EXPLORATION OF NOVEL SYNTHETIC UTILITY OF LITHIOACETONITRILE

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by

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ABSTRACT

Exploring "green" chemical technologies is of great importance in the synthetic community. In particular, the one-pot reaction approach is a highly efficient and environmentally friendly protocol, which often (1) minimizes total process waste, (2) reduces operational complexity, and (3) improves cost effectiveness. Our research group has been interested in such practical "one-pot" methods, which enable easy access to a variety of useful organic molecules.

Acetonitrile is known as a common solvent in synthetic chemistry, but ionization of acetonitrile by a suitable base (*n*-BuLi, LDA etc.) in an appropriate solvent (THF) leads to the formation an interesting organic reagent, lithioacetonitrile ($LiCH_2CN$). This resulting ionized acetonitrile can be further utilized mainly in two ways, (i) as a nucleophile (ii) as a base. Lithioacetonitrile ($LiCH_2CN$) was originally introduced simultaneously by Kaiser and Seebach in 1968. Due to its synthetic versatility, the utilization of this reagent in organic synthesis has been continuously increasing since its introduction. Our group has explored novel and practical "one-pot" reactions using $LiCH_2CN$ and its derivatives in combination with organoboron reagents especially with α-boryl carbanion. α-Boryl carbanion is an interesting species in the synthetic community with an excellent olefinating ability *via* bora-Wittig olefination.

In one project, a one-pot stereoselective olefination for use in the synthesis of α,β-disubstituted acrylonitriles has been developed. The protocol efficiently produced a variety of α-substituted-α-diaminoboryl acetonitrile reagents *in situ* that underwent subsequent olefination with an aldehyde. The use of an aryl or conjugated aldehyde preferentially led to a (*Z*)-acrylonitrile, whereas an aliphatic aldehyde gave an (*E*)-isomer as the major product. This

strategy was successfully applied for synthesis of a natural product, an alarm pheromone compound, as well as for the synthesis of 2-amino quinolone derivatives.

In the second project, a mixture of *n*-butyllithium and lithiated acetonitrile ($LiCH_2CN$) unexpectedly converted styrene oxide into a *C1*-homologated allyl alcohol in an unusual regioselective manner. The reaction seemed to involve a carbene-like intermediate which underwent subsequent methylenation with $LiCH_2CN$. This protocol was extended to prepare a variety of 2,3-diaryl allyl alcohols. The use of 2-aryl acetonitriles in place of simple acetonitrile for the homologation reaction successfully provided the corresponding 2,3-diaryl allyl alcohols in a stereoselective manner with the (*Z*)-isomer predominating. The prepared allyl alcohols were subsequently utilized for the synthesis of the respective indene derivatives by means of the Lautens' intramolecular Friedel-Crafts alkylation. In a further improvement of this protocol, an alternative reagent, trimethylsulphonium iodide ($(CH_3)_3S^+I^-$), was utilized in place of CH_3CN to carry out a similar transformation that avoids the toxic by-product of this reaction. The by-product of the reaction using trimethylsulphonium iodide is dimethylsulfide (CH_3S), which is much safer than cyanide (CN^-).

DEDICATION

I dedicate this dissertation to my family and friends, especially……

To my wife, Divya Nallamothu for her tremendous support, love, encouragement, and for her patience throughout my graduation

To my grandparents, for their support and love since my childhood

And to my parents, for their love and extended support.

LIST OF ABBREVIATIONS AND SYMBOLS

Ac	Acetyl
aq	aqueous
Ar	aryl
Bn	benzyl
Bu	butyl
°C	degree Celcius
calcd	calculated
cat.	Catalytic
cm^{-1}	wavenumber(s)
Cy	cyclohexyl
DCM	dichloromethane
DIBAL(H)	diisobutylaluminum hydride
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
eq (equiv)	equivalent
Et	ethyl
EtOAc	ethyl acetate
EWG	electron-withdrawing group
g	gram(s)

h or hr(s)	hour(s)
Hex	hexanes/hexyl
HMPA	hexamethylphosphoramide
HR	high resolution
Hz	Hertz
i-Pr	isopropyl
KHMDS	potassium hexamethyldisilazane
LHMDS	lithium hexamethyldisilazane
lit	literature value
m	meta
M	molarity
Me	methyl
MeOH	methanol
Mes	mesityl
min	minute
mL	milliliter
Ms	mesyl (methanesulfonyl)
MS	mass spectrometry
n	normal (*e.g.*, alkyl chain unbranched)
NMR	nuclear magnetic resonance
NR	no reaction
Nu	nucleophile
o	ortho

p	para
%	percent
Ph	phenyl
Pr	*n*-propyl
quant	quantitative
r.t. (rt)	room temperature
R_f	retention factor
sat.	saturated
sec	secondary
SiO_2	silica gel
t or *tert*	tertiary
TEA	triethylamine
Temp	temperature
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMEDA	*N*,*N*,*N*',*N*'-tetramethyl-1,2-ethylenediamine
TOF	time of flight
Tol	toluene
UV	ultraviolet
vol	volume

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CHAPTER I

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1.1. Introduction

1.1.1. Green chemistry and one-pot reaction strategy

One of the main driving forces in synthetic organic chemistry has always been the capability of doing synthesis in a more efficient way. Chemists always strive to come up with better ideas and combinations of reactions which will result in a quicker access to the synthetic target with higher overall yields. Hence in recent years, exploring "green" chemical technologies became of great importance in the synthetic community.[1-2] According to P. T. Anastas, “green chemistry is the utilization of a set of principles that reduces or eliminates the use or generation of hazardous substances in the design, manufacture and application of chemical products”.[3] P. T. Anastas and J. C. Warner formulated 12 principles which are well known as “Green Chemistry Principles” to achieve sustainability in the field of chemistry.

One of the ways to implement the real purpose of green chemistry is by designing a shorter route towards the target and also reducing the number of reaction steps. This kind of approach saves time, and utilization of solvents. Based on all these facts, by combining more than one step in the same reaction flask, the one-pot reaction strategy emerged. In particular, the one-pot reaction approach **(Figure 1)** is a highly efficient and environmentally friendly protocol, which often (1) minimizes total process waste, (2) reduces operational complexity, and (3) improves cost effectiveness, *etc.* In fact, better yields were often reported by implementing multi-component one-pot reactions when compared to a traditional multi-step synthetic strategy. More importantly, a one-pot reaction is highly advantageous when an intermediate in the reaction is short lived or cannot be isolable. Since one-pot reactions are useful for constructing complex organic structures with the minimal use of solvent and reducing the number of reaction steps, which saves precious time, it has been considered as a powerful “Green Chemistry” tool in

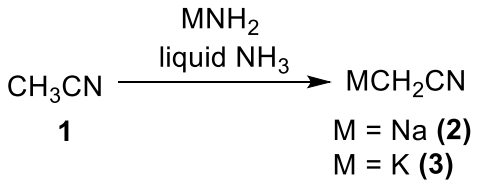
the field of synthetic chemistry. So, our research group has been interested in such practical "one-pot" methods, which enable an easy access to a variety of useful organic molecules.

Figure 1: Representation of one-pot reaction strategy compared to multi-step approach

1.1.2. History of lithioacetonitrile

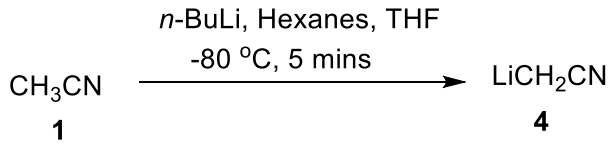
Acetonitrile is a common solvent in synthetic chemistry reactions and commonly used as a useful mobile phase in HPLC. On the other side, ionization of acetonitrile by a suitable base in an appropriate solvent leads to the formation a useful organic reagent, alkali acetonitrile, MCH_2CN (M = Li, Na and K). This resulting ionized acetonitrile can be further used mainly in two ways, i) as a nucleophile and ii) as a base.

In 1945, Bergstrom and his co-authors were the first who prepared 'a soluble salt', MCH_2CN (M = Na or K), by treating acetonitrile **1** with sodium amide in liquid ammonia, and utilized it for alkylations, benzoylation and arylation of acetonitrile **(Scheme 1)**.[4]



Scheme 1: Bergstrom's method of preparation of ionized acetonitrile

Although this was an interesting discovery, due to the complexity in handling the reaction, further applications were not explored. Later, in 1968, Kaiser[5] and Seebach[6] independently reported the preparation of lithioacetonitrile **4** ($LiCH_2CN$) by treating acetonitrile (CH_3CN) with *n*-butyllithium (*n*-BuLi) in tetrahydrofuran-hexane solvent system **(Scheme 2)**. Both Kaiser and Seebach reported the condensation of lithioacetonitrile with ketones or aldehydes to give monoaldol products. In Kaiser's report, lithioacetonitrile **4** was prepared in two ways, treating acetonitrile either with *n*-BuLi in THF-hexanes at -80 ^oC or with MNH_2 (M = Li or K) in liquid NH_3 at -33 ^oC, whereas Seebach reported the preparation of lithioacetonitrile by treating acetonitrile **1** with *n*-BuLi in THF at -78 ^oC. The *in situ* formed lithioacetonitrile **4**, upon nucleophilic addition reactions with a variety of aldehydes and ketones, resulted in *β*-hydroxynitriles in fair to good yields.



Scheme 2: Kaiser's scheme for generation of lithioacetonitrile

After Kaiser and Seebach's report, because of its ease of preparation and use, lithioacetonitrile has been widely used in organic reactions[7-10]. Although lithioacetonitrile was mostly used as a nucleophile in synthetic reactions, using this reagent as a base has been an unexplored area in synthetic chemistry.

