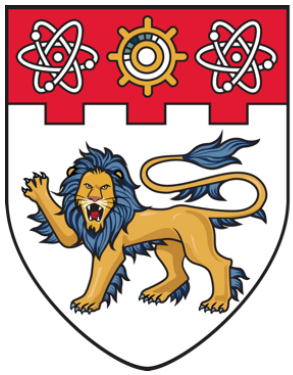

NANYANG TECHNOLOGICAL UNIVERSITY
SINGAPORE

NUCLEOPHILIC AROMATIC AMINATION AND HYDROALKYLATION OF STYRENES WITH ALKYL AMINES MEDIATED BY ALKALI METAL HYDRIDES

PANG JIA HAO

SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

2021

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SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

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

2021

Statement of Originality

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

14 July 2021

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Date

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Pang Jia Hao

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12 July 2021 Shunsuke Chiba

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Date

Authorship Attribution Statement

This thesis contains material from 3 paper(s) published in the following peer-reviewed journals in which I am listed as an author.

Chapter 1 is published as Ong, D. Y.; Pang, J. H.; Chiba, S., Sodium and Potassium. In *Reference Module in Chemistry, Molecular Sciences and Chemical Engineering*, Elsevier: 2021. DOI: https://doi.org/10.1016/B978-0-12-820206-7.00016-0.

The contributions of the co-authors are as follows:

- Prof. S. Chiba provided the overall book chapter direction.
- The book chapter was prepared and revised by Prof. Chiba, S., Dr. Ong, D. Y., and the author.

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The contributions of the co-authors are as follows:

- Prof. S. Chiba provided overall project direction.
- The manuscript was prepared and revised by Prof. Chiba, S., Dr. Kaga, A., and the author.
- The author and Dr. Kaga, A., designed the study and performed all the experimental work at the School of Physical and Mathematical Sciences.

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- The author, Dr. Kaga, A., Mr. Roediger, S. and Mr. Lin, M. H. designed the study and performed all the experimental work at the School of Physical and Mathematical Sciences.

Note: If published materials are not inserted as thesis chapters, students must acknowledge co-worker contributions in the acknowledgement section of their thesis.

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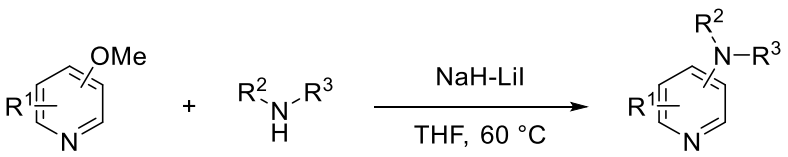
Abstract

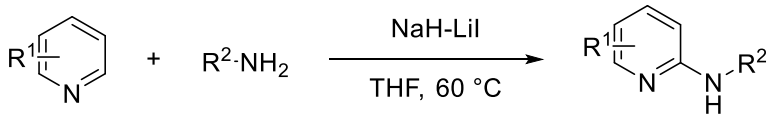
The alkali metal hydrides are one of the most widely used Brønsted bases in synthetic chemistry. Our group has recently discovered that solvothermal treatment of sodium hydride with various dissolving iodide salts in THF imparts both a unique hydridic reactivity and an significant increase in its Brønsted basicity to sodium hydride. The resulting sodium hydride-iodide composite is capable of deprotonative metalations on less acidic aliphatic amines (pK_a of H_2 = 36, pK_a of pyrrolidine = 44), directed sodiation of arenes, hydride reduction of various π-polar electrophiles and hydrodehalogenation of haloarenes. The thesis describes the utilization of readily available sodium and potassium hydrides as bases for generation of alkali metal amide anions and their nucleophilic addition reactions.

Chapter 1 provides an overview on the methods for the generation of sodium and potassium organometallic compounds from organic molecules. The chapter is divided into two sections, the first section focuses on the state-of-the-art reagents available for metalations of organic molecules, whereas the second section focuses on the generation of sodium/potassium organometallic compounds from sodium/potassium hydride and the use of activated sodium/potassium hydride for reductive transformations.

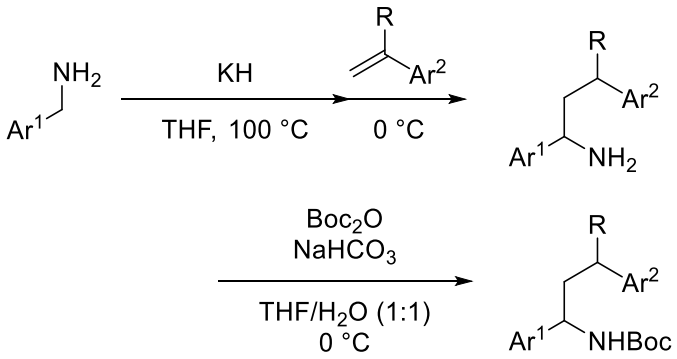
Chapter 2 will describe the nucleophilic aromatic substitution of methoxypyridines using sodium alkylamides generated from alkylamines and sodium hydride-iodide composite. The reaction was able to effect amination at the C3 position of pyridines which was rarely achieved by the conventional methods without using transition metals.



Chapter 3 demonstrates the utility of the NaH/LiI composite in the Chichibabin amination of pyridines for the synthesis of C-2 aminated pyridines. This protocol showed higher process efficiency with wider substrate scope under milder reaction conditions over the traditional Chichibabin amination.



Chapter 4 describes the selective hydroalkylation of styrenes with benzylamines mediated by potassium hydride. The use of heavier counter cations on the amide anions is found to be the key in influencing the selectivity switch from conventional hydroamination to unusual hydroalkylation via reversible 1,2-anion shift from the amide anion to the benzylic carbanion.



Chapter 5 lists the experimental data for the respective chapter 2, 3 and 4.

Chapter 6 gives a conclusion and summary to thesis.

Acknowledgements

First and foremost, I would like to thank my supervisor, Professor Chiba Shunsuke for his guidance and advice throughout the 4 years of my PhD course. His strict discipline and insistence on only the highest quality of work allowed me to perform to a standard that I would not have achieved without him. I would also like to thank Prof. John Murphy for hosting me during my overseas research attachment to the University of Strathclyde. His insights and knowledge of chemistry was very inspiring and made me rethink what chemistry is capable of.

I would also like to extend my thanks to the following mentors, Dr. Tejo Ciputra and Dr. Kaga Atsushi, who had imparted the skills and knowledge required to finish my PhD work. I would not have managed without their supervision and guidance in the early years of my PhD.

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The work published over the 4 years would not have been made possible without my co-authors, Dr. Wang Bin, Dr. Kaga Atushi, Dr. Li Haoyu, Dr. Tejo Ciputra, Dr. Ong, Sven Roediger and Lin Min Htoo, who had contributed greatly for the experimental works and discussions

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With deepest gratitude,

Jia Hao

Table of Contents

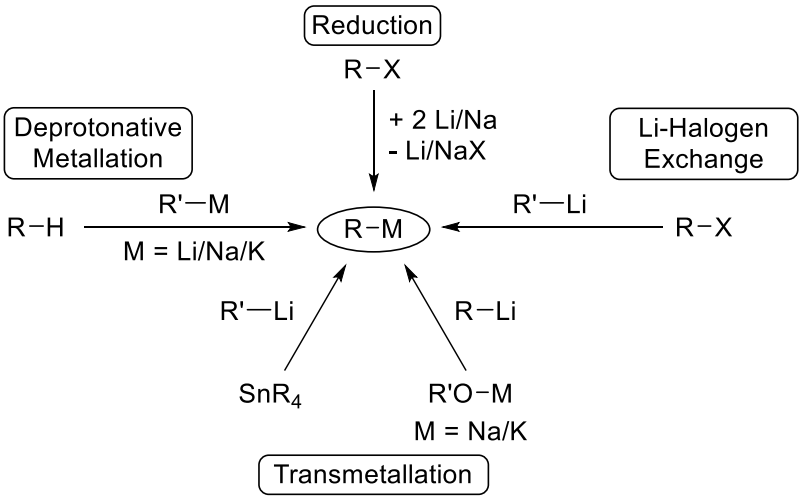
List of Abbreviations

δ	chemical shift
°C	degree celsius
%	percent
ANRORC	addition of the nucleophile, ring opening and ring closing
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
ByBroP	bromo-tris-pyrrolidino-phosphonium hexafluorophosphate
DA	diisopropylamide
DFT	density functional theory
DMAT	((2-(dimethylamino)phenyl)(trimethylsilyl)methyl)
DME	dimethoxyethane
DMEA	*N*,*N*-dimethylethylamine
EtOAc	ethyl acetate
equiv	equivalent(s)
FDA	Food and Drug Administration
h	hour(s)
HMDS	1,1,1,3,3,3-hexamethyldisilazide
Hz	hertz
i-Pr	isopropyl
J	coupling constant(s)
K_a	acid dissociation constant
kJ	kilojoule

KH	potassium hydride
LiH	lithium hydride
Me	methyl
mg	milligram(s)
min	minutes(s)
mL	milliliter(s)
NaH	sodium hydride
n-Bu	*n*-butyl
NMR	nuclear magnetic resonance
OMe	methoxy
Ph	phenyl
PMDETA	*N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine
ppm	parts per million
PyBox	pyridinebisoxazoline
s-Bu	*sec*-butyl
rt	room temperature
t-Bu	*tert*-butyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMP	2,2,6,6-tetramethylpiperidide
TMS	trimethylsilyl

Chapter 1. General Introduction

Group 1 and 2 organometallic compounds are one of the most useful anionic synthons in synthetic chemistry. In general, Group 1 organometallic reagents are typically more nucleophilic and act as stronger bases as compared to their Group 2 counterparts due to the more polarized nature of the alkali metal-carbon bond as compared to the alkaline earth metal-carbon bond. There are four classical methods of generating Group 1 organometallics (Scheme 1): 1) Reduction of organohalides using alkali metals. 2) Deprotonative metalation of acidic C-H bonds with the use of alkali metal organometallic reagents. 3) Metal-halogen exchange between an alkali metal organometallic reagents and organohalides. 4) Transmetallation between organolithium reagents with other organometallics to generate organolithium compounds or with sodium/potassium alkoxides to generate organosodium or organopotassium compounds.[1] In contrast, generation of alkali metal organometallics from alkali metal hydrides remain extremely scarce despite their commercially availability (LiH, NaH and KH) and their thermodynamic stability.



Scheme 1. Classical Methods to generate alkali metal organometallics.

In the following sections, the latest advances in the Lochmann-Schlosser bases will be covered along with the current state-of-the-art reagents used for sodiation/potassiation of organic

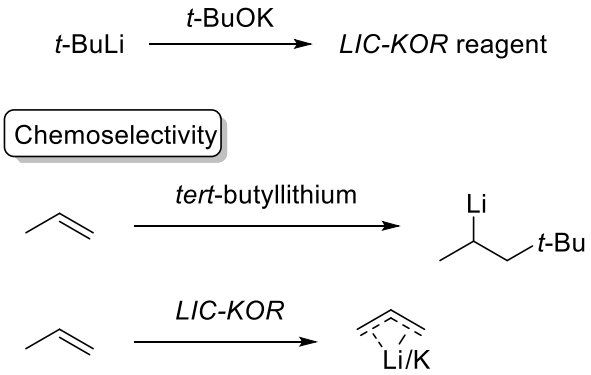
molecules. Recent developments in the use of alkali metal hydrides for hydride reductions and deprotonative metalations of non-acidic protons will also be covered in the subsequent section.

1.1 Sodiation/potassiation Reagents – Structures and Preparation

1.1.1. Lochmann-Schlosser bases

One of the earliest reports in using a mixture of alkylmetal and metal alkoxides was its use in the catalytic polymerization of unsaturated hydrocarbons by Morton and co-workers.[2] Their seminal discovery of so called 'alfin' catalyst, named after its *al*cholic and ole*fin*ic components, had led to an extensive study for the use of this reagent in both metalation[3-4] and polymerization[2, 5-6] reactions as well as some rudimentary studies into its structural properties.[7-8] The alfin catalyst, however, never gained widespread use as a metalation agent due to stringent requirements of high speed stirring in the specialized apparatus, longer reaction times and unsatisfactory yields.

It was until the Schlosser's discovery that alkyllithium reagents ('*LIC*') can be made significantly more reactive in the presence of potassium alkoxide ('*KOR*') that led to a breakthrough in the use of alkylmetal and metal alkoxide mixtures as a metalation reagent.[9] In the ensuing studies, the '*LIC-KOR* superbase' was found to have excellent chemoselectivity, i.e. *tert*-butyllithium (*t*-BuLi) adds to the double bond of simple alkenes while *LIC-KOR*, prepared from an equimolar of *tert*-butyllithium and potassium *tert*-butoxide (*t*-BuOK), and promotes highly regioselective deprotonations (Scheme 2).[10] This 1:1 combination of an alkyllithium reagent and a potassium alcoholate soon after became famously known as the Lochmann-Schlosser base and is now introduced as a textbook methodology for metalation reactions. Multiple reviews[10-13] have been published on this topic and thus, the section shall only cover the most recent literatures since 2007.

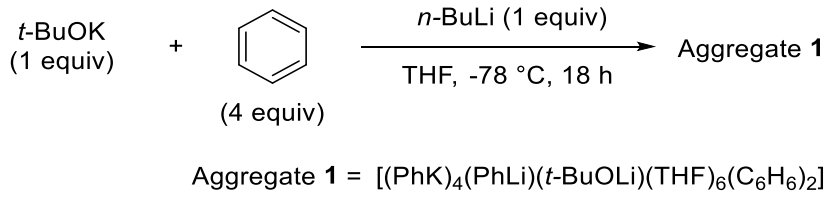


Scheme 2. Chemoselectivity of *LIC-KOR* reagents.

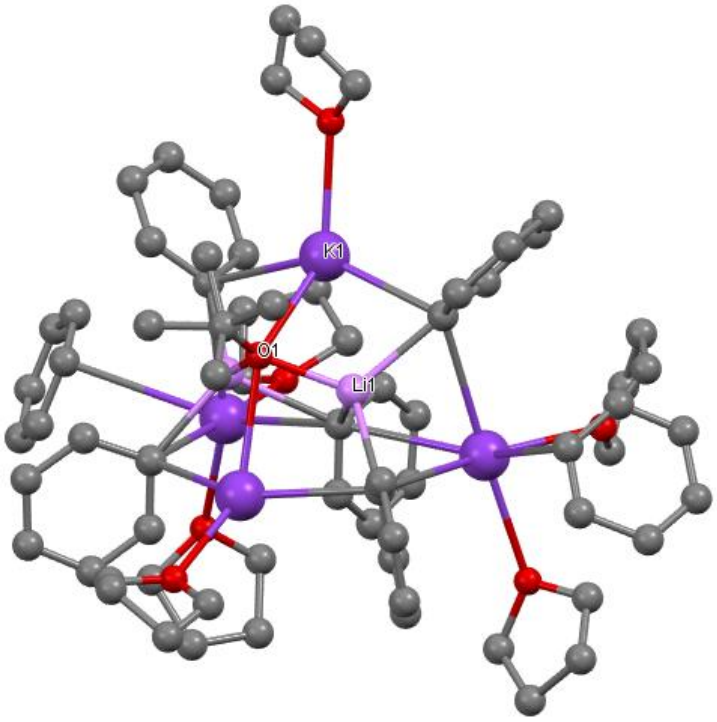
Despite being widely used reagents, structural information of the metalated products derived from *LIC-KOR* bases remain scarce. This is due to the low solubility of the generated alkyl alkali metal compounds and their propensity to undergo β-hydride elimination.[14-16] There is much ambiguity in the key species responsible for the exceptional reactivities afforded by these superbasic mixtures. It has been proposed that the formation of alkylpotassium[17-20] is solely responsible for the unique reactivities, while others argue that the formation of mixed alkyl/alkoxy aggregates[21-22] is crucial. Mulvey and co-workers discussed in great details the synergistic effects when alkyllithium and potassium alkoxide are mixed to form the aggregated superbases, where the individual components are unable to achieve such reactivities,[23-24] highlighting the importance in elucidating the species responsible for the privileged reactivities afforded by the Lochmann-Schlosser base.

In 2014, Strohmann and co-workers reported a glimpse of the molecular structure of metalated benzene through deprotonation using the Lochmann-Schlosser's base.[25] Treatment of a mixture of *n*-BuLi and *t*-BuOK in THF with excess amounts of benzene led to the crystallization of aggregate **1** (Scheme 3). The core of the aggregate comprises of a lithium center, surrounded by an 8-membered ring arrangement of potassium cations. The lithium center is coordinated by the hard butoxide and phenyl anions. In contrast, the potassium centers are arranged approximately perpendicular to the phenyl anions. This is a good illustration of the preference

for an ‘in-plane’ interaction between the hard lithium cation with the localized charge on the phenyl carbanion, while the softer potassium cation prefers to interact with the π-electrons at 90˚ to the phenyl ring.



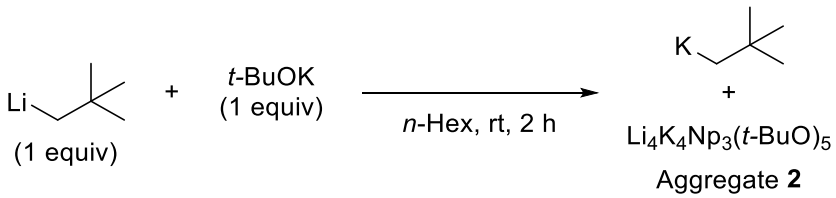
Aggregate **1** = $[(PhK)_4(PhLi)(t\text{-}BuOLi)(THF)_6(C_6H_6)_2]$

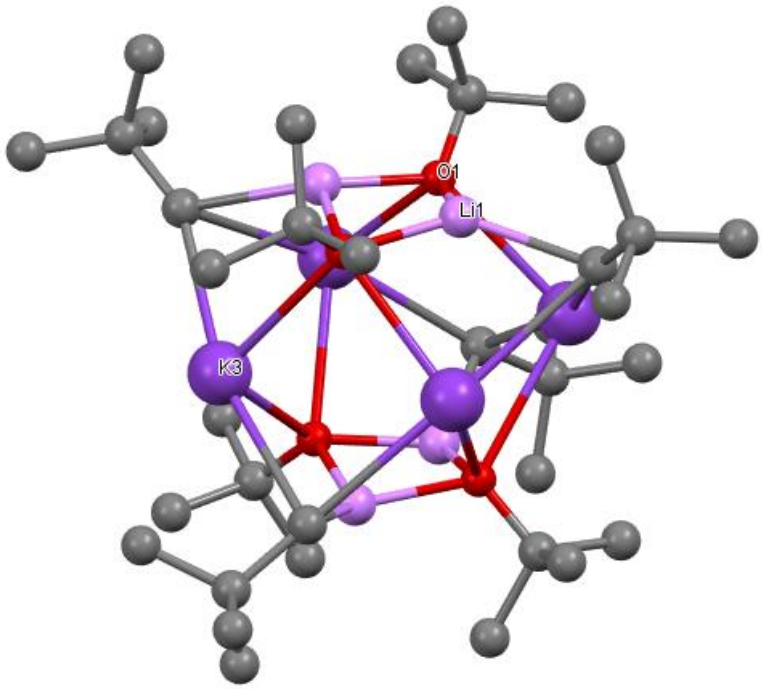


Scheme 3. Synthesis and characterization of metalated benzene (CCDC for aggregate **1**: 931570).

In 2016, Klett and co-workers reported the crystal structure of an alkane-soluble Lochmann-Schlosser superbase (Scheme 4).[26] Using a mixture of neopentyllithium, which lacks β-hydrogen atoms, and *t*-BuOK offers higher stability and solubility than the conventional Lochmann-Schlosser superbase derived from *n*-BuLi and *t*-BuOK. The observation of substitutional disorder in the crystals and ^{1}H NMR studies led the conclusion that the *LIC-KOR*

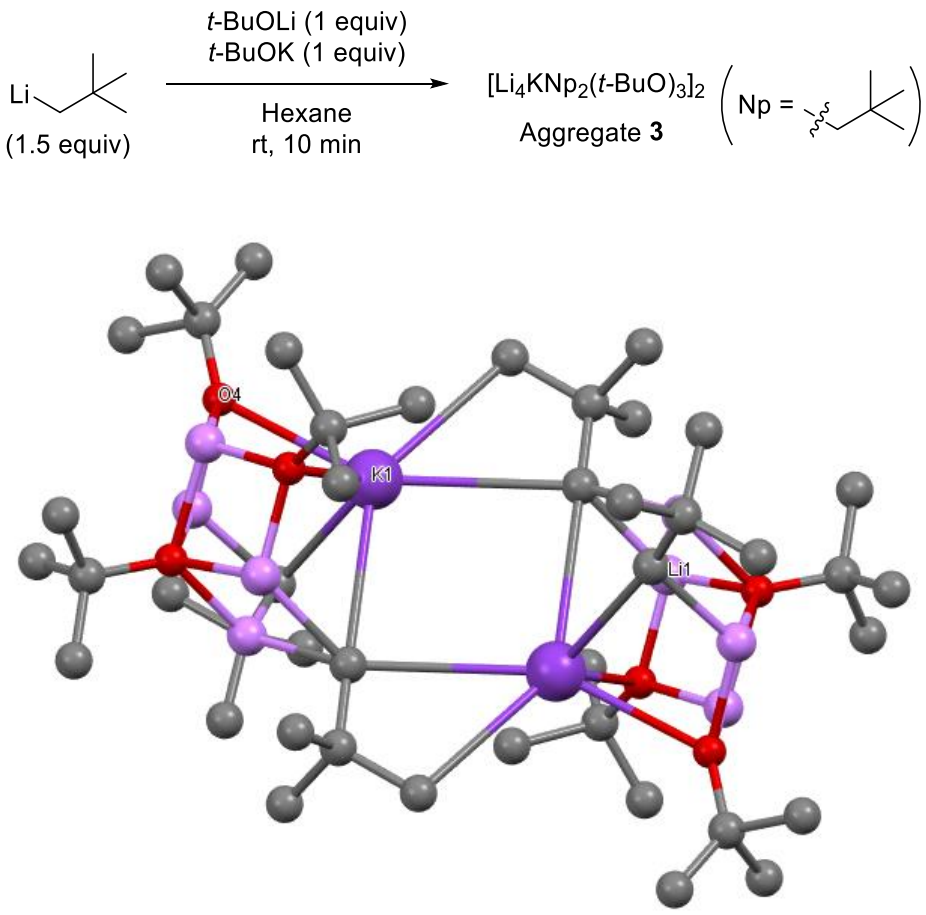
base is in fact made of a mixture of neopentyl/butoxide aggregates of varying stoichiometry in solution. The butoxide groups on aggregate **2** could be increasingly substituted ($Li_4K_4Np_n$(*t*-BuO)$_{8-n}$, up to n = 3) by the neopentyl group through the addition of increasing amounts of neopentyllithium. The coordination of the alkyl group to both the lithium and potassium led to a hybrid Li/K-C bond polarity, while the electrophilic LiK_2 moiety allows for co-ordination to both hard and soft Lewis bases, namely, Li to hard Lewis bases and K to soft Lewis bases. The combination of both factors is proposed to account for the unique reactivities of these *LIC-KOR* bases.





Scheme 4. Synthesis and characterization of an alkane-soluble $Li_4K_4Np_3$(*t*-BuO)$_5$ (CCDC for aggregate **2**: 1455868).

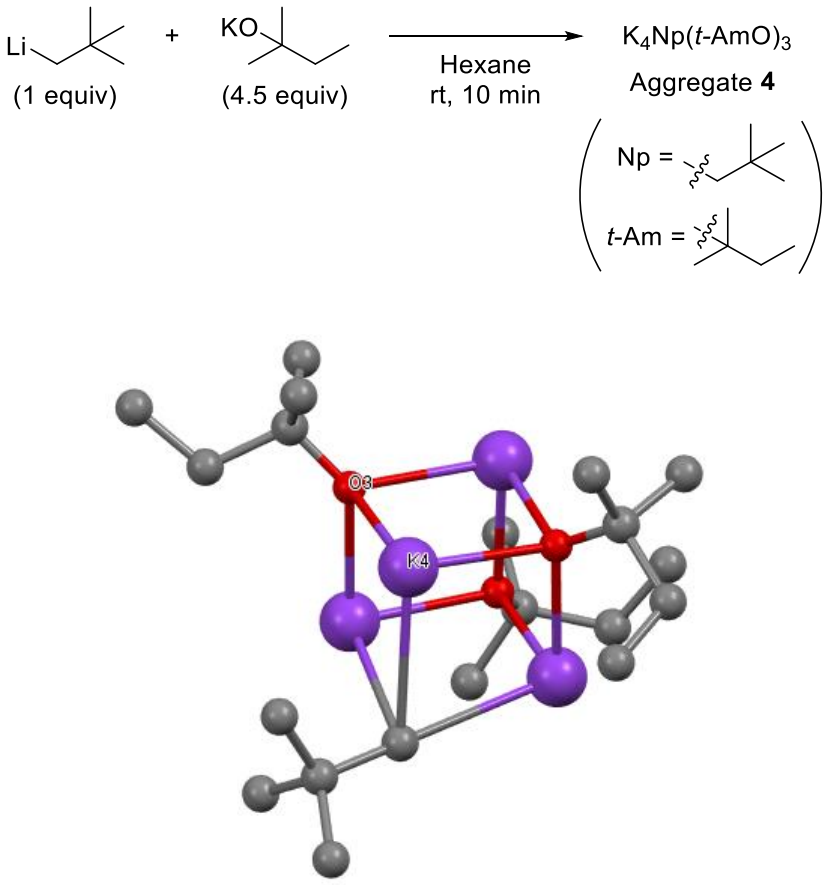
Shortly thereafter, the same group reported the isolation of a new alkane-soluble alkyl/alkoxy base, which is thermally stable and has a well-defined stoichiometry.[27] By mixing neopentyllithium, *t*-BuOLi and *t*-BuOK in a 1.5:1.0:1.0 mixture, aggregate $[Li_4KNp_2(t\text{-}BuO)_3]_2$ **3**, which is of high lithium to potassium content, was isolated and characterized (Scheme 5). The absence of aggregates with high potassium to lithium content is likely due to the low solubility of alkylpotassium, which precipitates out of the solution.



Scheme 5. Synthesis and characterization of an alkane-soluble $[Li_4KNp_2(t\text{-}BuO)_3]_2$ (CCDC for aggregate **3**: 1579177).

To simplify the reaction mixture, treatment of neopentyllithium with potassium *tert*-amylate was attempted. The resulting crystals of aggregate 4 $K_4Np(Ot\text{-}Am)_3$ (Scheme 6) are thermally stable and highly soluble in hexanes. This superbasic potassium aggregate was then used for

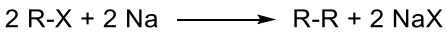
polymetalations of ferrocene, yielding a mixture of tetra, tri- and di-substituted ferrocene upon quenching with CO_2.



Scheme 6. Synthesis and characterization of $K_4Np(t\text{-}AmO)_3$ **4** (CCDC: 1579178).

1.1.2. Alkylsodium and alkylpotassium

Amongst the alkyl alkali metal reagents, alkyllithium is the most accessible due to their higher stability in general and ease of generation from alkyl halides and lithium. In contrast, preparation of alkylsodium reagents are more tedious as it generally requires cryogenic reaction conditions and high speed mechanical stirring to form.[28] Furthermore, alkylsodium compounds are degraded in ethereal solvents via unwanted side reactions such as Wurtz coupling (Scheme 7).[29] Therefore, alkylsodium reagents have not been typically employed as the reagent of choice for organic synthesis.



Scheme 7. Wurtz coupling.

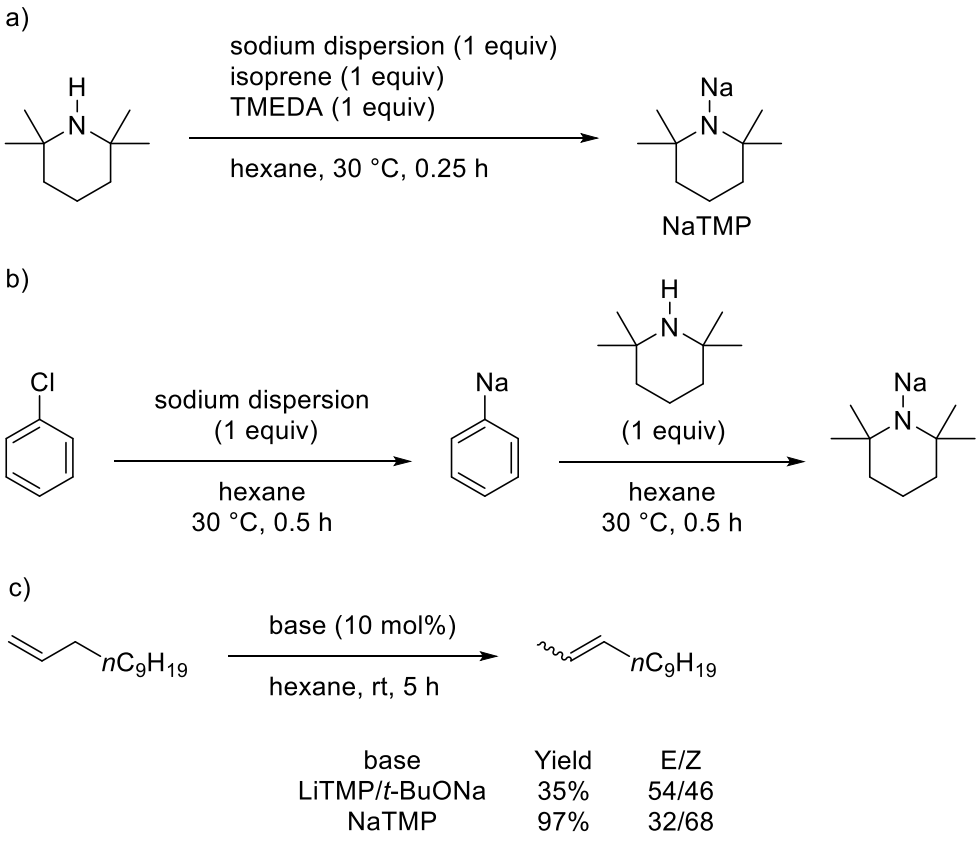
Butylpotassium can be easily prepared from butyllithium and potassium *tert*-amylate in hexane, where the resulting butylpotassium is insoluble and can be easily separated and isolated.[18] Similarly to alkylsodium compounds, alkylpotassium reagents are also highly unstable in ethereal solvents (for example, deprotonation of THF occurs even at –100 °C).[18] Thus, alkylpotassium reagents have also been rarely used as a reagent in organic synthesis.

1.1.3. Sodium and potassium amides

Despite the frequent utilities of the *LIC-KOR* bases, several limitations have been identified in their use. For example, cryogenic reaction conditions (usually at -50 °C and below) are needed to suppress the attack of *LIC-KOR* on THF.[30] Moreover, exploration into generation of carbon-based sodium and potassium bases has also been restricted due to the inherent unstable nature of such reagents as they are prone to undergo the Wurtz coupling and readily deprotonate ethereal solvents as described in Section 2.2. To overcome these shortcomings, researchers have recently revisited to the use of sodium and potassium amides as an alternative to the *LIC-KOR* base. The three most utilized sodium and potassium amides are as such: alkali-metal 1,1,1,3,3,3-hexamethyldisilazide (HMDS), alkali-metal 2,2,6,6-tetramethylpiperidide (TMP) and lastly alkali-metal diisopropylamide (DA). The structural aspects of the alkali metal amides have been nicely reviewed by Mulvey and Robertson in 2013.[31] The following section will discuss the recent advances in the preparation and structural discussion of the sodium and potassium amides.

1.1.3.1. Sodium 2,2,6,6-tetramethylpiperidide (NaTMP)

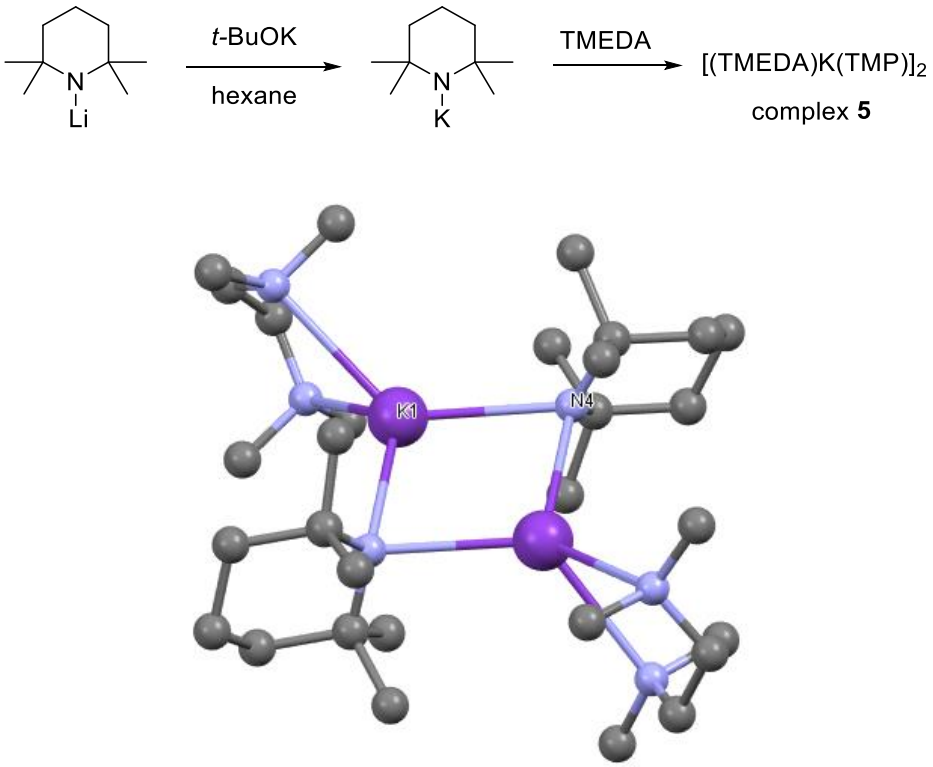
Use of lithium 2,2,6,6-tetramethylpiperidide (LiTMP) has been widely explored than its sodium counterpart (NaTMP). This is likely due to the lack of practical protocols for the preparation of NaTMP. Asako and Takai reported two lithium-free protocols for preparation of NaTMP using sodium dispersion (Scheme 8a and Scheme 8b).[32] The difference in reactivity caused by the presence of lithium cation was nicely demonstrated in the base-catalyzed isomerization of 1-dodecene, where the presence of lithium cation resulted in lower yield and *E*-selectivity. (Scheme 8c).



Scheme 8. Preparation and reactivity of NaTMP: a) preparation using sodium dispersion; b) preparation via phenylsodium; c) reactivity difference of NaTMP with Li and NaTMP without Li.

1.1.3.2. Potassium 2,2,6,6-tetramethylpiperidide (KTMP)

In 2008, Mulvey reported the synthesis and characterization of KTMP•TMEDA complex.[33] The complex was synthesized by the addition of *t*-BuOK to a solution of LiTMP in hexanes, generating KTMP as a precipitate. KTMP was then suspended in hexane and subsequent treatment with TMEDA formed KTMP•TMEDA complex **5** (Scheme 9).

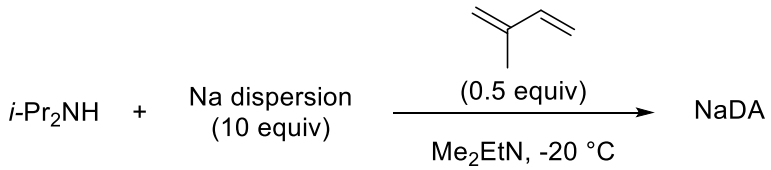


Scheme 9. Synthesis and characterization of $[(TMEDA)K(TMP)]_2$ **5** (CCDC: 675684).

1.1.3.3. Sodium diisopropylamide (NaDA)

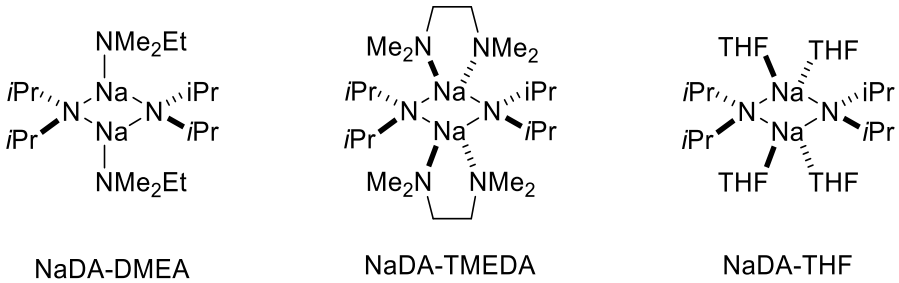
In 1950, use of lithium diisopropylamide (LDA) was reported for α-deprotonation of esters by Hamell and Levine.[34] Due to its superior stability and its higher tolerance towards polar Lewis donor solvent like THF, LDA is the preferred reagent for deprotonations over its Na/K counterpart. On the other hand, there is a growing interest in using sodium over lithium due to the high natural abundance of sodium[35] and the increasing price of lithium due to the development of lithium batteries for energy storage and electric vehicles.[36-37] NaDA was first

prepared by Levine in 1959 using phenylsodium and diisopropylamine.[38] Since then, several procedures were reported for the preparation of NaDA.[39-40] Recent efforts by Collum and co-workers revealed much details about its preparation, stability and structure. NaDA can be prepared easily using diisopropylamine and sodium dispersion in the presence of isoprene as an electron carrier[40] with *N*,*N*-dimethylethylamine (DMEA) as a solvent (Scheme 10).[41] In this protocol, no pre-drying is required for diisopropylamine as sodium dispersion can serve as a drying agent. Furthermore, NaDA can be stored as a solid for months or as a 1 M solution in DMEA at room temperature for weeks or at –20 °C for months. The ease of preparation and storage could stimulate organic chemists to further utilize this reagent.



Scheme 10. Collum's method for the preparation of NaDA.

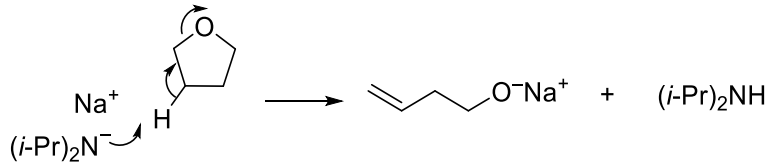
Collum and co-workers elucidated the structure of NaDA in solutions determined based on the DFT and NMR studies.[42] It was found that NaDA exists primarily as a dimeric structure in solutions which are either di-solvated or tetra-solvated (Scheme 11).



Scheme 11. Structures of NaDA in solution.

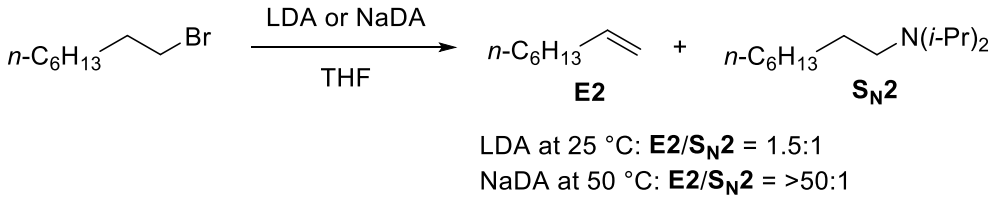
The stability of NaDA in ethereal solution was also studied, revealing that NaDA decomposed in THF solution with a half-life of 1 h through deprotonative ring-opening of THF (Scheme 12).[42] It was also noted that the utility of NaDA as a metalation reagent was not lost as the rate

of metalation by NaDA far exceeds its decomposition rate in THF. The key would be to moderate the amounts of ethereal solvent as its use is still critical in metalation reactions due to its ability in stabilizing the metalated species as a Lewis base.



Scheme 12. Decomposition of NaDA in THF.

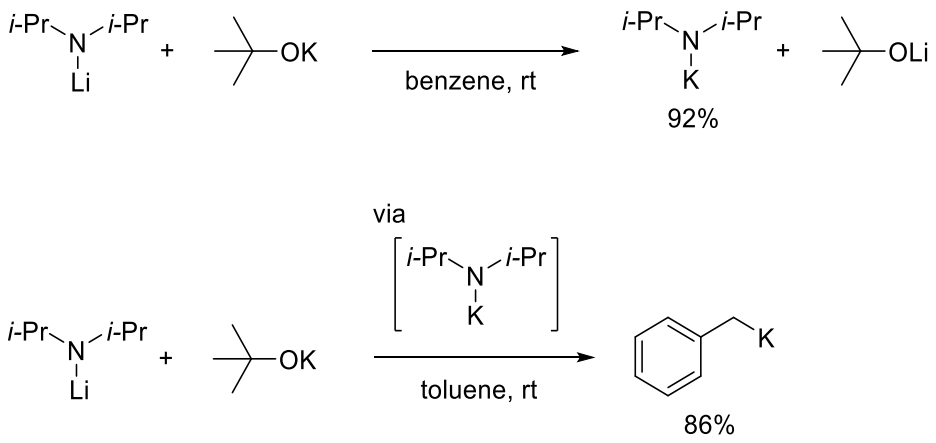
Collum disclosed an interesting counter cation effect on amide bases in E2-elimination of alkyl bromides (Scheme 13). Treatment of 1-bromooctane with LDA underwent both E2-elimination and nucleophilic substitution to form the corresponding alkene and amine. Interestingly, employment of sodium diisopropylamide (NaDA) as a base resulted in E2-elimination exclusively.[43]



Scheme 13. Reaction of 1-bromooctane with alkali metal diisopropylamides.

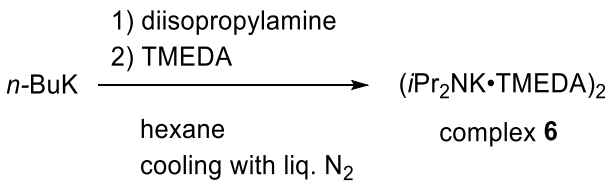
1.1.3.4. Potassium diisopropylamide (KDA)

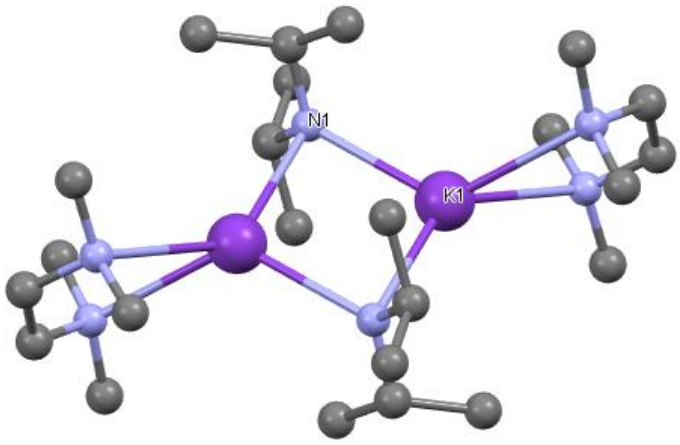
Lochmann reported the synthesis of *N*-potassium dialkylamides through the reaction of the corresponding lithium dialkylamides and potassium alkoxides.[20] The potassium diisopropylamides are significantly more reactive than LDA and can readily metalate the benzylic C-H bond of toluene at ambient temperature (Scheme 14).



Scheme 14. Preparation of KDA and its deprotonative metalation of toluene.

The first crystal structure of a potassium diisopropylamide complex was reported by Clegg in 1998 (Scheme 15).[44] The potassium complex was synthesized by reacting a suspension of *n*-butylpotassium with diisopropylamine while being cooled by liquid nitrogen. The resulting mixture was warmed to room temperature before complexation with TMEDA.





Scheme 15. Synthesis and characterization of complex (KDA•TMEDA)$_2$ **6** (CCDC: 1170183).

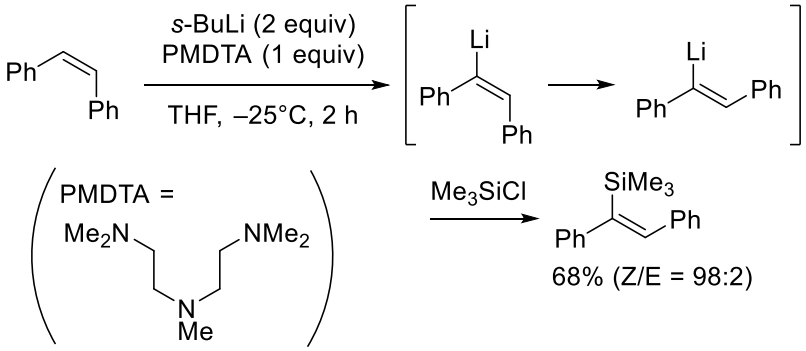
1.2. Metalations

Bergmann and Schlenk reported the first use of ethyllithium for the metalation of fluorene to 9-fluorenyllitihum.[45] The highly nucleophilic nature of the resulting polarized carbon-alkali metal bond allows for facile addition of the generated carbanion species towards electrophiles, and is still one of the most widely used reactions in organic synthesis.[12-13] Further development of directed metalations became a significant milestone in metalation chemistry, serving as key molecular transformations towards the synthesis of natural products, pharmaceutical drugs and organic materials.[11, 46-50] This section highlights recent state-of-the-art metalation methodologies classified depending on the types of the substrates being metalated.

1.2.1. Metalation of alkenes

1.2.1.1. Metalation of vinylic positions

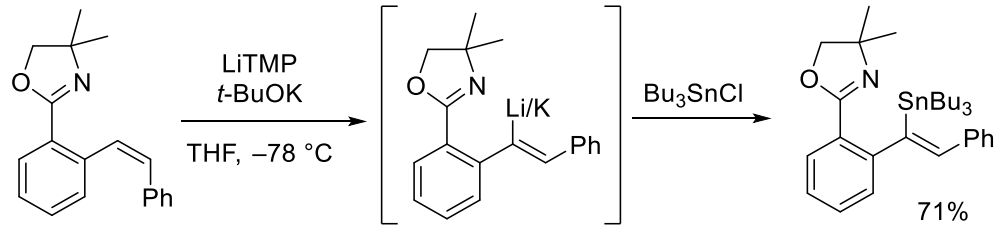
Disubstituted *trans*-aryl alkenes such as *trans*-stilbene typically undergo carbolithiation with alkyllithium reagents.[51] O'Shea and co-workers exploited more acidic nature of vinyl protons of *cis*-stilbene than that of *trans*-stilbene to induce deprotonation of symmetrical *cis*-stilbene with *s*-BuLi selectively over the carbolithiation (Scheme 16).[52]



Scheme 16. Metalation of *cis*-stilbene.

The resulting lithiated *cis*-stilbene undergoes isomerization to the more thermodynamically stable lithiated *trans*-isomer. The same group went on to further explore regioselective

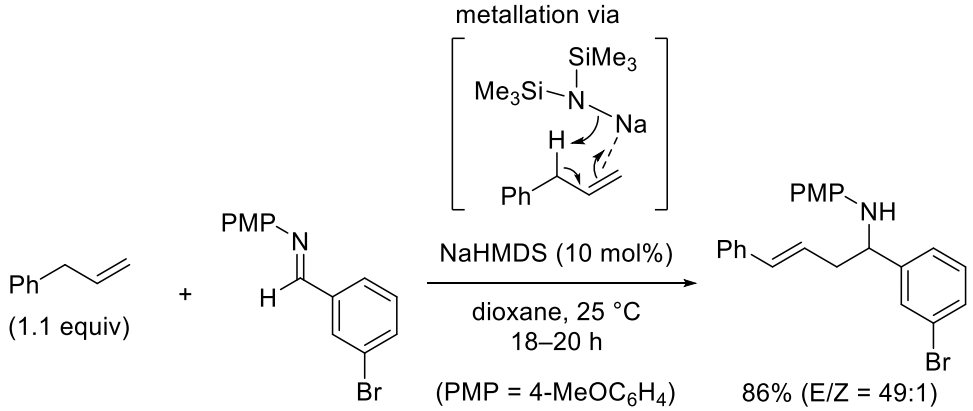
metalation of *cis*-stilbene with various ortho-directing groups using the *LIC-KOR* superbases (Scheme 17).[53] This metalated species were further functionalized with various electrophiles.



Scheme 17. Directed metalation of *cis*-stilbenes.

1.2.1.2. Metalation of allylic positions

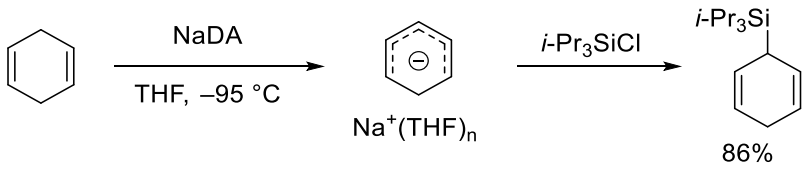
Schneider and co-workers recently reported the use of a catalytic amount of sodium hexamethyldisilazide (NaHMDS) for deprotonation of allylic C-H bond followed by the electrophilic functionalization with imines (Scheme 18).[54] The reported pK_a value of the allylic proton is about 33,[55] whereas the pK_a of HMDS is about 26 due to the α-silicon effect. Therefore, direct deprotonation of allylic proton is thermodynamically not feasible. It was proposed that π-Lewis acidity of sodium cation facilitates deprotonation of the allylic proton.



Scheme 18. Allylic nucleophilic addition towards imines.

Collum and co-workers reported the successful metalation of dienes with NaDA in THF to afford useful dienyl sodium species (Scheme 19).[56] Interestingly, the rate of sodiation of dienes

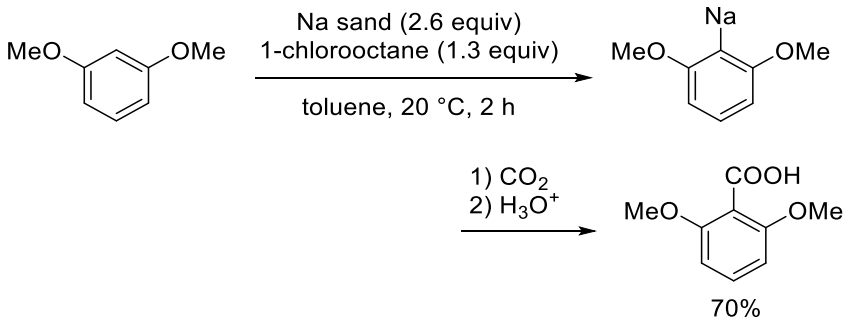
with NaDA outperformed use of more conventional choices like *n*-BuLi/TMEDA or LDA in THF.



Scheme 19. Metalation of 1,3-cyclohexadiene.

1.2.2. Metalation of (hetero)arenes

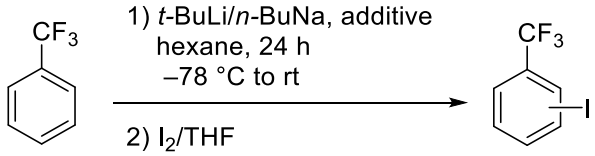
Unlike the use of organolithium reagents for the directed aromatic lithiation, the precedents on the directed aromatic sodiation/potassiation remain extremely rare. Mioskowski and Wagner reported the use of 1-chlorooctane and finely dispersed sodium sand to generate octylsodium *in situ* for the immediate sodiation of mono-, dimethoxy arenes and heteroarenes such as thiophene and benzofuran (Scheme 20).[57] The major drawback of using metallic sodium is its high reactivity towards electron-poor aromatic compounds, forming complex mixtures even before the addition of electrophiles.



Scheme 20. Sodiation using sodium sand.

Mulvey and co-workers explored the reactivity differences between *t*-BuLi and *n*-BuNa with different Lewis basic donors such as THF, TMEDA and *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (PMDETA) with the use of trifluoromethyl benzene as the substrate.[58] Significant regioselectivity differences were observed with use of *n*-BuNa over *t*-

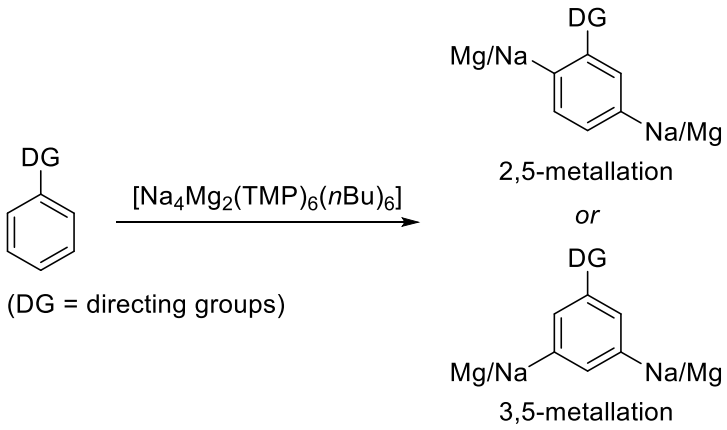
BuLi in iodine quenching experiments (Scheme 21). In all cases, the use of a Lewis base additive results in regioselective *ortho*-metalation in the reaction with *n*-BuNa over that with *t*-BuLi. The DFT studies revealed larger energy differences between the *ortho*-, *meta*-, and *para*-regioisomers of the sodiated species over the lithiated species, which are in line with the experimental observations.



metalating agent	additive	product yield (%)		
		ortho	*meta*	*para*
t-BuLi	TMEDA	65	10	6
n-BuNa	TMEDA	72	0	0
n-BuNa	PMDETA	80	1	1

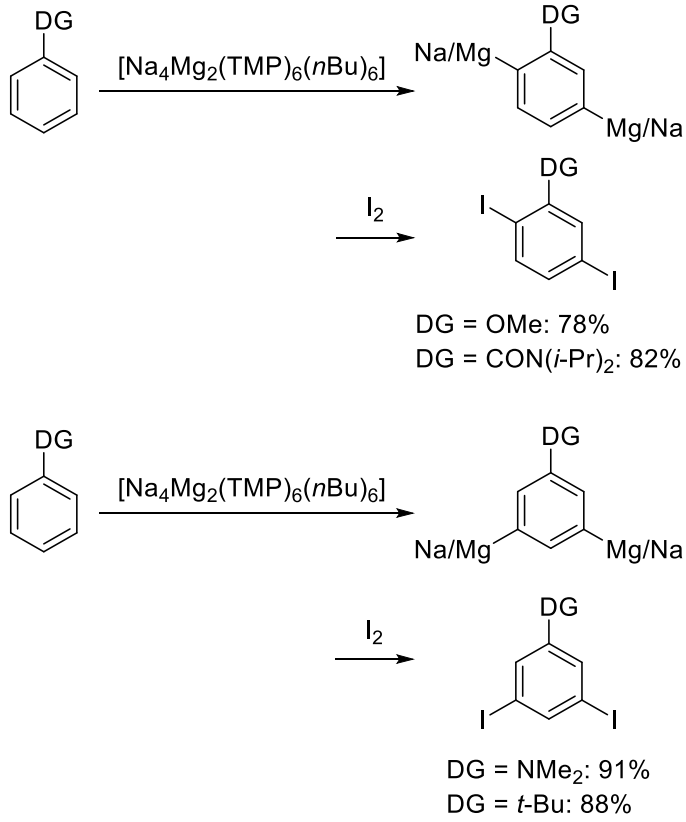
Scheme 21. Regioselective metalation of *t*-BuLi vs *n*-BuNa.

Mulvey, O'Hara and co-workers developed mixed sodium magnesium TMP amide [$Na_4Mg_2(TMP)_6(n\text{-}Bu)_6$] as a seminal templated metalating agent capable of unprecedented *ortho-meta' or meta-meta'* directed remote metalations on arenes having a directing group such as methoxy or oxazoline moiety (Scheme 22).[59]



Scheme 22. Templated metalations.

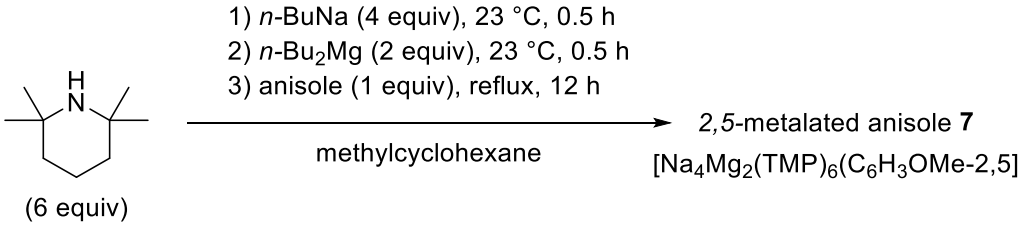
The key behind these regioselective metalations is the formation of an symmetrical inverse crown metal complex. This complex acts as a 'template', trapping the substrates in specific conformations. This allows for regioselective deprotonation at the specific sites of the arene substrates. Various arenes having different directing groups could be engaged in the templated metalation, showcasing the applicability of this protocol for regioselective metalations on distal carbons (Scheme 23). It should be noted that the regioselectivity could be uniquely switched by varying the directing group. Namely, methoxy and carboxamide groups direct metalation at *ortho*- and *meta*-positions, whereas sterically bulkier *N,N*-dimethylamine and even weakly directing *tert*-butyl groups result in *meta-meta* metalation.

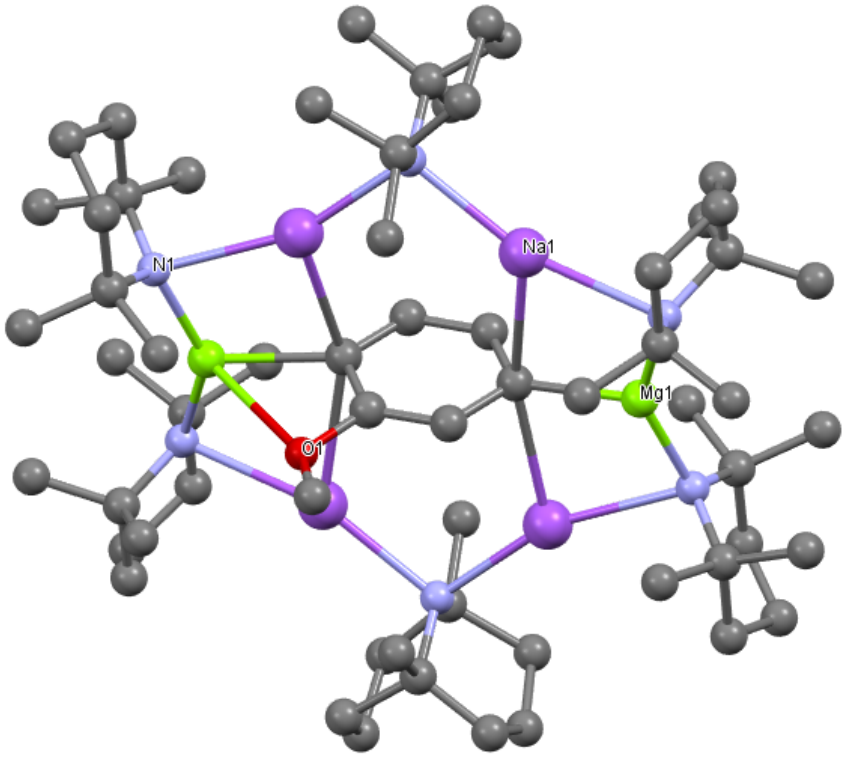


Scheme 23. Regioselective metalation using $[Na_4Mg_2(TMP)_6(n\text{-}Bu)_6]_2$.

The templated metalating agent was prepared by stirring TMP(H) with *n*-BuNa followed by *n*-Bu_2Mg. Anisole was then refluxed with the metalating agent in methylcyclohexane, providing 2,5-metalated arene **7**. The crystal structure of **7** (Scheme 24) provided valuable insights to

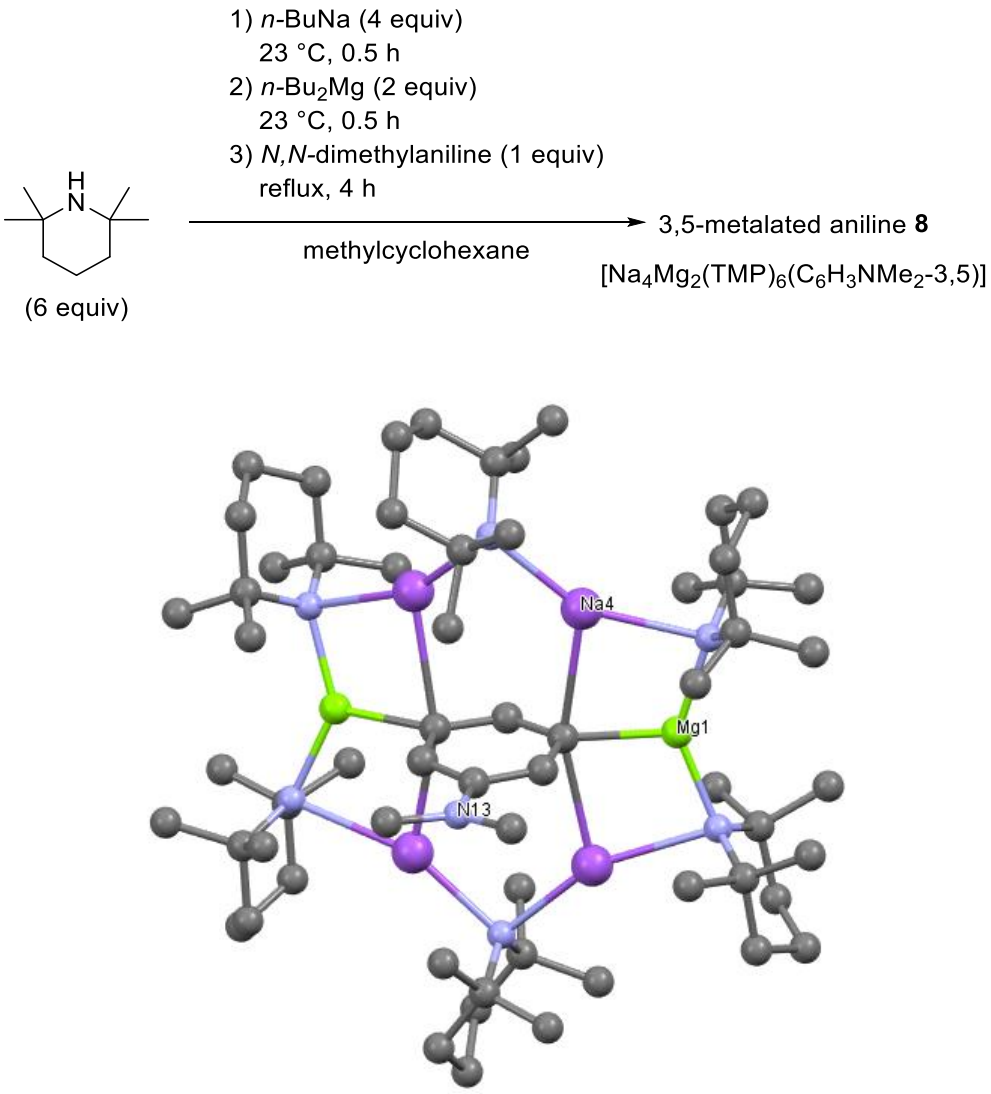
how the templated metalating agent interacts with the substrate to obtain regioselectivity. In the crystal structure of **7**, the presence of an ionic contact between Na and O atoms orientates the anisole such that the magnesium ions are directly facing towards the *2*- and *5*-position of the anisole.





Scheme 24. 2,5-metalated anisole **7** (CCDC: 1017351).

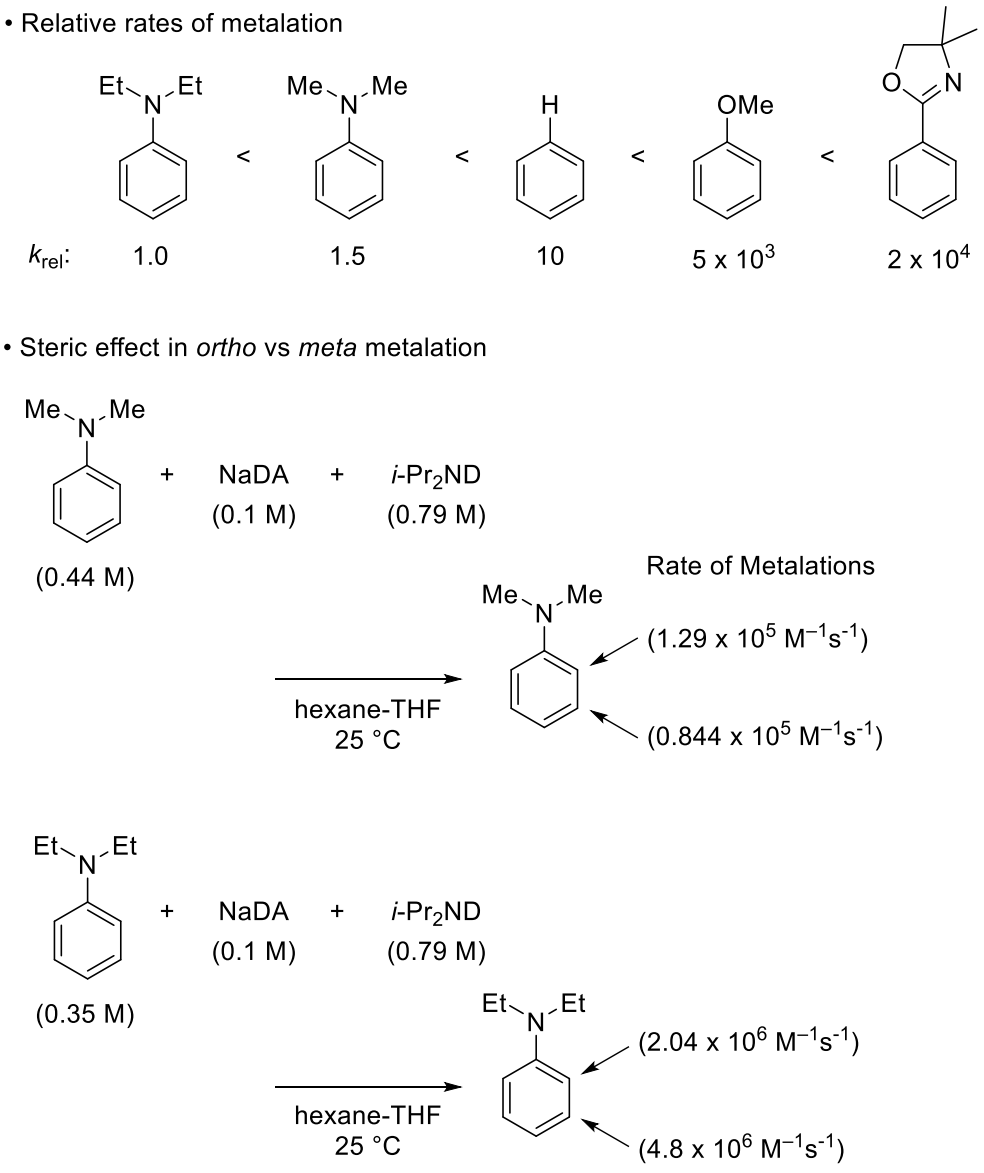
Similarly, *N*,*N*-dimethylaniline was refluxed with the templated metalating agent to obtain 3,5-metalated aniline **8**. In crystal structure of **8** (Scheme 25), steric hinderance from the dimethyl on the nitrogen atom prevents metalation on the *ortho*-position on the *N*,*N*-dimethylaniline, resulting in the 3,5-metalation.



Scheme 25. 3,5-metalated aniline **8** (CCDC: 1017352).

Collum and co-workers carried out an extensive study on the directing group effects on the aromatic ring towards *ortho/meta/para*-metalations by sodium diisopropylamide (NaDA).[60] By comparing the relative rates of metalations on substituted arenes, it was concluded that there are largely four major factors affecting the directed metalations: 1) electron-rich arenes inhibit metalation due to resonance effects, 2) the presence of a directing group (such as methoxy) significantly improves metalation rates, 3) metalation rates are promoted by functional groups that withdraw electrons through the inductive effect (such as trifluoromethyl); 4) sterically hindered substituents disturb the metalation on the *ortho*-position (Scheme 26). The kinetic

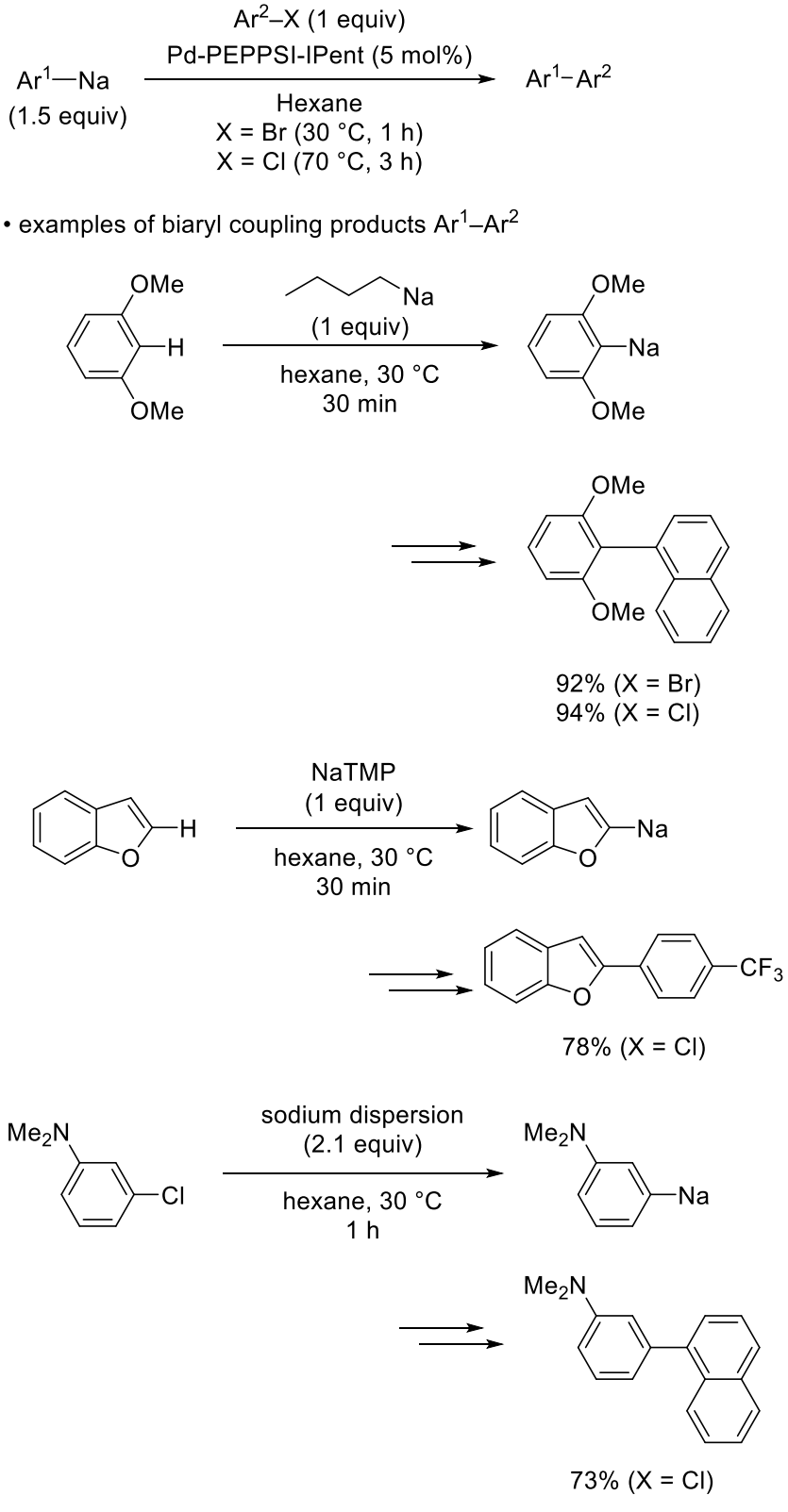
studies show an approximate half-order dependence on NaDA, showing that the species that induces the metalation should likely be monomeric in nature. The plots of rate against THF concentrations show non-zero intercepts and linear dependencies on THF concentration, which are consistent with di- and tri-solvated NaDA monomers.



Scheme 26. Factors affecting regioselectivity.

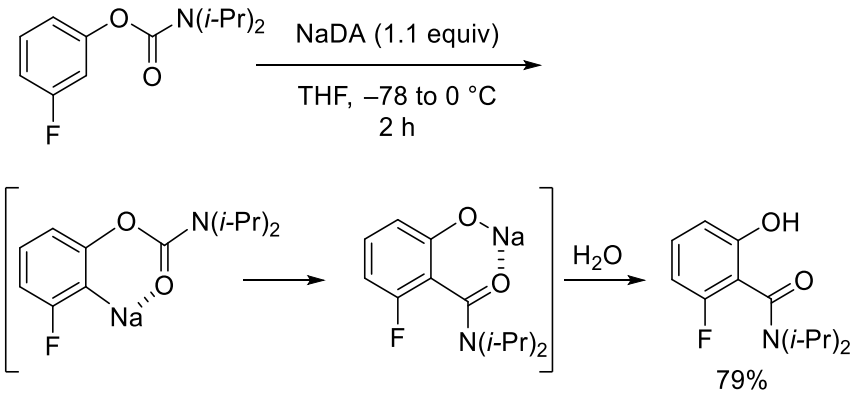
Asako and Takai recently reported the direct use of arylsodium for biaryl cross-coupling reaction under palladium catalysis (Scheme 27).[61] This methodology is complementary to the Negishi and Suzuki-Miyaura aryl cross-coupling reactions. The protocol bypasses the need to

use arylzinc and arylboron reagents, which are generally prepared from the corresponding organolithium and organomagnesium species. On the other hand, the preparation of arylsodium reagents is mediated by directed sodiation by *in-situ* generated pentylsodium, deprotonation *via* NaTMP or reduction of organohalides with sodium dispersion. The ensuing cross-coupling with bromo- and chloroarenes was practiced under palladium catalysis.



Scheme 27. Biaryl cross-coupling between arylsodium and aryl halides with palladium catalysis.

