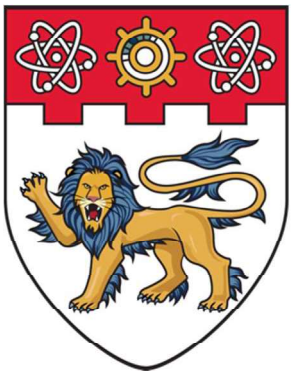

NANYANG TECHNOLOGICAL UNIVERSITY
SINGAPORE

# Reductive Molecular Transformations by Sodium or Zinc Hydrides

**Ong Yiren Derek**

**SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES**

**2020**

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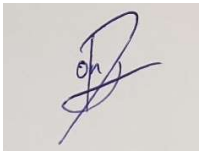
A thesis submitted to the Nanyang Technological University in partial fulfilment of the requirement for the degree of Doctor of Philosophy

**2020**

## Statement of Originality

I hereby certify that the work embodied in this thesis is the result of original research done by me except where otherwise stated in this thesis. The thesis work has not been submitted for a degree or professional qualification to any other university or institution. I declare that this thesis is written by myself and is free of plagiarism and of sufficient grammatical clarity to be examined. I confirm that the investigations were conducted in accord with the ethics policies and integrity standards of Nanyang Technological University and that the research data are presented honestly and without prejudice.



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Prof. Chiba Shunsuke

# Authorship Attribution Statement

This thesis contains material from 2 papers published in the following peer-reviewed journals which I am listed as the first author.

Chapter 2 is published as D. Y. Ong, C. Tejo, K. Xu, H. Hirao, and S. Chiba. Hydrodehalogenation of Haloarenes by a Sodium Hydride-Iodide Composite. *Angew. Chem. Int. Ed.* **56**, 1840-1844 (2017). DOI: 10.1002/anie.201611495.

The contributions of the co-authors are as follows:

- Prof. S. Chiba provided the initial project direction.
- The manuscript was prepared and revised by Prof. S. Chiba, Prof. H. Hirao, Dr. C. Tejo and the author.
- Dr. C. Tejo and the author designed the study and performed all the experimental work at the School of Physical and Mathematical Sciences.
- DFT calculations were performed and written by Mr. K. Xu and Prof. H. Hirao.

Chapter 4 is published as D. Y. Ong, Z. Yen, A. Yoshii, J. R. Imbernon, R. Takita, and S. Chiba. Controlled Reduction of Carboxamides into Alcohols or Amines by Zinc Hydrides. *Angew. Chem. Int. Ed.* **58**, 4992-4997 (2019). DOI: 10.1002/anie.201900233.

The contributions of the co-authors are as follows:

- Prof. S. Chiba provided the initial project direction.
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- The author, Mr. Z. Yen, Ms. A. Yoshii and Ms. J. R. Imbernon designed the study and performed all the experimental work at the School of Physical and Mathematical Sciences.
- The author conducted the different spectroscopic measurements for the characterization of zinc hydrides species at the School of Physical and Mathematical Sciences.
- DFT calculations were performed and written by Prof. Takita.

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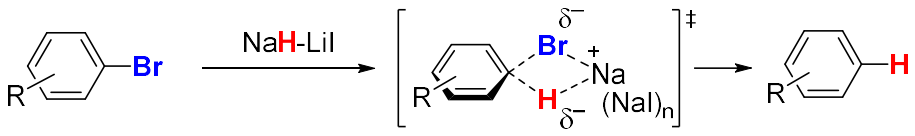
# Abstract

Reductive molecular transformations are highly valuable and important protocols for their synthetic applications in various fields. The use of sodium hydride as the hydride source has been underdeveloped due to its inert reactivity as a hydride donor. This thesis describes new utilization of sodium hydride as an unprecedented hydride source by combined use with main group metal halides to develop several types of reductive transformations.

Chapter 1 provides a brief review on the use of alkali metal hydrides as hydride source for preparation of synthetically useful hydride reagents and the direct activation of alkali metal hydrides for reduction reactions.

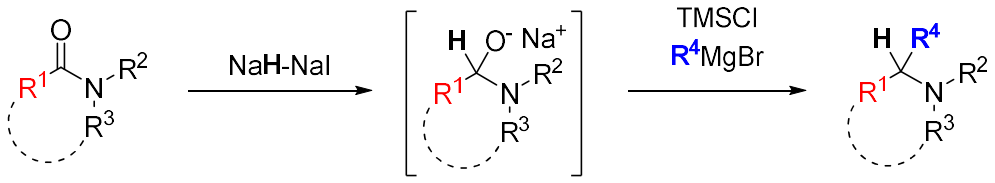
Chapter 2 describes the discovery and development of hydrodehalogenation of halo (hetero)arenes using sodium hydrides in the presence of lithium iodides, that proceeds through an unusual concerted nucleophilic aromatic substitution mechanism.

**Chapter 2. Hydrodehalogenation by NaH-LiI composite**



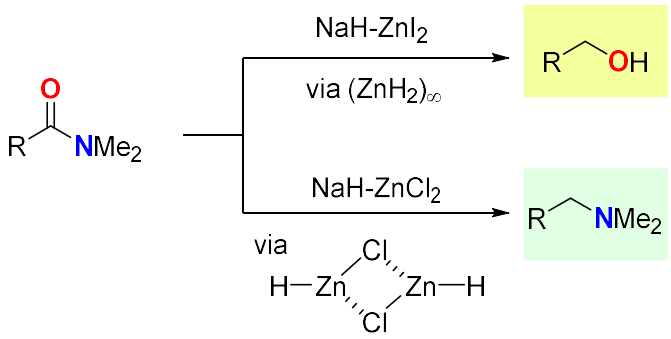

Chapter 3 shows development of transition-metal free reductive functionalization of carboxamides and lactams for synthesis of α-branched amines. The protocol relies on formation of stable anionic carbinol amine intermediates via the reduction of tertiary carboxamides with the sodium hydride-sodium iodide system and their subsequent treatment with trimethylsilylchloride and carbon nucleophiles such as Grignard reagents.

**Chapter 3. Transition-metal free synthesis of α-branched tertiary amines**



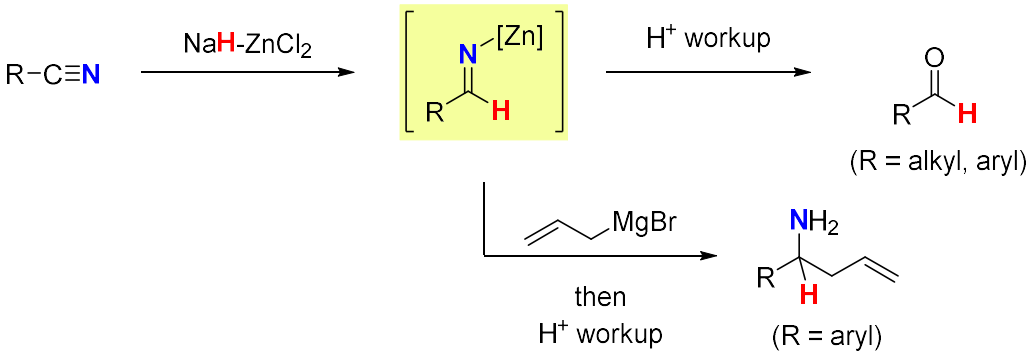

Chapter 4 discusses on the controlled reduction of carboxamides to either alcohols or amines using sodium hydride and zinc halides. The halides ions on the zinc dictates the process selectivity through generation of different types of zinc hydrides. These protocols tolerate a wide array of (hetero)aromatic and aliphatic amides and retains α-chirality for α-enantioenriched amides.

**Chapter 4. Controlled reduction of carboxamides to alcohols and amines by zinc hydrides**




Chapter 5 demonstrates the further synthetic application of zinc hydrides derived from sodium hydride and zinc chloride to perform controlled reduction of carbonitriles to aldehydes. The iminyl zinc intermediates formed through the hydride delivery to nitriles could also be further allylated with allyl metal reagents to afford the corresponding homoallyl amines.

**Chapter 5. Controlled reduction of carbonitriles to aldehydes by zinc hydrides**




Chapter 6 presents the experimental and computational data for the respective chapters 2, 3, 4 and 5.

Chapter 7 gives a brief conclusion and perspective.

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With deepest gratitude,

Derek

# Table of Contents

## List of Abbreviations

| | |
|---|---|
| % | percent |
| Δ | heat |
| $\Delta H_{lattic}$ | lattice energy |
| °C | degree Celsius |
| μm | micrometer |
| α | alpha |
| Ac | acetyl |
| AIBN | azobisisobutyronitrile |
| Bn | Benzyl |
| Boc | *tert*-butoxycarbonyl |
| brs | broad singlet |
| Calcd | calculated |
| cat. | catalytic |
| $cm^{-1}$ | wavenumber |
| CRA | complex reducing agents |
| d | doublet |
| dd | doublet of doublet |
| DFT | density function theory |
| DIBAL-H | diisobutylaluminum hydride |
| Dip | 2,6-diisopropylbenzene |
| DMF | *N*,*N*-dimethylformamide |
| dr | diastereomeric ratio |
| DTBMP | ditertbutylmethylpyridine |
| ee | enantiomeric excess |
| equiv | equivalent |
| ESIHRMS | Electrospray Ionization High Resolution Mass Spectrometry |
| Et | ethyl |
| FLP | frustrated Lewis pair |
| FTIR | Fourier Transform Infrared Spectroscopy |
| g | gram |
| h | hour |
| Hz | Hertz |

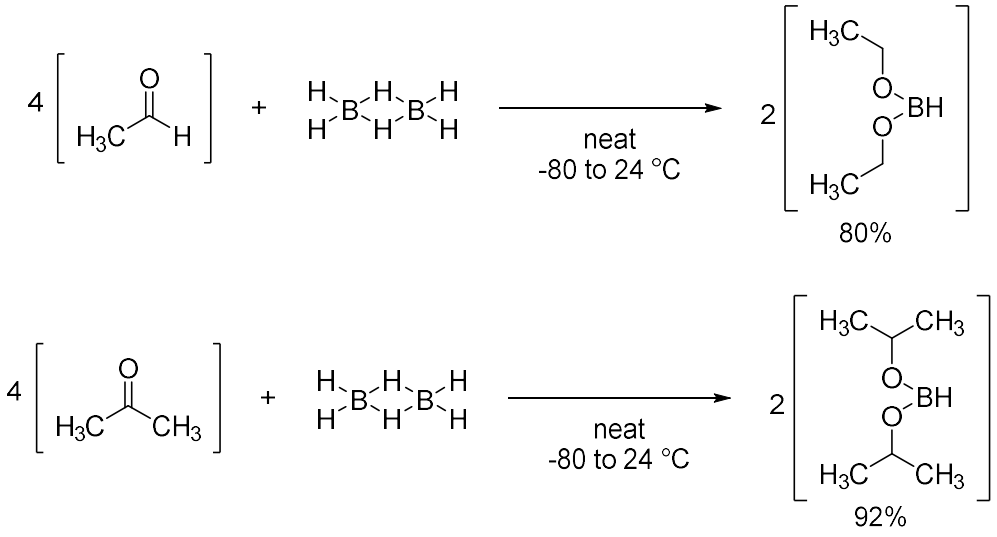
| | |
|---|---|
| INT | intermediate |
| *i*Pr | *iso*-propyl |
| *J* | coupling constants |
| kcal | kilocalorie |
| KJ | kilojoule |
| LDA | lithium diisopropylamide |
| m | multiplet |
| M | Molar (mol/L) |
| Me | methyl |
| Mes | 1,3,5-trimethylbenzene |
| min | minutes |
| mL | millilitre |
| mol | mole |
| Na(pz) | sodium pyrazolate |
| NaHMDS | sodium hexamethyldisilazane |
| *n*-Bu | *n*-butyl |
| Nu | nucleophile |
| Ph | phenyl |
| pzH | pyrazole |
| q | quartet |
| rt | room temperature |
| s | singlet |
| *s*-Bu | *sec*-butyl |
| sext | sextet |
| $S_NAr$ | nucleophilic aromatic substitution |
| t | triplet |
| TBACN | tetrabutylammonium cyanide |
| *t*-Bu | *tert*-butyl |
| td | triplet of doublet |
| TEA | triethylamine |
| Tf | trifluoromethylsulfonyl |
| THF | tetrahydrofuran |
| TIPS | triisopropylsilyl |

| | |
|---|---|
| TLC | thin layer chromatography |
| TMDS | tetramethyldisiloxane |
| TMEDA | tetramethylethylenediamine |
| TMS | trimethylsilane |
| TMSCl | trimethylchlorosilane |
| TMSCN | trimethylsilyl cyanide |
| TMSOTf | trimethylsilyl trifluoromethanesulfonate |
| TS | transition state |
| Ts | toluenesulfonyl |
| UV | ultraviolet |
| XRD | X-ray diffraction |
| δ | chemical shift (ppm) |
| ρ | rho |
| % | percent |

## Chapter 1. General Introduction

Reductive molecular transformations are well established and highly appreciated for their utilization in various opportunities for the synthesis of pharmaceutical and fine chemicals.[1] Most of the reported reduction protocols can be categorized into these three types of methodologies: 1) the use of stoichiometric amount of hydride reagents for reduction; 2) catalytic hydrogenation under hydrogen gas atmosphere; 3) catalytic hydrosilylation.

The use of hydride reagents for the reduction of polar π-electrophiles such as carbonitriles, imines, nitros, and carbonyl compounds as well as non-polar ones such as alkynes and alkenes are one of the most reliable protocols due to conveniences and availabilities of those reagents. In 1936, Schlesinger first reported the reaction of diborane with carbon monoxide to generate borane-carbonyl compounds,[2] while there were debates on whether it was a simple addition of carbon monoxide to borane or a hydride transfer from boron to carbon center.[3] It was only later in 1939, Schlesinger and Brown confirmed the first application of diborane as a hydride source for the reduction of carbonyl compounds (Scheme 1.1).[4]




**Scheme 1.1.** Reduction of carbonyl groups with diborane.

The typically employed hydrides for reduction processes were covalent hydrides such as boranes, borohydrides, alanes, aluminum hydrides and silanes/siloxanes (Figure 1.1).[3, 5] The use of these hydrides is able to realize well-controlled regio-[6] stereo-[7] and chemo-[8] selectivity.

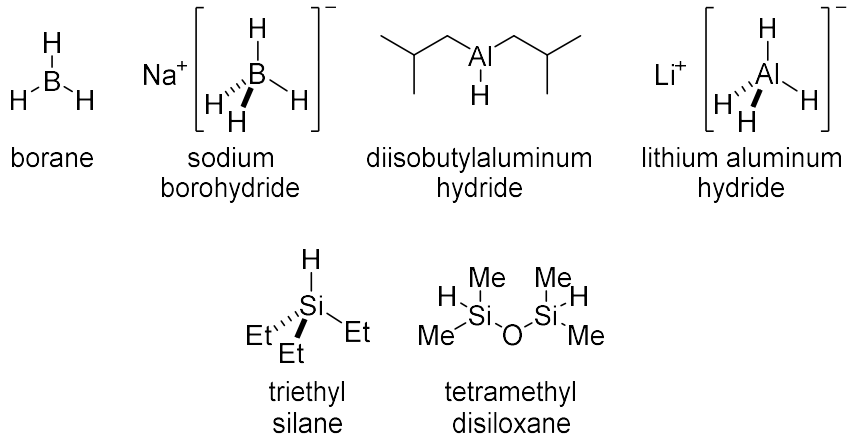



**Figure 1.1.** Various type of covalent hydrides.

In contrast to these covalent hydrides, ionic hydrides such as alkali metal or alkaline earth metal hydrides are rarely used as hydride source for the reduction of polar or non-polar π-electrophiles. Actually, these ionic hydrides have been exclusively used as a Brønsted base to perform deprotonation reactions.[9] It is described in Organic Chemistry 2nd editions by Clayden et al. that "sodium hydride, NaH, has such a high charge density that it only ever reacts as a base".[10] Therefore, the common practice and belief shared in the community of chemical synthesis is that ionic hydrides are exclusively used as a Brønsted base and not as a hydride source.

The main reason why these ionic hydrides based on alkali metals or alkaline earth metals are employed only as a Brønsted base is because of their very high lattice energy, $\Delta H_{lattice}$ (Table 1.1).[11] In general, the lattice energy per mole of metal hydrides will

decrease down the group. For group 1 elements, lithium to cesium and for Group 2 elements, from beryllium to barium as shown in Table 1.1.

**Table 1.1.** Lattices energy of various alkali metal or alkaline earth metal hydrides.

| Alkali Metal hydrides | $\Delta H_{lattice}$ (KJ $mol^{-1}$) | Alkaline earth metal hydrides | $\Delta H_{lattice}$ (KJ $mol^{-1}$) |
|---|---|---|---|
| LiH | 858 | $BeH_2$ | 3205 |
| NaH | 782 | $MgH_2$ | 2791 |
| KH | 699 | $CaH_2$ | 2410 |
| RbH | 674 | $SrH_2$ | 2250 |
| CsH | 648 | $BaH_2$ | 2171 |

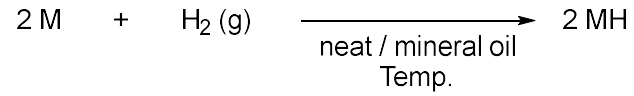
Such high lattice energy prevents the alkali metal hydrides from being soluble in aprotic organic solvents. Owning to the high natural abundance of alkali metals, it should be attractive to make use of alkali metal hydrides for the reduction processes. Nonetheless, several reports have been published on use of alkali metal hydrides for reduction reactions of π-electrophiles through their chemical activation.

In this chapter, the author will discuss and summarize the approaches for the utilization of alkali metal hydrides as hydride source and the direct activation of alkali metal hydrides for reduction protocols.

### 1.1. Alkali metal hydrides

The alkali metal hydrides are typically produced by the hydrogenation of the metal dispersion at high temperature (Scheme 1.2).[9] However, the direct hydrogenation of the metal dispersion is a very slow process due to the formation of a protective layer of metal hydrides during the process. The potential explosion hazard is also present as the

hydrogen source is typically attached directly to the reaction vessel to provide a continuous flow of hydrogen. Recent advances in the synthesis of alkali earth metal hydrides reported by Guérard et al. made use of modified mechanical alloying technique.[12] In this technique of mechanical alloying, the milling balls can effectively remove the protective metal hydride layers to allow for a fresh layer of metal to react with the hydrogen gas.[13] Guérard et al. concluded their protocol with the gram scale synthesis of various alkali metal hydrides from NaH (16 g) to CsH (89 g) within 16 h that exemplified its feasibility for commercialization.




| M: | Temp. (°C) |
|---|---|
| Li | 700-900 |
| Na | 250-300 |
| K | 90-200 |

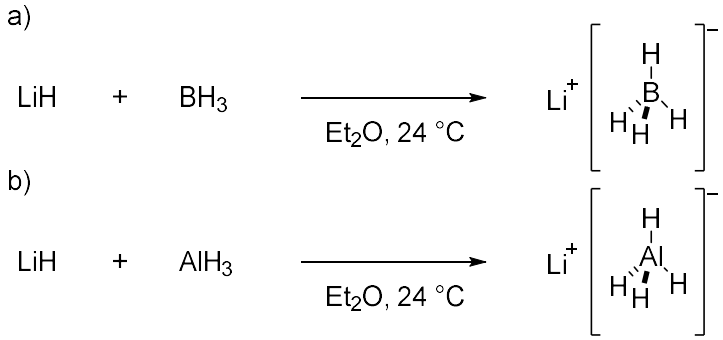
**Scheme 1.2.** Synthesis of alkali metal hydrides by hydrogenation of alkali metals.

Alkali metal hydrides have the cubic halite structure in which each metal cation is surrounded by six hydride ions and *vice versa*. These alkali metal hydrides have high lattice energy, which makes them insoluble in most of the aprotic organic solvents. The following section will discuss selected protocols for utilization of alkali metal hydrides as hydride source for reduction of π-electrophiles.

### 1.1.1. Activation by formation of "ate" complexes

Schlesinger and Brown et al. developed methods to convert alkali metal hydrides to their corresponding "ate" complexes by addition of borane[14] or alane[15] to lithium hydrides to afford lithium borohydride ($LiBH_4$)[16] (Scheme 1.3a) and lithium

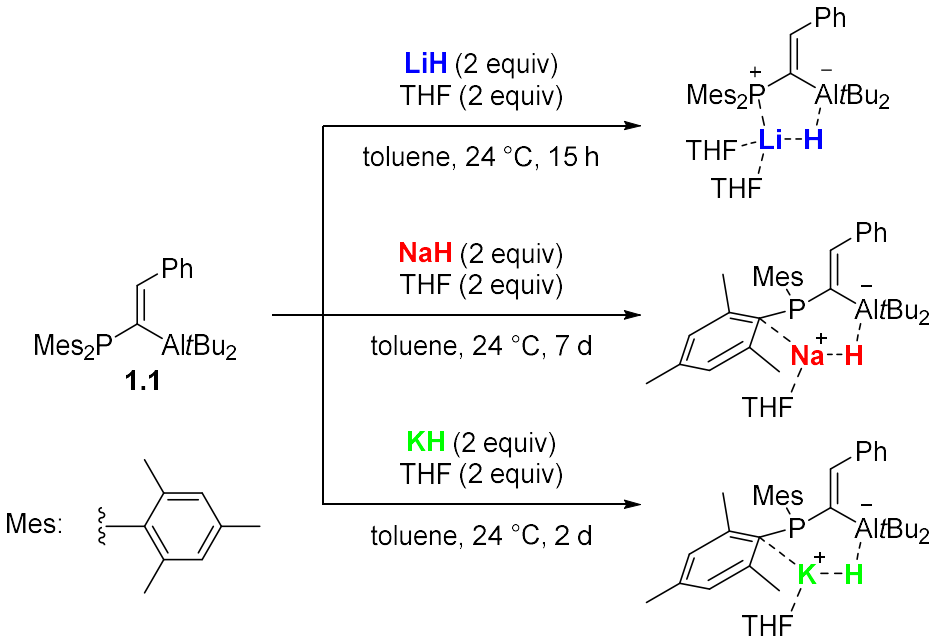
aluminum hydride ($LiAlH_4$)[17] respectively (Scheme 1.3b). Hence, alkali metal hydrides serve as the hydride source to form the corresponding ate covalent hydrides.




**Scheme 1.3.** Synthesis of "ate" complexes with a) Borane; b) Alane.

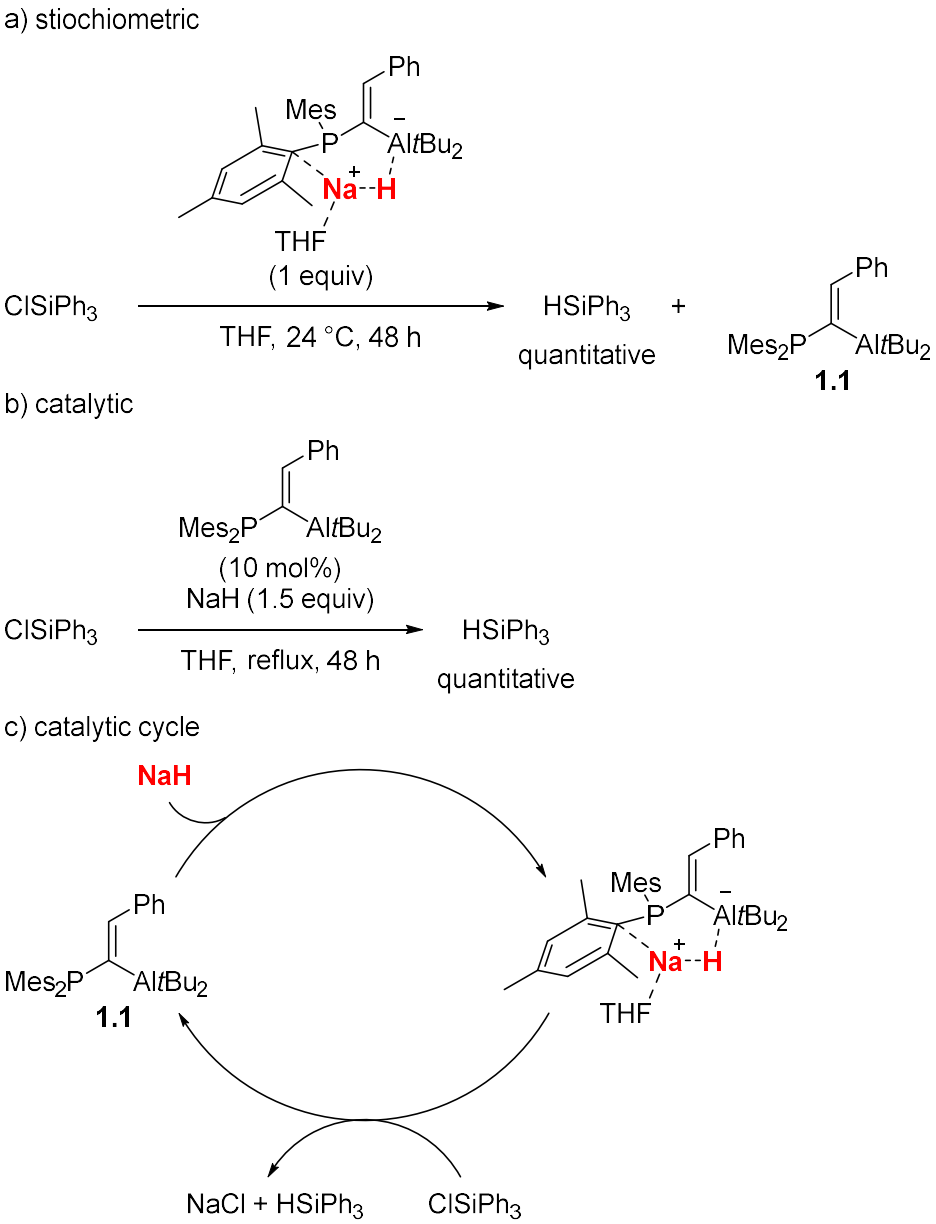
### 1.1.2. Mixed metal hydride complexes

Slootweg and Uhl et al. recently reported the use of a phosphorus/aluminum-based frustrated Lewis pair (FLP) **1.1** to activate commercial alkali metal hydrides (LiH, NaH, and KH) by generation of soluble FLP complexes with the respective alkali metal hydrides (Scheme 1.4).[18] Interestingly, the LiH-FLP complex has an unique coordination pattern that differs from those based on NaH and KH. This is because Na and K, which are larger and softer than Li, preferred to coordinate to arene through cation-π interaction rather than the phosphorus moiety.




**Scheme 1.4.** Synthesis of "ate" complexes with FLP.

These soluble alkaline metal-FLP complexes did show hydride donor reactivity. Slootweg and Uhl et al. demonstrated that stoichiometric amount of NaH-FLP complexes could reduce chlorotriphenylsilane to the corresponding triphenylsilane (scheme 1.5a). They realized that the FLP **1.1** was recovered after the stoichiometric reaction, hence they envisioned that development of the catalytic variant might be feasible. Using 10 mol% of FLP **1.1** and 1.5 equiv of commercial sodium hydride, they were able to convert chlorotriphenylsilane to triphenylsilane quantitatively. In contrast, no reaction was observed when chlorotriphenylsilane was treated with only commercial sodium hydride. This clearly demonstrated the enhanced hydricity of the alkali metal-FLP complexes.

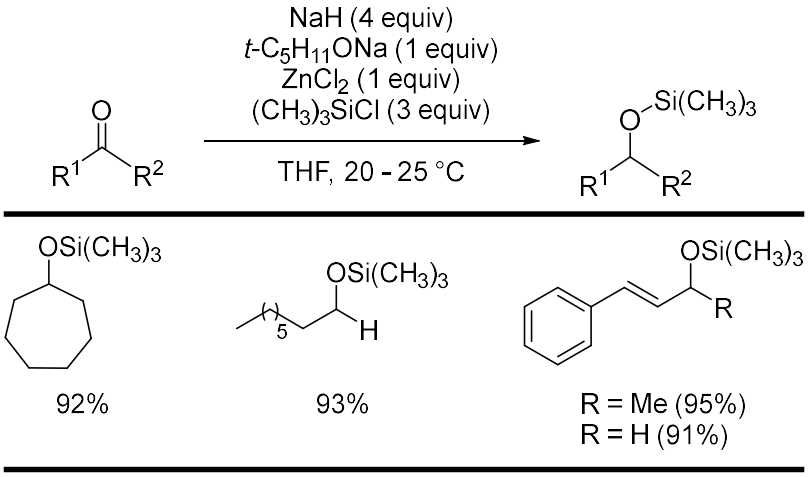



**Scheme 1.5.** Reduction of chlorotriphenylsilane using NaH-FLP complexes.

### 1.1.3. Complex reducing reagents

Caubere et al. has developed a new class of reducing agents known as complex reducing agents (CRA), particularly zinc CRA (ZnCRA) that worked in conjunction with chlorotrimethylsilane (TMSCl). The ZnCRA was prepared by first heating a mixture of NaH and $ZnCl_2$ in THF at 63 °C, followed by addition of *t*-amyl alcohol and TMSCl. Treatment of this ZnCRA with carbonyl substrates afforded the corresponding alkyl

silyl ethers (Scheme 1.6).[19] This protocol allowed for reductive silylation of ketones or aldehydes containing enolizable protons, whereas the use of commercial NaH would not enable reductive silylation of these substrates. This protocol also allowed the selective reductive silylation of unsaturated ketones and aldehydes while keeping the alkenyl groups intact.



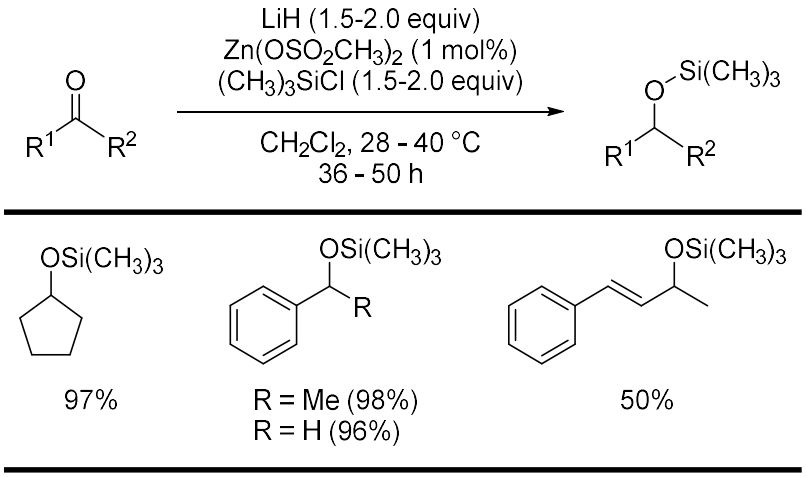

**Scheme 1.6.** Reductive silylation of carbonyl substrate with ZnCRA/TMSCl.

The mechanism of this protocol is unclear, however, Caubere et al. did investigate ZnCRA in detail and found a new species, $[(t\text{-}C_5H_{11}O)_xZn(Na)_x]_n$ that is associated with Zn metal and sodium *t*-pentoxide.[20] They proposed that $[(t\text{-}C_5H_{11}O)_xZn(Na)_x]_n$ will further interact with sodium hydride to form the reducing reagent for their protocol. This provided a simple yet effective method to use commercial sodium hydride as a hydride source to perform reductive silylation on carbonyl substrates.

### 1.1.4. Counter ion metathesis between alkali metal hydrides and metal salts

Noyori et al. reported the reductive silylation of carbonyl compounds with commercial lithium hydride and chlorotrimethylsilane (TMSCl) in the presence of zinc(II) mesylate

($Zn(OMs)_2$) as the catalyst (Scheme 1.7).[21] This protocol allowed for reductive silylation of saturated and unsaturated ketones and aldehydes to afford the corresponding alkyl silyl ethers in almost quantitative yields. Noyori et al. proposed that the commercial LiH is first activated by TMSCl, after which zinc(II) mesylate further interacted on the surface of the activated LiH that enabled the reductive silylation of carbonyl compounds.




**Scheme 1.7.** Reductive silylation of carbonyl substrate with $LiH/Zn(OMs)_2$/TMSCl.

Based on the reports above, the lithium hydrides acted as the hydride source for possible generation of zinc hydride species through counter ion metathesis with zinc(II) mesylate, which were responsible for the reductive transformation.

Ashby et al. reported the use of alkali metal hydrides for counter ion metathesis with other metal salts to generate the corresponding metal hydrides. Ashby et al. first reported the reaction of alkali metal hydrides with magnesium halides ($MgX_2$) to generate magnesium hydrides ($MgH_2$).[22] Ashby et al. conducted a series of reaction

between various alkali metal hydrides with $MgX_2$ to conclude the reactivity of alkali metal hydrides (Table 1.2).

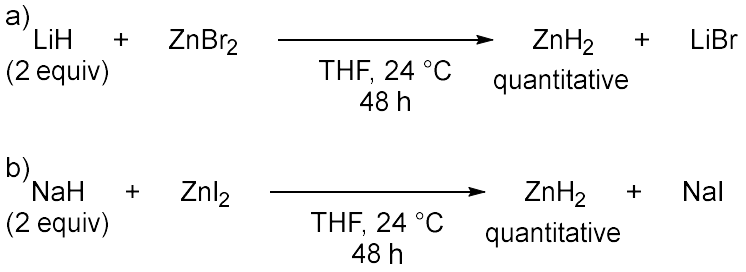
**Table 1.2.** Reaction of alkali metal hydrides with magnesium halides in various solvents.[a]

| Entry | 2MH + $MgX_2$ | Solvent | Yield of $MgH_2$ (%) |
|---|---|---|---|
| 1[b] | LiH + $MgBr_2$ | Tetrahydrofuran | 0 |
| 2[c] | LiH + $MgCl_2$ | Tetrahydrofuran | 64 |
| 3[c] | LiH + $MgBr_2$ | Tetrahydrofuran | 74 |
| 4[c] | LiH + $MgI_2$ | Tetrahydrofuran | 16 |
| 5 | NaH + $MgBr_2$ | Tetrahydrofuran | 15 |
| 6 | NaH + $MgBr_2$ | Diethyl ether | 10 |

[a] All reactions run in refluxing solvent for 5 h. [b] Commercial LiH. [c] LiH synthesized by hydrogenolysis of *t*-butyllithium.

They concluded that commercial LiH was unreactive to react with $MgX_2$, whereas a freshly prepared LiH by deprotonation of molecular hydrogen with *t*-BuLi was able to react with $MgX_2$ to give the corresponding $MgH_2$. The other trend that was observed for reactivity of magnesium halides was such that Br>Cl>I. They proposed that was due to $MgI_2 \cdot 6THF$ being poorly soluble in THF. Interestingly, this meant that solubilities of the metals salt in the respective solvent systems is an important factor for effective counter ion metathesis between metal salts and alkaline metal hydrides.

Ashby et al. also examined the reaction of alkali metal hydrides with zinc halides, $ZnX_2$. They reported the successful isolation of zinc hydride, $ZnH_2$ from the reaction between LiH and $ZnBr_2$ and NaH and $ZnI_2$ (Scheme 1.8).[23]

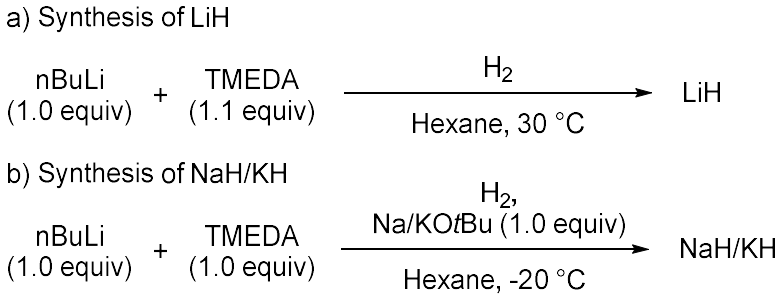



**Scheme 1.8.** Reaction of alkali metal hydrides with $ZnX_2$.

In principle, the utilization of alkali metal hydrides as the hydride source that involved the conversion of alkali metal hydrides to other complexes/compounds, where the hydride ligands are not or partially bonded to the alkali metal. This effectively led to new hydride species having a reactivity that is not theoretically similar from the original alkali metal hydrides. A more direct activation of alkali metal hydride will be discussed in the following sections.

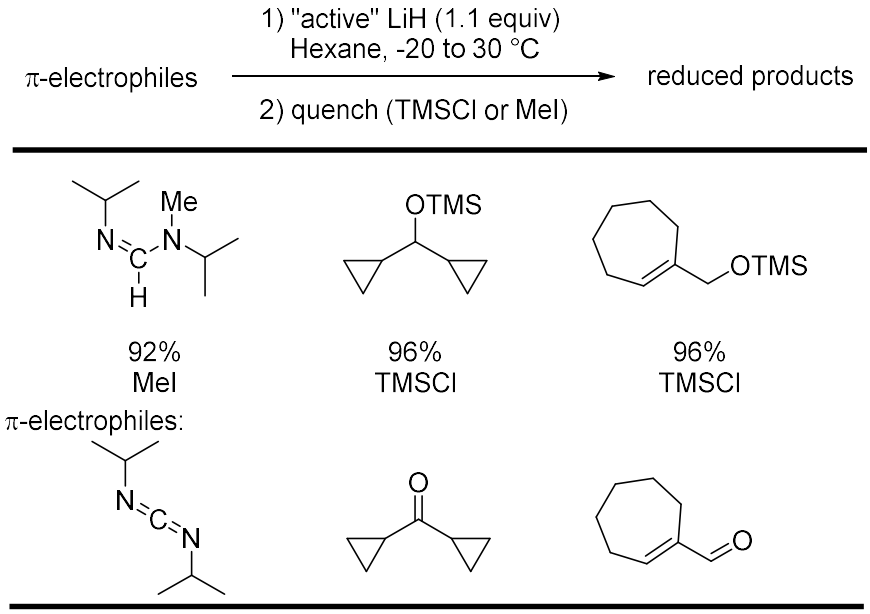
### 1.1.5. Activation by *in-situ* generation of alkali metal hydrides

Brandsma and Schleyer et al. reported the production of highly active alkali metal hydrides (LiH, NaH, KH) by deprotonation of molecular hydrogen with highly basic reagents such as *n*BuLi/TMEDA, *n*BuLi/TMEDA/NaO*t*Bu, and *n*BuLi/TMEDA/KO*t*Bu (Scheme 1.9).[24]



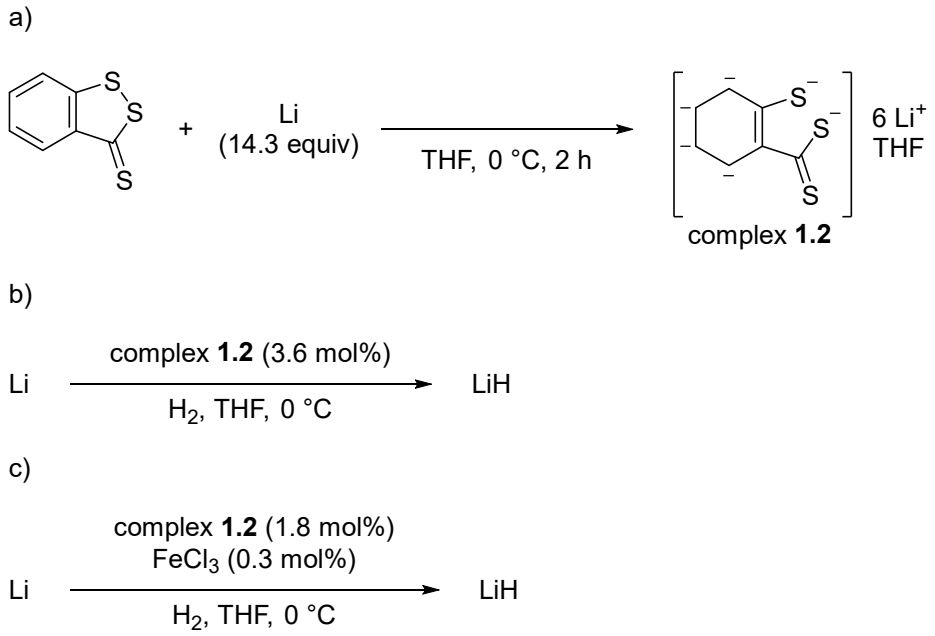

**Scheme 1.9.** Synthesis of highly active a) LiH; b) NaH and KH.

These protocols afforded more reactive alkali metal hydrides than the commercially available ones as commercial LiH tend to aggregate over time to form large polymeric form due to their high lattice energy, hence overall surface area to volume ratio is lower and correspondingly unreactive. The difference in the reactivity can be observed from the ability of their *in-situ* generated lithium hydride to reduce π-electrophiles like carbodiimides, ketones and aldehydes (Scheme 1.10)[25] whereas the commercially available lithium hydride could not reduce those π-electrophiles.



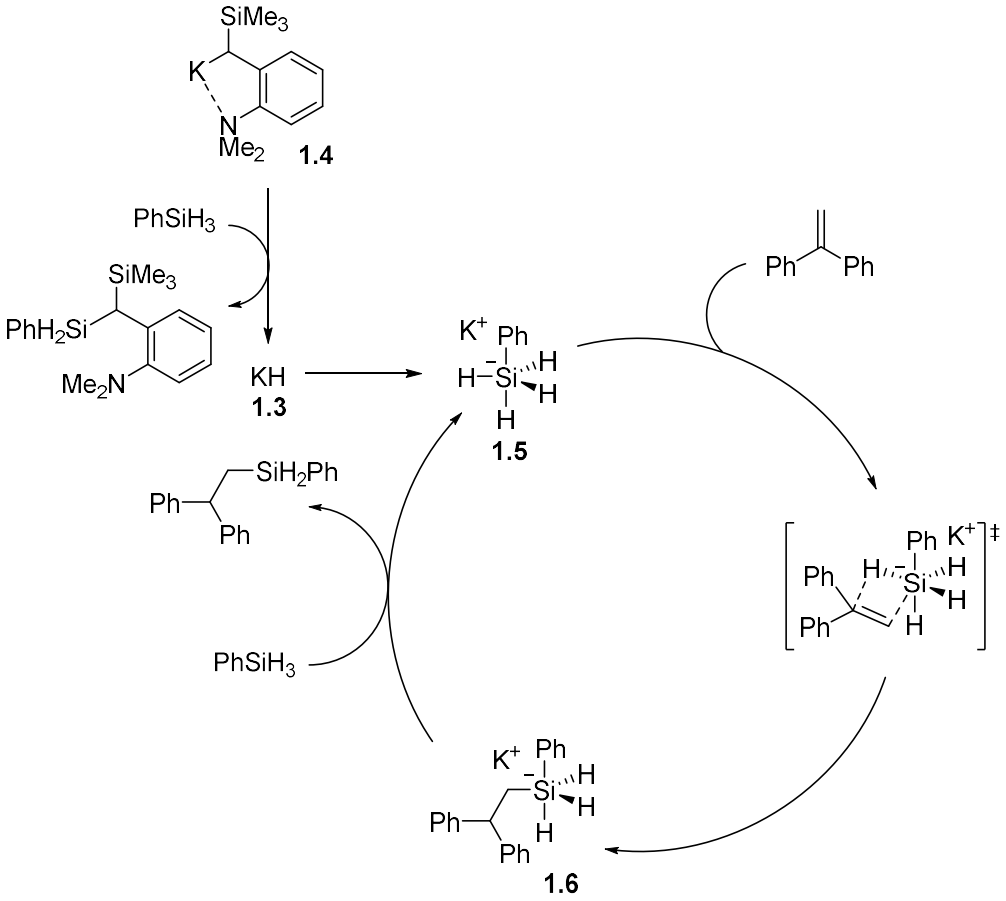

**Scheme 1.10.** Reduction of π-electrophiles using activated LiH.

Instead of the use of very basic reagents to deprotonate hydrogen gas, Bogdanovic et al. reported the direct hydrogenation of lithium sand at 0 °C using a catalytic amount of benzo-1,2-dithiol-3-thione hexalithium complex **1.2** in THF to generate highly active lithium hydride (Scheme 1.11b).[26] The complex **1.2** can be easily prepared by treatment of benzo-1,2-dithiol-3-thione with excess amount of lithium metal in THF (Scheme 1.11a). Finally, the rate of hydrogenation can be further increased by the addition of iron (III) chloride as a co-catalyst (Scheme 1.11c).



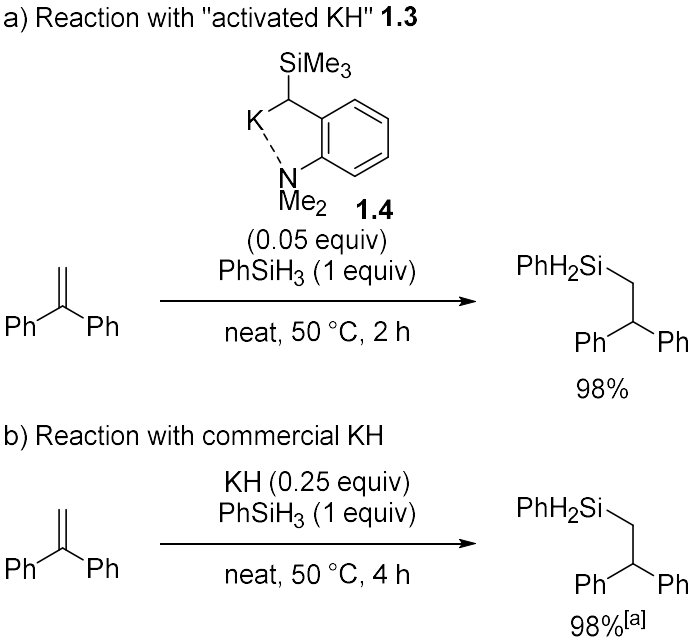

**Scheme 1.11.** Hydrogenation of Li with catalysis.

Recently, Harder et al. reported the generation of active potassium hydride **1.3** from the silylbenzylpotassium complex **1.4** and phenylsilane (Scheme 1.12). The activated potassium hydride **1.3** was first formed by transmetalation between silylbenzylpotassium complex **1.4** and phenylsilane. The resulting in-situ generated active potassium hydride reacted with another molecule of phenylsilane to generate the hypervalent silicon species **1.5**, which reacted with 1,1-diphenylethene to give hydrosilylated intermediate **1.6**. Subsequent σ-bond metathesis of **1.6** with another molecule of phenylsilane gave the *anti*-Markovnikov hydrosilylated product with the regeneration of **1.5** to maintain the catalytic cycle.



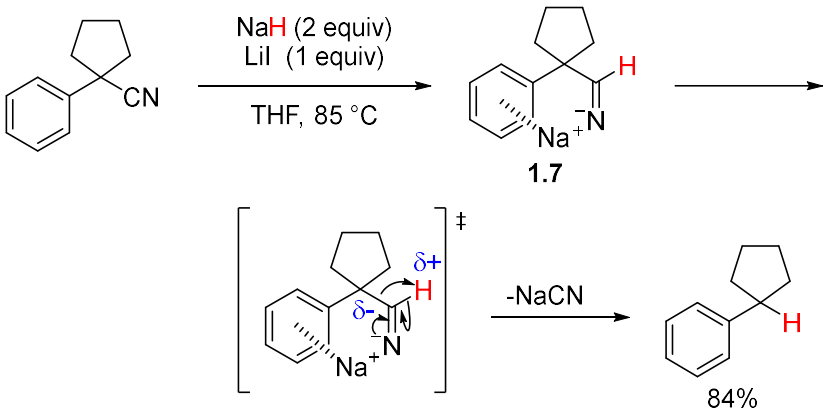

**Scheme 1.12.** Generation of active KH and mechanism of hydrosilylation.

The resulting reactive potassium hydride **1.3** enabled faster hydrosilylation of 1,1-diphenylethene in comparison with that by the commercially available potassium hydride (Scheme 1.13).[27]



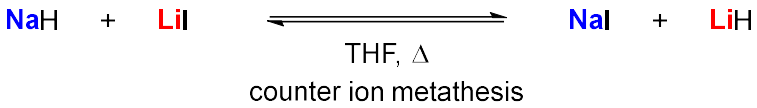

**Scheme 1.13.** Hydrosilylation of 1,1-diphenylethene. [a] 90 min incubation time.

Chiba et al. recently reported the use of commercial sodium hydride in the presence of sodium or lithium iodide for reductive decyanation of α-quaternary benzyl nitrile (Scheme 1.14).[28-29] In the absence of iodide salts, the reductive decyanation did not proceed. The process was assumed to be initiated by hydride addition of activated sodium hydride to the cyano group to form iminyl sodium intermediates **1.7**. Subsequent C-C bond cleavage was facilitated by 1,2-proton shift to form hydrodecyanated product along with formation of sodium cyanide.




**Scheme 1.14.** Reductive decyanation of α-aryl benzyl nitrile.

Intrigued by the enhanced hydricity of sodium hydride in the presence of sodium or lithium iodide, Chiba et al. employed various spectroscopic techniques and density function theory (DFT) calculation to understand this enhanced hydricity. It was proposed that sodium hydride and soluble iodide salts underwent solvothermal counter ion metathesis (Scheme 1.15).[29] This counter ion metathesis provided the system with fresh, likely nanometric sodium hydride that displayed the observed hydricity.

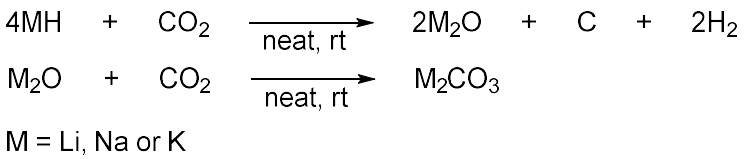



**Scheme 1.15.** Counter ion metathesis.

### 1.1.6. Activation by mechanical means

Commercially available alkali metal hydrides typically have larger particle sizes; hence, they have smaller surface area to volume ratio and correspondingly lower hydricity. Dong and Teng et al. reported the use of mechanical ball milling to reduce the particle size of commercially available alkali metal hydrides (LiH, NaH, KH) to enable the reduction of carbon dioxide to elemental carbon at room temperature (Scheme 1.16),[30]

while the commercially available alkali metal hydrides show no to little reduction of carbon dioxide.

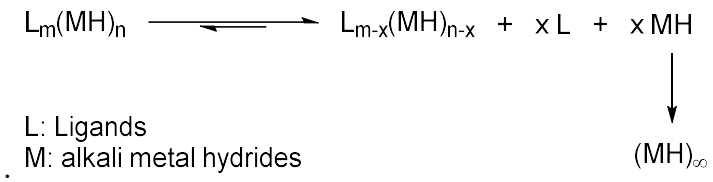



**Scheme 1.16.** Reduction of $CO_2$ using mechanically activated alkali metal hydrides.

They reported the average particle size of commercial LiH samples is around 2.3 – 18 μm. When this commercial LiH was subjected to mechanical ball milling processes for 48 h, the average size of the particles reduced to 0.55 – 8 μm. In summary, generation of alkali metal hydrides of nanometric size by mechanical means also helps to increase their hydricity. Although activation of alkali metal hydride by decreasing the particle size is an effective method, those metal hydrides remain in their halite cubic structures, which are insoluble in organic solvent. Therefore, more effective methods should be the design and synthesis of molecular alkali metal hydrides by using sophisticated ligands.

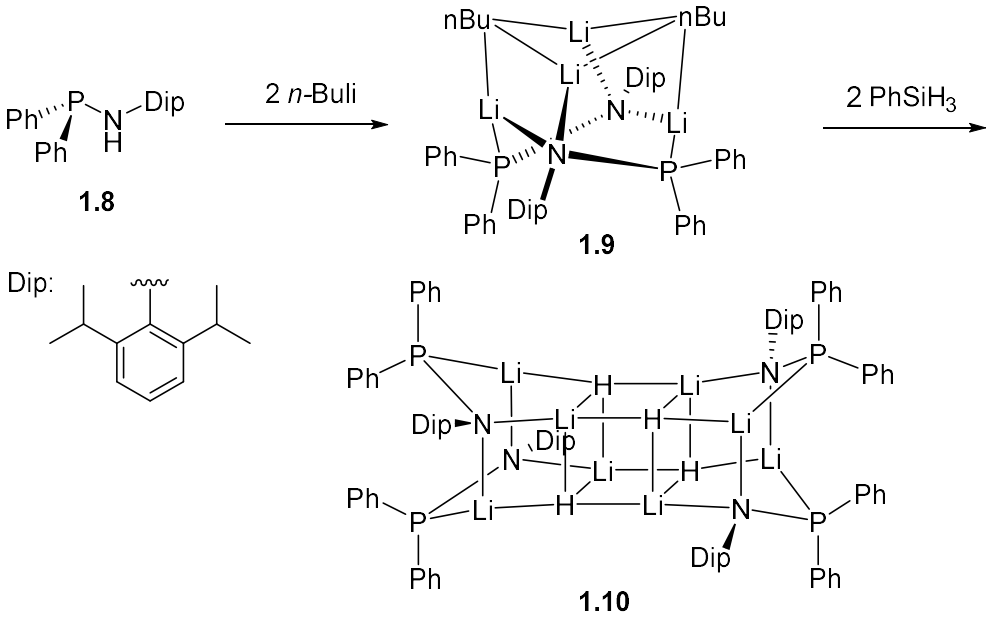
### 1.1.7. Activation by formation of molecular alkali metal hydride

Schlenk equilibrium of alkali metal hydrides complexes tend to shift towards the formation of polymeric state. This meant that monomeric alkali metal hydrides complexes inherently tend to aggregate into polymeric form due to their high lattice energy as mentioned in Table 1.1 (Scheme 1.17).[11] Therefore, the main challenge for the synthesis of molecular alkali metal hydride complexes is to design suitable ligands that stabilize the molecular forms.



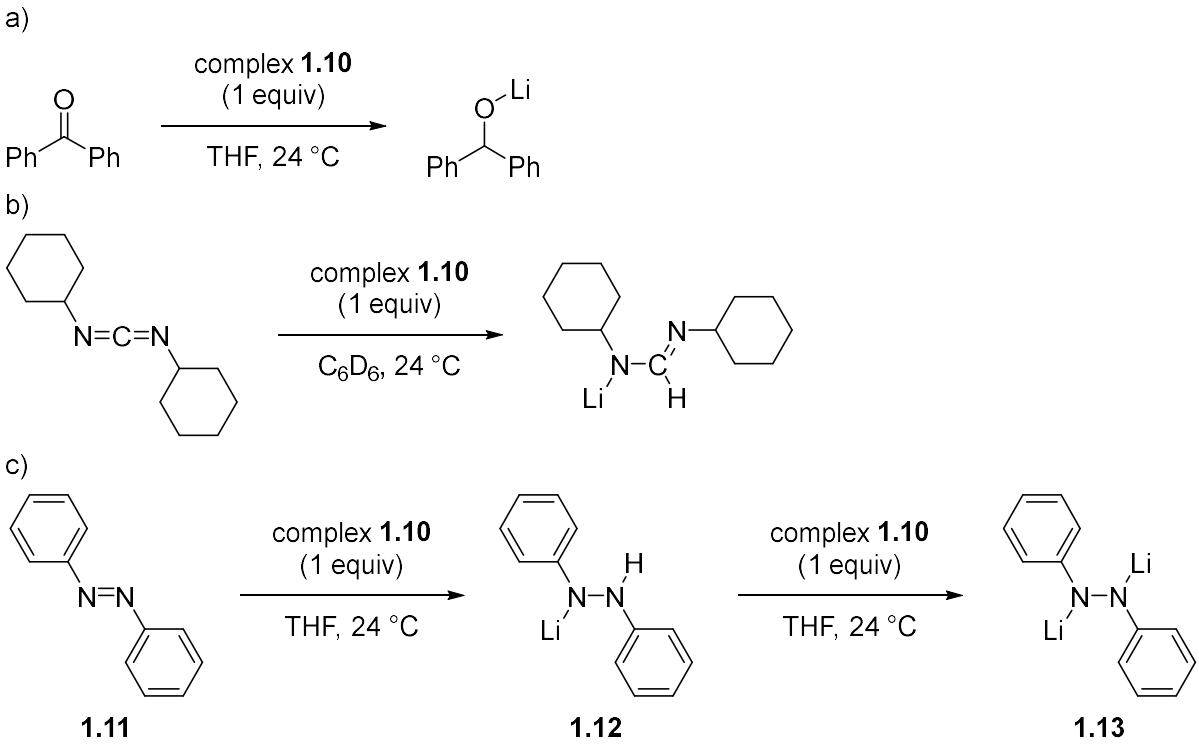

**Scheme 1.17.** Schlenk equilibrium for alkali metal hydrides complexes.

Stasch et al. reported the synthesis of a soluble molecular LiH cluster complex **1.10** having a central $(LiH)_4$ cube (Scheme 1.18).[31] This complex was synthesized via the 3-step process: 1) phosphinoamine, $DipNHPPh_2$ (**1.8**) was synthesized by nucleophilic substitution of $ClPPh_2$ with DipNHLi; 2) phosphinoamine **1.8** was treated with *n*-Buli to form the alkyl phosphinoamido lithium complex **1.9**; 3) addition of phenylsilane to **1.9** in toluene afforded the soluble molecular LiH cluster complex **1.10**, which is stable at 60 °C, while at temperature above 60 °C, Schlenk equilibrium will shift to result in the decomposition and the formation of polymeric lithium hydride.




**Scheme 1.18.** Synthesis of LiH cluster complexes **1.10.**

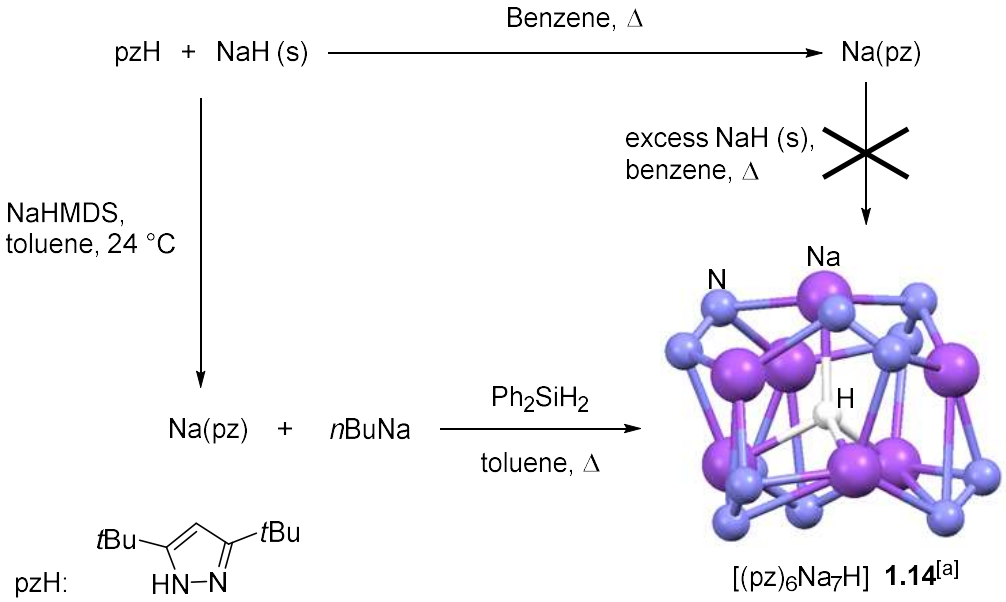
To demonstrate the enhanced hydricity of complex **1.10**, various π-electrophiles were treated with the complex **1.10** (Scheme 1.19).[32] Complex **1.10** was able to successfully reduce benzophenone (Scheme 1.19a) and dicyclohexylcarbodiimide (Scheme 1.19b). The reduction of diphenyldiazene **1.11** gave the expected mono lithiated diamine **1.12** with the umpolung of hydride to proton which underwent further deprotonation by complex **1.10** to afford the dilithiated diamine **1.13** (Scheme 1.19c). The application of this cluster complex **1.10** as a synthetic equivalent of LiH was limited to the reduction of only reactive and simple π-electrophiles.




**Scheme 1.19.** Hydrometallation of π-electrophiles using complex **1.10.**

Stasch et al. also reported the synthesis of the first known example of molecular NaH cluster complex (Scheme 1.20).[33] This was achieved using sterically bulky 3,5-di*tert*butyl-1H-pyrazole (pzH) as ligand to stabilize the molecular NaH cluster complex. Sodium pyrazolate, Na(pz) was first prepared from pyrazole (pzH) and sodium

hexamethyldisilazane (NaHMDS). The corresponding Na(pz) was subjected to *n*-butyl sodium and diphenylsilane to form the NaH cluster complex $[(pz)_6Na_7H]$ **1.14.** However, when Na(pz) was heated with sodium hydride in benzene, no reaction was observed. This highlighted the challenges of forming alkali metal complexes directly from commercial alkali metal hydrides having very high lattice energy. Stasch did not reported the thermal stability of this NaH complexes **1.14**, while it was reported that this complex was synthesized during reaction of Na(pz), *n*-butyl sodium and diphenylsilane in toluene at 90 °C. Stasch et al. also did not examine its reactivity.




**Scheme 1.20.** Synthesis of NaH cluster complex **1.14**. CCDC: 1043423 [a] Ligand pz was represented only by its N atoms in complex **1.14**

### 1.2. Perspective of this thesis

In summary, the utilization of alkali metal hydride as the hydride source for the formation of ate metal hydride complexes, mixed metal hydride, complex reducing reagents or for counter ion metathesis with other metal salts to generate active metal

hydrides are generally effective. However, the methods for reductive transformation with the use of alkali metal hydrides in the presence of metal salts are still very limited. Conversely, the direct activation of alkali metal hydrides can be classified into two types; 1) the generation of alkali metal hydrides with smaller particle size through *in-situ* generation or by mechanical means; 2) the synthesis of soluble molecular alkali metal hydrides.

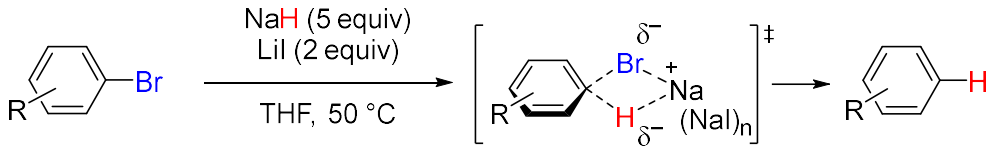
The author believed that there is still more possibility to explore the utilization of metal salts with alkali metal hydrides and further exploration into the actual species responsible for their reductive transformations. The use of alkali metal hydrides is still advantageous in term of atom economy[34] due to the higher hydride content of alkali metal hydrides comparing to other hydride reagents based on B, Al, and Si. Furthermore, sodium is the 6$^{th}$ most natural abundance element on earth [35] and the most natural abundance element of the group 1 alkali metals.

Based on these backgrounds, through this PhD study, the author has aimed to explore and develop general and practical protocols to make use of sodium hydride for reductive transformations and to utilize other metal salts with sodium hydride to generate possible new metal hydrides for new reductive molecular transformations. The contents of the PhD thesis are briefly summarized below.

### 1.2.1. Reductive molecular transformations with sodium hydride

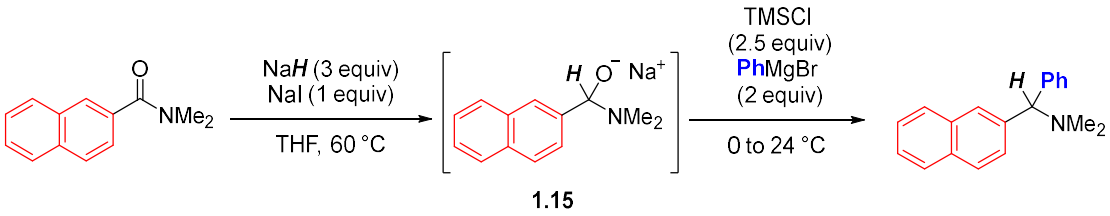
During the examination of substrate scope for hydrodecyanation of α-quaternary benzyl cyanide,[28] the author noticed that the substrate containing bromoarene underwent hydrodebromination to the corresponding reduced arene with sodium hydride-iodide composite. In chapter 2, the author investigated further the scope and limitation of hydrodehalogenation of haloarenes (Scheme 1.21).[36] The mechanistic studies revealed

that the hydrodehalogenation is mediated under an unusual concerted nucleophilic aromatic substitution.




**Scheme 1.21.** Hydrodebromination of halo (hetero)arenes using sodium hydride and lithium iodide.

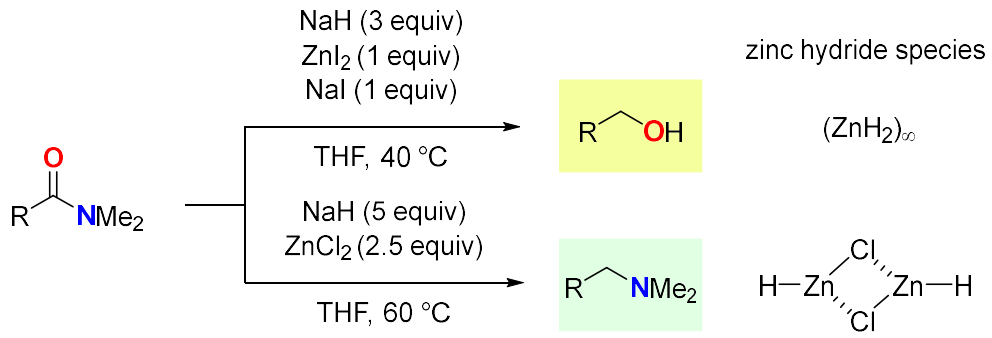
The author's group has developed a protocol for controlled reduction of carboxamides to aldehydes.[37] Intrigued by the reactivity difference between reduction of carboxamides with diisopropylaluminum hydride (DIBAL-H) and sodium hydride-iodide composite, a mechanistic study was conducted to understand the reactivities difference.[38] During the study, the author concluded that the anionic carbinol amine intermediate **1.15** can be formed as a stable species that could be confirmed by the NMR spectroscopies. To seek for further conversion of the intermediate **1.15**, in chapter 3, the author demonstrated a transition-metal-free reductive coupling of carboxamides with carbon nucleophiles such as Grignard reagents (Scheme 1.22).




**Scheme 1.22.** Synthesis of α-branched tertiary amines

### 1.2.2. Reductive molecular transformations with zinc hydride

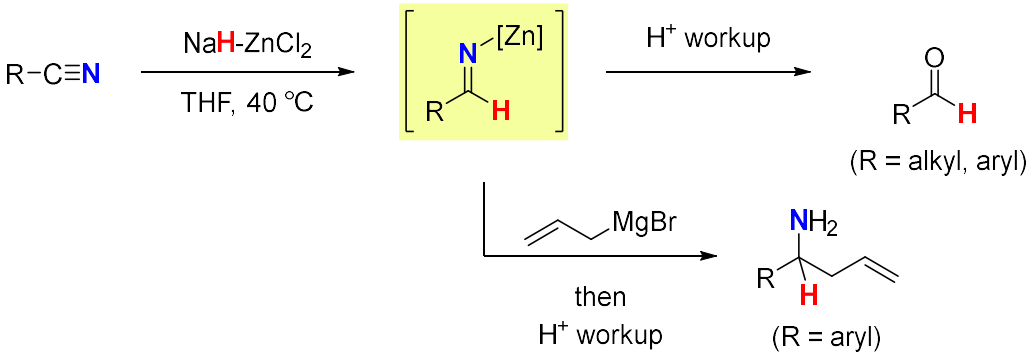
Having explored the unprecedented reductive transformation of sodium hydride-iodide composition, the author paid attention to the ability of sodium hydride in inducing counter ion metathesis with soluble alkali metal iodides. The author became interested in the generation of new metal hydrides species through counter ion metathesis. Previous reports on the synthesis of polymeric[23] or molecular[39] zinc hydrides suggested the feasibility of exploring zinc hydrides as the target. In chapter 4, the author discovered that counter ion metathesis between sodium hydride and various zinc halides resulted in the formation of distinct zinc hydride complexes. These zinc hydride complexes exhibited unique chemical reactivity on the controlled reduction of amides to amines and alcohols (Scheme 1.23).[40]




**Scheme 1.23.** Controlled reduction of amides using zinc hydrides.

The author was further interested to investigate if these zinc hydride complexes can perform hydride reduction on other π-electrophiles. As a result, the controlled reduction of aromatic and aliphatic carbonitriles to their corresponding aldehydes were demonstrated using sodium hydride and zinc chloride at mild reaction condition, that are described in chapter 5 (Scheme 1.24). The iminyl zinc intermediates generated via

the first hydride attack could be further allylated by subsequent addition of allyl metal reagents to afford homoallyl amines.




**Scheme 1.24.** Controlled reduction of carbonitriles to aldehydes using sodium hydride and zinc chloride.

## 1.3. References

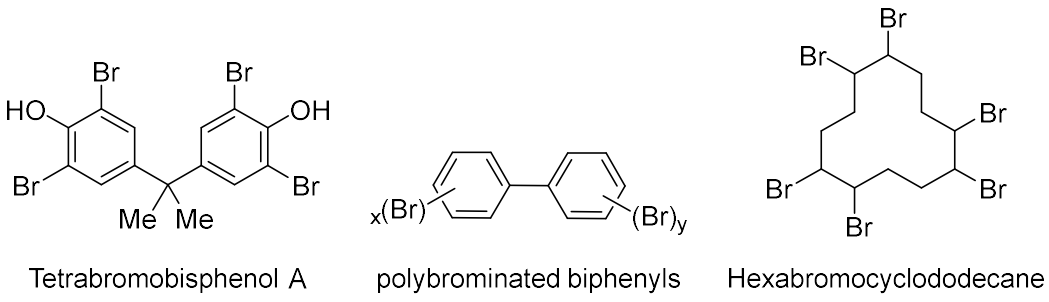

1. P. G. Andersson, I. J. Munslow, *Modern Reduction Methods*. Wiley: 2008.
2. A. B. Burg, H. I. Schlesinger, *J. Am. Chem. Soc.* **1937,** *59*, 780-787.
3. H. C. Brown, S. Krishnamurthy, *Tetrahedron* **1979,** *35*, 567-607.
4. H. C. Brown, H. I. Schlesinger, A. B. Burg, *J. Am. Chem. Soc.* **1939,** *61*, 673-680.
5. V. Ručilová, M. Soural, *Synthesis* **2018,** *50*, 3809-3824.
6. C. Soucy, D. Favreau, M. M. Kayser, *J. Org. Chem.* **1987,** *52*, 129-134.
7. N. Kennedy, T. Cohen, *J. Org. Chem.* **2015,** *80*, 8134-8141.
8. D. E. Ward, C. K. Rhee, *Synth. Commun.* **1988,** *18*, 1927-1933.
9. U. Wietelmann, M. Felderhoff, P. Rittmeyer, Hydrides. In *Ullmann's Encyclopedia of Industrial Chemistry*, 2012; pp 1-39.
10. J. Clayden, N. Greeves, S. Warren, *Organic Chemistry*. OUP Oxford: 2012.
11. S. Harder, *Chem. Commun.* **2012,** *48*, 11165-11177.
12. L. Elansari, L. Antoine, R. Janot, J. C. Gachon, J. J. Kuntz, D. Guérard, *J. Alloys Compd.* **2001,** *329*, L5-L8.
13. E. Gaffet, *Mater. Sci. Eng. A* **1991,** *132*, 181-193.
14. H. I. Schlesinger, H. C. Brown, H. R. Hoekstra, L. R. Rapp, *J. Am. Chem. Soc.* **1953,** *75*, 199-204.
15. A. E. Finholt, A. C. Bond, H. I. Schlesinger, *J. Am. Chem. Soc.* **1947,** *69*, 1199-1203.
16. L. Banfi, E. Narisano, R. Riva, E. W. Baxter, Lithium Borohydride. In *Encyclopedia of Reagents for Organic Synthesis*, 2005.
17. L. A. Paquette, T. Ollevier, V. Desyroy, Lithium Aluminum Hydride. In *Encyclopedia of Reagents for Organic Synthesis*, 2004.
18. C. Appelt, J. C. Slootweg, K. Lammertsma, W. Uhl, *Angew. Chem. Int. Ed.* **2012,** *51*, 5911-5914.

19. J.-J. Brunet, D. Besozzi, P. Caubère, *Synthesis* **1982,** *1982*, 721-723.
20. J. J. Brunet, D. Besozzi, A. Courtois, P. Caubere, *J. Am. Chem. Soc.* **1982,** *104*, 7130-7135.
21. T. Ohkuma, S. Hashiguchi, R. Noyori, *J. Org. Chem.* **1994,** *59*, 217-221.
22. E. C. Ashby, R. D. Schwartz, *Inorg. Chem.* **1971,** *10*, 355-357.
23. J. J. Watkins, E. C. Ashby, *Inorg. Chem.* **1974,** *13*, 2350-2354.
24. P. A. A. Klusener, L. Brandsma, H. D. Verkruijsse, P. von Ragué Schleyer, T. Friedl, R. Pi, *Angew. Chem. Int. Ed.* **1986,** *25*, 465-466.
25. R. Pi, T. Friedl, P. v. R. Schleyer, P. Klusener, L. Brandsma, *J. Org. Chem.* **1987,** *52*, 4299-4303.
26. B. Bogdanovic, US4370488A, **1978**.
27. F. Buch, J. Brettar, S. Harder, *Angew. Chem. Int. Ed.* **2006,** *45*, 2741-2745.
28. P. C. Too, G. H. Chan, Y. L. Tnay, H. Hirao, S. Chiba, *Angew. Chem. Int. Ed.* **2016,** *55*, 3719-3723.
29. G. H. Chan, D. Y. Ong, S. Chiba, *Org. Synth.* **2018,** *95*, 240-255.
30. J. Zhao, B.-X. Dong, Y.-L. Teng, L. Wang, C. Ping, Z.-W. Li, *Int. J. Hydrog. Energy* **2018,** *43*, 5068-5076.
31. A. Stasch, *Angew. Chem. Int. Ed.* **2012,** *51*, 1930-1933.
32. A. Stasch, *Dalton Transactions* **2014,** *43*, 7078-7086.
33. A. Stasch, *Chem. Commun.* **2015,** *51*, 5056-5058.
34. R. A. Sheldon, *Green Chem.* **2017,** *19*, 18-43.
35. W. M. Haynes, *CRC Handbook of Chemistry and Physics*. CRC Press: 2014.
36. D. Y. Ong, C. Tejo, K. Xu, H. Hirao, S. Chiba, *Angew. Chem. Int. Ed.* **2017,** *56*, 1840-1844.
37. G. H. Chan, D. Y. Ong, Z. Yen, S. Chiba, *Helv. Chim. Acta.* **2018,** *101*, e1800049.
38. D. Y. Ong, K. Watanabe, R. Takita, S. Chiba, *Helv. Chim. Acta.* **2019,** *102*, e1900166.
39. A.-K. Wiegand, A. Rit, J. Okuda, *Coord. Chem. Rev.* **2016,** *314*, 71-82.
40. D. Y. Ong, Z. Yen, A. Yoshii, J. Revillo Imbernon, R. Takita, S. Chiba, *Angew. Chem. Int. Ed.* **2019,** *58*, 4992-4997.

## Chapter 2. Hydrodehalogenation of Haloarenes by a Sodium Hydride-Iodide composite

### 2.1. Introduction

Among various types of reductive molecular transformations,[1] hydrodehalogenation of organic halides has particularly attracted a great deal of attention from the points of views on environmental chemistry. This is mainly due to its potential use for the detoxification of environmentally hazardous organic halide.[2] A group of such organic halides is flame retardants (Figure 2.1), which is persistent environment pollutants[3] with serious long term health impacts on animals and humans.[4] Hydrodehalogenation can remove the halogen atoms from such compounds and thus converting them to less environmentally harmful molecules.[5]

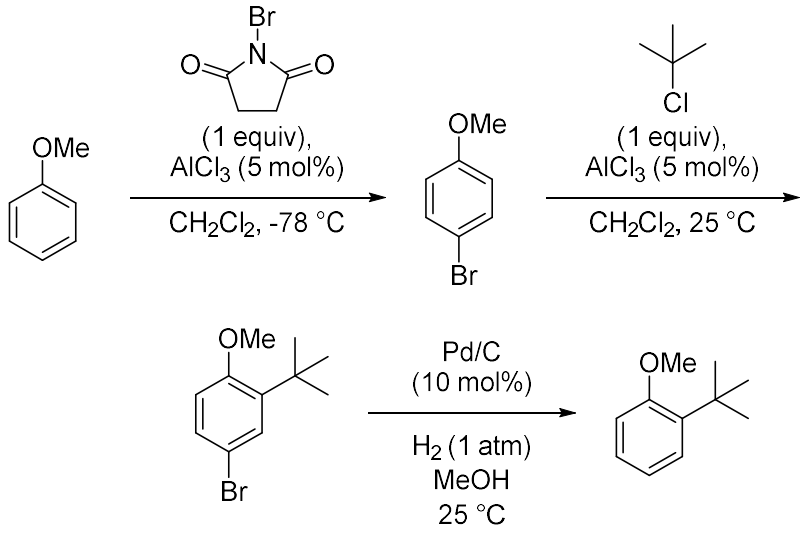



Tetrabromobisphenol A polybrominated biphenyls Hexabromocyclododecane

**Figure 2.1.** Flame retardants.

Hydrodehalogenation is also a useful tool in synthetic organic chemistry especially for the installation of functional groups selectively on the *ortho*-position in aromatic compounds. For example, *ortho*-selective electrophilic aromatic substitution of the aromatic ring could be realized by use of *para*-bromo- or chloro-arene substrates. The bromide or chloride blocking group can be removed via Pd-catalyzed hydrodehalogenation to yield the desired *ortho* substituted aromatic products (Scheme 2.1). Traditionally, sulfonic acids[6] and *tert*-butyl[7] groups have been used as effective

*para*-blocking groups but those methods are incompatible with acid sensitive functional groups. Such drawback has garnered interests to develop methods of a wider functional group tolerance. Although hydrodehalogenation has not been commonly used as part of the general organic synthetic strategy,[8] the development of hydrodehalogenation methodology with large functional group tolerance has become pivotal for the installation of functional groups on the desired *ortho* position in the aromatic ring by using halogen as *para*-blocking group (Scheme 2.1).[9]



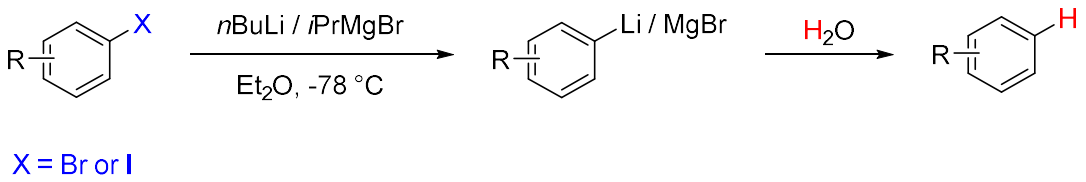

**Scheme 2.1.** Proposed steps for installing a *tert*-butyl on the ortho-position in anisole.

Consequently, hydrodehalogenation is considered important to both the chemical industry and organic synthesis in academic setting,[10-12] accordingly, various methodologies for the hydrodehalogenation have been developed.

## 2.2. Hydrodehalogenation

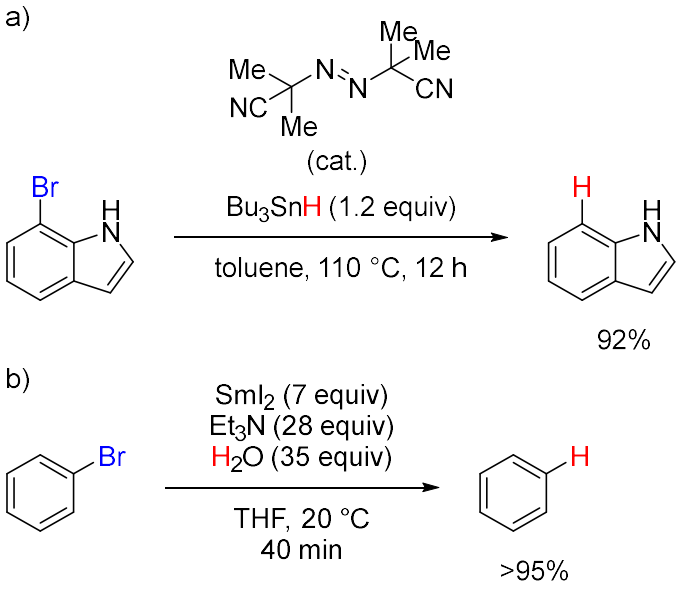
The reported procedures for hydrodehalogenation can be classified under various categories like the use of biological processes,[13-14] photochemical reduction,[15-16] electrochemical reduction,[17-18] halogen-metal exchange and subsequent

protonation,[19-20] transition-metal catalysis with hydrides sources,[21-26] and radical mediated processes.[27-35] Among them, halogen-metal exchanged followed by protonation is perhaps one of the most commonly employed procedures for hydrodehalogenation, while cryogenic reaction conditions are required for the use of highly reactive organo-magnesium or lithium reagents (Scheme 2.2). [19-20]



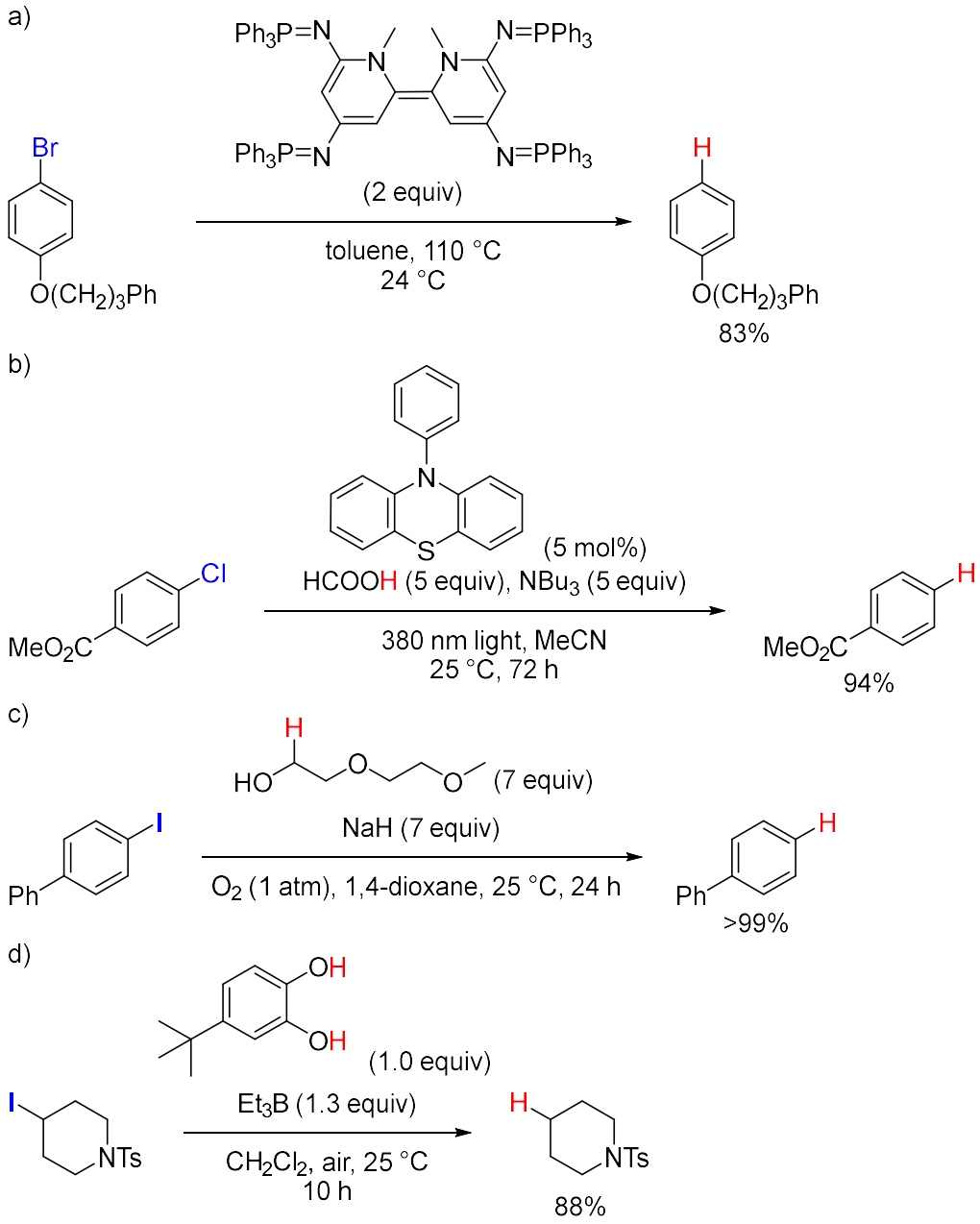

**Scheme 2.2.** Hydrodehalogenation via general halogen-metal exchange followed by protonation.

Radical-mediated dehalogenation is also a typical method for hydrodehalogenation, although there are several disadvantageous concerns in their use of explosive reagent (AIBN),[27] toxic reagent such as tin hydrides ($Bu_3SnH$) (scheme 2.3a)[28-31] and the difficulty in handling of air sensitive reagent such as $SmI_2$ (Scheme 2.3b).[32-33]




**Scheme 2.3.** Radical mediated dehalogenation using a) explosive, toxic and b) air sensitive reagents.

The recent developments such as the use of organic super electron donors (Scheme 2.4a), [36-38] photo-redox catalysis (Scheme 2.4b),[39] use of sodium alcoholates as the organic chain reductant for radical hydrodehalogenation (Scheme 2.4c)[34] and catechols as hydrogen radical source (Scheme 2.4d)[35] under milder reaction conditions could compensate for such drawbacks.

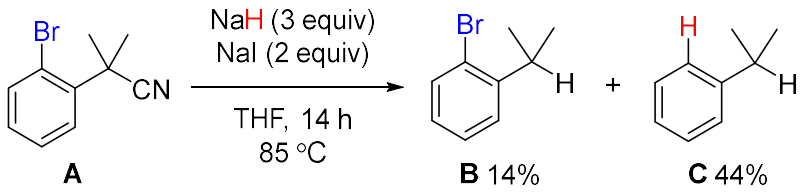



**Scheme 2.4.** Dehalogenation using a) Organic super electron donor, b) photo redox catalysis, c) sodium alcholates and d) catechols.

### 2.3. Serendipitous discovery

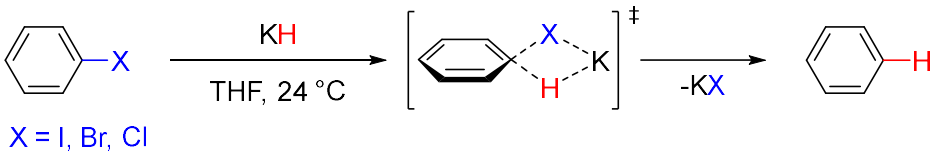
While studying the substrate scope of the hydrodecyanation by the NaH–NaI composite,[40] the author found that the reaction of bromoaryl substrate **A** provided not only 2-bromocumene **B** in 14% yield but also cumene **C** in 44% yield (Scheme 2.5). It

was tempting to assume that cumene **C** was formed through hydrodebromination by the NaH-NaI composite.




**Scheme 2.5.** Serendipitous observation of hydrodebromination during hydrodecyanation of **A**.

There is an early report by Pierre et al. on the hydrodehalogenation of haloarenes by potassium hydride (KH) in THF.[41] They observed that the rate of hydrodehalogenation was the fastest for iodobenzene (PhI), then bromobenzene (PhBr) and chlorobenzene (PhCl) while almost no amount of the dehalogenated product was detected from fluorobenzene (PhF). This order of rate is a reverse from the classical nucleophilic aromatic substitution, $S_NAr$ reactions as PhF with the highly polarized C-F bond should preferably undergo $S_NAr$ reaction with the highest rate. Furthermore, they demonstrated that the substituted hydrogen at the dehalogenated product originated from KH when they conducted their reaction in THF-$d_8$, the reaction also proceeded without any electron withdrawing groups unlike typical $S_NAr$ with an addition-elimination mechanism and no evolution of hydrogen gas suggesting unlikeness of benzyne mechanism. Based on their observation, Pierre et al. proposed a concerted $S_NAr$ reaction with a 4-centred transition state (Scheme 2.6). However, detailed mechanistic investigation was not conducted, and no substrate scope was investigated as well.




**Scheme 2.6.** Hydrodehalogenation using KH.

There are also previous reports on hydrodehalogenation of haloarenes that utilized NaH under harsh reaction conditions,[42-43] although these reports examined only very simple substrates and there has been no discussion of the reaction mechanism. Therefore, the author started to explore the scope and limitation as well as the reaction mechanism of this process.

## 2.4. Result and discussion

### 2.4.1. Preparation of starting materials

#### 2.4.1.1. Bromoarenes and iodoarene substrates

A series of bromoarenes shown in Figure 2.2 were commercially available and used as received.

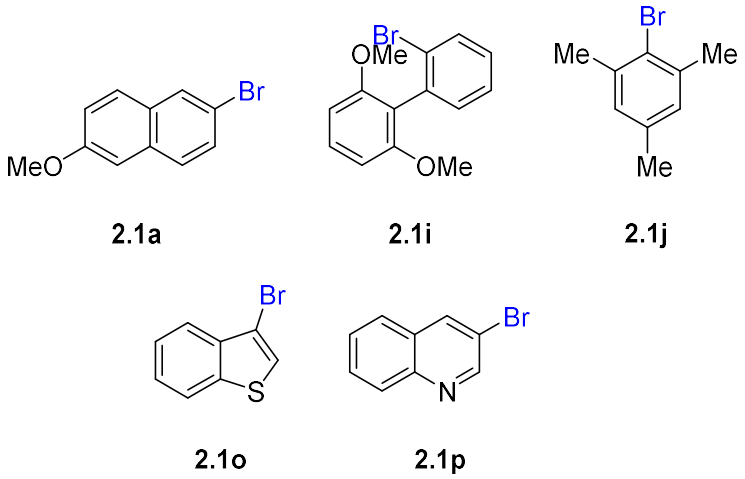



**Figure 2.2.** Commercially available bromoarenes.

A series of iodoarene **2.1a'**[44] and bromoarenes **2.1b**,[45] **2.1c**,[46] **2.1d**,[47] **2.1e-f**,[48] **2.1g**,[49] **2.1h**,[50] **2.1k**,[51] **2.1l**,[52] **2.1m**,[53] **2.1n**,[54] ***para*-2.1q**,[55] and ***ortho*-2.1q**[56] were synthesized based on the reported procedures (Figure 2.3).

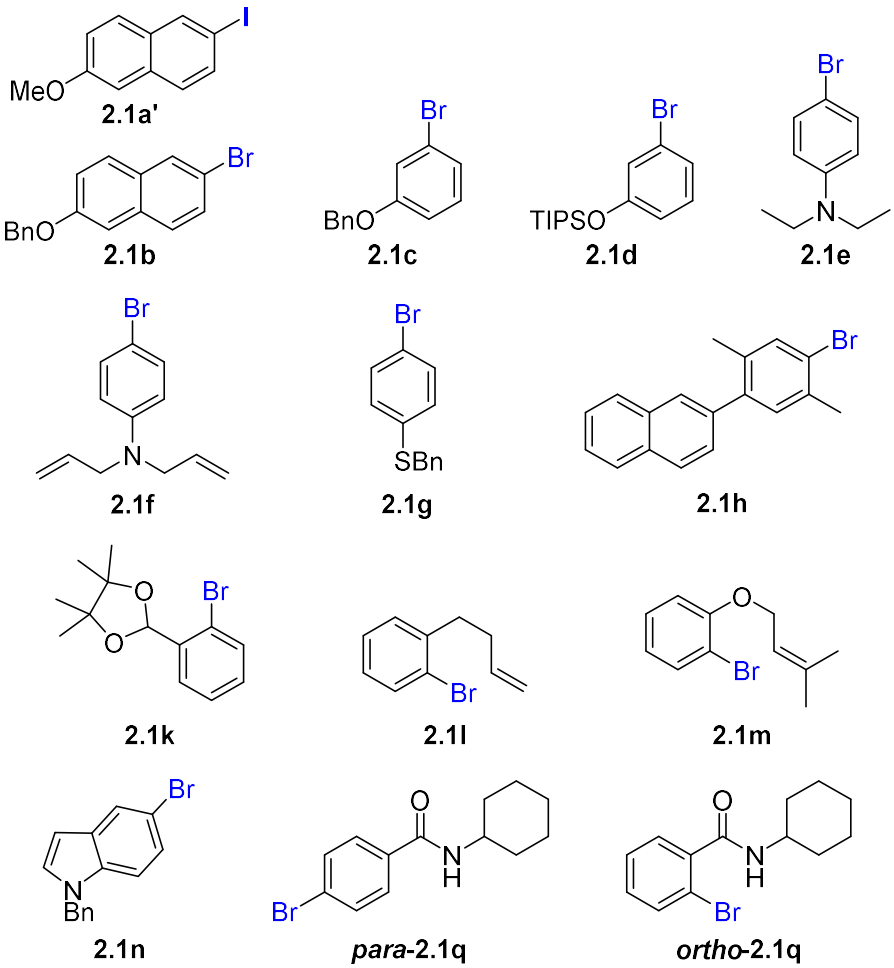
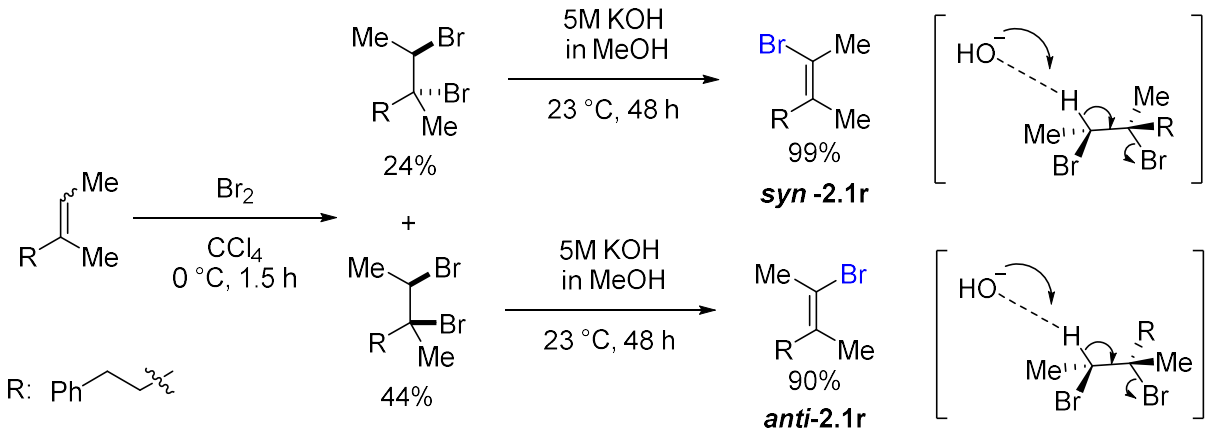



**Figure 2.3.** Known bromoarenes and iodoarenes.

### 2.4.1.2. Bromoalkenes substrate

The synthesis of bromoalkenes **2.1r** was conducted via 2-step sequence comprising of dibromination and base-mediated E2 elimination as shown below (Scheme 2.7).



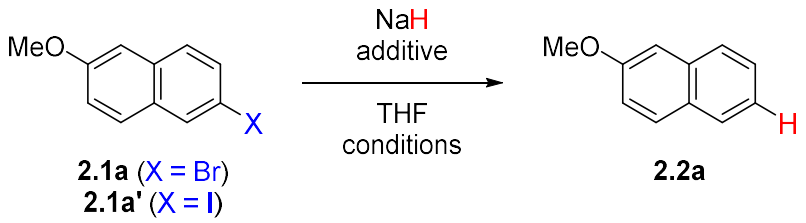

**Scheme 2.7.** Synthesis of Bromoalkenes **2.1r**.

### 2.4.2. Optimization of reaction conditions

The author commenced optimization of the reaction conditions for the hydrodebromination using 2-bromo-6-methoxynaphthalene (**2.1a**) (Table 2.1). The reaction of **2.1a** with NaH (5 equiv) in THF was completed within 12 h even at 60 ˚C when NaI (2 equiv) was used as an additive, affording 2-methoxynaphthalene (**2.2a**) in good yield (entry 1). Use of LiI instead of NaI rendered the process smoother, completing the process within 6 h (entry 2), while lowering the amounts of NaH and LiI slowed down the reaction rate (entry 3). Furthermore, the reaction temperature could be lowered to 40–50 ˚C without diminishment of the yields of **2.2a** (entries 4 and 5), although the reaction at room temperature (24 ˚C) became sluggish (entry 6). It should be noted that NaH alone is not enough to drive the hydrodebromination (entry 7), indicating that this unique hydride donor reactivity is conferred on the sodium hydride-iodide composite. Employment of more reactive iodide **2.1a'** allowed the

reaction to reach full conversion even at 30 ˚C (entries 8 and 9). Similarly, almost no reaction of **2.1a'** occurred without iodide additive (entry 10).

**Table 2.1**: Optimization of the reaction conditions[a]




**2.1a** (X = Br)
**2.1a'** (X = I)

**2.2a**

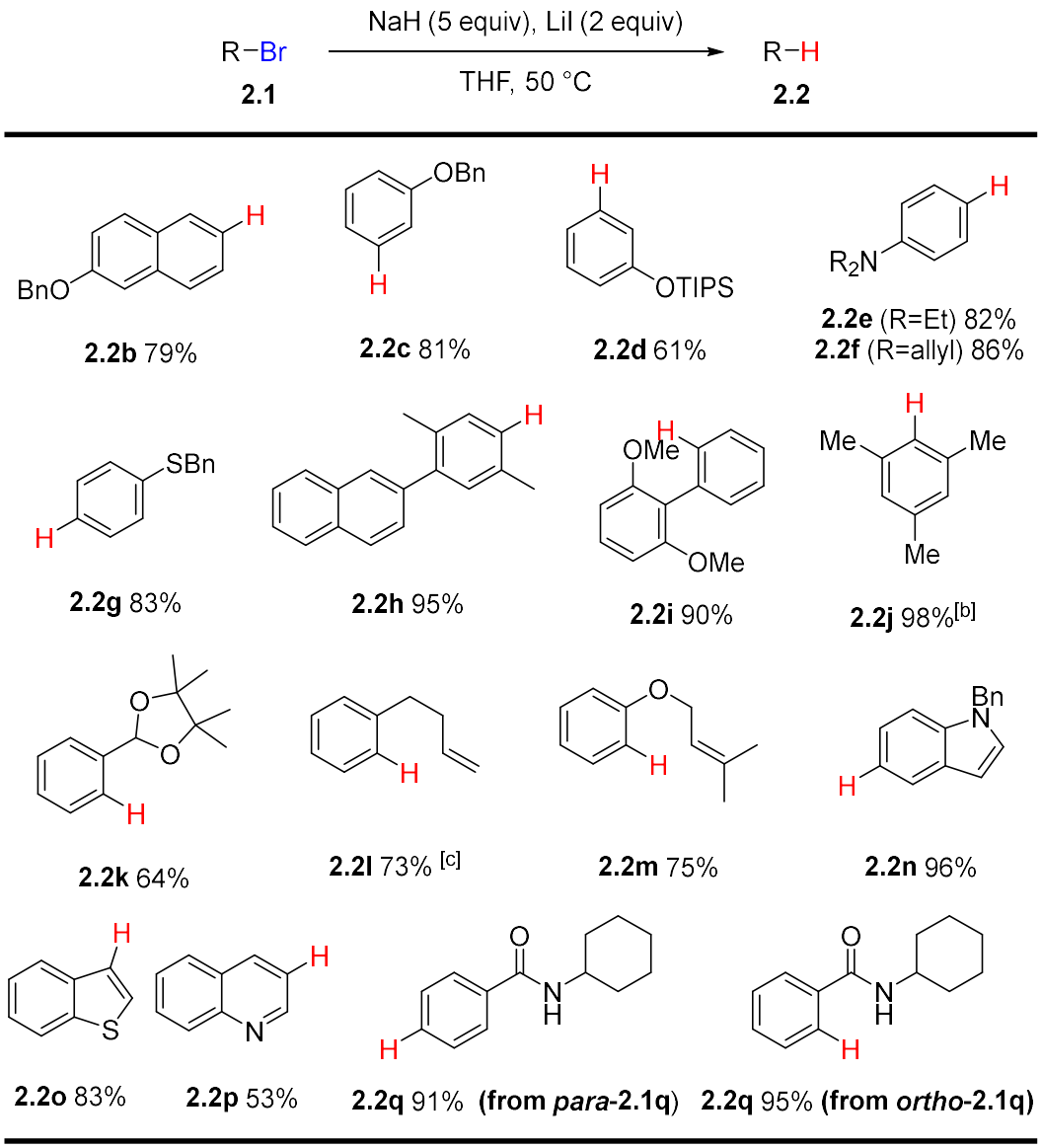
| Entry | X | NaH (equiv) | additive (equiv) | Temp. (°C) | *t* (h) | Yield of **2.2a** (%)[b] |
|---|---|---|---|---|---|---|
| 1 | Br | 5 | NaI (2) | 60 | 12 | 91 |
| 2 | Br | 5 | LiI (2) | 60 | 6 | 89 |
| 3 | Br | 3 | LiI (1) | 60 | 10 | 90 |
| 4 | Br | 5 | LiI (2) | 50 | 7 | 89 (81)[c] |
| 5 | Br | 5 | LiI (2) | 40 | 10 | 89 |
| 6 | Br | 5 | LiI (2) | 24 | 16 | 33[d] |
| 7 | Br | 5 | – | 50 | 10 | 4[e] |
| 8 | I | 5 | NaI (2) | 30 | 10 | 85 (75)[c] |
| 9 | I | 5 | LiI (2) | 30 | 10 | 61 |
| 10 | I | 5 | – | 30 | 10 | 0[e] |

[a] The reactions were conducted using 0.5 mmol of **2.1a** or **2.1a'** in THF (2.5 mL). [b] $^1$H NMR yields. [c] Isolated yield of **2.2a**. [d] Recovery of **2.1a** in 63% yield. [e] Recovery of **2.1a** or **2.1a'** in more than 90% yield.

### 2.4.3. Scope and limitation

With the optimized reaction conditions in hand (Table 2.1, entry 4), the substrate scope of hydrodebromination using various bromoarenes **2.1** was investigated (Scheme 2.8). As electron-donating substituents, benzyloxy (for **2.2b** and **2.2c**) and silyloxy (for **2.2d**)

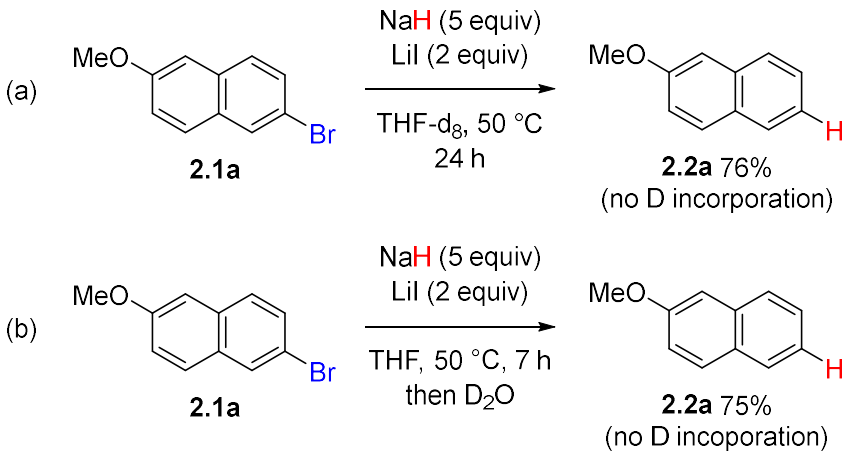
as well as dialkyl amino (for **2.2e** and **2.2f**) and benzyl sulfanyl (for **2.2g**) moieties could be tolerated, and the corresponding reduced arenes were obtained in 61–86% yields. Sterically hindered bromoarenes having *ortho*-methyl (for **2.2h**) and *ortho*-aryl (for **2.2i**) groups could be reduced smoothly. It should be worthy to note that hydrodebromination of 2-bromomesitylene (**2.1j**) worked very nicely to give mesitylene (**2.2j**) in quantitative yield, suggesting that benzyne is unlikely involved as an intermediate in the present hydrodebromination. The acetal moiety could be kept intact during the reduction process (for **2.2k**). Bromoarenes **2.1l** and **2.1m** having *ortho*-butenyl and *ortho*-O-allyl tethers, respectively, gave **2.2l** and **2.2m** while keeping the alkenyl moieties intact.[57-58] These results suggested that an aryl radical intermediate may not be involved in the reaction pathway. Hydrodebromination of 5-bromoindole (**2.1n**) and 3-bromobenzothiophene (**2.1o**) proceeded smoothly to give the corresponding heteroarenes **2.2n** and **2.2o** in high yields, whereas the reduction of 3-bromoquinoline (**2.1p**) afforded a moderate yield of **2.2p** (53% yield). Although the NaH–iodide composite could reduce tertiary amides to the corresponding aldehydes,[40] secondary amides could be kept intact because the amide anion generated through deprotonation by NaH is inert toward hydride reduction by the NaH–iodide composite. Taking advantage of this unique reactivity pattern, selective reduction of bromo-*N*-cyclohexyl benzamides ***para*-2.1q** and ***ortho*-2.1q** could be achieved, which afforded debrominated **2.2q** in excellent yields.




**Scheme 2.8.** Substrate scope for the hydrodebromination of bromoarenes **2.1**. [a] The reactions were conducted using 0.5 mmol of **2.1** in THF (2.5 mL) and isolated yields of **2.2** were noted above unless otherwise stated. [b] GC yield. [c] $^{1}$H NMR yield.

### 2.4.4. Mechanistic discussion

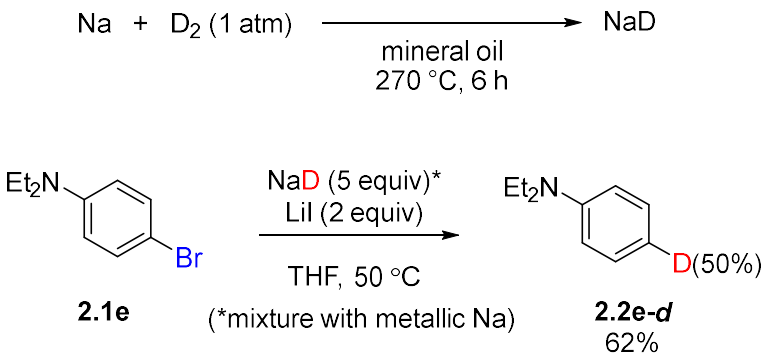
To investigate the reaction mechanism, especially how the hydrogen is installed during the hydrodehalogenation process, several deuterium labelling experiments were conducted. Incorporation of deuterium was not observed at all in the reactions of **2.1a** in THF-$d_8$ or with $D_2O$ quench (Scheme 2.9).




**Scheme 2.9.** Deuterium studies.

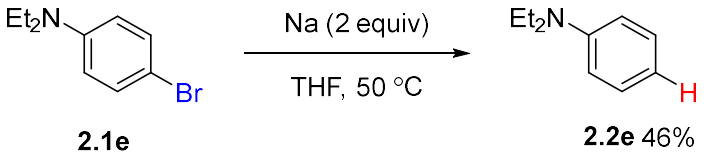
This implied that single-electron reduction of aryl bromides by NaH[59] should not be involved in the present process. Rather, NaH in the composite state functions as a hydrogen atom donor in the reduction process, most probably via nucleophilic aromatic substitution. To prove this hypothesis, the author prepared sodium deuteride (NaD) from metallic Na and $D_2$ gas following the reported procedure (Scheme 2.10).[60] Treatment of Na dispersion in mineral oil with $D_2$ gas (1 atm) at 270 °C afforded NaD containing metallic Na (ca. 9%), which was characterized by solid-state NMR ($^{23}$Na and $^{2}$H) spectroscopy as well as powder X-ray diffraction.

The hydrodebromination of **2.1e** by this NaD sample resulted in deuterium incorporation of 50% in the reduced product **2.2e** (Scheme 2.10b), which unambiguously exemplified the role of NaH as the hydrogen donor. The other 50% of H-incorporation was due to single-electron reduction by metallic sodium contaminant. This is most likely because the prepared NaD sample contained small amount of metallic sodium (ca. 9%) as confirmed by powder XRD.




**Scheme 2.10.** Preparation of NaD and a deuterium labelling experiment.

The metallic sodium competes to perform hydrodehalogenation of **2.1e** in single-electron-transfer mechanism, and thus hydrogen source could be either THF (via H-radical abstraction) or quenching $H_2O$ (via protonation of the resulting aryl anion that was generated from further reduction of aryl radical that was produced from one electron transfer from metallic sodium to the aryl group followed by homolytic cleavage). To confirm this competition reaction, the author examined the reaction of **2.1e** with metallic sodium. This demonstrated that metallic sodium also performs hydrodehalogenation on haloarenes (Scheme 2.11).




**Scheme 2.11.** Hydrodebromination of **2.1e** with Na.

The recent work of the author's group on materials characterization of the NaH–iodide composite indicated that a smaller nanometric unit of NaH dispersed on NaI might be produced by solvothermal treatment of NaH with NaI or LiI in THF, giving rise to unique hydride donor reactivity.[61] On this basis, to better understand the reaction

mechanism of the present hydrodehalogenation, DFT calculations were performed for a model reaction of bromobenzene with a single molecule of NaH, using Gaussian 09 software.[62] The bulk solvent effect of THF was described with an implicit model, and two molecules of THF were included explicitly. The experimental results showed that aryl iodide underwent deiodination with the fastest rate followed by aryl bromide. This protocol did not allow for the dechlorination of aryl chloride. These results are consistent with the work of Pierre at al. on the hydrodehalogenation of haloarenes by potassium hydride in THF with similar trend.[41] Hence, the halides ions were not considered during the DFT calculation as the trend of halides ions is known. A highly exothermic pathway having a single transition state (TS-I) for concerted nucleophilic aromatic substitution was obtained (Figure 2.4). The barrier for the reaction was not very high (20.9 kcal $mol^{-1}$), indicating that NaH, especially in a fragment state, is reactive toward an aromatic bromide.