1.1.3. Importance of organoboron reagents in synthetic chemistry

The organic derivatives of BH_3 are well known as organoboron compounds such as trialkyl boranes, boronic acids and esters, borates and carboranes etc. In fact, until the invention

of the hydroboration reaction by H.C. Brown,[11,12] the utilization of boron compounds in the synthetic world was minimal because only minor amounts were prepared for use and they required special techniques for handling.[13] After successful addition reactions by hydroboration-oxidation, the chemistry world realized the potential of boron compounds in organic synthesis. Since then, organoboron compounds have emerged as an important class of reagents in synthetic chemistry, enabling a number of key chemical transformations such as hydroboration-oxidation[14], reductions,[15] carbon-carbon bond formation reactions[16,17] and other key organic transformations.[18,19] In recent years, among all these applications, the utilization of borates such as boronic acid and esters became more popular, as it enables a crucial carbon-carbon bond formation (the Suzuki-Miyaura cross-coupling reaction) in the presence of Pd catalyst.[17]

1.1.4. Utility of the borate complex and path to α–boryl carbanion chemistry

In molecules, a boron atom possesses trigonal planar geometry with sp^2 hybridization. Trivalent organoboron compounds, having only six outer shell electrons, are normally expected to be more or less Lewis acidic due to the presence of an empty p orbital on the boron. Hence, when working along with a base/nucleophile, they are highly reactive and often form a stable tetravalent "*ate*"-complex product, *i.e., a* borate complex **(Figure 2).** By taking advantage of the borate complex, extensive research has been conducted in the field of synthetic chemistry, and a number of organoboron reagents and useful synthetic reactions have been developed so far, for example, sodium borohydride as a reducing agent[15]; boronic acids, boronate esters[17] and potassium trifluoroborates[19] for the Suzuki coupling reaction; *etc.* Interestingly, on rare occasions, some trivalent organoboron compounds are compatible with a base and, if they possess an acidic α- hydrogen, can produce another unique chemical species, *i.e.,* an α-boryl carbanion, without forming a typical "ate"-complex **(Figure 2).** By utilizing the “ate” complex,

several applications of the boron compounds have already been well established in synthetic chemistry,[20] but little has been explored on α-boryl carbanions, mainly due the limitation of preferential formation of "ate" complexes with base. Clearly, there is a lot of room to explore in α-boryl carbanion chemistry, so we focused on methods of generating α-boryl carbanions and utilizing them for synthetic applications.

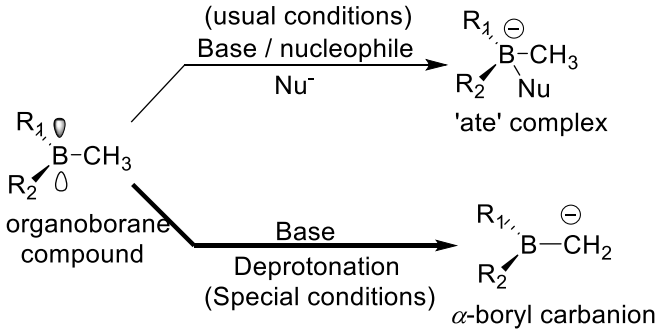
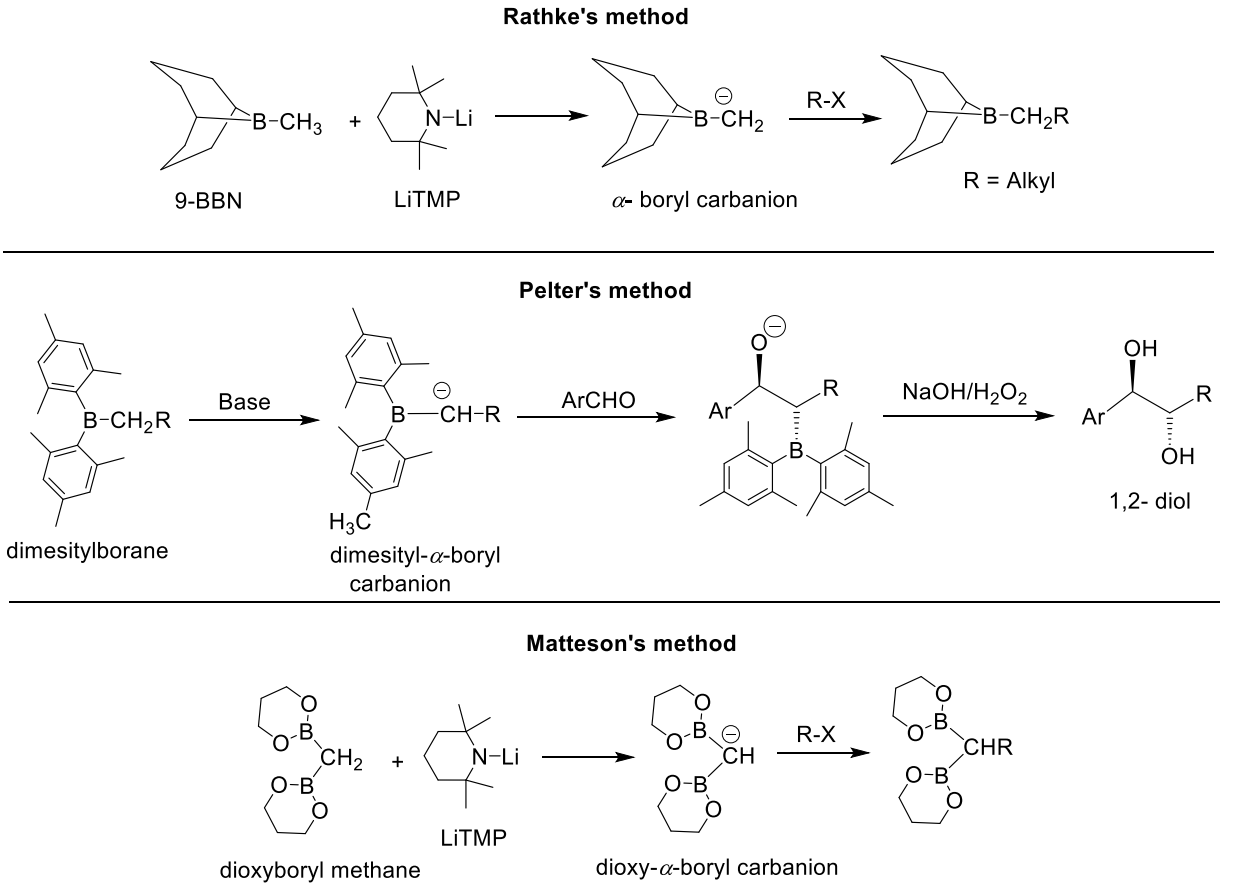


Figure 2: Generation of α-boryl carbanion

1.1.5. Possible routes to generate α-boryl carbanions

Prior to our research, studies on the generation and application of α-boryl carbanion in synthetic chemistry were carried out mainly by Rathke[21], Pelter[22,23], and Matteson[24] in the '70s and '80s. Although the carbanion should be readily generated upon direct deprotonation of the α-hydrogen, the Lewis acidic nature of the boron often makes this step complicated, and a competitive side reaction with a base leads to an undesired borate complex **(Figure 2).** Although the researchers above had different synthetic application goals, in the course of reaction the common intermediate was an α-boryl carbanion. First, Rathke prepared α-boryl carbanions by treating organoboron compounds with sterically hindered bases such as lithium tetramethyl piperidine (LiTMP). Pelter used sterically hindered boranes such as dimesityl borane along with a base to generate α-boryl carbanions, whereas Matteson prepared his by treating electron rich

boranes with sterically hindered base (LiTMP). By utilizing *in situ* generated α-boryl carbanions, all the above scientists could successfully prepare their respective target compounds (**Scheme 3**).



Scheme 3: Literature methods for generation of α-boryl carbanion

After their significant work for preparing α-boryl carbanions, however, further synthetic applications have rarely been investigated due to the limited accessibility and handling difficulties of the desired α-boryl carbanion species.

1.2. Preparation of α-boryl carbanion and one-pot synthesis of β–monosubstituted acrylonitriles

1.2.1. Importance of acrylonitriles

Acrylonitrile, an α,β-unsaturated cyanide is a versatile intermediate in synthetic chemistry. Since electron with drawing cyano group attached to the double bond, the molecule become electron deficient and acts as a useful reagent in various reactions such as dienophile in Diels-Alder reaction,[25] as a Michael acceptor in Michael addition reaction,[26] and as a coupling partner in Heck cross coupling reaction.[27] Along with that, acrylonitrile is also a key component in many biologically active natural products, dyes, and agrochemicals.[28] Interestingly, using appropriate reagents the cyano group in acrylonitrile can also be transformed into various useful functionalities such as amines, aldehydes, and amides. Because of this versatile nature, acrylonitriles are always interesting targets in synthetic chemistry.

1.2.2. Our approach to generate α-boryl carbanions

Based on Rathke, Pelter and Matteson's efforts, it became very clear that in organoboron reagents if two major parameters were controlled, it's not hard to generate the α-boryl carbanion. Those are i) steric[21-23] and ii) electronic factors.[24] If we could design an organoboron reagent that controlled those two factors, we believed that it would not be hard to work with boron compounds in the presence of a compatible base. So, to overcome the major drawback of the formation of an "ate" complex, we proposed a sterically-hindered and mildly Lewis acidic diaminoboryl acetonitrile reagent, **5 (Figure 3).**[29]

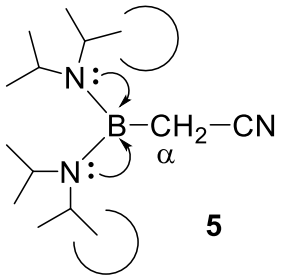
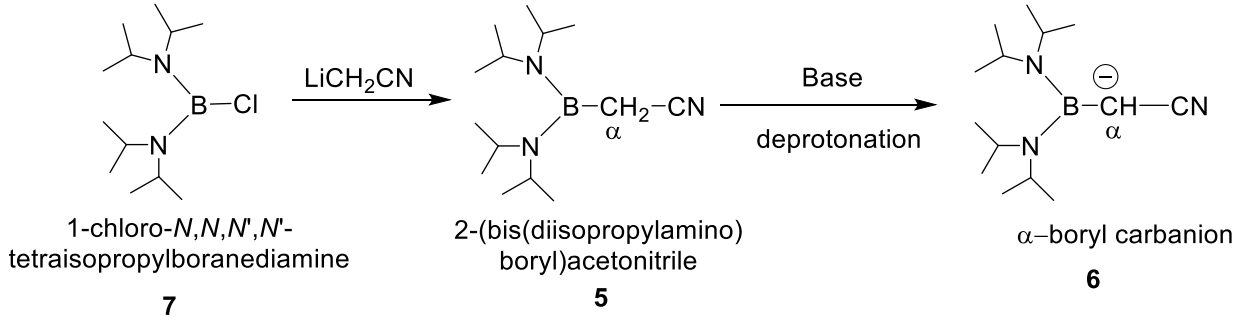