Building on the utility of metalation mediated by sodium diisopropylamide, Collum recently reported NaDA-mediated Snieckus-Fries Rearrangement (Scheme 28).[62] Although anionic Fries rearrangements were typically carried out using strong bases such as LDA,[63] use of NaDA results in a faster metalation to form the arylsodium intermediate.

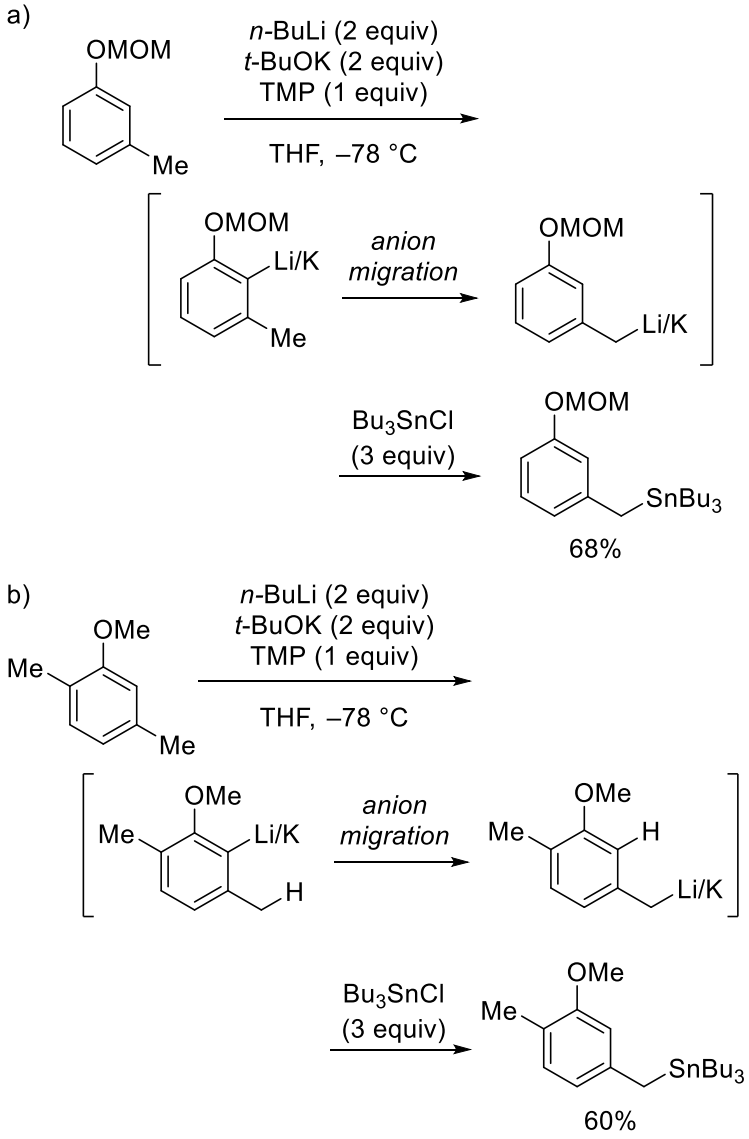


Scheme 28. NaDA mediated Snieckus-Fries rearrangement.

1.2.3. Metalation of alkyl(hetero)arenes

In contrast to the widespread use of metal amide bases for directed aryl metalation, metalations on the benzylic positions remains underutilized. This is largely due to the difficulty in achieving selective benzylic metalations in the presence of the directing groups, which commonly prefer to induce *ortho*-aromatic metalations. In this regards, O'Shea and co-workers reported a general protocol for the benzylic metalation of methylarenes having a directing group using a mixture of BuLi/*t*-BuOK/TMP at –78 °C,[64] where the migration of aryl anion, firstly formed by the kinetically favored *ortho*-aromatic metalation, to the thermodynamically more stable benzylic anion, is the key to enable remarkable selectivity for the benzylic metalation. The efficiency of the metalation is thus dependent on the relative acidity of the benzylic protons. The metalated benzylic anions were subsequently trapped by various electrophiles (Scheme 29a). Interestingly, treatment of 2,5-dimethylanisole led to the metalation of the *meta*-methyl

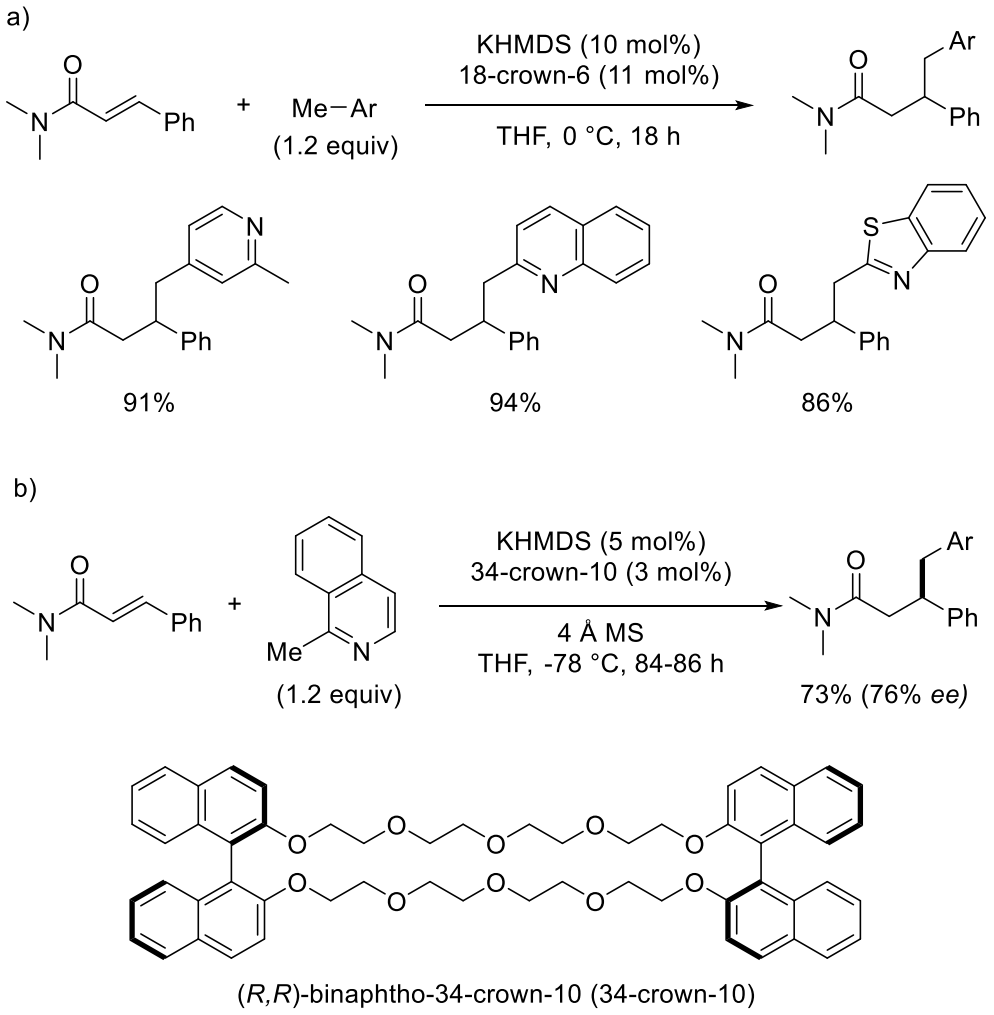
group over the *ortho*-methyl group. This highlights the fact that the heteroatom coordination is not a factor in the overall outcome for this benzylic metalation (Scheme 29b). Further improvements to the methodology with the use heptane as a solvent have allowed the process to take place at ambient temperature.[65]



Scheme 29. Regioselective metalation of benzylic protons.

The catalytic variant for the benzylic metalations of alkylarenes are extremely rare due to the low acidity of the benzylic protons, hindering any potential catalytic turnover with the regeneration of the reactive base. Kobayashi and co-workers developed 1,4-addition of alkylazaarenes to unsaturated amides by using catalytic KHMDS and 18-crown-6 in THF

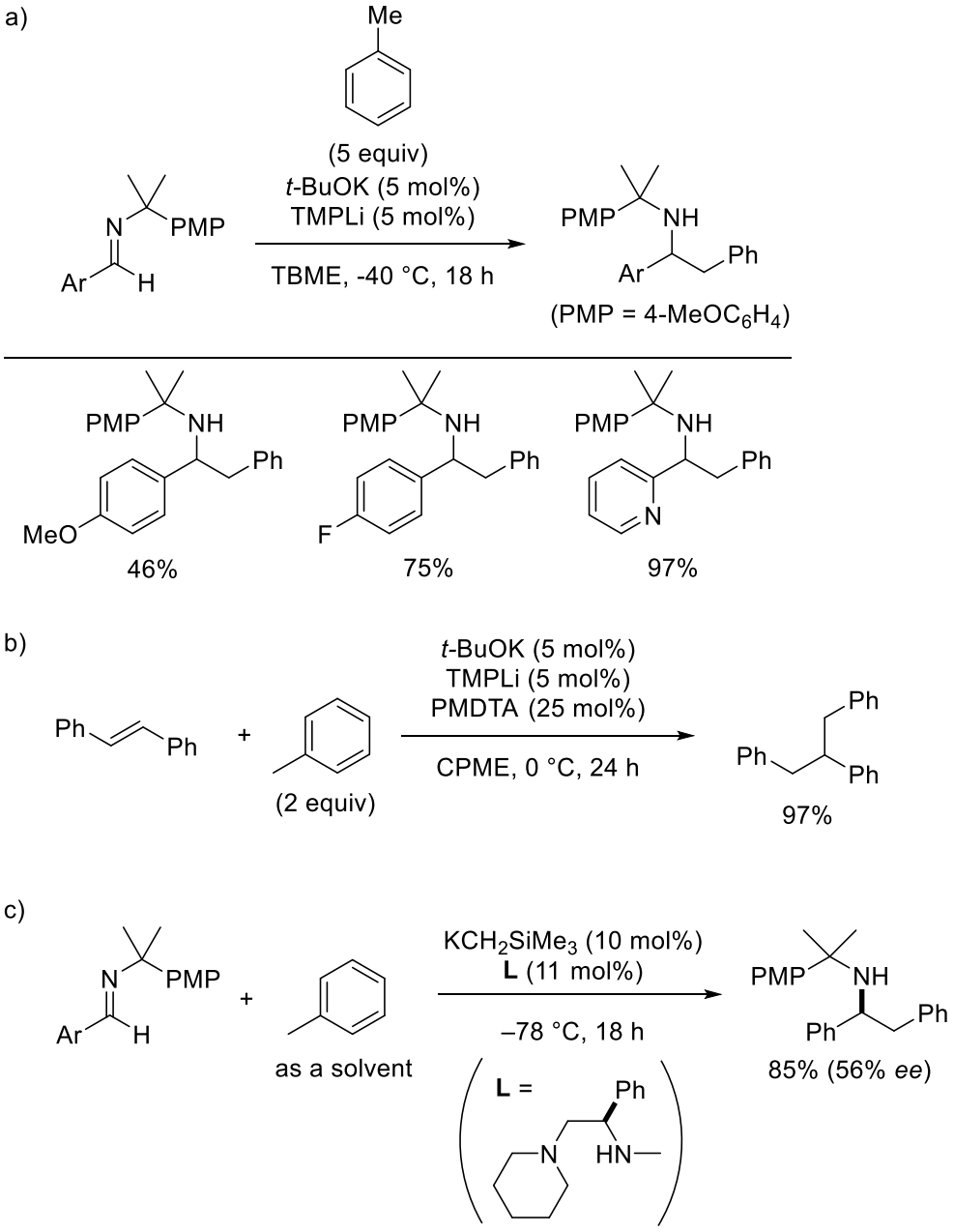
(Scheme 30a).[66] The reaction was regioselective towards more acidic benzylic protons. Namely, the reaction of 2,4-dimethylpyridine afforded a *para*-substituted product over *ortho*-substituted product.[67] The asymmetric variant was also achieved by engaging a chiral crown ether (Scheme 30b).



Scheme 30. Catalytic and enantioselective 1,4-additions towards unsaturated amides.

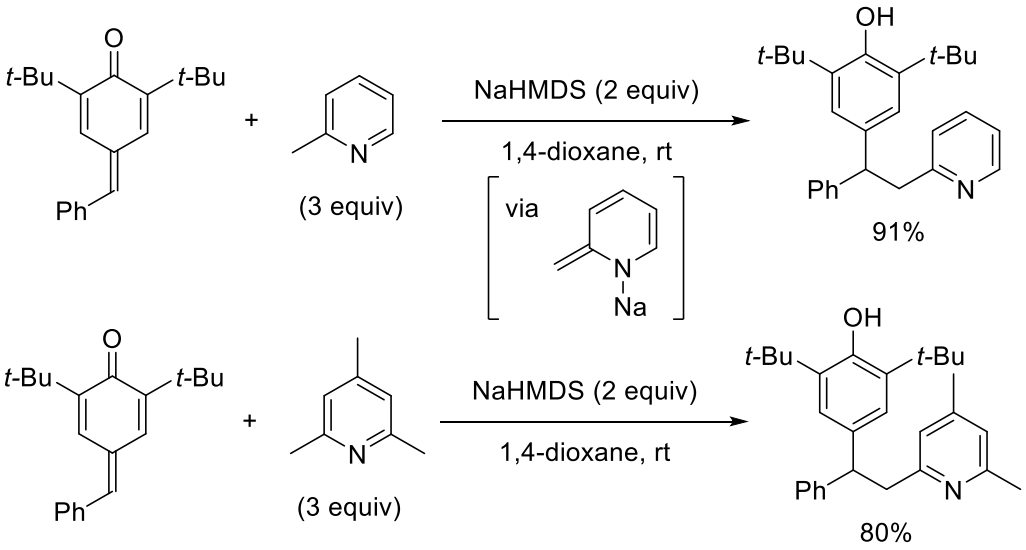
They have also developed a catalytic addition of alkylarenes to aldimines and styrenes (or conjugated alkenes) with the use of a mixture *t*-BuOK and LiTMP (Scheme 31).[68] Similar to the O'Shea's work,[64-65] both *t*-BuOK and LiTMP were found to be essential to facilitate the process. Both electron-rich and electron-poor arenes were found to react efficiently, while electron-poor imines tend to give higher yields under the reaction conditions (Scheme 31a).

The process is mediated via regeneration of active amide base (Li/KTMP) or direct regeneration of benzylic carbanion by metal amide intermediate, that is formed from aldimine and benzylic carbanion. The reaction was also amenable to conjugated alkenes such as *trans*-stilbene in the presence of *N*,*N*,*N*',*N*'',*N*''-pentamethyldiethylenetriamine (PMDTA) as an additive (Scheme 31b). A preliminary demonstration of an asymmetric variant of this reaction was shown using a chiral diamine ligand (Scheme 31c).



Scheme 31. Catalytic 1,2-addition of alkylarenes.

Kaliyamoorthy and co-workers developed base-promoted conjugate addition of alkylazaarenes to *para*-quinone methides (Scheme 32).[69] The reaction was amenable to quinone methides containing both electron-withdrawing and electron-donating groups and various heteroarenes could be engaged as the nucleophile. In sharp contrast to the Kobayashi's report,[66] C2-selective functionalization was observed in the reaction of 1,3,5-trimethylpyridine and the addition of crown ethers renders the reaction sluggish. These observations brought a mechanistic proposal that the metal cation acts as a Lewis acid coordinating to the nitrogen of the azaarenes, which allows for more facile deprotonation at the C-2 benzylic proton to form the sodium enamide nucleophile.

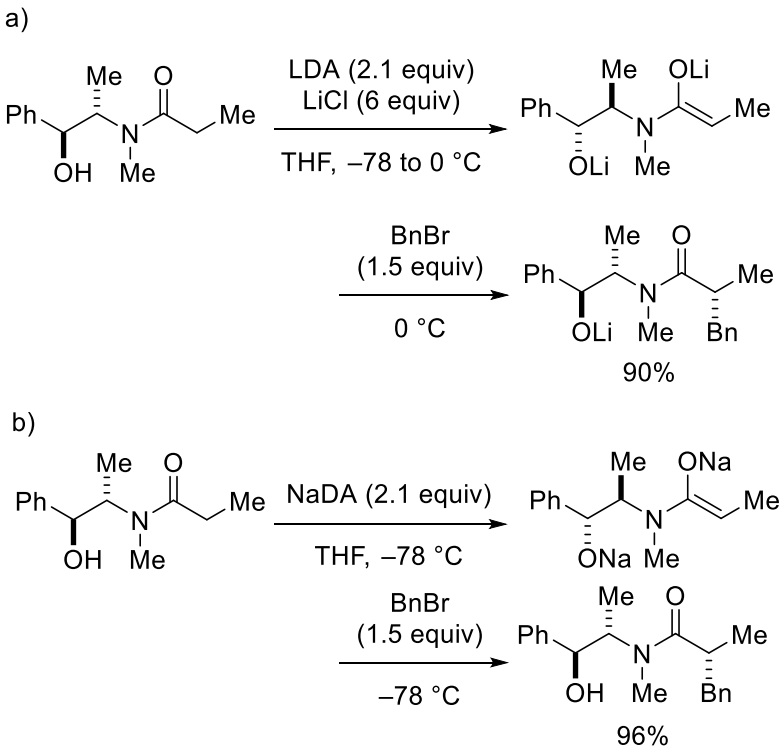


Scheme 32. Conjugate addition of alkylazaarenes to *para*-quinone methides.

1.2.4. Metalation of carbonyl compounds and their derivatives

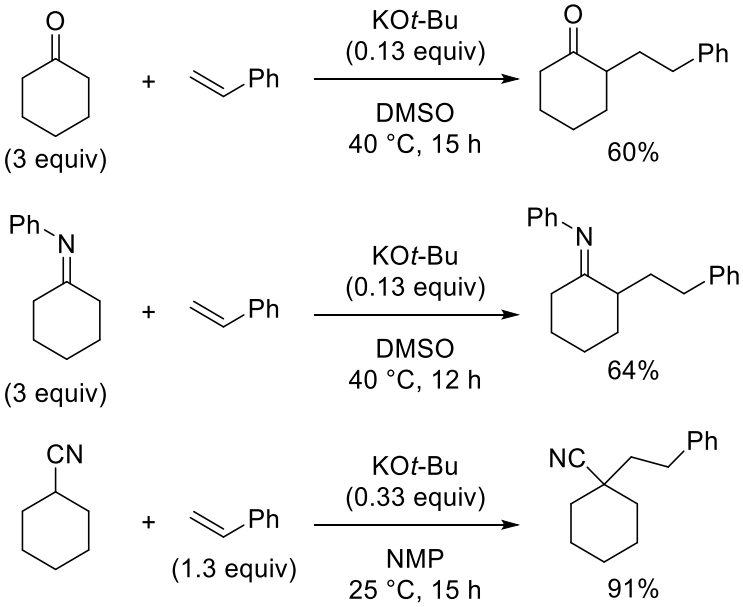
Sterically hindered alkali metal amides such as LDA are non-nucleophilic, thus serving only as a Brønsted base in general. This makes them ideal reagents for the generation of enolates via deprotonation of the α-proton from enolizable carbonyl compounds and their derivatives. For example, the preparation of the dianionic Myers chiral enolates engages LDA in the

presence of excess amounts of LiCl to induce the desired C-alkylation selectively by preventing the *O*-alkylation (Scheme 33a).[70] Collum recently reported a LiCl-free protocol that employs NaDA as an efficient base for diastereomeric alkylation of the Myers enolates (Scheme 33b).[71] The careful control of the reaction temperature prevents the formation of inert higher order aggregates.

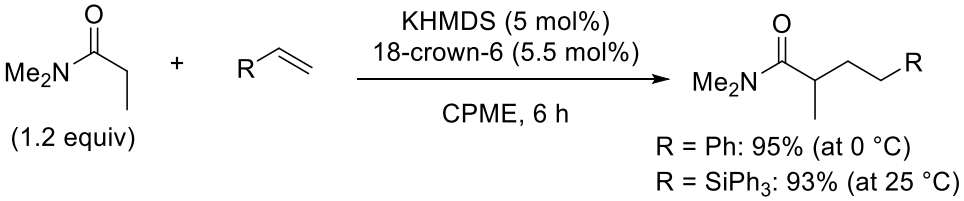


Scheme 33. Diastereoselective alkylation of the Myers enolates.

In 2000, Knochel reported α-alkylation of carbonyl compounds and their derivatives including ketones, imines and nitriles with styrenes mediated by potassium *tert*-butoxide (Scheme 34).[72] Recent contributions by Kobayashi[73] and Barham[74] successfully engage carboxamides having less acidic α-protons as a nucleophile, where not only styrenes but also vinyl silanes can be employed as an electrophile (Scheme 35).

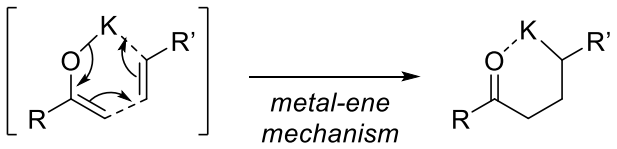


Scheme 34. Alkylation of enolates with styrenes catalyzed by KO*t*-Bu.



Scheme 35. Alkylation of carboxyamides catalyzed by KHMDS.

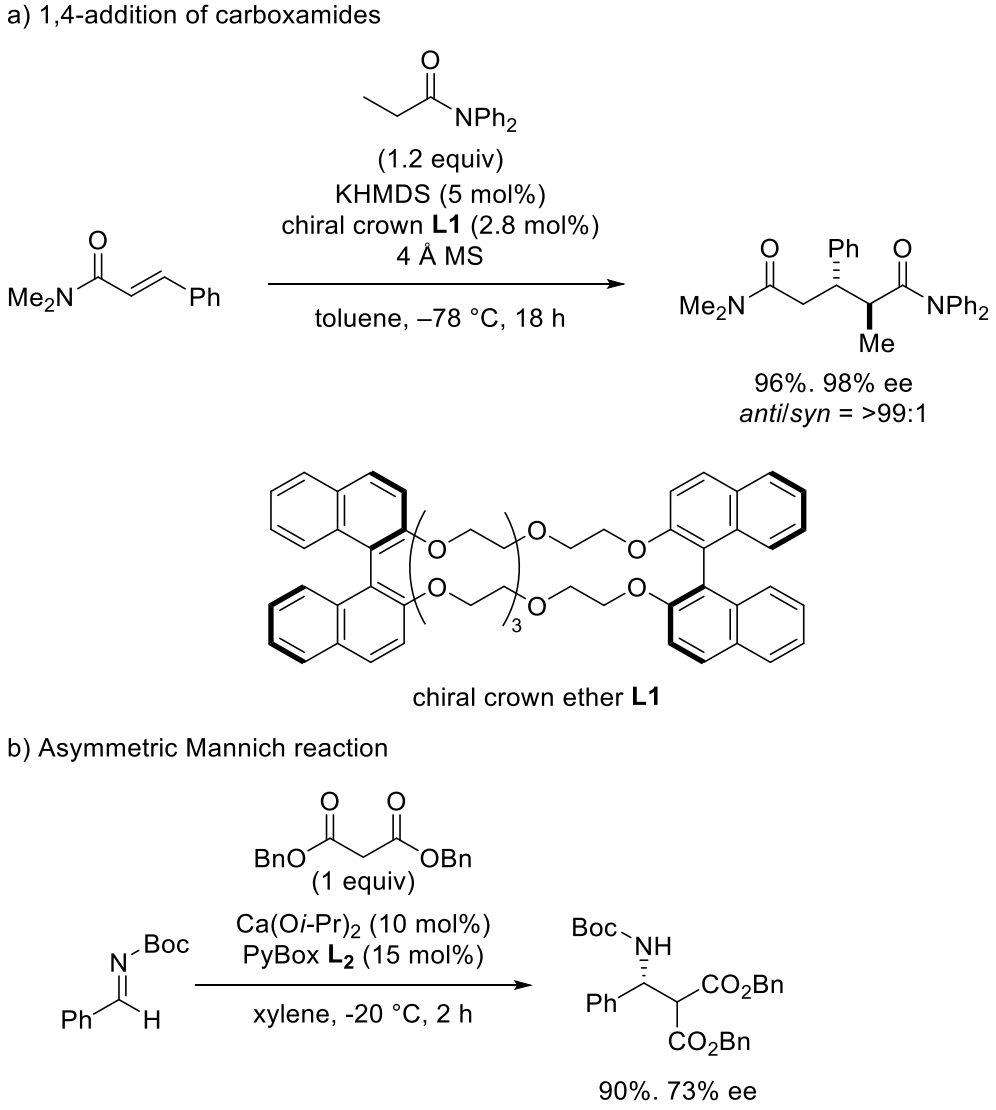
The mechanistic studies by Barham suggested that the process involves a rate-determining metal-ene type C-C bond formation step (Scheme 36).[75]



Scheme 36. Metal-ene mechanism.

Kobayashi recently reported an asymmetric *anti*-selective 1,4-addition of unactivated carboxamides to α,β-unsaturated carboxamides using a catalytic amount of KHMDS and chiral macro crown ether, binaphtho-34-crown-10 (Scheme 37a).[76] Interestingly, the use of other alkaline metal cations resulted in lower yields and/or lower diastereoselectivity. For

comparison, the use of a chiral calcium pyridinebisoxazoline (PyBox) complex for an asymmetric Mannich reaction between malonates and *N*-Boc imines gave only moderate enantioselectives (Scheme 37b).[77]



Scheme 37. Asymmetrical 1,4-addition of carboxamides to α,β-unsaturated carboxamides and asymmetric Mannich reaction.

1.3. Sodium and Potassium Hydrides

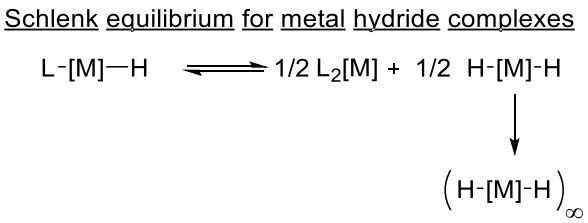
Alkali metal hydrides are one of the most used reagents for routine deprotonation of oxo-acids or acidic α-protons on carbonyls or nitriles.[78-80] These alkali metal hydrides form NaCl-type lattice structures, where each metal cation is surrounded by 6 hydride anions. An important property of these metal hydride is its inherent high lattice energies due to their highly ionic nature (**Table 1**). Generally, these lattice energies are reflective of their reactivities. Going down the group, as the lattice energies of the metal hydrides decrease, they become increasingly reactive. For instance, LiH is highly inert. It does not react with O_2 or even HCl[81] without heating and is unreactive towards tertiary alcohols[82] at room temperature.

Table 1. Lattice energies for group I metal hydrides.[83]

Alkali Metal Hydrides	Lattice Energy (kJ mol^{-1})
LiH	920
NaH	810
KH	710
RbH	690
CsH	650

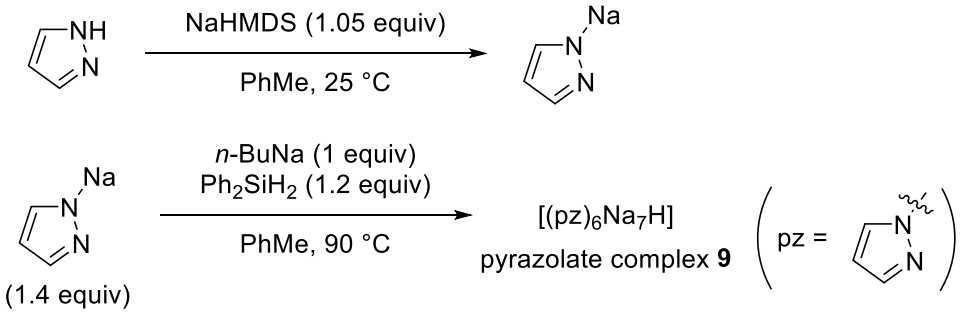
One way to improve the reactivity of these metal hydrides is to solubilize them in organic solvents. The most widely used reagents are the covalent hydride complexes such as borohydrides, aluminum hydrides.[84-85] However, these hydridic complexes are best viewed as $Li^+BH_4^-$ or $Li^+AlH_4^-$ where the metal cation is acting as charge balancers and as such, cannot be strictly considered as metal hydrides. These complexes are only distally related to the alkali metal hydrides and will not be discussed.

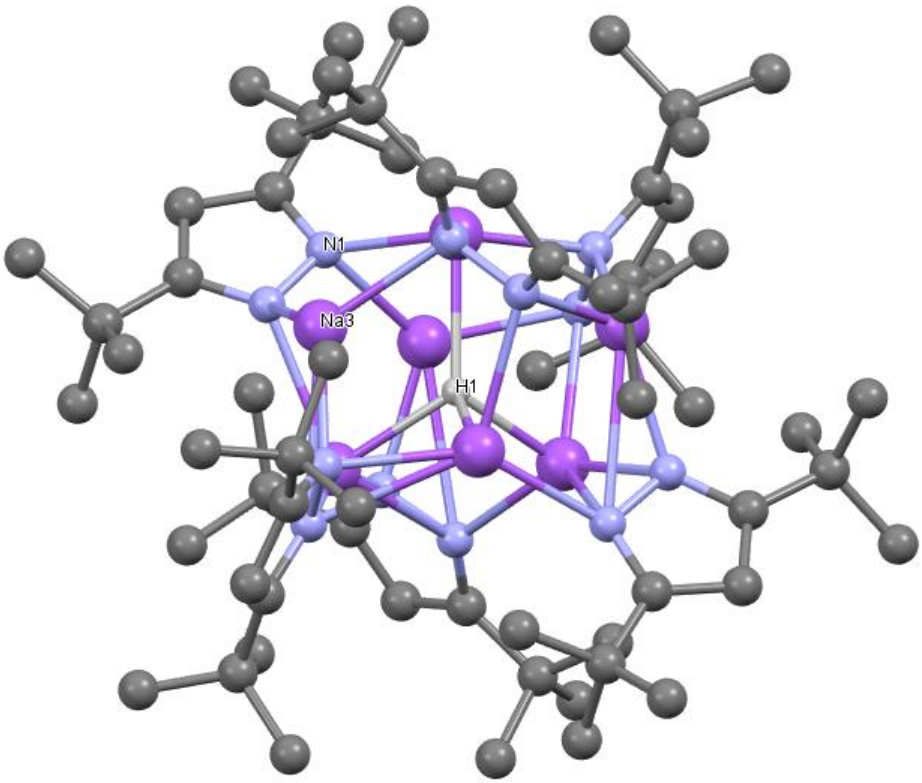
The major challenge in solubilizing metal hydrides is overcoming the Schlenk equilibrium.[86] Due to its high lattice energies and insolubility in organic solvents, formation of any form of molecular metal hydrides is highly unstable and will quickly aggregate to its polymeric form (Scheme 38).



Scheme 38. The Schlenk equilibrium of metal hydride complexes.

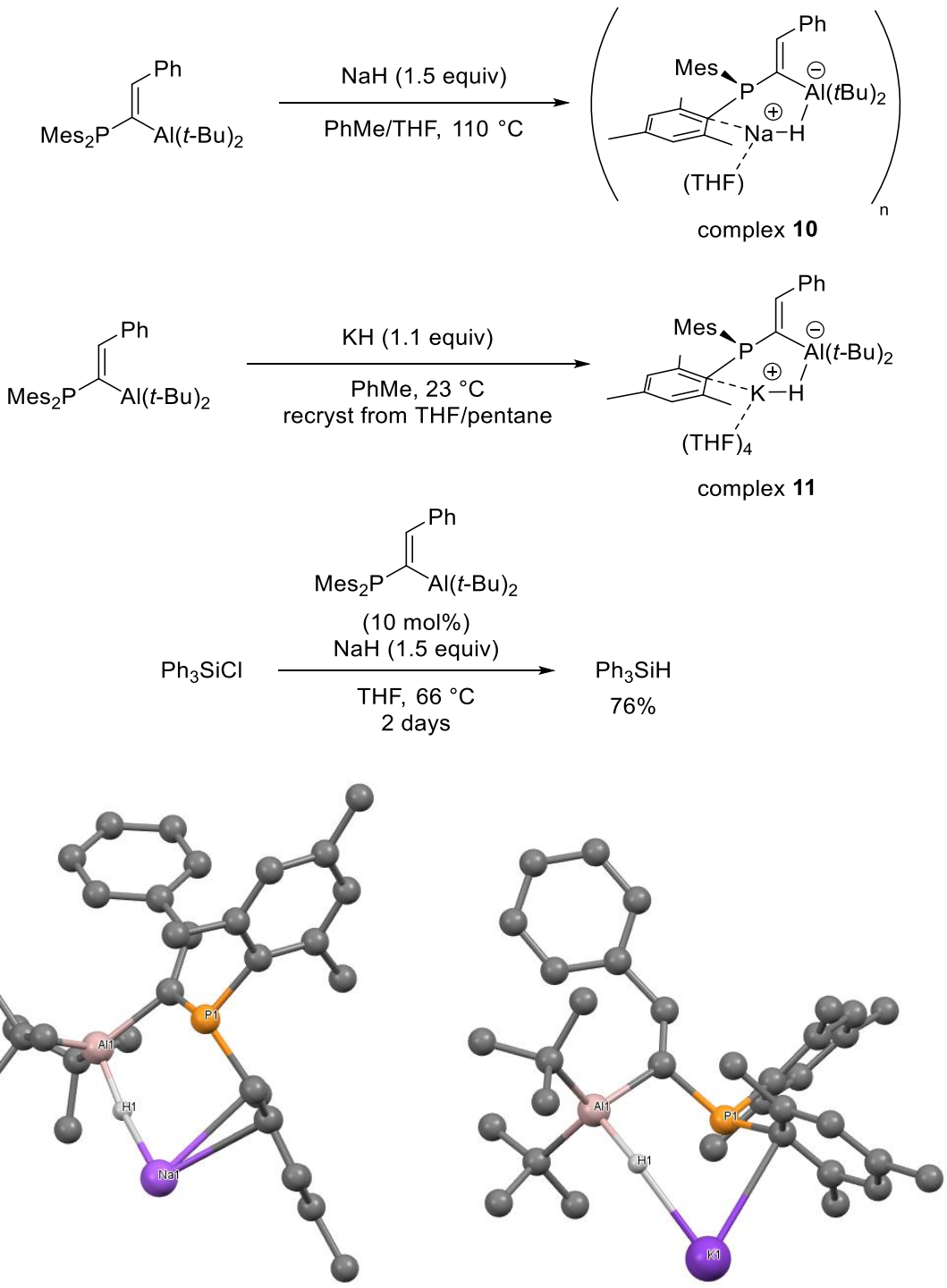
Stasch have managed to overcome the Schlenk equilibrium using a bulky pyrazolate ligand to stabilize the molecular sodium hydride complex. Sodium pyrazolate was first prepared from the deprotonation of pyrazole with NaHMDS. The sodium pyrazolate was then subjected to *n*-BuNa and diphenylsilane as the hydride source to form complex **9**. The synthetic utility of this sodium hydride complex was not explored.





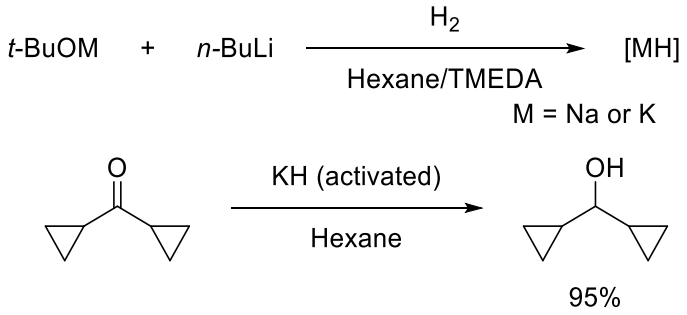
Scheme 39. Pyrazolate-stabilized sodium hydride complex **9** (CCDC: 1043423).

Uhl and coworkers[87] reported a frustrated Lewis pair (FLP) activated sodium hydride complex **10** and potassium hydride complex **11** (Scheme 40). The FLP alkali metal hydride complexes were prepared by reacting the phosphorus aluminum precursors directly with bulk sodium hydride and potassium hydride. The FLP is demonstrated to be able to catalytically activate sodium hydride for the reduction of triphenylchlorosilane into triphenylsilane.



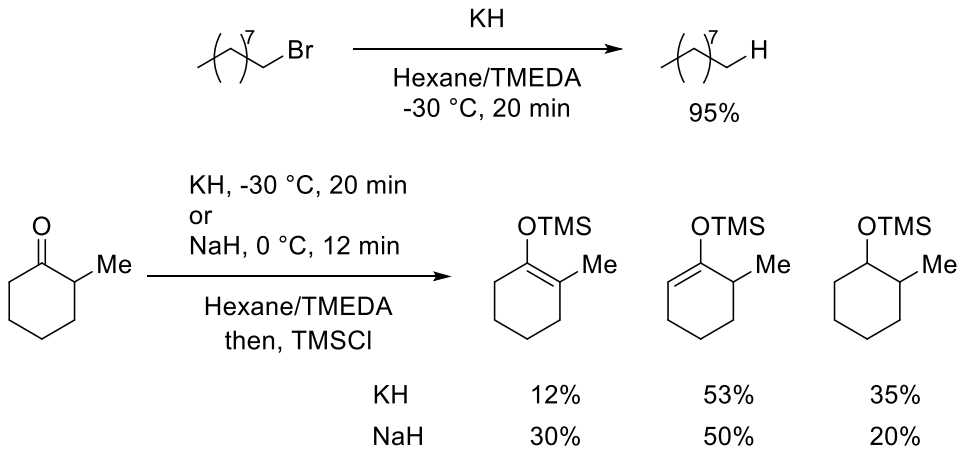
Scheme 40. FLP activated sodium complex **10** and potassium complex **11**. (CCDC: 866809 & 866810)

Early studies by Brandsma and coworkers showed that highly reactive alkali metal hydrides can be freshly generated through the deprotonation of molecular H_2 with a mixture of *n*-BuLi with *t*-BuOM (M = Na or K) in hexane/TMEDA (Scheme 41).[88] These highly active hydride species appear as insoluble fine precipitate in a suspension and are able to readily reduce dicyclopropyl ketone to its alcohol where their corresponding commercially available metal hydride are less reactive.



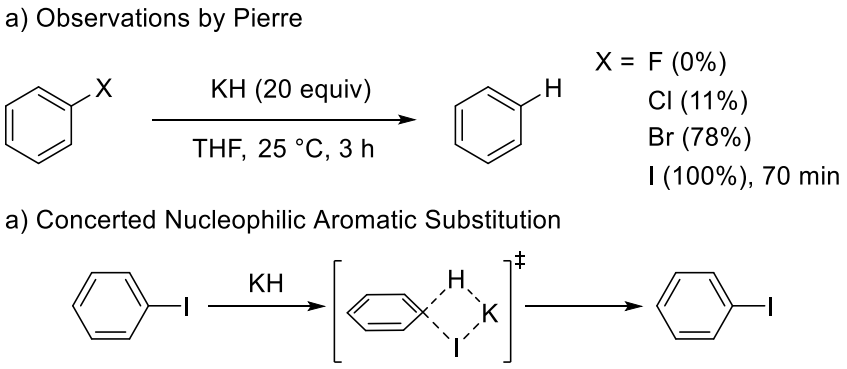
Scheme 41. Generation of active metal hydride species using superbase mixtures.

Further studies demonstrated that the *in situ* generated KH is capable to reducing 1-bromodecane to furnish *n*-decane (Scheme 42).[89] The use of the active metal hydrides and with 2-methylcyclohexanone afforded a mixture of TMS protected alcohol and silyl enol ether products upon quenching with TMSCl.



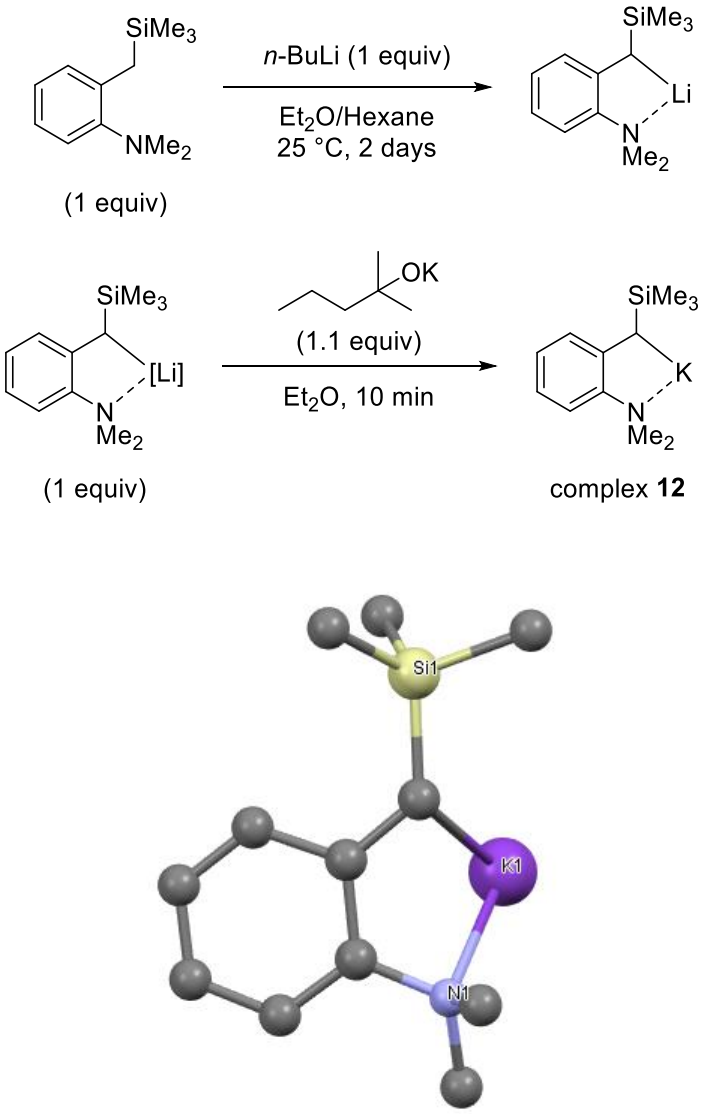
Scheme 42. Reactions of activated metal hydride.

Early studies by Pierre and coworkers[90] showed that hydrodehalogenation of halobenzenes can occur with the use of potassium hydride in THF (Scheme 43a). Interestingly, they observed that iodobenzene reacted in the fastest rate, followed by bromobenzene and finally chlorobenzene. Fluorobenzene did not undergo hydrodehalogenation at all. The rate of reactivities was inverse from classical nucleophilic aromatic substitution and simple halobenzenes without any electron withdrawing groups could be used. This led to their conclusion that a concerted nucleophilic aromatic substitution via a 4-membered ring transition state might be taking place instead of a classical addition-elimination nucleophilic aromatic substitution (Scheme 43b). This proposed mechanism was later confirmed via DFT by Murphy and Tuttle.[91]

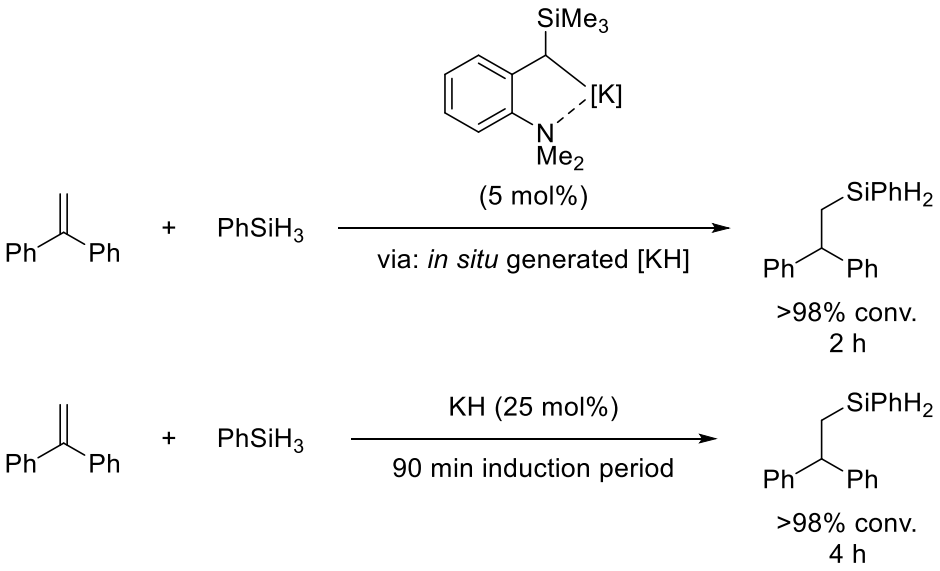


Scheme 43. Hydrodehalogenation of halobenzenes by potassium hydride.

Recent studies by Harder showed that highly reactive potassium hydride can also be generated through the reaction of phenylsilane and a benzylpotassium derivative, prepared from the reaction between ((2-(dimethylamino)phenyl)(trimethylsilyl)methyl)lithium ((DMAT)Li) and potassium 2-methylpentan-2-olate (Scheme 44).[92] While the hydrosilylation of diphenylethylene (DPE) using commercially available KH requires a 90 min induction period before the formation of any product, the *in situ* generated KH requires a lower catalytic loading and half the reaction time for reaction completion (Scheme 45. Difference in reactivities between *in situ* generated KH and commercially available KH.).

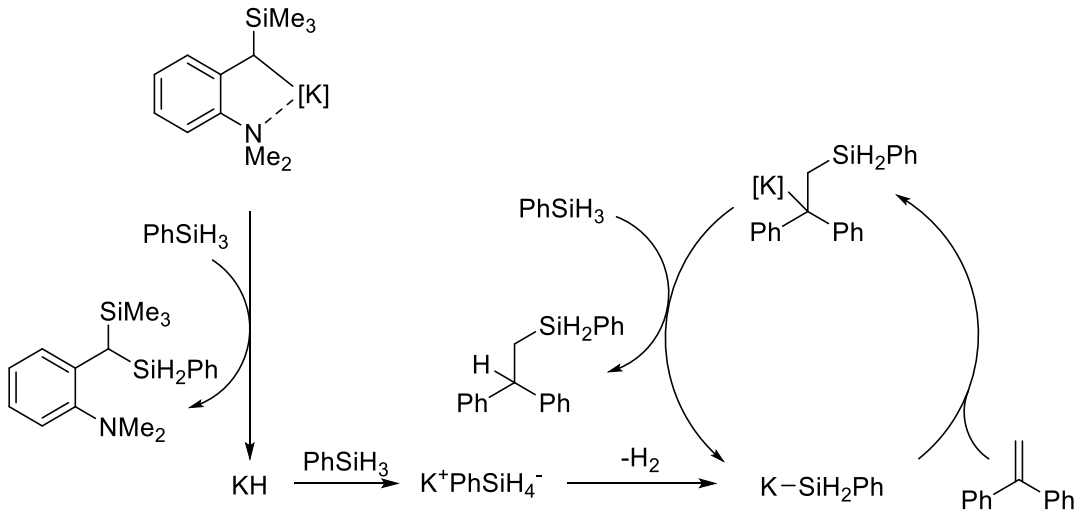


Scheme 44. (DMAT)K complex **12**. (CCDC: 181280).



Scheme 45. Difference in reactivities between *in situ* generated KH and commercially available KH.

The catalytic cycle involves the reaction between *in situ* generated KH with $PhSiH_3$ to form a hypervalent silicon species $PhSiH_4^-K^+$ which then decomposes to $PhSiH_2^-K^+$ with the loss of hydrogen (Scheme 46). The addition of DPE to the silane gives the metalated $PhSiH_2CH_2CPh_2^-K^+$ intermediate which undergoes σ-bond metathesis to furnish the hydrosilylated product along with the regeneration of potassium dihydrophenylsilane.

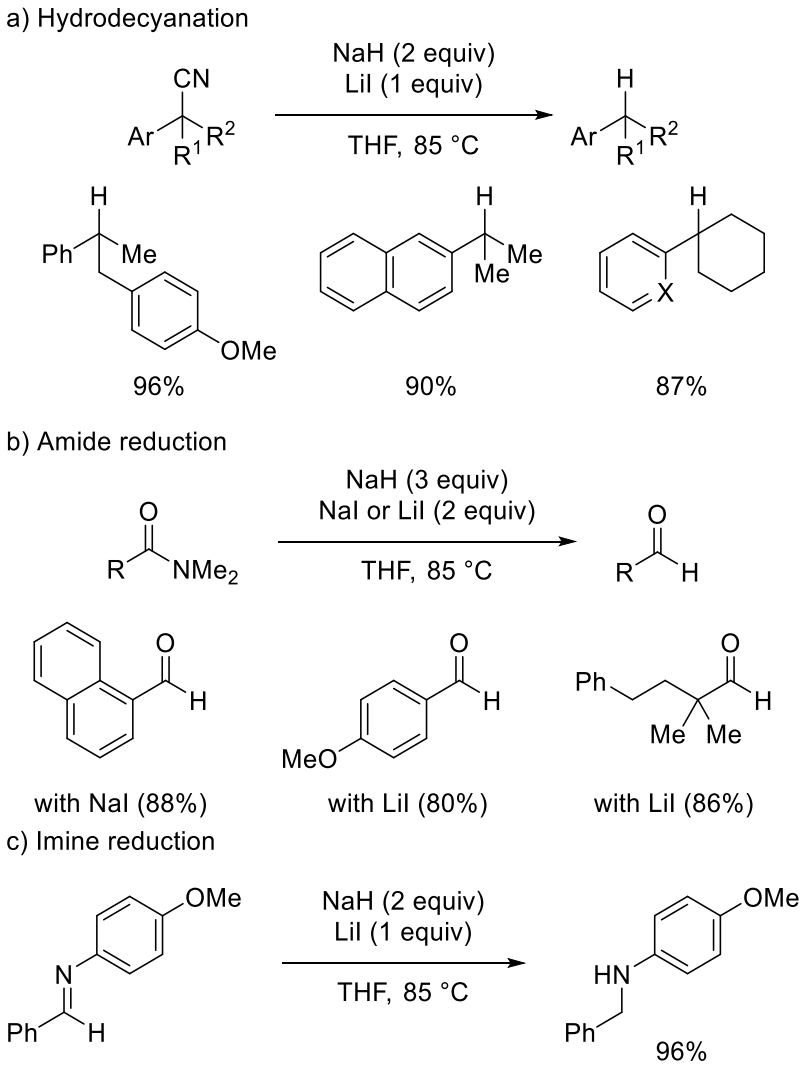


Scheme 46. Catalytic cycle of hydrosilylation of DPE by initiated by KH.

The reactivities of sodium hydride can also be enhanced through the addition of additives. Our group discovered that the solvothermal treatment of bulk sodium hydride with dissolving iodide salts in THF endows a unique hydridic character with sodium hydride. The composite was examined through powder X-ray diffraction, solid state NMR and X-ray photoelectron spectroscopy, revealing that it comprises of activated sodium hydride interlaced between sodium iodide.[93] It is proposed that counter-ion metathesis between sodium hydride and the iodide salt creates nanomeric sodium hydride (Scheme 47). The DFT calculations shows that these nanomeric sodium hydride shows hydridic reactivities similar to those of covalent hydrides.

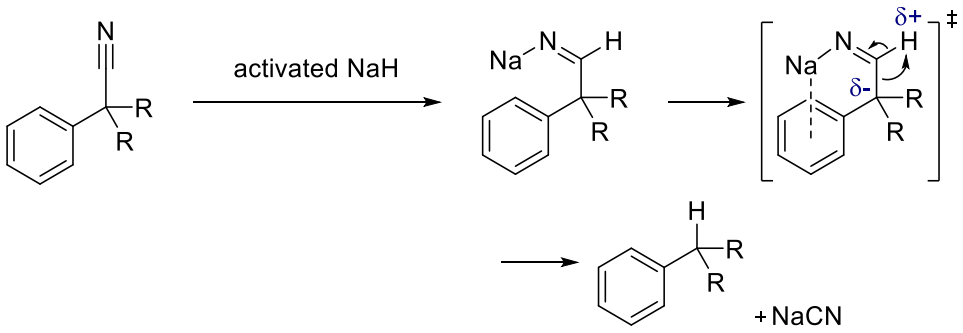
Scheme 47. Formation of NaH-NaI composite via counter-ion metathesis.

The sodium-iodide composite is able to effect the hydride reduction of various π-polar electrophiles such as α-quaternary nitriles (Scheme 48a), amides (Scheme 48b) and imines (Scheme 48c).



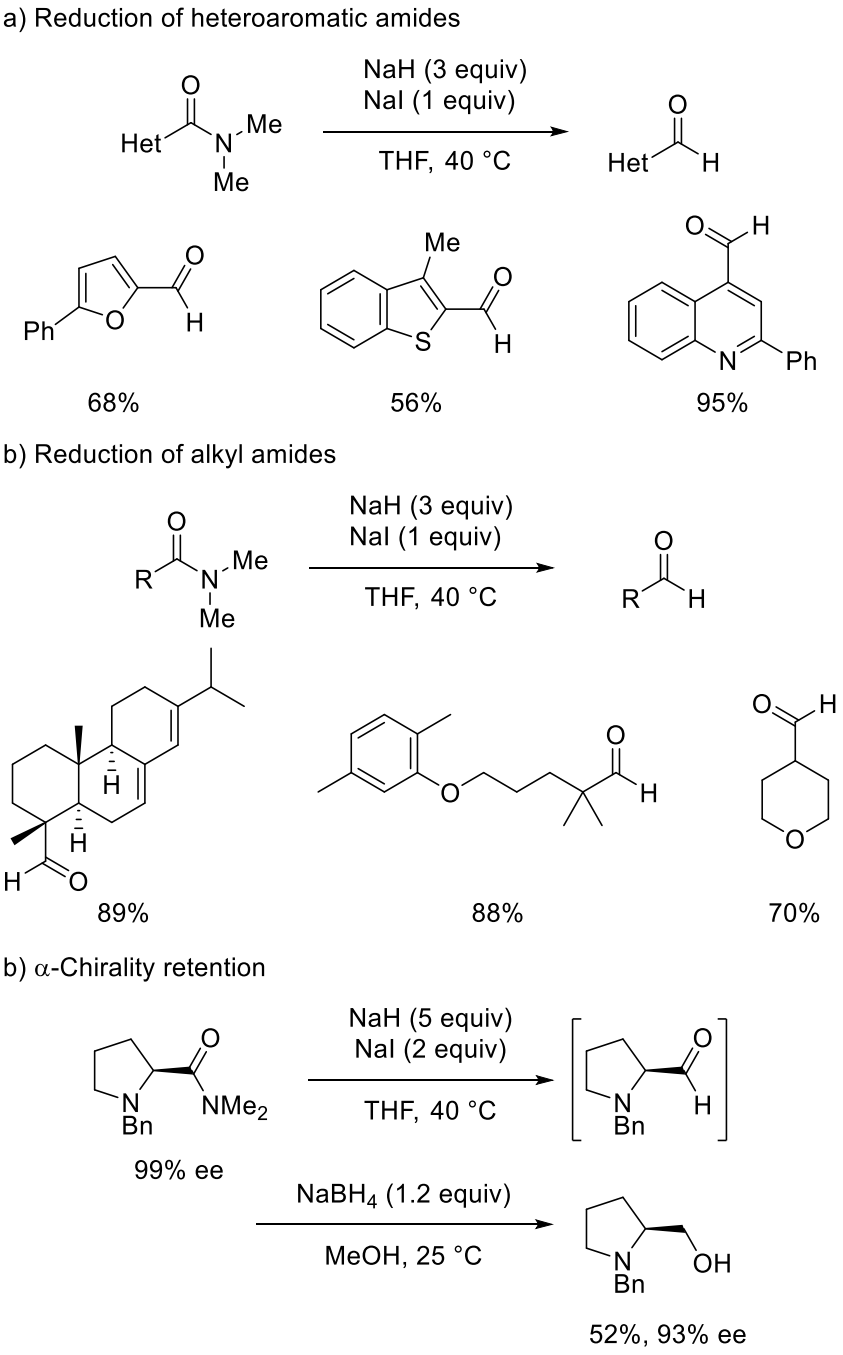
Scheme 48. Sodium hydride-iodide composite reduction of π-polar electrophiles.

The decyanation begins with a facile hydride reduction of the nitrile with sodium hydride to generate the sodium/lithium imines (Scheme 49). Cation-π interaction between the alkali metal and the aromatic ring facilitates a concerted C-C bond cleavage followed by a 1,2-proton shift to provide the hydrodecyanated product along with sodium/lithium cyanide. Due to the requirement for the cation-π interaction and high basicity of activated sodium hydride, the reaction scope is only limited towards α-quaternary benzylcyanides.



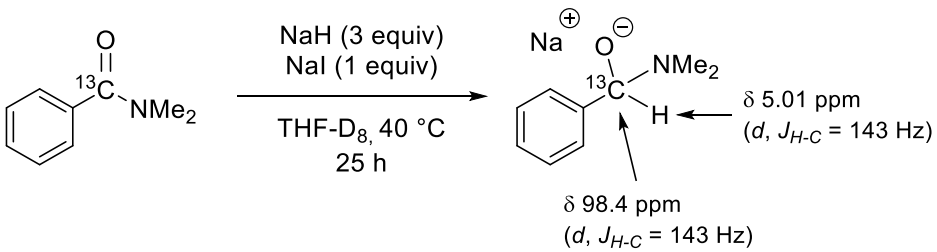
Scheme 49. Mechanism behind the hydrodecyanation of α-quaternary nitriles.

Our group has expanded the scope for the controlled reduction of *N*,*N*-dimethylcarboxamides to aldehydes with the sodium hydride-iodide composite.[94] The reaction conditions were optimized to be milder and various heteroaromatic (Scheme 50a) and alkyl amides (Scheme 50b) were reduced in good to excellent yields. α-Enantioenriched amides were also reduced with minor loss of enantiomeric excess (Scheme 50c), however, a reverse quench method, where the crude mixture was slowly quenched via addition into a pH 7 phosphate buffer solution, was required to minimize epimerization.



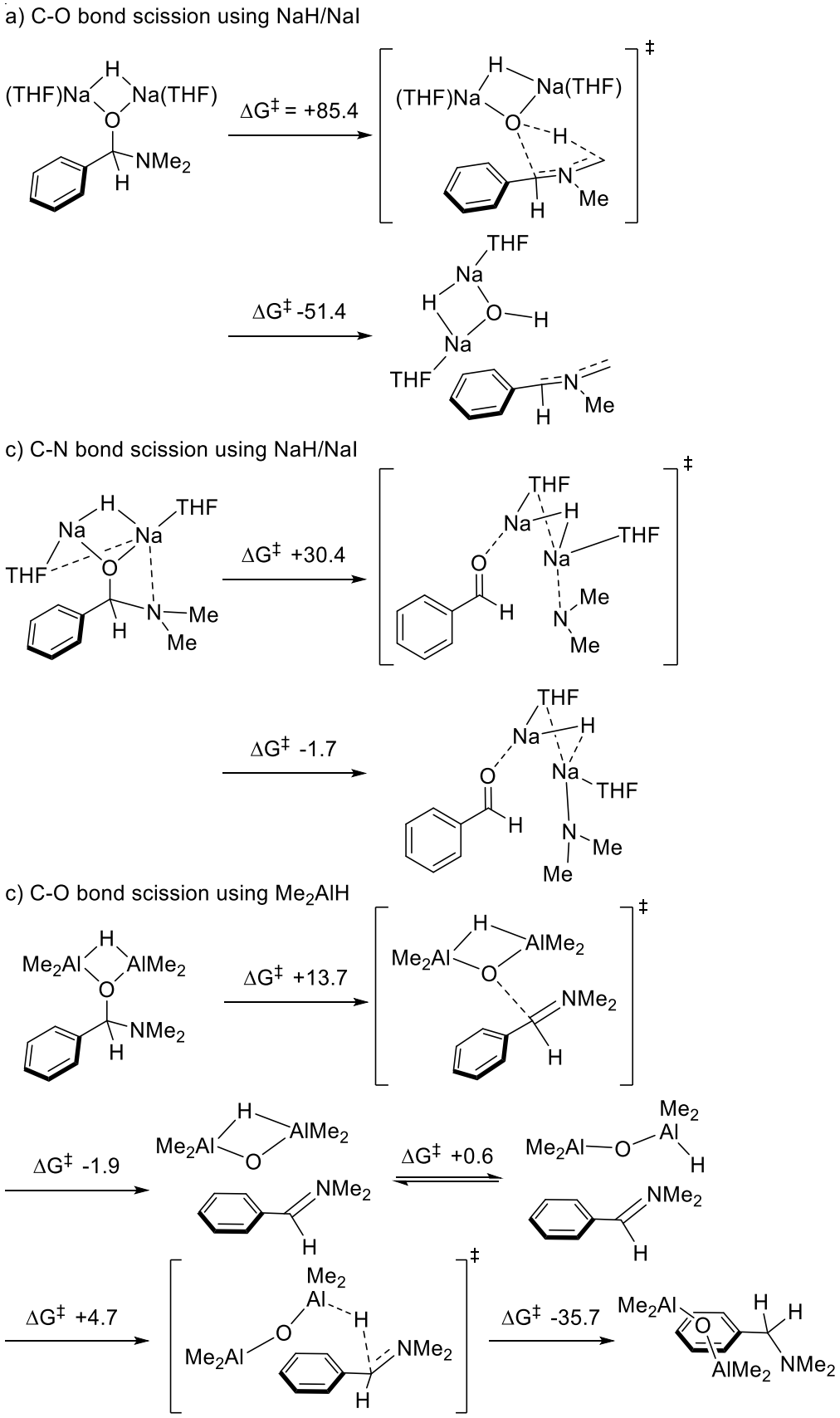
Scheme 50. Reduction of *N*,*N*-dimethylcarboxamides by sodium hydride-iodide composite.

The tetrahedral anionic carbinol amine intermediate generated from the first hydride reduction of the amide is extremely stable and was characterized with NMR spectroscopy (Scheme 51).[95]



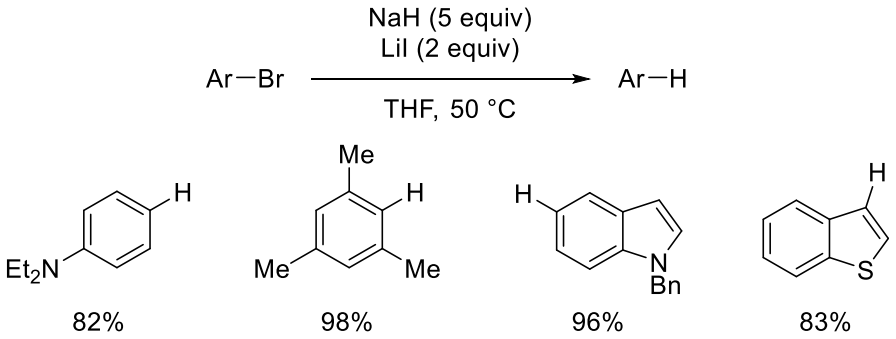
Scheme 51. Characterization of carbinol amine anion.

DFT calculations show that subsequent scission of either the C-N or C-O bond to form the corresponding aldehyde or imine is very endergonic and thus, unlikely to occur (Scheme 52a and Scheme 52b). In contrast, DFT calculations showed that C-O bond scission is found to be facile when using DIBAL as the reductant due to highly Lewis acidic and oxophilic nature of the aluminum cation (Scheme 52c).



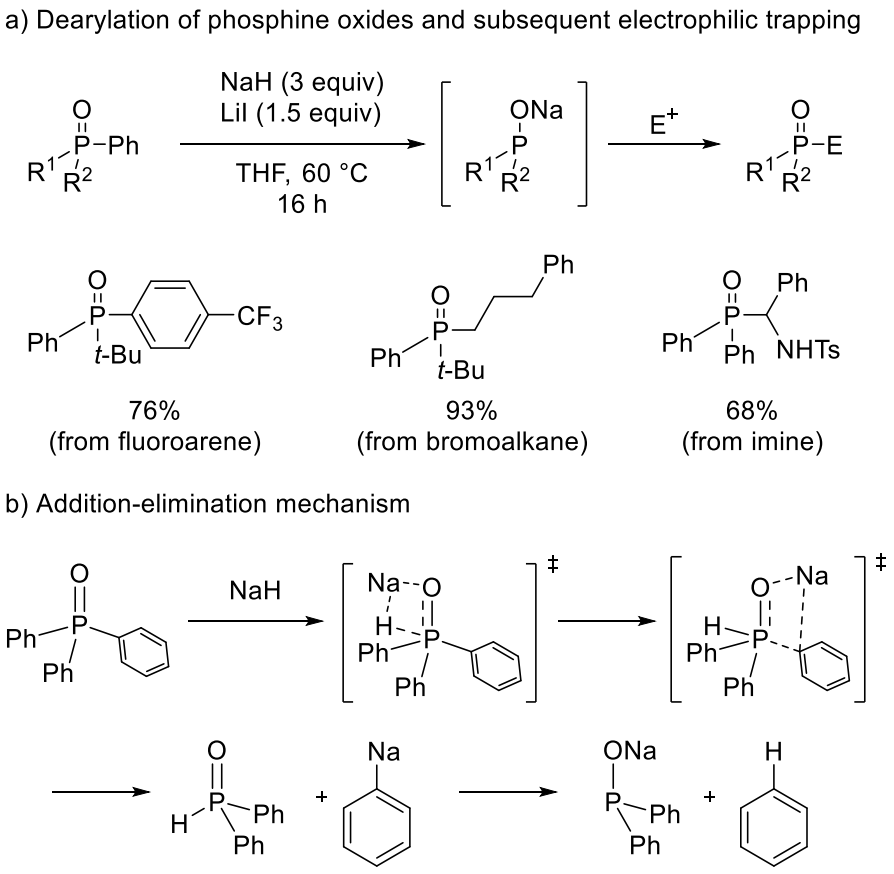
Scheme 52. Characterization and DFT studies of amide reduction with NaH/NaI and Me_2AlH. ($\Delta G^{‡}$ values are in kcal mol^{-1})

Similar to Pierre's report, our group also demonstrated the hydrodehalogenation of bromoarenes using the sodium hydride-iodide composite (Scheme 53).[96] Both electron-rich and sterically hindered bromoarenes are easily reduced to their corresponding arenes. The reaction is also amenable to heteroarenes, giving their respective products in high yields. The proposed mechanism is similar to that of Pierre's, where a concerted nucleophilic aromatic substitution takes place via a 4-membered ring transition state.



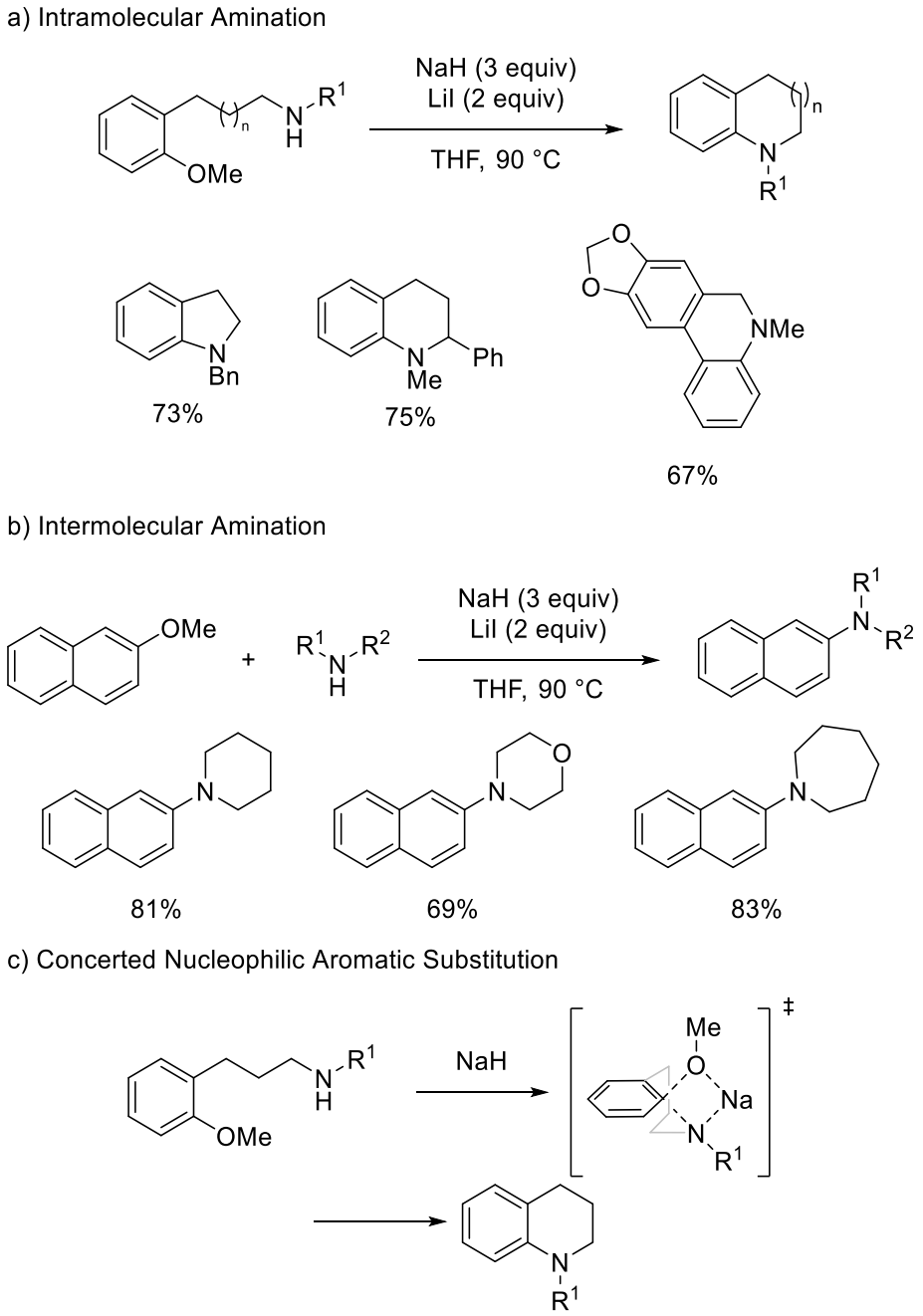
Scheme 53. Hydrodehalogenation of bromoarenes.

Arylphosphine oxides are also able to undergo a dearylation reaction with the use of the sodium hydride-iodide composite. The resulting sodium phosphinite intermediate could be trapped by various electrophiles to furnish tri-substituted phosphine oxides (Scheme 54a). In contrast to the hydrodehalogenation of bromoarenes, the reaction pathway consists of a hydride attack onto the phosphine center followed by elimination of phenylsodium and subsequent deprotonation of the resulting diphenylphosphine oxide, generating the sodium phosphinite intermediate (Scheme 54b).



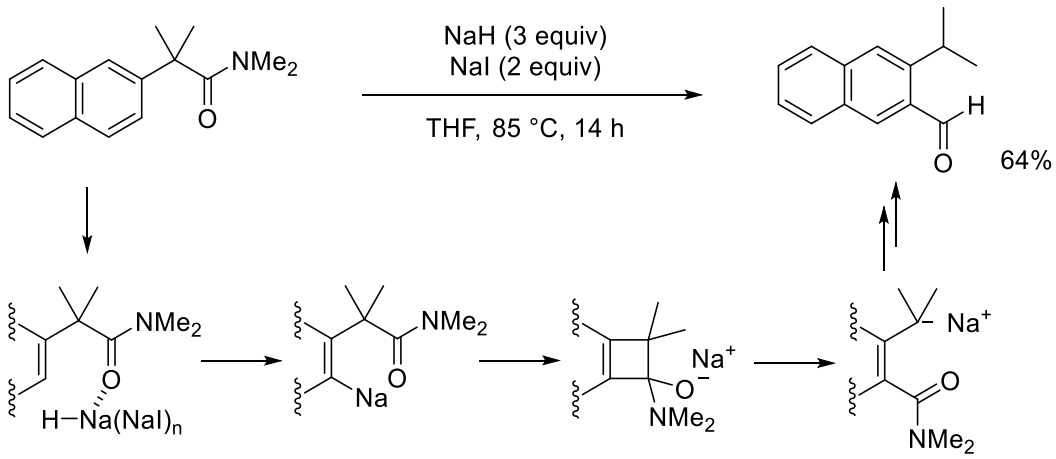
Scheme 54. Dearylation of diarylphosphine oxides using sodium hydride-iodide composite.

The enhanced Brønsted basicity of sodium hydride-iodide composite was nicely demonstrated by the nucleophilic amination of methoxy arenes, where a methoxide anion was used as a unusual leaving group.[97] Intramolecular (Scheme 55a) and intermolecular amination (Scheme 55b) was achieved with various methoxy arenes. However, the substrate scope was limited to simple aromatics due to the highly basic nature of the system. The reaction mechanism was similar to the ones proposed above for the hydrodehalogenation of arenes, in this case, that co-ordination of Lewis acidic sodium cation to the methoxy group enables the concerted nucleophilic aromatic substitution (Scheme 55c).



Scheme 55. Nucleophilic amination of methoxyarenes by sodium hydride-iodide composite.

Further capitalizing on the enhanced Brønsted basicity of sodium hydride-iodide composite, an amide-directed aromatic sodiation was developed. *Ortho*-deprotonation of the arene led to an unprecedented anionic C-Fries-type rearrangement (Scheme 56).[98] The resulting carboxamides are further reduced by activated NaH to afford aryl aldehydes as the final product.

