Molecular transformations using a sodium hydride-iodide composite

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**MOLECULAR TRANSFORMATIONS USING A
SODIUM HYDRIDE-IODIDE COMPOSITE**

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SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

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List of Abbreviation

δ	chemical shift (ppm)
%	percent
$^{\circ}\text{C}$	degree centigrade
μm	micrometre
acac	acetylacetonate
ATR-FTIR	attenuated total reflectance fourier transform infrared
Bn	benzyl
Calcd	calculated
cat.	catalytic
CIPE	complex-induced proximity effect
cod	1,5-cyclooctadiene
Cp	cyclopentadienyl
CPME	cyclopentyl methyl ether
cy	cyclohexyl
DIBAL	diisobutylaluminium hydride
Dip	2,6- <i>i</i> Pr ₂ C ₆ H ₃
DIPP-nacnac	HC[C(Me)N(2,6- <i>i</i> Pr-C ₆ H ₃)] ₂
DME	dimethoxyethane
DMEA	N,N-dimethylethylamine
DMF	dimethylformamide
DMPU	N,N'-dimethylpropyleneurea
dr	diastereomeric ratio
DTBP	di-tert-butyl peroxide
E ⁺	electrophile
E _a	activation energy

ee	enantiomeric excess
EIHRMS	high resolution electron ionization mass spectrometry
equiv	equivalent
ESIHRMS	high resolution electrospray ionization mass spectrometry
Et	ethyl
EtOAc	ethyl acetate
FLP	frustrated lewis pair
HMPA	hexamethylphosphoramide
HPLC	high-performance liquid chromatography
Hz	hertz
<i>i</i> -Pr	isopropyl
kcal	kilocalorie
KHMDS	potassium bis(trimethylsilyl)amide
LDA	lithium diisopropylamide
liq	liquid
M	concentration (mol/L)
Me	methyl
Me ₄ TACD	1,4,7,10-tetramethyl-1,4,7,10-tetraazacyclododecane
MHz	megahertz
min	minutes
mL	millilitre
mmHg	millimetre of mercury
mol	mole
MOM	methoxymethyl
MTPA	(-)- α -methoxy- α -trifluoromethyl)phenylacetic acid
NaDA	sodium diisopropylamide

<i>n</i> -Bu	butyl
NHC	N-heterocyclic carbene
nm	nanometer
NMR	nuclear magnetic resonance
OMs	mesylate
PCC	pyridinium chlorochromate
Ph	phenyl
pKa	Acid Dissociation Constant
PMDTA	N,N,N',N'',N''-pentamethyldiethylenetriamine
pz	3,5-di- <i>tert</i> -butylpyrazole
Red-Al	Sodium bis(2-methoxyethoxy)aluminium hydride
rt	room temperature
TBAB	tetrabutylammonium bromide
<i>t</i> -Bu	<i>tert</i> -butyl
Tf	triflate
THF	tetrahydrofuran
TMDS	tetramethyldisiloxane
TMEDA	tetramethylethylenediamine
TMP	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilane
TMSCl	chlorotrimethylsilane
TS	transition state
UV	ultraviolet

Abstract

Sodium hydride is used exclusively as a strong Brønsted base for the deprotonation reactions in chemical synthesis. This thesis describes development of new protocol for use of sodium hydride in a variety of unique hydride reduction processes by its combined use with alkali metal iodides.

In Chapter 1, various strategies for the manipulation of alkali and alkaline earth metal hydrides for the reduction of π -electrophiles are discussed.

Chapter 2 describes serendipitous discovery and development of unprecedented hydrodeacylation of α -quaternary benzylicyanides by a NaH-iodide. This simple protocol bestows NaH with an unique hydride-donor chemical reactivity. The composite can reduce a cyano functional group at the benzylic position to its respective alkanes (via the iminyl intermediate) with a retention of the preinstalled α -chirality.

Chapter 3 describes development of the sodium hydride-iodide composite for the selective hydride reduction of tertiary carboxamides into the corresponding aldehydes. This protocol displays interesting reactivity in the reduction of a wide variety of aryl, heteroaryl and aliphatic carboxamide amides into the aldehydes. Retention of α -chirality in α -enantioriched amides and chemoselective reduction of amides over ketones and tert-butyl esters feature prominently in the present reduction protocol. The chapter also describes the use of sodium deuteride as an economical alternative for the synthesis of various deuterated aldehydes in high deuterium incorporation.

Chapter 3. Reduction of *N,N*-dimethylcarboxamides by a NaH-NaI composite

Hydride (H^-) reactivity
Retention of α -chirality
Chemoselective reduction over ketones
and tert-butyl esters

In Chapter 4, discovery and development of the amide-directed C-H sodiation by the NaH-iodide composite are discussed. It was found that unique Lewis acidity is installed on sodium hydride in the presence of NaI or LiI, that enables amide-directed deprotonative sodiation of ortho-aromatic C-H or benzylic C-H bond to form nucleophilic organosodium intermediates. Subsequent transformations allowed for facile synthesis of ortho-secondary alkyl arylaldehydes, 2-indanones, and phenanthrenes.

Chapter 4. Amide directed C-H sodiation by a NaH-NaI composite

Unprecedented Lewis acid reactivity

Chapter 5 describes the experimental procedures and characterization of the compounds synthesized in each Chapter.

Chapter 1 General Introduction

Molecular hydrogen has a relatively high bond dissociation enthalpy of $104 \text{ kcal mol}^{-1}$ and a high pK_a value in water of 35.^[1] Nevertheless, it can be reduced with various metal elements in the periodic table at elevated temperatures to form binary compounds of hydrogen, which are termed as metal hydrides (Scheme 1.1).^[2]

Scheme 1.1. Synthesis of metal hydrides

Depending on the electronegativity of the metal, the nature of the metal hydride bond can be grouped under three categories, namely the ionic/saline hydrides, covalent hydrides. Electronegativity difference with hydrogen of approximately 1.2-1.3 units based on the Allred-Rochow values are being classified under the ionic/saline hydrides, while the electronegativity difference less than that are classified under the covalent hydrides or hydrides with mixed degree of covalent and ionic bonding.^[3] Therefore, based on this segregation, it can be determined that the metal hydrides from Group I (Li to Cs) and Group II (Ca to Ba) are ionic hydrides. Lighter Group II metal hydrides such as beryllium hydride are covalent in nature, while magnesium hydride have both covalent and ionic characters (Table 1.1).^[4]

Group 1 MH	$\Delta\chi^{[a]}$	Group 2 MH ₂	$\Delta\chi^{[a]}$
LiH	1.2	BeH ₂	0.7
NaH	1.2	MgH ₂	1.0
KH	1.3	CaH ₂	1.2
RbH	1.3	SrH ₂	1.2
CsH	1.3	BaH ₂	1.2
[a] Electronegativity differences based on Allred-Rochow values			

Table 1.1. Electronegativity difference of metal hydrides

These metal hydrides possess a very high lattice energy with those decreasing down the group from Li to Cs and from Be to Ba (Table 1.2).^[1]

Group 1 MH	Lattice energy ^[a] kcal mol ⁻¹	Group 2 MH ₂	Lattice energy ^[b] kcal mol ⁻¹
LiH	220	BeH ₂	766
NaH	193	MgH ₂	667
KH	171	CaH ₂	576
RbH	164	SrH ₂	537
CsH	154	BaH ₂	519

[a] Values taken from ref [1],
[b] Values taken from ref [9a].

Table 1.2. Lattice energies of metal hydrides

Compared with other Group I metal hydrides (from NaH to CsH), LiH has the highest lattice energy. This impedes the heterogeneous surface reaction to water as compared to NaH to CsH where the rate of reaction to water increases down the group.^[2, 3a, 5] Group II hydrides show similar trends whereby the lattice energies decrease down the group. However, Group II hydrides show starkly different reactivity due to a larger lattice energy as compared to Group I hydrides. Group I hydrides (NaH to CsH) can be used as a Brønsted base for deprotonation reaction in organic synthesis,^[5] while Group II hydrides such as CaH₂ is essentially unreactive to other common organic acids and a large variety of functional groups such as halides, carbonyl, imino, cyano and alkenes. CaH₂ only reacts vigorously with water, which makes it a common drying agent for a wide variety of organic solvent.^[6]

Alkali metal or alkaline earth metal hydrides have rarely been employed as hydride sources for the reduction of polar π -electrophiles, but have remained exclusively as a strong Brønsted base for deprotonation reactions in chemical synthesis.^[2, 3b] One of the possible reasons for this limited reactivity is that the high lattice energy of these hydrides make them insoluble in organic solvents.

Hydride reduction of π -electrophiles such as carbonyl compounds, carbonitriles, imines and alkenes are one of the most fundamental and important molecular transformations in chemical synthesis.^[7] In this context, a variety of covalent hydrides such as borane, alane, metal borohydrides, metal aluminum hydrides, and silanes have often been employed as the

reagents of choice for desired hydride transfer processes in stereo-, regio-, and chemo-selective fashion (Scheme 1.2).^[8]

Scheme 1.2. Typical covalent hydrides

Due to the importance of such reductive transformation and abundant availability of the alkali and alkali-earth metals, various strategies have been developed to overcome the limited reactivity of alkali metal or alkaline earth metal hydrides to the reduction of π -electrophiles. This general introduction will summarize and discuss about the adaptable strategies for the manipulation of ionic hydrides, specifically those based on Li to K as well as Ca to Ba for the reduction of π -electrophiles.^[9]

1.1. Strategies for use of Alkali Metal Hydrides

As stated above, alkali metal hydrides are insoluble in common organic solvents and are mainly used as a Brønsted base for deprotonation of organic acids instead of a reagent with polar hydride reactivity. In this section, representative examples of classical and modern methods for the manipulation of these ionic hydrides for the hydride reduction of π -electrophiles are presented.

1.1.1. Classical Methods

One classic example for the manipulation of these ionic hydrides is the conversion of these hydrides to the covalent hydrides by the formation of ‘ate’-type complexes with either the Lewis acidic borane or aluminium hydride derivatives. These reagents are commercially available in solutions and are widely used for the reduction of a variety of π -electrophiles. For example, LiH/AlH₃ solution can reduce practically most of the carbonyl π -electrophiles such as aldehydes, ketones, carboxylic acids, anhydrides, acid chlorides, esters, lactones, amides as well as other functional groups like imines, azides, oximes, and sulfoxides,^[10] while LiH/BH₃ solution can reduce esters, acid chlorides, aldehydes and ketones.^[11]

This remarkable protocol, discovered by Brown et al., treats LiH with stoichiometric amounts of aluminium hydride or aluminum chloride in ethereal solvents to form the ‘ate’-complex LiAlH_4 (lithium aluminium hydride), in which the hydrides are bound to the aluminum metal center instead of the lithium, and the lithium cation acts as a charge balancer (Scheme 1.3a).^[12] Analogously, treatment of LiH with stoichiometric amounts of borane in ethereal solvents to form the ‘ate’-complex LiBH_4 (lithium borohydride), wherein the hydride ligands are bound to the boron center (Scheme 1.3b).^[13] These procedures essentially convert the ionic hydrides to the covalent hydrides, thus enabling the resulting hydrides to be both soluble and have polar hydride reactivity.

Scheme 1.3. Synthesis of LiAlH_4 and LiBH_4

Changing of alkali metal hydrides and the substituents on the Lewis acidic metals allow for preparation of different types of the metal hydrides such as sodium borohydride (NaBH_4), lithium di/triethoxyaluminium hydrides $\text{LiAlH}_n(\text{OEt})_{4-n}$ ($n = 1$ or 2), diisobutylaluminium hydride, and sodium bis(2-methoxyethoxy)aluminium hydride (Red-Al). These offer different reduction capability for various functional groups.^[8, 14]

Although these compounds show polar hydridic reactivity, the structures and reactivity are technically not remotely related to the original alkali metal hydride since the hydride is bonded to the aluminum or boron metal center instead of the alkali metal. Thus, there is still a possibility for the direct activation of alkali metal hydride for hydridic reactivity.

Takacs et al. first demonstrated the combined use of NaH/KH and chlorotrimethylsilane to convert cyclohexanone to its silyl alkyl ether via the hydride reduction of the carbonyl group, although there is a need of harsh reaction conditions. The yield was low as the reaction is not selective, furnishing the silyl enol ethers as a side product due to the inherent basicity of NaH and KH (Scheme 1.4).^[15]

Scheme 1.4. Activation of NaH or KH with TMSCl for hydrosilylation

The process efficiency could be improved by using a less kinetically reactive basic hydride, LiH to suppress the side reaction. Noyori et al. developed a practical method for the activation of commercial LiH using chlorotrimethylsilane in the presence of a catalytic amount of zinc(II) mesylate for the reductive silylation of various simple ketones and non-enolizable aldehydes. The resulting silyl alkyl ethers are generated in high yields with milder reaction conditions albeit a long reaction time of 36 to 50 h (Scheme 1.5).^[16] It is proposed that the reductive silylation is heterogenous in nature and the reaction occurs on the surface of the insoluble species generated through mixing LiH, chlorotrimethylsilane and $\text{Zn}(\text{OMs})_2$ in the reaction mixture.

Scheme 1.5. Activation of LiH with TMSCl for hydrosilylation

Schleyer et al. developed a protocol for the *in-situ* generation of LiH, NaH and KH via the deprotonation of hydrogen gas with organolithium bases such as *n*-BuLi-TMEDA, and alkoxides such as *t*-BuOM (M = Li, Na or K) (Scheme 1.6a and 1.6b).^[17]

a) Preparation of LiH

b) Preparation of NaH/KH

Scheme 1.6. *In-situ* generation of alkali metal hydrides

This deprotonation of molecular hydrogen in such highly basic reaction conditions gives freshly generated LiH, NaH or KH, which are more reactive to perform the hydride reduction of simple π -electrophiles such as aldehydes, ketones and carbodiimide (Scheme 1.7).

Scheme 1.7. Hydride reduction with *in-situ* generated alkali metal hydrides

These active alkali metal hydrides are postulated to be possibly nanomeric in nature and they still retain their salts like lattice and the hydridic reactivity stems from the high surface area of these nanomeric hydrides that are finely dispersed although not necessarily soluble in organic solvents.

1.1.2. Modern Methods

Recently, Harder et al. developed a new strategy for the generation of activated KH from phenylsilane. As shown in Scheme 1.8a, the use of commercial KH with phenylsilane worked to reduced, but the reaction required a long incubation time. In contrast, by the new procedure of *in-situ* generation of activated KH via the reaction of a silyl benzylpotassium catalyst with phenylsilane (as shown in scheme 1.8b), shorter reaction time could be achieved to yield the same product. The mechanism is proposed as shown in Scheme 1.9; active KH is firstly generated by the addition of silane to the silyl benzylpotassium catalyst. The resulting active KH reacts with phenylsilane to form the hypervalent PhSiH_4K **A** which adds onto 1,1-diphenylethene to give the hydrosilylated intermediate **B**. Finally, σ -bond metathesis of **B** with phenylsilane gives hydrosilylated product in an anti-Markovnikov manner with regeneration of PhSiH_4K **A** (Scheme 1.9).^[18]

[a] There was a 90 min incubation time

Scheme 1.8. Reactivity comparison between *in-situ* generated KH and commercial KH

Scheme 1.9. Mechanism of hydrosilylation with *in-situ* generated KH

While the methods in activating the alkali metal hydrides are effective, the metal hydrides are in their salt like crystal form and are still insoluble in the reaction solvent. Therefore, there is a possibility to enhance hydridic activity for the reduction of polar π -electrophiles through design and synthesis of soluble molecular alkali metal hydride complexes.

However, the high lattice energies of the ionic hydrides result in difficulty for the synthesis of molecular alkali metal hydrides from the polymeric metal hydride salt. One of the ways to overcome this challenge is to form an 'ate'-complex (Section 1.1.1). Recently, Slootweg and Uhl et al. utilized a P-Al based frustrated lewis pair (FLP) to synthesize an 'ate'-complex. The easily accessible FLP can be used to react with commercially available LiH, NaH and KH at room temperature to form the respective soluble monomeric hydride complexes (Scheme 1.10).^[19] Interestingly, the coordination pattern for KH/NaH FLP complex is different from that of the LiH FLP complex. This is due to the Na and K being a softer Lewis acid metal as compared to Li.

Scheme 1.10. Synthesis of molecular alkali metal hydrides with FLP

These soluble molecular hydride complexes display enhanced hydridic reactivity. The NaH complex is able to convert chlorotriphenylsilane to triphenylsilane quantitatively in THF at reflux after 48 h. The generation of triphenylsilane released the FLP, and the FLP will react with excess NaH (1.5 equiv) to form the monomeric hydride complex, thus realizing the catalytic cycle. When chlorotriphenylsilane was treated with just sodium hydride alone, there is no reaction under otherwise the same reaction conditions (Scheme 1.11).

Stoichiometric version

Catalytic version

Catalytic cycle

Scheme 1.11. Reactivity of molecular sodium hydride

Another challenge is the Schlenk equilibrium, that converts molecular state of ionic hydrides into the polymeric form due to the high lattice energy and insolubility (Scheme 1.12a and b).^[9c, 20] Furthermore, the alkali/alkaline earth metal centers display ionic bonding, which causes the supporting ligands to be weakly bonded to the metal center, again, facilitating the formation of the polymeric hydride.

a) Schlenk equilibrium for Group I metal hydride complexes

b) Schlenk equilibrium for Group II metal hydride complexes

Scheme 1.12. Schlenk equilibrium

All in all, the sophisticated design of ligands is required to stabilize the molecular state of ionic hydrides. Stasch et al. developed a protocol for the synthesis of the molecular LiH complex $[(\text{DipNPPH}_2)_4\text{Li}_8\text{H}_4]$ ($\text{Dip} = 2,6\text{-}i\text{Pr}_2\text{C}_6\text{H}_3$) **1.1** by subsequent treatment of the sterically demanding phosphinoamine $\text{Ph}_2\text{PN}(\text{H})\text{Dip}$ with $n\text{-BuLi}$ (2 equiv) followed by phenyl silane in benzene to furnish the LiH complex **1.1** (Scheme 1.13).^[21]

Scheme 1.13. Synthetic route to LiH cluster complex

This LiH complex **1.1** is stable at temperatures below 60 °C, while forming the polymeric LiH at temperature higher than that. Even though it is not truly a monomeric complex, it is one of the simplest molecular LiH complex characterized to date.

The lithium hydride complex $[(\text{DipNPPH}_2)_4\text{Li}_8\text{H}_4]$ **1.1** has enhanced hydridic reactivity capable of reducing dicyclohexylcarbodiimide to the corresponding lithiated amidine (Scheme 1.14a), benzophenone to the corresponding lithium alkoxide (Scheme 1.14b) and azobenzene to the dilithiated hydrazine-1,2-diide (Scheme 1.14c).^[22]

Scheme 1.14. Reactivity of LiH cluster complex

However, there are some limitations to this protocol. The lithium hydride complex **1.1** is inert to 1,1-diphenylethene or 1,2-diphenylacetylene presumably due to the low Lewis acidity of Li cations (Scheme 1.15a). Furthermore, side reactions caused by the ligands via nucleophilic addition of the P and N centers to various unsaturated organic compounds can occur (Scheme 1.15b).

Scheme 1.15. Complications from using LiH cluster complex

The utilization of 3,5-di-*tert*-butyl-1H-pyrazole (pzH) as the sterically demanding ligand is able to stabilize a NaH complex, where a stoichiometric amount of [Na(pz)], *n*-BuNa and diphenylsilane in hydrocarbon solvents are mixed to form the NaH complex [(pz)₆Na₇H] **1.2** (Scheme 1.16). Simply reacting [Na(pz)] with excess amounts of NaH do not furnish the NaH complex **1.2**, exemplifying that it is difficult for the synthesis of such alkali metal hydrides complexes from the polymeric metal hydride salt itself due to the high lattice energy.^[23] To date, this is the only well-defined molecular NaH complex, while no investigation has been done to determine the hydridic reactivity of this complex. The attempt to extend this protocol to synthesis of the molecular potassium hydride was not successful.

Scheme 1.16. Synthesis of Napz and NaH cluster complex **1.2**. CCDC: 1043423^[23]

1.2. Strategies for use of Alkaline Earth Metal Hydrides

Due to their larger lattice energy, it is even more challenging to activate the alkaline earth metal hydrides as compared to the alkali metal hydrides. Therefore, development in this area has only begun in the recent two decades. In this section, representative examples for the synthesis and application of molecular alkaline earth metal hydrides are described.

Initial attempts to synthesize a stable molecular calcium hydride complex was met with difficulty. Harder et al. managed to generate a transient calcium hydride complex via the reaction between the heteroleptic calcium complex **1.3** or the homoleptic calcium complex **1.4** with phenylsilane. However, the complexes are not stable for characterization due to the formation of the polymeric CaH₂ (Scheme 1.17).^[18]

Scheme 1.17. Attempts to synthesized a stable CaH_2 complex

Nevertheless, this transient calcium hydride complex is able to catalyze the hydrosilylation with various olefins in excellent conversion. The mechanism is proposed as follows, the transient molecular calcium hydride complex undergoes hydrometallation onto the olefin in a Markovnikov manner to form the resonance stabilized organocalcium intermediate **D**, that is followed by silylation to form the hydrosilylated product **E** and regenerating the transient calcium hydride complex (Scheme 1.18).

Scheme 1.18. Mechanism for hydrosilylation with transient calcium hydride complex

The use of the bulky β -diketiminate ligand, DIPP-nacnac allows isolation of the stable molecular bridged calcium hydride dimer **1.6** via treatment of calcium silylamide complex **1.5** with phenylsilane (Scheme 1.19).^[24]

Scheme 1.19. Synthesis of calcium dimer complex **1.6**

The resulting calcium hydride complex is proven to be versatile for the hydride reduction of various π -electrophiles such as conjugated alkenes, dienes, ketones, imines, nitriles and isocyanides (Scheme 1.20).^[25]

Scheme 1.20. Reactions of calcium dimer complex **1.6**

However, molecular calcium hydride complex **1.6** was inert to the reduction of unactivated alkenes. Nevertheless, Hill and Maron et al. managed to tune the calcium hydride complex **1.6** to display hydridic reactivity with unactivated terminal alkene such as *n*-butene to form the alkyl calcium complex **1.8**. This enhanced reactivity to alkenes can be achieved by synthesizing a THF-free calcium hydride complex **1.7** from the THF-free calcium silylamide complex and phenylsilane in a 1:3 ratio. The resulting alkyl calcium complex **1.8** was able to perform a nucleophilic ($\text{S}_{\text{N}}2$) displacement of hydride on benzene forming alkylbenzene as a product and regenerating the calcium hydride complex **1.7** (Scheme 1.21).^[26]

Scheme 1.21. Synthesis and reactions of THF-free calcium dimer complex **1.7**

Although these experiments show that it is possible for such complex to react with π -electrophiles, it is not practically feasible as a stoichiometric amount of calcium hydride dimer is needed. The catalytic variants for reduction of several aromatic olefins were developed under a H_2 atmosphere, in which the calcium hydride complex can be regenerated through the reaction of the transient organocalcium intermediate with molecular hydrogen. Calcium hydride dimer **1.6** or even the homoleptic calcium complex **1.4** were used at relatively milder reaction temperature and hydrogen gas pressures (Scheme 1.22a).^[27] Freshly grounded commercial (polymeric) CaH_2 failed to catalyze the above reactions. This emphasizes the importance for *in-situ* generation and solubility of the molecular calcium hydride (Scheme 1.22b).

Scheme 1.22. Catalytic hydrosilylation of alkenes with catalyst **1.4** or **1.6**

Other bulky ligands were developed for the synthesis of soluble molecular calcium hydride complexes. Harder et al. demonstrated the synthesis of a neutral calcium hydride dimer **1.9** using a monoanionic amidinate ligands (Scheme 1.23a).^[20] This hydride complex is shown to be able to catalyze the reduction of imines via a hydride attack to the C-N double bond followed by hydrogenolysis to furnish the product and regenerating the catalyst (Scheme 1.23b).^[28]

Scheme 1.23. Synthesis and reactivity of calcium hydride complex **1.9**

Okuda et al. developed a cationic dicalcium trihydride complex **1.10** using the macrocyclic tetraamine ligand, Me_4TACD . The stability of the complex stems from the multiple coordination of the nitrogen to the calcium center on top of its steric bulk (Scheme 1.24).^[29] This complex shows the enhanced reactivity as compared to the catalyst developed by Harder et al. (Scheme 1.20), capable of catalyzing the hydrogenation of alkenes such as 1,1-diphenylethene, trans-stilbene, styrene and simple aliphatic alkenes under mild reaction conditions at lower hydrogen pressure of 1 bar. The enhanced reactivity is due to the cationic nature of the complex, which imbues high electrophilicity to the metal center. Nevertheless, the reaction is limited to terminal aliphatic alkenes, whereas internal alkenes such as cyclohexene is inert (Scheme 1.25).

Scheme 1.24. Synthesis of calcium hydride complex **1.10**

[a] %Conversion, [b] 25 °C, [c] 60 °C, [d] Dimer was observed in 5%

Scheme 1.25. Reactivity of calcium hydride complex **1.10**

Molecular metal hydrides complexes based on heavier alkaline earth metals such as strontium and barium are even harder to synthesize as compared to the calcium hydride derivatives. This is due to the increased metal sizes, resulting in a lower metal ligand-bond energies that cause the Schlenk equilibrium to shift to the polymeric hydride. Furthermore,

larger metal centers make it difficult to prevent the Schlenk equilibrium by steric bulk. It is only in the past two years that such complexes are being synthesized and characterized. Harder et al. managed to synthesize the strontium hydride complex **1.11** with PMDTA (*N,N,N',N'',N'''*-pentamethyldiethylenetriamine), phenylsilane and strontium silylamide at room temperature in hydrocarbon solvents (Scheme 1.26). However, no experiment was conducted to determine the hydridic reactivity of this complex.^[30]

Scheme 1.26. Synthesis of strontium hydride complex **1.11**. CCDC: 1559999^[30]

The same group succeeded in synthesizing the barium hydride complex **1.12** from the reaction of barium silylamide with phenylsilane at -90 °C. The neutral barium hydride complex is shown to be reactive for reduction of unactivated alkenes such as vinyl silane, and ethene, furnishing the respective alkane product under milder reaction conditions at room temperature (Scheme 1.27).^[31]

Scheme 1.27. Synthesis and reactivity of barium hydride complex **1.12**. CCDC: 1575322^[31]

1.3 Perspective of the thesis

In summary, activation of the ionic hydrides to enhance their hydridic reactivity can be classified broadly under these two categories: 1) *in situ* generation of ionic hydrides; 2) solubilization of ionic hydrides via the formation of a) mixed metal 'ate' complexes, or b) the respective molecular alkali metal and alkaline earth metal complexes using sterically demanding and multiple coordinating ligands. Although these strategies do effectively activate the ionic hydrides, it requires either harsh reaction conditions or long reaction time for generation of the active ionic hydrides. Furthermore, the reactivity of these active ionic hydrides is usually demonstrated on alkenes, ketones and imines instead of the other common functional groups commonly utilized in organic synthesis such as carboxylic acid, amides, ester, and cyano groups, etc.^[32] (with exception from the work done by Harder et al. and Brown et al.). Therefore, there is still a need to develop a robust and general methodology for the reduction of π -electrophiles using ionic hydrides. During the PhD study, the author aims to investigate the reactivity of a sodium hydride-iodide composite that was serendipitously discovered.

1.3.1 Sodium hydride-iodide composite as a hydride donor

During the preparation of α -quaternary benzyl cyanides for the studies in the Cu-catalyzed molecular transformation,^[33] the author serendipitously discovered that simple solvothermal treatment of NaH with LiI or NaI in THF installs unprecedented hydridic reactivity onto NaH. In Chapter 2, use of this NaH-I composite for the hydrodecyanation of α -quaternary benzyl cyanides was discussed. It was found that the hydrodecyanation proceeds via hydride transfer from NaH in the composite onto the cyano group, that affords an iminyl anion intermediate. This was followed by a concerted C–C bond cleavage and 1,2-H-atom transfer to allow for construction of a decyanated tertiary carbon center, which, interestingly, retains the original stereo-configuration installed onto the carbonitriles with generation of sodium cyanide (NaCN) (Scheme 1.28).^[34]

Scheme 1.28. Hydrodecyanation by a NaH-NaI composite

The author was then further intrigued if hydride reduction of other polar π -electrophiles beside the cyano group is possible with the NaH-I composite. It was found that the NaH-I composite was capable of reducing *N,N*-dimethylcarboxamides selectively to the corresponding aldehydes, that was described in the Chapter 3. This protocol displayed versatility and practicability in the reduction of a wide variety of aryl, heteroaryl and aliphatic carboxamide amides into the aldehydes. Retention of α -chirality in α -enantiomeriched amides and chemoselective reduction of amides over ketones and *tert*-butyl esters were featured prominently in the present reduction protocol. The chapter also described the use of sodium deuteride as an economical alternative for the synthesis of deuterated aldehydes in high deuterium incorporation (Scheme 1.29).^[35]

Scheme 1.29. Reduction of *N,N*-dimethylcarboxamides by a NaH-NaI composite

1.3.2 Sodium hydride-iodide composite as a Lewis acid

During the investigation on the controlled reduction of *N,N*-dimethylcarboxamides to the corresponding aldehydes with the NaH-I composite, the author found that the composite had unique Lewis acidity installed on sodium hydride, that enabled amide-directed deprotonative sodiation of ortho-aromatic C-H or benzylic C-H bond to form nucleophilic organosodium intermediates. Subsequent transformations allowed for facile synthesis of ortho-secondary alkyl arylaldehydes, 2-indanones, and phenanthrenes depending on the starting material used. These transformations showed unique reaction outcomes as compared to those mediated by typical amide-directed deprotonative lithiation (Scheme 1.30).^[36]

Unprecedented Lewis acid reactivity

Scheme 1.30. Amide directed C-H sodiation by a NaH-NaI composite

1.4 References

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Chapter 2 Hydrodeacylation of α -Aryl Tertiary Nitriles by a Sodium Hydride-Iodide Composite

2.1 Introduction

2.1.1 Classical Methods for Hydrodeacylation

The electron-withdrawing properties of the cyano group gives a useful functionality for the formation of various carbon-carbon bonds.^[1] This allows the cyano group to be a versatile motif for various manufacture of intermediates, pharmaceuticals and specialty chemicals. Furthermore, it can be cleanly and selectively transformed to a variety of functional groups such as amino, imino, hydroxymethyl, and formyl groups. Reduction of the cyano group into a methyl group or its hydrodeacylation is also possible.^[2]

Hydrodeacylation of nitriles to form the corresponding alkanes in synthesis of various molecular targets can allow the cyano group to be used as a traceless functionality.^[3] The earliest example of such transformation was demonstrated by Arapakos et al., where the treatment of various α -aryl nitriles, tertiary aliphatic nitriles and aromatic nitriles with alkali metal such as lithium or sodium in liquid ammonia under cryogenic reaction conditions furnish the corresponding alkane products.^[4] The mechanism involved a sequential twice single-electron-transfer to form the carbanion via the radical anion. Further protonation gives the reduced alkanes.

Scheme 2.1. Hydrodeacylation via radical/anion crossover

This protocol was adopted more recently by Rychnovsky et al. for the hydrodeacylation of various alkylated cyanohydrin acetonides, which are the key intermediates for the total synthesis of antibiotics roflamycoin and roxaticin.^[5] Interestingly, the reaction proceeds with a retention of original stereochemistry (Scheme 2.2).

Scheme 2.2. Alkylation and hydrodeacylation of cyanohydrin acetonide

Typical hydride source such as lithium aluminium hydride, sodium borohydride, diisobutylaluminum hydride (DIBAL) are used for the hydrodeacylation of substrates having an α -electron-withdrawing group such as sulfonyl,^[6] *gem*-nitrile,^[7] and aminocarbonyl groups.^[8] These stabilizing group are important because of the competing pathway of the expected hydride reduction of nitriles to amines or aldehydes depending on the type of hydride source used.

Chanon et al. described the use of LiAlH_4 for reduction of 2-(isopropylsulfonyl)bicyclo[2.2.1]hept-5-ene-carbonitrile (**2.1**) leading to the decyanated product **2.2** and expected amine **2.3** in 1:1 ratio, showing that the selectivity between hydrodeacylation and reduction of nitriles to amines is moderate (Scheme 2.3).^[6]

Scheme 2.3. Hydrodeacylation of 2-(isopropylsulfonyl)bicyclo[2.2.1]hept-5-ene-carbonitrile (**2.1**)

Another classical method is a base-mediated procedure for the hydrodeacylation of α -arylacetonitriles (Scheme 2.4).^[9]

Basic hydrodeacylation

Scheme 2.4. Acidic and Basic Mediated Hydrodeacylation

The reduction of α -aminoacetonitriles undergoes hydrodeacylation selectively through the formation of the iminium ions, in which various hydride sources such as NaBH_4 , LiAlH_4 , NaBH_3CN and BH_3 are used to furnish the decyanated amines in excellent yield and selectivity (Scheme 2.5).^[3]

Scheme 2.5. Mechanism of hydrodeacylation of α -aminonitriles

The requirement for either electron withdrawing or electron donating groups limits the substrate scope. There are a few reports on hydrodeacylation without these electron withdrawing or electron donating groups. Chanon et al.^[10] investigated the hydrodeacylation process of 2,2-diphenylpropionitrile (**2.4**). The authors were unable to suppress fully the formation of the amine product **2.6**, and thus the decyanated product **2.5** is formed in moderate yield (Scheme 2.6).

Scheme 2.6. Hydrodeacylation process of 2,2-diphenylpropionitrile (**2.1**)

The mechanism, involves a hydride attack on the cyano group to form the iminyl aluminium salt. The resulting imine salt undergoes fragmentation to form a solvent caged carbanion along with HCN and AlH₃. Further protonation in the solvent cage affords decyanated alkane product. Presence of the solvent caged intermediate is supported using LiAlD₄ which gave the reduced product with deuterium incorporating without any hydrogen incorporation (Scheme 2.7).^[10]

Scheme 2.7. Proposed mechanism for LiAlH_4 decyanation reaction

2.1.2 Modern Methods for Hydrodecyanation

There have recently been developed various new methods for versatile hydrodecyanation under milder reaction conditions. For example, Murphy et al. reported the use of organic super electron donor for hydrodecyanation of various malononitriles and α -cyanoacetates to furnish the decyanated products in high yields at room temperature (Scheme 2.8a).^[11] Kang et al. employed samarium(II) iodide and hexamethylphosphoramide (HMPA) for both malononitriles and cyanoacetates at 0 °C (Scheme 2.8b).^[12]

a) Murphy et al. radical/anion crossover

R = alkyl, benzyl, allyl
X = CN, CO_2R

Organic electron donor:

b) Kang et al. radical/anion crossover

R = alkyl, benzyl
X = CN, CO_2R

Scheme 2.8. Modern methods for radical/anion crossover hydrodecyanation

On the other hand, Curran et al. reported a radical hydrogen transfer method for the hydrodecyanation of various malononitriles using a stoichiometric amount of tributyltin

hydride.^[13] The same group recently demonstrated replacement of toxic tributyltin hydride with NHC-borane (Scheme 2.9).^[14]

Curran et al. radical hydrogen transfer

Scheme 2.9. Radical hydrogen transfer hydrodeacylation

The radical hydrogen transfer mechanism was postulated to be an addition of the tributyltin radical or NHC-borane radical to the cyano group, that is followed by fragmentation to give α -cyano radical. Subsequent hydrogen transfer from tributyltin hydride or NHC-borane furnishes the targeted product with regeneration of the tributyltin radical or NHC-borane radical to maintain the radical chain (Scheme 2.10).^{[13][14]}

Scheme 2.10. Radical hydrogen transfer hydrodeacylation mechanism

In 2018, Kawamoto et al. reported the use of methyl thiosalicylate as a catalyst with sodium borohydride for the hydrodeacylation of various unactivated primary and secondary aliphatic nitriles via the radical hydrogen transfer mechanism (Scheme 2.11).^[15]

Kawamoto et al. radical hydrogen transfer

Scheme 2.11. Thio catalysed radical hydrogen transfer hydrodeacyanation

A wider functional group and substrate compatibility can be achieved by transition metal-catalyzed hydrodeacyanation.^[16] Chatani et al. developed a protocol where various aromatic and heteroaromatic nitriles, α -aryl acetonitriles, primary to tertiary aliphatic carbonitriles were treated with diisopropylsilane in the presence of a Rh(I) catalyst, furnishing the corresponding alkanes in good to excellent yield with high functional group tolerance.^[17] This Rh(I)-catalyzed hydrodeacyanation relies on the oxidative addition of silane to the Rh(I) complex to form Si-Rh(III) complex **B**. The nitrile then coordinates to the Rh(III) in a η^2 -fashion to generate the iminoacyl intermediate **C** which undergo a silicon-assisted carbon-cyano bond cleavage to form complex **D**, that is followed by the C-H reductive elimination to form the decyanated product (Scheme 2.12).^[18]

Scheme 2.12. Rh catalysed hydrodeacylation (ligands omitted for clarity)

On the other hand, Maiti et al. demonstrated the Ni(0)-catalyzed hydrodeacylation with tetramethyldisiloxane (TMDS) as the hydride source with similar substrate scope compatibility and process efficiency.^[19] Ni(0)-Ni(II) catalytic cycle was proposed, in which the process is initiated by an oxidative addition of the C-CN bond to Ni(0) to form organo Ni(II) species **F**, that is followed by transmetalation with hydrosilane to form Ni(II) hydride complex **G**. Finally C-H reductive elimination completes the catalytic cycle to form the deacylated product with regeneration of the Ni(0) (Scheme 2.13).^[19]

Scheme 2.13. Ni catalysed hydrodeacylation

2.2 Preliminary Discovery and Working Hypothesis on Use of Sodium hydride (NaH) for Hydrodeacylation

During the course of investigation for the reactivity of tertiary nitriles in Cu-catalyzed molecular transformation in the author's group,^[20] there was a need for preparation of tertiary nitrile **2.8a**. Therefore, methylation of diphenylacetone nitrile under routine reaction conditions using NaH (3 equiv) and MeI (1.2 equiv) in THF was conducted (Scheme 2.14). Although the desired tertiary nitrile **2.8a** was isolated in 74% yield, we were intrigued to observe the formation of 1,1-diphenylethane (**2.9a**) in 25% yield as a side-product. With the assumption that **2.9a** might be formed via hydrodeacylation of nitrile **2.8a**, we expected that this hydrodeacylation reaction could be generalized to a more versatile synthetic strategy. Therefore, the author started to investigate details of this transformation, that can be complementary to the existing methods for hydrodeacylation as discussed in Section 2.1. The detailed results and discussion will be presented below.

Scheme 2.14. Reductive decyanation observed during methylation of (**2.7**)

2.3 Results and Discussion

2.3.1 Preparation of Various Tertiary Carbonitriles

Tertiary carbonitriles **2.8a-2.8w** were synthesized by the following procedures: the alkylation of secondary carbonitriles with alkyl halides (Method A); nucleophilic aromatic substitution of aryl fluorides with secondary carbonitriles (Method B); substitution of tertiary alcohols with cyanide (Method C) (Scheme 2.15 to Scheme 2.17).

Method A: **2.8a-2.8f** and **2.8q-t** and **2.8x** were synthesized via the alkylation of the corresponding secondary carbonitriles with alkyl halides (1.0 – 1.5 equiv) in the presence of NaH (1.2 equiv) at reflux for 2-24 h (Scheme 2.15). **2.8g-2.8j** and **2.8l-2.8o** were synthesized via the double alkylation of benzylnitriles with alkyl halides (1.2 – 3.5 equiv). Use of excess amounts of MeI (for **2.8a-2.8d**, **2.8g-2.8h**, **2.8x**) will caused hydrodeacylation to occur, and therefore it is paramount to add a limited amount of MeI.

Scheme 2.15. Method A

Method B: Nitriles **2.8k**, **2.8p** and **2.8z** were synthesized via the aromatic substitution of various aryl fluorides with carbonitriles (4 equiv) using potassium bis(trimethylsilyl)amide (KHMDs) (1.5 equiv) as a base at reflux (Scheme 2.16).^[21]

Scheme 2.16. Method B

Method C: Nitriles **2.8u-2.8w** were synthesized via the substitution of tertiary alcohols with trimethylsilylcyanide (1.2 equiv) catalyzed by tris(pentafluorophenyl)borane (3 mol%) (Scheme 2.17).^[22]

Scheme 2.17. Method C

2.3.2 Optimization of the Reaction Conditions

Using 2,2-diphenylpropanenitrile (**2.8a**) as the model substrate, optimization of the reaction conditions for hydrodeacylation were commenced (Table 2.1). Treatment of **2.8a** with just 3 equiv of NaH did not afford hydrodeacylated product **2.9a** (entry 1). During the methylation of **2.7** with NaH (3 equiv) and MeI (1.2 equiv) (page 9, Scheme 2.14), NaI should be generated. It could be hypothesized that the cooperation of NaH and NaI is the key to facilitate the hydrodeacylation. Expectedly, the reaction of **2.8a** with NaH (3 equiv) and NaI (2 equiv) gave the corresponding hydrodeacylated product **2.9a** in excellent yield of 96% (entry 2). Other iodide sources were then screened. LiI (2 equiv) rapidly gave 98% of the deacylated product within 3.5 hours (entry 3), while KI (2 equiv) was not sufficient to mediate the hydrodeacylation to occur, affording only 9% of **2.9a** (entry 4). Slower reaction rate was observed with MgI₂ (1 equiv) to give **2.9a** in 96% after 24 h (entry 5). Interestingly, LiBr (2 equiv) or LiCl (2 equiv) was ineffective for the hydrodeacylation (entries 6 and 7), indicating the importance of the dissolving iodide ions to enable the hydrodeacylation efficiently. Reducing the amount of LiI to 1 equiv and even to catalytic amount of 20 mol% allowed the full conversion of **2.8a** albeit with longer reaction time (entry 8 and 9). With LiI as the iodide source, the amount of NaH could be reduced to 2 equiv with full conversion of **2.8a** at an acceptable reaction rate (entry 10).

Entry	NaH (equiv)	Additive (equiv)	Yield of 2.9a (%) ^[b]	Time (h)
1	3	-	trace ^[c]	24
2	3	NaI (2)	96	14
3	3	LiI (2)	98	3.5
4	3	KI (2)	9 ^[c]	40
5	3	MgI ₂ (1)	96	20
6	3	LiBr (2)	8 ^[c]	24
7	3	LiCl (2)	3 ^[c]	24
8	3	LiI (1)	98	6
9	3	LiI (0.2)	98	48
10	2	LiI (1)	98	7

[a] The reactions were conducted using 0.3-0.5 mmol of nitrile **2.8a** in THF (2.5 mL). [b] Isolated yields were recorded. [c] Recovery of **2.8a** in >90% yield was confirmed by ¹H NMR of the crude materials.

[d] Recovery yield of **2.8a**.

Table 2.1. Optimization of the reaction conditions for deacylation of **2.8a**

2.3.3 Scope and Limitation

Having optimized the reaction conditions (Table 2.1, entry 10), the generality of the hydrodeacylation was investigated. This protocol enabled the facile construction of various monoaryl (for **2.9b-2.9p**) and diaryl (for **2.9q-2.9u**) tertiary carbons as well as synthesis of triarylmethanes (for **2.9v** and **2.9w**). Carbonitriles having a cycloalkyl moiety (for **2.9i-2.9p**) underwent hydrodeacylation smoothly to afford the corresponding cycloalkylarenes in good yields. It should be noted that an electron-deficient pyridine ring could be kept intact during the hydrodeacylation (for **2.9p**). It was observed that an electron-rich 4-methoxyphenyl group rendered the reaction rate of the hydrodeacylation slower (for **2.9j** vs **2.9k** and **2.9m** vs **2.9n**) (Scheme 2.18).

[a] The reaction was conducted at a 0.5 mmol scale using 3 equiv of NaH and 1 equiv of Lil.

Scheme 2.18. Substrate scope for the decyanation of various tertiary nitriles

It is worthy to note that the present hydrodecyanation of carbonitriles is complementary to their reduction by aluminium hydrides such as LiAlH_4 and $(i\text{-Bu})_2\text{AlH}$ (DIBAL), which generally provides the corresponding primary amines and aldehydes respectively (Scheme 2.19).^[23] It was also found that the larger scale reaction of **2.8I** in 47 mmol under reflux conditions afforded **2.9I** in 92% yield (Scheme 2.20).^[24]

Scheme 2.19. Typical reduction of nitriles with LiAlH_4 and DIBAL

Reaction set-up

Distillation set-up

Scheme 2.20. Upscaled hydrodecyanation reaction on **2.9I**

2.3.4 Mechanistic Discussion

During the investigation of the substrate scope (section 2.3.3.), it was found that substrates **2.8i** and **2.8t** having pentenyl tether(s) as well as **2.8u** having a cyclopropyl group showed negative effect toward radical clock (no cyclization/ring-opening product was observed).^[25] Moreover, the reactions of **2.8u** in THF-*d*₈ or quenching of the reaction of **2.8u** with D₂O showed no deuterium incorporation (Scheme 2.21a and Scheme 2.21b). The presence of NaOD in the process also did not provide deuterated product (Scheme 2.21c). These experiments unambiguously suggested that the present hydrodeacylation is operated neither via radical nor via step-wise elimination/protonation mechanism.

Scheme 2.21. Deuterium labeling experiments

On the other hand, several substrates provided critical evidence to the elucidation of the reaction mechanism that the present hydrodeacylation is indeed initiated by hydride transfer from NaH to the cyano group. The evidence of the hydride transfer could be obtained through the following two substrates. When the hydrodeacylation of **2.8k** was quenched at 2.5 h (completion of the process needs 24 h), the corresponding aldehyde **2.11k** was isolated in 42% yield together with the decyanated alkane **2.9k** in 37% yield (Scheme 2.22). Isolation of the aldehyde **2.11k** clearly indicated the presence of the iminyl anion intermediate **2.10**, which should be formed via 1,2-hydride addition from NaH to the cyano group.

Scheme 2.22. Investigation of intermediates formed from the reductive decyanation of **2.8k** and **2.8x**

The reaction of *ortho*-chloro substrate **2.8x** afforded not only decyanated product **2.9x** but also dihydroindole **2.12x** in 61% and 17% yield, respectively (Scheme 2.23a). Formation of dihydroindole **2.12x** should occur through *ipso*-aromatic substitution of the chloride by the iminyl anion followed by reduction of cyclic imine. Otherwise, it is also possible that C-N bond forming cyclization of iminyl anion onto the transient benzyne intermediate to form cyclic imine, that is reduced further to form **2.12x** (Scheme 2.23b).

Scheme 2.23. Investigation of intermediates formed from the reduction of **2.8x** and the proposed mechanism on the formation of **2.12x**

The possibility of the hydride transfer from NaH was further supported by the reaction of adamantan-1-carbonitrile (**2.8y**), which gave not only aldehyde **2.13y** in 29% yield but also primary amine **2.14y** in 7% yield, although the mass balance was not very good (Scheme 2.24).