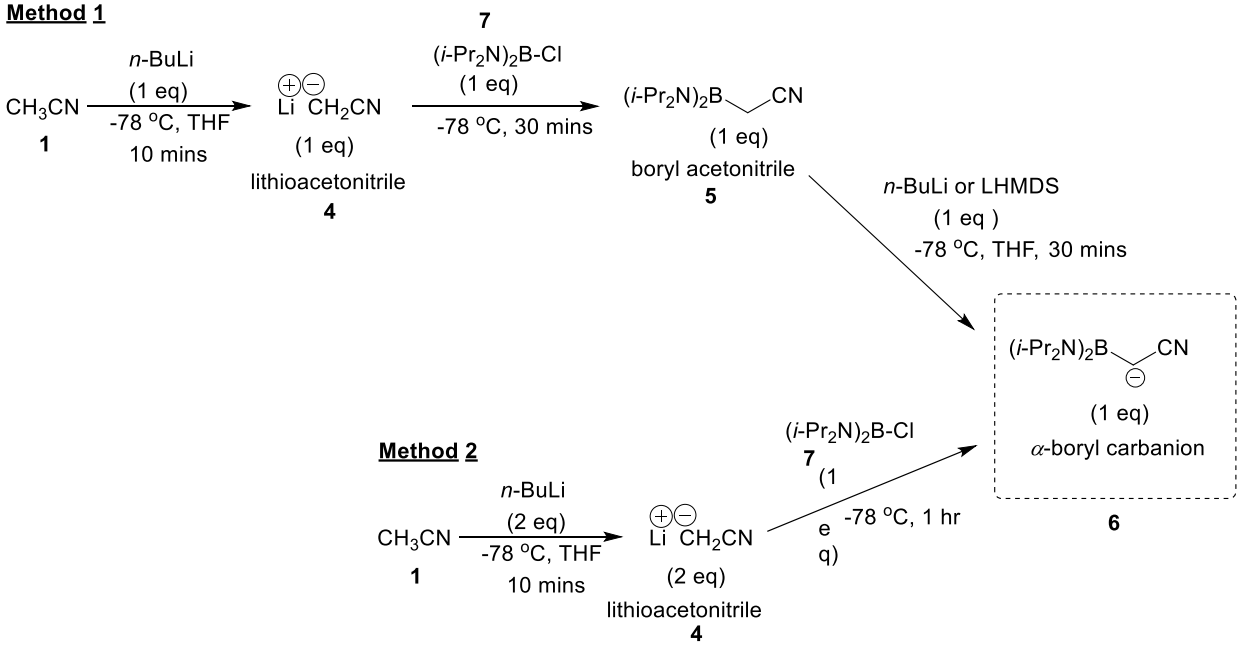
Figure 3: 2-(bis(diisopropylamino)boryl)acetonitrile

The proposed diaminoboryl reagent **5** comprises two diisopropyl amino groups, which sterically protect the boron from a base/nucleophile. In addition, since a nitrogen atom is known as a strong electron donor to boron, the attached two amino ligands also lower the Lewis acidity of the boryl moiety. Thus, we envisioned that such a diaminoboryl group could be useful under basic conditions and highly advantageous for the study of α-boryl cαrbanion chemistry. Furthermore, the electron-withdrawing cyano group (CN) attached to the α-carbon increases the acidity of the α-hydrogen for effective generation of a stable carbanion species **6 (Scheme 4).** To the best of our knowledge, there is no general synthetic path known in the literature to access such boryl acetonitriles, though the potassium salt form of the trifluoroborate (KBF_3CH_2CN) was recently reported by the Molander group.[30]



Scheme 4: Preparation of α-boryl carbanion from chloroboron reagent

The carbanion was prepared by treating the readily-available chloroborane reagent **7**, $(i\text{-Pr}_2\text{N})_2\text{BCl}$),[31] with one equivalent of LiCH_2CN **4**, which was followed by deprotonation of the product's α –carbon to boron with a suitable base (LHMDS, *n*-BuLi, *etc*.). The starting material, chloroboron reagent **7**, was prepared according to literature conditions by refluxing boron trichloride with diisopropylamine in hexanes/toluene solvent.[31] Furthermore, in the course of our research[29,32] we realized that the same α –boryl carbanion could be prepared by simply treating the original chloroborane with two equivalents of LiCH_2CN **(Scheme 5).** In fact, it was more effective than using an external base (*n*-BuLi) for deprotonation, was easier in terms of handling, and improved the yield of the reaction. In the reaction, LiCH_2CN **4** was playing two roles, one equiv acting as a nucleophile to be substituted on the boron atom, and the other as a base for deprotonation of α-carbon. The two methods used for preparation of the α-boryl carbanion are shown in Scheme 5.



Scheme 5: Methods to prepare α-boryl carbanion from acetonitrile

The *in situ* generated carbanion **6** was subsequently utilized for further synthetic applications, which will be discussed in the following sections.

1.2.3. Initial attempt for utilization of *α*-boryl carbanion

Once the scheme was designed to access the key intermediate *α*-boryl carbanion **6**, we focused on utilization of this reagent to prepare useful synthetic products. First, we recognized that the α-boryl carbanion had comparable structural features to cyano versions of the Horner-Witting reagent ($(OR)_2P(=O)CH^-CN$)[33] and Peterson's reagent (Me_3SiCH^-CN),[34] so we wanted to see whether the *α*-boryl carbanion would have similar olefinating ability with aldehydes; such an outcome would result in a bora-Wittig olefination **(Figure 4).**

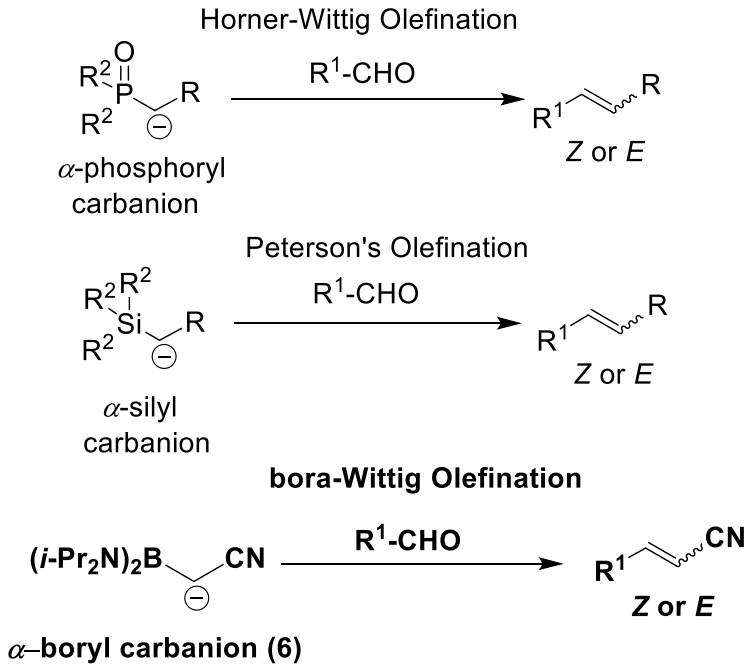
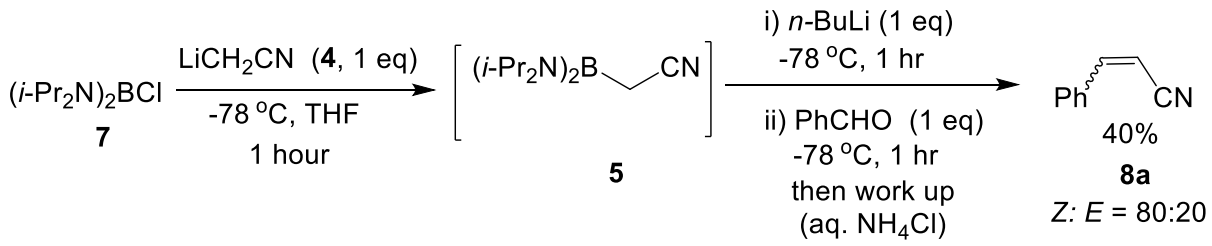


Figure 4: Proposed olefination reaction using *α*-boryl carbanion

1.2.4. Attempt for olefination using α-boryl carbanion

(The work of the section 1.2.4. was carried out by our former and present group members Yusuke Takahashi, Takayoshi Yanase and Trey G. Vaughan under the direction of Dr. Takashi Tomioka. I included these details of the reaction and optimization since a part of my dissertation work was developed based on this work and was directly/closely related to this work)

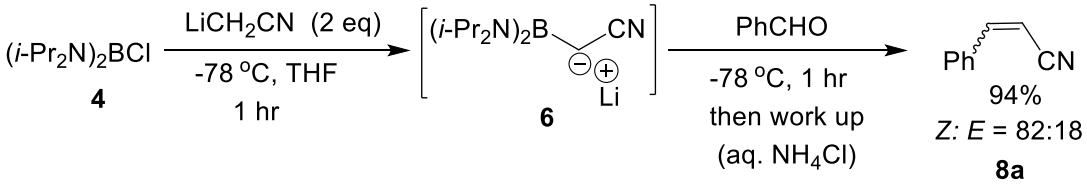
As an initial attempt, the olefinating ability of **6** was tested with benzaldehyde (PhCHO).[29] In the first step, treating 1 equiv of chloroboron reagent **7** with 1 equiv of *n*-BuLi in THF at -78 ^{o}C generated the boryl acetonitrile intermediate **5**, which was confirmed by crude proton NMR, followed by deprotonation of **5** with 1 more equiv of *n*-BuLi to generate α-boryl carbanion **6** *in situ*. At this point, addition of 1 equiv of benzaldehyde to the reaction flask produced the target β-phenyl acrylonitrile, **8a**. To our delight, the major product formed was the *Z*-isomer, which confirmed that the reaction was stereoselective. Fortunately, we could separate and isolate both *Z* and *E* isomers chromatographically using an ethyl acetate/hexanes eluting system. Interestingly, the selectivity of the bora-Wittig olefination reaction was exactly opposite to that of the Horner-Wittig and Peterson's selectivity at standard conditions **(Scheme 6).**



