(*On the Spine*)

TITLE OF RESEARCH

YIN PENG

2011

NANYANG TECHNOLOGICAL UNIVERSITY

PART I: INTERMOLECULAR HYDROAMINATION BETWEEN NONACTIVATED ALKENES AND ANILINE CATALYZED BY LANTHANIDE SALTS IN IONIC SOLVENTS
PART II: NHC-Pd COMPLEX CATALYZED ALLYLIC AMINATION USING AMMONIA FOR THE SYNTHESIS OF PRIMARY AMINES

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SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

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PART I

INTERMOLECULAR HYDROAMINATION BETWEEN NONACTIVATED ALKENES AND ANILINE CATALYZED BY LANTHANIDE SALTS IN IONIC SOLVENTS

PART II

NHC-PD COMPLEX CATALYZED ALLYLIC AMINATION USING AMMONIA FOR THE SYNTHESIS OF PRIMARY AMINES

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School of Physical and Mathematical Sciences

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

2011

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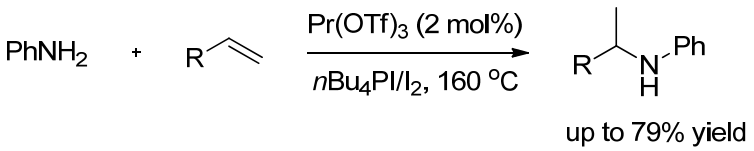
SUMMARY

This thesis comprises two main parts. Part I: Lanthanide salts-mediated intermolecular hydroamination and iodine-catalyzed intramolecular hydroamination. Part II: Allylic amination with ammonia for the synthesis of primary amines catalyzed by $Pd(PPh_3)_4$/SIPr·HCl and (SIPr)Pd(allyl)Cl/PPh_3.

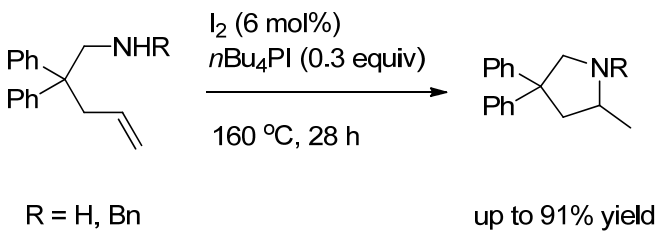
I. INTERMOLECULAR HYDROAMINATION BETWEEN NONACTIVATED ALKENES AND ANILINE

An efficient methodology for intermolecular hydroamination of unactivated alkenes and anilines catalyzed by lanthanide salts was developed. The Markovnikov products were obtained in moderate to good yields.



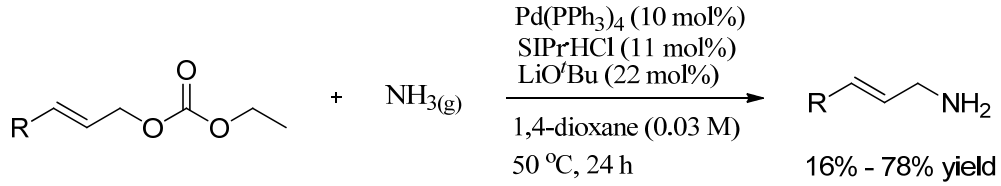
II. INTRAMOLECULAR HYDROAMINATION OF NONACTIVATED ALKENES WITH PRIMARY AND SECONDARY AMINES

A novel metal-free method for the cyclizations from secondary alkylamines and primary amines to the unactivated olefins was developed in good yields (up to 91% yield).



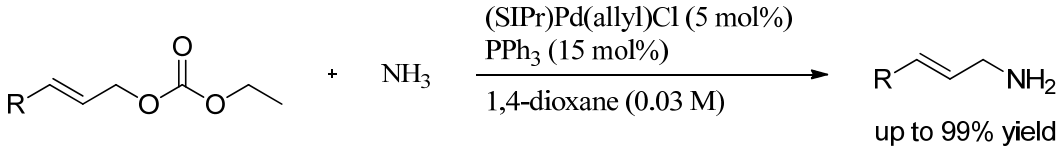
III. ALLYLIC AMINATION WITH AMMONIA GAS MEDIATED BY PD(PPH$_3$)$_4$ AND SIPR·HCL

Pd-NHC complex mediated allylic amination with ammonia gas was found to proceed effectively. The choice of the solvent and the base are crucial for this transformation. Primary amines were selectively obtained in moderate to good yields without formation of secondary amines.



IV. ALLYLIC AMINATION WITH AMMONIA SOLUTION AND AMMONIA GAS MEDIATED BY (SIPR)PD(ALLYL)CL AND PPH$_3$

A new method for the allylic amination with both ammonia solution and ammonia gas were developed. For the ammonia solution, reactions were conducted at room temperature for 12 h. Primary amines were selectively obtained with moderate to good yields.



INDEX OF ABBREVIATIONS

δ	chemical shift
Δ	reflux
ºC	degree centrigrade
ABq	AB quartet
Ac	acetyl
acac	acetoacetonate
Ar	Aryl
AcCl	acetyl chloride
AcOH	acetic acid
Ac_2O	acetic anhydride
Al_2O_3	Aluminium oxide
aq.	aqueous
Bn	benzyl
bs	broad singlet
BuLi	butyl lithium
C	Carbon
Cacld	calculated
Cat.	catalytic
$CDCl_3$	deuterated chloroform
CDC	Cross-Dehydrogenative Coupling
Cp	cyclopentadienyl
CH_4	Methane
CH_2Cl_2	dichoromethane
$CHCl_3$	chloroform
CCl_4	Carbon tetrachloride
cm^{-1}	inverse centimeter
COD	cyclooctadiene
CuBr	copper bromide
CuH	copper hydride
d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane

DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
dd	doublets of doublet
de	diastereomeric excess
DCE	dichloroethane
DIBAL-H	diisobutylaluminum hydride
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
dppf	diphenylphosphino ferrocenyl
dq	doublets of quartet
dt	doublets of triplet
ee	enantiomeric excess
equiv.	equivalent
EI	electron impact ionization
Et	ethyl
ether	diethyl ether
Et_3N	triethylamine
EtOAc	ethyl acetate
EtOH	ethanol
FG	Functional group
FTIR	Fourier transform infrared spectroscopy
g	gram
Gly	glycine
h	hour
H	hydrogen
Hex	hexane
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectroscopy
Hz	Hertz
IR	infrared
i-Pr	isopropyl

J	coupling constants
kg	kilogram
LDA	lithium diisopropylamide
M	concentration (mol/dm^{-3})
M^+	parent ion peak (mass spectrum)
m	multiplet
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MeCN	acetonitrile
MeOH	methanol
mg	milligram
MHz	Megahertz
min	minute
mmol	millimoles
mol	moles
MS	mass spectrum
Ms	methanesulfonyl
M	concentration (normality)
NaOAc	Sodium Acetate
NCS	*N*-chlorosuccinimide
NBS	*N*-bromosuccinimide
NIS	*N*-Iodosuccinimide
n-Bu	*n*-butyl
nmr	nuclear magnetic resonance
N.R.	no reaction
OTf	trifluoromethanesulfonate
Pt	Platinum
Pd	Pladium
$Pd(PPh_3)_4$	tetrakis(triphenylphosphine)palladium(0)
Pd / C	palladium on carbon
Ph	phenyl
PMP	*p*-methoxyphenyl
PNBA	4-nitrobenzoic acid
ppm	parts per million

Py	pyridine
q	quartet
rt.	room temperature
R_f	retention factor
s	singlet
t	triplet
t-Bu	*tert*-butyl
t-BuOLi	lithium *tert*-butyloxide
td	triplets of doublet
TFA	trifluoroacetic acid
TfOH	triflate acid
Tf_2O	triflate anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N*',*N*'-tetramethylethylenediamine
TON	turnover number
Ts	*p*-toluenesulfonyl
T.S.	transition state
vol	volume

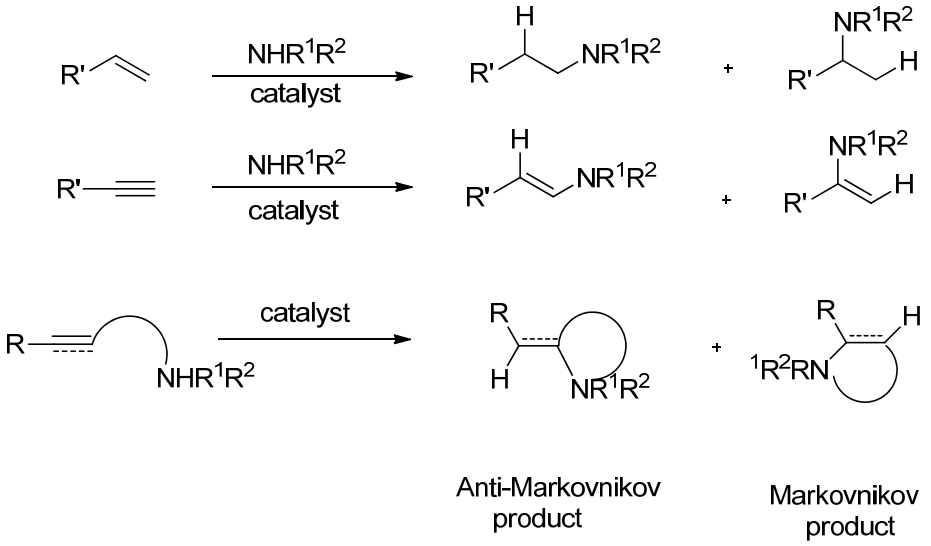
PART I

CHAPTER 1

Intermolecular Hydroamination between Nonactivated Alkenes and Aniline Catalyzed by Lanthanide Salts in Ionic Solvents

1.1 OVERVIEW OF THE BACKGROUND

Amines are a valuable and commercially important class of compounds used for bulk chemicals and pharmaceuticals. There are many methods for the synthesis of amines, including the reductive amination of ketone and aldehyde, reduction of nitro-compounds and nucleophilic substitution of organic halides. Hydroamination is one of the most efficient method (Scheme 1).[1]



Scheme 1 General reaction of hydroamintion.

Alkenes and alkynes are cheap and easily accessible, while the hydroamination reaction is slightly exothermic or thermoneutral approximately.[2] However, there is a high acitivation barrier due to the electrostatic repulsion between the lone pair of elections on the nitrogen atom and the electron rich π-bond of the alkenes and alkynes. The [2 + 2] cycloaddition of N-H across the carbon-carbon multiple bond is orbital-forbidden under thermal conditions.[3] It is impossible to

[1] Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675.
[2] (a) Taube, R. *Appl. Homogeneous Catal. Organomet. Compd.* **1996**, *1*, 507. (b) Johns, A. M.; Sakai, N.; Ridder, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 9306.
[3] Trost, B. M.; Tang, W. *J. Am. Chem. Soc.* **2002**, *124*, 14542.

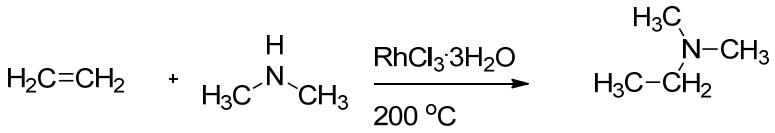
perform the hydroamination reaction simply by employing high temperature. Hydroamination reactions are always catalyzed by acids, bases or metal catalysts. The hydroamination of alkenes is more difficult than that of alkynes because of the lower reactivity and electron density of the carbon-carbon double bonds.[4] Therefore, the anti-Markovnikov addition of amines to olefins was listed as one of the "Ten Challenges for Catalysis".[4]

Extensive efforts have been devoted to develop new methods for hydroamination since the 1990s. The Markovnikov hydroamintion of protected amines with alkynes is a well-established strategy, described in many reviews covering various aspects of the hydroamination.[5] In comparison, intramolecular hydroamination is easier than intermolecular hydroamination. Though there has been much progress in this field in the last decade, especially for intramolecular hydroamination, the intermolecular hydroamination of unactivated alkenes is still an important challenge in organic synthesis. In addition, some studies of intermolecular hydroamination are limited to activated amines with alkenes or aniline derivatives with vinyl arenes,[6] 1,3-dienes,[7] and strained bicyclic alkenes.[8] Up to 2009, before our work was published, there had been no report on the hydroamination of aniline with unactivated alkenes. The followings are some examples of intermolecular

[4] Haggin, J. *Chem. Eng. News* **1993**, *71*, 23.
[5] (a) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675. (b) Seayad, J.; Tillack, A.; Hartung, C. G.; Beller, M. *Adv. Synth. Catal.* **2002**, *344*, 795. (c) Pohlki, F.; Doye, S. *Chem. Soc. Rev.* **2003**, *32*, 104. (d) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079. (e) Hultzsch, K. C. *Adv. Synth. Catal.* **2005**, *347*, 367. (f) Brunet, J.-J.; Chu, N.-C.; Rodriguez-Zubiri, M. *Eur. J. Inorg. Chem.* **2007**, 4711. (g) Muller Thomas, E.; Hultzsch Kai, C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795. (h) Doye, S. *Sci. Synth.* **2009**, *40a*, 241. (i) Reznichenko, A. L.; Hultzsch, K. C. *Chiral Amine Synth.* **2010**, 341. (j) Hesp, K. D.; Stradiotto, M. *ChemCatChem* **2010**, *2*, 1192. (k) Reznichenko, A. L.; Hultzsch, K. C. *Sci. Synth., Stereosel. Synth.* **2011**, *1*, 689.
[6] (a) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 9546. (b) Utsunomiya, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 14286. (c) Hu, A.; Ogasawara, M.; Sakamoto, T.; Okada, A.; Nakajima, K.; Takahashi, T.; Lin, W. *Adv. Synth. Catal.* **2006**, *348*, 2051.
[7] Loeber, O.; Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 4366.
[8] (a) Dorta, R.; Egli, P.; Zuercher, F.; Togni, A. *J. Am. Chem. Soc.* **1997**, *119*, 10857. (b) Zhou, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 12220.

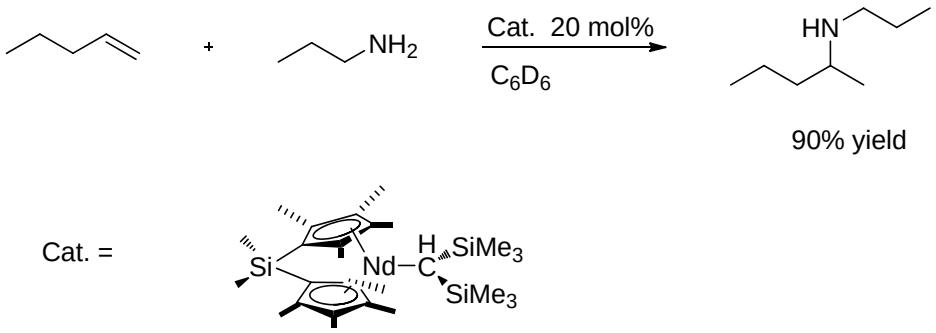
hydroamination using unactivated alkenes and brief review of asymmetric intermolecular hydroamination.

In 1971, Coulson reported the intermolecular hydroamination of ethylene with different secondary amines (Scheme 2).[9] This reaction required high temperature, and only dimethylamine and piperidine gave good results. Primary amines and ammonia were unreactive.



Scheme 2 Intermolecular hydroamintion of ethylene with amines reported by Coulson.

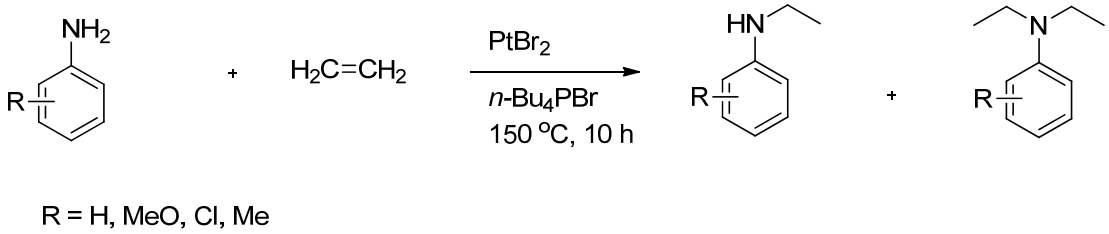
Lanthanide catalysts have been well-developed and proved to be useful catalysts for the intramolecular hydroamination. Marks and co-workers used Me_2-$SiCp_2NdCH(SiMe_3)_2$ as a precatalyst to catalyze the intermolecular hydroamination of 1-pentene with 1-propylamine in high yield (Scheme 3).[10] However, this was the only example of the intermolecular hydroamination of unactivated alkenes with alkylamines in their report.



Scheme 3 Intermolecular hydroamintion of 1-pentene with 1-propylamine reported by Marks and co-workers.

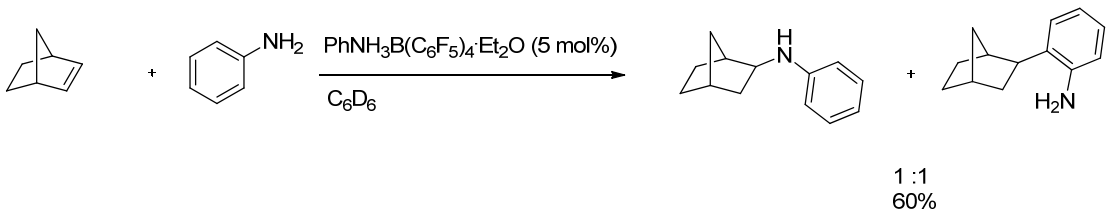
[9] Coulson, D. R. *Tetrahedron Lett.* **1971**, *12*, 429.
[10] (a) Li, Y.; Marks, T. J. *Organometallics* **1996**, *15*, 3770. (b) Ryu, J.-S.; Li, G. Y.; Marks, T. J. *J. Am. Chem. Soc.* **2003**, *125*, 12584.

Brunet and co-workers first used $PtBr_2$ to catalyze the intermolecular hydroamination of aniline derivatives with ethylene in 2004 (Scheme 4).[11] Tertiary amines were obtained as side products. For all reactions, the yields were rather low (< 35%), though the use of protic acid could increase the yields.



Scheme 4 Intermolecular hydroamintion of ethylene with aniline and aniline derivatives reported by Brunet and co-workers.

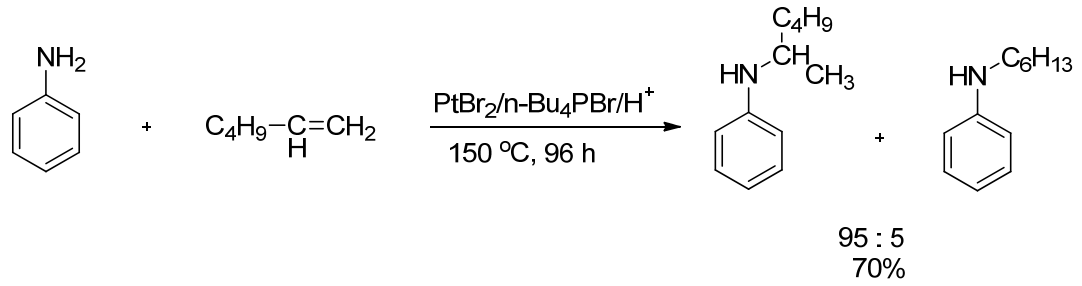
In 2005, Bergman and co-workers first reported the proton-catalyzed hydroamination and hydroarylation reactions of anilines with alkenes (Scheme 5).[12] Both hydroamination and hydroarylation products were obtained in a 1:1 ratio at 60% yield. They also found that the acid counteranion exerted a dramatic effect on the reaction efficiency. No reaction took place in the presence of an acid scavenger. For cyclopentene, only the hydroarylation product was obtained.



Scheme 5 Proton catalyzed hydroamintion and hydroarylation of alkenes with aniline reported by Bergman and co-workers.

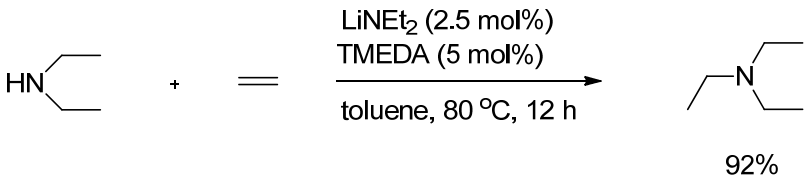
[11] Brunet, J.-J.; Cadena, M.; Chu, N. C.; Diallo, O.; Jacob, K.; Mothes, E. *Organometallics* **2004**, *23*, 1264.
[12] Anderson, L. L.; Arnold, J.; Bergman, R. G. *J. Am. Chem. Soc.* **2005**, *127*, 14542.

In 2005, Brunet and co-workers further studied the [$PtBr_2$-*n*-Bu_4PBr-H^+] catalytic system for the intermolecular hydroamination of aniline with alkenes (Scheme 6).[13] For 1-hexene, after stirring at 150 °C for 96 h, 70% yield with 95% Markovnikov regioselectivity was achieved.



Scheme 6 $PtBr_2$ catalyzed hydroamintion of alkenes with aniline reported by Brunet and co-workers.

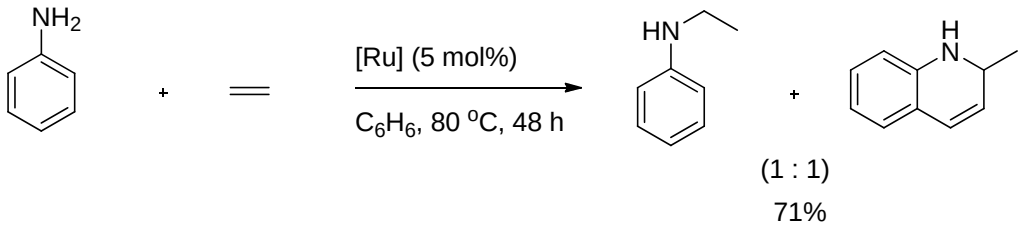
Besides acid catalysis, Beller and co-workers reported the base-catalyzed hydroamination of ethylene with diethylamine in 2005 (Scheme 7).[14] After screening solvents and ligands, toluene was found to be the best solvent and *N*, *N*, *N'*, *N'*-tetramethylethylenediamine (TMEDA) as the best ligand with 92% yield and 99% conversion. In addition, base-catalyzed hydroamination of olefins with longer chains is also possible at higher temperature.



Scheme 7 Base-catalyzed hydroamintion of ethylene with diethylamine reported by Beller and co-workers.

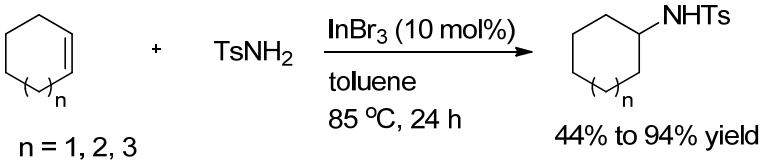
[13] Brunet, J. J.; Chu, N. C.; Diallo, O. *Organometallics* **2005**, *24*, 3104.
[14] Khedkar, V.; Tillack, A.; Benisch, C.; Melder, J.-P.; Beller, M. *J. Mol. Catal. A: Chem.* **2005**, *241*, 175.

In 2005, Yi and co-worker used ruthenium catalyst for the intermolecular hydroamination of arylamines with ethylene and 1,3-dienes (Scheme 8).[15] Using $[(PCy_3)_2(CO)(Cl)Ru=CH-CH=C(CH_3)_2]^+BF_4^-$ [Ru] as catalyst, a 1:1 mixture of *N*-ethylaniline and 2-methylquinoline was obtained in 71% combined yield. Noticeably, only ethylene was suitable for this catalytic system to give the coupling products among selected alkenes; no reaction was observed with alkyl-substitued alkenes and styrene.



Scheme 7 Ruthenium catalyzed hydroamintion of ethylene with aniline reported by Yi and co-worker.

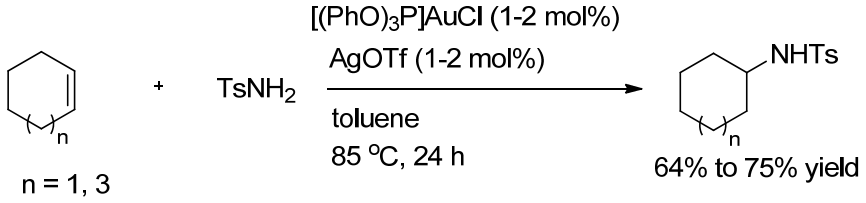
In 2007, our group reported the intermolecular hydroamination of unactivated alkenes with $TsNH_2$ catalyzed by $InBr_3$ (Scheme 8).[16] After screening different indium catalysts, $InBr_3$ was found to be the best. Moderate to good yields were obtained.



Scheme 8 $InBr_3$ catalyzed hydroamintion of unactivated alkenes with $TsNH_2$ reported by our group.

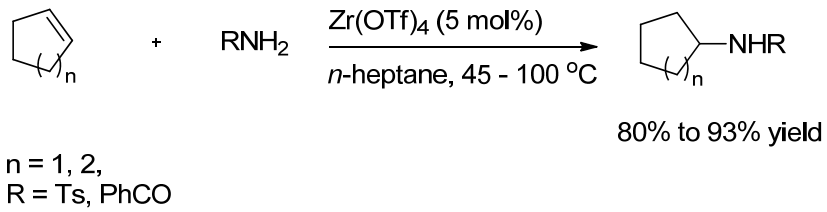
[15] Yi, C. S.; Yun, S. Y. *Org. Lett.* **2005**, *7*, 2181.
[16] Huang, J.-M.; Wong, C.-M.; Xu, F.-X.; Loh, T.-P. *Tetrahedron Lett.* **2007**, *48*, 3375.

In 2008, Najera and co-worker used a gold catalyst to perform the intermolecular hydroamination of non-activated alkenes with $TsNH_2$ (Scheme 9).[17] After screening different gold catalysts, the combination of $[(PhO)_3P]AuCl$ with AgOTf was found to show the best catalytic ability. The reaction could be performed with low catalyst loading in toluene as the solvent under conventional thermal or microwave conditions and at room temperature in the case of dienes.



Scheme 9 Gold catalyzed hydroamintion of unactivated alkenes with $TsNH_2$ reported by Najera and co-worker.

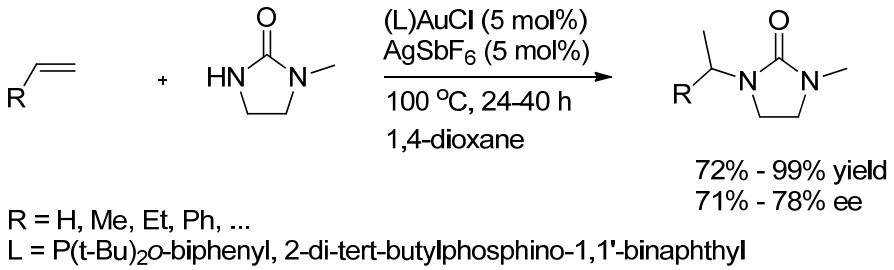
Xu and co-workers reported zirconium-catalyzed intermolecular hydroamination of unactivated olefins in 2009 (Scheme 10).[18] Their screening study revealed that $Zr(OTf)_4$ and *n*-heptane were the best catalyst and solvent, respectively. Only sulfonamides, carboxamides, and carbamates were effective for this transformation.



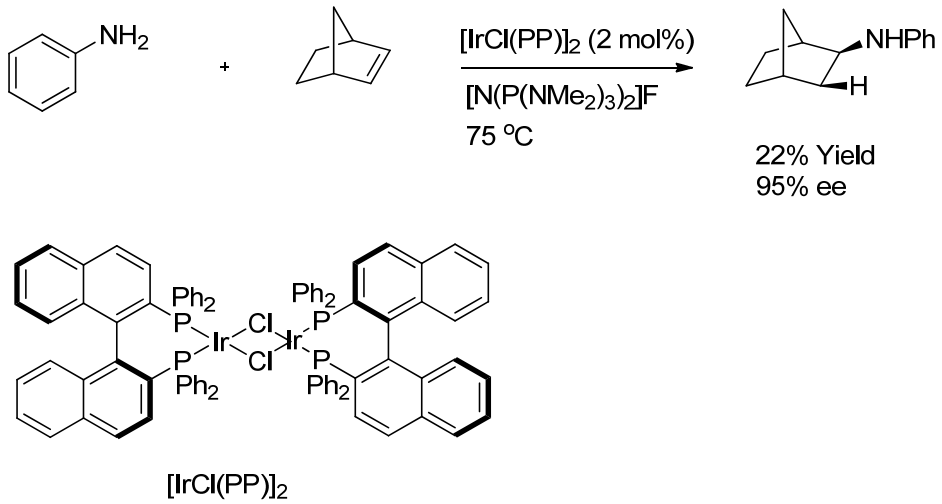
Scheme 10 $Zr(OTf)_4$ catalyzed hydroamintion of unactivated alkenes with activated amines reported by Xu and co-workers.

[17] Giner, X.; Najera, C. *Org. Lett.* **2008**, *10*, 2919.
[18] Yang, L.; Xu, L.-W.; Zhou, W.; Gao, Y.-H.; Sun, W.; Xia, C.-G. *Synlett* **2009**, 1167.

Meanwhile, Widenhoefer and co-workers used a gold catalyst and $AgSbF_6$ to catalyze the intermolecular hydroamination of ethylene and 1-alkenes with cyclic ureas (Scheme 11).[19] The silver salt is crucial to this reaction, as a poor result was obtained for the hydroamination of 1-octene in the absence of AgOTf. Chiral phoshine ligand was used to perform asymmetric hydroamination in good yields with 71-78% *ee*. However, the substrate scope was limited since activated amines such as urea had to be used.



Scheme 11 Intermolecular hydroamintion of unactivated alkenes with cyclic urea catalyzed by gold catalyst and $AgSbF_6$ reported by Widenhoefer and co-workers.

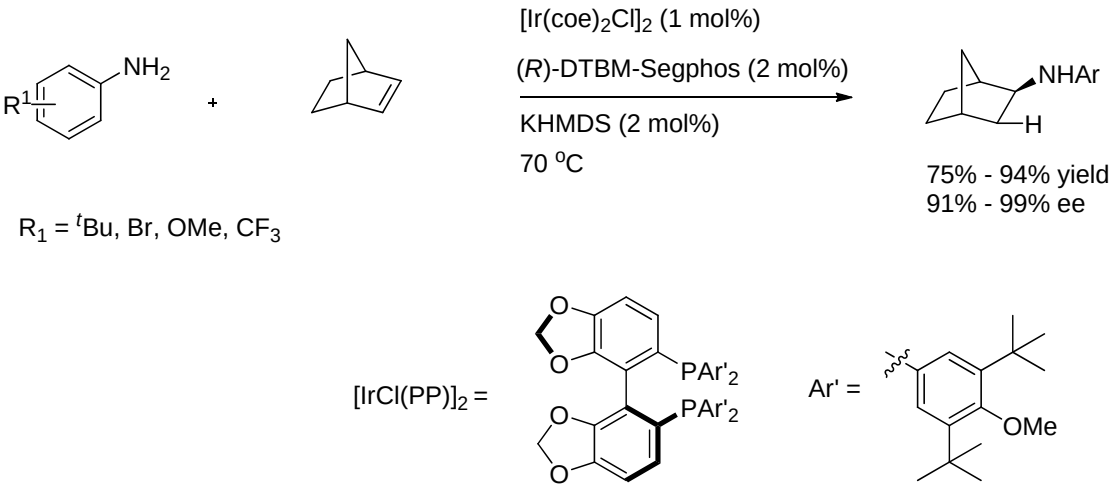


Scheme 12 Asymmetric hydroamination of aniline with norbornene reported by Togni and co-workers.

[19] Zhang, Z.; Lee, S. D.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2009**, *131*, 5372.

Asymmetric intermolecular hydroamination of olefins with amines is a long-standing goal in organic chemistry. Togni and co-workers first reported the asymmetric intermolecular hydroamination of aniline with norbornene catalyzed by iridium catalyst (Scheme 12).[21] The fluoride anion was required for high yields and enantioselectivity. However, the reaction occured in either high yield or high enantioselectivity, but not both.

In 2008, Hartwig and co-worker improved the iridium-catalyzed hydroamination to provide high yields and enantioselectivities for a wider scope of bicyclic alkenes (Scheme 13).[22] After screening different chiral phosphine ligands, (*R*)-DTBM-Segphos was found to give the best yields and enantioselectivities for various arylamines. However, no reaction with alkylamines was reported.

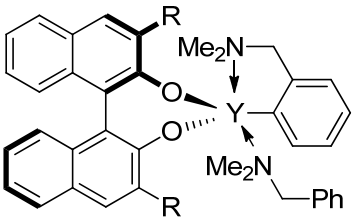


Scheme 13 Asymmetric hydroamination of aniline with norbornene reported by Hartwig and co-worker.

Until recently, Hultzsch and co-workers have explored binaphtholate yttrium complex (Figure 1), which they have earlier used to catalyze asymmetric

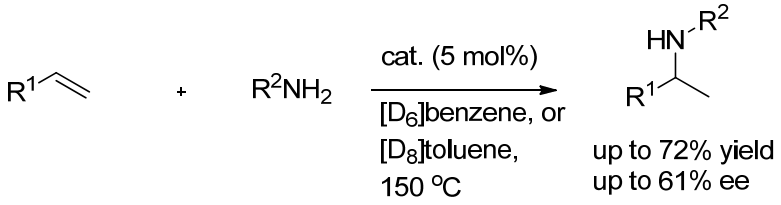
[21] Dorta, R.; Egli, P.; Zuercher, F.; Togni, A. *J. Am. Chem. Soc.* **1997**, *119*, 10857.
[22] Zhou, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 12220.

intramolecular hydroaminations, [23] to catalyze asymmetric intermolecular hydroamination at 150 ºC with high yields for the Markovnikov products (Scheme 14).[24] Though only moderate enantioselectivities were obtained. Catalysts with (*R*)-configuration yielded products with (*R*)-configuration exclusively. However, the substrate scope was limited, only a few amines were reported.



R = $SiPh_3$

Figure 1 The structure of the catalyst reported by Hultzsch and co-workers.



R^1 = alkyl, cycloalkyl;

R^2 = benzyl, cyclopentyl, 4-methoxybenzyl

Scheme 14 Asymmetric intermolecular hydroamination of unactivated alkenes with simple amines reported by Hultzsch and co-workers.

[23] (a) Gribkov, D. V.; Hultzsch, K. C.; Hampel, F. *J. Am. Chem. Soc.* **2006**, *128*, 3748. (b) Reznichenko, A. L.; Hampel, F.; Hultzsch, K. C. *Chem.--Eur. J.* **2009**, *15*, 12819. (c) Gribkov, D. V.; Hultzsch, K. C. *Chem. Commun.* **2004**, 730. (d) Gribkov, D. V.; Hampel, F.; Hultzsch, K. C. *Eur. J. Inorg. Chem.* **2004**, 4091.

[24] Reznichenko, A. L.; Nguyen, H. N.; Hultzsch, K. C. *Angew. Chem., Int. Ed.* **2010**, *49*, 8984.

