TRANSITION METAL-FREE AMINO-CYCLIZATION FOR THE SYNTHESIS OF SATURATED AZAHETEROCYCLES

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Part 1: Synthesis of Saturated Azaheterocycles via Alkali Metal-mediated Amino-cyclization 1

List of abbreviations

δ	chemical shift (ppm)
°C	degree centigrade
Ac	acetyl
Ar	aryl (substituted aromatic ring) or argon atmosphere
B3LYP	Becke, 3-parameter, Lee-Yang-Parr
BBN	9-borabicyclo[3.3.1]nonane
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
brs	broad singlet
Bu	butyl
Bz	benzoyl
Calcd	calculated
cat.	catalytic
cod	1,5-cyclooctadiene
cm^{-1}	wave number
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
dd	doublet of doublets
ddd	doublet of doublet of doublets
DEAD	diethyl azodicarboxylate
DFT	density functional theory
DIBAL	diisobutylaluminum hydride

DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
DPPA	diphenylphosphoryl azide
dppf	1,1'-bis(diphenylphosphino)ferrocene
dr	diastereomeric ratio
dt	doublet of triplets
ee	enantiomeric excess
equiv	equivalent
ESIHRMS	Electrospray Ionization High Resolution Mass Spectrometry
Et	ethyl
EWG	electron withdrawing group
FTIR	Fourier Transform Infrared Spectroscopy
g	gram
h	hour
HAT	hydrogen atom transfer
HFIP	hexafluoroisopropyl alcohol
HG	Hoveyda-Grubbs
Hz	hertz
INT	intermediate
J	coupling constants
k	reaction rate
kcal	kilocalorie
LDA	lithium diisopropylamide

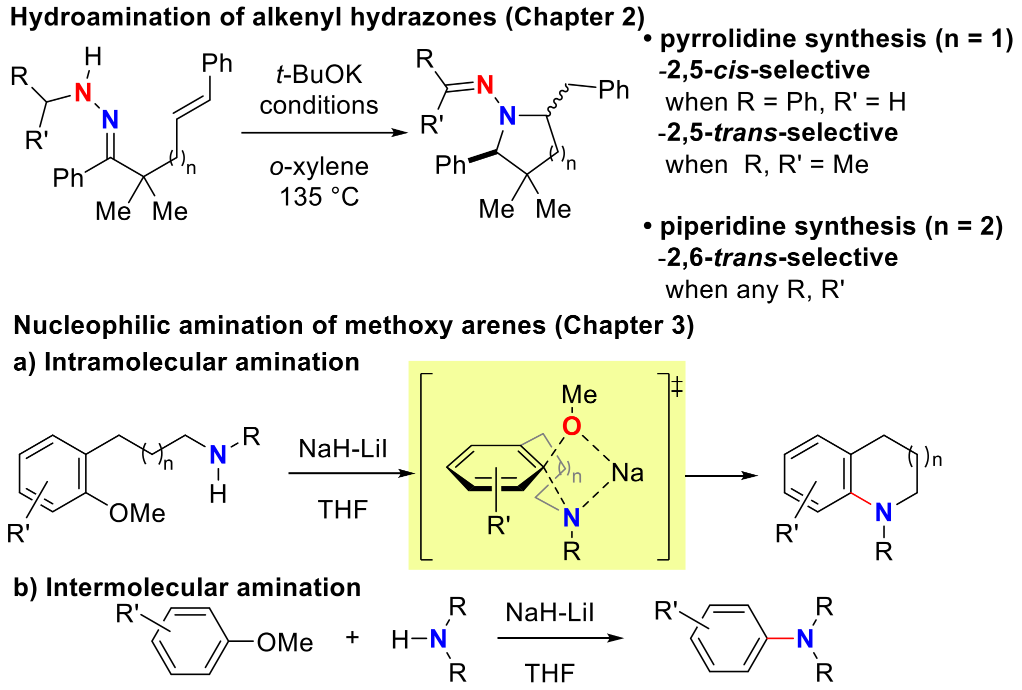
LED	light emitting diode
LG	leaving group
LHMDS	lithium bis(trimethylsilyl)amide
M	concentration (N, mol/dm^{-3})
M^+	parent ion peak (mass spectrum)
m	multiplet
Me	methyl
mg	milligram
MHz	megahertz
min	minutes
mL	milliliters
mmol	millimole
MOM	methoxymethyl
Ms	methanesulfonyl
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NMR	nuclear magnetic resonance
NPA	natural population analysis
Nu	nucleophile
OTf	trifluoromethanesulfonate
pcm	polarizable continuum model (SCRF)
PD	product
Ph	phenyl
PMB	*para*-methoxybenzyl
ppm	parts per million

PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl
q	quartet
ρ	reaction constant
Red-Al	sodium bis(2-methoxyethoxy)aluminum hydride
rt	room temperature
s	singlet
σ	substituent constant
sep	septet
S_NAr	nucleophilic aromatic substitution
t	triplet
TBAF	tetrabutylammonium fluoride
TBAT	tetrabutylammonium difluorotriphenylsilicate
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N*’,*N*’-tetramethylethylenediamine
TMS	trimethylsilyl
Ts	*para*-toluenesulfonyl
TS	transition state
tt	triplet of triplets

Abstract

This thesis focused on the development of transition metal-free amino-cyclization towards the synthesis of saturated azaheterocycles and benzannulated saturated azaheterocycles that are ubiquitous scaffolds in biologically active natural products as well as pharmaceuticals.

Part 1 of the thesis described alkali metal-mediated amino-cyclization for the synthesis of saturated azaheterocycles and benzannulated saturated azaheterocycles (Scheme 1). In Chapter 2, *t*-BuOK-mediated hydroamination of alkenyl hydrazones was discussed. Modification of the substituents on the hydrazones enabled diastereo-divergent synthesis of 2,5-disubstituted pyrrolidines whereas a unique 2,6-*trans* selectivity was observed in piperidine formation, which were rationalized by experiments and DFT computation. Chapter 3 described nucleophilic amination of methoxy arenes by means of sodium hydride in the presence of lithium iodide. This protocol served as an efficient route to benzo-fused saturated azaheterocycles as well as aryl amines via intermolecular amination. Mechanistic studies showed that the reaction proceeded through an unprecedented concerted nucleophilic aromatic substitution.


Hydroamination of alkenyl hydrazones (Chapter 2)

- pyrrolidine synthesis (n = 1)
  -2,5-*cis*-selective
  when R = Ph, R' = H
  -2,5-*trans*-selective
  when R, R' = Me
- piperidine synthesis (n = 2)
  -2,6-*trans*-selective
  when any R, R'

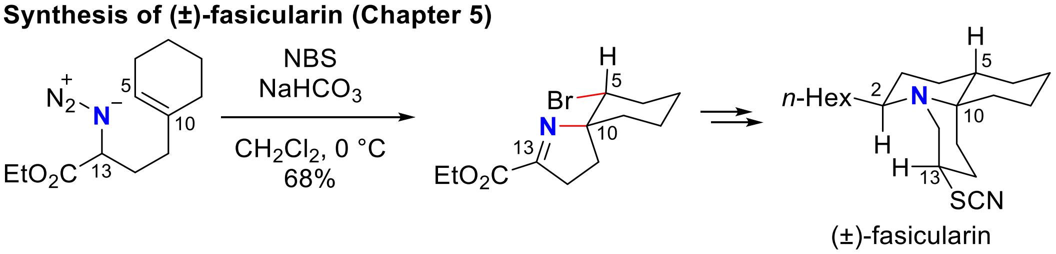
Nucleophilic amination of methoxy arenes (Chapter 3)

a) Intramolecular amination

b) Intermolecular amination

Scheme 1. Alkali metal-mediated amino-cyclization for the synthesis of saturated azaheterocycles and benzannulated saturated azaheterocycles.

In part 2 of the thesis, the author presented total synthesis of (±)-fasicularin having the DNA alkylation ability (Scheme 2). The synthesis was stemmed from NBS-mediated spirocyclizing bromoamination of alkenyl azidoester to construct key azaspirocycle. The resulting azaspirocycle was converted to (±)-fasicularin in 14 steps including stereoselective installation of β-hexyl side chain at C(2).


Synthesis of (±)-fasicularin (Chapter 5)

Scheme 2. Synthesis of (±)-fasicularin.

Chapter 6 disclosed the experimental and computational data for Chapter 2, 3, and 5.

Part 1: Synthesis of Saturated Azaheterocycles via Alkali Metal-mediated Amino-cyclization

Chapter 1: General Introduction

1.1. Importance of saturated azaheterocycles

Saturated nitrogen-containing heterocycles (azaheteorocycles) are ubiquitous scaffolds found in biologically active natural products as well as pharmaceutical drugs.[1] In particular, pyrrolidine and piperidine rings are the prevalent cyclic amines in prominent drugs such as Remoxipride (for schizophrenia) (**1.1**), Clindamycin (for bacterial infection) (**1.2**), and Tiagabine (for epilepsy) (**1.3**) (Figure 1.1).[2] On the other hand, benzannulated saturated azaheterocycles are also of particular importance in the pharmaceutical industry,[3] which are exemplified by a 5-hydroxy tryptamine (5-HT$_3$) receptor antagonist (**1.4**),[4] an tubulin polymerization inhibitor (**1.5**),[5] as well as a nonpeptide vasopressin V2-receptor antagonist, mozavaptan (**1.6**) (Figure 1.1).[6]

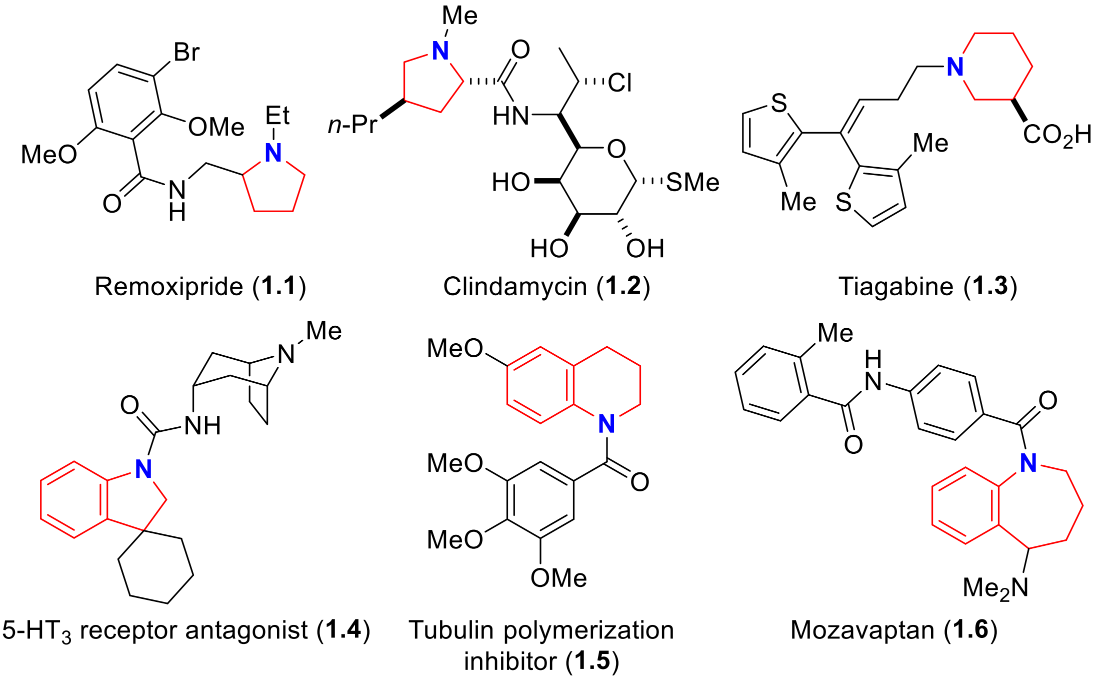

Remoxipride (**1.1**)
Clindamycin (**1.2**)
Tiagabine (**1.3**)
5-HT$_3$ receptor antagonist (**1.4**)
Tubulin polymerization inhibitor (**1.5**)
Mozavaptan (**1.6**)

Figure 1.1. Pharmaceuticals containing saturated azaheterocycles.

1.2. Necessity of transition metal-free molecular transformations

Transition-metal-catalyzed reactions for the synthesis of saturated azaheterocycles have attracted extensive attention over the past decades.[7] Representative preparative protocols involving C(sp^3)-nitrogen bond formation include alkene hydroamination,[8] C-H amination,[9] and recently emerging Cu-mediated stannyl amine protocol (SnAP).[10] For the construction of C(sp^2)-nitrogen bonds, the Buchwald-Hartwig amination is one of the most practical methods.[11] On the other hand, the development of transition metal-free processes has recently been of high demand. European Agency for the Evaluation of Medicinal Products (EMEA) recently established the strict guideline for the allowable level of contaminated metals in pharmaceuticals, which stated maximum concentrations for heavy metals typically used in organic synthesis should be minimized to ppm levels (Table 1.1).[12] Most of the transition metals are toxic owing to their coordinating abilities with amino acids, proteins, DNA, and other macromolecules, whereas the removal of contaminated transition-metal residues from the substances is energy intensive process.[13]

Table 1.1. Guideline for the concentration limits of contaminated transition metals in pharmaceuticals.

Elements	Oral concentration limit (ppm)	Parenteral concentration limit (ppm)
Pt, Pd, Ir, Rh, Ru, Os	10	1
Mo, Ni, Cr, V	25	2.5
Cu, Mn	250	25
Fe, Zn	1300	130

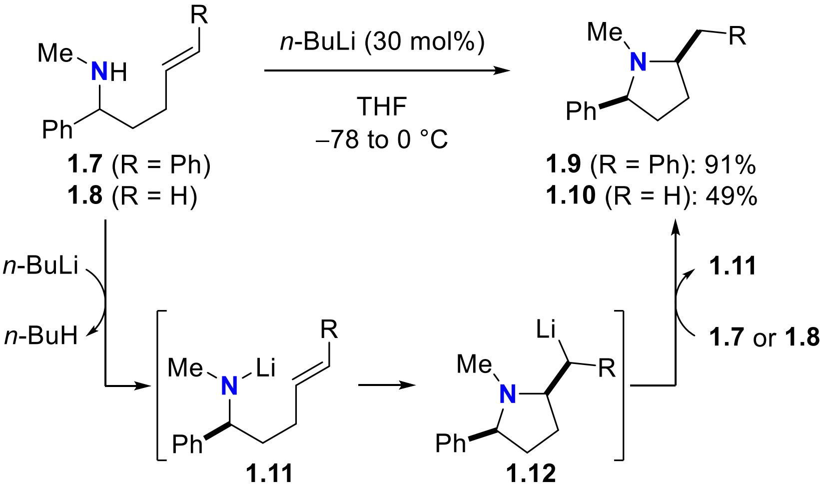
Moreover, large consumption of precious transition metals should be avoided from the viewpoint of environmental sustainability.[14] Therefore, alternative approaches to saturated azaheterocycles under transition metal-free conditions are highly desirable.

1.3. Diastereoselective alkene hydroamination to the synthesis of saturated azaheterocycles under transition metal-free conditions

Alkene hydroamination involving the addition of amine nucleophiles toward carbon-carbon double bonds has received a considerable interest for the synthesis of saturated azaheterocycles due to the abundance of amines and alkenes. This process is ideally atom-economical to construct carbon-nitrogen bonds in comparison to the other classical synthetic protocols such as nucleophilic substitution of alkyl halides by amines as well as reductive amination of carbonyl compounds.[8i] Although the direct addition of amines to alkenes is thermodynamically favorable, simple carbon-nitrogen bond formation has a high energy barrier due to the electronic repulsion between lone pair of amines and π-bond of the electron-enriched alkenes.[15] Therefore, intense research activities have been dedicated to the establishment of alkene hydroamination under metal-mediated or metal-free reaction conditions.[8] Especially, remarkable progress has been made in the field of stereoselective hydroamination including enantioselective as well as diastereoselective variants.[16] In this respect, diastereoselective preparation of 2,5-disubstituted pyrrolidines and 2,6-disubstituted piperidines has been extensively explored for their applications in agricultural and medicinal chemistry.[17] This section highlights selected examples of diastereoselective alkene hydroamination toward the synthesis of 2,5-disubstituted pyrrolidines and 2,6-disubstituted piperidines under transition metal-free conditions classified by the reaction promoters.

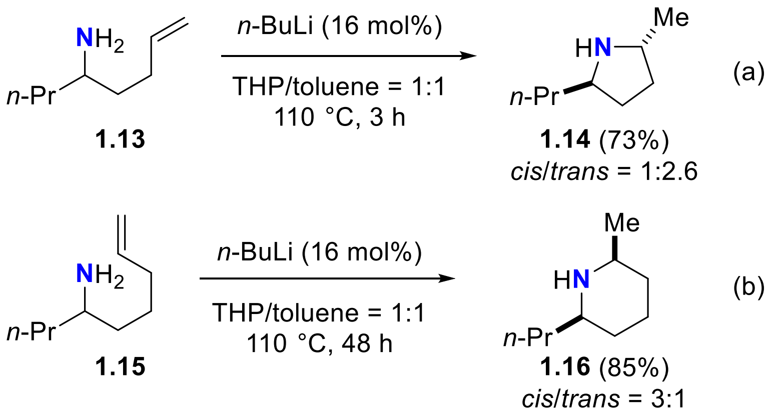
1.3.1. With alkali metals

Suginome and Tokuda in 1992 reported cyclohydroamination of alkenyl secondary amines using *n*-BuLi as an initiator (Scheme 1.1).[18] Their protocol could be applicable to not only conjugated alkene **1.7** but also unactivated one **1.8** for the synthesis of *cis*-pyrrolidines **1.9-1.10**. This reaction was initiated by deprotonation of amines by *n*-BuLi to form nucleophilic lithium amides **1.11**, which added onto the alkenes. The resulting organolithium species **1.12** undergoes deprotonation from the starting amines **1.7-1.8** to provide the products **1.9-1.10** and regenerate lithium amides **1.11** to maintain the process.



Scheme 1.1. *n*-BuLi-catalyzed cyclohydroamination of secondary amines.

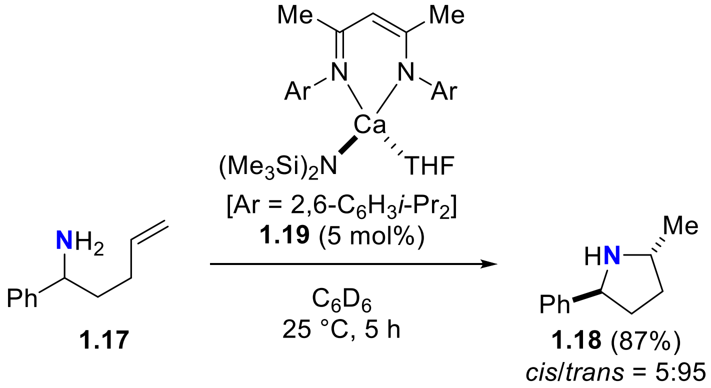
The employment of primary amines for the *n*-BuLi catalyzed intramolecular hydroamination was investigated by other groups.[19] The use of tetrahydropyran (THP)/toluene co-solvent system was critical to suppress the undesired alkene isomerization of **1.13**, affording *trans*-pyrrolidine **1.14** in moderate diastereoselectivity (*cis*/*trans* = 1:2.6) (Scheme 1.2a).[19a] Moreover, the reaction of amine **1.15** under the same reaction conditions enabled six-membered ring formation to deliver the alkaloid (±)-dihydropinidine (**1.16**) in 85% yield (Scheme 1.2b).



Scheme 1.2. *n*-BuLi-catalyzed cyclohydroamination of primary amines.

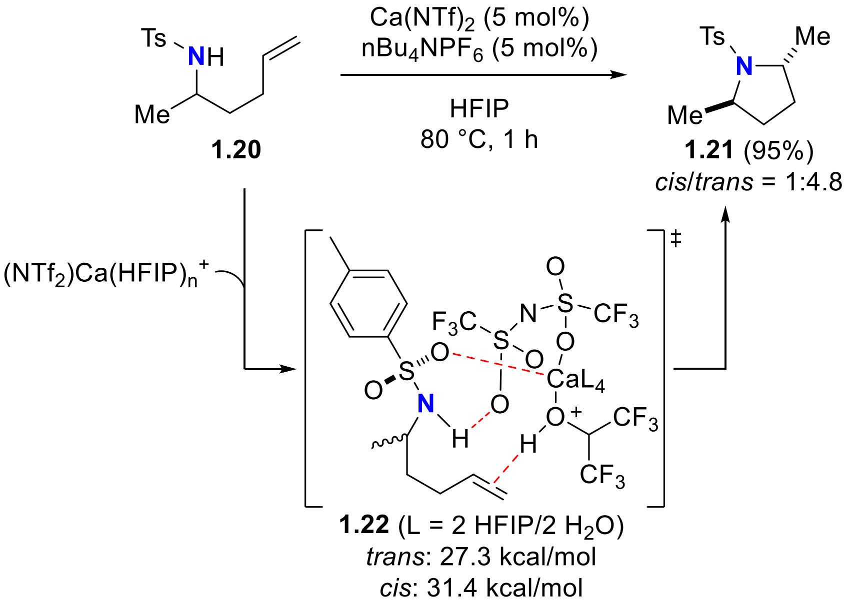
1.3.2. With alkali earth metals

Hill and co-workers developed the first alkali earth metal-catalyzed intramolecular hydroamination using an organocalcium compound as a catalyst.[20] The treatment of primary amine **1.17** with 5 mol% of β-diketiminato calcium bis(trimethylsilyl)amide **1.19** afforded pyrrolidine **1.18** in 93% yield with excellent *trans*-selectivity (Scheme 1.3).



Scheme 1.3. Organocalcium-catalyzed hydroamination of alkenes.

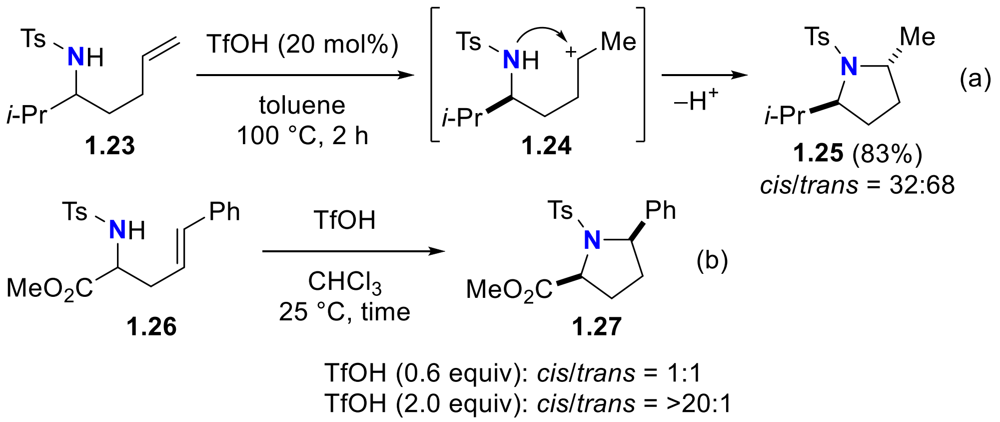
Very recently, Gandon and Lebœuf reported calcium-catalyzed hydroamination of alkenes in hexafluoroisopropyl alcohol (HFIP) solvent without the use of special ligands (Scheme 1.4).[21,22] Their reaction of aminoalkene **1.20** utilized a combination of $Ca(NTf_2)_2$ and *n*-Bu_4NPF_6 to generate highly Lewis acidic $[Ca(NTf_2)]^+[PF_6]^-$ via counter ion metathesis,[23] producing *trans*-pyrrolidine **1.21** as a major isomer. Their DFT computation showed that the key in this amino-cyclization was the formation of $(NTf_2)Ca(HFIP)_n^+$, which played a dual role of Lewis acid and Brønsted acid. The transition state **1.22** involves three types of attractive interaction that is, 1) hydrogen bonding between the NH amine substrate **1.20** and the sulfoxide on the sulfonimide ligand, 2) coordination of the tosyl oxygen of the substrate **1.20** to the $(NTf_2)Ca^+$ metal center, and 3) noncovalent interaction between the alkene **1.20** and the OH group of HFIP. Further DFT computation revealed that the transition state energy of *trans*-cyclization was 4.1 kcal/mol lower than that of *cis*-cyclization (*trans*: 27.3 kcal/mol, *cis*: 31.4 kcal/mol).



Scheme 1.4. Calcium-catalyzed hydroamination of alkenes under HFIP solvent.

1.3.3. With Brønsted acids

Hartwig and co-workers described the first Brønsted acid-catalyzed intramolecular hydroamination of alkenyl *N*-sulfonamides (Scheme 1.5a).[24] The treatment of tosylamide **1.23** in the presence of TfOH at an elevated temperature promoted cyclization of carbenium ion **1.24** generated *in situ* to provide pyrrolidine **1.25** in 83% yield with moderate diastereoselectivity (*cis*/*trans* = 32:68). On the other hand, Knight and Haskins found that stoichiometric use of TfOH for the reaction of **1.26** resulted in the formation of *cis*-pyrrolidine **1.27** exclusively (Scheme 1.5b). They proposed an isomerization mechanism of *trans*-**1.27** to thermodynamically more stable *cis*-**1.27** under highly acidic condition. Recently, intramolecular hydroamination using hydrogen iodide (HI) was also reported for the synthesis of 2,5-disubstituted pyrrolidines albeit in poor diastereoselectivity.[25]

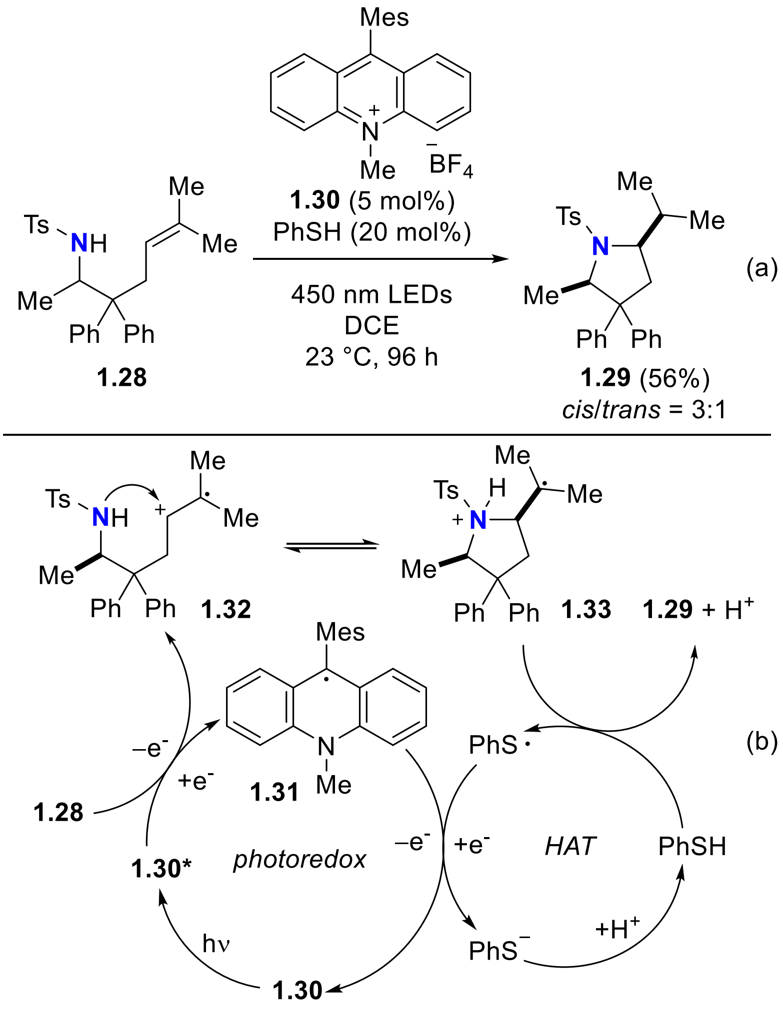


Scheme 1.5. Brønsted acid-catalyzed intramolecular hydroamination of alkenes.

1.3.4. With radical initiators

Organic photoredox catalysis has emerged in the synthetic organic community as a valuable tool to generate the key radicals smoothly under visible light irradiation without transition metals.[26] Nicewicz and Nguyen reported amino-cyclization of alkenyl sulfonamides using 9-mesityl-10-methylacridinium tetrafluoroborate (**1.30**) as a photocatalyst,[27] which possesses highly oxidizing ability in its excited state.[27c,28] They utilized thiophenol as a hydrogen atom donor for the reaction of sulfonamide **1.28** with acridinium salt **1.30** to deliver *cis*-pyrrolidine **1.29** as a major isomer

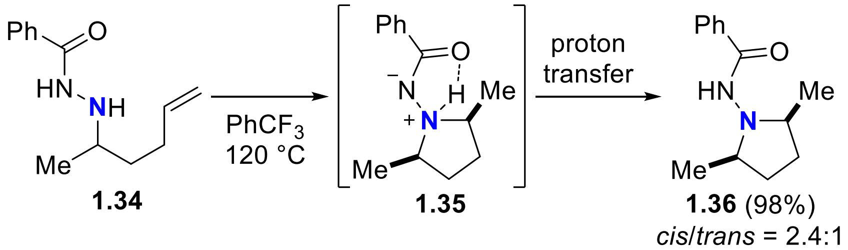
(Scheme 1.6a). The reaction involved a dual catalytic cycle of the photoredox and hydrogen atom transfer system (Scheme 1.6b).[29] Initial single electron oxidation of alkene **1.28** by the photo-excited acridinium catalyst **1.30*** generated acridinyl radical **1.31** and radical cation **1.32**, which was trapped by the internal amine nucleophile. The resulting radical cation **1.33** abstracted hydrogen atom from thiophenol to deliver the desired product **1.29** and a thiyl radical. The thiyl radical served as a reductant of the acridinyl radical **1.31** to regenerate the acridinium catalyst **1.30**.



Scheme 1.6. Organic photoredox-catalyzed hydroamination of alkenes.

1.3.5. Cope-type hydroamination

As a mechanistically distinct approach to typical alkene hydroamination, the Cope-type hydroamination has been explored since the first intramolecular cyclization of akenyl hydroxylamine was reported in 1976.[30,31] Recently, Beauchemin and co-workers demonstrated Claisen-type hydroamination of hydrazides instead of hydroxylamines due to the bench stability of hydrazides.[32] The reaction of benzoyl hydrazide **1.34** at 120 °C provided pyrrolidine derivative **1.36** as a diastereomeric mixture through intramolecular proton transfer of ammonium ylide **1.35** promoted by hydrazide moiety (Scheme 1.7).



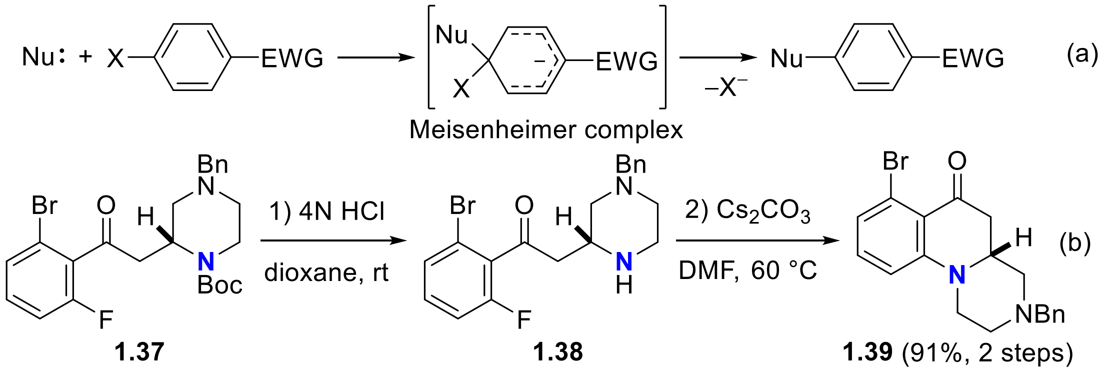
Scheme 1.7. Cope-type hydroamination of hydrazides.

1.4. Synthesis of benzannulated saturated azaheterocycles under transition-metal free reaction conditions

Transition metal-catalyzed C(sp^2)-N cross coupling has become the most practical protocol to construct benzannulated saturated azaheterocycles.[11] However, aforementioned rigid guideline for the residual contamination of transition metals in pharmaceuticals as well as consideration of environmental sustainability encouraged the development of transition metal-free N-aryl bond forming cyclization. In this context, nucleophilic aromatic substitution reaction under transition metal-free system has been a prevalent approach in medicinal chemistry.[33] Besides, electrophilic amination of carbanions has also been investigated as an alternative approach.[34] This section exemplifies the synthetic approaches to benzannulated saturated azaheterocycles under transition metal-free conditions by categorizing them into the following three reaction modes, that is, 1) nucleophilic aromatic substitution reaction via addition-elimination, 2) nucleophilic aromatic substitution reaction via elimination-addition, and 3) electrophilic amination.

1.4.1. Nucleophilic aromatic substitution reaction via addition-elimination

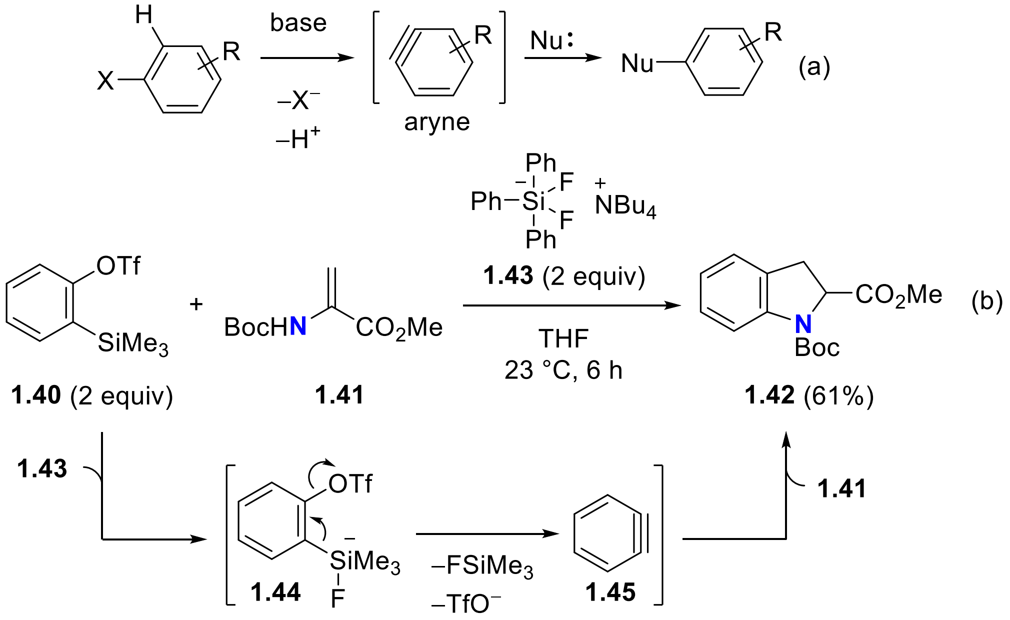
Nucleophilic aromatic substitution reaction via addition-elimination mechanism involves a two-step sequence of 1) addition of a nucleophile to the π^* orbital of the sp^2-hybridized carbon having a leaving group to generate a tetrahedral Meisenheimer complex, and 2) elimination of the leaving group (Scheme 1.8a).[35] Haloarenes are typical substrates in addition-elimination reaction and the order on the leaving group ability of halogen atoms is F > Cl > Br > I. Since the formation of the Meisemheimer complex is generally rate-determining step, the ease of carbon-halogen bond cleavage does not have an influence on the reaction efficiency. Therefore, the order of reactivity is largely attributed to the polar effect of the halogen atom in which the more electronegative halogen atom enhances the overall reaction rate.[36] A limitation of S_NAr reaction is the requirement for electron-withdrawing groups such as nitro, cyano, and acyl groups onto the starting haloarene to stabilize the substituted cyclohexadienyl anion. For example, basic treatment of amine **1.38** bearing an acyl group at the *ortho*-position, prepared by deprotection of *N*-Boc group of **1.37**, underwent amino-cyclization via C-F bond cleavage to deliver tricycle **1.39** in 91% yield (Scheme 1.8b).[37]



Scheme 1.8. Nucleophilic aromatic substitution via addition-elimination mechanism.

1.4.2. Nucleophilic aromatic substitution reaction via elimination-addition

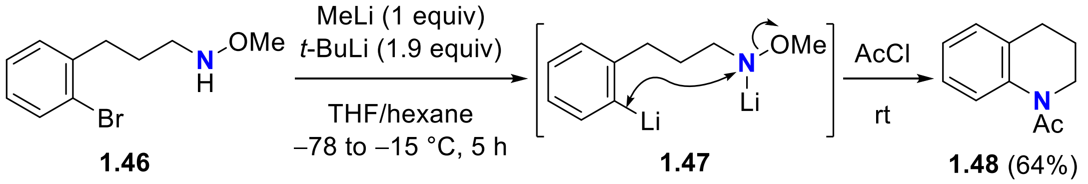
Elimination-addition pathway proceeds through nucleophilic attack of nitrogen-nucleophiles to the strained aryne intermediates generated *in situ* (Scheme 1.9a).[38] Classical generation protocols of aryne species required harsh reaction conditions such as treatment of aryl halides with strong bases as well as thermolysis of hazardous diazonium salts.[38] In 1983, Kobayashi and co-workers invented the mild generation method of arynes by the treatment of *ortho*-silylaryl triflates with fluoride sources.[39] Due to the bench-stability of silylaryl triflates and the good functional group tolerance of the reaction conditions, silyltriflate precursors have been frequently utilized in aryne chemistry. In this context, Stoltz and co-workers demonstrated formal [3+2]-annulation of benzyne **1.45** with enamide **1.41** using TBAT **1.43** as the fluoride source for the synthesis of indoline **1.42** (Scheme 1.9b).[40] The reaction mechanism involved nucleophilic addition of a fluoride anion to the silyl group on **1.40** followed by β-elimination of triflate **1.44** to generate benzyne **1.45**, which was trapped by enamide **1.41**.



Scheme 1.9. Nucleophilic aromatic substitution via elimination-addition mechanism.

1.4.3. Electrophilic amination

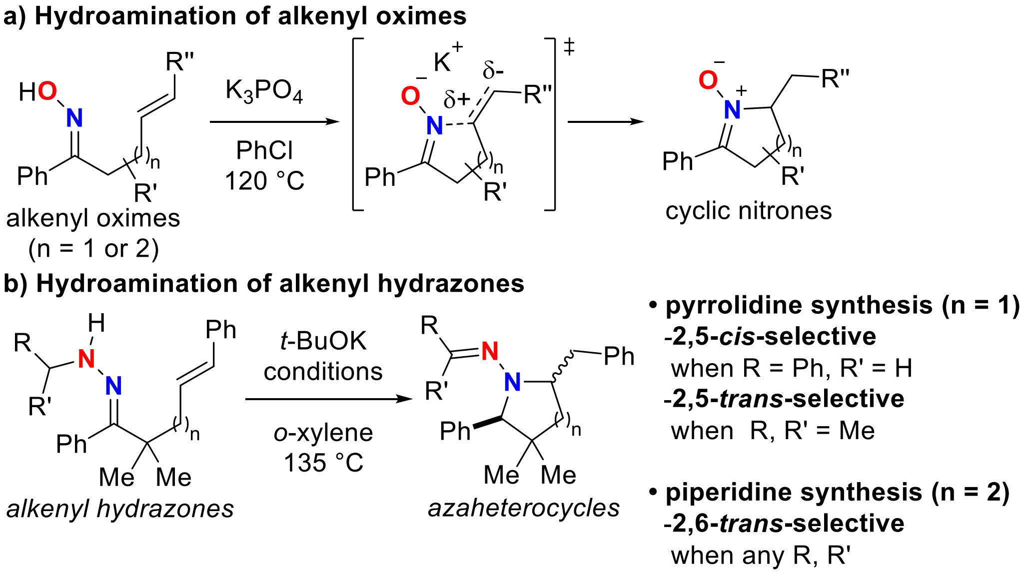
Intramolecular electrophilic amination of hydroxylamine derivatives was applied for the synthesis of benzannulated saturated azaheterocycles. Beak and co-workers reported alkyl lithium-mediated electrophilic amino-cyclization (Scheme 1.10).[41] Their protocol relied on double lithiation of aryl bromide **1.46** using combination of MeLi and *t*-BuLi followed by intramolecular displacement of the alkoxy group by organolithium **1.47** to form tetrahydroquinoline **1.48** after *N*-acetylation.



Scheme 1.10. Electrophilic aminative synthesis of tetrahydroquinoline.

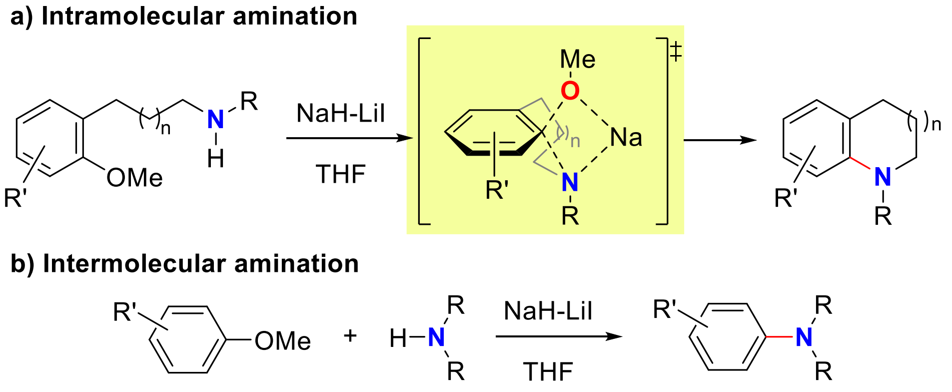
1.5. Perspective for the Chapter 2 and 3

The first part of this chapter demonstrated examples of diastereoselective alkene hydroamination for the synthesis of saturated azaheterocycles under transition metal-free conditions. However, diastereo-divergent approaches to saturated azaheterocycles using hydroamination of alkenes are still underexplored. In this context, Chapter 2 states diastereo-divergent synthesis of saturated azaheterocycles by hydroamination of alkenyl hydrazones using *t*-BuOK. The author's group has recently demonstrated that potassium base-mediated hydroamination of alkenyl oximes for the synthesis of cyclic nitrones (Scheme 1.11a).[42] Structural analogy of oximes with hydrazones encouraged us to investigate the reactivity of alkenyl hydrazones in the presence of a potassium base. In this transformation, notable diastereodivergence in the formation of 2,5-disubstituted pyrrolidines was enabled by changing the substituents on the hydrazones, whereas a unique 2,6-*trans* selective cyclization took place in piperidine formation, which was rationalized by experiments and DFT computation (Scheme 1.11b).[43]



Scheme 1.11. *t*-BuOK-mediated hydroamination of alkenyl hydrazones.

In the latter part of this chapter, transition metal-free syntheses of benzanulated saturated azaheterocycles via C(sp^2)-N bond formation were introduced. However, several drawbacks such as the requirement of installing activating groups onto arenes as well as the restricted ring sizes of the products should be circumvented by developing new protocols. In this respect, Chapter 3 presents NaH-mediated nucleophilic amination of methoxy arenes for the preparation of benzannulated saturated azaheterocycles. The author's group has recently found the hydride donor ability of NaH in the presence of NaI or LiI in THF solvent. The resulting NaH/iodide composites could be utilized for various hydride reductions such as hydrodecyanation of carbonitriles.[44] In Chapter 3, the author utilized the NaH/iodide composites as an enhanced Brønsted base to promote the intramolecular nucleophilic displacement of methoxy arenes by pendant amine nucleophiles (Scheme 1.12a). An intermolecular variant of this method was also explored to offer various aromatic amines (Scheme 1.12b). Mechanistic investigation revealed that the reaction involved unprecedented concerted nucleophilic aromatic substitution via four-membered chelation transition state.[45]



Scheme 1.12. Nucleophilic amination of methoxy arenes by means of NaH/iodide composite.

1.6. References

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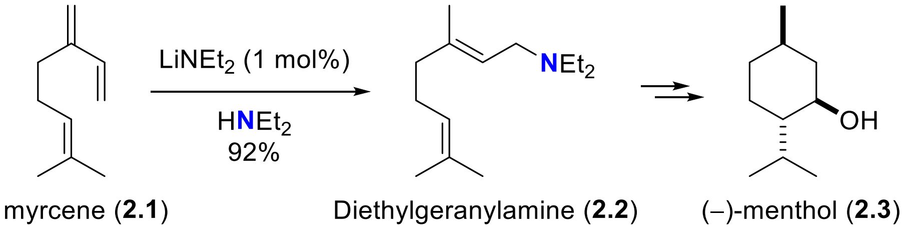
Chapter 2: Diastereo-divergent synthesis of saturated azaheterocycles enabled by *t*-BuOK-mediated hydroamination of alkenyl hydrazones

2.1. Introduction

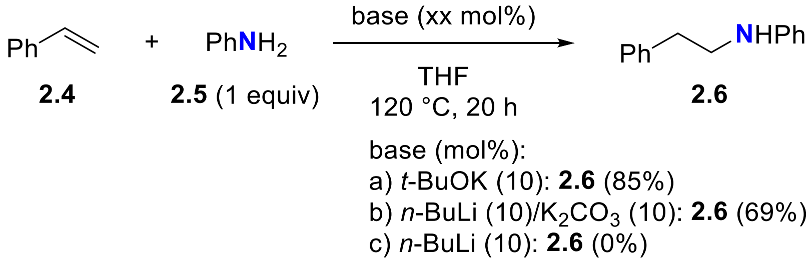
Hydroamination reactions promoted by inexpensive alkali metals have received considerable interests over the half century since the first alkali metal-catalyzed amination of ethylene with ammonia under the harsh conditions (175−200 °C and 800−1000 bar) was reported by Howk and co-workers in 1954.[1] Commonly employed alkali metals in alkene hydroamination are alkyl lithium reagents, lithium and sodium amides, as well as NaH, which serve as strong Brønsted bases to deprotonate the starting amines for the generation of nucleophilic metal amides.[2,3] Alkali-metal catalyzed hydroamination has been applied to the key steps for the industrial production of cyclic and acyclic monoterpenes.[4,5] For instance, the Takasago process for the industrial synthesis of (−)-menthol **2.3** includes the amination of myrcene **2.1** with diethyl amine in the presence of a catalytic amount of lithium diethylamide to produce *N*,*N*-diethylgeranylamine **2.2** as the key intermediate (Scheme 2.1).[4]



Scheme 2.1. Hydroamination as a key step in the Takasago process for (−)-menthol.

In contrast, there is an only report on the use of bench-stable *t*-BuOK for alkene hydroamination due to the lower basicity of *t*-BuOK than common alkali metal bases such as alkyl lithium reagents. In 1998, Beller and co-workers demonstrated the *t*-BuOK-induced intermolecular hydroamination of styrene **2.4** with aniline **2.5** at elevated temperature to provide pharmaceutically important 2-(arylethyl)amine **2.6** in

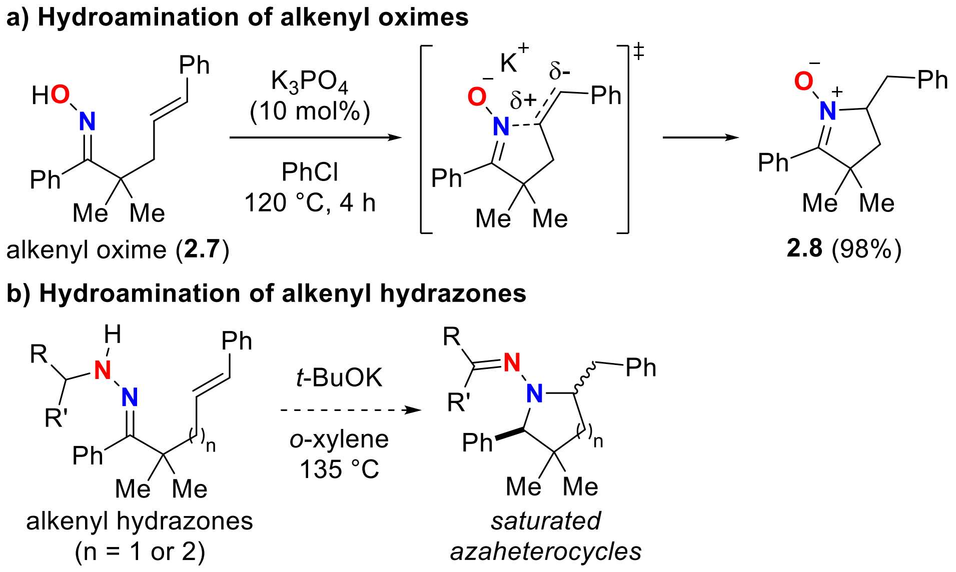
85% yield (Scheme 2.2).[6] Screening of bases for the same transformation revealed that the combination of K_2CO_3 and *n*-BuLi also promoted the desired hydroamination whereas the use of *n*-BuLi as a sole base resulted in no reaction. These results indicated that generation of potassium anilides is the key in this hydroamination due to their more ionic and nucleophilic character than lithium anilides. In the case of K_2CO_3/*n*-BuLi co-catalytic system, the mixed lithium-potassium anilide species was presumably formed during the reaction.[7]



Scheme 2.2. Hydroamination of styrene with aniline using *t*-BuOK by Beller *et al.*

2.2. Working hypothesis

Our research group recently disclosed the potassium base-mediated/catalyzed hydroamination of alkenyl oximes for the synthesis of cyclic nitrones (Scheme 2.3a).[8] The amino-cyclization of oxime **2.7** was induced by the ionic interaction between the potassium cation on the oxime oxygen atom and the negatively charged styrenyl unit in the transition state to afford nitrone **2.8**. Encouraged by this finding and the structural analogy between oximes and hydrazones, we commenced to investigate the *t*-BuOK-mediated hydroamination of alkenyl hydrazones to deliver various saturated azaheterocycles (Scheme 2.3b).

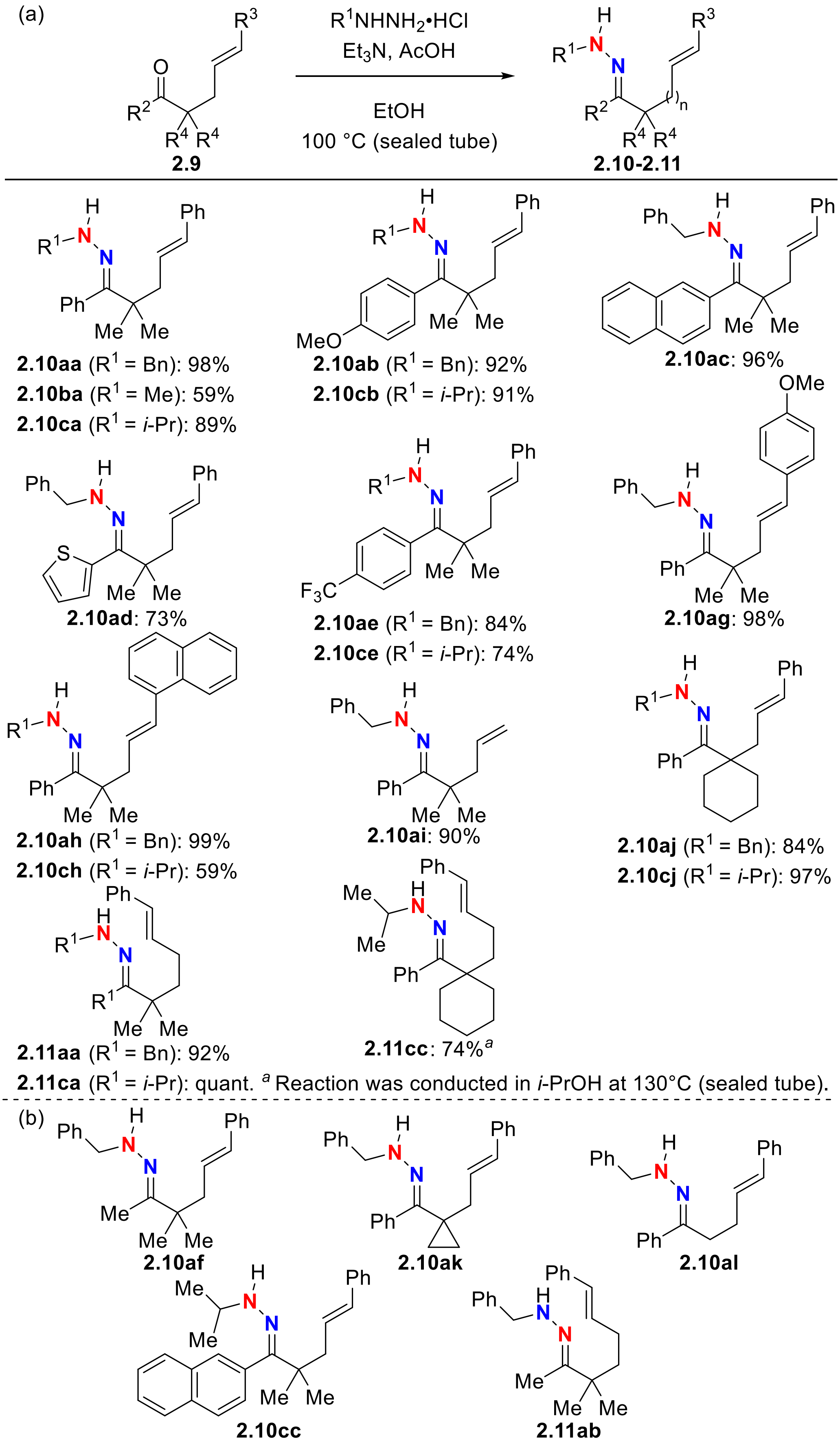


Scheme 2.3. Inorganic base-mediated hydroamination with alkenyl oximes and hydrazones.

2.3. Results and discussion

2.3.1. Preparation of alkenyl hydrazones

Alkenyl hydrazones were prepared by the condensation of corresponding ketones and hydrazines in the presence of Et_3N and AcOH in EtOH at 100 °C under sealed conditions as shown in Scheme 2.4a. As hydrazones **2.10af**, **2.10ak**, **2.10al**, **2.10cc**, and **2.11ab** were not stable enough to be characterized, these hydrazones were used immediately for next hydroamination without purification (Scheme 2.4b).



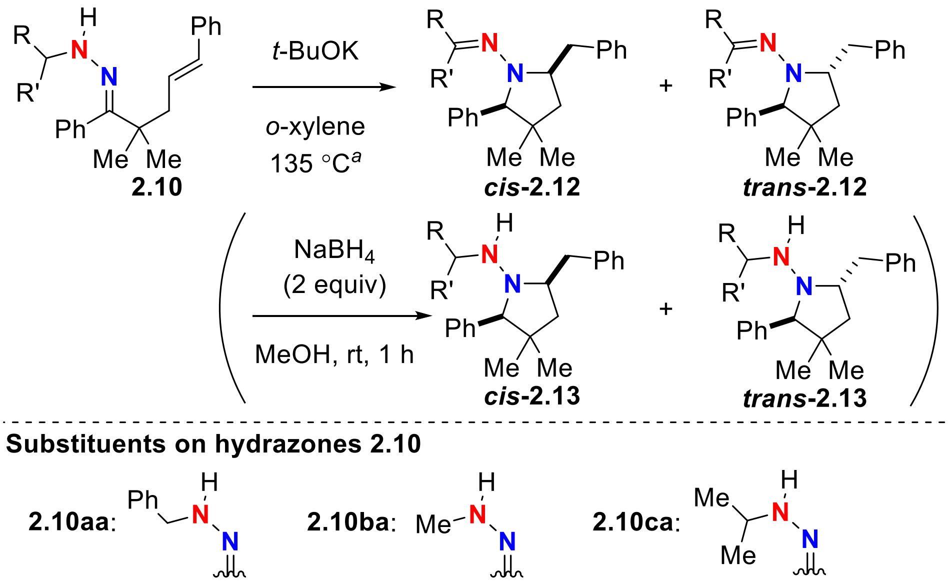
[a] Reaction was conducted in *i*-PrOH at 130°C (sealed tube).

Scheme 2.4. Synthesis of alkenyl hydrazones.

2.3.2. Optimization of reaction conditions

The author investigated the feasibility for amino-cyclization of γ,δ-alkenyl hydrazones **2.10aa-2.10ca** bearing various substituents on the terminal nitrogen of the hydrazones in the presence of inorganic bases (Table 2.1). Interestingly, the reaction of *N*-benzyl hydrazone **2.10aa** with *t*-BuOK in *o*-xylene at 135 °C provided *N*-imino pyrrolidine **2.12aa** in 94% yield with good 2,5-*cis* selectivity (*cis*/*trans* = 4.5:1) (entry 1). The use of tertiary alcohol, Et_3COH as a proton source for the reaction of **2.10aa** enhanced the yield of **2.12aa** albeit the 2,5-*cis* selectivity was diminished (*cis*/*trans* = 3.2:1) (entry 2). For further investigation on the substrate scope of *N*-benzyl hydrazone **2.10a** (*vide infra*), the reaction conditions using *t*-BuOK alone (entry 1) was selected to achieve higher 2,5-*cis*-selectivity. On the other hand, the use of other bases such as *t*-BuONa, Cs_2CO_3, or K_3PO_4 instead of *t*-BuOK for the reaction of **2.10aa** resulted in no reaction at all. In addition, the reaction of **2.10aa** with a stronger base, NaH in place of *t*-BuOK resulted in the formation of the desired **2.12aa** in only 10% yield along with a mixture of unidentified products. When *N*-methyl hydrazone **2.10ba** was subjected to the same condition, cyclization product **2.12ba** was obtained in lower yield (66%) and diastereoselectivity (*cis*:*trans* = 2.1:1) (entry 3). In contrast, the employment of *N*-isopropyl hydrazone **2.10ca** resulted in the opposite diastereoselectivity to afford *trans*-**2.12ca** as a major isomer (entry 4). As *N*-dimethylvinylidene pyrrolidine **2.12ca** was unstable under an aerobic atmosphere, the crude material of **2.12ca** was treated with $NaBH_4$ to afford more stable 2,5-*trans* *N*-amino pyrrolidine **2.13ca** (*cis*:*trans* = 1:3.7). Notably, the addition of the tertiary alcohol, Et_3COH, as a proton source for the reaction of **2.10ca** improved the *trans*-selectivity (*cis*:*trans* = 1:9.7) albeit with insufficient conversion of the starting hydrazone **2.10ca** (entry 5). Further optimization identified that the addition of 2 equivalents of *t*-BuOK in the presence of Et_3COH enabled the full conversion of **2.10ca** to furnish *N*-isopropyl amino pyrrolidine **2.13ca** in 92% yield with excellent 2,5-*trans*-selectivity (*cis*/*trans* =1:10.9) (entry 6). Reactions with *t*-BuOH as the proton source were found to be not reproducible in terms of the yields and diastereoselectivities, probably due to its lower boiling point (82 °C in 760 torr) than the reaction temperature (135 °C). The tertiary alcohol with a higher boiling point, Et_3COH (141 °C in 760 torr), was thus employed.

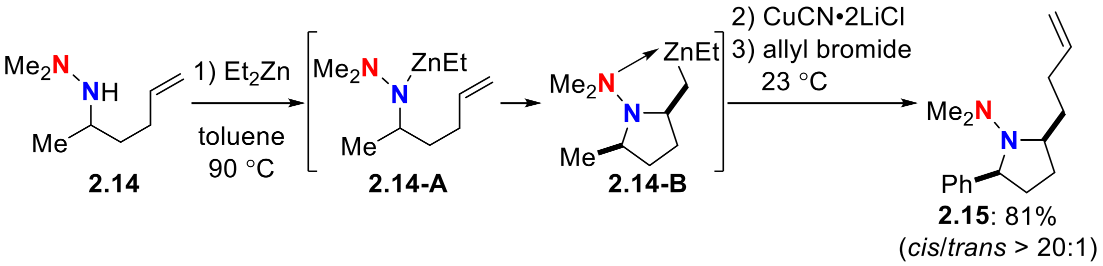
Table 2.1. Optimization of the reaction conditions.



entry	2.10	*t*-BuOK (equiv)	Additive (equiv)	Time (h)	yield of **2.12** or **2.13** (%)	*cis*:*trans*
1	**2.10aa**	1	-	2	**2.12aa**: 94[b]	4.5:1
2	**2.10aa**	1	Et_3COH (3)	2	**2.12aa**: 98[b]	3.3:1
3	**2.10ba**	1	-	4	**2.12ba**: 66[b]	2.1:1
4	**2.10ca**	1	-	24	**2.13ca**: 74[c]	1:3.7
5	**2.10ca**	1	Et_3COH (3)	24	**2.13ca**: 32[c] (45)[d]	1:9.7
6	**2.10ca**	2	Et_3COH (3)	24	**2.13ca**: 92[c]	1:10.9

[a] The reactions were conducted using 0.5 mmol of **2.10** in *o*-xylene (5 mL; 0.1 M). [b] Isolated yields of **2.12** as a *cis*:*trans* mixture were stated. Diastereoselectivities (*cis*:*trans*) were determined by ^{1}H-NMR analysis of the isolated mixture of **2.12**. [c] Combined isolated yields of 2,5-*cis* and 2,5-*trans*-**2.13ca** were stated. Diastereoselectivities (*cis*:*trans*) were determined by combined isolated yields. [d] Recovery yield of **2.10ca**.

The relevant work has been reported by the group of Livinghouse (Scheme 2.5) who demonstrated the zinc-mediated diastereoselective hydrohydrazination of *N*,*N*-dimethylhydrazinoalkene **2.14** to provide 2,5-*cis*-pyrrolidine **2.15** through the direct metalation of **2.14** with diethylzinc followed by the amino-cyclization of **2.14-A**, and allylation of **2.14-B** using CuCN·2LiCl and allyl bromide.[9] However, distereo-divergent synthesis of pyrrolidines using this protocol has not been achieved.

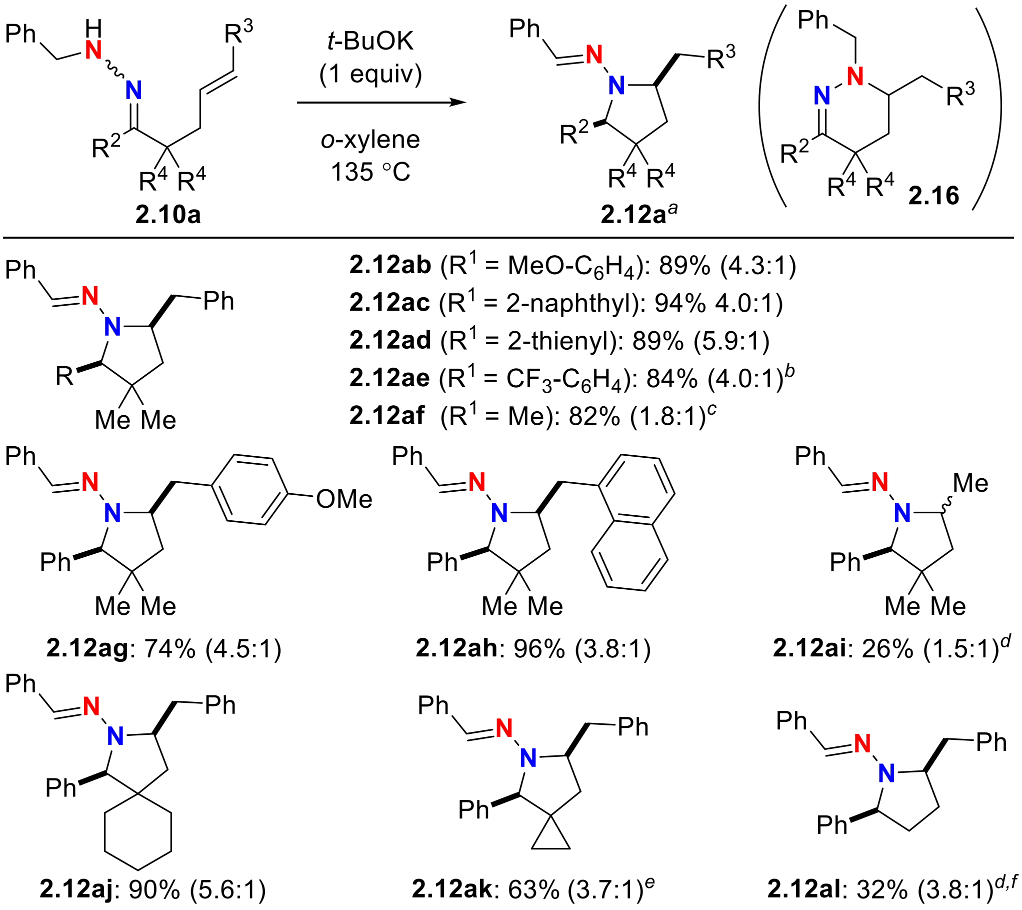


Scheme 2.5. Diastereoselective hydrohydrazination of *N*,*N*-dimethylhydrazinoalkene.

2.3.3. Scope and limitations

After the optimization of diastereo-divergent hydroamination, we surveyed the generality of the 2,5-*cis*-selective cyclizations of *N*-benzyl hydrazones **2.10a** (Scheme 2.6). For substituents R^2, various substrates having an electron-donating 4-methoxyphenyl (**2.10ab**), 2-naphthyl (**2.10ac**), or 2-thienyl (**2.10ad**) group could be transformed to the corresponding *N*-imino pyrrolidines **2.12ab-2.12ad** in good yields with 2,5-*cis*-selectivity. On the other hand, the reaction of hydrazone **2.12ae** having an electron-withdrawing trifluoromethylphenyl group provided the desired product **2.12ae** in 84% yield along with the generation of tetrahydropyridazine **2.16ae** in 8% yield through the competing 6-*exo* cyclization of N1 atom of the hydrazone moiety of **2.10ae**. An alkyl substituent (**2.10af**) was also tolerated under the optimized reaction conditions, although the moderate 2,5-*cis*-selectivity was observed (*cis*:*trans* = 1.8:1). As for the substituent compatibility of R^3 on the alkenyl moiety, a 4-methoxyphenyl

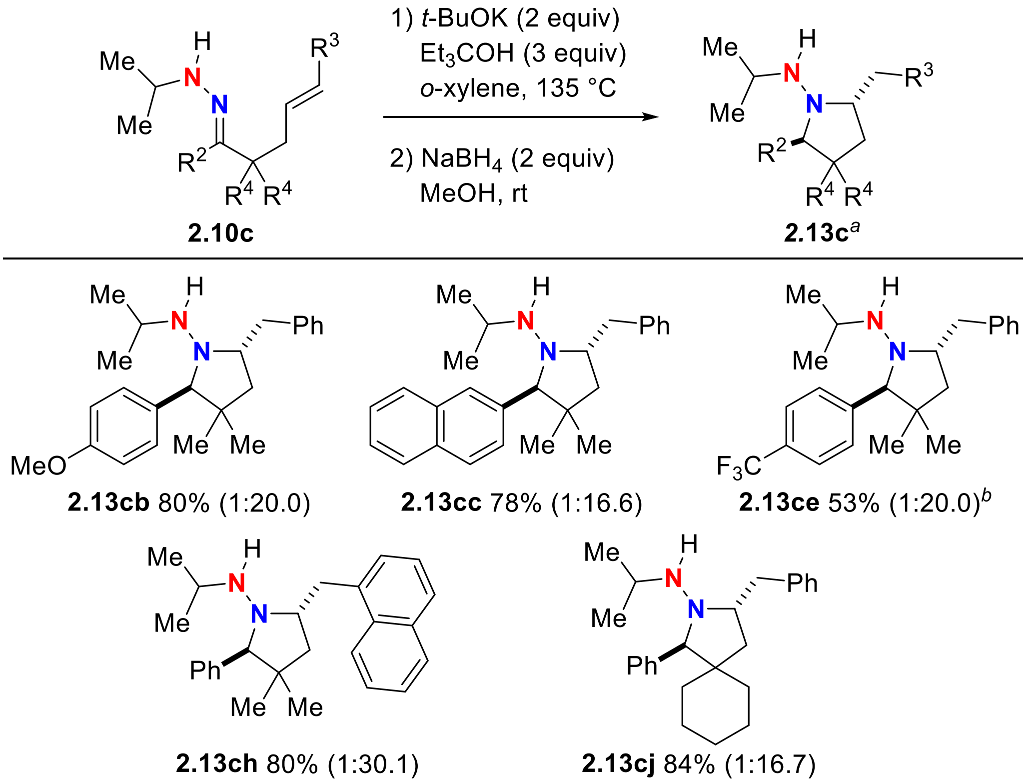
(**2.10ag**) as well as a sterically hindered 1-naphthyl (**2.10ah**) group could be installed while amino-cyclization toward the terminal alkene (for **2.10ai**) resulted in poor yield and diastereoselectivity. This protocol was capable of constructing spirocyclic pyrrolidines **2.12aj** and **2.12ak** with good 2,5-*cis*-selectivity whereas the reaction of substrate **2.10ak** having a cyclopropyl moiety generated six-membered tetrahydropyridazine **2.16ak** in 20% yield as a side product. Similarly, the hydroamination of α-nonsubstituted hydrazone **2.10al** formed pyrrolidine **2.12al** and tetrahydropyridazine **2.16al** in 32% and 25% yields, respectively.



[a] The reactions were conducted using 0.5 mmol of **2.10a** in *o*-xylene (0.1 M). Isolated yields of **2.12a** as a *cis*:*trans*-mixture were stated. Diastreoselectivities (*cis*:*trans*) were determined by ^{1}H-NMR analysis of the isolated mixture of **2.12a** and shown in parentheses. [b] **2.16ae** was obtained in 8% yield. [c] 3 equiv of *t*-BuOK was used. [d] 2 equiv of *t*-BuOK and 3 equiv of Et_3COH was used. [e] **2.16ak** was obtained in 20% yield. [f] **2.16al** was obtained in 25% yield.

Scheme 2.6. Substrate scope on the reactions of *N*-benzyl hydrazones **2.10a**.

We next turned our attention to the substrate scope of *N*-isopropyl hydrazones **2.10c** for the 2,5-*trans*-selective hydroamination (Scheme 2.7). The reactions under the optimized reaction conditions provided the desired pyrrolidines **2.13c** with excellent 2,5-*trans*-selectivity up to 1:30.1 *cis*/*trans* ratio in comparable yields.



2.10c

2.13c[a]

2.13cb 80% (1:20.0)

2.13cc 78% (1:16.6)

2.13ce 53% (1:20.0)[b]

2.13ch 80% (1:30.1)

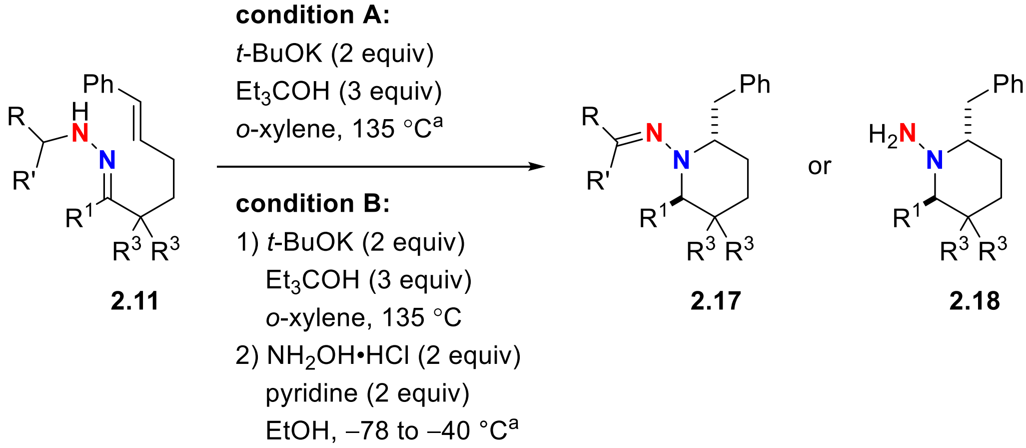
2.13cj 84% (1:16.7)

[a] The reactions were conducted using 0.5 mmol of **2.10c** in *o*-xylene (0.1 M). Isolated yields of *trans*-**2.13c** were stated. Diastereoselectivities (*cis*:*trans*) were determined by ^{1}H-NMR analysis of the crude mixture and shown in parentheses. [b] Tetrahydropyridazine **2.16ce** was obtained in 8% yield.

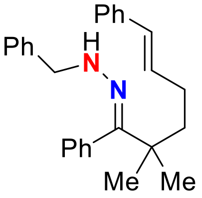
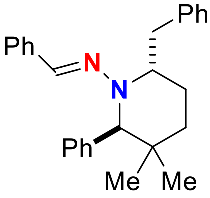
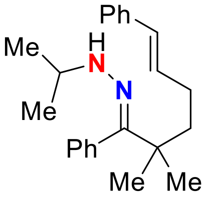
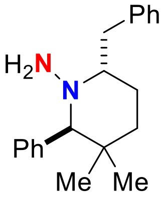
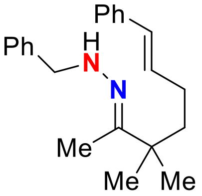
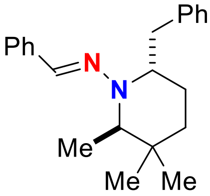
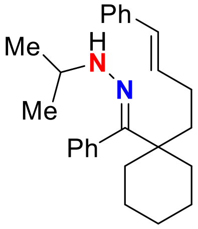
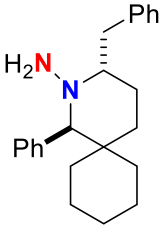
Scheme 2.7. Substrate scope on the reactions of *N*-isopropyl hydrazones **2.10c**.

The present protocol was also applicable to the stereoselective construction of 2,6-*trans*-disubstituted piperidines **2.17** and **2.18** regardless of the substituents on the nitrogen atom of the hydrazones (Table 2.2). It was noted that the addition of Et$_3$COH was essential to promote the cyclization of both *N*-benzyl and isopropyl δ,ε-alkenyl hydrazones **2.11aa-2.11ca** (entry 1-2). Interestingly, the reaction of *N*-isopropyl hydrazone **2.11ca** resulted in the exclusive formation of 2,6-*trans*-isomer **2.17ca** of which the *N*-dimethylvinylidene moiety was sequentially converted to hydrazine **2.18a** via the transimination with NH_2OH•HCl (entry 2).[10] By replacing the phenyl group with methyl substituent (**2.11ab**), 2,6-dialkyl substituted piperidine **2.17ab** was obtained with good *trans*-selectivity (*cis*:*trans* = 1:5.4) (entry 3). Furthermore, the reaction of **2.11cc** enabled the formation of 2,6-*trans*-spirocyclic hydrazine **2.18c** as a single isomer, while harsh reaction conditions (5 equivalents of *t*-BuOK at 170 °C) were required to promote the cyclization (entry 4). To the best of our knowledge, the stereoselective hydroamination for the synthesis of 2,6-*trans*-disubstituted piperidines is limited to the organoacitinide-catalyzed cyclization of 1,3-disubstituted primary aminoallene **2.19** to **2.20** albeit in moderate 2,6-*trans*-selectivity (Scheme 2.8).[11]

Table 2.2. Stereoselective synthesis of 2,6-*trans*-disubstituted piperidines.

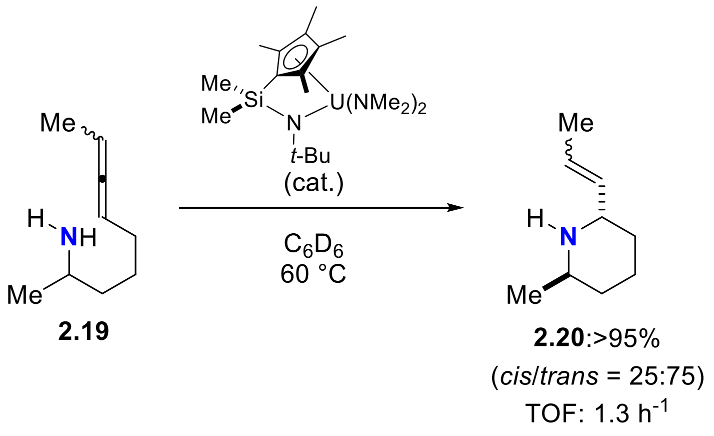


2.11 **2.17** **2.18**

entry	hydrazones		conditions	piperidines	
1		**2.11aa**	**A**		**2.17aa**: 58% (1:3.9)[b]
2		**2.11ca**	**B**		**2.18a**: 70% (pure *trans*)[c]
3		**2.11ab**	**A**		**2.17ab**: 72% (1:5.4)[d]
4		**2.11cc**	**B**		**2.18c**:45% (pure *trans*)[e]

[a] The reactions were conducted using 0.5 mmol of **2.11** in *o*-xylene (0.1 M). [b] Combined isolated yield of 2,6-*cis* and 2,6-*trans*-product **2.17aa** was stated. Diastereoselectivity (*cis*:*trans*) was shown in parentheses. [c] The reaction gave an only 2,6-*trans* isomer. [d] Isolated yield of **2.17ab** as a *cis*:*trans* mixture was stated. Diastereoselectivity (*cis*:*trans*) was determined by ^{1}H-NMR analysis of the isolated mixture of **2.17ab** and shown in parentheses. [e] The reaction was conducted using **2.11cc** (0.24 mmol) in the presence of 5 equiv of *t*-BuOK and 3 equiv of Et_3COH at 170 °C (sealed tube).

2,6-*trans*-selective cyclization of primary aminoallenes by Marks *et al* (ref 11)

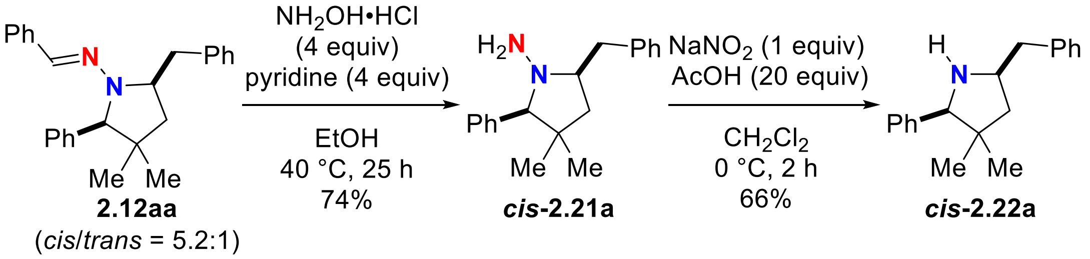


Scheme 2.8. Organoactinide-catalyzed 2,6-*trans*-selective cyclization of primary aminoallenes by Marks *et al.*

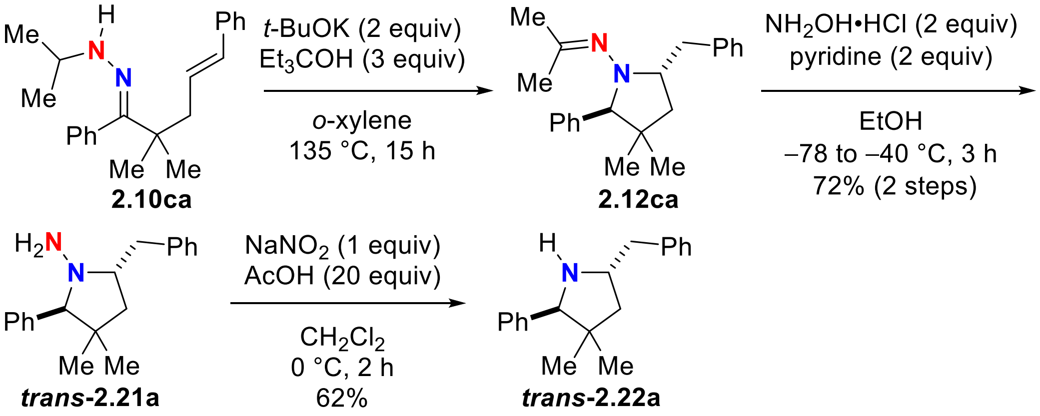
2.3.4. Synthesis of NH pyrrolidines and the piperidine

The synthetic utility of the present hydroamination was demonstrated by the derivatization of the cyclized products toward the diastreo-enriched saturated azaheterocycles (Scheme 2.9). For the preparation of 2,5-*cis*-pyrrolidine **2.22a**, diastereomeric mixture of **2.12aa** was treated under the transimination reaction conditions using $NH_2OH•HCl$ at 40 °C to provide hydrazine product *cis*-**2.21a** as a pure single isomer, because the *cis* and *trans* isomers of the hydrazine product **2.21a** were separable. However, the *trans*-**2.21a** was not isolated due to the its instability during the transimination step using $NH_2OH•HCl$ under thermal conditions (40 °C). The *cis*-**2.21a** was further converted to *cis*-**2.22a** through N-N bond cleavage of hydrazine with $NaNO_2$ in the presence of AcOH (Scheme 2.9a).[12] The synthesis of *trans*-**2.22a** was enabled by a three-step sequence of 1) hydroamination of **2.10ca** under the optimal reaction conditions, 2) the transimination of **2.12ca** with $NH_2OH•HCl$ at lower temperature (−78 to −40 °C), and 3) N-N bond cleavage of *trans*-**2.21a** under the treatment with $NaNO_2$/AcOH (Scheme 2.9b). Similarly, the six-membered cyclic hydrazine **2.18a** was also transformed to the pure 2,6-*trans*-piperidine **2.23a** using the same N-N bond cleavage protocol (Scheme 2.9c). Mechanistically, the N-N bond cleavage of hydrazines by a combination of $NaNO_2$ and AcOH involved the oxidation of hydrazines **A** with $NaNO_2$ under acidic condition (Scheme 2.9d). The resulting nitroso compounds **B** were converted to triazenes **C** via proton transfer followed by elimination of nitrous oxide for the production of desired amines **D**.

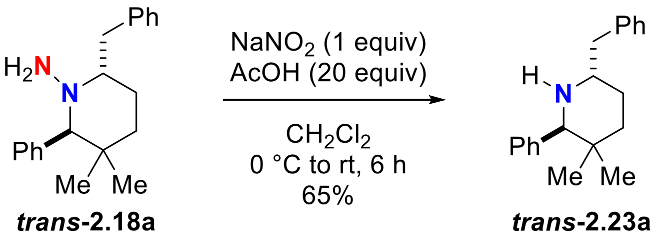
(a) Synthesis of *cis*-**2.22a**



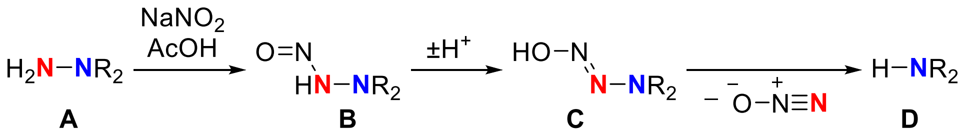
(b) Synthesis of *trans*-**2.22a**



(c) Synthesis of *trans*-**2.23a**



(d) Mechanism on N-N bond cleavage of hydrazines

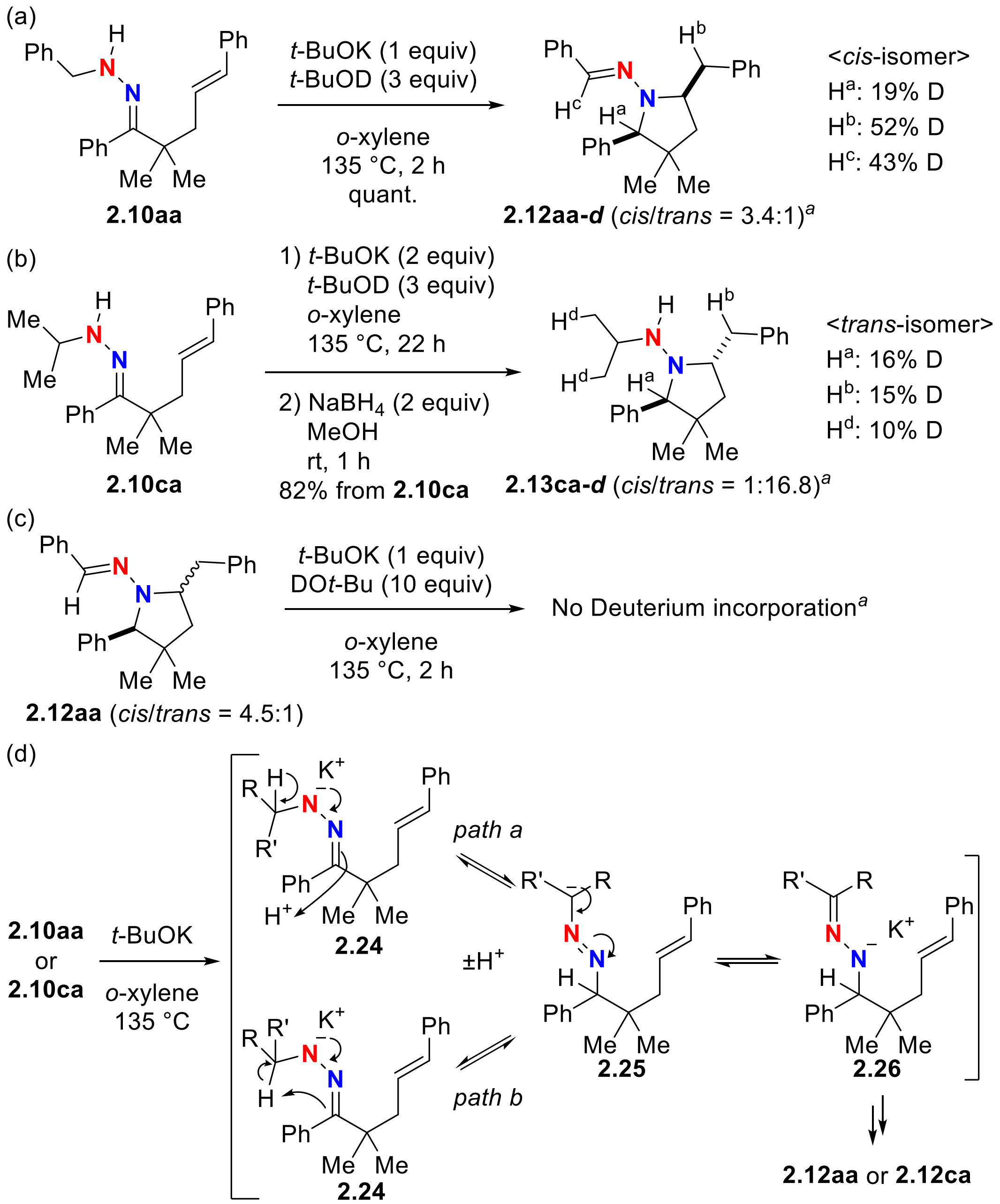


Scheme 2.9. Transformation to *N*-H pyrrolidines and piperidine.

2.4. Mechanistic insights

2.4.1. Deuterium labelling experiments

To gain mechanistic insight, deuterium labelling experiments for the reactions of **2.10aa**, **2.10ca**, and **2.12aa** were performed (Scheme 2.10). The reactions of **2.10aa** and **2.10ca** under the optimal reaction conditions in the presence of *t*-BuOD resulted in the moderate deuterium incorporations at H^a [*cis*-**2.12aa-*d*** (19%) and *trans*-**2.13ca-*d*** (16%)] and H^b [*cis*-**2.12aa-*d*** (52%) and *trans*-**2.13ca-*d*** (15%)] (Scheme 2.10a-b). In addition, the deuterium incorporations at hydrazone moiety [*cis*-**2.12aa-*d*** (H^c) and *trans*-**2.13ca-*d*** (H^d)] were also observed in 43% (for H^c) and 10% (for H^d), respectively. On the other hand, the treatment of *N*-imino pyrrolidine **2.12aa** in the presence of 10 equiv of *t*-BuOD resulted in no deuterium incorporation (Scheme 2.10c). These results suggested that this hydroamination involved the hydrazone-hydrazone isomerization to the *exo*-hydrazone **2.26** via intermolecular protonolysis of the potassium amide **2.24** followed by the isomerization of the azo intermediate **2.25** (path a) or intramolecular proton transfer of **2.24** to **2.25** through the 5-membered ring transition state (path b), analogous to the 1,3-proton shift of imines (Scheme 2.10d).[13] The deuterium incorporation at H^a and H^c supported the equilibrium between the potassium amide **2.24** and the *exo*-hydrazone **2.26**. On the other hand, the deuterium incorporation into H^d would be rationalized by the deprotonation of the α-position of either the hydrazone **2.26** or **2.12ca**. Furthermore, no deuterium incorporation from the reaction of the cyclized **2.12aa** in the presence of *t*-BuOD suggested that retro-cyclization of **2.12aa** does not proceed under the optimal conditions using *t*-BuOK. Besides, the employment of external proton source (tertiary alcohol, Et_3COH) might assist the hydrazone-hydrazone isomerization for the enhancement of reaction efficiency.



[a] The reactions were conducted using 0.5 mmol of hydrazones in *o*-xylene (0.1 M).

Scheme 2.10. Deuterium labelling experiments in the reaction of **2.10aa**, **2.10ca**, and **2.12aa**.

2.4.2. DFT calculations

2.4.2.1. 2,5-*cis*-selective hydroamination of γ,δ-alkenyl *N*-benzyl hydrazones

To rationalize the role of hydrazone substituents for the divergent diastereoinduction in the synthesis of 2,5-disubtituted pyrrolidines, DFT calculations were conducted using Gaussian 09 at the B3LYP-D3BJ(SCRF)/6-311+G(d,p)//B3LYP-D3BJ(SCRF)/6-31G(d) level.[14-18] The DFT calculations identified that the hydroamination of γ,δ-alkenyl *N*-benzyl hydrazone **2.10aa** was initiated by the hydrazone-hydrazone isomerization from INT_0-**2.10aa** to INT_1-**2.10aa** (Figure 2.1) supported by the deuterium labeling experiments (Scheme 2.8). In contrast, a local energy minimum for the direct formation of five-membered cyclic azomethineimine **2.27aa** was not observed on the potential surface, which was distinguished mechanism from the previous hydroaminative approach to the cyclic nitrone **2.8** (Scheme 2.3).[8] Further DFT computation elucidated the small energy difference of transition state free energy (0.3 kcal/mol) between the 2,5-*cis*-pathway (11.0 kcal/mol) and the 2,5-*trans*-pathway (11.3 kcal/mol) from INT_1-**2.10aa**. The lower transition state free energy for the 2,5-*cis*-pathway (TS-**2.10aa**-*cis*) might be attributed to the cation-π interaction by the association of potassium cation and three benzene rings to stabilize the 2,5-*cis*-transition state.[19] The necessity of the cation-π interaction for 2,5-*cis*-selectivity was in agreement with the poor diastereoinduction in the case of substrates having less number of aromatic π-systems such as *N*-methyl hydrazone **2.10ba** (*cis*/*trans* = 2.1:1, Table 2.1, entry 2) and methyl ketone hydrazone **2.10af** (*cis*/*trans* = 1.8:1, Scheme 2.6). Furthermore, the optimization for the cyclization of **2.10aa** showed that the use of *t*-BuONa in place of *t*-BuOK resulted in no reaction, which suggested that the cation-π interaction between K^+ and an aromatic ring in the styrene moiety might promote desired amino-cyclization as the previous hydroamination of alkenyl oximes was induced by the ionic interaction between K^+ on the oxime oxygen atom and benzene ring in the styrene unit.[8] Since the binding energy of Na^+ to the aromatic ring is smaller than that of K^+ in the solution state,[20] the use of *t*-BuONa might not induce the desired amino-cyclization of **2.10aa**.

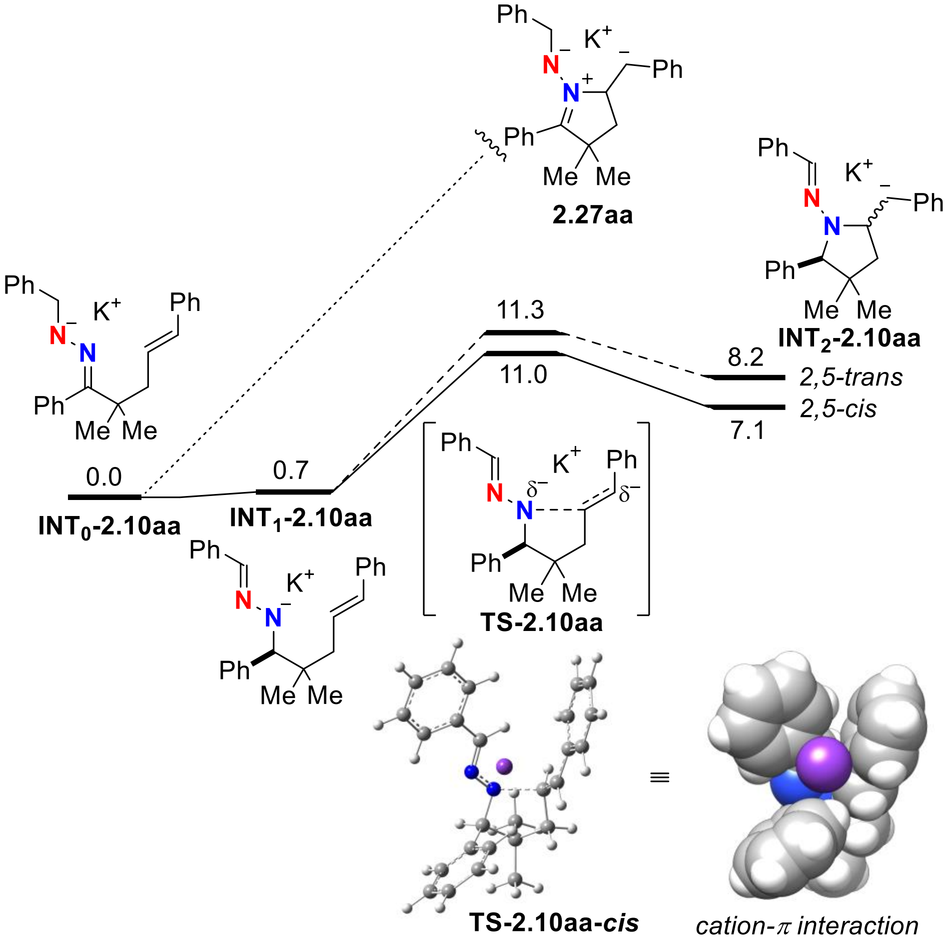


Figure 2.1. Energy diagram (in kcal/mol) for the reaction of *N*-benzyl hydrazone **2.10aa**.

2.4.2.2. 2,5-*trans*-selective hydroamination of γ,δ-alkenyl *N*-isopropyl hydrazones

DFT studies for the hydroamination of γ,δ-alkenyl *N*-isopropyl hydrazone **2.10ca** also revealed the initiation via hydrazone-hydrazone isomerization toward INT$_1$-**2.10ca** (Figure 2.2). In contrast to the 2,5-*cis* selectivity for *N*-benzyl substrate **2.10aa**

(Figure 2.1), the transition state free energy of TS-**2.10ca** for the 2,5-*trans*-pathway (12.1 kcal/mol) is 3.4 kcal/mol lower than that for 2,5-*cis*-pathway (15.5 kcal/mol). The energy difference would be originated from the steric repulsion between the *N*-dimethylvinylidene unit and the benzene ring of the styrene moiety in the 2,5-*cis*-transition state (TS-**2.10ca**-*cis*). Hence, the steric effect of *N*-isopropyl substituent enabled the opposite diastereoinduction toward the 2,5-*trans*-pathway.

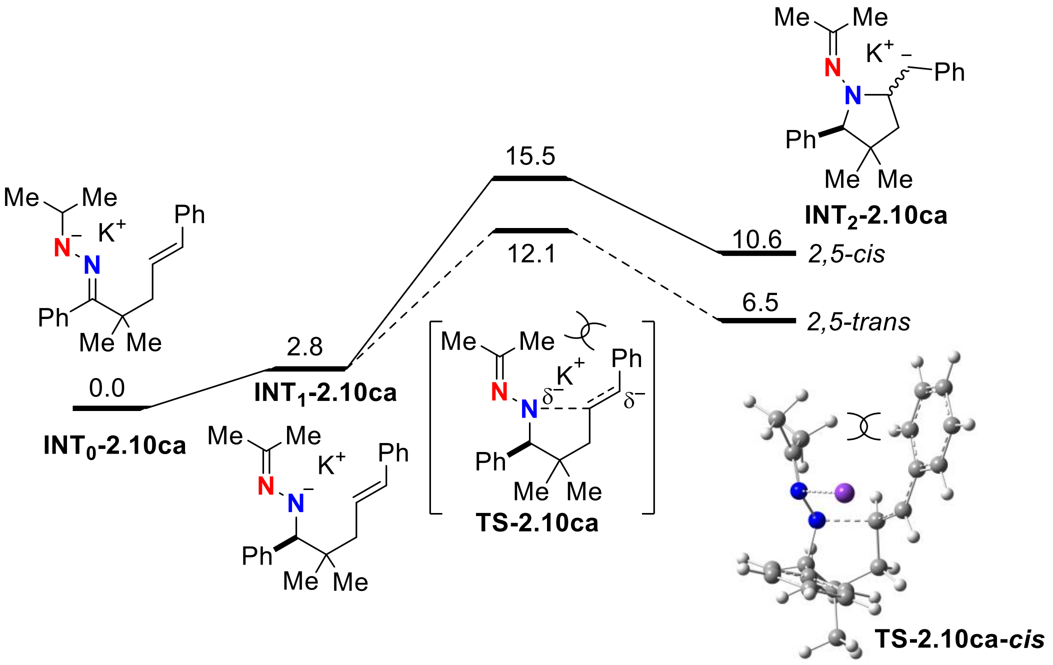
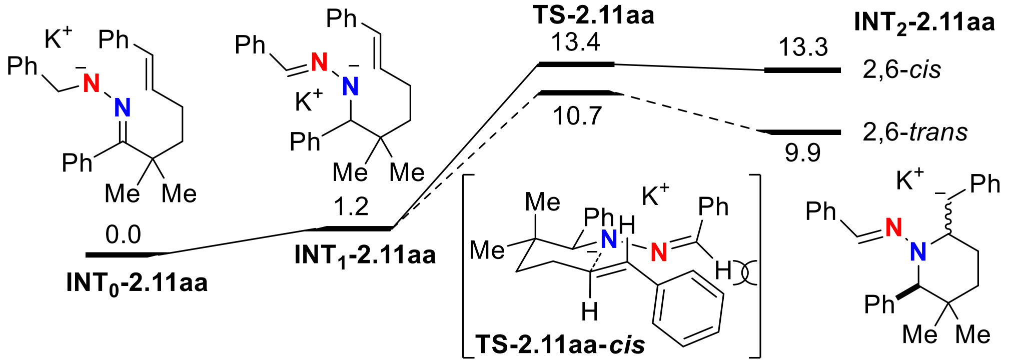


Figure 2.2. Energy diagram (in kcal/mol) for the reaction of *N*-isopropyl hydrazone **2.10ca**.

2.4.2.3. 2,6-*trans*-selective hydroamination of δ,ε-alkenyl hydrazones

Amino-cyclization of δ,ε-alkenyl hydrazones afforded 2,6-*trans*-disubstituted piperidines as the major product regardless of the hydrazone substituents (Table 2.2). DFT calculations for the reaction of **2.11** revealed that the transition state free energies for the 2,6-*trans*-pathway are lower than that for the 2,6-*cis*-pathway in both the reactions of *N*-benzyl **2.11aa** and *N*-isopropyl **2.11ca** of which the energy differences were 2.7 kcal/mol (for **2.11aa**) and 3.5 kcal/mol (for **2.11ca**), respectively (Figure 2.3). These 2,6-*trans* selectivity could be rationalized by the steric repulsion between the *N*-vinylidene unit and aromatic ring of styrene moiety in the *cis*-transition state. Moreover, cation-π interaction was also observed in 2,6-*trans*-transition state of *N*-benzyl **2.11a** to promote 2,6-*trans*-selectivity, while the steric effect was the dominant factor in this diastereoinduction.

(a) the reaction of *N*-benzyl hydrazone 2.11aa



(b) the reaction of *N*-isopropyl hydrazone 2.11ca

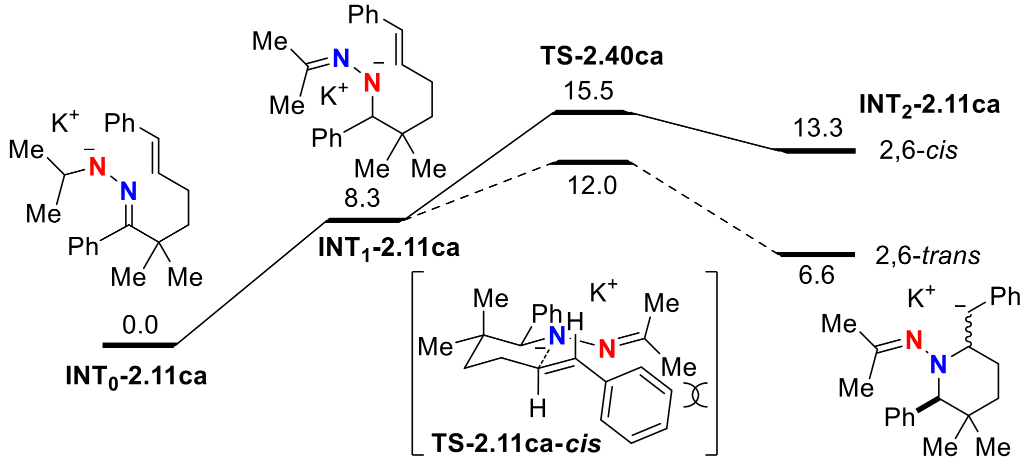


Figure 2.3. Energy diagram (in kcal/mol) for the reaction of **2.11aa** and **2.11ca**.

2.5. Conclusion

In conclusion, hydroamination reactions of alkenyl hydrazones using *t*-BuOK were established for the diastereo-divergent synthesis of azaheterocycles. The DFT calculations elucidated that the cation-π interaction between the potassium cation and multiple aryl substituents on hydrazones was the key in 2,5-*cis*-selective amino-cyclization of γ,δ-alkenyl *N*-benzyl hydrazones. In contrast, the tuning of a hydrazone substituent to the *N*-isopropyl group resulted in 2,5-*trans*-selectivity. An unprecedented 2,6-*trans*-selective amination in the preparation of piperidines was further demonstrated by means of the present protocol.

2.6. References

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Takaya, H.; Aiyashita, A.; Noyori, R. *J. Chem. Soc. Chem. Commun.* **1982**, 600. (c) Takabe, K.; Katagiri, T.; Tanaka, J. *Tetrahedron Lett.* **1975**, *16*, 3005.

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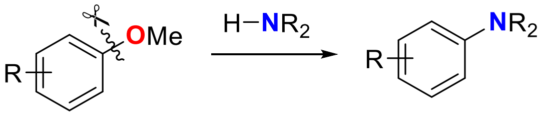
Chapter 3: Nucleophilic amination of methoxy arenes promoted by a sodium hydride/iodide composite

3.1. Introduction

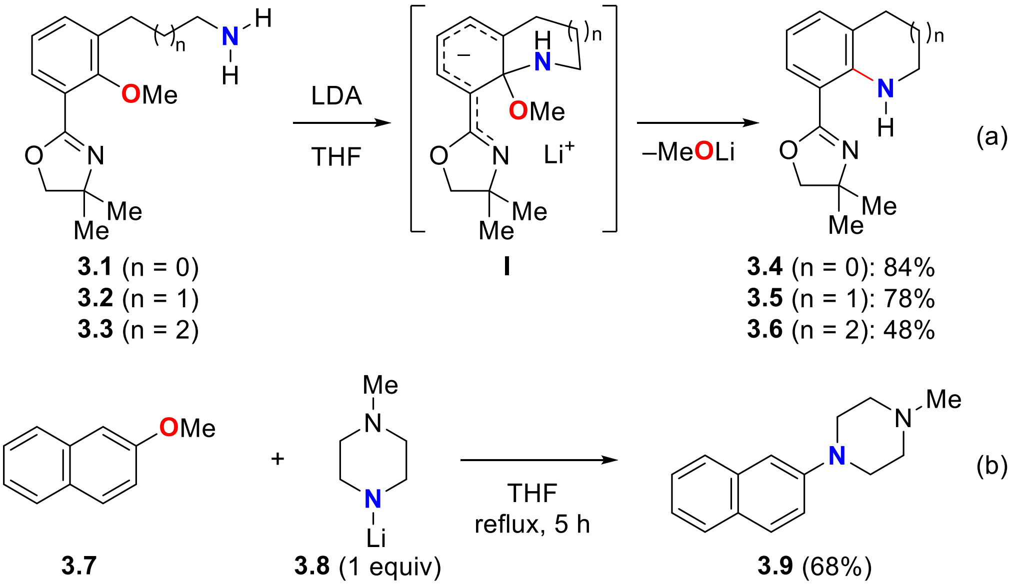
Over the past decade, C(sp^2)−O electrophiles have emerged as attractive alternatives to aryl halides in the fields of cross-coupling and nucleophilic substitution reactions due to the low cost and easy accessibility of phenols, which are abundant aromatic feedstocks from the coal-based chemical industry.[1] However, direct employment of phenols is limited because of the highly reactive acidic hydroxyl group and the high dissociation energy of the C(sp^2)−OH bond due to p−π conjugation.[1a,2] Therefore, pre-functionalization of phenols into various phenol derivatives such as sulfonates, esters and carbamates has been utilized as the general strategy to remove the acidic proton and lower the energy of the C(sp^2)−O bond, although the coupling reactions of such phenol derivatives generate considerable amounts of wastes.[1] In this respect, the use of methoxy arenes (aromatic ethers) is highly attractive in terms of atom-economic viewpoint as well as their easy accessibility while significant challenge still remains due to the inertness of the C(sp^2)−OMe bond (Scheme 3.1).[3] This section highlights amination of methoxy arenes under transition-metal free reaction conditions in accordance with the types of promoters.



Scheme 3.1. Amination of methoxy arenes.