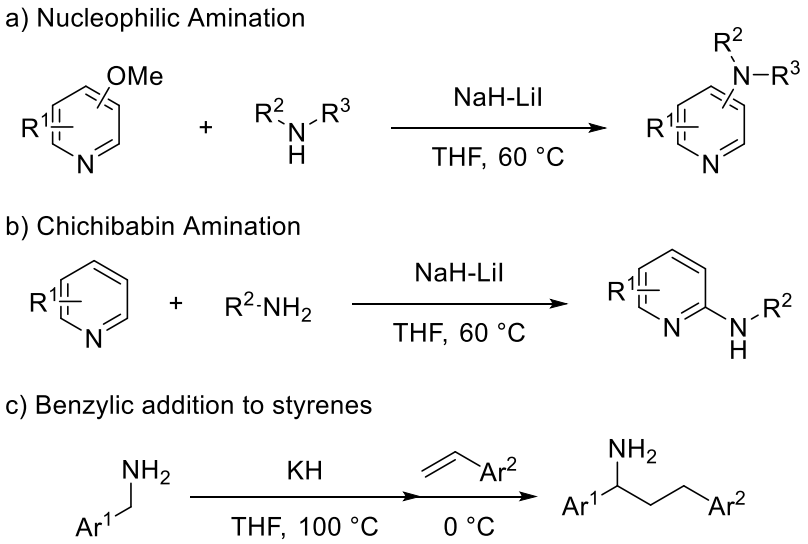


Scheme 56. Directed sodiation by NaH-NaI.

1.4. Conclusion

This chapter discussed the latest development on chemistry of organosodium/potassium reagents in terms of their generation, reactivity, and applications in chemical synthesis. The structural elucidations of the exotic yet attractively reactive organosodium and potassium species allowed for design and implementation of their synthetic applications, especially deprotonative metalations. On the other hand, direct formation of organosodium and organopotassium compounds via deprotonative metalations from readily available sodium and potassium hydrides are exceedingly rare. This is due to their relative inertness as compared to typical alkylsodium and alkylpotassium reagents. The use of sodium and potassium hydrides is still advantageous due to their relative ease of handling and high atom economy.

Based on these backgrounds, the author aims to exploit the enhanced basicity of the sodium hydride-iodide composite for deprotonative metalations of aliphatic amines and their use in for nucleophilic functionalization onto pyridines (Scheme 57a and Scheme 57b) and styrenes (Scheme 57c).



Scheme 57. Summary of thesis projects.

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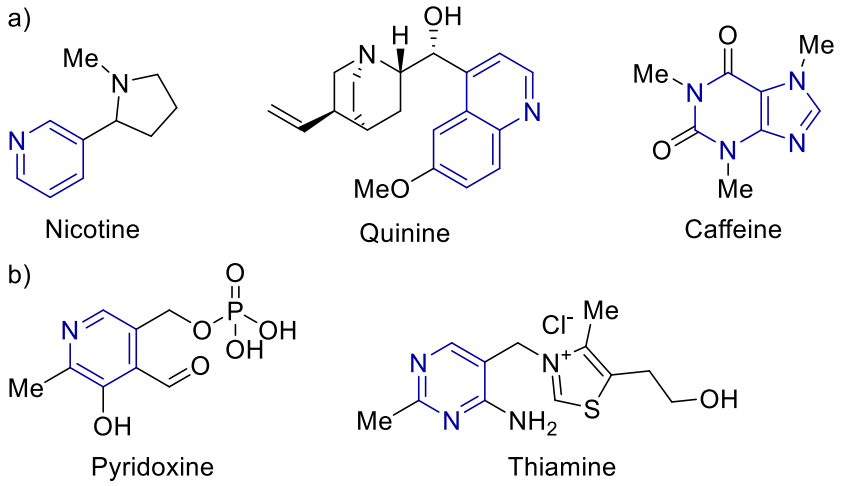
Chapter 2: Nucleophilic Amination of Methoxypyridines by a Sodium Hydride-Iodide Composite

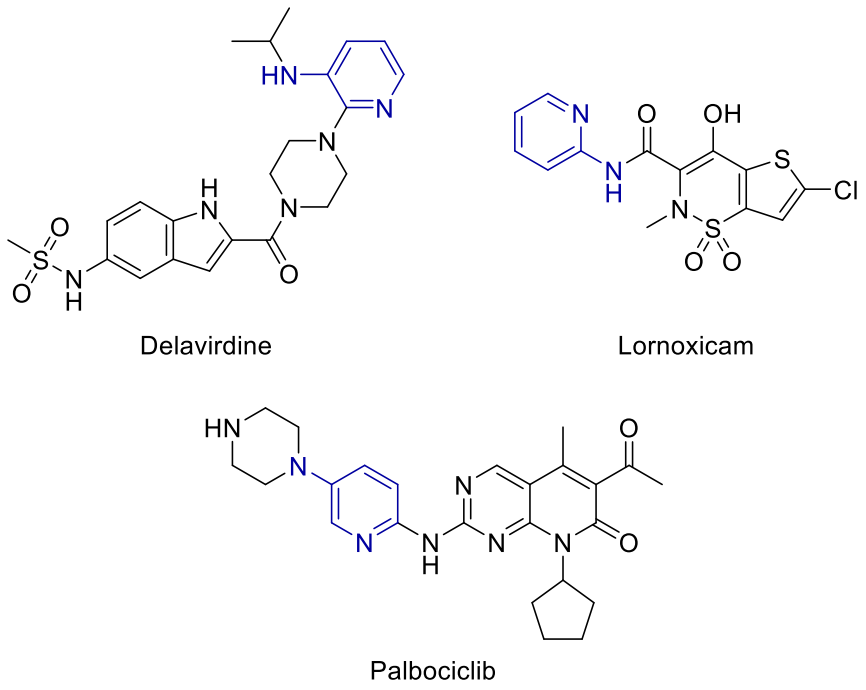
2.1. Introduction

Nitrogen heterocycles are one of the most privileged pharmacophores in drug design and discovery. A 2014 survey of U.S. FDA approved small molecule drugs showed that nitrogen heterocycles make up to 59% of all unique small molecule drugs.[1] After piperidine, the pyridine ring is the second most commonly found heterocycle in pharmaceuticals[1] and is a core structure in many biologically active compounds including alkaloids (Scheme 58a),[2] which have effects on our central nervous system, and vitamins (Scheme 58b),[3] which is an essential nutrient for human life.



Scheme 58. Bioactive molecules containing *N*-heterocycles.

Protocols for the installation of amino groups onto pyridine rings for the synthesis of aminopyridines are highly sought after as these moieties often form the core scaffold of many pharmaceuticals such as delaviridine,[4] which is used as a non-nucleoside reverse transcriptase inhibitors for treatment of HIV, lornoxicam, which is a nonsteroidal anti-inflammatory drug,[5] and palbociclib,[6] an cyclin-dependent kinases inhibitor used for treatment of breast cancer (Scheme 59).

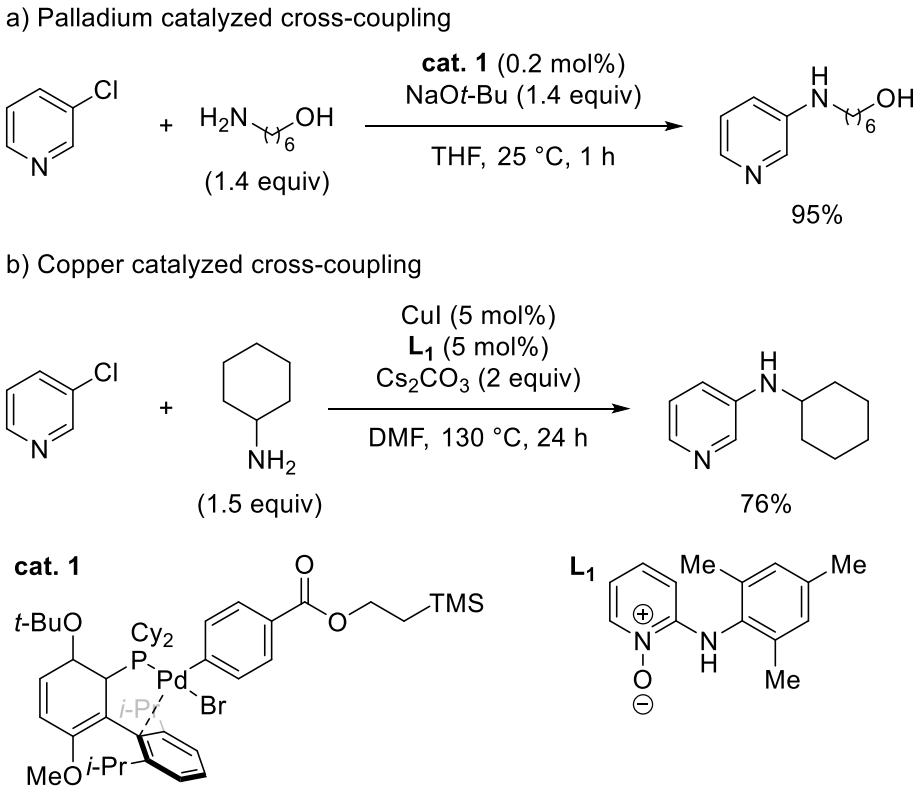


Scheme 59. Drug molecules containing the aminopyridine scaffold.

2.1.1. Typical Methods for the Synthesis of Aminopyridines

One of the most used methods to synthesize aminopyridines is the cross-coupling reactions between haloypyridines and amines. In the case of palladium catalysis (Buchwald-Hartwig amination),[7-9] the major difficulty faced by chemists is the displacement of ligands on the metal center by pyridine due to the inherent Lewis basicity of the pyridine nitrogen.[10-11] To overcome this, the use of highly hindered and basic ligands which chelate strongly to the metal center is required.[12-14] In the latest development, Buchwald and co-workers reported a new dialkylbiaryl monophsphine palladium catalyst (**cat. 1**) which improved catalyst stability, allowing these reactions to have catalytic loadings as low as 0.2 mol% at ambient temperature (Scheme 60a).[15] On the other hand, copper catalysis (the Ullmann reaction)[16-17] has been developed as an cheaper alternative to palladium catalysis. Liu and co-workers recently reported the use of 2-aminopyridine 1-oxide ligands for the Ullmann reaction of aryl chlorides and aliphatic amines

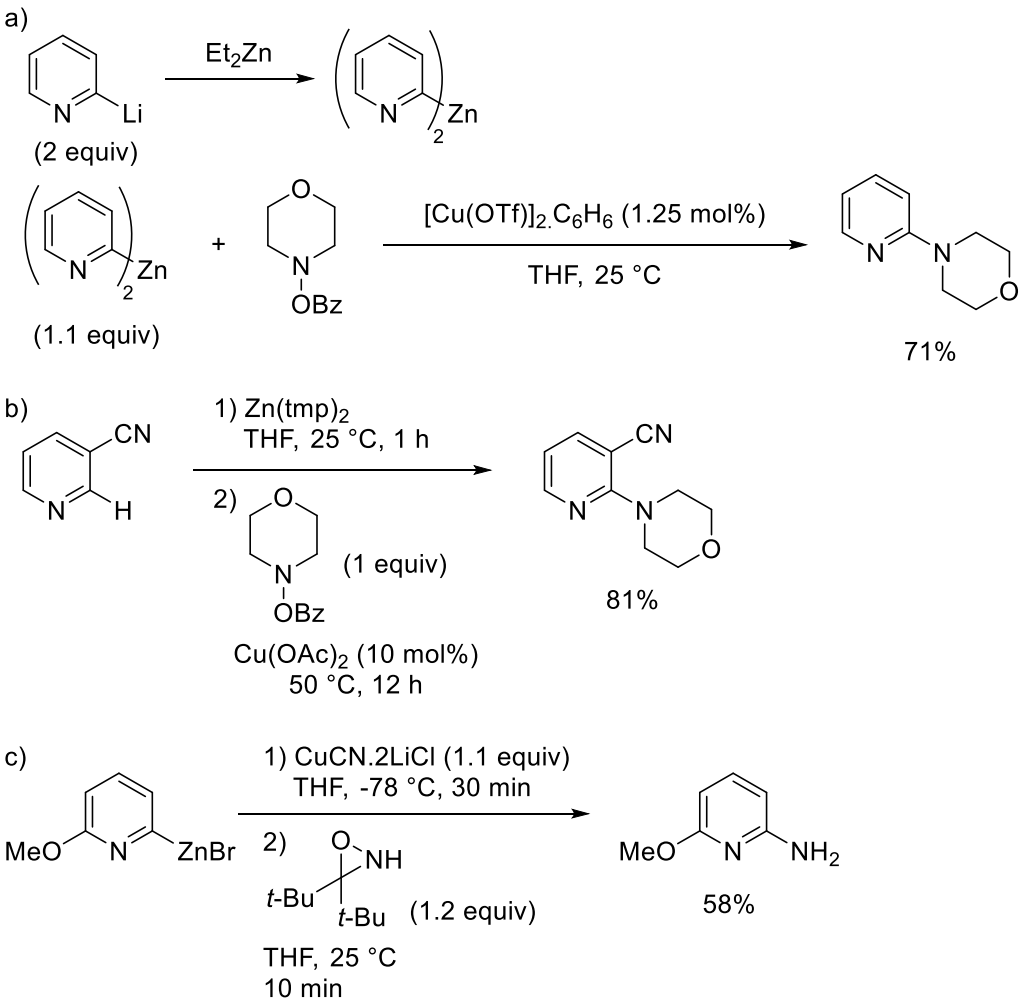
(Scheme 60b).[18] The authors postulated that the both the N and O atoms on the ligand can act as a bidentate chelating centers to the copper ion to form a highly stable 5-membered ring. However, copper-catalyzed reactions typically require higher catalytic loadings and harsher conditions as compared to the Buchwald-Hartwig amination.



Scheme 60. Transition metal catalyzed cross coupling reactions.

The electrophilic amination of pyridyl organometallic reagents with *N*-electrophiles have also been reported under copper catalysis. In their seminal publication, Johnson and co-workers reported the amination of bis(2-pyridyl)zinc using 4-benzoyloxymorpholine using copper trifluoromethanesulfonate as a catalyst in good yields (Scheme 61a).[19] A decade later, by using amidodialkylzincate complexes which are known to promote directing group mediated *ortho*- or C-2 zincation, Wang and co-workers reported a direct C-2 zincation of arenes and heteroarenes using zinc tetramethylpiperidide [$Zn(TMP)_2$] and subsequent electrophilic trapping with benzoyl amines under copper catalysis (Scheme 61b).[20] Kürti and co-workers

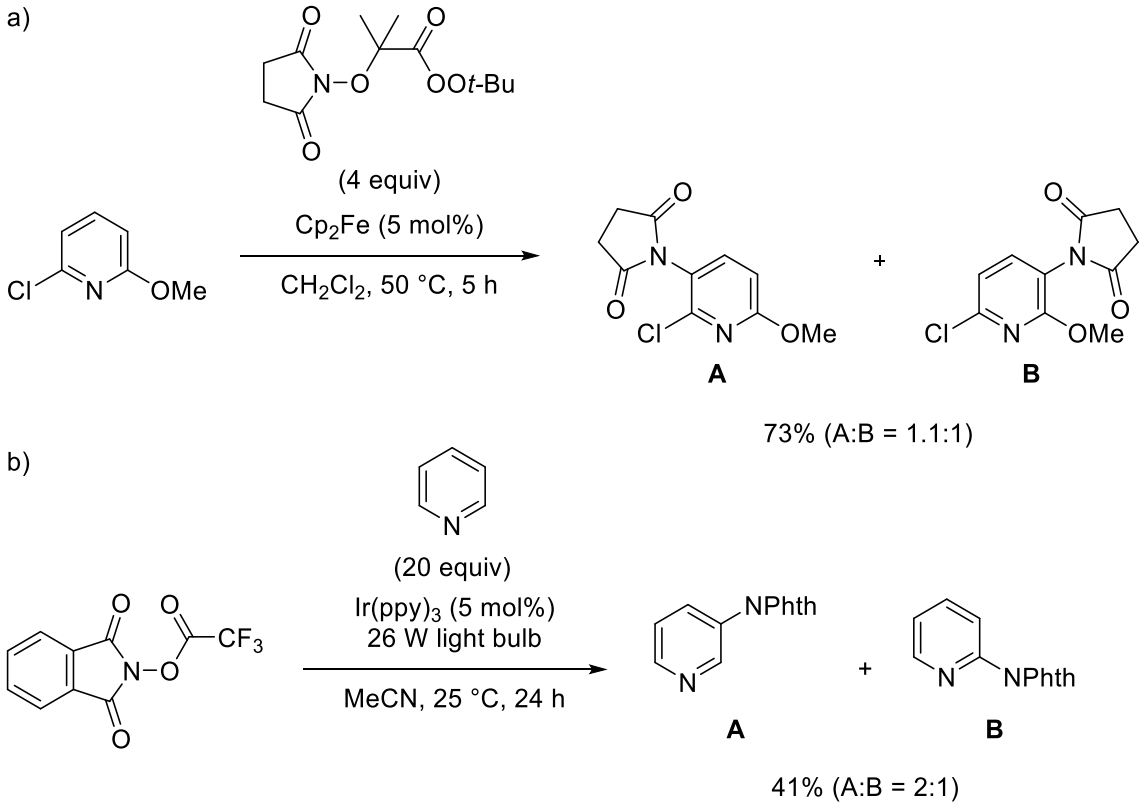
recently disclosed the amination of (hetero)aryl organometallic reagents using a novel *N*-H-oxaziridine as a NH_2 surrogate.[21] The organometallic reagents were transmetallated with stoichiometric amounts of copper before trapping with the *N*-H-oxaziridine to give the corresponding aminopyridines (Scheme 61c).



Scheme 61. Electrophilic amination using copper.

Transition-metal mediated radical imidation of pyridines has also been reported using ferrocene[22] or iridium[23-24] photocatalysts. In 2014, Baran and co-workers developed a novel perester reagent which can decompose in the presence of ferrocene to generate a succinimide radical (Scheme 62a).[22] This *N*-centered radical is electrophilic in nature and engages the most electron rich carbon on the heterocycle (following the regioselectivities of electrophilic

aromatic substitution), potentially giving rise to a mixture of regioisomers. For instance, the use of 2-chloro-6-methoxypyridine gave a mixture of 3- and 5- substituted pyridine. Similarly, Allen and co-workers designed a new *N*-acyloxyphthalimide as a precursor to the *N*-centered phthalimide radical (Scheme 62b).[23] Likewise, this protocol suffers from the formation of regioisomers due to the electrophilic nature of the nitrogen radical.

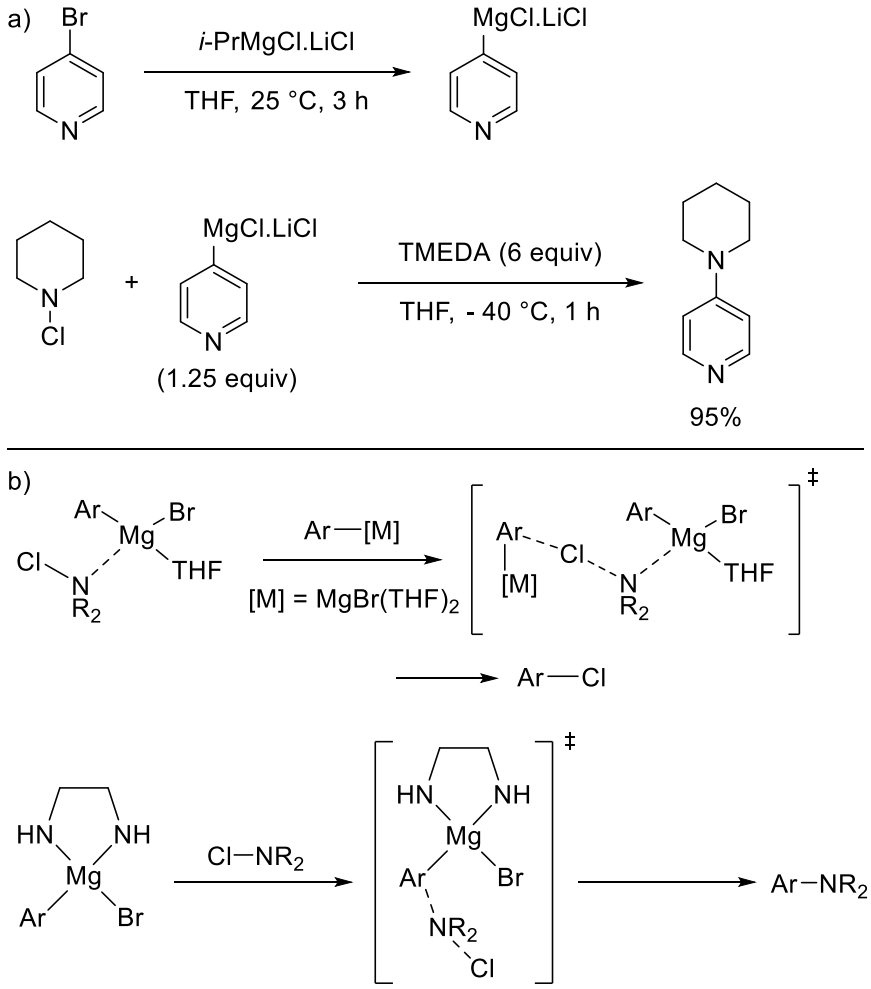


Scheme 62. Radical imidation of pyridines using transition metals.

Despite the utility of transition metals for catalytic C-N bond formation on the pyridine rings, stringent limitations on the amount of residual transition metals contaminants pharmaceuticals have led to the need for the development of transition metal free synthetic methods for C-N bond formation.[25-27]

One of the methods to synthesize aminopyridines without any transition metals is the electrophilic aromatic substitution of pyridines. However, due to the electron deficient nature

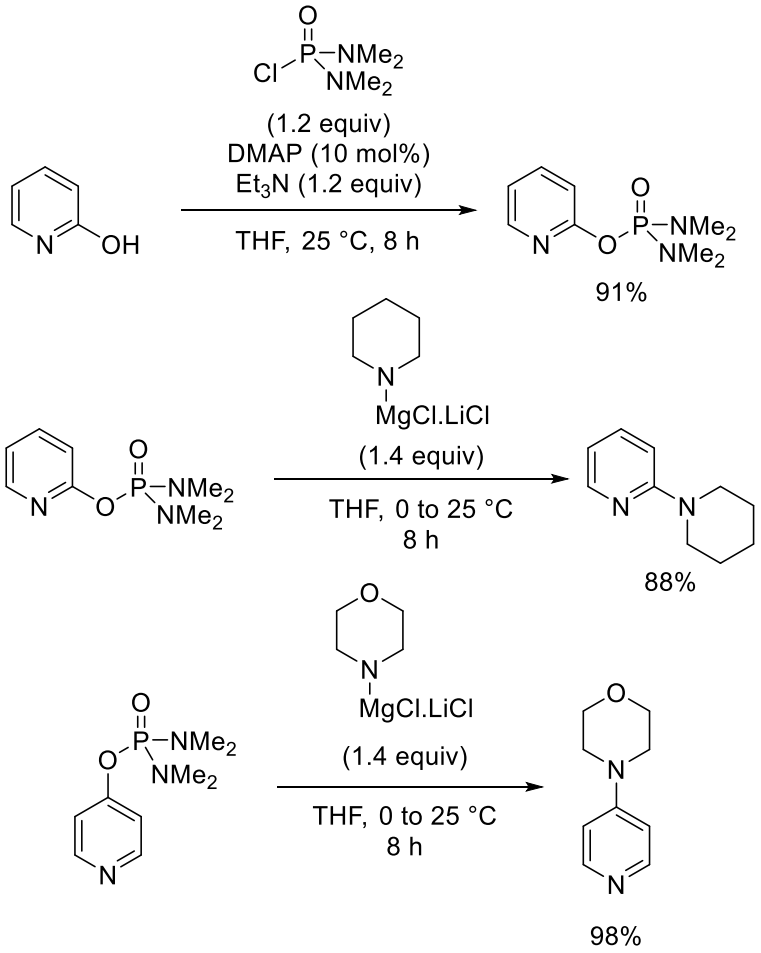
of the pyridine ring, the electrophilic aromatic substitution of pyridines is extremely rare. Nakamura and co-workers reported the amination of pyridyl Grignard reagents using *N*-chloroamines with TMEDA as an additive to give their respective aminopyridines (Scheme 63a).[28] They postulated that the TMEDA coordinates to the Grignard reagent to prevent any potential interaction of the chloroamine with the magnesium center, which can result in competitive electrophilic chlorination over amination (Scheme 63b).



Scheme 63. Transition metal free electrophilic amination of pyridines.

One of the most classical yet practical methods to synthesize aminopyridines is the nucleophilic aromatic substitution of 2- or 4-substituted (pseudo)halopyridines with amine nucleophiles under basic reaction conditions.[29-39] A recent development by Knochel and co-workers is the

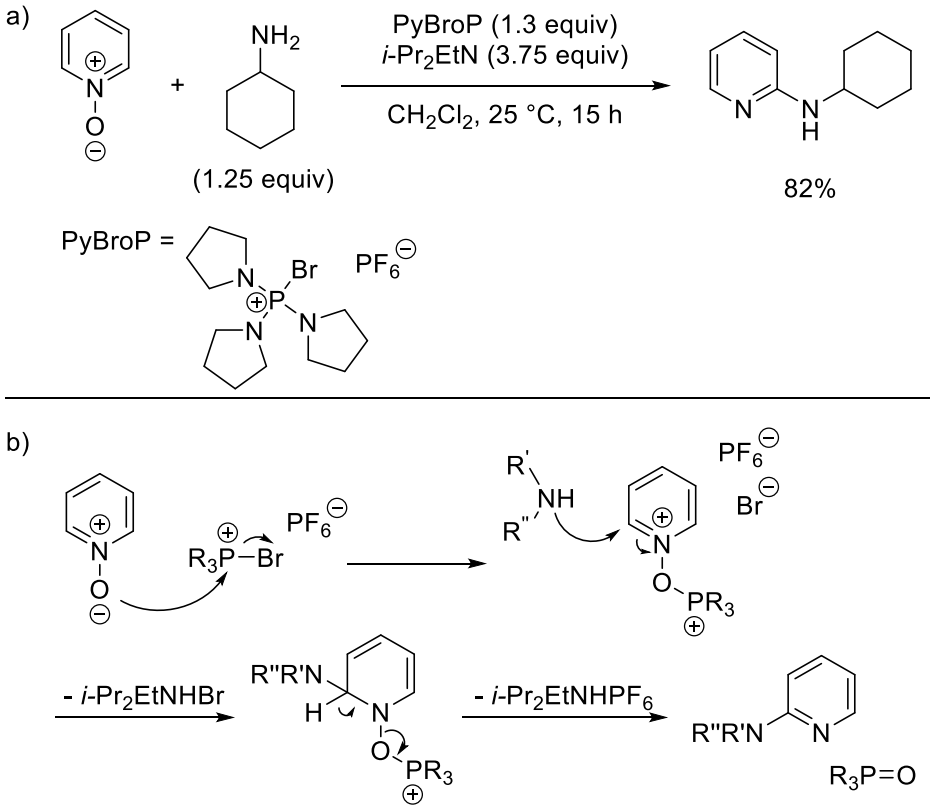
amination of various 2- or 4-phosphorodiamidate substituted pyridines with magnesium amides under mild conditions (Scheme 64).[40] The substituted pyridines were easily prepared from readily available hydroxylpyridines and were able to undergo a directed *ortho*-metalation and electrophilic functionalization prior to amination. However, this reaction was only limited to 2- and 4- substituted pyridines due to electron withdrawing effect the nitrogen atom has on stabilizing negative charges on these positions.



Scheme 64. Nucleophilic amination of phosphorodiamidate substituted pyridines.

Other types of nucleophilic aromatic substitution include C-2 nucleophilic amination onto activated pyridine *N*-oxides.[41-45] For example, Londregan and co-workers reported the synthesis of 2-aminopyridines through the activation pyridine *N*-oxide with bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBroP) followed by direct C-2 amination

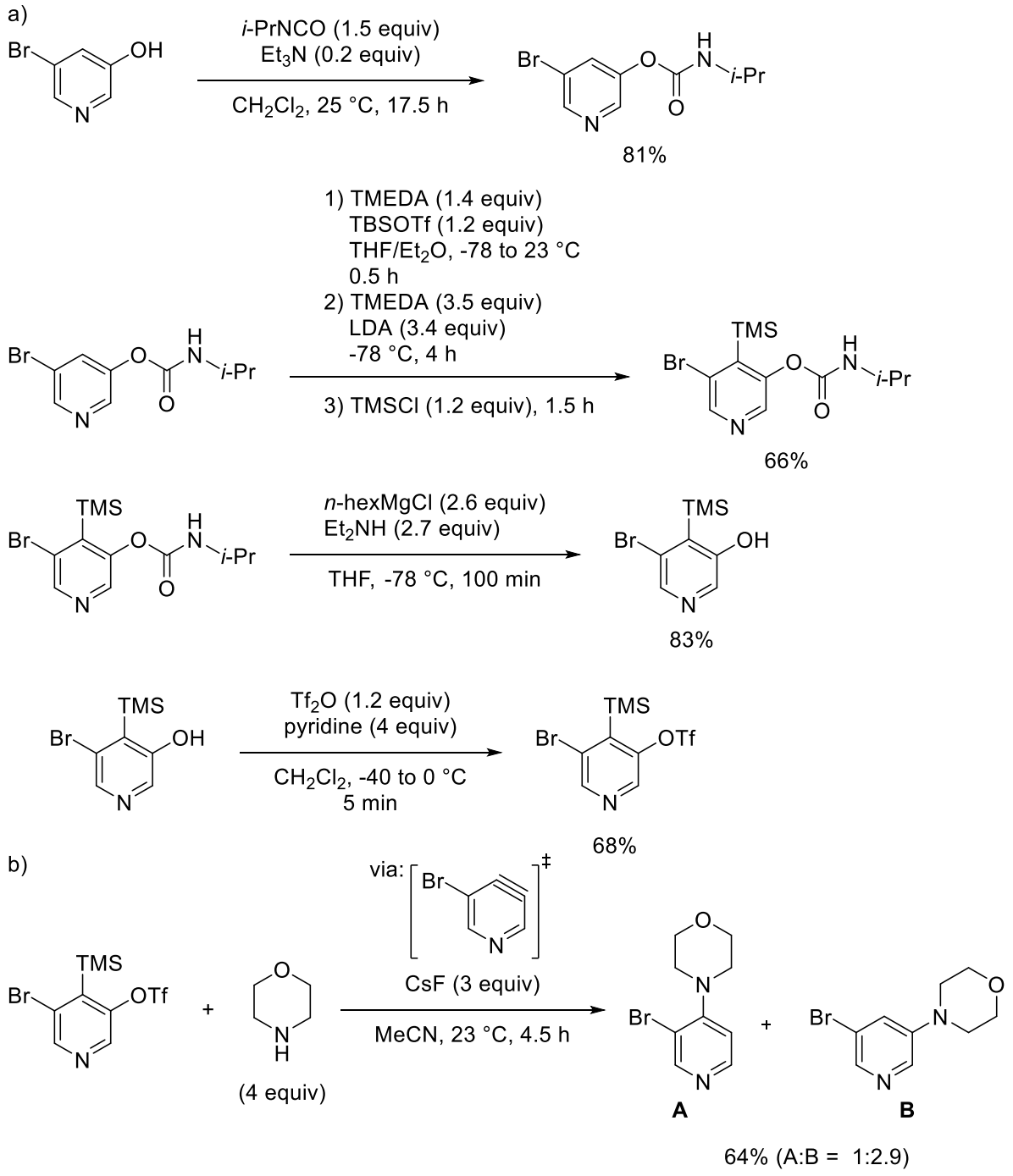
with amines.[42] In their proposed mechanism, attack of the pyridine *N*-oxide onto PyBroP forms the activated pyridine complex which is susceptible to C-2 amination. Deprotonative re-aromatization along with the expulsion of phosphoryltripyrrolidine gives the 2-aminopyridine. However, nucleophilic amination of pyridines typically only works for C-2 or C-4 substitutions due to the nitrogen atom on pyridine being able to stabilize negative charges on those carbons.



Scheme 65. C-2 Amination of activated pyridine *N*-oxides.

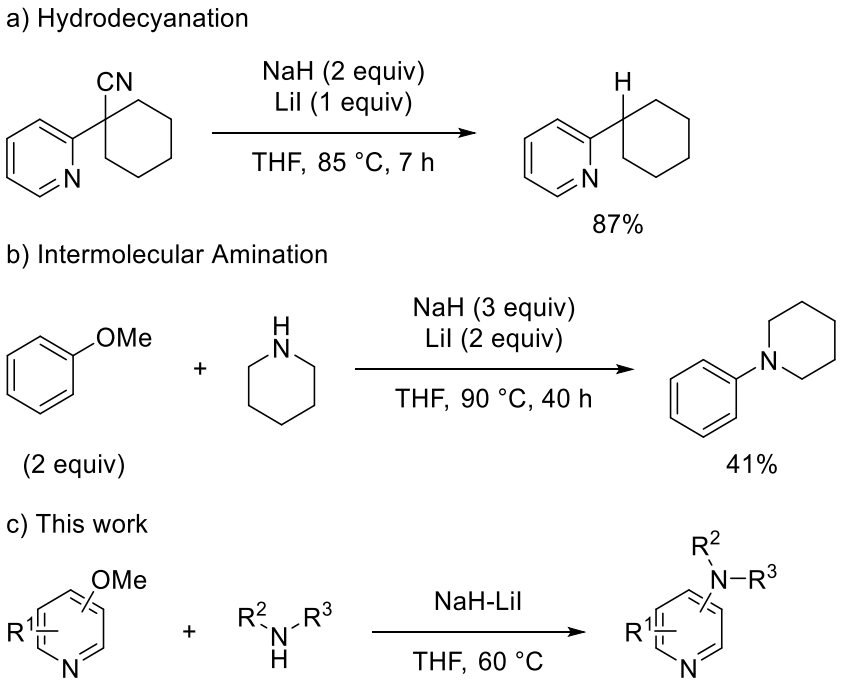
Nucleophilic addition to pyridyne intermediates were also reported for the synthesis of aminopyridines.[46-48] Garg and co-workers reported the amination of pyridines through a transient 3,4-pyridyne intermediate. The silyltriflate precursor can be easily prepared from the corresponding pyridine carbamate through an *ortho*-lithiation protocol followed by trapping with TMSCl. The resulting silylated pyridine is deprotected to afford the silylated hydroxy pyridine which is reacted with triflic anhydride to furnish the silyltriflate precursor (Scheme 66a). The precursor undergoes desilylation readily in the presence of CsF to form a highly

reactive 3,4-pyridyne intermediate which is trapped by morpholine to give a mixture of 3- and 4-aminated pyridine (Scheme 66b). The major drawback behind the nucleophilic aminations of pyridynes is the formation of regioisomers, which can complicate product purification.



Scheme 66. Nucleophilic amination of 3,4-pyridyne.

Prior studies by our group showed pyridine rings, which are typically reduced by hydride reagents,[49-50] were not reduced when treated with the sodium hydride-iodide composite (Scheme 67a).[51] Furthermore, intermolecular nucleophilic amination with methoxyarenes was enabled using the sodium hydride-iodide composite (Scheme 67b).[52] Hence, we envisioned that the enhanced Brønsted basicity of the composite can be used as a base to generate amide nucleophiles for nucleophilic aminations of readily available methoxypyridine without the decomposition of the pyridine rings (Scheme 67c). In contrast to other reports on the nucleophilic aromatic amination of pyridines, our reaction system is able effect a C-3 amination due to its unusual concerted nucleophilic aromatic substitution mechanism, bypassing any negative charge build up on the aromatic system. In this section of the thesis, the optimization, and the substrate scope of the nucleophilic amination of methoxypyridines as well as the comparison of the ability of leaving groups for nucleophilic aromatic amination using sodium hydride-iodide composite are described.



Scheme 67. Precedent works and the nucleophilic amination of methoxypyridines.

2.2. Results and Discussion

2.2.1. Preparation of starting materials

The methoxypyridines shown in **Figure 1**, apart from **2.1e**, **2.1k**, and **2.4**, were commercially available and used as received.

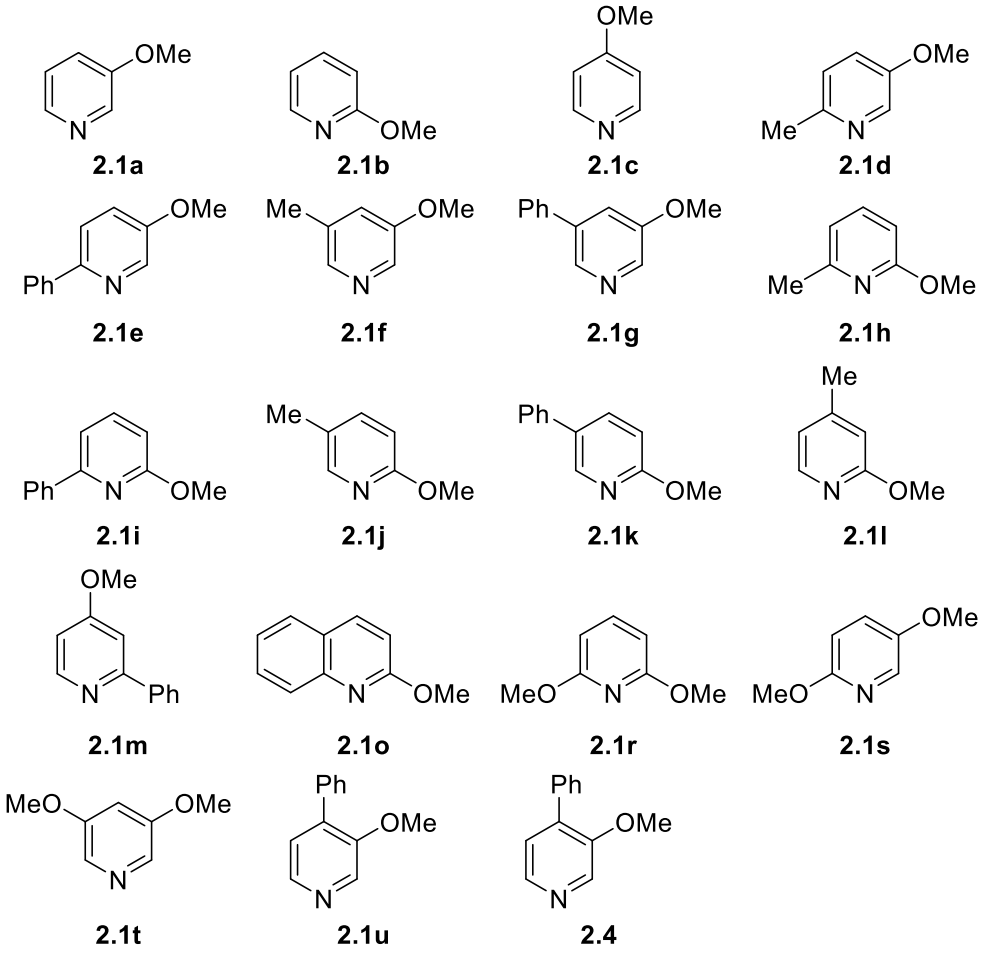
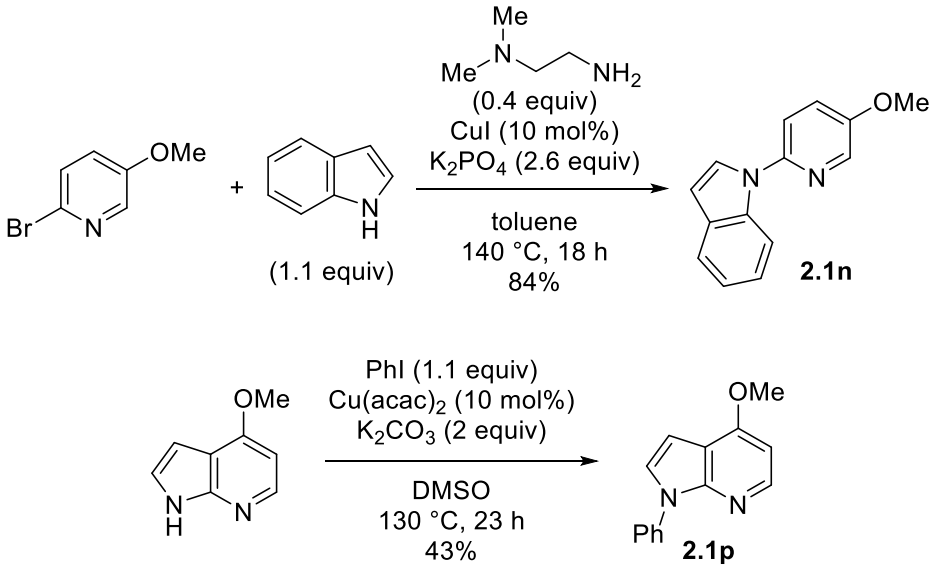


Figure 1. Methoxypyridines used.

Methoxypyridines **2.1e**[53], **2.1k**[54], and **2.4**[55] were synthesized based on the corresponding literature procedures (Figure 1). Their spectra data are identical to those reported. The remaining methoxypyridines were commercially available and used as received.

Indole **2.1n** and 7-azaindole **2.1p** were synthesized via Ullman reaction of the corresponding heterocycle and haloarene as shown below (Scheme 68).



Scheme 68. Ullman reaction for the synthesis of 1n and 1p.

The amines shown in Figure 2 were commercially available and used as received.

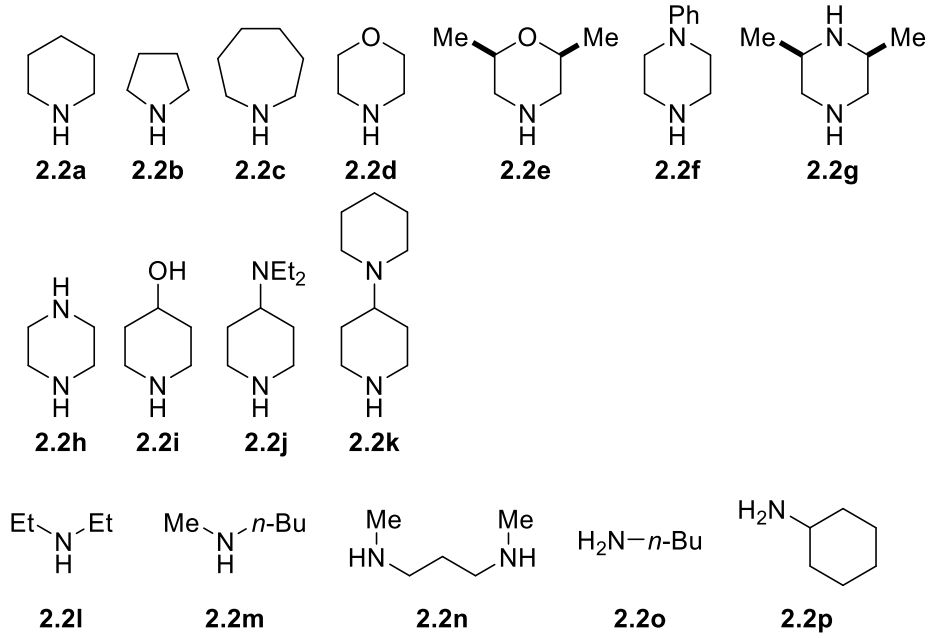


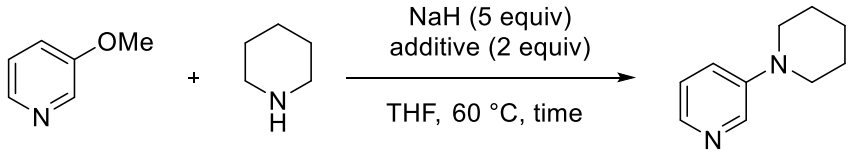
Figure 2. Commercially available amines.

2.2.2. Optimization of reaction conditions

We began our studies with the optimization of the reaction conditions. Treating 3-methoxypyridine **2.1a** with piperidine **2.2a** (2 equiv) in the presence of sodium hydride (5

equiv), sodium iodide (2 equiv) in THF at 60 °C yielded 3-piperidin-1-ylpyridine **2.3aa** in only 7% yield with incomplete conversion after 24 hours (Entry 1). Changing the additive from sodium iodide to lithium iodide greatly increased the efficiency of the reaction, furnishing product **2.3aa** in 88% yields after only 8 hours (Entry 2). Note that the use of only sodium hydride without any additive gave no products after 24 hours (Entry 3). The reaction can also be scaled up to 50 mmol without any difficulty.

Table 2. Optimization of reaction conditions.



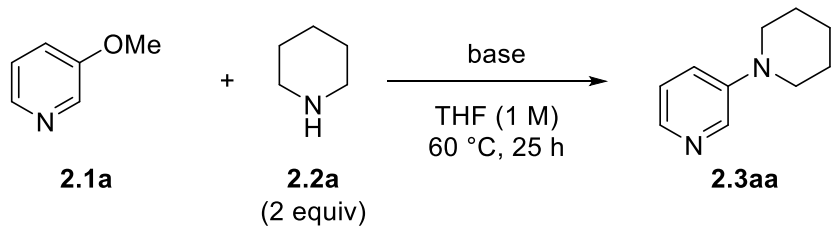
2.1a **2.2a** (2 equiv) **2.3aa**

Entry[a]	Additive	Time [h]	Yield [%]	Conversion[d] [%]
1	NaI	24	7	37
2	LiI	8	88[b] (92[c])	>99
3	-	24	0	23

[a]Reactions were carried out using 0.5 mmol of **2.1a** and 1 mmol of **2.2a.**[b]Isolated yields. [c]Isolated yields on a 50 mmol scale. [d]Yields calculated using ^{1}H NMR based on an internal standard.

The use of other bases such as *t*-BuOK, LHMDS and KHMDS led to no formation of the aminated product even after 25 h (Table 3, Entries 1 to 3). The use of *n*-BuLi as a base for the generation of the lithium amide proceeded quite efficiently, furnishing the desired aminated product in 77% yields. However, alkylated pyridines were also observed as side products with the use of *n*-BuLi as the base as opposed to the use of the sodium hydride-iodide composite.

Table 3. Screening of other bases.



2.1a **2.2a** (2 equiv) **2.3aa**

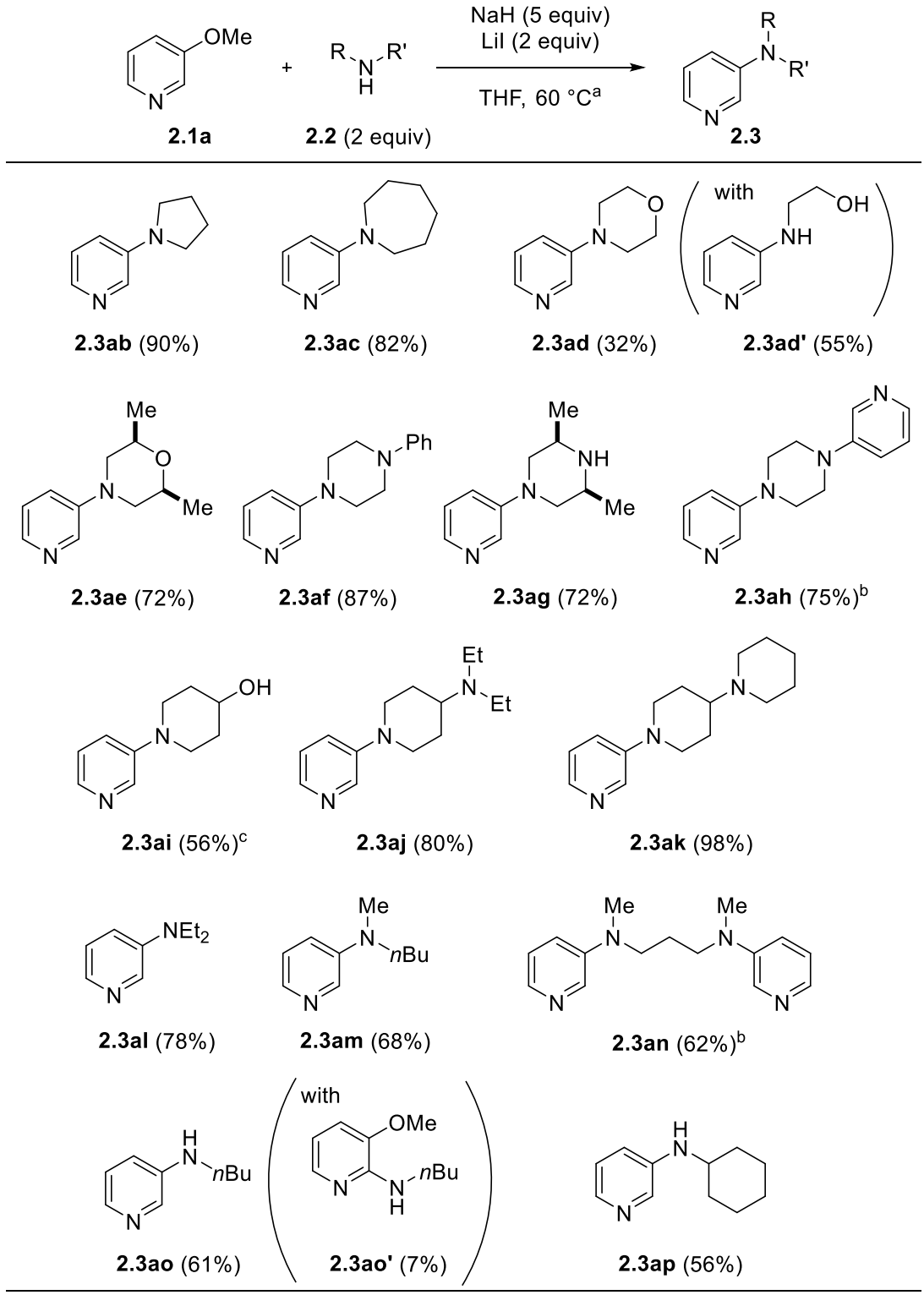
Entry[a]	Base (equiv)	Yield [%]	Conversion[%][c]
1	KO*t*-Bu (5)	0	12
2	LHMDS (2)	0	10
3	KHMDS (2)	0	8
4	*n*-BuLi (2)	77[b]	99

[a]Reactions were carried out using 0.5 mmol of **2.1a** and 1 mmol of **2.2a**.[b]Isolated yields. [c]Yields calculated using ^{1}H NMR based on an internal standard.

2.2.3. Substrate scope and limitations

With the optimized reaction conditions, we started screening the scope of C3-amination of 3-methoxypyridines with various amines (Scheme 69). The amination proceeded smoothly with saturated nitrogen heterocycles such as pyrrolidine (for **2.3ab)** and azepane (for **2.3ac**). Reactions with morpholine formed **2.3ad** and **2.3ad**' with yields of 32% and 55% respectively. The formation of **2.3ad**' is likely caused by the deprotonation of the relatively acidic α-oxy hydrogen followed by the ring opening of the morpholine adduct and hydrolysis of the enol ether intermediate formed. The use of cis-2,6-dimethylmorpholine prevented the fragmentation of the morpholine moiety, providing **2.3ae** as the sole product. Amination with piperazine derivatives proceeded smoothly (for **2.3af – 2.3ah**), with the adduct forming at the less sterically hindered side with the use of 2,6-dimethylpiperazine, affording product **2.3ag** in 72% yields. The use of unsubstituted piperazine as a substrate gave the double aminated product **2.3ah** in 75% yield. While the use of 4-hydroypiperidine as the substrate gave the desired aminated product with the hydroxyl group kept intact, indicating that the reaction is chemoselective with amides as the nucleophile. Use of 4-aminopiperidines gave products **2.3aj**

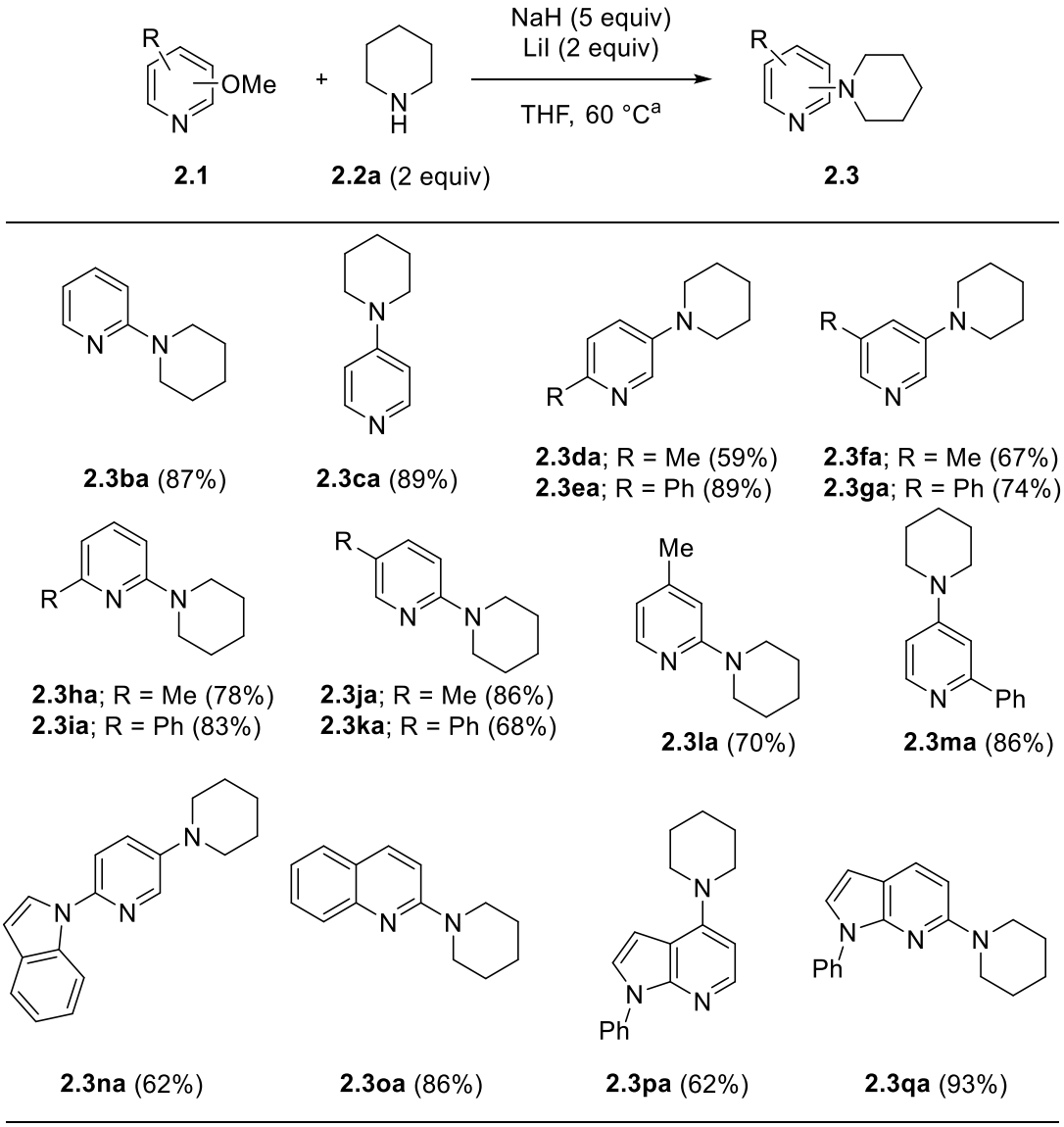
and **2.3ak** in good yields. Reactions with acyclic secondary amines also proceeded smoothly, affording products **2.3al** and **2.3am** in good yields. The use of 1,3-propanediamine afford the bispyridyl product **2.3an** in 62% yield. Chichibabin amination side products were observed with the use of *n*-butylamine, providing 2-aminopyridine **2.3ao'** in 7% yield along with 3-aminated pyridine **2.3ao** in 61% yield. The use of a bulkier cyclohexylamine provided **2.3ap** as the sole product in 56% yields.



[a]The reactions were conducted using 0.5 mmol of **2.1a** and 1 mmol of **2.2.** [b]The reaction was conducted using 1 mmol of **2.1a** and 0.5 mmol of **2.2.** Isolated yields were calculated based on **2.2.** [c] The reaction was conducted using NaH (7 equiv.) and LiI (2 equiv) at 90 °C in a sealed tube.

Scheme 69. Nucleophilic amination of 3-methoxypyridine using amines.

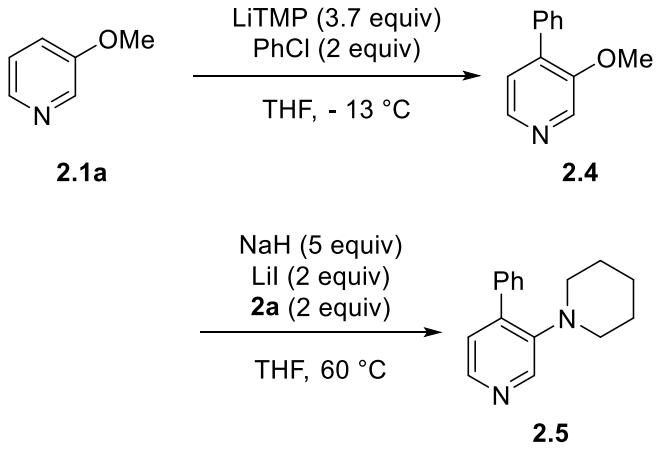
Using piperidine **2.2a** as the nucleophile, we explored the scope of methoxypyridine derivatives (Scheme 70). C-2 and C-4 nucleophilic amination reactions on the pyridine ring typically require electron withdrawing substituents to stabilize the Meisenheimer complex for the reaction to proceed.[56-58] Using our protocol, the C-2 and C-4 nucleophilic amination of the pyridine ring proceeded smoothly without the requirement of having an electron withdrawing substituent on the ring. Aminations of methyl or phenyl pyridines proceeded cleanly with good yields (**2.3da – 2.3la**). The use of 1-(5-methoxypyridin-2-yl)-1H-indole and 2-methoxyquinoline gave **2.3na** and **2.3oa** in 62% and 86% yields, respectively. 4- and 6-methoxy-1-phenyl-7-azaindoles were aminated readily, furnishing **2.3pa** and **2.3qa** in 62% and 93% yields, respectively.



[a]The reactions were conducted using 0.5 mmol of **2.1a** and 1 mmol of **2.2**.

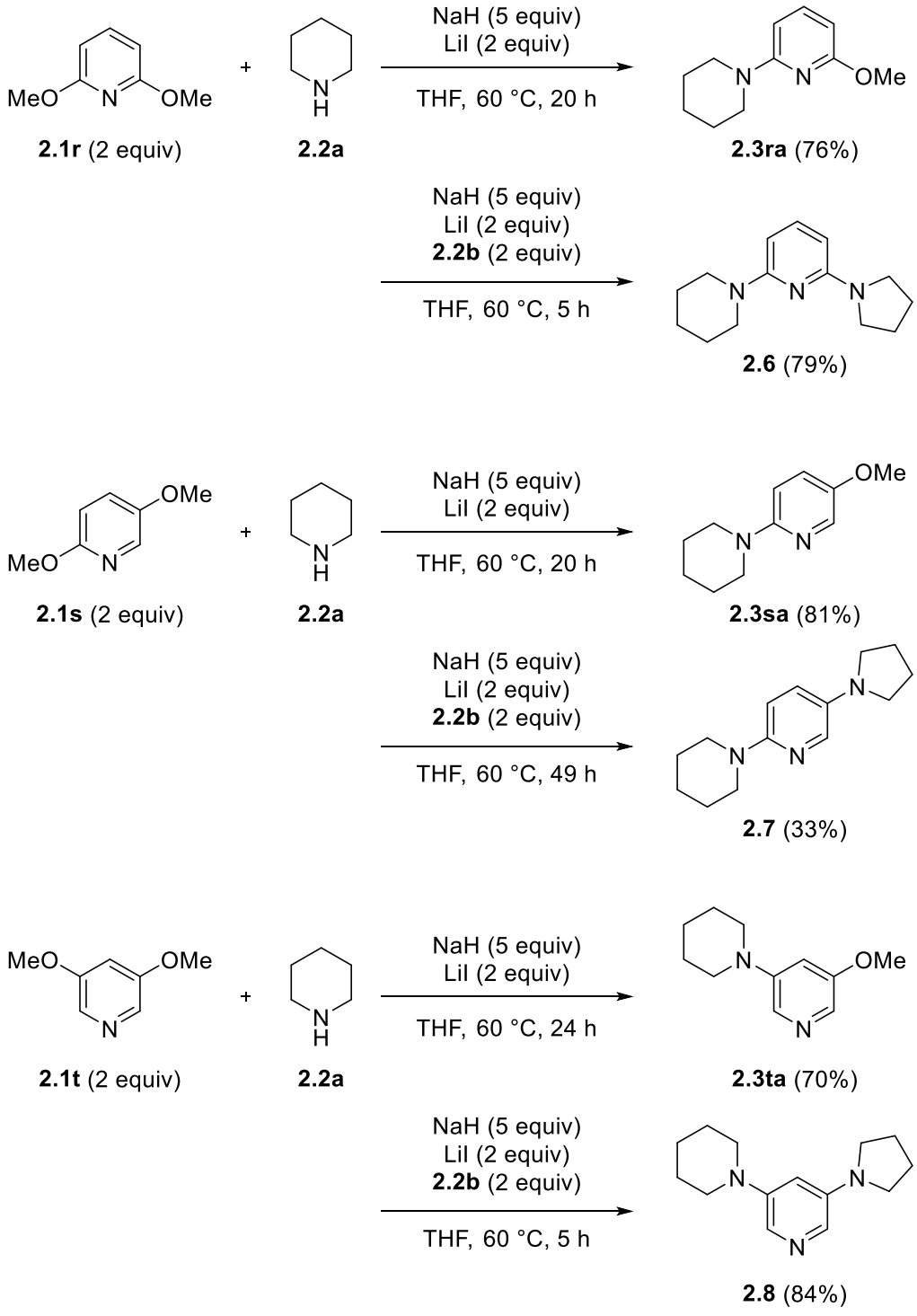
Scheme 70. Nucleophilic amination of methoxypyridines using piperidine.

The methoxy group on the pyridine ring could also be used as a directing group for *ortho*-metalation, allowing for further functionalization through the reaction of the generated pyridyl lithium species with electrophiles.[55, 59-61] As a demonstration, we used a protocol reported by Daugulis[55] for methoxy group directed ortho-lithiation followed by the arylation at the C-4 position to afford **2.4** (Scheme 71). The methoxy group on **2.4** can then be further transformed into an amine adduct using our reaction protocol to furnish 4-phenyl-3-(piperidin-1-yl)pyridine **2.5**.



Scheme 71. *Ortho*-phenylation of 3-methoxypyridine followed by amination.

The reaction conditions were also amenable to sequential diamination of dimethoxypyridines (Scheme 72). The use of 2 equivalent of dimethoxypyridines **2.1r**, **2.1s**, **2.1t** and 1 equivalent of piperidine **2.2a** exclusively gave mono-aminated methoxypyridines **2.3ra**, **2.3sa,** and **2.3ta** respectively in good yields. The second amination of **2.3ra** and **2.3ta** proceeded readily to furnish their respective diaminated products in good yields. Sequential amination of **2.3sa** proceeded less smoothly, giving the diaminated pyridine **2.7** in 33% yields after 49 hours.

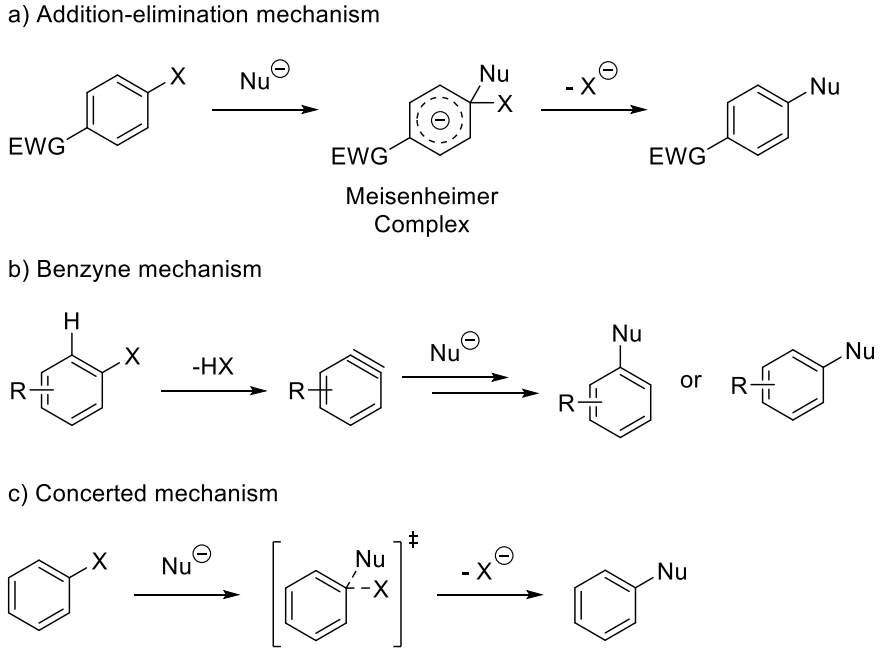


Scheme 72. Sequential diamination of dimethoxypyridines.

2.3. Mechanistic Studies

Typical nucleophilic aromatic substitution reactions (S_NAr) undergo two types of mechanisms: 1) an addition-elimination mechanism where the nucleophile adds onto the arene, forming a

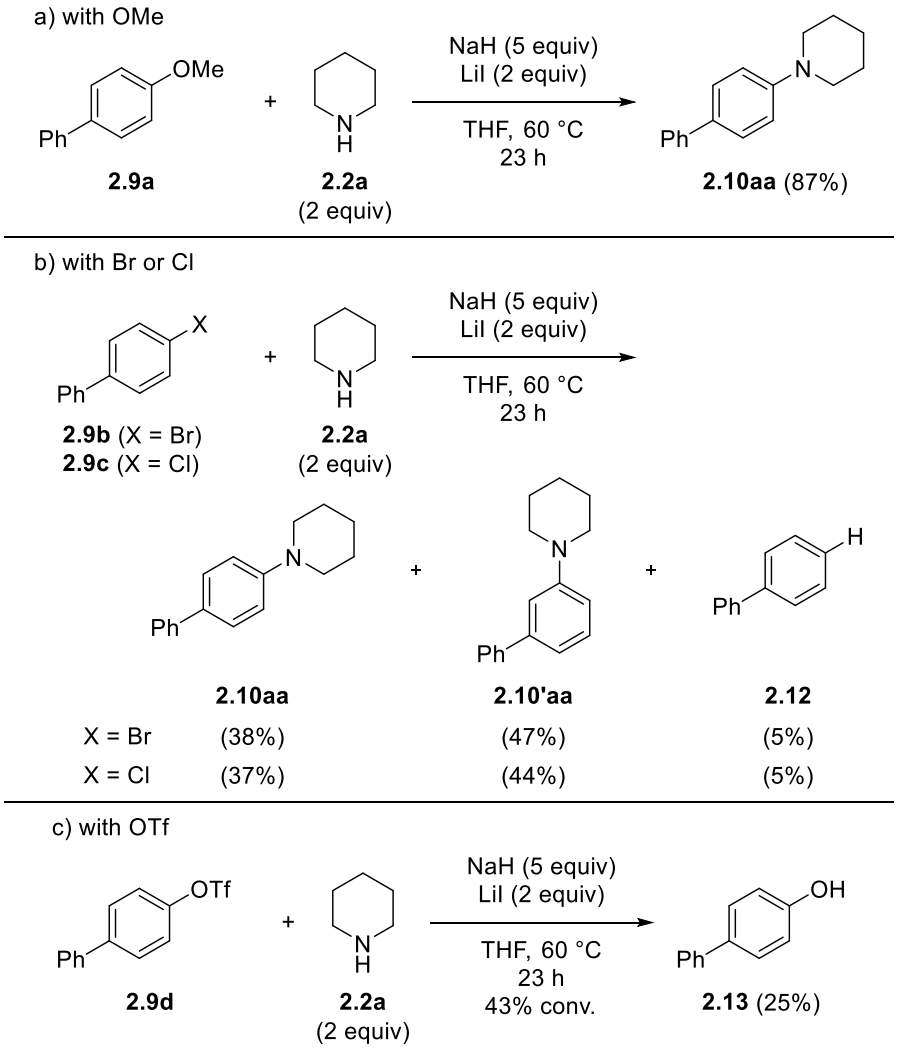
stabilized Meisenheimer complex followed by the elimination of a leaving group (Scheme 73a). In this case, leaving group effect is characterized by an 'element effect' where leaving group abilities follows as such: F > NO_2 > Cl ~ Br > I,[62] 2) an nucleophilic addition into a benzyne intermediate which usually provides a mixture of regioisomers (Scheme 73b).[55, 63-64] In contrast, a concerted nucleophilic aromatic substitution (cS_NAr), where the bond breaking and bond forming processes occur concurrently, the leaving group abilities are typically inversed as such: I > Br > C (Scheme 73c).[65-66] Recent computational and experimental studies by Jacobsen and co-workers showed that cS_NAr were not as rare as previously thought. Using DFT calculations, they found out that whether a nucleophilic aromatic substitution undergoes a concerted or stepwise process is highly dependent on the leaving groups and the ability of the substrate to stabilize the Meisenheimer intermediate.[67]



Scheme 73. Possible mechanisms behind nucleophilic aromatic substitutions.

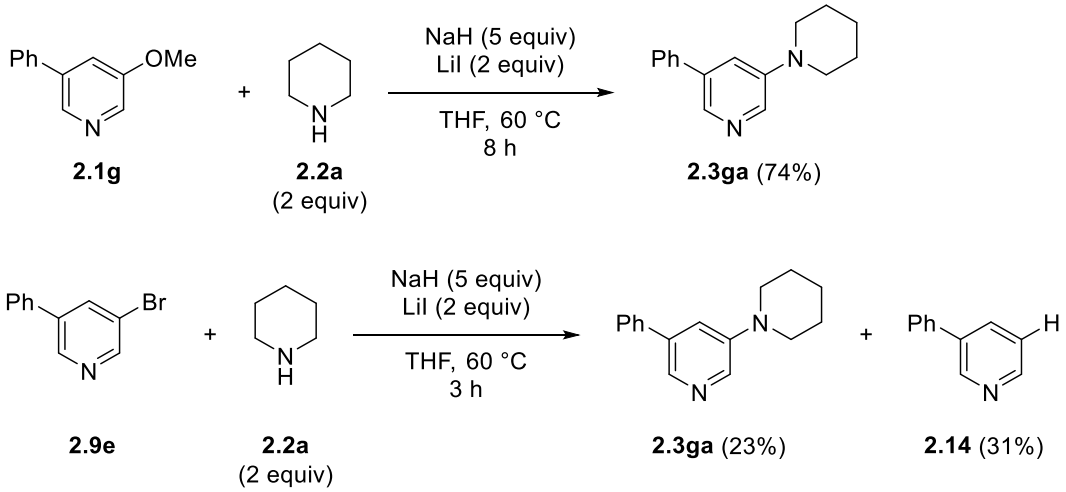
DFT calculations from our previous studies[68] showed that the amination of methoxy groups on arenes under our reaction system goes through a concerted nucleophilic substitution mechanism, hence allowing for C-3 substitutions. As noted in the introduction, typical

nucleophilic aromatic substitutions tend to undergo the traditional addition-elimination substitution reactions therefore allowing for only C-2 and C-4 aminations. Further investigations from our group had shown that the methoxy group is best leaving group under our amination reaction conditions (Scheme 74a). The use of haloarenes results in the formation of benzynes, resulting in a mixture of regioisomers **2.10aa** and **2.10'aa** being formed alongside some biphenyl **2.12** which is highly likely to be formed via hydrodehalogenation of the haloarene (Scheme 74b).[69] The use of triflates resulted in no substitution on the arene ring, only phenol **2.13** is formed (Scheme 74c).



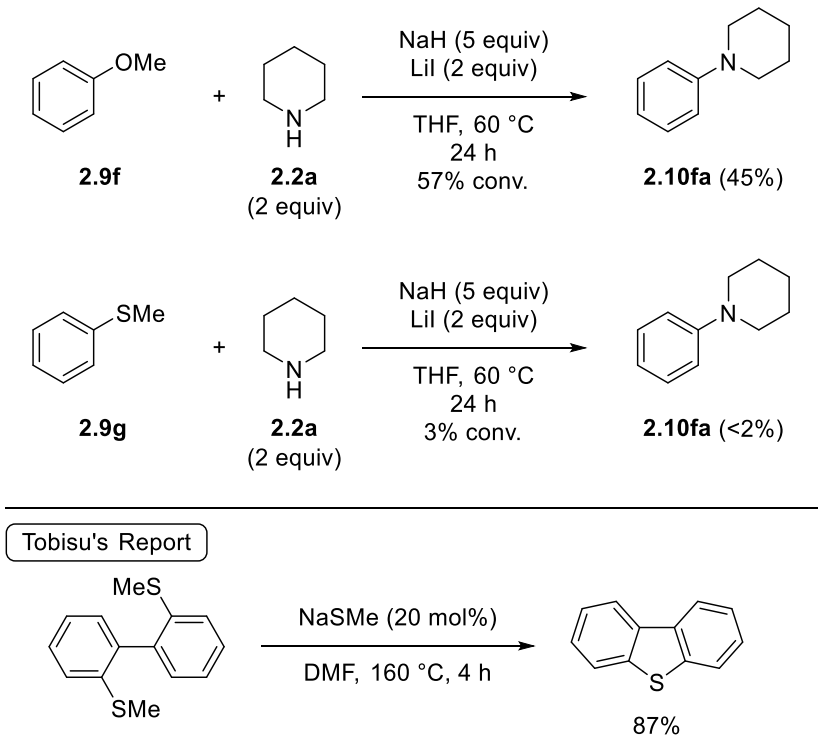
Scheme 74. Reactivity studies between different leaving groups for nucleophilic aromatic amination of arenes.

We then explored the use of halogens as leaving groups in the amination of pyridines. Using methoxypyridine **2.1g** afford aminated product **2.3ga** is 74% yields. In comparison, the use of bromopyridine **2.9e** resulted in the formation of **2.3ga** in only 23% yield and hydrodebrominated product **2.14** in 31% yield (Scheme 75).