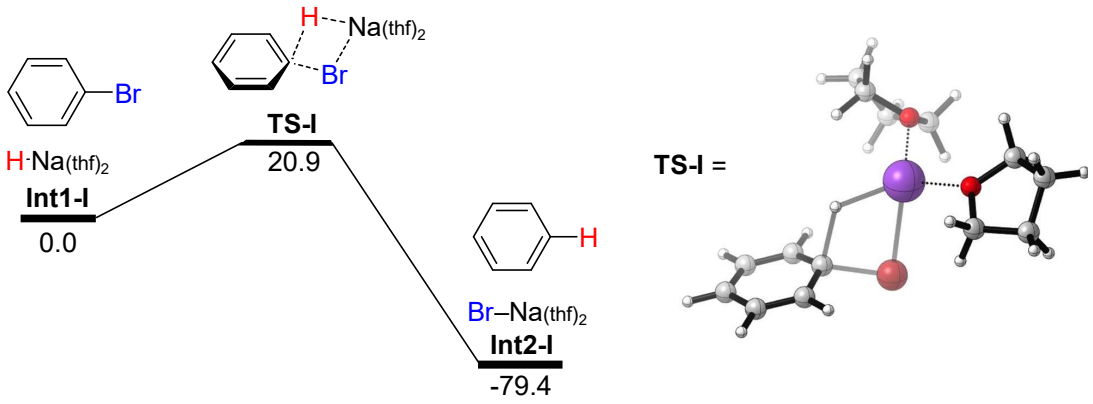
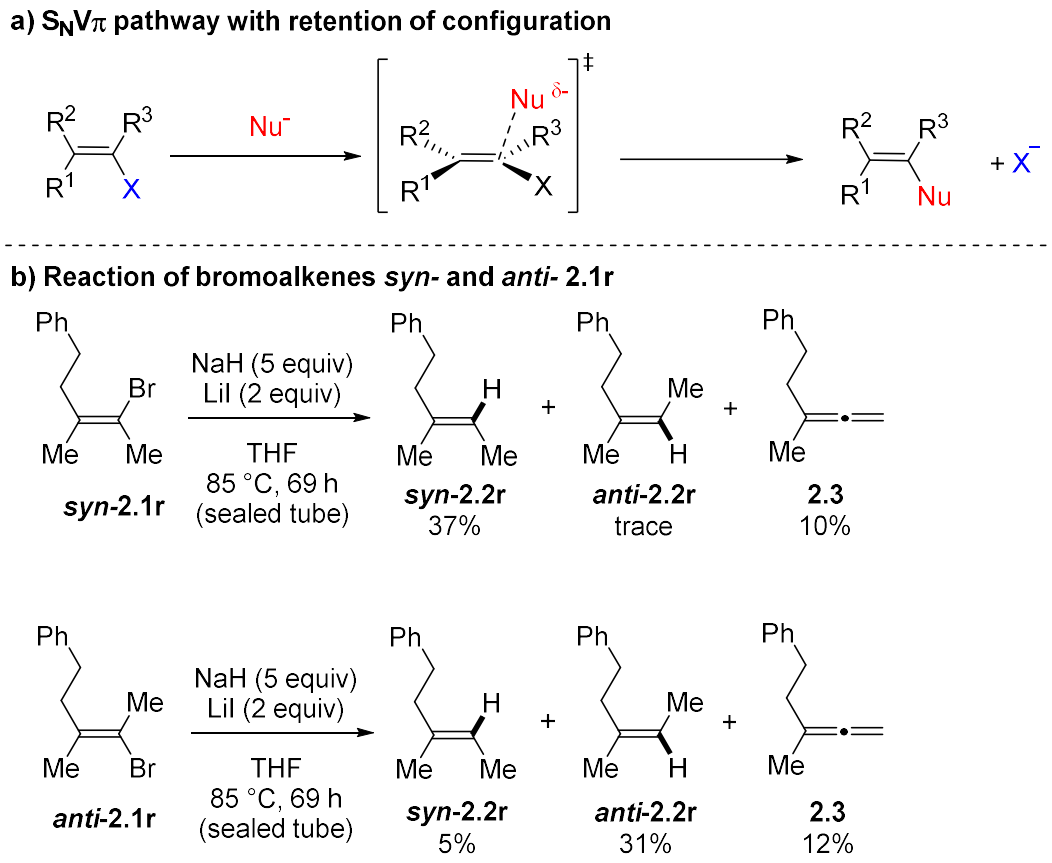



**Figure 2.4.** Free energy profile for hydrodebromination of bromobenzene by a single molecule of NaH in THF (in kcal $mol^{-1}$), determined at the B3LYP(SCRF)-D3(BJ)/def2-TZVP//B3LYP/def2-TZVP level. Key bond distances are indicated in Å.

Moreover, the Hammett plot of $\log(k_X/k_H)$ versus σ showed a linear correlation with a positive ρ value of 0.47. This trend supports the concerted nucleophilic aromatic

substitution mechanism via transition state of the rate determining step having a partial negative charge ($\delta^-$) (**TS-I** in Figure 2.4) without formation of a charged Meisenheimer complex, which is involved as an intermediate in typical aromatic substitution reactions proceeding via an addition–elimination mechanism. Nucleophilic aromatic substitution reactions via addition–elimination mechanism normally show larger ρ values between 3 and 8.[63-65]

The predicted concerted nucleophilic aromatic substitution reaction in the hydrodehalogenation is initiated by the interaction between the hydride and the π* orbital of the aromatic ring. An analogous concerted substitution reaction at the vinylic carbon through the hydride attack onto the π* orbital ($S_NV\pi$) should result in retention of the stereoconfiguration of the haloalkenes (Scheme 2.12a).[66-67] The author thus investigated the hydrodebromination of bromoalkenes ***syn*-2.1r** and ***anti*-2.1r** (Scheme 2.12b). The stereochemistry of bromoalkenes **2.1r** is discussed as following; the *syn*-isomer is defined as the substrate bearing the C-Br bond on the same side of the phenethyl group and *vice versa* for the *anti*-isomer. For the reduced alkenes **2.2r**; the *syn*-isomer is defined as the substrate bearing the C-H bond on the same side of the phenethyl group and *vice versa* for the *anti*-isomer.




**Scheme 2.12** Hydrodebromination of bromoalkenes **2.1r**.

The reduction of ***syn*-2.1r** at 85 ˚C afforded ***syn*-2.2r** in 37% yield. Similarly, the reduction of ***anti*-2.1r** delivered ***anti*-2.2r** in 31% yield along with a small amount of ***syn*-2.2r**. As expected, in both cases, reduction of the C-Br bond proceeded mostly with retention of the configuration. It is noted that both reactions also produced allene **2.3** via an elimination reaction.

DFT calculations of a model reaction of 2-bromo-3-methyl-2-butene with NaH provided **TS-II** for concerted vinylic substitution that involves attack of the hydride on the π* orbital ($S_NV\pi$) (Figure 2.5); the barrier for this reaction was again not very high (20.1 kcal $mol^{-1}$).

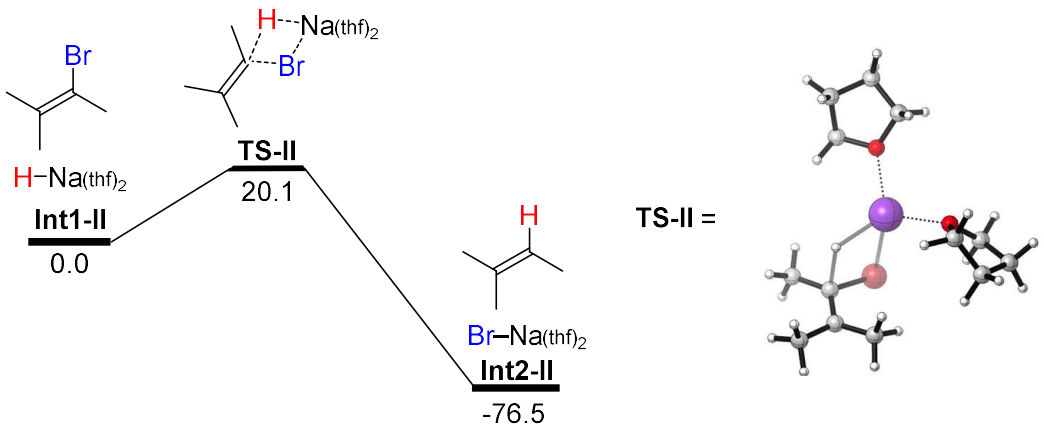



**Figure 2.5.** Free energy profiles for hydrodebromination of 2-bromo-3-methyl-2-butene by a single molecule of NaH in THF (in kcalmol$^{-1}$), determined at the B3LYP(SCRF)-D3(BJ)/def2-TZVP//B3LYP/def2-TZVP level.

An alternative pathway, in which the hydride attacks the σ* orbital of the C-Br bond ($S_NV\sigma$), could not be obtained. When calculations were performed without adding two explicit THF molecules, the transition state for the $S_NV\sigma$ pathway could be located; however, the barrier for this process was higher than that for the $S_NV\pi$ pathway by about 8 kcal mol$^{-1}$. (Figure 2.5) These results also suggest that the $S_NV\pi$ pathway should be the dominant process and are well consistent with the stereochemical outcomes in the hydrodebromination of ***syn***- and ***anti*-2.1r** (Scheme 2.12).

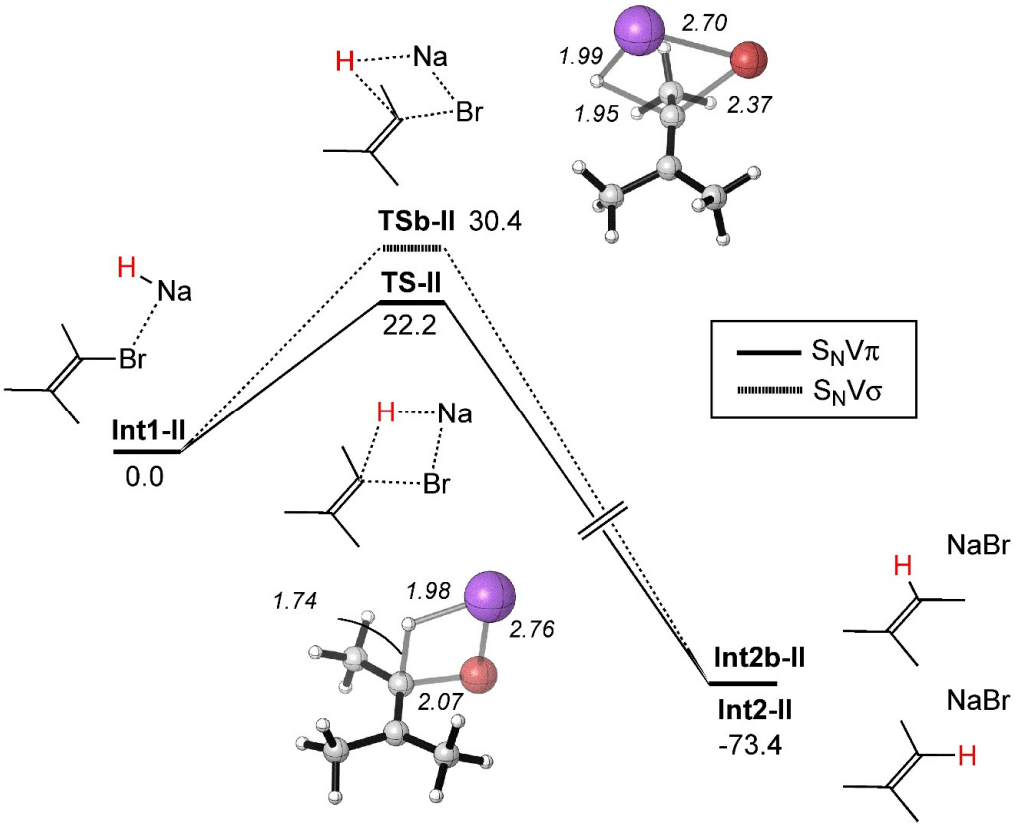
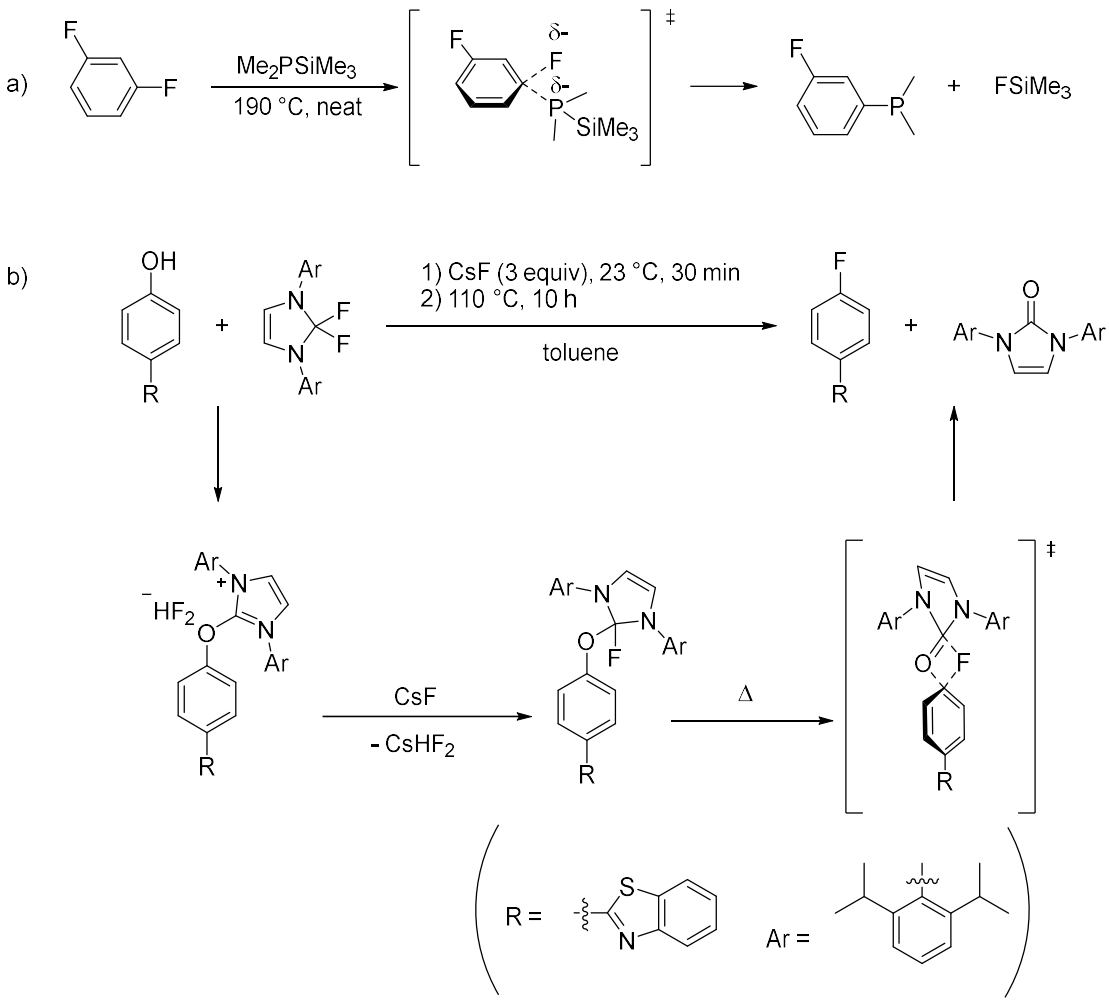



**Figure 2.6.** Free Energy Profiles for hydrodebromination of 2-bromo-3-methyl-2-butene by a single molecule of NaH in THF (in kcal/mol), determined at the B3LYP(SCRF)-D3(BJ)/def2-TZVP//B3LYP/def2-TZVP level. Here, not explicit THF molecules were added. Key bond distances are indicated in Å.

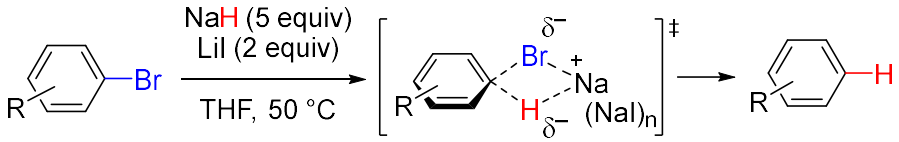
Analogous to this unusual mechanism for hydrodehalogenation by NaH, the author's protocol shared a similar mechanism of $cS_NAr$ with the hydrodehalogenation of haloarenes using KH as proposed by Pierre et al.[41] confirming the possibility of this mechanism. There have been several reports with comparable mechanism. Würthweinn et. al. reported the intermolecular concerted nucleophilic aromatic substitution of dimethyl (trimethylsilane) phosphane with 1,3-difluorobenzene to yield its corresponding (3-fluorophenyl) dimethyl phosphane and trimethyl fluorosilane (Scheme 2.13a).[68] Ritter et. al. reported a phenol deoxyfluorination reaction that proceeds via an intramolecular nucleophilic aromatic substitution (Scheme 2.14b).[69]




**Scheme 2.13.** a) Intermolecular and b) intramolecular concerted nucleophilic aromatic substitution.

## 2.5. Conclusion

A simple protocol for hydro-debromination and -deiodination of halo(hetero)arenes was enabled by sodium hydride (NaH) in the presence of lithium iodide (LiI) (Scheme 2.14). Mechanistic studies showed that an unusual concerted nucleophilic aromatic substitution operates in the present process.




**Scheme 2.14.** Hydrodehalogenation of haloarene by sodium hydride-iodide composite.

## 2.6 References


1. P. G. Andersson, I. J. Munslow, *Modern Reduction Methods*. Wiley: 2008.
2. F. Alonso, I. P. Beletskaya, M. Yus, *Chem. Rev.* **2002,** *102*, 4009-4092.
3. J. de Boer, P. G. Wester, H. J. C. Klamer, W. E. Lewis, J. P. Boon, *Nature* **1998,** *394*, 28-29.
4. G. F. Fries, *Sci. Total Environ.* **1996,** *185*, 93-108.
5. G. Cagnetta, J. Robertson, J. Huang, K. Zhang, G. Yu, *J. Hazard. Mater.* **2016,** *313*, 85-102.
6. E. Sakellarios, D. Jatrides, *Ber. Dtsch. Chem. Ges.* **1925,** *58*, 2286.
7. M. Tashiro, T. Yamato, K. Kobayashi, *J. Org. Chem.* **1984,** *49*, 4724.
8. M. B. Smith, J. March, *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*. Wiley: 2001.
9. A. Ramanathan, L. S. Jimenez, *Synthesis* **2010**, 217-220.
10. R. A. Hites, *Acc. Chem. Res.* **1990,** *23*, 194-201.
11. V. V. Grushin, H. Alper, *Chem. Rev.* **1994,** *94*, 1047-1062.
12. A. R. Pinder, *Synthesis* **1980**, 425-452.
13. A. El Gamal, V. Agarwal, I. Rahman, B. S. Moore, *J. Am. Chem. Soc.* **2016,** *138*, 13167-13170.
14. K. A. P. Payne, C. P. Quezada, K. Fisher, M. S. Dunstan, F. A. Collins, H. Sjuts, C. Levy, S. Hay, S. E. J. Rigby, D. Leys, *Nature* **2015,** *517*, 513-516.
15. J. T. Pinhey, R. D. G. Rigby, *Tetrahedron Lett.* **1969,** *10*, 1267-1270.
16. J. A. Barltrop, D. Bradbury, *J. Am. Chem. Soc.* **1973,** *95*, 5085-5086.
17. A. J. Fry, *Synthetic Organic Electrochemistry*. Wiley: 1989.
18. N. Bhuvaneswari, C. S. Venkatachalam, K. K. Balasubramanian, *Tetrahedron Lett.* **1992,** *33*, 1499-1502.
19. P. Knochel, W. Dohle, N. Gommermann, F. F. Kneisel, F. Kopp, T. Korn, I. Sapountzis, V. A. Vu, *Angew. Chem. Int. Ed.* **2003,** *42*, 4302-4320.
20. W. F. Bailey, J. J. Patricia, *J. Organomet. Chem.* **1988,** *352*, 1-46.

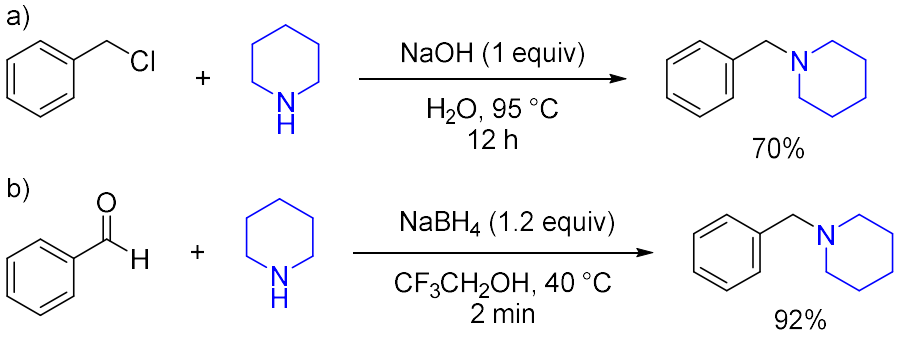
21. J. Chen, Y. Zhang, L. Yang, X. Zhang, J. Liu, L. Li, H. Zhang, *Synfacts* **2007**, 0750-0750.
22. H. Guo, K.-i. Kanno, T. Takahashi, *Chem. Lett.* **2004,** *33*, 1356-1357.
23. C. Desmarets, S. Kuhl, R. Schneider, Y. Fort, *Organometallics* **2002,** *21*, 1554-1559.
24. K.-i. Fujita, M. Owaki, R. Yamaguchi, *Chem. Commun.* **2002**, 2964-2965.
25. N. M. Yoon, Selective reduction of organic compounds with aluminum and boron hydrides. In *Pure and Applied Chemistry*, 1996; Vol. 68, p 843.
26. S. Giri, M. Bhaumik, R. Das, V. K. Gupta, A. Maity, *Appl. Catal., B: Environ.* **2017,** *202*, 207-216.
27. J. I. Kroschwitz, A. Seidel, *Kirk-Othmer Encyclopedia of Chemical Technology*. Wiley: 2006.
28. A. Dobbs, *J. Org. Chem.* **2001,** *66*, 638-641.
29. A. Studer, S. Amrein, *Synthesis* **2002**, 835-849.
30. C. Chatgilialoglu, A. Studer, *Encyclopedia of Radicals in Chemistry, Biology and Materials: Basic concepts and methodologies*. John Wiley & Sons: 2012.
31. P. Renaud, M. P. Sibi, *Radicals in Organic Synthesis*. Wiley: 2001.
32. A. Dahlén, G. Hilmersson, B. W. Knettle, R. A. Flowers, *J. Org. Chem.* **2003,** *68*, 4870-4875.
33. M. Szostak, M. Spain, D. J. Procter, *Chem. Soc. Rev.* **2013,** *42*, 9155-9183.
34. A. Dewanji, C. Mück-Lichtenfeld, A. Studer, *Angew. Chem. Int. Ed.* **2016,** *55*, 6749-6752.
35. G. Povie, L. Ford, D. Pozzi, V. Soulard, G. Villa, P. Renaud, *Angew. Chem. Int. Ed.* **2016,** *55*, 11221-11225.
36. E. Cahard, F. Schoenebeck, J. Garnier, S. P. Y. Cutulic, S. Zhou, J. A. Murphy, *Angew. Chem. Int. Ed.* **2012,** *51*, 3673-3676.
37. S. S. Hanson, E. Doni, K. T. Traboulsee, G. Coulthard, J. A. Murphy, C. A. Dyker, *Angew. Chem. Int. Ed.* **2015,** *54*, 11236-11239.
38. J. A. Murphy, T. A. Khan, S.-z. Zhou, D. W. Thomson, M. Mahesh, *Angew. Chem. Int. Ed.* **2005,** *44*, 1356-1360.
39. E. H. Discekici, N. J. Treat, S. O. Poelma, K. M. Mattson, Z. M. Hudson, Y. Luo, C. J. Hawker, J. R. de Alaniz, *Chem. Commun.* **2015,** *51*, 11705-11708.
40. P. C. Too, G. H. Chan, Y. L. Tnay, H. Hirao, S. Chiba, *Angew. Chem. Int. Ed.* **2016,** *55*, 3719-3723.
41. H. Handel, M. A. Pasquini, J. L. Pierre, *Tetrahedron* **1980,** *36*, 3205-3208.
42. W. Zhang, S. Liao, Y. Xu, Y. Zhang, *Synth. Commun.* **1997,** *27*, 3977-3983.
43. R. B. Nelson, G. W. Gribble, *J. Org. Chem.* **1974,** *39*, 1425-1426.
44. W. B. Smith, *J. Org. Chem.* **1985,** *50*, 3649-3651.
45. A. C. Donnelly, J. R. Mays, J. A. Burlison, J. T. Nelson, G. Vielhauer, J. Holzbeierlein, B. S. J. Blagg, *J. Org. Chem.* **2008,** *73*, 8901-8920.
46. J. Kim, Y. K. Kim, N. Park, J. H. Hahn, K. H. Ahn, *J. Org. Chem.* **2005,** *70*, 7087-7092.
47. R. Hesse, O. Kataeva, A. W. Schmidt, H.-J. Knölker, *Chem. Eur. J.* **2014,** *20*, 9504-9509.
48. T. Saitoh, J. Ichikawa, *J. Am. Chem. Soc.* **2005,** *127*, 9696-9697.
49. H. Sugimoto, Y. Tsuchiya, H. Sugumi, K. Higurashi, N. Karibe, Y. Iimura, A. Sasaki, Y. Kawakami, T. Nakamura, *J. Med. Chem.* **1990,** *33*, 1880-1887.
50. S. B. Lee, K. H. Park, C. W. Joo, J.-I. Lee, J. Lee, Y.-H. Kim, *Dyes Pigm.* **2016,** *128*, 19-25.
51. E. Anderson, B. Capon, *J. Chem. Soc., Perkin Trans. 2* **1972**, 515-522.

52. A. Katayama, H. Senboku, S. Hara, *Tetrahedron* **2016,** *72*, 4626-4636.
53. H.-X. Feng, Y.-Y. Wang, J. Chen, L. Zhou, *Adv. Synth. Catal.* **2015,** *357*, 940-944.
54. X.-H. Xu, G.-K. Liu, A. Azuma, E. Tokunaga, N. Shibata, *Org. Lett.* **2011,** *13*, 4854-4857.
55. W. S. Bechara, G. Pelletier, A. B. Charette, *Nat. Chem.* **2012,** *4*, 228-234.
56. S. Balalaie, M. Mahdidoust, R. Eshaghi-Najafabadi, *J. Iran. Chem. Soc.* **2007,** *4*, 364-369.
57. J. Garnier, D. W. Thomson, S. Zhou, P. I. Jolly, L. E. A. Berlouis, J. A. Murphy, *Beilstein J. Org. Chem.* **2012,** *8*, 994-1002.
58. L. J. Johnston, J. Lusztyk, D. D. M. Wayner, A. N. Abeywickreyma, A. L. J. Beckwith, J. C. Scaiano, K. U. Ingold, *J. Am. Chem. Soc.* **1985,** *107*, 4594-4596.
59. P. Caubère, *Angew. Chem. Int. Ed.* **1983,** *22*, 599-613.
60. H. Jenkner, US3116112A. US patent: 1963.
61. Z. Hong, D. Y. Ong, S. K. Muduli, P. C. Too, G. H. Chan, Y. L. Tnay, S. Chiba, Y. Nishiyama, H. Hirao, H. S. Soo, *Chem. Eur. J.* **2016,** *22*, 7108-7114.
62. M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. J. A. Montgomery, J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Coss, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, *Gaussian 09, revision B.01, Gaussian, Inc., Wallingford CT* **2010**.
63. V. M. Vlasov, *New. J. Chem.* **2010,** *34*, 2962-2970.
64. R. Y. Sung, H. Choi, J. P. Lee, J. K. Park, K. Yang, K. I. Sun, *Bull. Korean Chem. Soc.* **2009,** *30*, 1579-1582.
65. W. Greizerstein, R. A. Bonelli, J. A. Brieux, *J. Am. Chem. Soc.* **1962,** *84*, 1026-1032.
66. S. Chiba, K. Ando, K. Narasaka, *Synlett* **2009**, 2549-2564.
67. Z. Rappoport, *Acc. Chem. Res.* **1992,** *25*, 474-479.
68. L. I. Goryunov, J. Grobe, D. Le Van, V. D. Shteingarts, R. Mews, E. Lork, E.-U. Würthwein, *Eur. J. Org. Chem.* **2010**, 1111-1123.
69. C. N. Neumann, J. M. Hooker, T. Ritter, *Nature* **2016,** *534*, 369-373.

## Chapter 3. Transition-metal free synthesis of α-branched tertiary amines via reductive functionalization of carboxamides and lactams

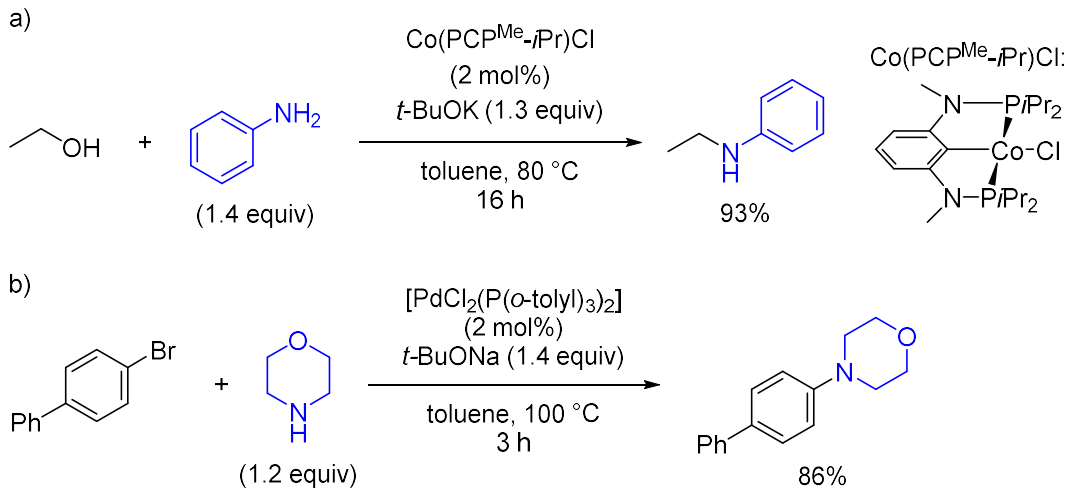
### 3.1. Introduction

The synthesis of amines are common and important protocols that are utilized in the production of drug molecules, agrochemical compounds, fragrances and dyes.[1-3] The synthesis of these classes of compounds heavily relies on the C-N bond formation reactions (i.e. amination) such as nucleophilic amination with alkyl (pseudo)halides (Scheme 3.1a)[4-6] and reductive amination (Scheme 3.1b).[7-8]




**Scheme 3.1.** a) Nucleophilic amination; b) Reductive amination.

Recent advancements by leveraging on transition metal catalysis allows for construction of more diverse array of amine derivatives. The representative examples are catalytic dehydrative *N*-alkylation of amines with alcohols, which proceeds via alcohol dehydrogenation and subsequent reductive amination with concomitantly generated metal hydride during the catalytic cycle (Scheme 3.2a)[3, 9] and transition-metal-catalyzed C-N cross-coupling reaction (Scheme 3.2b).[10, 11]




**Scheme 3.2.** a) *N*-Alkylation of amines with alcohols; b) Transition-metal catalyzed C-N cross-coupling.

Among organic amine compounds, α-branched amines are found as a key scaffold in various pharmaceutical drugs and natural products (see Figure 3.1 for selected examples of clinically used small molecule drugs based on the α-branched amine scaffold). Therefore, synthetic methods capable of their facile construction from readily available materials would be highly demanded.

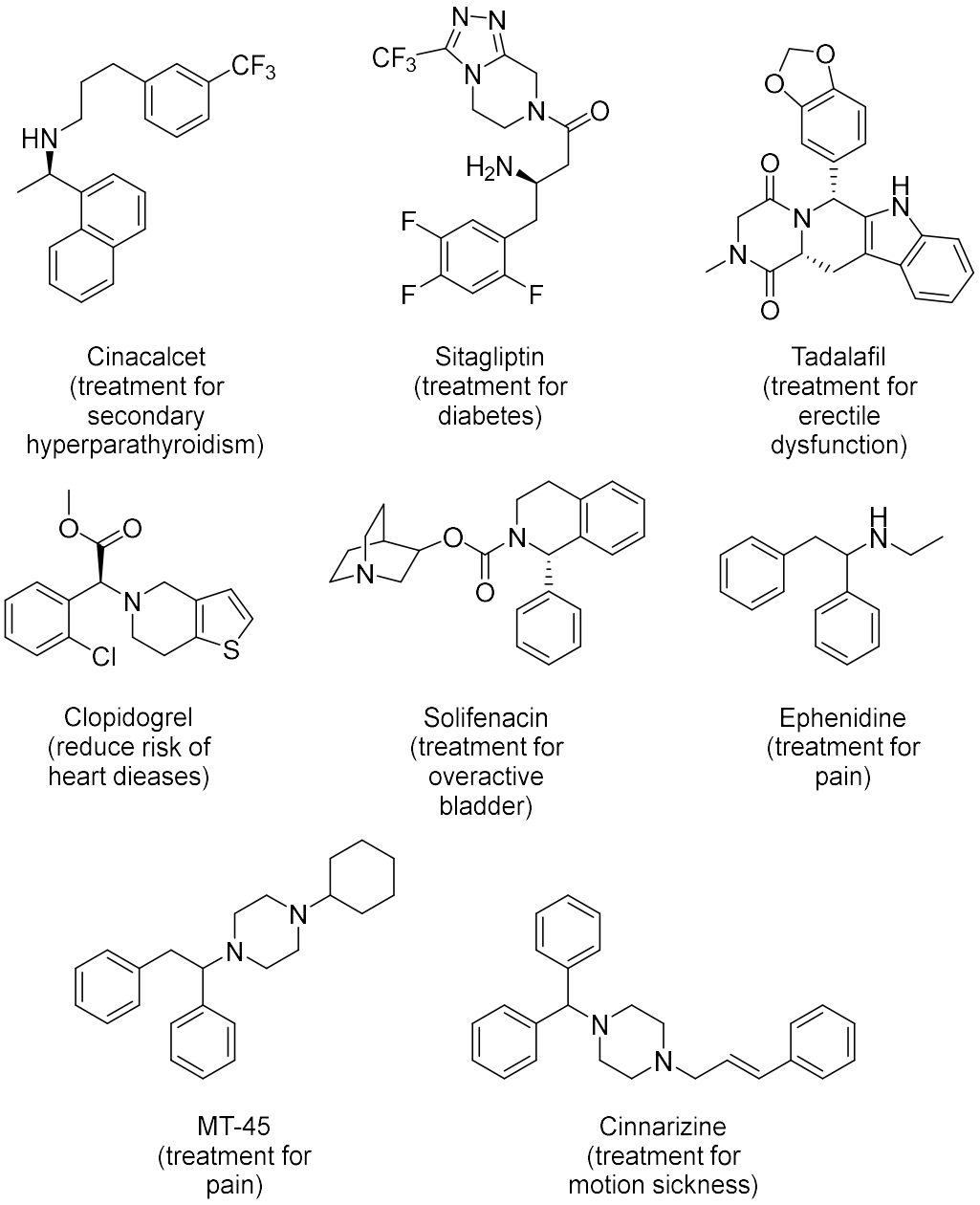
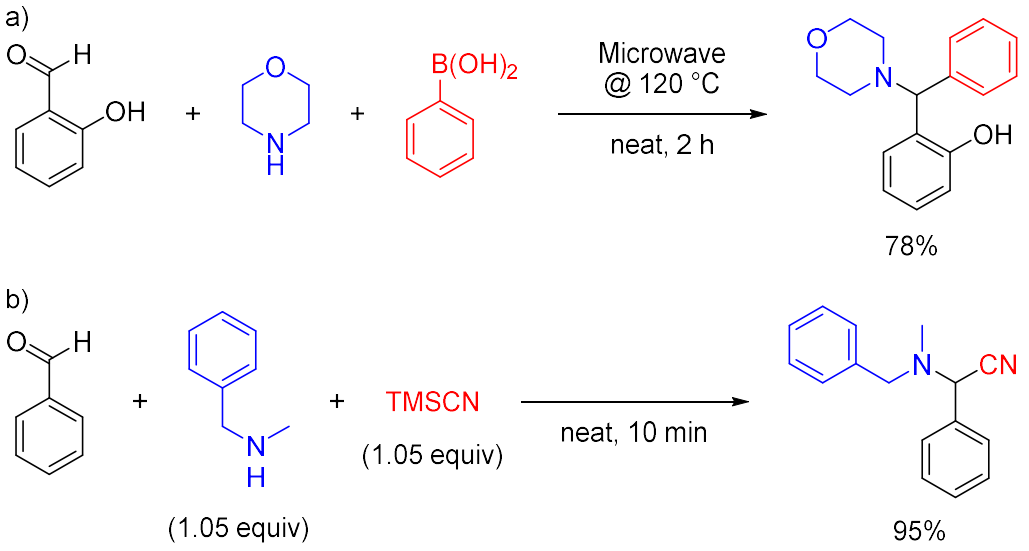


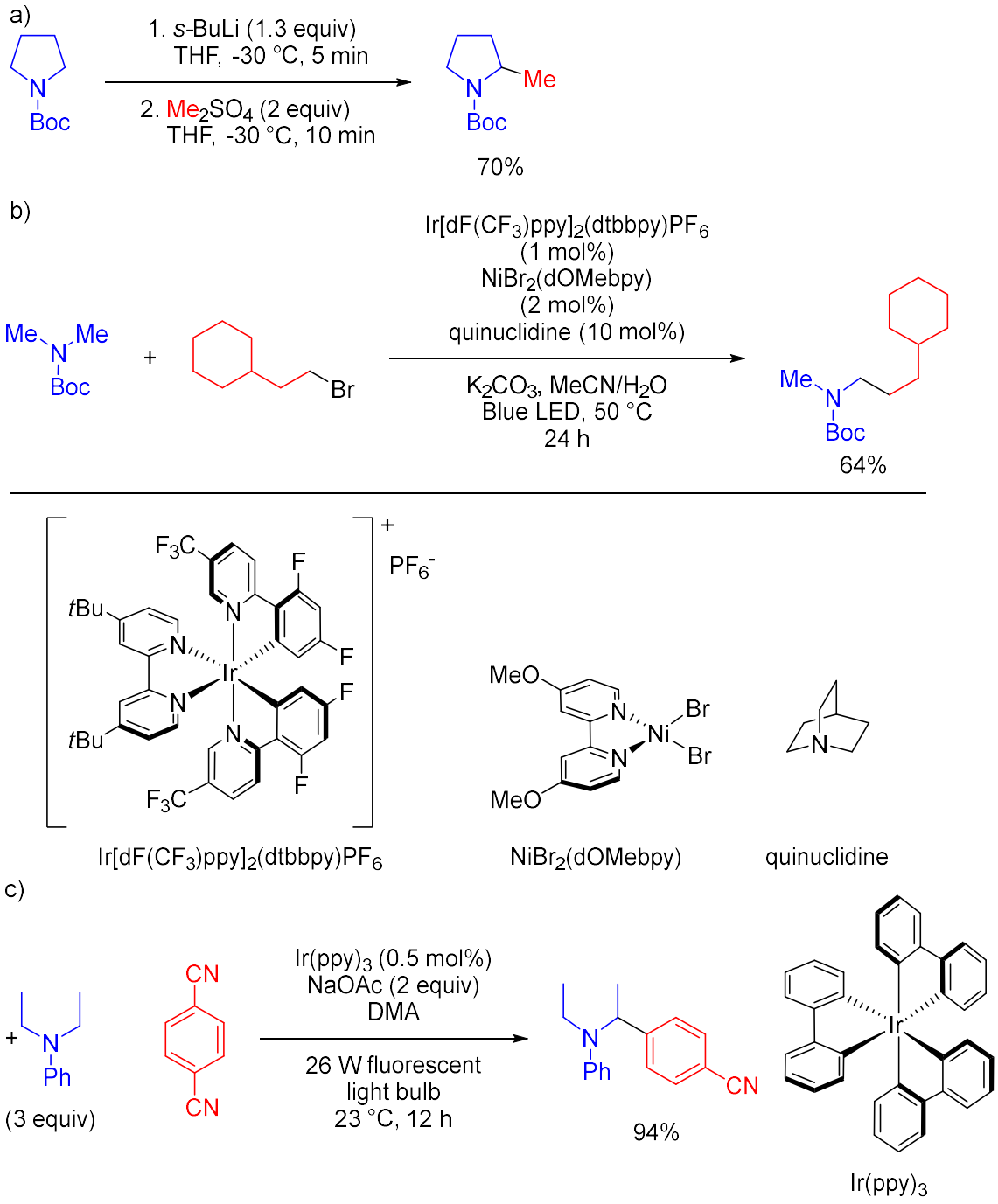

**Figure 3.1.** Drug molecules containing α-branched amine.

Use of a carbanion (or its precursor) in place of a hydride in reductive amination allows for synthesis of various α-branched amines. The Petasis-Mannich reaction (Scheme 3.3a)[12-13] and the Strecker reaction (Scheme 3.3b)[14-15] are the representative examples of this multi-component coupling approach.




**Scheme 3.3.** a) Microwave-assisted Petasis-Mannich reaction; b) Strecker reaction.

Directed lithiation at the α-carbon of *N*-Boc cyclic amines and subsequent trap of the resulting carbanion with appropriate carbon electrophiles is an alternative method to access to α-branched amines, while the method requires use of strong base for deprotonation and is commonly limited for functionalization of cyclic amines (Scheme 3.4a).[16-20] The α-C-H alkylation of acyclic or cyclic amines introduced recently by MacMillian et al., which took advantage of a combination of photoredox and nickel catalysis under much milder reaction conditions (Scheme 3.4b).[21] The same group also reported α-C-H arylation of amines with aryl nitriles under visible light photoredox catalysis (Scheme 3.4c).[22] Both protocols represented a significant advancement for the synthesis of α-branched amines.




**Scheme 3.4.** a) Directed lithiation/alkylation sequence at the α-carbon of tertiary amines; b) C-H alkylation of tertiary amines using a combination of catalysis; c) C-H arylation of tertiary amines using photoredox catalyst, $Ir(ppy)_3$.

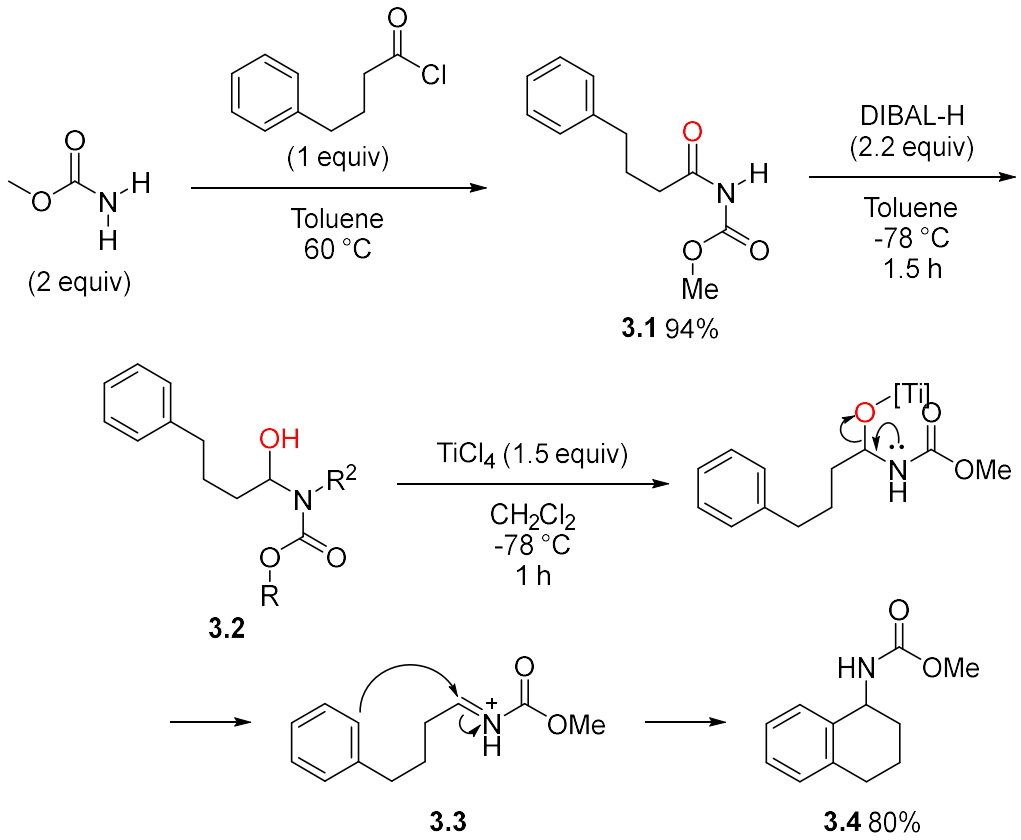
Another feasible approach to access α-branched amines would be to perform reductive functionalization on the readily accessible and bench-stable carboxamides. Several protocols had been developed, taking advantage of electrophilic activation or controlled hydride reduction including transition-metal-catalyzed hydrosilylation of amides as the process initiation to enable subsequent selective reductive functionalization with prevention of over-reduction of amides. The following section will discuss the recent approaches to the reductive functionalization of carboxamides for the synthesis of α-branched amines.

### 3.1.1. Reductive functionalization via electrophilic activation of amides

Electrophilic activation of amides prior to the reductive functionalization has been used as a viable option. There are two types of such amide activation protocols; one is the use of imides and another is by external electrophilic activators.

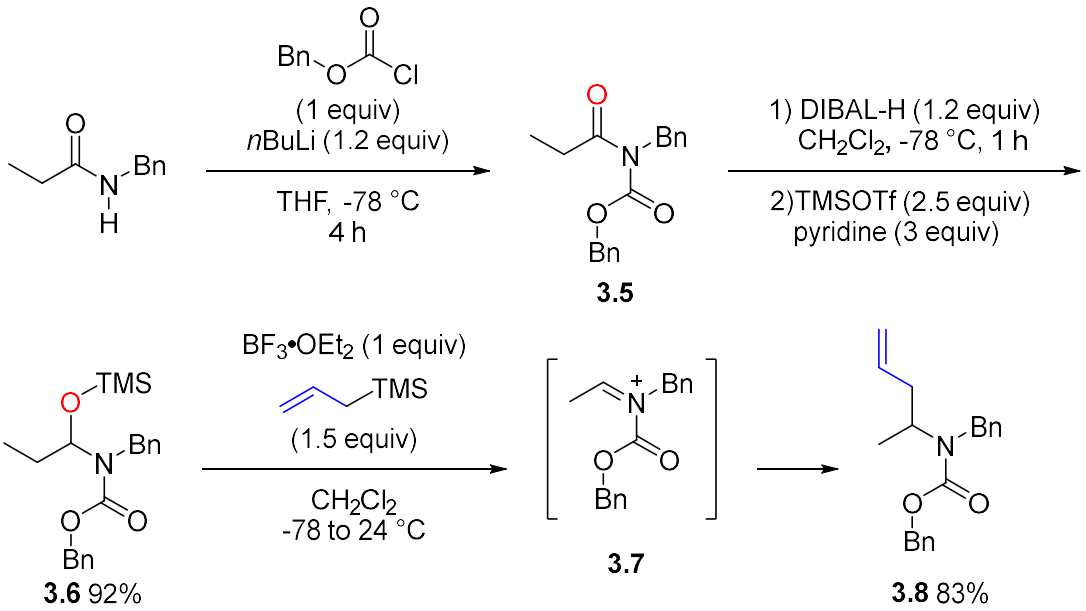
#### 3.1.1.1. Functionalization of primary/secondary amides via imides

DeNinno et al. demonstrated reductive functionalization of *N*-acylcarbamate **3.1**. Reduction of **3.1** by diisobutylaluminium hydride (DIBAL-H) resulted in formation of isolable *N,O*-hemiacetal **3.2**, that was subsequently treated with $TiCl_4$ to form *N*-acyliminium ion **3.3**. Finally, intramolecular Friedel-Crafts type cyclization took place to afford α-branched amine **3.4** (Scheme 3.5).[23-24]




**Scheme 3.5.** Generation of *N*-acyliminium ion and its intramolecular cyclization.

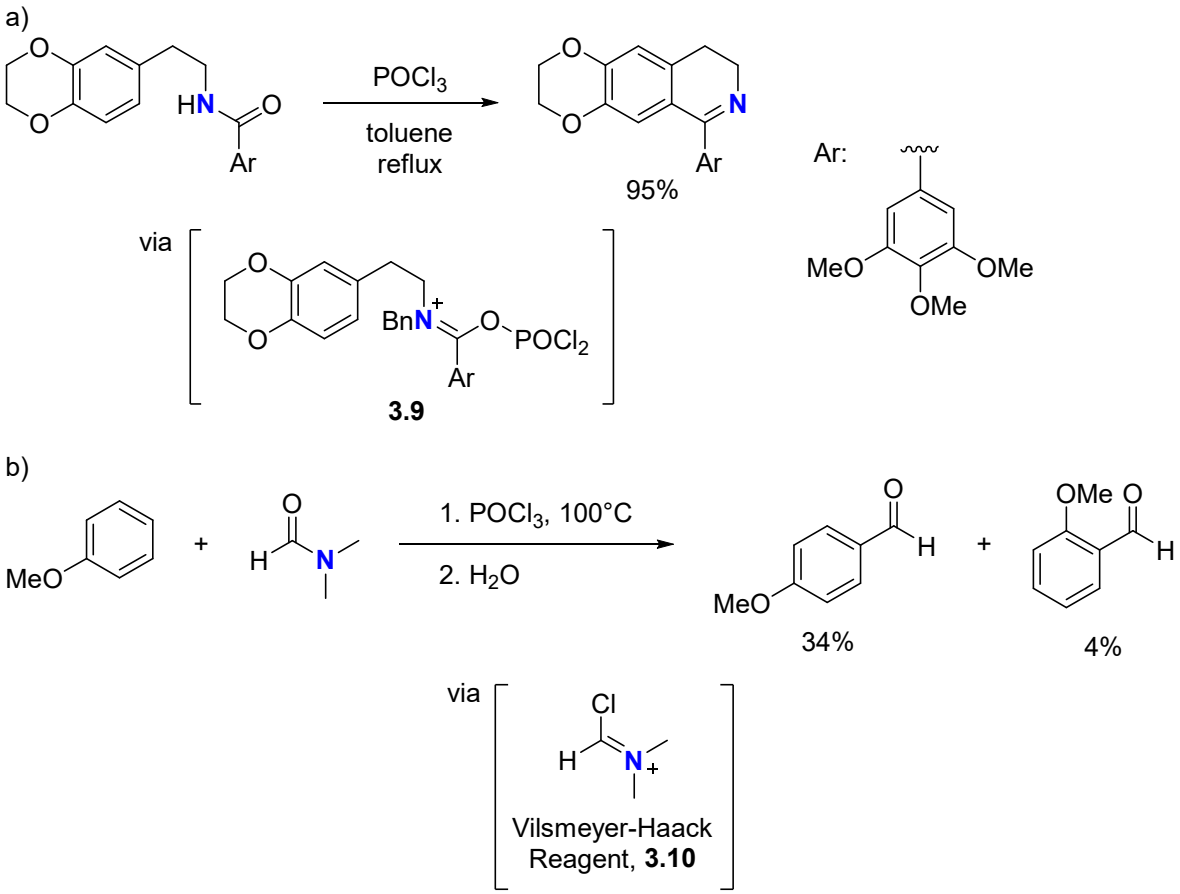
Similarly, Suh et al. generated *O*-silylated aminal intermediate **3.6** through DIBAL-H reduction of imide **3.5** followed by treatment with TMSOTf. The reaction of *O*-silylated aminal intermediate **3.6** with allyltrimethylsilane in the presence of $BF_3$•$OEt_2$ afforded α-branched amine **3.8** via *N*-acyliminium ion **3.7** (Scheme 3.6).[25-26]




**Scheme 3.6.** Reductive allylation of imides.

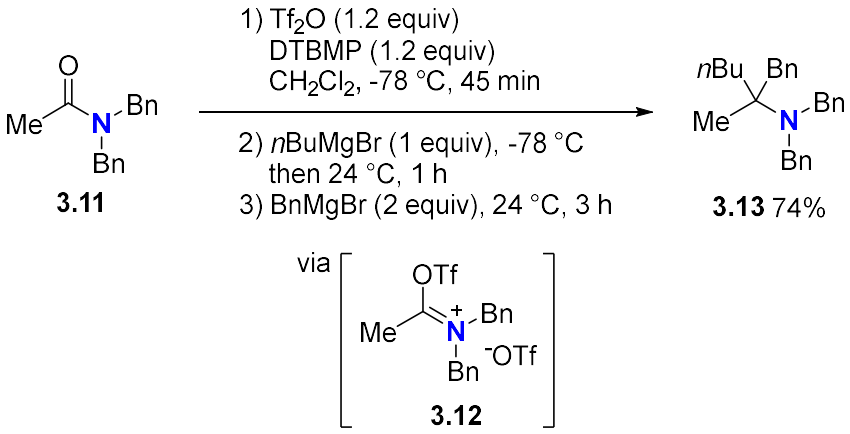
### 3.1.1.2. Functionalization of tertiary amides by electrophilic activation

There are classical name reactions such as Bischler-Napieralski reaction,[27] an intramolecular cyclization reaction of β-aryl ethylamides to yield dihydroisoquinolines (Scheme 3.7a), and Vilsmeier-Haack reaction[27] for the formylation of electron-rich arenes (Scheme 3.7b), while utilizing phosphorous(V) oxychloride ($POCl_3$) as an electrophilic activator of the amide oxygen to generate iminium ions (**3.9** and **3.10**) as the key intermediates.




**Scheme 3.7.** a) Bischler-Napieralski reaction; b) Vilsmeier-Haack reaction.

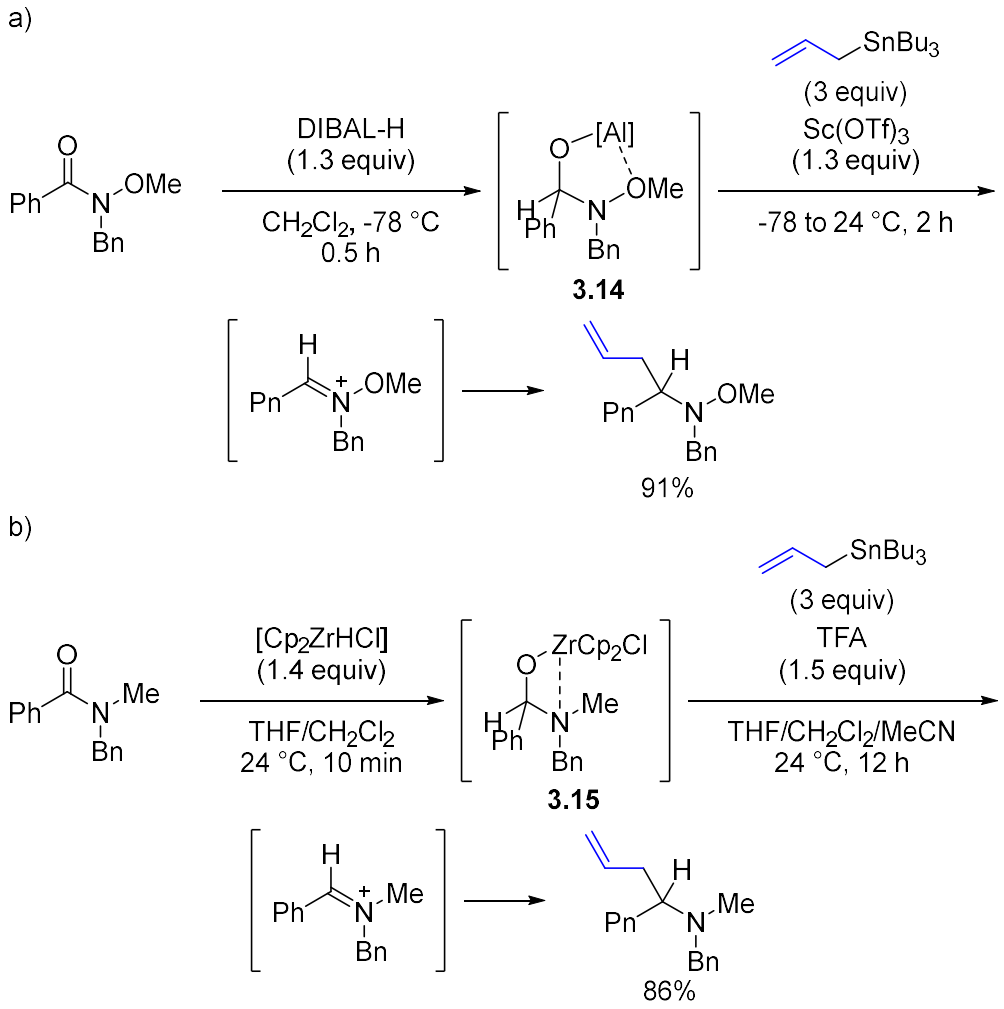
Analogous to these reactions, Huang et al. reported the electrophilic activation of tertiary amides **3.11** by triflic anhydride ($Tf_2O$) in the presence of ditertbutylmethylpyridine (DTBMP) to form the corresponding iminium triflate intermediate **3.12**. This iminium intermediate **3.12** could subsequently be functionalized twice by serial addition of Grignard reagents, allowing for di-alkylation at the α-position to afford α-dialkylated amines **3.13** (Scheme 3.8).[28]




**Scheme 3.8.** Sequential reductive alkylation of amides and lactams.

### 3.1.2. Reductive functionalization initiated by hydride reduction

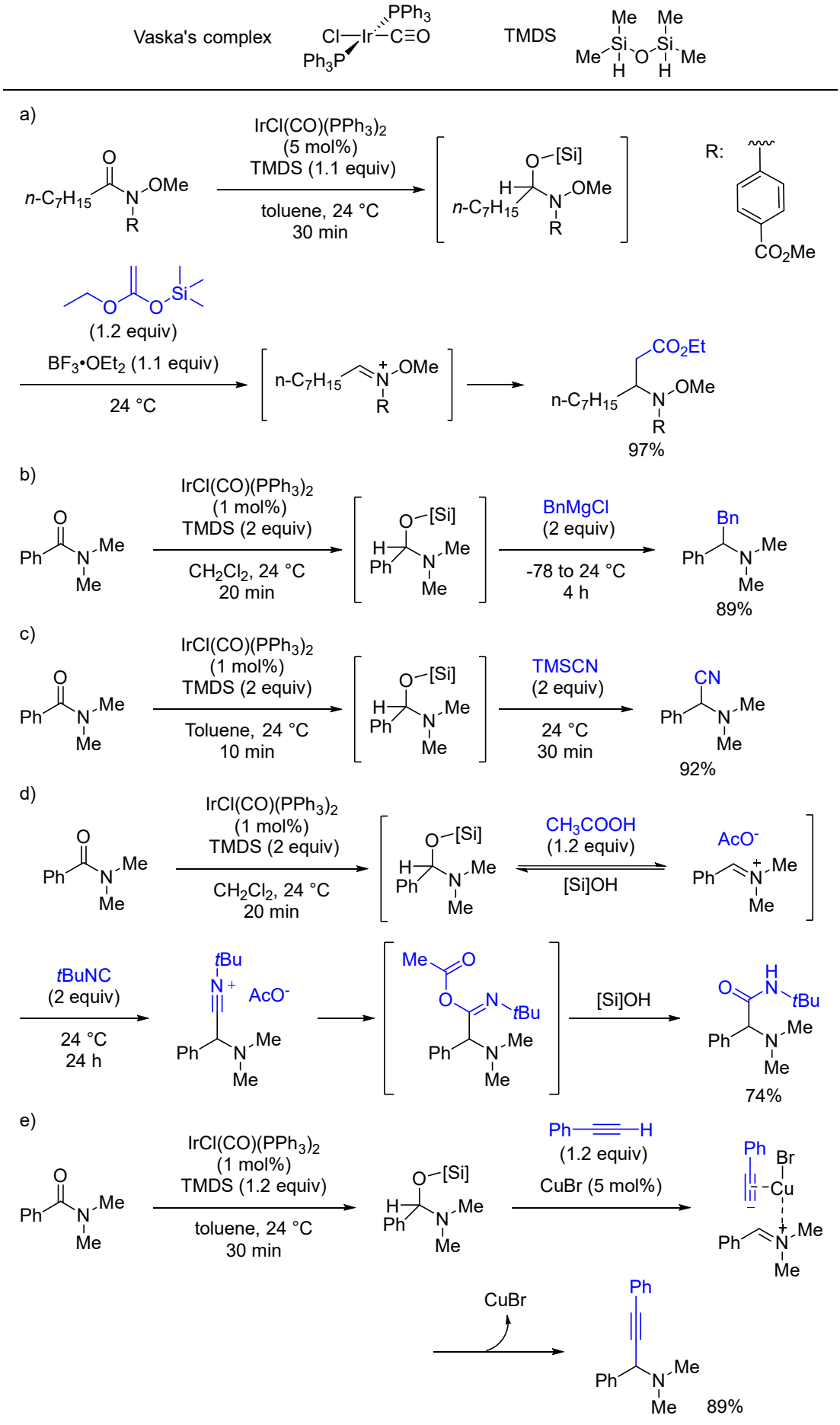
Reductive functionalization of amides can also be initiated by their hydride reduction. Chida et al. reported the use of DIBAL-H for reduction of *N*-methoxy amides (Scheme 3.9a)[29] and Schwartz's reagents ($Cp_2ZrHCl$) for reduction of tertiary amides (Scheme 3.9b),[30] generating the corresponding anionic carbinol amine intermediates **3.14** and **3.15** respectively. Further addition of acid reagents could collapse the intermediates to form reactive iminium ions that could be further functionalized with the addition of nucleophiles such as allyltributylstannane (Scheme 3.9).




**Scheme 3.9.** Reductive functionalization of tertiary carboxamides initiated with stoichiometric amount of a) DIBAL-H and b) Schwartz's reagents.

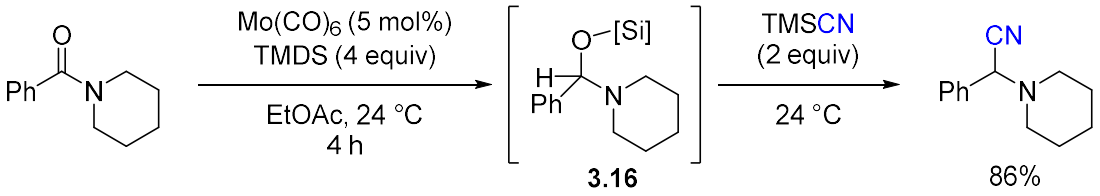
Catalytic hydrosilylation of carboxamides with siloxane has also been utilized to initiate the reductive functionalization. Nagashima et al. reported that the Vaska's complex [$IrCl(CO)(PPh_3)_2$] is a capable catalyst in hydrosilylation of tertiary amides with tetramethyldisiloxane (TMDS).[31] This methodology was ingeniously adopted by Chida, Dixon and Huang to perform the reductive transformations of tertiary amides through functionalization of the silylated carbinol amine intermediates generated by the hydrosilylation. Chida et al. reported the reductive conversion of aliphatic *N*-methoxy amides using $BF_3$-mediated addition of ketene silyl acetals as a carbon nucleophile

(Scheme 3.10a).[32] Dixon et al. reported reductive coupling of aliphatic or (hetero)aromatic tertiary amides using a variety of alkyl and aryl Grignard reagents (Scheme 3.10b).[33] The same group also disclosed the reductive Strecker reaction on tertiary amides and lactams (Scheme 3.10c)[34] as well as reductive Ugi-type reactions (Scheme 3.10d).[35] Huang et al. utilized Cu(I)-catalysed alkynylation (Scheme 3.10e).[36]


Vaska's complex
TMDS
a)
IrCl(CO)(PPh3)2
(5 mol%)
TMDS (1.1 equiv)
toluene, 24 °C
30 min
R:
CO2Me
(1.2 equiv)
BF3•OEt2 (1.1 equiv)
24 °C
97%
b)
IrCl(CO)(PPh3)2
(1 mol%)
TMDS (2 equiv)
CH2Cl2, 24 °C
20 min
BnMgCl
(2 equiv)
-78 to 24 °C
4 h
89%
c)
IrCl(CO)(PPh3)2
(1 mol%)
TMDS (2 equiv)
Toluene, 24 °C
10 min
TMSCN
(2 equiv)
24 °C
30 min
92%
d)
IrCl(CO)(PPh3)2
(1 mol%)
TMDS (2 equiv)
CH2Cl2, 24 °C
20 min
CH3COOH
(1.2 equiv)
[Si]OH
tBuNC
(2 equiv)
24 °C
24 h
[Si]OH
74%
e)
IrCl(CO)(PPh3)2
(1 mol%)
TMDS (1.2 equiv)
toluene, 24 °C
30 min
(1.2 equiv)
CuBr (5 mol%)
CuBr
89%

**Scheme 3.10.** Reductive transformation of amides initiated with Vaska's complex and TMDS.

Recently, Adolfsson et al. reported the use of molybdenum(VI) hexacarbonyl as a catalyst with TMDS to perform reductive Strecker reaction on tertiary amides (Scheme 3.11).[37] Their protocol goes through a similar *O*-silylated carbinol amine intermediates **3.16** before the addition of TMSCN to afford the α-amino nitriles.

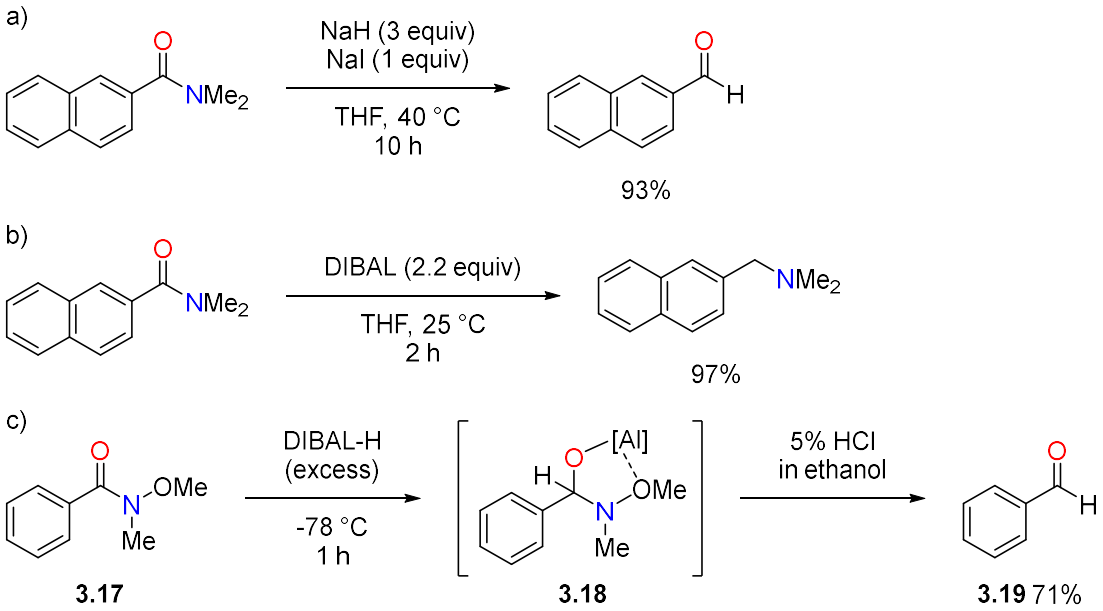



**Scheme 3.11.** Reductive Strecker initiated with $Mo(CO)_6$ and TMDS.

As discussed above, reductive functionalization of tertiary amides heavily relies on the use of transition-metal complexes. Thus, the exploration of a transition-metal free alternatives should make such a transformation more appealing.

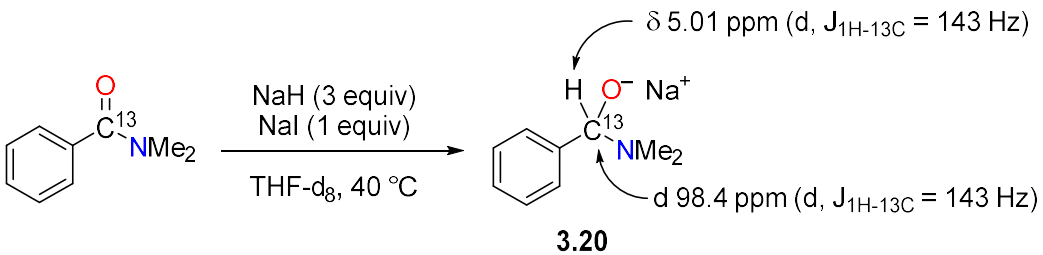
### 3.2. Perspective of this chapter

The author's group has recently developed controlled reduction of tertiary carboxamide to aldehydes[38] using the NaH-NaI composite (Scheme 3.12a). On the other hand, it is well known that DIBAL-H, which is one of the most commonly utilized hydride reagents in both academics and industries[39-41], reduces tertiary carboxamides to the corresponding amines (Scheme 3.12b).[42] Reduction of *N*-methoxy *N*-methyl amides **3.17** (the Weinreb amides) are the exceptional examples providing aldehydes **3.19** through the formation of stable 5-membered ring chelate **3.18** (Scheme 3.12c).[43-45]



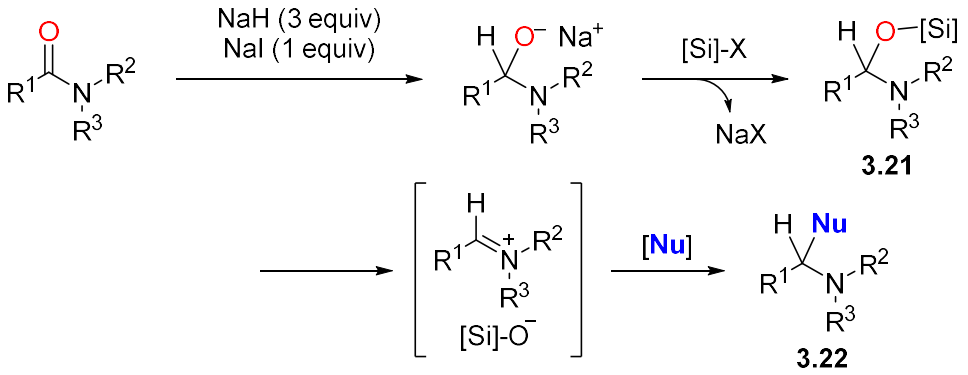

**Scheme 3.12.** Reduction of tertiary carboxamide a) by the NaH-I composite; b) by DIBAL-H. c) Reduction of the Weinreb amides by DIBAL-H.

Intrigued by the reactivity difference between reduction of tertiary carboxamide with diisopropylaluminum hydride and sodium hydride-iodide composite (Scheme 3.12), the author's group has conducted a mechanistic study to understand the difference of their reactivity.[46] The study confirmed that tetrahedral carbinol amine intermediate such as **3.20**, formed by the hydride attack from the NaH-NaI composite, is a stable species in THF even at high temperature (e.g. under reflux in THF). The formation of anionic carbinol amine intermediate **3.20**, derived from the reduction of $^{13}$C-labelled benzamide, was unambiguously detected in the $^{1}$H and proton-coupled $^{13}$C NMR spectroscopies (Scheme 3.13).




**Scheme 3.13.** Observation of tetrahedral carbinol amine intermediate **3.20**.

Thus, the author explored the possible use of this anionic carbinol amine intermediate **3.20** for further reductive functionalization. Namely, silylation of **3.20** and subsequent treatment of silylated **3.21** with external nucleophiles should provide α-branched amines **3.22** under transition-metal free fashion (Scheme 3.14). This chapter describes the detailed results on the reaction optimization and substrate scope.

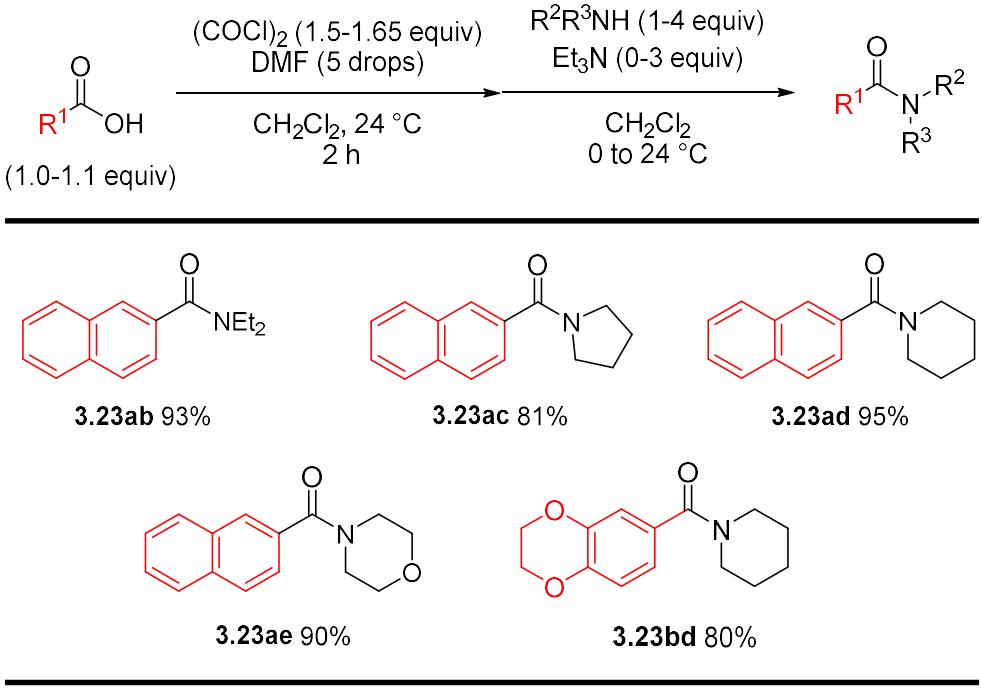



**Scheme 3.14.** Reductive functionalization of tertiary carboxamides.

### 3.3. Result and discussion

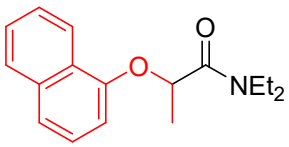
#### 3.3.1. Preparation of starting materials

Amides **3.23ab**, **3.23ac**, **3.23ad**, **3.23ae** and **3.23bd** were synthesized from the corresponding carboxylic acids (1.0 – 1.1 equiv) via the formation of acyl chlorides using oxalyl chloride (1.5 – 1.65 equiv) in the presence of catalytic amount of DMF in dichloromethane at 24 °C for 2 h. Subsequently, amidation was done by adding corresponding amine (1 – 4 equiv) and triethylamine (0 – 3 equiv) or excess corresponding amine as buffer. The isolated yields were summarized below (Scheme 3.15). It should be noted that amide **3.23bd** is known as CX546, which is utilized for treatment of schizophrenia.[47]




**Scheme 3.15.** Synthesis of amides via acyl chloride.

α-Aryoxyamide, napropamide **3.23rb** is commercially available and used as received (Figure 3.2). This compound is a herbicide, which is used in agriculture to minimize weeds growth in plantation by inhibiting their roots growth.[48]



**3.23rb**

**Figure 3.2.** Napropamide.

The series of aromatic amides **3.23aa**, **3.23ca**, **3.23da**, **3.23ea**, **3.23fa**, **3.23ga**, **3.23ha**, **3.23ia** and **3.23td** were synthesized based on the corresponding literature procedures (Figure 3.3).[33, 38]

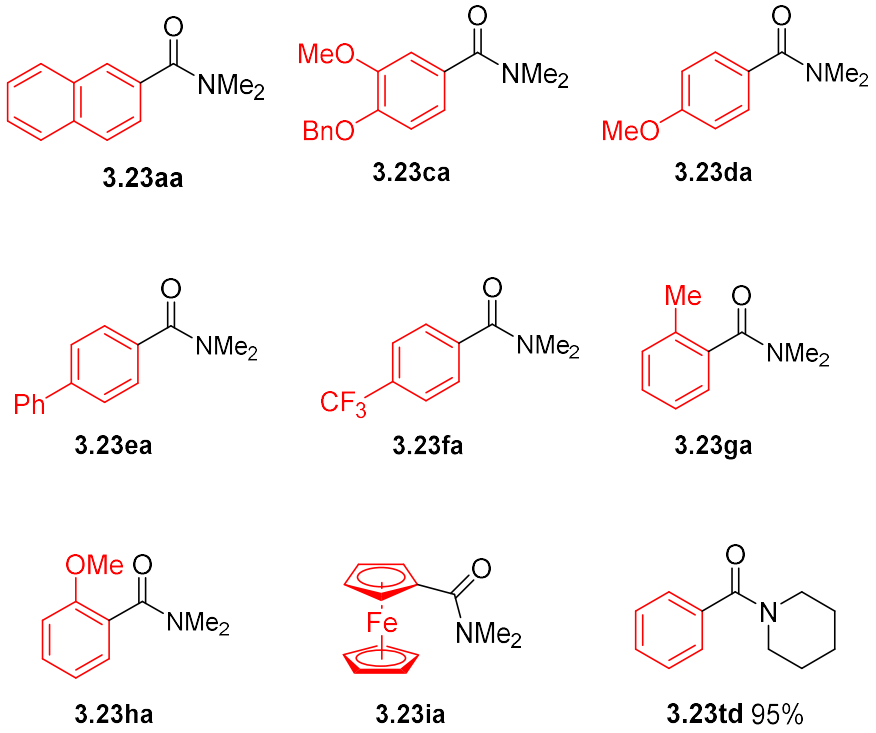



**Figure 3.3.** Known aromatic amides.

A series of heteroaromatic amides **3.23ja**, **3.23ka**, **3.23la** and **3.23ma** were synthesized based on the corresponding literature procedures (Figure 3.4).[38]

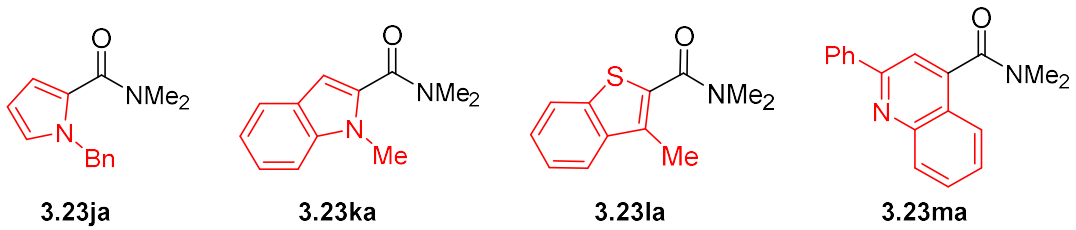



**Figure 3.3.** Known heteroaromatic amides.

Aliphatic amides **3.23na**, **3.23oa**, **3.23pa**, **3.23qa** and **3.23sa** were synthesized based on the corresponding literature procedures. (Figure 3.4).[38, 49] Amide **3.23na** was synthesized from gemfibrozil, which is an antihyperlipidemic agent that is used to reduce blood lipid and cholesterol level.[50]

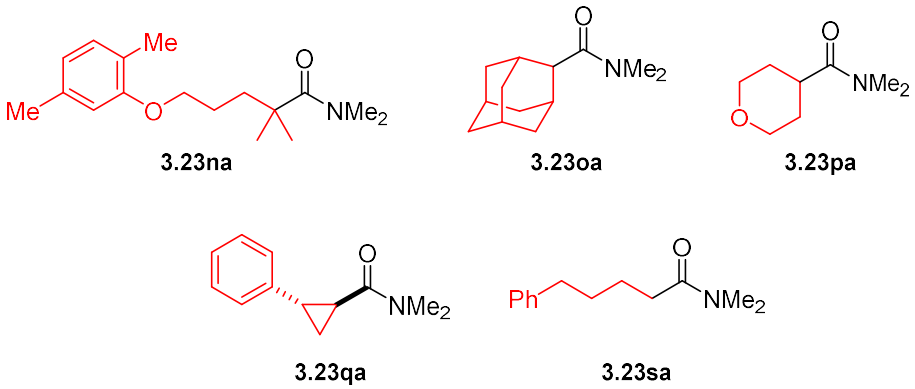



**Figure 3.4.** Known aliphatic amides.

Lactams **3.23u** and **3.23v** were synthesized based on the corresponding literature procedures (Figure 3.5).[51]

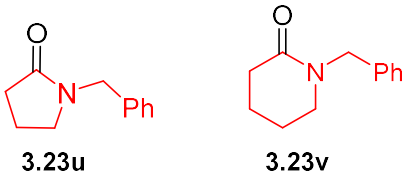


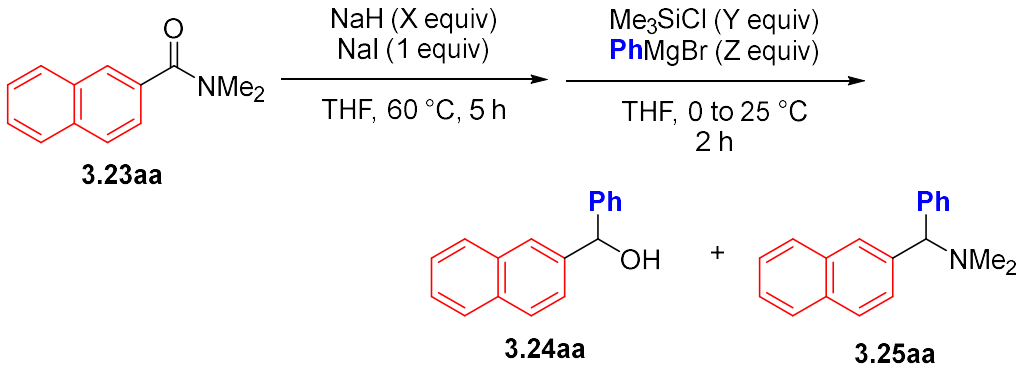

**Figure 3.5.** Known lactams.

### 3.3.2. Optimization of reaction conditions

We embarked on the optimization of the reaction conditions using napthamide **3.23aa**. The first reductive generation of sodiated carbinol amine intermediate was conducted by treatment of **3.23aa** with 3 equiv of NaH and 1 equiv of NaI at 60 °C.[38, 46] Chlorotrimethylsilane (TMSCl) was tested as a reagent for *O*-silylation of the sodiated carbinol amine intermediate. As expected, simultaneous addition of 1.5 equiv of TMSCl and 2 equiv of PhMgBr afforded desired α-branched **3.25aa** in 59% yield along with 26% yield of alcohol **3.24aa** (entry 1). Increase of the amount of PhMgBr to 3 equiv significantly improved the yield of **3.25aa** to 81% (entry 2). Use of 2.5 equiv of TMSCl allowed for further enhancement of the yield of **3.25aa** to 86% (entry 3). It was

found that with 2.5 equiv of TMSCl, the amount of PhMgBr could be reduced to 2 equiv with keeping the yield of **3.25aa** (entry 4).

**Table 3.1**: Optimization of the reaction conditions[a]

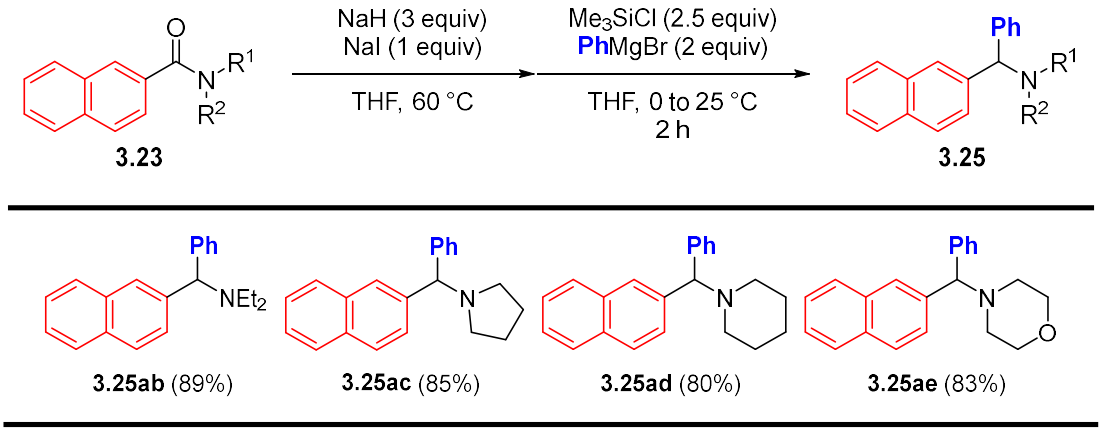



| Entry | NaH (X equiv) | $Me_3SiCl$ (Y equiv) | PhMgBr (Z equiv) | Yield of **3.24aa** (%)[b] | Yield of **3.25aa** (%)[b] |
|---|---|---|---|---|---|
| 1 | 3 | 1.5 | 2 | 26 | 59 |
| 2 | 3 | 1.5 | 3 | 16 | 81 |
| 3 | 3 | 2.5 | 3 | 11 | 87 |
| 4 | 3 | 2.5 | 2 | 11 | 89 (86)[c] |

[a] The reactions were conducted using 0.5 mmol of **3.23aa** in THF (2.5 mL). [b] Yields determined by $^1H$ NMR spectroscopy. [c] Isolated yield.

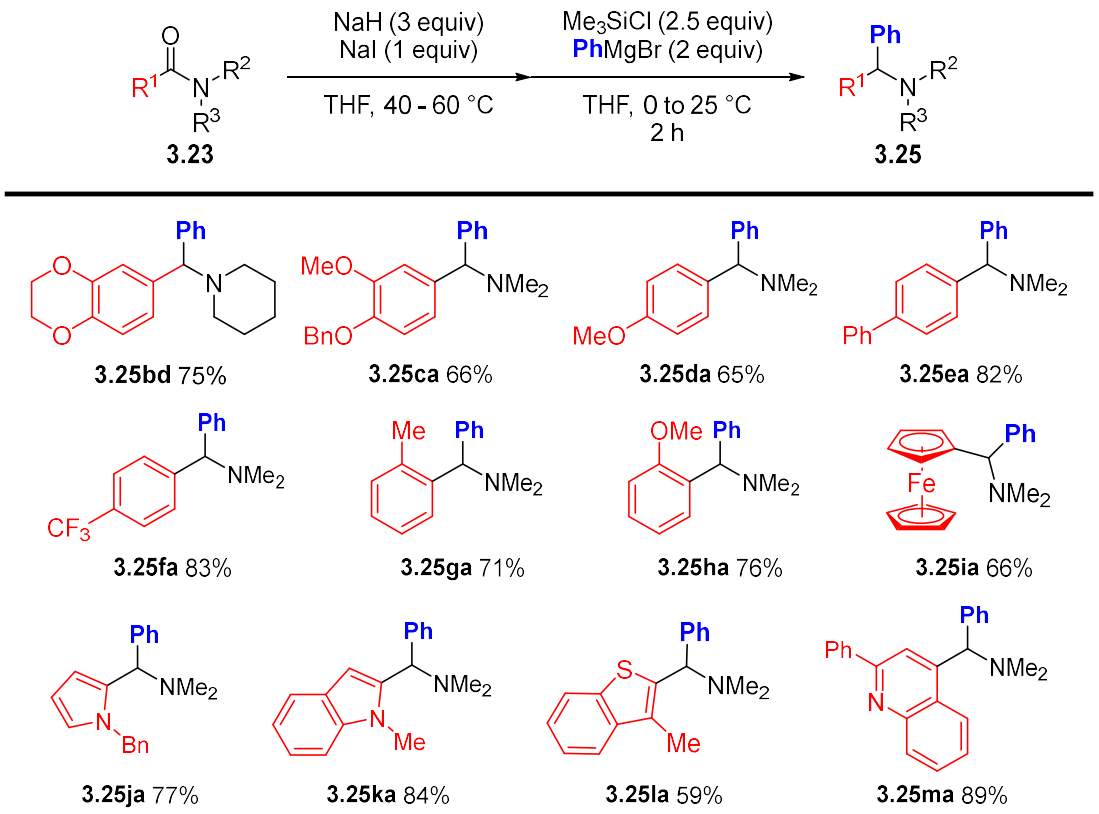
### 3.3.3. Scope and limitation

With the optimized condition in hand (Table 3.1, entry 4), the author began to investigate the scope and limitation of this protocol. As for the substituents on the amine, the method allowed for the synthesis of diethylamine **3.25ab** as well as cyclic amines like pyrrolidine **3.25ac**, piperidine **3.25ad** and morpholine **3.25ae** in good yields (Scheme 3.16).




**Scheme 3.16.** α-phenyl tertiary amine synthesis from various tertiary amides. [a] The reactions were conducted using 0.5 mmol of the amides **3.23** with isolated yields of tertiary amines **3.25** given.

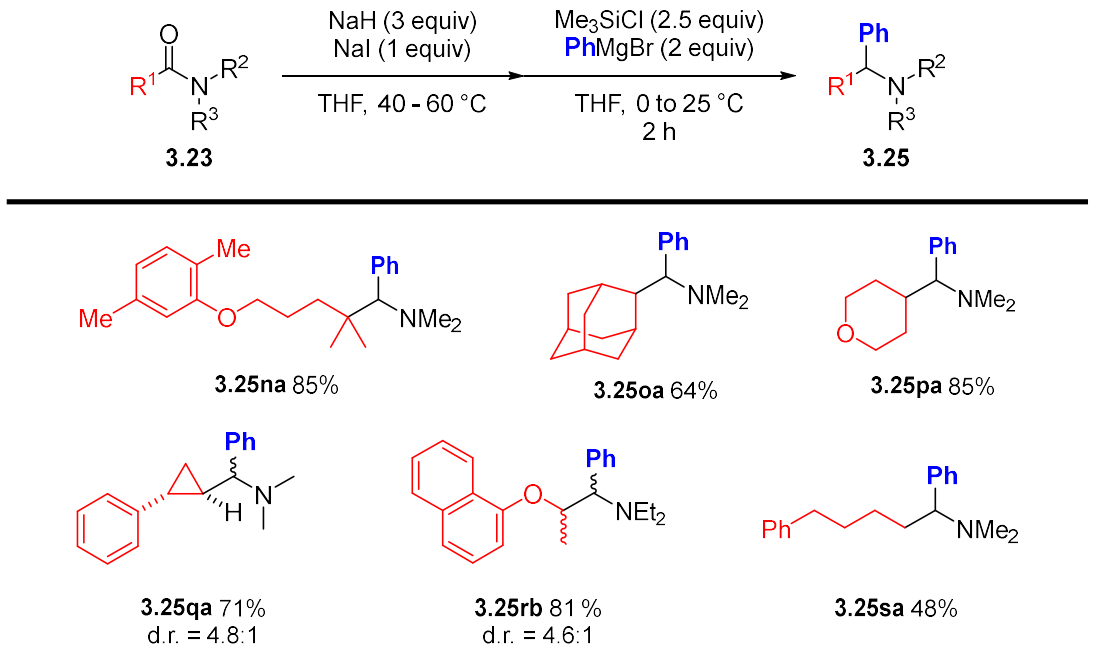
This protocol generally tolerated various aromatic and heteroaromatic amides to afford the corresponding α-branched amines in good yields (Scheme 3.17). Both electron-rich and -deficient arenes on the amides were also well tolerated (for **3.25b**, **3.25ca**, **3.25da** and **3.25ea** as well as **3.25fa**). This protocol was not affected by sterically bulky arene substituents (for **3.25ga** and **3.25ha**). Synthesis of tertiary amine **3.25ia** containing ferrocene was also achieved in 66% yield. Furthermore, the reductive phenylation of electron-rich heteroaromatic amides such as those based on pyrrole (**3.23ja**), indole (**3.23ka**) and benzothiophene (**3.23la**) as well as electron-deficient heteroaromatic amides based on quinoline (**3.23ma**) proceed smoothly to give the corresponding heteroaryl containing α-branched amines in good yields.




**Scheme 3.17.** α-phenyl tertiary amine synthesis from (hetero)aromatic amides. [a] The reactions were conducted using 0.5 mmol of the amides **3.23** with isolated yields of α-branched amines **3.25** given.

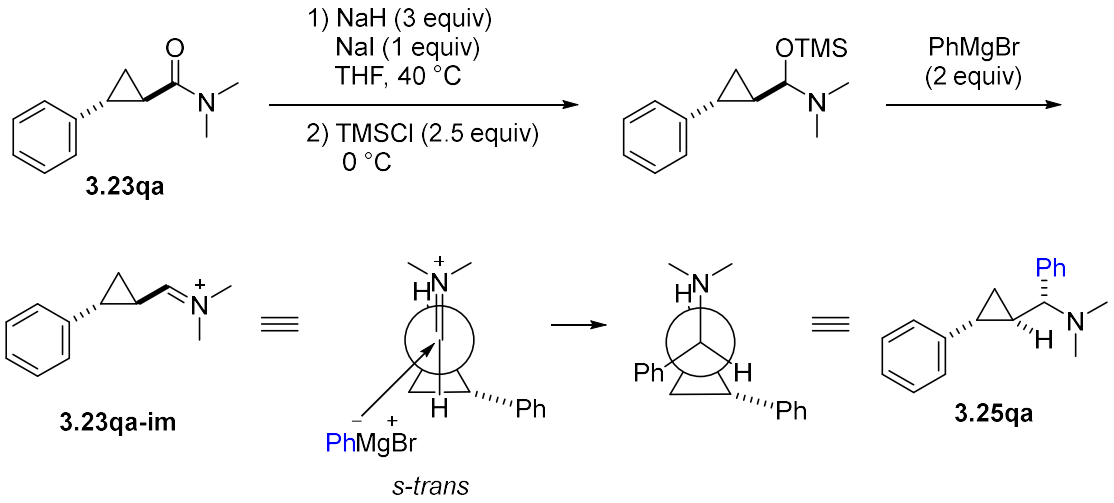
Next, the author investigated the use of aliphatic amides for reductive phenylation (Scheme 3.18). Sterically bulky α-quaternary aliphatic amides **3.23na** (derived from drug molecule, gemfibrozil)[50] underwent reductive phenylation smoothly to afford product **3.25na** in good yields. Tertiary amides containing an enolizable α-proton were converted into the corresponding α-branched amines (for **3.25oa**, **3.25pa**, **3.25qa** and **3.25rb**). The potential application of this protocol was demonstrated with the further derivatization of napropamide (**3.23rb**)[48] to afford the α-phenyl amine **3.25rb**. Noteworthy, the presence of β-oxygen did not disturb the process. The reductive phenylation

of α-secondary amides **3.23sa** also proceeded despite moderate yield of the product **3.25sa**.




**Scheme 3.18.** α-phenyl tertiary amine synthesis from aliphatic amides. [a] The reactions were conducted using 0.5 mmol of the amides **3.23** with isolated yields of tertiary amines **3.25** given.

Interestingly, the formation of α-phenyl tertiary amines **3.25qa** and **3.25rb** resulted in good diastereoselectivity of 4.8:1 and 4.6:1 respectively. The configuration of the major isomer was speculated as described below (Schemes 3.19 and 3.20). In the second step of the present process, the addition of PhMgBr, which also functioned as a Lewis acid, resulted in formation of the corresponding iminium ions **3.23qa-im** and **3.23rb-im**. The iminium ion **3.23qa-im** resembles cyclopropanecarboaldehyde bearing a bisected *S-trans* conformation.[52] The phenyl Grignard reagent should attack to the less hindered *Si*-face to give the (*R**,*R**,*R**)-tertiary amine **3.25qa** (Scheme 3.19).

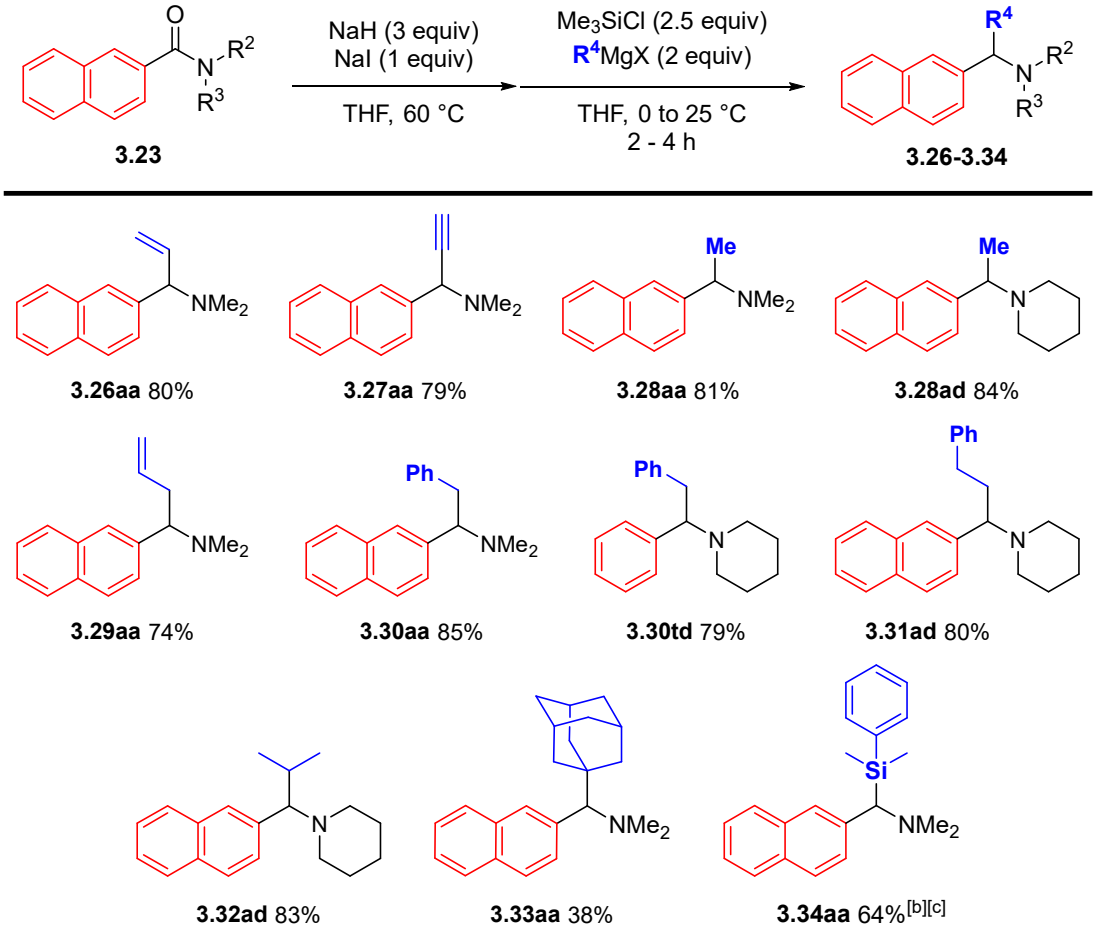



**Scheme 3.19.** Proposed configuration of the major isomer for amine **3.25qa**.

The diastereoselectivity in the formation of amine **3.25rb** cannot be estimated due to the presence of different possible model, further experimental work is needed to determine the diastereoselectivity.

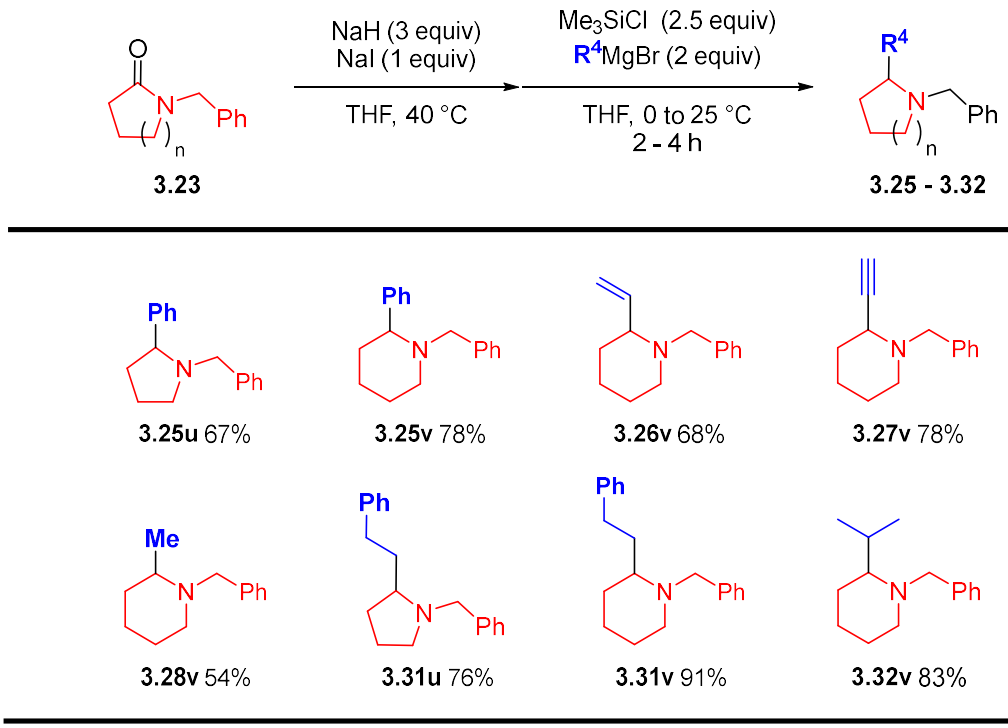
The author then investigated the scope of Grignard reagents for reductive functionalization of naphthamides **3.23aa** and **3.23ad** (Scheme 3.21). The present method was found compatible for reductive vinylation and alkynylation, providing the corresponding amines **3.26aa** and **3.27aa** in good yields. As for aliphatic Grignard reagents, methylmagnesium bromide as well as various primary alkyl Grignard reagents based on allyl, benzyl and phenethyl groups could be utilized for synthesis of corresponding amines **3.28aa**, **3.28ad**, **3.29aa**, **3.30aa**, **3.30td** and **3.31ad.** The successful synthesis of diphenidine **3.30td** (*N*-methyl-D-aspartate (NMDA) receptor antagonist[53] which is used for treatment of chronic pain[54]) showcased practicability of the present method. Installation of an isopropyl group was efficiently achieved (for **3.32ad**), while the reaction with an adamantyl Grignard reagent provided **3.33aa** only in moderate yield. In addition to the Grignard reagents as a carbon source,

dimethylphenylsilylmagnesium bromide was found compatible for a new carbon-silicon bond formation to yield α-silyl tertiary amine **3.34aa** in good yield, while the use of dimethylphenylsilyllithium resulted in lower yield of **3.34aa** with formation of a complex mixture of unidentified compounds.



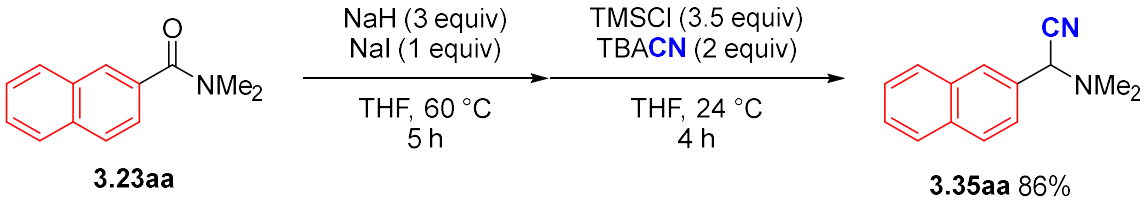

**Scheme 3.21.** Scope of Grignard reagents. [a] The reactions were conducted using 0.5 mmol of the amides **3.23** with isolated yields of tertiary amines **3.26-3.34** given; [b] Use of $PhMe_2SiMgBr$ (prepared from $MgBr_2$ + $PhMe_2SiLi$)[55]; [c] Use of $PhMe_2SiLi$ yielded **3.34aa** determined in 19% yield based on $^1H$ NMR with 1,1,2,2-tetrachloroethane as internal standard.

The present protocol was found applicable to the reductive functionalization of cyclic amides, lactams, enabling efficient construction of α-functionalized pyrrolidines and piperidines (Scheme 3.22). Reductive phenylation (for **3.25u**, **3.25v**), vinylation (for **3.26v**), and alkynylation (for **3.27v**) were successfully achieved. Similarly, the method was amenable to installation of methyl, phenethyl, and isopropyl groups (for **3.28v**, **3.31u**, **3.31v** and **3.32v**).




**Scheme 3.22.** Pyrrolidines and piperidines synthesized from lactams and various Grignard reagents. [a] The reactions were conducted using 0.5 mmol of the amides **3.23** with isolated yields of pyrrolidines and piperidines **3.25-3.32** given.

Synthetically valuable α-amino nitriles[56] could also be synthesized by the present method using tetrabutylammonium cyanide (TBACN) instead of Grignard reagents. Namely, after reduction of amide **3.23aa** by the NaH-NaI system, the mixture was subsequently treated with TMSCl and TBACN to yield the α-amino nitriles **3.35aa** in 86% yield (Scheme 3.23).




**3.23aa** **3.35aa** 86%

**Scheme 3.23.** Reductive Strecker reaction.

### 3.4. Conclusion

In conclusion, a new protocol for reductive functionalization of tertiary amides with carbon or silicon-based nucleophiles was achieved. The method is initiated by the controlled hydride reduction of carboxamides by the NaH-NaI system to form stable anionic carbinol amine intermediate, which is subsequently treated with TMSCl and the nucleophiles. Thus, the protocol can be operated under completely transition-metal free fashion.

### 3.5 References


1. A. Ricci, *Amino Group Chemistry: From Synthesis to the Life Sciences*. Wiley: 2008.
2. S. A. Lawrence, *Amines: Synthesis, Properties and Applications*. Cambridge University Press: 2006.
3. G. Guillena, D. J. Ramón, M. Yus, *Chem. Rev.* **2010,** *110*, 1611-1641.
4. Y. Ju, R. S. Varma, *Green Chem.* **2004,** *6*, 219-221.
5. M. Kurosu, S. S. Dey, D. C. Crick, *Tetrahedron Lett.* **2006,** *47*, 4871-4875.
6. S. A. I. Quadri, T. C. Das, S. Jadhav, M. Farooqui, *Synth. Commun.* **2018,** *48*, 267-277.
7. M. Tajbakhsh, R. Hosseinzadeh, H. Alinezhad, S. Ghahari, A. Heydari, S. Khaksar, *Synthesis* **2011,** *2011*, 490-496.
8. E. Podyacheva, O. I. Afanasyev, A. A. Tsygankov, M. Makarova, D. Chusov, *Synthesis* **2019,** *51*, 2667-2677.
9. M. Mastalir, G. Tomsu, E. Pittenauer, G. Allmaier, K. Kirchner, *Org. Lett.* **2016,** *18*, 3462-3465.
10. A. S. Guram, R. A. Rennels, S. L. Buchwald, *Angew. Chem. Int. Ed.* **1995,** *34*, 1348-1350.
11. J. F. Hartwig, *Acc. Chem. Res.* **2008,** *41*, 1534-1544.
12. P. Nun, J. Martinez, F. Lamaty, *Synthesis* **2010,** *2010*, 2063-2068.
13. N. R. Candeias, F. Montalbano, P. M. S. D. Cal, P. M. P. Gois, *Chem. Rev.* **2010,** *110*, 6169-6193.

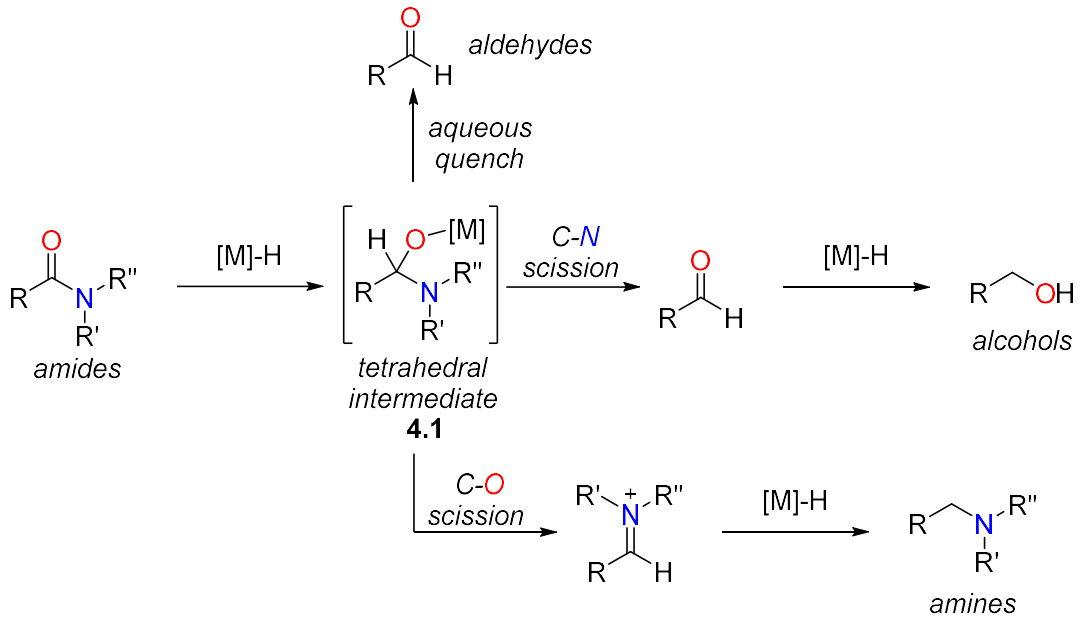
14. A. Baeza, C. Nájera, J. M. Sansano, *Synthesis* **2007,** *2007*, 1230-1234.
15. D. Bandyopadhyay, J. M. Velazquez, B. K. Banik, *Organic and Medicinal Chemistry Letters* **2011,** *1*, 11.
16. G. Barker, P. O'Brien, K. R. Campos, *Org. Lett.* **2010,** *12*, 4176-4179.
17. P. Beak, A. Basu, D. J. Gallagher, Y. S. Park, S. Thayumanavan, *Acc. Chem. Res.* **1996,** *29*, 552-560.
18. D. Hoppe, T. Hense, *Angew. Chem. Int. Ed.* **1997,** *36*, 2282-2316.
19. E. A. Mitchell, A. Peschiulli, N. Lefevre, L. Meerpoel, B. U. W. Maes, *Chem. Eur. J.* **2012,** *18*, 10092-10142.
20. X. Li, I. Coldham, *J. Am. Chem. Soc.* **2014,** *136*, 5551-5554.
21. C. Le, Y. Liang, R. W. Evans, X. Li, D. W. C. MacMillan, *Nature* **2017,** *547*, 79-83.
22. A. McNally, C. K. Prier, D. W. C. MacMillan, *Science* **2011,** *334*, 1114-1117.
23. M. P. DeNinno, C. Eller, *Tetrahedron Lett.* **1997,** *38*, 6545-6548.
24. M. P. DeNinno, C. Eller, J. B. Etienne, *J. Org. Chem.* **2001,** *66*, 6988-6993.
25. Y.-G. Suh, D.-Y. Shin, J.-K. Jung, S.-H. Kim, *Chem. Commun.* **2002**, 1064-1065.
26. Y.-G. Suh, S.-H. Kim, J.-K. Jung, D.-Y. Shin, *Tetrahedron Lett.* **2002,** *43*, 3165-3167.
27. J. J. Li, *Name Reactions: A Collection of Detailed Mechanisms and Synthetic Applications*. Springer Berlin Heidelberg: 2007.
28. K.-J. Xiao, J.-M. Luo, K.-Y. Ye, Y. Wang, P.-Q. Huang, *Angew. Chem. Int. Ed.* **2010,** *49*, 3037-3040.
29. K. Shirokane, Y. Kurosaki, T. Sato, N. Chida, *Angew. Chem. Int. Ed.* **2010,** *49*, 6369-6372.
30. M. Nakajima, Y. Oda, T. Wada, R. Minamikawa, K. Shirokane, T. Sato, N. Chida, *Chem. Eur. J.* **2014,** *20*, 17565-17571.
31. Y. Motoyama, M. Aoki, N. Takaoka, R. Aoto, H. Nagashima, *Chem. Commun.* **2009**, 1574-1576.
32. M. Nakajima, T. Sato, N. Chida, *Org. Lett.* **2015,** *17*, 1696-1699.
33. L.-G. Xie, D. J. Dixon, *Chem. Sci.* **2017,** *8*, 7492-7497.
34. Á. L. Fuentes de Arriba, E. Lenci, M. Sonawane, O. Formery, D. J. Dixon, *Angew. Chem. Int. Ed.* **2017,** *56*, 3655-3659.
35. L.-G. Xie, D. J. Dixon, *Nature Communications* **2018,** *9*, 2841.
36. P.-Q. Huang, W. Ou, F. Han, *Chem. Commun.* **2016,** *52*, 11967-11970.
37. P. Trillo, T. Slagbrand, H. Adolfsson, *Angew. Chem. Int. Ed.* **2018,** *57*, 12347-12351.
38. G. H. Chan, D. Y. Ong, Z. Yen, S. Chiba, *Helv. Chim. Acta.* **2018,** *101*, e1800049.
39. K. Ziegler, H. Martin, F. Krupp, *Justus Liebigs Annalen der Chemie* **1960,** *629*, 14-19.
40. E. Winterfeldt, *Synthesis* **1975,** *1975*, 617-630.
41. J. Magano, J. R. Dunetz, *Org. Process Res. Dev.* **2012,** *16*, 1156-1184.
42. P. Galatsis, M. Sollogoub, P. Sinaÿ, Diisobutylaluminum Hydride. In *Encyclopedia of Reagents for Organic Synthesis*, 2008.
43. S. Nahm, S. M. Weinreb, *Tetrahedron Lett.* **1981,** *22*, 3815-3818.
44. J. Singh, N. Satyamurthi, I. S. Aidhen, *Journal für praktische Chemie* **2000,** *342*, 340-347.
45. M. P. Sibi, *Org. Prep. Proced. Int.* **1993,** *25*, 15-40.