1.2 INTERMOLECULAR HYDROAMINATION BETWEEN NONACTIVATED ALKENES AND ANILINE CATALYZED BY LANTHANIDE SALTS IN IONIC SOLVENTS

The development of novel catalyst systems for hydroamination has seen great progress in the last two decades. Much success has been accomplished in this area, especially in the intramolecular and intermolecular hydroamination of activated alkenes or/and activated amines.[25] The catalytic intermolecular hydroamination of non-activated alkenes with unactivated amines is still a challenging task.[26] Brunet has reported a successful intermolecular hydroamination of unactivated alkenes with aniline catalyzed by $PtBr_2$ in *n*-Bu_4PBr in the presence of strong acid.[31] Despite significant progress in the development of intermolecular hydroamination reactions, addition of more basic amines such as aniline to non-activated alkenes using cheaper metal complexes under milder reaction conditions continues to pose significant challenges to synthetic chemists.[32] Marks has done a lot of work about intramolecular

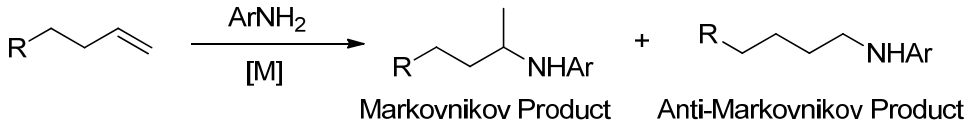
[25] For selected examples, see: (a) Liu, Z.; Yamamichi, H.; Madrahimov, S. T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 2772. (b) Manna, K.; Xu, S.; Sadow, A. D. *Angew. Chem., Int. Ed.* **2011**, *50*, 1865. (c) Neukom, J. D.; Perch, N. S.; Wolfe, J. P. *J. Am. Chem. Soc.* **2010**, *132*, 6276. (d) Le Roux, E.; Liang, Y.; Storz, M. P.; Anwander, R. *J. Am. Chem. Soc.* **2010**, *132*, 16368. (e) Hesp, K. D.; Tobisch, S.; Stradiotto, M. *J. Am. Chem. Soc.* **2010**, *132*, 413. (f) Shen, X.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2010**, *49*, 564. (g) Crimmin, M. R.; Arrowsmith, M.; Barrett, A. G. M.; Casely, I. J.; Hill, M. S.; Procopiou, P. A. *J. Am. Chem. Soc.* **2009**, *131*, 9670. (h) Hamann, T.; Boehler, E.; Swiderek, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 4643. (i) Hesp, K. D.; Stradiotto, M. *Org. Lett.* **2009**, *11*, 1449. (j) Tsuhako, A.; Oikawa, D.; Sakai, K.; Okamoto, S. *Tetrahedron Lett.* **2008**, *49*, 6529. (k) Liu, Z.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 1570. (l) Cho, J.; Hollis, T. K.; Helgert, T. R.; Valente, E. J. *Chem. Commun.* **2008**, 5001. (m) Carney, J. M.; Donoghue, P. J.; Wuest, W. M.; Wiest, O.; Helquist, P. *Org. Lett.* **2008**, *10*, 3903. (n) Komeyama, K.; Morimoto, T.; Takaki, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 2938. (o) Qin, H.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 1611. (p) Zhang, J.; Yang, C. G.; He, C. *J. Am. Chem. Soc.* **2006**, *128*, 1798. (q) Brouwer, C.; He, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1744. (r) Karshtedt, D.; Bell, A. T.; Tilley, T. D. *J. Am. Chem. Soc.* **2005**, *127*, 12640.

[26] (a) Zhao, J.; Marks, T. J. *Organometallics* **2006**, *25*, 4763. (b) Brunet, J.-J.; Chu, N. C.; Diallo, O. *Organometallics* **2005**, *24*, 3104.

[31] (a) Brunet, J. J.; Cadena, M.; Chu, N. C.; Diallo, O.; Jacob, K.; Mothes, E. *Organometallics* **2004**, *23*, 1264. (b) ref 13

[32] McBee, J. L.; Bell, A. T.; Tilley, T. D. *J. Am. Chem. Soc.* **2008**, *130*, 16562.

hydroamination using lanthanide catalyst.[33] Inspired by his work, we reported an efficient method for the catalytic intermolecular hydroamination of unactivated alkenes and aniline using $Pr(OTf)_3$ as catalyst (Scheme 15).

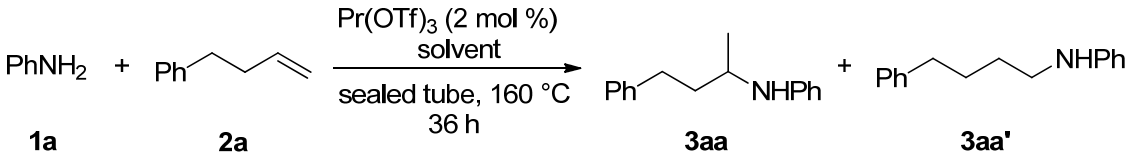


Scheme 15 General reaction of intermolecular hydroamination

Initially, we screened the hydroamination of 4-phenyl-1-butene and aniline using a catalytic amount of $Pr(OTf)_3$ (2 mol %) at 160 ^oC in a sealed tube under various conditions for 36 h. The results were summarized in Table 1. The reaction in *n*-Bu_4PBr without iodine afforded the product in low yield (22%, Table 1, entry 5). The addition of a catalytic amount of iodine increased the yield of the product (Table 1, entries 6 and 8). The best yield (75%) was obtained when the reaction was carried out in *n*-Bu_4PI in the presence of a catalytic amount of I_2 at 160 ^oC (Table 1, entry 8). No product was observed when the reaction was performed in toluene, DMF, [Omim]Cl or $[Omim]BF_4$ (Table 1, entries 1-4). It is important to note that contrary to the reaction conditions reported by Brunet,[16] our method does not require the use of strong acids.

[33] (a) Ryu, J.-S.; Li, G. Y.; Marks, T. J. *J. Am. Chem. Soc.* **2003**, *125*, 12584. (b) Motta, A.; Lanza, G.; Fragala, I. L.; Marks, T. J. *Organometallics* **2004**, *23*, 4097. (c) Hong, S.; Tian, S.; Metz, M. V.; Marks, T. J. *J. Am. Chem. Soc.* **2003**, *125*, 14768.

Table 1. Hydroamination between 4-Phenyl-1-butene and aniline under different conditions[a]



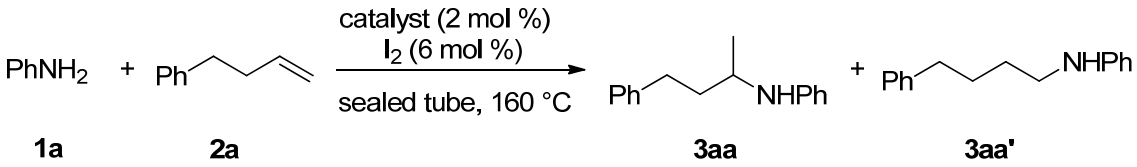
1a **2a** **3aa** **3aa'**

entry	solvent	iodine	yield[b] (%)	Ratio (3aa:3aa')[c]
1	DMF	6 mol %	0	–
2	toluene	6 mol %	0	–
3	[Omim]Cl	–[d]	0	–
4	[Omim]BF_4	–[d]	0	–
5	*n*-Bu_4PBr	–[d]	22	97:3
6	*n*-Bu_4PBr	6 mol %	69	91:9
7	*n*-Bu_4PI	–[d]	71	93:7
8	*n*-Bu_4PI	6 mol %	75	95:5
9	*n*-Bu_4PI	6 mol %	64	91:9[e]

[a] All reactions were performed with aniline (1 equiv), $Pr(OTf)_3$ (2 mol %), solvent (0.3 equiv), I_2 (indicated above) and 4-phenyl-1-butene (2 equiv) in sealed tube at 160 °C (oil temperature) for 36 h .
[b] Combined yield.
[c] Ratio of the two isomers as determined by ^1H NMR analysis.
[d] – : No iodine was added.
[e] No $Pr(OTf)_3$ was added.

Next, we investigated the catalytic activity of various rare earth metals using our optimized conditions. The results were summarized in Table 2. In all cases, the desired product was obtained in moderate to excellent yields. Dysprosium triflate exhibited better catalytic activity than dysprosium trichloride (Table 2, entries 5 and 6). Luterium triflate was the best catalyst, affording the desired product in 80% yield with the Markovnikov product as the major product (95:5, Table 2, entry 8). It was important to note that reaction carried out in the presence of TfOH resulted in only 10% yield of the product (Table 2, entry 9)

Table 2. The effects of different catalysts.



1a **2a** **3aa** **3aa'**

entry	catalyst	Yield[a] (%)	Ratio (3aa:3aa')[b]
1	$La(OTf)_3.H_2O$	60	98:2
2	$Ce(OTf)_3.H_2O$	48	94:6
3	$Pr(OTf)_3$	75	95:5
4	$Gd(OTf)_3$	76	94:6
5	$Dy(OTf)_3$	77	96:4
6	$DyCl_3$	70	94:6
7	$Er(OTf)_3$	78	96:4
8	$Lu(OTf)_3$	80	95:5
9	TfOH	10	–

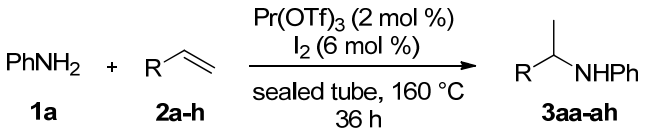
[a] Combined yield.
[b] Ratio of the two isomers as determined by ^{1}H NMR analysis.

Furthermore, since there were no notable differences in the catalytic abilities of these lanthanide triflates, reactions with various alkenes were investigated using the lower cost $Pr(OTf)_3$ as catalyst. The results were summarized in Table 3. Cyclopentene, cyclohexene and cycloheptene gave the desired products in good yields (Table 3, entries 2-4). In the case of terminal olefins, Markovnikov addition products were obtained as the major products (Table 3, entries 6-8). For allylbenzene, the Markovnikov product was obtained as a single isomer (Table 3, entry 8).

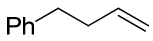
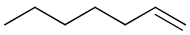
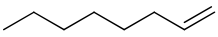
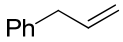
Noticeably, the reaction of 4-phenyl-1-butene with *p*-anisidine afforded the desired Markovnikov product (**3ba**) in moderate yield (32%) with 3% yield of the compound **3ba'** using praseodymium triflate as catalyst (Scheme 16). The formation of compound **3ba'** may be due to the isomerization of 4-phenyl-1-butene and low

reactivity of *p*-anisidine. Other nitrogen-containing compounds, such as *o*-anisidine, morpholine, benzylamine and diethylamine did not afford any of the desired products.

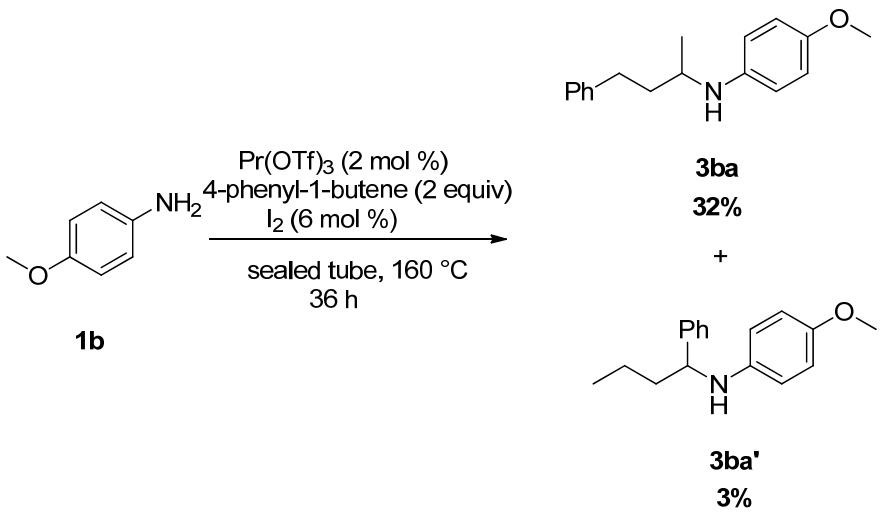
Table 3. Intermolecular Hydroamination of Aniline with Various Alkenes[a]



1a **2a-h** **3aa-ah**

entry	alkene	product	yield(%)[b]
1[c]		**3aa**	75
2		**3ab**	71[d]
3		**3ac**	75
4		**3ad**	70
5		**3ae**	61
6[c]		**3af**	79
7[c]		**3ag**	79
8[e]		**3ah**	56

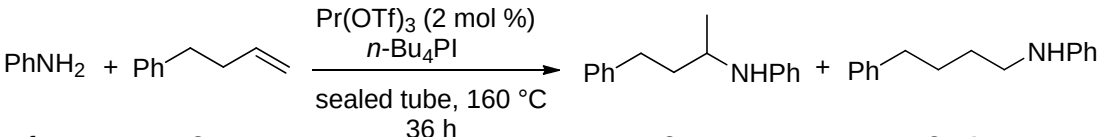
[a] All reactions were performed with aniline (1 equiv), $Pr(OTf)_3$ (2 mol %), I_2 (6 mol %), *n*-Bu_4PI (0.3 equiv) and alkenes (2 equiv) in sealed tube at 160 °C (oil temperature) for 36 h.
[b] Isolated yield.
[c] Up to 5% yield of other isomers were also observed.
[d] Reation time was 48 h.
[e] A single isomer was obtained.



Scheme 16 Intermolecular hydroamination of 4-phenyl-1-butene with *p*-anisidine.

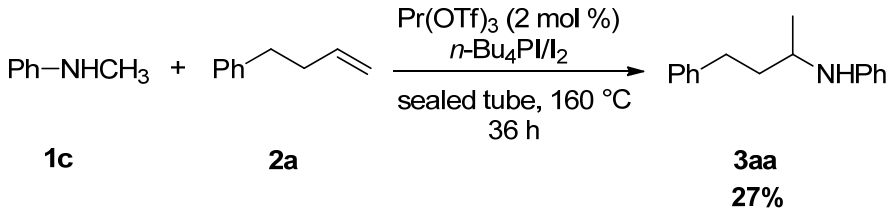
In order to probe the mechanism of the reaction, the following reaction (Table 4) was carried out in the presence of trapping reagents. The addition of three catalytic equivalents of NEt_3 or three catalytic equivalents of 2,6-di-*tert*-butylpyridine could not completely inhibit the hydroamination, both giving the two products in a combined yield of 40% and 60% respectively. Surprisingly, the reaction of 4- phenyl-1-butene with *N*-methylaniline gave the same product as with aniline in 27% yield (Scheme 17). Therefore, the reaction did not simply proceed *via* an acid-catalyzed mechanism.

Table 4. Intermolecular hydroamination of aniline with 4-phenyl-1-butene under different conditions



1a **2a** **3aa** **3aa'**

base	overall yield (%)	ratio (**3aa** : **3aa'**)
–	71	93 : 7
2,6-di-*tert*-butylpyridine	40	96 : 4
triethylamine	60	95 : 5



1c **2a** **3aa** **27%**

Scheme 17 Intermolecular hydroamination of 4-phenyl-1-butene with *N*-methylaniline

1.3 CONCLUSION AND FUTURE WORK

The catalytic system of $Pr(OTf)_3$/*n*-Bu_4PI/I_2 has been shown to exhibit excellent catalytic activity for the hydroamination of non-activated alkenes with aniline. This protocol offers several advantages including the use of simple and cheap catalyst, atom-economy, and offering products in high yields. Therefore, this new methodology offers an attractive strategy for the synthesis of synthetically and pharmaceutically useful amines. The detailed study of the mechanism and further work to explore new catalysts that tolerate a variety of functional groups under v mild reaction conditions are in progress. Further extension of this methodology is also in progress.

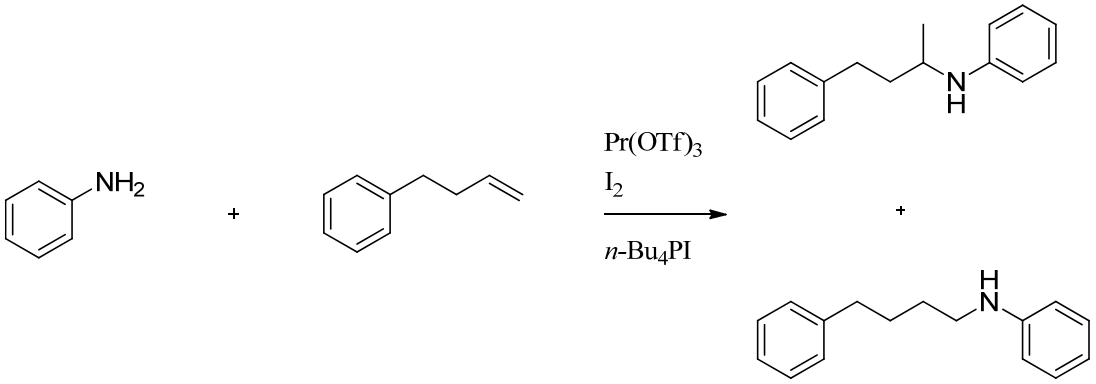
1.4 EXPERIMENTAL

General Information

Commercial solvents and reagents were used without further purification with the following exceptions: hexane and ethyl acetate were fractionally distilled. Aniline was distilled before use. Analytical thin layer chromatography (TLC) was performed using Merck 60 F_{254} precoated silica gel plate (0.2 mm thickness). Subsequent to elution, plates were visualized using UV radiation (254 nm) on Spectroline Model ENF-24061/F 254 nm. Further visualization was possible by staining with basic solution of potassium permanganate and iodine in the silica gel. Flash chromatography was performed using Merck silica gel 60 with freshly distilled solvents. Columns were typically packed as slurry and equilibrated with the appropriate solvent system prior to use. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a Bruker AMX 400 spectrophoto-meters ($CDCl_3$ as solvent). Chemical shifts for ^{1}H NMR spectra are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-d (δ 7.2600, singlet). Multiplicities were given as: s (singlet); d (doublet); t (triplet); q (quartet); qu(quintet); dd (doublets of doublet); ddd (doublets of doublets of doublet); dt (doublets of triplet); td (triplets of doublet) or m (multiplets). The number of protons (n) for a given resonance is indicated by nH. Coupling constants are reported as a J value in Hz. Carbon nuclear magnetic resonance spectra (^{13}C NMR) are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-d (δ 77.03, triplet). High Resolution Mass (HRMS) spectra were obtained using Waters Q-Tof Permies Mass Spectrometer.

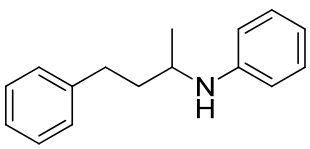
General procedure for hydroamination of alkenes and amines

The reaction conditions and yields for each reaction were shown in Table 3. A typical procedure was given in the following.



To a 5 mL sealed tube was added $Pr(OTf)_3$ (13.4 mg, 0.0228 mmol), I_2 (17.3 mg, 0.683 mmol) and *n*-Bu_4PI (132 mg, 0.341 mmol). The sealed tube was evacuated and refilled with nitrogen. This action was repeated three times. Then aniline (106 mg, 1.14 mmol) and 4-phenyl-1-butene (300 mg, 2.28 mmol) were added through syringe under the flush of nitrogen. After heated at 160 °C (oil temperature) for 36 h, the mixture in the sealed tube was cooled down to room temperature and dissolved in ethyl acetate, then transferred to 25 mL round-bottom flask and evaporated under reduced pressure. The resulting residue was purified by column chromatography (hexane:ethyl acetate = 100:1) to obtain the products.

***N*-(4-Phenylbutan-2-yl)aniline (3aa)**



R_f: 0.32 (Hexane:Ethyl acetate = 20:1)

This compound was prepared by the General Procedure described above and was obtained as a yellow oil.

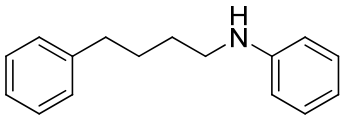
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30-7.13 (m, 7H), 6.68-6.64 (t, *J* = 7.2 Hz, 1H), 6.54-6.52 (d, *J* = 7.8 Hz, 2H), 3.51-3.42 (m, 2H), 2.74-2.71 (t, *J* = 7.8 Hz, 2H), 1.91-1.74 (m, 2H), 1.23-1.21 (d, *J* = 6.0 Hz, 3H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.6, 142.0, 129.3, 128.5, 128.4, 125.9, 117.0, 113.2, 47.9, 38.9, 32.5, 20.9 ppm.

FTIR (neat): *v* = 3418, 3017, 1605, 1504, 1219, 756, 671 cm^{-1}.

HRMS (ESI, m/z): calculated for $C_{16}H_{19}N$ $[M+H]^+$: 226.1590, found $[M + H]^+$: 226.1587.

N-(4-Phenylbutyl)aniline (3aa')



R_f: 0.26 (Hexane:Ethyl acetate = 20:1)

This compound was prepared by the General Procedure described above and was obtained as a yellow oil.

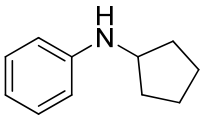
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30-7.15 (m, 7H), 6.70-6.67 (t, *J* = 7.5 Hz, 1H), 6.60-6.58 (d, *J* = 8.2 Hz, 2H), 3.57 (br, s, 1H), 3.15-3.11 (t, *J* = 7.0 Hz, 2H), 2.68-2.65 (t, *J* = 7.6 Hz, 2H), 1.77-1.64 (m, 4H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.4, 142.2, 129.2, 128.4, 128.3, 125.8, 117.2, 112.7, 43.8, 35.7, 29.2, 28.9 ppm.

FTIR (neat): *v* = 3417, 3017, 2924, 2855, 1605, 1505, 1219, 756, 671 cm^{-1}.

HRMS (ESI, m/z): calculated for $C_{16}H_{19}N$ $[M + H]^+$: 226.1590, found $[M + H]^+$: 226.1592.

N-Cyclopentylaniline (3ab)



R_f: 0.29 (Hexane:Ethyl acetate = 20:1).

This compound was prepared by the General Procedure described above and was obtained as a yellow oil.

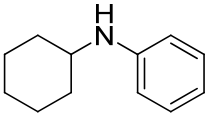
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19-7.16 (t, *J* = 7.8 Hz, 2H), 6.70-6.67 (t, *J* = 7.3 Hz, 1H), 6.62-6.60 (d, *J* = 8.2 Hz, 2H), 3.83-3.77 (m, 1H), 3.64 (br, s, 1H), 2.06-1.99 (m, 2H), 1.78-1.58 (m, 4H), 1.52-1.44 (m, 2H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.1, 129.2, 116.9, 113.2, 54.7, 33.6, 24.1ppm.

FTIR (neat): *v* = 3418, 2924, 2855, 1605, 1504, 1219, 756, 694 cm^{-1}.

HRMS (ESI, m/z): calculated for $C_{11}H_{15}N$ $[M+H]^+$: 162.1277, found $[M+H]^+$: 162.1277.

N-Cyclohexylaniline (3ac)



R_f: 0.28 (Hexane:Ethyl acetate = 20:1).

This compound was prepared by the General Procedure described above and was obtained as a yellow oil.

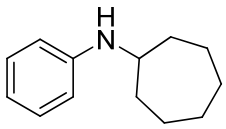
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18-7.14 (t, *J* = 7.8 Hz, 2H), 6.68-6.65 (t, *J* = 7.2 Hz, 1H), 6.61-6.59 (d, *J* = 8.2 Hz, 2H), 3.52 (br, s, 1H), 3.30-3.23 (m, 1H), 2.09-2.05 (m, 2H), 1.80-1.75 (m, 2H), 1.69-1.64 (m, 1H), 1.44-1.11 (m, 5H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.4, 129.3, 116.8, 113.2, 51.7, 33.5, 26.0, 25.1 ppm.

FTIR (neat): *v* = 3417, 3016, 2931, 2854, 1504,1219, 756, 671 cm^{-1}.

HRMS (ESI, m/z): calculated for $C_{12}H_{17}N$ $[M+H]^+$: 176.1434, found $[M+H]^+$: 176.1437.

N-Phenylcycloheptanamine (3ad)



R_f: 0.33 (Hexane:Ethyl acetate = 20:1).

This compound was prepared by the General Procedure described above and was obtained as a yellow oil.

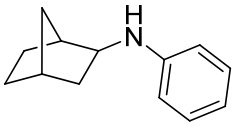
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18-7.15 (t, *J* = 7.9 Hz, 2H), 6.68-6.64 (t, *J* = 7.3 Hz, 1H), 6.56-6.54 (d, *J* = 8.3 Hz, 2H), 3.59 (br, s, 1H), 3.49-3.44 (m, 1H), 2.04-1.98 (m, 2H), 1.71-1.27 (m, 10H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.4, 129.3, 116.8, 113.2, 53.7, 34.9, 28.4, 24.4 ppm.

FTIR (neat): *v* = 3017, 2924, 2855, 1605, 1504, 1219, 756, 671 cm^{-1}.

HRMS (ESI, m/z): calculated for $C_{13}H_{19}N$ $[M+H]^+$: 190.1590, found $[M+H]^+$: 190.1593.

N-Phenylbicyclo[2.2.1]heptan-2-amine (3ae)



R_f: 0.42 (Hexane:Ethyl acetate = 20:1)

This compound was prepared by the General Procedure described above and was obtained as a yellow oil.

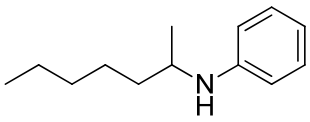
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18-7.14 (t, *J* = 7.9 Hz, 2H), 6.69-6.65 (t, *J* = 7.4 Hz, 1H), 6.58-6.56 (d, *J* = 8.0 Hz, 2H), 3.55 (bs, 1H), 3.25-3.22 (m, 1H), 2.29 (s, 2H), 1.85-1.80 (m, 1H), 1.60-1.43 (m, 3H), 1.23-1.14 (m, 4H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.6, 129.2, 116.9, 113.1, 56.6, 41.2, 41.1, 35.6, 35.3, 28.5, 26.4 ppm.

FTIR (neat): *v* = 3426, 3009, 2955, 2870, 1605, 1504, 1304, 1219, 756, 694, 671 cm^{-1}.

HRMS (ESI, m/z): calculated for $C_{13}H_{17}N$ $[M+H]^+$: 188.1434, found $[M+H]^+$: 188.1436.

N-(2-Methylhexyl)aniline (3af)



R_f: 0.39 (Hexane:Ethyl acetate = 20:1).

This compound was prepared by the General Procedure described above and was obtained as a yellow oil.

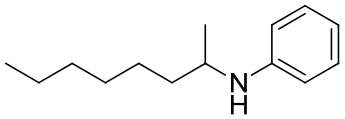
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19-7.15 (t, *J* = 7.8 Hz, 2H), 6.69-6.65 (t, *J* = 7.3 Hz, 1H), 6.60-6.58 (d, *J* = 8.0 Hz, 2H), 3.49-3.43 (m, 2H), 1.62-1.55 (m, 1H), 1.48-1.30 (m, 7H), 1.19-1.18 (d, *J* = 6.3 Hz, 3H), 0.92-0.89 (t, *J* = 6.6 Hz, 3H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.7, 129.3, 116.7, 113.1, 48.5, 37.2, 31.9, 25.9, 22.7, 20.8, 14.1 ppm.

FTIR (neat): *v* = 3017, 1651, 1636, 1219, 771, 671 cm^{-1}.

HRMS (ESI, m/z): calculated for $C_{13}H_{21}N$ $[M+H]^+$: 192.1747, found $[M+H]^+$: 192.1750.

N-(2-Methylheptyl)aniline (3ag)



R_f: 0.41 (Hexane:Ethyl acetate = 20:1).

This compound was prepared by the General Procedure described above and was obtained as a yellow oil.

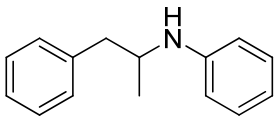
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19-7.15 (t, *J* = 8.1 Hz, 2H), 6.69-6.65 (t, *J* = 7.3 Hz, 1H), 6.60-6.58 (d, *J* = 8.0 Hz, 2H), 3.49-3.42 (m, 2H), 1.62-1.55 (m, 1H), 1.48-1.30 (m, 9H), 1.19-1.18 (d, *J* = 6.3 Hz, 3H), 0.92-0.88 (t, *J* = 6.5 Hz, 3H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.7, 129.3, 116.7, 113.1, 48.5, 37.3, 31.9, 29.4, 26.2, 22.6, 20.8, 14.1 ppm.

FTIR (neat): *v* = 3417, 3017, 2924, 1605, 1504, 1219, 756, 694, 671 cm^{-1}.

HRMS (ESI, m/z): calculated for $C_{14}H_{23}N$ $[M+H]^+$: 206.1903, found $[M+H]^+$: 206.1910.

N-(1-Phenylpropan-2-yl)aniline (3ah)



R_f: 0.27 (Hexane:Ethyl acetate = 20:1).

This compound was prepared by the General Procedure described above and was obtained as a yellow oil.

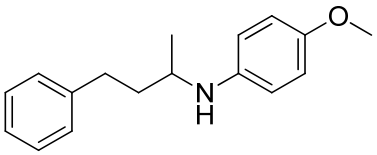
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31-7.16 (m, 7H), 6.71-6.67 (t, *J* = 7.3 Hz, 1H), 6.64-6.62 (d, *J* = 8.2 Hz, 2H), 3.79-3.74 (m, 1H), 3.53 (br, s, 1H), 2.96-2.92 (dd, *J* = 4.7, 13.4 Hz, 1H), 2.72-2.67 (dd, *J* = 7.3, 13.4 Hz, 1H), 1.16-1.14 (d, *J* = 7.3 Hz, 3H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.2, 138.6, 129.5, 129.4, 128.3, 126.3, 117.2, 113.4, 49.3, 42.3, 20.2 ppm.

FTIR (neat): *v* = 3417, 3017, 2924, 1605, 1504, 1319, 1219, 772, 702 cm^{-1}.

HRMS (ESI, m/z): calculated for $C_{15}H_{17}N$ $[M+H]^+$: 212.1434 found $[M+H]^+$: 212.1438.

4-Methoxy-*N*-(4-phenylbutan-2-yl)aniline (3ba)



R_f: 0.11 (Hexane:Ethylacetate = 20:1)

This compound was prepared by the General Procedure described above and was obtained as a brown oil.

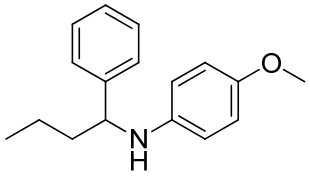
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34-7.17 (m, 5H), 6.77-6.74 (d, *J* = 8.7 Hz, 2H), 6.52-6.49 (d, *J* = 8.9 Hz, 2H), 3.74 (s, 3H), 3.44-3.36 (m, 1H), 2.74-2.70 (t, *J* = 8.0 Hz, 2H), 1.91-1.69 (m, 2H), 1.20-1.18 (d, *J* = 6.4 Hz, 3H) ppm;

^{13}C NMR (100MHz, $CDCl_3$): δ = 151.9, 142.1, 141.8, 128.5, 128.4, 125.8, 115.0, 114.8, 55.8, 49.0, 38.9, 32.5, 20.9 ppm.

FTIR (neat): *v* = 3017, 1512, 1219, 756, 671 cm^{-1}.

HRMS (ESI, m/z): calculated for $C_{17}H_{21}NO$ $[M+H]^+$: 256.1696, found $[M+H]^+$: 256.1702.

4-Methoxy-*N*-(1-phenylbutyl)aniline (3ba')



R_f: 0.16 (Hexane:Ethyl acetate = 20:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34-7.16 (m, 5H), 6.68-6.66 (d, *J* = 8.8 Hz, 2H), 6.47-6.45 (d, *J* = 8.8 Hz, 2H), 4.24-4.21 (t, *J* = 6.8 Hz, 1H), 3.68 (s, 3H), 1.87-1.67 (m, 2H), 1.47-1.29 (m, 2H), 0.94-0.91 (t, *J* = 7.4 Hz, 3H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.8, 144.6, 141.8, 128.5, 126.8, 126.4, 114.8, 114.4, 58.8, 55.8, 41.2, 19.5, 14.0 ppm.

FTIR (neat): *v* = 3015, 1515, 1218, 756, 671 cm^{-1}.

HRMS (ESI, m/z): calculated for $C_{17}H_{21}NO$ $[M+H]^+$: 256.1696, found $[M+H]^+$: 256.1692.

PART I

CHAPTER 2

Iodine-catalyzed Intramolecular Hydroamination of Unactivated Alkenes with Primary and Secondary amines

2.1 OVERVIEW OF THE BACKGROUND

The synthesis of nitrogen containing heterocyclic system is of great interest because of their presence in many natural, biological and pharmaceutical active compounds. Intramolecular hydroamination, the addition of amines to alkenes, alkynes and other unsaturated systems, presents an atom-economical method for the synthesis of these heterocycles. [1] Though hydroamination for unactivated aminoalkenes under mild reaction conditions and with wide substrate scope is difficult due to the high electron density of C=C bonds, there are significant advances in this area, and many catalytic systems have been developed to promote such cyclization.[2] The following are some lead examples of intramolecular hydroamination.

Rare earth elements and actinides are highly efficient catalysts for intramolecular hydroamination. [3] A number of relevant studies have been accomplished by the group of T. J. Marks. The following is one example about asymmetric intramolecular hydroamination, which was reported by Hultzsch and co-workers (Scheme 1).[3i] Enantioselectivities of up to 95% *ee* were achieved.

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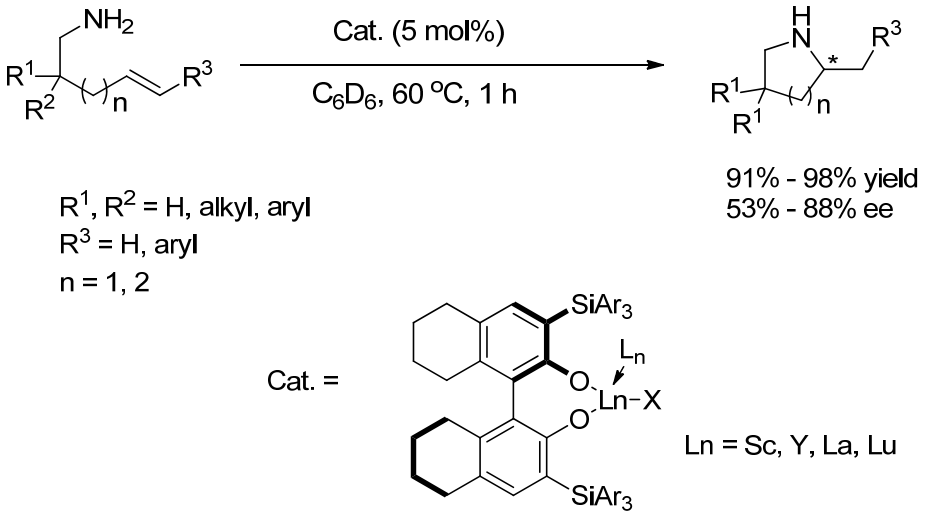
[1] (a) Hesp, K. D.; Tobisch, S.; Stradiotto, M. *J. Am. Chem. Soc.* **2010**, *132*, 413. (b) Hong, S.; Kawaoka, A. M.; Marks, T. J. *J. Am. Chem. Soc.* **2003**, *125*, 15878. (c) Trost, B. M.; Tang, W. *J. Am. Chem. Soc.* **2003**, *125*, 8744. (d) Molander, G. A.; Dowdy, E. D.; Pack, S. K. *J. Org. Chem.* **2001**, *66*, 4344. (e) Arredondo, V. M.; Tian, S.; McDonald, F. E.; Marks, T. J. *J. Am. Chem. Soc.* **1999**, *121*, 3633.

[2] Mueller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795.

[3] For a selection of recent lead references, see: (a) Tobisch, S. *Dalton Trans* **2011**, *40*, 249. (b) Le Roux, E.; Liang, Y.; Storz, M. P.; Anwander, R. *J. Am. Chem. Soc.* **2010**, *132*, 16368. (c) Yuen, H. F.; Marks, T. J. *Organometallics* **2009**, *28*, 2423. (d) Aillaud, I.; Collin, J.; Duhayon, C.; Guillot, R.; Lyubov, D.; Schulz, E.; Trifonov, A. *Chem.-Eur. J.* **2008**, *14*, 2189. (e) Zi, G.; Xiang, L.; Song, H. *Organometallics* **2008**, *27*, 1242. (f) Stubbert, B. D.; Marks, T. J. *J. Am. Chem. Soc.* **2007**, *129*, 4253. (g) Stubbert, B. D.; Marks, T. J. *J. Am. Chem. Soc.* **2007**, *129*, 6149. (h) Riegert, D.; Collin, J.; Daran, J.-C.; Fillebeen, T.; Schulz, E.; Lyubov, D.; Fukin, G.; Trifonov, A. *Eur. J. Inorg. Chem.* **2007**, 1159. (i) Gribkov, D. V.; Hultzsch, K. C.; Hampel, F. *J. Am. Chem. Soc.* **2006**, *128*, 3748. (j) Rastaetter, M.; Zulys, A.; Roesky, P. W. *Chem. Commun.* **2006**, 874. (k) Bambirra, S.; Tsurugi, H.; van Leusen, D.; Hessen, B. *Dalton Trans.* **2006**, 1157. (l) Kim, H.; Lee, P. H.; Livinghouse, T. *Chem. Commun.* **2005**, 5205. (m) Lauterwasser, F.; Hayes, P. G.; Braese, S.; Piers, W. E.; Schafer, L. L. *Organometallics* **2004**, *23*, 2234. (n) Hong, S.; Marks, T. J. *Acc. Chem. Res.* **2004**, *37*, 673.