Scheme 2.24. Reduction of adamantan-1-carbonitrile (**2.8y**)

Hydrodecyanation of *exo*-2-(4-methoxyphenyl)-*endo*-2-norbornyl carbonitrile (**2.8z**) afforded *only* *exo*-2-(4-methoxyphenyl)norbornane (**2.9z**) with retention of the original stereoconfiguration (Scheme 2.25a). Furthermore, the hydrodecyanation reaction of the enantioriched nitrile (+)-**2.8b** or (-)-**2.8b** resulted in construction of decyanated tertiary carbon with keeping high ee values, suggesting that the C-C bond cleavage and hydrogen transfer in the hydrodecyanation most likely take place in a concerted process (Scheme 2.25b).

Scheme 2.25. Hydrodecyanation of enantioriched carbonitriles

Based on these experimental outcomes, the following reaction mechanism is proposed (Scheme 2.26). The process is initiated by hydride transfer from NaH to the cyano group to afford iminyl sodium (lithium) intermediate **A**, which subsequently undergoes concerted C-C bond cleavage-1,2-proton shift to give hydrodecyanated product **2** and sodium (lithium) cyanide (NaCN). In the transition state **B** for this C-C bond cleavage, the imine hydrogen atom has partial positive charge (δ^+) and the benzylic carbon does partial negative charge (δ^-), and thus the hydrogen is rearranged to the adjacent carbon (δ^-) via 1,2-proton transfer.

This result demonstrates the unique *umpolung* nature of the decyanation, where the nucleophilic hydride originated from NaH is changed to the electrophilic proton in the later stage.

Scheme 2.26. A proposed reaction mechanism of hydrodeacylation

Formation of Na(Li)CN was further supported by the detection of cyanide ion (2086 cm^{-1}) from the attenuated total reflectance Fourier transform infrared (ATR-FTIR) spectroscopy of the reaction residue (Figure 2.2).

Figure 2.2. FT-IR spectrum for the NaH-NaI sample after the reduction of carbonitriles, showing conversion of the composite to NaCN.

2.4 Conclusion

This chapter described hydrodeacylation of α -quaternary benzyl cyanides by the NaH-LiI composite through the hydride reduction of carbonitriles followed by unique concerted C-C bond/1,2-proton transfer from the iminyl anion intermediate. This work also demonstrated unprecedented nature of NaH as a hydride donor installed by its facile treatment with LiI in THF.

2.5 References

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Chapter 3 Controlled Reduction of N,N-Dimethylcarboxamides to Aldehydes by Sodium Hydride-Iodide Composite

3.1 Introduction

Hydride reduction of carbonyl compounds is one of the most fundamental and important processes in organic synthesis.^[1] Among the various carbonyl compounds, the amide is one of the least susceptible to hydride reduction as compared to the other carbonyl groups.^[2] This is due to the resonance stability of the amide bond and the orbital overlap of the lone pair from the nitrogen to the *anti*-bonding orbital of the carbonyl group. The delocalization causes the amide bond to have a partial double-bond character, which induces the planarity of the bond thus reducing the electrophilicity of the carbonyl carbon. These bench-stable amides are used as versatile precursor to be reduced into amines and alcohols as well as aldehydes.^[3] To perform an efficient and selective reduction of amides to aldehydes, specific setups in the amide substituents, reductants, and/or reaction conditions are required to prevent the fragmentation of the transient tetrahedral metalated aminal intermediates, that are formed by the 1st hydride transfer to the amides, to imine/iminium or aldehyde intermediates. These imine/iminium or aldehyde intermediates are more reactive towards the hydride reduction, resulting in their over-reduction to amines and alcohols (Scheme 3.1). In this section, the representative examples of the reaction and substrate setups, that allow for controlled reduction of amides into aldehydes, will be briefly introduced.

Scheme 3.1. Different pathways for the reduction of amide

3.1.1 Reduction of Amides to Aldehydes Controlled by Amide Substituents

Use of *N*-methoxy-*N*-methyamides (the Weinreb amides) is perhaps one of the most promising ways to control the reduction of amides into aldehydes, that proceeds via the stabilized tetrahedral five-membered-chelate intermediates to prevent the over-reduction.^[4] Reactive hydride donors such as lithium aluminium hydride, diisobutylaluminium hydride and sodium bis(2-methoxyethoxy)aluminium hydride (Red-Al) are commonly used under cryogenic reaction conditions (commonly at $< 0\text{ }^{\circ}\text{C}$) (Scheme 3.2a). Another alternative to the Weinreb amides is the use of morpholides, which also induce formation of stabilized chelate intermediates (Scheme 3.2b).^[5]

Scheme 3.2. Weinreb and morpholine amides and their intermediates

The use of amides that reduces the electron-donating capabilities of the amide nitrogen to the carbonyl group has also been reported, such as *N*-acyl sultam,^[6] *N*-acyl saccharin,^[7] *N*-acyl carbazoles,^[8] and aziridine amides,^[9] while the substrate scope was not investigated in details. Similarly, in these cases, cryogenic reaction conditions must be used to prevent the over-reduction (Scheme 3.3).

Other specialized amides

Scheme 3.3. Other special amides for selective reduction to aldehydes

3.1.2 Hydride Reagents that Controls Reduction of Amides to Aldehydes

The reduction of simple *N,N*-dialkylamides using reactive hydride source such as lithium aluminium hydride typically gives the over reduction products. Nevertheless, the use of modified hydride reagents such as $\text{LiAlH}_n(\text{OEt})_{4-n}$ ($n = 1$ or 2),^[10] disiamylborane,^[11] and lithium diisobutylpiperidinoaluminum^[12] enables the controlled reduction of simple *N,N*-dimethylamides to its corresponding aldehydes. However, these typical aluminium hydride reagents requires tedious workup procedures to remove the aluminium salts generated upon aqueous quench of the processes, while disiamylborane reagents requires oxidative workup with NaOH and H_2O_2 to cleave the B-O bond in the tetrahedral intermediates.

It is recently revealed that the Schwartz's reagent $[\text{Cp}_2\text{Zr}(\text{H})\text{Cl}]$ is able to reduce a variety of simple amides to the corresponding aldehydes via a stable, 18-electron zirconacycle intermediate under very mild reaction conditions in a short duration.^[13] The reaction is chemoselective with a wide range of functional groups such as cyano (for **3.1**), nitro (for **3.2**), acetyl (for **3.3**) and alkoxy carbonyl (for **3.4**) groups (Scheme 3.4).

Scheme 3.4. Reduction with Schwartz's reagent and its representative examples

However, it is not chemoselective to the keto carbonyl groups and terminal alkyne as both functional groups are reduced by the Schwartz's reagent. The reagent is also sensitive to light, air and moisture. To overcome this shortcoming, Snieckus and co-worker developed a protocol for one pot *in-situ* generation of the Schwartz's reagent (Scheme 3.5).^[14] However, in large-scale processes, the need for stoichiometric use of Schwartz's reagent still hinders its application due to waste and cost.

Scheme 3.5. One pot *in-situ* generation of Schwartz's reagent

There are several methods of reducing amides to aldehydes by combined use of hydrosilanes and transition metals. Buchwald et al. developed a protocol to reduce simple secondary and tertiary amides into aldehydes using a stoichiometric amount of $\text{Ti}(\text{O}i\text{Pr})_4$ and diphenylsilane, that proceeds via the enamine intermediate.^[15] The process is tolerant of a wide range of functional groups such as cyano (for **3.5**), epoxide (for **3.6**), terminal alkyne (for **3.7**), alkenyl (**3.8-3.9**) groups (Scheme 3.6). However, as the process involves an enamine intermediate, reduction of α -quaternary amides was not suitable. Furthermore, the reduction of α -chiral amides will result in the complete racemization.

Hydrosilanes and $\text{Ti}(\text{O}i\text{Pr})_4$

Scheme 3.6. Reduction with catalyst and its representative examples

Adolfsson et al. developed $\text{Mo}(\text{CO})_6$ -catalyzed reduction of various piperidine amides using tetramethyldisiloxane (TMDS) as a hydride source, furnishing the respective aldehydes via the silylhemiaminal intermediate.^[16] Temperature control is the key to enable selective formation of aldehydes over that of amines (-5 to 60°C), and the process has a wide range of chemoselectivity over other reducible functional groups such as cyano (for **3.10**), nitro (for **3.11**), methoxycarbonyl (for **3.12**), acetyl (for **3.13**), vinyl (for **3.14**), formyl (for **3.15**) and even iminyl (for **3.16**) groups (Scheme 3.7).

Hydrosilanes and Mo catalyst

Scheme 3.7. Reduction with hydrosilanes and Mo catalyst and its representative examples

However, the limitation of this protocol is that only aryl, heteroaryl and α -quaternary amides undergo the reduction smoothly, whereas that with α -secondary amides such as 2-phenyl-1-(piperidin-1-yl)ethanone (for **3.17**) only gave the corresponding enamine (Scheme 3.8a) and 1-(piperidin-1-yl)pentan-1-one (for **3.18**) gave a mixture of enamine and amines (Scheme 3.8b).

[a] No yield was reported

Scheme 3.8. Limitations of Mo mediated amide reduction

Metal-free reduction of secondary amides was developed by Charette et al., that is mediated by conversion of secondary amides into O-Tf imidate salts with Tf_2O followed by subsequent

reduction by Et_3SiH to give aldehydes (Scheme 3.9).^[17] The reaction is of high tolerance to cyano (for **3.19**), nitro (for **3.20**), azido **3.21**, and methoxycarbonyl (for **3.22**) groups. Due to the mechanistic nature, this protocol is only applicable to the secondary amides. This nature can be used for chemoselective reduction of secondary amides over tertiary one (for **3.23**). Various aliphatic amide bearing α -quaternary carbon (for **3.24**), α -tertiary carbon (for **3.25**) and even α -secondary carbon (for **3.26**) are tolerated.

Hydrosilanes through electrophilic activation of 2°-amides

Scheme 3.9. Reduction with hydrosilanes through electrophilic activation of 2°-amides and its representative examples

3.2 A perspective of this chapter

Despite the recent progress, there is still ample room to develop methods for reducing simple amides to aldehydes that can be conducted in operationally simple and cost-effective manner under milder reaction conditions.

The author discovered that sodium hydride (NaH) could act as a hydride donor in the presence of NaI or LiI in THF, and is capable of performing hydrodeacylation of carbonitriles, that is supposed to proceed via hydride reduction of the cyano group to form iminylsodium intermediate followed by the C-C bond cleavage (Scheme 3.10a).^[18] In this context, the author became interested in use of the NaH-iodide composite for the reduction of amide and their derivatives.^[19] The detailed results and discussion will be described below (Scheme 3.10b).

a) Hydrodeacylation (Chapter 2)

b) Reduction of amides to aldehydes (this chapter)

Scheme 3.10. Various reductions by NaH-NaI composite

3.3 Results and Discussion

3.3.1 Preparation of Starting Materials

Various *N,N*-dimethylamides were synthesized through the following two procedures; amidation of carboxylic acid via the acyl chlorides (Method A) and amidation of carboxylic acid via the mixed anhydride (Method B).

Method A: Amides **3.27a-3.27u** and **3.28a-3.28j** and **3.28l** were synthesized from the corresponding carboxylic acids via their conversion into acyl chlorides using oxalyl chloride (1.5 equiv) in the presence of catalytic amount of DMF in dichloromethane at room temperature or thionyl chloride (solvent amount) at reflux for 2-16 h. Subsequently, amidation was done by adding dimethylamine (4 equiv) or diethylamine (4 equiv). Amidation with other amines such as diisopropylamine (1.2 equiv), morpholine (1.2 equiv) and piperidine (1.2 equiv) were conducted in the presence of triethylamine (3 equiv). The isolated yields were summarized (Scheme 3.11a and Scheme 3.11b).

Scheme 3.11a. Method A for aromatic amides

Scheme 3.11b. Method A for aliphatic amides

Method B: Amides **3.28k** and **3.29a-3.29m** were synthesized from the corresponding carboxylic acids via formation of the mixed anhydride using triethylamine (1.1 equiv) and ethyl chloroformate (1.1 equiv). The resulting mixed anhydrides were treated with dimethylamine (4 equiv) for the formation of the amides. The isolated yields were summarized below (Scheme 3.12).

Scheme 3.12. Method B

Amides **3.27c** and **3.27d** were synthesized via the base-mediated etherification of 4-hydroxyphenyl carboxamides. Alkylation was performed using MOMCl (1.1 equiv), BnBr (1.1 equiv) in the presence of NaH (1.2 equiv) as a base. On the other hand, amides **3.30-3.33** bearing an alkoxy carbonyl tether were synthesized by etherification with the corresponding 5-bromo-2,2-dimethylpentanoates (1.2 equiv) in the presence of K_2CO_3 (1.2 equiv) as a base and KI (0.3 equiv) as an additive (the Finkelstein reaction).^[20] The isolated yields were summarized below (Scheme 3.13).

[a] Method was used for synthesis of **3.27c-d**. [b] Method was used for synthesis of **3.30-3.33**

Scheme 3.13. Further derivatisation of 4-hydroxyphenyl carboxamide

The keto amide **3.34** was synthesized via the α -alkylation of N,N-dimethylisobutyramide with 2-(4-bromobutyl)-2-phenyl-1,3-dioxolane (1.2 equiv) using LDA (1.2 equiv) as a base. Deprotection of the acetal moiety was subsequently carried out with 3M HCl aqueous solution (10 equiv) (Scheme 3.14).

Scheme 3.14. Alkylation of N,N-dimethylisobutyramide

3.3.2 Optimization of the Reaction Conditions for Controlled Reduction of N,N-Dimethylamides into Aldehydes

Using N,N-dimethyl-2-naphthamide (**3.27a**) as the model substrate, the author started to investigate the reactivity of the NaH-iodide composites toward the reduction of **3.27a** (Table 3.1). The reduction of **3.27a** with NaH (3 equiv) and NaI (1 equiv) in THF at 85 °C (in sealed tube) was completed within 1 h to give 2-naphthaldehyde (**3.35a**) in 90% yield as a sole product (Table 3.1, entry 1). Surprisingly, the transient tetrahedral hemiaminal intermediate could be kept stable even at high reaction temperature (85 °C), enabling selective formation of aldehyde **3.35a**. This unprecedented discovery stimulated the author to further to optimize the reaction conditions to render the reduction process more selective and versatile.^[21] The reaction rate was rendered slower when the iodide additive was changed to LiI (entry 2), while maintaining its selectivity. Lowering of the reaction temperature to 40 °C for the NaH-NaI system could also complete the process and the yield of **3.35a** was improved to 93% (entry 3). This reduction of temperature, despite longer reaction time required, was advantageous to make the process more selective (vide infra). Further lowering of the reaction temperature to 25 °C or the amount of NaI to 0.1 equivalent made the reaction incomplete even after 24 h (entries 4 and 5). Again, the sole use of NaH in the absence of iodide additives was not sufficient to drive the hydride reduction, exhibiting the important role of the dissolving iodide ions to facilitate the hydride reduction (entry 6).

Entry	iodide (equiv)	Temperature (°C)	Time (h)	Yield 3.35a (%) ^[b]
1	NaI (1)	85	3	90
2	LiI (1)	85	6	89
3	NaI (1)	40	10	93
4	NaI (1)	25	24	(63) ^[c]
5	NaI (0.1)	40	24	(23) ^[d]
6	-	40	10	— ^[e]

[a] The reactions were conducted using 0.5 mmol of amide **3.27a** in THF (0.2 M). [b] Yields of isolated products. [c] ¹H-NMR yield based on internal standard. **3.27a** was recovered in 36% yield. [d] ¹H-NMR yield based on internal standard. **3.27a** was recovered in 74% yield. [e] **3.27a** was recovered in >95% yield based on internal standard.

Table 3.1. Optimization of reaction conditions

3.3.3 Scope and Limitation

Having optimized the reaction conditions, the author next investigated the substituent effect of the amide nitrogen (Scheme 3.15). As the steric demand increases, the reaction become more sluggish. The reduction of diisopropylamide **3.27bc** was not completed even after 24 h, providing only 7% yield of aldehyde **3.35bc** with 70% recovery of **3.27bc**. Cyclic piperidine and morpholine amides **3.27bd** and **3.27be** showed similar reactivity as that of diethylamide **3.27bb**.

Scheme 3.15. Investigation of the substituent effect on the amide nitrogen

Reduction of various aromatic N,N-dimethylamides was then examined (Scheme 3.16). Electron-donating substituents, such as methoxy, methoxymethoxy (MOMO-), benzyloxy, methylenedioxy as well as dimethylamino moieties could be well tolerated, and the corresponding aldehydes were obtained in 78-94% yields (for **3.35b-3.35h**). Sterically hindered benzamides having *ortho*-methyl **3.27i** and *ortho*-benzyl **3.27j** groups and 1-naphthamide **3.27k** could be reduced smoothly to its corresponding aldehydes (**3.35i-3.35k**). However, the reduction of 2,6-dimethylbenzamide (**3.27l**) became sluggish, indicating that this protocol is sensitive to the steric hindrance for aromatic substrates.

Ferrocenecarboxamide **3.27m** was reduced to ferrocenecarboxaldehyde (**3.35m**) in 93% yield. It should be worthy to note that the present reaction conditions allowed for chemoselective reduction of amides into benzaldehydes keeping C-halogen bonds such as the C-Cl (for **3.35o**) and C-Br (for **3.35p**) bond intact. Reduction of electron-deficient amides (**3.27q-3.27s**) also worked well, giving the corresponding aldehydes (**3.35q-3.35s**) in good yields, while that of α,β -unsaturated amide **3.27u** afforded **3.35u** in moderate yield.

[a] Unless otherwise stated, the reactions were conducted using 0.5 mmol of **3.27** with 3 equiv of NaH and 1 equiv of NaI in THF (2.5 mL: 0.2 M) at 40 °C and isolated yields of aldehydes **3.35** were noted above. [b] ¹H NMR yield with aid of internal standard. [c] **3.27l** was recovered in 81% yield based on internal standard. [d] The reaction was conducted using N¹,N¹,N⁴,N⁴-tetramethylterephthalamide (**3.27t**) with 5 equiv of NaH and 2 equiv of NaI at 85 °C

Scheme 3.16. Substrate scope for aromatic amides

The reduction of various heteroaromatic amides were also tested (Scheme 3.17 and 3.18). Electron-rich 5-membered heteroaromatic substrates were first screened (Scheme 3.17). Reduction of N-methyl-2-indolecarboxamide **3.29a** and N-benzyl-2-pyrrolicarboxamide **3.29b** gave the corresponding aldehydes (**3.36a** and **3.36b**, respectively) in excellent yields. N-Unprotected 2-pyrrolicarboxamide **3.29c** could also be reduced in good yield, while the use of 5 equivalents of NaH and, 2 equivalents of NaI was required to complete the process. Dilution of the reaction mixture (from 0.2 M to 0.1 M), which was required to realize efficient stirring to ensure the completion of the process. Other electron-rich heteroaromatic amides based on furan **3.29d**, thiophene **3.29e**, and benzothiophene **3.29f** could be converted into the corresponding aldehydes in good to moderate yields (for **3.36d-3.36f**).

Scheme 3.17. Substrate scope for electron-rich heteroaromatic amides

On the other hand, it is known that electron-deficient 6-membered-ring aromatic heterocycles are susceptible to the conventional hydride reductants.^[22] In this regard, use of the NaH-NaI composite is advantageous as quinoline and pyridine scaffolds were tolerated during the hydride reduction of the amide moiety (for **3.36g-3.36m**). In order for the yields to be reproducible, there is a need to maintain these electron-deficient heteroaromatic aldehydes at a neutral pH. Therefore, the reaction should be reversely quench with pH 7 phosphate buffer to maintain the bulk solution at neutral pH. When the reaction of **3.29g** was

quenched normally the product **3.36g** obtained was 38% as compared to 53% when the reaction was quenched inversely (Scheme 3.18).

Scheme 3.18. Substrate scope for electron-poor heteroaromatic amides

Various quinoline (**3.29g-3.29j**) and pyridinecarboxamides (**3.29k-3.29m**) were reduced to the corresponding aldehydes (**3.36g-3.36m**) in good to moderate yields. Nevertheless, this protocol is capable of reducing 7-chloro-2-phenylquinoline-4-carboxamide **3.29i** to 7-chloro-2-phenylquinoline-4-carboxaldehyde (**3.36i**), which is a key intermediate for supplying a quinolone-based anti-cancer agent.^[23] The controlled reduction of carboxamide **3.29i** to aldehyde **3.36i** avoids the oxidation step and the usage of transition metal as compared to the patented route (Scheme 3.19).

Scheme 3.19. Comparison with patented route

Finally, the reduction of aliphatic amides was investigated (Scheme 3.20). The present protocol is capable of reducing α -quaternary carbon (**3.28a-3.28e**) (Scheme 3.20a), including those derived from drug molecule, gemfibrozil (for **3.37d**) and natural product, abietic acid (for **3.37e**). It was also found that the reduction of α -tertiary amides having one enolizable proton (**3.28f-3.28k**) gave the corresponding aldehydes (**3.37f-3.37k**) in good yields, emphasizing that the mild reaction conditions enables such functional group tolerance (Scheme 3.20b). The method is compatible with aldehydes based on aliphatic heterocycles such as tetrahydropyran **3.37i**, piperidine **3.37j**, and pyrrolidine **3.37k** moieties. Piperidine-4-carboxaldehyde **3.37j** was used for the production of donepezil hydrochloride, an *anti*-Alzheimer drug (Scheme 3.21).^[24] The reduction of amide **3.28j** in 4.1 mmol scale afforded aldehyde **3.37j** in 75% yield. The reaction conditions were optimal for the reduction of α -secondary amide **3.28l** giving the aldehyde **3.37l** in 77% when the reaction was reversely quenched with pH 7 phosphate buffer. Normal quenching furnished the aldehyde **3.37l** in 18% yield (Scheme 3.20).

a) Reduction of α -quaternary amides

b) Reduction of α -tertiary/secondary amides

[a] The reactions were conducted using 0.5 mmol of amides **3.28** with 3 equiv of NaH and 1 equiv of NaI at 40 °C in THF (0.2 M) and isolated yields of aldehydes **3.37** were noted above. [b] The reaction was conducted using 1 g (4.1 mmol) of **3.28j** at 60 °C. [c] The reactions were conducted using 5 equiv of NaH and 2 equiv of NaI.

Scheme 3.20. Substrate scope for aliphatic amides

Scheme 3.21. Synthetic route to donepezil hydrochloride

Encouraged by the mild reaction conditions and the tolerance to substrates containing enolizable α -protons (for **3.37f**-**3.37l**), the author investigated the possibility of the retention of stereochemistry in the reduction of α -enantiomerized amides. It was found that the current protocol, even with the inherent basicity of NaH, is amenable to reduce α -enantiomerized amides **3.28f**^[25] and **3.28k** to afford the corresponding aldehydes **3.37f** and **3.37k** in high ee (Scheme 3.22). Prolinal **3.37k** was further converted into alcohol **2.34k** for the purpose to measure the ee by the Mosher method.^[26] It should be noted that inverse quench with pH 7 phosphate buffer was required to prevent unwanted epimerization of the product, as normal quenching caused the enantiomeric excess of **3.38k** to be reduced to 80% ee due to the generation of NaOH in the aqueous layer when quenching with water.

[a] The reaction mixture was quenched by pouring the reaction mixture into pH 7 phosphate buffer solution.
 [b] Parenthesis are the yields and ee obtained by quenching the reaction mixture with water

Scheme 3.22. Reduction of various α -enantiomerized amides

To prove that NaH is acting as the hydride donor in the present reduction, use of NaD^[27] was attempted. The reduction of aromatic amides (**3.27a**-**3.27b**) by NaD resulted in formation of the corresponding deuterated aromatic aldehydes **3.35a**-[D] and **3.35b**-[D] with high

deuterium incorporation rate of 93% and 95%, respectively (Scheme 3.23). Similarly, the reduction of aliphatic amide **3.28a** afforded 90% deuterium incorporation in **3.37a-[D]**. These results unambiguously support the role of sodium hydride as a hydride donor. Moreover, this protocol provides a direct and concise method to supply deuterated aldehydes with high deuterium incorporation rate, given the fact that existing methods involve use of expensive reagents and/or require multistep routes for their preparation.^[28]

Scheme 3.23. Deuterium labeling experiments

It was also found that the NaH-NaI composite shows unprecedented chemoselectivity for reduction of amide over ketone. The reaction of benzamide **3.30** having a tethered keto carbonyl group with the NaH-NaI composite proceeded smoothly to give benzaldehyde **3.39** in 88% yield keeping the keto moiety intact (Scheme 3.24). Remarkably, the reduction of keto amide **3.34** exclusively afforded keto aldehyde, which spontaneously cyclized to 2-hydroxycyclohexyl phenyl ketone **3.40** as a sole diastereomer via the Schmidt-Claisen type aldol condensation due to the inherent basicity of NaH.^[29]

Scheme 3.24. Chemoselective reduction of amides over ketones

The author also examined the chemoselectivity for the reduction of amide over ester. However, this chemoselectivity can only be observed when the sterically hindered tert-butyl ester **3.33** was used giving the corresponding aldehyde **3.44** in 76% yield. The reduction of less sterically hindered methyl and isopropyl esters **3.31** and **3.32** resulted in incomplete conversion with formation of carboxylic acid **3.42** even after 24 h (Scheme 3.25). Formation of carboxylic acid **3.42** is probably due to the presence of NaOH in NaH and that somehow hampered the hydride reduction.

[a] Starting material **3.31** was recovered in 84% yield. [b] Starting material **3.32** was recovered in 71% yield

Scheme 3.25. Chemoselective reduction of amides over esters

It was found that the reduction of ethyl benzoate **3.45** at higher temperature gave a mixture of alcohol **3.46**, mixed ester **3.47**, and carboxylic acid **3.48** due to the inherent basic nature of NaH (Scheme 3.26).

Scheme 3.26. Hydride reduction of ethyl esters

3.4 Conclusion

The author has developed a new and concise protocol for selective reduction of a series of N,N-dimethyl amides into the corresponding aldehydes using the NaH-NaI composite under mild reaction conditions. The protocol is capable of reducing variety of amides ranging from aromatic, heteroaromatic and a wide variety of aliphatic amides. Remarkably, the reduction of α -enantioriched aliphatic amides proceeded with retention of enantiomeric excess. Use of sodium deuteride (NaD) offers a new step-economical alternative to prepare deuterated aldehydes with high deuterium incorporation rate. The method exhibits unique chemoselectivity for reduction of amides over other carbonyl functions such as ketones and tert-butyl esters.

3.5 References

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Chapter 4 Amide-Directed C-H Sodiation by a Sodium Hydride-Iodide Composite

4.1 Introduction

Directed C-H metalation has been used as one of the most efficient tools for the regioselective way of converting relatively inert C-H bonds into nucleophilic organometallic species, which are used for synthesis of functionalized aromatic compounds.^[1]

Directed C-H metalation commonly requires the utilization of a strong base, typically organolithium/magnesium reagents and lithium/magnesium amides with a series of directing group. Representative examples are shown in Scheme 4.1.

a) Strong Directing Group

b) Moderate Directing Group

c) Weak Directing Group

Scheme 4.1. Different directing group

These directing groups enhance the rate and regioselectivity of the metalations depending on their relative strength in directing the metalation. In this aspect, several mechanistic concepts to explain these metalations have been presented, that are summarized in the following sections.

4.1.1 Complex-induced Proximity Effect

Complex-induced proximity effect (CIPE) is used to describe the situation before the metalation step, where the reactive groups, both base and substrates, are brought together in close proximity via the coordination of the Lewis basic directing group and the Lewis acidic metal base, thus accounting for the observed regioselectivity (Scheme 4.2). This lowers the activation energy to enable the smooth C-H metalation.

a) *ortho*-metalation

b) lateral metalation

Scheme 4.2. CIPE effect on directed *ortho*- and lateral metalation

4.1.2 Kinetically Enhanced Metalation

In another mechanistic proposal, Schleyer et al. has proposed that the complexation of the base with the directing group and the proton abstraction occurs in a concerted fashion (Scheme 4.3).^[2] It was suggested that the directing and kinetic enhancement for the metalation are attributed to the transition state structure during the deprotonation step instead of the pre-metalation complex explained in the CIPE mechanism. Kinetically enhanced metalation focuses on both the agnostic interaction between the metal and the acidic hydrogen atom which lowers the energy level of the transition state.

a) *ortho*-metalation

b) lateral metalation

Scheme 4.3. Kinetically enhanced metalation effect on directed *ortho*- and lateral metalation

These two metalation can thus be combined together to explain the complete picture of directed C-H metalation as described by Mortier et al., in which the metalation proceeds by a two-step mechanism is suggested.^[3] Firstly, the reversible CIPE effect takes place, that is followed by the kinetically enhanced metalation, that is rate-determining (Figure 4.1). This considers both mechanistic proposals where firstly, the reactants are brought into close proximity with each other via the chelation of the base and the directing group. Secondly,

they are held in exactly the right orientation before deprotonation can occur. Both lower the activation energy of the transition state due to complexation and this combined mechanism can be used even when the geometries of the precursor complex and transition structure are totally different.

Figure 4.1. Energy level diagram for combined mechanism^[3]

These mechanistic proposals are used to explain widely utilized directed lithiation reactions.^[1, 3] Although they can also be extended to sodiation reactions, the examples are still rare probably due to the instability and accessibility of organosodium intermediate despite the lower cost of metallic sodium and its derivatives.^[4] In the following section, the reported examples of directed sodiation are highlighted.

4.1.3 Directed C-H Sodiation

The first example on directed C-H sodiation for aromatic $C(sp^2)$ -H bonds was reported by Gilman et al. in 1939. *n*-Butylsodium was used for *ortho*-sodiation of anisole **4.1** to generate arylsodium intermediate, that was captured with carbon dioxide to form benzoic acid **4.2** (Scheme 4.4a).^[5] On the other hand, the first example on directed benzylic $C(sp^3)$ -H sodiation was reported by Morton et al. in 1954, whereby *o*-methyl anisole **4.3** was laterally metalated with *n*-amylsodium and subsequent treatment of the resulting benzylnsodium with carbon dioxide gave the corresponding phenylacetic acid **4.4**, while the isolated yield was very low (Scheme 4.4b).^[6]

a) First example on directed *ortho*-sodiation

b) First example on lateral sodiation

Scheme 4.3. First examples on directed *ortho*- and lateral metalation

The poor yields for both reactions were due to the instability of alkylsodium reagents in ethereal solvents. In addition, the high basicity of alkylsodium deprotonates the relatively acidic α -proton of the THF to furnish the sodium enolate and ethylene (Scheme 4.4a). Similarly, the reaction in diethyl ether causes α -deprotonation followed by deprotonative fragmentation to form sodium ethoxide and ethylene (Scheme 4.4b).^[7]

Scheme 4.4. Alkylsodium reactions with ethereal solvents

Another issue is the Wurtz coupling, happening during the treatment of organohalides with sodium for the preparation of alkylsodium. The resulting alkylsodium is highly reactive and reacts with the remaining organohalides (Scheme 4.5).^[4]

Synthesis of organosodium

Wurtz coupling

Scheme 4.5. Wurtz coupling of organosodium

Furthermore, the alkylsodium reagents are unstable thermally as it will undergo β -hydride elimination. Ethylsodium is known to decompose at 100 °C to form ethene and sodium hydride (NaH) (Scheme 4.6a).^[8] Similar decomposition profile was encountered with higher analogues of alkylsodium reagents. Pentylsodium decomposes to form *trans*-pent-2-ene and NaH via the base mediated isomerization of pentene with pentylsodium give *trans*-pent-2-ene (Scheme 4.6b).^[9]

Scheme 4.6. Thermal decomposition of alkylsodium compounds

In 2002, Mioskowski et al. managed to overcome these issues by developing a one-pot *ortho*-sodiation protocol by generating the alkylsodium *in-situ* to avoid its handling and storage.^[10] This protocol enabled the *ortho*-sodiation of 1,3-dimethoxybenzene (**4.5**), and treatment of the resulting arylsodium intermediate with various electrophiles gave the corresponding products in high yields. The protocol was extended for the synthesis of biaryls using either chlorobenzene or chloroanisole as electrophiles via either the $\text{S}_{\text{N}}\text{Ar}$ or the aryne pathway depending on the position of the methoxy group (Scheme 4.7). When the methoxy group is at the *ortho*-position, the mechanism follows a chelation driven $\text{S}_{\text{N}}\text{Ar}$. However, when the methoxy group is located at the *meta*- or *para*-position, the coupling proceed via the benzyne intermediate. It should be noted that the reaction rate of the biaryl coupling with the arylsodium is much faster than that of aryllithium.^[11]

Scheme 4.7. *In-situ* generation of alkylsodium for *ortho*-metalation

Collum et al. recently developed a protocol for *ortho*-sodiation by sodium diisopropylamide (NaDA), which can be generated rapidly using diisopropylamine with sodium dispersion, in *N,N*-dimethylethylamine (DMEA) solution and formed as a dimer bridged with Na cations.^[12] The resulting NaDA underwent directed metalation of a variety of arenes including mono and di-substituted benzenes as well as pyridines and furans (Scheme 4.8).

Scheme 4.8. Synthesis of sodium diisopropylamide (NaDA) and its reactions

Mulvey et al. reported use of bimetallic sodium-magnesium monoalkyl bisamido complex [(TMEDA)Na(μ -Bu)(μ -TMP)Mg(TMP)] (**4.6**), which was prepared by combining the individual monometallic alkyl base and treating it with 2,2,6,6-tetramethylpiperidine (TMP) and tetramethylethylenediamine (TMEDA) (Scheme 4.9a).^[13] This bimetallic base was able to metalate benzene and toluene efficiently, while their respective alkyl bases gave either low or no yield. Furthermore, this synergic approach allowed access to *meta*-substituted derivatives as treatment of the metalated toluene **4.7** with TMSOTf gave the trimethyl *meta*-tolylsilane **4.8** quantitatively (Scheme 4.9b).

Scheme 4.9. Synthesis of $[(\text{tmEDA})\text{Na}(\mu\text{-Bu})(\mu\text{-tmp})\text{Mg}(\text{tmp})]$ and the *meta* metalation of toluene

More recently, Mulvey et al. have extended this work to *ortho-meta'*- and *meta-meta'* dimetalations using sodium magnesiate complex **4.9** prepared by mixing of a 2:1:3 ratio of *n*-BuNa, *n*-Bu₂Mg and TMP (Scheme 4.10).^[14]

Scheme 4.10. Synthesis of bimetallic base $[\text{Na}_4\text{Mg}_2(\text{TMP})_6(n\text{-Bu})_2]$ (**4.9**)

This bimetallic base **4.9** was able to metalate either at the *ortho-meta'*- and *meta-meta'* position depending on the directing groups; amino and sterically hindered directing group gave the latter, while methoxy, tert-butoxy and trifluoromethyl directed *ortho-meta'*-positions. Metalated aromatic compounds were treated with a variety of electrophiles such as iodine, carbon dioxide and D₂O, providing the functionalized arenes in moderate to excellent yields (Scheme 4.11).

Scheme 4.11. Various directed metalation using bimetallic base $[\text{Na}_4\text{Mg}_2(\text{TMP})_6(n\text{-Bu})_2]$

4.2 Result and Discussion

4.2.1. A Preliminary Finding

During the investigation of the reduction of N,N-dimethylamides into aldehydes using the NaH-NaI system (Chapter 3), the author found that the reduction of α -arylamide **4.10a** did not afford expected α -quaternary aldehyde **4.12** at all, but provided 3-isopropyl-2-naphthaldehyde (**4.11a**) in 64% yield (Scheme 4.12a). This outcome is in sharp contrast to that from reduction of amide **4.13**, that delivered the corresponding α -quaternary aldehyde **4.14** as a sole product (Scheme 4.12b).

a) Reaction of α -arylacetamide

b) Hydride reduction of *N,N*-dimethyl amides to aldehydes

[a] Reactions were conducted using 0.5 mmol of **4.10a** in THF (2.5 ml: 0.2 M) and yields of isolated **4.11a** are noted above. No reaction was observed without NaI

Scheme 4.12. Reactions of aliphatic amides with NaH-I composite.

This migration of the formyl group in the formation of **4.11a** was supposed to be mediated by a sequence of directed sodiation and anionic C-Fries type rearrangement (Scheme 4.13).^[15] Namely, the NaH-NaI composite should bear reasonable Lewis acidity to form acid-base complex **A** with the Lewis basic amide moiety. With complex induced proximity effect (CIPE), subsequent *ortho*-deprotonation takes place to form arylsodium **B**, that undergoes nucleophilic addition to the amide carbonyl group to form 4-membered ring anionic carbinolamine **C**. To release the ring strain of **C**, further ring-opening takes place through C-C bond cleavage to generate arylamide **D** (1,3-carbamoyl migration). Finally, hydride reduction of the amide moiety of **D** by the NaH-NaI composite results in the formation of aldehyde **4.11a** after aqueous quench.

Scheme 4.13. Proposed reaction mechanism of rearrangement reaction of **4.10a**.

With this preliminary finding, the author started to investigate the chemical reactivity of the NaH-I composite for the unprecedented amide directed C-H sodiation of aromatic sp^2 C-H bonds and lateral sodiation for benzylic sp^3 C-H bonds to furnish useful aromatic building blocks such as arylaldehydes having *ortho*-secondary aliphatic groups, 2-indanones, and polycyclic aromatic hydrocarbons. The detailed results and discussion will be presented below.

4.2.2 Preparation of Starting Materials

α -quaternary α -arylamides **4.10a-4.10d** and **4.10j-4.10t** and various biaryl secondary and tertiary amides **4.19a-4.19g** were synthesized from the corresponding carboxylic acid via the amidation of the acyl chlorides. The carboxylic acid was obtained through the hydrolysis of either α -substituted benzyl cyanide (Method A) or α -substituted acetic esters (Method B) or the Pinnick oxidation of the aldehydes (Method C).^[16]

Other methods include the hydrolysis of various α -substituted *o*-tolylbenzyl cyanide to its corresponding primary amide followed by alkylation to its tertiary amides (Method D). Lastly, the synthesis of **4.10i** was done via the α -methylation of diphenylacetamides (Method E).

Method A: Starting material **4.10a-4.10h**, **4.10j**, **4.20c** and **4.20g** were synthesized via the hydrolysis of α -substituted benzyl cyanide or biaryl cyanide by using KOH (4 equiv) in a mixture of ethylene glycol and water (5:1) at reflux. The corresponding acid was then treated with oxalyl chloride (1.5 equiv) with catalytic amount of DMF in dichloromethane at room temperature. Amidation was done with dimethylamine (4 equiv) or monomethylamine (4 equiv). The isolated yields were summarized below (Scheme 4.14).

Scheme 4.14. Method A

Method B: Starting material **4.10e**, **4.10o**, **4.17**, **4.20a-4.20b**, were synthesized via the hydrolysis of α -substituted acetic esters or biaryl ester by using KOH (4 equiv) in a mixture of methanol and water (1:1) at reflux. The corresponding acids were then treated with oxalyl chloride (1.5 equiv) with a catalytic amount of DMF in dichloromethane at room temperature. Amidation was done with dimethylamine (4 equiv), monomethylamine (4 equiv) or benzylamine (4 equiv). The isolated yields were summarized below (Scheme 4.15).

[a] $\text{EtOH:H}_2\text{O}$ (1:1) was used for hydrolysis.

Scheme 4.15. Method B

Method C: Starting material **4.20d-4.20e** were synthesized via Pinnick oxidation of the corresponding biaryl aldehydes to acids by using sodium chlorite (8.7 equiv), sodium hydrogen phosphate (6.9 equiv) and 2-methyl-2-butene (7.3 equiv) as a scavenger of hypochlorous acid HClO generated during the reaction. The acid was treated with oxalyl chloride and catalytic amount of DMF , followed by amidation using monomethylamine (5 equiv) in the presence of triethylamine (2 equiv). The isolated yields were summarized below (Scheme 4.16).

Scheme 4.16. Method C

Method D: Starting material **4.10k-4.10n**, **4.10p-4.10t** were synthesized via the hydrolysis of the corresponding α -substituted *ortho*-substituted benzyl cyanide by using KOH (4 equiv) in a mixture of ethylene glycol and water (5:1) at reflux. The resulting acids were then treated with oxalyl chloride (1.5 equiv) with a catalytic amount of DMF in dichloromethane at room temperature. Amidation was done with dimethylamine (4 equiv). The isolated yields were summarized below (Scheme 4.17).

Scheme 4.17. Method D

Method E: **4.10i** was synthesized via the α -methylation of diphenylacetamides by using LDA (1.5 equiv) as base and MeI (1.5 equiv) as the electrophile (Scheme 4.18).

Scheme 4.18. Method E

4.2.3 Scope and Limitation

Firstly, the author investigated the commonly used lithiated base for the possibility to induce anionic Fries rearrangement. When α -arylacetamide **4.10a** was treated with LDA (1.2 equiv) or *sec*-BuLi, there was no formation aldehyde **4.11a** (Scheme 4.19a). Furthermore, the reaction of **4.10a** with NaH without additives did not give any product (Scheme 4.19b). These reactions showed the unprecedented reactivity the NaH-Nal composite, which allowed the anionic C-Fries-type rearrangement and amide reduction in a simple protocol.

Scheme 4.19. Reaction of **4.10a** with typical lithiation base and NaH

The author next investigated the scope and limitations of this multistep molecular transformations (Scheme 4.20). An electron-donating methoxy group on the aryl ring was tolerated forming the aryl aldehyde **4.11b**. A phenyl group was also compatible for the present transformation (for **4.11c-4.11d**). The reaction with the *meta*-phenyl substrate **4.10d** resulted in the selective metalation in the less hindered *ortho*-position to form the corresponding biaryl aldehyde **4.11d** in 49% yield. Interestingly, when *ortho*-phenyl substrate **4.10e** was used, not only the biaryl aldehyde **4.11e**, but also the 9,10-dihydrophenanthren-9-ol (**4.15**) were isolated in 54% and 10% yields respectively. The formation of **4.15** suggested that the remote sodiation at the biaryl C-H bond occurred, followed by a sequence of cyclization and reduction (Scheme 4.21).^[17] Electron-poor pyridyl motif was tolerated (for **4.11f**). The protocol enabled the synthesis of benzaldehydes having cyclohexyl **4.11g** and tetrahydropyranyl **4.11h** moieties in moderate yields. The reaction of α -diphenylacetamide (**4.10i**) provided the corresponding benzaldehyde **4.11i** in 65% yield, while the reaction of α -triphenylacetamide (**4.10j**) afforded the *N,N*-dimethylbenzamide **4.11j** in 61% yield. Further reduction of **4.10j** to its corresponding aldehyde was not observed, possibly due to the bulky *ortho*-diphenylmethyl moiety which might impede further hydride reduction after the rearrangement. Furthermore, this methodology did not work for primary or secondary amides due to the formation of inert amide anions through deprotonation

[a] The reactions were conducted using 0.5 mmol of **4.10** in THF (2.5 mL: 0.2 M) for 14 h and the isolated yield was noted above. [b] 9,10-dihydrophenanthren-9-ol **4.15** was obtained together with aldehyde **4.11e** from the reaction of amide **4.10e**. [c] The reaction was completed at 18 h to afford benzamide **4.11j** in 61% yield instead of the corresponding benzaldehyde

Scheme 4.20. Substrate scope for the synthesis of aryl aldehydes **4.11**

Scheme 4.21. Proposed mechanism for the formation of **4.15**

Interestingly, the treatment of α -(2-tolyl)acetamide **4.10k** with the NaH-I composites provided 2-indanone **4.16k** as a sole product (Scheme 4.22), and the used of NaH-LiI system

rendered the process faster in rate. Again, NaH alone resulted in recovery of starting material, indicating the unique reactivity from the NaH-I composite.

[a] The reactions were conducted using 0.5 mmol of **4.10k** in THF (2.5 mL: 0.2 M) and yields of isolated **4.16k** was noted above.

Scheme 4.22. Lateral sodiation for the synthesis of **4.16**

In this reaction, it was observed that the transient NaH-amide complex **E** undergoes lateral benzylic sp^3 C-H sodiation exclusively to generate benzyl sodium **F**, which cyclized with the amide moiety to give a 5-membered ring anionic carbinol amine **G** (Scheme 4.23). Elimination of sodium dimethylamide produced 2-indanone **4.16k**. Further hydride reduction of the carbonyl group could be prevented by formation of enolate **H** through α -deprotonation, which is converted into **4.16k** upon aqueous workup.

Scheme 4.23. Proposed mechanism for the formation of **4.16k**

2-Indanones are a privileged scaffold for production of pharmaceutical drugs based on the 2-aminoindane core.^[18] As the current protocol with the NaH-LiI composite could be an attractive alternative to synthesize 2-indanones,^[19] the scope and limitation were explored (Scheme 4.24). The method allowed for construction of spirocyclic 2-indanones **4.16l-4.16n** efficiently. Installation of two different alkyl groups (benzyl and methyl groups) at the C1 of 2-indanone **4.16o** was readily accomplished. Lateral sodiation besides the methylene

moiety also worked with the current protocol, furnishing **4.16p** and **4.16q** in moderate to good yields. As for the substituent R⁴ on the benzene ring, methyl, methoxy, and fluoro groups were introduced (for **4.16r-4.16t**), while the yield of 5-fluoro-2-indanone (**4.16t**) was moderate.

[a] Unless otherwise stated, the reactions were conducted using 0.3-0.5 mmol of **4.10** in THF (0.2 M) for 2-4 h and yields of isolated **4.16** were noted above. [b] NaI (2 equiv) was used instead of Lil and the reaction was run for 6 h

Scheme 4.24. Substrate scope for the synthesis of 2-indanones **4.16**

Encouraged by both the success of directed *ortho*- and lateral sodiation, the author was then curious if the construction of the phenanthrene scaffold could be achieved by a sequence of lateral sodiation-cyclization of biaryl amides using the NaH-I composite. Actually, Snieckus et al. reported synthesis of 9-phenanthrenol (**4.18**) by the treatment of biaryl tertiary carboxamides with LDA (Scheme 4.25a).^[20] However, use of the NaH-I composite for the transformation of N,N-dimethylbenzamide **4.17** was not optimal, affording 9-phenanthrenol (**4.18**) only in 4% yield (Scheme 4.25b). The major product formed in this case was biarylaldehyde **4.19** through the hydride reduction.

a) Construction of 9-phenanthrenol with LDA by Snieckus et al.

b) Reduction of amide into aldehyde by NaH-I composite

[a] The reaction was conducted using 0.5 mmol of amide **4.17** in THF (2.5 mL: 0.2 M) and yields of isolated products were noted above unless otherwise stated.