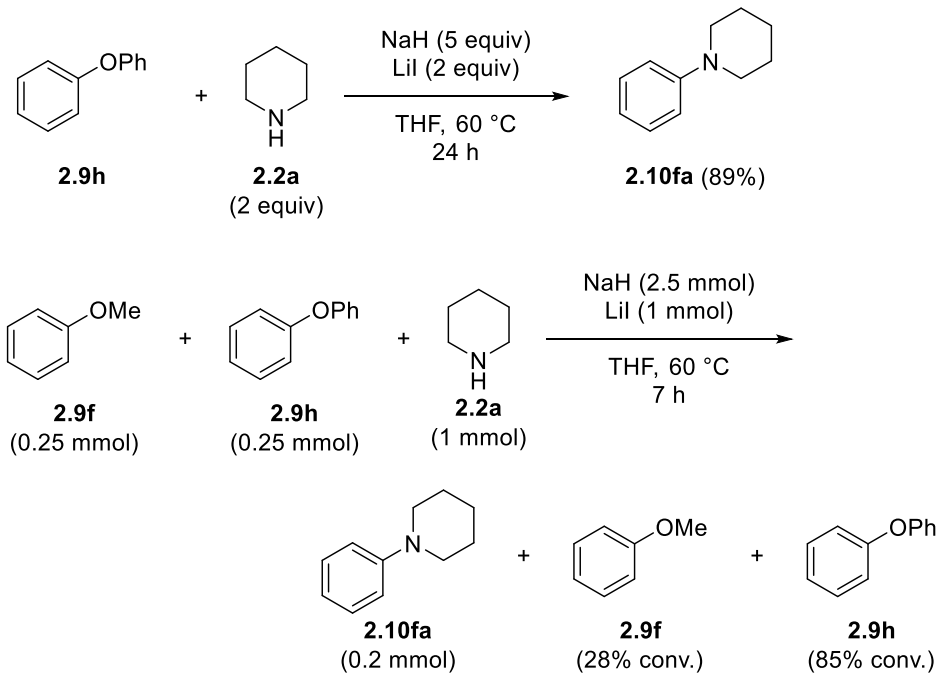
Scheme 75. Leaving group comparison in the nucleophilic amination of pyridines.

The recent report by Tobisu and co-workers for the construction of dibenzothiophenes via a intramolecular displacement of a thiolate anion by a benzothiolate anion prompted us to investigate the reactivity differences between thiolate and methoxide as a leaving groups (Scheme 76).[70] The use of anisole **2.9f** gave aminated product **2.10fa** in 45% yields while almost no reaction was observed with the use of thioanisole **2.9g**. Our DFT studies pointed out a significantly lowered activation energy for the case of using methoxy as a leaving group due to a stronger interaction between the counter cation and the oxygen atom as compared to that with the sulfur atom.



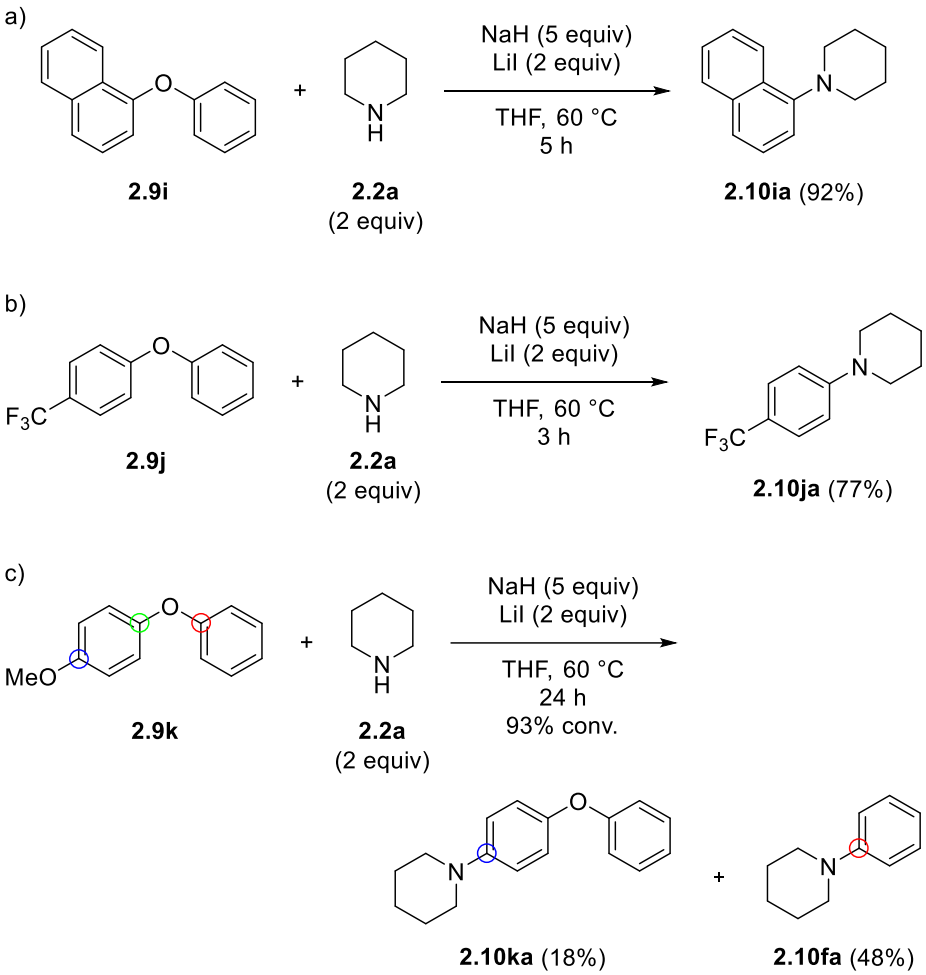
Scheme 76. Comparison between methoxide and thiolate as leaving groups.

As expected, the use of phenoxy as a leaving group is better as compared to methoxy. This is due to the phenoxy group being able to better stabilize the negative charge upon nucleophilic displacement as compared to the methoxy group. This is exemplified in the competitive reaction between anisole **2.9f** and diphenyl ether **2.9h**, where most of the diphenyl ether is consumed as compared to that of anisole (Scheme 77).



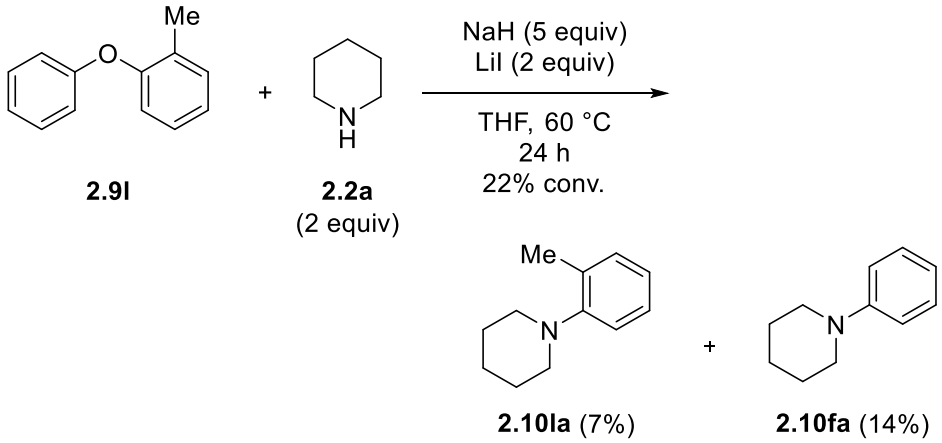
Scheme 77. Comparison between phenoxy and methoxy as leaving groups.

We then proceeded to investigate the electronic and steric influence on diaryl ethers bearing multiple sites for nucleophilic substitutions. The reaction of 1-phenoxynaphthalene **2.9i** gave only 1-(naphthalen-1-yl)piperidine **2.10ia** in 92% yields, showing that the nucleophilic amination preferentially takes place on the arene ring with a lowered LUMO (due to higher π-conjugation on the arene ring) (Scheme 78a). This effect is observed again with the use of 1-phenoxy-4-(trifluoromethyl)benzene **2.9j**, where the more electron deficient arene ring is preferentially attacked (Scheme 78b). The use of 1-methoxy-4-phenoxybenzene **2.9k** with 3 different sites of substitution gave a mixture of 1-(4-phenoxyphenyl)piperidine **2.10ka** and 1-phenylpiperidine **2.10fa** (Scheme 78c). It is clear that the nucleophilic aminations avoid attack on the most electron rich carbon labelled in green.



Scheme 78. Nucleophilic aminations on substrates with multiple substitution sites.

The nucleophilic amination of biaryl ethers is also sensitive to steric effects. The use of 1-methyl-2-phenoxybenzene **2.9l** with an *ortho* methyl group rendered the reaction sluggish with only 14% of 1-phenylpiperidine **2.10fa** and 7% of the more hindered 1-(o-tolyl)piperidine **2.10la** being formed after 24 h.



Scheme 79. Steric effects on the nucleophilic aminations of diaryl ethers.

2.4. Conclusion

In this work, the author demonstrated a novel use of the sodium hydride-iodide composite for amination of methoxypyridines in a concise manner. The broad scope and ability to synthesize aminated pyridines described in the report could be used to as an alternative to transition metal catalyzed amination of pyridines. Mechanistic studies showed that the nucleophilic amination is sensitive to steric and electronic factors. Furthermore, the methoxy group, which is typically considered a poor leaving group, is in fact the best leaving group under our reaction conditions for the nucleophilic aminations of arenes in terms of reaction efficiency and atom economy.

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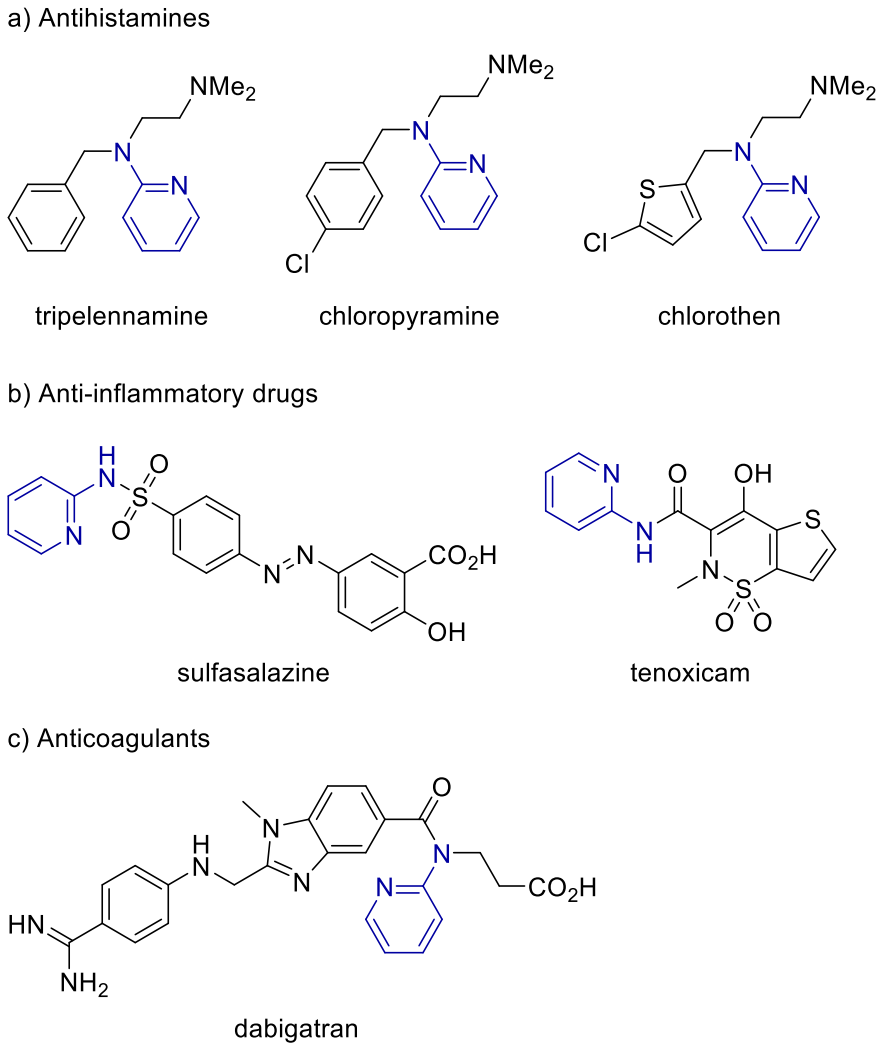
Chapter 3: Revisiting the Chichibabin Reaction: C2 Amination of Pyridines with a NaH-Iodide Composite

3.1. Introduction

Amongst all pyridine containing biologically active molecules, 2-aminopyridines play a central role as a crucial pharmacophore in various drugs.[1] This is exemplified in antihistamines such as tripelennamine[2-3] and its analogues[3-6] which feature a 2-aminopyridine moiety as its core scaffold (Scheme 80a). Other drugs include sulfasalazine[7] and tenoxicam[8] which are anti-inflammatory drugs for rheumatoid arthritis (Scheme 80b), and dabigatran[9-10] which is an anticoagulant used for the prevention of blood clots in people with risks of stroke (Scheme 80c).

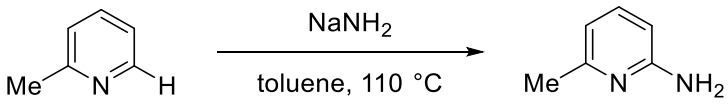


Scheme 80. Pharmaceuticals bearing the 2-aminopyridine pharmacophore.

As mentioned in the preceding chapter, one of the most powerful methods for C-2 amination *N*-heterocycles is the use of transition metal catalyzed cross coupling reactions with 2-halopyridines. The use of transition metals has major drawbacks including their relatively high costs, their high toxicity leading to stringent limitations on residual heavy metals found on pharmaceuticals, and their adverse environmental and social impacts during their extraction.[11-13]

Unlike the other C-2 amination methods mentioned previously, the Chichibabin reaction offers access to synthetically valuable 2-aminopyridines directly from pyridine without any pre-

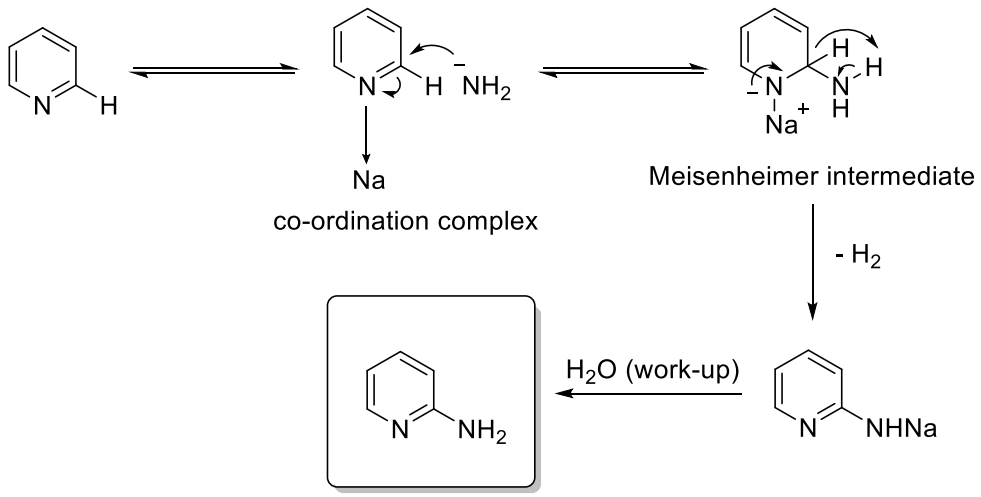
functionalization. In their seminal report, Chichibabin and co-workers described the formation of 6-methylpyridin-2-amine in the reaction with 2-picoline with sodium amide (Scheme 81).[14] The reaction was one of the first examples of an aromatic nucleophilic substitution of hydrogen and greatly influenced the development of heterocyclic chemistry in the 20th century. The Chichibabin reaction is typically carried out under heterogenous conditions at elevated temperatures in toluene, tetrahydrofuran, 1,2-dimethoxyethane, tetralin or in the case of highly electron deficient *N*-heterocycles such as pyrimidines, in liquid ammonia.[15-17]



Scheme 81. Chichibabin's seminal report on the amination of 2-picoline.

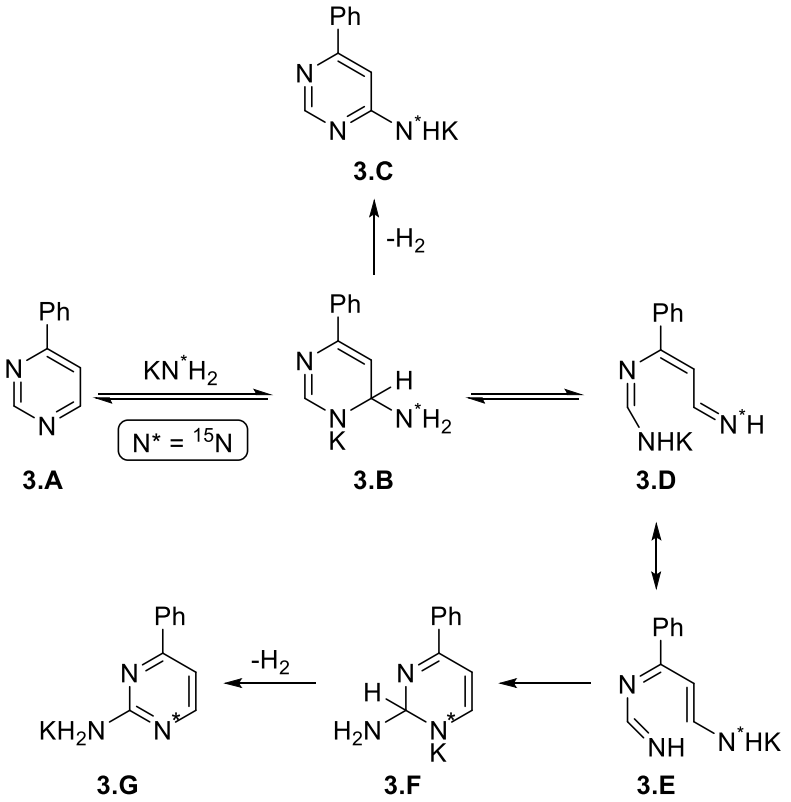
3.1.1. Mechanism of the Chichibabin Reaction

There are 2 generally accepted mechanisms for the Chichibabin reaction, the addition-elimination mechanism, most commonly seen under heterogenous conditions in aprotic solvents, and the S_N(ANRORC) (addition of the nucleophile, ring opening and ring closing) mechanism, typically seen under homogenous conditions with electron poor heterocycles.[15, 17] The addition-elimination mechanism is characterized by the formation of an Meisenheimer intermediate (Scheme 82). The reaction generally begins with the sorption of the Lewis acidic sodium cation to pyridine, increasing the heterocycle's susceptibility to nucleophilic attacks at the C-2 position. The amide nucleophile then adds onto the 2-position of the pyridine ring to generate the Meisenheimer intermediate. Expulsion of the hydride anion is driven by the re-aromatization of the pyridine ring which immediately deprotonates the amine, forming sodium pyridylamide, which upon quenching, furnishes 2-aminopyridine as the product. This proposed mechanism was later supported through DFT calculations with NH_3 as the solvent by Dransfield and co-workers.[18]



Scheme 82. Addition-elimination mechanism of the Chichibabin reaction.

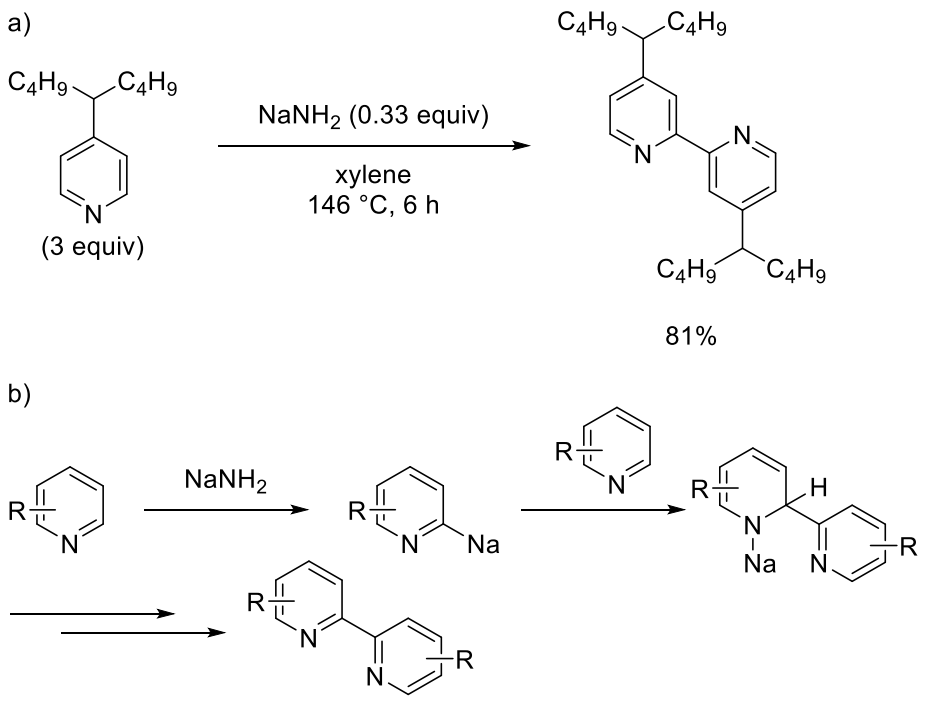
Under homogenous conditions, with liquid ammonia as a solvent, the Chichibabin reaction of highly electron poor *N*-heterocycles such as pyrimidines were proposed to undergo a S_N(ANRORC) mechanism. Studies by Plas and co-workers using ^{15}N-labelled potassium amide showed the inclusion of the ^{15}N into the ring of the aminopyrimidine product (Scheme 83).[19] In their proposed mechanism, attack of the ^{15}N labelled potassium amide onto the C-6 position of pyrimidine **3.A** forms Meisenheimer intermediate **3.B**. Subsequently, **3**.**B** can liberate H_2 to give isotopically labelled product **3.C** or undergo ring opening to give species **3.D**. Species **3.D** is in resonance with species **3.E** which can undergo ring closure to form **3.F**. Expulsion of H_2 can give ^{15}N incorporated amino pyrimidine **3.G**. The S_N(ANRORC) mechanism is uncommon and most Chichibabin reactions occur under heterogenous conditions which follows the addition-elimination mechanism.



Scheme 83. S_N(ANRORC) mechanism of the Chichibabin reaction.

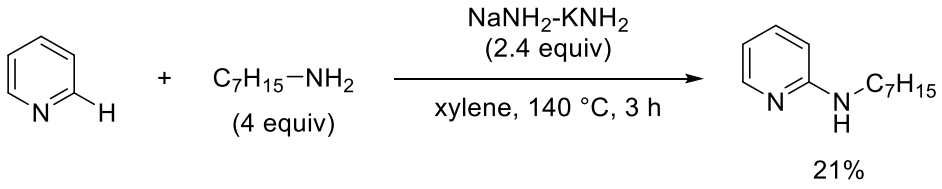
3.1.2. Limitations of the Chichibabin Reaction

Due to the high temperatures required for the Chichibabin reaction, dimers are often observed as side products, significantly lowering the yields of the aminated products (Scheme 84a).[15, 17] With the use of some alkylpyridines, dimers are the only products being formed. For example McGill reported that treatment of 4-(nonan-5-yl)pyridine with sodium amide gave only 4,4'-di(nonan-5-yl)-2,2'-bipyridine as the sole product.[20] Although the mechanism behind the dimerization is not entirely clear, the generally accepted pathway begins with the C2-metalation of the pyridine ring followed by the attack of the resulting pyridyl anion onto another equivalent of pyridine (Scheme 84b).[17]



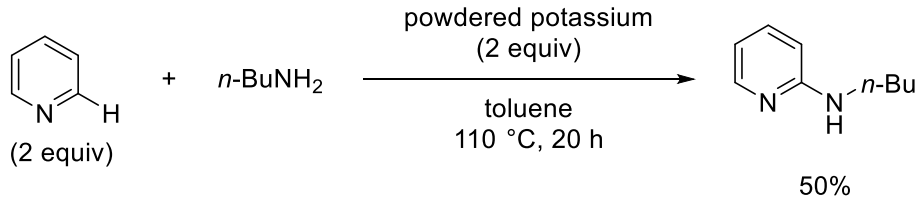
Scheme 84. Formation of dimers in the Chichibabin reaction.

Studies pertaining to the Chichibabin reaction were mainly limited to the use of sodium amides due to the difficulty of forming metalated primary alkylamides. One of the earliest reports was in 1945, where Bergstrom and co-workers reported the alkylamination of pyridine and quinolines using a sodium amide-potassium amide eutectic.[21] The sodium amide-potassium amide eutectic was prepared by bubbling ammonia gas through molten sodium and potassium and used as a base for deprotonation of the alkylamines. Their reported yields were typically low, and the use of a highly pyrophoric sodium-potassium eutectic made this methodology highly impractical (Scheme 85).



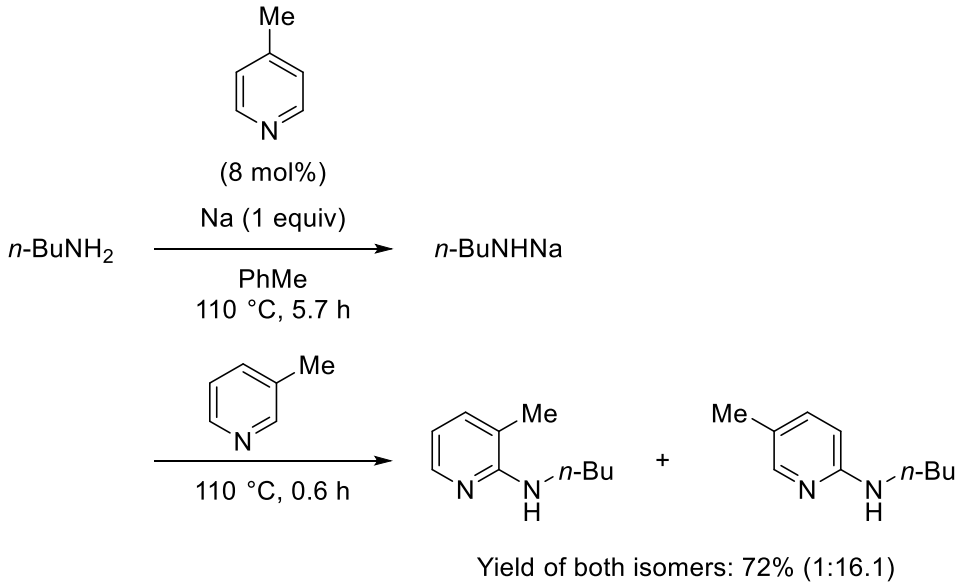
Scheme 85. Alkylamination of pyridine using sodium-potassium amide eutectic.

Later in 1961, Vajda and co-workers reported the amination of pyridines, picolines and quinolines by refluxing primary alkylamine with finely divided sodium or potassium in toluene (Scheme 86).[22] However, a major drawback in the reaction was the formation of dimers and tarry material as side products and the reported yields were typically less than 50%. The dimers were postulated to be formed from the dimerization of heterocyclic radical anions generated by single electron transfer from the alkali metal present in the reaction system.



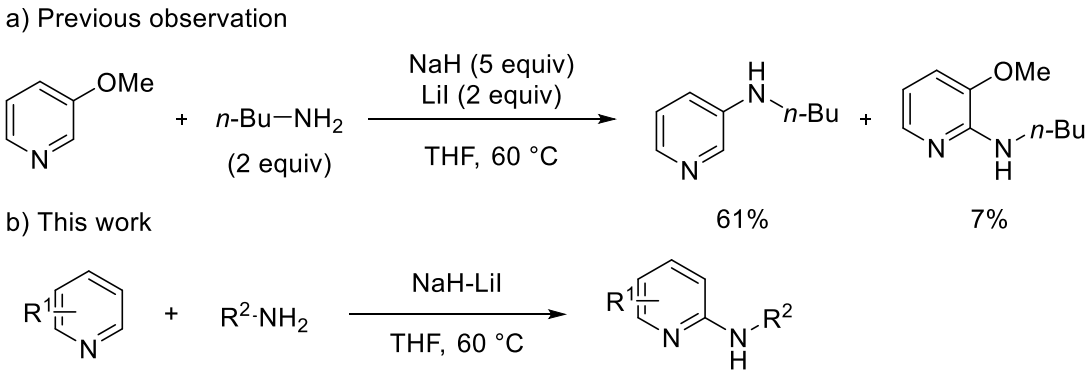
Scheme 86. Amination of pyridine using butylamine and powdered potassium.

A significant advancement in the Chichibabin reaction was discovered by McGill and co-workers in 1983. Their patent outlined the use of alkylpyridines dialkyl-2,2'-bipyridines as catalysts to pre-form the sodium alkylamide. Alkylpyridines were then aminated with the pre-formed sodium alkylamide to furnish a mixture of 2,3- and 2,5'-substituted alkylaminoalkylpyridines (Scheme 87). As compared to Vajda's protocol, this method generally gave better yields and less side products. A significant drawback is the formation of isomeric products which complicates the purification process, and the yields were still typically less than 80%. In general, the few successful reports for the amination of pyridines using alkylamines stem mainly from the difficulty in generating metalated primary alkylamines. Furthermore, the use of highly reactive alkali metals and harsh temperatures severely limits the substrate scope and yields for these reactions.



Scheme 87. Chichibabin reaction with pre-formed sodium alkylamides.

During our studies in the nucleophilic amination of methoxypyridines, we found that 2-butylamino-3-methoxypyridine was formed via the Chichibabin reaction, alongside the expected 3-butylaminopyridine (Scheme 88a). Expanding on that observation, we hypothesized that the highly basic nature of the sodium hydride-iodide composite can readily deprotonate primary alkyl amines under milder conditions, thereby improving the efficiency and scope of the Chichibabin reaction. In this section of the thesis, the author will demonstrate that the Chichibabin reaction using the sodium hydride-iodide composite offers access to a wider range of 2-aminopyridines whilst giving higher yields (Scheme 88b).



Scheme 88. Preceding observations and this work.

3.2. Results and Discussion

3.2.1. Starting materials

The pyridines shown in Figure 3 were commercially available and used as received.

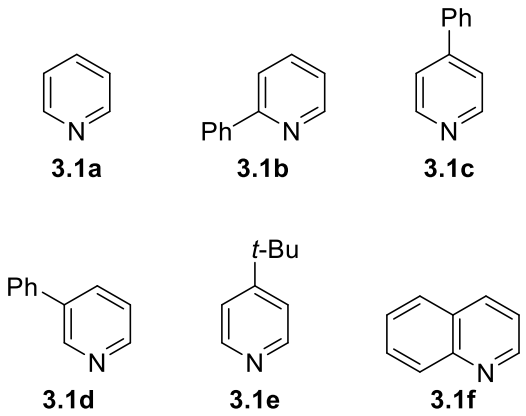


Figure 3. Pyridines used.

The amines shown in Figure 4 were commercially available and used as received.

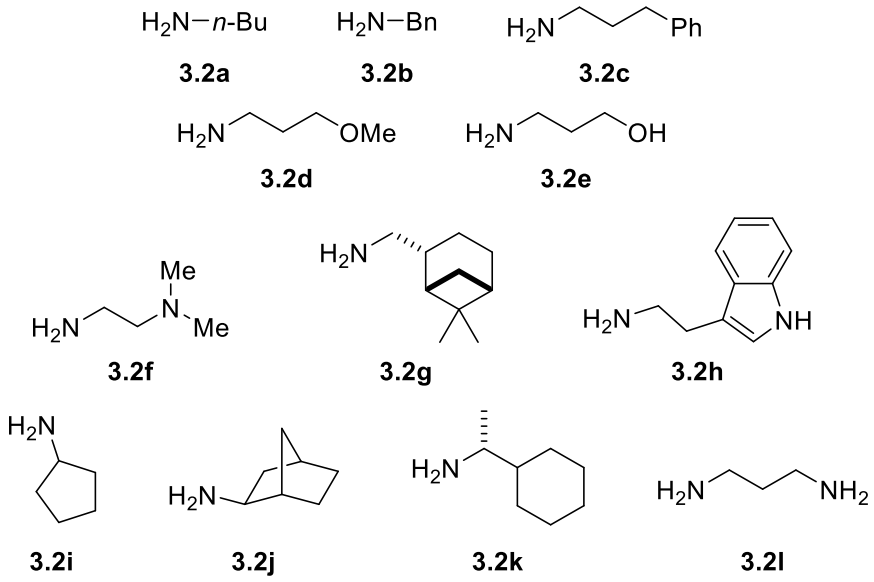


Figure 4. Amines used.

The bipyridines shown in **Figure 5** were commercially available and used as received.

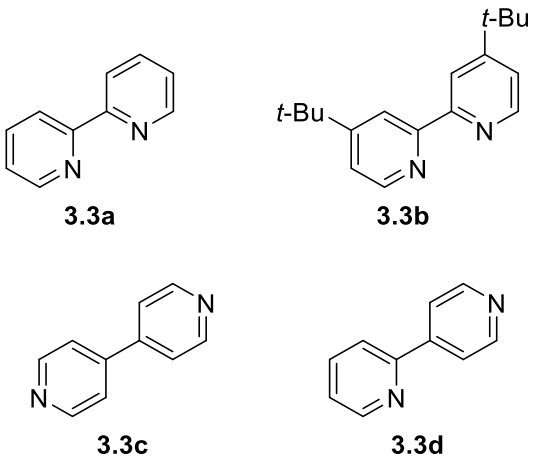
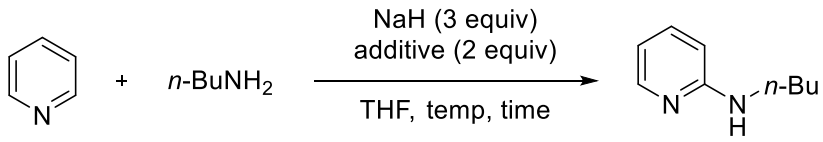


Figure 5. Bipyridines used.

3.2.2. Optimization of reaction conditions

We began our studies by optimizing the reaction conditions using pyridine **3.1a** (1 equiv) and *n*-butylamine **3.2a** (2 equiv) (Table 4). The use of NaH (3 equiv) and LiI (2 equiv) gave *N*-butylpyridin-2-amine **3.3aa** in 95% after 18 h at 65 ℃ (Entry 1). The use of just NaH gave **3.3aa** in only 21%, highlighting the importance of the iodide additive in enhancing the Brønsted basicity of NaH (Entry 2). Increasing the reaction temperature to 85 ℃ accelerated the reaction significantly, providing product **3.3aa** in 93% yields in just 7 h (Entry 3). The use of NaI instead of LiI rendered the reaction sluggish, giving only 75% yield of **3.3aa** even after 24 h while the use of less reactive LiH instead of NaH gave poor yields.

Table 4. Optimization of reaction conditions.



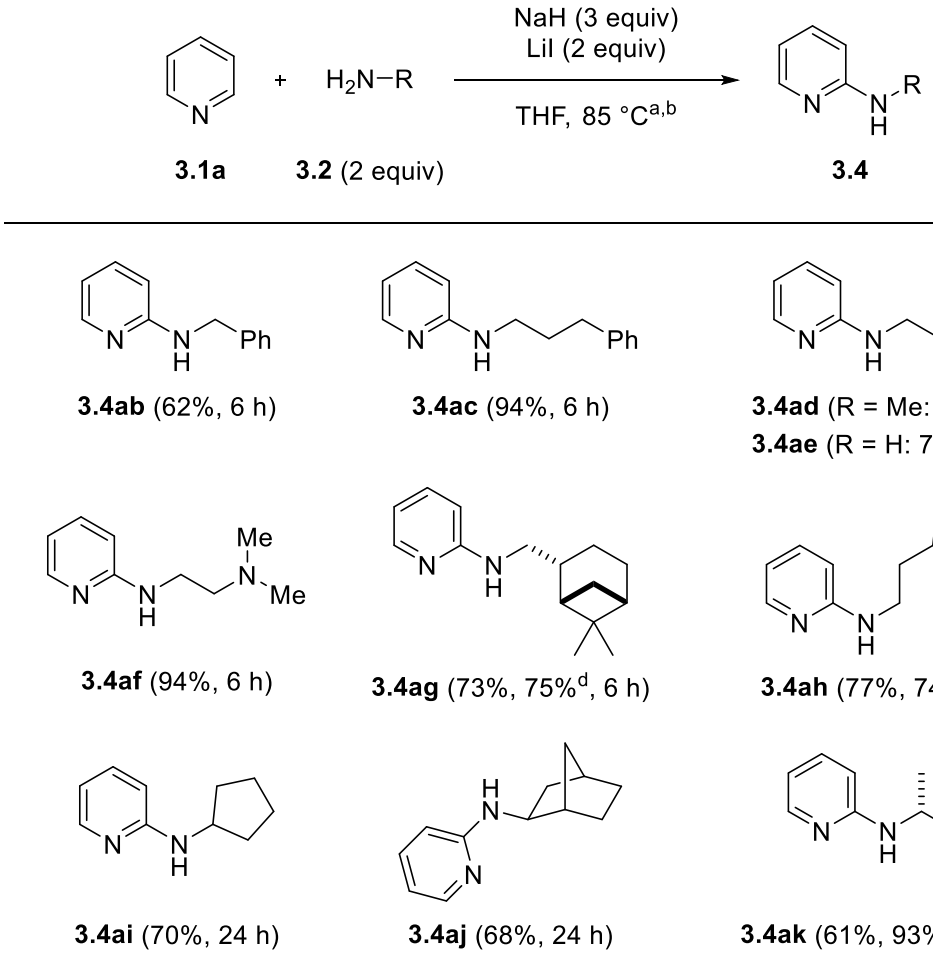
3.1a **3.2a** (2 equiv) **3.4aa**

Entry[a]	Additive	Time [h]	Temp [°C]	Yields [%][b]
1	LiI	18	65	95
2	none	18	65	21
3	LiI	7	85	93
4	NaI	24	85	75
5[c]	LiI	24	85	7[d]

[a]Reactions were carried out using 0.5 mmol of **3.1a** and 1 mmol of **3.2a.**[b]Isolated yields. [c]LiH (3 equiv) was used instead of NaH. [d]Yields calculated using ^{1}H NMR based on an internal standard.

3.2.3. Substrate scope and limitations

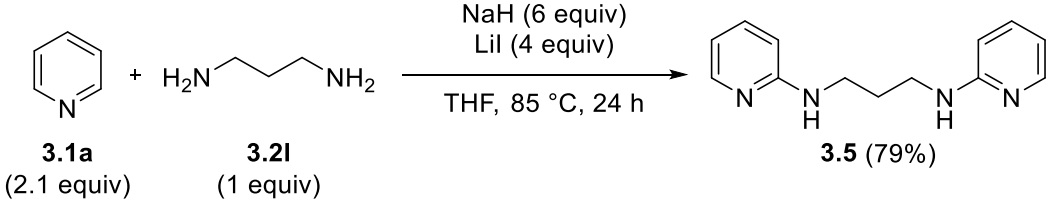
Using the optimized conditions, we started screening a series of primary amines for Chichibabin reaction using pyridine **3.1a** as the substrate (Scheme 89). Primary amines bearing primary alkyl groups reacted smoothly (**3.4ab**, **3.4ac, 3,4ad** and **3.4af**) under the reaction conditions. Amines bearing other acidic protons such as amino alcohols or indoles were also tolerated but required higher loadings of NaH (7 equiv) to form their corresponding 2-aminopyridines (**3.4ae** and **3.4ah**). Chiral (-)-*cis*-myrtanylamine could also be used to give **3.4ag** in good yields. Amines bearing more sterically demanding secondary alkyl groups such as cyclopentyl amine or *exo*-2-aminonorbornane required extended reaction times to give their corresponding products (**3.4ai** and **3.4aj**) in good yields. The reaction of pyridine with (*R*)-cyclohexylethylamine (94.5% ee) gave aminopyridine **3.4ak** in good yields with minimal loss of enantiomeric excess.



[a]The reactions were conducted using 0.5 mmol of **3.1a** and 1 mmol of **3.2.** [b]Isolated yields were based on **3.1a.** [c]Reaction was carried out using NaH (7 equiv). [d]Isolated yields were based on **3.2** using **3.1a** (3 equiv). [e]The reaction was carried out using (*R*)-(–)-cyclohexylethylamine (94.5% ee) using NaH (4 equiv).

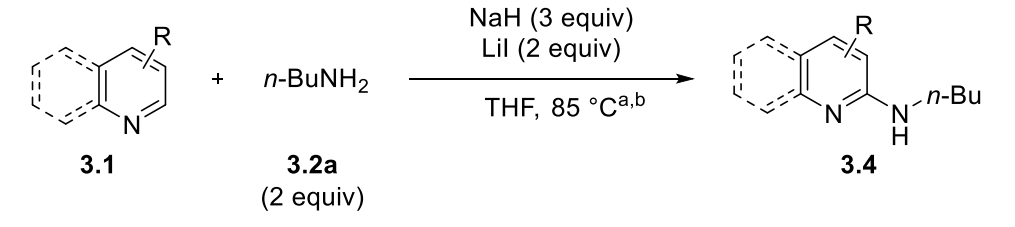
Scheme 89. Substrate scope of amines.

The reaction was also amenable to diamination by using 2.1 equivalent of pyridine **3.1a** with 1 equivalent of propane-1,3-diamine **3.2l** and higher loadings of NaH to form bispyridine **3.5** in good yields (Scheme 90).

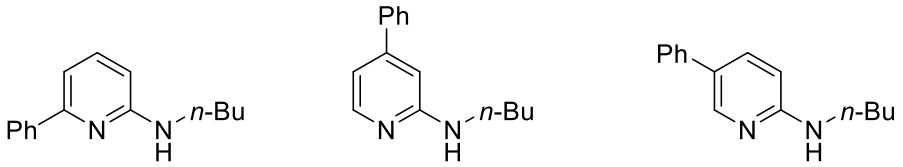


Scheme 90. Diamination of 1,3-propanediamine.

Next, we examined pyridines bearing different substituents by using *n*-butylamine **3.2a** as the nucleophile (Scheme 91). Phenyl and *t*-butyl substituted pyridines gave their aminated products excellent yields (**3.4ba**, **3.4ca**, **3.4da** and **3.4ea**) while quinoline **3.4fa** gave 2-aminoquinoline in excellent yields as well.



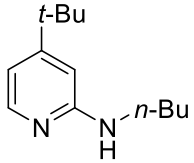
3.1 **3.2a** (2 equiv) **3.4**



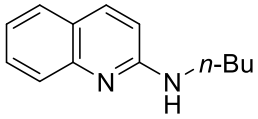
3.4ba (88%, 9 h)

3.4ca (96%, 7 h)

3.4da (82%, 24 h)



3.4ea (87%, 24 h)



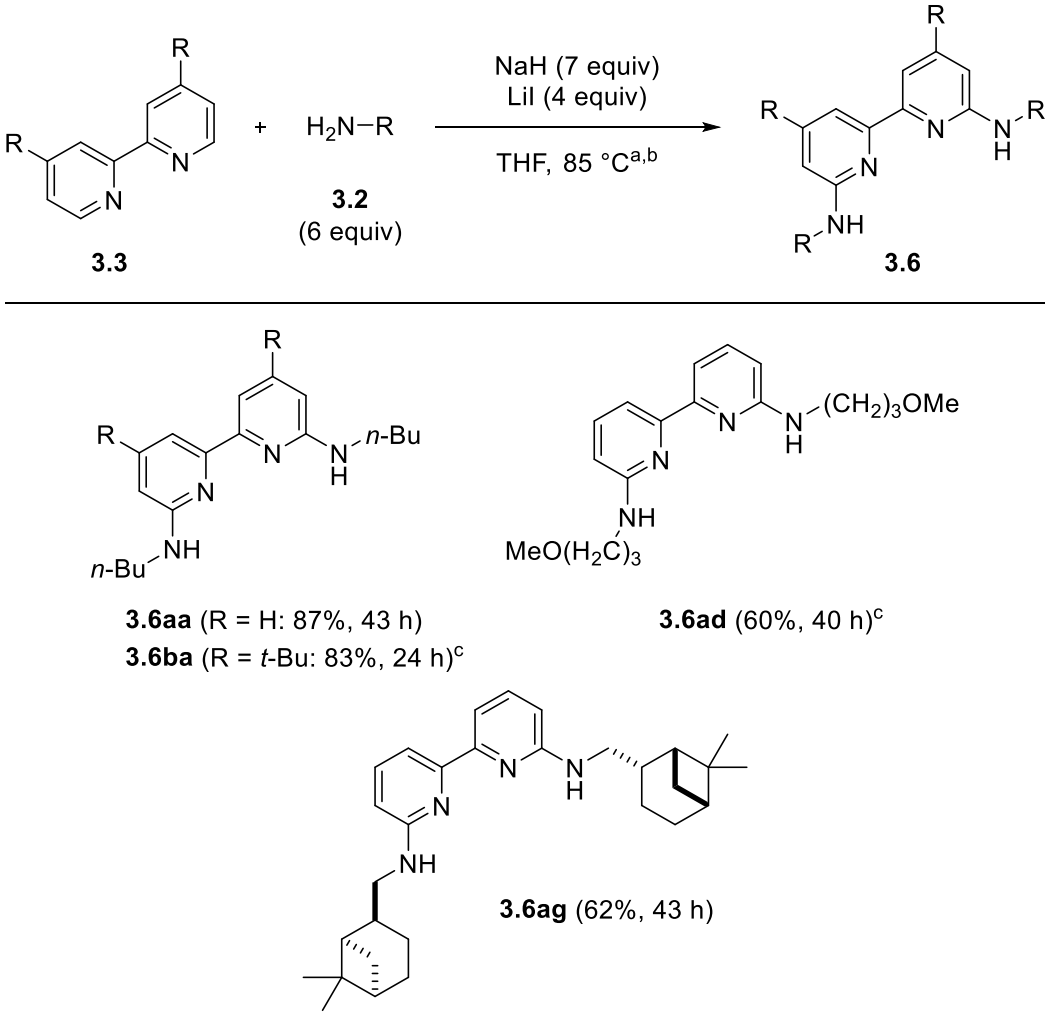
3.4fa (84%, 5 h)

[a]The reactions were conducted using 0.5 mmol of **3.1** and 1 mmol of **3.2a.** [b]Isolated yields were based on **3.1.**

Scheme 91. Substrate scope of pyridines.

Using commercially available 2,2'-bipyridines as substrates, we were able to synthesize 6,6'-diamino-2,2'-bipyridines via a diamination reaction (Scheme 92). Conventional synthesis of these bipyridines typically requires multiple step synthesis starting from C2 halogenated pyridines or bipyridines.[23-24] Diamination with *n*-butylamine and 3-methoxypropylamine proceeded smoothly to give 6,6'-diamino-2,2'-bipyridines (**3.6aa**, **3.6ba** and **3.6ad** respectively) in good to excellent yields. The use of (-)-*cis*-myrtanylamine gave diamino-bipyridine **3.6ag** in good yields. This protocol offers a direct and concise access to 6,6'-

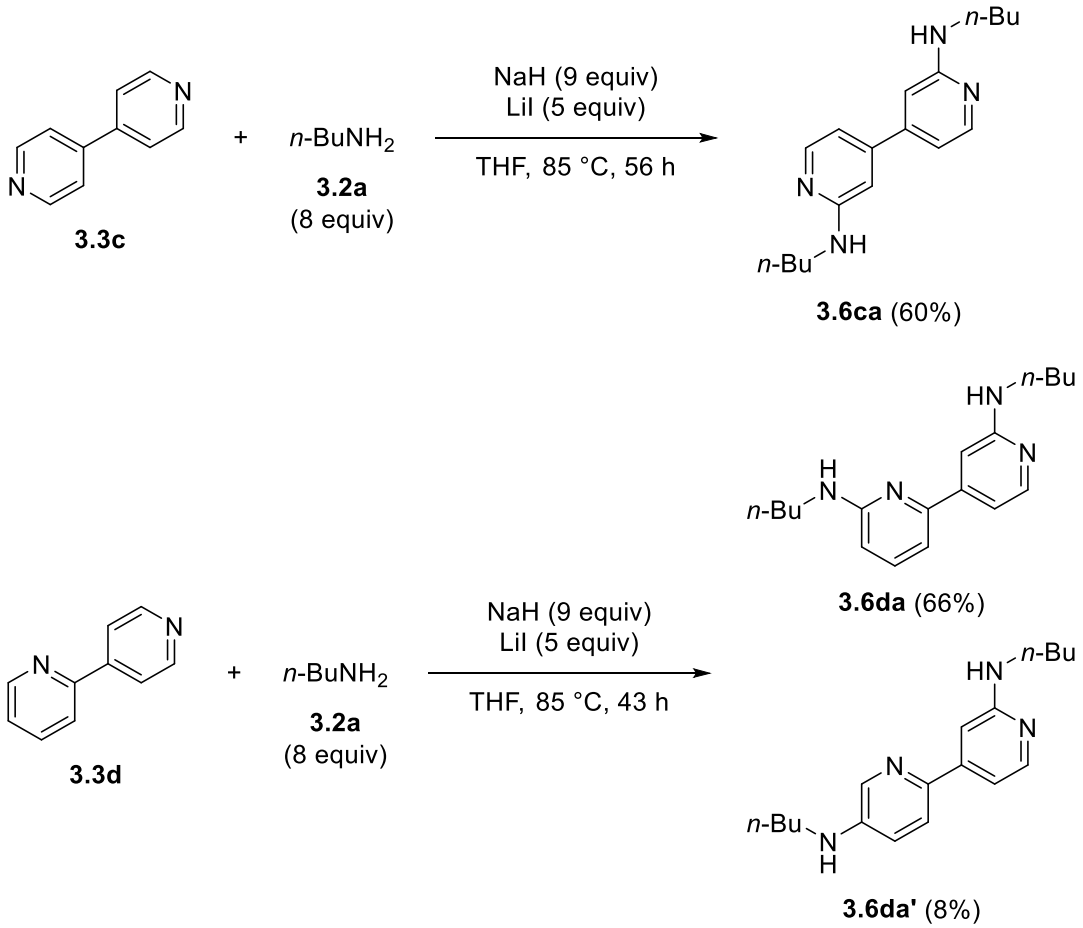
diamino-2,2'-bipyridines which may be used as potential ligands for transition metal catalysis.[25-27]



[a]The reactions were conducted using 1 mmol of **3.3** and 6 mmol of **3.2.** [b]Isolated yields were based on **3.3.**
[c]The reactions were conducted using 0.5 mmol of **3.6**, 8 equiv. of **3.2**, 10 equiv. of NaH and 7 equiv. of LiI.

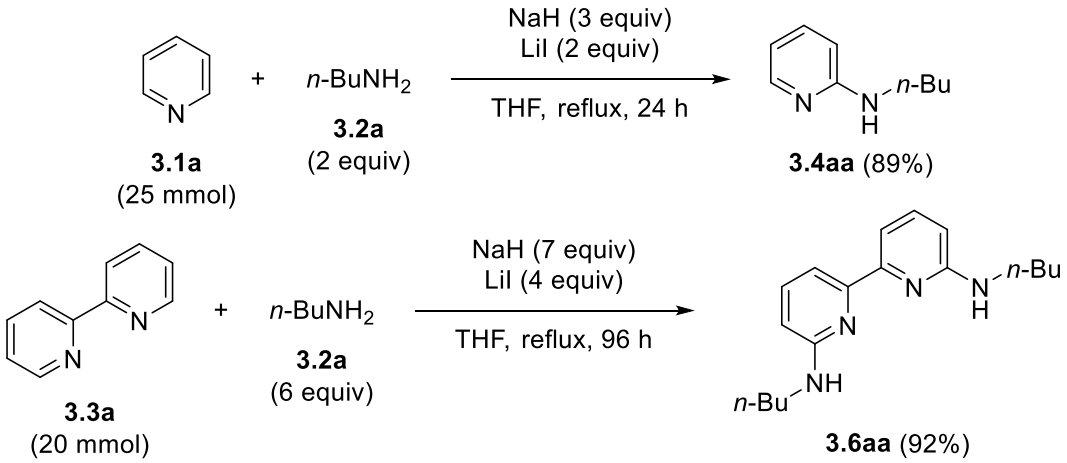
Scheme 92. Diamination of substituted 2,2'-bipyridines.

Diamination of 4,4'-bipyridine and 2,4'-bipyridine furnished their corresponding diamino-bipyridine in good yields (Scheme 93). Formation of some 5,2'-diaminated bipyridine **3.6da'** was observed in 8% yields alongside the expected 3,2'-diaminated bipyridine **3.6da**. The formation of **3.6da'** is arose from the ability of the of the nitrogen atom on the 4' location of the opposing pyridine ring to stabilize the Meisenheimer intermediate formed from the attack of the amine nucleophile onto the C-5 position of the bipyridine ring.



Scheme 93. Diamination of 4,4'-bipyridine and 2,4'-bipyridine.

Refluxing instead of super heating THF under pressure allowed us to safely scale the Chichibabin reaction for the multigram synthesis of (di)amino(bi)pyridines (Scheme 94). Large scale synthesis of 2-aminopyridine **3.4aa** with 20 mmol of pyridine **3.1a** and *n*-butylamine **3.2a** proceeded smoothly with excellent yields. Diamination of bipyridine **3.3a** was also feasible at a 20 mmol scale, giving diaminated bipyridine **3.6aa** in excellent yields.



Scheme 94. Multigram synthesis of (di)amino(bi)pyridines.

3.3. Conclusion

In conclusion, the author showcased the use of the sodium hydride-iodide composite for the C2-amination of *N*-heterocycles under mild and user-friendly conditions to furnish pharmaceutical and synthetically interesting 2-aminopyridines and diamino-bipyridines in good yields. Furthermore, the Chichibabin reaction under our conditions is easily scalable and would be a viable synthetic route towards the large-scale production of pharmaceutically valuable 2-aminopyridines.

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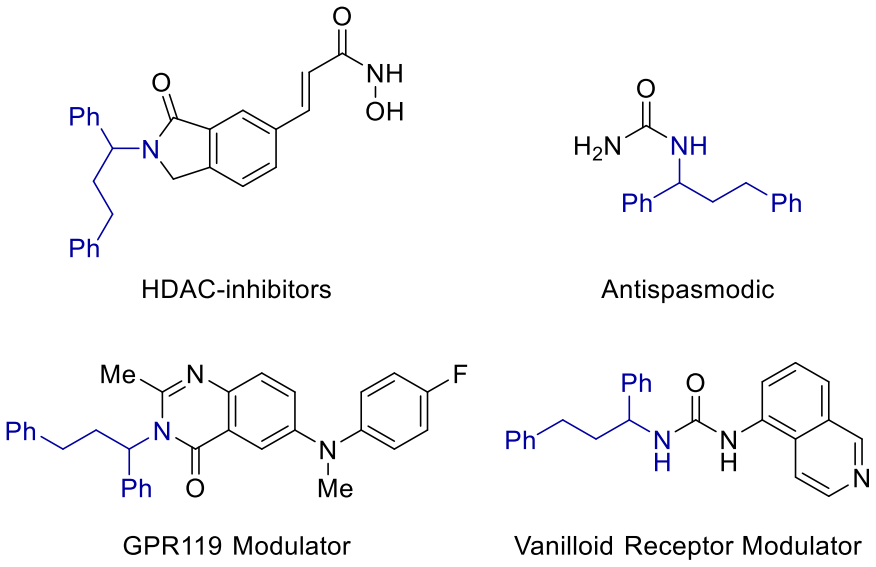
Chapter 4: Hydroalkylation of Styrenes with Benzylamines by Potassium Hydride

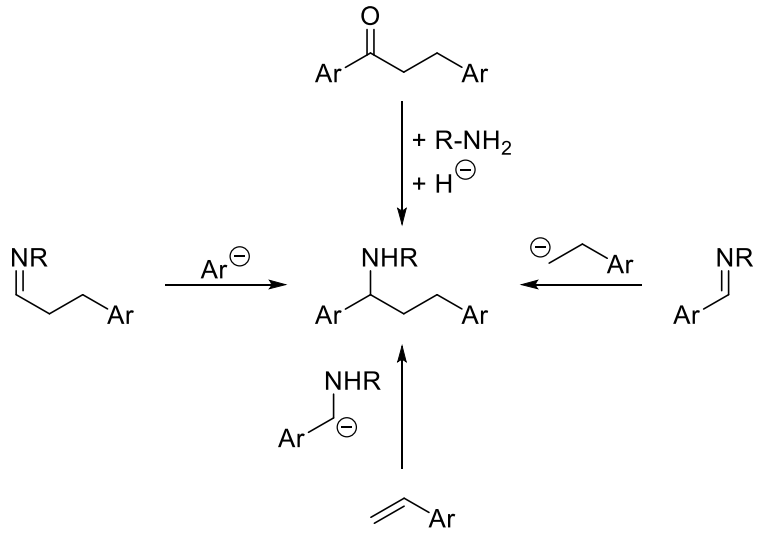
4.1. Introduction

Due to their high affinity for binding with proteins and neurotransmitters in the human body, amines are one of the most common functional group found in drug molecules.[1-2] Specifically, the 1,3-diarylpropylamines moiety has found use as various clinical candidates such as histone deacetylase (HDAC) inhibitors,[3] antispasmodic drugs,[4] G protein-coupled receptor modulators[5] and vanilloid receptor modulators (Scheme 95).[6]



Scheme 95. Examples of drugs containing the 1,3-diarylpropylamine moiety.

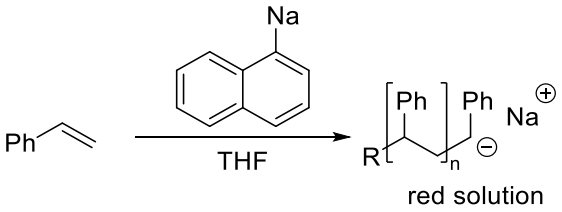
Typical synthetic paths towards the synthesis of 1,3-diarylpropylamines include the reductive amination of 1,3-diarylpropanones[6-8] and Mannich/Petasis reactions through the nucleophilic additions of aryl anions to phenylethylaldimines or addition of arylethylanions to arylaldimines (Scheme 96). Even so, the development of novel protocols from readily available starting materials would be useful for easy access to more chemically diverse 1,3-diarylpropylamine scaffolds.



Scheme 96. Typical methods to synthesize 1,3-diarylpropylamines.

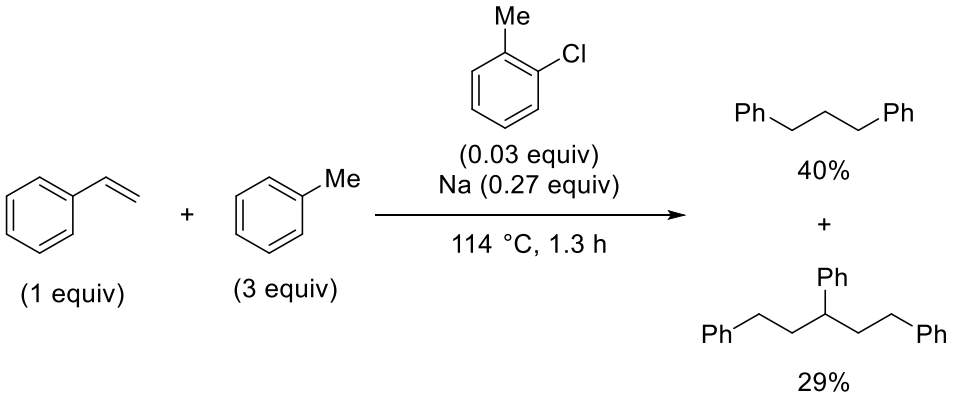
4.1.1. Addition of Carbanions towards Styrenes

The addition of carbanions towards styrenes is extremely well known in polymerization reactions.[9-12] In the seminal work by Szwarc on living polymerization of styrenes, it was observed that the addition of sodium naphthalene to styrene in THF resulted in the formation of an intense red solution of benzylic anions (Scheme 97).[13] The addition of more styrene monomers to the reaction mixture led to an increase in viscosity, indicating that the polystyrene chain is growing. Furthermore, the intense red coloration (the benzylic anion) persists for several days in the absence of air or moisture. This led to the conclusion that unless the reaction is quenched by an external source, the reaction will not terminate on its own, thus coining the term 'living polymerization'.



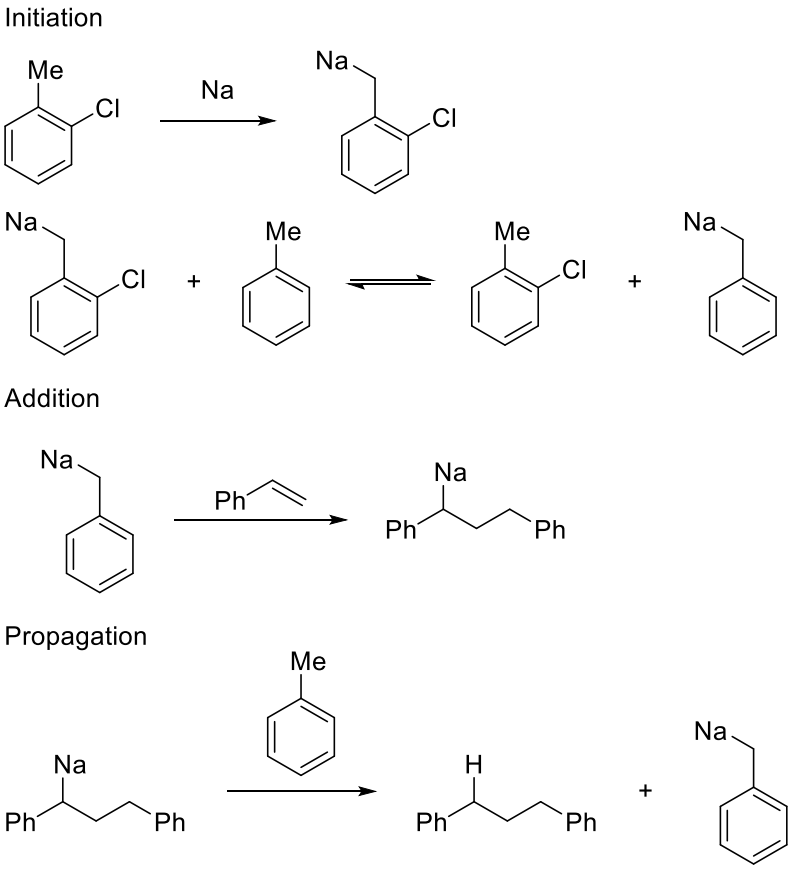
Scheme 97. Living polymerization of styrene.

Subsequent work by Pines and co-workers throughout the 1950s to 1970s showed that various alkylbenzenes and alkylheteroaromatics can be added to styrenes under highly basic conditions.[14-21] In their seminal work, they demonstrated that alkylbenzenes can form mono- and di-adducts with styrenes in the presence of catalytic amount of sodium and a promoter such as *o*-chlorotoluene (Scheme 98).[21]



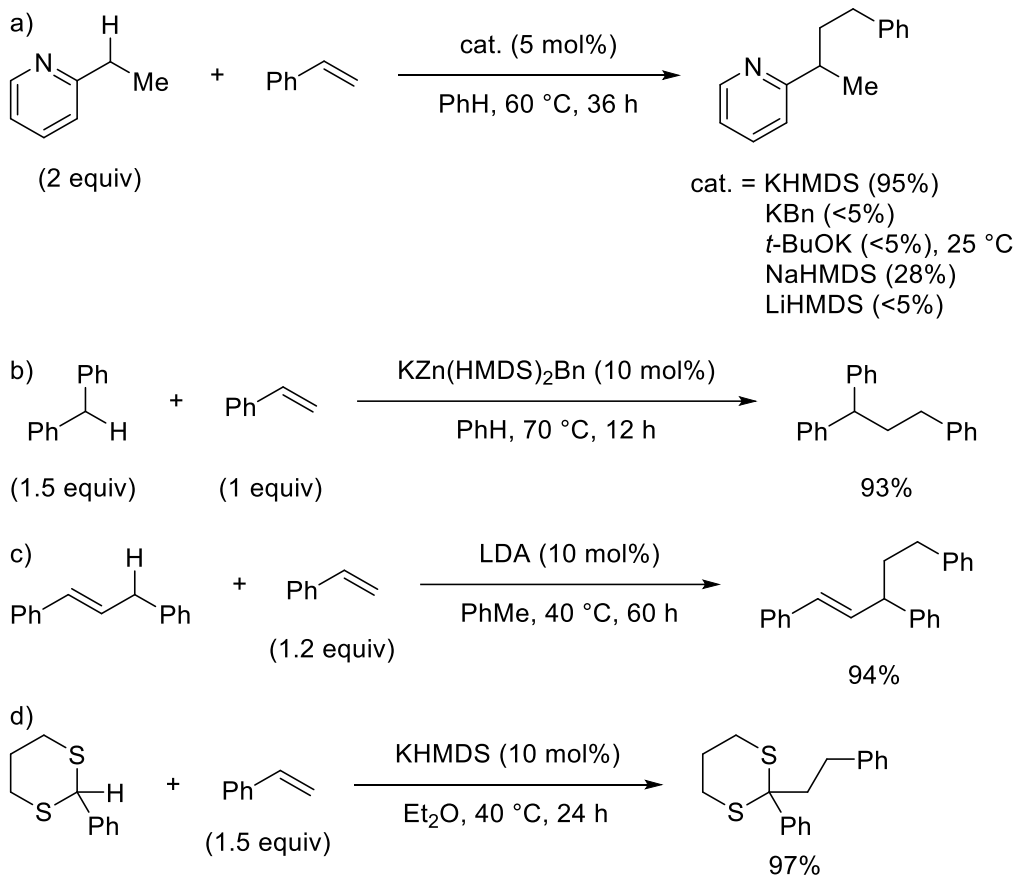
Scheme 98. Addition of toluene to styrenes.

They postulated that the promoters such as *o*-chlorotoluene readily form benzyl sodium in the presence of sodium metal which readily deprotonates the alkylbenzene (**Scheme 99**).[14] The benzylic anion adds onto styrene, forming a secondary anion which readily deprotonates another molecule of toluene, regenerating the benzylic anion and thereby propagating the anionic chain reaction.



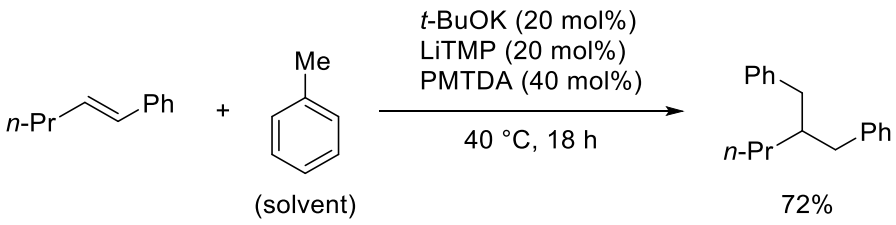
Scheme 99. Anionic chain mechanism using catalytic sodium.

More recently, by utilizing substrates bearing relatively acidic C-H bonds, Guan and co-workers demonstrated the addition of various carbanions towards styrenes using strong bases. In their first report, alkylpyridines was deprotonated using catalytic amount of KHMDS and subsequently trapped with styrenes as an electrophile (Scheme 100a).[22] They observed that the use of KHMDS is essential for the reaction to occur – stronger bases such as benzylpotassium led to the polymerization of styrene while weak bases like *t*-BuOK gave no reaction. Furthermore, the use of a potassium counter cation is also essential in their reactions, where both NaHMDS and LiHMDS gave poor yields and conversions in the reaction. In their following studies, other substrates such as diarylmethanes (Scheme 100b),[23] 1,3-diarylpropenes (Scheme 100c)[24] and 1,3-dithianes (Scheme 100d)[25] were demonstrated to add readily to styrenes upon deprotonation with various organometallic bases.



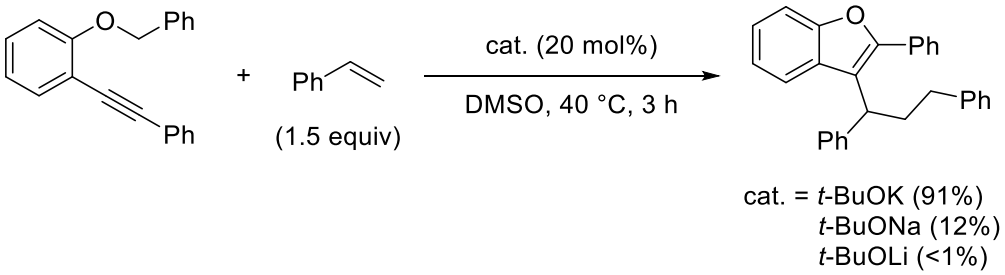
Scheme 100. Addition of various nucleophiles to styrenes using organometallic bases.

As mentioned in the introduction, Kobayashi and co-workers realized the addition of toluene towards activated diarylalkenes using a super-basic mixture of *t*-BuOK and TMPLi in the presence of PMDTA (Scheme 101).[26] In their reaction, unsymmetrical diarylalkenes gave the desired adducts in complete regioselectivity, resulting from intermediates where the anion was formed in the more stabilized benzylic position.



Scheme 101. Addition of toluene to diarylalkenes.

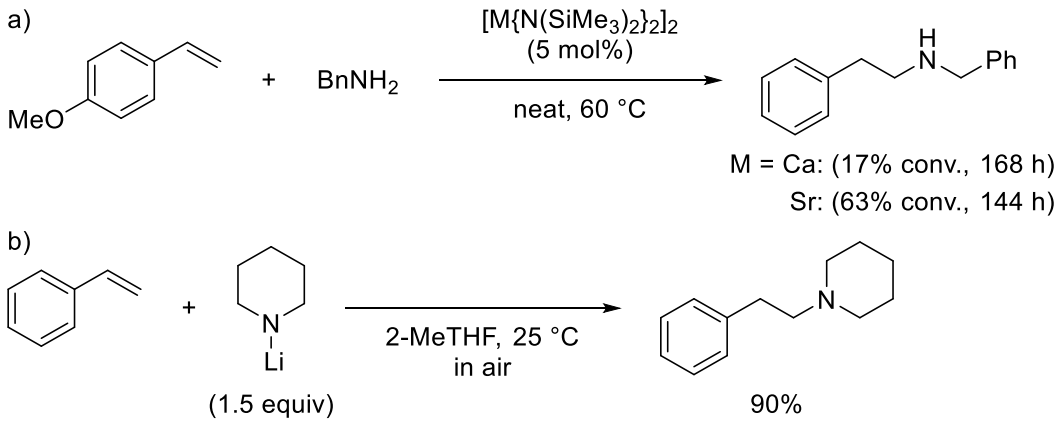
In the most recent example, Terada and co-workers demonstrated the synthesis of benzofurans using a tandem intramolecular cyclization followed by intermolecular addition strategy (Scheme 102).[27] Similar to Guan's reaction with alkylpyridines, they reported that the role of the counter cation of the base is highly influential towards the reaction outcomes. The use of *t*-BuOLi or *t*-BuONa led to little to no yields while *t*-BuOK is found to be optimal for the reaction.



Scheme 102. Base mediated synthesis of substituted benzofurans.

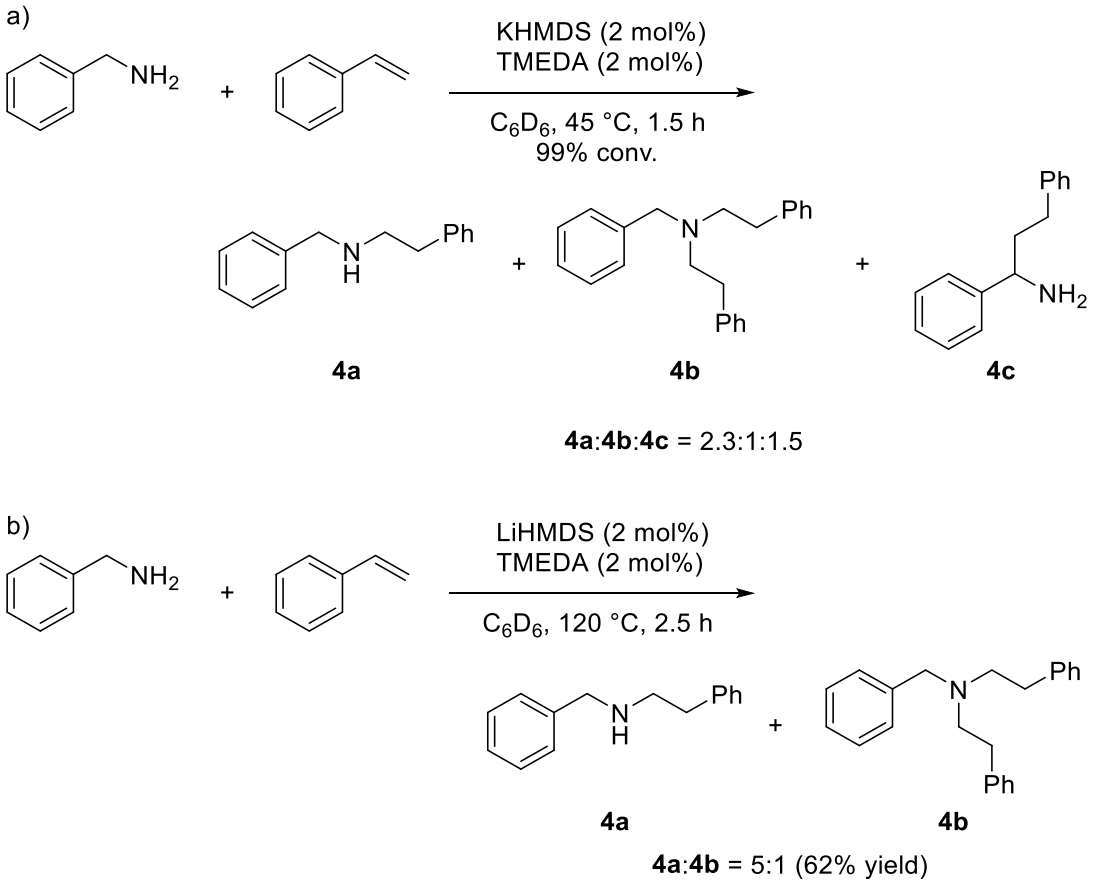
4.1.2. Hydroamination of Styrenes

In contrast, deprotonative benzylic alkylation of benzylamines, which bears an acidic N-H bond, remain exceeding rare. Primary and secondary amines tend to undergo deprotonation on the N-H bond in the presence of alkali/alkaline earth metal bases to generate the amide anion. The amide anion readily adds onto olefins to form the hydroaminated product.[28-35] In one of the earliest reports, Hill and co-workers carried out an assessment of using heavier group 2 metals for intermolecular hydroaminations.[33] Their experimental results showed that the heavier strontium catalyst showed superior catalytic performance over the calcium catalyst, providing the hydroaminated products in higher conversion and lower reaction times (Scheme 103a). In a more recent example, Hevia and co-workers reported the hydroamination of vinylarenes with lithium piperidide under ambient conditions in air (Scheme 103b).[28] They showed that the presence of a proton source, such as moisture in air, is crucial to quench anionic intermediate to prevent polymerization of styrenes.