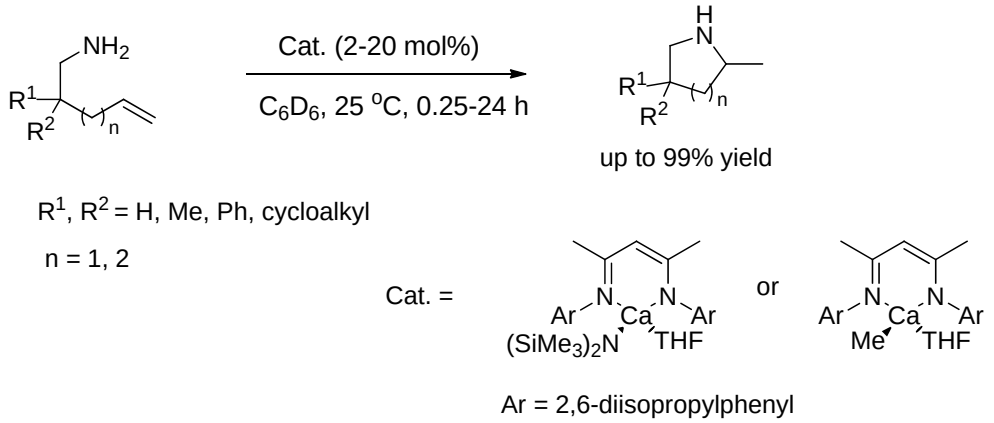
Scheme 1 Asymmetric Intramolecular hydroamination of unactivated aminoalkenes reported by Hultzsch and co-workers.

For rare-earth metal complexes and actinides, despite their effectiveness and excellent stereochemistry in hydroamination, their uses in many applications are limited because of their sensitivity to oxygen and moisture and their low tolerance for polar functional groups.

Alkali and alkaline earth metals are also investigated in hydroamination.[4] In 2009, Barrett and co-wrokers reported intramolecular hydroamination of unactivated aminoalkenes catalyzed by calcium and magnesium complexes (Scheme 2).[5] The reaction conditions were mild and the reactions proceeded quickly (0.25 – 24 h). The detailed mechanism was also studied.

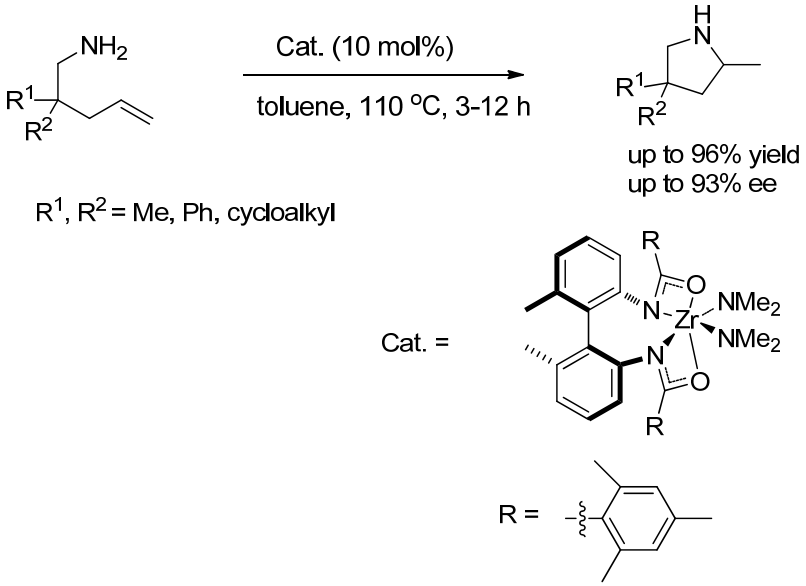
[4] some examples: (a) Zhang, W.; Werness, J. B.; Tang, W. *Tetrahedron* **2009**, *65*, 3090. (b) Arrowsmith, M.; Hill, M. S.; Kociok-Kohn, G. *Organometallics* **2009**, *28*, 1730. (c) Arrowsmith, M.; Hill, M. S.; Kociok-Kohn, G. *Organometallics* **2009**, *28*, 1730. (d) Datta, S.; Gamer, M. T.; Roesky, P. W. *Organometallics* **2008**, *27*, 1207. (e) Martinez, P. H.; Hultzsch, K. C.; Hampel, F. *Chem. Commun.* **2006**, 2221. (f) Crimmin, M. R.; Casely, I. J.; Hill, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 2042.

[5] Crimmin, M. R.; Arrowsmith, M.; Barrett, A. G. M.; Casely, I. J.; Hill, M. S.; Procopiou, P. A. *J. Am. Chem. Soc.* **2009**, *131*, 9670.



Scheme 2 Calcium and magnesium complexes catalyzed intramolecular hydroamination of unactivated aminoalkenes reported by Hultzsch and co-workers.

Group 4 metal catalysts are particularly attractive in organic synthesis and applied widely in hydroamination, due to their low cost, low toxicity and high reactivity.[6] In 2006, Schafer and co-workers used chiral neutral zirconium

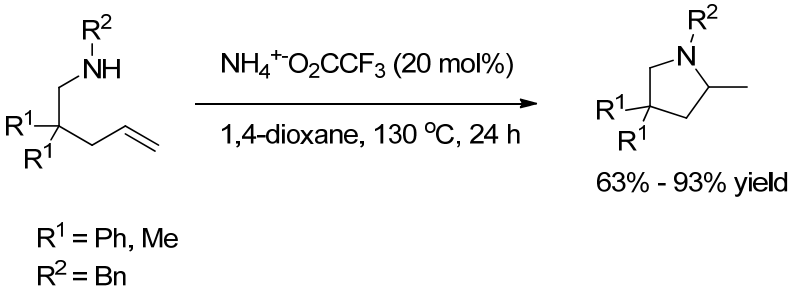


Scheme 3 Zr complexes catalyzed asymmetric intramolecular hydroamination of unactivated aminoalkenes reported by Schafer and co-workers.

[6] (a) Lee, A. V.; Sajitz, M.; Schafer, L. L. *Synthesis* **2009**, 97. (b) Lian, B.; Spaniol, T. P.; Horrillo-Martinez, P.; Hultzsch, K. C.; Okuda, J. *Eur. J. Inorg. Chem.* **2009**, 429. (c) Cho, J.; Hollis, T. K.; Helgert, T. R.; Valente, E. J. *Chem. Commun.* **2008**, 5001. (d) Majumder, S.; Odom, A. L. *Organometallics* **2008**, *27*, 1174. (e) Lee, A. V.; Schafer, L. L. *Eur. J. Inorg. Chem.* **2007**, 2243. (f) Gott, A. L.; Clarke, A. J.; Clarkson, G. J.; Scott, P. *Organometallics* **2007**, *26*, 1729. (g) Watson, D. A.; Chiu, M.; Bergman, R. G. *Organometallics* **2006**, *25*, 4731. (h) Knight, P. D.; Munslow, I.; O'Shaughnessy, P. N.; Scott, P. *Chem. Commun.* **2004**, 894.

amidate complexes to catalyze asymmetric intramolecular hydroamination (Scheme 3).[7] Up to 96% yield and up to 93 % *ee* were obtained. Nevertheless, no desired product was obtained with secondary amines.

Hartwig and co-workers reported the intramolecular hydroamination of tosyl-protected aminoalkenes catalyzed by several common Brønsted acids.[8] However, there were no reactions for primary amines. In 2007, Ackermann and co-workers reported a Brønsted-acid catalyzed intramolecular hydroamination (Scheme 4).[9] However, there was only one example involving primary amine.

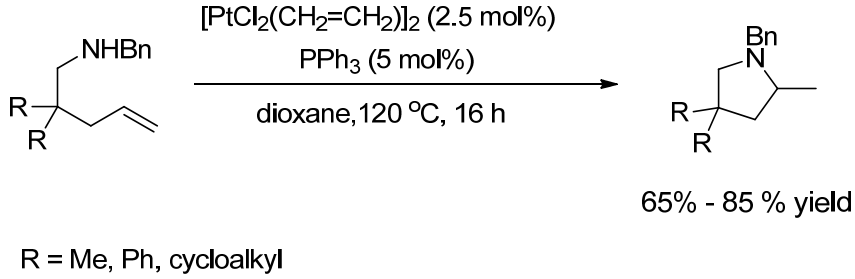


Scheme 4 Bronsted acid catalyzed intramolecular hydroamination of unactivated aminoalkenes reported by Ackermann and co-workers.

In contrast to early transition metals and lanthanides complexes, late transition metals have the advantage of better functional group tolerance and low oxophilicity. A variety of transition metal complexes have been developed to promote intramolecular hydroamination. At the same time, for the intramolecular hydroamination of secondary amides, carbamates, or ureas to unactivated alkenes,

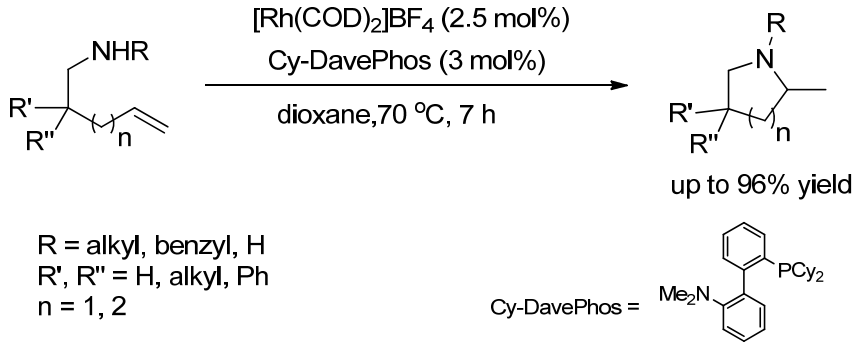
[7] Wood, M. C.; Leitch, D. C.; Yeung, C. S.; Kozak, J. A.; Schafer, L. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 354.
[8] Schlummer, B.; Hartwig, J. F. *Org. Lett.* **2002**, *4*, 1471.
[9] Ackermann, L.; Kaspar, L. T.; Althammer, A. *Org. Biomol. Chem.* **2007**, *5*, 1975.

much progress has been made using Fe, [10] Pd,[11] and Au[12] catalysts. Late transition metal catalysts for intramolecular hydroamination of secondary alkyl, arylamines and primary amines with unactivated olefins were published recently. The first example of this type was reported by Widenhoefer and co-workers in 2005 (Scheme 5).[13] They used $[PtCl_2(H_2C=CH_2)]_2/PPh_3$ as catalyst. Moderate to good yields were achieved. However, no primary amine was reported.



Scheme 5 Pt catalyst complexes catalyzed intramolecular hydroamination of unactivated aminoalkenes reported by Widenhoefer and co-workers.

In 2008, Hartwig and co-worker used $[Rh(COD)_2]BF_4$/Cy-DavePhos (Cy-DavePhos = 2-dicyclohexylphosphino-2′-*N*,*N*-dimethylaminobiphenyl) for the hydro-

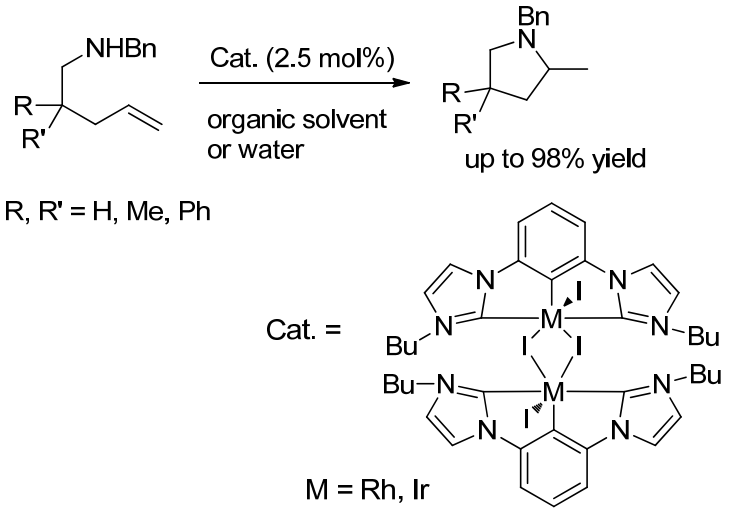


Scheme 6 Rh catalyst complexes catalyzed intramolecular hydroamination of unactivated aminoalkenes reported by Hartwig and co-worker.

[10] Komeyama, K.; Morimoto, T.; Takaki, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 2938.
[11] (a) Cochran, B. M.; Michael, F. E. *J. Am. Chem. Soc.* **2008**, *130*, 2786. (b) Michael, F. E.; Cochran, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 4246.
[12] (a) Bender, C. F.; Widenhoefer, R. A. *Chem. Commun.* **2006**, 4143. (b) Zhang, J.; Yang, C.-G.; He, C. *J. Am. Chem. Soc.* **2006**, *128*, 1798. (c) Liu, X.-Y.; Li, C.-H.; Che, C.-M. *Org. Lett.* **2006**, *8*, 2707. (d) Brouwer, C.; He, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1744.
[13] Bender, C. F.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2005**, *127*, 1070.

amination of aminoalkenes (Scheme 6).[15] Reactions of primary and secondary alkylamines with terminal and internal alkenes were successful.

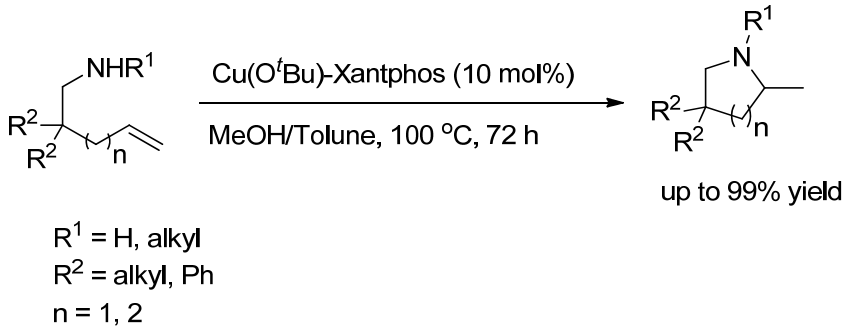
In the same year, Hollis and co-workers described the Rh and Ir complexes supported by NHC ligands to catalyze the cyclization of terminal alkenes with pendant secondary alkyl and phenylamines (Scheme 7).[16] The reactions could proceed in both organic solvent and water.



Scheme 7 Rh and Ir catalyst complexes catalyzed intramolecular hydroamination of unactivated aminoalkenes reported by Hollis and co-workers.

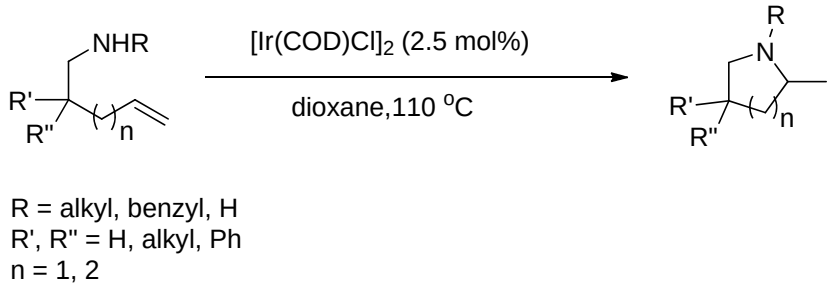
In 2009, Sawamura and co-workers reported the use of Cu(O^{t}Bu)/Xantphos (Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene) for the hydro-amination of unactivated alkenes by tethered primary or secondary alkylamine (Scheme 8).[17] Pyrrolidine and piperidine derivatives were produced in excellent yields.

[15] Liu, Z.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 1570.
[16] Bauer, E. B.; Andavan, G. T. S.; Hollis, T. K.; Rubio, R. J.; Cho, J.; Kuchenbeiser, G. R.; Helgert, T. R.; Letko, C. S.; Tham, F. S. *Org. Lett.* **2008**, *10*, 1175.
[17] Ohmiya, H.; Moriya, T.; Sawamura, M. *Org. Lett.* **2009**, *11*, 2145.



Scheme 8 Cu catalyst complexes catalyzed intramolecular hydroamination of unactivated aminoalkenes reported by Sawamura and co-workers.

In the same year, Stradiotto and co-workers developed an Ir catalyst for intramolecular hydroamination (Scheme 9).[18] They explored the substrate scope and studied the detailed mechanism.[18a] However, for primary amines, additional $HNEt_3Cl$ was needed to promote the reaction.



Scheme 9 $[Ir(COD)Cl]_2$ catalyzed intramolecular hydroamination of unactivated aminoalkenes reported by Stradiotto and co-workers.

2.2 IODINE-CATALYZED INTRAMOLECULAR HYDROAMINATION OF UNACTIVATED ALKENES WITH PRIMARY AND SECONDARY AMINES

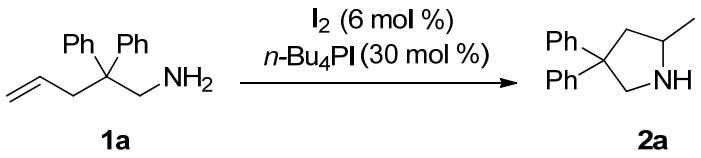
Despite the development of numerous catalytic systems in the recent years, the addition of primary or secondary amines across unactivated olefins still poses to be a

[18] (a) Hesp, K. D.; Tobisch, S.; Stradiotto, M. *J. Am. Chem. Soc.* **2010**, *132*, 413. (b) Hesp, K. D.; Stradiotto, M. *Org. Lett.* **2009**, *11*, 1449.

challenge. In chapter 1, we had discovered that iodine can be used to catalyze intermolecular hydroamination between unactivated alkenes and aniline. Here, we report the use of iodine as the catalyst for the intramolecular hydroamination of various unactivated aminoalkenes.

First, we chose 2,2-diphenylpent-4-en-1-amine, which was often used in the intramolecular hydroamination, as the model to ascertain the reaction temperature and time (Table 1). With reference to the Chapter 1, 6 mol% of iodine and 30 mol% of nBu$_4$PI were used. As shown Table 1, when the temperature was 135 ºC, longer reaction time did not help to increase the yield (entries 1 and 2, Table 1). Higher temperature, 160 ºC, was necessary to achieve high conversion (no starting material was seen in the crude ^{1}H NMR) and high yield (89% isolated yield) (entry 3, Table 1). No iodo byproduct was observed.

Table 1. Intramolecular hydroamination of 2,2-Diphenylpent-4-en-1-amine under different reaction conditions [a]



1a **2a**

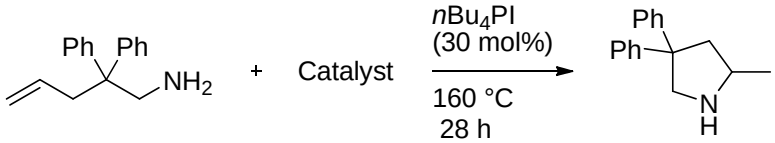
entry	temperature (ºC)	time (h)	result[b] (%)
1	135	24	50
2	135	48	54
3	160	28	89

[a] Conditions: 2,2-Diphenylpent-4-en-1-amine (0.5 mmol), I_2 (6 mol %), nBu$_4$PI (30 mol%) were heated in a sealed tube.
[b] Isolated yield.

Next, different catalysts were screened at 160 ºC for 28h (Table 2). Iodine gave the best yield (entry 1, Table 2). No desired product was obtained when KI or KF was employed as the catalyst (entries 2 and 6, Table 2). With PhI(OAc)$_2$, only 14% yield

was obtained (entry 3, table 2). NBS was inferior to NIS (entries 4 and 5, Table 2), both giving moderate yields.

Table 2. Different catalysts for the intramolecular hydroamination[a]

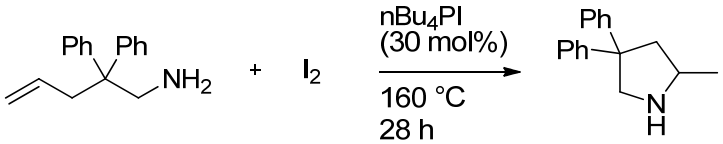


entry	catalyst	conversion[b] (%)	yield[c] (%)
1[d]	I_2	>99	89
2	KI	19	-[e]
3[d]	$PhI(OAc)_2$	26	14
4	NIS	76	58
5	NBS	62	55
6	KF	7	-[e]

[a] Conditions: 2,2-Diphenylpent-4-en-1-amine (0.5 mmol), catalyst (10 mol %), *n*Bu4PI (30 mol%) were heated in a sealed tube for 28 h at 160 ºC.
[b] Judged by crude ^{1}H NMR.
[c] Isolated yield.
[d] The amount of the catalyst was 6 mol%
[e] No desired product was obtained.

Next, the effect of iodine was also studied in details. When the amount of iodine was decreased, the yields also decreased accordingly (entries 1, 2 and 3, Table 3). If no iodine was added, no reaction occurred (entry 4, Table 3), which showed that the iodine is essential for this reaction. In order to check the temperature effect, the amount of iodine was increased to about 10 mol %, while decreasing the reaction temperature to 135^{o}C. A significant decrease of yield was observed (entry 5, Table 3). Further increasing to 20 mol % of iodine at the same temperature did not give better yield either (entry 6, Table 3). Furthermore, ^{i}Pr$_2$NH was added to determine whether

Table 3. The effects of the amount of iodine for the intramolecular hydroamination[a]



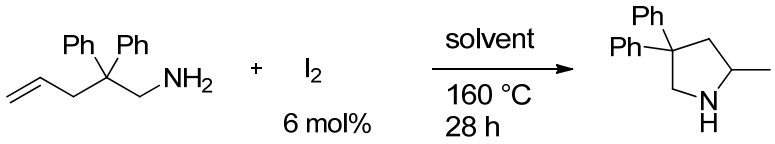
entry	amount of I_2 (mol%)	conversion[b] (%)	yield[c] (%)
1	6	>99	89
2	4	91	77
3	1	67	63
4	-[d]	9	-[e]
5[f]	10	78	61
6[f]	20	-	72
7[g]	6	91	81

[a] Conditions: 2,2-Diphenylpent-4-en-1-amine (0.5 mmol), I_2 (stated in the table), *n*Bu_4PI (30 mol%) were heated in a sealed tube for 28 h at 160 ºC.
[b] Judged by crude ^1H NMR.
[c] Isolated yield.
[d] No iodine was added
[e] No desired product was obtained.
[f] The reation was conducted at 135 ºC.
[g] 30 mol% of $^iPr_2NH$ was added.

the reaction was acid-catalyzed or not. No significant difference was observed (entry 7, Table 3).

As stated in chapter 1, the use of ionic solvents is crucial for the intermolecular hydroamination of aniline with unactivated alkenes. Thus, we also examined various solvents as shown in Table 4. For toluene and 1,4-dioxane, low yields were given (entries 1 and 5, Table 4). But for the polar coordinating solvents, such as DMSO, NMP, and DMF, no desired products were obtained (entries 2, 3 and 4, Table 4). Ionic solvent *n*Bu_4PBr did not perform as good as *n*Bu_4PI (64% yield, entry 6, Table 4). Another two I^- containing ionic liquids were also tested, but only moderate yields were obtained (entries 7 and 8, Table 4). In conclusion, *n*Bu_4PI was proved to be the best solvent for our catalytic system.

Table 4. Different solvents for the iodine catalyzed intramolecular hydroamination[a]



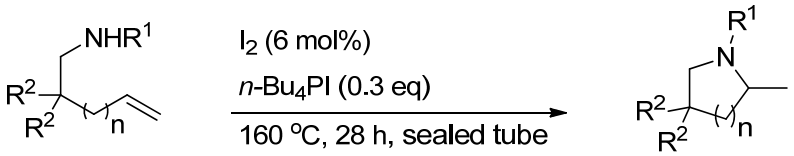
entry	solvent	Conversion[b] (%)	Yield[c] (%)
1	Toluene	57	30
2	DMSO	-	-[d]
3	NMP	-	-[d]
4	DMF	-	-[d]
5	1,4-dioxane	37	22
6[e]	*n*Bu$_4$PBr	83	64
7[e]	Tetrahexylammonium iodide	-	24
8[e]	1-Methyl-3-propyl-imidazolium iodide	-	57

[a] Conditions: 2,2-Diphenylpent-4-en-1-amine (0.5 mmol), I_2 (stated in the table), solvent (1 mL) were heated in a sealed tube for 28 h at 160 ºC.
[b] Judged by crude ^{1}H NMR.
[c] Isolated yield.
[d] No desired product was obtained.
[e] 30 mol% of the solvent was used.

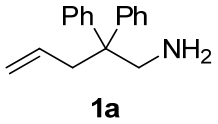
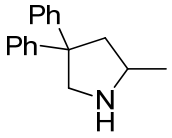
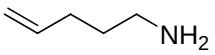
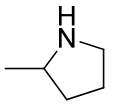
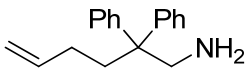
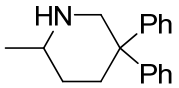
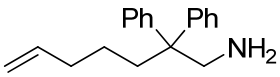
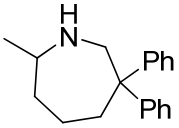
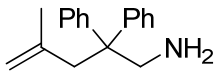
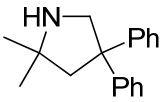
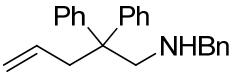
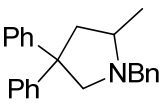
With the optimized reaction conditions, the scope of this reaction was investigated (Table 5). A series of aminoalkenes with secondary alkyl, arylamines and primary amines were synthesised. Initially, primary alkylamine **1b** was subjected to this catalytic system. Unfortunately, no desired product was obtained due to the absence of Thorpe-Ingold effect. For the formation of six and seven member ring, the reactions either did not proceed as expected (entries 3 and 4, Table 5). For substrate **1e**, high yield was achieved (entry 5, Table 5). Note that the HCl salt of **1e** could also produce compound **2e** without iodine under the same reaction condition in 85% yield. However, when 1,2-disubstituted alkenes was incorporated, no reaction occurred (entry 9, Table 5). For the secondary alkylamines, good results were achieved (entries

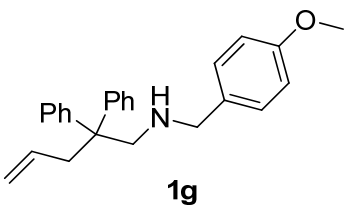
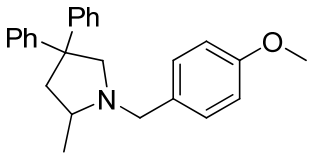
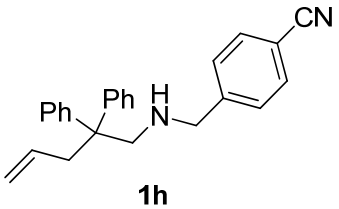
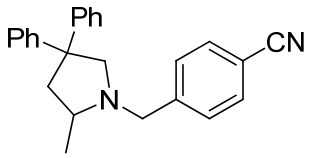
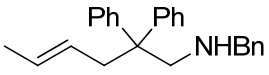
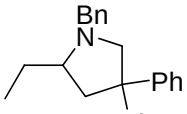
6, 7 and 8, Table 5). Functional groups such as methoxy and cyano groups were tolerated to this catalytic system. The application to more substrates are in progress.

Table 5. Intramolecular hydroamination of different aminoalkenes under optimized conditionsa



R^1, R^2 = H, Ph
n = 1, 2

entry	substrate	product	yield(%)[b]
1	 **1a**	 **2b**	89
2	 **1b**	 **2b**	-[c]
3	 **1c**	 **2c**	-[c]
4	 **1d**	 **2d**	-[c]
5	 **1e**	 **2e**	90
6	 **1f**	 **2f**	83

7	 **1g**	 **2g**	91
8	 **1h**	 **2h**	78
9	 **1i**	 **2i**	-[c]

[a] Conditions: substrates (0.5 mmol), I_2 (6 mol%), nBu$_4$PI (30 mol%) were heated in a sealed tube for 28 h at 160 ºC.
[b] Isolated yield.
[c] No desired product was obtained.

Conclusion

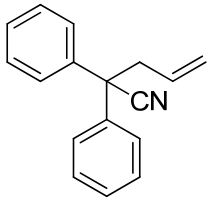
In summary, a new metal-free method for the intramolecular cyclizations of secondary alkyl amines and primary amines with unactivated olefins was discovered. This catalytic system shows great potential in the development of cheap, metal-free systems in the catalysis of intramolecular hydroamination. Further works to explore the reaction mechanism and more substrates are still in progress.

2.3 EXPERIMENTAL

General

All reactions were carried out in a seal tube unless otherwise noted. Reactions were monitored by thin-layer chromatography (TLC) using on Merck silica gel plates (60 F254) with visulization by UV or iodine staining. Flash chromatography was performed using Merck silica gel 60 (230-400 mesh) using compressed air. NMR spectra were obtained on Bruker Avance-500, Avance-400 or Avance-300 instruments using trimethylsilane (TMS) (0.00 ppm for ^{1}H NMR) and residue undeuterated chloroform as internal references (7.26 ppm for ^{1}H NMR and 77.00 ppm for ^{13}C NMR).

2,2-Diphenylpent-4-enenitrile[1] (S1)

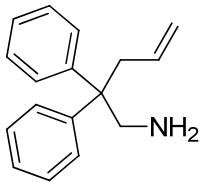


A solution of diphenylacetonitrile (1.93 g, 10.0 mmol) in DMF (3 mL) was added slowly to a suspension of NaH (252 mg, 10.5 mmol) in DMF (10 mL) and the resulting mixture was stirred at room temperature for 1 h. The resulting bright yellow suspension was cooled to 0 ºC, treated with allyl bromide (1.33 g, 11.0 mmol) and warmed to room temperature, then stirred overnight. The resulting solution was poured into an ice/water mixture and extracted with ethylacetate The combined organic layers were washed with water, dried ($MgSO_4$), and concentrated to give 2,2-diphenyl-4-pentenenitrile, which was used in the subsequent step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26 - 7.42 (m, 10H), 5.65 - 5.78 (m, 1H), 5.14 - 5.25 (m, 2H), 3.13 (d, *J* = 7.02 Hz, 2H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.8, 131.8, 128.9, 128.0, 127.1, 122.0, 120.4, 51.8, 44.0 ppm.

2,2-Diphenylpent-4-en-1-amine[2] (1a)

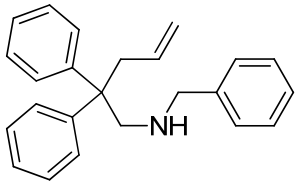


A suspension of $LiAlH_4$ (311 mg, 8.20 mmol) in diethylether (3 mL) was treated with crude 2,2-diphenylpent-4-enenitrile (478 mg, 2.05 mmol) at 0 ºC and then warm slowly to room temperature and stirred overnight. The resulting suspension was diluted with diethylether and then cooled to 0 ºC. To the cooled solution was added H_2O (0.3 mL) slowly. Then slowly add 0.3 mL NaOH (15%) and 0.9 mL H_2O successively to the mixture. The resulting suspension was warmed to room temperature and stirred for 30 minutes. After dried with $MgSO_4$, the solution was filtered and the filtrate was concentrated to give the product.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.14 - 7.32 (m, 10H), 5.33 - 5.46 (m, 1H), 4.94 - 5.09 (m, 2H), 3.32 (s, 2H), 2.92 (d, *J* = 7.02 Hz, 2H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.3, 134.7, 128.2, 128.1, 126.1, 117.7, 51.4, 48.6, 41.2 ppm.

N-Benzyl-2,2-diphenylpent-4-en-1-amine[2] (1f)

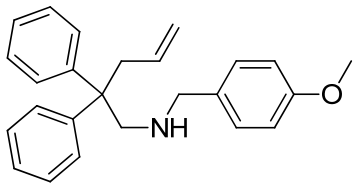


A solution of 2,2-diphenylpent-4-en-1-amine (300 mg, 1.27 mmol) and benzaldehyde (140 mg, 1.33 mmol) in 10 mL of MeOH was stirred at room temperature for 3.5 h, then treated with $NaBH_4$ (72 mg, 1.90 mmol) and stirred overnight. The resulting mixture was treated with water and 1M NaOH solution. Then the solution was extracted with dichoromethane for three tiemes. The combined extracts ware dried over $MgSO_4$ and concentrated. The resulting oily residue was purified by column chromatography to obtain the product.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.10 - 7.30 (m, 15H), 5.27 - 5.40 (m, 1H), 4.84 - 5.04 (m, 2H), 3.70 (s, 2H), 3.19 (s, 2H), 3.03 (d, *J* = 7.02 Hz, 2H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.9, 140.8, 135.0, 128.3, 128.2, 128.0, 128.0, 126.8, 126.1, 117.7, 55.4, 54.3, 50.3, 41.7 ppm.

N-(4-Methoxybenzyl)-2,2-diphenylpent-4-en-1-amine[2] (1g)

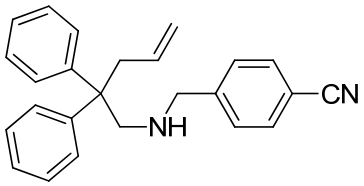


The procedure was similar to the preparation of **1f**.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 - 7.29 (m, 4H), 7.08 - 7.20 (m, 8H), 6.81 (d, *J* = 8.54 Hz, 2H), 5.28 - 5.40 (m, 1H), 4.84 - 5.02 (m, 2H), 3.78 (s, 3H), 3.64 (s, 2H), 3.18 (s, 2H), 3.02 (d, *J* = 7.02 Hz, 2H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.5, 146.9, 135.0, 132.9, 129.1, 128.1, 128.0, 126.0, 117.6, 113.6, 55.3, 55.2, 53.6, 50.2, 41.7 ppm.

4-(((2,2-diphenylpent-4-en-1-yl)amino)methyl)benzonitrile[2]

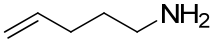


The procedure was similar to the preparation of **1f**.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54 (d, *J* = 8.24 Hz, 2H), 7.12 - 7.34 (m, 12H), 5.24 - 5.37 (m, 1H), 4.86 - 5.02 (m, 2H), 3.75 (s, 2H), 3.17 (s, 2H), 3.03 (d, *J* = 7.02 Hz, 2H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.6, 146.5, 134.8, 132.1, 128.5, 128.1, 128.0, 126.2, 119.1, 117.7, 110.5, 55.4, 53.7, 50.2, 41.6 ppm.

Pent-4-en-1-amine[2] (1b)

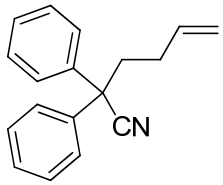


This compound was prepared from pent-4-enenitrile using the similar procedure as compound **1a**.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.79 (ddt, *J* = 6.60, 10.34, 17.05 Hz, 1H), 4.89 - 5.06 (m, 2H), 2.68 (t, *J* = 7.17 Hz, 2H), 2.07 (q, *J* = 7.22 Hz, 2H), 1.52 (q, *J* = 7.32 Hz, 2H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.4, 114.7, 41.6, 32.8, 31.1 ppm.

2,2-Diphenylhex-5-enenitrile[2] (S2)

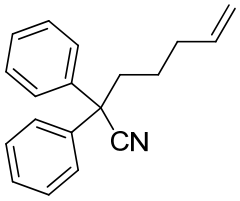


This compound was prepared from diphenylacetonitrile and 4-bromobut-1-ene using the similar procedure as compound **S1**.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26 - 7.44 (m, 10H), 5.81 (dd, *J* = 10.38, 17.09 Hz, 1H), 4.94 - 5.11 (m, 2H), 2.41 - 2.52 (m, 2H), 2.13 - 2.24 (m, 2H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.1, 136.7, 132.5, 130.1, 128.9, 128.3, 127.9, 126.9, 122.2, 115.7, 51.5, 38.9, 29.9 ppm.

2,2-Diphenylhept-6-enenitrile[2] (S3)

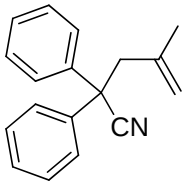


This compound was prepared from diphenylacetonitrile and 5-bromopent-1-ene using the similar procedure as compound **S1**.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26 - 7.42 (m, 10H), 5.74 (dd, *J* = 10.07, 17.09 Hz, 1H), 4.93 - 5.06 (m, 2H), 2.32 - 2.42 (m, 2H), 2.12 (q, *J* = 7.02 Hz, 2H), 1.48 - 1.61 (m, 2H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.3, 137.7, 132.4, 130.1, 128.9, 128.3, 127.9, 126.9, 122.4, 115.5, 51.7, 39.0, 33.4, 24.8 ppm.

4-Methyl-2,2-diphenylpent-4-enenitrile[2] (S4)

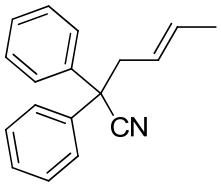


This compound was prepared from diphenylacetonitrile and 3-bromo-2-methylprop-1-ene using the similar procedure as compound **S1**.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 - 7.46 (m, 10H), 4.92 (t, *J* = 1.53 Hz, 1H), 4.76 (s, 1H), 3.12 (s, 2H), 1.51 (s, 3H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.0, 131.4, 128.8, 128.8, 127.8, 127.1, 124.2, 122.2, 52.2, 49.0, 24.1 ppm.