Scheme 4.25. a) Typical synthesis of 9-phenanthrenols. b) Initial cyclization attempts using NaH-Lil composite

However, it was found that secondary amides could not be reduced to the corresponding aldehydes by the NaH-I composite due to the formation of the inert anionic amidides through deprotonation. Thus, the reaction of secondary N-methyl biarylamide **4.20a** were tested (Scheme 4.26). It was found that the construction of the phenanthrene skeleton proceeded smoothly. More fascinatingly, the product distribution could be switched by changing the iodide additive. Namely, the reaction with NaH-NaI system predominantly provided 9-phenanthrenol (**4.18**) via the C-N bond cleavage of the anionic carbinolamine intermediate. On the other hand, the use of the NaH-Lil system delivered N-methyl-9-phenanthrenamine (**4.21a**) via the C-O bond cleavage as the major product. Although the origin of the selectivity observed by the change of the iodide additives is not certain at this moment, one of the possible speculations is that the higher oxophilicity of the lithium cation renders the C-O bond of the tetrahedral intermediate X weaker.^[21]

[a] The reactions were conducted using 0.5 mmol of amide **4.20a** in THF (2.5 mL: 0.2 M) and yields of isolated products were noted above unless otherwise stated. [b] Yields within the parenthesis are determined based on ¹H NMR spectroscopy with the aid of an internal standard.

Scheme 4.26. Reactions of N-methyl biaryl amide **4.20**

Since the construction of aminoarene motifs have been rarely achieved by the lateral metalation-cyclization strategy and the 9-phenanthrenamine scaffolds are found as the core of dioxoaporphine alkaloids,^[22] the scope and limitation of the reaction employing the NaH-Lil system was briefly examined (Scheme 4.27). On the nitrogen, a cleavable benzyl group could be installed (for **4.21b**). On the phenanthrene core, methyl and methoxy groups were successfully introduced (for **4.21c-4.21f**) by the present protocol.

[a] The reactions were conducted using 0.5 mmol of amide **4.20** in THF (2.5 mL: 0.2 M) and yield of isolated product were noted above unless otherwise stated.

Scheme 4.27. Directed remote metalation of biaryl amides **4.20**

Moreover, the present protocol was applicable to the construction of [4]helicene, which was otherwise difficult to be achieved by the conventional method with LDA (developed by Snieckus et al.) due to the hindered rotation on the biaryl axis (Scheme 4.28a).^[1f] Namely, the reaction of biaryl amide **4.20g** under the NaH-Lil system provided 5-N-methylamino-[4]helicene **4.22g** together with 5-hydroxy-[4]helicene **4.21g** in good combined yield (Scheme 4.28b). While the reaction of **4.20g** with the NaH-Nal composite provided 5-hydroxy-[4]helicene **4.21g** as a sole product, albeit the slow reaction rate even with higher loadings of NaH and Nal and longer reaction time, gave **4.22** in 32% yield along with 60% recovery of **4.20g** (Scheme 4.29c). Use of thermally stable NaH for the lateral metalation-cyclization strategy allowed for running the process at higher temperature, which might be the key to enable such a challenging transformation.

a) No cyclization by LDA (Snieckus et al.)

b) with NaH-LiI composite

c) with NaH-NaI composite

[a] The reactions were conducted using 0.5 mmol of amide substrate **4.20g** in THF (2.5 mL: 0.2 M) and yields of isolated products were noted above unless otherwise stated. [b] Yields within the parenthesis are determined based on ¹H NMR spectroscopy with the aid of an internal standard.

Scheme 4.29. Construction of [4]helicenes

4.3 Conclusion

This work demonstrated the use of NaH-I composite for directed C-H sodiation under concise manners. This simple protocol conferred unprecedented Lewis acidity on NaH, enabling the facile synthesis of various important scaffolds not easily synthesized via the typical directed C-H lithiation such as arylaldehydes containing secondary aliphatic groups at the *ortho*-position and 2-indanones. More impressively polycyclic aromatic hydrocarbons specifically the 9-phenanthrenamines and 9-phenanthrenol could be synthesized from the same starting material by just changing the additives.

4.4 References

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Chapter 5 Experimental Section

5.1 General

^1H and ^{13}C NMR spectra were recorded on Bruker Avance 400 spectrometers or JEOL ECA400 and ECA400SL spectrometers in CDCl_3 using TMS ($\delta = 0.00$) for ^1H 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, ddd = doublet of doublet of doublet, t = triplet, q = quartet, sept = septet, m = multiplet. High-resolution mass spectra were obtained with Q-Tof Premier LC HR mass spectrometer. Optical rotations were obtained with a JASCO P-1030 polarimeter. Flash column chromatography was performed using Merck silica gel 60 with distilled solvents. NaH (60% dispersion in oil), NaI and LiI were purchased from Sigma-Aldrich, Inc. Due to moisture sensitivity of NaH, it was consistently handled under an N_2 atmosphere in a glovebox or with Schlenk techniques under an inert (N_2 or Ar) atmosphere. Due to the hygroscopic nature of NaI and LiI, they were dried over P_2O_5 under reduced pressure at 60 °C and 120 °C, respectively, before use.^[1]

5.2 Experimental data for Chapter 2

5.2.1 Synthesis of Tertiary Carbonitriles

Three methods A-C were applied for the synthesis of tertiary nitriles **2.8a-2.8w**.

Method A: For synthesis of tertiary carbonitriles 2.8a-2.8j, 2.8l-2.8o, 2.8q-2.8t and 2.8x

Typical Procedure for Synthesis of **2.8a**^[2]

Diphenylacetonitrile (3.86 g, 20.0 mmol) and methyl iodide (4.26 g, 30.0 mmol) in THF (50 mL) was added dropwise to a solution of sodium hydride (60% dispersion in mineral oil; 960 mg, 24 mmol) in THF (50 mL) at 85 °C (reflux). Upon reaction completion the reaction was quenched with water at 0 °C. The organic materials were extracted twice with diethyl ether and the combined organic extracts were washed with brine and dried over MgSO_4 . Volatiles was removed *in vacuo* and the crude material was purified by flash column chromatography (silica gel, hexane:ethyl acetate = 90:10) to give 2,2-diphenylpropanenitrile (**2.8a**) (4.10 g, 19.8 mmol) in 99% yield.

¹H NMR (400 MHz, CDCl₃): δ = 2.08 (s, 3H), 7.26 - 7.44 (m, 10H).

¹³C NMR (100 MHz, CDCl₃): δ = 28.1, 46.1, 123.4, 126.6, 127.9, 128.8, 141.2.

3-(4-Methoxyphenyl)-2-methyl-2-phenylpropanenitrile (2.8b)^[3]

Prepared by following **Method A** from 3-(4-methoxyphenyl)-2-phenyl propanenitrile (1.36 g, 5.72 mmol) and methyl iodide (1.5 equiv) to give **2.8b** (1.27 g, 5.06 mmol) in 89% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.73 (s, 3H), 3.06 (d, *J* = 13.6 Hz, 1H), 3.10 (d, *J* = 13.6 Hz, 1H), 3.77 (s, 3H), 6.76 (ddd, *J* = 2.0, 2.8, 8.8 Hz, 2H), 6.93 (ddd, *J* = 2.4, 2.8, 8.8 Hz, 2H), 7.28 - 7.35 (m, 1H), 7.35-7.38 (m, 4H)

¹³C NMR (100 MHz, CDCl₃): δ = 25.9, 43.7, 47.8, 55.2, 113.5, 123.3, 126.0, 127.2, 127.8, 128.7, 131.4, 139.8, 158.9.

Synthesis of 3-(4-methoxyphenyl)-2-phenyl propanenitrile

2-phenylacetonitrile (1.29 g, 11.0 mmol) was added to a suspension of sodium hydride (60% dispersion in mineral oil; 440 mg, 11.0 mmol) in DMF (20 mL) at 0 °C. The reaction was stirred for 30 mins at room temperature before, 4-methoxybenzyl chloride (1.57 g, 10.0 mmol) was added dropwise and was further stirred for 12 h. The reaction was quenched with water at 0 °C and the organic materials were extracted twice with diethyl ether. The combined extracts were washed with thrice with H₂O and brine and dried over MgSO₄. Volatiles were removed *in vacuo* and the crude material was purified by flash column chromatography (silica gel, hexane:ethyl acetate = 85:15) to give 3-(4-methoxyphenyl)-2-phenylpropanenitrile (1.49 g, 6.27 mmol) in 57% yield along with 2-(4-methoxybenzyl)-3-(4-methoxyphenyl)-2-phenylpropanenitrile (**2.8e**) (1.06 g, 2.97 mmol) in 27%.

3-(4-Methoxyphenyl)-2-phenylpropanenitrile^[4]

^1H NMR (400 MHz, CDCl_3): δ = 3.07 (dd, J = 6.8, 14.0 Hz, 1H), 3.12 (dd, J = 8.4, 14.0 Hz, 1H), 3.78 (s, 3H), 3.95 (dd, J = 6.8, 8.0 Hz, 1H), 6.82 (ddd, J = 2.0, 2.8, 8.8 Hz, 2H), 7.04 (ddd, J = 2.0, 2.8, 8.8 Hz, 2H), 7.22 - 7.27 (m, 2H), 7.30-7.40 (m, 3H)

^{13}C NMR (100 MHz, CDCl_3): δ = 40.0, 41.3, 55.2, 113.9, 120.4, 127.5, 127.9, 128.3, 128.9, 130.2, 135.2, 158.8.

2-(4-Methoxybenzyl)-3-(4-methoxyphenyl)-2-phenylpropanenitrile (2.8e)

^1H NMR (400 MHz, CDCl_3): δ = 3.20 (d, J = 13.6 Hz, 2H), 3.25 (d, J = 14.0 Hz, 2H), 3.71 (s, 6H), 6.70 (ddd, J = 2.0, 2.8, 8.8 Hz, 4H), 6.93 (ddd, J = 2.0, 3.2, 8.4 Hz, 4H), 7.22 - 7.31 (m, 5H).

^{13}C NMR (100 MHz, CDCl_3): δ = 45.5, 51.6, 55.0, 113.4, 121.4, 126.8, 127.1, 127.7, 128.5, 131.3, 137.4, 158.7

ESIHRMS: Found: m/z 358.1806. Calcd for $\text{C}_{24}\text{H}_{23}\text{NO}_2$: $(\text{M}+\text{H})^+$ 358.1807.

3-(4-Methoxyphenyl)-2-methyl-2-(2-methylphenyl)propanenitrile (2.8c)

Prepared by following **Method A** from 3-(4-methoxyphenyl)-2-(2-methylphenyl)propanenitrile (503 mg, 2.00 mmol) and methyl iodide (1.5 equiv) to give **2.8c** (524 mg, 1.97 mmol) in 99% yield.

^1H NMR (400 MHz, CDCl_3): δ = 1.74 (s, 3H), 2.67 (s, 3H), 3.04 (d, J = 13.6 Hz, 1H), 3.25 (d, J = 13.6 Hz, 1H), 3.76 (s, 3H), 6.77 (ddd, J = 2.0, 2.8, 8.8 Hz, 2H), 6.94 (ddd, J = 2.0, 2.8, 8.8 Hz, 2H), 7.12 - 7.18 (m, 2H), 7.20 - 7.26 (m, 2H)

^{13}C NMR (100 MHz, CDCl_3): δ = 21.5, 25.3, 40.9, 44.8, 55.1, 113.5, 123.6, 126.1, 126.3, 127.0, 128.0, 131.4, 132.7, 136.2, 136.7, 158.9

ESIHRMS: Found: m/z 266.1544. Calcd for $\text{C}_{18}\text{H}_{19}\text{NO}$: $(\text{M}+\text{H})^+$ 266.1545.

Synthesis of 3-(4-Methoxyphenyl)-2-(2-methylphenyl)propanenitrile

Prepared by following the **Synthesis of 3-(4-methoxyphenyl)-2-phenyl propanenitrile** from 2-(2-methylphenyl)acetonitrile (656 mg, 5.00 mmol) in THF under reflux conditions to give 3-(4-Methoxyphenyl)-2-(2-methylphenyl)propanenitrile (1.14 g, 4.52 mmol) in 90% yield.

^1H NMR (400 MHz, CDCl_3): δ = 2.25 (s, 3H), 3.02 (dd, J = 6.4, 14.0 Hz, 1H), 3.09 (dd, J = 7.6, 14.0 Hz, 1H), 3.79 (s, 3H), 4.10 (dd, J = 6.4, 7.6 Hz, 1H), 6.83 (ddd, J = 2.0, 2.8, 8.8 Hz, 2H), 7.07 (ddd, J = 2.0, 2.8, 8.8 Hz, 2H), 7.14 - 7.19 (m, 1H), 7.19 - 7.27 (m, 2H), 7.38 - 7.43 (m, 1H)

^{13}C NMR (100 MHz, CDCl_3): δ = 19.0, 36.8, 40.1, 55.2, 114.0, 120.8, 126.8, 127.7, 128.2, 128.5, 130.2, 130.9, 133.7, 135.0, 158.9

ESIHRMS: Found: m/z 252.1393. Calcd for $\text{C}_{17}\text{H}_{17}\text{NO}$: $(\text{M}+\text{H})^+$ 252.1388.

2-(3-Fluorophenyl)-3-(4-methoxyphenyl)-2-methylpropanenitrile (2.8d)

Prepared by following **Method A** from 2-(3-fluorophenyl)-3-(4-methoxyphenyl)propanenitrile (478 mg, 1.87 mmol) and methyl iodide (1.5 equiv) to give **2.8d** (412 mg, 1.53 mmol) in 82% yield

¹H NMR (400 MHz, CDCl₃): δ = 1.73 (s, 3H), 3.07 (s, 2H), 3.77 (s, 3H), 6.77 (ddd, J = 2.0, 2.8, 8.8 Hz, 2H), 6.94 (ddd, J = 2.0, 3.2, 8.4 Hz, 2H), 7.01 (dddd, J = 0.8, 2.4, 8.0, 8.4 Hz, 1H), 7.07 (ddd, J = 2.0, 2.4, 10.4 Hz, 1H), 7.15 (ddd, J = 0.8, 2.0, 8.0 Hz, 1H), 7.33 (ddd, J = 6.4, 8.0, 8.4 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 25.8, 43.6, 47.6, 55.1, 113.2 ($J_{\text{H-F}}$ = 23.1 Hz), 113.6, 114.8 ($J_{\text{H-F}}$ = 20.9 Hz), 121.7 ($J_{\text{H-F}}$ = 2.9 Hz), 122.7, 126.7, 130.3 ($J_{\text{H-F}}$ = 8.3 Hz), 131.3, 142.3 ($J_{\text{H-F}}$ = 7.1 Hz), 159.0, 162.8 ($J_{\text{H-F}}$ = 245.6 Hz)

ESIHRMS: Found: m/z 270.1293. Calcd for C₁₇H₁₆FNO: (M+H)⁺ 270.1294.

Synthesis of 2-(3-Fluorophenyl)-3-(4-methoxyphenyl)propanenitrile

Prepared by following the **Synthesis of 3-(4-methoxyphenyl)-2-phenyl propanenitrile** from 2-(3-fluorophenyl)acetonitrile (676 mg, 5.0 mmol) in THF under reflux conditions to give 2-(3-Fluorophenyl)-3-(4-methoxyphenyl)propanenitrile (484 mg, 1.89 mmol) in 38% yield.

¹H NMR (400 MHz, CDCl₃): δ = 3.07 (dd, J = 6.4, 13.6 Hz, 1H), 3.13 (dd, J = 8.0, 13.6 Hz, 1H), 3.78 (s, 3H), 3.96 (dd, J = 6.8, 8.0 Hz, 1H), 6.82 (ddd, J = 2.0, 3.2, 8.4 Hz, 2H), 6.97 (ddd, J = 2.0, 2.4, 9.6 Hz, 1H), 7.00 - 7.08 (m, 4H), 7.32 (ddd, J = 5.6, 8.0, 8.0 Hz, 1H)

¹³C NMR (100 MHz, CDCl₃): δ = 39.7, 41.2, 55.2, 114.1, 114.7 ($J_{\text{H-F}}$ = 22.4 Hz), 115.2 ($J_{\text{H-F}}$ = 20.8 Hz), 119.9, 123.3 ($J_{\text{H-F}}$ = 3.0 Hz), 127.8, 130.3, 130.6 ($J_{\text{H-F}}$ = 8.1 Hz), 137.6 ($J_{\text{H-F}}$ = 7.3 Hz), 159.0, 162.9 ($J_{\text{H-F}}$ = 246.4 Hz).

2-Cyclohexyl-3-(4-methoxyphenyl)-2-phenylpropanenitrile (2.8f)

Prepared by following **Method A** from 2-cyclohexyl-2-phenylacetonitrile (598 mg, 3.00 mmol) and 1-(chloromethyl)-4-methoxybenzene (1.0 equiv) to give **2.8f** (639 mg, 2.00 mmol) in 67% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.02 - 1.28 (m, 3H), 1.28 - 1.40 (m, 2H), 1.47 (dq, J = 3.2, 12.4 Hz, 1H), 1.62 - 1.72 (m, 2H), 1.89 - 2.00 (m, 2H), 2.22 - 2.30 (m, 1H), 2.96 (d, J = 13.6 Hz, 1H), 3.32 (d, J = 13.6 Hz, 1H), 3.70 (s, 3H), 6.61 (d, J = 8.4 Hz, 2H), 6.74 (d, J = 8.8 Hz, 2H), 7.20 - 7.31 (m, 5H).

¹³C NMR (100 MHz, CDCl₃): δ = 25.9, 26.2, 26.3, 28.8, 28.9, 42.8, 45.8, 55.0, 55.1, 113.1, 121.1, 127.0, 127.39, 127.44, 128.4, 131.2, 137.4, 158.4.

ESIHRMS: Found: m/z 320.2014. Calcd for C₂₂H₂₅NO: (M+H)⁺ 320.2014.

Synthesis of 2-cyclohexyl-2-phenylacetonitrile^[5]

60% aqueous KOH (140.0 mmol) was added dropwise to a solution of 2-phenylacetonitrile (2.34 g, 20.0 mmol), cyclohexyl bromide (6.52 g, 40.0 mmol) and tetrabutylammonium bromide (TBAB, 129 mg, 0.4 mmol) at such a rate so that the reaction temperature is at 50 °C. The reaction was quenched with water upon reaction completion and the organic materials were extracted twice with diethyl ether washed with brine and dried over MgSO₄. Volatile materials were removed *in vacuo* and the crude residue was purified by flash column chromatography (silica gel, hexane:ethyl acetate = 85:15) to give 2-cyclohexyl-2-phenylacetonitrile^[6] (1.71 g, 8.6 mmol) in 43% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.08 - 1.28 (m, 5H), 1.62-1.88 (m, 6H), 3.63 (d, J = 6.8 Hz, 1H), 7.26 - 7.39 (m, 5H)

¹³C NMR (100 MHz, CDCl₃): δ = 25.75, 25.80, 25.9, 29.5, 31.2, 42.7, 44.3, 120.1, 127.86, 127.94, 128.7, 134.7.

3-(4-Methoxyphenyl)-2,2-diphenylpropanenitrile (2.8q)

Prepared by following **Method A** from diphenylacetonitrile (1.93 g, 10.0 mmol) and 1-(chloromethyl)-4-methoxybenzene (1.0 equiv) to give **2.8q** in (2.99 g, 9.55 mmol) in 96% yield.

^1H NMR (400 MHz, CDCl_3): δ = 3.60 (s, 2H), 3.74 (s, 3H), 6.68 (d, J = 8.4 Hz, 2H), 6.78 (d, J = 8.4 Hz, 2H), 7.26 - 7.36 (m, 10H).

^{13}C NMR (100 MHz, CDCl_3): δ = 44.5, 53.2, 55.1, 113.3, 121.9, 126.6, 127.4, 127.9, 128.6, 131.5, 140.1, 158.8

ESIHRMS: Found: m/z 314.1544. Calcd for $\text{C}_{22}\text{H}_{19}\text{NO}$: $(\text{M}+\text{H})^+$ 314.1545.

4-Methoxy-2,2-diphenylbutanenitrile (2.8r)

Prepared by following **Method A** from diphenylacetonitrile (966 mg, 5.00 mmol) and 1-bromo-2-methoxyethane (1.2 equiv) to give **2.8r** (1.22 g, 4.85 mmol) in 97% yield.

^1H NMR (400 MHz, CDCl_3): δ = 2.70 (t, J = 7.4 Hz, 2H), 3.28 (s, 3H), 3.45 (t, J = 7.4 Hz, 2H), 7.27 - 7.41 (m, 10H)

^{13}C NMR (100 MHz, CDCl_3): δ = 38.6, 48.9, 58.8, 69.2, 121.9, 126.7, 128.0, 128.9, 139.9.

ESIHRMS: Found: m/z 252.1389. Calcd for $\text{C}_{17}\text{H}_{17}\text{NO}$: $(\text{M}+\text{H})^+$ 252.1388.

2,2,6,6-Tetraphenylhexanenitrile (2.8s)

Prepared following **Method A** from NaH (2.5 equiv), diphenylacetonitrile (2.0 equiv) and 1,3-dibromopropane (2.02 g, 10.0 mmol) to give **2.8s** (3.97 g, 9.30 mmol) in 93% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.57 - 1.67 (m, 2H), 2.39 - 2.47 (m, 4H), 7.24 - 7.35 (m, 20H).

¹³C NMR (100 MHz, CDCl₃): δ = 21.8, 39.3, 51.4, 122.0, 126.7, 127.9, 128.9, 139.8.

ESIHRMS: Found: m/z 427.2173. Calcd for C₃₁H₂₆N₂: (M+H)⁺ 427.2174.

2,2-Diphenylhept-6-enenitrile (2.8t)

Prepared by following **Method A** from diphenylacetone nitrile (1.93 g, 10.0 mmol) and 5-bromopent-1-ene (1.1 equiv) to give **2.8t** (2.59 g, 9.90 mmol) in 99% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.49 - 1.58 (m, 2H), 2.12 (td, J = 6.8, 7.2 Hz, 2H), 2.33 - 2.40 (m, 2H), 4.95 - 5.00 (m, 1H), 5.05 (tdd, J = 1.2, 1.6, 17.2 Hz, 1H), 5.74 (tdd, J = 6.4, 10.4, 17.2 Hz, 1H), 7.26 - 7.32 (m, 2H), 7.32 - 7.40 (m, 8H).

¹³C NMR (100 MHz, CDCl₃): δ = 24.7, 33.3, 39.0, 51.7, 115.4, 122.4, 126.8, 127.8, 128.8, 137.6, 140.2.

ESIHRMS: Found: m/z 262.1599. Calcd for C₁₉H₁₉N: (M+H)⁺ 262.1596.

2-(2-Chlorophenyl)-3-(4-methoxyphenyl)-2-methylpropanenitrile (2.8x)

Prepared by following **Method A** from 2-(2-chlorophenyl)-3-(4-methoxyphenyl)propanenitrile (543 mg, 2.00 mmol) and methyl iodide (1.5 equiv) to give **2.8x** (551 mg, 1.93 mmol) in 96% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.88 (s, 3H), 3.25 (d, J = 14.0 Hz, 1H), 3.58 (d, J = 13.6 Hz, 1H), 3.76 (s, 3H), 6.74 (ddd, J = 2.0, 2.8, 8.8 Hz, 2H), 6.99 (ddd, J = 2.0, 3.2, 8.4 Hz, 2H), 7.19 (ddd, J = 1.6, 7.6, 7.6 Hz, 1H), 7.27 (ddd, J = 1.6, 7.6, 7.6 Hz, 1H), 7.32 (dd, J = 1.6, 7.6 Hz, 1H), 7.47 (dd, J = 1.6, 8.0 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 24.6, 42.6, 43.5, 55.1, 113.5, 122.7, 127.1, 127.2, 129.1, 129.4, 131.3, 132.0, 132.7, 135.3, 158.8.

ESIHRMS: Found: m/z 286.1000. Calcd for C₁₇H₁₆³⁵CINO: (M+H)⁺ 286.0999.

Synthesis of 2-(2-Chlorophenyl)-3-(4-methoxyphenyl)propanenitrile

Prepared by following the **Synthesis of 3-(4-methoxyphenyl)-2-phenylpropanenitrile** from 2-(2-chlorophenyl)acetonitrile (454 mg, 3.00 mmol) in THF under reflux conditions to give 2-(2-Chlorophenyl)-3-(4-methoxyphenyl)propanenitrile (746 mg, 2.75 mmol) in 92% yield

¹H NMR (400 MHz, CDCl₃): δ = 3.00 (dd, *J* = 9.2, 13.6 Hz, 1H), 3.16 (dd, *J* = 4.8, 13.6 Hz, 1H), 3.79 (s, 3H), 4.48 (dd, *J* = 4.8, 9.2 Hz, 1H), 6.84 (ddd, *J* = 2.0, 2.8, 8.8 Hz, 2H), 7.13 (d, *J* = 8.8 Hz, 2H), 7.25 - 7.31 (m, 2H), 7.39 - 7.47 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ = 37.6, 39.3, 55.2, 114.0, 119.8, 127.5, 128.1, 129.2, 129.6, 130.0, 130.3, 132.6, 133.0, 159.0.

ESIHRMS: Found: m/z 272.0837. Calcd for C₁₇H₁₆³⁵CINO: (M+H)⁺ 272.0842.

2-Methyl-2-(naphthalen-2-yl)propanenitrile (2.8g)^[7]

Prepared by following **Method A** from 2-(naphthalen-2-yl)acetonitrile (3.34 g, 20.0 mmol) with NaH (2.5 equiv) and methyl iodide (3.0 equiv) to give **2.8g** (3.87 g, 19.8 mmol) in 99% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.81 (s, 3H), 7.47 - 7.53 (m, 2H), 7.55 (dd, *J* = 2.0, 8.8 Hz, 1H), 7.81 - 7.90 (m, 3H), 7.94 (d, *J* = 1.6 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 29.0, 37.3, 123.0, 123.8, 124.5, 126.4, 126.6, 127.5, 128.1, 128.9, 132.6, 133.1, 138.6.

2-(2',6'-Dimethoxy-[1,1'-biphenyl]-2-yl)-2-methylpropanenitrile (2.8h)

Prepared by following **Method A** from 2-(2',6'-dimethoxy-[1,1'-biphenyl]-2-yl)acetonitrile (2.53 g, 10.0 mmol) with NaH (3.0 equiv) and methyl iodide (3.5 equiv) to give **2.8h** (2.64 g, 9.40 mmol) in 94% yield

¹H NMR (400 MHz, CDCl₃): δ = 1.59 (s, 6H), 3.70 (s, 6H), 6.62 (d, J = 8.4 Hz, 2H), 7.03 (d, J = 7.2 Hz, 1H), 7.31 - 7.41 (m, 3H), 7.62 (d, J = 7.2 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 29.0, 37.6, 55.4, 103.6, 118.7, 124.9, 126.5, 127.5, 127.8, 129.7, 133.1, 133.4, 139.0, 158.1.

ESIHRMS: Found: m/z 282.1494. Calcd for C₁₈H₁₉NO₂: (M+H)⁺ 282.1494.

Synthesis of 2-(2',6'-dimethoxy-[1,1'-biphenyl]-2-yl)acetonitrile^[8]

In a 2-necked rbf, 2-(2-bromophenyl)acetonitrile (3.92 g, 20.0 mmol, prepared by the literature procedure^[9]) and Pd(PPh₃)₄ (1.85g, 1.6 mmol) in cyclopentyl methyl ether (45 mL), was added a solution of (2,6-dimethoxyphenyl)boronic acid (4.37 g, 24.0 mmol) in ethanol (35 mL). Subsequently, 2 M aqueous solution of Na₂CO₃ (35 mL, 70.0 mmol) was added and the reaction mixture was allowed to stir at reflux condition for 24 h. The reaction mixture was cooled to room temperature before the solvents were removed *in vacuo*. The organic materials were then extracted twice with dichloromethane after addition of H₂O (50 mL) and the combined extracts were washed with brine and dried over MgSO₄. Volatiles were removed *in vacuo* and the crude residue was purified by flash column chromatography (silica gel, hexane:ethyl acetate = 80:20) to give 2-(2',6'-dimethoxy-[1,1'-biphenyl]-2-yl)acetonitrile (4.00 g, 15.8 mmol) in 79% yield.

¹H NMR (400 MHz, CDCl₃): δ = 3.47 (s, 2H), 3.71 (s, 6H), 6.65 (d, J = 8.4 Hz, 2H), 7.18 - 7.25 (m, 1H), 7.31 - 7.41 (m, 3H), 7.52 - 7.58 (m, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 21.6, 55.7, 104.0, 116.4, 118.3, 127.6, 127.9, 128.0, 129.6, 129.7, 131.6, 133.9, 157.5.

ESIHRMS: Found: m/z 254.1181. Calcd for C₁₆H₁₅NO₂: (M+H)⁺ 254.1181.

2-(Pent-4-en-1-yl)-2-phenylhept-6-enenitrile (2.8i)

Prepared by following **Method A** from 2-phenylacetonitrile (1.15 ml, 10.0 mmol) with NaH (2.5 equiv) and 5-bromopent-1-ene (2.2 equiv) to give **2.8i** (2.52 g, 9.95 mmol) in 99% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.13 - 1.26 (m, 2H), 1.50 - 1.63 (m, 2H), 1.87 (ddd, J = 4.8, 12.4, 13.6 Hz, 2H), 1.93 - 2.09 (m, 6H), 4.92 - 4.97 (m, 2H), 4.96 (tdd, J = 1.6, 2.0, 16.8 Hz, 2H), 5.69 (tdd, J = 6.8, 10.4, 16.8 Hz, 2H), 7.28 - 7.34 (m, 1H), 7.35 - 7.42 (m, 4H).

¹³C NMR (100 MHz, CDCl₃): δ = 24.3, 33.3, 40.4, 48.1, 115.2, 122.4, 125.8, 127.6, 128.8, 137.7, 138.4.

ESIHRMS: Found: m/z 254.1915. Calcd for C₁₈H₂₃N: (M+H)⁺ 254.1909.

1-(4-Chlorophenyl)cyclohexanecarbonitrile (2.8j)

Prepared by following **Method A** from 2-(4-chlorophenyl)acetonitrile (455 mg, 3.00 mmol) with NaH (2.5 equiv) and 1,5-dibromopentane (1.2 equiv) to give **2.8j** (569 mg, 2.59 mmol) in 86% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.20 - 1.34 (m, 1H), 1.67 - 1.77 (m, 2H), 1.77 - 1.92 (m, 5H), 2.09 - 2.18 (m, 2H), 7.36 (ddd, J = 2.4, 2.8, 8.8 Hz, 2H), 7.43 (ddd, J = 2.4, 3.2, 8.8 Hz, 2H).

¹³C NMR (100 MHz, CDCl₃): δ = 23.5, 24.9, 37.4, 44.0, 122.3, 127.0, 129.0, 133.7, 140.0.

ESIHRMS: Found: m/z 220.0895. Calcd for C₁₃H₁₄³⁵ClN: (M+H)⁺ 220.0893.

1-Phenylcyclopentanecarbonitrile (2.8l)^[7]

Prepared by following **Method A** from 2-phenylacetonitrile (2.34 g, 20.0 mmol) with NaH (2.5 equiv) and 1,4-dibromopentane (1.2 equiv) to give **2.8i** (2.87 g, 16.8 mmol) in 84% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.88 - 2.13 (m, 6H), 2.42 - 2.52 (m, 2H), 7.29 (tt, J = 1.2, 7.2 Hz, 1H), 7.34 - 7.40 (m, 2H), 7.43 - 7.48 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ = 24.2, 40.4, 47.7, 124.3, 125.9, 127.7, 128.8, 139.8.

2-([1,1'-Biphenyl]-4-yl)cyclobutane-1-carbonitrile (**2.8m**)

Prepared by following **Method A** from 2-([1,1'-biphenyl]-4-yl)acetonitrile (580 mg, 3.00 mmol) with NaH (2.2 equiv) and 1,3-dibromopropane (2.2 equiv) in DMSO and diethyl ether at room temperature to give **2.8m** (462 mg, 1.98 mmol) in 66% yield.

¹H NMR (400 MHz, CDCl₃): δ = 2.11 (ttd, J = 3.6, 7.2, 10.8 Hz, 1H), 2.46 (ttd, J = 8.8, 8.8, 11.6 Hz, 1H), 2.62 - 2.72 (m, 2H), 2.81 - 2.91 (m, 2H), 7.37 (t, J = 7.2 Hz, 1H), 7.45 (dd, J = 7.2, 7.6 Hz, 2H), 7.49 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 7.2 Hz, 2H), 7.62 (d, J = 8.4 Hz, 2H).

¹³C NMR (400 MHz, CDCl₃): δ = 17.1, 34.7, 40.0, 124.4, 126.0, 127.1, 127.56, 127.62, 128.8, 138.7, 140.3, 140.8.

ESIHRMS: Found: m/z 234.1281. Calcd for C₁₇H₁₅N: (M+H)⁺ 234.1283.

1-(4-Methoxyphenyl)cyclobutane-1-carbonitrile (**2.8n**)^[10]

Prepared by following **Method A** from 2-(4-methoxyphenyl)acetonitrile (736 mg, 5.00 mmol) with NaH (2.2 equiv) and 1,3-dibromopropane (2.2 equiv) in DMSO and diethyl ether at room temperature to give **2.8n** (554 mg, 2.96 mmol) in 60% yield

¹H NMR (400 MHz, CDCl₃): δ = 2.01 - 2.10 (m, 1H), 2.40 (ttd, J = 8.4, 8.8, 11.6 Hz, 1H), 2.54 - 2.62 (m, 2H), 2.76 - 2.84 (m, 2H), 3.82 (s, 3H), 6.92 (ddd, J = 2.4, 3.2, 8.8 Hz, 2H) 7.33 (ddd, J = 2.0, 3.2, 8.8 Hz, 2H).

¹³C NMR (400 MHz, CDCl₃): δ = 17.0, 34.8, 39.6, 55.3, 114.2, 124.6, 126.8, 131.9, 159.1.

4-Phenyltetrahydro-2H-pyran-4-carbonitrile (**2.8o**)

Prepared by following **Method A** from 2-phenylacetonitrile (586 mg, 5.00 mmol) with NaH (3.0 equiv) and 1-chloro-2-(2-chloroethoxy)ethane (1.2 equiv) in DMSO at room temperature to give **2.8o** (928 mg, 4.96 mmol) in 99% yield

¹H NMR (400 MHz, CDCl₃): δ = 2.02 - 2.09 (m, 2H), 2.14 (ddd, J = 4.4, 11.6, 14.0 Hz, 2H), 3.91 (ddd, J = 2.0, 12.0, 12.4 Hz, 2H), 7.09 (ddd, J = 1.6, 4.0, 12.0 Hz, 2H), 7.35 (tt, J = 1.2, 7.2 Hz, 1H), 7.39 - 7.46 (m, 2H), 7.46 - 7.52 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ = 36.6, 41.8, 65.0, 121.7, 125.4, 128.3, 129.1, 139.8.

ESIHRMS: Found: m/z 188.1082. Calcd for C₁₂H₁₃NO: (M+H)⁺ 188.1075.

Method B: For synthesis of tertiary carbonitriles **2.8k**, **2.8p** and **2.8z**

Typical Procedure for Synthesis of **2.8k**^[11]

To a stirred solution of 1-fluoro-4-methoxybenzene (1.26 g, 10.0 mmol) in THF (10 mL) at room temperature was added cyclohexanecarbonitrile (4.37 g, 40.0 mmol) and potassium bis(trimethylsilyl)amide (KHMDS, 1.0 M in THF; 15.0 mL, 15.0 mmol). The reaction mixture was allowed stir at 60 °C for 4 days. After cooling to room temperature, the crude mixture was poured into 1N aqueous and extracted twice with diethyl ether. The combined extracts were washed with brine and dried over MgSO₄. After removal of the solvent, the crude material was purified by flash column chromatography (silica gel, hexane:ethyl acetate = 80:20) to give 1-(4-methoxyphenyl)cyclohexanecarbonitrile^[12] (**2.8k**) (667 mg, 3.10 mmol) in 31% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.18 - 1.33 (m, 1H), 1.66 - 1.90 (m, 7H), 2.08 - 2.18 (m, 2H), 3.80 (s, 3H), 6.89 (ddd, J = 2.0, 3.2, 8.8 Hz, 2H), 7.39 (ddd, J = 2.4, 2.8, 8.8 Hz, 2H).

¹³C NMR (100 MHz, CDCl₃): δ = 23.6, 24.9, 37.5, 43.5, 55.3, 114.1, 122.9, 126.6, 133.6, 159.0.

1-(Pyridin-2-yl)cyclohexanecarbonitrile (2.8p)

Prepared by following **Method B** from 2-fluoropyridine (485 mg, 5.00 mmol) in toluene to give **2.8p** (924 mg, 4.96 mmol) in 99% yield

¹H NMR (400 MHz, CDCl₃): δ = 1.25 - 1.41 (m, 1H), 1.78 - 1.93 (m, 5H), 2.03 (ddd, J = 3.6, 12.4, 13.6 Hz, 2H), 2.08 - 2.16 (m, 2H), 7.23 (dd, J = 4.8, 7.2 Hz, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.72 (ddd, J = 2.0, 7.6, 8.0 Hz, 1H), 8.60 (d, J = 4.8 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 23.3, 24.9, 35.9, 46.7, 120.5, 122.5, 122.7, 137.1, 149.4, 159.5.

ESIHRMS: Found: m/z 187.1233. Calcd for C₁₂H₁₄N₂: (M+H)⁺ 187.1235.

2-(3-Methoxyphenyl)bicyclo[2.2.1]heptane-2-carbonitrile (2.8z)

Prepared by following **Method B** from 2-norbornanecarbonitrile (mixture of *endo* and *exo*) (4.0 equiv) and 1-fluoro-3-methoxybenzene (630 mg, 5.00 mmol) in THF at 75 °C to give **2.8z** (850 mg, 3.74 mmol) in 75% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.36 (tdd, J = 1.2, 2.4, 10.4 Hz, 1H), 1.42 - 1.50 (m, 1H), 1.50 - 1.56 (m, 1H), 1.63 - 1.79 (m, 2H), 2.07 - 2.16 (m, 2H), 2.32 (ddd, J = 2.4, 4.4, 13.2 Hz, 1H), 2.41 - 2.46 (m, 1H), 2.76 - 2.80 (m, 1H), 3.82 (s, 3H), 6.81 (ddd, J = 0.8, 2.4, 8.4 Hz, 1H), 6.97 (dd, J = 2.0, 2.4 Hz, 1H), 7.02 (ddd, J = 0.8, 1.6, 7.6 Hz, 1H), 7.28 (dd, J = 7.6, 8.4 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 26.5, 28.5, 36.7, 37.3, 45.4, 46.0, 46.6 55.3, 112.4, 113.0, 118.8, 124.9, 129.7, 143.0, 159.8.

ESIHRMS: Found: m/z 228.1388. Calcd for C₁₅H₁₇NO: [(M-H₂O)+H]⁺ 228.1388.

Method C: For synthesis of tertiary carbonitriles 2.8u-2.8w

Typical Procedure for Synthesis of 2.8u

To a stirred solution of cyclopropyl(4-methoxyphenyl)(phenyl)methanol (1.27 g, 5.0 mmol) and B(C₆F₅)₃ (77 mg, 0.15 mmol) in CH₃CN (5 mL) was added dropwise trimethylsilyl cyanide (0.6 g, 6.0 mmol). The reaction mixture was stirred at room temperature for 12 h. Volatile materials were removed *in vacuo* and the crude residue was purified by flash column chromatography (silica gel, hexane:ethyl acetate = 80:20) to give 2-cyclopropyl-2-(4-methoxyphenyl)-2-phenylacetonitrile (**2.8u**) (1.04 g, 3.95 mmol) in 79% yield.

¹H NMR (400 MHz, CDCl₃): δ = 0.61 - 0.72 (m, 2H), 0.72 - 0.84 (m, 2H), 1.63 (tt, *J* = 5.2, 8.0 Hz, 1H), 3.81 (s, 3H), 6.88 (ddd, *J* = 2.0, 3.2, 8.4 Hz, 2H), 7.28 - 7.39 (m, 5H), 7.39 - 7.44 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ = 3.4, 3.7, 19.8, 52.9, 55.3, 113.9, 120.6, 127.4, 127.8, 128.6, 128.8, 132.7, 141.0, 159.1.

ESIHRMS: Found: m/z 264.1385. Calcd for C₁₈H₁₇NO: (M+H)⁺ 264.1388.

Synthesis of cyclopropyl(4-methoxyphenyl)(phenyl)methanol

To a solution of cyclopropyl(phenyl)methanone (1.46 g, 10.0 mmol) in anhydrous THF (10 mL) was added (4-methoxyphenyl)magnesium bromide [prepared from 1-bromo-4-methoxybenzene (2.24 g, 12.0 mmol) and Mg (0.37 g, 15.0 mmol) in 10 mL of THF] dropwise at -78 °C. The reaction was then allowed to warm up to room temperature and stirred for 2 h. After completion, the reaction was quenched with 1N aqueous HCl

at 0 °C and the organic materials were extracted twice with diethyl ether. The combined extracts were washed with brine, and dried over MgSO₄. Volatile materials were removed *in vacuo* and the crude material was purified by flash column chromatography (Si gel, hexane:ethyl acetate = 70:30) to give cyclopropyl(4-methoxyphenyl)(phenyl)methanol (2.49 g, 9.8 mmol) in 98% yield.

¹H NMR (400 MHz, CDCl₃): δ = 0.42 - 0.50 (m, 2H), 0.50 - 0.64 (m, 2H), 1.60 (tt, J = 5.6, 8.4 Hz, 1H), 1.85 (s, 1H), 3.79 (s, 3H), 6.84 (ddd, J = 2.0, 3.2, 8.8 Hz, 2H), 7.24 (tt, J = 1.2, 7.2 Hz, 1H), 7.27 - 7.33 (m, 2H), 7.36 (ddd, J = 2.0, 3.2, 8.8 Hz, 2H), 7.40 - 7.45 (m, 2H,).

¹³C NMR (100 MHz, CDCl₃): δ = 1.5, 1.9, 21.7, 55.2, 113.2, 126.7 (overlapped), 126.8, 127.8, 128.1, 139.5, 147.5, 158.5.

ESIHRMS: Found: m/z 237.1276. Calcd for C₁₇H₁₈O₂: [(M-H₂O)+H]⁺ 237.1279.

2,2,2-Triphenylacetonitrile (**2.8v**)^[13]

Prepared by following **Method C** from triphenylmethanol (2.08 g, 8.00 mmol) to give **2.8v** (1.23 g, 4.56 mmol) in 57% yield.

¹H NMR (400 MHz, CDCl₃): δ = 7.18 - 7.28 (m, 6H), 7.30 - 7.39 (m, 9H).

¹³C NMR (100 MHz, CDCl₃): δ = 57.4, 123.5, 128.1, 128.7, 128.8, 140.2.

2,2-Bis(4-methoxyphenyl)-2-phenylacetonitrile (**2.8w**)

Prepared by following **Method C** from bis(4-methoxyphenyl)(phenyl)methanol (1.10 g, 3.43 mmol) to give **2.8w** (1.03 g, 3.13 mmol) in 91% yield.

¹H NMR (400 MHz, CDCl₃): δ = 3.81 (s, 6H), 6.86 (ddd, J = 2.0, 3.2, 8.8 Hz, 4H), 7.12 (ddd, J = 2.0, 3.2, 8.8 Hz, 4H), 7.20 - 7.25 (m, 2H), 7.30 - 7.38 (m, 3H).

¹³C NMR (400 MHz, CDCl₃): δ = 55.3, 56.1, 113.9, 123.7, 128.0, 128.57, 128.63, 129.9, 132.5, 140.8, 159.2.

ESIHRMS: Found: m/z 330.1495. Calcd for C₂₂H₁₉NO₂: (M+H)⁺ 330.1494.

Synthesis of Bis(4-methoxyphenyl)(phenyl)methanol

Prepared from methyl benzoate (1.36 g, 10.0 mmol) and (4-methoxyphenyl)magnesium bromide (2.4 equiv) according to the experimental procedure for the **Synthesis of cyclopropyl(4-methoxyphenyl) (phenyl)methanol** to give bis(4-methoxyphenyl)(phenyl)methanol (3.00 g, 9.36 mmol) 94% yield.

¹H NMR (400 MHz, CDCl₃): δ = 2.71 (s, 1H), 3.79 (s, 6H), 6.83 (ddd, J = 2.0, 3.2, 8.8 Hz, 4H), 7.17 (ddd, J = 2.0, 3.2, 8.8 Hz, 4H), 7.22 - 7.33 (m, 5H).

¹³C NMR (400 MHz, CDCl₃): δ = 55.2, 81.4, 113.1, 127.0, 127.7, 127.8, 129.1, 139.4, 147.3, 158.6.

5.2.2 Hydrodeacylation of Tertiary Carbonitriles

Typical procedure for synthesis of 2.9a

To a mixture of NaH (60% dispersion in mineral oil; 40 mg, 1.0 mmol) and Lil (67 mg, 0.5 mmol) in 25 mL sealed tube was added a solution of 2,2-diphenylpropanenitrile (**2.8a**) (104 mg, 0.50 mmol) in THF (2.5 mL). The reaction mixture was stirred at 85 °C for 7 h. After cooling to room temperature, the reaction was then quenched with water at 0 °C and extracted thrice with diethyl ether (20 mLx3). The combined extracts were washed with brine, and dried over MgSO₄. Volatile materials were removed *in vacuo* and the crude

residue was purified by flash column chromatography (silica gel, hexane:ethyl acetate = 95:5) to give 1,1-diphenylethane^[14] (**2.9a**) (89.7 mg, 0.49 mmol) in 98% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.64 (d, J = 7.2 Hz, 3H), 4.15 (q, J = 7.2 Hz, 1H), 7.17 (t, J = 7.2 Hz, 2H), 7.22 (d, J = 7.2 Hz, 4H), 7.28 (dd, J = 7.2, 7.6 Hz, 4H).

¹³C NMR (100 MHz, CDCl₃): δ = 21.8, 44.8, 126.0, 127.6, 128.3, 146.3.

1-Methoxy-4-(2-phenylpropyl)benzene (**2.9b**)^[15]

Prepared from carbonitrile **2.8b** (126 mg, 0.500 mmol) to give **2.9b** (108 mg, 0.478 mmol) in 96% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.22 (d, J = 6.8 Hz, 3H), 2.70 (dd, J = 8.0, 13.2 Hz, 1H), 2.88 (dd, J = 6.4, 13.6 Hz, 1H), 2.95 (dq, J = 6.4, 6.8, 8.0 Hz, 1H), 3.76 (s, 3H), 6.77 (d, J = 8.4 Hz, 2H), 6.98 (d, J = 8.8 Hz, 2H), 7.14 - 7.20 (m, 3H), 7.24 - 7.30 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ = 21.1, 42.0, 44.1, 55.2, 113.5, 125.9, 127.1, 128.2, 130.0, 132.9, 147.0, 157.8.