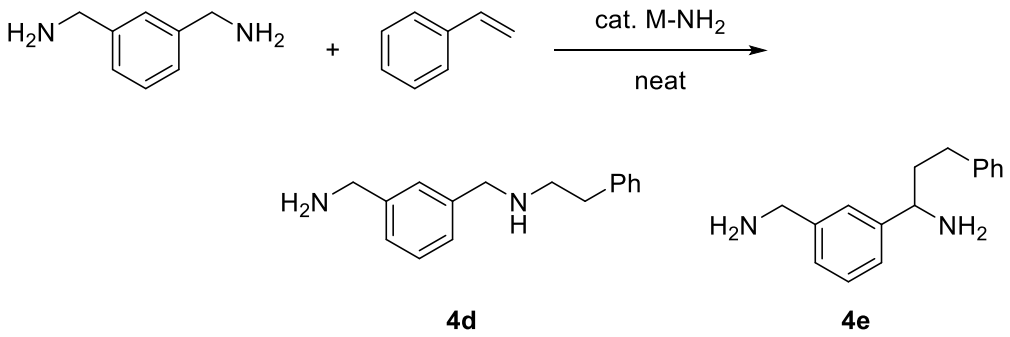
Scheme 103. Hydroamination of styrenes.

Interestingly, Hultz and co-workers has observed the formation of hydroaminated products, **4a** and **4b**, along with hydroalkylated product **4c** when using KHMDS and TMEDA (Scheme 104a).[36] In their reactions using LiHMDS, only hydroaminated products were formed (Scheme 104b). This led us to hypothesize that there might be an equilibrium between the amide anion and benzylic anion and the presence of a potassium cation might influence the reaction outcomes.



Scheme 104. Formation of hydroalkylated and hydroaminated products using alkali metal amides.

Similarly, researchers at Mitsubishi Gas Chemical Company have observed a similar counter cation ion effect in their reaction of 1,3-phenylenedimethanamine with styrene using catalytic alkali metal amides (Scheme 105).[37] The use of lithium and sodium amide gave hydroaminated **4d** as the major product. When *t*-BuOK was used as an additive together with $NaNH_2$, a selectivity switch occurred, giving hydroalkylated **4e** as the major product.



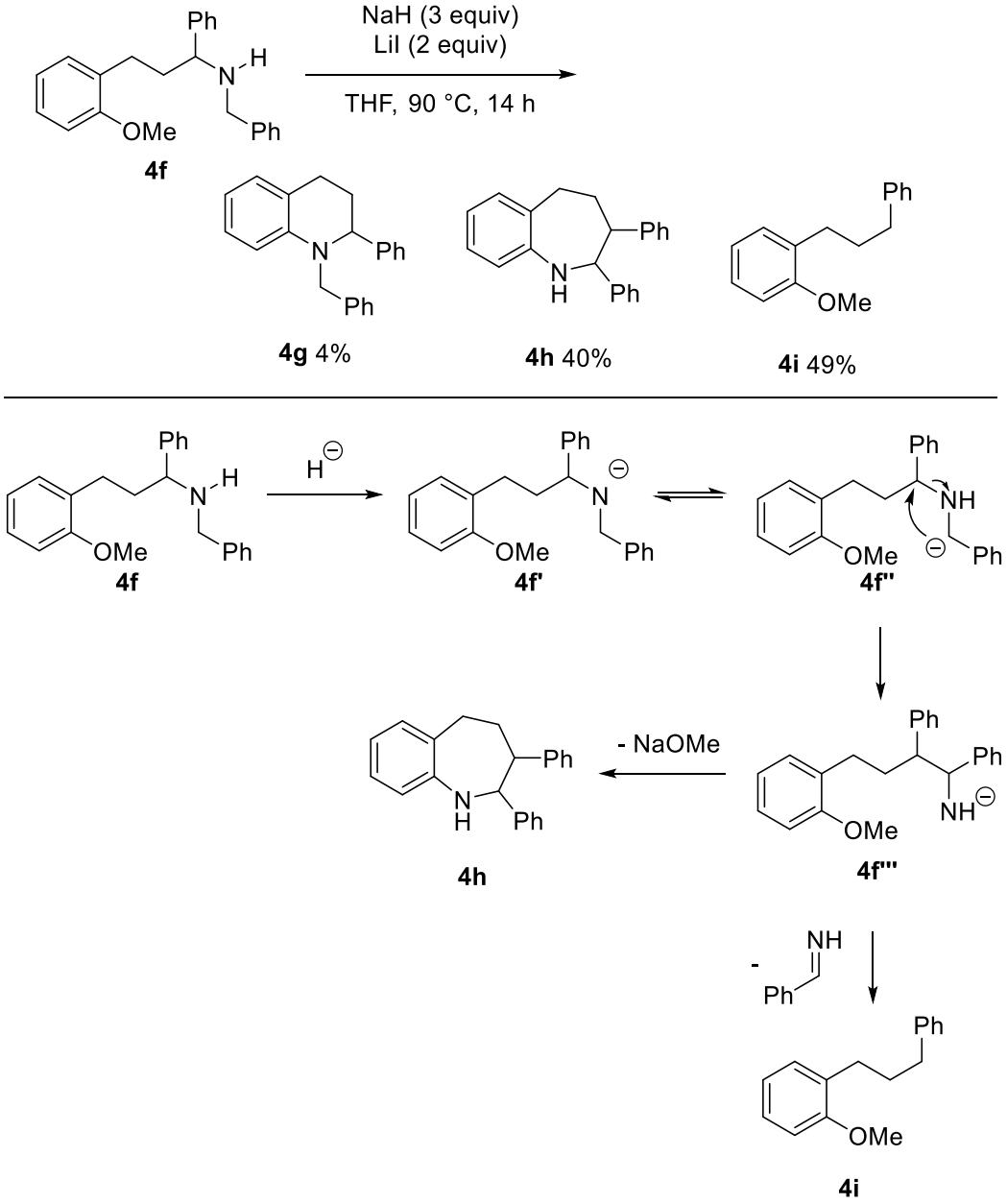
M-NH_2 = $LiNH_2$: **4d**:**4e** = 89:11

= $NaNH_2$: **4d**:**4e** = 61:39

= $NaNH_2$ + *t*-BuOK: **4d**:**4e** = 22:78

Scheme 105. Counter cation effects on the selectivity between hydroamination and hydroalkylation of styrenes.

Furthermore, during our studies in the nucleophilic amination of methoxyarenes using alkali metal amides generated using the sodium hydride-iodide composite, we observed an equilibrium between the amide anion and its benzylic anion (Scheme 106). Treatment of *N*-benzyl-3-(2-methoxyphenyl)-1-phenylpropan-1-amine **4f** with NaH (3 equiv) and LiI (2 equiv) in THF at 90 ℃ gave tetrahydroquinoline **4g**, benzo[b]azepine **4h**, and 1-methoxy-2-(3-phenylpropyl)benzene **4i**. We proposed that deprotonation of **4d** by the sodium hydride composite forms amide anion **4f'** which is in equilibrium with benzylic anion **4f''**. A aza-[1,2]-Wittig rearrangement would form amide anion **4f'''** which either undergo cyclization to form **4h** or a β-elimination of imine to form **4i**.



Scheme 106. Previous studies showing the presence of an equilibrium between amide anion and benzylic carbanion.

Based on these observations, we postulated that we could capitalize on the amide-benzylic anion equilibrium and selectively react the benzylic anion with styrene through the careful selection of counter cation to give hydroalkylated products. This is an example of an non-traditional bond disconnection for functionalization of substrates bearing pharmaceutically important amine groups and is highly sought after in drug synthesis and discovery.[38] In this

chapter, we report the selective hydroalkylation of styrene using benzylic amines in the presence of potassium hydride.

4.2. Results and Discussion

4.2.1. Preparation of starting materials

The amines shown in **Figure 6** were commercially available and used as received.

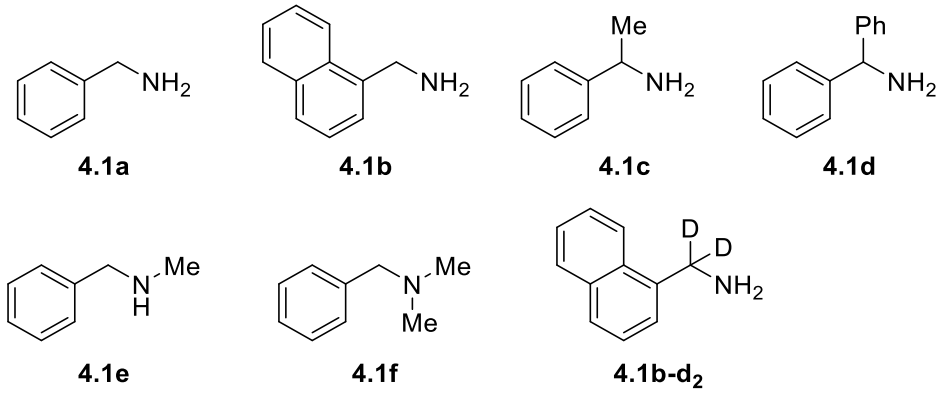


Figure 6. Amines used.

The styrenes shown in **Figure 7** were commercially available and used as received.

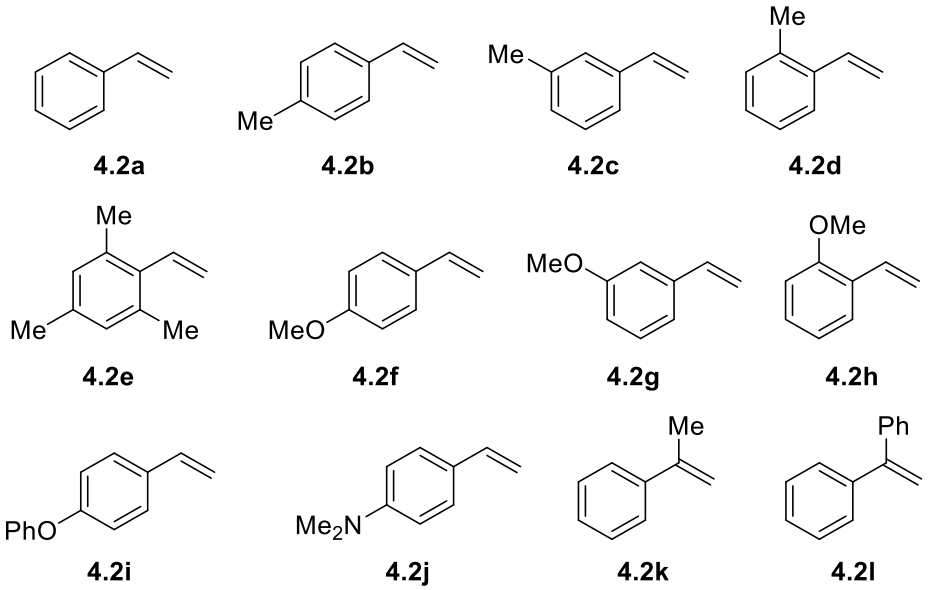
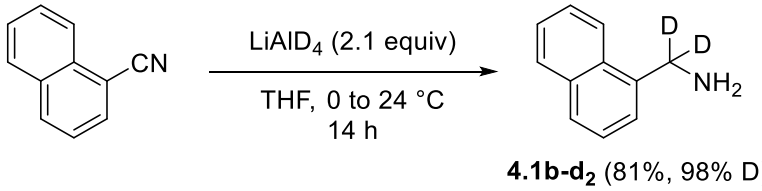


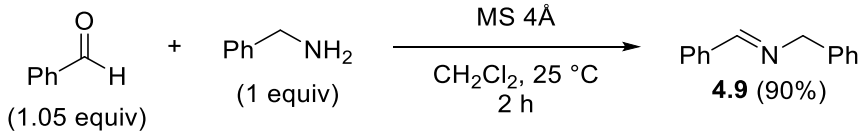
Figure 7. Styrenes used.

Deuterated naphthylamine **4.2b-d2** was synthesized via reduction of 1-naphthylnitrile using lithium aluminum deuteride (Scheme 107).



Scheme 107. Synthesis of deuterated 1-naphthylmethylamine.

Imine **4.9** was synthesized via reductive amination using 4Å molecular sieves and distilled using a bulb-to-bulb distillation set up (Scheme 108).



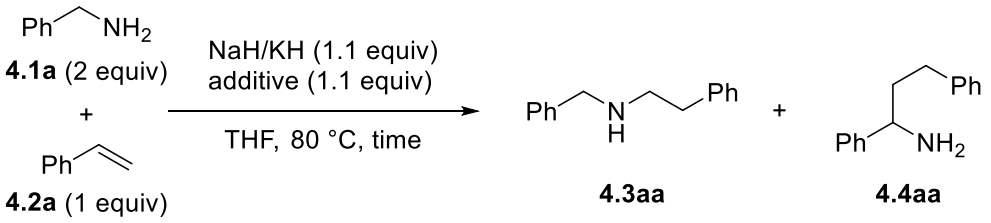
Scheme 108. Reductive amination of benzaldehyde and benzylamine.

4.2.2. Optimization of reaction conditions

We began our studies by using benzylamine **4.1a** and styrene **4.2a** as model substrates for our optimization reaction (Table 5). Using just NaH without any additives gave poor yields and selectivity of both hydroaminated product **4.3aa** and hydroalkylated product **4.4aa** (Table 5, Entry 1). The use of LiI as an additive did not improve the yields of the reaction and we postulated that the poor mass balance of the reaction was caused by anionic polymerization of styrene under our reaction conditions (Table 5, Entry 2). We then examined the use of larger counter cations in hope of minimizing the deleterious polymerization reaction and discovered that the use of CsI led to better yields of both **4.3aa** and **4.4aa** (Table 5, Entry 3). We envisioned using CsF will enhance the counter ion metathesis between the additive and sodium hydride due to the higher lattice energies of NaF (910 kJ mol^{-1}) as compared to that of NaH (682 kJ mol^{-1}). Indeed, using CsF in combination with NaH resulted in good yields and better

selectivity towards formation of **4.4aa** while the yields of **4.3aa** remained largely the same (Table 5, Entry 4). Increasing the amounts of amine to 2.5 equiv improved the yields significantly (Table 5, Entry 5) while the use of more reactive KH allowed for a quicker consumption of styrene but led to lowered yields (Table 5, Entries 6 and 7).

Table 5. Optimization of reaction conditions



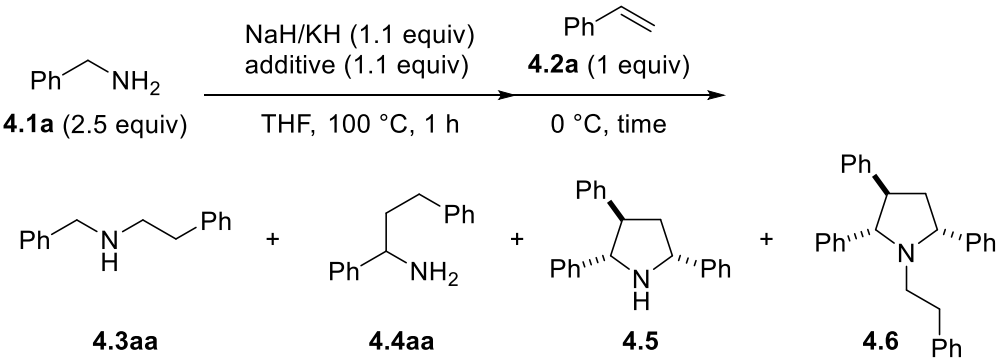
Entry[a]	[MH]	Additive	Time [h]	Yield **4.3aa** [%][b]	Yield **4.4aa** [%][b]
1	NaH	none	3	17	19
2	NaH	LiI	3	11	16
3	NaH	CsI	3	40	21
4	NaH	CsF	3	5	59
5[c]	NaH	CsF	3	11	74
6[c]	KH	CsF	0.5	0	58
7[c]	KH	none	0.5	0	57

[a]Reactions were carried out using 1 mmol of **4.1a** and 0.5 mmol of **4.2a.** [b]1H NMR yields of an inseperable mixture containing **4.3aa** and **4.4aa** based on an internal standard. [c]Reactions were carried out using **4.1a** (2.5 equiv)

The greatly improved rate of reaction using the more reactive KH stimulated us to tune the reaction conditions to maximize the reaction efficiency. We observed that using KH required a significant shorter incubation period to form the deep red suspension indicative of the formation of benzylic anions.[13] Hence, by incubating KH and the benzylamine to preform the nucleophile followed by electrophilic trapping with styrene at 0 °C, we were able to obtain the hydroalkylated product in good yields and short reaction times (Table 6, Entries 1 and 2). In this case, the use of KH with CsF as an additive led to poor yields, possibility due to the enhanced Brønsted basicity caused by the addition of halide salts as an additive as noted in the introduction. This enhanced basicity led to the formation of side products arising from anionic

polymerizations. Note that pyrrolidines **4.5** and **4.6** were also observed as side products arising from the known [3+2] cycloaddition of styrene and aza-allyl anions being formed in the reaction.[39] This will be further discussed in the mechanistic studies. In contrast, the use of NaH/CsF did not give any products under this protocol (Table 6, Entry 3). This is possibly due to nucleophiles bearing the potassium counter cation having enhanced nucleophilicity as potassium is more electropositive than sodium, leading to a more polarized C-M bond.

Table 6. Optimization of conditions by prior incubation of benzyl amine and KH.

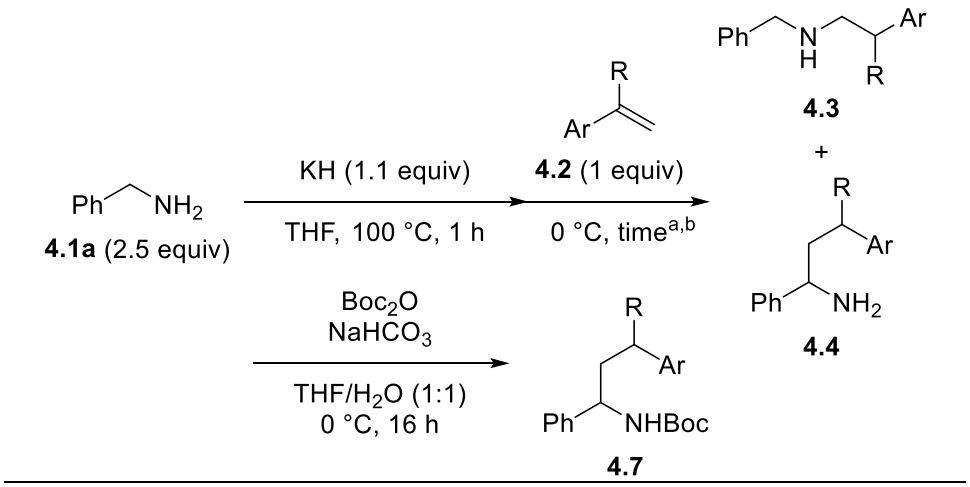


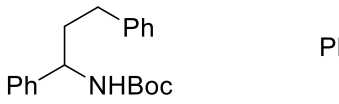
Entry[a]	[MH]	Additive	Time [h]	Yields[b]			
				4.3aa	**4.4aa**	**4.5**	**4.6**
1	KH	CsF	0.3	12	45	5	5
2	KH	None	0.3	10	63	4	12
3	NaH	CsF	24	0	0	0	0

[a]Reactions were carried out using 1.25 mmol of **4.1a** and 0.5 mmol of **4.2a.** [b]1H NMR yields based on an internal standard.

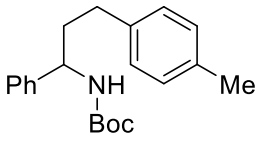
4.2.3. Substrate scope and limitations

With the optimized conditions in hand, we started investigating the use of various styrenes using benzylamine **4.1a** as the nucleophile. Due to the difficulty in separating regioisomers **4.3** and **4.4**, we established a protocol where amines **4.3** and **4.4** were isolated as a mixture before treatment with di-tert-butyl decarbonate (Boc_2O) to allow for the clean isolation of *boc*-protected amine **4.7** (Scheme 109). The reaction is amenable to various styrenes bearing methyl groups (**4.7ab**, **4.7ac**, **4.7ad**) substituted on the ring. Sterically hindered 1,3,5-trimethyl styrene **4.7ae** required an extended reaction time at 30 ℃ for reaction completion. The use of electron rich styrenes such as methoxy (**4.7af**, **4.7ag**, **4.7ah**), phenoxy (**4.7ai**) and *N*,*N*-dimethylamino styrenes (**4.7aj**) did not reduce the reaction efficiency, giving the hydroalkylated products in good yields. Interestingly, the use of 2-methoxystyrene (**4.7ah**) resulted in a significant acceleration in the nucleophilic addition to the styrene, indicating the possibility of chelation between the potassium cation and the methoxy group on the phenyl ring. The use of electron poor styrenes bearing halogens or a trifluoromethyl groups on the phenyl ring resulted in anionic polymerization. Next, we examined styrenes bearing various substituents on the alkene. The reaction using α-methylstyrene (**4.7ak**) gave the hydroalkylated product in good yields while the use of diphenylethylene gave poor yields with side products.

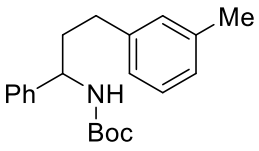




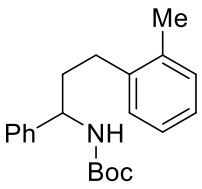
4.7aa
(61%, 14:86, 0.3 h)



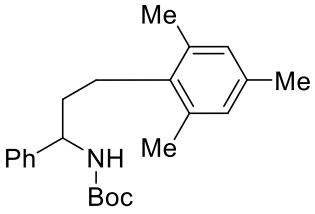
4.7ab
(69%, 7:93, 3.5 h)



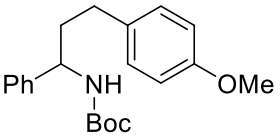
4.7ac
(55%, 2:98, 3.5 h)



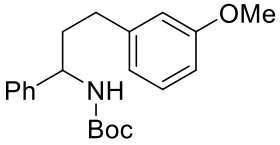
4.7ad
(62%, 0:100, 3.5 h)



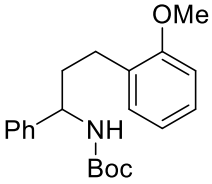
4.7ae
(71%, 0:100, 7 h)[c]



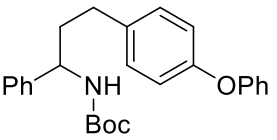
4.7af
(79%, 5:95, 3.5 h)



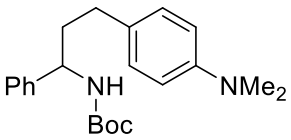
4.7ag
(62%, 10:90, 1 h)



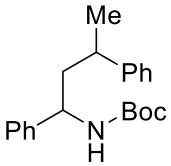
4.7ah
(61%, 8:92, 0.2 h)



4.7ai
(60%, 11:89, 1 h)



4.7aj
(62%, 0:100, 23 h)

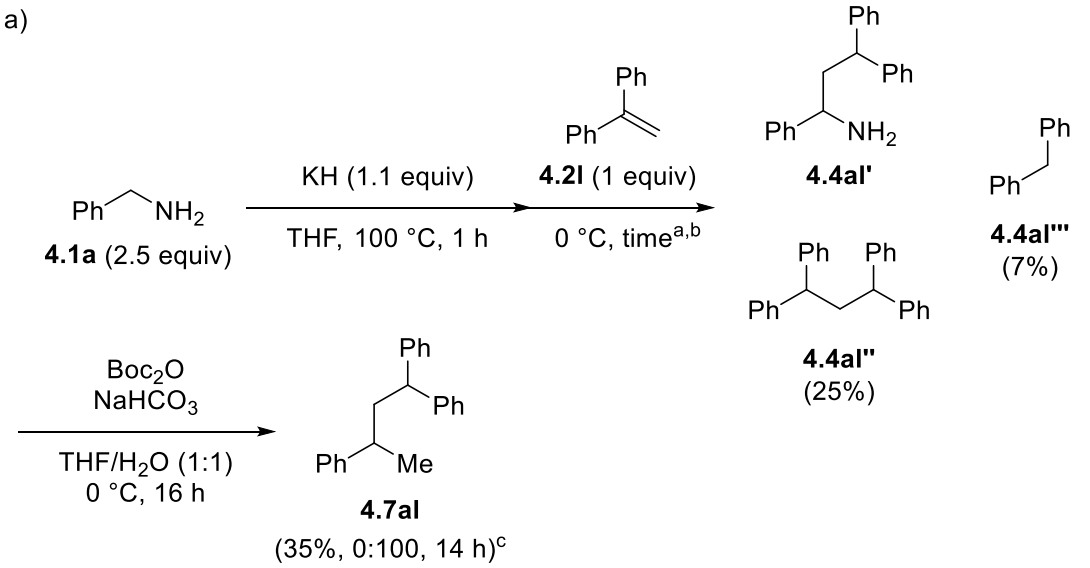


4.7ak
(84%, dr = 1:1
0:100, 23 h)

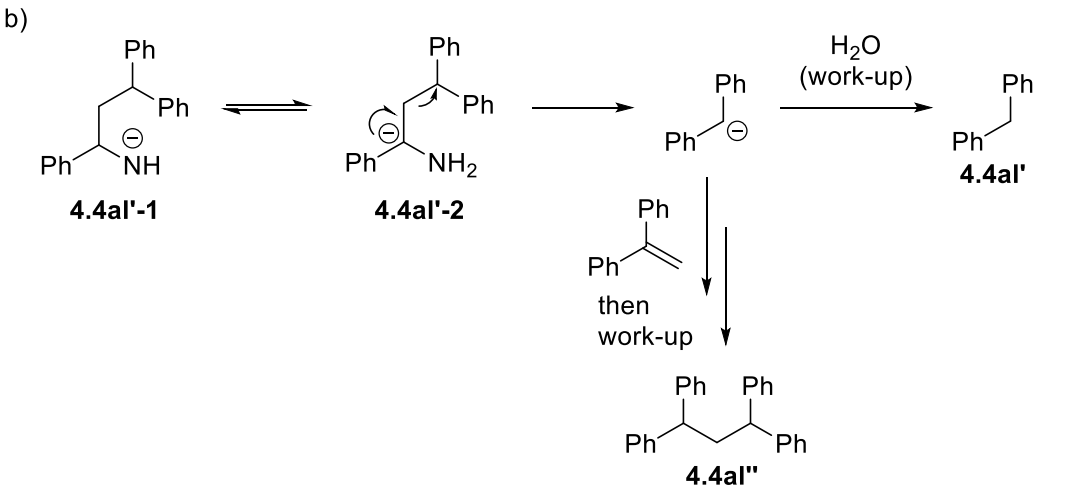
[a]Reactions were carried out using 1.25 mmol of **4.1a** and 0.5 mmol of **4.2.** [b]Ratios of hydroaminated to hydroalkylated products are noted in parentheis. [c]Reaction was carried out at 30 °C.

Scheme 109. Scope of styrenes.

Interestingly, using 1,1-diphenylethylene **4.2l** gave not only hydroalkylated **4.4al'**, the formation of 1,1,3,3-tetraphenylpropane **4.4al''** and diphenylmethane **4.4al'''** is also observed (Scheme 110). We presumed that amide anion **4.4al'-1** is in equilibrium with benzylic carbanion **4.4al'-2** which can undergo a β-carbon elimination to form a more stabilized diphenylmethyl carbanion which can either attack another equivalent of **4.2l** to form **4.4al''** or be quenched upon work-up to give **4.4al'''**.

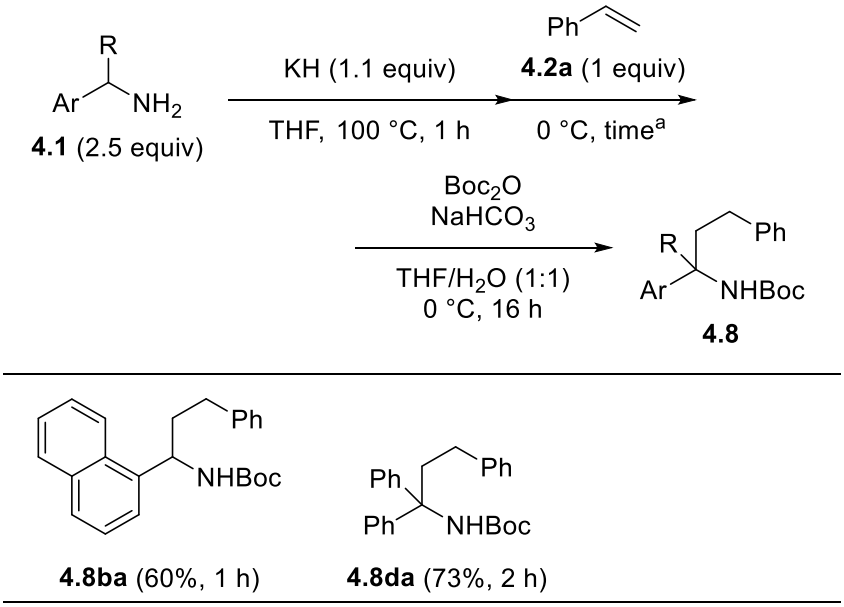


[a]Reactions were carried out using 1.25 mmol of **4.1a** and 0.5 mmol of **4.2.** [b]Ratios of hydroaminated to hydroalkylated products are noted in parenthesis. [c]Reaction was carried out at 30 °C.



Scheme 110. Using 1,1-diphenylethylene as the electrophile.

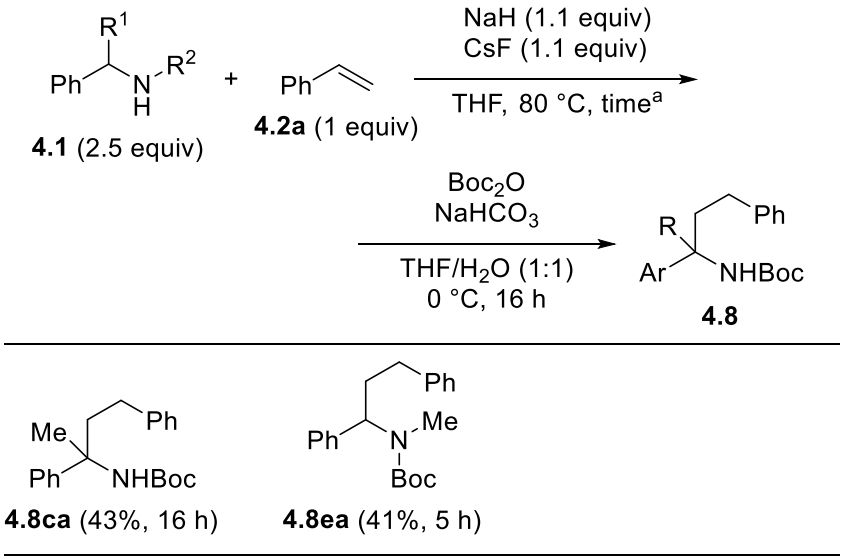
Next, with styrene **4.2a** as the substrate, we examined the use of various benzylamines as the nucleophile (Scheme 111). The hydroalkylation proceeded well using both 1-naphthylmethylamine and benzhydryl amine as nucleophiles.



[a]Reactions were carried out using 1.25 mmol of **4.1** and 0.5 mmol of **4.2a**.

Scheme 111. Scope of amines.

We observed that using NaH/CsF works best while using α-methylbenzylamine and *N*-methylbenzylamine as substrates, giving hydroalkylated products **4.8ca** and **4.8ea** in moderate yields (Scheme 112).

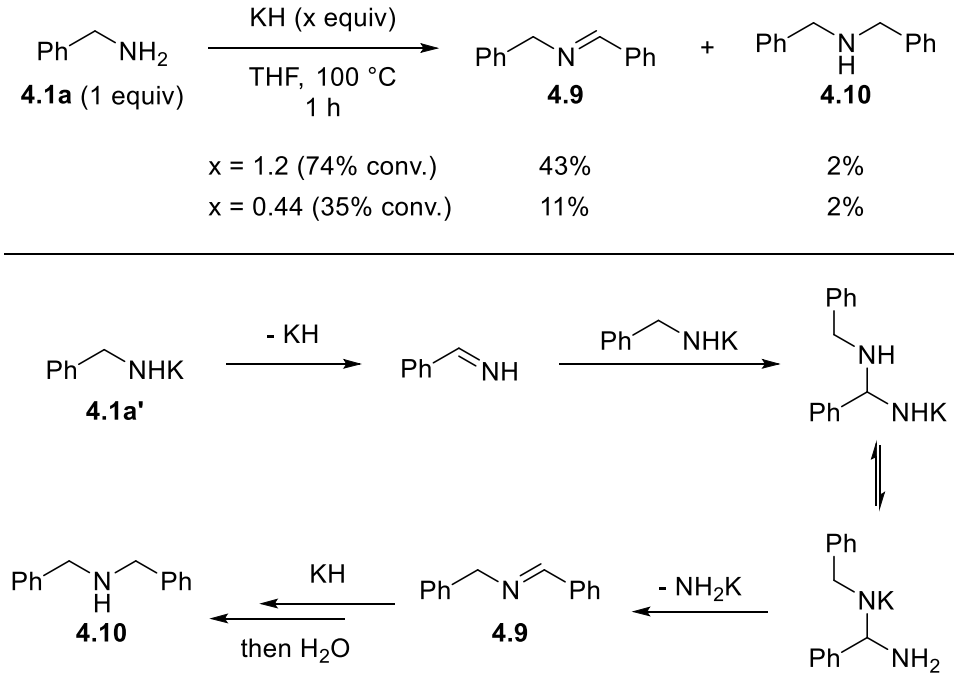


[a]Reactions were carried out using 1.25 mmol of **4.1** and 0.5 mmol of **4.2a.**

Scheme 112. Scope of amines.

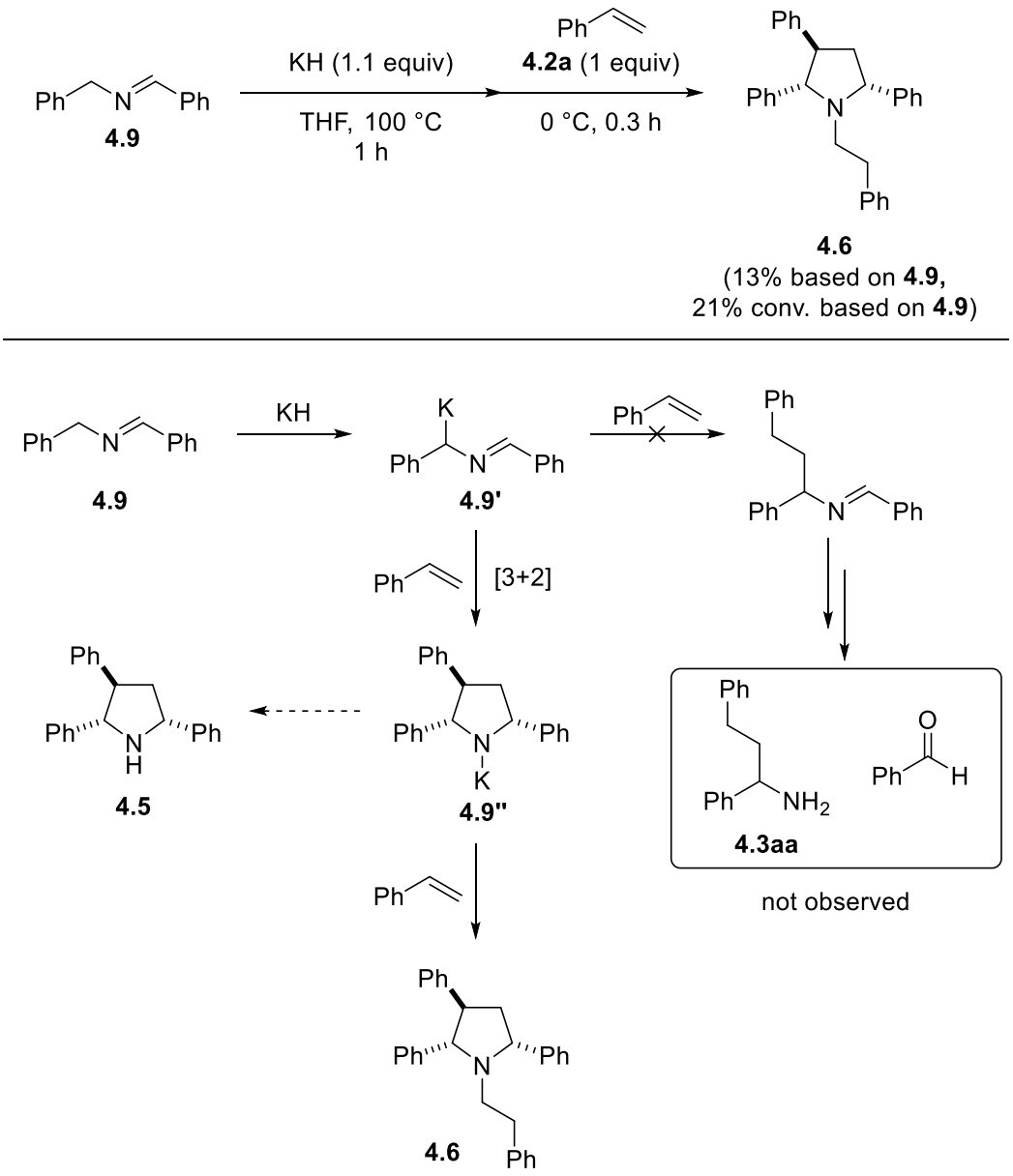
4.3. Mechanistic Studies

In theory, only one equivalent of benzylamine **4.1a** is required for the hydroalkylation of styrene **4.2a** but the optimized conditions required an excess (2.5 equiv) of amine for the reaction to proceed smoothly. Furthermore, the formation of pyrrolidines **4.5** and **4.6** hints to the formation of an aza-allyl anionic intermediate so we were wondering if imine **4.9** is being formed under the reaction conditions. A control experiment comparing the difference in KH loadings with respect to the amounts of amine **4.1a** revealed that significant amounts of imine **4.9** is being formed in the reaction when a slight excess of KH (1.2 equiv) is used (Scheme 113). β-Hydride elimination of amide **4.1a'** will give phenylmethanimine which can undergo a condensation reaction via the elimination of potassium amide to give **4.9**. Further hydride reduction of imine **4.9** will yield dibenzylamine **4.10** as a product. Using 0.44 equiv of KH (the same stoichiometry as the optimized reaction conditions) can suppress the formation of **4.9** and **4.10**.



Scheme 113. Formation of imine in the presence of high loadings of KH.

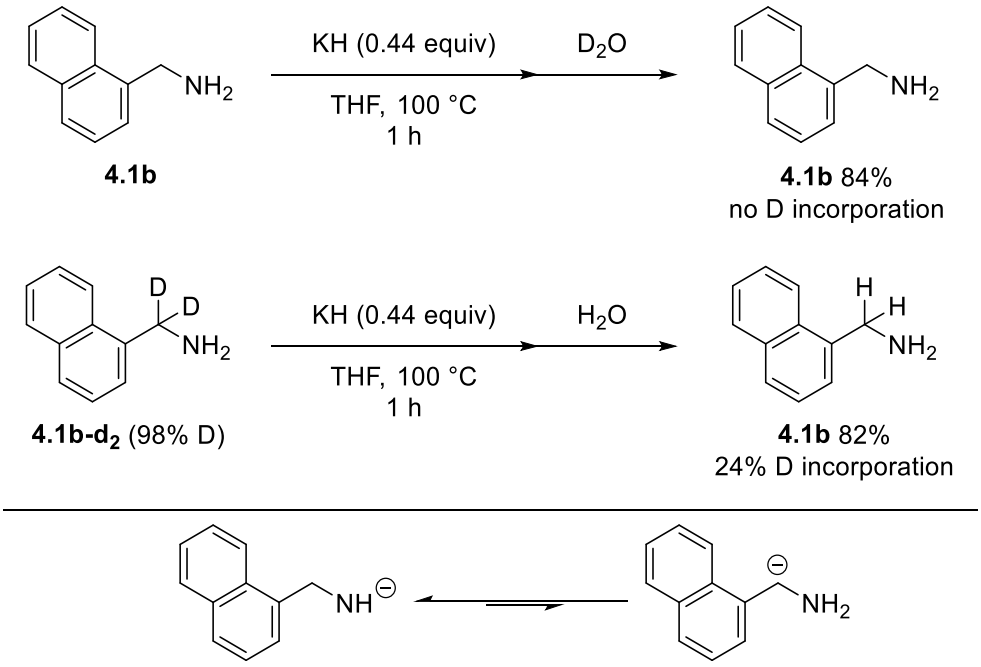
We also determined that the hydroalkylated product **4.3aa** were not derived from aza-allyl anion **4.9'** generated from the deprotonation of **4.9**. Treatment of imine **4.9** with KH followed by addition of styrene **4.2a** as an electrophile resulted in the formation of pyrrolidine **4.6** as the major product along with recovery of starting material (Scheme 114). Formation of hydroalkylated product **4.33aa** was not observed under these reaction conditions. Instead, a [3+2] cycloaddition reaction occurs between **4.9**' and styrene to form pyrrolidine **4.9''** which is further trapped by another equivalent of styrene to form **4.6**. Note that **4.5**, stemming from the protonation of **4.9''**, was also observed as a minor side product under our optimized reaction conditions.



Scheme 114. Formation of pyrrolidine side products.

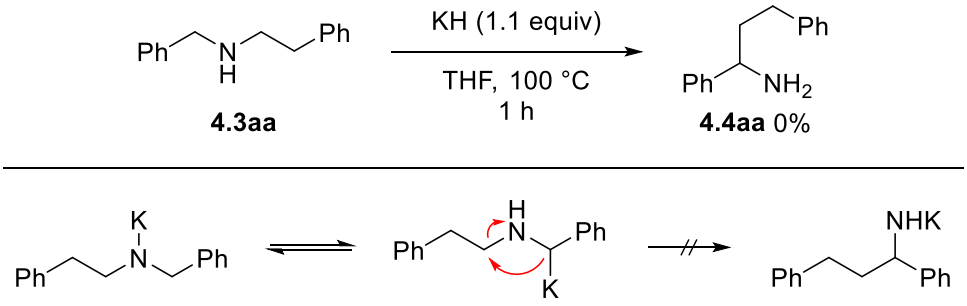
Next, we carried out deuterium labelling experiments to probe any potential equilibrium between the amide anion and benzylic carbanions in solution. Treatment of **4.1b** with KH followed by a D_2O quench resulted in recovery of the amine with no deuterium incorporation at the benzylic position (Scheme 115). From this observation, we can assume that most of the naphthylamine **4.1b** is resting in its amide anionic state. The treatment of **4.1b-d$_2$** with KH followed by quenching with H_2O resulted in a loss of 76% of deuterium, signifying that D/H exchange is occurring between the hydrogens on the amines and deuterium on the benzylic

position. This shows that there is an equilibrium between the amide anion and the benzylic carbanion, and that the equilibrium lies heavily towards the amide anion.



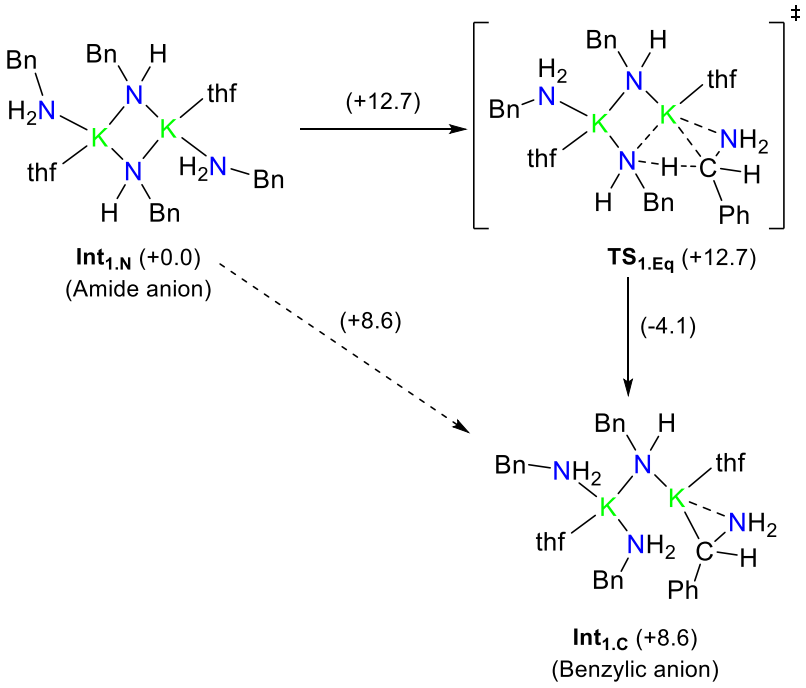
Scheme 115. Deuterium labelling experiments.

Next, we subjected hydroaminated product **4.3aa** to our reaction conditions and observed no hydroalkylation product (Scheme 116). Hence, we concluded that a aza-[1,2]-Wittig rearrangement where the hydroaminated product undergoes a 1,2-proton transfer to form the benzylic carbanion followed by rearrangement was unlikely.



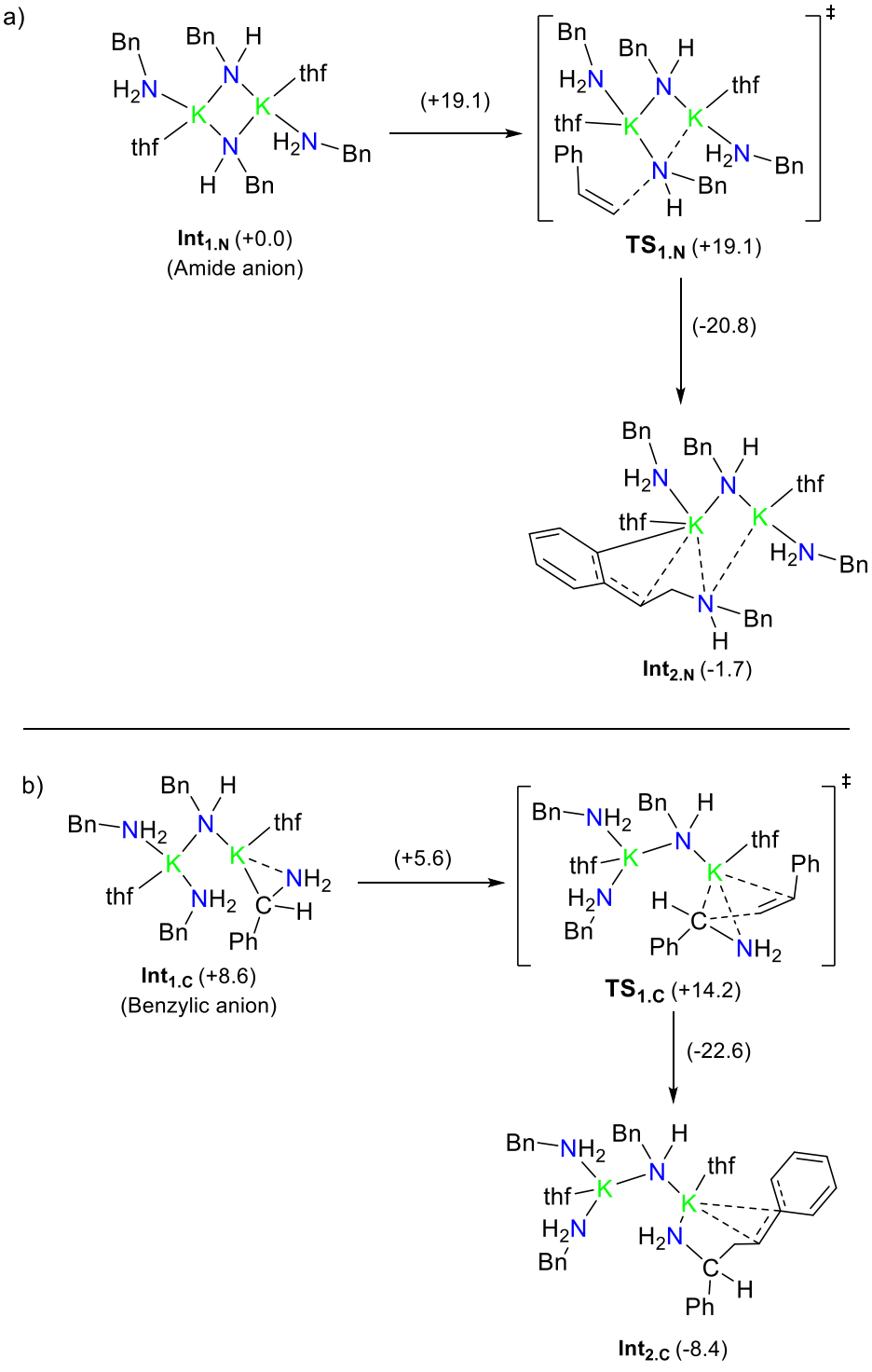
Scheme 116. Reaction probing for conversion of 4.3aa to 4.4aa via aza-[1,2]-Wittig rearrangement.

To better understand the selectivity of C-alkylation over hydroamination we carried out DFT calculations at the M06-2X/6-311+ + G*/SMD(THF)//M06-2X/6-31 + G* level of theory. level of theory. As more than 2 equivalents of amine is required for the reaction to proceed smoothly, we postulated that co-ordination of the benzylamine to the potassium cation plays a crucial role in the observed reactivities. Furthermore, previous reports have shown that potassium amides form dimeric or oligomeric structures in solution[40-42] and hence we started calculations using potassium amide dimer **Int$_{1.N}$** as a model. From the DFT models, the benzylic proton is deprotonated through transition state **TS$_{1.Eq}$** through a proximal potassium amide anion to give benzylic anion **Int$_{1.C}$** (Scheme 117. DFT calculations at a M06-2X/6-311+ + G*/SMD(THF)//M06-2X/6-31 + G* level of theory for the equilibrium between the amide anion and benzylic anion. Energies are in parentheses and are shown in Kcal mol-1.). The reaction is kinetically feasible and the benzylic anion is more unstable than its amide counterpart, suggesting that the equilibrium between the potassium amide and its benzylic anion lies heavily towards the former.



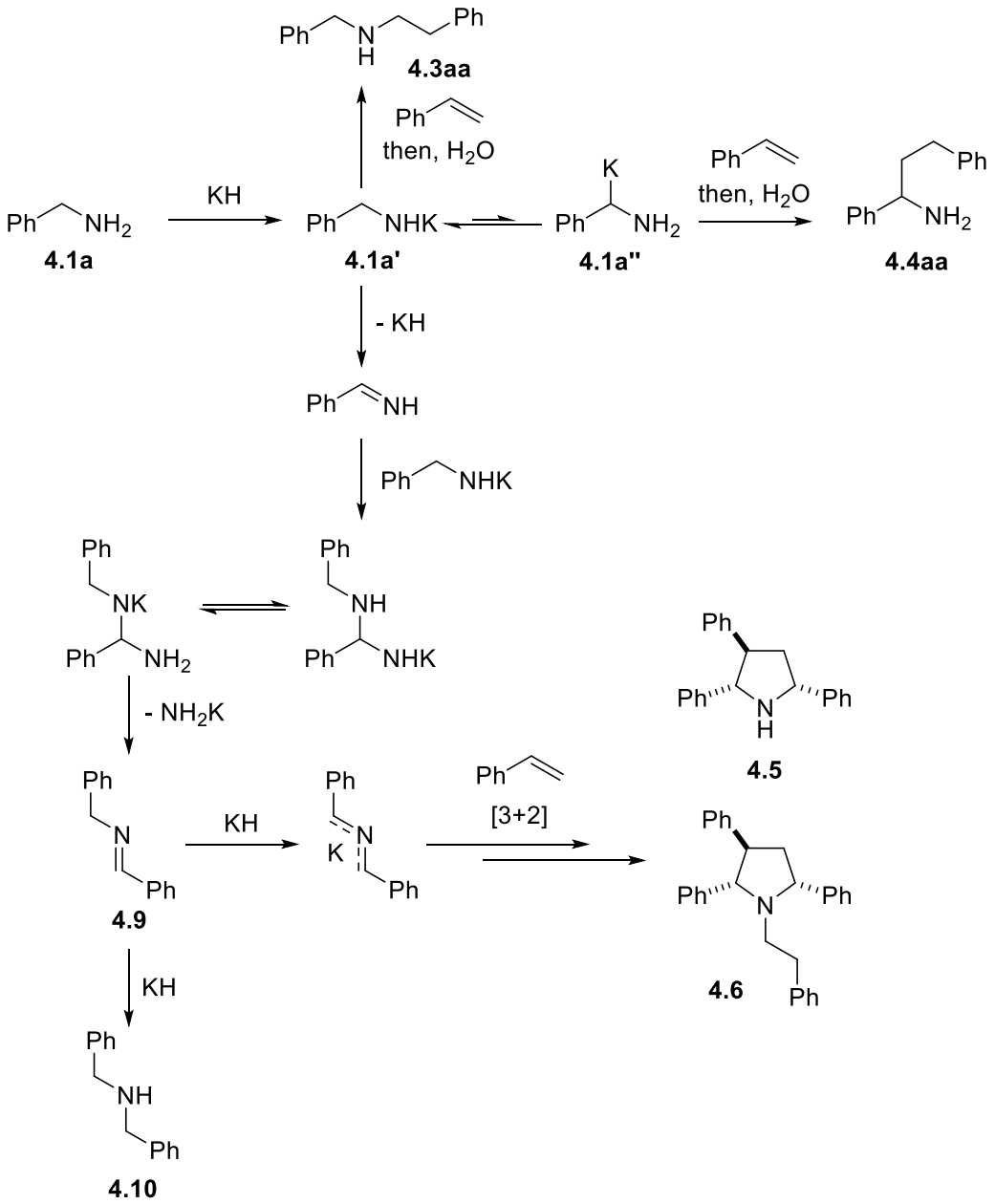
Scheme 117. DFT calculations at a M06-2X/6-311+ + G*/SMD(THF)//M06-2X/6-31 + G* level of theory for the equilibrium between the amide anion and benzylic anion. Energies are in parentheses and are shown in Kcal mol^{-1}.

While the hydroamination pathway starting from the more stable amide anion **INT$_{1.N}$** requires 19.1 kcal/mol to give **Int$_{2.N}$** via **TS$_{1.N}$** (Scheme 118a), the hydroalkylation product is easily accessible via **TS$_{1.C}$** at mere 5.6 kcal/mol starting from benzylic anion **Int$_{1.C}$** (Scheme 118. DFT calculations at the M06-2X/6-311+ + G*/SMD(THF)//M06-2X/6-31 + G* level of theory, modelling reaction pathway. Energies are in parentheses and are shown in Kcal mol-1.). This like likely due to the styrene molecule being able to coordinate to the potassium cation more readily as it is less sterically crowded compared to amide anion **INT$_{1.N}$**. These calculations are in line with the observed selectivity of our KH-mediated hydroalkylation reactions.



Scheme 118. DFT calculations at the M06-2X/6-311+ + G*/SMD(THF)//M06-2X/6-31 + G* level of theory, modelling reaction pathway. Energies are in parentheses and are shown in Kcal mol^{-1}.

From these observations, we propose an overall mechanism for the hydroalkylation of styrenes (Scheme 119). Deprotonation of the benzylamine forms amide anion **4.1a'**, which is in equilibrium with benzylic carbanion **4.1a''**. Amide anion **4.1a'** can undergo hydroamination with styrene to give hydroaminated product **4.3aa** upon workup while benzylic carbanion **4.1a''** undergoes hydroalkylation with one equivalent of styrene to give **4.4aa** upon workup. As we know that the equilibrium between **4.1a'** and **4.1a''** lies heavily towards the amide anion, we can assume that hydroalkylation between **4.1a''** and styrene is significantly faster than the hydroamination between **4.1a'** and styrene. On the other hand, **4.1a'** can also undergo a β-hydride elimination and a condensation reaction with another equivalent of **4.1a'** to give aldimine **4.9**. Aldimine **4.9** can either undergo a hydride reduction to give dibenzylamine **4.10** or deprotonation to give an aza-allyl anion which can undergo a [3+2] cycloaddition reaction with styrene to give pyrrolidines **4.5** and **4.6**.



Scheme 119. Overview of the mechanism for the hydroalkylation of styrene.

4.4. Conclusion

In this chapter, the author demonstrated a novel C-C bond disconnection for the synthesis of pharmaceutically useful 1,3-diarylpropylamines. Mechanistic studies showed that a quick equilibrium between the amide anion and benzylic carbanion is present, where the equilibrium

lies heavily towards the amide anion. The use of potassium hydride allows for the unusual selectively towards hydroalkylation over the more commonly seen hydroamination of styrenes.

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Chapter 5: Experimental data

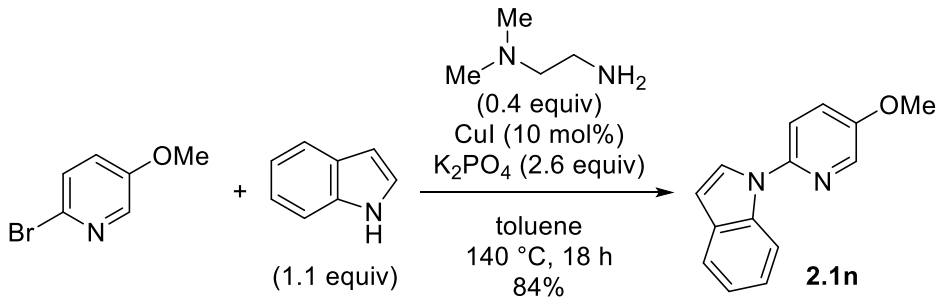
5.1. General Information for Chapter 2

^{1}H NMR spectra (300, 400 or 500 MHz) were recorded on a Bruker Avance 300, 400 or 500 spectrometers in $CDCl_3$ [using TMS (for ^{1}H, $\delta = 0.00$) as internal standard]. ^{13}C NMR spectra (75, 100 or 125 MHz) were recorded on a Bruker Avance 300, 400 or 500 spectrometers in $CDCl_3$ [using $CDCl_3$ (for ^{13}C, $\delta = 77.00$) as internal standard]. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, br = broad. High-resolution mass spectra were obtained with a Waters Q-Tof Premier mass spectrometer. Flash chromatography was performed using Merck silica gel 60 with distilled solvents. Tetrahydrofuran (THF) was taken from a solvent purification system (PS-400-5, innovative technology Inc.). NaH (60% dispersion in mineral oil), NaI and LiI were purchased from Sigma-Aldrich, Inc. Due to moisture sensitivity of NaH, it was consistently handled under an Ar atmosphere in a glovebox or with Schlenk techniques under an inert (N_2 or Ar) atmosphere. NaI and LiI were dried over P_2O_5 under reduced pressure at 60 °C and 120 °C, respectively. Other solvents and reagents, otherwise noted, were commercially available and used as received.

5.2. Experimental Data for Chapter 2

5.2.1. Synthesis of Starting Materials

Synthesis of 1-(5-methoxypyridin-2-yl)-1*H*-indole (2.1n)



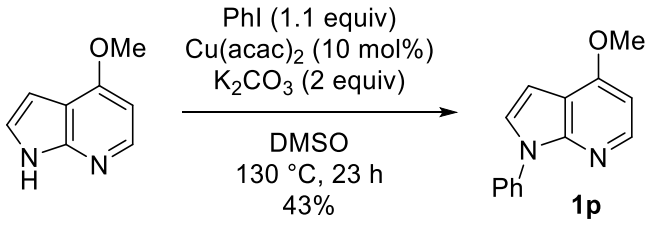
To a 100 mL sealed tube containing 2-bromo-5-methoxypyridine (CAS: 105170-27-2) (545 mg, 2.90 mmol), indole (391 mg, 3.34 mmol), CuI (67.8 mg, 0.356 mmol) and K_3PO_4 (1.72 g, 8.08 mmol) in toluene (30 mL) was added *N*,*N*-dimethylethylenediamine (131 μL, 1.20 mmol) at 23 °C under a N_2 atmosphere. The tube was sealed, and the solution was then stirred at 140 °C for 18 h. The reaction mixture was filtered through a Celite pad with washing with EtOAc. The collected filtrate was washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting crude material was purified by flash column chromatography (hexane: EtOAc =20:1) to yield (**2.1n**) (544 mg, 2.43 mmol) in 84% yield as an orange oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (d, *J* = 2.8 Hz, 1H), 8.01 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.60 (d, *J* = 3.4 Hz, 1H), 7.38 (d, *J* = 8.8 Hz, 1H), 7.31 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.28-7.24 (m, 1H), 7.19-7.15 (m, 1H), 6.674-6.665 (m, 1H), 3.87 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 153.4, 146.0, 135.4, 135.2, 130.0, 126.4, 123.8, 122.8, 121.1, 120.9, 115.7, 112.2, 104.6, 56.0.

ESIHRMS: Found m/z 225.1028; Calcd for $C_{14}H_{13}N_2O$ $[M+H]^+$ 225.1028.

Synthesis of 4-methoxy-1-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine (2.1p)



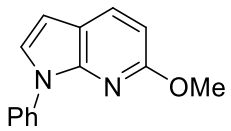
To a 10 mL sealed tube containing 4-methoxy-1*H*-pyrrolo[2,3-*b*]pyridine (CAS: 122379-63-9) (369 mg, 2.49 mmol), $Cu(acac)_2$ (66.4 mg, 0.254 mmol) and K_2CO_3 (695 mg, 5.03 mmol) in DMSO (5 mL) was added iodobenzene (0.31 mL, 2.77 mmol) at 23 °C under a N_2 atmosphere. The tube was sealed, and the solution was then stirred at 130 °C for 23 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution at 0 °C. The reaction mixture was filtered through a Celite pad with washing with CH_2Cl_2. The collected filtrate was extracted thrice with CH_2Cl_2, and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting crude material was purified by flash column chromatography (hexane : EtOAc =20:1) to yield (**2.1p**) (238 mg, 1.06 mmol) in 43% yield as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (d, *J* = 5.6 Hz, 1H), 7.73 (d, *J* = 7.2 Hz, 2H), 7.52 (d, *J* = 2.0 Hz, 1H), 7.49 (d, *J* = 8.4 Hz, 1H), 7.35 (d, *J* = 3.6 Hz, 1H), 7.32 (t, *J* = 7.2 Hz, 1H), 6.70 (d, *J* = 3.6 Hz, 1H), 6.58 (d, *J* = 5.6 Hz, 1H), 4.01 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.9, 149.2, 145.6, 138.7, 129.3, 126.3, 125.7, 124.1, 111.7, 98.9, 98.6, 55.5.

ESIHRMS: Found m/z 225.1024; Calcd for $C_{14}H_{13}N_2O$ $[M+H]^+$ 225.1028.

Synthesis of 6-methoxy-1-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine (2.1q)



2.1q

Prepared using 6-methoxy-1*H*-pyrrolo[2,3-*b*]pyridine (CAS: 896722-53-5) (296 mg, 2.00 mmol) for 13 h by the procedure described in section 2.1.2. Purification by flash chromatography (silica gel, hexane: EtOAc = 40:1) gave 6-methoxy-1-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine (**2.1q**) (398.0 mg, 1.78 mmol) in 89% yield as a pale-yellow oil.

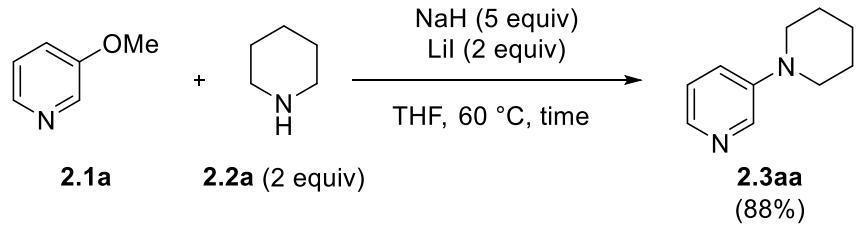
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83-7.82 (m, 2H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.48–7.44 (m, 2H), 7.31 (d, *J* = 3.6 Hz, 1H), 7.28-7.24 (m, 1H), 6.62 (d, *J* = 8.4 Hz, 1H), 6.51 (d, *J* = 3.6 Hz, 1H), 3.94 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 161.0, 144.9, 138.9, 131.9, 129.1, 125.6, 124.3, 123.1, 115.4, 104.8, 102.2, 53.4.

ESIHRMS: Found m/z 225.1033; Calcd for $C_{14}H_{13}N_2O$ $[M+H]^+$ 225.1028.

5.2.2. Compound Data and Procedures

5.2.2.1. Synthesis of 3-(piperidin-1-yl)pyridine (3aa)[1] (a typical procedure)



2.1a **2.2a** (2 equiv) **2.3aa** (88%)

To a 10 mL sealed tube containing 3-methoxypyridine (**2.1a**) (55.0 mg, 0.504 mmol), NaH (101 mg, 2.53 mmol), and LiI (134 mg, 1.00 mmol) in THF (0.5 mL) was added amine (**2.2a**) (98.8 μL, 1.00 mmol) at 23 °C under a N_2 atmosphere. The tube was sealed, and the solution was then stirred at 60 °C for 8 h. The reaction mixture was quenched with cold water at 0 °C and the organic materials were extracted thrice with CH_2Cl_2. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting crude material was purified by flash column chromatography (hexane: EtOAc = 3:1) to yield (**2.3aa**) (72.1 mg, 0.444 mmol) in 88% yield as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (d, *J* = 2.8 Hz, 1H), 8.05 (dd, *J* = 4.4, 1.6 Hz, 1H), 7.18 (dd, *J* = 8.4, 4.4 Hz, 1H), 7.13 (ddd, *J* = 8.4, 2.8, 1.6 Hz, 1H), 3.19 (t, *J* = 5.2 Hz, 4H), 1.74-1.69 (m, 4H), 1.62-1.57 (m, 2H).

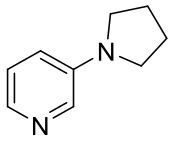
^{13}C NMR (100 MHz, $CDCl_3$): δ 147.7, 140.0, 138.9, 123.3, 122.6, 49.8, 25.5, 24.0.

Large scale (50 mmol) synthesis of 3-(piperidin-1-yl)pyridine (2.3aa)

To a 250 mL sealed tube containing 3-methoxypyridine (**2.1a**) (5.492 g, 50.3 mmol), NaH (10.0 g, 250 mmol), and LiI (13.4 g, 100.0 mmol) in THF (50 mL) was added amine **2.2a** (9.95 L, 100.7 mmol) at 23 °C under a N_2 atmosphere. The tube was sealed, and the solution was then stirred at 60 °C for 6 h. The reaction mixture was quenched with cold water at 0 °C and

the organic materials were extracted thrice with CH_2Cl_2. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting crude material was purified by flash column chromatography (hexane: EtOAc =3:1) to yield (**2.3aa**) (7.49 g, 46.2 mmol) in 92% yield as a dark orange oil.

5.2.2.2. Synthesis of 3-(pyrrolidin-1-yl)pyridine (2.3ab)[2]

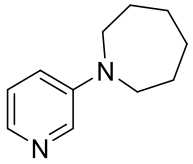


Prepared using 3-methoxypyridine (**2.1a**) (51.4 mg, 0.471 mmol) and amine (**2.2b**) (83.5 μL, 1.00 mmol) for 4 h. Purification by flash chromatography (silica gel, hexane: EtOAc = 2:1) gave 3-(pyrrolidin-1-yl)pyridine (**2.3ab**) (63.2 mg, 0.426 mmol) in 90% yield as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, *J* = 2.8 Hz, 1H), 7.92 (d, *J* = 4.4 Hz, 1H), 7.10 (dd, *J* = 8.4, 4.4 Hz, 1H), 6.80 (dd, *J* = 8.4, 2.8 Hz, 1H), 3.29 (t, *J* = 6.4 Hz, 4H), 2.04-2.01 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.7, 136.9, 134.4, 123.5, 117.7, 47.3, 25.4.

5.2.2.3. Synthesis of 1-(pyridin-3-yl)azepane (2.3ac)[3]

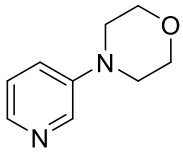


Prepared using 3-methoxypyridine (**2.1a**) (54.9 mg, 0.503 mmol) and amine (**2.2c**) (114 μL, 1.01 mmol) for 9 h. Purification by flash chromatography (silica gel, hexane: Et_2O = 1:2) gave 1-(pyridin-3-yl)azepane (**2.3ac**) (76.3 mg, 0.433 mmol) in 82% yield as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, *J* = 2.4 Hz, 1H), 7.89 (d, *J* = 4.4 Hz, 1H), 7.08 (dd, *J* = 8.4, 4.4 Hz, 1H), 6.93 (dd, *J* = 8.4, 2.4 Hz, 1H), 3.46 (t, *J* = 6.0 Hz, 4H), 1.81-1.79 (m, 4H), 1.57-1.54 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.6, 136.6, 134.1, 123.6, 117.3, 48.9, 27.4, 27.0.

5.2.2.4. Synthesis of 4-(pyridin-3-yl)morpholine (2.3ad)[3]

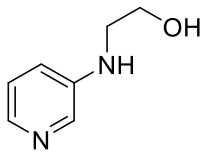


Prepared using 3-methoxypyridine (**2.1a**) (54.1 mg, 0.496 mmol) and amine (**2.2d**) (87.1 μL, 0.996 mmol) for 5 h. Purification by flash chromatography (silica gel, MeOH: CH_2Cl_2 = 1:20) gave 4-(pyridin-3-yl)morpholine (**2.3ad**) (26.1 mg, 0.159 mmol) in 32% yield as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (m, 1H), 8.13 (m, 1H), 7.18-7.17 (m, 2H), 3.88 (t, *J* = 4.8 Hz, 4H), 3.19 (t, *J* = 4.8 Hz, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 146.9, 141.1, 138.3, 123.5, 122.1, 66.7, 48.6.

5.2.2.5. Synthesis of 2-(pyridin-3-ylamino)ethan-1-ol (2.3ad')



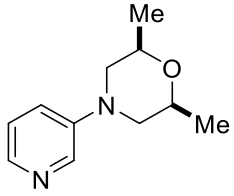
Prepared using 3-methoxypyridine (**2.1a**) (54.1 mg, 0.496 mmol) and amine (**2.2d**) (87.1 μL, 0.996 mmol) for 5 h. Purification by flash chromatography (silica gel, MeOH: CH_2Cl_2 = 1:20) gave 2-(pyridin-3-ylamino)ethan-1-ol (**2.3ad'**) (37.8 mg, 0.274 mmol) in 55% yield as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (m, 1H), 7.89 (d, *J* = 4.2 Hz, 1H), 7.07 (dd, *J* = 7.7, 4.2 Hz, 1H), 6.90 (d, *J* = 7.7 Hz, 1H), 4.12 (brs, 2H), 3.84 (t, *J* = 5.1 Hz, 2H), 3.26 (t, *J* = 5.1 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.6, 138.2, 135.7, 124.0, 119.1, 60.5, 45.7.

ESIHRMS: Found *m/z* 139.0868; Calcd for $C_7H_{11}N_2O$ $[M+H]^+$ 139.0871.

5.2.2.6. Synthesis of (2*S**,6*R**)-2,6-dimethyl-4-(pyridin-3-yl)morpholine (2.3ae)



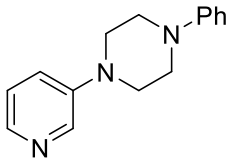
Prepared using 3-methoxypyridine (**2.1a**) (56.7 mg, 0.520 mmol) and amine (**2.2e**) (129 μL, 1.04 mmol) for 6 h. Purification by flash chromatography (silica gel, hexane: EtOAc = 1:1) gave (2*S**,6*R**)-2,6-dimethyl-4-(pyridin-3-yl)morpholine (**2.3ae**) (72.3 mg, 0.376 mmol) in 72% yield as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (m, 1H), 8.12-8.10 (m, 1H), 7.16 (m, 2H), 3.84-3.78 (m, 2H), 3.45 (d, *J* =11.3 Hz, 2H), 2.46 (t, *J* = 11.3 Hz, 2H), 1.27 (d, *J* = 6.2 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 146.6, 140.8, 138.3, 123.5, 122.1, 71.5, 54.0, 19.0.

ESIHRMS: Found *m/z* 193.1341; Calcd for $C_{11}H_{17}N_2O$ $[M+H]^+$ 193.1341.