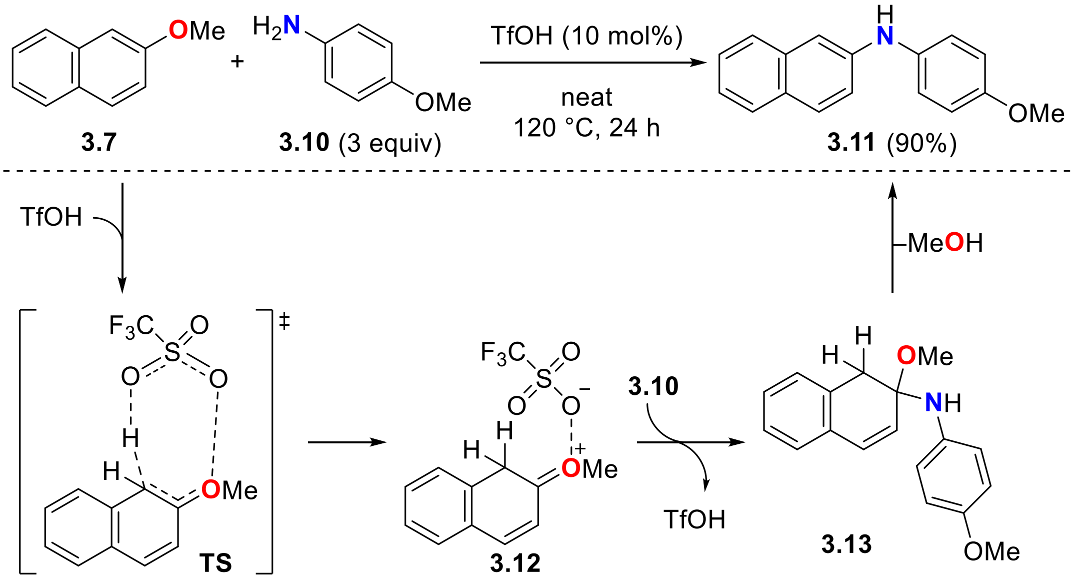
Early examples of the amination of methoxy arenes have utilized Brønsted bases as promoters. The first example of Brønsted base-mediated amination was reported by Meyers and co-workers in 1981 (Scheme 3.2a).[4] Their method utilized LDA as a

Brønsted base to induce aminative substitution of methoxy arenes **3.1**-**3.3** bearing an electron-withdrawing oxazolinyl functionality at the *ortho*-position. The reaction involved the addition-elimination mechanism through the formation of the Meisenheimer complex **I** stabilized by the oxazoline ring and subsequent elimination of lithium methoxide, providing the corresponding benzannulated azaheterocycles **3.4**-**3.6** in good to moderate yields. However, this protocol required the installation of an electron-withdrawing group onto the methoxy arenes. In this context, Wynberg and co-workers found the intermolecular amination by lithiated secondary amines onto unactivated methoxy arenes (Scheme 3.2b).[5] The lithium amide **3.8** was prepared from *N*-methyl piperazine and *n*-BuLi *in situ* and treated with the methoxy arene **3.7** under reflux conditions to produce the aromatic amine **3.9**. In this report, a variety of simple aromatic ethers and dialkyl amines were employed while the intramolecular variants were not explored.



Scheme 3.2. Brønsted base-mediated amination of methoxy arenes.

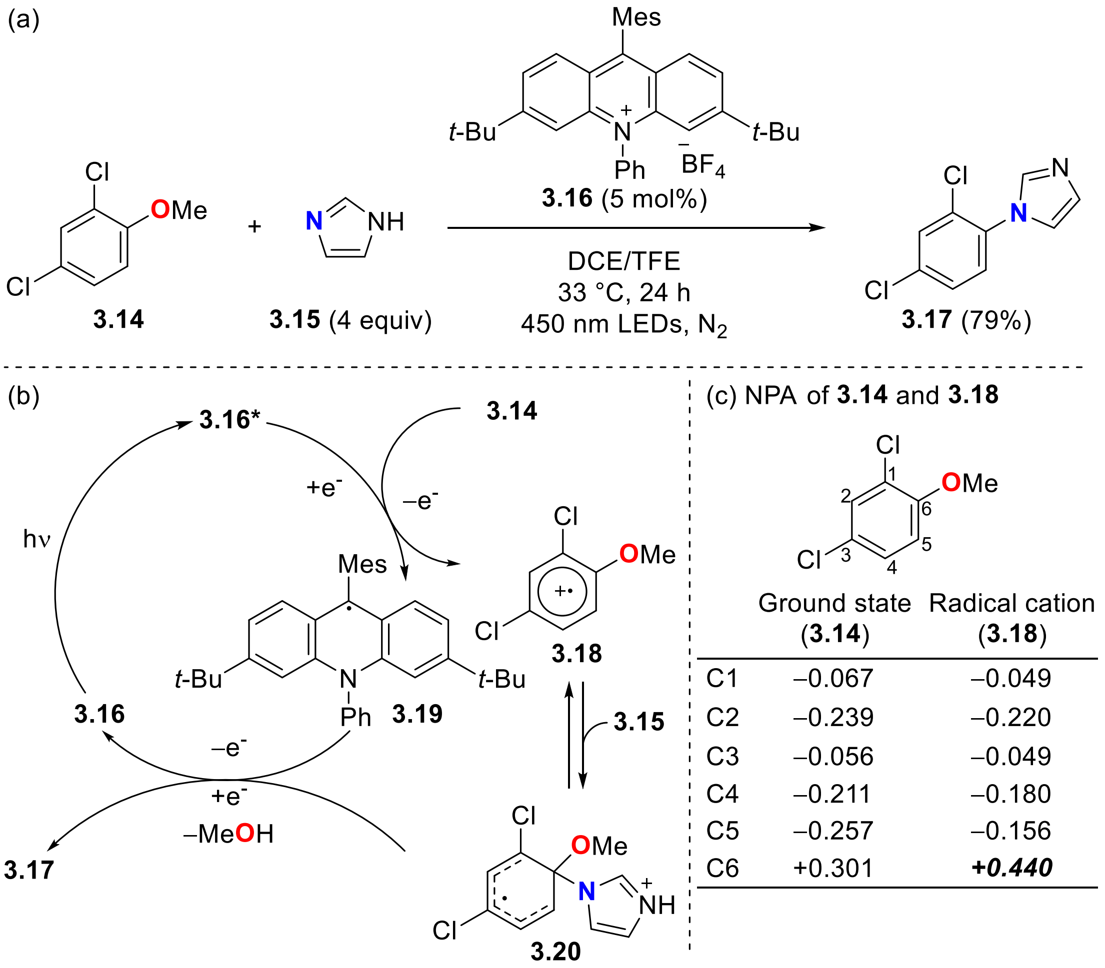
Recently, a Brønsted acid was used for the amination of methoxy arenes by Biswas and co-workers (Scheme 3.3).[6] TfOH was employed as a catalyst for the reaction of methoxy arene **3.7** with aniline **3.10** under solvent free conditions to provide diarylamine **3.11** in 90% yield. This amination would be initiated by the C(1)-protonation of the methoxy arene **3.7** by TfOH through a cyclic transition state **TS** to form an oxocarbenium ion **3.12**, which would react with the aniline **3.10** to give an aminal **3.13** and regenerate TfOH. Subsequent rearomatization of **3.13** via the loss of MeOH produced the desired product **3.11**.



Scheme 3.3. Brønsted acid-catalyzed amination of methoxy arenes.

Very recently, photoredox-catalyzed amination of methoxyarenes has been demonstrated by Nicewicz and Tay (Scheme 3.4a).[7] The coupling reaction of 2,4-dichloroanisole (**3.14**) and imidazole (**3.15**) was induced by the use of an acridinium ion **3.16** with blue LED irradiation under an inert atmosphere, providing the amination product **3.17** in 79% yield. In their proposed mechanism (Scheme 3.4b), the key is the single electron oxidation of **3.14** by the photo-excited acridinium ion **3.16*** to form a radical cation **3.18** along with the generation of the radical **3.19**. The natural population analysis (NPA) of the radical cation **3.18** revealed that the methoxy-bearing carbon at C6 is the most electrophilic site (Scheme 3.4c).[8]

Therefore, addition of imidazole **3.15** onto the reactive radical cation **3.18** underwent at the *ipso*-position relative to the methoxy group. Finally, single-electron-reduction of the resulting intermediate **3.20** by the radical **3.19** followed by the expulsion of MeOH afforded **3.17** and regenerated acridinium **3.16** in an overall redox-neutral mechanism. Although this amination proceeded under extraordinarily mild reaction conditions at room temperature, amine nucleophiles were mainly limited to heteroaromatics such as imidazoles, benzimidazoles, and pyrazoles.



	Ground state (**3.14**)	Radical cation (**3.18**)
C1	–0.067	–0.049
C2	–0.239	–0.220
C3	–0.056	–0.049
C4	–0.211	–0.180
C5	–0.257	–0.156
C6	+0.301	***+0.440***

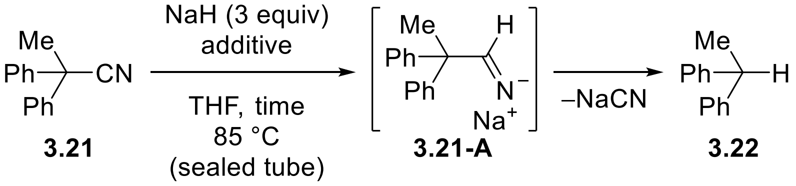
Scheme 3.4. photoredox-catalyzed amination of methoxy arenes.

3.2. Results and discussion

3.2.1. Molecular transformations using a sodium hydride-iodide composite

The author's group has recently found that the NaH gains hydride donor ability upon solvothermal treatment with NaI or LiI in a THF solvent. The resulting NaH/iodide composites could be utilized for various hydride reductions of carbonitriles and amides, hydrodehalogenation of aryl halides as well as dearylation of arylphosphine oxides.[9] For instance, the use of NaH-NaI or NaH-LiI composite induced the hydrodecyanation of carbonitrile **3.21** via iminyl anion intermediate **3.21-A** to provide decyanated alkane **3.22** (Table 3.1, entry 1-3).[9f] It was also found that the use of low loadings of LiI enabled full conversion of **3.21** with a longer reaction time (entry 3 and 4). Notebly, the desired decyanation of carbonitrile **3.21** was not promoted by the treatment with only NaH (entry 5).

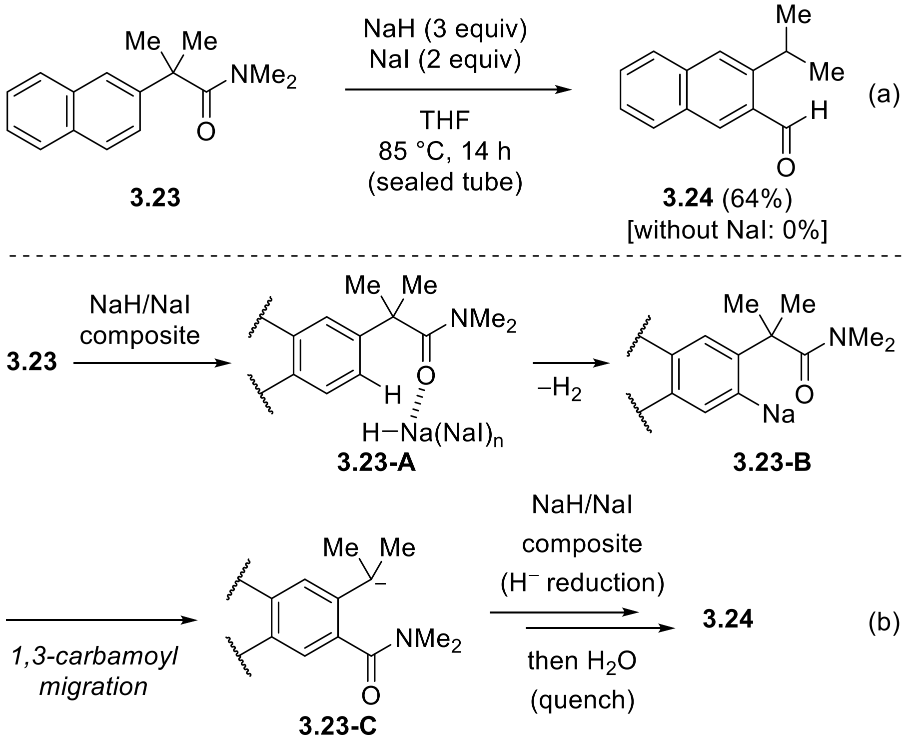
Table 3.1. Decyanation of carbonitrile **3.21** using the NaH-iodide composite.



entry	additive (equiv)	time (h)	yield (%)
1	NaI (2)	14	96
2	LiI (2)	3.5	98
3	LiI (1)	6	98
4	LiI (0.2)	48	98
5	-	24	trace

Continuous studies revealed the enhanced Lewis acidity of the NaH in the NaH-iodide composite in addition to its nucleophilic hydride donor ability. The reaction of α-quaternary α-arylacetamide **3.23** in the presence of the NaH-NaI composite provided 3-isopropyl-2-naphthaldehyde (**3.24**) in 64% yield via a sequence of anionic

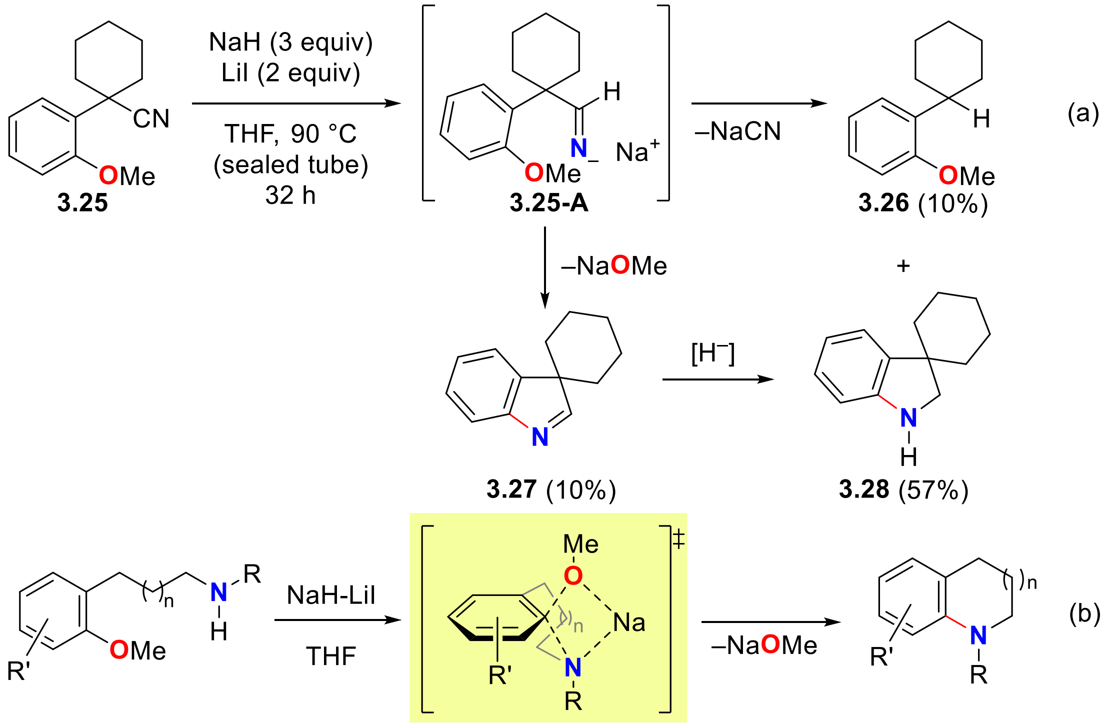
C-Fries-type rearrangement[10] and reduction of amide (Scheme 3.5a).[9c] Importantly, the treatment of **3.23** with NaH alone resulted in no reaction at all. It was proposed that the unprecedented reaction was induced by the enhanced Lewis acidity of NaH in the the NaH-NaI composite to proceed an *ortho*-deprotonation of a complex **3.23-A** directed by the Lewis-basic amide moiety. The subsequent 1,3-carbamoyl migration of an aryl sodium **3.23-B** followed by the hydride reduction of amide **3.23-C** delivered the aldehyde **3.24** (Scheme 3.5b).



Scheme 3.5. Amide-directed C-H sodiation by a sodium hydride-iodide composite.

3.2.2. Serendipitous aminative cyclization of *ortho*-methoxy benzyl cyanide

Continuous investigation of the substrate scope in the hydrodecyanation of carbonitriles revealed that the treatment of *ortho*-methoxy benzyl cyanide **3.25** with the NaH-LiI composite afforded the decyanated product **3.26** in only 10% yield along with the formation of 3*H*-indole **3.27** and indoline **3.28** in 10% and 57% yields, respectively (Scheme 3.6a). The unprecedented amino-cyclization presumably proceeded through the nucleophilic displacement of methoxy group by an anionic imine nucleophile **3.25-A** to form cyclic imine **3.27**. The imine moiety was further reduced to amine **3.28**. Since the employment of carbonitriles under the treatment with the NaH/iodide composites causes competing decyanation, simple amines are selected as starting materials for the development of general nucleophilic amination of methoxyarenes by means of NaH/iodide composites, which enables the synthesis of benzannulated azaheterocycles under transition-metal free conditions (Scheme 3.6b).

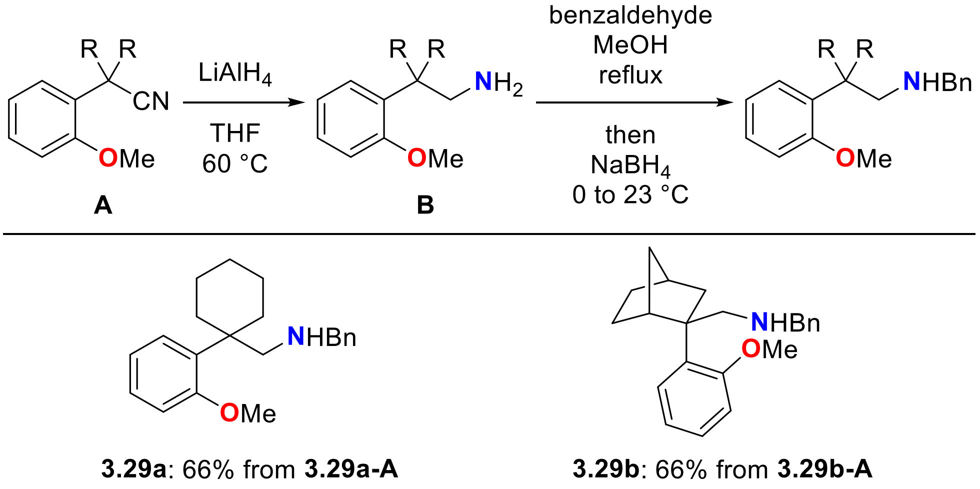


Scheme 3.6. Reactions with the NaH-iodide composites.

3.2.3. Substrate synthesis

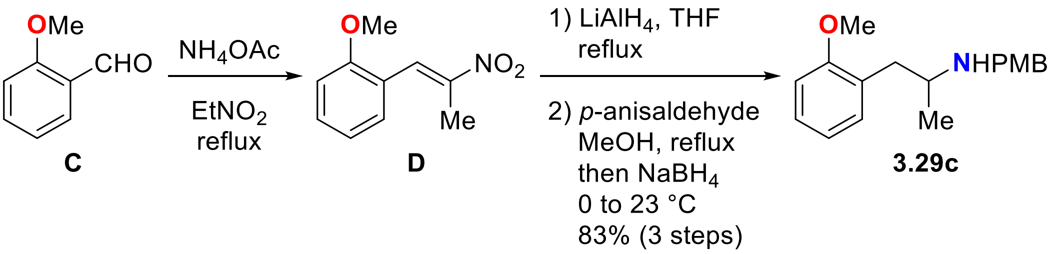
3.2.3.1. Substrates for five-membered ring formation

C(3)-Disubstituted *N*-benzyl amines **3.29a-3.29b** were prepared by the $LiAlH_4$ reduction of carbonitriles **A** followed by reductive amination of amines **B** with benzaldehyde in the presence of $NaBH_4$ (Scheme 3.7).



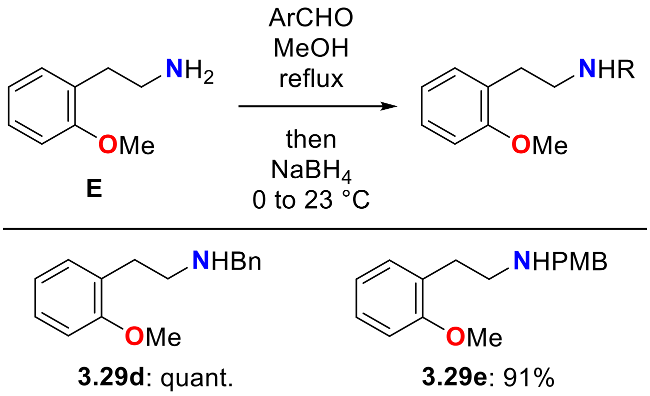
Scheme 3.7. Synthesis of C(3)-disubstituted *N*-benzylamines.

The preparation of a C(2)-substituted amine **3.29c** having a *para*-methoxybenzyl group was conducted by a three-step sequence of nitroaldol reaction of 2-methoxybenzaldehyde (**C**) with nitroethane,[11] reduction of the nitroalkene **D** by $LiAlH_4$, and reductive amination of the amine and *para*-anisaldehyde (Scheme 3.8).



Scheme 3.8. Synthesis of a C(2)-substituted *N*-PMB amine.

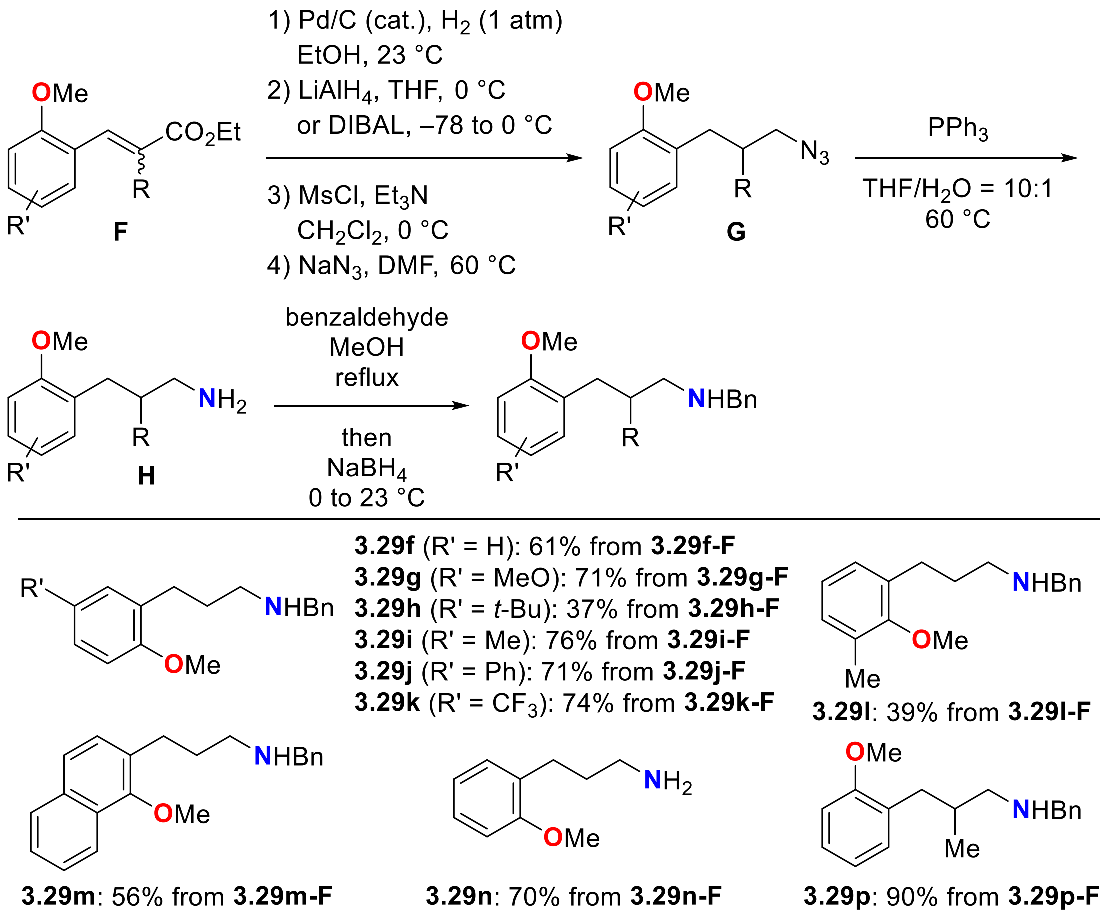
Non-substituted amines **3.29d-3.29e** were obtained by the reductive amination of 2-(2-methoxyphenyl)ethan-1-amine (**E**) and the corresponding aldehydes (Scheme 3.9).



Scheme 3.9. Synthesis of non-substituted amines.

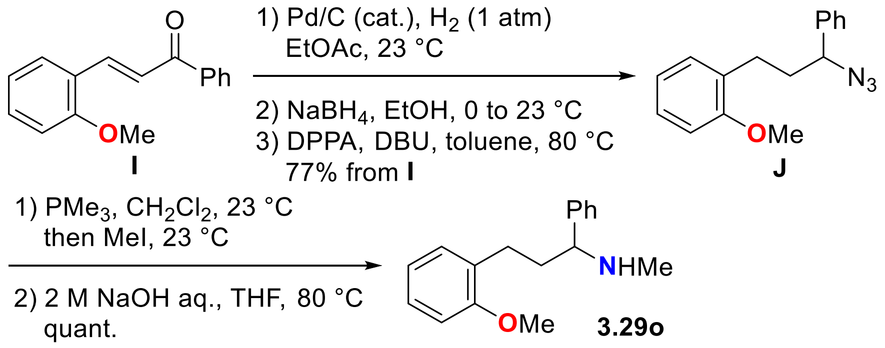
3.2.3.2. Substrates for six-membered ring formation

The synthesis of substrates **3.29f-3.29n** and **3.29p** for six-membered ring formation were initiated by hydrogenation of alkenes **F**, $LiAlH_4$-reduction of the corresponding esters, and azidation. The resulting azides **G** were further treated under the Staudinger reaction conditions followed by reductive amination with benzaldehyde (Scheme 3.10).



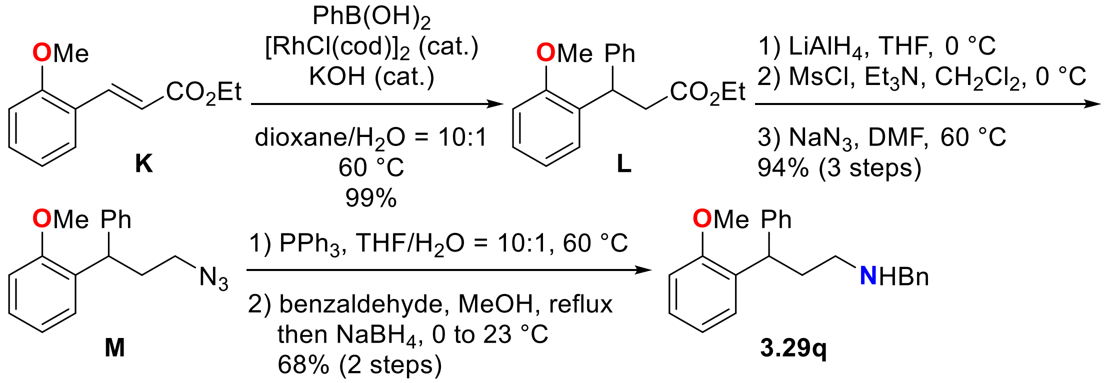
Scheme 3.10. Synthesis of substrates **3.29f-3.29n** and **3.29p**.

An *N*-methyl amine **3.29o** was accessed by hydrogenation of alkene **I**, $NaBH_4$-reduction of the corresponding ketone, and subsequent azidation of the alcohol using diphenylphosphoryl azide (Scheme 3.11). The resulting azide **J** was treated with PMe_3 followed by MeI to generate the corresponding iminophosphonium salt, which was hydrolysed to amine **3.29o** under basic conditions based on the reported procedure.[12]



Scheme 3.11. Synthesis of C(2)-substituted *N*-methylamine **3.29o**.

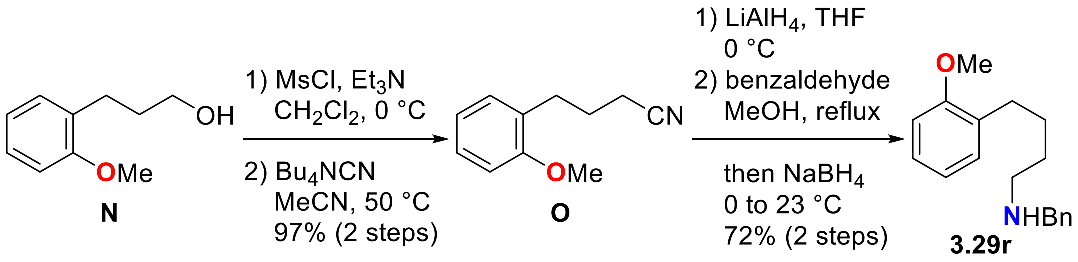
The synthesis of a C(4)-substituted *N*-benzyl amine **3.29q** was commenced with rhodium-catalyzed conjugate addition of phenylboronic acid to enone **K** (Scheme 3.12).[13] The resulting ester **L** was converted to *N*-benzyl amine **3.29q** via azide **M** according to the similar procedure in Scheme 3.10.



Scheme 3.12. Synthesis of a C(4)-substituted *N*-benzyl amine **3.29q**.

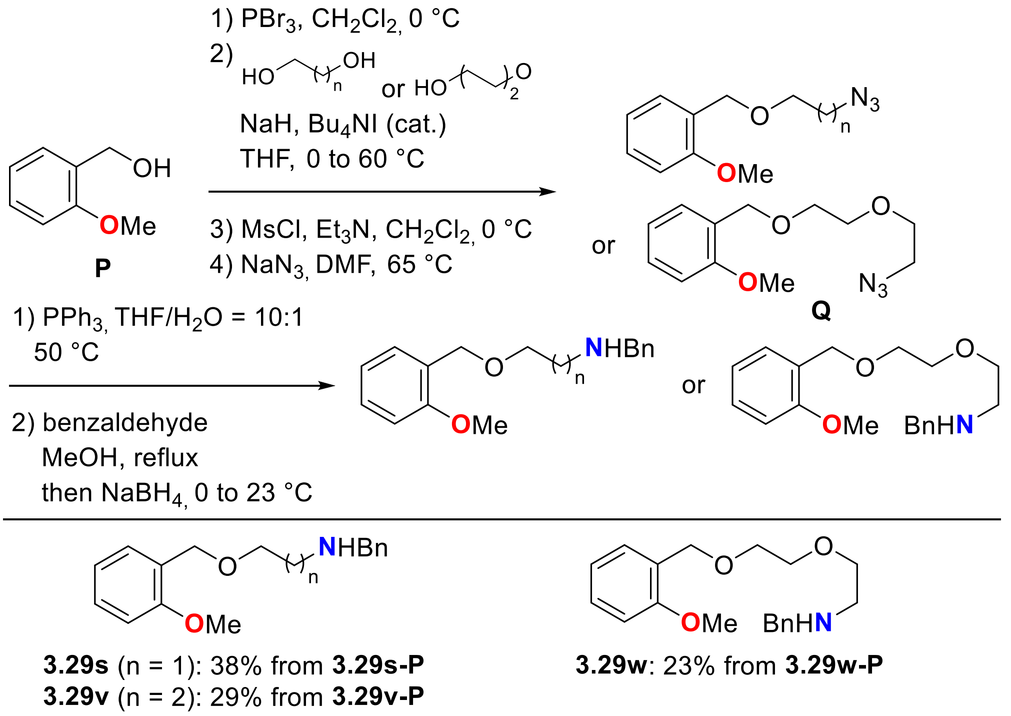
3.2.3.3. Substrates for medium ring formation

A substrate **3.29r** for seven-memebred ring formation was obtained by mesylation of an alcohol **N**, cyanation of the mesylate, followed by the conversion of the nitrile **O** to amine **3.29r** (Scheme 3.13) according to the similar procedure in Scheme 3.7.



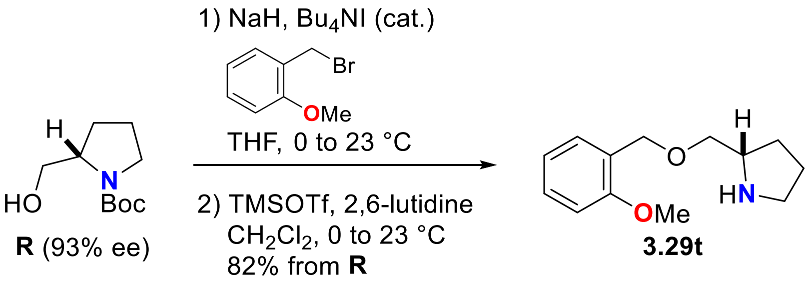
Scheme 3.13. Synthesis of substrate **3.29r**.

The preparation of substrates **3.29s** and **3.29v-3.29w** for seven- to ten-membered ring azaheterocycles having oxygen atoms was began with a sequence of bromination of an alcohol **P**, mono-benzylation of the corresponding diols, mesylation and azidation (Scheme 3.14). The resulting azides **Q** were transformed into *N*-benzylamines **3.29s** and **3.29v-3.29w** following the similar procedure in Scheme 3.10.



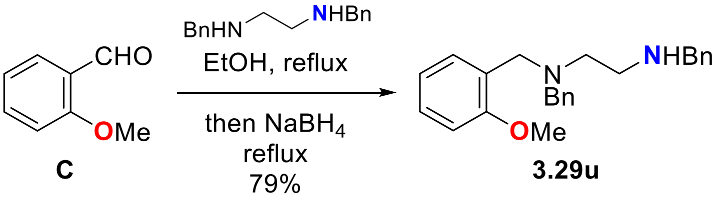
Scheme 3.14. Synthesis of substrates **3.29s** and **3.29v-3.29w**.

A chiral substrate **3.29t** was prepared by benzylation of *N*-Boc (L)-prolinol **R**, followed by deprotection of the *N*-Boc group using TMSOTf in the presence of 2,6-lutidine (Scheme 3.15).[14]



Scheme 3.15. Synthesis of chiral substrate **3.29t**.

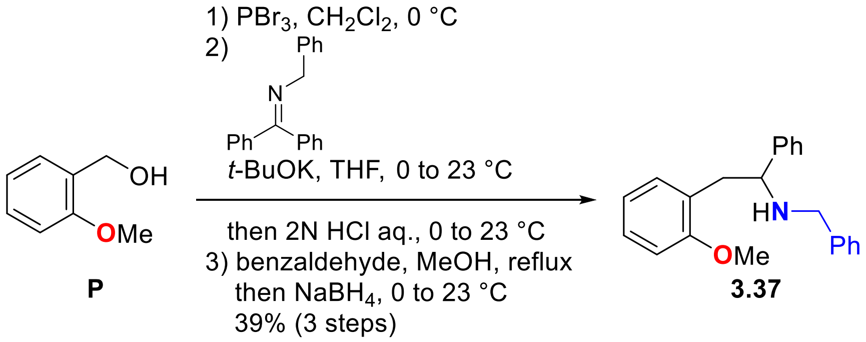
A substrate **3.29u** for additional nitrogen atom-containing azaheterocycle was prepared by the condensation of an aldehyde **C** and N^1,N^2-dibenzylethane-1,2-diamine and ensuing hydride reduction with $NaBH_4$ (Scheme 3.16).[15]



Scheme 3.16. Synthesis of substrate **3.29u**.

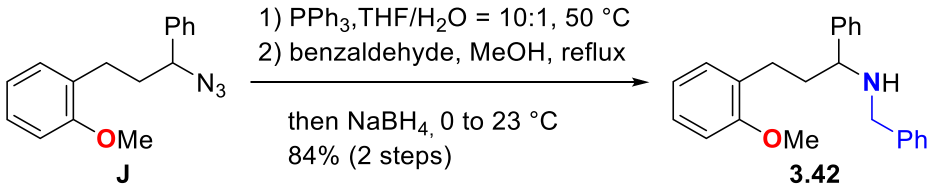
3.2.3.4. C(2)-phenylated *N*-benzylamines

A substrate **3.37** was provided through bromination of the alcohol **P**, benzylation of benzophenone imine followed by acidic hydrolysis,[16] and reductive amination of the corresponding amine and benzaldehyde (Scheme 3.17).



Scheme 3.17. Synthesis of substrate **3.37**.

A homologated *N*-benzyl amine **3.42** was obtained by the reduction of azide **J** and the subsequent reductive amination, (Scheme 3.18) in accordance with the procedure in Scheme 3.10.



Scheme 3.18. Synthesis of substrate **3.42**.

3.2.3.5. Substrates for the intermolecular amination

A series of amines and methoxy arenes for the intermolecular amination are commercially available and used as received (Figure 3.1). Dextromethorphan was prepared according to the reported procedure.[17]

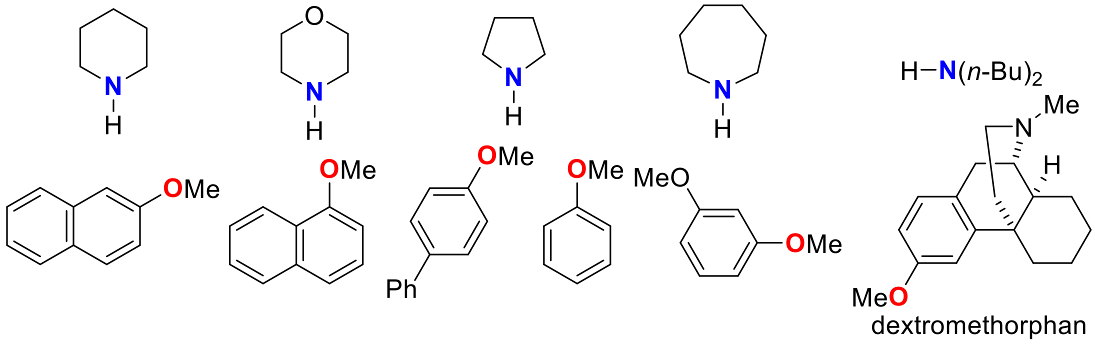
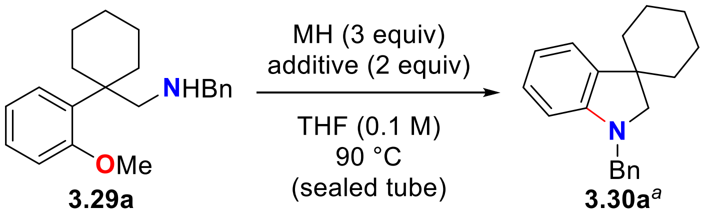


Figure 3.1. Substrates for the intermolecular amination.

3.2.4. Optimization of the reaction conditions

Our studies commenced with the additive screening for the reaction of *N*-benzylamine **3.29a** in the presence of NaH. It was found that the addition of LiI or NaI at 90 °C promoted the amino-cyclization to deliver the indoline **3.30a** (Table 3.2, entry 1-2). In particular, the combination of NaH (3 equiv) and LiI (2 equiv) enabled a full conversion of the starting amine **3.29a** to give **3.30a** in 90% yield (entry 1). Control experiments established the importance of NaH-LiI composite as the indoline **3.30a** was not formed in the absence of LiI (entry 3), under the treatment of LiH (entry 4), or LiH-LiI composite (entry 5) instead of the NaH-LiI composite.

Table 3.2. Optimization of reaction conditions.



3.29a **3.30a**[a]

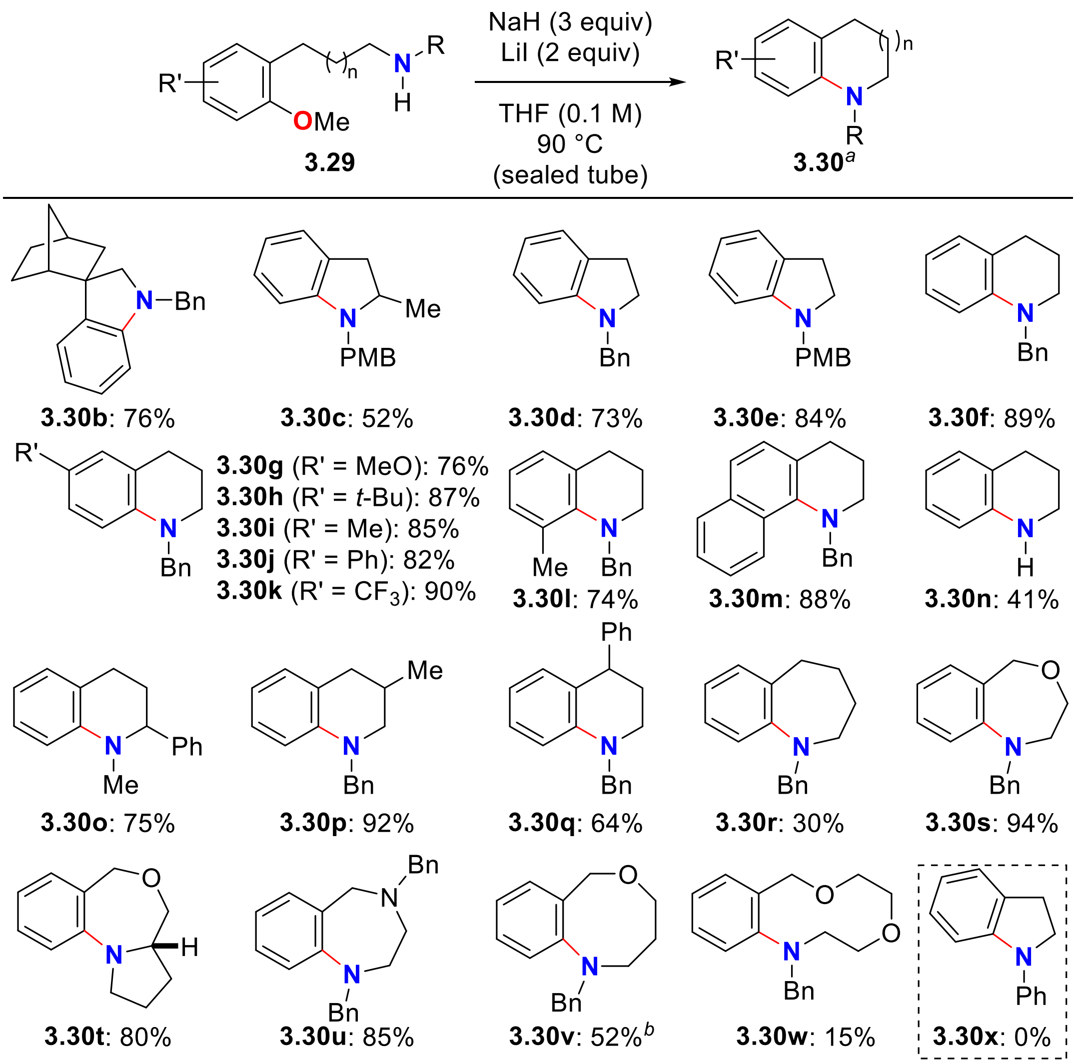
entry	MH	additive	time (h)	conv. (%)	yield (%)[b]
1	NaH	LiI	19	>99	90
2	NaH	NaI	24	37	31
3	NaH	none	24	<1	<1
4	LiH	none	24	2	0
5	LiH	LiI	24	9	0

[a] The reactions were conducted using 0.3-0.5 mmol of **3.29a** in THF (0.1 M). [b] Isolated yields.

3.2.5. Scope and limitation

3.2.5.1. Intramolecular amination

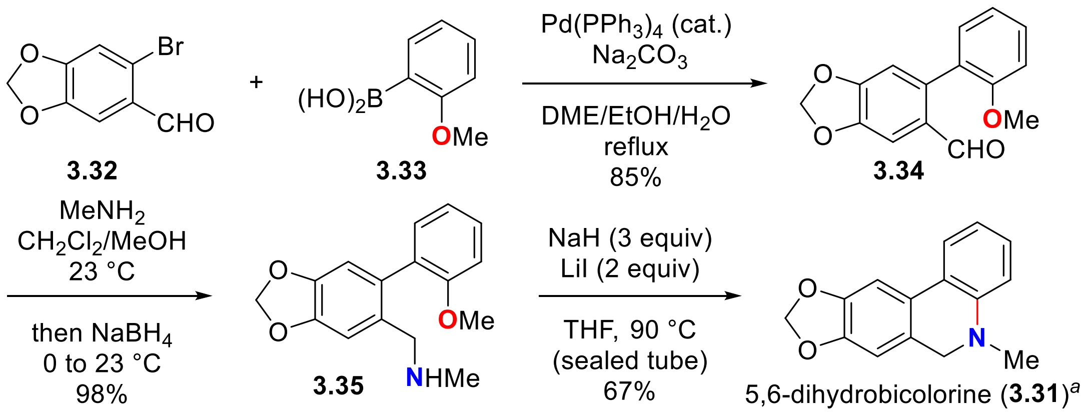
The optimized conditions using the NaH-LiI composite were applied for the amination of unactivated methoxy arenes (Scheme 3.19). Various 2-methoxyphenethylamine derivatives **3.29b-3.29e** were successfully converted to substituted indolines **3.30b**-**3.30c** and nonsubstituted indolines **3.30d**-**3.30e** bearing cleavable *N*-benzyl and *para*-methoxybenzyl groups. This method was also able to construct a series of tetrahydroquinolines **3.30f**-**3.30q**. Notably, reactions of substrates having electron-donating groups (for **3.29g**-**3.29i**) and sterically hindered substituents (for **3.29l**-**3.29m**) underwent smoothly to afford good yields of the desired tetrahydroquinolines. We found the amenability of a primary amine (for **3.29n**), an *N*-methylamine (for **3.29o**), and C(2)-C(4) substituted *N*-benzyl amines (for **3.29o**-**3.29q**) as compatible substrates in the current transformation. Further evaluation of the generality for the synthesis of larger ring azaheterocycles resulted in a broad substrate scope. Constructions of the 7-membered rings such as tetrahydro-1*H*-benzo[*b*]azepine (**3.30r**), tetrahydrobenzo[*e*][1,4]oxazepine (**3.30s**-**3.30t**), and -[1,4]diazepine (**3.30u**) were accomplished using this protocol albeit the moderate yield of **3.30r** was observed. For the synthesis of tricycle **3.30t**, the preinstalled chirality derived from (L)-prolinol was retained after the amination. An 8-membered ring, tetrahydro-2*H*-benzo[*c*][1,5]oxazocine **3.30v**, was also produced by the excess use of the NaH-LiI composite, while the preparation of the 10-membered ring **3.30w** resulted in lower yield. Unfortunately, the trial of excess use of the NaH-LiI composite or highly diluted reaction conditions for the synthesis of **3.30w** did not improve the reaction efficiency. The method was not applicable to the secondary aryl amine (for **3.30x**), presumably because of the delocalization the resulting anionic charge.



[a] The reactions were conducted using 0.3-0.5 mmol of **3.29** in THF (0.1 M) and isolated yields of **3.30** were stated. [b] NaH (6 equiv) and LiI (4 equiv) were used.

Scheme 3.19. Substrate scope on intramolecular amination of methoxy arenes.

Synthetic applicability of this protocol was demonstrated by a facile synthesis of 5,6-dihydrobicolorine (**3.31**) in three steps via palladium-catalyzed Suzuki coupling of commercially available 6-bromopiperonal (**3.32**) and 2-methoxyphenylboronic acid (**3.33**), reductive amination of biarylaldehyde **3.34** with methylamine, and the nucleophilic amination of **3.35** with the NaH-LiI composite (Scheme 3.20).[18]

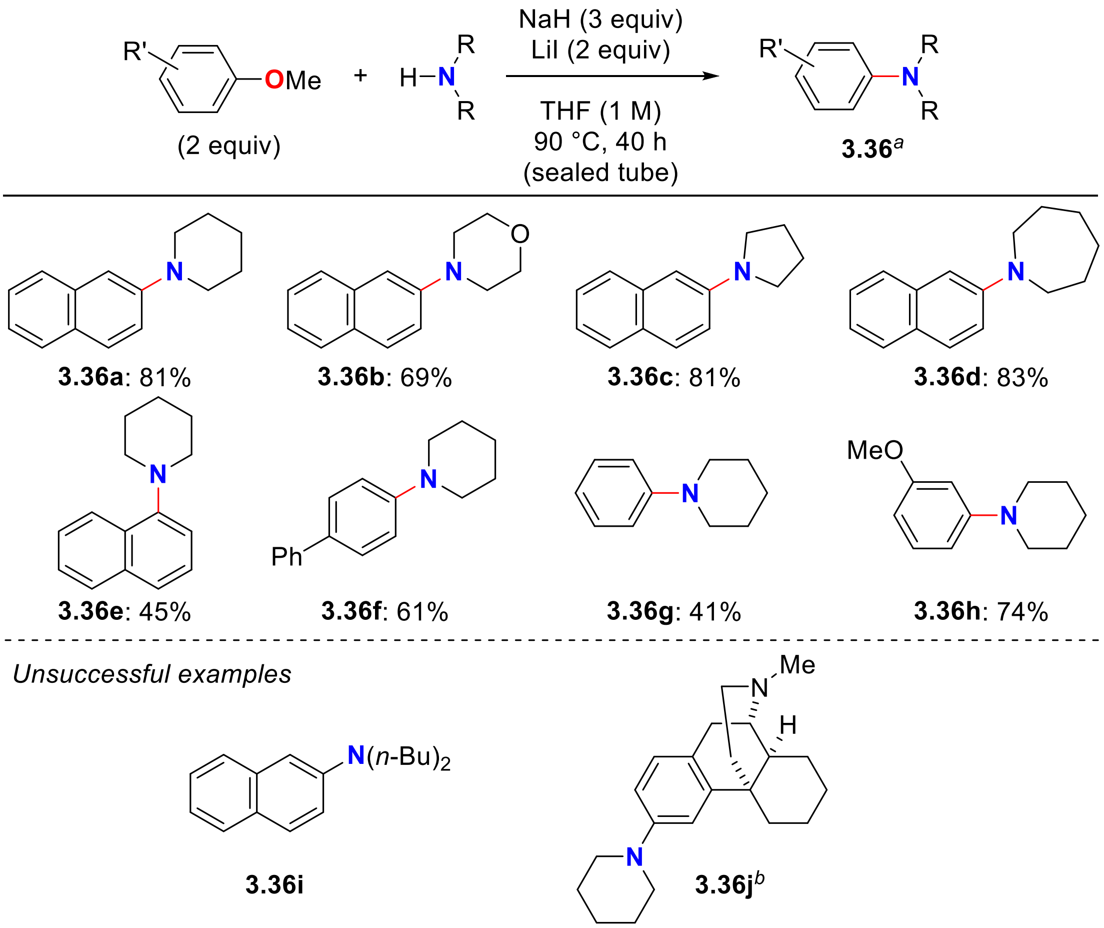


[a] The reaction was conducted using 0.5 mmol of **3.35** in THF (0.1 M) and isolated yield of **3.31** was stated.

Scheme 3.20. Three-step synthesis of 5,6-dihydrobicolorine (**3.31**).

3.2.5.2. Intermolecular amination

The transformation using the NaH-LiI composite could be extended to intermolecular variants for the synthesis of aromatic amines (Scheme 3.21). The intermolecular amination of various cyclic secondary amines and methoxy arenes required a higher concentration of 1 M to enhance the reaction efficiency, delivering aminated products **3.36a-3.36h** in good to moderate yields. This reaction system is not applicable to the acyclic amine (for **3.36i**), or dextromethorphan, a blockbuster drug of the morphinan class (for **3.36j**).



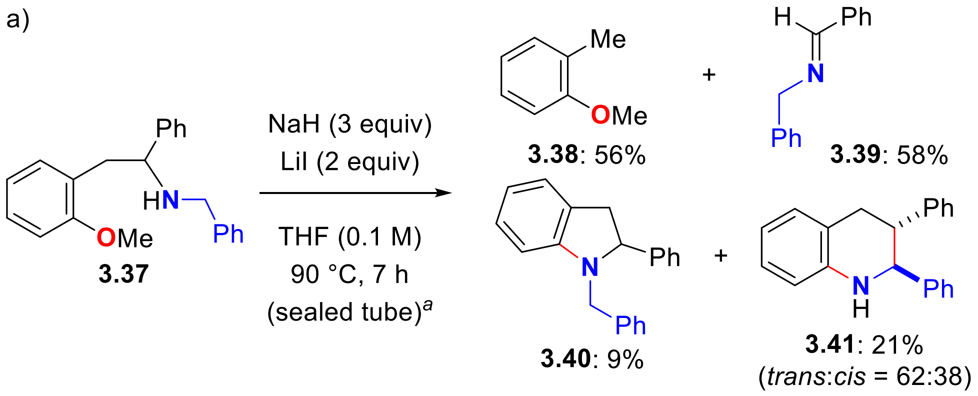
[a] The reactions were conducted using amines (0.5 mmol) and methoxy arenes (2 equiv) in THF (1 M) and isolated yields of the aminated arenes **3.36** are noted. [b] The reaction was conducted using dextromethorphan (0.5 mmol) and piperidine (2 equiv) in the presence of NaH (5 equiv) and LiI (2 equiv) in THF (1 M) at 90 °C for 42 h.

Scheme 3.21. Intermolecular amination of methoxy arenes.

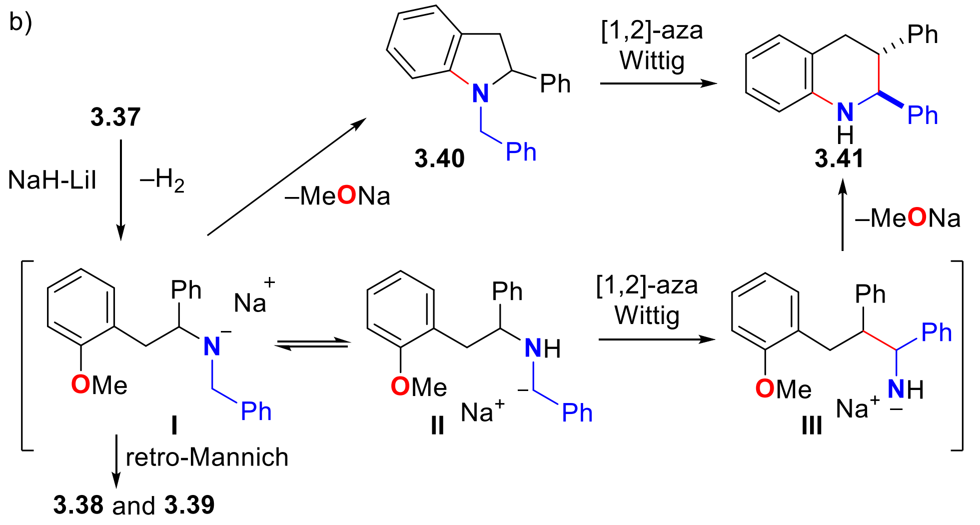
3.2.5.3. Retro-Mannich reactions and skeletal rearrangements

In contrast to the formation of indolines **3.29b-3.29e** (Scheme 3.19), a treatment of amine **3.37** under the optimal reaction conditions caused the retro-Mannich reaction to furnish 2-methylanisole (**3.38**) and aldimine **3.39** as the major products along with the formation of indoline **3.40** and tetrahydroquinoline **3.41** (Scheme 3.22a). The reaction was initiated by the formation of sodium amide **I** through the deprotonation of amines **3.37** by the NaH-LiI composite (Scheme 3.22b). The resulting amide **I** prefers to undergo retro-Mannich reaction to generate stabilized benzyl anion (as a precursor of

2-methylanisole **3.38**) and conjugated benzaldimine **3.39**. The amide **I** could also undergo amino-cyclization to provide **3.40**, which might undergo ring-expansion via aza-[1,2]-Wittig rearrangement to afford **3.41**.[19] Alternative mechanism for the formation of **3.41** would involve aza-[1,2]-Wittig rearrangement of newly formed benzyl sodium **II** to deliver sodium amide **III** through C-N bond scission.[20] Subsequent aminative displacement of the methoxy group in the sodium amide **III** provided **3.41**.

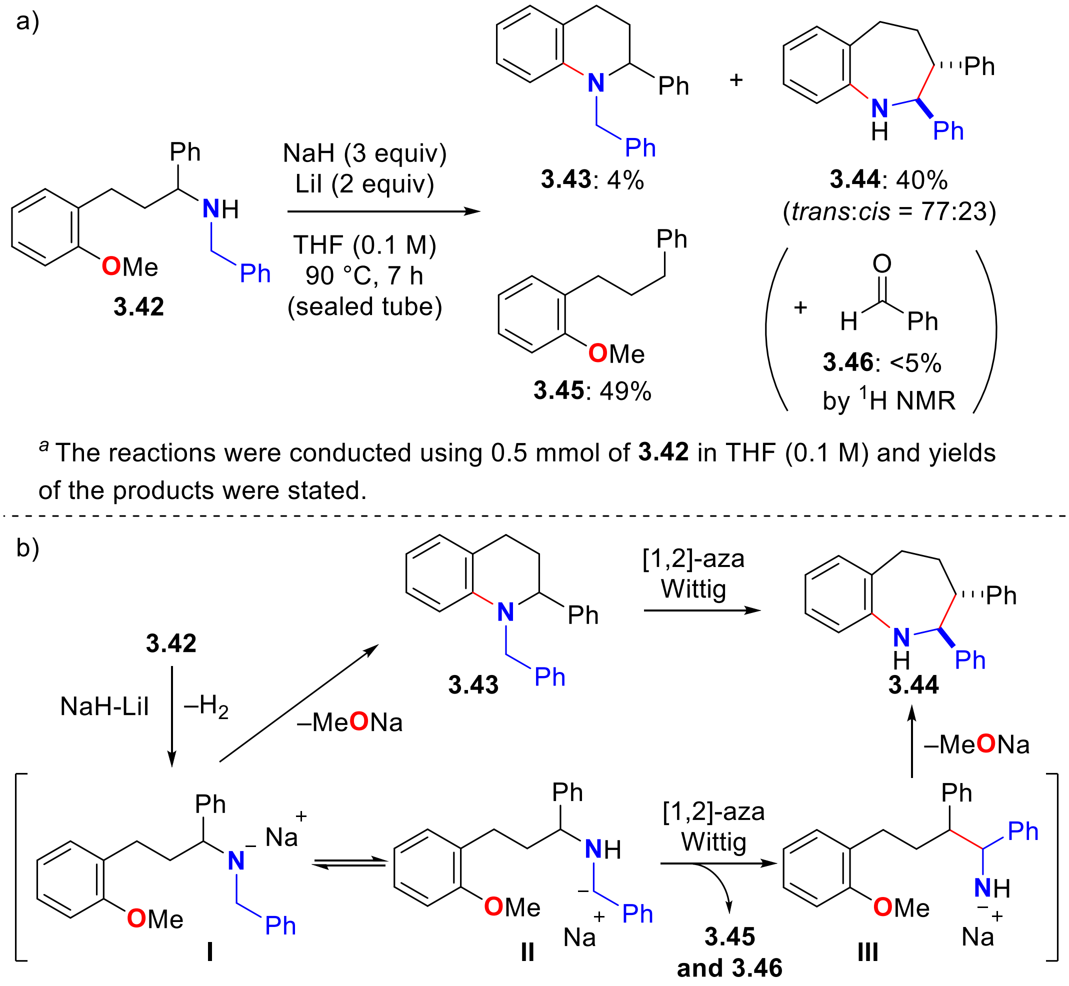


[a] The reactions were conducted using 0.5 mmol of **3.37** in THF (0.1 M) and yields of the products were stated.



Scheme 3.22. Reactions of *N*-benzylamines **3.37**.

To avoid the retro-Mannich reaction, the reaction of one-carbon homologated amine **3.42** was examined (Scheme 3.23a). As a result, tetrahydroquinoline **3.43** was formeed in merely 4% yield. On the other hand, tetrahydro-1*H*-benzo[*b*]azepine **3.44** and fragmentated alkane **3.45** were obtained in 40% and 49% yields, respectively, along with a trace amount of benzaldehyde (**3.46**), which was in sharp contrast to the reaction of *N*-methyl amine **3.29o** (Scheme 3.19). The mechanism for the reaction of **3.42** is analogous to that of **3.37** (Scheme 3.22) whereas the alkane **3.45** and benzaldehyde (**3.46**) were presumably formed through the C-N bond cleavage of benzyl sodium **II** (Scheme 3.23b).[20]

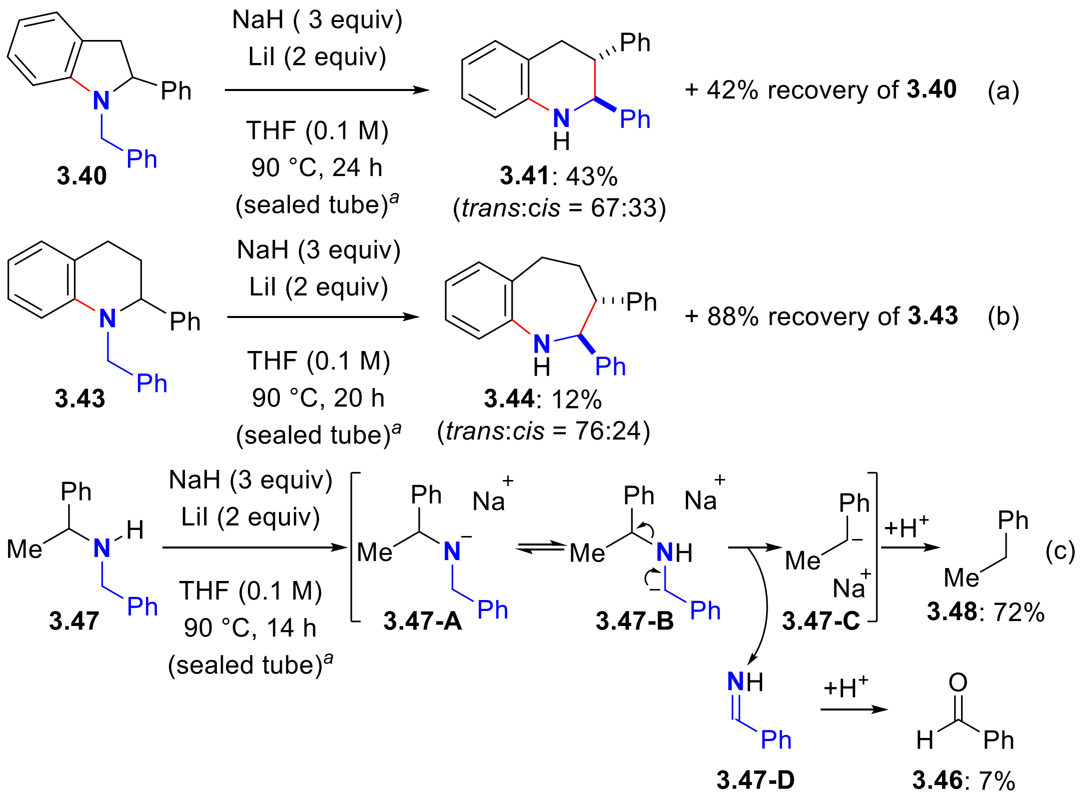


[a] The reactions were conducted using 0.5 mmol of **3.42** in THF (0.1 M) and yields of the products were stated.

Scheme 3.23. Reactions of *N*-benzylamines **3.42**.

Control experiments of indoline **3.40** and tetrahydroquinoline **3.43** under the optimal reaction conditions provided the ring-expansion products **3.41** and **3.44** in 43% and 12% yields, respectively, which indicated the formation of **3.41** and **3.44** involves

[1,2]-aza Wittig rearrangement after amino-cyclization (Scheme 3.24a,b). On the other hand, the reaction of *N*-benzyl-1-phenylethan-1-amine (**3.47**) with the NaH-LiI composite generated ethylbenzene (**3.48**) and benzaldehyde (**3.46**) in 72% and 7% yields, respectively, along with a mixture of unidentified compounds (Scheme 3.24c). The mechanism for the formation of ethylbenzene (**3.48**) and benzaldehyde (**3.46**) would involve the C-N bond cleavage of **3.47-B** via sodium amide **3.47-A** to generate benzyl sodium **3.47-C** and phenylmethanimine (**3.47-D**) which were hydrolyzed to **3.48** and **3.46**, respectively. The formation of ethylbenzene (**3.48**) suggested that the C-N bond scission of **3.42** for the generation of alkane **3.45** likely occurs prior to the cyclization. The lower yield of benzaldehyde (**3.46**) than that of **3.48** might be originated from the decomposition of imine **3.47-D** under thermal reaction conditions in the presence of the NaH-LiI composite.



[a] The reactions were conducted using 0.3-0.5 mmol of amines in THF (0.1 M) and yields of the products were stated.

Scheme 3.24. Control experiments.

3.3. Mechanistic insights

3.3.1. From the DFT calculation

To elucidate the mechanism of the amino-cyclization for the synthesis of *N*-methyl tetrahydroquinoline as the model reaction (Figure 3.2), DFT calculations were conducted using Gaussian 09 at the B3LYP- 6-31+G* level of theory [SCRF (pcm, solvent = THF)] taking into consideration the solvent effect of THF in which the two molecules of THF were included.[21] It was found that the cyclization of the resulting Na amide involves a four-membered ring transition state (TS) having a partial negative charge with a reasonable energy barrier (+14.7 kcal/mol), which supported the concerted nucleophilic aromatic substitution mechanism.[9d, 22] The unusual nucleophilic amination of methoxy arenes could be presumably induced by an enhanced Lewis acidity of NaH in the NaH-LiI composite.[9c]

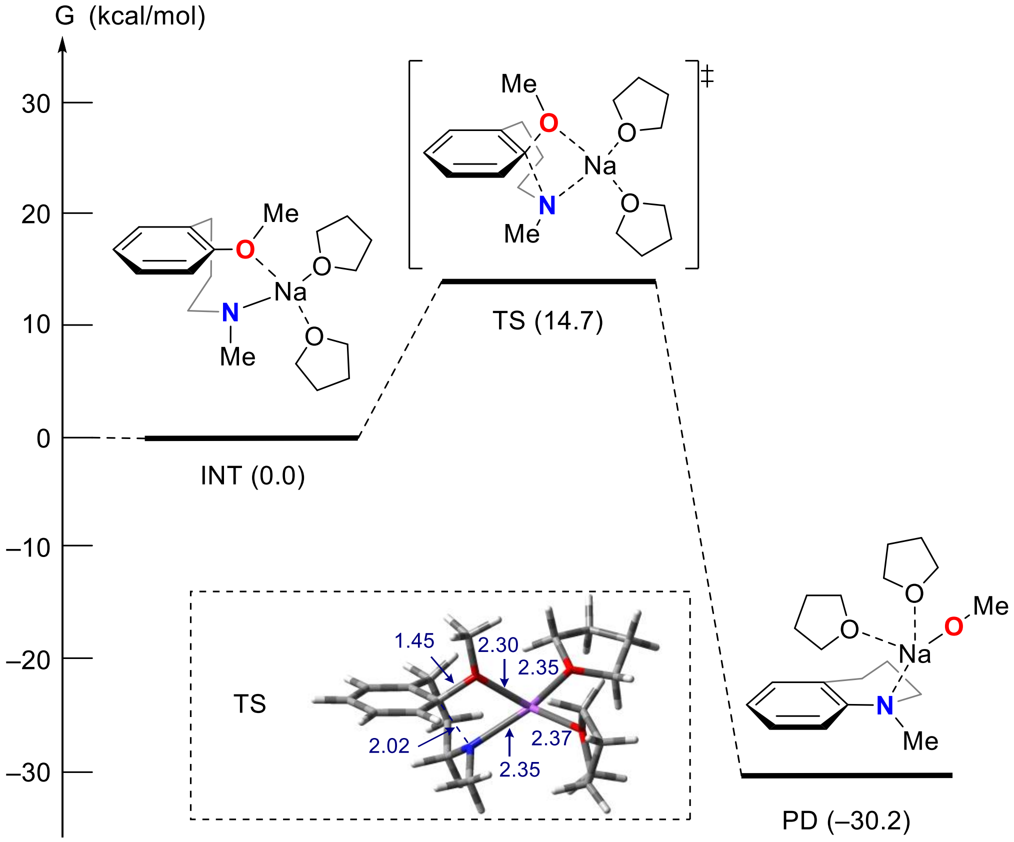
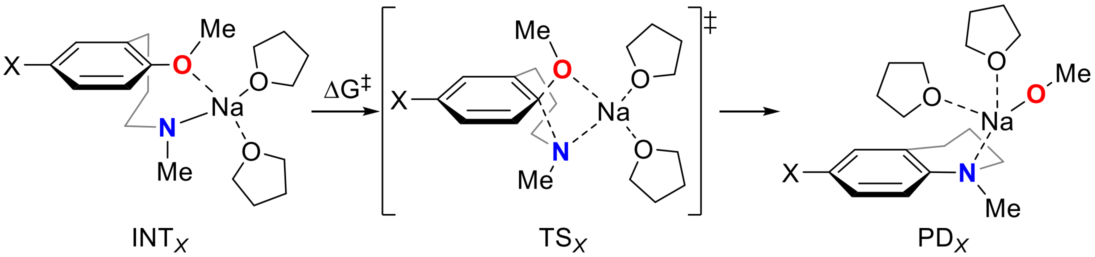


Figure 3.2. Energy diagram for the synthesis of *N*-methyl tetrahydroquinoline.

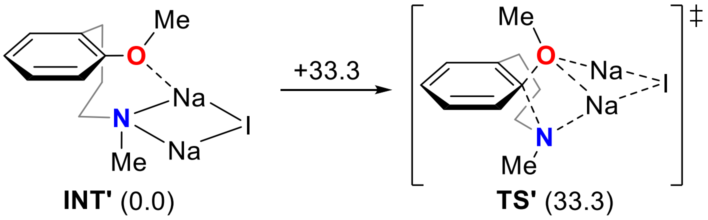
The DFT calculations of the transition state free energy for the reactions of methoxyarenes having several substituents (Table 3.3) are in good agreement with experimental liner Hammett correlation (*vide infra*, Figure 3.4), supporting the concerted nucleophilic aromatic substitution mechanism.

Table 3.3. The calculated transition state free energy of substituted methoxy arenes.



Entry	Substituents (X)	$\Delta G^{\ddagger}$ (kcal/mol)
1	CF_3	+9.6
2	H	+14.7
3	Me	+16.9
4	*t*-Bu	+18.2
5	OMe	+21.0

Our group previously investigated material characterization of the NaH-LiI composite.[9e] In the report, the solvothermal reaction of NaH and LiI in a THF solvent generates a mixture of NaH, NaI, and LiH via counter ion metathesis, where a smaller activated unit of NaH are dispersed on NaI. Besides, the optimization of the current amino-cyclization revealed that the use of LiH did not promote the desired reaction at all (Table 3.2). In consideration of these results, we conducted DFT computations of the alternative mechanism involving the coordination of NaI onto the methoxy arene (Scheme 3.25). As a result, this mechanism required a high activation barrier (+33.3 kcal/mol, **INT'** to **TS'**), which suggested that the pathway via coordination of NaI might be unfavourable.



Scheme 3.25. DFT calculations of alternative mechanism for the reaction of *N*-methyl amine based on B3LYP-6-31+G* level of theory [SCRF (pcm, solvent = THF)] in kcal/mol.

3.3.2. From the experimental results

Based on the experimental results, the amination of methoxy arenes using the NaH-LiI composite proceeded via neither addition-elimination mechanism through the Meisenheimer complex (path A) nor elimination-addition mechanism through the aryne intermediate (path B) because the current method tolerated electron-rich arenes **3.30g-3.30i** as well as 2,6-disubstituted arenes **3.30l-3.30m** (Figure 3.3).

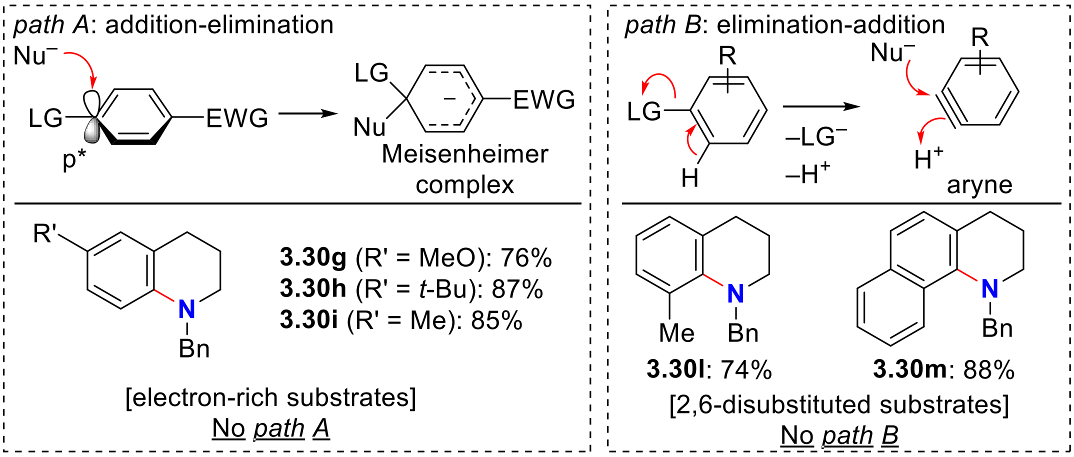
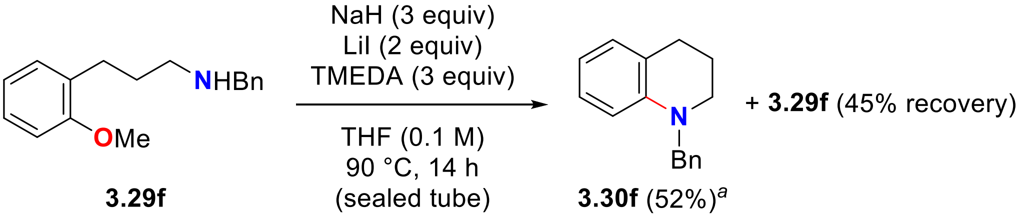


Figure 3.3. Mechanistic insights based on experimental results.

The addition of *N*,*N*,*N*',*N*'-tetramethylethylenediamine (TMEDA, 3 equiv) to the reaction of **3.29f** decreased the reaction efficiency (Scheme 3.26). This result supports that chelation of the Na cation in a four-membered ring transition state is a key to promote the concerted nucleophilic aromatic substitution reactions (Figure 3.2).

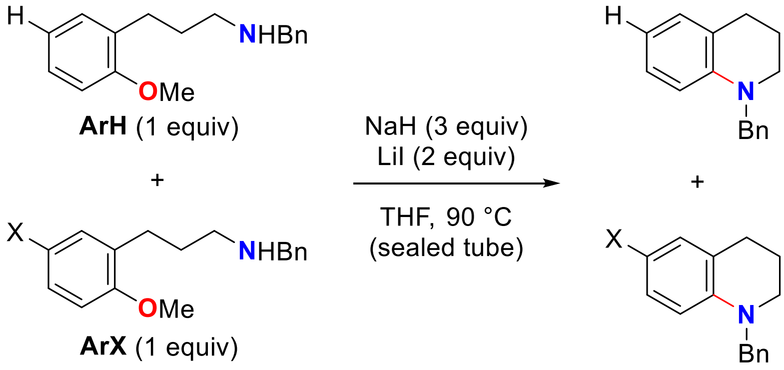


(without TMEDA: 89% yield of **3.30f** with full conversion for 14 h)

[a] The reaction was conducted using 0.3 mmol of **3.29f** in THF (0.1 M) and isolated yields of **3.30** was stated.

Scheme 3.26. Reaction of **3.29f** in the presence of TMEDA.

Linear free energy relationships of log(k_X/k_H) against σ_p were examined by the competition experiments between ArH and ArX (Figure 3.4). The Hammett plot resulted in a moderate linearity, which indicated a substituent-independent rate determining step. The small positive ρ value of 2.0 illustrated that only modest negative charge develops on the aromatic ring in the transition state of concerted nucleophilic aromatic substitution. This is distinct from the stepwise nucleophilic aromatic substitution through a Meisenheimer complex, which commonly exhibits higher ρ values between 3.0 to 8.6.[23]



Entry	X-substituent	σ_p[24]	log(k_X/k_H)
1	CF_3	0.54	+0.98
2	H	0	0
3	Me	−0.17	−0.54
4	*t*-Bu	−0.20	−0.44
5	OMe	−0.27	−0.61

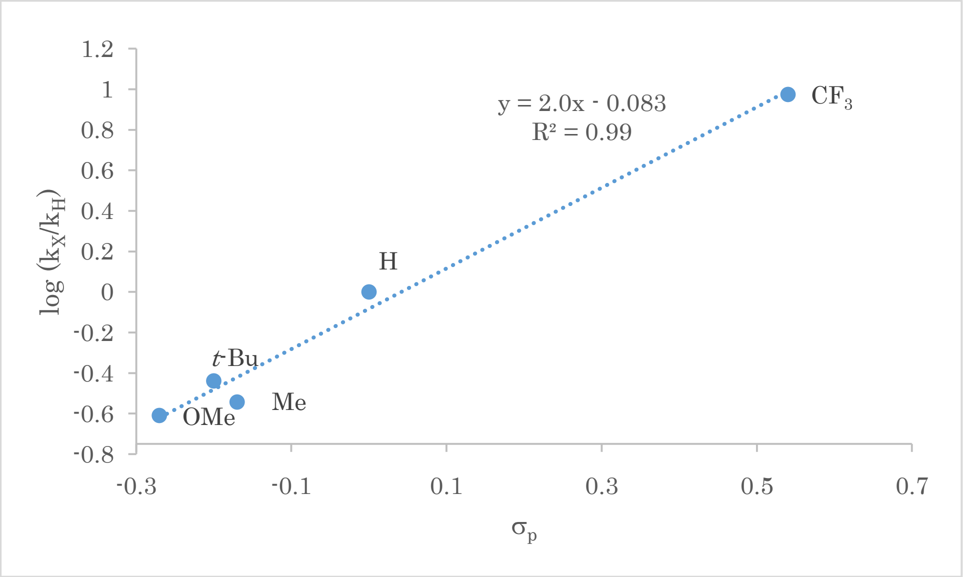


Figure 3.4. Hammett plot for log(k_X/k_H) against σ_p.

3.4. Conclusion

The Chapter 3 discloses the applicability of NaH-LiI composite toward nucleophilic amination of methoxy arenes for the synthesis of diverse benzannulated saturated azaheterocycles as well as aromatic amines. DFT computation has revealed that this transformation proceeds via a concerted nucleophilic aromatic substitution mechanism.

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Part 2: Synthesis of tricyclic marine alkaloid, fasicularin

Chapter 4: General information

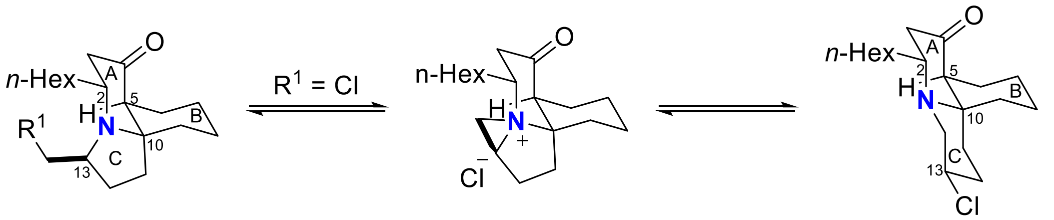
4.1. Isolation, Structural determination, and biological activity of tricyclic alkaloids

Tricyclic alkaloids bearing perhydropyrrolo[2,1-*j*]quinoline **4.1** or perhydropyrido[2,1-*j*]quinoline **4.2** have been isolated from diverse marine tunicates (Figure 4.1).[1]

perhydropyrrolo[2,1-j]quinoline (**4.1**) perhydropyrido[2,1-j]quinoline (**4.2**)

Figure 4.1. The chemical structure of common framework in tricyclic alkaloids.

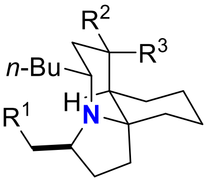
Cylindricine A (**4.3**) and B (**4.4**) were isolated from Tasmanian ascidians *Clavelina cylindrica* and the first members of the family of the tricyclic alkaloids in 1993 (Figure 4.2).[2] The structures of cylindricines (**4.3-4.4**) were proved by X-ray crystallography of corresponding picrate salts. Cylindricine A (**4.3**) and B (**4.4**) interconvert gradually and form a 3:2 equilibrium mixture of **4.3** and **4.4** via aziridinum ion **4.3'** in aqueous media. Cylindricines (**4.3-4.4**) exhibited some inhibitory activity in brine shrimp assay. Continuous investigations revealed the additional congeners, cylindricine C-K (**4.5-4.13**), whose structures were elucidated by the NMR experiments as well as the chemical conversion.[3] Although numerous research groups achieved the asymmetric syntheses of cylindricines,[4] their absolute configurations as natural samples have been undetermined. The structural feature of all the cylindricines is the *cis*-1-azadecalin AB ring bearing an C(2)-alkyl side chain linked to the diverse C-ring.

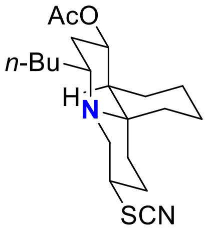


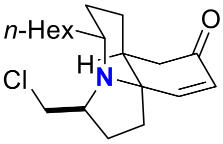
R^1 = Cl: Cylindricine A (**4.3**)
R^1 = OH: Cylindricine C (**4.5**)
R^1 = OMe: Cylindricine D (**4.6**)
R^1 = OAc: Cylindricine E (**4.7**)
R^1 = SCN: Cylindricine F (**4.8**)

4.3'

Cylindricine B (**4.4**)







R^1 = SCN, R^2 = R^3 = O: Cylindricine G (**4.9**)
R^1 = SCN, R^2 = OAc, R^3 = H: Cylindricine H (**4.10**)
R^1 = NCS, R^2 = OAc, R^3 = H: Cylindricine I (**4.11**)

Cylindricine J (**4.12**)

Cylindricine K (**4.13**)

Figure 4.2. The chemical structure of cylindricines.

Lepadiformine A (**4.14**) was collected from the ascidian *Clavelina lepadiformis* by Biard and co-workers in 1994 (Figure 4.3).[5] The exact structure of lepadiformine A (**4.14**) was determined by the first total synthesis of (±)-lepadiformine A (**4.14**) by Kibayashi and co-workers.[6] Ensuing asymmetric syntheses of (−)-lepadiformine A (**4.14**) confirmed its absolute configuration.[7] This tricyclic alkaloid possesses the unusual twist boat−chair *trans*-1-azadecalin AB-ring connected with the C(13)-hydroxymethylated C-ring similar to cylindricine C (**4.5**) while they differ in the conformation of 1-azadecalin AB ring as well as the oxidation state at C(4). In 2006, its structural analogues, lepadiformine B (**4.15**) and C (**4.16**) were found from *C. moluccensis* by Sauviat and co-workers.[8] The absolute configuration of (−)-lepadiformine B (**4.15**) was proved by the Rychnovsky's asymmetric synthesis of (−)-**4.15** in 2012.[9] For the absolute configuration of lepadiformine C (**4.16**), its optical rotation was opposite to that of lepadiformine A (**4.14**) and B (**4.15**) based on asymmetric synthesis of (+)-**4.16** by Morimoto and co-workers.[10] Lepadiformines (**4.14**-**4.16**) showed potent antiarrhythmic character as well as moderate cytotoxicity against various tumor cell lines.[11]

R = *n*-Hex: (–)-Lepadiformine A (**4.14**)
R = *n*-Bu: (–)-lepadiformine B (**4.15**)

(+)-Lepadiformine C (**4.16**)

Figure 4.3. The chemical structure of lepadiformines.

Fasicularin (**4.17**) was discovered in the ascidian *Nephteis fasicularis* by Patil and co-workers in 1997 (Figure 4.4).[12] The structure of fasicularin (**4.17**) was elucidated by the NMR analyses that showed the perhydropyrido[2,1-j]quinoline ABC tricycle including a *trans*-1-azadecalin AB ring analogous to that of lepadiformine A (**4.14**) but its C(2)-epimer. However the absolute configuration of natural one remains uncertain. Fasicularin (**4.17**) has unique biological activities as an alkylating agent toward a cellular DNA (Figure 4.4).[13] DNA alkylation using fasicularin (**4.17**) would involve the extrusion of thiocyanate anion to form aziridinium ion **4.18**, which was trapped by the guanine residues in DNA for the production of N(7)-guanine adduct **4.19**. Finally, strand scission of **4.19** would form the alkylated guanine fragment **4.20**.

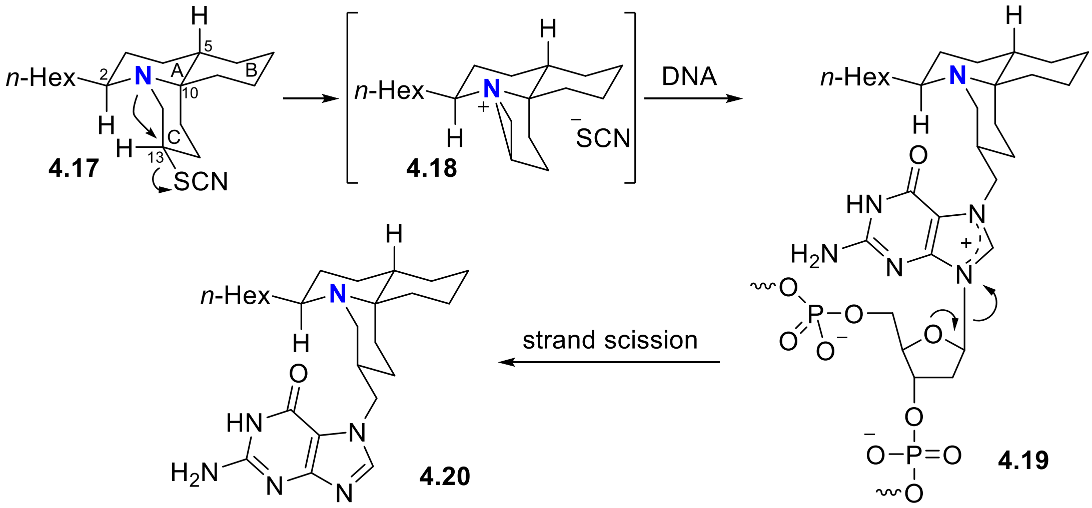
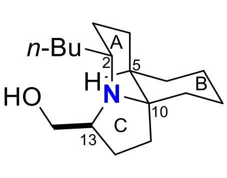
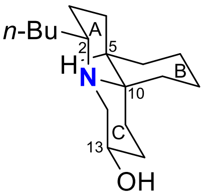


Figure 4.4. The chemical structure of fasicularin and its DNA-alkylation ability.

New congeners of tricyclic alkaloids, polycitorols (**4.21-22**) were recently obtained from a marine ascidian of the family *Polycitoridae* (Figure 4.5).[14] Their structures include *cis*-1-azadecalin AB units similar to cylindricines whereas the C(4)-carbonyl functionality does not exist in polycitorols. The Kim's first syntheses of polycitorols identified that the NMR spectroscopic data of the synthetic products were not matched with those of the natural samples,[15] which indicated that the assigned structures of the natural polycitorols are incorrect. Biological activity of polycitorols has not been investigated yet.



Polycitorol A (**4.21**)



Polycitorol B (**4.22**)

Figure 4.5. The chemical structure of polycitorols.

4.2. Total syntheses of fasicularin

Challenges in the syntheses of tricyclic alkaloids are stereoselective installation of fully substituted carbon center at C(10) and the alkyl side chain at C(2) in the 1-azadecalin AB ring. Their unique structures stimulated numerous synthetic chemists to approach the tricyclic alkaloids over the past two decades, which have been comprehensively reviewed.[16] Specifically, the useful biological activity of fasicularin (**4.17**) has aroused attention to pursue its synthesis. In this chapter, syntheses of fasicularin (**4.17**) will be discussed by categorizing three strategies based on the key bicyclic intermediates, namely azaspirocycle (BC ring) and azadecalin (AB ring) and indolizidine (AC ring) approaches in chronological order.

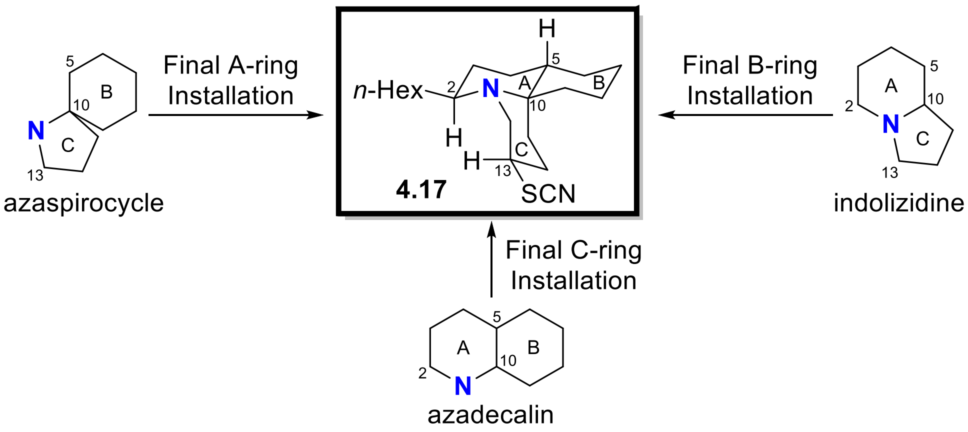
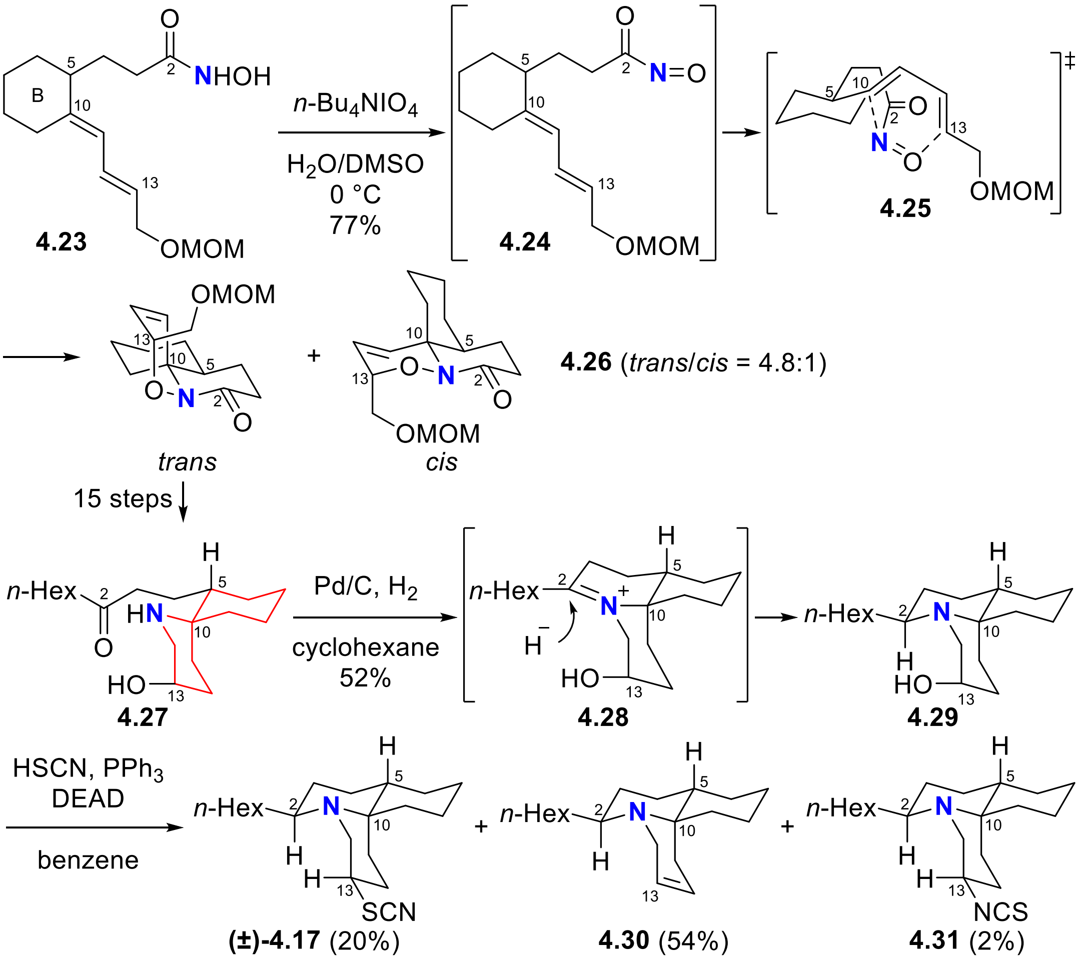


Figure 4.6. Strategies toward the synthesis of fasicularin.

4.2.1. Azaspirocycle (BC ring) approaches

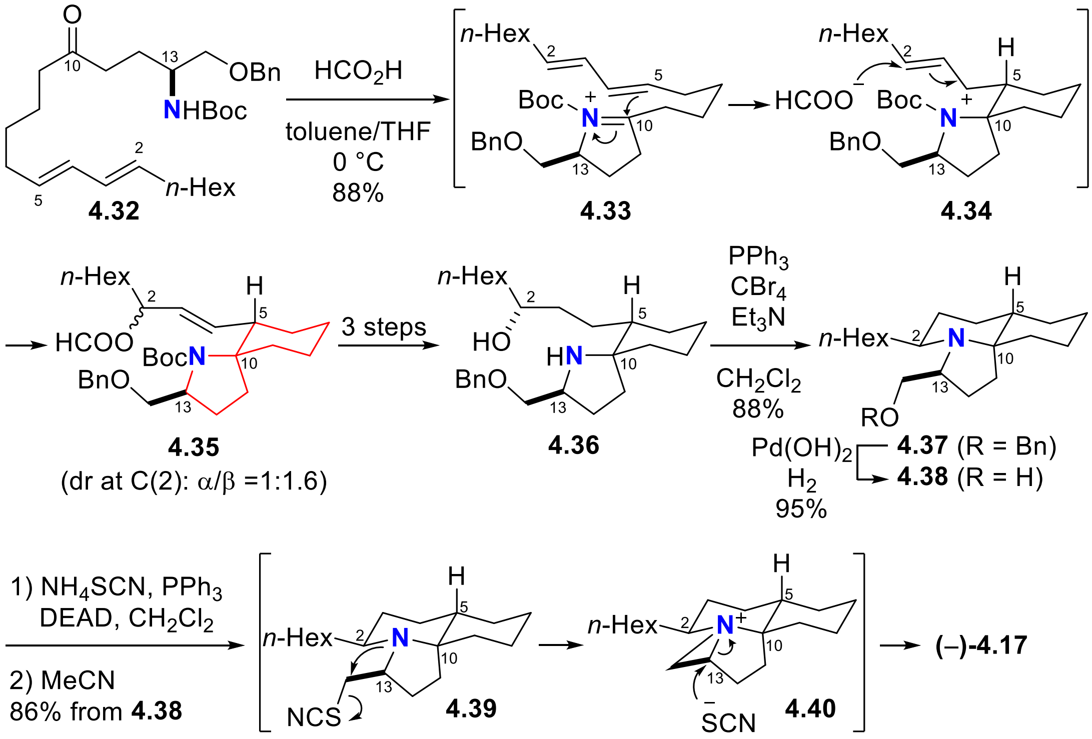
4.2.1.1. Kibayashi's synthesis

Kibayashi and co-workers achieved the first total synthesis of (±)-fasicularin [(±)-**4.17**] in 2000 (Scheme 4.1).[6] Their synthesis was stemmed from the intramolecular [4+2]-cycloaddition of an *N*-acylnitroso compound for the construction of the fully substituted carbon center at C(10). The key Diels-Alder reaction was initiated by the oxidation of a hydroxamic acid **4.23** with tetrabutylammonium periodate in aqueous DMSO to generate an acyl nitroso compound **4.24** *in situ*, which underwent cycloaddition via transition state **4.25** to afford the tricyclic lactam **4.26** as a *trans*/*cis* mixture (*trans*/*cis* = 4.8:1). The two diastereomers were separable and *trans*-**4.26** was converted to a bicyclic ketone **4.27** in 15 steps. Catalytic hydrogenation of the ketone **4.27** in cyclohexane formed an iminium species **4.28** *in situ*. Ensuing hydride reduction of the iminium **4.28** proceeded from the α-face at the C(2) position induced by the directing effect of the C(13)-hydroxyl group to deliver the tricycle **4.29**. Finally, **4.29** was converted to (±)-fasicularin [(±)-**4.17**] in 20% yield by Mitsunobu reaction with thiocyano acid along with the formation of the elimination product **4.30** and the isothiocyanate **4.31** in 54% and 2% yields, respectively.



Scheme 4.1. Kibayashi's total synthesis of (±)-fasicularin.

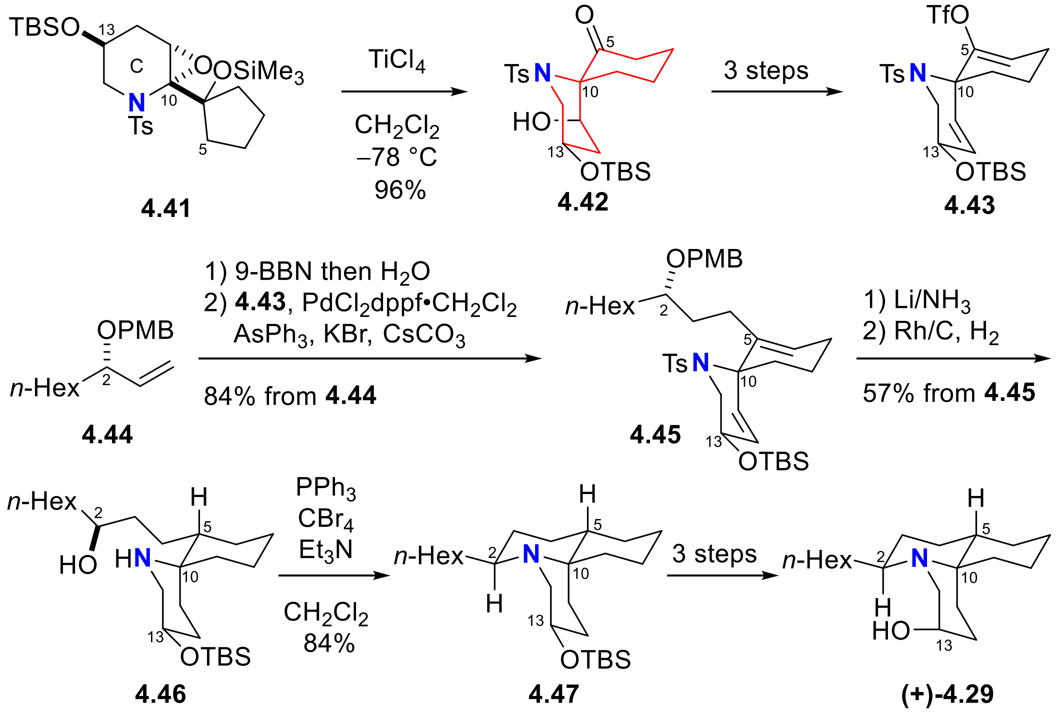
In 2005, the same research group demonstrated the first enantioselective total synthesis of (−)-fasicularin [(−)-**4.17**] by utilizing the conjugate azaspirocyclization of *N*-acyliminium ion as a new strategy (Scheme 4.2).[4b] The *N*-acyliminium ion **4.33** was prepared by the treatment of a ketoamide **4.32** having a conjugated diene in the presence of formic acid. The key azaspirocyclization of the iminium **4.33** took place from the opposite site to the benzyloxymethyl group at C(13) to generate the allyl cation **4.34**, which was trapped by formate ion to give the azaspirocycle **4.35**. The formate **4.35** was transformed to the alcohol **4.36** in 3 steps. Exposure of **4.36** under the cyclodehydration condition with PPh_3/CBr_4 led the C-ring closure to yield the tricycle **4.37**. After debenzylation of **4.37**, the resulting tricycle **4.38** was subjected to Mitsunobu reaction conditions using ammonium thiocyanate to generate **4.39**, which further underwent the ring expansion of pyrrolidine C-ring via aziridinium ion intermediate **4.40** for the completion of the total synthesis of (−)-fasicularin [(−)-**4.17**] in excellent yield.



Scheme 4.2. Kibayashi's total synthesis of (−)-fasicularin.

4.2.1.2. Dake's synthesis

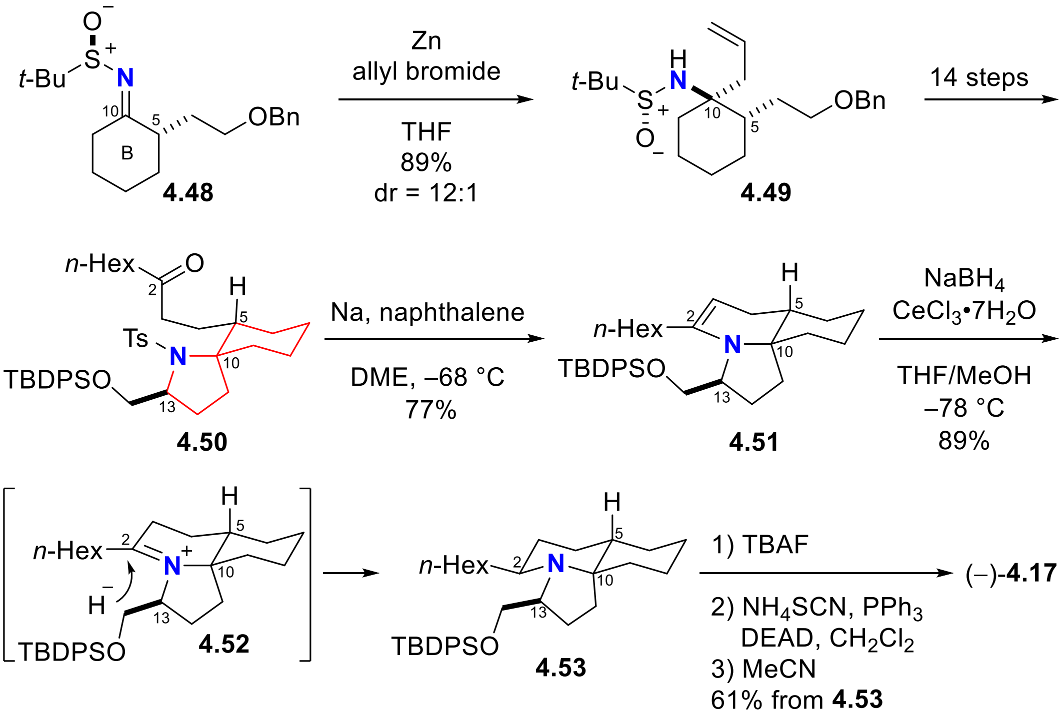
Dake and Fenster reported the formal synthesis of (+)-fasicularin [(+)-**4.17**] based on azaspirocyclic BC ring strategy (Scheme 4.3).[17] Their synthesis relied on the semipinacol rearrangement of an epoxide **4.41** in the presence of $TiCl_4$ to construct the azaspirocycle **4.42** as a single diastereomer. After the conversion of **4.42** to the enol triflate **4.43** in 3 steps, a sequence of hydroboration of an alkene **4.44** followed by palladium-catalyzed cross coupling with the triflate **4.43** under the Johnson's reaction conditions delivered the diene **4.45**.[18] Reductive removal of the *para*-toluenesulfonyl and *para*-methoxybenzyl groups in **4.45**, and subsequent stereoselective hydrogenation of the diene afforded the azaspirocycle **4.46** in a diastereoselective manner. Conversion of **4.46** to the Kibayashi intermediate (+)-**4.29** was achieved by cyclocondensation of **4.46** under Kibayashi's prorocol,[6] followed by the stereochemical adjustment at C(13) of tricycle **4.47** in 3 steps.



Scheme 4.3. Dake's formal synthesis of (+)-fasicularin.

4.2.1.3. Zhao's synthesis

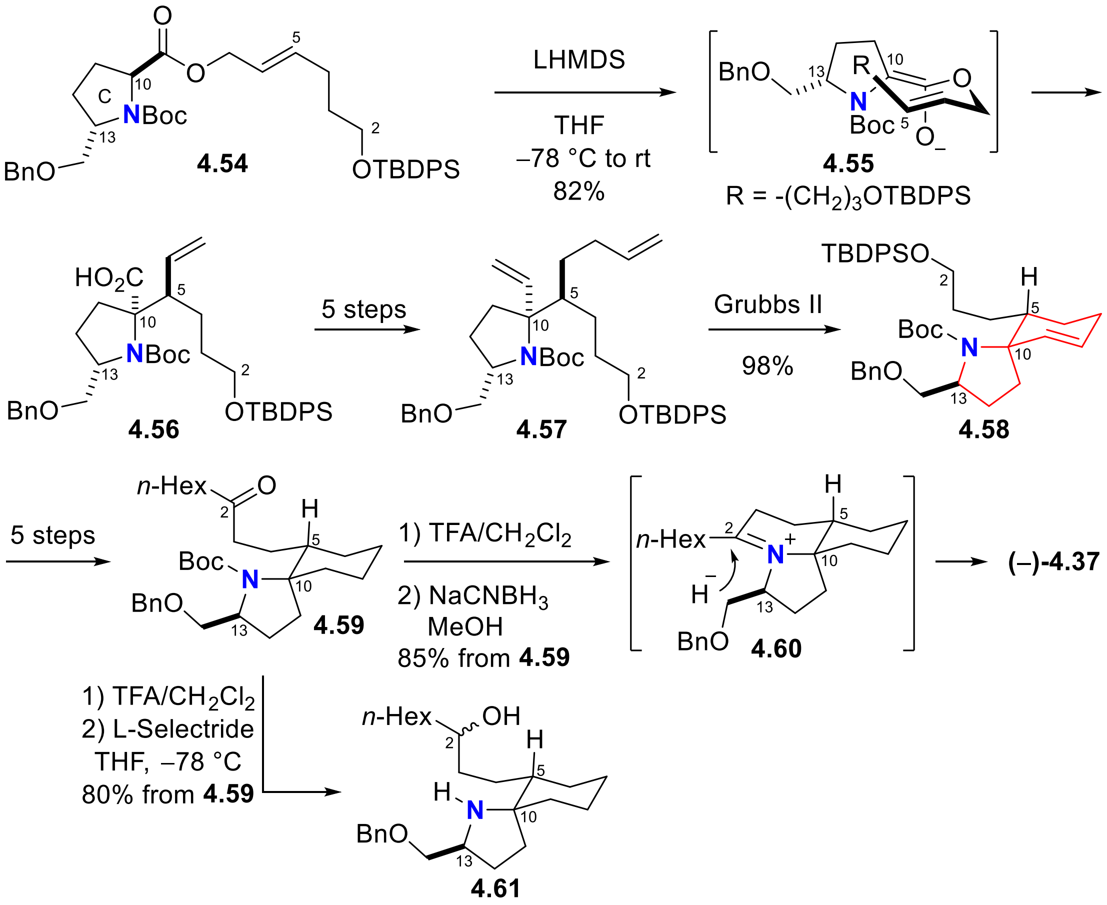
In 2010, Zhao and Mei employed the zinc-mediated allylation of chiral sulfinimines for the stereoselective installation of the C(10)-fully substituted carbon center in their synthesis of (−)-fasicularin [(−)-**4.17**] (Scheme 4.4).[19] The reaction of a chiral *N*-*tert*-butanesulfinylimine **4.48** with an allyl zinc nucleophile provided the sulfinamide **4.49** having a fully substituted carbon center at C(10) in excellent diastereoselectivity (dr = 12:1). Upon derivatization of the sulfinamide **4.49** to a key azaspirocycle **4.50** in 14 steps, desulfonylative A-ring closure of **4.50** formed the enamine **4.51**. Subsequent C(2)α-selective reduction of the iminium **4.52** generated *in situ* under the Luche conditions produced the tricycle **4.53**. This stereochemical outcome could be explained by the stereoelectronic principle in which the nitrogen lone pair prefers to be located *anti*-coplanar relationship with the installed C-H bond in **4.53**.[20] Finally, the removal of TBDPS group in **4.53** followed by the Mitsunobu reaction according to the Kibayashi protocol afforded (−)-fasicularin [(−)-**4.17**].[6]



Scheme 4.4. Zhao's total synthesis of (−)-fasicularin.