1-(1-(4-Methoxyphenyl)propan-2-yl)-2-methylbenzene (**2.9c**)

Prepared from carbonitrile **2.8c** (133 mg, 0.501 mmol) to give **2.9c** (106 mg, 0.439 mmol) in 88% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.19 (d, J = 7.2 Hz, 3H), 2.22 (s, 3H), 2.66 (dd, J = 8.8, 13.6 Hz, 1H), 2.85 (dd, J = 6.0, 13.6 Hz, 1H), 3.20 (dq, J = 6.0, 7.2, 8.8 Hz, 1H), 3.76 (s, 3H), 6.77 (d, J = 8.4 Hz, 2H), 6.99 (d, J = 8.4 Hz, 2H), 7.04 - 7.12 (m, 2H), 7.16 - 7.22 (m, 1H), 7.26 (d, J = 8.0 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 19.4, 20.4, 36.8, 43.5, 55.2, 113.5, 125.4, 125.6, 126.1, 129.9, 130.2, 133.1, 135.3, 145.2, 157.8.

ESIHRMS: Found: m/z 241.1583. Calcd for $C_{17}H_{20}O$: $(M+H)^+$ 241.1592.

1-Fluoro-3-(1-(4-methoxyphenyl)propan-2-yl)benzene (2.9d)

Prepared from carbonitrile **2.8d** (135 mg, 0.501 mmol) to give **2.9d** (119 mg, 0.486 mmol) in 97% yield.

1H NMR (400 MHz, $CDCl_3$): δ = 1.22 (d, J = 7.2 Hz, 3H), 2.71 (dd, J = 8.0, 13.6 Hz, 1H), 2.84 (dd, J = 6.8, 13.6 Hz, 1H), 2.95 (dq, J = 6.8, 7.2, 8.0 Hz, 1H), 3.77 (s, 3H), 6.77 (d, J = 8.4 Hz, 2H), 6.82 - 6.90 (m, 2H), 6.92 (d, J = 7.6 Hz, 1H), 6.96 (d, J = 8.4 Hz, 2H), 7.17 - 7.24 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.0, 41.9, 43.9, 55.2, 112.7 (d, J = 20.9 Hz), 113.5, 113.8 (d, J = 20.8 Hz), 122.8 (d, J = 2.4 Hz), 129.6 (d, J = 8.2 Hz), 130.0, 132.4, 149.7 (d, J = 6.8 Hz), 157.9, 162.9 (d, J = 243.5 Hz).

ESIHRMS: Found: m/z 245.1340. Calcd for $C_{16}H_{17}FO$: $(M+H)^+$ 245.1342.

4,4'-(2-Phenylpropane-1,3-diyl)bis(methoxybenzene) (2.9e)

Prepared from carbonitrile **2.8e** (190 mg, 0.530 mmol) to give **2.9e** (165 mg, 0.496 mmol) in 94% yield.

1H NMR (400 MHz, $CDCl_3$): δ = 2.82 (dd, J = 7.6, 13.6 Hz, 2H), 2.90 (dd, J = 6.4, 13.6 Hz, 2H), 3.03 (tt, J = 6.4, 7.6 Hz, 1H), 3.73 (s, 6H), 6.71 (ddd, J = 2.0, 2.8, 8.8 Hz, 4H), 6.89 (d, J = 8.8 Hz, 4H), 7.03 (dd, J = 1.6, 7.6 Hz, 2H), 7.12 (tt, J = 1.2, 7.2 Hz, 1H), 7.17 - 7.22 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.5, 50.2, 55.1, 113.4, 126.0, 127.9, 128.0, 130.0, 132.6, 144.4, 157.7.

ESIHRMS: Found: m/z 333.1857. Calcd for $C_{23}H_{24}O_2$: $(M+H)^+$ 333.1855.

1-(2-Cyclohexyl-2-phenylethyl)-4-methoxybenzene (2.8f)

Prepared from carbonitrile **2.8f** (160 mg, 0.501 mmol) to give **2.9f** (146 mg, 0.497 mmol) in 99% yield.

1H NMR (400 MHz, $CDCl_3$): δ = 0.74 - 0.86 (m, 1H), 0.93 - 1.18 (m, 3H), 1.18 - 1.31 (m, 1H), 1.50 - 1.68 (m, 4H), 1.70 - 1.78 (m, 1H), 1.90 - 1.99 (m, 1H), 2.57 (ddd, J = 5.2, 6.8, 9.6 Hz, 1H), 2.74 (dd, J = 9.6, 13.6 Hz, 1H), 3.10 (dd, J = 5.2, 13.6 Hz, 1H), 3.71 (s, 3H), 6.67 (ddd, J = 2.0, 2.8, 8.8 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 7.01 (dd, J = 1.6, 7.6 Hz, 2H), 7.09 - 7.15 (m, 1H), 7.19 (dd, J = 7.2, 7.6 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.49, 26.55, 26.59, 30.5, 31.8, 38.3, 42.2, 54.5, 55.1, 113.3, 125.7, 127.7, 128.8, 129.9, 133.4, 143.7, 157.4.

ESIHRMS: Found: m/z 295.2064. Calcd for $C_{21}H_{26}O$: $(M+H)^+$ 295.2062.

2-Isopropyl-naphthalene (2.8g)^[16]

Prepared from carbonitrile **2.8g** (97.8 mg, 0.501 mmol) to give **2.9g** (76.6 mg, 0.450 mmol) in 90% yield.

1H NMR (400 MHz, $CDCl_3$): δ = 1.34 (d, J = 6.8 Hz, 6H), 3.07 (septet, J = 6.8 Hz, 1H), 7.37 - 7.47 (m, 3H), 7.64 (s, 1H), 7.75 - 7.82 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.9, 34.2, 124.1, 125.0, 125.7, 125.8, 127.5, 127.6, 127.8, 132.1, 133.7, 146.3.

2'-Isopropyl-2,6-dimethoxy-1,1'-biphenyl (2.9h)

Prepared from carbonitrile **2.8h** (141 mg, 0.501 mmol) to give **2.9h** (126 mg, 0.491 mmol) in 98% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.10 (d, J = 6.8 Hz, 6H), 2.65 (septet, J = 6.8 Hz, 1H), 3.68 (s, 6H), 6.63 (d, J = 8.4 Hz, 2H), 7.07 (dd, J = 0.8, 7.6 Hz, 1H), 7.21 (ddd, J = 1.6, 6.8, 7.2 Hz, 1H), 7.29 (t, J = 8.4 Hz, 1H), 7.33 (ddd, J = 1.2, 6.8, 7.6 Hz, 1H), 7.37 (dd, J = 1.6, 7.6 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 23.7, 30.3, 55.7, 103.8, 119.0, 124.9, 125.2, 127.6, 128.5, 130.6, 133.0, 147.8, 157.9.

ESIHRMS: Found: m/z 257.1542. Calcd for C₁₇H₂₀O₂: (M+H)⁺ 257.1542.

Undeca-1,10-dien-6-ylbenzene (**2.9i**)

Prepared from carbonitrile **2.8i** (126 mg, 0.497 mmol) to give **2.9i** (111 mg, 0.487 mmol) in 98% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.14 - 1.33 (m, 4H), 1.50 - 1.69 (m, 4H), 1.90 - 2.07 (m, 4H), 2.48 (tt, J = 5.2, 9.2 Hz, 1H), 4.89 (tdd, J = 0.8, 2.0, 10.4 Hz, 2H), 4.94 (tdd, J = 1.6, 2.0, 17.2 Hz, 2H), 5.73 (tdd, J = 3.2, 10.4, 17.2 Hz, 2H), 7.12 (dd, J = 1.6, 8.4 Hz, 2H), 7.17 (tt, J = 1.2, 7.6 Hz, 1H), 7.27 (dd, J = 7.6, 8.4 Hz, 2H).

¹³C NMR (100 MHz, CDCl₃): δ = 26.9, 33.8, 36.4, 45.9, 114.3, 125.8, 127.6, 128.2, 138.9, 145.9.

ESIHRMS: Found: m/z 229.1949. Calcd for C₁₇H₂₄: (M+H)⁺ 229.1956.

1-Chloro-4-cyclohexylbenzene (**2.9j**)^[17]

Prepared from carbonitrile **2.8j** (110 mg, 0.500 mmol) to give **2.9j** (79.0 mg, 0.403 mmol) in 81% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.20 - 1.30 (m, 1H), 1.30 - 1.45 (m, 4H), 1.70 - 1.78 (m, 1H), 1.78 - 1.90 (m, 4H), 2.46 (tt, J = 2.4, 8.8 Hz, 1H), 7.12 (ddd, J = 1.6, 2.4, 8.4 Hz, 2H), 7.24 (ddd, J = 2.0, 2.4, 8.8 Hz, 2H).

¹³C NMR (100 MHz, CDCl₃): δ = 26.1, 26.8, 34.4, 44.0, 128.1, 128.3, 131.3, 146.5.

1-Cyclohexyl-4-methoxybenzene (**2.9k**)^[18]

Prepared from carbonitrile **2.8i** (109 mg, 0.504 mmol) to give **2.9i** (88.0 mg, 0.462 mmol) in 92% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.17 - 1.30 (m, 1H), 1.30 - 1.45 (m, 4H), 1.69 - 1.77 (m, 1H), 1.77 - 1.90 (m, 4H), 2.44 (tt, J = 3.2, 11.2 Hz, 1H), 3.78 (s, 3H), 6.83 (d, J = 8.4 Hz, 2H), 7.12 (d, J = 8.4 Hz, 2H).

¹³C NMR (100 MHz, CDCl₃): δ = 26.2, 26.9, 34.7, 43.7, 55.2, 113.6, 127.6, 140.4, 157.6.

Cyclopentylbenzene (**2.9l**)^[19]

Prepared from carbonitrile **2.8l** (85.6 mg, 0.500 mmol) to give **2.9l** (61.3 mg, 0.419 mmol) in 84% yield.

Large scale: Prepared from carbonitrile **2.8l** (8.02 g, 46.8 mmol) (see Chapter 2, Scheme 2.20 for picture of reaction setup) at reflux for 5 h and purified by vacuum distillation (5.0 mmHg, 60-61 °C) to give **2.9l** (6.31 g, 43.1 mmol) in 92% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.53 - 1.74 (m, 4H), 1.74 - 1.87 (m, 2H), 2.00 - 2.13 (m, 2H), 2.98 (tt, J = 7.4, 9.6 Hz, 1H), 7.13 - 7.19 (m, 1H), 7.21 - 7.31 (m, 4H).

^{13}C NMR (100 MHz, CDCl_3): δ = 25.5, 34.6, 45.9, 125.6, 127.1, 128.2, 146.5.

4-Cyclobutyl-1,1'-biphenyl (2.9m)

Prepared from carbonitrile **2.8m** (116 mg, 0.498 mmol) to give **2.9m** (88.0 mg, 0.423 mmol) in 85% yield.

^1H NMR (400 MHz, CDCl_3): δ = 1.87 - 1.97 (m, 1H), 2.08 (ttd, J = 8.0, 10.0, 10.0 Hz, 1H), 2.17 - 2.29 (m, 2H), 2.37 - 2.46 (m, 2H), 3.63 (tt, J = 8.8, 8.8 Hz, 1H), 7.31 - 7.39 (m, 3H), 7.46 (dd, J = 7.6 Hz, 2H), 7.57 (d, J = 8.4 Hz, 2H), 7.60 - 7.65 (m, 2H).

^{13}C NMR (400 MHz, CDCl_3): δ = 18.3, 29.8, 40.1, 126.7, 126.95 (overlapped), 127.01, 128.7, 138.7, 141.2, 145.4.

ESIHRMS: Found: m/z 209.1338. Calcd for $\text{C}_{16}\text{H}_{16}$: $(\text{M}+\text{H})^+$ 209.1330.

1-Cyclobutyl-4-methoxybenzene (2.9n)

Prepared from carbonitrile **2.8n** (100 mg, 0.500 mmol) to give **2.9n** (56.6 mg, 0.349 mmol) in 70% yield.

^1H NMR (400 MHz, CDCl_3): δ = 1.83 - 1.92 (m, 1H), 2.03 (tdt, J = 8.4, 9.6, 10.0 Hz, 1H), 2.09 - 2.22 (m, 2H), 2.32 - 2.41 (m, 2H), 3.54 (tt, J = 8.4, 8.8 Hz, 1H), 3.83 (s, 3H), 6.89 (ddd, J = 2.0, 3.2, 8.8 Hz, 2H), 7.20 (ddd, J = 2.0, 2.8, 8.4 Hz, 2H).

^{13}C NMR (400 MHz, CDCl_3): δ = 18.1, 30.1, 39.7, 55.2, 113.6, 127.2, 138.5, 157.6.

ESIHRMS: Found: m/z 163.1127. Calcd for $\text{C}_{11}\text{H}_{14}\text{O}$: $(\text{M}+\text{H})^+$ 163.1123.

4-Phenyltetrahydro-2H-pyran (2.9o)^[20]

Prepared from carbonitrile **2.8o** (93.8 mg, 0.501 mmol) to give **2.9o** (66 mg, 0.407 mmol) in 81% yield.

^1H NMR (400 MHz, CDCl_3): δ = 1.72 - 1.89 (m, 4H), 2.75 (tt, J = 4.4, 11.6 Hz, 1H), 3.53 (ddd, J = 2.4, 11.2, 11.6 Hz, 2H), 4.08 (dd, J = 1.2, 4.4, 11.2 Hz, 2H), 7.18 - 7.26 (m, 3H), 7.31 (dd, J = 7.2, 7.6 Hz, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ = 33.9, 41.5, 68.4, 126.3, 126.7, 128.5, 145.8.

2-Cyclohexylpyridine (**2.9p**)^[21]

Prepared from carbonitrile **2.8p** (93.6 mg, 0.503 mmol) to give **2.9p** (71.0 mg, 0.437 mmol) in 87% yield.

^1H NMR (400 MHz, CDCl_3): δ = 1.28 (ttt, J = 3.2, 12.4, 12.4 Hz, 1H), 1.42 (ttt, J = 3.2, 12.4, 12.8 Hz, 2H), 1.53 (dt, J = 2.8, 3.2, 12.4 Hz, 2H), 1.71 - 1.80 (m, 1H), 1.82 - 1.91 (m, 2H), 1.91 - 2.00 (m, 2H), 2.69 (tt, J = 3.2, 12.0 Hz, 1H), 7.08 (ddd, J = 0.8, 4.8, 7.6 Hz, 1H), 7.14 (d, J = 8.0 Hz, 1H), 7.59 (ddd, J = 1.6, 7.6, 8.0 Hz, 1H), 8.53 (dd, J = 0.4, 4.8 Hz, 1H).

^{13}C NMR (100 MHz, CDCl_3): δ = 26.1, 26.6, 32.9, 45.6, 120.9, 136.3, 149.0, 166.5.

(2-(4-Methoxyphenyl)ethane-1,1-diyl)dibenzene (**2.9q**)

Prepared from carbonitrile **2.8q** (157 mg, 0.501 mmol) to give **2.9q** (137 mg, 0.475 mmol) in 95% yield.

^1H NMR (400 MHz, CDCl_3): δ = 3.30 (d, J = 7.6 Hz, 2H), 3.73 (s, 3H), 4.17 (t, J = 7.6 Hz, 1H), 6.70 (d, J = 8.4 Hz, 2H), 6.90 (d, J = 8.4 Hz, 2H), 7.15 (t, J = 7.2 Hz, 2H), 7.17 - 7.28 (m, 8H).

^{13}C NMR (100 MHz, CDCl_3): δ = 41.2, 53.3, 55.1, 113.5, 126.1, 128.1, 128.3, 129.9, 132.4, 144.6, 157.8.

ESIHRMS: Found: m/z 289.1600. Calcd for $C_{21}H_{20}O$: $(M+H)^+$ 289.1592.

(3-Methoxypropane-1,1-diyl)dibenzene (2.9r)

Prepared from carbonitrile **2.8r** (126 mg, 0.500 mmol) to give **2.9r** (112 mg, 0.493 mmol) in 99% yield.

1H NMR (400 MHz, $CDCl_3$): δ = 2.31 (td, J = 6.4, 8.0 Hz, 2H), 3.27 (s, 3H), 3.29 (t, J = 6.4 Hz, 2H), 4.11 (t, J = 8.0 Hz, 1H), 7.13 - 7.19 (m, 2H), 7.22 - 7.30 (m, 8H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 35.3, 47.2, 58.5, 70.6, 126.1, 127.9, 128.4, 144.6.

ESIHRMS: Found: m/z 227.1438. Calcd for $C_{16}H_{18}O$: $(M+H)^+$ 227.1436.

1,1,5,5-Tetraphenylpentane (2.9s)

Prepared from carbonitrile **2.8s** (214 mg, 0.502 mmol) with NaH (3 equiv) and Lil (1 equiv) to give **2.9s** (189 mg, 0.501 mmol) in 99% yield.

1H NMR (400 MHz, $CDCl_3$): δ = 1.22 - 1.32 (m, 2H), 2.07 (td, J = 7.6, 7.6 Hz, 4H), 3.84 (t, J = 7.6 Hz, 2H), 7.11 - 7.20 (m, 12H), 7.20 - 7.28 (m, 8H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.1, 35.5, 50.9, 126.0, 127.8, 128.4, 145.1.

ESIHRMS: Found: m/z 377.2278. Calcd for $C_{29}H_{28}$: $(M+H)^+$ 377.2269.

Hex-5-ene-1,1-diylidibenzene (2.9t)

Prepared from carbonitrile **2.8t** (132 mg, 0.505 mmol) to give **2.9t** (119 mg, 0.503 mmol) in 99% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.32 - 1.41 (m, 2H), 2.01 - 2.12 (m, 4H), 3.89 (t, J = 8.0 Hz, 1H), 4.89 - 4.95 (m, 1H), 4.98 (tdd, J = 1.6, 2.0, 17.2 Hz, 1H), 5.76 (tdd, J = 2.8, 10.4, 17.2 Hz, 1H), 7.13 - 7.20 (m, 2H), 7.20 - 7.30 (m, 8H).

¹³C NMR (100 MHz, CDCl₃): δ = 27.3, 33.7, 35.1, 51.3, 114.6, 126.0, 127.8, 128.4, 138.7, 145.1.

ESIHRMS: Found: m/z 237.1651. Calcd for C₁₈H₂₀: (M+H)⁺ 237.1643.

1-(Cyclopropyl(phenyl)methyl)-4-methoxybenzene (2.9u)

Prepared from carbonitrile **2.8u** (132 mg, 0.503 mmol) to give **2.9u** (120 mg, 0.503 mmol) in 99% yield.

¹H NMR (400 MHz, CDCl₃): δ = 0.25 - 0.30 (m, 2H), 0.59 - 0.69 (m, 2H), 1.34 (ttd, J = 5.2, 8.0, 9.6 Hz, 1H), 3.16 (d, J = 9.6 Hz, 1H), 3.76 (s, 3H), 6.82 (ddd, J = 2.4, 2.8, 8.8 Hz, 2H), 7.17 (ddd, J = 2.0, 2.8, 8.8 Hz, 2H), 7.15 - 7.20 (m, 1H), 7.22 - 7.30 (m, 4H).

¹³C NMR (100 MHz, CDCl₃): δ = 5.2, 5.3, 16.9, 54.8, 55.2, 113.6, 126.0, 128.2 (overlapped), 129.1, 137.4, 145.5, 157.9.

ESIHRMS: Found: m/z 239.1436. Calcd for C₁₇H₁₈O: (M+H)⁺ 239.1436.

Triphenylmethane (2.9v)^[22]

Prepared from carbonitrile **2.8v** (135 mg, 0.500 mmol) to give **2.9v** (110 mg, 0.450 mmol) in 90% yield.

¹H NMR (400 MHz, CDCl₃): δ = 5.55 (s, 1H), 7.11 (d, J = 7.2 Hz, 6H), 7.20 (t, J = 7.6 Hz, 3H), 7.27 (dd, J = 7.2, 7.6 Hz, 6H).

¹³C NMR (100 MHz, CDCl₃): δ = 56.8, 126.3, 128.3, 129.4, 143.9.

4,4'-(Phenylmethylene)bis(methoxybenzene) (**2.9w**)^[23]

Prepared from carbonitrile **2.8w** (164 mg, 0.497 mmol) to give **2.9w** (114 mg, 0.373 mmol) in 75% yield.

¹H NMR (400 MHz, CDCl₃): δ = 3.77 (s, 6H), 5.44 (s, 1H), 6.81 (d, J = 8.8 Hz, 4H), 7.01 (d, J = 8.8 Hz, 4H), 7.10 (d, J = 7.2 Hz, 2H), 7.19 (t, J = 7.2 Hz, 1H), 7.27 (dd, J = 7.2, 7.6 Hz, 2H).

¹³C NMR (400 MHz, CDCl₃): δ = 55.18, 55.21, 113.6, 126.1, 128.2, 129.3, 130.3, 136.4, 144.6, 158.0.

5.2.3 A procedure for Scheme 2.22 and characterization of the products

Prepared by following the experimental procedure in Section 5.2.2 with carbonitrile **2.8k** (108 mg, 0.50 mmol) for 2.5 h to give **2.9k** (35 mg, 0.185 mmol) in 37% yield and **2.11k** (46 mg, 0.21 mmol) in 42% yield.

1-(4-Methoxyphenyl)cyclohexanecarbaldehyde (**2.11k**)^[24]

¹H NMR (400 MHz, CDCl₃): δ = 1.24 - 1.35 (m, 1H), 1.41 - 1.53 (m, 2H), 1.55 - 1.71 (m, 3H), 1.75 - 1.86 (m, 2H), 2.23 - 2.32 (m, 2H), 3.79 (s, 3H), 6.90 (ddd, J = 2.0, 3.2, 8.8 Hz, 2H), 7.23 (ddd, J = 2.0, 3.2, 8.8 Hz, 2H), 9.31 (s, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 22.8, 25.6, 31.3, 53.6, 55.2, 114.2, 128.2, 131.5, 158.6, 202.2.

5.2.4 A procedure for Scheme 2.23 and characterization of the products

Prepared by following the experimental procedure in Section 5.2.2 with carbonitrile **2.8x** (143 mg, 0.50 mmol) to give **2.9x** (79.5 mg, 0.31 mmol) in 61% yield and **2.12x** (21.5 mg, 0.085 mmol) 17% yield.

1-Chloro-2-(1-(4-methoxyphenyl)propan-2-yl)benzene (**2.9x**)

¹H NMR (400 MHz, CDCl₃): δ = 1.19 (d, J = 6.8 Hz, 3H), 2.60 (dd, J = 8.8, 13.6 Hz, 1H), 2.95 (dd, J = 5.2, 13.6 Hz, 1H), 3.53 (dq, J = 5.2, 6.8, 8.8 Hz, 1H), 3.78 (s, 3H), 6.80 (ddd, J = 2.0, 3.2, 8.4 Hz, 2H), 7.06 (ddd, J = 2.0, 3.2, 8.8 Hz, 2H), 7.12 (ddd, J = 1.6, 7.2, 7.6 Hz, 1H), 7.22 (ddd, J = 1.2, 7.2, 8.0 Hz, 1H), 7.27 (dd, J = 1.6, 7.6 Hz, 1H), 7.34 (dd, J = 1.2, 8.0 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 19.3, 37.3, 42.5, 55.2, 113.5, 126.8, 127.0, 127.3, 129.5, 130.0, 132.4, 133.7, 144.1, 157.9.

ESIHRMS: Found: m/z 261.1050. Calcd for C₁₆H₁₇ClO: (M+H)⁺ 261.1046.

3-(4-Methoxybenzyl)-3-methylindoline (**2.12x**)

¹H NMR (400 MHz, CDCl₃): δ = 1.29 (s, 3H), 2.79 (s, 2H), 3.14 (d, J = 13.2 Hz, 1H), 3.48 (d, J = 13.2 Hz, 1H), 3.63 (brs, 1H), 3.78 (s, 3H), 6.63 (d, J = 7.6 Hz, 1H), 6.71 (ddd, J = 0.8, 7.2, 7.6 Hz, 1H), 6.77 (ddd, J = 2.0, 2.8, 8.4 Hz, 2H), 6.86 (dd, J = 0.8, 7.6 Hz, 1H), 6.94 (ddd, J = 2.0, 2.8, 8.8 Hz, 2H), 7.04 (ddd, J = 1.2, 7.2, 7.6 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 24.6, 45.1, 46.1, 55.1, 58.9, 109.7, 113.1, 118.4, 123.1, 127.4, 130.5, 131.4, 136.8, 150.6, 158.0.

ESIHRMS: Found: m/z 254.1542. Calcd for C₁₇H₁₉NO: (M+H)⁺ 254.1545.

5.2.5 A procedure for Scheme 2.24 and characterization of the products

Prepared by following the experimental procedure in Section 5.2.2 with carbonitrile **2.8y** (161.2 mg, 1.0 mmol) and NaH (3 equiv) and NaI (2 equiv) to give **2.13y** (47 mg, 0.29 mmol) in 29% yield and **2.14y** (11 mg, 0.066 mmol) in 7% yield.

Adamantane-1-carbaldehyde (**2.13y**)^[25]

¹H NMR (400 MHz, CDCl₃): δ = 1.66 - 1.82 (m, 9H), 2.0 - 2.10 (m, 6H), 9.32 (s, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 27.0, 35.8, 36.5, 44.8, 205.9.

Adamantan-1-ylmethanamine (**2.14y**)^[26]

¹H NMR (400 MHz, CDCl₃): δ = 1.51 (d, J = 2.4 Hz, 6H), 1.60 - 1.75 (m, 6H), 1.92 - 1.98 (m, 3H), 2.21 (s, 2H).

¹³C NMR (100 MHz, CDCl₃): δ = 28.6, 34.0, 37.3, 41.0, 64.3.

5.2.6 A procedure for Scheme 2.25a and characterization of the products

Prepared by following the experimental procedure in Section 5.2.2 with carbonitrile **2.8z** (114 mg, 0.50 mmol) to give **2.9z** (97 mg, 0.48 mmol) in 96% yield.

2-(3-Methoxyphenyl)bicyclo[2.2.1]heptane (**2.9z**)^[27]

¹H NMR (400 MHz, CDCl₃): δ = 1.18 (dtd, J = 0.8, 1.6, 9.6 Hz, 1H), 1.21 - 1.30 (m, 1H), 1.30 - 1.38 (m, 1H), 1.50 - 1.68 (m, 4H), 1.75 (ddd, J = 2.0, 9.2, 12.4 Hz, 1H), 2.30 - 2.38 (m, 2H), 2.71 (dd, J = 6.0, 8.8 Hz, 1H), 3.79 (s, 3H), 6.69 (dd, J = 2.4, 8.0 Hz, 1H), 6.77 (dd, J = 0.8, 2.4 Hz, 1H), 6.81 (dd, J = 0.8, 7.6 Hz, 1H), 7.18 (dd, J = 7.6, 8.0 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 28.8, 30.6, 36.2, 36.7, 39.2, 42.8, 47.3, 55.1, 110.3, 113.1, 119.5, 129.1, 149.4, 159.5.

5.2.7 A procedure for Scheme 2.25b and characterization of the products

The enantioenriched (+)-**2.8b** and (–)-**2.8b** were obtained by separation of racemic carbonitrile (±)-**2.8b** using CombiFlash® Rf 200 with chiral column Daicel ChiralPak IC (30 mm ϕ $\times$ 100 mmL; particle size 20 μ m) hexane/isopropyl alcohol (97/3), flow rate 12 mL/min. The optically active carbonitrile (+)-**2.8b** was isolated in 93% ee and carbonitrile (–)-**2.8b** in 98% ee.

HPLC analysis for (+)-2.8b and (–)-2.8b

Chiral column: Daicel ChiralPak IC (4.0mm ϕ $\times$ 10mmL; particle size 5 μ m)

Eluent: hexane/isopropyl alcohol (96/4)

Flow rate: 0.5 mL/min

Diode array detector: 278 nm

Retention time for (+)-**2.8b**: 16.5 min

Retention time for (–)-**2.8b**: 18.8 mins

Racemic carbonitrile (±)-**2.8b**

PeakTable		
UV Detector Ch2 278nm		
Peak#	Ret. Time	Area %
1	16.666	50.085
2	18.840	49.915
Total		100.000

Optically active carbonitrile (+)-**2.8b**

PeakTable		
UV Detector Ch2 278nm		
Peak#	Ret. Time	Area %
1	16.234	96.856
2	18.105	3.144
Total		100.000

Optically active carbonitrile (–)-**2.8b**

PeakTable		
UV Detector Ch2 278nm		
Peak#	Ret. Time	Area %
1	16.557	1.025
2	18.762	98.975
Total		100.000

Optical rotation for (+)-**2.8b** and (–)-**2.8b**

For (+)-**2.8b** (94% ee): $[\alpha]_D^{21} +70.6^\circ$ ($c = 0.01914$ g/mL, CHCl_3)

For (–)-**2.8b** (97% ee): $[\alpha]_D^{21} -70.1^\circ$ ($c = 0.01286$ g/mL, CHCl_3)

The reaction with (+)-**2.8b** (0.500 mmol) was conducted by following the procedure described in section 5.2.2, affording the decyanated product (+)-**2.9f** in 91% yield and 89% ee.

The reaction with (–)-**2.8f** (0.303 mmol) was conducted by following the procedure described in section 5.2.2, affording the decyanated product (–)-**2.9f** in 89% yield with 95% ee.

HPLC analysis for (+)-2.9b and (–)-2.9b

Chiral column: Daicel ChiralPak OD-H (4.0mm ø × 10mmL; particle size 5 µm)

Eluent: hexane (100%)

Flow rate: 0.8 mL/min

Diode array detector: 278 nm

Retention time for (+)-**2.9b**: 23.0 min

Retention time for (–)-**2.9b**: 31.5 mins

Racemic carbonitrile (±)-2.9b

PeakTable
UV Detector Ch2 278nm

Peak#	Ret. Time	Area %
1	23.230	50.530
2	31.989	49.470
Total		100.000

Optically active carbonitrile (+)-2.9b

PeakTable
UV Detector Ch2 278nm

Peak#	Ret. Time	Area %
1	23.000	94.674
2	31.962	5.326
Total		100.000

Optically active carbonitrile (–)-**2.9b**

Optical rotation for (+)-**2.9b** and (–)-**2.9b**

For (+)-**2.9b** (89% ee): $[\alpha]_D^{21} +77.3^\circ$ ($c = 0.0547$ g/mL, CHCl_3)

For (–)-**2.9b** (95% ee): $[\alpha]_D^{21} -82.6^\circ$ ($c = 0.0614$ g/mL, CHCl_3)

5.2.8 Detection of NaCN after the decyanation of **2.8a** with NaH-Nal composite

To a mixture of NaH (60% dispersion in mineral oil; 0.30 g, 7.5 mmol), NaI (0.75 g, 5.0 mmol) in a flamed-dried 100 mL sealed tube was added a solution of nitrile **2.8a** (0.518 g, 2.5 mmol) in 12.5 mL of THF. The reaction mixture was stirred for 24 h at 85 °C. After the suspension was allowed to stand undisturbed at around 60 °C, the particles in the suspension deposited. Before further cooling to room temperature, most of the supernatant was removed via a syringe and the remaining solvent was removed *in vacuo*. The vacuum-dried mixture was taken into a glovebox and washed with anhydrous pentane (3 mL × 8) to remove the mineral oil. This sample was used for the attenuated total reflectance Fourier transform infrared (ATR-FTIR) spectroscopy. The ATR-FTIR spectrum revealed the presence of CN^- (2086 cm^{-1}) in the bulk material as anticipated (Chapter 2, Figure 2.2).

5.2.9 References for Section 5.2

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5.3 Experimental data for Chapter 3

5.3.1 Synthesis of Aromatic, Heteroaromatic and Aliphatic Amides

Two methods **A** and **B** were applied for the synthesis of aromatic amides **3.27a-3.27b**, **3.27bb-3.27be** and **3.27e-3.27u**, heteroaromatic amides **3.29a-3.29k** and aliphatic amides **3.28a-3.28l**.

Amides **3.27c-3.27d** and **3.30-3.33** were synthesized via the base-mediated etherification of 4-hydroxyphenyl carboxamides. Keto amide **3.34** was synthesized via the α -alkylation of *N,N*-dimethylisobutyramide.

Method A: For synthesis of aromatic amides 3.27a-3.27b, 3.27bb-3.27be and 3.27e-3.27u and aliphatic amides 3.28a-3.28j and 3.28l.

Typical Procedure for Synthesis of 3.27a^[1]

To a solution of 2-naphthoic acid (1.72 g, 10.0 mmol) in CH_2Cl_2 (40 mL) was added $(\text{COCl})_2$ (1.30 mL, 15.0 mmol) and DMF (5 drops) 23 °C. The reaction mixture was stirred at room temperature for 2 h, before adding Me_2NH (40 w/w% in water; 5.06 mL, 40.0 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 1M aqueous HCl solution followed by saturated aqueous NaHCO_3 solution and brine, and then 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 = 50:50) to give **3.27a** (1.26 g, 6.33 mmol) in 63% yield.

¹H NMR (400 MHz, CDCl_3): δ = 3.03 (s, 3H), 3.16 (s, 3H), 7.49 – 7.54 (m, 3H), 7.84 – 7.88 (m, 3H), 7.91 (s, 1H).

¹³C NMR (100 MHz, CDCl_3): δ = 35.5, 39.7, 124.5, 126.7, 126.9, 127.1, 127.9, 128.3, 128.5, 132.8, 133.7, 133.8, 171.7.

4-methoxy-N,N-dimethylbenzamide (3.27b)^[2]

Prepared by following **Method A** from 4-methoxybenzoic acid (1.22 g, 8.00 mmol) to give **3.27b** (1.22 g, 6.80 mmol) in 85% yield.

¹H NMR (400 MHz, CDCl₃): δ = 3.05 (brs, 6H), 3.82 (s, 3H), 6.89 (d, J = 8.8 Hz, 2H), 7.39 (d, J = 8.8 Hz, 2H).

¹³C NMR (100 MHz, CDCl₃): δ = 35.6, 39.9, 55.4, 113.6, 128.5, 129.2, 160.6, 171.5.

N,N-diethyl-4-methoxybenzamide (3.27bb)^[3]

Prepared by following **Method A** with slight modification from 4-methoxybenzoic acid (761 mg, 5.01 mmol) and diethylamine to give **3.27bb** (1.00 g, 4.83 mmol) in 96% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.17 (brs, 6H), 3.39 (brs, 4H), 3.81 (s, 3H), 6.89 (d, J = 8.8 Hz, 2H), 7.33 (d, J = 8.8 Hz, 2H).

¹³C NMR (100 MHz, CDCl₃): δ = 13.6, 39.4, 43.2, 55.3, 113.7, 128.2, 129.6, 160.3, 171.2.

N,N-diisopropyl-4-methoxybenzamide (3.27bc)

Prepared by following **Method A** with slight modification from 4-methoxybenzoic acid (3.59 g, 20.0 mmol) with diisopropylamine in the presence of triethylamine to give **3.27bc** (556 mg, 2.36 mmol) in 12% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.32 (brs, 12H), 3.69 (brs, 2H), 3.81 (s, 3H), 6.89 (d, J = 8.8 Hz, 2H), 7.26 (d, J = 8.8 Hz, 2H).

¹³C NMR (100 MHz, CDCl₃): δ = 20.9, 47.9, 55.4, 113.7, 127.5, 131.4, 160.0, 171.0.

ESIHRMS: Found: m/z 236.1657; Calcd for C₁₄H₂₂NO₂: (M+H)⁺ 236.1651.

(4-methoxyphenyl)(piperidin-1-yl)methanone (3.27bd)

Prepared by following **Method A** from 4-methoxybenzoic acid (760 mg, 5.00 mmol) and piperidine to give **3.27bd** (592 mg, 2.70 mmol) in 54% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.58 (brs, 3H), 1.66 (brs, 3H), 3.52 (brs, 4H), 3.82 (s, 3H), 6.89 (d, *J* = 8.5 Hz, 2H), 7.36 (d, *J* = 8.5 Hz, 2H).

¹³C NMR (100 MHz, CDCl₃): δ = 24.6, 26.2, 29.6, 43.9, 48.5, 55.2, 113.5, 128.6, 128.8, 160.4, 170.2.

ESIHRMS: Found: m/z 220.1347; Calcd for C₁₃H₁₈NO₂: (M+H)⁺ 220.1338.

(4-methoxyphenyl)(morpholino)methanone (3.27be)

Prepared by following **Method A** from 4-methoxybenzoic acid (1.52 g, 10.0 mmol) and morpholine to give **3.27be** (2.08 g, 9.40 mmol) in 94% yield.

¹H NMR (400 MHz, CDCl₃): δ = 3.47 – 3.79 (m, 8H), 3.82 (s, 3H), 6.90 (d, *J* = 8.8 Hz, 2H), 7.37 (d, *J* = 8.8 Hz, 2H).

¹³C NMR (100 MHz, CDCl₃): δ = 43.3, 47.5, 55.4, 66.9, 113.8, 127.4, 129.2, 160.9, 170.4.

ESIHRMS: Found: m/z 222.1125; Calcd for C₁₂H₁₆NO₃: (M+H)⁺ 222.1130.

2-methoxy-N,N-dimethylbenzamide (3.27e)^[4]

Prepared by following **Method A** from 2-methoxybenzoic acid (1.46 g, 9.58 mmol) to give **3.27e** (1.56 g, 8.70 mmol) in 91% yield.

¹H NMR (400 MHz, CDCl₃): δ = 2.84 (s, 3H), 3.11 (s, 3H), 3.83 (s, 3H), 6.90 (d, J = 8.4 Hz, 1H), 6.98 (dd, J = 8.4, 7.5 Hz, 1H), 7.22 (d, J = 8.4 Hz, 1H), 7.34 (dd, J = 8.4, 7.5 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 34.8, 38.3, 55.6, 111.0, 120.9, 126.4, 127.9, 130.3, 155.4, 169.5.

N,N-dimethylbenzo[d][1,3]dioxole-5-carboxamide (3.27f)

Prepared by following **Method A** from benzo[d][1,3]dioxole-5-carboxylic acid (1.66 g, 10.0 mmol) to give **3.27f** (1.74 g, 9.00 mmol) in 90% yield.

¹H NMR (400 MHz, CDCl₃): δ = 3.03 (brs, 6H), 5.98 (s, 2H), 6.80 (d, J = 7.8 Hz, 1H), 6.90 - 6.94 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ = 35.5, 39.8, 101.4, 108.09, 108.10, 121.6, 129.9, 147.5, 148.7, 171.1.

ESIHRMS: Found: m/z 194.0820; Calcd for C₁₀H₁₂NO₃: (M+H)⁺ 194.0817

4-(benzyloxy)-3-methoxy-N,N-dimethylbenzamide (3.27g)

Prepared by following **Method A** from 4-(benzyloxy)-3-methoxybenzoic acid^[5] (2.51 g, 9.73 mmol) to give **3.27g** (2.03 g, 7.11 mmol) in 71% yield.

¹H NMR (400 MHz, CDCl₃): δ = 3.05 (brs, 6H), 3.90 (s, 3H), 5.18 (s, 2H), 6.86 (d, J = 8.2 Hz, 1H), 6.92 (dd, J = 8.2, 1.9 Hz, 1H), 7.03 (d, J = 1.9 Hz, 1H), 7.30 (t, J = 7.2 Hz, 1H), 7.36 (dd, J = 7.2, 7.1 Hz, 2H), 7.43 (d, J = 7.1 Hz, 2H),.

¹³C NMR (100 MHz, CDCl₃): δ = 35.6, 39.8, 56.1, 71.0, 111.5, 113.1, 120.1, 127.3, 128.0, 128.6, 129.2, 136.8, 149.3, 149.5, 171.4.

ESIHRMS: Found: m/z 276.1448; Calcd for C₁₇H₂₀NO₃: (M+H)⁺ 286.1443

3-(dimethylamino)-N,N-dimethylbenzamide (3.27h)

Prepared by following **Method A** from 3-(dimethylamino)benzoic acid (1.32 g, 8.00 mmol) to give **3.27h** (768 mg, 4.00 mmol) in 50% yield.

¹H NMR (400 MHz, CDCl₃): δ = 2.93 (s, 6H), 2.95 (s, 3H), 3.08 (s, 3H), 6.67 (d, *J* = 7.4 Hz, 1H), 6.71 - 6.72 (m, 2H), 7.20 (dd, *J* = 9.0, 7.4 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 35.3, 39.6, 40.6, 110.9, 113.4, 114.8, 129.0, 137.2, 150.6, 172.5.

ESIHRMS: Found: m/z 193.1351; Calcd for C₁₁H₁₇N₂O: (M+H)⁺ 193.1341.

N,N,2-trimethylbenzamide (3.27i)^[6]

Prepared by following **Method A** from 2-methylbenzoic acid (1.37 g, 10.1 mmol) to give **3.27i** (1.55 g, 9.47 mmol) in 94% yield.

¹H NMR (400 MHz, CDCl₃): δ = 2.29 (s, 3H), 2.83 (s, 3H), 3.13 (s, 3H), 7.14 - 7.22 (m, 3H), 7.24 - 7.29 (m, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 19.0, 34.6, 38.4, 125.8, 126.0, 128.8, 130.4, 134.0, 136.8, 171.6.

2-benzyl-N,N-dimethylbenzamide (3.27j)

Prepared by following **Method A** from 2-benzylbenzoic acid (2.12 g, 10.0 mmol) to give **3.27j** (2.30 g, 9.61 mmol) in 96% yield.

¹H NMR (400 MHz, CDCl₃): δ = 2.31 (s, 3H), 2.93 (s, 3H), 3.99 (brs, 2H), 7.10 - 7.31 (m, 9H).

¹³C NMR (100 MHz, CDCl₃): δ = 34.3, 38.4, 39.3, 126.2, 126.3, 126.4, 128.3, 128.9, 129.3, 130.6, 136.9, 138.0, 140.2, 171.2.

ESIHRMS: Found: m/z 240.1379; Calcd for C₁₆H₁₈NO: (M+H)⁺ 240.1388.

N,N-dimethyl-1-naphthamide (3.27k)^[1]

Prepared by following **Method A** from 1-naphthoic acid (2.36 g, 13.7 mmol) to give **3.27k** (2.59 g, 13.0 mmol) in 95% yield.

¹H NMR (400 MHz, CDCl₃): δ = 2.79 (s, 3H), 3.24 (s, 3H), 7.40 (dd, J = 7.2, 1.2 Hz, 1H), 7.45 - 7.51 (m, 3H), 7.76 - 7.79 (m, 1H), 7.83 - 7.86 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ = 35.0, 39.0, 124.0, 124.9, 125.3, 126.4, 127.1, 128.5, 129.1, 129.6, 133.6, 134.8, 171.0.

N,N,2,6-tetramethylbenzamide (3.27l)^[6]

Prepared by following **Method A** from 2,6-dimethylbenzoic acid (1.20 g, 8.00 mmol) to give **3.27l** (1.39 g, 7.76 mmol) in 97% yield.

¹H NMR (400 MHz, CDCl₃): δ = 2.23 (s, 6H), 2.79 (s, 3H), 3.15 (s, 3H), 7.01 (d, J = 7.4 Hz, 2H), 7.13 (t, J = 7.4 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 19.0, 34.2, 37.5, 127.5, 128.3, 133.5, 136.7, 171.4.

N,N-dimethylferroceneamide (3.27m)

Prepared by following **Method A** from ferrocenecarboxylic acid (2.30 g, 10.0 mmol) to give **3.27m** (1.16 g, 4.52 mmol) in 45% yield.

^1H NMR (400 MHz, CDCl_3): δ = 3.13 (brs, 6H), 4.23 (s, 5H), 4.29 - 4.33 (m, 2H), 4.61 - 4.64 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ = 36.7, 38.8, 69.3, 69.8, 70.7, 78.5, 170.9.

ESIHRMS: Found: m/z 258.0576; Calcd for $\text{C}_{13}\text{H}_{16}\text{NOFe}$: $(\text{M}+\text{H})^+$ 258.0581.

N,N-dimethyl-[1,1'-biphenyl]-4-carboxamide (3.27n)^[2]

Prepared by following **Method A** from [1,1'-biphenyl]-4-carboxylic acid (1.98 g, 10.0 mmol) to give **3.27n** (1.95 g, 8.67 mmol) in 87% yield.

^1H NMR (400 MHz, CDCl_3): δ = 3.04 (s, 3H), 3.13 (s, 3H), 7.37 (t, J = 7.7 Hz, 1H), 7.45 (dd, J = 8.2, 7.7 Hz, 2H), 7.50 (d, J = 8.2 Hz, 2H), 7.58 - 7.63 (m, 4H).

^{13}C NMR (100 MHz, CDCl_3): δ = 35.5, 39.7, 127.1, 127.2, 127.8, 127.8, 129.0, 135.2, 140.4, 142.5, 171.5.

4-chloro-N,N-dimethylbenzamide (3.27o)^[2]

Prepared by following **Method A** from 4-chlorobenzoic acid (1.25 g, 8.00 mmol) to give **3.27o** (1.32 g, 7.2 mmol) in 90% yield.

^1H NMR (400 MHz, CDCl_3): δ = 2.96 (s, 3H), 3.09 (s, 3H), 7.34 - 7.38 (m, 4H).

^{13}C NMR (100 MHz, CDCl_3): δ = 35.5, 39.6, 128.7(overlap), 134.7, 135.7, 170.6.

4-bromo-N,N-dimethylbenzamide (3.27p)^[2]

Prepared by following **Method A** from 4-bromobenzoic acid (2.10 g, 10.0 mmol) to give **3.27p** (2.05 g, 9.0 mmol) in 90% yield.

¹H NMR (400 MHz, CDCl₃): δ = 2.93 (s, 3H), 3.06 (s, 3H), 7.26 (d, J = 8.2 Hz, 2H), 7.50 (d, J = 8.2 Hz, 2H).

¹³C NMR (100 MHz, CDCl₃): δ = 35.5, 39.6, 123.9, 128.9, 131.6, 135.2, 170.6.

4-fluoro-N,N-dimethylbenzamide (3.27q)^[2]

Prepared by following **Method A** from 4-fluorobenzoic acid (1.05 g, 7.50 mmol) to give **3.27q** (1.21 g, 7.23 mmol) in 96% yield.

¹H NMR (400 MHz, CDCl₃): δ = 2.99 (s, 3H), 3.10 (s, 3H), 7.09 (dd, J_{H-H} = 8.4 Hz, J_{H-F} = 8.4 Hz, 2H), 7.43 (dd, J_{H-H} = 8.4 Hz, J_{H-F} = 5.4 Hz, 2H).

¹³C NMR (100 MHz, CDCl₃): δ = 35.6, 39.7, 115.5 (d, J = 21.9 Hz), 129.5 (d, J = 8.5 Hz), 132.4 (d, J = 3.4 Hz), 163.4 (d, J = 250.4 Hz), 170.7.