46. D. Y. Ong, K. Watanabe, R. Takita, S. Chiba, *Helv. Chim. Acta.* **2019,** *102*, e1900166.
47. T. Lipina, K. Weiss, J. Roder, *Neuropsychopharmacology* **2007,** *32*, 745-756.
48. Y. Qi, D. Liu, W. Zhao, C. Liu, Z. Zhou, P. Wang, *Pesticide Biochemistry and Physiology* **2015,** *125*, 38-44.
49. D. Y. Ong, Z. Yen, A. Yoshii, J. Revillo Imbernon, R. Takita, S. Chiba, *Angew. Chem. Int. Ed.* **2019,** *58*, 4992-4997.
50. R. M. Hodges, *Proceedings of the Royal Society of Medicine* **1976,** *69 Suppl 2*, 1-2.
51. X. Xing, N. R. O'Connor, B. M. Stoltz, *Angew. Chem. Int. Ed.* **2015,** *54*, 11186-11190.
52. S. Ono, S. Shuto, A. Matsuda, *Tetrahedron Lett.* **1996,** *37*, 221-224.
53. M. L. Berger, A. Schweifer, P. Rebernik, F. Hammerschmidt, *Bioorg. Med. Chem.* **2009,** *17*, 3456-3462.
54. D. J. Hewitt, *The Clinical Journal of Pain* **2000,** *16*, S73-S79.
55. W. Xue, R. Shishido, M. Oestreich, *Angew. Chem. Int. Ed.* **2018,** *57*, 12141-12145.
56. F. F. Fleming, *Natural Product Reports* **1999,** *16*, 597-606.

## Chapter 4. Controlled reduction of carboxamides by Zinc Hydrides

### 4.1. Introduction

Carboxamides have enriched chemical reactivity, and thus have been utilized as adaptive materials in a series of synthetic transformations for production of fine chemicals in various fields.[1-2] Among them, reduction of carboxamides, commonly mediated by metal hydrides, is one of the most frequently used processes, that potentially delivers three possible products; aldehydes, alcohols, and amines (Scheme 4.1).[3-8]




**Scheme 4.1.** Reduction of carboxamides.

Aldehydes are synthesized when tetrahedral anionic carbinol amine intermediates **4.1,** formed via the first hydride transfer, are kept intact prior to the aqueous quench. On the other hand, alcohols or amines could be formed when the tetrahedral intermediates **4.1** fragment through C-N or C-O bond scission, respectively, and the resulting aldehydes or imine/iminium intermediates are reduced by the second hydride. In the

following section, the discussion will focus on the reduction of amides to amines and alcohols.

### 4.1.1. Typical methods for amide reduction

In general, there are three types of methodologies for the reduction of amides (Figure 4.1).[4] The first one is transition-metal-catalysed hydrogenation, which, is generally ideal as the theoretical by-product is only water. [9] However, typical drawbacks are the need of elevated temperature and high pressure of hydrogen gas.[5] The second is hydrosilylation using silanes or siloxanes as hydride sources mediated by metal or non-metal-based catalyst. This protocol is widely explored by many research groups and generally showed good chemoselectivity.[4] The last type is the stoichiometric use of hydride reagents for the reduction of amides, where the general concerns are the tedious work-up like the use of the aluminum hydride agents or the high cost relating to the stoichiometric use of reagents like zirconium hydride.

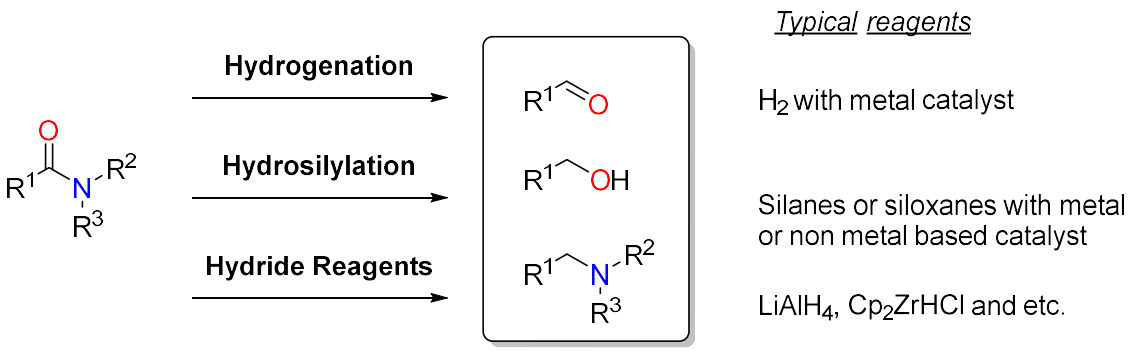



**Figure 4.1.** Typical methods for amide reduction.

### 4.1.2. Latest development for amide reduction

At present, the state-of-the-art approaches for reduction of amides into alcohols are catalytic hydrogenation by well-defined pincer complexes based on Ru,[10-12] Fe,[13] and

Mn[14] under a highly pressurized $H_2$ atmosphere (Figure 4.2). However, these reaction conditions are typically very harsh requiring high temperature and high $H_2$ pressure.

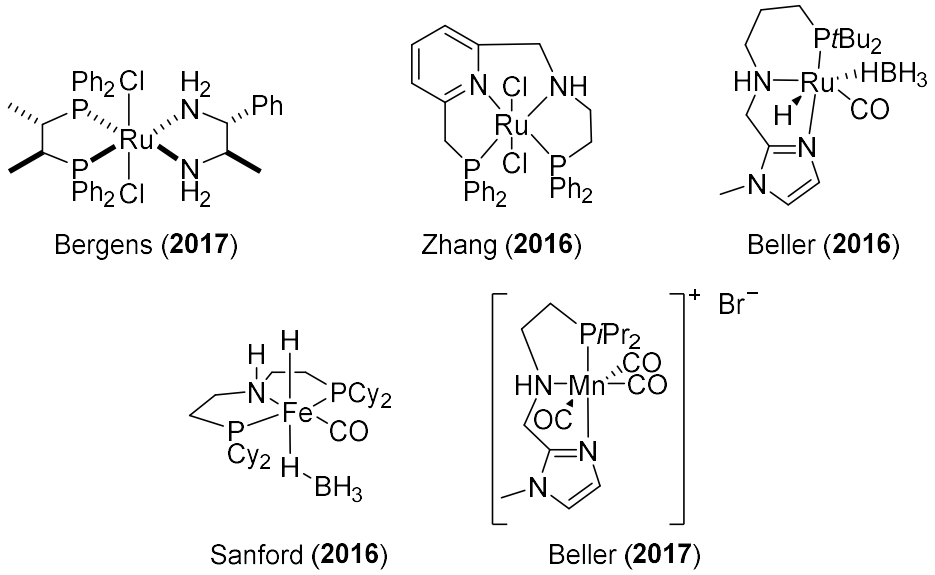
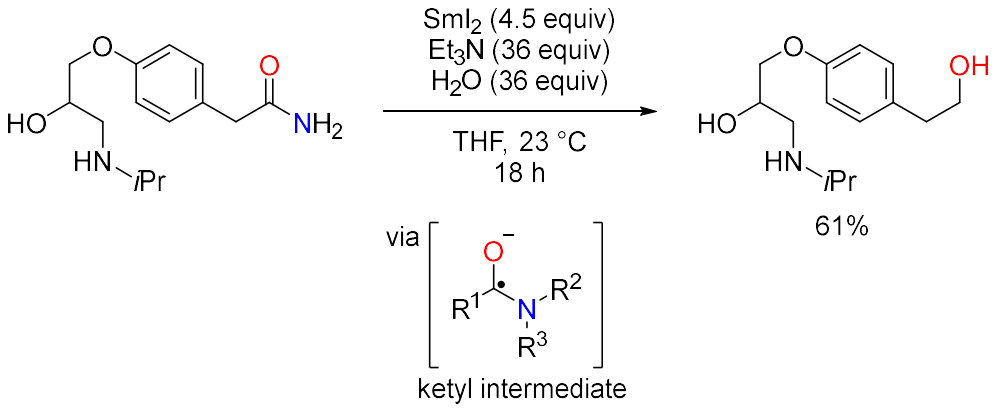


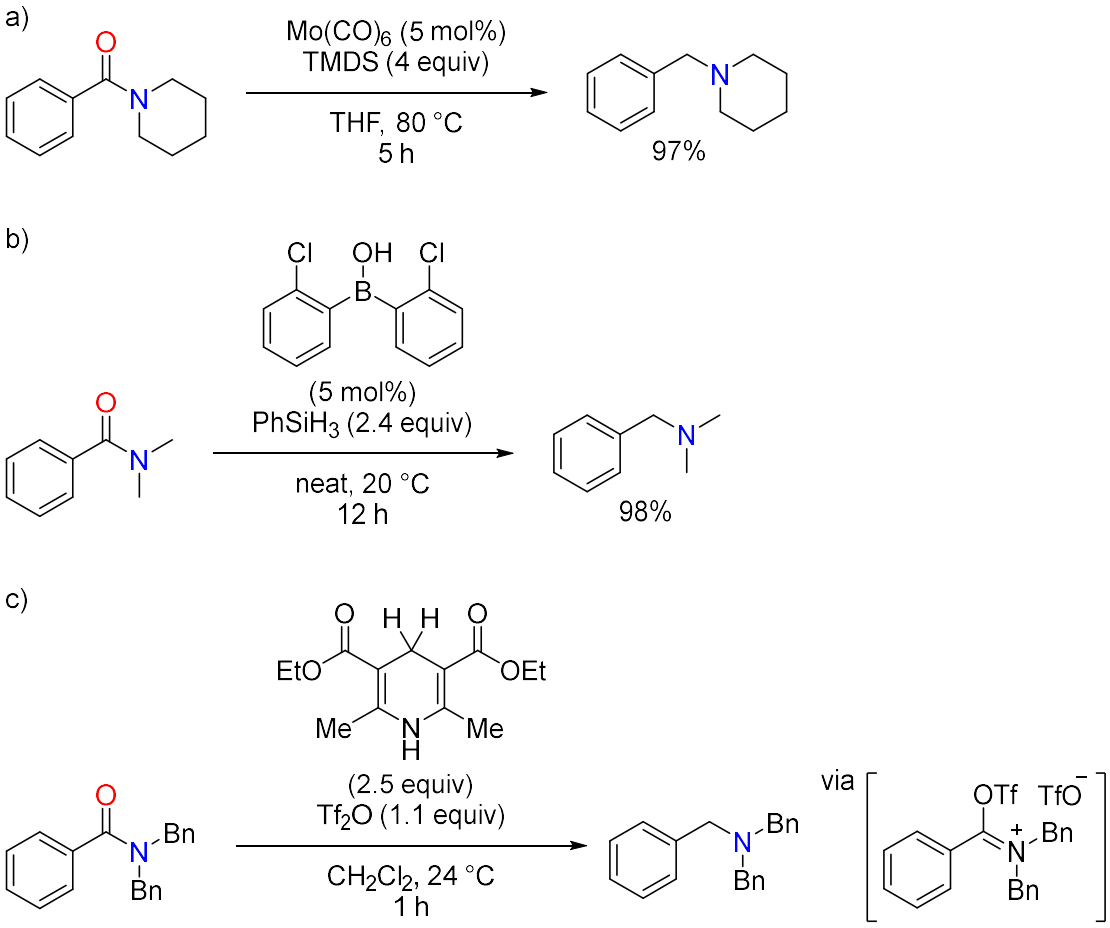

**Figure 4.2.** Pincer complexes for hydrogenation of amides to alcohols.

Procter et al. recently disclosed use of $SmI_2$ for the highly chemoselective reduction of amides to alcohols under milder reaction conditions.[15] The protocol allowed for the reduction of a broad scope of tertiary, secondary and primary amides in the presence of $SmI_2$, triethylamine and water via a single electron transfer mechanism (Scheme 4.2). They also demonstrated the selective reduction of primary amides in the presence of esters or alkyl halides, showing high chemoselectivity of the protocol.



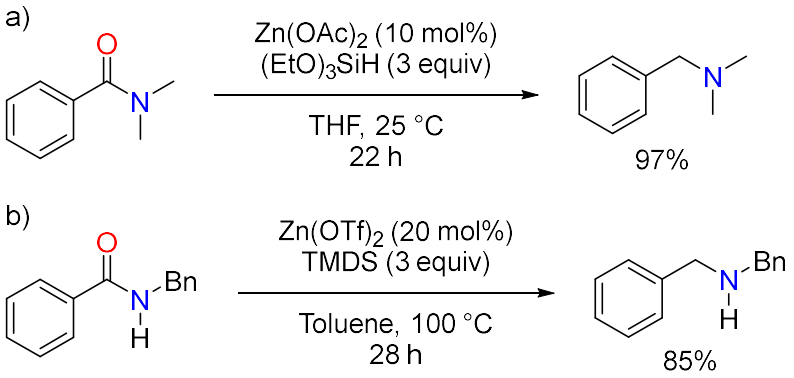

**Scheme 4.2.** Reduction of amides to alcohol via single electron transfer.

The recent advances for the reduction of amides to amines are facilitated by hydrosilylation[16] with many various transition-metal-based catalysts (Scheme 4.3a) such as Mo,[17-18] Rh,[19] Ir,[20-21] Pt,[22] Fe,[23-25] Ni,[26] Cu,[27] and Zn[28-29] or the use of organoboranes[30-34] as catalysts (Scheme 4.3b) for a transition-metal-free protocol. Reduction of amides to amines can also be initiated by electrophilic activation of amides with trifluoromethanesulfonic anhydride followed by reduction using tris(pentafluorophenyl)borane catalysed hydrosilylation[35] or Hantzsch esters (Scheme 4.3c).[36]



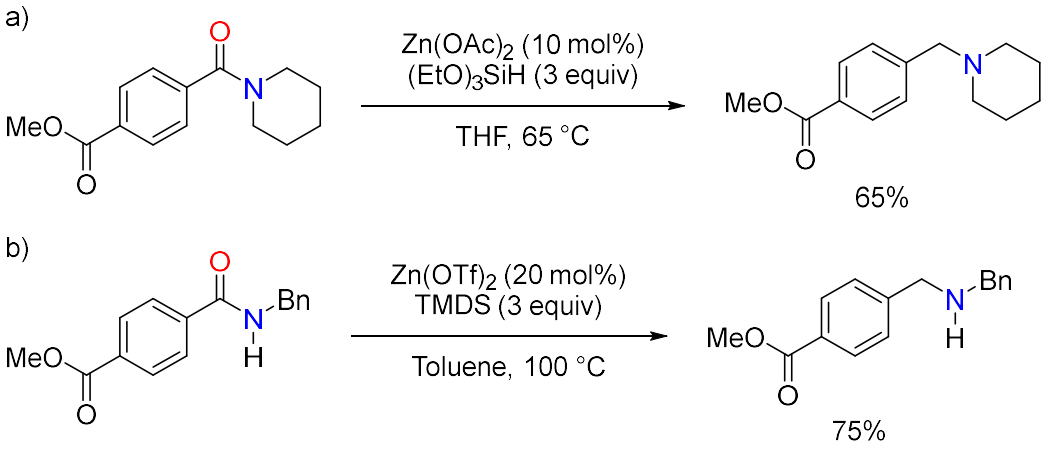

**Scheme 4.3.** Selected examples for reduction of amides to amines by hydrosilylation with a) $Mo(CO)_6$; b)Boronic acid as catalyst. c)Reduction of amides initiated by electrophilic activation.

Beller et al. recently reported the use of commercially available zinc(II) acetate and zinc(II) triflate with triethoxysilane or 1,1,3,3-tetramethyldisiloxane to perform reduction of both tertiary and secondary amides to amines[29, 37] (Scheme 4.4).




**Scheme 4.4.** Reduction of a) tertiary and b) secondary amides.

Beller et al. also uncovered that their protocols were chemoselective and reduced both tertiary and secondary amides selectively in the presences of nitro, cyano, diazo, alkenyl and alkynyl groups. They also demonstrated the chemoselective reduction of both tertiary and secondary amides over esters (Scheme 4.5).



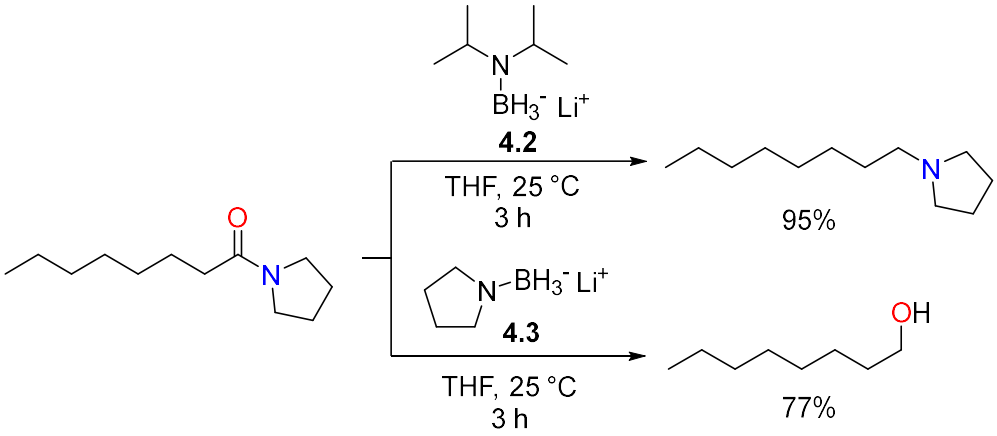

**Scheme 4.5.** Chemoselective reduction of a) tertiary and b) secondary amides over esters.

Beller et al. summarized that the mechanism for their protocols is based on the activation of hydride on the silane or siloxane by zinc(II) acetate and not by the Lewis acid, zinc(II) acetate, activation of the carbonyl group that facilitated the direct hydride

attack by silanes. This was based on the observation that a new peak in $^{1}H$ NMR was observed when triethoxysilane reacted with zinc(II) acetate and the absence of a new C=O stretch in the IR spectrum when amides were allowed to react with zinc(II) acetate.

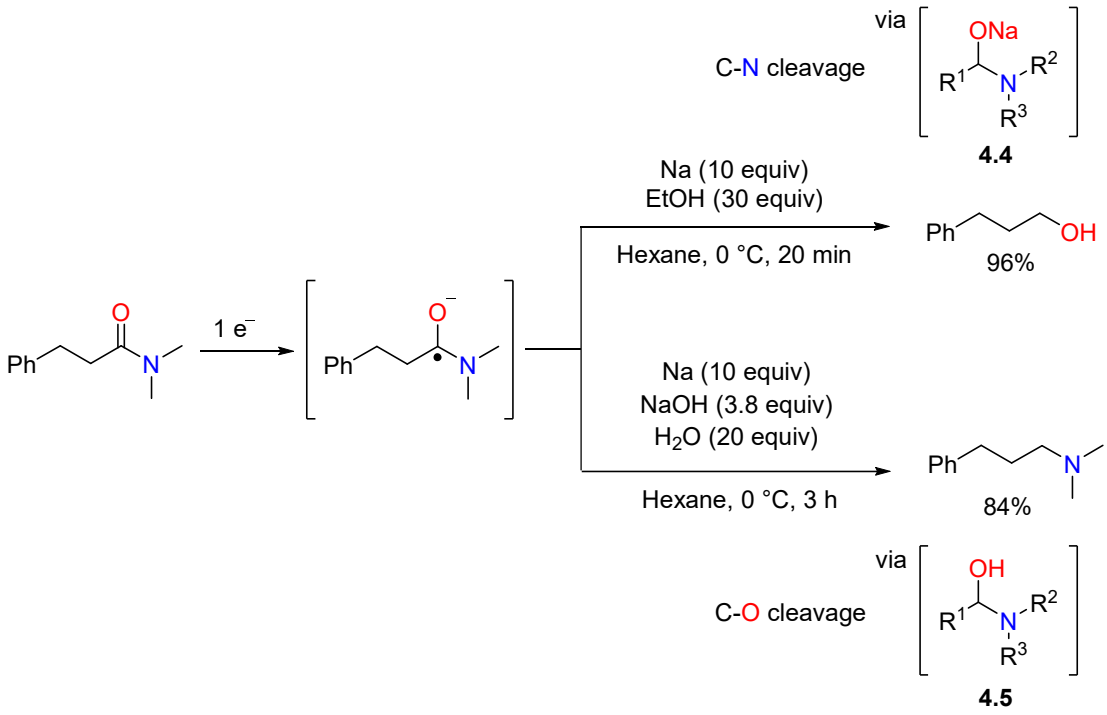
### 4.1.3. Controlled reduction of amides

Despite the recent advancement in amide reduction, there are few reports on controlled reduction via selectively C-N/C-O bond cleavage in the same amide substrates. Singaram et al. reported the use of lithium aminoborohydride with varying alkyl group size to perform controlled reduction of amides to amines and alcohols (Scheme 4.6).[38] The key to their design is based on the steric requirement of the tertiary amides and lithium aminoborohydride that were used to synthesize the corresponding amines or alcohols. In the reduction of α-secondary alkyl amides, the utilization of sterically bulky lithium diisopropylaminoborohydride (**4.2**) provided amines as the main product, whereas the employment of less hindered lithium pyrrolidinoborohydride (**4.3**) afforded alcohols as the major product.




**Scheme 4.6.** Controlled reduction of tertiary amides with lithium aminoborohydride.

An et al. reported the reduction of tertiary amides to the corresponding amines and alcohols mediated by sodium dispersions (Scheme 4.7).[39] This methodology leveraged on single-electron-reduction followed by protonation using varying acidity of the proton source which enabled the controlled reduction of amides. When the reduction of amides to sodiated carbinol amine intermediates **4.4** was conducted in the presence of EtOH, intermediate **4.4** was not protonated and induced selective C-N bond cleavage to afford the corresponding alcohols. On the other hand, $H_2O$, bearing more acidic protons than that of EtOH, protonated **4.4** to generated hemiaminal **4.5**, which in turn underwent selective C-O cleavage to yield the amine.

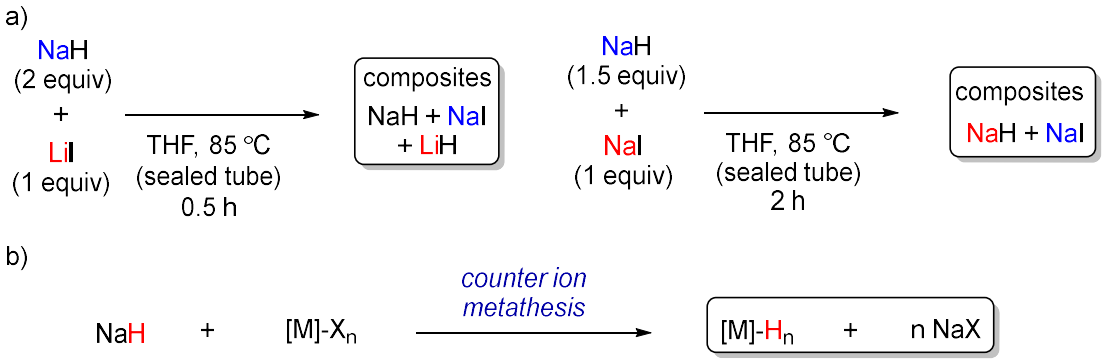



**Scheme 4.7.** Controlled reduction of tertiary amides with sodium dispersion.

Nonetheless, implementation of the reduction of amides with precise and predictable control of the C-N/C-O cleavage for the formation of alcohols/amines remains a challenge, that requires the sophisticated design of the reaction settings.

### 4.2. Perspective of this chapter

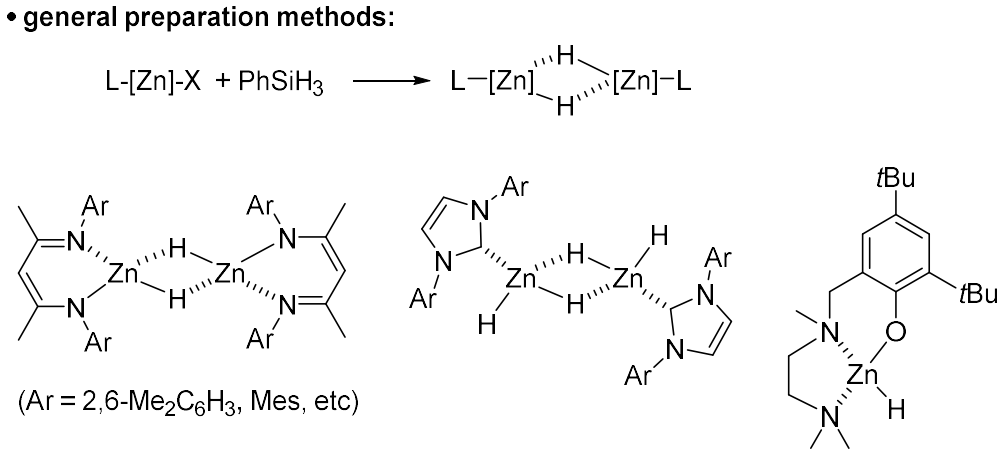
The author's group recently uncovered a concise protocol to activate NaH in the presence of dissolving iodides such as NaI/LiI in tetrahydrofuran (THF) and the composite performed unprecedented reductive transformations such as hydrodecyanation of α-quaternary benzyl cyanides,[40, 41] hydrodehalogenation of haloarenes,[42] and controlled reduction of *N,N*-dimethyl carboxamides to aldehydes.[40, 43] In these reactions, it was assumed that activated NaH could be generated through counter ion metathesis between polymeric NaH with dissolving NaI/LiI(Scheme 4.8a).[44] Stimulated by these findings, the author's attention was directed to use of NaH for generation of new metal hydrides of interest through counter ion metathesis with the corresponding metal halides (Scheme 4.8b) and exploration of their reactivities.




**Scheme 4.8.** Counter ions metathesis.

There have been a number of examples reported on the synthesis and characterization of molecular zinc hydrides in either dimeric bridged hydride form or monomeric monohydride form with proper chelating ligands (Scheme 4.9), but their reactivity has been examined only for reduction of simple and reactive carbonyl compounds.[45-47] Watkins and Ashby previously reported formation of polymeric $(ZnH_2)_\infty$ by mixing NaH and $ZnI_2$ in THF for 24 hours,[48] but its detailed reactivity for the hydride

reduction has thus far not been examined. Considering that the counter ion metathesis between NaH and $ZnX_2$ (X=I, Br, Cl) includes a double hydride–halide exchange, the author assumed that their reaction kinetics will be varied depending on the halide ions, thus resulting in formation of distinct zinc hydride complexes having unique chemical reactivity. The detailed result and discussion will be described below.

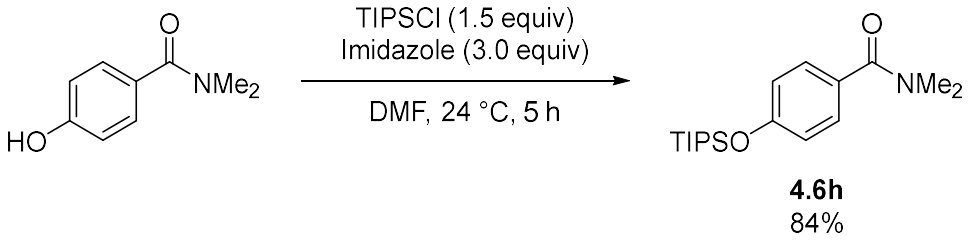



**Scheme 4.9.** Molecular zinc hydrides.

## 4.3. Result and discussion

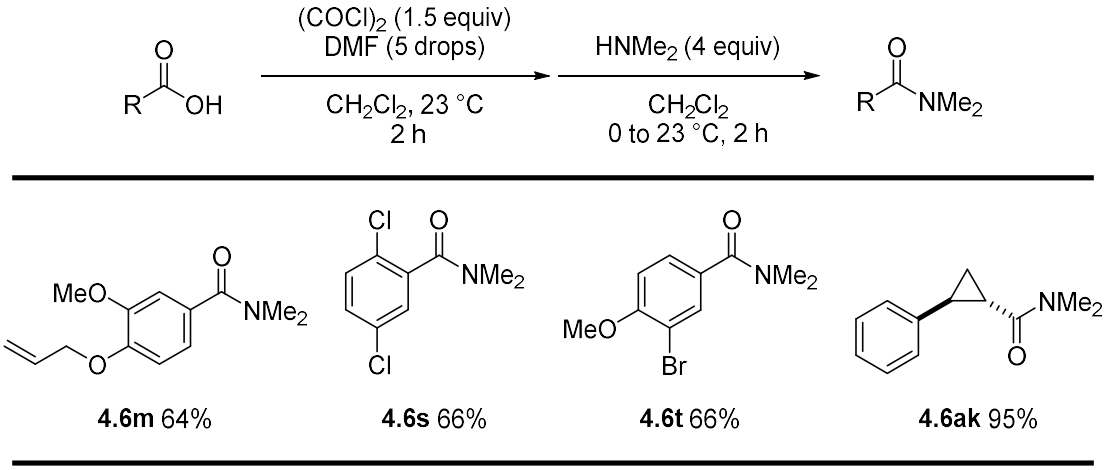
### 4.3.1. Preparation of starting materials

Amide **4.6h** was synthesized via silylation of 4-hydroxy-*N,N*-dimethylbenzamide with triisopropylsilylchloride (1.5 equiv) using imidazole (3 equiv) as a base (Scheme 4.10).



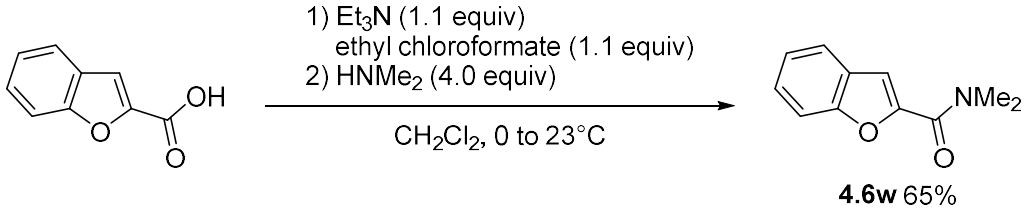

**Scheme 4.10.** Silylation of hydroxy benzamide **4.6h**.

Amides **4.6m**, **4.6s, 4.6t** and **4.6ak** were synthesized from the corresponding carboxylic acids via the formation of acyl chlorides using oxalyl chloride (1.5 equiv) in the presence of catalytic amount of DMF in dichloromethane at 23 °C for 2 h. Subsequent amidation was done by adding dimethylamine (4 equiv). The isolated yields were summarized below. (Scheme 4.11)




**Scheme 4.11.** Synthesize of amide via acyl chloride.

Amide **4.6w** was synthesized from the corresponding carboxylic acid via formation of the mixed anhydride using triethylamine (1.1 equiv) and ethylchloroformate (1.1 equiv). The resulting mixed anhydride was treated with dimethylamine (4 equiv) for the formation of the amide (Scheme 4.12).




**Scheme 4.12.** Synthesize of amide via mixed anhydride.

Aromatic amides **4.6a** – **4.6g**, **4.6i** – **4.6l**, **4.6n** – **4.6r** were synthesized based on the reported procedures (Figure 4.3).[43]

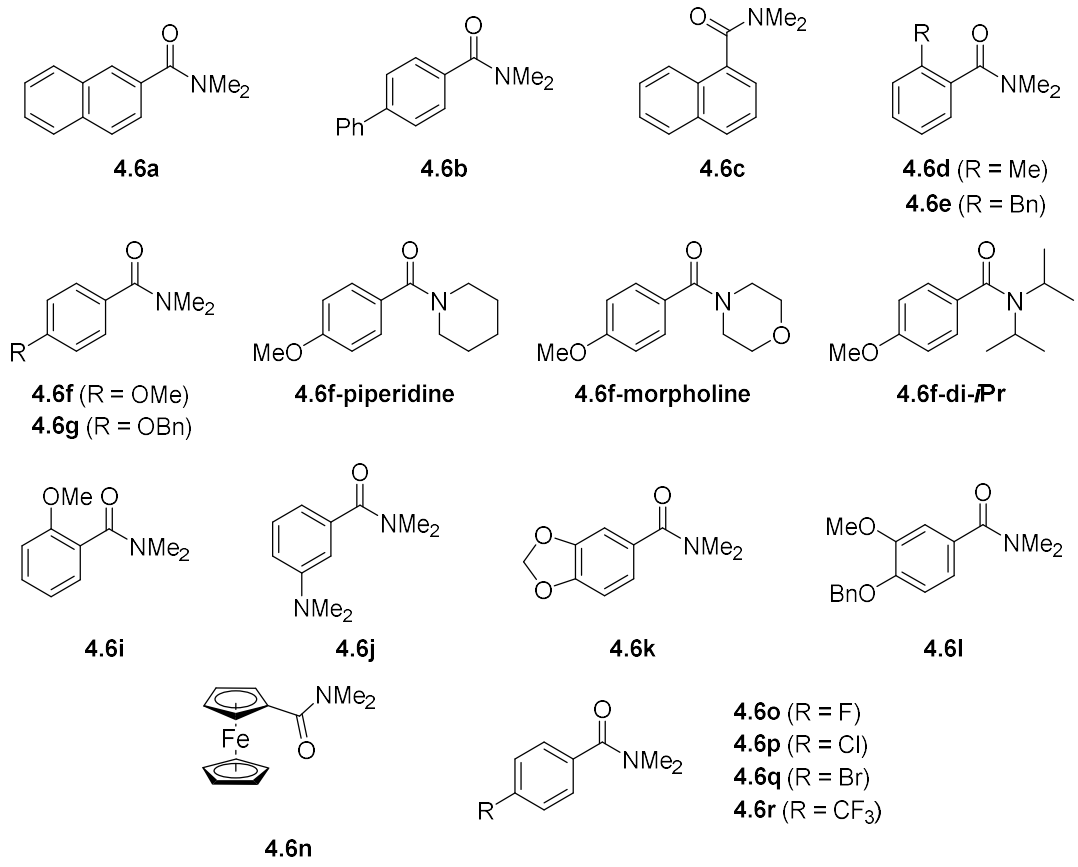



**Figure 4.3.** Known aromatic amides.

Heteroaromatic amides **4.6u**, **4.6v, 4.6x** – **4.6aa** were synthesized based on the reported protocols (Figure 4.4).[43]

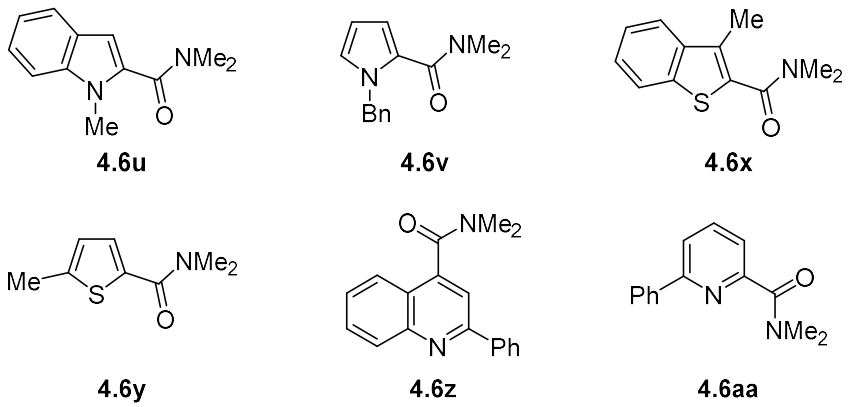



**Figure 4.4.** Known heteroaromatic amides.

Aliphatic amides **4.6ab – 4.6aj**,[43] **4.6al**,[43] **4.6m,**[49] and **4.6m'**[49] were synthesized by following the reported methods (Figure 4.5). Amides **4.6ae** was synthesized from gemfibrozil, which is an antihyperlipidemic agent used to reduce blood lipid and cholesterol level.[50] Amides **4.6af** was synthesized from abietic acid, which is a natural product found in trees.[51]

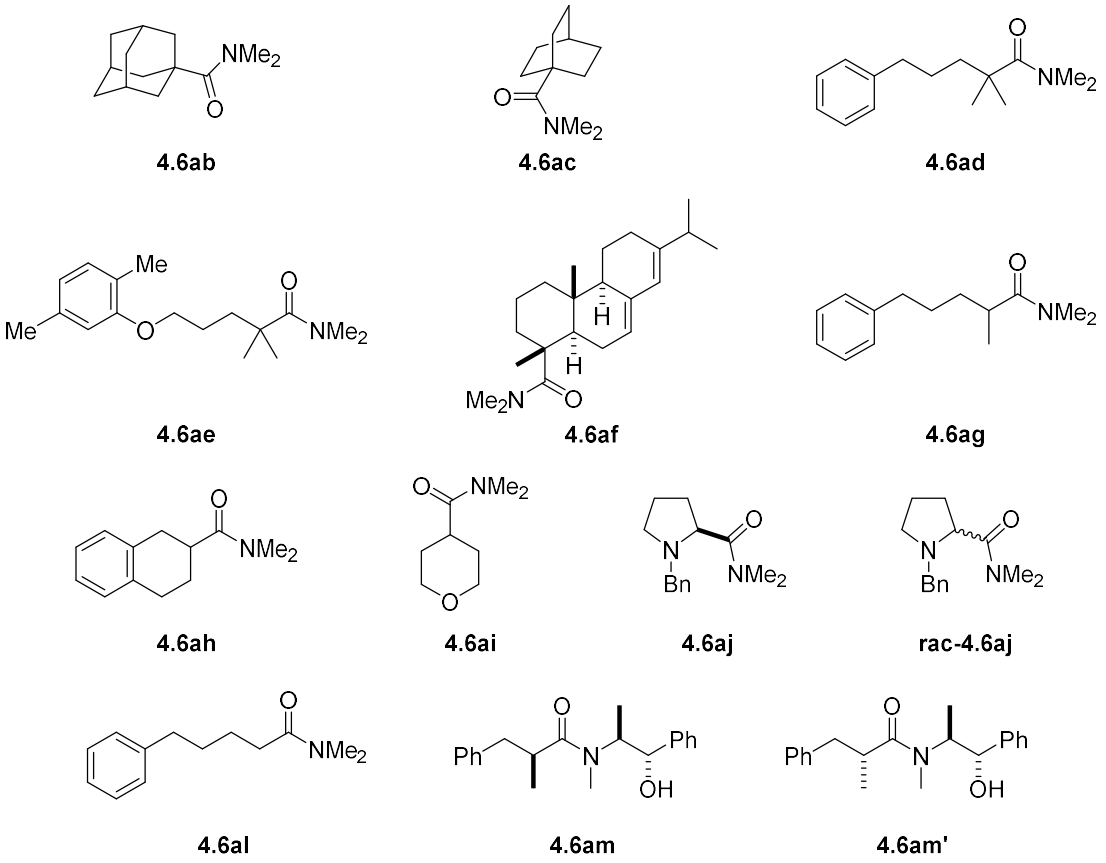


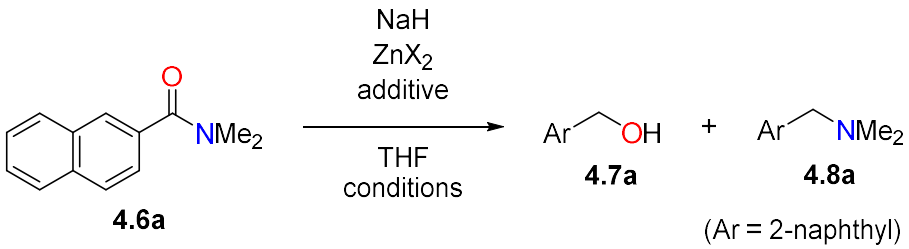

**Figure 4.5.** Known aliphatic amides.

### 4.3.2. Optimization of reaction conditions

The author first examined the reaction of the amide **4.6a** with NaH (3 equiv) and $ZnI_2$ (1.5 equiv) in THF (Table 4.1, entry 1). The author found that the reaction at 40 °C afforded the alcohol **4.7a** in 76% yield as the major product with 22% yield of amine **4.8a**. Interestingly, decreasing the amount of $ZnI_2$ to 1 equiv could improve the yield

of **4.7a** to 88% (entry 2). Moreover, addition of 1 equiv of NaI could suppress the formation of amine completely to form **4.7a** as a sole product in 95% yield (entry 3). In the sharp contrast, it was found that the reaction with either $ZnBr_2$ or $ZnCl_2$ (1.5 equiv) in the presence of NaH (3 equiv) delivered the amine **4.8a** as the major product (entries 4 and 5). Furthermore, increase of the amounts of NaH and $ZnCl_2$ to 5 and 2.5 equivalents, respectively, renders the process more selective and efficient (entry 6). The reaction at 60 °C completed the process within 30 min, giving **4.8a** in 90% yield (entry 7). It should be noted that both protocols could be implemented in 40 mmol scale, emphasizing the scalable nature of the present protocols (entries 3 and 7).

**Table 4.1**: Optimization of the reaction conditions[a]




**4.6a** **4.7a** **4.8a**

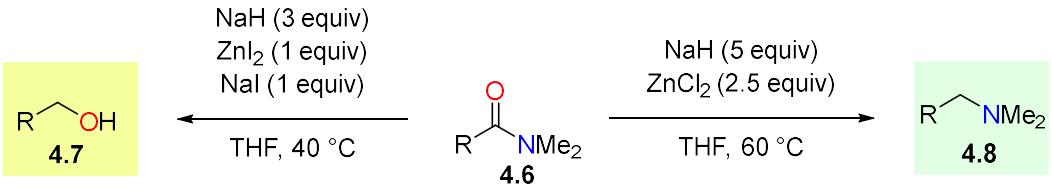
(Ar = 2-naphthyl)

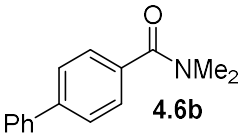
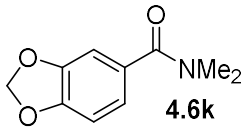
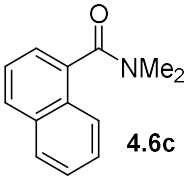
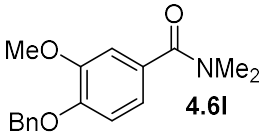
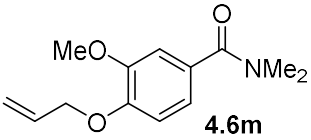
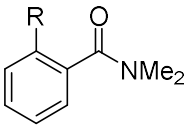
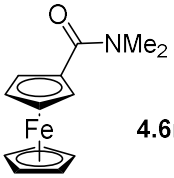
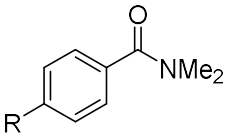
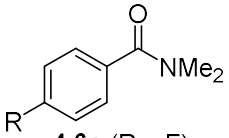
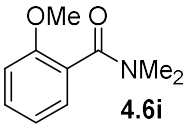
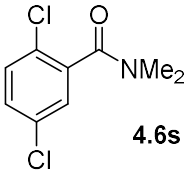
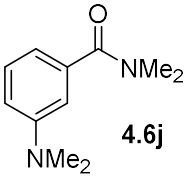
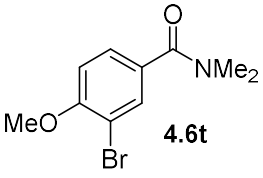
| Entry | NaH (equiv) | $ZnX_2$ (equiv) | Additive (equiv) | Temp. (°C) | *t* (h) | Yield of **4.7a** (%)[b] | Yield of **4.8a** (%)[b] |
|---|---|---|---|---|---|---|---|
| 1 | 3 | $ZnI_2$ (1.5) | – | 40 | 1.5 | 76 | 22 |
| 2 | 3 | $ZnI_2$ (1) | – | 40 | 3 | 88 | 11 |
| 3 | 3 | $ZnI_2$ (1) | NaI (1) | 40 | 7 | 95 (97)[c] | 0 |
| 4 | 3 | $ZnBr_2$ (1.5) | – | 40 | 7 | 18 | 53 |
| 5 | 3 | $ZnBr_2$ (1.5) | – | 40 | 6 | 8 | 62 |
| 6 | 5 | $ZnBr_2$ (2.5) | – | 40 | 2.5 | 6 | 88 |
| 7 | 5 | $ZnBr_2$ (2.5) | – | 60 | 0.5 | 4 | 90 (89)[c] |

[a] The reactions were conducted using 0.5 mmol of **4.6a** in THF (2.5 mL). [b] Yields determined by $^1$H NMR spectroscopy. [c] Yields of products isolated from the reactions run on 40 mmol scale.

### 4.3.3. Scope and Limitation.

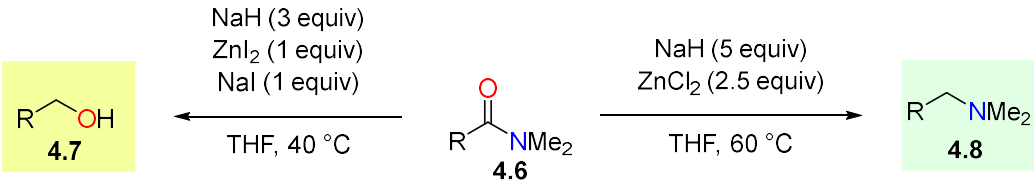
With the optimized reaction conditions (Table 4.1, entry 3) for formation of alcohols **4.7**; entry 7 for formation of amines **4.8**), the author next investigated the scope and limitations of this controlled reduction of the carboxamides **4.6**. For reduction of aromatic amides (**4.6b** – **4.6t**), the process was not influenced by the presence of a sterically demanding aromatic ring (for **4.6c** – **4.6e**) and tolerated substitutions of varying electronic natures, such as electron-donating groups (for **4.6f** – **4.6n**) and electron-withdrawing groups, including halogen atoms, which are often susceptible to the common hydride reduction conditions (for **4.6o** – **4.6t**) (Scheme 4.13).

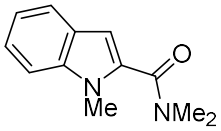
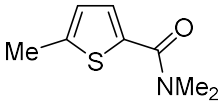
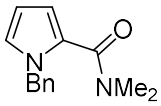
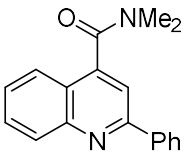
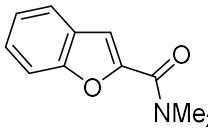
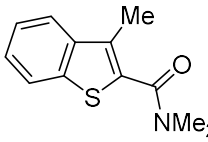
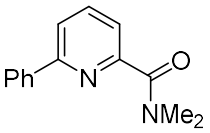



| | alcohols 4.7 | amines 4.8 | | alcohols 4.7 | amines 4.8 |
|---|---|---|---|---|---|
|  **4.6b** | **4.7b** 89% | **4.8b** 81% |  **4.6k** | **4.7k** 87% | **4.8k** 83% |
|  **4.6c** | **4.7c** 98% | **4.8c** 80% |  **4.6l** | **4.7l** 82% | **4.8l** 82% |
| | | |  **4.6m** | **4.7m** 88% | **4.8m** 82% |
|  **4.6d** (R = Me) | **4.7d** 89% | **4.8d** 74% |  **4.6n** | **4.7n** 69%[b] | **4.8n** 86% |
| **4.6e** (R = Bn) | **4.7e** 98% | **4.8e** 67% | | | |
|  **4.6f** (R = OMe) | **4.7f** 95% | **4.8f** 75% |  **4.6o** (R = F) | **4.7o** 76% | **4.8o** 86% |
| **4.6g** (R = OBn) | **4.7g** 97% | **4.8g** 78% | **4.6p** (R = Cl) | **4.7p** 87% | **4.8p** 70% |
| **4.6h** (R = OTIPS) | **4.7h** 89% | **4.8h** 86% | **4.6q** (R = Br) | **4.7q** 87% | **4.8q** 70% |
| | | | **4.6r** (R = $CF_3$) | **4.7r** 95% | **4.8r** 58% |
|  **4.6i** | **4.7i** 66% | **4.8i** 62% |  **4.6s** | **4.7s** 86% | **4.8s** 63% |
|  **4.6j** | **4.7j** 92% | **4.8j** 89% |  **4.6t** | **4.7t** 90% | **4.8t** 77% |

**Scheme 4.13.** Reduction of aromatic amides. [a] The reactions were conducted using 0.5 mmol of the amides **4.6** with isolated yields of alcohols **4.7** and amines **4.8** given. [b] The reaction was conducted using 5 equiv of NaH, 2 equiv of $ZnI_2$ and 2 equiv of NaI.

Amides based on electron-rich five-membered heteroaromatic rings such as the indole **4.6u**, pyrrole **4.6v**, benzofuran **4.6w**, benzothiophene **4.6x**, and thiophene **4.6y**, as well as electron-deficient six-membered ring ones including quinoline **4.6z** and pyridine **4.6aa** were also compatible (Scheme 4.14).

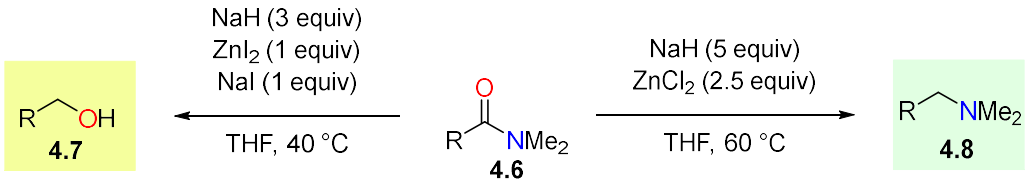


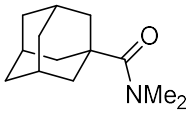
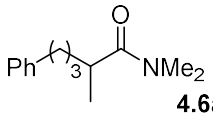
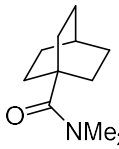
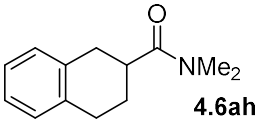
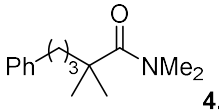
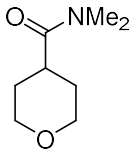
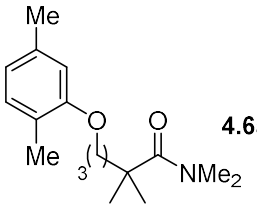
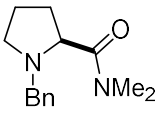
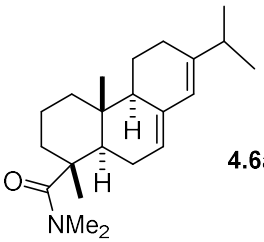
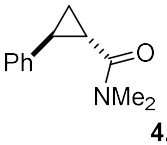
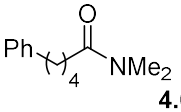

| | | alcohols **4.7** | amines **4.8** | | | alcohols **4.7** | amines **4.8** |
|---|---|---|---|---|---|---|---|
|  | **4.6u** | **4.7u** 89% | **4.8u** 78% |  | **4.6y** | **4.7y** 74% | **4.8y** 75% |
|  | **4.6v** | **4.7v** 75% | **4.8v** 78% |  | **4.6z** | **4.7z** 93% | **4.8z** 56% |
|  | **4.6w** | **4.7w** 76% | **4.8w** 80% | | | | |
|  | **4.6x** | **4.7x** 82% | **4.8x** 88% |  | **4.6aa** | **4.7aa** 84% | **4.8aa** 55% |

**Scheme 4.14.** Reduction of heteroaromatic amides. [a] The reactions were conducted using 0.5 mmol of the amides **4.6** with isolated yields of alcohols **4.7** and amines **4.8** given.

We found that the current protocols are amenable to reducing a series of aliphatic amides (Scheme 4.15). The sterically congested α-quaternary amides **4.6ab** – **4.6af** were reduced smoothly and selectively to either the corresponding alcohols **4.7** or amines **4.8**. We also observed that the reduction of amides **4.6ag** – **4.6al**, having enolizable α-protons, proceeds well in general to afford the corresponding alcohols or

amines in good yields, except for conversion of the cyclopropanecarboxamide **4.6ak** and α-secondary amide **4.6al** into the corresponding alcohols **4.7ak** and **4.7al**, respectively, with concomitant formation of a significant amount of the corresponding amines **4.8**.

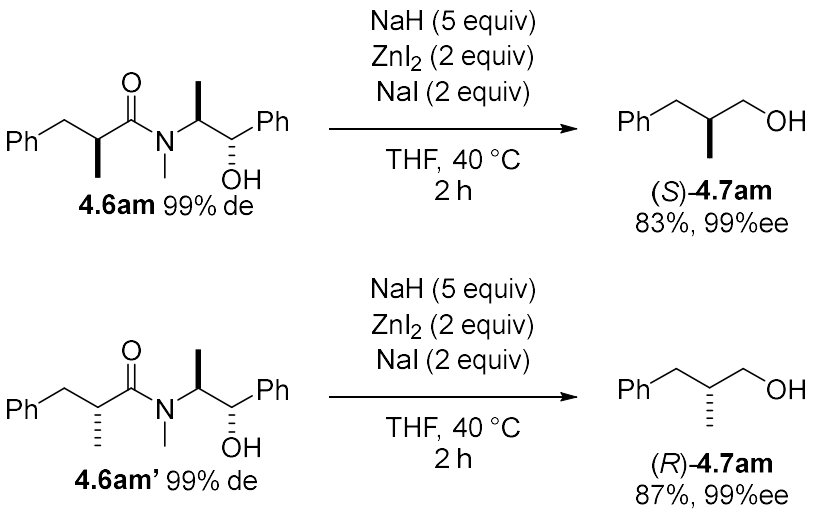



| | alcohols 4.7 | amines 4.8 | | alcohols 4.3 | amines 4.8 |
|---|---|---|---|---|---|
|  **4.6ab** | **4.7ab** 97% | **4.8ab** 77% |  **4.6ag** | **4.7ag** 92% | **4.8ag** 68% |
|  **4.6ac** | **4.7ac** 86% | **4.8ac** 77% |  **4.6ah** | **4.7ah** 76% | **4.8ah** 81% |
|  **4.6ad** | **4.7ad** 92% | **4.8ad** 68% |  **4.6ai** | **4.7ai** 74% | **4.8ai** 77% |
|  **4.6ae** | **4.7ae** 90% | **4.8ae** 72% |  **4.6aj**[c] | **4.7aj** 91% | **4.8aj** 84% |
|  **4.6af** | **4.7af** 88% | **4.8af** 68%[b] |  **4.6ak** | **4.7ak** 56%[d] | **4.8ak** 76% |
| | | |  **4.6al** | **4.7al** 44%[e] | **4.8al** 79% |

**Scheme 4.15**. Reduction of aliphatic amide. [a] The reactions were conducted using 0.5 mmol of the amides **4.6** with isolated yields of alcohols **4.7** and amines **4.8** given. [b] The reaction was conducted using 7 equiv of NaH and 3.5 equiv of $ZnCl_2$. [c] **4.6aj** >98%ee; **4.7aj** >97%ee; **4.8aj** >98%ee as measured by the Mosher method which used a chiral derivatising agent to react with the chiral compound to form

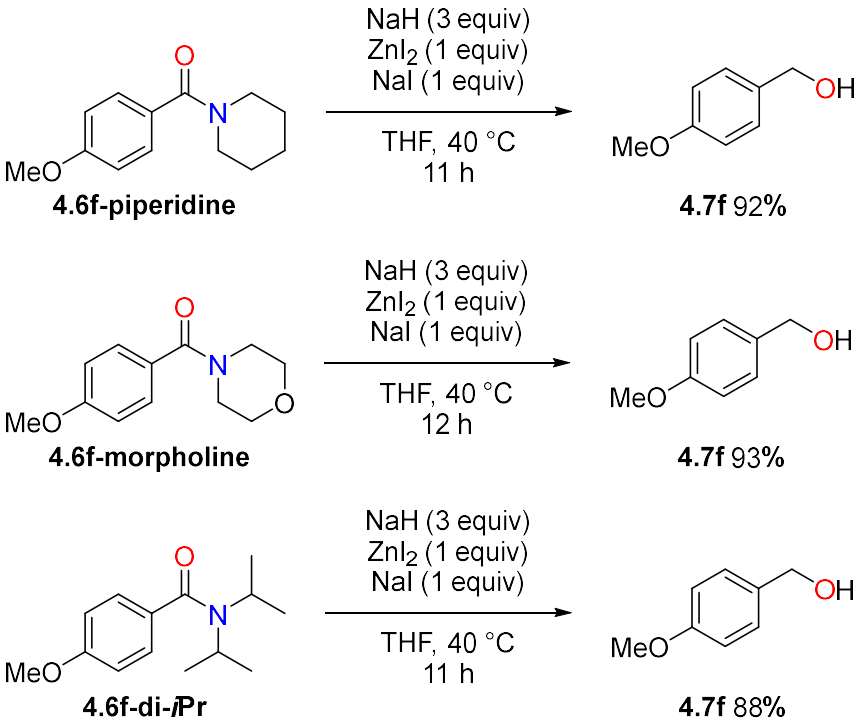
diastereomer, which allowed the %ee to be determined base on the diastereomeric ratio in proton nmr. [d] Amine **4.8ak** was formed in 35% yield. [e] Amine **4.8al** was formed in 31% yield.

It is noteworthy that the reactions of the α-enantioenriched amides **4.6am** and **4.6am'**, derived from the Myers chiral auxiliary,[49] under the NaH-$ZnI_2$ system delivered the alcohols (S)- and (R)-**4.7am** with complete retention of the α-chirality (Scheme 4.16).



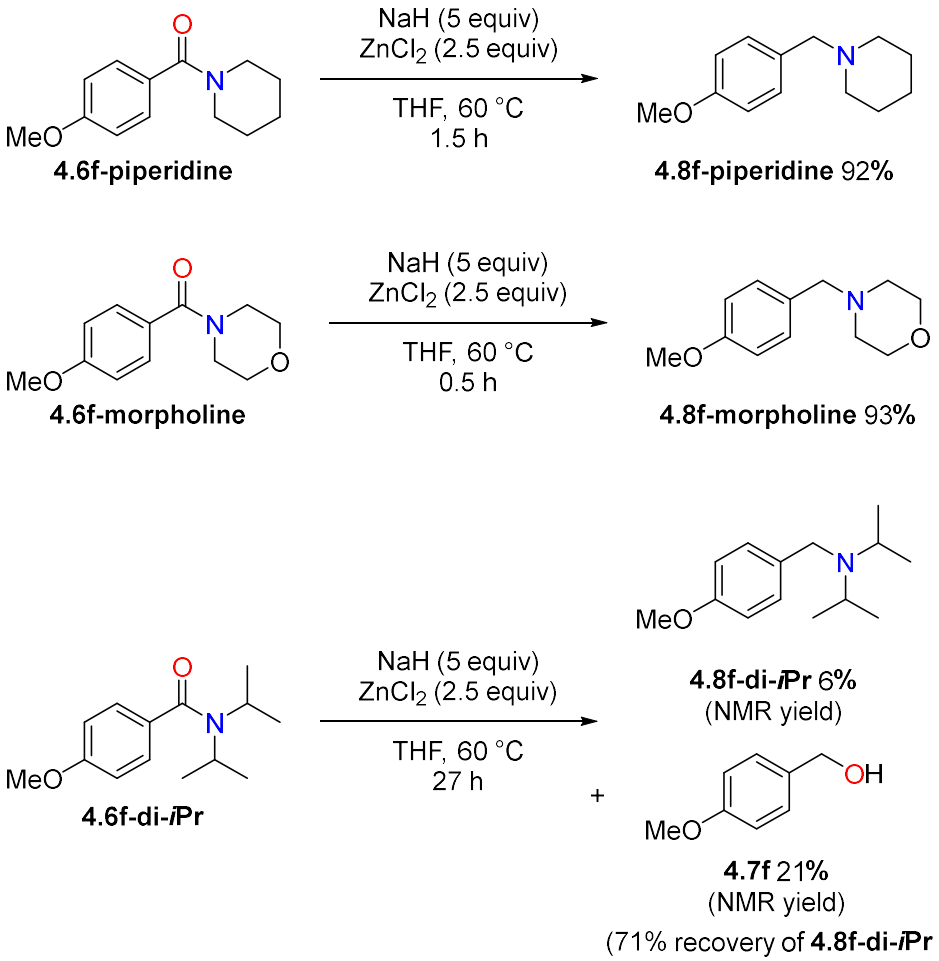

**Scheme 4.16.** Reduction of enantioenriched amides to amines.

Next, the effect of substituents on the amide nitrogen was investigated. The reactions of piperidine and morpholine amides as well as sterically bulky *N,N*-diisopropylamide worked well to afford corresponding alcohol **4.7f** in good yields (Scheme 4.17).




**Scheme 4.17.** Effect of the substituents for controlled reduction of amides to alcohol.

The reactions of piperidine and morpholine amides proceeded smoothly to give the corresponding amines **4.8** in good yields. However, the reduction of sterically hindered *N,N*-diisopropylamide became sluggish, resulting in incomplete conversion with a mixture of amine **4.8f-di-*i*Pr**, and alcohol **4.7f** in 6% and 21% yields (based on the crude $^{1}$H NMR), respectively, with recovery of amide **4.6f-di-*i*Pr** in 71% yield (Scheme 4.18). Zinc hydride dimeric species with bridging chloride which is more sterically bulky due to the bridging chloride than zinc hydride dimeric species with bridging hydride. Hence, the reduction of sterically bulky **4.6f-di-*i*Pr** is not effective using zinc hydride dimeric species with bridging chloride (generated from sodium hydride and zinc chloride).

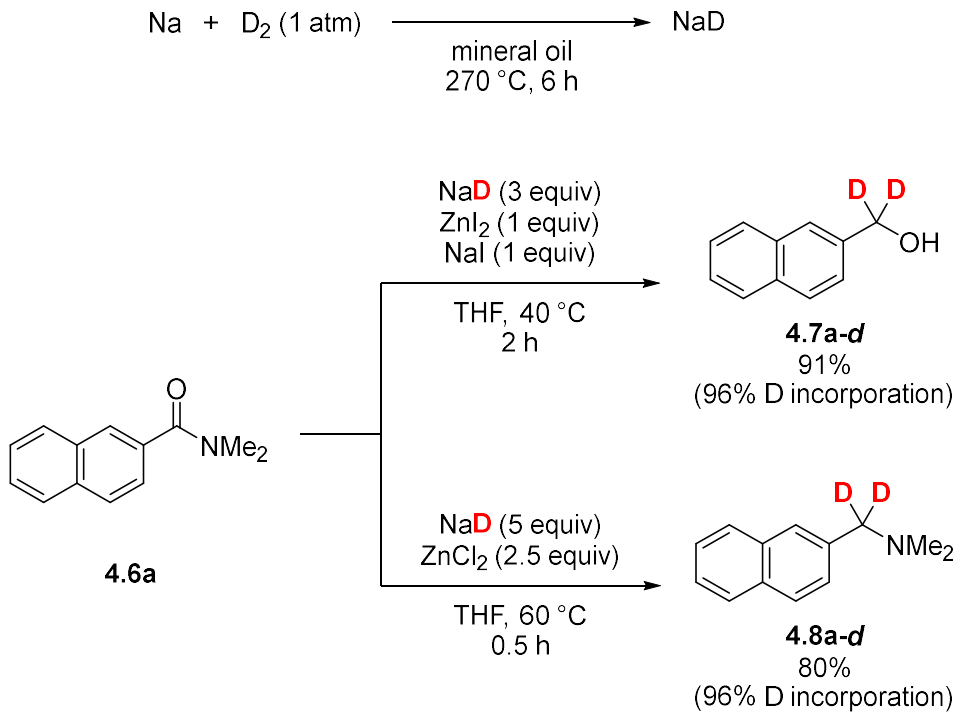



**Scheme 4.18.** Effect of the substituents for controlled reduction of amides to amines.

## 4.4. Mechanistic studies

### 4.4.1. Deuterium labelling experiments

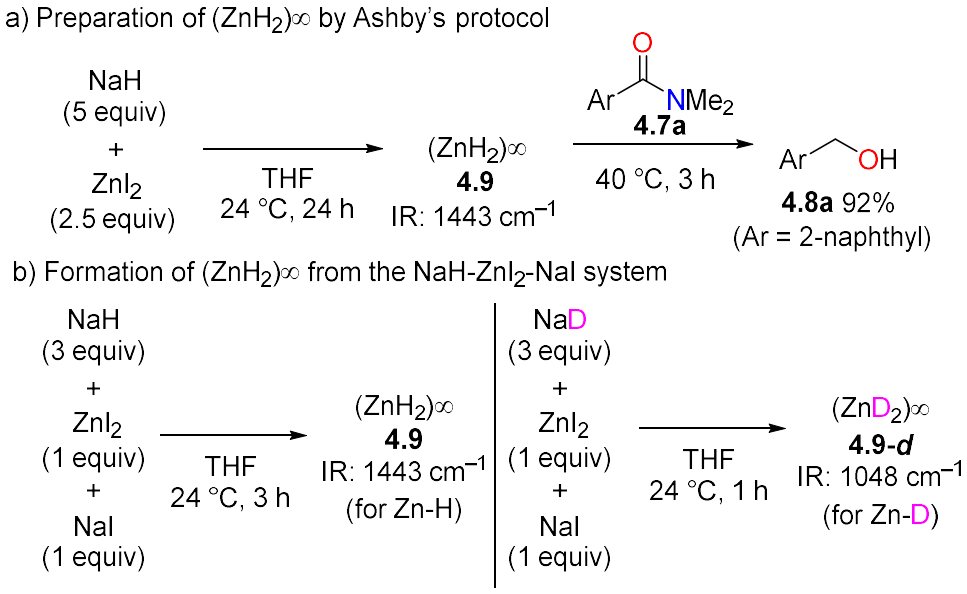
Use of NaD[52] (containing metallic Na in ca. 4%) for the reduction of amide **4.6a** resulted in high deuterium incorporation in both alcohol **4.7a** and amine **4.8a**. This observation as well as the reactivity of NaH itself that reduced amide to aldehyde in the presence of NaI[43] unambiguously indicated that NaH serves as the hydride source for zinc hydrides, which are responsible for the present transformations.




**Scheme 4.19.** Preparation of NaD and deuterium labelling experiment.

### 4.4.2. Characterization of zinc hydride species

To identify the active zinc hydride species, the author designed several experiments as shown in Scheme 4.20 and 4.21. By following the Ashby's protocol,[48] the zinc hydride polymer $(ZnH_2)_\infty$ (**4.9**) was prepared and its infrared (IR) spectroscopy analysis showed one strong absorption band at 1443 $cm^{-1}$ (Scheme 4.20a), which is similar to the reported literature value of 1540 $cm^{-1}$.[53] The amide **4.6a** was then added to the mixture of the resulting $(ZnH_2)_\infty$ (**4.9**), and it provided **4.7a** in 92% yield.

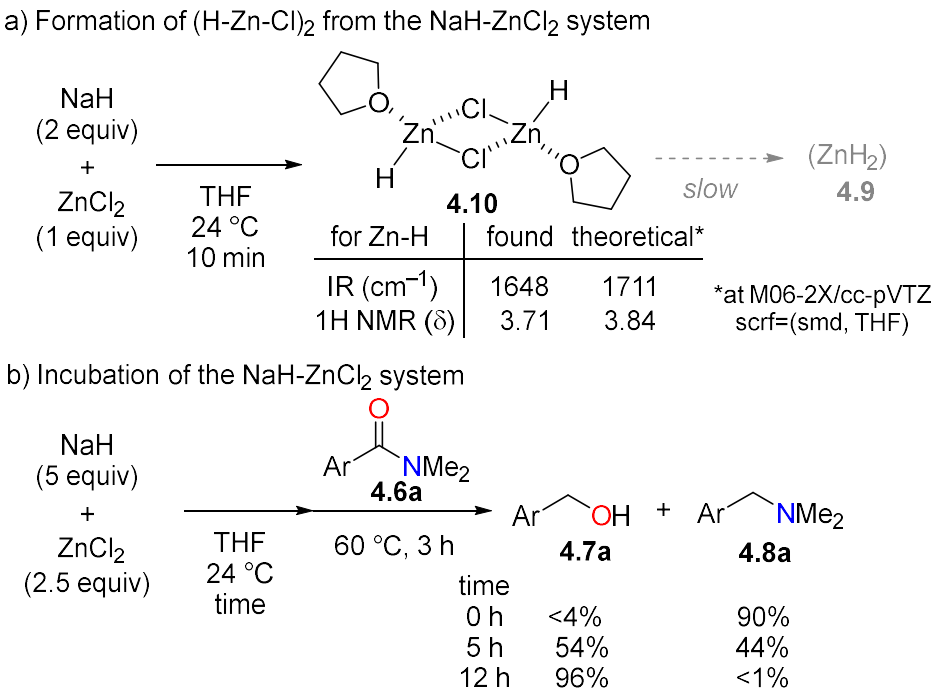



**Scheme 4.20.** Characterization of zinc hydride species from NaH-NaI-$ZnI_2$ system.

Interestingly, when a 3:1:1 mixture of NaH, $ZnI_2$, and NaI was stirred at 24 °C for 3 h, formation of $(ZnH_2)_\infty$ (**4.9**) was observed by IR spectroscopy (scheme 4.20b). Lower frequency shift of the band was observed when NaD was used as a deuteride source. When $(ZnH_2)_\infty$ (**4.9**) was use directly for powder X-ray diffraction (XRD), the author observed only the presence of NaH, the absence of $ZnH_2$ is possibly due to the amorphous nature of the prepared sample. $(ZnH_2)_\infty$ (**4.9**) was also subjected to elemental analysis (EA) and inductively coupled plasma – optical emission spectrometry (ICP-OES) measurement. The interpretation of the data from EA and ICP-OES was based on the assumption that the isolated solid material only comprised of $ZnH_2$, NaH (based on powder XRD), and THF (based on the IR). Based on the comparison of total calculated %mass of hydrogen from the separate components presented in the isolated solid material with %mass of hydrogen determined based on EA, the most probable zinc species would be $ZnH_2$. Judging from the various spectroscopic data, the author did not observe other zinc hydride species in the mixture

(Scheme 4.20). All these experimental observations suggested that $(ZnH_2)_\infty$ (**4.9**) should be responsible for the alcohol formation.

In contrast, treatment of a 2:1 mixture of NaH and $ZnCl_2$ within 10 min in THF afforded a distinct zinc hydride species having an absorption at 1648 $cm^{-1}$ in the IR spectrum and a broad peak at δ=3.71 ppm in the $^1H$ NMR spectrum (Scheme 4.21).




**Scheme 4.21.** Characterization of zinc hydride species from NaH-$ZnCl_2$ system.

The author detected the mass of zinc hydride chloride dimer with two THF molecules by the cold-spray time-of-flight (TOF) mass. Based on the experimental data, there are 2 possible isomers of this zinc hydride chloride dimer; hydride bridge terminal chloride or chloride bridge terminal hydride species. The DFT calculations at the M06-2X/cc-pVTZ (scrf=smd, THF) level of theory indicated that the hydride bridge terminal chloride species is less stable than the chloride bridge terminal hydride **4.10**. In addition,

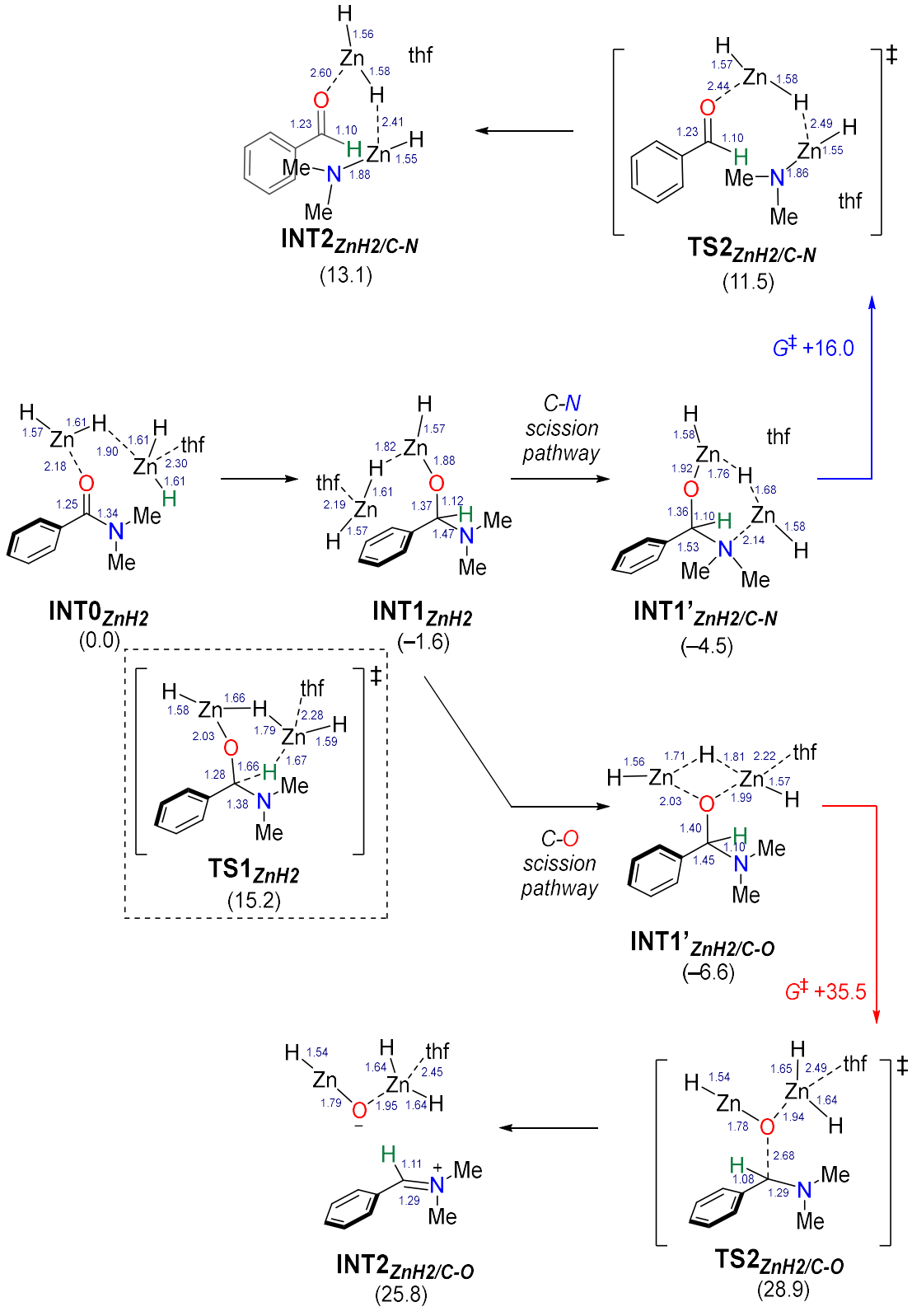
the amide reduction with this bridging hydride species was expected to perform reduction in slower rate than species **4.10** does. Based on the reported data,[54-56] as well as the close agreement of the theoretical prediction for terminal hydride species with the experimental data, we characterized this zinc hydride chloride dimer as the chloride bridged terminal hydride **4.10**. This should be the reactive species for the formation of amines.

The author found that the second hydride–chloride exchange from **4.10** to $(ZnH_2)_\infty$ (**4.9**) could be happening slowly. This exchange was ascertained by the incubation study of the NaH-$ZnCl_2$ system for the reduction of **4.6a** (Scheme 4.21b). While the direct treatment of **4.6a** with NaH and $ZnCl_2$ gave alcohol **4.7a** in less than 4% yield with 90% yield of amine **4.8a** (Table 4.1, entry 7), treatment of **4.6a** after the incubation of the mixture of NaH and $ZnCl_2$ for 5 h significantly increased the amount of alcohol **4.7a** to 54% yield with 44% yield of amine **4.8a**. Incubation for 12 h completely switched the selectivity toward formation of alcohol **4.7a**.

### 4.4.3. DFT calculation

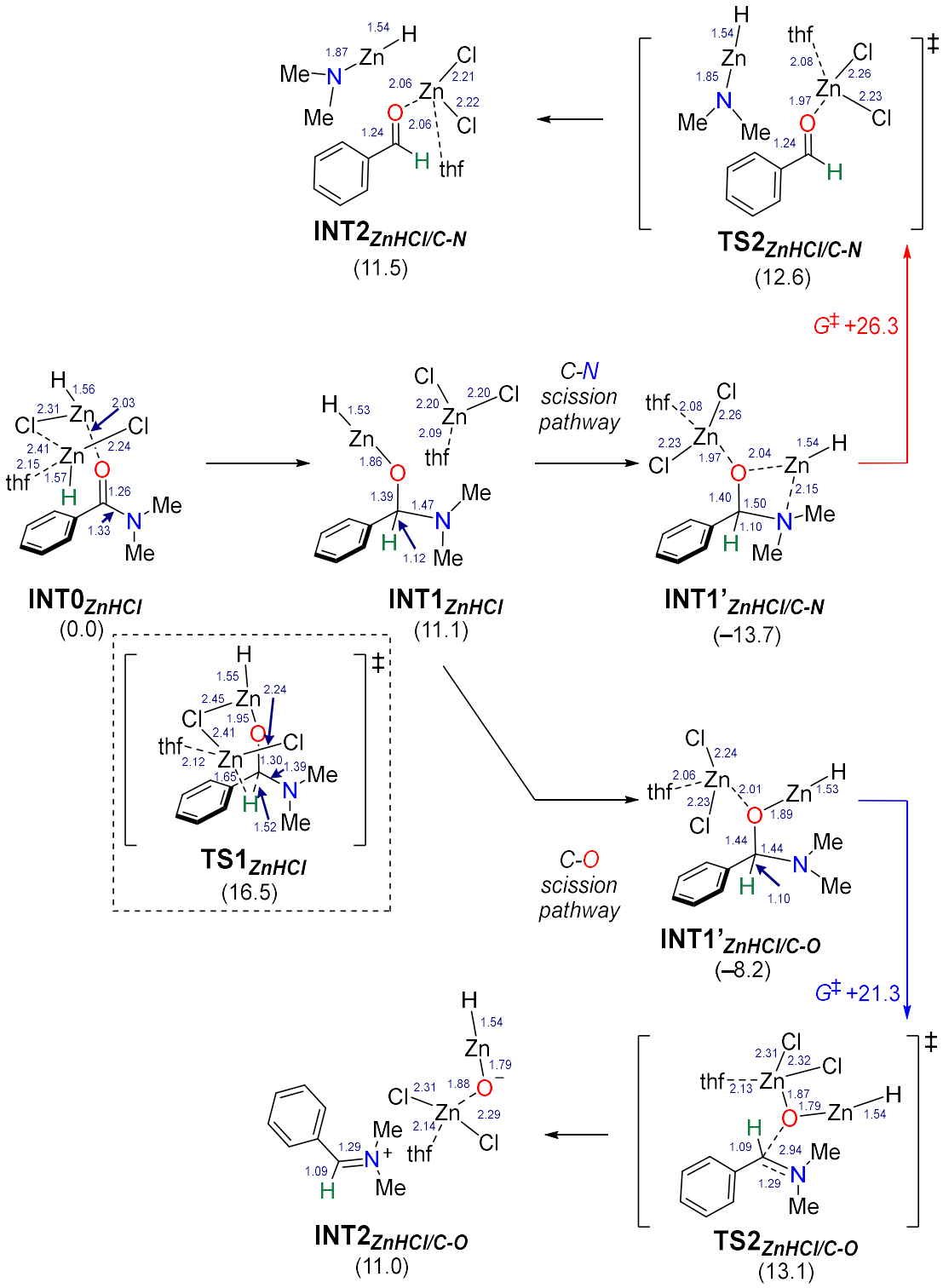
To gain insight into the detailed reaction pathway and selectivity, density-functional theory (DFT) calculations for model reactions of benzamide with $ZnH_2$ dimer as the model of $(ZnH_2)_\infty$ (**4.9**) or the zinc hydride chloride dimer **4.10** were thus carried out at the $\omega$B97XD/SDD&6-31 + G* (scrf=smd, THF) level of theory. In the cases of both complexes, by taking advantage of the flexible conformation change in dimeric structures, the efficient amide reduction lead to the formation of stable tetrahedral intermediates (i.e. **INT1'** complexes). Thus, the selectivity for benzyl alcohol or amine formation should be determined kinetically by the energy barriers of the subsequent C-O/C-N bond scission processes.

Using $ZnH_2$ dimer as the model species for $(ZnH_2)_\infty$ (Scheme 4.22), both oxygen and nitrogen atoms can coordinate to two zinc centers in **INT1'**$_{ZnH2/C\text{-}N}$, and the C-N bond scission efficiently proceeds with the activation barrier of +16.0 kcal $mol^{-1}$. In contrast, the C-O scission process begins from the stable **INT1'**$_{ZnH2/C\text{-}O}$, in which two zinc centers of dimeric species activates the oxygen atom. The C-O bond is cleaved, concomitant with the degradation of dimeric structure and formation of Zn-O-Zn species in **INT2**$_{ZnH2/C\text{-}O}$, which requires a rather high energy ($\Delta G^{\ddagger}$ +35.5 $kcalmol^{-1}$). The further reductions into benzyl alcohol/amine were found to proceed readily with the generated zinc hydride in **INT2** complexes, while other hydride species may also be possibly involved. DFT calculation shows that the second reduction proceeds with lower activation barriers than those of the previous C–O/C-N scissions. Therefore, the second reduction steps should not affect the kinetic reaction outcome or selectivity between benzyl alcohol and amine formation.




**Scheme 4.22.** Reaction pathways of benzamide reduction promoted by $ZnH_2$ dimeric species.

Scheme 4.23 depicts the reaction pathways promoted by the zinc hydride chloride dimer. With the aid of Lewis-acidic monomeric $ZnCl_2$(thf) generated in the formation of tetrahedral intermediate, the C-O bond cleavage is kinetically feasible via **TS2**$_{ZnHCl/C\text{-}O}$ ($\Delta G^{\ddagger}$ +21.3 kcal mol$^{-1}$) to afford the iminium intermediate **INT2**$_{ZnHCl/C\text{-}O}$. On the other hand, the C-N bond scission starts from the stable complex **INT1'**$_{ZnHCl/C\text{-}N}$ having the O,N-chelation to one zinc center, and requires a higher activation energy ($\Delta G^{\ddagger}$ +26.3 kcal mol$^{-1}$). Thus, these calculated results clearly explain that the amide reduction by both NaH-$ZnI_2$ and NaH-$ZnCl_2$ system proceeds smoothly and selectively.




**Scheme 4.23.** Reaction pathways of benzamide reduction promoted by ZnHCl dimeric species.

In summary, given that 1) the flexible conformation change is profitable for the first amide reduction, 2) the dimeric $ZnH_2$ species efficiently activates the tetrahedral intermediate for the C-N scission process, and 3) the formation of Lewis-acidic $ZnCl_2$ facilitates the dissociation of Zn-O-Zn species, the structural and electronical requirements on each active species are responsible for the controlled reduction process.

## 4.5. Conclusion

New protocols for controlled reduction of carboxamides to either alcohols or amines were established using a combination of NaH and zinc halides ($ZnX_2$). Halogen atoms on $ZnX_2$ dictates the selectivity, wherein the NaH-$ZnI_2$ system delivered alcohols and NaH-$ZnCl_2$ gave amines. Extensive mechanistic studies by experimental and theoretical approaches indicated that polymeric zinc hydride $(ZnH_2)_\infty$ is responsible for alcohol formation, whereas dimeric zinc chloride hydride $(H\text{-}Zn\text{-}Cl)_2$ is the key species for the production of amines.

## 4.6. References


1. D. Kaiser, A. Bauer, M. Lemmerer, N. Maulide, *Chem. Soc. Rev.* **2018,** *47*, 7899-7925.
2. D. Kaiser, N. Maulide, *J. Org. Chem.* **2016,** *81*, 4421-4428.
3. J. Seyden-Penne, *Reductions by the Alumino- and Borohydrides in Organic Synthesis*. Wiley: 1997.
4. A. Volkov, F. Tinnis, T. Slagbrand, P. Trillo, H. Adolfsson, *Chem. Soc. Rev.* **2016,** *45*, 6685-6697.
5. A. M. Smith, R. Whyman, *Chem. Rev.* **2014,** *114*, 5477-5510.
6. J. Magano, J. R. Dunetz, *Org. Process Res. Dev.* **2012,** *16*, 1156-1184.
7. P. A. Dub, T. Ikariya, *ACS Catal.* **2012,** *2*, 1718-1741.
8. D. Addis, S. Das, K. Junge, M. Beller, *Angew. Chem. Int. Ed.* **2011,** *50*, 6004-6011.
9. M. C. Bryan, P. J. Dunn, D. Entwistle, F. Gallou, S. G. Koenig, J. D. Hayler, M. R. Hickey, S. Hughes, M. E. Kopach, G. Moine, P. Richardson, F. Roschangar, A. Steven, F. J. Weiberth, *Green Chem.* **2018,** *20*, 5082-5103.
10. L. Rasu, J. M. John, E. Stephenson, R. Endean, S. Kalapugama, R. Clément, S. H. Bergens, *J. Am. Chem. Soc.* **2017,** *139*, 3065-3071.

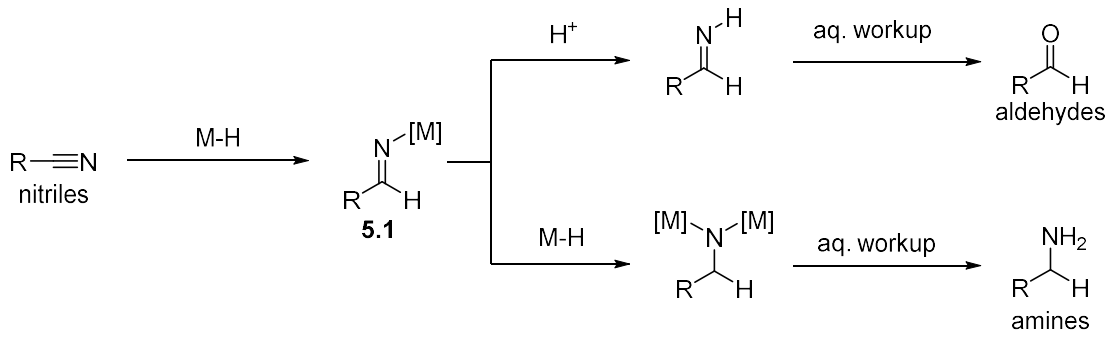
11. L. Shi, X. Tan, J. Long, X. Xiong, S. Yang, P. Xue, H. Lv, X. Zhang, *Chem. Eur. J.* **2017,** *23*, 546-548.
12. J. R. Cabrero-Antonino, E. Alberico, H.-J. Drexler, W. Baumann, K. Junge, H. Junge, M. Beller, *ACS Catal.* **2016,** *6*, 47-54.
13. N. M. Rezayee, D. C. Samblanet, M. S. Sanford, *ACS Catal.* **2016,** *6*, 6377-6383.
14. V. Papa, J. R. Cabrero-Antonino, E. Alberico, A. Spanneberg, K. Junge, H. Junge, M. Beller, *Chem. Sci.* **2017,** *8*, 3576-3585.
15. M. Szostak, M. Spain, A. J. Eberhart, D. J. Procter, *J. Am. Chem. Soc.* **2014,** *136*, 2268-2271.
16. J. Pesti, G. L. Larson, *Org. Process Res. Dev.* **2016,** *20*, 1164-1181.
17. F. Tinnis, A. Volkov, T. Slagbrand, H. Adolfsson, *Angew. Chem. Int. Ed.* **2016,** *55*, 4562-4566.
18. A. Volkov, F. Tinnis, T. Slagbrand, I. Pershagen, H. Adolfsson, *Chem. Commun.* **2014,** *50*, 14508-14511.
19. S. Das, Y. Li, C. Bornschein, S. Pisiewicz, K. Kiersch, D. Michalik, F. Gallou, K. Junge, M. Beller, *Angew. Chem. Int. Ed.* **2015,** *54*, 12389-12393.
20. C. Cheng, M. Brookhart, *J. Am. Chem. Soc.* **2012,** *134*, 11304-11307.
21. S. Park, M. Brookhart, *J. Am. Chem. Soc.* **2012,** *134*, 640-653.
22. S. Hanada, E. Tsutsumi, Y. Motoyama, H. Nagashima, *J. Am. Chem. Soc.* **2009,** *131*, 15032-15040.
23. J. T. Reeves, Z. Tan, M. A. Marsini, Z. S. Han, Y. Xu, D. C. Reeves, H. Lee, B. Z. Lu, C. H. Senanayake, *Adv. Synth. Catal.* **2013,** *355*, 47-52.
24. Y. Sunada, H. Kawakami, T. Imaoka, Y. Motoyama, H. Nagashima, *Angew. Chem. Int. Ed.* **2009,** *48*, 9511-9514.
25. S. Zhou, K. Junge, D. Addis, S. Das, M. Beller, *Angew. Chem.* **2009,** *121*, 9671-9674.
26. B. J. Simmons, M. Hoffmann, J. Hwang, M. K. Jackl, N. K. Garg, *Org. Lett.* **2017,** *19*, 1910-1913.
27. S. Das, B. Join, K. Junge, M. Beller, *Chem. Commun.* **2012,** *48*, 2683-2685.
28. O. O. Kovalenko, A. Volkov, H. Adolfsson, *Org. Lett.* **2015,** *17*, 446-449.
29. S. Das, D. Addis, S. Zhou, K. Junge, M. Beller, *J. Am. Chem. Soc.* **2010,** *132*, 1770-1771.
30. A. Chardon, T. Mohy El Dine, R. Legay, M. De Paolis, J. Rouden, J. Blanchet, *Chem. Eur. J.* **2017,** *23*, 2005-2009.
31. D. Mukherjee, S. Shirase, K. Mashima, J. Okuda, *Angew. Chem. Int. Ed.* **2016,** *55*, 13326-13329.
32. E. Blondiaux, T. Cantat, *Chem. Commun.* **2014,** *50*, 9349-9352.
33. R. C. Chadwick, V. Kardelis, P. Lim, A. Adronov, *J. Org. Chem.* **2014,** *79*, 7728-7733.
34. Y. Li, J. A. Molina de La Torre, K. Grabow, U. Bentrup, K. Junge, S. Zhou, A. Brückner, M. Beller, *Angew. Chem. Int. Ed.* **2013,** *52*, 11577-11580.
35. P.-Q. Huang, Q.-W. Lang, Y.-R. Wang, *J. Org. Chem.* **2016,** *81*, 4235-4243.
36. G. Barbe, A. B. Charette, *J. Am. Chem. Soc.* **2008,** *130*, 18-19.
37. S. Das, D. Addis, K. Junge, M. Beller, *Chem. Eur. J.* **2011,** *17*, 12186-12192.
38. C. L. Bailey, A. Y. Joh, Z. Q. Hurley, C. L. Anderson, B. Singaram, *J. Org. Chem.* **2016,** *81*, 3619-3628.
39. B. Zhang, H. Li, Y. Ding, Y. Yan, J. An, *J. Org. Chem.* **2018,** *83*, 6006-6014.
40. P. C. Too, G. H. Chan, Y. L. Tnay, H. Hirao, S. Chiba, *Angew. Chem. Int. Ed.* **2016,** *55*, 3719-3723.

41. G. H. Chan, D. Y. Ong, S. Chiba, *Org. Synth.* **2018,** *95*, 240-255.
42. D. Y. Ong, C. Tejo, K. Xu, H. Hirao, S. Chiba, *Angew. Chem. Int. Ed.* **2017,** *56*, 1840-1844.
43. G. H. Chan, D. Y. Ong, Z. Yen, S. Chiba, *Helv. Chim. Acta.* **2018,** *101*, e1800049.
44. Z. Hong, D. Y. Ong, S. K. Muduli, P. C. Too, G. H. Chan, Y. L. Tnay, S. Chiba, Y. Nishiyama, H. Hirao, H. S. Soo, *Chem. Eur. J.* **2016,** *22*, 7108-7114.
45. A.-K. Wiegand, A. Rit, J. Okuda, *Coord. Chem. Rev.* **2016,** *314*, 71-82.
46. T. Ohkuma, S. Hashiguchi, R. Noyori, *J. Org. Chem.* **1994,** *59*, 217-221.
47. M. Uchiyama, S. Furumoto, M. Saito, Y. Kondo, T. Sakamoto, *J. Am. Chem. Soc.* **1997,** *119*, 11425-11433.
48. J. J. Watkins, E. C. Ashby, *Inorg. Chem.* **1974,** *13*, 2350-2354.
49. A. G. Myers, B. H. Yang, H. Chen, L. McKinstry, D. J. Kopecky, J. L. Gleason, *J. Am. Chem. Soc.* **1997,** *119*, 6496-6511.
50. R. M. Hodges, *Proc R Soc Med* **1976,** *69 Suppl 2*, 1-2.
51. G. C. Harris, T. F. Sanderson, *Org. Synth.* **1952**, 1-3.
52. H. Jenkner, US3116112A. US patent: 1963.
53. D. F. Shriver, G. J. Kubas, J. A. Marshall, *J. Am. Chem. Soc*. **1971**, 93, 5076-5079.
54. A. Rit, A.-K. Wiegand, D. Mukherjee, T. P. Spaniol, J. Okuda, *Eur. J. Inorg. Chem* **2018,** *2018*, 1114-1119.
55. P. A. Lummis, M. R. Momeni, M. W. Lui, R. McDonald, M. J. Ferguson, M. Miskolzie, A. Brown, E. Rivard, *Angew. Chem. Int. Ed.* **2014,** *53*, 9347-9351.
56. E. C. Ashby, A. B. Goel, *Inorg. Chem.* **1981,** *20*, 1096-1101.

## Chapter 5. Controlled reduction of nitriles into aldehydes by zinc hydrides

### 5.1. Introduction

Carbonitriles (organic cyanides) are important synthons for chemical synthesis that facilitate various types of bond-forming reactions owing to the electron-withdrawing ability of the cyano group.[1-2] Furthermore, among the organic polar π-electrophiles, the cyano group is also considered as a versatile functional group that can be hydrolyzed to carboxylic acids, and reduced into either formyl, iminyl, or amino groups. Especially, controlled mono-hydride reduction of nitriles is regarded as one of the valuable synthetic methodologies, which produces the corresponding aldehydes from the hydrolysis of the aldimine intermediates **5.1**. The challenge for this conversion of nitriles to aldehydes via mono-hydride reduction is the formation of generally more electrophilic aldimine intermediates **5.1** which can easily receive the second hydride to form the corresponding amines (Scheme 5.1).[3] The following discussion will focus on the reduction of nitriles to the corresponding aldehydes in controlled fashion.

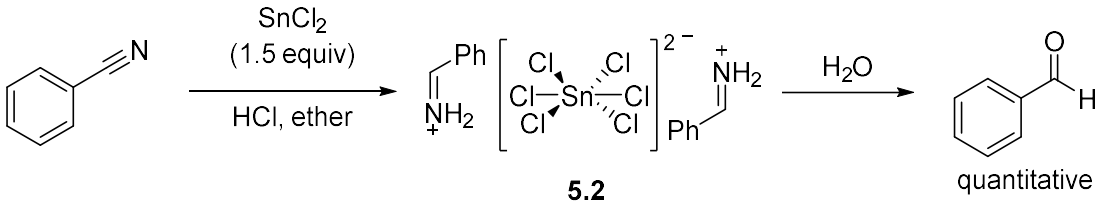



**Scheme 5.1.** Possible pathways for reduction of nitriles.

#### 5.1.1. First reported aldehyde synthesis from nitrile

In 1925, Stephen reported one of the first methodologies for the synthesis of aldehydes from nitriles.[4] Treatment of nitriles in the presence of tin(II) chloride in ether saturated

with dry hydrogen chloride provided the corresponding aldimine tin(IV) chloride salts **5.2** through single-electron-transfer. This aldimine was subsequently hydrolyzed to afford the aldehydes (Scheme 5.2).

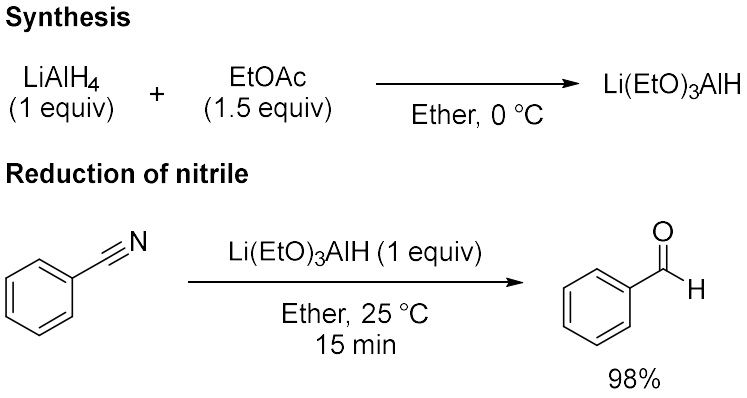



**Scheme 5.2.** Stephen reaction.

This methodology works on both aliphatic and aromatic nitriles, although the yields of aldehydes generated from aliphatic nitriles were typically much lower than those from aromatic nitriles. Furthermore, this reaction was reported to be sensitive to the steric factor of the substrates and of low functional group tolerance. Knight et al. also reported poor reproducibility for the reduction of aliphatic nitriles using the Stephen reaction.[5]

### 5.1.2. Use of aluminum hydride

Lithium aluminum hydride ($LiAlH_4$) can reduce nitriles to primary amines[6] as the highly reactive $LiAlH_4$ rapidly reacts with the aldimine intermediates for the second hydride reduction. Brown et al. began to investigate the controlled reduction of acid chlorides and phenyl esters to their corresponding aldehydes with alkoxy substituted lithium aluminum hydrides such as lithium triethoxyaluminum hydride. Having found success in these controlled reduction, they successively reported the use of lithium triethoxyaluminohydride for the controlled reduction of aromatic and aliphatic nitriles to their corresponding aldehydes (Scheme 5.3)[7]




**Scheme 5.3.** Use of $Li(EtO)_3AlH$ for the reduction of nitriles.

Complementary to alkoxy substituted lithium aluminum hydrides, Cha et al. also reported the synthesis and usage of amino substituted lithium aluminum hydrides such as lithium *N*,*N*'-dimethylethylenediaminoaluminum hydride (LDMEDAH)[8] and lithium tris(dihexylamino)aluminum hydride (LTDHA)[9] (Figure 5.1). These lithium amino aluminum hydrides were used to selectively reduce aromatic nitriles over aliphatic nitriles to their corresponding aldehydes at 0 °C.

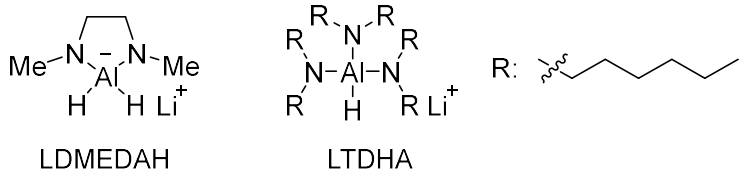
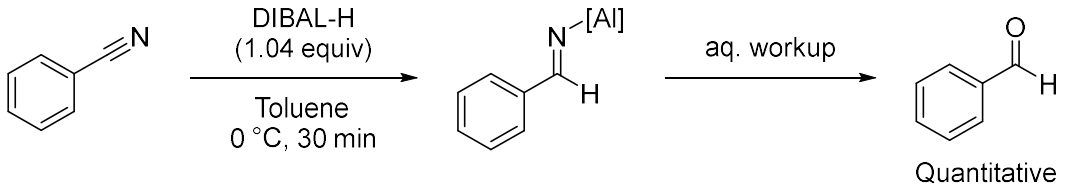


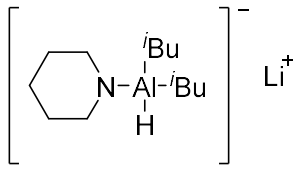

**Figure 5.1.** Lithium amino aluminium hydrides.

Diisobutylaluminum hydride (DIBAL-H) is the most commonly used reagents for the reduction of nitriles to the aldehydes (Scheme 5.4).[10-12] However, the usage of DIBAL-H comes with certain drawbacks such as the need for cryogenic reaction conditions to control the selectivity, the inherent functional groups compatibility and the tedious workup protocol needed to remove the aluminum residues.

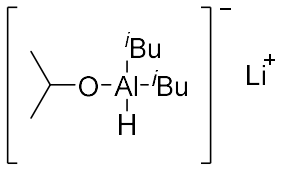



**Scheme 5.4.** Reduction of nitrile using DIBAL-H.

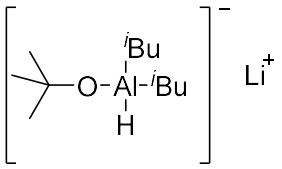
An et al. reported the derivatization of DIBAL-H by reacting DIBAL-H with variety of lithium alkoxide[13-14] and lithium dialkylamide[15-16] (Figure 5.2). This allowed for the reduction of aromatic nitriles to the aldehydes under mild reaction conditions. These protocols also enabled selective reduction of aromatic nitriles over aliphatic ones. In other words, these reagents could reduce only aromatic nitriles.



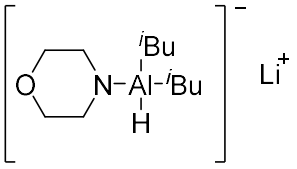

Lithium Diisobutylpiperidinohydroaluminate (2006)




Lithium Diisobutyl-iso-propoxyaluminum Hydride (2010)




Lithium Diisobutyl-t-butoxyaluminum Hydrides (2008)

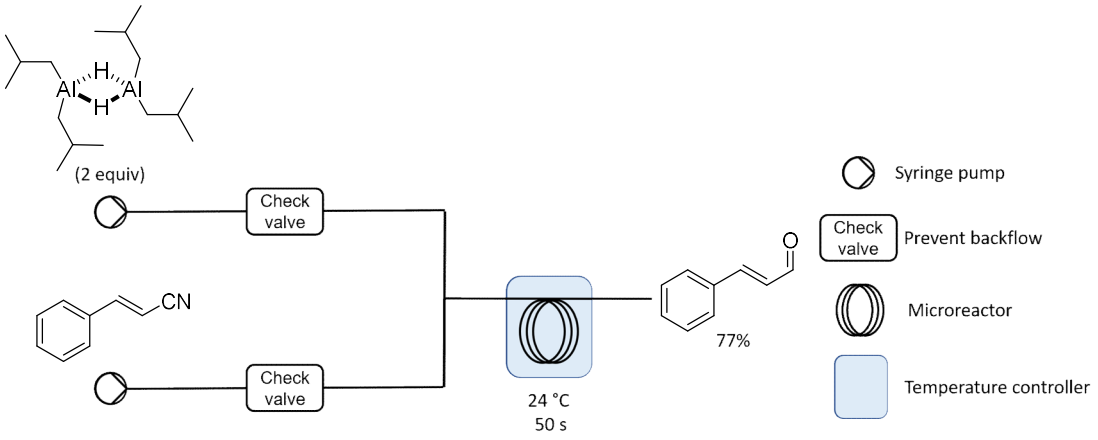



Lithium Diisobutylmorpholinoaluminum Hydride (2012)

**Figure 5.2.** Derivatized DIBAL-H.

Utilization of DIBAL-H for the controlled reduction of nitriles could be upgraded to the continuous flow system (Scheme 5.5).[17-18] The use of flow system is able to avoid the problem caused by the highly exothermic reaction as there is a high surface area to volume ratio in the microreactor to dissipate the heat. Safety issue due to handling of

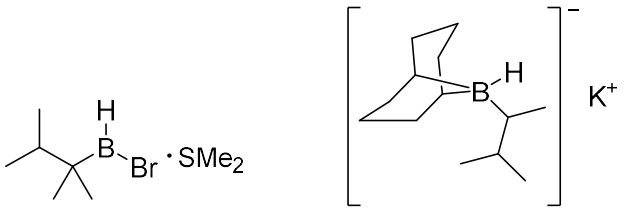
air and moisture sensitive compounds is also mitigated as the volume is greatly reduced in the microflow reactors. The simple flow setup could achieve a product yield of 3 g $h^{-1}$.




**Scheme 5.5.** Schematics for reduction of nitriles to aldehydes in the continuous flow system.

### 5.1.3. Use of boron hydride

Reactivity of sodium borohydride ($NaBH_4$) is too weak to reduce the cyano groups. In the presence of metallic transition-metals or transition-metal salts such as $CoCl_2$,[19] Ni(0),[20] $NiCl_2$,[21] $CuSO_4$[22] or $InCl_3$[23] the reactivity of $NaBH_4$ could be enhanced enabling reduction of nitriles to amines. Complementary to the reactivity of $NaBH_4$ with transition-metals or transition-metal salts, Cha et al. developed a new borohydride reagent, thexylbromoborane-methyl sulphide complex (ThxBHBr•$SMe_2$) (Scheme 5.6)[24] This reagent allowed for the reduction of aromatic and aliphatic nitriles to the corresponding aldehydes. The same group also reported potassium 9-sec-amyl-9-boratabicyclo[3.3.1]nonane (K 9-sec-Am-9-BBNH) could reduce aromatic nitriles to aldehydes selectively over aliphatic nitriles (Scheme 5.6).[25]

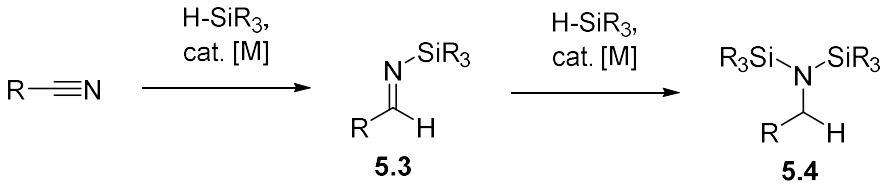



ThxBHBr•$SMe_2$ K 9-sec-Am-9-BBNH

**Figure 5.3.** Borohydride reagents for aromatic nitriles reduction to aldehydes.

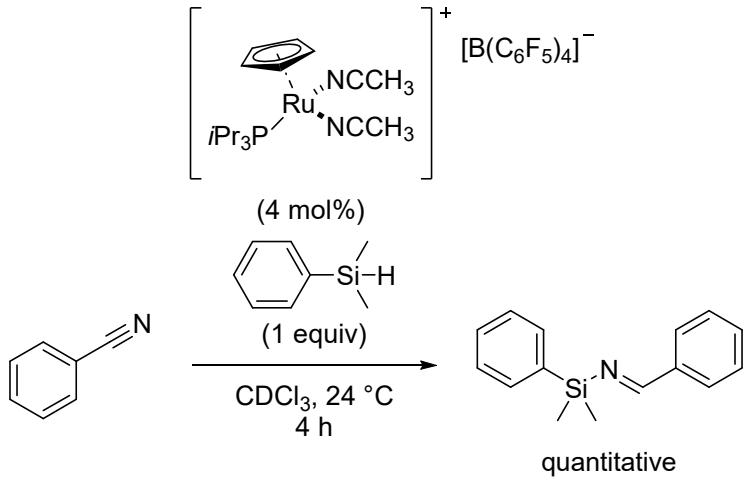
### 5.1.4. Use silanes or siloxanes

The first example of hydrosilylation of nitriles was a zinc(II) chloride-catalysed process reported by Calas et al. [26] Mono-hydrosilyation of nitriles is challenging because the mono-hydrosilyated product **5.3**, N-silylaldimines, are more reactive than nitriles and second hydrosilylation should proceed to yield disilylamines **5.4** (Scheme 5.6).[27]



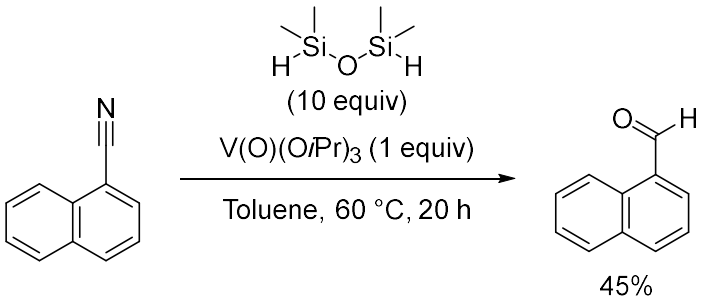

**Scheme 5.6.** Hydrosilylation of nitriles.

Nikonov et al. recently reported a controlled hydrosilylation of both aliphatic and aromatic nitriles using the cationic cyclopentadienyl ruthenium(II) complex (Scheme 5.7).[28] Functional groups like carbonyl (on aldehydes, ketones and esters), nitro, and alkenyl groups were well tolerated in this protocol.




**Scheme 5.7.** Hydrosilylation of nitriles.

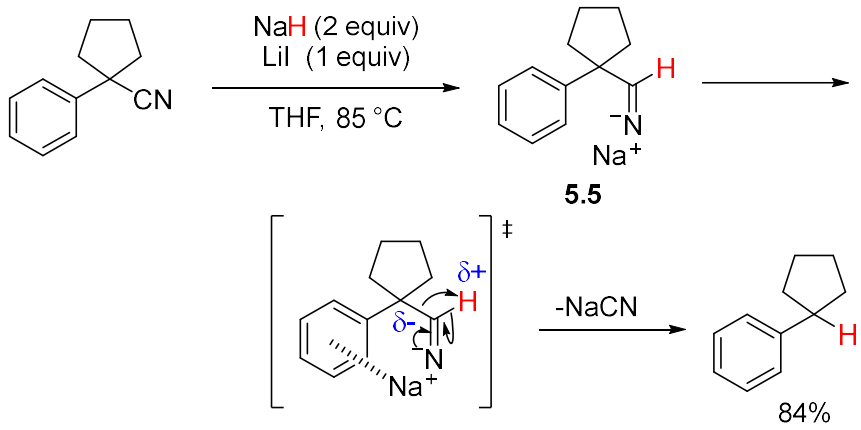
Typically, hydrosilanes like triethoxysilane is a fire hazard because it can undergo disproportionation to generate $SiH_4$ which is highly flammable.[29] In this regard, hydrosiloxanes are the safer alternatives to hydrosilanes. Lemaire et al. reported the use of 1,1,3,3-tetramethyldisiloxanes (TMDS) for the reduction of aromatic and aliphatic nitriles to the corresponding aldehydes in moderate to good yields in the presence of an oxovanadium(V) complex (Scheme 5.8).[3]




**Scheme 5.8.** Reduction of nitrile to aldehyde using TMDS/V(O)(O*i*Pr)$_3$.

## 5.2. Perspective of this chapter

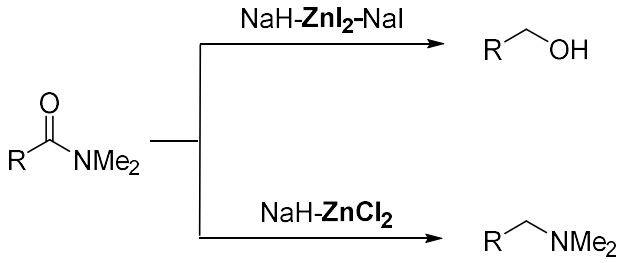
The author's group recently reported on hydrodecyanation of α-quaternary benzyl cyanides using the NaH in the presences of LiI (Scheme 5.9). This reduction process is assumed to be initiated with the hydride attack onto the cyano group from the activated NaH to generate iminyl sodium/lithium intermediates **5.5**. This intermediate subsequently undergoes a concerted C-C bond cleavage and 1,2-proton shift to afford the hydrodecyanated alkane products together with generation of sodium/lithium cyanide. This reaction is, however, limited to the use of benzyl cyanides as the cation-π interaction between the sodium/lithium cation and the aryl group is essential to facilitate the concerted C-C bond cleavage event to happen. Nonetheless, this protocol with the NaH-LiI system cannot be utilized to perform general hydride reduction of nitriles to the corresponding aldehydes.




**Scheme 5.9.** Hydrodecyanation of α-quaternary benzyl cyanides.

In turn, the author developed use of NaH as the hydride source for the generation of a well-defined zinc hydrides by counter ion metathesis with zinc halides as discussed in chapter 4 of this thesis (Scheme 5.10). Lewis acidity of the Zn(II) center should be the key to mediate further decomposition of anionic carbinolamine intermediates via C-O

or C-N bond cleavage. Based on these backgrounds, the author wondered if the zinc hydrides derived from NaH and zinc halides could show reactivity toward the reduction of nitriles.



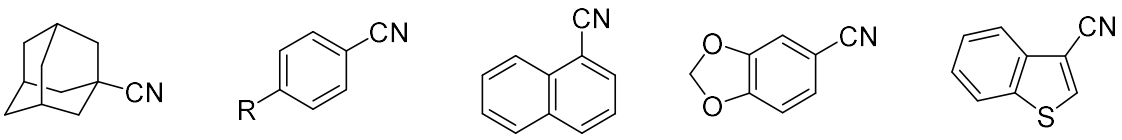

**Scheme 5.10.** Controlled reduction of carboxamides with NaH and $ZnX_2$.

This chapter will discuss the controlled reduction of nitriles to their corresponding aldehydes using the NaH and $ZnCl_2$ system. Details of reaction optimization, scope and limitation, reactivity comparison between the author's protocol and that with DIBAL-H will be described in this chapter.

## 5.3. Result and discussion

### 5.3.1. Preparation of starting materials

The following nitriles **5.6n, 5.8a-5.8e** and **5.8n** were commercially available and used as received (Figure 5.4).