Scheme 6: Initial bora-Wittig olefination attempt using α-boryl carbanion

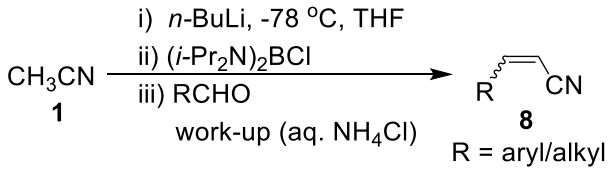
Although the olefination reaction using the α-boryl carbanion seemed successful, for some reason the isolated yield of **8a** was low (~ 45%). The reaction conditions were further

optimized by changing several parameters like temperature (-20 ^{o}C, -40 ^{o}C, and -78 ^{o}C), concentration of reagents, additive (TMEDA), different bases (LiTMP, KHMDS, LDA, and MeMgBr) and finally time of reaction, but no significant improvement of yield was observed in the reaction. After further optimization, when 2 equiv of $LiCH_2CN$ **4** was used in the reaction at the beginning instead of 1 equiv, the yield of **8a** was dramatically improved to 94% **(Scheme 7).** This result indicated that $LiCH_2CN$ **4** was performing two important functions, one equiv of **4** acting as a nucleophile, which substituted the chloro group on boron, and the other equiv as a base to deprotonate **5** and form the key intermediate α- boryl carbanion **6.**

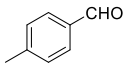
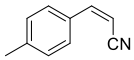
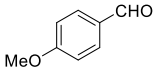
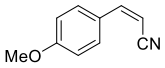
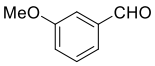
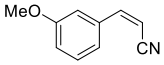
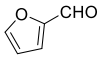
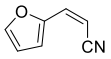
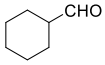
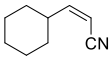
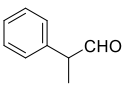
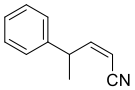
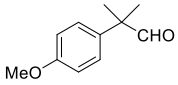
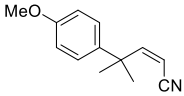
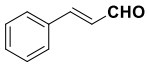
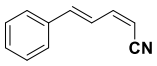


Scheme 7: Optimized bora-Wittig olefination conditions

The course of optimization of the reaction also revealed that using *n*-BuLi for the deprotonation step or increasing the amount of any base (either *n*-BuLi or $LiCH_2CN$ **4**) further reduced the yield of the olefination product **8a.** Once the reaction conditions were optimized, a series of aromatic aldehydes (Ar–CHO) (**entries 1-4, Table 1**) and non-aromatic aldehydes (**entries 5-8, Table 1**) were tested and they were smoothly converted into the corresponding acrylonitriles in one-pot reactions (80–98% yields, 13 examples), all with *Z*-stereoselectivities **(up to *Z:E* = 96:4).**



Scheme 8: General scheme for one-pot bora-Wittig olefination reaction

Entry	aldehyde	Product	Z:E[a]		yield(%)[b]
1			81:19	8**b**	97%
2			83:17	**8c**	86%
3			78:22	**8d**	80%
4			80:20	**8e**	82%
5			88:12	**8f**	92%
6			83:17	**8g**	94%
7			94:6	**8h**	86%
8			65:35	**8i**	88%

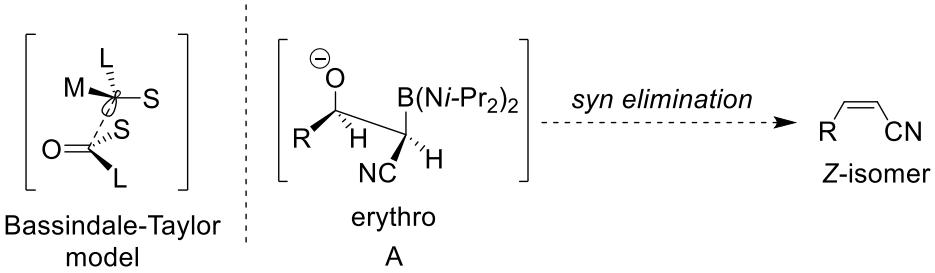
[a]determined by crude ^{1}H NMR
[b]combined isolated yield of *Z* and *E* isomers

Table 1: One-pot bora-Wittg olefination reaction of α-boryl carbanion

1.2.5. Stereochemical discussion

From **Table 1**, it was clearly indicated that the selectivity was sensitive to steric factors but not very dependent on electronic factors. In **Table 1**, when more sterically congested aldehydes were used, the selectivity was higher, ranging up to 94:6 **(entry 7),** whereas when a less sterically hindered aldehyde was used, the selectivity dropped **(entry 8).** But the presence of either electron-deficient or electron-rich substituents did not have much effect on the selectivities

of the products. Based on these facts, the reaction selectivity was rationalized by the Bassindale-Taylor approach model,[35] the common steric approach model **(Scheme 9).**



Scheme 9: Bora-Wittig olefination reaction mechanism

1.3. Synthesis of α,β-disubstituted acrylonitriles

1.3.1. Limitations of the established methodology and attempted synthesis of α,β-disubstituted acrylonitriles

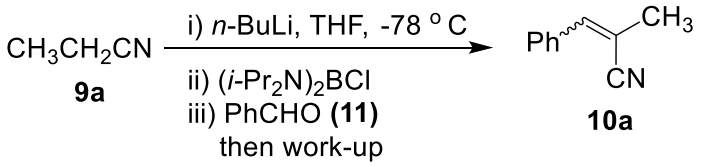
Although it was a scintillating effort from our group members to establish a novel route to prepare acrylonitriles, the earlier methodology **(Scheme 8)** developed by our group had its own limitations. Using this protocol, with aldehydes, only mono-substituted acrylonitriles could be synthesized, and it was ineffective for synthesizing multi-substituted olefins. In fact, preparing tri- and tetra- substituted olefins in a stereoselective manner has always been challenging. However, the success of the earlier report laid a platform and also raised our curiosity to develop more substituted or functionalized olefins.

So, we planned to further extend the synthetic utility of the α –boryl carbanion **6** by introducing more functionalities or substitutions on the α–carbon to boron, and utilizing those multifunctionalized reagents in organic synthesis, especially in olefination reactions. The possibilities for more-substituted acrylonitriles would include β,β- and α,β- disubstituted

acrylonitriles. In fact, to prepare *β,β*-disubstituted acrylonitriles, several methods[36-38] were available in the literature either from an aldehyde or a ketone by using standard olefination techniques, such as Wittig/Horner-Emmons[33] and Peterson type reactions[34], but those strategies are less commonly employed for the synthesis of *α,β*- disubstituted acrylonitriles, since prior modification of starting materials would be required.[39-42] Alternatively, the target acrylonitriles can also be prepared by the Baylis – Hillman reaction,[43-52] but that was a multi-step approach.

1.3.2. Linear approach for acrylonitrile synthesis

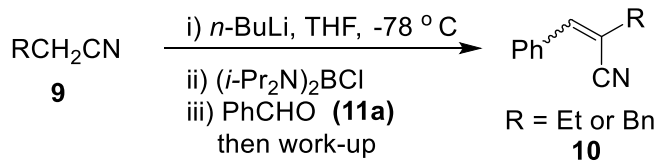
To prepare *α,β*- disubstituted acrylonitriles, we initially proposed two approaches, one linear and the other divergent. The linear approach **(Scheme 10)** was designed with similar reaction conditions to **Scheme 8**, but chloroborane **7** was treated with 2 equiv of lithiated propionitrile **9a**, which was followed by the addition of benzaldehyde **11**, yielding the target *α,β*-disubstituted acrylonitrile **10a** with a good yield of 94%.



Scheme 10: Linear approach for synthesis of *α,β*- disubstituted acrylonitriles

Later, similar procedures were examined with two other alkyl-substituted lithiated nitriles to see the feasibility of the reaction **(Scheme 11).** As expected, this linear approach gave the corresponding *α,β*- disubstituted acrylonitriles in fair to good yields, and the reaction was *Z*-selective. Although this linear approach confirmed that the *α* –substituted-*α* –boryl carbanion had adequate olefination ability and could drive the reaction stereoselectively, the results, after

testing the generality of the reaction with three different nitriles, revealed the fact that the reaction was substrate dependent **(Scheme 11).** The results were summarized in **Table 2.**



Scheme 11: Synthesis of α,β– disubstituted acrylonitriles using linear approach

R	*Z:E*		yield[a]
Me	70:30	**10a**	94%
Et	70:30	**10b**	90%
Bn	87:13	**10c**	61%

[a]isolated yield

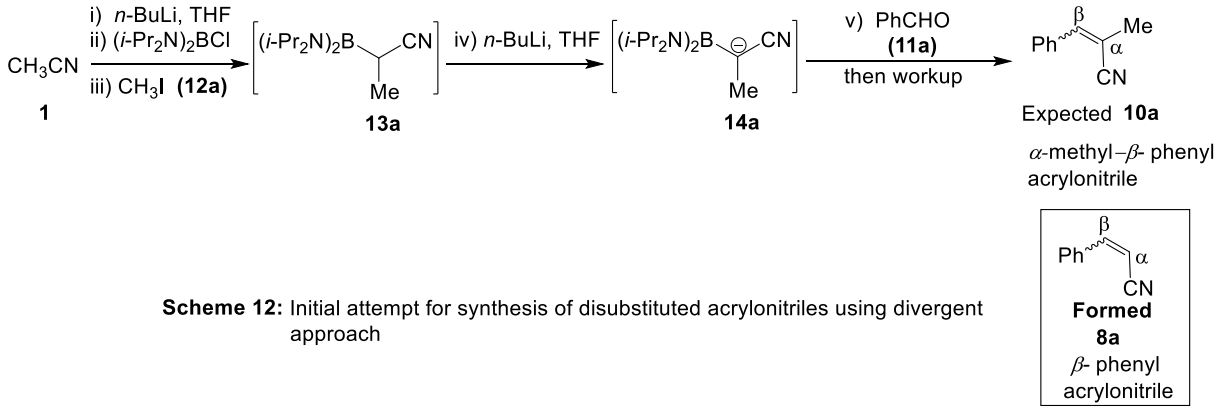
Table 2: Synthesis of α,β– disubstituted acrylonitriles by linear approach

From **Table 2**, the reaction starting with proponitrile **9a** and butyronitrile **9b** gave good yields (94 % and 90 %, respectively), but the yield dropped to 61% when benzylcyanide **9c** was used. This trend revealed the fact that the reaction yield was substrate dependent. Another drawback of this linear approach was that it required two equiv of the nitrile to complete the reaction. Since only a few aryl/alkyl nitriles are commercially available and they were expensive, the reaction was not economical. Based on these factors, we proposed an alternate, divergent approach to prepare the target α,β-disubstituted acrylonitriles.