¹⁹F NMR (376 MHz, CDCl₃): δ = -110.6 (m).

2-fluoro-N,N-dimethylbenzamide (3.27r)^[1]

Prepared by following **Method A** from 2-fluorobenzoic acid (1.41 g, 10.0 mmol) to give **3.27r** (1.55 g, 9.24 mmol) in 92% yield.

¹H NMR (400 MHz, CDCl₃): δ = 2.93 (s, 3H), 3.13 (s, 3H), 7.05 (dd, J_{H-H} = 8.5 Hz, J_{H-F} = 8.5 Hz, 1H), 7.16 (dd, J_{H-H} = 7.5 Hz, J_{H-H} = 7.5 Hz, 1H), 7.29 - 7.43 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ = 34.9, 38.3, 115.7 (d, J = 21.6 Hz), 124.6 (d, J = 3.3 Hz), 124.7 (d, J = 14.5 Hz), 129.0 (d, J = 3.8 Hz), 131.2 (d, J = 8.0 Hz), 158.2 (d, J = 248.5 Hz), 166.8.

¹⁹F NMR (376 MHz, CDCl₃): δ = -115.1 (m).

ESIHRMS: Found: m/z 168.0825; Calcd for C₉H₁₁NOF: (M+H)⁺ 168.0825.

N,N-dimethyl-4-(trifluoromethyl)benzamide (3.27s)^[2]

Prepared by following **Method A** from 4-(trifluoromethyl)benzoic acid (1.90 g, 10.0 mmol) to give **3.27s** (2.05g, 9.44 mmol) in 94% yield.

¹H NMR (400 MHz, CDCl₃): δ = 2.96 (s, 3H), 3.13 (s, 3H), 7.53 (d, J_{H-H} = 8.6 Hz, 2H), 7.67 (d, J_{H-H} = 8.6 Hz, 2H).

¹³C NMR (100 MHz, CDCl₃): δ = 35.2, 39.3, 123.8 (q, J = 266.3 Hz), 125.5 (q, J = 3.4 Hz), 127.4, 131.4 (q, J = 32.6 Hz), 140.0, 170.1.

¹⁹F NMR (376 MHz, CDCl₃): δ = -62.8.

N¹,N¹,N⁴,N⁴-tetramethylterephthalamide (3.27t)^[6]

A solution of terephthalic acid (1.66 g, 10.0 mmol) in SOCl₂ (27.7 mL) was stirred at reflux temperature for 14 h, and then the volatile materials were removed *in vacuo*. The resulting residue was then dissolved in CH₂Cl₂ (40 mL) before adding Me₂NH (40 w/w% in water; 5.06 mL, 40.0 mmol) dropwise at 0 °C. The reaction mixture was stirred continuously at 23 °C for 2 h. The reaction was then quenched with water and the organic materials were extracted twice with CH₂Cl₂. The combined extracts were washed with brine and dried over MgSO₄. The solvent was removed *in vacuo* and the resulting crude mixture was purified by flash column chromatography (silica gel, hexane:ethyl acetate = 60:40) to give **3.27t** (2.02 g, 9.19 mmol) in 92% yield.

^1H NMR (400 MHz, CDCl_3): δ = 2.94 (s, 6H), 3.10 (s, 6H), 7.43 (s, 4H).

^{13}C NMR (100 MHz, CDCl_3): δ = 35.4, 39.6, 127.2, 137.6, 170.9.

N,N-dimethylcinnamamide (3.27u)^[7]

Prepared by following **Method A** from cinnamic acid (1.11 g, 7.50 mmol) to give **3.27u** (1.20 g, 6.82 mmol) in 91% yield.

^1H NMR (400 MHz, CDCl_3): δ = 3.07 (s, 3H), 3.17 (s, 3H), 6.89 (d, J = 15.5 Hz, 1H), 7.32 - 7.39 (m, 3H), 7.51 - 7.53 (m, 2H), 7.67 (d, J = 15.5 Hz, 1H),.

^{13}C NMR (100 MHz, CDCl_3): δ = 35.9, 37.4, 117.4, 127.7, 128.7, 129.5, 135.3, 142.3, 166.7.

Preparation of aliphatic N,N-dimethylamides

N,N,2,2-tetramethyl-5-phenylpentanamide (3.28a)

Prepared by following **Method A** from crude 2,2-dimethyl-5-phenylpentanoic acid (preparation see below) to give **3.28a** (1.12 g, 4.78 mmol) in 88% yield.

^1H NMR (400 MHz, CDCl_3): δ = 1.22 (s, 6H), 1.57 - 1.61 (m, 4H), 2.50 - 2.68 (m, 2H), 2.90 (s, 6H), 7.09 - 7.19 (m, 3H), 7.21 - 7.29 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ = 26.7, 27.0, 36.2, 38.1, 39.9, 42.6, 125.8, 128.3, 128.5, 142.3, 176.7.

ESIHRMS: Found: m/z 234.1857; Calcd for $\text{C}_{15}\text{H}_{24}\text{NO}$: $(\text{M}+\text{H})^+$ 234.1858.

Preparation of crude 2,2-dimethyl-5-phenylpentanoic acid

Preparation of crude 2,2-dimethyl-5-phenylpentanoic acid: To a solution of diisopropylamine (1.25 mL, 9.11 mmol) in THF (30 mL) at $-78\text{ }^{\circ}\text{C}$ was added n-BuLi (1.55 M in hexane, 3.65 mL, 9.11 mmol) was added slowly and the mixture was stirred for 30 min. To the mixture was added a solution of methyl 2-methyl-5-phenylpentanoate^[8] (1.25 g, 6.07 mmol) in THF (20 mL). After being stirred at the same temperature for 30 min, MeI (0.80 mL, 12.4 mmol) was added dropwise, and the reaction mixture was slowly warmed up to $23\text{ }^{\circ}\text{C}$ with stirring overnight. The reaction mixture was then quenched with saturated aqueous NH_4Cl solution and the organic materials were extracted twice with diethyl ether. The combined extracts were washed with brine and dried over MgSO_4 . The solvent was removed in vacuo to give the crude residue, which was purified by flash column chromatography (silica gel, hexane:ethyl acetate = 90:10) to afford methyl 2,2-dimethyl-5-phenylpentanoate (1.20 g, 5.44 mmol) in 90% yield.

To a solution of methyl 2,2-dimethyl-5-phenylpentanoate (1.20 g, 5.43 mmol) in MeOH (20 mL) and water (20 mL) was added KOH (1.22 g, 21.7 mmol), and the reaction mixture was stirred under reflux conditions for 4 h. After the reaction mixture was cooled down to $23\text{ }^{\circ}\text{C}$, the volatile materials were removed *in vacuo* and the resulting residue was diluted with water (20 mL). The basic organic materials were extracted twice with diethyl ether. The aqueous layer was then acidified to pH 1 with 1M aqueous HCl solution and the acidic organic materials were extracted twice with dichloromethane. The combined acidic extracts were washed with brine and dried over MgSO_4 . After removal of the solvent, the resulting crude materials including carboxylic acid were used for the next amidation without any further purification.

methyl 2,2-dimethyl-5-phenylpentanoate

^1H NMR (400 MHz, CDCl_3): δ = 1.16 (s, 6H), 1.44 - 1.71 (m, 4H), 2.47 - 2.69 (m, 2H), 3.64 (s, 3H), 7.13 - 7.21 (m, 3H), 7.22 - 7.31 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ = 25.2, 26.9, 36.3, 40.4, 42.3, 51.7, 125.8, 128.36, 128.43, 142.3, 178.5.

ESIHRMS: Found: m/z 221.1541; Calcd for $\text{C}_{14}\text{H}_{21}\text{O}_2$: $(\text{M}+\text{H})^+$ 221.1542.

N,N-dimethyladamantane-1-carboxamide (3.28b)

Prepared by following **Method A** from 1-adamantanecarboxylic acid (1.64 g, 9.11 mmol) to give **3.28b** (1.35 g, 6.51 mmol) in 71% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.64 - 1.77 (m, 6H), 1.98 - 2.03 (m, 9H), 3.04 (s, 6H).

¹³C NMR (100 MHz, CDCl₃): δ = 28.6, 36.8, 38.6, 38.8, 41.7, 177.0.

ESIHRMS: Found: m/z 208.1707; Calcd for C₁₃H₂₂NO: (M+H)⁺ 208.1701.

N,N-dimethylbicyclo[2.2.2]octane-1-carboxamide (**3.28c**)

Prepared by following **Method A** from bicyclo[2.2.2]octane-1-carboxylic acid (75.5 mg, 4.90 mmol) to give **3.28c** (610 mg, 3.37 mmol) in 69% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.54 - 1.63 (m, 7H), 1.81 - 1.85 (m, 6H), 3.00 (s, 6H).

¹³C NMR (100 MHz, CDCl₃): δ = 23.9, 25.7, 27.9, 38.6, 39.2, 177.2.

ESIHRMS: Found: m/z 182.1548; Calcd for C₁₁H₂₀NO: (M+H)⁺ 182.1545.

5-(2,5-dimethylphenoxy)-N,N,2,2-tetramethylpentanamide (**3.28d**)

Prepared by following **Method A** from gemfibrozil (1.88 g, 7.50 mmol) to give **3.28d** (1.97 g, 7.11 mmol) in 95% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.30 (s, 6H), 1.71 - 1.84 (m, 4H), 2.16 (s, 3H), 2.30 (s, 3H), 3.03 (s, 6H), 3.93 (t, J = 5.7 Hz, 2H), 6.60 (s, 1H), 6.65 (d, J = 7.5 Hz, 1H), 6.99 (d, J = 7.5 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 15.9, 21.5, 25.4, 27.0 (overlap), 37.3, 38.3, 42.4, 67.8, 111.9, 120.7, 123.4, 130.4, 136.6, 157.0, 176.6,.

ESIHRMS: Found: m/z 278.2122; Calcd for C₁₇H₂₈NO₂: (M+H)⁺ 278.2120.

N,N-dimethylabietic amide (3.28e)

Prepared by following **Method A** from abietic acid (2.27 g, 7.50 mmol) to give **3.28e** (1.90 g, 5.76 mmol) in 77% yield.

¹H NMR (400 MHz, CDCl₃): δ = 0.85 (s, 3H), 0.99 (d, J = 3.4 Hz, 3H), 1.00 (d, J = 3.4 Hz, 3H), 1.08 - 1.28 (m, 3H), 1.32 (s, 3H), 1.57 - 1.72 (m, 3H), 1.77 - 1.97 (m, 4H), 2.00 - 2.10 (m, 3H), 2.17 - 2.26 (m, 2H), 3.04 (s, 6H), 5.36 - 5.37 (m, 1H), 5.76 (s, 1H),.

¹³C NMR (100 MHz, CDCl₃): δ = 14.2, 18.5, 20.2, 20.9, 21.5, 22.7, 26.0, 27.5, 34.9, 35.0, 35.4, 38.0, 39.5, 44.6, 46.5, 51.4, 121.4, 122.6, 135.3, 145.1, 177.9.

ESIHRMS: Found: m/z 330.2799; Calcd for C₂₂H₃₆NO: (M+H)⁺ 330.2797.

N,N,2-trimethyl-5-phenylpentanamide (3.28f)

Prepared by following **Method A** from crude methyl 2-methyl-5-phenylpentanoic acid (prepared from methyl 2-methyl-5-phenylpentanoate^[8] (678 mg, 3.29 mmol) by following the procedure for the preparation of crude 2,2-dimethyl-5-phenylpentanoic acid) to give **3.28f** (639 mg, 2.92 mmol) in 89% yield (2-steps).

¹H NMR (400 MHz, CDCl₃): δ = 1.08 (d, J = 6.8 Hz, 3H), 1.36 - 1.45 (m, 1H), 1.54 - 1.62 (m, 2H), 1.70 - 1.79 (m, 1H), 2.52 - 2.64 (m, 2H), 2.69 (q, J = 6.8 Hz, 1H), 2.93 (s, 3H), 2.99 (s, 3H), 7.15 - 7.17 (m, 3H), 7.24 - 7.28 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ = 17.6, 29.6, 33.9, 35.6, 35.7, 36.1, 37.3, 125.8, 128.4, 128.5, 142.5, 176.6.

ESIHRMS: Found: m/z 220.1711; Calcd for C₁₄H₂₂NO: (M+H)⁺ 220.1701.

N,N-dimethyl-1,2,3,4-tetrahydronaphthalene-2-carboxamide (3.28g)

Prepared by following **Method A** from 1,2,3,4-tetrahydronaphthalene-2-carboxylic acid (1.32 g, 2.50 mmol) to give **3.28g** (1.43 g, 7.05 mmol) in 94% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.82 - 1.96 (m, 1H), 1.98 - 2.05 (m, 1H), 2.79 - 2.96 (m, 4H), 2.99 (s, 3H), 3.09 (s, 3H), 3.06 - 3.11 (m, 1H), 7.07 - 7.12 (m, 4H).

¹³C NMR (100 MHz, CDCl₃): δ = 26.4, 29.0, 32.4, 35.8, 37.2, 37.4, 125.8, 125.9, 128.9, 129.1, 135.8, 135.9, 175.4.

ESIHRMS: Found: m/z 204.1380; Calcd for C₁₃H₁₈NO: (M+H)⁺ 204.1388.

N,N-dimethyladamantane-2-carboxamide (3.28h)

Prepared by following **Method A** from adamantane-2-carboxylic acid (509 mg, 2.82 mmol) to give **3.28h** (553 mg, 2.66 mmol) in 95% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.54 - 1.57 (m, 2H), 1.71 - 1.76 (m, 4H), 1.83 - 1.90 (m, 4H), 2.03 (s, 2H), 2.31 - 2.34 (m, 2H), 2.77 (s, 1H), 2.90 (s, 3H), 2.97 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 27.4, 28.1, 30.3, 32.8, 35.6, 37.7, 37.8, 39.3, 46.5, 175.5.

ESIHRMS: Found: m/z 208.1696; Calcd for C₁₃H₂₂NO: (M+H)⁺ 208.1701.

N,N-dimethyltetrahydro-2H-pyran-4-carboxamide (3.28i)^[6]

Prepared by following **Method A** from tetrahydro-2H-pyran-4-carboxylic acid (976 mg, 7.50 mmol) to give **3.28i** (937 mg, 5.96 mmol) in 79% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.57 - 1.60 (m, 2H), 1.83 - 1.93 (m, 2H), 2.73 (tt, J = 11.3, 3.8 Hz, 1H), 2.93 (s, 3H), 3.04 (s, 3H), 3.43 (ddd, J = 11.8, 11.8, 1.6 Hz, 2H), 4.00 (ddd, J = 11.8, 3.3, 1.6 Hz, 2H),.

¹³C NMR (100 MHz, CDCl₃): δ = 29.0, 35.7, 37.1, 37.9, 67.4, 174.3.

benzyl-N,N-dimethylpiperidine-4-carboxamide (3.28j)^[6]

Prepared by following **Method A** from 1-benzylpiperidine-4-carboxylic acid (3.29 g, 15.0 mmol) to give **3.28j** (2.02 g, 8.20 mmol) in 55% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.63 - 1.69 (m, 2H), 1.82 - 1.92 (m, 2H), 2.00 (ddd, J = 11.7, 11.7, 2.3 Hz, 2H), 2.47 (tt, J = 11.3, 3.8 Hz, 1H), 2.93 - 2.97 (m, 5H), 3.03 (s, 3H), 3.51 (s, 2H), 7.22 - 7.32 (m, 5H),.

¹³C NMR (100 MHz, CDCl₃): δ = 28.6, 35.7, 37.1, 39.0, 53.3, 63.3, 127.0, 128.2, 129.1, 138.5, 175.2.

N,N-dimethyl-5-phenylpentanamide (3.28l)

Prepared by following **Method A** from 5-phenylpentanoic acid (1.43 g, 8.00 mmol) to give **3.28l** (1.56 g, 7.60 mmol) in 95% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.66 - 1.68 (m, 4H), 2.31 (t, J = 6.8 Hz, 2H), 2.63 (t, J = 6.9 Hz, 2H), 2.92 (s, 3H), 2.96 (s, 3H), 7.14 - 7.18 (m, 3H), 7.24 - 7.27 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ = 24.9, 31.4, 33.3, 35.5, 35.9, 37.4, 125.8, 128.4, 128.5, 142.4, 173.1.

ESIHRMS: Found: m/z 206.1542; Calcd for C₁₃H₂₀NO: (M+H)⁺ 206.1545.

Method B: For synthesis of heteroaromatic amides 3.29a-3.29m and aliphatic amide 3.28k

Typical Procedure for Synthesis of **3.29a**^[9]

To a solution of 1-methyl-1H-indole-2-carboxylic acid (1.75 g, 10.0 mmol) in CH₂Cl₂ (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 the same temperature for 1 h before HNMe₂ (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 till the reaction was completed. Subsequently, the reaction was quenched with water, and the organic materials were extracted twice with CH₂Cl₂. The combined extracts were washed with brine and dried over MgSO₄. After removal of the volatile materials *in vacuo*, the resulting crude residue was purified by flash column chromatography (silica gel, hexane:ethyl acetate = 20:80) to give **3.29a** (1.49 g, 7.37 mmol) in 74% yield.

¹H NMR (400 MHz, CDCl₃): δ = 3.18 (brs, 6H), 3.84 (s, 3H), 6.63 (s, 1H), 7.13 (dd, *J* = 7.9, 6.9 Hz, 1H), 7.29 (dd, *J* = 8.2, 6.9 Hz, 1H), 7.36 (d, *J* = 8.2 Hz, 1H), 7.62 (d, *J* = 7.9 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 31.2, 35.3, 39.6, 104.1, 109.9, 120.2, 121.6, 123.3, 126.5, 132.1, 137.9, 164.5.

1-benzyl-N,N-dimethyl-1H-pyrrole-2-carboxamide (**3.29b**)

Prepared from N,N-dimethyl-1H-pyrrole-2-carboxamide (**3.29c**) (602 mg, 4.36 mmol) (prepared by following the procedure in **Method B** from 1H-pyrrole-2-carboxylic acid) and BnBr (0.60 mL, 4.80 mmol) and NaH (211 mg, 5.28 mmol) by following the procedure in 5.3.2 to give **3.29b** (924 mg, 4.05 mmol) in 93% yield.

¹H NMR (400 MHz, CDCl₃): δ = 2.98 (s, 6H), 5.34 (s, 2H), 6.11 (dd, *J* = 3.7, 2.6 Hz, 1H), 6.36 (dd, *J* = 3.7, 1.7 Hz, 1H), 6.76 (dd, *J* = 2.6, 1.7 Hz, 1H), 7.08 (d, *J* = 6.8 Hz, 2H), 7.19 - 7.29 (m, 3H),.

¹³C NMR (100 MHz, CDCl₃): δ = 38.4(brs), 51.6, 107.2, 113.1, 125.2, 125.6, 127.3, 127.4, 128.5, 138.8, 164.5.

ESIHRMS: Found: m/z 229.1340; Calcd for $C_{14}H_{17}N_2O$: $(M+H)^+$ 229.1341.

N,N-dimethyl-1H-pyrrole-2-carboxamide (3.29c)

Prepared by following **Method B** from 1H-pyrrole-2-carboxylic acid (556 mg, 5.00 mmol) to give **3.29c** (610 mg, 4.42 mmol) in 88% yield.

1H NMR (400 MHz, $CDCl_3$): δ = 3.22 (brs, 6H), 6.23 (dd, J = 3.0, 3.0 Hz, 1H), 6.55 - 6.57 (m, 1H), 6.91 (dd, J = 3.0, 1.9 Hz, 1H), 10.06 (brs, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 37.5, 38.2, 109.6, 112.7, 121.0, 125.2, 162.7.

ESIHRMS: Found: m/z 139.0865; Calcd for $C_7H_{11}N_2O$: $(M+H)^+$ 139.0871.

N,N-dimethyl-5-phenylfuran-2-carboxamide (3.29d)

Prepared by following **Method B** from 5-phenylfuran-2-carboxylic acid (1.08 g, 5.76 mmol) to give **3.29d** (921 mg, 4.28 mmol) in 74% yield.

1H NMR (400 MHz, $CDCl_3$): δ = 3.15 (brs, 3H), 3.38 (brs, 3H), 6.71 (d, J = 3.6 Hz, 1H), 7.11 (d, J = 3.6 Hz, 1H), 7.31 (t, J = 7.5 Hz, 1H), 7.40 (dd, J = 7.6, 7.5 Hz, 2H), 7.69 (d, J = 7.6 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.8, 38.4, 106.5, 118.6, 124.4, 128.5, 128.9, 130.1, 147.5, 155.2, 160.3.

ESIHRMS: Found: m/z 216.1026; Calcd for $C_{13}H_{14}NO_2$: $(M+H)^+$ 216.1025.

N,N,3-trimethylbenzo[b]thiophene-2-carboxamide (3.29e)

Prepared by following **Method B** from 3-methylbenzo[b]thiophene-2-carboxylic acid (500 mg, 2.60 mmol) to give **3.29e** (232 mg, 1.06 mmol) in 41% yield.

¹H NMR (400 MHz, CDCl₃): δ = 2.40 (s, 3H), 3.10 (brs, 6H), 7.35 - 7.43 (m, 2H), 7.69 - 7.72 (m, 1H), 7.79 - 7.82 (m, 1H),.

¹³C NMR (100 MHz, CDCl₃): δ = 12.8, 35.4, 39.0, 122.5, 122.6, 124.5, 125.4, 130.9(overlap), 139.3, 139.5, 166.0.

ESIHRMS: Found: m/z 220.0799; Calcd for C₁₂H₁₄NOS: (M+H)⁺ 220.0796

N,N,5-trimethylthiophene-2-carboxamide (3.29f)

Prepared by following **Method B** from 5-methylthiophene-2-carboxylic acid (1.17 g, 8.24 mmol) to give **3.29f** (574 mg, 3.39 mmol) in 41% yield.

¹H NMR (400 MHz, CDCl₃): δ = 2.48 (s, 3H), 3.16 (brs, 6H), 6.68 (d, *J* = 3.5 Hz, 1H), 7.16 (d, *J* = 3.5 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 15.3, 37.1, 38.5, 125.2, 129.8, 135.6, 144.1, 164.4.

ESIHRMS: Found: m/z 170.0640; Calcd for C₈H₁₂NOS: (M+H)⁺ 170.0640.

N,N-dimethylquinoline-3-carboxamide (3.29g)^[6]

Prepared by following **Method B** from quinoline-3-carboxylic acid (1.73 g, 10.0 mmol) to give **3.29g** (1.82 g, 9.07 mmol) in 90% yield.

¹H NMR (400 MHz, CDCl₃): δ = 3.03 (s, 3H), 3.14 (s, 3H), 7.55 (ddd, *J* = 8.2, 7.1, 1.1 Hz, 1H), 7.73 (ddd, *J* = 8.5, 7.1, 1.1 Hz, 1H), 7.81 (d, *J* = 8.2 Hz, 1H), 8.09 (d, *J* = 8.5 Hz, 1H), 8.21 (d, *J* = 2.0 Hz, 1H), 8.94 (d, *J* = 2.0 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 35.6, 39.7, 127.1, 127.5, 128.3, 129.3, 129.4, 130.7, 135.1, 148.3, 148.6, 169.2.

N,N-dimethyl-2-phenylquinoline-4-carboxamide (3.29h)

Prepared by following **Method B** from 2-phenylquinoline-4-carboxylic acid (997 mg, 4.00 mmol) to give **3.29h** (674 mg, 2.44 mmol) in 61% yield.

¹H NMR (400 MHz, CDCl₃): δ = 2.85 (s, 3H), 3.28 (s, 3H), 7.45 - 7.57 (m, 4H), 7.73 - 7.77 (m, 2H), 7.80 (s, 1H), 8.14 - 8.17 (m, 2H), 8.20 (d, J = 8.5 Hz, 1H),.

¹³C NMR (100 MHz, CDCl₃): δ = 34.9, 38.8, 116.1, 123.2, 124.6, 127.4, 127.6, 129.0, 129.8, 130.3, 130.4, 139.1, 143.7, 148.6, 157.1, 168.8.

ESIHRMS: Found: m/z 277.1326; Calcd for C₁₈H₁₇N₂O: (M+H)⁺ 277.1341.

7-chloro-N,N-dimethyl-2-phenylquinoline-4-carboxamide (3.29i)

Prepared by following **Method B** from 7-chloro-2-phenylquinoline-4-carboxylic acid prepared from the literature procedure^[10] (2.26 g, 7.96 mmol) to give **3.29i** (1.44 g, 4.62 mmol) in 58% yield.

¹H NMR (400 MHz, CDCl₃): δ = 2.85 (s, 3H), 3.27 (s, 3H), 7.46 - 7.55 (m, 4H), 7.71 (d, J = 8.8 Hz, 1H), 7.79 (s, 1H), 8.13 - 8.16 (m, 2H), 8.20 (d, J = 2.1 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 35.0, 38.8, 116.2, 121.6, 126.0, 127.6, 128.3, 129.1, 129.3, 130.1, 136.3, 138.6, 143.6, 149.0, 158.1, 168.3.

ESIHRMS: Found: m/z 311.0954; Calcd for C₁₈H₁₆N₂OCl: (M+H)⁺ 311.0951.

N,N-dimethylisoquinoline-1-carboxamide (3.29j)

Prepared by following **Method B** from isoquinoline-1-carboxylic acid (1.73 g, 10.0 mmol) to give **3.29j** (1.64 g, 8.18 mmol) in 82% yield.

¹H NMR (400 MHz, CDCl₃): δ = 2.85 (s, 3H), 3.25 (s, 3H), 7.60 (ddd, *J* = 8.3, 6.9, 1.2 Hz, 1H), 7.70 (ddd, *J* = 8.4, 6.9, 1.2 Hz, 1H), 7.84 (d, *J* = 8.3 Hz, 1H), 8.01 (d, *J* = 8.4 Hz, 1H), 8.50 (d, *J* = 5.7 Hz, 1H),.

¹³C NMR (100 MHz, CDCl₃): δ = 35.0, 38.5, 121.3, 125.5, 126.1, 127.1, 128.1, 130.8, 136.6, 141.8, 155.8, 168.4.

ESIHRMS: Found: *m/z* 201.1033; Calcd for C₁₂H₁₃N₂O: (M+H)⁺ 201.1028

N,N-dimethylnicotinamide (3.29k)^[8]

Prepared by following **Method B** from quinoline-3-carboxylic acid (1.23 g, 10.0 mmol) to give **3.29k** (799 mg, 5.17 mmol) in 52% yield.

¹H NMR (400 MHz, CDCl₃): δ = 2.99 (s, 3H), 3.11 (s, 3H), 7.33 (dd, *J* = 7.7, 4.9 Hz, 1H), 7.74 (d, *J* = 7.7 Hz, 1H), 8.63 (d, *J* = 4.9 Hz, 1H), 8.66 (s, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 35.5, 39.6, 123.5, 132.2, 135.1, 148.1, 150.7, 169.0.

N,N-dimethyl-6-phenylpicolinamide (3.29l)

Prepared by following **Method B** from 6-phenylpicolinic acid (500 mg, 2.51 mmol) to give **3.29l** (471 mg, 2.08 mmol) in 83% yield.

¹H NMR (400 MHz, CDCl₃): δ = 3.16 (s, 3H), 3.18 (s, 3H), 7.39 - 7.48 (m, 3H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.75 (d, *J* = 7.8 Hz, 1H), 7.83 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.98 - 8.01 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ = 36.0, 39.3, 121.0, 122.2, 127.0, 128.9, 129.3, 137.8, 138.8, 154.3, 155.8, 169.0.

ESIHRMS: Found: *m/z* 227.1185; Calcd for C₁₄H₁₅N₂O: (M+H)⁺ 227.1184.

2,6-bis(4-fluorophenyl)-N,N-dimethylisonicotinamide (3.27m)

Prepared by following **Method B** from 2,6-bis(4-fluorophenyl)isonicotinic acid (501 mg, 1.61 mmol) to give **3.29m** (442 mg, 1.31 mmol) in 81% yield.

¹H NMR (400 MHz, CDCl₃): δ = 3.02 (s, 3H), 3.17 (s, 3H), 7.17 (dd, J_{H-H} = 8.9 Hz, J_{H-F} = 8.7 Hz, 4H), 7.61 (s, 2H), 8.11 (dd, J_{H-H} = 8.9 Hz, J_{H-F} = 5.4 Hz, 4H).

¹³C NMR (100 MHz, CDCl₃): δ = 35.3, 39.4, 115.8 (d, J = 21.6 Hz), 129.0 (d, J = 8.4 Hz), 134.9 (d, J = 2.7 Hz), 146.0, 156.5(overlap), 163.9 (d, J = 250.4 Hz), 169.5.

¹⁹F NMR (376 MHz, CDCl₃): δ = -112.02(m).

ESIHRMS: Found: m/z 339.1319; Calcd for C₂₀H₁₇N₂OF₂: (M+H)⁺ 339.1309.

1-benzyl-N,N-dimethylpyrrolidine-2-carboxamide (**5k**)^[11]

For both racemic ($\pm$)-**3.28k** and enantioenriched (*S*)-**5k**: Prepared by following **Method B** from racemic N-benzyl-proline hydrochloride salt (1.26 g, 5.21 mmol) or benzyl-L-proline hydrochloride salt (1.21 g, 5.01 mmol) to give ($\pm$)-**3.28k** (545 mg, 2.35 mmol) and (*S*)-**3.28k** (533 mg, 2.29 mmol) in 45% yield and 46% yield respectively. (*S*)-**3.28k** obtained with 99% ee: $[\alpha]^{25}_D$ = 101.8 ° (c = 0.005 g/mL, CHCl₃). (See section 5.3.11. for the ee measurement.)

¹H NMR (400 MHz, CDCl₃): δ = 1.73 - 1.92 (m, 3H), 2.06 - 2.11 (m, 1H), 2.31 - 2.37 (m, 1H), 2.90 (s, 3H), 2.98 (s, 3H), 3.06 (ddd, J = 8.2, 7.8, 3.1 Hz, 1H), 3.39 (dd, J = 8.8, 8.6 Hz, 1H), 3.45 (d, J = 12.9 Hz, 1H), 3.92 (d, J = 12.9 Hz, 1H), 7.19 - 7.23 (m, 1H), 7.25 - 7.32 (m, 4H).

¹³C NMR (100 MHz, CDCl₃): δ = 22.9, 28.6, 36.1, 36.8, 52.9, 58.1, 64.2, 127.0, 128.2, 129.3, 138.7, 173.1.

Base-mediated etherification of 4-hydroxyphenyl carboxamides for synthesis of amides 3.27c-3.27d and 3.30-3.33.

Typical Procedure for Synthesis of 3.27c

To an ice cold solution of 4-hydroxy-N,N-dimethylbenzamide^[12] (330 mg, 2.00 mmol) in DMF (6 mL) was added NaH (60% dispersion in mineral oil; 960 mg, 2.40 mmol), and the reaction mixture was stirred at the same temperature for 1 h before MOMCl (0.20 mL, 2.20 mmol) was added. After being stirred at 23 °C for 4 h, the reaction was quenched with water under an ice bath, and the organic materials were extracted twice with ether. The combined extracts were washed twice with water followed by brine and dried over MgSO₄. The solvent was removed *in vacuo* and the resulting crude mixture was purified by flash column chromatography (silica gel, ethyl acetate) to give **3.27c** (311 mg, 1.48 mmol) in 74% yield.

¹H NMR (400 MHz, CDCl₃): δ = 3.04 (brs, 6H), 3.47 (s, 3H), 5.19 (s, 2H), 7.04 (d, J = 8.6 Hz, 2H), 7.39 (d, J = 8.6 Hz, 2H).

¹³C NMR (100 MHz, CDCl₃): δ = 35.6, 39.8, 56.2, 94.3, 115.9, 129.1, 129.7, 158.3, 171.4.

ESIHRMS: Found: m/z 210.1123; Calcd for C₁₁H₁₆NO₃: (M+H)⁺ 210.1130.

4-(benzyloxy)-N,N-dimethylbenzamide (3.27d)

Prepared by following the **Typical Procedure for Synthesis of 3.27c** from 4-hydroxy-N,N-dimethylbenzamide (825 mg, 5.00 mmol) with BnBr to give **3.27d** (1.18 g, 4.63 mmol) in 93% yield.

¹H NMR (400 MHz, CDCl₃): δ = 3.05 (brs, 6H), 5.08 (s, 2H), 6.97 (d, J = 8.8 Hz, 2H), 7.31-7.44 (m, 7H).

¹³C NMR (100 MHz, CDCl₃): δ = 35.6, 39.9, 70.1, 114.6, 127.5, 128.2, 128.7, 128.8, 129.2, 136.7, 159.9, 171.5.

ESIHRMS: Found: m/z 256.1346; Calcd for C₁₆H₁₈NO₂: (M+H)⁺ 256.1338.

Typical Procedure for Synthesis of 3.30

To a suspension of K_2CO_3 (829 mg, 6.00 mmol) and KI (99.6 mg, 0.60 mmol) in acetone (20 mL) was added 4-hydroxy-N,N-dimethylbenzamide (332 mg, 2.00 mmol) and 5-bromo-1-phenylpentan-1-one (629 mg, 2.60 mmol).^[13] The reaction mixture was stirred under reflux for 16 h and the suspension was cooled to 23 °C before filtering through celite pad. The volatile materials were removed *in vacuo* and the residue was purified by flash column chromatography (silica gel, hexane:ethyl acetate = 1:1) to give **3.30** (545 mg, 1.68 mmol).

^1H NMR (400 MHz, CDCl_3): δ = 1.83 - 1.94 (m, 4H), 3.02 - 3.06 (m, 8H), 4.00 (t, J = 5.9 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 7.36 (d, J = 8.6 Hz, 2H), 7.43 (dd, J = 7.8, 6.8 Hz, 2H), 7.53 (t, J = 6.8 Hz, 1H), 7.94 (d, J = 7.8 Hz, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ = 20.9, 28.8, 35.6, 38.1, 40.0, 67.8, 114.1, 128.1, 128.4, 128.7, 129.2, 133.1, 137.0, 160.1, 171.6, 200.0.

ESIHRMS: Found: m/z 326.1773; Calcd for $\text{C}_{13}\text{H}_{24}\text{NO}_3$: $(\text{M}+\text{H})^+$ 326.1756.

methyl 5-(4-(dimethylcarbamoyl)phenoxy)-2,2-dimethylpentanoate (3.31)

Prepared by following the **Typical Procedure for Synthesis of 3.30** using 4-hydroxy-N,N-dimethylbenzamide (1.11 g, 6.69 mmol) and methyl 5-bromo-2,2-dimethylpentanoate (procedure below) to give **3.31** (1.82 g, 5.93 mmol) in 89% yield.

^1H NMR (400 MHz, CDCl_3): δ = 1.20 (s, 6H), 1.65 - 1.76 (m, 4H), 3.03 (brs, 6H), 3.65 (s, 3H), 3.93 (t, J = 5.9 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 7.37 (d, J = 8.6 Hz, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ = 25.0, 25.2, 35.7, 37.0, 39.7, 42.1, 51.9, 68.2, 114.1, 128.4, 129.2, 160.1, 171.6, 178.3.

ESIHRMS: Found: m/z 308.1869; Calcd for $\text{C}_{17}\text{H}_{26}\text{NO}_4$: $(\text{M}+\text{H})^+$ 308.1862.

methyl 5-bromo-2,2-dimethylpentanoate

To a solution of diisopropylamine (1.70 mL, 12.2 mmol) in THF (40 mL) at 0 °C was added n-BuLi (2.0 M in cyclohexane, 6.0 mL, 12.0 mmol) slowly and the mixture was stirred for 30 min. To the mixture at -78 °C was added a solution of methyl isobutyrate (1.02 g, 10.0 mmol) in THF (10 mL). After being stirred at the same temperature for 1 h, 1,3-dibromopropane (5.10 mL, 50.0 mmol) was added, and the reaction mixture was slowly warmed up to 23 °C with stirring overnight. The reaction mixture was then quenched with saturated aqueous NH₄Cl solution and the organic materials were extracted twice with diethyl ether. The combined extracts were washed with brine and dried over MgSO₄. The solvent was removed in vacuo to give the crude residue, which was purified by flash column chromatography (silica gel, hexane:ethyl acetate = 95:5) to afford methyl 5-bromo-2,2-dimethylpentanoate (1.87 g, 8.37 mmol) in 84% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.17 (s, 6H), 1.62 - 1.66 (m, 2H), 1.75 - 1.83 (m, 2H), 3.36 (t, *J* = 6.6 Hz, 2H), 3.66 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 25.3, 28.6, 33.9, 39.2, 42.0, 51.9, 178.1.

ESIHRMS: Found: *m/z* 223.0338; Calcd for C₈H₁₆O₂Br: (M+H)⁺ 223.0334.

isopropyl 5-(4-(dimethylcarbamoyl)phenoxy)-2,2-dimethylpentanoate (3.32)

Prepared by following the **Typical Procedure for Synthesis of 3.30** using 4-hydroxy-N,N-dimethylbenzamide (662 mg, 4.00 mmol) and isopropyl 5-bromo-2,2-dimethylpentanoate (procedure below) to give **3.32** (1.30 g, 3.88 mmol) in 97% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.18 (s, 6H), 1.21 (d, J = 6.2 Hz, 6H), 1.62 - 1.77 (m, 4H), 3.04 (brs, 6H), 3.94 (t, J = 6.1 Hz, 2H), 4.98 (hept, J = 6.2 Hz, 1H), 6.86 (d, J = 8.9 Hz, 2H), 7.37 (d, J = 8.9 Hz, 2H).

¹³C NMR (100 MHz, CDCl₃): δ = 21.8, 24.9, 25.1, 35.5, 36.8, 39.9, 41.9, 67.4, 68.2, 114.1, 128.3, 129.1, 160.1, 171.5, 177.1.

ESIHRMS: Found: m/z 336.2179; Calcd for C₁₉H₃₀NO₄: (M+H)⁺ 336.2175.

isopropyl 5-bromo-2,2-dimethylpentanoate

To a solution of diisopropylamine (1.65 mL, 12.0 mmol) in THF (40 mL) at 0 °C was added *n*-BuLi (2.0 M in cyclohexane, 6.0 mL, 12.0 mmol) slowly and the mixture was stirred for 30 min. To the mixture at -78 °C was added a solution of isopropyl isobutyrate (1.30 g, 10.0 mmol) in THF (10 mL). After being stirred at the same temperature for 1 h, 1,3-dibromopropane (5.10 mL, 50.0 mmol) was added, and the reaction mixture was slowly warmed up to 23 °C with stirring overnight. The reaction mixture was then quenched with saturated aqueous NH₄Cl solution and the organic materials were extracted twice with diethyl ether. The combined extracts were washed with brine and dried over MgSO₄. The solvent was removed in vacuo to give the crude residue, which was purified by flash column chromatography (silica gel, hexane:ethyl acetate = 95:5) to afford isopropyl 5-bromo-2,2-dimethylpentanoate (2.09 g, 8.31 mmol) in 83% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.15 (s, 6H), 1.21 (d, J = 6.2 Hz, 6H), 1.60 - 1.65 (m, 2H), 1.75 - 1.83 (m, 2H), 3.36 (t, J = 6.6 Hz, 2H), 4.96 (hept, J = 6.2 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 21.8, 25.2, 28.6, 34.0, 39.1, 41.8, 67.6, 177.0.

ESIHRMS: Found: m/z 251.0644; Calcd for C₁₀H₂₀O₂Br: (M+H)⁺ 251.0647.

tert-butyl 5-(4-(dimethylcarbamoyl)phenoxy)-2,2-dimethylpentanoate (3.33c)

Prepared by following the **Typical Procedure for Synthesis of 3.30** using 4-hydroxy-N,N-dimethylbenzamide (496 mg, 3.00 mmol) and tert-butyl 5-bromo-2,2-dimethylpentanoate (procedure below) to give **3.33** (968 mg, 2.77 mmol) in 90% yield.

^1H NMR (400 MHz, CDCl_3): δ = 1.15 (s, 6H), 1.43 (s, 9H), 1.61 - 1.67 (m, 2H), 1.69 - 1.78 (m, 2H), 3.04 (brs, 6H), 3.95 (t, J = 6.3 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 7.37 (d, J = 8.8 Hz, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ = 25.0, 25.3, 28.1, 35.6, 37.0, 39.8, 42.5, 68.3, 79.9, 114.1, 128.3, 129.2, 160.1, 171.6, 177.1.

ESIHRMS: Found: m/z 350.2332; Calcd for $\text{C}_{20}\text{H}_{32}\text{NO}_4$: $(\text{M}+\text{H})^+$ 350.2331

Preparation of t-butyl 5-bromo-2,2-dimethylpentanoate

To a solution of diisopropylamine (1.70 mL, 12.2 mmol) in THF (40 mL) at 0 °C was added n-BuLi (2.0 M in cyclohexane, 6.10 mL, 12.2 mmol) slowly and the mixture was stirred for 30 min. To the mixture at -78 °C was added a solution of tert-butyl isobutyrate (1.44 g, 9.99 mmol) in THF (10 mL). After being stirred at the same temperature for 1 h, 1,3-dibromopropane (5.10 mL, 50.0 mmol) was added, and the reaction mixture was slowly warmed up to 23 °C with stirring overnight. The reaction mixture was then quenched with saturated aqueous NH_4Cl solution and the organic materials were extracted twice with diethyl ether. The combined extracts were washed with brine and dried over MgSO_4 . The solvent was removed in vacuo to give the crude residue, which was purified by flash column chromatography (silica gel, hexane:ethyl acetate = 95:5) to afford tert-butyl 5-bromo-2,2-dimethylpentanoate (1.49 g, 5.62 mmol) in 56% yield.

^1H NMR (400 MHz, CDCl_3): δ = 1.12 (s, 6H), 1.43 (s, 9H), 1.57 - 1.62 (m, 2H), 1.77 - 1.84 (m, 2H), 3.37 (t, J = 6.6 Hz, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ = 25.3, 28.1, 28.6, 34.2, 39.3, 42.4, 80.1, 176.9.

ESIHRMS: Found: m/z 265.0800; Calcd for $C_{11}H_{22}O_2Br$: $(M+H)^+$ 265.0803.

α -alkylation of N,N-dimethylisobutyramide for synthesis of amide 3.34

To an ice cold solution of diisopropylamine (0.35 mL, 2.40 mmol) in THF (10 mL) was slowly added BuLi (2.0 M in cyclohexane, 1.20 mL, 2.40 mmol) and the mixture was stirred for 30 min at the same temperature. To the mixture was added a solution of N,N-dimethylisobutyramide (231 mg, 2.00 mmol) in THF (1 mL) at -78°C . After being stirred for 1 h at the same temperature, 2-(4-bromobutyl)-2-phenyl-1,3-dioxolane (preparation below) (684 mg, 2.40 mmol) was added, and the reaction mixture was slowly warmed up to room temperature with stirring for 4 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution and the organic materials were extracted twice with diethyl ether. The combined extracts were washed with brine and dried over MgSO_4 . The solvent was removed in vacuo to give the crude residue, which was dissolved in THF (5 mL) and treated with 3M HCl (6.70 mL, 20.1 mmol). The mixture was stirred for 1 h at room temperature. The solution was diluted with water (10 mL) and the organic materials were extracted twice with diethyl ether. The combined extracts were washed with brine and dried over MgSO_4 . The solvent was removed in vacuo to give the crude residue, which was purified by flash column chromatography (silica gel, hexane:ethyl acetate = 60:40) to afford **3.34** (334 mg, 1.21 mmol) in 61% yield (2-step).

^1H NMR (400 MHz, CDCl_3): δ = 1.25 (s, 6H), 1.29 - 1.37 (m, 2H), 1.58 - 1.76 (m, 4H), 2.96 (t, J = 7.3 Hz, 2H), 3.02 (s, 6H), 7.43 - 7.47 (m, 2H), 7.52 - 7.57 (m, 1H), 7.92 - 7.94 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ = 24.9, 25.0, 27.0, 38.3, 38.6, 40.8, 42.6, 128.1, 128.7, 133.0, 137.1, 176.8, 200.4.

ESIHRMS: Found: m/z 276.1969; Calcd for $C_{17}H_{26}O_2N$: $(M+H)^+$ 276.1964.

2-(4-bromobutyl)-2-phenyl-1,3-dioxolane

To a solution of ethylene glycol (4.50 mL, 80.2 mmol) and *p*-TsOH monohydrate (153 mg, 0.804 mmol) in benzene 80 mL was added 5-bromo-1-phenylpentan-1-one (1.93 g, 8.02 mmol).^[13] The reaction mixture was stirred under reflux for 18 h under azeotropic conditions with a Dean-Stark apparatus, and then the reaction mixture was cooled to 23 °C. The solution was then poured into saturated aqueous sodium bicarbonate solution and the organic layer was separated. From the aqueous layer, the organic materials were extracted twice with dichloromethane (40 mL) and the combined extracts were washed with brine and dried over MgSO₄. The solvent was removed *in vacuo* to give the crude residue, which was purified by flash column chromatography (silica gel, hexane:ethyl acetate = 95:5) to afford 2-(4-bromobutyl)-2-phenyl-1,3-dioxolane (2.24 g, 7.86 mmol) in 98% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.45 - 1.53 (m, 2H), 1.80 - 1.87 (m, 2H), 1.89 - 1.93 (m, 2H), 3.35 (t, *J* = 6.9 Hz, 2H), 3.74 - 3.78 (m, 2H), 3.99 - 4.02 (m, 2H), 7.26 - 7.30 (m, 1H), 7.32 - 7.36 (m, 2H), 7.42 - 7.45 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ = 22.5, 32.9, 33.7, 39.6, 64.6, 110.3, 125.8, 127.9, 128.2, 142.5.

ESIHRMS: Found: *m/z* 285.0496; Calcd for C₁₃H₁₈O₂Br: (M+H)⁺ 285.0490.

5.3.2 Synthesis of aromatic aldehydes

Typical procedure for synthesis of 3.35a [CAS: 66-99-9]

To a mixture of NaH (60% dispersion in mineral oil; 60.5 mg, 1.51 mmol) and NaI (76.0 mg, 0.50 mmol) was added a solution of amide *N,N*-dimethyl-1-naphthamide (**3.27a**) (99.6 mg, 0.500 mmol) in 2.5 mL of THF, and the reaction mixture was stirred at 40 °C for 10 h. The reaction was quenched with water at 0 °C and the organic materials were extracted with diethyl ether (20 mL × 3). The combined extracts were washed with brine and dried over MgSO₄. The volatile materials were removed *in vacuo* and the resulting crude residue was

purified with flash column chromatography (silica gel, hexane:ethyl acetate = 98:2) to give **3.35a** (72.6 mg, 0.465 mmol) in 93% yield.