**5.6n** | **5.8a** (R = Ph), **5.8b** (R = OMe), **5.8c** (R = Br) | **5.8d** | **5.8e** | **5.8n**

**Figure 5.4.** Commercially available nitriles

The nitriles **5.6b**,[30] **5.6c,**[31] **5.6d,** [30] **5.6e,**[32] **5.6f,**[33] **5.6i,**[34] **5.6j,**[35] **5.6k,**[30] **5.6l,**[36] **5.6q,** [30] **5.6r,**[37] **5.8f,**[38] **5.8g,**[39] **5.8h,**[40] **5.8i,**[41] **5.8j,**[42] **5.8k**[43] and **5.8m**[30] were prepared by following the literature methods (Figure 5.5).

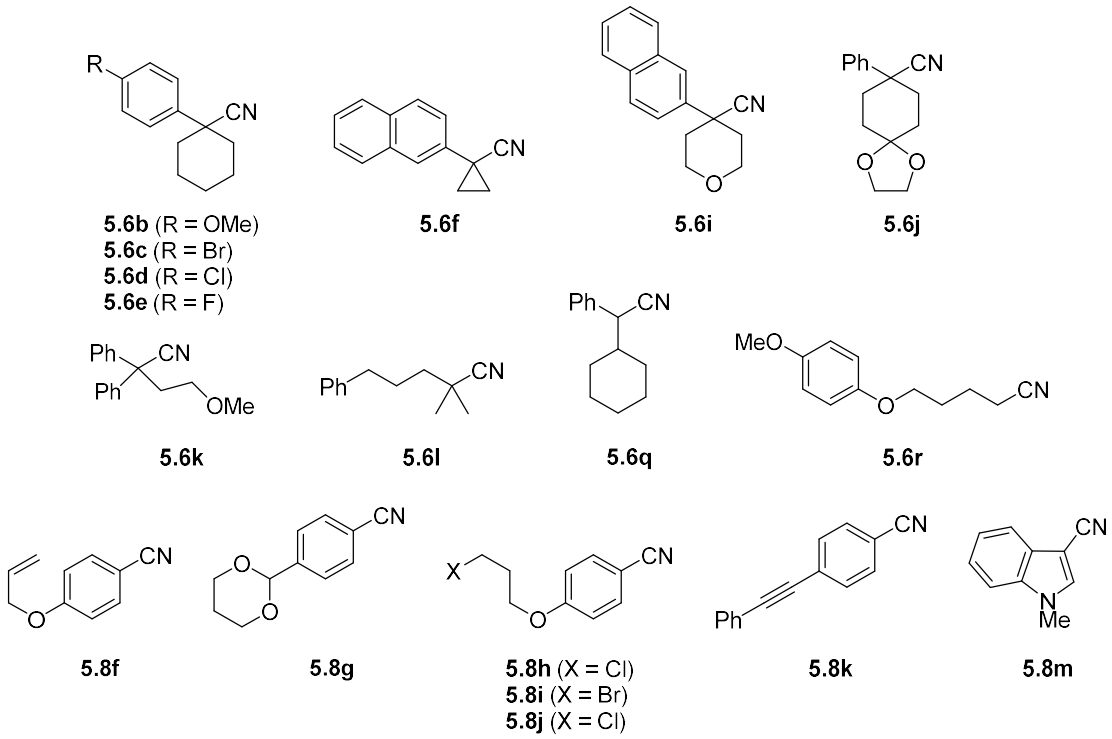
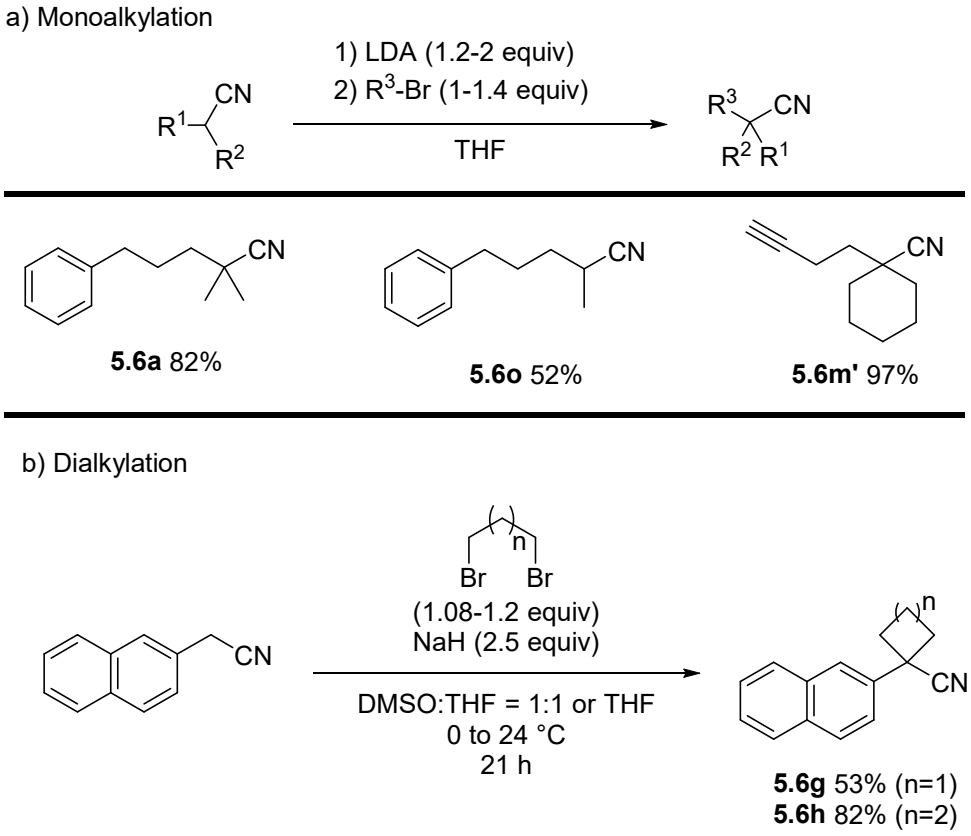


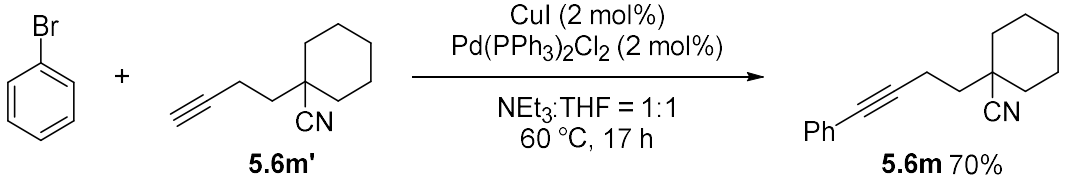

**Figure 5.5.** Known nitriles prepared by the literature methods.

Nitriles **5.6a, 5.6o** and **5.6m'** were synthesized via sequential deprotonation-alkylation of α-secondary/tertiary carbonitriles with alkyl bromides (1.0–1.4 equiv) in the presence of lithium diisopropylamide (1.2–2.0 equiv) and nitriles **5.6g** and **5.6h** were synthesized via dialkylation of 2-naphthylacetonitriles with alkyl halides (1.08–1.2 equiv) in the presence of NaH (2.5 equiv) as a base (Scheme 5.11).



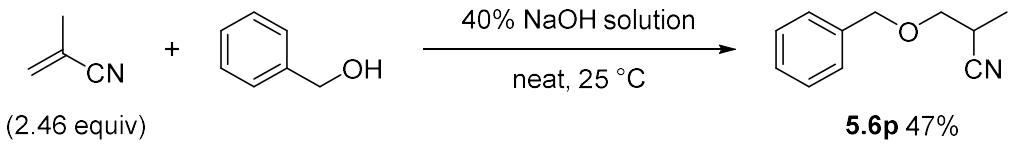

**Scheme 5.11.** a) Monoalkylation; b) Dialkylation of carbonitriles.

Nitrile **5.6m** was synthesized via Sonogashira coupling of terminal alkyne **5.6m'** and bromobenzene in the presence of copper(I) iodide and bis(triphenylphosphine)palladium(II) dichloride (Scheme 5.12).



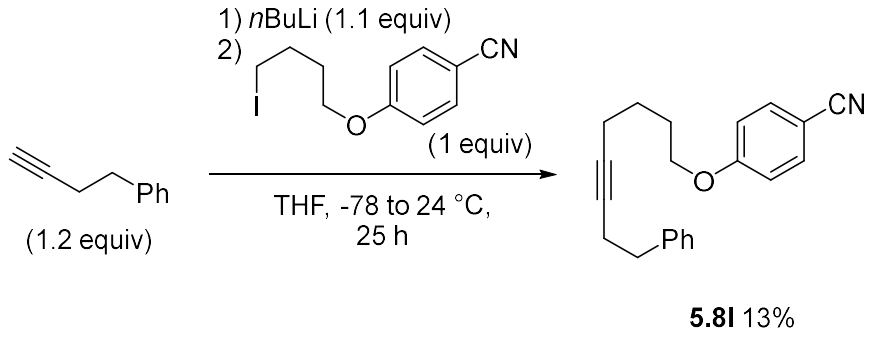

**Scheme 5.12.** Sonogashira coupling.

Nitrile **5.6p** was obtained via oxa-Michael addition of benzyl alcohol to methacrylonitrile in the presence of NaOH (Scheme 5.13).




**Scheme 5.13.** Oxa-Michael addition.

Nitrile **5.8l** was prepared by nucleophilic substitution of the corresponding alkyl iodide with lithium acetylide. (Scheme 5.14)



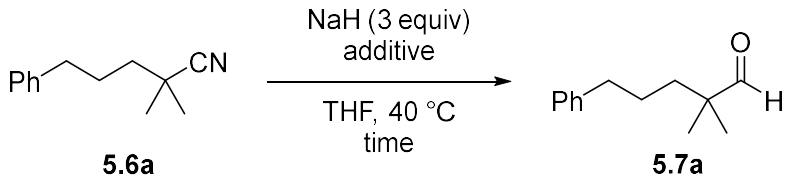

**Scheme 5.14.** Nucleophilic substitution of alkyl iodide.

### 5.3.2. Optimization of reaction conditions

Using α-quaternary carbonitrile **5.6a** as a model substrate, the author first pursued the reaction optimization. The reduction of **5.6a** in the presence of NaH (3 equiv) and $ZnI_2$ (1.5 equiv) in THF proceeded rapidly at 40 °C, resulting in full conversion of **5.6a** within 2.5 h to give aldehyde **5.7a** in 70% yield (Table 5.1, entry 1). Changing the halides on the zinc centre from iodide to bromide rendered the reaction slower (entry 2), while the yield of **5.7a** was improved to 88%. Use of $ZnCl_2$ allowed for rapid reduction and good yield of **5.7a** (entry 3). The protocol was amenable to use of even

LiH in the presence of $ZnCl_2$, providing aldehyde **5.7a** in 70% yield (entry 4). With NaH as a hydride source, lowering the amount of $ZnCl_2$ from 1.5 to 1.0 equiv caused the slower reaction (entry 5). Further reduction of the amount of $ZnCl_2$ to 0.5 equiv resulted in incomplete conversion of **5.6a** (entry 6).

**Table 5.1**: Optimization of the reaction conditions[a]




**5.6a** **5.7a**

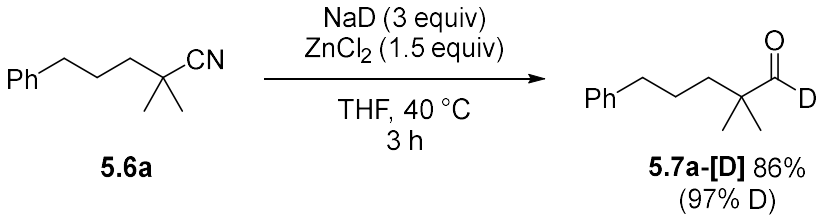
| Entry | additive (equiv) | time (h) | Conv. (%) | Yield of **5.7a** (%)[b] |
|---|---|---|---|---|
| 1 | $ZnI_2$ (1.5) | 2.5 | >99 | 70 |
| 2 | $ZnBr_2$ (1) | 5 | >99 | 88 |
| 3 | $ZnCl_2$ (1) | 3 | >99 | 85 |
| 4[b] | $ZnCl_2$ (1.5) | 3 | >99 | 70 |
| 5 | $ZnCl_2$ (1.0) | 7 | >99 | 91 |
| 6 | $ZnCl_2$ (0.5) | 24 | 83 | 74 |

[a] The reactions were conducted using 0.5 mmol of **5.6a** in THF (2.5 mL). [b] LiH was used instead of NaH.

### 5.3.3. Synthesis of deuterated aldehyde

Sodium deuteride (NaD)[44] was used in place of NaH, the reduction of carbonitrile **5.6a** proceeded with similar efficiency to give the deuterated aldehyde **5.7a-[D]** in similar yield and high deuterium incorporation of 97% (Scheme 5.15). This provided direct

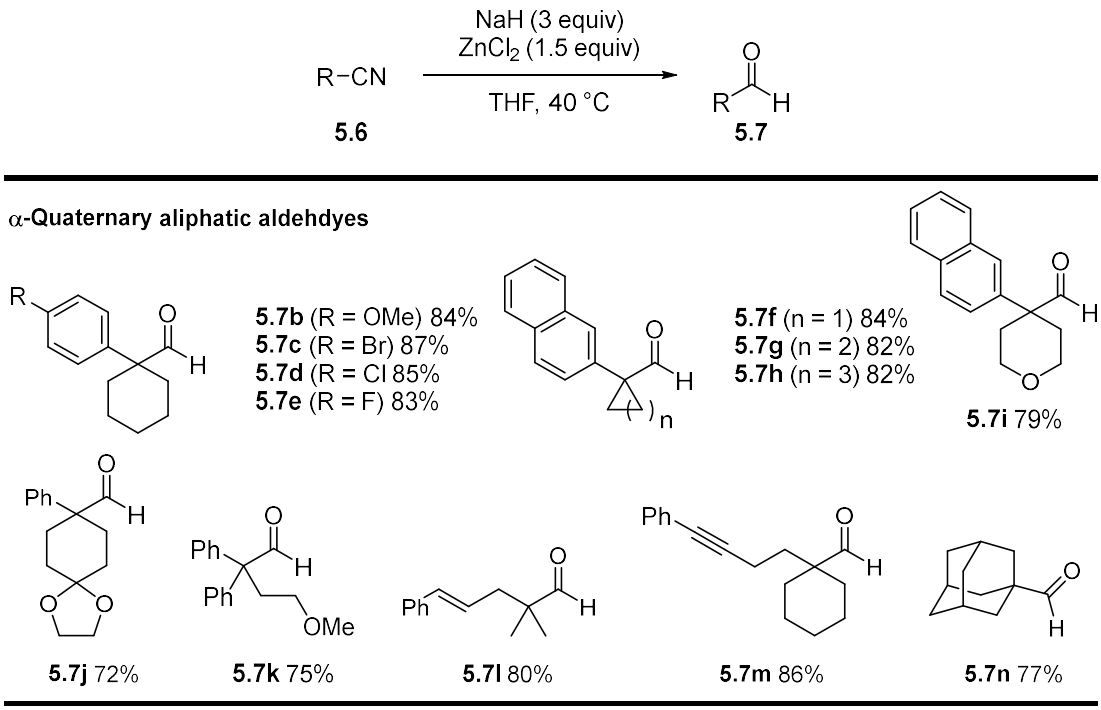
evidence that sodium hydride is the hydride source for the reduction process. Furthermore, this protocol provides a simple and direct synthesis of deuterated aldehydes with high deuterium incorporation, this contrasted with the existing methods that usually required multistep routes and/or expensive reagents for the synthesis of deuterated aldehydes.[45-50]




**Scheme 5.15.** Reduction of nitrile to aldehyde with NaD and $ZnCl_2$.

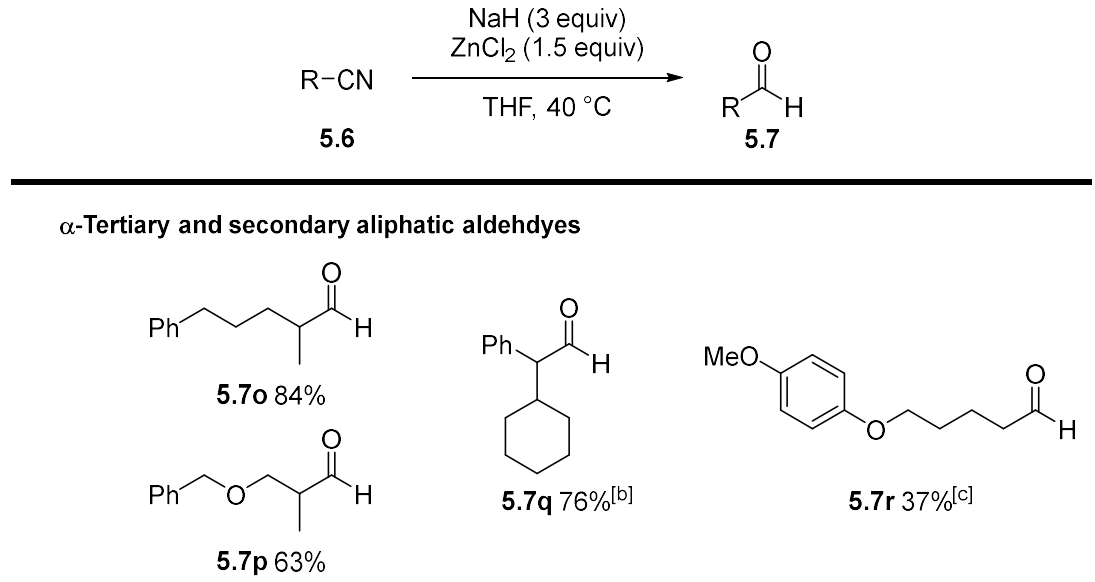
### 5.3.4. Scope and limitation

With the optimised reaction conditions in hand (Table 5.1, entry 3), the author started to investigate the scope and limitation of this methodology. This protocol allowed for the reduction of both aliphatic and aryl nitriles to their corresponding aldehydes with a wide functional group compatibility (Schemes 5.16 to 5.18). Sterically hindered α-quaternary aliphatic nitriles could be reduced smoothly to the corresponding aldehydes in good yields (72%-87%) (Scheme 5.16). Complementary to the hydrodecyanation of α-quaternary benzyl cyanides under the NaH-LiI system developed by the author's group,[51] this protocol with the NaH-$ZnCl_2$ system enabled controlled reduction of α-quaternary benzyl cyanides to the corresponding aldehydes (for **5.7b** – **5.7k**).



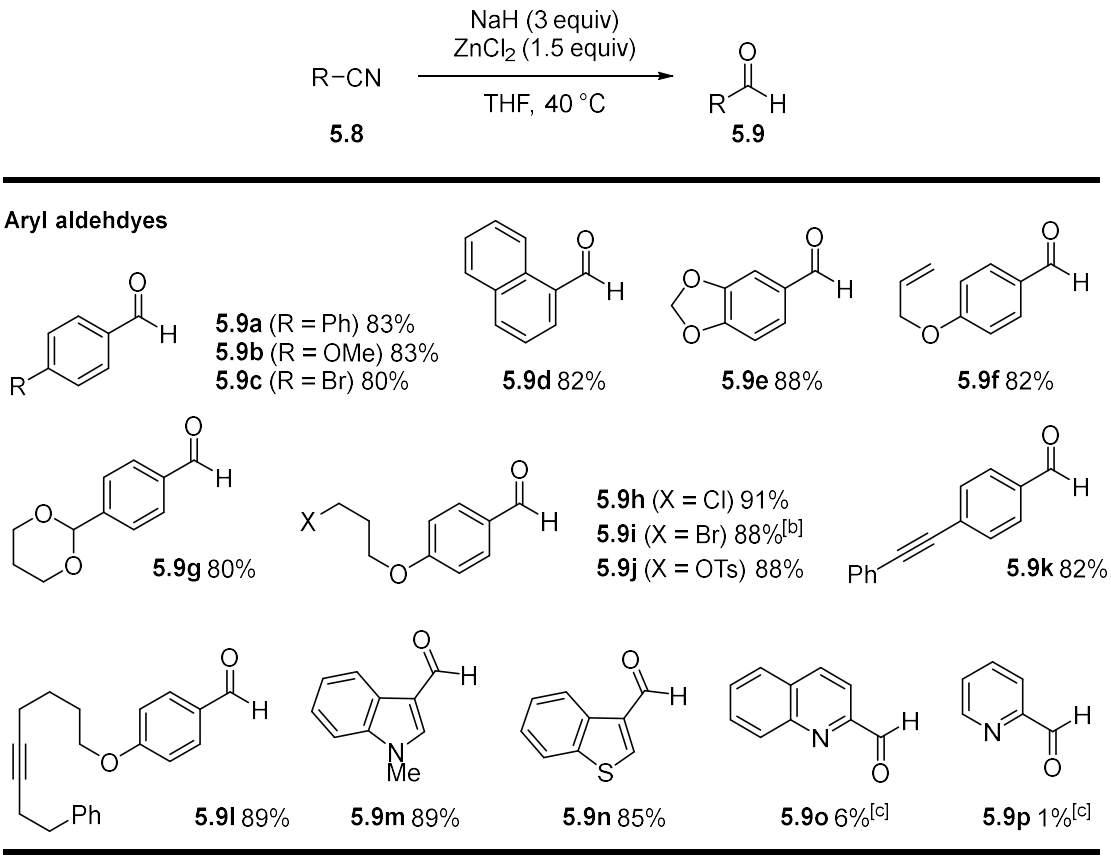

**Scheme 5.16.** Reduction of α-quaternary aliphatic aldehydes. [a] The reactions were conducted using 0.5 mmol of the nitriles **5.6** with isolated yields of aldehydes **5.7** given.

The reduction of α-tertiary aliphatic nitriles having an α-enolizable proton also proceeded smoothly to give the corresponding α-tertiary aldehydes in good yield (for **5.7o** – **5.7q**) (Scheme 5.17). However, the reduction of α-secondary aliphatic nitrile **5.6r** became sluggish and required an elevated temperature to complete the reaction. The reduction of **5.6r** provided the α-secondary aldehyde **5.7r** in moderate yield (Scheme 5.17).




**Scheme 5.17.** Reduction of α-tertiary and secondary aliphatic aldehydes. [a] The reactions were conducted using 0.5 mmol of the nitriles **5.6** with isolated yields of aldehydes **5.7** given. [b] Reaction was conducted using NaH (6 equiv) and $ZnCl_2$ (3 equiv). [c] The reaction was conducted at 60 °C.

Controlled reduction of (hetero)aryl nitriles also proceeded efficiently with the current protocol (Scheme 5.18). Both electron-donating (for **5.9b**) or electron-withdrawing (for **5.9c**) groups were tolerated. Electron-rich 5-membered ring heteroaryl aldehydes based on indole **5.9m** and benzothiophene **5.9n** could be prepared in high yields. Synthesis of electron-deficient 6-membered ring heteroaryl aldehydes based on quinoline **5.9o** or pyridine **5.9p** were, however, not efficient with over-reduction of aromatic moieties, affording the corresponding aldehydes only in poor yields.




**Scheme 5.18.** Reduction of aryl aldehydes. [a] The reactions were conducted using 0.5 mmol of the nitriles **5.8** with isolated yields of aldehydes **5.9** given. [b] 4% of hydrodebrominated product was observed. [c] $^{1}$H NMR yield based on 1,1,2,2-tetrachloroethane as internal standard.

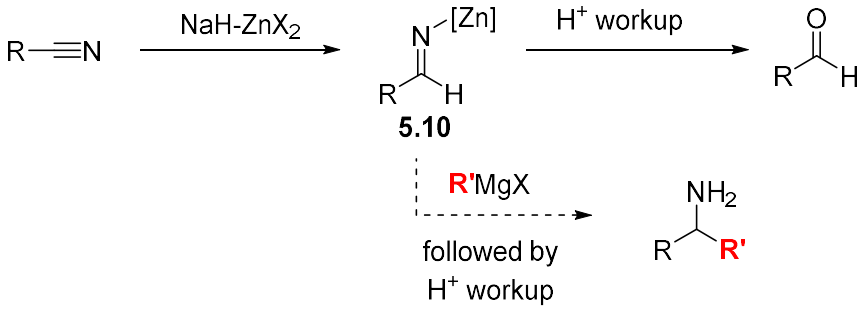
In the reduction of nitriles possessing aryl halides (**5.6c** – **5.6e**, **5.8c**) and alkyl (pseudo)halides (for **5.8h** and **5.8j**), hydrodehalogenation was not observed. However, a small amount of hydrodebrominated product (in 4% yield) was observed during the reduction of nitrile **5.8i** having a $sp^3$-C–Br bond.

The author compared the ability of the present NaH-$ZnCl_2$ system with that of diisopropylaluminum hydride (DIBAL-H) in the reduction of nitriles to aldehydes. The current protocol could keep various internal alkyne motifs (for **5.7m**, **5.9k**, and **5.9l**)

completely intact during the reduction processes. This contrasts with the reactivity of DIBAL-H that is well known to perform hydroalumination of alkynes. [52] Lewis acidity of DIBAL-H has been employed for several useful molecular transformations. For example, Claisen rearrangement of allyl phenyl ethers can be mediated by DIBAL-H under milder reaction conditions.[53] On the other hand, the reduction of 4-(allyloxy)benzonitrile (**5.8f**) using the NaH-$ZnCl_2$ system only provided 4-(allyloxy)benzaldehyde (**5.9f**) without observation of the Claisen rearrangement. DIBAL-H could be used for the cleavage of benzylidene acetals of 1,2- and 1,3-glycols to mono-benzyl-protected diols.[54] In the current protocol, Nitrile **5.8g** having a benzylidene acetal moiety was successfully reduced to the aldehyde **5.9g** without cleavage of the acetal moiety. All the results exemplified the wide functional groups tolerance of the current protocol.

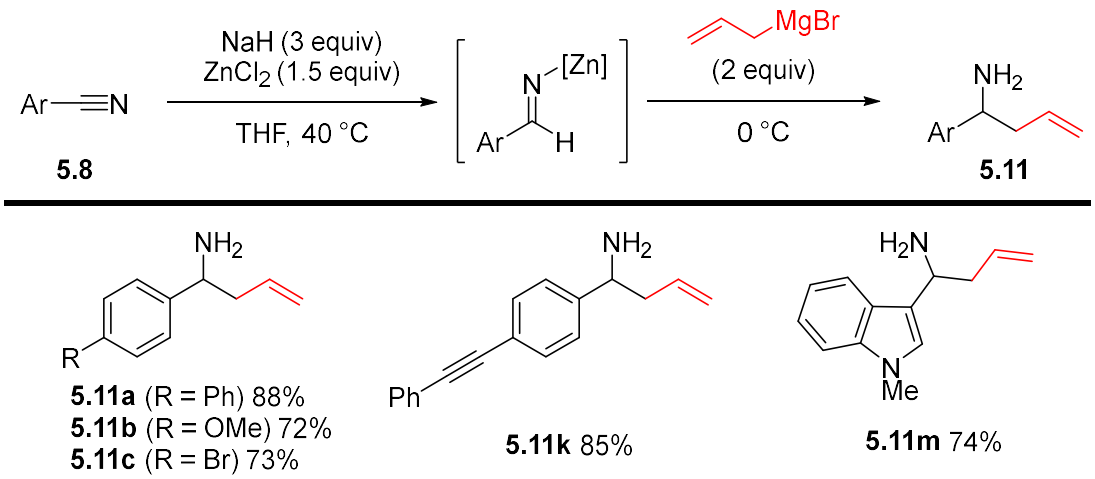
### 5.4. Allylation of iminyl zinc

The reduction of nitriles to aldehydes using the NaH-$ZnCl_2$ system should proceed via the iminyl zinc species **5.10** (Scheme 5.19). The author wondered if iminyl zinc species **5.10** could be further functionalized with another carbon nucleophile.



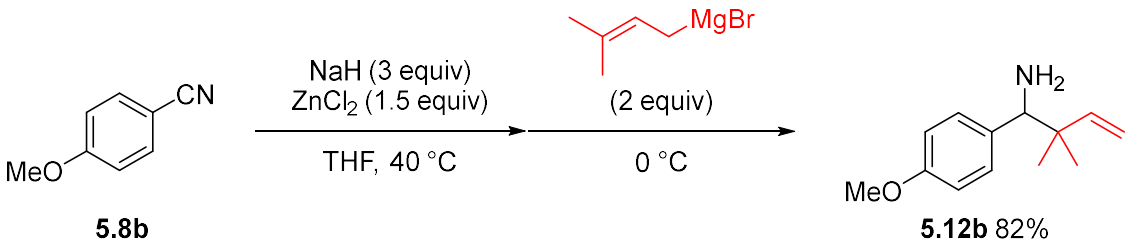

**Scheme 5.19.** Possible pathway for reduction of nitriles.

The initial trial for use of phenylmagnesium bromide or phenethylmagnesium bromide to the iminyl zinc species was unsuccessful, just yielding the corresponding aldehydes. These Grignard reagents were not effective most likely because the Grignard reagents are not nucleophilic enough to directly attacked the iminyl zinc intermediate. On the other hand, the author found that addition of allylmagnesium bromide to the iminyl zinc derived from aromatic nitriles could result in formation of homoallylic primary amine **5.11** (Scheme 5.20). Various (hetero)aromatic were tolerated to give the corresponding homoallylic primary amines (for **5.11a**–**5.11c**, **5.11k**, and **5.11m**) in good yields.




**Scheme 5.20.** Hydride reduction followed by allylation with allylmagnesium bromide. [a] The reactions were conducted using 0.5 mmol of the nitriles **5.8** with isolated yields of homoallylic amine **5.11** given.

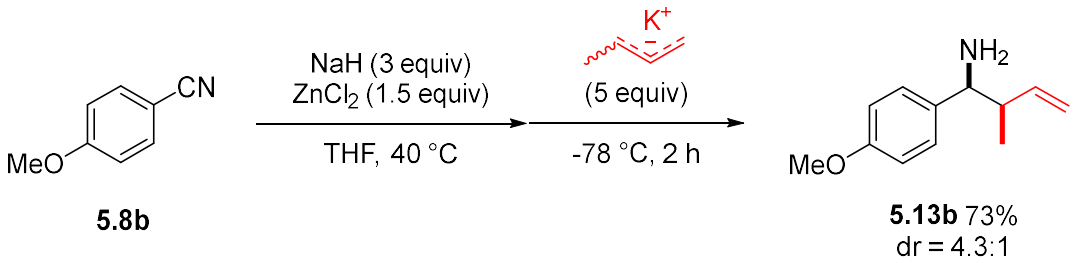
Since the discovery that only allyl Grignard reagent work for allylation, the allyl metal reagents were studies in detail to understand the mechanism. Interestingly, the reduction of nitrile **5.8b** followed by subsequent addition of 3,3-dimethylallyl magnesium bromide gave branched homoallyl amine **5.12b** as a single product (Scheme 5.21).




**5.8b** **5.12b** 82%

**Scheme 5.21.** Hydride reduction followed by allylation with 3,3-dimethyl allyl magnesium bromide.

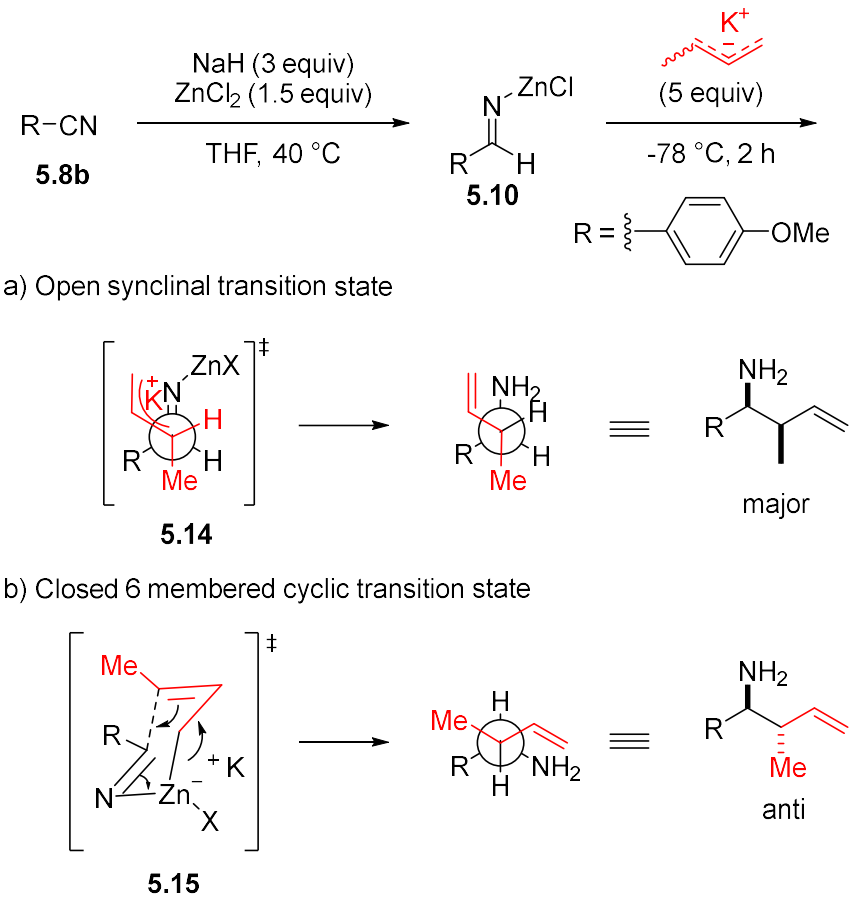
Furthermore, addition of *trans*-crotyl potassium,[55-57] prepared from *trans*-butene by following the Schlosser's protocol, at -78 °C could afford branched homoallylic amine **5.13b** with *syn*-diastereoselectivity. The same diastereoselectivity was observed when *cis*-crotyl potassium was used. These results indicated that the *syn*-diastereoselectivity is irrespective of the stereochemistry of the crotyl potassium used (Scheme 5.22).




**5.8b** **5.13b** 73%
dr = 4.3:1

**Scheme 5.22.** Hydride reduction followed by allylation with crotyl potassium.

These observations suggested that the allyl metal nucleophile reacted with the iminyl zinc species **5.10** via an open synclinal transition-state **5.14** (Scheme5.23a)[58,59] as the major pathway rather than a closed six membered cyclic transition state **5.15** (Scheme 5.23b).




**Scheme 5.23.** Proposed mechanism for allylation with crotyl potassium.

## 5.5. Conclusion

A new protocol for the controlled reduction of carbonitriles to the corresponding aldehydes was developed using a combination of NaH and $ZnCl_2$. This protocol allowed for the reduction of both aliphatic and (hetero)aromatic nitriles under milder reaction conditions and showed wider functional group compatibility than DIBAL-H does. The further allylation of the iminyl zinc intermediates provided homoallylamines.

## 5.6. References


1. X.-Q. Chu, D. Ge, Z.-L. Shen, T.-P. Loh, *ACS Catal.* **2018,** *8*, 258-271.
2. F. F. Fleming, Q. Wang, *Chem. Rev.* **2003,** *103*, 2035-2078.
3. S. Laval, W. Dayoub, L. Pehlivan, E. Métay, D. Delbrayelle, G. Mignani, M. Lemaire, *Tetrahedron Lett.* **2014,** *55*, 23-26.
4. H. Stephen, *J. Chem. Soc., Trans.* **1925,** *127*, 1874-1877.

5. J. A. Knight, H. D. Zook, *J. Am. Chem. Soc.* **1952,** *74*, 4560-4562.
6. L. H. Amundsen, L. S. Nelson, *J. Am. Chem. Soc.* **1951,** *73*, 242-244.
7. H. C. Brown, C. J. Shoaf, *J. Am. Chem. Soc.* **1964,** *86*, 1079-1085.
8. J. S. Cha, S. H. Jang, S. Y. Kwon, *Bull. Korean Chem. Soc.* **2002,** *23*, 1697-1698.
9. J. S. Cha, *Bull. Korean Chem. Soc.* **1992,** *13*, 670-676.
10. P. Galatsis, M. Sollogoub, P. Sinaÿ, Diisobutylaluminum Hydride. In *Encyclopedia of Reagents for Organic Synthesis*, 2008.
11. A. E. G. Miller, J. W. Biss, L. H. Schwartzman, *J. Org. Chem.* **1959,** *24*, 627-630.
12. N. M. Yoon, Y. S. Gyoung, *J. Org. Chem.* **1985,** *50*, 2443-2450.
13. Y.-M. Choi, S.-J. Choi, K.-Y. Eom, H. Hwang, D. K. An, *Bull. Korean Chem. Soc.* **2008,** *29*, 2303.
14. Y.-M. Choi, M. Yoo, D.-K. An, *Bull. Korean Chem. Soc.* **2010,** *31*, 473-474.
15. J.-H. Ha, J.-H. Ahn, D.-K. An, *Bull. Korean Chem. Soc.* **2006,** *27*, 121-122.
16. Y. R. Kim, D. K. An, *Bull. Korean Chem. Soc.* **2012,** *33*, 4194-4196.
17. T. Fukuyama, M. T. Rahman, I. Ryu, I. R. Baxendale, J. J. Hayward, S. Lanners, S. V. Ley, C. D. Smith, B. Ahmed-Omer, T. Wirth, V. Hessel, P. Löb, H. Löwe, K. Koch, F. P. J. T. Rutjes, J. C. M. van Hest, Organic Chemistry in Microreactors. In *Microreactors in Organic Synthesis and Catalysis*, 2008; pp 59-209.
18. J. d. M. Muñoz, J. Alcázar, A. d. l. Hoz, A. Díaz-Ortiz, *Tetrahedron Lett.* **2011,** *52*, 6058-6060.
19. J. O. Osby, S. W. Heinzman, B. Ganem, *J. Am. Chem. Soc.* **1986,** *108*, 67-72.
20. S. Liu, Y. Yang, X. Zhen, J. Li, H. He, J. Feng, A. Whiting, *Org. Biomol. Chem.* **2012,** *10*, 663-670.
21. S. Caddick, D. B. Judd, A. K. d. K. Lewis, M. T. Reich, M. R. V. Williams, *Tetrahedron* **2003,** *59*, 5417-5423.
22. S.-e. Yoo, S.-h. Lee, *Synlett* **1990,** *1990*, 419-420.
23. J. Z. Saavedra, A. Resendez, A. Rovira, S. Eagon, D. Haddenham, B. Singaram, *J. Org. Chem.* **2012,** *77*, 221-228.
24. J. S. Cha, S. Y. Oh, J. E. Kim, *Bull. Korean Chem. Soc.* **1987,** *8*, 301-304.
25. J. S. Cha, M. S. Yoon, *Tetrahedron Lett.* **1989,** *30*, 3677-3680.
26. R. Calas, SUR QUELQUES ASPECTS DE LA REACTIVITE DES HYDROGENOSILANES EN CHIMIE ORGANIQUE. In *Organosilicon Chemistry*, Butterworth-Heinemann: 1966; pp 61-79.
27. T. Murai, T. Sakane, S. Kato, *J. Org. Chem.* **1990,** *55*, 449-453.
28. D. V. Gutsulyak, G. I. Nikonov, *Angew. Chem. Int. Ed.* **2010,** *49*, 7553-7556.
29. S. C. Berk, S. L. Buchwald, *J. Org. Chem.* **1993,** *58*, 3221-3221.
30. Y. Nakao, K. S. Kanyiva, S. Oda, T. Hiyama, *J. Am. Chem. Soc.* **2006,** *128*, 8146-8147.
31. J. Zhao, T. Nanjo, E. C. de Lucca, M. C. White, *Nat. Chem.* **2019,** *11*, 213-221.
32. S. Watanuki, K. Matsuura, Y. Tomura, M. Okada, T. Okazaki, M. Ohta, S.-i. Tsukamoto, *Bioorg. Med. Chem.* **2011,** *19*, 5628-5638.
33. J. M. McCabe Dunn, J. T. Kuethe, R. K. Orr, M. Tudge, L.-C. Campeau, *Org. Lett.* **2014,** *16*, 6314-6317.
34. Y. Huang, G. H. Chan, S. Chiba, *Angew. Chem. Int. Ed.* **2017,** *56*, 6544-6547.

35. Y.-J. Wu, H. He, R. Bertekap, R. Westphal, S. Lelas, A. Newton, T. Wallace, M. Taber, C. Davis, J. E. Macor, J. Bronson, *Bioorg. Med. Chem.* **2013,** *21*, 2217-2228.
36. X. Peng, B. M. K. Tong, H. Hirao, S. Chiba, *Angew. Chem. Int. Ed.* **2014,** *53*, 1959-1962.
37. J. E. T. Corrie, A. Barth, G. Papageorgiou, *J Label Compd Radiopharm* **2001,** *44*, 619-626.
38. Y. Mao, Y. Liu, Y. Hu, L. Wang, S. Zhang, W. Wang, *ACS Catal.* **2018,** *8*, 3016-3020.
39. S. He, G. Dong, Z. Wang, W. Chen, Y. Huang, Z. Li, Y. Jiang, N. Liu, J. Yao, Z. Miao, W. Zhang, C. Sheng, *ACS Med. Chem. Lett.* **2015,** *6*, 239-243.
40. S. Xu, A. Aguilar, T. Xu, K. Zheng, L. Huang, J. Stuckey, K. Chinnaswamy, D. Bernard, E. Fernández-Salas, L. Liu, M. Wang, D. McEachern, S. Przybranowski, C. Foster, S. Wang, *Angew. Chem. Int. Ed.* **2018,** *57*, 1601-1605.
41. M. Rahimian, A. Kumar, M. Say, S. A. Bakunov, D. W. Boykin, R. R. Tidwell, W. D. Wilson, *Biochemistry* **2009,** *48*, 1573-1583.
42. D. Cladingboel, G. Ensor, WO2006137770, **2006**.
43. F. Pape, N. O. Thiel, J. F. Teichert, *Chem. Eur. J.* **2015,** *21*, 15934-15938.
44. H. Jenkner, US3116112A, **1953**.
45. X. Li, S. Wu, S. Chen, Z. Lai, H.-B. Luo, C. Sheng, *Org. Lett.* **2018,** *20*, 1712-1715.
46. E. S. Isbrandt, J. K. Vandavasi, W. Zhang, M. P. Jamshidi, S. G. Newman, *Synlett* **2017,** *28*, 2851-2854.
47. W. J. Kerr, M. Reid, T. Tuttle, *Angew. Chem. Int. Ed.* **2017,** *56*, 7808-7812.
48. G.-H. Niu, P.-R. Huang, G. J. Chuang, *Asian J. Org. Chem.* **2016,** *5*, 57-61.
49. S. Korsager, R. H. Taaning, A. T. Lindhardt, T. Skrydstrup, *J. Org. Chem.* **2013,** *78*, 6112-6120.
50. J. T. Spletstoser, J. M. White, G. I. Georg, *Tetrahedron Lett.* **2004,** *45*, 2787-2789.
51. P. C. Too, G. H. Chan, Y. L. Tnay, H. Hirao, S. Chiba, *Angew. Chem. Int. Ed.* **2016,** *55*, 3719-3723.
52. W. Uhl, *Coord. Chem. Rev.* **2008,** *252*, 1540-1563.
53. G. V. M. Sharma, A. Ilangovan, P. Sreenivas, A. K. Mahalingam, *Synlett* **2000,** *2000*, 0615-0618.
54. T. Seiichi, A. Masashi, S. Seiji, O. Kunio, *Chem. Lett.* **1983,** *12*, 1593-1596.
55. W. R. Roush, K. Ando, D. B. Powers, A. D. Palkowitz, R. L. Halterman, *J. Am. Chem. Soc.* **1990,** *112*, 6339-6348.
56. R. W. Hoffmann, *Angew. Chem. Int. Ed.* **1982,** *21*, 555-566.
57. B. M. Trost, I. Fleming, *Comprehensive Organic Synthesis*. Elsevier Science: 1991; Vol. 2.
58. G. E. Keck, K. A. Savin, E. N. K. Cressman, D. E. Abbott, *J. Org. Chem.* **1994,** *59*, 7889-7896.
59. W. J. Lee, W. Jeong, J. Park, Y. H. Rhee, *Asian J. Org. Chem*. **2017,** 6, 441.

## Chapter 6. Experimental data and Computational calculation

### 6.1. General information

$^{1}H$ and $^{13}C$ NMR spectra were recorded on Bruker Avance 400 spectrometers in $CDCl_3$ using TMS ($\delta = 0.00$) or $C_6D_6$ ($\delta = 7.16$) for $^{1}H$ and $CDCl_3$ ($\delta = 77.00$) for $^{13}C$ as internal standard. The following abbreviations were used to explain the multiplicities: s = singlet, brs = broad singlet, d = doublet, dd = doublet of doublet, t = triplet, td = triplet of doublet, q = quartet, sext = sextet, m = multiplet.

IR spectra were recorded on a Shimadzu IR Prestige-21 FT-IR spectrometer or a Bruker alpha Platinum ATR inside a glovebox. High-resolution mass spectra were obtained with Q-Tof Premier LC HR mass spectrometer and JEOL AccuTOF-CS JMS-T100CS mass spectrometer. Thermo Polaris Q GCMS and Thermo LCQ Fleet LCMS were used to monitor the progress of the reaction. Shimadzu GC-2010 was used for GC analysis. Flash column chromatography was performed using Merck silica gel 60 with distilled solvents. Optical rotations were measured on an Anton Paar MCP 200 polarimeter. Enantiomeric excesses (ee) were determined by HPLC analysis on Shimadzu HPLC with Daicel chiral columns. Elemental analyses were measured on a 2400 Series II CHNS/O Elemental Analysis instrument. Zinc and Sodium content was measured on a Thermo Fisher iCAP6000 inductively coupled plasma - optical emission spectrometer.

The powder XRD experiments were conducted using a Bruker D8 Advance X-ray diffractometer with a copper ($K_{\alpha1}(1.54060)/K_{\alpha2}(1.54439) = 2$) target X-ray tube set to 40 kV and 40 mA. In a glovebox, the vacuum-dried, freshly prepared NaD sample was loaded into an airtight specimen holder.

NaH (60% dispersion in oil), NaI, LiI, $ZnI_2$ and $ZnCl_2$ was purchased from Sigma-Aldrich, Inc. Due to moisture sensitivity of NaH, NaI, LiI, $ZnI_2$ and $ZnCl_2$, they were consistently handled under an $N_2$ atmosphere in a glovebox or with Schlenk techniques under an inert ($N_2$ or Ar) atmosphere. NaI and LiI were dried over $P_2O_5$ under reduced pressure at 60 °C and 120 °C, respectively.[1] Deuterium gas (99.6% D) was purchased from Cambridge Isotope Laboratories, Inc.

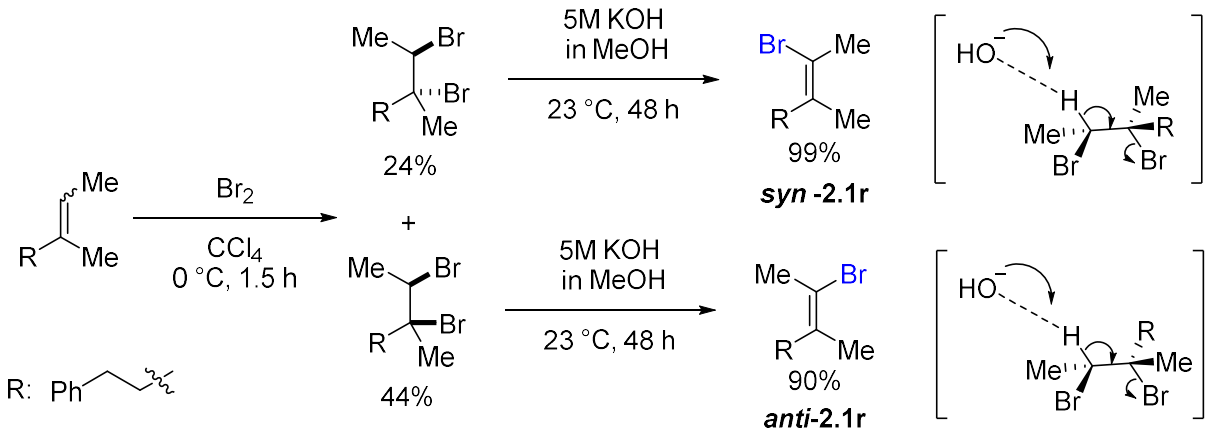
### 6.1.1. Reference for section 6.1

1. W. L. F. Armarego, C. L. L. Chai, Chapter 5 - Purification of Inorganic and Metal-Organic Chemicals: (Including Organic compounds of B, Bi, P, Se, Si, and ammonium and metal salts of organic acids). In *Purification of Laboratory Chemicals (Sixth Edition)*, Butterworth-Heinemann: Oxford, 2009; pp 445-576.

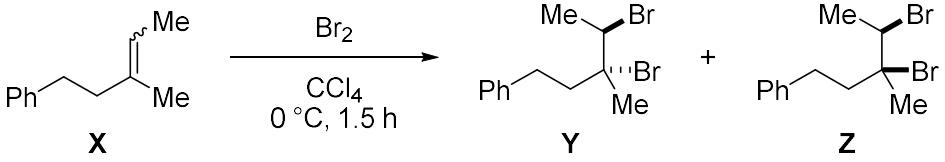
## 6.2. Experimental data for Chapter 2

### 6.2.1. Synthesis of bromoalkenes 2.1r

The synthesis of bromoalkenes **2.1r** was conducted via 2-steps sequence comprising of dibromination and base-mediated E2 elimination as shown below.

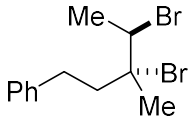



**A procedure for dibromination:**




To an ice-cold solution of (3-methylpent-3-en-1-yl) benzene (**X**)[1] (3.14 g, 19.6 mmol) in $CCl_4$ (100 mL) was added a solution of bromine (1.06 mL, 20.5 mmol) in $CCl_4$ (30 mL). After stirring for 1.5 h, the reaction mixture was concentrated in vacuo and the resulting residue was purified by flash column chromatography (silica gel, *n*-Hex) to give ((3*R**,4*R**)-3,4-dibromo-3-methylpentyl)benzene (**Y**) in 24% yield (1.50 g, 4.69 mmol) and ((3*S**,4*R**)-3,4-dibromo-3-methylpentyl)benzene (**Z**) in 44% yield (2.79 g, 8.69 mmol).

**((3*R**,4*R**)-3,4-dibromo-3-methylpentyl)benzene (Y)**




**$^{1}$H NMR** ($CDCl_3$, 400 MHz) $\delta$ 7.32–7.18 (m, 5H), 4.54 (q, $J$ = 6.7 Hz, 1H), 2.95–2.81 (m, 2H), 2.38–2.20 (m, 2H), 1.96 (d, $J$ = 6.4 Hz, 3H), 1.84 (s, 3H).

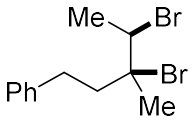
**$^{13}$C NMR** ($CDCl_3$, 100 MHz) $\delta$ 141.2, 128.5 (2C, overlapped), 126.1, 73.2, 56.3, 47.8, 31.8, 26.1, 23.1.

**IR** ($cm^{-1}$, neat) 3024, 2982, 2932, 1601, 1493, 1450, 698 (C–Br).

**LRMS** (GC-EI): Found *m/z* 159.09; Calcd for $C_{12}H_{15}$ [M-$HBr_2$] 159.12.

**ESIHRMS**: Found *m/z* 160.1251; Calcd for $C_{12}H_{16}$ [M-$Br_2$]$^{+}$ 160.1252.

**((3*S**,4*R**)-3,4-dibromo-3-methylpentyl)benzene (Z)**




**$^{1}$H NMR** ($CDCl_3$, 400 MHz) $\delta$ 7.32–7.29 (m, 2H), 7.23–7.21 (m, 3H), 4.49 (q, $J$ = 6.7 Hz, 1H), 2.94–2.77 (m, 2H), 2.28–2.22 (m, 2H), 1.95 (s, 3H), 1.91 (d, $J$ = 6.8 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 100 MHz) $\delta$ 141.2, 128.53, 128.46, 126.2, 73.5, 59.7, 41.6, 32.1, 31.1, 23.0.

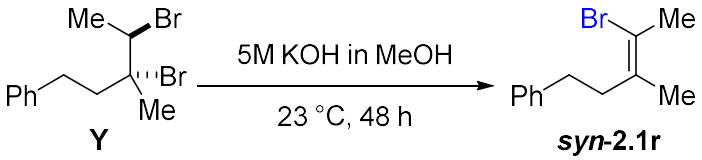
**IR** ($cm^{-1}$, neat) 3024, 2955, 2932, 1601, 1497, 1450, 698 (C–Br).

**LRMS** (GC-EI): Found *m/z* 159.09; Calcd for $C_{12}H_{15}$ [M-$HBr_2$] 159.12;

**ESIHRMS**: Found *m/z* 160.1247; Calcd for $C_{12}H_{16}$ [M-$Br_2$]$^{+}$ 160.1252.

**Procedures for E2 elimination:**

**Synthesis of (*Z*)-(4-bromo-3-methylpent-3-en-1-yl)benzene (*syn*-2.1r)**




To a round-bottom flask containing dibromide **Y** (1.21 g, 3.78 mmol) was added 5 M KOH solution in MeOH (9.0 mL, 46.3 mmol) and the mixture was stirred for 48 h at 23 °C. The reaction mixture was concentrated under reduced pressure and then diluted with water. The organic materials were extracted with $Et_2O$ (3 x 15 mL) and the combined extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by flash column chromatography (silica gel, Hex) to give bromoalkene ***syn*-2.1r** in 99% yield (895 mg, 3.74 mmol) as colourless oil with >97% purity based on $^1$H NMR.

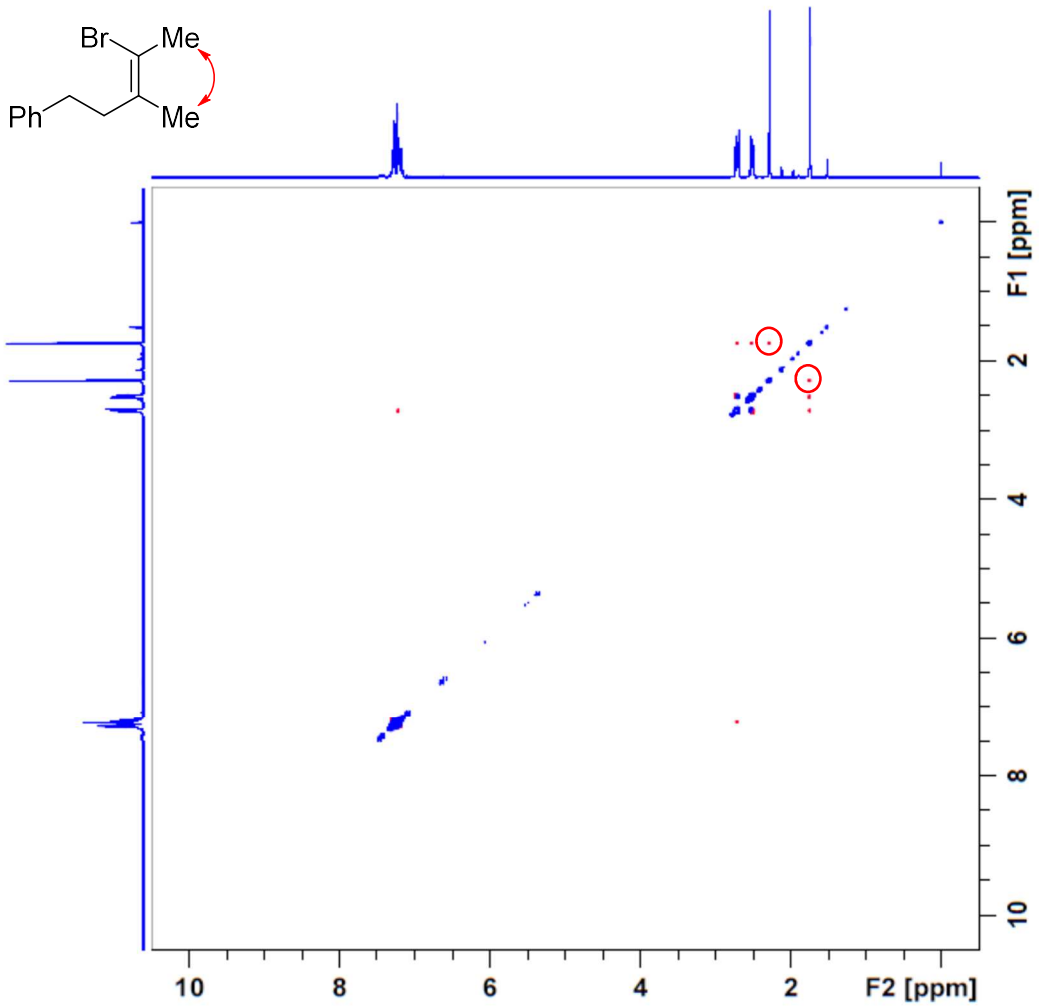
**$^1$H NMR** ($CDCl_3$, 400 MHz) $\delta$ 7.30–7.17 (m, 5H), 2.74–2.70 (m, 2H), 2.53–2.49 (m, 2H), 2.29 (s, 3H), 1.75 (d, $J$ = 0.8 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 100 MHz) $\delta$ 141.8, 133.1, 128.4, 128.3, 125.9, 116.1, 41.0, 33.4, 25.3, 18.7; **IR** ($cm^{-1}$, neat) 3063, 3024, 2920, 2859, 1655, 1600, 1493, 1454, 698 (C–Br).

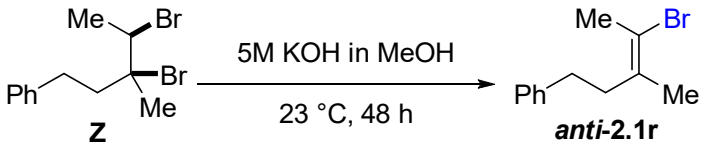
**LRMS** (GC-EI): Found *m/z* 159.09; Calcd for $C_{12}H_{15}$ [M-Br] 159.12.

**ESIHRMS**: Found *m/z* 160.1252; Calcd for $C_{12}H_{16}$ $[M\text{-}Br+H]^+$ 160.1252.

**NOESY of (*Z*)-(4-bromo-3-methylpent-3-en-1-yl)benzene (*syn*-2.1r)**




**Synthesis of (*E*)-(4-bromo-3-methylpent-3-en-1-yl)benzene (*anti*-2.1r)**




Dibromide **Z** (638 mg, 1.99 mmol) was treated with 5 M KOH solution in MeOH (4.8 mL, 23.9 mmol) under the same procedure to give bromoalkene ***anti*-2.1r** in 90% yield (430 mg, 1.80 mmol) as colourless oil.

**$^1$H NMR** ($CDCl_3$, 400 MHz) $\delta$ 7.28 (t, $J$ = 7.2 Hz, 2H), 7.21–7.14 (m, 3H), 2.70 (t, $J$ = 8.0 Hz, 2H), 2.41 (t, $J$ = 7.8 Hz, 2H), 2.12 (d, $J$ = 1.2 Hz, 3H), 1.89 (d, $J$ = 1.2 Hz, 3H).

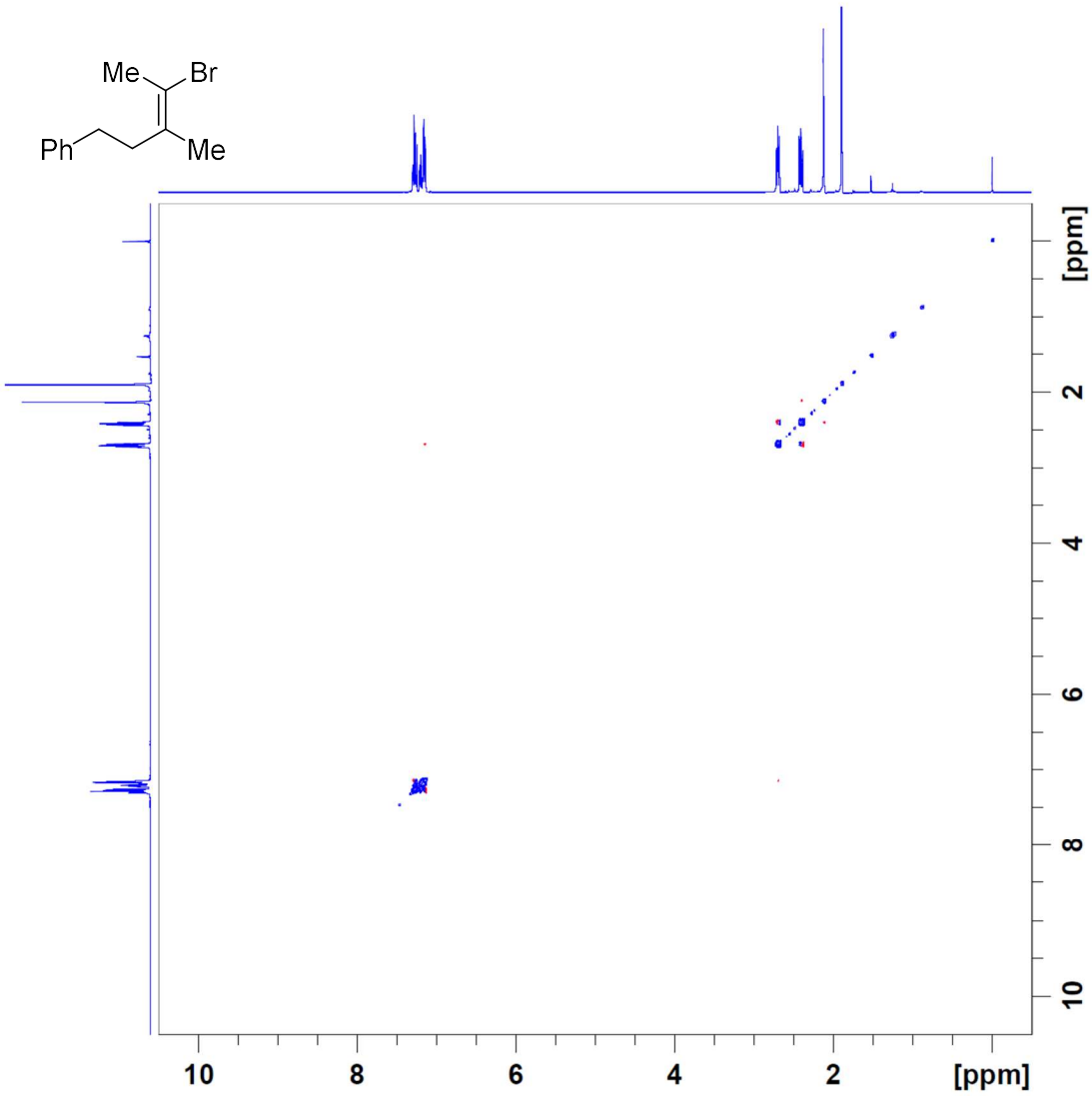
**$^{13}$C NMR** ($CDCl_3$, 100 MHz) $\delta$ 141.3, 133.0, 128.4 (2C, overlapped), 126.0, 117.5, 36.5, 34.1, 24.8, 23.4.

**IR** ($cm^{-1}$, neat) 3063, 3024, 2924, 2859, 1654, 1605, 1493, 1454, 698 (C–Br).

**GCMS** (EI): Found *m/z* 159.12; Calcd for $C_{12}H_{15}$ [M-Br] 159.12;

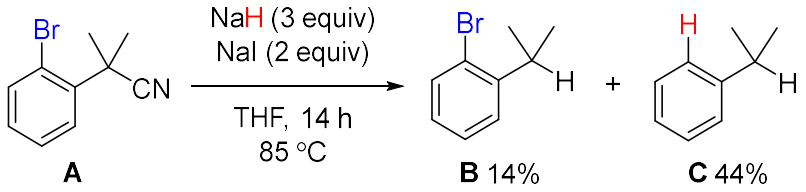
**ESIHRMS**: Found *m/z* 160.1254; Calcd for $C_{12}H_{16}$ $[M\text{-}Br+H]^+$ 160.1252.

**NOESY of (E)-(4-bromo-3-methylpent-3-en-1-yl)benzene (*anti*-2.1r)**



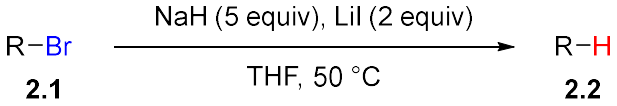
### 6.2.2. Hydrodehalogenation of bromoarenes

#### 6.2.2.1. Hydrodecyanation/debromination of A (Scheme 2.5)




To a mixture of NaH (60.3 mg, 1.51 mmol) and NaI (150 mg, 1.00 mmol) in 25 mL sealed tube was added a solution of nitrile **A** (113 mg, 0.506 mmol) in THF (2.5 mL) and stirred at 85 °C. With confirmation of full conversion of **A** based on TLC analysis, the reaction mixture was cooled to 0 °C and quenched with cold water. The organic materials were extracted with $Et_2O$ (3 x 10 mL) and the combined extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was then analysed by $^1H$ NMR with 1,1,2,2-tetrachloroethane as internal standard to give 14% crude NMR yield of **B** and 44% crude NMR yield of **C,** which might be partially lost during evaporation (boiling point of **C** = 152–153 °C at 760 Torr).[2]

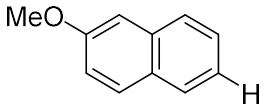
#### 6.2.2.2. Hydrodebromination of bromoarenes




To a mixture of NaH (100 mg, 2.50 mmol) and LiI (134 mg, 1.00 mmol) in 25 mL sealed tube was added a solution of bromoarene **2.1** (0.50 mmol) in THF (2.5 mL). The reaction mixture was stirred at 50 °C and monitored by GCMS or LCMS until full consumption of **2.1**. The reaction mixture was then cooled to 0 °C and quenched with cold water. The organic materials were extracted with $Et_2O$ (3 x 10 mL) and the combined extracts was washed with brine, dried over $MgSO_4$ and concentrated under

reduced pressure. The resulting crude material was purified by flash column chromatography (silica gel) to give the hydrodehalogenated product **2.2**.

#### 6.2.2.2.1. Synthesis of 2-methoxynaphthalene (2.2a) [CAS: 93-04-9]




Prepared from **2.1a** (119 mg, 0.502 mmol) for 7 h or **2.1a'** (142 mg, 0.500 mmol) with NaI instead of LiI for 10 h at 30 °C.

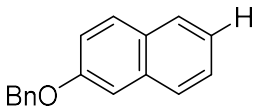
Purification: Hex:EtOAc = 97:3

Yield: 81% yield (64.0 mg, 0.405 mmol) from **2.1a** or 75% yield (59.2 mg, 0.374 mmol) from iodide **2.1a'** as white solid.

**$^1$H NMR** ($CDCl_3$, 400 MHz) $\delta$ 7.77–7.72 (m, 3H), 7.44 (dd, $J$ = 7.8, 7.8 Hz, 1H), 7.33 (dd, $J$ = 7.8, 7.8 Hz, 1H), 7.16–7.13 (m, 2H), 3.92 (s, 3H).

**$^{13}$C NMR** ($CDCl_3$, 100 MHz) $\delta$ 157.6, 134.6, 129.4, 128.9, 127.6, 126.7, 126.3, 123.6, 118.7, 105.7, 55.2.

#### 6.2.2.2.2. Synthesis of 2-(benzyloxy)naphthalene (2.2b) [CAS: 613-62-7]




Prepared from **2.1b** (157 mg, 0.501 mmol) for 8 h.

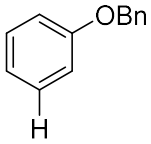
Purification: Hex:EtOAc = 97:3

Yield: 79% yield (92.4 mg, 0.394 mmol) as off-white solid.

**$^1$H NMR** ($CDCl_3$, 400 MHz) $\delta$ 7.77–7.71 (m, 3H), 7.48 (d, $J$ = 7.2 Hz, 2H), 7.44–7.38 (m, 3H), 7.35–7.31 (m, 2H), 7.24–7.22 (m, 2H), 5.17 (s, 2H).

**$^{13}$C NMR** ($CDCl_3$, 100 MHz) $\delta$ 156.7, 136.9, 134.5, 129.4, 129.0, 128.6, 128.0, 127.6, 127.5, 126.8, 126.3, 123.7, 119.0, 107.1, 70.0.

#### 6.2.2.2.3. Synthesis of benzyl phenyl ether (2.2c) [CAS: 946-80-5]




Prepared from **2.1c** (132 mg, 0.502 mmol) for 11 h.

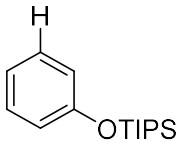
Purification: Hex:EtOAc = 99:1

Yield: 81% yield (75.3 mg, 0.409 mmol) as white solid.

**$^{1}$H NMR** ($CDCl_3$, 400 MHz) $\delta$ 7.44–7.42 (m, 2H), 7.37 (t, $J$ = 7.2 Hz, 2H), 7.33–7.26 (m, 3H), 6.98–6.93 (m, 3H), 5.05 (s, 2H).

**$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 158.8, 137.0, 129.4, 128.5, 127.9, 127.4, 120.9, 114.8, 69.8.

#### 6.2.2.2.4. Synthesis of triisopropyl(phenoxy)silane (2.2d) [CAS: 1529-17-5]




Prepared from **2.1d** (165 mg, 0.501 mmol) for 9 h.

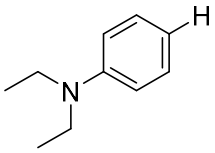
Purification: Hex

Yield: 60% yield (75.0 mg, 0.299 mmol) as colourless oil.

**$^{1}$H NMR** ($CDCl_3$, 400 MHz) $\delta$ 7.21 (t, $J$ = 8.0 Hz, 2H), 6.94–6.87 (m, 3H), 1.30–1.20 (m, 3H), 1.10 (d, $J$ = 7.2 Hz, 18H).

**$^{13}$C NMR** ($CDCl_3$, 100 MHz) $\delta$ 156.0, 129.3, 121.0, 119.9, 17.9, 12.7.

**6.2.2.2.5. Synthesis of *N*,*N*-diethylaniline (2.2e) [CAS: 91-66-7]**



Prepared from **2.1e** (114 mg, 0.500 mmol) for 12 h.

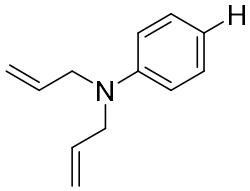
Purification: Hex:EtOAc = 99:1

Yield: 82% yield (61.4 mg, 0.411 mmol) as yellow oil.

**$^{1}$H NMR** ($CDCl_3$, 400 MHz) $\delta$ 7.20 (t, $J$ = 7.8 Hz, 2H), 6.68, (d, $J$ = 8.4 Hz, 2H), 6.63 (t, $J$ = 7.2 Hz, 1H), 3.34 (q, $J$ = 7.2 Hz, 4H), 1.15 (t, $J$ = 7.2 Hz, 6H).

**$^{13}$C NMR** ($CDCl_3$, 100 MHz) $\delta$ 147.8, 129.2, 115.3, 111.8, 44.3, 12.5.

**6.2.2.2.6. Synthesis of *N*,*N*-diallylaniline (2.2f) [CAS: 6247-00-3]**



Prepared from **2.1f** (126 mg, 0.500 mmol) for 12 h.

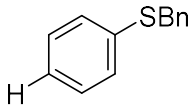
Purification: Hex:EtOAc = 99:1

Yield: 86% yield (74.8 mg, 0.430 mmol) as pale yellow oil.

**$^{1}$H NMR** ($CDCl_3$, 400 MHz) $\delta$ 7.19 (t, $J$ = 8.0 Hz, 2H), 6.71–6.66 (m, 3H), 5.90–5.81 (m, 2H), 5.20–5.13 (m, 4H), 3.92–3.91 (m, 4H).

**$^{13}$C NMR** ($CDCl_3$, 100 MHz) $\delta$ 148.8, 134.1, 129.1, 116.4, 116.0, 112.4, 52.8.

**6.2.2.2.7. Synthesis of benzyl(phenyl)sulfane (2.2g) [CAS: 831-91-4]**



Prepared from **2.1g** (140 mg, 0.501 mmol) for 8 h.

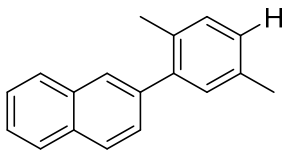
Purification: *n*-Hex

Yield: 83% yield (83.8 mg, 0.418 mmol) as off-white solid.

**$^1$H NMR** ($CDCl_3$, 400 MHz) $\delta$ 7.32–7.22 (m, 9H), 7.20–7.10 (m, 1H), 4.11 (s, 2H).

**$^{13}$C NMR** ($CDCl_3$, 100 MHz) $\delta$ 137.4, 136.3, 129.8, 128.8 (2C, overlapped), 128.4, 127.1, 126.3, 39.0.

### 6.2.2.2.8. Synthesis of 2-(2,5-dimethylphenyl)naphthalene (2.2h) [CAS: 54753-92-3]




Prepared from **2.1h** (153 mg, 0.501 mmol) for 14 h.

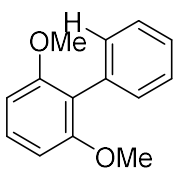
Purification: *n*-Hex

Yield: 95% yield (110.9 mg, 0.477 mmol) as white solid.

**$^1$H NMR** ($CDCl_3$, 400 MHz) $\delta$ 7.88–7.84 (m, 3H), 7.76 (s, 1H), 7.52–7.45 (m, 3H), 7.20 (d, $J$ = 7.6 Hz, 1H), 7.15 (s, 1H), 7.11 (d, $J$ = 7.6 Hz, 1H), 2.37 (s, 3H), 2.27 (s, 3H).

**$^{13}$C NMR** ($CDCl_3$, 100 MHz) $\delta$ 141.7, 139.7, 135.2, 133.3, 132.4, 132.2, 130.7, 130.3, 128.1, 128.0, 127.8, 127.7, 127.6, 127.4, 126.1, 125.8, 20.9, 20.0.

### 6.2.2.2.9. Synthesis of 2,6-dimethoxy-1,1'-biphenyl (2.2i) [CAS: 13732-86-0]




Prepared from **2.1i** (147 mg, 0.501 mmol) for 10 h.

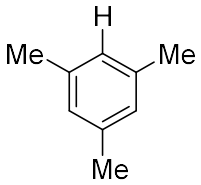
Purification: Hex:EtOAc = 97:3

Yield: 90% yield (96.4 mg, 0.450 mmol) as white solid.

**$^{1}$H NMR** ($CDCl_3$, 400 MHz) $\delta$ 7.42–7.38 (m, 2H), 7.35–7.30 (m, 3H), 7.28–7.24 (m, 1H), 6.65 (d, $J$ = 8.4 Hz, 2H), 3.72 (s, 6H)

**$^{13}$C NMR** ($CDCl_3$, 100 MHz) $\delta$ 157.6, 134.1, 130.8, 128.6, 127.6, 126.7, 119.5, 104.2, 55.8.

### 6.2.2.2.10. Synthesis of mesitylene (2.2j) [CAS: 108-67-8]

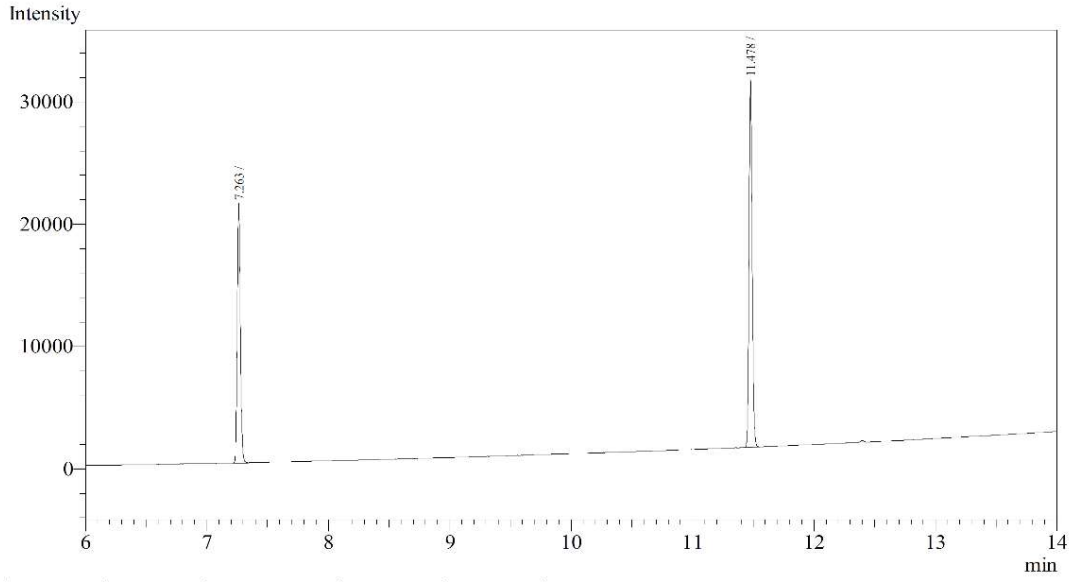



Prepared from **2.1j** (100 mg, 0.502 mmol) for 18 h.

Yield: GC analysis with dodecane as an internal standard to give 98% yield of **2.2j**.

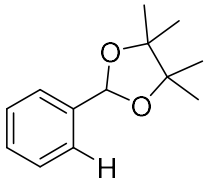
Retention time of mesitylene, **2.2j** = 7.26 min.

Retention time of dodecane = 11.48 min.




| Peak# | Ret.Time | Area | Area% | Height |
|---|---|---|---|---|
| 1 | 7.263 | 37556 | 41.2544 | 20928 |
| 2 | 11.478 | 53478 | 58.7456 | 29801 |
| Total | | 91034 | 100.0000 | 50729 |

**6.2.2.2.11. Synthesis of 4,4,5,5-tetramethyl-2-phenyl-1,3-dioxolane (2.2k) [CAS: 1831-57-8]**



Prepared from **2.1k** (143 mg, 0.501 mmol) for 5 h.

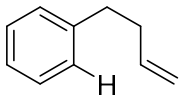
Purification: Hex:EtOAc = 99:1

Yield: 64% yield (66.0 mg, 0.320 mmol) as white solid.

**$^{1}$H NMR** ($CDCl_3$, 400 MHz) $\delta$ 7.49 (d, $J$ = 6.8 Hz, 2H), 7.38–7.31 (m, 3H), 5.98 (s, 1H), 1.33 (s, 6H), 1.27 (s, 6H).

**$^{13}$C NMR** ($CDCl_3$, 100 MHz) $\delta$ 139.7, 128.6, 128.2, 126.2, 99.9, 82.6, 24.3, 22.2.

**6.2.2.2.12. Synthesis of but-3-en-1-ylbenzene (2.2l) [CAS: 768-56-9]**



Prepared from **2.1l** (106 mg, 0.502 mmol) for 13 h. The crude mixture was then analysed by $^{1}$H NMR to give 73% crude NMR yield using 1,1,2,2-tetrachloroethane as an internal standard.

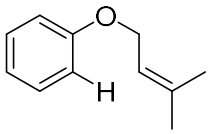
Purification: Hex

Yield: 49% yield (32.7 mg, 0.246 mmol) as colourless oil, which might be partially lost during evaporation (boiling point = 178–179 °C at 760 Torr).[3]

**$^{1}$H NMR** ($CDCl_3$, 400 MHz) $\delta$ 7.30–7.26 (m, 2H), 7.19–7.16 (m, 3H), 5.91–5.81 (m, 1H), 5.04 (dd, $J$ = 17.2, 2.0 Hz, 1H), 4.97 (dd, $J$ = 10.4, 1.2 Hz, 1H), 2.71 (t, $J$ = 7.8 Hz, 2H), 2.40–2.34 (m, 2H).

**$^{13}$C NMR** ($CDCl_3$, 100 MHz) $\delta$ 141.8, 138.1, 128.4, 128.3, 125.8, 114.9, 35.5, 35.4.

**6.2.2.2.13. Synthesis of ((3-methylbut-2-en-1-yl)oxy)benzene (2.2m) [CAS: 14309-15-0]**



Prepared from **2.1m** (121 mg, 0.502 mmol) for 5 h.

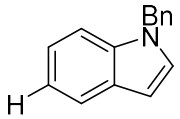
Purification: Hex:EtOAc = 97:3

Yield: 75% yield (61.0 mg, 0.376 mmol) as colourless oil.

**$^{1}$H NMR** ($CDCl_3$, 400 MHz) $\delta$ 7.28 (t, $J$ = 8.5 Hz, 2H), 6.95–6.91 (m, 3H), 5.50 (t, $J$ = 6.8 Hz, 1H), 4.51 (d, $J$ = 6.7 Hz, 2H), 1.80 (s, 3H), 1.74 (s, 3H).

**$^{13}$C NMR** ($CDCl_3$, 100 MHz) $\delta$ 158.8, 138.0, 129.4, 120.5, 119.8, 114.6, 64.6, 25.8, 18.1.

**6.2.2.2.13. Synthesis of 1-benzyl-1*H*-indole (2.2n) [CAS: 3377-71-7]**



Prepared from **2.1n** (143 mg, 0.500 mmol) for 16 h.

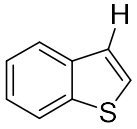
Purification: Hex

Yield: **5n** in 96% yield (100 mg, 0.483 mmol) as pale yellow solid.

**$^{1}$H NMR** ($CDCl_3$, 400 MHz) $\delta$ 7.65 (d, $J$ = 7.6 Hz, 1H), 7.28–7.23 (m, 4H), 7.16 (t, $J$ = 7.0 Hz, 1H), 7.12–7.09 (m, 4H), 6.55 (d, $J$ = 2.8 Hz, 1H), 5.32 (s, 2H).

**$^{13}$C NMR** ($CDCl_3$, 100 MHz) $\delta$ 137.5, 136.3, 128.7 (2C, overlapped), 128.2, 127.5, 126.7, 121.6, 120.9, 119.5, 109.6, 101.6, 50.0.

#### 6.2.2.2.14. Synthesis of benzo[*b*]thiophene (2.2o) [CAS: 95-15-8]



Prepared from **2.1o** (112 mg, 0.500 mmol) for 8 h.

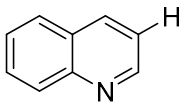
Purification: Hex

Yield: 83% yield (56.0 mg, 0.417 mmol) as white solid.

**$^1$H NMR** ($CDCl_3$, 400 MHz) $\delta$ 7.86 (dd, $J$ = 7.2, 0.4 Hz, 1H), 7.80 (dd, $J$ = 6.8, 2.0 Hz, 1H), 7.40 (d, $J$ = 5.6 Hz, 1H), 7.36–7.30 (m, 3H).

**$^{13}$C NMR** ($CDCl_3$, 100 MHz) $\delta$ 139.8, 139.6, 126.3, 124.24, 124.19, 123.9, 123.6, 122.5.

#### 6.2.2.2.15. Synthesis of quinoline (2.2p) [CAS: 91-22-5]



Prepared from **2.1p** (104 mg, 0.500 mmol) for 12 h.

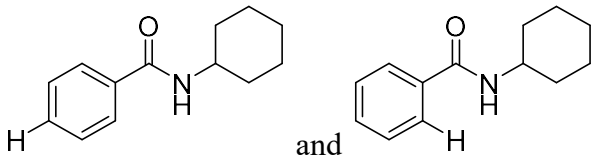
Purification: Hex:EtOAc = 9:1

Yield: 53% yield (34.7 mg, 0.267 mmol) as yellow oil.

**$^1$H NMR** ($CDCl_3$, 400 MHz) $\delta$ 8.91 (dd, $J$ = 4.0, 1.4 Hz, 1H), 8.16 (d, $J$ = 8.0 Hz, 1H), 8.12 (d, $J$ = 8.4 Hz, 1H), 7.82 (d, $J$ = 8.4 Hz, 1H), 7.72 (td, $J$ = 7.6, 2.2 Hz, 1H), 7.55 (t, $J$ = 7.3 Hz, 1H), 7.40 (dd, $J$ = 8.2, 3.8 Hz, 1H).

**$^{13}$C NMR** ($CDCl_3$, 100 MHz) $\delta$ 150.4, 148.2, 136.1, 129.5, 129.4, 128.3, 127.8, 126.6, 121.1.

### 6.2.2.2.16. Synthesis of *N*-cyclohexylbenzamide (2.2q) [CAS: 1759-68-8]



Prepared from ***para*-2.1q** (141 mg, 0.500 mmol) for 13 h or ***ortho*-2.1q** (141 mg, 0.500 mmol) for 23 h.

Purification: Hex:EtOAc = 85:15

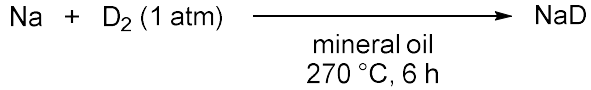
Yield: 91% yield (92.2 mg, 0.454 mmol) from ***para*-2.1q** or 95% yield (97.0 mg, 0.477 mmol) from ***ortho*-2.1q**.

**$^1$H NMR** ($CDCl_3$, 400 MHz) $\delta$ 7.75 (d, $J$ = 7.4 Hz, 2H), 7.48 (t, $J$ = 7.6 Hz, 1H), 7.42 (t, $J$ = 7.4 Hz, 2H), 5.99 (brs, 1H), 4.03–3.94 (m, 1H), 2.05–2.01 (m, 2H), 1.78–1.73 (m, 2H), 1.69–1.63 (m, 1H), 1.48–1.38 (m, 2H), 1.29–1.15 (m, 3H).

**$^{13}$C NMR** ($CDCl_3$, 100 MHz) $\delta$166.6, 135.0, 131.0, 128.3, 126.8, 48.6, 33.0, 25.4, 24.8.

## 6.2.3. Deuterium labeling experiments

### 6.2.3.1. Synthesis of NaD from metallic sodium and deuterium gas




To a 100 mL sealed tube was added sodium pieces (1.63 g, 70.9 mmol) under an Ar atmosphere. Mineral oil (3.5 mL) was then added and the reaction vessel was evacuated and backfilled with argon (three times). The reaction vessel was then heated to 270 °C for 2 h. The reaction vessel was subsequently evacuated and backfilled with deuterium gas (twice). The reaction mixture was stirred for 6 h at the same temperature ($D_2$ gas balloon was refilled every 3 hours). The reaction mixture was then cooled to room temperature, evacuated, and transferred to the glove box. The solid materials were filtered, washed with pentane (7 x 5 mL) and THF (5 x 5 mL). Subsequently, the solid

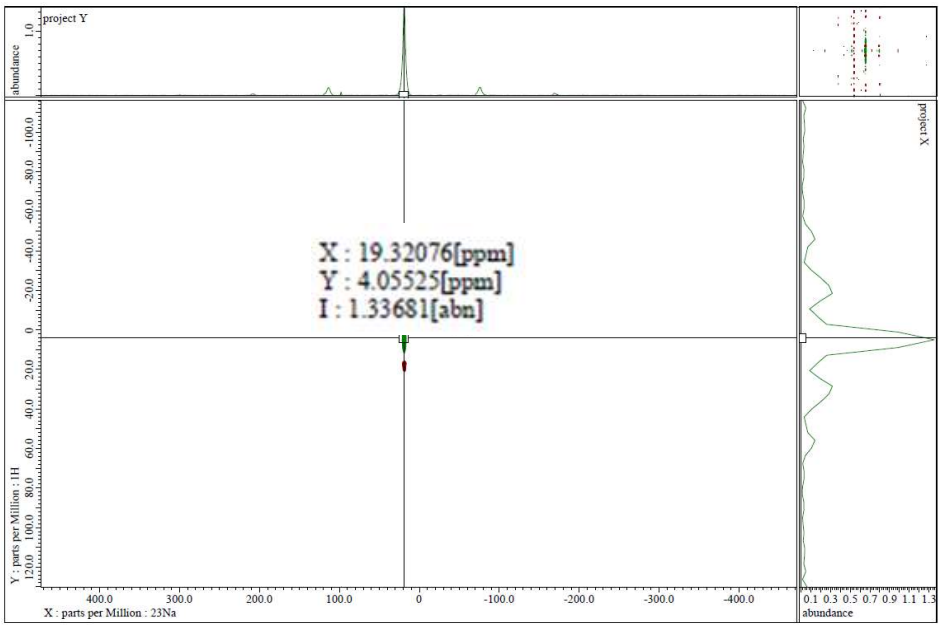
was suspended in 1,4-dioxane to separate the unreacted metallic sodium to give an 84% yield of NaD containing around 9% of metallic Na (1.50 g, 59.9 mmol) as grey solid.

### 6.2.3.2. Characterisation of NaD

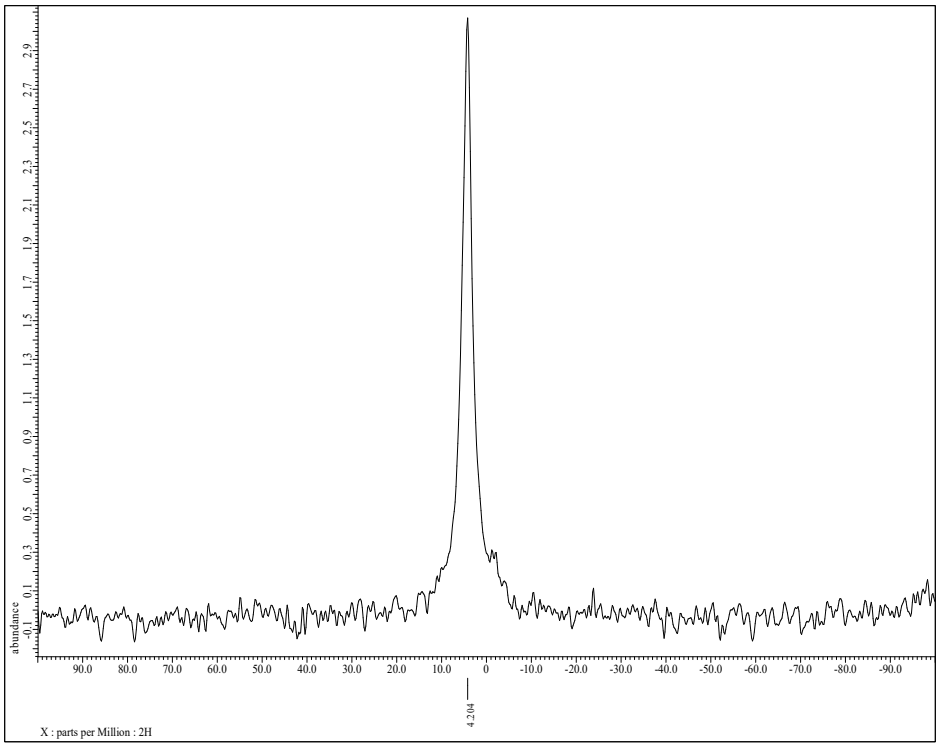
#### 6.2.3.2.1. Solid state NMR measurement

We conducted solid state $^{23}Na$ and $^{2}H$ measurement on NaD (and NaH as the reference). The peak positions will be very sensitive to local environments and thus, if two samples show NMR spectra with the peaks at the same positions, it could be safely concluded that the local structures around the observed nuclei are very similar to each other.

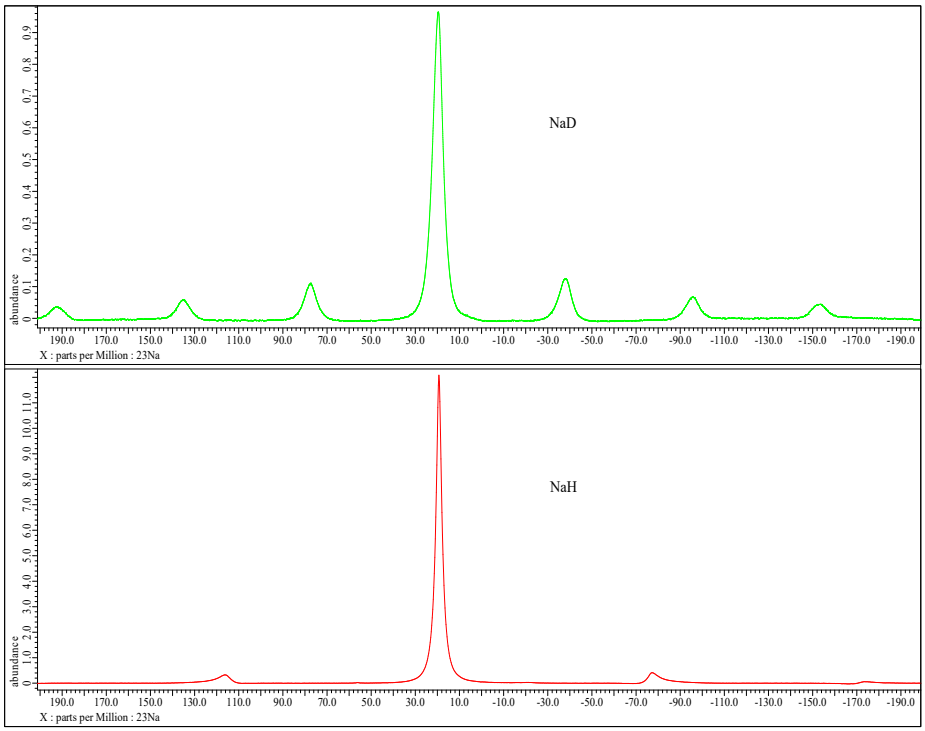
#### 6.2.3.2.2. $^{1}H/^{23}Na$ Hetcor of NaH



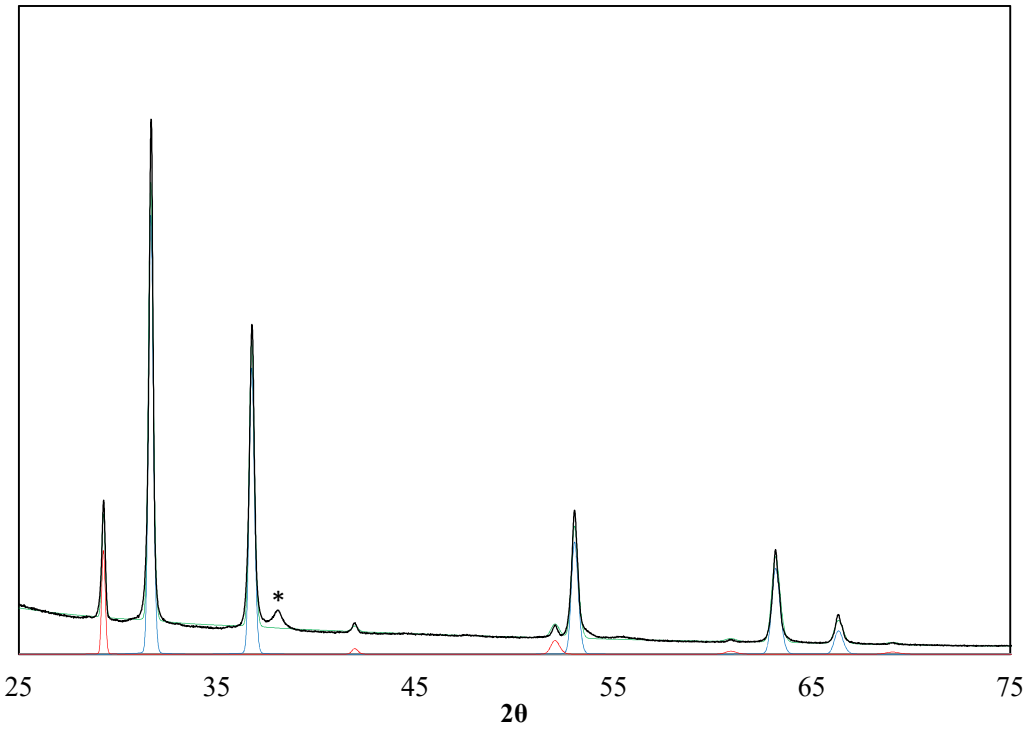
### 6.2.3.2.3. Solid state $^{2}H$ NMR spectrum of NaD




### 6.2.3.2.4. Overlay of $^{23}Na$ Spectrum of NaD and NaH



### 6.2.3.2.5. Powder XRD data of NaD



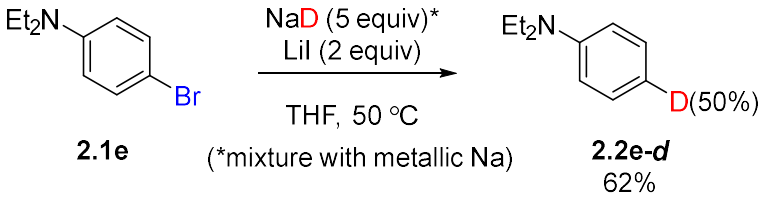

Powder X-ray diffraction data for freshly prepared NaD sample (black). The Rietveld refinement (green) is overlaid with the independently collected data for the components NaD (blue) and metallic Na (red). The peak at 2θ = 38.1° (marked with *) corresponds to NaOH (a trace amount).

**6.2.3.2.6. Rietveld refinement[4-5] results of the powder X-ray diffraction data for the NaD and Na samples.**

| | Atom | Site | x | y | z | Occupancy | $B_{eq.}$ |
|---|---|---|---|---|---|---|---|
| **NaD + Na** | | | | | | | |
| $R_{wp}$: 10.4 | | | | | | | |
| GOF: 7.41 | | | | | | | |
| **NaD** | Na | 4a | 0 | 0 | 0 | 1 | 1 |
| Fm-3m (No. 225) | | | | | | | |
| a: 4.8688(6) | | | | | | | |
| $R_B$: 3.00 | D | 4b | 0.5 | 0.5 | 0.5 | 1 | 1 |
| wt: 91.5% | | | | | | | |
| **Na** | Na | 2a | 0 | 0 | 0 | 1 | 1 |
| Im-3m (No. 229) | | | | | | | |
| a: 4.2904(1) | | | | | | | |
| $R_B$: 6.35 | | | | | | | |
| wt: 8.5% | | | | | | | |

The slightly larger $R_{wp}$ and GOF values could be due to the presence of amorphous NaOH in the sample.

**6.2.3.3. Hydrodehalogenation of 4-bromo-*N*,*N*-diethylaniline (2.1e) by the NaD-LiI composite (Scheme 2.10)**




To a mixture of NaD containing ca. 9% of metallic Na (66.0 mg, 2.64 mmol) and LiI (134 mg, 1.00 mmol) in 25 mL sealed tube was added a solution of 4-bromo-*N*,*N*-diethylaniline **2.1e** (114 mg, 0.500 mmol). The reaction vessel was stirred at 50 °C and the progress was monitored by GCMS until full conversion of **2.1e** (10 h). The reaction mixture was then cooled to 0 °C and quenched with cold water. The organic materials

were extracted with $Et_2O$ (3 x 10 mL) and the combined extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting crude material was purified by flash column chromatography (silica gel, *n*-Hex:EtOAc = 99:1) to give **2.2e** as pale yellow oil in 62% yield (46.5 mg, 0.313 mmol) with 50% deuterium incorporation.

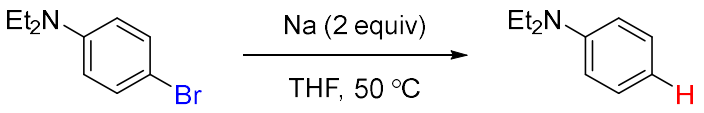
**$^1$H NMR** ($CDCl_3$, 400 MHz) $\delta$ 7.22–7.18 (m, 2H), 6.67 (d, $J$ = 8.4 Hz, 2H), 6.63 (t, $J$ = 7.2 Hz, 0.5H), 3.34 (q, $J$ = 7.0 Hz, 4H), 1.15 (t, $J$ = 7.0 Hz, 6H);

**$^{13}$C NMR** ($CDCl_3$, 100 MHz) $\delta$ 147.8, 129.2, 129.1 (*ortho*-carbon with respect to deutrated carbon), 115.3, 111.8, 44.3, 12.5.

**GCMS** (EI) *m/z* 149.08 [M] for **2.2e**, 150.11 [M] for **2.2e-D**.

### 6.2.3.4. Hydrodehalogenation of 4-bromo-*N*,*N*-diethylaniline 2.1e by metallic sodium (Scheme 2.11)

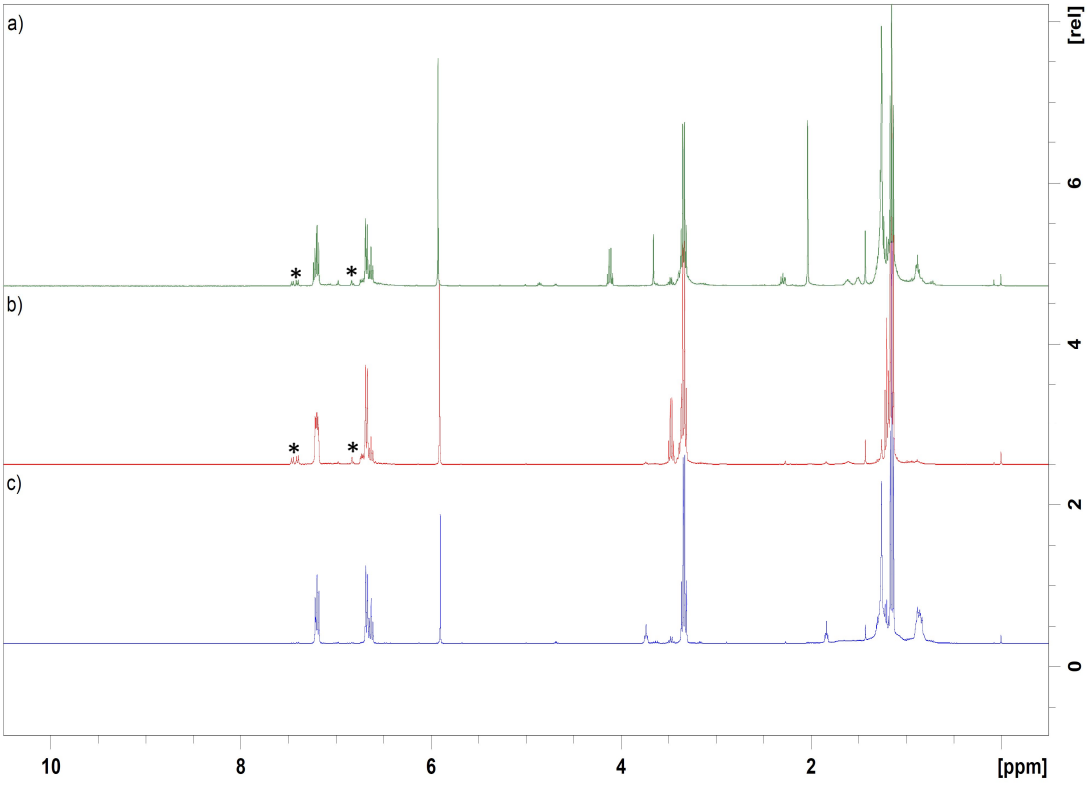
The deuterium incorporation was 50% (another 50% is hydrogen incorporation) most likely because the prepared NaD sample contained small amount of metallic sodium (ca. 9%) as confirmed by powder XRD. The metallic sodium competes to perform hydrodehalogenation of **2.1e** in single-electron-transfer mechanism, and thus hydrogen source could be either THF (via H-radical abstraction) or quenching $H_2O$ (via protonation of the resulting aryl anion). To confirm this competition reaction, we examined the reaction of **2.1e** with metallic sodium below, that actually demonstrated that metallic sodium also performs hydrodehalogenation.




**2.1e** **2.2e** 46%

To a 25 mL sealed tube containing metallic sodium (18 mg, 0.783 mmol) was added solution of 4-bromo-*N*,*N*-diethylaniline **2.1e** (89 mg, 0.391 mmol) in THF (2 mL). The reaction was stirred at 50 °C and the progress was monitored by GCMS until full consumption of **2.1e** (2 h). The reaction mixture was then cooled to 0 °C and quenched with methanol before the volatile materials were removed under reduced pressure. The resulting residue was diluted with water and extracted with $Et_2O$ (3 x 10 mL). The combined extracts were then washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting crude material was purified by flash column chromatography (silica gel, *n*-Hex:EtOAc = 99:1) to give *N*,*N*-diethylaniline **2.2e** in 46% yield (27 mg, 0.181 mmol) as pale yellow oil.

### 6.2.3.5. Crude $^{1}$H spectra overlay of debromination of 2.1e with a) metallic sodium, b) NaD + LiI and c) NaH + LiI.

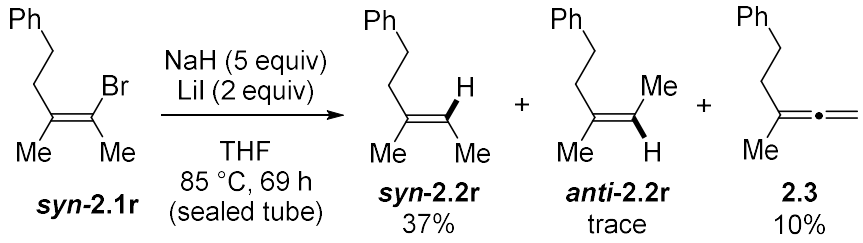



*Side products observed when metallic sodium was used or present for hydrodebromination.

During hydrodebromination of **2.1e** with metallic Na, side products were observed in the crude $^{1}$H NMR (6.2.3.5a). These side products (marked with *) were also observed with those formed during hydrodebromination of substrate **2.1e** with our prepared NaD (6.2.3.5b). However, such side products were not detected in the crude mixture of the reaction conducted with NaH (6.2.3.5c). These observations also provided a solid proof that our prepared NaD contains metallic Na.

### 6.2.4. Hydrodebromination of bromoalkenes 2.1r (Scheme 2.12)

#### 6.2.4.1. Hydrodebromination of *syn*-2.1r (Scheme 2.12b)




Hydrodebromination of ***syn*-2.1r** (160 mg, 0.500 mmol) was conducted following the general procedure at 85 °C. Purification by flash column chromatography (silica gel, *n*-Hex) gave inseparable mixture of ***syn*-2.2r** and **2.3** (37.9 mg) in 37% and 10% yield, respectively. The yields were calculated based on $^{1}$H NMR analysis of the mixture.

**(*E*)-(3-methylpent-3-en-1-yl)benzene (*syn*-2.2r)**:

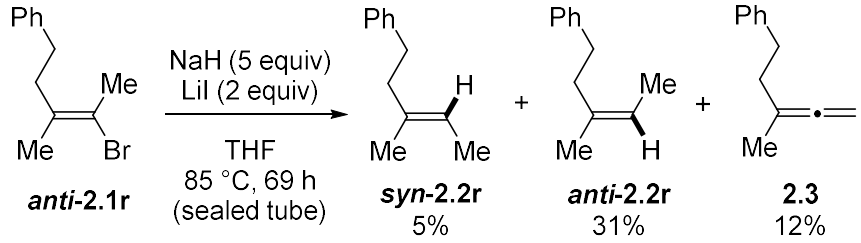
**$^{1}$H NMR** ($CDCl_3$, 400 MHz) $\delta$ 7.28–7.24 (m, 2H), 7.20–7.16 (m, 3H), 5.22 (q, $J$ = 6.7 Hz, 1H), 2.71–2.67 (m, 2H), 2.29–2.25 (m, 2H), 1.65 (s, 3H), 1.57 (d, $J$ = 6.6 Hz, 3H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz) $\delta$ 142.5, 135.3, 128.3, 128.2, 125.6, 118.8, 41.6, 34.8, 15.8, 13.3; **ESIHRMS**: Found *m/z* 161.1327; Calcd for $C_{12}H_{17}$ $[M+H]^+$ 161.1330.

**(3-methylpenta-3,4-dien-1-yl)benzene (2.3):**

**$^{1}$H NMR** ($CDCl_3$, 400 MHz) $\delta$ 7.28–7.24 (m, 2H), 7.20–7.16 (m, 3H), 4.61 (sext, $J$ = 3.1 Hz, 2H), 2.75–2.71 (m, 2H), 2.25–2.20 (m, 2H), 1.71 (t, $J$ = 3.0 Hz, 3H);

**$^{13}$C NMR** ($CDCl_3$, 100 MHz) $\delta$206.2, 142.2, 128.4, 128.2, 125.7, 98.1, 74.6, 35.2, 33.9, 18.9; **ESIHRMS**: Found *m/z* 159.1179; Calcd for $C_{12}H_{15}$ $[M+H]^+$ 159.1174.

### 6.2.4.2. Hydrodehalogenation of *anti*-2.1r (Scheme 2.12b)




Hydrodebromination of ***anti*-2.1r** (160 mg, 0.500 mmol) was conducted following the general procedure at 85 °C. Purification by flash column chromatography (silica gel, *n*-Hex) gave inseparable mixture of ***syn*-2.2r**, ***anti*-2.2r** and **2.3** (38.1 mg) in 5%, 31%, and 12% yield, respectively.

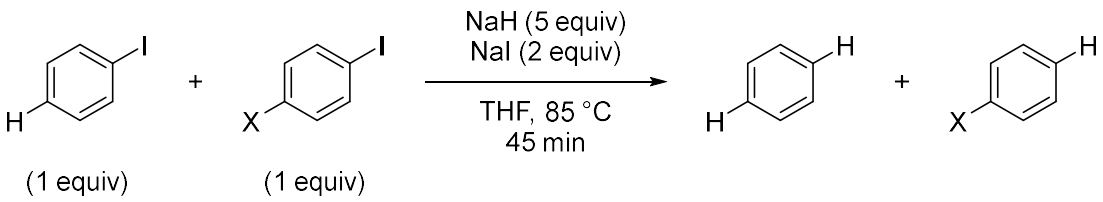
**(*Z*)-(3-methylpent-3-en-1-yl)benzene (*anti*-2.2r):**

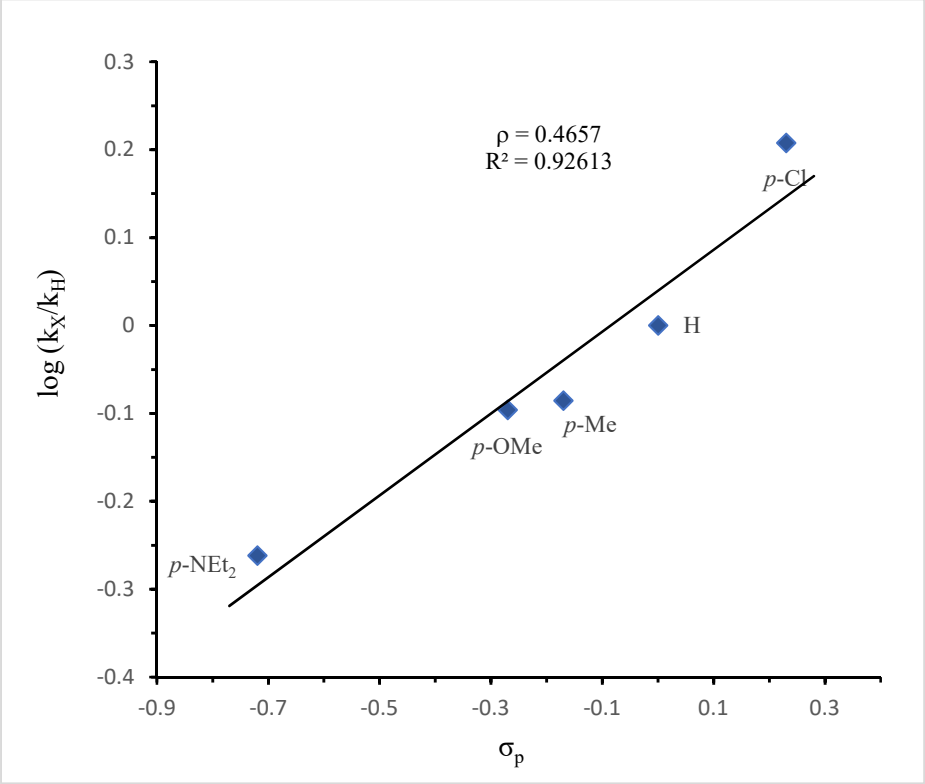
**$^{1}$H NMR** ($CDCl_3$, 400 MHz) $\delta$ 7.28–7.25 (m, 2H), 7.20–7.15 (m, 3H), 5.22 (q, $J$ = 6.7 Hz, 1H), 2.67 (t, $J$ = 7.7 Hz, 2H), 2.32 (t, $J$ = 8.4 Hz, 2H), 1.71 (s, 3H), 1.47 (d, $J$ = 7.0 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 100 MHz) $\delta$ 142.4, 135.2, 128.23, 128.21, 125.7, 119.6, 34.1, 33.6, 23.4, 13.1.