(*E*)-2,2-Diphenylhex-4-enenitrile[2] (S5)

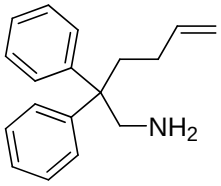


This compound was prepared from diphenylacetonitrile and (*E*)-1-bromobut-2-ene using the similar procedure as compound **S1**.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24 - 7.43 (m, 10H), 5.56 - 5.70 (m, *J* = 6.40 Hz, 1H), 5.27 - 5.41 (m, 1H), 3.05 (dt, *J* = 1.07, 7.02 Hz, 2H), 1.63 (dd, *J* = 1.53, 6.41 Hz, 3H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.0, 131.4, 128.8, 128.8, 127.8, 127.1, 124.2, 122.2, 52.2, 43.0, 18.1 ppm.

2,2-Diphenylhex-5-en-1-amine[2] (1c)

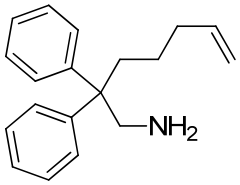


This compound was prepared from crude compound **S2** using the similar procedure as compound **1a**.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.11 - 7.37 (m, 10H), 5.77 (dd, *J* = 10.22, 16.94 Hz, 1H), 4.85 - 5.00 (m, 2H), 3.33 (s, 2H), 2.15 - 2.25 (m, 2H), 1.71 - 1.80 (m, 2H), 0.89 (br. s., 2H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.3, 138.8, 128.3, 128.1, 126.1, 114.4, 51.8, 49.2, 35.8, 28.6 ppm.

2,2-Diphenylhept-6-en-1-amine[2] (1d)

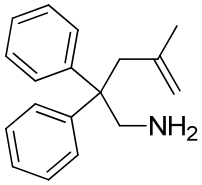


This compound was prepared from crude compound **S3** using the similar procedure as compound **1a**.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27 - 7.33 (m, 4H), 7.15 - 7.24 (m, 6H), 5.65 - 5.78 (m, 1H), 4.88 - 5.02 (m, 2H), 3.33 (s, 2H), 2.07 - 2.15 (m, 2H), 2.02 (q, *J* = 7.22 Hz, 2H), 1.06 - 1.17 (m, 2H), 0.89 (br. s., 2H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.0, 138.5, 128.7, 127.8, 127.1, 114.8, 48.9, 46.3, 35.4, 33.7, 23.2 ppm.

4-Methyl-2,2-diphenylpent-4-en-1-amine[2] (1e)

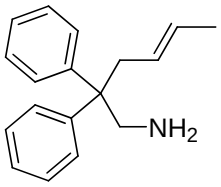


This compound was prepared from crude compound **S4** using the similar procedure as compound **1a**.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.14 - 7.31 (m, 10H), 4.82 (dd, *J* = 1.53, 2.14 Hz, 1H), 4.59 (d, *J* = 0.61 Hz, 1H), 3.41 (s, 2H), 2.92 (s, 2H), 1.07 (s, 3H), 0.84 (br. s., 2H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.5, 128.3, 128.3, 128.0, 126.8, 126.0, 51.6, 48.6, 49.0, 23.8 ppm.

(*E*)-2,2-diphenylhex-4-en-1-amine[2]

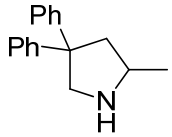


This compound was prepared from crude compound **S5** using the similar procedure as compound **1a**.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.12 - 7.34 (m, 10H), 5.44 (dd, *J* = 6.41, 15.26 Hz, 1H), 4.93 - 5.09 (m, 1H), 3.26 - 3.34 (m, 2H), 2.83 (d, *J* = 7.02 Hz, 2H), 1.56 (d, *J* = 6.41 Hz, 3H), 0.93 (br. s, 2H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.5, 128.3, 128.3, 128.0, 126.8, 126.0, 51.6, 48.6, 39.9, 18.1 ppm.

2-Methyl-4,4-diphenylpyrrolidine[2] (2a)



The compound was purified by flash column chromatography on silica gel (hexanes:EtOAc:Et_3N = 40:10:1) in 89 % yield (53 mg) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.12 - 7.34 (m, 10H), 3.68 (dd, *J* = 1.07, 11.44 Hz, 1H), 3.47 (d, *J* = 11.29 Hz, 1H), 3.38 (dt, *J* = 6.41, 8.85 Hz, 1H), 2.74 (dd, *J* = 6.56,

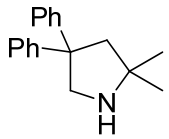
12.66 Hz, 1H), 2.54 (br. s., 1H), 2.04 (dd, *J* = 9.16, 12.51 Hz, 1H), 1.21 (d, *J* = 6.41 Hz, 3H) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ = 147.8, 147.1, 128.4, 128.3, 127.1, 127.0, 126.1, 126.0, 57.8, 57.3, 53.1, 47.1, 22.3 ppm.

FTIR (neat): *v* = 3017, 2963, 1489, 1450, 1219, 756, 702, 664 cm^{-1}.

HRMS (ESI, m/z): calculated for $C_{17}H_{19}N$ $[M+H]^+$: 238.1590, found $[M+H]^+$: 238.1598.

2,2-Dimethyl-4,4-diphenylpyrrolidine[2] (2e)



The compound was purified by flash column chromatography on silica gel (hexanes:EtOAc :Et_3N = 40:10:1) in 90 % yield (53 mg) as a faint yellow oil.

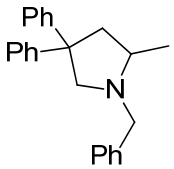
^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.07 - 7.33 (m, 10H), 3.64 (s, 2H), 2.54 (s, 2H), 1.15 (s, 6H) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ = 147.6, 128.4, 127.0, 125.9, 59.3, 58.4, 57.3, 52.1, 30.8 ppm.

FTIR (neat): *v* = 3017, 2963, 1489, 1450, 1219, 756, 702, 664 cm^{-1}.

HRMS (ESI, m/z): calculated for $C_{18}H_{21}N$ $[M+H]^+$: 252.1747, found $[M+H]^+$: 252.1760.

1-Benzyl-2-methyl-4,4-diphenylpyrrolidine[2] (2f)



The compound was purified by flash chromatography on silica gel (hexanes:EtOAc = 20:1) in 83 % yield as a white solid.

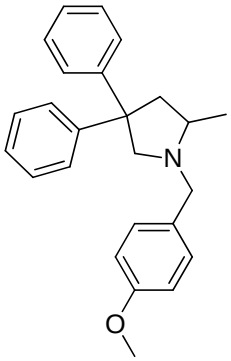
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.04 - 7.42 (m, 15H), 4.08 (d, *J* = 13.12 Hz, 1H), 3.64 (d, *J* = 9.77 Hz, 1H), 3.25 (d, *J* = 13.12 Hz, 1H), 2.87 - 2.95 (m, 1H), 2.81 - 2.87 (m, 1H), 2.78 (d, *J* = 10.07 Hz, 1H), 2.20 (dd, *J* = 7.78, 12.66 Hz, 1H), 1.16 (d, *J* = 6.10 Hz, 3H) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ = 150.6, 148.7, 140.1, 128.6, 128.2, 128.2, 127.8, 127.5, 127.3, 126.8, 125.8, 125.4, 66.5, 59.7, 58.0, 52.6, 48.0, 19.5 ppm.

FTIR (neat): *v* = 3017, 2970, 2793, 1489, 1450, 1219, 756, 702, 671 cm^{-1}.

HRMS (ESI, m/z): calculated for $C_{24}H_{25}N$ $[M+H]^+$: 328.2060, found $[M+H]^+$: 328.2057.

1-(4-Methoxybenzyl)-2-methyl-4,4-diphenylpyrrolidine[2] (2g)

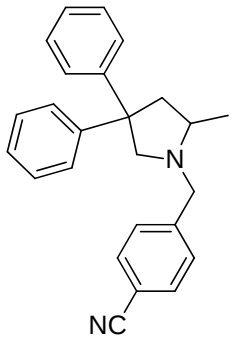


The compound was purified by flash chromatography on silica gel (hexane:EtOAc = 20:1) in 91 % yield as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.04 - 7.31 (m, 12H), 6.85 (d, *J* = 8.54 Hz, 2H), 4.01 (d, *J* = 12.82 Hz, 1H), 3.79 (s, 3H), 3.62 (d, *J* = 9.77 Hz, 1H), 3.19 (d, *J* = 13.12 Hz, 1H), 2.90 (dd, *J* = 7.63, 12.82 Hz, 1H), 2.72 - 2.85 (m, 2H), 2.19 (dd, *J* = 7.78, 12.66 Hz, 1H), 1.15 (d, *J* = 6.10 Hz, 3H) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.5, 150.6, 148.7, 132.0, 129.7, 128.1, 127.8, 127.4, 127.2, 125.7, 125.3, 113.5, 66.2, 59.5, 57.2, 55.2, 52.4, 48.0, 19.5 ppm.

4-((2-Methyl-4,4-diphenylpyrrolidin-1-yl)methyl)benzonitrile[2] (2h)



The compound was purified by flash chromatography on silica gel (hexane:EtOAc = 20:1) in 78 % yield as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (d, *J* = 7.93 Hz, 2H), 7.46 (d, *J* = 7.63 Hz, 2H), 7.09 - 7.31 (m, 10H), 4.08 (d, *J* = 14.34 Hz, 1H), 3.58 (d, *J* = 9.77 Hz, 1H), 3.35 (d, *J* = 14.34 Hz, 1H), 2.85 - 2.96 (m, 2H), 2.82 (d, *J* = 9.77 Hz, 1H), 2.17 - 2.31 (m, 1H), 1.16 (d, *J* = 5.19 Hz, 3H) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.3, 150.1, 148.4, 146.1, 132.1, 129.0, 128.2, 128.0, 127.3, 127.1, 126.0, 125.7, 119.1, 110.7, 66.5, 59.7, 57.6, 52.7, 47.7, 19.5 ppm.

(1) Bender, C. F.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2005**, *127*, 1070-1071.
(2) Hesp, K. D.; Tobisch, S.; Stradiotto, M. *J. Am. Chem. Soc.* **2010**, *132*, 413-426.

PART II

CHAPTER 3

Advances in the Application of Ammonia in Homogeneous Catalysis

3.1 GENERAL INTRODUCTION OF AMMONIA

Ammonia is very important to the nutritional needs of terrestrial organisms by serving as a precursor to food and fertilizers. It, either directly or indirectly, is also a valuable building block for the synthesis of numerous pharmachemicals, cleaners, polymer additives and many bulk chemicals, such as nitric acid, and ammonium hydroxide. For its many uses, ammonia is one of the most highly produced inorganic chemicals. Industrial production of NH_3 involves mainly reacting N_2 and H_2 at high pressure.[1] The worldwide ammonia production in 2004 was 109 million metric tonnes.[2] Despite its importance in industry, coupled with extremely low cost and great abundance, the study of metal catalyzed reactions with ammonia is still very limited. Currently, industrial amines are mainly produced by reaction of amine precursor with alkyl halides (*via* salt elimination) or alcohols (*via* dehydration routes).[3] Anti-Markovnikov addition of ammonia to olefins for the synthesis of primary amines and the direct catalytic addition of ammonia with aromatics to yield aromatic amines are listed among the ten most challenging goals for catalysis.[4] There are several reasons for the difficulty in utilizing ammonia as the nitrogen source to carry out catalytic reactions.[5] First, transition-metal catalysts are often deactivated by ammonia through formation of stable Werner amine complexes. Second, ancillary ligands from the transition metal are displaced by ammonia, generating inactive species. Third, strength of the N-H bond in ammonia (107 kcal mol^{-1}) renders "N-H activation" by

[1] Yandulov, D. V.; Schrock, R. R. *Science* **2003**, *301*, 76.
[2] *"United States Geological Survey publication".* Retrieved 2009-07-07
[3] Hayes, K. S. *Appl. Catal., A* **2001**, *221*, 187.
[4] Haggin, J. *Chem. Eng. News* **1993**, *71*.
[5] (a) Roundhill, D. M. *Chem. Rev.* **1992**, *92*, 1. (b) Zhao, J.; Goldman Alan, S.; Hartwig John, F. *Science* **2005**, *307*, 1080. (c) Lang, F.; Zewge, D.; Houpis, I. N.; Volante, R. P. *Tetrahedron Lett.* **2001**, *42*, 3251. (d) Aubin, Y.; Fischmeister, C.; Thomas, C. M.; Renaud, J.-L. *Chem. Soc. Rev.* **2010**, *39*, 4130. (e) van der Vlugt, J. I. *Chem. Soc. Rev.* **2010**, *39*, 2302. (f) Klinkenberg, J. L.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2010**, *50*, 86.

the metal centre challenging. Fourth, the moderate basicity of ammonia makes proton transferring difficult. Despite the existence of these difficulties, increasingly more attention is being directed to the use of ammonia in organic synthesis, with much progress achieved in this area. Amination of aryl halides with ammonia and dehydrogenative coupling with alcohols will be dealt with in the following sections.

3.2 DIRECT AMINATION OF ARYL HALIDES WITH AMMONIA

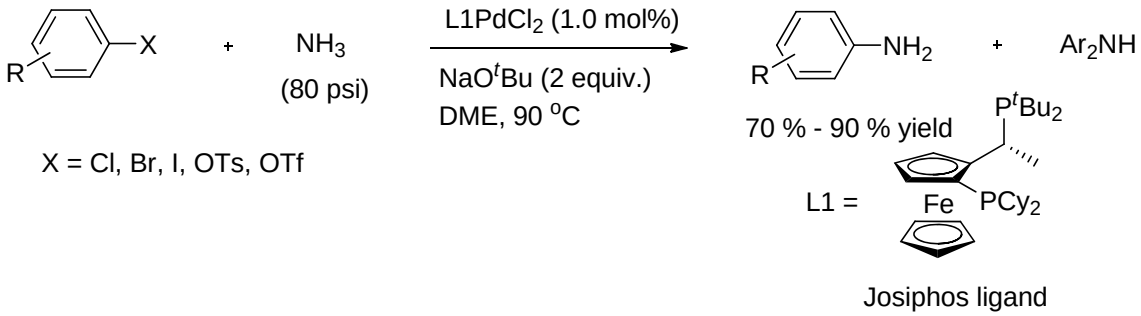
Primary aromatic amines are very important feedstocks that are frequently used in the synthesis of pharmaceuticals, insecticides and material sciences. One of the most desirable synthetic methods for the primary aromatic amines is the direct reaction of aryl halides with ammonia. Indeed, the synthesis of aromatic amines by the direct reaction of aromatics with ammonia is also regarded as one of the ten challenges for catalysis.[6] The preparation of aniline *via* "C-H activation" of benzene with ammonia is also a dream for organic chemists. Although there are many reports on the use of aryl halides for the synthesis of secondary and tertiary amines,[7] the reactions of aryl halides with ammonia are only reported in recent years. There are also a number of papers pertaining to the reactions of aryl halide with ammonia surrogates for the synthesis of primary aromatic amines.[8] However, this is not

[6] Haggin, J. *Chem. Eng. News* **1993**, *71*.
[7] (a) Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338. (b) Navarro, O.; Marion, N.; Mei, J.; Nolan, S. P. *Chem.-Eur. J.* **2006**, *12*, 5142. (c) Anderson, K. W.; Tundel, R. E.; Ikawa, T.; Altman, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 6523. (d) Shen, Q.; Ogata, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 6586. (e) Fors, B. P.; Watson, D. A.; Biscoe, M. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 13552. (f) Guram, A. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 7901. (g) Paul, F.; Patt, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 5969.
[8] (a) Grasa, G. A.; Viciu, M. S.; Huang, J.; Nolan, S. P. *J. Org. Chem.* **2001**, *66*, 7729. (b) Zheng, Z.; Elmkaddem, M. K.; Fischmeister, C.; Roisnel, T.; Thomas, C. M.; Carpentier, J.-F.; Renaud, J.-L. *New J. Chem.* **2008**, *32*, 2150. (c) Ikawa, T.; Barder, T. E.; Biscoe, M. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 13001. (d) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158. (e) Lee, D.-Y.; Hartwig, J. F. *Org. Lett.* **2005**, *7*, 1169. (f) Leung, S. K.-Y.; Huang, J.-S.; Liang, J.-L.; Che, C.-M.; Zhou, Z.-Y. *Angew. Chem., Int. Ed.* **2003**, *42*, 340.

economical and additional steps are needed to remove the protecting groups which produce a lot of waste. Hence, ammonia is the most promising N-nucleophile. There are two main kinds of transition metal complexes that can catalyze the reaction of aryl halides and ammonia: Palladium and copper complexes.

Palladium.

The first example of palladium catalyzed amination of aryl halides with ammonia was reported by Hartwig *et al*. in 2006.[9] They used a bulky diphosphine Josiphos as the ligand, which could not be replaced by ammonia (Scheme 1). The base, solvent, pressure of ammonia and concentration are crucial for high conversions and the selectivity of primary amine *vs*. secondary amine. Unfortunately, only phenols were obtained with aryl sulfonats as substrates. In 2009, Vo and Hartwig[10] extended the formation of primary aryl amines by using the highly active, air-stable combination of [Pd(P-*o*-tol$_3$)$_2$] and Josiphos ligand as catalyst with the aim to overcome the limitations of the previous report.[9] A wide variety of functional groups on the aryl halides were tolerated. The loading of the catalyst was also decreased.

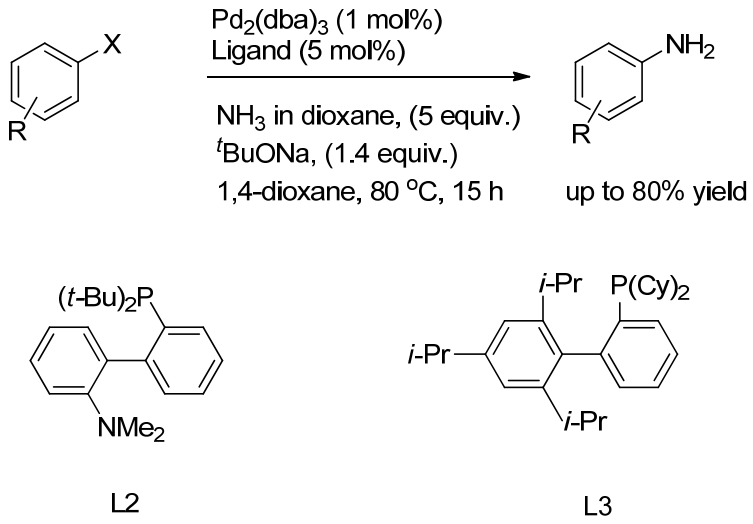


Scheme 1 Coupling of aryl halides with ammonia reported by Hartwig.

In 2007, Buchwald and co-workers reported a similar amination of aryl halides with ammonia using $Pd_2(dba)_3$(dba = *trans*,*trans*-dibenzylideneacetone) and different

[9] Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 10028.
[10] Vo, G. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2009**, *131*, 11049.

phosphine ligands to obtain mono-, bis- and triarylamines selectively.[11] With biaryl phosphine ligand L2, primary amine was efficiently obtained, whereas the use of ligand **L3** afforded secondary amines (Scheme 2). Triarylamines could also be



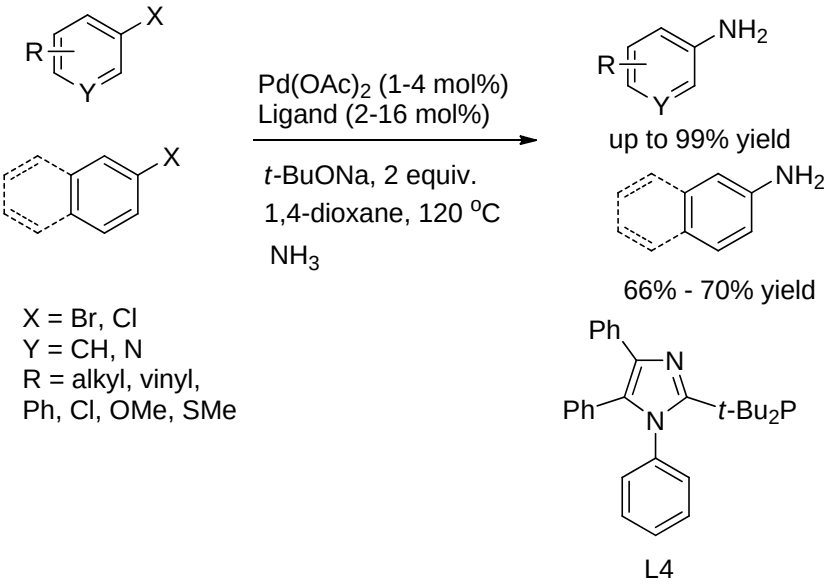
Scheme 2 $Pd_2(dba)_3$ catalyzed coupling of ammonia with aryl halides reported by Buchwald.

obtained using ligand **L2** at a higher concentration at 100 ºC. Interestingly, unsymmetrical diarylamines and triarylamines were successfully synthesized by using $Pd_2(dba)_3$/L2 and then $Pd_2(dba)_3$/L3 at different concentrations and different temperatures in a one-pot manner.

In 2009, Beller *et al.* used bulky indoxyl- or imidazolylphosphine ligands to extend this methodology for more challenging substrates, such as aminoaryl halides, halostyrenes and halopyridines.[12] The ligand is air stable, and only primary amines were observed at high reaction temperature of 120 ºC (Scheme 3). Note that a high pressure of nitrogen was used along with ammonia gas.

[11] Surry, D. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 10354.
[12] Schulz, T.; Torborg, C.; Enthaler, S.; Schaeffner, B.; Dumrath, A.; Spannenberg, A.; Neumann, H.; Boerner, A.; Beller, M. *Chem.--Eur. J.* **2009**, *15*, 4528.

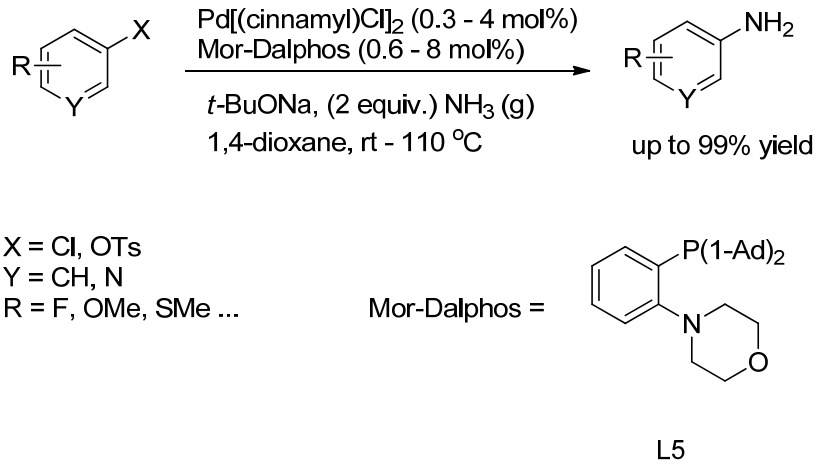
In 2010, Stradiotto and co-workers have developed P,N ligands for the cross-coupling of ammonia with deactivated aryl chlorides and aryl tosylates at room temperature.[13] After screening a series of P,N ligands, Mor-Dalphos ligand was found



Scheme 3 Pd-catalyzed cross-coupling of aryl bromides and chlorides with ammonia using imidazole-based ligands.

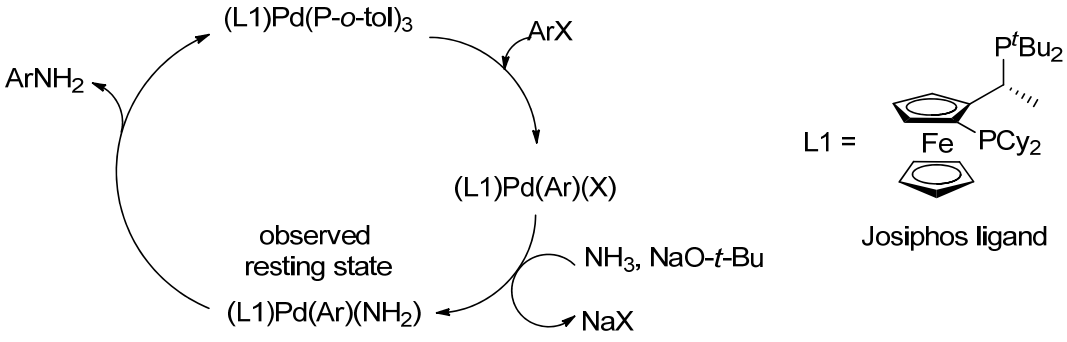
to be the most effective ligand with Pd[(cinnamyl)Cl]$_2$ as Pd source and *t*-BuONa as base in 1,4-dioxane (Scheme 4). With a moderate catalyst loading, the reaction proceeded at lower pressures and temperatures. A variety of substituents on the aryl chloride were tolerated. However, only a few aryl tosylates were reported.

[13] Lundgren, R. J.; Peters, B. D.; Alsabeh, P. G.; Stradiotto, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 4071.



Scheme 4 Mor-Dalphos-ligated Pd-catalyzed cross-coupling of aryl chlorides and tosylates with ammonia reported by Stradiotto.

Recently, Hartwig and co-workers reported a detailed mechanism study of Pd catalyzed amination of aryl halides with ammonia using Josiphos ligand.[14] The CyPf-*t*-Bu-ligated arylpalladium parent amido complexes were formed more rapidly and more stable than the arylamido complexes. The catalytic cycle was presented in the paper (Scheme 5). The slow rate of reductive elimination resulted in the arylpalladium amido complex being the resting state in the coupling of aryl halides and ammonia, which is different from that in the reactions of aryl halides



Scheme 5 Mechanism of Pd-Catalyzed amination with ammonia and observed arylpalladium parent amido resting state reported by Hartwig.

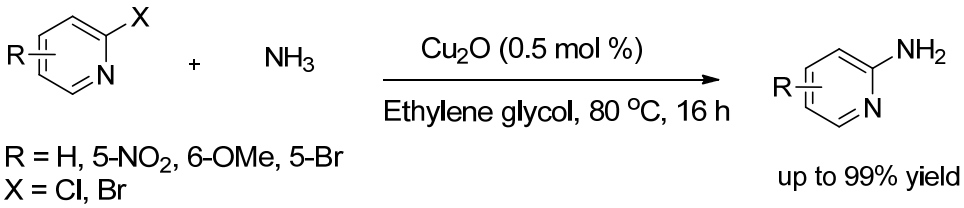
[14] Klinkenberg, J. L.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 11830.

with amines, catalyzed by most palladium complexes.

Copper

Although palladium catalysts are successful in the cross-coupling of aryl halides with ammonia, the cost of catalysts and ligands is one major drawback. Copper salts are readily available and cheap, and have been used in the Ullmann and Goldberg reactions of aryl halides with amines and other nitrogen nucleophiles for many years.[15]

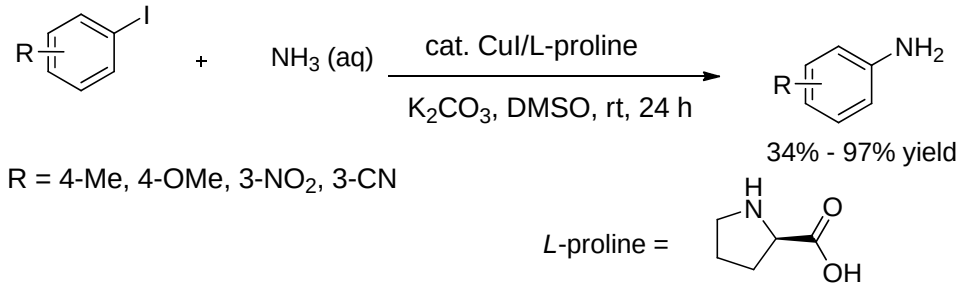
In 2001, researchers in Merck reported the first copper-catalyzed aryl amination reaction with ammonia.[16] It involved the use of ligand-free copper oxide as catalyst in 8M solution of ammonia in ethylene glycol at 80 ^{o}C and low pressure. This reaction proceeded with excellent selectivity in the formation of a monoarylamine, despite its limited substrate scope (Scheme 6).



Scheme 6 Copper-catalyzed coupling of heteroaryl halides with ammonia.

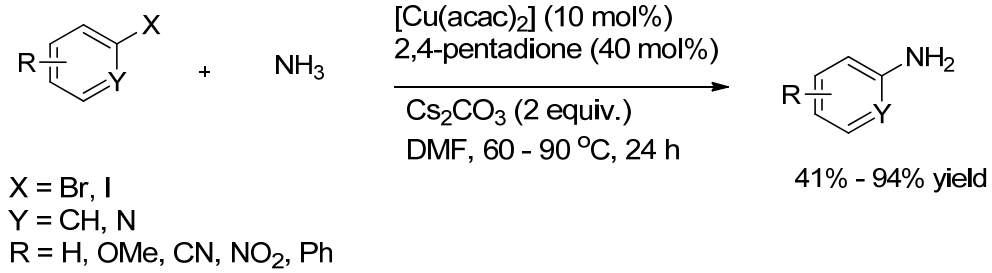
In 2008, Chang and co-worker reported the amination of aryl iodides and activated aryl bromides with solid NH_4Cl and aqueous ammonia, catalyzed by CuI and L-proline at room temperature.[17] This transformation was favoured by the presence of electron-withdrawing substituent on the aryl iodides (Scheme 7).

[15] Ullmann, F. *Ber.* **1903**, *36*, 2382.
[16] Lang, F.; Zewge, D.; Houpis, I. N.; Volante, R. P. *Tetrahedron Lett.* **2001**, *42*, 3251.
[17] Kim, J.; Chang, S. *Chem. Commun. (Cambridge, U. K.)* **2008**, 3052.



Scheme 7 CuI/proline-catalyzed N-arylation of aryl iodides with aqueous NH_3 solution reported by Chang.

In 2009, Taillefer and Xia described the coupling reaction between less reactive substrates with ammonia, using [$Cu(acac)_2$] as catalyst, 2,4-pentadione as ligand, and

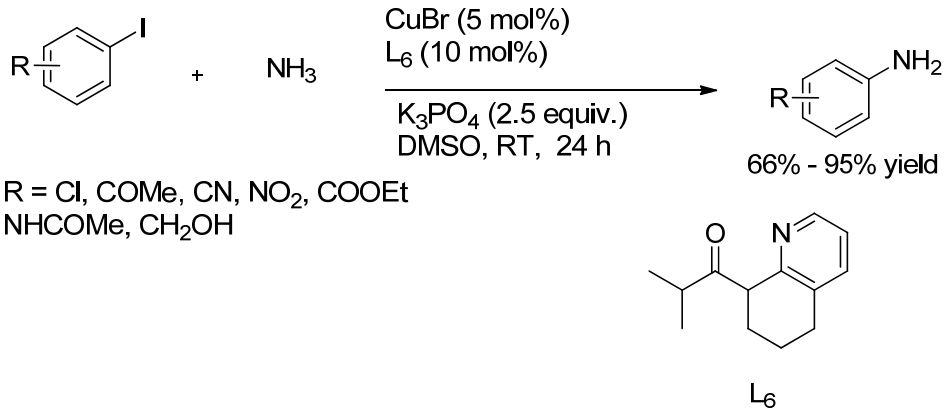


Scheme 8 Arylation of ammonia with aryl bromides and iodides catalyzed by Cu and 2,4-pentadione.

Cs_2CO_3 as base (Scheme 8).[18] Besides aryl iodides, unactivated aryl bromides were also coupled with aqueous ammonia in DMF at 90 ºC.

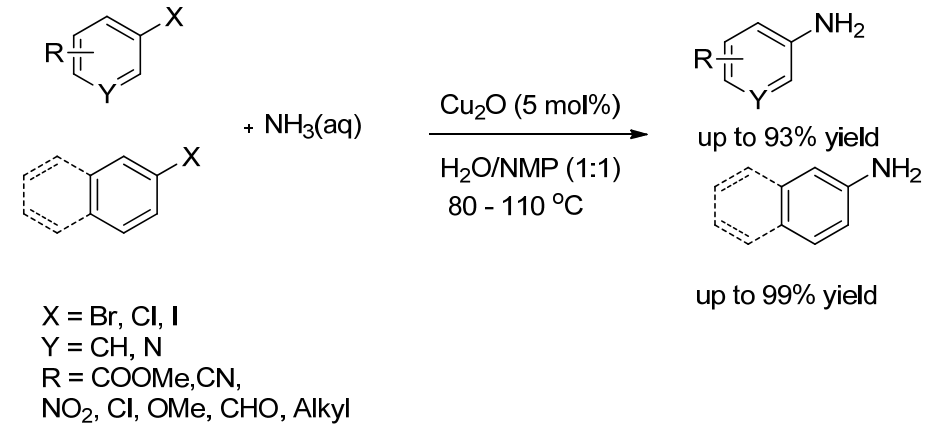
Subsequently, Ding and co-workers reported similar coupling reaction of aryl iodides with aqueous ammonia at room temperature.[19] They used CuBr as the catalyst and 2-pyridinyl-β-ketone as lthe igand with K_3PO_4 as the base in DMSO (Scheme 9). A wide range of substrates were reported for this reaction. Only a few substrates required high temperature to achieve high yields.

[18] Xia, N.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 337.
[19] Wang, D.; Cai, Q.; Ding, K. *Adv. Synth. Catal.* **2009**, *351*, 1722.



Scheme 9 Cross coupling of aryl iodides with aqueous ammonia at room temperature reported by Ding.

Wolf and Xu reported a simple method for the coupling of both activated and

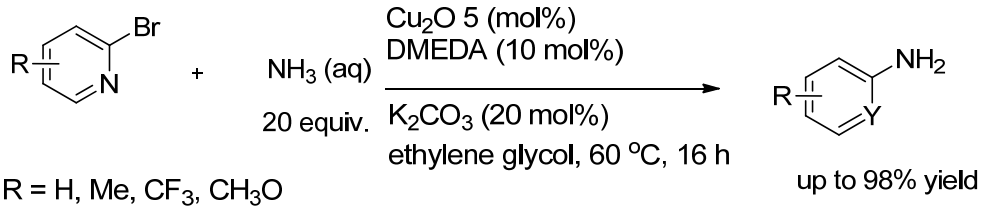


Scheme 10 Cross coupling of aryl halides with aqueousammonia catalyzed by ligand-free Cu reported by Wolf.

non-activated aryl halides with aqueous ammonia, catalyzed by Cu_2O in aqueous NMP (*N*-methyl pyrrolidinone).[20] Many functional groups were tolerated by this catalytic system, and no base was needed (Scheme 10). For aryl chlorides, microwave irradiation was conducted at 110 ºC for good yields.

[20] Xu, H.; Wolf, C. *Chem. Commun. (Cambridge, U. K.)* **2009**, 3035.

In 2010, Renaud and co-workers reported an efficient method for the synthesis of aminopyridines using aqueous ammonia.[21] They used Cu_2O as catalyst, K_2CO_3 as base and DMEDA (dimethylethylenediamine) as ligand in ethylene glycol at 60 ºC (Scheme 11). In addition, only a few substrates were tolerated.



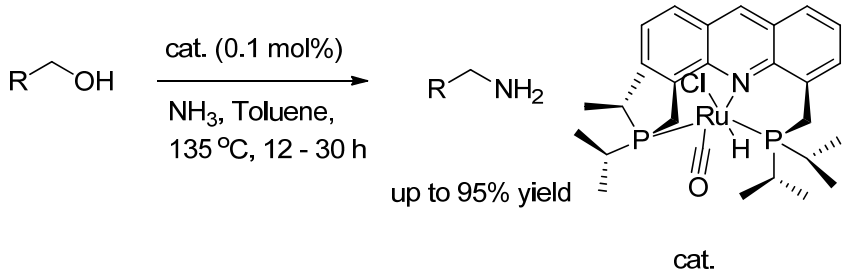
Scheme 11 Amination of pyridine bromide with aqueous ammonia catalyzed by Cu_2O reported by Renaud.

3.3 ALKYLATION OF AMMONIA WITH ALCOHOLS

Besides coupling with aryl halides, another main aspect for the utility of ammonia in homogeneous catalysis is the dehydrogenative coupling of ammonia with alcohols. Conventional methods for the conversion of alcohols to amines typically involve two or three steps, and each step always requires isolation and purification, which makes scaling-up difficult. In industry, amination of alcohols using ammonia is performed with heterogeneous catalysts on a multithousand-ton scale, which is very atom-efficient with water as the only side product. However, there are some drawbacks for heterogeneous catalysis: high temperature, high pressure, difficulty in controlling the chemoselectivity and narrow substrate scopes. Besides the heterogeneous catalysis, the homogeneous catalysis for this kind of reaction is very challenging.