¹H NMR (400 MHz, CDCl₃): δ = 7.58 (ddd, J = 8.2, 6.9, 1.4 Hz, 1H), 7.64 (ddd, J = 8.2, 6.9, 1.4 Hz, 1H), 7.90 (d, J = 8.0 Hz, 1H), 7.93 - 7.98 (m, 2H), 8.00 (d, J = 8.0 Hz, 1H), 8.33 (s, 1H), 10.16 (s, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 122.9, 127.2, 128.2, 129.2(overlap), 129.6, 132.7, 134.2, 134.6, 136.6, 192.4.

4-methoxybenzaldehyde (**3.35b**) [CAS: 123-11-5]

Prepared from amide **3.27b** (90.0 mg, 0.502 mmol) for 9 h to give **3.35b** (64.1 mg, 0.471 mmol) in 94% yield.

¹H NMR (400 MHz, CDCl₃): δ = 3.89 (s, 3H), 7.01 (d, J = 8.9 Hz, 2H), 7.84, (d, J = 8.9 Hz, 2H), 9.89 (s, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 55.5, 114.3, 129.9, 131.9, 164.6, 190.8.

4-(methoxymethoxy)benzaldehyde (**3.35c**)

Prepared from amide **3.27c** (62.6 mg, 0.299 mmol) for 24 h to give **3.35c** (43.3 mg, 0.261 mmol) in 87% yield.

¹H NMR (400 MHz, CDCl₃): δ = 3.50 (s, 3H), 5.26 (s, 2H), 7.15 (d, J = 8.7 Hz, 2H), 7.84 (d, J = 8.7 Hz, 2H), 9.91 (s, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 56.3, 94.1, 116.3, 130.7, 131.9, 162.2, 190.9.

ESIHRMS: Found: m/z 167.0710; Calcd for C₉H₁₁O₃: (M+H)⁺ 167.0708.

4-(benzyloxy)benzaldehyde (**3.35d**)

Prepared from amide **3.27d** (128.2 mg, 0.502 mmol) for 26 h to give **3.35d** (100 mg, 0.472 mmol) in 94% yield.

¹H NMR (400 MHz, CDCl₃): δ = 5.15 (s, 2H), 7.08 (d, J = 8.8 Hz, 2H), 7.33 - 7.45 (m, 5H), 7.84 (d, J = 8.8 Hz, 2H), 9.89 (s, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 70.3, 115.1, 127.5, 128.3, 128.7, 130.1, 132.0, 135.9, 163.7, 190.8.

ESIHRMS: Found: m/z 213.0918; Calcd for C₁₄H₁₃O₂: (M+H)⁺ 213.0918.

2-methoxybenzaldehyde (**3.35e**) [CAS: 135-02-4]

Prepared from amide **3.27e** (90.0 mg, 0.502 mmol) for 24 h to give **3.35e** (58.0 mg, 0.426 mmol) in 85% yield.

¹H NMR (400 MHz, CDCl₃): δ = 3.93 (s, 3H), 6.98 - 7.05 (m, 2H), 7.54 - 7.58 (m, 1H), 7.83 (dd, J = 7.7, 1.8 Hz, 1H), 10.48 (s, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 55.6, 111.6, 120.6, 124.8, 128.5, 135.9, 161.8, 189.8.

benzo[d][1,3]dioxole-5-carbaldehyde (**3.35f**) [CAS: 120-57-0]

Prepared from amide **3.27f** (97.6 mg, 0.505 mmol) at 40 °C for 12 h to give **3.35f** (61.7 mg, 0.411 mmol) in 81% yield.

¹H NMR (400 MHz, CDCl₃): δ = 6.07 (s, 2H), 6.92 (d, J = 7.9 Hz, 1H), 7.32 (s, 1H), 7.40 (d, J = 7.9 Hz, 1H), 9.80 (s, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 102.1, 106.9, 108.3, 128.6, 131.8, 148.7, 153.1, 190.3.

4-(benzyloxy)-3-methoxybenzaldehyde (3.35g)

Prepared from amide **3.27g** (142 mg, 0.499 mmol) for 23 h to give **3.35g** (94.8 mg, 0.391 mmol) in 78% yield.

^1H NMR (400 MHz, CDCl_3): δ = 3.94 (s, 3H), 5.24 (s, 2H), 6.99 (d, J = 8.2 Hz, 1H), 7.30 - 7.45 (m, 7H), 9.83 (s, 1H).

^{13}C NMR (100 MHz, CDCl_3): δ = 56.0, 70.8, 109.3, 112.3, 126.5, 127.1, 128.1, 128.6, 130.2, 135.9, 150.0, 153.5, 190.8.

ESIHRMS: Found: m/z 243.1022; Calcd for $\text{C}_{15}\text{H}_{15}\text{O}_3$: $(\text{M}+\text{H})^+$ 243.1021.

3-(dimethylamino)benzaldehyde (3.35h)^[14]

Prepared from amide **3.27h** (96.0 mg, 0.499 mmol) for 22 h to give **3.35h** (67.8 mg, 0.454 mmol) in 91% yield.

^1H NMR (400 MHz, CDCl_3): δ = 3.01 (s, 6H), 6.95 - 6.98 (m, 1H), 7.18 - 7.20 (m, 2H), 7.38 (dd, J = 7.8, 7.8 Hz, 1H), 9.95 (s, 1H).

^{13}C NMR (100 MHz, CDCl_3): δ = 40.4, 111.5, 118.3, 118.9, 129.6, 137.2, 150.7, 193.2.

2-methylbenzaldehyde (3.35i) [CAS: 529-20-4]

Prepared from amide **3.27i** (81.0 mg, 0.496 mmol) for 10 h to give **3.35i** (39.3 mg, 0.327 mmol) in 66% yield.

^1H NMR (400 MHz, CDCl_3): δ = 2.67 (s, 3H), 7.26 (d, J = 7.6 Hz, 1H), 7.36 (dd, J = 7.6, 7.6 Hz, 1H), 7.48 (dd, J = 7.6, 7.6 Hz, 1H), 7.80 (d, J = 7.6 Hz, 1H), 10.27 (s, 1H).

^{13}C NMR (100 MHz, CDCl_3): δ = 19.6, 126.3, 131.7, 132.0, 133.6, 134.1, 140.6, 192.8.

2-benzylbenzaldehyde (3.35j)^[15]

Prepared from amide **3.27j** (121 mg, 0.504 mmol) for 12 h to give **3.35j** (91.8 mg, 0.468 mmol) in 93% yield.

^1H NMR (400 MHz, CDCl_3): δ = 4.45 (s, 2H), 7.13 - 7.21 (m, 3H), 7.25 - 7.30 (m, 3H), 7.41 (dd, J = 7.6, 7.6 Hz, 1H), 7.52 (dd, J = 7.6, 7.6 Hz, 1H), 7.86 (d, J = 7.6 Hz, 1H), 10.25 (s, 1H).

^{13}C NMR (100 MHz, CDCl_3): δ = 38.1, 126.4, 127.1, 128.7, 128.9, 131.8, 132.1, 134.0(overlap), 140.4, 143.1, 192.5.

1-naphthaldehyde (3.35k) [CAS: 66-77-3]

Prepared from amide **3.27k** (101 mg, 0.505 mmol) for 15 h to give **3.35k** (73.0 mg, 0.467 mmol) in 93% yield.

^1H NMR (400 MHz, CDCl_3): δ = 7.56 - 7.64 (m, 2H), 7.66 - 7.71 (m, 1H), 7.91 (d, J = 8.2 Hz, 1H), 7.98 (d, J = 7.1 Hz, 1H), 8.09 (d, J = 8.2 Hz, 1H), 9.25 (d, J = 8.6 Hz, 1H), 10.39 (s, 1H).

^{13}C NMR (100 MHz, CDCl_3): δ = 124.8 (overlap), 126.9, 128.4, 129.0, 130.5, 131.4, 133.7, 135.2, 136.6, 193.5.

2,6-dimethylbenzaldehyde (3.35l) [CAS: 1123-56-4]

Prepared from amide **3.27l** (89.4 mg, 0.504 mmol) for 24 h to give 12% crude NMR yield of **3.35l** with 81% recovery of **3.27l** with 1,1,2,2-tetrachloroethane as the internal standard

Ferrocenecarboxaldehyde (3.35m)

Prepared from amide **3.27m** (128 mg, 0.499 mmol) for 23 h to give **3.35m** (101 mg, 0.470 mmol) in 94% yield.

¹H NMR (400 MHz, CDCl₃): δ = 4.28 (s, 5H), 4.60 - 4.61 (m, 2H), 4.79 - 4.80 (m, 2H), 9.96 (s, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 69.7, 73.3(overlap), 79.5, 193.5.

ESIHRMS: Found: m/z 215.0163; Calcd for C₁₁H₁₁OFe: (M+H)⁺ 215.0159.

[1,1'-biphenyl]-4-carbaldehyde (3.35n) [CAS: 3218-36-8]

Prepared from **3.27n** (113 mg, 0.501 mmol) for 24 h to **3.35n** (78.9 mg, 0.433 mmol) in 86% yield.

¹H NMR (400 MHz, CDCl₃): δ = 7.40 - 7.44 (m, 1H), 7.46 - 7.51 (m, 2H), 7.64 (d, J = 7.2 Hz, 2H), 7.76 (d, J = 8.5 Hz, 2H), 7.95 (d, J = 8.5 Hz, 2H), 10.06 (s, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 127.3, 127.7, 128.5, 129.0, 130.3, 135.2, 139.7, 147.2, 191.9.

4-chlorobenzaldehyde (3.35o) [CAS: 104-88-1]

Prepared from amide **3.27o** (92.2 mg, 0.502 mmol) for 7 h to give **3.35o** (49.9 mg, 0.355 mmol) in 71% yield.

¹H NMR (400 MHz, CDCl₃): δ = 7.52 (d, J = 8.5 Hz, 2H), 7.83 (d, J = 8.5 Hz, 2H), 9.99 (s, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 129.6, 131.0, 134.8, 141.1, 190.9.

4-bromobenzaldehyde (3.35p) [CAS: 1122-91-4]

Prepared from amide **3.27p** (114 mg, 0.498 mmol) for 18 h to give **3.35p** (71.1 mg, 0.384 mmol) in 77% yield.

^1H NMR (400 MHz, CDCl_3): δ = 7.69 (d, J = 8.5 Hz, 2H), 7.75 (d, J = 8.5 Hz, 2H), 9.98 (s, 1H).

^{13}C NMR (100 MHz, CDCl_3): δ = 129.8, 131.0, 132.4, 135.1, 191.1.

4-fluorobenzaldehyde (3.35q) [CAS: 459-57-4]

Prepared from amide **3.27q** (84.0 mg, 0.502 mmol) for 6.5 h to give **3.35q** (43.3 mg, 0.349 mmol) in 70% yield.

^1H NMR (400 MHz, CDCl_3): δ = 7.22 (dd, $J_{\text{H-H}}$ = 8.7 Hz, $J_{\text{H-F}}$ = 8.7 Hz, 1H), 7.92 (dd, $J_{\text{H-H}}$ = 8.7 Hz, $J_{\text{H-F}}$ = 5.4 Hz, 2H), 9.97 (s, 1H).

^{13}C NMR (100 MHz, CDCl_3): δ = 116.3 (d, J = 22.2 Hz), 132.2 (d, J = 9.8 Hz), 133.0 (d, J = 2.7 Hz), 166.5 (d, J = 255.6 Hz), 190.5.

^{19}F NMR (376 MHz, CDCl_3): δ = -102.29 (m).

2-fluorobenzaldehyde (3.35r) [CAS: 446-52-6]

Prepared from amide **3.27r** (83.8 mg, 0.501 mmol) for 8 h to give **3.35r** in 66% crude NMR yield with 1,1,2,2-tetrachloroethane as the internal standard. Isolated yield of **3.35r** (24.6 mg, 0.198 mmol) was 40% yield. Decrease in the isolated yield is due to the volatile nature of **3.35r**.

^1H NMR (400 MHz, CDCl_3): δ = 7.13 - 7.18 (m, 1H), 7.23 - 7.28 (m, 1H), 7.56 - 7.62 (m, 1H), 7.86 (dd, $J_{\text{H-H}}$ = 9.7 Hz, $J_{\text{H-F}}$ = 7.6 Hz, 1H), 10.36 (s, 1H).

^{13}C NMR (100 MHz, CDCl_3): δ = 116.6 (d, J = 20.6 Hz), 124.3 (d, J = 8.1 Hz), 124.7 (d, J = 3.8 Hz), 128.8 (d, J = 1.9 Hz), 136.4 (d, J = 9.2 Hz), 164.8 (d, J = 259.9 Hz), 187.3.
 ^{19}F NMR (376 MHz, CDCl_3): δ = -121.88(m).

4-(trifluoromethyl)benzaldehyde (3.35s) [CAS: 455-19-6]

Prepared from amide **3.27s** (108 mg, 0.498 mmol) for 14 h to give **3.35s** in 62% crude NMR yield with 1,1,2,2-tetrachloroethane as the internal standard. Isolated yield of **3.35s** (42.1 mg, 0.242 mmol) in 49% yield. Decrease in the isolated yield is due to the volatile nature of **3.35s**.

^1H NMR (400 MHz, CDCl_3): δ = 7.80 (d, $J_{\text{H-H}}$ = 8.3 Hz, 2H), 8.00 (d, $J_{\text{H-H}}$ = 8.3 Hz, 2H), 10.10 (s, 1H).

^{13}C NMR (100 MHz, CDCl_3): δ = 123.5 (q, J = 274.3 Hz), 126.2 (q, 3.6 Hz), 130.0, 135.7 (q, J = 32.7 Hz), 138.7, 191.1.

^{19}F NMR (376 MHz, CDCl_3): δ = -63.12.

Terephthalaldehyde (3.35t) [CAS: 623-27-8]

Prepared from amide **3.27t** (110 mg, 0.500 mmol) with NaH (5 equiv) and NaI (2 equiv) at 85 °C for 14 h to give **3.35t** (37.9 mg, 0.283 mmol) in 57% yield.

^1H NMR (400 MHz, CDCl_3): δ = 8.06 (s, 4H), 10.14 (s, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ = 130.1, 140.0, 191.5.

Cinnamaldehyde (3.35u) [CAS: 14371-10-9]

Prepared from amide **3.27u** (88.0 mg, 0.503 mmol) for 7 h to give **3.35u** (24.0 mg, 0.181

mmol) in 36% yield.

¹H NMR (400 MHz, CDCl₃): δ = 6.73 (dd, *J* = 16.0, 7.7 Hz, 1H), 7.42 - 7.47 (m, 3H), 7.49 (d, *J* = 16.0 Hz, 1H), 7.56 - 7.59 (m, 2H), 9.72 (d, *J* = 7.7 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 128.5, 128.6, 129.1, 131.3, 134.0, 152.8, 193.7.

5.3.3 Synthesis of electron-rich heteroaromatic aldehydes

Typical procedure for synthesis of **3.36a** [CAS: 27421-51-8]

To a mixture of NaH (60% dispersion in mineral oil; 61.6 mg, 1.54 mmol) and NaI (75.9 mg, 0.506 mmol) was added a solution of N,N,1-trimethyl-1H-indole-2-carboxamide (**3.29a**) (102 mg, 0.502 mmol) in THF (2.5 mL), and the reaction mixture was stirred at 40 °C for 14 h. The reaction was carefully quenched with pH 7 phosphate buffer solution at 0 °C and the organic materials were extracted with dichloromethane (20 mL × 3). The combined extracts were washed with brine and dried over MgSO₄. The volatile materials were removed *in vacuo* and the resulting crude residue was purified by flash column chromatography (silica gel, hexane:ethyl acetate = 80:20) to give **3.36a** (72.1 mg, 0.453 mmol) in 90% yield.

¹H NMR (400 MHz, CDCl₃): δ = 4.10 (s, 3H), 7.18 (dd, *J* = 8.1, 6.2 Hz, 1H), 7.25 (s, 1H), 7.38 - 7.45 (m, 2H), 7.73 (d, *J* = 8.1, Hz, 1H), 9.89 (s, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 31.6, 110.5, 117.6, 121.0, 123.5, 126.4, 127.0, 135.8, 141.0, 183.0.

1-benzyl-1H-pyrrole-2-carbaldehyde (**3.36b**)^[16]

Prepared from amide **3.29b** (68.9 mg, 0.302 mmol) for 14 h to give **3.36b** (53.3 mg, 0.288 mmol) in 95% yield.

¹H NMR (400 MHz, CDCl₃): δ = 5.56 (s, 2H), 6.27 (dd, *J* = 3.4, 3.4 Hz, 1H), 6.97 (d, *J* = 3.4 Hz, 2H), 7.14 (d, *J* = 6.9 Hz, 2H), 7.23 - 7.33 (m, 3H), 9.56 (s, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 52.0, 110.2, 124.9, 127.4, 127.8, 128.8, 131.5, 131.7, 137.6, 179.6.

1H-pyrrole-2-carbaldehyde (3.36c) [CAS: 1003-29-8]

Prepared from amide **3.29c** (41.2 mg, 0.298 mmol) with NaH (5 equiv) and NaI (2 equiv) in THF (3.0 mL) for 25 h to give **3.36c** (22.3 mg, 0.234 mmol) in 79% yield.

¹H NMR (400 MHz, CDCl₃): δ = 6.34 - 6.36 (m, 1H), 6.98 - 6.99 (m, 1H), 7.130 - 7.133 (m, 1H), 9.52 (s, 1H), 9.66 (brs, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 111.4, 121.8, 126.9, 133.0, 179.5.

5-phenylfuran-2-carbaldehyde (3.36d) [CAS: 13803-39-9]

Prepared from amide **3.29d** (65.0 mg, 0.302 mmol) for 24 h to give **3.36d** (35.2 mg, 0.204 mmol) in 68% yield.

¹H NMR (400 MHz, CDCl₃): δ = 6.84 (d, J = 3.7 Hz, 1H), 7.31 (d, J = 3.7 Hz, 1H), 7.37 - 7.46 (m, 3H), 7.82 (d, J = 7.0 Hz, 2H), 9.65 (s, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 107.8, 123.7, 125.4, 129.1(overlap), 129.8, 152.1, 159.5, 177.3.

3-methylbenzo[b]thiophene-2-carbaldehyde (3.36e) [CAS: 22053-74-3]

Prepared from amide **3.29e** (88.0 mg, 0.401 mmol) for 19 h to give **3.36e** (39.6 mg, 0.225 mmol) in 56% yield.

¹H NMR (400 MHz, CDCl₃): δ = 2.78 (s, 3H), 7.44 (dd, J = 8.3, 7.0 Hz, 1H), 7.50 (dd, J = 8.3, 7.0 Hz, 1H), 7.85 - 7.89 (m, 2H), 10.33 (s, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 12.2, 123.4, 124.0, 124.9, 128.5, 137.6, 140.2, 142.2, 143.1, 184.1.

5-methylthiophene-2-carbaldehyde (**3.36f**) [CAS: 13679-70-4]

Prepared from amide **3.29f** (50.5 mg, 0.298 mmol) for 16 h to give **3.36f** (20.5 mg, 0.162 mmol) in 55% yield.

¹H NMR (400 MHz, CDCl₃): δ = 2.56 (s, 3H), 6.87 (d, J = 3.7 Hz, 1H), 7.58 (d, J = 3.7 Hz, 1H), 9.79 (s, 1H),

¹³C NMR (100 MHz, CDCl₃): δ = 16.3, 127.1, 137.3, 142.1, 151.7, 182.7.

5.3.4 Synthesis of electron-poor heteroaromatic aldehydes

Typical procedure for synthesis of (**3.36g**) [CAS 13669-42-6]

To a mixture of NaH (60% dispersion in mineral oil; 60.2 mg, 1.51 mmol) and NaI (75.1 mg, 0.501 mmol) in a 25 mL sealed tube was added a solution of amide from N,N-dimethylquinoline-3-carboxamide (**3.29g**) (100 mg, 0.501 mmol) in 1.5 mL of THF, and the reaction mixture was sealed and stirred at 40 °C for 17 h. The reaction mixture was slowly added into pH 7 mono-potassium phosphate buffer solution (40 mL) at 0 °C and the organic materials were extracted with dichloromethane (20 mL $\times$ 3). The combined extracts were washed with brine and dried over MgSO₄. The volatile materials were removed *in vacuo* and the resulting crude residue was purified by flash column chromatography (silica gel, hexane:ethyl acetate = 90:10) to give **3.36g** (42.0 mg, 0.267 mmol) in 53% yield.

¹H NMR (400 MHz, CDCl₃): δ = 7.63 (dd, J = 8.1, 6.9 Hz, 1H), 7.85 (dd, J = 8.5, 6.9 Hz, 1H), 7.96 (d, J = 8.1 Hz, 1H), 8.15 (d, J = 8.5 Hz, 1H), 8.59 (s, 1H), 9.33 (s, 1H), 10.22 (s, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 127.1, 128.0, 128.7, 129.5, 129.8, 132.7, 140.2, 149.2, 150.7, 190.8.

2-phenylquinoline-4-carbaldehyde (3.36h)

Prepared from amide **3.29h** (83.1 mg, 0.301 mmol) for 21 h to give **3.36h** (66.7 mg, 0.289 mmol) in 95% yield.

¹H NMR (400 MHz, CDCl₃): δ = 7.48 - 7.58 (m, 3H), 7.68 (ddd, J = 8.5, 6.9, 1.3 Hz, 1H), 7.80 (ddd, J = 8.4, 6.9, 1.4 Hz, 1H), 8.21 - 8.26 (m, 4H), 8.97 (dd, J = 8.5, 1.4 Hz, 1H), 10.56 (s, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 123.0, 124.2, 124.3, 127.5, 129.0, 129.2, 130.1, 130.3, 130.4, 137.8, 138.5, 149.5, 157.4, 193.1.

ESIHRMS: Found: m/z 234.0930; Calcd for C₁₆H₁₂NO: (M+H)⁺ 234.0919.

7-chloro-2-phenylquinoline-4-carbaldehyde (3.36i)

Prepared from amide **3.29i** (1.00 g, 3.22 mmol) for 22 h to give **3.36i** (792 mg, 2.96 mmol) in 92% yield.

¹H NMR (400 MHz, CDCl₃): δ = 7.52 - 7.60 (m, 3H), 7.63 (dd, J = 9.1, 2.2 Hz, 1H), 8.21 - 8.26 (m, 4H), 8.96 (d, J = 9.1 Hz, 1H), 10.51 (s, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 121.2, 124.5, 125.9, 127.5, 129.19, 129.22, 129.8, 130.5, 136.6, 137.8, 138.0, 150.0, 158.5, 192.8.

ESIHRMS: Found: m/z 268.0529; Calcd for C₁₆H₁₁NOCl: (M+H)⁺ 268.0529.

isoquinoline-1-carbaldehyde (3.36j)^[17]

Prepared from amide **3.29j** (99.9 mg, 0.499 mmol) for 22 h to give **3.36j** (61.7 mg, 0.393 mmol) in 79% yield.

¹H NMR (400 MHz, CDCl₃): δ = 7.72 - 7.77 (m, 2H), 7.87 - 7.92 (m, 2H), 8.74 (d, J = 5.5 Hz, 1H), 9.29 - 9.32 (m, 1H), 10.38 (s, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 125.6, 125.8, 126.4, 127.0, 130.1, 130.9, 137.0, 142.5, 149.9, 195.7.

nicotinaldehyde (**3.36k**) [CAS: 500-22-1]

Prepared from amide **3.29k** (75.3 mg, 0.501 mmol) for 23 h to give **3.36k** in 50% crude NMR yield with 1,1,2,2-tetrachloroethane as the internal standard. Isolated yield of **3.36k** (17.9 mg, 0.188 mmol) in 33% yield. Decrease in the isolated yield is due to the volatile nature of **3.36k**.

¹H NMR (400 MHz, CDCl₃): δ = 7.48 (dd, J = 7.9, 4.8 Hz, 1H), 8.17 (dd, J = 7.9, 1.4 Hz 1H), 8.84 (dd, J = 4.8, 1.4 Hz, 1H), 9.08 (s, 1H), 10.12 (s, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 124.2, 131.5, 135.9, 152.2, 154.9, 190.8.

6-phenylpicolinaldehyde (**3.36l**)^[18]

Prepared from amide **3.29l** (67.5 mg, 0.298 mmol) with NaH (3 equiv) and NaI (2 equiv) for 11 h to give **3.36l** (34.5 mg, 0.188 mmol) in 63% yield.

¹H NMR (400 MHz, CDCl₃): δ = 7.45 - 7.54 (m, 3H), 7.88 - 7.97 (m, 3H), 8.09 (d, J = 7.1 Hz, 2H), 10.17 (s, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 119.9, 124.6, 127.1, 129.0, 129.8, 137.9, 138.2, 152.8, 158.0, 194.1.

2,6-bis(4-fluorophenyl)isonicotinaldehyde (**3.36m**)

Prepared from **3.29m** (101 mg, 0.297 mmol) for 14 h to give **3.36m** (65.5 mg, 0.222 mmol) in 75% yield.

¹H NMR (400 MHz, CDCl₃): δ = 7.21 (dd, J_{H-H} = 8.7 Hz, J_{H-F} = 8.7 Hz, 4H), 8.02 (s, 2H), 8.18 (dd, J_{H-H} = 8.7 Hz, J_{H-F} = 5.5 Hz, 4H), 10.18 (s, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 116.0 (d, J = 21.7 Hz), 116.8, 129.1 (d, J = 8.5 Hz), 134.5 (d, J = 3.2 Hz), 143.8, 157.6, 164.1 (d, J = 251.1 Hz), 191.7.

¹⁹F NMR (376 MHz, CDCl₃): δ = -111.44(m).

ESIHRMS: Found: m/z 296.0891; Calcd for C₁₈H₁₂NOF₂: (M+H)⁺ 296.0887.

5.3.5 Synthesis of aliphatic aldehydes

2,2-dimethyl-5-phenylpentanal (**3.37a**)^[19]

Prepared by following the method described in 5.3.4 from amide **3.28a** (117 mg, 0.500 mmol) for 17 h to give **3.37a** (87.4 mg, 0.459 mmol) in 92% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.04 (s, 6H), 1.48 - 1.60 (m, 4H), 2.61 (t, J = 7.0 Hz, 2H), 7.15 - 7.21 (m, 3H), 7.26 - 7.30 (m, 2H), 9.43 (s, 1H)

¹³C NMR (100 MHz, CDCl₃): δ = 21.4, 26.2, 36.4, 36.8, 45.9, 126.0, 128.4(overlap), 142.0, 206.4.

adamantane-1-carbaldehyde (**3.37b**)^[20]

Prepared by following the method described in 5.3.4 from amide **3.28b** (104 mg, 0.503 mmol) for 15 h. Purified with flash column chromatography (silica gel, hexane:ethyl acetate = 98:2) to give **3.37b** (71.9 mg, 0.438 mmol) in 87% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.67 - 1.79 (m, 12H), 2.06 - 2.06 (m, 3H), 9.31 (s, 1H),

^{13}C NMR (100 MHz, CDCl_3): δ = 27.4, 35.9, 36.7, 44.9, 206.1.

bicyclo[2.2.2]octane-1-carbaldehyde (3.37c)

Prepared by following the method described in 5.3.4 from amide **3.28c** (91.1 mg, 0.503 mmol) for 14 h to give **3.37c** (46.8 mg, 0.339 mmol) in 67% yield.

^1H NMR (400 MHz, CDCl_3): δ = 1.58 – 1.58 (m, 12H), 1.67 – 1.67 (m, 1H), 9.38 (s, 1H).

^{13}C NMR (100 MHz, CDCl_3): δ = 24.6, 25.0, 25.4, 43.1, 206.6.

ESIHRMS: Found: m/z 139.1136; Calcd for $\text{C}_9\text{H}_{15}\text{O}$: $(\text{M}+\text{H})^+$ 139.1123.

5-(2,5-dimethylphenoxy)-2,2-dimethylpentanal (3.37d)

Prepared by following the method described in 5.3.4 from amide **3.28d** (139 mg, 0.501 mmol) for 14 h to give **3.37d** (103 mg, 0.441 mmol) in 88% yield.

^1H NMR (400 MHz, CDCl_3): δ = 1.10 (s, 6H), 1.65 - 1.77 (m, 4H), 2.17 (s, 3H), 2.31 (s, 3H), 3.92 (t, J = 5.7 Hz, 2H), 6.60 (s, 1H), 6.66 (d, J = 7.5 Hz, 1H), 7.00 (d, J = 7.5 Hz, 1H), 9.49 (s, 1H).

^{13}C NMR (100 MHz, CDCl_3): δ = 15.8, 21.4(overlap), 24.6, 33.7, 45.7, 67.9, 112.0, 120.9, 123.6, 130.4, 136.6, 156.9, 206.2.

ESIHRMS: Found: m/z 235.1692; Calcd for $\text{C}_{15}\text{H}_{23}\text{O}_2$: $(\text{M}+\text{H})^+$ 235.1698.

(1R,4aR,4bR,10aR)-7-isopropyl-1,4a-dimethyl-1,2,3,4,4a,4b,5,6,10,10a-decahydrophenanthrene-1-carbaldehyde (3.37e)^[21]

Prepared by following the method described in 5.3.4 from amide **3.28e** (164 mg, 0.499 mmol) for 18 h to give **3.37e** (127 mg, 0.443 mmol) in 89% yield.

¹H NMR (400 MHz, CDCl₃): δ = 0.84 (s, 3H), 1.00 (d, J = 3.2 Hz, 3H), 1.01 (d, J = 3.2 Hz, 3H), 1.06 - 1.12 (m, 1H), 1.13 (s, 3H), 1.18 - 1.26 (m, 1H), 1.29 - 1.34 (m, 1H), 1.41 - 1.49 (m, 1H), 1.61 - 1.67 (m, 3H), 1.75 - 1.85 (m, 2H), 1.90 - 2.10 (m, 5H), 2.18 - 2.25 (m, 1H), 5.34 - 5.35 (m, 1H), 5.76 - 5.78 (m, 1H), 9.21 (s, 1H)

¹³C NMR (100 MHz, CDCl₃): δ = 14.2, 14.5, 17.4, 20.9, 21.5, 22.6, 25.6, 27.5, 33.0, 33.9, 35.0, 38.4, 42.6, 49.2, 50.7, 120.2, 122.4, 135.8, 145.7, 206.4.

2-methyl-5-phenylpentanal (**3.37f**)

Prepared by following the method described in 5.3.5 from amide **3.28f** (63.5 mg, 0.290 mmol) for 14 h. Purified with flash column chromatography (silica gel, hexane:ethyl acetate = 98:2) to give **3.37f** (41.5 mg, 0.235 mmol) in 81% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.09 (d, J = 7.2 Hz, 3H), 1.37 - 1.45 (m, 1H), 1.63 - 1.80 (m, 3H), 2.31 - 2.40 (m, 1H), 2.64 (t, J = 7.4 Hz, 2H), 7.16 - 7.20 (m, 3H), 7.26 - 7.30 (m, 2H), 9.60 (s, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 13.4, 28.8, 30.1, 35.9, 46.3, 126.0, 128.5(overlap), 142.0, 205.2.

ESIHRMS: Found: m/z 177.1274; Calcd for C₁₂H₁₇O: (M+H)⁺ 177.1279.

1,2,3,4-tetrahydronaphthalene-2-carbaldehyde (**3.37g**)

Prepared by following the method described in 5.3.5 from amide **3.28g** (101 mg, 0.498 mmol) for 14 h to give **3.37g** (56.3 mg, 0.351 mmol) in 71% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.75 - 1.85 (m, 1H), 2.19 - 2.26 (m, 1H), 2.67 - 2.74 (m, 1H), 2.82 - 3.02 (m, 4H), 7.09 - 7.14 (m, 4H), 9.79 (s, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 23.0, 28.2, 28.5, 47.0, 126.1, 126.2, 129.0, 129.3, 134.4, 136.0, 203.9.

ESIHRMS: Found: m/z 161.0960; Calcd for C₁₁H₁₃O: (M+H)⁺ 161.0966.

adamantane-2-carbaldehyde (3.37h)

Prepared by following the method described in 5.3.5 from amide **3.28h** (104 mg, 0.500 mmol) for 14 h to give **3.37h** (77.0 mg, 0.469 mmol) in 94% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.62 - 1.97 (m, 12H), 2.36 - 2.42 (m, 3H), 9.72 (s, 1H)

¹³C NMR (100 MHz, CDCl₃): δ = 27.6, 28.0, 28.2, 33.6, 37.1, 37.9, 56.7, 206.0.

ESIHRMS: Found: m/z 165.1285; Calcd for C₁₁H₁₇O: (M+H)⁺ 165.1279.

tetrahydro-2H-pyran-4-carbaldehyde (3.37i)^[22]

Prepared by following the method described in 5.3.5 from amide **3.28i** (78.8 mg, 0.501 mmol) for 15 h to give **3.37i** (40.1 mg, 0.351 mmol) in 70% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.63 - 1.73 (m, 2H), 1.82 - 1.86 (m, 2H), 2.48 (tt, J = 10.6, 5.3 Hz, 1H), 3.47 (ddd, J = 11.3, 10.8, 2.5 Hz, 2H), 3.94 (ddd, J = 11.3, 7.6, 3.8 Hz, 2H), 9.63 (s, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 25.9, 47.0, 66.9, 202.9.

benzylpiperidine-4-carbaldehyde (3.37j)

Prepared by following the method described in 5.3.5 from amide **3.28j** (1.00 g, 4.07 mmol) at 60 °C for 20 h. Purification was conducted in the slightly modified way: The crude product was dissolved in CH₂Cl₂ (10 mL) and was stirred vigorously for 1 min in saturated NaHSO₃ (40 mL) to give the bisulfite adduct. The aqueous layer was then washed thrice with 10% ethyl acetate in hexane, basified carefully with 50% NaOH and extracted twice with CH₂Cl₂. The organic layer was then washed thrice with water, once with brine and dried over MgSO₄. The volatiles were then removed *in vacuo* to give **3.37j** (619 mg, 3.04 mmol) in 75% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.64 - 1.73 (m, 2H), 1.84 - 1.91 (m, 2H), 2.10 (ddd, J = 13.4, 11.2, 2.5 Hz, 2H), 2.23 (tt, J = 10.6, 5.2 Hz, 1H), 2.81 (ddd, J = 11.2, 7.6, 3.4 Hz, 2H), 3.49 (s, 2H), 7.22 - 7.33 (m, 5H), 9.64 (s, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 25.6, 48.1, 52.6, 63.3, 127.1, 128.3, 129.2, 138.3, 204.1.

ESIHRMS: Found: m/z 204.1386; Calcd for C₁₃H₁₈NO: (M+H)⁺ 204.1388.

1-benzylpyrrolidine-2-carbaldehyde (3.37k)

Prepared by following the method described in 5.3.5 from amide **3.28k** (117 mg, 0.503 mmol) with NaH (5 equiv) and NaI (2 equiv) at 40 °C for 24 h. Purified by flash column chromatography with nitrogen gas (silica gel treated with Et₃N, hexane:EtOAc:Et₃N = 69:30:1) to give **3.37k** (61.5 mg, 0.325 mmol) in 65% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.80 - 1.94 (m, 3H), 1.95 - 2.06 (m, 1H), 2.36 - 2.43 (m, 1H), 2.96 - 3.01 (m, 1H), 3.09 - 3.14 (m, 1H), 3.66 (d, J = 12.9 Hz, 1H), 3.75 (d, J = 12.9 Hz, 1H), 7.23 - 7.33 (m, 5H), 9.30 (d, J = 4.1 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 23.9, 26.7, 54.4, 59.6, 71.7, 127.5, 128.5, 129.2, 138.5, 203.0.

ESIHRMS: Found: m/z 190.1228; Calcd for C₁₂H₁₆NO: (M+H)⁺ 190.1232.

5-phenylpentanal (3.37l)^[23]

Prepared by following the method described in 5.3.6 from amide **3.28l** (103 mg, 0.500 mmol) for 22 h. to give **3.37l** (62.5 mg, 0.385 mmol) in 77% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.65 - 1.69 (m, 4H), 2.43 - 2.46 (m, 2H), 2.64 (t, J = 7.0 Hz, 2H), 7.16 - 7.20 (m, 3H), 7.25 - 7.30 (m, 2H), 9.75 (t, J = 1.8 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 21.8, 31.0, 35.7, 43.8, 125.9, 128.5(overlap), 142.0, 202.6.

5.3.6 Deuterium labelling experiments

Preparation of NaD and its characterization

To a 100 mL sealed tube was added sodium pieces (2.90 g, 125 mmol) under an Ar atmosphere. Mineral oil (5.4 mL) was then added and the reaction vessel was evacuated and backfilled with argon (three times). The reaction vessel was then heated to 285 °C for 3 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 (D₂ 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.

Powder XRD data of NaD

Figure S1. 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 $2\theta = 38.1^\circ$ (marked with *) corresponds to NaOH (a trace amount).

Table S1. Rietveld refinement^[24] 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.

	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%							

Synthesis of deuterated aldehydes **3.35a-[D]**, **3.35b-[D]** and **3.37a-[D]**

Deuterated 2-naphthaldehyde (**3.35a-[D]**)

Prepared by following the method described in 5.3.4 from amide **3.27a** (99.7 mg, 0.500 mmol) with NaD (3 equiv) and NaI (1 equiv) for 24 h to give **3.35a-[D]** (62.0 mg, 0.399 mmol) in 80% yield with 93% deuterium incorporation.

¹H NMR (400 MHz, CDCl₃): δ = 7.58 (ddd, J = 8.2, 6.9, 1.3 Hz, 1H), 7.64 (ddd, J = 8.1, 6.9, 1.3 Hz, 1H), 7.89 (d, J = 8.1 Hz, 1H), 7.92 - 7.97 (m, 2H), 7.99 (d, J = 8.1 Hz, 1H), 8.32 (s, 1H), 10.14 (s, 0.07H),.

¹³C NMR (100 MHz, CDCl₃): δ = 122.8, 127.2, 128.2, 129.2, 129.2, 129.6, 132.7, 134.1, 134.6, 136.5, 192.0 (t, J = 26.6 Hz),.

ESIHRMS: Found: m/z 158.0713; Calcd for C₁₃O₁H₈2H: (M+H)⁺ 158.0716.

Deuterated 4-methoxybenzaldehyde (**3.35b-[D]**)

Prepared by following the method described in 5.3.4 from amide **3.27b** (89.6 mg, 0.499 mmol) with NaD (3 equiv) and NaI (1 equiv) for 18 h to give deuterated **3.35b-[D]** (55.1 mg, 0.405 mmol) in 81% yield with 95% deuterium incorporation.

¹H NMR (400 MHz, CDCl₃): δ = 3.89 (s, 3H), 7.01 (d, J = 8.6 Hz, 2H), 7.84 (d, J = 8.6 Hz, 2H), 9.89 (s, 0.05H).

¹³C NMR (100 MHz, CDCl₃): δ = 55.5, 114.3, 129.8, 131.9, 164.6, 190.4 (t, J = 26.4 Hz).

ESIHRMS: Found: m/z 138.0669; Calcd for C₁₃O₂1H₈2H: (M+H)⁺ 138.0665.

Deuterated 2,2-dimethyl-5-phenylpentanal (**3.37a-[D]**)

Prepared by following the method described in 5.3.4 from amide **3.28a** (116 mg, 0.498 mmol) with NaD (3 equiv) and NaI (1 equiv) for 26 h to give deuterated **3.37a-[D]** (82.3 mg, 0.430 mmol) in 86% yield with 90% deuterium incorporation.

¹H NMR (400 MHz, CDCl₃): δ = 1.03 (s, 6H), 1.48 - 1.58 (m, 4H), 2.60 (t, J = 6.9 Hz, 2H), 7.14 - 7.20 (m, 3H), 7.25 - 7.30 (m, 2H), 9.42 (s, 0.1H).

¹³C NMR (100 MHz, CDCl₃): δ = 21.4, 26.2, 36.4, 36.8, 45.7, 126.0, 128.4 (overlap), 142.0, 206.1 (t, J = 25.7 Hz),.

ESIHRMS: Found: m/z 192.1498; Calcd for C₁₃O₁H₁₈2H: (M+H)⁺ 192.1499.

5.3.7 Chemoselective reduction of amides over ketones

The reaction for N,N-dimethyl-4-((5-oxo-5-phenylpentyl)oxy)benzamide (**3.30**)

Prepared by following the method described in 5.3.5 from keto amide **3.30** (163 mg, 0.500 mmol) with NaH (5 equiv) and NaI (2 equiv) for 24 h to give 4-((5-oxo-5-phenylpentyl)oxy)benzaldehyde (**3.39**) (124 mg, 0.438 mmol) in 88% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.91 - 1.97 (m, 4H), 3.08 (t, J = 6.2 Hz, 2H), 4.10 (t, J = 5.7 Hz, 2H), 6.98 (d, J = 8.7 Hz, 2H), 7.46 (dd, J = 8.4, 7.8 Hz, 2H), 7.57 (t, J = 7.8 Hz, 1H), 7.82 (d, J = 8.7 Hz, 2H), 7.96 (d, J = 8.4 Hz, 2H), 9.87 (s, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 20.7, 28.6, 37.9, 68.0, 114.7, 127.9, 128.6, 129.8, 131.9, 133.0, 136.9, 164.0, 190.7, 199.7.

ESIHRMS: Found: m/z 283.1338; Calcd for C₁₈H₁₉O₃: (M+H)⁺ 283.1334.

The reaction for N,N,2,2-tetramethyl-7-oxo-7-phenylheptanamide (**3.34**)

Prepared by following the method described in 5.3.5 from keto amide **3.34** (137 mg, 0.499 mmol) with NaH (5 equiv) and NaI (2 equiv) for 20 h to give ((1*R**,2*R**)-2-hydroxy-3,3-dimethylcyclohexyl)(phenyl)methanone (**3.40**) (100 mg, 0.432 mmol) in 87% yield as a single diastereomer.

¹H NMR (400 MHz, CDCl₃): δ = 1.03 (s, 6H), 1.19 - 1.24 (m, 1H), 1.63 - 1.72 (m, 4H), 1.81 - 1.91 (m, 1H), 3.65 (ddd, J = 12.9, 3.1, 1.8 Hz, 1H), 3.70 (s, 1H), 3.72 (d, J = 1.8 Hz, 1H), 7.46 - 7.50 (m, 2H), 7.57 - 7.61 (m, 1H), 7.92 - 7.94 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ = 21.4, 23.4, 24.1, 28.0, 32.1, 34.8, 44.3, 74.4, 128.3, 128.7, 133.4, 136.0, 205.8.

ESIHRMS: Found: m/z 233.1545; Calcd for C₁₅H₂₁O₂: (M+H)⁺ 233.1542.

5.3.8 Chemoselective reduction of amides over esters

The chemoselective reduction following the method describe in 5.3.5 of amides over esters was enabled only when t-Bu ester **3.33** was used as the ester moiety, affording aldehyde **3.44** in 76% yield (Chapter 3, Scheme 3.24). Methyl and isopropyl esters **3.31** and **3.32** were partially converted into carboxylic acid **3.42** (carboxylate before aqueous quench) probably due to the presence of NaOH in NaH, that somehow hampered reduction of amides.

Characterization of products in Chapter 3, Scheme 3.24

4-((5-oxo-5-phenylpentyl)oxy)benzaldehyde (**3.43c**)

^1H NMR (400 MHz, CDCl_3): δ = 1.15 (s, 6H), 1.42 (s, 9H), 1.62 - 1.67 (m, 2H), 1.73 - 1.80 (m, 2H), 4.01 (t, J = 6.2 Hz, 2H), 6.97 (d, J = 8.6 Hz, 2H), 7.81 (d, J = 8.6 Hz, 2H), 9.86 (s, 1H).

^{13}C NMR (100 MHz, CDCl_3): δ = 24.9, 25.3, 28.1, 36.9, 42.5, 68.7, 80.0, 114.8, 129.9, 132.1, 164.2, 177.0, 190.9.

ESIHRMS: Found: m/z 307.1902; Calcd for $\text{C}_{18}\text{H}_{27}\text{O}_4$: $(\text{M}+\text{H})^+$ 307.1909.

5-(4-(dimethylcarbamoyl)phenoxy)-2,2-dimethylpentanoic acid (3.42)

^1H NMR (400 MHz, CDCl_3): δ = 1.23 (s, 6H), 1.66 - 1.79 (m, 4H), 3.06 (brs, 6H), 3.94 (t, J = 6.1 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 7.39 (d, J = 8.7 Hz, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ = 25.0, 25.1, 35.6, 36.9, 39.9, 41.9, 68.3, 114.1, 128.1, 129.3, 160.2, 171.9, 183.0.

ESIHRMS: Found: m/z 294.1706; Calcd for $\text{C}_{16}\text{H}_{24}\text{NO}_4$: $(\text{M}+\text{H})^+$ 294.1705.

Characterization of the products in Chapter 4, Scheme 3.26.

The procedure for the reduction of ester is as described in Section 5.2.2

[1,1'-Biphenyl]-4-ylmethanol^[25]

^1H NMR (400 MHz, CDCl_3): δ = 1.70 (brs, 1H), 4.75 (s, 2H), 7.35 (tt, J = 1.2, 7.2 Hz, 1H), 7.41 - 7.47 (m, 4H), 7.57 - 7.62 (m, 4H).

^{13}C NMR (100 MHz, CDCl_3): δ = 65.1, 127.1, 127.3 (overlapped), 127.5, 128.8, 139.9, 140.7, 140.8.

[1,1'-Biphenyl]-4-ylmethyl [1,1'-biphenyl]-4-carboxylate^[26]

^1H NMR (400 MHz, CDCl_3): δ = 5.43 (s, 2H), 7.32 - 7.41 (m, 2H), 7.41 - 7.49 (m, 4H), 7.54 (d, J = 8.0 Hz, 2H), 7.57 - 7.64 (m, 6H), 7.66 (d, J = 7.6 Hz, 2H), 8.16 (d, J = 7.6 Hz, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ = 66.4, 127.06, 127.12, 127.26, 127.35, 127.42, 128.1, 128.7, 128.79, 128.82, 128.9, 130.2, 135.1, 140.0, 140.7, 141.2, 145.8, 166.3.

[1,1'-Biphenyl]-4-carboxylic acid^[27]

^1H NMR (400 MHz, CD_3OD): δ = 7.38 (tt, J = 1.2, 7.6 Hz, 1H), 7.47 (dd, J = 7.6, 7.6 Hz, 2H), 7.67 (d, J = 7.2 Hz, 2H), 7.72 (d, J = 8.4 Hz, 2H), 8.09 (d, J = 8.4 Hz, 2H).

^{13}C NMR (100 MHz, CD_3OD): δ = 126.6, 126.8, 127.8, 128.6, 129.3, 129.9, 139.9, 145.6, 168.3.

5.3.9 Reduction of enantio-enriched amides

Reduction of **3.28f**

The enantioenriched (+)-**3.28f** (99% ee) and (–)-**3.28f** (99% ee) were obtained by separation of racemic (±)-**3.28f** using LaboACE recycling preparative HPLC with chiral column Daicel ChiralPak IG (20 mm ø x 250 mmL; particle size 5 µm) hexane/isopropyl alcohol (95/5), flow rate 8 mL/min.