**ESIHRMS**: Found *m/z* 161.1334; Calcd for $C_{12}H_{17}$ $[M+H]^+$ 161.1330.

### 6.2.5. Linear free-energy correlation of log($k_X/k_H$) against $\sigma_p$ plot [a]






| Entry | X-Substituent | $\sigma_p$ | $\log(k_X/k_H)$[b] |
|---|---|---|---|
| 1 | $NEt_2$ | -0.72 | -0.262 |
| 2 | OMe | -0.27 | -0.096 |
| 3 | Me | -0.17 | -0.085 |
| 4 | H | 0 | 0 |
| 5 | Cl[c] | 0.23 | 0.2078 |

[a] The reactions were carried out at 0.5 mmol scale in 25 mL sealed tube at 85 °C for 45 min with NaH:NaI:ArH:ArX = 5:2:1:1. [b] Measurement at 45 min time based on GC analysis with mesitylene as an internal standard. [c] Full conversion was observed to form chlorobenzene as a sole product, that proves chemoselectivity of the present method toward hydrodebromination and -deiodination.

The Hammett correlation gave a moderate linearity and showed that there is no change of rate determining step in the reaction. The small $\rho$ value of 0.47 indicated that minimum charge is built up in the transition state, that supports our DFT calculation for concerted nucleophilic aromatic substitution. Typical mechanism of nucleophilic aromatic substitution includes a Meisenheimer complex as an intermediate. The reported $\rho$ values for this stepwise mechanism fall between 3.0 to 8.6.[6] This, in turn, disapprove addition elimination pathway since the $\rho$ value for the hydrodehalogenation reaction is much smaller to those reported for stepwise $S_NAr$.[7]

### 6.2.6. DFT calculation

#### 6.2.6.1. Computational method

All density functional theory (DFT) calculations were performed using Gaussian 09. Geometries of intermediates and transition states were optimized at the B3LYP/def2-TZVP level of theory.[8-11] Free energy correction values ($G_{corr}$) were obtained from harmonic frequency calculations. Single-point energy calculations were performed to evaluate the solvent effect of THF with a self-consistent reaction field (SCRF) method called IEFECM.[12] Dispersion energies for the optimized geometries were evaluated by the DFT-D3 method with Becke-Johnson (BJ) damping.[13-17] Free energy G was calculated as follows:

$$G = E(SCRF) + G_{corr} + E_{disp}$$

#### 6.2.6.2. Complete list of authors of Gaussian 09

Gaussian 09 (Revision B.01), M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng,

J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai,; T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, Gaussian Inc., Wallingford CT, **2010**.

### 6.2.6.3. Raw energy data

#### 6.2.6.3.1. Data for the reaction of PhBr (with 2 explicit THF molecules)

| | E(Gas) (a.u.) | E(SCRF) (a.u.) | ZPE (a.u.) | $G_{corr}$ (a.u.) | $E_{disp}$ (a.u.) | ΔG (kcal/mol) |
|---|---|---|---|---|---|---|
| **Int1-I** | -3433.911485 | -3433.936306 | 0.329601 | 0.267897 | -0.071191 | 0.0 |
| **TS-I** | -3433.879748 | -3433.899582 | 0.328679 | 0.266475 | -0.073196 | 20.9 |
| **Int2-I** | -3434.043632 | -3434.066552 | 0.337449 | 0.274095 | -0.073699 | -79.4 |

#### 6.2.6.3.2. Data for the reaction of 2-bromo-3-methyl-2-butene (with 2 explicit THF molecules)

| | E(gas) (a.u.) | E(SCRF) (a.u.) | ZPE (a.u.) | $G_{corr}$ (a.u.) | $E_{disp}$ (a.u.) | ΔG (kcal/mol) |
|---|---|---|---|---|---|---|
| **Int1-II** | -3398.195825 | -3398.21679 | 0.365423 | 0.301423 | -0.076107 | 0.0 |
| **TS-II** | -3398.169742 | -3398.18665 | 0.364815 | 0.302651 | -0.075491 | 20.1 |
| **Int2-II** | -3398.326479 | -3398.34854 | 0.372716 | 0.309376 | -0.074170 | -76.5 |
| **Int2b-II** | -3398.328024 | -3398.348084 | 0.373021 | 0.309546 | -0.076604 | -77.6 |

#### 6.2.6.3.3. Data for the reaction of PhBr (without explicit THF molecules)

| | E(gas) (a.u.) | E(SCRF) (a.u.) | ZPE (a.u.) | $G_{corr}$ (a.u.) | $E_{disp}$ (a.u.) | ΔG (kcal/mol) |
|---|---|---|---|---|---|---|
| **Int1-I** | -2968.790801 | -2968.829252 | 0.093674 | 0.053866 | -0.027794 | 0.0 |
| **TS-I** | -2968.756705 | -2968.790014 | 0.093605 | 0.058740 | -0.029986 | 26.3 |
| **Int2-I** | -2968.920437 | -2968.957058 | 0.102152 | 0.063198 | -0.025667 | -73.0 |

#### 6.2.6.3.4. Data for the reaction of 2-bromo-3-methyl-2-butene (without explicit THF molecules)

| | E(gas) (a.u.) | E(SCRF) (a.u.) | ZPE (a.u.) | $G_{corr}$ (a.u.) | $E_{disp}$ (a.u.) | ΔG (kcal/mol) |
|---|---|---|---|---|---|---|
| **Int1-II** | -2933.077466 | -2933.112629 | 0.129514 | 0.089342 | -0.029037 | 0.0 |
| **TS-II** | -2933.047972 | -2933.076798 | 0.129261 | 0.091599 | -0.031822 | 22.2 |
| **TSb-II** | -2933.037152 | -2933.064089 | 0.128572 | 0.090984 | -0.030810 | 30.4 |
| **Int2-II** | -2933.201504 | -2933.239048 | 0.137109 | 0.096535 | -0.026797 | -73.4 |
| **Int2b-II** | -2933.201479 | -2933.238996 | 0.137083 | 0.096217 | -0.026816 | -73.6 |

## 6.2.6.4. XYZ coordinates of optimized geometry (in Å)

With 2 THF molecules

===Int1-I with 2 THF molecules===

| | | | |
|---|---|---|---|
| C | 1.082980 | 1.280265 | -2.297450 |
| C | 1.537407 | 1.333127 | -3.607312 |
| C | 2.323498 | 2.413587 | -3.994036 |
| C | 2.640259 | 3.412558 | -3.079660 |
| C | 2.169912 | 3.330463 | -1.774203 |
| C | 1.381148 | 2.258355 | -1.364060 |
| H | 1.284878 | 0.552442 | -4.311461 |
| H | 2.685244 | 2.469279 | -5.013139 |
| H | 3.251874 | 4.251913 | -3.385740 |
| H | 2.410790 | 4.102637 | -1.054117 |
| H | 1.021851 | 2.203077 | -0.335662 |
| Br | -0.012612 | -0.223769 | -1.778150 |
| Na | -0.450473 | 0.282477 | 1.497378 |
| H | 0.414183 | 2.054499 | 1.710206 |
| C | -3.759955 | 0.200611 | 1.175100 |
| O | -2.604662 | -0.620071 | 1.465217 |
| C | -3.021188 | -1.918219 | 1.933149 |
| C | -4.498261 | -1.775880 | 2.281273 |
| C | -4.965470 | -0.731107 | 1.261197 |
| H | -3.811109 | 1.000766 | 1.918556 |
| H | -3.625107 | 0.648364 | 0.190096 |
| H | -2.868469 | -2.649674 | 1.132457 |
| H | -2.392349 | -2.193444 | 2.780287 |
| H | -5.036166 | -2.720774 | 2.207375 |
| H | -4.615409 | -1.396103 | 3.298595 |
| H | -5.155102 | -1.202385 | 0.294406 |
| H | -5.871280 | -0.207534 | 1.565372 |
| C | 1.717385 | -2.321593 | 1.732796 |
| O | 0.889603 | -1.412435 | 2.474462 |
| C | 1.677294 | -0.791710 | 3.527501 |
| C | 3.115479 | -1.292150 | 3.347761 |
| C | 3.134254 | -1.791461 | 1.897054 |
| H | 1.618380 | -3.332509 | 2.147684 |
| H | 1.366574 | -2.331576 | 0.700296 |
| H | 1.590971 | 0.289964 | 3.399099 |
| H | 1.252315 | -1.075435 | 4.492802 |
| H | 3.844622 | -0.504201 | 3.532912 |
| H | 3.328031 | -2.115046 | 4.033440 |
| H | 3.304111 | -0.962752 | 1.207546 |
| H | 3.892851 | -2.553197 | 1.715692 |

===TS-I with 2 THF molecules===

| | | | |
|---|---|---|---|
| C | 0.497936 | -2.393049 | 0.579696 |
| C | 1.881986 | -2.491985 | 0.377278 |
| C | 2.596002 | -1.363486 | 0.007988 |
| C | 1.951470 | -0.157242 | -0.259028 |
| C | 0.559640 | -0.114929 | -0.188487 |
| C | -0.175080 | -1.229727 | 0.179377 |
| H | 2.394534 | -3.422208 | 0.577032 |
| H | 3.673324 | -1.435523 | -0.089409 |
| H | 2.516170 | 0.717390 | -0.552925 |
| H | 0.032017 | 0.798315 | -0.438843 |
| H | -1.253186 | -1.181576 | 0.232799 |
| Br | -0.530842 | -4.131058 | 0.258492 |
| Na | -0.715973 | -4.133210 | 3.203740 |
| H | 0.227000 | -2.504486 | 2.446248 |
| C | -3.969836 | -3.835211 | 3.101892 |
| O | -2.925860 | -4.587088 | 3.764392 |
| C | -3.505707 | -5.593119 | 4.621692 |
| C | -5.003259 | -5.300294 | 4.660426 |
| C | -5.242505 | -4.649768 | 3.293127 |
| H | -4.046179 | -2.850917 | 3.573694 |
| H | -3.682196 | -3.703161 | 2.059002 |
| H | -3.299905 | -6.578235 | 4.191831 |
| H | -3.026572 | -5.532941 | 5.599970 |
| H | -5.596734 | -6.200127 | 4.819767 |
| H | -5.234307 | -4.595770 | 5.462268 |
| H | -5.327473 | -5.412279 | 2.515921 |
| H | -6.139227 | -4.031601 | 3.262097 |
| C | 1.312068 | -6.789080 | 3.644058 |
| O | 0.820316 | -5.571978 | 4.234901 |
| C | 1.926201 | -4.819795 | 4.802253 |
| C | 3.181763 | -5.662202 | 4.570766 |
| C | 2.789150 | -6.538677 | 3.375154 |
| H | 1.167540 | -7.617335 | 4.347360 |
| H | 0.730159 | -6.988193 | 2.743337 |
| H | 1.969067 | -3.856612 | 4.287481 |
| H | 1.719557 | -4.646852 | 5.860027 |
| H | 4.057765 | -5.044165 | 4.377336 |
| H | 3.394684 | -6.285037 | 5.442209 |
| H | 2.911980 | -5.990910 | 2.439077 |
| H | 3.366097 | -7.461167 | 3.311587 |

===Int2-I with 2 THF molecules===

| | | | |
|---|---|---|---|
| C | -0.091331 | 2.013952 | -1.760259 |
| C | 1.175646 | 1.469156 | -1.962292 |
| C | 2.285660 | 2.060678 | -1.364331 |
| C | 2.130042 | 3.188849 | -0.564371 |
| C | 0.863709 | 3.728223 | -0.358618 |
| C | -0.247053 | 3.141598 | -0.957381 |
| H | 1.282335 | 0.584047 | -2.576928 |
| H | 3.272125 | 1.645299 | -1.529703 |
| H | 2.995206 | 3.650948 | -0.104912 |
| H | 0.743804 | 4.607393 | 0.262182 |
| H | -1.231803 | 3.565849 | -0.805537 |
| Br | -0.516375 | -2.132327 | -1.974748 |
| Na | -0.273106 | -0.388392 | 0.016340 |
| H | -0.948651 | 1.556466 | -2.239247 |
| C | -3.441654 | -0.659710 | 0.224652 |
| O | -2.346628 | -0.128613 | 1.012257 |
| C | -2.669041 | -0.209919 | 2.417305 |
| C | -4.065420 | -0.832920 | 2.507243 |
| C | -4.191127 | -1.580061 | 1.173834 |
| H | -4.072931 | 0.171289 | -0.109442 |
| H | -3.010562 | -1.162506 | -0.641408 |
| H | -1.912627 | -0.831838 | 2.903583 |
| H | -2.624220 | 0.792210 | 2.849436 |
| H | -4.170246 | -1.481617 | 3.376560 |
| H | -4.827189 | -0.053614 | 2.576838 |
| H | -3.694205 | -2.551077 | 1.221952 |
| H | -5.225421 | -1.740722 | 0.870479 |
| C | 1.685864 | -2.519668 | 1.275758 |
| O | 1.358138 | -1.125392 | 1.490131 |
| C | 2.488676 | -0.449531 | 2.082521 |

| | | | |
|---|---|---|---|
| C | 3.636939 | -1.467819 | 2.124978 |
| C | 3.196217 | -2.534376 | 1.113661 |
| H | 1.370680 | -3.099984 | 2.150625 |
| H | 1.135980 | -2.855629 | 0.396192 |
| H | 2.725208 | 0.414667 | 1.457720 |
| H | 2.209929 | -0.092521 | 3.076906 |
| H | 4.596076 | -1.013687 | 1.877611 |
| H | 3.723108 | -1.904843 | 3.121668 |
| H | 3.461787 | -2.243767 | 0.095448 |
| H | 3.629751 | -3.514141 | 1.313017 |

===Int1-II with 2 THF molecules===

| | | | |
|---|---|---|---|
| C | -0.878123 | 0.683648 | 0.434050 |
| C | 0.354291 | 0.189767 | 0.302242 |
| C | -2.149320 | -0.113544 | 0.396638 |
| H | -2.575132 | -0.137195 | 1.406265 |
| H | -2.876017 | 0.378737 | -0.255178 |
| H | -2.005699 | -1.132506 | 0.047813 |
| C | -1.119100 | 2.145190 | 0.720252 |
| H | -1.806514 | 2.563344 | -0.020113 |
| H | -1.599068 | 2.222816 | 1.700662 |
| H | -0.218827 | 2.752928 | 0.731577 |
| C | 1.678607 | 0.884988 | 0.324250 |
| H | 2.283085 | 0.551722 | 1.171274 |
| H | 2.242500 | 0.668589 | -0.585722 |
| H | 1.555571 | 1.963683 | 0.397676 |
| Br | 0.616347 | -1.739913 | 0.069408 |
| Na | -0.111311 | -1.002201 | 3.246868 |
| H | -1.603688 | 0.202733 | 3.837520 |
| C | -1.575234 | -3.122406 | 5.024772 |
| O | -0.497034 | -3.180618 | 4.062666 |
| C | -0.541604 | -4.436804 | 3.353622 |
| C | -1.756721 | -5.200305 | 3.892365 |
| C | -2.623754 | -4.085731 | 4.491801 |
| H | -1.199420 | -3.441323 | 6.004009 |
| H | -1.906150 | -2.083577 | 5.079384 |
| H | -0.634035 | -4.218738 | 2.286699 |
| H | 0.397666 | -4.970210 | 3.516774 |
| H | -2.263726 | -5.767855 | 3.112222 |
| H | -1.452479 | -5.901906 | 4.671926 |
| H | -3.218913 | -3.596092 | 3.718171 |
| H | -3.299906 | -4.441690 | 5.269075 |
| C | 1.674046 | 1.199241 | 4.594072 |
| O | 1.933643 | -0.099574 | 4.012135 |
| C | 2.955693 | -0.780818 | 4.769339 |
| C | 3.355407 | 0.161519 | 5.910054 |
| C | 2.132826 | 1.078761 | 6.038766 |
| H | 2.253290 | 1.956015 | 4.052356 |
| H | 0.607214 | 1.399172 | 4.477284 |
| H | 2.532907 | -1.717435 | 5.142650 |
| H | 3.789532 | -1.018563 | 4.105107 |
| H | 3.586834 | -0.379426 | 6.827520 |
| H | 4.237091 | 0.743691 | 5.633861 |
| H | 1.352285 | 0.606129 | 6.638878 |
| H | 2.368800 | 2.044576 | 6.485453 |

===TS-II with 2 THF molecules===

| | | | |
|---|---|---|---|
| C | -1.440771 | 0.411906 | 0.180276 |
| C | -0.157890 | 0.520991 | 0.605053 |
| C | -2.272863 | -0.798850 | 0.459016 |
| H | -2.595078 | -0.797808 | 1.519738 |
| H | -3.179404 | -0.813108 | -0.150186 |
| H | -1.733529 | -1.729163 | 0.286149 |
| C | -2.221887 | 1.685792 | -0.027681 |
| H | -3.089071 | 1.502935 | -0.667228 |
| H | -2.605613 | 2.078760 | 0.929993 |
| H | -1.635608 | 2.478472 | -0.490761 |
| C | 0.743727 | 1.698333 | 0.366360 |
| H | 1.685325 | 1.584167 | 0.896449 |
| H | 0.955225 | 1.823289 | -0.700577 |
| H | 0.263162 | 2.601461 | 0.745562 |
| Br | 0.956960 | -1.196805 | 0.489002 |
| Na | 0.628057 | -0.982702 | 3.398133 |
| H | -0.098740 | 0.639322 | 2.382557 |
| C | -1.904330 | -2.760883 | 4.513879 |
| O | -0.534543 | -2.900372 | 4.078387 |
| C | -0.364152 | -4.155707 | 3.377471 |
| C | -1.686394 | -4.907091 | 3.522736 |
| C | -2.698204 | -3.768097 | 3.693746 |
| H | -1.959773 | -2.980389 | 5.585586 |
| H | -2.209029 | -1.726694 | 4.348184 |
| H | -0.134544 | -3.934749 | 2.331912 |
| H | 0.481356 | -4.685374 | 3.819711 |
| H | -1.895401 | -5.540274 | 2.661107 |
| H | -1.672362 | -5.540426 | 4.412506 |
| H | -2.962588 | -3.339654 | 2.725308 |
| H | -3.615386 | -4.080316 | 4.192746 |
| C | 3.014357 | 0.704002 | 4.746238 |
| O | 2.366328 | -0.579061 | 4.895728 |
| C | 2.676388 | -1.141830 | 6.187925 |
| C | 3.651706 | -0.170933 | 6.856402 |
| C | 3.327747 | 1.158403 | 6.164183 |
| H | 3.927182 | 0.575946 | 4.154934 |
| H | 2.331149 | 1.358307 | 4.204070 |
| H | 1.744630 | -1.235443 | 6.752667 |
| H | 3.097452 | -2.138836 | 6.045609 |
| H | 3.522875 | -0.136798 | 7.937926 |
| H | 4.683425 | -0.462643 | 6.649529 |
| H | 2.449294 | 1.624922 | 6.615288 |
| H | 4.150037 | 1.872536 | 6.201363 |

===Int2-II with 2 THF molecules===

| | | | |
|---|---|---|---|
| C | -1.513505 | 0.881284 | 1.064754 |
| C | -0.282509 | 1.409210 | 1.108083 |
| C | -1.834802 | -0.248602 | 0.120097 |
| H | -2.307855 | -1.082088 | 0.648818 |
| H | -2.553180 | 0.083111 | -0.636809 |
| H | -0.947521 | -0.625554 | -0.388337 |
| C | -2.683564 | 1.364767 | 1.878562 |
| H | -3.478609 | 1.726161 | 1.218570 |
| H | -3.115100 | 0.541696 | 2.456441 |
| H | -2.431656 | 2.168060 | 2.567777 |
| C | 0.205802 | 2.571810 | 1.921049 |
| H | 1.078041 | 2.292177 | 2.518977 |
| H | 0.530275 | 3.383835 | 1.263052 |
| H | -0.548177 | 2.974668 | 2.595841 |
| Br | 1.949560 | -2.307571 | 0.684091 |
| Na | 0.466256 | -1.007503 | 2.461854 |
| H | 0.461960 | 0.974741 | 0.443438 |
| C | -1.230553 | -3.700065 | 2.503257 |

| | | | |
|---|---|---|---|
| O | -1.131185 | -2.488165 | 3.295903 |
| C | -1.503108 | -2.766139 | 4.661790 |
| C | -1.874941 | -4.250728 | 4.719156 |
| C | -1.129677 | -4.832282 | 3.511772 |
| H | -2.198371 | -3.707039 | 1.990067 |
| H | -0.426986 | -3.679011 | 1.766736 |
| H | -0.645100 | -2.539483 | 5.301647 |
| H | -2.329677 | -2.110699 | 4.945349 |
| H | -1.589158 | -4.709458 | 5.665438 |
| H | -2.952346 | -4.379037 | 4.596314 |
| H | -0.082574 | -5.024534 | 3.754627 |
| H | -1.569994 | -5.758817 | 3.144156 |
| C | 3.310954 | -0.229057 | 3.676744 |
| O | 1.920533 | -0.112474 | 4.047346 |
| C | 1.881445 | 0.256313 | 5.433668 |
| C | 3.171443 | -0.300737 | 6.075054 |
| C | 3.956666 | -0.893083 | 4.884588 |
| H | 3.356275 | -0.809674 | 2.755624 |
| H | 3.721300 | 0.773030 | 3.500609 |
| H | 1.834533 | 1.347214 | 5.516549 |
| H | 0.968821 | -0.160133 | 5.860907 |
| H | 3.730413 | 0.498674 | 6.561920 |
| H | 2.954989 | -1.054847 | 6.830908 |
| H | 5.026380 | -0.694788 | 4.945721 |
| H | 3.817080 | -1.972925 | 4.825443 |

====Int2b-II with 2 THF molecules====

| | | | |
|---|---|---|---|
| C | -0.439745 | 0.513711 | 0.078030 |
| C | 0.860062 | 0.289020 | -0.163988 |
| C | -1.431722 | -0.532563 | 0.506420 |
| H | -1.883627 | -0.247420 | 1.461320 |
| H | -2.246448 | -0.594296 | -0.221568 |
| H | -0.999664 | -1.526161 | 0.608939 |
| C | -1.031462 | 1.890096 | -0.078717 |
| H | -1.483630 | 2.224118 | 0.860107 |
| H | -0.286183 | 2.622470 | -0.391912 |
| H | -1.829563 | 1.876060 | -0.827590 |
| C | 1.608985 | -1.012310 | -0.117829 |
| H | 2.483200 | -0.949673 | 0.537844 |
| H | 0.997954 | -1.846125 | 0.223495 |
| H | 1.989895 | -1.266993 | -1.111890 |
| Br | -1.194660 | 1.740954 | 4.035258 |
| Na | 0.980605 | 1.189286 | 2.596067 |
| H | 1.453791 | 1.141928 | -0.488626 |
| C | 2.296331 | -0.047214 | 5.202702 |
| O | 1.939212 | -0.523983 | 3.880626 |
| C | 1.103210 | -1.698527 | 3.997437 |
| C | 0.618366 | -1.719181 | 5.439827 |
| C | 1.810980 | -1.109974 | 6.184702 |
| H | 3.376885 | 0.105492 | 5.228121 |
| H | 1.787277 | 0.905387 | 5.372593 |
| H | 0.288219 | -1.612700 | 3.277860 |
| H | 1.704127 | -2.580890 | 3.752655 |
| H | -0.259722 | -1.079741 | 5.540500 |
| H | 0.368254 | -2.724274 | 5.779741 |
| H | 1.536289 | -0.679499 | 7.147171 |
| H | 2.585833 | -1.861397 | 6.355461 |
| C | 3.710330 | 3.312923 | 2.554222 |
| O | 2.285623 | 3.102423 | 2.461863 |
| C | 1.583076 | 4.310335 | 2.848431 |
| C | 2.571719 | 5.071865 | 3.715992 |
| C | 3.906194 | 4.755970 | 3.028974 |
| H | 4.114998 | 2.590760 | 3.268738 |
| H | 4.161659 | 3.123423 | 1.577813 |
| H | 1.326499 | 4.875479 | 1.945619 |
| H | 0.666798 | 4.008619 | 3.356267 |
| H | 2.355175 | 6.139055 | 3.757361 |
| H | 2.556417 | 4.681058 | 4.735573 |
| H | 4.058015 | 5.421043 | 2.176435 |
| H | 4.766816 | 4.857760 | 3.689585 |

Without THF molecules

===Int1-I===

| | | | |
|---|---|---|---|
| C | 0.613898 | -1.841713 | -0.317402 |
| C | 1.998507 | -1.831627 | -0.391158 |
| C | 2.657735 | -0.608027 | -0.331917 |
| C | 1.937858 | 0.573903 | -0.201599 |
| C | 0.550214 | 0.537778 | -0.131305 |
| C | -0.126663 | -0.676349 | -0.189806 |
| H | 2.553007 | -2.753699 | -0.493574 |
| H | 3.738431 | -0.585699 | -0.386576 |
| H | 2.457725 | 1.521612 | -0.153283 |
| H | -0.015325 | 1.454821 | -0.028775 |
| H | -1.205844 | -0.709684 | -0.138996 |
| Br | -0.310320 | -3.530231 | -0.397427 |
| Na | -0.542916 | -3.753691 | 2.663951 |
| H | -0.735321 | -3.756216 | 4.553400 |

===TS-I===

| | | | |
|---|---|---|---|
| C | 0.541322 | -1.924462 | 0.297047 |
| C | 1.924995 | -1.907571 | 0.072441 |
| C | 2.567788 | -0.690322 | -0.084518 |
| C | 1.852093 | 0.504792 | -0.110590 |
| C | 0.463272 | 0.457696 | -0.009307 |
| C | -0.203767 | -0.746417 | 0.148365 |
| H | 2.490651 | -2.827977 | 0.088913 |
| H | 3.644750 | -0.681005 | -0.204183 |
| H | 2.362832 | 1.449406 | -0.240072 |
| H | -0.116668 | 1.371083 | -0.069824 |
| H | -1.281340 | -0.770361 | 0.223388 |
| Br | -0.407079 | -3.617276 | -0.419703 |
| Na | -0.590416 | -4.138440 | 2.345977 |
| H | 0.322554 | -2.437968 | 2.017594 |

===Int2-I===

| | | | |
|---|---|---|---|
| C | 0.841107 | -1.454356 | 1.748662 |
| C | 2.081204 | -1.661735 | 1.146086 |
| C | 2.426458 | -0.949001 | -0.001391 |
| C | 1.531679 | -0.028928 | -0.546129 |
| C | 0.291575 | 0.178441 | 0.056434 |
| C | -0.053747 | -0.534460 | 1.203799 |
| H | 2.777058 | -2.373613 | 1.571092 |
| H | 3.390404 | -1.107711 | -0.467486 |
| H | 1.800997 | 0.526362 | -1.435374 |
| H | -0.401827 | 0.894779 | -0.365076 |
| H | -1.015363 | -0.371555 | 1.673238 |
| Br | -0.838108 | -4.457238 | -2.304406 |
| Na | 0.165371 | -2.614502 | -0.865242 |
| H | 0.574180 | -2.005300 | 2.641324 |

===Int1-II===

| | | | |
|---|---|---|---|
| C | -1.089663 | 0.746356 | -0.296954 |
| C | 0.212961 | 0.759332 | -0.017138 |
| C | -1.910284 | -0.470147 | -0.618379 |
| H | -2.723489 | -0.574095 | 0.106129 |
| H | -2.379763 | -0.354024 | -1.599597 |
| H | -1.333469 | -1.389801 | -0.621824 |
| C | -1.898135 | 2.022595 | -0.309242 |
| H | -2.372936 | 2.152528 | -1.285921 |
| H | -2.702576 | 1.954896 | 0.428468 |
| H | -1.319916 | 2.914380 | -0.089845 |
| C | 1.124589 | 1.891024 | 0.327802 |
| H | 1.454599 | 1.825868 | 1.370595 |
| H | 2.011091 | 1.883138 | -0.309056 |
| H | 0.623522 | 2.848377 | 0.198694 |
| Br | 1.210860 | -0.941091 | -0.001485 |
| Na | 1.581494 | -0.655815 | 2.966736 |
| H | 1.551982 | 1.005150 | 3.904870 |

===TS-II===

| | | | |
|---|---|---|---|
| C | -0.923814 | 0.787865 | -0.247249 |
| C | 0.323040 | 0.835218 | 0.289617 |
| C | -1.723115 | -0.473348 | -0.235079 |
| H | -1.943128 | -0.759141 | 0.817666 |
| H | -2.682667 | -0.349488 | -0.738205 |
| H | -1.205556 | -1.316284 | -0.690945 |
| C | -1.717518 | 2.067712 | -0.314973 |
| H | -2.511305 | 1.985438 | -1.060520 |
| H | -2.203646 | 2.283571 | 0.650928 |
| H | -1.110676 | 2.933731 | -0.574463 |
| C | 1.225643 | 2.033330 | 0.345335 |
| H | 2.093206 | 1.839457 | 0.970656 |
| H | 1.569980 | 2.315541 | -0.653624 |
| H | 0.685184 | 2.871326 | 0.787821 |
| Br | 1.461295 | -0.838431 | -0.033369 |
| Na | 0.544267 | -1.199457 | 2.640047 |
| H | 0.176592 | 0.625815 | 2.002400 |

===Int2-II===

| | | | |
|---|---|---|---|
| C | -0.808219 | 0.883476 | -0.160425 |
| C | 0.454457 | 1.261927 | -0.421997 |
| C | -1.425361 | -0.296413 | -0.866482 |
| H | -1.774045 | -1.044499 | -0.147577 |
| H | -2.305171 | 0.023205 | -1.432569 |
| H | -0.731252 | -0.770325 | -1.561924 |
| C | -1.728204 | 1.569348 | 0.812263 |
| H | -2.618330 | 1.926908 | 0.286221 |
| H | -2.076232 | 0.860545 | 1.569972 |
| H | -1.274732 | 2.419156 | 1.317788 |
| C | 1.203913 | 2.446455 | 0.121277 |
| H | 2.208844 | 2.169651 | 0.454925 |
| H | 1.345017 | 3.197741 | -0.661885 |
| H | 0.696648 | 2.932478 | 0.953102 |
| Br | -0.807783 | -1.966216 | 3.113321 |
| Na | 0.726812 | -0.643951 | 1.567840 |
| H | 0.988335 | 0.697553 | -1.185618 |

===TSb-II===

| | | | |
|---|---|---|---|
| C | -0.986155 | 0.867247 | -0.269410 |
| C | 0.241231 | 1.028222 | 0.235313 |
| C | -1.672493 | -0.429225 | -0.588782 |
| H | -2.571888 | -0.548626 | 0.027726 |
| H | -2.008674 | -0.422379 | -1.630254 |
| H | -1.025461 | -1.287258 | -0.438745 |
| C | -1.838268 | 2.113002 | -0.364025 |
| H | -2.849470 | 1.862192 | -0.688830 |
| H | -1.856715 | 2.600236 | 0.621049 |
| H | -1.429099 | 2.848757 | -1.060270 |
| C | 1.520432 | 1.644467 | -0.181017 |
| H | 2.213972 | 1.782608 | 0.645230 |
| H | 1.989840 | 1.038695 | -0.962282 |
| H | 1.289900 | 2.626227 | -0.603945 |
| Br | 1.095457 | -1.009042 | 1.200906 |
| Na | 0.268600 | 0.937129 | 2.951048 |
| H | -0.012549 | 2.417303 | 1.653915 |

===Int2b-II===

| | | | |
|---|---|---|---|
| C | -0.856163 | 1.278982 | -0.179400 |
| C | 0.338504 | 1.893678 | -0.213726 |
| C | -1.138650 | -0.084519 | -0.748787 |
| H | -1.544397 | -0.742523 | 0.025664 |
| H | -1.905034 | -0.006818 | -1.525681 |
| H | -0.266298 | -0.564286 | -1.187241 |
| C | -2.053692 | 1.947622 | 0.445328 |
| H | -2.468383 | 1.334152 | 1.251493 |
| H | -1.814286 | 2.935905 | 0.840283 |
| H | -2.849043 | 2.064036 | -0.296631 |
| C | 1.612736 | 1.418383 | -0.854290 |
| H | 2.469594 | 1.535441 | -0.183587 |
| H | 1.572730 | 0.376990 | -1.168960 |
| H | 1.840368 | 2.020834 | -1.739094 |
| Br | -1.232240 | -0.991227 | 3.495258 |
| Na | 0.303746 | 0.613031 | 2.247026 |
| H | 0.384525 | 2.901072 | 0.198220 |

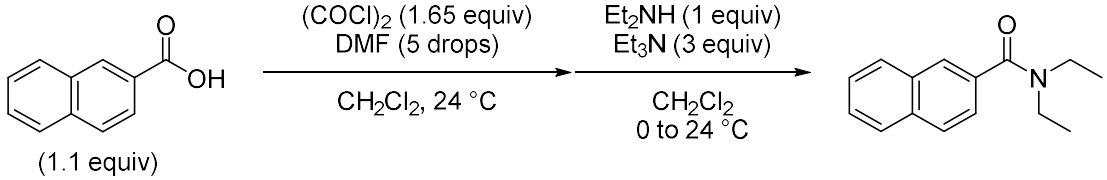
### 6.2.7. References for section 6.2


1. S. W. Youn, S. J. Pastine, D. Sames, *Org. Lett.* **2004,** *6*, 581-584.
2. C. G. Overberger, H. Gainer, *J. Am. Chem. Soc.* **1958,** *80*, 4561-4565.
3. D. F. DeTar, C. Weis, *J. Am. Chem. Soc.* **1956,** *78*, 4296-4301.
4. C. G. Shull, E. O. Wollan, G. A. Morton, W. L. Davidson, *Phys. Rev.* **1948,** *73*, 842-847.
5. A. W. Hull, *Phys. Rev.* **1917,** *10*, 661-696.
6. V. M. Vlasov, *New. J. Chem.* **2010,** *34*, 2962-2970.
7. C. N. Neumann, J. M. Hooker, T. Ritter, *Nature* **2016,** *534*, 369-373.
8. A. D. Becke, *J. Chem. Phys.* **1993,** *98*, 5648-5652.
9. C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988,** *37*, 785-789.
10. S. H. Vosko, L. Wilk, M. Nusair, *Can. J. Phys.* **1980,** *58*, 1200-1211.
11. F. Weigend, R. Ahlrichs, *Phys. Chem. Chem. Phys.* **2005,** *7*, 3297-3305.
12. J. Tomasi, B. Mennucci, R. Cammi, *Chem. Rev.* **2005,** *105*, 2999-3094.
13. S. Grimme, S. Ehrlich, L. Goerigk, *J. Comp. Chem.* **2011,** *32*, 1456-1465.
14. S. Grimme, J. Antony, S. Ehrlich, H. Krieg, *J. Chem. Phys.* **2010,** *132*, 154104.
15. E. R. Johnson, A. D. Becke, *J. Chem. Phys.* **2006,** *124*, 174104.
16. A. D. Becke, E. R. Johnson, *J. Chem. Phys.* **2005,** *123*, 154101.
17. E. R. Johnson, A. D. Becke, *J. Chem. Phys.* **2005,** *123*, 024101.

## 6.3. Experimental data for Chapter 3

### 6.3.1. Synthesis of amides

#### 6.3.1.1. Synthesis of *N,N*-diethyl-2-naphthamide (3.23ab)[1]

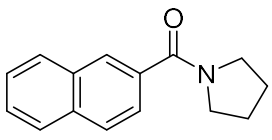



To a solution of 2-naphthoic acid (1.51 g, 8.79 mmol) in $CH_2Cl_2$ (20 mL) was added $(COCl)_2$ (1.1 mL, 13.2 mmol) and DMF (5 drops) at 23 °C. The reaction mixture was stirred at 23 °C for 2 h, before adding triethylamine (3.4 mL, 24.4 mmol) and diethylamine (830 µL, 8.03 mmol) dropwise at 0 °C, and the reaction mixture was stirred continuously at 23 °C for 5 h. The reaction was then quenched with water and organic materials were extracted twice with $CH_2Cl_2$. The combined organic layers was washed with saturated aqueous $NaHCO_3$ solution and then dried over $MgSO_4$. The volatile materials was removed *in vacuo* and the resulting crude mixture was purified by flash column chromatography (silica gel, Hex:EtOAc = 1:1) to give a pale yellow oil **3.23ab** (1.69 g, 7.44 mmol) in 93% yield.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.88 – 7.84 (m, 4H), 7.54 – 7.50 (m, 2H), 7.47 (dd, *J* = 8.3, 1.7 Hz, 1H), 3.60 (brs, 2H), 3.31 (brs, 2H), 1.29 (brs, 3H), 1.14 (brs, 3H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 171.2, 134.6, 133.3, 132.7, 128.24, 128.20, 127.7, 126.7, 126.5, 125.7, 123.9, 43.3, 39.3, 14.2, 12.9.

#### 6.3.1.2. Synthesis of naphthalen-2-yl(pyrrolidin-1-yl)methanone (3.23ac)[2]

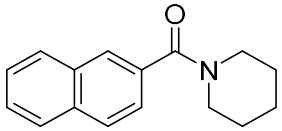


Prepared by following the experimental procedure in section 6.3.1.1 from 2-napthoic acid (1.51 g, 8.79 mmol) with slight modification of the procedure for the formation of amide using pyrrolidine (660 µL, 8.04 mmol) in the presence of triethylamine (3.4 mL, 24.4 mmol). Purified by flash column chromatography (silica gel, Hex:EtOAc = 1:1) to give an white solid **3.23ac** (1.47 g, 6.52 mmol) in 81% yield.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 8.01 (s, 1H), 7.88 – 7.84 (m, 3H), 7.62 (dd, J = 8.5, 1.4 Hz, 1H), 7.56 – 7.49 (m, 2H), 3.71 (t, *J* = 7.0 Hz, 2H), 3.49 (t, *J* = 6.6 Hz, 2H), 2.03 – 1.96 (m, 2H), 1.92 – 1.85 (m, 2H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 169.5, 134.3, 133.6, 132.4, 128.3, 127.9, 127.6, 126.83, 126.75, 126.3, 124.2, 49.5, 46.1, 26.2, 24.3.

### 6.3.1.3. Synthesis of naphthalen-2-yl(piperidin-1-yl)methanone (3.23ad)[3]

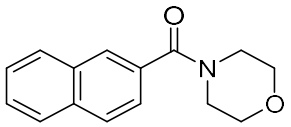



Prepared by following the experimental procedure in section 6.3.1.1 from 2-napthoic acid (1.50 g, 8.70 mmol) with slight modification of the procedure for the formation of amide using piperidine (780 µL, 7.90 mmol) in the presence of triethylamine (3.4 mL, 24.4 mmol). Purified by flash column chromatography (silica gel, Hex:EtOAc = 1:1) to give an white solid **3.23ad** (1.82 g, 7.61 mmol) in 95% yield.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.88 – 7.84 (m, 4H), 7.54 – 7.50 (m, 2H), 7.48 (dd, *J* = 8.4, 1.6 Hz, 1H), 3.75 (brs, 2H), 3.39 (brs, 2H), 1.69 – 1.55 (m, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 170.3, 133.8, 133.5, 132.7, 128.3, 128.2, 127.7, 126.8, 126.54, 126.45, 124.2, 48.8, 43.2, 26.6, 25.7, 24.6.

### 6.3.1.4. Synthesis of morpholino(naphthalen-2-yl)methanone (3.23ae)[4]

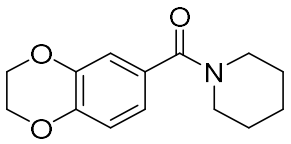


Prepared by following the experimental procedure in section 6.3.1.1 from 2-naphthoic acid (1.52 g, 8.82 mmol) with slight modification of the procedure for the formation of amide using morpholine (690 µL, 7.98 mmol) in the presence of triethylamine (3.4 mL, 24.4 mmol). Purified by flash column chromatography (silica gel, Hex:EtOAc = 1:1) to give an white solid **3.23ae** (1.73 g, 7.17 mmol) in 90% yield.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.91 (s, 1H), 7.90 – 7.85 (m, 3H), 7.56 – 7.53 (m, 2H), 7.49 (dd, *J* = 8.4, 1.6 Hz, 1H), 3.74 – 3.55 (m, 8H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 170.3, 133.6, 132.6, 132.5, 128.30, 128.27, 127.7, 127.1, 126.9, 126.7, 124.1, 66.8, 48.2, 42.6.

### 6.3.1.5. Synthesis of (2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)(piperidin-1-yl)methanone (3.23bd)[5]

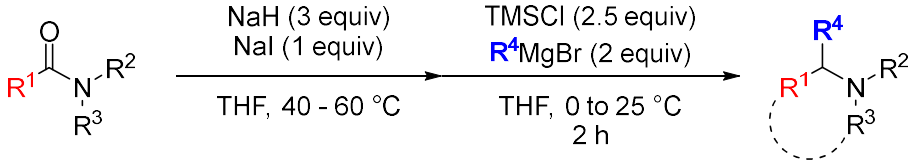


Prepared by following the experimental procedure in section **6.3.1.1** from 2,3-dihydrobenzo[*b*][1,4]dioxine-6-carboxylic acid (1.81 g, 10.0 mmol) with slight modification of the procedure for the formation of amide using morpholine (4.0 mL, 40.5 mmol). Purified by flash column chromatography (silica gel, Hex:EtOAc = 1:4) to give an off white solid **3.23bd** (1.98 g, 8.03 mmol) in 80% yield.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 6.90 (s, 1H), 6.86 (d, *J* = 8.3 Hz, 1H), 6.82 (d, *J* = 8.3 Hz, 1H), 4.23 (s, 4H), 3.56 – 3.43 (m, 4H), 1.63 – 1.55 (m, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 169.7, 144.6, 143.2, 129.5, 120.3, 117.0, 116.4, 64.4, 64.2, 48.8, 43.2, 26.0, 24.6.

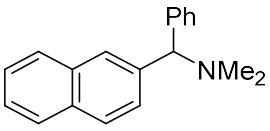
### 6.3.2. General procedure for reductive transformation of amides/lactams 6.23




To a mixture of NaH (60% dispersion in mineral oil; 60.0 mg, 1.50 mmol) and NaI (75.0 mg, 0.500 mmol) was added a solution of amide or lactam (0.500 mmol) in 2.5 mL of THF, and the reaction mixture was stirred at 40 °C or 60 °C. Upon full consumption of amide/lactam based on TLC, the reaction was cooled down to 0 °C. TMSCl (160 µL, 1.26 mmol) and Grignard reagent (1 mmol) were added at 0 °C and stirred at 24 °C for 2 h. The reaction was quenched with ammonium pH 10 buffer at 0 °C and the organic materials were extracted with dichloromethane (20 mL × 3). The combined extracts were dried over $MgSO_4$. The volatile materials were removed *in vacuo* and the resulting crude residue was purified by flash column chromatography to give the corresponding α-branched tertiary amines.

### 6.3.3. Synthesis of α-phenyl tertiary amines 6.23

#### 6.3.3.1. Synthesis of *N*,*N*-dimethyl-1-(naphthalen-2-yl)-1-phenylmethanamine (3.25aa)




Prepared from amide **3.23aa** (99.6 mg, 0.500 mmol) and heated at 60 °C for 5 h, followed by addition of phenylmagnesium bromide.

Purification: Hex:EtOAc:Triethylamine = 98:2:1

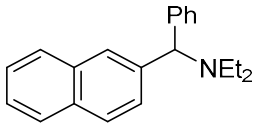
Yield: 86% yield (112 mg, 0.429 mmol) as white solid.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.86 (s, 1H), 7.79 (d, *J* = 7.7 Hz, 1H), 7.76 – 7.74 (m, 2H), 7.60 (d, *J* = 8.5 Hz, 1H), 7.48 (d, *J* = 7.2 Hz, 2H), 7.45 – 7.38 (m, 2H), 7.27 (dd, *J* = 7.7, 7.7 Hz, 2H), 7.16 (t, *J* = 7.2 Hz, 1H), 4.23 (s, 1H), 2.25 (s, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 143.2, 141.0, 133.5, 132.7, 128.5, 128.2, 127.8 (overlapped), 127.6, 126.9, 126.2, 125.9, 125.8, 125.6, 78.1, 44.8.

**ESIHRMS**: Found m/z 262.1597; Calcd for $C_{19}H_{20}N$ $[M+H]^+$ 262.1596.

### 6.3.3.2. Synthesis of *N*-ethyl-*N*-(naphthalen-2-yl(phenyl)methyl)ethanamine (3.25ab)




Prepared from amide **3.23ab** (114 mg, 0.502 mmol) and heated at 60 °C for 9 h, followed by addition of phenylmagnesium bromide.

Purification: Hex:EtOAc:Triethylamine = 99:1:1

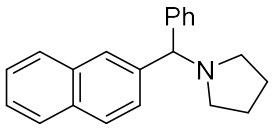
Yield: 89% yield (130 mg, 0.449 mmol) as colorless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.82 (s, 1H), 7.79 – 7.72 (m, 3H), 7.62 (d, *J* = 8.6 Hz, 1H), 7.48 (d, *J* = 7.3 Hz, 2H), 7.44 – 7.36 (m, 2H), 7.25 (dd, *J* = 7.3, 7.3 Hz, 2H), 7.15 (t, *J* = 7.3 Hz, 1H), 4.87 (s, 1H), 2.62 (q, *J* = 7.1 Hz, 4H), 1.00 (t, *J* = 7.1 Hz, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 143.3, 141.1, 133.4, 132.6, 128.3, 128.2, 128.0, 127.8, 127.5, 126.7, 126.6, 126.4, 125.8, 125.4, 71.5, 42.9, 11.0.

**ESIHRMS**: Found m/z 290.1914; Calcd for $C_{21}H_{24}N$ $[M+H]^+$ 290.1909.

### 6.3.3.3. Synthesis of 1-(naphthalen-2-yl(phenyl)methyl)pyrrolidine (3.25ac)




Prepared from amide **3.23ac** (113 mg, 0.499 mmol) and heated at 60 °C for 6 h, followed by addition of phenylmagnesium bromide.

Purification: Hex:EtOAc:Triethylamine = 98:2:1

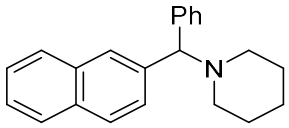
Yield: 85% yield (122 mg, 0.424 mmol) as off-white solid.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.95 (s, 1H), 7.86 (d, *J* = 7.7 Hz, 1H), 7.82 – 7.79 (m, 2H), 7.68 (d, *J* = 8.5 Hz, 1H), 7.58 (d, *J* = 7.4 Hz, 2H), 7.51 – 7.43 (m, 2H), 7.32 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.21 (t, *J* = 7.4 Hz, 1H), 4.40 (s, 1H), 2.54 (brs, 4H), 1.88 – 1.84 (m, 4H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 144.2, 142.0, 133.6, 132.8, 128.5, 128.2, 127.9, 127.68, 127.65, 126.9, 126.0, 125.93, 125.87, 125.6, 76.7, 53.8, 23.7.

**ESIHRMS**: Found m/z 288.1754; Calcd for $C_{21}H_{22}N$ $[M+H]^+$ 288.1752.

### 6.3.3.4. Synthesis of 1-(naphthalen-2-yl(phenyl)methyl)piperidine (3.25ad)




Prepared from amide **3.23ad** (120 mg, 0.501 mmol) and heated at 60 °C for 6 h, followed by addition of phenylmagnesium bromide.

Purification: Hex:EtOAc:Triethylamine = 98:2:1

Yield: 86% yield (130 mg, 0.431 mmol) as white solid.

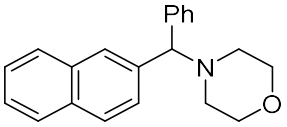
**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.82 (s, 1H), 7.79 – 7.72 (m, 3H), 7.58 (d, *J* = 8.5 Hz, 1H), 7.46 (d, *J* = 7.4 Hz, 2H), 7.45 – 7.37 (m, 2H), 7.26 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.15

(t, *J* = 7.4 Hz, 1H), 4.39 (s, 1H), 2.36 (brs, 4H), 1.61 – 1.56 (m, 4H), 1.47 – 1.41 (m, 2H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 143.1, 140.9, 133.4, 132.6, 128.3, 128.0 (overlapped), 127.8, 127.5, 126.7, 126.5, 126.2, 125.8, 125.4, 76.9, 53.3, 26.2, 24.7.

**ESIHRMS**: Found m/z 302.1913; Calcd for $C_{22}H_{24}N$ $[M+H]^+$ 302.1909.

### 6.3.3.5. Synthesis of 4-(naphthalen-2-yl(phenyl)methyl)morpholine (3.25ae)




Prepared from amide **3.23ae** (121 mg, 0.499 mmol) and heated at 60 °C for 5 h, followed by addition of phenylmagnesium bromide.

Purification: Hex:EtOAc:Triethylamine = 98:2:1

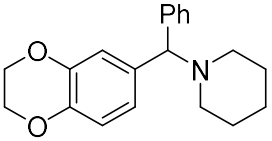
Yield: 83% yield (125 mg, 0.413 mmol) as white solid.

**$^{1}$H NMR** (400 MHz, $CDCl_3$): δ 7.84 (s, 1H), 7.79 (d, *J* = 7.6 Hz, 1H), 7.75 (d, *J* = 8.5 Hz, 2H), 7.60 (d, *J* = 8.5 Hz, 1H), 7.49 (d, *J* = 7.4 Hz, 2H), 7.45 – 7.38 (m, 2H), 7.27 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.16 (t, *J* = 7.4 Hz, 1H), 4.37 (s, 1H), 3.74 – 3.72 (m, 4H), 2.44 – 2.43 (m, 4H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 142.2, 139.9, 133.4, 132.7, 128.6, 128.4, 128.0, 127.8, 127.6, 127.1, 126.7, 126.0, 125.8, 125.7, 76.8, 67.2, 52.8.

**ESIHRMS**: Found m/z 304.1702; Calcd for $C_{21}H_{22}NO$ $[M+H]^+$ 304.1701.

### 6.3.3.6. Synthesis of 1-((2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)(phenyl)methyl)piperidine (3.25bd)



Prepared from amide **3.23bd** (124 mg, 0.501 mmol) and heated at 40 °C for 29 h, followed by addition of phenylmagnesium bromide.

Purification: Hex:EtOAc:Triethylamine = 80:20:1

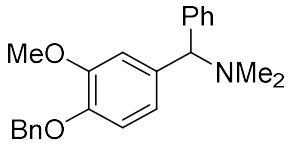
Yield: 75% yield (117 mg, 0.377 mmol) as white solid.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.37 (d, *J* = 7.4 Hz, 2H), 7.25 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.15 (t, *J* = 7.4 Hz, 1H), 6.92 (d, *J* = 2.0 Hz, 1H), 6.84 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.74 (d, *J* = 8.3 Hz, 1H), 4.21 – 4.17 (m, 4H), 4.09 (s, 1H), 2.29 (brs, 4H), 1.57 – 1.52 (m, 4H), 1.44 – 1.38 (m, 2H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 143.5, 143.2, 142.2, 136.7, 128.3, 127.9, 126.6, 120.9, 116.9, 116.6, 76.1, 64.32, 64.26, 53.1, 26.2, 24.7.

**ESIHRMS**: Found m/z 310.1804; Calcd for $C_{20}H_{24}NO_2$ $[M+H]^+$ 310.1807.

### 6.3.3.7. Synthesis of 1-(4-(benzyloxy)-3-methoxyphenyl)-*N*,*N*-dimethyl-1-phenylmethanamine (3.25ca)




Prepared from amide **3.23ca** (143 mg, 0.501 mmol) and heated at 60 °C for 5 h, followed by addition of phenylmagnesium bromide.

Purification: Hex:EtOAc:Triethylamine = 97:3:1

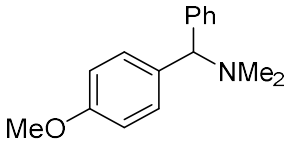
Yield: 66% yield (115 mg, 0.331 mmol) as white solid.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.41 – 7.39 (m, 4H), 7.33 (dd, *J* = 7.3, 7.3 Hz, 2H), 7.29 – 7.24 (m, 3H), 7.17 (t, *J* = 7.3 Hz, 1H), 7.01 (d, *J* = 2.0 Hz, 1H), 6.85 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.76 (d, *J* = 8.2 Hz, 1H), 5.08 (s, 2H), 3.97 (s, 1H), 3.87 (s, 3H), 2.18 (s, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 149.6, 147.1, 143.5, 137.3, 136.7, 128.44, 128.39, 127.7, 127.5, 127.2, 126.8, 119.9, 113.6, 111.0, 77.7, 71.0, 56.0, 44.7.

**ESIHRMS**: Found m/z 348.1960; Calcd for $C_{23}H_{26}NO_2$ $[M+H]^+$ 348.1964.

### 6.3.3.8. Synthesis of 1-(4-methoxyphenyl)-*N*,*N*-dimethyl-1-phenylmethanamine (3.25da)




Prepared from amide **3.23da** (90.0 mg, 0.502 mmol) and heated at 60 °C for 5 h, followed by addition of phenylmagnesium bromide.

Purification: Hex:EtOAc:Triethylamine = 97:3:1

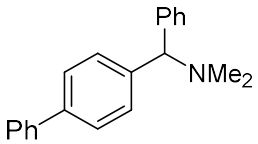
Yield: 65% yield (78.0 mg, 0.323 mmol) as white solid.

**$^{1}$H NMR** (400 MHz, $CDCl_3$): δ 7.41 (d, *J* = 7.3 Hz, 2H), 7.32 (d, *J* = 8.6 Hz, 2H), 7.26 (dd, *J* = 7.3, 7.3 Hz, 2H), 7.16 (t, *J* = 7.3 Hz, 1H), 6.81 (d, *J* = 8.6 Hz, 2H), 4.02 (s, 1H), 3.75 (s, 3H), 2.18 (s, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 158.5, 143.8, 135.6, 128.7, 128.4, 127.6, 126.7, 113.8, 77.3, 55.2, 44.7.

**ESIHRMS**: Found m/z 242.1546; Calcd for $C_{16}H_{20}NO$ $[M+H]^+$ 242.1545.

### 6.3.3.9. Synthesis of 1-([1,1'-biphenyl]-4-yl)-*N*,*N*-dimethyl-1-phenylmethanamine (3.25ea)



Prepared from amide **3.23ea** (112 mg, 0.499 mmol) and heated at 60 °C for 10 h, followed by addition of phenylmagnesium bromide.

Purification: Hex:EtOAc:Triethylamine = 96:4:1

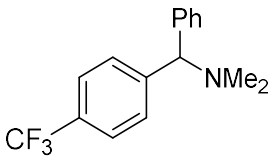
Yield: 62% yield (89.4 mg, 0.311 mmol) as white solid.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.54 (d, *J* = 7.3 Hz, 2H), 7.51 – 7.48 (m, 4H), 7.46 (d, *J* = 7.8 Hz, 2H), 7.40 (dd, *J* = 7.3, 7.3 Hz, 2H), 7.34 – 7.25 (m, 3H), 7.19 (t, *J* = 7.8 Hz, 1H), 4.11 (s, 1H), 2.23 (s, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 143.4, 142.5, 140.9, 139.7, 128.7, 128.5, 128.1, 127.7, 127.2, 127.1, 127.0, 126.9, 77.7, 44.8.

**ESIHRMS**: Found m/z 288.1756; Calcd for $C_{21}H_{22}N$ $[M+H]^+$ 288.1752.

### 6.3.3.10. Synthesis of *N*,*N*-dimethyl-1-phenyl-1-(4-(trifluoromethyl)phenyl)methanamine (3.25fa)




Prepared from amide **3.23fa** (108 mg, 0.499 mmol) and heated at 60 °C for 5 h, followed by addition of phenylmagnesium bromide.

Purification: Hex:EtOAc:Triethylamine = 97:3:1

Yield: 83% yield (116 mg, 0.415 mmol) as white solid.

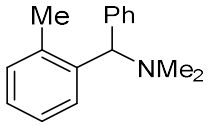
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.59 – 7.50 (m, 4H), 7.39 (d, *J* = 7.5 Hz, 2H), 7.29 (dd, *J* = 11.1, 3.9 Hz, 2H), 7.20 (dd, *J* = 11.1, 3.9 Hz, 1H), 4.13 (s, 1H), 2.19 (s, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 147.6, 142.4, 129.1 (q, *J* = 32.1), 128.6, 127.9, 127.7, 127.3, 125.5 (q, *J* = 3.6), 124.2 (q, *J* = 270.7), 77.5, 44.6.

**$^{19}$F NMR** (376 MHz, $CDCl_3$) δ -62.33.

**ESIHRMS**: Found m/z 280.1317; Calcd for $C_{16}H_{17}N^{19}F_3$ $[M+H]^+$ 280.1313.

### 6.3.3.11. Synthesis of *N*,*N*-dimethyl-1-phenyl-1-(o-tolyl)methanamine (3.25ga)




Prepared from amide **3.23ga** (81.9 mg, 0.502 mmol) and heated at 60 °C for 23 h, followed by addition of phenylmagnesium bromide.

Purification: Hex:EtOAc:Triethylamine = 97:3:1

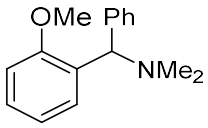
Yield: 71% yield (79.8 mg, 0.354 mmol) as white solid.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.79 (d, *J* = 7.3 Hz, 1H), 7.39 (d, *J* = 7.3 Hz, 2H), 7.28 – 7.19 (m, 3H), 7.16 (t, *J* = 7.3 Hz, 1H), 7.11 – 6.97 (m, 2H), 4.26 (s, 1H), 2.34 (s, 3H), 2.18 (s, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 142.5, 141.5, 135.5, 130.4, 128.5, 128.3, 127.1, 126.8, 126.3, 126.2, 72.9, 44.9, 19.9.

**ESIHRMS**: Found m/z 226.1593; Calcd for $C_{16}H_{20}N$ $[M+H]^+$ 226.1596.

### 6.3.3.12. Synthesis of 1-(2-methoxyphenyl)-*N*,*N*-dimethyl-1-phenylmethanamine (3.25ha)




Prepared from amide **3.23ha** (89.2 mg, 0.498 mmol) and heated at 60 °C for 23 h, followed by addition of phenylmagnesium bromide.

Purification: Hex:EtOAc:Triethylamine = 97:3:1

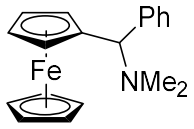
Yield: 76% yield (92.8 mg, 0.380 mmol) as off white solid.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 7.9 Hz, 1H), 7.44 (d, *J* = 7.2 Hz, 2H), 7.26 – 7.21 (m, 2H), 7.14 (dd, *J* = 7.2, 7.2 Hz, 2H), 6.94 (t, *J* = 7.2 Hz, 1H), 6.80 (d, *J* = 7.9 Hz, 1H), 4.62 (s, 1H), 3.79 (s, 3H), 2.20 (s, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 156.8, 143.4, 131.7, 128.11, 128.09, 127.9, 127.4, 126.5, 120.8, 110.8, 68.6, 55.4, 44.8.

**ESIHRMS**: Found m/z 242.1544; Calcd for $C_{16}H_{20}NO$ $[M+H]^+$ 242.1545.

### 6.3.3.13. Synthesis of ((dimethylamino)(phenyl)methyl)ferrocene (3.25ia)




Prepared from amide **3.23ia** (129 mg, 0.500 mmol) and heated at 60 °C for 16 h, followed by addition of phenylmagnesium bromide.

Purification: Hex:EtOAc:Triethylamine = 96:4:1

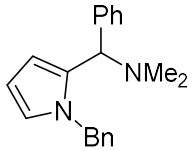
Yield: 66% yield (105 mg, 0.329 mmol) as pale brown solid.

**$^{1}$H NMR** (400 MHz, $CDCl_3$): δ 7.49 (d, *J* = 7.3 Hz, 2H), 7.39 (dd, *J* = 7.3, 7.3 Hz, 2H), 7.30 (t, *J* = 7.3 Hz, 1H), 4.20 (s, 1H), 4.18 (s, 1H), 4.14 (s, 1H), 4.09 (s, 1H), 3.79 (s, 1H), 3.72 (s, 5H), 2.07 (s, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 143.3, 128.5, 128.0, 127.1, 90.2, 72.3, 70.5, 68.7, 68.5, 67.3, 66.4, 44.4.

**ESIHRMS**: Found m/z 320.1099; Calcd for $C_{19}H_{22}NFe$ $[M+H]^+$ 320.1102.

### 6.3.3.14. Synthesis of 1-(1-benzyl-1*H*-pyrrol-2-yl)-*N*,*N*-dimethyl-1-phenylmethanamine (3.25ja)




Prepared from amide **3.23ja** (114 mg, 0.499 mmol) and heated at 40 °C for 24 h, followed by addition of phenylmagnesium bromide.

Purification: Hex:EtOAc:Triethylamine = 97:3:1

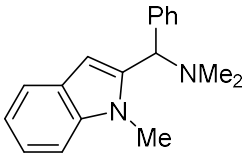
Yield: 77% yield (111 mg, 0.382 mmol) as pale brown solid.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.28 – 7.14 (m, 8H), 6.91 (d, *J* = 7.0 Hz, 2H), 6.56 (d, *J* = 3.2 Hz, 1H), 6.25 (d, *J* = 3.2 Hz, 1H), 6.15 (t, *J* = 3.2 Hz, 1H), 5.14 (d, *J* = 16.2 Hz, 1H), 5.05 (d, *J* = 16.2 Hz, 1H), 4.16 (s, 1H), 2.14 (s, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 140.6, 138.5, 133.4, 128.6, 128.5, 128.1, 127.2, 127.0, 126.5, 121.8, 108.2, 107.3, 68.5, 50.7, 43.8.

**ESIHRMS**: Found m/z 291.1863; Calcd for $C_{20}H_{23}N_2$ $[M+H]^+$ 291.1861.

### 6.3.3.15. Synthesis of *N*,*N*-dimethyl-1-(1-methyl-1*H*-indol-2-yl)-1-phenylmethanamine (3.25ka)




Prepared from amide **3.23ka** (101 mg, 0.500 mmol) and heated at 40 °C for 17 h, followed by addition of phenylmagnesium bromide.

Purification: Hex:EtOAc:Triethylamine = 97:3:1

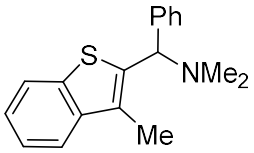
Yield: 84% yield (131 mg, 0.422 mmol) as pale brown oil.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.57 (d, *J* = 7.2 Hz, 1H), 7.43 (d, *J* = 7.2 Hz, 2H), 7.29 (dd, *J* = 7.2, 7.2 Hz, 2H), 7.25 – 7.18 (m, 2H), 7.14 (t, *J* = 7.2 Hz, 1H), 7.06 (dd, *J* = 7.2, 7.2 Hz, 1H), 6.57 (s, 1H), 4.52 (s, 1H), 3.69 (s, 3H), 2.30 (s, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 141.1, 139.9, 137.6, 128.7, 128.3, 127.6, 127.3, 120.9, 120.3, 119.3, 108.8, 100.8, 69.6, 44.2, 30.2.

**ESIHRMS**: Found m/z 265.1703; Calcd for $C_{18}H_{21}N_2$ $[M+H]^+$ 265.1705.

### 6.3.3.16. Synthesis of *N*,*N*-dimethyl-1-(3-methylbenzo[*b*]thiophen-2-yl)-1-phenylmethanamine (3.25la)




Prepared from amide **3.23la** (110 mg, 0.502 mmol) and heated at 40 °C for 20 h, followed by addition of phenylmagnesium bromide.

Purification: Hex:EtOAc:Triethylamine = 98:2:1

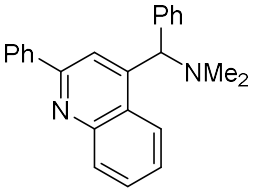
Yield: 59% yield (83.0 mg, 0.295 mmol) as pale yellow solid.

**$^{1}$H NMR** (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 7.8 Hz, 1H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.51 (d, *J* = 7.7 Hz, 2H), 7.32 – 7.28 (m, 3H), 7.25 (d, *J* = 7.8 Hz, 1H), 7.20 (t, *J* = 7.7 Hz, 1H), 4.56 (s, 1H), 2.42 (s, 3H), 2.29 (s, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 142.6, 141.9, 140.5, 139.2, 128.5, 128.0, 127.3, 123.9, 123.6, 122.3, 121.4, 71.1, 45.0, 12.2.

**ESIHRMS**: Found m/z 282.1316; Calcd for $C_{18}H_{20}NS$ $[M+H]^+$ 282.1316.

### 6.3.3.17. Synthesis of *N*,*N*-dimethyl-1-(3-methylbenzo[*b*]thiophen-2-yl)-1-phenylmethanamine (3.25ma)




Prepared from amide **3.25ma** (138 mg, 0.500 mmol) and heated at 40 °C for 24 h, followed by addition of phenylmagnesium bromide.

Purification: Hex:EtOAc:Triethylamine = 97:3:1

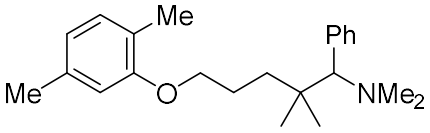
Yield: 89% yield (151 mg, 0.446 mmol) as off-white solid.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.44 (s, 1H), 8.32 (d, *J* = 8.5 Hz, 1H), 8.27 – 8.21 (m, 2H), 8.15 (d, *J* = 8.5 Hz, 1H), 7.70 – 7.60 (m, 1H), 7.60 – 7.42 (m, 6H), 7.31 – 7.22 (m, 2H), 7.21 – 7.12 (m, 1H), 4.90 (s, 1H), 2.29 (s, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 157.3, 149.2, 148.9, 141.1, 140.0, 130.7, 129.2, 129.0, 128.8, 128.6, 128.5, 127.7, 127.5, 126.0, 125.7, 123.1, 117.0, 72.4, 45.0.

**ESIHRMS**: Found m/z 339.1862; Calcd for $C_{24}H_{23}N_2$ $[M+H]^+$ 339.1861.

### 6.3.3.18. Synthesis of 5-(2,5-dimethylphenoxy)-*N*,*N*,2,2-tetramethyl-1-phenylpentan-1-amine (3.25na)




Prepared from amide **3.23na** (139 mg, 0.501 mmol) and heated at 40 °C for 24 h, followed by addition of phenylmagnesium bromider.

Purification: Hex:EtOAc:Triethylamine = 98:2:1

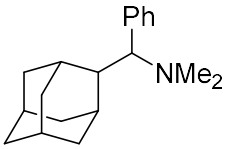
Yield: 85% yield (145 mg, 0.426 mmol) as colorless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.32 – 7.22 (m, 5H), 6.98 (d, *J* = 7.5 Hz, 1H), 6.63 (d, *J* = 7.5 Hz, 1H), 6.58 (s, 1H), 3.86 (t, *J* = 6.6 Hz, 2H), 3.24 (s, 1H), 2.29 (s, 3H), 2.22 (s, 6H), 2.13 (s, 3H), 1.84 – 1.71 (m, 2H), 1.56 – 1.43 (m, 2H), 1.13 (s, 3H), 0.96 (s, 3H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 157.1, 136.9, 136.4, 130.9, 130.2, 127.4, 126.6, 123.6, 120.5, 112.0, 77.7, 68.6, 44.8, 38.6, 37.4, 25.6, 24.3, 21.4, 15.8.

**ESIHRMS**: Found m/z 340.2641; Calcd for $C_{23}H_{34}NO$ $[M+H]^+$ 340.2640.

### 6.3.3.19. Synthesis of 1-((1*r*,3*r*,5*r*,7*r*)-adamantan-2-yl)-N,N-dimethyl-1-phenylmethanamine (3.25oa)




Prepared from amide **3.23oa** (104 mg, 0.502 mmol) and heated at 40 °C for 16 h, followed by addition of phenylmagnesium bromide.

Purification: Hex:EtOAc:Triethylamine = 98:2:1

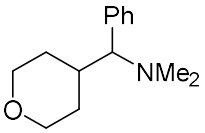
Yield: 64% yield (86.6 mg, 0.321 mmol) as white solid.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.33 (dd, *J* = 7.0, 7.0 Hz, 2H), 7.26 (t, *J* = 7.0 Hz, 1H), 7.13 (d, *J* = 7.0 Hz, 2H), 3.83 (d, *J* = 12.0 Hz, 1H), 2.27 – 2.20 (m, 2H), 2.12 – 2.06 (m, 6H), 2.02 – 1.91 (m, 2H), 1.91 – 1.86 (m, 1H), 1.86 – 1.79 (m, 2H), 1.79 – 1.75 (m, 1H), 1.75 – 1.58 (m, 5H), 1.38 – 1.31 (m, 1H), 1.27 – 1.21 (m, 1H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 135.5, 129.5, 127.6, 126.8, 68.3, 43.8, 40.7, 39.3, 39.2, 38.4, 31.7, 31.4, 29.1, 28.4, 28.1, 27.8.

**ESIHRMS**: Found m/z 270.2218; Calcd for $C_{19}H_{28}N$ $[M+H]^+$ 270.2222.

### 6.3.3.20. Synthesis of *N*,*N*-dimethyl-1-phenyl-1-(tetrahydro-2*H*-pyran-4-yl)methanamine (3.25pa)




Prepared from amide **3.23pa** (78.7 mg, 0.501 mmol) and heated at 40 °C for 14 h, followed by addition of phenylmagnesium bromide.

Purification: EtOAc:Triethylamine = 100:1

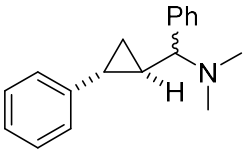
Yield: 85% yield (93.6 mg, 0.427 mmol) as off-white solid.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.33 (dd, *J* = 7.2, 7.2 Hz, 2H), 7.26 (t, *J* = 7.2 Hz, 1H), 7.12 (d, *J* = 7.2 Hz, 2H), 4.02 (dd, *J* = 11.3, 3.4 Hz, 1H), 3.86 (dd, *J* = 11.3, 3.4 Hz, 1H), 3.44 (ddd, *J* = 12.0, 12.0, 2.2 Hz, 1H), 3.32 (ddd, *J* = 12.0, 12.0, 2.2 Hz, 1H), 3.11 (d, *J* = 9.5 Hz, 1H), 2.18 – 2.08 (m, 7H), 1.93 – 1.89 (m, 1H), 1.38 – 1.26 (m, 2H), 1.20 – 1.10 (m, 1H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 135.9, 129.4, 127.7, 127.0, 74.8, 68.2, 68.0, 41.5, 35.9, 31.3, 30.2.

**ESIHRMS**: Found m/z 220.1699 ; Calcd for $C_{14}H_{22}NO$ $[M+H]^+$ 220.1701.

### 6.3.3.21. Synthesis of *N*,*N*-dimethyl-1-phenyl-1-((1*R**,2*R**)-2-phenylcyclopropyl)methanamine (3.25qa)




Prepared from amide **3.23qa** (94.9 mg, 0.502 mmol) and heated at 40 °C for 24 h, followed by addition of phenylmagnesium bromide.

Purification: Hex:EtOAc:Triethylamine = 97:3:1

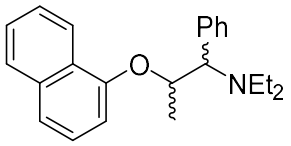
Yield: 71% yield (89.7 mg, 0.358 mmol) as pale yellow oil with an estimated 83:17 diastereomeric mixture (based on $^1$H NMR spectroscopy analysis).

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.34 – 7.24 (m, 0.83 X 7H + 0.17 X 7H), 7.17 – 7.12 (m, 0.83 X 1H + 0.17 X 1H), 7.05 (d, *J* = 7.7 Hz, 0.83 X 2H), 6.82 (d, *J* = 7.7 Hz, 0.17 X 2H), 2.46 (d, *J* = 9.1 Hz, 0.17 X 1H), 2.33 (d, *J* = 9.1 Hz, 0.83 X 1H), 2.31 (s, 0.17 X 6H), 2.25 (s, 0.83 X 6H), 1.94 – 1.89 (m, 0.83 X 1H), 1.63 – 1.58 (m, 0.17 X 1H), 1.41 – 1.34 (m, 0.83 X 1H + 0.17 X 1H), 1.25 – 1.21 (m, 0.17 X 1H), 1.07 – 1.02 (m, 0.17 X 1H), 0.85 – 0.80 (m, 0.83 X 1H), 0.73 – 0.68 (m, 0.83 X 1H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 143.6, 143.4, 142.4, 141.8, 128.5, 128.4, 128.3, 128.2, 128.0, 127.8, 127.1, 127.1, 126.4, 125.7, 125.6, 125.5, 77.3, 76.6, 44.5, 44.0, 29.1, 27.0, 26.8, 20.8, 17.8, 13.5.

**ESIHRMS**: Found m/z 252.1756; Calcd for $C_{18}H_{22}N$ $[M+H]^+$ 252.1752.

### 6.3.3.22. Synthesis of *N*,*N*-diethyl-2-(naphthalen-1-yloxy)-1-phenylpropan-1-amine (3.25rb)




Prepared from amide **3.23rb** (136 mg, 0.501 mmol) and heated at 40 °C for 24 h, followed by addition of phenylmagnesium bromide.

Purification: Hex:EtOAc:Triethylamine = 98:2:1

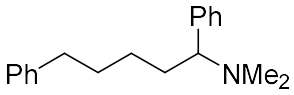
Yield: 81% yield (136 mg, 0.407 mmol) as pale yellow oil with an estimated 82:18 diastereomeric mixture (based on $^1$H NMR spectroscopy analysis).

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 8.21 (d, *J* = 8.1 Hz, 0.82 X 1H), 7.85 (d, *J* = 8.1 Hz, 0.18 X 1H), 7.78 (d, *J* = 8.1 Hz, 0.82 X 1H), 7.71 (d, *J* = 8.1 Hz, 0.18 X 1H), 7.48 – 7.16 (m, 0.82 X 10H + 0.18 X 10H), 6.92 – 6.89 (m, 0.82 X 1H + 0.18 X 1H), 5.16 – 5.03 (m, 0.82 X 1H + 0.18 X 1H), 4.07 (d, *J* = 6.6 Hz, 0.82 X 1H), 4.00 (d, *J* = 7.5 Hz, 0.18 X 1H), 2.82 – 2.66 (m, 0.82 X 2H + 0.18 X 2H), 2.51 (dq, *J* = 13.7, 6.9 Hz, 0.82 X 2H), 2.33 (dq, *J* = 13.7, 6.9 Hz, 0.18 X 2H), 1.52 (d, *J* = 6.0 Hz, 0.18 X 3H), 1.25 (d, *J* = 6.0 Hz, 0.82 X 3H), 1.07 (t, *J* = 7.1 Hz, 0.18 X 6H), 1.00 (t, *J* = 7.1 Hz, 0.82 X 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 153.9, 153.8, 139.2, 137.9, 134.8, 134.6, 129.5, 129.3, 127.8, 127.7, 127.3, 127.13, 127.05, 126.8, 126.6, 126.5, 126.2, 126.1, 125.8, 125.7, 124.9, 124.8, 122.8, 122.4, 119.9 (overlapped), 105.7 (overlapped), 74.3, 73.9, 68.9, 68.6, 43.8, 43.6, 17.9, 16.8, 13.3, 12.5.

**ESIHRMS**: Found m/z 334.2174; Calcd for $C_{23}H_{28}NO$ $[M+H]^+$ 334.2171.

### 6.3.3.23. Synthesis of *N*,*N*-dimethyl-1,5-diphenylpentan-1-amine (3.25sa)




Prepared from amide **3.23sa** (103 mg, 0.502 mmol) at 40 °C for 17 h, followed by addition of phenylmagnesium bromide.

Purification: Hex:EtOAc:Triethylamine = 97:3:1

Yield: 48% yield (64.0 mg, 0.239mmol) as colorless oil.

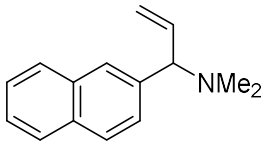
**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.31 (dd, *J* = 7.2, 7.2 Hz, 2H), 7.27 – 7.19 (m, 5H), 7.14 (t, *J* = 7.2 Hz, 1H), 7.12 (d, *J* = 7.0 Hz, 2H), 3.15 (dd, *J* = 9.6, 4.9 Hz, 1H), 2.58 – 2.45 (m, 2H), 2.16 (s, 6H), 1.96 – 1.87 (m, 1H), 1.81 – 1.71 (m, 1H), 1.64 – 1.51 (m, 2H), 1.26 – 1.07 (m, 2H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 142.7, 140.3, 128.6, 128.3, 128.2, 128.0, 127.0, 125.5, 70.8, 42.7, 35.8, 33.0, 31.6, 26.2.

**ESIHRMS**: Found m/z 268.2070; Calcd for $C_{19}H_{26}N$ $[M+H]^+$ 268.2065.

## 6.3.4. Synthesis of α-functionalized tertiary amines 3.26-3.34

### 6.3.4.1. Synthesis of *N*,*N*-dimethyl-1-(naphthalen-2-yl)prop-2-en-1-amine (3.26aa)




Prepared from amide **3.23aa** (99.4 mg, 0.499 mmol) heat at 60 °C for 5 h, followed by addition of vinylmagnesium chloride.

Purification: Hex:EtOAc:Triethylamine = 70:30:1

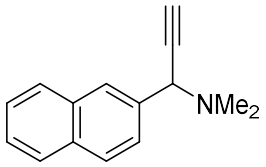
Yield: 80% yield 84.1 mg, 0.398 mmol) as pale yellow oil.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.82 – 7.79 (m, 3H), 7.75 (s, 1H), 7.51 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.48 – 7.41 (m, 2H), 6.08 (ddd, *J* = 17.1, 10.1, 8.8 Hz, 1H), 5.27 (dd, *J* = 17.1, 0.9 Hz, 1H), 5.12 (dd, *J* = 10.1, 1.5 Hz, 1H), 3.71 (d, *J* = 8.8 Hz, 1H), 2.24 (s, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 140.0, 139.9, 133.5, 132.9, 128.3, 127.8, 127.6, 126.4, 126.0, 125.9, 125.6, 116.4, 76.2, 43.7.

**ESIHRMS**: Found m/z 212.1438; Calcd for $C_{15}H_{18}N$ $[M+H]^+$ 212.1439.

### 6.3.4.2. Synthesis of *N*,*N*-dimethyl-1-(naphthalen-2-yl)prop-2-yn-1-amine (3.27aa)




Prepared from amide **3.23aa** (99.6 mg, 0.500 mmol) heat at 60 °C for 5 h, followed by addition of ethynylmagnesium bromide.

Purification: Hex:EtOAc = 92:8

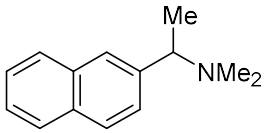
Yield: 79% yield (82.6 mg, 0.395 mmol) as pale yellow solid.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 8.04 (s, 1H), 7.87 – 7.82 (m, 3H), 7.66 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.50 – 7.45 (m, 2H), 4.78 (d, *J* = 2.1 Hz, 1H), 2.63 (d, *J* = 2.1 Hz, 1H), 2.29 (s, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 135.7, 133.1, 133.0, 128.1, 127.9, 127.6, 127.1, 126.3, 126.0, 126.0, 78.7, 76.2, 61.7, 41.4.

**ESIHRMS**: Found m/z 210.1284; Calcd for $C_{15}H_{16}N$ $[M+H]^+$ 210.1283.

### 6.3.4.3. Synthesis of *N*,*N*-dimethyl-1-(naphthalen-2-yl)ethan-1-amine (3.28aa)




Prepared from amide **3.23aa** (99.4 mg, 0.499 mmol) heat at 60 °C for 5 h, followed by addition of methylmagnesium bromide.

Purification: Hex:EtOAc:Triethylamine = 98:2:1

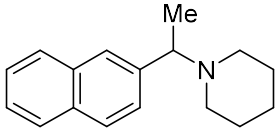
Yield: 81% yield (80.9 mg, 0.406 mmol) as pale yellow oil.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.82 – 7.79 (m, 3H), 7.71 (s, 1H), 7.50 – 7.41 (m, 3H), 3.39 (q, *J* = 6.7 Hz, 1H), 2.24 (s, 6H), 1.44 (d, *J* = 6.7 Hz, 3H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 142.0, 133.4, 132.8, 127.9, 127.8, 127.6, 125.91, 125.85 (overlapped), 125.4, 66.2, 43.4, 20.3.

**ESIHRMS**: Found m/z 200.1441; Calcd for $C_{14}H_{18}N$ $[M+H]^+$ 200.1439.

### 6.3.4.4. Synthesis of 1-(1-(naphthalen-2-yl)ethyl)piperidine (3.28ad)




Prepared from amide **3.23ad** (120 mg, 0.500 mmol) and heated at 60 °C for 5 h, followed by addition of methylmagnesium bromide.

Purification: Hex:EtOAc:Triethylamine = 60:40:1

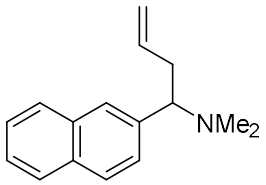
Yield: 84% yield (101 mg, 0.420 mmol) as pale yellow oil.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.83 – 7.78 (m, 3H), 7.69 (s, 1H), 7.51 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.47 – 7.40 (m, 2H), 3.53 (q, *J* = 6.7 Hz, 1H), 2.47 – 2.45 (m, 2H), 2.40 – 2.34 (m, 2H), 1.59 – 1.53 (m, 4H), 1.44 (d, *J* = 6.7 Hz, 3H), 1.41 – 1.35 (m, 2H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 141.8, 133.3, 132.7, 127.8, 127.64, 127.56, 126.3, 126.1, 125.8, 125.4, 65.3, 51.7, 26.2, 24.6, 19.4.

**ESIHRMS**: Found m/z 240.1757; Calcd for $C_{17}H_{22}N$ $[M+H]^+$ 240.1752.

### 6.3.4.5. Synthesis of *N*,*N*-dimethyl-1-(naphthalen-2-yl)but-3-en-1-amine (3.29aa)




Prepared from amide **3.23aa** (99.7 mg, 0.500 mmol) and heated at 60 °C for 5 h, followed by addition of allylmagnesium bromide.

Purification: Hex:EtOAc:Triethylamine = 80:20:1

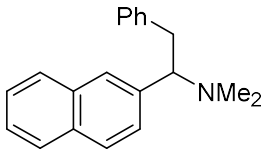
Yield: 74% yield (83.1 mg, 0.369 mmol) as pale yellow oil.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.83 – 7.79 (m, 3H), 7.65 (s, 1H), 7.49 – 7.41 (m, 3H), 5.60 (ddt, *J* = 17.1, 10.1, 7.0 Hz, 1H), 4.98 (ddd, *J* = 17.1, 3.3, 1.5 Hz, 1H), 4.90 (ddt, *J* = 10.1, 2.0, 1.0 Hz, 1H), 3.39 (dd, *J* = 9.0, 5.2 Hz, 1H), 2.77 – 2.70 (m, 1H), 2.67 – 2.58 (m, 1H), 2.25 (s, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 138.1, 135.5, 133.2, 132.8, 127.8, 127.7, 127.6, 127.4, 126.6, 125.9, 125.6, 116.6, 70.9, 43.1, 37.9.

**ESIHRMS**: Found m/z 226.1597; Calcd for $C_{16}H_{20}N$ $[M+H]^+$ 226.1596.

### 6.3.4.6. Synthesis of *N*,*N*-dimethyl-1-(naphthalen-2-yl)-2-phenylethan-1-amine (3.30aa)




Prepared from amide **3.23aa** (99.6 mg, 0.500 mmol) and heated at 60 °C for 5 h, followed by addition of benzylmagnesium chloride.

Purification: Hex:EtOAc:Triethylamine = 50:50:1

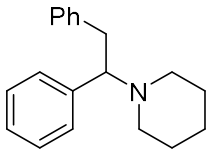
Yield: 85% yield (117 mg, 0.426 mmol) as white solid.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.80 – 7.76 (m, 1H), 7.75 – 7.70 (m, 2H), 7.49 (s, 1H), 7.44 – 7.39 (m, 2H), 7.36 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.10 – 7.01 (m, 3H), 6.95 (d, *J* = 8.1 Hz, 1H), 3.61 (dd, *J* = 9.8, 4.7 Hz, 1H), 3.39 (dd, *J* = 13.3, 4.7 Hz, 1H), 3.07 (dd, *J* = 13.3, 9.8 Hz, 1H), 2.30 (s, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 139.3, 137.4, 133.0, 132.7, 129.3, 128.0, 127.8, 127.7, 127.51, 127.49, 126.7, 125.8, 125.7, 125.5, 72.9, 43.1, 39.9.

**ESIHRMS**: Found m/z 276.1754; Calcd for $C_{20}H_{22}N$ $[M+H]^+$ 276.1752.

### 6.3.4.7. Synthesis of 1-(1,2-diphenylethyl)piperidine (3.30td)




Prepared from amide **3.23td** (94.2 mg, 0.498 mmol) and heated at 60 °C for 4 h, followed by addition of benzylmagnesium chloride.

Purification: Hex:EtOAc:Triethylamine = 90:10:1

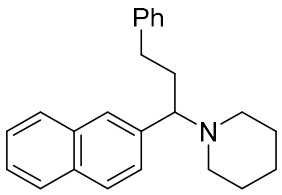
Yield: 79% yield (104 mg, 0.394 mmol) as colorless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.23 (dd, *J* = 7.0 Hz, 2H), 7.18 (t, *J* = 7.0 Hz, 1H), 7.14 – 7.10 (m, 4H), 7.07 (t, *J* = 7.0 Hz, 1H), 6.99 (d, *J* = 7.0 Hz, 2H), 3.59 (dd, *J* = 9.4, 5.2 Hz, 1H), 3.30 (dd, *J* = 13.3, 5.2 Hz, 1H), 2.99 (dd, *J* = 13.3, 9.4 Hz, 1H), 2.45 – 2.40 (m, 4H), 1.61 – 1.50 (m, 4H), 1.39 – 1.33 (m, 2H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 134.0, 139.4, 129.4, 128.9, 127.8, 127.6, 126.8, 125.6, 72.3, 51.4, 39.2, 26.3, 24.6.

**ESIHRMS**: Found m/z 266.1913; Calcd for $C_{19}H_{24}N$ $[M+H]^+$ 266.1909.

### 6.3.4.8. Synthesis of 1-(1-(naphthalen-2-yl)-3-phenylpropyl)piperidine (3.31ad)




Prepared from amide **3.23ad** (120 mg, 0.501 mmol) and heated at 60 °C for 5 h, followed by addition of phenethylmagnesium bromide.

Purification: Hex:EtOAc:Triethylamine = 70:30:1

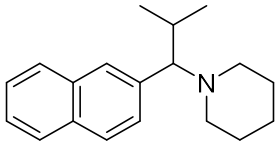
Yield: 80% yield (131 mg, 0.399 mmol) as colorless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.85 – 7.81 (m, 3H), 7.64 (s, 1H), 7.50 – 7.41 (m, 3H), 7.24 (dd, *J* = 7.3, 7.3 Hz, 2H), 7.15 (t, *J* = 7.3 Hz, 1H), 7.11 (d, *J* = 7.3 Hz, 2H), 3.52 (dd, *J* = 9.1, 5.2 Hz, 1H), 2.56 – 2.29 (m, 7H), 2.23 – 2.13 (m, 1H), 1.62 – 1.48 (m, 4H), 1.35 – 1.29 (m, 2H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 142.3, 137.1, 133.1, 132.8, 128.4, 128.2, 127.83, 127.81, 127.6, 127.5, 126.9, 125.9, 125.7, 125.6, 69.7, 51.2, 34.1, 32.8, 26.2, 24.5.

**ESIHRMS**: Found m/z 330.2217; Calcd for $C_{24}H_{28}N$ $[M+H]^+$ 330.2222.

### 6.3.4.9. Synthesis of 1-(2-methyl-1-(naphthalen-2-yl)propyl)piperidine (3.32ad)




Prepared from amide **3.23ad** (120 mg, 0.501 mmol) and heated at 60 °C for 5 h, followed by addition of isopropylmagnesium chloride.

Purification: Hex:EtOAc:Triethylamine = 98:2:1

Yield: 83% yield (110 mg, 0.413 mmol) as pale yellow solid.

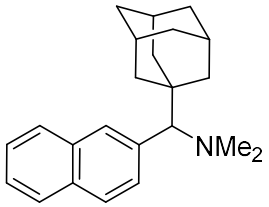
**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.83 – 7.81 (m, 2H), 7.76 (d, *J* = 8.5 Hz, 1H), 7.55 (s, 1H), 7.47 – 7.41 (m, 2H), 7.32 (dd, *J* = 8.5, 1.6 Hz, 1H), 3.13 (d, *J* = 9.3 Hz, 1H), 2.41

– 2.32 (m, 3H), 2.27 (brs, 2H), 1.60 – 1.45 (m, 4H), 1.30 – 1.25 (m, 2H), 1.04 (d, *J* = 6.5 Hz, 3H), 0.72 (d, *J* = 6.5 Hz, 3H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 136.1, 133.0, 132.6, 128.0, 127.8, 127.6, 127.5, 126.7, 125.6, 125.2, 77.0, 50.9, 28.0, 26.6, 24.9, 20.7, 19.6.

**ESIHRMS**: Found m/z 268.2063; Calcd for $C_{19}H_{26}N$ $[M+H]^+$ 268.2065.

### 6.3.4.10. Synthesis of 1-((3*r*,5*r*,7*r*)-adamantan-1-yl)-*N*,*N*-dimethyl-1-(naphthalen-2-yl)methanamine (3.33aa)




Prepared from amide **3.23aa** (99.8 mg, 0.5009 mmol) and heated at 60 °C for 5 h, followed by addition of 1-adamantylmagnesium bromide.[6]

Purification: Hex:EtOAc:Triethylamine = 98:2:1

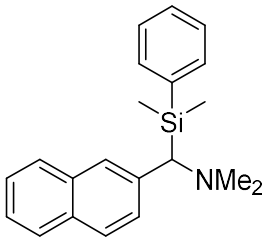
Yield: 38% yield (60.2 mg, 0.188 mmol) as white solid.

**$^{1}$H NMR** (400 MHz, $CDCl_3$): δ 7.84 – 7.82 (m, 2H), 7.77 (d, *J* = 8.5 Hz, 1H), 7.62 (s, 1H), 7.49 – 7.42 (m, 3H), 3.16 (s, 1H), 2.28 (s, 6H), 1.95 – 1.88 (m, 6H), 1.69 – 1.62 (m, 9H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 134.4, 132.9, 132.3, 130.1, 129.3, 127.9, 127.4, 126.4, 125.7, 125.5, 81.1, 45.2, 41.1, 38.3, 37.1, 28.8.

**ESIHRMS**: Found m/z 320.2379; Calcd for $C_{23}H_{30}N$ $[M+H]^+$ 320.2378.

### 6.3.4.11. Synthesis of 1-(dimethyl(phenyl)silyl)-*N*,*N*-dimethyl-1-(naphthalen-2-yl)methanamine (3.34aa)




Prepared from amide **3.23aa** (99.4 mg, 0.497 mmol) and heated at 60 °C for 5 h, followed by addition of dimethylphenylsilylmagnesium bromide.[7]

Purification: Hex:EtOAc:Triethylamine = 98:2:1

Yield: 64% yield (102 mg, 0.320 mmol) as pale yellow oil.

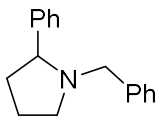
**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.78 (d, *J* = 7.6 Hz, 1H), 7.72 (dd, *J* = 7.6, 7.6 Hz, 2H), 7.59 (s, 1H), 7.51 – 7.49 (m, 2H), 7.45 – 7.39 (m, 2H), 7.35 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.33 – 7.27 (m, 3H), 3.17 (s, 1H), 2.23 (s, 6H), 0.41 (s, 3H), 0.02 (s, 3H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ140.1, 138.9, 133.9, 133.5, 132.1, 128.9, 127.7 (overlapped), 127.5 (overlapped), 127.3, 126.5, 125.8, 125.0, 67.6, 47.3, -1.4, -4.7.

**ESIHRMS**: Found m/z 320.1838; Calcd for $C_{21}H_{26}NSi$ $[M+H]^+$ 320.1835.

### 6.3.5. Synthesis of α-functionalized pyrrolidines and piperidines 3.25-3.32

#### 6.3.5.1. Synthesis of 1-benzyl-2-phenylpyrrolidine (3.25u)




Prepared from amide **3.23u** (87.3 mg, 0.498 mmol) and heated at 40 °C for 16 h, followed by addition of phenylmagnesium bromide.

Purification: Hex:EtOAc = 97:3

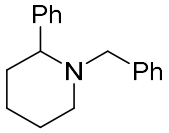
Yield: 67% yield (79.6 mg, 0.335 mmol) as white solid.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.47 (d, *J* = 7.1 Hz, 2H), 7.34 (dd, *J* = 7.5, 7.5 Hz, 2H), 7.28 – 7.26 (m, 4H), 7.25 – 7.18 (m, 2H), 3.85 (d, *J* = 13.1 Hz, 1H), 3.36 (t, *J* = 8.0 Hz, 1H), 3.12 – 3.07 (m, 1H), 3.03 (d, *J* = 13.1 Hz, 1H), 2.23 – 2.14 (m, 2H), 1.93 – 1.84 (m, 1H), 1.82 – 1.68 (m, 2H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 143.9, 139.8, 128.7, 128.4, 128.1, 127.5, 127.0, 126.6, 69.6, 58.1, 53.3, 35.2, 22.3.

**ESIHRMS**: Found m/z 238.1595; Calcd for $C_{17}H_{20}N$ $[M+H]^+$ 238.1596.

### 6.3.5.2. Synthesis of 1-benzyl-2-phenylpiperidine (3.25v)




Prepared from amide **3.23v** (94.3 mg, 0.498 mmol) and heated at 40 °C for 16 h, followed by addition of phenylmagnesium bromide.

Purification: Hex:EtOAc = 98:2

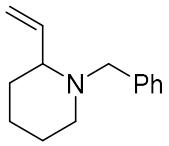
Yield: 78% yield (97.6 mg, 0.388 mmol) as white solid.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.45 (d, *J* = 7.2 Hz, 2H), 7.32 (dd, *J* = 7.7 Hz, 2H), 7.26 – 7.25 (m, 4H), 7.23 – 7.16 (m, 2H), 3.76 (d, *J* = 13.5 Hz, 1H), 3.10 (dd, *J* = 11.2, 2.7 Hz, 1H), 2.96 (d, *J* = 11.2 Hz, 1H), 2.80 (d, *J* = 13.5 Hz, 1H), 1.96 – 1.90 (m, 1H), 1.79 – 1.76 (m, 2H), 1.67 – 1.51 (m, 3H), 1.42 – 1.31 (m, 1H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 145.7, 139.8, 128.7, 128.5, 128.0, 127.4 126.8, 126.5, 69.2, 59.8, 53.3, 37.0, 26.0, 25.2.

**ESIHRMS**: Found m/z 252.1752; Calcd for $C_{18}H_{22}N$ $[M+H]^+$ 252.1752.

### 6.3.5.3. Synthesis of 1-benzyl-2-vinylpiperidine (3.26v)




Prepared from amide **3.23v** (94.4 mg, 0.497 mmol) and heated at 40 °C for 16 h, followed by addition of vinylmagnesium chloride.

Purification: Hex:EtOAc = 97:3

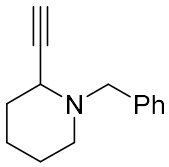
Yield: 68% yield (68.1 mg, 0.338 mmol) as colorless oil.

**$^{1}$H NMR** (400 MHz, $CDCl_3$): δ 7.32 – 7.26 (m, 4H), 7.23 – 7.19 (m, 1H), 5.88 (ddd, *J* = 17.3, 10.2, 8.6 Hz, 1H), 5.18 (dd, *J* = 17.3, 1.6 Hz, 1H), 5.09 (dd, *J* = 10.2, 1.6 Hz, 1H), 4.04 (d, *J* = 13.6 Hz, 1H), 3.04 (d, *J* = 13.6 Hz, 1H), 2.79 (dt, *J* = 6.9, 3.1 Hz, 1H), 2.69 – 2.64 (m, 1H), 1.87 (td, *J* = 11.4, 3.1 Hz, 1H), 1.72 – 1.60 (m, 2H), 1.55 – 1.43 (m, 3H), 1.34 – 1.26 (m, 1H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 142.5, 139.4, 129.1, 128.0, 126.6, 115.6, 66.7, 59.8, 52.1, 33.7, 25.8, 23.9.

**ESIHRMS**: Found m/z 202.1595; Calcd for $C_{14}H_{20}N$ $[M+H]^+$ 202.1596.

### 6.3.5.4. Synthesis of 1-benzyl-2-ethynylpiperidine (3.27v)




Prepared from amide **3.23v** (94.9 mg, 0.502 mmol) and heated at 40 °C for 16 h, followed by addition of ethynylmagnesium bromide.

Purification: Hex:EtOAc:Triethylamine = 99:1

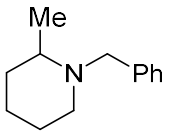
Yield: 78% yield (77.5 mg, 0.391mmol) as colorless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.36 (d, *J* = 7.2 Hz, 2H), 7.30 (dd, *J* = 7.2 Hz, 2H), 7.23 (t, *J* = 7.2 Hz, 1H), 3.64 (d, *J* = 13.1 Hz, 1H), 3.55 (d, *J* = 13.1 Hz, 1H), 3.52 – 3.51 (m, 1H), 2.55 – 2.47 (m, 2H), 2.34 (d, *J* = 2.2 Hz, 1H), 1.77 – 1.71 (m, 2H), 1.67 – 1.61 (m, 1H), 1.58 – 1.47 (m, 3H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 138.6, 129.2, 128.1, 126.9, 81.4, 74.0, 60.3, 50.9, 48.9, 31.1, 25.7, 20.4.

**ESIHRMS**: Found m/z 200.1441; Calcd for $C_{14}H_{18}N$ $[M+H]^+$ 200.1439.

### 6.3.5.5. Synthesis of 1-benzyl-2-methylpiperidine (3.28v)




Prepared from amide **3.23v** (94.8 mg, 0.502 mmol) and heated at 40 °C for 16 h, followed by addition of methylmagnesium bromide.

Purification: Hex:EtOAc = 88:12

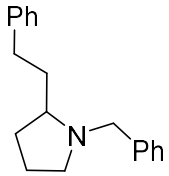
Yield: 54% yield (51.1 mg, 0.269 mmol) as colorless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.33 – 7.27 (m, 4H), 7.24 – 7.20 (m, 1H), 3.99 (d, *J* = 13.4 Hz, 1H), 3.20 (d, *J* = 13.4 Hz, 1H), 2.75 – 2.70 (m, 1H), 2.32 – 2.27 (m, 1H), 1.98 – 1.91 (m, 1H), 1.67 – 1.61 (m, 2H), 1.54 – 1.22 (m, 4H), 1.17 (d, *J* = 6.2 Hz, 3H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 139.2, 129.2, 128.0, 126.7, 58.4, 56.3, 52.1, 34.6, 25.9, 24.0, 19.5.

**ESIHRMS**: Found m/z 190.1591; Calcd for $C_{13}H_{20}N$ $[M+H]^+$ 190.1596.

### 6.3.5.6. Synthesis of 1-benzyl-2-phenethylpyrrolidine (3.31u)




Prepared from amide **3.23u** (87.4 mg, 0.499 mmol) and heated at 40 °C for 16 h, followed by addition of phenethylmagnesium bromide.

Purification: Hex:EtOAc:Triethylamine = 95:5:1

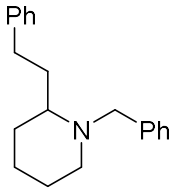
Yield: 76% yield (101 mg, 0.380 mmol) as pale yellow oil.

**$^{1}$H NMR** (400 MHz, $CDCl_3$): δ 7.30 – 7.26 (m, 6H), 7.24 – 7.16 (m, 4H), 4.02 (d, *J* = 12.9 Hz, 1H), 3.17 (d, *J* = 12.9 Hz, 1H), 2.94 – 2.89 (m, 1H), 2.79 – 2.72 (m, 1H), 2.62 – 2.55 (m, 1H), 2.44 – 2.37 (m, 1H), 2.14 – 1.94 (m, 3H), 1.75 – 1.54 (m, 4H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 142.7, 139.6, 129.0, 128.4 (overlapped), 128.2, 126.8, 125.7, 63.7, 58.6, 54.2, 35.9, 32.6, 30.3, 22.1.

**ESIHRMS**: Found m/z 266.1910; Calcd for $C_{19}H_{24}N$ $[M+H]^+$ 266.1909.

### 6.3.5.7. Synthesis of 1-benzyl-2-phenethylpiperidine (3.31v)




Prepared from amide **3.23v** (94.9 mg, 0.501 mmol) and heated at 40 °C for 16 h, followed by addition of phenethylmagnesium bromide.

Purification: Hex:EtOAc:Triethylamine = 95:5:1

Yield: 91% yield (121 mg, 0.456 mmol) as pale orange solid.

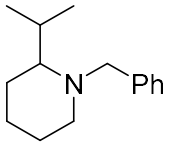
**$^{1}$H NMR** (400 MHz, $CDCl_3$): δ 7.33 (d, *J* = 7.0 Hz, 2H), 7.31 – 7.22 (m, 5H), 7.20 – 7.14 (m, 3H), 3.99 (d, *J* = 13.5 Hz, 1H), 3.27 (d, *J* = 13.5 Hz, 1H), 2.78 – 2.71 (m, 2H),

2.65 – 2.58 (m, 1H), 2.42 – 2.38 (m, 1H), 2.10 – 2.04 (m, 1H), 1.99 – 1.83 (m, 2H), 1.72 – 1.67 (m, 2H), 1.58 – 1.45 (m, 3H), 1.39 – 1.29 (m, 1H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 143.0, 139.8, 128.9, 128.3 (overlapped), 128.1, 126.6, 125.6, 60.1, 57.4, 51.4, 33.5, 31.7, 29.9, 24.9, 23.5.

**ESIHRMS**: Found m/z 280.2061; Calcd for $C_{20}H_{26}N$ $[M+H]^+$ 280.2065.

### 6.3.5.8. Synthesis of 1-benzyl-2-isopropylpiperidine (3.32v)




Prepared from amide **3.23v** (94.6 mg, 0.500 mmol) and heated at 40 °C for 16 h, followed by addition of isopropylmagnesium chloride.

Purification: Hex:EtOAc:Triethylamine = 98:2:1

Yield: 83% yield (90.2 mg, 0.415 mmol) as pale yellow oil.

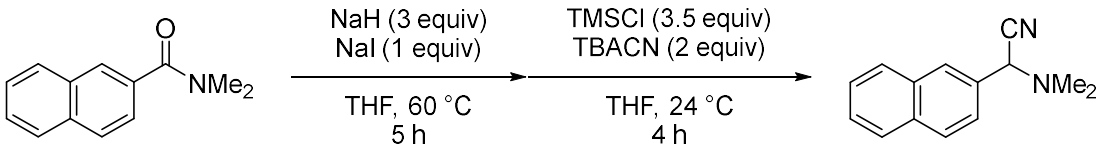
**$^{1}$H NMR** (400 MHz, $CDCl_3$): δ 7.33 (d, *J* = 7.0 Hz, 2H), 7.29 (dd, *J* = 7.0 Hz, 2H), 7.21 (t, *J* = 7.0 Hz, 1H), 4.10 (d, *J* = 13.4 Hz, 1H), 3.09 (d, *J* = 13.4 Hz, 1H), 2.81 (dtd, *J* = 11.8, 3.6, 1.3 Hz, 1H), 2.31 – 2.20 (m, 1H), 2.04 – 2.00 (m, 1H), 1.98 – 1.91 (m, 1H), 1.75 – 1.71 (m, 1H), 1.63 – 1.58 (m, 1H), 1.48 – 1.37 (m, 2H), 1.31 – 1.21 (m, 2H), 0.94 (d, *J* = 5.1 Hz, 3H), 0.92 (d, *J* = 5.1 Hz, 3H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 140.3, 128.8, 128.1, 126.5, 66.5, 56.5, 52.6, 27.6, 24.7, 24.5, 23.5, 20.1, 16.0.

**ESIHRMS**: Found m/z 218.1908; Calcd for $C_{15}H_{24}N$ $[M+H]^+$ 218.1909.

### 6.3.6. Synthesis of α-amino nitriles

#### 6.3.6.1. Synthesis of 2-(dimethylamino)-2-(naphthalen-2-yl)acetonitrile (3.35aa)




**3.23aa** **3.35aa** 86%

Prepared from amide **3.23aa** (99.6 mg, 0.500mmol) and heated at 60 °C for 5 h, followed by slight modification of the procedure with full consumption of amide based on TLC, the reaction mixture was cooled down to 24 °C. TMSCl (220 μL, 1.73 mmol) and tetrabutylammonium cyanide (270 mg, 1.00 mmol) was added and stirred at 24 °C for 4 h.

Purification: Hex:EtOAc: = 88:12

Yield: 86% yield (93.9 mg, 0.430 mmol) as white solid.

**$^{1}$H NMR** (400 MHz, $CDCl_3$): δ 8.02 (s, 1H), 7.89 – 7.84 (m, 3H), 7.59 – 7.56 (m, 1H), 7.55 – 7.51 (m, 2H), 5.00 (s, 1H), 2.36 (s, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 133.3, 132.9, 131.1, 128.7, 128.2, 127.6, 126.9, 126.8, 126.6, 125.1, 115.0, 63.3, 41.8.

**ESIHRMS**: Found m/z 211.1239; Calcd for $C_{14}H_{15}N_2$ $[M+H]^+$ 211.1235.

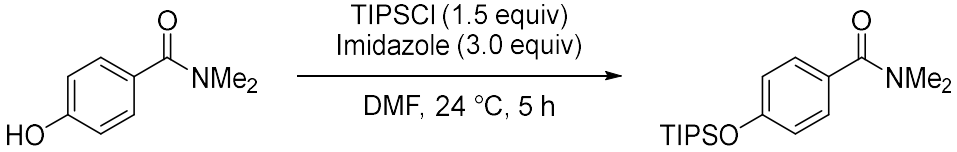
### 6.3.7. References for section 6.3


1. S. Wangngae, C. Duangkamol, M. Pattarawarapan, W. Phakhodee, *RSC Adv.* **2015,** *5*, 25789-25793.
2. M. Kim, S. Sharma, N. K. Mishra, S. Han, J. Park, M. Kim, Y. Shin, J. H. Kwak, S. H. Han, I. S. Kim, *Chem. Commun.* **2014,** *50*, 11303-11306.
3. A. Volkov, E. Buitrago, H. Adolfsson, *Eur. J. Org. Chem.* **2013,** *2013*, 2066-2070.
4. C. G. Jørgensen, B. Frølund, J. Kehler, A. A. Jensen, *ChemMedChem* **2011,** *6*, 725-736.
5. S. N. Gockel, K. L. Hull, *Org. Lett.* **2015,** *17*, 3236-3239.
6. G. Molle, P. Bauer, J. E. Dubois, *J. Org. Chem.* **1982,** *47*, 4120-4128.
7. W. Xue, R. Shishido, M. Oestreich, *Angew. Chem. Int. Ed.* **2018,** *57*, 12141-12145.

## 6.4 Experimental data for Chapter 4

### 6.4.1 Synthesis of amides

#### 6.4.1.1 Synthesis of *N,N*-dimethyl-4-((triisopropylsilyl)oxy)benzamide (4.6h)[1]



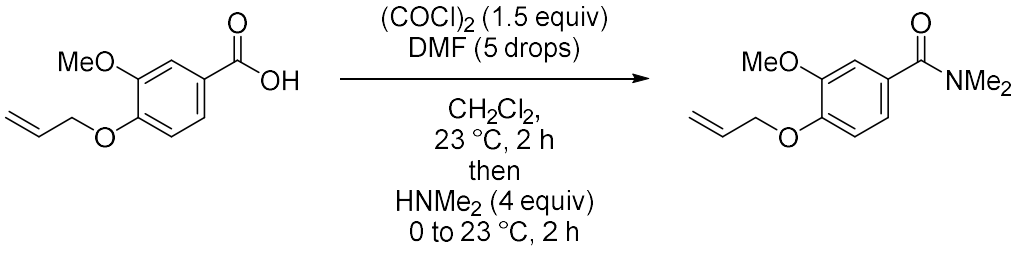

To a solution of 4-hydroxy-N,N-dimethylbenzamide[2] (1.32 g, 8.01 mmol) and imidazole (1.63 g, 24.0 mmol) in DMF (20 mL) was added TIPSCl (2.60 mL, 12.2 mmol), and the reaction mixture was stirred at 24 °C for 5 h. The reaction was quenched with water, and the organic materials were extracted thrice with ether. The combined extracts were washed thrice with water followed by sat. aq. $NaHCO_3$ and dried over $MgSO_4$. The solvent was removed *in vacuo* and the resulting crude mixture was purified by flash column chromatography (silica gel, Hex:EtOAc = 7:3) to give a pale yellow oil **4.6h** (2.16 g, 6.70 mmol) in 84% yield.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.33 (d, $J$ = 8.6 Hz, 2H), 6.88 (d, $J$ = 8.6 Hz, 2H), 3.05 (brs, 6H), 1.27 (sept, $J$ = 7.2 Hz, 3H), 1.10 (d, $J$ = 7.2 Hz, 18H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 171.6, 157.3, 129.0, 128.7, 119.5, 77.0, 39.7, 35.6, 17.8, 12.6.

**ESIHRMS**: Found m/z 322.2202; Calcd for $C_{18}H_{32}NO_2Si$: $(M+H)^+$ 322.2202

#### 6.4.1.2 Synthesis of 4-(allyloxy)-3-methoxy-*N,N*-dimethylbenzamide (4.6m)



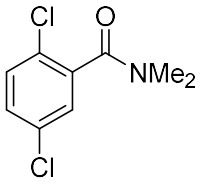
To a solution of 4-(allyloxy)-3-methoxybenzoic acid[3] (1.97 g, 9.46 mmol) in $CH_2Cl_2$ (20 mL) was added $(COCl)_2$ (1.2 mL, 14.2 mmol) and DMF (5 drops) at 23 °C. The reaction mixture was stirred at 23 °C for 2 h, before adding $Me_2NH$ (40 w/w% in water; 4.79 mL, 37.8 mmol) dropwise at 0 °C, and the reaction mixture was stirred continuously at 23 °C for 2 h. The reaction was then quenched with water and organic materials were extracted twice with $CH_2Cl_2$, washed with saturated aqueous $NaHCO_3$ solution and then dried over $MgSO_4$. The volatile materials was removed *in vacuo* and the resulting crude mixture was purified by flash column chromatography (silica gel, Hex:EtOAc = 1:1) to give a white solid **4.6m** (1.42 g, 6.05 mmol) in 64% yield.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.02 (d, *J* = 1.6 Hz, 1H), 6.96 (dd, *J* = 8.2, 1.6 Hz, 1H), 6.86 (d, *J* = 8.2 Hz, 1H), 6.08 (ddd, *J* = 17.3, 10.6, 5.4 Hz, 1H), 5.41 (dd, *J* = 17.3, 1.3 Hz, 1H), 5.30 (dd, *J* = 10.5, 1.3 Hz, 1H), 4.64 (d, *J* = 5.4 Hz, 2H), 3.89 (s, 3H), 3.06 (brs, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 171.4, 149.1, 149.0, 132.8, 128.9, 120.0, 118.1, 112.4, 111.2, 69.7, 55.9, 39.9, 35.6.

**ESIHRMS**: Found: m/z 236.1288; Calcd for $C_{13}H_{18}NO_3$: $(M+H)^+$ 236.1287

### 6.4.1.3. Synthesis of 2,5-dichloro-*N,N*-dimethylbenzamide (4.6s)



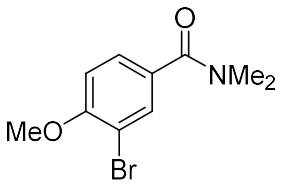

Prepared by following the experimental procedure in section 6.4.1.2 from 2,5-dichlorobenzoic acid (1.91 g, 10.0 mmol) and purified by flash column chromatography (silica gel, Hex:EtOAc:$CH_2Cl_2$ = 6:3:1) to give a white solid **4.6s** (1.85 g, 8.48 mmol) in 85% yield.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.34 – 7.28 (m, 3H), 3.13 (s, 3H), 2.88 (s, 3H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 166.9, 137.7, 133.2, 130.8, 130.1, 128.6, 127.8, 77.0, 38.0, 34.7.