[21] Elmkaddem, M. K.; Fischmeister, C.; Thomas, C. M.; Renaud, J.-L. *Chem. Commun. (Cambridge, U. K.)* **2010**, *46*, 925.

There are many methods for the synthesis of primary amines, such as reduction of amides.[22] The first homogeneously catalyzed amination of alcohols with ammonia was reported by Gunanathan and Milstein in 2008.[23] In 2007, this group reported the direct synthesis of amide from amines and alcohols with liberation of H_2 using PNP [2,6-bis(di-tert-butylphosphinomethyl)pyridine] pincer-type Ru(II) complex as catalyst.[24] Changing the cooperative ligand PNP to an acridine-based pincer complex significantly altered the properties of the catalyst. Instead of yielding amides, the corresponding primary amines with conversions of up to 100% and selectivity of up to 87% were obtained when they used [RuHCl(A-*i*PrPNP)(CO)] as catalyst with 7.5 atm of ammonia (Scheme 12). The major side product was the secondary imine. There are also some drawbacks in this system: high temperature and no desired transformation with secondary alcohols.

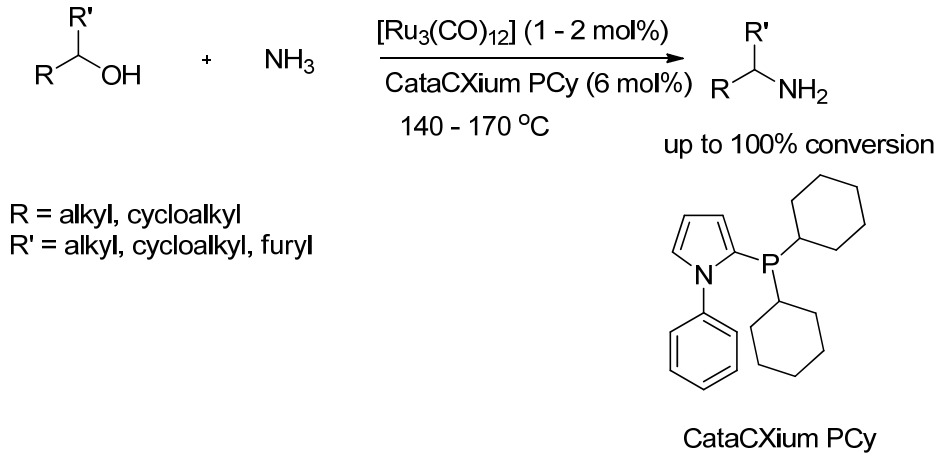


Scheme 12 Ru/PNP pincer complex for primary alcohol amination reported by Gunanathan and Milstein.

In 2010, Beller's group[25] and Vogt's group[26] reported the same catalytic system for the direct amination of secondary alcohols using ammonia. They developed the ideas from the catalytic system for the aminations of alcohols with

[22] Nunez Magro, A. A.; Eastham, G. R.; Cole-Hamilton, D. J. *Chem. Commun. (Cambridge, U. K.)* **2007**, 3154.
[23] Gunanathan, C.; Milstein, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 8661.
[24] Gunanathan, C.; Ben-David, Y.; Milstein, D. *Science (Washington, DC, U. S.)* **2007**, *317*, 790.
[25] Imm, S.; Baehn, S.; Neubert, L.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 8126.
[26] Pingen, D.; Mueller, C.; Vogt, D. *Angew. Chem., Int. Ed.* **2010**, *49*, 8130.

primary and secondary amines using ruthenium catalyst.[27] Both of them screened a series of ruthenium catalysts as catalyst precursors in combination with numerous phosphorus ligands. They found the best catalyst was the combination of $[Ru_3(CO)_{12}]$ with CataCXium PCy (Scheme 13). The only difference between the two papers was the solvent used. Beller used *tert*-amyl alcohol as the solvent, while Vogt used cyclohexane. In addition, Beller and co-workers added molecular sieves to improve the yield. The corresponding secondary imines and ketone were the main side products. The main drawbacks for the two papers were the need of high temperature (140 ºC and 170 ^{o}C) and the use of autoclave.



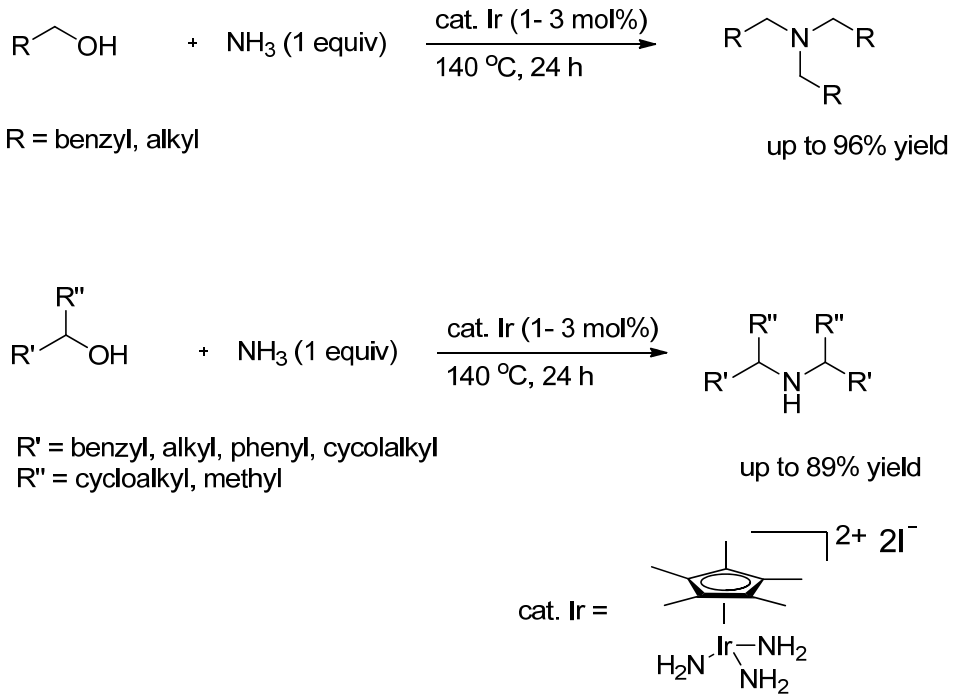
Scheme 13 $[Ru_3(CO)_{12}]$/CataCXium PCy for secondary alcohols amination with ammonia reported by Beller and Vogt.

In 2010, Yamaguchi and co-workers reported the multialkylation of aqueous ammonia with alcohols catalyzed by Cp*Ir-amine complexes.[28] A series of $[Cp^*IrX_2]_2$ (X = Cl, Br, I) were reacted with ammonia to give water soluble

[27] (a) Watanabe, Y.; Tsuji, Y.; Ohsugi, Y. *Tetrahedron Lett.* **1981**, *22*, 2667. (b) Grigg, R.; Mitchell, T. R. B.; Sutthivaiyakit, S.; Tongpenyai, N. *J. Chem. Soc., Chem. Commun.* **1981**, 611. (c) Moon, M. P.; Komin, A. P.; Wolfe, J. F.; Morris, G. F. *J. Org. Chem.* **1983**, *48*, 2392. (d) Tillack, A.; Hollmann, D.; Mevius, K.; Michalik, D.; Bähn, S.; Beller, M. *Eur. J. Org. Chem.* **2008**, 4745. (e) Bähn, S.; Imm, S.; Mevius, K.; Neubert, L.; Tillack, A.; Williams, J. M. J.; Beller, M. *Chem – Eur. J.* **2010**, *16*, 3590. (f) Hamid, M. H. S. A.; Allen, C. L.; Lamb, G. W.; Maxwell, A. C.; Maytum, H. C.; Watson, A. J. A.; Williams, J. M. J. *J. Am. Chem. Soc.* **2009**, *131*, 1766. (g) Bähn, S.; Imm, S.; Mevius, K.; Neubert, L.; Tillack, A.; Williams, J. M. J.; Beller, M. *Chem – Eur. J.* **2010**, *16*, 3590.

[28] Kawahara, R.; Fujita, K. I.; Yamaguchi, R. *J. Am. Chem. Soc.* **2010**, *132*, 15108.

$[Cp^*Ir(NH_3)_3][X]_2$ (X = Cl, Br, I), which were used to catalyze the reaction of benzyl alcohol with ammonia. Among these iridium catalysts, $[Cp^*Ir(NH_3)_3][I]_2$ was found to have the best catalytic ability, with which a series of alcohols were converted to amine products (Scheme 14). For primary alcohols, trialkylamines were obtained. For



Scheme 14 $[Cp^*Ir(NH_3)_3][I]_2$ catalyzed multialkylation of alcohols with aqueous ammonia reported by Yamaguchi and co-workers.

secondary alcohols, only secondary amines were obtained due to the steric hinderance. Noticeably, only one equivalent of ammonia was used. The iodide ion (I^-) was also important for this transformation. The catalyst could be recycled and used for three times without significant drop in the catalytic ability.

PART II

CHAPTER 4

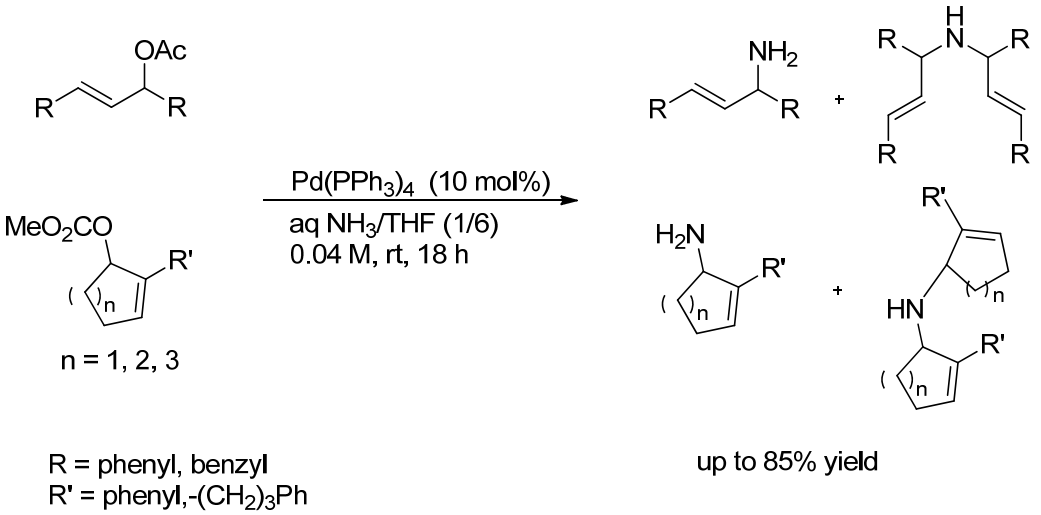
Pd-NHC Complex Catalyzed Allylic Amination Using Ammonia for the Synthesis of Primary Amines

4.1 GENERAL INTRODUCTION FOR ALLYLIC AMINATION WITH AMMONIA

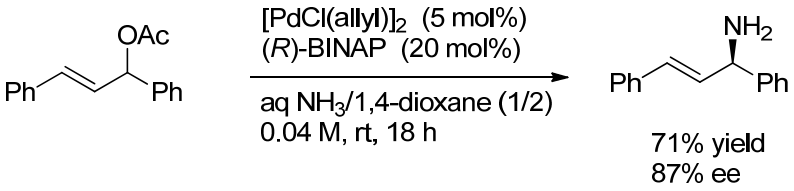
Allylamines are important building blocks in organic synthesis, being used for the synthesis of many compounds such as amino acids,[1] and different alkaloids.[2] The allylamine moiety is also widely featured in a vast number of natural products. During the past four decades, the palladium-catalyzed allylic amination has been well-established for the synthesis of allylamines. For the preparation of primary amines, using ammonia as the nitrogen source in allylic amination is the most effective and atom-economical. However, due to the difficulties plaguing the use of ammonia, which are listed in the chapter 3, ammonia was regarded as an ineffective nucleophile in π-allylpalladium chemistry.[3] Therefore, numerous ammonia surrogates, such as *p*-toluenesulfonamides,[4] phthalimide,[5] di-tert-butyl iminodicarbonate,[6] and sodium azide,[7] are used in allylic amination for the synthesis of primary amines followed by deprotection after reaction. In 2009, Kobayashi and Nagano reported the first example of palladium-catalyzed allylic amination with aqueous ammonia for the synthesis of primary amines.[8] They used a catalytic amount of $Pd(PPh_3)_4$ to catalyze the reaction of allyl acetates and carbonates with aqueous ammonia in 1,4-dioxane to obtain the primary allylamines with good yield at room temperature (Scheme 1). However, no reaction was observed with ammonia gas under the same reaction conditions. In

[1] (a) Hayashi, T.; Yamamoto, A.; Ito, Y.; Nishioka, E.; Miura, H.; Yanagi, K. *J. Am. Chem. Soc.* **1989**, *111*, 6301. (b) Bower, J. F.; Jumnah, R.; Williams, A. C.; Williams, J. M. J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1411. (c) Burgess, K.; Liu, L. T.; Pal, B. *J. Org. Chem.* **1993**, *58*, 4758.
[2] (a) Magnus, P.; Lacour, J.; Coldham, I.; Mugrage, B.; Bauta, W. B. *Tetrahedron* **1995**, *51*, 11087. (b) Trost, B. M. *Angew. Chem.* **1989**, *101*, 1199.
[3] Godleski, S. A. *Comprehensive Organic Synthesis* **1991**, *4*, 585.
[4] Byström, S. E.; Aslanian, R.; Bäckvall, J. E. *Tetrahedron Lett.* **1985**, *26*, 1749.
[5] Inoue, Y.; Taguchi, M.; Toyofuku, M.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 3021.
[6] Connell, R. D.; Rein, T.; Åkermark, B.; Helquist, P. *J. Org. Chem.* **1988**, *53*, 3845.
[7] Murahashi, S.; Taniguchi, Y.; Imada, Y.; Tanigawa, Y. *J. Org. Chem.* **1989**, *54*, 3292.
[8] Nagano, T.; Kobayashi, S. *J. Am. Chem. Soc.* **2009**, *131*, 4200.

addition, the 0.04 M concentration was critical for this reaction as further dilution resulted in no conversion, which was probably due to deactivation of the palladium catalyst upon liberation of phosphine ligands. Chiral phosphine ligand (*R*)-BINAP was used for the asymmetric variant of this reaction to afford primary amines in good yield and high enantioselectivity (Scheme 2). However, no substrates possessing less sterically hindered groups or unsymmetrical linear allyl carbonates were reported.



Scheme 1. $Pd(PPh_3)_4$-catalyzed allylic amination with aqueous ammonia for the synthesis of primary amines reported by Kobayashi and Nagano.

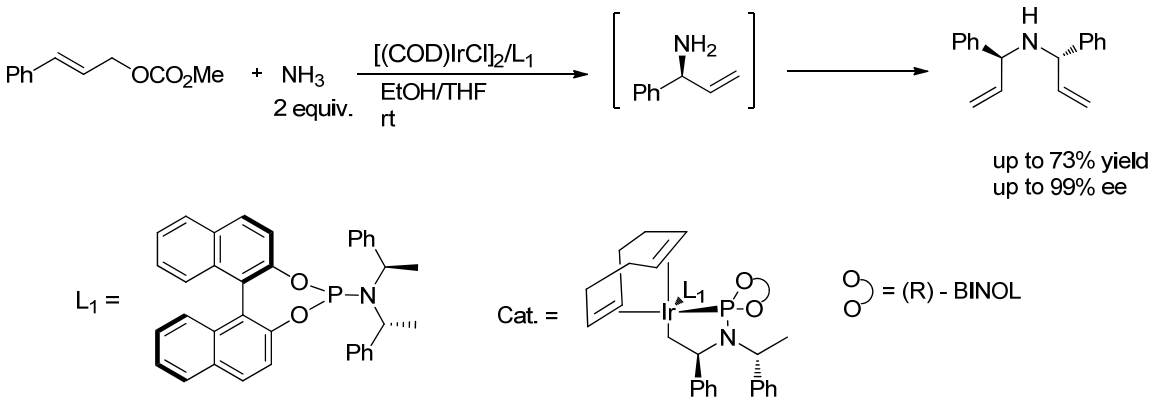


Scheme 2. Preliminary Investigation of asymmetric allylic amination using aqueous ammonia reported by Kobayashi and Nagano.

Subsequently, Hartwig and co-workers reported the iridium-catalyzed enantioselective monoallylation of ammonia.[9] In 2007, Hartwig and co-workers

[9] Pouy, M. J.; Stanley, L. M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2009**, *131*, 11312.

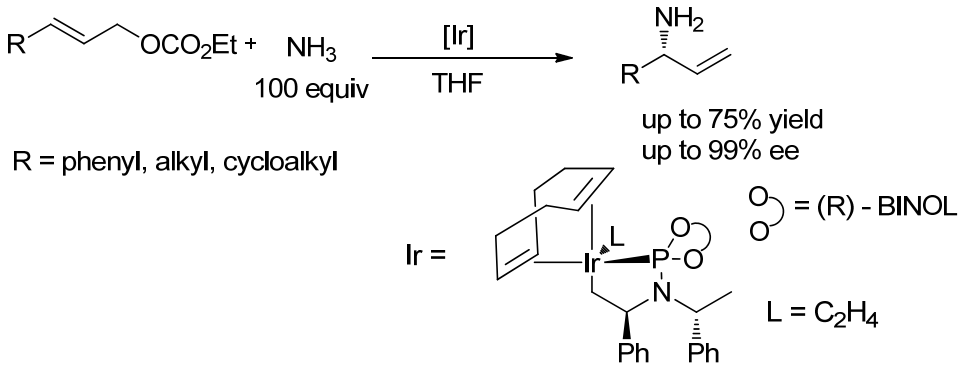
reported a similar reaction.[10] They first synthesized the active Ir catalyst (cat. in Scheme 3) *in situ* by heating $[Ir(COD)Cl]_2$ with the phosphoramidite ligand (L_1) and propylamine in THF for 30 minutes. Subsquently, they used the catalyst with additional $[Ir(COD)Cl]_2$ to catalyze the reaction of cinnamyl methyl carbonate with ethanolic ammonia in THF at room temperature (Scheme 3). Instead of chiral primary amine, only symmetrical diallylamine was obtained in 93% yield, 94:6 dr and



Scheme 3. Ir-catalyst for asymmetric allylic amination using ammonia reported by Hartwig and co-workers.

99% *ee*. Later in 2009, they found that the metalacyclic complex $[Ir(COD)(\kappa^2\text{-}L_1)L_1]$ (cat. in Scheme 1) would liberate the phosphoramidite ligand (L_1) to give $[Ir(COD)Cl]_2$, and the latter could react with ammonia to form an unidentified species. It was also found that the amount of ammonia was important to generate the primary amines. Therefore, 100 equivalents of ammonia were needed at 30 ºC to produce the best result (Scheme 4). Another Ir catalyst (Ir in Scheme 4) without additive was also explored, and the best yield, chemical selectivity and enantioselectivity could be achieved when ethyl carbonates were employed as the leaving group.

[10] Pouy, M. J.; Leitner, A.; Weix, D. J.; Ueno, S.; Hartwig, J. F. *Org. Lett.* **2007**, *9*, 3949.



Scheme 4. Ir catalyst for asymmetric allylic amination using ammonia reported by Hartwig and co-workers.

4.2 PD-NHC CATALYZED ALLYLIC AMINATION USING AMMONIA FOR THE SYNTHESIS OF PRIMARY AMINES

4.2.1 Design

Up to now, for the synthesis of primary amines *via* allylic amination with ammonia catalyzed by palladium catalyst, only one paper has been reported by Kobayashi,[8] where several limitations exist. Firstly, no reaction was observed using ammonia gas in their catalytic system, since ammonia gas behaves differently from aqueous ammonia. Secondly, secondary amines were still formed as side products in small quantity. Thirdly, when the concentration decreased to 0.03 M, no reaction occurred with $Pd(PPh_3)_4$ for it may liberate PPh_3 under high dilute conditions, where the active Pd(0) species failed to be stabilized. Additional PPh_3 was needed to restore the catalytic activity. Thus, it still remains a challenge to use palladium catalyst to execute allylic aminations with ammonia. Considering the above limitations, we designed a $Pd(NHC)(PPh)_n$ (n = 1, 2, 3) system to catalyze the allylic amination with

ammonia gas, based on the properties of N-heterocyclic carbenes (NHCs) and the differences between NHC and PPh_3 as ligand.

N-Heterocyclic carbenes (NHCs) were firstly reported by Wanzlick and Schönherr [11] and Öfele [12] in 1968 independently. In 1991,[13] Arduengo and co-workers revealed the first stable, crystalline NHC(IAd) (Figure 1). A lot of NHC complexes

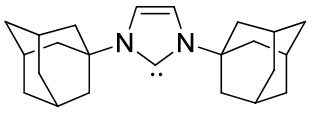


Figure 1 The structure of IAd

with main-group and transition metals have been reported.[14] Similar to other transition metals, for palladium complexes, the NHCs serve as powerful, neutral two electron donors to form a single bond to the palladium,[15] while the π-back donation from the Pd to the NHC π* orbital is always negligible.[16] Although using NHCs as phosphine mimics proved to be an effective way to catalyst refinement by simply replacing phosphine ligands with NHCs,[17] studies on the electronic and steric effects of NHC substituents in transition-metal-NHC complexes are not as extensive as that for phosphine ligands.[18] Compared to phosphine ligands, NHCs have similar electronic structure, but with huge differences in their topology (Figure 2).[19] As shown in the figure, the three substituents on the phosphine are directed away from the metal, like a cone, while the substituents on the NHC nitrogen atoms are pointing forward, forming

[11] Wanzlick, H. W.; Schönherr, H. J. *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 141.
[12] Öfele, K. *J. Organomet. Chem.* **1968**, *12*, P42.
[13] Arduengo, A. J., III; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1991**, *113*, 361.
[14] Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290.
[15] (a) Scott, N. M.; Nolan, S. P. *Eur. J. Inorg. Chem.* **2005**, 1815. (b) Crabtree, R. H. *J. Organomet. Chem.* **2005**, *690*, 5451.
[16] (a) Green, J. C.; Herbert, B. J. *Dalton Trans.* **2005**, 1214. (b) Green, J. C.; Scurr, R. G.; Arnold, P. L.; Cloke, F. G. N. *Chem. Commun. (Cambridge)* **1997**, 1963.
[17] (a) Scott, N. M.; Nolan, S. P. *Eur. J. Inorg. Chem.* **2005**, 1815. (b) Crabtree, R. H. *J. Organomet. Chem.* **2005**, *690*, 5451.
[18] (a) Cavallo, L.; Correa, A.; Costabile, C.; Jacobsen, H. *J. Organomet. Chem.* **2005**, *690*, 5407. (b) Tolman, C. A. *Chem. Rev.* **1977**, *77*, 313.
[19] (a) Orpen, A. G.; Connelly, N. G. *J. Chem. Soc., Chem. Commun.* **1985**, 1310. (b) Herrmann, W. A.; Schütz, J.; Frey, G. D.; Herdtweck, E. *Organometallics* **2006**, *25*, 2437.

a cage around the metal centre, generating stronger impact since NHC ligands are stronger σ-donors with weaker π-acidity;[20] as a result, they can form stronger bonds

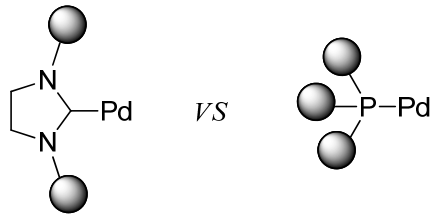


Figure 2 Comparison of the steric topographies of phosphane-Pd and NHC-Pd.

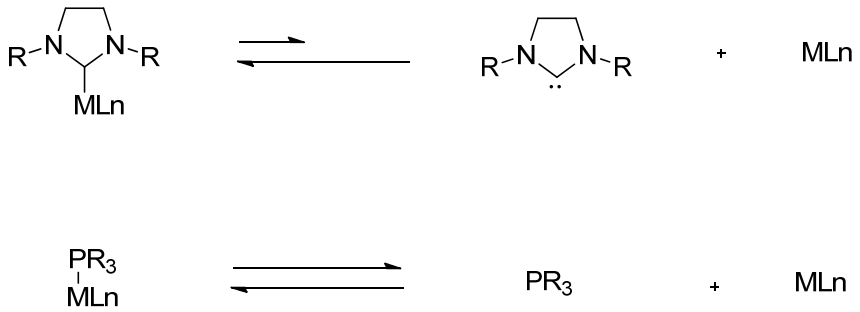


Figure 3 Comparison of the stability of phosphane-metal and NHC-metal.

with the metal centre than phosphines (Figure 3).

Currently, though NHCs can be used as catalysts, they are mainly used as ligands for transition metal catalysts in three aspects: metathesis, Pd-catalyzed reactions and hydrosilylation. Recent advancements are focused on various reactions catalyzed by Pd-NHC complexes, such as oxidations,[21] allylic alkylations,[22] Heck

[20] (a) Cavallo, L.; Correa, A.; Costabile, C.; Jacobsen, H. *J. Organomet. Chem.* **2005**, *690*, 5407. (b) Penka, E. F.; Schlaepfer, C. W.; Atanasov, M.; Albrecht, M.; Daul, C. *J. Organomet. Chem.* **2007**, *692*, 5709. (c) Diez-Gonzalez, S.; Nolan, S. P. *Coord. Chem. Rev.* **2007**, *251*, 874. (d) Fantasia, S.; Petersen, J. L.; Jacobsen, H.; Cavallo, L.; Nolan, S. P. *Organometallics* **2007**, *26*, 5880. (e) Khramov, D. M.; Lynch, V. M.; Bielawski, C. W. *Organometallics* **2007**, *26*, 6042.

[21] (a) Muehlhofer, M.; Strassner, T.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1745. (b) Schultz, M. J.; Hamilton, S. S.; Jensen, D. R.; Sigman, M. S. *J. Org. Chem.* **2005**, *70*, 3343.

[22] (a) Sato, Y.; Yoshino, T.; Mori, M. *Org Lett* **2003**, *5*, 31. (b) Bonnet, L. G.; Douthwaite, R. E.; Kariuki, B. M. *Organometallics* **2003**, *22*, 4187. (c) Flahaut, A.; Baltaze, J.-P.; Roland, S.; Mangeney, P. *J. Organomet. Chem.* **2006**, *691*, 3498.

reactions,[23] Negishi couplings,[24] Suzuki couplings,[25] Hiyama reactions,[26] Kumada-Tamao-Corriu reactions, [27] Sonogashira reaction,[28] Buchwald-Hartwig amination,[29] and Stille reactions.[30] Among all the NHCs investigated, the most bulky *N*,*N'*-diaryl ligand precursors IPr·HCl and SIPr·HCl (Figure 4) are found to give the best performance in many cases. The less hindered IMes·HCl and SMes·HCl (Figure 4) are also commonly used.

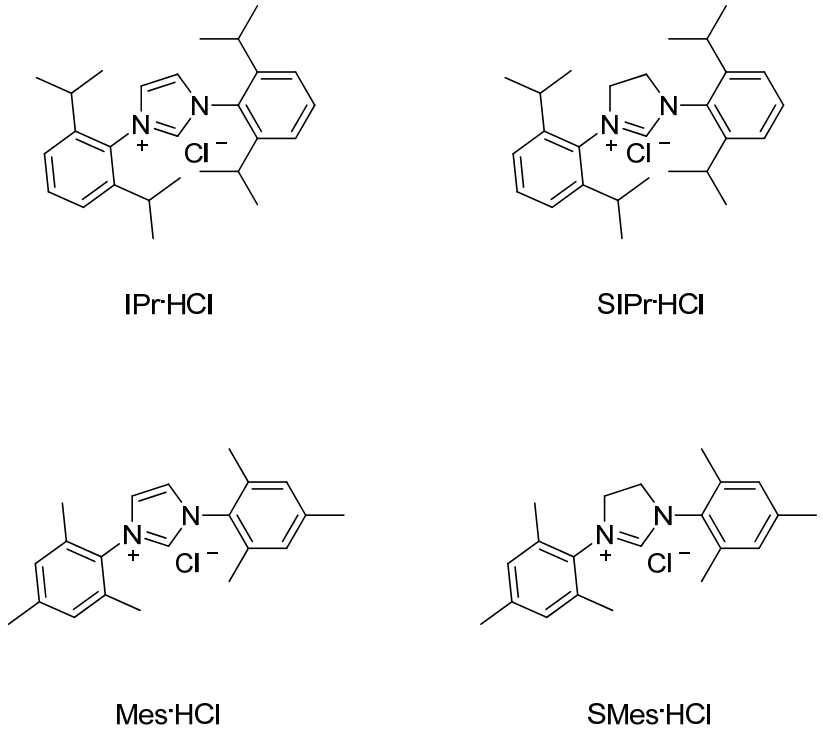
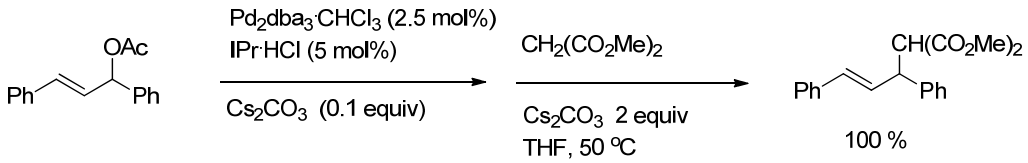


Figure 4 Structures of IPr·HCl, SIPr·HCl, IMes·HCl and SMes·HCl.

[23] (a) Herrmann, W. A.; Elison, M.; Fischer, J.; Koecher, C.; Artus, G. R. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2371. (b) Clyne, D. S.; Jin, J.; Genest, E.; Gallucci, J. C.; RajanBabu, T. V. *Org. Lett.* **2000**, *2*, 1125.
[24] Hadei, N.; Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. *Org. Lett.* **2005**, *7*, 3805.
[25] (a) Grasa, G. A.; Viciu, M. S.; Huang, J.; Zhang, C.; Trudell, M. L.; Nolan, S. P. *Organometallics* **2002**, *21*, 2866. (b) Marion, N.; Navarro, O.; Mei, J.; Stevens, E. D.; Scott, N. M.; Nolan, S. P. *J. Am. Chem. Soc.* **2006**, *128*, 4101.
[26] Lee, H. M.; Nolan, S. P. *Org. Lett.* **2000**, *2*, 2053.
[27] (a) Huang, J.; Nolan, S. P. *J. Am. Chem. Soc.* **1999**, *121*, 9889. (b) Organ, M. G.; Abdel-Hadi, M.; Avola, S.; Hadei, N.; Nasielski, J.; O'Brien, C. J.; Valente, C. *Chem. Eur. J.* **2007**, *13*, 150.
[28] (a) Caddick, S.; Cloke, F. G. N.; Clentsmith, G. K. B.; Hitchcock, P. B.; McKerrecher, D.; Titcomb, L. R.; Williams, M. R. V. *J. Organomet. Chem.* **2001**, *617-618*, 635. (b) Batey, R. A.; Shen, M.; Lough, A. J. *Org. Lett.* **2002**, *4*, 1411. (c) Yang, C.; Nolan, S. P. *Organometallics* **2002**, *21*, 1020.
[29] (a) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234. (b) Conesa Lerma, I.; Cawley, M. J.; Cloke, F. G. N.; Arentsen, K.; Scott, J. S.; Pearson, S. E.; Hayler, J.; Caddick, S. *J. Organomet. Chem.* **2005**, *690*, 5841. (c) Cheng, J.; Trudell, M. L. *Org. Lett.* **2001**, *3*, 1371. (d) Viciu, M. S.; Kelly, R. A., III; Stevens, E. D.; Naud, F.; Studer, M.; Nolan, S. P. *Org. Lett.* **2003**, *5*, 1479.
[30] Weskamp, T.; Böhm, V. P. W.; Herrmann, W. A. *J. Organomet. Chem.* **1999**, *585*, 348.

In 2003, Mori and Sato reported the first allylic alkylation reaction catalyzed by Pd-NHC complexes (Scheme 5).[31] The combination of Pd_2dba_3 with IPr·HCl was found to be the most effective, and Cs_2CO_3 was the best base. Cyclic acetates

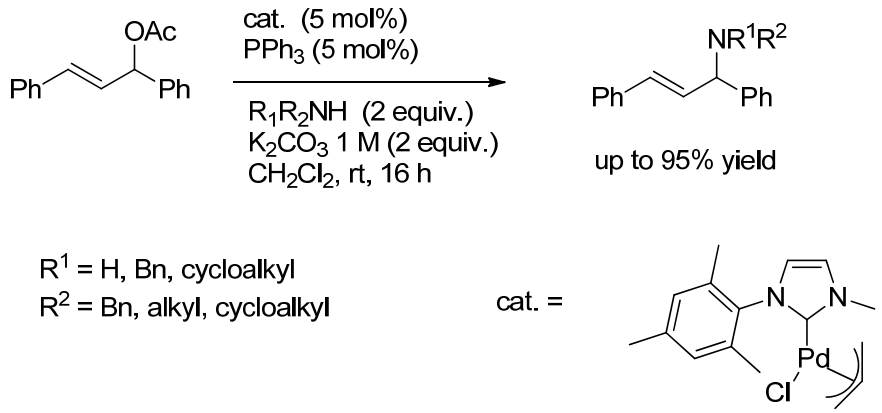


Scheme 5. Allylic alkylation catalyzed by Pd-NHC reported by Mori and Sato.

or lactones could also react, giving moderate to excellent yields. It is worthy to note that C-N substitution with nitrogen nucleophiles (amines and tosylamides) did not occur under their catalytic system.

In 2007, Togni and Visentin reported the synthesis and characterization of palladium π-allyl complexes bearing NHC ligands.[32] When they attempted allylic amination, NHC-P ligands gave lower reactions rates than isostructural P-N ligands in the nucleophilic attack of amines on the cationic π-allylpalladium complex. In 2009, Mangeney and co-workers reported allylic amination with the [(NHC)Pd(η^3-ally)Cl] complexes and PPh_3 (Scheme 6).[33] For cinnamyl acetate, a mixture of linear (mono and dialkylamines) and branched products were obtained. It was found that the PPh_3 was essential for this transformation. Without PPh_3, no reaction occurred.

[31] Sato, Y.; Yoshino, T.; Mori, M. *Org Lett* **2003**, *5*, 31.
[32] Visentin, F.; Togni, A. *Organometallics* **2007**, *26*, 3746.
[33] Roland, S.; Cotet, W.; Mangeney, P. *Eur. J. Inorg. Chem.* **2009**, 1796.



Scheme 6. Allylic amination catalyzed by Pd-NHC and PPh_3 reported by Mangeney and co-workers.

Up to now, to the best of our knowledge, there is no report on allylic amination with ammonia gas by palladium catalyst. Considering the properties of NHCs, and the inherent differences between phosphine ligands and NHCs, we envisage the possibility of using the Pd-NHC complexes to catalyze allylic amination with ammonia gas. In the following sections, detailed experimental procedures and results will be described.

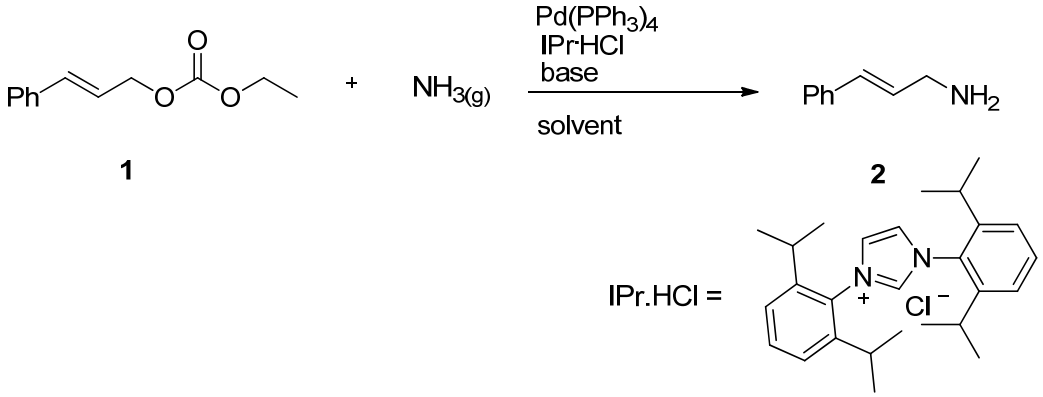
4.2.2 Results

The most common method to generate NHCs is by treating azolium salts with a stong base, such as NaO^{t}Bu, LiO^{t}Bu.[34] Isolated NHCs are very air and moisture sensitive and always require strict inert conditions, such as glovebox. For Pd-NHC complexes catalyzed reactions, the catalyst is usually generated by simply mixing the NHC precursor and common palladium source with base. For our project, cinnamyl carbonate was selected for the model study, since allyl carbonates were the best

[34] (a) Arduengo, A. J., III; Dias, H. V. R.; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1992**, *114*, 5530. (b) Arduengo, A. J., III; Goerlich, J. R.; Marshall, W. J. *J. Am. Chem. Soc.* **1995**, *117*, 11027.

substrates in Hartwig's paper.[9] Due to the significant influence of both bases and solvents on the catalytic ability of Pd-NHC complexes, we first screened various bases and solvents using $Pd(PPh_3)_4$ with IPr·HCl (Table 1).