HPLC analysis for (+)-**3.28f** and (–)-**3.28f**

Chiral column: Daicel ChiralPak IG (4.6mm ø × 250mmL; particle size 5 µm)

Eluent: hexane/isopropyl alcohol (90/10)

Flow rate: 1.0 mL/min

Diode array detector: 230 nm

Retention time for (+)-**3.28f**: 10.5 min

Retention time for (–)-**3.28f**: 12.9 min

HPLC trace for (±)-**3.28f**

HPLC trace for (+)-**3.28f**

HPLC trace for (–)-**3.28f**

Optical rotation for (+)-3.28f and (–)-3.28f

For (+)-**3.28f** (99% ee): $[\alpha]_D^{25} = +27.7^\circ$ ($c = 0.01$ g/mL, CHCl_3)

For (–)-**3.28f** (99% ee): $[\alpha]_D^{25} = -24.4^\circ$ ($c = 0.01$ g/mL, CHCl_3)

The reaction with (+)-**3.28f** (0.290 mmol) was conducted by following the procedure described in section 5.3.6, affording aldehyde (+)-**3.37f** in 81% yield (41.5 mg, 0.235 mmol) with 90% ee.

The reaction with (–)-**3.28f** (0.384 mmol) was conducted by following the procedure described in section 5.3.4, affording aldehyde (–)-**3.37f** in 79% yield (53.4 mg, 0.303 mmol) with 80% ee.

The reaction with (–)-**3.28f** (0.303 mmol) was conducted by following the procedure described in section 5.3.6, affording aldehyde (–)-**3.37f** in 78% yield (41.7 mg, 0.237 mmol) with 93% ee.

HPLC analysis for (+)-3.37f and (–)-3.37f

Chiral column: Daicel ChiralPak IG (4.6mm $\varnothing$ × 250mmL; particle size 5 μm)

Eluent: hexane/isopropyl alcohol (99/1)

Flow rate: 0.6 mL/min

Diode array detector: 280 nm

Retention time for (+)-**3.37f**: 12.7 min

Retention time for (–)-**3.37f**: 12.1 min

HPLC trace for (±)-**3.37f**

HPLC trace for (+)-**3.37f** (70% ee)

<Chromatogram>

<Peak Table>

UV Channel 1 280nm

Peak#	Ret. Time	Area	Height	Area%
1	11.768	31461	2512	15.213
2	12.359	175346	12972	84.787
Total		206808	15485	100.000

HPLC trace for (+)-**3.37f** (90% ee)

<Chromatogram>

<Peak Table>

UV Channel 1 280nm

Peak#	Ret. Time	Area	Height	Area%
1	12.116	7207	594	4.955
2	12.704	138236	10557	95.045
Total		145443	11152	100.000

HPLC trace for (–)-**3.37f** (80% ee)

<Chromatogram>

<Peak Table>

UV Channel 1 280nm

Peak#	Ret. Time	Area	Height	Area%
1	12.174	128573	10581	89.873
2	12.666	14487	1104	10.127
Total		143060	11685	100.000

HPLC trace for (–)-**3.37f** (93% ee)

<Chromatogram>

<Peak Table>

UV Channel 1 280nm

Peak#	Ret. Time	Area	Height	Area%
1	12.564	142806	10578	96.375
2	13.092	5372	425	3.625
Total		148178	11003	100.000

Optical rotation for (+)-**3.37f** and (–)-**3.37f**

For (+)-**3.37f** (90% ee): $[\alpha]_D^{25} +16.0^\circ$ ($c = 0.005$ g/mL, CHCl_3)

For (–)-**3.37f** (80% ee): $[\alpha]_D^{25} -14.8^\circ$ ($c = 0.010$ g/mL, CHCl_3)

For (–)-**3.37f** (93% ee): $[\alpha]_D^{25} -17.4^\circ$ ($c = 0.005$ g/mL, CHCl_3)

Reduction of (S)-**3.28k** for synthesis of (S)-(1-benzylpyrrolidin-2-yl)methanol (**3.38k**)

[CAS: 53912-80-4]

Prepared from (S)-**3.28k** (70.0 mg, 0.301 mmol) under the standard conditions described in section 4.2.1 with NaH (60% dispersion in mineral oil; 60.2 mg, 1.51 mmol) and NaI (90.5 mg, 0.60 mmol). After extraction the crude mixture was dissolved in 2 mL of MeOH and was treated with NaBH₄ (13.7 mg, 0.361 mmol) for 30 min at room temperature. The solvent was removed *in vacuo* and the product was extracted twice with dichloromethane, wash with brine and dried over MgSO₄. The volatiles was removed *in vacuo* and purified with flash column chromatography (silica gel, hexane:ethyl acetate:Et₃N = 50:48:2) to give (S)-**3.38k** (30.0 mg, 0.157 mmol) in 52% 2-step yield with 93% ee, which was measured by the Mosher method with (–)-MTPA derivatization (see below for experimental details).^[28]

For racemic (±)-**3.38k**: prepared by following the experimental procedure in section 5.3.11.2 from 1-benzyl-N,N-dimethylpyrrolidine-2-carboxamide (**3.28k**) (70.3 mg, 0.303 mmol) and purified by flash column chromatography (silica gel, hexane:ethyl acetate:Et₃N = 50:48:2) to give 1-benzylpyrrolidin-2-ylmethanol ((±)-**3.38k**) (33.0 mg, 0.172 mmol) in 57% 2-step yield.

Optical Rotation: For (S)-**3.38k** (93% ee): $[\alpha]_D^{25} -49.6^\circ$ (c = 0.011 g/mL, CHCl₃)

¹H NMR (400 MHz, CDCl₃): δ = 1.67 - 1.73 (m, 2H), 1.78 - 2.00 (m, 2H), 2.25 - 2.35 (m, 1H), 2.64 (brs, 1H), 2.74 (ddd, J = 9.0, 5.9, 2.9 Hz, 1H), 2.95 - 3.00 (m, 1H), 3.37 (d, J = 13.0 Hz, 1H), 3.43 (dd, J = 10.8, 2.3 Hz, 1H), 3.65 (dd, J = 10.8, 3.5 Hz, 1H), 3.97 (d, J = 13.0 Hz, 1H), 7.23 - 7.34 (m, 5H).

¹³C NMR (100 MHz, CDCl₃): δ = 23.5, 27.8, 54.5, 58.6, 61.8, 64.4, 127.2, 128.4, 128.8, 139.2.

The Moscher method for **3.28k**

For derivatisation of (±)-**3.28k** and (S)-**3.28k**: (±)-**3.28k** (5.05 mg, 0.022 mmol) or (S)-**3.28k** (5.01 mg, 0.022 mmol) and (–)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) (6.55 mg, 0.028 mmol) was dissolved in CDCl₃ (1.0 mL) and was stirred at room temperature for

15 min. The resulting solution was then analyzed using ^1H NMR without any further purification.

^1H NMR spectrum for ($\pm$)-3.28k-MTPA complex

^1H NMR spectrum for (S)-3.28k-MTPA complex

The Moscher method for **3.38k**

For derivatisation of (±)-**3.38k** and (S)-**3.38k**: (±)-**3.38k** (4.95 mg, 0.026 mmol) or (S)-**3.38k** (5.00 mg, 0.026 mmol) and (–)-MTPA (6.60 mg, 0.028 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 ^1H NMR without any further purification.

^1H NMR spectrum for (±)-**3.38k**-MTPA complex

¹H NMR spectrum for (S)-3.38k-MTPA complex

5.3.10 References for Section 5.3

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5.4 Experimental data for Chapter 4

5.4.1 Synthesis of α -quaternary α -arylacetamides and Biaryl Secondary and Tertiary Amides Derivatives

Five methods **A-E** were applied for the synthesis of α -quaternary α -arylacetamides **4.10a-4.10t** and biaryl secondary and tertiary amides **4.17** and **4.20a-4.20g**.

Method A: For synthesis of α -arylacetamides 4.10a-4.10h, 4.10j and biaryl secondary amides 4.20c and 4.20g

Typical Procedure for Synthesis of 4.10a

In a 100 mL round bottom flask, 2-methyl-2-(naphthalen-2-yl)propanenitrile^[1] (3.91 g, 10.0 mmol) was dissolved in ethylene glycol (20 mL) and water (4 mL) and was added KOH (2.24 g, 40.0 mmol). The reaction mixture was then stirred at reflux and upon consumption of the starting material (for 14 h). After cooling down to room temperature, water (20 mL) was added into the reaction mixture and the neutral organic materials were extracted twice with diethyl ether. The aqueous layer was then acidified to pH 1 by adding 1M aqueous HCl and the acidic organic materials were extracted with CH_2Cl_2 (20 mL x 3). The combined extracts were then washed with water and brine and dried over MgSO_4 . After removal of the solvent, the resulting crude residue including carboxylic acid was used in the amide synthesis without further purification.

The crude material obtained above was dissolved in CH_2Cl_2 (40 mL) and was added $(\text{COCl})_2$ (1.35 mL, 15.0 mmol) and DMF (5 drops). The reaction mixture was stirred at room temperature for 3 h, before adding Me_2NH (40 w/w% in water; 5.06 mL, 40.0 mmol) dropwise at 0 °C. The reaction mixture was stirred continuously at room temperature for 3 h. The reaction was then quenched with water and the organic materials were extracted twice with CH_2Cl_2 , 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 = 80:20) to give *N,N*,2-trimethyl-2-(naphthalen-2-yl)propanamide **4.10a** (2.06 g, 8.54 mmol) in 85% yield for 2 steps.

¹H NMR (400 MHz, CDCl₃): δ = 1.64 (s, 6H), 2.50 (br s, 3H), 2.96 (br s, 3H), 7.31 (dd, *J* = 8.5 Hz, 1.9 Hz, 1H), 7.43-7.51 (m, 2H), 7.69 (d, *J* = 1.5 Hz, 1H), 7.79-7.83 (m, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 28.3, 37.4 (br), 38.3 (br), 47.3, 122.5, 124.2, 125.8, 126.3, 127.7, 127.9, 128.8, 132.1, 133.7, 144.2, 176.1.

ESIHRMS: Found 242.1547; Calcd for C₁₆H₂₀NO: (M+H)⁺ 242.1545.

2-(4-methoxyphenyl)-N,N,2-trimethylpropanamide (4.10b)^[2]

Prepared by following **Method A** from 2-(4-methoxyphenyl)-2-methylpropanenitrile (2.40 g, 13.7 mmol)^[3] to give **4.10b** (2.66g, 12.0 mmol) in 88% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.50 (s, 6H), 2.52 (br s, 3H), 2.91 (br s, 3H), 3.79 (s, 3H), 6.85 (d, *J* = 9.0 Hz, 2H), 7.11 (d, *J* = 9.0 Hz, 2H).

¹³C NMR (100 MHz, CDCl₃): δ = 28.3, 37.3 (br), 38.2 (br), 46.3, 55.2, 114.2, 125.7, 138.6, 157.9, 176.4.

2-([1,1'-biphenyl]-4-yl)-N,N,2-trimethylpropanamide (4.10c)

Prepared by following **Method A** from 2-([1,1'-biphenyl]-4-yl)-2-methylpropanenitrile (472 mg, 2.13 mmol)^[4] to give **4.10c** (471 mg, 1.76 mmol) in 83% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.57 (s, 6H), 2.56 (br s, 3H), 2.93 (br s, 3H), 7.25-7.29 (m, 2H), 7.30-7.35 (m, 1H), 7.40-7.45 (m, 2H), 7.54-7.60 (m, 4H).

¹³C NMR (100 MHz, CDCl₃): δ = 28.3, 37.4 (br), 38.3 (br), 46.9, 125.3, 127.0, 127.4, 127.6, 128.9, 139.1, 140.6, 145.7, 176.2.

ESIHRMS: Found 268.1707; Calcd for C₁₈H₂₂NO: (M+H)⁺ 268.1701.

2-([1,1'-biphenyl]-3-yl)-N,N,2-trimethylpropanamide (4.10d)

Prepared by following **Method A** from 2-([1,1'-biphenyl]-3-yl)-2-methylpropanenitrile (2.57 g, 11.7 mmol) to give **4.10d** (2.48 g, 9.28 mmol) in 79% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.60 (s, 6H), 2.54 (br s, 3H), 2.95 (br s, 3H), 7.21 (ddd, J = 7.7 Hz, 1.5 Hz, 1.4 Hz, 1H), 7.33-7.47 (m, 6H), 7.57-7.59 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ = 28.4, 37.5 (br), 38.5 (br), 47.2, 123.6, 123.8, 125.2, 127.3, 127.5, 128.9, 129.4, 141.1, 141.9, 147.2, 176.2.

ESIHRMS: Found 268.1701; Calcd for C₁₈H₂₂NO: (M+H)⁺ 268.1701.

Synthesis of 2-([1,1'-biphenyl]-3-yl)-2-methyl-propanenitrile (dialkylation procedure A):

To an ice-cold solution of 2-([1,1'-biphenyl]-3-yl)acetonitrile^[5] (2.63 g, 13.6 mmol) in THF (40 mL) was added NaH (60% dispersion in mineral oil; 1.63 g, 40.9 mmol) portion-wise and the reaction mixture was stirred at that temperature for 1 h. MeI (3.0 mL, 47.7 mmol) was then added and the reaction was stirred at room temperature for 16 h. The reaction was quenched by careful addition of water and the organic material was extracted twice with diethyl ether. The combined organic extracts were washed with brine and dried over MgSO₄. The solvent was removed *in vacuo* and the resulting crude material was purified by flash column chromatography (silica gel, hexane:ethylacetate = 95:5) to give 2-([1,1'-biphenyl]-3-yl)-2-methylpropane-nitrile (2.77g, 12.5 mmol) in 92% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.80 (s, 6H), 7.37-7.41 (m, 1H), 7.46-7.51 (m, 4H), 7.53-7.57 (m, 1H), 7.60-7.62 (m, 2H), 7.70-7.71 (m, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 29.3, 37.4, 124.0, 124.1, 124.6, 126.8, 127.4, 127.8, 129.0, 129.5, 140.8, 142.1, 142.2.

ESIHRMS: Found 222.1279; Calcd for C₁₆H₁₆N: (M+H)⁺ 222.1283.

N,N-dimethyl-1-(naphthalen-2-yl)cyclohexane-1-carboxamide (4.10g)

Prepared by following **Method A** from 1-(naphthalen-2-yl)cyclohexane-1-carbonitrile (1.88 g, 8.00 mmol)^[6] to give **4.10g** (1.17 g, 4.17 mmol) in 52% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.24-1.39 (m, 1H), 1.67-1.84 (m, 7H), 2.41-2.49 (m, 2H), 2.74 (br s, 6H), 7.38 (dd, *J* = 8.7 Hz, 1.9 Hz, 1H), 7.42-7.49 (m, 2H), 7.73 (d, *J* = 1.5 Hz, 1H), 7.78-7.82 (m, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 23.7, 26.1, 36.7, 38.0 (br), 51.4, 123.3, 124.5, 125.7, 126.2, 127.6, 128.0, 128.6, 132.1, 133.7, 144.0, 175.0.

ESIHRMS: Found 282.1864; Calcd for C₁₉H₂₄NO: (M+H)⁺ 282.1858.

***N,N*-dimethyl-2,2,2-triphenylacetamide (4.10j)**^[7]

Prepared by following **Method A** with modifications. Full procedure as follows: To a solution of commercially available 2,2,2-triphenylacetic acid (2.88 g, 10.0 mmol) in CH₂Cl₂ (50 mL) was added (COCl)₂ (6.35 g, 50.0 mmol) and DMF (3 drops), and the reaction mixture was stirred at reflux temperature for 4 h. The volatile materials were removed *in vacuo*. The resulting residue containing acid chloride was dissolved in 20 mL of THF, which was added dropwise into a solution of Me₂NH (2 M in THF; 20 mL, 40.0 mmol) and Et₃N (1.40 mL, 10.0 mmol) and THF (20 mL) at 0 °C. After being stirred for 14 h at room temperature, the reaction mixture was then quenched with water and acidified to pH 1 with 1 M aqueous HCl solution. The organic materials were extracted thrice with Et₂O (30 mL x 3). The combined extracts were washed with saturated aqueous Na₂CO₃ and brine, and dried over MgSO₄. The solvent was removed *in vacuo* to give the crude product, which was purified by flash column chromatography (silica gel, CH₂Cl₂) followed by recrystallization from EtOH-H₂O to give *N,N*-dimethyl-2,2,2-triphenylacetamide (**4.10j**) (1.61 g, 5.10 mmol) in 51% yield.

¹H NMR (400 MHz, CDCl₃): δ = 2.36 (s, 3H), 3.05 (s, 3H), 7.19-7.31 (m, 15H).

¹³C NMR (100 MHz, CDCl₃): δ = 37.5, 39.6, 67.4, 126.5, 127.7, 130.2, 143.2, 172.8.

ESIHRMS: Found 316.1709; Calcd for C₂₂H₂₂NO: (M+H)⁺ 316.1701.

***N*,2',6'-trimethyl-[1,1'-biphenyl]-2-carboxamide (4.20c)**

Prepared by following **Method A** with slight modification from 2-(2,6-dimethylphenyl)benzonitrile^[8] (837 mg, 4.04 mmol) (use of ethylene glycol as the solvent for hydrolysis and MeNH₂ (4 equiv) for amidation).to give **4.20c** (540 mg, 2.26 mmol) in 56% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.99 (s, 6H), 2.61 (d, J = 3.9 Hz, 3H), 5.43 (br s, 1H), 7.07-7.26 (m, 4H), 7.42-7.52 (m, 2H), 8.08 (d, J = 7.2 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 20.6, 26.8, 127.6, 128.0, 128.1, 130.0, 130.1, 131.0, 133.6, 136.0, 138.3, 139.8, 168.2.

ESIHRMS: Found 240.1387; Calcd for C₁₆H₁₈NO: (M+H)⁺ 240.1388.

N-methyl-2-(2-methylnaphthalen-1-yl)benzamide (4.20g)

Prepared by following **Method A** with slight modification from 2-(2-methylnaphthalen-1-yl)benzonitrile^[8] (1.59 g, 6.54 mmol) (use of ethylene glycol as the solvent for hydrolysis and MeNH₂ (4 equiv) was used for amidation) to give **4.20g** (931 mg, 3.41 mmol) in 52% yield.

¹H NMR (400 MHz, CDCl₃): δ = 2.20 (s, 3H), 2.37 (d, J = 4.9 Hz, 3H), 5.23 (br s, 1H), 7.18-7.20 (m, 1H), 7.30 (d, J = 8.5 Hz, 1H), 7.35 (dd, J = 8.5 Hz, 7.9 Hz, 1H), 7.42-7.46 (m, 2H), 7.52-7.59 (m, 2H), 7.82 (d, J = 8.5 Hz, 1H), 7.86 (d, J = 7.9 Hz, 1H), 8.05-8.08 (m, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 20.7, 26.6, 125.3, 125.4, 126.9, 128.1, 128.20, 128.23, 128.8, 129.9, 130.8, 131.2, 132.1, 132.5, 134.0, 135.7, 136.0, 136.9, 168.6.

ESIHRMS: Found 276.1389; Calcd for C₁₉H₁₈NO: (M+H)⁺ 276.1388.

Method B: For synthesis of α -arylacetamides 4.10e, 4.10o, biaryl tertiary amide 4.18 and biaryl secondary amide 4.20a and 4.20b

Typical Procedure for Synthesis of 4.10e

To a solution of methyl 2-([1,1'-biphenyl]-2-yl)-2-methylpropanoate^[9] (605 mg, 2.38 mmol) in MeOH (15 mL) and water (15 mL) was added KOH (534 mg, 9.52 mmol), and the reaction mixture was stirred under reflux conditions for 16 h. After the reaction mixture was cooled down to room temperature, water (20 mL) was added and the basic organic materials were extracted twice with diethyl ether. The aqueous layer was acidified to pH 1 with 1M HCl and the acidic organic materials were extracted twice with CH₂Cl₂. The combined extracts were washed with water (100 mL) and brine, followingly dried over MgSO₄. After removal of the solvent, the resulting crude residue including carboxylic acid was used for the next amidation without any further purification.

To a solution of the crude carboxylic acid obtained above in CH₂Cl₂ (40 mL) was added (COCl)₂ (0.32 mL, 3.57 mmol) and DMF (5 drops) and the reaction mixture was stirred at room temperature for 2 h. To the reaction mixture was then added HNMe₂ (2 M in THF; 4.76 mL, 9.52 mmol) dropwise at 0 °C. After being stirred for 2 h at room temperature, the reaction was then quenched with water, and the organic material were extracted twice with CH₂Cl₂. The combined extracts were washed with brine and dried over MgSO₄. After removal of the volatile materials *in vacuo*, the resulting crude residue was purified by flash column chromatography (silica gel, hexane:ethyl acetate = 80:20) to give N,N,2-trimethyl-2-(naphthalen-2-yl)propanamide **4.10e** (576 mg, 2.16 mmol) in 91% yield (2-steps).

¹H NMR (400 MHz, CDCl₃): δ = 1.47 (s, 6H), 2.55 (s, 3H), 2.58 (s, 3H), 7.07 (d, *J* = 7.3 Hz, 1H), 7.16-7.25 (m, 3H), 7.32-7.39 (m, 5H).

¹³C NMR (100 MHz, CDCl₃): δ = 29.5, 36.6, 38.1, 47.1, 125.5, 125.9, 127.3, 127.4, 128.1, 129.4, 132.7, 141.0, 141.9, 143.7, 175.2.

ESIHRMS: Found 268.1701; Calcd for C₁₈H₂₂NO: (M+H)⁺ 268.1701.

N,N,2-trimethyl-2-(pyridin-2-yl)propanamide (**4.10f**)^[10]

Prepared by following **Method B** from ethyl 2-methyl-2-(pyridin-2-yl)propanoate (1.35 g, 7.00 mmol)^[11] with slight modification (MeOH was used for hydrolysis, 50 °C, 3 h. After hydrolysis, extraction was not done, the solvent including water was removed *in vacuo* and directly used for next step) **4.10f** (941 mg, 4.90 mmol) in 70% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.50 (s, 6H), 2.34 (s, 3H), 2.86 (s, 3H), 7.05 (dd, *J* = 7.5 Hz, 4.9 Hz, 1H), 7.10 (d, *J* = 7.1 Hz, 1H), 7.56 (dd, *J* = 7.5 Hz, 7.1 Hz, 1H), 8.48 (d, *J* = 4.9 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 27.0, 36.9 (br), 37.7 (br), 49.5, 120.0, 121.2, 136.8, 149.1, 165.1, 175.4.

ESIHRMS: Found 193.1338; Calcd for C₁₁H₁₇N₂O: (M+H)⁺ 193.1341;

N,N,2-trimethyl-3-phenyl-2-(o-tolyl)propanamide (4.10o)

Prepared by following **Method B** with slight modification from methyl 2-methyl-3-phenyl-2-(o-tolyl)propanoate (376 mg, 1.40 mmol) (use of ethanol and water as the solvent for hydrolysis) to give **4.10o** (240 mg, 0.852 mmol) in 61% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.51 (s, 3H), 2.29 (s, 3H), 2.51 (s, 3H), 2.97 (s, 3H), 3.33 (s, 2H), 6.52 (br s, 2H), 6.71 (br s, 1H), 6.96-7.18 (m, 6H).

¹³C NMR (100 MHz, CDCl₃): δ = 20.1, 22.5 (br), 37.3, 38.0, 44.4, 50.1, 126.0, 126.1, 126.4 (br), 126.7, 127.2, 131.4, 132.1, 136.1, 137.7, 141.4, 176.4.

ESIHRMS: Found 282.1865; Calcd for C₁₉H₂₄NO: (M+H)⁺ 282.1858.

methyl 2-methyl-3-phenyl-2-(o-tolyl)propanoate (for the synthesis of 4.10o)

To a solution of diisopropylamine (1.05 mL, 7.58 mmol) in THF (6 mL) at –78 °C was slowly added *n*-BuLi (1.55 M in hexane, 4.90 mL, 7.58 mmol), and the reaction mixture was stirred for 30 min before addition of a solution of methyl 2-(o-tolyl)propanoate^[12] (900 mg, 5.05 mmol) in THF (6 mL) dropwise. After the reaction mixture was stirred at the same temperature for 1 h, a solution of benzyl bromide (1.2 mL, 10.1 mmol) in THF (6 mL) was added dropwise. The reaction mixture was slowly warmed up to room temperature with stirring for 4 h, and then quenched with saturated aqueous NH₄Cl

solution. The organic materials were extracted twice with diethyl ether. The combined 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, hexane:ethyl acetate = 99:1) to give methyl 2-methyl-3-phenyl-2-(o-tolyl)propanoate (945 mg, 3.52 mmol) in 70% yield.

^1H NMR (400 MHz, CDCl_3): δ = 1.51 (s, 3H), 2.27 (s, 3H), 3.29 (d, J = 13.4 Hz, 1H), 3.37 (d, J = 13.4 Hz, 1H), 3.69 (s, 3H), 6.67-6.70 (m, 2H), 6.94 (d, J = 7.9 Hz, 1H), 7.05-7.19 (m, 6H).

^{13}C NMR (100 MHz, CDCl_3): δ = 20.3, 24.0, 43.3, 50.6, 52.3, 125.8, 126.4, 126.8, 127.0, 127.6, 130.9, 131.8, 136.1, 137.0, 140.7, 178.1.

ESIHRMS: Found 269.1537; Calcd for $\text{C}_{18}\text{H}_{21}\text{O}_2$: $(\text{M}+\text{H})^+$ 269.1542.

N,N,2'-trimethyl-[1,1'-biphenyl]-2-carboxamide (4.17)

Prepared by following **Method B** from methyl 2'-methyl-[1,1'-biphenyl]-2-carboxylate^[13] (457 mg, 2.02 mmol) to give **4.17** (405 mg, 1.69 mmol) in 84% yield.

^1H NMR (400 MHz, CDCl_3): δ = 2.23 (s, 3H), 2.58 (br s, 3H), 2.78 (s, 3H), 7.14-7.27 (m, 5H), 7.36-7.43 (m, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ = 20.3, 34.5, 38.4, 125.4, 127.1, 127.5, 127.8, 128.5, 129.7 (br), 130.3, 130.4, 135.8 (br), 136.8, 138.5 (br), 139.3 (br), 171.0.

ESIHRMS: Found 240.1388; Calcd for $\text{C}_{16}\text{H}_{18}\text{NO}$: $(\text{M}+\text{H})^+$ 240.1388.

N,2'-Dimethylbiphenyl-2-carboxamide (4.20a)^[14]

Prepared by following **Method B** from methyl 2'-methyl-[1,1'-biphenyl]-2-carboxylate (487 mg, 2.15 mmol)^[13] and MeNH_2 to give **4.20a** (250 mg, 1.11 mmol) in 52% yield.

¹H NMR (400 MHz, CDCl₃): δ = 2.10 (s, 3H), 2.61 (d, J = 4.9 Hz, 3H), 5.23 (br s, 1H), 7.17-7.20 (m, 2H), 7.23-7.32 (m, 3H), 7.40-7.49 (m, 2H), 7.90-7.92 (m, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 20.1, 26.8, 126.3, 127.8, 128.3, 129.2, 129.37, 129.40, 130.4, 130.5, 134.9, 136.2, 139.2, 140.3, 169.0.

***N*-benzyl-2'-methyl-[1,1'-biphenyl]-2-carboxamide (4.20b)**

Prepared by following **Method B** from methyl 2'-methyl-[1,1'-biphenyl]-2-carboxylate (1.61 g, 7.12 mmol) and benzyl amine (915 mg, 8.54 mmol) to give **4.20b** (1.75 g, 5.81 mmol) in 82% yield.

¹H NMR (400 MHz, CDCl₃): δ = 2.06 (s, 3H), 4.22 (dd, J = 14.5 Hz, 5.1 Hz, 1H), 4.37 (dd, J = 14.5 Hz, 5.7 Hz, 1H), 5.65 (br s, 1H), 6.85-6.88 (m, 2H), 7.11-7.31 (m, 8H), 7.41-7.51 (m, 2H), 7.95 (dd, J = 7.5 Hz, 1.6 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 20.0, 44.1, 126.2, 127.3, 127.67, 127.71, 128.2, 128.5, 129.1, 129.4, 130.36, 130.42, 130.6, 134.8, 136.2, 137.5, 139.1, 140.1, 168.1.

ESIHRMS: Found 302.1547; Calcd for C₂₁H₂₀NO: (M+H)⁺ 302.1545.

Method C: For synthesis of biaryl secondary amide 4.20d to 4.20e

Typical Synthesis for 4.20d

Pinnick oxidation:^[15] To a solution of 4'-Methoxy-2'-methyl[1,1'-biphenyl]-2-carboxaldehyde (792 mg, 3.50 mmol) in *t*-BuOH (60 mL) was added 2-methyl-2-butene (2.7 mL, 25.5 mmol), aqueous solution containing NaClO₂ (80%, 30 mL, 3.44 g, 30.4 mmol) and NaH₂PO₄•2H₂O (3.76 g, 24.1 mmol) was added dropwise over a period of 15 min. The reaction mixture was stirred for 24 h at room temperature before removing the volatile materials in vacuo. The

resulting residue was diluted with water (20 mL) and the solution was acidified to pH 1 with 1M aqueous HCl solution. The organic materials were extracted with EtOAc (3x 30 mL) and the combined extracts were washed with brine and dried over MgSO₄. The volatile materials were removed in vacuo to afford the crude material containing carboxylic acid, which was used for the next amide formation without purification.

Amide formation: The crude carboxylic acid obtained above was treated with (COCl₂) (2.22 g, 17.5 mmol) in CH₂Cl₂ (10 mL) in the presence of 3 drops of DMF and the mixture was stirred at room temperature for 4 h. The volatile materials were then removed in vacuo and the resulting residue containing acid chloride was dissolved in 20 mL of CH₂Cl₂, which was added dropwise into a solution of Et₃N (1.0 mL, 7.0 mmol) and MeNH₂ (1.36 g, 40% wt% in H₂O, 17.5 mmol) in CH₂Cl₂ (20 mL) at 0 °C. The reaction mixture was stirred overnight at room temperature. After removal of the volatile materials in vacuo, the resulting crude residue was dispersed in 1 M aqueous HCl solution and EtOAc. The organic phase was separated and the organic materials were extracted twice with EtOAc from the aqueous phase. The combined extracts were washed with brine and dried over MgSO₄. The solvent was removed in vacuo to provide the crude residue, which was purified by flash column chromatography (silica gel, hexane:ethyl acetate = 3:1) to give N-methyl amide **4.20d** (813 mg, 3.19 mmol) in 91% yield (2 steps).

¹H NMR (400 MHz, CDCl₃): δ = 2.09 (s, 3H), 2.65 (d, *J* = 4.9 Hz, 3H), 3.84 (s, 3H), 5.34 (br s, 1H), 6.79-6.83 (m, 2H), 7.11 (d, *J* = 8.1 Hz, 1H), 7.17 (d, *J* = 7.2 Hz, 1H), 7.39-7.47 (m, 2H), 7.89-7.93 (m, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 20.3, 26.8, 55.2, 111.4, 115.8, 127.5, 129.2, 130.20, 130.23, 130.9, 132.5, 135.1, 137.6, 138.8, 159.3, 169.1.

ESIHRMS: Found 256.1341; Calcd for C₁₆H₁₈NO₂: (M+H)⁺ 256.1388.

Typical Biaryl Aldehyde Synthesis Procedure (for synthesis of **4.20d**, **4.20e** and **4.20f**)

4'-Methoxy-2'-methyl[1,1'-biphenyl]-2-carboxaldehyde

Suzuki coupling:^[16] To a solution of 2-bromobenzaldehyde (925 mg, 5.00 mmol) in DME (10 mL) was added Pd(PPh₃)₄ (60 mg, 0.052 mmol), and the solution was stirred for 20 min before adding 2-methyl-4-methoxyphenyl boronic ester (1.29 g, 5.50 mmol) (preparation method was described below) and EtOH (16 mL). After the mixture was stirred for 20 min, aqueous Na₂CO₃ solution (2M, 5 mL) was added, and the reaction mixture was stirred at reflux temperature for 14 h. The mixture was cooled down to room temperature, and the resulting precipitate was filtered off. The volatile materials were removed from the filtrate in vacuo. The resulting residue was dissolved in EtOAc (30 mL), and the solution was washed with water (3 × 10 mL), and dried over MgSO₄. After evaporation of the solvent under reduced pressure, the resulting crude material was purified by flash chromatography (silica gel, hexane:ethyl acetate = 10:1) to afford 4'-Methoxy-2'-methyl[1,1'-biphenyl]-2-carboxaldehyde (1.09 g, 4.80 mmol) in 96% yield.

¹H NMR (400 MHz, CDCl₃): δ = 2.09 (s, 3H), 3.84 (s, 3H), 6.80-6.85 (m, 2H), 7.10 (d, *J* = 8.2 Hz, 1H), 7.28 (s, 1H), 7.45 (dd, *J* = 7.7 Hz, 7.5 Hz, 1H), 7.61 (dd, *J* = 8.2 Hz, 6.8 Hz, 1H), 8.00 (d, *J* = 7.7 Hz, 1H), 9.78 (s, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 20.6, 55.3, 111.1, 115.6, 127.1, 127.6, 129.8, 131.3, 131.4, 133.6, 134.3, 137.6, 145.5, 159.5, 192.4.

ESIHRMS: Found 227.1074; Calcd for C₁₅H₁₅O₂: (M+H)⁺ 227.1072.

2-(4-methoxy-2-methylphenyl)-5,5-dimethyl-1,3,2-dioxaborinane

A solution of 4-methoxy-2-methylphenylboronic acid (1.66 g, 10.0 mmol) and 2,2-dimethylpropane-1,3-diol (1.15 g, 11.0 mmol) in toluene (60 mL) was stirred under reflux conditions for 3 h with a Dean-Stark apparatus. The solvent was removed under reduced pressure and the resulting residue was purified by flash chromatography (silica gel, hexane:ethyl acetate = 10:1) to afford 2-(4-methoxy-2-methylphenyl)-5,5-dimethyl-1,3,2-dioxaboronane (2.13 g, 9.10 mmol) in 91% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.03 (s, 6H), 2.51 (s, 3H), 3.76 (s, 4H), 3.80 (s, 3H), 6.70-6.72 (m, 2H), 7.71 (d, *J* = 9.0 Hz, 1H).

^{13}C NMR (100 MHz, CDCl_3): δ = 21.9, 22.6, 31.6, 55.0, 72.2, 110.0, 115.7, 136.8, 146.4, 161.1.

ESIHRMS: Found 235.1506; Calcd for $\text{C}_{13}\text{H}_{19}\text{BO}_3$: $(\text{M}+\text{H})^+$ 235.1506.

N,2',5-trimethyl-[1,1'-biphenyl]-2-carboxamide (4.20e)

Prepared by following **Method C** with the slight modification using SOCl_2 (10 mL) for acid chloride formation from 2',5-dimethyl-[1,1'-biphenyl]-2-carbaldehyde (947 mg, 4.50 mmol, see below) to give **4.20e** (1.02 g, 4.26 mmol) in 95% yield.

^1H NMR (400 MHz, CDCl_3): δ = 2.08 (s, 3H), 2.36 (s, 3H), 2.57 (d, J = 4.8 Hz, 3H), 5.36 (br s, 1H), 6.97 (s, 1H), 7.14-7.28 (m, 5H), 7.78 (d, J = 8.0 Hz, 1H).

^{13}C NMR (100 MHz, CDCl_3): δ = 20.0, 21.3, 26.6, 126.1, 128.1, 128.3, 129.0, 129.4, 130.3, 131.0, 131.9, 136.1, 139.2, 140.4, 140.5, 168.9.

ESIHRMS: Found 240.1391; Calcd for $\text{C}_{16}\text{H}_{18}\text{NO}$: $(\text{M}+\text{H})^+$ 240.1388.

2',5-dimethyl-[1,1'-biphenyl]-2-carbaldehyde

Prepared by following **Typical Biaryl Aldehyde Synthesis Procedure** from 2-bromo-4-methylbenzaldehyde (995 mg, 5.00 mmol) and *o*-tolyl boronic ester (1.12 g, 5.49 mmol)^[17] to give the product (947 mg, 4.50 mmol) in 90% yield.

^1H NMR (400 MHz, CDCl_3): δ = 2.11 (s, 3H), 2.45 (s, 3H), 7.11 (s, 1H), 7.18 (d, J = 7.2 Hz, 1H), 7.24-7.34 (m, 4H), 7.94 (d, J = 8.0 Hz, 1H), 9.71 (s, 1H).

^{13}C NMR (100 MHz, CDCl_3): δ = 20.3, 21.8, 125.6, 127.2, 128.2, 128.7, 130.0, 130.1, 131.3, 131.7, 136.1, 137.7, 144.7, 145.8, 191.9.

ESIHRMS: Found 211.1122; Calcd for $\text{C}_{15}\text{H}_{15}\text{O}$: $(\text{M}+\text{H})^+$ 211.1123.

4-methoxy-N,2'-dimethyl-[1,1'-biphenyl]-2-carboxamide (4.20f)

Prepared by following **Method C** with slight modification using SOCl_2 (10 mL) for acid chloride formation from 4-methoxy-2'-methyl-[1,1'-biphenyl]-2-carbaldehyde (1.07 g, 4.73 mmol, see below) to give **4.20f** (1.12 g, 4.39 mmol) in 93% yield.

^1H NMR (400 MHz, CDCl_3): δ = 2.09 (s, 3H), 2.59 (d, J = 4.9 Hz, 3H), 3.86 (s, 3H), 5.29 (br s, 1H), 7.00 (dd, J = 8.4 Hz, 2.8 Hz, 1H), 7.10 (d, J = 8.4 Hz, 1H), 7.16 (d, J = 6.9 Hz, 1H), 7.21-7.27 (m, 3H), 7.46 (d, J = 2.8 Hz, 1H).

^{13}C NMR (100 MHz, CDCl_3): δ = 20.0, 26.7, 55.5, 113.4, 117.0, 126.2, 128.0, 129.5, 130.4, 131.4, 131.6, 135.8, 136.5, 139.9, 158.9, 168.7.

ESIHRMS: Found 256.1337; Calcd for $\text{C}_{16}\text{H}_{18}\text{NO}_2$: $(\text{M}+\text{H})^+$ 256.1338.

4-methoxy-2'-methyl-[1,1'-biphenyl]-2-carbaldehyde

Prepared by following **Typical Biaryl Aldehyde Synthesis Procedure** from 2-bromo-5-methoxybenzaldehyde (1.08 g, 4.98 mmol) and *o*-tolyl boronic ester (1.12g, 5.49 mmol), to give the product (1.07 g, 4.73 mmol) in 95% yield.

^1H NMR (400 MHz, CDCl_3): δ = 2.11 (s, 3H), 3.91 (s, 3H), 7.13-7.15 (m, 6H), 7.51 (d, J = 2.4 Hz, 1H), 9.70 (s, 1H).

^{13}C NMR (100 MHz, CDCl_3): δ = 20.4, 55.6, 109.4, 121.5, 125.6, 128.1, 130.1, 130.7, 132.0, 134.7, 136.6, 137.2, 138.7, 159.1, 192.1.

ESIHRMS: Found 227.1076; Calcd for $\text{C}_{15}\text{H}_{15}\text{O}_2$: $(\text{M}+\text{H})^+$ 227.1072.

Method D: For synthesis of α -quaternary *ortho*-substituted α -arylacetamides 4.10k-4.10n and 4.10p-4.10t

Typical Synthesis for 4.10k

To a solution of 2-methyl-2-(*o*-tolyl)propanenitrile^[18] (4.32 g, 27.2 mmol) in ethylene glycol (30 mL) and water (6 mL) was added KOH (6.10 g, 109 mmol), and the reaction mixture was stirred under reflux conditions for 16 h. After being cooled down to room temperature, the reaction mixture was diluted with water (20 mL) and the organic extracts were extracted twice with diethyl ether. The combined extracts were washed with water and brine, followingly dried over MgSO₄. After removal of the volatile materials *in vacuo*, the resulting crude residue containing primary amide was used for the next step without purification.

To an ice cold solution of the crude material obtained above in THF (40 mL) was added NaH (60% dispersion in oil, 2.07 g, 51.9 mmol) portion-wise and the mixture was stirred at the same temperature for 1 h before adding MeI (2.70 mL, 43.2 mmol). After being stirred for 16 h at room temperature, the reaction was quenched with water and the organic materials were extracted twice with diethyl ether. The combined extracts were washed with brine and dried over MgSO₄. The solvent was removed *in vacuo* to give the crude residue, which was purified by flash column chromatography (silica gel, hexane:ethyl acetate = 80:20) to give N,N-dimethyl-2-(*o*-tolyl)propanamide (**4.10k**) (2.62 g, 12.8 mmol) in 47% yield (2 steps).

¹H NMR (400 MHz, CDCl₃): δ = 1.54 (s, 6H), 2.19 (s, 3H), 2.46 (s, 3H), 2.92 (s, 3H), 7.09-7.14 (m, 2H), 7.16-7.21 (m, 1H), 7.32 (d, *J* = 9.2 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 19.8, 27.5 (br), 37.1, 38.0, 46.4, 124.1, 126.5, 126.8, 132.3, 135.8, 144.4, 176.7.

ESIHRMS: Found 206.1543; Calcd for C₁₃H₂₀NO: (M+H)⁺ 206.1545.

N,N-dimethyl-1-(*o*-tolyl)cyclohexane-1-carboxamide (**4.10l**)

Prepared by following **Method D** from 1-(*o*-tolyl)cyclohexane-1-carbonitrile (1.66 g, 8.34 mmol)^[19] to give **4.10l** (777 mg, 3.17 mmol) in 38% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.28-1.38 (m, 1H), 1.57-1.93 (m, 7H), 2.25 (s, 3H), 2.30-2.33 (m, 2H), 2.46 (br s, 3H), 2.91 (br s, 3H), 7.09-7.11 (m, 2H), 7.17-7.21 (m, 1H), 7.43 (d, J = 7.8 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 20.3, 22.9, 26.1, 35.2 (br), 37.2 (br), 38.1 (br), 50.2, 125.2, 126.2, 126.5, 132.7, 136.3, 144.5, 175.8.

ESIHRMS: Found 246.1863; Calcd for C₁₆H₂₄NO: (M+H)⁺ 246.1858.

N,N-dimethyl-4-(o-tolyl)tetrahydro-2H-pyran-4-carboxamide (4.10m)

Prepared by following **Method D** from 4-(o-tolyl)tetrahydro-2H-pyran-4-carbonitrile (534 mg, 2.65 mmol)^[20] to give **4.10n** (498 mg, 2.01 mmol) in 76% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.96-2.17 (m, 2H), 2.25 (s, 3H), 2.25-2.46 (m, 2H), 2.46 (br s, 3H), 2.93 (br s, 3H), 3.83-3.85 (m, 2H), 3.94-4.10 (m, 2H), 7.11-7.16 (m, 2H), 7.20-7.24 (m, 1H), 7.40 (d, J = 7.9 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 20.2, 34.8 (br), 37.3 (br), 37.8 (br), 48.0, 64.7, 124.9, 126.7, 126.8, 133.0, 136.3, 143.0, 174.6.

ESIHRMS: Found 248.1653; Calcd for C₁₅H₂₂NO₂: (M+H)⁺ 248.1651.

N,N-dimethyl-1-(o-tolyl)cyclopentane-1-carboxamide (4.10n)

Prepared by following **Method D** from 1-(o-tolyl)cyclopentane-1-carbonitrile (1.34 g, 7.23 mmol)^[21] to give **4.10n** (1.14 g, 4.91 mmol) in 68% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.65-1.84 (m, 4H), 1.99-2.13 (m, 2H), 2.20 (s, 3H), 2.37-2.54 (m, 2H), 2.49 (br s, 3H), 2.92 (br s, 3H), 7.08-7.12 (m, 2H), 7.13-7.18 (m, 1H), 7.27 (d, J = 7.6 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 20.4, 25.2, 37.0 (br), 37.9, 57.9, 124.7, 126.1, 126.2, 132.2, 136.2, 143.8, 176.4.

ESIHRMS: Found 232.1708; Calcd for C₁₅H₂₂NO: (M+H)⁺ 232.1701.

2-(2-ethylphenyl)-N,N,2-trimethylpropanamide (4.10p)

Prepared by following **Method D** from 2-(2-ethylphenyl)-2-methylpropanenitrile (1.47 g, 8.48 mmol) (preparation methods of this nitrile were described below) to give **4.10p** (1.02 g, 4.65 mmol) in 55% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.14 (t, J = 7.5 Hz, 3H), 1.55 (s, 6H), 2.46 (s, 3H), 2.54 (q, J = 7.5 Hz, 2H), 2.91 (s, 3H), 7.15-7.25 (m, 3H), 7.30-7.34 (m, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 15.4, 24.2, 37.2, 38.2, 46.4, 124.1, 126.4, 126.7, 130.2, 142.1, 143.6, 177.1.

ESIHRMS: Found 220.1705; Calcd for C₁₄H₂₂NO: (M+H)⁺ 220.1701.

Synthesis of 2-(2-ethylphenyl)-2-methylpropanenitrile

Conversion of benzyl alcohol to benzyl cyanide: To an ice cold solution of commercially available (2-ethylphenyl)methanol (1.74 g, 12.8 mmol) in CH₂Cl₂ (60 mL) was added PBr₃ (1.35 mL, 14.1 mmol), and the reaction mixture was stirred at the same temperature for 1 h. The reaction was carefully quenched with water and the organic material was extracted twice with diethyl ether. The combined organic extracts were then washed with brine and dried over MgSO₄. The solvent was removed *in vacuo* to provide the crude material containing benzyl bromide, which was dissolved in EtOH (20 mL) and H₂O (4 mL). To the solution was added KCN (919 mg, 14.1 mmol), and the reaction mixture was stirred under reflux conditions for 3 h. After the reaction mixture was cooled down to room temperature, the volatile materials were then removed *in vacuo*. The resulting residue was diluted with water and the organic materials were extracted twice with diethyl ether. The combined extracts were then washed with brine and dried over MgSO₄. The solvents were removed *in vacuo* and

the resulting crude material was purified by flash column chromatography (silica gel, hexane:ethyl acetate = 94:6) to give 2-(2-ethylphenyl)acetonitrile (1.29 g, 8.85 mmol) in 69% yield (2 steps).

¹H NMR (400 MHz, CDCl₃): δ = 1.27 (t, J = 7.6 Hz, 3H), 2.67 (q, J = 7.6 Hz, 2H), 3.71 (s, 2H), 7.21-7.26 (m, 2H), 7.29-7.33 (m, 3H), 7.37 (d, J = 7.8 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 14.5, 21.4, 25.7, 118.0, 126.7, 127.9, 128.7, 128.9, 129.0, 141.9.