4.2.1.4. Kim's synthesis

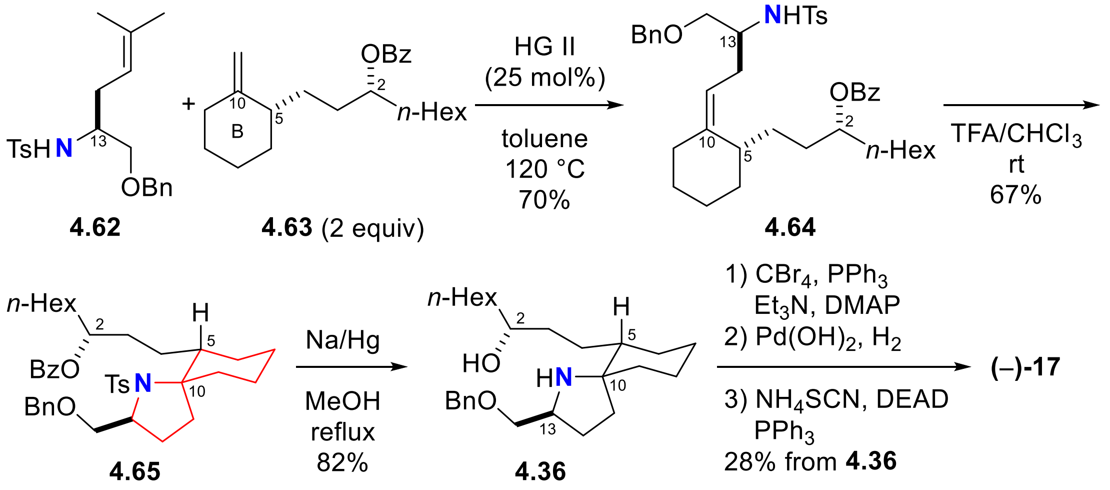
Kim and co-workers achieved the formal synthesis of (−)-fasicularin [(−)-**4.17**] using the Claisen rearrangement of an ester enolate (Scheme 4.5).[15] The treatment of an amino acid ester **4.54** with LHMDS generated the key (*E*)-enolate **4.55** to avoid the steric repulsion between the *N*-Boc group and the alkyl side chain at C(13). The Claisen rearrangement of the enolate **4.55** resulted in the formation of the rearrangement product **4.56** bearing a fully substituted carbon center at C(10). After 5-step conversion of the amino acid **4.56** to a diene **4.57**, the ring closing metathesis of the diene **4.57** using Grubbs 2nd generation catalyst furnished the azaspirocycle **4.58** in 98% yield. The azaspirocycle **4.58** was then transformed into a ketone **4.59** in 5 steps. Finally, acidic treatment of the ketone **4.59** followed by α-face selective hydride reduction of the iminium salt **4.60** afforded the Kibayashi intermediate (−)-**4.37**.[4b] On the other hand, the use of L-selectride as a bulky hydride reductant failed to reduce the iminium **4.60** whereas the secondary alcohol **4.61** was obtained in 80% yield probably via the reduction of the ketone **4.59** generated by *in situ* hydrolysis of **4.60** during the second step.



Scheme 4.5. Kim's formal synthesis of (−)-fasicularin.

4.2.1.5. Robinson's synthesis

Robinson and co-workers demonstrated the use of olefin cross-metathesis reaction for the synthesis of (−)-fasicularin [(−)-**4.17**] in 2017 (Scheme 4.6).[21] The olefin metathesis between a sterically hindered tri-substituted alkenyl amine **4.62** and an *exo*-cyclic alkene **4.63** with the Hoveyda-Grubbs 2nd generation catalyst afforded the metathesized alkene **4.64**. The key azaspirocycle **4.65** was constructed by the TFA-promoted 5-*endo*-trig spirocyclization of **4.64** in a diastereoselective fashion. After the concomitant removal of the *N*-tosyl and *O*-benzoyl groups, the amino alcohol **4.36** was subjected to the modified Kibayashi cyclodehydration condition,[19] followed by the Mitsunobu reaction to provide (−)-fasicularin [(−)-**4.17**].[4b]

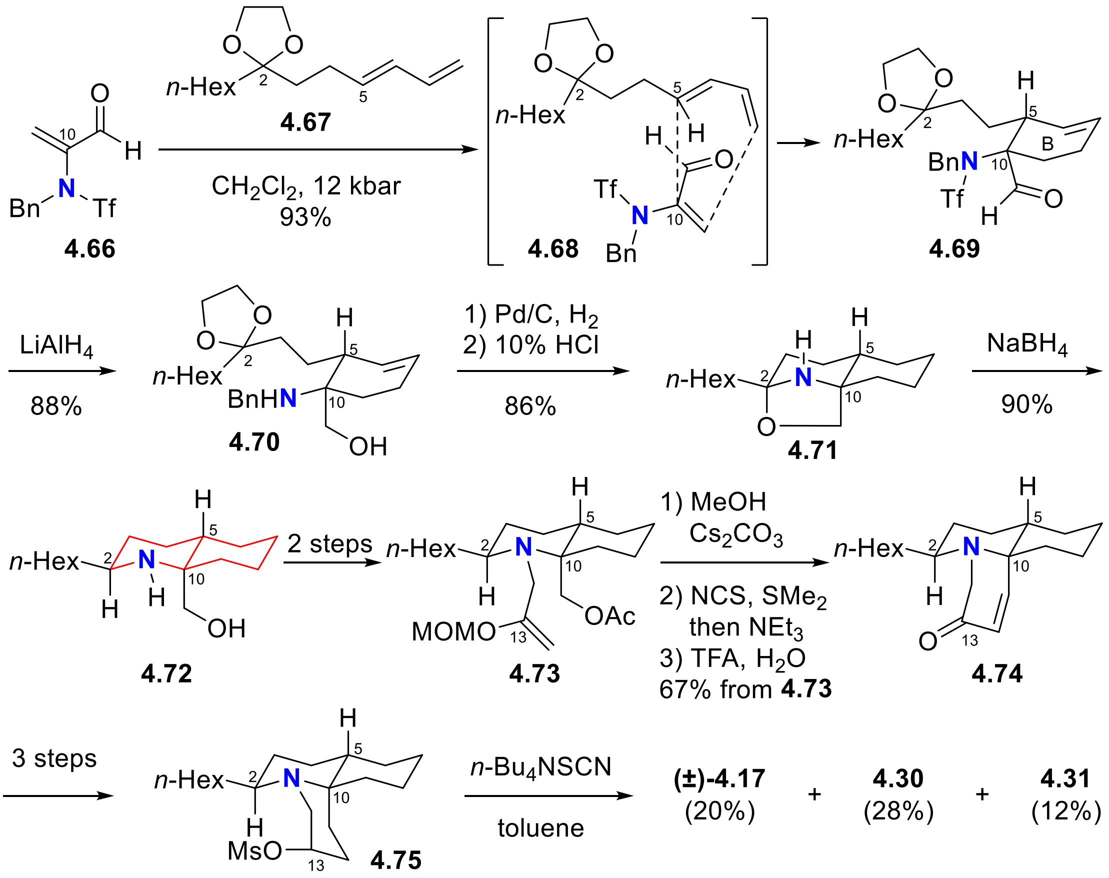


Scheme 4.6. Robinson's total synthesis of (−)-fasicularin.

4.2.2. Azadecalin (AB ring) approaches

4.2.2.1. Funk's synthesis

Funk and Maeng established the azadecalin approach for the synthesis of (±)-fasicularin [(±)-**4.17**] in 2002 (Scheme 4.7).[22] Their synthesis was based on the Diels-Alder reaction of an amidoacrolein **4.66** with a diene **4.67** having a hexyl side chain. The [4+2] annulation of the dienophile **4.66** and the diene **4.67** under high-pressure (12 kbar) resulted in the exclusive formation of the cycloadduct **4.69** via the *endo*-transition state **4.68**. Subsequent $LiAlH_4$ reduction of the aldehyde **4.69** and concomitant removal of the trifluoromethanesulfonyl group provided the aminoalcohol **4.70**. The aminoalcohol **4.70** was derivatized to a tricyclic oxazolidine **4.71** by alkene hydrogenation followed by acidic hydrolysis. Stereoselective hydride reduction of the oxazolidine **4.71** with $NaBH_4$ delivered the *trans*-azadecalin **4.72** via α-hydride attack at C(2). After the *N*-allylation of **4.72** in two steps, a three step sequence of 1) transesterification of the acetate **4.73** to the corresponding alcohol, 2) oxidation under Corey-Kim condition to the aldehyde, 3) TFA-mediated hydrolysis of methoxymethyl group and aldol condensation, afforded the tricycle **4.74**. Upon transformation of the enone **4.74** to a mesylate **4.75** in three steps, nucleophilic substitution of **4.75** with tetrabutylammonium thiocyanate furnished (±)-fasicularin [**(±)-4.17**] (20%), the alkene **4.30** (28%) and the isocyanate **4.31** (12%) similar to the result in Kibayashi's 1st generation synthesis of (±)-fasicularin [**(±)-4.17**] (Scheme 4.1).[6]

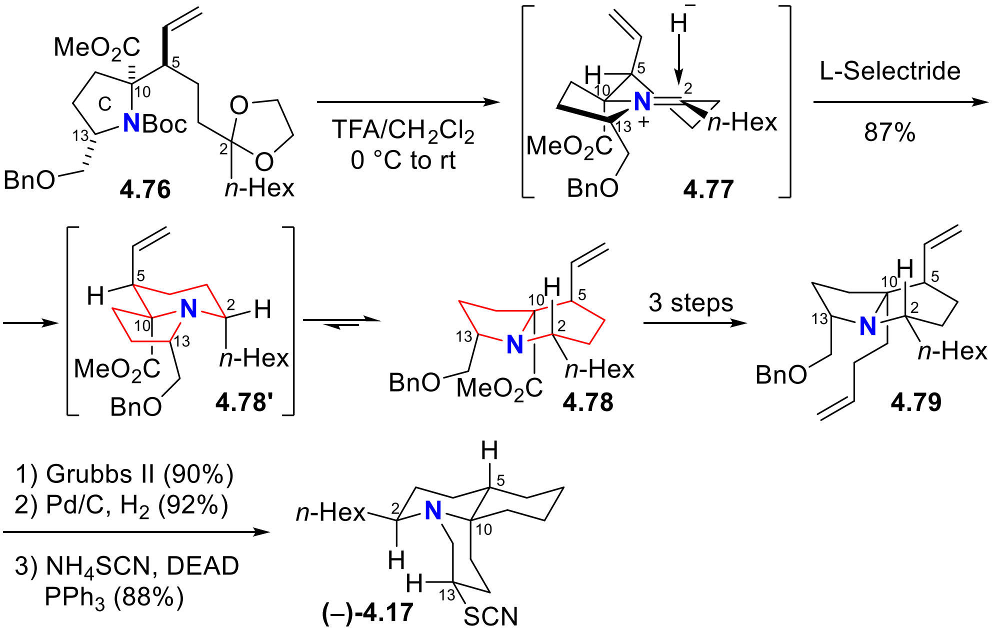


Scheme 4.7. Funk's total synthesis of (±)-fasicularin.

4.2.3. Indolizidine (AC ring) approaches

4.2.3.1. Kim's synthesis

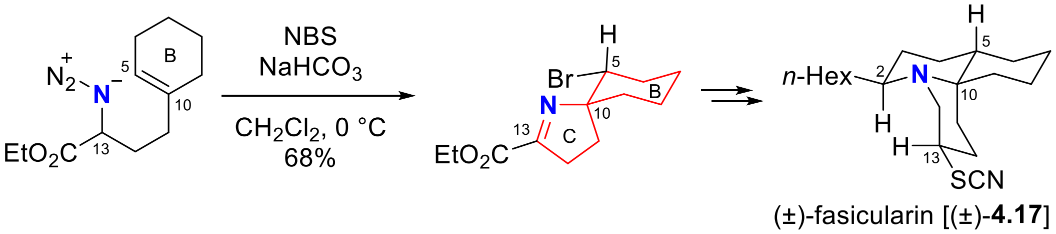
Kim and co-workers developed a novel strategy for the total synthesis of (−)-fasicularin [(−)-**4.17**] based on the construction of the key indolizidine as their 2nd generation synthesis of (−)-**4.17** (Scheme 4.8).[15] Their updated approach made use of the stereoselective reduction of a bicyclic iminium ion. The iminium salt **4.77** was prepared by the treatment of **4.76** with TFA via concomitant removal of the acetal and Boc groups followed by cyclocondensation. Subsequent hydride reduction of the iminium **4.77** by bulky L-selectride led to the formation of chair-**4.78'** as a major isomer, which was inverted to the more stable boat-**4.78**. This unusual stereoselection using a bulky reducing agent would be attributed to β-hydride attack at C(2) to avoid steric repulsion between the reductant and the methoxycarbonyl group at C(10). After homologation of the ester **4.78** to a homoallyl derivative **4.79**, a sequence of 1) ring-closing metathesis, 2) hydrogenolysis, and 3) Mitsunobu reaction under the Kibayashi's condition provided (−)-fasicularin [(−)-**4.17**].[4b]



Scheme 4.8. Kim's total synthesis of (−)-fasicularin.

4.3. Perspective for the Chapter 5

This chapter discussed the previous syntheses of fasicularin (**4.17**) according to the classification of the key azabicyclic intermediates. Especially, a synthetic strategy via azaspirobicyclic BC ring intermediates have been the most frequent approach in the synthesis of fasicularin (**4.17**) as well as other tricyclic alkaloids.[16] In this respect, Chapter 5 describes our original approach for the construction of azaspirocyclic BC ring by NBS-induced bromoamination of alkenyl azidoester.[23] The key azaspirocycle can be converted to (±)-fasicularin [(±)-**4.17**] including stereoselective installation of hexyl side chain at C(2) (Scheme 4.9). Synthetic efforts on another tricyclic alkaloid, (±)-lepadiformine A [(±)-**4.14**], via a common synthetic intermediate are also discussed.



Scheme 4.9. Synthesis of (±)-fasicularin via bromoamination of alkenyl azidoester.

4.4. References

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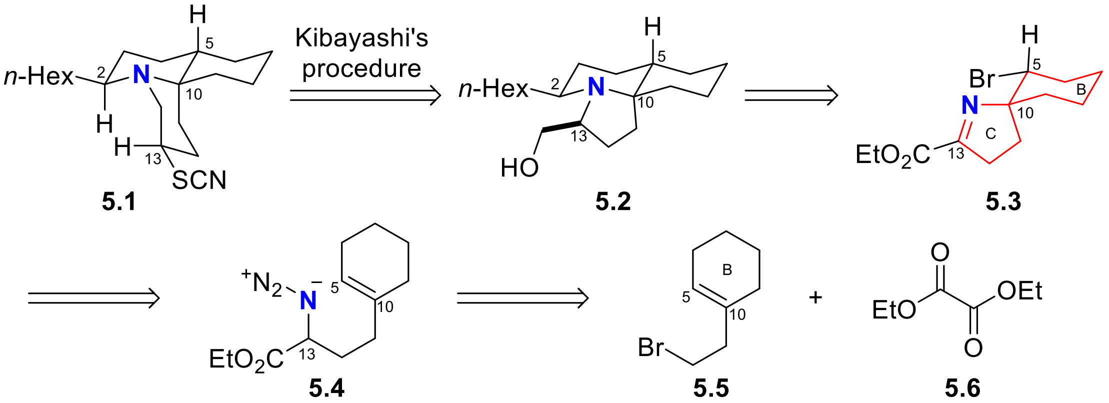
Chapter 5: Synthesis of tricyclic marine alkaloid, fasicularin

5.1. Retrosynthetic analysis

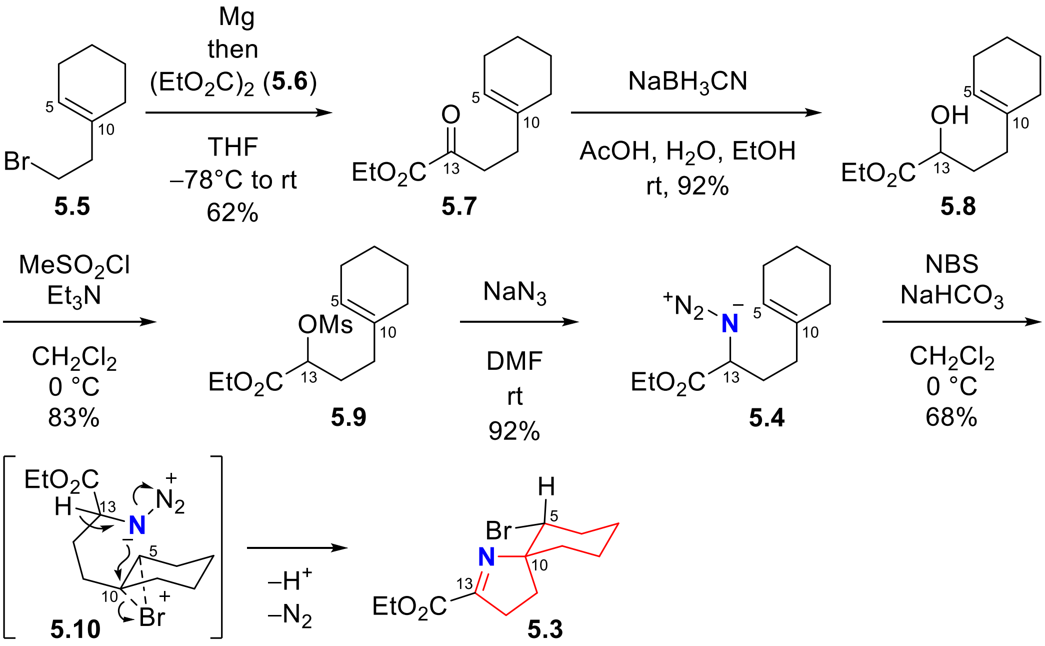
Our retrosynthetic analysis of fasicularin (**5.1**) is shown in Scheme 5.1. On the basis of the aforementioned Kibayashi's 2nd generation synthesis of (−)-fasicularin (**5.1**) (Scheme 4.2),[1] fasicularin (**5.1**) would be prepared from C2-*epi*-lepadiformine A (**5.2**). We envisioned that the tricycle **5.2** would be constructed via an azaspirocyclic BC ring **5.3**, the C(10)-N bond of which is *trans*-relationship to C(5)-bromo substituent. For the synthesis of the key azaspirocycle, spirocyclizing bromoamination of an alkenyl α-azido ester **5.4** would be employed.[2] The starting alkenyl azide **5.4** would be elaborated from 1-(2-bromoethyl)cyclohexene (**5.5**)[3] and diethyl oxalate (**5.6**).



Scheme 5.1. Retrosynthetic analysis of (±)-fasicularin.

5.2. Diastereoselective bromoamination of an alkenyl azide for construction of azaspirocyclic BC-ring

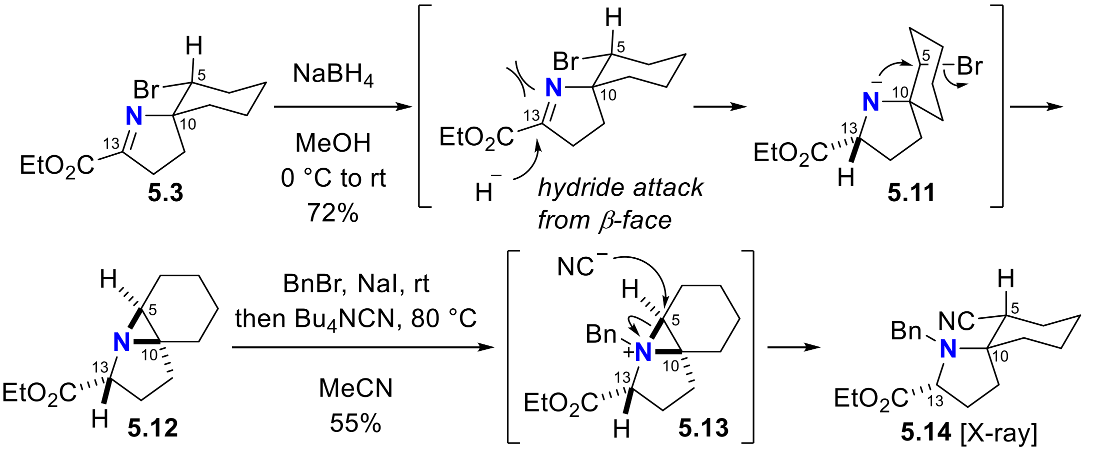
The construction of the key azaspirocyclic BC ring is illustrated in Scheme 5.2. Our investigation began with the nucleophilic addition of a Grignard reagent generated from 1-(2-bromoethyl)cyclohexene (**5.5**) onto diethyl oxalate (**5.6**) for the preparation of the α-keto ester **5.7**. The α-keto ester **5.7** was transformed to the azide **5.4** in three steps via hydride reduction of the keto carbonyl group in **5.7**, *O*-mesylation of the resulting alcohol **5.8**, and substitution of the corresponding mesylate **5.9** with NaN_3. The key bromoamination of the α-azido ester **5.4** was promoted by the employment of NBS in the presence of $NaHCO_3$ via formation of a bromonium ion **5.10**, affording a single diastereomer of the azaspirocyclic BC ring **5.3**, whose C(5) bromo substituent was *trans* relative to a C(10)-N bond.



Scheme 5.2. Construction of azaspirocycle **5.3** through the aminobromination of α-azido ester **5.4**.

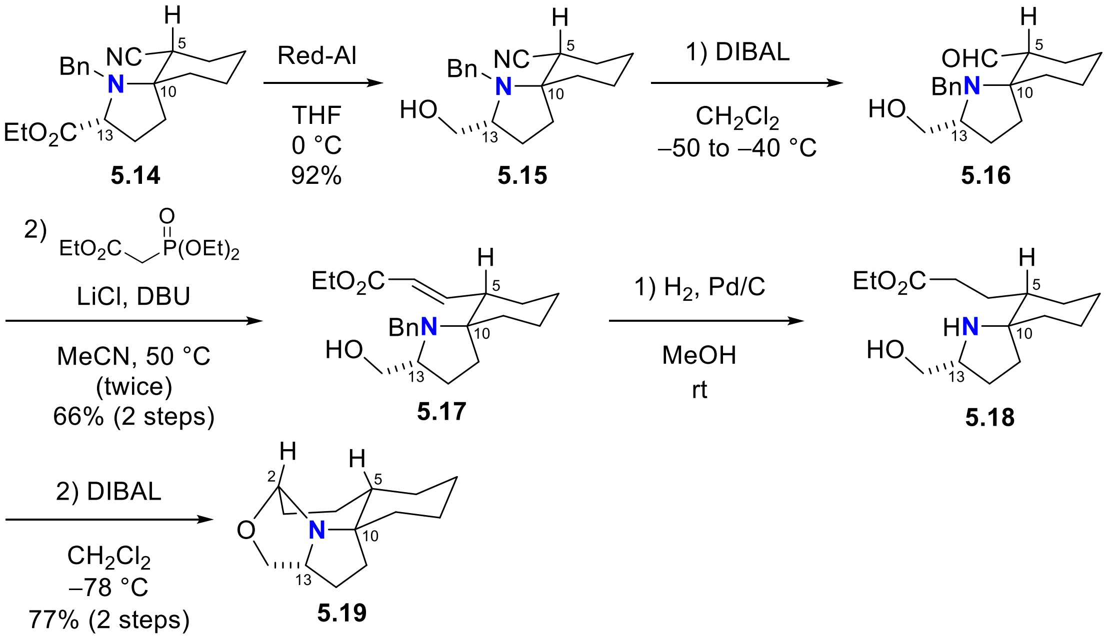
5.3. Synthesis of tetracyclic *N,O*-acetal

The spirocyclic iminoester **5.3** was converted into a tricyclic aziridine **5.12** by β-selective reduction of the imine moiety using $NaBH_4$ and ensuing intramolecular nucleophilic substitution in the intermediate **5.11**.[4] This stereoselective hydride reduction for the generation of **5.11** is attributed to the smaller steric hindrance of the β-face of the C=N bond in **5.3**. In order to install the C(5)-carbon functionality, we next attempted ring-opening of the aziridine **5.12** by a carbon nucleophile.[5] The reaction of **5.12** with *in situ* generated benzyl iodide formed the *N*-benzyl aziridinium salt **5.13**, which was subsequently treated with Bu_4NCN for regio- and stereoselective ring-opening of the aziridinium ion **5.13** at the C(5) position, giving the azaspirocycle **5.14** having the C(5)-α-cyano group, the structure of which was secured by X-ray crystallographic analysis.



Scheme 5.3. Synthesis of azaspirocycle **5.14**.

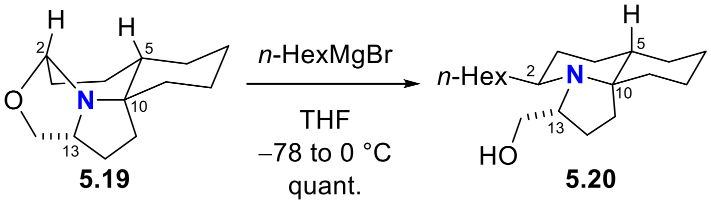
Having succeeded in the synthesis of the azaspirocyclic BC ring **5.14**, we next turned our attention to the construction of the A ring. The reaction of **5.14** with Red-Al provided the alcohol **5.15** via chemoselective reduction of the ethoxycarbonyl group in the presence of the cyano group (Scheme 5.4).[6] The alcohol **5.15** was further transformed to an α,β-unsaturated ester **5.17** through a two-step sequence involving reduction of the cyano group to the formyl group using DIBAL followed by the Horner-Wadsworth-Emmons reaction of the aldehyde **5.16** with triethyl phosphonoacetate under the Masamune-Roush conditions.[7] After hydrogenation of the alkene and concomitant removal of the *N*-benzyl group in **5.17**, the resulting amino alcohol **5.18** was carefully treated with DIBAL at −78 °C to reduce the ester, delivering the tetracyclic *N*,*O*-acetal **5.19** having the A ring.



Scheme 5.4. Synthesis of tetracyclic *N*,*O*-acetal **5.19**.

5.4. Stereoselective alkylation of *N*,*O*-acetal

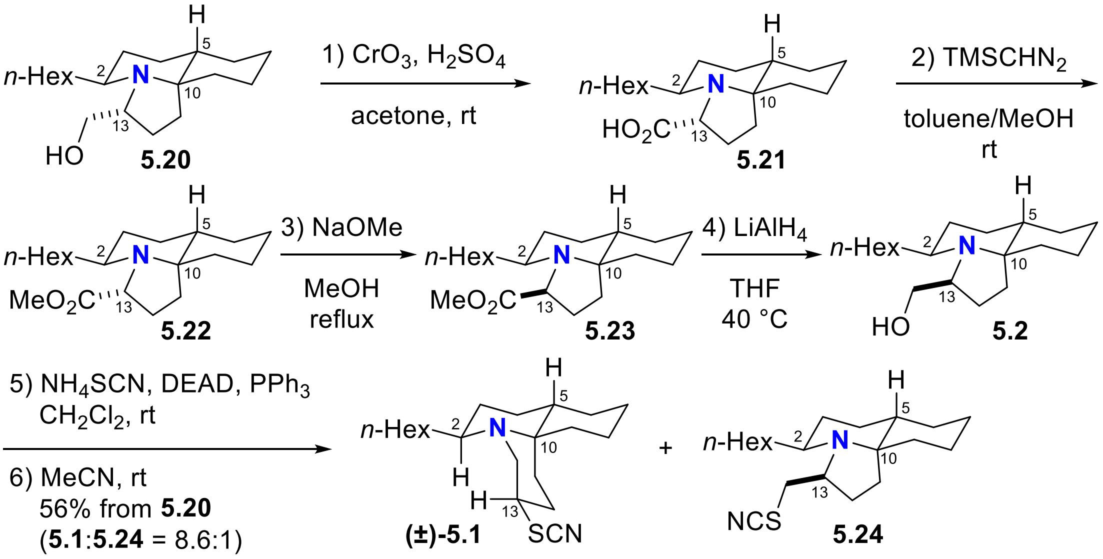
With the *N*,*O*-acetal **5.19** in hand, the stage was set for the stereoselective installation of a hexyl side chain at C(2). The desired β-hexyl group at C(2) was completed by the treatment of the *N*,*O*-acetal **5.19** with hexylmagnesium bromide to afford the alcohol **5.20** in quantitative yield (Scheme 5.5). The stereoselective alkylation of the *N*,*O*-acetal **5.19** presumably involves S_N2-like displacement of **5.19** by the alkyl nucleophile.



Scheme 5.5. Stereoselective alkylation of *N*,*O*-acetal.

5.5. Completion of the synthesis of fasicularin

For the total synthesis of fasicularin (**5.1**), the stereochemical configuration of C(13) was adjusted by a four-step sequence through 1) the Jones oxidation of **5.20**; 2) esterification of **5.21** using trimethylsilyl diazomethane to **5.22**; 3) base-mediated epimerization of **5.22**; 4) $LiAlH_4$-reduction of the methoxycarbonyl group in **5.23** to yield C(2)-*epi*-lepadiformine A (**5.2**) (Scheme 5.6). Finally, the treatment of the alcohol **5.2** under the Kibayashi's protocol provided (±)-fasicularin (**5.1**) along with the generation of its structural isomer **5.24**.[1] The spectroscopic data (^{1}H, ^{13}C NMR, and MS) of our synthetic sample were identical with those of the reported one.[1]



Scheme 5.6. Total synthesis of (±)-fasicularin (**5.1**).

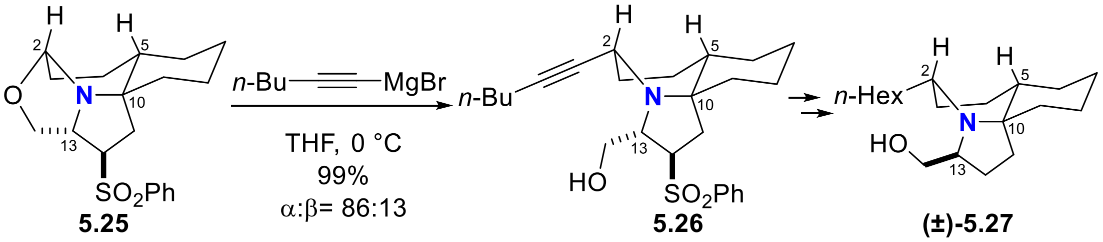
5.6. Attempts for the synthesis of lepadiformine A

5.6.1. Stereoselective alkynylation of *N*,*O*-acetal

As a key strategy in the synthesis of (±)-lepadiformine A (**5.27**) by Craig and Caldwell, the alkynylation of a sulfone-containing *N*,*O*-acetal **5.25** with a 1-hexynyl Grignard reagent furnished the alcohol **5.26** having a *α*-hexynyl side chain (Scheme 5.7a).[8] This α-selective alkynylation presumably involved S_N1-like ring opening of

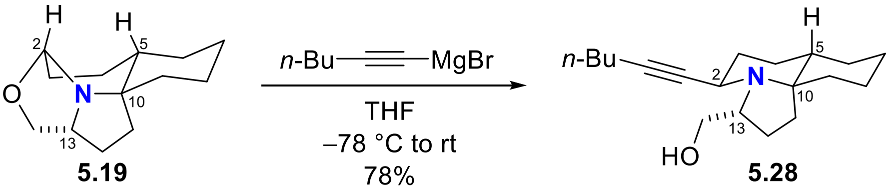
5.25 by less-sterically hindered alkynyl Grignard reagent as a predominant mechanism. Stimulated by this observation, we examined the alkynylation of *N*,*O*-acetal **5.19**. In contrast to the Craig's result (Scheme 5.7a), the addition of 1-hexynyl Grignard reagent to the *N*,*O*-acetal **5.19** resulted in the exclusive formation of the β-alkynylated alcohol **5.28**, which corresponds to the same diastereodirection with the alkylation of the *N*,*O*-acetal (Scheme 5.5). These results indicated that the presence of sulfonyl group might be crucial to achieve α-selective alkynylation of *N*,*O*-acetal.

a) Alkynylation of sulfone-containing *N*,*O*-acetal **5.25** by Craig *et al.* (ref 8)



5.25 **5.26** **(±)-5.27**

b) Alkynylation of *N*,*O*-acetal **5.19**



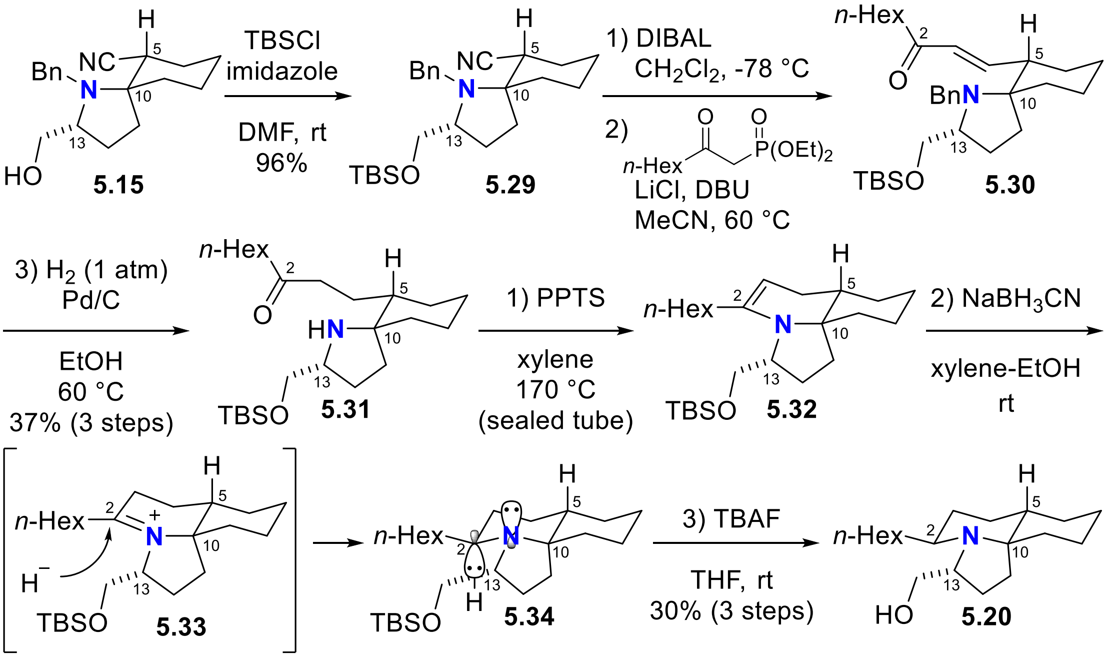
5.19 **5.28**

Scheme 5.7. Stereoselective alkynylation of *N,O*-acetals.

5.6.2. Stereoselective hydride reduction of tricyclic enamine

For the installation of the α-hexyl side chain at the C2 position toward synthesis of (±)-lepadiformine A (**5.27**), we next surveyed the feasibility of stereoselective hydride reduction of a tricyclic enamine **5.32**. The preparation of the tricyclic enamine **5.32** was initiated by the TBS-protection of the hydroxyl group in **5.15** to the silyl ether **5.29** (Scheme 5.8). Further conversion of **5.29** to an amino ketone **5.31** was accomplished by reduction of the cyano group in **5.29** using DIBAL, the

Horner-Wadsworth-Emmons reaction of the corresponding aldehyde to the α,β-unsaturated ketone **5.30**, and ensuing hydrogenation of the alkene and simultaneous removal of the *N*-benzyl group. The treatment of the amino ketone **5.31** in the presence of PPTS at 170 °C in *o*-xylene enabled the formation of the highly strained cyclic enamine **5.32**. With the cyclic enamine **5.32** in hand, stereoselective hydride reduction of **5.32** was attempted. The treatment of enamine **5.32** with $NaBH_3CN$ resulted in α-selective hydride reduction of the iminium **5.33** to provide the amino ether **5.34** bearing the β-hexyl group as a single diastereomer, which was converted to **5.20** via deprotection of the TBS group. This stereochemical outcome might be originated from the stereoelectronic principle in which the nitrogen lone pair favors to be located in *anti*-coplanar relationship with the installed C-H bond in **5.34**.[9]

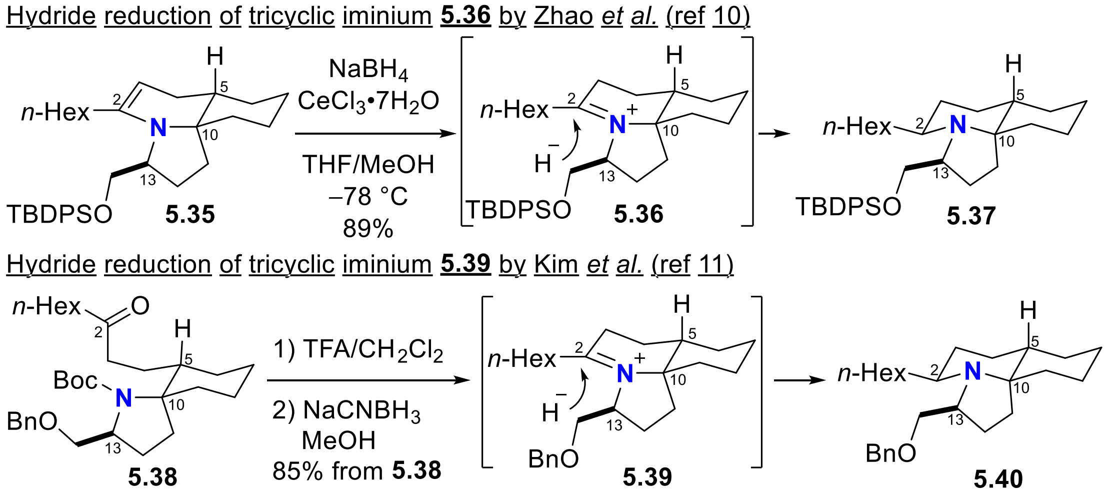


Hydride attack from α-face

Scheme 5.8. Diastereoselective hydride reduction of cyclic enamine **5.32**.

To install the α-hexyl side chain at C(2) for the synthesis of lepadiformine A (**5.27**), the same strategy utilizing stereoselective hydride reduction of tricyclic iminium ions **5.36** or **5.39** has also been examined by the groups of Zhao or Kim, respectively.[10,11]

However, their attempts also resulted in the α-selective hydride reduction of tricyclic iminium **5.36** or **5.39** to deliver the amino ether **5.37** or **5.40** having β-hexyl side chain.

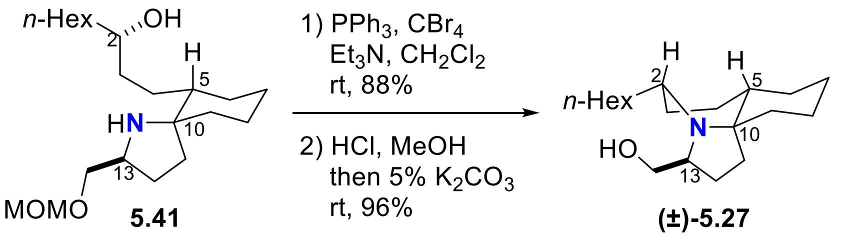

Hydride reduction of tricyclic iminium **5.36** by Zhao *et al.* (ref 10)

Hydride reduction of tricyclic iminium **5.39** by Kim *et al.* (ref 11)

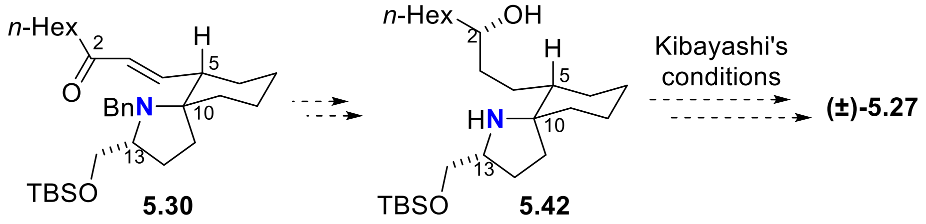
Scheme 5.9. The α-selective hydride reduction of tricyclic iminium **5.36** or **5.39** by the group of Zhao or Kim.

As an another approach to construct the tricycle bearing the α-alkyl side chain for the synthesis of (±)-lepadiformine A (**5.27**), the cyclohydration of the aminoalcohol has been demonstrated by the several groups,[1,10,12] since the first synthesis of (±)-**5.27** using aminoalcohol **5.41** by Kibayashi and co-workers.[12g] This strategy can be applied to our future synthesis of (±)-**5.27** using the aminoalcohol **5.42** as a potential precursor which would be prepared by the aminoketone **5.30**.

Cyclohydration of the aminoalcohol **5.41** by Kibayashi *et al.* (ref 12g)



Future plan: Cyclohydration of the aminoalcohol **5.42**



Scheme 5.10. Our future work for the synthesis of (±)-lepadiformine A (**5.27**).

5.7. Conclusion

This chapter disclosed the synthesis of (±)-fasicularin (**5.1**) in 3.1% overall yield in 19 steps in which the key transformations include 1) denitrogenative bromoamination of an alkenyl azide for the construction of a spirocyclic BC ring intermediate **5.3**, 2) displacement of a bromo group in the azaspirocycle **5.3** to a cyano group with the retention of the configuration at C(5) through an aziridinium salt **5.13**, and 3) stereoselective alkylation of a tetracyclic *N*,*O*-acetal **5.19**. The advantage of the present synthesis in comparison with the previously reported total syntheses is the rapid construction of the key azaspirocyclic BC ring **5.3** having vicinal stereogenic centers from the known starting material **5.5** in only 5 steps under the transition metal-free conditions. In addition, the synthesis of lepadiformine A (**5.27**) has been examined in which the key challenge is the stereoselective installation of α-hexyl side chain. However, all the attempts resulted in the exclusive installation of β-hexyl group.

5.8. References

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Chapter 6. Experimental and Computational Section

6.1. General Information

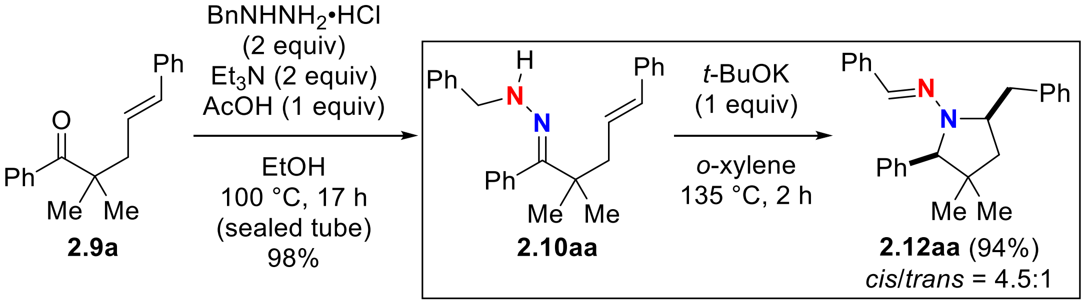
^{1}H NMR spectra (300, 400, or 500 MHz) were recorded on a Bruker Avance 300, 400, 500, or JEOL ECA400 spectrometer in $CDCl_3$ [using TMS (for ^{1}H, $\delta = 0.00$) as internal standard]. ^{13}C NMR spectra (75, 100, or 125 MHz) were recorded on a Bruker Avance 300, 400, or 500 spectrometer in $CDCl_3$ [using $CDCl_3$ (for ^{13}C, $\delta = 77.00$) as internal standard]. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, br = broad. IR spectra were recorded on a Shimadzu IR IRAffinity-1 FT-IR Spectrometer. High-resolution mass spectra were obtained with a Waters Q-Tof Premier mass spectrometer. Melting points are uncorrected and were recorded on a MPA 100 OptiMelt Automated Melting Point System. X-ray crystallography analysis was performed on Bruker X8 APEX X-ray diffractionmeter. Optical rotations were measured on an Anton Paar MCP 200 polarimeter. Enantiomeric excesses (ee) were determined by HPLC analysis on Shimadzu HPLC with Daicel chiral columns. Flash chromatography was performed using Merck silica gel 60 with distilled solvents. Tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), acetonitrile (MeCN) and diethyl ether (Et_2O) were taken from a solvent purification system (PS-400-5, innovative technology Inc.). NaH (60% dispersion in mineral oil), NaI and LiI were purchased from Sigma-Aldrich, Inc. Due to moisture sensitivity of NaH, it was consistently handled under an Ar atmosphere in a glovebox or with Schlenk techniques under an inert (N_2 or Ar) atmosphere. NaI and LiI were dried over P_2O_5 under reduced pressure at 60 °C and 120 °C, respectively. *o*-Xylene was distilled over CaH_2. *t*-BuOK (≥98%, reagent grade, CAS Number 865-47-4) was purchased from Sigma-Aldrich, Et_3COH (≥99%, reagent grade, CAS Number 597-49-9) was purchased from TCI, and *t*-BuOD was purchased from

Cambridge Isotope Laboratories, Inc. and used as received. Other solvents and reagents, otherwise noted, were commercially available and used as received.

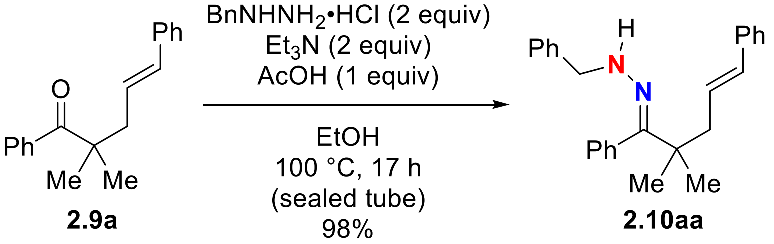
6.2. Experimental data for Chapter 2

6.2.1. Hydroamination of γ,δ-alkenyl hydrazones 2.10 for synthesis of N-imino pyrrolidines 2.12 (Table 2.1 and Scheme 2.6)

6.2.1.1. Synthesis of 2.12aa (Table 2.1, entry 1)



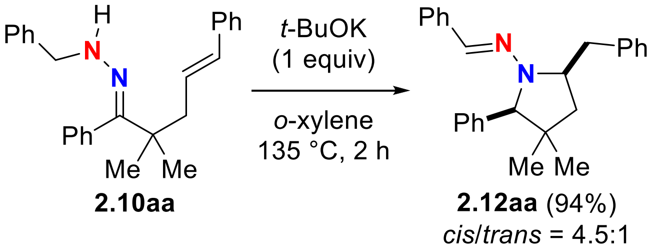
6.2.1.1.1. Synthesis of (*Z*)-1-benzyl-2-((*E*)-2,2-dimethyl-1,5-diphenylpent-4-en-1-ylidene)hydrazine (2.10aa)



To a sealed tube containing ketone **2.9a**[1] (2.32 g, 8.79 mmol) and benzylhydrazine monohydrochloride (2.75 g, 17.6 mmol) in degassed EtOH (18 mL) was added Et_3N (2.4 mL, 17.6 mmol) and AcOH (0.50 mL, 8.79 mmol) under an Ar atmosphere. The tube was sealed and the solution was then stirred at 100 °C for 17 h. After the mixture was cooled down to room temperature, the solvent was removed under reduced pressure. The resulting crude product was purified immediately by flash column chromatography (hexane:Et_2O = 30:1) to yield hydrazone **2.10aa** (3.17 g, 8.62 mmol, 98% yield) as a yellow oil, which was used immediately or stored under -20 °C under a N_2 atmosphere as hydrazones are not very stable with moisture and air. [2]

IR (NaCl) 3444, 3026, 2964, 1599, 1494, 1454, 1383, 1072, 968 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.11 (6H, s), 2.39 (2H, d, *J* = 7.0 Hz), 4.27 (2H, s), 4.81 (1H, s br), 6.23 (1H, dt, *J* = 15.5, 7.0 Hz), 6.35 (1H, d, *J* = 15.5 Hz), 6.93 (2H, d, *J* = 8.0 Hz), 7.19-7.33 (11H, m), 7.38 (2H, t, *J* = 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.9, 41.4, 44.4, 55.2, 126.3, 127.0, 127.1, 128.2, 128.3(0), 128.3(4), 128.5, 128.6, 128.7, 129.2, 132.3, 134.6, 138.1, 140.5, 156.0.; ESIHRMS: Found: m/z 369.2332. Calcd for $C_{26}H_{29}N_2$: $(M+H)^+$ 369.2331.

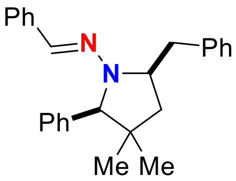
6.2.1.1.2. Synthesis of (*E*)-*N*-5-benzyl-3,3-dimethyl-2-phenylpyrrolidin-1-yl)-1-phenylmethanimine (2.12aa) (Typical procedure A)



To a 25 mL Schlenk tube containing *t*-BuOK (56.7 mg, 0.505 mmol) was added hydrazone **2.10aa** (184 mg, 0.499 mmol) in degassed *o*-xylene (5.0 mL) under an Ar atmosphere. The solution was stirred at 135 °C for 2 h and then cooled down to room temperature. After dilution with water and ethyl acetate, the mixture was extracted thrice with ethyl acetate. The combined extracts were washed with brine, dried over

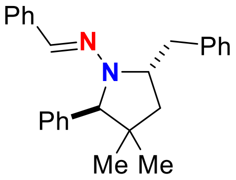
$MgSO_4$, and concentrated under reduced pressure. The resulting crude material was purified by flash column chromatography (hexane:Et_2O = 50:1) to yield *N*-imino pyrrolidine **2.12aa** (173 mg, 0.468 mmol) in 94% yield as a 2,5-*cis*/2,5-*trans* mixture (*cis*:*trans* = 4.5:1). Two diastereomers could be isolated partially by preparative TLC for characterization.

(*E*)-*N*-((2*S**,5*S**)-5-benzyl-3,3-dimethyl-2-phenylpyrrolidin-1-yl)-1-phenylmethanimine (*cis*-2.12aa)



Sticky yellow oil; IR (NaCl) 3024, 2958, 2866, 1589, 1556, 1452, 1215, 916, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.55 (3H, s), 1.15 (3H, s), 1.57-1.64 (2H, m), 3.01 (1H, dd, *J* = 13.2, 8.8 Hz), 3.62 (1H, dd, *J* = 13.2, 3.6 Hz), 3.96-4.03 (1H, m), 4.12 (1H, s), 6.93 (1H, s), 7.10-7.15 (3H, m), 7.21-7.29 (10H, m), 7.44 (2H, d, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.1, 30.1, 40.5, 41.2, 42.4, 64.2, 75.7, 125.3, 126.1, 126.8, 126.9, 127.0, 128.2, 128.3, 128.4, 129.9, 131.5, 137.3, 139.1, 141.2.; ESIHRMS: Found: m/z 369.2334. Calcd for $C_{26}H_{29}N_2$: $(M+H)^+$ 369.2331.

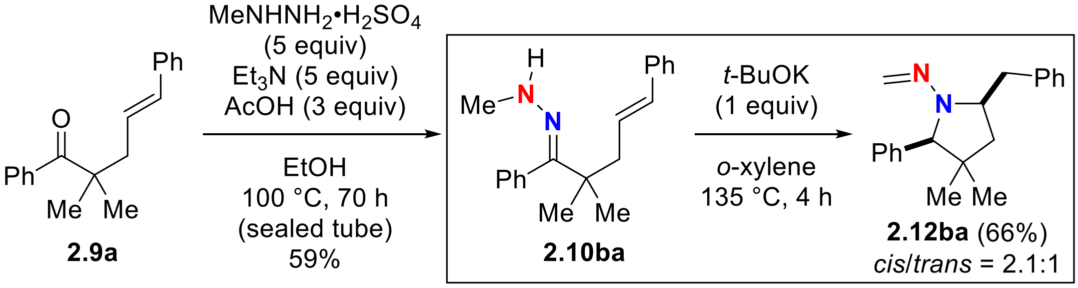
(*E*)-*N*-((2*S**,5*R**)-5-benzyl-3,3-dimethyl-2-phenylpyrrolidin-1-yl)-1-phenylmethanimine (*trans*-2.12aa)



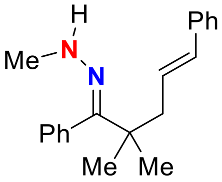
[X-ray]

Pale yellow crystal (*trans*-**2.12aa** could be recrystallized from $CHCl_3$/hexane) (CCDC 1424791); mp: 100-101 °C; IR (NaCl) 3026, 2958, 2866, 1587, 1556, 1452, 1330, 1217, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.58 (3H, s), 1.26 (3H, s), 1.60 (1H, dd, *J* = 12.8, 8.4 Hz), 1.74 (1H, dd, *J* = 12.8, 6.8 Hz), 2.68 (1H, dd, *J* = 13.2, 10.0 Hz), 3.81 (1H, dd, *J* = 13.2, 4.4 Hz), 4.36 (1H, s), 4.38-4.42 (1H, dddd, *J* = 10.0, 8.4, 6.8, 4.4 Hz), 6.75 (1H, s), 7.09 (1H, t, *J* = 7.6 Hz), 7.16-7.35 (14H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7, 28.9, 40.5, 41.3, 44.5, 64.5, 74.2, 124.9, 126.0, 126.4, 126.9, 127.0, 128.2(5), 128.3(2), 128.3(7), 129.4, 130.3, 137.7, 138.5, 139.7.; ESIHRMS: Found: m/z 369.2328. Calcd for $C_{26}H_{29}N_2$: $(M+H)^+$ 369.2331.

6.2.1.2. Synthesis of 2.12ba (Table 2.1, entry 2)



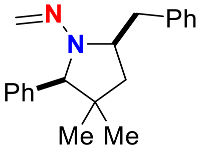
6.2.1.2.1. Synthesis of (*Z*)-1-((*E*)-2,2-dimethyl-1,5-diphenylpent-4-en-1-ylidene)-2-methylhydrazine (2.10ba)



59% yield (516 mg, 1.76 mmol) from ketone **2.9a**[1] (793 mg, 3.00 mmol) following the procedure described in section 6.2.1.1.1. (page 105)

A yellow sticky oil; IR (NaCl) 3285, 3025, 2965, 1597, 1474, 1447, 1217, 1119, 966, 756 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (6H, s), 2.42 (2H, d, *J* = 6.4 Hz), 2.84 (3H, s), 4.37 (1H, s br), 6.34 (1H, dt, *J* = 16.0, 6.4 Hz), 6.40 (1H, d, *J* = 16.0 Hz), 7.08 (2H, d, *J* = 7.6 Hz), 7.20 (1H, t, *J* = 7.2 Hz), 7.31 (2H, t, *J* = 7.2 Hz), 7.35-7.38 (3H, m), 7.44 (2H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.5, 37.9, 41.0, 44.1, 126.0, 126.8, 128.0, 128.1, 128.4(3), 128.4(4), 129.0, 132.1, 134.5, 138.0, 155.3.; ESIHRMS: Found: m/z 293.2022. Calcd for $C_{20}H_{25}N_2$: $(M+H)^+$ 293.2018.

6.2.1.2.2. Synthesis of *N*-((2*S**,5*S**)-5-benzyl-3,3-dimethyl-2-phenylpyrrolidin-1-yl)methanimine (2.12ba)



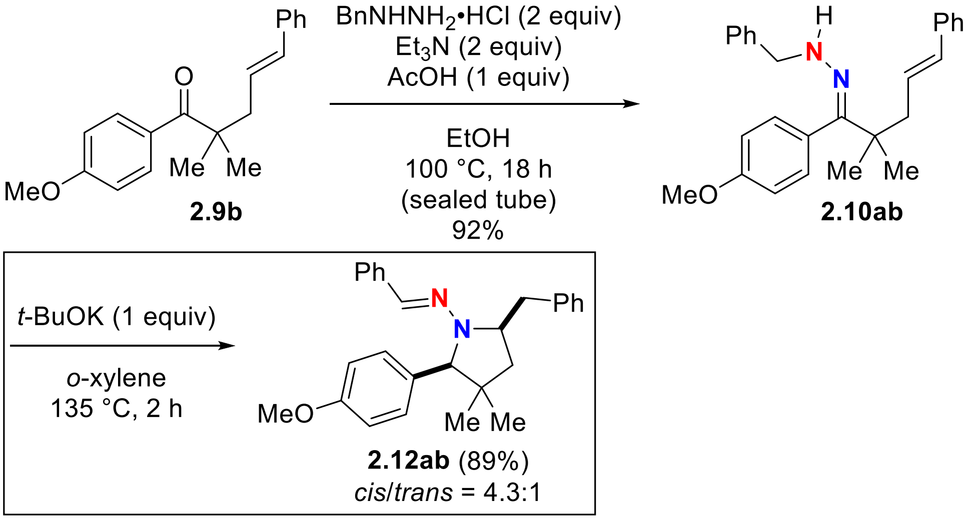
66% yield (96.5 mg, 0.330 mmol) (*cis*:*trans* = 2.1 : 1) from **2.10ba** (146 mg, 0.498 mmol) for 4 h by the typical procedure A (page 106).

The major *cis*-isomer was isolated partially for characterization.

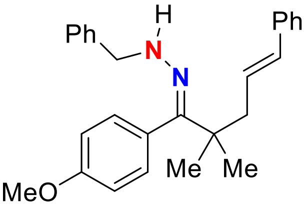
Pale yellow oil; IR (NaCl) 3027, 2955, 2964, 1603, 1568, 1495, 1454, 1332, 1238, 1152, 881, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.53-0.54 (3H, s+3H×0.49, s), 1.11 (3H, s), 1.25 (3H×0.49, s) 1.55-1.57 (2H+1H×0.49, m), 1.70 (1H×0.49, dd, *J* = 12.4, 7.2 Hz), 2.59 (1H×0.49, dd, *J* = 13.2, 10.4 Hz), 2.88 (1H, dd, *J* = 13.2, 9.6 Hz), 3.53 (1H, dd, *J* = 13.2, 3.6 Hz), 3.65 (1H×0.49, dd, *J* = 13.2, 4.0 Hz), 3.81-3.89 (1H, m), 3.94 (1H, s), 4.21-4.29 (2H×0.49, m), 5.68 (1H×0.49, d, *J* = 11.6 Hz), 5.78 (1H×0.49, d, *J* = 11.6 Hz), 5.86-5.92 (2H, m), 7.08-7.10 (2H+2H×0.49, m), 7.19-7.33 (8H+8H×0.49, m).; ESIHRMS: Found: m/z 293.2017. Calcd for $C_{20}H_{25}N_2$: $(M+H)^+$ 293.2018.

***cis*-2.12ba**: ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.53 (3H, s), 1.11 (3H, s), 1.54-1.57 (2H, m), 2.88 (1H, dd, *J* = 13.2, 9.6 Hz), 3.53 (1H, dd, *J* = 13.2, 3.6 Hz), 3.81-3.89 (1H, m), 3.94 (1H, s), 5.86-5.92 (2H, m), 7.09 (2H, d, *J* = 6.8 Hz), 7.19-7.33 (8H, m); ^{13}C NMR (100 MHz, CDCl$_3$) δ 26.2, 30.2, 40.6, 41.5, 42.8, 64.3, 75.9, 121.8, 126.4, 127.0, 127.2, 128.5, 128.6, 130.0, 139.2, 141.4.

6.2.1.3. Synthesis of 2.12ab (Scheme 2.6)



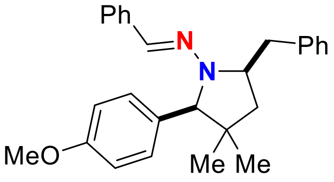
6.2.1.3.1. Synthesis of (*Z*)-1-benzyl-2-((*E*)-1-(4-methoxyphenyl)-2,2-dimethyl-5-phenylpent-4-en-1-ylidene)hydrazine (2.10ab)



92% yield (657 mg, 1.65 mmol) from ketone **2.9b**[1] (530 mg, 1.80 mmol) following the procedure described in section 6.2.1.1.1. (page 105)

A yellow oil; IR (NaCl) 3396, 3026, 2964, 1606, 1510, 1454 1248, 1109, 968 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (6H, s), 2.37 (2H, d, *J* = 7.2 Hz), 3.79 (3H, s), 4.27 (2H, s), 4.88 (1H, s br), 6.21 (1H, dt, *J* = 16.0, 7.2 Hz), 6.34 (1H, d, *J* = 16.0 Hz), 6.85 (2H, d, *J* = 8.5 Hz), 6.90 (2H, d, *J* = 8.5 Hz), 7.18-7.29 (10H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.6, 41.3, 44.1, 54.9, 55.2, 114.4, 126.0, 126.2, 126.7, 126.8, 128.1 (overlapped), 128.2, 128.4, 129.6, 131.9, 137.9, 140.2, 155.7, 159.2.; ESIHRMS: Found: m/z 399.2438. Calcd for $C_{27}H_{31}N_2O$: $(M+H)^+$ 399.2436.

6.2.1.3.2. Synthesis of (*E*)-*N*-((2*S**,5*S**)-5-benzyl-2-(4-methoxyphenyl)-3,3-dimethylpyrrolidin-1-yl)-1-phenylmethanimine (2.12ab)



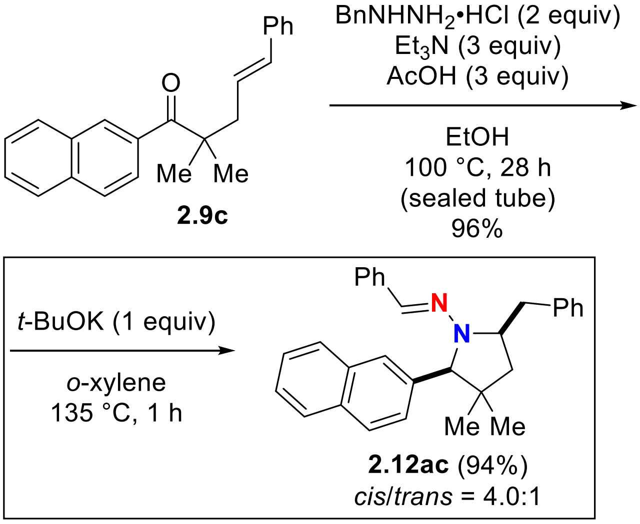
89% yield (175 mg, 0.440 mmol) (*cis*:*trans* = 4.3 : 1) from **2.10ab** (197 mg, 0.494 mmol) for 2 h by the typical procedure A (page 106)

The major *cis*-isomer was isolated partially for characterization.

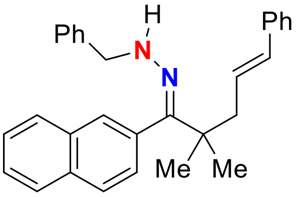
Yellow sticky oil; IR (NaCl) 3024, 2956, 1587, 1556, 1510, 1452, 1246, 1035, 754 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.55 (3H, s), 0.58 (3H×0.23, s), 1.13 (3H, s), 1.23 (3H×0.23, s), 1.54-1.59 (2H+1H×0.23, m), 1.73 (1H×0.23, dd, *J* = 12.0, 6.8 Hz), 2.64-2.70 (1H×0.23, m), 3.00 (1H, dd, *J* = 13.2, 9.2 Hz), 3.60 (1H, dd, *J* = 13.2, 3.6 Hz), 3.78 (3H, s+3H×0.23, s), 3.94-4.01 (1H, m), 4.08 (1H, s), 4.32-4.37 (2H×0.23, m), 6.78-6.85 (2H+3H×0.23, m), 6.94 (1H, s), 7.01 (2H, d, *J* = 8.4 Hz), 7.07-7.36 (8H+12H×0.23, m), 7.44 (2H, d, *J* = 7.2 Hz).; ESIHRMS: Found: m/z 399.2436. Calcd for $C_{27}H_{31}N_2O$: $(M+H)^+$ 399.2436.

***cis*-2.12ab**: ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.55 (3H, s), 1.13 (3H, s), 1.54-1.59 (2H, m), 3.00 (1H, dd, *J* = 13.2, 9.2 Hz), 3.60 (1H, dd, *J* = 13.2, 3.6 Hz), 3.78 (3H, s), 3.94-4.01 (1H, m), 4.08 (1H, s), 6.80 (2H, d, *J* = 8.4 Hz), 6.94 (1H, s), 7.01 (2H, d, *J* = 8.4 Hz), 7.13 (1H, t, *J* = 7.6 Hz), 7.22-7.33 (7H, m), 7.44 (2H, d, *J* = 7.2 Hz).; ^{13}C NMR (100 MHz, CDCl$_3$) δ 26.3, 30.2, 40.7, 41.5, 42.6, 55.4, 64.3, 75.3, 114.0, 125.5, 126.3, 127.0, 128.1, 128.5, 128.6, 130.2, 131.6, 133.5, 137.6, 139.4, 158.9.

6.2.1.4. Synthesis of 2.12ac (Scheme 2.6)



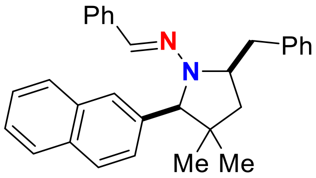
6.2.1.4.1. Synthesis of (*Z*)-1-benzyl-2-((*E*)-2,2-dimethyl-1-(naphthalen-2-yl)-5-phenylpent-4-en-1-ylidene)hydrazine (2.10ac)



96% yield (689 mg, 1.65 mmol) from ketone **2.9c**[1] (537 mg, 1.71 mmol) following the procedure described in section 6.2.1.1.1. (page 105)

A yellow sticky oil; IR (NaCl) 3264, 3026, 2967, 1597, 1495, 1454, 1360, 1126, 968 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (6H, s), 2.44 (2H, d, *J* = 6.8 Hz), 4.27 (2H, s), 4.86 (1H, s br), 6.28 (1H, dt, *J* = 15.6, 6.8 Hz), 6.36 (1H, d, *J* = 15.6 Hz), 7.03 (2H, d, *J* = 8.4 Hz), 7.19-7.31 (10H, m), 7.39 (1H, s), 7.47-7.52 (2H, m), 7.75-7.77 (1H, m), 7.82-7.86 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.7, 41.4, 44.3, 55.0, 126.1, 126.2, 126.4, 126.5, 126.8, 126.9, 127.5, 127.7, 127.9(7), 128.0(9), 128.1(2), 128.3, 128.4, 128.7, 131.9, 132.1, 132.8, 133.3, 137.9, 140.1, 155.8.; ESIHRMS: Found: m/z 419.2481. Calcd for $C_{30}H_{31}N_2$: $(M+H)^+$ 419.2487.

6.2.1.4.2. Synthesis of (*E*)-*N*-((2*S**,5*S**)-5-benzyl-3,3-dimethyl-2-(naphthalen-2-yl)pyrrolidin-1-yl)-1-phenylmethanimine (2.12ac)



94% yield (197 mg, 0.471 mmol) (*cis*:*trans* = 4.0 : 1) from **2.10ac** (209 mg, 0.498 mmol) for 1 h by the typical procedure A (page 106)

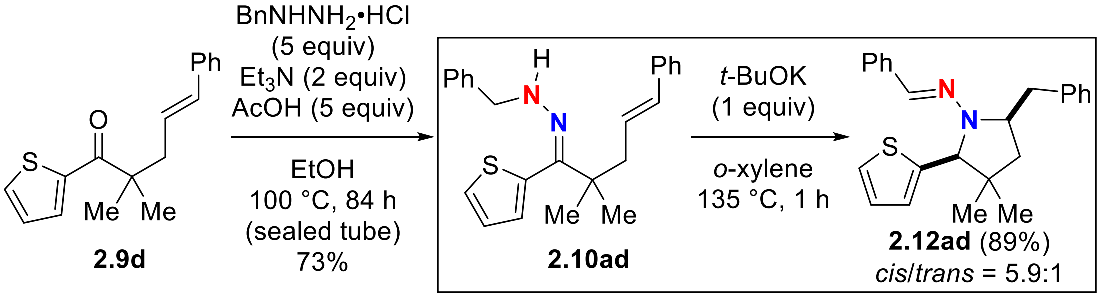
The major *cis*-isomer was isolated partially for characterization.

Pale yellow solid; mp: 70-71°C; IR (NaCl) 3024, 2956, 1589, 1556, 1446, 1371, 1217, 916, 821 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.55 (3H, s), 0.59 (3H×0.25, s), 1.21 (3H, s), 1.31 (3H×0.25, s), 1.60-1.72 (2H+1H×0.25, m), 1.78 (1H×0.25, dd, *J* = 12.8, 6.4 Hz), 2.72 (1H×0.25, dd, *J* = 13.2, 10.0 Hz), 3.17 (1H, dd, *J* = 13.2, 8.4 Hz), 3.60 (1H, dd, *J* = 13.2, 3.6 Hz), 3.86 (1H×0.25, dd, *J* = 13.2, 4.4 Hz), 4.01-4.08 (1H, m), 4.26 (1H, s), 4.44-4.51 (1H×0.25, m), 4.53 (1H×0.25, s), 6.81 (1H×0.25, s), 6.97 (1H, s), 7.05-7.47 (13H+13H×0.25, m), 7.51 (1H, s), 7.64 (1H×0.25, s), 7.73-7.81

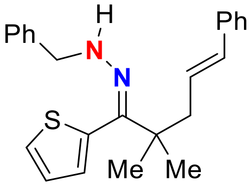
(3H+3H×0.25, m).; ESIHRMS: Found: m/z 419.2484. Calcd for $C_{30}H_{31}N_2$: $(M+H)^+$ 419.2487.

cis-**2.12ac**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.55 (3H, s), 1.21 (3H, s), 1.60-1.72 (2H, m), 3.17 (1H, dd, *J* = 13.2, 8.4 Hz), 3.60 (1H, dd, *J* = 13.2, 3.6 Hz), 4.01-4.08 (1H, m), 4.26 (1H, s), 6.97 (1H, s), 7.12 (1H, t, *J* = 7.2 Hz), 7.20-7.47 (12H, m), 7.51 (1H, s), 7.74 (2H, t, *J* =7.2 Hz), 7.79-7.81 (1H, m).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.2, 30.2, 40.7, 40.8, 42.3, 64.1, 75.8, 125.2, 125.3, 125.4(9), 125.5(3), 125.9, 126.2, 126.9, 127.6, 127.9, 128.0, 128.2(5), 128.2(8), 130.2, 131.8, 132.8, 133.5, 137.2, 138.9, 139.0.

6.2.1.5. Synthesis of 2.12ad (Scheme 2.6)



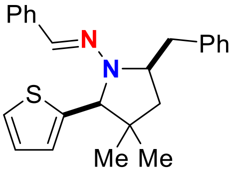
6.2.1.5.1. Synthesis of (*Z*)-1-benzyl-2-((*E*)-2,2-dimethyl-5-phenyl-1-(thiophen-2-yl)pent-4-en-1-ylidene)hydrazine (2.10ad)



73% yield (528 mg, 1.41 mmol) from ketone **2.9d**[1] (524 mg, 1.94 mmol) following the procedure described in section 6.2.1.1.1. (page 105)

An orange oil; IR (NaCl) 3395, 3026, 2965, 1651, 1599, 1495, 1454, 1361, 1126, 966 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.16 (6H, s), 2.39 (2H, d, *J* = 7.5 Hz), 4.33 (2H, s), 5.30 (1H, s br), 6.18 (1H, dt, *J* = 15.5, 7.5 Hz), 6.35 (1H, d, *J* = 15.5 Hz), 6.76 (1H, d, *J* = 3.0 Hz), 7.08 (1H, dd, *J* = 5.0, 3.0 Hz), 7.19-7.29 (10H, m), 7.40 (1H, d, *J* = 5.0 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ 26.5, 41.3, 44.1, 54.8, 126.1, 126.8(1), 126.8(4), 126.8(9), 127.3, 127.5, 127.8, 127.9, 128.3, 128.4, 132.1, 132.3, 137.8, 140.0, 147.2.; ESIHRMS: Found: m/z 375.1898. Calcd for $C_{24}H_{27}N_2S$: $(M+H)^+$ 375.1895.

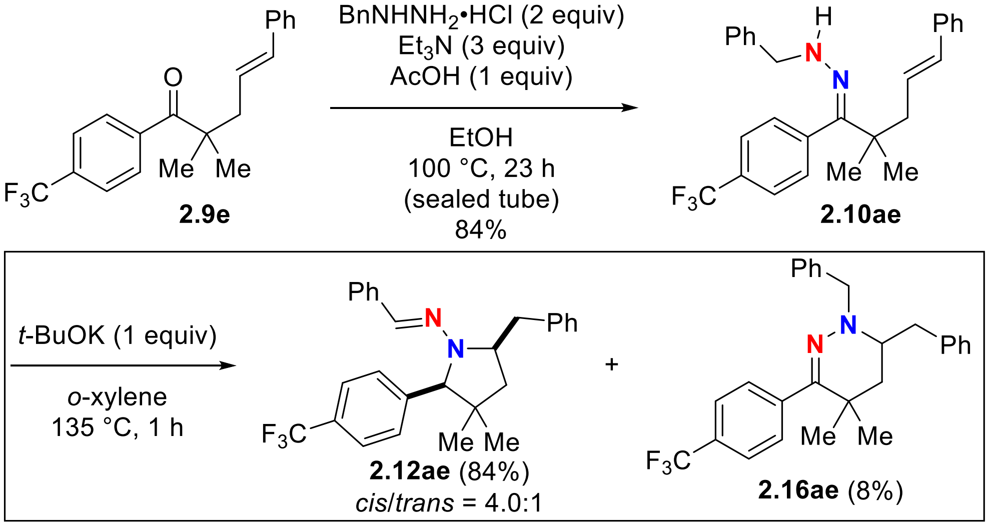
6.2.1.5.2. Synthesis of (*E*)-*N*-((2*S**,5*S**)-5-benzyl-3,3-dimethyl-2-(thiophen-2-yl)pyrrolidin-1-yl)-1-phenylmethanimine (2.12ad)



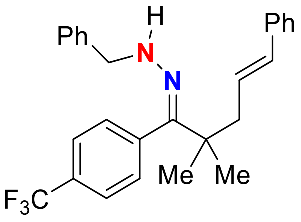
89% yield (167 mg, 0.445 mmol) (*cis*:*trans* = 5.9 : 1) (as an inseparable *cis*/*trans*-mixture) from **2.10ad** (186 mg, 0.497 mmol) for 1 h by the typical procedure A (page 106)

Yellow oil; IR (NaCl) 3026, 2958, 1589, 1562, 1454, 1328, 1143, 910, 752 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.75 (3H, s), 0.77 (3H×0.17, s), 1.15 (3H, s), 1.31 (3H×0.17, s), 1.63 (1H, dd, *J* = 12.8, 6.0 Hz + 1H×0.17, m), 1.73 (1H, dd, *J* = 12.8, 10.8 Hz), 1.89 (1H×0.17, dd, *J* = 12.8, 7.6 Hz), 2.73 (1H×0.17, dd, *J* = 13.2, 10.0 Hz), 2.95 (1H, dd, *J* = 13.2, 8.8 Hz), 3.66 (1H, dd, *J* = 13.2, 3.6 Hz), 3.78 (1H×0.17, dd, *J* = 13.2, 4.0 Hz), 3.95-4.02 (1H, dddd, *J* = 10.8, 8.8, 6.0, 3.6 Hz), 4.31-4.38 (1H×0.17, m), 4.46 (1H, s), 4.67 (1H×0.17, s), 6.87 (1H, d, *J* = 3.2 Hz), 6.92 (1H×0.17, d, *J* = 3.2 Hz), 6.98-7.02 (1H+1H×0.17, m), 7.09 (1H×0.17, s), 7.20-7.37 (10H+9H×0.17, m), 7.46 (2H×0.17, d, *J* = 8.0 Hz), 7.52 (2H, d, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) (for *cis*-**2.12ad**) δ 25.2, 29.1, 40.7, 41.7, 42.2, 64.5, 71.3, 123.7, 124.0, 125.5, 126.1, 127.0(0), 127.0(7), 128.3, 128.4, 129.7, 131.8, 137.2, 139.3, 146.7.; ESIHRMS: Found: m/z 375.1892. Calcd for $C_{24}H_{27}N_2S$: $(M+H)^+$ 375.1895.

6.2.1.6. Synthesis of 2.12ae and 2.16ae (Scheme 2.6)



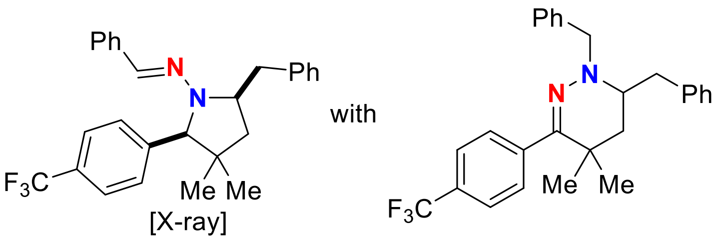
6.2.1.6.1. Synthesis of (*Z*)-1-benzyl-2-(*E*-2,2-dimethyl-5-phenyl-1-(4-(trifluoromethyl)phenyl)pent-4-en-1-ylidene)hydrazine (2.10ae)



84% yield (416 mg, 0.953 mmol) from ketone **2.9e**[1] (377 mg, 1.13 mmol) following the procedure described in section 6.2.1.1.1. (page 105)

A white solid; mp: 78-79 °C; IR (NaCl) 3420, 3024, 2967, 1616, 1495, 1454, 1323, 1130, 845 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (6H, s), 2.38 (2H, d, *J* = 7.2 Hz), 4.28 (2H, s), 4.69 (1H, s br), 6.21 (1H, dt, *J* = 15.6, 7.2 Hz), 6.35 (1H, d, *J* = 15.6 Hz), 7.07 (2H, d, *J* = 8.4 Hz), 7.20-7.30 (10H, m), 7.65 (2H, d, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.6, 41.1, 44.1, 55.0, 123.9 (q, *J* = 270.6 Hz), 125.9 (q, *J* = 3.7 Hz), 126.1, 126.9, 127.0, 127.5, 128.1, 128.4, 128.5, 129.0, 130.3 (q, *J* = 32.4 Hz), 132.3, 137.7, 138.4, 139.9, 153.8.; ESIHRMS: Found: m/z 437.2204. Calcd for $C_{27}H_{28}N_2F_3$: $(M+H)^+$ 437.2205.

6.2.1.6.2. Synthesis of *E*-*N*-((2*S**,5*S**)-5-benzyl-3,3-dimethyl-2-(4-(trifluoromethyl)phenyl)pyrrolidin-1-yl)-1-phenylmethanimine (2.12ae) and 1,6-dibenzyl-4,4-dimethyl-3-(4-(trifluoromethyl)phenyl)-1,4,5,6-tetrahydropyridazine (2.16ae)



84% yield (183 mg, 0.420 mmol) (*cis*:*trans* = 4.0 : 1) of **2.12ae** and 8% yield (18.0 mg, 0.0412 mmol) of **2.16ae** from **2.10ae** (218 mg, 0.499 mmol) for 1 h by the typical procedure A (page 106).

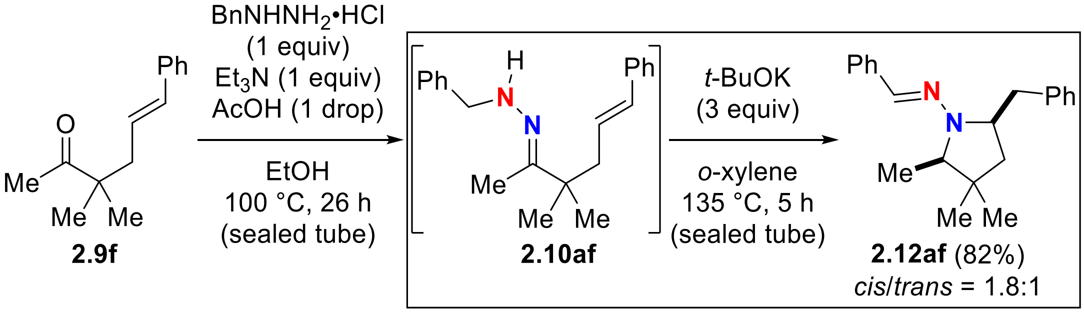
(the major *cis*-isomer of **2.12ae** could be recrystallized from *i*-PrOH as a colorless crystal)

Characterization of **2.12ae**; Yellow solid; mp: 95-96 °C; IR (NaCl) 3057, 2960, 1589, 1562, 1325, 1126, 754 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.54 (3H, s), 0.56 (3H×0.25, s), 1.19 (3H, s), 1.26 (3H×0.25, s), 1.56-1.66 (2H+1H×0.25, m), 1.74 (1H×0.25, dd, *J* = 12.4, 6.4 Hz), 2.68 (1H×0.25, dd, *J* = 13.2, 10.0 Hz), 3.10 (1H, dd, *J* = 13.2, 8.4 Hz), 3.53 (1H, dd, *J* = 13.2, 3.6 Hz), 3.80 (1H×0.25, dd, *J* = 13.2, 4.0 Hz), 3.98-4.05 (1H, m), 4.15 (1H, s), 4.36-4.44 (2H×0.25, m), 6.69 (1H×0.25, s), 6.87 (1H, s), 7.12-7.35 (10H+12H×0.25, m), 7.45 (2H, d, *J* = 8.0 Hz), 7.50 (2H, d, *J* = 8.0 Hz), 7.57 (2H×0.25, d, *J* = 8.0 Hz).; ^{13}C NMR (100 MHz, $CDCl_3$) (for *cis*-**2.12ae**) δ 26.1, 30.1, 40.7, 42.1, 64.0, 75.2, 124.2 (q, *J* = 270.2 Hz), 125.4 (m), 126.3 (overlapped), 127.2, 128.3, 128.4, 129.4 (q, *J* = 32.1 Hz), 130.1, 132.0 (overlapped), 137.0, 138.7, 145.5.; ESIHRMS: Found: m/z 437.2209. Calcd for $C_{27}H_{28}N_2F_3$: $(M+H)^+$ 437.2205.

cis-**2.12ae** (CCDC 1424732); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.54 (3H, s), 1.19 (3H, s), 1.56-1.66 (2H, m), 3.10 (1H, dd, *J* = 13.2, 8.4 Hz), 3.53 (1H, dd, *J* = 13.2, 3.6 Hz), 3.98-4.05 (1H, m), 4.15 (1H, s), 6.87 (1H, s), 7.16-7.18 (3H, m), 7.24-7.34 (7H, m), 7.45 (2H, d, *J* = 8.0 Hz), 7.50 (2H, d, *J* = 8.0 Hz).

Characterization of **2.16ae**; Pale yellow sticky oil; IR (NaCl) 3026, 2960, 1616, 1494, 1454, 1325, 1124, 845 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (3H, s), 1.04 (3H, s), 1.41 (1H, dd, *J* = 13.2, 2.8 Hz), 1.56-1.62 (1H, m), 2.51 (1H, dd, *J* = 12.8, 10.0 Hz), 3.06-3.12 (1H, m), 3.40 (1H, dd, *J* = 12.8, 3.6 Hz), 4.60 (1H, d, *J* = 14.8 Hz), 4.84 (1H, d, *J* = 14.8 Hz), 7.01 (2H, d, *J* = 7.6 Hz), 7.18-7.35 (8H, m), 7.55-7.60 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.8, 29.9, 32.1, 38.9, 41.4, 52.2, 57.9, 124.2 (q, *J* = 270.2 Hz), 124.7 (q, *J* = 3.7 Hz), 126.4, 127.3, 128.2(9), 128.3(7), 128.4, 128.5, 128.8 (q, *J* = 32.4 Hz), 129.2, 137.6, 137.9, 142.6, 148.6.; ESIHRMS: Found: m/z 437.2204. Calcd for $C_{27}H_{28}N_2F_3$: $(M+H)^+$ 437.2205.

6.2.1.7. Synthesis of 2.12af from ketone 2.9f (Scheme 2.6) (Typical procedure B)



To a 25 mL sealed tube containing ketone **2.9f** (101 mg, 0.499 mmol) and benzylhydrazine hydrochloride (85.5 mg, 0.539 mmol) in degassed EtOH (2.0 mL) was added Et_3N (70 μL, 0.504 mmol) and AcOH (1 drop) under an Ar atmosphere. The tube was sealed and the solution was then stirred at 100 °C for 26 h. After the mixture was cooled down to room temperature, the solvent was removed under reduced pressure. The degassed heptane was then added and the resulting mixture was concentrated. The resulting crude material including hydrazone **2.10af** was used immediately for the next hydroamination.

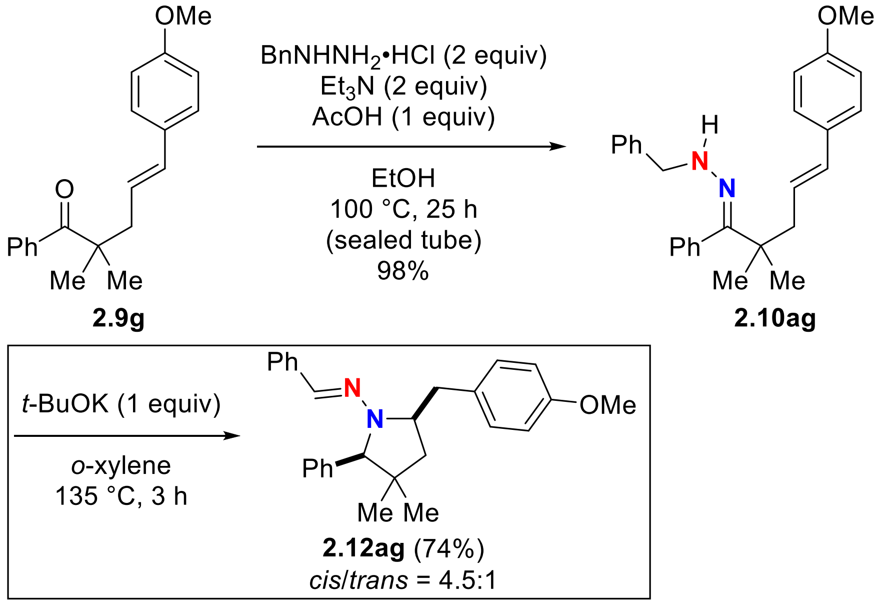
To the same 25 mL sealed tube containing crude material obtained above in *o*-xylene (5.0 mL) was added *t*-BuOK (169 mg, 1.51 mmol) under an Ar atmosphere. The tube was sealed and the solution was stirred at 135 °C for 5 h. The solution was then cooled down to room temperature and diluted with water and ethyl acetate. The mixture was extracted thrice with ethyl acetate and the combined extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting crude material was purified by flash column chromatography (hexane:Et_2O = 90:1) to yield *N*-imino pyrrolidine **2.12af** (126 mg, 0.411 mmol) in 82 % yield (from ketone **2.9f**, *cis*:*trans* = 1.8:1; the major *cis*-**2.12af** was separated partially for characterization) as a yellow oil.

IR (NaCl) 3024, 2954, 1583, 1556, 1446, 1330, 1182, 858, 752 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.73 (3H×0.57, s), 0.95 (3H, s), 0.98 (3H, s), 0.99 (3H×0.57, m), 1.01 (3H, d, *J* = 6.8 Hz), 1.16 (3H×0.57, d, *J* = 6.4 Hz), 1.51-1.62 (2H+1H×0.57, m), 1.83 (1H×0.57, dd, *J* = 12.4, 8.0 Hz), 2.65 (1H×0.57, dd, *J* = 13.2, 8.8 Hz), 2.77 (1H, dd, *J* = 13.2, 8.8 Hz), 3.27-3.33 (2H+1H×0.57, m), 3.40 (1H×0.57, q, *J* = 6.4 Hz), 3.78-3.89 (1H +1H×0.57, m), 7.13-7.33 (9H+9H×0.57, m), 7.53-7.56 (2H+2H×0.57, m).; ESIHRMS: Found: m/z 307.2170. Calcd for $C_{21}H_{27}N_2$: $(M+H)^+$ 307.2174.

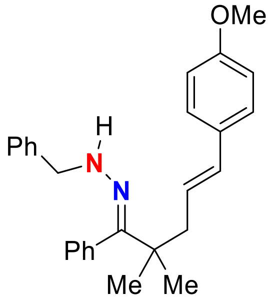
***cis*-2.12af**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, s), 0.98 (3H, s), 1.01 (3H, d, *J* = 6.8 Hz), 1.52-1.63 (2H, m), 2.77 (1H, dd, *J* = 13.2, 8.8 Hz), 3.28-3.33 (2H, m), 3.78-3.85 (1H, m), 7.16-7.33 (9H, m), 7.56 (2H, d, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.8, 23.8, 28.6, 38.7, 41.8, 42.3, 63.2, 66.8, 125.3, 126.3, 126.8, 128.4, 128.7 (overlapped), 129.9, 138.0, 139.3.

The stereochemistry of ***cis*-2.12af** was determined by X-ray crystallographic analysis of the corresponding pyrrolidine ***cis*-2.22f**, which was prepared from **2.12af** (see section 6.2.4.4. for the detailed procedure).

6.2.1.8. Synthesis of 2.12ag (Scheme 2.6)



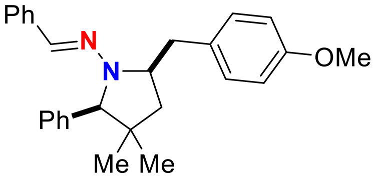
6.2.1.8.1. Synthesis of (*Z*)-1-benzyl-2-((*E*)-5-(4-methoxyphenyl)-2,2-dimethyl-1-phenylpent-4-en-1-ylidene)hydrazine (2.10ag)



98% yield (581 mg, 1.46 mmol) from ketone **2.9g**[1] (440 mg, 1.49 mmol) following the procedure described in section 6.2.1.1.1. (page 105)

A white solid; mp: 51-52 °C; IR (NaCl) 3444, 3026, 2963, 1607, 1510, 1458, 1247, 1035, 754 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (6H, s), 2.35 (2H, d, *J* = 7.2 Hz), 3.81 (3H, s), 4.27 (2H, s), 4.82 (1H, s br), 6.08 (1H, dt, *J* = 15.6, 7.2 Hz), 6.29 (1H, d, *J* = 15.6 Hz), 6.83 (2H, d, *J* = 8.8 Hz), 6.93 (2H, d, *J* = 8.8 Hz), 7.20-7.40 (10H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.5, 41.1, 44.1, 54.9, 55.3, 113.8, 125.7, 126.8, 127.1, 128.1 (overlapped), 128.2(6), 128.3(4), 128.9, 130.8, 131.3, 134.4, 140.2, 156.0, 158.6.; ESIHRMS: Found: m/z 399.2430. Calcd for $C_{27}H_{31}N_2O$: $(M+H)^+$ 399.2436.

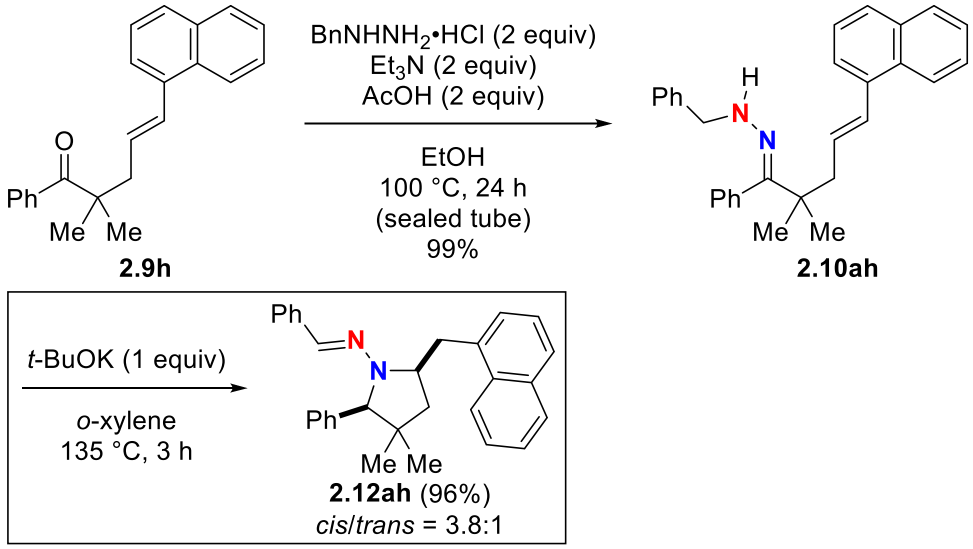
6.2.1.8.2. Synthesis of (*E*)-*N*-((2*S**,5*S**)-5-(4-methoxybenzyl)-3,3-dimethyl-2-phenylpyrrolidin-1-yl)-1-phenylmethanimine (2.12ag)



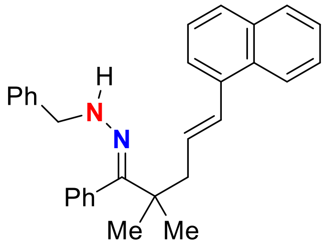
74% yield (149 mg, 0.374 mmol) (*cis*:*trans* = 4.5 : 1) (as an inseparable *cis*/*trans*-mixture) from **2.10ag** (199 mg, 0.499 mmol) for 3 h by the typical procedure A (page 106).

White solid; mp: 96-97 °C; IR(NaCl) 3026, 2954, 1614, 1587, 1556, 1514, 1033, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.54 (3H, s), 0.57 (3H×0.22, s), 1.15 (3H, s), 1.25 (3H×0.22, s), 1.54-1.63 (2H+1H×0.22, m), 1.74 (1H×0.22, dd, J = 12.4, 6.4 Hz), 2.64 (1H×0.22, dd, J = 13.2, 10.0 Hz), 2.98 (1H, dd, J = 13.2, 8.8 Hz), 3.53 (1H, dd, J = 13.2, 3.6 Hz), 3.73 (1H×0.22, dd, J = 13.2, 4.0 Hz), 3.80 (3H×0.22, s), 3.82 (3H, s), 3.92-3.99 (1H, m), 4.11 (1H, s), 4.30-4.35 (2H×0.22, m), 6.74 (1H×0.22, s), 6.87 (2H+2H×0.22, m), 6.92 (1H, s), 7.09-7.34 (10H+12H×0.22, m), 7.44 (2H, d, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) (for *cis*-**2.12ag**) δ 26.1, 30.1, 40.1, 40.5, 42.3, 55.3, 64.2, 75.6, 113.6, 125.3, 126.8, 126.9, 127.0, 128.3, 128.4, 130.8, 131.1, 131.3, 137.3, 141.2, 158.1.; ESIHRMS: Found: m/z 399.2434. Calcd for $C_{27}H_{31}N_2O$: $(M+H)^+$ 399.2436.

6.2.1.9. Synthesis of 2.12ah (Scheme 2.6)



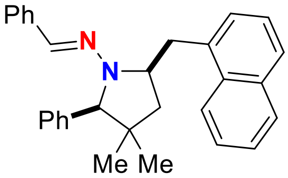
6.2.1.9.1. Synthesis of (*Z*)-1-benzyl-2-((*E*)-2,2-dimethyl-5-(naphthalen-1-yl)-1-phenylpent-4-en-1-ylidene)hydrazine (2.10ah)



99% yield (745 mg, 1.78 mmol) from ketone **2.9h**[1] (567 mg, 1.80 mmol) following the procedure described in section 6.2.1.1.1. (page 105)

A yellow oil; IR (NaCl) 3446, 3059, 2965, 1589, 1495, 1462, 1088, 970 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (6H, s), 2.50 (2H, d, *J* = 7.2 Hz), 4.27 (2H, s), 4.83 (1H, s br), 6.24 (1H, dt, *J* = 15.6, 7.2 Hz), 6.96 (2H, d, *J* = 8.0 Hz), 7.09 (1H, d, *J* = 15.6 Hz), 7.14-7.23 (5H, m), 7.31-7.50 (7H, m), 7.75 (1H, d, *J* = 8.0 Hz), 7.83-7.85 (1H, m), 8.10-8.12 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.7, 41.2, 44.5, 54.9, 123.7, 124.0, 125.6, 125.7, 125.8, 126.8, 127.2, 128.0, 128.1, 128.2, 128.3(9), 128.4(2), 129.0, 129.3, 131.1, 131.3, 133.6, 134.3, 135.8, 140.1, 155.7.;ESIHRMS: Found: m/z 419.2490. Calcd for $C_{30}H_{31}N_2$: $(M+H)^+$ 419.2487.

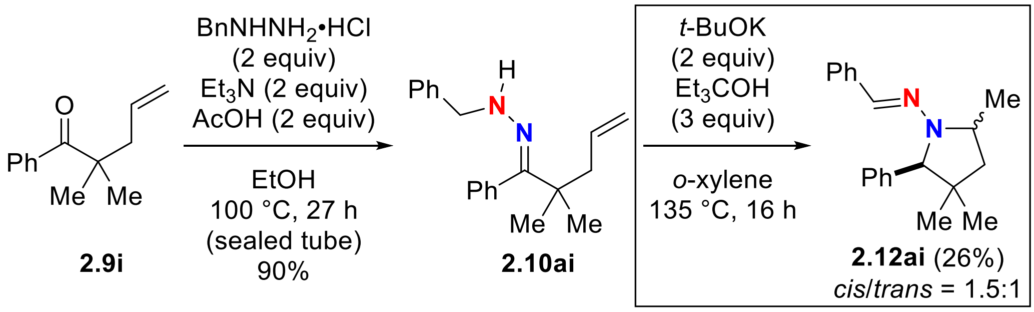
6.2.1.9.2. Synthesis of (*E*)-*N*-((2*S**,5*S**)-3,3-dimethyl-5-(naphthalen-1-ylmethyl)-2-phenylpyrrolidin-1-yl)-1-phenylmethanimine (2.12ah)



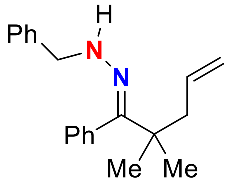
96% yield (202 mg, 0.482 mmol) (*cis*:*trans* = 3.8:1) (as an inseparable *cis*/*trans*-mixture) from **2.10ah** (209 mg, 0.499 mmol) for 3 h by the typical procedure A (page 106)

White solid; mp:68-69 °C; IR (NaCl) 3024, 2958, 1587, 1556, 1446, 1320, 1215, 916, 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.54 (3H×0.26, s), 0.56 (3H, s), 1.08 (3H, s), 1.34 (3H×0.26, s), 1.56 (1H, dd, J = 12.4, 5.6 Hz), 1.64-1.70 (1H+2H×0.26, m), 3.00 (1H×0.26, dd, J = 13.6, 10.4 Hz), 3.20 (1H, dd, J = 13.6, 10.0 Hz), 4.11-4.18 (2H, m), 4.39-4.48 (1H+2H×0.26, m), 4.52-4.59 (1H×0.26, m), 6.81(1H×0.26, s), 6.98 (1H, s), 7.10-7.19 (8H+8H×0.26, m), 7.41-7.63 (6H+6H×0.26, m), 7.78 (1H+1H×0.26, m), 7.89 (1H+1H×0.26, m), 8.41 (1H×0.26, d, J = 8.4 Hz), 8.47 (1H, d, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) (for *cis*-**2.12ah**) δ 26.2, 30.1, 39.3, 40.9, 43.4, 63.8, 75.7, 124.7, 125.4, 125.5, 125.6, 126.0, 126.9(5), 127.0(0), 127.0(8), 127.2, 127.5, 128.4, 128.6, 128.7, 131.9, 132.5, 134.0, 135.9, 137.4, 141.2.; ESIHRMS: Found: m/z 419.2489. Calcd for $C_{30}H_{31}N_2$: $(M+H)^+$ 419.2487.

6.2.1.10. Synthesis of 2.12ai (Scheme 2.6)



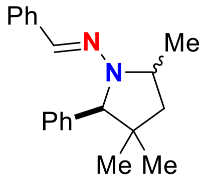
6.2.1.10.1. Synthesis of (*Z*)-1-benzyl-2-(2,2-dimethyl-1-phenylpent-4-en-1-ylidene)hydrazine (2.10ai)



90% yield (530 mg, 1.81 mmol) from ketone **2.9i**[1] (376 mg, 2.00 mmol) following the procedure described in section 6.2.1.1.1. (page 105)

A yellow liquid; IR (NaCl) 3393, 3071, 2967, 1638, 1495, 1454, 1383, 1088, 912, 754 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (6H, s), 2.19 (2H, d, *J* = 7.2 Hz), 4.24 (2H, s), 4.76 (1H, br s), 4.96-5.01 (2H, m), 5.71-5.81 (1H, m), 6.89 (2H, d, *J* = 8.4 Hz), 7.19-7.38 (8H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.3, 40.6, 44.8, 55.0, 116.7, 126.9, 128.0, 128.2(0), 128.2(3), 128.3, 128.9, 134.3, 135.9, 140.1, 156.0.; ESIHRMS: Found: m/z 293.2019. Calcd for $C_{20}H_{25}N_2$: $(M+H)^+$ 293.2018.

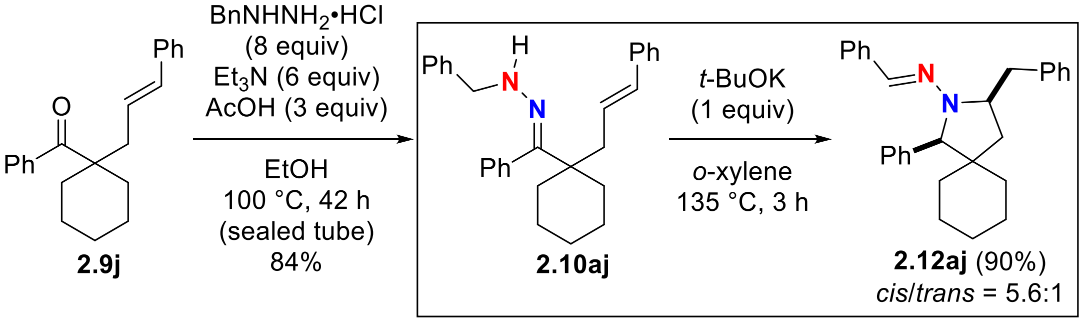
6.2.1.10.2. Synthesis of (*E*)-1-phenyl-*N*-((2*S**,5*S**)-3,3,5-trimethyl-2-phenylpyrrolidin-1-yl)methanimine (2.12ai)



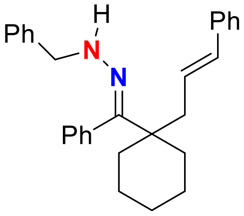
26% yield (38.6 mg, 0.132 mmol) (*cis*:*trans* = 1.5:1) (as an inseparable *cis*/*trans*-mixture) from **2.10ai** (144 mg, 0.493 mmol) with *t*-BuOK (2 equiv) and Et_3COH (3 equiv) for 16 h by the typical procedure A (page 106)

Yellow oil; IR (NaCl) 3059, 2960, 2926, 1587, 1556, 1446, 1373, 1192, 912, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.60 (3H×0.66, s), 0.63 (3H, s), 1.21 (3H×0.66, s), 1.26 (3H, s), 1.46 (3H, d, *J* = 6.4 Hz), 1.49-1.56 (1H+4H×0.66, m), 1.77 (1H×0.66, dd, *J* = 6.0, 12.4 Hz), 1.98 (1H, dd, *J* = 6.4, 12.0 Hz), 3.80-3.89 (1H×0.66, m), 4.13 (1H×0.66, s), 4.21-4.30 (2H, m), 6.69 (1H, s), 6.89 (1H×0.66, s), 7.05-7.33 (10H+8H×0.66, m), 7.40 (2H×0.66, d, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5, 20.6, 24.6, 26.1, 28.6, 30.0, 40.5, 40.7, 45.2, 47.4, 58.0, 58.2, 73.8, 75.6, 124.8, 125.2, 126.2, 126.6, 126.8, 126.9, 126.9, 127.0, 128.2, 128.3, 128.4, 129.9, 131.1, 137.4, 137.8, 138.7, 141.1.; ESIHRMS: Found: m/z 293.2014. Calcd for $C_{20}H_{25}N_2$: $(M+H)^+$293.2018.

6.2.1.11. Synthesis of 2.12aj (Scheme 2.6)



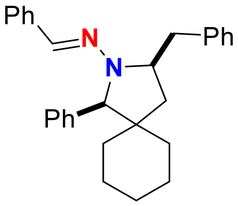
6.2.1.11.1. Synthesis of (*Z*)-1-benzyl-2-((1-cinnamylcyclohexyl)(phenyl)methylene)hydrazine (2.10aj)



84% yield (375 mg, 0.919 mmol) from ketone **2.9j**[1] (333 mg, 1.09 mmol) following the procedure described in section 6.2.1.1.1. (page 105)

A white solid; mp. 105-106 °C; IR (NaCl) 3269, 3026, 2922, 1595, 1495, 1454, 1215, 1083, 754 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33-1.54 (8H, m), 1.74-1.79 (2H, m), 2.37 (2H, d, *J* = 6.4 Hz), 4.28 (2H, s), 4.91 (1H, s br), 6.20 (1H, dt, *J* = 6.4, 16.0 Hz), 6.37 (1H, d, *J* = 16.0 Hz), 7.00 (2H, d, *J* = 6.8 Hz), 7.19-7.34 (11H, m), 7.39 (2H, t, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.3, 26.1, 34.1, 41.1, 44.3, 54.9. 126.1, 126.8, 127.5, 127.9, 128.1, 128.2, 128.3, 128.4, 128.9, 131.7, 134.3, 137.9, 140.4, 153.7.; ESIHRMS: Found: m/z 409.2649. Calcd for $C_{29}H_{33}N_2$: $(M+H)^+$ 409.2644.

6.2.1.11.2. Synthesis of (*E*)-*N*-((1*S**,3*S**)-3-benzyl-1-phenyl-2-azaspiro[4.5]decan-2-yl)-1-phenylmethanimine (2.12aj)



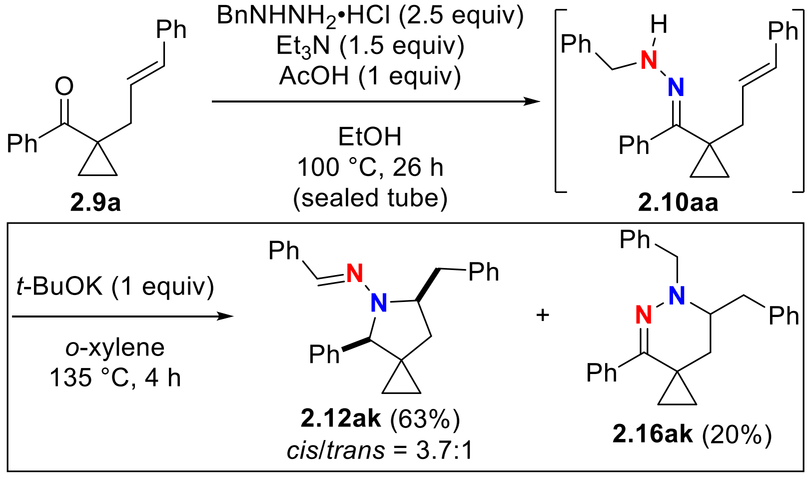
90% yield (184 mg, 0.451 mmol) (*cis*:*trans* = 5.6 : 1) from **2.10aj** (204 mg, 0.500 mmol) for 6 h by the typical procedure A (page 106)

The major *cis*-**2.12aj** was isolated partially for characterization.