1.3.3. Divergent approach for acrylonitrile synthesis

This approach was a two-step, one-pot reaction starting from simple acetonitrile **1 (Scheme 12)**.

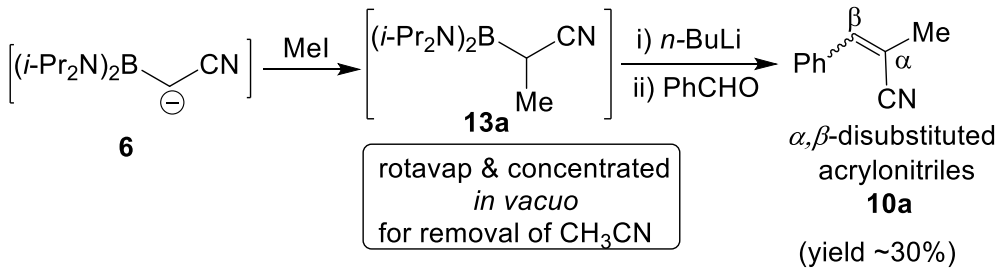
First, as a test reaction, iodomethane **12a** was used for alkylation of the α-boryl carbanion **6**. This step quantitatively afforded α-methyl-α-borylacetonitrile **13a**, which was confirmed by ^{1}H NMR analysis of crude reaction mixture. On subsequent treatment with a base (e.g., *n*-BuLi), a second α-boryl carbanion **14a** should be generated *in situ*; subsequent treatment with benzaldehyde was expected to provide the corresponding β- phenyl-α–methyl acrylonitrile **10a** through bora-Wittig olefination. Surprisingly, the target product was not found; instead, the observed major product was β- phenyl acrylonitrile **8a**. In the overall reaction, the product formed lacked the initial methyl group on the α-carbon**.**



Scheme 12: Initial attempt for synthesis of disubstituted acrylonitriles using divergent approach

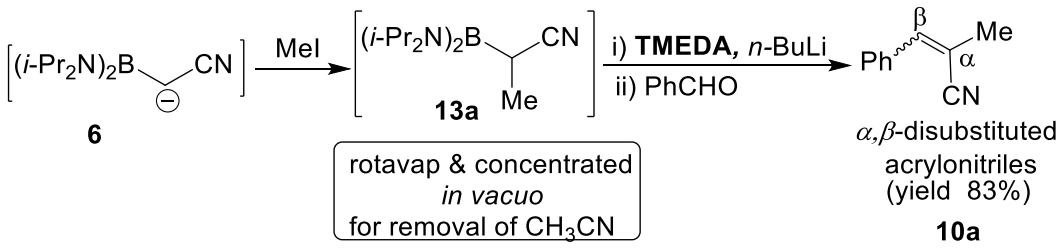
Although this result was not as expected, this failure drove us to look deeply into the reaction to identify the problem. After a careful investigation, we could identify the problem in the reaction which was actually limiting the formation of the target acrylonitrile. The reaction was started with 3 equiv of CH_3CN **1** (excess amount of CH_3CN than needed for the reaction) and 2 equiv of *n*-BuLi, which resulted in the formation 2 equiv of $LiCH_2CN$ for the reaction. The boryl carbanion **6** species was generated from chlorodiaminoborane **7** by treating it with 2 equiv of $LiCH_2CN$ **4** (1 equiv of $LiCH_2CN$ substituted –chloro group on boron and another equiv of

$LiCH_2CN$ deprotonated the α-carbon to boron which again generating 1 more equiv of CH_3CN, so a total of 2 equiv of CH_3CN existed in the reaction flask).[53] Addition of 1 equiv of iodomethane **12a** to the reaction gave one equiv of methyl-substituted intermediate **13a.** At this stage, two equiv of acetonitrile (reaction started with 3 equiv of CH_3CN where only 2 equiv of CH_3CN still in the reaction flask) was should still exist in the reaction flask. In the next step, for attempted deprotonation of the **13a,** the acetonitrile which remained in the reaction flask would be more rapidly deprotonated by *n*-BuLi than the sterically congested methylated boryl acetonitrile **13a.** As a result, $LiCH_2CN$ **4** was generated again, and it added to the benzaldehyde **11a** to form an oxyanion intermediate. This intermediate presumably underwent β-elimination with the assistance of boryl group, yielding the undesired β-monosubstituted acrylonitrile **8a.** Since the problem in the reaction was identified, we slightly changed the reaction procedure. To get rid of the excess of CH_3CN **1**, after the alkylation step, the reaction mixture was concentrated under reduced pressure, and then used for the following olefination reaction without further purification. Encouragingly, this modified procedure was effective and afforded the target acrylonitrile **10a** in moderate yield (30%) **(Scheme 13).**



Scheme 13: Improved procedure for divergent approach

In the process of further improvement, we inspected the reaction deeper to find the problem behind the low yield. We hypothesized that in the second step of the reaction, in **13a** the α- carbon to boron was too sterically crowded to be efficiently deprotonated by *n*- BuLi. In solutions like hexanes, usually *n*- BuLi exists as hexamer. Addition of an additive like TMEDA or HMPA etc., cleaves the polymeric form into more effective base of tetramer or monomer respectively. Due to the toxicity of HMPA, it's usage was limited unless it is necessary. Hence to resolve the issue, an additive, TMEDA, was added to the reaction mixture for more effective deprotonation of **13a** by *n*- BuLi. The addition of TMEDA before adding *n*- BuLi in the second step was effective, and the reaction finally yielded 83% of the target acrylonitrile **(Scheme 14).**



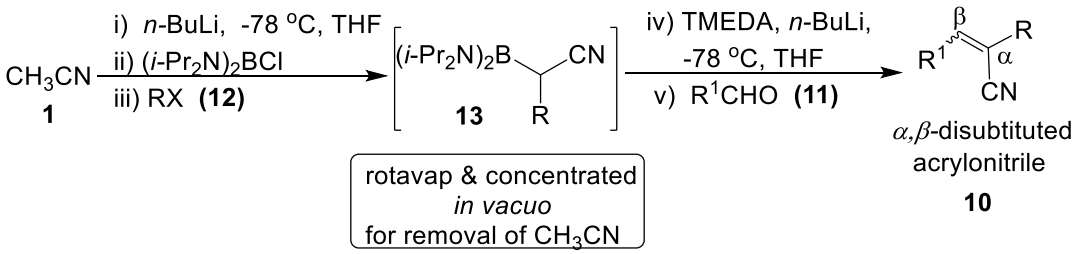
Scheme 14: Optimization for divergent approach for synsthesis of disubstituted acrylonitriles

The configuration of the formed product from this divergent approach was identical to that of the product formed from the linear approach. This implied that in both approaches, the same carbanion intermediate **14a** was involved in the olefination reaction.

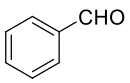
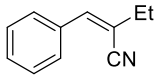
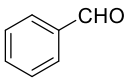
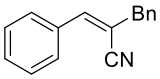
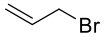
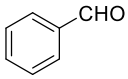
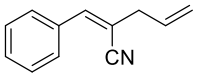
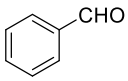
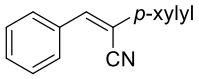
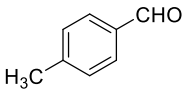
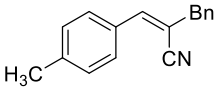
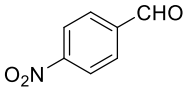
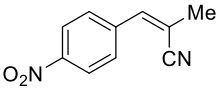
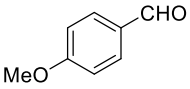
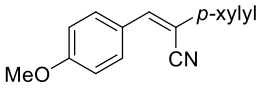
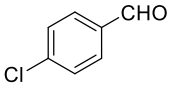
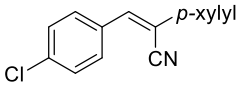
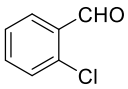
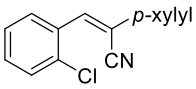
1.3.4. Results & discussion

Upon optimization of the reaction conditions, a series of alkyl halides **12** with a combination of different aromatic aldehydes **11** were tested to demonstrate the generality of the reaction **(Table 3).** Similar to iodomethane, other alkyl halides such as ethyl iodide, allyl

bromide, benzyl bromide, and p-xylyl bromide underwent alkylation with the carbanion, and on subsequent olefination with benzaldehyde produced the target acrylonitriles. Later, aromatic aldehydes functionalized with methyl, nitro, methoxy, or chloro groups were also examined **(entries 5-8, Table 3).** Both electron-rich and electron-deficient aldehydes were efficiently converted into the corresponding products in good to excellent yields (72-96%). All of the target acrylonitriles were consistently *Z*-stereoselective. The *E/Z* isomers were separable by silica gel column chromatography using toluene as eluent.