Table 1. Allylic amination with ammonia catalyzed by $Pd(PPh_3)_4$ and IPr·HCl[a]



entry	solvent	base	conc. (mmol/mL)	result
1[b]	THF	LiO^tBu	0.3	-
2[b]	toluene	NaO^tBu	0.3	trialkylamine **3**[c]
3[d]	toluene	NaO^tBu	0.1	**4** and **5**
4[d]	THF	NaO^tBu	0.1	trace of **5**
5[d]	1,4-dioxane	NaO^tBu	0.1	trace of **5**
6[d]	THF	LiO^tBu	0.1	trace
7[d]	toluene	LiO^tBu	0.1	trace
8[d]	1,4-dioxane	LiO^tBu	0.1	33[e]

[a] Conditions: cinnamyl carbonate (0.3 mmol), $Pd(PPh_3)_4$ (10 mmol%), base (11 mmol%), under argon atmosphere.
[b] NH_3 (1 equiv.), the reaction was conducted at 80 ºC for 12 h.
[c] Yield was 33%.
[d] NH_3 (100 equiv.), the reaction was conducted at 50 ºC for 12 h.
[e] Dicinnamylamine **6** was also obtained with 29% yield. The ratio of primary amine with secondary is 53:47.

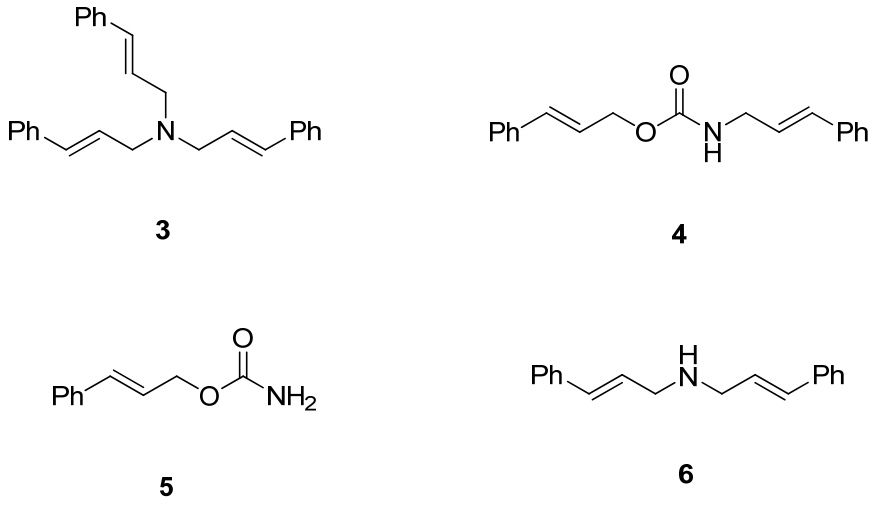


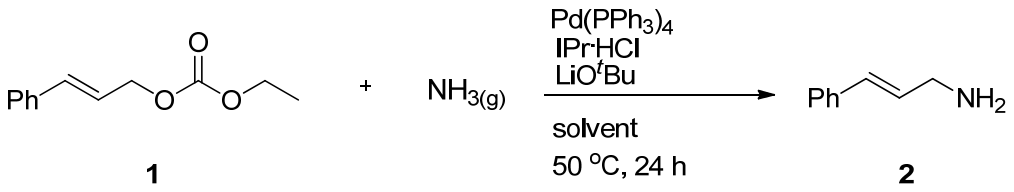
Figure 5 Structures of compounds 3, 4, 5 and 6.

For convenience, only one equivalent of NH_3 was used in the preliminary studies. When the combination of THF and LiO^tBu was used, no reaction took place, and the starting material was recovered (entry 1, Table 1). When the temperature was increased to 80 ºC, tricinnamylamine (**3**) was obtained in 33% yield (entry 2, Table 1), providing encouragement to the project, although the product was not the desired one. Then we decreased the concentration from 0.3 M to 0.1 M, and increased the ammonia to 100 equivalents. Surprisingly, instead of tricinnamylamine, two new compounds **4** and **5** were obtained in 7% and 79% yields respectively (entry 4, Table 1), which might involve another synthetic pathway. If the solvent was switched to THF or 1,4-dioxane, only trace amount of compound **5** was seen (entries 4 and 5, Table 1). After changing the base to LiO^tBu, our desired product primary amine **2** was obtained in 33% yield, but together with dicinnamylamine (**6**) in 29% yield. The ratio of **2** and **6** was 53:47. When reactions were done in toluene or THF, no desired product was observed. Only the cinnamyl alcohol was formed, which was the hydrolyzed product of the starting material. Other common bases, such as NaH, Cs_2CO_3 and K_3PO_4 combined with THF, toluene and 1,4-dioxane were respectively,

gave no desired product. In one bid to achieve better results, using the two solvent and base systems, NaO^{t}Bu with toluene, and LiO^{t}Bu with 1,4-dioxane, many transition metal catalysts, such as $Pt(PPh_3)(C_2H_4)$, $Pt(C_6H_5CN)_2Cl_2$, $Pt(COD)Cl_2$, $AuCl_3$, AuCl, $Au(PPh_3)Cl$, $Ir(CO)(PPh_3)Cl$, $IrCl_3$, $Ni(COD)_2$, $Ni(PPh_3)_2Cl_2$ were also screened. None of them gave the desired results. Hence, $Pd(PPh_3)_4$ remained as the best catalyst for this transformation.

As noted in many papers, the amount of ammonia and concentration are critical factors for the reactions with ammonia, for the products are more reactive than ammonia. Thus, we tried to use 500 equivalents of ammonia and further reduced the concentration down to 0.03 M, in which there was no reaction as reported in Kobayashi's paper.[8]

Table 2. Optimization of the reaction conditions [a]



entry	solvent	conc. (mmol/mL)	yield (%)
1	1,4-dioxane	0.03	62
2[b]	1,4-dioxane	0.03	70
3[c]	1,4-dioxane	0.03	trace
4[d]	1,4-dioxane	0.03	-
5[e]	1,4-dioxane	0.03	5
6	1,4-dioxane	0.05	55[f]
7	1,4-dioxane	0.1	25
8[g]	1,4-dioxane	0.03	35
9	THF	0.03	-
10	toluene	0.03	-
11[h]	1,4-dioxane	0.03	-

[a] Conditions: cinnamyl carbonate (0.3 mmol), $Pd(PPh_3)_4$ (10 mmol%), LiO^{t}Bu (11 mmol%), NH_3 (500 equiv.), The reaction was conducted under argon atmosphere at 50 ºC for 24 h.

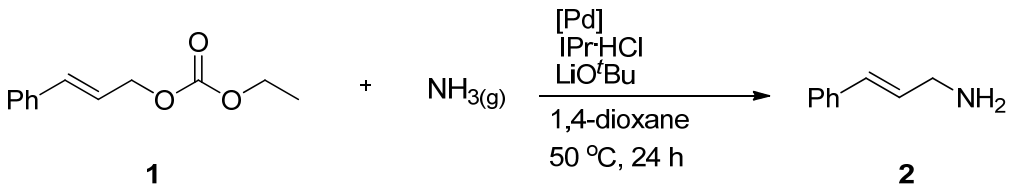
[b] The reaction was conducted at 80 ºC for 12 h.
[c] $Pd(PPh_3)_4$ (5 mol%), LiO^tBu (5.5 mmol%),
[d] No $Pd(PPh_3)_4$ was added
[e] No IPr·HCl or LiO^tBu.
[f] Containing 4% of dicinnamylamine.
[g] NH_3 (100 equiv.).
[h] NaO^tBu (11 mol%) was used as base.

As shown in Table 1, the combination of LiO^tBu with 1,4-dioxane was the best system. When the reaction was conducted using 500 equivalents of ammonia in 10 mL anhydrous 1,4-dioxane at 50 ºC for 24 h, all of the starting material was consumed, and only primary amine **2** was obtained (entry 1, Table 2) in 62% yield. No secondary amine was observed. The main side product was cinnamyl alcohol (20% yield), and compound **5** was also isolated in 15% yield. Increasing the reaction temperature to 80 ºC could reduce the reaction time to 12 h and increase the yield slightly (70%) (entry 2, Table 2). Since the difference in the yields (entry 1 with entry 2 in Table 2) were not significant, and higher temperature which required special equipments for handling ammonia was unsafe and uneconomical, we chose 50 ºC as the reaction temperature. If the amount of $Pd(PPh_3)_4$ was reduced to 5 mol%, only trace of the product was observed (entry 3, Table 2), which might be due to the highly diluted reaction mixture. When the reaction was carried out without $Pd(PPh_3)_4$, no reaction occurred. Note that cinnamyl chloride by itself reacted with ammonia without catalyst to give cinnamylamine in 93% yield. Without IPr·HCl or base only 5% of cinnamylamine **2** was obtained, proving that the NHC ligand is crucial for this transformation (entry 5, Table 2). We also checked the effect of concentration on the reaction. When the concentration was 0.05 M, the mixture of primary and secondary amines was obtained in a combined yield of 55% (entry 6, Table 2). The ratio of primary amine to secondary amine was 96:4. The yields of side products (cinnamyl alcohol and compound **5**) were increased to 27% and 21% respectively, which were

higher than those in entry 1 of Table 2. If the concentration was increased to 0.1 M, surprisingly, 25% of the primary amine was obtained. together with 55% of the cinnamyl alcohol (entry 7, Table 2). Under this condition, a higher proportion of the starting material was decomposed to the alcohol. While reducing the amount of ammonia to 100 equivalents, the yield of primary amine was decreased to 35% with 25% of the side product **5**. The use of THF and toluene as solvents were also tested employing the same reaction conditions, and no desired product was obtained (entries 9 and 10, Table 2). The main side products for this reaction were cinnamyl alcohol and compound **5** which was the main product in entry 3 of Table 1. We also checked the combination of NaO^{t}Bu and 1,4-dioxane (entry 11, Table 2). No primary amine was observed. In conclusion, the best yield for the synthesis of primary amine was 62% using 500 equivalents of ammonia with a concentration of 0.03 M.

We also checked the influence of different palladium sources, and that found only $Pd(PPh_3)_4$ was the effective catalyst (table 3). Neither $PdCl_2$, $Pd(CH_3CN)_2Cl_2$ nor Pd_2dba_3 can catalyze this reaction. Our findings are consistent with the results from Mangeney.[34] The phosphine ligands are also essential for our reactions.

Table 3. Influences of different palladium sources [a]



1 **2**

entry	[Pd]	Yield (%)
1	**$Pd(PPh_3)_4$**	62
2	**$PdCl_2$**	-[b]
3	**$Pd(CH_3CN)_2Cl_2$**	-[b]
4	**Pd_2dba_3**	-[b]

[a] Conditions: cinnamyl carbonate (0.3 mmol), [Pd] (10 mmol%), IPr·HCl (11 mol%), LiO^{t}Bu (22 mmol%), NH_3 (500 equiv.), 1,4-dionaxe (10 mL),

The reaction was conducted under argon atmosphere at 50 ºC for 24 h.
[b] No reaction was occurred.

Compared to phosphine ligands, the electron donating abilities of NHCs span a very narrow range. The electronics can be altered by changing the nature of the azole ring. The general order of electron donating ability is: benzimidazole < imidazole < imidazoline. The following are the general commercially available NHC precursors we have screened (Figure 6). As shown in Table 4, SIPr·HCl gave the best result (entry 2, Table 4). In this reaction, the catalytic ability of IMes·HCl was not as good as SIMes·HCl (entries 3 and 4, Table 4), for the electon-donating ability of SIMes·HCl is stronger than that of IMes·HCl. The NHC precursor SIPr·HCl displayed better result than SIMes·HCl (entries 2 and 4, Table 4), which may be due to steric hinderance of the isopropyl group. NHCs bearing *N*-alkyl substituents ehibited poorer catalytic activity (entries 5-7, Table 4). For the I*i*Pr·HCl, no desired product was observed.

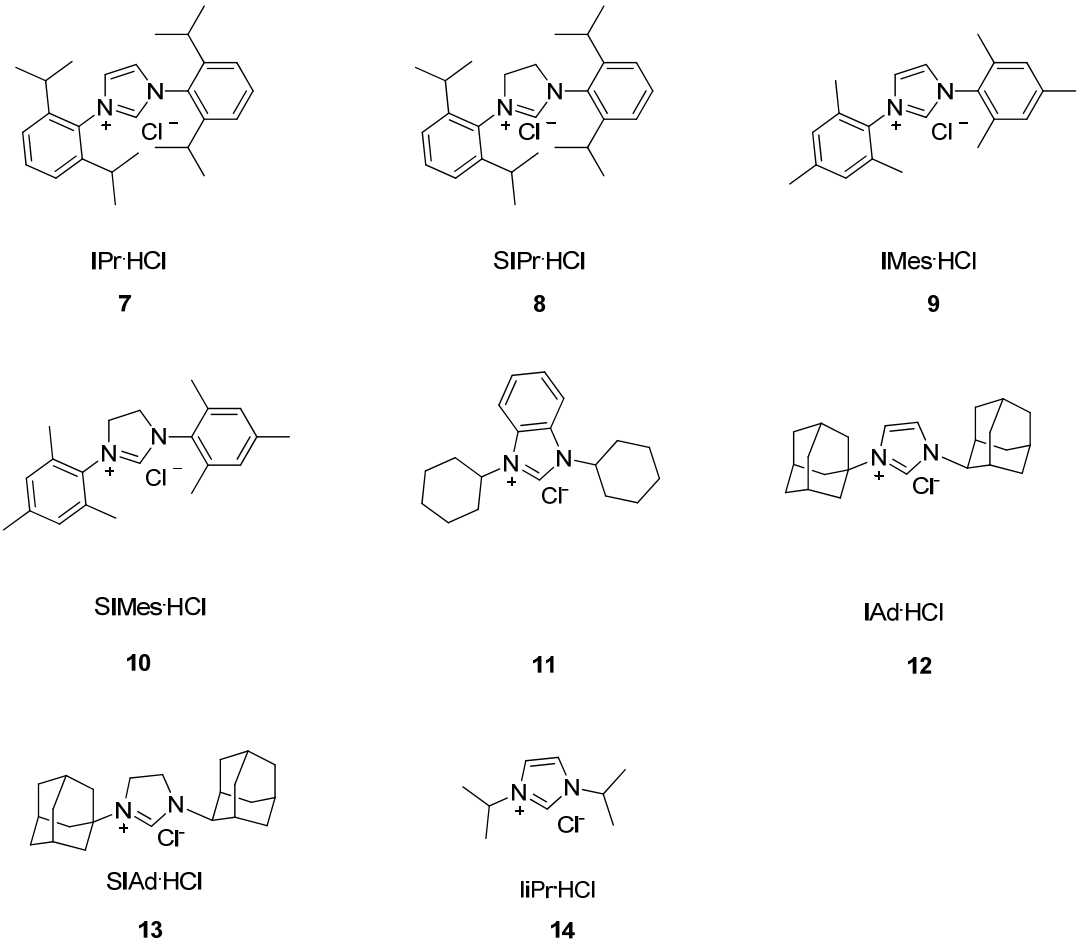
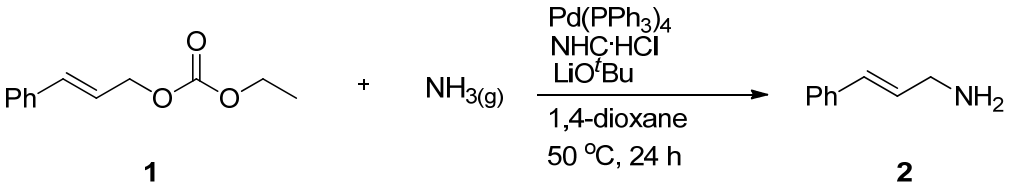


Figure 6 Structures of NHC precursors

Table 4. Effects of the different NHC·HCls [a]



entry	NHC·HCl	Yield (%)
1	**7**	62
2	**8**	75
3	**9**	23
4	**10**	60
5	**11**	30
6	**12**	25

7	**13**	15
8	**14**	-[b]

[a] Conditions: cinnamyl carbonate (0.3 mmol), $Pd(PPh_3)_4$ (10 mmol%), NHC·HCl (11 mol%), LiO^{t}Bu (22 mmol%), NH_3 (500 equiv.), 1,4-dionaxe (10 mL), The reaction was conducted under argon atmosphere at 50 ºC for 24 h.
[b] No reaction occurred.

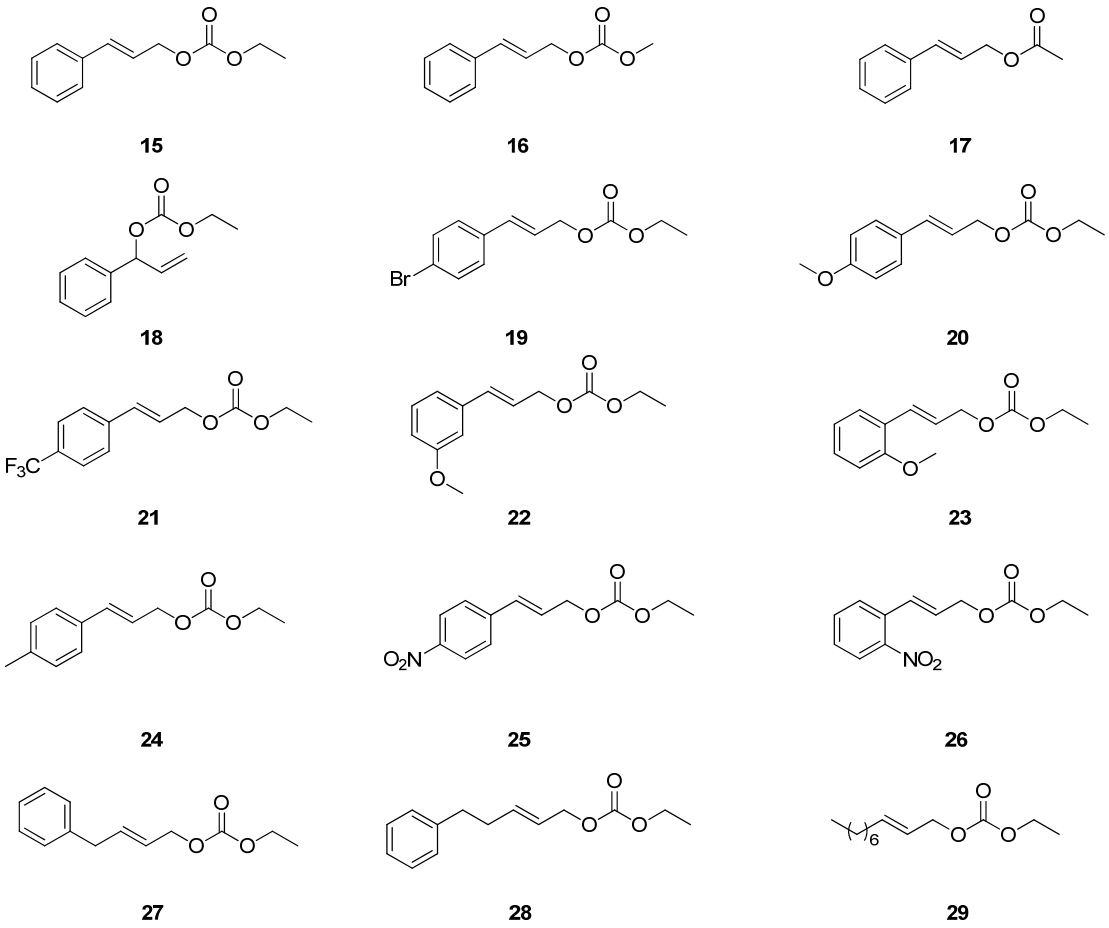
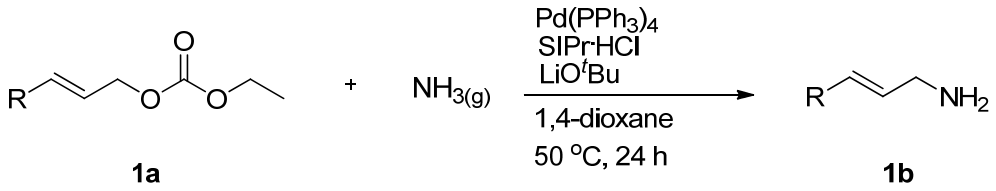


Figure 7 Structures of the substrates.

Table 5. Allylic amination with ammonia gas [a]



entry	subtrate	yield (%)
1	**15**	75
2	**16**	65
3	**17**	68
4	**18**	73
5	**19**	60
6	**20**	76
7	**21**	43
8	**22**	59
9	**23**	73
10	**24**	77
11	**25**	-[b]
12	**26**	-[b]
13	**27**	57 (64 : 36)[c]
14	**28**	78 (53 : 47)[c]
15	**29**	16[d]

[a] Conditions: cinnamyl carbonate (0.3 mmol), $Pd(PPh_3)_4$ (10 mmol%), SIPr·HCl (11 mol%), LiO^{t}Bu (22 mmol%), NH_3 (500 equiv.), 1,4-dioxane (10 mL), The reaction was conducted under argon atmosphere at 50 ºC for 24 h.
[b] No desired product was observed.
[c] Ratio of linear and branch primary amines.
[d] The ratio cannot be determined by H NMR.

With the optimized reaction conditions, the scope of this transformation was investigated. A series of substrates were synthesized and tested (Table 5). Cinnamyl acetate and methyl cinnamyl carbonate gave slightly lower yields (entries 1-3, Table 5). Thus, we focused on ethyl cinnamyl carbonates and prepared them from their

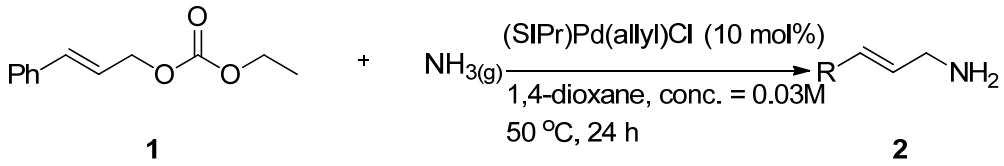
corresponding alcohols with ethyl chloroformate. Branched substrate afforded linear product, isolated in 73% yield (entry 4, Table 5), similar to entry 1. For the substrates with *para* or *ortho* electron-donating group on the phenyl ring, there is little difference in the yields (entries 6, 9 and 10, Table 5). However, when a methoxy group was on the *meta* position of the phenyl ring, the yield was decreased to 59% (entry 8, Table 5). In contrast, electron-withdrawing groups exhibited dramatic influence on the yield. With a *para*-trifluoromethyl group on the phenyl ring, only 43% yield was isolated (entry 7, Table 5). Substrates with nitro group even gave no desired products (entries 11 and 12, Table 5). From entry 1 to entry 10 in Table 5, surprisingly, primary linear amines were isolated without the necessity to perform column chromatography with a trace of the branched primary amine. However, allylic carbanates with aliphatic substituents afforded a mixture of linear and branched products (entries 13 to 15, Table 5). For substrate **27**, the total yield was 57% and the ratio of the linear amine to branched amine was 64:36, judging from ^{1}H NMR. For substrate **28**, the total yield was 78% with a ratio of 53:47 for the linear to branched products. However, for substrate **29**, the yield was only 16%, which might be due to the low boiling point of the product, being lost with the solvent upon evaporation. The ratio of the branched amine to linear amine was very difficult to determine from ^{1}H NMR, but could be readily concluded from ^{13}C NMR.

4.2.3 Mechanistic Study

The Tsuji-Trost reaction is a well-known method for C-C bond, C-N bond, C-S bond and C-O bond formations.[35] With this reaction being widely applied in organic synthesis, its mechanism has also been well studied.[36] However, the investigations of Pd-NHC complexes catalyzed allyl alkylations were rather limited, and its mechanism has yet to be studied.

In the beginning, we thought that the real catalyst might be [(SIPr)Pd(PPh_3)]. Unfortunately, we could not isolate this compound in our hands due to its air sensitivity. Then we investigated the reactions with the catalyst preformed *in situ* (Table 6).

Table 6. Mechanism study [a]



entry	additive	LiO^tBu	PPh_3	Yield (%)
1	-	-	-	-
2	**^{i}PrOH**	-	-	-
3	-	22 mol%	-	-
4	**^{i}PrOH**	22 mol%	-	-
5	-	22 mol%	10 mol%	-[b]
6	**^{i}PrOH**	22 mol%	10 mol%	-[b]

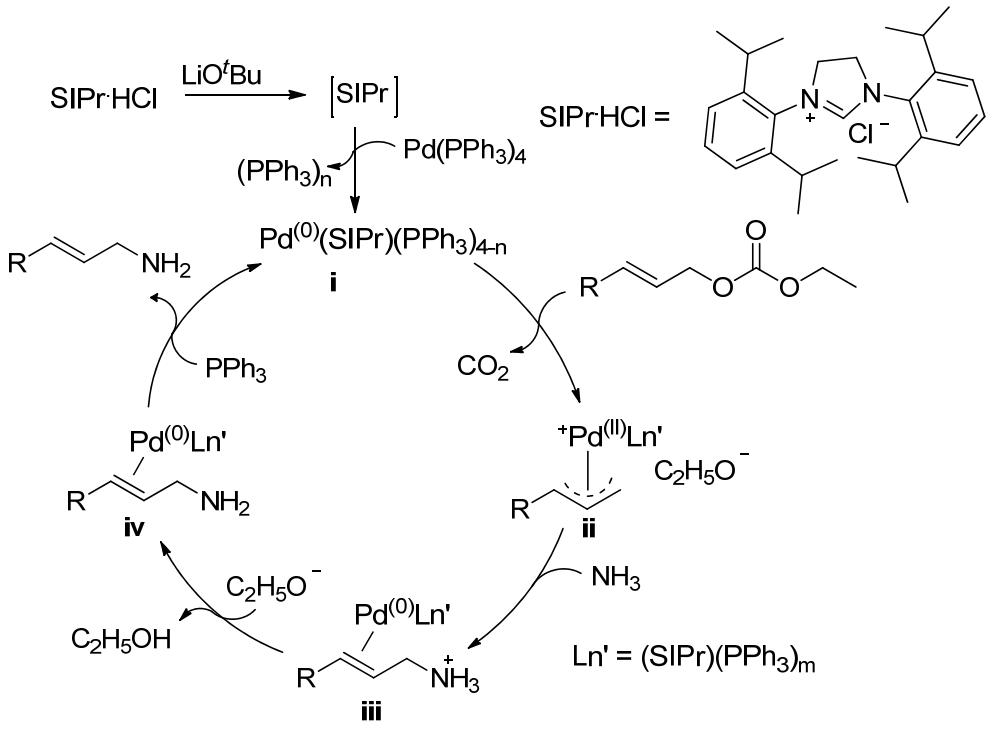
[a] Conditions: cinnamyl carbonate (0.3 mmol), (SIPr)Pd(allyl)Cl (10 mmol%), LiO^tBu (22 mmol%), NH_3 (500 equiv.), 1,4-dioxane (10 mL), The reaction was conducted under argon atmosphere at 50 ºC for 24 h. [b] 95% yield of the cinnamyl alcohol was obtained.

[35] (a) Morikawa, M.; Takahashi, J.; Tsuji, J. *Tetrahedron Lett.* **1965**, *6*, 4387. (b) Trost, B. M.; Fullerton, T. J. *J. Am. Chem. Soc.* **1973**, *95*, 292.
[36] Nomura, N.; Tsurugi, K.; Okada, M. *Angew. Chem., Int. Ed.***2001**, *40*, 1932.

Unfortunately, no desired product was observed. Instead only the decomposed product, i.e., cinnamyl alcohol, was obtained in 95% yield (entries 5 and 6, Table 6). So the real catalyst may not be [(SIPr)Pd(PPh_3)]. We also tested KO^{t}Bu as the base, but did not obtain any positive results.

Based on the general mechanism for the Tsuji-Trost reaction, we propose a plausible mechanism for our reactions (Scheme 7). As shown in the scheme, firstly, the SIPr·HCl reacts with LiO^{t}Bu to give the carbene, the general method to access the NHC. Then, the resulting SIPr reacts with $Pd(PPh_3)_4$ to form the Pd(0) catalyst through the release of PPh_3. After workup, PPh_3 and trace amount of $OPPh_3$ could be isolated. However, it was very difficult to prove the exact number of equivalents of PPh_3 released upon substituition by SIPr. Then, the palladium(0) intermediate reacts with the carbonates *via* oxidative addition with release of CO_2. The resulting intermediate **ii** reacts with ammonia to give the intermediate **iii**, a process without direct coordination to the metal.[37] After deprotonation by the base and dissociation from the palladium catalyst, the desired primary amine is obtained.

[37] Klinkenberg, J. L.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2011**, *50*, 86.



Scheme 7. Plausible reaction mechanism.

4.3 CONCLUSION AND FUTURE WORK

To the best of our knowledge so far, there is no report on the palladium-catalyzed allylic amination with ammonia gas. Thus it is scientifically interesting to develop a catalytic system suitable with ammonia gas. Fortunately, we are the first to report the above in situ formed Pd-NHC complex for allylic amintion using ammonia gas. Primary amines were selectively obtained in moderate to good yields. No secondary amines were observed.

In general, for allylic substitutions, palladium catalysts often give linear, achiral products.[38] The selective synthesis of branched primary amines is very challenging. Our future work will focus on the synthesis of branched primary amines

[38] Hartwig, J. F.; Stanley, L. M. *Acc. Chem. Res.* **2010**, *43*, 1461.

with ammonia.

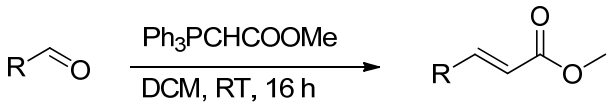
The mechanism needs to be studied in details, and the real intermediates should be isolated and characterized.

4.4 EXPERIMENTAL

General Information

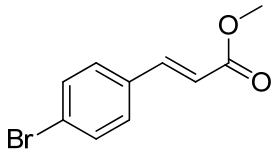
All aminations reactions were carried out using schlenk line in a seal tube until otherwise noted. All other reagents were obtained from commercial sources and used without further purification. Reactions were monitored by thin-layer chromatography (TLC) carried out on Merck silica gel plates (60 F254) and visualized by UV or iodine staining. NMR spectra were obtained on Avance-400 or Avance-300 instruments as indicated and calibrated using trimethylsilane (TMS) (0.00 ppm for ^{1}H NMR) and residue deuterated chloroform as an internal reference (7.26 ppm for ^{1}H NMR and 77.00 ppm for ^{13}C NMR).

General procedure for Wittig Reaction[1]



To a solution of aldehyde (1 equiv) in anhydrous dichloromethane (10 mL/g) was added methyl(triphenylphosphoranylidene)acetate (1.05 equiv) under an inert atmosphere (N_2). The solution was stirred for 16 h at room temperature. Volatiles were removed *in vacuo* and the resulting solid was purified by flash chromatography to give the desired α,β-unsaturated ester.

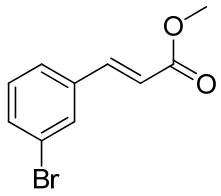
Methyl (*E*)-3-(4-bromophenyl)-2-propenoate



^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 15.90 Hz, 1H), 7.52 (d, *J* = 8.70 Hz, 2H), 7.38 (d, *J* = 8.40 Hz, 2H), 6.43 (d, *J* = 15.90 Hz, 1H), 3.81 (s, 3H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.1, 143.5, 133.3, 132.1, 129.4, 124.6, 118.5, 51.8 ppm.

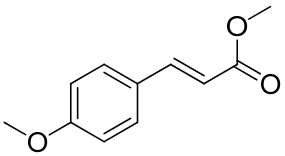
Methyl (*E*)-3-(3-bromophenyl)-2-propenoate



^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 15.90 Hz, 1H), 7.55 (s, 1H), 7.41 (d, *J* = 8.00 Hz, 1H), 7.32 (d, *J* = 7.93 Hz, 1H), 7.20 (t, *J* = 7.90 Hz, 1H), 6.42 (d, *J* = 15.90 Hz, 1H) 3.81 (s, 3H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.4, 138.3, 132.9, 131.0, 130.1, 129.6, 125.3, 124.5, 118.7, 51.6 ppm.

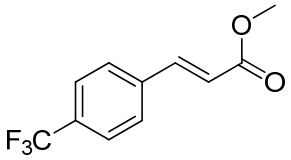
Methyl (*E*)-3-(4-methoxyphenyl)-2-propenoate



^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 15.90 Hz, 1H), 7.47 (d, *J* = 8.70 Hz, 2H), 6.90 (d, *J* = 8.70 Hz, 2H), 6.31 (d, *J* = 15.90 Hz, 1H), 3.83 (s, 3H), 3.79 (s, 3H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.0, 164.0, 144.0, 130.1, 127.5, 116.0, 114.7, 60.7, 56.0 ppm.

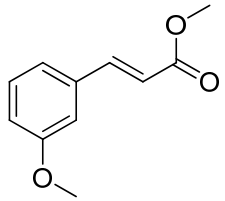
Methyl (*E*)-3-(4-(trifluoromethyl)phenyl)-2-propenoate



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67 (d, *J* = 15.99, 1H), 7.42 (d, *J* = 7.98, 2H), 7.19 (d, *J* = 7.98 Hz, 2H), 5.39 (d, *J* = 15.99 Hz, 1H), 3.80 (s, 3H), 2.37 (s, 3H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.1, 132.8, 127.4, 126.8, 125.6, 124.6, 110.5, 51.8 ppm.

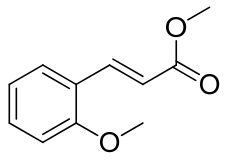
(*E*)-Methyl 3-(3-methoxyphenyl)acrylate



^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 16.02 Hz, 1H), 7.27-7.33 (m, 1H), 7.11 (d, *J* = 7.56 Hz, 1H), 7.04 (s, 1H), 6.91-6.95 (m, 1H), 6.43 (d, *J* = 16.02 Hz, 1H), 3.83 (s, 3H), 3.81 (s, 3H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.3, 159.9, 144.8, 135.7, 129.8, 120.7, 118.1, 116.1, 113.0, 55.3, 51.7 ppm.

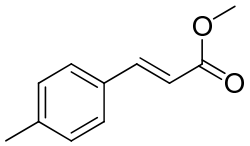
(*E*)-Methyl 3-(2-methoxyphenyl)acrylate



^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00 (d, *J* = 16.17 Hz, 1H), 7.49 (dd, *J* = 7.65, 1.47 Hz, 1H), 7.33 (m, 1H), 6.88-6.97 (m, 1H), 6.52 (d, *J* = 16.17 Hz, 1H), 3.86 (s, 3H), 3.79 (s, 3H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.3, 129.9, 129.2, 127.3, 125.1, 123.2, 120.6, 110.9, 55.5, 51.6 ppm.

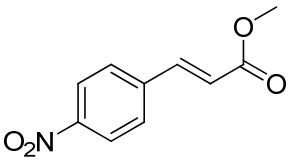
Methyl (*E*)-3-(4-methylphenyl)-2-propenoate



^{1}H NMR (300MHz, $CDCl_3$): δ = 7.65 (d, 1 H), 7.47 (d, *J* = 8.70 Hz, 2H), 6.90 (d, *J* = 8.76 Hz, 2H), 6.31 (d, *J* = 15.9 Hz, 1H), 3.83 (s, 3H), 3.79 (s, 3H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.0, 137.6, 133.87, 131.2, 129.3, 127.4, 126.3, 63.9, 22.7 ppm.

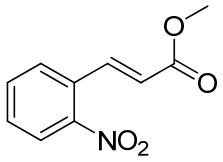
Methyl (*E*)-3-(4-nitrophenyl)-2-propenoate



^{1}H NMR (300MHz, $CDCl_3$): δ = 8.30 (d, *J* = 8.8 Hz, 2 H), 7.70 (d, *J* = 8.8 Hz, 2H), 7.80 (d, *J* = 16.1 Hz, 1H), 6.60 (d, *J* = 16.1 Hz, 1H), 4.30 (s, 3H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.8, 148.9, 142.1, 139.6, 129.0, 124.6, 123.0, 61.5 ppm.