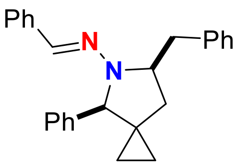
White solid; mp: 64-65 °C; IR (NaCl) 3061, 2927, 1587, 1556, 1494, 1454, 1151, 1070, 914, 752 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.68-0.71 (1H+1H×0.18, m), 0.83-0.90 (1H, m), 1.00-1.70 (9H+10H×0.18, m), 1.95 (1H, dd, *J* = 12.4, 5.6 Hz +1H×0.18, m), 2.70 (1H×0.18, dd, *J* = 13.2, 10.0 Hz), 3.05 (1H, dd, *J* = 13.2, 8.4 Hz), 3.56 (1H, dd, *J* = 13.2, 3.2 Hz), 3.75 (1H×0.18, dd, *J* = 13.2, 4.0 Hz), 3.91-3.98 (1H, m), 4.11 (1H, s), 4.32-4.39 (1H×0.18, m), 4.43 (1H×0.18, s), 6.80 (1H×0.18, s), 6.97 (1H, s), 7.10-7.34 (13H+15H×0.18, m), 7.43 (2H, d, *J* = 8.0 Hz).; ESIHRMS: Found: m/z 409.2646. Calcd for $C_{29}H_{33}N_2$: $(M+H)^+$ 409.2644.

cis-**2.12aj**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.68-0.71 (1H, m), 0.83-0.90 (1H, m), 1.09-1.66 (9H, m), 1.95 (1H, dd, *J* = 12.4, 5.6 Hz), 3.05 (1H, dd, *J* = 13.2, 8.4 Hz), 3.56 (1H, dd, *J* = 13.2, 3.2 Hz), 3.91-3.98 (1H, m), 4.11 (1H, s), 6.97 (1H, s), 7.10-7.34 (13H, m), 7.43 (2H, d, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.7, 22.8, 25.9, 35.4, 37.5, 37.6, 41.1, 44.1, 63.7, 76.4, 125.3, 126.0, 126.8, 127.0, 127.5, 128.2 (overlapped), 128.3, 130.0, 131.4, 137.4, 139.1, 140.7.

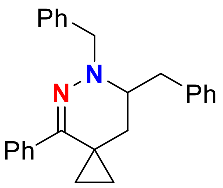
6.2.1.12. Synthesis of 2.12ak and 2.16ak (Scheme 2.6)



6.2.1.12.1. Synthesis of (*E*)-*N*-((4*S**,6*S**)-6-benzyl-4-phenyl-5-azaspiro[2.4]heptan-5-yl)-1-phenylmethanimine (2.12ak) and 6,7-dibenzyl-4-phenyl-5,6-diazaspiro[2.5]oct-4-ene (2.16ak)



with



63% yield (115 mg, 0.315 mmol) (*cis*:*trans* = 3.7 : 1) of **2.12ak** and 20% yield (36.8 mg, 0.100 mmol) of **2.16ak** from ketone **2.9k** (131 mg, 0.499 mmol) for 4 h by the typical procedure B (page 119).

cis-**2.12ak** was separated partially for characterization.

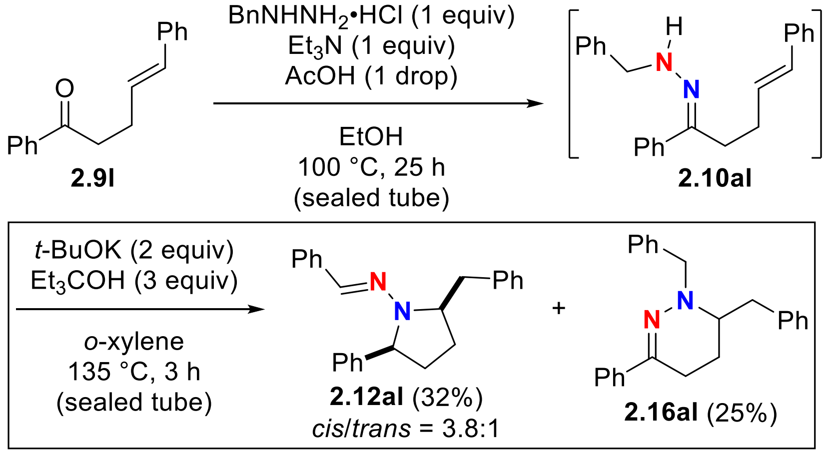
Characterization of **2.12ak**; Yellow oil; IR (NaCl) 3061, 3024, 1589, 1556, 1494, 1452, 1217, 1151, 1072, 912, 754 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.21-0.31 (2H+2H×0.27, m), 0.54-0.62 (2H, m), 0.68 (1H×0.27, ddd, *J* = 9.6, 5.6, 4.0 Hz), 0.80 (1H×0.27, ddd, *J* = 10.4, 5.6, 4.8 Hz), 1.40 (1H×0.27, dd, *J* = 12.4, 1.6 Hz), 1.49-1.52 (1H, m), 1.95 (1H, dd, *J* = 12.0, 9.2 Hz), 2.29 (1H×0.27, dd, *J* = 12.4, 7.2 Hz), 2.91 (1H×0.27, dd, *J* = 12.8, 9.6 Hz), 3.09 (1H, dd, *J* = 12.8, 9.2 Hz), 3.49 (1H×0.27, dd, *J*

= 13.2, 3.6 Hz), 3.60 (1H, dd, *J* = 13.2, 3.2 Hz), 4.05-4.09 (2H, m), 4.22 (1H×0.27, s), 4.44 (1H×0.27, dddd, *J* = 9.6, 7.2, 3.6, 1.6 Hz), 6.87 (1H×0.27, s), 6.98 (1H, s), 7.10-7.33 (13H+13H×0.27, m), 7.39 (2H×0.27, d, *J* = 7.6 Hz), 7.43 (2H, d, *J* = 7.6 Hz).; ESIHRMS: Found: m/z 367.2171. Calcd for $C_{26}H_{27}N_2$: $(M+H)^+$ 367.2174.

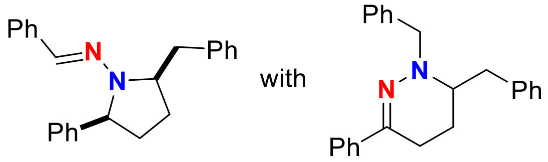
cis-**2.12ak**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.23-0.29 (2H, m), 0.54-0.62 (2H, m), 1.49-1.52 (1H, m), 1.93-1.98 (1H, m), 3.09 (1H, dd, *J* = 13.2, 9.2 Hz), 3.60 (1H, dd, *J* = 13.2, 3.2 Hz), 4.05-4.09 (2H, m), 6.98 (1H, s), 7.11-7.16 (3H, m), 7.23-7.33 (10H, m), 7.43 (2H, d, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.2, 13.8, 26.4, 37.5, 40.8, 66.2, 71.8, 125.4, 126.1, 126.3, 127.0, 127.2, 128.2, 128.3, 128.6, 129.9, 132.4, 137.1, 139.1, 141.5.

Characterization of **2.16ak**; Yellow oil; IR (NaCl) 3061, 3026, 2945, 1600, 1494, 1454, 1355, 1217, 1072 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.34 (1H, ddd, *J* = 10.0, 6.0, 4.0 Hz), 0.60 (1H, ddd, *J* = 9.6, 5.2, 4.4 Hz), 0.77 (1H, ddd, *J* = 10.0, 6.0, 4.0 Hz), 0.94 (1H, ddd, *J* = 9.6, 5.2, 4.4 Hz), 1.52 (1H, dd, *J* = 13.2, 5.6 Hz), 1.76 (1H, dd, *J* = 13.2, 4.0 Hz), 2.78 (1H, dd, *J* = 13.2, 10.0 Hz), 3.26 (1H, dd, *J* = 13.2, 4.4 Hz), 3.35 (1H, dddd, *J* = 10.0, 5.6, 4.4, 4.0 Hz), 4.39 (1H, d, *J* = 14.8 Hz), 4.72 (1H, d, *J* = 14.8 Hz), 7.06 (2H, d, *J* = 7.2 Hz), 7.18 (1H, t, *J* = 8.0 Hz), 7.23-7.37 (10H, m), 7.43 (2H, d, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.3, 14.9, 16.1, 34.5, 35.2, 55.6, 59.1, 126.2, 127.2, 127.5, 128.0, 128.3, 128.4, 128.7, 128.9, 129.2, 137.2, 138.4, 139.1, 149.0.; ESIHRMS: Found: m/z 367.2176. Calcd for $C_{26}H_{27}N_2$: $(M+H)^+$ 367.2174.

6.2.1.13. Synthesis of 2.12al and 2.16al (Scheme 2.6)



6.2.1.13.1. Synthesis of (*E*)-*N*-((2*R**,5*S**)-2-benzyl-5-phenylpyrrolidin-1-yl)-1-phenylmethanimine (2.12al) and 1,6-dibenzyl-3-phenyl-1,4,5,6-tetrahydropyridazine (2.16al)



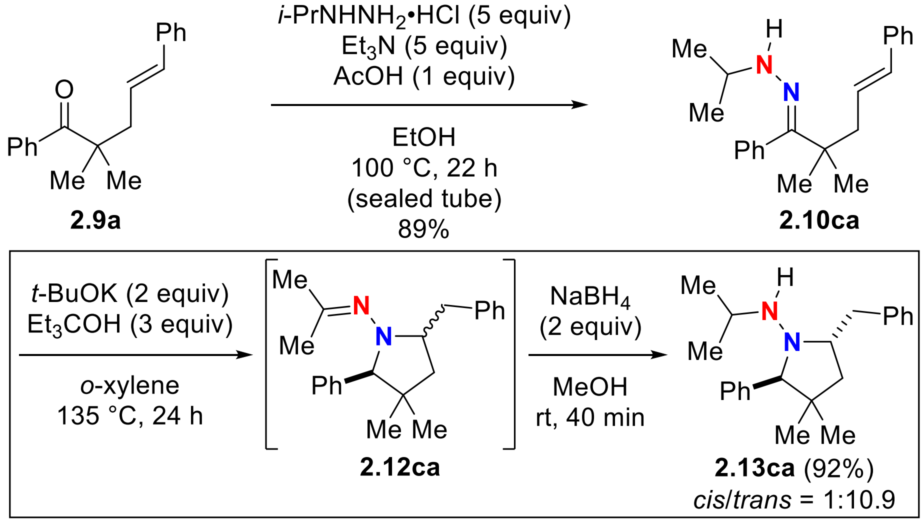
32% yield (54.6 mg, 0.160 mmol) (*cis*:*trans* = 3.8:1 as an inseparable mixture) of **2.12al** and 25% yield (42.0 mg, 0.123 mmol) of **2.16al** from ketone **2.9l** (116 mg, 0.491 mmol) with *t*-BuOK (2 equiv) and Et_3COH (3 equiv) for 3 h by the typical procedure B (page 119).

Characterization of **2.12al**; Yellow oil; IR (NaCl) 3061, 3026 2939, 1587, 1555, 1494, 1454, 1328, 1153, 1091, 910, 752 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.63-1.75 (1H+2H×0.26, m), 1.78-1.86 (2H, m), 1.95-2.04 (1H×0.26, m), 2.18-2.28 (1H×0.26, m), 2.31-2.40 (1H, m), 2.82 (1H×0.26, dd, *J* = 13.2, 8.8 Hz), 2.97 (1H, dd, *J* = 13.2, 8.8 Hz), 3.34 (1H×0.26, dd, *J* = 13.2, 3.6 Hz), 3.54 (1H, dd, *J* = 13.2, 4.0 Hz), 3.87-3.94 (1H, m), 4.32-4.36 (1H×0.26, m), 4.50 (1H, dd, *J* = 9.2, 3.2 Hz), 4.66-4.69 (1H×0.26, m), 6.85 (1H×0.26, s), 6.98 (1H, s), 7.12-7.32 (13H+13H×0.26, m), 7.42-7.46 (2H+2H×0.26, m); ^{13}C NMR (100 MHz, $CDCl_3$) (for *cis*-**2.12al**) δ 27.5, 33.7, 41.0, 65.3, 67.0, 125.4, 125.8, 126.1, 126.8, 127.0, 128.2, 128.3, 128.6, 129.8, 132.4, 137.2, 139.2, 143.8.; ESIHRMS: Found: m/z 341.2021. Calcd for $C_{24}H_{25}N_2$: $(M+H)^+$ 341.2018.

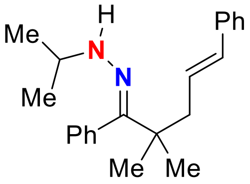
Characterization of **2.16al**; Orange oil; IR (NaCl) 3061, 2933, 1681, 1583, 1556, 1494, 1122, 908, 692 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.65-1.79 (2H, m), 2.47-2.51 (2H, m), 2.57 (1H, dd, *J* = 13.2, 9.6 Hz), 3.09 (1H, dd, *J* = 13.2, 4.8 Hz), 3.23-3.29 (1H, m), 4.36 (1H, d, *J* = 14.4 Hz), 4.73 (1H, d, *J* = 14.4 Hz), 7.07 (2H, d, *J* = 8.0 Hz), 7.18-7.39 (11H, m), 7.72 (2H, d, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.0, 21.8, 35.6, 54.1, 59.8, 123.9, 126.3, 127.0, 127.2, 128.2, 128.3, 128.4, 128.5, 129.2, 138.5, 138.6, 138.8, 139.0.; ESIHRMS: Found: m/z 341.2019. Calcd for $C_{24}H_{25}N_2$: $(M+H)^+$ 341.2018.

6.2.2. Hydroamination of γ,δ-alkenyl hydrazones 2.10c for synthesis of *N*-amino pyrrolidines 2.13c (Table 2.1, entry 6 and Scheme 2.7)

6.2.2.1. Synthesis of 2.13ca (Table 2.1, entry 6)



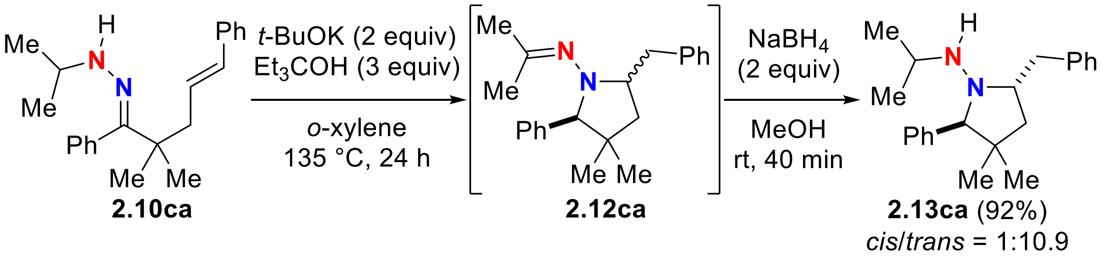
6.2.2.1.1. Synthesis of (*Z*)-1-((*E*)-2,2-dimethyl-1,5-diphenylpent-4-en-1-ylidene)-2-isopropylhydrazine (2.10ca)



89% yield (1.84 g, 5.74 mmol) from ketone **2.9a**[1] (1.70 g, 6.44 mmol) following the procedure described in section 6.2.1.1.1. (page 105)

A white solid; mp: 57-58 °C; IR (NaCl) 3290, 3024, 2964, 1597, 1494, 1469, 1381, 1362, 1217, 962, 756 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.05 (6H, d, *J* = 6.4 Hz), 1.14 (6H, s), 2.43 (2H, d, *J* = 6.0 Hz), 3.40 (1H, septet, *J* = 6.4 Hz), 4.27 (1H, s br), 6.36 (1H, dt, *J* = 16.0, 6.0 Hz), 6.41 (1H, d, *J* = 16.0 Hz), 7.07 (2H, d, *J* = 8.0 Hz), 7.19-7.22 (1H, m), 7.30 (2H, t, *J* = 7.6 Hz), 7.36-7.39 (3H, m), 7.45 (2H, m); ^{13}C NMR (100 MHz, CDCl$_3$) δ 22.0, 26.6, 41.2, 44.1, 50.6, 126.0, 126.8, 128.0, 128.2, 128.4, 128.5, 129.0, 131.9, 134.6, 138.0, 154.8.; ESIHRMS: Found: m/z 321.2335. Calcd for $C_{22}H_{29}N_2$: $(M+H)^+$ 321.2331.

6.2.2.1.2. Synthesis of 2.13ca (Table 2.1, entry 6) (Typical procedure C)

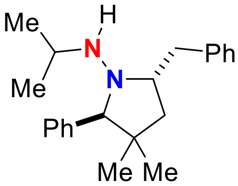


To a 25 mL Schlenk tube containing hydrazone **2.10ca** (160 mg, 0.499 mmol) and *t*-BuOK (114 mg, 1.02 mmol) in *o*-xylene (5.0 mL) was added Et$_3$COH (210 μL, 1.49 mmol) under an Ar atmosphere. The solution was then stirred at 135 °C for 24 h and cooled down to room temperature. After dilution with water and ethyl acetate, the mixture was extracted thrice with ethyl acetate. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting crude material was used immediately for the next reduction as *N*-iminopyrrolidine **2.12ca** was not very stable under an aerobic conditions (the chemical structure of the major isomer, *trans*-**2.12ca** could be confirmed by X-ray crystallographic analysis).

To a 50 mL round bottom flask containing crude material obtained above in MeOH (4.0 mL) was added $NaBH_4$ (40.3 mg, 1.07 mmol) under a N_2 atmosphere and the solution was stirred at room temperature for 40 min. The solution was quenched with saturated aqueous NH_4Cl and basified with 1 M NaOH. After dilution with ethyl acetate, the mixture was extracted with ethyl acetate. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting crude material was purified by flash column chromatography (hexane:Et_2O = 60:1) to yield *trans*-**2.13ca** (136 mg, 0.420 mmol) in 84% yield and *cis*-**2.13ca** (12.5 mg, 0.0388 mmol) in 8% yield (total yield, 92% from hydrazone **2.10ca**; *cis*:*trans* = 1:10.9).

6.2.2.1.3.

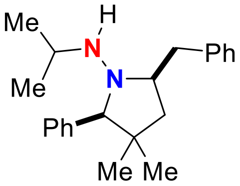
(2*R**,5*S**)-5-benzyl-*N*-isopropyl-3,3-dimethyl-2-phenylpyrrolidin-1-amine (*trans*-2.13ca)



Yellow oil; IR (NaCl) 3393, 3026, 2968, 2955, 1603, 1495, 1452, 1361, 1118, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.64 (3H, s), 0.80 (3H, d, J = 6.4 Hz), 1.07 (3H, d, J = 6.4 Hz), 1.32 (3H, s), 1.52 (1H, dd, J = 13.2, 4.4 Hz), 1.79 (1H, dd, J = 13.2, 9.6 Hz), 2.45 (1H, dd, J = 12.8, 10.8 Hz), 2.62 (1H, s br), 2.89 (1H, septet, J = 6.4 Hz), 3.37 (1H, dd, J = 12.8, 3.6 Hz), 3.53 (1H, dddd, J = 10.8, 9.6, 4.4, 3.6 Hz), 3.96 (1H, s), 7.17-7.32 (10H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 21.6, 26.5, 32.0, 39.4, 41.0, 42.0, 47.7, 65.3, 76.7, 125.7, 127.0, 128.1, 128.2, 129.3, 129.4, 139.0, 140.8. ESIHRMS: Found: m/z 323.2489. Calcd for $C_{22}H_{31}N_2$: $(M+H)^+$ 323.2487.

6.2.2.1.4.

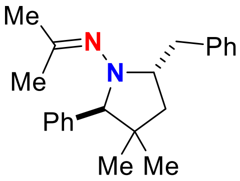
(2*S**,5*S**)-5-benzyl-*N*-isopropyl-3,3-dimethyl-2-phenylpyrrolidin-1-amine (*cis*-2.13ca)



Yellow oil; IR (NaCl) 3026, 2957, 1601, 1495, 1454, 1364, 1029, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.52 (3H, s), 0.76 (3H, d, J = 6.4 Hz), 0.97 (3H, d, J = 6.4 Hz), 1.00 (3H, s), 1.42 (1H, dd, J = 12.8, 9.6 Hz), 1.52 (1H, dd, J = 12.8, 6.8 Hz), 2.29 (1H, s br), 2.51 (1H, dd, J = 13.2, 10.0 Hz), 2.74 (1H, septet, J = 6.4 Hz), 2.97 (1H, dddd, J = 10.0, 9.6, 6.8, 4.4 Hz), 3.34 (1H, s), 3.43 (1H, dd, J = 13.2, 4.4 Hz), 7.17-7.36 (10H, m).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8(8), 21.8(9), 27.3, 30.4, 39.2, 41.8, 44.2, 48.2, 67.8, 85.9, 125.7, 126.8, 127.4, 128.1, 128.5, 129.2, 140.7, 142.4.; ESIHRMS: Found: m/z 323.2491. Calcd for $C_{22}H_{31}N_2$: $(M+H)^+$ 323.2487.

6.2.2.1.5.

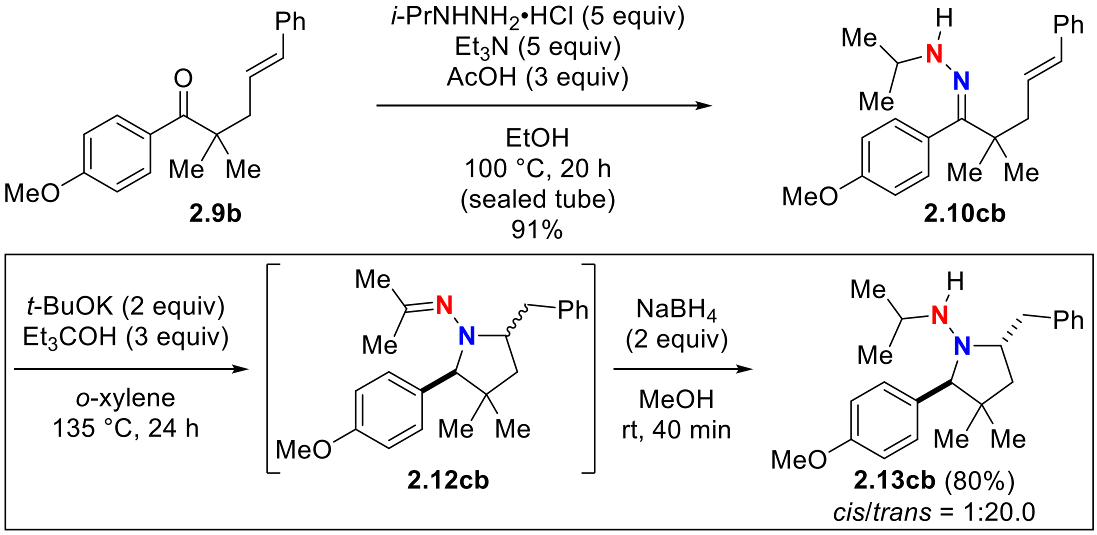
N-((2*S**,5*R**)-5-benzyl-3,3-dimethyl-2-phenylpyrrolidin-1-yl)propan-2-imine (*trans*-2.12ca)



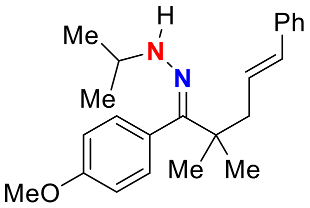
[X-ray]

Yellow crystal (*trans*-**2.12ca** could be recrystallized from $CHCl_3$/hexane) (CCDC 1424733); mp: 92-93 °C; IR (NaCl) 3019, 2954, 2933, 1637, 1602, 1494, 1452, 1363, 1215, 1029 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.63 (3H, s), 1.10 (3H, s), 1.67 (1H, dd, *J* = 12.8, 6.4 Hz), 1.77 (1H, dd, *J* = 12.8, 7.6 Hz), 1.86 (3H, s), 2.02 (3H, s), 2.42 (1H, dd, *J* = 13.2, 10.4 Hz), 2.88 (1H, dd, *J* = 13.2, 4.4 Hz), 3.94 (1H, dddd, *J* = 10.4, 7.6, 6.4, 4.4 Hz), 4.37 (1H, s), 7.14-7.30 (10H, m).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 24.7, 25.0, 28.0, 37.6, 39.4, 45.6, 61.4, 77.4, 125.8, 126.3, 127.3, 128.3, 128.4, 129.1, 140.1(5), 140.1(9), 163.2.; ESIHRMS: Found: m/z 321.2327. Calcd for $C_{22}H_{29}N_2$: $(M+H)^+$ 321.2331.

6.2.2.2. Synthesis of 2.13cb (Scheme 2.7)



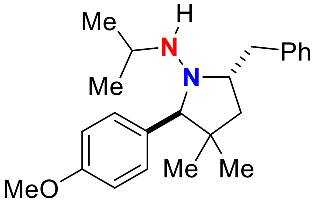
6.2.2.2.1. Synthesis of (*Z*)-1-isopropyl-2-((*E*)-1-(4-methoxyphenyl)-2,2-dimethyl-5-phenylpent-4-en-1-ylidene)hydrazine (2.10cb)



91% yield (632 mg, 1.80 mmol) from ketone **2.9b**[1] (584 mg, 1.98 mmol) following the procedure described in section 6.2.1.1.1. (page 105)

A yellow oil; IR (NaCl) 3026, 2965, 1607, 1506, 1447, 1381, 1248, 1175, 835 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (6H, d, *J* = 6.4 Hz), 1.12 (6H, s), 2.41 (2H, d, *J* = 6.0 Hz), 3.39 (1H, septet, *J* = 6.4 Hz), 3.83 (3H, s), 4.31 (1H, s br), 6.32 (1H, dt, *J* = 16.0, 6.4 Hz), 6.38 (1H, d, *J* = 16.0 Hz), 6.95 (2H, d, *J* = 8.8 Hz), 7.00 (2H, d, *J* = 8.8 Hz), 7.19 (1H, t, *J* = 7.2 Hz), 7.29 (2H, t, *J* = 7.2 Hz), 7.35 (2H, d, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0, 26.6, 41.3, 44.1, 50.5, 55.2, 114.4, 126.0, 126.5, 126.8, 128.3, 128.4, 129.7, 131.8, 138.0, 154.7, 159.1.; ESIHRMS: Found: m/z 351.2438. Calcd for $C_{23}H_{31}N_2O$: $(M+H)^+$ 351.2436.

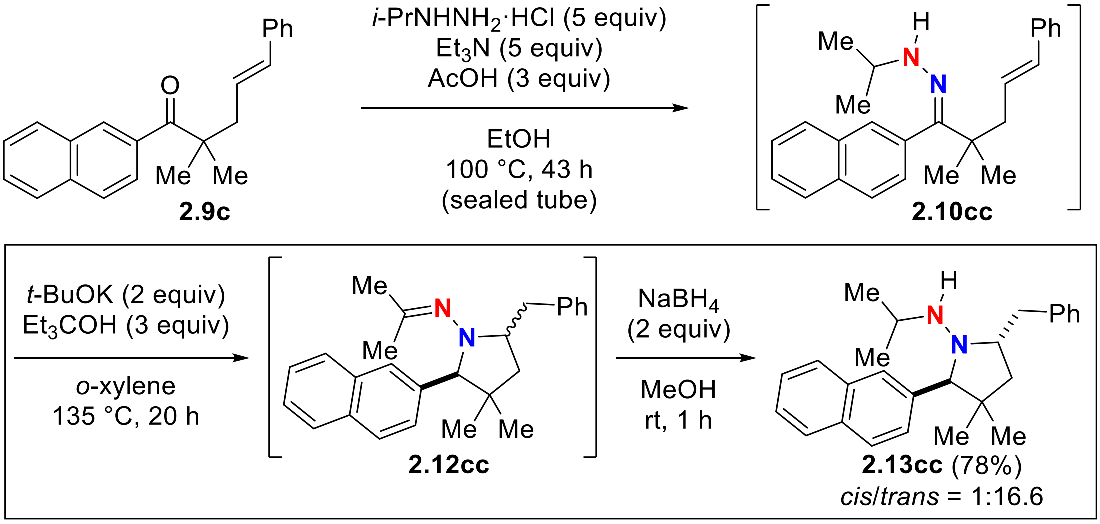
6.2.2.2.2. Synthesis of (2*R**,5*S**)-5-benzyl-*N*-isopropyl-2-(4-methoxyphenyl)-3,3-dimethylpyrrolidin-1-amine (2.13cb)



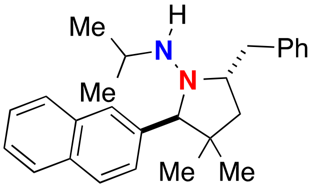
80% yield (141 mg, 0.401 mmol) (*cis*:*trans* = 1:20.0, determined by crude ^{1}H NMR) from **2.10cb** (174 mg, 0.497 mmol) for 24 h by the typical procedure C (page 133).

Orange oil; IR (NaCl) 3026, 2954, 1667, 1607, 1514, 1454, 1361, 1250, 1179, 1038, 833, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.64 (3H, s), 0.81 (6H, d, *J* = 6.0 Hz), 1.07 (3H, d, *J* = 6.0 Hz), 1.30 (3H, s), 1.50 (1H, dd, *J* = 13.2, 4.4 Hz), 1.77 (1H, dd, *J* = 13.2, 9.6 Hz), 2.44 (1H, dd, *J* = 12.8, 10.8 Hz), 2.88 (1H, septet, *J* = 6.0 Hz), 3.37 (1H, dd, *J* = 13.2, 3.6 Hz), 3.48 (1H, dddd, *J* = 10.8, 9.6, 4.4, 3.6 Hz), 3.81 (3H, s), 3.92 (1H, s), 6.86 (2H, d, *J* = 8.4 Hz), 7.09 (2H, d, *J* = 8.4 Hz), 7.18 (1H, t, *J* =7.2 Hz), 7.23-7.30 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 21.7, 26.5, 32.1, 39.3, 42.0, 47.7, 55.2, 76.0, 113.5, 125.6, 128.2, 129.4, 130.6, 130.8, 140.9, 158.6. ESIHRMS: Found: m/z 353.2597. Calcd for $C_{23}H_{33}N_2O$: $(M+H)^+$ 353.2593.

6.2.2.3. Synthesis of 2.13cc (Scheme 2.7)



6.2.2.3.1. Synthesis of (2*R**,5*S**)-5-benzyl-*N*-isopropyl-3,3-dimethyl-2-(naphthalen-2-yl)pyrrolidin-1-amine (2.13cc)

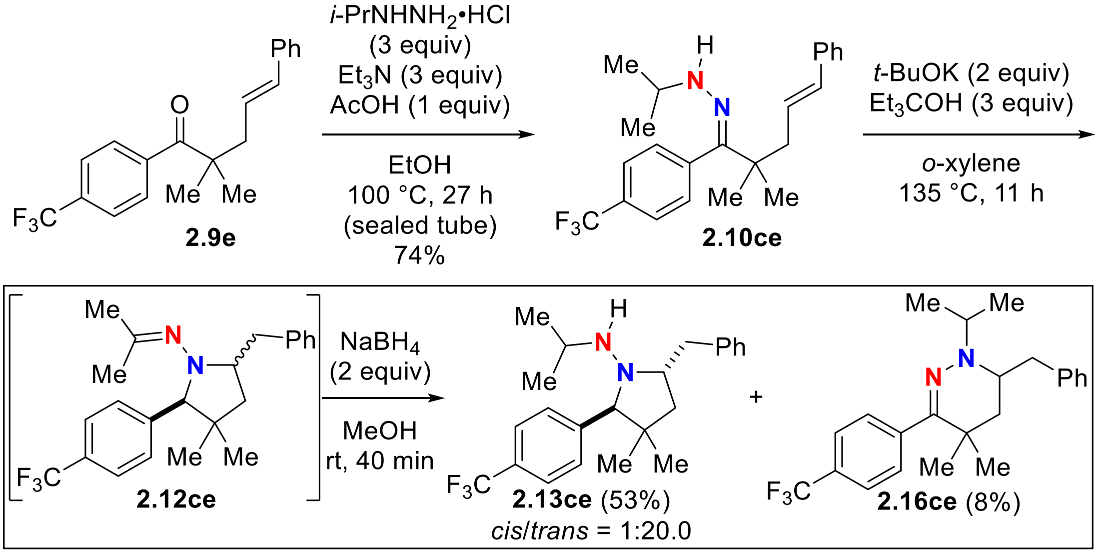


Synthesis of **2.13cc** was conducted by 3-step procedure from ketone **2.9c** including 1) formation of hydrazone **2.10cc**; 2) hydroamination; 3) $NaBH_4$ reduction.

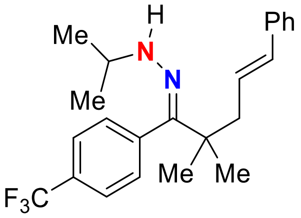
78% yield (232 mg, 0.622 mmol) (*cis*:*trans* = 1:16.6, determined by crude ^{1}H NMR) from ketone **2.9c** (252 mg, 0.801 mmol) for 20 h.

Brown sticky oil; IR (NaCl) 3196, 3059, 2957, 1601, 1470, 1454, 1377, 1217, 1120, 756 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.65 (3H, s), 0.78 (3H, d, *J* = 6.0 Hz), 1.08 (3H, d, *J* = 6.0 Hz), 1.36 (3H, s), 1.58 (1H, dd, *J* = 13.0, 4.0 Hz), 1.87 (1H, dd, *J* = 13.0, 7.6 Hz), 2.47-2.52 (1H, m), 2.82 (1H, s br), 2.95 (1H, septet, *J* = 6.0 Hz), 3.40-3.42 (1H, m), 3.65-3.69 (1H, m), 4.13 (1H, s), 7.19-7.22 (1H, m), 7.27-7.37 (5H, m), 7.44-7.48 (2H, m), 7.63 (1H, s), 7.79-7.83 (3H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.4, 21.6, 26.5, 32.0, 39.7, 42.2, 47.8, 77.0, 125.6, 125.7, 125.9, 127.4, 127.5(6), 127.5(9), 127.8, 128.2, 128.3, 129.4, 132.7, 133.3, 137.0, 140.8.; ESIHRMS: Found: m/z 373.2640. Calcd for $C_{26}H_{33}N_2$: $(M+H)^+$ 373.2644.

6.2.2.4. Synthesis of 2.13ce and 2.16ce (Scheme 2.7)



6.2.2.4.1. Synthesis of (*Z*)-1-((*E*)-2,2-dimethyl-5-phenyl-1-(4-(trifluoromethyl)phenyl)pent-4-en-1-ylidene)-2-isopropylhydrazine (2.10ce)

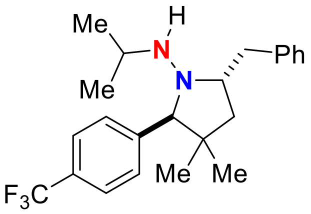


74% yield (575 mg, 1.48 mmol) from ketone **2.9e**[1] (664 mg, 2.00 mmol) following the procedure described in section 6.2.1.1.1. (page 105)

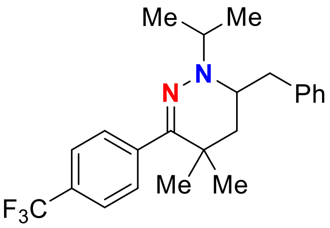
A white solid; mp. 58-59 °C; IR (NaCl) 3026, 2967, 1614, 1470, 1447, 1325, 1128, 1067, 843, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.05 (6H, d, *J* = 6.4 Hz), 1.13 (6H, s), 2.42 (2H, d, *J* = 6.8 Hz), 3.40 (1H, septet, *J* = 6.4 Hz), 4.15 (1H, s br), 6.32 (1H, dt, *J* = 16.0, 6.8 Hz), 6.34 (1H, d, *J* = 16.0 Hz), 7.20-7.22 (3H, m), 7.30 (2H, t, *J* = 7.6 Hz), 7.35 (2H, d, *J* = 7.2 Hz), 7.70 (2H, d, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0, 26.7, 41.2, 44.2, 50.8, 124.0 (q, *J* = 270.4 Hz), 126.0(1), 126.0(3) (q, *J*

= 3.5 Hz), 127.0, 127.7, 128.5, 129.1, 130.3 (q, *J* = 32.5 Hz), 132.2, 137.8, 138.6, 152.8.; ESIHRMS: Found: m/z 389.2207. Calcd for $C_{23}H_{28}N_2F_3$: $(M+H)^+$ 389.2205.

6.2.2.4.2. Synthesis of (2*R**,5*S**)-5-benzyl-*N*-isopropyl-3,3-dimethyl-2-(4-(trifluoromethyl)phenyl)pyrrolidin-1-amine (2.13ce) and 6-benzyl-1-isopropyl-4,4-dimethyl-3-(4-(trifluoromethyl)phenyl)-1,4,5,6-tetrahydropyridazine (2.16ce)



with

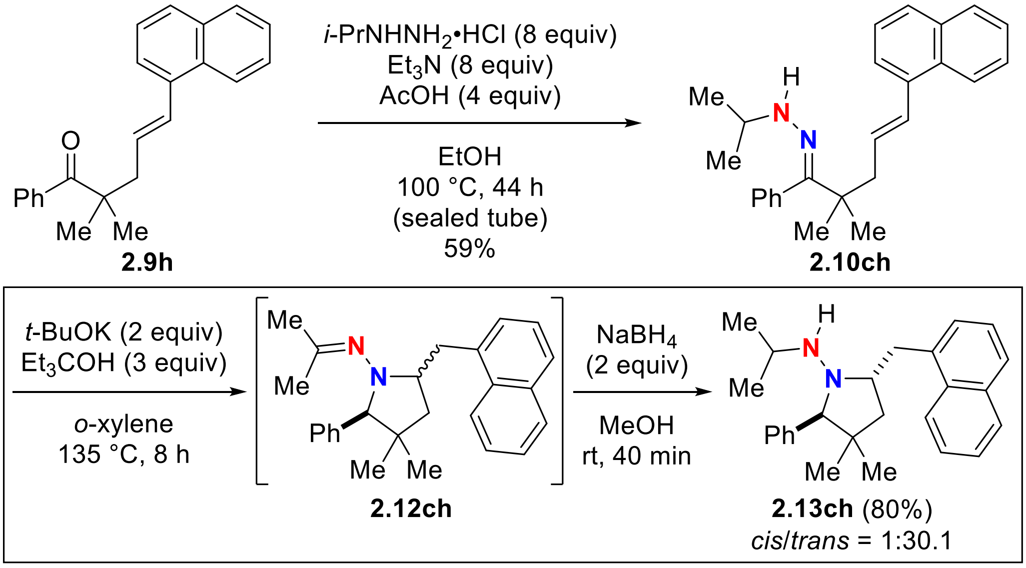


53% yield (104 mg, 0.266 mmol) (*cis*:*trans* = 1:20.0, determined by crude ^{1}H NMR) of **2.13ce** and 8% yield (15.4 mg, 0.0396 mmol) of **2.16ce** from **2.10ce** (193 mg, 0.496 mmol) for 11 h by the typical procedure C (page 133).

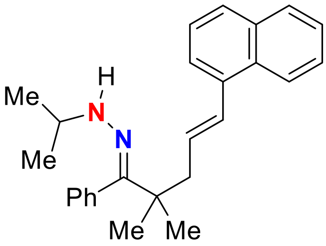
Characterization of **2.13ce**; White solid; mp. 65-66 °C; IR (NaCl) 3196, 3028, 2957, 2870, 1618, 1454, 1362, 1325, 1125, 1069, 756 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.60 (3H, s), 0.85 (3H, d, *J* = 6.4 Hz), 1.07 (3H, d, *J* = 6.4 Hz), 1.26 (3H, s), 1.56 (1H, dd, *J* = 13.2, 4.4 Hz), 1.75 (1H, dd, *J* = 13.2, 8.8 Hz), 2.44 (1H, dd, *J* = 12.8, 10.8 Hz), 2.66 (1H, s br), 2.94 (1H, septet, *J* = 6.4 Hz), 3.31 (1H, dd, *J* = 12.8, 3.6 Hz), 3.63 (1H, dddd, *J* = 10.8, 8.8, 4.4, 3.6 Hz), 3.96 (1H, s), 7.19-7.35 (7H, m), 7.58 (2H, d, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 26.3, 30.3, 31.1, 39.0, 39.3, 42.6, 47.8, 63.7, 76.8, 124.3 (q, *J* = 270.2 Hz), 124.8 (q, *J* = 3.6 Hz), 125.9, 128.3, 129.2 (q, *J* = 32.0 Hz), 129.3, 129.4, 140.3, 143.9.； ESIHRMS: Found: m/z 391.2360. Calcd for $C_{23}H_{30}N_2F_3$: $(M+H)^+$ 391.2361.

Characterization of **2.16ce**; Yellow solid; mp. 112-113 °C; IR (NaCl) 3022, 2963, 1614, 1454, 1325, 1215, 1120, 1018, 756 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (3H, d, *J* = 6.4 Hz), 1.06 (3H, s), 1.23 (3H, s), 1.41 (3H, d, *J* = 6.4 Hz), 1.47 (1H, dd, *J* = 13.2, 2.8 Hz), 1.56-1.62 (1H, m), 2.57 (1H, dd, *J* = 12.8, 8.8 Hz), 3.24-3.35 (2H, m), 3.84 (1H, septet, *J* = 6.4 Hz), 7.19-7.26 (3H, m), 7.32 (2H, t, *J* = 7.6 Hz), 7.53 (2H, d, *J* = 8.4 Hz), 7.61 (2H, d, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.0, 21.3, 27.8, 30.5, 32.2, 39.3, 42.5, 50.2, 52.1, 124.4 (q, *J* = 270.1 Hz), 124.5 (q, *J* = 3.7 Hz), 126.4, 128.0, 128.3 (q, *J* = 32.1 Hz), 128.5, 129.3, 138.3, 143.1, 147.3.; ESIHRMS: Found: m/z 389.2209. Calcd for $C_{23}H_{28}N_2F_3$: $(M+H)^+$ 389.2205.

6.2.2.5. Synthesis of 2.13ch (Scheme 2.7)



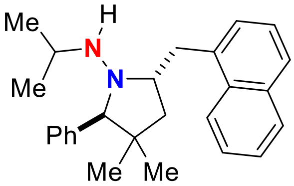
6.2.2.5.1. Synthesis of (*Z*)-1-((*E*)-2,2-dimethyl-5-(naphthalen-1-yl)-1-phenylpent-4-en-1-ylidene)-2-isopropylhydrazine (2.10ch)



59% yield (349 mg, 0.940 mmol) from ketone **2.9h**[1] (503 mg, 1.60 mmol) following the procedure described in section 6.2.1.1.1. (page 105)

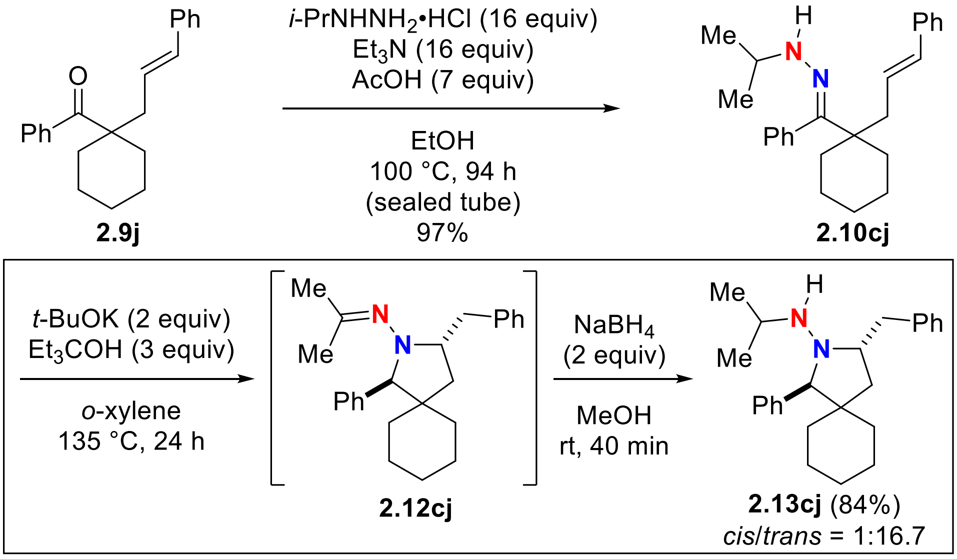
A yellow oil; IR (NaCl) 3057, 2965, 1589, 1508, 1466, 1441, 1362, 1165, 1072, 970, 775 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.04 (6H, d, *J* = 6.4 Hz), 1.20 (6H, s), 2.55 (1H, d, *J* = 7.2 Hz), 3.39 (1H, septet, *J* = 6.4 Hz), 4.28 (1H, s br), 6.35 (1H, dt, *J* = 15.6, 7.2 Hz), 7.09 (2H, d, *J* = 8.4 Hz), 7.12 (1H, d, *J* = 15.6 Hz), 7.34-7.38 (1H, m), 7.41-7.51 (5H, m), 7.57 (1H, d, *J* = 7.2 Hz), 7.74 (1H, d, *J* = 8.4 Hz), 7.83 (1H, d, *J* = 7.2 Hz), 8.13 (1H, d, *J* = 8.8 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 22.0, 26.7, 41.3, 44.5, 50.6, 123.6, 124.0, 125.5(8), 125.6(4), 125.8, 127.2, 128.0, 128.4, 128.5, 129.0, 129.3, 131.1, 131.5, 133.6, 134.6, 135.8, 154.8.; ESIHRMS: Found: m/z 371.2484. Calcd for $C_{26}H_{31}N_2$: $(M+H)^+$ 371.2487.

6.2.2.5.2. Synthesis of (2*R**,5*S**)-*N*-isopropyl-3,3-dimethyl-5-(naphthalen-1-ylmethyl)-2-phenylpyrrolidin-1-amine (2.13ch)

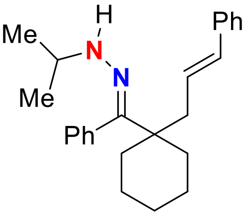


80% yield (150 mg, 0.403 mmol) (*cis*:*trans* = 1:30.1, determined by crude ^{1}H NMR) from **2.10ch** (185 mg, 0.499 mmol) for 8 h by the typical procedure C (page 133). Brown oil; IR (NaCl) 3198, 3043, 2955, 2866, 1597, 1454, 1362, 1190, 1119, 791 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.68 (3H, s), 0.90 (3H, d, J = 6.0 Hz), 1.20 (3H, d, J = 6.0 Hz), 1.47 (3H, s), 1.65 (1H, dd, J = 13.2, 3.6 Hz), 1.80 (1H, dd, J = 13.2, 9.6 Hz), 2.82-2.88 (1H, m), 2.99 (1H, septet, J = 6.0 Hz), 3.70-3.74 (1H, m), 4.04-4.08 (2H, m), 7.18 (2H, d, J =7.2 Hz), 7.27-7.31 (3H, m), 7.43-7.58 (4H, m), 7.76 (1H, d, J = 7.2 Hz), 7.89 (1H, d, J = 8.0 Hz), 8.33 (1H, d, J = 8.4 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 21.5, 21.8, 26.5, 32.4, 38.9, 39.8, 42.2, 47.7, 64.7, 76.6, 124.7, 125.4(2), 125.4(5), 125.7, 126.5, 126.9, 127.1, 128.2, 128.6, 129.5, 132.4, 133.9, 137.2, 139.0. ESIHRMS: Found: m/z 373.2640. Calcd for $C_{26}H_{33}N_2$: (M+H)$^+$ 373.2644.

6.2.2.6. Synthesis of 2.13cj (Scheme 2.7)



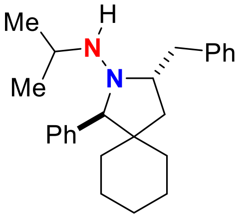
6.2.2.6.1. Synthesis of (*Z*)-1-((1-cinnamylcyclohexyl)(phenyl)methylene)-2-isopropylhydrazine (2.10cj)



97% yield (362 mg, 1.00 mmol) from ketone **2.9j**[1] (313 mg, 1.03 mmol) following the procedure described in section 6.2.1.1.1. (page 105)

A white solid; mp: 52-53 °C; IR (NaCl) 3420, 3026, 2930, 1597, 1494, 1450, 1362, 1217, 1074, 965, 752 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (6H, d, *J* = 6.4 Hz), 1.34-1.61 (8H, m), 1.80-1.85 (2H, m), 2.40 (2H, d, *J* = 6.4 Hz), 3.38 (1H, septet, *J* = 6.4 Hz), 4.33 (1H, s br), 6.32 (1H, dt, *J* = 15.6, 6.4 Hz), 6.42 (1H, d, *J* = 15.6 Hz), 7.11 (2H, d, *J* = 6.8 Hz), 7.19 (1H, t, *J* = 7.2 Hz), 7.29 (2H, t, *J* = 7.2 Hz), 7.33-7.37 (3H, m), 7.43 (2H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.1, 22.5, 26.2, 34.2, 41.4, 44.5, 50.6, 126.0, 126.8, 127.7, 128.0, 128.3(9), 128.4(2), 129.0, 131.6, 134.5, 137.9, 152.6.; ESIHRMS: Found: m/z 361.2647. Calcd for $C_{25}H_{33}N_2$: $(M+H)^+$ 361.2644.

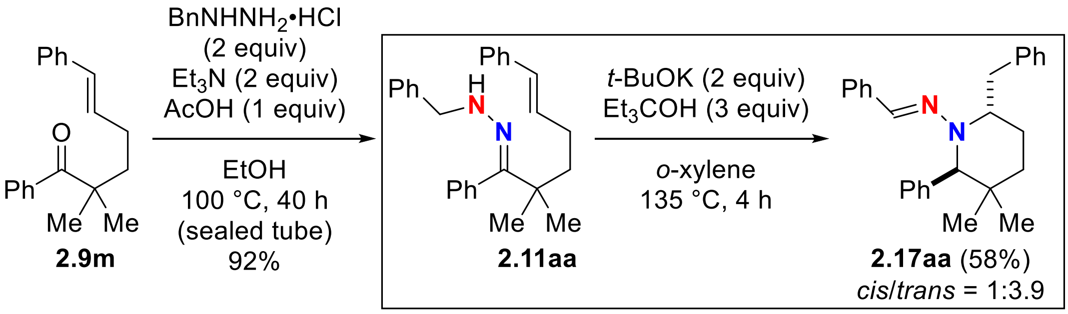
6.2.2.6.2. Synthesis of (1*R**,3*S**)-3-benzyl-*N*-isopropyl-1-phenyl-2-azaspiro[4.5]decan-2-amine (2.13cj)



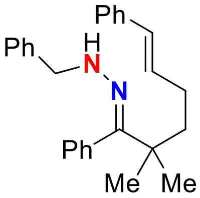
84% yield (153 mg, 0.422 mmol) (*cis*:*trans* = 1:16.7, determined by crude ^{1}H NMR) from **2.10cj** (180 mg, 0.499 mmol) for 24 h by the typical procedure C (page 133). Orange oil; IR (NaCl) 3201, 3022, 2920, 2841, 1600, 1493, 1452, 1360, 1217, 866, 752 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.77 (3H, d, *J* = 6.4 Hz), 0.89-0.95 (2H, m), 1.06 (3H, d, *J* = 6.4 Hz), 1.10-1.43 (5H, m), 1.52-1.77 (5H, m), 2.40 (1H, dd, *J* = 13.2, 10.4 Hz), 2.65 (1H, s br), 2.89 (1H, septet, *J* = 6.4 Hz), 3.36 (1H, dd, *J* = 13.2, 3.6 Hz), 3.42-3.48 (1H, m), 4.11 (1H, s), 7.17-7.26 (5H, m), 7.28-7.34 (5H, m).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 21.7, 23.0, 23.4, 26.1, 35.6, 38.4, 39.9, 43.1, 47.5, 65.0, 75.5, 125.7, 127.1, 128.1, 128.2, 129.4, 130.0, 138.2, 141.0.; ESIHRMS: Found: m/z 363.2803. Calcd for $C_{25}H_{35}N_2$: $(M+H)^+$ 363.2800.

6.2.3. Hydroamination of δ,ε-Alkenyl Hydrazones 2.11 for synthesis of 2,6-*trans*-piperidine (Table 2.2)

6.2.3.1. Synthesis of 2.17aa (Table 2.2, entry 1)



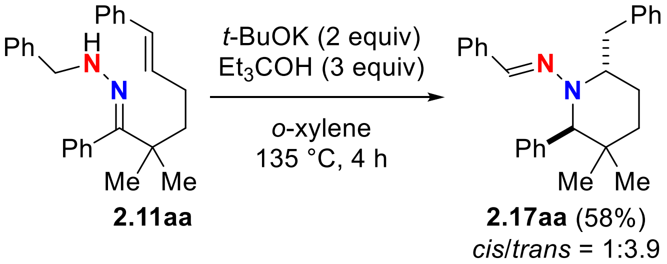
6.2.3.1.1. Synthesis of (*Z*)-1-benzyl-2-((*E*)-2,2-dimethyl-1,6-diphenylhex-5-en-1-ylidene)hydrazine (2.11aa)



92% yield (3.36 g, 8.78 mmol) from ketone **2.9m**[1] (2.66 g, 9.55 mmol) following the procedure described in section 6.2.1.1.1. (page 105)

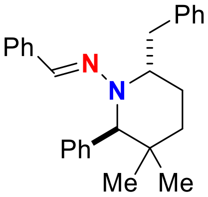
Pale yellow sticky oil; IR (NaCl) 3025, 2963, 1599, 1495, 1454, 1362, 1202, 1074, 964, 743 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (6H, s), 1.52-1.58 (2H, m), 2.11-2.17 (2H, m), 4.25 (2H, s), 4.79 (1H, s br), 6.19 (1H, dt, *J* = 16.0, 7.2 Hz), 6.32 (1H, d, *J* = 16.0 Hz), 6.88 (2H, d, *J* =7.2 Hz), 7.16-7.33 (10H, m), 7.37 (2H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.6, 28.4, 39.8, 40.8, 55.0, 125.8, 126.7, 126.9, 128.0, 128.1, 128.2(3), 128.2(4), 128.4, 129.0, 129.3, 131.4, 134.3, 138.0, 140.2, 155.8.; ESIHRMS: Found: m/z 383.2483. Calcd for $C_{27}H_{31}N_2$: $(M+H)^+$ 383.2487.

6.2.3.1.2. Synthesis of 2.17aa (Table 2.2, entry 1)



To a 25 mL Schlenk tube containing hydrazone **2.11aa** (190 mg, 0.497 mmol) and *t*-BuOK (112 mg, 0.999 mmol) in *o*-xylene (5.0 mL) was added Et_3COH (210 μL, 1.50 mmol) under an Ar atmosphere. The solution was then stirred at 135 °C for 4 h and cooled down to room temperature. After dilution with water and ethyl acetate, the mixture was extracted thrice with ethyl acetate. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting crude material was purified by flash column chromatography (hexane:Et_2O = 100:1) to yield *trans*-**2.17aa** (88.5 mg, 0.231 mmol) in 46% yield and *cis*-**2.17aa** (22.5 mg, 0.0588 mmol) in 12% yield (total yield, 58% from hydrazone **2.11aa**; *cis*:*trans* = 1:3.9).

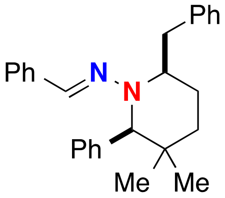
(*E*)-*N*-((2*S**,6*S**)-6-benzyl-3,3-dimethyl-2-phenylpiperidin-1-yl)-1-phenylmethanimine (*trans*-2.17aa)



White solid; mp:121-122°C; IR (NaCl) 3420, 3024, 2945, 1591, 1494, 1454, 1354, 1217, 1120, 1070 cm^{-1}; ^1H NMR(400 MHz, $CDCl_3$) δ 0.90 (3H, s), 0.94 (3H, s), 1.50-1.55 (1H, m), 1.68-1.75 (2H, m), 1.85-1.93 (1H, m), 2.89 (1H, dd, *J* = 13.2, 10.4 Hz), 3.21 (1H, dd, *J* = 13.2, 2.4 Hz), 4.24-4.27 (2H, m), 7.11 (1H, t, *J* = 7.2 Hz), 7.18

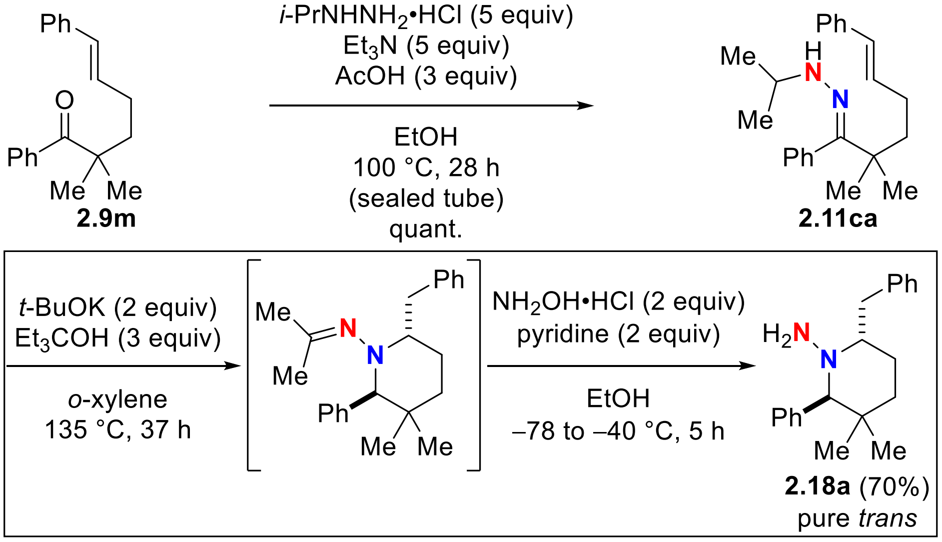
(2H, t, *J* = 7.2 Hz), 7.21-7.35 (12H, m), 7.52 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.9, 23.2, 29.2, 31.9, 33.5, 34.9, 57.1, 72.2, 125.5, 126.1, 126.4, 126.9, 127.1, 128.3, 128.5, 129.4, 130.5, 132.9, 137.5, 139.3, 140.0.; ESIHRMS: Found: m/z 383.2493. Calcd for $C_{27}H_{31}N_2$: $(M+H)^+$ 383.2487.

(*E*)-*N*-((2*S,6*R**)-6-benzyl-3,3-dimethyl-2-phenylpiperidin-1-yl)-1-phenylmethanimine (*cis*-2.17aa)**

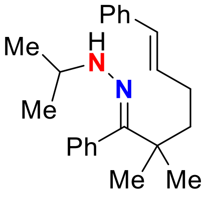


Pale yellow solid; mp: 69-70 °C; IR (NaCl) 3026, 2947, 2864, 1626, 1600, 1295, 1450, 1364, 1217, 1103, 914 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.79 (3H, s), 0.94 (3H, s), 1.40-1.74 (4H, m), 2.56 (1H, dd, *J* = 12.8, 9.6 Hz), 2.98-3.05 (1H, m), 3.13 (1H, dd, *J* = 12.8, 3.2 Hz), 3.62 (1H, s), 7.08 (1H, t, *J* = 7.6 Hz), 7.16-7.28 (12H, m), 7.39 (2H, d, *J* = 7.6 Hz), 8.01 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0, 26.2, 30.0, 34.7, 39.2, 41.9, 65.9, 77.9, 125.8, 126.3, 127.2, 127.3, 128.1, 128.3, 129.6(9), 129.7(3), 129.9, 134.8, 139.8, 140.3, 158.7.; ESIHRMS: Found: m/z 383.2488. Calcd for $C_{27}H_{31}N_2$: $(M+H)^+$ 383.2487.

6.2.3.2. Synthesis of 2.18a (Table 2.2, entry 2)



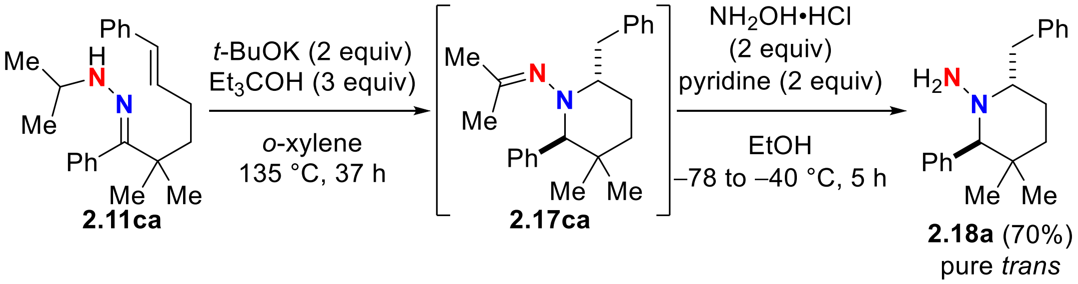
6.2.3.2.1. Synthesis of (*Z*)-1-((*E*)-2,2-dimethyl-1,6-diphenylhex-5-en-1-ylidene)-2-isopropylhydrazine (2.11ca)



Quantitative yield (1.34 g, 4.00 mmol) from ketone **2.9m**[1] (1.12 g, 4.01 mmol) following the procedure described in section 6.2.1.1.1. (page 105)

A white solid; mp: 49-50 °C; IR (NaCl) 3022, 2963, 1597, 1472, 1447, 1361, 1217, 1072, 962, 756 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (6H, d, *J* = 6.4 Hz), 1.13 (6H, s), 1.59-1.63 (2H, m), 2.26-2.32 (2H, m), 3.38 (1H, septet, *J* = 6.4 Hz), 4.25 (1H, s br), 6.23 (1H, dt, *J* = 16.0, 6.8 Hz), 6.39 (1H, d, *J* = 16.0 Hz), 7.03-7.05 (2H, m), 7.17 (1H, t, *J* = 7.2 Hz), 7.24-7.37 (5H, m), 7.43 (2H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0, 26.7, 28.6, 40.0, 40.8, 50.6, 125.8, 126.7, 127.9, 128.3, 128.4, 129.0, 129.3, 131.4, 134.6, 137.9, 154.6.; ESIHRMS: Found: m/z 335.2482. Calcd for $C_{23}H_{31}N_2$: $(M+H)^+$ 335.2487.

6.2.3.2.2. Synthesis of (2*S**,6*S**)-6-benzyl-3,3-dimethyl-2-phenylpiperidin-1-amine (2.18a)

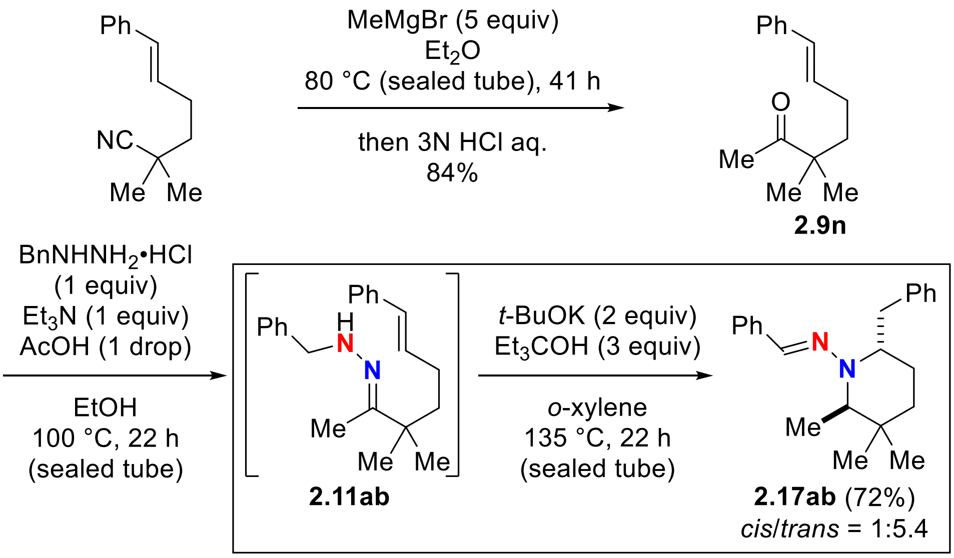


To a 25 mL Schlenk tube containing hydrazone **2.11ca** (166 mg, 0.496 mmol) and *t*-BuOK (116 mg, 1.03 mmol) in degassed *o*-xylene (5.0 mL) was added Et_3COH (220 µL, 1.56 mmol) under an Ar atmosphere. The solution was stirred at 135 °C for 37 h and then cooled to room temperature. After dilution with water and ethyl acetate, the mixture was extracted thrice with ethyl acetate. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting crude material including hydrazone **2.17ca** was used immediately for the next *trans*-imination.

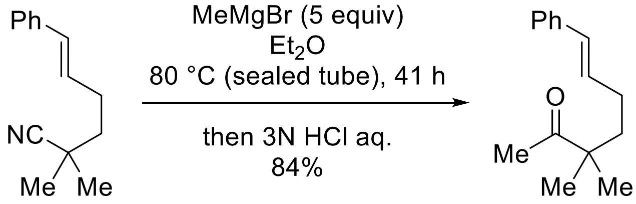
To a 50 mL round bottom flask containing the crude material obtained above in degassed EtOH (6.0 mL) was added pyridine (90 µL, 1.11 mmol) at –78 °C under an Ar atmosphere. NH_2OH•HCl (72.1 mg, 1.04 mmol) was then added and the solution was stirred at -40 °C for 5 h. The reaction was quenched with saturated aqueous $NaHCO_3$ and basified with 1 M NaOH. After dilution with ethyl acetate, the mixture was extracted thrice with ethyl acetate. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting crude material was purified by flash column chromatography (hexane:Et_2O = 2:1) to yield hydrazine **2.18a** (103 mg, 0.350 mmol) in 70% yield (from hydrazone **2.11ca**), pure *trans*-diastereomer as a white solid.

mp:107-108 °C; IR (NaCl) 3018, 2947, 1493, 1454, 1215, 756 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (3H, s), 0.90 (3H, s), 1.26-1.31 (1H, m), 1.38-1.43 (1H, m), 1.69-1.75 (1H, m), 1.81-1.90 (1H, m), 2.80-2.89 (3H, m), 3.10 (1H, dd, *J* = 12.8, 3.2 Hz), 3.51 (1H, s), 3.53-3.54 (1H, m), 7.18-7.35 (10H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 22.7, 27.8, 29.8, 33.8, 35.4, 64.1, 76.6, 125.7, 127.1, 127.8, 128.3, 129.3 (overlapped), 139.2, 140.7.; ESIHRMS: Found: m/z 295.2172. Calcd for $C_{20}H_{27}N_2$: $(M+H)^+$ 295.2174.

6.2.3.3. Synthesis of 2.17ab (Table 2.2, entry 3)



6.2.3.3.1. Synthesis of (*E*)-3,3-dimethyl-7-phenylhept-6-en-2-one (2.9n)

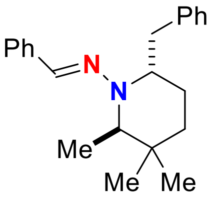


2.9n

To a 100 mL sealed tube containing (*E*)-2,2-dimethyl-6-phenylhex-5-enenitrile[1] (1.59 g, 7.98 mmol) in anhydrous Et_2O (15 mL) was added MeMgBr (3.0 M in Et_2O) (13 mL, 39.0 mmol). The tube was sealed and the solution was stirred at 80 °C for 41 h. The solution was cooled to 0 °C and 3N HCl aq. was then added dropwise. After completion of the hydrolysis, the resulting mixture was extracted with Et_2O. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting crude material was purified by flash column chromatography (hexane:Et_2O = 15:1) to yield **2.9n** (1.45 g, 6.72 mmol) in 84% yield as a colorless liquid.

IR (NaCl) 3024, 2966, 2931, 1699, 1469, 1446, 1354, 1122, 964, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.16 (6H, s), 1.68-1.72 (2H, m), 2.07-2.11 (2H, m), 2.14 (3H, s), 6.17 (1H, dt, *J* = 15.6, 6.8 Hz), 6.37 (1H, d, *J* = 15.6 Hz), 7.19 (1H, t, *J* = 7.2 Hz), 7.25-7.33 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.3, 25.1, 28.4, 39.5, 47.6, 125.9, 126.9, 128.5, 130.1, 130.2, 137.6, 213.7.; ESIHRMS: Found: m/z 217.1600. Calcd for $C_{15}H_{21}O$: $(M+H)^+$ 217.1592.

6.2.3.3.2. Synthesis of (*E*)-*N*-((2*R**,6*S**)-6-benzyl-2,3,3-trimethylpiperidin-1-yl)-1-phenylmethanimine (*trans*-2.17ab)



Synthesis of **2.17ab** was conducted by 2-step procedure from ketone **2.9n** including 1) formation of hydrazone **2.11ab**; 2) hydroamination following the procedure described in section 6.2.3.1.2. (page 146)

72% yield (115 mg, 0.360 mmol) (*cis*:*trans* = 1:5.4) from ketone **2.9n** (108 mg, 0.499 mmol).

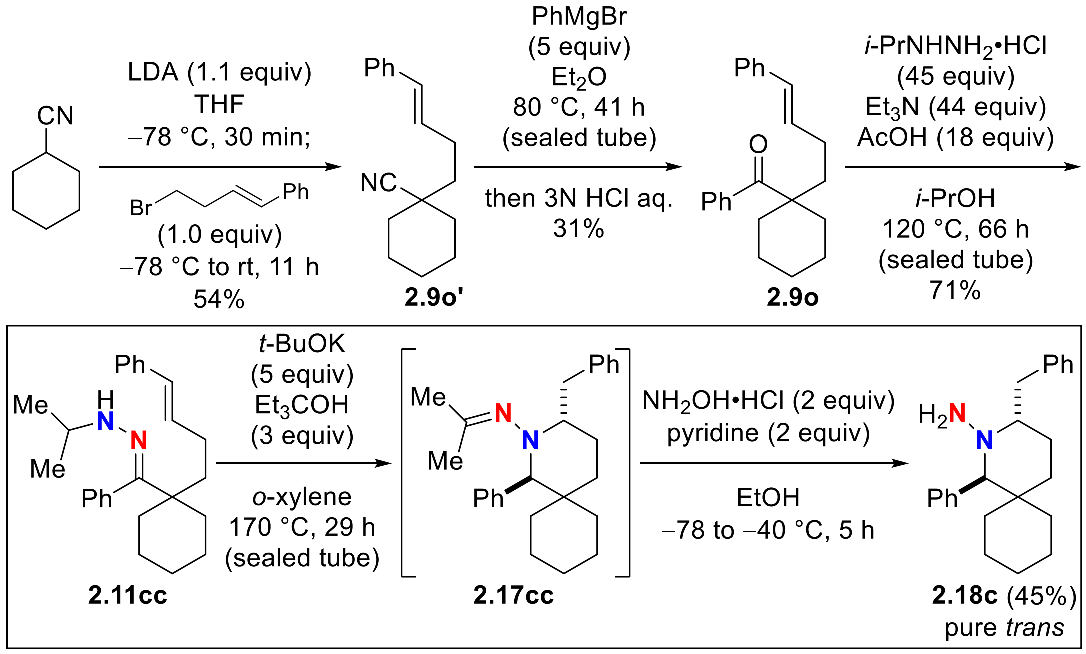
The mixture was partially separated by column chromatography to give pure *trans*-**2.17ab** in 29% yield (45.7 mg, 0.143 mmol) and the mixture of **2.17ab** (*cis*:*trans* = 1:2.9) in 43% yield (69.7 mg, 0.217 mmol).

Yellow oil; IR (NaCl) 3061, 3024, 2968, 1587, 1556, 1166, 1076, 912, 752 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.92 (3H, s), 1.04 (3H, s), 1.13 (3H, d, *J* = 6.8 Hz), 1.37-1.47 (2H, m), 1.48-1.57 (2H, m), 2.80 (1H, dd, *J* = 13.2, 9.2 Hz), 3.47 (1H, dd, *J* = 13.6, 4.0 Hz), 3.53 (1H, q, *J* = 6.8 Hz), 3.62-3.68 (1H, m), 7.17-7.33 (8H, m), 7.43 (1H, s), 7.57 (2H, d, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 9.3, 24.9, 25.3, 27.8, 32.9, 34.0, 36.3, 56.5, 59.2, 125.4, 125.9, 126.8, 128.3, 128.4, 129.6, 129.8, 138.1, 140.2.; ESIHRMS: Found: m/z 321.2330. Calcd for $C_{22}H_{29}N_2$: (M+H)$^+$ 321.2331.

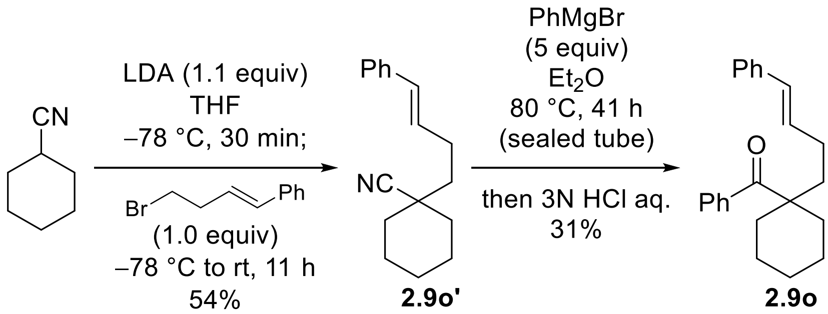
The mixture of two diastereomers (*cis*:*trans* = 1:2.9)

Yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.92 (3H, s), 1.00 (3H×0.35, s), 1.04 (3H, s), 1.07 (3H×0.35, d, *J* = 6.8 Hz), 1.08 (3H×0.35, s), 1.13 (3H, d, *J* = 6.8 Hz), 1.35-1.61 (4H+2H×0.35, m), 1.78-1.80 (2H×0.35, m), 2.51-2.57 (1H×0.35, m), 2.80 (1H, dd, J = 13.2, 9.2 Hz), 2.87 (1H×0.35, dd, J = 13.2, 2.4 Hz), 3.47-3.55 (2H+1H×0.35, m), 3.53 (1H, q, J = 6.8 Hz), 3.62-3.68 (1H, m), 3.83-3.88 (1H×0.35, m), 7.17-7.33 (8H+8H×0.35, m), 7.43 (1H, s), 7.49 (1H×0.35, s), 7.57 (2H, d, J = 7.2 Hz), 7.63 (2H×0.35, d, J = 7.2 Hz).

6.2.3.4. Synthesis of 2.18c (Table 2.2, entry 4)



6.2.3.4.1. Synthesis of (*E*)-phenyl(1-(4-phenylbut-3-en-1-yl)cyclohexyl)methanone (2.9o)



To a freshly prepared LDA [from *n*-BuLi (11.5 mmol) and diisopropylamine (11.5 mmol) in THF (14 mL) at 0 °C for 30 min] was added cyclohexane carbonitrile (1.2 mL, 10.0 mmol) dropwise at -78 °C under a N_2 atmosphere. The resulting mixture was stirred at the same temperature for 30 min. (*E*)-(4-bromobut-1-en-1-yl)benzene[3] (2.11 g, 10.0 mmol) in THF (7.0 mL) was then added dropwise and the reaction mixture was warmed up to room temperature. After stirring for 11 h, the reaction mixture was quenched with saturated aqueous NH_4Cl at 0 °C and extracted thrice with ethyl acetate. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting crude material was purified by flash column chromatography (hexane:Et_2O = 80:1) to yield (*E*)-1-(4-phenylbut-3-en-1-yl)cyclohexane-1-carbonitrile (**2.9o’**) (1.29 g, 5.38 mmol) in 54% yield as a white solid.

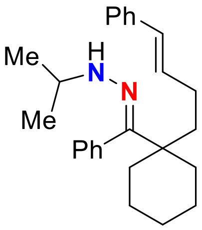
To a 50 mL sealed tube containing **2.9o’** (957 mg, 4.00 mmol) in anhydrous Et_2O (4.0 mL) was added PhMgBr (3.0 M in Et_2O) (6.0 mL, 24 mmol) under a N_2 atmosphere. The tube was sealed and the solution was then stirred at 80 °C for 41 h. The solution was cooled down to 0 °C and 3N HCl was then added dropwise. After completion of the hydrolysis, the resulting mixture was extracted with Et_2O. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure.

The resulting crude material was purified by flash column chromatography (hexane:Et_2O = 90:1) to yield ketone **2.9o** (393 mg, 1.24 mmol) in 31% yield as a colorless liquid.

Characterization of **2.9o'**; mp: 66-67 °C; IR (NaCl) 3018, 2937, 2858, 2225, 1490, 1450, 1217, 966, 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.14-1.30 (3H, m), 1.63-1.77 (7H, m), 2.00-2.04 (2H, m), 2.39-2.46 (2H, m), 6.19 (1H, dt, *J* = 16.0, 6.8 Hz), 6.44 (1H, d, *J* = 16.0 Hz), 7.20 (1H, t, *J* = 7.2 Hz), 7.27-7.34 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.0, 25.4, 28.1, 35.7, 38.9, 40.1, 123.5, 126.0, 127.1, 128.5, 129.0, 130.8, 137.4.; ESIHRMS: Found: m/z 240.1749. Calcd for $C_{17}H_{22}N$: $(M+H)^+$ 240.1752.

Characterization of **2.9o**; IR (NaCl) 3024, 2931, 2852, 1722, 1681, 1446, 1251, 1207, 972, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.30-1.47 (8H, m), 1.95-1.99 (2H, m), 2.14-2.18 (2H, m), 2.23-2.27 (2H, m), 6.15 (1H, dt, *J* = 15.6, 6.4 Hz), 6.34 (1H, d, *J* = 15.6 Hz), 7.16-7.20 (1H, m), 7.27-7.32 (4H, m), 7.38-7.48 (3H, m), 7.64 (2H, d, *J* = 6.8 Hz).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.9, 26.0, 27.8. 34.7, 38.8, 52.3, 125.9, 126.9, 127.2, 128.1, 128.5, 130.1, 130.2, 130.7, 137.6, 140.0, 209.0.; ESIHRMS: Found: m/z 319.2059. Calcd for $C_{23}H_{27}O$: $(M+H)^+$ 319.2062.

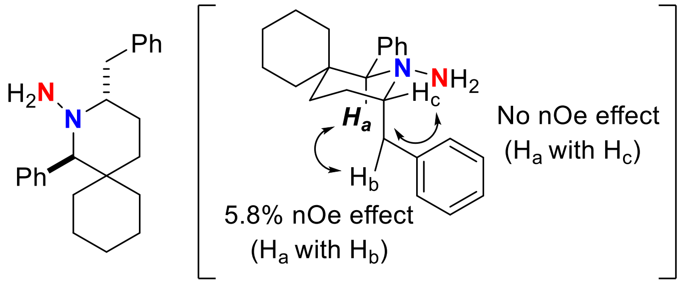
6.2.3.4.2. Synthesis of (*Z*)-1-isopropyl-2-(phenyl(1-((*E*)-4-phenylbut-3-en-1-yl)cyclohexyl)methylene)hydrazine (2.11cc)



74% yield (198 mg, 0.529 mmol) as from ketone **2.9o** (236 mg, 0.741 mmol) following the procedure described in section 6.2.1.1.1. (page 105)

A white solid; mp: 61-62 °C; IR (NaCl) 3024, 2927, 2852, 1492, 1454, 1072, 962, 756 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (6H, d, *J* = 6.4 Hz), 1.28-1.60 (10H, m), 1.83-1.86 (2H, m), 2.27-2.29 (2H, m), 3.39 (1H, septet, *J* = 6.4 Hz), 4.33 (1H, s br), 6.24 (1H, dt, *J* = 16.0, 6.8 Hz), 6.40 (1H, d, *J* = 16.0 Hz), 7.07 (2H, d, *J* = 7.6 Hz), 7.17 (1H, t, *J* = 6.8 Hz), 7.26-7.36 (5H, m), 7.42 (2H, t, *J* = 7.2 Hz).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.1, 22.6, 26.5, 27.6, 34.3, 37.5, 44.2, 50.6, 125.9, 126.7, 127.9, 128.1, 128.4, 129.0, 129.3, 131.4, 134.4, 137.9, 152.4.; ESIHRMS: Found: m/z 375.2804. Calcd for $C_{26}H_{35}N_2$: $(M+H)^+$ 375.2800.

6.2.3.4.3. Synthesis of (1*S**,3*S**)-3-benzyl-1-phenyl-2-azaspiro[5.5]undecan-2-amine (2.18c)



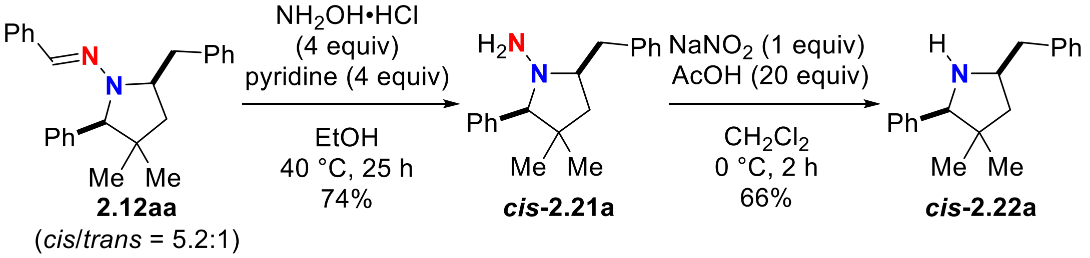
45% yield (36.2 mg, 0.108 mmol) from **2.11cc** (90.4 mg, 0.241 mmol) following the procedure described in section 6.2.3.2.2. (page 149)

Pale-yellow sticky oil; IR (NaCl) 3649, 3026, 2933, 2860, 1492, 1454, 1217, 912, 758 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94-1.04 (2H, m), 1.21-1.49 (9H, m), 1,67-1.73 (2H, m), 1.90-1.96 (1H, m), 2.63 (2H, s br), 2.67-2.73 (1H, m), 3.20 (1H, dd, *J* = 12.8, 3.2 Hz), 3.39-3.43 (1H, m), 3.60 (1H, s), 7.17-7.35 (10H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 21.4, 23.1, 25.6, 26.4, 29.8, 31.5, 36.8, 37.8, 63.3, 78.2, 125.8, 127.1, 127.7, 128.3, 129.5, 131.1, 138.4, 140.6.; ESIHRMS: Found: m/z 335.2480. Calcd for $C_{23}H_{31}N_2$: $(M+H)^+$ 335.2487.

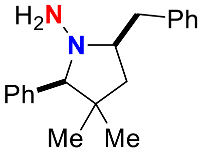
5.8% of NOE enhancement between H_a and H_b was observed, while the absence of NOE enhancement between H_a and H_c was detected. These data established the 2,6-*trans* relationship between H_a and H_c.

6.2.4. Conversion to *N*-H pyrrolidines 2.22a and piperidine 2.23a (Scheme 2.9)

6.2.4.1. Synthesis of *cis*-2.22a (Scheme 2.9a)

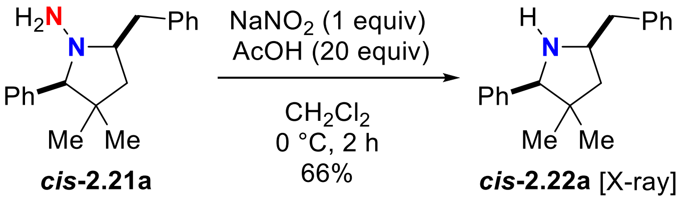


6.2.4.1.1. Synthesis of (2*S**,5*S**)-5-benzyl-3,3-dimethyl-2-phenylpyrrolidin-1-amine (*cis*-2.21a)



74% yield (62.6 mg, 0.223 mmol) from *N*-iminopyrrolidine **2.12aa** (*cis*/*trans* = 5.2:1) (110 mg, 0.298 mmol) via treatment with $NH_2OH{\cdot}HCl$ (4 equiv) and pyridine (4 equiv) at 40 °C following the procedure described in the section 6.2.3.2.2. (page 149) Yellow oil; IR (NaCl) 3342, 3026, 2953, 1600, 1494, 1454, 1384, 1029, 918, 746 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.53 (3H, s), 1.00 (3H, s), 1.44 (1H, dd, *J* = 13.2, 8.0 Hz), 1.72 (1H, dd, *J* = 13.2, 8.4 Hz), 2.65-2.78 (2H, m), 2.81 (2H, s br), 3.10 (1H, s), 3.31 (1H, dd, *J* = 12.4, 3.2 Hz), 7.19-7.36 (10H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.0, 29.0, 38.3, 40.7, 43.8, 68.0, 85.8, 125.9, 127.1, 128.0, 128.1, 128.4, 129.5, 139.2, 139.9.; ESIHRMS: Found: m/z 281.2014. Calcd for $C_{19}H_{25}N_2$: $(M+H)^+$ 281.2018.

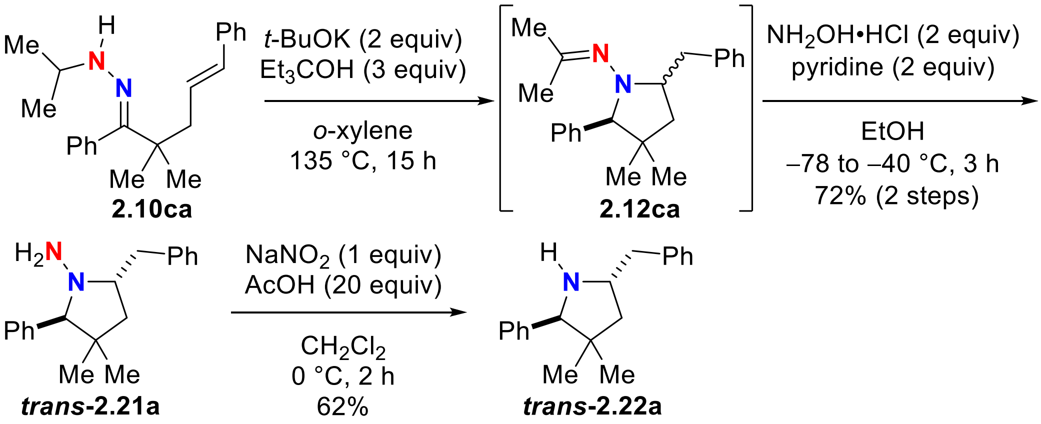
6.2.4.1.2. Synthesis of (2*S**,5*S**)-5-benzyl-3,3-dimethyl-2-phenylpyrrolidine (*cis*-2.22a)



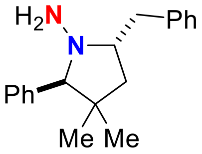
To a 25 mL round bottom flask containing hydrazine *cis*-**2.21a** (55.4 mg, 0.198 mmol) and AcOH (200 µL, 4.02 mmol) in CH_2Cl_2 (4.0 mL) was added $NaNO_2$ (15.0 mg, 0.217 mmol) at 0 °C under a N_2 atmosphere and the solution was stirred for 2 h. The solution was quenched with 1 M NaOH and extracted with CH_2Cl_2. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting crude material was purified by flash column chromatography (hexane:Et_2O = 10:1) to yield *cis*-**2.22a** (35.0 mg, 0.132 mmol) in 66% yield as a beige solid, which was recrystallized from CH_2Cl_2/hexane for X-ray crystallographic analysis.

Colorless crystal (recrystallized from CH_2Cl_2/hexane) (CCDC 1424734); mp: 76-77 °C; IR (NaCl) 3333, 3027, 2955, 2934, 1603, 1495, 1452, 1364, 1217, 1028 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.61 (3H, s), 1.07 (3H, s), 1.45 (1H, dd, *J* = 12.0, 7.2 Hz), 1.78 (1H, dd, *J* = 12.0, 7.6 Hz), 1.79 (1H, s br), 2.84 (2H, d, *J* = 6.8 Hz), 3.44 (1H, tdd, *J* = 7.6, 7.2, 6.8 Hz), 3.81 (1H, s),7.19-7.30 (8H, m), 7.36 (2H, d, *J* =7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.6, 28.8, 41.3, 43.9, 47.1, 57.5, 72.4, 126.2, 126.9, 127.8, 127.9, 128.5, 129.4, 140.8, 142.2. ESIHRMS: Found: m/z 266.1912. Calcd for $C_{19}H_{24}N$: $(M+H)^+$ 266.1909.

6.2.4.2. Synthesis of *trans*-2.22a (Scheme 2.9b)



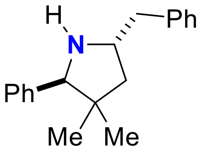
6.2.4.2.1. Synthesis of (2*S**,5*R**)-5-benzyl-3,3-dimethyl-2-phenylpyrrolidin-1-amine (*trans*-2.21a)



72% yield (60.6 mg, 0.216 mmol) from hydrazone **2.10ca** (95.7 mg, 0.299 mmol) via 2 steps including 1) hydroamination of **2.10ca**; 2) treatment of **2.12ca** with $NH_2OH \cdot HCl$ (2 equiv) and pyridine (2 equiv) at –78 to –40 °C following the procedure described in the section 6.2.3.2.2. (page 149)

Yellow oil; IR (NaCl) 3026, 2953, 2866, 1602, 1495, 1454, 1364, 1072, 1030, 926, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.60 (3H, s), 1.14 (3H, s), 1.56 (1H, dd, J = 13.2, 4.4 Hz), 1.68 (1H, dd, J = 13.2, 7.6 Hz), 2.46-2.52 (1H, m), 2.86 (2H, s br), 3.41 (1H, dd, J = 12.4, 4.0 Hz), 3.64 (1H, s), 3.67-3.74 (1H, m), 7.18-7.38 (10H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.2, 29.5, 35.9, 39.5, 43.4, 64.0, 81.5, 125.8, 127.1, 128.2, 128.3, 128.6, 129.4, 139.0, 139.9.; ESIHRMS: Found: m/z 281.2019. Calcd for $C_{19}H_{25}N_2$: $(M+H)^+$ 281.2018.

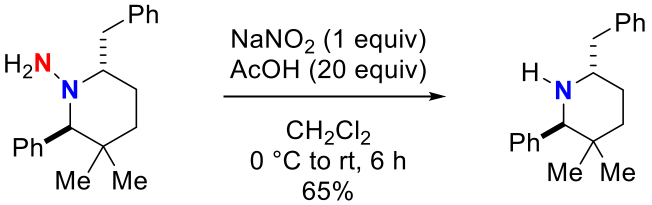
6.2.4.2.2. Synthesis of (2*S**,5*R**)-5-benzyl-3,3-dimethyl-2-phenylpyrrolidine (***trans*-2.22a**)



62% yield (33.0 mg, 0.124 mmol) from *trans*-**2.21a** (56.0 mg, 0.200 mmol) as a yellow oil following the procedure described in the section 6.2.4.1.2. (page 159)

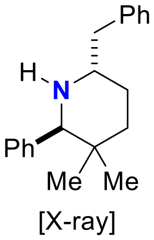
IR (NaCl) 3350, 3026, 2953, 2864, 1600, 1494, 1452, 1365, 1093, 1070, 744 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.64 (3H, s), 1.05 (3H, s), 1.56 (1H, dd, *J* = 12.4, 8.4 Hz), 1.81 (1H, s br), 1.86 (1H, dd, *J* = 12.4, 6.8 Hz), 2.75 (1H, dd, *J* = 13.2, 6.4 Hz), 2.84 (1H, dd, *J* = 13.2, 7.6 Hz), 3.73 (1H, dddd, *J* = 8.4, 7.6, 6.8, 6.4 Hz), 4.06 (1H, s), 7.20-7.32 (10H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.8, 26.8, 42.6, 44.3, 48.2, 56.5, 70.4, 126.1, 126.8, 127.5, 127.7, 128.4, 129.0, 139.8, 141.1.; ESIHRMS: Found: m/z 266.1907. Calcd for $C_{19}H_{24}N$: $(M+H)^+$ 266.1909.

6.2.4.3. Synthesis of *trans*-2.23a (Scheme 2.9c)



***trans*-2.18a** ***trans*-2.23a**

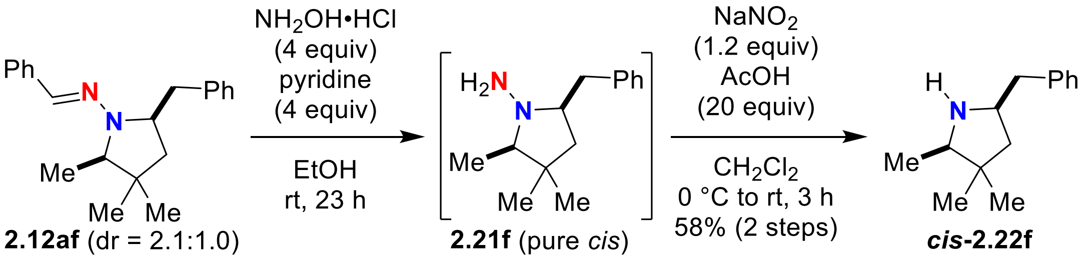
6.2.4.3.1. Synthesis of (2*S**,6*S**)-6-benzyl-3,3-dimethyl-2-phenylpiperidine (***trans*-2.23a**)



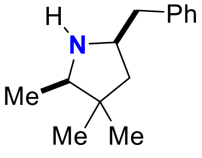
65% yield (45.6 mg, 0.163 mmol) from *trans*-**2.18a** (72.6 mg, 0.247 mmol) as a colorless crystal (recrystallized from *i*-PrOH) (CCDC 1424735) following the procedure described in the section 6.2.4.1.2. (page 159)

mp: 94-95 °C; IR (NaCl) 3020, 2943, 1490, 1452, 1361, 1215, 1029, 702 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.81 (3H, s), 0.88 (3H, s), 1.37-1.42 (1H, m), 1.48-1.54 (2H, m) 1.69-1.76 (1H, m), 2.06-2.15 (1H, m), 2.77 (1H, dd, *J* = 13.2, 5.6 Hz), 3.10 (1H, dd, *J* = 13.2, 9.2 Hz), 3.37-3.41 (1H, m), 3.86 (1H, s), 7.12-7.33 (10H, m); ^{13}C NMR (100 MHz, CDCl$_3$) δ 19.4, 25.2, 29.2, 34.1, 35.4, 37.2, 54.7, 63.4, 125.9, 126.9, 127.4, 128.5, 128.8, 129.0, 140.2, 142.0.; ESIHRMS: Found: m/z 280.2066. Calcd for $C_{20}H_{26}N$: $(M+H)^+$ 280.2065.

6.2.4.4. Synthesis of *cis*-2.22f for elucidation of the stereochemistry



6.2.4.4.1. Synthesis of (2*R**,5*S**)-5-benzyl-2,3,3-trimethylpyrrolidine (*cis*-2.22f).



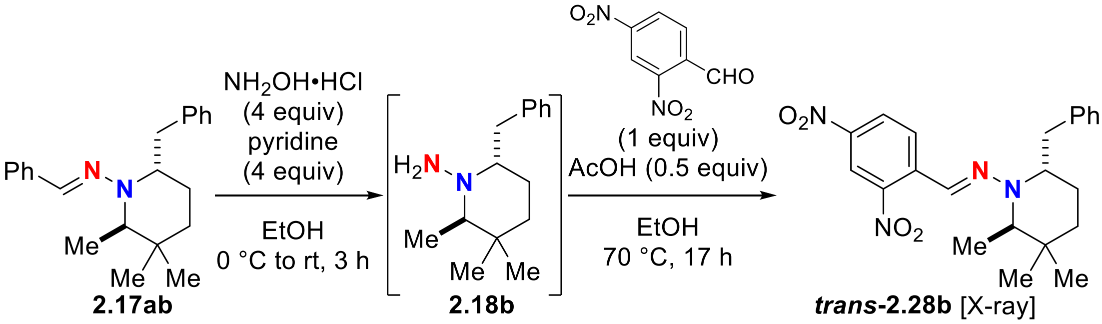
[X-ray]

Synthesis of *cis*-**2.22f** was conducted by 2-step procedure from **2.12af** including 1) treatment of *cis*-**2.12af** with $NH_2OH \cdot HCl$ (4 equiv) and pyridine (4 equiv) at room temperature; 2) subsequent treatment of the resulting hydrazine **2.21f** with $NaNO_2$ in the presence of AcOH.

58% yield (116 mg, 0.568 mmol) from **2.12af** (299 mg, 0.976 mmol) as a yellow crystal as HCl salt (recrystallized from $CHCl_3$/*i*-PrOH) (CCDC 1424736); mp: 247-248 °C; IR (NaCl) 2945, 2833, 1655, 1450, 1026 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.01 (3H, s), 1.02 (3H, s), 1.23 (3H, d, *J* = 6.8 Hz), 1.51 (1H, dd, *J* = 13.2, 8.4 Hz), 1.73 (1H, dd, *J* = 13.2, 8.4 Hz), 2.87 (1H, dd, *J* = 13.2, 9.2 Hz), 2.99 (3H, q, *J* = 6.8 Hz), 3.15 (1H, dd, *J* = 13.2, 5.6 Hz), 3.55 (1H, dddd, *J* = 9.2, 8.4, 8.4, 5.6 Hz), 7.18-7.30 (5H, m).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 24.2, 27.6, 39.9, 41.3, 45.6, 58.0, 63.8, 126.5, 128.5, 129.0, 138.4.; ESIHRMS: Found: m/z 204.1749. Calcd for $C_{14}H_{22}N$: $(M+H)^+$ 204.1752.

6.2.5. Conversion of 2.17ab to 2,4-dinitrophenyl hydrazone 2.28b for elucidation of the stereochemistry

6.2.5.1. Synthesis of (*E*)-*N*-((2*R**,6*S**)-6-benzyl-2,3,3-trimethylpiperidin-1-yl)-1-(2,4-dinitrophenyl)methanimine (*trans*-2.28b)



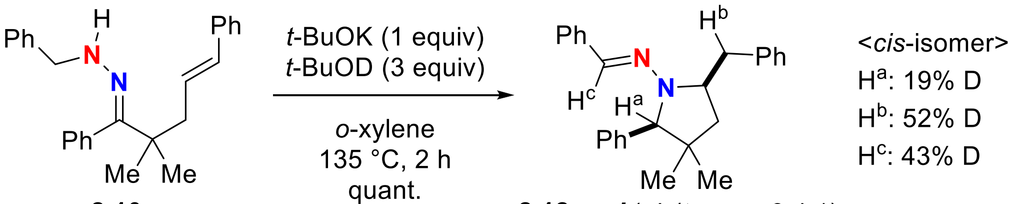
To a 25 mL Schlenk tube containing **2.17ab** (112 mg, 0.350 mmol) in degassed EtOH (3.4 mL) was added pyridine (120 µL, 1.4 mmol) at 0 °C under an Ar atmosphere. $NH_2OH·HCl$ (104 mg, 1.49 mmol) was then added and the solution was stirred at room temperature for 3 h. The reaction was quenched with saturated aqueous $NaHCO_3$ and basified with 1M NaOH. After dilution with ethyl acetate, the mixture was extracted with ethyl acetate. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting crude material including **2.18b** was used immediately for the next step.

To a 50 mL round bottom flask containing crude material obtained above in degassed EtOH (2.0 mL) was added 2,4-dinitrobenzaldehyde (70.0 mg, 0.357 mmol) and AcOH (10 µL, 0.175 mmol) under an Ar atmosphere and the solution was stirred at 70 °C for 17 h. After the mixture was cooled down to room temperature, the solvent was removed under reduced pressure. The resulting crude product was purified immediately by flash column chromatography (hexane:ethyl acetate = 50:1) to yield hydrazone (*trans*-**2.28b**) (93.7 mg, 0.228 mmol) in 65% yield as a red solid, which was recrystallized from CH_2Cl_2/hexane to yield red crystal for X-ray crystallographic analysis.

Red crystal (recrystallized from CH_2Cl_2/hexane) (CCDC 1424737); mp: 146 °C; IR (NaCl) 2945, 2832 1450, 1417, 1115, 1030 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, s), 1.03 (3H, s), 1.28 (3H, d, J = 6.8 Hz), 1.40-1.46 (1H, m), 1.58-1.74 (3H, m), 2.84 (1H, dd, J = 13.6, 8.8 Hz), 3.22 (1H, dd, J = 13.6, 4.0 Hz), 3.65 (1H, q, J = 6.8 Hz), 4.06 (1H, m), 7.21-7.26 (3H, m), 7.30-7.34 (2H, m), 7.96 (1H, s), 8.19 (2H, m), 8.82 (1H, s).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.3, 22.9, 24.5, 27.7, 33.7, 34.9, 35.6, 57.2, 61.6, 118.8, 121.5, 126.3, 126.5, 126.7, 128.6, 129.2, 138.3, 139.4, 143.7, 144.0.; ESIHRMS: Found: m/z 411.2028. Calcd for $C_{22}H_{27}N_4O_4$: $(M+H)^+$ 411.2032.

6.2.6. Deuterium labelling experiments (Scheme 2.10)

6.2.6.1. Reaction of 2.10aa in the presence of *t*-BuOD (Scheme 2.10a)



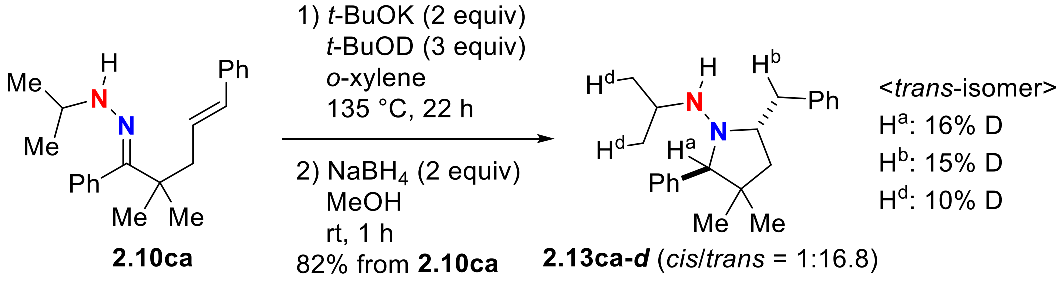
2.10aa

2.12aa-*d* (*cis*/*trans* = 3.4:1)

<*cis*-isomer>
H^a: 19% D
H^b: 52% D
H^c: 43% D

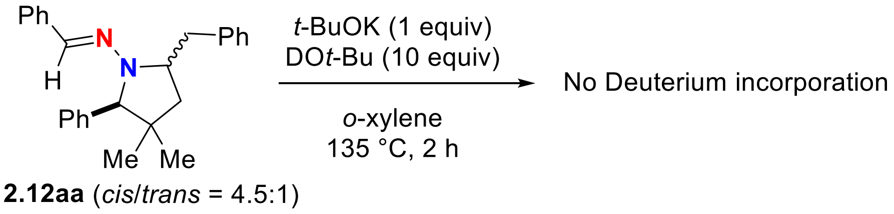
Quantitative yield (185 mg, 0.500 mmol, *cis*/*trans* = 3.4:1 as an inseparable mixture) of **2.12aa-*d*** from **2.10aa** (184 mg, 0.500 mmol) with *t*-BuOK (1 equiv) in the presence of *t*-BuOD (3 equiv) in accordance with the typical procedure A (page 106).

6.2.6.2. Reaction of 2.10ca in the presence of *t*-BuOD (Scheme 2.10b)



77% yield (124 mg, 0.387 mmol) of *trans*-**2.13ca-*d*** and 5% yield (7.4 mg, 0.0229 mmol) of *cis*-**2.13ca-*d*** from **2.10ca** (160 mg, 0.499 mmol) with *t*-BuOK (2 equiv) in the presence of *t*-BuOD (3 equiv) in accordance with the typical procedure C (page 133).

6.2.6.3. Reaction of 2.12aa in the presence of *t*-BuOD (Scheme 2.10c)



The reaction was conducted using **2.12aa** (*cis*/*trans* = 4.5:1) (184 mg, 0.499 mmol) with *t*-BuOK (1 equiv) in the presence of *t*-BuOD (10 equiv) in accordance with the typical procedure A (page 106). We observed no deuterium incorporation (>99% recovery) of **2.12aa** in the crude material by ^{1}H NMR analysis with 1,1,2,2-tetrachloroethane as an internal standard.

6.2.7. DFT calculation

6.2.7.1. General

DFT calculations were performed at the B3LYP-D3BJ(SCRF)/6-311+G(d,p)// B3LYP-D3BJ(SCRF)/6-31G(d) level using Gaussian 09.[4-8] Here, the default SCRF (self-consistent reaction field) method in Gaussian was used to describe the solvent effect of *o*-xylene. Reported relative energy values contain zero-point energy (ZPE) corrections. In what follows, E1 and E2 refer to total energies calculated at the B3LYP-D3BJ(SCRF)/6-31G(d) and B3LYP-D3BJ(SCRF)/6-311+G(d,p)// B3LYP-D3BJ(SCRF)/6-31G(d) levels, respectively.