Scheme 15: Optimized procedure for divergent approach for synthesis of α,β-disubtituted acrylonitrile

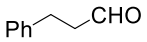
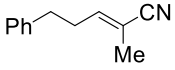
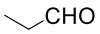
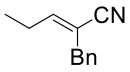
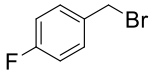
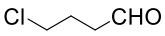
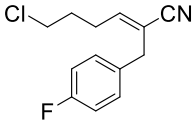
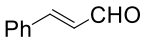
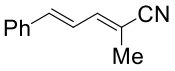
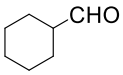
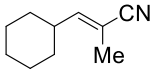
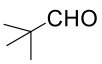
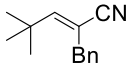
Entry	RX (12)	R^1CHO (11)	Product (10)		*Z:E*[a]	Yield(%)[b]
1	EtI			**10b**	70:30	71
2	BnBr			**10c**	86:14	84
3				**10d**	70:30	83
4	*p*-xylyl bromide			**10e**	88:12	89
5	BnBr			**10f**	88:12	96
6	MeI			**10g**	81:19	80
7	*p*-xylyl bromide			**10h**	*n.d.*[c]	72[d]
8	*p*-xylyl bromide			**10i**	86:14	90
9	*p*-xylyl bromide			**10j**	85:15	72

[a]Determined by ^{1}H NMR of the crude reaction mixture. [b]Combined isolated yield of Z and E isomers. [c]Not determined. [d]Isolated yield of Z isomer.

Table 3: α,β-disubtituted acrylonitrile synthesis using aromatic aldehydes

Later, aliphatic aldehydes were investigated **(Table 4).** Interestingly, unlike the aromatic aldehydes, all primary and secondary aliphatic aldehydes examined led to *E*-olefinic isomers as the major product **(entries 1-4, Table 4).** A tertiary aliphatic aldehyde **(entry 6**, **Table 4)**) did

not give any desired product due to steric interference. A conjugated aldehyde, *trans*-cinnamaldehyde, underwent *Z*-olefination **(entry 4, Table 4)**.

Entry	RX	R^1CHO	Product		*Z:E*[a]	Yield(%)[b]
1	MeI			**10k**	11:89	87
2	BnBr			**10l**	16:84	99
3				**10m**	12:88	76
4	MeI			**10n**	69:31	82
5	MeI			**10o**	24:76 (23:77)[c]	84 (83)[c]
6	BnBr			**10p**	--	0 (0)[c]

[a]Determined by ^1H NMR of the crude reaction mixture.
[b]Combined isolated yield of Z and E isomers.
[c] by linear approach

Table 4: *a,b*-disubtituted acrylonitrile synthesis using aliphatic aldehydes

1.3.5. Stereochemical discussion

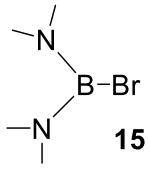
In the previous report by Tomioka et al. **(Scheme 8),** the *Z*-selectivity of the *β*-monosubstituted acrylonitrile products was explained by taking advantage of the Bassindale-Taylor model **(Scheme 9),** which is a common steric approach model. In that report, the reaction yielded the *Z*-isomer as the major compound irrespective of whether aromatic or aliphatic aldehyde was used for olefination.

However, the selectivities in the syntheses of *α, β*-disubstituted acrylonitriles **(Scheme 15)** could not be explained by using the same steric approach model because of reversed

selectivities of some reactions (aromatic aldehydes gave *Z*-isomers whereas aliphatic aldehydes gave *E*-isomers as major products). The mechanistic rationale for these reversed selectivities between aromatic and aliphatic aldehydes is still inconclusive.

1.3.6. Alternate boron reagents for synthesis of α, β- disubstituted acrylonitriles

Although using bis(diisopropylamino)chloroborane **7** for the synthesis of disubstituted acrylonitriles was successful, we thought an alternative reagent would be worth testing. So, a commercially available and sterically less crowded bis(dimethylamino)bromoborane ($(Me_2N)_2BBr$) **15 (Figure 5)** was tested in place of the bis(diisopropylamino)chloroborane reagent. Unfortunately, when we applied identical reaction conditions as in **Scheme 15**, we could not find any of the expected olefinic peaks for the final acrylonitrile product in the crude ^1H NMR spectrum, even though we altered a variety of reaction conditions like reaction time, amount of reagents, and reaction temperature; all the efforts were in vain. The major reason for the failure might be that the amount of steric crowding around the boron atom in **15** was not sufficient to prevent the nucleophilic attack on boron of either lithioacetonitrile or *n*-BuLi in the initial step of the reaction.



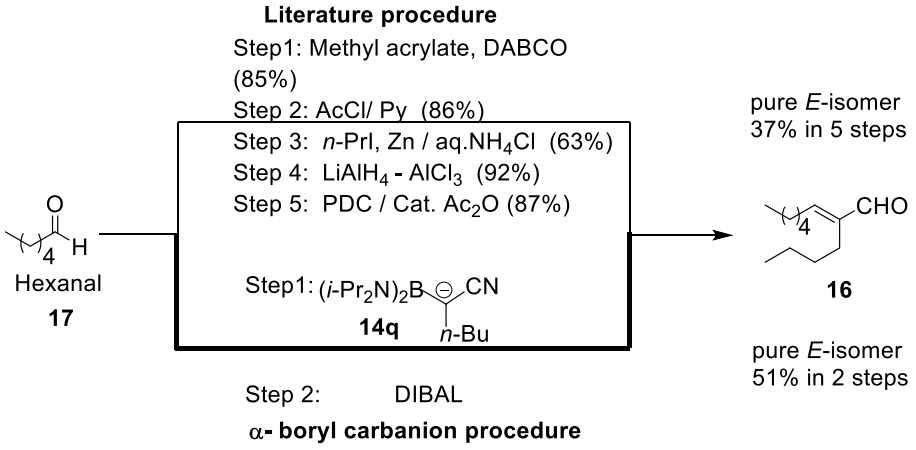
15

Figure 5: 1-bromo-*N*,*N*,*N*',*N*'-tetramethylboranediamine

1.4. Application of the one-pot strategy

1.4.1. For natural product synthesis

Since the reaction to synthesize α, β- disubstituted acrylonitriles was successful, we looked to implement this strategy for synthetic applications. As a part of that, we applied the methodology to synthesize a natural product, (*E*)-2-butyl-2-octenal, **16.** This is known as an alarm pheromone of the African weaver ant, *Oecophylla longinoda*.[54,55] Prior to our report, **16** was synthesized by using a Baylis-Hillman reaction strategy that took five steps starting from hexanal **17** with an overall reaction yield of 37%.[46] By using the α- boryl carbanion methodology, the target natural product **16** was prepared in two steps starting from the same hexanal **17**, and the yield was 51%. The target alarm pheromone compound was prepared by treating *n*-hexanal **17** with the carbanion **6**, followed by DIBAL reduction of the crude nitrile **14q** (*E/Z* = 86:14) **(Scheme 16)**. This synthesis proved the superiority of the one-pot α- boryl carbanion methodology over a multi-step reaction strategy.



Scheme 16: Synthesis of *(E)*-2-Butyl-2-octenal

1.4.2. For synthesis of 2-aminoquinoline based alkaloids

(The work of section 1.4.2. to 1.4.4. was carried out by our former group members Yusuke Takahashi, and Toshihide Maejima under the direction of Dr. Takashi Tomioka. I included these details of the reaction and optimization since this work was developed based on my dissertation work and was direct applications of Scheme 15)[56]

Numerous natural products are found to have 2-aminoquinoline either as the basic skeleton or as part of the structure. These are medicinally important molecules showing biological activities such as antidepressant, antihypertensive, and anthelmintic. Recent studies have revealed that some of the 2-aminoquinoline derivatives are potent against Alzheimer disease and exhibit anti-proliferative properties. Hence, 2-aminoquinolines are attractive targets for synthesis.

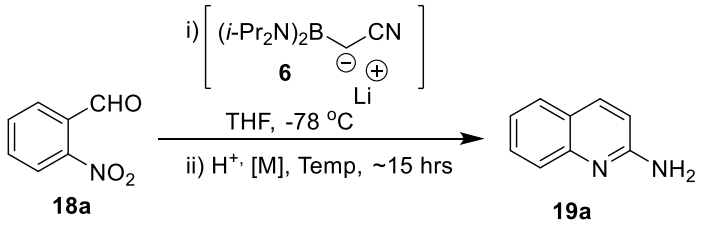
1.4.3. Advantages of our protocol compared to earlier approaches for the synthesis of 2-aminoquinoline derivatives

The common precursor for synthesizing 2-aminoquinoline derivative **19** is 2-nitrophenylacrylonitrile **18a**, and only *Z*-acrylonitriles are useful for synthesizing such targets. 2-Nitrophenylacrylonitriles are prepared using the Horner-Emmon's reaction, but the highest reported selectivity of *Z* to *E* acrylonitriles was low (2:1), and as a result the yields of target 2-aminoquinolines **19** were low as well. From our protocol, the obtained acrylonitrile product *Z:E* selectivities were as high as 4:1. So we envisioned that it would be advantageous to apply our methodology towards the synthesis of such 2-aminoquinoline derivative targets, **19**.

1.4.4. Modification of the protocol and establishment of reaction scheme

According to the literature reports, *Z*-acrylonitriles usually undergo reductive cyclization to 2-aminoquinolines in the presence of a metal (Fe, Sn, Zn, Sm or In)[57-60] in an acidic environment. Since we quench the reaction by adding saturated aqueous NH_4Cl after the

olefination step, directly adding Zn powder during the quenching step yielded 2-aminoquinoline **19a** in 65 – 68% yield. Upon the addition of aqueous NH_4Cl to the reaction flask, the reaction mixture became biphasic (THF: aq. NH_4Cl), which could be a reason for the lower yield than expected. This made us test an organic acid, CH_3COOH, in place of aqueous NH_4Cl. Fortunately, the use CH_3COOH improved the yield of **19a** to 76%. This yield was very close to the experimental yield of *Z*-isomer portion of **8a** after the olefination reaction (80%) from **Scheme 7**.