**ESIHRMS**: Found: m/z 218.0141; Calcd for $C_9H_{10}NO_3{}^{35}Cl_2$: $(M+H)^+$ 218.0139

### 6.4.1.4. Synthesis of 3-bromo-4-methoxy-*N*,*N*-dimethylbenzamide (4.6t)



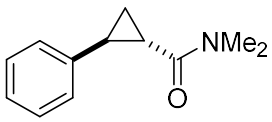

Prepared by following the experimental procedure in section 6.4.1.2 from 3-bromo-4-methoxybenzoic acid (2.31 g, 9.99 mmol) and purified by flash column chromatography (silica gel, Hex:EtOAc = 3:2) to give an off white solid **4.6t** (1.71 g, 6.61 mmol) in 66% yield.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.65 (d, $J$ = 2.0 Hz, 1H), 7.39 (dd, $J$ = 8.4, 2.0 Hz, 1H), 6.91 (d, $J$ = 8.4 Hz, 1H), 3.92 (s, 3H), 3.05 (s, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 169.8, 156.8, 132.5, 129.6, 127.9, 111.3, 111.2, 56.2, 39.6, 35.5.

**ESIHRMS**: Found: m/z 258.0127; Calcd for $C_{10}H_{13}NO_2{}^{79}Br$: $(M+H)^+$ 258.0130

### 6.4.1.5. Synthesis of (*1S*,2S**)-*N*,*N*-dimethyl-2-phenylcyclopropane-1-carboxamide (4.6ak)



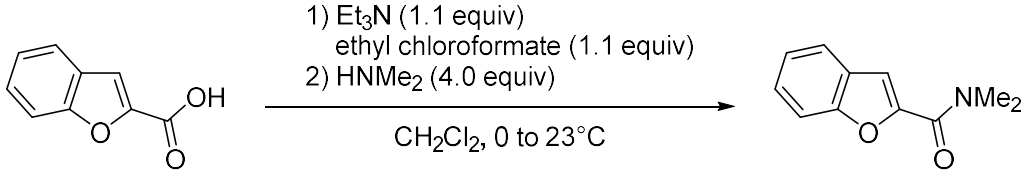
Prepared by following the experimental procedure in section 6.4.1.2 from (*1S*,2S**)-2-phenylcyclopropane-1-carboxylic acid[4] (1.30 g, 8.00 mmol) and purified by flash column chromatography (silica gel, Hex:EtOAc:$CH_2Cl_2$ = 6:3:1) to give **4.6ak** (1.44 g, 7.60 mmol) in 95% yield.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.28 (dd, *J* = 7.2, 7.2 Hz, 2H), 7.19 (t, *J* = 7.2 Hz, 1H), 7.12 (d, *J* = 7.2 Hz, 2H), 3.13 (s, 3H), 2.99 (s, 3H), 2.48 (ddd, *J* = 9.1, 6.2, 4.3 Hz, 1H), 1.99 (ddd, *J* = 8.3, 5.3, 4.3 Hz, 1H), 1.66 – 1.61 (m, 1H), 1.26 (ddd, *J* = 8.3, 6.2, 4.3 Hz, 1H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 171.9, 141.1, 128.4, 126.1, 126.1, 37.2, 35.8, 25.4, 23.1, 16.2.

**ESIHRMS**: Found: m/z 190.1234; Calcd for $C_{12}H_{16}NO$: $(M+H)^+$ 190.1232

### 6.4.1.6. Synthesis of *N,N*-dimethylbenzofuran-2-carboxamide (4.6w)




To a solution of benzofuran-2-carboxylic acid (1.62 g, 10.0 mmol) in $CH_2Cl_2$ (40 mL), triethylamine (1.55 mL, 11.1 mmol) and ethyl chloroformate (1.05 mL, 11.0 mmol) were added in this order at 0 °C. The reaction mixture was stirred at 0 °C for 1 h before $HNMe_2$ (7.9 M in water; 5.05 mL, 39.9 mmol) was added dropwise at 0 °C. The reaction mixture was then stirred at 23 °C. Upon full consumption of acid based on TLC, the reaction was quenched with water. The organic materials were extracted twice with $CH_2Cl_2$. The combined organic extracts were washed with brine and dried over $MgSO_4$. After removal of the volatile materials in vacuo, the resulting crude residue was purified

by flash column chromatography (silica gel, Hex:EtOAc = 20:80) to give a white solid **4.6w** (1.23 g, 6.51 mmol) in 65% yield.

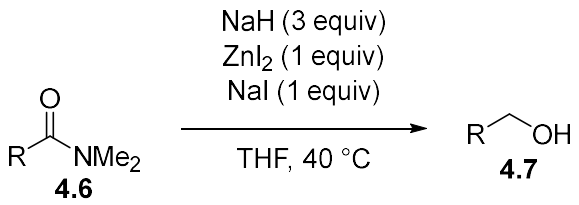
**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.65 (d, *J* = 7.8 Hz, 1H), 7.53 (d, *J* = 8.3 Hz, 1H), 7.41 – 7.37 (m, 1H), 7.31 – 7.26 (m, 2H), 3.35 (brs, 3H), 3.15 (brs, 3H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 160.9, 154.6, 149.2, 127.0, 126.3, 123.4, 122.1, 111.8, 111.6, 38.5, 36.4.

**ESIHRMS**: Found: m/z 190.0870; Calcd for $C_{11}H_{12}NO_2$: $(M+H)^+$ 190.0868

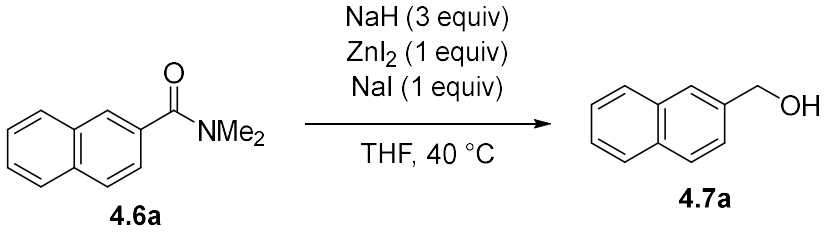
### 6.4.2. Synthesis of alcohols 4.7

#### 6.4.2.1. General procedure for reduction of amides 4.6 to alcohols 4.7




To a mixture of NaH (60% dispersion in mineral oil; 60.0 mg, 1.50 mmol), NaI (75.0 mg, 0.500 mmol) and $ZnI_2$ (160 mg, 0.500 mmol) in a 25 mL sealed tube was added a solution of amide **4.6** (0.500 mmol) in 2.5 mL of THF, the reaction mixture was sealed and stirred at 40 °C. The reaction was quenched with ammonium pH 10 buffer at 0 °C and the organic materials were extracted with dichloromethane (20 mL × 3). The combined extracts were dried over $MgSO_4$. The volatile materials were removed *in vacuo* and the resulting crude residue was purified by flash column chromatography (silica gel) to give the corresponding alcohol **4.7**.

### 6.4.2.2. Reduction of amide to alcohol in 40 mmol scale (Table 4.1, entry 3)

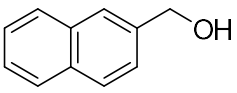



**4.6a** **4.7a**

To a mixture of NaH (60% dispersion in mineral oil; 4.80 g, 120 mmol), NaI (6.01 g, 40.1 mmol) and $ZnI_2$ (12.8 g, 40.0 mmol) in a 500 mL 2-neck round-bottom flask was added a solution of amide, **4.6a** (7.97g, 40.0 mmol) in 200 mL of THF. The reaction mixture was placed under $N_2$ atmosphere and stirred at 40 °C for 7 h. The reaction was quenched with ammonium pH 10 buffer at 0 °C and the organic materials were extracted with dichloromethane (50 mL × 3). The combined extracts were dried over $MgSO_4$. The volatile materials were removed *in vacuo* and the resulting crude residue was purified by flash column chromatography (silica gel, Hex:EtOAc = 4:1) to give the corresponding alcohol, **4.7a** (6.11g, 38.6 mmol) in 97% yield.

### 6.4.2.3. Reduction of aromatic amides to alcohols

#### 6.4.2.3.1. Synthesis of naphthalen-2-ylmethanol (4.7a) [CAS: 1592-38-7]




Prepared from amide **4.6a** (89.9 mg, 0.502 mmol) for 7 h.

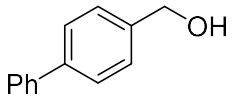
Purification: Hex:EtOAc = 4:1.

Yield: 95% yield (65.9 mg, 0.477 mmol) as white solid.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.83 – 7.80 (m, 3H), 7.78 (s, 1H), 7.49 – 7.44 (m, 3H), 4.82 (s, 2H). 1.96 (s, 1H)

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 138.3, 133.3, 132.9, 128.3, 127.9, 127.7, 126.2, 125.9, 125.4, 125.1, 65.4.

**6.4.2.3.2. Synthesis of [1,1'-biphenyl]-4-ylmethanol (4.7b)** [CAS: 3597-91-9]




Prepared from **4.6b** (113 mg, 0.502 mmol) for 10 h.

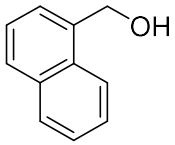
Purification: Hex:EtOAc = 4:1.

Yield: 89% yield (82.5 mg, 0.448 mmol) as white solid.

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.58 – 7.56 (m, 4H), 7.44 – 7.40 (m, 4H), 7.33 (dd, *J* = 7.3, 7.3 Hz, 1H), 4.70 (s, 2H), 2.01 (s, 1H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 140.8, 140.6, 139.8, 128.7, 127.4, 127.27, 127.25, 127.0, 65.0.

**6.4.2.3.3. Synthesis of naphthalen-1-ylmethanol (4.7c)** [CAS: 4780-79-4]




Prepared from **4.6c** (99.6 mg, 0.500 mmol) for 12 h.

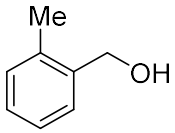
Purification: Hex:EtOAc = 4:1.

Yield: 98% yield (77.4 mg, 0.489 mmol) as colorless oil.

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.1 Hz, 1H), 7.88 (d, *J* = 7.9 Hz, 1H), 7.81 (d, *J* = 8.1 Hz, 1H), 7.57 – 7.49 (m, 3H), 7.44 (dd, *J* = 7.5, 7.5Hz, 1H), 5.14 (s, 2H), 1.80 (s, 1H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 136.2, 133.8, 131.2, 128.7, 128.6, 126.3, 125.9, 125.4, 125.3, 123.6, 63.7.

**6.4.2.3.4. Synthesis of *o*-tolylmethanol (4.7d)** [CAS: 89-95-2]




Prepared from **4.6d** (81.9 mg, 0.502mmol) for 15 h.

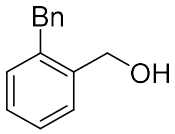
Purification: Pentane:Diethyl Ether = 3:2.

Yield: 89% yield (54.5 mg, 0.446 mmol) as white solid.

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.36 – 7.34 (m, 1H), 7.23 – 7.16 (m, 3H), 4.69 (s, 2H), 2.36 (s, 3H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 138.7, 136.1, 130.3, 127.8, 127.5, 126.0, 63.5, 18.6.

**6.4.2.3.5. Synthesis of (2-benzylphenyl)methanol (4.7e)**




Prepared from **4.6e** (120 mg, 0.501 mmol) for 21 h.

Purification: Hex:EtOAc = 4:1.

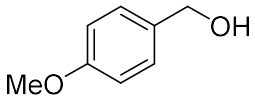
Yield: 98% yield (97.6 mg, 0.492 mmol) as pale yellow oil.

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.42 (dd, $J$ = 5.3, 3.7 Hz, 1H), 7.30 – 7.27 (m, 4H), 7.22 – 7.17 (m, 2H), 7.16 – 7.14 (m, 2H), 4.65 (d, $J$ = 5.2 Hz, 2H), 4.10 (s, 2H), 1.48 (t, $J$ = 5.2 Hz, 1H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 140.5, 138.8, 138.6, 130.6, 128.6, 128.5, 128.4, 128.0, 126.8, 126.2, 63.2, 38.5.

**ESIHRMS**: Found: m/z 199.1122; Calcd for $C_{14}H_{15}O$: $(M+H)^+$ 199.1123.

**6.4.2.3.6. Synthesis of (4-methoxyphenyl)methanol (4.7f)** [CAS: 105-13-5]




Prepared from **4.6f** (89.9 mg 0.502 mmol) for 12 h.

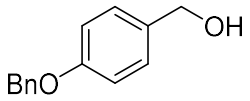
Purification: Hex:EtOAc = 7:3.

Yield: 95% yield (65.9 mg, 0.477 mmol) as colorless oil.

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 4.58 (s, 2H), 3.79 (s, 3H), 2.02 (brs, 1H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 159.1, 133.1, 128.6, 113.8, 64.8, 55.2.

**6.4.2.3.7. Synthesis of (4-(benzyloxy)phenyl)methanol (4.7g)**[5]




Prepared from **4.6g** (128 mg, 0.500 mmol) for 12 h.

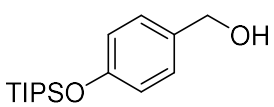
Purification: Hex:EtOAc = 7:3.

Yield: 97% yield (104 mg, 0.486 mmol) as white crystalline solid.

**$^{1}$H NMR** (400 MHz, $CDCl_3$) 7.43 (d, *J* = 7.1 Hz, 2H), 7.38 (dd, *J* = 7.1, 7.1 Hz, 2H), 7.33 (d, *J* = 7.1 Hz, 1H), 7.29 (d, *J* = 8.6 Hz, 2H), 6.97 (d, *J* = 8.6 Hz, 2H), 5.07 (s, 2H), 4.62 (s, 2H), 1.56 (s, 1H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 158.4, 136.9, 133.4, 128.64, 128.58, 128.0, 127.4, 114.9, 70.0, 65.1.

**6.4.2.3.8. Synthesis of (4-((triisopropylsilyl)oxy)phenyl)methanol (4.7h)**




Prepared from **4.6h** (160.4 mg, 0.499 mmol) for 8 h.

Purification: Hex:EtOAc = 4:1.

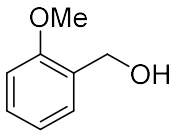
Yield: 89% yield (125 mg, 0.445 mmol) as a colorless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.3 Hz, 2H), 6.86 (d, *J* = 8.3 Hz, 2H), 4.60 (d, *J* = 4.2 Hz, 2H), 1.54 (t, *J* = 4.2 Hz, 1H), 1.26 (sept, *J* = 7.3 Hz, 3H), 1.10 (d, *J* = 7.3 Hz, 18H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 155.7, 133.4, 128.5, 119.9, 65.2, 17.9, 12.7.

**ESIHRMS**: Found: m/z 281.1941; Calcd for $C_{16}H_{29}O_2Si$: $(M+H)^+$ 281.1937.

**6.4.2.3.9. Synthesis of (2-methoxyphenyl)methanol (4.7i)** [CAS: 612-16-8]




Prepared from **4.6i** (89.3 mg, 0.498 mmol) for 6 h.

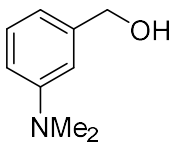
Purification: Hex:EtOAc = 7:3.

Yield: 66% yield (45.4 mg, 0.329 mmol) as a colorless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.30 – 7.26 (m, 2H), 6.94 (dd, *J* = 7.6, 7.6 Hz, 1H), 6.89 (d, *J* = 7.6 Hz, 1H), 4.68 (s, 2H), 3.87 (s, 3H), 2.32 (s, 1H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 157.4, 129.0, 128.9, 128.7, 120.6, 110.2, 62.1, 55.2.

**6.4.2.3.10. Synthesis of (3-(dimethylamino)phenyl)methanol (4.7j)**




Prepared from **4.6j** (96.2 mg, 0.500 mmol) for 11 h.

Purification: Hex:EtOAc = 7:3.

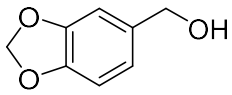
Yield: 92% yield (69.6 mg, 0.460 mmol) as pale yellow oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.23 (dd, *J* = 7.9, 7.9 Hz, 1H), 6.75 (s, 1H), 6.72 – 6.66 (m, 2H), 4.64 (s, 2H), 2.95 (s, 6H), 1.68 (brs, 1H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 150.9, 141.8, 129.3, 1152, 112.0, 111.1, 66.0, 40.6.

**ESIHRMS**: Found: m/z 152.1072; Calcd for $C_9H_{14}NO$: $(M+H)^+$ 152.1075.

**6.4.2.3.11. Synthesis of benzo[d][1,3]dioxol-5-ylmethanol (4.7k)** [CAS: 495-76-1]




Prepared from **4.6k** (96.9 mg, 0.5002 mmol) for 7 h.

Purification: Hex:EtOAc = 4:1.

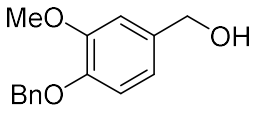
Yield: 87% yield (66.8 mg, 0.439 mmol) as off white solid.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 6.85 (s, 1H), 6.81 – 6.76 (m, 2H), 5.94 (s, 2H), 4.55 (s, 2H), 1.94 (brs, 1H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 147.8, 147.0, 134.8, 120.5, 108.2, 107.8, 101.0, 65.2.

**6.4.2.3.12. Synthesis of (4-(benzyloxy)-3-methoxyphenyl)methanol (4.7l)**

[CAS: 33693-48-0]




Prepared from **4.6l** (143 mg, 0.499 mmol) for 14 h.

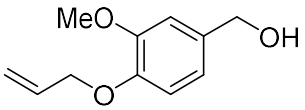
Purification: Hex:EtOAc = 3:2.

Yield: 82% yield (101 mg, 0.411 mmol) as white solid.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.3 Hz, 2H), 7.36 (dd, *J* = 7.3, 7.3 Hz, 2H), 7.29 (t, *J* = 7.3 Hz, 1H), 6.94 (s, 1H), 6.86 – 6.80 (m, 2H), 5.15 (s, 2H), 4.60 (s, 2H), 3.89 (s, 3H), 1.69 (s, 1H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 149.8, 147.7, 137.1, 134.2, 128.5, 127.8, 127.2, 119.3, 114.0, 111.0, 71.1, 65.3, 56.0.

### 6.4.2.3.13. Synthesis of (4-(allyloxy)-3-methoxyphenyl)methanol (4.7m)




Prepared from **4.6m** (118 mg, 0.500 mmol) for 14 h.

Purification: Hex:EtOAc = 3:2.

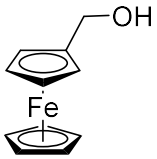
Yield: 88% yield (85.6 mg, 0.441 mmol) as white solid.

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 6.93 (s, 1H), 6.85-6.85 (m, 2H), 6.08 (ddt, *J* = 17.2, 10.6, 5.4 Hz, 1H), 5.40 (dd, *J* = 17.2, 1.5 Hz, 1H), 5.28 (dd, *J* = 10.6, 1.5 Hz, 1H), 4.61 – 4.60 (m, 4H), 3.88 (s, 3H), 1.74 (s, 1H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 149.6, 147.5, 134.0, 133.3, 119.3, 117.9, 113.4, 110.8, 69.9, 65.3, 55.9.

**ESIHRMS**: Found: m/z 195.1026; Calcd for $C_{11}H_{15}O_3$: $(M+H)^+$ 195.1021.

### 6.4.2.3.14. Synthesis of 1-ferrocene-methanol (4.7n) [CAS: 1273-86-5]




Prepared from **4.6n** (129 mg, 0.501 mmol) by the slightly modified procedure using NaH (100 mg, 2.50 mmol, 5 equiv), NaI (150 mg, 1.00 mmol, 2 equiv) and $ZnI_2$ (319 mg, 1.00 mmol, 2 equiv) for 12 h.

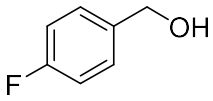
Purification: Hex:EtOAc = 4:1.

Yield: 69% yield (74.4 mg, 0.344 mmol, 69% yield, 12 h) as pale yellow solid.

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 4.33 (s, 2H), 4.24 (t, *J* = 1.8 Hz, 2H), 4.18-4.17 (m, 7H), 1.58 (s, 1H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 88.3, 68.23, 68.22, 67.8, 60.7

**6.4.2.3.15. Synthesis of (4-fluorophenyl)methanol (4.7o)** [CAS: 459-56-3]




Prepared from **4.6o** (83.9 mg, 0.502 mmol) for 7 h.

Purification: Pentane:Diethyl Ether = 4:1.

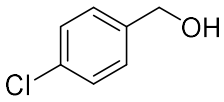
Yield: 76% yield (48.0 mg, 0.381 mmol) as a pale yellow oil.

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.29 (dd, *J* = 8.6, 5.6 Hz, 2H), 7.02 (dd, *J* = 8.6, 8.6 Hz, 2H), 4.59 (s, 2H), 2.40 (s, 1H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 162.3 (d, *J* = 245.4 Hz), 136.6 (d, *J* = 3.2 Hz), 128.8 (d, *J* = 8.2 Hz), 115.3 (d, *J* = 21.4 Hz), 64.5.

**$^{19}$F NMR** (376 MHz, $CDCl_3$): δ -114.9 (m).

**6.4.2.3.16. Synthesis of (4-chlorophenyl)methanol (4.7p)** [CAS: 873-76-7]




Prepared from **4.6p** (92.1 mg, 0.502 mmol) for 7 h.

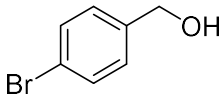
Purification: Hex:EtOAc = 4:1.

Yield: 87% yield (62.0 mg, 0.435 mmol) as white solid.

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.5 Hz, 2H), 7.28 (d, *J* = 8.5 Hz, 2H), 4.64 (s, 2H), 1.95 (s, 1H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 139.2, 133.3, 128.6, 128.2, 64.5.

**6.4.2.3.17. Synthesis of (4-bromophenyl)methanol (4.7q)** [CAS: 873-75-6]




Prepared from **4.6q** (114 mg, 0.500 mmol) for 7 h.

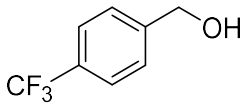
Purification: Hex:EtOAc = 4:1

Yield: 87% yield (81.7 mg, 0.437 mmol) as white solid.

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 4.62 (s, 2H), 1.99 (s, 1H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ139.7, 131.6, 128.5, 121.4, 64.5.

**6.4.2.3.18. Synthesis of (4-(trifluoromethyl)phenyl)methanol (4.7r)** [CAS: 349-95-1]




Prepared from **4.6r** (109 mg, 0.502 mmol) for 5 h.

Purification: Pentane:Diethyl Ether = 4:1.

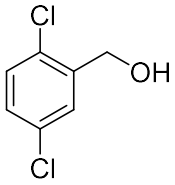
Yield: 95% yield (83.7 mg, 0.475 mmol) as a pale yellow oil.

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 2H), 4.73 (s, 2H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 144.7 (q, *J* = 1.3 Hz), 129.7 (q, *J* = 32.3 Hz), 126.8, 125.4 (q, *J* = 3.8 Hz), 124.1 (q, *J* = 271.9 Hz), 64.4.

**$^{19}$F NMR** (376 MHz, $CDCl_3$): δ -62.5 (s).

**6.4.2.3.19. Synthesis of (2,5-dichlorophenyl)methanol (4.7s)** [CAS: 34145-05-6]




Prepared from **4.6s** (109 mg, 0.501 mmol) for 5 h.

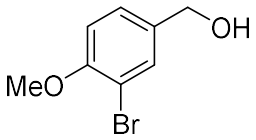
Purification: Hex:EtOAc = 4:1

Yield: 86% yield (76.3 mg, 0.431 mmol) as a white solid.

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 2.4 Hz, 1H), 7.30 (d, *J* = 8.5 Hz, 1H), 7.23 (dd, *J* = 8.5, 2.4 Hz, 1H), 4.77 (s, 2H), 2.09 (s, 1H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 139.9, 133.0, 130.5, 130.3, 128.6, 128.3, 62.2.

**6.4.2.3.20. Synthesis of (3-bromo-4-methoxyphenyl)methanol (4.7t)**




Prepared from **4.6t** (129 mg, 0.500 mmol) for 4 h.

Purification: Hex:EtOAc = 7:3

Yield: 90% yield (97.9 mg, 0.451 mmol) as a white solid.

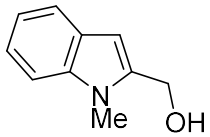
**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 1.9 Hz, 1H), 7.24 (dd, *J* = 8.4, 1.9 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 4.58 (s, 2H), 3.88 (s, 3H), 1.97 (s, 1H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 155.3, 134.5, 132.2, 127.3, 111.9, 111.6, 64.2, 56.3.

**ESIHRMS**: Found: m/z 216.9870; Calcd for $C_8H_{10}O_2{}^{79}Br$: $(M+H)^+$ 216.9864.

### 6.4.2.4. Reduction of heteroaromatic amides to alcohol

#### 6.4.2.4.1. Synthesis of (1-methyl-1H-indol-2-yl)methanol (4.7u)




Prepared from **4.6u** (101 mg, 0.500 mmol) for 11 h.

Purification: Hex:EtOAc = 3:2.

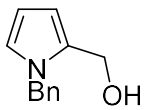
Yield: 89% yield (71.8 mg, 0.445 mmol) as off white solid.

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.23 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.10 (dd, *J* = 8.0, 8.0 Hz, 1H), 6.45 (s, 1H), 4.81 (d, *J* = 4.8 Hz, 2H), 3.81 (s, 3H), 1.52 (t, *J* = 4.8 Hz, 1H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 138.6, 138.0, 127.1, 121.9, 120.7, 119.5, 109.1, 101.2, 57.3, 29.6.

**ESIHRMS**: Found: m/z 162.0921; Calcd for $C_{10}H_{12}NO$: $(M+H)^+$ 162.0919.

#### 6.4.2.4.2. Synthesis of (1-benzyl-1H-pyrrol-2-yl)methanol (4.7v)




Prepared from **4.6v** (114 mg, 0.499 mmol) for 6h.

Purification: Hex:EtOAc = 4:1.

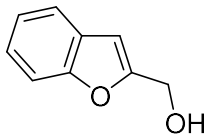
Yield: 75% yield (70.2 mg, 0.375 mmol) as a yellow oil.

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.31 (dd, *J* = 7.0, 7.0 Hz, 2H), 7.27 (t, *J* = 7.0 Hz, 1H), 7.06 (d, *J* = 7.0 Hz, 2H), 6.71 (dd, *J* = 2.6, 1.8 Hz, 1H), 6.17 (dd, *J* = 3.4, 1.8 Hz, 1H), 6.13 (dd, *J* = 3.4, 2.6 Hz, 1H), 5.20 (s, 2H), 4.51 (d, *J* = 5.5 Hz, 2H), 1.28 (t, *J* = 5.5 Hz, 1H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 138.3, 131.8, 128.7, 127.5, 126.5, 123.2, 109.4, 107.3, 56.7, 50.5.

**ESIHRMS**: Found: m/z 188.1080; Calcd for $C_{12}H_{14}NO$: $(M+H)^+$ 188.1075.

#### 6.4.2.4.3. Synthesis of benzofuran-2-ylmethanol (4.7w)[6]




Prepared from **4.6w** (94.5 mg, 0.499 mmol) for 7 h.

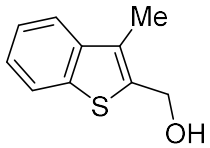
Purification: Hex:EtOAc = 7:3.

Yield: 76% yield (56.4 mg, 0.380 mmol) as pale yellow oil.

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.5 Hz, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.28 (dd, *J* = 8.0, 7.5 Hz, 1H), 7.22 (dd, *J* = 7.5, 7.5 Hz, 1H), 6.66 (s, 1H), 4.78 (s, 2H), 1.93 (s, 1H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 156.4, 155.0, 128.1, 124.3, 122.8, 121.1, 111.2, 104.1, 58.0.

#### 6.4.2.4.4. Synthesis of (3-methylbenzo[b]thiophen-2-yl)methanol (4.7x)




Prepared from **4.6x** (109 mg, 0.498 mmol) for 10 h.

Purification: Hex:EtOAc = 4:1.

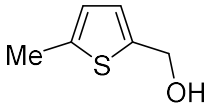
Yield: 82% yield (72.7 mg, 0.408 mmol) as a white solid.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.5 Hz, 1H), 7.67 (d, *J* = 7.5 Hz, 1H), 7.38 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.33 (d, *J* = 7.5, 7.5 Hz, 1H), 4.92 (d, *J* = 5.8 Hz, 2H), 2.40 (s, 3H), 1.75 (t, *J* = 5.8 Hz, 1H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 140.6, 138.8, 137.6, 128.6, 124.4, 124.0, 122.4, 121.8, 58.4, 11.4.

**ESIHRMS**: Found: m/z 179.0536; Calcd for $C_{10}H_{11}OS$: $(M+H)^+$ 179.0531.

#### 6.4.2.4.5. Synthesis of (5-methylthiophen-2-yl)methanol (4.7y)




Prepared from **4.6y** (84.4 mg, 0.499 mmol) for 3 h.

Purification: Hex:EtOAc = 7:3.

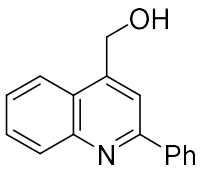
Yield: 73% yield (47.0 mg, 0.367 mmol) as pale yellow oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 6.78 (d, *J* = 3.3 Hz, 1H), 6.60 (dq, *J* = 3.3, 0.8 Hz, 1H), 4.71 (s, 2H), 2.46 (d, *J* = 0.8 Hz, 3H), 1.96 (s, 1H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 141.6, 140.4, 125.6, 124.8, 60.1, 15.3.

**ESIHRMS**: Found: m/z 129.0370; Calcd for $C_6H_9OS$: $(M+H)^+$ 129.0374.

#### 6.4.2.4.6. Synthesis of (2-phenylquinolin-4-yl)methanol (4.7z)




Prepared from **4.6z** (138 mg, 0.501 mmol) for 6 h.

Purification: Hex:EtOAc = 7:3.

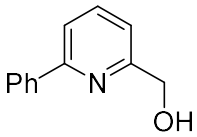
Yield: 93% yield (110 mg, 0.468 mmol) as a white crystalline solid.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 8.4 Hz, 1H), 7.93 (d, *J* = 7.4 Hz, 2H), 7.74 – 7.72 (m, 2H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.44 – 7.36 (m, 4H), 5.01 (s, 2H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 157.2, 147.6, 147.2, 139.3, 129.7, 129.4, 129.2, 128.6, 127.4, 126.2, 124.6, 122.6, 116.0, 61.3.

**ESIHRMS**: Found: m/z 236.1079; Calcd for $C_{16}H_{14}NO$: $(M+H)^+$ 236.1075.

#### 6.4.2.4.7. Synthesis of (6-phenylpyridin-2-yl)methanol (4.7aa)




Prepared from **4.6aa** (113 mg 0.501 mmol) for 3 h.

Purification: Hex:EtOAc = 7:3.

Yield: 84% yield (77.9 mg, 0.421 mmol) as a pale yellow solid.

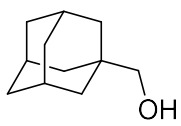
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.1 Hz, 2H), 7.74 (t, *J* = 7.7 Hz, 1H), 7.64 (d, *J* = 7.7 Hz, 1H), 7.48 (dd, *J* = 7.1, 7.1 Hz, 2H), 7.42 (t, *J* = 7.1 Hz, 1H), 7.15 (d, *J* = 7.7 Hz, 1H), 4.81 (s, 2H), 4.15 (s, 1H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 158.5, 156.1, 138.8, 137.4, 129.1, 128.7, 126.9, 119.0, 118.7, 63.9.

**ESIHRMS**: Found: m/z 186.0918; Calcd for $C_{12}H_{12}NO$: $(M+H)^+$ 186.0919.

### 6.4.2.5. Reduction of aliphatic amides to alcohols

#### 6.4.2.5.1 Synthesis of ((3r,5r,7r)-adamantan-1-yl)methanol (4.7ab) [CAS: 770-71-8]




Prepared from **4.6ab** (104 mg, 0.501 mmol) for 12 h.

Purification: Hex:EtOAc = 7:3.

Yield: 97% yield (80.6 mg, 0.485 mmol) as a colorless crystal.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 3.20 (s, 2H), 1.99 (s, 3H), 1.74 (d, *J* = 12.2 Hz, 3H), 1.65 (d, *J* = 12.2 Hz, 3H), 1.51-1.51 (m, 6H), 1.33 (s, 1H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 73.9, 39.0, 37.2, 34.5, 28.2.

### 6.4.2.5.2. Synthesis of bicyclo[2.2.2]octan-1-ylmethanol (4.7ac)


Prepared from **4.6ac** (90.7 mg, 0.500 mmol) for 7 h.

Purification: Hex:EtOAc = 7:3.

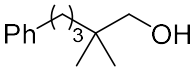
Yield: 86% yield (60.1 mg, 0.429 mmol) as a white solid.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 3.21 (s, 2H), 1.58 – 1.55 (m, 7H), 1.38 – 1.34 (m, 6H), 1.23 (s, 1H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 72.0, 32.4, 27.7, 25.7, 24.6.

**ESIHRMS**: Found: m/z 141.1281; Calcd for $C_9H_{17}O$: $(M+H)^+$ 141.1279.

### 6.4.2.5.3. Synthesis of 2,2-dimethyl-5-phenylpentan-1-ol (4.7ad)




Prepared from **4.6ad** (117 mg, 0.501 mmol) for 12 h.

Purification: Hex:EtOAc = 4:1.

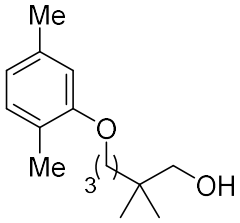
Yield: 92% yield (88.3 mg, 0.459 mmol) as a colorless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.28 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.19 – 7.16 (m, 3H), 3.30 (s, 2H), 2.59 (t, *J* = 7.7 Hz, 2H), 1.63 – 1.55 (m, 2H), 1.32 – 1.26 (m, 2H), 0.86 (s, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 142.7, 128.4, 128.3, 125.7, 71.9, 38.3, 36.8, 35.0, 26.0, 23.8.

**ESIHRMS**: Found: m/z 193.1589; Calcd for $C_{13}H_{21}O$: $(M+H)^+$ 193.1592.

### 6.4.2.5.4. Synthesis of 5-(2,5-dimethylphenoxy)-2,2-dimethylpentan-1-ol (4.7ae)




Prepared from **4.6ae** (139 mg, 0.500 mmol) for 12 h.

Purification: Hex:EtOAc = 4:1.

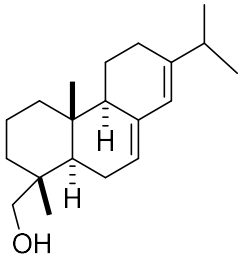
Yield: 90% yield (107 mg, 0.451 mmol) as colorless oil.

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.00 (d, $J$ = 7.4 Hz, 1H), 6.65 (d, $J$ = 7.4 Hz, 1H), 6.62(s, 1H), 3.93 (t, $J$ = 6.4 Hz, 2H), 3.36 (s, 2H), 2.30 (s, 3H), 2.18 (s, 3H), 1.81 – 1.73 (m, 2H), 1.61 (s, 1H), 1.45 – 1.39 (m, 2H), 0.92 (s, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 157.0, 136.4, 130.3, 123.6, 120.7, 112.1, 71.8, 68.6, 34.9, 34.8, 24.1, 23.8, 21.4, 15.8.

**ESIHRMS**: Found: m/z 237.1858; Calcd for $C_{15}H_{25}O_2$: $(M+H)^+$ 237.1855.

### 6.4.2.5.5. Synthesis of ((1*R*,4a*R*,4b*R*,10a*R*)-7-isopropyl-1,4a-dimethyl-1,2,3,4,4a,4b,5,6,10,10a-decahydrophenanthren-1-yl)methanol (4.7af)




Prepared from **4.6af** (164 mg, 0.500 mmol) for 12 h.

Purification: Hex:EtOAc = 9:1.

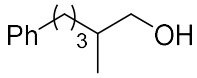
Yield: 88% yield (127 mg, 0.440 mmol) as a pale yellow oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 5.78 (s, 1H), 5.40 (s, 1H), 3.36 (d, *J* = 10.8 Hz, 1H), 3.14 (d, *J* = 10.8 Hz, 1H), 2.22 (dt, *J* = 13.6, 6.8 Hz, 1H), 2.08 – 2.06 (m, 2H), 2.01 – 1.98 (m, 2H), 1.90 – 1.78 (m, 3H), 1.63 – 1.50 (m, 3H), 1.44 – 1.32 (m, 3H), 1.26 – 1.15 (m, 1H), 1.03 – 1.00(m, 7H), 0.88 (s, 3H), 0.83 (s, 3H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 145.3, 135.5, 122.4, 120.9, 72.2, 50.8, 43.7, 38.9, 37.5, 35.7, 34.9, 34.6, 27.5, 23.8, 22.7, 21.4, 20.9, 18.2, 17.7, 14.2.

**ESIHRMS**: Found: m/z 289.2534; Calcd for $C_{20}H_{33}O$: $(M+H)^+$ 289.2531.

### 6.4.2.5.6. Synthesis of 2-methyl-5-phenylpentan-1-ol (4.7ag)




Prepared from **4.6ag** (110 mg, 0.501 mmol) for 12 h.

Purification: Hex:EtOAc = 7:3.

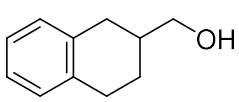
Yield: 83% yield (73.9 mg, 0.415 mmol) as a colorless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.29 – 7.25 (m, 2H), 7.19 – 7.16 (m, 3H), 3.50 (dd, *J* = 10.4, 5.8 Hz, 1H), 3.42 (dd, *J* = 10.4, 6.5 Hz, 1H), 2.67 – 2.55 (m, 2H), 1.70 – 1.60 (m, 4H), 1.50 – 1.42 (m, 1H), 1.21 – 1.12 (m, 1H), 0.92 (d, *J* = 6.8 Hz, 3H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 142.6, 128.4, 128.3, 125.7, 68.3, 36.2, 35.7, 32.8, 28.9, 16.5.

**ESIHRMS**: Found: m/z 179.1436; Calcd for $C_{12}H_{19}O$: $(M+H)^+$ 179.1436.

### 6.4.2.5.7. Synthesis of (1,2,3,4-tetrahydronaphthalen-2-yl)methanol (4.7ah)



Prepared from **4.6ah** (101 mg, 0.499 mmol) for 10 h.

Purification: Hex:EtOAc = 7:3.

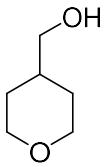
Yield: 76% yield (61.2 mg, 0.377 mmol) as a pale yellow oil

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.10 – 7.05 (m, 4H), 3.65 – 3.57 (m, 2H), 2.90 – 2.80 (m, 3H), 2.53 – 2.46 (m, 1H), 2.03 – 1.92 (m, 2H), 1.77 (s, 1H), 1.48 – 1.38 (m, 1H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 136.7, 135.9, 129.2, 128.8, 125.6, 125.6, 67.6, 37.0, 32.4, 28.7, 25.9.

**ESIHRMS**: Found: m/z 163.1128; Calcd for $C_{11}H_{15}O$: $(M+H)^+$ 163.1123.

### 6.4.2.5.8. Synthesis of (tetrahydro-2H-pyran-4-yl)methanol (4.7ai)




Prepared from **4.6ai** (78.4 mg, 0.499 mmol) for 5 h.

Purification: Hex:EtOAc = 1:9.

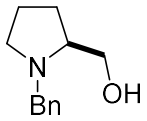
Yield: 74% yield (43.0 mg, 0.370 mmol) as a colorless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 4.00 (dd, *J* = 11.7, 4.6 Hz, 2H), 3.51 (d, *J* = 6.4 Hz, 2H), 3.41 (td, *J* = 11.7, 2.1 Hz, 2H), 1.81 – 1.71 (m, 1H), 1.68 – 1.62 (m, 3H), 1.37 (dd, *J* = 12.1, 4.5 Hz, 1H), 1.31 (dd, *J* = 12.1, 4.5 Hz, 1H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 67.9, 67.7, 37.7, 29.4

**ESIHRMS**: Found: m/z 117.0919; Calcd for $C_6H_{13}O_2$: $(M+H)^+$ 117.0916.

### 6.4.2.5.9. Synthesis of (*S*)-prolinol (4.7aj)



Prepared from **4.6aj** (116 mg, 0.499 mmol) for 4 h.

Purification: Hex:EtOAc:TEA = 50:50:1.

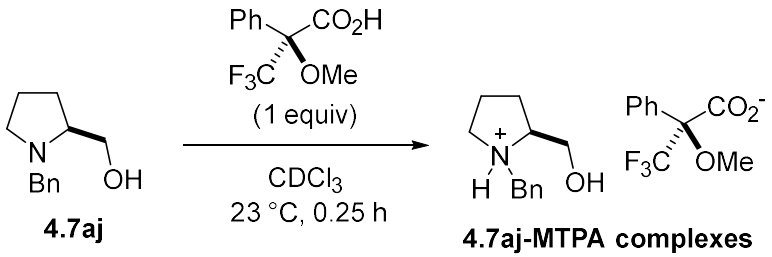
Yield: 91% yield (87.0 mg, 0.455 mmol, >97% ee) as a pale yellow oil.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.34 – 7.23 (m, 5H), 3.97 (d, *J* = 13.0 Hz, 1H), 3.66 (dd, *J* = 10.7, 3.5 Hz, 1H), 3.43 (dd, *J* = 10.7, 2.0 Hz, 1H), 3.36 (d, *J* = 13.0 Hz, 1H), 3.00 – 2.95 (m, 1H), 2.76 – 2.71 (m, 1H), 2.33 – 2.24 (m, 1H), 1.98 – 1.91 (m, 1H), 1.89 – 1.79 (m, 1H), 1.73 – 1.65 (m, 2H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 139.3, 128.7, 128.3, 127.0, 64.3, 61.8, 58.5, 54.4, 27.8, 23.4.

**Optical Rotation**: $[\alpha]^{25}_D$ –49.6° (c = 0.011 g/mL, $CHCl_3$)

**Enantiomeric excess:** measured by the Mosher method[7] with (−)-MTPA derivatization (see below for the experimental details).

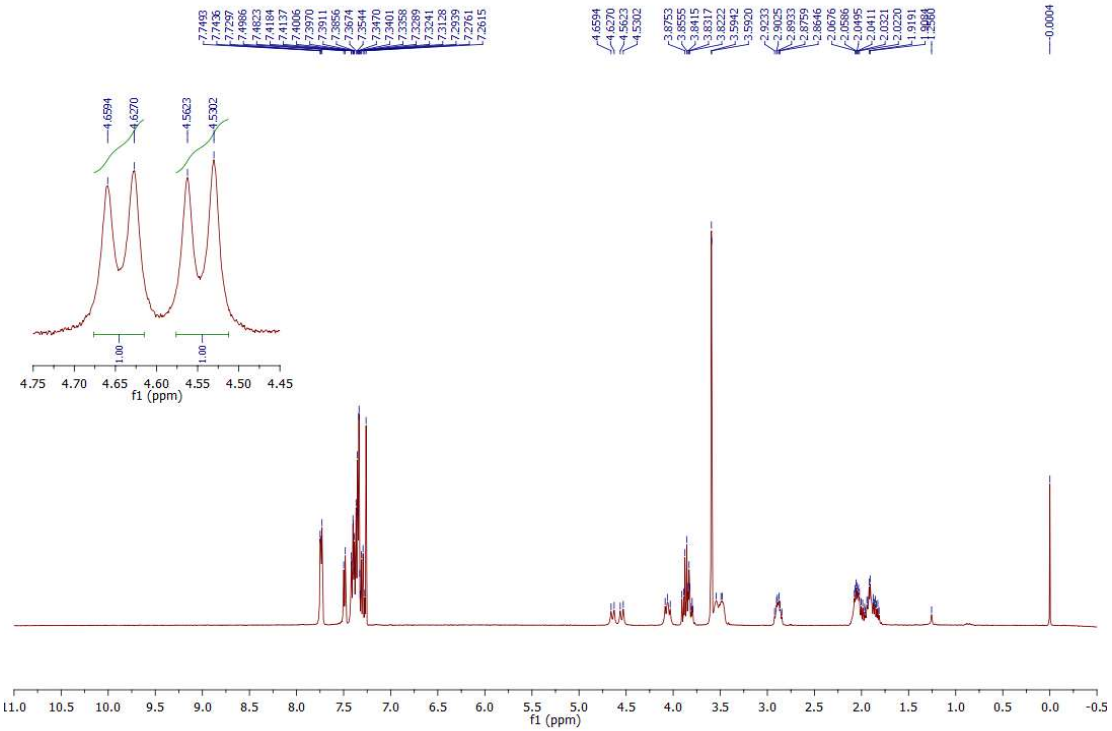



**4.7aj** **4.7aj-MTPA complexes**

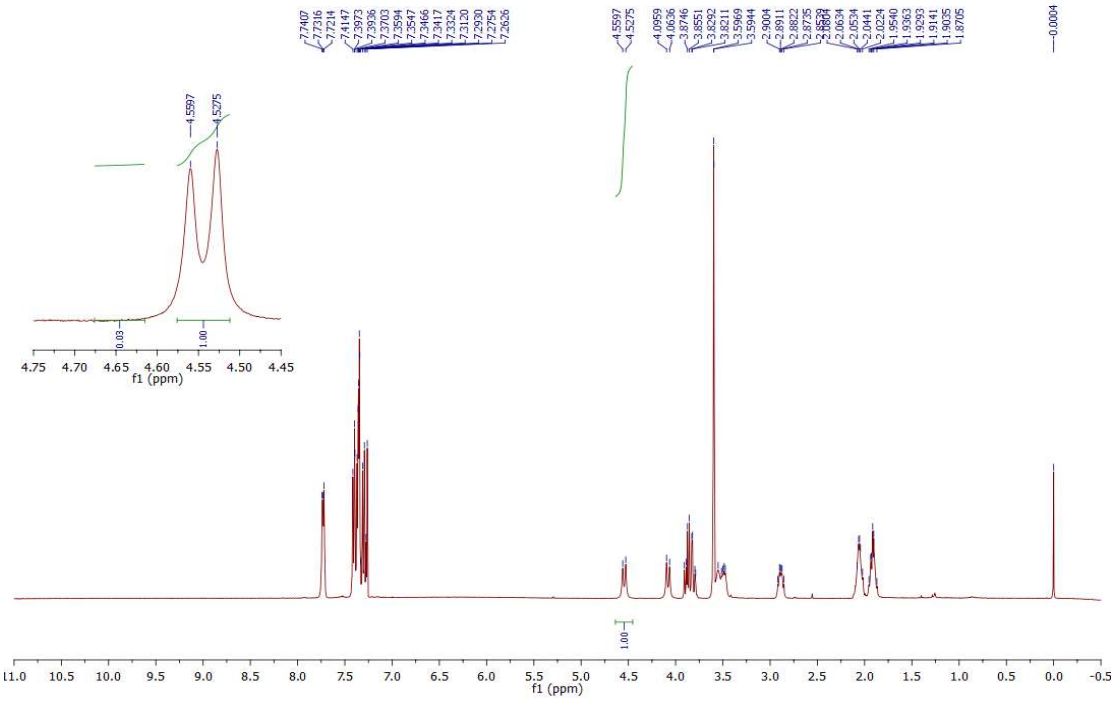
For derivatisation of **rac-4.7aj**: **rac-4.7aj** (7.00 mg, 0.0366 mmol) and (−)-MTPA (8.60 mg, 0.0367 mmol) was dissolved in $CDCl_3$ (1.0 mL) and was stirred at room temperature for 15 min. The resulting solution was then analyzed using $^1$H NMR without any further purification.

For derivatisation of **4.7aj**: **4.7aj** (6.40 mg, 0.0335 mmol) and (−)-MTPA (8.50 mg, 0.0363 mmol) was dissolved in $CDCl_3$ (1.0 mL) and was stirred at room temperature for 15 min. The resulting solution was then analyzed using $^1$H NMR without any further purification.

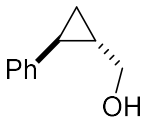
## $^{1}$H NMR spectrum for rac-4.7aj-MTPA complex



## $^{1}$H NMR spectrum for 4.7aj-MTPA complex



**6.4.2.5.10. Synthesis of ((1*S**,2*S**)-2-phenylcyclopropyl)methanol (4.7ak)**




Prepared from **4.6aj** (94.8 mg, 0.501 mmol) for 11 h.

Purification: Pentane:Diethyl Ether = 2:3.

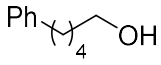
Yield: 56% yield (46.1 mg, 0.279 mmol) as a colorless oil with formation of 35% yield of amine **4.8aj** based on $^1$H NMR using 1,1,2,2-tetrachloroethane as the internal standard.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.25 (dd, *J* = 7.5, 7.5 Hz, 2H), 7.15 (t, *J* = 7.5 Hz, 1H), 7.07 (d, *J* = 7.5 Hz, 2H), 3.66 – 3.57 (m, 2H), 1.84 – 1.80 (m, 1H), 1.54 (s, 1H), 1.49 – 1.41 (m, 1H), 0.99 – 0.90 (m, 2H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 142.4, 128.3, 125.8, 125.6, 66.5, 25.3, 21.3, 13.8.

**ESIHRMS**: Found: m/z 149.0963; Calcd for $C_{10}H_{13}O$: $(M+H)^+$ 149.0966.

**6.4.2.5.11. Synthesis of 5-phenylpentan-1-ol (4.7al)** [CAS: 10521-91-2]




Prepared from **4.6ak** (102 mg, 0.498 mmol) for 9 h.

Purification: Hex:EtOAc = 7:3.

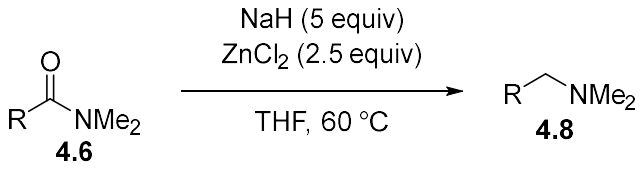
Yield: 45% yield (39.9 mg, 0.224 mmol) as a colorless oil with formation of 31% yield of amine **4.8ak** based on $^1$H NMR using 1,1,2,2-tetrachloroethane as the internal standard.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 1H NMR (400 MHz, CDCl3) δ 7.29 – 7.25 (m, 2H), 7.18 – 7.16 (m, 3H), 3.63 (t, *J* = 6.6 Hz, 2H), 2.62(t, *J* = 7.6 Hz, 2H), 1.69 – 1.56 (m, 4H), 1.44 – 1.36 (m, 2H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 142.3, 128.4, 128.2, 125.6, 62.9, 35.9, 32.6, 31.2, 25.4.

### 6.4.3. Synthesis of amines 4.8

#### 6.4.3.1. General procedure for reduction of amide to amine




To a mixture of NaH (60% dispersion in mineral oil; 100 mg, 2.50 mmol) and $ZnCl_2$ (170 mg, 1.25 mmol) in a 25 mL sealed tube was added a solution of amide **4.6** (0.500 mmol) in 2.5 mL of THF, and the reaction mixture was sealed and stirred at 60 °C. The reaction was quenched by following one of the two protocols shown below:

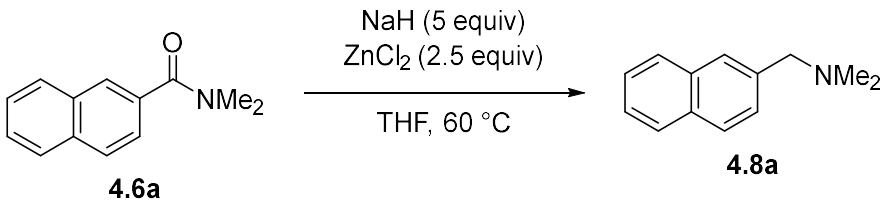
**Work-up protocol 1:**

Upon full consumption of amide based on TLC, the reaction was quenched with pH 10 ammonium buffer at 0 °C and the organic materials were extracted with dichloromethane (20 mL × 3). The combined extracts were dried over $MgSO_4$. The volatile materials were removed in vacuo and the resulting crude residue was purified by flash column chromatography to give the corresponding amine **4.8**.

**Work-up protocol 2:**

Upon full consumption of amide based on TLC, the reaction was quenched with aqueous 1M HCl solution at 0 °C. The aqueous layer was washed with diethyl ether (20 mL × 3) and basified with aqueous 3M NaOH solution. The organic materials were then extracted from the basified aqueous layer with dichloromethane (20 mL × 3). The combined organic extracts were dried over $MgSO_4$. The volatile materials were removed in vacuo to give the corresponding amine **4.8**.

### 6.4.3.2. Reduction in 40 mmol scale (Table 4.1, entry 7)

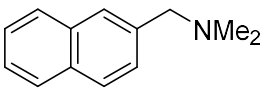



**4.6a** **4.8a**

To a mixture of NaH (60% dispersion in mineral oil; 8.02 g, 201 mmol) and $ZnCl_2$ (13.7 g, 100 mmol) in a 500 mL 2-neck round-bottom flask was added a solution of amide, **4.6a** (7.95 g, 39.9 mmol) in 200 mL of THF. The reaction mixture was placed under $N_2$ atmosphere and stirred at 60 °C for 0.5 h. The reaction was quenched with ammonium pH 10 buffer at 0 °C and the organic materials were extracted with dichloromethane (50 mL × 3). The combined extracts were dried over $MgSO_4$. The volatile materials were removed *in vacuo* and the resulting crude residue was purified by flash column chromatography (silica gel, Hex:EtOAc:TEA = 80:20:1) to give the corresponding amine, **4.8a** (6.57 g, 35.4 mmol) in 89% yield.

### 6.4.3.3. Reduction of aromatic amides 4.6 to amines 4.8

#### 6.4.3.3.1. Synthesis of *N,N*-dimethyl-1-(naphthalen-2-yl)methanamine (4.8a)[8]




Prepared from **4.6a** (99.7 mg, 0.501 mmol) for 0.25 h with work-up protocol 1.

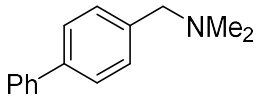
Purification: Hex:EtOAc:$Et_3N$ = 80:20:1

Yield: 80% yield (74.0 mg, 0.400 mmol) as a colorless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.83 – 7.80 (m, 3H), 7.73 (s, 1H), 7.49 – 7.44 (m, 3H), 3.58 (s, 2H), 2.29 (s, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 134.8, 133.8, 132.5, 128.4, 128.0, 127.4, 126.0, 125.5, 125.1, 124.5, 62.5, 45.7.

#### 6.4.3.3.2. Synthesis of 1-([1,1'-biphenyl]-4-yl)-*N,N*-dimethylmethanamine (4.8b)




Prepared from **4.6b** (113 mg, 0.500 mmol) for 0.25 h with work-up protocol 1.

Purification: Hex:EtOAc:$CH_2Cl_2$:$Et_3N$ = 70:20:10:1

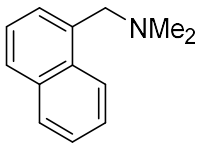
Yield: 81% yield (85.5 mg, 0.405 mmol) as a colorless oil

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.61 – 7.58 (m, 2H), 7.57 – 7.54 (m, 2H), 7.45 – 7.41 (m, 2H), 7.39 – 7.36 (m, 2H), 7.35 – 7.31 (m, 1H), 3.46 (s, 2H), 2.27 (s, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 141.0, 139.9, 138.0, 129.5, 128.7, 127.1, 127.0, 126.9, 64.0, 45.4.

**ESIHRMS**: Found: m/z 212.1444; Calcd for $C_{15}H_{18}N$: $(M+H)^+$ 212.1439.

#### 6.4.3.3.3. Synthesis of *N,N*-dimethyl-1-(naphthalen-1-yl)methanamine (4.8c)




Prepared from **4.6c** (99.7 mg, 0.500 mmol) for 1.5 h with work-up protocol 1.

Purification: Hex:EtOAc:$Et_3N$ = 80:20:1

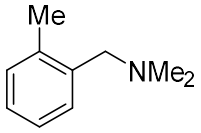
Yield: 80% yield (74.3 mg, 0.401 mmol) as a colorless oil

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 8.26 (d, $J$ = 7.9 Hz, 1H), 7.84 (d, $J$ = 7.9 Hz, 1H), 7.79 – 7.76 (m, 1H), 7.54 – 7.45 (m, 2H), 7.41 – 7.39 (m, 2H), 3.82 (s, 2H), 2.30 (s, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 134.8, 133.8, 132.5, 128.4, 128.0, 127.4, 126.0, 125.6, 125.1, 124.5, 62.6, 45.7.

**ESIHRMS**: Found: m/z 186.1286; Calcd for $C_{13}H_{16}N$: $(M+H)^+$ 186.1283

#### 6.4.3.3.4. Synthesis of *N,N*-dimethyl-1-(o-tolyl)methanamine (4.8d)[8]



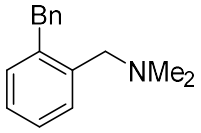

Prepared from **4.6d** (81.8 mg, 0.501 mmol) for 3 h with work-up protocol 2.

Yield: 74% yield (55.7 mg, 0.373 mmol) as a colorless oil

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.25 – 7.23 (m, 1H), 7.16 – 7.14 (m, 3H), 3.37 (s, 2H), 2.36 (s, 3H), 2.24 (s, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 137.2, 137.1, 130.2, 129.8, 127.0, 125.5, 62.0, 45.6, 19.1.

#### 6.4.3.3.5. Synthesis of 1-(2-benzylphenyl)-*N,N*-dimethylmethanamine (4.8e)




Prepared from **4.6e** (120 mg, 0.501 mmol) for 4 h with work-up protocol 1.

Purification: Hex:EtOAc:$Et_3N$ = 80:20:1

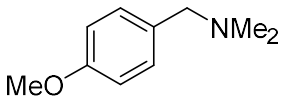
Yield: 67% yield (75.2 mg, 0.334 mmol) as a pale yellow oil.

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.32 – 7.11 (m, 9H), 4.15 (s, 2H), 3.36 (s, 2H), 2.21 (s, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 141.0, 139.9, 136.8, 130.6, 130.4, 128.8, 128.3, 127.3, 126.2, 125.8, 61.8, 45.4, 38.3.

**ESIHRMS**: Found: m/z 226.1590; Calcd for $C_{16}H_{20}N$: $(M+H)^+$ 226.1596.

#### 6.4.3.3.6. Synthesis of 1-(4-methoxyphenyl)-*N,N*-dimethylmethanamine (4.8f)[8]




Prepared from **4.6f** (90.7 mg, 0.506 mmol) for 1.25 h with work-up protocol 1.

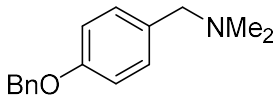
Purification: Hex:EtOAc:$CH_2Cl_2$:$Et_3N$ = 10:90:10:1

Yield: 75% yield (62.8 mg, 0.380 mmol) as pale yellow oil.

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 3.80 (s, 3H), 3.35 (s, 2H), 2.22 (s, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 158.7, 130.9, 130.2, 113.6, 63.7, 55.2, 45.2.

#### 6.4.3.3.7. Synthesis of 1-(4-(benzyloxy)phenyl)-*N,N*-dimethylmethanamine (4.8g)




Prepared from **4.6g** (128 mg, 0.501 mmol) for 1.5 h with work-up protocol 1.

Purification: Hex:EtOAc:$CH_2Cl_2$:$Et_3N$ = 5:90:5:1

Yield: 78% yield (94.2 mg, 0.390 mmol) as pale yellow oil

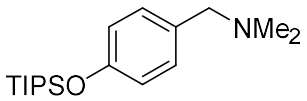
**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.2 Hz, 2H), 7.38 (dd, *J* = 7.2, 7.2 Hz, 2H), 7.32 (t, J = 7.2 Hz, 1H), 7.21 (d, *J* = 8.5 Hz, 2H), 6.93 (d, *J* = 8.5 Hz, 2H), 5.05 (s, 2H), 3.36 (s, 2H), 2.22 (s, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 157.9, 137.1, 131.2, 130.2, 128.5, 127.9, 127.4, 114.5,

70.0, 63.7, 45.2.

**ESIHRMS**: Found: m/z 242.1545; Calcd for $C_{16}H_{20}O$: $(M+H)^+$ 242.1545.

#### 6.4.3.3.8. Synthesis of *N,N*-dimethyl-1-(4-((triisopropylsilyl)oxy)phenyl)methanamine (4.8h)




Prepared from **4.6h** (161 mg, 0.500 mmol) for 1.75 h with work-up protocol 1.

Purification: Hex:EtOAc:$CH_2Cl_2$:$Et_3N$ = 5:90:5:2

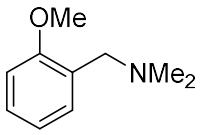
Yield: 86% yield (132 mg, 0.428 mmol) as colorless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.13 (d, *J* = 8.6 Hz, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 3.34 (s, 2H), 2.21 (s, 6H), 1.25 (d, *J* = 7.3 Hz, 3H), 1.09 (d, *J* = 7.3 Hz, 18H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ = 155.1, 131.2, 130.2, 119.6, 63.8, 45.1, 17.9, 12.6.

**ESIHRMS**: Found: m/z 308.2411; Calcd for $C_{18}H_{34}NOSi$: $(M+H)^+$ 308.2410.

#### 6.4.3.3.9. Synthesis of 1-(2-methoxyphenyl)-*N,N*-dimethylmethanamine (4.8i)[8]



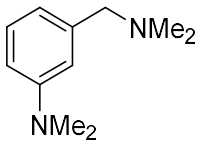

Prepared from **4.6i** (89.2 mg, 0.498 mmol) for 3.5 h with work-up protocol 2.

Yield: 62% yield (51.1 mg, 0.309 mmol) as colorless clear oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.28 – 7.21 (m, 2H), 6.92 (d, *J* = 7.8, 7.8 Hz, 1H), 6.87 (d, *J* = 7.8 Hz, 1H), 3.82 (s, 3H), 3.45 (s, 2H), 2.26 (s, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 157.9, 130.9, 128.2, 126.8, 120.1, 110.4, 57.9, 55.4, 45.4.

### 6.4.3.3.10. Synthesis of 3-((dimethylamino)methyl)-*N*,*N*-dimethylaniline (4.8j)




Prepared from **4.6j** (96.6 mg, 0.502 mmol) for 1 h with work-up protocol 1.

Purification: Hex:EtOAc:$CH_2Cl_2$:$Et_3N$ = 5:90:5:2

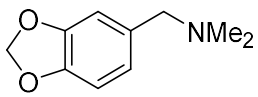
Yield: 89% yield (79.3 mg, 0.445 mmol) as pale yellow oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.18 (dd, *J* = 7.8, 7.8 Hz, 1H), 6.69 (s, 1H), 6.67 – 6.63 (m, 2H), 3.38 (s, 2H), 2.94 (s, 6H), 2.24 (s, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 150.8, 139.8, 128.9, 117.8, 113.4, 111.5, 65.1, 45.6, 40.8.

**ESIHRMS**: Found: m/z 179.1547; Calcd for $C_{11}H_{19}N_2$: $(M+H)^+$ 179.1548.

### 6.4.3.3.11. Synthesis of 1-(benzo[*d*][1,3]dioxol-5-yl)-*N*,*N*-dimethylmethanamine (4.8k)[8]




Prepared from **4.6k** (97.6 mg, 0.505 mmol) for 0.5 h with work-up protocol 1.

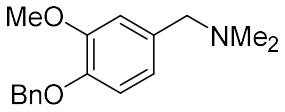
Purification: Hex:EtOAc:$CH_2Cl_2$:$Et_3N$ = 5:90:5:1

Yield: 83% yield (75.3 mg, 0.420 mmol) as pale yellow oil

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 6.83 – 6.82 (m, 1H), 6.74 – 6.74 (m, 2H), 5.94 (s, 2H), 3.32 (s, 2H), 2.22 (s, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 147.6, 146.5, 132.7, 122.1, 109.5, 107.8, 100.8, 64.1, 45.1.

#### 6.4.3.3.12. Synthesis of 1-(4-(benzyloxy)-3-methoxyphenyl)-*N*,*N*-dimethylmethanamine (4.8l)




Prepared from **4.6l** (104 mg, 0.501 mmol) for 1 h with work-up protocol 1.

Purification: Hex:EtOAc:$CH_2Cl_2$:$Et_3N$ = 40:50:10:1 to 0:90:10:1

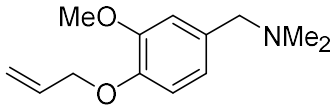
Yield: 82% yield (111 mg, 0.409 mmol) of pale pink crystalline solid

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.3 Hz, 2H), 7.35 (dd, *J* = 7.3, 7.3 Hz, 2H), 7.29 (t, *J* = 7.3 Hz, 1H), 6.90 (d, *J* = 1.7 Hz, 1H), 6.82 (d, *J* = 8.1 Hz, 1H), 6.73 (dd, *J* = 8.1, 1.7 Hz, 1H), 5.14 (s, 2H), 3.89 (s, 3H), 3.34 (s, 2H), 2.22 (s, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 149.6, 147.3, 137.3, 132.2, 128.5, 127.7, 127.3, 121.2, 113.7, 112.6, 71.1, 64.2, 56.0, 45.3.

**ESIHRMS**: Found: m/z 272.1655; Calcd for $C_{17}H_{22}NO_2$: $(M+H)^+$ 272.1651.

#### 6.4.3.3.13. Synthesis of 1-(4-(allyloxy)-3-methoxyphenyl)-*N*,*N*-dimethylmethanamine (4.8m)




Prepared from **4.6m** (118 mg, 0.500 mmol) for 1 h with work-up protocol 1.

Purification: Hex:EtOAc:$CH_2Cl_2$:$Et_3N$ = 40:50:10:1 to 0:90:10:1

Yield: 82% yield (91.1 mg, 0.412 mmol) as pale brown oil

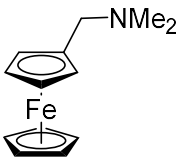
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 6.88 (d, *J* = 1.6 Hz, 1H), 6.81 (d, *J* = 8.1 Hz, 1H), 6.77 (dd, *J* = 8.1, 1.6 Hz, 1H), 6.09 (ddt, *J* = 17.3, 10.6, 5.4 Hz, 1H), 5.40 (dd, *J* = 17.3, 1.4

Hz, 1H), 5.27 (dd, *J* = 10.6, 1.4 Hz, 1H), 4.60 (d, *J* = 5.4 Hz, 2H), 3.88 (s, 3H), 3.35 (s, 2H), 2.23 (s, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 149.4, 147.0, 133.5, 132.0, 121.1, 117.8, 113.0, 112.4, 69.9, 64.2, 55.9, 45.3.

**ESIHRMS**: Found: m/z 222.1498; Calcd for $C_{13}H_{20}NO_2$: $(M+H)^+$ 222.1494.

**6.4.3.3.14. Synthesis of 1-ferrocene-*N,N*-dimethylmethanamine (4.8n)** [CAS: 1271-86-9]




Prepared from **4.6n** (129 mg, 0.501 mmol) for 5 h with work-up protocol 1.

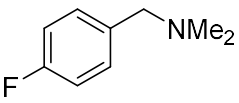
Purification: Hex:EtOAc:$CH_2Cl_2$:$Et_3N$ = 50:40:10:1

Yield: 86% yield (105 mg, 0.431 mmol) as pale brown oil

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 4.16 (t, *J* = 1.8Hz, 2H), 4.11 – 4.10 (m, 7H), 3.28 (s, 2H), 2.17 (s, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 83.1, 70.1, 68.4, 68.0, 59.1, 44.6.

**6.4.3.3.15. Synthesis of 1-(4-fluorophenyl)-*N,N*-dimethylmethanamine (4.8o)**[8]




Prepared from **4.6o** (83.6 mg, 0.500 mmol) for 0.25 h with work-up protocol 2.

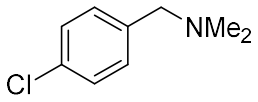
Yield: 86% yield (65.9 mg,0.430 mmol) as a colorless oil

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.26 (dd, *J* = 8.7, 5.6 Hz, 2H), 7.00 (dd, *J* = 8.7, 8.7 Hz, 2H), 3.38 (s, 2H), 2.22 (s, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 162.0 (d, *J* = 244.7 Hz), 134.6 (d, *J* = 3.1 Hz), 130.5 (d, *J* = 7.8 Hz), 115.0 (d, *J* = 21.4 Hz), 63.6, 45.2.

**$^{19}$F NMR** (376 MHz, $CDCl_3$): δ -115.6 (m).

### 6.4.3.3.16. Synthesis of 1-(4-chlorophenyl)-*N,N*-dimethylmethanamine (4.8p)[8]




Prepared from **4.6p** (91.9 mg, 0.500 mmol) for 0.25 h with work-up protocol 1.

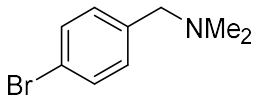
Purification: Hex:EtOAc:$CH_2Cl_2$:$Et_3N$ = 5:90:5:1

Yield: 70% yield (59.4 mg, 0.350 mmol) as a colorless oil.

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.6 Hz, 2H), 7.24 (d, *J* = 8.6 Hz, 2H), 3.38 (s, 2H), 2.22 (s, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 137.4, 132.7, 130.3, 128.4, 63.6, 45.3.

### 6.4.3.3.17. Synthesis of 1-(4-bromophenyl)-*N,N*-dimethylmethanamine (4.8q)[9]




Prepared from **4.6q** (114 mg, 0.501 mmol) for 0.25 h with work-up protocol 1.

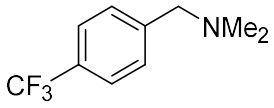
Purification: Hex:EtOAc:$CH_2Cl_2$:$Et_3N$ = 30:60:10:1

Yield: 70% yield (75.4 mg, 0.352 mmol) as a colorless oil

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.3 Hz, 2H), 7.18 (d, *J* = 8.3 Hz, 2H), 3.36 (s, 2H), 2.22 (s, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 138.0, 131.3, 130.7, 120.8, 63.6, 45.3.

### 6.4.3.3.18. Synthesis of *N,N*-dimethyl-1-(4-(trifluoromethyl)phenyl)methanamine (4.8r)[8]




Prepared from **4.6r** (109 mg, 0.503 mmol) for 0.25 h with work-up protocol 2.

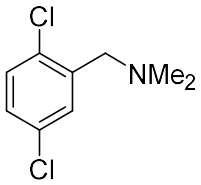
Yield: 58% yield (58.6 mg, 0.288 mmol) as a colorless oil

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.1 Hz, 2H), 7.43 (d, *J* = 8.1 Hz, 2H), 3.47 (s, 2H), 2.25 (s, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 143.2, 129.1, 125.2 (q, *J* = 3.8 Hz), 124.3 (q, *J* = 271.8 Hz), 63.8, 45.4.

**$^{19}$F NMR** (376 MHz, $CDCl_3$): δ -62.7 (s).

### 6.4.3.3.19. Synthesis of 1-(2,5-dichlorophenyl)-*N,N*-dimethylmethanamine (4.8s)




Prepared from **4.6s** (109 mg, 0.498 mmol) for 1.5 h with work-up protocol 2

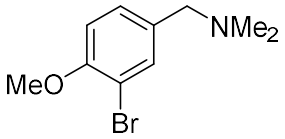
Yield: 52% yield (53.4 mg, 0.262 mmol) as a colorless oil.

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 2.3 Hz, 1H), 7.27 (d, *J* = 8.5 Hz, 1H), 7.16 (dd, *J* = 8.5, 2.3 Hz, 1H), 3.49 (s, 2H), 2.30 (s, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 138.4, 132.6, 132.3, 130.5, 130.4, 128.1, 60.4, 45.6.

**ESIHRMS**: Found: m/z 204.0350; Calcd for $C_9H_{12}N^{35}Cl_2$: $(M+H)^+$ 204.0347.

#### 6.4.3.3.20. Synthesis of 1-(3-bromo-4-methoxyphenyl)-*N,N*-dimethylmethanamine (4.8t)




Prepared from **4.6t** (129 mg, 0.499 mmol) for 0.67 h with work-up protocol 2.

Yield: 77% yield (93.7 mg, 0.384 mmol) as a pale yellow oil.

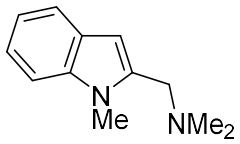
**$^{1}$H NMR** (400 MHz, $CDCl_3$) 7.50 (d, *J* = 2.1 Hz, 1H), 7.19 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.84 (d, *J* = 8.3 Hz, 1H), 3.88 (s, 3H), 3.33 (s, 2H), 2.22 (s, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) 154.9, 133.8, 132.7, 129.0, 111.6, 111.4, 63.1, 56.2, 45.2.

**ESIHRMS**: Found: m/z 244.0342; Calcd for $C_{10}H_{15}NO^{79}Br$: $(M+H)^+$ 244.0337.

### 6.4.3.4. Reduction of heteroaromatic amides to amine

#### 6.4.3.4.1. Synthesis of *N,N*-dimethyl-1-(1-methyl-1H-indol-2-yl)methanamine (4.8u)




Prepared from **4.6u** (101 mg, 0.501 mmol) for 2.5 h with work-up protocol 1.

Purification: Hex:EtOAc:$CH_2Cl_2$:$Et_3N$ = 30:60:10:1 to 10:80:10:1

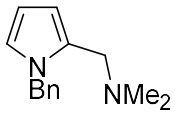
Yield: 78% yield (73.3 mg, 0.389 mmol) as a pale yellow oil

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.8 Hz, 1H), 7.30 (d, *J* = 7.8 Hz, 1H), 7.22 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.12 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.00 (s, 1H), 3.77 (s, 3H), 3.62 (s, 2H), 2.28 (s, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 136.9, 128.3 (overlapped), 121.4, 119.3, 119.0, 111.7, 109.1, 54.3, 45.2, 32.6.

**ESIHRMS**: Found: m/z 189.1389; Calcd for $C_{12}H_{17}N_2$: $(M+H)^+$ 189.1392.

### 6.4.3.4.2. Synthesis of 1-(1-benzyl-1H-pyrrol-2-yl)-*N,N*-dimethylmethanamine (4.8v)




Prepared from **4.6v** (114 mg, 0.500 mmol) for 4 h with work-up protocol 1.

Purification: Hex:EtOAc:$CH_2Cl_2$:$Et_3N$ = 10:80:10:1

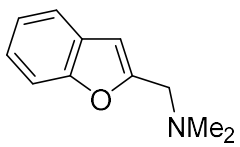
Yield: 78% yield (83.3 mg, 0.387 mmol)as a pale yellow oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.29 (dd, *J* = 7.3, 7.3 Hz, 2H), 7.23 (t, *J* = 7.3 Hz, 1H), 7.03 (d, *J* = 7.3 Hz, 2H), 6.65 – 6.64 (m, 1H), 6.09 (dd, *J* = 3.0, 3.0 Hz, 1H), 6.04 – 6.03 (m, 1H), 5.22 (s, 2H), 3.22 (s, 2H), 2.16 (s, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 138.9, 129.8, 128.5, 127.1, 126.6, 122.1, 109.5, 106.7, 55.6, 50.3, 45.0.

**ESIHRMS**: Found: m/z 215.1545; Calcd for $C_{14}H_{19}N_2$: $(M+H)^+$ 215.1548.

### 6.4.3.4.3. Synthesis of 1-(benzofuran-2-yl)-*N,N*-dimethylmethanamine (4.8w)




Prepared from **4.6w** (94.3 mg, 0.501 mmol) for 4 h with work-up protocol 1.

Purification: Hex:EtOAc:$CH_2Cl_2$:$Et_3N$ = 5:90:5:1

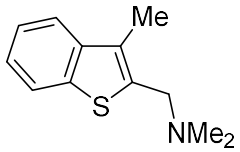
Yield: 80% yield (69.6 mg, 0.399 mmol)as a colorless oil

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.4 Hz, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.25 – 7.17 (m, 2H), 6.57 (s, 1H), 3.61 (s, 2H), 2.32 (s, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 155.1, 155.0, 128.2, 123.8, 122.5, 120.6, 111.2, 105.1, 56.3, 45.1.

**ESIHRMS**: Found: m/z 176.1078; Calcd for $C_{11}H_{14}NO$: $(M+H)^+$ 176.1075.

### 6.4.3.4.4. Synthesis of *N,N*-dimethyl-1-(3-methylbenzo[b]thiophen-2-yl)methanamine (4.8x)




Prepared from **4.6x** (110 mg, 0.499 mmol) for 0.5 h with work-up protocol 1

Purification: Hex:EtOAc = 1:1 to 0:1

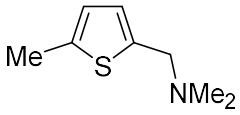
Yield: 88% yield (90.6 mg, 0.441 mmol) as a pale yellow oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.6 Hz, 1H), 7.64 (d, *J* = 7.6 Hz, 1H), 7.35 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.29 (dd, *J* = 7.6, 7.6 Hz, 1H), 3.68 (s, 2H), 2.36 (s, 3H), 2.32 (s, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 140.7, 139.1, 137.2, 128.3, 123.9, 123.6, 122.2, 121.4, 56.7, 45.4, 11.7.

**ESIHRMS**: Found: m/z 206.0999; Calcd for $C_{12}H_{16}NS$: $(M+H)^+$ 206.1003.

### 6.4.3.4.5. Synthesis of *N,N*-dimethyl-1-(5-methylthiophen-2-yl)methanamine (4.8y)




Prepared from **4.6y** (84.9 mg, 0.501mmol,) for 0.5 h with work-up protocol 1.

Purification: Hex:EtOAc:$CH_2Cl_2$:$Et_3N$ = 40:50:10:1

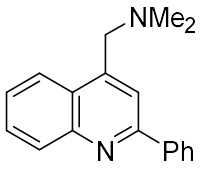
Yield: 75% yield (58.1 mg, 0.374 mmol) as a pale pink oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 6.67 (d, *J* = 3.1 Hz, 1H), 6.57 (d, *J* = 3.1 Hz, 1H), 3.55 (s, 2H), 2.45 (s, 3H), 2.26 (s, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 139.7, 139.4, 125.8, 124.3, 58.5, 44.9, 15.4.

**ESIHRMS**: Found: m/z 156.0847; Calcd for $C_8H_{14}NS$: $(M+H)^+$ 156.0847.

### 6.4.3.4.6. Synthesis of *N,N*-dimethyl-1-(2-phenylquinolin-3-yl)methanamine (4.8z)




Prepared from **4.6z** (139 mg, 0.501 mmol) for 3 h with work-up protocol 1.

Purification: Hex:EtOAc:$Et_3N$ = 70:20:10:1

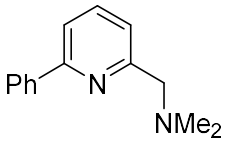
Yield: 56% yield (73.6 mg, 0.281 mmol) as a pale yellow powder

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.21 – 8.17 (m, 4H), 7.88 (s, 1H), 7.70 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.55 – 7.50 (m, 3H), 7.45 (t, *J* = 7.2 Hz, 1H), 3.89 (s, 2H), 2.35 (s, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 157.0, 148.6, 145.1, 139.8, 130.3, 129.3, 129.2, 128.8, 127.6, 126.6, 126.1, 123.8, 119.2, 61.4, 45.9.

**ESIHRMS**: Found: m/z 263.1542; Calcd for $C_{18}H_{19}N_2$: $(M+H)^+$ 263.1548.

#### 6.4.3.4.7. Synthesis of *N,N*-dimethyl-1-(6-phenylpyridin-2-yl)methanamine (4.8aa)




Prepared from **4.6aa** (113 mg, 0.501 mmol) for 0.75 h with work-up protocol 1.

Purification: Hex:EtOAc:$CH_2Cl_2$:$Et_3N$ = 50:50:1

Yield: 55% yield (58.6 mg, 0.276 mmol) as a pale yellow oil

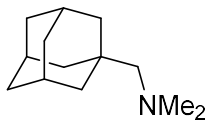
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 7.4 Hz, 2H), 7.72 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.59 (d, *J* = 7.7 Hz, 1H), 7.46 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.41 – 7.36 (m, 2H), 3.69 (s, 2H), 2.35 (s, 3H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 159.1, 156.7, 139.6, 137.0, 128.7, 128.6, 127.0, 121.3, 118.7, 66.0, 45.7.

**ESIHRMS**: Found: m/z 213.1387; Calcd for $C_{14}H_{17}N_2$: $(M+H)^+$ 213.1392.

### 6.4.3.5. Reduction of α-Quaternary/Tertiary/Secondary amides to amine

#### 6.4.3.5.1. Synthesis of 1-((3r,5r,7r)-adamantan-1-yl)-*N,N*-dimethylmethanamine (4.8ab)




Prepared from **4.6ab** (104 mg, 0.501 mmol) for 1.5 h with work-up protocol 1.

Purification: Hex:EtOAc:$CH_2Cl_2$:$Et_3N$ = 5:90:5:1

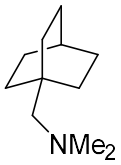
Yield: 77% yield (74.4 mg, 0.359 mmol) as a pale yellow oil

**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 2.27 (s, 6H), 1.95 – 1.93 (m, 5H), 1.71 – 1.63 (m, 6H), 1.51 – 1.51 (m, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 73.2, 49.2, 41.1, 37.2, 34.7, 28.5.

**ESIHRMS**: Found: m/z 194.1904; Calcd for $C_{13}H_{24}N$: $(M+H)^+$ 194.1909.

### 6.4.3.5.2. Synthesis of 1-(bicyclo[2.2.2]octan-1-yl)-*N*,*N*-dimethylmethanamine (4.8ac)




Prepared from **4.6ac** (90.7 mg, 0.500 mmol) for 2.5 h with work-up protocol 2.

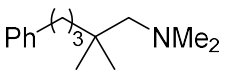
Yield: 77% yield (64.5 mg, 0.386 mmol) as a pale pink oil

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 2.25 (s, 6H), 1.95 (s, 2H), 1.55 – 1.52 (m, 7H), 1.39 – 1.35 (m, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 71.0, 48.9, 32.4, 29.6, 26.1, 24.6.

**ESIHRMS**: Found: m/z 168.1748; Calcd for $C_{11}H_{22}N$: $(M+H)^+$ 168.1752.

### 6.4.3.5.3. Synthesis of *N*,*N*,2,2-tetramethyl-5-phenylpentan-1-amine (4.8ad)




Prepared from **4.6ad** (117 mg, 0.500 mmol) for 2.5 h with work-up protocol 1.

Purification: Hex:EtOAc:$CH_2Cl_2$:TEA = 10:80:10:1

Yield: 68% yield (75.0 mg, 0.342 mmol) as a pale yellow oil

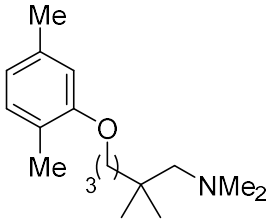
**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.29 – 7.26 (m, 2H), 7.19 – 7.15 (m, 3H), 2.58 (t, *J* = 8.0, 2H), 2.27 (s, 6H), 2.06 (s, 2H), 1.60 – 1.53 (m, 2H), 1.32 – 1.27 (m, 2H), 0.85 (s, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 142.9, 128.3, 128.2, 125.6, 70.8, 48.9, 40.2, 36.9, 35.3,

26.3, 25.6.

**ESIHRMS**: Found: m/z 220.2071; Calcd for $C_{15}H_{26}N$: $(M+H)^+$ 220.2065.

### 6.4.3.5.4. Synthesis of 5-(2,5-dimethylphenoxy)-*N*,*N*,2,2-tetramethylpentan-1-amine (4.8ae)




Prepared from **4.6ae** (139 mg, 0.501 mmol) for 1.5 h with work-up protocol 1.

Purification: Hex:EtOAc:$CH_2Cl_2$:$Et_3N$ = 40:50:10:0 to 40:50:10:1

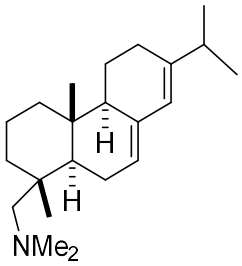
Yield: 72% yield (95.2 mg, 0.361 mmol) as a colorless oil

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.00 (d, *J* = 7.4 Hz, 1H), 6.65 (d, *J* = 7.4 Hz, 1H), 6.63 (s, 1H), 3.92 (t, *J* = 6.8 Hz, 2H), 2.31 (s, 9H), 2.18 (s, 3H), 2.11 (s, 2H), 1.80 – 1.72 (m, 2H), 1.42 – 1.38 (m, 2H), 0.91 (s, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 157.1, 136.4, 130.2, 123.5, 120.5, 111.9, 70.7, 68.7, 48.9, 36.5, 35.1, 25.6, 24.3, 21.4, 15.8.

**ESIHRMS**: Found: m/z 264.2330; Calcd for $C_{17}H_{30}NO$: $(M+H)^+$ 264.2327.

**6.4.3.5.5. Synthesis of 1-((1*R*,4a*R*,4b*R*,10a*R*)-7-isopropyl-1,4a-dimethyl-1,2,3,4,4a,4b,5,6,10,10a-decahydrophenanthren-1-yl)-*N*,*N*-dimethylmethanamine (4.8af)**




Prepared from **4.6af** (164.7 mg, 0.500 mmol) by the slightly modified procedure using NaH (142 mg, 3.55 mmol, 7.0 equiv) and $ZnCl_2$ (239 mg, 1.75 mmol, 3.5 equiv) for 3 h with work-up protocol 1.

Purification: Hex:EtOAc = 4:1 to 1:1

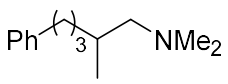
Yield: 68% yield (108 mg, 0.342 mmol) as a colorless oil

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 5.78 (s, 1H), 5.40 (d, *J* = 4.9 Hz, 1H), 2.30 – 2.25 (m, 8H), 2.13 – 2.03 (m, 3H), 1.98 – 1.90 (m, 3H), 1.83 – 1.78 (m, 2H), 1.54 – 1.36 (m, 4H), 1.25 – 1.15 (m, 2H), 1.09 – 1.05 (m, 1H), 1.02 – 0.99 (m, 6H), 0.85 (s, 3H), 0.81 (s, 3H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 145.0, 135.7, 122.5, 121.1, 71.3, 50.8, 49.3, 44.8, 38.9, 38.3, 37.3, 34.9, 34.8, 27.5, 24.1, 22.7, 21.4, 20.8, 19.3, 18.4, 14.4.

**ESIHRMS**: Found: m/z 316.3003; Calcd for $C_{22}H_{38}N$: $(M+H)^+$ 316.3004.

**6.4.3.5.6. Synthesis of *N*,*N*,2-trimethyl-5-phenylpentan-1-amine (4.8ag)**




Prepared from **4.6ag** (110 mg, 0.500 mmol) for 3.5 h with work-up protocol 1.

Purification: Hex:EtOAc:$CH_2Cl_2$:$Et_3N$ = 5:90:5:1

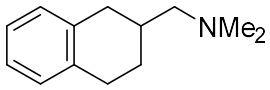
Yield: 76% yield (78.0 mg, 0.380 mmol) as a colourless oil

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.29 – 7.24 (m, 2H), 7.18 – 7.15 (m, 3H), 2.66 – 2.52 (m, 2H), 2.17 (s, 6H), 2.09 – 1.98 (m, 2H), 1.72 – 1.65 (m, 1H), 1.64 – 1.54 (m, 2H), 1.50 – 1.42 (m, 1H), 1.17 – 1.07 (m, 1H), 0.89 (d, *J* = 6.6 Hz, 3H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 142.8, 128.3, 128.2, 125.6, 67.2, 45.9, 36.3, 34.9, 31.0, 29.0, 18.2.

**ESIHRMS**: Found: m/z 206.1907; Calcd for $C_{14}H_{24}N$: $(M+H)^+$ 206.1909.

### 6.4.3.5.7. Synthesis of *N,N*-dimethyl-1-(1,2,3,4-tetrahydronaphthalen-2-yl)methanamine (4.8ah)




Prepared from **4.6ah** (102 mg, 0.501 mmol) for 0.5 h with work-up protocol 1

Purification: Hex:EtOAc:$CH_2Cl_2$:$Et_3N$ = 80:10:10:1

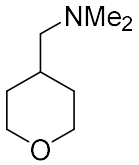
Yield: 81% yield (76.4 mg, 0.404 mmol) as a pale yellow oil

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.09 (m, 4H), 2.93 (dd, *J* = 16.6, 6.3 Hz, 1H), 2.84 – 2.80 (m, 2H), 2.43 (dd, *J* = 16.6, 10.3 Hz, 1H), 2.29 – 2.19 (m, 8H), 1.98 – 1.94 (m, 2H), 1.45 – 1.35 (m, 1H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 136.9, 136.4, 129.2, 128.8, 125.5, 125.5, 66.2, 46.0, 34.5, 32.33, 28.9, 27.8.

**ESIHRMS**: Found: m/z 190.1594; Calcd for $C_{13}H_{20}N$: $(M+H)^+$ 190.1596.

**6.4.3.5.8. Synthesis of *N,N*-dimethyl-1-(tetrahydro-2H-pyran-4-yl)methanamine (4.8ai)**




Prepared from **4.6ai** (78.6 mg, 0.500 mmol) for 1.5 h with work-up protocol 2.

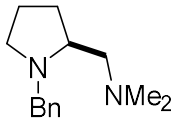
Yield: 77% yield (55.0 mg (0.384 mmol, 77%, 1.5 h) of clear oil

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 3.96 (dd, *J* = 11.4, 3.7 Hz, 2H), 3.39 (t, *J* = 11.4 Hz, 2H), 2.21 (s, 6H), 2.12 (d, *J* = 6.8 Hz, 2H), 1.72 – 1.64 (m, 3H), 1.31 – 1.21 (m, 2H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 67.9, 66.4, 45.9, 33.1, 31.6.

**ESIHRMS**: Found: m/z 144.1386; Calcd for $C_8H_{18}NO$: $(M+H)^+$ 144.1388.

**6.4.3.5.9. Synthesis of (*S*)-1-(1-benzylpyrrolidin-2-yl)-N,N-dimethylmethanamine (4.8aj)**




Prepared from **4.6aj** (116 mg, 0.498 mmol) for 4 h with work up protocol 1.

Purification: EtOAc:$Et_3N$ = 100:0 to 100:2.

Yield: 84% yield (91.4 mg, 0.419 mmol, >98% ee) as a pale yellow oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.34 – 7.20 (m, 5H), 4.12 (d, *J* = 12.9 Hz, 1H), 3.28 (d, *J* = 12.9 Hz, 1H), 2.94 – 2.89 (m, 1H), 2.61 – 2.54 (m, 1H), 2.43 (dd, *J* = 12.2, 3.9 Hz, 1H), 2.29 (dd, *J* = 12.2, 8.4 Hz, 1H), 2.24 (s, 6H), 2.18 – 2.11 (m, 1H), 2.03 – 1.96 (m, 1H), 1.75 – 1.60 (m, 3H).

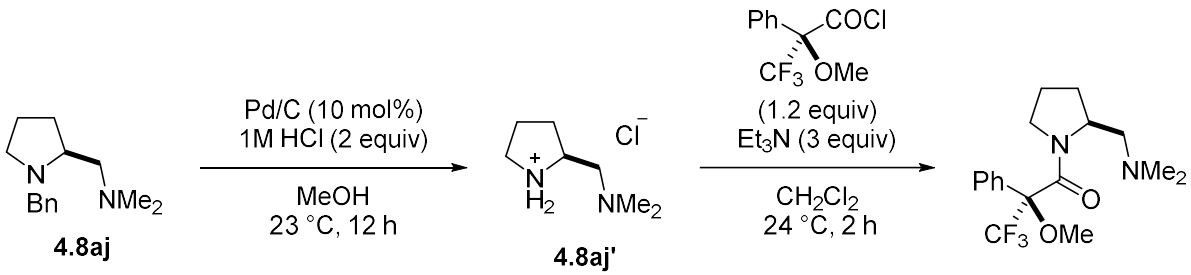
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 139.7, 128.9, 128.1, 126.7, 65.2, 62.0, 59.4, 54.4, 46.3,

30.4, 22.6.

**Optical Rotation**: $[\alpha]^{25}_{D}$ –66.0° (c = 0.011 g/mL, $CHCl_3$)

**Enantiomeric excess:** measured by the Mosher method[7] with (−)-MTPA derivatization (see below for the experimental details).

**The Moscher method for 4.8aj**




To a mixture of amine, **4.8aj** (79.8 mg, 0.365 mmol), palladium on carbon (10% wt; 38.9 mg, 0.0366mmol), and MeOH (3 mL) was added aq. 1M HCl (1 ml) in a 2 necked round bottom flask. The reaction vessel was evacuated and backfilled with hydrogen (three times). The reaction mixture was stirred at 24 °C for 12 h. The crude mixture was filtered through a pad of celite and a yellow solution was collected. After removing volatile materials in vacuo, the resulting crude material including debenzylated amine **4.8aj'** was used without further purification.

To a solution of (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid (103 mg, 0.440 mmol) in $CH_2Cl_2$ (2 mL) was added $(COCl)_2$ (55.7 µL, 0.658 mmol) and DMF (1 drop) at 23 °C. The reaction mixture was stirred at 24 °C for 1 h. After removing volatile materials in vacuo, the resulting crude material including acyl chloride **MTPA-Cl** was used without further purification.

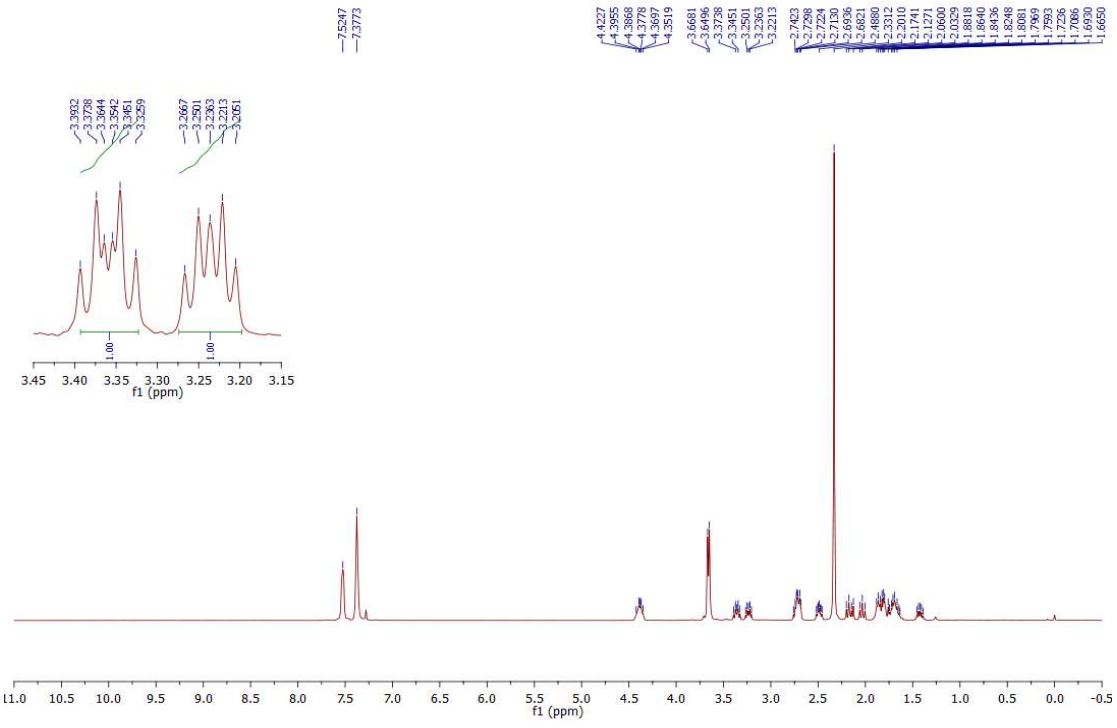
To a solution of **4.8aj'** and triethylamine (153 µL, 1.10 mmol) in $CH_2Cl_2$ (2 mL) was added dropwise of **MTPA-Cl** in $CH_2Cl_2$ (2 mL). The reaction mixture was stirred at

24 °C for 2 h. The reaction was then quenched with water and organic materials were extracted twice with $CH_2Cl_2$, washed with saturated aqueous $NaHCO_3$ solution and then dried over $MgSO_4$. The volatile materials was removed *in vacuo* and the resulting crude mixture was purified by flash column chromatography (silica gel, $CH_2Cl_2$:MeOH = 1:0 to 43:2) to give a white solid **4.8aj'-MTPA** (89.3 mg, 0.259 mmol) in 71% yield over 2 steps.

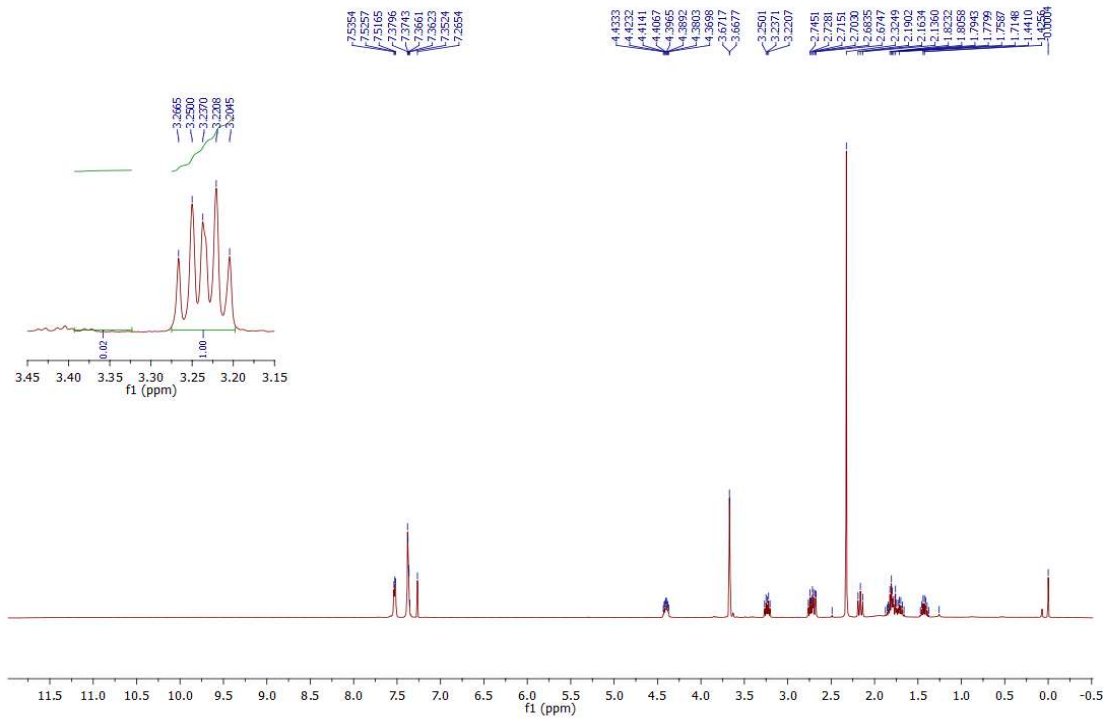
**For derivatisation of rac-4.8aj:**

Prepared from **rac-4.8j** (95.2 mg, 0.436 mmol) by following the procedure described above to give **rac-4.8j'-MTPA** (109 mg, 0.317 mmol) in 73% yield over 2 steps.

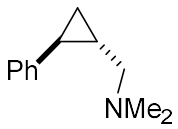
**<u>$^1$H NMR spectrum for rac-4.8aj'-MTPA</u>**



**$^1$H NMR spectrum for 4.8aj'-MTPA**




**6.4.3.5.10. Synthesis of *N,N*-dimethyl-1-((1*S**,2*S**)-2-phenylcyclopropyl)methanamine (4.8ak)**




Prepared from **4.6ak** (94.6 mg, 0.500 mmol) for 2 h with work-up protocol 1.

Purification: Hex:EtOAc:$CH_2Cl_2$:$Et_3N$ = 10:80:10:2

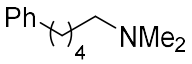
Yield: 76% yield (66.2 mg, 0.378 mmol) as a colorless oil

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.25 (dd, *J* = 7.3, 7.3 Hz, 2H), 7.14 (t, *J* = 7.3 Hz, 1H), 7.06 (d, *J* = 7.3 Hz, 2H), 2.41 (dd, *J* = 12.5, 6.3 Hz, 1H), 2.33 – 2.24 (m, 7H), 1.71 – 1.66 (m, 1H), 1.27 – 1.19 (m, 1H), 0.99 – 0.94 (m, 1H), 0.86 – 0.81 (m, 1H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 142.8, 128.2, 125.6, 125.4, 63.9, 45.4, 22.5, 21.4, 14.9.

**ESIHRMS**: Found: m/z 176.1445; Calcd for $C_{12}H_{18}N$: $(M+H)^+$ 176.1439.

### 6.4.3.5.11. Synthesis of *N,N*-dimethyl-5-phenylpentan-1-amine (4.8al)



Prepared from **4.6al** (103 mg, 0.501 mmol) for 0.75 h with work-up protocol 1.

Purification: Hex:EtOAc:$CH_2Cl_2$:$Et_3N$ = 5:90:5:2

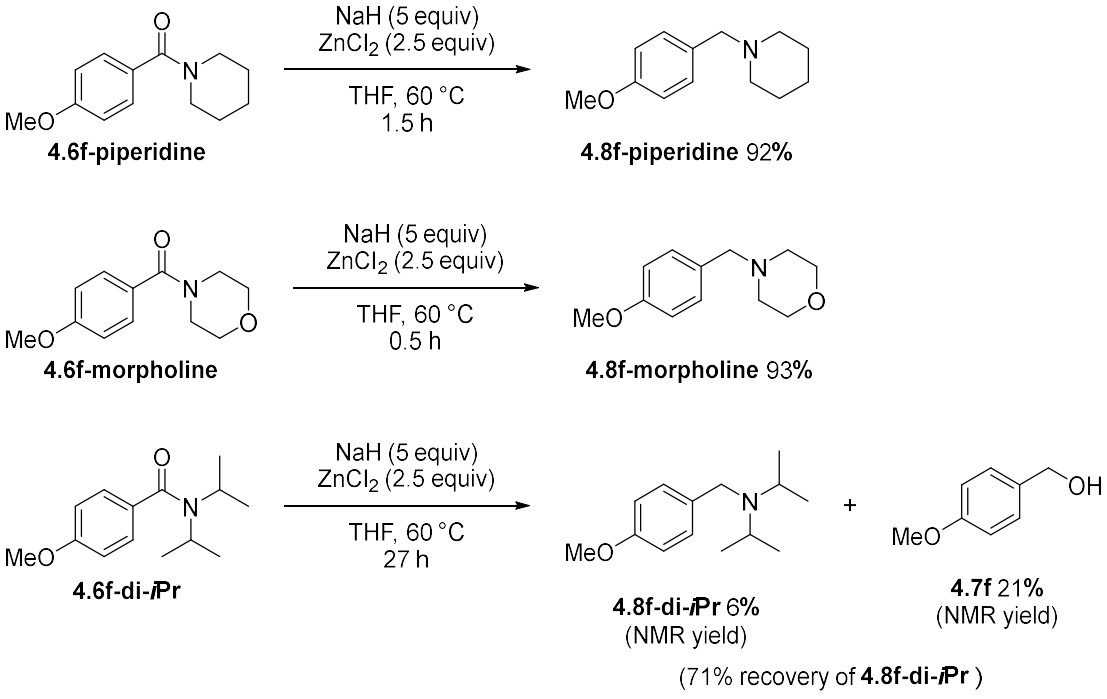
Yield: 79% yield (75.9 mg, 0.397 mmol) as a colorless oil

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.29 – 7.25 (m, 2H), 7.19 – 7.15 (m, 3H), 2.61 (t, *J* = 8.0 Hz, 2H), 2.26 – 2.21 (m, 8H), 1.68 – 1.60 (m, 2H), 1.53 – 1.45 (m, 2H), 1.39 – 1.31 (m, 2H).

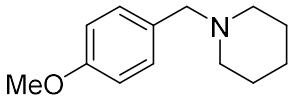
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 142.8, 128.5, 128.3, 125.7, 59.8, 45.5, 36.0, 31.5, 27.6, 27.2.

**ESIHRMS**: Found: m/z 192.1757; Calcd for $C_{13}H_{22}N$: $(M+H)^+$ 192.1752.

### 6.4.3.6. Effect of the substituents on the amide nitrogen



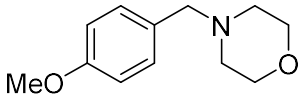
#### 6.4.3.6.1. Spectral data for 1-(4-methoxybenzyl)piperidine (4.8f-piperidine)[10]




**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.22 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 3.80 (s, 3H), 3.41 (s, 2H), 2.35 (brs, 4H), 1.59 – 1.53 (m, 4H), 1.45 – 1.42 (m, 2H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 158.5, 130.5, 130.4, 113.4, 63.2, 55.2, 54.3, 25.9, 24.4.

#### 6.4.3.6.2. Spectral data for 1-(4-methoxybenzyl)piperidine (4.8f-morpholine)[11]

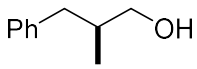



**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.28 (d, *J* = 7.8 Hz, 2H), 6.88 (d, *J* = 7.8Hz, 2H), 3.83 (s, 3H), 3.74 – 3.71 (m, 4H), 3.46 (s, 2H), 2.45 (brs, 4H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 158.7, 130.3, 129.6, 113.6, 67.0, 62.8, 55.2, 53.5.

### 6.4.4. Reduction of α-enantioenriched amides 4.6am and 4.6am'

#### 6.4.4.1. Synthesis of (*S*)-2-methyl-3-phenylpropan-1-ol ((*S*)-4.7am)




Prepared from **4.6am** (155 mg, 0.499 mmol) for 2 h by the slightly modified procedure described in section 3.1. using NaH (100mg, 2.50 mmol), NaI (150 mg, 1.00 mmol) and $ZnI_2$ (319 mg, 1.00 mmol)

Purification: Hex:EtOAc = 4:1.

Yield: 83% yield (61.9 mg, 0.412 mmol, 99% ee) as a colorless oil.

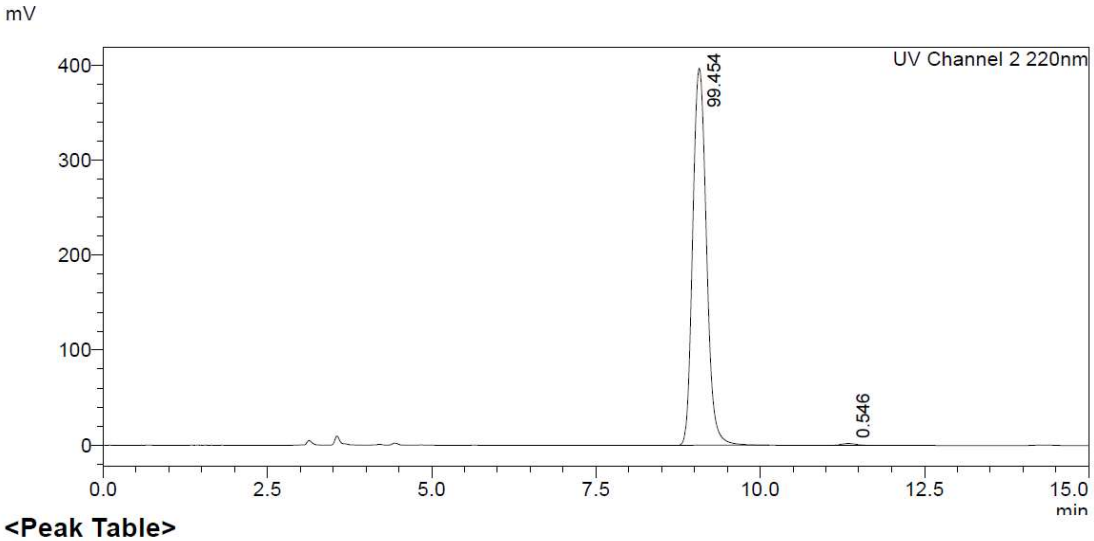
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.28 (t, *J* = 7.3 Hz, 2H), 7.21 – 7.16 (m, 3H), 3.53 (dd, *J* = 10.5, 5.9 Hz, 1H), 3.47 (dd, *J* = 10.5, 5.9 Hz, 1H), 2.75 (dd, *J* = 13.4, 6.3 Hz, 1H), 2.43 (dd, *J* = 13.4, 8.0 Hz, 1H), 2.01 – 1.89 (m, 1H), 1.36 (s, 1H), 0.92 (d, *J* = 6.7 Hz, 3H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 140.6, 129.1, 128.2, 125.8, 67.6, 39.7, 37.8, 16.4.

**Enantiomeric excess:** 99% ee measured by HPLC analysis (chiracel OD-H, hexanes/*i*-PrOH 95/5, 1.0 mL/min, 220 nm): $t_R$ (minor) = 11.3 minutes, $t_R$ (major) = 9.07 minutes

**HPLC trace for (*S*)-4.7am (99%ee)**

<Chromatogram>

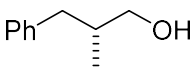



<Peak Table>

UV Channel 2 220nm

| Peak# | Ret. Time | Area | Height | Area% |
|---|---|---|---|---|
| 1 | 9.071 | 5797283 | 396507 | 99.454 |
| 2 | 11.341 | 31803 | 1995 | 0.546 |
| Total | | 5829086 | 398501 | 100.000 |

### 6.4.4.2. Synthesis of (*R*)-2-methyl-3-phenylpropan-1-ol ((*R*)-4.7am))




Prepared from **4.6am'** (156 mg, 0.500 mmol) for 2 h by the slightly modified procedure described in section 3.1. using NaH (100mg, 2.50 mmol), NaI (150 mg, 1.00 mmol) and $ZnI_2$ (319 mg, 1.00 mmol).

Purification: Hex:EtOAc = 4:1.

Yield: 87% yield (65.4 mg, 0.435 mmol, 99% ee) as a colorless oil.

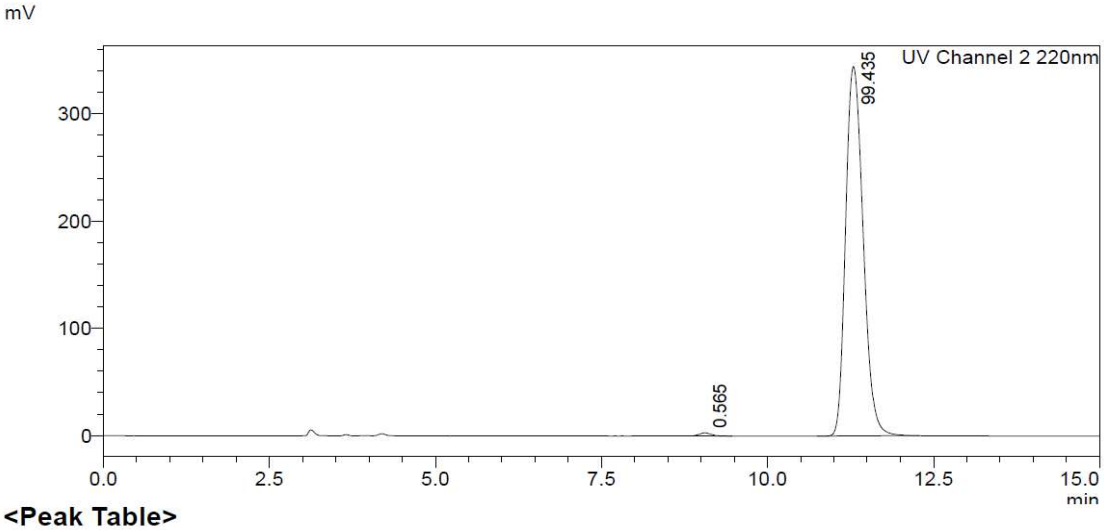
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.28 (t, *J* = 7.3 Hz, 2H), 7.21 – 7.16 (m, 3H), 3.53 (dd, *J* = 10.5, 5.9 Hz, 1H), 3.47 (dd, *J* = 10.5, 5.9 Hz, 1H), 2.75 (dd, *J* = 13.4, 6.3 Hz, 1H), 2.43 (dd, *J* = 13.4, 8.0 Hz, 1H), 2.01 – 1.89 (m, 1H), 1.36 (s, 1H), 0.92 (d, *J* = 6.7 Hz, 3H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 140.6, 129.1, 128.2, 125.8, 67.6, 39.7, 37.8, 16.4.