6.2.7.2. For Figure 2.1

Table 6.1. Raw energy data for the reaction of 2.10aa

	E1 [hartree]	ZPE [hartree]	E2 [hartree]	Δ(E2+ZPE) [kcal/mol]
INT$_0$-2.10aa	-1716.568196	0.464235	-1716.888213	0.0
INT$_1$-2.10aa	-1716.565341	0.463884	-1716.886694	0.7
TS-2.10aa (*cis*)	-1716.547731	0.464066	-1716.870473	11.0
TS-2.10aa (*trans*)	-1716.545708	0.463701	-1716.869691	11.3
INT$_2$-2.10aa (*cis*)	-1716.553831	0.465554	-1716.878252	7.1
INT$_2$-2.10aa (*trans*)	-1716.551080	0.465197	-1716.876055	8.2

6.2.7.3. For Figure 2.2

Table 6.2. Raw energy data for the reaction of 2.10ca

	E1 [hartree]	ZPE [hartree]	E2 [hartree]	Δ(E2+ZPE) [kcal/mol]
INT$_0$-2.10ca	-1564.124069	0.439129	-1564.411146	0.0
INT$_1$-2.10ca	-1564.116074	0.438671	-1564.405672	2.8
TS-2.10ca (*cis*)	-1564.097119	0.438106	-1564.384785	15.5
TS-2.10ca (*trans*)	-1564.101306	0.437780	-1564.389949	12.1
INT$_2$-2.10ca (*cis*)	-1564.105235	0.440117	-1564.394619	10.6
INT$_2$-2.10ca (*trans*)	-1564.110077	0.439871	-1564.401027	6.5

6.2.7.4. For Figure 2.3 (piperidine formation)

Table 6.3. Raw energy data for the reaction of 2.11aa

	E1 [hartree]	ZPE [hartree]	E2 [hartree]	Δ(E2+ZPE) [kcal/mol]
INT$_0$-2.11aa	-1755.886454	0.492535	-1756.217655	0.0
INT$_1$-2.11aa	-1755.883971	0.492946	-1756.216213	1.2
TS-2.11aa (*cis*)	-1755.864016	0.492780	-1756.196466	13.4
TS-2.11aa (*trans*)	-1755.869458	0.492769	-1756.200798	10.7
INT$_2$-2.11aa (*cis*)	-1755.865187	0.493972	-1756.197872	13.3
INT$_2$-2.11aa (*trans*)	-1755.869458	0.492769	-1756.203804	8.8

Table 6.4. Raw energy data for the reaction of 2.11ca

	E1 [hartree]	ZPE [hartree]	E2 [hartree]	Δ(E2+ZPE) [kcal/mol]
INT$_0$-2.11ca	-1603.445871	0.467855	-1603.742932	0.0
INT$_1$-211ca	-1603.430635	0.467228	-1603.729074	8.3
TS-2.11ca (*cis*)	-1603.418960	0.467609	-1603.718055	15.5
TS-2.11ca (*trans*)	-1603.425850	0.467720	-1603.723649	12.0
INT$_2$-2.11ca (*cis*)	-1603.422925	0.468944	-1603.722884	13.3
INT$_2$-2.11ca (*trans*)	-1603.433942	0.469326	-1603.733909	6.6

6.2.7.5. XYZ coordinates of optimized geometries

[Figure 2.1]

=== **INT$_0$-2.10aa** ===

C	-3.778104	0.388913	-0.286844
C	-3.005564	0.767414	0.845377
C	-2.424051	2.029920	0.952595
C	-2.579212	2.980955	-0.062311
C	-3.310440	2.626167	-1.198743
C	-3.890334	1.363128	-1.311557
H	-2.885244	0.047513	1.643419
H	-1.833766	2.268500	1.835008
H	-2.129520	3.966205	0.024155
H	-3.432673	3.339652	-2.010690
H	-4.454649	1.138581	-2.205303
C	-4.429740	-0.930459	-0.349273
N	-4.860517	-1.601619	0.712338
N	-4.804471	-1.142429	1.950040
C	-4.703890	-1.632482	-1.698987
C	-3.455089	-1.623351	-2.603999
H	-2.646750	-2.197643	-2.137054
H	-3.679082	-2.080472	-3.576314
H	-3.081478	-0.611953	-2.786412
C	-5.090358	-3.106374	-1.465709
H	-5.169365	-3.615913	-2.434586
H	-4.340600	-3.618609	-0.857189
H	-6.047513	-3.199443	-0.946866
C	-5.898829	-0.965926	-2.480489
H	-5.538310	-0.190924	-3.166040
H	-6.361560	-1.733846	-3.117990
C	-6.921672	-0.374703	-1.558739
C	-7.307707	0.911255	-1.601838
H	-7.302595	-1.034017	-0.780366
H	-6.869673	1.554354	-2.365191
C	-8.182300	1.603268	-0.643516
C	-8.970380	0.928135	0.311769
C	-8.177907	3.012573	-0.616546
C	-9.692628	1.636847	1.270259
H	-9.003876	-0.156166	0.321783
C	-8.904132	3.720487	0.341852
H	-7.582654	3.551021	-1.350117
C	-9.660536	3.035763	1.296492
H	-10.276983	1.088236	2.001926
H	-8.879130	4.806793	0.342082
H	-10.227309	3.583499	2.043803
C	-5.453980	-2.114424	2.850384
K	-5.965438	1.339041	1.765900
H	-5.180645	-3.141742	2.570717
H	-5.075310	-1.926041	3.863440
C	-6.964652	-1.981682	2.855119
C	-7.622700	-1.196728	3.814508
C	-7.738946	-2.585831	1.850987
C	-9.009681	-1.022788	3.779718
H	-7.040559	-0.737602	4.612562
C	-9.123662	-2.419835	1.815124
H	-7.239792	-3.193923	1.103507
C	-9.766628	-1.639283	2.781546
H	-9.499414	-0.421891	4.542140
H	-9.706239	-2.908968	1.038415
H	-10.846485	-1.520893	2.759876

=== **INT$_1$-2.10aa** ===

C	-3.783879	-0.025287	-0.075445
C	-3.214152	-0.007915	1.211078
C	-2.898534	1.187080	1.859968
C	-3.131044	2.412827	1.226853
C	-3.669344	2.418142	-0.063575
C	-3.994688	1.213969	-0.700899
H	-3.036183	-0.953093	1.714258
H	-2.468443	1.161790	2.857762
H	-2.877224	3.346186	1.722002
H	-3.829492	3.359428	-0.584150
H	-4.421137	1.254681	-1.691875

C	-4.253159	-1.370916	-0.613412
N	-5.596512	-1.769228	-0.126823
N	-5.867976	-1.373578	1.079164
C	-4.214586	-1.611087	-2.156738
C	-2.799515	-1.326714	-2.687693
H	-2.060919	-1.958572	-2.180277
H	-2.741267	-1.541649	-3.761621
H	-2.508190	-0.282441	-2.534895
C	-4.528532	-3.102986	-2.388005
H	-4.429635	-3.353130	-3.451354
H	-3.832283	-3.736445	-1.825343
H	-5.539015	-3.345243	-2.053664
C	-5.227567	-0.764147	-3.005510
H	-4.768396	0.184190	-3.307556
H	-5.381124	-1.321895	-3.941428
C	-6.558341	-0.486338	-2.374591
C	-7.060079	0.752523	-2.222676
H	-7.098111	-1.345351	-1.995183
H	-6.487769	1.596253	-2.610144
C	-8.259473	1.128409	-1.464117
C	-9.084980	0.188705	-0.808073
C	-8.549522	2.496461	-1.277347
C	-10.126776	0.603766	0.017817
H	-8.881331	-0.871035	-0.914868
C	-9.596657	2.911090	-0.450543
H	-7.932838	3.238291	-1.780288
C	-10.387732	1.966941	0.208433
H	-10.732216	-0.140373	0.527368
H	-9.793846	3.972276	-0.323754
H	-11.198619	2.284558	0.857037
C	-7.047657	-1.705689	1.603363
K	-6.684440	1.305841	1.463442
H	-7.763235	-2.284092	1.010485
H	-3.525604	-2.103385	-0.217654
C	-7.436680	-1.242494	2.907151
C	-6.532517	-0.614908	3.812937
C	-8.789149	-1.341463	3.330135
C	-6.970241	-0.090389	5.026712
H	-5.479238	-0.574151	3.548899
C	-9.211995	-0.822534	4.548050
H	-9.506082	-1.826681	2.671119
C	-8.313750	-0.178725	5.409355
H	-6.247203	0.375985	5.693303
H	-10.257967	-0.917456	4.831648
H	-8.648259	0.222860	6.361213

=== TS-2.10aa (cis) ===

C	-3.398319	-0.148496	0.056486
C	-2.139090	-0.330285	0.638093
C	-1.408759	0.750995	1.136321
C	-1.930773	2.042705	1.063856
C	-3.188731	2.239197	0.487180
C	-3.913179	1.153744	-0.006594
H	-1.727161	-1.334255	0.705613
H	-0.433170	0.582312	1.584262
H	-1.365674	2.886305	1.450054
H	-3.601098	3.243673	0.413673
H	-4.891271	1.308260	-0.449808
C	-4.164637	-1.347700	-0.481009
N	-5.594480	-1.347290	-0.185177
N	-5.903733	-1.111135	1.069197
C	-4.134237	-1.516219	-2.030006
C	-2.774158	-1.175636	-2.644016
H	-1.983941	-1.815206	-2.232065
H	-2.798550	-1.331794	-3.729074
H	-2.494499	-0.134644	-2.455651
C	-4.493744	-2.974748	-2.365357
H	-4.586719	-3.108396	-3.449727
H	-3.713775	-3.657950	-2.008064
H	-5.437518	-3.268150	-1.896879
C	-5.232281	-0.563322	-2.544979
H	-4.841832	0.460716	-2.569470
H	-5.498134	-0.819254	-3.578817
C	-6.481496	-0.594634	-1.674159

C	-7.156976	0.632461	-1.462593
H	-7.116851	-1.458846	-1.855117
H	-6.582955	1.544137	-1.642700
C	-8.541253	0.825684	-1.155142
C	-9.483681	-0.228840	-0.969754
C	-9.061182	2.146007	-0.984994
C	-10.800244	0.021032	-0.601977
H	-9.168861	-1.255690	-1.131430
C	-10.382452	2.385320	-0.615063
H	-8.404663	2.992654	-1.195029
C	-11.270755	1.325783	-0.402434
H	-11.477641	-0.820636	-0.472584
H	-10.725308	3.412662	-0.506508
H	-12.301154	1.509720	-0.114279
C	-7.166970	-1.027344	1.411000
K	-7.142077	1.957556	1.389486
H	-7.966787	-1.178092	0.686033
H	-3.707470	-2.243026	-0.035198
C	-7.562792	-0.732726	2.780182
C	-6.628536	-0.545806	3.827924
C	-8.933985	-0.552949	3.078243
C	-7.053567	-0.189519	5.104056
H	-5.573974	-0.685707	3.611451
C	-9.348510	-0.192087	4.359691
H	-9.665702	-0.687516	2.284510
C	-8.414374	-0.005228	5.382406
H	-6.317847	-0.056954	5.893811
H	-10.408624	-0.059208	4.560894
H	-8.738959	0.271231	6.381277

=== **TS-2.10aa (trans)** ===

C	-3.191345	-0.491879	0.220223
C	-2.342943	-1.559355	0.537681
C	-1.102697	-1.338417	1.138815
C	-0.694473	-0.038405	1.439934
C	-1.538537	1.032974	1.138655
C	-2.775764	0.807448	0.536596
H	-2.661217	-2.575241	0.315747
H	-0.460115	-2.181876	1.377677
H	0.267847	0.138108	1.912699
H	-1.234154	2.048580	1.378152
H	-3.439275	1.636300	0.316460
C	-4.510964	-0.755751	-0.477282
N	-5.530960	0.249585	-0.191287
N	-5.927450	0.253782	1.069591
C	-4.432409	-0.766131	-2.030099
C	-3.794847	0.520823	-2.576132
H	-2.739724	0.589344	-2.293345
H	-3.854766	0.532340	-3.671068
H	-4.302038	1.411520	-2.194509
C	-3.663679	-1.981006	-2.554415
H	-3.703292	-2.016974	-3.649699
H	-2.609916	-1.940992	-2.258055
H	-4.088755	-2.917199	-2.171521
C	-5.919141	-0.841928	-2.425209
H	-6.047385	-0.631123	-3.495083
H	-6.277287	-1.866730	-2.257588
C	-6.775878	0.110214	-1.604146
C	-8.078536	-0.324478	-1.261281
H	-6.697480	1.147841	-1.921251
H	-8.250885	-1.404126	-1.287757
C	-9.232854	0.491203	-1.042480
C	-9.212708	1.917062	-0.982791
C	-10.514169	-0.108738	-0.836335
C	-10.353174	2.655035	-0.692828
H	-8.281048	2.441755	-1.173001
C	-11.651523	0.641443	-0.545298
H	-10.607202	-1.189492	-0.960056
C	-11.587482	2.035327	-0.452969
H	-10.280457	3.740150	-0.655907
H	-12.602210	0.130044	-0.405269
H	-12.472365	2.622052	-0.226450
C	-6.902259	1.059983	1.405598
K	-9.035585	-1.105938	1.589368

H	-7.360508	1.734010	0.681032
H	-4.854482	-1.759114	-0.165844
C	-7.396667	1.129170	2.773206
C	-6.838008	0.372291	3.831145
C	-8.523095	1.935138	3.059185
C	-7.394002	0.415750	5.106028
H	-5.964337	-0.238224	3.625471
C	-9.074902	1.968777	4.339606
H	-8.966662	2.520426	2.256560
C	-8.518793	1.208309	5.372028
H	-6.943661	-0.168253	5.905099
H	-9.942270	2.595204	4.531890
H	-8.945805	1.238988	6.370106

=== INT$_2$-2.10aa (cis) ===

C	-3.284812	0.022261	0.004252
C	-1.964300	-0.185224	0.417873
C	-1.139363	0.889078	0.752641
C	-1.628318	2.194831	0.683360
C	-2.947705	2.412182	0.281207
C	-3.769705	1.334329	-0.050895
H	-1.580142	-1.200594	0.482239
H	-0.117354	0.705811	1.072976
H	-0.989161	3.033484	0.944716
H	-3.338055	3.425798	0.224658
H	-4.799360	1.502647	-0.351231
C	-4.147948	-1.169705	-0.376838
N	-5.566877	-0.969237	-0.107400
N	-5.951658	-0.986781	1.152984
C	-4.162703	-1.544560	-1.893654
C	-2.846156	-1.264803	-2.619213
H	-2.019910	-1.842791	-2.188039
H	-2.935020	-1.546691	-3.674825
H	-2.576272	-0.205813	-2.570953
C	-4.519485	-3.035339	-2.020538
H	-4.669036	-3.305305	-3.072228
H	-3.715466	-3.664517	-1.620713
H	-5.437713	-3.275904	-1.474369
C	-5.313781	-0.667832	-2.423478
H	-4.942387	0.346491	-2.609323
H	-5.719234	-1.043262	-3.368293
C	-6.403978	-0.603893	-1.333736
C	-7.103862	0.710313	-1.274688
H	-7.117908	-1.429205	-1.464257
H	-6.516241	1.558758	-1.630618
C	-8.494560	0.922177	-1.180291
C	-9.480456	-0.097805	-0.935245
C	-9.034732	2.259619	-1.242535
C	-10.814044	0.206350	-0.686481
H	-9.183341	-1.142553	-0.965338
C	-10.370907	2.542327	-0.991276
H	-8.360306	3.071917	-1.520168
C	-11.287764	1.525361	-0.680477
H	-11.507715	-0.613107	-0.502929
H	-10.710178	3.575745	-1.053579
H	-12.332742	1.748388	-0.489043
C	-7.213101	-0.889170	1.466840
K	-7.510200	2.099077	1.367826
H	-8.004512	-0.847090	0.721056
H	-3.797845	-2.029705	0.205499
C	-7.638728	-0.818071	2.862928
C	-6.731434	-0.811175	3.943614
C	-9.014901	-0.687891	3.145828
C	-7.189391	-0.688027	5.251227
H	-5.671044	-0.907055	3.732789
C	-9.466096	-0.558192	4.459451
H	-9.724289	-0.688797	2.320284
C	-8.557742	-0.558045	5.520142
H	-6.475489	-0.692574	6.071061
H	-10.531146	-0.461773	4.653731
H	-8.908540	-0.461594	6.543515

=== INT$_2$-2.10aa (trans) ===

C	-3.321039	-0.635211	0.253382

C	-2.471099	-1.715903	0.514653
C	-1.268803	-1.535740	1.200625
C	-0.904594	-0.265160	1.646400
C	-1.751618	0.818291	1.400692
C	-2.948519	0.635404	0.710393
H	-2.756688	-2.709831	0.178539
H	-0.623285	-2.388661	1.392040
H	0.026618	-0.120264	2.186994
H	-1.480641	1.810557	1.751216
H	-3.606877	1.477973	0.533608
C	-4.572842	-0.868400	-0.558561
N	-5.679694	0.031663	-0.239946
N	-5.952972	0.243826	1.036505
C	-4.420757	-0.656604	-2.095486
C	-3.722816	0.669538	-2.428331
H	-2.680678	0.669569	-2.094897
H	-3.733911	0.828809	-3.512689
H	-4.226754	1.519405	-1.957232
C	-3.676105	-1.817470	-2.755177
H	-3.653384	-1.690210	-3.843644
H	-2.640081	-1.873489	-2.402055
H	-4.162108	-2.776396	-2.538260
C	-5.904074	-0.599474	-2.506692
H	-6.049609	-0.131441	-3.485460
H	-6.298622	-1.620922	-2.571546
C	-6.678299	0.156393	-1.404127
C	-8.035993	-0.396102	-1.158654
H	-6.724698	1.226112	-1.643575
H	-8.134564	-1.469202	-1.341388
C	-9.233236	0.341107	-1.081656
C	-9.319110	1.775320	-0.973823
C	-10.510909	-0.329563	-1.022091
C	-10.522056	2.429233	-0.739744
H	-8.418532	2.371804	-1.092784
C	-11.703317	0.343996	-0.787065
H	-10.532166	-1.407201	-1.196325
C	-11.735119	1.736419	-0.614623
H	-10.515256	3.515620	-0.661021
H	-12.631071	-0.226458	-0.754667
H	-12.668506	2.261234	-0.436521
C	-6.947299	1.014605	1.372021
K	-9.200648	-1.004931	1.565697
H	-7.557884	1.545564	0.643428
H	-4.879240	-1.918457	-0.405496
C	-7.292196	1.223432	2.776786
C	-6.606222	0.588827	3.834890
C	-8.392239	2.049118	3.092621
C	-7.008380	0.779381	5.152739
H	-5.757874	-0.044729	3.596253
C	-8.793148	2.229769	4.416763
H	-8.930013	2.540994	2.284238
C	-8.105407	1.596806	5.454445
H	-6.463001	0.289094	5.955217
H	-9.642481	2.871080	4.637312
H	-8.414478	1.740483	6.485674

[Figure 2.2]

=== **INT$_0$-2.10ca** ===

C	-4.143838	-0.861700	-0.032039
C	-4.103273	-2.271248	-0.161861
C	-3.647775	-3.093912	0.872894
C	-3.209562	-2.546876	2.080486
C	-3.217580	-1.151375	2.227786
C	-3.673722	-0.331548	1.199041
H	-4.452394	-2.733638	-1.076641
H	-3.637511	-4.172248	0.729927
H	-2.855180	-3.187170	2.883450
H	-2.854635	-0.700757	3.149212
H	-3.692473	0.742899	1.332064
C	-4.663813	0.040278	-1.073894
N	-5.463526	1.065967	-0.811227
N	-5.935314	1.321527	0.395731
C	-4.439075	-0.243686	-2.572658
C	-4.642930	1.047305	-3.389475

H	-3.973762	1.836708	-3.032787
H	-4.422914	0.853948	-4.447103
H	-5.662121	1.428199	-3.303008
C	-3.012164	-0.747398	-2.857370
H	-2.888303	-0.966866	-3.925473
H	-2.278222	0.018293	-2.580524
H	-2.770604	-1.655879	-2.298577
C	-5.469668	-1.313830	-3.106088
H	-5.596288	-1.168846	-4.189348
H	-5.079673	-2.330210	-2.977158
C	-6.779791	-1.181528	-2.395290
C	-7.367744	-2.155641	-1.682831
H	-7.204263	-0.180884	-2.389339
H	-6.907193	-3.143823	-1.669700
C	-8.526813	-1.999841	-0.792074
C	-9.251544	-0.793997	-0.669597
C	-8.881326	-3.065188	0.060944
C	-10.259839	-0.657955	0.282077
H	-9.007194	0.049052	-1.307273
C	-9.891262	-2.926760	1.016019
H	-8.343282	-4.006799	-0.022807
C	-10.582716	-1.718917	1.137499
H	-10.796377	0.283689	0.359243
H	-10.139559	-3.765017	1.661482
H	-11.369519	-1.607138	1.877608
C	-6.760643	2.531129	0.361812
K	-6.722228	-0.857056	1.793881
H	-7.295206	2.586075	-0.603288
C	-7.798131	2.465336	1.487387
H	-7.300612	2.346424	2.460231
H	-8.400176	3.380342	1.534714
H	-8.487577	1.622661	1.341706
C	-5.894826	3.793915	0.486988
H	-5.343309	3.781096	1.436445
H	-5.163944	3.818121	-0.327933
H	-6.494552	4.713345	0.446549

=== INT$_1$-2.10ca ===

C	-3.410822	0.183606	0.124591
C	-2.457717	-0.042947	1.128358
C	-1.544602	0.943107	1.510275
C	-1.558335	2.193321	0.891010
C	-2.496208	2.440710	-0.115881
C	-3.408538	1.451012	-0.488443
H	-2.439394	-1.010377	1.623004
H	-0.821470	0.732197	2.294103
H	-0.847727	2.961685	1.182795
H	-2.512267	3.404191	-0.621240
H	-4.131597	1.668915	-1.265708
C	-4.474720	-0.877859	-0.157748
N	-5.812755	-0.423474	0.238835
N	-5.977791	-0.583721	1.563022
C	-4.492184	-1.440164	-1.615075
C	-3.089615	-1.964590	-1.967932
H	-2.771712	-2.734181	-1.254734
H	-3.081499	-2.410660	-2.970081
H	-2.344927	-1.161508	-1.948378
C	-5.481951	-2.618335	-1.644453
H	-5.504979	-3.082157	-2.638459
H	-5.183109	-3.385111	-0.919910
H	-6.488778	-2.291501	-1.376201
C	-4.889807	-0.416671	-2.721389
H	-4.053218	0.261940	-2.926370
H	-5.026697	-1.003578	-3.643726
C	-6.130441	0.385244	-2.468216
C	-6.228917	1.708126	-2.693815
H	-6.967796	-0.154680	-2.041491
H	-5.363066	2.235355	-3.098341
C	-7.359730	2.569637	-2.323776
C	-8.586444	2.066393	-1.839916
C	-7.196178	3.969466	-2.357947
C	-9.590436	2.926221	-1.399846
H	-8.750372	0.994563	-1.802983
C	-8.202990	4.829542	-1.917802

H	-6.261549	4.380315	-2.733659
C	-9.405907	4.312727	-1.431733
H	-10.524465	2.510651	-1.031425
H	-8.047759	5.904336	-1.958403
H	-10.192777	4.978997	-1.090682
C	-7.165851	-0.373854	2.081401
K	-6.148308	2.162883	0.870150
H	-4.191854	-1.742928	0.463167
C	-7.329747	-0.538018	3.569137
H	-7.718837	0.369590	4.060899
H	-8.038316	-1.343930	3.821725
H	-6.363005	-0.778615	4.022835
C	-8.400380	-0.160805	1.236375
H	-8.616919	0.887252	0.958587
H	-8.284859	-0.702368	0.288532
H	-9.295880	-0.519497	1.758968

=== **TS-2.10ca (cis)** ===

C	-3.409888	0.054590	0.025377
C	-2.973033	0.105349	1.360480
C	-2.163491	1.142341	1.831690
C	-1.750011	2.158177	0.964077
C	-2.154831	2.115766	-0.374502
C	-2.979662	1.081990	-0.831309
H	-3.288926	-0.679829	2.041866
H	-1.849405	1.152514	2.872204
H	-1.108687	2.959894	1.319850
H	-1.825167	2.884558	-1.069070
H	-3.290513	1.087215	-1.866849
C	-4.399979	-1.049005	-0.348763
N	-5.813115	-0.713362	-0.175538
N	-6.102937	0.013441	0.950689
C	-4.377708	-1.609601	-1.799849
C	-2.963960	-1.821971	-2.354525
H	-2.397997	-2.512078	-1.716592
H	-3.013875	-2.263631	-3.357171
H	-2.392342	-0.893255	-2.426962
C	-5.091399	-2.976894	-1.789103
H	-5.140156	-3.388096	-2.804710
H	-4.547976	-3.695265	-1.162614
H	-6.106132	-2.882269	-1.396890
C	-5.197339	-0.608665	-2.660324
H	-4.526146	0.120535	-3.126793
H	-5.671761	-1.147450	-3.490581
C	-6.262382	0.143969	-1.864083
C	-6.237745	1.553457	-1.931359
H	-7.244028	-0.322873	-1.859513
H	-5.299322	2.013434	-2.242565
C	-7.269485	2.473682	-1.562234
C	-8.573604	2.098009	-1.121743
C	-7.015053	3.881369	-1.579983
C	-9.510436	3.036785	-0.712173
H	-8.839168	1.046865	-1.111594
C	-7.963409	4.815552	-1.168080
H	-6.053382	4.228718	-1.959593
C	-9.223699	4.410807	-0.716935
H	-10.490431	2.692956	-0.386464
H	-7.715972	5.874809	-1.210677
H	-9.964121	5.137250	-0.396246
C	-7.320980	-0.086344	1.398047
K	-5.414935	2.695521	0.795511
H	-4.157456	-1.889387	0.324211
C	-7.740860	0.825724	2.515912
H	-8.404367	1.620737	2.136490
H	-8.307684	0.287580	3.286340
H	-6.872655	1.292920	2.996360
C	-8.359044	-1.023187	0.849687
H	-9.090037	-0.496955	0.221886
H	-7.873134	-1.788480	0.239566
H	-8.925373	-1.487468	1.667147

=== **TS-2.10ca (trans)** ===

C	-3.760656	-0.652527	0.351556
C	-3.282749	-1.832689	0.937075

C	-2.279758	-1.803934	1.908940
C	-1.742317	-0.583073	2.318545
C	-2.218436	0.601941	1.750455
C	-3.218699	0.566896	0.779861
H	-3.702215	-2.786705	0.622811
H	-1.922117	-2.732728	2.346248
H	-0.964190	-0.553754	3.076369
H	-1.810065	1.557813	2.068491
H	-3.602330	1.484936	0.348285
C	-4.842121	-0.712075	-0.706012
N	-5.724694	0.434448	-0.740437
N	-6.417906	0.579422	0.442778
C	-4.336585	-0.825365	-2.181570
C	-3.161648	0.122595	-2.457134
H	-2.266747	-0.166408	-1.895483
H	-2.910815	0.107927	-3.524979
H	-3.424062	1.148725	-2.181956
C	-3.907557	-2.264716	-2.491738
H	-3.565010	-2.352310	-3.529700
H	-3.082536	-2.578063	-1.840790
H	-4.737967	-2.966699	-2.351330
C	-5.568761	-0.388156	-3.054600
H	-5.348172	0.573782	-3.525416
H	-5.731693	-1.113522	-3.860670
C	-6.821885	-0.253118	-2.202219
C	-7.551079	-1.425690	-1.923481
H	-7.376537	0.675652	-2.310961
H	-7.077846	-2.377739	-2.164157
C	-8.791022	-1.515138	-1.216305
C	-9.523048	-0.387449	-0.731060
C	-9.345343	-2.791460	-0.884358
C	-10.676511	-0.531862	0.030488
H	-9.152089	0.609754	-0.943282
C	-10.497720	-2.924631	-0.114243
H	-8.841548	-3.683798	-1.253766
C	-11.179171	-1.798656	0.367308
H	-11.192808	0.361878	0.376274
H	-10.873110	-3.921625	0.109338
H	-12.078501	-1.902081	0.966731
C	-7.060195	1.694017	0.608683
K	-7.363476	-1.799927	1.427420
H	-5.414468	-1.646612	-0.518645
C	-7.928303	1.833958	1.826316
H	-7.826008	2.825741	2.284427
H	-8.991779	1.708365	1.566903
H	-7.675059	1.080026	2.580520
C	-7.040417	2.827362	-0.379744
H	-6.151985	2.742352	-1.011167
H	-7.920134	2.803282	-1.038746
H	-7.054942	3.795800	0.134650

=== INT$_2$-2.10ca (cis) ===

C	-3.444220	0.111983	-0.003083
C	-3.024104	0.182727	1.334541
C	-2.196297	1.212810	1.791906
C	-1.752348	2.196896	0.904764
C	-2.142046	2.131559	-0.438059
C	-2.982032	1.106255	-0.882082
H	-3.366023	-0.577952	2.031774
H	-1.893312	1.240441	2.835274
H	-1.099617	2.994502	1.248743
H	-1.791776	2.880056	-1.144188
H	-3.286619	1.096471	-1.919672
C	-4.450182	-0.979425	-0.369573
N	-5.860728	-0.572057	-0.339090
N	-6.223133	0.169346	0.814440
C	-4.385423	-1.624364	-1.784928
C	-2.968613	-1.801626	-2.340107
H	-2.365781	-2.432731	-1.675563
H	-3.010461	-2.295662	-3.318061
H	-2.439953	-0.854666	-2.467768
C	-5.045210	-3.015150	-1.705306
H	-5.109693	-3.462024	-2.704307
H	-4.459268	-3.692464	-1.071718

H	-6.054570	-2.945228	-1.291475
C	-5.268679	-0.672819	-2.637307
H	-4.648206	0.057631	-3.165042
H	-5.811462	-1.231685	-3.406833
C	-6.244672	0.070420	-1.684055
C	-6.170251	1.554883	-1.816437
H	-7.273832	-0.277600	-1.847377
H	-5.279475	1.957680	-2.296180
C	-7.182304	2.472372	-1.506846
C	-8.465753	2.134577	-0.937512
C	-6.969400	3.896750	-1.661761
C	-9.371721	3.099224	-0.522031
H	-8.730288	1.087405	-0.836715
C	-7.889015	4.844667	-1.231821
H	-6.051640	4.226210	-2.151505
C	-9.104574	4.474930	-0.633113
H	-10.322684	2.771521	-0.101605
H	-7.659494	5.900049	-1.378734
H	-9.824104	5.219106	-0.305962
C	-7.385026	-0.112025	1.293056
K	-5.446696	2.877187	0.782921
H	-4.321918	-1.765950	0.386435
C	-7.878531	0.715618	2.447611
H	-8.650956	1.410884	2.091420
H	-8.331138	0.089074	3.224329
H	-7.064262	1.295967	2.893534
C	-8.309973	-1.178293	0.774989
H	-9.151547	-0.730180	0.233017
H	-7.771182	-1.842081	0.097625
H	-8.735007	-1.744768	1.611446

=== INT$_2$-2.10ca (trans) ===

C	-3.682535	-0.587650	0.345492
C	-3.012731	-1.663979	0.940489
C	-1.986937	-1.451770	1.863448
C	-1.623897	-0.151068	2.215512
C	-2.293926	0.930030	1.637202
C	-3.313189	0.713178	0.711112
H	-3.298149	-2.679574	0.674414
H	-1.476411	-2.301008	2.309861
H	-0.829563	0.019450	2.936857
H	-2.021092	1.946264	1.909547
H	-3.838287	1.550256	0.264333
C	-4.758323	-0.849653	-0.677087
N	-5.778962	0.190175	-0.736073
N	-6.460726	0.299158	0.505012
C	-4.293356	-0.947135	-2.169348
C	-3.124893	-0.001734	-2.475653
H	-2.215828	-0.290898	-1.937585
H	-2.905479	-0.019688	-3.549929
H	-3.372079	1.027780	-2.197880
C	-3.888678	-2.386724	-2.504585
H	-3.584887	-2.469594	-3.554716
H	-3.042689	-2.711475	-1.886147
H	-4.721084	-3.080070	-2.338121
C	-5.569071	-0.491818	-2.950879
H	-5.355207	0.432805	-3.495890
H	-5.884543	-1.241122	-3.681878
C	-6.679104	-0.251703	-1.906651
C	-7.531539	-1.454818	-1.676057
H	-7.276259	0.632138	-2.159732
H	-7.157919	-2.399710	-2.070788
C	-8.848488	-1.448239	-1.190148
C	-9.556784	-0.274132	-0.738674
C	-9.583450	-2.680809	-1.007349
C	-10.800917	-0.346153	-0.126638
H	-9.097185	0.699258	-0.876719
C	-10.823354	-2.729879	-0.385234
H	-9.133785	-3.602948	-1.377656
C	-11.457075	-1.568966	0.089914
H	-11.277531	0.581167	0.191457
H	-11.316101	-3.695729	-0.275317
H	-12.430552	-1.611587	0.568532
C	-7.023929	1.433181	0.729634

K	-7.523211	-2.147816	1.259751
H	-5.227185	-1.821930	-0.431530
C	-7.831154	1.572448	1.990041
H	-7.603973	2.513093	2.504792
H	-8.901989	1.580435	1.745932
H	-7.639988	0.740362	2.674758
C	-6.970968	2.617483	-0.195174
H	-6.122623	2.519306	-0.876022
H	-7.885850	2.676509	-0.798719
H	-6.901354	3.549056	0.376616

[Figure 2.3a]

=== **INT$_0$-2.11aa** ===

C	-4.603928	-0.680531	0.068027
C	-5.448818	-1.752720	-0.283139
C	-5.603158	-2.871659	0.542172
C	-4.914220	-2.961662	1.752514
C	-4.044299	-1.921120	2.113267
C	-3.895872	-0.808288	1.287667
H	-6.006293	-1.705227	-1.211052
H	-6.268020	-3.675449	0.234350
H	-5.032325	-3.831016	2.393555
H	-3.469939	-1.987616	3.035056
H	-3.230043	-0.004164	1.578808
C	-4.429522	0.540994	-0.755688
N	-4.501712	1.754298	-0.243195
N	-4.870979	1.954588	1.014498
C	-4.082625	0.445486	-2.249140
C	-3.361310	1.730016	-2.703120
H	-2.464594	1.898343	-2.098780
H	-3.062044	1.635631	-3.754921
H	-3.991851	2.613859	-2.593095
C	-3.125603	-0.736689	-2.510474
H	-2.870746	-0.798495	-3.576050
H	-2.194978	-0.610698	-1.945030
H	-3.567094	-1.693776	-2.215619
C	-5.331641	0.249483	-3.164604
H	-5.011286	0.389924	-4.206277
H	-5.678174	-0.791153	-3.103325
C	-7.412233	0.695749	-1.774391
C	-7.894611	1.431856	-0.762079
H	-7.712553	-0.349299	-1.855144
H	-7.612831	2.481131	-0.697574
C	-8.762632	0.943262	0.317553
C	-8.923607	-0.429848	0.608027
C	-9.423825	1.867384	1.151020
C	-9.704001	-0.851712	1.683983
H	-8.402442	-1.168640	0.008136
C	-10.195966	1.446204	2.233857
H	-9.312481	2.928108	0.949612
C	-10.339361	0.083603	2.510429
H	-9.806298	-1.914756	1.886316
H	-10.682351	2.184613	2.865072
H	-10.939078	-0.246507	3.353529
C	-4.764171	3.381207	1.338653
K	-6.512173	0.482791	2.578329
H	-5.061258	4.010323	0.484020
H	-3.725285	3.667448	1.592488
C	-5.651611	3.667286	2.527608
C	-5.212572	3.378314	3.829523
C	-6.974707	4.094437	2.352922
C	-6.078655	3.490265	4.922199
H	-4.184109	3.057892	3.980189
C	-7.842740	4.216473	3.440356
H	-7.323437	4.322712	1.349018
C	-7.399823	3.905460	4.729134
H	-5.720543	3.264042	5.923412
H	-8.864790	4.550944	3.283176
H	-8.073013	4.000014	5.576707
C	-6.524081	1.183637	-2.878107
H	-6.175603	2.197404	-2.656280
H	-7.127548	1.246715	-3.797605

=== **INT$_1$-2.11aa** ===

C	-3.662245	-0.939048	-0.066862
C	-3.815329	-2.291390	0.271790
C	-2.880782	-2.949541	1.077297
C	-1.767486	-2.258886	1.557997
C	-1.604535	-0.909424	1.231144
C	-2.545279	-0.256807	0.435139
H	-4.671366	-2.842002	-0.117499
H	-3.021297	-3.999178	1.324016
H	-1.036789	-2.764175	2.183497
H	-0.744210	-0.361069	1.606023
H	-2.441507	0.799653	0.213970
C	-4.707288	-0.216996	-0.915240
N	-4.956904	1.148595	-0.457995
N	-5.403697	1.164154	0.777735
C	-4.369370	-0.176876	-2.445375
C	-3.284075	0.870841	-2.737371
H	-2.347809	0.609418	-2.232066
H	-3.079885	0.915701	-3.814573
H	-3.587766	1.858556	-2.387109
C	-3.859759	-1.552259	-2.914597
H	-3.712560	-1.550741	-4.001263
H	-2.906214	-1.809572	-2.444903
H	-4.576477	-2.348781	-2.677009
C	-5.646514	0.114810	-3.279238
H	-5.332764	0.162052	-4.330949
H	-6.310534	-0.757348	-3.206755
C	-7.338437	1.310881	-1.746629
C	-8.222885	0.328488	-1.494647
H	-7.231183	2.124107	-1.037131
H	-8.323533	-0.489539	-2.208745
C	-9.030719	0.179811	-0.277266
C	-9.076225	1.152122	0.747103
C	-9.747918	-1.017609	-0.067083
C	-9.775423	0.924964	1.930797
H	-8.526119	2.078117	0.632825
C	-10.450619	-1.246955	1.119126
H	-9.742431	-1.777676	-0.845431
C	-10.462507	-0.280661	2.129810
H	-9.758918	1.684156	2.707542
H	-10.991454	-2.180527	1.251122
H	-11.004490	-0.458124	3.054244
C	-5.774107	2.329771	1.290916
K	-6.834601	-0.997856	1.806239
H	-5.749548	3.227002	0.664480
H	-5.630945	-0.829856	-0.852958
C	-6.326672	2.412639	2.620452
C	-6.057023	1.447443	3.627796
C	-7.211697	3.461947	2.970729
C	-6.696243	1.487728	4.865582
H	-5.283254	0.705817	3.442123
C	-7.837228	3.504161	4.212372
H	-7.421789	4.234695	2.234323
C	-7.605280	2.506921	5.168121
H	-6.456317	0.735595	5.614818
H	-8.518975	4.320943	4.438055
H	-8.095346	2.543101	6.136549
C	-6.472374	1.383963	-2.980642
H	-5.807865	2.246374	-2.895494
H	-7.117159	1.565476	-3.854481

=== **TS-2.11aa (cis)** ===

C	-3.903006	-0.462275	0.362675
C	-4.020078	-1.756553	0.885426
C	-3.156357	-2.218714	1.884072
C	-2.157013	-1.382613	2.380903
C	-2.030911	-0.086677	1.870207
C	-2.894988	0.368182	0.876217
H	-4.794401	-2.415377	0.497308
H	-3.265343	-3.229867	2.267943
H	-1.482438	-1.734085	3.156683
H	-1.258473	0.574727	2.253550
H	-2.811706	1.385509	0.512922
C	-4.882660	0.011353	-0.695071
N	-5.414306	1.355738	-0.427055

N	-5.604432	1.589268	0.891257
C	-4.321337	0.031513	-2.156490
C	-3.176495	1.045650	-2.304461
H	-2.301330	0.744698	-1.719722
H	-2.867256	1.108898	-3.354713
H	-3.486817	2.038862	-1.971160
C	-3.805390	-1.365341	-2.534056
H	-3.494712	-1.386187	-3.585349
H	-2.944712	-1.653768	-1.921828
H	-4.584372	-2.126758	-2.401004
C	-5.479507	0.395564	-3.122623
H	-5.058160	0.520970	-4.128882
H	-6.155901	-0.470316	-3.181617
C	-6.965915	1.450491	-1.386688
C	-7.911447	2.365074	-0.869163
H	-7.266070	0.409339	-1.244868
H	-7.850501	3.411820	-1.162574
C	-8.894989	2.021564	0.105890
C	-9.187677	0.681514	0.517883
C	-9.684733	3.029210	0.741218
C	-10.157237	0.395510	1.482519
H	-8.693194	-0.149687	0.019426
C	-10.628697	2.736723	1.712113
H	-9.524085	4.064564	0.447146
C	-10.878433	1.413602	2.113464
H	-10.366358	-0.646590	1.726449
H	-11.188191	3.551490	2.167485
H	-11.630618	1.187168	2.863112
C	-5.975477	2.806718	1.184527
K	-7.067682	0.041279	2.604032
H	-6.069760	3.569089	0.413917
H	-5.699119	-0.738366	-0.704468
C	-6.246715	3.170040	2.571951
C	-5.582506	2.530029	3.643848
C	-7.197670	4.160769	2.880483
C	-5.895673	2.838650	4.966516
H	-4.789659	1.821330	3.416121
C	-7.505476	4.467885	4.204185
H	-7.714510	4.664070	2.070095
C	-6.867420	3.803070	5.254989
H	-5.363202	2.343649	5.775174
H	-8.253698	5.226470	4.418042
H	-7.108328	4.047461	6.285517
C	-6.331128	1.621981	-2.754946
H	-5.737360	2.542404	-2.773759
H	-7.121018	1.733747	-3.510276

=== **TS-2.11aa (trans)** ===

C	-4.263130	-0.786127	0.203548
C	-4.342577	-2.128386	0.602942
C	-3.512073	-2.639584	1.606320
C	-2.582892	-1.807826	2.231568
C	-2.491590	-0.467957	1.842253
C	-3.322514	0.036135	0.842732
H	-5.058477	-2.785768	0.111963
H	-3.590707	-3.685315	1.892408
H	-1.935485	-2.197631	3.012024
H	-1.772658	0.189308	2.323939
H	-3.263970	1.082774	0.568577
C	-5.194134	-0.268681	-0.879025
N	-5.744834	1.064906	-0.596516
N	-6.010607	1.249798	0.717352
C	-4.538106	-0.208419	-2.302240
C	-3.397919	0.820930	-2.345444
H	-2.562333	0.511522	-1.709251
H	-3.017034	0.916946	-3.369416
H	-3.738481	1.802150	-2.006056
C	-3.981186	-1.588668	-2.682473
H	-3.615103	-1.576494	-3.715924
H	-3.149931	-1.882491	-2.033807
H	-4.755477	-2.363183	-2.612752
C	-5.632326	0.161124	-3.335975
H	-5.145151	0.316814	-4.307827
H	-6.293276	-0.704962	-3.466469

C	-7.221763	1.237105	-1.670269
C	-8.146278	0.164896	-1.553304
H	-7.542579	2.188834	-1.247504
H	-8.027093	-0.683136	-2.224070
C	-9.114895	-0.008414	-0.523587
C	-9.425042	0.968355	0.477272
C	-9.835415	-1.242410	-0.403721
C	-10.345121	0.726593	1.492853
H	-8.919103	1.926512	0.452478
C	-10.743352	-1.479964	0.623096
H	-9.656102	-2.015941	-1.148660
C	-11.009798	-0.505845	1.599739
H	-10.533080	1.510893	2.223859
H	-11.255783	-2.439501	0.663830
H	-11.719255	-0.693343	2.399963
C	-6.412167	2.429763	1.096658
K	-7.425325	-0.893120	1.898980
H	-6.546072	3.243446	0.377625
H	-6.018044	-1.001385	-0.964954
C	-6.769683	2.671753	2.488502
C	-6.252470	1.880469	3.539809
C	-7.676901	3.696776	2.819454
C	-6.661359	2.084678	4.855145
H	-5.498304	1.133236	3.305809
C	-8.080690	3.899909	4.137775
H	-8.078275	4.322905	2.026286
C	-7.584756	3.090506	5.163127
H	-6.242562	1.471149	5.649295
H	-8.788906	4.691962	4.365837
H	-7.898978	3.251025	6.190235
C	-6.481247	1.392411	-2.991672
H	-5.842554	2.280043	-2.940016
H	-7.209998	1.559866	-3.796026

=== INT$_2$-2.11aa (cis) ===

C	-3.866124	-0.385359	0.462974
C	-3.888704	-1.682650	0.987311
C	-2.951525	-2.097403	1.937983
C	-1.974148	-1.209509	2.385712
C	-1.942984	0.091093	1.872850
C	-2.878186	0.497844	0.923489
H	-4.648624	-2.380002	0.641943
H	-2.988062	-3.112197	2.325634
H	-1.243406	-1.524504	3.125477
H	-1.187837	0.792792	2.217041
H	-2.863636	1.515431	0.551758
C	-4.900284	0.021277	-0.568544
N	-5.452774	1.361192	-0.309758
N	-5.616973	1.588043	1.047418
C	-4.370686	-0.011413	-2.042577
C	-3.214349	0.979671	-2.249356
H	-2.326886	0.678502	-1.684285
H	-2.938649	1.012022	-3.310122
H	-3.494893	1.987417	-1.932973
C	-3.885476	-1.426938	-2.389037
H	-3.600378	-1.480196	-3.446341
H	-3.015475	-1.713259	-1.789637
H	-4.673969	-2.170608	-2.217912
C	-5.546926	0.345909	-2.981166
H	-5.167707	0.424707	-4.008713
H	-6.255673	-0.495533	-2.978063
C	-6.816980	1.520271	-1.149486
C	-7.722933	2.567142	-0.689175
H	-7.295279	0.537417	-1.029324
H	-7.550153	3.585093	-1.034128
C	-8.813948	2.342839	0.172781
C	-9.260916	1.043507	0.608512
C	-9.585436	3.437145	0.700610
C	-10.336095	0.880398	1.486657
H	-8.809591	0.153180	0.175149
C	-10.630926	3.258545	1.586704
H	-9.320699	4.444363	0.382470
C	-11.025427	1.975428	2.015791
H	-10.653942	-0.131589	1.741801

H	-11.163898	4.133841	1.954747
H	-11.861123	1.841625	2.695913
C	-5.859517	2.835521	1.316714
K	-7.372804	0.389002	2.833678
H	-5.824774	3.598539	0.542948
H	-5.707188	-0.737271	-0.519048
C	-6.131645	3.251290	2.695387
C	-5.489593	2.621666	3.783304
C	-7.059489	4.273132	2.961157
C	-5.794811	2.983892	5.094873
H	-4.728910	1.872475	3.577928
C	-7.363902	4.628834	4.274279
H	-7.567337	4.754030	2.132213
C	-6.740863	3.983725	5.345987
H	-5.281106	2.499634	5.921471
H	-8.095993	5.409190	4.462605
H	-6.977350	4.267855	6.367299
C	-6.318680	1.611888	-2.591267
H	-5.698142	2.508999	-2.701797
H	-7.180675	1.730939	-3.258150

=== INT$_2$-2.11aa (trans) ===

C	-4.304016	-0.685893	0.236175
C	-4.364909	-1.997933	0.725882
C	-3.550267	-2.418252	1.783282
C	-2.657312	-1.522924	2.371252
C	-2.582959	-0.212132	1.889427
C	-3.396246	0.200933	0.835800
H	-5.054969	-2.703013	0.265782
H	-3.613931	-3.442858	2.140087
H	-2.023017	-1.841052	3.193754
H	-1.890993	0.493586	2.340860
H	-3.349489	1.227010	0.491443
C	-5.219082	-0.282202	-0.902794
N	-5.879474	1.020899	-0.684221
N	-6.077173	1.302234	0.638396
C	-4.517452	-0.238081	-2.303067
C	-3.407977	0.824008	-2.346627
H	-2.569930	0.549368	-1.698433
H	-3.020263	0.918045	-3.367906
H	-3.779332	1.801495	-2.027648
C	-3.912404	-1.612974	-2.620309
H	-3.505569	-1.620045	-3.638229
H	-3.101139	-1.866043	-1.930265
H	-4.669942	-2.404236	-2.558582
C	-5.601078	0.074836	-3.364034
H	-5.109063	0.216142	-4.335249
H	-6.245678	-0.806048	-3.473686
C	-7.117793	1.178168	-1.651501
C	-8.110877	0.088807	-1.539416
H	-7.532554	2.149044	-1.369044
H	-7.973984	-0.774237	-2.186754
C	-9.102049	-0.032378	-0.554302
C	-9.456052	0.988857	0.404253
C	-9.842430	-1.265326	-0.389643
C	-10.383242	0.777421	1.417722
H	-8.976859	1.959174	0.336670
C	-10.757350	-1.462452	0.634295
H	-9.656834	-2.068485	-1.101761
C	-11.037543	-0.456631	1.581758
H	-10.592172	1.595095	2.106727
H	-11.268512	-2.422172	0.702454
H	-11.757931	-0.614406	2.378298
C	-6.539984	2.458710	0.986463
K	-7.549463	-0.830652	1.892043
H	-6.819948	3.222865	0.255951
H	-5.995380	-1.060725	-0.983041
C	-6.773661	2.753891	2.399516
C	-6.124715	2.034375	3.426542
C	-7.690785	3.755927	2.761795
C	-6.412335	2.294669	4.763561
H	-5.376383	1.294110	3.155164
C	-7.974829	4.013557	4.102309
H	-8.193504	4.321875	1.981450

C	-7.343877	3.280737	5.109714
H	-5.896921	1.738398	5.542498
H	-8.693063	4.786741	4.360450
H	-7.563931	3.482866	6.153830
C	-6.467646	1.296597	-3.036154
H	-5.854277	2.204773	-3.067283
H	-7.255407	1.403339	-3.790371

[Figure 2.3b]

=== **INT$_0$-2.11ca** ===

C	-4.345428	-0.863648	0.018105
C	-4.806591	-2.194177	-0.017322
C	-4.445209	-3.120199	0.971516
C	-3.620135	-2.738043	2.030864
C	-3.148734	-1.416842	2.086383
C	-3.506572	-0.502454	1.097331
H	-5.481474	-2.499650	-0.807443
H	-4.814513	-4.141483	0.911012
H	-3.335980	-3.456151	2.795389
H	-2.491991	-1.108156	2.896411
H	-3.144770	0.519391	1.145215
C	-4.710507	0.175460	-0.987533
N	-5.359799	1.264499	-0.643440
N	-5.859554	1.425547	0.579371
C	-4.245955	0.035983	-2.443180
C	-4.348922	1.385460	-3.173877
H	-3.705990	2.130544	-2.695198
H	-4.030835	1.269536	-4.218283
H	-5.364668	1.784174	-3.154966
C	-2.765126	-0.407250	-2.469651
H	-2.397355	-0.488946	-3.500365
H	-2.139041	0.319675	-1.939620
H	-2.629565	-1.380598	-1.985538
C	-5.049498	-1.034066	-3.235775
H	-4.603914	-1.125512	-4.237305
H	-4.914935	-2.011342	-2.758125
C	-7.356342	-0.668851	-2.155005
C	-8.004935	-1.690581	-1.572233
H	-7.356856	0.303386	-1.671803
H	-7.939506	-2.685890	-2.014979
C	-8.747828	-1.601143	-0.306618
C	-9.357834	-0.404451	0.124848
C	-8.844946	-2.728310	0.533643
C	-10.005786	-0.331839	1.358117
H	-9.317921	0.471375	-0.514705
C	-9.488466	-2.655567	1.771857
H	-8.393185	-3.664360	0.214355
C	-10.068320	-1.454374	2.195058
H	-10.471477	0.600955	1.664498
H	-9.544589	-3.539123	2.402275
H	-10.582145	-1.398895	3.150524
C	-6.449524	2.759057	0.696180
K	-6.568678	-0.516882	2.265526
H	-7.027451	2.996893	-0.216227
C	-7.415166	2.776270	1.885234
H	-6.882226	2.534682	2.817235
H	-7.873751	3.762652	2.020079
H	-8.222471	2.045659	1.746603
C	-5.376254	3.847996	0.854118
H	-4.788577	3.668764	1.764913
H	-4.693971	3.814821	-0.001393
H	-5.811858	4.854953	0.915489
C	-6.564057	-0.786031	-3.427269
H	-6.704388	0.125816	-4.020412
H	-6.960817	-1.615764	-4.026805

=== **INT$_1$-2.11ca** ===

C	-3.856544	-0.896812	0.266705
C	-3.769728	-2.213939	0.743614
C	-2.859667	-2.568956	1.744785
C	-2.010867	-1.602798	2.287883
C	-2.087520	-0.285897	1.824021
C	-3.005183	0.062391	0.833227
H	-4.418012	-2.976499	0.310935

H	-2.811729	-3.597528	2.094930
H	-1.300816	-1.870848	3.065593
H	-1.434135	0.474747	2.244332
H	-3.099472	1.089628	0.498099
C	-4.892289	-0.497819	-0.791577
N	-5.450629	0.820920	-0.573928
N	-6.078173	0.888842	0.622297
C	-4.331652	-0.562579	-2.257199
C	-3.401946	0.628726	-2.536657
H	-2.532949	0.608393	-1.869486
H	-3.030709	0.586349	-3.568930
H	-3.921893	1.574426	-2.377453
C	-3.536553	-1.862318	-2.477942
H	-3.237405	-1.948676	-3.529795
H	-2.629468	-1.892122	-1.867078
H	-4.137887	-2.746526	-2.230095
C	-5.493760	-0.588934	-3.286126
H	-5.039242	-0.538415	-4.285252
H	-5.978347	-1.573104	-3.233604
C	-7.538749	0.349359	-2.050208
C	-8.164435	-0.806521	-1.736070
H	-7.789010	1.255843	-1.512050
H	-7.925123	-1.705782	-2.302512
C	-9.089387	-1.018927	-0.624299
C	-9.523164	0.015127	0.239406
C	-9.542806	-2.327592	-0.338063
C	-10.341284	-0.252576	1.334402
H	-9.186109	1.030493	0.064740
C	-10.355741	-2.595985	0.764906
H	-9.237292	-3.141431	-0.992337
C	-10.757346	-1.561623	1.616406
H	-10.650950	0.566134	1.979024
H	-10.680724	-3.615578	0.956315
H	-11.392985	-1.766047	2.472926
C	-6.524862	2.059151	0.998800
K	-6.971797	-1.407052	1.790321
H	-5.673960	-1.295726	-0.758767
C	-7.299754	2.170679	2.282144
H	-6.952291	3.013462	2.897392
H	-8.379904	2.334275	2.120699
H	-7.198527	1.263516	2.891947
C	-6.302675	3.296749	0.173108
H	-5.266619	3.319526	-0.189241
H	-6.930913	3.317168	-0.730517
H	-6.513242	4.207307	0.746073
C	-6.576939	0.501682	-3.201983
H	-6.106166	1.484814	-3.139519
H	-7.145520	0.478072	-4.146410

=== TS-2.11ca (cis) ===

C	-4.135818	-0.800174	0.464019
C	-4.067016	-2.063687	1.068508
C	-3.173935	-2.322249	2.113242
C	-2.329050	-1.311695	2.573062
C	-2.388358	-0.046582	1.980361
C	-3.284331	0.206686	0.943051
H	-4.713283	-2.860494	0.704035
H	-3.137259	-3.312131	2.561269
H	-1.632344	-1.505639	3.383866
H	-1.736611	0.748457	2.333192
H	-3.350708	1.196821	0.507433
C	-5.131784	-0.539000	-0.656129
N	-5.752272	0.777988	-0.576586
N	-6.190589	1.074804	0.689837
C	-4.515549	-0.672918	-2.092254
C	-3.448850	0.404149	-2.341869
H	-2.593928	0.278825	-1.669229
H	-3.076507	0.329534	-3.370962
H	-3.860157	1.403578	-2.187029
C	-3.872619	-2.058143	-2.264705
H	-3.525517	-2.189058	-3.296529
H	-3.012462	-2.188990	-1.600530
H	-4.590297	-2.860558	-2.050737
C	-5.649159	-0.545134	-3.140813

H	-5.188813	-0.540046	-4.138195
H	-6.261033	-1.458894	-3.094871
C	-7.324180	0.627588	-1.671762
C	-8.308986	1.562273	-1.317501
H	-7.552066	-0.400275	-1.374731
H	-8.249151	2.565501	-1.733620
C	-9.306772	1.339722	-0.320742
C	-9.633480	0.054618	0.219165
C	-10.082163	2.421243	0.197941
C	-10.615599	-0.114702	1.196068
H	-9.162332	-0.829971	-0.206093
C	-11.045368	2.245623	1.181468
H	-9.895834	3.418684	-0.195684
C	-11.323563	0.976548	1.712601
H	-10.852306	-1.122851	1.538745
H	-11.596422	3.112297	1.541896
H	-12.087815	0.841118	2.472045
C	-6.510698	2.320505	0.891577
K	-7.379787	-0.836614	2.190265
H	-5.886956	-1.356728	-0.585459
C	-7.157655	2.686590	2.196710
H	-6.717498	3.598536	2.621602
H	-8.231428	2.878946	2.049514
H	-7.054046	1.889050	2.942679
C	-6.183534	3.467375	-0.028149
H	-5.738454	3.101507	-0.952536
H	-7.075466	4.056940	-0.266516
H	-5.476072	4.147862	0.472628
C	-6.598370	0.654173	-3.000555
H	-6.062100	1.603167	-3.112267
H	-7.332471	0.608122	-3.817875

=== **TS-2.11ca (trans)** ===

C	-4.215697	-0.806440	0.410562
C	-4.054326	-2.079972	0.976361
C	-3.189314	-2.293295	2.054378
C	-2.465778	-1.225917	2.588144
C	-2.616824	0.048869	2.034482
C	-3.484480	0.255703	0.962739
H	-4.607205	-2.919020	0.555868
H	-3.079823	-3.291349	2.471385
H	-1.792259	-1.384215	3.425861
H	-2.059985	0.887376	2.444743
H	-3.621879	1.250504	0.554406
C	-5.177583	-0.597525	-0.750727
N	-5.914032	0.659649	-0.669373
N	-6.435642	0.836742	0.600627
C	-4.472775	-0.653732	-2.151773
C	-3.498667	0.520991	-2.331673
H	-2.680116	0.467239	-1.606486
H	-3.056806	0.492421	-3.335384
H	-4.006533	1.478295	-2.197543
C	-3.692747	-1.969769	-2.301027
H	-3.293095	-2.057478	-3.318456
H	-2.851370	-2.025911	-1.603347
H	-4.339537	-2.838002	-2.121503
C	-5.550725	-0.626530	-3.264283
H	-5.037988	-0.538579	-4.231860
H	-6.057499	-1.599793	-3.281920
C	-7.428681	0.378361	-1.878922
C	-8.159807	-0.799946	-1.634473
H	-7.893814	1.313878	-1.576740
H	-7.862501	-1.705050	-2.160484
C	-9.175177	-0.979248	-0.645631
C	-9.705444	0.068038	0.172353
C	-9.702052	-2.283243	-0.376221
C	-10.639355	-0.175898	1.173896
H	-9.357553	1.083133	0.015422
C	-10.627244	-2.520113	0.635744
H	-9.352252	-3.114411	-0.986506
C	-11.103823	-1.474076	1.441869
H	-11.007595	0.661518	1.764009
H	-10.985521	-3.534924	0.798883
H	-11.829178	-1.658542	2.228423

C	-6.854844	2.026353	0.901385
K	-7.444402	-1.436532	1.795920
H	-5.877933	-1.461659	-0.740097
C	-7.519345	2.222552	2.235810
H	-7.165163	3.136720	2.729094
H	-8.610938	2.320543	2.129175
H	-7.324201	1.376838	2.905001
C	-6.741681	3.221462	-0.006327
H	-6.003329	3.016007	-0.785584
H	-7.696631	3.454177	-0.497883
H	-6.454806	4.114221	0.563758
C	-6.603602	0.483287	-3.149295
H	-6.115320	1.462154	-3.180561
H	-7.271892	0.427142	-4.020898

=== **INT$_2$-2.11ca (cis)** ===

C	-3.931789	-0.700092	0.429259
C	-3.821777	-1.915557	1.117530
C	-2.817239	-2.122308	2.068024
C	-1.901829	-1.107300	2.344921
C	-2.001042	0.110560	1.664720
C	-3.005739	0.312428	0.720708
H	-4.525623	-2.715571	0.895094
H	-2.750433	-3.075798	2.585564
H	-1.118438	-1.261129	3.081705
H	-1.294012	0.908523	1.875392
H	-3.093350	1.267442	0.215809
C	-5.033864	-0.511164	-0.594322
N	-5.656544	0.813717	-0.495764
N	-5.884316	1.154425	0.856490
C	-4.565440	-0.741953	-2.071325
C	-3.482551	0.267077	-2.483499
H	-2.558679	0.112852	-1.917356
H	-3.246269	0.144217	-3.547168
H	-3.815443	1.294278	-2.318598
C	-4.008732	-2.164680	-2.226580
H	-3.766945	-2.361378	-3.277564
H	-3.097642	-2.308260	-1.637144
H	-4.741676	-2.916379	-1.907168
C	-5.802281	-0.595761	-2.986492
H	-5.477426	-0.658736	-4.033756
H	-6.460500	-1.460634	-2.815091
C	-7.030338	0.801701	-1.278706
C	-7.927664	1.913562	-0.950096
H	-7.494478	-0.157529	-0.988758
H	-7.742153	2.868677	-1.435813
C	-8.900908	1.867676	0.056753
C	-9.345572	0.664704	0.723249
C	-9.556453	3.065430	0.523113
C	-10.305447	0.681670	1.737412
H	-9.022528	-0.300364	0.333683
C	-10.484148	3.063710	1.547989
H	-9.292634	4.006461	0.042181
C	-10.873607	1.873979	2.196565
H	-10.637764	-0.268823	2.159971
H	-10.929034	4.009877	1.854154
H	-11.616009	1.879772	2.988895
C	-5.970389	2.429265	1.064798
K	-7.145412	-0.623542	2.454497
H	-5.789405	-1.304341	-0.395102
C	-6.469337	2.887221	2.405776
H	-5.895145	3.743091	2.779459
H	-7.517667	3.204131	2.302243
H	-6.424810	2.090065	3.156215
C	-5.522752	3.521541	0.130599
H	-5.206626	3.113236	-0.827508
H	-6.322025	4.250740	-0.032663
H	-4.683772	4.061644	0.597076
C	-6.619686	0.677150	-2.746320
H	-6.057254	1.572314	-3.038655
H	-7.525217	0.653433	-3.363245

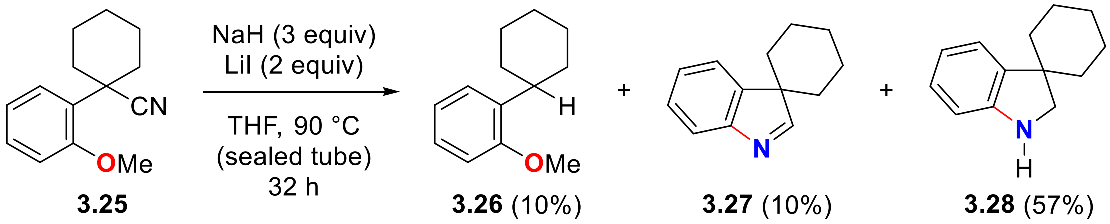
=== **INT$_2$-2.11ca (trans)** ===

C	-4.195307	-0.692006	0.401719

C	-3.847272	-1.880296	1.056363
C	-2.959375	-1.880412	2.135529
C	-2.405716	-0.680233	2.581578
C	-2.747150	0.513217	1.939133
C	-3.633205	0.506752	0.863392
H	-4.269580	-2.820878	0.707369
H	-2.701878	-2.816557	2.624003
H	-1.715820	-0.672904	3.420732
H	-2.323143	1.453829	2.280632
H	-3.910218	1.437743	0.381707
C	-5.151407	-0.732415	-0.773453
N	-6.118364	0.377128	-0.723926
N	-6.628287	0.486292	0.608147
C	-4.430084	-0.725699	-2.163323
C	-3.588986	0.544744	-2.365409
H	-2.745343	0.577658	-1.669042
H	-3.181783	0.562993	-3.383403
H	-4.185698	1.447783	-2.215979
C	-3.513170	-1.952767	-2.274659
H	-3.078593	-2.006431	-3.279727
H	-2.691423	-1.911275	-1.552865
H	-4.071094	-2.881820	-2.102364
C	-5.517170	-0.825849	-3.257507
H	-5.041159	-0.719749	-4.241293
H	-5.948017	-1.834753	-3.231324
C	-7.283223	0.119972	-1.704485
C	-8.063531	-1.134399	-1.487615
H	-7.922774	0.998797	-1.574097
H	-7.778281	-2.006166	-2.073847
C	-9.239687	-1.246915	-0.734672
C	-9.827984	-0.187924	0.053795
C	-9.916368	-2.519443	-0.594533
C	-10.886908	-0.407349	0.926485
H	-9.418828	0.814053	-0.025947
C	-10.964940	-2.719065	0.289980
H	-9.562535	-3.352973	-1.201356
C	-11.463566	-1.676788	1.095808
H	-11.273953	0.437968	1.495711
H	-11.414624	-3.709712	0.353832
H	-12.292279	-1.836559	1.778553
C	-7.027335	1.657841	0.953940
K	-7.648984	-1.934398	1.501860
H	-5.695600	-1.694844	-0.723439
C	-7.637116	1.807760	2.320709
H	-7.220162	2.676487	2.843291
H	-8.720614	1.965801	2.237462
H	-7.466412	0.914941	2.929276
C	-6.963047	2.885571	0.087826
H	-6.239509	2.735172	-0.716102
H	-7.941511	3.088316	-0.367122
H	-6.697902	3.764012	0.686231
C	-6.636553	0.205072	-3.095389
H	-6.235450	1.214278	-3.249314
H	-7.410574	0.040220	-3.853095

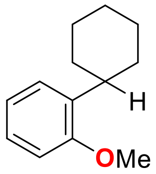
6.3. Experimental data for Chapter 3

6.3.1. Hydrodecyanation and nucleophilic aromatic substitution of 3.25 (Scheme 3.6a)



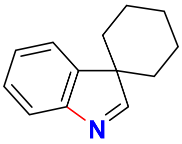
To a 25 mL sealed tube containing NaH (37.9 mg, 0.948 mmol) and LiI (80.6 mg, 0.602 mmol) in THF (1 mL) was added a solution of 1-(2-methoxyphenyl)cyclohexane-1-carbonitrile (**3.25**) (64.0 mg, 0.297 mmol) in THF (2 mL) at 0 °C under a N_2 atmosphere. The tube was sealed and the solution was then stirred at 90 °C. With confirmation of full conversion of **3.25** based on TLC analysis, the reaction mixture was cooled to 0 °C and quenched with cold water. The organic materials were extracted thrice with EtOAc and the combined extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting crude material was purified by flash column chromatography (hexane : EtOAc =120:1 to 100:1 to 10:1) to yield **3.26** (5.5 mg, 0.0289 mmol) in 10% yield as a pale-yellow oil, **3.27** (5.7 mg, 0.0308 mmol) in 10% yield as a pale yellow oil, and **3.28** (32.0 mg, 0.170 mmol) in 57% yield as a pale orange solid.

1-cyclohexyl-2-methoxybenzene (3.26)[9]



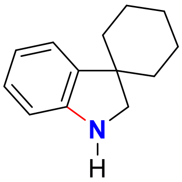
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24-1.44 (5H, m), 1.73-1.84 (5H, m), 2.93-2.98 (1H, m), 3.82 (3H, s), 6.85 (1H, d, J = 8.1 Hz), 6.92 (1H, dd, J = 7.6, 7.4 Hz), 7.15 (1H, dd, *J* = 8.1, 7.6 Hz), 7.19 (1H, d, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.4, 27.1, 33.2, 36.7, 55.4, 110.3, 120.5, 126.4, 126.5, 136.3, 156.7.

spiro[cyclohexane-1,3'-indole] (3.27) [10]



^{1}H NMR (400 MHz, $CDCl_3$) δ 1.57-1.91 (10H, m), 7.25 (1H, dd, *J* = 7.8, 7.7 Hz), 7.34 (1H, dd, *J* = 7.7, 7.3 Hz), 7.40 (1H, d, *J* = 7.3 Hz), 7.64 (1H, d, *J* = 7.8 Hz), 8.35 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.0, 25.6, 31.7, 57.8, 121.2, 122.2, 125.9, 127.7, 144.6, 154.5, 178.4.

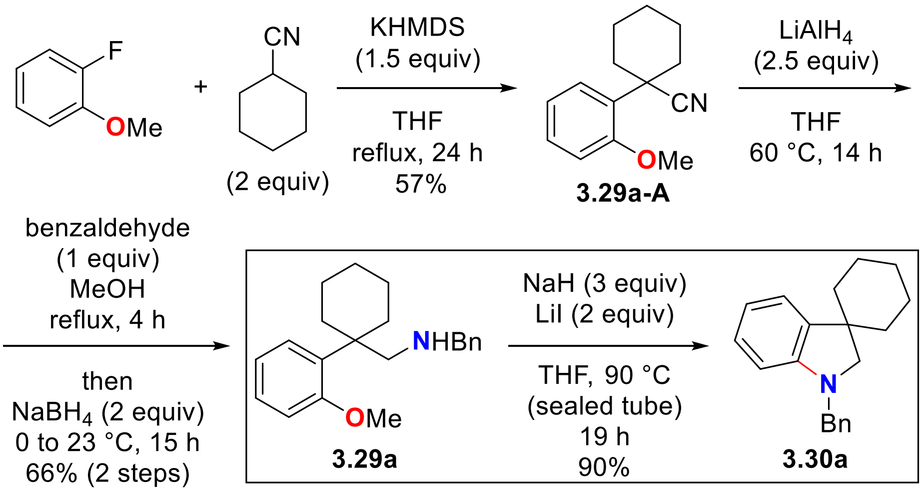
spiro[cyclohexane-1,3'-indoline] (3.28)[11]



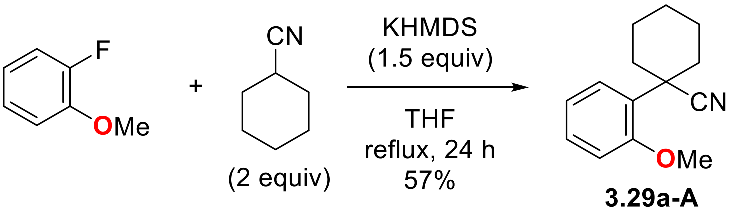
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26-1.75 (10H, m), 3.22 (1H, brs), 3.41 (2H, s), 6.63 (1H, d, *J* = 7.8 Hz), 6.73 (1H, dd, *J* = 7.4, 7.3 Hz), 7.00 (1H, dd, *J* = 7.8, 7.4 Hz), 7.05 (1H, d, *J* = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.2, 25.8, 36.4, 46.1, 56.7, 109.6, 118.6, 122.5, 127.4, 138.4, 150.4.

6.3.2. Synthesis of indolines 3.30a-3.30e (Table 3.2, entry 1 and Scheme 3.19)

6.3.2.1. Synthesis of 3.30a (Table 3.2, entry 1)



6.3.2.1.1. Synthesis of 1-(2-methoxyphenyl)cyclohexane-1-carbonitrile (3.29a-A)[12]

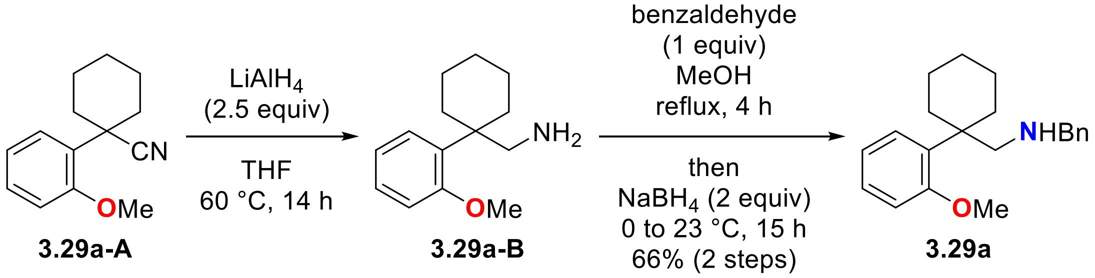


3.29a-A

Following the reported procedure,[13] to a mixture of 2-fluoroanisole (2.01 g, 16.0 mmol) and cyclohexanecarbonitrile (3.80 mL, 32.0 mmol) in THF (16 mL) was added KHMDS (24.0 mL, 24.0 mmol, 1.0 M solution in THF) at 23 °C under a N_2 atmosphere. The reaction mixture was stirred under reflux conditions for 24 h. The solution was quenched at 0 °C with saturated aqueous NH_4Cl solution and the organic materials were extracted thrice with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude material was purified by recrystallization (from Et_2O) to give **3.29a-A** (1.97 g, 9.16 mmol) in 57% yield as a white solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.24-1.27 (1H, m), 1.74-1.90 (7H, m), 2.37 (2H, d, *J* = 12.3 Hz), 3.92 (3H, s), 6.95-6.98 (2H, m), 7.25-7.33 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.3, 25.3, 34.5, 40.8, 55.5, 112.1, 120.8, 122.5, 125.9, 129.1 (overlapped), 157.5.

6.3.2.1.2. Synthesis of *N*-benzyl-1-(1-(2-methoxyphenyl)cyclohexyl)methanamine (3.29a) (Typical procedure A)

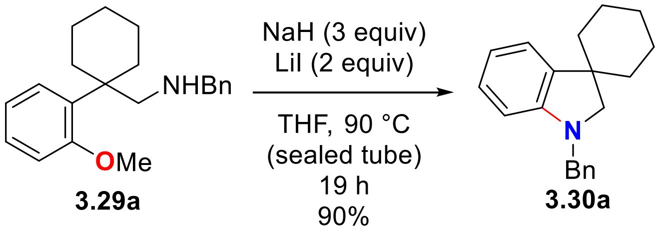


To an ice cold suspension of $LiAlH_4$ (697 mg, 18.4 mmol) in THF (20 mL) was added a solution of **3.29a-A** (1.57 g, 7.29 mmol) in THF (20 mL) dropwise under a N_2 atmosphere. The reaction mixture was then warmed to 60 ºC and stirred for 14 h. The reaction mixture was then cooled to 0 ºC and H_2O (0.70 mL), 15% aqueous NaOH (0.70 mL), and H_2O (2.10 mL) was cautiously dropped in this order into the reaction mixture. The resulting suspension was filtered through a Celite pad with washing with EtOAc and the collected filtrate was concentrated *in vacuo* to afford crude material including amine **3.29a-B**, which was used to the next step without purification.

To a solution of crude amine **3.29a-B** in anhydrous MeOH (20 mL) was added benzaldehyde (0.740 mL, 7.28 mmol) under a N_2 atmosphere and the mixture was stirred under reflux conditions for 4 h. With confirmation of full conversion of amine **3.29a-B** based on ^{1}H NMR analysis, the reaction mixture was then cooled to 0 ºC and $NaBH_4$ (555 mg, 14.7 mmol) was added portion-wise. After stirring at 23 °C for 15 h, the reaction mixture was quenched with saturated aqueous NH_4Cl and then basified with 1 M aqueous NaOH. The organic materials were extracted four times with CH_2Cl_2 and the combined extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude material was purified by flash column chromatography (silica gel; CH_2Cl_2 : hexane = 5: 1 then EtOAc : hexane = 20 : 1) to give N-benzylamine **3.29a** (1.49 g, 4.82 mmol) in 66% yield based on nitrile **3.29a-A** as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41-1.51 (6H, m), 1.73-1.77 (2H, m), 2.21-2.26 (2H, m), 2.89 (2H, s), 3.63 (3H, s), 3.64 (2H, s), 6.82 (1H, d, *J* = 8.1 Hz), 6.91-6.95 (1H, m), 7.10 (2H, d, *J* = 7.2 Hz), 7.15-7.25 (4H, m), 7.31 (1H, d, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.5, 26.8, 34.3, 43.1, 54.0, 54.8, 55.3, 111.7, 120.3, 126.4, 127.2, 127.8, 128.1, 130.1, 132.9, 141.0, 158.7; ESIHRMS: Found: m/z 310.2176. Calcd for $C_{21}H_{28}NO$: $(M+H)^+$ 310.2171.

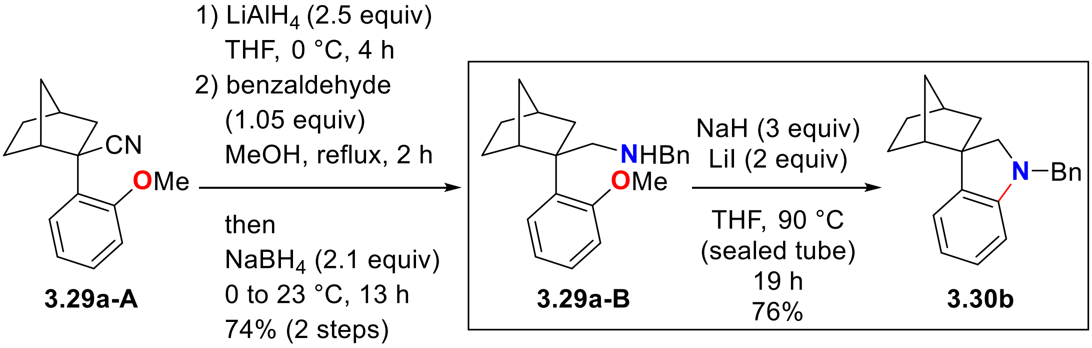
6.3.2.1.3. Nucleophilic amination of methoxy arenes: synthesis of 1'-benzylspiro[cyclohexane-1,3'-indoline] (3.30a)[11] (Typical procedure B)



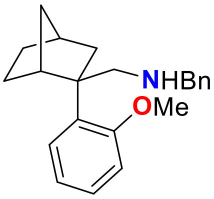
To a 25 mL sealed tube containing NaH (61.4 mg, 1.54 mmol) and LiI (138 mg, 1.03 mmol) in THF (2 mL) was added a solution of **3.29a** (153 mg, 0.496 mmol) in THF (3 mL) at 0 °C under a N_2 atmosphere. The tube was sealed and the solution was then stirred at 90 °C. With confirmation of full conversion of **3.29a** based on TLC analysis, the reaction mixture was cooled to 0 °C and quenched with cold water. The organic materials were extracted thrice with EtOAc and the combined extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting crude material was purified by flash column chromatography (hexane : EtOAc =130:1) to yield **3.30a** (124 mg, 0.448 mmol) in 90% yield as a pale yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30-1.38 (3H, m), 1.56-1.76 (7H, m), 3.21 (2H, s), 4.29 (2H, s), 6.46 (1H, d, J = 8.0 Hz), 6.68 (1H, dd, J = 7.4, 7.3 Hz), 7.03-7.07 (2H, m), 7.26-7.34 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.1, 25.7, 36.5, 44.6, 52.8, 63.1, 106.7, 117.4, 122.3, 127.0, 127.6 (overlapped), 128.5, 138.7, 138.8, 151.2.

6.3.2.2. Synthesis of 3.30b (Scheme 3.19)



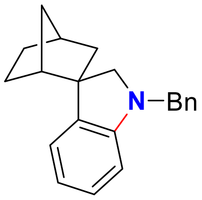
6.3.2.2.1. Synthesis of *N*-benzyl-1-((1*R**,2*R**,4*S**)-2-(2-methoxyphenyl)bicyclo[2.2.1]heptan-2-yl)methanamine (3.29a-B)



74% yield (639 mg, 1.99 mmol) from **3.29a-A**[13] (609 mg, 2.68 mmol) by the typical procedure A (page 194).

Colorless oil; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.12-1.16 (2H, m), 1.19-1.32 (2H, m), 1.41-1.43 (1H, m), 1.49-1.59 (2H, m), 1.68-1.72 (1H, m), 1.90-1.92 (1H, m), 2.15 (1H, m), 2.59 (1H, d, *J* = 11.4 Hz), 2.97 (1H, brs), 3.22 (1H, d, *J* = 11.4 Hz), 3.57 (1H, d, *J* = 14.0 Hz), 3.61 (3H, s), 3.64 (1H, d, *J* = 14.0 Hz), 6.81 (1H, d, *J* = 8.4 Hz), 6.90 (1H, ddd, *J* = 7.6, 7.4, 1.0 Hz), 7.02 (2H, d, *J* = 6.8 Hz), 7.14-7.22 (4H, m), 7.40 (1H, dd, *J* = 6.7, 1.3 Hz); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 24.3, 29.4, 37.8, 38.0, 41.0, 45.4, 49.3, 53.2, 53.8, 54.7, 111.7, 120.0, 126.4, 126.9, 127.6, 127.8, 128.0, 136.2, 141.0 158.0; ESIHRMS: Found: *m/z* 322.2180. Calcd for $C_{22}H_{28}NO$: $(M+H)^+$ 322.2171.

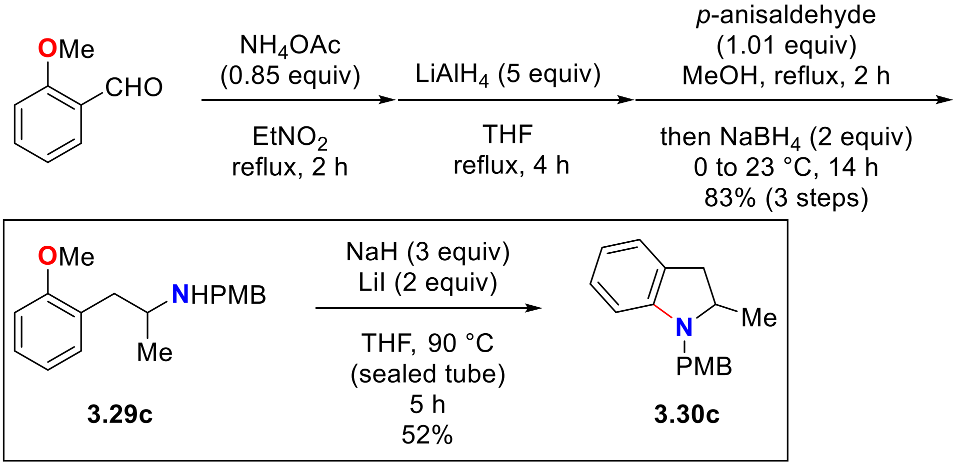
6.3.2.2.2. Synthesis of (1*R**,2*R**,4*S**)-1'-benzylspiro[bicyclo[2.2.1]heptane-2,3'-indoline] (3.30b)



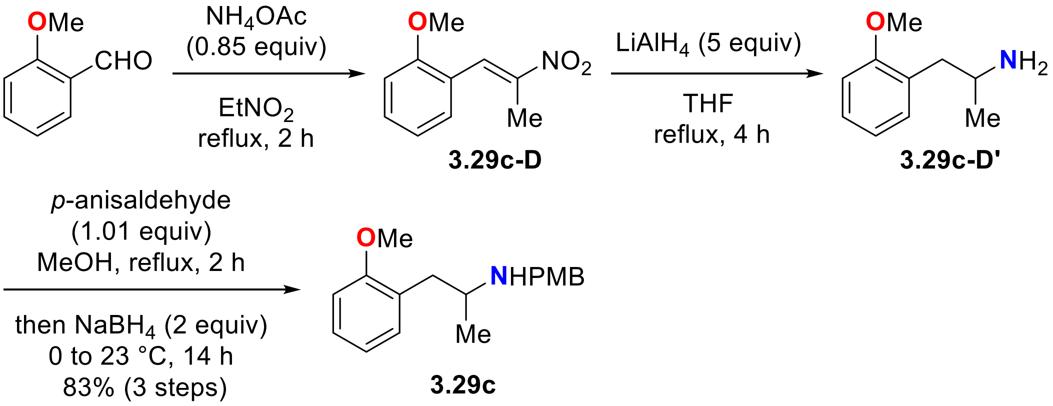
76% yield (87.7 mg, 0.303 mmol) from **3.29b** (128 mg, 0.400 mmol) for 19 h by the typical procedure B (page 195).

Pale yellow oil; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.15-1.18 (1H, m), 1.35-1.60 (5H, m), 1.84-1.87 (1H, m), 1.98-2.00 (1H, m), 2.27 (1H, m), 2.33 (1H, m), 3.03 (1H, d, *J* = 8.6 Hz), 3.29 (1H, d, *J* = 8.6 Hz), 4.17 (1H, d, *J* = 14.9 Hz), 4.27 (1H, d, *J* = 14.9 Hz), 6.49 (1H, d, *J* = 7.8 Hz), 6.70 (1H, dd, *J* = 7.4, 7.4 Hz), 7.05 (1H, dd, *J* = 7.8, 7.4 Hz), 7.16 (1H, d, *J* = 7.4 Hz), 7.24-7.28 (1H, m), 7.32-7.38 (4H, m); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 25.3, 28.2, 37.0, 38.7, 45.9, 46.5, 49.7, 53.5, 64.8, 107.1, 118.0, 122.5, 127.0, 127.1, 127.7, 128.4, 138.5, 140.0, 151.4; ESIHRMS: Found: *m/z* 290.1909. Calcd for $C_{21}H_{24}N$: $(M+H)^+$ 290.1909.

6.3.2.3. Synthesis of 3.30c (Scheme 3.19)



6.3.2.3.1. Synthesis of *N*-(4-methoxybenzyl)-1-(2-methoxyphenyl)propan-2-amine (3.29c)



To a mixture of ammonium acetate (689 mg, 8.94 mmol) in nitroethane (10 mL) was added a solution of 2-methoxybenzaldehyde (1.36 g, 10.0 mmol) in nitroethane (15 mL) under a N_2 atmosphere. The reaction mixture was stirred under reflux conditions for 2 h and then concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 and washed sequentially with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*.

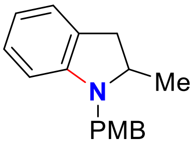
The resulting crude material including nitroalkene **3.29c-D** was used to the next step without purification.

To an ice cold suspension of $LiAlH_4$ (1.89 g, 49.9 mmol) in THF (15 mL) was added a solution of crude nitroalkene **3.29c-D** in THF (30 mL) dropwise under a N_2 atmosphere. The reaction mixture was stirred under reflux conditions for 4 h and then cooled to 0 ºC. H_2O (1.90 mL), 15% aqueous NaOH (1.90 mL), and H_2O (5.70 mL) was cautiously dropped in this order into the reaction mixture. The resulting suspension was filtered through a Celite pad with washing with EtOAc. The collected filtrate was concentrated *in vacuo* to afford crude material including alkylamine **3.29c-D'**, which was used to the next step without purification.

To a solution of crude amine **3.29c-D'** in anhydrous MeOH (20 mL) was added *p*-anisaldehyde (1.23 mL, 10.1 mmol) under a N_2 atmosphere and the mixture was stirred under reflux conditions for 2 h. With confirmation of full conversion of amine **3.29c-D'** based on ^{1}H NMR analysis, the reaction mixture was then cooled to 0 ºC and $NaBH_4$ (755 mg, 20.0 mmol) was added portion-wise. After stirring at 23 °C for 14 h, the reaction mixture was quenched with saturated aqueous NH_4Cl and then basified with 1 M aqueous NaOH. The organic materials were extracted four times with CH_2Cl_2 and the combined extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude material was purified by flash column chromatography (silica gel; CH_2Cl_2 : hexane = 8 : 1 then EtOAc only) to give *N*-PMB amine **3.29c** (2.37 g, 8.30 mmol) in 83% yield based on 2-methoxybenzaldehyde as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (3H, d, J = 6.2 Hz), 2.58 (1H, dd, J = 13.0, 6.5 Hz), 2.85 (1H, dd, J = 13.0, 6.7 Hz), 2.93-3.01 (1H, m), 3.68 (1H, d, J = 13.0 Hz), 3.76-3.82 (1H, d, *J* = 13.0 Hz + 3H, s + 3H, s), 6.80-6.89 (4H, m), 7.10-7.21 (4H, m); ^{13}C NMR (100 MHz, CDCl$_3$) δ 20.4, 38.0, 50.6, 52.2, 55.1, 55.2, 110.3, 113.6, 120.3, 127.4, 128.0, 129.0, 131.0, 133.0, 157.7, 158.4; ESIHRMS: Found: m/z 286.1810. Calcd for $C_{18}H_{24}NO_2$: $(M+H)^+$ 286.1807.

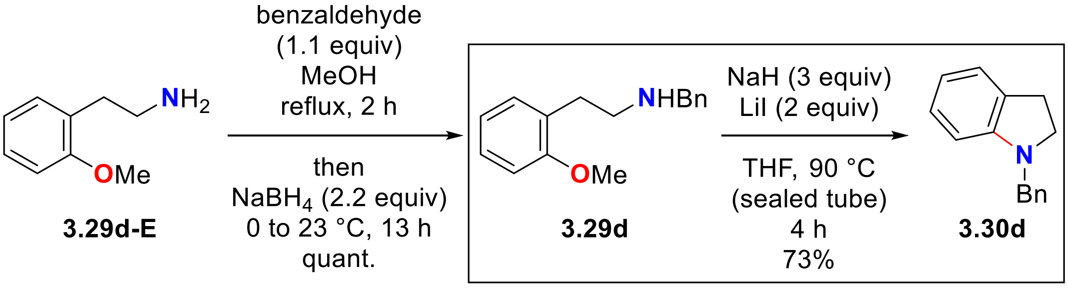
6.3.2.3.2. Synthesis of 1-(4-methoxybenzyl)-2-methylindoline (3.30c)[14]



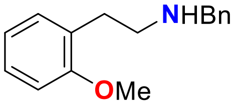
52% yield (66.1 mg, 0.261 mmol) from **3.29c** (143 mg, 0.500 mmol) for 5 h by typical procedure B (page 195).

Pale-yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.31 (3H, d, *J* = 6.0 Hz), 2.67 (1H, dd, *J* = 15.3, 9.5 Hz), 3.17 (1H, dd, *J* = 15.3, 8.6 Hz), 3.67-3.77 (1H, m), 3.81 (3H, s), 4.14 (1H, d, *J* = 15.7 Hz), 4.34 (1H, d, *J* = 15.7 Hz), 6.36 (1H, d, *J* = 7.8 Hz), 6.64 (1H, dd, *J* = 7.3, 7.1 Hz), 6.87 (2H, d, *J* = 7.9 Hz), 7.01 (1H, dd, *J* = 7.8, 7.3 Hz), 7.06 (1H, d, *J* = 7.1 Hz), 7.28 (2H, d, *J* = 7.9 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 19.6, 37.3, 50.3, 55.2, 60.2, 106.8, 113.8, 117.2, 124.1, 127.3, 128.5, 128.8, 131.1, 152.6, 158.6.

6.3.2.4. Synthesis of 3.30d (Scheme 3.19)



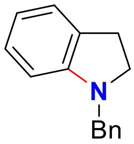
6.3.2.4.1. Synthesis of *N*-benzyl-2-(2-methoxyphenyl)ethan-1-amine (3.29d)[15]



Synthesis of **3.29d** was conducted by reductive amination from 2-methoxyphenethylamine (CAS: 2045-79-6) (2.29 g, 15.2 mmol) and benzaldehyde (a part of the typical procedure A; page 194) in quantitative yield (3.65 g, 15.1 mmol).

Colorless liquid; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.43 (1H, brs), 2.83-2.89 (4H, m), 3.77 (3H, s), 3.80 (2H, s), 6.82 (1H, d, *J* = 8.4 Hz), 6.86 (1H, ddd, *J* = 7.4, 7.4, 1.0 Hz), 7.13-7.15 (2H, m), 7.16-7.23 (1H, m), 7.26-7.31 (4H, m); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 30.8, 49.1, 53.7, 55.1, 110.3, 120.3, 126.7, 127.3, 128.0, 128.2, 128.4, 130.2, 140.5, 157.5.

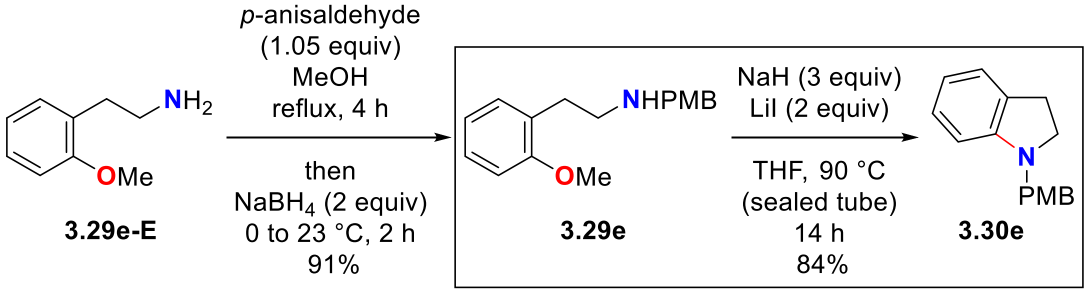
6.3.2.4.2. Synthesis of 1-benzylindoline (3.30d)[16]



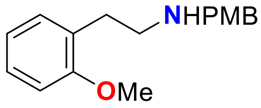
73% yield (70.2 mg, 0.336 mmol) from **3.29d** (91.7 mg, 0.426 mmol) for 4 h by the typical procedure B (page 195).

Pale yellow oil; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 2.96 (2H, t, *J* = 8.3 Hz), 3.30 (2H, t, *J* = 8.3 Hz), 4.24 (2H, s), 6.50 (1H, d, *J* = 7.8 Hz), 6.66 (1H, dd, *J* = 7.4, 7.3 Hz), 7.05 (1H, dd, *J* = 7.8, 7.4 Hz), 7.09 (1H, d, *J* = 7.3 Hz), 7.24-7.27 (1H, m), 7.31-7.36 (4H, m); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 28.5, 53.5, 53.6, 107.0, 117.6, 124.4, 127.1, 127.3, 127.9, 128.4, 129.9, 138.5, 152.5.

6.3.2.5. Synthesis of 3.30e (Scheme 3.19)



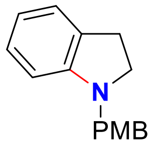
6.3.2.5.1. Synthesis of *N*-(4-methoxybenzyl)-2-(2-methoxyphenyl)ethan-1-amine (3.29e)



Synthesis of **3.29e** was conducted by reductive amination from 2-methoxyphenethylamine (CAS:2045-79-6) (2.00 g, 13.2 mmol) and *p*-anisaldehyde (CAS: 123-11-5) (a part of the typical procedure A; page 194) in 91% yield (3.26 g 12.0 mmol).

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54 (1H, brs), 2.85 (4H, m), 3.73 (2H, s), 3.77 (3H, s), 3.78 (3H, s), 6.82-6.84 (3H, m), 6.87 (1H, d, J = 7.4 Hz), 7.13 (1H, d, J = 7.4 Hz), 7.15-7.21 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.7, 49.0, 53.1, 55.12, 55.14, 110.2, 113.6, 120.3, 127.3, 128.4, 129.2, 130.2, 132.6, 157.5, 158.4; ESIHRMS: Found: m/z 272.1652. Calcd for $C_{17}H_{22}NO_2$: $(M+H)^+$ 272.1651.

6.3.2.5.2. Synthesis of 1-(4-methoxybenzyl)indoline (3.30e)[17]

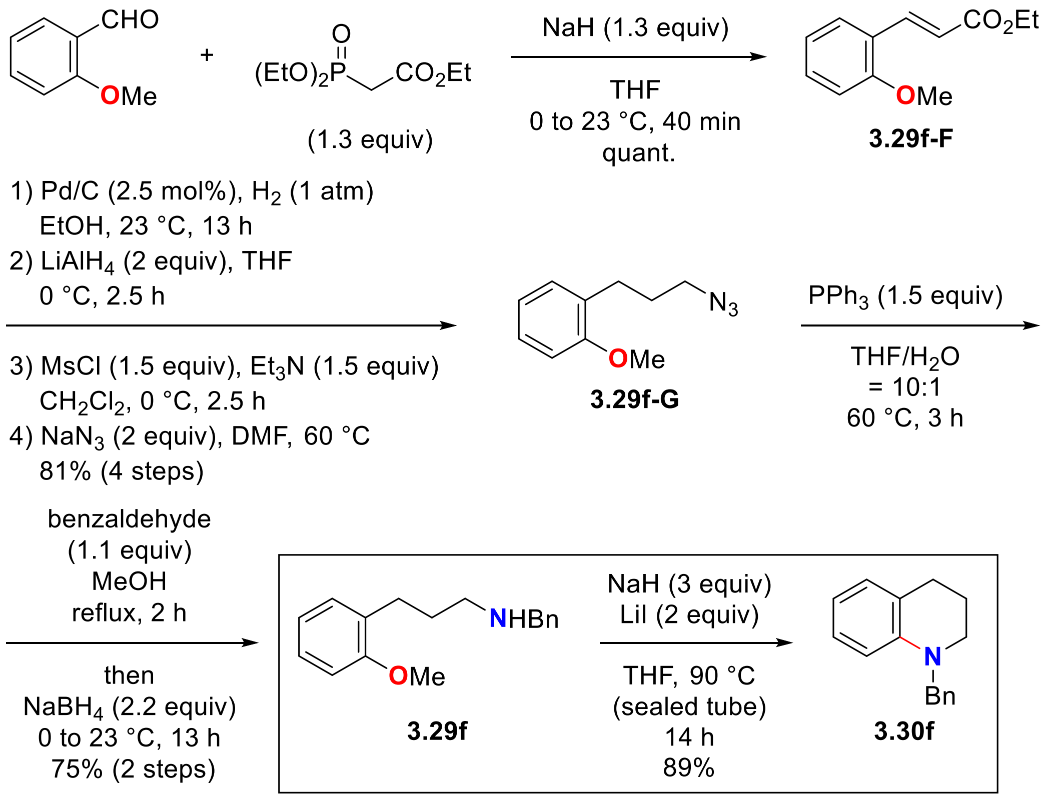


84% yield (103 mg, 0.430 mmol) from **3.29e** (139 mg, 0.512 mmol) for 14 h by the typical procedure B (page 195).

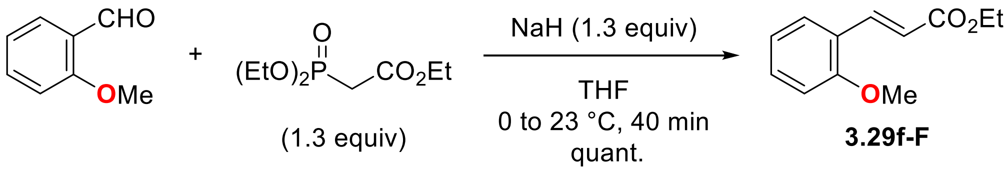
Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.94 (2H, t, *J* = 8.0 Hz), 3.26 (2H, t, *J* = 8.0 Hz), 3.79 (3H, s), 4.17 (2H, s), 6.51 (1H, d, *J* = 7.6 Hz), 6.63-6.67 (1H, m), 6.86 (2H, d, *J* = 8.4 Hz), 7.03-7.09 (2H, m), 7.26 (2H, d, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.5, 53.0, 53.4, 55.2, 107.0, 113.8, 117.6, 124.4, 127.2, 129.1, 130.0, 130.4, 152.5, 158.7.

6.3.3. Synthesis of tetrahydroquinolines 3.30f-3.30q (Scheme 3.19)

6.3.3.1. Synthesis of 3.30f



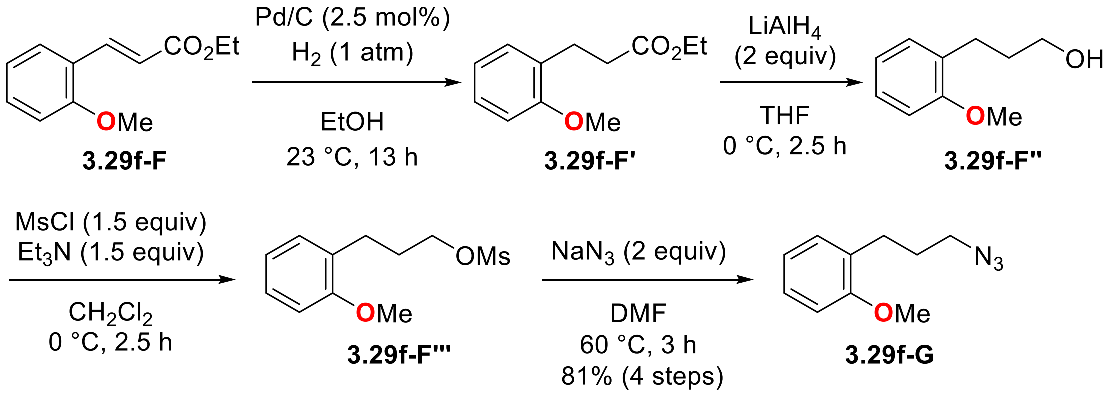
6.3.3.1.1. Synthesis of ethyl (*E*)-3-(2-methoxyphenyl)acrylate (3.29f-F)[18] (typical procedure C)



To an ice cold suspension of NaH (2.62 g, 65.5 mmol) in THF (100 mL) was added triethyl phosphonoacetate (13.0 mL, 65.5 mmol) under a N_2 atmosphere. After stirring at 23 °C for 30 min, the mixture was cooled to 0 °C and a solution of 2-methoxybenzaldehyde (6.78 g, 49.8 mmol) in THF (20 mL) was added dropwise. The reaction mixture was stirred at 23 °C for 40 min. The solution was quenched with saturated aqueous NH_4Cl and the organic materials were extracted thrice with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude material was purified by flash column chromatography (silica gel; hexane : EtOAc = 10 : 1) to give α,β-unsaturated ester **3.29f-F** (10.3 g, 49.8 mmol) in quantitative yield as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (3H, t, *J* = 7.2 Hz), 3.88 (3H, s), 4.26 (2H, q, *J* = 7.2 Hz), 6.52 (1H, d, *J* = 16.2 Hz), 6.91 (1H, d, *J* = 8.3 Hz), 6.95 (1H, dd, *J* = 7.6, 7.5 Hz), 7.34 (1H, dd, *J* = 8.3, 7.5 Hz), 7.50 (1H, d, *J* = 7.6 Hz), 7.99 (1H, d, *J* = 16.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 55.4, 60.3, 111.1, 118.8, 120.6, 123.4, 128.9, 131.3, 140.0, 158.3, 167.5.

6.3.3.1.2. Synthesis of 1-(3-azidopropyl)-2-methoxybenzene (3.29f-G) (typical procedure D)



To a mixture of α,β-unsaturated ester **3.29f-F** (4.04 g, 19.6 mmol) and Pd/C (521 mg, 0.490 mmol, 10% Pd wt/wt on carbon) was added EtOH (40 mL) at 23 ºC under a N_2 atmosphere. The mixture was charged with H_2 gas (1 atm balloon) and stirred at 23 ºC for 13 h. H_2 gas was then removed and the reaction vessel was back filled with N_2 gas. The resulting suspension was filtered through a Celite pad with washing with EtOAc. The collected filtrate was concentrated *in vacuo* to afford crude material including saturated ester **3.29f-F'**, which was used to the next step without purification.

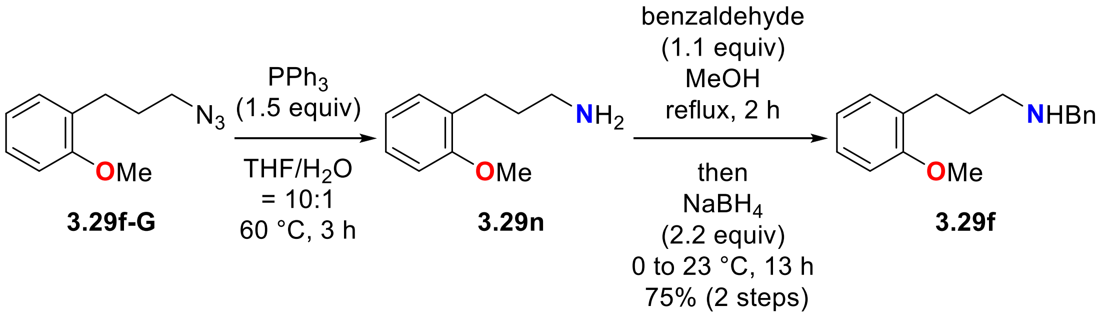
To an ice cold suspension of $LiAlH_4$ (1.49 g, 39.3 mmol) in THF (30 mL) was added a solution of crude ester **3.29f-F'** in THF (30 mL) dropwise at 0 ºC under a N_2 atmosphere. The reaction mixture was stirred at 0 °C for 2.5 h and H_2O (1.50 mL), 15% aqueous NaOH (1.50 mL), and H_2O (1.50 mL) was cautiously dropped in this order into the reaction mixture. The resulting suspension was filtered through a Celite pad with washing with EtOAc. The collected filtrate was concentrated *in vacuo* to afford crude material including alcohol **3.29f-F''**, which was used to the next step without purification.

To an ice cold solution of the crude alcohol **3.29f-F''** in CH_2Cl_2 (30 mL) was added Et_3N (4.1 mL, 29.4 mmol) under a N_2 atmosphere. A solution of methanesulfonyl chloride (2.3 mL, 29.4 mmol) in CH_2Cl_2 (20 mL) was then added dropwise into the reaction mixture at 0 °C. The reaction mixture was stirred at 0 °C for 2.5 h and quenched with saturated aqueous Na_2CO_3, and the organic materials were extracted three times with CH_2Cl_2. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude material mesylate **3.29f-F’’’** was used for the next step without any further purification.

To a solution of mesylate **3.29f-F’’’** in DMF (40 mL) was added NaN_3 (2.55 g, 39.2 mmol) portion-wise at 0 °C. The reaction mixture was stirred at 60 °C for 3 h and then cooled to 23 °C. The mixture was quenched with H_2O and the organic materials were extracted thrice with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude material was purified by flash column chromatography (silica gel; EtOAc was gradually increased from 5% to 10% in hexane) to give azide **3.29f** (3.05 g, 16.0 mmol) in 82% yield based on α,β-unsaturated ester **3.29f-F** as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.88 (2H, tt, *J* = 7.5, 6.9 Hz), 2.70 (2H, t, *J* = 7.5 Hz), 3.27 (2H, t, *J* = 6.9 Hz), 3.82 (3H, s), 6.84 (1H, d, *J* = 8.0 Hz), 6.88 (1H, dd, *J* = 7.4, 7.3 Hz), 7.12 (1H, d, *J* = 7.3 Hz), 7.19 (1H, dd, *J* = 8.0, 7.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.5, 28.8, 51.0, 55.2, 110.3, 120.4, 127.4, 129.3, 130.0, 157.4; ESIHRMS: Found: *m/z* 192.1143. Calcd for $C_{10}H_{14}N_3O$: $(M+H)^+$ 192.1137.

6.3.3.1.3. Synthesis of *N*-benzyl-3-(2-methoxyphenyl)propan-1-amine (3.29f)[15] (typical procedure E)

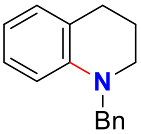


To a solution of azide **3.29f-G** (2.04 g, 10.7 mmol) in THF (30 mL) and H_2O (3 mL) was added PPh_3 (4.19 g, 16.0 mmol) at 23 °C. The reaction mixture was stirred at 60 °C for 3 h and then cooled to 23 °C. After dilution with 1M aqueous HCl, the aqueous layer was washed four times with Et_2O. The aqueous layer was basified with 2M aqueous NaOH and the organic layer was extracted four times with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude material including amine **3.29n** was used for the next step without any further purification.

To a solution of crude amine **3.29n** in anhydrous MeOH (20 mL) was added benzaldehyde (1.2 mL, 11.8 mmol) under a N_2 atmosphere and the mixture was stirred under reflux conditions for 2 h. With confirmation of full conversion of amine **3.29n** based on ^1H NMR analysis, the reaction mixture was then cooled to 0 °C and $NaBH_4$ (846 mg, 22.4 mmol) was added portion-wise. The reaction mixture was stirred at 23 °C for 13 h and quenched with saturated aqueous NH_4Cl and then basified with 1 M aqueous NaOH. The organic materials were extracted four times with CH_2Cl_2 and the combined extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude material was purified by flash column chromatography (silica gel; CH_2Cl_2 : hexane = 5: 1 then EtOAc only) to give **3.29f** (2.05 g, 8.04 mmol) in 75% yield based on **3.29f-G** as a colorless liquid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.61 (1H, br), 1.80 (2H, tt, *J* = 7.3, 7.2 Hz), 2.63-2.67 (4H, m), 3.75 (2H, s +3H, s), 6.80 (1H, d, *J* = 8.1 Hz), 6.85 (1H, dd, *J* = 7.4, 7.4 Hz), 7.09 (1H, d, *J* = 7.4 Hz) 7.14 (1H, ddd, *J* = 8.1, 7.4, 1.5 Hz), 7.19-7.24 (1H, m), 7.28-7.30 (4H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.7, 29.9, 49.0, 53.8, 55.0, 110.1, 120.3, 126.7, 126.9, 128.0, 128.2, 129.7, 130.4, 140.4, 157.3.