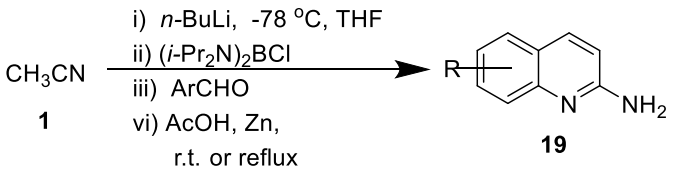


Scheme 17: Optimization for 2-aminoquinoline synthesis

Entry	H^+ source (mL)	[M] (equiv)	Temp	yield (%)
1	sat. NH_4Cl (5)	Zn (5)	rt	68
2	sat. NH_4Cl (5)	Zn (5)	reflux	65
3	sat. NH_4Cl (5)	Fe (5)	rt	38
4	AcOH(1)	Zn (5)	rt	76
5	AcOH(1)	Zn (5)	reflux	76
6	AcOH(1)	Zn (5)	rt	37
7	AcOH(1)	Fe (5)	rt	16
8	MeOH(10)	Zn (5)	reflux	28

Table 5: Optimization of conditions for 2-aminoquinoline synthesis

Once the reaction conditions were optimized, a variety of 2-aminoquinoline derivatives were obtained from six nitrobenzaldehydes **(Table 6)** and acetonitriles alkylated with five alkyl halides **(Table 7).**



Scheme 18: General scheme for 2-aminoquinoline derivatives synthesis in one-pot

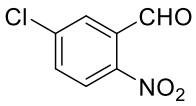
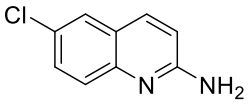
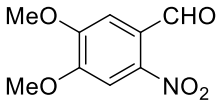
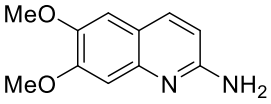
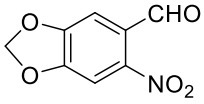
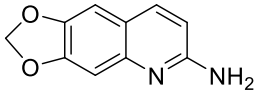
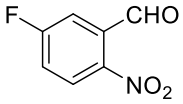
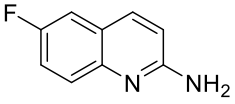
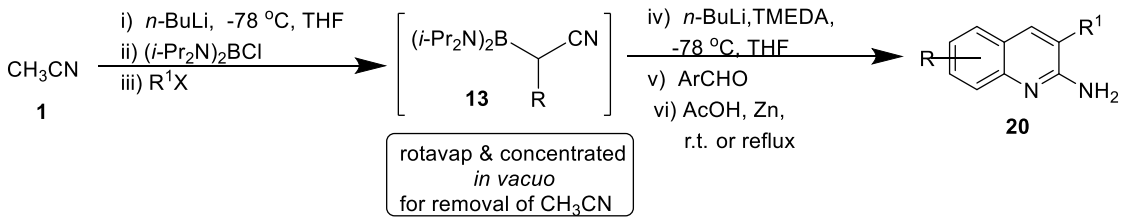
Entry	R^1CHO	Product		Yield(%)
1			**19b**	67
2			**19c**	55
3			**19d**	77
4			**19e**	67

Table 6: Synthesis of 2-aminoquinoline derivatives



Scheme 19: General scheme for 3-alkyl-2-aminoquinoline derivatives synthesis in one-pot

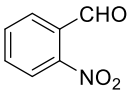
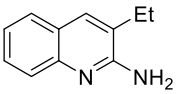
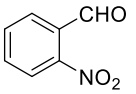
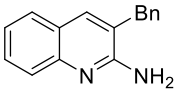
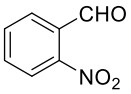
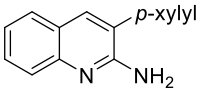
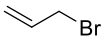
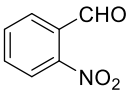
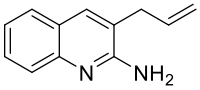
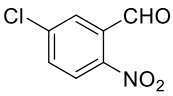
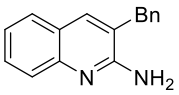
Entry	R^1X	ArCHO	Product		Yield(%)
1	EtI			**20a**	66
2	BnBr			**20b**	73
3	*p*-Xylyl Bromide			**20c**	72
4				**20d**	66
5	BnBr			**20e**	62

Table 7: Synthesis of 3-alkyl-2-aminoquinoline derivatives

1.4.5. Summary

An α-diaminoboryl carbanion-mediated one-pot approach to prepare α,β-disubstituted acrylonitriles has been successfully established. Two alternative approaches were proposed which were complementary and efficiently provided the target acrylonitriles in good to excellent yields with good stereoselectivities. Upon olefination, aryl aldehydes preferentially yielded the (*Z*)-isomer as the major product, whereas aliphatic aldehydes gave the (*E*)-isomer as the major product. This protocol was successfully applied for the synthesis of a natural product, (*E*)-2-

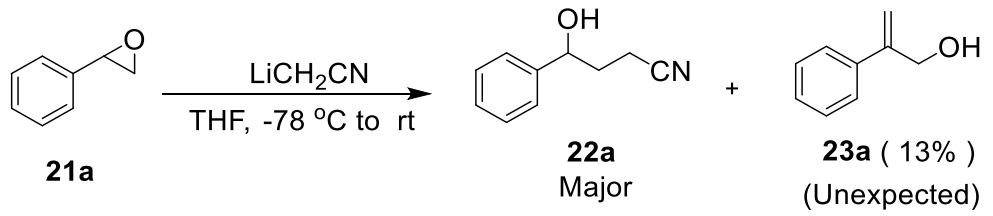
butyl-2-octenal **16**. This work was published in *The Journal of Organic Chemistry* in August, 2011, with the help of Trey G. Vaughan and Toshihide Maejima, under the guidance of Dr. Takashi Tomioka.

CHAPTER II

ONE-CARBON HOMOLOGATION OF ARYL EPOXIDES INTO CONJUGATED ALLYL ALCOHOLS

2.1. Introduction and background

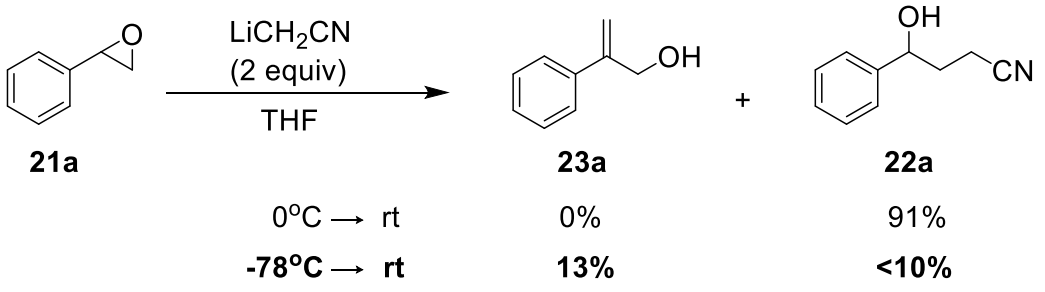
As described in chapter I, using α–boryl carbanion chemistry, a series of α, β-disubstituted acrylonitriles were synthesized by bora-Wittig Olefination **(Scheme 15).** This protocol was also applied to the synthesis of a natural product **16** and a series of 2-aminoquinoline derivatives **(Schemes 18 & 19)**. Since the α–boryl carbanion was the key intermediate in these reactions, we continually sought further applications of this nucleophilic species with other electrophiles, such as epoxide, acyl halide, ester, imine, *etc.* During the study with an epoxide, we serendipitously discovered a unique chemical transformation of styrene oxide **21a** into 2-phenyl-2-propen-1-ol **23a (Scheme 20).** By treating **21a** with lithioacetonitrile **4** in tetrahydrofuran at lower temperatures (< 0 ^{o}C), the reaction was regioselective and the unexpected homologated allyl alcohol **23a** was obtained in non-negligible amounts (> 10%). After further screening, we realized that the yield of **23a** was inversely proportional to the temperature of the reaction. When we looked for literature precedents for a similar transformation, to our surprise, we could find only one literature report for conversion of **21a** to **23a**. We also found that the literature report[61] used a toxic organotin reagent $(Me_3Sn)_2CH_2$, the yields were low, and no synthetic generality had been explored (only two examples were described).[61,62] Apart from that, if we carefully look into the reaction, it seems like the transformation of **21a** to **23a** is not a simple epoxide ring opening reaction. Although it was hard to conclude which mechanism was operating in the reaction to lead to the product **23a**, we believed that it was a mechanistically unique reaction pathway. Based on all these factors, we initiated this *C1*-homologation project, as our one-pot method was operationally simple and potentially versatile for the purpose of molecular functionalization.



Scheme 20: Reaction of lithioacetonitrile with styreneoxide (our conditions)

2.2. Experimental results and discussion

According to a literature report,[63] styrene oxide **21a** normally undergoes a ring-opening S_N2 reaction in the presence of $LiCH_2CN$ **4** at 0 °C and produces alcohol **22a (Scheme 21).** However, when we operated this reaction at a lower temperature (-78 °C),[64] an unusual side-product, allyl alcohol **23a,** was unexpectedly obtained (13%). To confirm this curious observation, we then tested the reaction with the exact literature conditions (namely 0 °C) and, as expected, we could isolate only product **22a** nearly quantitatively; the allyl alcohol **23a** was not observed at all. Concluding with this observation, our incidentally applied lower reaction temperature (-78 °C) seemed to be important in leading to **23a (Scheme 20)**.