ESIHRMS: Found 146.0973; Calcd for C₁₀H₁₂N: (M+H)⁺ 146.0970.

Typical Dimethylation Procedure (for synthesis of precursor for 4.10p-4.10t)

General Procedure for Dimethylation of Benzyl Cyanide: To an ice cold solution of 2-(2-ethylphenyl)acetonitrile (1.29 g, 8.85 mmol) in THF (40 mL) was added NaH (60% dispersion in mineral oil, 1.06 g, 26.6 mmol) portion-wise and the reaction mixture was stirred at the same temperature for 1 h. To the solution was then added MeI (1.4 mL, 22.1 mmol), and the reaction mixture was stirred under reflux conditions for 8 h. The reaction was quenched with water and the organic materials were extracted twice with diethyl ether. The combined extracts were then washed with brine and dried over MgSO₄. The solvent was removed *in vacuo* to provide the crude residue, which was purified by flash column chromatography (silica gel, hexane:ethyl acetate = 95:5) to give 2-(2-ethylphenyl)-2-methylpropanenitrile (1.47 g, 8.48 mmol) in 96% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.36 (t, J = 7.5 Hz, 3H), 1.80 (s, 6H), 3.00 (q, J = 7.5 Hz, 2H), 7.18-7.22 (m, 1H), 7.28-7.34 (m, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 16.1, 25.7, 29.0, 34.7, 124.6, 125.2, 126.2, 128.3, 131.0, 137.6, 142.8.

ESIHRMS: Found 174.1278; Calcd for C₁₂H₁₆N: (M+H)⁺ 174.1283.

2-(2-benzylphenyl)-N,N,2-trimethylpropanamide (4.10q)

Prepared by following **Method D** from 2-(2-benzylphenyl)-2-methylpropanenitrile (1.89 g, 8.01 mmol) (preparation methods of this nitrile were described below) to give **4.10q** (1.61 g, 5.71 mmol) in 71% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.60 (s, 6H), 2.44 (s, 3H), 2.55 (s, 3H), 3.98 (s, 2H), 7.04-7.08 (m, 3H), 7.14-7.20 (m, 2H), 7.23-7.28 (m, 3H), 7.42 (dd, J = 7.9 Hz, 1.3 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 36.7, 37.4, 38.0, 46.4, 124.5, 125.9, 126.5, 127.1, 128.2, 128.8, 132.9, 138.0, 140.9, 144.5, 176.4.

ESIHRMS: Found 282.1860; Calcd for C₁₉H₂₄NO (M+H)⁺ 282.1858.

Synthesis of 2-(2-benzylphenyl)-2-methylpropanenitrile

Prepared by the **Typical Dimethylation Procedure** described above from 2-(2-benzylphenyl)acetonitrile^[22] (1.78 g, 8.59 mmol) to give the product (1.89 g, 8.01 mmol) in 93% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.82 (s, 6H), 4.45 (s, 2H), 7.10-7.12 (m, 1H), 7.15-7.17 (m, 2H), 7.21-7.33 (m, 5H), 7.38-7.41 (m, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 29.0, 34.9, 38.6, 124.9, 125.1, 126.3, 126.9, 128.2, 128.6, 129.4, 132.9, 138.2, 139.3, 140.9.

ESIHRMS: Found 236.1438; Calcd for C₁₇H₁₈N: (M+H)⁺ 236.1439.

2-(2,6-dimethylphenyl)-N,N,2-trimethylpropanamide (4.10r)

Prepared by following **Method D** from 2-(2,6-dimethylphenyl)-2-methylpropanenitrile (675 mg, 3.90 mmol) (preparation methods of this nitrile were described below) to give **4.10r** (537 mg, 2.45 mmol) in 63% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.66 (s, 6H), 2.35 (s, 6H), 2.48 (s, 3H), 2.92 (s, 3H), 6.93-6.99 (m, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 23.2, 28.1, 36.7, 38.1, 48.6, 125.9, 131.4, 135.7, 142.4, 178.4.

ESIHRMS: Found 220.1703; Calcd for C₁₄H₂₂NO: (M+H)⁺ 220.1701.

Synthesis of 2-(2,6-dimethylphenyl)-2-methylpropanenitrile

Prepared according to the **Typical Dimethylation Procedure** described above from 2-(2,6-dimethylphenyl)acetonitrile^[23] (1.01 g, 6.98 mmol) to give the product (675 mg, 3.90 mmol) in 56% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.95 (s, 6H), 2.59 (s, 6H), 7.01-7.09 (m, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 24.4, 29.5, 37.9, 126.4, 127.2, 131.6, 136.2, 136.8.

ESIHRMS: Found 174.1280; Calcd for C₁₂H₁₆N: (M+H)⁺ 174.1283.

2-(4-methoxy-2-methylphenyl)-N,N,2-trimethylpropanamide (4.10s)

Prepared by following **Method D** from 2-(4-methoxy-2-methylphenyl)-2-methylpropanenitrile (1.32 g, 6.97 mmol) (preparation methods of this nitrile were described below) to give **4.10s** (675 mg, 2.87 mmol) in 41% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.49 (s, 6H), 2.14 (s, 3H), 2.47 (s, 3H), 2.89 (s, 3H), 3.74 (s, 3H), 6.64 (d, J = 2.8 Hz, 1H), 6.69 (dd, J = 8.6 Hz, 2.8 Hz, 1H), 7.20 (d, J = 8.6 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 19.8, 27.8 (br), 37.0, 37.9, 45.6, 55.0, 111.4, 117.6, 125.1, 136.6, 137.0, 157.7, 176.8.

ESIHRMS: Found 236.1652; Calcd for C₁₄H₂₂NO₂: (M+H)⁺ 236.1651.

2-(4-methoxy-2-methylphenyl)-2-methylpropanenitrile

Prepared according to the **Typical Dimethylation Procedure** described above from commercially available 2-(4-methoxy-2-methylphenyl)acetonitrile (2.42 g, 15.0 mmol) to give the product (1.39 g, 7.34 mmol) in 49% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.76 (s, 6H), 2.62 (s, 3H), 3.80 (s, 3H), 6.72 (dd, J = 8.8 Hz, 2.6 Hz, 1H), 6.77 (d, J = 2.6 Hz, 1H), 7.21 (d, J = 8.8 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 21.4, 28.5, 34.5, 55.3, 111.2, 118.2, 124.9, 126.1, 130.4, 138.0, 159.0.

ESIHRMS: Found 190.1243; Calcd for C₁₂H₁₆NO: (M+H)⁺ 190.1232.

2-(4-fluoro-2-methylphenyl)-N,N,2-trimethylpropanamide (4.10t)

Prepared by following **Method D** from 2-(4-fluoro-2-methylphenyl)-2-methylpropanenitrile (886 mg, 5.00 mmol) (preparation methods of this nitrile were described below) to give **4.10t** (837 mg, 3.75 mmol) in 75% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.50 (s, 6H), 2.15 (s, 3H), 2.45 (s, 3H), 2.89 (s, 3H), 6.79 (dd, *J*_{H-F} = 9.7 Hz, *J*_{H-H} = 2.7 Hz, 1H), 6.84 (ddd, *J*_{H-F} = 11.1 Hz, *J*_{H-H} = 8.6 Hz, *J*_{H-H} = 2.7 Hz, 1H), 7.25 (dd, *J*_{H-H} = 8.6 Hz, *J*_{H-F} = 5.8 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 19.7 (d, *J* = 1.4 Hz), 27.6 (br), 37.0, 37.9, 45.8, 113.0 (d, *J* = 20.3 Hz), 118.5 (d, *J* = 20.5 Hz), 125.6 (d, *J* = 8.0 Hz), 138.1 (d, *J* = 7.2 Hz), 140.1 (d, *J* = 3.2 Hz), 161.0 (d, *J* = 243.4 Hz), 176.2.

¹⁹F NMR (CDCl₃, 282 MHz): δ = -117.7 (m).

ESIHRMS: Found 224.1450; Calcd for C₁₃H₁₉NOF: (M+H)⁺ 224.1451.

2-(4-fluoro-2-methylphenyl)-2-methylpropanenitrile

Prepared according to the **Typical Dimethylation Procedure** described above from commercially available 2-(4-fluoro-2-methylphenyl)acetonitrile (1.49 g, 10.0 mmol) to give the product (1.44 g, 8.13 mmol) in 81% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.77 (s, 6H), 2.64 (s, 3H), 6.86-6.96 (m, 2H), 7.26 (dd, *J*_{H-H} = 8.8 Hz, *J*_{H-F} = 5.7 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 21.3, 28.4, 34.6, 113.0 (d, *J* = 20.9 Hz), 119.3 (d, *J* = 21.1 Hz), 124.4, 126.6 (d, *J* = 8.6 Hz), 134.0 (d, *J* = 3.2 Hz), 139.1 (d, *J* = 7.8 Hz), 162.1 (d, *J* = 248.3 Hz).

¹⁹F NMR (CDCl₃, 282 MHz): δ = -115.4 (m, 1F).

ESIHRMS: Found 178.1037; Calcd for C₁₁H₁₃NF: (M+H)⁺ 178.1032.

Method E: For synthesis of 4.10i

To a solution of diisopropylamine (0.84 mL, 6.0 mmol) in THF (10 mL) at -78°C was added *n*-BuLi (1.55 M in hexane, 3.9 mL, 6.0 mmol) was added slowly and the mixture was stirred for 30 min. To the mixture was added a solution of N,N-dimethyl-2,2-diphenylacetamide^[7] (957 mg, 4.00 mmol) in THF (5 mL) dropwise. After being stirred at the same temperature for 30 min, MeI (0.40 mL, 6.0 mmol) was added dropwise, and the reaction mixture was slowly warmed up to room temperature with stirring for 2 h. The reaction mixture was then quenched with saturated aqueous NH₄Cl solution and the organic materials were extracted twice with diethyl ether. The combined extracts were washed with brine and dried over MgSO₄. The solvent was removed *in vacuo* to give the crude residue, which was purified by flash column chromatography (silica gel, hexane:ethyl acetate = 80:20) to afford N,N-dimethyl-2,2-diphenylpropanamide (**4.10i**) (962 mg, 3.80 mmol) in 95% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.90 (s, 3H), 2.39 (br s, 3H), 3.00 (br s, 3H), 7.22-7.27 (m, 2H), 7.29-7.36 (m, 8H).

¹³C NMR (100 MHz, CDCl₃): δ = 32.7, 37.3(br), 39.2 (br), 57.1, 126.6, 127.8, 128.4, 143.5, 174.6.

ESIHRMS: Found 254.1550; Calcd for C₁₇H₂₀NO: (M+H)⁺ 254.1545;

5.4.2 Synthesis of arylaldehydes having *ortho*-secondary aliphatic groups

Typical Procedure for synthesis of 4.11a

To a mixture of NaH (60% dispersion in mineral oil; 60.0 mg, 1.50 mmol) and NaI (150 mg, 1.00 mmol) in a 25 mL sealed tube was added a solution of amide **4.10a** (121 mg, 0.500

mmol) in 2.5 mL of THF, and the reaction mixture was sealed and stirred at 85 °C for 14 h. The reaction was quenched with water at 0 °C and the organic materials were extracted with diethyl ether (20 mL × 3). The combined extracts were washed with brine and dried over MgSO₄. The volatile materials were removed *in vacuo* and the resulting crude residue was purified by flash column chromatography (silica gel, hexane:ethyl acetate = 95:5) to give 3-isopropyl-2-naphthaldehyde (**4.11a**) (63.4 mg, 0.320 mmol) in 64% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.39 (d, *J* = 6.9 Hz, 6H), 4.10 (sept, *J* = 6.9 Hz, 1H), 7.51 (dd, *J* = 8.2 Hz, 6.8 Hz, 1H), 7.60 (dd, *J* = 8.2 Hz, 6.8 Hz, 1H), 7.82 (s, 1H), 7.84 (d, *J* = 8.2 Hz, 1H), 7.94 (d, *J* = 8.2 Hz, 1H), 8.32 (s, 1H), 10.39 (s, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 23.9, 28.2, 124.9, 126.3, 127.5, 129.08, 129.11, 131.0, 132.2, 136.0, 136.3, 146.1, 192.9.

ESIHRMS: Found 199.1122; Calcd for C₁₄H₁₅O: (M+H)⁺ 199.1123.

2-isopropyl-5-methoxybenzaldehyde (**4.11b**)

Prepared from **4.10b** (111 mg, 0.500 mmol) to give **4.11b** (47.8 mg, 0.268 mmol) in 54% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.29 (d, *J* = 6.9 Hz, 6H), 3.84 (s, 3H), 3.85 (sept, *J* = 6.9 Hz, 1H), 7.11 (dd, *J* = 8.7 Hz, 2.9 Hz, 1H), 7.33 (d, *J* = 2.9 Hz, 1H), 7.35 (d, *J* = 8.7 Hz, 1H), 10.39 (s, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 24.3, 27.1, 55.6, 113.2, 121.5, 127.5, 133.8, 144.1, 157.9, 191.6.

4-isopropyl-[1,1'-biphenyl]-3-carbaldehyde (**4.11c**)

Prepared from **4.10c** (134 mg, 0.500 mmol) to give **4.11c** (74.9 mg, 0.334 mmol) in 67% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.36 (d, *J* = 6.9 Hz, 6H), 4.01 (sept, *J* = 6.9 Hz, 1H), 7.38 (tt, *J* = 7.5 Hz, 1.2 Hz, 1H), 7.44-7.49 (m, 2H), 7.54 (d, *J* = 8.2 Hz, 1H), 7.61-7.63 (m, 2H), 7.79 (dd, *J* = 8.2 Hz, 2.1 Hz, 1H), 8.06 (d, *J* = 2.1 Hz, 1H), 10.44 (s, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 23.9, 27.5, 126.8, 126.9, 127.7, 128.9, 129.8, 132.4, 133.3, 139.1, 139.7, 150.3, 192.2.

ESIHRMS: Found 225.1283; Calcd for C₁₆H₁₇O: (M+H)⁺ 225.1279.

3-isopropyl-[1,1'-biphenyl]-4-carbaldehyde (4.11d)

Prepared from **4.10d** (134 mg, 0.500 mmol) to give **4.11d** (55.0 mg, 0.245 mmol) in 49% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.38 (d, J = 6.8 Hz, 6H), 4.05 (sept, J = 6.8 Hz, 1H), 7.42 (t, J = 7.3 Hz, 1H), 7.47-7.51 (m, 2H), 7.57 (dd, J = 8.0 Hz, 1.8 Hz, 1H), 7.64 (s, 1H), 7.64-7.67 (m, 2H), 7.90 (d, J = 8.0 Hz, 1H), 10.40 (s, 1H):

¹³C NMR (100 MHz, CDCl₃): δ = 23.9, 27.9, 124.9, 125.0, 127.4, 128.3, 129.0, 131.9, 132.3, 140.2, 146.7, 151.9, 191.9:

ESIHRMS: Found 225.1281; calcd for C₁₆H₁₇O: (M+H)⁺ 225.1279.

2-isopropyl-[1,1'-biphenyl]-3-carbaldehyde (4.11e)

Prepared from **4.10e** (134 mg, 0.500 mmol) to give **4.11e** (60.6 mg, 0.270 mmol) in 54% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.41 (d, J = 7.4 Hz, 6H), 3.40 (sept, J = 7.4 Hz, 1H), 7.28 (m, 2H), 7.36 (t, J = 7.5 Hz, 1H), 7.40-7.48 (m, 4H), 8.00 (dd, J = 7.5 Hz, 1.7 Hz, 1H), 10.77 (s, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 24.6, 30.3, 125.8, 127.2, 128.2, 129.0, 129.4, 135.6, 135.8, 141.9, 143.2, 148.5, 192.3.

ESIHRMS: Found 225.1280; Calcd for C₁₆H₁₇O: (M+H)⁺ 225.1279.

10,10-dimethyl-9,10-dihydrophenanthren-9-ol (4.15)

Prepared from **4.10e** (134 mg, 0.500 mmol) to give **4.15** (11.2 mg, 0.050 mmol) in 10% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.18 (s, 3H), 1.40 (s, 3H), 4.42 (d, J = 5.6 Hz, 1H), 7.31-7.36 (m, 3H), 7.41 (dd, J = 7.7 Hz, 7.5 Hz, 1H), 7.45-7.48 (m, 2H), 7.78-7.82 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ = 22.6, 26.5, 39.5, 123.8, 124.1, 125.8, 127.0, 127.7,

128.0, 128.5, 128.7, 132.1, 132.7, 137.1, 142.6.

ESIHRMS: Found 225.1280; Calcd for $C_{16}H_{17}O$: $(M+H)^+$ 225.1279.

Derivatization of 4.15 for the structural confirmation: The structure of **4.15** was confirmed by converting **4.15** into the known ketone (see below). The 1H and ^{13}C NMR spectra of the ketone were identical to those reported.^[24]

To a suspension of PCC (21.6 mg, 0.100 mmol) and celite (0.50 g) in CH_2Cl_2 (3 mL) was added a solution of **4.15** (11.2 mg, 0.050 mmol) in CH_2Cl_2 (2 mL), and the mixture was stirred at room temperature for 3 h. The solid materials were filtered off and the filtrate was evaporated under reduced pressure. The resulting crude product was purified by flash column chromatography (silica gel, hexane:ethyl acetate = 95:5) to give the corresponding ketone, 10,10-dimethylphenanthren-9(10H)-one (10.1 mg, 0.046 mmol) in 92% yield.

1H NMR (400 MHz, $CDCl_3$): δ = 1.55 (s, 6H), 7.35-7.39 (m, 2H), 7.43 (ddd, J = 8.3 Hz, 7.4 Hz, 1.1 Hz, 1H), 7.51-7.53 (m, 1H), 7.67 (ddd, J = 8.4 Hz, 7.3 Hz, 1.5 Hz, 1H), 7.98-8.03 (m, 2H), 8.08 (dd, J = 7.8 Hz, 1.5 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.3, 47.4, 122.9, 124.0, 126.3, 127.0, 127.8, 128.1, 128.9, 129.1, 134.2, 137.1, 144.0, 203.2.

2-isopropylnicotinaldehyde (**4.11f**)

Prepared from **4.10f** (96.1 mg, 0.500 mmol) to give **4.11f** (38.0 mg, 0.255 mmol) in 51% yield.

1H NMR (400 MHz, $CDCl_3$): δ = 1.35 (d, J = 6.8 Hz, 6H), 3.92 (sept, J = 6.8 Hz, 1H), 7.28 (dd, J = 7.8 Hz, 4.7 Hz, 1H), 8.09 (dd, J = 7.8 Hz, 1.9 Hz, 1H), 8.74 (dd, J = 4.7 Hz, 1.9 Hz, 1H), 10.42 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.3, 30.7, 121.5, 128.3, 137.6, 153.5, 168.7, 191.0.

ESIHRMS: Found 150.0921.; Calcd for $C_9H_{12}NO$: $(M+H)^+$ 150.0919.

3-cyclohexyl-2-naphthaldehyde (**4.11g**)

Prepared from **4.10g** (141 mg, 0.500 mmol) to give **4.11g** (71.2 mg, 0.299 mmol) in 60% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.25-1.36 (m, 1H), 1.48-1.60 (m, 4H), 1.80-2.30 (m, 5H), 3.62-3.68 (m, 1H), 7.49 (dd, J = 8.1 Hz, 6.9 Hz, 1H), 7.59 (dd, J = 8.2 Hz, 6.9 Hz, 1H), 7.78 (s, 1H), 7.82 (d, J = 8.2 Hz, 1H), 7.93 (d, J = 8.1 Hz, 1H), 8.32 (s, 1H), 10.38 (s, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 26.4, 27.1, 34.7, 38.6, 125.4, 126.3, 127.6, 129.1, 129.2, 131.0, 132.2, 136.0, 145.4, 193.0.

ESIHRMS: Found 239.1435; Calcd for C₁₇H₁₉O: (M+H)⁺ 239.1436.

3-(tetrahydro-2H-pyran-4-yl)-2-naphthaldehyde (**4.11h**)

Prepared from **4.10g** (141 mg, 0.500 mmol) to give **4.11h** (49.3 mg, 0.205 mmol) in 41% yield;

¹H NMR (400 MHz, CDCl₃): δ = 1.84-1.96 (m, 4H), 3.68 (ddd, J = 11.4 Hz, 9.4 Hz, 3.6 Hz, 2H), 3.98-4.07 (m, 1H), 4.13 (ddd, J = 11.4 Hz, 5.9 Hz, 2.8 Hz, 2H), 7.54 (dd, J = 8.2 Hz, 6.8 Hz, 1H), 7.63 (dd, J = 8.2 Hz, 6.8 Hz, 1H), 7.80 (s, 1H), 7.86 (d, J = 8.2 Hz, 1H), 7.96 (d, J = 8.2 Hz, 1H), 8.30 (s, 1H), 10.30 (s, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 34.0, 36.0, 68.5, 125.8, 126.6, 127.6, 129.0, 129.4, 131.1, 132.1, 135.8, 138.5, 143.0, 193.3.

ESIHRMS: Found 241.1230; Calcd for C₁₆H₁₇O₂: (M+H)⁺ 241.1229.

2-(1-phenylethyl)benzaldehyde (**4.11i**)

Prepared from **4.10i** (127 mg, 0.500 mmol) to give **4.11i** (68.6 mg, 0.326 mmol) in 65% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.67 (d, J = 7.2 Hz, 3H), 5.25 (q, J = 7.2 Hz, 1H), 7.17-7.22 (m, 3H), 7.27-7.30 (m, 2H), 7.36-7.39 (m, 2H), 7.53 (ddd, J = 9.6 Hz, 7.8 Hz, 1.5 Hz, 1H), 7.82 (dd, J = 8.2 Hz, 1.5 Hz, 1H), 10.32 (s, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 22.3, 39.0, 126.3, 126.7, 127.9, 128.5, 128.6, 132.1, 133.4, 134.0, 145.7, 148.7, 192.5.

ESIHRMS: Found 211.1131; Calcd for C₁₅H₁₅O: (M+H)⁺ 211.1123.

2-benzhydryl-N,N-dimethylbenzamide (4.11j)

Prepared from **4.10j** (158 mg, 0.500 mmol) to give **4.11j** (96.2 mg, 0.305 mmol) in 61% yield (reaction time: 18 h).

¹H NMR (400 MHz, CDCl₃): δ = 2.09 (s, 3H), 2.87 (s, 3H), 5.90 (s, 1H), 7.03 (d, *J* = 7.7 Hz, 1H), 7.13-7.29 (m, 13H).

¹³C NMR (100 MHz, CDCl₃): δ = 34.1, 38.3, 52.6, 126.0, 126.1, 126.4 (br), 128.3, 128.5, 129.6 (br), 129.8 (br), 129.9, 137.3, 141.4, 171.0.

ESIHRMS: Found 316.1702; Calcd for C₂₂H₂₂NO: (M+H)⁺ 316.1701.

5.4.3 Synthesis of 2-indanones

Typical Procedure for synthesis of 4.11k^[25]

To a mixture of NaH (60% dispersion in mineral oil; 60.0 mg, 1.50 mmol) and Lil (134 mg, 1.00 mmol) in a 25 mL sealed tube was added a solution of α-arylamide **4.10k** (103 mg, 0.500 mmol) in 2.5 mL of THF. The reaction mixture was sealed and stirred at 85 °C for 3 h. The reaction was then quenched with water at 0 °C and the organic materials were extracted with diethyl ether (20 mL × 3). The combined extracts were washed with brine and dried over MgSO₄. The volatile materials were removed *in vacuo* and the resulting crude residue was purified by flash column chromatography (silica gel, hexane:ethyl acetate = 95:5) to give **4.11k** (67.1 mg, 0.419 mmol) in 84% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.33 (s, 6H), 3.59 (s, 2H), 7.23-7.28 (m, 2H), 7.29-7.33 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ = 25.3, 41.6, 50.2, 123.1, 124.8, 127.3, 127.7, 134.8, 148.3, 220.5.

spiro[cyclohexane-1,1'-inden]-2'(3'H)-one (4.11l)

Prepared from **4.10l** (123 mg, 0.500 mmol) to give **4.11l** (86.1 mg, 0.430 mmol) in 86% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.43-1.93 (m, 10H), 3.55 (s, 2H), 7.22-7.36 (m, 4H).

¹³C NMR (100 MHz, CDCl₃): δ = 21.6, 25.5, 34.4, 42.2, 52.8, 123.9, 124.7, 127.1, 127.5, 135.3, 148.7, 219.8.

ESIHRMS: Found 201.1282; Calcd for C₁₄H₁₇O: (M+H)⁺ 201.1279.

2',3',5',6'-tetrahydrospiro[indene-1,4'-pyran]-2(3H)-one (4.11m)

Prepared from **4.10m** (124 mg, 0.500 mol) to give **4.11m** (70.6 mg, 0.349 mmol) in 70% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.72-1.76 (m, 2H), 1.91 (ddd, J = 14.2 Hz, 11.0 Hz, 4.3 Hz, 2H), 3.59 (s, 2H), 3.88 (ddd, J = 14.7 Hz, 11.5 Hz, 4.3 Hz, 2H), 4.08 (ddd, J = 14.2 Hz, 11.5 Hz, 2.7 Hz, 2H), 7.25-7.35 (m, 4H).

¹³C NMR (100 MHz, CDCl₃): δ = 34.0, 42.1, 49.7, 63.6, 123.5, 124.8, 127.6, 128.0, 135.2, 147.1, 219.1.

ESIHRMS: Found 203.1072; Calcd for C₁₃H₁₅O₂: (M+H)⁺ 203.1072.

spiro[cyclopentane-1,1'-inden]-2'(3'H)-one (4.11n)^[25]

Prepared from **4.10n** (116 mg, 0.500 mol) to give **4.11n** (78.9 mg, 0.424 mmol) in 85% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.68-1.74 (m, 2H), 1.84-1.92 (m, 4H), 2.04-2.11 (m, 2H), 3.51 (s, 2H), 7.16-7.27 (m, 4H).

¹³C NMR (100 MHz, CDCl₃): δ = 27.1, 39.8, 42.3, 60.6, 123.2, 124.4, 127.0, 128.0, 135.5, 149.1, 221.2.

1-benzyl-1-methyl-1,3-dihydro-2H-inden-2-one (4.11o)

Prepared from **4.10o** (141 mg, 0.500 mmol) to give **4.11o** (77.9 mg, 0.330 mmol) in 66% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.44 (s, 3H), 2.79 (d, J = 22.9 Hz, 1H), 2.92 (d, J = 13.1 Hz, 1H), 3.09 (d, J = 13.1 Hz, 1H), 3.27 (d, J = 22.9 Hz, 1H), 6.73-6.77 (m, 2H), 7.03-7.12 (m, 4H), 7.20-7.24 (m, 2H), 7.32 (dd, J = 7.7 Hz, 6.7 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 23.8, 42.9, 46.8, 56.1, 124.2, 124.6, 126.5, 127.4, 127.5, 127.8, 130.0, 136.2, 136.6, 145.6, 220.6.

ESIHRMS: Found 237.1288; Calcd for C₁₇H₁₇O: (M+H)⁺ 237.1279.

1,1,3-trimethyl-1,3-dihydro-2H-inden-2-one (4.11p)

Prepared from **4.10p** (65.8 mg, 0.300 mmol) using NaI (89.9 mg, 0.600 mmol) as an additive to give **4.11p** (26.0 mg, 0.149 mmol) in 50% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.31 (s, 3H), 1.33 (s, 3H), 1.42 (d, J = 7.6 Hz, 3H), 3.55 (q, J = 7.6 Hz, 1H), 7.24-7.31 (m, 4H).

¹³C NMR (100 MHz, CDCl₃): δ = 16.0, 25.1, 26.6, 45.5, 49.5, 123.0, 124.0, 127.5, 127.8, 140.8, 143.0, 147.2, 223.3.

ESIHRMS: Found 175.1128; Calcd for C₁₂H₁₅O: (M+H)⁺ 175.1123.

1,1-dimethyl-3-phenyl-1,3-dihydro-2H-inden-2-one (4.11q)

Prepared from **4.10q** (141 mg, 0.500 mmol) to give **4.11q** (108 mg, 0.455 mmol) in 91% yield.

¹H NMR (400 MHz, CDCl₃): δ = 1.34 (s, 3H), 1.40 (s, 3H), 4.74 (s, 1H), 7.10-7.13 (m, 2H), 7.18-7.21 (m, 1H), 7.23-7.40 (m, 6H).

¹³C NMR (100 MHz, CDCl₃): δ = 26.0, 26.3, 49.9, 57.8, 123.0, 125.9, 127.3, 127.8, 128.4, 128.7, 128.8, 138.5, 138.7, 148.1, 219.3.

ESIHRMS: Found 237.1285; Calcd for $C_{17}H_{17}O$: $(M+H)^+$ 237.1279.

1,1,7-trimethyl-1,3-dihydro-2H-inden-2-one (4.11r)

Prepared from **4.10r** (110 mg, 0.500 mmol) to give **4.11r** (82.8 mg, 0.475 mmol) in 95% yield.

1H NMR (400 MHz, $CDCl_3$): δ = 1.41 (s, 6H), 2.42 (s, 3H), 3.58 (s, 2H), 7.05-7.08 (m, 1H), 7.13-7.18 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.1, 23.6, 41.8, 51.4, 122.6, 127.2, 130.3, 134.7, 135.4, 145.3, 221.0.

ESIHRMS: Found 175.1124; Calcd for $C_{12}H_{15}O$: $(M+H)^+$ 175.1123.

5-methoxy-1,1-dimethyl-1,3-dihydro-2H-inden-2-one (4.11s)

Prepared from **4.10s** (118 mg, 0.500 mmol) to give **4.11s** (76.1 mg, 0.400 mmol) in 80% yield.

1H NMR (400 MHz, $CDCl_3$): δ = 1.30 (s, 6H), 3.57 (s, 2H), 3.81 (s, 3H), 6.85-6.88 (m, 2H), 7.15 (d, J = 9.1 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.6, 41.9, 49.7, 55.4, 109.9, 114.0, 124.0, 136.0, 140.5, 159.0, 220.5.

ESIHRMS: Found 191.1074; Calcd for $C_{12}H_{15}O_2$: $(M+H)^+$ 191.1072.

5-fluoro-1,1-dimethyl-1,3-dihydro-2H-inden-2-one (4.11t)

Prepared from **4.10t** (112 mg, 0.500 mmol) to give **4.11t** (40.9 mg, 0.215 mmol) in 43% yield.

1H NMR (400 MHz, $CDCl_3$): δ = 1.30 (s, 6H), 3.58 (s, 2H), 6.97-7.02 (m, 2H), 7.19 (dd, J = 5.2 Hz, 9.1 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.5, 41.7 (d, J = 1.9 Hz), 49.8, 111.9 (d, J = 22.3 Hz), 114.9 (d, J = 22.2 Hz), 124.5 (d, J = 8.6 Hz), 136.7 (d, J = 8.5 Hz), 143.9 (d, J = 2.7 Hz), 162.0 (d, J = 243.4 Hz), 219.4.

¹⁹F NMR (CDCl₃, 282 MHz): δ = -114.5 (m, 1F).

ESIHRMS: Found 179.0870; Calcd for C₁₁H₁₂OF: (M+H)⁺ 179.0872.

5.4.4 Synthesis of polycyclic aromatic hydrocarbons

The reaction of N,N-dimethyl amide **5**: Scheme 6a

To a mixture of NaH (60% dispersion in mineral oil; 60.0 mg, 1.50 mmol) and Lil (133 mg, 1.00 mmol) in a 25 mL sealed tube was added a solution of N,N,2'-trimethyl-[1,1'-biphenyl]-2-carboxamide (**4.17**) (120 mg, 0.500 mmol) in 2.5 mL of THF. The reaction mixture was sealed and stirred at 85 °C for 3 h. After cooling to 0 °C, the reaction was quenched with water and the organic materials were extracted with diethyl ether (20 mL $\times$ 3). The combined extracts were washed with brine and dried over MgSO₄. The volatile materials were removed *in vacuo* to provide the crude residue, which was purified by flash column chromatography with nitrogen gas (silica gel, hexane:ethyl acetate = 95:5 to 90:10) to give **4.18** (4.1 mg, 0.021 mmol) in 4% yield and aldehyde **4.19** (87.8 mg, 0.447 mmol) in 89% yield. Phenanthren-9-ol (**4.18**) was found unstable under an air atmosphere as well as under basic conditions

Phenanthren-9-ol (**4.18**)^[26]

¹H NMR (400 MHz, CDCl₃): δ = 5.40 (br s, 1H), 7.01 (s, 1H), 7.49-7.56 (m, 2H), 7.64-7.73 (m, 3H), 8.32 (d, *J* = 8.1 Hz, 1H), 8.61 (d, *J* = 7.9 Hz, 1H), 8.68 (d, *J* = 7.9 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 106.2, 122.4, 122.7, 122.8, 124.4, 125.6, 126.5, 126.8, 127.0, 127.3, 131.6, 132.7, 149.6.

2'-Methyl-[1,1'-biphenyl]-2-carbaldehyde (**4.19**)^[27]

¹H NMR (400 MHz, CDCl₃): δ = 2.11 (s, 3H), 7.19 (dd, J = 7.4 Hz, 1.4 Hz, 1H), 7.25-7.36 (m, 4H), 7.48-7.52 (m, 1H), 7.64 (ddd, J = 8.2 Hz, 7.4 Hz, 1.4 Hz, 1H), 8.03 (dd, J = 7.8 Hz, 1.4 Hz, 1H), 9.75 (s, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 20.4, 125.8, 127.2, 127.9, 128.4, 130.2, 130.3, 130.9, 133.8, 133.9, 136.2, 137.6, 145.8, 192.4.

Typical Synthesis for 4.21a

To a mixture of NaH (60% dispersion in mineral oil; 100 mg, 2.50 mmol) and Lil (201 mg, 1.50 mmol) in a 25 mL sealed tube was added a solution of N,2'-dimethyl-[1,1'-biphenyl]-2-carboxamide (**4.20a**) (113 mg, 0.500 mmol) in 2.5 mL of THF. The reaction mixture was sealed and stirred at 85 °C for 14 h. After cooling to 0 °C, the reaction was quenched with water and the organic materials were extracted with diethyl ether (20 mL $\times$ 3). The combined extracts were washed with brine and dried over MgSO₄. The volatile materials were removed *in vacuo* and the resulting crude residue was purified by flash column chromatography (silica gel, hexane:EtOAc:Et₃N = from 94:5:1 to 79:20:1) to give N-methylphenanthren-9-amine (**4.21a**) (86.7 mg, 0.418 mmol) in 84% yield (90% yield based on the ¹H NMR of the crude reaction mixture using 1,1,2,2-tetrachloroethane as an internal standard). Yield of phenanthren-9-ol (**4.18**) (5%) was measured by ¹H NMR of the crude mixture as **4.18** is decomposed under the flash column with basic eluents, that was needed to isolate **4.21a**.

When NaI (225 mg, 1.50 mmol) was used instead of Lil under otherwise the same reaction conditions (with **4.20**, 113 mg, 0.500 mmol; NaH, 100 mg, 2.50 mmol), only phenanthren-9-ol (**4.18**) (68.3 mg, 0.352 mmol) was isolated in 70% yield (by flash column chromatography

with nitrogen gas, silica gel, hexane:ethyl acetate = 90:10).

N-methylphenanthren-9-amine (4.21a)^[28]

¹H NMR (400 MHz, CDCl₃): δ = 3.11 (s, 3H), 4.44 (br s, 1H), 6.78 (s, 1H), 7.40 (dd, J = 8.2 Hz, 8.2 Hz, 1H), 7.50 (dd, J = 7.9 Hz, 7.9 Hz, 1H), 7.61 (dd, J = 8.2 Hz, 8.2 Hz, 1H), 7.67 (dd, J = 7.9 Hz, 7.9 Hz, 1H), 7.73 (d, J = 7.9 Hz, 1H), 7.88 (d, J = 7.9 Hz, 1H), 8.54 (d, J = 8.2 Hz, 1H), 8.71 (d, J = 8.2 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 31.1, 101.6, 120.2, 122.4, 122.8, 123.5, 125.3, 125.4, 126.2, 126.5, 126.6, 126.9, 131.0, 133.8, 142.2.

N-benzylphenanthren-9-amine (4.21b)

Prepared from amide **4.20b** (151 mg, 0.500 mmol) to give **4.21b** (101 mg, 0.356 mmol) in 71% yield.

¹H NMR (400 MHz, CDCl₃): δ = 4.59 (s, 2H), 4.65 (br s, 1H), 6.85 (s, 1H), 7.34 (tt, J = 7.2 Hz, 1.5 Hz, 1H), 7.38-7.45 (m, 3H), 7.46-7.55 (m, 3H), 7.64 (dd, J = 8.2 Hz, 6.9 Hz, 1H), 7.64-7.72 (m, 2H), 7.93 (d, J = 8.2 Hz, 1H), 8.55 (d, J = 8.2 Hz, 1H), 8.73 (d, J = 8.1 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 48.7, 102.7, 120.4, 122.4, 123.1, 123.6, 125.4, 125.5, 126.3, 126.6, 126.7, 127.0, 127.5, 128.0, 128.8, 131.2, 133.7, 139.1, 141.0.

ESIHRMS: Found 284.1447; Calcd for C₂₁H₁₈N: (M+H)⁺ 284.1439.

N,4-dimethylphenanthren-9-amine (4.21c)

Prepared from amide **4.20c** (120 mg, 0.500 mmol) to give **4.21c** (71.9 mg, 0.325 mmol) in 65%

yield.

¹H NMR (400 MHz, CDCl₃): δ = 3.10 (s, 3H), 3.12 (s, 3H), 4.33 (br s, 1H), 6.81 (s, 1H), 7.29 (d, J = 7.2 Hz, 1H), 7.43 (dd, J = 7.8 Hz, 7.4 Hz, 1H), 7.60-7.68 (m, 3H), 7.93 (dd, J = 7.8 Hz, 1.8 Hz, 1H), 8.93 (d, J = 8.7 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 27.3, 31.1, 103.2, 120.0, 125.3, 125.4, 125.5, 125.6, 126.2, 126.7, 127.9, 128.2, 132.4, 135.0, 135.3, 141.8.

ESIHRMS: Found 222.1286; Calcd for C₁₆H₁₆N: (M+H)⁺ 222.1283.

2-methoxy-N-methylphenanthren-9-amine (4.21d)

Prepared from amide **4.20d** (128 mg, 0.500 mmol) to give **4.21d** (93.7 mg, 0.395 mmol) in 79% yield.

¹H NMR (400 MHz, CDCl₃): δ = 3.09 (s, 3H), 3.96 (s, 3H), 4.44 (br s, 1H), 6.72 (s, 1H), 7.04 (dd, J = 9.0 Hz, 2.7 Hz, 1H), 7.14 (d, J = 2.7 Hz, 1H), 7.53 (ddd, J = 8.2 Hz, 6.9 Hz, 1.3 Hz, 1H), 7.63 (ddd, J = 8.2 Hz, 6.9 Hz, 1.3 Hz, 1H), 7.82 (d, J = 8.2 Hz, 1H), 8.43 (d, J = 9.0 Hz, 1H), 8.59 (d, J = 8.2 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 31.0, 55.3, 101.3, 107.0, 113.0, 119.6, 120.2, 123.0, 124.1, 124.3, 125.2, 126.6, 131.2, 135.3, 142.9, 158.7.

ESIHRMS: Found 238.1228; Calcd for C₁₆H₁₆NO: (M+H)⁺ 238.1232.

N,6-dimethylphenanthren-9-amine (4.21e)

Prepared from amide **4.20e** (120 mg, 0.500 mmol) to give **4.21e** (94.0 mg, 0.425 mmol) in 85% yield.

¹H NMR (400 MHz, CDCl₃): δ = 2.65 (s, 3H), 3.07 (s, 3H), 4.34 (br s, 1H), 6.75 (s, 1H), 7.41-7.46 (m, 2H), 7.54 (dd, J = 8.2 Hz, 7.9 Hz, 1H), 7.73-7.78 (m, 2H), 8.53 (s, 1H), 8.58 (d, J = 8.2 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 21.9, 31.0, 100.9, 120.2, 122.4, 122.7, 123.35, 123.43, 125.2, 126.6, 126.8, 127.9, 131.2, 134.1, 136.2, 142.4.

ESIHRMS: Found 222.1282; Calcd for C₁₆H₁₆N: (M+H)⁺ 222.1283.

7-methoxy-N-methylphenanthren-9-amine (4.21f)

Prepared from amide **4.20f** (128 mg, 0.500 mmol) to give **4.21f** (94.9 mg, 0.400 mmol) in 80% yield.

¹H NMR (400 MHz, CDCl₃): δ = 3.08 (s, 3H), 3.96 (s, 3H), 4.18 (br s, 1H), 6.81 (s, 1H), 7.22 (d, J = 2.6 Hz, 1H), 7.29 (dd, J = 9.0 Hz, 2.6 Hz, 1H), 7.41 (ddd, J = 8.3 Hz, 7.9 Hz, 1.5 Hz, 1H), 7.48 (dd, J = 8.3 Hz, 7.9 Hz, 1H), 7.74 (dd, J = 7.9 Hz, 1.5 Hz, 1H), 8.46 (d, J = 8.3 Hz, 1H), 8.61 (d, J = 9.0 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 31.2, 55.5, 102.0, 102.6, 116.0, 121.9, 123.1, 125.1, 125.2, 125.6, 126.0, 126.6, 126.9, 132.6, 141.8, 158.3.

ESIHRMS: Found 138.1234; Calcd for C₁₆H₁₆NO: (M+H)⁺ 238.1232.

Construction of [4]helicenes (Scheme 4.29b)

Synthesis of 4.21g (Scheme 4.29b)

To a mixture of NaH (60% dispersion in mineral oil; 100 mg, 2.50 mmol), Lil (201 mg, 1.50 mmol), and N-methyl-2-(2-methylnaphthalen-1-yl)benzamide (**4.20g**) (138 mg, 0.500 mmol) in a 25 mL sealed tube was added 2.5 mL of dry THF. The reaction mixture was sealed and stirred at 85 °C for 14 h. After cooling to 0 °C, the reaction was then quenched with water and extracted with diethyl ether (20 mL $\times$ 3). The combined extracts were washed with brine, and dried over MgSO₄. The volatile materials were removed *in vacuo* to give the crude residue containing N-methylbenzo[c]phenanthren-5-amine (**4.21g**) and benzo[c]phenanthren-5-ol (**4.22**) in 47% and 48% yields, respectively, based on the ¹H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. Purification by flash column chromatography (silica gel, hexane:ethyl acetate:Et₃N 94:5:1 to 79:20:1) gave **4.21g** (56.6 mg, 0.220 mmol) in 44% yield.

N-methylbenzo[c]phenanthren-5-amine (4.21g)

¹H NMR (400 MHz, CDCl₃): δ = 3.13 (s, 3H), 4.53 (br s, 1H), 6.87 (s, 1H), 7.53 (ddd, J = 8.0 Hz, 6.9 Hz, 1.1 Hz, 1H), 7.60-7.66 (m, 2H), 7.69 (dd, J = 8.5 Hz, 6.9 Hz, 1H), 7.74 (d, J = 8.5 Hz, 1H), 7.84 (d, J = 8.5 Hz, 1H), 7.94-7.99 (m, 2H), 8.97 (d, J = 8.6 Hz, 1H), 9.14 (d, J = 8.5 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 31.2, 102.7, 102.7, 120.2, 120.3, 124.2, 125.5, 125.6, 126.0, 126.2, 126.6, 127.1, 128.0, 128.7, 128.9, 130.7, 131.3, 132.1, 132.8, 143.1.

ESIHRMS: Found 258.1279; Calcd for C₁₉H₁₆N: (M+H)⁺ 258.1283.

Synthesis of benzo[c]phenanthren-5-ol (4.22) (Scheme 4.29c)

When **4.20g** (82.6 mg, 0.300 mmol) was treated with NaH (100 mg, 2.50 mmol, 8.3 equiv) and NaI (225 mg, 1.50 mmol, 5 equiv) under otherwise the same reaction conditions for 24 h, only formation of benzo[c]phenanthren-5-ol (**4.22**) was observed in slower conversion. The crude residue was purified by flash column chromatography with nitrogen gas (silica gel, hexane:ethyl acetate = 85:15) to give **4.22** (23.7 mg, 0.097 mmol) in 32% yield with 60 % recovery of **4.20g** (49.2 mg, 0.179 mmol).

¹H NMR (400 MHz, CDCl₃): δ = 5.51 (br s, 1H), 7.10 (s, 1H), 7.57 (dd, J = 7.4 Hz, 7.1 Hz, 1H), 7.65-7.70 (m, 3H), 7.73 (dd, J = 8.6 Hz, 7.1 Hz, 1H), 7.85 (d, J = 8.6 Hz, 1H), 7.99 (d, J = 7.9 Hz, 1H), 8.44 (d, J = 7.9 Hz, 1H), 9.04 (d, J = 8.6 Hz, 1H), 9.13 (d, J = 8.6 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ = 107.3, 122.2, 122.7, 125.0, 125.7, 125.9, 126.0, 126.3, 126.8, 127.4, 127.9, 128.0, 128.7, 130.5, 131.70, 131.73, 132.6, 150.0.

ESIHRMS: Found 245.0970; Calcd for C₁₈H₁₃O: (M+H)⁺ 245.0966.

5.4.5 References for Section 5.4

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List of Publications

- 1) Pei Chui TOO, Guo Hao CHAN, Ya Lin TNAY, Hajime HIRAO, Shunsuke CHIBA. Hydride Reduction by a Sodium Hydride-Iodide Composite. *Angew. Chem. Int. Ed.* **2016**, *55*, 3719-3723.
- 2) Zhonghan HONG, Yiren Derek ONG, Kumar Muduli SUBAS, Pei Chui TOO, Guo Hao CHAN, Ya Lin TNAY, Shunsuke CHIBA, Yusuke NISHIYAMA, Hajime HIRAO, Han Sen SOO. Understanding the Origins of Nucleophilic Hydride Reactivity of a Sodium Hydride–Iodide Composite. *Chem. Eur. J.* **2016**, *22*, 7108-7114.
- 3) Yinhua HUANG, Guo Hao CHAN, Shunsuke CHIBA. Amide-Directed C-H Sodiation by a Sodium Hydride/Iodide Composite. *Angew. Chem. Int. Ed.* **2017**, *56*, 6544-6547.
- 4) Guo Hao CHAN, Yiren Derek ONG, Zhihao YEN, Shunsuke CHIBA. Reduction of N,N-Dimethylcarboxamides to Aldehydes by Sodium Hydride-Iodide Composite. *Helv. Chim. Acta.* **2018**, *101*, e1800049.
- 5) Guo Hao CHAN, Yiren Derek ONG, Shunsuke CHIBA. Hydrodeacylation by a Sodium Hydride-Iodide Composite. *Org. Synth.* **2018**, *95*, 240-255.