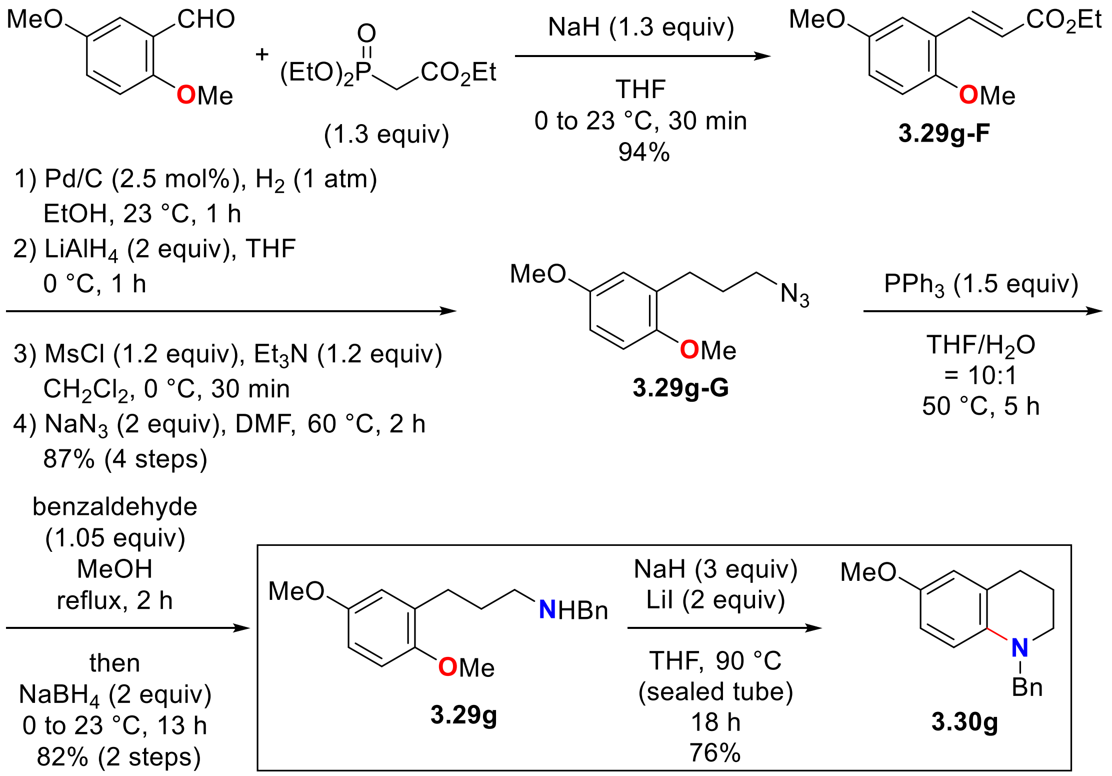
6.3.3.1.4. Synthesis of 1-benzyl-1,2,3,4-tetrahydroquinoline (3.30f)[19]



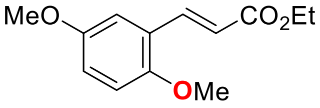
89% yield (99.3 mg, 0.445 mmol) from **3.29f** (127 mg, 0.498 mmol) for 14 h by typical procedure B (page 195).

Pale yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.99 (2H, tt, *J* = 6.3, 5.7 Hz), 2.80 (2H, t, *J* = 6.3 Hz), 3.33 (2H, t, *J* = 5.7 Hz), 4.45 (2H, s), 6.49 (1H, d, *J* = 8.4 Hz), 6.56 (1H, dd, *J* = 7.3, 7.3 Hz), 6.93-6.97 (1H, m + 1H, m), 7.19-7.31 (5H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.3, 28.2, 49.8, 55.1, 110.9, 115.8, 122.2, 126.5, 126.7, 127.1, 128.5, 128.9, 138.9, 145.5.

6.3.3.2. Synthesis of 3.30g



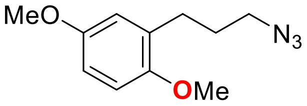
6.3.3.2.1. Synthesis of ethyl (*E*)-3-(2,5-dimethoxyphenyl)acrylate (3.29g-F)[20]



94% yield (6.64 g, 28.1 mmol) from 2,5-dimethoxybenzaldehyde (CAS:93-02-7) (4.97 g, 29.9 mmol) by the typical procedure C (page 204).

Pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (3H, t, *J* = 7.1 Hz), 3.78 (3H, s), 3.83 (3H, s), 4.26 (2H, q, *J* = 7.1 Hz), 6.49 (1H, d, *J* = 16.1 Hz), 6.83 (1H, d, *J* = 9.0 Hz), 6.89 (1H, dd, *J* = 9.0, 2.9 Hz), 7.04 (1H, d, *J* = 2.9 Hz), 7.96 (1H, d, *J* = 16.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 55.7, 56.0, 60.3, 112.4, 113.2, 117.0, 118.9, 124.0, 139.7, 152.7, 153.4, 167.3.

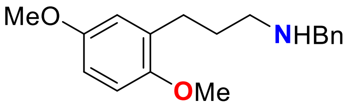
6.3.3.2.2. Synthesis of 2-(3-azidopropyl)-1,4-dimethoxybenzene (3.29g-G)



87% yield (5.29 g, 23.9 mmol) from **3.29g-F** (6.50 g, 27.5 mmol) by the typical procedure D (page 207).

Colorless oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.88 (2H, tt, *J* = 7.6, 6.8 Hz), 2.67 (2H, t, *J* = 7.6 Hz), 3.28 (2H, t, *J* = 6.8 Hz), 3.76 (3H, s), 3.78 (3H, s), 6.69-6.78 (3H, m); ^{13}C NMR (100 MHz, CDCl$_3$) δ 27.6, 28.9, 50.9, 55.6, 55.8, 111.1, 111.2, 116.4, 130.5, 151.7, 153.4; ESIHRMS: Found: m/z 222.1245. Calcd for $C_{11}H_{16}N_3O_2$: $(M+H)^+$ 222.1243.

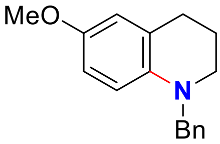
6.3.3.2.3. Synthesis of *N*-benzyl-3-(2,5-dimethoxyphenyl)propan-1-amine (3.29g)



82% yield (1.07 g, 3.75 mmol) from **3.29g-G** (1.01 g, 4.56 mmol) by the typical procedure E (page 207).

Colorless oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.57 (1H, brs), 1.77-1.84 (2H, m), 2.61-2.69 (4H, m), 3.74 (3H, s), 3.75 (3H, s), 3.78 (2H, s), 6.67-6.72 (2H, m), 6.75 (1H, d, *J* = 8.7 Hz), 7.21-7.32 (5H, m); ^{13}C NMR (100 MHz, CDCl$_3$) δ 27.9, 30.1, 49.0, 53.9, 55.6, 55.8, 110.8, 111.1, 116.2, 126.8, 128.1, 128.3, 131.7, 140.5, 151.7, 153.4; ESIHRMS: Found: m/z 286.1802. Calcd for $C_{18}H_{24}NO_2$: $(M+H)^+$ 286.1807.

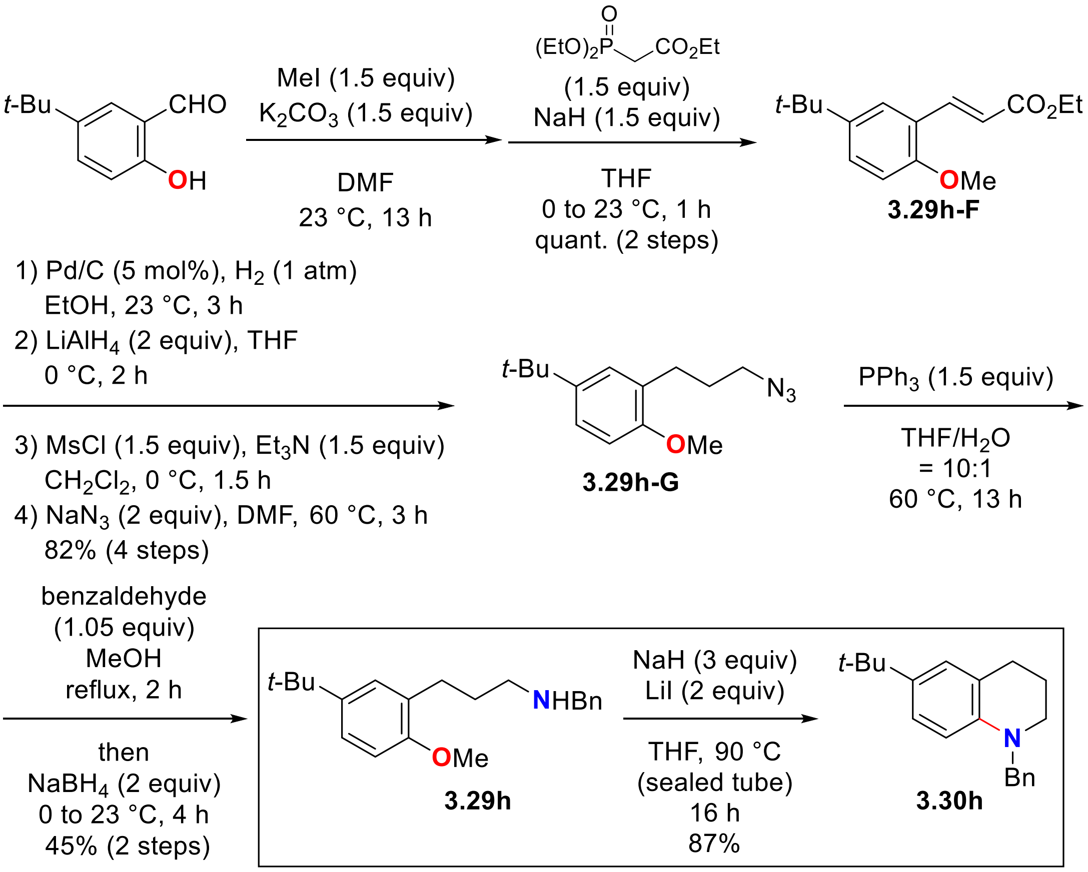
6.3.3.2.4. Synthesis of 1-benzyl-6-methoxy-1,2,3,4-tetrahydroquinoline (3.30g)[21]



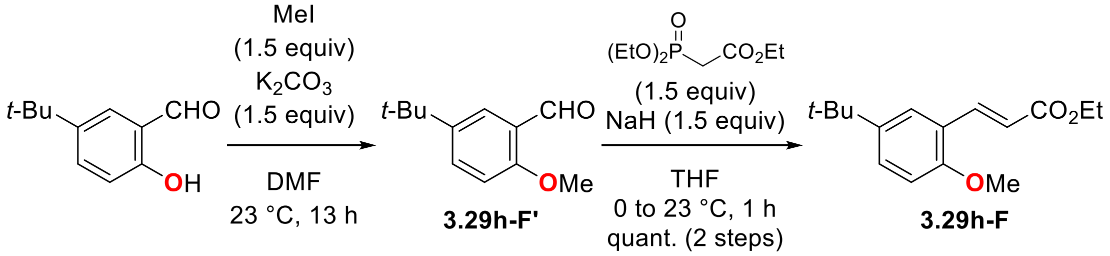
76% yield (97.9 mg, 0.387 mmol) from **15-c** (145 mg, 0.508 mmol) for 18 h by typical procedure B (page 195).

Pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.99 (2H, tt, *J* = 6.4, 5.6 Hz), 2.80 (2H, t, *J* = 6.4 Hz), 3.28 (2H, t, *J* = 5.6 Hz), 3.71 (3H, s), 4.40 (2H, s), 6.44 (1H, d, *J* = 8.8 Hz), 6.57 (1H, dd, *J* = 8.8, 3.0 Hz), 6.60 (1H, d, *J* = 3.0 Hz), 7.21-7.23 (1H, m), 7.26-7.32 (4H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.5, 28.4, 49.9, 55.7, 55.9, 112.2, 112.3, 115.2, 123.7, 126.6, 126.7, 128.5, 139.3, 140.3, 150.8.

6.3.3.3. Synthesis of 3.30h



6.3.3.3.1. Synthesis of ethyl (*E*)-3-(5-(*tert*-butyl)-2-methoxyphenyl)acrylate (3.29h-F)

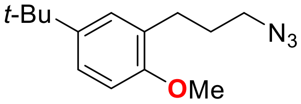


To a solution of 5-(*tert*-butyl)-2-hydroxybenzaldehyde (2.07 g, 11.6 mmol) (CAS: 2725-53-3) in DMF (20 mL) was added MeI (1.1 mL, 17.7 mmol) followed by K_2CO_3 (2.41 g, 17.3 mmol) at 23 °C under a N_2 atmosphere. The reaction mixture was stirred at 23 ºC for 13 h. The reaction mixture was quenched with 0.5 M aqueous NaOH and then extracted thrice with Et_2O. The combined organic extracts were washed thrice with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material including aldehyde **3.29h-F'** was used to the next step without purification.

To an ice cold suspension of NaH (699 mg, 17.5 mmol) in THF (20 mL) was added a solution of triethyl phosphonoacetate (3.5 mL, 17.6 mmol) in THF (10 mL) dropwise under a N_2 atmosphere. After stirring at 23 °C for 30 min, a solution of crude aldehyde **3.29h-F'** in THF (20 mL) was added dropwise at 0 °C and the reaction mixture was stirred at 23 °C for 1 h. The solution was quenched with saturated aqueous NH_4Cl and the organic materials were extracted thrice with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude material was purified by flash column chromatography (silica gel; hexane : EtOAc = 95 : 5) to give α,β-unsaturated ester **3.29h-F** (3.05 g, 11.6 mmol) in quantitative yield based on 5-(*tert*-butyl)-2-hydroxybenzaldehyde as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.31 (9H, s), 1.34 (3H, t, J = 7.1 Hz), 3.87 (3H, s), 4.27 (2H, q, J = 7.1 Hz), 6.55 (1H, d, J = 16.2 Hz), 6.85 (1H, d, J = 8.7 Hz), 7.36 (1H, dd, J = 8.7, 2.5 Hz), 7.52 (1H, d, J = 2.5 Hz), 7.98 (1H, d, J = 16.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.3, 31.4, 34.1, 55.5, 60.3, 110.8, 118.5, 122.7, 126.0, 128.3, 140.6, 143.3, 156.3, 167.6; ESIHRMS: Found: *m/z* 285.1462. Calcd for $C_{16}H_{22}O_3Na$: $(M+Na)^+$ 285.1467.

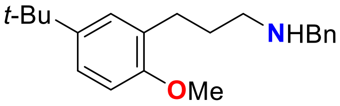
6.3.3.3.2. Synthesis of 2-(3-azidopropyl)-4-(*tert*-butyl)-1-methoxybenzene (3.29h-G)



80% yield (1.11 g, 4.50 mmol) from α,β-unsaturated ester **3.29h-F** (1.48 g, 5.66 mmol) by the typical procedure D (page 207).

Colorless oil; H NMR ($CDCl_3$, 400 MHz) δ 1.31 (9H, s), 1.90 (2H, tt, J = 7.1, 6.9 Hz), 2.70 (2H, t, J = 7.1 Hz), 3.29 (2H, t, J = 6.9 Hz), 3.81 (3H, s), 6.79 (1H, d, J = 8.5 Hz), 7.15 (1H, d, J = 2.4 Hz), 7.21 (1H, dd, J = 8.5, 2.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.9, 29.0, 31.5, 34.0, 51.1, 55.2, 109.8, 123.8, 127.3, 128.6, 143.1, 155.2; ESIHRMS: Found: *m/z* 270.1591. Calcd for $C_{14}H_{21}N_3ONa$: $(M+Na)^+$ 270.1582.

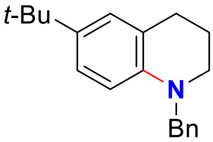
6.3.3.3.3. Synthesis of *N*-benzyl-3-(5-(*tert*-butyl)-2-methoxyphenyl)propan-1-amine (3.29h)



45% yield (578 mg, 1.86 mmol) from **3.29h-G** (1.02 g, 4.13 mmol) by the typical procedure E (page 207).

Colorless oil; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.28 (9H, s), 1.53 (1H, brs), 1.82 (2H, tt, *J* = 7.3, 7.3 Hz), 2.63-2.70 (4H, m), 3.78 (3H, s), 3.79 (2H, s), 6.76 (1H, d, *J* = 8.3 Hz), 7.14-7.18 (2H, m), 7.22-7.27 (1H, m), 7.31-7.32 (4H, m); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 28.2, 30.3, 31.5, 34.0, 49.2, 54.0, 55.3, 109.6, 123.4, 126.8, 127.1, 128.1, 128.3, 129.8, 140.5, 142.9, 155.2; ESIHRMS: Found: *m/z* 312.2320. Calcd for $C_{21}H_{30}NO$: $(M+H)^+$ 312.2327.

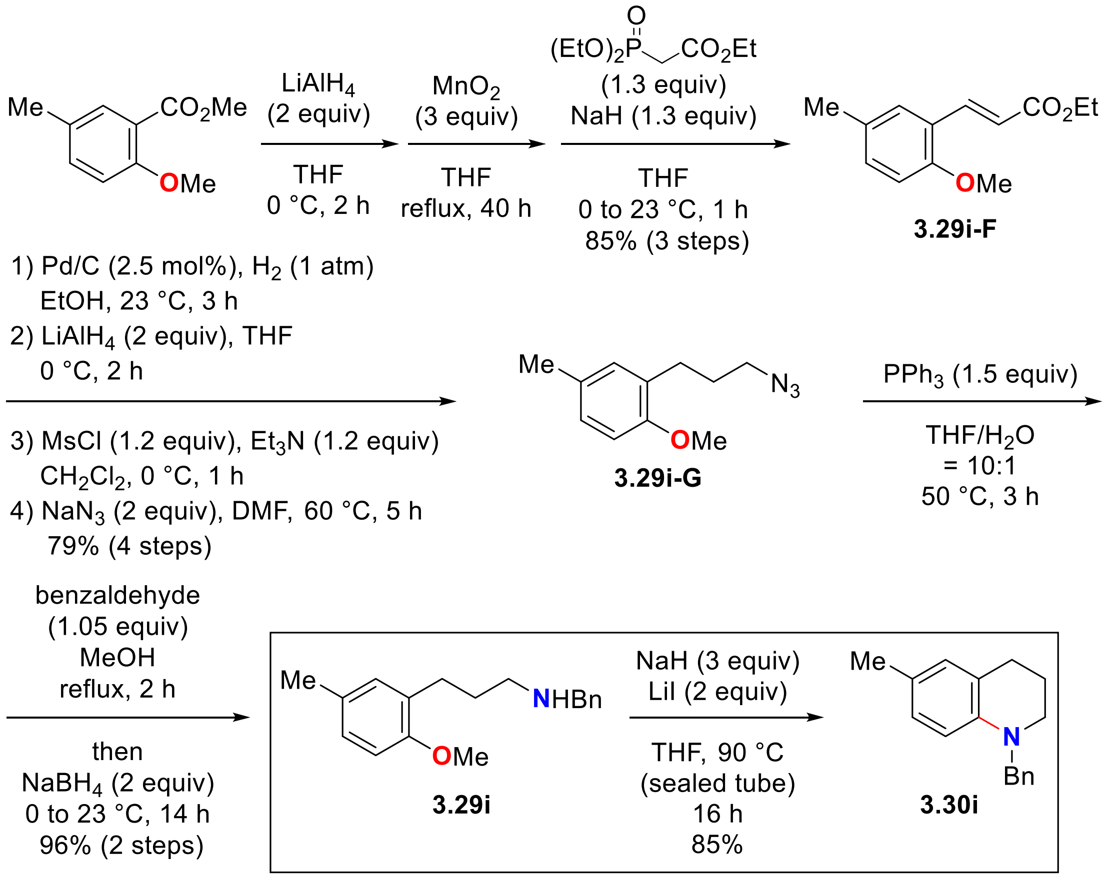
6.3.3.3.4. Synthesis of 1-benzyl-6-(*tert*-butyl)-1,2,3,4-tetrahydroquinoline (3.30h)



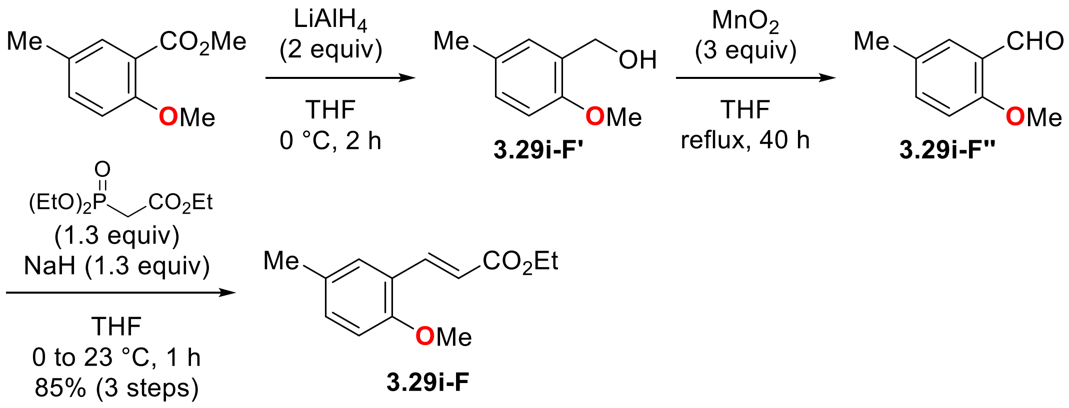
87% yield (101 mg, 0.361 mmol) from **3.29h** (129 mg, 0.415 mmol) for 16 h by the typical procedure B (page 195).

White solid; mp 69-70 °C; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.26 (9H, s), 2.01 (2H, tt, *J* = 6.4, 5.7 Hz), 2.82 (2H, t, *J* = 6.4 Hz), 3.31 (2H, t, *J* = 5.7 Hz), 4.43 (2H, s), 6.46 (1H, d, *J* = 9.2 Hz), 6.98-7.00 (2H, m), 7.21-7.24 (1H, m), 7.27-7.33 (4H, m); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 22.6, 28.4, 31.5, 33.6, 49.9, 55.5, 110.8, 121.7, 123.8, 126.0 (overlapped), 126.7, 128.5, 138.5, 139.4, 143.5; ESIHRMS: Found: *m/z* 280.2063. Calcd for $C_{20}H_{26}N$: $(M+H)^+$ 280.2065.

6.3.3.4. Synthesis of 3.30i



6.3.3.4.1. Synthesis of ethyl (*E*)-3-(2-methoxy-5-methylphenyl)acrylate (3.29i-F) (typical procedure F)



To an ice cold suspension of $LiAlH_4$ (1.38 g, 36.4 mmol) in THF (20 mL) was added a solution of methyl 2-methoxy-5-methylbenzoate[22] (3.29 g, 18.2 mmol) in THF (41 mL) under a N_2 atmosphere. The reaction mixture was stirred at 0 ºC for 2 h and H_2O

(1.40 mL), 15% aqueous NaOH (1.40 mL), and H_2O (4.20 mL) was cautiously dropped in this order into the reaction mixture. The resulting suspension was filtered through a Celite pad with washing with EtOAc and the collected filtrate was concentrated *in vacuo* to afford crude material including benzyl alcohol **3.29i-F’**, which was used to the next step without purification.

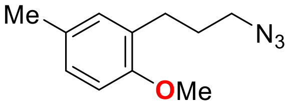
MnO_2 (4.75 g, 54.6 mmol) was at first activated at 120 °C for 1.5 h under vacuum. After cooling to 23 °C, THF (10 mL) followed by a solution of crude benzyl alcohol **3.29i-F’** in THF (20 mL) was added under a N_2 atmosphere. The reaction mixture was stirred under reflux conditions for 40 h and then cooled to 23 °C. The mixture was filtered through a Celite pad with washing with Et_2O. The collected filtrate was concentrated *in vacuo* to afford crude material including benzaldehyde **3.29i-F’’**, which was used to the next step without purification.

To an ice cold suspension of NaH (948 mg, 23.7 mmol) in THF (15 mL) was added triethyl phosphonoacetate (4.69 mL, 23.7 mmol) under a N_2 atmosphere. After stirring at 23 °C for 20 min, a solution of crude benzaldehyde **3.29i-F’’** in THF (31 mL) was added dropwise at 0 °C and the reaction mixture was stirred at 23 °C for 1 h. The solution was quenched with saturated aqueous NH_4Cl and the organic materials were extracted thrice with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude material was purified by flash column chromatography (silica gel; hexane : EtOAc = 10 : 1) to give α,β-unsaturated ester **3.29i-F** (3.41 g, 15.5 mmol) in 85% yield based on methyl 2-methoxy-5-methylbenzoate as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (3H, t, J = 7.2 Hz), 2.29 (3H, s), 3.85 (3H, s), 4.25 (2H, q, J = 7.2 Hz), 6.51 (1H, d, J = 16.0 Hz), 6.80 (1H, d, J = 8.4 Hz), 7.13 (1H, d, J

= 8.4 Hz), 7.31 (1H, s), 7.96 (1H, d, *J* = 16.0 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 14.3, 20.3, 55.5, 60.2, 111.1, 118.5, 123.1, 129.3, 129.8, 131.9, 140.0, 156.3, 167.5; ESIHRMS: Found: m/z 221.1180. Calcd for $C_{13}H_{17}O_3$: $(M+H)^+$ 221.1178.

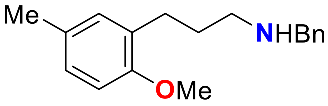
6.3.3.4.2. Synthesis of 2-(3-azidopropyl)-1-methoxy-4-methylbenzene (3.29i-G)



79% yield (2.47 g, 12.0 mmol) from **3.29i-F** (3.35 g, 15.2 mmol) by the typical procedure D (page 207).

Colorless oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.87 (2H, tt, *J* = 7.2, 6.9 Hz), 2.27 (3H, s), 2.66 (2H, t, *J* = 7.2 Hz), 3.27 (2H, t, *J* = 6.9 Hz), 3.79 (3H, s), 6.74 (1H, d, *J* = 8.2 Hz), 6.93 (1H, d, *J* = 1.6 Hz), 6.98 (1H, dd, *J* = 8.2, 1.6 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 20.4, 27.4, 28.9, 51.0, 55.3, 110.2, 127.5, 129.0, 129.5, 130.8, 155.3; ESIHRMS: Found: m/z 206.1295. Calcd for $C_{11}H_{16}N_3O$: $(M+H)^+$ 206.1293.

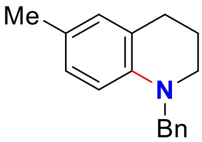
6.3.3.4.3. Synthesis of *N*-benzyl-3-(2-methoxy-5-methylphenyl)propan-1-amine (3.29i)



96% yield (1.28 g, 4.75 mmol) from **3.29i-G** (1.02 g, 4.97 mmol) by the typical procedure E (page 207).

Colorless oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.61 (1H, brs), 1.80 (2H, tt, *J* = 7.6, 7.2 Hz), 2.25 (3H, s), 2.62 (2H, t, *J* = 7.6 Hz), 2.66 (2H, t, *J* = 7.2 Hz), 3.75 (3H, s), 3.77 (2H, s), 6.71 (1H, d, *J* = 8.4 Hz), 6.92 (1H, s), 6.94 (1H, d, *J* = 8.4 Hz), 7.22-7.25 (1H, m), 7.30-7.31 (4H, m); ^{13}C NMR (100 MHz, CDCl$_3$) δ 20.4, 27.7, 30.1, 49.0, 53.9, 55.3, 110.1, 126.8, 127.1, 128.1, 128.3, 129.4, 130.2, 130.6, 140.5, 155.3; ESIHRMS: Found: m/z 270.1853. Calcd for $C_{18}H_{24}NO$: $(M+H)^+$ 270.1858.

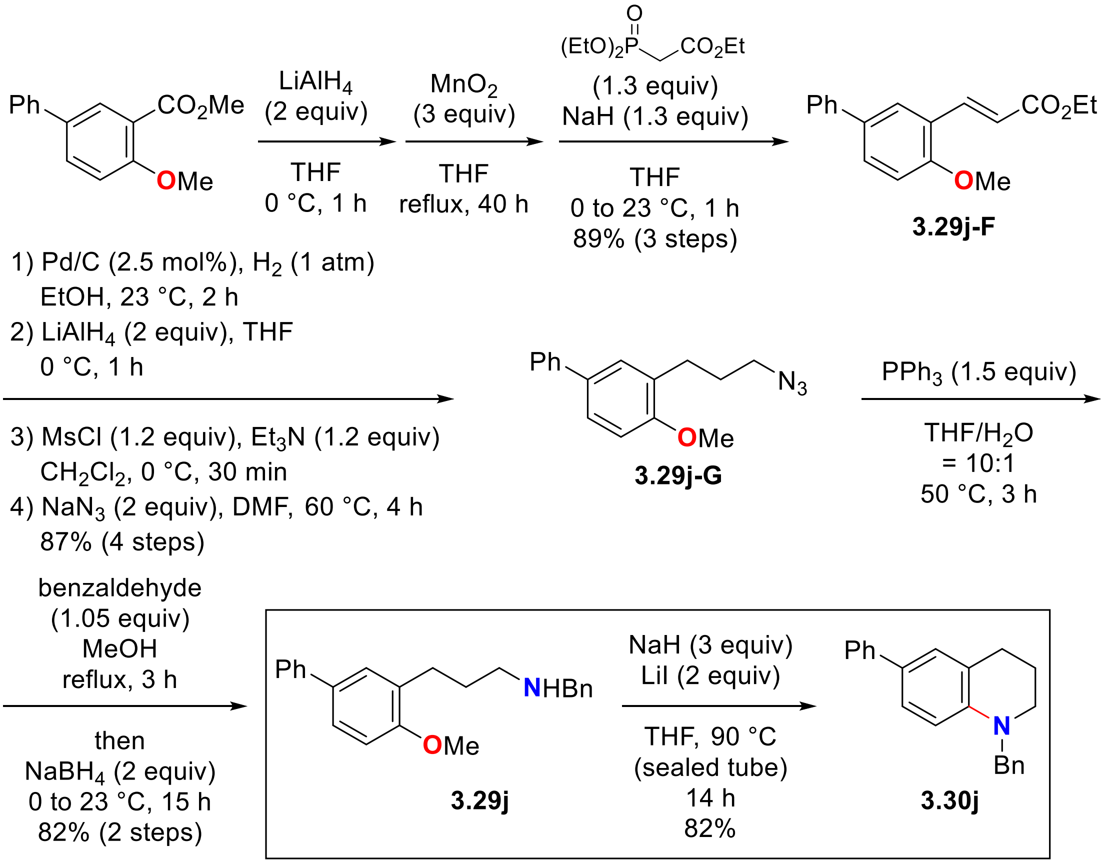
6.3.3.4.4. Synthesis of 1-benzyl-6-methyl-1,2,3,4-tetrahydroquinoline (3.30i)



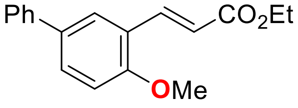
85% yield (105 mg, 0.442 mmol) from **3.29i** (141 mg, 0.523 mmol) for 16 h by the typical procedure B (page 195).

Pale orange oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.00 (2H, tt, *J* = 6.4, 5.6 Hz), 2.19 (3H, s), 2.79 (2H, t, *J* = 6.4 Hz), 3.32 (2H, t, *J* = 5.6 Hz), 4.44 (2H, s), 6.42 (1H, d, *J* = 8.4 Hz), 6.77 (1H, d, *J* = 8.4 Hz), 6.81 (1H, s), 7.20-7.32 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.1, 22.5, 28.1, 49.8, 55.3, 111.1, 122.2, 124.9, 126.56, 126.60, 127.5, 128.5, 129.7, 139.2, 143.4; ESIHRMS: Found: m/z 260.1417. Calcd for $C_{17}H_{19}NNa$: $(M+Na)^+$ 260.1415.

6.3.3.5. Synthesis of 3.30j



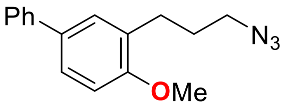
6.3.3.5.1. Synthesis of ethyl (*E*)-3-(4-methoxy-[1,1'-biphenyl]-3-yl)acrylate (3.29j-F)



89% yield (1.96 g, 6.94 mmol) from methyl 4-methoxy-[1,1'-biphenyl]-3-carboxylate[23] (1.89 g, 7.81 mmol) by typical procedure F (page 215).

White solid; mp: 101-102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (3H, t, *J* = 7.2 Hz), 3.93 (3H, s), 4.28 (2H, q, *J* = 7.2 Hz), 6.60 (1H, d, *J* = 16.2 Hz), 6.98 (1H, d, *J* = 8.6 Hz), 7.30-7.35 (1H, m), 7.41-7.45 (2H, m), 7.53-7.56 (2H, m), 7.57 (1H, dd, *J* = 8.6, 2.3 Hz), 7.73 (1H, d, *J* = 2.3 Hz), 8.03 (1H, d, *J* = 16.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 55.6, 60.3, 111.5, 119.1, 123.6, 126.7, 127.0, 127.5, 128.8, 129.9, 133.8, 139.9, 140.1, 157.8, 167.4; ESIHRMS: Found: m/z 283.1339. Calcd for $C_{18}H_{19}O_3$: $(M+H)^+$ 283.1334.

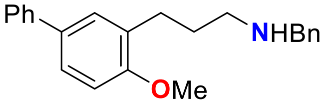
6.3.3.5.2. Synthesis of 3-(3-azidopropyl)-4-methoxy-1,1'-biphenyl (3.29j-G)



87% yield (1.56 g, 5.84 mmol) from **3.29j-F** (1.90 g, 6.73 mmol) by the typical procedure D (page 207).

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.93 (2H, tt, *J* = 7.2, 6.8 Hz), 2.76 (2H, t, *J* = 7.2 Hz), 3.31 (2H, t, *J* = 6.8 Hz), 3.86 (3H, s), 6.92 (1H, d, *J* = 8.4 Hz), 7.28-7.31 (1H, m), 7.36 (1H, d, *J* = 2.2 Hz), 7.39-7.44 (3H, m), 7.55 (2H, d, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.6, 28.8, 50.9, 55.2, 110.5, 125.9, 126.5, 126.6, 128.6, 128.7, 129.5, 133.4, 140.7, 157.0; ESIHRMS: Found: m/z 268.1445. Calcd for $C_{16}H_{18}N_3O$: $(M+H)^+$ 268.1450.

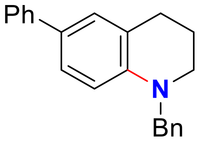
6.3.3.5.3. Synthesis of *N*-benzyl-3-(4-methoxy-[1,1'-biphenyl]-3-yl)propan-1-amine (3.29j)



82% yield (1.12 g, 3.38 mmol) from **3.29j-G** (1.10 g, 4.11 mmol) by the typical procedure E (page 207).

Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.83-1.90 (2H, m), 2.69-2.74 (4H, m), 3.79 (2H, s), 3.84 (3H, s), 6.90 (1H, d, *J* = 8.4 Hz), 7.21-7.31 (6H, m), 7.36-7.43 (4H, m), 7.52-7.55 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.0, 30.1, 49.1, 54.0, 55.3, 110.4, 125.5, 126.5, 126.7, 126.8, 128.1, 128.3, 128.62, 128.66, 130.8, 133.4, 140.5, 141.0, 157.0; ESIHRMS: Found: m/z 332.2010. Calcd for $C_{23}H_{26}NO$: $(M+H)^+$ 332.2014.

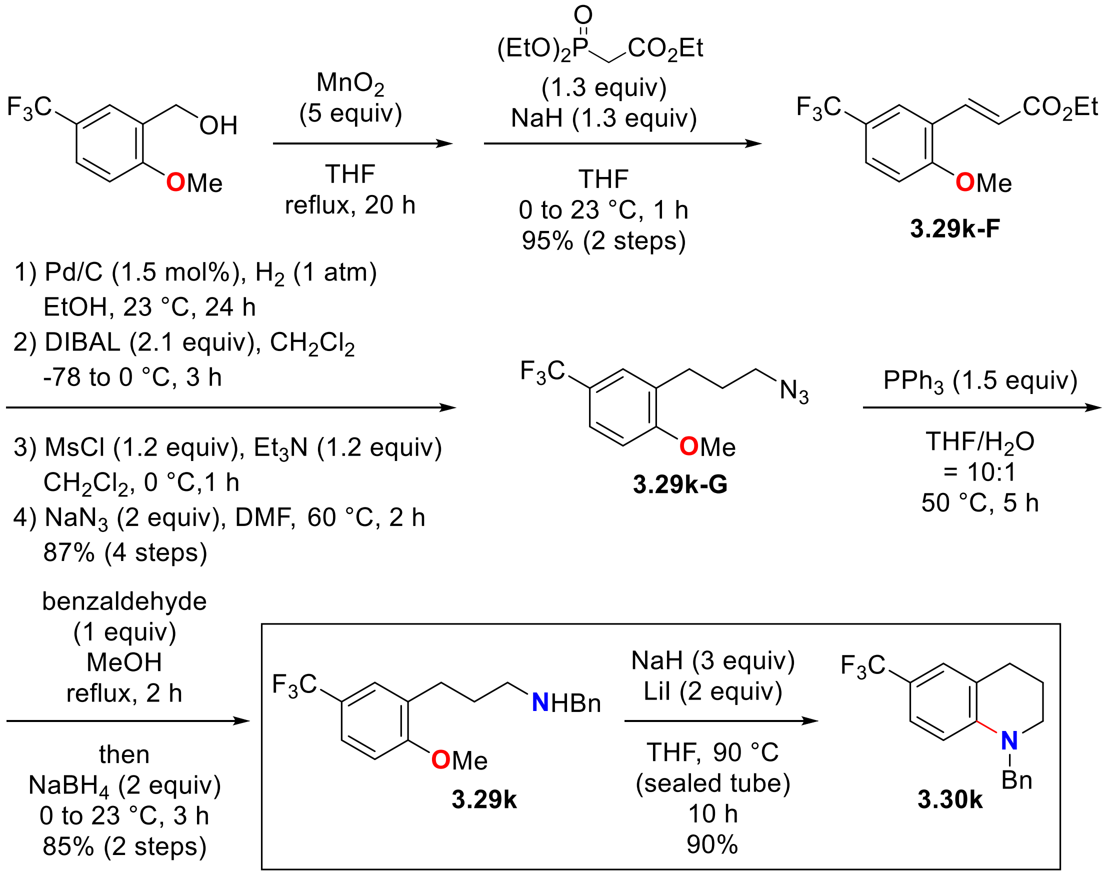
6.3.3.5.4. Synthesis of 1-benzyl-6-phenyl-1,2,3,4-tetrahydroquinoline (3.30j)



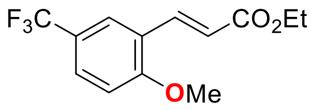
82% yield (118 mg, 0.395 mmol) from **3.30j** (159 mg, 0.480 mmol) for 14 h by the typical procedure B (page 195).

Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.05 (2H, tt, *J* = 6.4, 5.6 Hz), 2.88 (2H, t, *J* = 6.4 Hz), 3.40 (2H, t, *J* = 5.6 Hz), 4.52 (2H, s), 6.57 (1H, d, *J* = 8.4 Hz), 7.19-7.37 (10H, m), 7.51 (2H, d, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.4, 28.3, 49.9, 55.1, 111.2, 122.4, 125.7 (overlapped), 126.1, 126.5, 126.8, 127.6, 128.5, 128.59, 128.62, 138.7, 141.3, 145.0; ESIHRMS: Found: m/z 190.1230. Calcd for $C_{12}H_{16}NO$: $(M+H)^+$190.1232.

6.3.3.6. Synthesis of 3.30k



6.3.3.6.1. Synthesis of ethyl (*E*)-3-(2-methoxy-5-(trifluoromethyl)phenyl)acrylate (3.29k-F)

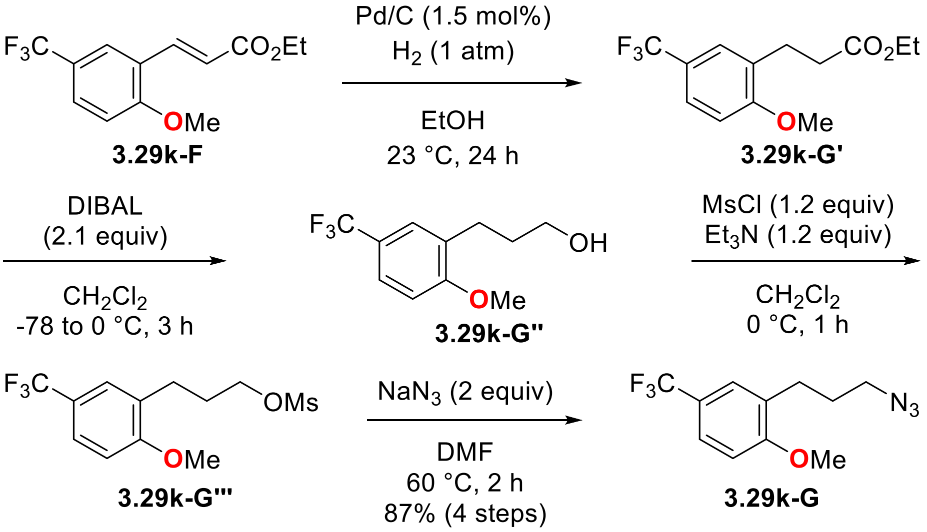


Synthesis of **3.29k-F** was conducted by 1) MnO_2 oxidation & 2) HWE reaction (a part of the typical procedure F; page 215) from (2-methoxy-5-(trifluoromethyl)phenyl)methanol (CAS: 685126-89-0) (6.17 g, 29.9 mmol) in 95% yield (7.81 g, 28.5 mmol).

White solid; mp: 34-35 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (3H, t, *J* = 7.2 Hz), 3.93 (3H, s), 4.26 (2H, q, *J* = 7.2 Hz), 6.55 (1H, d, *J* = 16.2 Hz), 6.97 (1H, d, *J* = 8.7 Hz), 7.57 (1H, dd, *J* = 8.7, 1.6 Hz), 7.73 (1H, d, *J* = 1.6 Hz), 7.94 (1H, d, *J* = 16.2

Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 55.8, 60.5, 111.1, 120.6, 123.1 (q, J = 32.8 Hz), 123.9, 124.1 (q, J = 269.7 Hz), 125.8 (q, J = 3.6 Hz), 128.1 (q, J = 3.6 Hz), 138.4, 160.3, 166.9; ESIHRMS: Found: m/z 275.0898. Calcd for $C_{13}H_{14}O_3F_3$: $(M+H)^+$ 275.0895.

6.3.3.6.2. Synthesis of 2-(3-azidopropyl)-1-methoxy-4-(trifluoromethyl)benzene (3.29k-G)



To a mixture of α,β-unsaturated ester **3.29k-F** (6.86 g, 25.0 mmol) and Pd/C (396 mg, 0.372 mmol, 10% Pd wt/wt on carbon) was added EtOH (50 mL) at 23 ºC under a N_2 atmosphere. The mixture was charged with H_2 gas (1 atm balloon) and stirred at 23 ºC for 13 h. H_2 gas was then removed and the reaction vessel was back filled with N_2 gas. The resulting suspension was filtered through a Celite pad with washing with EtOAc. The collected filtrate was concentrated *in vacuo* to afford crude material including saturated ester **3.29k-G'**, which was used to the next step without purification.

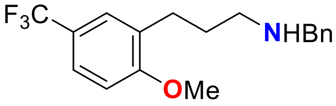
To a solution of the crude ester **3.29k-G'** in CH_2Cl_2 (50 mL) was cooled to –78 ºC before DIBAL (51 mL, 51.0 mmol, 1.0 M solution in THF) was added dropwise to the mixture. The mixture was gradually warmed to 0 ºC for 1 h and then stirred at 0 ºC for additional 2 h. The reaction was quenched with MeOH and saturated aqueous Rochelle salt was subsequently added to the mixture. The slurry mixture was then stirred at 23 ºC for additional 1 h. The organic materials were extracted thrice with CH_2Cl_2 and the combined extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude material including alcohol **3.29k-G”** was used to the next step without further purification.

To an ice cold solution of the crude alcohol **3.29k-G”** in CH_2Cl_2 (63 mL) was added Et_3N (4.20 mL, 30.1 mmol) followed by methanesulfonyl chloride (2.30 mL, 29.7 mmol) slowly under a N_2 atmosphere. The reaction mixture was stirred at 0 °C for 1 h and quenched with saturated aqueous $NaHCO_3$. The organic materials were extracted twice with CH_2Cl_2 and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude material mesylate **3.29k-G’”** was used for the next step without any further purification.

To a solution of crude mesylate **3.29k-G’”** in DMF (62 mL) was added NaN_3 (3.26 g, 50.1 mmol) portion-wise at 0 °C. The reaction mixture was stirred at 60 °C for 3 h and then cooled to 23 °C. The mixture was quenched with H_2O and the organic materials were extracted thrice with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude material was purified by flash column chromatography (silica gel, hexane/EtOAc = 60:1) to give azide **3.29k-G** (5.65 g, 21.8 mmol) in 87% yield based on α,β-unsaturated ester **3.29k-F** as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.89 (2H, tt, *J* = 7.4, 6.8 Hz), 2.72 (2H, t, *J* = 7.4 Hz), 3.29 (2H, t, *J* = 6.8 Hz), 3.87 (3H, s), 6.89 (1H, d, *J* = 8.6 Hz), 7.37 (1H, d, *J* = 2.0 Hz), 7.46 (1H, dd, *J* = 8.6, 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.4, 28.6, 50.9, 55.5, 109.9, 122.6 (q, *J* = 32.3 Hz), 124.5 (q, *J* = 269.3 Hz), 124.9 (q, *J* = 3.8 Hz), 126.8 (q, *J* = 3.6 Hz), 130.0, 159.9; ESIHRMS: Found: m/z 260.1015. Calcd for $C_{11}H_{13}N_3OF_3$: $(M+H)^+$ 260.1011.

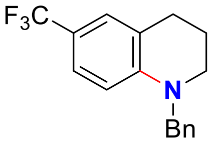
6.3.3.6.3. Synthesis of *N*-benzyl-3-(2-methoxy-5-(trifluoromethyl)phenyl)propan-1-amine (3.29k)



85% yield (2.95 g, 9.12 mmol) from azide **3.29k-G** (2.79 g, 10.7 mmol) by the typical procedure E (page 207).

Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50 (1H, brs), 1.77-1.84 (2H, m), 2.65-2.70 (4H, m), 3.78 (2H, s), 3.83 (3H s), 6.85 (1H, d, *J* = 8.4 Hz), 7.23-7.37 (6H, m), 7.42-7.44 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.8, 29.8, 48.9, 54.0, 55.4, 109.8, 122.4 (q, *J* = 32.2 Hz), 124.4 (q, *J* = 3.9 Hz), 124.5 (q, *J* = 269.6 Hz), 126.6 (q, *J* = 3.6 Hz), 126.9, 128.1, 128.3, 131.2, 140.5, 159.8; ESIHRMS: Found: m/z 324.1578. Calcd for $C_{18}H_{21}NOF_3$: $(M+H)^+$ 324.1575.

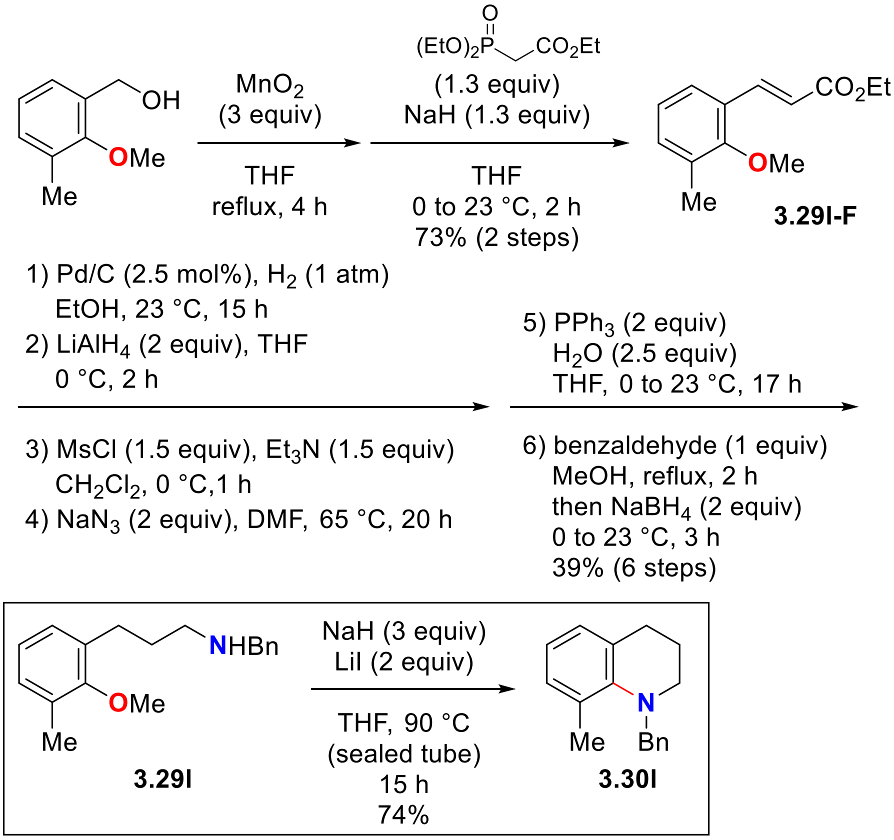
6.3.3.6.4. Synthesis of 1-benzyl-6-(trifluoromethyl)-1,2,3,4-tetrahydroquinoline (3.30k)



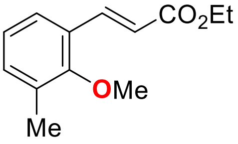
90% yield (131 mg, 0.450 mmol) from **3.29k** (162 mg, 0.501 mmol) for 10 h by the typical procedure B (page 195).

Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.01 (2H, tt, *J* = 6.2, 5.6 Hz), 2.82 (2H, t, *J* = 6.2 Hz), 3.42 (2H, t, *J* = 5.6 Hz), 4.51 (2H, s), 6.47 (1H, d, *J* = 8.4 Hz), 7.16-7.34 (7H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 28.1, 49.9, 54.8, 109.9, 117.1 (q, *J* = 32.2 Hz), 121.8, 124.5 (q, *J* = 3.9 Hz), 125.2 (q, *J* = 268.3 Hz), 125.7 (q, *J* = 3.6 Hz), 126.3, 127.0, 128.7, 137.7, 147.8; ESIHRMS: Found: m/z 292.1316. Calcd for $C_{17}H_{17}NF_3$: $(M+H)^+$ 292.1313.

6.3.3.7. Synthesis of 3.30l



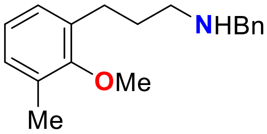
6.3.3.7.1. Synthesis of ethyl (*E*)-3-(2-methoxy-3-methylphenyl)acrylate (3.29l-F)



Synthesis of **3.29l-F** was conducted by 1) MnO_2 oxidation & 2) HWE reaction from from (2-methoxy-3-methylphenyl)methanol[24] (1.52 g, 9.99 mmol) (a part of the typical procedure F; page 215) in 73% yield (1.58 g, 7.17 mmol).

Colorless liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.34 (3H, t, *J* = 7.1 Hz), 2.31 (3H, s), 3.75 (3H, s), 4.27 (2H, q, *J* = 7.1 Hz), 6.48 (1H, d, *J* = 16.2 Hz), 7.03 (1H, dd, *J* = 7.7, 7.4 Hz), 7.21 (1H, d, *J* = 7.4 Hz), 7.40 (1H, d, *J* = 7.7 Hz), 7.97 (1H, d, *J* = 16.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.3, 15.9, 60.4, 61.3, 119.2, 124.2, 125.5, 127.9, 131.8, 133.2, 139.7, 157.8, 167.2; ESIHRMS: Found: *m/z* 221.1179. Calcd for $C_{13}H_{17}NO_3$: $(M+H)^+$221.1178.

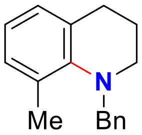
6.3.3.7.2. Synthesis of *N*-benzyl-3-(2-methoxy-3-methylphenyl)propan-1-amine (3.29l)



Synthesis of **3.29l** was conducted by a sequence of the typical procedure D (page 207) and E (page 207) in 39% yield (528 mg, 1.96 mmol) from α,β-unsaturated ester **3.29l-F** (1.11 g, 5.04 mmol).

Colorless liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.41 (1H, brs), 1.82 (2H, tt, *J* = 7.4, 7.1 Hz), 2.28 (3H, s), 2.65-2.69 (2H, m +2H, m), 3.70 (3H, s), 3.77 (2H, s), 6.92 (1H, ddd, *J* = 6.7, 6.6, 1.4 Hz), 6.99-7.00 (2H, m), 7.20-7.23 (1H, m), 7.29-7.30 (4H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.3, 27.5, 31.1, 49.2, 54.1, 60.4, 124.0, 126.9, 127.8, 128.2, 128.4, 129.1, 131.0, 135.0, 140.7, 156.8; ESIHRMS: Found: *m/z* 270.1850. Calcd for $C_{18}H_{24}NO$: $(M+H)^+$ 270.1858.

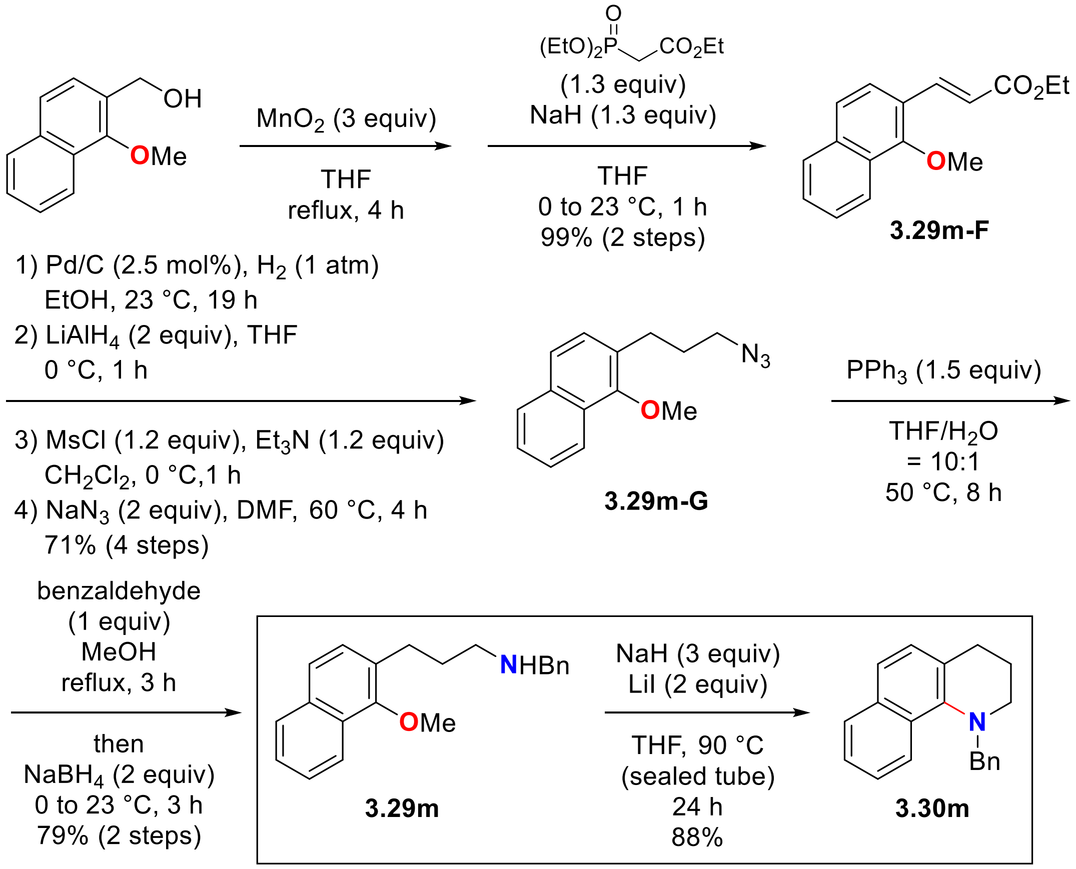
6.3.3.7.3. Synthesis of 1-benzyl-8-methyl-1,2,3,4-tetrahydroquinoline (3.30l)



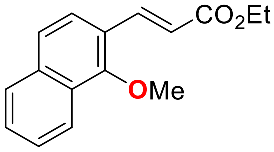
74% yield (59.5 mg, 0.251 mmol) from **3.29l** (90.6 mg, 0.337 mmol) for 15 h by the typical procedure B (page 195).

Pale yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.75-1.81 (2H, m), 2.31 (3H, s), 2.81 (2H, t, *J* = 6.7 Hz), 2.96-2.98 (2H, m), 4.04 (2H, s), 6.84 (1H, dd, *J* = 7.4, 7.4 Hz), 6.92 (1H, d, *J* = 7.4 Hz), 7.00 (1H, d, *J* = 7.4 Hz), 7.25 (1H, t, *J* = 7.4 Hz), 7.34 (2H, dd, *J* = 7.6, 7.4 Hz), 7.50 (2H, d, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.8, 18.7, 27.8, 46.9, 57.7, 121.6, 126.8, 127.4, 127.5, 128.4, 128.9, 129.2, 131.4, 139.7, 147.8; ESIHRMS: Found: *m/z* 238.1601. Calcd for $C_{17}H_{20}N$: $(M+H)^+$ 238.1596.

6.3.3.8. Synthesis of 3.30m



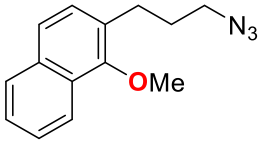
6.3.3.8.1. Synthesis of ethyl (*E*)-3-(1-methoxynaphthalen-2-yl)acrylate (3.29m-F)



Synthesis of **3.29m-F** was conducted by 1) MnO_2 oxidation & 2) HWE reaction (a part of the typical procedure F; page 215) from (1-methoxynaphthalen-2-yl)methanol[25] (5.89 g, 31.3 mmol) in 99% yield (8.01 g, 31.2 mmol).

Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (3H, t, *J* = 7.1 Hz), 3.96 (3H, s), 4.29 (2H, q, *J* = 7.1 Hz), 6.54 (1H, d, *J* = 16.2 Hz), 7.47-7.61 (4H, m), 7.77-7.79 (1H, m), 8.13-8.15 (1H, m), 8.20 (1H, d, *J* = 16.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 60.4, 63.3, 118.9, 122.8, 123.1, 123.4, 124.4, 126.5, 127.3, 127.97, 127.99, 135.7, 138.8, 156.2, 167.1; ESIHRMS: Found: m/z 257.1179. Calcd for $C_{16}H_{17}O_3$: $(M+H)^+$ 257.1178.

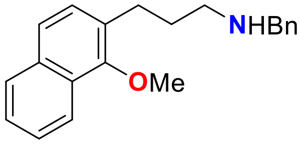
6.3.3.8.2. Synthesis of 2-(3-azidopropyl)-1-methoxynaphthalene (3.29m-G)



71% yield (5.26 g, 21.8 mmol) from **3.29m-F** (7.91 g, 30.9 mmol) by the typical procedure D (page 207).

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.98 (2H, tt, *J* = 7.4, 6.8 Hz), 2.89 (2H, t, *J* = 7.4 Hz), 3.33 (2H, t, *J* = 6.8 Hz), 3.93 (3H, s), 7.29 (1H, d, *J* = 8.4 Hz), 7.42-7.52 (2H, m), 7.57 (1H, d, *J* = 8.4 Hz), 7.81 (1H, d, *J* = 8.0 Hz), 8.07 (1H, d, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.9, 29.8, 50.9, 62.0, 122.0, 124.2, 125.6, 126.0, 127.97 (overlapped), 128.04, 129.1, 133.9, 153.6; ESIHRMS: Found: m/z 242.1289. Calcd for $C_{14}H_{16}N_3O$: $(M+H)^+$ 242.1293.

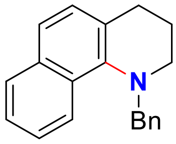
6.3.3.8.3. Synthesis of *N*-benzyl-3-(1-methoxynaphthalen-2-yl)propan-1-amine (3.29m)



79% yield (2.63 g, 8.61 mmol) from **3.29m-G** (2.63 g, 10.9 mmol) by the typical procedure E (page 207).

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54 (1H, brs), 1.91 (2H, tt, *J* = 7.5, 7.0 Hz), 2.70 (2H, t, *J* = 7.0 Hz), 2.86 (2H, t, *J* = 7.5 Hz), 3.78 (2H, s), 3.91 (3H, s), 7.21-7.32 (6H, m), 7.41-7.51 (2H, m), 7.56 (1H, d, *J* = 8.4 Hz), 7.80 (1H, d, *J* = 8.1 Hz), 8.08 (1H, d, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.2, 31.0, 49.0, 54.0, 62.0, 122.0, 124.0, 125.3, 125.8, 126.8, 127.9, 128.0, 128.1 (overlapped), 128.3, 130.2, 133.7, 140.5, 153.3; ESIHRMS: Found: m/z 306.1859. Calcd for $C_{21}H_{24}NO$: $(M+H)^+$ 306.1858.

6.3.3.8.4. Synthesis of 1-benzyl-1,2,3,4-tetrahydrobenzo[h]quinolone (3.30m)

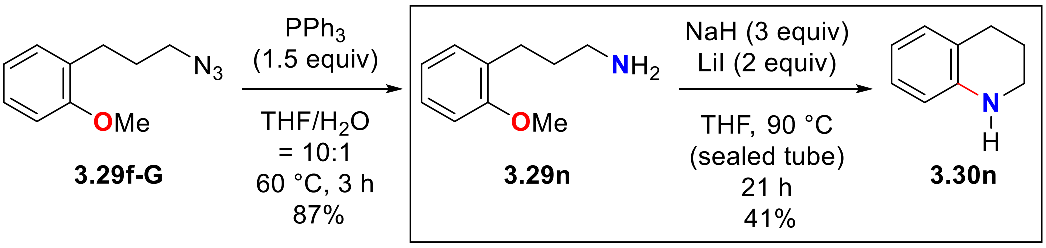


88% yield (120 mg, 0.439 mmol) from **3.29m** (152 mg, 0.498 mmol) for 24 h by the typical procedure B (page 195).

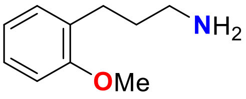
Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.91-1.97 (2H, m), 2.99 (2H, t, *J* = 6.4 Hz), 3.20-3.22 (2H, m), 4.39 (2H, s), 7.22 (1H, d, *J* = 8.2 Hz), 7.38-7.51 (6H, m), 7.68

(2H, d, *J* = 7.0 Hz), 7.81-7.83 (1H, m), 8.20-8.21 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.5, 27.9, 46.9, 59.0, 122.1, 122.9, 125.0, 125.2, 125.3, 126.9, 127.3, 128.2, 128.3, 128.6, 128.8, 133.4, 139.7, 144.1; ESIHRMS: Found: m/z 274.1599. Calcd for $C_{20}H_{20}N$: $(M+H)^+$ 274.1596.

6.3.3.9. Synthesis of 3.30n



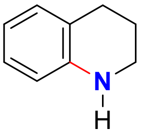
6.3.3.9.1. Synthesis of 3-(2-methoxyphenyl)propan-1-amine (3.29n)



Synthesis of amine **3.29n** was conducted by reduction of alkyl azide **3.29f-G** (422 mg, 2.21 mmol) by PPh_3 (a part of the typical procedure E; page 207) in 87% yield (317 mg, 1.92 mmol).

Colorless liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.55 (2H, brs), 1.74 (2H, tt, *J* = 7.6, 6.9 Hz), 2.66 (2H, t, *J* = 7.6 Hz), 2.71 (2H, t, *J* = 6.9 Hz), 3.82 (3H, s), 6.84 (1H, d, *J* = 8.0 Hz), 6.89 (1H, dd, *J* = 7.5, 7.4 Hz), 7.13 (1H, d, *J* = 7.4 Hz), 7.17 (1H, dd, *J* = 8.0, 7.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.3, 33.9, 41.8, 55.2, 110.2, 120.4, 127.0, 129.8, 130.4, 157.4; ESIHRMS: Found: *m/z* 166.1234. Calcd for $C_{10}H_{16}NO$: $(M+H)^+$ 166.1232.

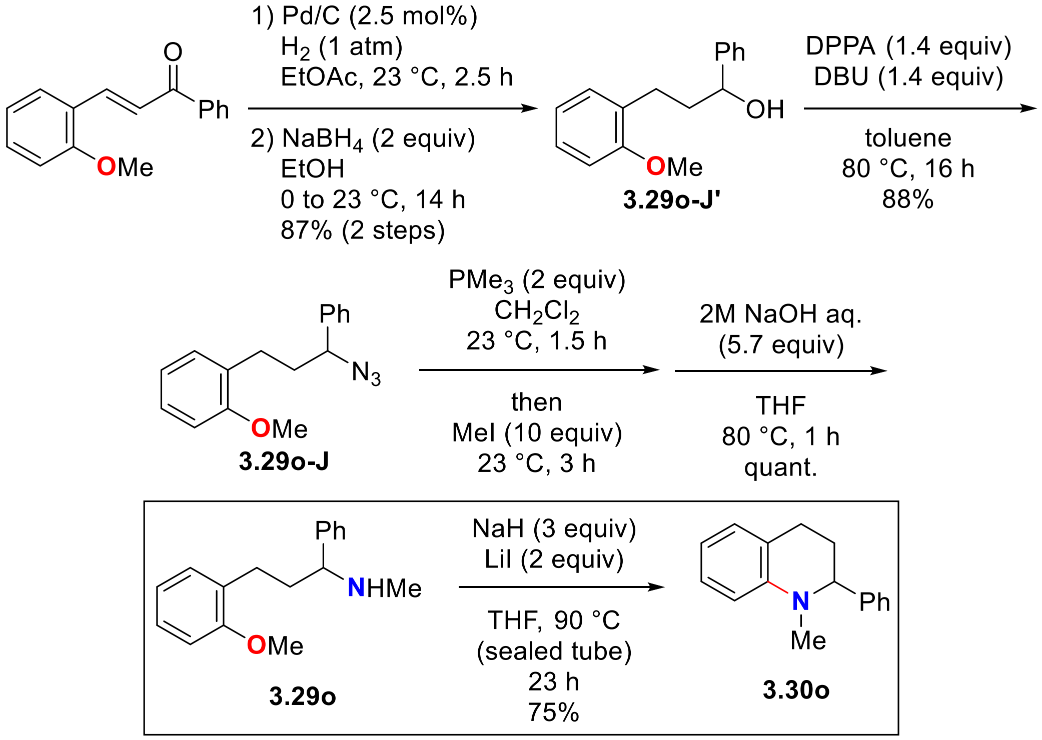
6.3.3.9.2. Synthesis of 1,2,3,4-tetrahydroquinoline (3.30n)[19]



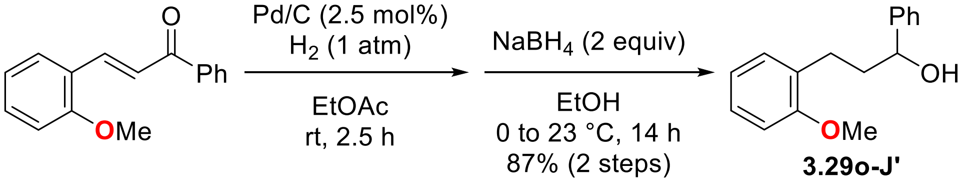
41% yield (25.4 mg, 0.191 mmol) from **3.29n** (76.3 mg, 0.462 mmol) for 21 h by typical procedure B (page 195).

Colorless liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.94 (2H, tt, *J* = 6.4, 5.4 Hz), 2.76 (2H, t, *J* = 6.4 Hz), 3.29 (2H, t, *J* = 5.4 Hz), 3.79 (1H, brs), 6.46 (1H, d, *J* = 7.8 Hz), 6.59 (1H, dd, *J* = 7.4, 7.2 Hz), 6.93-6.97 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.2, 26.9, 42.0, 114.2, 116.9, 121.4, 126.7, 129.5, 144.7.

6.3.3.10. Synthesis of 3.30o



6.3.3.10.1. Synthesis of 3-(2-methoxyphenyl)-1-phenylpropan-1-ol (3.29o-J')[26]

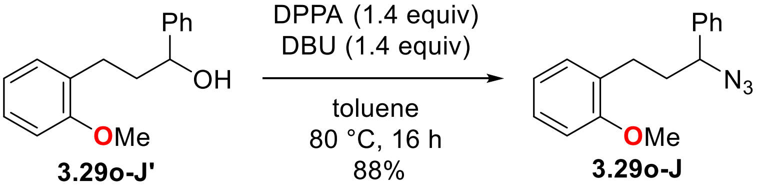


To a mixture of (*E*)-3-(2-methoxyphenyl)-1-phenylprop-2-en-1-one[27] (3.27 g, 13.7 mmol) and Pd/C (365 mg, 0.343 mmol, 10% Pd wt/wt on carbon) was added EtOAc (46 mL) at 23 ºC under a N_2 atmosphere. The mixture was charged with H_2 gas (1 atm balloon) and stirred at 23 ºC for 2.5 h. H_2 gas was then removed and the reaction vessel was back filled with N_2 gas. The resulting suspension was filtered through a Celite pad with washing with EtOAc. The collected filtrate was concentrated *in vacuo* to afford crude materials, which was used to the next step without purification.

To an ice cold solution of crude material in EtOH (46 mL) was added $NaBH_4$ (1.04 g, 27.4 mmol) under a N_2 atmosphere. After stirring at 23 ºC for 14 h, the reaction was quenched with several drops of acetic acid at 0 °C and the solvent was removed *in vacuo*. After dilution with EtOAc and saturated aqueous $NaHCO_3$, the organic materials were extracted thrice with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude material was purified by flash column chromatography (silica gel; hexane: Et_2O = 4:1 to 3:1) to give alcohol **3.29o-J'** (2.88 g, 11.9 mmol) in 87% yield as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.92-2.11 (2H, m), 2.47 (1H, d, *J* = 3.6 Hz), 2.73 (2H, t, *J* = 7.3 Hz), 3.79 (3H, s), 4.57-4.61 (1H, m), 6.83 (1H, d, *J* = 8.1 Hz), 6.86-6.90 (1H, m), 7.11-7.32 (7H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.4, 39.3, 55.2, 73.5, 110.3, 120.6, 125.8, 127.1, 127.3, 128.3, 129.95, 129.99, 144.6, 157.3.

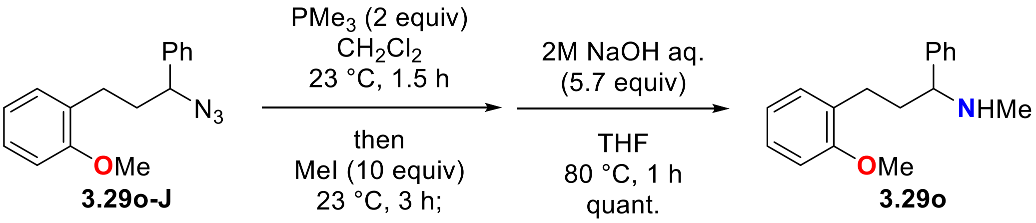
6.3.3.10.2. Synthesis of 1-(3-azido-3-phenylpropyl)-2-methoxybenzene (3.29o-J)



To an ice cold solution of **3.29o-J’** (1.10 g, 4.54 mmol) in toluene (23 mL) was added diphenyl phosphoryl azide (1.37 mL, 6.36 mmol) and DBU (949 μL, 6.36 mmol) slowly under a N_2 atmosphere. The reaction mixture was stirred at 80 °C for 16 h. The mixture was cooled to 23 °C and diluted with EtOAc. The resulting mixture was washed with 1M aqueous HCl, H_2O, and brine. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude material was purified by flash column chromatography (silica gel; hexane:toluene = 4:1) to give azide **3.29o-J** (1.07 g, 3.99 mmol) in 88% yield as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.01-2.17 (2H, m), 2.60-2.76 (2H, m), 3.81 (3H, s), 4.38-4.41 (1H, m), 6.84 (1H, d, J = 8.2 Hz), 6.88 (1H, d, J = 7.4 Hz), 7.09 (1H, d, J = 7.3 Hz), 7.16-7.21 (1H, m), 7.30-7.34 (3H, m), 7.36-7.40 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.3, 35.8, 55.2, 65.8, 110.3, 120.4, 127.0, 127.4, 128.2, 128.7, 129.3, 130.0, 139.8, 157.5; ESIHRMS: Found: m/z 268.1448. Calcd for $C_{16}H_{18}N_3O$: $(M+H)^+$ 268.1450.

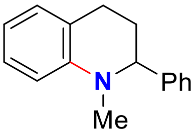
6.3.3.10.3. Synthesis of 3-(2-methoxyphenyl)-*N*-methyl-1-phenylpropan-1-amine (3.29o)



Following the reported procedure,[28] to a solution of azide **3.29o-J** (235 mg, 0.879 mmol) in CH_2Cl_2 (8.8 mL) was added PMe_3 (1.76 mL, 1.76 mmol, 1.0 M THF solution) slowly at 23 °C under a N_2 atmosphere. After stirring at 23 °C for 1.5 h, a solution of iodomethane (547 μL, 8.79 mmol) in CH_2Cl_2 (4.4 mL) was added to the mixture. After stirring at 23 °C for 3 h, the solvent was removed *in vacuo*. The resulting material was diluted with THF (10 mL) and 2M aqueous NaOH (10 mL) and then stirred at 80 °C for 1 h. The mixture was cooled to 23 °C and extracted thrice with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resulting crude material was purified by flash column chromatography (silica gel; CH_2Cl_2:EtOAc:MeOH= 4:4:1 to 3:0:1 to 1:0:1) to give **3.29o** (224 mg, 0.877 mmol) in quantitative yield as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.90-1.99 (1H, m), 2.04-2.13 (1H, m), 2.26 (3H, s), 2.43 (1H, brs), 2.47-2.61 (2H, m), 3.50 (1H, dd, J = 7.4, 6.4 Hz), 3.77 (3H, s), 6.81 (1H, d, J = 8.2 Hz), 6.84 (1H, dd, J = 8.2, 7.4 Hz), 7.05 (1H, d, J = 7.4 Hz), 7.15 (1H, dd, J = 8.2, 8.2 Hz), 7.24-7.37 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.1, 34.0, 37.2, 55.2, 65.1, 110.2, 120.4, 127.1, 127.3, 127.6, 128.5, 129.8, 130.2, 142.7, 157.4; ESIHRMS: Found: m/z 256.1705. Calcd for $C_{17}H_{22}NO$: $(M+H)^+$ 256.1701.

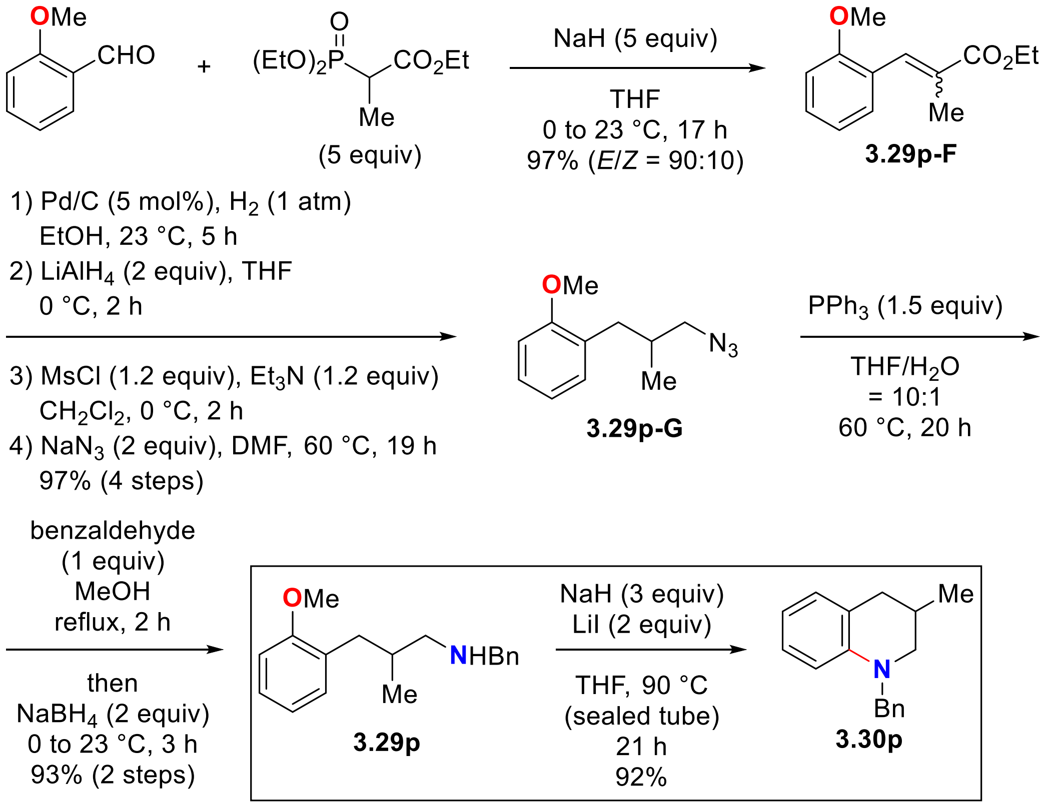
6.3.3.10.4. Synthesis of 1-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline (3.30o)[29]



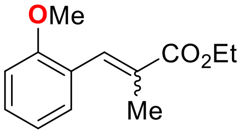
75% yield (50.4 mg, 0.226 mmol) from **3.29o** (76.7 mg, 0.300 mmol) for 23 h by the typical procedure B (page 195).

Pale yellow foam; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.97-2.03 (1H, m), 2.14-2.22 (1H, m), 2.52-2.65 (2H, m), 2.86 (3H, s), 4.47 (1H, t, *J* = 4.7 Hz), 6.61-6.64 (1H, m), 6.66 (1H, d, *J* = 8.2 Hz), 6.97 (1H, d, *J* = 7.2 Hz), 7.12-7.18 (3H, m), 7.21-7.31 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.2, 30.2, 37.7, 63.3, 109.9, 115.6, 122.6, 126.5, 126.8, 127.3, 128.4 (overlapped), 144.3, 146.1.

6.3.3.11. Synthesis of 3.30p



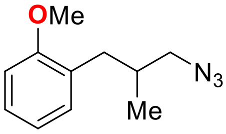
6.3.3.11.1. Synthesis of ethyl 3-(2-methoxyphenyl)-2-methylacrylate (3.29p-F)[30]



97% yield (427 mg, 1.94 mmol, *E*/*Z* = 90:10) from 2-methoxybenzaldehyde (272 mg, 2.00 mmol) with triethyl 2-phosphonopropionate (CAS: 3699-66-9) by the typical procedure C (page 204).

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (1H×0.11, t, *J* = 7.2 Hz), 1.34 (1H, t, *J* = 6.8 Hz), 2.04 (3H, s), 2.11 (3H×0.11, s), 3.82 (3H×0.11, s), 3.85 (3H, s), 4.06 (2H×0.11, q, *J* = 7.2 Hz), 4.27 (2H, q, *J* = 6.8 Hz), 6.83-6.87 (3H×0.11, m), 6.91 (1H, d, *J* = 8.0 Hz), 6.95-6.99 (1H, m), 7.15 (1H×0.11, d, *J* = 7.2 Hz), 7.22 (1H×0.11, d, *J* = 8.0 Hz), 7.28-7.33 (2H, m), 7.83 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) (for ***E*_3.29p-F**) δ 14.1, 14.3, 55.4, 60.7, 110.4, 120.0, 124.9, 128.6, 129.6, 130.1, 134.6, 157.5, 168.6.

6.3.3.11.2. Synthesis of 1-(3-azido-2-methylpropyl)-2-methoxybenzene (3.29p-G)

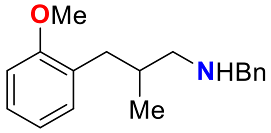


97% yield (4.86 g, 23.7 mmol) from **3.29p-F** (5.37 g, 24.4 mmol) by the typical procedure D (page 207).

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, d, *J* = 6.7 Hz), 2.04-2.14 (1H, m), 2.45 (1H, dd, *J* = 13.2¸ 7.4 Hz), 2.71 (1H, dd, *J* = 6.8, 13.2 Hz), 3.12 (1H, dd, *J* = 12.0, 6.9 Hz), 3.22 (1H, dd, *J* = 12.0, 5.5 Hz), 3.81 (3H, s), 6.85 (1H, d, *J* = 8.6 Hz), 6.88 (1H, d, *J* = 7.4 Hz), 7.07-7.09 (1H, m), 7.17-7.21 (1H, m); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 17.8, 33.9, 35.0, 55.2, 57.3, 110.3, 120.2, 127.4, 128.3, 130.9, 157.6; ESIHRMS: Found: m/z 178.1234. Calcd for $C_{11}H_{16}NO$: $(M-N_2+H)^+$ 178.1232.

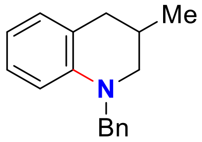
6.3.3.11.3. Synthesis of *N*-benzyl-3-(2-methoxyphenyl)-2-methylpropan-1-amine (3.29p)



93% yield (3.07 g, 11.4 mmol) from **3.29p-G** (2.50 g, 12.2 mmol) by the typical procedure E (page 207).

Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, d, *J* = 6.7 Hz), 1.99-2.07 (1H, m), 2.39 (1H, dd, *J* = 13.2, 8.0 Hz), 2.47 (1H, dd, *J* = 12.0, 6.8 Hz), 2.58 (1H, dd, *J* = 12.0, 6.1 Hz), 2.74 (1H, dd, *J* = 13.2, 6.0 Hz), 3.76 (2H, s), 3.77 (3H, s), 6.83 (1H, d, *J* = 8.5 Hz), 6.86 (1H, d, *J* = 7.4 Hz), 7.08 (1H, d, *J* = 7.3 Hz), 7.15-7.31 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.3, 33.7, 35.6, 54.1, 55.2, 55.7, 110.3, 120.2, 126.8, 127.0, 128.1, 128.3, 129.4, 130.9, 140.8, 157.7; ESIHRMS: Found: m/z 270.1854. Calcd for $C_{18}H_{24}NO$: $(M+H)^+$ 270.1858.

6.3.3.11.4. Synthesis of 1-benzyl-3-methyl-1,2,3,4-tetrahydroquinoline (3.30p)

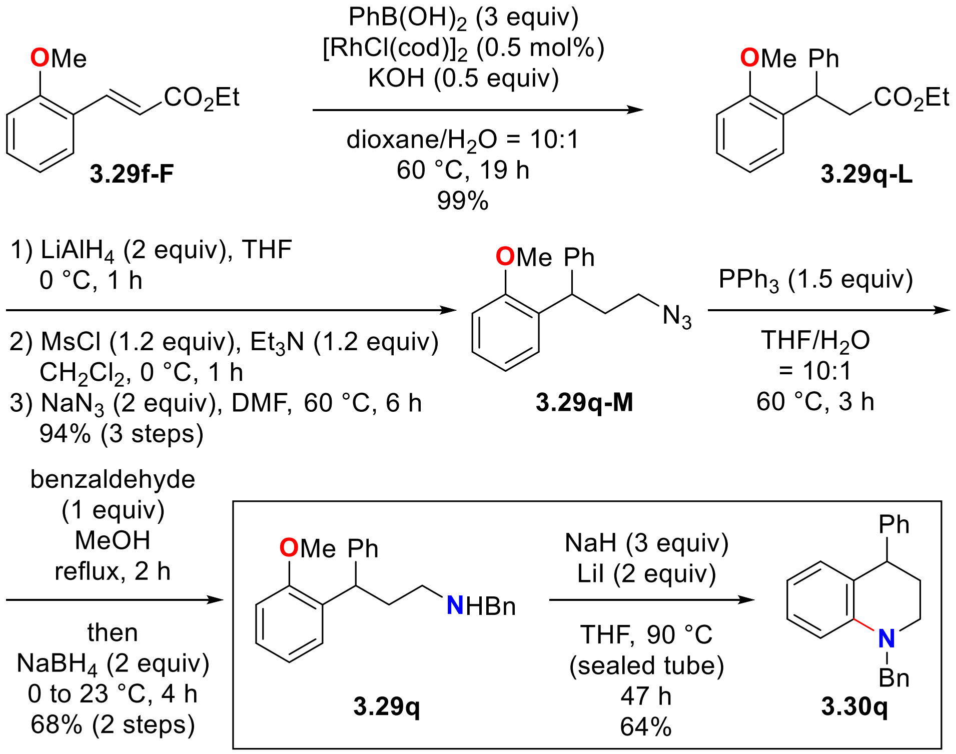


92% yield (109 mg, 0.459 mmol) from **3.29p** (134 mg, 0.497 mmol) for 21 h by the typical procedure B (page 195).

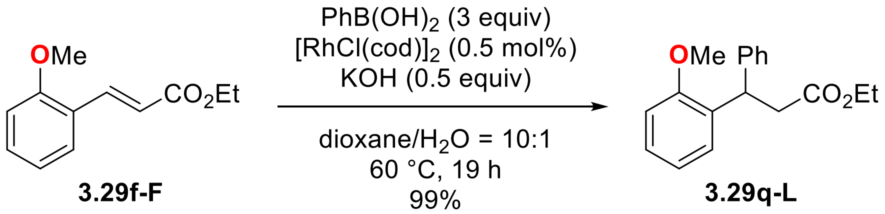
Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (3H, d, *J* = 6.6 Hz), 2.11-2.19 (1H, m), 2.49 (1H, dd, *J* = 15.6, 10.6 Hz), 2.81 (1H, dd, *J* = 15.6, 2.6 Hz), 2.99-3.04

(1H, m), 3.25-3.29 (1H, m), 4.42-4.51 (2H, m), 6.50 (1H, d, *J* = 8.6 Hz), 6.55-6.58 (1H, m), 6.95-6.97 (2H, m), 7.20-7.32 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.0, 27.3, 36.5, 55.1, 56.8, 110.7, 115.8, 121.8, 126.5, 126.7, 127.1, 128.5, 129.1, 139.0, 145.1; ESIHRMS: Found: m/z 238.1595. Calcd for $C_{17}H_{20}N$: $(M+H)^+$ 238.1596.

6.3.3.11. Synthesis of 3.30q



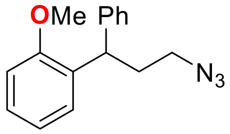
6.3.3.11.1. Synthesis of ethyl 3-(2-methoxyphenyl)-3-phenylpropanoate (3.29q-L)



To a mixture of chloro(1,5-cyclooctadiene)rhodium(I) dimer (49.2 mg, 0.100 mmol), phenylboronic acid (7.29 g, 59.8 mmol), and KOH (578 mg, 10.3 mmol) in degassed water (6 mL) was added a solution of **3.29f-F** (4.12 g, 20.0 mmol) in degassed dioxane (60 mL) at 23 °C under an Ar atmosphere. The mixture was stirred at 60 °C for 19 h and then cooled to 23 °C. After dilution with water and EtOAc, the organic materials were extracted thrice with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude material was purified by flash column chromatography (silica gel; hexane : EtOAc = 80 : 1) to give **3.29q-L** (5.61 g, 19.7 mmol) in 99% yield as a pale yellow solid.

mp: 48-49 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (3H, t, *J* = 7.1 Hz), 2.97-3.09 (2H, m), 3.77 (3H, s), 4.01 (2H, q, *J* = 7.1 Hz), 4.94 (1H, t, *J* = 8.1 Hz), 6.82 (1H, d, *J* = 8.2 Hz), 6.87-6.90 (1H, m), 7.13-7.28 (7H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 39.7, 40.4, 55.4, 60.2, 110.8, 120.4, 126.1, 127.6, 127.8, 127.9, 128.2, 131.9, 143.2, 156.9, 172.1; ESIHRMS: Found: m/z 307.1308. Calcd for $C_{18}H_{20}O_3Na$: $(M+Na)^+$ 307.1310.

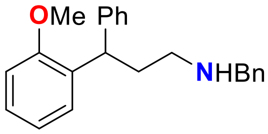
6.3.3.11.2. Synthesis of 1-(3-azido-1-phenylpropyl)-2-methoxybenzene (3.29q-M)



Synthesis of **3.29q-M** was conducted by 1) $LiAlH_4$ reduction, 2) mesylation & 3) azidation (a part of the typical procedure D; page 207) in 94% yield (4.95 g, 18.5 mmol) from **3.29q-L** (5.61 g, 19.7 mmol).

White solid; mp: 53-54 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.26-2.32 (2H, m), 3.15-3.28 (2H, m), 3.78 (3H, s), 4.52 (1H, t, *J* = 7.9 Hz), 6.84 (1H, d, *J* = 8.3 Hz), 6.89-6.92 (1H, m), 7.15-7.27 (7H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.8, 40.5, 49.9, 55.4, 110.8, 120.6, 126.2, 127.5, 127.6, 128.1, 128.3, 132.2, 143.5, 157.0; ESIHRMS: Found: m/z 268.1449. Calcd for $C_{16}H_{18}N_3O$: $(M+H)^+$ 268.1450.

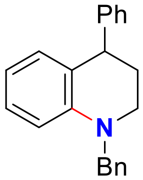
6.3.3.11.3. Synthesis of *N*-benzyl-3-(2-methoxyphenyl)-3-phenylpropan-1-amine (3.29q)



68% yield (2.23 g, 6.72 mmol) from **3.29q-M** (2.64 g, 9.87 mmol) by the typical procedure E (page 207).

White solid; mp: 69-70 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (1H, brs), 2.23 (2H, dt, *J* = 7.8, 7.2 Hz), 2.61 (2H, t, *J* = 7.2 Hz), 3.72 (2H, s), 3.75 (3H, s), 4.49 (1H, t, *J* = 7.8 Hz), 6.81 (1H, d, *J* = 8.2 Hz), 6.88-6.91 (1H, m), 7.12-7.30 (12H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.1, 40.9, 47.8, 53.8, 55.4, 110.6, 120.6, 125.8, 126.8, 127.1, 127.7, 128.0, 128.08, 128.12, 128.3, 133.2, 140.5, 144.7, 156.9; ESIHRMS: Found: m/z 332.2018. Calcd for $C_{23}H_{26}NO$: $(M+H)^+$ 332.2014.

6.3.3.11.4. Synthesis of 1-benzyl-4-phenyl-1,2,3,4-tetrahydroquinoline (3.30q)

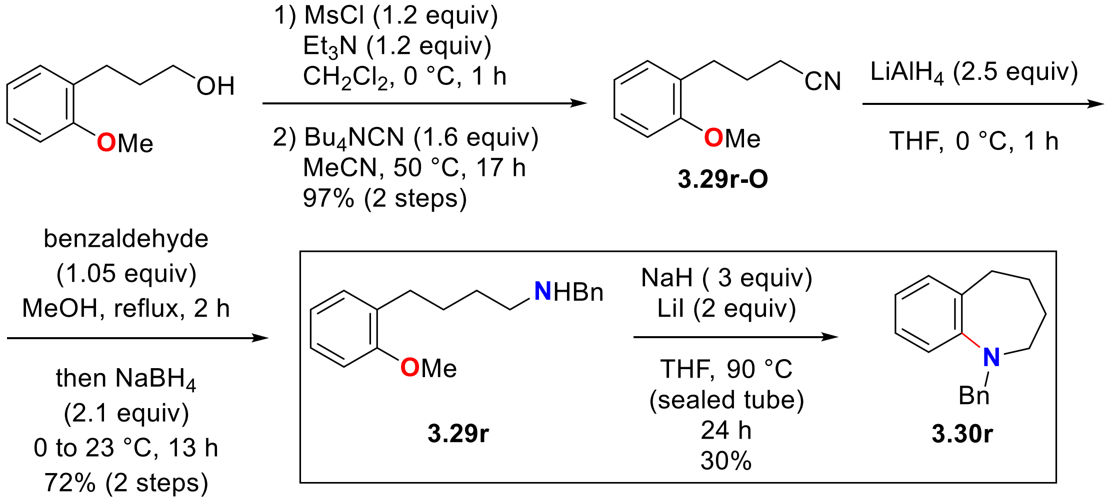


64% yield (57.2 mg, 0.191 mmol) from **3.29q** (98.6 mg, 0.297 mmol) for 47 h by the typical procedure B (page 195).

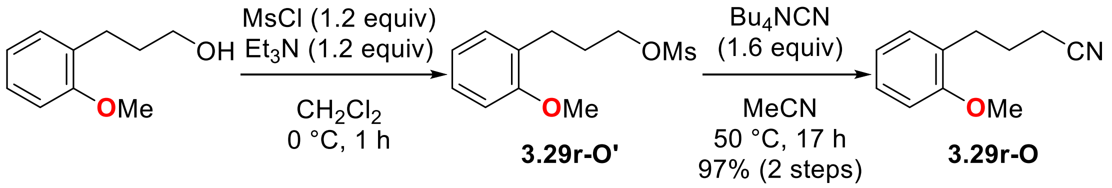
Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.10-2.17 (1H, m), 2.25-2.33 (1H, m), 3.23-3.35 (2H, m), 4.18 (1H, t, *J* = 5.7 Hz), 4.48-4.57 (2H, m), 6.52-6.56 (1H, m), 6.60 (1H, d, *J* = 8.3 Hz), 6.79 (1H, d, *J* = 7.5 Hz), 7.00-7.04 (1H, m), 7.13 (2H, d, *J* = 8.0 Hz), 7.19-7.34 (8H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.6, 43.4, 46.6, 55.2, 111.1, 115.9, 124.0, 126.1, 126.6, 126.8, 127.7, 128.3, 128.58, 128.62, 130.0, 138.8, 145.7, 146.1; ESIHRMS: Found: m/z 300.1756. Calcd for $C_{22}H_{22}N$: $(M+H)^+$ 300.1752.

6.3.4. Synthesis of medium-ring heterocycles 3.30r-3.30w (Scheme 3.19)

6.3.4.1. Synthesis of 3.30r (Scheme 3.19)



6.3.4.1.1. Synthesis of 4-(2-methoxyphenyl)butanenitrile (3.29r-O)

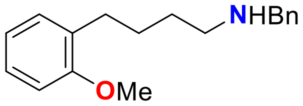


To an ice cold solution of 3-(2-methoxyphenyl)propan-1-ol[31] (1.36 g, 8.18 mmol) and Et_3N (1.40 mL, 10.0 mmol) in CH_2Cl_2 (21 mL) was added methanesulfonyl chloride (0.760 mL, 9.82 mmol) dropwise under a N_2 atmosphere. The solution was stirred at 0 ºC for 1 h and quenched with saturated aqueous $NaHCO_3$. The organic materials were extracted twice with CH_2Cl_2 and the combined extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude material including mesylate **3.29r-O’** was used to the next step without purification.

To a solution of crude mesylate **3.29r-O'** in MeCN (26 mL) was added Bu_4NCN (3.43 g, 12.8 mmol) at 23 ºC under a N_2 atmosphere and the mixture was stirred at 50 ºC for 17 h. The reaction mixture was cooled to 0 ºC and quenched with saturated aqueous NH_4Cl. The organic materials were extracted twice with EtOAc and the combined extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude material was purified by flash column chromatography (silica gel; hexane : EtOAc = 10 : 1) to give nitrile **3.29r-O** (1.39 g, 7.93 mmol) in 97% yield as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.95 (2H, tt, *J* = 7.2, 7.3 Hz), 2.30 (2H, t, *J* = 7.2 Hz), 2.76 (2H, t, *J* = 7.3 Hz), 3.82 (3H, s), 6.85 (1H, d, *J* = 8.0 Hz), 6.89 (1H, dd, *J* = 7.5, 7.4 Hz), 7.11 (1H, d, *J* = 7.4 Hz), 7.21 (1H, dd, *J* = 8.0, 7.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.6, 25.4, 29.3, 55.1, 110.3, 119.8, 120.4, 127.8, 128.1, 130.1, 157.4; ESIHRMS: Found: *m/z* 176.1077. Calcd for $C_{11}H_{14}NO$: $(M+H)^+$ 176.1075.

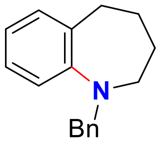
6.3.4.1.2. Synthesis of *N*-benzyl-4-(2-methoxyphenyl)butan-1-amine (3.29r)



72% yield (722 mg, 2.68 mmol) from **3.29r-O** (650 mg, 3.71 mmol) by the typical procedure A (page 194).

Colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.39 (1H, brs), 1.54-1.64 (2H, m + 2H, m), 2.62 (2H, t, *J* = 7.3 Hz), 2.66 (2H, t, *J* = 6.8 Hz), 3.78 (2H, s), 3.80 (3H, s), 6.83 (1H, d, *J* = 8.2 Hz), 6.86 (1H, dd, *J* = 7.5, 7.4 Hz), 7.11 (1H, dd, *J* = 7.4 Hz), 7.16 (1H, dd, *J* = 8.2, 7.5 Hz), 7.23-7.26 (1H, m), 7.30-7.32 (4H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.5, 29.9, 30.0, 49.4, 54.1, 55.2, 110.2, 120.3, 126.8, 126.9, 128.1, 128.3, 129.8, 130.9, 140.6, 157.4; ESIHRMS: Found: *m/z* 270.1861. Calcd for $C_{18}H_{24}NO$: $(M+H)^+$ 270.1858.

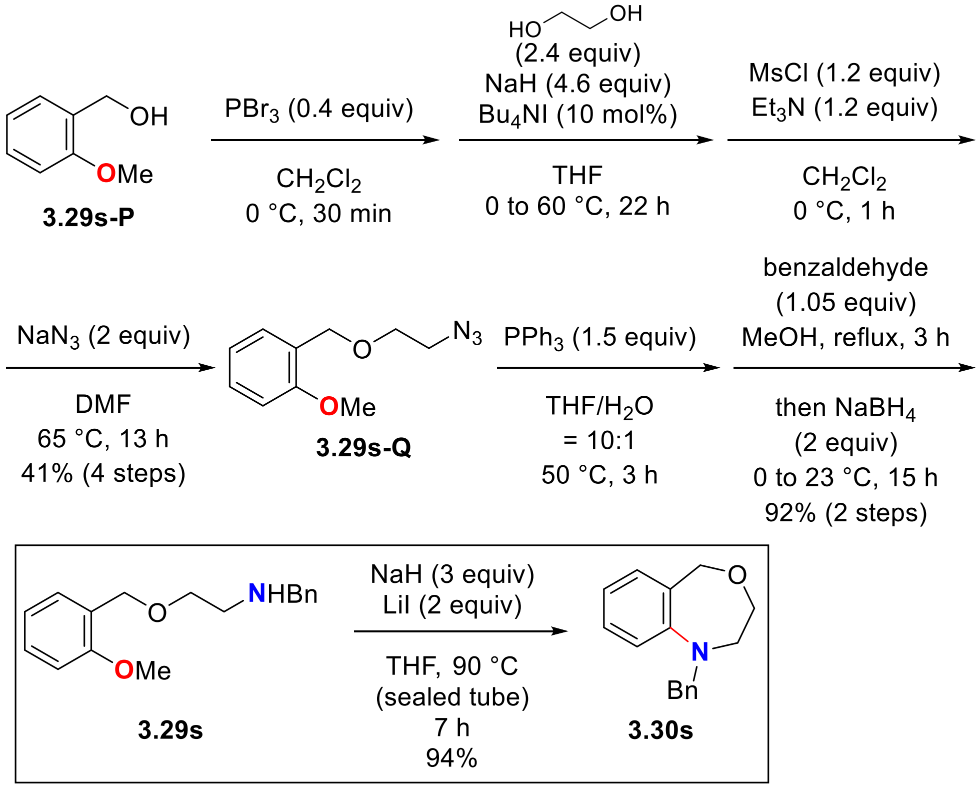
6.3.4.1.3. Synthesis of 1-benzyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine (3.30r)[16]



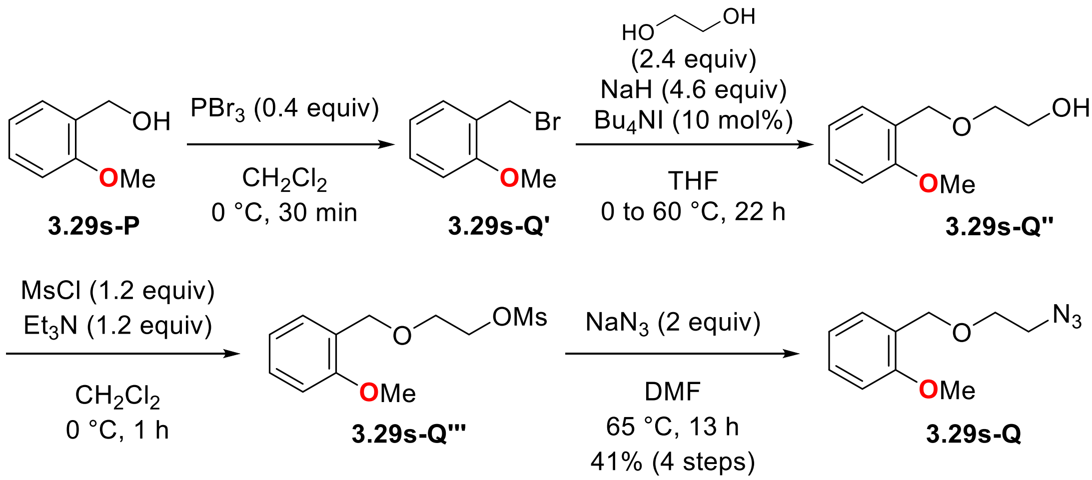
30% yield (23.0 mg, 0.0970 mmol) from **3.29r** (87.0 mg, 0.323 mmol) for 24 h by the typical procedure B (page 195).

Pale yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.59-1.60 (2H, m + 2H, m), 2.86-2.88 (2H, m + 2H, m), 4.30 (2H, s), 6.87 (1H, dd, *J* = 7.4, 7.4 Hz), 6.97 (1H, d, *J* = 8.0 Hz), 7.11-7.15 (1H, m + 1H, m), 7.23 (1H, t, *J* = 7.3 Hz), 7.31 (2H, dd, *J* = 7.3, 7.3 Hz), 7.42 (2H, d, *J* = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.8, 30.0, 35.0, 53.4, 58.5, 117.6, 121.2, 126.6, 126.9, 128.25, 128.31, 129.9, 136.1, 139.9, 152.6.

6.3.4.2. Synthesis of 3.30s (Scheme 3.19)



6.3.4.2.1. Synthesis of 1-((2-azidoethoxy)methyl)-2-methoxybenzene (3.29s-Q) (typical procedure G):



To an ice cold solution of 2-methoxybenzyl alcohol (1.09 g, 7.88 mmol) in CH_2Cl_2 (20 mL) was added dropwise a solution of phosphorus tribromide (0.30 mL, 3.15 mmol) in CH_2Cl_2 (10 mL) under a N_2 atmosphere. The reaction mixture was stirred at

0 °C for 30 min and quenched with saturated aqueous Na_2CO_3 solution. The organic materials were extracted thrice with CH_2Cl_2 and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude material including bromide **3.29s-Q’** were used immediately for the next step without further purification.

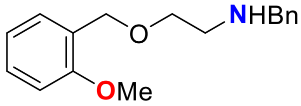
To an ice cold suspension of NaH (1.45 g, 36.3 mmol) in THF (20 mL) was added a solution of ethylene glycol (1.17 g, 18.9 mmol) (CAS: 107-21-1) in THF (10 mL) dropwise under a N_2 atmosphere. After stirring at 0 °C for 30 min, a solution of crude bromide **3.29s-Q’** in THF (20 mL) was added dropwise into the reaction mixture at 0 °C. After stirring at 0 °C for 30 min, Bu_4NI (291 mg, 0.788 mmol) was added into the reaction mixture at 0 °C and the mixture was stirred at 23 ºC for 15 h. The mixture was then warmed to 60 ºC and stirred for 7 h. The reaction mixture was cooled to 0 °C and quenched with saturated aqueous NH_4Cl solution and the organic materials were extracted thrice with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude material including alcohol **3.29s-Q’’** was used for the next step without any further purification.

To an ice cold solution of the crude alcohol **3.29s-Q”** in CH_2Cl_2 (20 mL) was added Et_3N (1.3 mL, 9.33 mmol) under a N_2 atmosphere. A solution of methanesulfonyl chloride (732 μL, 9.45 mmol) in CH_2Cl_2 (20 mL) was then added dropwise into the reaction mixture at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and quenched with saturated aqueous Na_2CO_3. The organic materials were extracted thrice with CH_2Cl_2. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude material including mesylate **3.29s-Q”’** was used for the next step without any further purification.

To a solution of crude mesylate **3.29s-Q'''** in DMF (20 mL) was added NaN_3 (1.02 g, 15.7 mmol) portion-wise at 0 °C. The reaction mixture was stirred at 65 °C for 13 h and then cooled to 23 °C. The mixture was quenched with H_2O and the organic materials were extracted thrice with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude material was purified by flash column chromatography (silica gel, hexane:EtOAc = 95 : 5) to give azide **3.29s-Q** (669 mg, 3.23 mmol) in 41% yield based on 2-methoxybenzyl alcohol as a colorless liquid.

^1H NMR ($CDCl_3$, 400 MHz) δ 3.42 (2H, t, *J* = 5.1 Hz), 3.70 (2H, t, *J* = 5.1 Hz), 3.84 (3H, s), 4.62 (2H, s), 6.87 (1H, d, *J* = 8.2 Hz), 6.97 (1H, dd, *J* = 7.4, 6.8 Hz), 7.28 (1H, dd, *J* = 8.2, 7.4 Hz), 7.39 (1H, d, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 50.8, 55.3, 68.0, 69.0, 110.2, 120.5, 126.2, 128.9 (overlapped), 157.0; ESIHRMS: Found: *m/z* 208.1087. Calcd for $C_{10}H_{14}N_3O_2$: $(M+H)^+$ 208.1086.

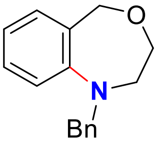
6.3.4.2.2. Synthesis of *N*-benzyl-2-((2-methoxybenzyl)oxy)ethan-1-amine (3.29s)



92% yield (558 mg, 2.05 mmol) from **3.29s-Q** (460 mg, 2.22 mmol) by typical procedure E (page 207).

Pale-yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 1.87 (1H, brs), 2.85 (2H, t, *J* = 5.0 Hz), 3.66 (2H, t, *J* = 5.0 Hz), 3.79 (3H, s), 3.81 (2H, s), 4.56 (2H, s), 6.85 (1H, d, *J* = 8.2 Hz), 6.92-6.96 (1H, m), 7.24-7.36 (7H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 48.9, 53.8, 55.3, 67.9, 69.7, 110.2, 120.4, 126.6, 126.8, 128.1, 128.3, 128.7, 129.1, 140.3, 157.2; ESIHRMS: Found: *m/z* 272.1655. Calcd for $C_{17}H_{22}NO_2$: $(M+H)^+$ 272.1651.