**Enantiomeric excess:** 99% ee measured by HPLC analysis (chiracel OD-H, hexanes/*i*-PrOH 95/5, 1.0 mL/min, 220 nm): $t_R$ (minor) = 9.06 minutes, $t_R$ (major) = 11.3 minutes

**HPLC trace for (*R*)-4.7am (99%ee)**

<Chromatogram>




<Peak Table>

UV Channel 2 220nm

| Peak# | Ret. Time | Area | Height | Area% |
|---|---|---|---|---|
| 1 | 9.055 | 36079 | 2815 | 0.565 |
| 2 | 11.293 | 6347334 | 344095 | 99.435 |
| Total | | 6383413 | 346910 | 100.000 |

### 6.4.5. Deuterium labelling experiments

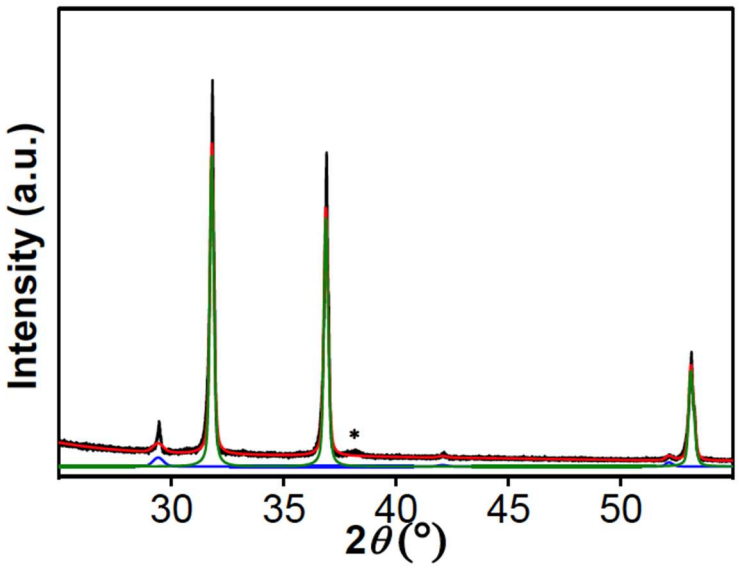
#### 6.4.5.1. Preparation and Characterisation of NaD

##### 6.4.5.1.1. Preparation of NaD[12]

To a 100 mL sealed tube were added sodium pieces (2.90 g, 125 mmol) and mineral oil (5.4 mL). The reaction vessel was evacuated and backfilled with argon (three times). The mixture was then heated to 285 °C and stirred for 3 h. The reaction vessel was subsequently evacuated and backfilled with $D_2$ gas (twice). The reaction mixture was stirred for 6 h at the same temperature ($D_2$ gas balloon was refilled every 3 hours). The reaction mixture was then cooled to room temperature, evacuated, and transferred to the glove box. The solid materials were filtered, washed with pentane (7 x 5 mL) and THF (5 x 5 mL). Subsequently, the solid was suspended in 1,4-dioxane to separate the unreacted metallic sodium to give an 81% yield of NaD containing around 3.7% of metallic Na (2.52 g, 101 mmol) as grey solid.

##### 6.4.5.1.2. Powder XRD data of NaD

###### 6.4.5.1.2.1. Powder X-ray diffraction data



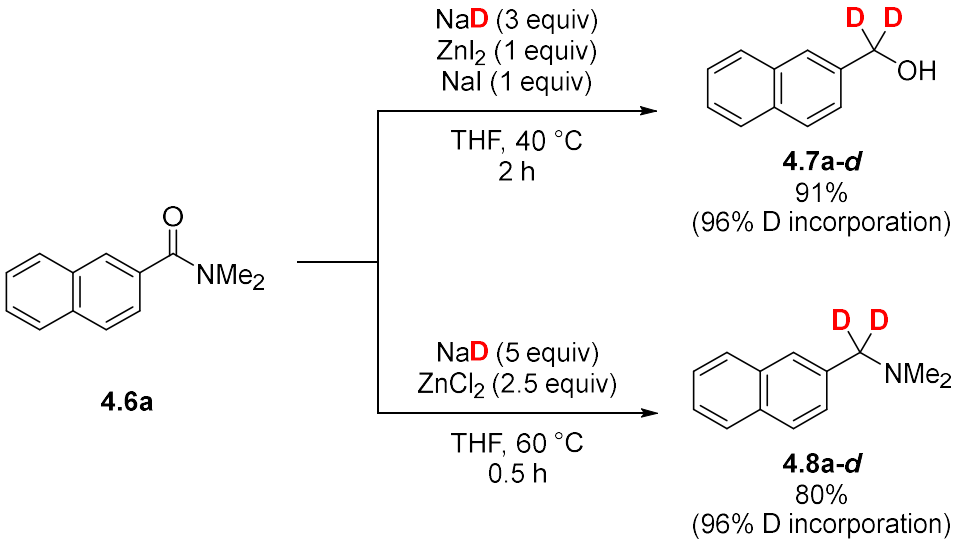
Powder X-ray diffraction data for freshly prepared NaD sample (black). The Rietveld refinement (red) is overlaid with the independently collected data for the components NaD (green) and metallic Na (blue). The peak at 2θ = 38.1° (marked with *) corresponds to NaOH (a trace amount).

### 6.4.5.1.2.2. Rietveld refinement results [13-14]

| | Atom | Site | x | y | z | Occupancy | $B_{eq.}$ |
|---|---|---|---|---|---|---|---|
| **NaD + Na** | | | | | | | |
| $R_{wp}$: 15.87 | | | | | | | |
| GOF: 2.56 | | | | | | | |
| **NaD** | Na | 4a | 0 | 0 | 0 | 1 | 1 |
| Fm-3m (No. 225) | | | | | | | |
| a: 4.8750669 | | | | | | | |
| $R_B$: 4.25 | D | 4b | 0.5 | 0.5 | 0.5 | 1 | 1 |
| wt: 96.3% | | | | | | | |
| **Na** | Na | 2a | 0 | 0 | 0 | 1 | 1 |
| Im-3m (No. 229) | | | | | | | |
| a: 4.2955808 | | | | | | | |
| $R_B$: 6.63 | | | | | | | |
| wt: 3.7% | | | | | | | |

Rietveld refinement results of the powder X-ray diffraction data for the NaD and Na samples. The slightly larger $R_{wp}$ and GOF values could be due to the presence of amorphous NaOH in the sample and the low content of Na.

### 6.4.5.2. Reduction of amide 4.6a with NaD




#### 6.4.5.2.1. Synthesis of deuterated naphthalen-2-ylmethanol (4.7a-d)

Prepared from **4.6a** (99.7 mg, 0.500 mmol) for 2 h by following the procedure described in section 3.1. using NaD containing ca. 4% of metallic Na (40.5 mg, 1.62 mmol).

Purification: Hex:EtOAc = 4:1.

Yield: 91% (72.9 mg, 0.455 mmol, 96% D incorporation) as a white solid.

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.84 – 7.79 (m, 4H), 7.49 – 7.44 (m, 3H), 4.81 (s, 0.08H of **2a**), 1.89 (s, 1H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 138.1, 133.3, 132.9, 128.2, 127.8, 127.7, 126.1, 125.8, 125.4, 125.1, 65.2 – 64.2 (m).

**ESIHRMS**: Found: m/z 161.0932; Calcd for $C_{11}{}^{1}H_9{}^{2}H_2O$: $(M+H)^+$ 161.0935.

#### 6.4.5.2.2. Synthesis of deuterated *N,N*-dimethyl-1-(naphthalen-2-yl)methanamine (4.8a-d)

Prepared from **4.6a** (99.3 mg, 0.498 mmol) for 0.5 h with work up protocol 1 by following the procedure described in section 4.1 using NaD containing ca. 4% of metallic Na (62.6 mg, 2.50 mmol)

Purification: Hex:EtOAc:TEA = 80:20:1

Yield: 80% yield (73.9 mg, 0.399 mmol, 96% D incorporation) as a colorless oil.

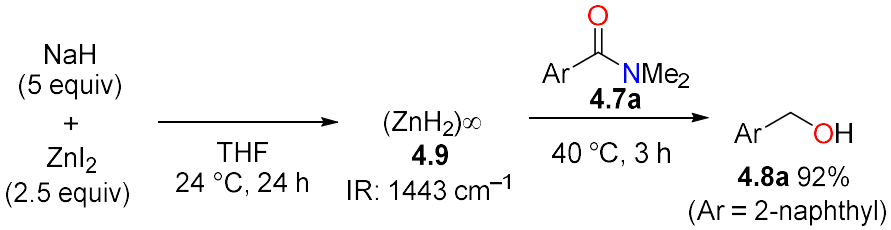
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.83 – 7.80 (m, 3H), 7.73 (s, 1H), 7.48 – 7.42 (m, 3H), 3.54 (s, 0.08H of **3a**), 2.28 (s, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 136.4, 133.3, 132.7, 127.9, 127.7, 127.6, 127.5, 127.3, 125.8, 125.5, 64.1 – 63.3 (m), 45.4.

**ESIHRMS**: Found: m/z 188.1413; Calcd for $C_{13}{}^1H_{14}{}^2H_2N$: $(M+H)^+$ 188.1408.

### 6.4.6. Characterization of the active zinc hydride species

#### 6.4.6.1. Reduction of amide using $(ZnH_2)_\infty$ 4.9 synthesized by the Ashby's protocol[15] (Scheme 4.20a)



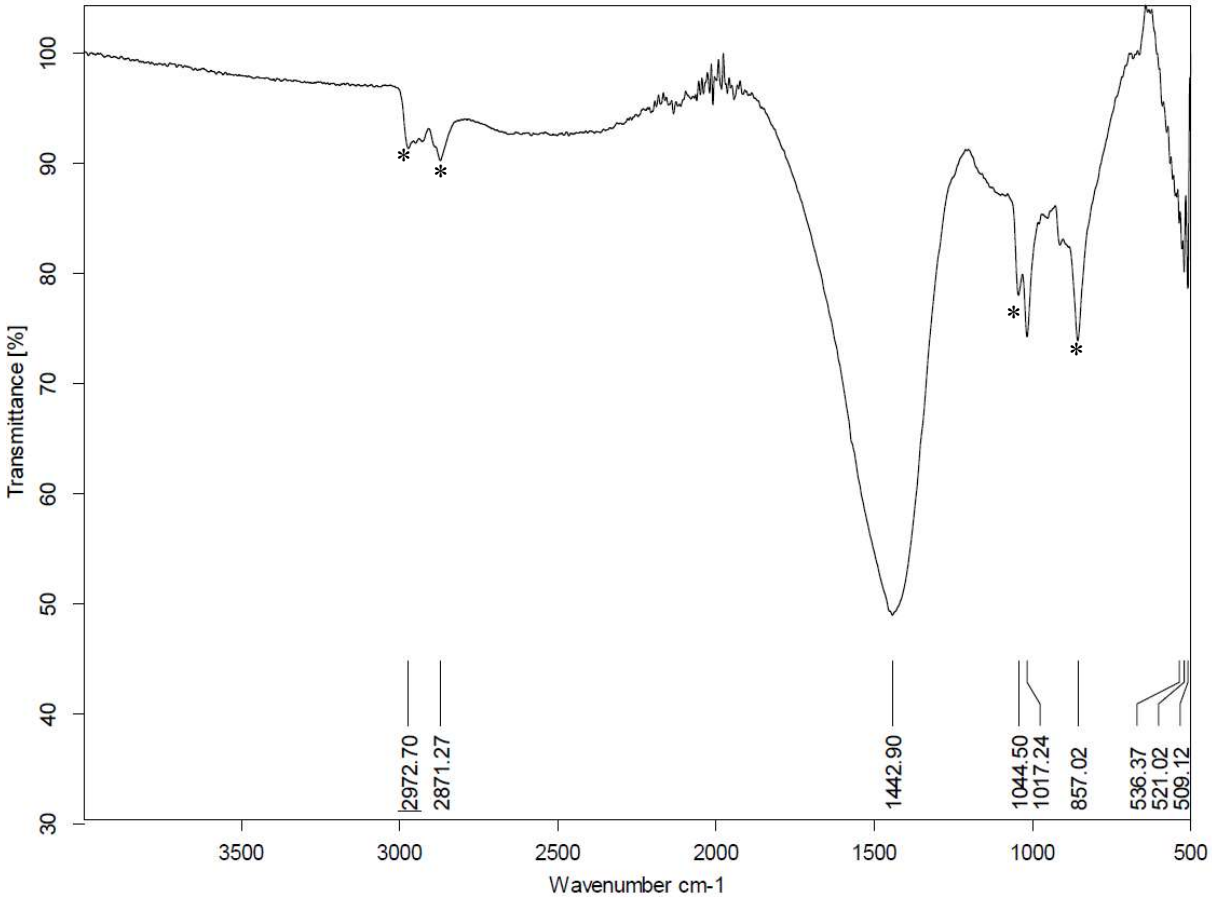

To a mixture of NaH (dry; 61.1 mg, 2.54 mmol) and $ZnI_2$ (400 mg, 1.25 mmol) in a 25 mL sealed tube was added 2.5 mL of THF, the reaction mixture was sealed and stirred at 24 °C for 24 h. The reaction mixture was transferred to a glovebox and a sample of the reaction mixture containing $(ZnH_2)_\infty$ **4.9** was directly taken for IR spectroscopy analysis.

ν (Zn-H): 1443 $cm^{-1}$

Amide **4.6a** (99.5 mg, 0.499 mmol) was added directly into the reaction mixture and was sealed and stirred at 40 °C for 3 h. The reaction was quenched with ammonium pH 10 buffer at 0 °C and the organic materials were extracted with dichloromethane (20 mL×3). The combined extracts were dried over $MgSO_4$. The volatile materials were

removed *in vacuo* and the resulting crude residue was purified by flash column chromatography (silica gel, Hex:EtOAc = 4:1) to give a white solid **4.7a** (72.6 mg, 0.459 mmol) in 92% yield.

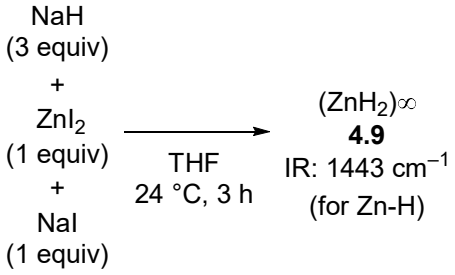
### 6.4.6.1.1. IR spectrum of $(ZnH_2)_\infty$ 4.9 synthesized following Ashby's protocol.




The peaks marked with * corresponds to IR absorptions of THF

### 6.4.6.2. Characterization of $(ZnH_2)_\infty$ 4.9 prepared from the NaH-$ZnI_2$-NaI system (Scheme 4.20b)

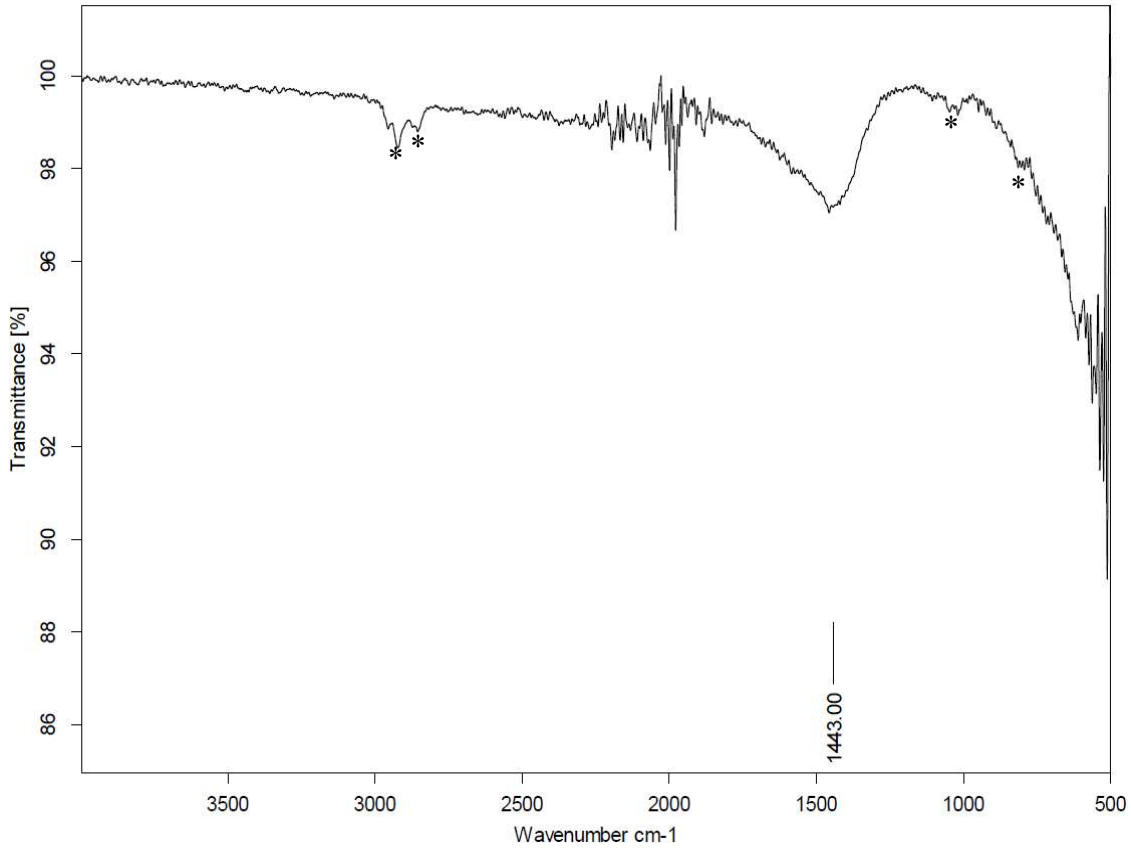
#### 6.4.6.2.1. Synthesis of $(ZnH_2)_\infty$ 4.9 from the NaH-$ZnI_2$-NaI system




To a mixture of NaH (dry; 37.2 mg, 1.55 mmol), $ZnI_2$ (161 mg, 0.504 mmol) and NaI (75.5 mg, 0.504 mmol) in a 25 mL sealed tube was added 2.5 mL of THF, the reaction mixture was sealed and stirred at 24 °C for 3 h. The reaction mixture was transferred to a glovebox and a sample of the reaction mixture was directly taken for IR spectroscopy analysis.

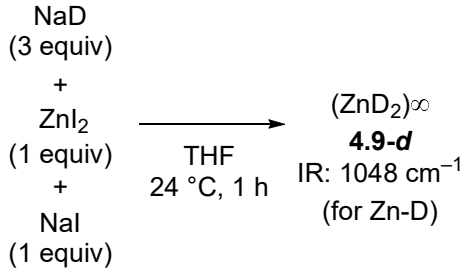
ν (Zn-H): 1443 $cm^{-1}$

### 6.4.6.2.1.1. IR spectrum of $(ZnH_2)_\infty$ from NaH-$ZnI_2$-NaI system




The peaks marked with * corresponds to IR absorptions of THF.

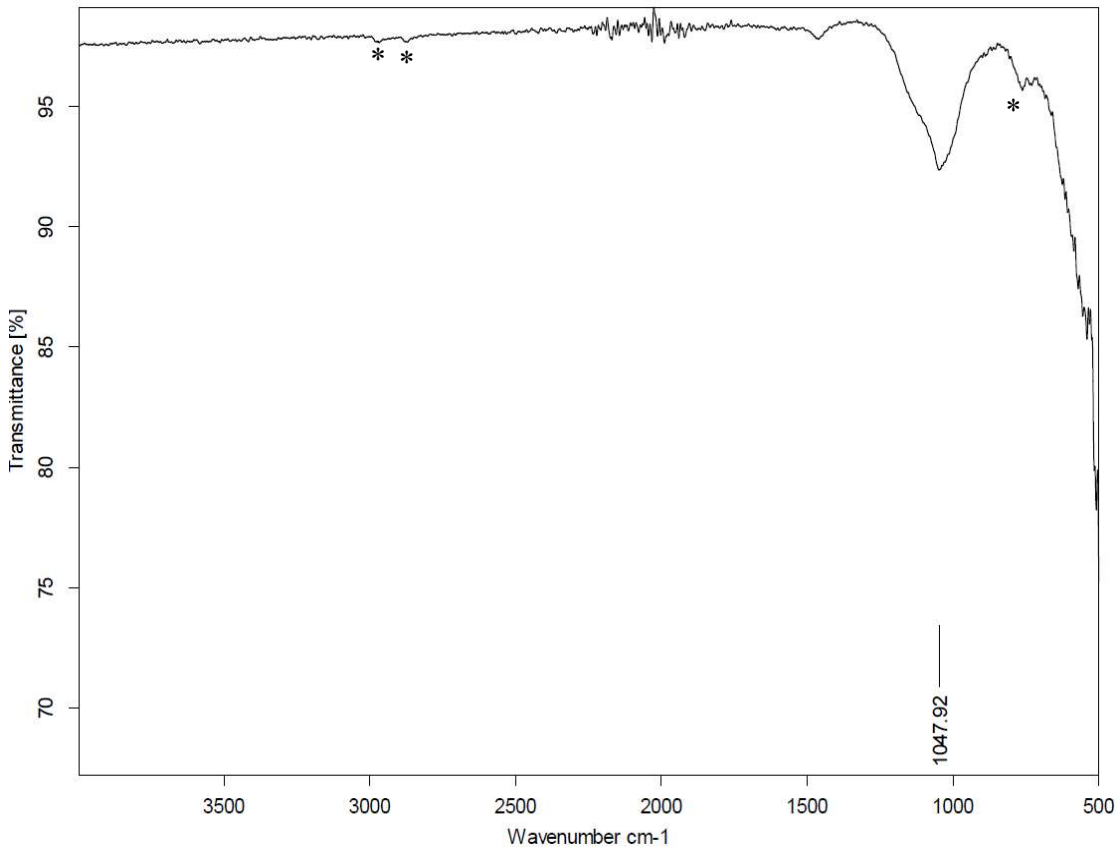
### 6.4.6.2.2. Synthesis of $(ZnD_2)_\infty$ 4.9-*d* from the NaD-$ZnI_2$-NaI system




To a mixture of NaD (38.1 mg, 1.52 mmol), $ZnI_2$ (160 mg, 0.500 mmol) and NaI (75.9 mg, 0.506 mmol) in a 25 mL sealed tube was added 2.5 mL of THF, the reaction mixture was sealed and stirred at 24 °C for 1 h. Reaction mixture was transferred to a glovebox and a sample of reaction mixture was directly taken for IR spectroscopy analysis.

ν (Zn-D): 1048 $cm^{-1}$

### 6.4.6.2.2.1. IR spectrum of $(ZnD_2)_\infty$ from NaD-$ZnI_2$-NaI system.




The peaks marked with * corresponds to IR absorptions of THF.

### 6.4.6.2.3. Theoretical prediction of IR peaks of $(ZnH_2)_\infty$ 4.9 and $(ZnD_2)_\infty$ 4.9-*d*

According to the Hooke's law,[16]

$$\nu_{max} = \frac{1}{2\pi c}\sqrt{\frac{k}{\mu}}$$

where c = speed of light, $k$ = force constant, $\mu = \frac{m_1 m_2}{m_1 + m_2}$, reduced mass.

given that mass of Zn = 65.4, H = 1.01 and D = 2.01

In the case of Zn-H stretch for $(ZnH_2)_\infty$ **4.9**:

$$\nu_{max} = \frac{1}{2\pi c}\sqrt{\frac{k}{\mu}}$$

$$1443 = \frac{1}{2\pi c}\sqrt{k}\sqrt{\frac{m_1 + m_2}{m_1 m_2}}$$

$$1443 = \frac{1}{2\pi c}\sqrt{k}\sqrt{\frac{65.4 + 1.01}{65.4 \times 1.01}}$$

$$\frac{1}{2\pi c}\sqrt{k} = 1439$$

In the case of Zn-D stretch for $(ZnH_2)_\infty$ **4.9-*d***:

Assuming that force constant is similar to in both Zn-H and Zn-D,

$$\nu_{max} = \frac{1}{2\pi c}\sqrt{\frac{k}{\mu}}$$

$$\nu_{max} = \frac{1}{2\pi c}\sqrt{k}\sqrt{\frac{m_1 + m_2}{m_1 m_2}}$$

$$\nu_{max} = 1447\sqrt{\frac{65.4 + 2.01}{65.4 \times 2.01}}$$

$$\nu_{max} = 1030$$

Theoretical $\nu_{max}$ for Zn-D stretch calculated from Zn-H stretch is 1030 $cm^{-1}$.

Experimental $\nu_{max}$ for Zn-D stretch is 1048 $cm^{-1}$.

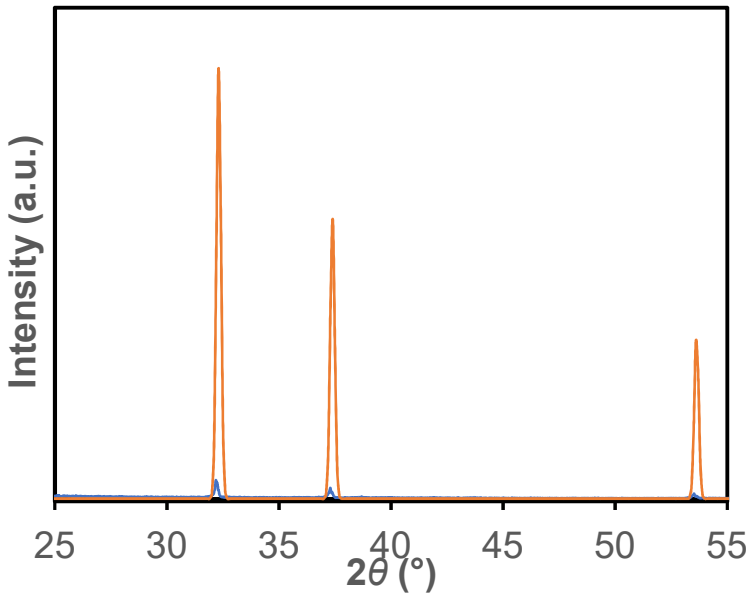
The theoretical and experimental values are similar to each other thus proving the identification of true Zn-H stretch.

**6.4.6.2.4. Powder X-ray diffraction (XRD), elemental analysis (EA) and inductively coupled plasma - optical emission spectrometry (ICP-OES)**

**Sample preparation:** To a mixture of NaH (dry; 72.0 mg, 3.00 mmol), $ZnI_2$ (320 mg, 1.00 mmol) and NaI (150 mg, 1.00 mmol) in a 25 mL sealed tube was added 5 mL of THF, the reaction mixture was sealed and stirred at 24 °C for 3 h. Reaction mixture

was transferred to a glovebox. The reaction mixture was filtered through a sinter funnel (porosity M), the reside was washed with THF (4 x 5 mL). The resulting solid was use directly for powder XRF, EA and ICP-OES measurements.

#### 6.4.6.2.4.1. Powder X-ray diffraction (XRD)




Powder X-ray diffraction data for freshly prepared **4.9** (blue) and the independently collected data for the component NaH (orange).

Based on the overlaid spectra of NaH with the prepared $ZnH_2$ polymer using our protocol, we can only observe NaH in the prepared $ZnH_2$ polymer. The absence of $ZnH_2$ peak is possibly due to the amorphous nature of the prepared $ZnH_2$ polymer.

**Inductively coupled plasma - optical emission spectrometry (ICP-OES):** 8.6 mg of resulting solid was first dissolved in 5 mL of nitric acid (67%, VWR Chemical, Ultrapure NORMATON®), followed by membrane filtration (MiniSart, 0.2 µm). The resulting solution was diluted to 100 mL with ultrapure water (generated by a Milli-Q® Integral Water Purification System for Ultrapure Water) in a 100 mL volumetric flask.

The solution was used without further dilution. A 86 ppm stock solution was obtained to perform ICP-OES measurement.

The ICP-OES determination was carried out by an external standard calibration prepared by four-fold serial dilutions with the sodium and zinc concentration of 1, 10, 50, 100 ppm in 3% nitric acid. The stock solution of the two-elements standard was prepared by the mixture of single element standards, 1000 µg/mL Zn in 2% $HNO_3$ (High purity standards, Charleston, SC, USA) and 1000 µg/mL Na in 0.1% $HNO_3$ (Inorganic Venture (Christiansburg, VA, USA))

**6.4.6.2.4.2. Result obtained from ICP-OES**

| Element | Na | Zn |
|---|---|---|
| Unit | ppm | ppm |
| Avg. | 45.89 | 13.21 |
| Stddev. | 0.29 | 0.4 |
| %RSD | 0.6313 | 0.3301 |
| Run 1 | 45.94 | 13.25 |
| Run 2 | 45.58 | 13.22 |
| Run 3 | 45.18 | 13.16 |

**6.4.6.2.4.3. Elemental analysis (EA):** Sample was prepared inside an argon filled glovebox and used directly for EA measurement.

Result obtained from EA

| Weight | Carbon | Hydrogen | Nitrogen |
|---|---|---|---|
| 2.150 mg | 2.67% | 3.32% | 0.07% |

**Analysis and interpretation of the data:** with the assumption that the isolated solid material is comprised of $ZnH_2$, NaH (based on powder XRD), and THF (based on the IR), the total percentage mass (%mass) of hydrogen present in the resulting solid can be calculated based on the different element detected:

%mass of zinc present =

$$\frac{13.21}{86} \times 100\% = 15.360\%$$

%mass of zinc hydride's corresponding hydrogen =

$$\frac{1.00794 \times 2}{65.38} \times 15.360\% = 0.474\%$$

%mass of sodium present =

$$\frac{45.89}{86} \times 100\% = 53.360\%$$

%mass of sodium hydride's corresponding hydrogen =

$$\frac{1.00794}{22.98977} \times 53.360\% = 2.339\%$$

%mass of carbon present = 2.67%

%mass of THF's corresponding hydrogen =

$$\frac{1.00794 \times 8}{12.0107 \times 4} \times 2.67\% = 0.448\%$$

**6.4.6.2.4.4.** %mass of the different element and its corresponding H

| Element | Zinc | Sodium | Carbon |
|---|---|---|---|
| %mass | 15.36 | 53.36 | 2.67 |
| Mole ratio | 4.2 | 41.8 | 1.0 |
| %mass of corresponding H | 0.474 | 2.339 | 0.448 |

Total %mass of hydrogen present in the isolated solid material

= 0.474% + 2.339% + 0.448%

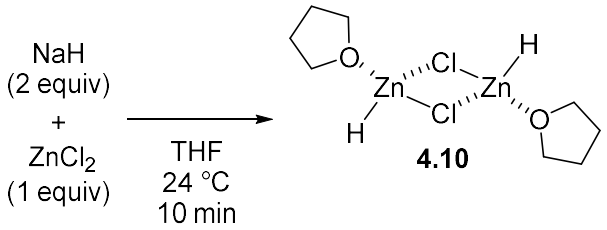
= 3.261%

%mass of hydrogen determined based on EA = 3.32%

Based on the comparison of total %mass of hydrogen present in the isolated solid material with %mass of hydrogen determined based on EA, the most probable zinc species would be $ZnH_2$.

### 6.4.6.3. Characterization of $(H\text{-}Zn\text{-}Cl)_2$ 4.10 obtained from the $NaH\text{-}ZnCl_2$ system (Scheme 4.21a)

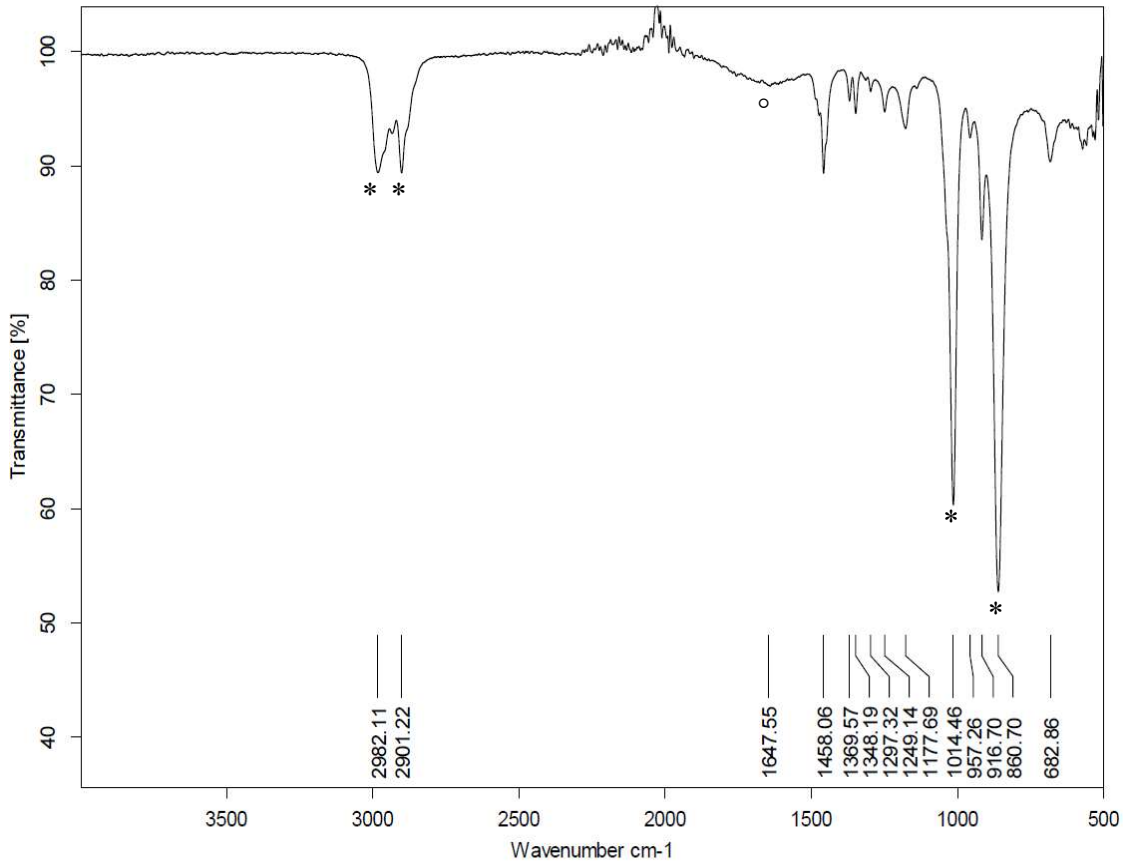
#### 6.4.6.3.1. IR analyses



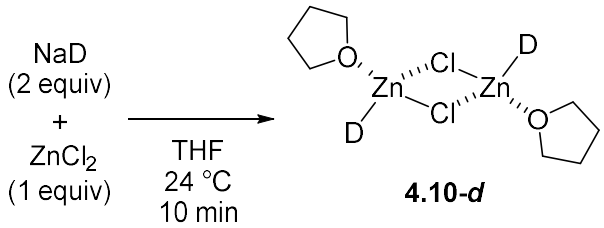

To a mixture of NaH (dry; 60.5 mg, 2.52 mmol), $ZnCl_2$ (170 mg, 1.25 mmol) in a 25 mL sealed tube was added 2.5 mL of THF, the reaction mixture was sealed and stirred at 24 °C for 10 min. Reaction mixture was transferred to a glovebox and a sample of the reaction mixture containing **4.10** was directly taken for the IR spectroscopy analysis.

ν(Zn-H): 1648 $cm^{-1}$

### 6.4.6.3.1.1. IR spectrum of $(H\text{-}Zn\text{-}Cl)_2 \cdot 2THF$ from NaH-$ZnCl_2$ system




The peaks marked with * corresponds to IR absorptions of THF and the peak mark with ° corresponds to IR absorption of Zn-H.



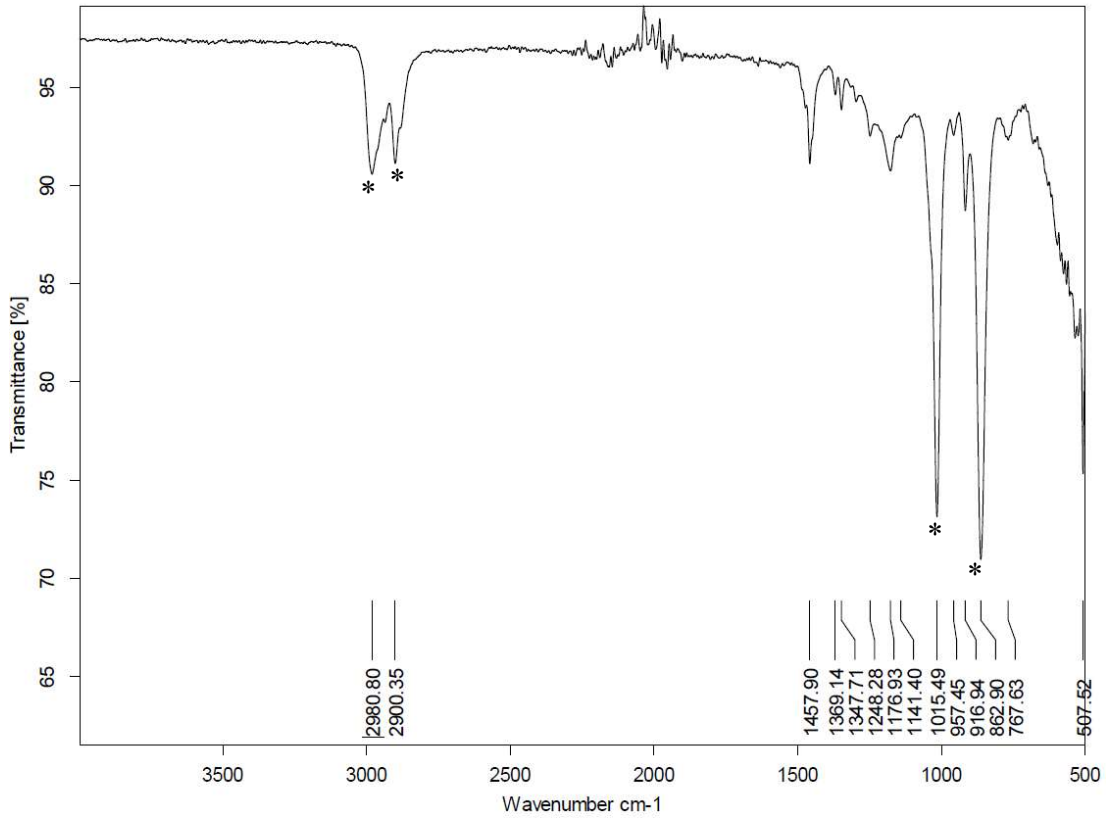

**4.10-*d***

To a mixture of NaD (62.6 mg, 2.50 mmol), $ZnCl_2$ (170 mg, 1.25 mmol) in a 25 mL sealed tube was added 2.5 mL of THF, the reaction mixture was sealed and stirred at

24 °C for 10 min. Reaction mixture was transferred to a glovebox and a sample of the reaction mixture containing **4.10-*d*** was directly taken for the IR spectroscopy analysis.

The absence of the absorption at 1648 $cm^{-1}$ in 6.4.6.3.1.1. indicted the correct identification of Zn-H stretch in Figure S6 as the peak of Zn-D will be shifted to a lower wavenumber region in accordance with the Hooke's law.

**6.4.6.3.1.1. IR spectrum of $(D\text{-}Zn\text{-}Cl)_2 \cdot 2THF$ from $NaD\text{-}ZnCl_2$ system**.



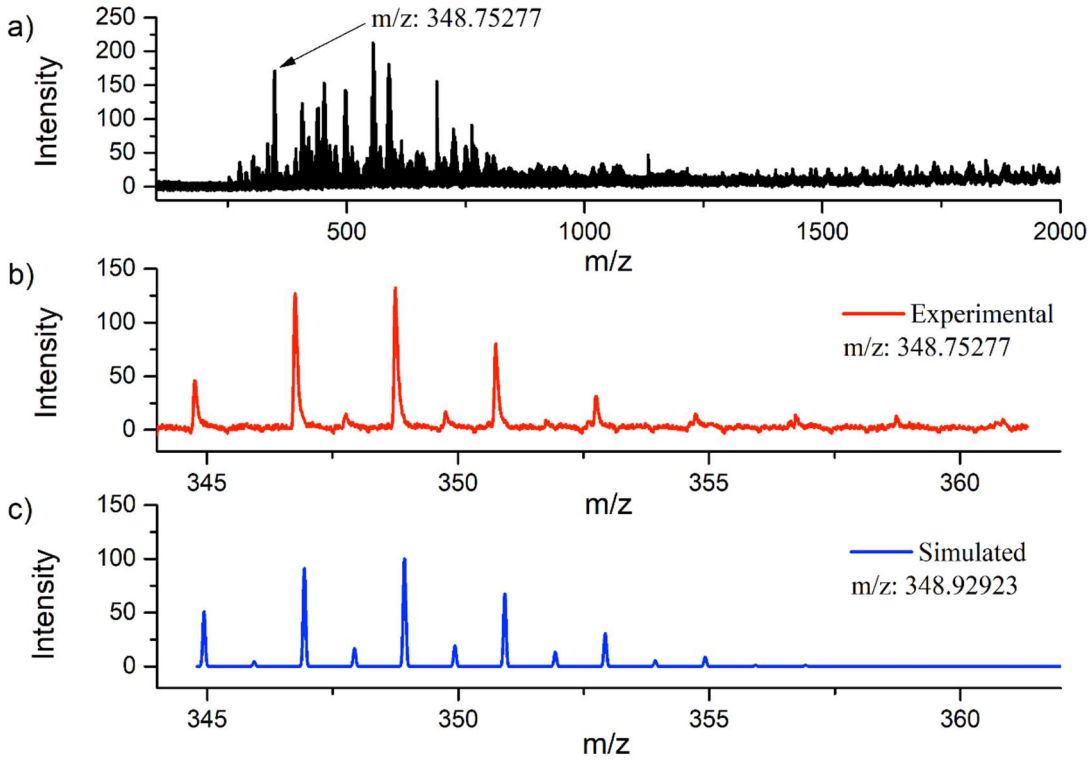

The peaks marked with * corresponds to IR absorptions of THF.

**6.4.6.3.2. Cold spray ionisation TOF mass**

To a mixture of NaH (dry; 60.0 mg, 2.50 mmol), $ZnCl_2$ (170 mg, 1.25 mmol) in a 25 mL sealed tube was added 2.5 mL of THF, the reaction mixture was sealed and stirred

at 24 °C for 10 min. Reaction mixture was transferred to a glovebox. The reaction mixture was filtered through glass microfiber filter and the resulting clear solution was directly injected into the cold spray ionization TOF mass spectrometer (injection temperature = 233 K). For clarity, only the parent ion of $(H\text{-}Zn\text{-}Cl)_2 \cdot 2THF$ is assigned.

### 6.4.6.3.2. Cold spray ionisation TOF mass spectrum of $(H\text{-}Zn\text{-}Cl)_2 \cdot 2THF$ from NaH-ZnCl system




### 6.4.6.3.3. $^{1}H$ and $^{2}H$ NMR

To a mixture of NaH (dry; 36.5 mg, 1.52 mmol), $ZnCl_2$ (102 mg, 0.75 mmol) in a 10 mL sealed tube was added 1.5 mL of THF-d8, the reaction mixture was sealed and stirred at 24 °C for 10 min inside a glovebox. The reaction mixture was allowed to stand

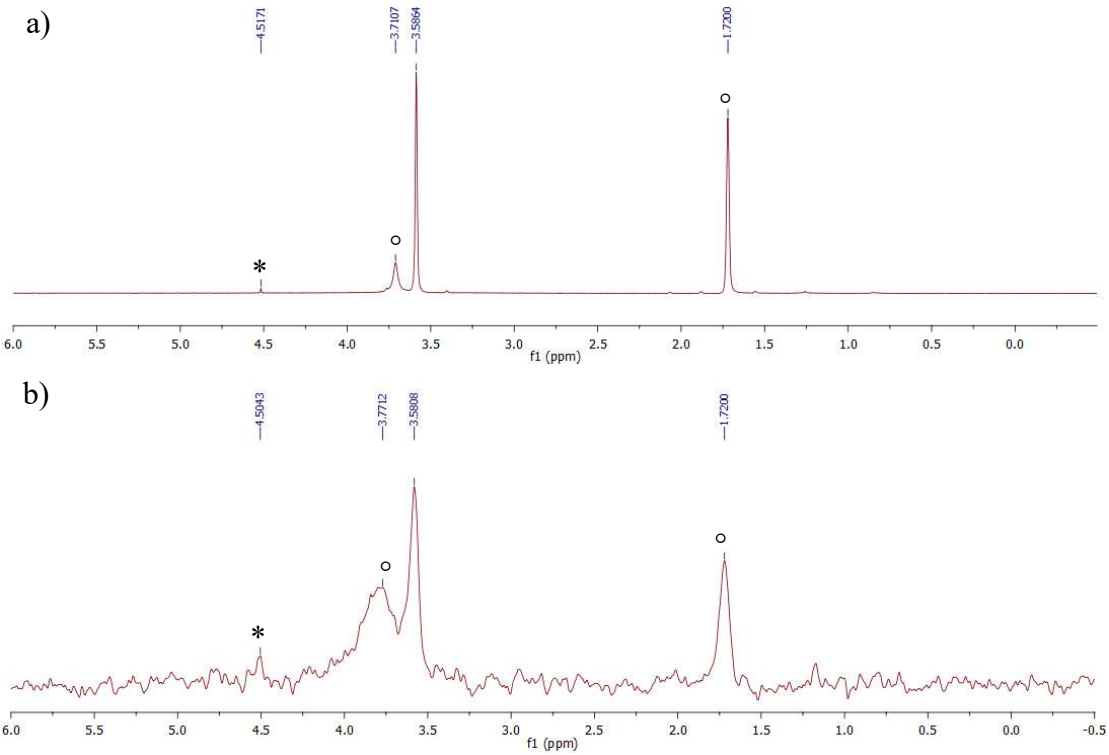
for 5 min and the top clear solution was collected and directly use for the $^{1}$H NMR spectroscopy analysis.

**$^{1}$H NMR** (400 MHz, THF-d8) δ 3.71 (brs)

To a mixture of NaD (37.8 mg, 1.51 mmol), $ZnCl_2$ (102 mg, 0.75 mmol) in a 10 mL sealed tube was added 1.5 mL of THF, the reaction mixture was sealed and stirred at 24 °C for 10 min inside a glovebox. The reaction mixture was allowed to stand for 5 min and the top clear solution was collected and directly use for the $^{2}$H NMR spectroscopy analysis.

**$^{2}$H NMR** (400 MHz, THF) δ 3.77 (brs)

**6.4.6.3.3.1. a) $^{1}$H NMR spectrum of 4.10. b) $^{2}$H NMR spectrum of 4.10-*d*.**



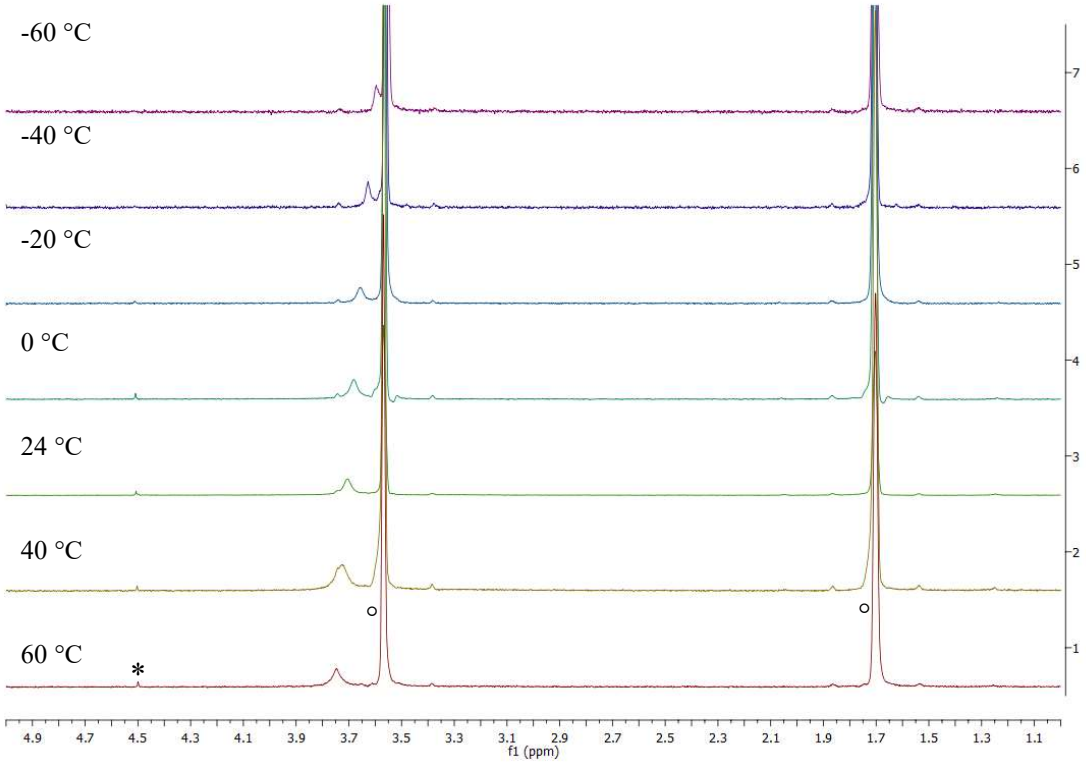

The peak at δ 4.5 (marked with *) corresponds to molecular $H_2$. The peaks at δ 1.7 and 3.6 (marked with °) correspond to THF.

### 6.4.6.3.4. Variable Temperature $^{1}H$ NMR spectra

There is no splitting of the ZnH resonances of **4.10** in the variable temperature spectra and no other $^{1}H$ signal was observed below 0 °C. Both observations suggest that **4.10** is the predominate zinc hydride species present in the reaction mixture.

To a mixture of NaH (dry; 36.5 mg, 1.52 mmol), $ZnCl_2$ (102 mg, 0.75 mmol) in a 10 mL sealed tube was added 1.5 mL of THF-d8, the reaction mixture was sealed and stirred at 24 °C for 10 min inside a glovebox. The reaction mixture was allowed to stand for 5 min and the top clear solution was collected and directly use for the variable temperature experiment.

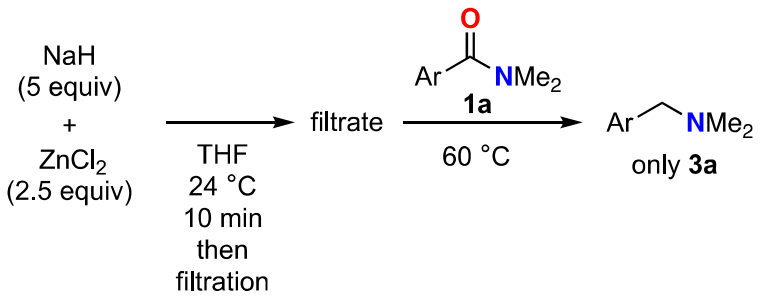
#### 6.4.6.3.4.1. Stacked NMR spectra of 4.10 performed at variable temperature.



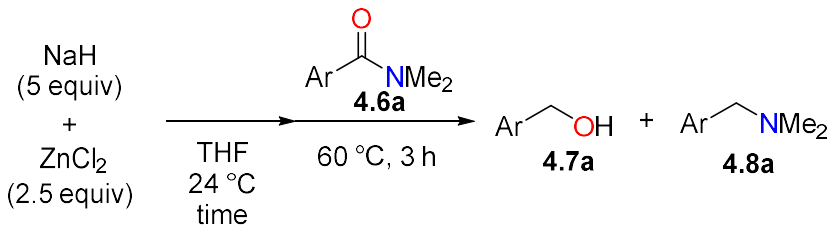

The peak at δ 4.5 (marked with *) corresponds to molecular $H_2$. The peaks at δ 1.7 and 3.6 (marked with °) correspond to THF.

### 6.4.6.3.5. Use of filtrate from the suspension of NaH-$ZnCl_2$ in THF for reduction of 4.6a

To a mixture of NaH (dry; 60.0 mg, 2.50 mmol), $ZnCl_2$ (170 mg, 1.25 mmol) in a 25 mL sealed tube was added 2.5 mL of THF, the reaction mixture was sealed and stirred at 24 °C for 10 min. Reaction mixture was transferred to a glovebox. The reaction mixture was filtered through glass microfiber filter and the resulting filtrate was added to amide, **4.6a** (99.2 mg, 0.498 mmol) in a 25 mL sealed tube. The reaction mixture was stirred at 60 °C for 4 h. This produce only amine **4.8a** in 5% yield ($^1$H crude NMR yield based on 1,1,2,2-tetrachloroethane as internal standard) and recovery of **4.6a** in 94% yield ($^1$H crude NMR yield). This observation suggested that dissolving species **4.10** is formed and responsible for the controlled reduction of amides **4.6** into amines **4.8**.




### 6.4.6.4. Reduction of amide by varying incubation time of NaH and $ZnCl_2$ (Scheme 4.21b)



To a mixture of NaH (60% dispersion in oil; 100 mg, 2.50 mmol) and $ZnCl_2$ (170 mg, 1.25 mmol) in a 25 mL sealed tube was added 2.5 mL of THF, the reaction mixture was sealed and stirred at 24 °C for X h. Afterwhich, amide, **4.6a** (99.5mg, 0.499 mmol) was added directly into the reaction mixture and was sealed and stirred at 60 °C. Upon full consumption of amide based on TLC, the reaction was quenched with ammonium pH 10 buffer at 0 °C and the organic materials were extracted with dichloromethane (20 mL × 3). The combined extracts were dried over $MgSO_4$. The volatile materials were removed *in vacuo* and the resulting crude residue was added $C_2H_2Cl_4$ (20 μL, 0.189 mmol) in $CDCl_3$.

#### 6.4.6.4.1. Outcome of varying incubation time against products obtained

| Incubation time (h) | Yield of **4.7a**[a] | Yield of **4.8a**[a] |
|---|---|---|
| 0 | 4% | 90% |
| 5 | 54% | 44% |
| 12 | 96% | 1% |

[a] Crude $^1H$ NMR yields based on 1,1,2,2-tetrachloroethane as an internal standard.

### 6.4.7. Computational studies

#### 6.4.7.1. Computational details

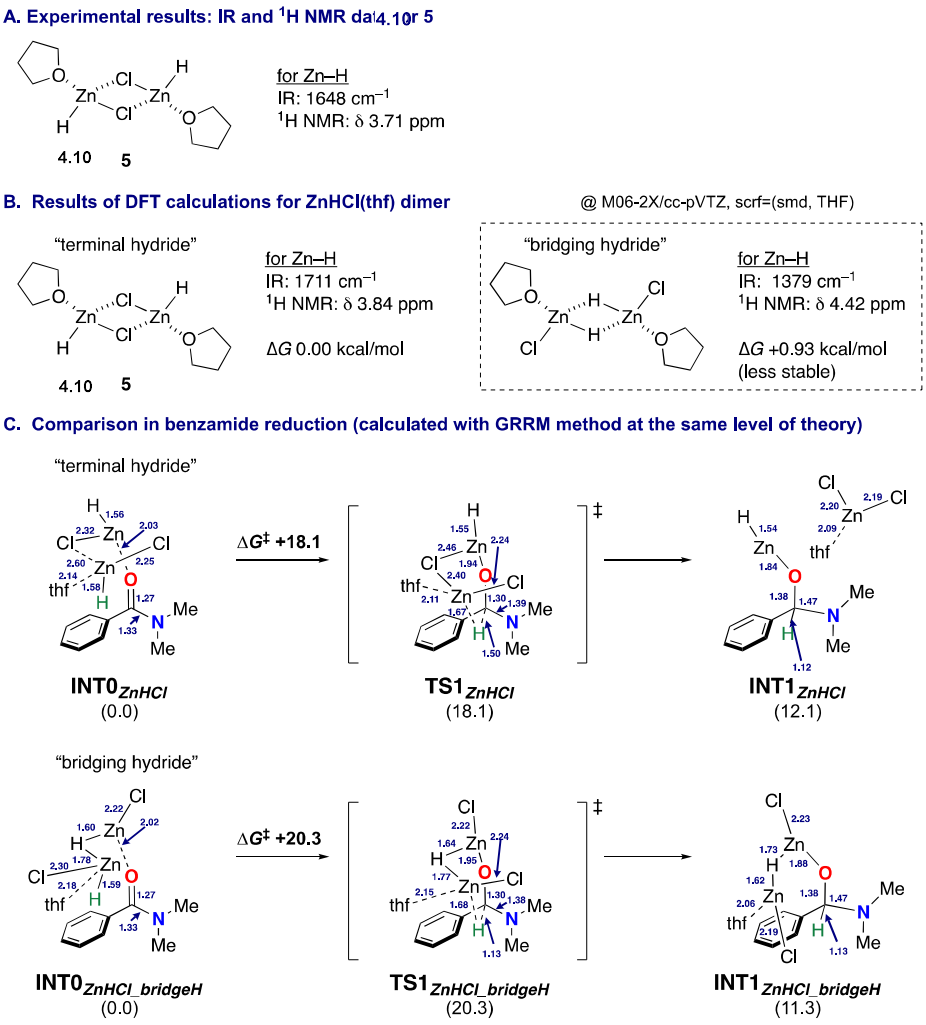
All calculations were carried with the Gaussian 16 (revision B.01) program package.[17] Unless otherwise noted, the molecular structures and harmonic vibrational frequencies were obtained using the hybrid density functional method based on the long-range corrected hybrid density functional including a version of Grimme's D2 dispersion model developed by Chai and Head-Gordon ($\omega$B97XD).[18-19] We used SDD basis set[20-21] for Cu and I atoms and 6–31+G* basis set[22] for all other atoms. Geometry optimization and vibrational analysis were performed at the same level. All stationary points were optimized without any symmetry assumptions and characterized by normal coordinate analysis at the same level of theory (number of imaginary frequencies, NIMAG, 0 for minima and 1 for TSs). The intrinsic reaction coordinate (IRC) method was used to track minimum energy paths from transition structures to the corresponding local minima.[23-25] The self-consistent reaction field (SCRF) method based on the SMD[26] was employed to evaluate the solvent reaction field (THF; $\varepsilon = 7.58$). In Scheme 5C, the molecular structures, harmonic vibrational frequencies, and NMR parameters (nmr=giao) were obtained using the hybrid density functional method based on M06-2X,[27-28] and cc-pVTZ[29] basis set was used. In section 6.4.7.2.1c, the calculations were performed using GRRM program (ver. 14.01, based on Gaussian 09)[30-34] for tracking the reaction pathway.

#### 6.4.7.2. The structure of $[ZnHCl]_2$: IR and NMR assignment, stability, and reaction analysis

The DFT calculations for ZnHCl(thf) dimers were performed at the M06-2X/cc-pVTZ (scrf = smd, THF) level of theory. The calculated results for IR and $^1$H NMR data of

ZnHCl(thf) dimer having the terminal hydride structure were well matched with those of experimentally observed data. The largely shifted parameters obtained by the DFT calculations of ZnHCl(thf) dimer having the bridging hydride structure. The latter one was found to be less stable (+0.93 kcal/mol) than the former structure. In addition, the calculation suggested that the amide reduction with the bridging hydride species proceed slower than that with the terminal hydride species (Scheme 4.23 in the chapter 4). From the combination of both experimental and theoretical results, the structure of **4.10** was assigned as the terminal hydride structure as shown in Scheme 4.21a.

**6.4.7.2.1. A) Experimentally observed IR and NMR data of 5: B) DFT calculations for ZnHCl(thf) dimers at the M06-2X/cc-pVTZ (scrf = smd, THF) level of theory: C) The amide reduction pathway with the terminal and bridging hydride species calculated with GRRM method at the ωB97XD/SDD&6-31+G* (scrf = smd, THF) level of theory.**

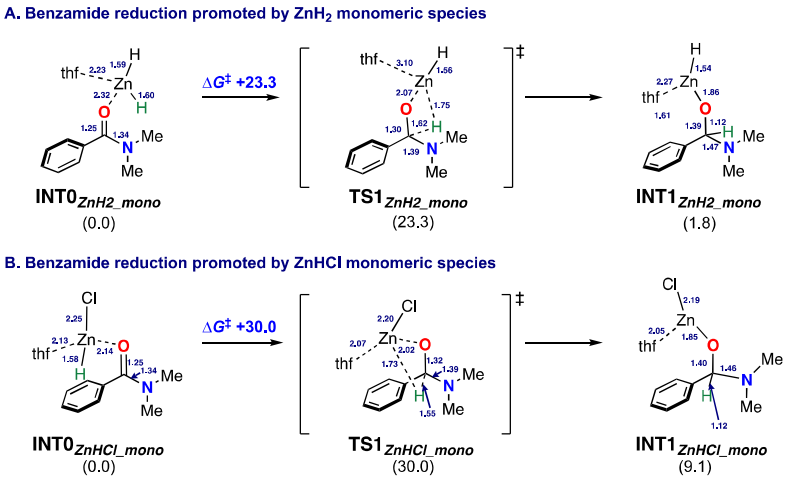



## 6.4.7.3. The reduction with monomeric species

The calculations for the reduction of benzamide with the monomeric $ZnH_2$ or ZnHCl species were carried out (section 6.4.7.3.1). Compared with the reactions with the corresponding dimeric species, the higher activation barriers ($\Delta G^{‡}$ +23.3 and 30.0 kcal/mol, respectively) are required, probably due to the strained four-membered

transition state structures. The flexible conformation change with the dimeric species should facilitate the efficient reduction process and subsequent C–O/C–N bond scissions.

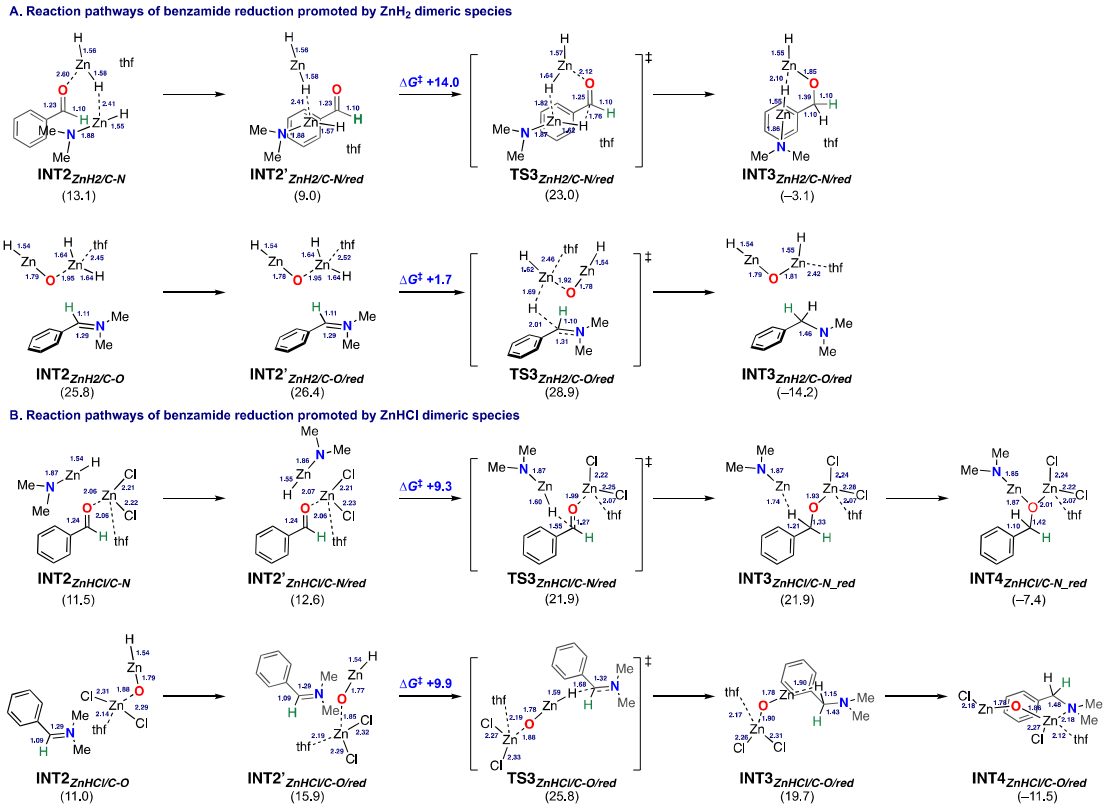
**6.4.7.3.1. DFT calculations for model reaction of benzamide with $ZnH_2$ or ZnHCl species. Energy changes and bond lengths at the ωB97XD/SDD&6-31+G* (scrf = smd, THF) level of theory are shown in kcal/mol and Å, respectively.**




### 6.4.7.4. The second reduction steps from INT2 complexes

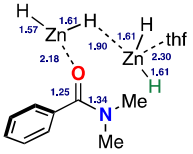
There are many possibilities of what kind of hydride species generated in situ are involved in the second reduction steps from **INT2** complexes to afford benzyl alcohol amine products. Section 6.4.7.4.1 presents one of those possibilities, where the zinc hydride moieties in **INT2** are utilized. In all cases shown here, the reductions proceed with the lower activation barriers than those of the previous C–O/C-N scissions. So, the second reduction steps should not affect the kinetic reaction outcome or selectivity between benzyl alcohol and amine formation. These steps may proceed faster with other hydride species.

**6.4.7.4.1. DFT calculations for model reactions with $(ZnH_2)_2$ or $(ZnHCl)_2$ species, starting from INT2 complexes. Energy changes and bond lengths at the *ω*B97XD/SDD&6-31+G* (scrf = smd, THF) level of theory are shown in kcal/mol and Å, respectively.**



### 6.4.7.5. Cartesian coordinates and energies

INT0_ZnH2




**INT0$_{ZnH2}$**

Energy (RwB97XD): -1168.52373894 A.U.

Gibbs Free Energy: -1168.245664 A.U.

---

Zn 0.615900 -2.271040 -0.930517
H 1.658315 -3.494667 -0.952373
H 0.062301 -2.233583 0.882821
H -0.463276 -1.520113 -1.852112
Zn -0.460599 -1.202930 2.010667
H -0.395228 -0.530104 3.430034
C 2.562939 -0.083541 0.745578
H 2.561722 -0.941110 1.424157
H 1.913359 0.702341 1.154783
C 2.806223 0.010011 -1.602710
H 2.121961 0.458951 -2.329247
H 3.331138 -0.826961 -2.080648
C 3.779190 1.006232 -0.979072
H 3.332063 2.004958 -0.934768
H 4.715769 1.069847 -1.539860
C 3.958826 0.443301 0.434384
H 4.288045 1.193806 1.158299
H 4.682391 -0.379667 0.430580
O 2.026851 -0.508590 -0.514452
O -2.240133 -0.527593 0.955410
C -2.220609 0.331611 0.041479
N -3.073862 0.247595 -0.984863
C -1.221557 1.443714 0.098178
C -3.904987 -0.941237 -1.116159
C -3.343322 1.313246 -1.941415
C -1.049238 2.127278 1.306463
C -0.407122 1.749715 -0.995844
H -4.123473 -1.093201 -2.176147
H -3.373384 -1.810973 -0.729526
H -4.847404 -0.821752 -0.568259
H -2.933512 1.059906 -2.925092
H -4.427972 1.432670 -2.029868
H -2.920617 2.258683 -1.603697
C -0.087809 3.129910 1.409939
H -1.671067 1.876702 2.160947
C 0.557249 2.747118 -0.886715
H -0.514776 1.196149 -1.923638
C 0.715832 3.441054 0.312923
H 0.035297 3.664325 2.347561
H 1.189799 2.978612 -1.738897
H 1.469099 4.220107 0.394650

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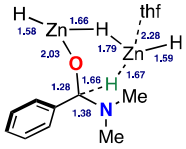
TS1_ZnH2




**TS1$_{ZnH2}$**

Energy (RwB97XD): -1168.50264896 A.U.

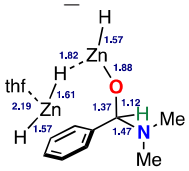
Gibbs Free Energy: -1168.221400 A.U.

---

Zn -0.238914 -1.808278 -1.192885
H 0.151148 -2.819166 -2.359696
H -0.553401 -2.385371 0.469378
H -1.065647 -0.368668 -1.038154
Zn -0.936561 -1.506620 1.827108
H -0.730166 -1.530531 3.391034
C 2.264692 -0.730113 0.772083
H 1.939405 -1.506806 1.469174
H 1.791401 0.223065 1.041598
C 2.820923 -0.737442 -1.523914
H 2.344322 -0.086523 -2.264271
H 3.159017 -1.651725 -2.023778
C 3.945546 -0.044484 -0.752930
H 3.798882 1.040307 -0.753113
H 4.927302 -0.260054 -1.183221
C 3.776760 -0.596658 0.666675
H 4.187000 0.065082 1.434434
H 4.251698 -1.579703 0.760536
O 1.839190 -1.117033 -0.542036
O -2.063179 0.003243 1.057992
C -1.752158 0.698014 0.025808
N -2.794913 1.104220 -0.789364
C -0.550581 1.619702 0.159203
C -3.888067 0.150736 -0.888152
C -2.497025 1.766698 -2.045927
C -0.379700 2.254444 1.393246
C 0.386615 1.839886 -0.851881
H -4.715178 0.610897 -1.433451
H -3.557477 -0.752581 -1.432366
H -4.229373 -0.142410 0.104059
H -2.015162 1.070579 -2.754217
H -3.432583 2.121423 -2.484628
H -1.844882 2.627555 -1.892496
C 0.703467 3.106398 1.607247
H -1.096131 2.074138 2.189282
C 1.464308 2.695452 -0.642788
H 0.286390 1.321017 -1.799906
C 1.628570 3.330396 0.588843
H 0.823813 3.591808 2.571951
H 2.184759 2.856046 -1.440305

H 2.475317 3.991172 0.754296
---

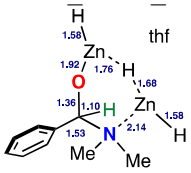
INT1_ZnH2




**INT1$_{ZnH2}$**

Energy (RwB97XD): -1168.53225004 A.U.
Gibbs Free Energy: -1168.248209 A.U.
---
Zn 0.875050 -1.392748 -1.512982
H 1.076123 -1.067800 -3.032590
H 0.167087 -2.068122 -0.234496
H -2.033987 -0.364309 -1.165913
Zn -0.800428 -1.886431 1.297200
H -0.240639 -2.656702 2.544967
C 2.542000 -0.388256 0.973706
H 2.396948 -1.335525 1.498097
H 1.671417 0.258728 1.137514
C 3.652710 0.152538 -1.056052
H 3.201380 0.660008 -1.912944
H 4.451447 -0.507409 -1.410546
C 4.132856 1.104676 0.035210
H 3.552417 2.032279 0.016827
H 5.190611 1.354815 -0.082173
C 3.840980 0.321881 1.320017
H 3.732147 0.965563 2.197059
H 4.633777 -0.408224 1.517391
O 2.645436 -0.680868 -0.436765
O -2.300471 -0.858158 0.814119
C -2.255092 0.099737 -0.169874
N -3.569519 0.761609 -0.267223
C -1.162663 1.138336 0.091445
C -4.619543 -0.224560 -0.481599
C -3.604765 1.758423 -1.327045
C -1.013877 1.685473 1.369934
C -0.289387 1.541985 -0.919953
H -5.591938 0.279330 -0.500611
H -4.493204 -0.765444 -1.441722
H -4.614517 -0.954700 0.328552
H -3.359767 1.331651 -2.320507
H -4.610494 2.187207 -1.384574
H -2.903700 2.572138 -1.122059
C -0.012972 2.619148 1.629445
H -1.690905 1.370854 2.159737
C 0.719903 2.472548 -0.664196
H -0.408613 1.140559 -1.924848
C 0.859273 3.014580 0.611996
H 0.089822 3.039534 2.626755
H 1.393244 2.773312 -1.462871
H 1.643064 3.739517 0.815925
---

INT1'_ZnH2_C-N

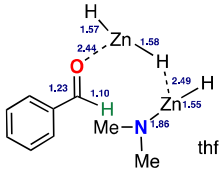



**INT1'$_{ZnH2/C-N}$**

Energy (RwB97XD): -1168.54408873 A.U.
Gibbs Free Energy: -1168.252907 A.U.
---
Zn -1.735615 1.123627 -1.303277
H -2.474884 0.551298 -2.575710
H -2.180895 1.988429 0.065991
H 0.211264 -0.814066 -0.033145
Zn -1.395938 1.556381 1.578066
H -2.062729 1.866453 2.972079
C -1.334735 -2.446745 1.409631
H -0.536903 -1.855341 1.870234
H -1.671611 -3.204318 2.131039
C -1.722048 -2.978849 -0.840455
H -1.829841 -3.956599 -1.321067
H -1.306089 -2.275052 -1.577033
C -3.025158 -2.444574 -0.251485
H -3.646799 -3.267574 0.119782
H -3.606256 -1.870052 -0.978681
C -2.505834 -1.604231 0.916384
H -3.250168 -1.416862 1.694951
H -2.146277 -0.633418 0.545066
O -0.807789 -3.104955 0.251820
O 0.337169 0.814854 1.221660
C 0.738883 0.144947 0.109276
N 0.385714 0.904250 -1.168081
C 2.231211 -0.171024 0.183908
C 0.788270 0.163830 -2.374523
C 0.957835 2.258183 -1.204168
C 3.136778 0.757518 0.706168
C 2.711889 -1.405860 -0.257592
H 0.382310 0.663492 -3.258855
H 1.880455 0.111277 -2.471975
H 0.387125 -0.853247 -2.336015
H 2.045909 2.233083 -1.350221
H 0.511476 2.814169 -2.035844
H 0.734561 2.775167 -0.268925
C 4.498794 0.467614 0.759093
H 2.764488 1.704033 1.086848
C 4.074177 -1.703875 -0.201262
H 2.012309 -2.145632 -0.641590
C 4.972639 -0.763786 0.301632
H 5.192158 1.200090 1.164982

H 4.431318 -2.671559 -0.544273
H 6.034411 -0.991828 0.347777
---

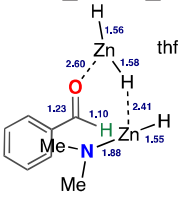
TS2_ZnH2_C-N




**TS2$_{ZnH2/C-N}$**

Energy (RwB97XD): -1168.50286305 A.U.
Gibbs Free Energy: -1168.227456 A.U.
---
Zn 1.487053 -1.879416 -1.047251
H 2.756465 -1.395597 -1.795024
H 2.087310 -0.663011 1.035627
H -0.094373 0.276337 0.064028
Zn 1.961863 0.136015 2.390043
H 2.147436 0.923595 3.733214
C 1.645822 2.755449 -0.378203
H 1.540132 2.405517 0.656431
H 1.784829 3.843557 -0.358304
C 0.728980 1.701483 -2.254562
H 0.058385 2.026379 -3.055717
H 0.537504 0.633567 -2.054993
C 2.205998 1.934929 -2.546595
H 2.341313 2.872689 -3.098057
H 2.652228 1.120418 -3.124587
C 2.777077 2.050378 -1.130254
H 3.714987 2.611111 -1.085834
H 2.952223 1.051936 -0.713867
O 0.435246 2.472849 -1.091163
O -0.402104 0.615076 2.025569
C -0.803806 0.491797 0.873274
N -0.181114 -2.458873 -0.472875
C -2.215270 0.592208 0.477306
C -1.206216 -2.888760 -1.394060
C -0.504386 -2.811841 0.887770
C -3.220217 0.846208 1.419672
C -2.544580 0.411040 -0.870224
H -1.351781 -3.987770 -1.393918
H -2.190080 -2.444308 -1.148423
H -0.962944 -2.592434 -2.422209
H -1.470308 -2.374755 1.207952
H -0.593314 -3.906585 1.036614
H 0.263861 -2.448684 1.580389
C -4.545921 0.921424 1.009760
H -2.952987 0.982315 2.463679
C -3.872952 0.487429 -1.279085
H -1.757258 0.206285 -1.590974
C -4.871104 0.742368 -0.338349
H -5.329421 1.118045 1.735884
H -4.130592 0.346231 -2.324712
H -5.908996 0.801234 -0.654783
---

INT2_ZnH2_C-N

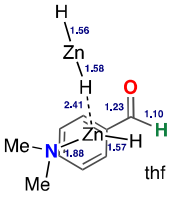



**INT2$_{ZnH2/C-N}$**

Energy (RwB97XD): -1168.50478565 A.U.
Gibbs Free Energy: -1168.224868 A.U.
---
Zn -1.251161 -0.815554 1.910320
H -2.556367 -0.174715 2.453672
H -2.211333 -1.894706 -0.022803
H 0.044504 0.666473 -0.437772
Zn -2.301231 -1.675656 -1.580623
H -2.621199 -1.501365 -3.101941
C -1.374419 2.805021 -1.355920
H -0.865741 2.192961 -2.108190
H -1.720609 3.729860 -1.837850
C -1.035522 2.965540 0.957927
H -0.798136 3.837952 1.574970
H -0.602187 2.073835 1.439279
C -2.529556 2.780696 0.708828
H -3.029422 3.753934 0.639432
H -3.013978 2.194558 1.494399
C -2.525106 2.087786 -0.656083
H -3.469197 2.180700 -1.199797
H -2.299162 1.019133 -0.536310
O -0.433459 3.139036 -0.328243
O 0.182310 -0.902740 -1.708387
C 0.675970 -0.066075 -0.958402
N 0.532552 -1.247975 1.498593
C 2.128901 0.135649 -0.798359
C 1.560801 -0.758601 2.393879
C 0.858362 -2.567663 1.008364
C 3.047374 -0.792853 -1.300407
C 2.582000 1.277505 -0.130752
H 1.683735 -1.380744 3.302288
H 2.544687 -0.734224 1.892096
H 1.339230 0.264786 2.722672
H 1.835192 -2.566887 0.490438
H 0.928155 -3.328279 1.810607
H 0.106093 -2.909769 0.288692
C 4.411613 -0.581952 -1.125478
H 2.684367 -1.674035 -1.821647
C 3.947919 1.493251 0.033635
H 1.858200 1.996079 0.247786
C 4.861925 0.560689 -0.459119

H 5.126285 -1.305467 -1.508058
H 4.300359 2.383380 0.547237
H 5.928046 0.724318 -0.325895
---

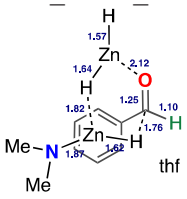
INT2'_ZnH2_C-N_red




**INT2'** ***ZnH2/C-N/red***

Energy (RwB97XD): -1168.50791397 A.U.
Gibbs Free Energy: -1168.231359 A.U.
---
Zn -0.058714 1.146169 -0.907339
H 0.486732 0.302226 -2.111398
H -1.958525 0.646273 -0.814394
H 0.415954 -2.653922 -1.355088
Zn -3.497348 0.341707 -0.956445
H -5.017969 0.034934 -1.104480
C 4.221896 -1.560354 -0.362585
H 3.809866 -2.561944 -0.200362
H 5.318954 -1.634902 -0.386222
C 3.475377 0.572652 0.258227
H 4.023445 1.320618 0.841171
H 2.400449 0.725670 0.424905
C 3.817868 0.602554 -1.231742
H 4.845958 0.950763 -1.384675
H 3.145063 1.252865 -1.798655
C 3.692427 -0.873936 -1.616935
H 4.262318 -1.139280 -2.512077
H 2.640544 -1.134494 -1.785365
O 3.826288 -0.732149 0.733632
O -1.557106 -3.053836 -1.469469
C -0.582445 -2.623886 -0.877825
N -0.042324 2.486593 0.404752
C -0.613617 -2.030683 0.474242
C 1.163318 3.231495 0.687270
C -0.953152 2.532441 1.521321
C -1.798546 -1.979222 1.220568
C 0.561766 -1.475511 0.989072
H 0.946352 4.297170 0.894040
H 1.712871 2.848491 1.571874
H 1.854512 3.201102 -0.164291
H -0.519296 2.112571 2.451889
H -1.255748 3.570496 1.760644
H -1.867024 1.965312 1.305882
C -1.801380 -1.371534 2.470186
H -2.706016 -2.417791 0.813956
C 0.555723 -0.857818 2.237661
H 1.484390 -1.521902 0.415880
C -0.625318 -0.806989 2.976077
H -2.716613 -1.332377 3.054181
H 1.468881 -0.416604 2.626479
H -0.633891 -0.325091 3.949825
---

TS3_ZnH2_C-N_red

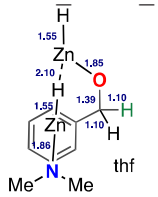



**TS3**$_{ZnH2/C-N/red}$

Energy (RwB97XD): -1168.48761885 A.U.
Gibbs Free Energy: -1168.209039 A.U.
---
Zn 0.133679 1.437904 -0.103540
H -0.308380 0.097947 0.699115
H 1.879450 1.384082 0.424619
H -0.371216 -1.582624 1.763968
Zn 2.949251 0.518894 1.308496
H 4.378125 0.275063 1.908374
C -3.739191 -1.494964 1.587711
H -3.242671 -2.336982 2.080097
H -4.824654 -1.589287 1.742967
C -3.328519 -0.247891 -0.349672
H -4.070981 -0.119873 -1.145788
H -2.327628 -0.154509 -0.791522
C -3.534660 0.733231 0.811272
H -4.571273 1.087467 0.835066
H -2.878831 1.606227 0.735125
C -3.238507 -0.129707 2.042614
H -3.745497 0.222248 2.945835
H -2.160995 -0.163215 2.236596
O -3.446374 -1.568148 0.192762
O 1.531180 -0.923274 1.951920
C 0.568625 -1.328138 1.256719
N -0.382113 2.915083 -1.136535
C 0.746737 -1.944833 -0.088977
C -1.579730 2.922800 -1.944980
C 0.597644 3.851953 -1.637559
C 2.007808 -2.045618 -0.681455
C -0.377612 -2.447901 -0.754733
H -2.053289 3.923027 -1.962781
H -1.390308 2.648308 -3.002813
H -2.324358 2.219009 -1.554498
H 0.906153 3.640342 -2.681784
H 0.211894 4.889262 -1.630320
H 1.503735 3.837637 -1.019195
C 2.141260 -2.623305 -1.943765
H 2.893247 -1.699184 -0.153665
C -0.241973 -3.025525 -2.012277

H -1.361871 -2.360047 -0.294258
C 1.017898 -3.109081 -2.611714
H 3.123756 -2.701251 -2.400886
H -1.117848 -3.409157 -2.528410
H 1.123197 -3.558756 -3.595347
---

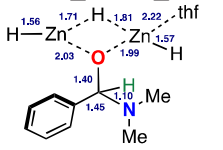
INT3_ZnH2_C-N_red




**INT3**$_{ZnH2/C\text{-}N/red}$

Energy (RwB97XD): -1168.53514697 A.U.
Gibbs Free Energy: -1168.250596 A.U.
---
Zn 0.187853 -0.186535 -1.593721
H -0.750199 -1.176520 1.341714
H -0.933402 -1.187424 -1.196499
H -1.686974 -0.687482 2.746203
Zn -2.955036 -1.466452 -0.696818
H -3.662753 -2.008838 -1.961219
C 2.095017 -2.002798 2.364709
H 1.138930 -1.884286 2.887271
H 2.748805 -2.637730 2.977612
C 3.111545 -0.504726 0.872866
H 4.100400 -0.036077 0.879181
H 2.404260 0.183429 0.385309
C 3.091453 -1.878609 0.209204
H 4.034841 -2.406082 0.391492
H 2.934004 -1.818917 -0.871756
C 1.940860 -2.563364 0.951706
H 1.996290 -3.655414 0.929561
H 0.978474 -2.261765 0.520724
O 2.706393 -0.715105 2.227710
O -2.791318 -0.919136 1.059331
C -1.597639 -0.541578 1.655601
N 1.511701 0.957468 -2.213691
C -1.197510 0.909167 1.426229
C 1.633225 2.302590 -1.696620
C 2.784882 0.453388 -2.679176
C -2.076525 1.829667 0.853437
C 0.069557 1.349442 1.833889
H 2.319818 2.375322 -0.829496
H 2.025111 2.990746 -2.467940
H 0.659247 2.688829 -1.375783
H 3.195104 1.091577 -3.483029
H 3.555913 0.416749 -1.883619
H 2.682578 -0.559098 -3.088256
C -1.706626 3.169670 0.705108
H -3.060553 1.492610 0.539018
C 0.437575 2.685234 1.692597
H 0.777154 0.641464 2.265654
C -0.452401 3.603582 1.130140
H -2.404882 3.875809 0.262182
H 1.424667 3.009044 2.013530
H -0.164309 4.645308 1.015702
---

INT1'_ZnH2_C-O

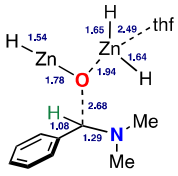



**INT1'**$_{ZnH2/C\text{-}O}$

Energy (RwB97XD): -1168.54100948 A.U.
Gibbs Free Energy: -1168.256229 A.U.
---
Zn 1.085690 -0.024114 1.340861
H 1.226119 -0.637417 2.780564
H 1.419876 1.676426 0.821377
H -1.167829 -0.660979 -1.841727
Zn 0.390875 1.900179 -0.523925
H 0.008851 2.900079 -1.662338
C 2.856802 -0.642568 -1.246825
H 1.842617 -0.491747 -1.618629
H 3.284214 -1.535775 -1.720068
C 4.066563 -0.607649 0.694449
H 4.721478 -1.461585 0.476142
H 3.970090 -0.497240 1.776695
C 4.519998 0.656097 -0.037080
H 5.607395 0.686986 -0.146658
H 4.207322 1.545318 0.518104
C 3.784100 0.573847 -1.395664
H 4.474019 0.434142 -2.232328
H 3.210991 1.486559 -1.585268
O 2.762608 -0.888720 0.164545
O -0.174724 -0.020935 -0.199025
C -1.247355 -0.740252 -0.746031
N -1.226043 -2.164833 -0.463625
C -2.597260 -0.144462 -0.348006
C -0.066382 -2.835798 -1.029675
C -1.420342 -2.533583 0.931218
C -2.729832 0.764497 0.701044
C -3.740119 -0.523186 -1.059985
H 0.871616 -2.597961 -0.501273
H -0.217118 -3.920453 -0.980945
H 0.049000 -2.554245 -2.082362
H -1.571995 -3.617195 0.992658
H -0.562210 -2.278230 1.575607
H -2.311761 -2.044789 1.334706
C -3.981196 1.284766 1.038457
H -1.851305 1.063099 1.266303

C -4.990033 -0.005247 -0.730198
H -3.646062 -1.233310 -1.878820
C -5.114775 0.902794 0.323825
H -4.067785 1.989435 1.861659
H -5.867573 -0.307277 -1.296229
H -6.088717 1.309734 0.582773
---

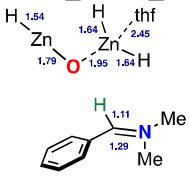
TS2_ZnH2_C-O




**TS2$_{ZnH2/C-O}$**

Energy (RwB97XD): -1168.48160742 A.U.
Gibbs Free Energy: -1168.199733 A.U.
---
Zn -0.878709 0.101798 1.169891
H -0.057063 1.475075 1.525573
H -1.821908 -0.751891 2.221281
H 1.269917 -0.141076 -1.639954
Zn -0.654553 -2.590206 -0.453508
H -0.912504 -4.105630 -0.586056
C -3.281887 0.480792 -1.030954
H -2.440008 -0.028549 -1.504395
H -3.794088 1.129763 -1.758889
C -3.829703 1.592398 0.889588
H -4.339317 2.493041 0.517602
H -3.406659 1.806177 1.874288
C -4.767546 0.369880 0.866161
H -5.808392 0.682738 0.738325
H -4.696443 -0.199383 1.796719
C -4.262983 -0.462084 -0.334408
H -5.069999 -0.781507 -1.000590
H -3.731242 -1.352878 0.015417
O -2.743242 1.282493 0.017475
O -0.354508 -0.832442 -0.445708
C 1.757382 0.670529 -1.111542
N 1.201967 1.830356 -1.237152
C 2.948035 0.336312 -0.333431
C -0.061870 1.953724 -1.966370
C 1.696540 3.079197 -0.660305
C 3.254070 0.905856 0.911410
C 3.769738 -0.675962 -0.853131
H -0.805288 2.379972 -1.287316
H 0.085843 2.614408 -2.825215
H -0.396216 0.964996 -2.275383
H 1.455306 3.885126 -1.356119
H 1.192503 3.260402 0.293185
H 2.775921 3.034072 -0.518513
C 4.387544 0.489655 1.602324
H 2.587075 1.631817 1.362771
C 4.914678 -1.069778 -0.169798
H 3.508354 -1.148973 -1.796141
C 5.224836 -0.484881 1.058570
H 4.611870 0.921942 2.572880
H 5.554502 -1.842552 -0.585280
H 6.110933 -0.801577 1.601560
---

INT2_ZnH2_C-O

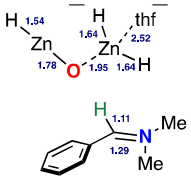



**INT2$_{ZnH2/C-O}$**

Energy (RwB97XD): -1168.48470016 A.U.
Gibbs Free Energy: -1168.204680 A.U.
---
Zn 0.973379 0.006138 1.204959
H -0.122772 -1.152561 1.603936
H 2.000115 0.800948 2.208493
H -1.053686 0.122298 -0.701476
Zn 1.292180 2.475894 -0.746679
H 1.901297 3.868308 -1.015118
C 3.327521 -0.895303 -0.908321
H 2.571887 -0.351459 -1.478277
H 3.756750 -1.700525 -1.524785
C 3.702617 -1.808207 1.149074
H 4.090991 -2.805573 0.897746
H 3.249674 -1.844171 2.142826
C 4.792534 -0.729568 0.999150
H 5.785295 -1.186708 0.945840
H 4.782346 -0.038693 1.846192
C 4.418893 -0.005342 -0.314033
H 5.268462 0.111657 -0.993352
H 4.010929 0.987933 -0.099518
O 2.671770 -1.468005 0.220687
O 0.576734 0.858267 -0.505354
C -1.894645 -0.603307 -0.693929
N -1.632207 -1.753231 -1.224260
C -3.161396 -0.172284 -0.108678
C -0.266129 -2.034320 -1.680220
C -2.574793 -2.860091 -1.383608
C -4.006167 -0.998933 0.647667
C -3.481690 1.185819 -0.264869
H 0.112743 -2.892219 -1.117756
H -0.294517 -2.277284 -2.746032
H 0.357602 -1.158135 -1.491603
H -2.313828 -3.394141 -2.299000
H -2.484567 -3.542899 -0.534049
H -3.595889 -2.487042 -1.460984

C -5.169295 -0.477764 1.204492
H -3.737064 -2.031577 0.841112
C -4.660455 1.694268 0.269394
H -2.803803 1.835968 -0.811546
C -5.505535 0.861643 1.003476
H -5.811370 -1.117224 1.802858
H -4.910174 2.741790 0.129809
H -6.418549 1.261202 1.435876
---

INT2'_ZnH2_C-O_red




**INT2'$_{ZnH2/C-O/red}$**

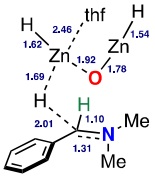
Energy (RwB97XD): -1168.48457622 A.U.

Gibbs Free Energy: -1168.203408 A.U.

---

Zn -0.843245 0.107159 -1.211352
H 0.319432 -0.996925 -1.561247
H -1.955485 0.739089 -2.238688
H 1.132853 0.347223 0.736496
Zn -1.713371 2.385730 0.726088
H -2.729521 3.499527 1.030365
C -3.259781 -1.043008 0.848792
H -2.615459 -0.420023 1.472547
H -3.647244 -1.882135 1.447817
C -3.380973 -2.009171 -1.210878
H -3.682708 -3.038760 -0.969697
H -2.852889 -2.009191 -2.167443
C -4.584857 -1.049044 -1.163715
H -5.526541 -1.606063 -1.181459
H -4.577627 -0.366556 -2.017487
C -4.393325 -0.279946 0.162822
H -5.299094 -0.252630 0.775761
H -4.083609 0.751459 -0.035608
O -2.464323 -1.551538 -0.216620
O -0.544839 1.062390 0.462868
C 1.933998 -0.415522 0.767551
N 1.617836 -1.514259 1.371902
C 3.215989 -0.092637 0.145781
C 0.243244 -1.697482 1.851208
C 2.503571 -2.657317 1.588557
C 3.994139 -1.010456 -0.576246
C 3.623134 1.248303 0.225060
H -0.185773 -2.561328 1.336018
H 0.269188 -1.886230 2.928056
H -0.333420 -0.799463 1.615739
H 2.229824 -3.118674 2.539104
H 2.363320 -3.385364 0.784527
H 3.543809 -2.334975 1.628467
C 5.178264 -0.594520 -1.175473
H 3.657103 -2.032306 -0.712363
C 4.822739 1.651569 -0.351440
H 2.996571 1.968971 0.743854
C 5.601439 0.729445 -1.051024
H 5.768297 -1.304218 -1.747718
H 5.140127 2.686920 -0.271656
H 6.530270 1.046691 -1.516723
---

TS3_ZnH2_C-O_red




**TS3$_{ZnH2/C-O/red}$**

Energy (RwB97XD): -1168.48027412 A.U.

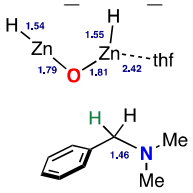
Gibbs Free Energy: -1168.200744 A.U.

---

Zn 0.658606 0.009164 1.112317
H -0.724824 -0.927392 0.850256
H 1.446171 0.166325 2.516426
H -1.026010 0.472768 -0.804013
Zn 1.912814 2.508409 -0.570831
H 2.977095 3.591394 -0.817573
C 3.123973 -1.074727 -0.797140
H 2.565411 -0.344715 -1.385529
H 3.497664 -1.873101 -1.456458
C 3.039369 -2.262570 1.142502
H 3.324267 -3.262668 0.785111
H 2.438296 -2.365566 2.048665
C 4.271410 -1.356462 1.309472
H 5.186750 -1.951115 1.383570
H 4.187701 -0.747505 2.213588
C 4.251470 -0.469983 0.042069
H 5.204640 -0.471069 -0.494631
H 4.009086 0.565565 0.303501
O 2.221683 -1.636519 0.152826
O 0.682397 1.238656 -0.361504
C -1.765453 -0.336692 -0.768137
N -1.557487 -1.320186 -1.608622
C -3.050355 -0.051692 -0.100488
C -0.224889 -1.455110 -2.188326
C -2.417328 -2.486716 -1.749700
C -3.771941 -0.987322 0.650715
C -3.533880 1.257108 -0.219598
H 0.306013 -2.259016 -1.664600
H -0.313228 -1.700063 -3.250027
H 0.323103 -0.521721 -2.046600
H -2.260190 -2.911941 -2.742867

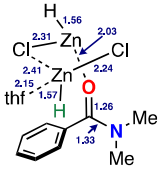
H -2.152209 -3.236019 -0.993708
H -3.466536 -2.209859 -1.643264
C -4.974849 -0.623510 1.246991
H -3.374832 -1.986502 0.799303
C -4.746750 1.614308 0.365929
H -2.959145 1.994484 -0.774230
C -5.469244 0.673894 1.098137
H -5.523477 -1.351400 1.837837
H -5.118543 2.629389 0.260113
H -6.409237 0.953579 1.565771
---

INT3_ZnH2_C-O_red




Energy (RwB97XD): -1168.55403870 A.U.
Gibbs Free Energy: -1168.269371 A.U.
---
Zn -0.760285 -0.678481 1.216816
H 1.227763 1.465556 0.572017
H -0.517365 -0.493562 2.732107
H 0.874496 0.712001 -0.987634
Zn -2.388357 -2.120869 -1.104994
H -3.632413 -2.805594 -1.690244
C -2.026873 1.748691 -0.603687
H -1.469407 1.058376 -1.238010
H -1.814054 2.784331 -0.898817
C -2.634561 1.922424 1.596326
H -2.696701 3.019330 1.649954
H -2.418881 1.527402 2.592021
C -3.868166 1.324171 0.927640
H -4.790295 1.834537 1.219524
H -3.959895 0.267220 1.202522
C -3.544641 1.473068 -0.574433
H -4.096485 2.305025 -1.021996
H -3.800314 0.566669 -1.131979
O -1.557254 1.551050 0.735752
O -0.939579 -1.265947 -0.488373
C 1.689277 1.101757 -0.366314
N 2.324630 2.201142 -1.090608
C 2.642855 -0.028515 -0.054448
C 1.322627 3.146567 -1.556379
C 3.320850 2.872842 -0.270480
C 2.907686 -0.407310 1.263278
C 3.265066 -0.729453 -1.094089
H 0.760325 3.611272 -0.723193
H 1.806762 3.945720 -2.127973
H 0.607293 2.639132 -2.212156
H 3.792804 3.675205 -0.847295
H 2.879411 3.315325 0.644465
H 4.100520 2.167579 0.033516
C 3.771338 -1.469106 1.542325
H 2.436674 0.134615 2.080863
C 4.131341 -1.784934 -0.821672
H 3.064601 -0.441068 -2.123443
C 4.385990 -2.160036 0.500120
H 3.964799 -1.751623 2.574005
H 4.605728 -2.320665 -1.640027
H 5.059409 -2.986121 0.713217
---

INT0_ZnHCl

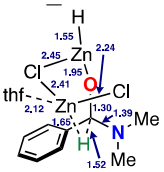



**INT0$_{ZnHCl}$**

Energy (RwB97XD): -2087.85380396 A.U.
Gibbs Free Energy: -2087.589156 A.U.
---
Zn -1.637238 -0.990640 -0.664724
Zn 1.364374 -0.405096 2.383096
H -0.527382 -0.906988 -1.772058
Cl -0.775050 0.058309 1.648069
Cl -3.165828 -2.458108 0.073676
H 2.087658 -0.119878 3.732780
O -2.790411 0.818420 -0.758346
C -3.932077 1.075770 0.091026
C -2.078466 2.048111 -1.036038
C -4.151182 2.578694 0.003986
H -4.764328 0.477434 -0.284400
H -3.687265 0.758923 1.110868
C -2.718656 3.100762 -0.140424
H -1.017662 1.887902 -0.827762
H -2.209865 2.273593 -2.100215
H -4.663058 2.967402 0.888360
H -4.744472 2.830041 -0.882617
H -2.220961 3.123263 0.835147
H -2.665009 4.099305 -0.582575
O 2.011698 -1.447135 0.761375
C 2.237640 -0.982629 -0.392758
N 2.189211 -1.786267 -1.448318
C 2.551175 0.469109 -0.542730
C 1.702338 -3.151985 -1.291876
C 2.616641 -1.421557 -2.793266
C 1.824853 1.284549 -1.415554
C 3.529466 1.027508 0.286503
H 1.188161 -3.440352 -2.211718
H 2.537405 -3.838568 -1.113028
H 1.005231 -3.207349 -0.455873

H 3.202050 -2.250039 -3.202521
H 1.744614 -1.250308 -3.433665
H 3.241697 -0.529638 -2.777243
C 2.079149 2.652762 -1.457513
H 1.050608 0.853051 -2.042831
C 3.792274 2.394021 0.227666
H 4.090821 0.393643 0.967914
C 3.064841 3.207709 -0.641006
H 1.503615 3.286190 -2.126590
H 4.561672 2.822792 0.863065
H 3.264542 4.274882 -0.679925
---

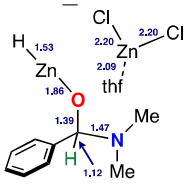
TS1_ZnHCl




**TS1$_{ZnHCl}$**

Energy (RwB97XD): -2087.82889603 A.U.
Gibbs Free Energy: -2087.562784 A.U.
---
Zn -1.288285 -0.851276 -0.300431
Zn 1.474423 -0.541557 2.336190
H 0.284171 -0.702428 -0.779867
Cl -0.952497 -0.367221 2.031940
Cl -2.813991 -2.440604 -0.685513
H 2.154025 -0.146550 3.672188
O -2.398882 0.919252 -0.634653
C -3.827453 0.899835 -0.366770
C -1.842087 2.213903 -0.286380
C -4.207782 2.358202 -0.168876
H -4.314839 0.416137 -1.214652
H -4.000735 0.309181 0.539071
C -2.944137 2.933447 0.475727
H -0.935646 2.052419 0.300244
H -1.587562 2.725296 -1.220891
H -5.096289 2.460782 0.459527
H -4.402789 2.840700 -1.133221
H -2.904172 2.673561 1.539284
H -2.863870 4.019163 0.377298
O 1.903662 -1.389419 0.637595
C 1.772378 -0.852520 -0.535901
N 2.072714 -1.677078 -1.609886
C 2.164866 0.612613 -0.662826
C 1.724178 -3.074900 -1.414298
C 1.760681 -1.188353 -2.940785
C 1.402843 1.564942 -1.338484
C 3.360956 1.002042 -0.049927
H 0.627144 -3.191133 -1.345006
H 2.086655 -3.653191 -2.266899
H 2.174952 -3.457515 -0.499369
H 2.149119 -1.896078 -3.676028
H 0.667910 -1.098911 -3.078016
H 2.221455 -0.215774 -3.120335
C 1.824465 2.891230 -1.401347
H 0.471812 1.268897 -1.813098
C 3.784011 2.328318 -0.112857
H 3.963045 0.264325 0.473677
C 3.015421 3.276935 -0.787077
H 1.218094 3.624371 -1.926366
H 4.714248 2.619316 0.367018
H 3.342161 4.312145 -0.832109
---

INT1_ZnHCl

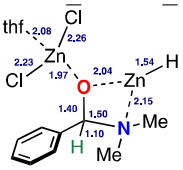



**INT1$_{ZnHCl}$**

Energy (RwB97XD): -2087.84554949 A.U.
Gibbs Free Energy: -2087.571450 A.U.
---
Zn 3.215366 -0.805746 -0.284074
Zn -4.294978 -1.571044 -0.707750
H -1.261934 -1.120154 -0.408542
Cl 2.357607 -1.993037 -1.921602
Cl 4.430468 -0.576975 1.533464
H -5.400023 -1.692373 -1.762313
O 2.479291 1.134211 -0.570922
C 2.432140 2.146258 0.474291
C 1.552072 1.461462 -1.638119
C 1.260413 3.043511 0.101251
H 2.317712 1.642002 1.435274
H 3.388076 2.678353 0.456003
C 1.230028 2.930010 -1.424780
H 2.047196 1.239347 -2.585094
H 0.665474 0.827996 -1.527873
H 1.409024 4.067072 0.454663
H 0.326439 2.659580 0.527359
H 2.002811 3.561791 -1.876828
H 0.261400 3.198655 -1.853208
O -2.990672 -1.587262 0.612711
C -1.823816 -0.841765 0.514853
N -0.974699 -1.143098 1.672071
C -2.137707 0.647739 0.427514
C -0.701547 -2.572323 1.749911
C 0.273895 -0.403506 1.624558
C -2.090777 1.297508 -0.806355
C -2.556236 1.363386 1.554584
H -0.142272 -2.936082 0.864553

H -0.100544 -2.777874 2.641788
H -1.637525 -3.127800 1.819510
H 0.907662 -0.696282 2.467119
H 0.832714 -0.600601 0.686971
H 0.096100 0.672543 1.687599
C -2.454760 2.641407 -0.920414
H -1.766655 0.749076 -1.689562
C -2.906348 2.706555 1.448608
H -2.593621 0.859966 2.517081
C -2.857242 3.350915 0.208775
H -2.415591 3.133517 -1.888822
H -3.219703 3.255132 2.333325
H -3.132407 4.399179 0.127164
---

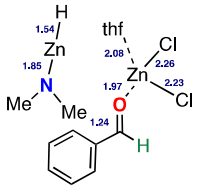
INT1'_ZnHCl_C-N




**INT1'$_{ZnHCl/C-N}$**

Energy (RwB97XD): -2087.88311753 A.U.
Gibbs Free Energy: -2087.610990 A.U.
---
Zn 1.229818 -0.158443 0.902130
Zn -0.554577 -2.475082 -0.919325
H -1.667587 -0.725706 1.353601
Cl 2.071038 -2.090052 1.706317
Cl 1.104571 1.656746 2.199329
H 0.098131 -3.724945 -1.548711
O 2.477045 0.327106 -0.686110
C 2.040120 1.327439 -1.637194
C 3.914324 0.404050 -0.490332
C 3.309844 1.758380 -2.353267
H 1.294255 0.859648 -2.282730
H 1.581552 2.156622 -1.086127
C 4.353082 1.656904 -1.236533
H 4.115377 0.439516 0.583099
H 4.349345 -0.507988 -0.910744
H 3.221208 2.766042 -2.767575
H 3.545855 1.063586 -3.167183
H 4.294076 2.531672 -0.579768
H 5.376641 1.568780 -1.609808
O -0.338021 -0.572260 -0.220809
C -1.634551 -0.448434 0.291347
N -2.412559 -1.514741 -0.421685
C -2.196727 0.950693 0.146550
C -3.402813 -2.183672 0.431032
C -3.034440 -1.077237 -1.682769
C -3.203489 1.380191 1.013857
C -1.734420 1.816406 -0.846142
H -4.218535 -1.501160 0.707220
H -3.825391 -3.031058 -0.115321
H -2.920646 -2.555518 1.338941
H -3.387821 -1.961756 -2.219855
H -3.883738 -0.405644 -1.501724
H -2.301266 -0.560009 -2.307094
C -3.754227 2.654637 0.881403
H -3.548644 0.720773 1.807353
C -2.279471 3.091603 -0.978173
H -0.936322 1.488795 -1.505478
C -3.293595 3.512782 -0.116651
H -4.532830 2.981288 1.565453
H -1.907909 3.761217 -1.749473
H -3.714428 4.509775 -0.215827
---

TS2_ZnHCl_C-N

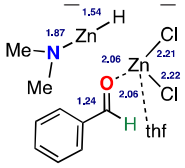



**TS2$_{ZnHCl/C-N}$**

Energy (RwB97XD): -2087.83281718 A.U.
Gibbs Free Energy: -2087.569141 A.U.
---
Zn 1.626842 -1.056430 -0.738443
Zn -0.196918 2.788427 -0.099189
H -1.038284 -2.582294 -0.880321
Cl 1.926032 0.208113 -2.531162
Cl 2.151707 -3.204995 -0.518512
H 1.137564 3.155170 0.581267
O 2.361410 -0.017862 0.857562
C 1.929987 -0.213313 2.225949
C 3.583256 0.764049 0.800451
C 2.741059 0.792543 3.027295
H 0.851455 -0.046219 2.259572
H 2.151899 -1.247736 2.510647
C 4.056686 0.848576 2.244200
H 4.281373 0.252664 0.133570
H 3.328450 1.744141 0.385867
H 2.872849 0.473137 4.064232
H 2.248703 1.771093 3.019562
H 4.686491 -0.012875 2.491751
H 4.625996 1.762900 2.429467
O -0.314146 -0.889183 -0.048371
C -1.228301 -1.693261 -0.260953
N -1.844641 2.311864 -0.799375
C -2.567940 -1.537571 0.281911
C -2.005312 1.441163 -1.938631
C -3.072455 2.991331 -0.463621
C -3.505046 -2.554214 0.049388
C -2.922081 -0.396723 1.019387

H -2.772824 0.664302 -1.755087
H -2.324484 1.986452 -2.849197
H -1.068289 0.925986 -2.177583
H -3.446045 3.635986 -1.284267
H -3.886505 2.275901 -0.235165
H -2.942232 3.629702 0.419239
C -4.792842 -2.436090 0.561471
H -3.220060 -3.430372 -0.528105
C -4.210170 -0.282476 1.522171
H -2.195796 0.399365 1.150895
C -5.141237 -1.302109 1.296241
H -5.522929 -3.220703 0.388209
H -4.497565 0.599716 2.086339
H -6.148294 -1.207336 1.693076
---

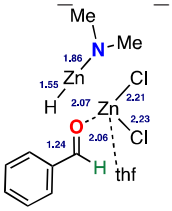
INT2_ZnHCl_C-N




**INT2$_{ZnHCl/C-N}$**

Energy (RwB97XD): -2087.83370799 A.U.
Gibbs Free Energy: -2087.570930 A.U.
---
Zn 1.701010 -1.045897 -0.807054
Zn 0.137763 2.956113 0.074085
H -0.799427 -2.931962 -0.596573
Cl 2.480962 0.419383 -2.265825
Cl 2.262880 -3.184902 -0.569837
H 1.468270 3.305923 0.775144
O 1.843484 -0.129458 1.033721
C 0.862608 -0.243851 2.092244
C 3.117257 0.333321 1.551684
C 1.479943 0.495843 3.268999
H -0.070534 0.194426 1.730812
H 0.708885 -1.307981 2.306340
C 2.977338 0.245726 3.064209
H 3.902026 -0.306868 1.140912
H 3.260663 1.361218 1.204272
H 1.108061 0.119047 4.225201
H 1.259098 1.566969 3.202819
H 3.250885 -0.754795 3.416740
H 3.607263 0.980264 3.572225
O -0.349468 -0.963468 -0.665597
C -1.138464 -1.893340 -0.466733
N -1.508954 2.491578 -0.668146
C -2.513991 -1.683929 -0.047770
C -1.565462 1.965843 -2.015662
C -2.697396 3.253242 -0.351097
C -3.336320 -2.806739 0.125582
C -3.002805 -0.389877 0.202060
H -2.437480 1.297145 -2.148707
H -1.656735 2.755738 -2.787192
H -0.670307 1.377176 -2.244461
H -2.849000 4.128784 -1.013478
H -3.606899 2.630671 -0.448614
H -2.663335 3.622471 0.681504
C -4.652206 -2.640326 0.543244
H -2.940353 -3.801037 -0.067448
C -4.316982 -0.235565 0.623792
H -2.351206 0.475886 0.062991
C -5.137919 -1.355741 0.792010
H -5.296469 -3.503978 0.676511
H -4.709558 0.757165 0.822733
H -6.165422 -1.224215 1.120239
---

INT2'_ZnHCl_C-N_red

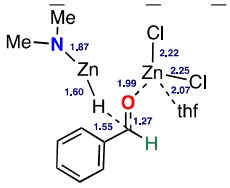



**INT2'$_{ZnHCl/C-N/red}$**

Energy (RwB97XD): -2087.83163300 A.U.
Gibbs Free Energy: -2087.569216 A.U.
---
Zn -0.617625 1.099302 0.210179
Zn -1.612480 -2.567816 -0.394396
H 1.371303 -0.584313 -1.362450
Cl -1.935707 0.875985 1.965456
Cl -1.114129 0.829683 -1.946315
H -0.096271 -2.731484 -0.662647
O 0.305206 2.935255 0.361726
C 1.545585 3.196669 -0.343055
C -0.512666 4.137478 0.420434
C 1.647435 4.712717 -0.393160
H 2.348486 2.711469 0.215311
H 1.473658 2.758985 -1.345490
C 0.177942 5.129936 -0.502967
H -1.527611 3.878228 0.109209
H -0.525042 4.471929 1.462191
H 2.253659 5.050371 -1.237574
H 2.089577 5.097401 0.532529
H -0.178822 5.005748 -1.531244
H -0.000092 6.162750 -0.192951
O 1.145313 0.070588 0.536278
C 1.751943 -0.569098 -0.331360
N -3.454123 -2.520660 -0.122845
C 2.975994 -1.308442 -0.065795
C -4.283185 -1.615280 -0.890915
C -3.995046 -2.727326 1.204266
C 3.586762 -1.982864 -1.132049

C 3.538465 -1.352616 1.219869
H -5.313644 -2.004811 -0.987851
H -4.364995 -0.607794 -0.437407
H -3.886981 -1.487328 -1.905488
H -4.088556 -1.790404 1.787816
H -5.006332 -3.172631 1.158242
H -3.363617 -3.413680 1.782097
C 4.760648 -2.697288 -0.916272
H 3.136852 -1.945882 -2.121257
C 4.709015 -2.067580 1.429120
H 3.052750 -0.829712 2.038222
C 5.318089 -2.737240 0.362083
H 5.238991 -3.221769 -1.737679
H 5.151308 -2.109036 2.419882
H 6.234560 -3.295474 0.532342
---

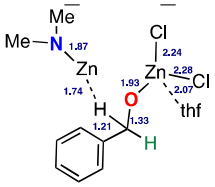
TS3_ZnHCl_C-N_red




**TS3**$_{ZnHCl/C\text{-}N/red}$

Energy (RwB97XD): -2087.81671172 A.U.
Gibbs Free Energy: -2087.554448 A.U.
---
Zn -1.686731 -0.895675 0.407456
Zn 2.727496 -0.959921 -0.356833
H 0.059727 0.873160 -1.285767
Cl -1.911966 -2.151725 2.225061
Cl -1.311832 -1.788197 -1.623835
H 1.444594 0.001958 -0.362759
O -3.418630 0.216121 0.191872
C -3.389782 1.399376 -0.643796
C -4.711761 -0.440635 0.101880
C -4.851120 1.697828 -0.936236
H -2.870891 2.181576 -0.086739
H -2.832895 1.165851 -1.559120
C -5.454497 0.291720 -1.007409
H -4.546687 -1.500893 -0.105147
H -5.199885 -0.331677 1.075267
H -4.972864 2.264437 -1.863018
H -5.297053 2.268987 -0.114398
H -5.238033 -0.167183 -1.978349
H -6.535729 0.278794 -0.847980
O -0.469613 0.653479 0.676558
C 0.317001 1.060382 -0.234195
N 4.388550 -1.811544 -0.372540
C 1.150144 2.273995 0.005731
C 4.515222 -3.087985 -1.049262
C 5.194324 -1.771593 0.832628
C 1.757832 2.909144 -1.080521
C 1.315211 2.782709 1.296045
H 5.564349 -3.273121 -1.341151
H 4.201961 -3.949184 -0.427354
H 3.913285 -3.104495 -1.965789
H 4.922783 -2.552137 1.570070
H 6.262378 -1.920137 0.593319
H 5.103609 -0.798588 1.330403
C 2.532097 4.048686 -0.878439
H 1.626531 2.507308 -2.083426
C 2.091152 3.921626 1.496986
H 0.833645 2.286128 2.133341
C 2.701030 4.554136 0.411842
H 3.002253 4.542676 -1.724017
H 2.219740 4.318166 2.500262
H 3.305772 5.442609 0.571630
---

INT3_ZnHCl_C-N_red

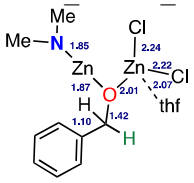



**INT3**$_{ZnHCl/C\text{-}N\_red}$

Energy (RwB97XD): -2087.821624889 A.U.
Gibbs Free Energy: -2087.55446907325 A.U.
---
Zn -1.620589 -0.805657 0.452269
Zn 2.641362 -0.953240 -0.413083
H 0.081235 0.990047 -1.301929
Cl -1.899386 -2.122491 2.245263
Cl -1.277342 -1.814700 -1.561463
H 1.291697 0.136391 -0.353298
O -3.407134 0.220055 0.207009
C -3.403827 1.404581 -0.624943
C -4.678180 -0.471780 0.106397
C -4.870111 1.660942 -0.934671
H -2.912341 2.199859 -0.062162
H -2.829457 1.191326 -1.534370
C -5.431717 0.237552 -1.011318
H -4.482328 -1.527431 -0.096385
H -5.180118 -0.375408 1.074338
H -4.998634 2.222445 -1.863794
H -5.342767 2.218908 -0.118682
H -5.192713 -0.216005 -1.979412
H -6.513755 0.192065 -0.862934
O -0.426324 0.697594 0.676986
C 0.454476 1.010996 -0.263513
N 4.311192 -1.791102 -0.436144
C 1.259153 2.268604 -0.007365
C 4.396524 -3.095165 -1.072381

C 5.077699 -1.754126 0.798590
C 1.916373 2.902698 -1.065293
C 1.361321 2.796547 1.280192
H 5.447470 -3.328571 -1.313412
H 4.020254 -3.921880 -0.441522
H 3.833532 -3.106856 -2.012802
H 4.750724 -2.502045 1.544798
H 6.142067 -1.954312 0.589237
H 5.015174 -0.764672 1.265624
C 2.674168 4.050218 -0.838799
H 1.828484 2.499887 -2.073286
C 2.119276 3.945181 1.508613
H 0.835950 2.307928 2.095736
C 2.778331 4.573513 0.451274
H 3.176199 4.540228 -1.668850
H 2.192388 4.353642 2.513189
H 3.363855 5.471337 0.630150
---

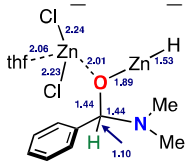
INT4_ZnHCl_C-N_red




**INT4**$_{ZnHCl/C\text{-}N\_red}$

Energy (RwB97XD): -2087.87231164 A.U.
Gibbs Free Energy: -2087.601176 A.U.
---
Zn -0.170136 -1.792388 -0.141215
Zn 2.271645 0.502423 -0.428355
H -0.930875 0.002919 -2.341495
Cl 1.229983 -2.124194 1.572460
Cl -0.822360 -3.272887 -1.666844
H 0.421197 1.078550 -2.662178
O -1.911558 -1.030081 0.649013
C -3.126778 -0.824388 -0.107946
C -2.092778 -0.629123 2.030711
C -3.883530 0.227106 0.682353
H -2.845730 -0.512317 -1.115161
H -3.668278 -1.775729 -0.159535
C -3.540077 -0.151382 2.127347
H -1.874114 -1.489876 2.666831
H -1.374029 0.167538 2.239346
H -4.957087 0.196255 0.478558
H -3.506231 1.226151 0.440026
H -4.188194 -0.964405 2.471200
H -3.639544 0.686958 2.821711
O 0.643409 -0.187150 -1.047421
C -0.180080 0.638866 -1.854729
N 3.827717 1.246469 0.234857
C -0.875539 1.751817 -1.092625
C 5.081387 0.585755 -0.085237
C 3.802450 1.690786 1.618086
C -1.788667 2.563878 -1.776005
C -0.635416 2.004278 0.257538
H 5.927826 1.278017 0.062245
H 5.280799 -0.304489 0.540675
H 5.096483 0.267511 -1.134122
H 3.916598 0.865984 2.346730
H 4.624259 2.402448 1.806619
H 2.862807 2.209193 1.843388
C -2.441285 3.606299 -1.123718
H -1.990636 2.374219 -2.828806
C -1.281881 3.053823 0.914096
H 0.040720 1.368098 0.822418
C -2.186813 3.858206 0.226945
H -3.149376 4.224792 -1.668949
H -1.081879 3.232167 1.967546
H -2.694342 4.672383 0.736965
---

INT1'_ZnHCl_C-O



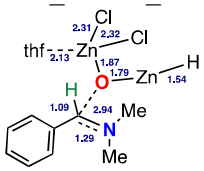

**INT1'**$_{ZnHCl/C\text{-}O}$

Energy (RwB97XD): -2087.87682227 A.U.
Gibbs Free Energy: -2087.602177 A.U.
---
Zn -1.092133 -1.361493 0.226406
Zn -2.060275 1.411709 -1.349643
H 0.041262 0.715449 1.716899
Cl -2.072878 -2.145146 -1.626666
Cl -1.743028 -1.818054 2.309537
H -2.954938 2.016111 -2.427120
O 0.870176 -1.974163 0.142239
C 1.787401 -1.942248 1.261081
C 1.538035 -2.420418 -1.064157
C 3.163549 -1.929250 0.619819
H 1.564925 -1.053948 1.855709
H 1.618280 -2.838361 1.868310
C 2.948066 -2.797922 -0.623663
H 0.967833 -3.255197 -1.477285
H 1.531847 -1.588572 -1.774278
H 3.928915 -2.326996 1.291457
H 3.438333 -0.907847 0.336746
H 2.994557 -3.860083 -0.360182
H 3.680445 -2.603854 -1.411647
O -0.936652 0.622354 -0.053851
C -0.033469 1.330278 0.810331
N -0.496795 2.614375 1.257658
C 1.356175 1.431034 0.192437
C -1.689250 2.560413 2.085729

C -0.534730 3.700923 0.294185
C 2.412913 1.868559 0.998352
C 1.613819 1.098309 -1.135386
H -1.816884 3.520575 2.597499
H -2.610392 2.359449 1.510863
H -1.583318 1.776209 2.841859
H -1.416726 3.680468 -0.375199
H -0.576128 4.653251 0.834340
H 0.367736 3.700147 -0.322580
C 3.700753 1.980139 0.482002
H 2.219633 2.125693 2.037256
C 2.902957 1.215665 -1.659882
H 0.809404 0.734179 -1.766805
C 3.949501 1.657677 -0.854437
H 4.511951 2.317791 1.121657
H 3.086869 0.953780 -2.698749
H 4.954076 1.744585 -1.259629

---

TS2_ZnHCl_C-O




**TS2$_{ZnHCl/C-O}$**

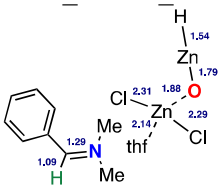
Energy (RwB97XD): -2087.83741380 A.U.
Gibbs Free Energy: -2087.568217 A.U.