5.2.2.7. Synthesis of 1-phenyl-4-(pyridin-3-yl)piperazine (2.3af)[3]

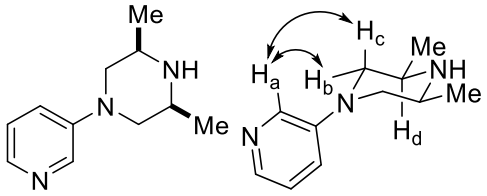


Prepared using 3-methoxypyridine (**2.1a**) (55.9 mg, 0.512 mmol) and amine (**2.2f**) (153 μL, 1.00 mmol) for 5 h. Purification by flash chromatography (silica gel, hexane: CH_2Cl_2 = 1:8) gave 1-phenyl-4-(pyridin-3-yl)piperazine (**2.3af**) (107.0 mg, 0.446 mmol) in 87% yield as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (d, *J* = 2.8 Hz, 1H), 8.13 (dd, *J* = 4.4, 1.2 Hz, 1H), 7.30 (dd, *J* = 8.4, 7.4 Hz, 2H), 7.24 (dd, *J* = 8.4, 4.4 Hz, 1H), 7.18 (ddd, *J* = 8.4, 2.8, 1.2 Hz, 1H), 6.99 (d, *J* = 8.4 Hz, 2H), 6.91 (t, *J* = 7.4 Hz, 1H), 3.37-3.36 (m, 8H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 151.1, 146.9, 141.1, 138.9, 129.3, 123.5, 122.6, 120.3, 116.5, 49.3, 48.7.

5.2.2.8. Synthesis of (3*S**,5*R**)-3,5-dimethyl-1-(pyridin-3-yl)piperazine (2.3ag)



NOESY correlation
(between H_a and H_b as well as H_a and H_c)

No NOESY correlation
(between H_a and H_d)

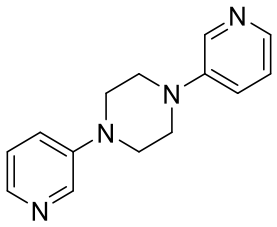
Prepared using 3-methoxypyridine (**2.1a**) (56.1 mg, 0.514 mmol) and amine (**2.2g**) (114 mg, 0.998 mmol) for 21 h. Purification by flash chromatography (silica gel, CH_2Cl_2: NEt_3 = 40:1) gave (3*S**,5*R**)-3,5-dimethyl-1-(pyridin-3-yl)piperazine (**2.3ag**) (71.2 mg, 0.372 mmol) in 72% yield as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (d, *J* = 2.1 Hz, 1H), 8.10 (d, *J* = 3.9 Hz, 1H), 7.17-7.16 (m, 2H), 3.52 (dd, *J* = 12.0, 1.8 Hz, 2H), 3.15-3.10 (m, 2H), 2.49 (t, *J* = 11.2 Hz, 2H), 1.24 (d, *J* = 6.3 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 146.9, 140.4, 138.6, 123.4, 122.3, 55.3, 50.5, 19.7.

ESIHRMS: Found m/z 192.1500; Calcd for $C_{11}H_{18}N_3$ $[M+H]^+$ 192.1501.

5.2.2.9. Synthesis of 1,4-di(pyridin-3-yl)piperazine (2.3ah)[3]



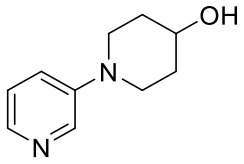
Prepared using 3-methoxypyridine (**2.1a**) (115 mg, 1.05 mmol) and amine (**2.2h**) (41.6 mg, 0.483 mmol) for 7 h. Purification by flash chromatography (silica gel, MeOH: CH_2Cl_2 = 1:4)

gave 1,4-di(pyridin-3-yl)piperazine (**2.3ah**) (86.5 mg, 0.360 mmol) in 75% yield as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (d, *J* = 2.6 Hz, 2H), 8.16 (dd, *J* = 4.4, 1.2 Hz, 2H), 7.26-7.19 (m, 4H), 3.39 (s, 8H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 146.7, 141.4, 139.0, 123.6, 122.8, 48.6.

5.2.2.10. Synthesis of 1-(pyridin-3-yl)piperidin-4-ol (2.3ai)



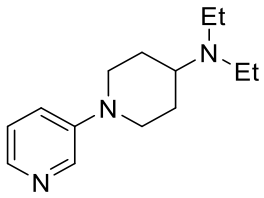
Prepared using 3-methoxypyridine (**2.1a**) (53.4 mg, 0.490 mmol), amine (**2.2i**) (105 mg, 1.04 mmol), NaH (142 mg, 3.55 mmol), and LiI (133 mg, 0.997 mmol) at 90 °C for 25 h. Purification by flash chromatography (silica gel, EtOAc: MeOH = 10:1) gave 1-(pyridin-3-yl)piperidin-4-ol (**2.3ai**) (47.0 mg, 0.264 mmol) in 56% yield as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (m, 1H), 8.08 (m, 1H), 7.23-7.18 (m, 2H), 3.89 (quintet, *J* = 4.2 Hz, 1H), 3.60-3.55 (m, 2H), 3.02-2.96 (m, 2H), 2.05-2.00 (m, 2H), 1.75-1.69 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 147.1, 139.9, 138.5, 123.7, 122.9, 67.2, 46.4, 33.8.

ESIHRMS: Found m/z 179.1178; Calcd for $C_{10}H_{15}N_2O$ $[M+H]^+$ 179.1184.

5.2.2.11. Synthesis of *N*,*N*-diethyl-1-(pyridin-3-yl)piperidin-4-amine (2.3aj)



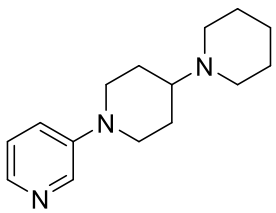
Prepared using 3-methoxypyridine (**2.1a**) (55.6 mg, 0.509 mmol) and amine (**2.2j**) (157 mg, 1.00 mmol) for 7 h. Purification by flash chromatography (silica gel, CH_2Cl_2: NEt_3 = 40:1) gave *N*,*N*-diethyl-1-(pyridin-3-yl)piperidin-4-amine (**2.3aj**) (95.6 mg, 0.410 mmol) in 80% yield as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (d, *J* = 2.7 Hz, 1H), 8.06 (dd, *J* = 4.4, 1.4 Hz, 1H), 7.19 (ddd, *J* = 8.0, 2.7, 1.4 Hz, 1H), 7.13 (dd, *J* = 8.0, 4.4 Hz, 1H), 3.77-3.74 (m, 2H), 2.79-2.73 (m, 2H), 2.69-2.63 (m, 1H), 2.60 (q, *J* = 7.2 Hz, 4H), 1.90-1.87 (m, 2H), 1.71-1.65 (m, 2H), 1.06 (t, *J* = 7.2 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 147.0, 140.2, 138.9, 123.4, 122.6, 57.7, 49.0, 43.5, 28.3, 13.7.

ESIHRMS: Found m/z 234.1973; Calcd for $C_{14}H_{24}N_3$ $[M+H]^+$ 234.1970.

5.2.2.12. Synthesis of 1'-(pyridin-3-yl)-1,4'-bipiperidine (2.3ak)



Prepared using 3-methoxypyridines (**2.1a**) (51.9 mg, 0.476 mmol) and amine (**2.2k**) (168 mg, 0.998 mmol) for 24 h. Purification by flash chromatography (silica gel, CH_2Cl_2: MeOH = 10:1)

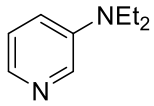
gave 1'-(pyridin-3-yl)-1,4'-bipiperidine (**2.3ak**) (115 mg, 0.469 mmol) in 98% yield as an orange solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (d, *J* = 2.4 Hz, 1H), 8.06 (dd, *J* = 4.4, 0.8 Hz, 1H), 7.18 (ddd, *J* = 8.4, 2.4, 0.8 Hz, 1H), 7.13 (dd, *J* = 8.4, 4.4 Hz, 1H), 3.78-3.75 (m, 2H), 2.76 (dt, *J* = 12.4, 2.4 Hz, 2H), 2.56 (t, *J* = 5.1 Hz, 4H), 2.47-2.43 (m, 1H), 1.97-1.94 (m, 2H), 1.70 (dt, *J* = 12.4, 4.0 Hz, 2H), 1.66-1.60 (m, 4H), 1.49-1.43 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 147.0, 140.3, 138.9, 123.4, 122.6, 62.4, 50.2, 48.8, 27.6, 26.2, 24.7.

ESIHRMS: Found m/z 246.1971; Calcd for $C_{15}H_{24}N_3$ $[M+H]^+$ 246.1970.

5.2.2.13. Synthesis of *N*,*N*-diethylpyridin-3-amine (2.3al)[3]

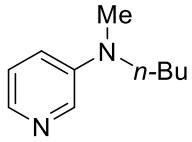


Prepared using 3-methoxypyridine (**2.1a**) (54.3 mg, 0.498 mmol) and amine (**2.2l**) (103 μL, 0.996 mmol) for 27 h. Purification by flash chromatography (silica gel, hexane: CH_2Cl_2 = 1:8) gave *N*,*N*-diethylpyridin-3-amine (**2.3al**) (58.2 mg, 0.387 mmol) in 78% yield as a pale-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, *J* = 3.2 Hz, 1H), 7.89 (d, *J* = 4.5 Hz, 1H), 7.09 (dd, *J* = 8.4, 4.5 Hz, 1H), 6.93 (ddd, *J* = 8.4, 3.2, 1.2 Hz, 1H), 3.36 (q, *J* = 7.2 Hz, 4H), 1.17 (t, *J* = 7.2 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.6, 136.8, 134.7, 123.6, 117.9, 44.1, 12.4.

5.2.2.14. Synthesis of *N*-butyl-*N*-methylpyridin-3-amine (2.3am)[2]

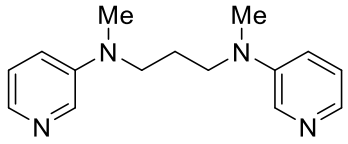


Prepared using 3-methoxypyridine (**2.1a**) (55.9 mg, 0.512 mmol) and amine (**2.2m**) (119 μL, 1.00 mmol) for 24 h. Purification by flash chromatography (silica gel, hexane: Et_2O = 1:1) gave *N*-butyl-*N*-methylpyridin-3-amine (**2.3am**) (56.9 mg, 0.346 mmol) in 68% yield as a pale-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, *J* = 3.0 Hz, 1H), 7.94 (dd, *J* = 4.4, 0.8 Hz, 1H). 7.11 (dd, *J* = 8.4, 4.4 Hz, 1H), 6.94 (ddd, *J* = 8.4, 3.0, 0.8 Hz, 1H), 3.33 (t, *J* = 7.4 Hz, 2H), 2.95 (s, 3H), 1.61-1.53 (m, 2H), 1.36 (sextet, *J* = 7.4 Hz, 2H), 0.96 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 145.1, 137.2, 134.8, 123.4, 118.1, 52.1, 37.9, 28.6, 20.3, 13.9.

5.2.2.15. N^1,N^3-dimethyl-N^1,N^3-di(pyridin-3-yl)propane-1,3-diamine (2.3an)



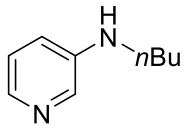
Prepared using 3-methoxypyridine (**2.1a**) (106 □L, 1.05 mmol) and amine (**2.2n**) (51.8 mg, 0.507 mmol) for 13 h. Purification by flash chromatography (silica gel, CH_2Cl_2: MeOH = 20:1) gave N^1,N^3-dimethyl-N^1,N^3-di(pyridin-3-yl)propane-1,3-diamine (**2.3an**) (79.9 mg, 0.312 mmol) in 62% yield as an orange oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, *J* = 2.2 Hz, 2H), 7.96 (d, *J* = 4.3 Hz, 2H), 7.10 (dd, *J* = 8.4, 4.3 Hz, 2H), 6.94 (dd, *J* = 8.4, 2.2 Hz, 2H), 3.39 (t, *J* = 7.3 Hz, 4H), 2.95 (s, 6H), 1.89 (quintet, *J* = 7.3 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 145.0, 137.9, 135.1, 123.5, 118.6, 49.9, 38.1, 23.9.

ESIHRMS: Found m/z 257.1764; Calcd for $C_{15}H_{21}N_4$ $[M+H]^+$ 257.1766.

5.2.2.16. Synthesis of *N*-butylpyridin-3-amine (2.3ao)[4]

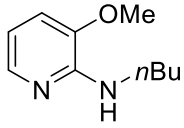


Prepared using 3-methoxypyridine (**2.1a**) (56.4 mg, 0.517 mmol) and amine (**2.2o**) (100 μL, 1.01 mmol) for 10 h. Purification by flash chromatography (silica gel, hexane: EtOAc = 1:1) gave *N*-butylpyridin-3-amine (**2.3ao**) (47.6 mg, 0.317 mmol) in 61% yield as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (m, 1H), 7.96 (d, *J* = 4.8 Hz, 1H), 7.08 (dd, *J* = 8.4, 4.8 Hz, 1H), 6.87 (dd, *J* = 8.4, 1.6 Hz, 1H), 3.64 (brs, 1H), 3.12 (t, *J* = 7.2 Hz, 2H), 1.62 (tt, *J* = 7.2, 7.2 Hz, 2H), 1.44 (tq, *J* = 7.2, 7.2 Hz, 2H), 0.97 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 145.0, 138.3, 135.8, 123.8, 118.4, 43.3, 31.5, 20.2, 13.9.

5.2.2.17. Synthesis of *N*-butyl-3-methoxypyridin-2-amine (2.3ao')



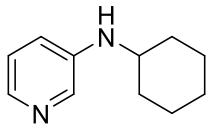
Prepared using 3-methoxypyridine (**2.1a**) (56.4 mg, 0.517 mmol) and amine (**2.2o**) (100 μL, 1.01 mmol) for 10 h. Purification by flash chromatography (silica gel, hexane: EtOAc = 10:1) gave *N*-butyl-3-methoxypyridin-2-amine (**2.3ao'**) (6.9 mg, 0.0383 mmol) in 7% yield as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, *J* = 5.2 Hz, 1H), 6.79 (d, *J* = 7.6 Hz, 1H), 6.48 (dd, *J* = 7.6, 5.2 Hz, 1H), 4.85 (brs, 1H), 3.82 (s, 3H), 3.47-3.42 (2H, m), 1.63 (tt, *J* = 7.6, 7.6 Hz, 2H), 1.44 (tq, *J* = 7.6, 7.6 Hz, 2H), 0.96 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.2, 142.2, 138.7, 113.3, 111.1, 55.1, 40.8, 32.0, 20.3, 13.9.

ESIHRMS: Found m/z 181.1333; Calcd for $C_{10}H_{17}N_2O$ $[M+H]^+$ 181.1341.

5.2.2.18. Synthesis of *N*-cyclohexylpyridin-3-amine (2.3ap)[5]

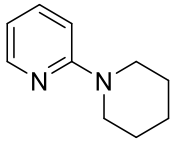


Prepared using 3-methoxypyridine (**2.1a**) (55.8 mg, 0.511 mmol) and amine (**2.2p**) (120 μL, 1.05 mmol) for 22 h. Purification by flash chromatography (silica gel, hexane: Et_2O = 1:2) gave *N*-cyclohexylpyridin-3-amine (**2.3ap**) (50.6 mg, 0.287 mmol) in 56% yield as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, *J* = 2.4 Hz, 1H), 7.90 (d, *J* = 4.4 Hz, 1H), 7.05 (dd, *J* = 8.0, 4.4 Hz, 1H), 6.84 (dd, *J* = 8.0, 2.4 Hz, 1H), 3.58 (brs, 1H), 3.25-3.24 (m, 1H), 2.06-2.03 (m, 2H), 1.80-1.75 (m, 2H), 1.68-1.65 (m, 1H), 1.43-1.33 (m, 2H), 1.28-1.12 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.3, 138.2, 136.4, 123.7, 118.7, 51.4, 33.2, 25.8, 24.8.

5.2.2.19. Synthesis of 2-(piperidin-1-yl)pyridine (2.3ba)[5]

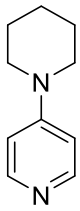


Prepared using methoxypyridine (**2.1b**) (54.6 mg, 0.500 mmol) and amine (**2.2a**) (100 μL, 1.01 mmol) for 5 h. Purification by flash chromatography (silica gel, hexane: EtOAc = 100:1) gave 2-(piperidin-1-yl)pyridine (**2.3ba**) (70.9 mg, 0.437 mmol) in 87% yield as a pale-yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.17 (d, *J* = 4.8 Hz, 1H), 7.43 (dd, *J* = 8.4, 7.2 Hz, 1H), 6.63 (d, *J* = 8.4 Hz, 1H), 6.55 (dd, *J* = 7.2, 4.8 Hz, 1H), 3.52 (4H, m), 1.64 (6H, m).

^{13}C NMR (75 MHz, $CDCl_3$): δ 159.8, 148.0, 137.3, 112.4, 107.1, 46.3, 25.5, 24.7.

5.2.2.20. Synthesis of 4-(piperidin-1-yl)pyridine (2.3ca)[6]

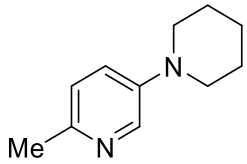


Prepared using methoxypyridine (**2.1c**) (56.2 mg, 0.515 mmol) and amine (**2.2a**) (100 μL, 1.01 mmol) for 6 h. Purification by flash chromatography (silica gel, hexane: EtOAc = 1:50) gave 4-(piperidin-1-yl)pyridine (**2.3ca**) (74.1 mg, 0.457 mmol) in 89% yield as an orange oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.22 (2H, d, *J* = 6.3 Hz), 6.64 (2H, d, *J* = 6.3 Hz), 3.33 (4H, m), 1.65 (6H, m).

^{13}C NMR (75 MHz, $CDCl_3$): δ 154.9, 150.1, 108.2, 47.2, 25.1, 24.3.

5.2.2.21. Synthesis of 2-methyl-5-(piperidin-1-yl)pyridine (2.3da)



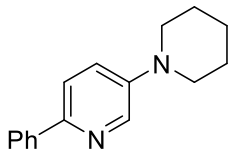
Prepared using methoxypyridine (**2.1d**) (61.4 mg, 0.499 mmol) and amine (**2.2a**) (98.8 μL, 1.00 mmol) for 5 h. Purification by flash chromatography (silica gel, EtOAc) gave 2-methyl-5-(piperidin-1-yl)pyridine (**2.3da**) (51.7 mg, 0.293 mmol) in 59% yield as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (d, *J* = 2.8 Hz, 1H), 7.13 (dd, *J* = 8.5, 2.8 Hz, 1H), 7.00 (d, *J* = 8.5 Hz, 1H), 3.12 (t, *J* = 5.6 Hz, 4H), 2.45 (s, 3H), 1.74-1.68 (m, 4H), 1.60-1.55 (m, 2H).

^{13}C NMR 100 MHz, $CDCl_3$): δ 148.6, 145.8, 138.4, 124.2, 122.9, 50.6, 25.7, 24.1, 23.2.

ESIHRMS: Found m/z 177.1396; Calcd for $C_{11}H_{17}N_2$ $[M+H]^+$ 177.1392.

5.2.2.22. Synthesis of 2-phenyl-5-(piperidin-1-yl)pyridine (2.3ea)



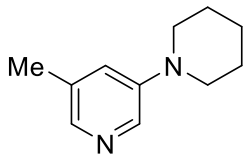
Prepared using methoxypyridine (**2.1e**) (92.7 mg, 0.500 mmol) and amine (**2.2a**) (98.8 μL, 1.00 mmol) for 7 h. Purification by flash chromatography (silica gel, CH_2Cl_2) gave 2-phenyl-5-(piperidin-1-yl)pyridine (**2.3ea**) (106 mg, 0.444 mmol) in 89% yield as a pale brown solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.38 (d, *J* = 3.0 Hz, 1H), 7.93 (d, *J* = 7.5 Hz, 2H), 7.60 (d, *J* = 8.5 Hz, 1H), 7.43 (dd, *J* = 7.5, 7.5 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.25 (dd, *J* = 8.5, 3.0 Hz, 1H), 3.24 (t, *J* = 5.5 Hz, 4H), 1.74-1.71 (m, 4H), 1.64-1.59 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 147.6, 146.5, 139.5, 138.3, 128.6, 127.7, 126.1, 123.2, 120.4, 49.8, 25.5, 24.1.

ESIHRMS: Found m/z 239.1543; Calcd for $C_{16}H_{19}N_2$ $[M+H]^+$ 239.1548.

5.2.2.23. Synthesis of 3-methyl-5-(piperidin-1-yl)pyridine (2.3fa)



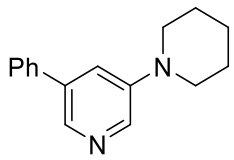
Prepared using methoxypyridine (**2.1f**) (62.9 mg, 0.511 mmol) and amine (**2.2a**) (98.8 μL, 1.00 mmol) for 5 h. Purification by flash chromatography (silica gel, hexane: EtOAc = 1:1) gave 3-methyl-5-(piperidin-1-yl)pyridine (**2.3fa**) (60.7 mg, 0.344 mmol) in 67% yield as a brown oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, *J* = 2.5 Hz, 1H), 7.90 (m, 1H), 6.99 (m, 1H), 3.17 (t, *J* = 5.4 Hz, 4H), 2.27 (s, 3H), 1.73-1.68 (m, 4H), 1.61-1.57 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 147.5, 140.7, 136.3, 132.9, 123.4, 50.0, 25.6, 24.1, 18.5.

ESIHRMS: Found m/z 177.1397; Calcd for $C_{11}H_{17}N_2$ $[M+H]^+$ 177.1392.

5.2.2.24. Synthesis of 3-phenyl-5-(piperidin-1-yl)pyridine (2.3ga)



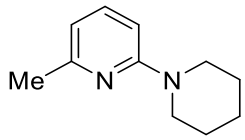
Prepared using methoxypyridine (**2.1g**) (93.2 mg, 0.503 mmol) and amine (**2.2a**) (98.8 μL, 1.00 mmol) for 23 h. Purification by flash chromatography (silica gel, CH_2Cl_2: EtOAc = 20:1) gave 3-phenyl-5-(piperidin-1-yl)pyridine (**2.3ga**) (88.2 mg, 0.370 mmol) in 74% yield as an orange solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29-8.28 (m, 2H), 7.56 (d, *J* = 7.2 Hz, 2H), 7.45 (dd, *J* = 7.2, 7.2 Hz, 2H), 7.36 (t, *J* = 7.2 Hz, 1H), 7.34 (m, 1H), 3.26 (t, *J* = 5.4 Hz, 4H), 1.76-1.71 (m, 4H), 1.65-1.60 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 147.7, 138.64, 138.62, 137.7, 136.7, 128.9, 127.9, 127.3, 121.2, 49.9, 25.6, 24.1.

ESIHRMS: Found m/z 239.1546; Calcd for $C_{16}H_{19}N_2$ $[M+H]^+$ 239.1548.

5.2.2.25. Synthesis of 2-methyl-6-(piperidin-1-yl)pyridine (2.3ha)[7]



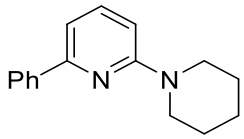
Prepared using methoxypyridine (**2.1h**) (61.4 mg, 0.499 mmol) and amine (**2.2a**) (98.8 μL, 1.00 mmol) for 5 h. Purification by flash chromatography (silica gel, hexane: EtOAc = 20:1) gave 2-methyl-6-(piperidin-1-yl)pyridine (**2.3ha**) (68.5 mg, 0.389 mmol) in 78% yield as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (dd, *J* = 8.4, 7.3 Hz, 1H), 6.44-6.42 (m, 2H), 3.50-3.49 (m, 4H), 2.38 (s, 3H), 1.65-1.63 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.6, 156.7, 137.6, 111.8, 103.7, 46.4, 25.6, 24.8, 24.7.

ESIHRMS: Found m/z 177.1392; Calcd for $C_{11}H_{17}N_2$ $[M+H]^+$ 177.1392.

5.2.2.26. Synthesis of 2-phenyl-6-(piperidin-1-yl)pyridine (2.3ia)



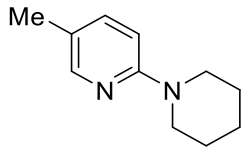
Prepared using methoxypyridine (**2.1i**) (91.4 mg, 0.493 mmol) and amine (**2.2a**) (98.8 μL, 1.00 mmol) for 3 h. Purification by flash chromatography (silica gel, hexane: EtOAc = 20:1) gave 2-phenyl-6-(piperidin-1-yl)pyridine (**2.3ia**) (97.6 mg, 0.410 mmol) in 83% yield as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, *J* = 7.2 Hz, 2H), 7.49 (dd, *J* = 8.4, 7.6 Hz, 1H), 7.40 (dd, *J* = 7.2, 7.2 Hz, 2H), 7.34 (t, *J* = 7.2 Hz, 1H), 7.04 (d, *J* = 7.6 Hz, 1H), 6.58 (d, *J* = 8.4 Hz, 1H), 3.62-3.61 (m, 4H), 1.66 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.4, 155.1, 140.2, 138.0, 128.4 (overlapped), 126.8, 108.9, 105.5, 46.3, 25.6, 24.9.

ESIHRMS: Found m/z 239.1542; Calcd for $C_{16}H_{19}N_2$ $[M+H]^+$ 239.1548.

5.2.2.27. Synthesis of 5-methyl-2-(piperidin-1-yl)pyridine (2.3ja)



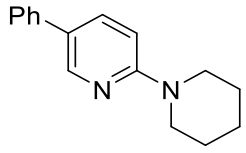
Prepared using methoxypyridine (**2.1j**) (61.7 mg, 0.501 mmol) and amine (**2.2a**) (98.8 μL, 1.00 mmol) for 5 h. Purification by flash chromatography (silica gel, hexane: EtOAc = 20:1) gave 5-methyl-2-(piperidin-1-yl)pyridine (**2.3ja**) (75.9 mg, 0.431 mmol) in 86% yield as a pale-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, *J* = 2.4 Hz, 1H), 7.30 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.61 (d, *J* = 8.4 Hz, 1H), 3.48-3.46 (m, 4H), 2.20 (s, 3H), 1.67-1.65 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.5, 147.6, 138.3, 121.4, 107.1, 46.8, 25.5, 24.7, 17.3.

ESIHRMS: Found m/z 177.1399; Calcd for $C_{11}H_{17}N_2$ $[M+H]^+$ 177.1392.

5.2.2.28. Synthesis of 5-phenyl-2-(piperidin-1-yl)pyridine (2.3ka)



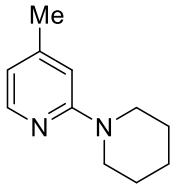
Prepared using methoxypyridine (**2.1k**) (95.6 mg, 0.516 mmol) and amine (**2.2a**) (98.8 μL, 1.00 mmol) for 9 h. Purification by flash chromatography (silica gel, hexane: EtOAc = 20:1) gave 5-phenyl-2-(piperidin-1-yl)pyridine (**2.3ka**) (83.2 mg, 0.349 mmol) in 68% yield as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.44 (d, *J* = 2.5 Hz, 1H), 7.69 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.52 (d, *J* = 7.2 Hz, 2H), 7.41 (dd, *J* = 7.2 ,7.2 Hz, 2H), 7.30 (t, *J* = 7.2 Hz, 1H), 6.71 (d, *J* = 8.9 Hz, 1H), 3.58 (m, 4H), 1.67 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.9, 146.2, 138.6, 136.0, 128.9, 126.6, 126.1, 125.3, 106.8, 46.4, 25.6, 24.8.

ESIHRMS: Found m/z 239.1543; Calcd for $C_{16}H_{19}N_2$ $[M+H]^+$ 239.1548.

5.2.2.29. Synthesis of 4-methyl-2-(piperidin-1-yl)pyridine (2.3la)



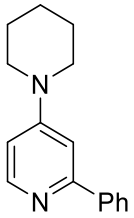
Prepared using methoxypyridine (**2.1l**) (61.0 mg, 0.495 mmol) and amine (**2.2a**) (98.8 μL, 1.00 mmol) for 5 h. Purification by flash chromatography (silica gel, hexane: EtOAc = 20:1) gave 4-methyl-2-(piperidin-1-yl)pyridine (**2.3la**) (61.2 mg, 0.347 mmol) in 70% yield as a pale-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, *J* = 5.0 Hz, 1H), 6.46 (m, 1H), 6.41 (dd, *J* = 5.0, 0.5 Hz, 1H), 3.51 (m, 4H), 2.24 (s, 3H), 1.63 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 160.1, 148.1, 147.6, 114.1, 107.5, 46.4, 25.6, 24.8, 21.4.

ESIHRMS: Found m/z 177.1398; Calcd for $C_{11}H_{17}N_2$ $[M+H]^+$ 177.1392.

5.2.2.30. Synthesis of 2-phenyl-4-(piperidin-1-yl)pyridine (2.3ma)



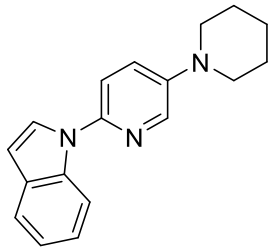
Prepared using methoxypyridine (**2.1m**) (90.4 mg, 0.488 mmol) and amine (**2.2a**) (98.8 μL, 1.00 mmol) for 5 h. Purification by flash chromatography (silica gel, hexane: EtOAc = 5:1) gave 2-phenyl-4-(piperidin-1-yl)pyridine (**2.3ma**) (100 mg, 0.421 mmol) in 86% yield as a pale-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (d, *J* = 6.0 Hz, 1H), 7.91 (d, *J* = 7.2 Hz, 2H), 7.44 (dd, *J* = 7.2, 7.2 Hz, 2H), 7.38 (t, *J* = 7.2 Hz, 1H), 7.07 (d, *J* = 2.5 Hz, 1H), 6.62 (dd, *J* = 6.0, 2.5 Hz, 1H), 3.38 (m, 4H), 1.66 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.4, 155.8, 150.1, 140.7, 128.51, 128.48, 127.0, 107.2, 105.5, 47.5, 25.2, 24.4.

ESIHRMS: Found m/z 239.1543; Calcd for $C_{16}H_{19}N_2$ $[M+H]^+$ 239.1548.

5.2.2.31. Synthesis of 1-(5-(piperidin-1-yl)pyridin-2-yl)-1*H*-indole (2.3na)



Prepared using methoxypyridine (**2.1n**) (116 mg, 0.516 mmol) and amine (**2.2a**) (98.8 μL, 1.00 mmol) for 7 h. Purification by flash chromatography (silica gel, hexane: Et_2O = 4:1) gave 1-

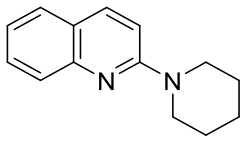
(5-(piperidin-1-yl)pyridin-2-yl)-1*H*-indole (**2.3na**) (88.5 mg, 0.319 mmol) in 62% yield as a brown solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, *J* = 3.2 Hz, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.61 (d, *J* = 3.4 Hz, 1H), 7.35 (d, *J* = 2.0 Hz, 2H), 7.27-7.23 (m, 1H), 7.18-7.14 (m, 1H), 6.66 (d, *J* = 3.4 Hz, 1H), 3.20 (t, *J* = 5.5 Hz, 4H), 1.77-1.72 (m, 4H), 1.64-1.59 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 145.7, 144.4, 137.2, 135.2, 129.9, 126.4, 125.9, 122.6, 121.0, 120.6, 115.6, 112.1, 104.2, 50.4, 25.6, 24.0.

ESIHRMS: Found m/z 278.1653; Calcd for $C_{18}H_{20}N_3$ $[M+H]^+$ 278.1657.

5.2.2.32. Synthesis of 2-(piperidin-1-yl)quinoline (2.3oa)[8]

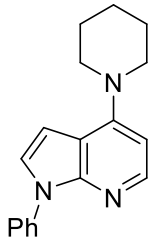


Prepared using 2-methoxyquinoline (**2.1o**) (82.0 mg, 0.515 mmol) and amine (**2.2a**) (98.8 μL, 1.00 mmol) for 4 h. Purification by flash chromatography (silica gel, hexane: EtOAc = 20:1) gave 2-(piperidin-1-yl)quinoline (**2.3oa**) (94.3 mg, 0.444 mmol) in 86% yield as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, *J* = 8.8 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.56 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.50 (ddd, *J* = 8.4, 7.2, 1.5 Hz, 1H), 7.20-7.16 (m, 1H), 6.97 (d, *J* = 9.2 Hz, 1H), 3.72-3.71 (m, 4H), 1.67 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 157.7, 148.1, 137.2, 129.4, 127.1, 126.5, 122.8, 122.0, 109.9, 46.3, 25.8, 24.9.

5.2.2.33. Synthesis of 1-phenyl-4-(piperidin-1-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (2.3pa)



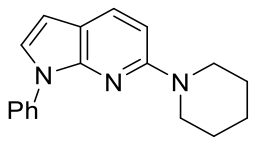
Prepared using methoxypyridine (**2.1p**) (109 mg, 0.488 mmol) and amine (**2.2a**) (98.8 μL, 1.00 mmol) for 23 h. Purification by flash chromatography (silica gel, hexane: EtOAc = 5:1) gave 1-phenyl-4-(piperidin-1-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (**2.3pa**) (84.0 mg, 0.303 mmol) in 62% yield as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, *J* = 5.5 Hz, 1H), 7.71 (d, *J* = 7.6 Hz, 2H), 7.49 (dd, *J* = 7.6, 7.6 Hz, 2H), 7.32-7.28 (d, *J* = 6.0 Hz, 1H + t, *J* = 7.6 Hz, 1H), 6.62 (d, *J* = 3.7 Hz, 1H), 6.47 (d, *J* = 5.5 Hz, 1H), 3.46 (t, *J* = 5.3 Hz, 4H), 1.80-1.75 (m, 4H), 1.72-1.69 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 152.4, 149.1, 145.0, 138.9, 129.3, 126.2, 124.39, 124.35, 112.0, 103.0, 101.2, 50.8, 25.9, 24.7.

ESIHRMS: Found m/z 278.1663; Calcd for $C_{18}H_{20}N_3$ $[M+H]^+$ 278.1657.

5.2.2.34. Synthesis of 1-phenyl-6-(piperidin-1-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (2.3qa)



Prepared using methoxypyridine (**2.1q**) (111 mg, 0.496 mmol) and amine (**2.2a**) (98.8 μL, 1.00 mmol) for 21 h. Purification by flash chromatography (silica gel, hexane: EtOAc = 100:1) gave

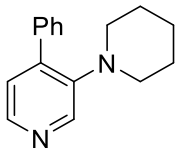
1-phenyl-6-(piperidin-1-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (**2.3qa**) (128 mg, 0.461 mmol) in 93% yield as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, *J* = 7.6 Hz, 2H), 7.72 (d, *J* = 8.7 Hz, 1H), 7.46 (dd, *J* = 7.6, 7.6 Hz, 2H), 7.26-7.22 (m, 1H + t, *J* = 7.6 Hz, 1H), 6.62 (d, *J* = 8.7 Hz, 1H), 6.44 (d, *J* = 3.6 Hz, 1H), 3.55 (t, *J* = 5.6 Hz, 4H), 1.66-1.64 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 156.8, 146.6, 139.4, 130.7, 128.9, 125.1, 123.3, 123.0, 113.0, 102.8, 102.0, 47.4, 25.7, 24.9.

ESIHRMS: Found m/z 278.1651; Calcd for $C_{18}H_{20}N_3$ $[M+H]^+$ 278.1657.

5.2.2.35. Synthesis of 4-phenyl-3-(piperidin-1-yl)pyridine (2.5)



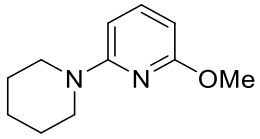
Prepared using methoxypyridine (**2.4**) (92.6 mg, 0.500 mmol) and amine (**2.2a**) (98.8 μL, 1.00 mmol) for 5 h. Purification by flash chromatography (silica gel, hexane: Et_2O = 1:1) gave 4-phenyl-3-(piperidin-1-yl)pyridine (**2.5**) (82.8 mg, 0.347 mmol) in 69% yield as a pale-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (m, 1H), 8.29 (d, *J* = 4.6 Hz, 1H), 7.70 (d, *J* = 7.2 Hz, 2H), 7.45 (dd, *J* = 7.2, 7.2 Hz, 2H), 7.37 (t, *J* = 7.2 Hz, 1H), 7.13 (d, *J* = 4.6 Hz, 1H), 2.86-2.85 (m, 4H), 1.49 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 146.7, 143.8, 141.4, 141.0, 138.9, 128.4, 128.1, 127.9, 125.1, 52.2, 25.9, 24.0.

ESIHRMS: Found m/z 239.1552; Calcd for $C_{16}H_{19}N_2$ $[M+H]^+$ 239.1548.

5.2.2.36. Synthesis of 2-methoxy-6-(piperidin-1-yl)pyridine (2.3ra)



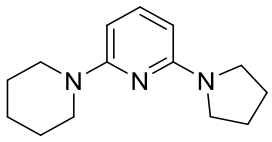
Prepared using methoxypyridine (**2.1r**) (141 mg, 1.01 mmol) and amine (**2.2a**) (42.8 mg, 0.503 mmol) for 20 h. Purification by flash chromatography (silica gel, hexane: EtOAc = 20:1) gave 2-methoxy-6-(piperidin-1-yl)pyridine (**2.3ra**) (73.5 mg, 0.382 mmol) in 76% yield as a pale-orange oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (dd, *J* = 8.4, 7.6 Hz, 1H), 6.15 (d, *J* = 8.4 Hz, 1H), 6.01 (d, *J* = 7.6 Hz, 1H), 3.86 (s, 3H), 3.50 (m, 4H), 1.63 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 163.1, 158.6, 140.0, 98.1, 97.0, 52.9, 46.3, 25.5, 24.8.

ESIHRMS: Found m/z 193.1341; Calcd for $C_{11}H_{17}N_2O$ $[M+H]^+$ 193.1341.

5.2.2.37. Synthesis of 2-(piperidin-1-yl)-6-(pyrrolidin-1-yl)pyridine (2.6)



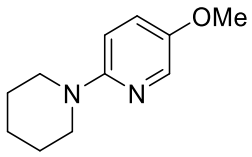
Prepared using methoxypyridine (**2.3ra**) (98.6 mg, 0.513 mmol) and amine **(2.2b**) (83.3 μL, 1.00 mmol) for 5 h. Purification by flash chromatography (silica gel, hexane: EtOAc = 100:1) gave 2-(piperidin-1-yl)-6-(pyrrolidin-1-yl)pyridine (**2.6**) (93.3 mg, 0.403 mmol) in 79% yield as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): 7.26 (dd, *J* = 8.0, 8.0 Hz, 1H), 5.89 (d, *J* = 8.0 Hz, 1H), 5.68 (d, *J* = 8.0 Hz, 1H), 3.48-3.47 (m, 4H), 3.42 (t, *J* = 6.6 Hz, 4H), 1.96-1.92 (m, 4H), 1.61 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.0, 156.6, 138.4, 94.7, 93.5, 46.4, 46.3, 25.6, 25.5, 25.0.

ESIHRMS: Found m/z 232.1812; Calcd for $C_{14}H_{22}N_3$ $[M+H]^+$ 232.1814.

5.2.2.38. Synthesis of 5-methoxy-2-(piperidin-1-yl)pyridine (2.3sa)



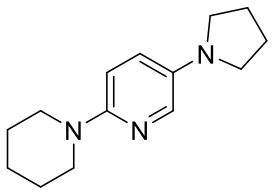
Prepared using methoxypyridine (**2.1s**) (140 mg, 1.01 mmol) and amine (**2.2a**) (42.0 mg, 0.493 mmol) for 20 h. Purification by flash chromatography (silica gel, hexane: EtOAc = 20:1) gave 5-methoxy-2-(piperidin-1-yl)pyridine (**2.3sa**) (74.3 mg, 0.386 mmol) in 81% yield as a pale-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, *J* = 3.0 Hz, 1H), 7.12 (dd, *J* = 9.1, 3.0 Hz, 1H), 6.64 (d, *J* = 9.1 Hz, 1H), 3.78 (s, 3H), 3.40 (t, *J* = 5.6 Hz, 4H), 1.67-1.60 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.7, 148.6, 133.5, 124.9, 108.4, 56.3, 47.6, 25.6, 24.6.

ESIHRMS: Found m/z 193.1349; Calcd for $C_{11}H_{17}N_2O$ $[M+H]^+$ 193.1341.

5.2.2.39. Synthesis of 2-(piperidin-1-yl)-5-(pyrrolidin-1-yl)pyridine (2.7)



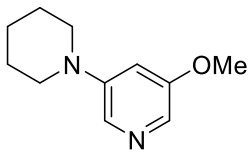
Prepared using methoxypyridine (**2.3sa**) (96.1 mg, 0.500 mmol) and amine (**2.2b**) (83.3 μL, 1.00 mmol) for 49 h. Purification by flash chromatography (silica gel, hexane: Et_2O = 1:10) gave 2-(piperidin-1-yl)-5-(pyrrolidin-1-yl)pyridine (**2.7**) (37.6 mg, 0.163 mmol) in 33% yield (76% yield based on recovered starting material) as a green solid along with recovery of methoxypyridine (**2.3sa**) (54.9 mg, 0.286 mmol).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, *J* = 2.8 Hz, 1H), 6.89 (dd, *J* = 9.0, 2.8 Hz, 1H), 6.67 (d, *J* = 9.0 Hz, 1H), 3.32 (t, *J* = 5.3 Hz, 4H), 3.22 (t, *J* = 6.2 Hz, 4H), 2.00-1.97 (m, 4H), 1.71-1.65 (m, 4H), 1.61-1.58 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 153.3, 138.2, 131.6, 122.3, 109.4, 48.5, 48.1, 25.7, 25.2, 24.6.

ESIHRMS: Found m/z 232.1814; Calcd for $C_{14}H_{22}N_3$ $[M+H]^+$ 232.1814.

5.2.2.40. Synthesis of 3-methoxy-5-(piperidin-1-yl)pyridine (2.3ta)



Prepared using methoxypyridine (**2.1t**) (144 mg, 1.03 mmol) and amine (**2.2a**) (43.0 mg, 0.505 mmol) for 24 h. Purification by flash chromatography (silica gel, hexane: Et_2O = 2:1) gave 3-

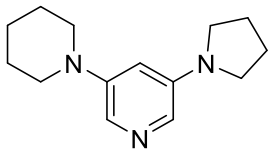
methoxy-5-(piperidin-1-yl)pyridine (**2.3ta**) (67.5 mg, 0.351 mmol) in 70% yield as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, *J* = 1.8 Hz, 1H), 7.77 (d, *J* = 1.8 Hz, 1H), 6.70 (dd, *J* = 1.8, 1.8 Hz, 1H), 3.84 (s, 3H), 3.19 (t, *J* = 5.5 Hz, 4H), 1.73-1.68 (m, 4H), 1.63-1.59 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 156.2, 148.6, 131.9, 126.7, 108.3, 55.5, 49.9, 25.5, 24.1.

ESIHRMS: Found m/z 193.1343; Calcd for $C_{11}H_{17}N_2O$ $[M+H]^+$ 193.1341.

5.2.2.41. Synthesis of 3-(piperidin-1-yl)-5-(pyrrolidin-1-yl)pyridine (2.8)



Prepared using methoxypyridine (**2.3ta**) (96.2 mg, 0.500 mmol) and amine (**2.2b**) (83.3 μL, 1.00 mmol) for 5 h. Purification by flash chromatography (silica gel, hexane:Et_2O = 2:1) gave 3-(piperidin-1-yl)-5-(pyrrolidin-1-yl)pyridine (**2.8**) (97.6 mg, 0.422 mmol) in 84% yield as a brown solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, *J* = 2.3 Hz, 1H), 7.52 (d, *J* = 2.3 Hz, 1H), 6.32 (dd, *J* = 2.3, 2.3 Hz, 1H), 3.28 (t, *J* = 6.6 Hz, 4H), 3.17 (t, *J* = 5.4 Hz, 4H), 2.02-1.98 (m, 4H), 1.74-1.68 (m, 4H), 1.61-1.57 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 148.4, 144.2, 127.4, 126.1, 105.5, 50.4, 47.4, 25.7, 25.4, 24.3.

ESIHRMS: Found m/z 232.1808; Calcd for $C_{14}H_{22}N_3$ $[M+H]^+$ 232.1814.

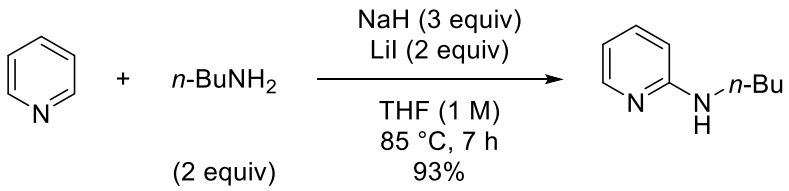
5.3. General Information for Chapter 3

H NMR spectra (400 MHz) were recorded on a Bruker Avance 400 spectrometer in $CDCl_3$ [using TMS (for ^1H, $\delta = 0.00$) as internal standard]. ^{13}C NMR spectra (100 MHz) were recorded on a Bruker Avance 400 or JEOL ECA400 spectrometer in $CDCl_3$ [using $CDCl_3$ (for ^{13}C, $\delta = 77.00$) as internal standard]. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sext = sextet, br = broad. High-resolution mass spectra were obtained with a Waters Q-Tof Premier mass spectrometer. Enantiomeric excesses (ee) were determined by HPLC analysis on Shimadzu HPLC with Daicel chiral columns. Flash chromatography was performed using Merck silica gel 60 with distilled solvents. Tetrahydrofuran (THF) was taken from a solvent purification system (PS-400-5, innovative technology Inc.). NaH (60% dispersion in mineral oil), NaI and LiI were purchased from Sigma-Aldrich, Inc. Due to moisture sensitivity of NaH, it was consistently handled under an Ar atmosphere in a glovebox or with Schlenk techniques under an inert (N_2 or Ar) atmosphere. NaI and LiI were dried over P_2O_5 under reduced pressure at 60 °C and 120 °C, respectively. Other solvents and reagents, otherwise noted, were commercially available and used as received. All the pyridines and amines were commercially available were used as received.

5.4. Experimental Data for Chapter 2

5.4.1. Compound Data and Procedures

5.4.1.1. Synthesis of *N*-butylpyridin-2-amine (3.4aa)[4] (a typical procedure)

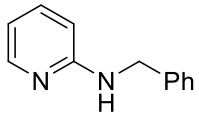


To a 10 mL sealed tube containing pyridine (**3.1a**) (38.9 mg, 0.492 mmol), NaH (60% dispersion in mineral oil, 61.7 mg, 1.54 mmol), and LiI (136 mg, 1.02 mmol) in THF (500 μL) was added *n*-butylamine (**3.2a**) (98.8 μL, 1.00 mmol) at room temperature under a N_2 atmosphere. The tube was sealed, and the solution was then stirred at 85 °C for 7 h. The reaction mixture was quenched with ice-cold water at 0 °C and the organic materials were extracted thrice with CH_2Cl_2. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The resulting crude material was purified by flash column chromatography (hexane: EtOAc = 4:1) to yield *N*-butylpyridin-2-amine (**3.4aa**) (68.5 mg, 0.456 mmol) in 93% yield as a pale-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (dd, *J* = 5.6, 1.9 Hz, 1H), 7.40 (ddd, *J* = 8.6, 6.4, 1.9 Hz, 1H), 6.54 (dd, *J* = 6.4, 5.6 Hz, 1H), 6.36 (d, *J* = 8.6 Hz, 1H), 4.61 (br, 1H), 3.24 (t, *J* = 6.9 Hz, 2H), 1.60 (quin, *J* = 7.3 Hz, 2H), 1.44 (sext, *J* = 7.4 Hz, 2H), 0.95 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.9, 148.0, 137.3, 112.5, 106.2, 41.9, 31.6, 20.1, 13.8.

5.4.1.2. Synthesis of *N*-benzylpyridin-2-amine (3.4ab)[9]

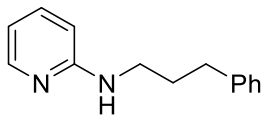


Prepared using pyridine (**3.1a**) (42.7 mg, 0.540 mmol) and benzylamine (**3.2b**) (109 μL, 1.00 mmol) for 6 h. Purification by flash chromatography (silica gel, hexane: EtOAc = 4:1) gave *N*-benzylpyridin-2-amine (**3.4ab**) (61.3 mg, 0.333 mmol) in 62% yield as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (dd, *J* = 5.1, 1.4 Hz, 1H), 7.40 (ddd, *J* = 8.6, 7.0, 1.4 Hz, 1H), 7.38-7.32 (m, 4H), 7.29-7.27 (m, 1H), 6.59 (ddd, *J* = 7.0, 5.1, 0.8 Hz, 1H), 6.37 (dd, *J* = 8.6, 0.8 Hz, 1H), 4.84 (br, 1H), 4.51 (d, *J* = 5.8 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.6, 148.2, 139.2, 137.5, 128.6, 127.4, 127.3, 113.2, 106.8, 46.3.

5.4.1.3. Synthesis of *N*-(3-phenylpropyl)pyridin-2-amine (3.4ac)



Prepared using pyridine (**3.1a**) (38.7 mg, 0.489 mmol) and 3-phenylpropan-1-amine (**3.2c**) (142 μL, 1.00 mmol) for 6 h. Purification by flash chromatography (silica gel, hexane: EtOAc = 4:1) gave *N*-(3-phenylpropyl)pyridin-2-amine (**3.4ac**) (98.0 mg, 0.462 mmol) in 94% yield as a yellow oil.

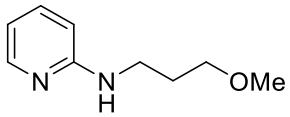
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (dd, *J* = 5.1, 1.5 Hz, 1H), 7.40 (ddd, *J* = 8.6, 7.0, 1.5 Hz, 1H), 7.30-7.27 (m, 2H), 7.21-7.17 (m, 3H), 6.55 (ddd, *J* = 7.0, 5.1, 0.8 Hz, 1H), 6.33 (dd, *J* =

8.6, 0.8 Hz, 1H), 4.49 (br, 1H), 3.29 (dt, *J* = 6.9, 6.5 Hz, 2H), 2.73 (t, *J* = 7.7 Hz, 2H), 1.96 (tt, *J* = 7.7, 6.5 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.9, 148.2, 141.6, 137.4, 128.45, 128.42, 126.0, 112.8, 106.4, 41.7, 33.3, 31.2.

ESIHRMS: Found *m/z* 213.1398; Calcd for $C_{14}H_{17}N_2$ $[M+H]^+$ 213.1392.

5.4.1.4. Synthesis of *N*-(3-methoxypropyl)pyridin-2-amine (3.4ad)



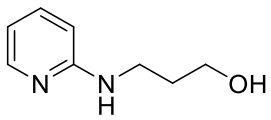
Prepared using pyridine (**3.1a**) (40.2 mg, 0.508 mmol) and 3-methoxypropan-1-amine (**3.2d**) (103 μL, 1.00 mmol) for 7 h. Purification by flash chromatography (silica gel, hexane: EtOAc = 1:1) gave *N*-(3-methoxypropyl)pyridin-2-amine (**3.4ad**) (73.4 mg, 0.442 mmol) in 87% yield as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (dd, *J* = 5.1, 1.5 Hz, 1H), 7.40 (ddd, *J* = 8.6, 6.0, 1.5 Hz, 1H), 6.54 (ddd, *J* = 6.0, 5.1, 0.8 Hz, 1H), 6.38 (dd, *J* = 8.6, 0.8 Hz, 1H), 4.77 (br, 1H), 3.51 (t, *J* = 5.9 Hz, 2H), 3.38 (dt, *J* = 6.4, 6.1 Hz, 2H), 3.35 (s, 3H), 1.89 (quin, *J* = 6.3 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.0, 148.2, 137.4, 112.7, 106.6, 71.1, 58.8, 40.1, 29.5.

ESIHRMS: Found *m/z* 167.1183; Calcd for $C_9H_{15}N_2O$ $[M+H]^+$ 167.1184.

5.4.1.5. Synthesis of 3-(pyridin-2-ylamino)propan-1-ol (3.4ae)



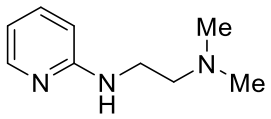
Prepared using pyridine (**3.1a**) (39.6 mg, 0.500 mmol) and 3-aminopropan-1-ol (**3.2e**) (76.5 μL, 1.00 mmol) in the presence of NaH (5 equiv) and LiI (2 equiv) for 10 h. Purification by flash chromatography (silica gel, CH_2Cl_2: MeOH = 19:1) gave 3-(pyridin-2-ylamino)propan-1-ol (**3.4ad**) (55.8 mg, 0.367 mmol) in 73% yield as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (dd, *J* = 5.1, 1.0 Hz, 1H), 7.37 (ddd, *J* = 8.7, 6.8, 1.0 Hz, 1H), 6.54 (ddd, *J* = 6.8, 5.1, 0.9 Hz, 1H), 6.38 (dd, *J* = 8.7, 0.9 Hz, 1H), 4.54 (br, 1H), 3.64 (t, *J* = 5.6 Hz, 2H), 3.55 (dt, *J* = 6.3, 6.1 Hz, 2H), 1.75 (quin, *J* = 5.9 Hz, 2H), 1.62 (br, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.0, 147.4, 137.5, 112.6, 108.2, 58.8, 38.1, 33.3.

ESIHRMS Found *m/z* 153.1032; Calcd for $C_8H_{13}N_2O$ $[M+H]^+$ 153.1028.

5.4.1.6. Synthesis of N^1,N^1-dimethyl-N^2-(pyridin-2-yl)ethane-1,2-diamine (3.4af)[10]

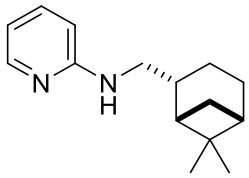


Prepared using pyridine (**3.1a**) (38.4 mg, 0.485 mmol) and N^1,N^1-dimethylethane-1,2-diamine (**3.2f**) (109 μL, 1.00 mmol) for 6 h. Purification by flash chromatography (silica gel, MeOH: CH_2Cl_2 = 1:5) gave N^1,N^1-dimethyl-N^2-(pyridin-2-yl)ethane-1,2-diamine (**3.4af**) (76.9 mg, 0.465 mmol) in 96% yield as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (dd, *J* = 5.1, 1.5 Hz, 1H), 7.38 (ddd, *J* = 8.6, 7.0, 1.5 Hz, 1H), 6.54 (ddd, *J* = 7.0, 5.1, 0.8 Hz, 1H), 6.42 (dd, *J* = 8.6, 0.8 Hz, 1H), 5.15 (brs, 1H), 3.38 (dt, *J* = 5.6, 4.6 Hz, 2H), 2.59 (t, *J* = 5.6 Hz, 2H), 2.30 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.8, 148.0, 137.1, 112.6, 107.7, 58.1, 45.1, 39.2.

5.4.1.7. Synthesis of *N*-(((1*S*,2*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl)methyl)pyridin-2-amine (3.4ag)



Prepared using pyridine (**3.1a**) (39.7 mg, 0.502 mmol) and ((1*S*,2*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl)methanamine (**3.2g**) (168 μL, 1.00 mmol) for 6 h. Purification by flash chromatography (silica gel, hexane: EtOAc = 4:1) gave *N*-(((1*S*,2*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl)methyl)pyridin-2-amine (**3.4ag**) (84.4 mg, 0.366 mmol) in 73% yield as a pale-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (dd, *J* = 5.1, 1.5 Hz, 1H), 7.40 (ddd, *J* = 8.6, 7.0, 1.5 Hz, 1H), 6.54 (ddd, *J* = 7.0, 5.1, 0.8 Hz, 1H), 6.35 (dd, *J* = 8.6, 0.8 Hz, 1H), 4.56 (br, 1H), 3.26-3.22 (m, 2H), 2.41-2.27 (m, 2H), 2.03-2.01 (m, 1H), 1.99-1.98 (m, 1H), 1.95-1.89 (m, 2H), 1.88-1.84 (m, 1H), 1.59-1.52 (m, 1H), 1.20 (s, 3H), 1.05 (s, 3H), 0.92 (d, *J* = 9.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.0, 148.1, 137.4, 112.5, 106.3, 48.1, 44.0, 41.4, 41.2, 38.7, 33.4, 28.0, 26.1, 23.3, 20.2.

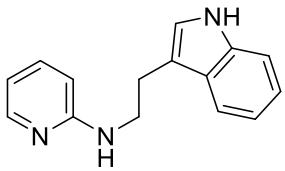
ESIHRMS: Found *m/z* 231.1859; Calcd for $C_{15}H_{23}N_2$ $[M+H]^+$ 231.1861.

$[\alpha]_D^{25}$: -12.45° (*c* = 0.4, $CHCl_3$)

The reaction with 3 equiv of pyridine (3.1a) to the amine:

Prepared using pyridine (**3.1a**) (121 μL, 1.50 mmol) and ((1*S*,2*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl)methanamine (**3.2g**) (76.4 mg, 0.498 mmol) for 6 h. Purification by flash chromatography (silica gel, hexane: EtOAc = 4:1) gave *N*-(((1*S*,2*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl)methyl)pyridin-2-amine (**3.4ag**) (86.6 mg, 0.376 mmol) in 75% yield as a pale-yellow oil.

5.4.1.8. Synthesis of *N*-(2-(1*H*-indol-3-yl)ethyl)pyridin-2-amine (3.4ah)



Prepared using pyridine (**3.1a**) (40.6 mg, 0.513 mmol) and 2-(1*H*-indol-3-yl)ethan-1-amine (**3.2h**) (162 mg, 1.01 mmol) in the presence of NaH (5 equiv) and LiI (2 equiv) for 6 h. Purification by flash chromatography (silica gel, hexane: EtOAc = 4:1) gave *N*-(2-(1*H*-indol-3-yl)ethyl)pyridin-2-amine (**3.4ah**) (93.8 mg, 0.395 mmol) in 77% yield as a pale-yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (br, 1H), 8.08 (dd, *J* = 5.1, 1.5 Hz, 1H), 7.62 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.41 (ddd, *J* = 8.7, 7.1, 1.5 Hz, 1H), 7.37 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.20 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H), 7.12 (ddd, *J* = 7.9, 7.0, 1.0 Hz, 1H), 7.05 (d, *J* = 2.2 Hz, 1H), 6.56 (ddd, *J* = 7.1, 5.1, 0.8 Hz, 1H), 6.37 (dd, *J* = 8.7, 0.8 Hz, 1H), 4.62 (br, 1H), 3.62 (dt, *J* = 6.7, 6.3 Hz, 2H), 3.10 (t, *J* = 6.7 Hz, 2H).

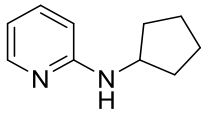
^{13}C NMR (100 MHz, $CDCl_3$): δ 158.8, 148.1, 137.5, 136.5, 127.4, 122.2, 122.1, 119.4, 118.7, 113.1, 112.8, 111.3, 106.8, 42.2, 25.3.

ESIHRMS: Found *m/z* 238.1342; Calcd for $C_{15}H_{16}N_3$ $[M+H]^+$ 238.1344.

The reaction with 3 equiv of pyridine (3.1a) to the amine:

Prepared using pyridine (**3.1a**) (121 μL, 1.50 mmol) and 2-(1*H*-indol-3-yl)ethan-1-amine (**3.2h**) (81.1 mg, 0.506 mmol) in the presence of NaH (5 equiv) and LiI (2 equiv) for 6 h. Purification by flash chromatography (silica gel, hexane: EtOAc = 4:1) gave *N*-(2-(1*H*-indol-3-yl)ethyl)pyridin-2-amine (**3.4ah**) (88.7 mg, 0.374 mmol) in 74% yield as a pale-yellow solid.

5.4.1.9. Synthesis of *N*-cyclopentylpyridin-2-amine (3.4ai)



Prepared using pyridine (**3.1a**) (42.2 mg, 0.533 mmol) and cyclopentanamine (**3.2i**) (98.7 μL, 1.00 mmol) for 24 h. Purification by flash chromatography (silica gel, hexane: EtOAc = 4:1) gave *N*-cyclopentylpyridin-2-amine (**3.4ai**) (60.3 mg, 0.372 mmol) in 70% yield as a yellow solid.

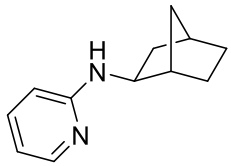
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (dd, *J* = 5.1, 1.5 Hz, 1H), 7.41 (ddd, *J* = 8.6, 6.0, 1.5 Hz, 1H), 6.54 (ddd, *J* = 7.0, 5.1, 0.9 Hz, 1H), 6.38 (dd, *J* = 8.6, 0.9 Hz, 1H), 4.52 (br, 1H), 3.97 (tt, *J* = 6.44, 6.41 Hz, 1H), 2.08-2.00 (m, 2H), 1.78-1.67 (m, 2H), 1.67-1.58 (m, 2H), 1.52-1.44 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.6, 148.3, 137.4, 112.5, 106.5, 53.4, 33.5, 23.8.

ESIHRMS: Found *m/z* 163.1239; Calcd for $C_{10}H_{15}N_2$ $[M+H]^+$ 163.1235.

5.4.1.10. Synthesis of

***N*-((1*S**,2*S**,4*R**)-bicyclo[2.2.1]heptan-2-yl)pyridin-2-amine (3.4aj)[11]**

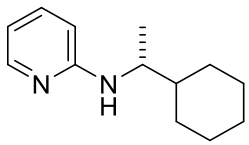


Prepared using pyridine (**3.1a**) (42.4 mg, 0.536 mmol) and (1*S**,2*S**,4*R**)-bicyclo[2.2.1]heptan-2-amine (**3.2j**) (119 μL, 1.00 mmol) for 24 h. Purification by flash chromatography (silica gel, hexane: EtOAc = 4:1) gave *N*-((1*S**,2*S**,4*R**)-bicyclo[2.2.1]heptan-2-yl)pyridin-2-amine (**3.4aj**) (68.8 mg, 0.365 mmol) in 68% yield as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (dd, *J* = 5.0, 1.5 Hz, 1H), 7.42 (ddd, *J* = 8.6, 7.0, 1.5 Hz, 1H), 6.54 (ddd, *J* = 7.0, 5.0, 0.9 Hz, 1H), 6.34 (dd, *J* = 8.6, 0.9 Hz, 1H), 4.50 (br, 1H), 3.41-3.37 (m, 1H), 2.30-2.26 (m, 2H), 1.85 (ddd, *J* = 12.9, 7.7, 2.4 Hz, 1H), 1.60-1.46 (m, 3H), 1.27-1.13 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.3, 148.4, 137.4, 112.6, 106.1, 55.3, 41.6, 41.0, 35.7, 35.4, 28.4, 26.4.

5.4.1.11. Synthesis of (*R*)-*N*-(1-cyclohexylethyl)pyridin-2-amine (3.4ak)



Prepared using pyridine (**3.1a**) (39.1 mg, 0.494 mmol) and (*R*)-1-cyclohexylethan-1-amine (**3.2k**) (purchased from TCI; 94.5% ee; Lot: EQG7L[12] (220 μL, 1.50 mmol) in the presence of NaH (4 equiv) and LiI (3 equiv) for 38 h. Purification by flash chromatography (silica gel, hexane: EtOAc = 5:1) gave (*R*)-*N*-(1-cyclohexylethyl)pyridin-2-amine (**3.4ak**) (62.1 mg, 0.302 mmol, 93% ee) in 61% yield as an orange oil.

The enantiomeric excess (ee) was measured by HPLC (Daicel Chiralpak OD-R column), *i*-PrOH/hexane = 10/90, flow 1.0 mL/min, 256 nm, t_1 = 4.60 min (minor), t_2 = 5.14 min (major).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (dd, *J* = 5.1, 1.5 Hz, 1H), 7.37 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H), 6.49 (ddd, *J* = 7.0, 5.1, 0.7 Hz, 1H), 6.33 (dd, *J* = 8.5, 0.7 Hz, 1H), 4.40 (d, *J* = 8.1 Hz, 1H), 3.64-3.55 (m, 1H), 1.84-1.64 (m, 4H), 1.46-1.38 (m, 1H), 1.14 (d, *J* = 6.6 Hz, 3H), 1.25-1.00 (m, 6H).

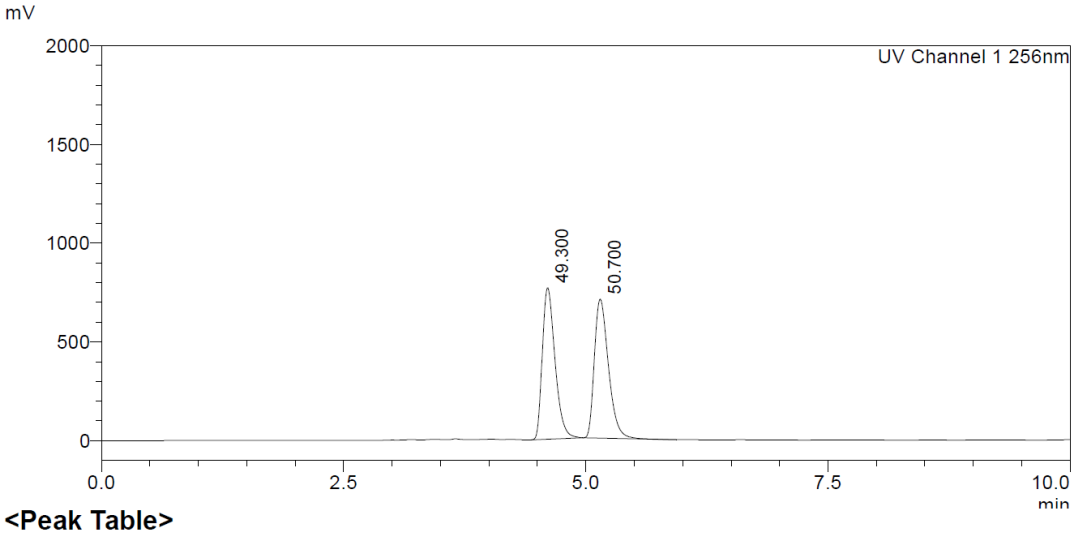
^{13}C NMR (100 MHz, $CDCl_3$): δ 158.6, 148.2, 137.3, 112.1, 106.5, 51.6, 43.4, 29.5, 28.8, 26.6, 26.4, 26.3, 17.8.

ESIHRMS: Found: m/z 205.1700; Calcd for $C_{13}H_{21}N_2$: $[M+H]^+$ 205.1705.

$[\alpha]_D^{25}$: -26.04° (*c* = 0.5, $CHCl_3$)

Chiral HPLC chart of racemic (**3.4ak**).

<Chromatogram>



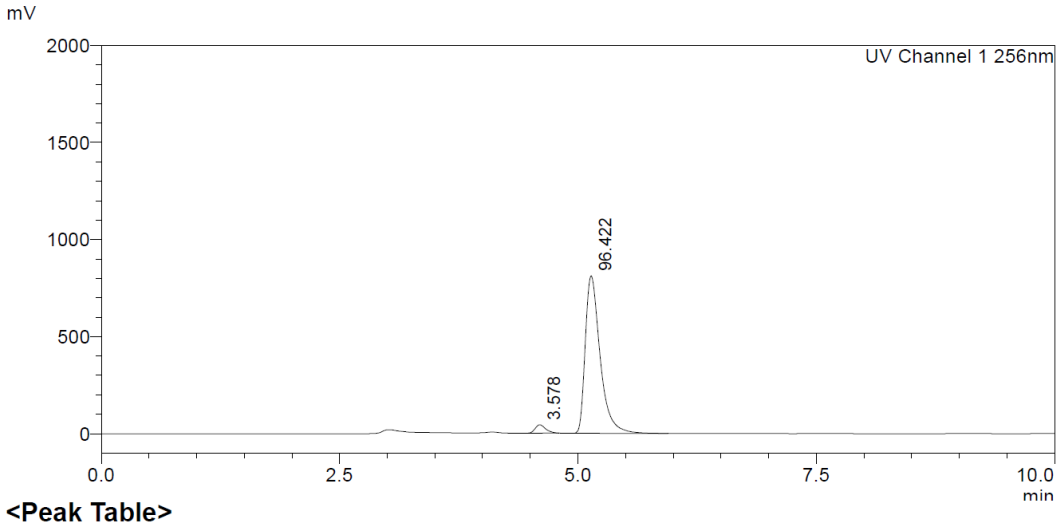
<Peak Table>

UV Channel 1 256nm

Peak#	Ret. Time	Area	Height	Area%
1	4.605	6976166	766377	49.300
2	5.148	7174160	704718	50.700
Total		14150326	1471094	100.000

Chiral HPLC chart of (**3.4ak**).

<Chromatogram>

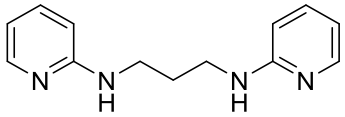


<Peak Table>

UV Channel 1 256nm

Peak#	Ret. Time	Area	Height	Area%
1	4.599	328380	43275	3.578
2	5.138	8850563	810054	96.422
Total		9178942	853329	100.000

5.4.1.12. Synthesis of N^1,N^3-di(pyridin-2-yl)propane-1,3-diamine (3.5)



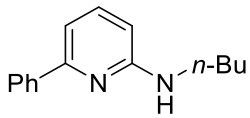
Prepared using pyridine (**3.1a**) (88.7 μL, 1.10 mmol) and propane-1,3-diamine (**3.2l**) (38.8 mg, 0.523 mmol) in the presence of NaH (6 equiv) and LiI (4 equiv) for 24 h. Purification by flash chromatography (silica gel, hexane: Acetone = 1:1) gave N^1,N^3-di(pyridin-2-yl)propane-1,3-diamine (**3.5**) (93.9 mg, 0.411 mmol) in 79% yield as a pale-yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (dd, *J* = 4.9, 1.1 Hz, 2H), 7.39 (ddd, *J* = 8.4, 6.8, 1.8 Hz, 2H). 6.55 (dd, *J* = 6.8, 4.9 Hz, 2H), 6.38 (d, *J* = 8.4 Hz, 2H), 4.75 (br, 2H), 3.44 (dt, *J* = 6.5, 6.3 Hz, 4H), 1.92 (quin, *J* = 6.5 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.8, 148.1, 137.3, 112.8, 107.2, 39.4, 29.7.

ESIHRMS: Found m/z 229.1462; Calcd for $C_{13}H_{17}N_4$ $[M+H]^+$ 229.1453.

5.4.1.13. Synthesis of *N*-butyl-6-phenylpyridin-2-amine (3.4ba)



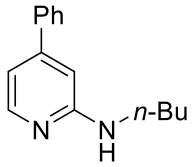
Prepared using 2-phenylpyridine (**3.1b**) (73.4 mg, 0.473 mmol) and *n*-butylamine (**3.2a**) (98.8 μL, 1.00 mmol) for 9 h. Purification by flash chromatography (silica gel, hexane: EtOAc = 4:1) gave *N*-butyl-6-phenylpyridin-2-amine (**3.4ba**) (94.6 mg, 0.418 mmol) in 88% yield as an off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, *J* = 7.5 Hz, 2H), 7.50 (dd, *J* = 8.0, 7.6, Hz, 1H), 7.44 (dd, *J* = 7.5, 7.4 Hz, 2H), 7.37 (t, *J* = 7.4 Hz, 1H), 7.04 (d, *J* = 7.6 Hz, 1H), 6.34 (d, *J* = 8.0 Hz, 1H), 4.61 (br, 1H), 3.34 (dt, *J* = 7.3, 6.5 Hz, 2H), 1.64 (quin, *J* = 7.3 Hz, 2H), 1.46 (sext, *J* = 7.5 Hz, 2H), 0.98 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.8, 155.9, 140.0, 138.1, 128.48, 128.45, 126.8, 109.4, 104.7, 42.1, 31.8, 20.3, 13.9.

ESIHRMS: Found *m/z* 249.1363; Calcd for $C_{15}H_{18}N_2Na$ $[M+Na]^+$ 249.1368.

5.4.1.14. Synthesis of *N*-butyl-4-phenylpyridin-2-amine (3.4ca)



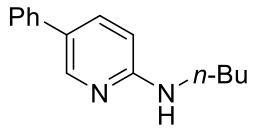
Prepared using 4-phenylpyridine (**3.1b**) (76.5 mg, 0.493 mmol) and *n*-butylamine (**3.2a**) (98.8 μL, 1.00 mmol) for 7 h. Purification by flash chromatography (silica gel, hexane: EtOAc = 4:1) gave *N*-butyl-4-phenylpyridin-2-amine (**3.4ca**) (107 mg, 0.473 mmol) in 96% yield as an off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, *J* = 5.3 Hz, 1H), 7.60 (d, *J* = 7.6 Hz, 2H), 7.45 (dd, *J* = 7.6, 7.1 Hz, 2H), 7.40 (t, *J* = 7.1 Hz, 1H), 6.79 (d, *J* = 5.3 Hz, 1H), 6.56 (s, 1H), 4.62 (br, 1H), 3.32 (dt, *J* = 6.6, 6.5 Hz, 2H), 1.65 (quin, *J* = 7.3 Hz, 2H), 1.46 (sext, *J* = 7.3 Hz, 2H), 0.97 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.5, 150.0, 148.6, 139.4, 128.9, 128.6, 126.9, 111.5, 104.0, 42.1, 31.7, 20.2, 13.9.

ESIHRMS: Found m/z 249.1377; Calcd for $C_{15}H_{18}N_2Na$ $[M+Na]^+$ 249.1368.

5.4.1.15. Synthesis of *N*-butyl-5-phenylpyridin-2-amine (3.4da)



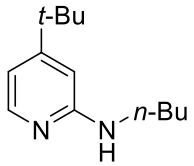
Prepared using 3-phenylpyridine (**3.1d**) (74.2 mg, 0.478 mmol) and *n*-butylamine (**3.2a**) (98.8 μL, 1.00 mmol) for 24 h. Purification by flash chromatography (silica gel, hexane: EtOAc = 4:1) gave *N*-butyl-5-phenylpyridin-2-amine (**3.4da**) (89.2 mg, 0.394 mmol) in 82% yield as an off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (d, *J* = 2.2 Hz, 1H), 7.67 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.51 (d, *J* = 7.4 Hz, 2H), 7.41 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.29 (t, *J* = 7.4 Hz, 1H), 6.45 (d, *J* = 8.6 Hz, 1H), 4.62 (br, 1H), 3.30 (dt, *J* = 7.3, 6.6 Hz, 2H), 1.64 (quin, *J* = 7.3 Hz, 2H), 1.46 (sext, *J* = 7.4 Hz, 2H), 0.97 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.2, 146.5, 138.6, 136.2, 128.9, 126.6, 126.1, 125.9, 106.2, 42.1, 31.7, 20.2, 13.9.