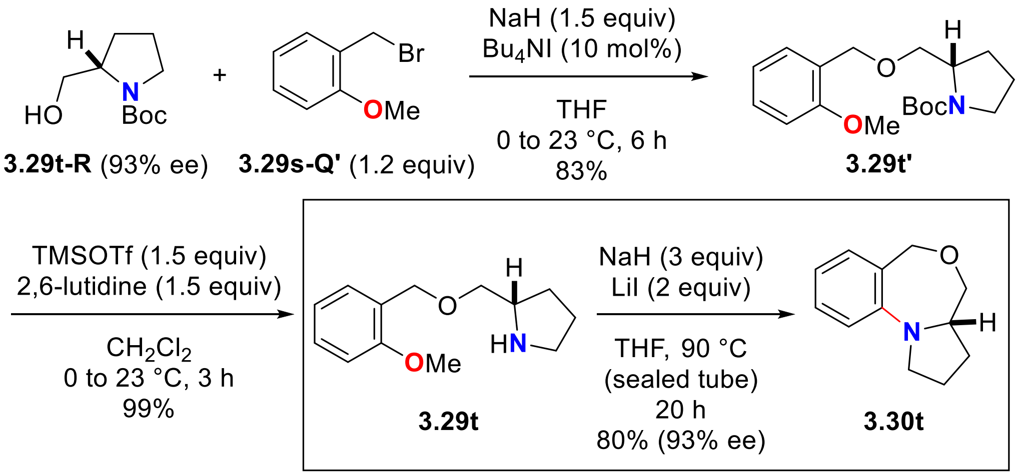
6.3.4.2.3. Synthesis of 1-benzyl-1,2,3,5-tetrahydrobenzo[*e*][1,4]oxazepine (3.30s)



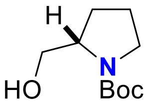
94% yield (113 mg, 0.472 mmol) from **3.30s** (135 mg, 0.499 mmol) for 7 h by the typical procedure B (page 195).

Colorless oil; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 2.98 (2H, t, *J* = 4.3 Hz), 3.69 (2H, t, *J* = 4.3 Hz), 4.39 (2H, s), 4.69 (2H, s), 6.93 (1H, dd, *J* = 7.4, 7.3 Hz), 7.03 (1H, d, *J* = 7.9 Hz), 7.23-7.27 (3H, m), 7.33-7.34 (2H, m), 7.41-7.43 (2H, m); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 54.6, 57.8, 71.7, 74.1, 116.9, 121.1, 127.2, 128.4, 128.5, 128.7, 129.9, 131.9, 139.0, 152.4; ESIHRMS: Found: *m/z* 240.1388. Calcd for $C_{16}H_{18}NO$: $(M+H)^+$ 240.1388.

6.3.4.3. Synthesis of 3.30t (Scheme 3.19)

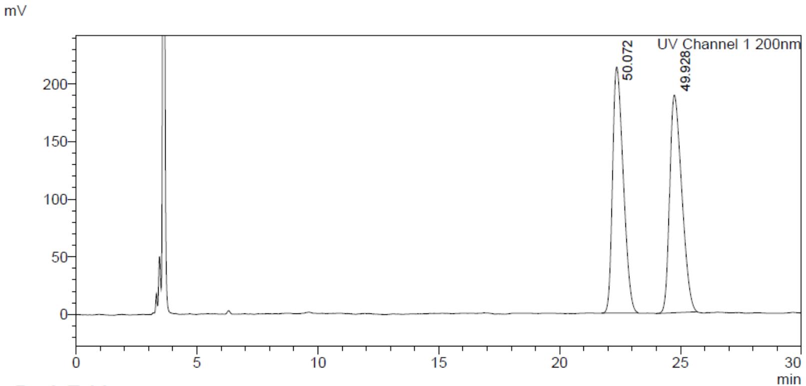


6.3.4.3.1 Synthesis of *tert*-butyl (*S*)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (3.29t-R)



The enantiopure (*S*)- **3.29t-R** was prepared according to a literature procedure.[32] The enantiomeric excess (ee) was measured by HPLC (Daicel Chiralpak IC column), *i*-PrOH/hexane = 5/95, flow 1.0 mL/min, 200 nm, t_1 = 22.1 min (major), t_2 = 25.0 min (minor); $[\alpha]_D^{20}$ = -45.9° (c = 1.00, $CHCl_3$), lit: -49.8° (c = 1.27, $CHCl_3$)[33] for 93% ee (*S*).

6.3.4.3.2. Chiral HPLC chart of racemic 3.29t-R:

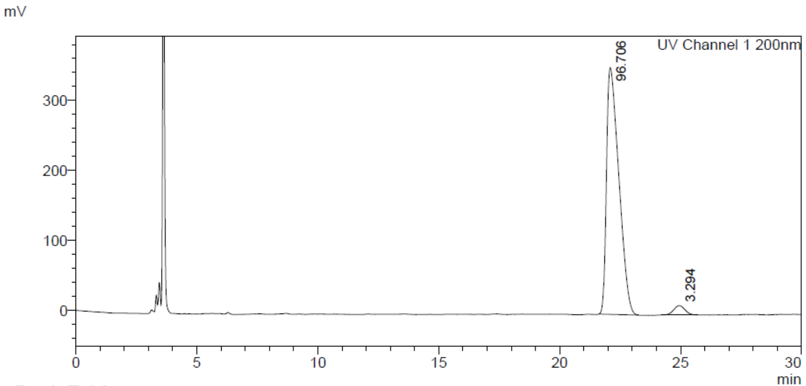


<Peak Table>

UV Channel 1 200nm

Peak#	Ret. Time	Area	Height	Area%
1	22.361	6624296	213582	50.072
2	24.745	6605250	189043	49.928
Total		13229546	402625	100.000

6.3.4.3.3. Chiral HPLC chart of 3.29t-R:

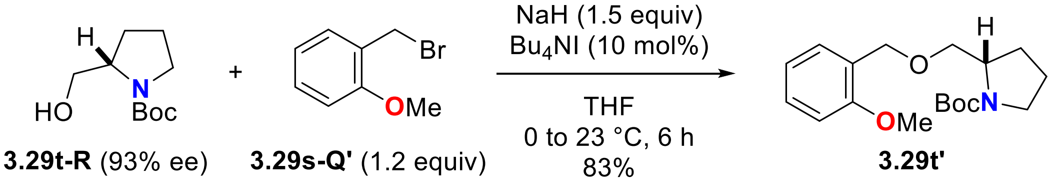


<Peak Table>

UV Channel 1 200nm

Peak#	Ret. Time	Area	Height	Area%
1	22.092	12546026	352444	96.706
2	24.952	427316	13209	3.294
Total		12973341	365652	100.000

6.3.4.3.4. Synthesis of *tert*-butyl (*S*)-2-(((2-methoxybenzyl)oxy)methyl)pyrrolidine-1-carboxylate (3.29t')

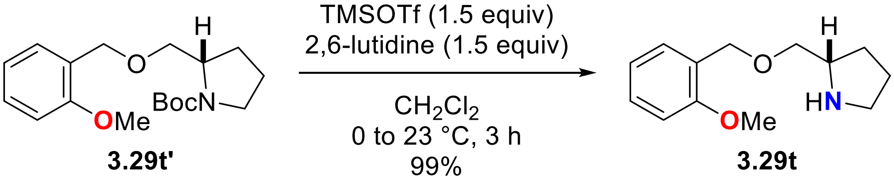


3.29t-R (93% ee) **3.29s-Q'** (1.2 equiv) **3.29t'**

To an ice cold solution of **3.29t-R** (2.00 g, 9.94 mmol) in THF (15 mL) was added NaH (596 mg, 14.9 mmol) under a N_2 atmosphere. After stirring at 0 °C for 30 min, a solution of benzyl bromide **3.29s-Q'** (11.9 mmol, prepared by the same way in typical procedure G, page 245) in THF (5 mL) and Bu_4NI (367 mg, 0.994 mmol) were added to the mixture successively at 0 °C. The reaction mixture was stirred at 23 °C for 6 h. The mixture was quenched with saturated aqueous NH_4Cl at 0 °C, and the resulting organic materials were extracted thrice with EtOAc. The combined extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude material was purified by flash column chromatography (silica gel; hexane:Et_2O = 2 : 1) to give **3.29t'** (2.65 g, 8.25 mmol) in 83% yield as a colorless oil.

^1H NMR (400 MHz, $CDCl_3$, mixture of rotamers) δ 1.44 (9H, s), 1.73-2.00 (4H, m), 3.34-3.67 (4H, m), 3.82 (3H, s), 3.93-4.04 (1H, m), 4.53-4.61 (2H, m), 6.85 (1H, d, *J* = 8.1 Hz), 6.94 (1H, dd, *J* = 7.3, 7.2 Hz), 7.23 (1H, dd, *J* = 8.1, 7.2 Hz), 7.35 (1H, d, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers) δ 22.7, 23.6, 27.9, 28.3, 28.7, 46.2, 46.7, 55.1, 56.4, 67.8, 70.7, 71.2, 78.8, 79.0, 109.9, 120.2, 126.7, 128.3, 154.4, 156.8; ESIHRMS: Found: m/z 322.2020. Calcd for $C_{18}H_{28}NO_4$: $(M+H)^+$ 322.2018; $[\alpha]_D^{20}$ = -42.1° (*c* = 1.03, $CHCl_3$)

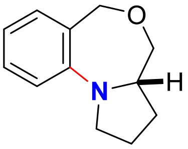
6.3.4.3.5. Synthesis of (*S*)-2-(((2-methoxybenzyl)oxy)methyl)pyrrolidine (3.29t)



To an ice cold solution of **3.29t'** (965 mg, 3.00 mmol) and 2,6-lutidine (540 μL, 4.64 mmol) in CH_2Cl_2 (28 mL) was added TMSOTf (830 μL, 4.59 mmol) slowly under a N_2 atmosphere. After stirring at 0 °C for 2 h, the mixture was warmed to 23 °C and stirred for 1 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and the resulting organic materials were extracted thrice with CH_2Cl_2.. The combined extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude material was purified by flash column chromatography (silica gel; hexane:EtOAc = 1:1 then CH_2Cl_2:MeOH:Et_3N = 100:20:1) to give **3.29t** (657 mg, 2.97 mmol) in 99% yield as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44-1.53 (1H, m), 1.70-1.90 (3H, m), 2.89-2.95 (1H, m), 2.99-3.04 (1H, m), 3.36-3.43 (1H, m), 3.44-3.48 (1H, m), 3.54 (1H, dd, *J* = 9.3, 4.4 Hz), 3.82 (3H, s), 3.91 (1H, brs), 4.58 (2H, s), 6.86 (1H, d, *J* = 8.2 Hz), 6.94 (1H, dd, *J* = 7.4, 6.8 Hz), 7.26 (1H, dd, *J* = 8.2, 6.8 Hz), 7.37 (1H. d, *J* = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.0, 27.7, 46.2, 55.1, 57.7, 67.8, 73.6, 110.0, 120.2, 126.6, 128.4, 128.7, 156.9; ESIHRMS: Found: m/z 222.1495. Calcd for $C_{13}H_{20}NO_2$: $(M+H)^+$ 222.1494; $[\alpha]_D^{20}$ = +1.65° (*c* = 0.970, $CHCl_3$).

6.3.4.3.6. Synthesis of (*S*)-2,3,3a,4-tetrahydro-1*H*,6*H*-benzo[*e*]pyrrolo[2,1-*c*][1,4]oxazepine (3.30t)

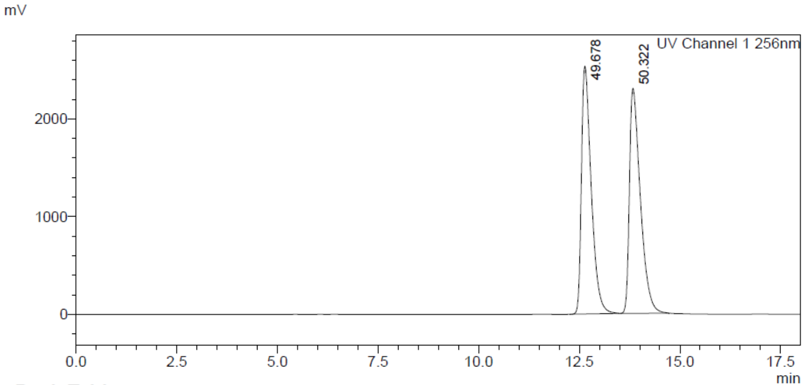


80% yield (82.2 mg, 0.434 mmol) from **3.29t** (120 mg, 0.542 mmol) for 20 h by the typical procedure B (page 195).

Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.51-1.58 (1H, m), 1.86-2.00 (2H, m), 2.09-2.19 (1H, m), 3.07-3.14 (1H, m), 3.29-3.32 (2H, m), 3.40 (1H, dd, *J* = 11.6, 10.1 Hz), 3.93 (1H, dd, *J* = 11.6, 2.4 Hz), 4.42 (1H, d, *J* = 13.1 Hz), 4.77 (1H, d, *J* = 13.1 Hz), 6.84-6.89 (2H, m), 7.15 (1H, d, *J* = 7.3 Hz), 7.21-7.25 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.7, 28.3, 51.6, 62.7, 74.5, 76.0, 115.1, 119.9, 128.5, 129.5, 130.1, 149.3; ESIHRMS: Found: m/z 190.1228. Calcd for $C_{12}H_{16}NO$: $(M+H)^+$ 190.1232.

The ee of **3.30t** was measured by HPLC (Daicel Chiralpak IB column), *i*-PrOH/hexane = 1/99, flow 1.0 mL/min, 256 nm, t_1 = 12.6 min (minor), t_2 = 13.6 min (major).; $[\alpha]_D^{20}$ = -47.7° (*c* = 0.970, $CHCl_3$) for 93% ee (*S*).

6.3.4.3.7. Chiral HPLC chart of racemic-3.30t:

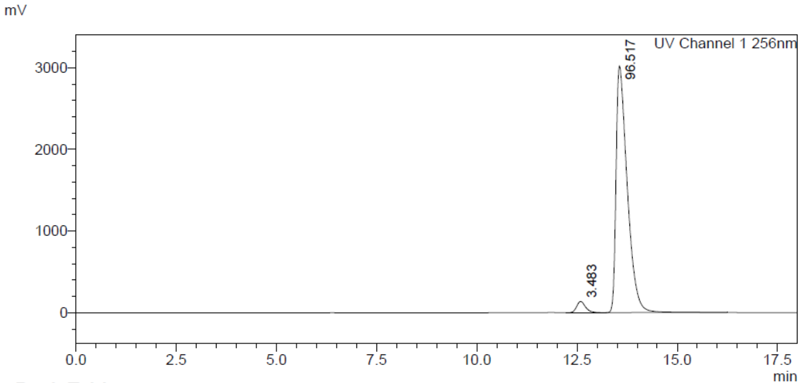


<Peak Table>

UV Channel 1 256nm

Peak#	Ret. Time	Area	Height	Area%
1	12.638	42864565	2535015	49.678
2	13.834	43419868	2300695	50.322
Total		86284433	4835710	100.000

6.3.4.3.8. Chiral HPLC chart of 3.30t:

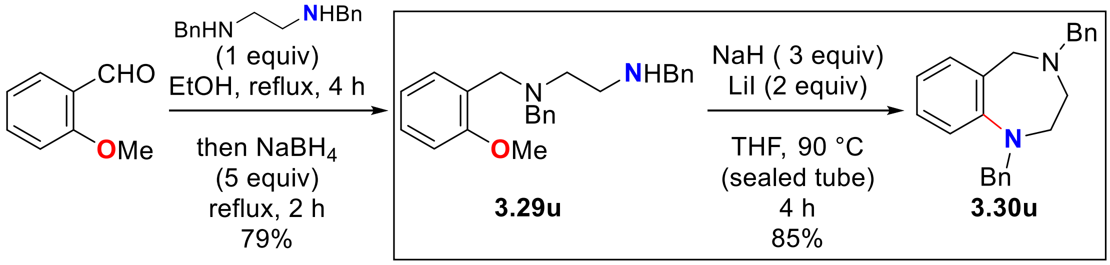


<Peak Table>

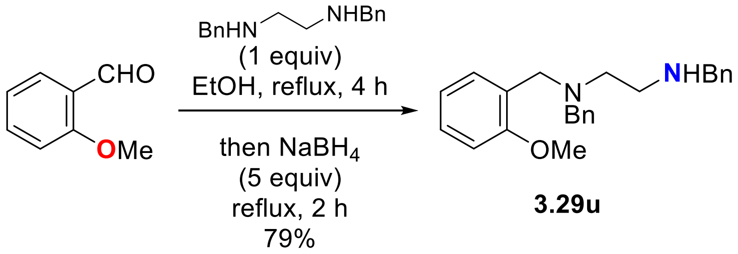
UV Channel 1 256nm

Peak#	Ret. Time	Area	Height	Area%
1	12.588	2121552	137735	3.483
2	13.561	58798729	3020058	96.517
Total		60920281	3157794	100.000

6.3.4.4. Synthesis of 3.30u (Scheme 3.19)



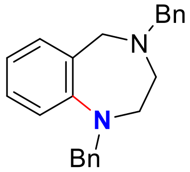
6.3.4.4.1. Synthesis of N^1,N^2-dibenzyl-N^1-(2-methoxybenzyl)ethane-1,2-diamine (3.29u)



To a solution of N^1,N^2-dibenzylethane-1,2-diamine[34] (960 mg, 4.00 mmol) in anhydrous EtOH (15 mL) was added 2-methoxybenzaldehyde (547 mg, 4.02 mmol) at 23 °C under a N_2 atmosphere and the mixture was stirred under reflux conditions for 4 h. With confirmation of full conversion of N^1,N^2-dibenzylethane-1,2-diamine based on ^{1}H NMR analysis, the reaction mixture was then cooled to 0 ºC and $NaBH_4$ (756 mg, 20.0 mmol) was added portion-wise. The reaction mixture was stirred under reflux conditions for 2 h and then cooled to 0 ºC. The mixture was quenched with saturated aqueous NH_4Cl and then basified with 1 M aqueous NaOH. The organic materials were extracted four times with CH_2Cl_2 and the combined extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude material was purified by flash column chromatography (silica gel; hexane : Et_2O= 5: 1 then EtOAc : hexane = 20 : 1) to give **3.29u** (1.14 g, 3.16 mmol) in 79% yield as a pale yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.95 (1H, brs), 2.64 (2H, t, *J* = 5.8 Hz), 2.71 (2H, t, *J* = 5.8 Hz), 3.57 (2H, s), 3.59 (2H, s), 3.62 (2H, s), 3.72 (3H, s), 6.83 (1H, d, *J* = 8.2 Hz), 6.92 (1H, dd, *J* = 7.4, 7.4 Hz), 7.20-7.32 (11H, m), 7.39 (1H, d, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 46.8, 52.4, 53.3, 53.6, 55.2, 59.0, 110.3, 120.3, 126.71, 126.77, 127.6, 128.0, 128.1, 128.2, 128.3, 128.8, 130.4, 140.0, 140.7, 157.8; ESIHRMS: Found: *m/z* 361.2283. Calcd for $C_{24}H_{29}N_2O$: $(M+H)^+$ 361.2280.

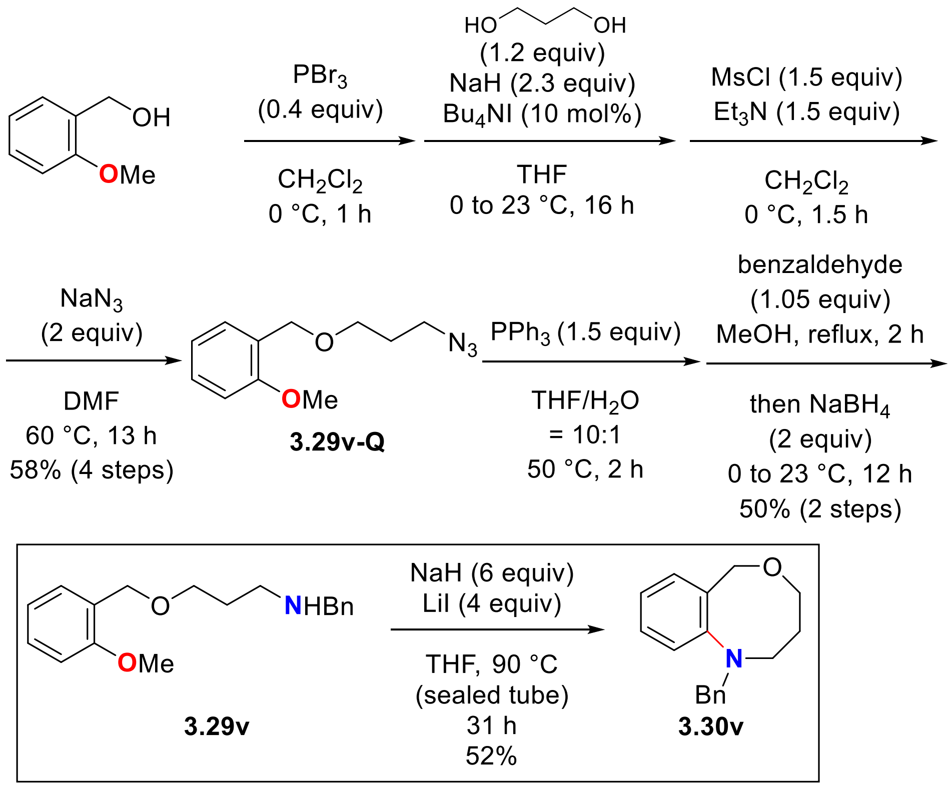
6.3.4.4.2. Synthesis of 1,4-dibenzyl-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepine (3.30u)



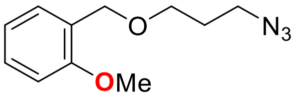
81% yield (80.2 mg, 0.244 mmol) from **3.29u** (109 mg, 0.302 mmol) for 4 h by the typical procedure B (page 195).

Pale yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.76-2.78 (2H, m), 2.97-2.99 (2H, m), 3.59 (2H, s), 3.87 (2H, s), 4.36 (2H, s), 6.87-6.91 (1H, m), 6.99 (1H, d, *J* = 7.6 Hz), 7.03 (1H, dd, *J* = 7.2, 1.6 Hz), 7.19-7.23 (4H, m), 7.27-7.35 (5H, m), 7.42 (2H, d, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 50.5, 56.5, 57.9, 58.7, 58.8, 116.7, 120.8, 126.9, 127.0, 128.0, 128.2, 128.3, 128.4, 129.0, 130.9, 131.0, 139.1, 139.2, 152.5; ESIHRMS: Found: *m/z* 329.2024. Calcd for $C_{23}H_{25}N_2$: $(M+H)^+$ 329.2018.

6.3.4.5. Synthesis of 3.30v (Scheme 3.19)



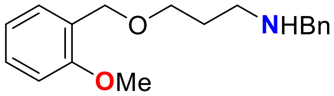
6.3.4.5.1. Synthesis of 1-((3-azidopropoxy)methyl)-2-methoxybenzene (3.29v-Q)



58% yield (1.41 g, 6.38 mmol) from 2-methoxybenzyl alcohol (1.52 g, 11.0 mmol) by the typical procedure G (page 245). For synthesis of **3.29v-Q**, 1,3-propanediol (CAS: 504-63-2) was used instead of ethylene glycol.

Colorless liquid; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.89 (2H, tt, *J* = 6.7, 6.0 Hz), 3.42 (2H, t, *J* = 6.7 Hz), 3.59 (2H, t, *J* = 6.0 Hz), 3.83 (3H, s), 4.55 (2H, s), 6.87 (1H, d, *J* = 8.2 Hz), 6.97 (1H, dd, *J* = 7.4, 7.4 Hz), 7.28 (1H, dd, *J* = 8.2, 7.4 Hz), 7.35 (1H, d, *J* = 7.4 Hz); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 29.2, 48.5, 55.3, 67.0, 67.7, 110.2, 120.4, 126.5, 128.7, 128.8, 157.1; ESIHRMS: Found: *m/z* 222.1242. Calcd for $C_{11}H_{16}N_3O_2$: (M+H)$^+$ 222.1243.

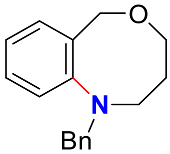
6.3.4.5.2. Synthesis of *N*-benzyl-3-((2-methoxybenzyl)oxy)propan-1-amine (3.29v)



50% yield (912 mg, 3.20 mmol) from **3.29v-Q** (1.41 g, 6.38 mmol) by the typical procedure E (page 207).

Pale-yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.52 (1H, brs), 1.84 (2H, tt, *J* = 6.8, 6.2 Hz), 2.75 (2H, t, *J* = 6.8 Hz), 3.59 (2H, t, *J* = 6.2 Hz), 3.77 (2H, s), 3.79 (3H, s), 4.53 (2H, s), 6.84 (1H, d, *J* = 8.2 Hz), 6.93 (1H, dd, *J* = 7.4, 7.4 Hz), 7.21-7.26 (2H, m), 7.29-7.30 (4H, m), 7.34 (1H, d, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.0, 46.9, 54.0, 55.2, 67.6, 69.1, 110.1, 120.4, 126.7, 126.8, 128.0, 128.3, 128.5, 128.7, 140.5, 157.0; ESIHRMS: Found: *m/z* 286.1803. Calcd for $C_{18}H_{24}NO_2$: $(M+H)^+$ 286.1807.

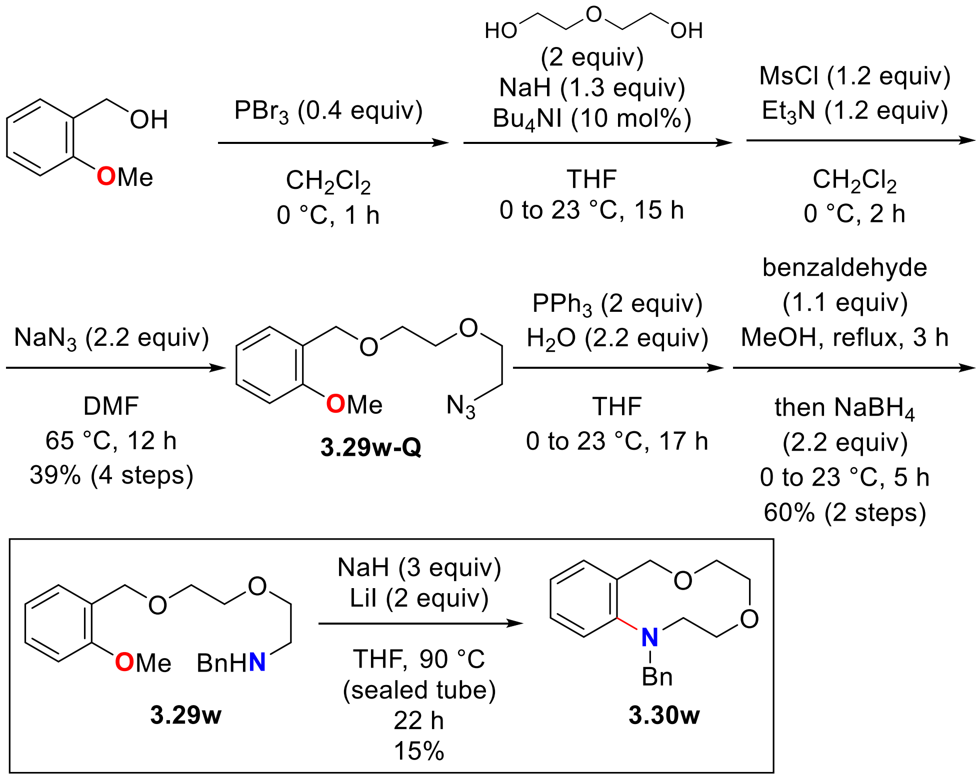
6.3.4.5.3. Synthesis of 1-benzyl-1,3,4,6-tetrahydro-2*H*-benzo[*c*][1,5]oxazocine (3.30v)



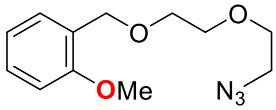
52% yield (54.4 mg, 0.215 mmol) from **3.29v** (117 mg, 0.410 mmol) with 6 equiv of NaH and 4 equiv of LiI for 31 h by the typical procedure B (page 195).

Pale yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.50 (2H, tt, *J* = 6.2, 4.6 Hz), 2.82 (2H, t, *J* = 6.2 Hz), 3.87 (2H, t, *J* = 4.6 Hz), 4.21 (2H, s), 4.75 (2H, s), 7.12 (1H, ddd, *J* = 7.4, 7.3, 1.4 Hz), 7.22-7.25 (1H, m), 7.29-7.37 (5H, m), 7.43-7.45 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.1, 56.8, 60.3, 70.5, 71.3, 122.6, 124.9, 127.0, 128.3, 128.6, 129.5, 130.9, 138.0, 139.5, 150.7; ESIHRMS: Found: *m/z* 254.1540. Calcd for $C_{17}H_{20}NO$: $(M+H)^+$ 254.1545.

6.3.4.6. Synthesis of 3.30w (Scheme 3.19)



6.3.4.6.1. Synthesis of 1-((2-(2-azidoethoxy)ethoxy)methyl)-2-methoxybenzene (3.29w-Q)

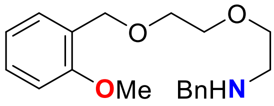


39% yield (967 mg, 3.85 mmol) from 2-methoxybenzyl alcohol (1.38 g, 10.0 mmol) by the typical procedure G (page 245). For synthesis of **3.29w-Q**, diethylene glycol (CAS: 111-46-6) was used instead of ethylene glycol.

Colorless liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.34 (2H, t, *J* = 5.0 Hz), 3.62-3.64 (2H, m + 2H, m + 2H, m), 3.77 (3H, s), 4.56 (2H, s), 6.81 (1H, d, *J* = 8.2 Hz), 6.90

(1H, dd, *J* = 7.4, 7.4 Hz), 7.20 (1H, dd, *J* = 8.2, 7.4 Hz), 7.34 (1H, d, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 50.8, 55.3, 68.0, 69.8, 70.0, 70.7, 110.2, 120.4, 126.6, 128.6, 128.9, 157.1; ESIHRMS: Found: *m/z* 252.1350. Calcd for $C_{12}H_{18}N_3O_3$: $(M+H)^+$ 252.1348.

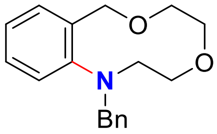
6.3.4.6.2. Synthesis of *N*-benzyl-2-(2-((2-methoxybenzyl)oxy)ethoxy)ethan-1-amine (3.29w)



56% yield (609 mg, 1.93 mmol) from **3.29w-Q** (860 mg, 3.42 mmol) by the typical procedure E (page 207).

Colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.80 (1H, brs), 2.82 (2H, t, *J* = 5.2 Hz), 3.62 (2H, t, *J* = 5.2 Hz), 3.66 (2H, m + 2H, m), 3.80 (2H, s + 3H, s), 4.60 (2H, s), 6.84 (1H, d, *J* = 8.2 Hz), 6.93 (1H, dd, *J* = 7.3, 7.2 Hz), 7.21-7.26 (2H, m), 7.28-7.31 (4H, m), 7.38 (1H, d, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 48.7, 53.9, 55.3, 67.9, 69.6, 70.4, 70.6, 110.2, 120.4, 126.7, 126.8, 128.1, 128.3, 128.5, 128.8, 140.4, 157.1; ESIHRMS: Found: *m/z* 316.1911. Calcd for $C_{19}H_{26}NO_3$: $(M+H)^+$ 316.1913.

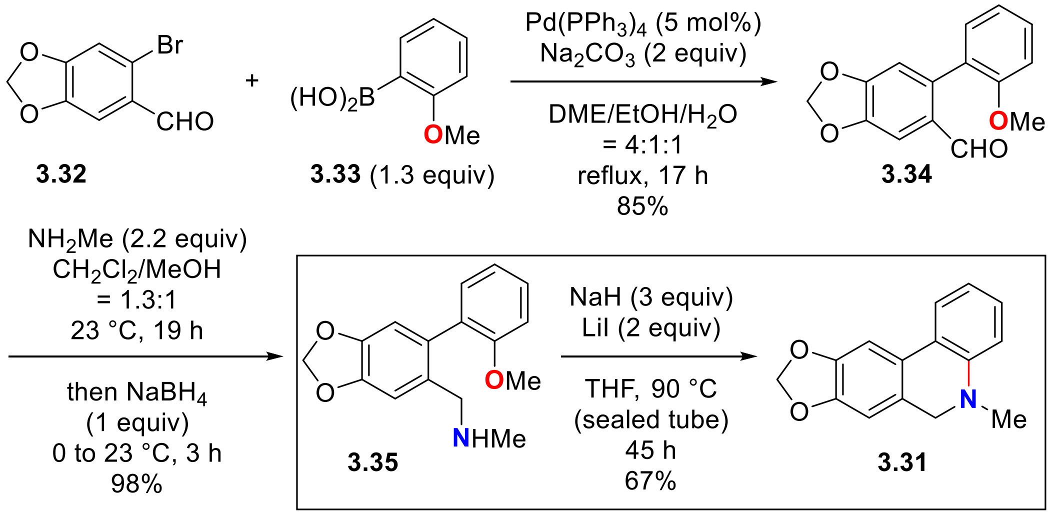
6.3.4.6.3. Synthesis of 1-benzyl-1,2,3,5,6,8-hexahydrobenzo[*h*][1,4,7]dioxazecine (3.30w)



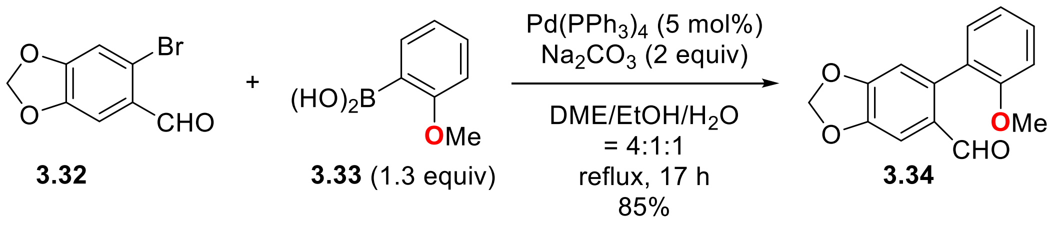
15% yield (16.4 mg, 0.0583 mmol) from **3.29w** (127 mg, 0.402 mmol) for 22 h by the typical procedure B (page 195).

Pale-yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.22 (2H, t, *J* = 4.3 Hz), 3.61 (2H, t, *J* = 4.3 Hz), 3.72 (2H, m + 2H, m), 4.21 (2H, s), 4.92 (2H, s), 7.06 (1H, dd, *J* = 7.4, 7.2 Hz), 7.14 (1H, dd, *J* = 7.3, 7.2 Hz), 7.19-7.23 (2H, m), 7.25-7.27 (1H, m), 7.28-7.31 (4H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 58.3, 58.9, 69.6, 69.8, 71.0, 72.3, 123.3, 124.6, 126.7, 128.1, 128.5, 129.0, 131.2, 136.1, 139.3, 151.3; ESIHRMS: Found: *m/z* 284.1650. Calcd for $C_{18}H_{22}NO_2$: $(M+H)^+$ 284.1651.

6.3.5. Synthesis of 5.6-dihydrobicolorine (3.31) (Scheme 3.20)



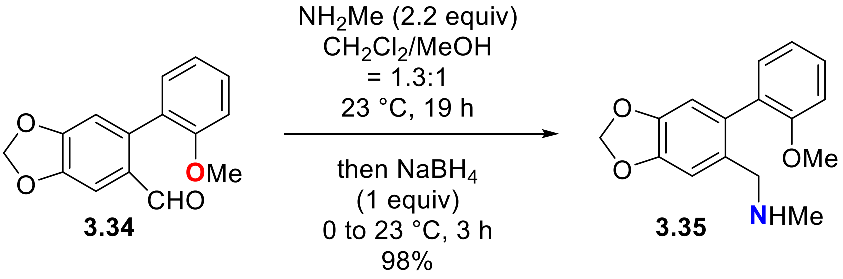
6.3.5.1. Synthesis of 6-bromobenzo[*d*][1,3]dioxole-5-carbaldehyde (3.34)



To a mixture of 6-bromopiperonal (**3.32**) (3.43 g, 15.0 mmol), 2-methoxyphenylboronic acid (**3.33**) (2.99 g, 19.7 mmol), and $Pd(PPh_3)_4$ (882 mg, 0.763 mmol) in degassed DME (50 mL) and EtOH (12 mL) was added Na_2CO_3 (3.14 g, 29.6 mmol) and degassed H_2O (12 mL) at 23 °C under an Ar atmosphere. The resulting mixture was stirred under reflux conditions for 17 h and cooled to 23 °C. After dilution with water and EtOAc, the organic materials were extracted thrice with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude material was purified by recrystallization (Et_2O) to give **3.34** (3.29 g, 12.8 mmol) in 85% yield as a pale-yellow solid.

mp: 146-147 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (3H, s), 6.06 (2H, d, *J* = 5.0 Hz), 6.78 (1H, s), 6.96 (1H, d, *J* = 8.3 Hz), 7.04 (1H, dd, *J* = 7.4, 8.4 Hz), 7.21 (1H, d, *J* = 7.4 Hz), 7.39 (1H, dd, *J* = 8.4, 8.3 Hz), 7.44 (1H, s), 9.57 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.4, 101.9, 105.7, 110.7, 110.8, 120.7, 126.4, 129.0, 129.9, 131.6, 139.2, 147.7, 152.1, 156.6, 190.9; ESIHRMS: Found: m/z 257.0817. Calcd for $C_{15}H_{13}O_4$: $(M+H)^+$ 257.0814.

6.3.5.2. Synthesis of 1-(6-(2-methoxyphenyl)benzo[*d*][1,3]dioxol-5-yl)-*N*-methylmethanamine (3.35)

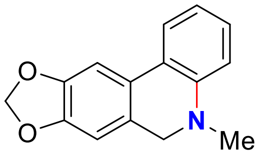


To a solution of **3.34** (1.03 g, 4.02 mmol) in anhydrous MeOH (20 mL) and CH_2Cl_2 (15 mL) was added NH_2Me (0.720 mL, 9.00 mmol, 33wt% in EtOH) under a N_2 atmosphere and the mixture was stirred at 23 ºC for 19 h. With confirmation of full conversion of **3.34** based on ^{1}H NMR analysis, the reaction mixture was then cooled to 0 ºC and $NaBH_4$ (152 mg, 4.02 mmol) was added portion-wise. After stirring at

23 °C for 3 h, The reaction mixture was quenched with saturated aqueous NH_4Cl and basified with 1 M aqueous NaOH. The organic materials were extracted five times with CH_2Cl_2 and the combined extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude material was purified by flash column chromatography (silica gel; EtOAc : hexane = 20 : 1) to give **3.35** (1.07 g, 3.94 mmol) in 98% yield as a brown oil.

^1H NMR (400 MHz, $CDCl_3$) δ 1.80 (1H, brs), 2.26 (3H, s), 3.39-3.49 (2H, m), 3.75 (3H, s), 5.96 (2H, s), 6.66 (1H, s), 6.95 (1H, d, *J* = 8.2 Hz), 6.98 (1H, dd, *J* = 9.1, 7.4 Hz), 6.99 (1H, s), 7.12 (1H, d, *J* = 7.4 Hz), 7.33 (1H, dd, *J* = 9.1, 8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.7, 53.1, 55.4, 101.0, 108.8, 110.3, 110.7, 120.5, 128.7, 129.8, 131.2 (overlapped), 132.1, 146.1, 147.0, 156.6; ESIHRMS: Found: m/z 272.1292. Calcd for $C_{16}H_{18}NO_3$: $(M+H)^+$ 272.1287.

6.3.5.3. Synthesis of 5.6-dihydrobicolorine (3.31)

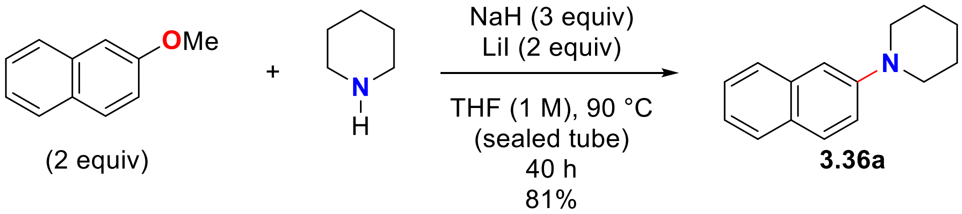


67% yield (80.2 mg, 0.335 mmol) from **3.35** (135 mg, 0.498 mmol) for 45 h by the typical procedure B (page 195).

Pale yellow solid; mp: 90-91 ºC; ^1H NMR (400 MHz, $CDCl_3$) δ 2.89 (3H, s), 4.07 (2H, s), 5.95 (2H, s), 6.62 (1H, s), 6.73 (1H, d, *J* = 8.1 Hz), 6.83-6.87 (1H, m), 7.17-7.21 (2H, m), 7.54 (1H, d, *J* = 7.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.5, 55.1, 100.9, 103.1, 106.1, 112.2, 118.7, 123.0, 123.6, 126.2, 127.2, 128.4, 146.5, 146.7, 147.5; ESIHRMS: Found: m/z 240.1029. Calcd for $C_{15}H_{14}NO_2$: $(M+H)^+$ 240.1025.

6.3.6. Intermolecular amination of methoxy arenes (Scheme 3.21)

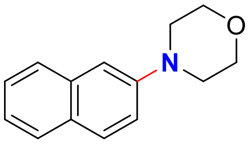
6.3.6.1. Intermolecular amination of methoxy arenes: synthesis of 1-(naphthalen-2-yl)piperidine (3.36a)[35] (Typical procedure H)



To a 10 mL sealed tube containing 2-methoxynaphthalene (CAS: 93-04-9) (158 mg, 1.00 mmol), NaH (63.1 mg, 1.57 mmol), and LiI (134 mg, 1.00 mmol) was added a solution of piperidine (CAS: 110-89-4) (42.5 mg, 0.499 mmol) in THF (0.5 mL) at 0 °C under a N_2 atmosphere. The tube was sealed and the solution was then stirred at 90 °C for 40 h. The reaction mixture was quenched with cold water at 0 °C and the solvent was removed *in vacuo*. After dilution with 1M aqueous HCl, the aqueous layer was washed twice with Et_2O. The aqueous layer was basified with 15% aqueous NaOH and the organic materials were extracted four times with CH_2Cl_2. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude material was purified by flash column chromatography (hexane : EtOAc =70:1) to yield **3.36a** (85.3 mg, 0.404 mmol) in 81% yield as a pale yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.57-1.62 (2H, m), 1.71-1.77 (4H, m), 3.23 (4H, t, J = 5.6 Hz), 7.10 (1H, d, J = 2.3 Hz), 7.23-7.28 (2H, m), 7.34-7.38 (1H, m), 7.65-7.69 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.3, 25.9, 51.0, 110.3, 120.1, 123.0, 126.0, 126.6, 127.3, 128.3, 128.4, 134.7, 150.1.

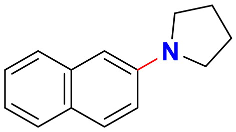
6.3.6.2. Synthesis of 4-(naphthalen-2-yl)morpholine (3.36b)[35]



69% yield (73.4 mg, 0.344 mmol) from 2-methoxynaphthalene (158 mg, 0.999 mmol) and morpholine (CAS: 110-91-8) (43.7 mg, 0.502 mmol) for 40 h by the typical procedure H (page 263).

White solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.25 (4H, t, *J* = 4.9 Hz), 3.90 (4H, t, *J* = 4.9 Hz), 7.10 (1H, d, *J* = 2.3 Hz), 7.24 (1H, dd, *J* = 9.0, 2.5 Hz), 7.27-7.32 (1H, m), 7.37-7.43 (1H, m), 7.68-7.75 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 49.8, 66.9, 110.1, 118.9, 123.5, 126.3, 126.7, 127.4, 128.7, 128.8, 134.5, 149.1.

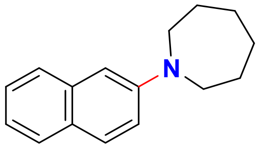
6.3.6.3. Synthesis of 1-(naphthalen-2-yl)pyrrolidine (3.36c)[35]



78% yield (77.1 mg, 0.391 mmol) from 2-methoxynaphthalene (158 mg, 1.00 mmol) and pyrrolidine (CAS: 123-75-1) (35.5 mg, 0.499 mmol) for 40 h by the typical procedure H (page 263). The acidic extracts also included **3.36c**, which was purified by the flash column chromatography and the yield was calculated by combined mass with **3.36c** obtained from the basic extracts.

White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.02-2.05 (4H, m), 3.37-3.40 (4H, m), 6.74 (1H, d, *J* = 2.0 Hz), 6.98 (1H, dd, *J* = 8.9, 2.4 Hz), 7.12-7.16 (1H, m), 7.31-7.35 (1H, m), 7.61 (1H, d, *J* = 8.3 Hz), 7.65-7.69 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.5, 47.8, 104.6, 115.7, 121.1, 125.7, 126.1, 126.2, 127.6, 128.7, 135.2, 145.9.

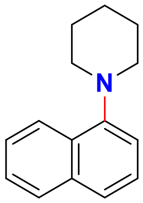
6.3.6.4. Synthesis of 1-(naphthalen-2-yl)azepane (3.36d)[36]



83% yield (94.1 mg, 0.417 mmol) from 2-methoxynaphthalene (158 mg, 1.00 mmol) and hexamethyleneimine (CAS: 111-49-9) (49.6 mg, 0.500 mmol) for 40 h by the typical procedure H (page 263). The acidic extracts also included **3.36d**, which was purified by the flash column chromatography and the yield was calculated by combined mass with **3.36d** obtained from the basic extracts.

Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.53-1.57 (4H, m), 1.84 (4H, m), 3.57 (4H, t, *J* = 5.9 Hz), 6.86 (1H, s), 7.09-7.15 (2H, m), 7.30-7.34 (1H, m), 7.59 (1H, d, *J* = 8.3 Hz), 7.63-7.67 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.0, 27.8, 49.5, 104.5, 115.1, 121.2, 125.8, 126.06, 126.11, 127.4, 128.8, 135.4, 146.8.

6.3.6.5. Synthesis of 1-(naphthalen-1-yl)piperidine (3.36e)[37]

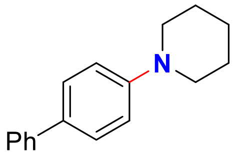


45% yield (46.1 mg, 0.218 mmol) from 1-methoxynaphthalene (CAS: 2216-69-5) (163 mg, 1.03 mmol) and piperidine (41.6 mg, 0.489 mmol) for 40 h by the typical procedure H (page 263).

Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.65 (2H, m), 1.81-1.86 (4H, m), 3.04 (4H, m), 7.04 (1H, d, *J* = 7.1 Hz), 7.35-7.48 (3H, m), 7.50 (1H, d, *J* = 8.2 Hz), 7.78-7.81

(1H, m), 8.18-8.20 (1H, m); ^{13}C NMR (100 MHz, CDCl$_3$): δ 24.6, 26.6, 54.6, 114.4, 122.9, 123.8, 125.1, 125.6, 125.8, 128.3, 129.1, 134.7, 151.1.

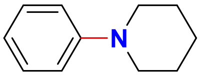
6.3.6.6. Synthesis of 1-([1,1'-biphenyl]-4-yl)piperidine (3.36f)[38]



61% yield (71.8 mg, 0.303 mmol) from 4-methoxybiphenyl (CAS: 613-37-6) (182 mg, 0.989 mmol) and piperidine (42.4 mg, 0.498 mmol) for 40 h by the typical procedure H (page 263).

White solid; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.56-1.61 (2H, m), 1.69-1.74 (4H, m), 3.20 (4H, t, *J* = 5.4 Hz), 6.99 (2H, d, *J* = 8.7 Hz), 7.26 (1H, t, *J* = 7.4 Hz), 7.39 (2H, dd, *J* = 7.3, 7.4 Hz), 7.49 (2H, d, *J* = 8.7 Hz), 7.55 (2H, d, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 24.3, 25.8, 50.4, 116.4, 126.2, 126.4, 127.6, 128.6, 131.6, 141.0, 151.4.

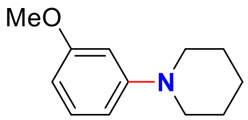
6.3.6.7. 1-phenylpiperidine (3.36g)[39]



41% yield (32.8 mg, 0.203 mmol) from anisole (CAS: 100-66-3) (109 mg, 1.01 mmol) and piperidine (42.2 mg, 0.496 mmol) for 40 h by the typical procedure H (page 263).

Pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.54-1.60 (2H, m), 1.67-1.74 (4H, m), 3.15 (4H, t, *J* = 5.5 Hz), 6.81 (1H, t, *J* = 7.3 Hz), 6.94 (2H, d, *J* = 7.9 Hz), 7.24 (2H, dd, *J* = 7.9, 7.3 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 24.3, 25.9, 50.7, 116.5, 119.2, 129.0, 152.3.

6.3.6.8. 1-(3-methoxyphenyl)piperidine (3.36h)[40]

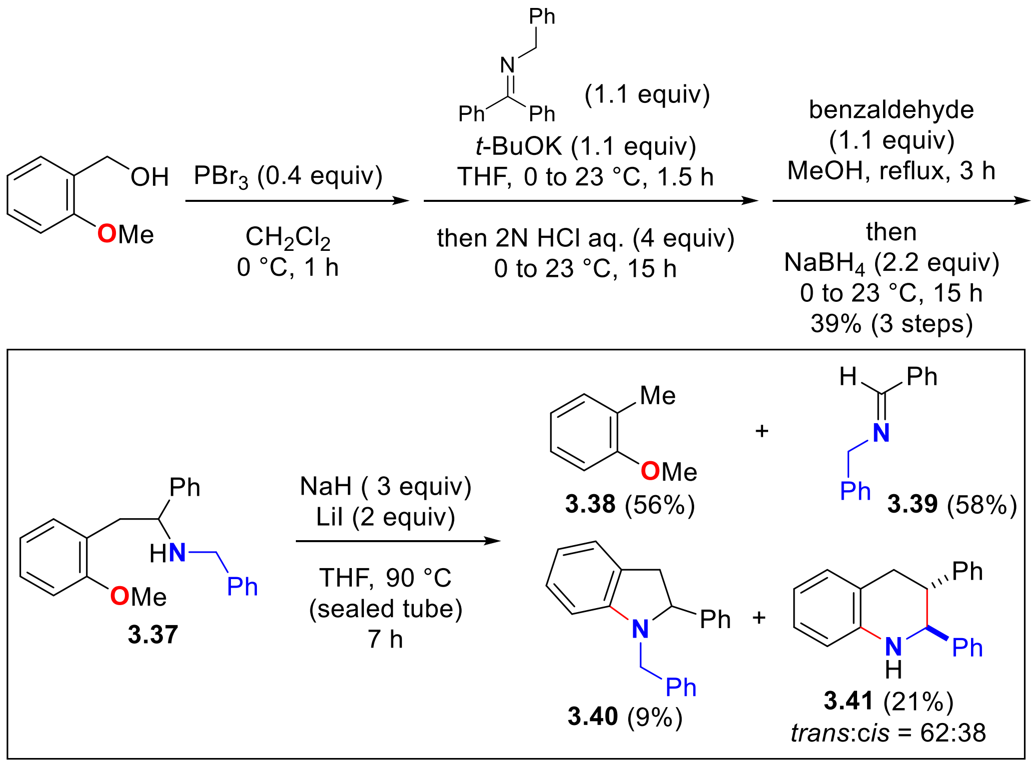


74% yield (69.6 mg, 0.364 mmol) from 1,3-Dimethoxybenzene (CAS: 151-10-0) (141 mg, 1.02 mmol) and piperidine (41.8 mg, 0.491 mmol) for 40 h by the typical procedure H (page 263).

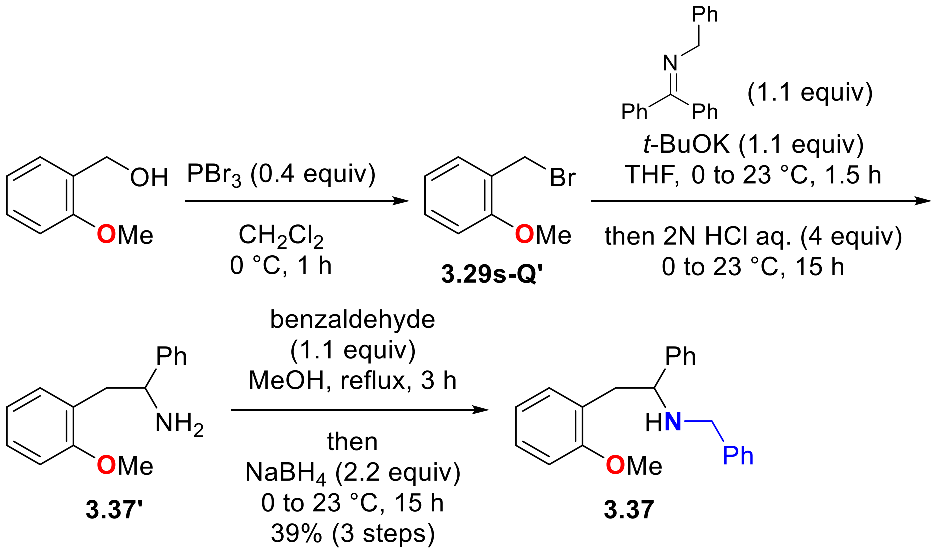
Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54-1.60 (2H, m), 1.66-1.72 (4H, m), 3.15 (4H, t, *J* = 5.4 Hz), 3.78 (3H, s), 6.37 (1H, dd, *J* = 8.1,2.2 Hz), 6.47 (1H, dd, *J* = 2.2, 2.0 Hz), 6.55 (1H, dd, *J* = 8.2, 2.0 Hz), 7.14 (1H, dd, *J* = 8.2, 8.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.3, 25.8, 50.5, 55.1, 102.7, 103.9, 109.3, 129.6, 153.6, 160.5.

6.3.7. Retro-Mannich reaction and skeletal rearrangement (Scheme 3.22-3.24)

6.3.7.1. The reaction of 3.37 (Scheme 3.22a)



6.3.7.1.1. Synthesis of *N*-benzyl-2-(2-methoxyphenyl)-1-phenylethan-1-amine (3.37)



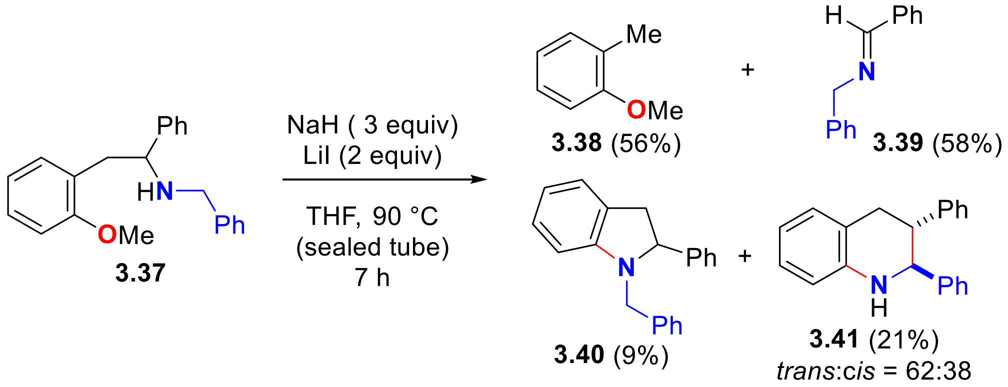
To an ice cold solution of 2-methoxybenzyl alcohol (707 mg, 5.12 mmol) in CH_2Cl_2 (20 mL) was added dropwise a solution of phosphorus tribromide (0.20 mL, 2.20 mmol) in CH_2Cl_2 (10 mL) under a N_2 atmosphere. The reaction mixture was stirred for 1 h at 0 °C and quenched with saturated aqueous Na_2CO_3 solution. The organic materials were extracted thrice with CH_2Cl_2 and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude material including benzyl bromide **3.29s-Q'** were used immediately for the next step without further purification.

To an ice cold solution of *N*-benzyl-1,1-diphenylmethanimine[41] (1.19 g, 4.38 mmol) in THF (30 mL) was added *t*-BuOK (491 mg, 4.38 mmol) portion-wise under a N_2 atmosphere. The reaction mixture was stirred at 0 °C for 5 min and then a solution of crude bromide **3.29s-Q'** in THF (10 mL) was added dropwise at 0 °C. After stirring at 0 °C for 1 h, the solvent was removed *in vacuo*. After addition of 2M aqueous HCl (8 mL) at 0 °C, the reaction mixture was gradually warmed to 23 °C. After completion of the reaction, the mixture was diluted with Et_2O and 1M aqueous HCl solution and the aqueous layer was washed five times with Et_2O. The aqueous layer was basified with 2M aqueous NaOH solution and the organic layer was extracted five times with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude material including amine **3.37’** was used immediately for the next step without further purification.

To a solution of crude amine **3.37’** in anhydrous MeOH (10 mL) was added benzaldehyde (426 μL, 4.18 mmol) under a N_2 atmosphere and the mixture was stirred under reflux conditions for 3 h. With confirmation of full conversion of amine **3.37’** based on ^1H NMR analysis, the reaction mixture was then cooled to 0 ºC and $NaBH_4$ (316 mg, 8.36 mmol) was added portion-wise. After stirring at 23 °C for 13 h, the reaction mixture was quenched with saturated aqueous NH_4Cl solution and then basified with 1 M aqueous NaOH solution. The organic materials were extracted thrice with EtOAc and the combined extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude material was purified by flash column chromatography (silica gel; hexane:EtOAc = 95 : 5) to give **3.37** (638 mg, 2.01 mmol) in 39% yield based on 2-methoxybenzyl alcohol as a colorless oil.

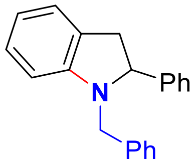
^1H NMR ($CDCl_3$, 400 MHz) δ 1.75 (1H, brs), 2.94 (2H, d, J = 6.9 Hz) 3.47 (1H, d, J = 13.6 Hz), 3.67 (1H, d, J = 13.6 Hz), 3.72 (3H, s), 3.95 (1H, t, J = 6.9 Hz), 6.79-6.83 (2H, m), 6.98 (1H, d, J = 7.7 Hz), 7.10 (2H, d, J = 7.0 Hz), 7.16-7.25 (5H, m), 7.31 (2H, dd, J = 7.6, 7.2 Hz), 7.36 (2H, d, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 39.8, 51.4, 55.2, 61.9, 110.3, 120.3, 126.5, 126.8, 127.3, 127.4, 127.6, 127.8, 128.16, 128.18, 131.0, 140.8, 144.4, 157.8; ESIHRMS: Found: m/z 318.1854. Calcd for $C_{22}H_{24}NO$: $(M+H)^+$ 318.1858.

6.3.7.1.2. The reaction of 3.37



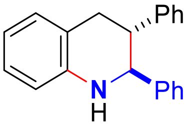
The reaction was performed by typical procedure B (page 195) from **3.37** (132 mg, 0.416 mmol) for 7 h. The resulting crude material was analyzed by ^{1}H NMR spectroscopy with 1,1,2,2-tetrachloroethane (20 µL) as an internal standard, that indicated 56% crude NMR yield of **3.38** (CAS:578-58-5), 58% crude NMR yield of **3.39** (CAS:780-25-6), 9% crude NMR yield of **3.40**, and 21% crude NMR yield of **3.41** (*trans*:*cis* = 62:38). Isolations of **3.40** and **3.41** were conducted by preparative TLC and GPC (Gel Permeation Chromatography) for characterization.

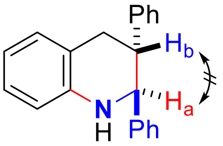
1-benzyl-2-phenylindoline (3.40)[42]



Pale yellow oil; ^{1}H NMR (500 MHz, CDCl$_3$) δ 3.06 (1H , dd, *J* = 15.7, 10.3 Hz), 3.42 (1H, dd, *J* = 15.7, 9.6 Hz), 3.98 (1H, d, *J* = 15.8 Hz), 4.41 (1H, d, *J* = 15.8 Hz), 4.89 (1H, t, *J* = 9.8 Hz), 6.44 (1H, d, *J* = 7.8 Hz), 6.72 (1H, dd, *J* = 7.5, 7.2 Hz), 7.07 (1H, dd, *J* = 7.8, 7.5 Hz), 7.10 (1H, d, *J* = 7.2 Hz), 7.23-7.33 (6H, m), 7.36-7.39 (2H, m), 7.47 (1H, d, *J* = 8.5 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ 39.4, 50.9, 69.3, 107.4, 117.9, 124.1, 126.8, 127.5, 127.56 (overlapped), 127.64, 128.3, 128.4, 128.5, 138.3, 142.5, 152.3.

(2*S**,3*R**)-2,3-diphenyl-1,2,3,4-tetrahydroquinoline (3.41-*trans*)

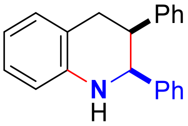


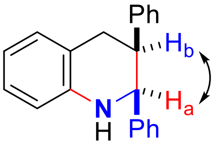


No NOESY correlation (between H_a and H_b)

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.00 (1H , dd, J = 15.6, 4.1 Hz), 3.08-3.15 (1H, m), 3.22 (1H, dd, J = 15.6, 11.2 Hz), 4.18 (1H, brs), 4.45 (1H, d, $J_{Ha\text{-}Hb}$ = 9.2 Hz), 6.57 (1H, d, J = 8.2 Hz), 6.67 (1H, dd, J = 7.4, 7.4 Hz), 6.98-7.00 (2H, m), 7.03-7.16 (10H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.9, 46.4, 62.5, 113.4, 117.0, 121.1, 126.4, 127.1, 127.4, 127.5, 128.0, 128.1, 128.2, 129.0, 142.61, 142.63, 144.2; ESIHRMS: Found: *m/z* 286.1599. Calcd for $C_{21}H_{20}N$: $(M+H)^+$ 286.1596. The relative *trans* configuration was assigned by the NOESY experiment and the coupling constant between H_a and H_b.[43]

(2*S**,3*S**)-2,3-diphenyl-1,2,3,4-tetrahydroquinoline (3.41-*cis*)



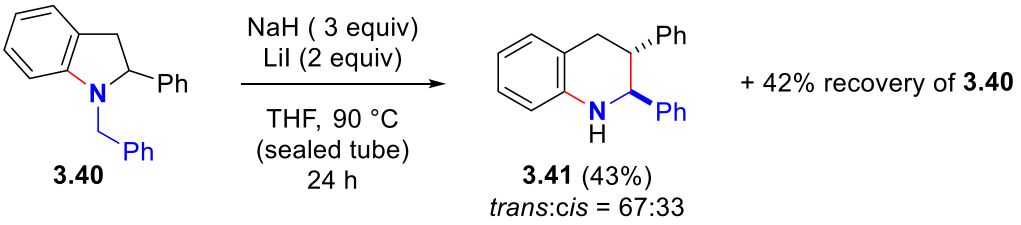


NOESY correlation (between H_a and H_b)

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.06-3.07 (1H, m + 1H , m), 3.52-3.55 (1H, m), 4.34 (1H, brs), 4.72 (1H, d, $J_{Ha\text{-}Hb}$ = 4.0 Hz), 6.62 (1H, d, J = 7.8 Hz), 6.71 (1H, ddd, J = 7.4, 7.4, 1.0 Hz), 6.78-6.82 (4H, m), 7.07-7.24 (8H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.6, 43.4, 60.3, 113.6, 117.2, 120.5, 126.4, 127.1, 127.2, 127.5, 127.6, 127.7, 128.7, 129.5, 141.2, 141.7, 144.3; ESIHRMS: Found: *m/z* 286.1597.

Calcd for $C_{21}H_{20}N$: $(M+H)^+$ 286.1596. The relative *cis* configuration was assigned by the NOESY experiment and the coupling constant between H_a and H_b.[43]

6.3.7.2. The control experiment of indoline 3.40

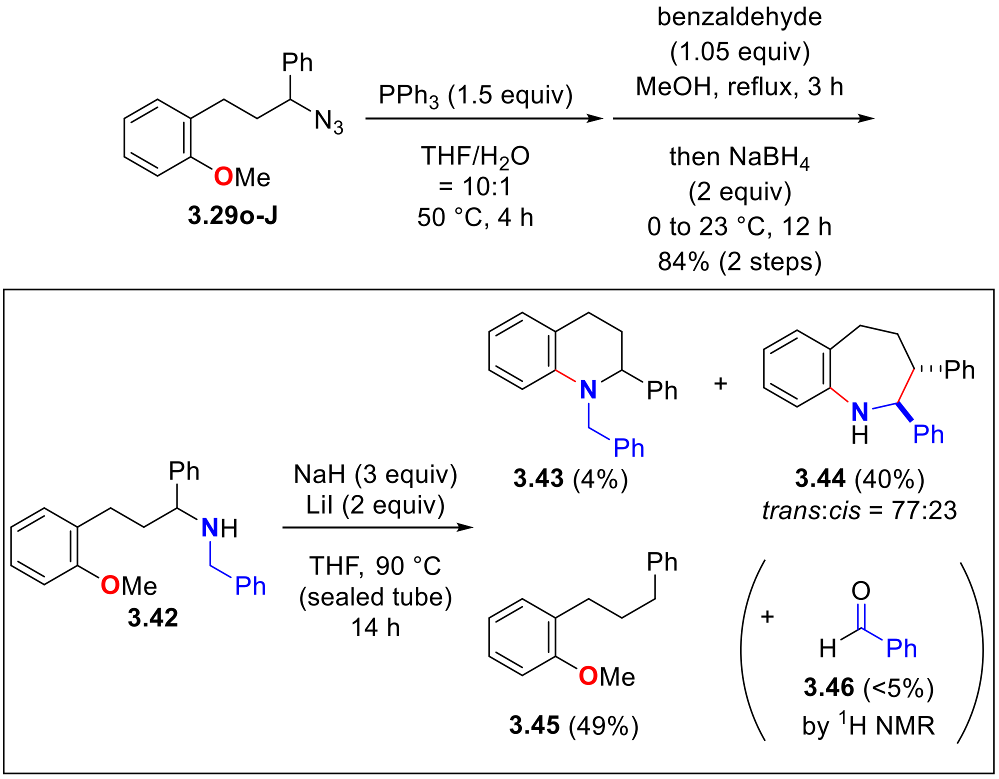


3.40

3.41 (43%)
trans:*cis* = 67:33

The reaction was performed by the typical procedure B (page 195) from **3.40** (148 mg, 0.520 mmol) for 24 h. The crude material was then analyzed by ^{1}H NMR with 1,1,2,2-tetrachloroethane (20 μL) as an internal standard to give 43% crude NMR yield of **3.41** (*trans*/*cis* = 67:33) and 42% crude NMR recovery of **3.40**.

6.3.7.3. The reaction of 3.42 (Scheme 3.23a)



3.29o-J

3.42

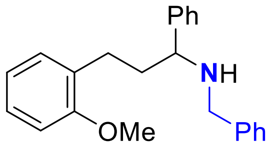
3.43 (4%)

3.44 (40%)
trans:*cis* = 77:23

3.45 (49%)

3.46 (<5%)

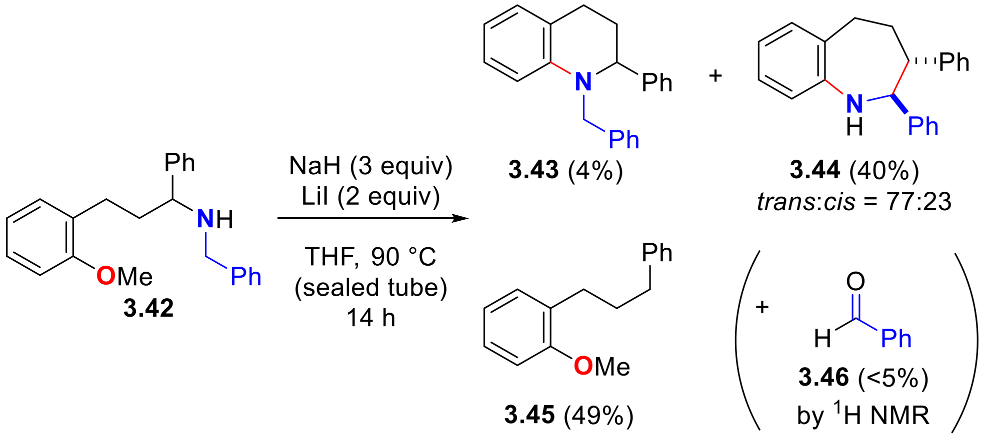
6.3.7.3.1. Synthesis of *N*-benzyl-3-(2-methoxyphenyl)-1-phenylpropan-1-amine (3.42)



84% yield (1.43 g 4.31 mmol) from **3.29o-J** (1.37 g, 5.13 mmol) by the typical procedure E (page 207).

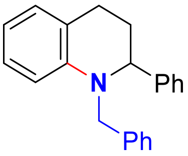
Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.69 (1H, brs), 1.88-2.06 (2H, m), 2.48-2.56 (1H, m), 2.58-2.66 (1H, m), 3.53 (1H, d, *J* = 13.1 Hz), 3.62-3.66 (1H, d, *J* = 13.1 Hz + 1H, m), 3.74 (3H, s), 6.78 (1H, d, *J* = 8.2 Hz), 6.81-6.85 (1H, m), 7.03 (1H, d, *J* = 7.3 Hz), 7.12-7.16 (1H, m), 7.19-7.34 (10H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.0, 38.1, 51.5, 55.1, 62.3, 110.1, 120.3, 126.7, 126.87, 126.92, 127.4, 128.1, 128.25, 128.29, 129.7, 130.4, 140.8, 144.3, 157.3; ESIHRMS: Found: m/z 332.2016. Calcd for $C_{23}H_{26}NO$: $(M+H)^+$ 332.2014.

6.3.7.3.2. The reaction of 3.42



The reaction was conducted using **3.42** (164 mg, 0.495 mmol) for 14 h by the typical procedure B (page 195). We observed formation of benzaldehyde (**3.46**) (<5% yield) in the crude material by ^{1}H NMR analysis with 1,1,2,2-tetrachloroethane as an internal standard.

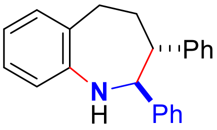
1-benzyl-2-phenyl-1,2,3,4-tetrahydroquinoline (3.43)[42]



4% yield (determined by crude ^{1}H-NMR using 1,1,2,2-tetrachloroethane as an internal standard). Authentic sample of **3.43** was prepared by the reported procedure.[42]

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.06-2.12 (1H, m), 2.25-2.34 (1H, m), 2.60-2.64 (2H, m), 4.23 (1H, d, J = 17.2 Hz), 4.69-4.73 (1H, d, J = 17.2 Hz + 1H, m), 6.56 (1H, d, J = 8.1 Hz), 6.59-6.63 (1H, m), 6.97-7.04 (2H, m), 7.17-7.32 (10H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.5, 29.4, 52.8, 61.2, 110.3, 115.6, 122.1, 126.3, 126.70, 126.71, 126.9, 127.4, 128.4, 128.6, 128.8, 138.6, 144.0, 145.1.

(2*S**,3*R**)-2,3-diphenyl-2,3,4,5-tetrahydro-1H-benzo[b]azepine (3.44-*trans*)

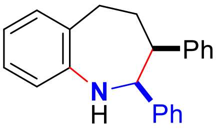


[X-ray]

31% yield (46.3 mg, 0.155 mmol).

Colorless crystal (recrystallization from CH_2Cl_2/hexane: CCDC 1554977); mp: 127-128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.78-1.88 (1H, m), 2.19-2.25 (1H, m), 2.94 (1H, dd, J = 14.1, 6.9 Hz), 3.03-3.15 (2H, m), 3.76 (1H, brs), 3.93 (1H, d, J = 10.2 Hz), 6.76 (1H, d, J = 7.7 Hz), 6.87 (2H, d, J = 7.8 Hz), 6.92-6.99 (2H, m), 7.01-7.16 (8H, m), 7.19 (1H, d, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.4, 34.9, 55.4, 68.7, 120.4, 121.9, 125.7, 126.9, 127.1, 127.4, 127.8, 127.9, 128.1, 130.1, 134.5, 143.9, 144.6, 148.8; ESIHRMS: Found: m/z 300.1755. Calcd for $C_{22}H_{22}N$: $(M+H)^+$ 300.1752.

(2*S,3*S**)-2,3-diphenyl-2,3,4,5-tetrahydro-1H-benzo[b]azepine (3.44-*cis*)**

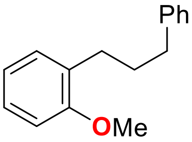


[X-ray]

9% yield (13.3 mg, 0.0444 mmol).

Colorless crystal (recrystallization from CH_2Cl_2/hexane: CCDC 1554978); mp: 149-150 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 2.16-2.23 (1H, m), 2.41-2.50 (1H, m), 3.07 (1H, dd, *J* = 15.8, 8.3 Hz), 3.17-3.26 (2H, m), 3.84 (1H, brs), 4.89 (1H, d, *J* = 3.9 Hz), 6.62 (1H, d, *J* = 7.8 Hz), 6.79-6.82 (1H, m), 6.84-6.87 (3H, m), 7.01-7.05 (1H, m), 7.06-7.13 (7H, m), 7.20-7.22 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.7, 32.2, 51.8, 65.0, 118.6, 119.8, 126.2, 126.7, 126.8, 127.1, 127.6, 127.8, 129.2, 129.5, 131.3, 142.1, 142.4, 148.9; ESIHRMS: Found: m/z 300.1756. Calcd for $C_{22}H_{22}N$: $(M+H)^+$ 300.1752.

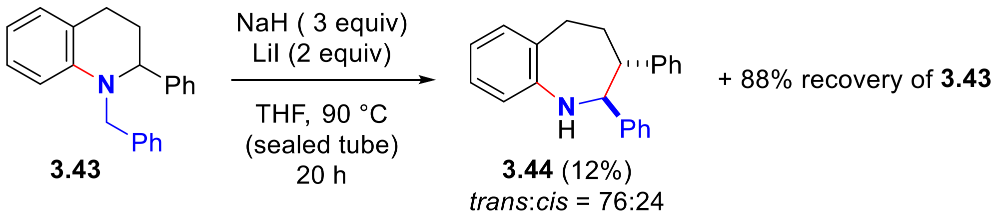
1-methoxy-2-(3-phenylpropyl)benzene (3.45)[44]



49% yield (54.6 mg, 0.241 mmol).

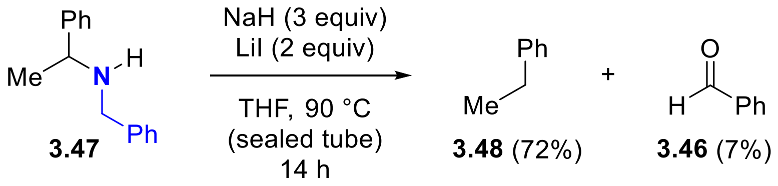
Colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 1.88-1.96 (2H, m), 2.64-2.68 (4H, m), 3.79 (3H, s), 6.82 (1H, d, *J* = 8.0 Hz), 6.85-6.89 (1H, m), 7.10-7.20 (5H, m), 7.24-7.28 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.9, 31.3, 35.7, 55.2, 110.2, 120.3, 125.6, 126.9, 128.2, 128.4, 129.8, 130.7, 142.6, 157.5.

6.3.7.4. The control experiment of tetrahydroquinoline 3.43



Reaction was performed by typical procedure B (page 195) from **3.43** (89.1 mg, 0.298 mmol) for 20 h. The crude material was then analyzed by ^{1}H NMR with 1,1,2,2-tetrachloroethane (30 μL) as an internal standard to give 12% crude NMR yield of **3.44** (*trans*/*cis* = 76:24) and 88% crude NMR recovery of **3.43**.

6.3.7.5. The control experiment to investigate a reaction pathway of the C-N bond cleavage to afford alkane 3.45



The reaction was performed by typical procedure B (page 195) from *N*-benzyl-1-phenylethan-1-amine (**3.47**) (105 mg, 0.497 mmol), which was prepared by the reported procedure,[45] for 14 h. We observed the formation of ethylbenzene (**3.48**) and benzaldehyde (**3.46**) in 72% and 7% yields, respectively, analyzed by ^{1}H NMR analysis with 1,1,2,2-tetrachloroethane (20 μL) as an internal standard, along with a mixture of unidentified compounds.

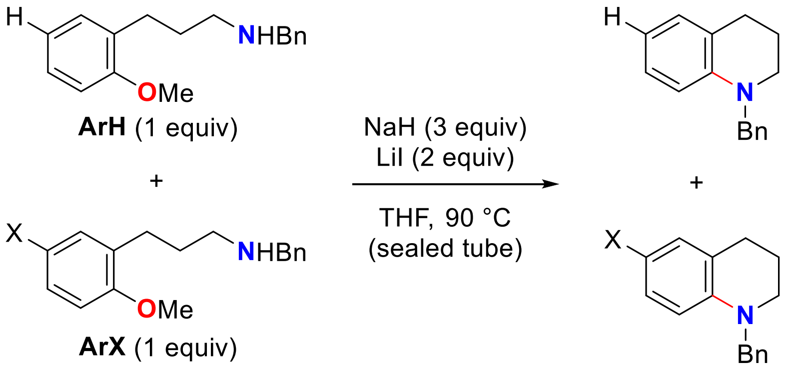
_N_-benzyl-1-phenylethan-1-amine (3.47)

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (3H, d, *J* = 6.6 Hz), 1.62 (1H brs), 3.58 (1H, d, *J* = 13.2 Hz), 3.66 (1H, d, *J* = 13.2 Hz), 3.80 (1H, q, *J* = 6.6 Hz), 7.20-7.37 (10H, m);

^{13}C NMR (75 MHz, $CDCl_3$) δ 24.4, 51.6, 57.5, 126.7, 126.8, 126.9, 128.1, 128.3, 128.4, 140.6, 145.6.

6.3.8. Linear free energy correlation of log(k_X/k_H) against σ_p plot

Procedure for competition reactions



To a 25 mL sealed tube containing NaH (0.600 mmol) and LiI (0.400 mmol) in THF (0.5 mL) was added a solution of ArH (0.200 mmol), ArX (0.200 mmol) and dodecane (45.4 μL, 0.200 mmol) in THF (1.5 mL) at 0 °C under a N_2 atmosphere. The molar ratio of NaH:LiI:ArH:ArX was 3:2:1:1. The tube was sealed and the solution was then stirred at 90 °C. The reactions were monitored by GC analysis. After conversion of both of the substrates was ceased (when k_x and k_H were reached to 0), yields of the corresponding products were calculated based on GC analysis with dodecane as an internal standard. The relative rates (k_x/k_H) were calculated from the yields of the corresponding products.

6.3.9. Computational details

6.3.9.1. Computational method

All calculations were carried with the Gaussian 09 program package. The molecular structures and harmonic vibrational frequencies were obtained using the hybrid density functionals based on Becke's three-parameter exchange function and the Lee-Yang-Parr nonlocal correlation functional (B3LYP).[5,46] We used 6–31+G* basis set. We used an additional Integral keyword to specify an ultrafine grid. All stationary points were optimized without any symmetry assumptions, and characterized by normal coordinate analysis at the B3LYP/6-31+G* of theory (number of imaginary frequencies, NIMAG, 0 for minima and 1 for TSs). The intrinsic reaction coordinate (IRC) method was used to track minimum energy paths from transition structures to the corresponding local minima.[47] The self-consistent reaction field (SCRF) method based on the Polarizable Continuum Model (PCM)[8,48] was employed to evaluate the solvent reaction field (THF; $\varepsilon = 7.58$).

6.3.9.2. Reaction pathways: the effects of coordination of solvent molecules

All calculations were performed at B3LYP/6-31+G* level of theory. The bulk solvent effect of THF was described with an implicit model (SCRF (solvent = THF, PCM)). The reaction proceeds *via* a concerted nucleophilic aromatic substitution mechanism with a reasonal activation barrier (17.5 kcal/mol) without coordination of THF (Figure 6.1). When two molecules of THF were included explicitly, the activation barrier is found to be slightly lowered (14.7 kcal/mol, Figure 3.2).

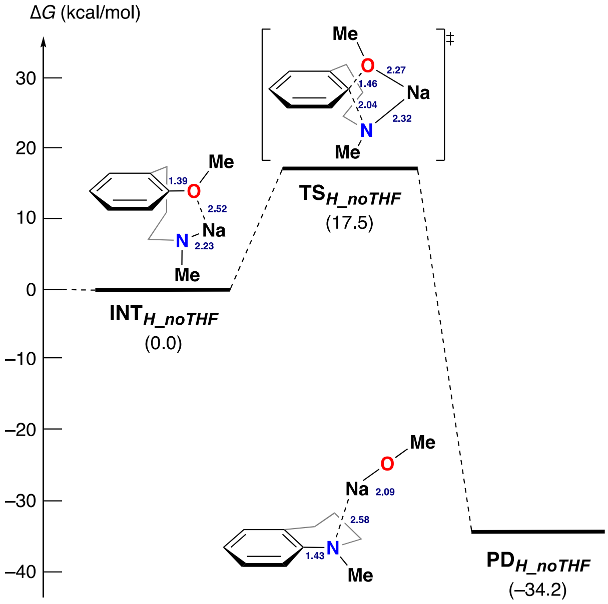


Figure 6.1. Reaction pathways of the nucleophilic amination with methoxy arenes (model for N-methyl tetrahydroquinoline) without consideration of the effects of THF. Energy changes and bond lengths at the B3LYP/6-31+G* level of theory (SCRF (pcm, solvent = THF)) are shown in kcal/mol and Å, respectively.

6.3.9.3. Coordination of NaI derived from NaH-LiI composite

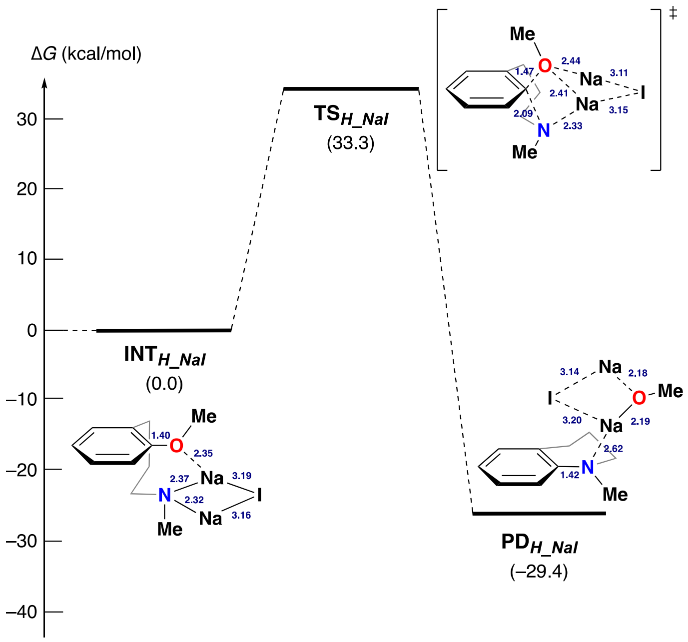
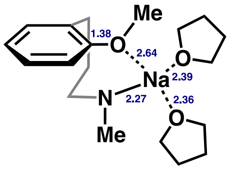


Figure 6.2. Reaction pathways of the nucleophilic amination with methoxy arenes in the composite with NaI. Energy changes and bond lengths at the B3LYP/6-31+G* level of theory (SCRF (pcm, solvent = THF)) are shown in kcal/mol and Å, respectively.

6.3.9.4. Cartesian coordinates and energies



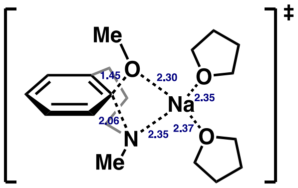
INT$_H$

Energy(RB3LYP): -1186.03814856 A.U.

Gibbs Free Energy: -1185.619285 A.U.

C	3.863347	1.575484	-0.909719
C	2.651160	1.144193	-1.461711
C	2.205062	-0.160995	-1.230707
C	2.964042	-1.073040	-0.467150
C	4.171079	-0.606936	0.069686
C	4.624383	0.701764	-0.134793
H	4.201101	2.592883	-1.090639
H	2.060165	1.831605	-2.057424
H	4.776168	-1.296162	0.654576
H	5.566902	1.026035	0.298535
C	2.559294	-2.523311	-0.292271
C	1.354470	-2.854582	0.623401
H	2.353722	-2.950731	-1.284335
H	1.329864	-3.951639	0.700941
H	0.418487	-2.569776	0.126426
H	3.435950	-3.057699	0.095727
O	0.991861	-0.623997	-1.709947
C	0.443107	0.008340	-2.871986
H	0.058602	1.009049	-2.643809
H	1.194968	0.075475	-3.666545
H	-0.381098	-0.628775	-3.197000
C	1.369909	-2.228737	2.034152
H	2.443006	-2.074844	2.331177
H	1.011017	-3.006480	2.763420
N	0.603424	-1.017807	2.118966
C	0.739269	-0.467907	3.437230
H	1.795945	-0.215311	3.720901
H	0.157837	0.462406	3.544097
H	0.390840	-1.153692	4.257058
O	-2.654715	-0.920098	-0.447117
C	-3.816385	-0.788704	0.409609
C	-2.780449	-2.109541	-1.267873
C	-4.523325	-2.143694	0.363658
H	-3.471025	-0.506003	1.408611
H	-4.454565	0.012878	0.013359
C	-4.211390	-2.615808	-1.065737
H	-2.557858	-1.835150	-2.304023
H	-2.038316	-2.843296	-0.928430
H	-5.595473	-2.059956	0.566720

H	-4.085585	-2.828714	1.099222
H	-4.892467	-2.141575	-1.782664
H	-4.287041	-3.700492	-1.189005
O	-1.033657	2.179999	0.201049
C	-2.155300	2.823442	-0.451686
C	-0.328663	3.137367	1.034149
C	-1.958511	4.325785	-0.237891
H	-2.154922	2.524130	-1.504449
H	-3.083082	2.467664	0.015388
C	-1.238987	4.363816	1.120343
H	-0.130151	2.664446	2.000406
H	0.629250	3.374604	0.554077
H	-2.906466	4.872647	-0.241195
H	-1.317933	4.745709	-1.022878
H	-1.959948	4.251301	1.939054
H	-0.675392	5.287191	1.285500
Na	-0.552460	-0.125628	0.377122



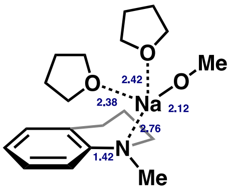
TS$_H$

Energy (RB3LYP): -1186.01364614 A.U.

Gibbs Free Energy: -1185.595933 A.U.

C	4.284843	1.684856	-0.093268
C	2.900086	1.544378	-0.178357
C	2.283001	0.259110	-0.304176
C	3.164180	-0.872540	-0.455474
C	4.539961	-0.693804	-0.355796
C	5.133396	0.573165	-0.183315
H	4.706460	2.683323	0.023743
H	2.258901	2.423258	-0.138711
H	5.177872	-1.576750	-0.421343
H	6.213553	0.680438	-0.126046
C	2.540990	-2.248612	-0.558356
C	1.582486	-2.549249	0.637592
H	1.988965	-2.364905	-1.502386
H	1.797884	-3.549597	1.037095
H	0.538890	-2.568436	0.295690
H	3.346895	-2.993077	-0.585039
O	1.065423	0.236666	-1.095383
C	1.292550	0.476362	-2.485689
H	1.723650	1.470930	-2.656183
H	1.965797	-0.277806	-2.914386
H	0.316117	0.413297	-2.976143
C	1.705200	-1.513927	1.763702

H	2.780187	-1.436608	2.043629
H	1.192453	-1.885353	2.673062
N	1.166605	-0.227499	1.360483
C	1.457429	0.763530	2.373189
H	2.545373	0.920250	2.534253
H	1.032730	1.739105	2.098245
H	1.028310	0.484655	3.355096
O	-2.532812	-1.577865	-0.123757
C	-3.266926	-2.170388	0.977104
C	-2.630108	-2.424399	-1.297426
C	-3.575714	-3.605724	0.547787
H	-2.645420	-2.103120	1.875404
H	-4.185250	-1.589474	1.136032
C	-3.708425	-3.462259	-0.977359
H	-2.872359	-1.789710	-2.155612
H	-1.652984	-2.894954	-1.468024
H	-4.479821	-3.995765	1.025221
H	-2.740500	-4.269930	0.799673
H	-4.701393	-3.078951	-1.241211
H	-3.550715	-4.402292	-1.514799
O	-2.035049	2.072740	0.020055
C	-3.452276	2.255111	0.262522
C	-1.403516	3.356382	-0.221733
C	-3.763553	3.695724	-0.148077
H	-3.995319	1.503304	-0.318141
H	-3.648246	2.088501	1.330236
C	-2.440253	4.411945	0.168117
H	-0.484866	3.400549	0.370837
H	-1.141608	3.418888	-1.285913
H	-4.618647	4.106917	0.397158
H	-3.982359	3.750532	-1.221308
H	-2.373784	4.639403	1.238804
H	-2.310193	5.345106	-0.388412
Na	-0.839764	0.051861	0.174807



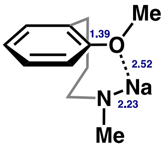
PD$_H$

Energy (RB3LYP): -1186.08614686 A.U.

Gibbs Free Energy: -1185.667425 A.U.

C	4.110088	-1.944494	0.905309
C	3.005379	-1.827439	0.061975
C	2.669250	-0.597139	-0.541595
C	3.493274	0.527962	-0.283388
C	4.592827	0.383516	0.571919
C	4.916394	-0.835384	1.169932

H	4.332686	-2.908449	1.356215
H	2.395234	-2.705815	-0.111735
H	5.211807	1.258245	0.765420
H	5.776992	-0.915904	1.828522
C	3.225479	1.875217	-0.928523
C	1.799051	1.970326	-1.471793
H	3.417681	2.677875	-0.205805
H	1.698589	2.832420	-2.141851
H	1.083524	2.108328	-0.651721
H	3.938075	2.029608	-1.752584
O	-0.525979	-1.025184	2.440124
C	-0.152167	-1.467545	3.686905
H	-0.839474	-2.239628	4.112326
H	0.861657	-1.936530	3.712340
H	-0.115757	-0.658502	4.457600
C	1.452890	0.695691	-2.233191
H	2.144618	0.569320	-3.086500
H	0.439288	0.754022	-2.643638
N	1.504501	-0.485405	-1.353004
C	1.082028	-1.702007	-2.057367
H	1.875282	-2.100594	-2.711166
H	0.783567	-2.484236	-1.356232
H	0.210319	-1.461290	-2.670823
O	-1.407943	1.919080	0.296327
C	-2.003034	2.681861	-0.781964
C	-1.469430	2.677588	1.530838
C	-2.308060	4.069889	-0.207068
H	-1.298801	2.705251	-1.620177
H	-2.916141	2.165497	-1.104124
C	-2.510589	3.768875	1.287209
H	-1.723598	1.981990	2.334529
H	-0.477708	3.105434	1.731910
H	-3.182000	4.529173	-0.679234
H	-1.452557	4.741355	-0.347592
H	-3.520796	3.382998	1.469899
H	-2.355645	4.642502	1.927918
O	-2.369210	-1.409471	-0.756102
C	-3.709351	-0.881105	-0.599980
C	-2.411477	-2.861007	-0.757953
C	-4.562916	-2.049811	-0.108226
H	-3.661493	-0.043040	0.101047
H	-4.056874	-0.511165	-1.574882
C	-3.893611	-3.245057	-0.805715
H	-1.842376	-3.218793	-1.621845
H	-1.928484	-3.217947	0.159915
H	-5.619153	-1.932747	-0.370562
H	-4.485827	-2.147076	0.980897
H	-4.238501	-3.324009	-1.843859
H	-4.088228	-4.199964	-0.307962
Na	-0.584409	-0.308684	0.442550

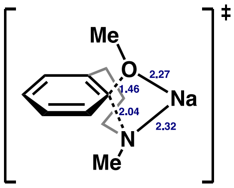


INT$_{H\_noTHF}$

Energy (RB3LYP): -721.096980174 A.U.

Gibbs Free Energy: -720.890003 A.U.

C	-2.563770	-1.419010	-1.105558
C	-2.307309	-0.069437	-0.836721
C	-1.352246	0.279909	0.122929
C	-0.649506	-0.698623	0.856449
C	-0.930526	-2.038905	0.558568
C	-1.867105	-2.408695	-0.413244
H	-3.305149	-1.684109	-1.854893
H	-2.846438	0.697633	-1.383056
H	-0.406931	-2.812223	1.116131
H	-2.056550	-3.459748	-0.614353
C	0.295297	-0.351135	1.990763
C	1.671231	0.281831	1.665349
H	-0.227441	0.326600	2.680951
H	2.208990	0.330745	2.623372
H	1.539555	1.325227	1.348284
H	0.476672	-1.277024	2.551058
O	-1.010662	1.602265	0.373940
C	-2.010094	2.609852	0.159845
H	-2.175794	2.794939	-0.907805
H	-2.954317	2.320603	0.633602
H	-1.623476	3.516839	0.627952
C	2.541992	-0.445364	0.620352
H	2.325935	-1.544746	0.698817
H	3.612643	-0.367222	0.951631
N	2.358068	0.052843	-0.714610
C	3.171720	-0.707193	-1.621904
H	2.925567	-1.800892	-1.648950
H	3.067308	-0.339616	-2.655378
H	4.268374	-0.674583	-1.384010
Na	0.977434	1.750925	-1.159415



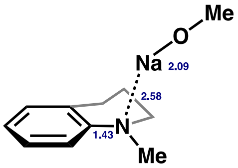
TS$_{H\_noTHF}$

Energy (RB3LYP): -721.070961956 A.U.

Gibbs Free Energy: -720.862055 A.U.

C	2.563626	0.608292	1.097950
C	1.256650	1.075024	0.963679
C	0.339991	0.484374	0.035224

C	0.867739	-0.542736	-0.830738
C	2.174596	-0.987094	-0.660158
C	3.052506	-0.426410	0.288938
H	3.216417	1.078282	1.833672
H	0.907007	1.901463	1.580065
H	2.526205	-1.800515	-1.296919
H	4.073899	-0.785281	0.385424
C	-0.087320	-1.213895	-1.794269
C	-1.321115	-1.828857	-1.058129
H	-0.437637	-0.508003	-2.561003
H	-1.466336	-2.867247	-1.384612
H	-2.238463	-1.288104	-1.332245
H	0.454967	-2.001411	-2.332299
O	-0.596184	1.420083	-0.577258
C	0.030718	2.342446	-1.471935
H	0.756751	2.976089	-0.948093
H	0.543521	1.817132	-2.288145
H	-0.767715	2.966906	-1.885237
C	-1.173147	-1.793209	0.468541
H	-0.213823	-2.289325	0.733593
H	-1.964164	-2.409128	0.937633
N	-1.223080	-0.430078	0.969824
C	-0.943729	-0.415097	2.390913
H	0.074445	-0.779920	2.639899
H	-1.023547	0.604302	2.792970
H	-1.656741	-1.047286	2.952346
Na	-2.728805	1.114992	0.129287



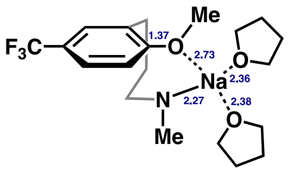
PD$_{H\_noTHF}$

Energy (RB3LYP): -721.148936104 A.U.

Gibbs Free Energy: -720.945090 A.U.

C	-2.087805	-2.411937	0.330268
C	-1.138614	-1.535488	0.857554
C	-1.068210	-0.190874	0.435974
C	-2.000888	0.265002	-0.530388
C	-2.939037	-0.637882	-1.046601
C	-2.997561	-1.969493	-0.632303
H	-2.109785	-3.441647	0.678105
H	-0.445078	-1.913107	1.599956
H	-3.644981	-0.275386	-1.791894
H	-3.738756	-2.644870	-1.050664
C	-2.021193	1.708392	-0.997777
C	-0.699566	2.417988	-0.701311
H	-2.250753	1.749231	-2.069443
H	-0.805288	3.501785	-0.823856

H	0.074631	2.090020	-1.407570
H	-2.838814	2.241054	-0.489930
O	4.011071	-0.503901	-0.577692
C	5.365518	-0.746007	-0.650987
H	5.984910	0.042610	-0.161588
H	5.672642	-1.702198	-0.164867
H	5.749180	-0.812377	-1.696502
C	-0.259379	2.112681	0.725695
H	-1.018924	2.483226	1.436833
H	0.681164	2.622248	0.957729
N	-0.037533	0.666198	0.927508
C	0.448470	0.389308	2.288926
H	-0.363546	0.425440	3.032225
H	0.934666	-0.586862	2.351054
H	1.195526	1.143705	2.547601
Na	1.953359	-0.178653	-0.481137



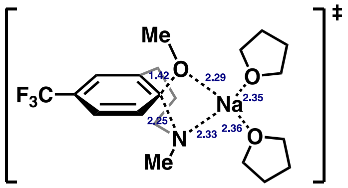
INT$_{CF3}$

Energy (RB3LYP): -1523.10216582 A.U.

Gibbs Free Energy: -1522.686752 A.U.

C	3.082872	0.893153	-1.206222
C	1.806539	0.640801	-1.715571
C	1.161230	-0.565903	-1.427965
C	1.785537	-1.563950	-0.643020
C	3.062664	-1.286686	-0.155562
C	3.711404	-0.070112	-0.420261
H	3.572780	1.834845	-1.429365
H	1.323998	1.396853	-2.323878
H	3.568592	-2.045184	0.435682
C	1.163439	-2.926682	-0.416960
C	-0.039001	-3.040746	0.552610
H	0.854108	-3.331908	-1.390693
H	-0.226568	-4.117970	0.670928
H	-0.941085	-2.628941	0.082659
H	1.958880	-3.586154	-0.048189
O	-0.107164	-0.850400	-1.870428
C	-0.632606	-0.091670	-2.968992
H	-0.861364	0.936924	-2.668679
H	0.071798	-0.087956	-3.807902
H	-1.552875	-0.598501	-3.262194
C	0.137720	-2.382539	1.934897
H	1.225185	-2.451028	2.210644

H	-0.361648	-3.040400	2.698354
N	-0.350714	-1.034035	1.977998
C	-0.040194	-0.462498	3.257724
H	1.057818	-0.426787	3.486751
H	-0.407338	0.574181	3.331822
H	-0.485852	-1.017327	4.127397
O	-3.770069	-0.563431	-0.297102
C	-4.803052	-0.328570	0.693613
C	-4.130437	-1.700659	-1.123326
C	-5.664564	-1.591402	0.703615
H	-4.314484	-0.121757	1.650823
H	-5.383109	0.553809	0.391185
C	-5.577805	-2.046481	-0.762242
H	-3.999250	-1.416403	-2.172323
H	-3.445961	-2.526427	-0.890838
H	-6.688697	-1.392692	1.034270
H	-5.228405	-2.346800	1.367732
H	-6.276948	-1.473338	-1.382965
H	-5.794071	-3.110551	-0.897895
O	-1.565399	2.301371	0.018137
C	-2.716650	3.102507	-0.350857
C	-0.572054	3.134149	0.670614
C	-2.314372	4.559532	-0.104927
H	-2.964453	2.886450	-1.395005
H	-3.562376	2.803350	0.281416
C	-1.298430	4.426745	1.041516
H	-0.179064	2.580524	1.527943
H	0.247480	3.319598	-0.036094
H	-3.173361	5.188418	0.148333
H	-1.832496	4.981565	-0.995071
H	-1.814870	4.314982	2.002503
H	-0.616798	5.279613	1.115770
Na	-1.534676	-0.039435	0.315627
C	5.074136	0.165400	0.152936
F	5.651781	1.308555	-0.298171
F	5.944670	-0.847110	-0.135613
F	5.062400	0.255708	1.516498



TS$_{CF3}$

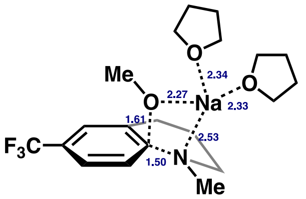
Energy (RB3LYP): -1523.08761763 A.U.

Gibbs Free Energy: -1522.671420 A.U.

C	3.297652	1.340674	-0.362802
C	1.917587	1.239503	-0.475941
C	1.265834	-0.023546	-0.444464

C	2.074219	-1.206172	-0.394661
C	3.447531	-1.078049	-0.273154
C	4.088581	0.184083	-0.274620
H	3.764250	2.321999	-0.370870
H	1.312604	2.136930	-0.580211
H	4.048840	-1.980985	-0.183135
C	1.390696	-2.553373	-0.306731
C	0.449558	-2.658804	0.935130
H	0.816108	-2.759564	-1.219944
H	0.593533	-3.639034	1.408672
H	-0.600720	-2.615178	0.618882
H	2.165583	-3.327510	-0.251555
O	0.006575	-0.106359	-1.101297
C	0.108583	-0.058556	-2.531800
H	0.538686	0.892432	-2.868391
H	0.724758	-0.883948	-2.909918
H	-0.910559	-0.157154	-2.915677
C	0.689867	-1.545094	1.965540
H	1.786303	-1.494534	2.163275
H	0.239757	-1.833923	2.939149
N	0.170397	-0.276781	1.501500
C	0.631172	0.789025	2.357878
H	1.738276	0.901655	2.364244
H	0.216656	1.756068	2.037124
H	0.330805	0.643858	3.416973
O	-3.623238	-1.371231	-0.119813
C	-4.577286	-1.804759	0.882483
C	-3.663169	-2.264377	-1.261464
C	-5.024605	-3.204475	0.456273
H	-4.081930	-1.779294	1.858133
H	-5.416506	-1.096701	0.891854
C	-4.914690	-3.124666	-1.075339
H	-3.679803	-1.653789	-2.169725
H	-2.749618	-2.873351	-1.259549
H	-6.034487	-3.440751	0.805135
H	-4.338925	-3.963670	0.850872
H	-5.793138	-2.621865	-1.497379
H	-4.818699	-4.104490	-1.552905
O	-2.868459	2.163217	0.146500
C	-4.293566	2.392843	0.272433
C	-2.185828	3.415235	-0.122109
C	-4.538028	3.792528	-0.292493
H	-4.811816	1.596874	-0.270331
H	-4.566351	2.334465	1.334939
C	-3.231817	4.515816	0.074974
H	-1.333552	3.493301	0.559879
H	-1.812888	3.389466	-1.154078
H	-5.427809	4.264046	0.135915
H	-4.661583	3.750954	-1.381435
H	-3.256112	4.840298	1.122083

H	-3.032476	5.392036	-0.549416
Na	-1.809316	0.076339	0.329201
C	5.555079	0.263660	-0.109735
F	6.077155	1.474884	-0.457295
F	6.237445	-0.673439	-0.844826
F	5.987319	0.049125	1.188364



INT2$_{CF3}$

Energy (RB3LYP): -1523.11087685 A.U.

Gibbs Free Energy: -1522.690742 A.U.

C	-3.568546	-1.469773	0.179432
C	-2.252777	-1.590972	0.565287
C	-1.280991	-0.483881	0.442250
C	-1.941533	0.822341	0.172318
C	-3.262080	0.898350	-0.194700
C	-4.111914	-0.239915	-0.261313
H	-4.208265	-2.349414	0.230722
H	-1.887914	-2.565194	0.875796
H	-3.676191	1.882032	-0.415730
C	-1.081264	2.044450	0.372013
C	-0.554224	2.097286	1.833470
H	-0.222097	2.027212	-0.314765
H	-1.161538	2.783306	2.437784
H	0.474380	2.481751	1.848449
H	-1.646709	2.952899	0.133039
O	-0.266946	-0.816990	-0.760423
C	-0.882399	-1.037035	-2.016284
H	-1.589485	-1.877654	-1.979691
H	-1.421971	-0.143846	-2.364951
H	-0.090617	-1.274728	-2.736488
C	-0.602290	0.704963	2.482346
H	-1.604100	0.515121	2.905686
H	0.109637	0.650562	3.313675
N	-0.246108	-0.350696	1.516635
C	0.073946	-1.601847	2.210595
H	-0.754592	-1.972831	2.837684
H	0.332181	-2.379886	1.486641
H	0.941020	-1.435475	2.859588
O	3.034345	1.787674	-0.334410
C	3.736206	2.543409	0.684767
C	3.015360	2.534146	-1.579807
C	3.879326	3.960298	0.127406
H	3.152710	2.490417	1.609193
H	4.714753	2.074849	0.854606

C	3.986673	3.700078	-1.384139
H	3.301855	1.854166	-2.388148
H	1.990563	2.885064	-1.756562
H	4.749184	4.481359	0.538640
H	2.985200	4.553684	0.352419
H	5.007227	3.399692	-1.649825
H	3.716606	4.568889	-1.991857
O	3.428496	-1.795687	-0.016268
C	4.846563	-1.528988	0.125501
C	3.221386	-3.177461	-0.413175
C	5.556779	-2.696230	-0.560110
H	5.051749	-0.554512	-0.327105
H	5.089726	-1.482767	1.195744
C	4.586960	-3.859034	-0.292800
H	2.456513	-3.609452	0.239103
H	2.851693	-3.186423	-1.446297
H	6.558831	-2.868063	-0.155327
H	5.648134	-2.511003	-1.637167
H	4.732678	-4.253119	0.720004
H	4.699065	-4.686203	-1.000191
Na	1.767697	-0.155138	-0.001237
C	-5.533251	-0.095638	-0.553950
F	-6.128862	-1.246740	-1.004795
F	-5.815161	0.874924	-1.488612
F	-6.342741	0.278893	0.535258

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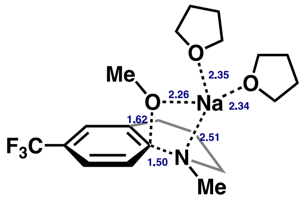


INT2'*CF3*

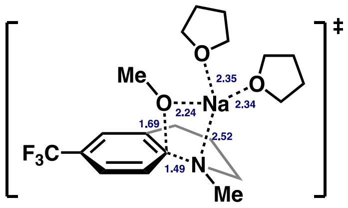
Energy (RB3LYP): -1523.11086505 A.U.

GIbbs Free Energy: -1522.692446 A.U.