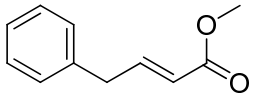
Methyl (*E*)-3-(2-nitrophenyl)-2-propenoate



^{1}H NMR (300MHz, $CDCl_3$): δ = 8.20–7.60 (m, 4H), 8.10 (d, *J* = 16.1 Hz, 1H), 6.55 (d, *J* = 16.1 Hz, 1H), 4.20 (s, 3H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.8, 142.6, 141.1, 135.6, 128.9, 127.3, 126.9, 123.8, 115.2, 61.2 ppm.

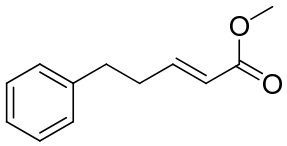
Methyl (*E*)-4-phenyl-2-butenoate



^{1}H NMR (400MHz, $CDCl_3$): δ = 7.27 - 7.34 (m, 2H), 7.19 - 7.27 (m, 3H), 6.37 (dt, *J* = 7.51, 11.52 Hz, 1H), 5.87 (d, *J* = 11.29 Hz, 1H), 4.03 (d, *J* = 7.63 Hz, 2H), 3.75 (s, 3H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.8, 148.3, 139.4, 128.7, 128.6, 126.4, 119.5, 51.2, 35.2 ppm.

Methyl (*E*)-5-phenyl-2-pentenoate



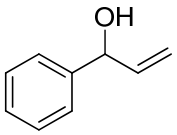
^{1}H NMR (400MHz, $CDCl_3$): δ = 7.26 - 7.33 (m, 2H), 7.14 - 7.24 (m, 3H), 6.95 - 7.06 (m, 1H), 5.85 (dd, *J* = 1.22, 15.56 Hz, 1H), 3.72 (s, 3H), 2.73 - 2.82 (m, 2H), 2.48 - 2.57 (m, 2H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.0, 148.4, 140.8, 128.5, 128.3, 126.2, 121.5, 51.5, 34.4, 33.9 ppm.

General Procedure for the Preparation of allylic alcohol [1]

To a cooled solution (-78 ^oC) of α,β-unsaturated ester (1.5 mmol, 1 equiv) in anhydrous dichloromethane (8 mL) under inert atmosphere, 1.0 M solution of DIBAL-H in heptane (3 equiv) was added dropwise over 30-60 minutes. The reaction was quenched after stirring for 90 min at -78 ^oC by the slow addition of 10% aqueous. NaOH (6 mL) at this temperature. After that, the resulting solution was warmed to room temperature and organic layer was separated. The aqueous phase was further extracted with dichloromethane three times. Combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the desired alcohol which was used directly in the next step without further purification.

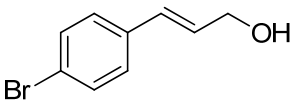
1-Phenylprop-2-en-1-ol



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44-7.29 (m, 5H), 6.73 (d, *J* = 15.92 Hz, 1H), 6.34 (dt, *J* = 15.88, 6.43 Hz, 1H), 4.82 (dd, *J* = 6.46, 1.22 Hz, 2H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): 138.4, 135.9, 128.6, 128.4, 127.1, 117.4, 73.0 ppm.

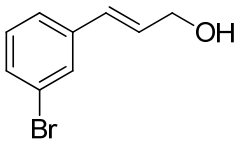
(*E*)-3-(4-Bromophenyl)prop-2-en-1-ol



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 (d, *J* = 8.46 Hz, 2H), 7.24 (d, *J* = 7.5 Hz, 2 H), 6.57 (d, *J* = 15.9 Hz, 1H), 6.35 (m, 1H), 4.32 (dd, *J* = 5.46, 1.29 Hz, 2H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.1, 133.3, 131.8, 128.2, 123.4, 122.1, 64.2 ppm

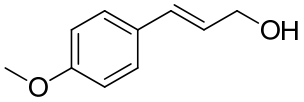
(*E*)-3-(3-Bromophenyl)prop-2-en-1-ol



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (s, 1H), 7.41 (d, *J* = 8.00 Hz, 1H), 7.32 (d, *J* = 7.93 Hz, 1H), 7.20 (t, *J* = 7.90 Hz, 1H), 6.63 (d, *J* = 16.17 Hz, 1H), 6.31 (dt, *J* = 6.22, 15.95 Hz, 1H), 4.80 (dd, *J* = 1.22, 6.10 Hz, 2H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.3, 132.9, 131.0, 130.1, 129.6, 125.3, 124.3, 122.8, 64.2 ppm.

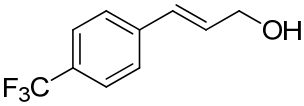
(*E*)-3-(4-Methoxyphenyl)prop-2-en-1-ol



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (d, *J* = 11.4 Hz, 2H), 6.86 (d, *J* = 11.4 Hz, 2H), 6.55 (d, *J* = 15.9 Hz, 1H), 6.28-6.19 (m, 1H), 4.29 (d, *J* = 5.7 Hz, 2H), 3.81 (s, 3H) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.1, 134.6, 128.0, 120.2, 114.0, 68.5, 64.0 ppm.

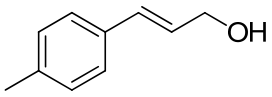
(*E*)-3-(4-(Trifluoromethyl)phenyl)prop-2-en-1-ol



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (d, *J* = 8.25 Hz, 2H), 7.47 (d, *J* = 8.25 Hz, 2H), 6.67 (d, *J* = 15.99 Hz, 1H), 6.46 (dt, *J* = 15.96 Hz, 5.30 Hz, 1H), 4.37 (d, *J* = 4.8 Hz, 2H), 1.60 (s, 1H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 132.8, 126.8, 125.6, 125.6, 125.4, 64.3 ppm.

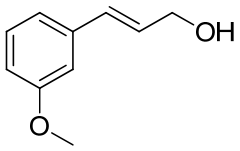
(*E*)-3-p-Tolylprop-2-en-1-ol



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28 (d, *J* = 8.07 Hz, 2H), 7.12 (d, *J* = 7.98 Hz, 2H), 6.58 (d, *J* = 15.9 Hz, 1H), 6.30 (dt, *J* = 15.06, 5.82 Hz, 1H), 4.30 (d, *J* = 5.52 Hz, 2H), 2.33 (s, 3H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 137.6, 133.9, 131.2, 129.3, 127.4, 126.4, 63.9, 22.7 ppm.

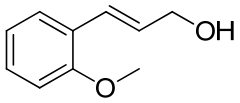
(*E*)-3-(3-Methoxyphenyl)prop-2-en-1-ol



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 (t, *J* = 7.98 Hz, 1 H), 6.97 (d, *J* = 7.68 Hz, 1 H), 6.91-6.92 (m, 1 H), 6.80 (dd, *J* = 8.16, 2.43 Hz, 1 H), 6.58 (d, *J* = 15.9 Hz, 1 H), 6.35 (dt, *J* = 15.9, 5.7 Hz, 1 H), 4.31 (d, *J* = 5.4 Hz, 2 H), 3.80 (s, 3 H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.0, 138.2, 130.2, 129.6, 128.9, 119.2, 113.3, 111.8, 63.6, 55.2 ppm.

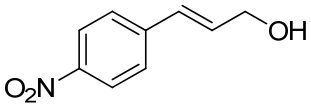
(*E*)-3-(2-Methoxyphenyl)prop-2-en-1-ol



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43 (dd, *J* = 7.58, 1.55 Hz, 1H), 7.20-7.23 (m, 1H), 6.85-6.94 (m, 1H), 6.37 (dt, *J* = 16.02, 5.90 Hz, 1H), 4.31 (s, 2H), 3.84 (s, 3H), 1.27 (s, 1H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.0, 129.9, 129.2, 127.3, 125.1, 123.2, 120.6, 110.9, 64.0, 55.2 ppm.

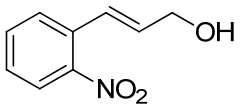
(*E*)-3-(4-Nitrophenyl)prop-2-en-1-ol



^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.20 (d, *J* = 8.6 Hz, 2H), 7.60 (d, *J* = 8.6 Hz, 2 H), 7.75 (d, *J* = 16.1 Hz, 1H), 6.57 (m, 1H), 4.30 (d, *J* = 6.0 Hz, 2H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.3, 144.5, 128.6, 127.4, 124.5, 123.0, 63.5ppm.

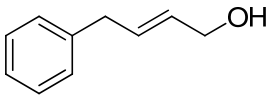
(*E*)-3-(2-Nitrophenyl)prop-2-en-1-ol



^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.00 (d, *J* = 8.2 Hz, 1H), 7.70–7.40 (m, 3H), 7.20 (d, *J* = 15.9 Hz, 1H), 6.40 (m, 1H), 4.40 (d, *J* = 6.0 Hz, 2H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.2, 134.7, 133.6, 132.9, 129.2, 128.5, 125.9, 124.7, 63.5 ppm.

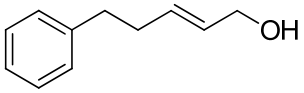
(*E*)-4-Phenylbut-2-en-1-ol



^{1}H NMR (400MHz, $CDCl_3$): δ = 7.24 - 7.33 (m, 2H), 7.16 - 7.23 (m, 3H), 5.80 - 5.93 (m, 1H), 5.63 - 5.77 (m, 1H), 4.12 (d, *J* = 5.49 Hz, 2H), 3.39 (d, *J* = 6.41 Hz, 2H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.0, 131.6, 130.3, 128.6, 128.5, 126.2, 63.6, 38.7 ppm.

(*E*)-5-Phenylpent-2-en-1-ol



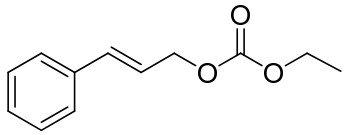
^{1}H NMR (400MHz, $CDCl_3$): δ = 7.26 - 7.31 (m, 2H), 7.15 - 7.22 (m, 3H), 5.62 - 5.78 (m, 2H), 4.08 (d, *J* = 5.49 Hz, 2H), 2.71 (t, *J* = 8.00 Hz, 2H), 2.39 (t, *J* = 8.00 Hz, 2H), 2.36 (s, 1H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.7, 132.3, 129.6, 129.1, 128.4, 128.4, 128.3, 125.9, 63.7, 35.6, 34.0 ppm.

General Procedure for the Preparation of Allylic Carbonates

To a well stirred solution of alcohol, which was obtained from previous step (4.5 mmol, 1 equiv), pyridine (3.8 equiv) and DMAP (0.02 equiv) in 10ml of anhydrous THF was added ethylchloroformate (3.4 equiv) slowly. The mixture was stirred at room temperature for 48 h. After which H_2O was added and the mixture was extracted with Et_2O three times. The combined organic layers were washed with 1M HCl, saturated $NaHCO_3$ and brine. Organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. Product was obtained by flash chromatography.

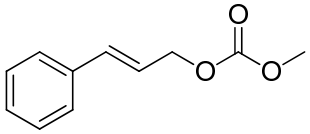
Ethyl Cinnamyl Carbonate



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (d, *J* = 5.61 Hz, 2H), 7.32 (t, *J* = 5.37 Hz, 2H), 7.27 (d, *J* = 5.52 Hz, 1H), 6.69 (d, *J* = 11.91 Hz, 1H), 6.30 (dt, *J* = 11.91, 4.83 Hz, 1H), 4.78 (d, *J* = 4.8 Hz, 2H) , 4.22 (q, *J* = 5.31 Hz, 2H), 1.32 (t, *J* = 5.33 Hz, 3H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.7, 136.1, 134.8, 128.6, 128.2, 126.7, 122.5, 68.4, 54.9, 14.3 ppm.

Methyl cinnamyl carbonate

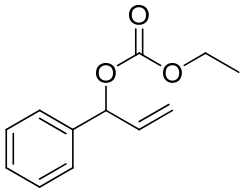


Methylchloroformate was used instead of Ethylchloroformate. Reaction was carried out with the general procedure.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 - 7.42 (m, 2H), 7.24 - 7.35 (m, 3H), 6.69 (d, *J* = 15.87 Hz, 1H), 6.29 (dt, *J* = 6.41, 15.87 Hz, 1H), 4.79 (dd, *J* = 1.37, 6.56 Hz, 2H), 3.81 (s, 3H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.7, 136.1, 134.8, 128.6, 128.2, 126.7, 122.5, 68.4, 54.9 ppm.

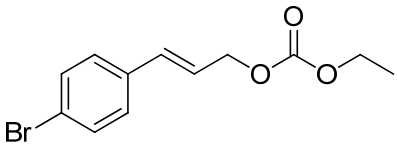
Ethyl 1-phenylallyl carbonate



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44-7.29 (m, 5H), 6.73 (d, *J* = 15.92 Hz, 1H), 6.34 (dt, *J* = 15.88, 6.43 Hz, 1H), 4.82 (dd, *J* = 6.46, 1.22 Hz, 2H), 4.26 (q, *J* = 7.13 Hz, 2H), 1.36 (t, *J* = 7.14 Hz, 3H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): 157.0, 138.4, 135.9, 128.6, 128.4, 127.1, 117.4, 80.0, 64.1, 14.3 ppm.

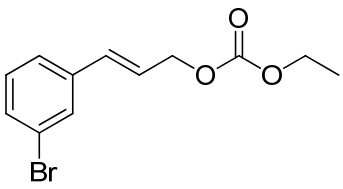
(*E*)-Ethyl-3-(4-bromophenyl)allyl carbonate



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 - 7.52 (m, 2H), 7.23 - 7.33 (m, 2H), 6.65 (d, *J* = 15.87 Hz, 1H), 6.31 (dt, *J* = 6.26, 15.87 Hz, 1H), 4.79 (dd, *J* = 1.37, 6.26 Hz, 2H), 4.25 (d, *J* = 7.32 Hz, 2H), 1.35 (t, *J* = 7.02 Hz, 3H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.0, 135.1, 133.3, 131.8, 128.2, 123.4, 122.1, 67.9, 64.2, 14.3 ppm.

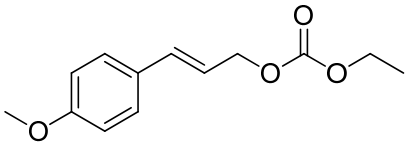
(*E*)-Ethyl-3-(3-bromophenyl)allyl carbonate



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (s, 1H), 7.41 (d, *J* = 8.00 Hz, 1H), 7.32 (d, *J* = 7.93 Hz, 1H), 7.20 (t, *J* = 7.90 Hz, 1H), 6.63 (d, *J* = 16.17 Hz, 1H), 6.31 (dt, *J* = 6.22, 15.95 Hz, 1H), 4.80 (dd, *J* = 1.22, 6.10 Hz, 2H), 4.25 (q, *J* = 7.02 Hz, 2H), 1.35 (t, *J* = 7.02 Hz, 3H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.0, 138.3, 132.9, 131.0, 130.1, 129.6, 125.3, 124.3, 122.8, 67.7, 64.2, 14.3 ppm.

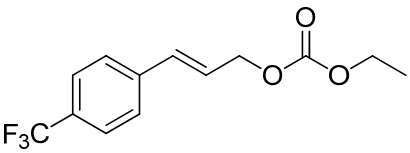
(*E*)-Ethyl 3-(4-methoxyphenyl)allyl carbonate



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (d, *J* = 8.73 Hz, 2H), 6.85 (d, *J* = 8.82 Hz, 2H), 6.63 (d, *J* = 15.87 Hz, 1H), 6.17 (dt, *J* = 6.64, 15.72 Hz, 1H), 4.76 (dd, *J* = 1.22, 6.41 Hz, 2H), 4.22 (q, *J* = 7.32 Hz, 2H), 3.81 (s, 3H), 1.32 (t, *J* = 7.30 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.7, 155.1, 134.6, 128.0, 120.2, 114.0, 68.5, 64.0, 55.3, 14.3 ppm.

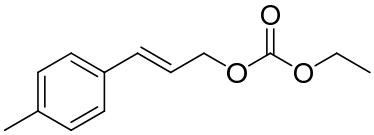
(*E*)-Ethyl 3-(4-(trifluoromethyl)phenyl)allyl carbonate



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (d, *J* = 8.24 Hz, 2H), 7.48 (d, *J* = 8.24 Hz, 2H), 6.71 (d, *J* = 15.87 Hz, 1H), 6.38 (dt, *J* = 6.22, 15.95 Hz, 1H), 4.80 (dd, *J* = 1.37, 6.26 Hz, 2H), 4.23 (q, *J* = 7.12 Hz, 2H), 1.33 (t, *J* = 7.17 Hz, 3H) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.0, 132.8, 126.8, 125.6, 125.6, 125.4, 67.6, 64.3, 14.3 ppm.

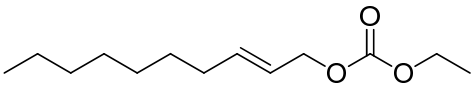
(*E*)-Ethyl 3-p-tolylallyl carbonate



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28 (d, *J* = 8.24 Hz, 2H), 7.13 (d, *J* = 7.93 Hz, 2H), 6.65 (d, *J* = 15.87 Hz, 1H), 6.25 (dt, *J* = 6.56, 15.87 Hz, 1H), 4.77 (dd, *J* = 1.22, 6.71 Hz, 2H), 4.22 (q, *J* = 7.02 Hz, 2H), 2.34 (s, 3H), 1.32 (t, *J* = 7.00 Hz, 3H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.1, 138.1, 134.8, 133.3, 129.3, 126.6, 121.5, 68.4, 64.1, 21.3, 14.3 ppm.

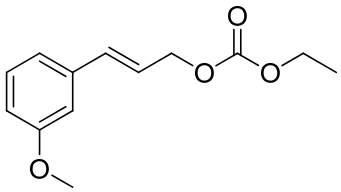
(*E*)-Ethyl-dec-2-en-1-yl carbonate



^{1}H NMR (400 MHz, $CDCl_3$): δ 5.74 - 5.88 (m, 1H), 5.53 - 5.65 (m, 1H), 4.56 (dd, *J* = 0.92, 6.41 Hz, 2H), 4.19 (q, *J* = 7.12 Hz, 2H), 2.05 (q, *J* = 7.12 Hz, 2H), 1.18 - 1.44 (m, 13H), 0.82 - 0.94 (m, 3H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.1, 137.5, 123.2, 68.5, 63.9, 32.2, 31.8, 29.1, 29.1, 28.8, 22.7, 14.3, 14.1 ppm.

(*E*)-Ethyl 3-(3-methoxyphenyl)allyl carbonate

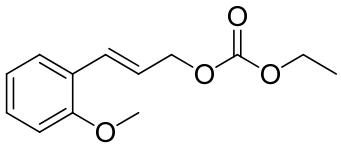


^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.14 (t, *J* = 7.93 Hz, 1H), 6.89 (d, *J* = 7.65 Hz, 1H), 6.84 (s, 1H), 6.78 (dd, *J* = 8.16, 2.43 Hz, 1H), 6.57 (d, *J* = 15.87 Hz, 1H), 6.20 (dt, *J* =

15.84, 6.38 Hz, 1H), 4.69 (dd, *J* = 6.38, 1.16 Hz, 2H), 4.13 (q, *J* = 7.13 Hz, 2H) ,3.71 (s, 3H), 1.23 (t, *J* = 7.10 Hz, 3H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.8, 155.0, 137.5, 134.5, 129.59, 122.9, 119.3, 113.9, 111.9, 68.1, 64.1, 55.2, 14.3 ppm.

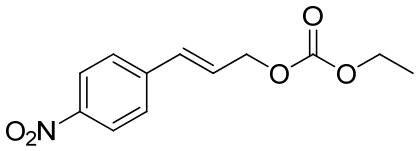
(*E*)-Ethyl 3-(2-methoxyphenyl)allyl carbonate



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42 (dd, *J* = 7.20, 1.52 Hz, 1H), 7.24-7.26 (m, 1H), 7.04 (d, 16.02 Hz, 1H), 6.85-6.94 (m, 2H), 6.61 (d, *J* = 15.9 Hz, 1H), 6.29 (dt, *J* = 15.60, 6.15 Hz, 1H), 4.78 (dd, *J* = 6.15, 1.35 Hz, 2H), 4.22 (q, *J* = 7.14 Hz, 2H), 3.84 (s, 3H), 1.32 (t, *J* = 7.13 Hz, 3H) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.0, 155.1, 129.9, 129.2, 127.3, 125.1, 123.2, 120.6, 110.9, 68.8, 64.0, 55.4, 14.3 ppm.

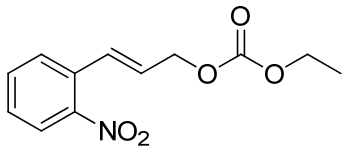
(*E*)-Ethyl 3-(4-nitrophenyl)allyl carbonate



^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (d, *J* = 8.54 Hz, 2H), 7.53 (d, *J* = 8.85 Hz, 2H), 6.76 (d, *J* = 16.17 Hz, 1H), 6.47 (dt, *J* = 5.91, 15.95 Hz, 1H), 4.84 (dd, *J* = 1.37, 5.95 Hz, 2H), 4.25 (q, *J* = 7.12 Hz, 2H), 1.34 (t, *J* = 7.17 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.9, 147.3, 142.5, 131.6, 127.6, 127.2, 124.0, 67.3, 64.4, 14.3 ppm.

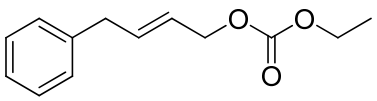
(*E*)-Ethyl 3-(2-nitrophenyl)allyl carbonate



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 7.93 Hz, 1H), 7.58 - 7.64 (m, 2H), 7.43 (ddd, *J* = 2.59, 6.18, 8.32 Hz, 1H), 7.17 (d, *J* = 15.87 Hz, 1H), 6.28 (dt, *J* = 5.99, 15.79 Hz, 1H), 4.83 (dd, *J* = 1.53, 6.10 Hz, 2H), 4.24 (q, *J* = 7.22 Hz, 2H), 1.34 (t, *J* = 7.17 Hz, 3H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.9, 147.9, 133.2, 132.0, 129.4, 128.9, 128.7, 128.1, 124.6, 67.5, 64.3, 14.3 ppm.

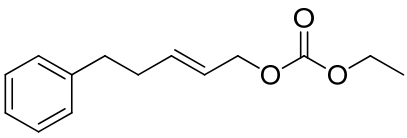
(*E*)-Ethyl (4-phenylbut-2-en-1-yl) carbonate



^{1}H NMR (400MHz, $CDCl_3$): δ = 7.26 - 7.32 (m, 2H), 7.15 - 7.23 (m, 3H), 5.90 - 6.03 (m, 1H), 5.59 - 5.71 (m, 1H), 4.60 (d, *J* = 6.41 Hz, 2H), 4.19 (q, *J* = 7.22 Hz, 2H), 3.40 (d, *J* = 6.71 Hz, 2H), 1.30 (t, *J* = 7.02 Hz, 3H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.0, 139.4, 135.3, 128.6, 128.5, 126.3, 124.8, 68.1, 64.0, 38.6, 14.3ppm.

(*E*)-Ethyl (5-phenylpent-2-en-1-yl) carbonate



^{1}H NMR (400MHz, $CDCl_3$): δ = 7.23 - 7.32 (m, 2H), 7.14 - 7.22 (m, 3H), 5.80 - 5.91 (m, 1H), 5.58 - 5.68 (m, 1H), 4.56 (d, *J* = 6.41 Hz, 2H), 4.19 (q, *J* = 7.02 Hz, 2H), 2.70 (t, *J* = 8.00 Hz, 2H), 2.38 (q, *J* = 8.00 Hz, 2H), 1.31 (t, *J* = 7.17 Hz, 3H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.1, 141.5, 136.1, 128.4, 128.4, 125.9, 124.0, 68.3, 63.9, 35.3, 34.0, 14.3 ppm.

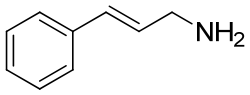
General Procedure for the Allylic Amination with Ammonia Gas

To a 25 mL sealed tube was added $Pd(PPh_3)_4$ (35 mg, 0.03 mmol) and NHC·HCl (0.033 mmol). The sealed tube was evacuated and refilled with argon. This action was repeated three times. Then lithium *tert*-butoxide (0.066 ml, 1 M in THF, 0.066 mmol) and 10 mL anhydrous 1,4-dioxane were added through syringe under the flow of argon. The mixture was stirred at room temperature for 1 h, followed by the addition of substrate (0.3 mmol) through syringe under the flow of argon. After stirring at room temperature for 10 min, the sealed tube was cooled to -78 ^{o}C in the acetone-dry ice bath. And liquid ammonia (4.4 mL, 500 equiv.) was added through syringe to the sealed tube under the flush of argon quickly. The reaction mixture was stirred at 50 ºC for indicated time.

The reaction mixture was cooled to room temperature and the cap of the sealed tube was slowly and carefully opened to release the ammonia gas. After the cap was totally opened, the mixture was stirred at room temperature for 10 min. The reaction mixture was acidified by 1 M HCl (pH < 2) and was extracted with dichloromethane three times. The aqueous layer was cooled in an ice bath and was made to be basic with solid NaOH (the solution becomes cloudy from the insoluble free amine). The amine was extracted by dichloromethane three times. The combined organic layers were

dried over anhydrous Na_2SO_4, the organic layer was filtered and concentrated under reduced pressure and the pure primary amine was obtained without further purification.

(*E*)-3-Phenylpro-2-en-1-amine



2

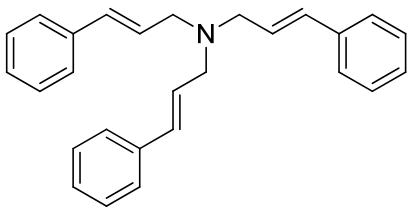
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 (t, *J* = 7.63 Hz, 2H), 7.19 - 7.25 (m, 3H), 6.50 (d, *J* = 15.88 Hz, 1H) 6.30 (tt, *J* = 15.84, 5.88 Hz, 1H) 3.47 (dd, *J* = 1.22, 5.80 Hz, 2H), 1.42 (br. s., 2H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.2, 131.3, 129.4, 128.6, 127.3, 126.3, 44.4 ppm.

FTIR (neat): *v* = 3017, 2924, 2855, 2253, 1651, 1636, 910, 733, 671, 648 cm^{-1}.

HRMS (ESI, m/z): calculated for $C_9H_{11}N$ $[M+H]^+$: 134.0961, found $[M+H]^+$: 134.0970.

Tri-cinnamylamine



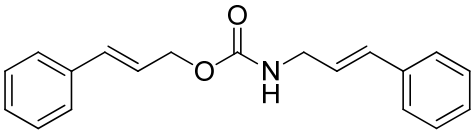
3

This compound was obtained by column chromatography.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40-7.21 (m, 15H), 6.55 (d, *J* = 15.84 Hz, 3H), 6.33 (tt, *J* = 15.88, 6.76 Hz, 3H), 3.36 (d, *J* = 6.60 Hz, 6H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.1, 133.1, 128.6, 127.5, 127.1, 126.3, 56.1 ppm.

Cinnamyl cinnamylcarbamate



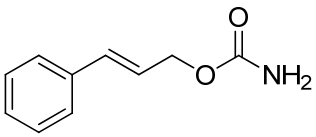
4

This compound was obtained by column chromatography.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19 - 7.44 (m, 10H), 6.48 - 6.71 (m, 2H), 6.15 - 6.36 (m, 2H), 4.76 (d, *J* = 5.80 Hz, 2H), 4.00 (t, *J* = 5.65 Hz, 2H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.2, 136.5, 136.3, 133.8, 131.9, 128.6, 128.0, 127.7, 126.6, 126.4, 125.8, 123.9, 65.6, 43.2 ppm.

Cinnamyl carbamate



5

This compound was obtained by column chromatography.

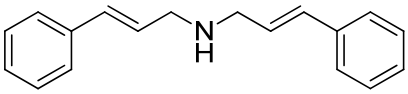
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 (d, *J* = 4.00 Hz, 2H), 7.35 (t, *J* = 7.48 Hz, 2H), 7.28 (t, *J* = 8.00 Hz, 1H), 6.68 (d, *J* = 15.87 Hz, 1H), 6.32 (dt, *J* = 6.29, 15.79 Hz, 1H), 4.81 (br. s., 2H), 4.75 (d, *J* = 6.41 Hz, 2H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.7, 136.3, 133.9, 128.6, 128.1, 126.6, 123.6, 65.7 ppm

FTIR (neat): *v* = 3017, 2253, 1651, 1636, 1219, 910, 733 cm^{-1}.

HRMS (ESI, m/z): calculated for $C_{10}H_{11}NO_2$ $[M+H]^+$: 178.0863, found $[M+H]^+$: 178.0864.

Di-cinnamylamine



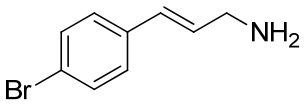
6

This compound was obtained by column chromatography.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18 - 7.43 (m, 10H), 6.55 (d, *J* = 15.87 Hz, 2H), 6.26 - 6.41 (m, 2H), 3.36 (d, *J* = 6.71 Hz, 4H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.1, 133.1, 128.6, 127.5, 127.1, 126.3, 56.1 ppm.

(*E*)-3-(4-Bromophenyl)prop-2-en-1-amine



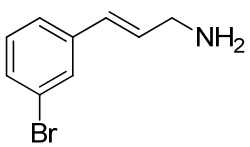
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 (d, *J* = 8.24 Hz, 2H), 7.22 (d, *J* = 8.24 Hz, 2H), 6.44 (d, *J* = 16.00 Hz, 1H), 6.26 - 6.36 (m, 1H), 3.46 (d, *J* = 5.49 Hz, 2H), 1.32 - 1.55 (m, 2H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.2, 132.2, 131.6, 128.2, 127.8, 44.2 ppm.

FTIR (neat): *v* = 3017, 2253, 1651, 1636, 1219, 910, 756,733, 671, 648 cm^{-1}.

HRMS (ESI, m/z): calculated for $C_9H_{10}BrN$ $[M+H]^+$: 212.0070, found $[M+H]^+$: 212.0069.

(*E*)-3-(3-Bromophenyl)prop-2-en-1-amine



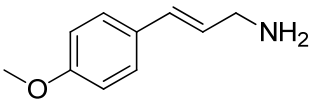
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53 (s, 1H), 7.35 (d, *J* = 7.93 Hz, 1H), 7.29 (d, *J* = 8.00 Hz, 1H), 7.18 (t, *J* = 8.00 Hz, 1H), 6.45 (d, *J* = 16.00 Hz, 1H), 6.29 - 6.39 (m, 1H), 3.50 (d, *J* = 3.97 Hz, 2H), 1.46 (br. s., 2H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.4, 132.9, 130.1, 130.1, 129.1, 128.0, 124.9, 122.8, 44.2 ppm.

FTIR (neat): *v* = 2855, 2253, 1558, 1474, 1072, 910, 733 cm^{-1}.

HRMS (ESI, m/z): calculated for $C_9H_{10}BrN$ $[M+H]^+$: 212.0070, found $[M+H]^+$: 212.0070.

(*E*)-3-(4-Methoxyphenyl)prop-2-en-1-amine



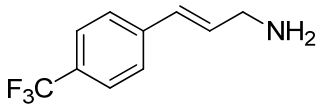
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 (d, *J* = 8.24 Hz, 2H), 6.84 (d, *J* = 8.85 Hz, 2H), 6.44 (d, *J* = 16.17 Hz, 1H), 6.10 - 6.24 (m, 1H), 3.80 (s, 3H), 3.44 (d, *J* = 5.80 Hz, 2H) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.0, 142.6, 130.0, 129.1, 127.4, 114.0, 55.3, 44.4 ppm.

FTIR (neat): *v* = 3017, 2253, 1651, 1512, 1219, 910, 756, 733 cm^{-1}.

HRMS (ESI, m/z): calculated for $C_{10}H_{13}NO$ $[M+Na]^+$: 186.0895, found $[M+Na]^+$: 186.0902.

(*E*)-3-(4-(Trifluoromethyl)phenyl)prop-2-en-1-amine



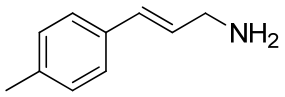
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (d, *J* = 8.24 Hz, 2H), 7.44 (d, *J* = 8.24 Hz, 2H), 6.54 (d, *J* = 15.95 Hz, 1H), 6.37 - 6.46 (dt, *J* = 5.55, 15.88 Hz, 1H), 3.51 (dd, *J* = 1.22, 5.49 Hz, 2H), 1.44 (br. s., 2H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.4, 133.7, 127.7, 126.0, 125.2, 125.2, 125.1, 43.8 ppm.

FTIR (neat): *v* = 3017, 2068, 1651, 1636, 1327, 1219, 1165, 1126, 756, 671 cm^{-1}.

HRMS (ESI, m/z): calculated for $C_{10}H_{10}F_3N$ $[M+H]^+$: 202.0838, found $[M+H]^+$: 202.0835.

(*E*)-3-*p*-Tolylprop-2-en-1-amine



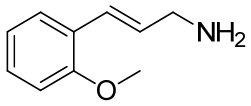
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18 (d, *J* = 8.24 Hz, 2H), 7.03 (d, *J* = 7.93 Hz, 2H), 6.38 (d, *J* = 15.87 Hz, 1H), 6.14 - 6.23 (m, 1H), 3.37 (dd, *J* = 1.37, 5.95 Hz, 2H), 2.25 (s, 3H), 1.37 (br. s., 2H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.1, 134.4, 130.3, 129.4, 129.3, 126.2, 44.4, 21.2 ppm.

FTIR (neat): *v* = 3017, 2361, 1651, 1636, 1219, 756, 671 cm^{-1}.

HRMS (ESI, m/z): calculated for $C_{10}H_{13}N$ $[M+H]^+$: 148.1121, found $[M+H]^+$: 148.1119.

(*E*)-3-(2-Methoxyphenyl)prop-2-en-1-amine



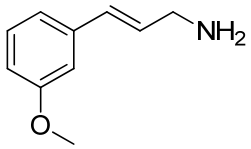
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42 (d, *J* = 7.63 Hz, 1H), 7.21 (t, *J* = 7.78 Hz, 1H), 6.92 (t, *J* = 7.63 Hz, 1H), 6.78 - 6.88 (m, 2H), 6.32 (dt, *J* = 5.87, 16.02 Hz, 1H), 3.84 (s, 3H), 3.48 (d, *J* = 5.80 Hz, 2H), 1.64 (br. s., 2H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.5, 132.0, 128.4, 126.8, 126.2, 124.3, 120.7, 110.8, 55.4, 44.8 ppm.

FTIR (neat): *v* = 2253, 1651, 1636, 1242, 910, 733, 648 cm^{-1}.

HRMS (ESI, m/z): calculated for $C_{10}H_{13}NO$ $[M+Na]^+$: 86.0895, found $[M+Na]^+$: 186.0897.

(*E*)-3-(3-Methoxyphenyl)prop-2-en-1-amine



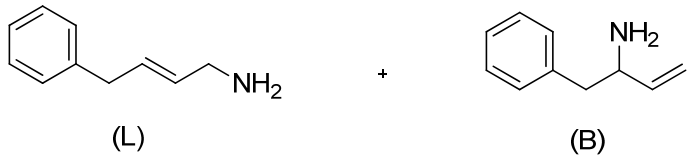
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 (t, *J* = 7.93 Hz, 1H), 6.89 - 6.99 (m, 2H), 6.77 (dd, *J* = 2.44, 8.24 Hz, 1H), 6.41 - 6.51 (m, 1H), 6.25 - 6.37 (m, 1H), 3.80 (s, 3H), 3.46 (d, *J* = 5.80 Hz, 2H), 1.54 (br. s., 2H) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.8, 138.7, 131.6, 129.5, 129.4, 118.9, 113.0, 111.6, 55.2, 44.3

FTIR (neat): *v* = 3017, 2839, 2399, 2253, 1597, 1219, 910, 756, 733 cm^{-1}.

HRMS (ESI, m/z): calculated for $C_{10}H_{13}NO$ $[M+Na]^+$: 186.0895, found $[M+Na]^+$: 186.0902.