ESIHRMS: Found m/z 227.1543; Calcd for $C_{15}H_{19}N_2$ $[M+H]^+$ 227.1548.

5.4.1.16. Synthesis of 4-(*tert*-butyl)-*N*-butylpyridin-2-amine (3.4ea)



Prepared using 4-*t*-butylpyridine (**3.1e**) (67.5 mg, 0.499 mmol) and *n*-butylamine (**3.2a**) (98.8 μL, 1.00 mmol) for 24 h. Purification by flash chromatography (silica gel, hexane: EtOAc =

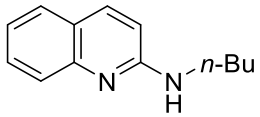
4:1) gave 4-(*tert*-butyl)-*N*-butylpyridin-2-amine (**3.4ea**) (89.6 mg, 0.434 mmol) in 87% yield as an white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, *J* = 5.5 Hz, 1H), 6.58 (dd, *J* = 5.5, 1.4 Hz, 1H), 6.33 (d, *J* = 1.4 Hz, 1H), 4.37 (br, 1H), 3.27 (dt, *J* = 7.3, 6.4 Hz, 2H), 1.61 (quin, *J* = 7.3 Hz, 2H), 1.44 (sext, *J* = 7.4 Hz, 2H), 1.27 (s, 9H), 0.96 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 161.3, 159.2, 147.8, 110.6, 103.1, 42.0, 34.6, 31.8, 30.5, 20.2, 13.9.

ESIHRMS: Found m/z 207.1858; Calcd for $C_{13}H_{23}N_2$ $[M+H]^+$ 207.1861.

5.4.1.17. Synthesis of *N*-butylquinolin-2-amine (3.4fa)



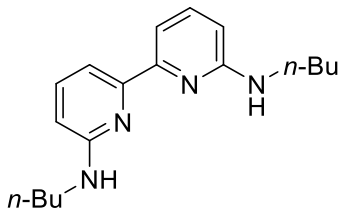
Prepared using quinoline (**3.1f**) (62.4 mg, 0.483 mmol) and *n*-butylamine (**3.2a**) (98.8 μL, 1.00 mmol) for 5 h. Purification by flash chromatography (silica gel, hexane: EtOAc = 3:1) gave *N*-butylquinolin-2-amine (**3.4fa**) (81.6 mg, 0.407 mmol) in 84% yield as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, *J* = 8.9 Hz, 1H), 7.66 (dd, *J* = 8.4, 1.0 Hz, 1H), 7.57 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.52 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.19 (ddd, *J* = 8.0, 6.9, 1.0 Hz, 1H), 6.64 (d, *J* = 8.9 Hz, 1H), 4.73 (br, 1H), 3.48 (dt, *J* = 6.9, 6.4 Hz, 2H), 1.66 (quin, *J* = 6.9 Hz, 2H), 1.47 (sext, *J* = 7.4 Hz, 2H), 0.98 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 157.1, 148.1, 137.4, 129.5, 127.4, 126.0, 123.3, 121.9, 110.9, 41.6, 31.9, 20.2, 13.9.

ESIHRMS: Found m/z 201.1386; Calcd for $C_{13}H_{17}N_2$ $[M+H]^+$ 201.1392.

5.4.1.18. Synthesis of N^6,$N^{6'}$-dibutyl-[2,2'-bipyridine]-6,6'-diamine (3.6aa)



Prepared using 2,2'-bipyridine (**3.3a**) (157 mg, 1.00 mmol) and *n*-butylamine (**3.2a**) (593 μL, 6.00 mmol) in the presence of NaH (7 equiv) and LiI (4 equiv) for 43 h. Purification by flash chromatography (silica gel, hexane: EtOAc = 4:1) gave N^6,$N^{6'}$-dibutyl-[2,2'-bipyridine]-6,6'-diamine (**3.6aa**) (260 mg, 0.870 mmol) in 87% yield as a pale-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, *J* = 6.9 Hz, 2H), 7.52 (dd, *J* = 8.1, 6.9 Hz, 2H). 6.37 (d, *J* = 8.1 Hz, 2H), 4.54 (br, 2H), 3.32 (dt, *J* = 7.3, 6.1 Hz, 4H), 1.64 (quin, *J* = 7.3 Hz, 4H), 1.45 (sext, *J* = 7.4 Hz, 4H), 0.97 (t, *J* = 7.3 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.5, 155.1, 138.1, 110.0, 106.1, 42.1, 31.8, 20.3, 13.9.

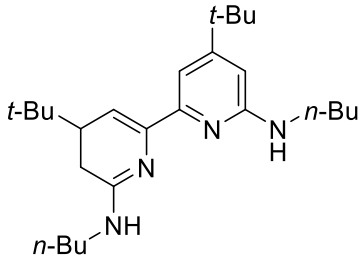
ESIHRMS: Found *m/z* 299.2242; Calcd for $C_{18}H_{27}N_4$ $[M+H]^+$ 299.2236.

Large scale (50 mmol) synthesis of N^6,$N^{6'}$-dibutyl-[2,2'-bipyridine]-6,6'-diamine (3.6aa):

To a 250 ml round bottomed flask fitted with a reflux condenser containing 2,2'-bipyridine (**3.3a**) (3.18 g, 20.3 mmol), mineral oil free NaH (prewashed by pentane in the glovebox) (3.37 g, 140 mmol), and LiI (10.7 g, 79.9 mmol) in THF (25 mL) was added *n*-butylamine (**3.2a**) (11.9 mL, 120 mmol) dropwise at room temperature under a N_2 atmosphere. The reaction mixture was then stirred at 23 °C for 15 min before being heated to reflux for 96 h. The reaction mixture was quenched with ice-cold water at 0 °C and the organic materials were extracted thrice with CH_2Cl_2. The combined organic extracts were washed with brine, dried over $MgSO_4$,

and concentrated *in vacuo*. The resulting crude material was purified by flash column chromatography (hexane: EtOAc = 5:1) to yield N^6,$N^{6'}$-dibutyl-[2,2'-bipyridine]-6,6'-diamine (**3.6aa**) (5.55 g, 18.6 mmol) in 92% yield as a pale-yellow oil.

5.4.1.19. Synthesis of 4,4'-di-*tert*-butyl-N^6,$N^{6'}$-dibutyl-[2,2'-bipyridine]-6,6'-diamine (3.6ba)



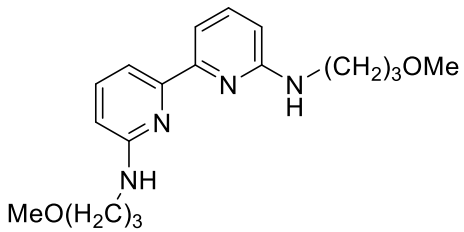
Prepared using 4,4'-di-*tert*-butyl-2,2'-bipyridine (**3.3b**) (134 mg, 0.501 mmol) and *n*-butylamine (**3.2a**) (400 □L, 4.05 mmol) in the presence of NaH (10 equiv) and LiI (7 equiv) for 24 h. Purification by flash chromatography (silica gel, hexane: EtOAc = 10:1) gave 4,4'-di-*tert*-butyl-N^6,$N^{6'}$-dibutyl-[2,2'-bipyridine]-6,6'-diamine (**3.6ba**) (170 mg, 0.415 mmol) in 83% yield as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (2H, d, *J* = 1.2 Hz, 2H), 6.34 (2H, d, *J* = 1.2 Hz, 2H), 4.50 (br, 2H), 3.33 (dt, *J* = 7.3, 6.4 Hz, 4H), 1.66 (quin, *J* = 7.3 Hz, 4H), 1.47 (sext, *J* = 7.4 Hz, 4H), 1.32 (s, 18H), 0.98 (t, *J* = 7.3 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 161.9, 158.8, 155.2, 108.3, 102.7, 42.2, 34.9, 31.9, 30.6, 20.3, 13.9.

ESIHRMS: Found: m/z 411.3489; Calcd for $C_{26}H_{43}N_4$: $[M+H]^+$ 411.3488.

5.4.1.20. Synthesis of N^6,$N^{6'}$-bis(3-methoxypropyl)-[2,2'-bipyridine]-6,6'-diamine (3.6ad)



Prepared using 2,2'-bipyridine (**3.3a**) (78.1 mg, 0.500 mmol) and 3-methoxypropan-1-amine (**3.2d**) (0.41 mL, 4.00 mmol) in the presence of NaH (10 equiv) and LiI (7 equiv) for 40 h. Purification by flash chromatography (silica gel, hexane: EtOAc = 2:1) gave N^6,$N^{6'}$-bis(3-methoxypropyl)-[2,2'-bipyridine]-6,6'-diamine (**3.6ad**) (99.5 mg, 0.301 mmol) in 60% yield as an orange oil.

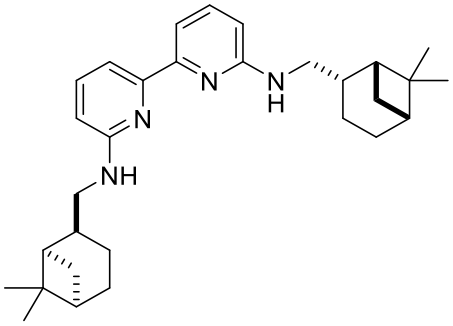
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, *J* = 7.6 Hz, 2H), 7.50 (dd, *J* = 8.0, 7.6 Hz, 2H), 6.39 (d, *J* = 8.0 Hz, 2H), 4.78 (br, 2H), 3.52 (t, *J* = 5.9 Hz, 4H), 3.45 (dt, *J* = 6.3, 6.1 Hz, 4H), 3.35 (s, 6H), 1.92 (quin, *J* = 6.3 Hz, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.3, 155.0, 138.0, 110.0, 106.4, 70.9, 58.7, 39.8, 29.6.

ESIHRMS: Found: m/z 331.2136; Calcd for $C_{18}H_{27}N_4O_2$: $[M+H]^+$ 331.2134.

5.4.1.21. Synthesis of

N^6,$N^{6'}$-bis(((1*S*,2*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl)methyl)-[2,2'-bipyridine]-6,6'-diamine (3.6ag)



Prepared using 2,2'-bipyridine (**3.3a**) (156 mg, 1.00 mmol) and ((1*S*,2*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl)methanamine (**3.2g**) (1.03 mL, 6.15 mmol) in the presence of NaH (7 equiv) and LiI (4 equiv) for 43 h. Purification by flash chromatography (silica gel, hexane: EtOAc = 5:1) followed by recrystallization from hexane gave N^6,$N^{6'}$-bis(((1*S*,2*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl)methyl)-[2,2'-bipyridine]-6,6'-diamine (**3.6ag**) (286 mg, 0.624 mmol) in 62% yield as a yellow solid.

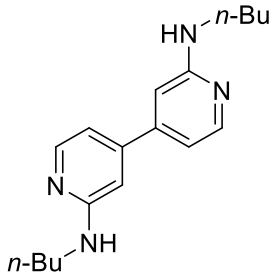
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, *J* = 6.8 Hz, 2H), 7.50 (dd, *J* = 8.0, 6.8 Hz, 2H), 6.35 (d, *J* = 8.0 Hz, 2H), 4.63 (br, 2H), 3.33-3.29 (m, 4H), 2.40-2.31 (m, 4H), 2.06-1.87 (m, 10H), 1.62-1.53 (m, 2H). 1.20 (s, 6H), 1.07 (s, 6H), 0.92 (d, *J* = 9.6 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.5, 155.1, 138.0, 110.0, 106.0, 48.2, 44.0, 41.5, 41.4, 38.7, 33.4, 28.0, 26.1, 23.3, 20.2.

ESIHRMS: Found: m/z 459.3484; Calcd for $C_{30}H_{43}N_4$: $[M+H]^+$ 459.3488.

$[\alpha]_D^{25}$: -7.82° (*c* = 0.2, $CHCl_3$)

5.4.1.22. Synthesis of N^2,$N^{2'}$-dibutyl-[4,4'-bipyridine]-2,2'-diamine (3.6ca)



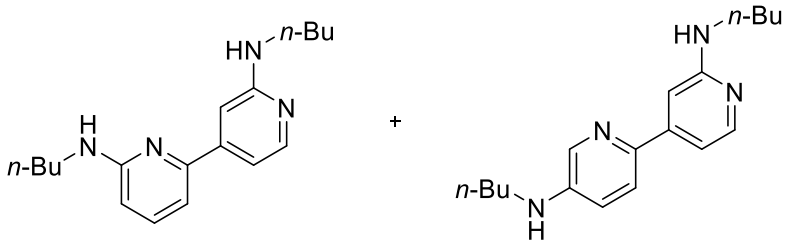
Prepared using 4,4'-bipyridine (**3.3c**) (157 mg, 1.01 mmol) and *n*-butylamine (**3.2a**) (790 □L, 7.99 mmol) in the presence of NaH (9 equiv) and LiI (5 equiv) for 56 h. Purification by flash chromatography (silica gel, hexane: EtOAc = 5:1) gave N^2,$N^{2'}$-dibutyl-[4,4'-bipyridine]-2,2'-diamine (**3.6ca**) (180 mg, 0.603 mmol) in 60% yield as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, *J* = 5.3 Hz, 2H), 6.74 (dd, *J* = 5.3, 1.4 Hz, 2H), 6.52 (s, 2H), 4.61 (br, 2H), 3.31 (dt, *J* = 7.0, 6.4 Hz, 4H), 1.64 (quin, *J* = 7.3 Hz, 4H), 1.46 (sext, *J* = 7.4 Hz, 4H), 0.97 (t, *J* = 7.3 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.5, 148.9, 148.4, 111.0, 103.9, 42.1, 31.7, 20.2, 13.9.

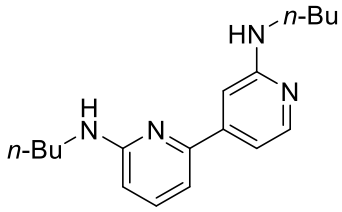
ESIHRMS: Found: m/z 299.2240; Calcd for $C_{18}H_{27}N_4$: $[M+H]^+$ 299.2236.

5.4.1.23. Synthesis of $N^{2'}$,N^6-dibutyl-[2,4'-bipyridine]-2',6-diamine (3.6da) and $N^{2'}$,N^5-dibutyl-[2,4'-bipyridine]-2',5-diamine (3.6da')



Prepared using 2,4'-bipyridine (**3.3d**) (157 mg, 0.999 mmol) and *n*-butylamine (**3.2a**) (790 □L, 7.99 mmol) in the presence of NaH (9 equiv) and LiI (5 equiv) for 43 h. Purification by flash chromatography (silica gel, hexane: Acetone = 19:1) gave $N^{2'}$,N^{6}-dibutyl-[2,4'-bipyridine]-2',6-diamine (**3.6da**) (198 mg, 0.664 mmol) in 66% yield as a pale-yellow oil and an impure mixture containing $N^{2'}$,N^{5}-dibutyl-[2,4'-bipyridine]-2',5-diamine (**3.6da'**) which was purified again by flash chromatography (silica gel, hexane: EtOAc = 5:1.) giving $N^{2'}$,N^{5}-dibutyl-[2,4'-bipyridine]-2',5-diamine (**3.6da'**) (23.3 mg 0.078 mmol) in 8% yield as a yellow oil.

$N^{2'}$,N^{6}-dibutyl-[2,4'-bipyridine]-2',6-diamine (3.6da)

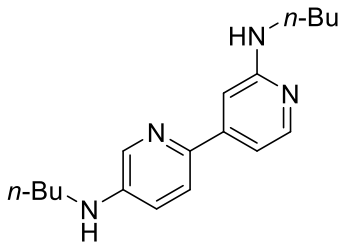


^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, *J* = 5.4 Hz, 1H), 7.49 (dd, *J* = 8.1, 7.9 Hz, 1H), 7.06 (dd, *J* = 5.4, 1.4 Hz, 1H), 7.02 (d, *J* = 7.9 Hz, 1H), 7.01 (d, *J* = 1.4 Hz, 1H), 6.39 (d, *J* = 8.1 Hz, 1H), 4.62 (t, *J* = 5.2 Hz, 1H), 4.55 (t, *J* = 5.3 Hz, 1H), 3.33 (dt, *J* = 6.9, 6.5 Hz, 4H), 1.65 (quin, *J* = 7.3 Hz, 2H), 1.64 (quin, *J* = 7.3 Hz, 2H), 1.46 (sext, *J* = 7.4 Hz, 2H), 1.45 (sext, *J* = 7.4 Hz, 2H), 0.97 (t, *J* = 7.3 Hz, 3H), 0.96 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7, 158.8, 153.9, 148.6, 148.4, 138.1, 110.7, 109.8, 106.3, 103.8, 42.1, 42.0, 31.8, 31.7, 20.3, 20.2, 13.9 (overlapped).

ESIHRMS: Found: m/z 299.2233; Calcd for $C_{18}H_{27}N_4$: $[M+H]^+$ 299.2236.

***N*$^{2'}$,*N*^{5}-dibutyl-[2,4'-bipyridine]-2',5-diamine (3.6da')**



^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53 (d, *J* = 2.0 Hz, 1H), 8.16 (d, *J* = 5.4 Hz, 1H), 7.65 (d, *J* = 8.1 Hz, 1H), 7.58 (dd, *J* = 8.1, 2.0 Hz, 1H), 7.07 (dd, *J* = 5.4, 1.3 Hz, 1H), 7.03 (s, 1H), 4.59 (br, 1H), 3.35 (dt, *J* = 6.9, 6.4 Hz, 2H), 2.66 (t, *J* = 7.7 Hz, 2H), 1.64 (quin, *J* = 7.0 Hz, 4H), 1.46 (sext, *J* = 7.4 Hz, 2H), 1.39 (sext, *J* = 7.3 Hz, 2H), 0.97 (t, *J* = 6.9 Hz, 3H), 0.95 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7, 153.1, 150.0, 148.7, 148.0, 138.0, 136.7, 120.5, 110.4, 103.6, 42.1, 33.2, 32.5, 31.7, 22.2, 20.2, 13.88, 13.85.

ESIHRMS: Found: m/z 299.2240; Calcd for $C_{18}H_{27}N_4$: $[M+H]^+$ 299.2236.

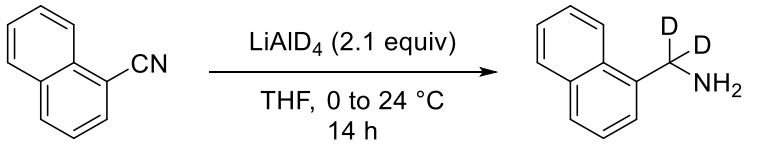
5.5. General Information for Chapter 4

^{1}H NMR spectra (400 MHz) were recorded on a Bruker Avance 400 spectrometer in $CDCl_3$ [using TMS (for ^{1}H, $\delta = 0.00$) as internal standard]. ^{13}C NMR spectra (100 MHz) were recorded on a Bruker Avance 400 spectrometer in $CDCl_3$ [using $CDCl_3$ (for ^{13}C, $\delta = 77.16$) as internal standard]. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet and br = broad. High-resolution mass spectra were obtained with a Waters Q-Tof Premier mass spectrometer. Flash chromatography was performed using Merck silica gel 60 with distilled solvents. Melting points are uncorrected and were recorded on an MPA 100 OptiMelt Automated Melting Point System. IR spectra were recorded on a Shimadzu IR Prestige-21 FT-IR spectrometer. KH (30% dispersion in mineral oil) was purchased from Sigma-Aldrich (product code: 215813). KH was dried by rinsing with pentanes multiple times to remove mineral oil and used as a dry powder. NaH (60% dispersion in mineral oil, product code: 452912) and CsF (99%, powder, product code: 198323) were purchased from Sigma-Aldrich and used as received. Due to moisture sensitivity of KH, NaH and CsF, they were stored in the glovebox and consistently handled under an Ar atmosphere in a glovebox or with Schlenk techniques under an Ar atmosphere.

5.6. Experimental Data for Chapter 4

5.6.1. Synthesis of Starting Materials

Synthesis of naphthalen-1-ylmethan-d$_2$-amine (2.1n)



4.2b-d$_2$ (81%, 98% D)

To a 25 mL Schlenk tube containing $LiAlD_4$ (883.5 mg, 21.1 mmol, 2.1 equiv) in THF (10 mL) was added a solution of 1-naphthonitrile (1.506 g, 9.83 mmol, 1 equiv) in THF (5 mL) dropwise at 0 ℃ under an Ar atmosphere. The reaction mixture allowed to warm to room temperature (24 ℃) and was stirred for 14 h. The reaction mixture was cooled to 0 °C before it was quenched with water (10 mL). The organic materials were extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, CH_2Cl_2:MeOH = 95:5) gave naphthalen-1-ylmethan-d$_2$-amine (**4.2b-d$_2$**) (81%, 7.96 mmol, 1.267 g, 98% D) as a yellow oil.

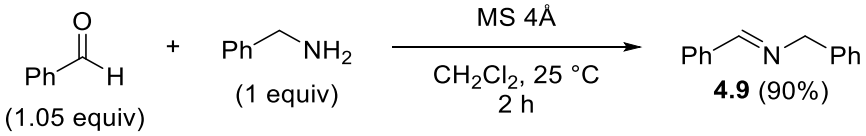
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.07 (d, *J* = 8.2 Hz, 1H), 7.87 (d, *J* = 7.7 Hz, 1H), 7.76 (d, *J* = 7.4 Hz, 1H), 7.56-7.42 (m, 4H), 4.31 (br, 2H), 1.57 (br, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 139.0, 134.0, 131.3, 129.0, 127.7, 126.3, 125.8, 125.7, 124.7, 123.3, 43.5 (quintet, *J* = 20.8 Hz).

MS (HRMS ESI): Calcd for $C_{11}H_{10}D_2N$ $[M+H]^+$ 160.1095, Found: 160.1100.

IR (neat, cm^{-1}): 3366 [υ(N-H)].

(E)-*N*-benzyl-1-phenylmethanimine (4.9)[13]



To a 50 mL Schlenk tube containing benzaldehyde (560.1 mg, 5.28 mmol, 1.05 equiv) and molecular sieves 4 Å (3.07 g) in THF (10 mL) was added benzylamine (**4.1a**) (537.7 mg, 5.02 mmol, 1 equiv) dropwise under an Ar atmosphere. The reaction was stirred for 2 h before it was quenched with water (10 mL). The organic materials were extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with brine, dried over MgSO4, and concentrated in vacuo. Purification by bulb-to-bulb distillation (203 °C, 5 millibar) gave (E)-*N*-benzyl-1-phenylmethanimine (**4.9**) (90%, 4.53 mmol, 884.8 mg) as a colorless oil.

1H NMR (400 MHz, CDCl3): δ (ppm) 8.40 (s, 1H), 7.80-7.77 (m, 2H), 7.43-7.41 (m, 3H), 7.35-7.34 (m, 4H), 7.29-7.26 (m, 1H), 4.83 (s, 2H).

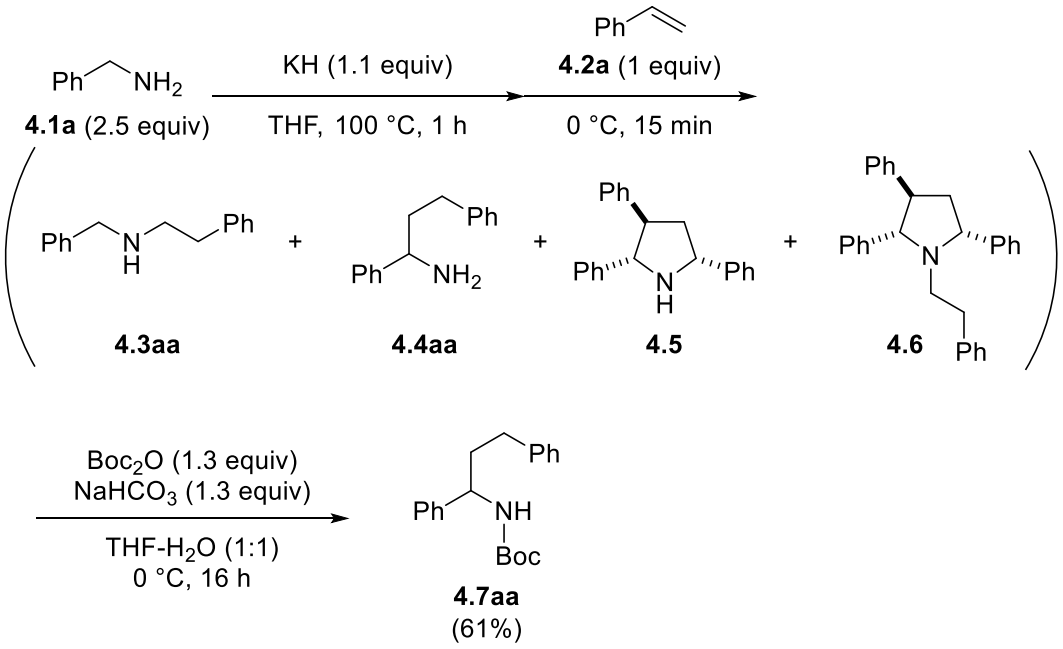
13C NMR (100 MHz, CDCl3): δ (ppm) 162.2, 139.4, 136.3, 130.9, 128.7, 128.6, 128.4, 128.1, 127.1, 65.2.

MS (HRMS ESI): Calcd for $C_{14}H_{15}N$ $[M+H]^+$ 197.1204, Found: 197.1199.

IR (neat, cm^{-1}): 1643 [υ(C=N)].

5.6.2. Protocols for hydroalkylation of styrenes with benzylamines

5.6.2.1. Synthesis of *tert*-butyl (1,3-diphenylpropyl)carbamate (4.7aa) (Protocol A)

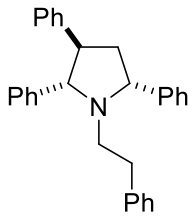


To a 25 mL sealed tube containing KH (22.3 mg, 0.556 mmol, 1.1 equiv) was added benzylamine (135.9 mg, 1.268 mmol, 2.5 equiv) in THF (2.0 mL) at room temperature under an Ar atmosphere. The tube was sealed, and the suspension was then stirred at 100 °C for 1 h. To the reaction mixture was added styrene (52.0 mg, 0.499 mmol, 1 equiv) at 0 °C with THF (0.5 mL). The reaction mixture was then stirred at 0 °C for 15 min before being quenched with water (20 mL) at 0 °C. The organic materials were extracted thrice with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The resulting crude material was analyzed by ^1H NMR with 1,1,2,2-tetrachloroethane (86.3 mg, 0.514 mmol) as an internal standard, revealing that pyrrolidines (**4.5**)[14] and (**4.6**) were formed in 4% and 12% yields, respectively, together with (**4.3aa**) and (**4.4aa**). Purification by flash column chromatography (CH_2Cl_2: MeOH = 95:5) gave an inseparable mixture containing *N*-benzyl-2-phenylethan-1-amine (**4.3aa**)[15] (in 10% NMR yield) and 1,3-diphenylpropan-1-amine (**4.4aa**) (in 63% NMR yield) as a pale yellow oil (ratio of **4.3aa**/**4.4aa**

= 14:86). The NMR yields were determined by the ^{1}H NMR spectrum with 1,1,2,2-tetrachloroethane (80.5 mg, 0.480 mmol) as an internal standard.

To a 100 mL sealed tube containing the mixture of (**4.3aa**) and (**4.4aa**) obtained above was added di-*tert*-butyl dicarbonate (108 μL, 0.470 mmol, 1.3 equiv to the calculated molar amounts of **4.3aa** and **4.4aa**) and sodium bicarbonate (40.0 mg, 0.476 mmol, 1.3 equiv to the calculated molar amounts of **4.3aa** and **4.4aa**) in THF (1.0 mL) and water (1.0 mL) at 0 ℃. The reaction mixture was stirred overnight before being diluted with water (20 mL). The organic materials were extracted thrice with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The resulting crude material was purified by flash column chromatography (EtOAc: hexane = 1:9) to yield *tert*-butyl (1,3-diphenylpropyl)carbamate (**4.7aa**) (95.2 mg, 0.306 mmol) in 61% yield over 2 steps based on styrene (**4.1a**) as a white solid.

(2*R,3*S**,5*S**)-1-Phenethyl-2,3,5-triphenylpyrrolidine (4.6)** (this compound was isolated and characterized in the reaction in section 5.2.)



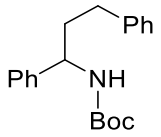
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.59 (d, *J* = 7.1 Hz, 2H), 7.39 (dd, *J* = 7.1, 7.1 Hz, 2H), 7.30-7.17 (m, 9H), 7.10-7.06 (m, 5H), 6.83 (d, *J* = 6.8 Hz, 2H), 4.19 (dd, *J* = 8.0, 8.0 Hz, 1H), 3.85 (d, *J* = 8.9 Hz, 1H), 3.27 (ddd, *J* = 8.9, 8.9, 8.9 Hz, 1H), 2.80-2.69 (m, 2H), 2.60-2.52 (m, 1H), 2.45 (dd, *J* = 7.6, 7.6 Hz, 2H), 2.29-2.22 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 146.2, 142.6, 142.5, 140.8, 128.7, 128.6, 128.4, 128.3, 128.2, 128.0, 127.8, 127.5, 127.3, 127.1, 126.5, 125.8, 77.3, 67.6, 53.9, 53.4, 43.3, 33.3.

MS (HRMS ESI): Calcd for $C_{30}H_{30}N$ $[M+H]^+$ 404.2378, Found: 404.2371.

IR (neat, cm^{-1}): 1144 [υ(C-N)].

***tert*-Butyl (1,3-diphenylpropyl)carbamate (4.7aa)**



^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.35-7.31 (m, 2H), 7.28-7.23 (m, 5H), 7.19-7.14 (m, 3H), 4.84 (br, 1H), 4.67 (br, 1H), 2.69-2.53 (m, 2H), 2.07-2.02 (m, 2H), 1.42 (s, 9H).

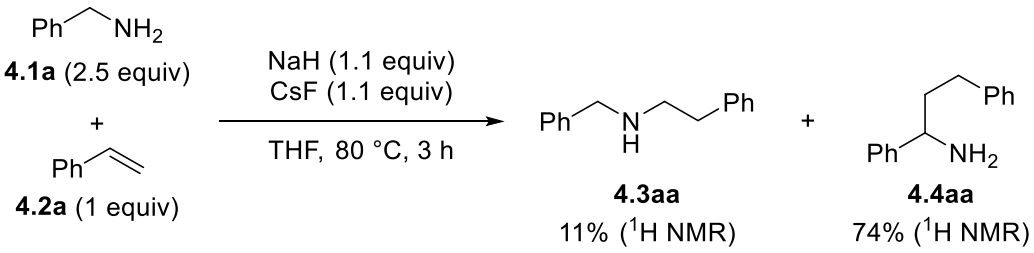
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 155.4, 142.8, 141.6, 128.8, 128.54, 128.48, 127.4, 126.5, 126.1, 79.6, 54.8, 38.7, 32.7, 28.5.

MS (HRMS ESI): Calcd for $C_{20}H_{26}NO_2$ $[M+H]^+$ 312.1964, Found: 312.1963.

IR (neat, cm^{-1}): 3364 [υ(N-H)], 1682 [υ(C=O)].

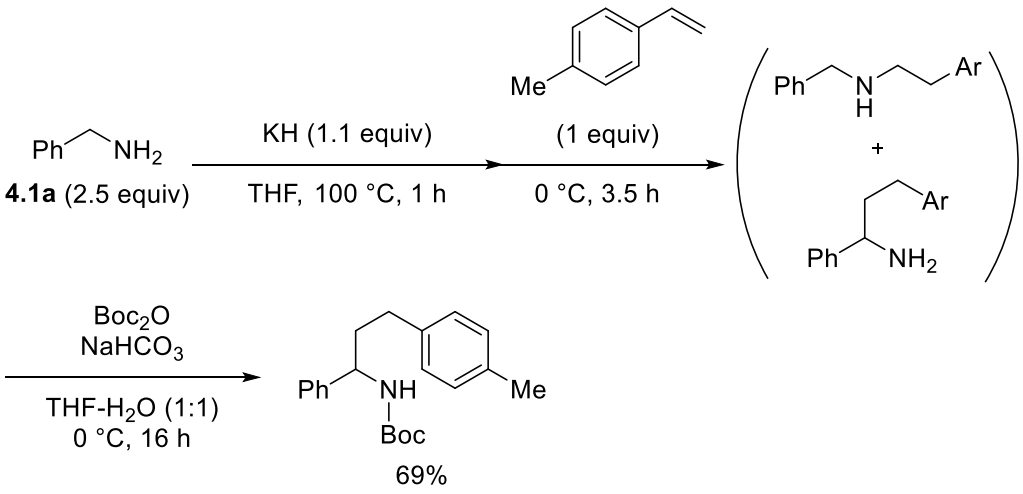
Melting point (°C): 97.4 - 98.7.

The reaction by NaH and CsF (Protocol B)



In 25 mL sealed tube containing a solution of styrene (51.4 mg, 0.494 mmol, 1 equiv) and benzylamine (134.0 mg, 1.251 mmol, 2.5 equiv) in THF (2.5 mL) was added NaH (60% in mineral oil, 22.3 mg, 0.558 mmol, 1.1 equiv) and CsF (83.4 mg, 0.549 mmol, 1.1 equiv) and the reaction mixture was stirred at 80 °C for 3 h. The reaction mixture was then quenched with water (20 mL) at 0 °C. The organic materials were extracted thrice with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The resulting crude material was purified by flash column chromatography (CH_2Cl_2: MeOH = 95:5) to give an inseparable mixture containing *N*-benzyl-2-phenylethan-1-amine (**4.3aa**) (in 11% NMR yield) and 1,3-diphenylpropan-1-amine (**4.4aa**) (in 74% NMR yield) as a pale-yellow oil (ratio of **4.3aa**/**4.4aa** = 13:87). The yields were determined via ^{1}H NMR with 1,1,2,2-tetrachloroethane (82.9 mg, 0.494 mmol) as an internal standard.

5.6.2.2. Synthesis of *tert*-butyl (1-phenyl-3-(*p*-tolyl)propyl)carbamate (4.7ab)



The 1st step was conducted using 1-methyl-4-vinylbenzene (61.1 mg, 0.517 mmol), potassium hydride (22.6 mg, 0.563 mmol) and benzylamine (**4.1a**) (137.9 mg, 1.287 mmol) at 0 ℃ for 3.5 h after addition of 1-methyl-4-vinylbenzene upon thermal incubation. Purification by flash column chromatography (silica gel, CH_2Cl_2:MeOH = 95:5) gave an inseparable mixture containing *N*-benzyl-2-(p-tolyl)ethan-1-amine (in 6% NMR yield) and 1-phenyl-3-(*p*-tolyl)propan-1-amine (in 76% NMR yield) as a light-yellow oil. The ratio of hydroamination/hydroalkylation products was 7:93. The yields were determined via ^{1}H NMR with 1,1,2,2-tetrachloroethane (79.8 mg, 0.475 mmol) as an internal standard.

The 2nd step was performed using di-*tert*-butyl dicarbonate (136 μL, 0.592 mmol, 1.40 equiv to the calculated amounts of amines) and sodium bicarbonate (50.3 mg, 0.599 mmol, 1.41 equiv to the calculated amounts of amines). Purification by flash column chromatography (EtOAc: hexane = 1:9) gave *tert*-butyl (1-phenyl-3-(*p*-tolyl)propyl)carbamate (**4.7ab**) (116.2 mg, 0.357 mmol) in 69% yield over 2 steps based on 1-methyl-4-vinylbenzene as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.35-7.31 (m, 2H), 7.27-7.23 (m, 3H), 7.08-7.03 (m, 4H), 4.82 (br, 1H), 4.66 (br, 1H), 2.65-2.49 (m, 2H), 2.31 (s, 3H), 2.06-2.04 (m, 2H), 1.42 (s, 9H).

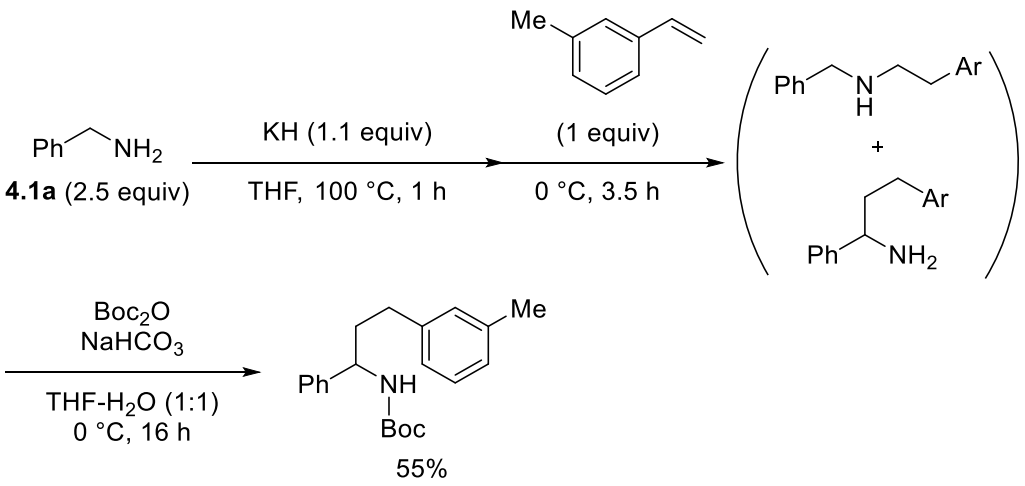
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 155.3, 142.9, 138.5, 135.5, 129.2, 128.7, 128.3, 127.3, 126.5, 79.5, 54.8, 38.8, 32.2, 28.5, 21.1.

MS (HRMS ESI): Calcd for $C_{21}H_{27}NO_2Na$ $[M+Na]^+$ 348.1939, Found: 348.1933.

IR (neat, cm^{-1}): 3375 [υ(N-H)], 1682 [υ(C=O)].

Melting point (°C): 120.0 – 121.6.

5.6.2.3. *tert*-butyl (1-phenyl-3-(*m*-tolyl)propyl)carbamate (4.7ac)



The 1st step was conducted using 1-methyl-3-vinylbenzene (60.1 mg, 0.509 mmol), potassium hydride (22.1 mg, 0.551 mmol) and benzylamine (**4.1a**) (137.5 mg, 1.283 mmol) at 0 ℃ for 3.5 h after addition of 1-methyl-3-vinylbenzene upon thermal incubation. Purification by flash column chromatography (silica gel, CH_2Cl_2:MeOH = 95:5) gave an inseparable mixture containing *N*-benzyl-2-(m-tolyl)ethan-1-amine (in 1% NMR yield) and 1-phenyl-3-(*m*-tolyl)propan-1-amine (in 63% NMR yield) as a yellow oil. The ratio of hydroamination/hydroalkylation products was 2:98. The yields were determined via ^{1}H NMR with 1,1,2,2-tetrachloroethane (81.9 mg, 0.488 mmol) as an internal standard.

The 2nd step was performed using di-*tert*-butyl dicarbonate (110 μL, 0.480 mmol, 1.47 equiv to the calculated amounts of amines) and sodium bicarbonate (40.5 mg, 0.482 mmol, 1.48 equiv to the calculated amounts of amines). Purification by flash column chromatography (EtOAc: hexane = 1:9) gave *tert*-butyl (1-phenyl-3-(*m*-tolyl)propyl)carbamate (**4.7ac**) (91.2 mg, 0.280 mmol) in 55% yield over 2 steps based on 1-methyl-3-vinylbenzene as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.35-7.32 (m, 2H), 7.28-7.23 (m, 3H), 7.17-7.13 (t, *J* = 7.4 Hz, 1H), 6.99 (d, *J* = 7.7, 1H), 6.96 (s, 1H), 6.95 (d, *J* = 8.0, 1H), 4.83 (br, 1H), 4.67 (br, 1H), 2.66-2.58 (m, 1H), 2.56-2.50 (m, 1H), 2.31 (s, 3H), 2.07-2.05 (m, 2H), 1.42 (s, 9H).

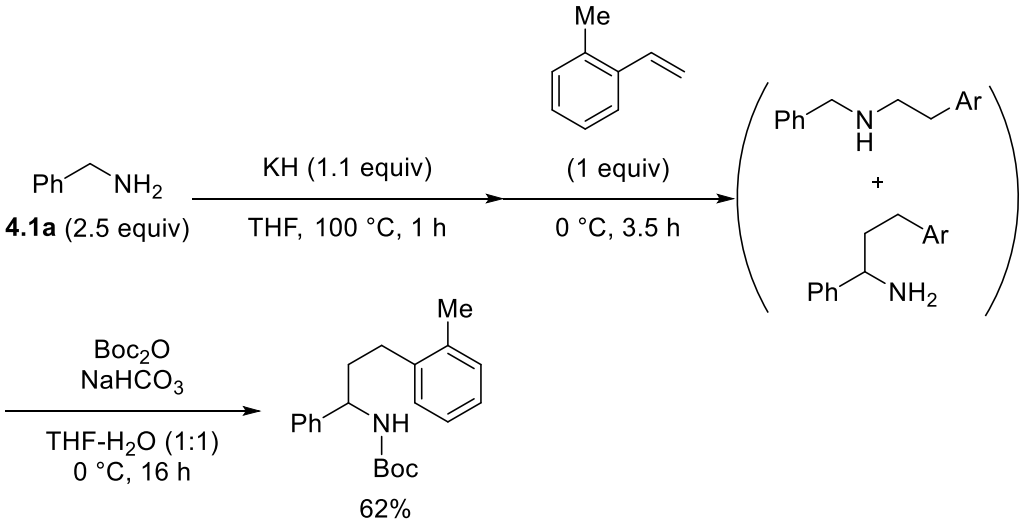
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 155.4, 142.9, 141.5, 138.1, 129.3, 128.8, 128.5, 127.4, 126.8, 126.5, 125.5, 79.6, 55.0, 38.8, 32.7, 28.5, 21.5.

MS (HRMS ESI): Calcd for $C_{21}H_{28}NO_2$ $[M+H]^+$ 326.2120, Found: 326.2122.

IR (neat, cm^{-1}): 3381 [υ(N-H)], 1683 [υ(C=O)].

Melting point (°C): 98.0 – 99.6.

5.6.2.4. *tert*-butyl (1-phenyl-3-(*o*-tolyl)propyl)carbamate (4.7ad)



The 1st step was conducted using 1-methyl-2-vinylbenzene (59.7 mg, 0.505 mmol), potassium hydride (22.1 mg, 0.551 mmol) and benzylamine (**4.1a**) (136.4 mg, 1.273 mmol) at 0 °C for 5 h after addition of 1-methyl-2-vinylbenzene upon thermal incubation. Purification by flash column chromatography (silica gel, CH_2Cl_2:MeOH = 95:5) gave an impure mixture containing 1-phenyl-3-(*o*-tolyl)propan-1-amine (in 65% NMR yield) as a yellow oil. No hydroamination

product was observed. The yields were determined via ^{1}H NMR with 1,1,2,2-tetrachloroethane (88.6 mg, 0.528 mmol) as an internal standard.

The 2nd step was performed using di-*tert*-butyl dicarbonate (113 μL, 0.492 mmol, 1.50 equiv to the calculated amounts of amine) and sodium bicarbonate (42.5 mg, 0.506 mmol, 1.54 equiv to the calculated amounts of amine). Purification by flash column chromatography (EtOAc: hexane = 1:9) gave *tert*-butyl (1-phenyl-3-(*o*-tolyl)propyl)carbamate (**4.7ad**) (101.5 mg, 0.312 mmol) in 62% yield over 2 steps based on 1-methyl-2-vinylbenzene as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.36 – 7.24 (m, 5H), 7.10 – 7.08 (m, 4H), 4.84 (br, 1H), 4.71 (br, 1H), 2.69 – 2.61 (m, 1H), 2.56 – 2.49 (m, 1H), 2.22 (s, 3H), 2.03 – 2.01 (m, 2H), 1.42 (s, 9H).

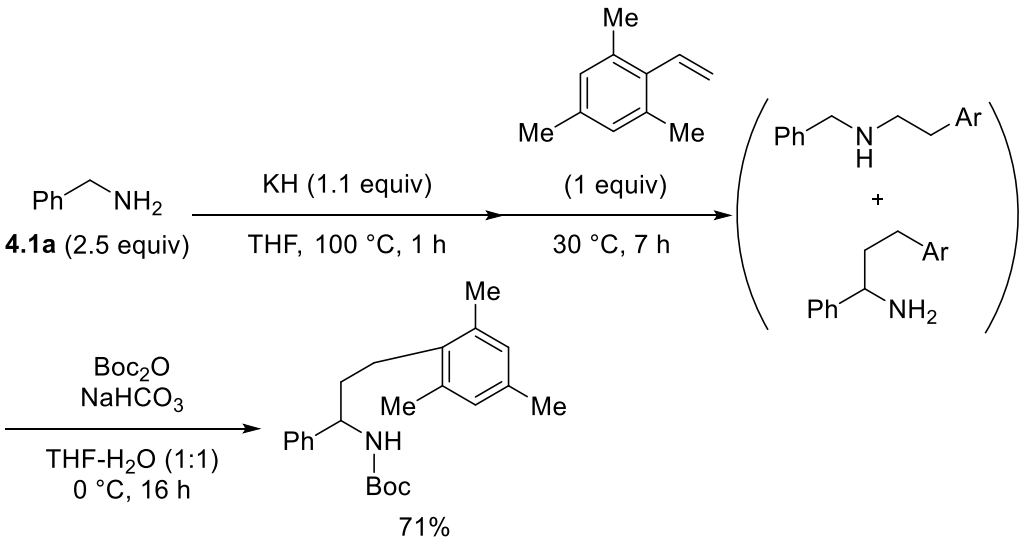
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 155.4, 142.8, 139.8, 135.9, 130.3, 128.8, 128.7, 127.4, 126.5, 126.2, 126.1, 79.6, 55.1, 37.5, 30.0, 28.5, 19.3.

MS (HRMS ESI): Calcd for $C_{21}H_{28}NO_2$ $[M+H]^+$ 326.2120, Found: 326.2116.

IR (neat, cm^{-1}): 3381 [υ(N-H)], 1683 [υ(C=O)].

Melting point (°C): 121.4 – 122.6.

5.6.2.5. *tert*-butyl (3-mesityl-1-phenylpropyl)carbamate (4.7ae)



The 1st step was conducted using 1,3,5-trimethyl-2-vinylbenzene (72.6 mg, 0.497 mmol), potassium hydride (22.3 mg, 0.556 mmol) and benzylamine (**4.1a**) (22.3 mg, 0.556 mmol) at 30 °C for 7 h after addition of 1,3,5-trimethyl-2-vinylbenzene upon thermal incubation. Purification by flash column chromatography (silica gel, CH_2Cl_2:MeOH = 95:5) gave an impure mixture containing 3-mesityl-1-phenylpropan-1-amine (in 72% NMR yield) as a yellow oil. No hydroamination product was observed. The yields were determined via ^1H NMR with 1,1,2,2-tetrachloroethane (75.9 mg, 0.452 mmol) as an internal standard.

The 2nd step was performed using di-*tert*-butyl dicarbonate (122 μL, 0.532 mmol, 1.49 equiv to the calculated amounts of amine) and sodium bicarbonate (44.5 mg, 0.530 mmol, 1.48 equiv to the calculated amounts of amine). Purification by flash column chromatography (EtOAc: hexane = 1:9) gave *tert*-butyl (3-mesityl-1-phenylpropyl)carbamate (**4.7ae**) (124.0 mg, 0.351 mmol) in 71% yield over 2 steps based on 1,3,5-trimethyl-2-vinylbenzene as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.37 – 7.24 (m, 5H), 6.79 (s, 2H), 4.84 (br, 1H), 4.71 (br, 1H), 2.61 (ddd, *J* = 12.6, 12.6, 5.4 Hz, 1H), 2.44 (ddd, *J* = 12.6, 12.6, 5.4 Hz, 1H), 2.22 (s, 3H), 2.18 (s, 6H), 1.92-1.86 (m, 2H), 1.42 (s, 9H).

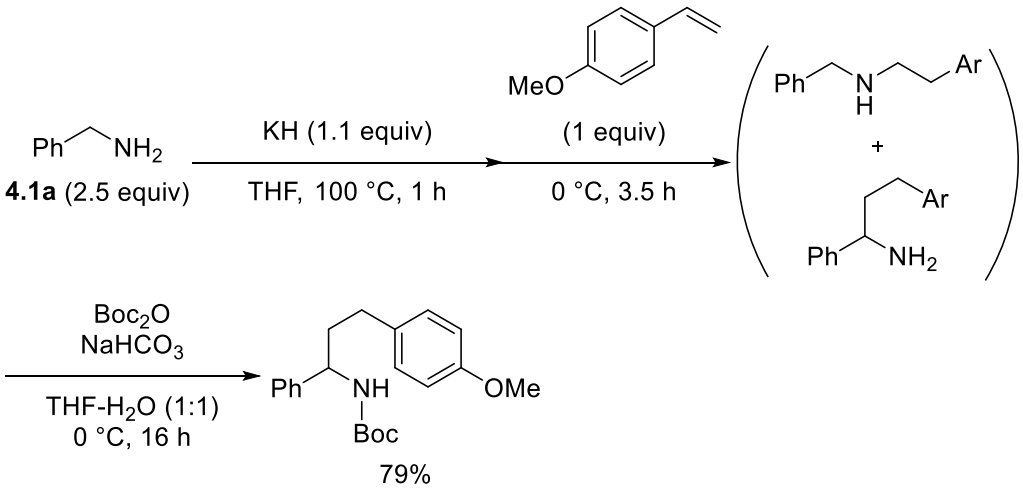
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 155.4, 142.7, 135.9, 135.4, 135.2, 129.0, 128.7, 127.5, 126.5, 79.6, 55.6, 36.2, 28.5, 26.2, 20.9, 19.7.

MS (HRMS ESI): Calcd for $C_{23}H_{32}NO_2$ $[M+H]^+$ 354.2433, Found: 354.2430.

IR (neat, cm^{-1}): 3447 [υ(N-H)], 1680 [υ(C=O)].

Melting point (°C): 153.1 – 154.7.

5.6.2.6. *tert*-butyl (3-(4-methoxyphenyl)-1-phenylpropyl)carbamate (4.7af)



The 1st step was conducted using 1-methoxy-4-vinylbenzene (67.9 mg, 0.506 mmol), potassium hydride (23.1 mg, 0.576 mmol) and benzylamine (**4.1a**) (133.7 mg, 1.248 mmol) at 0 °C for 3.5 h after addition of 1-methoxy-4-vinylbenzene upon thermal incubation. Purification by flash column chromatography (silica gel, CH_2Cl_2:MeOH = 95:5) gave an inseparable mixture containing *N*-benzyl-2-(4-methoxyphenyl)ethan-1-amine (in 4% NMR

yield) and 3-(4-methoxyphenyl)-1-phenylpropan-1-amine (in 81% NMR yield) as a light-yellow oil. The ratio of hydroamination/hydroalkylation products was 5:95. The yields were determined via ^{1}H NMR with 1,1,2,2-tetrachloroethane (84.9 mg, 0.506 mmol) as an internal standard.

The 2nd step was performed using di-*tert*-butyl dicarbonate (146 μL, 0.636 mmol, 1.48 equiv to the calculated amounts of amines) and sodium bicarbonate (54.0 mg, 0.643 mmol, 1.50 equiv to the calculated amounts of amines). Purification by flash column chromatography (EtOAc: hexane = 1:9) gave (*tert*-butyl (3-(4-methoxyphenyl)-1-phenylpropyl)carbamate) (**4.7af**) (135.2 mg, 0.396 mmol) in 79% yield over 2 steps based on 1-methoxy-4-vinylbenzene as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.35-7.31 (m, 2H), 7.27-7.23 (m, 3H), 7.06 (d, *J* = 8.6 Hz, 2H), 6.81 (d, *J* = 8.6 Hz, 2H), 4.80 (br, 1H), 4.66 (br, 1H), 3.78 (s, 3H), 2.63-2.47 (m, 2H), 2.04-2.01 (m, 2H), 1.42 (s, 9H).

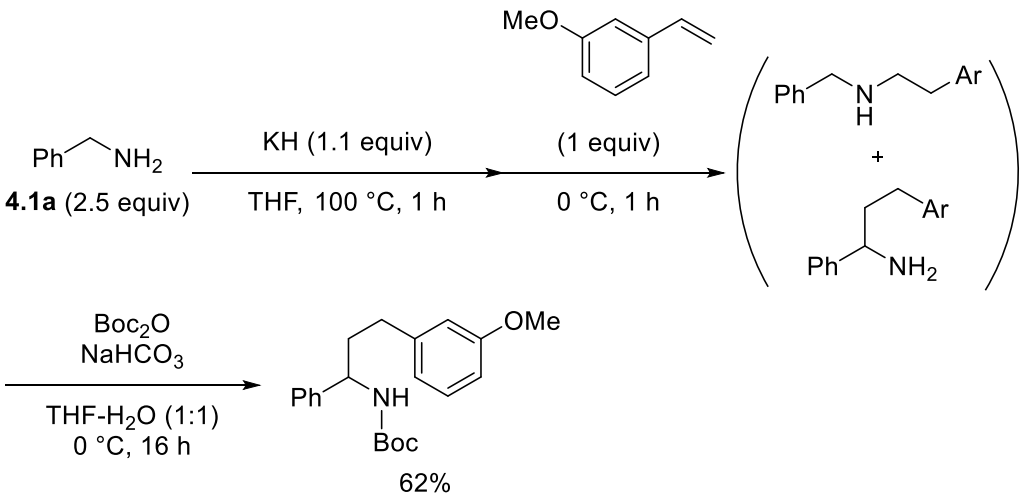
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 157.9, 155.3, 142.9, 133.5, 129.3, 128.6, 127.2, 126.4, 113.9, 79.3, 55.2, 54.6, 38.8, 31.7, 28.4.

MS (HRMS ESI): Calcd for $C_{21}H_{28}NO_3$ $[M+H]^+$ 342.2069, Found: 342.2065.

IR (neat, cm^{-1}): 3389 [υ(N-H)], 1684 [υ(C=O)].

Melting point (°C): 119.0 – 121.2.

5.6.2.7. *tert*-butyl (3-(3-methoxyphenyl)-1-phenylpropyl)carbamate (4.7ag)



The 1st step was conducted using 1-methoxy-3-vinylbenzene (67.5 mg, 0.503 mmol), potassium hydride (22.5 mg, 0.561 mmol) and benzylamine (**4.1a**) (134.9 mg, 1.259 mmol) at 0 ℃ for 1 h after addition of 1-methoxy-3-vinylbenzene upon thermal incubation. Purification by flash column chromatography (silica gel, CH_2Cl_2:MeOH = 95:5) gave an inseparable mixture containing *N*-benzyl-2-(3-methoxyphenyl)ethan-1-amine (in 7% NMR yield) and 3-(3-methoxyphenyl)-1-phenylpropan-1-amine (in 65% NMR yield) as a dark yellow oil. The ratio of hydroamination/hydroalkylation products was 10:90. The yields were determined via ^{1}H NMR with 1,1,2,2-tetrachloroethane (79.6 mg, 0.474 mmol) as an internal standard.

The 2nd step was performed using di-*tert*-butyl dicarbonate (113 μL, 0.492 mmol, 1.36 equiv to the calculated amounts of amines) and sodium bicarbonate (41.2 mg, 0.491 mmol, 1.36 equiv to the calculated amounts of amines). Purification by flash column chromatography (EtOAc: hexane = 1:9) gave *tert*-butyl (3-(3-methoxyphenyl)-1-phenylpropyl)carbamate (**4.7ag**) (106.0 mg, 0.310 mmol) in 62% yield over 2 steps based on 1-methoxy-3-vinylbenzene as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.34 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.32 (s, 1H), 7.28-7.24 (m, 3H), 7.18 (dd, *J* = 8.0, 7.7 Hz, 1H), 6.73 (dd, *J* = 8.2, 8.2 Hz, 2H), 6.71-6.70 (m, 1H), 4.81 (br, 1H), 4.68 (br, 1H), 3.78 (s, 3H), 2.67-2.51 (m, 2H), 2.08-2.02 (m, 2H), 1.42 (s, 9H).

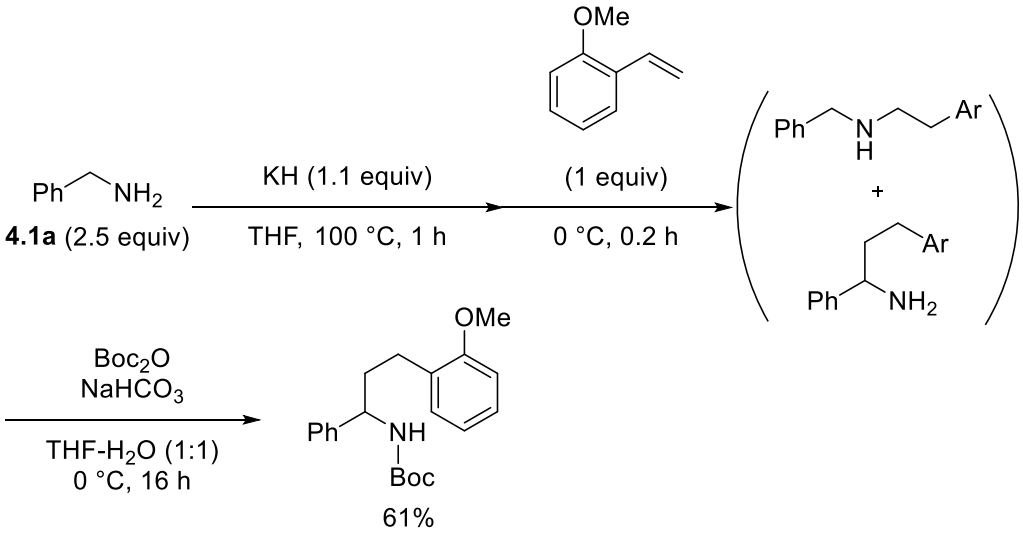
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 159.8, 155.4, 143.2, 142.8, 129.5, 128.7, 127.4, 126.5, 120.8, 114.2, 111.4, 79.5, 55.2, 54.8, 38.5, 32.7, 28.5.

MS (HRMS ESI): Calcd for $C_{21}H_{28}NO_3$ $[M+H]^+$ 342.2069, Found: 342.2064.

IR (neat, cm^{-1}): 3347 [υ(N-H)], 1697 [υ(C=O)].

Melting point (°C): 85.0 – 87.8.

5.6.2.8. *tert*-butyl (3-(2-methoxyphenyl)-1-phenylpropyl)carbamate (4.7ah)



The 1st step was conducted using 1-methoxy-2-vinylbenzene (66.4 mg, 0.495 mmol), potassium hydride (22.4 mg, 0.559 mmol) and benzylamine (**4.1a**) benzylamine (133.9 mg, 1.250 mmol) at 0 °C for 0.2 h after addition of 1-methoxy-2-vinylbenzene upon thermal incubation. Purification by flash column chromatography (silica gel, CH_2Cl_2:MeOH = 95:5) gave an inseparable mixture containing *N*-benzyl-2-(2-methoxyphenyl)ethan-1-amine (in 6%

NMR yield) and 3-(2-methoxyphenyl)-1-phenylpropan-1-amine (in 68% NMR yield) as a light-yellow oil. The ratio of hydroamination/hydroalkylation products was 8:92. The yields were determined via ^{1}H NMR with 1,1,2,2-tetrachloroethane (82.3 mg, 0.490 mmol) as an internal standard.

The 2nd step was performed using di-*tert*-butyl dicarbonate (118 μL, 0.514 mmol, 1.48 equiv to the calculated amounts of amines) and sodium bicarbonate (43.7 mg, 0.520 mmol, 1.42 equiv to the calculated amounts of amines). Purification by flash column chromatography (EtOAc: hexane = 1:9) gave *tert*-butyl (3-(2-methoxyphenyl)-1-phenylpropyl)carbamate (**4.7ah**) (103.4 mg, 0.303 mmol) in 61% yield over 2 steps based on 1-methoxy-2-vinylbenzene as a brown solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.34-7.29 (m, 3H), 7.28-7.21 (m, 2H), 7.16 (ddd, *J* = 7.8, 7.8, 1.5 Hz, 1H), 7.08 (dd, *J* = 7.3, 1.2 Hz, 1H), 7.88-6.84 (m, 1H), 6.82 (d, *J* = 8.3 Hz, 1H), 4.92 (br, 1H), 4.67 (br, 1H), 3.80 (s, 3H), 2.72-2.65 (m, 1H), 2.60-2.52 (m, 1H), 2.01-2.00 (m, 2H), 1.42 (s, 9H).

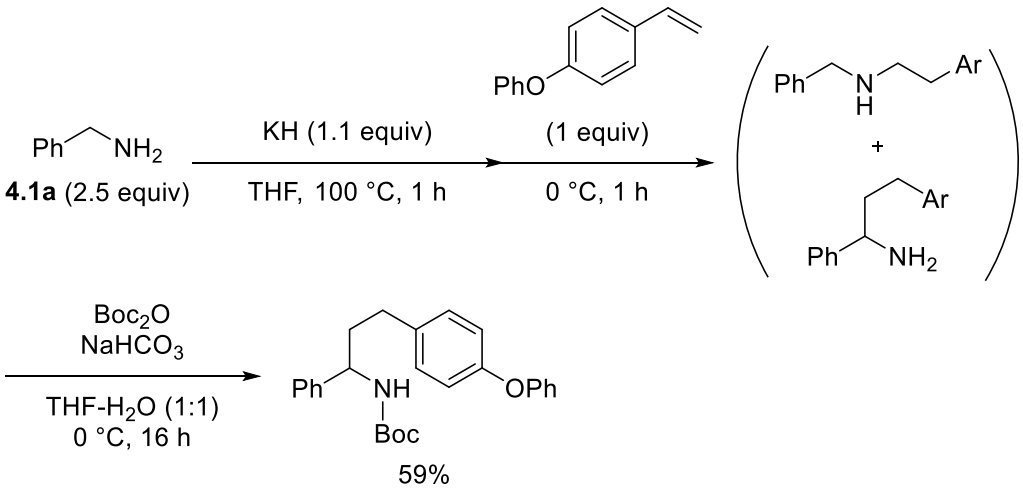
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 157.4, 155.4, 143.2, 130.1, 129.9, 128.5, 127.3, 127.1, 126.5, 120.5, 110.3, 79.3, 55.3, 55.0, 37.0, 28.5, 27.4.

MS (HRMS ESI): Calcd for $C_{21}H_{28}NO_3$ $[M+H]^+$ 342.2069, Found: 342.2061.

IR (neat, cm^{-1}): 3348 [υ(N-H)], 1697 [υ(C=O)].

Melting point (°C): 83.9 – 87.5.

5.6.2.9. *tert*-butyl (3-(4-phenoxyphenyl)-1-phenylpropyl)carbamate (4.7ai)



The 1st step was conducted using 1-phenoxy-4-vinylbenzene (98.4 mg, 0.501 mmol), potassium hydride (22.9 mg, 0.571 mmol) and benzylamine (**4.1a**) (135.5 mg, 1.265 mmol) at 0 ℃ for 1 h after addition of 1-phenoxy-4-vinylbenzene upon thermal incubation. Purification by flash column chromatography (silica gel, CH_2Cl_2:MeOH = 95:5) gave an inseparable mixture of *N*-benzyl-2-(4-phenoxyphenyl)ethan-1-amine (in 8% NMR yield) and 3-(4-phenoxyphenyl)-1-phenylpropan-1-amine (in 65% NMR yield) as a light-yellow oil. The ratio of hydroamination/hydroalkylation products was 11:89. The yields were determined via ^{1}H NMR with 1,1,2,2-tetrachloroethane (91.8 mg, 0.5469 mmol) as an internal standard.

The 2nd step was performed using di-*tert*-butyl dicarbonate (115 μL, 0.501 mmol, 1.37 equiv to the calculated amounts of amines) and sodium bicarbonate (42.3 mg, 0.504 mmol, 1.38 equiv to the calculated amounts of amines). Purification by flash column chromatography (EtOAc: hexane = 1:9) gave *tert*-butyl (3-(4-phenoxyphenyl)-1-phenylpropyl)carbamate (**4.7ai**) (121.1 mg, 0.300 mmol) in 60% yield over 2 steps based on 1-phenoxy-4-vinylbenzene as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.34-7.23 (m, 7H), 7.10 (d, *J* = 8.5 Hz, 2H), 7.06 (dd, *J* = 7.4, 7.4 Hz, 1H), 6.97 (d, *J* = 7.8, 2H), 6.91 (d, *J* = 8.4 Hz, 2H), 4.9 (d, *J* = 6.8 Hz, 1H), 4.68 (br, 1H), 2.67-2.51 (m, 2H), 2.07-2.03 (m, 2H), 1.42 (s, 9H).

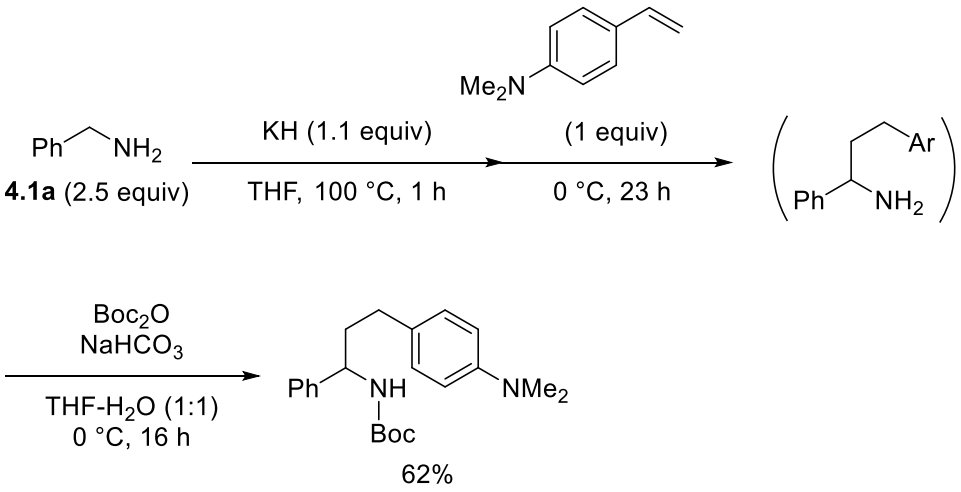
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 157.7 (overlapped), 155.3, 142.8, 136.5, 129.8, 129.7, 128.7, 127.4, 126.5, 123.0, 119.2, 118.6, 79.6, 54.7, 38.8, 31.9, 28.5.

MS (HRMS ESI): Calcd for $C_{26}H_{30}NO_3$ $[M+H]^+$ 404.2226, Found: 404.2227.

IR (neat, cm^{-1}): 3337 [υ(N-H)], 1697 [υ(C=O)].

Melting point (°C): 90.0 – 92.3.

5.6.2.10. *tert*-butyl (3-(4-(dimethylamino)phenyl)-1-phenylpropyl)carbamate (4.7aj)



The 1st step was conducted using *N*,*N*-dimethyl-4-vinylaniline (74.4 mg, 0.505 mmol), potassium hydride (22.5 mg, 0.561 mmol) and benzylamine (**4.1a**) (133.7 mg, 1.248 mmol) at 0 °C for 23 h after addition of *N*,*N*-dimethyl-4-vinylaniline upon thermal incubation. Purification by flash column chromatography (silica gel, CH_2Cl_2:MeOH = 95:5) gave an impure mixture containing 4-(3-amino-3-phenylpropyl)-*N*,*N*-dimethylaniline (in 67% NMR

yield) as a light-yellow oil. No hydroamination product was observed. The yields were determined via ^{1}H NMR with 1,1,2,2-tetrachloroethane (84.8 mg, 0.505 mmol) as an internal standard.

The 2nd step was performed using di-*tert*-butyl dicarbonate (118 μL, 0.514 mmol, 1.52 equiv to the calculated amounts of amines) and sodium bicarbonate (44.0 mg, 0.524 mmol, 1.55 equiv to the calculated amounts of amines). Purification by flash column chromatography (EtOAc: hexane = 1:9) gave *tert*-butyl (3-(4-(dimethylamino)phenyl)-1-phenylpropyl)carbamate (**4.7aj**) (111.1 mg, 0.313 mmol) in 62% yield over 2 steps based on *N*,*N*-dimethyl-4-vinylaniline as an orange solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.35-7.31 (m, 2H), 7.27-7.23 (m, 3H), 7.02 (d, *J* = 8.6 Hz, 2H), 6.68 (d, *J* = 8.6 Hz, 2H), 4.82 (br, 1H), 4.66 (br, 1H), 2.90 (s, 6H), 2.60-2.44 (m, 2H), 2.03-2.00 (m, 2H), 1.41 (s, 9H).

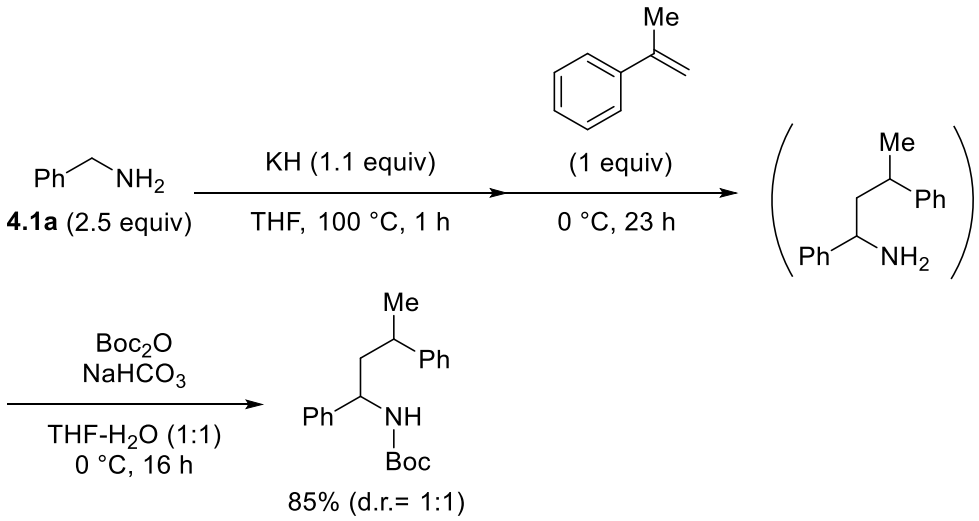
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 155.3, 149.2, 143.1, 129.7, 129.0, 128.6, 127.2, 126.5, 133.2, 79.4, 54.7, 41.0, 39.0, 31.6, 28.5.

MS (HRMS ESI): Calcd for $C_{22}H_{31}N_2O_2$ $[M+H]^+$ 355.2386, Found: 355.2389.

IR (neat, cm^{-1}): 3343 [υ(N-H)], 1697 [υ(C=O)].

Melting point (°C): 105.4 – 107.1.

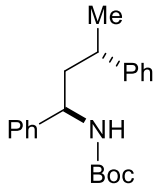
5.6.2.11. *tert*-butyl (1,3-diphenylbutyl)carbamate (4.7ak)



The 1st step was conducted using a-methylstyrene (60.0 mg, 0.508 mmol), potassium hydride (22.1 mg, 0.551 mmol) and benzylamine (**4.1a**) (133.9 mg, 1.250 mmol) at 0 ℃ for 23 h after addition of prop-1-en-2-ylbenzene upon thermal incubation. Purification by flash column chromatography (silica gel, CH_2Cl_2:MeOH = 95:5) gave an inseparable mixture containing 1,3-diphenylbutan-1-amine (in 87% NMR yield, d.r. = 1:1) as a light yellow oil. No hydroamination product was observed. The yields were determined via ^{1}H NMR with 1,1,2,2-tetrachloroethane (83.5 mg, 0.497 mmol) as an internal standard.

The 2nd step was performed using di-*tert*-butyl dicarbonate (152 μL, 0.672 mmol, 1.52 equiv to the calculated amounts of amines) and sodium bicarbonate (55.9 mg, 0.666 mmol, 1.51 equiv to the calculated amounts of amines). Purification by flash column chromatography (EtOAc: hexane = 1:9) gave *tert*-butyl (1,3-diphenylbutyl)carbamate (**4.7ak**) (139.9 mg, 0.429 mmol) as a 1:1 d.r. mixture as a colorless oil in 84% yield over 2 steps based on a-methylstyrene.

***tert*-Butyl ((1*R**,3*S**)-1,3-diphenylbutyl)carbamate[16]**



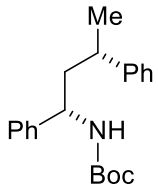
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.33-7.14 (m, 10H), 4.74 (br, 1H), 4.54 (br, 1H), 2.71 (m, 1H), 2.00 (m, 2H), 1.41 (s, 9H), 1.28 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 155.1, 146.7, 143.2, 128.6, 127.3, 127.1, 126.6, 126.34, 126.28, 79.4, 53.3, 45.8, 36.8, 28.5, 22.0.

MS (HRMS ESI): Calcd for $C_{21}H_{28}NO_2$ $[M+H]^+$ 326.2120, Found: 326.2123.

IR (neat, cm^{-1}): 3348 [υ(N-H)], 1697 [υ(C=O)].