---

Zn -0.699213 -1.065414 0.518903
Zn -3.027774 -0.113526 -1.302546
H -0.081922 1.925361 1.913368
Cl -1.387118 -3.260358 0.219399
Cl -0.377477 -0.609901 2.759246
H -4.425750 -0.297347 -1.925718
O 1.327069 -1.246433 -0.125346
C 2.388373 -1.667853 0.753388
C 1.557707 -1.726202 -1.467215
C 3.527928 -2.060938 -0.173665
H 2.617097 -0.833220 1.419190
H 2.037556 -2.519709 1.348377
C 2.770324 -2.645207 -1.369787
H 0.653489 -2.233757 -1.812842
H 1.748359 -0.854990 -2.102199
H 4.209968 -2.775451 0.295330
H 4.099178 -1.174823 -0.473593
H 2.453396 -3.671513 -1.153281
H 3.355757 -2.649279 -2.293360
O -1.410157 0.233144 -0.625528
C -0.024582 2.327749 0.904613
N -1.081862 2.940112 0.494023
C 1.243958 2.147583 0.211363
C -2.298432 2.929941 1.304850
C -1.232356 3.568936 -0.814750
C 2.391590 2.131672 1.019475
C 1.361148 1.927518 -1.168243
H -2.598409 3.960675 1.509907
H -3.081280 2.424084 0.733449
H -2.124319 2.392165 2.236358
H -1.606201 2.820081 -1.518164
H -1.956980 4.379418 -0.718867
H -0.279196 3.971265 -1.158345
C 3.647429 1.965936 0.447316
H 2.294013 2.252811 2.095468
C 2.618949 1.749067 -1.732073
H 0.471609 1.828796 -1.778291
C 3.760851 1.780313 -0.930753
H 4.533274 1.966125 1.075373
H 2.707958 1.567126 -2.799108
H 4.740555 1.639220 -1.379013

---

INT2_ZnHCl_C-O




**INT2$_{ZnHCl/C-O}$**

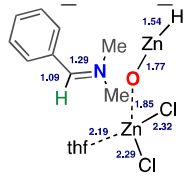
Energy (RwB97XD): -2087.84067736 A.U.
Gibbs Free Energy: -2087.571594 A.U.

---

Zn -1.219688 0.045243 0.760675
Zn -2.649396 0.970897 -1.884286
H 2.699634 1.985149 1.616446
Cl -3.254489 -0.854571 1.398103
Cl 0.016039 0.721793 2.566984
H -3.852653 0.990865 -2.848792
O -0.172014 -1.758254 0.260080
C 0.829054 -2.429561 1.049887
C -0.717167 -2.638755 -0.737827
C 1.074453 -3.757349 0.341978
H 1.711786 -1.786359 1.096880
H 0.430967 -2.569834 2.060902
C -0.281739 -4.034438 -0.314002
H -1.801051 -2.499951 -0.755009
H -0.301506 -2.356460 -1.712956
H 1.384032 -4.540144 1.039766
H 1.851941 -3.645134 -0.421990
H -0.986063 -4.444360 0.418478
H -0.219245 -4.722343 -1.161699
O -1.183275 0.988864 -0.860356
C 2.311729 1.919357 0.604176
N 1.585703 2.916677 0.224098
C 2.716779 0.756224 -0.174339
C 1.218412 3.964467 1.178013
C 1.008568 3.075176 -1.112570

C 3.963481 0.198369 0.158993
C 1.919603 0.151480 -1.159700
H 1.559148 4.928027 0.791047
H 0.129315 3.972408 1.273762
H 1.671366 3.764446 2.148292
H 0.060760 2.513223 -1.147159
H 0.840037 4.140261 -1.277905
H 1.704357 2.692714 -1.861829
C 4.441607 -0.908124 -0.531334
H 4.556475 0.642059 0.954752
C 2.403534 -0.965059 -1.834029
H 0.902593 0.496527 -1.342081
C 3.662000 -1.485666 -1.535333
H 5.411918 -1.326308 -0.280998
H 1.784434 -1.442437 -2.587796
H 4.028447 -2.357668 -2.070220
---

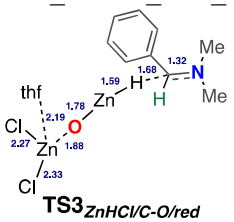
INT2'_ZnHCl_C-O_red




**INT2'$_{ZnHCl/C-O/red}$**

Energy (RwB97XD): -2087.83439532 A.U.
Gibbs Free Energy: -2087.563798 A.U.
---
Zn 1.955666 -0.746760 0.060149
Zn -0.599641 -1.977041 -1.684391
H -0.890605 -0.673756 1.427400
Cl 4.148586 -0.146704 -0.213750
Cl 1.478095 -1.268196 2.268922
H -2.051437 -2.331294 -2.048792
O 1.034469 1.237198 0.085492
C 1.577372 2.252538 0.958929
C 0.706558 1.808368 -1.197492
C 1.439901 3.570625 0.202297
H 1.021815 2.225715 1.900035
H 2.625068 2.002790 1.155363
C 1.479336 3.116286 -1.259752
H 0.980993 1.080259 -1.963750
H -0.377252 1.979130 -1.231869
H 2.240601 4.269629 0.458863
H 0.478280 4.046401 0.424817
H 2.511119 2.932628 -1.578916
H 1.021283 3.833852 -1.946377
O 1.093437 -1.566032 -1.362080
C -1.887384 -0.608069 0.987072
N -2.551449 -1.715415 0.947914
C -2.328294 0.707108 0.541140
C -1.928459 -2.970960 1.379215
C -3.938681 -1.848428 0.501983
C -1.883436 1.800994 1.299137
C -3.086713 0.923241 -0.619419
H -2.461031 -3.340801 2.259221
H -2.022864 -3.696522 0.566897
H -0.876351 -2.805410 1.614275
H -3.950677 -2.169337 -0.543599
H -4.412919 -2.613122 1.119161
H -4.467744 -0.903050 0.616502
C -2.242602 3.092249 0.934991
H -1.265536 1.630300 2.176031
C -3.412187 2.221573 -0.997443
H -3.386103 0.090007 -1.246765
C -3.003415 3.302835 -0.215917
H -1.915398 3.934397 1.536967
H -3.982992 2.389824 -1.905529
H -3.267653 4.314092 -0.511762
---

TS3_ZnHCl_C-O_red

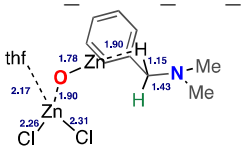



**TS3$_{ZnHCl/C-O/red}$**

Energy (RwB97XD): -2087.81651161 A.U.
Gibbs Free Energy: -2087.548054 A.U.
---
Zn 1.978370 -1.200804 -0.048485
Zn -0.800976 -1.613025 -1.012240
H -2.601261 -0.912414 1.460637
Cl 4.249966 -1.223190 -0.121426
Cl 1.125702 -1.627048 2.078239
H -2.276133 -1.360856 -0.480585
O 1.658802 0.961091 -0.017869
C 2.070196 1.733605 1.129466
C 1.944164 1.678544 -1.236265
C 2.390447 3.122988 0.592568
H 1.254267 1.714687 1.855643
H 2.953507 1.255970 1.568524
C 2.871019 2.815371 -0.828625
H 2.388072 0.980139 -1.949629
H 0.994884 2.049253 -1.641286
H 3.142956 3.631112 1.201902
H 1.487341 3.743201 0.565236
H 3.910677 2.469961 -0.814218
H 2.795898 3.670782 -1.505931
O 0.907581 -1.729269 -1.502991
C -3.065695 -0.387033 0.630934
N -4.325811 -0.721881 0.411563
C -2.491605 0.948909 0.324625
C -4.759760 -2.047822 0.831217
C -5.137087 -0.103370 -0.627305
C -1.985261 1.677277 1.405885

C -2.418385 1.482399 -0.966623
H -5.826547 -2.026089 1.061890
H -4.579208 -2.760003 0.013456
H -4.200506 -2.363068 1.713493
H -4.892117 -0.546461 -1.602162
H -6.188093 -0.292736 -0.403303
H -4.966574 0.972776 -0.659226
C -1.446539 2.946239 1.201622
H -2.010501 1.252434 2.405924
C -1.871330 2.745024 -1.167716
H -2.765761 0.902673 -1.816846
C -1.391844 3.481548 -0.083147
H -1.057894 3.507606 2.046184
H -1.808944 3.150062 -2.173492
H -0.962559 4.466390 -0.244161
---

INT3_ZnHCl_C-O_red




**INT3**$_{ZnHCl/C\text{-}O/red}$

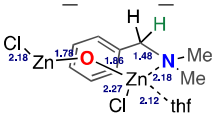
Energy (RwB97XD): -2087.83157496 A.U.

Gibbs Free Energy: -2087.557801 A.U.

---

Zn 2.095534 -0.986002 0.197475
Zn -0.454668 -1.994133 -1.023488
H -2.152101 -1.030690 1.272106
Cl 4.324542 -0.603684 0.251272
Cl 1.054730 -1.232993 2.242481
H -2.067511 -1.118284 -0.525047
O 1.373314 1.005355 -0.282192
C 1.328144 2.034495 0.734773
C 1.791913 1.569649 -1.538402
C 1.717618 3.335383 0.034271
H 0.319707 2.050403 1.157029
H 2.041752 1.760784 1.517903
C 2.531211 2.844545 -1.167606
H 2.405140 0.827706 -2.054698
H 0.898409 1.781068 -2.140600
H 2.286034 3.994628 0.695856
H 0.824975 3.872065 -0.304019
H 3.559211 2.609710 -0.871203
H 2.557658 3.562843 -1.991887
O 1.319415 -1.996080 -1.209985
C -2.632114 -0.651147 0.365700
N -3.978368 -1.129684 0.311545
C -2.459218 0.844949 0.268915
C -4.034844 -2.556461 0.574590
C -4.663948 -0.779715 -0.921754
C -2.768123 1.632342 1.382372
C -2.001000 1.462064 -0.895089
H -5.074027 -2.895770 0.569414
H -3.479583 -3.130998 -0.196946
H -3.597580 -2.776968 1.552832
H -4.167022 -1.231344 -1.803492
H -5.693778 -1.144301 -0.881188
H -4.685443 0.305025 -1.053266
C -2.625115 3.016763 1.327741
H -3.117961 1.155781 2.294932
C -1.857403 2.847633 -0.953493
H -1.755362 0.859501 -1.767262
C -2.169859 3.627578 0.158115
H -2.862958 3.618634 2.200468
H -1.497489 3.315875 -1.865603
H -2.052503 4.707020 0.117066
---

INT4_ZnHCl_C-O_red




**INT4**$_{ZnHCl/C\text{-}O/red}$

Energy (RwB97XD): -2087.88641403 A.U.

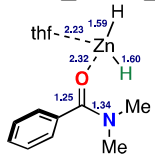
Gibbs Free Energy: -2087.607493 A.U.

---

Zn 0.999189 0.038969 0.544841
Zn -1.598859 1.815313 -0.055581
H -0.579697 -0.428400 -2.042706
Cl 1.314630 -0.798040 2.631716
Cl -3.668345 2.495803 -0.087770
H -0.696720 -2.161190 -2.358184
O 3.016951 0.528856 0.106400
C 3.375880 1.514387 -0.881807
C 4.189796 -0.175804 0.570188
C 4.689264 1.008240 -1.452931
H 2.554764 1.581919 -1.597191
H 3.493656 2.484122 -0.383371
C 5.363222 0.420726 -0.207814
H 4.269332 -0.039876 1.651106
H 4.046061 -1.240593 0.357517
H 5.273061 1.806458 -1.919029
H 4.503773 0.227726 -2.200076
H 5.840979 1.216637 0.373365
H 6.118744 -0.333585 -0.442736
O 0.164627 1.581577 -0.085759
C -0.629681 -1.409038 -1.556693
N 0.662115 -1.593262 -0.857811
C -1.911243 -1.469814 -0.745691
C 1.722119 -1.460228 -1.878333
C 0.763612 -2.939562 -0.264600
C -1.997578 -1.396661 0.647631
C -3.104449 -1.560418 -1.476971
H 2.698515 -1.614014 -1.416727
H 1.585939 -2.208014 -2.673255

H 1.687697 -0.462780 -2.323138
H 0.644306 -3.708572 -1.041809
H 1.744499 -3.051651 0.203116
H -0.000252 -3.087908 0.498612
C -3.238100 -1.415490 1.290453
H -1.106954 -1.342551 1.264508
C -4.341726 -1.571412 -0.840103
H -3.060850 -1.619443 -2.562913
C -4.414059 -1.500669 0.551916
H -3.274432 -1.360551 2.375080
H -5.250927 -1.635362 -1.431738
H -5.378012 -1.508954 1.052771
---

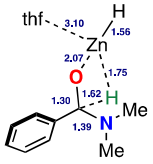
INT0_ZnH2_mono




**INT0**$_{ZnH2\_mono}$

Energy (RwB97XD): -940.176781316 A.U.
Gibbs Free Energy: -939.907855 A.U.
---
Zn 1.054320 -2.342350 -0.033440
O 1.282414 -0.335941 1.101224
C 1.399370 0.715140 0.438124
H 1.395952 -1.809408 -1.500666
N 2.563272 1.088537 -0.117330
C 3.736117 0.232025 -0.018488
H 4.453245 0.658143 0.693255
H 3.449294 -0.763266 0.316056
H 4.209930 0.161152 -1.002300
C 2.800211 2.369710 -0.770294
H 3.740815 2.784181 -0.393275
H 2.883207 2.238080 -1.854878
H 2.000898 3.076702 -0.552824
C 0.192526 1.583134 0.235376
C -0.316717 1.807146 -1.046056
C -0.466832 2.108342 1.348929
C -1.476967 2.560721 -1.213038
H 0.192561 1.388418 -1.910384
C -1.612729 2.882694 1.177452
H -0.079155 1.917600 2.345932
C -2.120096 3.108250 -0.102811
H -1.875692 2.722473 -2.210694
H -2.114999 3.302063 2.044731
H -3.019538 3.703501 -0.234334
H 1.228552 -3.380751 1.155901
O -1.142888 -1.971956 -0.058759
C -1.810374 -1.578106 -1.269530
C -1.872888 -1.517110 1.097931
C -3.225937 -1.217574 -0.842293
H -1.285149 -0.717107 -1.699796
H -1.755122 -2.415422 -1.970120
C -2.991953 -0.634628 0.554631
H -2.260131 -2.400694 1.618831
H -1.176323 -0.986398 1.751597
H -3.850809 -2.116496 -0.788238
H -3.693928 -0.507836 -1.530501
H -3.881899 -0.662442 1.189649
H -2.652799 0.402981 0.477248
---

TS1_ZnH2_mono

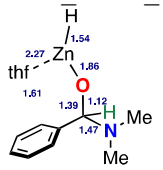



**TS1**$_{ZnH2\_mono}$

Energy (RwB97XD): -940.140967540 A.U.
Gibbs Free Energy: -939.870655 A.U.
---
Zn 0.961573 -1.967247 -0.094540
O 1.292378 -0.464084 1.287095
C 1.397882 0.385900 0.306987
H 1.211524 -0.515855 -1.031241
N 2.658005 0.912484 0.046268
C 3.754292 -0.016309 0.258139
H 4.702075 0.519037 0.164066
H 3.687117 -0.463205 1.249658
H 3.725627 -0.823693 -0.497920
C 2.826925 1.734587 -1.139973
H 3.833572 2.159569 -1.133578
H 2.702217 1.135543 -2.058572
H 2.109035 2.556259 -1.152771
C 0.231298 1.344224 0.117150
C -0.377104 1.607882 -1.108868
C -0.238118 1.989405 1.264965
C -1.434122 2.513498 -1.193377
H -0.022311 1.101166 -2.002114
C -1.291304 2.898044 1.182910
H 0.224547 1.773927 2.224050
C -1.892434 3.163717 -0.048138
H -1.901441 2.707296 -2.155282
H -1.645544 3.394912 2.082214
H -2.717790 3.867774 -0.112468
H 1.375818 -3.471202 -0.020556
O -1.189749 -1.787333 -0.023354
C -1.987753 -1.587225 -1.207657
C -1.899376 -1.349346 1.156095
C -3.375266 -1.211182 -0.700771
H -1.534476 -0.781292 -1.794494
H -1.966570 -2.512800 -1.789649
C -3.062221 -0.521843 0.631178
H -2.240779 -2.241102 1.695755

H -1.195996 -0.791379 1.777164
H -3.979512 -2.110101 -0.534434
H -3.903007 -0.563092 -1.405840
H -3.909032 -0.521011 1.323027
H -2.745511 0.512503 0.463534
---

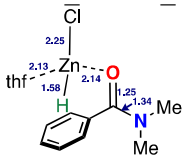
INT1_ZnH2_mono




**INT1**$_{ZnH2\_mono}$

Energy (RwB97XD): -940.180778900 A.U.
Gibbs Free Energy: -939.904911 A.U.
---
Zn 0.126589 -2.409648 0.113632
O -0.943187 -1.106769 -0.673411
C -1.582583 -0.188239 0.143428
H -1.589640 -0.527317 1.208533
N -2.983526 -0.033240 -0.280230
C -3.662227 -1.320960 -0.278097
H -4.693396 -1.189236 -0.622722
H -3.152815 -2.012840 -0.950240
H -3.693563 -1.773920 0.734287
C -3.701047 0.906246 0.569976
H -4.742249 0.973099 0.238253
H -3.701121 0.597515 1.634774
H -3.260854 1.905077 0.505417
C -0.868380 1.159138 0.106669
C -0.323733 1.715277 1.263577
C -0.741311 1.852443 -1.101507
C 0.326661 2.951807 1.225629
H -0.419771 1.184985 2.209623
C -0.097609 3.086040 -1.145496
H -1.161777 1.421111 -2.006110
C 0.436294 3.642659 0.020971
H 0.742417 3.373853 2.137221
H -0.011248 3.618488 -2.089471
H 0.938220 4.606146 -0.013868
H 0.515370 -3.730263 0.813933
O 2.095027 -1.302323 -0.138380
C 2.711904 -0.740321 1.034749
C 2.264717 -0.416485 -1.269396
C 3.696620 0.290306 0.503467
H 1.939537 -0.268453 1.656583
H 3.173348 -1.559769 1.591718
C 2.950137 0.830098 -0.720457
H 2.886450 -0.940698 -2.004191
H 1.278078 -0.219112 -1.695774
H 4.633247 -0.195180 0.206020
H 3.921907 1.063042 1.243701
H 3.610374 1.292469 -1.459411
H 2.203116 1.567789 -0.412380
---

INT0_ZnHCl_mono

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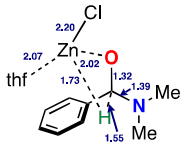
TS1_ZnHCl_mono




**TS1**$_{ZnHCl\_mono}$

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Gibbs Free Energy: -1399.536987 A.U.

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| H | 1.235667 | 3.337075 | 1.093460 |
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| C | 2.197923 | 1.119217 | -1.207886 |
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| H | 1.257424 | 0.644886 | 2.018915 |
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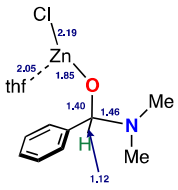
INT1_ZnHCl_mono




**INT1**$_{ZnHCl\_mono}$

Energy (RwB97XD): -1399.83854305 A.U.

Gibbs Free Energy: -1399.570306 A.U.

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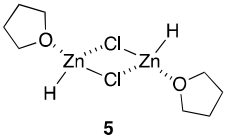


**5**

Energy (RM062X): -4945.52516323 A.U.
Gibbs Free Energy: -4945.322142 A.U.
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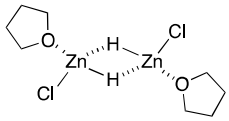


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### 6.4.8. References for section 6.4

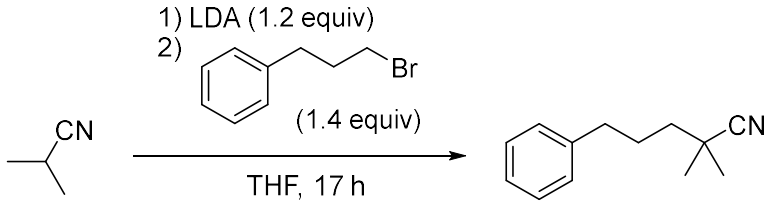

1. C. Dunst, P. Knochel, *Synlett* **2011,** *22*, 2064-2068.
2. G. H. Chan, D. Y. Ong, Z. Yen, C. Shunsuke, *Helv. Chim. Acta* **2018,** *101*, e1800049.
3. S. C. Wilson, P. W. Howard, D. E. Thurston, *Tetrahedron Lett.* **1995,** *36*, 6333-6336.
4. A. Armstrong, J. N. Scutt, *Org. Lett.* **2003,** *5*, 2331-2334.
5. A. K. Chakraborti, S. V. Chankeshwara, *J. Org. Chem.* **2009,** *74*, 1367-1370.
6. B. Gabriele, R. Mancuso, G. Salerno, *J. Org. Chem.* **2008,** *73*, 7336-7341.
7. T. J. Wenzel, *Discrimination of Chiral Compounds Using NMR Spectroscopy*. Wiley: 2007.
8. G. Cai, Y. Fu, Y. Li, X. Wan, Z. Shi, *J. Am. Chem. Soc.* **2007,** *129*, 7666-7673.
9. S. Hanada, E. Tsutsumi, Y. Motoyama, H. Nagashima, *J. Am. Chem. Soc.* **2009,** *131*, 15032-15040.
10. O. O. Kovalenko, A. Volkov, H. Adolfsson, *Org. Lett.* **2015,** *17*, 446-449.
11. F. Tinnis, A. Volkov, T. Slagbrand, H. Adolfsson, *Angew. Chem. Int. Ed.* **2016,** *55*, 4562-4566.
12. H. Jenkner, US3116112A, **1953**.
13. C. G. Shull, E. O. Wollan, G. A. Morton, W. L. Davidson, *Phys. Rev.* **1948,** *73*, 842-847.
14. A. W. Hull, *Phys. Rev.* **1917,** *10*, 661-696.
15. J. J. Watkins, E. C. Ashby, *Inorg. Chem.* **1974,** *13*, 2350-2354.
16. D. L. Pavia, G. M. Lampman, G. S. Kriz, J. R. Vyvyan, *Introduction to spectroscopy*. Stamford, CT : Cengage Learning, [2015] Fifth edition.: 2015.
17. M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. J. A. Montgomery, J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Coss, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, *Gaussian 09, revision B.01, Gaussian, Inc., Wallingford CT* **2010**.
18. J.-D. Chai, M. Head-Gordon, *Phys. Chem. Chem. Phys.* **2008,** *10*, 6615-6620.
19. J.-D. Chai, M. Head-Gordon, *J. Chem. Phys.* **2009,** *131*, 174105.
20. P. Fuentealba, H. Preuss, H. Stoll, L. Von Szentpály, *Chemical Physics Letters* **1982,** *89*, 418-422.
21. L. von Szentpály, P. Fuentealba, H. Preuss, H. Stoll, *Chemical Physics Letters* **1982,** *93*, 555-559.
22. M. J. Frisch, J. A. Pople, J. S. Binkley, *J. Chem. Phys.* **1984,** *80*, 3265-3269.
23. K. Fukui, *Acc. Chem. Res.* **1981,** *14*, 363-368.

24. K. Ishida, K. Morokuma, A. Komornicki, *J. Chem. Phys.* **1977,** *66*, 2153-2156.
25. C. Gonzalez, H. B. Schlegel, *The Journal of Physical Chemistry* **1990,** *94*, 5523-5527.
26. A. V. Marenich, C. J. Cramer, D. G. Truhlar, *The Journal of Physical Chemistry B* **2009,** *113*, 6378-6396.
27. Y. Zhao, D. G. Truhlar, *Theoretical Chemistry Accounts* **2008,** *120*, 215-241.
28. Y. Zhao, D. G. Truhlar, *Acc. Chem. Res.* **2008,** *41*, 157-167.
29. T. H. D. Jr., *J. Chem. Phys.* **1989,** *90*, 1007-1023.
30. S. Maeda, Y. Harabuchi, Y. Osada, T. Taketsugu, K. Morokuma, K. Ohno, *GRRM 14, Version 14.01* **2014**.
31. S. Maeda, K. Ohno, K. Morokuma, *Phys. Chem. Chem. Phys.* **2013,** *15*, 3683-3701.
32. K. Ohno, S. Maeda, *Chemical Physics Letters* **2004,** *384*, 277-282.
33. S. Maeda, K. Ohno, *J. Phy. Chem. A* **2005,** *109*, 5742-5753.
34. K. Ohno, S. Maeda, *J. Phy. Chem. A* **2006,** *110*, 8933-8941.

## 6.5. Experimental data for Chapter 5

### 6.5.1. Synthesis of nitriles

#### 6.5.1.1. Synthesis of 2,2-dimethyl-5-phenylpentanenitrile (5.6a)



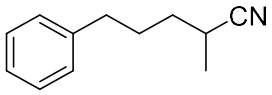

To a solution of diisopropylamine (3.70 mL, 26.4 mmol) in THF (66 mL) at -78 °C was added n-BuLi (2.2 M in *n*-hexane, 11.0 mL, 24.2 mmol) slowly and the mixture was stirred for 30 min. To the mixture at -78 °C was added isobutyronitrile (1.39 g, 20.1 mmol). After being stirred at the same temperature for 30 min, (3-bromopropyl)benzene (4.30 mL, 28.3 mmol) was added. The reaction mixture was slowly warmed up to 24 °C with stirring overnight. The reaction mixture was then quenched with saturated aqueous $NH_4Cl$ solution and the organic materials were extracted thrice with diethyl ether. The combined extracts were washed with brine and dried over $MgSO_4$. The solvent was removed *in vacuo* and the resulting crude mixture was purified by flash column chromatography (silica gel, hexane:ethyl acetate = 24:1) to give a colourless oil **5.6a** (3.08 g, 16.5 mmol) in 82% yield.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.29 (dd, $J$ = 7.3, 7.3 Hz, 2H), 7.21 – 7.17 (m, 3H), 2.66 (t, $J$ = 7.6 Hz, 2H), 1.86 – 1.78 (m, 2H), 1.57 – 1.52 (m, 2H), 1.32 (s, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 141.4, 128.1, 128.3, 126.0, 125.1, 40.5, 35.7, 32.3, 26.9, 26.6.

**ESIHRMS**: Found: m/z 188.1432; Calcd for $C_{13}H_{18}N$: $(M+H)^+$ 188.1439

### 6.5.1.2. Synthesis of 2-methyl-5-phenylpentanenitrile (5.6o)



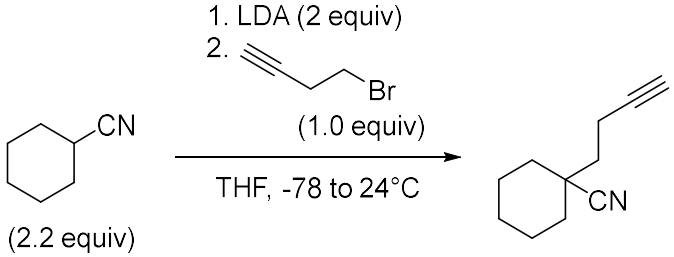

Prepared by following the experimental procedure in section **6.5.1.1.** from propiononitrile (1.10 g, 20.0) and purified by flash column chromatography (silica gel, Hex:EtOAc = 99:1) to give a colourless oil **5.6o** (1.81 g, 10.5 mmol) in 52% yield

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.29 (t, *J* = 7.3 Hz, 2H), 7.21 – 7.16 (m, 3H), 2.66 (t, *J* = 7.5 Hz, 1H), 2.63 – 2.56 (m, 1H), 1.93 – 1.83 (m, 1H), 1.80 – 1.71 (m, 1H), 1.69 – 1.52 (m,2), 1.30 (d, *J* = 7.1 Hz, 3H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 141.3, 128.4, 128.3, 126.0, 122.8, 35.2, 33.4, 28.6, 25.4, 17.9

**ESIHRMS**: Found: m/z 174.1285; Calcd for $C_{12}H_{16}N$: $(M+H)^+$ 174.1283

### 6.5.1.3. Synthesis of 1-(but-3-yn-1-yl)cyclohexane-1-carbonitrile (5.6m')




**5.6m'**

To a solution of diisopropylamine (2.95 mL, 20.9 mmol) in THF (40 mL) at -78 °C was added n-BuLi (1.5 M in *n*-hexane, 13.6 mL, 20.0 mmol) slowly and the mixture was stirred for 30 min. To the mixture at -78 °C was added cyclohexanecarbonitrile (2.6 mL g, 21.9 mmol). After being stirred at the same temperature for 30 min, 4-bromobut-1-yne (0.94 mL, 10.0 mmol) was added. The reaction mixture was slowly warmed up to

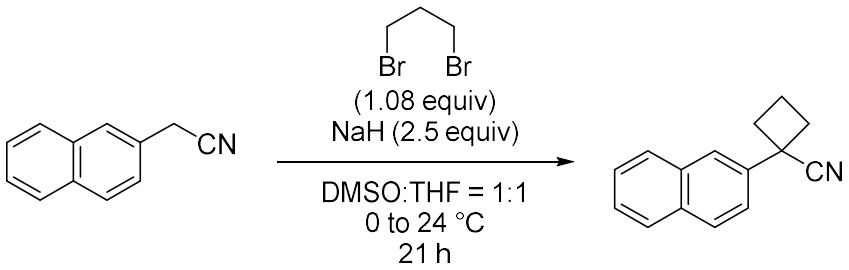
24 °C with stirring overnight. The reaction mixture was then quenched with 1M HCl solution and the organic materials were extracted three times with diethyl ether. The combined extracts were washed with brine and dried over $MgSO_4$. The solvent was removed *in vacuo* and the resulting crude mixture was purified by flash column chromatography (silica gel, hexane:ethyl acetate = 24:1) to give a colourless oil **5.6m'** (1.57 g, 9.76 mmol) in 97% yield.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 2.43 – 2.38 (m, 2H), 2.00 – 1.97 (m, 3H), 1.84 – 1.80 (m, 2H), 1.76 – 1.72 (m, 3H), 1.67 – 1.56 (m, 2H), 1.30 – 1.14 (m, 3H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 122.8, 83.0, 69.1, 39.1, 38.8, 35.4, 25.3, 22.9, 14.2.

**ESIHRMS**: Found: 162.1278 m/z; Calcd for $C_{11}H_{16}N$: $(M+H)^+$ 162.1283

### 6.5.1.4. Synthesis of 1-(naphthalen-2-yl)cyclobutane-1-carbonitrile (5.6g)




2-(naphthalen-2-yl)acetonitrile (1.67 g, 10.0 mmol) and 1,3-dibromopropane (1.1 mL, 10.8 mmol) in THF (20 mL) was added dropwise to a mixture of sodium hydride (60% dispersion in mineral oil; 1.00 g, 25.0 mmol) in DMSO (20 mL) at 0 °C. The mixture was allowed to warm up to 25 °C and stirred for 21 h. The reaction mixture was quenched with water at 0 °C. The organic materials were extracted three times with diethyl ether. The combined extracts were washed with brine and dried over $MgSO_4$. The solvent was removed *in vacuo* and the resulting crude mixture was purified by flash

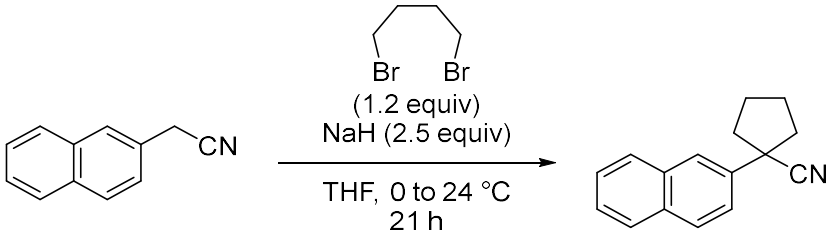
column chromatography (silica gel, hexane:ethyl acetate = 49:1) to give a white solid **5.6g** (1.10 g, 5.29 mmol) in 53% yield.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.90 – 7.83 (m, 4H), 7.54 – 7.48 (m, 3H), 2.94 – 2.87 (m, 2H), 2.78 – 2.70 (m, 2H), 2.49 (dtt, *J* = 11.7, 8.9, 8.9 Hz, 1H), 2.14 (dtt, *J* = 11.7, 8.9, 4.6 Hz, 1H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 136.9, 133.1, 132.6, 129.1, 128.0, 127.6, 126.7, 126.5, 124.4 (overlapped), 123.4, 40.3, 34.6, 17.1.

**ESIHRMS**: Found: m/z 208.1132; Calcd for $C_{15}H_{14}N$: $(M+H)^+$ 208.1126

### 6.5.1.5. Synthesis of 1-(naphthalen-2-yl)cyclopentane-1-carbonitrile (5.6h)



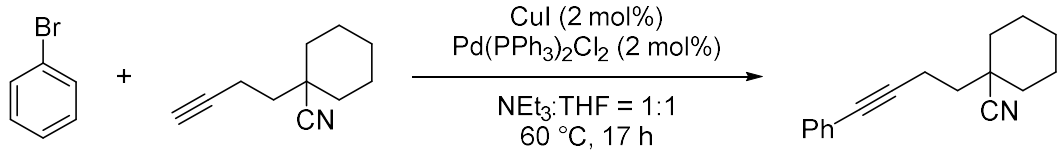

A mixture of sodium hydride (60% dispersion in mineral oil; 1.00 g, 25.0 mmol) in THF (10 mL) at 0 °C was added a solution of 2-(naphthalen-2-yl)acetonitrile (1.69 g, 10.1 mmol) in THF (10 mL). The reaction mixture was allowed to stir for 1 h at 24 °C. To the resulting mixture at 0 °C, 1,4-dibromobutane (1.4 mL, 11.7 mmol) was added. The mixture was allowed to warm up to 24 °C and stirred for another 21 h. The reaction mixture was quenched with water at 0 °C. The organic materials were extracted thrice with diethyl ether. The combined extracts were washed with brine and dried over $MgSO_4$. The solvent was removed *in vacuo* and the resulting crude mixture was purified by flash column chromatography (silica gel, hexane:ethyl acetate = 49:1) to give a white solid **5.6h** (1.83 g, 8.19 mmol) in 82% yield.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.94 (d, *J* = 1.7 Hz, 1H), 7.87 – 7.81 (m, 3H), 7.53 – 7.47 (m, 3H), 2.58 – 2.52 (m, 2H), 2.23 – 2.16 (m, 2H), 2.15 – 2.04 (m, 2H), 2.03 – 1.94 (m, 2H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 137.0, 133.1, 132.6, 128.8, 128.0, 127.5, 126.6, 126.4, 124.8, 124.4, 123.8, 47.9, 40.5, 24.4.

**ESIHRMS**: Found: m/z 222.1285; Calcd for $C_{16}H_{16}N$: $(M+H)^+$ 222.1283

### 6.5.1.6. Synthesis of 1-(3-phenylprop-2-yn-1-yl)cyclohexane-1-carbonitrile (5.6m)




**5.6m'**

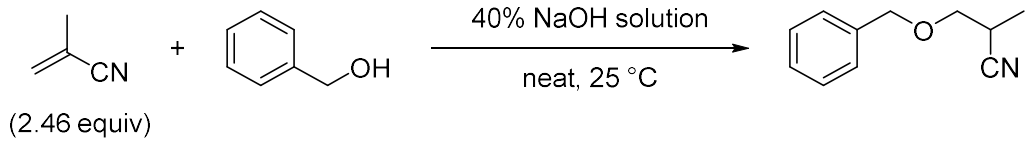
A mixture of **5.6m'** (646 mg, 4.01 mmol), bromobenzene (420 µL, 3.99 mmol), $PdCl_2(PPh_3)_2$ (56.5 mg, 0.0805 mmol), CuI (15.5 mg, 0.0814 mmol), $NEt_3$ (4.0 mL) and THF (4 mL) were stirred at 60 ˚C for 17 h. The reaction mixture was filtered through a pad of celite and the solvent was removed from the filtrate *in vacuo*. the resulting crude mixture was purified by flash column chromatography (silica gel, hexane:ethyl acetate = 48:1) to give a pale yellow oil **5.6m** (665 mg, 2.80 mmol) in 70% yield.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.41 – 7.37 (m, 2H), 7.31 – 7.27 (m, 3H), 2.64 (d, *J* = 7.9 Hz, 1H), 2.62 (d, *J* = 8.2 Hz, 1H), 2.03 (d, *J* = 13.3 Hz, 2H), 1.90 (d, *J* = 8.2 Hz, 1H), 1.88 (d, *J* = 7.9 Hz, 1H), 1.78 – 1.72 (m, 3H), 1.69 – 1.58 (m, 2H), 1.30 (td, J = 13.1, 3.5 Hz, 2H), 1.20 (tdd, J = 13.1, 9.1, 4.1 Hz, 1H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 131.5, 128.2, 127.8, 123.5, 123.0, 88.5, 81.3, 39.3, 38.8, 35.5, 25.3, 23.0, 15.2.

**ESIHRMS**: Found: m/z 238.1595; Calcd for $C_{17}H_{20}N$: $(M+H)^+$ 238.1596

### 6.5.1.7. Synthesis of 3-(benzyloxy)-2-methylpropanenitrile (5.6p)



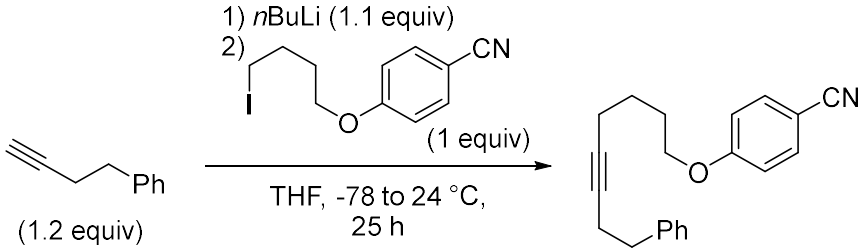

To a mixture of phenylmethanol (1.00 mL, 9.66 mmol) and 40% NaOH solution in water (100 µL) was added methacrylonitrile [CAS: 126-98-7] (2 mL, 23.8 mmol). The reaction mixture was stirred at 25 °C for 75 h. The reaction was neutralized with 1M HCl to about pH 7. The organic materials were extracted with EtOAc (20 mL × 3). The combined organic layer was washed with saturated $NaHCO_3$ solution and dried with $MgSO_4$. The volatile materials was removed in vacuo and the resulting crude mixture was purified by flash column chromatography (silica gel, Hex:EtOAc = 19:1) to give a colorless oil (E)-2,2-dimethyl-5-phenylpent-4-enenitrile **5.6p** (0.803 g, 4.58 mmol) in 47% yield.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.39 – 7.28 (m, 5H), 4.59 (s, 2H), 3.57 (dd, *J* = 9.2, 7.1 Hz, 1H), 3.52 (dd, *J* = 9.2, 6.1 Hz, 1H)., 2.88 (qdd, *J* = 7.1, 7.1, 6.1 Hz, 1H), 1.33 (d, *J* = 7.1 Hz, 3H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 137.3, 128.5, 127.9, 127.7, 121.4, 73.3, 70.6, 26.5, 14.7.

**ESIHRMS**: Found: m/z 176.1071; Calcd for $C_{11}H_{14}NO$: $(M+H)^+$ 176.1075

### 6.5.1.8. Synthesis of 4-((8-phenyloct-5-yn-1-yl)oxy)benzonitrile (5.6l)




To a solution of but-3-yn-1-ylbenzene [CAS: 16520-62-0] (1.0 mL, (0.711 mmol) in THF (12.0 mL) at -78 °C was added nBuLi (1.47 M in n-hexane, 4.5 mL, 6.62 mmol) slowly and the reaction mixture was stirred for 1 hr. To the mixture at -78 °C was added a solution of 4-(4-iodobutoxy)benzonitrile[1] (1.81 g, 6.00 mmol) in THF (12.0 mL). The reaction mixture was slowly warmed up to 24 °C with stirring overnight. The reaction mixture was then quenched with saturated aqueous $NH_4Cl$ solution and the organic materials were extracted thrice with diethyl ether. The combined extracts were washed with brine and dried over $MgSO_4$. The solvent was removed *in vacuo* and the resulting crude mixture was purified by flash column chromatography (silica gel, hexane:ethyl acetate = 49:1) to give a colourless oil **5.6l** (0.236 g, 0.778 mmol) in 13% yield.

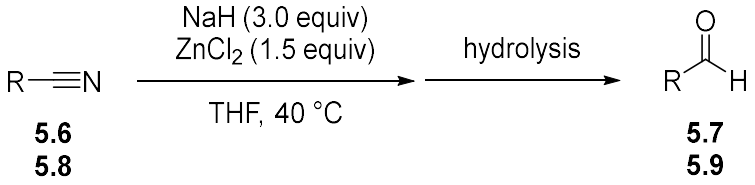
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.8 Hz, 2H), 7.28 (dd, *J* = 8.6, 8.6 Hz, 2H), 7.22 – 7.18 (m, 3H), 6.92 (d, *J* = 8.8 Hz, 2H), 3.99 (t, *J* = 6.3 Hz, 2H), 2.79 (t, *J* = 7.5 Hz, 2H), 2.44 (t, *J* = 7.5 Hz, 2H), 2.22 (t, *J* = 6.9 Hz, 2H), 1.90 – 1.83 (m, 2H), 1.68 – 1.60 (m, 2H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 162.3, 140.9, 134.0, 128.4, 128.3, 126.2, 119.3, 115.2, 103.8, 80.17, 80.15, 67.8, 35.5, 28.0, 25.3, 20.9, 18.4.

**ESIHRMS**: Found: 304.1709 m/z; Calcd for $C_{21}H_{22}NO$: $(M+H)^+$ 304.1661

### 6.5.2. Synthesis of aldehydes 5.7 and 5.9

#### 6.5.2.1. General procedure for reduction of nitriles 5.6 or 5.8 to aldehydes 5.7 or 5.9




**5.6**
**5.8**

**5.7**
**5.9**

To a mixture of NaH (60% dispersion in mineral oil; 60.0 mg, 1.50 mmol) and $ZnCl_2$ (102 mg, 0.750 mmol) in a 25 mL sealed tube was added a solution of nitrile **5.6** or **5.8** (0.500 mmol) in 2.5 mL of THF. The reaction mixture was sealed and stirred at 40 °C. The reaction was quenched by following one of the two protocols described below.

**Work-up protocol 1:**

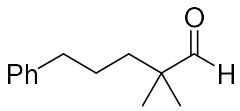
Upon full consumption of nitrile based on TLC or GC, Silica gel (2.0 g) was added to the reaction mixture and was diluted with hexane (10 mL) at 0°C. The resulting reaction mixture was stirred for 1 h at 24 °C. The mixture was then filtered through layers of cotton and sand and wash with ethyl acetate. The volatile materials were removed in vacuo from the resulting filtrate. The crude residue was purified by flash column chromatography to give the corresponding aldehyde **5.7** or **5.9**.

**Work-up protocol 2:**

Upon full consumption of amide based on TLC or GC, the reaction was quenched with pH 10 ammonium buffer at 0 °C and the organic materials were extracted with dichloromethane (20 mL × 3). The combined organic extracts were dried over MgSO4. The volatile materials were removed in vacuo and the resulting crude residue was purified by flash column chromatography to give the corresponding aldehyde **5.7** or **5.9.**

### 6.5.2.2. Synthesis of α-quaternary aliphatic aldehydes 5.7

#### 6.5.2.2.1. Synthesis of 2,2-dimethyl-5-phenylpentanal (5.7a)[2]




Prepared from nitrile **5.7a** (93.6 mg, 0.500 mmol) for 3 h with work-up protocol 2.

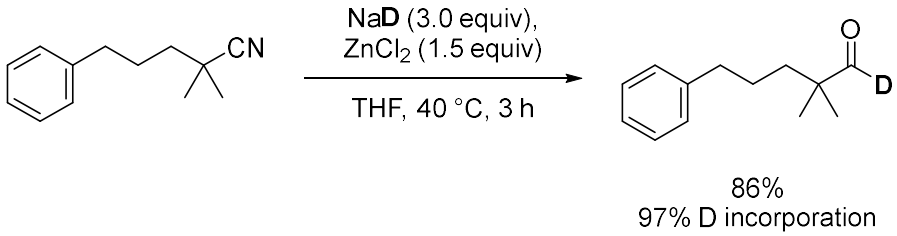
Purification: Hex:EtOAc = 98:2.

Yield: 85% yield (80.5 mg, 0.423 mmol) as clear oil.

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 9.42 (s, 1H), 7.28 (dd, *J* = 7.3, 7.3 Hz, 2H), 7.20 – 7.15 (m, 3H), 2.60 (t, *J* = 7.1 Hz, 2H), 1.57 – 1.48 (m, 4H), 1.03 (s, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 206.3, 141.9, 128.33, 128.32, 125.8, 45.7, 36.7, 36.3, 26.1, 21.3.

#### 6.5.2.2.2. Synthesis of deuterated 2,2-dimethyl-5-phenylpentanal (5.7a-*d*)[2]




Prepared from **5.6a** (93.7 mg, 0.500 mmol) for 3 h by slightly modifying the procedure described in section **6.5.2.1** using NaD[3] containing ca. 4% of metallic Na (39.0 mg, 1.56 mmol) instead of NaH.

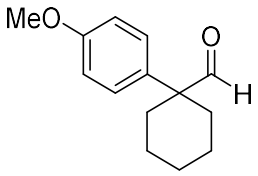
Purification: Hex:EtOAc = 49:1

Yield: 86% (82.4 mg, 0.431mmol, 97% D incorporation) as a clear oil.

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 9.42 (s, 0.03H of **5.7a**), 7.27 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.19 – 7.14 (m, 3H), 2.59 (t, *J* = 7.1 Hz, 2H), 1.59 – 1.46 (m, 4H), 1.03 (s, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 205.9 (t, *J* = 25.7 Hz), 141.9, 128.3, 125.8, 45.53 (t, *J* = 3.1 Hz), 36.7, 36.3, 26.0, 21.2.

#### 6.5.2.2.3. Synthesis of 1-(4-methoxyphenyl)cyclohexane-1-carbaldehyde (5.7b)[4]




Prepared from nitrile **5.6b** (107 mg, 0.499 mmol) for 4 h with work-up protocol 2.

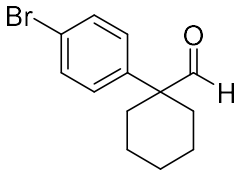
Purification: Hex:EtOAc = 97:3.

Yield: 84% yield (91.2 mg, 0.418 mmol) as clear oil.

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 9.32 (s, 1H), 7.23 (d, *J* = 8.9 Hz, 2H), 6.90 (d, *J* = 8.9 Hz, 2H), 3.80 (s, 3H), 2.30 – 2.24 (m, 2H), 1.84 – 1.77 (m, 2H), 1.70 – 1.63 (m, 3H), 1.52 – 1.42 (m, 2H), 1.34 – 1.26 (m, 1H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 202.3, 158.7, 131.5, 128.3, 114.2, 55.2, 53.6, 31.3, 25.6, 22.8.

#### 6.5.2.2.4. Synthesis of 1-(4-bromophenyl)cyclohexane-1-carbaldehyde (5.7c)[5]




Prepared from nitrile **5.6c** (132 mg, 0.499 mmol) for 3 h with work-up protocol 1.

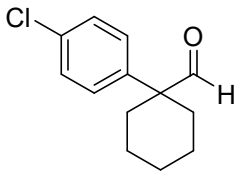
Purification: Hex:EtOAc = 98:2.

Yield: 87% yield (116 mg, 0.434 mmol) as white solid.

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 9.35 (s, 1H), 7.49 (d, *J* = 8.7 Hz, 2H), 7.19 (d, *J* = 8.7 Hz, 2H), 2.28 – 2.24 (m, 2H), 1.85 – 1.78 (m, 2H), 1.69 – 1.56 (m, 3H), 1.52 – 1.42 (m, 2H), 1.37 – 1.26 (m, 1H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 201.9, 138.8, 131.9, 128.9, 121.4, 54.1, 31.2, 25.5, 22.7.

### 6.5.2.2.5. Synthesis of 1-(4-chlorophenyl)cyclohexane-1-carbaldehyde (5.7d)[5]




Prepared from nitrile **5.6d** (110 mg, 0.498 mmol) for 3 h with work-up protocol 1.

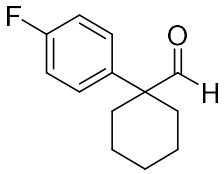
Purification: Hex:EtOAc = 98:2.

Yield: 85% yield (94.3 mg, 0.423 mmol) as white solid.

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 9.35 (s, 1H), 7.34 (d, *J* = 8.6 Hz, 2H), 7.25 (d, *J* = 8.6 Hz, 2H), 2.29 – 2.26 (m, 2H), 1.85 – 1.78 (m, 2H), 1.67 – 1.63 (m, 3H), 1.53 – 1.44 (m, 2H), 1.35 – 1.31 (m, 1H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 201.9, 138.2, 133.3, 129.0, 128.5, 54.0, 31.3, 25.5, 22.7.

### 6.5.2.2.6. Synthesis of 1-(4-fluorophenyl)cyclohexane-1-carbaldehyde (5.7e)[5]




Prepared from nitrile **5.6e** (101 mg, 0.499 mmol) for 3 h with work-up protocol 1.

Purification: Hex:EtOAc = 98:2.

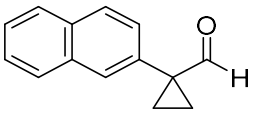
Yield: 83% yield (85.5 mg, 0.415 mmol) as clear oil.

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 9.34 (s, 1H), 7.28 (dd, *J* = 8.7, 5.4 Hz, 2H), 7.05 (dd, *J* = 8.7, 8.7 Hz, 2H), 2.31 – 2.27 (m, 2H), 1.84 – 1.77 (m, 2H), 1.68 – 1.59 (m, 3H), 1.52 – 1.43 (m, 2H), 1.35 – 1.26 (m, 1H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 202.1, 161.9 (d, *J* = 246.7 Hz), 135.4, 128.7 (d, *J* = 8.0 Hz), 115.7 (d, *J* = 21.2 Hz), 53.8, 31.4, 25.5, 22.7.

**$^{19}$F NMR** (376 MHz, $CDCl_3$): δ -115.3 – -115.4 (m).

#### 6.5.2.2.7. Synthesis of 1-(naphthalen-2-yl)cyclopropane-1-carbaldehyde (5.7f)




Prepared from nitrile **5.6f** (96.7 mg, 0.500 mmol) for 4 h with work-up protocol 2.

Purification: Hex:EtOAc = 96:4.

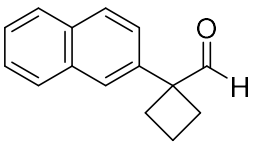
Yield: 84% yield (82.3 mg, 0.419 mmol) as white solid.

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 9.35 (s, 1H), 7.85 – 7.80 (m, 3H), 7.76 (s, 1H), 7.50 – 7.45 (m, 2H), 7.43 (dd, *J* = 8.5, 1.7 Hz, 1H), 1.66 – 1.63 (m, 2H), 1.52 – 1.49 (m, 2H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 201.0, 135.0, 133.3, 132.8, 128.8, 128.3, 128.0, 127.71, 127.65, 126.3, 126.1, 37.6, 16.2.

**ESIHRMS**: Found: m/z 197.0969; Calcd for $C_{14}H_{13}O$: $(M+H)^+$ 197.0966

#### 6.5.2.2.8. Synthesis of 1-(naphthalen-2-yl)cyclobutane-1-carbaldehyde (5.7g)




Prepared from nitrile **5.6g** (104 mg, 0.500 mmol) for 3 h with work-up protocol 2.

Purification: Hex:EtOAc = 98:2.

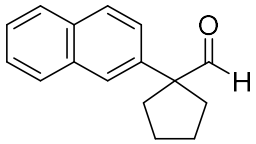
Yield: 82% yield (85.9 mg, 0.409 mmol) as clear oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 9.61 (s, 1H), 7.85 – 7.81 (m, 3H), 7.62 (s, 1H), 7.51 – 7.45 (m, 2H), 7.24 (dd, *J* = 8.4, 1.9 Hz, 1H), 2.85 – 2.79 (m, 2H), 2.55 – 2.48 (m, 2H), 2.12 – 1.92 (m, 2H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 199.4, 138.2, 133.4, 132.3, 128.7, 127.72, 127.68, 126.4, 126.0, 125.2, 124.4, 57.7, 28.4, 15.9

**ESIHRMS**: Found: m/z 211.1122; Calcd for $C_{15}H_{15}O$: $(M+H)^+$ 211.1123

### 6.5.2.2.9. Synthesis of 1-(naphthalen-2-yl)cyclopentane-1-carbaldehyde (5.7h)




Prepared from nitrile **5.6h** (111 mg, 0.500 mmol) for 3 h with work-up protocol 2.

Purification: Hex:EtOAc = 98:2.

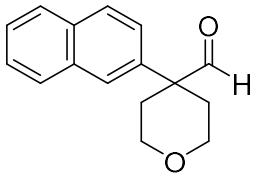
Yield: 82% yield (91.5 mg, 0.408 mmol) as white solid.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 9.48 (s, 1H), 7.83 – 7.80 (m, 3H), 7.72 (s, 1H), 7.51 – 7.45 (m, 2H), 7.35 (dd, *J* = 8.6, 1.8 Hz, 1H), 2.65 – 2.59 (m, 2H), 2.04 – 1.97 (m, 2H), 1.84 – 1.76 (m, 2H), 1.74 – 1.67 (m, 2H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 200.7, 137.7, 133.4, 132.4, 128.5, 127.9, 127.5, 126.33, 126.28, 126.1, 125.8, 63.8, 32.5, 24.3.

**ESIHRMS**: Found: m/z 225.1276; Calcd for $C_{16}H_{17}O$: $(M+H)^+$ 225.1279

**6.5.2.2.10. Synthesis of 4-(naphthalen-2-yl)tetrahydro-2*H*-pyran-4-carbaldehyde (5.7i)**



Prepared from nitrile **5.6i** (119 mg, 0.499 mmol) for 3 h with work-up protocol 1.

Purification: Hex:EtOAc = 90:10.

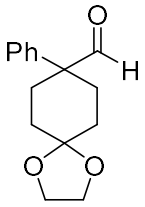
Yield: 79% yield (94.8 mg, 0.394 mmol) as white solid.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 9.47 (s, 1H), 7.87 – 7.82 (m, 3H), 7.75 (s, 1H), 7.53 – 7.48 (m, 2H), 7.38 (dd, *J* = 8.7, 1.9 Hz, 1H), 3.95 (ddd, *J* = 11.8, 4.0, 4.0 Hz, 2H), 3.65 (ddd, *J* = 11.8, 11.8, 2.4 Hz, 2H), 2.52 – 2.49 (m, 2H), 2.24 – 2.16 (m, 2H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 200.8, 135.8, 133.4, 132.6, 128.9, 128.0, 127.5, 126.5 (overlapped), 126.2, 124.2, 64.9, 52.3, 31.2.

**ESIHRMS**: Found: m/z 241.1230; Calcd for $C_{16}H_{17}O_2$: $(M+H)^+$ 241.1229

**6.5.2.2.11. Synthesis of 8-phenyl-1,4-dioxaspiro[4.5]decane-8-carbaldehyde (5.7j)[6]**



Prepared from nitrile **5.6j** (122 mg, 0.501 mmol) for 3 h with work-up protocol 2.

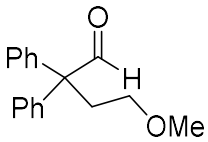
Purification: Hex:EtOAc = 85:15.

Yield: 72% yield (88.3 mg, 0.359 mmol) as white solid.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 9.41 (s, 1H), 7.37 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.32 (d, *J* = 7.5 Hz, 2H), 7.27 (t, *J* = 7.4 Hz, 1H), 3.97 – 3.91 (m, 4H), 2.38 – 2.35 (m, 2H), 2.18 – 2.11 (m, 2H), 1.77 – 1.65 (m, 4H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 201.4, 138.3, 128.9, 127.4, 127.1, 108.1, 64.31, 64.28, 53.5, 31.5, 28.4.

### 6.5.2.2.12. Synthesis of 4-methoxy-2,2-diphenylbutanal (5.7k)




Prepared from nitrile **5.6k** (126 mg, 0.500mmol) for 3 h with work-up protocol 1.

Purification: Hex:EtOAc = 96:4.

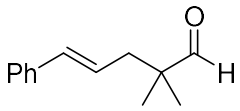
Yield: 75% yield (94.8 mg, 0.373 mmol) as clear oil.

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 9.74 (s, 1H), 7.36 (dd, *J* = 7.2, 7.2 Hz, 4H), 7.30 (t, *J* = 7.2 Hz, 2H), 7.21 (d, *J* = 7.2 Hz, 4H), 3.22 (s, 3H), 3.16 (t, *J* = 7.0 Hz, 2H), 2.60 (t, *J* = 7.0 Hz, 2H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 197.9, 140.0, 129.0, 128.6, 127.4, 69.1, 61.7, 58.6, 34.4.

**ESIHRMS**: Found: m/z 255.1380; Calcd for $C_{17}H_{19}O_2$: $(M+H)^+$ 255.1385

### 6.5.2.2.13. Synthesis of (E)-2,2-dimethyl-5-phenylpent-4-enal (5.7l)[7]




Prepared from nitrile **5.6l** (92.4 mg, 0.499 mmol) for 3 h with work-up protocol 2.

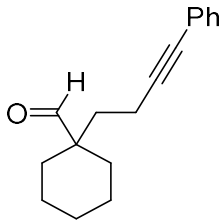
Purification: Hex:EtOAc = 98:2.

Yield: 80% yield (75.4 mg, 0.401 mmol) as clear oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 9.54 (s, 1H), 7.33 (d, *J* = 7.3 Hz, 2H), 7.29 (dd, *J* = 7.3, 7.3 Hz, 2H), 7.21 (t, *J* = 7.3 Hz, 1H), 6.42 (dt, *J* = 15.6, 1.2 Hz, 1H), 6.11 (dt, *J* = 15.6, 7.6 Hz, 1H), 2.37 (dd, *J* = 7.6, 1.2 Hz, 2H), 1.11 (s, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 205.9, 137.1, 133.5, 128.5, 127.3, 126.1, 124.8, 46.3, 40.6, 21.4.

### 6.5.2.2.14. Synthesis of 1-(4-phenylbut-3-yn-1-yl)cyclohexane-1-carbaldehyde (5.7m)




Prepared from nitrile **5.6m** (119 mg, 0.501 mmol) for 3 h with work-up protocol 2.

Purification: Hex:EtOAc = 98:2.

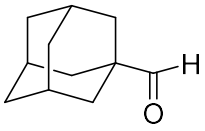
Yield: 81% yield (97.1 mg, 0.404 mmol) as pale yellow oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 9.53 (s, 1H), 7.37 (d, *J* = 7.4 Hz, 2H), 7.28 – 7.26 (m, 3H), 2.32 (t, *J* = 7.8 Hz, 2H), 1.93 – 1.89 (m, 2H), 1.83 (t, *J* = 7.8 Hz, 2H), 1.63 – 1.52 (m, 3H), 1.42 – 1.29 (m, 4H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 206.4, 131.4, 128.2, 127.7, 123.6, 89.5, 81.3, 49.3, 35.2, 30.7, 25.7, 22.3, 14.3.

**ESIHRMS**: Found: m/z 241.1600; Calcd for $C_{17}H_{21}O$: $(M+H)^+$ 241.1592

### 6.5.2.2.15. Synthesis of (3*r*,5*r*,7*r*)-adamantane-1-carbaldehyde (5.7n)[8]



Prepared from nitrile **5.6n** (80.8 mg, 0.501 mmol) for 1 h with work-up protocol 2.

Purification: Pentane:EtOAc = 98:2.

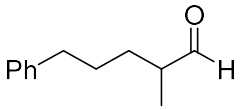
Yield: 77% yield (63.1 mg, 0.387 mmol) as white solid.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 9.32 (s, 1H), 2.08 – 2.07 (m, 3H), 1.80 – 1.68 (m, 12H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 206.0, 44.8, 36.6, 35.9, 27.4.

### 6.5.2.3. Synthesis of α-tertiary and secondary aliphatic aldehydes 5.7

#### 6.5.2.3.1. Synthesis of 2-methyl-5-phenylpentanal (5.7o)[2]




Prepared from nitrile **5.6o** (86.5 mg, 0.499 mmol) for 4 h with work-up protocol 2.

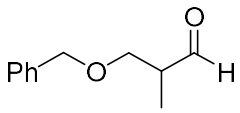
Purification: Hex:EtOAc = 98:2.

Yield: 84% yield (74.1 mg, 0.420 mmol) as clear oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 9.60 (d, $J$ = 1.9 Hz, 1H), 7.28 (dd, $J$ = 7.3, 7.3 Hz, 2H), 7.20 – 7.16 (m, 3H), 2.63 (t, $J$ = 7.4 Hz, 2H), 2.40 – 2.31 (m, 1H), 1.80 – 1.61 (m, 3H), 1.45 – 1.36 (m, 1H), 1.09 (d, $J$ = 7.0 Hz, 3H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 205.0, 141.9, 128.4 (overlapped), 125.9, 46.2, 35.8, 30.0, 28.7, 13.3.

#### 6.5.2.3.2. Synthesis of 3-(benzyloxy)-2-methylpropanal (5.7p)[9]




Prepared from nitrile **5.6p** (87.8 mg, 0.501 mmol) for 2.5 h with work-up protocol 2.

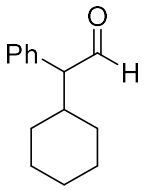
Purification: Hex:EtOAc = 90:10.

Yield: 63% yield (56.3 mg, 0.316 mmol) as clear oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 9.73 (d, *J* = 1.4 Hz, 1H), 7.37 – 7.26 (m, 5H), 4.53 (s, 2H), 3.69 (dd, *J* = 9.4, 6.9 Hz, 1H), 3.64 (dd, *J* = 9.4, 5.4 Hz, 1H), 2.67 (qddd, *J* = 6.9, 6.9, 5.4, 1.4 Hz, 1H), 1.13 (d, *J* = 6.9 Hz, 3H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 203.8, 137.9, 128.4, 127.7, 127.6, 73.3, 70.1, 46.8, 10.7.

### 6.5.2.3.3. Synthesis of 2-cyclohexyl-2-phenylacetaldehyde (5.7q)[10]




Prepared from nitrile **5.6q** (99.2 mg, 0.498 mmol) by the slightly modified procedure using NaH (120 mg, 3.00 mmol, 6 equiv) and $ZnCl_2$ (204 mg, 1.50 mmol, 3 equiv) for 4 h with work-up protocol 2.

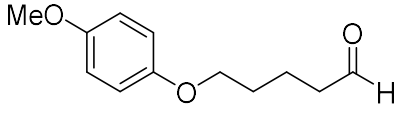
Purification: Hex:EtOAc = 98:2.

Yield: 76% yield (78.9 mg, 0.379 mmol) as clear oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 9.70 (d, *J* = 3.5 Hz, 1H), 7.36 (dd, *J* = 7.3, 7.3 Hz, 2H), 7.28 (t, *J* = 7.3 Hz, 1H), 7.18 (d, *J* = 7.3 Hz, 2H), 3.24 (dd, *J* = 9.6, 3.5 Hz, 1H), 2.15 – 2.06 (m, 1H), 1.85 – 1.81 (m, 1H), 1.78 – 1.72 (m, 1H), 1.66 – 1.62 (m, 2H), 1.43 – 1.37 (m, 1H), 1.34 – 1.26 (m, 1H), 1.22 – 1.01 (m, 3H), 0.85 – 0.75 (m, 1H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 201.2, 135.2, 129.3, 128.9, 127.4, 65.8, 38.2, 31.8, 30.2, 26.2, 26.1, 26.0.

### 6.5.2.3.4. Synthesis of 5-(4-methoxyphenoxy)pentanal (5.7r)



Prepared from nitrile **5.6r** (103 mg, 0.500 mmol) for 4 h with work-up protocol 2.

Purification: Hex:EtOAc = 88:12.

Yield: 46% yield (48.1 mg, 0.231 mmol) as clear oil.

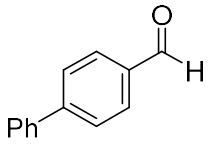
**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 9.80 (t, *J* = 1.5 Hz, 1H), 6.83 (s, 4H), 3.93 (t, *J* = 5.7 Hz, 2H), 3.77 (s, 3H), 2.53 (td, *J* = 6.9, 1.5 Hz, 2H), 1.85 – 1.79 (m, 4H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 202.3, 153.8, 153.0, 115.4, 114.6, 68.0, 55.7, 43.5, 28.7, 18.8.

**ESIHRMS**: Found: m/z 209.1171; Calcd for $C_{12}H_{17}O_3$: $(M+H)^+$ 209.1178

### 6.5.2.4. Synthesis of aromatic aldehydes 5.9

#### 6.5.2.4.1. Synthesis of [1,1'-biphenyl]-4-carbaldehyde (5.9a) [CAS No.: 3218-36-8]




Prepared from nitrile **5.8a** (89.7 mg, 0.501 mmol) for 3 h with work-up protocol 2.

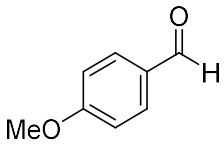
Purification: Hex:EtOAc = 96:4.

Yield: 83% yield (75.5 mg, 0.414 mmol) as white solid.

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 10.06 (s, 1H), 7.95 (d, *J* = 8.3 Hz, 2H), 7.76 (d, *J* = 8.3 Hz, 2H), 7.64 (d, *J* = 7.2 Hz, 2H), 7.48 (dd, *J* = 7.2, 7.2 Hz, 2H), 7.42 (t, *J* = 7.2 Hz, 1H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 191.9, 147.2, 139.7, 135.2, 130.3, 129.0, 128.5, 127.7, 127.4.

**6.5.2.4.2. Synthesis of 4-methoxybenzaldehyde (5.9b) [CAS No.: 123-11-5]**




Prepared from nitrile **5.8b** (66.6 mg, 0.500 mmol) for 3 h with work-up protocol 1.

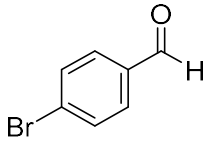
Purification: Hex:EtOAc = 94:6.

Yield: 83% yield (56.9 mg, 0.418 mmol) as clear oil.

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 9.89 (s, 1H), 7.84 (d, *J* = 8.7 Hz, 2H), 7.01 (d, *J* = 8.7 Hz, 2H), 3.89 (s, 3H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 190.8, 164.6, 132.0, 129.9, 114.3, 55.6.

**6.5.2.4.3. Synthesis of 4-bromobenzaldehyde (5.9c) [CAS No.: 1122-91-4]**




Prepared from nitrile **5.8c** (90.8 mg, 0.499 mmol) for 0.5 h with work-up protocol 1.

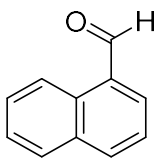
Purification: Hex:EtOAc = 98:2.

Yield: 80% yield (74.0 mg, 0.400 mmol) as white solid.

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 9.98 (s, 1H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.69 (d, *J* = 8.4 Hz, 2H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 191.0, 135.1, 132.4, 131.0, 129.8.

**6.5.2.4.4. Synthesis of 1-naphthaldehyde (5.9d) [CAS No.: 66-77-3]**




Prepared from nitrile **5.8d** (76.5 mg, 0.499 mmol) for 8 h with work-up protocol 1.

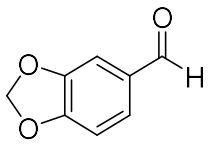
Purification: Hex:EtOAc = 98:2.

Yield: 82% yield (64.0 mg, 0.410 mmol) as pale yellow oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 10.41 (s, 1H), 9.25 (d, *J* = 8.6 Hz, 1H), 8.10 (d, *J* = 8.2 Hz, 1H), 8.00 (d, *J* = 7.0 Hz, 1H), 7.92 (d, *J* = 8.2 Hz, 1H), 7.70 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.65 – 7.58 (m, 2H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 193.5, 136.6, 135.3, 133.7, 131.4, 130.5, 129.1, 128.5, 127.0, 124.863, 124.857.

### 6.5.2.4.5. Synthesis of benzo[*d*][1,3]dioxole-5-carbaldehyde (5.9e) [CAS No.: 120-57-0]



Prepared from nitrile **5.8e** (73.7 mg, 0.501 mmol) for 2 h with work-up protocol 1.

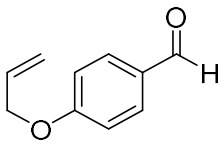
Purification: Hex:EtOAc = 90:10.

Yield: 88% yield (66.3 mg, 0.442 mmol) as white solid.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 9.81 (s, 1H), 7.42 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.34 (d, *J* = 1.5 Hz, 1H), 6.93 (d, *J* = 7.9 Hz, 1H), 6.08 (s, 2H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 190.3, 153.1, 148.7, 131.9, 128.6, 108.3, 106.9, 102.1.

### 6.5.2.4.6. Synthesis of 4-(allyloxy)benzaldehyde (5.9f)[11]



Prepared from nitrile **5.8f** (75.8 mg, 0.476 mmol) for 2.5 h with work-up protocol 1.

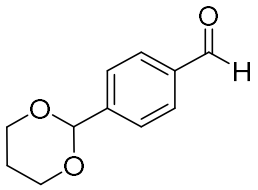
Purification: Hex:EtOAc = 94:6.

Yield: 81% yield (62.8 mg, 0.387 mmol) as clear oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 9.88 (s, 1H), 7.83 (d, *J* = 8.8 Hz, 2H), 7.02 (d, *J* = 8.7 Hz, 2H), 6.06 (ddt, *J* = 17.2, 10.5, 5.3 Hz, 1H), 5.44 (dd, J = 17.2, 1.4 Hz, 1H), 5.33 (dd, J = 10.5, 1.4 Hz, 1H), 4.63 (dt, J = 5.3, 1.4 Hz, 2H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 190.8, 163.6, 132.2, 131.9, 130.0, 118.3, 115.0, 69.0.

### 6.5.2.4.7. Synthesis of 4-(1,3-dioxan-2-yl)benzaldehyde (5.9g)[12]




Prepared from nitrile **5.8g** (94.5 mg, 0.499 mmol) for 3 h with work-up protocol 1.

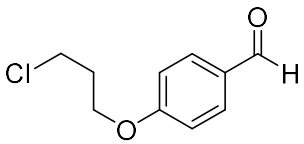
Purification: Hex:EtOAc = 80:20.

Yield: 83% yield (80.1 mg, 0.417 mmol) as white solid.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 10.02 (s, 1H), 7.89 (d, *J* = 8.2 Hz, 2H), 7.66 (d, *J* = 8.2 Hz, 2H), 5.56 (s, 1H), 4.29 (ddd, *J* = 12.1, 5.0, 1.3 Hz, 2H), 4.01 (ddd, *J* = 12.3, 12.1, 2.5 Hz, 2H), 2.24 (dtt, J = 13.5, 12.3, 5.0 Hz, 1H), 1.48 (dtt, J = 13.5, 2.5, 1.3 Hz, 1H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 192.0, 144.7, 136.6, 129.7, 126.8, 100.6, 67.4, 25.7.

### 6.5.2.4.8. Synthesis of 4-(3-chloropropoxy)benzaldehyde (5.9h)[13]




Prepared from nitrile **5.8j** (97.8 mg, 0.500 mmol) for 3 h with work-up protocol 1.

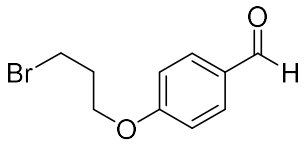
Purification: Hex:EtOAc = 90:10.

Yield: 91% yield (90.8 mg, 0.457 mmol) as clear oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 9.89 (s, 1H), 7.84 (d, *J* = 8.8 Hz, 2H), 7.01 (d, *J* = 8.8 Hz, 2H), 4.21 (t, *J* = 6.0 Hz, 2H), 3.76 (t, *J* = 6.0 Hz, 2H), 2.28 (tt, *J* = 6.0, 6.0 Hz, 2H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 190.7, 163.7, 132.0, 130.1, 114.7, 64.6, 41.2, 32.0.

#### 6.5.2.4.9. Synthesis of 4-(3-bromopropoxy)benzaldehyde (5.9i)[14]




Prepared from nitrile **5.8i** (120 mg, 0.502 mmol) for 3 h with work-up protocol 1.

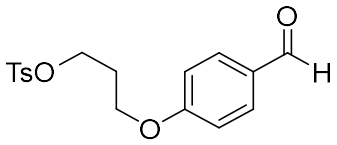
Purification: Hex:EtOAc = 90:10.

Yield: 88% yield (107 mg, 0.442 mmol) as clear oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 9.89 (s, 1H), 7.84 (d, *J* = 8.8 Hz, 2H), 7.01 (d, *J* = 8.8 Hz, 2H), 4.20 (t, *J* = 6.1 Hz, 2H), 3.61 (t, *J* = 6.1 Hz, 2H), 2.36 (tt, *J* = 6.1, 6.1 Hz, 2H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 190.7, 163.7, 132.0, 130.1, 114.8, 65.6, 32.0, 29.5.

#### 6.5.2.4.10. Synthesis of 3-(4-formylphenoxy)propyl 4-methylbenzenesulfonate (5.9j)




Prepared from nitrile **5.8h** (155 mg, 0.500 mmol) for 3 h with work-up protocol 1.

Purification: Hex:EtOAc = 60:40.

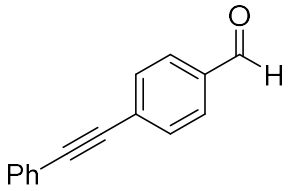
Yield: 88% yield (137 mg, 0.439 mmol) as white solid.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 9.89 (s, 1H), 7.81 (d, *J* = 8.7 Hz, 2H), 7.75 (d, *J* = 8.2 Hz, 2H), 7.24 (d, *J* = 8.2 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 4.25 (t, *J* = 5.9 Hz, 2H), 4.05 (t, *J* = 5.9 Hz, 2H), 2.37 (s, 3H), 2.16 (tt, *J* = 5.9, 5.9 Hz, 2H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 190.7, 163.4, 144.9, 132.7, 131.9, 130.1, 129.8, 127.8, 114.6, 66.6, 63.5, 28.7, 21.6.

**ESIHRMS**: Found: m/z 335.0950; Calcd for $C_{17}H_{18}O_5S$: $(M+H)^+$ 335.0953

### 6.5.2.4.11. Synthesis of 4-(phenylethynyl)benzaldehyde (5.9k)[15]




Prepared from nitrile **5.8k** (101 mg, 0.499 mmol) for 2 h with work-up protocol 1.

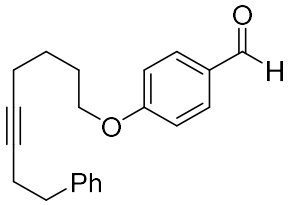
Purification: Hex:EtOAc = 98:2.

Yield: 82% yield (83.9 mg, 0.407 mmol) as white solid.

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 10.02 (s, 1H), 7.86 (d, $J$ = 8.2 Hz, 2H), 7.67 (d, $J$ = 8.2 Hz, 2H), 7.57 – 7.55 (m, 2H), 7.38 – 7.37 (m, 3H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 191.4, 135.4, 132.1, 131.8, 129.60, 129.56, 129.0, 128.5, 122.5, 93.4, 88.5.

### 6.5.2.4.12. Synthesis of 4-((8-phenyloct-5-yn-1-yl)oxy)benzaldehyde (5.9l)




Prepared from nitrile **5.8l** (152 mg, 0.500 mmol) for 3 h with work-up protocol 1.

Purification: Hex:EtOAc = 90:10.

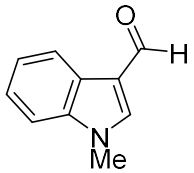
Yield: 89% yield (136 mg, 0.444 mmol) as clear oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 9.88 (s, 1H), 7.83 (d, *J* = 8.7 Hz, 2H), 7.28 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.22 – 7.18 (m, 3H), 6.98 (d, *J* = 8.7 Hz, 2H), 4.04 (t, *J* = 6.3 Hz, 2H), 2.80 (t, *J* = 7.5 Hz, 2H), 2.44 (tt, *J* = 7.5, 2.3 Hz, 2H), 2.23 (tt, *J* = 6.9, 2.3 Hz, 2H), 1.91 – 1.84 (m, 2H), 1.69 – 1.61 (m, 2H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 190.8, 164.1, 140.9, 132.0, 129.8, 128.4, 128.3, 126.1, 114.7, 80.2, 80.1, 67.8, 35.5, 28.0, 25.3, 20.9, 18.4.

**ESIHRMS**: Found: m/z 307.1693; Calcd for $C_{21}H_{23}O_2$: $(M+H)^+$ 307.1698

### 6.5.2.4.13. Synthesis of 1-methyl-1*H*-indole-3-carbaldehyde (5.9m) [CAS No.: 19012-03-4]




Prepared from nitrile **5.8m** (78.2 mg, 0.501 mmol) for 2 h with work-up protocol 1.

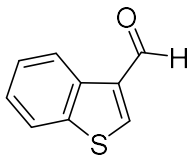
Purification: Hex:EtOAc = 60:40.

Yield: 89% yield (71.3 mg, 0.448 mmol) as pale brown solid.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 9.99 (s, 1H), 8.32 – 8.29 (m, 1H), 7.67 (s, 1H), 7.37 – 7.31 (m, 3H), 3.87 (s, 3H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 184.4, 139.2, 137.9, 125.3, 124.0, 122.9, 122.0, 118.0, 109.8, 33.6.

### 6.5.2.4.14. Synthesis of benzo[*b*]thiophene-3-carbaldehyde (5.9n)[16]



Prepared from nitrile **5.8n** (79.6 mg, 0.500 mmol) for 2.5 h with work-up protocol 1.

Purification: Hex:EtOAc = 97:3.

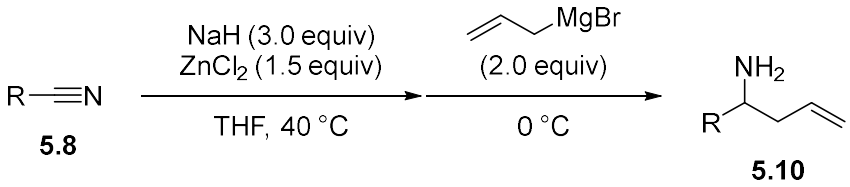
Yield: 85% yield (68.7 mg, 0.424 mmol) as pale yellow solid.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 10.15 (s, 1H), 8.68 (d, *J* = 7.7 Hz, 1H), 8.32 (s, 1H), 7.89 (d, *J* = 7.7 Hz, 1H), 7.52 (dd, *J* = 7.7 Hz, 1H), 7.46 (dd, *J* = 7.7, 7.7 Hz, 1H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 185.4, 143.2, 140.5, 136.5, 135.2, 126.2, 126.1, 124.8, 122.4.

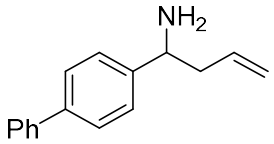
### 6.5.3. Synthesis of homoallylic amines 5.10 and 5.11

#### 6.5.3.1. General procedure for iterative reduction of nitrile 5.8 followed by allylation




To a mixture of NaH (60% dispersion in mineral oil; 60.0 mg, 1.50 mmol) and $ZnCl_2$ (102 mg, 0.750 mmol) in a 25 mL sealed tube was added a solution of nitrile **1** (0.500 mmol) in 2.5 mL of THF. The reaction mixture was sealed and stirred at 40 °C and monitored by GCMS or TLC until full consumption of **1**. Allyl magnesium bromide in diethyl ether (1.0 M; 1 mL. 1.00 mmol) was added to the reaction mixture and was stirred for 2 h at 0 °C. Silica gel (2.00 g) was added to the reaction mixture and was diluted with hexane (10 mL) at 0°C. The resulting reaction mixture was stirred for 1 h at 24 °C, followed by addition of Triethylamine (3mL). The mixture was then filtered through layers of sand and cotton and wash with ethyl acetate. The volatile materials were removed *in vacuo* from the resulting filtrate. The crude residue was purified by flash column chromatography to give the corresponding amine **3**.

### 6.5.3.3. Synthesis of 1-([1,1'-biphenyl]-4-yl)but-3-en-1-amine (5.10a)[17]




Prepared from nitrile **5.8a** (89.6 mg, 0.500 mmol) for 3 h.

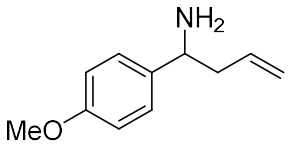
Purification: Hex:EtOAc:TEA = 50:50:1.

Yield: 88% yield (92.0 mg, 0.438 mmol) as pale yellow oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.58 (m, 4H), 7.45 – 7.40 (m, 4H), 7.33 (t, *J* = 6.9 Hz, 1H), 5.84 – 5.73 (m, 1H), 5.17 – 5.09 (m, 2H), 4.04 (dd, *J* = 7.9, 5.4 Hz, 1H), 2.54 – 2.48 (m, 1H), 2.44 – 2.36 (m, 1H), 1.86 (s, 2H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 144.8, 140.9, 139.9, 135.3, 128.7, 127.1(overlapped), 127.0, 126.7, 117.8, 55.1, 44.1.

### 6.5.3.4. Synthesis of 1-(4-methoxyphenyl)but-3-en-1-amine (5.10b)[18]




Prepared from nitrile **5.8b** (66.6 mg, 0.500 mmol) for 3 h.

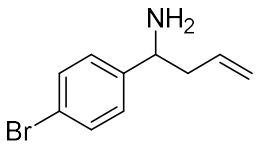
Purification: EtOAc:TEA = 100:1.

Yield: 89% yield (63.8 mg, 0.360 mmol) as pale yellow oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.79 – 5.70 (m, 1H), 5.13 – 5.06 (m, 2H), 3.95 (dd, *J* = 7.8, 5.5 Hz, 1H), 3.80 (s, 3H), 2.47 – 2.40 (m, 1H), 2.38 – 2.30 (m, 1H), 1.72 (s, 2H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 158.5, 137.9, 135.5, 127.3, 117.5, 113.7, 55.2, 54.7, 44.2.

### 6.5.3.5. Synthesis of 1-(4-bromophenyl)but-3-en-1-amine (5.10c) [18]




Prepared from nitrile **5.8c** (91.1 mg, 0.501 mmol) for 0.5 h.

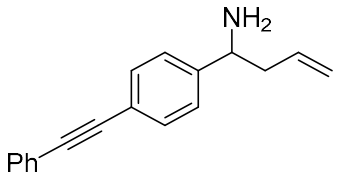
Purification: Hex:EtOAc:TEA = 50:50:1.

Yield: 73% yield (82.9 mg, 0.367 mmol) as pale yellow oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 5.77 – 5.66 (m, 1H), 5.13 – 5.07 (m, 2H), 3.97 (dd, *J* = 7.8 Hz, 5.5 Hz, 1H), 2.45 – 2.39 (m, 1H), 2.35 – 2.28 (m, 1H), 1.72 (s, 2H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 144.7, 134.9, 131.4, 128.1, 120.6, 118.0, 54.8, 44.1.

### 6.5.3.6. Synthesis of 1-(4-(phenylethynyl)phenyl)but-3-en-1-amine (5.10k)




Prepared from nitrile **5.8k** (102 mg, 0.500 mmol) for 2 h.

Purification: Hex:EtOAc:TEA = 50:50:1.

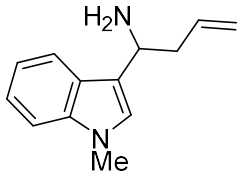
Yield: 85% yield (106 mg, 0.427 mmol) as pale yellow oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.54 – 7.49 (m, 4H), 7.37 – 7.31 (m, 5H), 5.79 – 5.68 (m, 1H), 5.14 – 5.08 (m, 2H), 4.01 (dd, *J* = 7.9, 5.4 Hz, 1H), 2.49 – 2.43 (m, 1H), 2.39 – 2.32 (m, 1H), 1.75 (s, 2H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 146.0, 135.0, 131.7, 131.6, 128.3, 128.2, 126.4, 123.3, 121.8, 117.9, 89.3, 89.1, 55.2, 44.0.

**ESIHRMS**: Found: m/z 248.1436; Calcd for $C_{18}H_{18}N$: $(M+H)^+$ 248.1439

### 6.5.3.7. Synthesis of 1-(1-methyl-1H-indol-3-yl)but-3-en-1-amine (5.10m)




Prepared from nitrile **5.8m** (78.1 mg, 0.500 mmol) for 2 h.

Purification: EtOAc:TEA = 100:1.

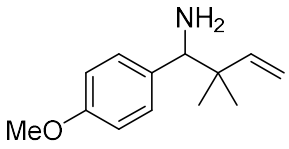
Yield: 74% yield (74.4 mg, 0.372 mmol) as pale yellow oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.7 Hz, 1H), 7.30 (d, *J* = 7.7 Hz, 1H), 7.23 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.11 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.00 (s, 1H), 5.90 – 5.80 (m, 1H), 5.16 (d, *J* = 17.1 Hz, 1H), 5.10 (d, *J* = 10.1 Hz, 1H), 4.36 (dd, *J* = 7.9, 5.2 Hz, 1H), 3.75 (s, 3H), 2.73 – 2.67 (m, 1H), 2.53 – 2.46 (m, 1H), 2.12 (s, 2H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 137.2, 136.0, 126.4, 125.4, 121.6, 119.4, 119.2, 118.8, 117.4, 109.3, 48.0, 43.1, 32.7.

**ESIHRMS**: Found: m/z 201.1394; Calcd for $C_{13}H_{17}N_2$: $(M+H)^+$ 201.1392

### 6.5.3.8. Synthesis of 1-(4-methoxyphenyl)-2,2-dimethylbut-3-en-1-amine (5.11b)




Prepared from nitrile **5.8b** (66.5 mg, 0.499 mmol) by modified procedure using (3-methylbut-2-en-1-yl)magnesium bromide (0.394 M in THF, 2.6 mL, 1.00 mmol) instead of allyl magnesium bromide for 2 h.

Purification: EtOAc:Hex:TEA = 50:50:1.

Yield: 82% yield (84.3 mg, 0.411 mmol) as clear oil.

**5.11b** was also synthesis by modified procedure adding (3-methylbut-2-en-1-yl)magnesium bromide (0.394 M in THF, 2.6 mL, 1.00 mmol) at -78 °C for 2 h instead of allyl magnesium bromide at 0 °C for 2 h.

Yield: 79% yield (80.9 mg, 0.394 mmol) as clear oil.

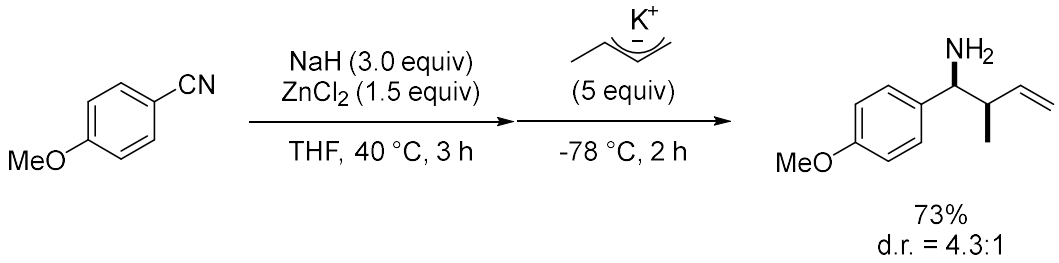
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 5.86 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.08 (d, *J* = 10.8 Hz, 1H), 5.03 (d, *J* = 17.5 Hz, 1H), 3.80 (s, 3H), 3.71 (s, 1H), 1.72 (s, 2H), 0.97 (s, 3H), 0.93 (s, 3H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 158.6, 145.9, 134.8, 129.3, 112.93, 112.86, 63.4, 55.2, 41.5, 25.5, 21.6.

**ESIHRMS**: Found: m/z 206.1547; Calcd for $C_{13}H_{20}NO$: $(M+H)^+$ 206.1545

### 6.5.4. Synthesis of homoallylic amines 5.13 with crotyl potassium

#### 6.5.4.1. Iterative reduction of nitrile 5.8 followed by addition of trans crotyl potassium (5.13b)[19]



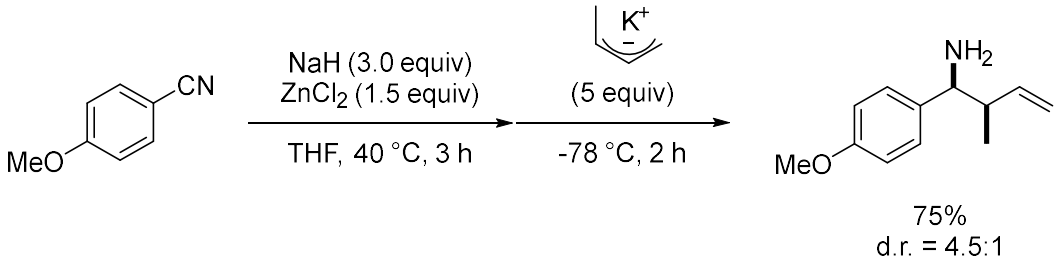

In a 25 mL sealed tube, a solution of *t*BuOK (287 mg, 2.56 mmol) in THF (1.3 mL) was added trans-2-butene (condensed from a gas lecture cylinder into a 5-mL graduated cylinder immersed in a dry ice/acetone bath, 0.5 mL) via cannula at -78 °C. *n*BuLi (1.51 M in *n*-hexane, 1.65 mL, 2.49 mmol) is added dropwise over 50 min using a syringe pump at -78 °C. After the addition is complete, the resultant yellow mixture is allowed to warm to –55 °C for 25 min and then immediately recooled to –78 °C. This gave the resulting trans crotyl potassium mixture.

To a mixture of NaH (60% dispersion in mineral oil; 60.0 mg, 1.50 mmol) and $ZnCl_2$ (102 mg, 0.750 mmol) in a separate 25 mL sealed tube was added a solution of **5.8b** (66.9 mg, 0.502 mmol) in 2.5 mL of THF. The reaction mixture was sealed and stirred at 40 °C for 3 h. This resulting mixture was added directly into the resulting trans crotyl potassium mixture at -78 °C and was stirred for 2 h at -78 °C. Silica gel (2.00 g) was added to the reaction mixture and was diluted with hexane (10 mL) at 0°C. The resulting reaction mixture was stirred for 1 h at 24 °C, followed by addition of Triethylamine (3mL). The mixture was then filtered through layers of sand and cotton and wash with ethyl acetate. The volatile materials were removed *in vacuo* from the resulting filtrate. The crude residue was purified by flash column chromatography (silica gel, ethyl acetate: triethylamine = 100:1) to give a colourless oil **5.13b** (70.1 mg, 0.367 mmol) in 73% yield with an estimated 81:19 diastereomeric mixture (based on $^1$H NMR spectroscopy analysis)

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.6 Hz, 0.19 X 2H), 7.19 (d, *J* = 8.6 Hz, 0.81 X 2H), 6.85 (d, *J* = 8.6 Hz, 0.19 X 2H + 0.81 X 2H), 5.78 – 5.62 (m, 0.19 X 1H + 0.81 X 1H), 5.18 – 5.09 (m, 0.19 X 2H), 5.01 (dd, *J* = 14.0, 3.1 Hz, 0.81 X 2H), 3.83 (d, *J* = 5.6 Hz, 0.81 X 1H), 3.80 (s, 0.19 X 3H + 0.81 X 3H), 3.59 (d, *J* = 8.5 Hz, 0.19 X 1H), 2.50 – 2.42 (m, 0.81 X 2H), 2.37 – 2.27 (m, 0.19 X 1H), 0.97 (d, *J* = 6.8 Hz, 0.81 X 3H), 0.80 (d, *J* = 6.8 Hz, 0.19 X 2H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 158.6, 158.4, 141.9, 141.0, 136.6, 136.4, 128.2, 128.1, 115.7, 114.9, 113.6, 113.4, 60.0, 59.4, 55.21, 55.19, 46.5, 44.7, 17.7, 15.2.

**6.5.4.2. Iterative reduction of nitrile 5.8 followed by addition of cis crotyl potassium (5.13b)[19]**




In a 25 mL sealed tube, a solution of *t*BuOK (287 mg, 2.56 mmol) in THF (1.3 mL) was added trans-2-butene (condensed from a gas lecture cylinder into a 5-mL graduated cylinder immersed in a dry ice/acetone bath, 0.5 mL) via cannula at -78 °C. *n*BuLi (1.51 M in *n*-hexane, 1.65 mL, 2.49 mmol) is added dropwise over 50 min using a syringe pump at 78 °C. After the addition is complete, the resultant yellow mixture is allowed to warm to –55 °C for 25 min and then warm up to –20 °C for 3 h. The mixture was finally recooled to –78 °C. This give the resulting racemic crotyl potassium mixture.

To a mixture of NaH (60% dispersion in mineral oil; 60.0 mg, 1.50 mmol) and $ZnCl_2$ (102 mg, 0.750 mmol) in a separate 25 mL sealed tube was added a solution of **5.8b** (66.9 mg, 0.502 mmol) in 2.5 mL of THF. The reaction mixture was sealed and stirred at 40 °C for 3 h. This resulting mixture was added directly into the resulting racemic crotyl potassium mixture at -78 °C and was stirred for 2 h at -78 °C. Silica gel (2.00 g) was added to the reaction mixture and was diluted with hexane (10 mL) at 0°C. The resulting reaction mixture was stirred for 1 h at 24 °C, followed by addition of Triethylamine (3mL). The mixture was then filtered through layers of sand and cotton and wash with ethyl acetate. The volatile materials were removed *in vacuo* from the resulting filtrate. The crude residue was purified by flash column chromatography (silica gel, ethyl acetate: triethylamine = 100:1) to give a colourless oil **5.13b** (71.7 mg,

0.375 mmol) in 75% yield with an estimated 82:18 diastereomeric mixture (based on $^{1}$H NMR spectroscopy analysis)

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.6 Hz, 0.18 X 2H), 7.19 (d, *J* = 8.6 Hz, 0.82 X 2H), 6.85 (d, *J* = 8.6 Hz, 0.18 X 2H + 0.82 X 2H), 5.78 – 5.62 (m, 0.18 X 1H + 0.82 X 1H), 5.18 – 5.09 (m, 0.18 X 2H), 5.01 (dd, *J* = 14.0, 3.1 Hz, 0.82 X 2H), 3.83 (d, *J* = 5.6 Hz, 0.82 X 1H), 3.80 (s, 0.18 X 3H + 0.82 X 3H), 3.59 (d, *J* = 8.5 Hz, 0.18 X 1H), 2.50 – 2.42 (m, 0.82 X 2H), 2.37 – 2.27 (m, 0.18 X 1H), 0.97 (d, *J* = 6.8 Hz, 0.82 X 3H), 0.80 (d, *J* = 6.8 Hz, 0.18 X 2H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 158.6, 158.4, 141.9, 141.0, 136.6, 136.4, 128.2, 128.1, 115.7, 114.9, 113.6, 113.4, 60.0, 59.4, 55.21, 55.19, 46.5, 44.7, 17.7, 15.2.

### 6.5.5. References for section 6.5


1. L. Wang, X. Jiang, P. Tang, *Org. Chem. Front.* **2017,** *4*, 1958-1961.
2. G. H. Chan, D. Y. Ong, Z. Yen, C. Shunsuke, *Helv. Chim. Acta* **2018,** *101*, e1800049.
3. H. Jenkner, US3116112A, **1953**.
4. R. Martín, S. L. Buchwald, *Org. Lett.* **2008,** *10*, 4561-4564.
5. Á. Gutiérrez-Bonet, A. Flores-Gaspar, R. Martin, *J. Am. Chem. Soc.* **2013,** *135*, 12576-12579.
6. Y.-J. Wu, H. He, R. Bertekap, R. Westphal, S. Lelas, A. Newton, T. Wallace, M. Taber, C. Davis, J. E. Macor, J. Bronson, *Bioorg. Med. Chem.* **2013,** *21*, 2217-2228.
7. S. G. Jarboe, P. Beak, *Org. Lett.* **2000,** *2*, 357-360.
8. G. Pelletier, W. S. Bechara, A. B. Charette, *J. Am. Chem. Soc.* **2010,** *132*, 12817-12819.
9. T. Nishimura, T. Onoue, K. Ohe, S. Uemura, *J. Org. Chem.* **1999,** *64*, 6750-6755.
10. D. J. Vyas, E. Larionov, C. Besnard, L. Guénée, C. Mazet, *J. Am. Chem. Soc.* **2013,** *135*, 6177-6183.
11. D. Zhu, L. Lv, C.-C. Li, S. Ung, J. Gao, C.-J. Li, *Angew. Chem. Int. Ed.* **2018,** *57*, 16520-16524.
12. Z.-L. Shen, K. Sommer, P. Knochel, *Synthesis* **2015,** *47*, 2617-2630.
13. A. Ouach, S. Gmouh, M. Pucheault, M. Vaultier, *Tetrahedron* **2008,** *64*, 1962-1970.
14. C. Le Sann, A. Baron, J. Mann, H. van den Berg, M. Gunaratnam, S. Neidle, *Org. Biomol. Chem.* **2006,** *4*, 1305-1312.
15. M. M. Hansmann, A. López-Andarias, E. Rettenmeier, C. Egler-Lucas, F. Rominger, A. S. K. Hashmi, C. Romero-Nieto, *Angew. Chem. Int. Ed.* **2016,** *55*, 1196-1199.
16. S. Tripathi, S. N. Singh, L. D. S. Yadav, *RSC Adv.* **2016,** *6*, 14547-14551.
17. S. Pramanik, R. R. Reddy, P. Ghorai, *J. Org. Chem.* **2015,** *80*, 3656-3663.
18. M. Sugiura, K. Hirano, S. Kobayashi, *J. Am. Chem. Soc.* **2004,** *126*, 7182-7183.
19. P. V. Ramachandran, W. Mitsuhashi, D. Biswas, D. R. Nicponski, *Tetrahedron Lett.* **2013,** *54*, 4830-4833.

## 7. Conclusion and perspective

In conclusion, this thesis explores the utilization of sodium hydride as an unprecedented hydride source by combined use with main group metal halides to develop several types of reductive transformations. Hydrodehalogenation of halo (hetero)arenes using sodium hydrides in the presence of lithium iodides was developed, which proceeds through an unusual concerted nucleophilic aromatic substitution mechanism (Chapter 2). The stable anionic carbinol amine intermediates, which were formed via the reduction of tertiary carboxamides with the sodium hydride-sodium iodide system, were utilized for the transition-metal free reductive functionalization of carboxamides and lactams for synthesis of α-branched amines (Chapter 3).

Further investigation of sodium hydrides with zinc halides also established the controlled reduction of carboxamides to either alcohols or amines, where the halides ions on the zinc dictates the process selectivity through generation of different types of zinc hydrides (Chapter 4). Further synthetic applications of zinc hydrides derived from sodium hydride and zinc chloride developed the controlled reduction of carbonitriles to aldehydes (Chapter 5).

In summary, the use of sodium hydride in the presence of different alkali metals and zinc halides salt have allowed for the development of a simple yet effective protocol for the different reductive molecular transformation.

The author believed that the use of alkali metal hydrides like sodium hydride is valuable in term of atom economy due to the higher hydride content of alkali metal hydrides comparing to other hydride reagents based on boron, aluminum and silicon. Furthermore, sodium is the sixth most natural abundance element on earth and the most natural abundance element of the group 1 alkali metals.

There are still more opportunities to explore utilization of alkali metal hydrides with different main group metal salts. The author envisions the generation of new main group metal hydride reagents with possibly new exciting reactivities by using sodium hydrides as a hydride source for counter ion metathesis with other main group metal salts. Further exploration into the actual species of the new main group metal hydrides responsible for their reductive transformations should generate more in depth understanding for additional development of other main group metal hydrides.

The simple protocol of mixing the alkali metal hydrides and main group metal salts to generate new main group metal hydrides for reductive transformation will be more advantageous and effective than those protocols requiring the use of ligands to stabilise the newly formed molecular hydrides.

For further studies, there is a need to utilise the transition metal-free reductive functionalization protocol for additional development of other synthetic protocols for the preparation of tertiary amines and cyclic amines like piperidine and pyrrolidine. These molecules are of importance to the pharmaceutical or agrochemical industries and providing a transition metal-free protocol to synthesize them would be highly sought after by the industries.

All in all, this thesis does not signify the end of exploration for sodium hydride as a hydride source but initiates the limitless possibilities in the quest for generation of new hydrides species.

## List of publications

1. Zonghan Hong, Derek Yiren Ong, Subas Kumar Muduli, Pei Chui Too, Guo Hao Chan, Ya Lin Tnay, Shunsuke Chiba, Yusuke Nishiyama, Hajime Hirao, and Han Sen Soo
"Understanding the Origins of Nucleophilic Hydride Reactivity of Sodium Hydride-Iodide Composite"
*Chem. Eur. J.* **2016**, *22*, 7108-7114.

2. Derek Yiren Ong, Ciputra Tejo, Kai Xu, Hajime Hirao, and Shunsuke Chiba
"Hydrodehalogenation of Haloarenes by a Sodium Hydride-Iodide Composite"
*Angew. Chem. Int. Ed*. **2017**, *56*, 1840-1844.

3. Geoffroy Hervé Lonca, Derek Yiren Ong, Thi Mai Huong Tran, Ciputra Tejo, Shunsuke Chiba, and Fabien Gagosz
"Anti-Markovnikov Hydrofunctionalization of Alkenes - Use of a Benzyl Group as a Traceless Redox-active Hydrogen Donor"
*Angew. Chem. Int. Ed*. **2017**, *56*, 11440-11444.

4. Ciputra Tejo, Jia Hao Pang, Derek Yiren Ong, Miku Oi, Masanobu Uchiyama, Ryu Takita, and Shunsuke Chiba
"Dearylation of Arylphosphine Oxides by a Sodium Hydride-Iodide Composite"
*Chem. Commun*. **2018**, *54*, 1782-1785.

5. Guo Hao Chan, Derek Yiren Ong, Zihao Yen, and Shunsuke Chiba
"Reduction of N,N-Dimethylcarboxamides to Aldehydes by Sodium Hydride-Iodide Composite"
*Helv. Chim. Acta* **2018**, *101,* e1800049.

6. Guo Hao Chan, Derek Yiren Ong, and Shunsuke Chiba
"Hydrodecyanation by Sodium Hydride-Iodide Composite"
*Org. Synth.* **2018**, *95,* 240-255.

7. Derek Yiren Ong, Zihao Yen, Asami Yoshii, Julia Revillo Imbernon, Ryo Takita, and Shunsuke Chiba
"Controlled Reduction of Carboxamides into Alcohols or Amines by Zinc Hydrides"
*Angew. Chem. Int. Ed*. **2019**, *58*, 4992-4997.

8. Jia Hao Pang, Derek Yiren Ong, Kohei Watanabe, Ryo Takita, and Shunsuke Chiba
"Leaving Group Ability in Nucleophilic Aromatic Amination by Sodium Hydride-Lithium Iodide Composite"
*Synthesis, accepted for publication (DOI: 10.1055/s-0039-1690010)*

9. Derek Yiren Ong, Kohei Watanabe, Ryo Takita, and Shunsuke Chiba
"Mechanistic Insights on Reduction of Carboxamides by Diisobutylaluminum Hydride and Sodium Hydride−Iodide Composite"
*Helv. Chim. Acta.* **2019***,102,* e1900166

10. Derek Yiren Ong, Jia Hao Pang, Shunsuke Chiba
"Synthetic Organic Reactions Mediated by Sodium Hydride"
*J. Synth. Org. Chem. Jpn*. **2019**, *77*, 1060