(*E*)-4-Phenylbut-2-en-1-amine (L) + 1-Phenylbut-3-en-2-amine (B)



(L) (B)

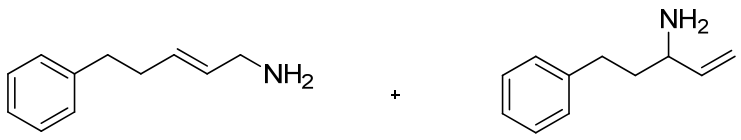
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.14 - 7.34 (m, 7.85H, L + B), 5.89 (ddd, *J* = 6.26, 10.53, 17.09 Hz, 0.57H, B), 5.57 - 5.77 (m, 2H, L), 4.99 - 5.19 (m, 1.14H, B), 3.56 - 3.63 (m, 0.57H, B), 3.35 (d, *J* = 6.41 Hz, 2H, L), 3.28 (d, *J* = 5.19 Hz, 2H, L), 2.83 (dd, *J* = 5.49, 13.43 Hz, 0.57H, B), 2.61 (dd, *J* = 8.24, 13.43 Hz, 0.57H, B), 1.42 (br. s., 3.14H, L + B) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ = 142.4, 140.5, 138.8, 132.8, 129.4, 129.2, 128.5, 128.5, 128.4, 128.4, 128.3, 126.4, 126.1, 113.7, 55.5, 44.4, 44.0, 38.8 ppm.

FTIR (neat): *v* = 2963, 2855, 2253, 1651, 1636, 910, 733, 648 cm^{-1}.

HRMS (ESI, m/z): calculated for $C_{10}H_{13}N$ $[M+H]^+$: 148.1121, found $[M+H]^+$: 148.1132.

(E)-5-Phenylpent-2-en-1-amine (L) + 5-Phenylpent-1-en-3-amine (B)



(L) (B)

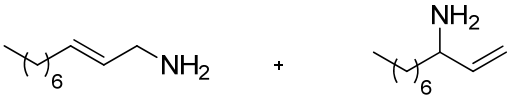
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.12 - 7.32 (m, 9.35H, L + B), 5.76 - 5.89 (m, 0.87H, B), 5.55 - 5.61 (m, 2H, L), 5.01 - 5.19 (m, 1.14H, B), 3.29 – 3.34 (m, 0.87H, B), 3.23 (d, *J* = 3.36 Hz, 2H, L), 2.63 - 2.75 (m, 3.74H, B + L), 2.34 – 2.36 (m, 2H, L), 1.72 - 1.78 (m, 1.74H, B), 1.34 (br. s., 3.74H, L + B) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.2, 142.1, 141.9, 132.0, 129.7, 128.6, 128.5, 128.4, 128.4, 128.3, 125.8, 113.8, 54.1, 44.1, 39.2, 35.8, 34.1, 32.4 ppm.

FTIR (neat): ν = 3024, 2924, 2855, 2253, 1636, 1489, 1450, 910, 733, 702 cm^{-1}.

HRMS (ESI, m/z): calculated for $C_{11}H_{15}N$ $[M+H]^+$: 162.1277, found $[M+H]^+$: 162.1290.

(*E*)-Dec-2-en-1-amine (L) + Dec-1-en-3-amine (B)



(L) (B)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.73 - 5.87 (m, 1H, B), 5.52 - 5.60 (m, 1H, L), 4.98 - 5.16 (m, 2H, B), 3.21 - 3.37 (m, 2H, B + L), 1.95 - 2.12 (m, 1.5H, B + L), 1.10 - 1.79 (m, 18H, B + L), 0.90 (m, 4.5H, B + L) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.7, 131.1, 130.9, 113.2, 54.5, 37.7, 32.3, 31.9, 31.8, 29.6, 29.4, 29.3, 29.2, 29.2, 26.1, 22.7, 14.1 ppm.

FTIR (neat): ν = 3055, 2986, 2307, 1651, 1636, 1265, 895, 741, 702 cm^{-1}.

HRMS (ESI, m/z): calculated for $C_{10}H_{21}N$ $[M+H]^+$: 156.1747, found $[M+H]^+$: 156.1758.

[1] Charette, A. B.; Molinaro, C.; Brochu, C. *J. Am. Chem. Soc.* **2001**, *123*, 12168.

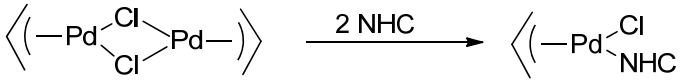
PART II

CHAPTER 5

Allylic Amination with Ammonia for the Synthesis of Primary Amines Catalyzed by (SIPr)Pd(allyl)Cl and PPh_3

5.1 OVERVIEW OF THE BACKGROUND

N-heterocyclic carbenes (NHCs) are widely applied as supporting ligands in transition metal-catalyzed reactions.[1] Pd complexes bearing NHCs and/or PR_3 have been employed in many transformations. Nolan's group has made much contribution in this area. In 2002, Nolan and co-workers reported a simple method for the preparation of various (NHC)Pd(allyl)Cl complexes (Scheme 1).[2] They found the real catalyst in NHC-Pd catalyzed cross-coupling reactions was the (NHC)Pd(0) complexes *via* the activation of (NHC)Pd(allyl)Cl by strong base. Later, many reactions catalyzed by (NHC)Pd(allyl)Cl as the precatalyst were developed.[3]



Scheme 1. The preparation of (NHC)Pd(allyl)Cl reported by Nolan and co-workers.

Metal NHC bonds are relatively stronger compared to metal phosphine bonds, and the mixed NHC-phosphine Pd complexes might offer a superior class of pre-catalysts.[4] In 2001, Cloke and co-workers reported the amination of 4-chlorotoluene

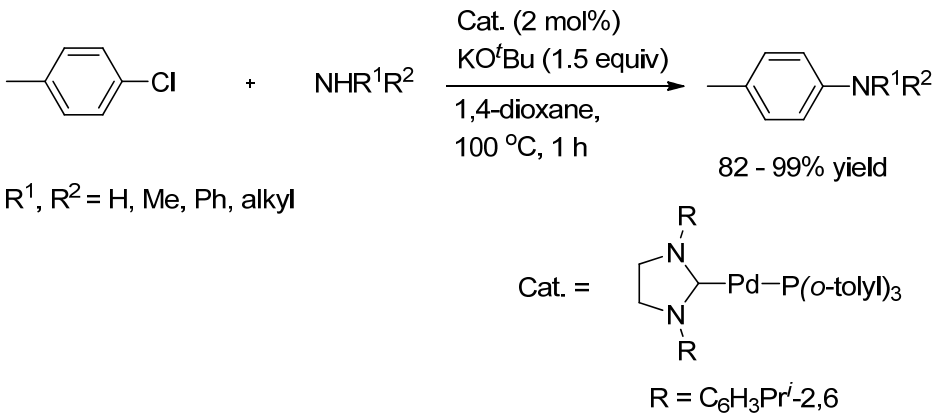
[1] For reviews, see: (a) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400. (b) Nishimura, T.; Uemura, S. *Synlett* **2004**, 201. (c) Sigman, M. S.; Jensen, D. R. *Acc. Chem. Res.* **2006**, *39*, 221. (d) Chen, X.; Engle, K. M.; Wang, D. H.; Jin-Quan, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (e) Diez-Gonzalez, S.; Marion, N.; Nolan, S. P. *Chem. Rev.* **2009**, *109*, 3612.

[2] Viciu, M. S.; Germaneau, R. F.; Navarro-Fernandez, O.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2002**, *21*, 5470.

[3] Some examples, see: (a) Viciu, M. S.; Germaneau, R. F.; Nolan, S. P. *Org. Lett.* **2002**, *4*, 4053. (b) Caemmerer, S. S.; Viciu, M. S.; Stevens, E. D.; Nolan, S. P. *Synlett* **2003**, 1871. (c) Viciu, M. S.; Navarro, O.; Germaneau, R. F.; Kelly, R. A., III; Sommer, W.; Marion, N.; Stevens, E. D.; Cavallo, L.; Nolan, S. P. *Organometallics* **2004**, *23*, 1629. (d) Marion, N.; Navarro, O.; Mei, J.; Stevens, E. D.; Scott, N. M.; Nolan, S. P. *J. Am. Chem. Soc.* **2006**, *128*, 4101. (f) Cawley, M. J.; Cloke, F. G. N.; Fitzmaurice, R. J.; Pearson, S. E.; Scott, J. S.; Caddick, S. *Org. Biomol. Chem.* **2008**, *6*, 2820. (g) Spergel, S. H.; Okoro, D. R.; Pitts, W. *J. Org. Chem.* **2010**, *75*, 5316.

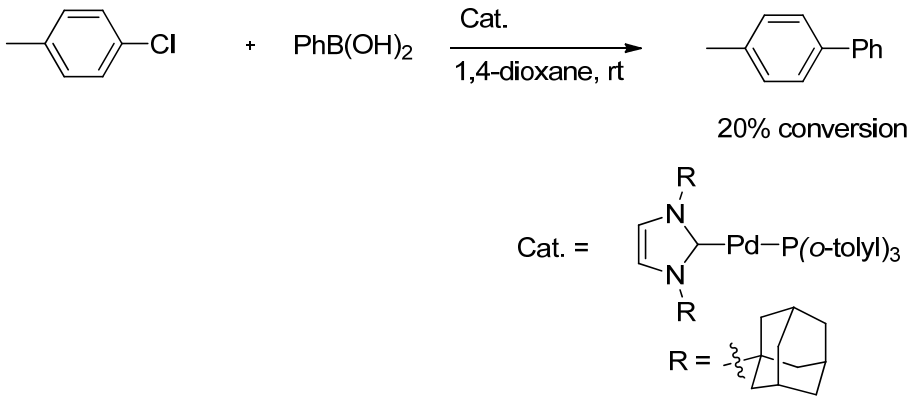
[4] (a) Danopoulos, A. A.; Tsoureas, N.; Macgregor, S. A.; Smith, C. *Organometallics* **2007**, *26*, 253. (b) Barczak, N. T.; Grote, R. E.; Jarvo, E. R. *Organometallics* **2007**, *26*, 4863. (c) Visentin, F.; Togni, A. *Organometallics* **2007**, *26*, 3746.

catalyzed by (SIPr)PdP[(*o*-tolyl)]$_3$ (Scheme 2).[5] Excellent yields were obtained for various amines.



Scheme 2. (SIPr)PdP[(*o*-tolyl)]$_3$ catalyzed amination of 4-chlorotolune reported by Cloke and co-workers.

In 2002, Herrmann and co-workers reported the use of NHC-Pd complexes to catalyze the Suzuki cross-coupling of aryl chlorides at room temperature (Scheme 3),[6] where a rather low 20% conversion was obtained when using (IAd)PdP[(*o*-tolyl)]$_3$. In addition only [Pd(IAd)$_2$] displayed good catalytic activity for this transformation.



Scheme 3. (IAd)PdP[(*o*-tolyl)]$_3$ catalyzed Suzuki coupling of 4-chlorotolune with phenylboronic acid reported by Herrmann and co-workers.

[5] Titcomb, L. R.; Caddick, S.; Cloke, F. G. N.; Wilson, D. J.; McKerrecher, D. *Chem. Commun.* **2001**, 1388.
[6] Gstottmayr, C. W. K.; Bohm, V. P. W.; Herdtweck, E.; Grosche, M.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1363.

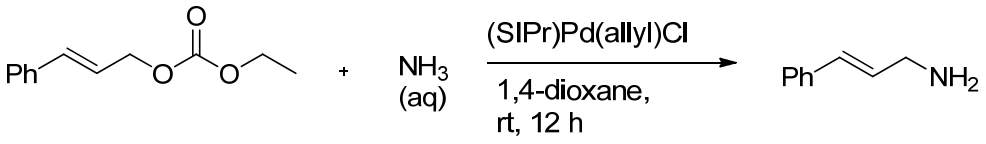
In conclusion, mixed NHC-phosphine Pd complexes possess specific characteristics, which can be applied widely in organic synthesis. More and mre attention has been being directed to this new area.

5.2 ALLYLIC AMINATION WITH AMMONIA FOR THE SYNTHESIS OF PRIMARY AMINES CATALYZED BY (SIPR)PD(ALLYL)CL AND PPH_3

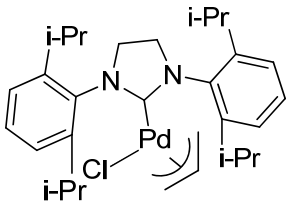
From Chapter 4, we found that the $Pd(PPh_3)_4$-SIPr·HCl-LiO^tBu combination worked well for allylic amination with NH_3 gas. Based on this result and our proposed mechanism, we envisioned that a well-defined preformed Pd-NHC complex could also serve as a catalyst for allylic amination with NH_3.

First, ethyl cinnamyl carbonate was selected as the model for the screening of the reaction conditions (Table 1). As shown in Table 1, when the concentration was 0.03 M, more PPh_3 helped to improve the yield (entries 1 – 3, Table 1). Increasing the concentration to 0.04 M, the yield dropped to 57% (entry 4, Table 1). In order to maximize the yield, we changed the ratio of aqueous NH_3 to 1,4-dioxane from 1:2 to 1:1. Nevertheless, the yield still dropped a little (entry 5, Table 1). Increasing the amount of aqueous ammonia did not increase the yield (entry 6, Table 1). Next, we reduced the catalyst loading to 5%, and the yield was almost the same as using 10% loading (entry 7, Table 1). However, no reaction occurred when the catalyst loading was further decreased to 1 mol%. A control reaction in the absence of PPh_3 gave no product

Table 1. Optimization of the reaction conditions[a]



(SIPr)Pd(allyl)Cl =

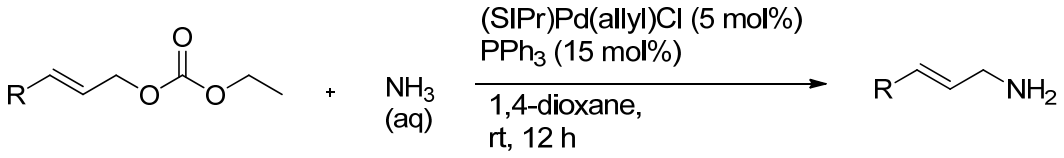


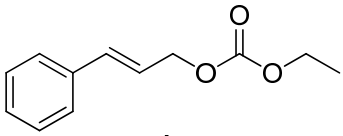
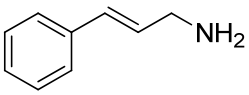
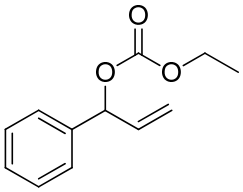
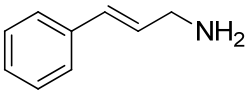
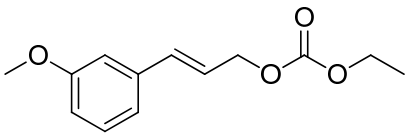
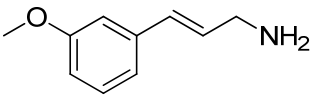
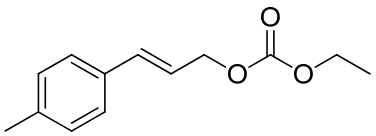
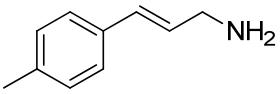
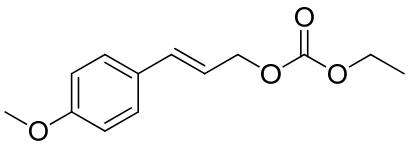
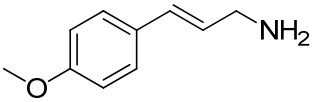
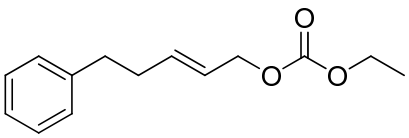
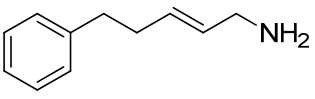
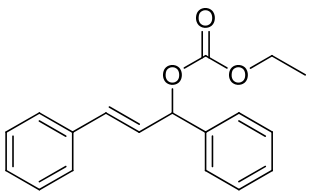
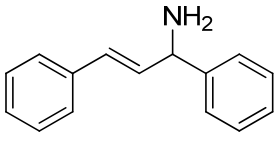
entry	NH_3/1,4-dioxane	conc. (M)	cat. (mol%)	PPh_3 (mol%)	yield[b] (%)
1	1 : 2	0.03	10	10	43
2	1 : 2	0.03	10	20	50
3	1 : 2	0.03	10	30	63
4	1 : 2	0.04	10	30	57
5	1 : 1	0.03	10	30	55
6	2 : 1	0.03	10	30	43
7	1 : 2	0.03	5	15	62
8	1 : 2	0.03	1	3	-[d]
9	1 : 2	0.03	10	-[c]	-[d]

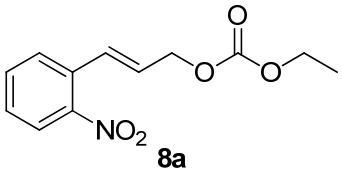
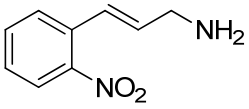
[a] Conditions: (SIPr)Pd(allyl)Cl and PPh_3 were added to 1,4-dioxane and stirred for 30 min, then ethyl cinnamyl carbonate (0.3 mmol) and aqueous ammonia (25%) were added to the solution successively. The solution was stirred at room temperature for 12 h.
[b] Isolated yields containing 4% of the branched primary amines.
[c] No PPh_3 was added.
[d] No desired product was obtained.

With the optimized reaction conditions, different substrates were investigated. Good yields were achieved for various substrates. No secondary amines were obtained. Judging from the ^{1}H NMR, 4% of the branched primary amines were formed (entries 1–4, Table 2). Substrate with a *p*-methoxy group (**5a)** gave relative lower yield and L/B selectivity (entry 5, Table 2). Less steric hindered substrate (**6a)** produced more branched product as expected (entry 6, Table 2). A substrate derived from 1,3-diphenylallyl alcohol (**7a**) gave the product in only 35% yield, presumably due to the steric hindrance (entry 7, Table 2). The substrate **8a** bearing a 2-nitro group reacted sluggishly to afford the product in a moderate yield of 52% (entry 8, Table 2).

Table 2. Allylic amination using aqueous ammonia[a]



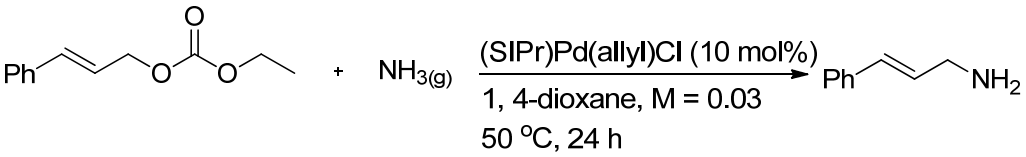
entry	substrate	product	yield(%)[b]
1	 **1a**	 **1b**	62
2	 **2a**	 **2b**	68
3	 **3a**	 **3b**	61
4	 **4a**	 **4b**	60
5	 **5a**	 **5b**	57[c] (84 : 16)[d]
6	 **6a**	 **6b**	50[c] (55 : 45)[d]
7	 **7a**	 **7b**	35

8	 **8a**	 **8b**	52[e]

[a] Conditions: (SIPr)Pd(allyl)Cl (5 mol%) and PPh_3 (15 mol%) were added to 1,4-dioxane (6.8 mL) and stirred for 30 min, then substrates (0.3 mmol) and aqueous ammonia (25%, 3.4 mL) were added to the solution successively. The solution was stirred at room temperature for 12 h.
[b] Isolated yields containing 4% of the branched primary amines.
[c] Combined yield.
[d] Ratio of the linear primary amine to the branched primary amine.
[e] The reaction time was 40 h. Only linear primary amine was obtained.

Next, based on the results in Chapter 4, allylic aminations with ammonia gas were also investigated. With 10 mol% of PPh_3, almost no reaction occurred regardless of the presence of LiO^tBu (entries 1 and 2, Table 3). Increase of the loading of PPh_3 to 30 mol%, together with the use of LiO^tBu, led to the formation of the product in 25% yield, while the rest of the substrate was hydrolyzed to cinnamyl alcohol.

Table 3. Optimization of the reaction conditions[a]



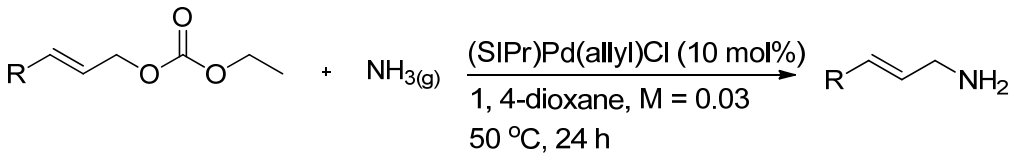
entry	LiO^tBu (mol%)	PPh_3 (mol%)	yield[b] (%)
1	11	10	trace
2	-	10	-
3	11	30	25
4	-	30	99
5[c]	-	30	trace

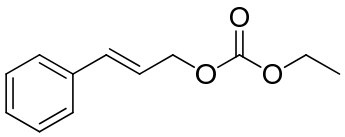
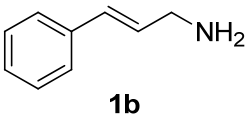
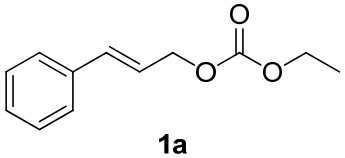
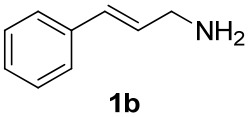
[a] Conditions: (SIPr)Pd(allyl)Cl, LiO^tBu and PPh_3 were added to 1,4-dioxane (10 mL) and stirred for 30 min, then ethyl cinnamyl carbonate (0.3 mmol) and liquid ammonia (4.5 mL) were added to the solution successively. The solution was stirred at 50 °C for 24 h.
[b] Isolated yields containing 4% of the branched primary amines (1-Phenylprop-2-en-1-amine).
[c] The reaction was proceeded at room temperature for 12 h.

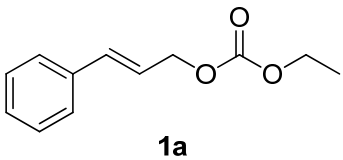
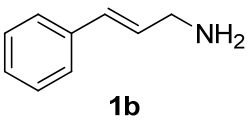
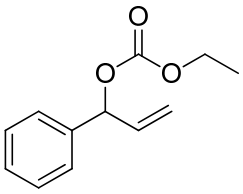
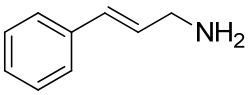
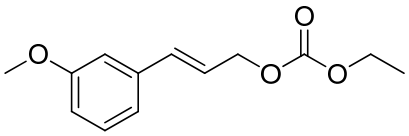
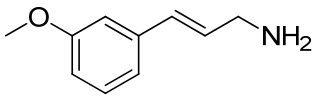
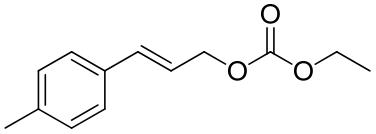
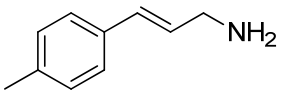
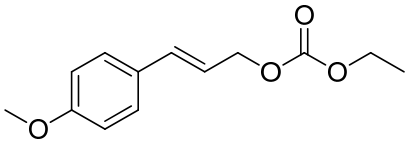
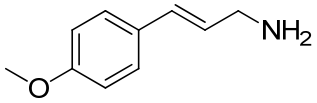
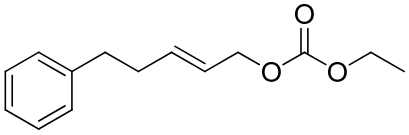
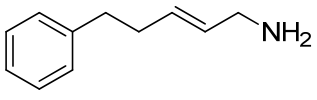
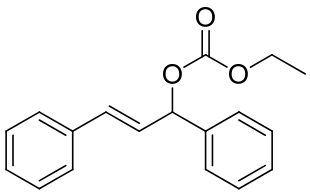
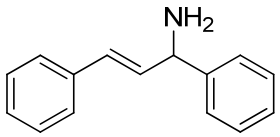
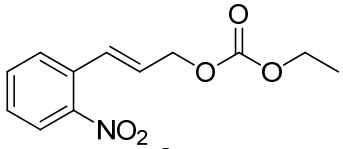
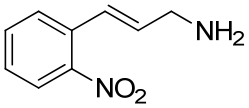
(entry 3, Table 3). On the other hand, almost quantitative yield was achieved in the absence of base (entry 4, table 3), which was different from the result using aqueous ammonia. When the reaction was conducted at room temperature for 12 h, only trace amount of the product was observed, which means that ammonia gas was less active than the aqueous solution.

The scope of the reaction with ammonia gas was also investigated. With the reaction time reduced to 12 h, the yield decreased dramatically (entry 2, Table 4). The amount of the catalyst loading was critical for this reaction, and no reaction occured when only 5 mol% of the (SIPr)Pd(allyl)Cl was used, which was different from the allylic amination with aqueous ammonia (entry 3, Table 4). Moderate to good yields were achieved for other substrates (entries 4 – 6, Table 4). Substrates **5a** and **6a** gave more branched primary amines (entries 7 and 8, Table 4). More stericlly hindered substrate **7a** afforded only 10% yield (entry 9, Table 4). The 2-nitro group bearing substrate **8a** could not give the desired product even after longer reaction time (entry 10, Table 4).

Table 4. Allylic amination using ammonia gas[a]



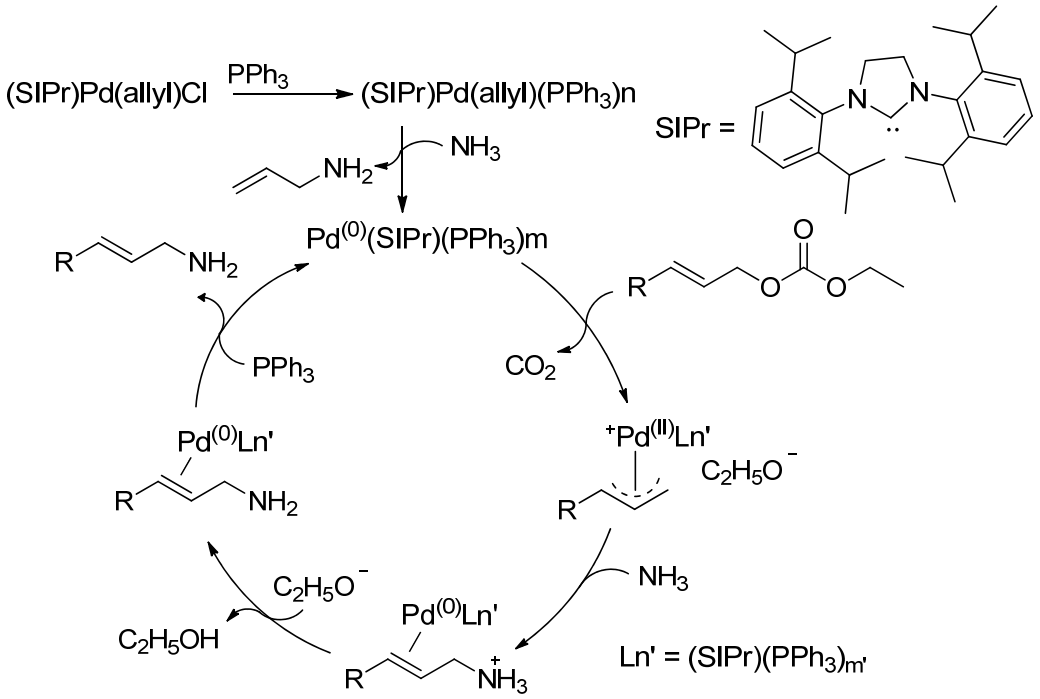
entry	substrate	product	yield(%)[b]
1	 **1a**	 **1b**	99
2[c]	 **1a**	 **1b**	30

3[d]	 **1a**	 **1b**	-
4	 **2a**	 **2b**	75
5	 **3a**	 **3b**	69
6	 **4a**	 **4b**	82
7	 **5a**	 **5b**	51[e] (81 : 19)[f]
8	 **6a**	 **6b**	63[e] (51 : 49)[f]
9	 **7a**	 **7b**	10
10	 **8a**	 **8b**	trace[g]

[a] Conditions: (SIPr)Pd(allyl)Cl (10 mol%) and PPh_3 (30 mol%) were added to 1,4-dioxane (10 mL) and stirred for 30 min, then substrates (0.3 mmol) and liquid ammonia (500 equiv) were added to the solution successively. The solution was stirred at 50 ºC for 24 h.
[b] Isolated yields containing 4% of the branched primary amines.
[c] The reaction time was 12 h.
[d] (SIPr)Pd(allyl)Cl (5 mol%) and PPh_3 (15 mol%) were used.
[e] Combined yield.

[f] Ratio of the linear primary amine to the branched primary amine.
[g] The reaction time was 40 h.

A plausible catalytic cycle is proposed below, which is similar to that in Chapter 4. Work towards the support of this proposal is in progress.



Scheme 4. A plausible mechanism.

CONCLUSION AND FUTURE WORK

To the best of our knowledge so far, there has been no report on palladium-catalyzed allylic amination with ammonia gas. A new catalytic system for allylic amination has been developed, which is suitable for both ammonia solution and

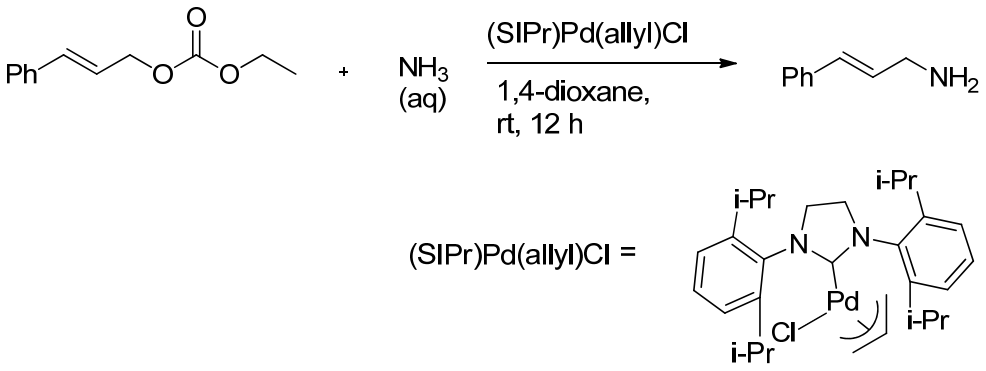
ammonia gas. Primary amines could be selectively obtained in moderate to good yields with our system. No secondary amines were observed.

Our future work will focus on the mechanism study, and expand our catalytic system to other reactions.

5.3 EXPERIMENTAL

The preparations and NMR characters of the starting materials were the same as the Section 4.4 in Chapter 4.

General procedure for the allylic amintion with aqueous ammonia

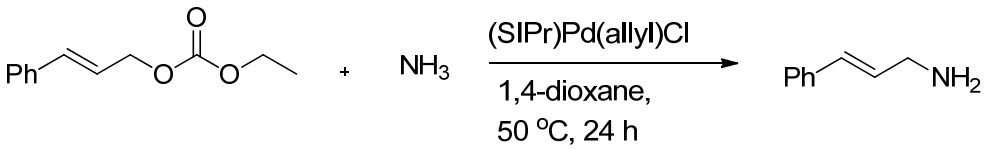


A 50 mL sealed tube was charged with PPh_3 (12 mg, 15 mol%), (SIPr)Pd(ally)Cl (9 mg, 5 mol%) and 6.8 mL 1,4-dioxane. The resulting solution was stirred at room temperature for 30 min. Then ethyl cinnamyl carbonate (62 mg, 0.3 mmol) and aqueous ammnonia (3.4 mL, 25%) were added to the sealed tube. The reaction mixture was stirred at room temperature for 12h.

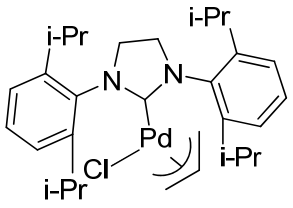
The reaction mixture was acidified by 3 M HCl (pH < 2) and was extracted with dichloromethane three times. The aqueous layer was cooled in an ice bath and was made to be basic with solid NaOH (the solution becomes cloudy from the insoluble free amine). The amine was extracted by dichloromethane three times. The combined organic layers were dried over anhydrous Na_2SO_4, the organic layer was filtered and concentrated under reduced pressure and the pure primary amine was obtained without further purification.

Other products were prepared as the same procedure. The NMR spectra of the products are the same as those in Section 4.4 of Chapter 4.

General procedure for the allylic amintion with ammonia gas

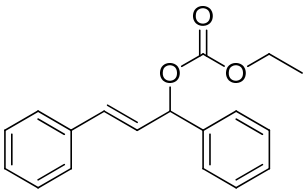


(SIPr)Pd(allyl)Cl =



The procedure was the same as that in in Section 4.4 of Chapter 4.

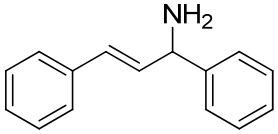
(*E*)-1,3-Diphenylallyl ethyl carbonate



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.17 - 7.49 (m, 10H), 6.69 (d, *J* = 15.87 Hz, 1H), 6.32 - 6.43 (m, 1H), 6.26 (d, *J* = 6.71 Hz, 1H), 4.21 (qd, *J* = 3.51, 7.17 Hz, 2H), 1.30 (t, *J* = 7.17 Hz, 3H)ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.5, 138.7, 136.1, 132.9, 128.7, 128.6, 128.4, 128.2, 127.0, 127.0, 126.8, 80.0, 64.2, 14.3 ppm.

(*E*)-1,3-Diphenylprop-2-en-1-amine[177]



This compound was purified by purified on silica gel PTLC (hexane/*i*-PrNH2 = 19/1).

[177] Nagano, T.; Kobayashi, S. *J. Am. Chem. Soc.* **2009**, *131*, 4200.

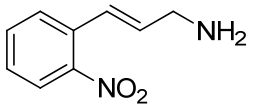
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.14 - 7.47 (m, 10H), 6.59 (d, *J* = 15.87 Hz, 1H), 6.37 (dd, *J* = 6.41, 15.87 Hz, 1H), 4.71 (d, *J* = 6.41 Hz, 1H), 1.66 (br. s., 2H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.6, 137.0, 133.9, 129.1, 128.7, 128.6, 127.5, 127.2, 126.7, 126.4, 58.0 ppm.

FTIR (neat): *v* = 3032, 2253, 1651, 910, 733, 648 cm^{-1}.

HRMS (ESI, m/z): calculated for $C_{15}H_{15}N$ $[M+H]^+$: 210.1277, found $[M+H]^+$: 210.1290.

(*E*)-3-(2-Nitrophenyl)prop-2-en-1-amine



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 8.24 Hz, 1H), 7.51 - 7.65 (m, 2H), 7.31 - 7.43 (m, 1H), 6.98 (d, *J* = 15.87 Hz, 1H), 6.33 (dt, *J* = 5.76, 15.64 Hz, 1H), 3.54 (dd, *J* = 1.37, 5.65 Hz, 2H), 1.32 (brs, 2H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.8, 137.0, 133.0, 132.9, 128.6, 127.8, 124.5, 124.5, 44.3 ppm.

FTIR (neat): *v* = 3156, 2963, 2855, 2253, 1519, 1350, 1119, 1096, 910, 733, 648 cm^{-1}.

HRMS (ESI, m/z): calculated for $C_9H_{10}N_2O_2$ $[M+H]^+$: 179.0815, found $[M+H]^+$: 179.0813.

List of Publication

1. Yin, P.; Loh, T. P. Intermolecular Hydroamination between Nonactivated Alkenes and Aniline Catalyzed by Lanthanide Salts in Ionic Solvents. *Org. Lett.*, **2009**, *17*, 3791-3793.

2. Yin, P.; Tham, Jieying; Loh, T. P. NHC-Pd Complex Catalyzed Allylic Amination Using Ammonia for the Synthesis of Primary Amines. *Manuscript in preparation.* **2011**.

3. Yin, P.; Tham, Jieying; Loh, T. P. Allylic Amination with Ammonia for the Synthesis of Primary Amines Catalyzed by (SIPr)Pd(allyl)Cl and PPh3. *Manuscript in preparation.* **2011**.

4. Yin, P.; Tham, Jieying; Yap Ting Gina; Loh, T. P. Iodine-Catalyzed Intramolecular Hydroamination of Unactivated Alkenes with Primary and Secondary Amines. *Manuscript in preparation.* **2011**.

Conferences

1. Yin, P.; Loh, T. P. International Symposium on Catalysis and Fine Chemicals, Singapore, 2007.

2. Yin, P.; Loh, T. P. 6th Asian-European Symposium on Metal Mediated Efficient Reactions. Singapore, 2010.