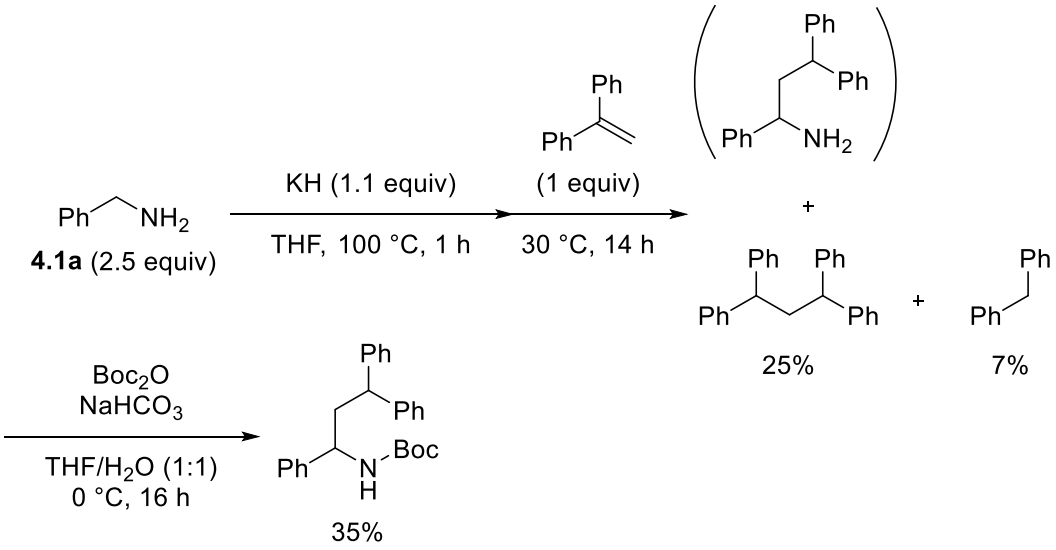
***tert*-Butyl ((1*S**,3*S**)-1,3-diphenylbutyl)carbamate**



^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.33-7.14 (m, 10H), 4.69 (br, 1H), 4.54 (br, 1H), 2.68-2.59 (m, 1H), 2.16-2.09 (m, 1H), 1.96-1.89 (m, 1H), 1.38 (s, 9H), 1.25 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 155.1, 146.7, 143.2, 128.6, 127.3, 127.1, 126.6, 126.34, 126.28, 79.4, 53.5, 45.3, 37.0, 28.5, 22.8.

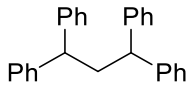
5.6.2.12. *tert*-Butyl (1,3,3-triphenylpropyl)carbamate (4.7al)



The 1st step was conducted using diphenylethylene (90.8 mg, 0.504 mmol), potassium hydride (22.5 mg, 0.561 mmol) and benzylamine (**4.1a**) (133.1 mg, 1.242 mmol) at 30 ℃ for 14 h after addition of ethene-1,1-diyldibenzene upon thermal incubation. Purification by flash column chromatography (silica gel, gradient elution from CH_2Cl_2:hexanes = 1:10 to CH_2Cl_2:MeOH = 95:5) gave 1,1,3,3-tetraphenylpropane (22.4 mg, 0.064 mmol) in 25% yield as a white solid, diphenylmethane (6.3 mg, 0.037 mmol) in 7% yield as a clear oil and an impure mixture containing 1,3,3-triphenylpropan-1-amine (in 39% NMR yield) as a dark yellow oil. No hydroamination product was observed. The yields were determined via ^{1}H NMR with 1,1,2,2-tetrachloroethane (72.1 mg, 0.430 mmol) as an internal standard.

The 2nd step was performed using di-*tert*-butyl dicarbonate (67.7 μL, 0.295 mmol, 1.50 equiv to the calculated amounts of amine) and sodium bicarbonate (25.1 mg, 0.299 mmol, 1.52 equiv to the calculated amounts of amine). Purification by flash column chromatography (EtOAc: hexane = 1:9) gave *tert*-butyl (1,3,3-triphenylpropyl)carbamate (**4.7al**) (67.9 mg, 0.175 mmol) in 35% yield over 2 steps based on ethene-1,1-diyldibenzene as a white solid.

1,1,3,3-tetraphenylpropane (4.4al'')[17]



^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.29-7.26 (m, 9 H), 7.19-7.17 (m, 11H), 3.78 (t, *J* = 7.8 Hz, 2H), 2.80 (t, *J* = 7.8 Hz, 2H).

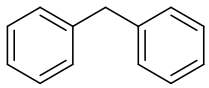
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 144.7, 128.7 128.1, 126.4, 48.8, 41.8.

MS (HRMS ESI): Calcd for $C_{27}H_{25}$ $[M+H]^+$ 349.1956, Found: 349.1954.

IR (neat, cm^{-1}): 696 [υ(C-H)].

Melting point (°C): 137.2 – 137.8.

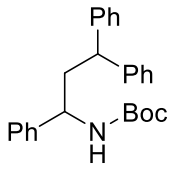
diphenylmethane (4.4al''')[18]



^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.28 (dd, *J* = 7.5, 7.5 Hz, 4H), 7.20-7.18 (m, 6H), 3.99 (s, 2H)

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 141.3, 129.1, 128.6, 126.2, 42.1.

***tert*-butyl (1,3,3-triphenylpropyl)carbamate (4.7al)**



^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.33-7.29 (m, 3H), 7.27-7.22 (m, 6H), 7.19-7.16 (m, 6H), 4.76 (br, 1H), 4.50 (br, 1H), 3.84 (br, 1H), 2.59 (br, 1H), 2.44-2.37 (m, 1H), 1.40 (s, 9H).

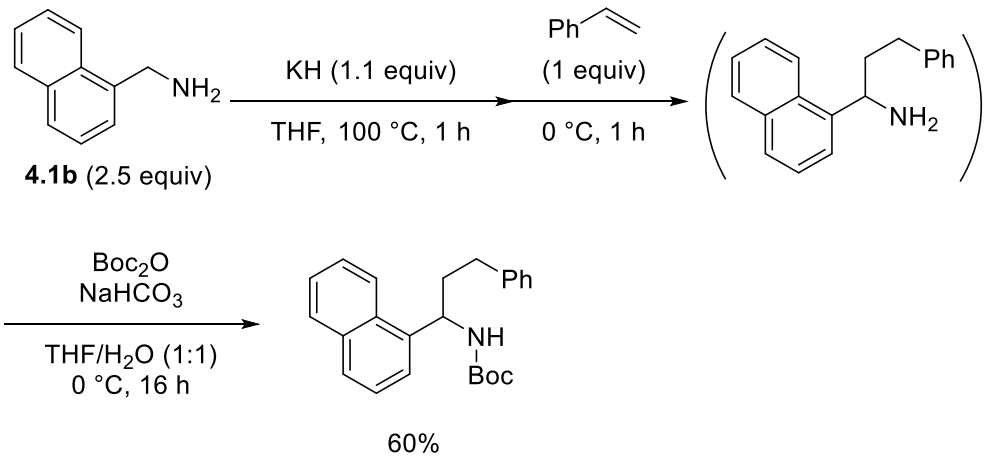
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 155.0, 144.6, 143.8, 142.8, 128.7 (overlapped), 128.7, 128.0, 127.9, 127.5, 126.6, 126.52, 126.46, 79.4, 53.5, 48.1, 42.9, 28.5.

MS (HRMS ESI): Calcd for $C_{26}H_{30}NO_2$ $[M+H]^+$ 388.2277, Found: 388.2280.

IR (neat, cm^{-1}): 3347 [υ(N-H)], 1694 [υ(C=O)].

Melting point (°C): 163.7 – 165.1.

5.6.2.13. *tert*-butyl (1-(naphthalen-1-yl)-3-phenylpropyl)carbamate (4.8ba)



The 1st step was conducted using styrene (52.5 mg, 0.504 mmol), potassium hydride (22.1 mg, 0.551 mmol) and naphthalen-1-ylmethanamine (**4.1b**) (197.0 mg, 1.253 mmol) at 0 °C for 1 h

after addition of styrene upon thermal incubation. Purification by flash column chromatography (silica gel, CH_2Cl_2:MeOH = 95:5) gave an impure mixture containing 1-(naphthalen-1-yl)-3-phenylpropan-1-amine (in 63% NMR yield) as a brown oil. No hydroamination product was observed. The yields were determined via ^{1}H NMR with 1,1,2,2-tetrachloroethane (78.8 mg, 0.469 mmol) as an internal standard.

The 2nd step was performed using di-*tert*-butyl dicarbonate (115 μL, 0.501 mmol, 1.58 equiv to the calculated amounts of amine) and sodium bicarbonate (43.0 mg, 0.512 mmol, 1.61 equiv to the calculated amounts of amine). Purification by flash column chromatography (EtOAc: hexane = 1:9) gave *tert*-butyl (1-(naphthalen-1-yl)-3-phenylpropyl)carbamate (**4.8ba**) (109.9 mg, 0.304 mmol) in 60% yield over 2 steps based on styrene as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.02 (m, 1H), 7.86-7.84 (m, 1H), 7.77-7.75 (m, 1H), 7.49-7.42 (m, 4H), 7.30-7.24 (m, 2H), 7.20-7.18 (m, 3H), 5.53 (br, 1H), 4.93 (br, 1H), 2.84-2.68 (m, 2H), 2.24-2.23 (m, 2H), 1.44 (s, 9H).

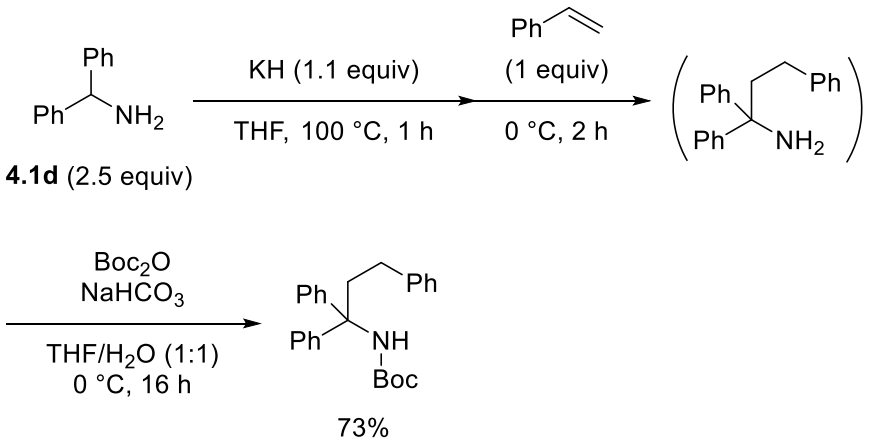
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 155.4, 141.6, 138.6, 134.1, 131.1, 128.9, 128.6, 128.5, 128.1, 126.4, 126.1, 125.8, 125.4, 123.3, 122.5, 79.6, 50.3, 38.4, 33.0, 28.5.

MS (HRMS ESI): Calcd for $C_{24}H_{28}NO_2$ $[M+H]^+$ 362.2120, Found: 362.2121.

IR (neat, cm^{-1}): 3420 [υ(N-H)], 1699 [υ(C=O)].

Melting point (°C): 120.3 – 121.9.

5.6.2.14. *tert*-butyl (1,1,3-triphenylpropyl)carbamate (4.8da)



The 1st step was conducted using styrene (53.7 mg, 0.516 mmol), potassium hydride (22.5 mg, 0.561 mmol) and diphenylmethanamine (**4.1d**) (229.1 mg, 1.250 mmol) at 0 ℃ for 2 h after addition of styrene upon thermal incubation. Purification by flash column chromatography (silica gel, CH_2Cl_2:MeOH = 95:5) gave an impure mixture containing 1,1,3-triphenylpropan-1-amine (in 82% NMR yield) as a dark yellow oil. No hydroamination product was observed. The yields were determined via ^{1}H NMR with 1,1,2,2-tetrachloroethane (73.4 mg, 0.437 mmol) as an internal standard.

The 2nd step was performed using di-*tert*-butyl dicarbonate (146 μL, 0.636 mmol, 1.50 equiv to the calculated amounts of amine) and sodium bicarbonate (54.3 mg, 0.652 mmol, 1.54 equiv to the calculated amounts of amine). Purification by flash column chromatography (EtOAc: hexane = 1:9) gave *tert*-butyl (1,1,3-triphenylpropyl)carbamate (**4.8da**) (146.1 mg, 0.377 mmol) in 73% yield over 2 steps based on styrene as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.36-7.34 (m, 4H), 7.30-7.26 (m, 4H), 7.26-7.22 (m, 2H), 7.21-7.17 (m, 2H), 7.17-7.12 (m, 3H), 5.58 (br, 1H), 2.87 (br, 2H), 2.55-2.51 (m, 2H), 1.34 (s, 9H).

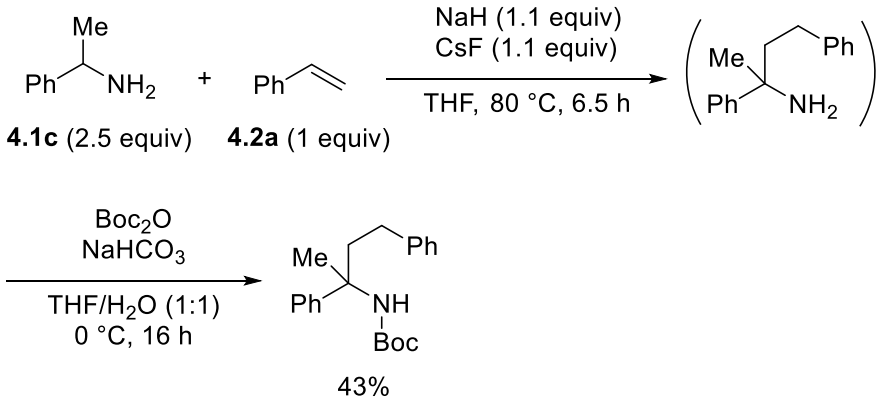
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 154.6, 145.8, 142.3, 128.6, 128.5, 128.3, 126.8, 126.5, 125.9, 79.7, 64.1, 40.3, 30.8, 28.3.

MS (HRMS ESI): Calcd for $C_{26}H_{30}NO_2$ $[M+H]^+$ 388.2277, Found: 388.2280.

IR (neat, cm^{-1}): 3343 [υ(N-H)], 1690 [υ(C=O)].

Melting point (°C): 85.3 – 86.9.

5.6.2.15. *tert*-butyl (2,4-diphenylbutan-2-yl)carbamate (4.8ca)



The 1st step was conducted using styrene (52.0 mg, 0.499 mmol), sodium hydride (21.7 mg, 0.543 mmol), cesium fluoride (83.9 mg, 0.552 mmol) and 1-phenylethan-1-amine (**4.1c**) (197.0 mg, 1.253 mmol) for 6.5 h at 80 °C. Purification by flash column chromatography (silica gel, CH_2Cl_2:MeOH = 95:5) gave an impure mixture containing 2,4-diphenylbutan-2-amine (in 45% NMR yield) as a dark yellow oil. No hydroamination product was observed. The yields were determined via ^{1}H NMR with 1,1,2,2-tetrachloroethane (78.2 mg, 0.466 mmol) as an internal standard.

The 2nd step was performed using di-*tert*-butyl dicarbonate (76.6 μL, 0.333 mmol, 1.49 equiv to the calculated amounts of amine) and sodium bicarbonate (28.7 mg, 0.342 mmol, 1.52 equiv

to the calculated amounts of amine). Purification by flash column chromatography (EtOAc: Hexanes = 1:9) gave *tert*-butyl (2,4-diphenylbutan-2-yl)carbamate (**4.8ca**) (68.4 mg, 0.212 mmol) in 43% yield over 2 steps based on styrene as a colorless oil.

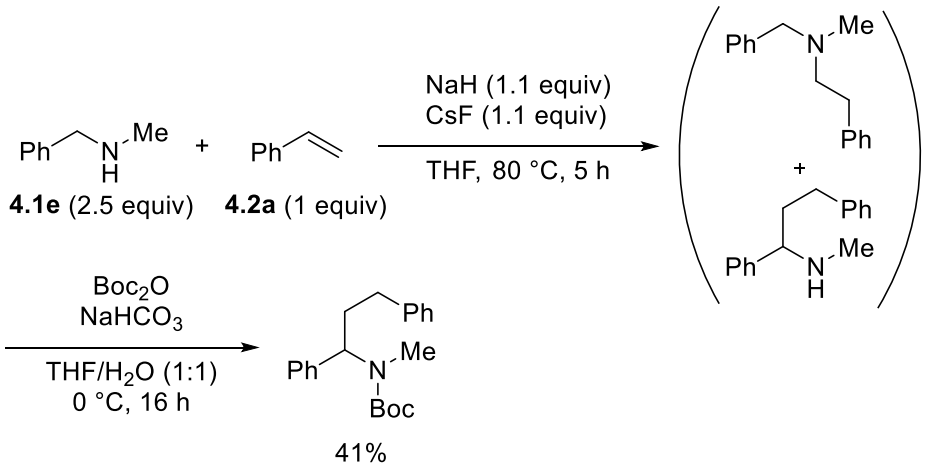
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.41-7.38 (m, 2H), 7.33 (dd, *J* = 7.7, 7.7 Hz, 2H), 7.27-7.21 (m, 3H), 7.16 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.13-7.11 (m, 2H), 4.94 (br, 1H), 2.53 (m, 1H), 2.46 (ddd, *J* = 12.5, 12.5, 4.9 Hz, 1H), 2.32 (m, 1H), 2.16 (m, 1H), 1.71 (s, 3H), 1.41 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 154.3, 146.5, 142.1, 128.54, 128.47, 128.4, 126.6, 126.0, 125.3, 79.3, 58.0, 43.8, 30.7, 28.5, 26.7.

MS (HRMS ESI): Calcd for $C_{21}H_{28}NO_2$ $[M+H]^+$ 326.2120, Found: 326.2115.

IR (neat, cm^{-1}): 3347 [υ(N-H)], 1694 [υ(C=O)].

5.6.2.16. *tert*-butyl (1,3-diphenylpropyl)(methyl)carbamate (4.8ea)



The 1st step was conducted using styrene (52.1 mg, 0.500 mmol), sodium hydride (22.9 mg, 0.560 mmol), cesium fluoride (83.6 mg, 0.550 mmol) and *N*-methyl-1-phenylmethanamine (**4.1e**) (152.0 mg, 1.254 mmol) at 80 ℃ for 5 h. Purification by flash column chromatography (silica gel, CH_2Cl_2:MeOH = 95:5) gave an impure mixture containing *N*-benzyl-*N*-methyl-2-phenylethan-1-amine[19] (in 20% NMR yield) as a yellow oil and another mixture containing *N*-methyl-1,3-diphenylpropan-1-amine (in 45% NMR yield) as a yellow oil. The ratio of hydroamination/hydroalkylation products was 31:69. The yields were determined via ^{1}H NMR with 1,1,2,2-tetrachloroethane (88.3 mg, 0.526 mmol) as an internal standard.

The 2nd step was performed for the mixture containing *N*-methyl-1,3-diphenylpropan-1-amine using di-*tert*-butyl dicarbonate (76.7 μL, 0.334 mmol, 1.48 equiv to the calculated amount of amine) and sodium bicarbonate (28.3 mg, 0.337 mmol, 1.50 equiv to the calculated amounts of amine). Purification by flash column chromatography (EtOAc: hexane = 1:9) gave *tert*-butyl (1,3-diphenylpropyl)(methyl)carbamate (**4.8ea**) (66.7 mg, 0.205 mmol) in 41% yield over 2 steps based on styrene as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.35-7.26 (m, 7H), 7.26-7.19 (m, 3H), 5.48-5.24 (m, 1H), 2.67-2.65 (m, 2H), 2.62 (s, 3H), 2.27-2.18 (m, 2H), 1.48 (s, 9H).

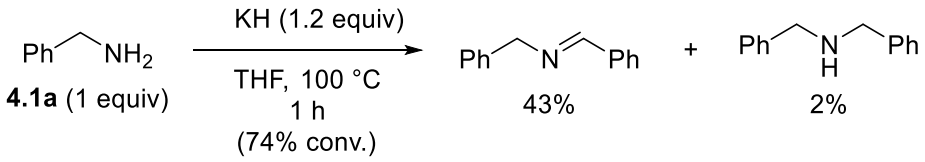
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 156.3, 141.8, 140.6, 128.6, 128.54, 127.52, 127.5, 127.4, 126.1, 79.8, 56.8, 32.9, 32.3, 28.6, 28.3.

MS (HRMS ESI): Calcd for $C_{21}H_{28}NO_2$ $[M+H]^+$ 326.2120, Found: 326.2115.

IR (neat, cm^{-1}): 1694 [υ(C=O)].

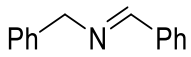
5.6.3. Mechanistic Studies

5.6.3.1. The reaction of benzylamine (4.1a) with KH



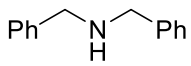
To a 25 mL sealed tube containing KH (60.3 mg, 1.50 mmol, 1.2 equiv) was added benzylamine (**4.1a**) (133.9 mg, 1.250 mmol, 1 equiv) in THF (2.0 mL) at room temperature under an Ar atmosphere. The tube was sealed, and the suspension was then stirred at 100 °C for 1 h. The reaction mixture was then cooled to 0 °C before being quenched with water (20 mL). The organic materials were extracted thrice with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The resulting crude material was analyzed by ^{1}H NMR spectroscopy, revealing that (E)-*N*-benzyl-1-phenylmethanimine (**4.9**) (in 43% NMR yield) and dibenzylamine (**4.10**) (in 2% NMR yield) were formed. The NMR yields were determined by the ^{1}H NMR spectrum with 1,1,2,2-tetrachloroethane (87.9 mg, 0.524 mmol) as an internal standard.

(E)-*N*-benzyl-1-phenylmethanimine (4.9)[20]



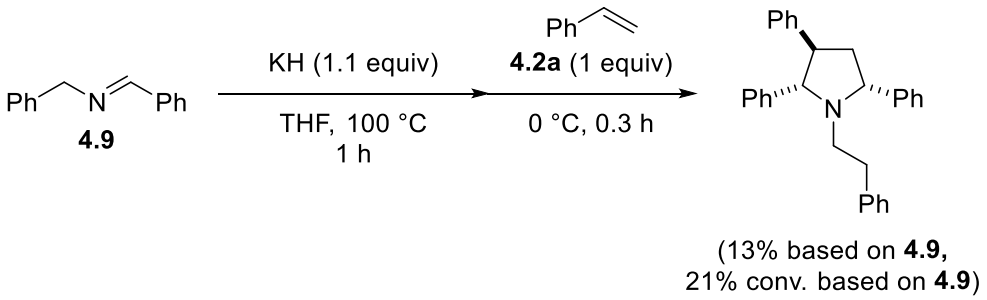
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.39 (s, 1H), 7.79-7.77 (m, 2H), 7.42-7.39 (m, 3H), 7.34-7.29 (4H), 7.26-7.22 (m, 1H), 4.82 (s, 2H).

Dibenzylamine (4.10)[20]



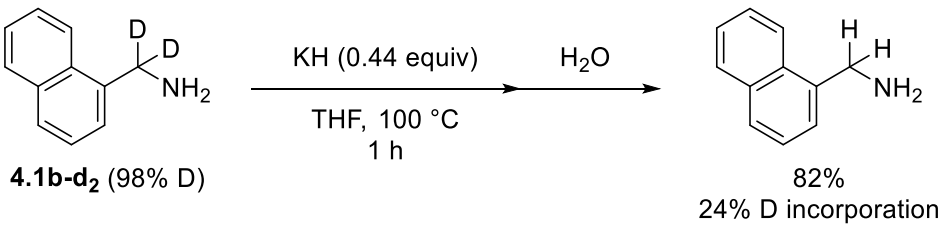
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.34-7.29 (m, 8H), 7.26-7.22 (m, 2H), 3.80 (s, 4H).

5.6.3.2. The reaction of *N*-benzylimine (4.9) with styrene (4.2a) in the presence of KH



To a 25 mL sealed tube containing KH (22.0 mg, 0.548 mmol, 1.2 equiv) was added (E)-*N*-benzyl-1-phenylmethanimine (**4.9**) (92.6 mg, 0.500 mmol, 1 equiv) in THF (2.0 mL) at room temperature under an Ar atmosphere. The tube was sealed, and the suspension was then stirred at 100 °C for 1 h. To the reaction mixture was added styrene (51.8 mg, 0.497 mmol, 1 equiv) at 0 °C with THF (0.5 mL). The reaction mixture was then stirred at 0 °C for 15 min before being quenched with water (20 mL) at 0 ℃. The organic materials were extracted thrice with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The resulting crude material was purified by flash column chromatography (CH_2Cl_2: hexane = 1:9) to give (2*R**,3*S**,5*S**)-1-phenethyl-2,3,5-triphenylpyrrolidine (**4.6**) (21%, 20.5 mg, 0.051 mmol) as a colorless oil.

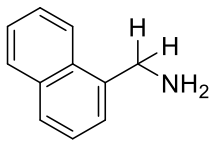
5.6.3.3. Deuterium labelling experiment



To a 25 mL sealed tube containing KH (22.5 mg, 0.561 mmol, 0.44 equiv) was added naphthalen-1-ylmethan-d_2-amine (**4.1b-d2**) (195.7 mg, 1.223 mmol, 1 equiv, 98% D) in THF

(2.0 mL) at room temperature under an Ar atmosphere. The tube was sealed, and the suspension was then stirred at 100 °C for 1 h. The reaction mixture was then cooled to 0 °C before being quenched with water (20 mL). The organic materials were extracted thrice with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The resulting crude material was analyzed by ^1H NMR spectroscopy, revealing that naphthalen-1-ylmethanamine (**29**) (in 82% NMR yield) was formed. Purification by flash column chromatography (EtOAc: hexane = 1:9) gave naphthalen-1-ylmethanamine (**4.1b**) (68%, 130.0 mg, 0.827 mmol, 24% D) as an yellow oil.

Naphthalen-1-ylmethanamine (4.1b)[21]



^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.05 (d, *J* = 8.2 Hz, 1H), 7.87 (d, *J* = 7.7 Hz, 1H), 7.76 (d, *J* = 7.4 Hz, 1H), 7.55-7.42 (m, 4H), 4.31 (s) + 4.29 (br, 2H), 1.88 (br, 2H).

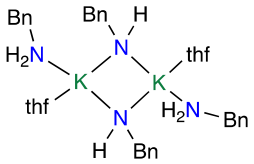
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 138.8, 133.9, 131.2, 128.8, 127.6, 126.2, 125.7, 125.6, 124.5, 123.2, 43.9 + 43.6 (*t*, *J* = 20.7 Hz).

5.7. Computational Details for Chapter 4

5.7.1. General Information

All calculations were carried with the Gaussian 16 (revision C.01) program package.[22] The molecular structures and harmonic vibrational frequencies were obtained using the M06-2X functional[23,24] and 6-31+G* basis set.[25] Geometry optimization and vibrational analysis were performed at the same level. All stationary points were optimized without any symmetry assumptions and characterized by normal coordinate analysis at the same level of theory (number of imaginary frequencies, NIMAG, 0 for minima and 1 for TSs). The thermal corrections were computed at 298.15 K and 1 atm. Connectivity of the stationary points was the "pseudo" intrinsic reaction coordinate (IRC) method,[26-29] where IRC calculations were performed for 20 to 50 steps form the TS (in both forward and backward directions) and subsequent structures were optimized to obtain the corresponding local minima.[30] Single point energies were calculated at the M06-2X/6-311++G*[31] level of theory and the self-consistent reaction field (SCRF) method based on the SMD[32] was employed to evaluate the solvent reaction field (THF; e = 7.58).

5.7.2. Cartesian Coordinates and Energies



$INT_{1\text{-}N}$
(+0.0)

at M06-2X/6-31+G*

Energy = -2970.43704780 A.U.

Thermal correction to Gibbs Free Energy = 0.7087648 A.U.

Sum of electronic and thermal Free Energies = -2969.728283 A.U.

at M06-2X/6-311++G*/SMD(THF)

Energy = -2970.96367493 A.U.

C -2.906858 1.922204 -1.147162

C -4.266046 2.219313 -0.963366

C -2.577982 0.870746 -2.005085

C -5.262596 1.487525 -1.604275

H -4.542554 3.046232 -0.306830

C -3.571485 0.136469 -2.661220

H -1.524666 0.636717 -2.151632

C -4.916834 0.437609 -2.460046

H -6.310130 1.719698 -1.427132

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H -1.931976 3.776581 -0.814840

N -0.473484 2.228464 -0.443662

H -0.114001 2.346667 -1.398128

O -1.878258 -2.562695 -0.269300

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C -2.912633 -3.278192 -0.929932

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N -3.727024 0.305323 1.812779

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C	-4.421699 -0.660941 0.966214	H	5.517199 -3.691019 0.794981
H	-4.122476 -1.667315 1.289760	H	4.555480 -2.900011 -3.316898
H	-4.034348 -0.540182 -0.054409	H	6.040213 -3.952944 -1.616764
C	-5.937302 -0.587331 0.903802	C	1.609370 -1.203202 -0.076366
C	-6.620817 -1.524481 0.120136	H	0.792302 -1.855583 -0.483868
C	-6.675718 0.393324 1.563673	H	1.542795 -0.303659 -0.722134
C	-8.004716 -1.479117 -0.007754	N	1.451057 -0.796006 1.295555
H	-6.054342 -2.290065 -0.408834	H	1.541859 -1.624800 1.890627
C	-8.066535 0.442867 1.441068	O	2.056897 4.562266 1.119501
H	-6.170242 1.139159 2.171840	C	3.058448 4.800548 0.138871
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H	-8.516118 -2.212672 -0.624726	C	2.325424 4.643175 -1.188430
H	-8.624596 1.216599 1.960879	H	3.467198 5.816551 0.254309
H	-9.816078 -0.450150 0.556608	H	3.861732 4.074390 0.299145
K	-1.161252 -0.174310 0.681367	C	0.971503 5.303777 -0.879692
C	2.888713 -1.940072 -0.491788	H	0.022822 4.468846 0.911260
C	3.738668 -2.526407 0.446941	H	0.695380 6.119950 1.147989
C	3.205547 -2.085938 -1.849999	H	2.189263 3.577737 -1.406956
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H 3.789264 0.480611 -1.011222

H 4.686939 1.848044 -0.952462

C 4.716263 0.745984 0.784664

H 3.981783 0.112781 1.305212

H 4.934739 1.597694 1.445130

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C 6.632966 -0.583337 1.711987

C 6.540740 -0.299165 -0.671076

C 7.788289 -1.345900 1.584993

H 6.206995 -0.404993 2.698215

C 7.702658 -1.062686 -0.803964

H 6.049501 0.075163 -1.565480

C 8.329856 -1.589119 0.319997

H 8.267616 -1.754363 2.470552

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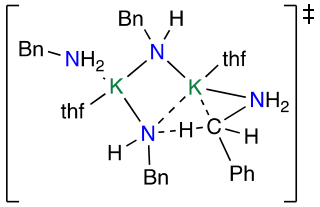
K 1.708306 1.852291 1.066356



$TS_{N\text{-}C}$
(+12.7)

at M06-2X/6-31+G*

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Thermal correction to Gibbs Free Energy = 0.7028507 A.U.

Sum of electronic and thermal Free Energies = -2969.709104 A.U.

at M06-2X/6-311++G*/SMD(THF)

Energy = -2970.93748924 A.U.

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C -5.480740 1.189561 -1.127712

H -4.548076 2.837968 -0.106603

C -4.079500 -0.017546 -2.671566

H -2.034238 0.693573 -2.823968

C -5.317593 0.158973 -2.058480

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H 2.033588 -3.316817 -2.736003
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H	3.290869	-5.445496	-2.608252
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H	1.074945	-1.493194	-1.449328
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C	2.400671	5.787037	1.071880
C	0.342099	5.222319	0.285817
C	1.912446	7.058269	0.347664
H	2.190314	5.842701	2.149736
H	3.461786	5.571094	0.931032
C	0.573709	6.619838	-0.295530
H	-0.168459	4.520241	-0.382023
H	-0.187472	5.278133	1.250116
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C	5.329471	-0.076090	2.194929
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C	7.188082	-1.437755	0.653303
H	6.406986	-0.342556	-1.014427
C	7.115871	-1.701018	2.019428
H	6.111805	-1.181995	3.858294
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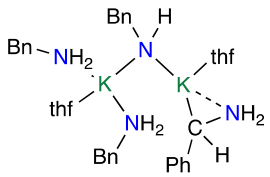

INT$_{1\text{-}C}$
(+8.6)

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Thermal correction to Gibbs Free Energy = 0.7120626 A.U.

Sum of electronic and thermal Free Energies = -2969.712722 A.U.

at M06-2X/6-311++G*/SMD(THF)

Energy = -2970.95324731 A.U.

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C -3.290056 2.571638 -0.496727

C -1.915106 1.137055 -1.838919

C -4.436518 2.005775 -1.047067

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H -2.959456 -0.208067 -3.160263

H -5.219074 0.550523 -2.435691

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H -0.825696 3.861539 -0.564304

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H -2.153478 -4.404016 1.651531

H -1.697515 -5.558479 0.394049

H -4.002354 -3.742090 0.406929

H -3.557909 -4.821741 -0.918272

N -2.647020 0.468952 2.098456

H -2.836681 0.363117 3.093564

H -2.781026 1.454421 1.871392

C -3.570078 -0.343410 1.307406

H -3.378200 -1.398080 1.544178

H -3.295965 -0.215372 0.251840

C -5.054973 -0.057395 1.442605

C	-5.951038	-0.811044	0.675076
C	-5.563832	0.943724	2.267704
C	-7.318712	-0.565978	0.723872
H	-5.564091	-1.590023	0.019042
C	-6.937580	1.193758	2.322500
H	-4.891553	1.548679	2.870944
C	-7.818549	0.443319	1.550355
H	-7.997356	-1.158975	0.117197
H	-7.315314	1.980013	2.970048
H	-8.885911	0.638845	1.590699
K	-0.309500	-0.193517	0.635937
C	1.916194	-2.264636	-1.590560
C	2.465949	-3.552625	-1.557031
C	0.861290	-2.006224	-2.467158
C	1.966259	-4.558295	-2.381027
H	3.297735	-3.756813	-0.883271
C	0.360276	-3.009450	-3.298523
H	0.432195	-1.006604	-2.504715
C	0.910728	-4.289126	-3.255699
H	2.405608	-5.551410	-2.348682
H	-0.453731	-2.787952	-3.984180
H	0.527046	-5.071022	-3.905126
C	2.464280	-1.196564	-0.676225
H	2.028840	-0.223561	-0.949370
H	3.554312	-1.128757	-0.810396
N	2.125490	-1.476208	0.731396
H	2.486476	-2.402731	0.974266
O	2.882094	5.154057	0.311891
C	3.516917	6.089910	-0.552505
C	1.487181	5.443819	0.232714
C	2.581401	6.233310	-1.769550
H	3.627766	7.047377	-0.023761
H	4.510054	5.703871	-0.791783
C	1.229714	5.677294	-1.257098
H	0.943339	4.585209	0.633698
H	1.271778	6.342429	0.830345
H	2.947486	5.652290	-2.619778
H	2.507840	7.276355	-2.088106
H	0.996832	4.718068	-1.730116
H	0.394838	6.360556	-1.431527
N	5.421997	1.084646	0.217964
H	5.195159	0.569241	-0.633098
H	6.446823	1.102944	0.245536
C	4.845550	0.409835	1.379630
H	2.717118	-0.844345	1.283148
H	4.804523	1.052813	2.262639

C 5.050345 -0.972204 1.612732

C 4.629764 -1.586301 2.838422

C 5.558458 -1.876025 0.629514

C 4.605641 -2.956858 3.007443

H 4.281656 -0.939708 3.643940

C 5.527730 -3.255739 0.814911

H 5.974621 -1.482645 -0.296001

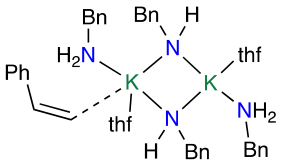
C 5.025490 -3.828317 1.985045

H 4.258432 -3.367018 3.954229

H 5.917139 -3.898393 0.025870

H 5.010634 -4.904678 2.124096

K 3.052334 2.465690 0.452784



$INT_{2\text{-}N}$
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at M06-2X/6-31+G*

Energy = -3279.97186049 A.U.

Thermal correction to Gibbs Free Energy = 0.8404295 A.U.

Sum of electronic and thermal Free Energies = -3279.131431 A.U.

at M06-2X/6-311++G*/SMD(THF)

Energy = -3280.5648582 A.U.

C 0.493622 -2.390574 1.569392

C 1.439666 -2.719120 0.593987

C -0.440164 -3.370011 1.931256

C 1.443701 -3.974773 -0.016441

H 2.190208 -1.981369 0.304821

C -0.454196 -4.619848 1.318111

H -1.170072 -3.137674 2.707157

C 0.489046 -4.927036 0.334155

H 2.194042 -4.209704 -0.768484

H -1.192766 -5.361547 1.613376

H 0.487041 -5.903340 -0.142188

C 0.390337 -0.992780 2.159987

H 1.365128 -0.492369 2.020340

H 0.285347 -1.112734 3.264432

N -0.642172 -0.180461 1.548221

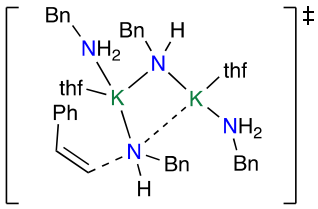
H -1.527789 -0.658671 1.755189

O 0.117356 -0.538619 -2.769305

C 0.156913 -1.965115 -2.677250

C	-1.254777	-0.105112	-2.830970
C	-1.139656	-2.339195	-1.977055
H	0.210665	-2.398603	-3.687478
H	1.058529	-2.238533	-2.122171
C	-2.117856	-1.360788	-2.640178
H	-1.406612	0.640978	-2.038074
H	-1.419291	0.385895	-3.796484
H	-1.053315	-2.139134	-0.899550
H	-1.414317	-3.387898	-2.115592
H	-3.009347	-1.164885	-2.038014
H	-2.445554	-1.754717	-3.609021
N	3.342047	1.361911	0.847856
H	3.751120	1.932080	0.107700
H	3.344025	1.926990	1.695495
C	4.130312	0.147355	1.036788
H	4.041378	-0.447486	0.118018
H	3.656205	-0.441117	1.831863
C	5.608949	0.298340	1.349974
C	6.364259	-0.860895	1.563296
C	6.255017	1.532436	1.391097
C	7.732900	-0.789476	1.798791
H	5.868586	-1.830063	1.530838
C	7.629896	1.610415	1.628151
H	5.691767	2.448429	1.229482
C	8.373766	0.451517	1.828555
H	8.302825	-1.700375	1.959357
H	8.116904	2.581223	1.654722
H	9.442568	0.511294	2.011140
K	0.870643	0.768848	-0.491393
C	-2.869109	3.173193	-1.816025
C	-3.500241	3.815305	-0.740975
C	-3.642185	2.315493	-2.603933
C	-4.842525	3.593411	-0.448527
H	-2.908812	4.506746	-0.142000
C	-4.991012	2.080376	-2.316985
H	-3.182922	1.823986	-3.458937
C	-5.594817	2.711634	-1.231647
H	-5.310691	4.109233	0.386365
H	-5.564839	1.400054	-2.941656
H	-6.641900	2.531600	-1.003187
C	-1.391894	3.424142	-2.084638
H	-1.307925	4.492161	-2.365783
H	-1.151318	2.870357	-3.025051
N	-0.575818	3.070548	-0.939916
H	0.234996	3.696758	-0.956801
O	-2.193112	2.063328	4.110357

C	-3.521064	1.531907	4.073855
C	-1.282329	1.087209	4.646556
C	-3.508471	0.319617	5.000555
H	-4.211312	2.319631	4.389741
H	-3.764947	1.236849	3.041613
C	-2.084417	-0.204671	4.793307
H	-0.447728	0.971518	3.947660
H	-0.920857	1.456016	5.614613
H	-4.282866	-0.409614	4.746566
H	-3.655177	0.634229	6.039974
H	-2.019745	-0.778212	3.861327
H	-1.726284	-0.829375	5.615645
N	-3.402887	0.498863	0.421894
H	-3.796412	0.868251	-0.444846
H	-2.507706	0.058087	0.182338
C	-4.308708	-0.501417	0.992675
H	-5.254306	0.001796	1.230199
H	-3.876486	-0.846020	1.942188
C	-4.564228	-1.692365	0.096590
C	-3.740234	-2.818158	0.167576
C	-5.563651	-1.647240	-0.880677
C	-3.902797	-3.876011	-0.725096
H	-2.944259	-2.855350	0.909917
C	-5.727143	-2.700194	-1.778799
H	-6.208932	-0.772234	-0.942843
C	-4.894504	-3.817945	-1.703541
H	-3.245299	-4.739563	-0.660108
H	-6.504911	-2.651571	-2.535942
H	-5.021287	-4.639643	-2.402665
K	-1.631029	2.376909	1.459268
C	5.420853	-1.325221	-2.069719
C	6.002405	-0.077487	-1.857970
C	5.257557	1.082152	-2.066884
C	3.922576	1.023850	-2.491958
C	3.347752	-0.241450	-2.703716
C	4.090722	-1.399891	-2.493470
H	5.995174	-2.231742	-1.902101
H	7.028614	-0.002907	-1.507680
H	5.720570	2.052990	-1.897806
H	2.319909	-0.314701	-3.049952
H	3.630973	-2.369567	-2.669418
C	3.175631	2.281560	-2.694196
H	3.750064	3.189211	-2.504584
C	1.896688	2.403733	-3.071224
H	1.438057	3.381172	-3.178139
H	1.256937	1.548880	-3.286615



$TS_{1\text{-}N}$
(+19.1)

at M06-2X/6-31+G*

Energy = -3279.95299654 A.U.

Thermal correction to Gibbs Free Energy = 0.8466555 A.U.

Sum of electronic and thermal Free Energies = -3279.106341 A.U.

at M06-2X/6-311++G*/SMD(THF)

Energy = -3280.54793555 A.U.

C -0.689971 2.896329 0.499618

C -1.680165 2.739402 -0.476567

C 0.077580 4.066974 0.469652

C -1.886516 3.703698 -1.461762

H -2.304535 1.846202 -0.468422

C -0.113812 5.033589 -0.517446

H 0.831853 4.219213 1.241740

C -1.095772 4.852840 -1.491962

H -2.665637 3.557101 -2.206407

H 0.493102 5.935875 -0.518993

H -1.251829 5.605525 -2.259456

C -0.366060 1.801729 1.498566

H -1.299842 1.264032 1.746492

H -0.077985 2.315956 2.448239

N 0.608875 0.849533 1.000105

H 1.317448 1.400774 0.503488

O 0.271507 -0.401017 -2.508746

C -0.253559 0.807175 -3.083214

C 1.660505 -0.223782 -2.211169

C 0.838924 1.861910 -2.922229

H -0.483951 0.615100 -4.140073

H -1.181473 1.069258 -2.564250

C 2.100365 0.999627 -3.007547

H 1.761982 -0.042513 -1.129538

H 2.187973 -1.143577 -2.482849

H 0.767641 2.333671 -1.933391

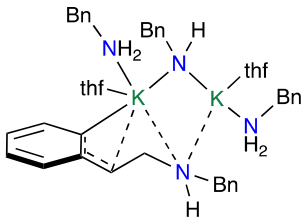
H 0.784183 2.643132 -3.685179

H 2.987548 1.481577 -2.591166

H 2.307400 0.720197 -4.047836

N	-3.326986 -0.787767 1.599016	C	5.035967 -3.581048 -1.125235
H	-3.688050 -1.664762 1.221273	H	3.502420 -3.140444 -2.569718
H	-3.379175 -0.849325 2.614093	C	5.318811 -4.025368 0.165543
C	-4.126074 0.331321 1.109029	H	4.474788 -4.740279 2.015216
H	-4.008759 0.369532 0.016704	H	5.845991 -3.317754 -1.801167
H	-3.688233 1.257129 1.503864	H	6.347250 -4.110661 0.505204
C	-5.615660 0.324806 1.404726	C	1.209178 -3.738063 -1.217821
C	-6.385518 1.408252 0.965682	H	0.959111 -4.748844 -1.606593
C	-6.254988 -0.727747 2.056797	H	1.205754 -3.084028 -2.102248
C	-7.761430 1.435074 1.165818	N	0.208696 -3.234875 -0.295466
H	-5.895128 2.231528 0.448263	H	0.036434 -3.960795 0.407230
C	-7.636816 -0.705772 2.261353	O	2.591624 -0.314437 3.793358
H	-5.680560 -1.584822 2.399662	C	3.847039 0.167096 4.260386
C	-8.394655 0.372687 1.815043	C	1.614684 0.660690 4.161269
H	-8.343237 2.282408 0.813803	C	3.776823 1.710019 4.194339
H	-8.118931 -1.537747 2.767166	H	4.005826 -0.176879 5.291933
H	-9.469380 0.388777 1.970532	H	4.622261 -0.270319 3.624635
K	-1.127799 -0.872876 -0.202037	C	2.293435 1.995872 3.874099
C	2.645126 -3.818659 -0.717331	H	0.731570 0.493526 3.540595
C	2.947968 -4.276563 0.570882	H	1.371174 0.545987 5.228827
C	3.712709 -3.477078 -1.555789	H	4.438629 2.117438 3.424706
C	4.266397 -4.376179 1.012511	H	4.075097 2.149354 5.150254
H	2.134833 -4.570836 1.233528	H	2.153217 2.222809 2.811488

H	1.880264	2.815601	4.467236
N	4.232382	-0.665398	0.316433
H	5.142677	-1.116671	0.297064
H	3.889723	-0.688951	-0.643744
C	4.306880	0.718516	0.811103
H	5.151211	0.777476	1.509382
H	3.400675	0.932735	1.394923
C	4.447888	1.780067	-0.259832
C	3.576676	2.871597	-0.285935
C	5.431678	1.680677	-1.250258
C	3.674798	3.841733	-1.283851
H	2.799327	2.953720	0.470520
C	5.539754	2.650630	-2.243895
H	6.113336	0.831798	-1.247137
C	4.657337	3.733091	-2.265528
H	2.968447	4.667323	-1.300385
H	6.308187	2.560721	-3.006522
H	4.733568	4.482140	-3.048225
K	1.831797	-1.493149	1.489779
C	-5.223718	-0.177481	-2.406133
C	-5.717169	-1.129210	-1.509363
C	-4.903880	-2.155116	-1.046360
C	-3.556313	-2.301658	-1.462840
C	-3.085137	-1.333031	-2.386778
C	-3.901426	-0.299202	-2.839898
H	-5.854634	0.631767	-2.760742
H	-6.741138	-1.057828	-1.148739
H	-5.315809	-2.887245	-0.352285
H	-2.068324	-1.404470	-2.772012
H	-3.497718	0.418362	-3.552056
C	-2.762131	-3.401923	-0.957989
H	-3.261406	-4.051599	-0.240152
C	-1.491249	-3.756619	-1.383270
H	-1.186940	-4.792950	-1.251277
H	-1.081022	-3.292210	-2.280597



INT$_{3\text{-}N}$
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at M06-2X/6-31+G*

Energy = -3279.98294280 A.U.

Thermal correction to Gibbs Free Energy = 0.8489698 A.U.

Sum of electronic and thermal Free Energies = -3279.133973 A.U.

at M06-2X/6-311++G*/SMD(THF)

Energy = -3280.58336819 A.U.

C -0.269192 2.444165 2.040598

C -1.472267 2.900593 1.488962

C 0.711517 3.394817 2.353399

C -1.685592 4.258247 1.237462

H -2.271452 2.192117 1.269313

C 0.505245 4.750618 2.112214

H 1.651196 3.055183 2.788413

C -0.695369 5.188340 1.547730

H -2.629794 4.582585 0.807807

H 1.279840 5.470276 2.365183

H -0.858073 6.245412 1.358114

C 0.029860 0.964967 2.224145

H -0.933314 0.429365 2.235490

H 0.447979 0.838534 3.248509

N 0.864309 0.410352 1.167698

H 1.682394 1.029383 1.114563

O 1.116224 1.799360 -2.476879

C 0.855668 3.199018 -2.568547

C 2.338674 1.634716 -1.742127

C 1.268528 3.736267 -1.204235

H 1.457195 3.639589 -3.378098

H -0.204384 3.326476 -2.808540

C 2.543611 2.926514 -0.922543

H 2.222912 0.743936 -1.114866

H 3.163983 1.471855 -2.448681

H 0.495990 3.506546 -0.461773

H 1.432991 4.817000 -1.195781

H 2.679583 2.721691 0.143058

H 3.431508 3.463237 -1.271443

N -2.494859 -1.410172 0.322010

H -2.739247 -1.498412 -0.673247

H -2.606073 -2.334805 0.741247

C -3.419814 -0.480000 0.977224

H -3.493424 0.420637 0.349252

H -2.983815 -0.171448 1.936011

C -4.833414 -0.969313 1.233092

C -5.667395 -0.191464 2.042948

C -5.346909 -2.136182 0.669507

C -6.986919 -0.564941 2.276920

H -5.277808 0.726752 2.479657
C -6.668852 -2.518210 0.904667
H -4.725789 -2.744951 0.016910
C -7.493589 -1.733965 1.706702
H -7.621810 0.055712 2.902962
H -7.054876 -3.426884 0.451238
H -8.523422 -2.028508 1.885998
K -0.876522 0.774505 -0.923511
C 2.314064 -2.141856 -2.919843
C 2.062462 -3.410214 -2.379369
C 3.623209 -1.651493 -2.860824
C 3.075836 -4.150100 -1.772568
H 1.066310 -3.845237 -2.452897
C 4.646118 -2.397200 -2.273441
H 3.842929 -0.675375 -3.287059
C 4.373560 -3.644129 -1.714922
H 2.854264 -5.127615 -1.353368
H 5.657685 -2.000505 -2.249756
H 5.164928 -4.219325 -1.243847
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H 1.084830 -1.730634 -4.625950
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N -0.040975 -1.341610 -2.857375
H -0.381873 -2.303833 -2.798192
O 0.411921 -3.417521 2.360674
C 1.716029 -3.930611 2.692025
C 0.027712 -2.418099 3.313742
C 2.158707 -3.190259 3.959630
H 1.637964 -5.013049 2.835381
H 2.385076 -3.713275 1.850869
C 1.337399 -1.898453 3.889600
H -0.549817 -1.650776 2.787400
H -0.604573 -2.876022 4.087065
H 3.238475 -3.021218 3.980401
H 1.887872 -3.761077 4.854907
H 1.772299 -1.180003 3.182302
H 1.208765 -1.412964 4.860569
N 3.045645 -1.509320 0.639416
H 3.184612 -1.314751 -0.354898
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C 4.306811 -1.230493 1.329996
H 5.089182 -1.869802 0.902827
H 4.190580 -1.522019 2.381277
C 4.730177 0.223882 1.259415
C 4.359273 1.126294 2.261255
C 5.456308 0.703046 0.163998

C 4.726096 2.469870 2.183338

H 3.777292 0.769936 3.110220

C 5.824027 2.044991 0.079720

H 5.746626 0.010525 -0.624755

C 5.465359 2.931252 1.094978

H 4.439297 3.156249 2.975652

H 6.397266 2.397835 -0.773527

H 5.755314 3.976376 1.035397

K 0.362093 -2.058127 0.075051

C -5.142191 2.066056 -1.371033

C -5.506186 0.714006 -1.508062

C -4.668032 -0.202243 -2.109585

C -3.364325 0.143262 -2.611372

C -3.086033 1.554293 -2.576462

C -3.935778 2.463976 -1.951225

H -5.800934 2.781173 -0.889626

H -6.461169 0.369316 -1.113639

H -4.983745 -1.242514 -2.184374

H -2.200918 1.939849 -3.082475

H -3.655003 3.516820 -1.943489

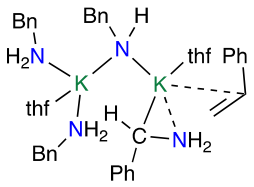
C -2.469351 -0.861816 -3.028958

H -2.902635 -1.847666 -3.210144

C -1.123434 -0.634306 -3.627437

H -1.061126 -0.979040 -4.678079

H -0.841222 0.426878 -3.650881



INT$_{2\text{-}C}$
(+10.2)

at M06-2X/6-31+G*

Energy = -3279.96184145 A.U.

Thermal correction to Gibbs Free Energy = 0.8410024 A.U.

Sum of electronic and thermal Free Energies = -3279.120839 A.U.

at M06-2X/6-311++G*/SMD(THF)

Energy = -3280.55642939 A.U.

C 1.238322 -2.928931 0.116376

C 0.996591 -3.642076 -1.067257

C 0.683471 -3.417443 1.298913

C 0.219835 -4.795497 -1.072610

H 1.431743 -3.276195 -1.998023

C -0.089796 -4.584580 1.306826
H 0.880223 -2.871785 2.220377
C -0.327961 -5.276053 0.123012
H 0.038016 -5.325820 -2.004179
H -0.501379 -4.956436 2.243293
H -0.927083 -6.182932 0.125887
C 2.104587 -1.660050 0.092336
H 1.659647 -1.010400 -0.688014
H 3.065948 -1.991330 -0.375096
N 2.234001 -0.900638 1.304433
H 2.647521 -1.515571 2.014305
O -2.610930 -1.078740 2.478560
C -4.005910 -0.934669 2.213707
C -2.465126 -2.335469 3.132274
C -4.535023 -2.351191 1.902860
H -4.496226 -0.509558 3.100876
H -4.112795 -0.233787 1.382899
C -3.390563 -3.282026 2.365541
H -1.408852 -2.613529 3.093598
H -2.773858 -2.237853 4.184423
H -4.739666 -2.478730 0.835902
H -5.464296 -2.545351 2.444727
H -2.860672 -3.701925 1.504659
H -3.740292 -4.111230 2.986247
N -1.201246 -1.204656 -1.457224
H -1.608945 -0.324806 -1.773065
H -0.806628 -1.677577 -2.268275
C -2.196240 -2.053503 -0.806886
H -2.626209 -1.463270 0.013382
H -1.670290 -2.902228 -0.352263
C -3.329009 -2.571876 -1.669200
C -3.650149 -3.931062 -1.679767
C -4.094548 -1.693710 -2.444470
C -4.717590 -4.406448 -2.443242
H -3.051427 -4.620770 -1.086933
C -5.158914 -2.163188 -3.209622
H -3.850079 -0.632224 -2.453395
C -5.474762 -3.523155 -3.209369
H -4.953435 -5.467052 -2.443098
H -5.743652 -1.469058 -3.806685
H -6.304015 -3.890395 -3.806942
K -0.425666 -0.197629 1.021884
C -3.744719 3.159599 1.319848
C -4.175667 3.953657 0.251352
C -4.365184 3.308883 2.562353
C -5.198629 4.882207 0.428759

H	-3.699073	3.844544	-0.720609
C	-5.388659	4.239299	2.743843
H	-4.044100	2.687350	3.396594
C	-5.807944	5.029212	1.675650
H	-5.520983	5.494492	-0.408893
H	-5.861942	4.341091	3.716504
H	-6.607015	5.752299	1.811366
C	-2.624392	2.155383	1.137738
H	-2.618270	1.485264	2.010143
H	-1.656829	2.674699	1.119757
N	-2.682504	1.348156	-0.088082
H	-3.656445	1.177901	-0.339136
O	5.748874	0.032721	1.780937
C	6.264550	-0.598019	2.945172
C	5.615369	-0.988763	0.781958
C	5.505784	-1.919756	3.021218
H	7.346852	-0.765729	2.829234
H	6.099740	0.071124	3.793435
C	5.397521	-2.317798	1.536436
H	4.771853	-0.720087	0.137536
H	6.531467	-1.010956	0.178696
H	4.511301	-1.746079	3.444208
H	6.017556	-2.669016	3.631032
H	4.425247	-2.757955	1.301409
H	6.171793	-3.042727	1.267886
N	1.321251	3.182123	1.165755
H	0.559229	3.381856	1.815645
H	1.613017	4.096353	0.807071
C	0.932107	2.287456	0.097175
H	-2.279320	1.882133	-0.861757
H	1.486408	1.352111	0.019948
C	0.141004	2.666392	-0.988700
C	-0.040449	1.793702	-2.121530
C	-0.570907	3.911617	-1.063789
C	-0.900205	2.100668	-3.158654
H	0.498180	0.844837	-2.129484
C	-1.419714	4.203080	-2.126716
H	-0.467996	4.633913	-0.256119
C	-1.627792	3.306435	-3.179264
H	-1.006215	1.395552	-3.982531
H	-1.941187	5.159441	-2.127301
H	-2.289839	3.548201	-4.003871
K	3.516185	1.474180	1.358033
C	4.940455	-0.639241	-2.864337
C	6.110177	0.020856	-2.493625
C	6.041811	1.285708	-1.913672

C 4.809152 1.922820 -1.715610

C 3.635987 1.252278 -2.102146

C 3.705706 -0.018247 -2.664488

H 4.987303 -1.630196 -3.306681

H 7.076407 -0.451726 -2.647450

H 6.956160 1.795136 -1.616665

H 2.667439 1.728940 -1.971687

H 2.788060 -0.525092 -2.951438

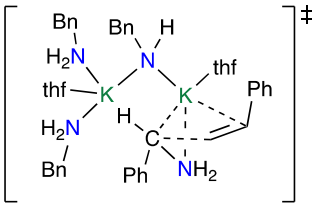
C 4.786961 3.274030 -1.121218

H 5.758051 3.647317 -0.793700

C 3.711637 4.057815 -0.971239

H 3.814040 5.044876 -0.529608

H 2.714833 3.758644 -1.292325



$TS_{1\text{-}C}$
(+14.2)

at M06-2X/6-31+G*

Energy = -3279.95347415 A.U.

Thermal correction to Gibbs Free Energy = 0.8411202 A.U.

Sum of electronic and thermal Free Energies = -3279.112354 A.U.

at M06-2X/6-311++G*/SMD(THF)

Energy = -3280.55018357 A.U.

C -2.801247 -0.896415 0.599074

C -3.886263 -0.761353 -0.280197

C -2.901805 -0.309507 1.860613

C -5.026642 -0.049526 0.079664

H -3.829702 -1.227272 -1.265772

C -4.053271 0.389486 2.238901

H -2.058768 -0.416907 2.540800

C -5.115375 0.529782 1.348871

H -5.841813 0.071354 -0.629960

H -4.121601 0.825062 3.234197

H -6.004889 1.085423 1.633285

C -1.555603 -1.699009 0.188695

H -1.249806 -1.312764 -0.806854

H -1.948769 -2.716590 -0.051310

N -0.416568 -1.671739 1.059043

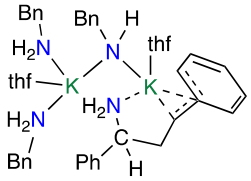
H -0.699927 -2.095280 1.950720

O	-0.682477	2.839597	2.090035
C	-0.623994	4.182748	1.615426
C	-1.521008	2.850475	3.237747
C	-1.975743	4.837020	1.986522
H	0.213741	4.700330	2.104460
H	-0.423914	4.139406	0.542197
C	-2.678817	3.764078	2.844478
H	-1.810471	1.819473	3.449598
H	-0.966242	3.256797	4.098147
H	-2.562576	5.096524	1.100903
H	-1.814419	5.757507	2.554295
H	-3.399160	3.195018	2.247350
H	-3.201108	4.183244	3.708493
N	-1.793385	1.623370	-1.419861
H	-1.492482	2.057562	-2.290987
H	-2.208549	0.722413	-1.656953
C	-2.778017	2.451391	-0.731515
H	-2.303952	3.416697	-0.514443
H	-2.982167	1.981729	0.239701
C	-4.103573	2.705641	-1.428100
C	-5.084146	3.439154	-0.749724
C	-4.397509	2.217228	-2.699536
C	-6.329272	3.672317	-1.322927
H	-4.869514	3.814528	0.250503
C	-5.646893	2.448145	-3.281140
H	-3.656111	1.639703	-3.246039
C	-6.616786	3.172976	-2.595638
H	-7.079314	4.239151	-0.778281
H	-5.859042	2.056227	-4.271938
H	-7.588926	3.350184	-3.046024
K	0.227685	0.913889	0.427211
C	4.486567	2.921078	1.056657
C	5.000585	3.786690	0.091634
C	5.329798	2.485880	2.085401
C	6.330155	4.208186	0.151311
H	4.366687	4.124355	-0.724235
C	6.656832	2.900705	2.147151
H	4.937808	1.813430	2.847437
C	7.162574	3.766783	1.176443
H	6.715078	4.880302	-0.610620
H	7.296374	2.551975	2.953195
H	8.197118	4.094078	1.221242
C	3.051838	2.419394	1.021375
H	2.617664	2.529051	2.024974
H	3.070127	1.341990	0.804134
N	2.135117	3.026783	0.064390

H	2.117599	4.037963	0.186979
O	0.306085	-4.858169	2.356812
C	-0.098863	-5.028312	3.706891
C	-0.871730	-5.013071	1.555085
C	-1.421079	-4.269198	3.804016
H	-0.239456	-6.099784	3.919394
H	0.695041	-4.640287	4.349359
C	-2.053593	-4.520220	2.418490
H	-0.736483	-4.429836	0.639304
H	-0.979462	-6.071635	1.284872
H	-1.224159	-3.202154	3.949183
H	-2.047092	-4.617581	4.629759
H	-2.500821	-3.609888	2.009493
H	-2.836185	-5.282434	2.470933
N	3.586446	-1.337357	-0.013171
H	4.011204	-0.589067	0.537708
H	4.354203	-1.770765	-0.534473
C	2.551587	-0.873195	-0.904477
H	2.449173	2.848808	-0.892033
H	1.536973	-1.179048	-0.643569
C	2.690591	0.262727	-1.732427
C	1.581126	0.744208	-2.496002
C	3.927836	0.943328	-1.934645
C	1.689677	1.843331	-3.331647
H	0.624307	0.225139	-2.408023
C	4.021316	2.038951	-2.785372
H	4.813940	0.613425	-1.396339
C	2.908410	2.523105	-3.481805
H	0.816447	2.178304	-3.888797
H	4.984430	2.532938	-2.898804
H	2.991773	3.378294	-4.144525
K	1.744244	-3.261974	0.741229
C	-1.035135	-5.914179	-1.879092
C	0.182543	-6.572268	-1.686868
C	1.382280	-5.873271	-1.758124
C	1.417371	-4.488043	-2.033603
C	0.172606	-3.832147	-2.168006
C	-1.026100	-4.538601	-2.112504
H	-1.972483	-6.460697	-1.832804
H	0.197266	-7.641209	-1.489136
H	2.323635	-6.405191	-1.632067
H	0.147841	-2.756395	-2.324962
H	-1.964215	-4.002953	-2.237287
C	2.686382	-3.783341	-2.142751
H	3.580646	-4.341862	-1.866853
C	2.803790	-2.479438	-2.545584

H 3.791532 -2.055842 -2.723617

H 1.997800 -1.980416 -3.080435



INT$_{3\text{-}c}$
(–8.4)

at M06-2X/6-31+G*

Energy = -3279.99084500 A.U.

Thermal correction to Gibbs Free Energy = 0.847215 A.U.

Sum of electronic and thermal Free Energies =

Gibbs Free Energy: -3279.143630 A.U.

at M06-2X/6-311++G*/SMD(THF)

Energy = -3280.59226022 A.U.

C 1.757504 0.952884 1.464924

C 2.929892 1.461941 0.881769

C 1.882128 0.076218 2.543794

C 4.186348 1.084518 1.344453

H 2.838938 2.164307 0.051638

C 3.143822 -0.293901 3.024308

H 0.970447 -0.296473 3.010563

C 4.298448 0.198700 2.420711

H 5.081308 1.465027 0.857683

H 3.225308 -0.963034 3.879082

H 5.279072 -0.097124 2.784508

C 0.390114 1.373521 0.912384

H 0.438610 1.189873 -0.177538

H 0.413081 2.487781 0.966930

N -0.798842 0.740757 1.423288

H -0.911248 1.007419 2.409384

O 1.511833 -3.767640 1.230262

C 2.177644 -4.805061 0.518086

C 2.104556 -3.744130 2.523516

C 3.646907 -4.773999 0.993486

H 1.704418 -5.766859 0.760101

H 2.048029 -4.611426 -0.549746

C 3.603424 -3.879063 2.254284

H 1.819018 -2.807334 3.007513

H 1.723854 -4.589742 3.116574

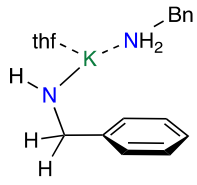
H 4.309117 -4.355584 0.230345

H 4.002759 -5.782170 1.220920

H 4.023771 -2.889315 2.047615

H	4.143382 -4.309653 3.101388	H	-5.124049 -3.277757 0.614596
N	1.992294 -0.964657 -1.357169	C	-6.453766 0.144552 1.840986
H	2.030504 -1.099032 -2.367257	H	-4.406695 0.575509 2.360238
H	1.970022 0.046495 -1.208380	C	-7.336545 -0.788575 1.292624
C	3.175774 -1.537867 -0.716985	H	-7.529257 -2.751864 0.431971
H	3.141919 -2.623757 -0.871733	H	-6.822239 1.108959 2.179327
H	3.077913 -1.379777 0.366357	H	-8.393361 -0.555066 1.203483
C	4.537878 -1.024528 -1.151475	C	-3.106155 -1.645147 1.631403
C	5.670775 -1.464935 -0.456382	H	-2.834333 -1.671977 2.694739
C	4.708359 -0.121118 -2.198242	H	-2.558930 -0.773037 1.235507
C	6.940238 -1.008560 -0.792417	N	-2.573927 -2.859233 1.010285
H	5.548854 -2.157184 0.376014	H	-2.903379 -3.691089 1.495201
C	5.981354 0.344339 -2.538583	O	-1.038813 4.389628 1.833198
H	3.848457 0.240005 -2.755417	C	-1.029596 4.089074 3.222279
C	7.099682 -0.095032 -1.837427	C	0.172388 5.096958 1.554251
H	7.806221 -1.357042 -0.236380	C	0.415914 3.696297 3.532561
H	6.091457 1.055240 -3.352436	H	-1.332247 4.981467 3.792447
H	8.088612 0.269385 -2.099120	H	-1.755296 3.289603 3.394284
K	-0.067271 -1.697031 0.475571	C	1.231415 4.549025 2.535020
C	-4.598747 -1.391642 1.512826	H	0.419695 4.925571 0.502453
C	-5.490202 -2.317531 0.970109	H	-0.000049 6.170742 1.711840
C	-5.099885 -0.157190 1.948543	H	0.567031 2.629845 3.338756
C	-6.850489 -2.019306 0.860196	H	0.681597 3.893440 4.574608

H	1.978926	3.940726	2.018068
H	1.755438	5.367814	3.035875
N	-3.675321	0.775483	-1.120508
H	-3.982387	0.156902	-0.371264
H	-4.481901	0.946294	-1.720264
C	-2.582652	0.183365	-1.896017
H	-2.894854	-2.939241	0.044308
H	-1.647626	0.366104	-1.337649
C	-2.679255	-1.312263	-2.106545
C	-1.504794	-2.038051	-2.356360
C	-3.895775	-2.002079	-2.116444
C	-1.537032	-3.413502	-2.570531
H	-0.552682	-1.505417	-2.380247
C	-3.934826	-3.380014	-2.341177
H	-4.822024	-1.465383	-1.925793
C	-2.756940	-4.094089	-2.557689
H	-0.612725	-3.956172	-2.752368
H	-4.891257	-3.896730	-2.338958
H	-2.788125	-5.166903	-2.723254
K	-1.992602	2.771670	-0.102815
C	1.761719	3.880127	-2.112639
C	0.640893	4.727958	-2.198110
C	-0.610131	4.250560	-2.534427
C	-0.865624	2.854850	-2.826782
C	0.306549	2.012576	-2.724587
C	1.555589	2.528052	-2.407816
H	2.747169	4.264285	-1.869213
H	0.759117	5.794077	-2.005916
H	-1.442612	4.949368	-2.623182
H	0.217082	0.950657	-2.953502
H	2.413208	1.854067	-2.390706
C	-2.141307	2.386971	-3.118118
H	-2.950208	3.106550	-3.228928
C	-2.457328	0.934724	-3.259281
H	-3.411206	0.783768	-3.789164
H	-1.701245	0.396596	-3.854101



INT$_{1\text{-}H}$

at M06-2X/6-31+G*

Energy = -1485.20023320 A.U.

Thermal correction to Gibbs Free Energy = 0.3476222 A.U.

Sum of electronic and thermal Free Energies =

-1484.852611 A.U.

at M06-2X/6-311++G*/SMD(THF)

Energy = -1485.46694212 A.U.

C -0.365180 2.345509 -0.318330

C -0.257858 1.372203 0.675772

C -1.514369 3.146392 -0.348841

C -1.266820 1.197796 1.624086

H 0.607546 0.719602 0.732674

C -2.518393 2.986693 0.602783

H -1.621098 3.902614 -1.124457

C -2.395128 2.012454 1.597656

H -1.150578 0.406860 2.360686

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C -2.670382 -2.593716 -0.386300

C -3.291154 -0.422624 -1.060053

C -3.243145 -1.863206 0.821279

H -3.349127 -3.372730 -0.758355

H -1.684585 -3.025815 -0.184328

C -4.135236 -0.815165 0.150712

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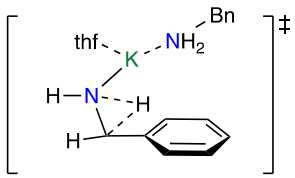

TS_H

at M06-2X/6-31+G*

Energy = -1485.11771418 A.U.

Thermal correction to Gibbs Free Energy = 0.3420842 A.U.

Sum of electronic and thermal Free Energies =

-1484.775630 A.U.

at M06-2X/6-311++G*/SMD(THF)

Energy = -1485.38343923 A.U.

C -0.446393 2.390551 -0.319403

C -0.338509 1.481094 0.736750

C -1.619338 3.144490 -0.437634

C -1.376459 1.335410 1.658849

H 0.556669 0.878047 0.873743

C -2.654295 3.006866 0.485845

H -1.720937 3.851354 -1.258993

C -2.533672 2.102746 1.542264

H -1.259876 0.622318 2.471325

H -3.555632 3.604024 0.378971

H -3.336089 1.999302 2.267522

C 0.693941 2.607684 -1.292437

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N 1.511676 1.401071 -1.474064

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H -3.331348 -3.308651 -0.862916

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C -4.099928 -0.863077 0.183292

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H 2.680106 -2.351594 -0.629415

C 4.638729 0.422004 -0.237483

H 4.486199 1.773495 1.441067

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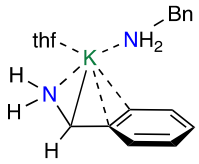

INT$_{2\text{-}H}$

at M06-2X/6-31+G*

Energy = -1485.20146172 A.U.

Thermal correction to Gibbs Free Energy = 0.3489727 A.U.

Sum of electronic and thermal Free Energies = -1484.852489 A.U.

at M06-2X/6-311++G*/SMD(THF)

Energy = -1485.47064008 A.U.

C -0.511757 2.451471 -0.332411

C -0.419168 1.539048 0.724210

C -1.684905 3.201073 -0.470436

C -1.469181 1.398755 1.633200

H 0.475924 0.936856 0.865309

C -2.733410 3.065097 0.438085
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H -1.369469 0.685676 2.448248
H -3.633833 3.660852 0.317117
H -3.435674 2.068226 2.216544
C 0.646044 2.678266 -1.282408
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H 0.246751 2.980791 -2.256638
N 1.458269 1.471339 -1.474633
H 2.132247 1.636758 -2.220082
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C -3.221618 -0.561392 -0.908429
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H -3.250153 -3.392868 -0.940355
H -1.497553 -3.282206 -0.615027
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H -2.635686 0.355480 -0.771996
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H -1.882176 -1.730581 1.251355
H -3.192317 -2.920628 1.492033
H -3.871321 -0.290410 1.166922
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N 0.856947 -2.925413 0.779649
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K 0.285576 -1.050496 -1.242731

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Chapter 6: Conclusion and Summary of the thesis.

In summary, this thesis showcased the use of readily available alkali metal hydrides in the presence of additives for the deprotonative metalations of less acidic N-H bonds of aliphatic amines. The generated metal amide anions are capable of C-3 nucleophilic aminations onto methoxypyridines due to its unusual concerted nucleophilic aromatic substitution mechanism (Chapter 2). Furthermore, Chichibabin amination using alkylamines onto various substituted pyridines was also achieved. The significantly milder conditions allowed for a wider scope and higher yields as compared to the typically harsh conditions reported previously (Chapter 3). On the other hand, the use of more reactive potassium hydrides allowed for a direct deprotonation of benzylamines, and the presence of the potassium cation influenced the selectivity of the reaction towards hydroalkylation over hydroamination of styrenes. (Chapter 4).

Future works can include elucidating the active species via X-ray crystallography or NMR experiments to characterize the active benzylic anionic species mentioned in Chapter 4. Reaction kinetic studies can also be designed to determine exactly how much faster the hydroalkylation pathway is over the hydroamination pathway in the reaction. The order of the reactions with regards to reagents used, especially the benzylamine as 2 equiv was required, would give insights to the intermediates involved in the reaction. The scalability of the reactions can also be expanded for Chapter 3 and Chapter 4 as these protocols might be of interest to medical chemists for the synthesis of pharmaceutically relevant molecules containing aminopyridines of 1,3-diarylpropylamines. One of the potential shortcomings of these completed projects is the use of sealed tubes as the reaction vessel for the reactions. However, this can simply be overcome via simple optimization as demonstrated in the large-scale protocol of the Chichibabin amination.

While this thesis has mainly explored the use of sodium hydride-iodide composite as a strong Brønsted base for nucleophilic substitutions or additions, it will be interesting to see if the use of potassium hydride composite, which is a much stronger base due to its lower lattice energies, will be an even stronger base. Potential π-cation effect of the potassium cation, being able to lower the LUMO of arenes such as benzene, might allow for facile deprotonation of benzenes to generate phenyl potassium.

The use of alkali metal hydrides holds considerable potential for further exploitation in chemistry. Furthermore, its high natural abundance and significantly lower atom economy as compared to other alkali metal bases makes it ideal as an alternative reagent for the metalation of organic molecules. Moreover, as the thesis has demonstrated, the ease of use of alkali metal hydrides for the synthesis of biologically active aminopyridines and 1,3-diarylpropylamines in a transition metal free protocol can be of interest to the pharmaceutical industry.