- -

C	-3.528751	-1.541569	-0.119635
C	-2.223924	-1.733078	0.276020
C	-1.263841	-0.618620	0.411495
C	-1.931775	0.710350	0.408811
C	-3.241280	0.854292	0.022222
C	-4.072899	-0.249724	-0.311175
H	-4.159261	-2.415832	-0.273862
H	-1.856571	-2.748311	0.389807
H	-3.661453	1.859712	0.000255
C	-1.092865	1.867993	0.888114
C	-0.601905	1.611242	2.339903
H	-0.216983	2.005752	0.237346
H	-1.239246	2.138683	3.061127
H	0.416332	2.002713	2.467587
H	-1.664785	2.801891	0.834473

O	-0.222334	-0.683555	-0.821631
C	-0.815043	-0.629449	-2.105716
H	-1.522813	-1.455913	-2.260706
H	-1.348872	0.319150	-2.266421
H	-0.011250	-0.711681	-2.847021
C	-0.632842	0.110324	2.671137
H	-1.635756	-0.181630	3.028567
H	0.070327	-0.112589	3.481508
N	-0.247458	-0.707918	1.506173
C	0.083794	-2.074826	1.921517
H	-0.744995	-2.579313	2.446696
H	0.356558	-2.677636	1.051087
H	0.943848	-2.040235	2.599710
O	2.836015	1.886485	-0.249800
C	3.523252	2.710329	0.726349
C	2.691804	2.612510	-1.498152
C	3.576941	4.116682	0.125274
H	2.969425	2.657541	1.669087
H	4.528393	2.296693	0.881220
C	3.619945	3.822396	-1.383309
H	2.950667	1.933002	-2.315936
H	1.642308	2.915850	-1.605825
H	4.442454	4.684739	0.479468
H	2.670510	4.678422	0.379988
H	4.637612	3.557488	-1.694486
H	3.281959	4.663169	-1.996503
O	3.576072	-1.652580	-0.089304
C	4.970722	-1.276354	0.037000
C	3.472583	-3.032268	-0.530419
C	5.761037	-2.368108	-0.685099
H	5.090666	-0.279413	-0.396975
H	5.226545	-1.233284	1.104355
C	4.887373	-3.609226	-0.439437
H	2.748772	-3.542789	0.111860
H	3.096767	-3.036981	-1.561433
H	6.777829	-2.471725	-0.294136
H	5.825817	-2.149774	-1.757807
H	5.073456	-4.015926	0.561732
H	5.055628	-4.407196	-1.168896
Na	1.770851	-0.173035	0.105262
C	-5.485323	-0.056053	-0.620303
F	-6.044889	-1.085140	-1.335404
F	-5.747999	1.093159	-1.330443
F	-6.339454	0.063134	0.491553



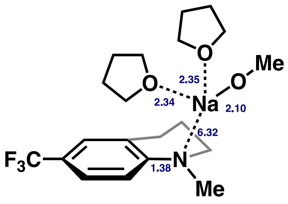
$\mathbf{TS2}_{CF3}$

Energy (RB3LYP): -1523.11071414 A.U.

Gibbs Free Energy: -1522.691370 A.U.

C	-3.532131	-1.539378	-0.095557
C	-2.232034	-1.727268	0.323964
C	-1.287023	-0.614758	0.469021
C	-1.937745	0.710569	0.438229
C	-3.241654	0.856407	0.026989
C	-4.069351	-0.249227	-0.301777
H	-4.160867	-2.413961	-0.253006
H	-1.868354	-2.741330	0.455181
H	-3.657088	1.862723	-0.017156
C	-1.094986	1.873293	0.898078
C	-0.581157	1.633006	2.344496
H	-0.229415	2.003079	0.232500
H	-1.206918	2.168332	3.069877
H	0.438285	2.027195	2.450391
H	-1.668349	2.806055	0.842707
O	-0.204940	-0.693942	-0.830835
C	-0.814566	-0.654601	-2.101011
H	-1.543576	-1.469308	-2.229874
H	-1.334944	0.300604	-2.278255
H	-0.033119	-0.768921	-2.864370
C	-0.604407	0.136308	2.694749
H	-1.597958	-0.150130	3.081622
H	0.119804	-0.077684	3.488654
N	-0.251156	-0.698172	1.529871
C	0.088181	-2.060925	1.950319
H	-0.731199	-2.561051	2.494406
H	0.345396	-2.669745	1.079631
H	0.959810	-2.020417	2.612976
O	2.833803	1.883832	-0.252385
C	3.534857	2.708561	0.712740
C	2.680172	2.605002	-1.502482
C	3.586041	4.112727	0.106359
H	2.991896	2.660654	1.662062
H	4.540551	2.292486	0.857521
C	3.612589	3.812912	-1.401513
H	2.929514	1.921401	-2.319788
H	1.630505	2.910491	-1.601802
H	4.456650	4.679763	0.449569
H	2.683734	4.677726	0.368473
H	4.626330	3.544338	-1.722238
H	3.270452	4.652355	-2.014247
O	3.566858	-1.656927	-0.080248
C	4.963661	-1.281873	0.019905
C	3.454178	-3.037487	-0.516408
C	5.739136	-2.373171	-0.718694

H	5.075868	-0.284370	-0.414843
H	5.240295	-1.240477	1.082202
C	4.870740	-3.614308	-0.455132
H	2.744638	-3.547040	0.142386
H	3.055706	-3.043978	-1.538807
H	6.763874	-2.476817	-0.349008
H	5.781517	-2.154494	-1.792456
H	5.077843	-4.021168	0.541859
H	5.023755	-4.412184	-1.188049
Na	1.761065	-0.173976	0.103983
C	-5.478822	-0.055369	-0.639518
F	-6.024810	-1.090716	-1.353889
F	-5.723167	1.085090	-1.367623
F	-6.345144	0.076802	0.455976



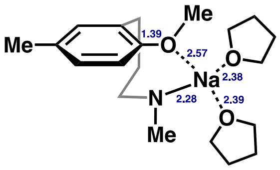
PD*CF3*

Energy (RB3LYP): -1523.15370861 A.U.

Gibbs Free Energy: -1522.744298 A.U.

C	-3.768420	-0.409340	-1.475941
C	-2.878642	-1.477886	-1.512043
C	-2.357937	-2.046244	-0.323536
C	-2.749346	-1.471357	0.924015
C	-3.645672	-0.409539	0.932186
C	-4.163483	0.137067	-0.252130
H	-4.146386	-0.002844	-2.408444
H	-2.587639	-1.871125	-2.478129
H	-3.942985	0.008853	1.891113
C	-2.184157	-2.000838	2.227174
C	-1.685450	-3.439378	2.074182
H	-1.346798	-1.363421	2.548558
H	-2.534543	-4.126613	1.967550
H	-1.121456	-3.746207	2.961751
H	-2.941724	-1.935091	3.017082
O	2.979986	0.948504	-3.160062
C	2.836281	0.900720	-4.528071
H	2.804656	-0.137704	-4.937999
H	1.900973	1.387281	-4.896030
H	3.663907	1.406181	-5.081636
C	-0.793424	-3.552300	0.840904
H	-0.475702	-4.589505	0.697941
H	0.119109	-2.945910	0.977509
N	-1.510708	-3.138087	-0.367597
C	-0.953313	-3.572940	-1.641185
H	-1.745399	-3.865706	-2.339340

H	-0.338927	-2.793923	-2.118564
H	-0.324077	-4.447875	-1.466812
O	2.090318	2.428399	0.438973
C	2.141001	2.405975	1.887902
C	1.070090	3.356800	-0.008815
C	0.951214	3.244981	2.366542
H	2.100489	1.363348	2.220155
H	3.098737	2.839518	2.202901
C	0.756211	4.232126	1.203615
H	1.470650	3.906622	-0.865068
H	0.190408	2.785378	-0.333205
H	1.151747	3.738012	3.322653
H	0.060833	2.616576	2.486386
H	1.473250	5.058782	1.275371
H	-0.252299	4.654478	1.161520
O	4.624761	-0.299613	0.248696
C	5.802247	0.153641	0.962785
C	4.699934	-1.731138	0.024938
C	6.785018	-1.018543	0.938360
H	6.179448	1.051842	0.464134
H	5.506973	0.413726	1.987676
C	5.840240	-2.231127	0.913797
H	3.725729	-2.164619	0.272032
H	4.907037	-1.906608	-1.038575
H	7.458238	-1.012250	1.800950
H	7.394014	-0.989105	0.027363
H	5.472326	-2.451439	1.922955
H	6.309739	-3.135428	0.515391
Na	3.199454	1.021573	-1.070688
C	-5.150481	1.251558	-0.179972
F	-5.333402	1.881006	-1.370063
F	-4.793517	2.217300	0.719287
F	-6.397675	0.838621	0.220160



INT$_{Me}$

Energy (RB3LYP): -1225.35582026 A.U.

Gibbs Free Energy: -1224.913174 A.U.

C	3.705053	1.132467	-1.271608
C	2.439562	0.728409	-1.716696
C	1.912692	-0.496305	-1.304393
C	2.646870	-1.353982	-0.458325
C	3.905954	-0.911926	-0.037155
C	4.456648	0.324211	-0.416142
H	4.100001	2.091343	-1.600931

H	1.874533	1.380337	-2.374712
H	4.488424	-1.569413	0.606544
C	2.164447	-2.741091	-0.082072
C	0.993203	-2.876725	0.922733
H	1.881517	-3.274420	-1.001161
H	0.923424	-3.948847	1.159168
H	0.046668	-2.618964	0.431134
H	3.027043	-3.279533	0.330879
O	0.645467	-0.923125	-1.672818
C	0.103603	-0.418807	-2.899328
H	-0.205959	0.628418	-2.802136
H	0.833331	-0.512997	-3.711483
H	-0.770898	-1.034880	-3.115528
C	1.107129	-2.059440	2.226245
H	2.199286	-1.952614	2.470331
H	0.717475	-2.695056	3.068879
N	0.437182	-0.792189	2.153679
C	0.656117	-0.073566	3.375373
H	1.737306	0.136320	3.595965
H	0.146409	0.903554	3.360965
H	0.287278	-0.608600	4.293073
O	-2.946850	-0.912663	-0.176661
C	-3.808490	-1.360991	0.900504
C	-3.571056	-1.184390	-1.454689
C	-4.864648	-2.250394	0.243446
H	-3.186054	-1.877689	1.636525
H	-4.261524	-0.479914	1.374887
C	-5.011155	-1.600273	-1.142108
H	-3.500295	-0.281538	-2.070059
H	-3.016084	-1.993732	-1.947404
H	-5.799928	-2.272876	0.811191
H	-4.495587	-3.278647	0.148426
H	-5.662017	-0.719474	-1.084458
H	-5.419689	-2.278133	-1.897879
O	-1.136640	2.193165	-0.030484
C	-2.448055	2.798650	-0.156390
C	-0.191570	3.164538	0.486318
C	-2.251672	4.294973	0.106533
H	-2.833658	2.578500	-1.157174
H	-3.112393	2.338958	0.586300
C	-1.039800	4.302866	1.052733
H	0.434946	2.661829	1.228368
H	0.444688	3.509115	-0.339918
H	-3.142825	4.759119	0.540187
H	-2.011494	4.821334	-0.825164
H	-1.351051	4.075321	2.079342
H	-0.503650	5.256927	1.060193
Na	-0.753436	-0.125430	0.332438
C	5.817387	0.751011	0.088080
H	5.800139	0.945172	1.168695

H	6.573002	-0.025255	-0.086252
H	6.156033	1.666959	-0.408006

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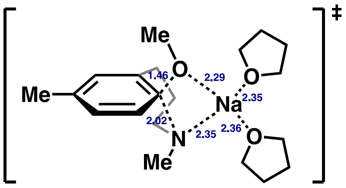

TS$_{Me}$

Energy (RB3LYP): -1225.32889112 A.U.

Gibbs Free Energy: -1224.886210 A.U.

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C	3.998648	1.580292	-0.324894
C	2.612433	1.411717	-0.355606
C	2.011038	0.114261	-0.303101
C	2.919894	-1.006687	-0.354072
C	4.292619	-0.790388	-0.310015
C	4.882993	0.493365	-0.300163
H	4.400466	2.594936	-0.340842
H	1.961701	2.283441	-0.406775
H	4.944133	-1.667369	-0.291371
C	2.328378	-2.400727	-0.303039
C	1.318229	-2.565253	0.873194
H	1.826816	-2.658417	-1.248076
H	1.475852	-3.537275	1.359988
H	0.287878	-2.568414	0.493909
H	3.149447	-3.120634	-0.190722
O	0.782337	-0.026758	-1.079066
C	0.993811	0.044954	-2.489170
H	1.398056	1.020881	-2.787102
H	1.683398	-0.739264	-2.828869
H	0.016114	-0.103487	-2.958901
C	1.452899	-1.442557	1.909885
H	2.526384	-1.368309	2.195649
H	0.918968	-1.717304	2.840250
N	0.952999	-0.179725	1.390675
C	1.293036	0.890225	2.304737
H	2.387780	1.020500	2.437797
H	0.899734	1.850925	1.945550
H	0.866532	0.715894	3.310521
O	-2.808360	-1.514653	-0.019662
C	-3.147126	-2.524968	0.963645
C	-3.389498	-1.857507	-1.303145
C	-3.698621	-3.709869	0.169301
H	-2.243464	-2.758424	1.534754
H	-3.901129	-2.109186	1.645342
C	-4.358373	-3.010839	-1.030792
H	-3.873697	-0.962987	-1.707551
H	-2.580415	-2.160313	-1.980670
H	-4.398179	-4.313051	0.756053

H	-2.882113	-4.360214	-0.166466
H	-5.346891	-2.625431	-0.753456
H	-4.477847	-3.665063	-1.899741
O	-2.319531	2.058139	0.032626
C	-3.658792	2.245279	0.554610
C	-1.787004	3.324538	-0.433911
C	-4.091254	3.640225	0.099587
H	-4.288215	1.438167	0.168013
H	-3.620774	2.171932	1.649818
C	-2.753161	4.397193	0.073870
H	-0.769110	3.429709	-0.046551
H	-1.747941	3.300289	-1.530722
H	-4.827463	4.087093	0.774736
H	-4.528064	3.598386	-0.905495
H	-2.475095	4.717621	1.085017
H	-2.768276	5.279986	-0.572513
Na	-1.084196	0.075824	0.250382
C	6.384537	0.673156	-0.247700
H	6.814953	0.362924	0.717712
H	6.902596	0.089079	-1.022405
H	6.659342	1.725117	-0.396310

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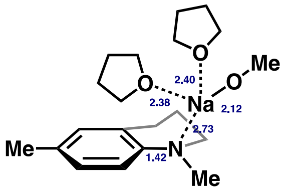

PD$_{Me}$

Energy (RB3LYP): -1225.40484637 A.U.

Gibbs Free Energy: -1224.963908 A.U.

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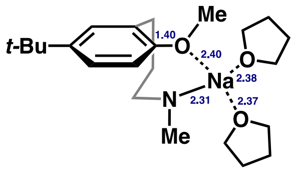
C	-3.844058	0.795020	-0.915208
C	-2.555240	0.427281	-1.306149
C	-1.975469	-0.783202	-0.877600
C	-2.752710	-1.638432	-0.056415
C	-4.038515	-1.236459	0.320973
C	-4.614596	-0.025541	-0.083930
H	-4.250968	1.739959	-1.270651
H	-2.002520	1.100616	-1.950965
H	-4.614871	-1.908271	0.957139
C	-2.237895	-2.994354	0.392446
C	-0.722918	-3.121023	0.218106
H	-2.519855	-3.171779	1.437540
H	-0.414227	-4.170941	0.284359
H	-0.202622	-2.577903	1.016790
H	-2.737567	-3.778515	-0.196015
O	0.747781	-0.029689	2.736447
C	0.469449	-0.149413	4.076962
H	0.043831	0.778642	4.531800
H	-0.272125	-0.951847	4.312017

H	1.364690	-0.391786	4.701034
C	-0.303543	-2.550857	-1.132819
H	-0.791925	-3.113892	-1.949741
H	0.778288	-2.642628	-1.268635
N	-0.636481	-1.118552	-1.224086
C	-0.102203	-0.501525	-2.441535
H	-0.717746	-0.723655	-3.329427
H	-0.024819	0.583107	-2.330936
H	0.905360	-0.889596	-2.609546
O	2.895609	-0.915231	-0.213437
C	3.896084	-0.339290	-1.087492
C	3.478986	-1.998496	0.557592
C	5.076960	-1.312159	-1.073909
H	3.448634	-0.204679	-2.077455
H	4.182876	0.644455	-0.692363
C	4.990528	-1.896643	0.345309
H	3.168133	-1.877500	1.598854
H	3.080991	-2.947816	0.174861
H	6.028491	-0.812263	-1.279764
H	4.934445	-2.100443	-1.823094
H	5.434721	-1.206063	1.072055
H	5.488994	-2.865791	0.445045
O	0.763349	2.383138	-0.145426
C	1.820221	3.217105	-0.680677
C	-0.235444	3.209386	0.507315
C	1.549707	4.634170	-0.164352
H	2.781916	2.812102	-0.349687
H	1.774392	3.167934	-1.776703
C	0.022308	4.632020	0.012080
H	-1.219714	2.814673	0.240522
H	-0.102377	3.126809	1.593867
H	1.904567	5.401883	-0.858938
H	2.044302	4.791462	0.801357
H	-0.477085	4.801306	-0.949818
H	-0.330677	5.388592	0.719644
Na	0.913865	0.140938	0.632049
C	-5.996909	0.380594	0.375709
H	-6.674604	-0.480014	0.422571
H	-5.971214	0.826107	1.379871
H	-6.439246	1.122457	-0.298628



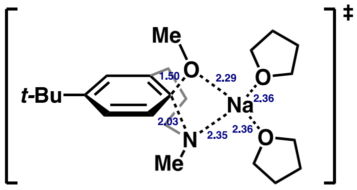
INT$_{t\text{-}Bu}$

Energy (RB3LYP): -1343.29746272 A.U.

Gibbs Free Energy: -1342.774500 A.U.

C	3.365608	0.842030	-1.460905
C	2.004544	0.695860	-1.739767
C	1.261373	-0.304915	-1.114578
C	1.856227	-1.175972	-0.186861
C	3.224463	-0.999559	0.067069
C	4.008739	-0.009928	-0.549250
H	3.912908	1.631943	-1.963629
H	1.512192	1.363309	-2.442656
H	3.690208	-1.673763	0.781383
C	1.070503	-2.278511	0.497721
C	1.120467	-2.282594	2.041042
H	0.027293	-2.227431	0.178022
H	2.149579	-2.487353	2.371599
H	0.512245	-3.134577	2.378687
H	1.452278	-3.248350	0.143722
O	-0.102215	-0.409703	-1.401070
C	-0.403178	-1.124840	-2.610452
H	0.021727	-0.609824	-3.479948
H	-0.009313	-2.147299	-2.561385
H	-1.491785	-1.152309	-2.691413
C	0.626166	-1.011418	2.751143
H	1.379826	-0.198001	2.561828
H	0.740669	-1.217987	3.848709
N	-0.711051	-0.613236	2.419755
C	-1.107051	0.437705	3.319794
H	-0.460121	1.356208	3.273136
H	-2.136559	0.776428	3.115211
H	-1.085770	0.141875	4.402214
Na	-1.688792	-0.137247	0.380690
O	-3.587400	-1.268911	-0.471541
C	-4.667181	-0.689793	-1.245873
C	-3.969511	-2.584300	0.004457
C	-5.690173	-1.811110	-1.449226
H	-5.090893	0.147107	-0.676120
H	-4.250131	-0.302371	-2.180986
C	-5.483420	-2.670420	-0.191082
H	-3.442682	-3.340061	-0.593791
H	-3.648729	-2.671733	1.046404
H	-5.453284	-2.389846	-2.350177
H	-6.710189	-1.427346	-1.548722
H	-5.828952	-3.701882	-0.310692
H	-6.006800	-2.229957	0.666092
O	-2.360395	2.095513	-0.088612
C	-3.445825	2.768992	0.593011
C	-1.380307	3.066525	-0.538173
C	-2.943833	4.185006	0.878908
H	-4.323575	2.778245	-0.067825
H	-3.687640	2.196907	1.494006
C	-2.018048	4.441675	-0.321554
H	-0.470408	2.941002	0.061929

H	-1.144665	2.853015	-1.585283
H	-2.373959	4.207317	1.815296
H	-3.761652	4.908123	0.956853
H	-1.270970	5.218580	-0.132251
H	-2.604111	4.737370	-1.200188
C	5.507883	0.105571	-0.210405
C	6.223772	-1.220954	-0.564630
H	7.292352	-1.151233	-0.324442
H	5.811462	-2.068840	-0.006857
H	6.129775	-1.443493	-1.634584
C	6.199000	1.242852	-0.988343
H	5.763055	2.221786	-0.755859
H	7.260007	1.281029	-0.714712
H	6.142880	1.090640	-2.072933
C	5.677927	0.387235	1.302482
H	6.742686	0.468644	1.555803
H	5.188271	1.327474	1.583200
H	5.248045	-0.410985	1.917080



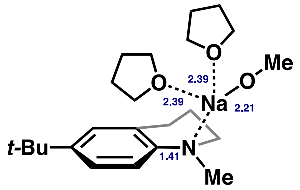
TS$_{t\text{-}Bu}$

Energy (RB3LYP): -1343.26893771 A.U.

Gibbs Free Energy: -1342.745547 A.U.

C	3.386589	1.342722	-0.631945
C	1.989189	1.303215	-0.652437
C	1.257525	0.135193	-0.276507
C	2.056252	-1.026400	0.034765
C	3.442781	-0.939684	0.046728
C	4.168602	0.228095	-0.292373
H	3.862791	2.278213	-0.917119
H	1.433193	2.187514	-0.960206
H	3.988209	-1.838781	0.337175
C	1.327609	-2.259098	0.521224
C	0.569523	-1.984311	1.862516
H	0.610487	-2.605986	-0.235364
H	0.954899	-2.648756	2.648106
H	-0.498584	-2.219478	1.751051
H	2.048063	-3.075276	0.657872
O	0.035986	-0.101163	-1.040096
C	0.282343	-0.441421	-2.404442
H	0.801977	0.367729	-2.933281
H	0.884787	-1.356545	-2.483730
H	-0.696090	-0.609311	-2.865906
C	0.709955	-0.531362	2.337152
H	1.791021	-0.326342	2.500245

H	0.235153	-0.420817	3.331148
N	0.131020	0.400807	1.387245
C	0.353367	1.759499	1.832228
H	1.428381	2.039120	1.863196
H	-0.139596	2.475077	1.159130
H	-0.051544	1.928324	2.847724
Na	-1.878007	0.071523	0.211170
O	-3.328139	-1.737248	-0.225749
C	-4.666317	-1.862579	0.319016
C	-2.916933	-2.992694	-0.823601
C	-5.209141	-3.194928	-0.203441
H	-4.596770	-1.855962	1.414805
H	-5.247888	-0.993497	-0.003391
C	-3.927993	-4.033837	-0.341117
H	-2.940114	-2.883011	-1.916044
H	-1.888588	-3.196212	-0.510561
H	-5.684784	-3.059277	-1.182183
H	-5.944415	-3.637242	0.475653
H	-4.030870	-4.867940	-1.041923
H	-3.627456	-4.438655	0.632704
O	-3.377849	1.885374	0.016370
C	-3.647466	2.842007	1.071820
C	-3.881586	2.385875	-1.247724
C	-4.057339	4.135376	0.365577
H	-4.459206	2.449780	1.699162
H	-2.743551	2.938131	1.680583
C	-4.743125	3.603342	-0.903703
H	-3.025725	2.660566	-1.878044
H	-4.436779	1.578994	-1.736569
H	-3.172006	4.727147	0.104116
H	-4.713863	4.755448	0.983634
H	-4.771509	4.333769	-1.717995
H	-5.772502	3.296227	-0.682842
C	5.707071	0.227623	-0.273509
C	6.255204	-0.835164	-1.259088
H	7.354015	-0.854607	-1.242734
H	5.900070	-1.840747	-1.005902
H	5.933580	-0.616027	-2.284967
C	6.296250	1.592991	-0.680804
H	5.979543	2.392500	0.000109
H	7.392439	1.548690	-0.653722
H	6.000624	1.876709	-1.698345
C	6.225550	-0.104168	1.148721
H	7.324295	-0.121118	1.171049
H	5.881775	0.645435	1.872342
H	5.870021	-1.083653	1.488913



PD$_{t\text{-}Bu}$

Energy (RB3LYP): -1343.34300646 A.U.

Gibbs Free Energy: -1342.815853 A.U.

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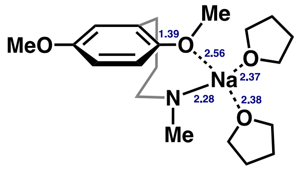
C	3.344410	0.911086	-1.311374
C	2.076153	1.457756	-1.549832
C	1.139924	1.579941	-0.511735
C	1.518695	1.146003	0.783084
C	2.794278	0.628645	0.993462
C	3.742699	0.484592	-0.039065
H	4.023977	0.835990	-2.153991
H	1.834069	1.782179	-2.555831
H	3.048967	0.323235	2.006653
C	0.511147	1.321600	1.889605
C	-0.122425	2.713613	1.742968
H	-0.272123	0.550787	1.824358
H	0.666098	3.465637	1.867312
H	-0.867419	2.897006	2.526037
H	0.988321	1.210222	2.869934
O	-2.231865	-0.791702	-2.872693
C	-2.560953	-1.131351	-4.163221
H	-2.529830	-0.270123	-4.875258
H	-1.885061	-1.900454	-4.610621
H	-3.589642	-1.555209	-4.267816
C	-0.790461	2.877578	0.368776
H	-0.747412	3.936897	0.069451
H	-1.848923	2.598583	0.421991
N	-0.178758	2.047206	-0.704577
C	-0.530941	2.549367	-2.031124
H	0.028641	3.463247	-2.295055
H	-0.353491	1.788454	-2.794747
H	-1.598580	2.786670	-2.040459
Na	-1.725330	-0.269359	-0.886758
O	-0.879532	-2.071376	0.433693
C	-1.784045	-3.117798	0.871420
C	0.392516	-2.651288	0.050362
C	-1.062606	-4.445993	0.613943
H	-1.987074	-2.964648	1.939147
H	-2.722358	-3.022055	0.315285
C	0.417962	-4.038014	0.691129
H	0.437494	-2.715983	-1.045361
H	1.181584	-1.979999	0.399114
H	-1.301040	-4.824024	-0.386977
H	-1.338871	-5.213614	1.343474
H	1.082928	-4.728575	0.163136
H	0.747470	-3.972763	1.735415
O	-3.553066	0.487097	0.456069
C	-3.815845	0.208935	1.853695

C	-4.738074	1.042659	-0.168760
C	-5.176249	0.840322	2.163087
H	-3.834475	-0.879640	1.992084
H	-2.994721	0.624815	2.446492
C	-5.885975	0.762785	0.801244
H	-4.586025	2.121503	-0.310750
H	-4.854934	0.570418	-1.147986
H	-5.054868	1.885796	2.471472
H	-5.707155	0.309411	2.959262
H	-6.702616	1.483958	0.697958
H	-6.291829	-0.242379	0.635411
C	5.133656	-0.104242	0.261016
C	4.984128	-1.535137	0.833203
H	5.970344	-1.961389	1.058173
H	4.398319	-1.544601	1.759142
H	4.485453	-2.194361	0.112303
C	6.018381	-0.185240	-0.998536
H	6.200350	0.804066	-1.435124
H	6.992666	-0.614528	-0.736019
H	5.572462	-0.823576	-1.770645
C	5.860931	0.782600	1.301793
H	6.852807	0.370522	1.528467
H	5.995245	1.802339	0.920830
H	5.303047	0.846024	2.242742



INT$_{OMe}$

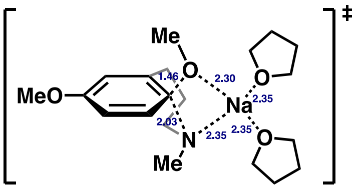
Energy (RB3LYP): -1300.56443514 A.U.

Gibbs Free Energy: -1300.116598 A.U.

C	3.591610	0.604582	-1.139339
C	2.292966	0.399351	-1.631246
C	1.564138	-0.730613	-1.269682
C	2.119772	-1.707247	-0.413451
C	3.410362	-1.483389	0.067373
C	4.148746	-0.339692	-0.276749
H	4.133950	1.494192	-1.438713
H	1.863242	1.145033	-2.292018
H	3.874410	-2.217046	0.721325
C	1.401955	-2.998937	-0.076353
C	0.194800	-2.940479	0.893238
H	1.061729	-3.463955	-1.012558
H	-0.063308	-3.986540	1.115007
H	-0.679834	-2.520367	0.380325
H	2.147601	-3.680243	0.352334
O	0.256876	-0.942754	-1.690329

C	-0.128729	-0.389604	-2.953753
H	-0.262845	0.696997	-2.894122
H	0.616450	-0.626293	-3.721892
H	-1.082310	-0.855766	-3.208163
C	0.412942	-2.162552	2.207489
H	1.502433	-2.237920	2.473197
H	-0.093928	-2.730562	3.035902
N	-0.037151	-0.801211	2.133713
C	0.283451	-0.133868	3.362271
H	1.381212	-0.109907	3.597640
H	-0.054459	0.915200	3.347146
H	-0.182346	-0.602058	4.272339
O	-3.287764	-0.531970	-0.227033
C	-4.184531	-0.821163	0.876109
C	-3.799136	-1.123168	-1.447092
C	-5.109340	-1.931714	0.377396
H	-3.574423	-1.104021	1.738749
H	-4.745095	0.091869	1.118856
C	-5.214695	-1.608919	-1.122126
H	-3.768900	-0.363760	-2.235249
H	-3.142020	-1.955766	-1.730586
H	-6.076770	-1.927443	0.888999
H	-4.645087	-2.913637	0.527985
H	-5.944352	-0.807745	-1.290604
H	-5.506377	-2.470150	-1.731063

O	-1.044778	2.399303	-0.103913
C	-2.247125	3.194215	-0.268443
C	0.018785	3.220040	0.441760
C	-1.842711	4.643003	0.023307
H	-2.623100	3.043051	-1.285540
H	-2.999124	2.830388	0.443040
C	-0.669441	4.464627	1.001021
H	0.549584	2.627330	1.191978
H	0.716555	3.475050	-0.367384
H	-2.669161	5.226318	0.440782
H	-1.503085	5.140054	-0.893333
H	-1.038634	4.274946	2.016043
H	-0.000562	5.330179	1.035152
Na	-1.039169	0.062695	0.277776
O	5.405578	-0.253418	0.270584
C	6.193935	0.894201	-0.032919
H	5.702315	1.814535	0.306828
H	7.132551	0.762346	0.507684
H	6.398773	0.963201	-1.108970



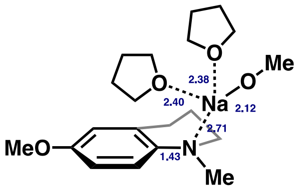
$\textbf{TS}_{\textit{OMe}}$

Energy (RB3LYP): -1300.53506179 A.U.

Gibbs Free Energy: -1300.088784 A.U.

C	3.806091	1.395407	-0.034443
C	2.424739	1.269527	-0.195168
C	1.778049	-0.008335	-0.211943
C	2.641200	-1.165284	-0.184648
C	4.012764	-1.005570	-0.010849
C	4.614797	0.262168	0.058506
H	4.261048	2.384245	0.007067
H	1.809919	2.162725	-0.289183
H	4.642733	-1.891326	0.075135
C	1.995671	-2.535972	-0.187365
C	0.884490	-2.664004	0.898783
H	1.567471	-2.773082	-1.172784
H	0.967483	-3.640720	1.394312
H	-0.109351	-2.632379	0.433261
H	2.776994	-3.285836	-0.009139
O	0.618067	-0.097724	-1.089585
C	0.953338	-0.024761	-2.476186
H	1.420879	0.935949	-2.727136
H	1.636838	-0.834690	-2.763903
H	0.014316	-0.128826	-3.028900
C	0.967338	-1.545819	1.945860
H	2.014663	-1.506068	2.322086
H	0.348814	-1.804117	2.827479
N	0.552433	-0.269520	1.388555
C	0.835657	0.790345	2.332681
H	1.914966	0.886510	2.575523
H	0.509822	1.762358	1.937988
H	0.306963	0.632361	3.291919
O	-3.189387	-1.422765	-0.147640
C	-3.577056	-2.384860	0.865699
C	-3.900341	-1.689485	-1.382889
C	-4.325728	-3.492086	0.122257
H	-2.669592	-2.727420	1.371821
H	-4.223001	-1.880410	1.596678
C	-4.980436	-2.715955	-1.032392
H	-4.300152	-0.741863	-1.757538
H	-3.186104	-2.087850	-2.115432
H	-5.049494	-4.005442	0.762631
H	-3.621711	-4.237536	-0.266513
H	-5.891636	-2.212787	-0.687297
H	-5.241837	-3.349462	-1.885446
O	-2.441700	2.126537	-0.105374
C	-3.718953	2.429266	0.510752
C	-1.793203	3.352286	-0.530216
C	-3.995404	3.901931	0.199678

H	-4.465898	1.744048	0.098570
H	-3.634337	2.253272	1.591259
C	-2.575795	4.488348	0.130647
H	-0.743447	3.304460	-0.225710
H	-1.842555	3.410372	-1.625638
H	-4.621960	4.375570	0.961616
H	-4.499061	4.002340	-0.769317
H	-2.191689	4.683425	1.139010
H	-2.519846	5.418492	-0.443048
Na	-1.362080	0.047410	0.065741
O	5.997595	0.381694	0.263605
C	6.770803	0.367805	-0.936997
H	6.497394	1.206818	-1.592306
H	7.820331	0.463992	-0.642135
H	6.632145	-0.573646	-1.486614



PD*OMe*

Energy (RB3LYP): -1300.61293696 A.U.

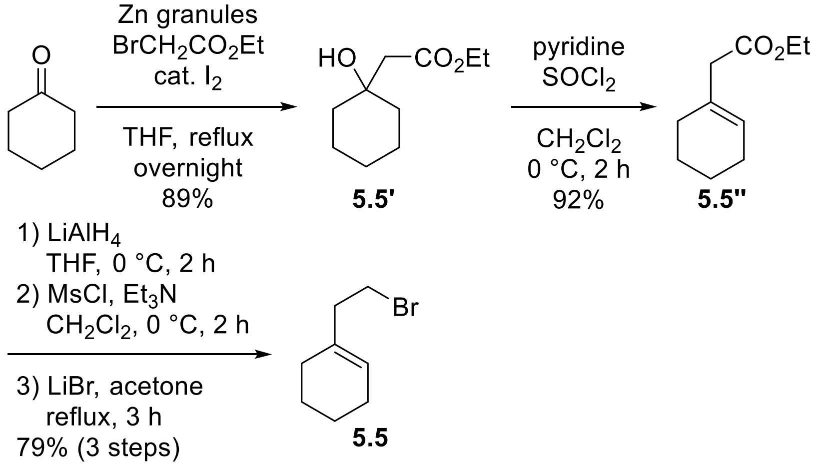
Gibbs Free Energy: -1300.165625 A.U.

C	-3.475381	1.284242	-0.804366
C	-2.254616	0.770247	-1.227524
C	-1.877265	-0.563257	-0.960875
C	-2.787334	-1.379280	-0.254147
C	-4.015826	-0.847954	0.172159
C	-4.370931	0.475331	-0.094902
H	-3.743118	2.315081	-1.019074
H	-1.584660	1.430321	-1.765411
H	-4.688296	-1.502150	0.718262
C	-2.489146	-2.837873	0.043605
C	-1.009795	-3.174892	-0.156155
H	-2.802437	-3.079417	1.066721
H	-0.868408	-4.260202	-0.218830
H	-0.419541	-2.819334	0.697352
H	-3.099210	-3.469171	-0.619639
O	0.773881	-0.259323	2.655618
C	0.362557	-0.444993	3.953628
H	-0.060015	0.475396	4.426455
H	-0.435461	-1.219367	4.066501
H	1.181493	-0.772113	4.640945
C	-0.496928	-2.520142	-1.433827
H	-1.068010	-2.895527	-2.303711
H	0.554666	-2.774403	-1.601192
N	-0.591324	-1.052032	-1.353404
C	0.002923	-0.411238	-2.532589

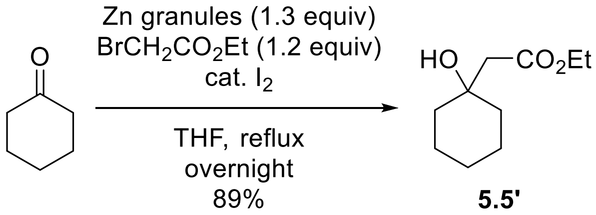
H	-0.650886	-0.477442	-3.418772
H	0.227581	0.639030	-2.336567
H	0.947259	-0.913427	-2.759792
O	3.276311	-0.824758	-0.028811
C	3.664569	-1.988686	-0.799959
C	4.341886	-0.463670	0.884950
C	5.003377	-2.461805	-0.221751
H	2.871812	-2.739648	-0.718768
H	3.758269	-1.685849	-1.850925
C	5.591704	-1.162230	0.351680
H	4.413425	0.627868	0.899888
H	4.080429	-0.814604	1.891431
H	5.639447	-2.927560	-0.980745
H	4.838862	-3.190838	0.580327
H	6.057329	-0.565478	-0.442205
H	6.337297	-1.335338	1.133853
O	1.223328	2.129108	-0.318647
C	2.336017	2.653988	-1.080196
C	0.605596	3.194317	0.453129
C	2.657161	4.014029	-0.459961
H	3.154438	1.930644	-1.021333
H	2.029111	2.755964	-2.130930
C	1.265411	4.494430	-0.016436
H	-0.473682	3.160719	0.276408
H	0.795047	2.998421	1.515387
H	3.142764	4.691407	-1.169440
H	3.316641	3.893377	0.407862
H	0.719607	4.919121	-0.867681
H	1.300863	5.248533	0.775758
Na	1.067027	-0.082164	0.560402
O	-5.553151	1.063042	0.286446
C	-6.488838	0.280628	1.023733
H	-6.059302	-0.062371	1.973367
H	-7.335131	0.939656	1.224205
H	-6.830003	-0.584977	0.441680

6.4. Experimental data for Chapter 5

6.4.1. Synthesis of 1-(2-bromoethyl)cyclohex-1-ene (5.5)



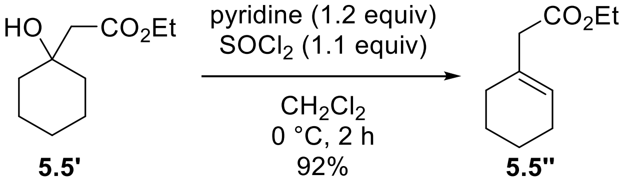
6.4.1.1. Synthesis of ethyl 2-(1-hydroxycyclohexyl)acetate (5.5')[49]



In a 1 L three-necked round-bottomed flask with reflux condenser were mixed zinc granules (42.5 g, 650 mmol), 1 crystal of iodine, cyclohexanone (51.8 mL, 500 mmol) in anhydrous THF (500 mL) under a N_2 atmosphere. Ethyl 2-bromoacetate (66.8 mL, 600 mmol) was then dropped into the mixture via dropping funnel at room temperature. The reaction mixture was first stirred at 50 ºC for 30 min and then refluxed at 65 ºC overnight. The reaction was cooled to room temperature and then quenched with 1 M aqueous HCl solution and the organic materials were extracted thrice with Et_2O. The combined organic extracts were washed once with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude product was purified by flash column chromatography (silica gel; hexane:EtOAc = 9:1) to give ethyl 2-(1-hydroxycyclohexyl)acetate (**5.5'**) (82.9 g, 445 mmol) in 89% yield.

Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (3H, t, *J* = 7.2 Hz), 1.38-1.71 (10H, m), 2.47 (2H, s), 3.43 (1H, br s), 4.16 (2H, q, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 22.0, 25.6, 37.4, 45.3, 60.5, 69.9, 172.9.

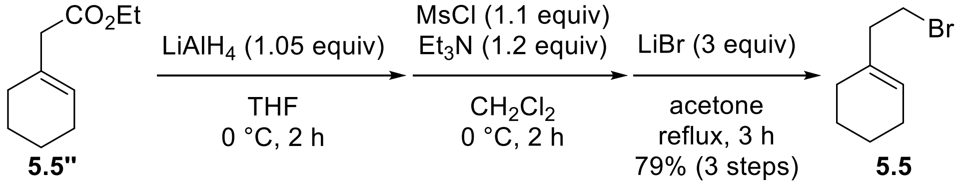
6.4.1.2. Synthesis of ethyl 2-(cyclohex-1-en-1-yl)acetate (5.5')[50]



To an ice cooled solution of ethyl 2-(1-hydroxycyclohexyl)acetate (**5.5'**) (79.5 g, 427 mmol) and pyridine (41.4 mL, 512 mmol) in anhydrous CH_2Cl_2 (570 mL) was added thionyl chloride (34.3 mL, 470 mmol) via a dropping funnel over 20 min under a N_2 atmosphere. The mixture was then stirred at 0 ºC for 2 h. The reaction was quenched with H_2O and the organic materials were extracted thrice with CH_2Cl_2. The combined organic extracts were washed twice with saturated aqueous $NaHCO_3$ and once with brine. The combined extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting crude residue was purified by flash column chromatography (silica gel; hexane:EtOAc = 9:1) to give ethyl 2-(cyclohex-1-en-1-yl)acetate (**5.5''**) (66.3 g, 394 mmol) in 92% yield.

Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (3H, t, *J* = 7.2 Hz), 1.53-1.66 (4H, m), 1.99-2.02 (4H, m), 2.94 (2H, s), 4.13 (2H, q, *J* = 7.2 Hz), 5.56 (1H, br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 22.0, 22.7, 25.3, 28.4, 43.7, 60.4, 125.5, 131.2, 172.0.

6.4.1.3. Synthesis of 1-(2-bromoethyl)cyclohex-1-ene (5.5)[49]

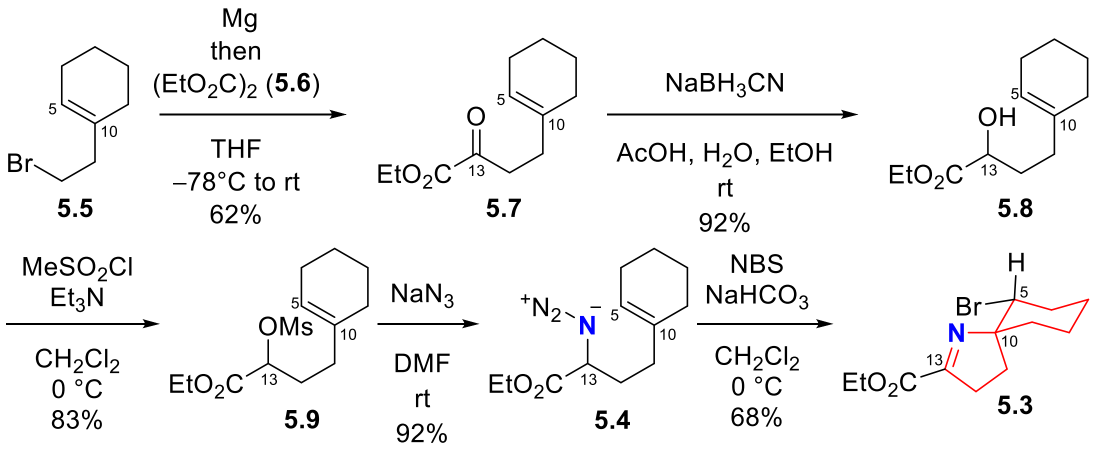


To an ice cooled suspension of lithium aluminum hydride (15.7 g, 414 mmol) in anhydrous THF (300 mL) was added a solution of ethyl 2-(cyclohex-1-en-1-yl)acetate (**5.5''**) (66.3 g, 394 mmol) in anhydrous THF (80 mL) via a dropping funnel over 45 min under a N_2 atmosphere. The mixture was then stirred at 0 ºC for 2 h before the reaction was carefully quenched at 0 ºC by dropping ice-cold H_2O into the reaction mixture until there was no effervescence. The resulting slurry was diluted with H_2O and the organic materials were extracted thrice with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* after filtration. The resulting crude alcohol was used for the next step without further purification.

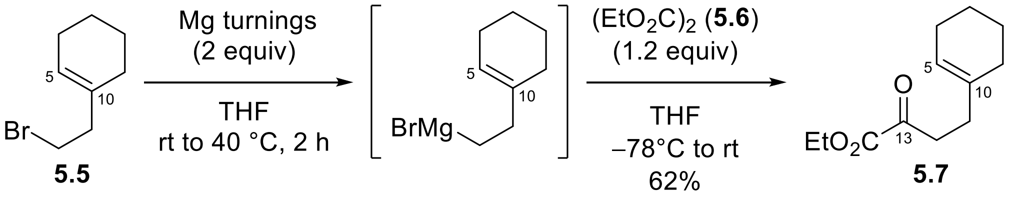
To an ice cooled solution of above crude alcohol (50.1 g) and Et_3N (65.9 mL, 473 mmol) in anhydrous CH_2Cl_2 (500 ml) was added methanesulfonyl chloride (33.5 mL, 433 mmol) via a dropping funnel over 15 min at 0 ºC under a N_2 atmosphere. The mixture was stirred for 2 h at 0 ºC before the reaction was quenched with H_2O. The organic materials were extracted thrice with CH_2Cl_2. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* after filtration. The resulting crude material including mesylate was then, without purification, dissolved in acetone (800 mL) before addition of lithium bromide (103 g, 1.19 mol) at room temperature. The mixture was stirred at 65 ºC for 3 h. The reaction was then cooled to room temperature and acetone was removed under reduced pressure. The resulting residue was diluted with H_2O and the organic materials were extracted thrice with hexane. The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* after filtration. The resulting residue was passed through a short silica gel column with hexane and concentrated *in vacuo*. The obtained crude materials were further purified by vacuum distillation (0.1 mbar, 60 ºC) to give 1-(2-bromoethyl)cyclohex-1-ene (**5.5**) (58.6 g, 310 mmol) in 79% overall yield in 3 steps from **5.5''**.

Colorless oil, bp 60 ºC at 0.1 mbar; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.55–1.65 (4H, m), 1.93– 2.00 (4H, m), 2.49 (2H, t, *J* = 7.5 Hz), 3.43 (2H, t, *J* = 7.5 Hz), 5.50 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.2, 22.8, 25.2, 27.9, 31.6, 41.4, 124.1, 134.8.

6.4.2. Synthesis of azaspirocycle 5.3 (Scheme 5.2)



6.4.2.1. Synthesis of ethyl 4-cyclohexenyl-2-oxobutanoate (5.7)

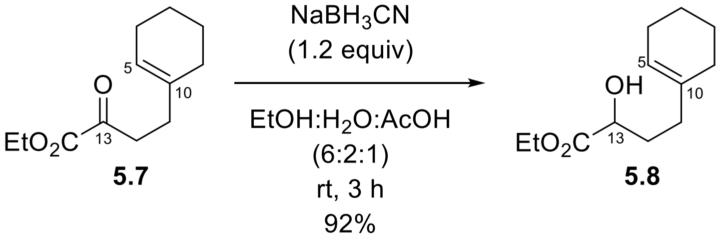


To a 250 mL two-necked round-bottomed flask installed with a reflux condenser was added Mg turnings (4.90 g, 202 mmol) and anhydrous THF (20 mL) under a N_2 atmosphere. A solution of 1-(2-bromoethyl)cyclohex-1-ene (**5.5**) (19.1 g, 101 mmol) in anhydrous THF (10 mL) was added dropwise into the stirred Mg suspension at room temperature until gentle reflux of the reaction mixture was initiated. The remaining bromide **5.5** in dropping funnel was then diluted with 190 mL of anhydrous THF and added dropped wise over 30 min to maintain a gentle reflux. After the addition was completed, the mixture was further stirred for 2 h at 40 ºC. The resulting Grignard reagent was cooled down to room temperature and transferred into another dropping funnel via cannula.

To a 500 mL two neck round bottomed flask installed with the dropping funnel containing the Grignard reagent prepared above was charged with a solution of freshly distilled diethyl oxalate (**5.6**) (16.4 mL, 121 mmol) in anhydrous THF (50 mL) under a N_2 atmosphere. The solution was cooled to –78 ºC in a dry ice-acetone bath, and the Grignard reagent was added into the solution via dropping funnel over 1 h at –78 ºC. The resulting mixture was stirred for 2 h at –78 ºC and then warmed up to room temperature over 1 h. The reaction mixture was then quenched with saturated aqueous NH_4Cl and the organic materials were extracted thrice with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* after filtration. The resulting crude material was purified by flash column chromatography (silica gel; hexane:EtOAc = 19:1) to afford ethyl 4-cyclohexenyl-2-oxobutanoate (**5.7**) (13.1 g, 62.4 mmol) in 62% yield.

Light yellow oil; IR (NaCl, neat) 3055, 2927, 1728, 1444, 1265, 1068, 1024 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (3H, t, *J* = 8.0 Hz), 1.52–1.65 (4H, m), 1.92–1.99 (4H, m), 2.26 (2H, t, *J* = 8.0 Hz), 2.93 (2H, t, *J* = 8.0 Hz), 4.31 (2H, q, *J* = 8.0 Hz), 5.42 (1H, t, *J* = 1.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.3, 22.8, 25.1, 28.3, 31.1, 37.7, 62.3, 122.0, 135.5, 161.2, 194.5. ESI (HRMS): Found: m/z 211.1329. Calcd for $C_{12}H_{19}O_3$: $(M+H)^+$ 211.1334.

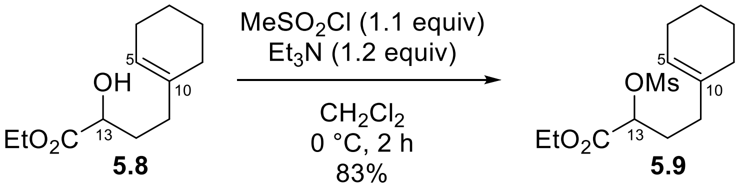
6.4.2.2. Synthesis of ethyl 4-cyclohexenyl-2-hydroxybutanoate (5.8)



To a 1 L round-bottomed flask with a solution of ethyl 4-cyclohexenyl-2-oxobutanoate (**5.7**) (28.8 g, 137 mmol) in EtOH (300 mL), H_2O (100 mL) and AcOH (50 mL) was added sodium cyanoborohydride (10.3 g, 164 mmol) at 0 °C under a N_2 atmosphere. The mixture was stirred at room temperature for 3 h. The reaction was then quenched with saturated aqueous NH_4Cl and the volatile materials were removed under reduced pressure. The resulting residue was diluted with H_2O and extracted thrice with ethyl acetate. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* after filtration. The resulting crude material was purified by flash column chromatography (silica gel; hexane:EtOAc = 9:1) to afford ethyl 4-cyclohexenyl-2-hydroxybutanoate (**5.8**) (26.7 g, 126 mmol) in 92% yield.

Colorless oil; IR (NaCl, neat) 3035, 2985, 2304, 1728, 1421, 1265 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (3H, t, *J* = 7.0 Hz), 1.52–1.64 (4H, m), 1.68–1.75 (1H, m), 1.89–2.00 (5H, m), 2.03–2.09 (2H, m), 2.73 (1H, m), 4.15-4.18 (1H, m), 4.24 (2H, q, *J* = 7.0 Hz), 5.45 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 22.4, 22.9, 25.2, 28.2, 32.5, 33.0, 61.6, 70.1, 121.7, 136.6, 175.3. ESI (HRMS): Found: m/z 213.1493. Calcd for $C_{12}H_{21}O_3$: $(M+H)^+$ 213.1491.

6.4.2.3. Synthesis of ethyl 4-(cyclohex-1-en-1-yl)-2-((methylsulfonyl)oxy)butanoate (5.9)

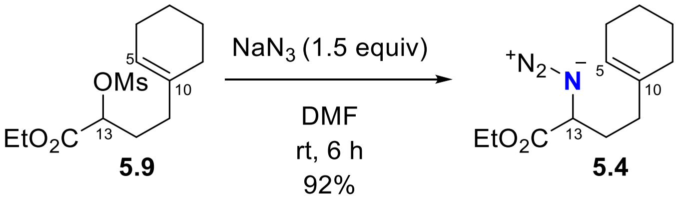


To an ice cooled 1 L three-necked round-bottomed flask with a solution of ethyl 4-cyclohexenyl-2-hydroxybutanoate (**5.8**) (26.7 g, 126 mmol) and Et_3N (21.1 mL, 151 mmol) in anhydrous CH_2Cl_2 (420 mL) under a N_2 atmosphere was added methanesulfonyl chloride (10.7 mL, 139 mmol) via a dropping funnel over 30 min at 0 ºC. The solution was continuously stirred for 2 h at 0 ºC. The reaction was then quenched with H_2O and the organic materials were extracted thrice with CH_2Cl_2. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* after filtration. The resulting crude material was purified by flash column chromatography (silica gel; hexane:EtOAc = 9:1) to afford ethyl

4-(cyclohex-1-en-1-yl)-2-((methylsulfonyl)oxy)butanoate (**5.9**) (30.3 g, 104 mmol) in 83% yield.

Colorless oil; IR (NaCl, neat) 2927, 2854, 1751, 1446, 1361, 1176, 1037, 960 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.31 (3H, t, *J* = 7.0 Hz), 1.55-1.63 (4H, m), 1.91-2.08 (8H, m), 3.15 (3H, s), 4.25 (2H, q, *J* = 7.0 Hz), 4.99-5.01 (1H, m), 5.47 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.3, 22.8, 25.2, 28.1, 30.1, 32.9, 39.1, 61.9, 77.5, 122.8, 135.2, 169.3; ESI (HRMS): Found: m/z 291.1270. Calcd for $C_{13}H_{23}O_5S$: $(M+H)^+$ 291.1266.

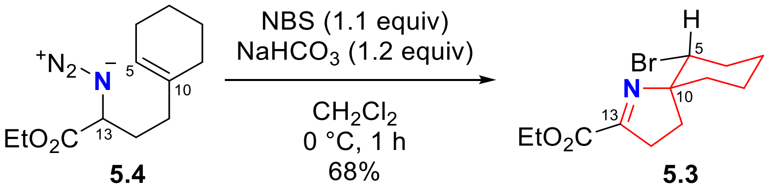
6.4.2.4. Synthesis of ethyl 2-azido-4-cyclohexenylbutanoate (5.4)



To a 500 mL two-necked round-bottomed flask was charged with a solution of mesylate **5.9** (26.6 g, 91.7 mmol) in anhydrous DMF (175 mL). The solution was cooled to 0 °C before addition of NaN_3 (9.01 g, 139 mmol) in two portions. The reaction mixture was then warmed up to room temperature and stirred for 6 h. The reaction was then quenched with H_2O and the organic materials were extracted thrice with Et_2O. The combined extracts were washed with water and brine, dried over $MgSO_4$ and concentrated *in vacuo* after filtration. The resulting crude materials were purified by flash column chromatography (silica gel; hexane:EtOAc = 50:1) to afford ethyl 2-azido-4-cyclohexenylbutanoate (**5.4**) (20.0 g, 84.6 mmol) in 92% yield.

Colorless oil; IR (NaCl, neat) 3053, 2985, 2927, 2304, 2106, 1737, 1446, 1421, 1371, 1265, 1195,1031 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.32 (3H, t, *J* = 7.0 Hz), 1.54–1.57 (2H, m), 1.60–1.65 (2H, m), 1.78–1.86 (1H, m), 1.91–1.99 (5H, m), 2.04–2.08 (2H, m), 3.78 (1H, dd, *J* = 10.0, 5.0 Hz), 4.25 (2H, q, *J* = 7.0 Hz), 5.46 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 22.4, 22.9, 25.2, 28.1, 29.5, 34.0, 61.6, 61.7, 122.6, 135.6, 170.7; ESI (HRMS): Found: m/z 238.1546. Calcd for $C_{12}H_{20}N_3O_2$: $(M+H)^+$ 238.1556.

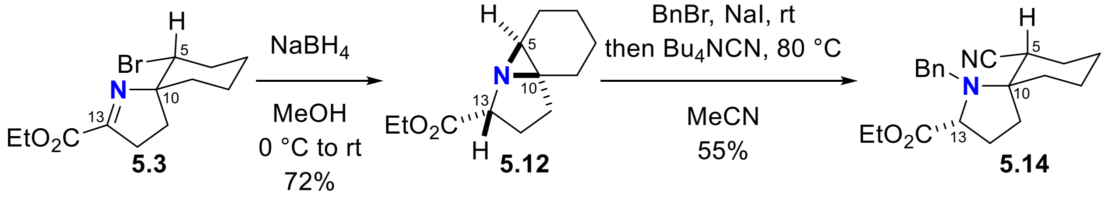
6.4.2.5. Synthesis of Ethyl (5*R**,6*S**)-6-bromo-1-azaspiro[4.5]dec-1-ene-2-carboxylate (5.3)



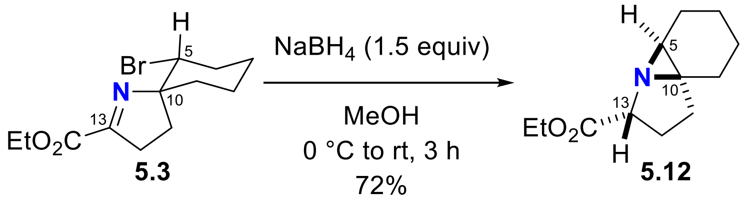
A 1 L three-necked round-bottomed flask was charged with a solution of ethyl 2-azido-4-cyclohexenylbutanoate (**5.4**) (17.6 g, 74.3 mmol) in anhydrous CH_2Cl_2 (250 mL) and cooled to 0 ºC under a N_2 atmosphere. To this solution, $NaHCO_3$ (7.49 g, 89.2 mmol) and *N*-bromosuccinimide (14.5 g, 81.7 mmol) were added in one portion at 0 ºC and the mixture was stirred at the same temperature for 1 h. The reaction mixture was quenched with H_2O and extracted thrice with CH_2Cl_2. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated under *vacuo* after filtration. The crude product was purified by flash column chromatography (silica gel; hexane:EtOAc = 19:1 to 4:1) to afford ethyl (5*R**,6*S**)-6-bromo-1-azaspiro[4.5]dec-1-ene-2-carboxylate (**5.3**) (14.5 g, 50.4 mmol) as a light yellow oil in 68% yield.

Light yellow oil; IR (NaCl) 3419, 3053, 2941, 2304, 1720, 1637, 1448, 1421, 1375, 1265, 1128, 1101, 1018 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (3H, t, *J* = 7.2 Hz), 1.421–1.46 (2H, m), 1.67–1.83 (5H, m), 1.97-1.99 (1H, m), 2.23 (1H, ddd, *J* = 13.2, 10.8, 6.0 Hz), 2.32–2.36 (1H, m), 2.87 (1H, ddd, *J* = 18.4, 10.4, 6.0 Hz), 2.97 (1H, ddd, *J* = 18.8, 10.8, 6.0 Hz), 4.36 (2H, q, *J* = 7.2 Hz), 4.53 (1H, dd, *J* = 12.0, 4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 22.1, 26.8, 27.9, 34.7, 36.7, 37.8, 61.3, 62.0, 82.7, 162.9, 166.3. ESI (HRMS): Found: m/z 288.0598. Calcd for $C_{12}H_{19}NO_2{}^{79}Br$: $(M+H)^+$ 288.0599.

6.4.3. Synthesis of 5.14 (Scheme 5.3)



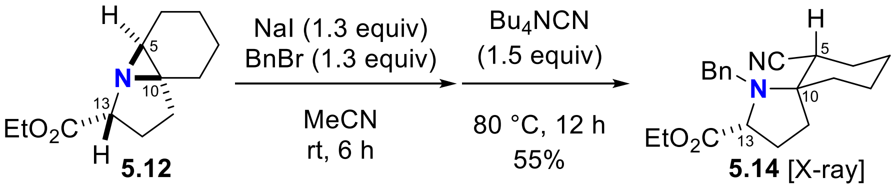
6.4.3.1. Synthesis of ethyl (3*R**, 8a*R**)-hexahydro-1*H*,6*H*-benzo[2,3]azirino[1,2-*a*]pyrrole-3-carboxylate (5.12)



A 1 L round-bottomed flask was a charged with a solution of ethyl (5*R**,6*S**)-6-bromo-1-azaspiro[4.5]dec-1-ene-2-carboxylate (**5.3**) (14.5 g, 50.4 mmol) in MeOH (170 mL) under a N_2 atmosphere. Sodium borohydride (2.86 g, 75.6 mmol) was then added in 3 portions over 15 min at 0 ºC. The reaction was then warmed up to room temperature and stirred for 3 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and the volatile materials were removed *in vacuo*. The resulting residue was diluted with H_2O and the organic materials were extracted thrice with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated under *vacuo* after filtration. The crude product was purified by flash column chromatography (silica gel; hexane:EtOAc = 4:1) to afford the ethyl (3*R**,8a*R**)-hexahydro-1*H*,6*H*-benzo[2,3]azirino[1,2-*a*]pyrrole-3-carboxylate (**5.12**) (7.60 g, 36.3 mmol) as a colorless oil in 72% yield.

Colorless oil; IR (NaCl) 3414, 3053, 2983, 2937, 2860, 2304, 1732, 1637, 1438, 1421, 1377, 1265, 1203, 1172, 1147, 1095, 1026 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.27 (3H, t, *J* = 7.5 Hz), 1.20-1.28 (2H, m), 1.37-1.41 (2H, m), 1.66-1.91 (7H, m), 2.06 (1H, d, *J* = 5.0 Hz), 2.13 (1H, dd, *J* = 12.5, 7.5 Hz), 3.89 (1H, dd, *J* = 10.5, 7.5 Hz), 4.12-4.25 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 20.5, 21.4, 24.2, 25.1, 27.6, 32.5, 35.6, 50.1, 60.6, 65.2, 173.0; ESI (HRMS): Found: m/z 210.1491. Calcd for $C_{12}H_{20}NO_2$: $(M+H)^+$ 210.1494.

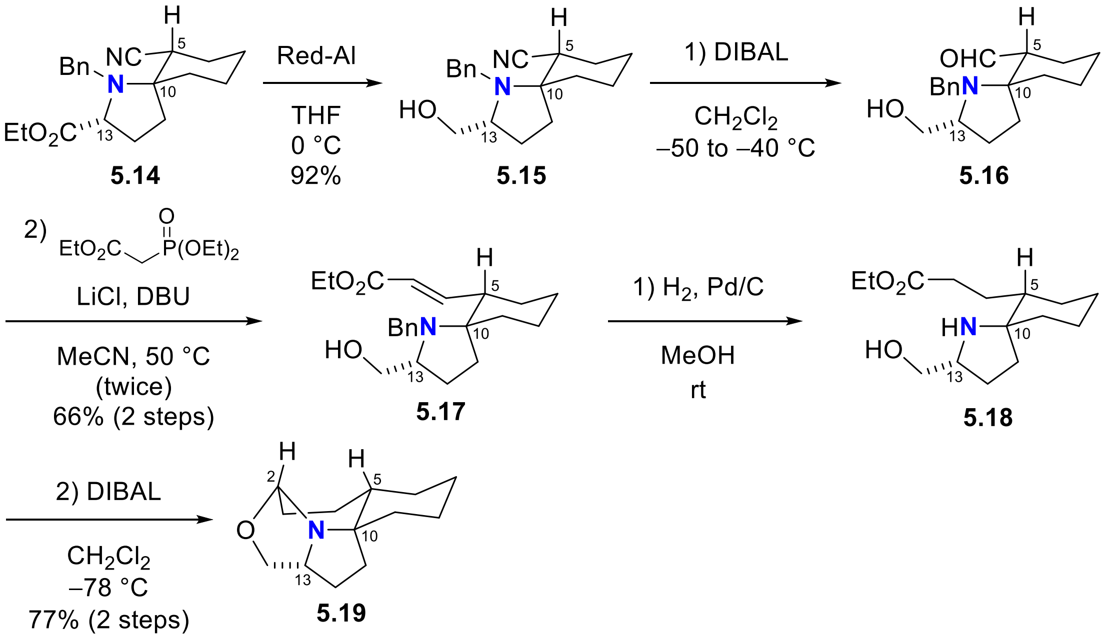
6.4.3.2. Synthesis of ethyl (1*R**, 2*R**, 5*S**, 6*R**)-1-benzyl-6-cyano-1-methyl-1λ⁴-azaspiro[4.5]decane-2-carboxylate (5.14)



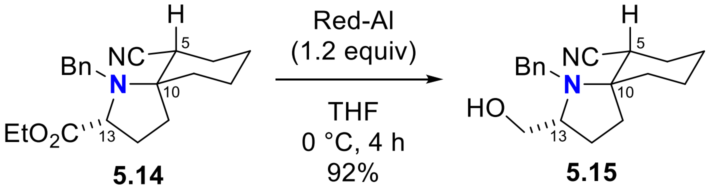
To a 100 mL Schlenk tube containing NaI (2.21 g, 14.8 mmol) in anhydrous MeCN (20 mL) was added benzyl bromide (2.19 g, 12.8 mmol) under a N_2 atmosphere, and the mixture was stirred at room temperature for 30 min. To this mixture, a solution of ethyl (3*R**,8a*R**)-hexahydro-1*H*,6*H*-benzo[2,3]azirino[1,2-*a*]pyrrole-3-carboxylate (**5.12**) (2.06 g, 9.84 mmol) in anhydrous MeCN (10 mL) was then added, and the mixture was stirred at room temperature for another 6 h. Finally, tetrabutylammonium cyanide (3.96 g, 14.8 mmol) was added to the mixture and the mixture was stirred at 80 ºC for 12 h, before the reaction was cooled to room temperature and quenched with saturated aqueous NH_4Cl. The organic materials were extracted thrice with EtOAc and the combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* filtration. The crude product was purified by flash column chromatography (silica gel; hexane:EtOAc = 9:1) to afford ethyl (1*R**,2*R**,5*S**,6*R**)-1-benzyl-6-cyano-1-methyl-1λ^4-azaspiro[4.5]decane-2-carboxylate (**5.14**) (1.78 g, 5.45 mmol) as a white solid in 55% yield. Further recrystallization from hexane-CH_2Cl_2 afforded colorless crystal, the structure of which was secured by X-ray crystallographic analysis.

Colorless crystal (CCDC-1483783); mp 92-93 ºC; IR (NaCl) 3055, 2982, 2239, 1740, 1495, 1454, 1369, 1265, 1028; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.06 (1H, qt, *J* = 13.0, 4.0 Hz), 1.13 (3H, t, *J* = 7.0 Hz), 1.32-1.40 (1H, m), 1.48-1.77 (5H, m), 1.91 (1H, ddd, *J* = 12.0, 8.0, 4.5 Hz), 2.01-2.21 (4H, m), 2.46 (1H, dd, *J* = 12.5, 3.5 Hz), 3.49 (1H, dd, *J* = 8.5, 5.5 Hz), 3.62 (1H, d, *J* = 14.0 Hz), 3.76–3.87 (2H, m), 3.99 (1H, d, *J* = 14.0 Hz), 7.21 (1H, t, *J* = 7.5 Hz), 7.27-7.30 (2H, m), 7.46 (2H, d, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 23.1, 24.7, 27.3, 29.3, 30.6, 31.2, 38.8, 52.0, 60.5, 66.0, 66.2, 121.2, 127.2, 128.1, 129.0, 139.2, 174.2; ESI (HRMS): Found: *m/z* 327.2070. Calcd for $C_{20}H_{27}N_2O_2$: $(M+H)^+$ 327.2073.

6.4.4. Synthesis of *N,O*-acetal 5.19 (Scheme 5.4)



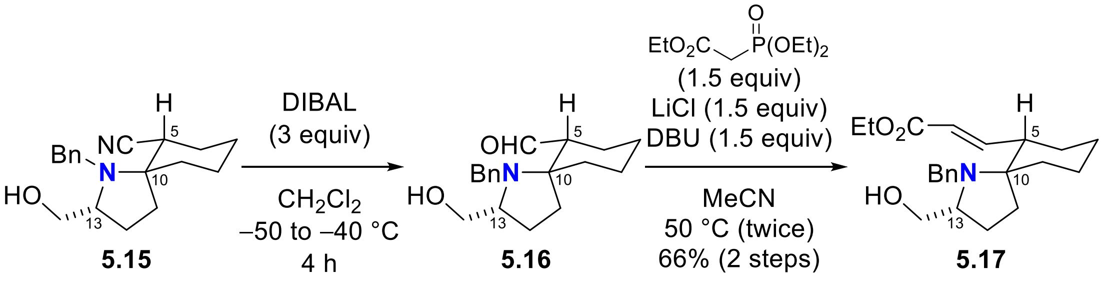
6.4.4.1. Synthesis of (1*R**, 2*R**, 5*S**, 6*R**)-1-benzyl-2-(hydroxymethyl)-1-methyl-1λ^4-azaspiro[4.5]decane-6-carbonitrile (5.15)



To a THF (12 mL) solution of ethyl (1*R**,2*R**,5*S**,6*R**)-1-benzyl-6-cyano-1-methyl-1λ^4-azaspiro[4.5]decane-2-carboxylate (**5.14**) (2.22 g, 6.52 mmol) in a 100 mL two-necked round-bottomed flask was added Red-Al (2.5 mL, 7.82 mmol, 60% wt/wt in toluene) dropwise at 0 ºC under a N_2 atmosphere. After 4 h, the reaction was quenched with saturated aqueous NH_4Cl and the organic materials were extracted thrice with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* after filtration. The crude product was purified by flash column chromatography (silica gel; hexane:EtOAc = 5:1) to give (1*R**,2*R**,5*S**,6*R**)-1-benzyl-2-(hydroxymethyl)-1-methyl-1λ^4-azaspiro[4.5]decane-6-carbonitrile (**5.15**) (1.80 g, 6.02 mmol) as a white solid in 92% yield.

White solid; mp 101-102 ºC; IR (NaCl) 3528, 3053, 2980, 2237, 1495, 1452, 1265, 1078; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.08 (1H, qt, *J* = 13.2, 3.6 Hz), 1.38-2.06 (11H, m), 2.31 (1H, d, *J* = 10.8 Hz), 2.58 (1H, dd, *J* = 12.8, 3.6 Hz), 2.99-3.04 (2H, m), 3.16 (1H, t, *J* = 10.0 Hz), 3.49 (1H, d, *J* = 14.0 Hz), 3.98 (1H, d, *J* = 14.0 Hz), 7.26 (1H, t, *J* = 6.4 Hz), 7.33 (2H, t, *J* = 7.2 Hz), 7.41 (2H, d, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 23.0, 24.7, 26.0, 28.6, 28.9, 30.4, 39.0, 52.4, 64.4, 65.4, 66.4, 121.9, 127.4, 128.3, 128.7, 140.2; ESI (HRMS): Found: *m/z* 285.1968. Calcd for $C_{18}H_{25}N_2O$: $(M+H)^+$ 285.1967.

6.4.4.2. Synthesis of ethyl (*E*)-3-((2*R**, 5*S**, 6*S**)-1-benzyl-2-(hydroxymethyl)-1-azaspiro[4.5]decan-6-yl)acrylate (5.17)



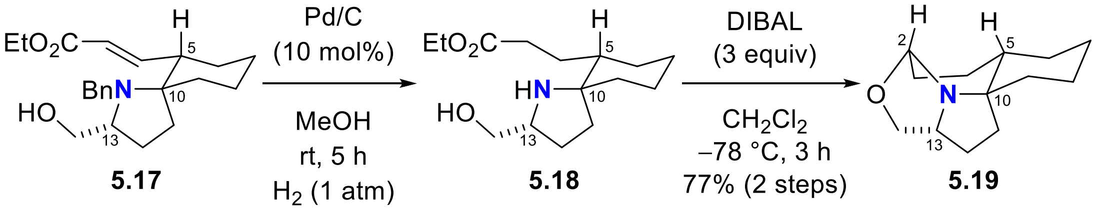
A 100 mL two-necked round-bottomed flask with a solution of (1*R**,2*R**,5*S**,6*R**)-1-benzyl-2-(hydroxymethyl)-1-methyl-1λ^4-azaspiro[4.5]decane-6-carbonitrile (**5.15**) (983 mg, 3.28 mmol) in anhydrous CH_2Cl_2 (11 mL) was cooled to –50 ºC under a N_2 atmosphere. To the solution was added DIBAL (10 mL, 10.0 mmol, 1.0 M solution in cyclohexane) and the mixture was stirred at the same temperature for 3 h. The reaction mixture was then warmed up to –40 ºC and stirred for additional 1 h. The reaction was quenched with MeOH and saturated aqueous Rochelle salt was added. The resulting slurry mixture was stirred at room temperature for 1 h. The organic materials were extracted thrice with CH_2Cl_2 and the combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* after filtration. The resulting crude materials including aldehyde **5.16** was used to the next step without further purification.

The resulting crude aldehyde **5.16** was dissolved in anhydrous acetonitrile (10 mL) in a 100 mL two-necked round-bottomed flask. To the mixture were added LiCl (213 mg, 5.02 mmol), DBU (0.75 mL, 5.02 mmol), and triethyl phosphonoacetate (1.0 mL, 5.04 mmol), and the reaction mixture was stirred at 50 ºC for 24 h.[51] The reaction was then cooled down to room temperatures and quenched with saturated aqueous NH_4Cl. The organic materials were extracted thrice with EtOAc and the combined extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* after filtration. As the resulting crude materials still contained unreacted aldehyde **5.16** (aldehyde **5.16** : α,β-unsaturated ester **5.17** = 1:3.9), the mixture was subjected under the same reaction conditions described above and the reaction mixture was stirred for 6 h before the same work-up procedure described above was conducted. The crude product was purified by flash column chromatography (silica gel; hexane:EtOAc = 10:1) to give ethyl (*E*)-3-((2*R**,5*S**,6*S**)-1-benzyl-2-(hydroxymethyl)-1-azaspiro[4.5]decan-6-yl)acrylate (**5.17**) (773 mg, 2.16 mmol) in 66% overall yield from **5.15**.

Pale yellow oil; IR (NaCl, $CHCl_3$) 3466, 3013, 1709, 1647, 1454, 1273 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.24–1.97 (16H, m), 2.38-2.43 (1H, m), 2.86 (1H, dd, *J* =

10.8, 3.6 Hz), 2.94-2.97 (1H, m), 3.05-3.07 (1H, m), 3.41 (1H, d, *J* = 13.6 Hz), 4.07 (1H, d, *J* = 13.6 Hz), 4.21 (2H, q, *J* = 7.2 Hz), 5.78 (1H, dd, *J* = 16.0, 1.2 Hz), 7.23-7.32 (5H, m), 7.41 (1H, dd, *J* = 16.0, 6.8 Hz) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 23.6, 25.6, 26.2, 28.0, 29.7, 30.0, 45.8, 52.2, 60.2, 64.3, 64.9, 68.9, 121.8, 127.2, 128.5 (overlapped), 141.1, 151.1, 166.5; ESI (HRMS): Found: m/z 358.2386. Calcd for $C_{22}H_{32}NO_3$: $(M+H)^+$ 358.2382.

6.4.4.3. Synthesis of (2a*R**, 4a*S**, 10a*R**)-dodecahydrobenzo[h]oxazolo[4,3,2-cd]indolizine (5.19)



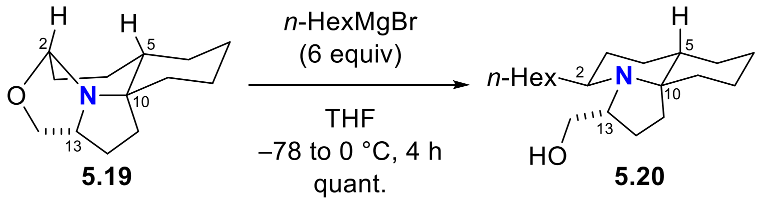
To a 50 mL Schlenk tube containing a solution of ethyl (*E*)-3-((2*R**,5*S**,6*S**)-1-benzyl-2-(hydroxymethyl)-1-azaspiro[4.5]decan-6-yl)acrylate (**5.17**) (739 mg, 2.07 mmol) in MeOH (20 mL) was added Pd/C (215 mg, 0.202 mmol, 10% Pd wt/wt on carbon) at room temperature under a N_2 atmosphere. The mixture was then charge with H_2 gas (1 atm) and the mixture was stirred at the same temperature for 5 h before the reaction tube was backfilled with N_2 gas. The reaction mixture was then filtered over Celite pad and the collected filtrate was concentrated *in vacuo*. The resulting crude materials including spirocyclic pyrrolidine **5.18** were used for the next step without further purification.

To a solution of the crude mixture prepared above in anhydrous CH_2Cl_2 (20 mL) was cooled down to –78 °C before DIBAL (6.2 mL, 6.20 mmol, 1.0 M solution in cyclohexane) was added dropwise to the mixture. The mixture was then stirred at the same temperature for 3 h. The reaction was quenched with MeOH and saturated aqueous Rochelle salt was subsequently added to the mixture. The slurry mixture was then stirred at room temperature for additional 1 h. The organic materials were extracted thrice with CH_2Cl_2 and the combined extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* after filtration. The resulting residue was purified by flash column chromatography (basic alumina; hexane:EtOAc = 1:1) to give (2a*R**,4a*S**,10a*R**)-dodecahydrobenzo[*h*]oxazolo[4,3,2-*cd*]indolizine (**5.19**) (332 mg, 1.60 mmol) in 77% overall yield from **5.17**.

Pale yellow oil; IR (NaCl, neat) 2929, 2856, 2104, 1743, 1446, 1224, 1165, 1029 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.09–1.70 (14H, m), 1.84-1.93 (1H, m), 2.04-2.14 (2H, m), 3.64–3.70 (3H, m), 4.35 (1H, d, $J = 4.0$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 23.4, 26.0, 26.2, 28.8, 31.0, 32.5, 38.9, 44.3, 62.4, 67.2, 74.1, 91.2; ESI (HRMS): Found: m/z 208.1703. Calcd for $C_{13}H_{22}NO$: $(M+H)^+$ 208.1701.

6.4.5. Stereoselective alkylation of *N*,*O*-acetal 5.19

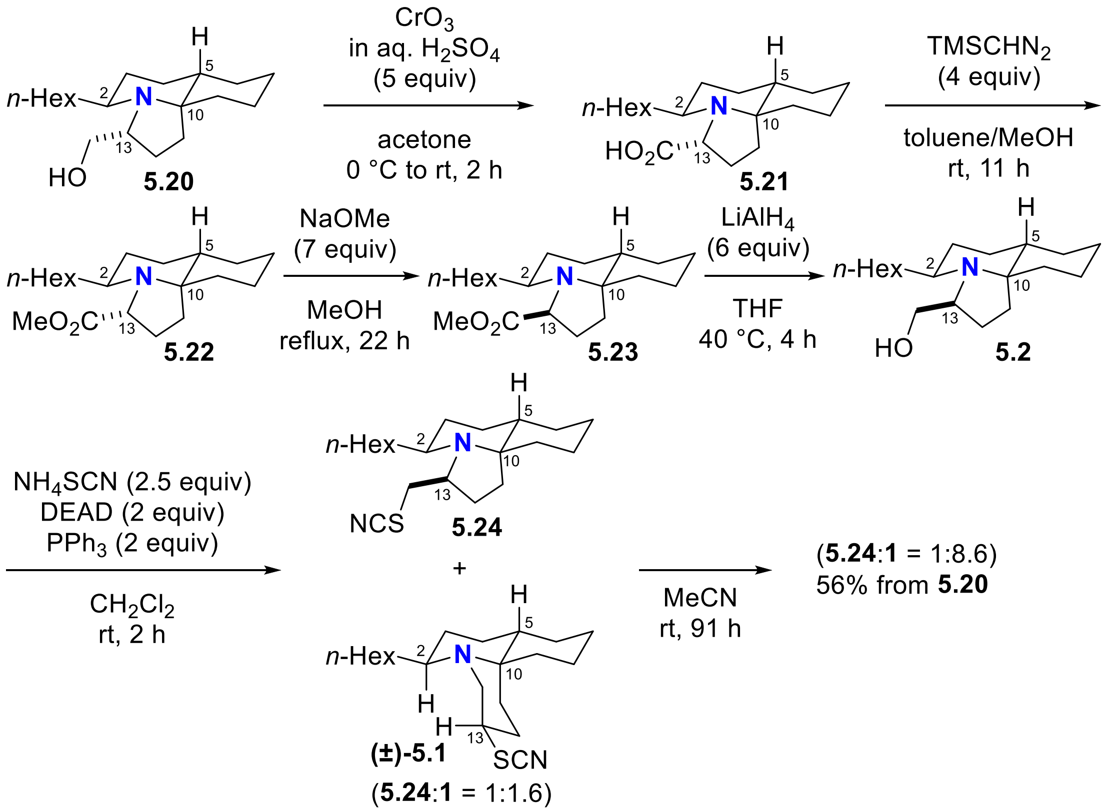
6.4.5.1. Synthesis of ((3*R**, 5*S**, 7a*S**, 11a*S**)-5-hexyldecahydro-1*H*-pyrrolo[2,1-*j*]quinolin-3-yl)methanol (5.20)



To a 25 mL Schlenk tube containing a solution of tetracyclic aminal **5.19** (179 mg, 0.865 mmol) in anhydrous THF (16 mL) was added *n*-hexylmagnesium bromide (2.6 mL, 5.20 mmol, 2M solution in Et_2O) dropwise at –78 ºC under a N_2 atmosphere. The reaction mixture was warmed up to 0 ºC and stirred for 4 h before the reaction was quenched with saturated aqueous NH_4Cl. The organic materials were extracted thrice with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, and concentrated *in vacuo* after filtration. The crude product was purified by flash column chromatography (basic alumina; hexane:EtOAc = 1:4, then CH_2Cl_2:MeOH = 4:1) to give ((3*R**,5*S**,7a*S**,11a*S**)-5-hexyldecahydro-1*H*-pyrrolo[2,1-*j*]quinolin-3-yl)methanol (**5.20**) (254 mg, 0.864 mmol) in quantitative yield.

Pale yellow oil; IR (NaCl, $CHCl_3$) 3329, 2859, 1450, 1240, 1042 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.87 (3H, t, *J* = 6.5 Hz), 1.04 (1H, qd, *J* = 13.0, 3.5 Hz), 1.17-1.91 (26H, m), 2.21 (1H, brs), 2.47-2.48 (1H, m), 3.55-3.58 (1H, m) 3.61 (1H, dd, *J* = 10.5, 6.0 Hz), 3.90 (1H, dd, *J* = 10.5, 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.6, 23.8, 24.4, 25.2, 26.2, 26.4, 27.3, 29.6, 30.7, 31.4, 31.9, 39.1, 40.1, 41.5, 52.1, 63.3, 64.1, 68.3; ESI (HRMS): Found: m/z 294.2802. Calcd for $C_{19}H_{36}NO$: $(M+H)^+$ 294.2797.

6.4.6. Synthesis of fasicularin (5.1)



To a solution of ((3*R**,5*S**,7a*S**,11a*S**)-5-hexyldecahydro-1*H*-pyrrolo[2,1-*j*]quinolin-3-yl)methanol (**5.20**) (195 mg, 0.665 mmol) in acetone (13 mL) was added Jones reagent (1.1 mL, 3.30 mmol, 3 M solution in H_2O) dropwise at 0 ºC. The mixture was then warmed up to room temperature and stirred for 2 h. To the mixture were added H_2O (5 mL) and CH_2Cl_2 (5 mL) and then the mixture was neutralized by adding saturated aqueous $NaHCO_3$ to render the solution pH 6-7. The organic materials were extracted seven times with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, filtered, and then passed through a short plug of basic alumina with 10% MeOH in CH_2Cl_2. The filtrate was concentrated under reduced pressure to give the crude residue containing carboxylic acid **5.21**, which was used for the next step without further purification.

To a solution of the crude carboxylic acid **5.21** in toluene (12 mL) and MeOH (2.4 mL) was added TMSCHN$_2$ (1.4 mL, 2.80 mmol, 2.0 M in hexane) at room temperature. After the reaction mixture was stirred for 11 h, the volatile materials were removed *in vacuo* to afford a mixture containing methyl ester **5.22**, which was used for the next step without further purification.

To a solution of methyl ester **5.22** in anhydrous MeOH (11 mL) was added NaOMe (2.2 mL, 4.40 mmol, 2 M in MeOH) under inert atmosphere and the mixture was stirred under reflux conditions for 22 h. The reaction mixture was then cooled down to room temperature and quenched with saturated aqueous NH$_4$Cl. The organic materials were extracted six times with CH$_2$Cl$_2$. The combined organic extracts were dried over Na$_2$SO$_4$, and concentrated *in vacuo* after filtration to give epimerized ester **5.23**, which was used for the next step without further purification.

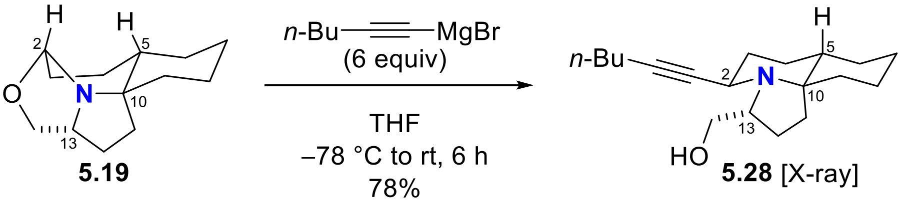
To a solution of ester **5.23** in anhydrous THF (50 mL) was added LiAlH$_4$ (155 mg, 4.07 mmol) portion-wise at 0 ºC under a N$_2$ atmosphere. The reaction mixture was then warmed up to 40 ºC and stirred for 4 h. The reaction mixture was then cooled down to 0 ºC and H$_2$O (0.15 mL), 15% aqueous NaOH solution (0.15 mL), and H$_2$O (0.45 mL) was cautiously dropped in this order into the reaction mixture. The resulting suspension was filtered through a Celite pad with washing with EtOAc and the collected filtrate was concentrated *in vacuo* to afford crude materials including C2-*epi*-lepadiformine A (**5.2**), which was used to the next step without purification.

To a solution of DEAD (233 mg, 1.33 mmol), PPh$_3$ (351 mg, 1.34 mmol), and NH$_4$SCN (128 mg, 1.69 mmol) in CH$_2$Cl$_2$ (4 mL) was added a solution of crude alcohol **5.2** in CH$_2$Cl$_2$ (10 mL) dropwise at room temperature. After the mixture was stirred for 2 h at room temperature, the reaction was quenched with saturated aqueous NaHCO$_3$ and the organic materials were extracted thrice with CH$_2$Cl$_2$. The combined organic extracts were dried over Na_2SO_4, and concentrated *in vacuo* after filtration. The resulting crude materials were purified by flash column chromatography (silica gel; hexane:EtOAc = 80:1) to give a mixture of fasicularin (**5.1**) and its structural isomer **5.24** in the ratio of 1.6:1. The resulting mixture was dissolved in MeCN (14 mL) and stirred at room temperature for 91 h. After removal of the solvent under reduced pressure, the resulting residue was purified by flash column chromatography (silica gel; hexane:EtOAc = 60:1) to give a mixture of fasicularin (**5.1**) and **5.24** (125 mg, 0.375 mmol, **5.1**:**5.24** = 8.6:1) in 56% overall yield from **5.20**. Fasicularin (**5.1**) could be separated partially for the characterization.

Pale pink solid; mp 46-47 ^{o}C:IR (NaCl, $CHCl_3$) 2927, 2858, 2355, 2152, 2054, 1060 cm^{-1}; ^{1}H NMR (400 MHz, pyridine-d_5) δ 0.89 (3H, t, *J* = 6.4 Hz), 1.00-1.04 (2H, m), 1.16-1.58 (21H, m), 1.76-1.90 (2H, m), 1.92-1.97 (1H, m), 2.54 (1H, d, *J* = 12.4 Hz), 2.90-2.94 (1H, m), 3.26-3.30 (1H, m), 3.38 (1H, dd, *J* = 14.4, 12.0 Hz), 3.53-3.60 (1H, m); ^{13}C NMR (100 MHz, pyridine-d_5) δ 14.3, 19.3, 22.7, 22.9, 24.0, 26.3, 27.2, 27.7, 29.5, 30.2, 32.1, 32.3, 34.1, 34.3, 40.2, 46.1, 46.5, 52.3, 56.3, 111.6; ESI (HRMS): Found: m/z 335.2519. Calcd for $C_{20}H_{35}N_2S$: $(M+H)^+$ 335.2521.

NMR spectra of the natural fasicularin (**5.1**)[52]: ^{1}H NMR (400 MHz, pyridine-d_5) δ 0.84 (3H, t, *J* = 6.4 Hz), 0.95-1.10 (2H , m), 1.11-1.32 (14H, m), 1.33-1.58 (7H , m), 1.78 (1H, td, *J* = 12.9, 4.6 Hz), 1.87 (1H, qd, *J* = 12.4, 3.9 Hz), 1.92-1.99 (1H, m), 2.54 (1H, d, *J* = 12.2 Hz), 2.92 (1H, ddt, *J* = 11.2, 5.6, 2.7 Hz), 3.28 (1H, ddd, *J* = 14.5, 4.4, 1.8 Hz), 3.38 (1H, dd, *J* = 14.5, 12.0 Hz), 3.52–3.62 (m, 1H); ^{13}C NMR (100 MHz, pyridine-d_5) δ 14.2, 19.3, 22.7, 22.9, 24.0, 26.3, 27.2, 27.7, 29.5, 30.2, 32.1, 32.4, 34.1, 34.3, 40.2, 46.1, 46.5, 52.3, 56.3, 111.5.

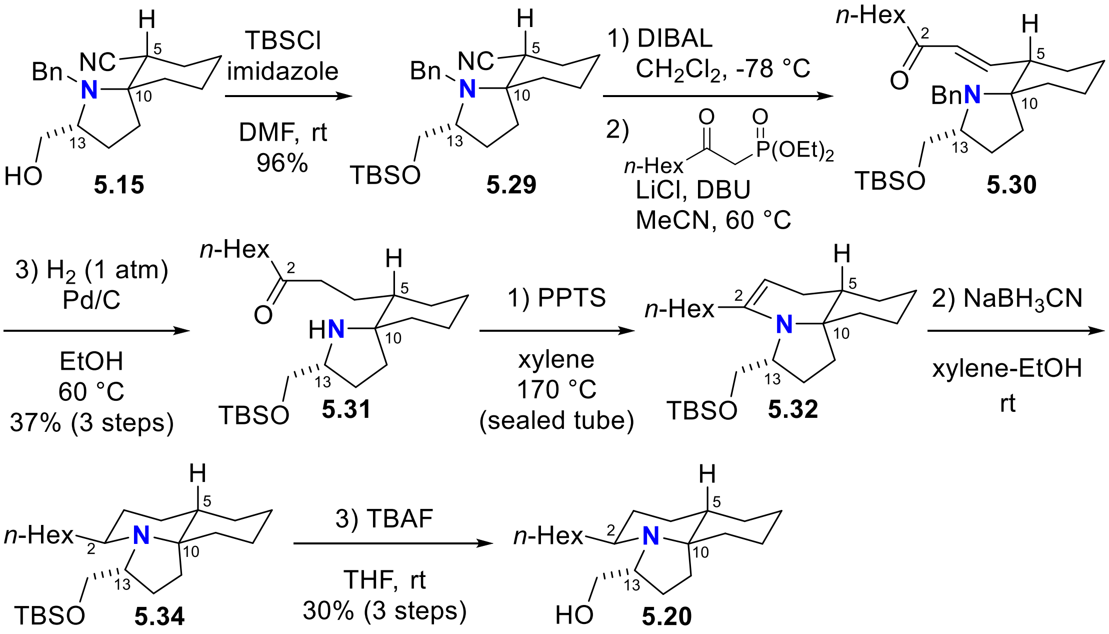
6.4.7. Stereoselective alkynylation of *N,O*-acetal 5.19 (Scheme 5.7)



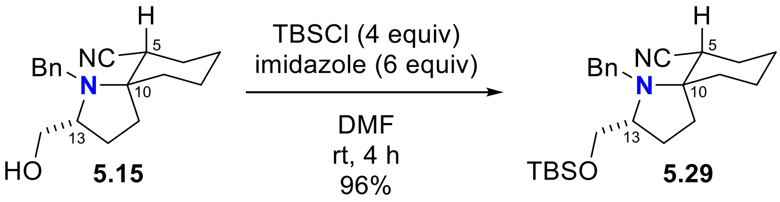
To a solution of 1-hexyne (0.7 mL, 6.09 mmol) in anhydrous THF (6 mL) was added methylmagnesium bromide (4.3 mL, 6.02 mmol, 1.4 M solution in THF/toluene) at room temperature under a N_2 atmosphere. After the mixture was stirred for 12 h, the preformed solution of 1-hexynylmagnesium bromide was added dropwise to a solution of tetracyclic aminal **5.19** (207 mg, 1.00 mmol) in anhydrous THF (4 mL) at –78 ºC. The resulting mixture was warmed up to 0 °C and stirred for another 6 h while warming up to room temperature gradually. The reaction was quenched with water and the organic materials were extracted thrice with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* after filtration. The crude product was purified by flash column chromatography (silica gel; MeOH:EtOAc:Et_3N = 10:89:1) to give ((3*R**,5*R**,7a*S**,11a*S**)-5-(hex-1-yn-1-yl)decahydro-1*H*-pyrrolo[2,1-*j*]quinolin-3-yl) methanol (**5.28**) (225 mg, 0.777 mmol) in 78% yield as a yellow solid. Recrystallization from EtOAc/hexane provide colorless crystal, the structure of which was elucidated by X-ray crystallographic analysis.

Colorless crystal (CCDC-1483784); mp 109-101 ºC; IR (NaCl, $CHCl_3$) 3543, 2956, 2860, 1448, 1033 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.89 (3H, t, *J* = 7.5 Hz), 1.03 (1H, qd, *J* = 12.5, 3.5 Hz), 1.20–1.88 (18H, m), 1.99–2.05 (2H, m), 2.19 (2H, dt, *J* = 7.5, 2.0 Hz), 3.01 (1H, br s), 3.20 (1H, d, *J* = 11.5 Hz), 3.68 (1H, dd, *J* = 13.0, 7.0 Hz), 3.78-3.84 (1H, m), 4.18 (1H, dd, *J* = 13.0, 9.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.5, 18.5, 22.0, 22.1, 22.8, 23.6, 25.9. 26.1, 30.6, 30.9, 34.9, 36.6, 43.1, 45.4, 61.9, 64.2, 70.3, 83.5, 83.8; ESI (HRMS): Found: m/z 290.2488. Calcd for $C_{19}H_{32}NO$: $(M+H)^+$ 290.2484.

6.4.8. Stereoselective hydride reduction of tricyclic enamine 5.32 (Scheme 5.8)



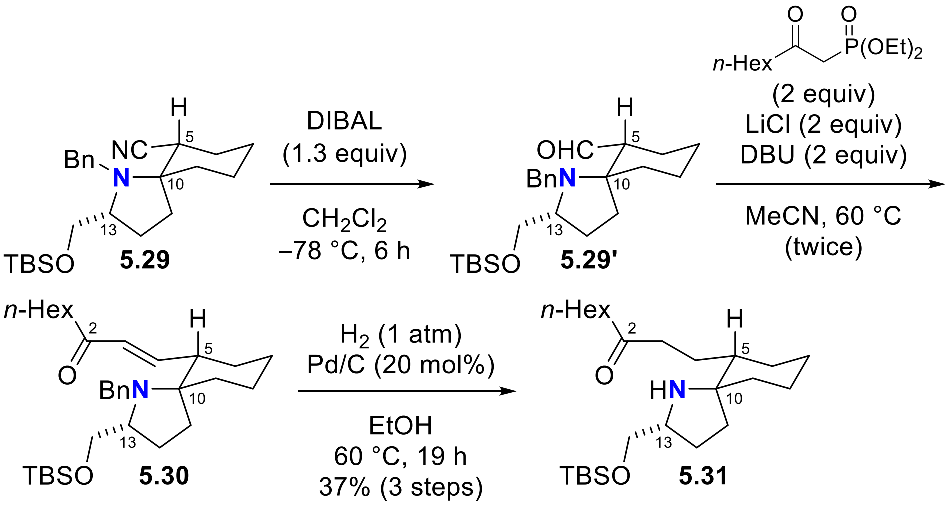
6.4.8.1. Synthesis of (2*R**,5*S**,6*R**)-1-benzyl-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-1-azaspiro[4.5]decane-6-carbonitrile (5.29)



To an ice cold solution of (1*R**,2*R**,5*S**,6*R**)-1-benzyl-2-(hydroxymethyl)-1-methyl-1λ^4-azaspiro[4.5]decane-6-carbonitrile (**5.15**) (265 mg, 0.884 mmol) and imidazole (354 mg, 5.20 mmol) in anhydrous DMF (2.4 ml) was added TBSCl (556 mg, 3.69 mmol) at 0 ºC under a N_2 atmosphere. The solution was then stirred for 4 h at room temperature before the reaction was quenched with H_2O. The organic materials were extracted twice with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* after filtration. The resulting crude material was purified by flash column chromatography (silica gel; hexane:EtOAc = 50:1) to afford (2*R**,5*S**,6*R**)-1-benzyl-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-1-azaspiro[4.5]decane-6-carbonitrile (**5.29**) (350 mg, 0.845 mmol) in 96% yield.

White solid; mp 81-82 ºC: IR (NaCl, $CHCl_3$) 2933, 2856, 2320, 2237, 1469, 1454, 1255, 1089 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ -0.16 (3H, s), -0.14 (3H, s), 0.77 (9H, s), 0.99-1.10 (1H, m), 1.33-2.04 (11H, m), 2.46 (1H, dd, *J* = 12.8, 4.0 Hz), 2.92-2.96 (1H, m), 3.08 (1H, dd, *J* = 10.0, 4.8 Hz), 3.15-3.19 (1H, m), 3.60 (1H, d, *J* = 14.0 Hz), 3.94 (1H, d, *J* = 14.0 Hz), 7.22 (1H, t, *J* = 7.2 Hz), 7.30 (2H, t, *J* = 7.2 Hz), 7.41 (2H, d, *J* = 7.2 Hz) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.4(8), -5.4(6), 18.1, 23.2, 24.8, 25.8, 25.9, 29.1, 29.5, 30.1, 39.3, 52.3, 65.8, 66.2, 66.5, 121.7, 127.0, 128.3, 128.6, 141.2.; ESI (HRMS): Found: m/z 399.2828. Calcd for $C_{24}H_{39}N_2OSi$: $(M+H)^+$ 399.2832.

6.4.8.2. Synthesis of (*E*)-1-((2*R**,5*S**,6*S**)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-1-azaspiro[4.5]decan-6-yl)non-1-en-3-one (5.31)



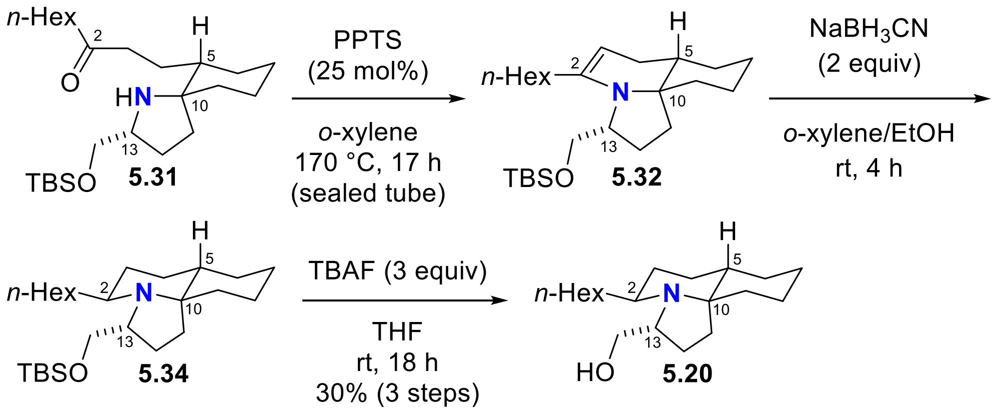
To a solution of (2*R**,5*S**,6*R**)-1-benzyl-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-1-azaspiro[4.5]decane-6-carbonitrile (**5.29**) (335 mg, 0.810 mmol) in anhydrous CH_2Cl_2 (2.7 mL) was added DIBAL (1.1 mL, 1.10 mmol, 1.0 M solution in cyclohexane) dropwise at –78 ºC under a N_2 atmosphere. The reaction mixture was stirred at the same temperature for 6 h. The reaction was quenched with MeOH and saturated aqueous Rochelle salt was added to the mixture. The resulting mixture was stirred at room temperature for additional 1 h. The resulting mixture was extracted twice with CH_2Cl_2 and the combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* after filtration. The resulting crude material including aldehyde **5.29’** was used for the next step without further purification.

To a solution of aldehyde **5.29’** in anhydrous acetonitrile (2.7 mL) were added LiCl (70.0 mg, 1.65 mmol), DBU (0.24 mL, 1.61 mmol), and diethyl (2-oxooctyl)phosphonate (426 mg, 1.61 mmol) at room temperature under a N_2 atmosphere. The reaction mixture was then stirred at 60 ºC for 11 h. The reaction was cooled down to room temperature and quenched with saturated aqueous NH_4Cl. The organic materials were extracted twice with Et_2O and the combined extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* after filtration. As the resulting crude materials still contained unreacted aldehyde **5.29’** (aldehyde **5.29’**: α,β-unsaturated ketone **5.30** = 1.61:1), the mixture was subjected under the same reaction conditions described above and stirred for 20 h before the same work-up procedure described above was conducted. The crude residue including α,β-unsaturated ketone **5.30** was passed through a short plug of silica gel with elution of *n*-hexane : acetone = 80 : 1, before it was subjected to the next step.

To a solution of the materials containing ketone **5.30** in MeOH (2.0 mL) was added Pd/C (64.0 mg, 0.0601 mmol, 10% Pd wt/wt on carbon) at room temperature under a N_2 atmosphere. The mixture was then charge with H_2 gas (1 atm balloon) and stirred at 60 °C for 19 h. The reaction vessel was then backfilled with N_2 gas. The reaction mixture was filtered over Celite pad and the collected filtrate was concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica gel; hexane:EtOAc = 2:1) to give (*E*)-1-((2*R**,5*S**,6*S**)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-1-azaspiro[4.5]decan-6-yl)non-1-en-3-one (**5.31**) (127 mg, 0.299 mmol) in 37% overall yield in three steps from **5.29**.

Yellow oil; IR (NaCl, $CHCl_3$) 2954, 2926, 2854, 1807, 1714, 1556, 1080, 831 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.034 (6H, s), 0.87 (9H, s), 0.84-0.88 (2H, m), 0.94-1.03 (1H, m), 1.08-1.80 (22H, m),1.95-2.02 (1H, m), 2.29-2.46 (4H, m), 3.22-3.28 (1H, m), 3.52 (1H, dd, J = 9.6, 5.0 Hz), 3.60 (1H, dd, J = 10.0, 5.0 Hz) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.3, 14.0, 18.3, 22.5, 23.49, 23.54, 23.9, 25.0, 25.9, 28.5, 28.9, 29.3, 30.3, 31.6, 39.4, 41.7, 42.7, 45.7, 58.2, 64.6, 66.6, 211.7; ESI (HRMS): Found: m/z 424.3616. Calcd for $C_{25}H_{50}NO_2Si$: $(M+H)^+$ 424.3611.

6.4.8.3. Synthesis of ((3*R**,5*S**,7a*S**,11a*S**)-5-hexyldecahydro-1*H*-pyrrolo[2,1-*j*]quinolin-3-yl)methanol (5.20)



To a solution of ketone **5.31** (20.9 mg, 0.0493 mmol) in anhydrous *o*-xylene (1.8 mL) in a sealed tube was added PPTS (3.0 mg, 0.0119 mmol) at room temperature under a N_2 atmosphere. The tube was then sealed and heated at 170 ºC. After the reaction was stirred for 17 h, the mixture was cooled down to room temperature and concentrated *in vacuo* to afford a crude mixture including cyclic enamine **5.32**, which was immediately used for the next step without further purification.

To a solution of cyclic enamine **5.32** in anhydrous *o*-xylene (1.8 mL) was added $NaBH_3CN$ (6.0 mg, 0.0955 mmol) and anhydrous EtOH (0.2 mL) at room temperature under a N_2 atmosphere. After the reaction mixture was stirred for 4 h, saturated aqueous $NaHCO_3$ was added to the mixture. The resulting mixture was extracted thrice with CH_2Cl_2 and the combined organic extracts were dried over Na_2SO_4, and concentrated *in vacuo* after filtration. The crude product was purified by flash column chromatography (silica gel; hexane:EtOAc = 4:1 then CH_2Cl_2:MeOH

= 15:1) to give **5.34** (8.2 mg, 0.0201 mmol) in 40% yield with recovery of **5.31** (6.2 mg, 0.0146 mmol) in 29% yield recovery. The structure of **5.34** was confirmed after subsequent removal of TBS.

To a solution of **5.34** (8.2 mg, 0.0201 mmol) obtained above in anhydrous THF (0.4 mL) was added TBAF (0.060 mL, 0.0600 mmol, 1.0 M in THF) at room temperature under a N_2 atmosphere. After being stirred for 18 h, the mixture was quenched with water. The organic materials were extracted thrice with EtOAc and the combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* after filtration. The crude product was purified by flash column chromatography (silica gel; hexane:EtOAc = 1:1, then CH_2Cl_2:MeOH = 4:1) to give ((3*R**,5*S**,7a*S**,11a*S**)-5-hexyldecahydro-1*H*-pyrrolo[2,1-*j*]quinolin-3-yl)methanol (**5.20**) (4.5 mg, 0.0153 mmol) in 76% yield (30% overall yield in three steps from **5.31**).

6.5. References

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Summary and perspective

In summary, this thesis described the development of amino-cycliation for the synthesis of various (benzannulated) saturated azaheterocycles under transition-metal free conditions. As a perspective for the thesis, more challenges and opportunities remain for the exploration of asymmetric hydroamination of alkenyl hydrazones with chiral bases (for Chapter 2), the nucleophilic amination of heteroaromatic methoxy ethers such as methoxypyridines using the NaH-iodide composite (for Chapter 3), and synthesis of (±)-lepadiformine A as well as asymmetric total synthesis of (−)-fasicularin (for Chapter 5).

List of Publication

[1] Atsushi Kaga[#], Hirohito Hayashi[#], Hiroyuki Hakamata[#], Miku Oi, Masanobu Uchiyama, Ryo Takita*, Shunsuke Chiba* ([#] equal contribution)

"Nucleophilic Amination of Methoxy Arenes Promoted by a Sodium Hydride/Iodide Composite"

Angew. Chem. Int. Ed. **2017**, *56*, 11807.

[2] Atsushi Kaga, Ya Lin Tnay, Shunsuke Chiba*

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Chem. Eur. J. **2015**, *21*, 19112.

The results of the following publications are not included in this thesis.

[4] Hirohito Hayashi, Atsushi Kaga, Bin Wang, Fabien Gagosz*, Shunsuke Chiba*

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Reviews

[9] Atsushi Kaga, Shunsuke Chiba*

“Synthesis of Tricyclic Marine Alkaloids, Cylindricines, Lepadiformines, Fasicularin, and Polycitorols: A Recent Update”

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