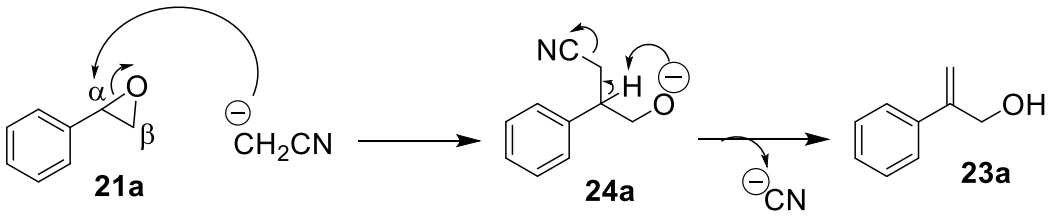


Scheme 21: Transformation of styrene oxide to arylallyl alcohol; comparison to literature report.

2.2.1. Mechanism I for C1-homologation Reaction

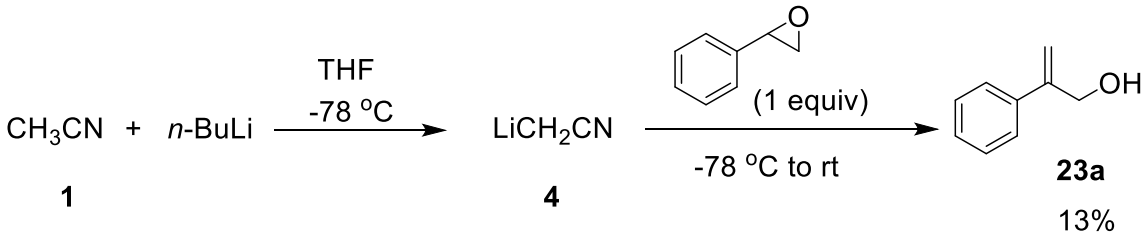
Before further optimization, we proposed a simple anionic path for this reaction

(Mechanism I, Scheme 22). According to this mechanism, the nucleophilic attack of **4** on the benzylic carbon of styrene oxide **21a** opens the epoxide ring, which leaves oxyanion intermediate **24a**. The final product **23a** can be obtained by either intramolecular or intermolecular β-elimination from intermediate **24a**.



Scheme 22: Mechanism I for transformation of styrene oxide to arylallyl alcohol

This pathway seemed reasonable at that point, and various reaction conditions were subsequently varied (i.e., reaction time, temperature, concentration, amount of $LiCH_2CN$ reagent, solvent, and additive). To our surprise, the yield of **23a** hardly improved, and even became worse if the initial conditions were changed; in addition, the reaction was poorly reproducible **(Scheme 23).**



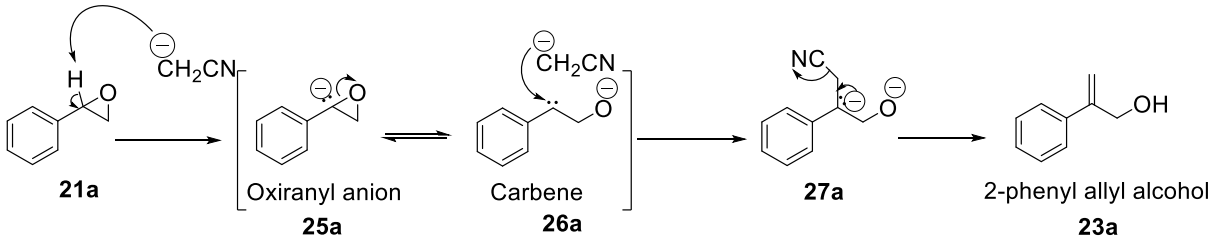
Scheme 23: *C1*-homologation of styrene oxide

As a result, we set aside "Mechanism I" and proposed an unusual pathway, Mechanism

II, which involved a carbene intermediate.

2.2.2. Mechanism II for C1-homologation reaction

According to Mechanism II **(Scheme 24)**, first, oxiranyl anion **25a** was generated with deprotonation of the acidic α-hydrogen of styrene oxide **21a** by $LiCH_2CN$, followed by unimolecular ring opening of the epoxide to give the carbene intermediate **26a**. Subsequently, nucleophilic addition of $LiCH_2CN$ to carbene **26a**, followed by elimination of a cyanide ion from dianion **27a**, afforded allyl alcohol 2**3a**

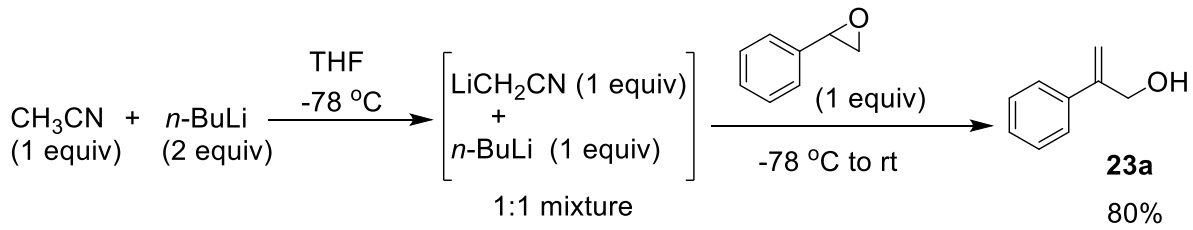


Scheme 24: Mechanism II for *C1*-homologation of styrene oxide to arylallyl alcohol

2.2.2. Optimization of the C1-homologation reaction

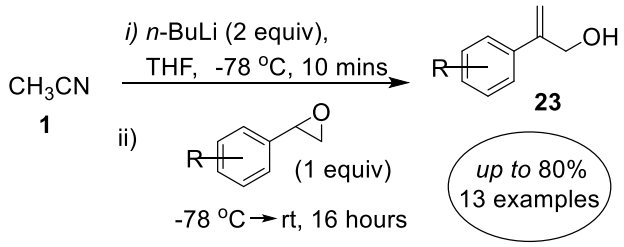
From a literature search, we learned that carbene intermediate **26a** was typically formed at very low temperatures (below -78 ^oC) because of thermal instability at higher temperatures,[65-67] explaining why alcohol **23a** was not produced at 0 ^oC, but could be produced at -78 ^oC **(Scheme 21).**[68] According to Mechanism II, $LiCH_2CN$ was playing two different roles in the reaction, *i.e.*, one as a base to generate oxiranyl anion **25a** and another as a nucleophile to react with carbene species **26a**. We anticipated that the use of a stronger base than $LiCH_2CN$ would make the initial deprotonation step dominant and generate the key carbene intermediate **26a** more efficiently. So we tested different concentration combinations of *n*-BuLi - $LiCH_2CN$ to improve the yield of the reaction. Finally, to our delight, the use of a 1:1 mixture of *n*-BuLi (as a

base) and $LiCH_2CN$ (as a nucleophile) greatly improved the yield of *C1*-homologated allyl alcohol, **23a**, from 13% to 80% **(Scheme 25).**

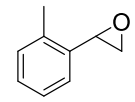
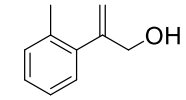
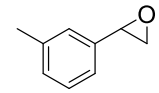
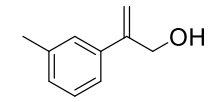
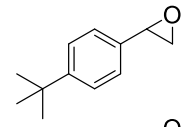
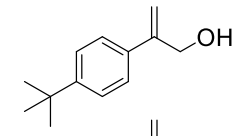
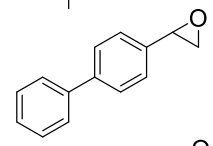
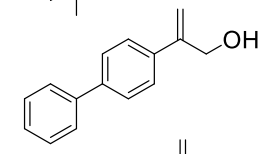
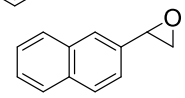
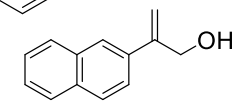
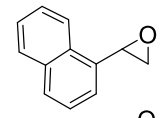
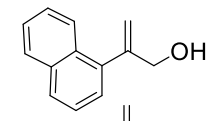
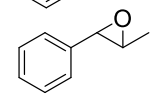
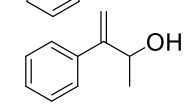
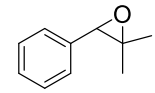
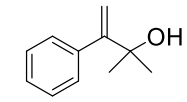
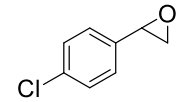
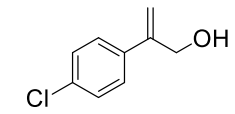
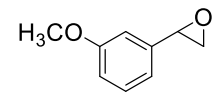
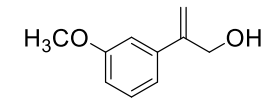
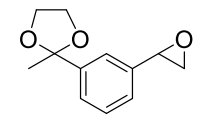
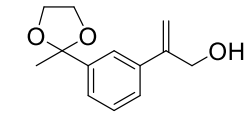


Scheme 25: Optimized conditions for C1-homologation of styrene oxide

This procedure also demonstrated broad substrate generality with respect to various aryl epoxides **(Table 8).** Styrene oxides with ortho-, meta-, and para-alkyl substituents **(entries 1-3)** as well as an arylated styrene oxide **(entry 4)** yielded their corresponding allyl alcohols in good yields (51-81%). Aromatic epoxides (2- and 1-naphthalene-based) **(entries 5 and 6)** also underwent the transformation smoothly (71% and 77%, respectively). Di- and tri- substituted aromatic epoxides **(entries 7 and 8)** got converted into their respective alcohol products with good efficiency (65%). Substituted styrene oxides were also investigated. Styrene oxide with *p*-chloro substitution **(entry 9)** gave a slightly inferior result (44%), maybe due to the susceptibility of the halogen group to *n*-BuLi. *m*-Substituted styrene oxides with a methoxy group **(entry 10)** or an acetal group **(entry 11)** were also compatible, and the yields were 60% and 65%, respectively.



Scheme 26: Synthesis of 2-arylallyl alcohols from aryl epoxides[a]

Entry	Aryl Oxide	allyl alcohol		yield
1			**23b**	80
2			**23c**	72
3			**23d**	51
4			**23e**	64
5			**23f**	71
6			**23g**	77
7			**23h**	65
8			**23i**	65
9			**23j**	44
10			**23k**	60
11			**23l**	65

[a] CH_3CN (2.1 m.mol), *n*-BuLi (4.1 m.mol), arylepoxide (2.0 m.mol), THF (3.0 mL)

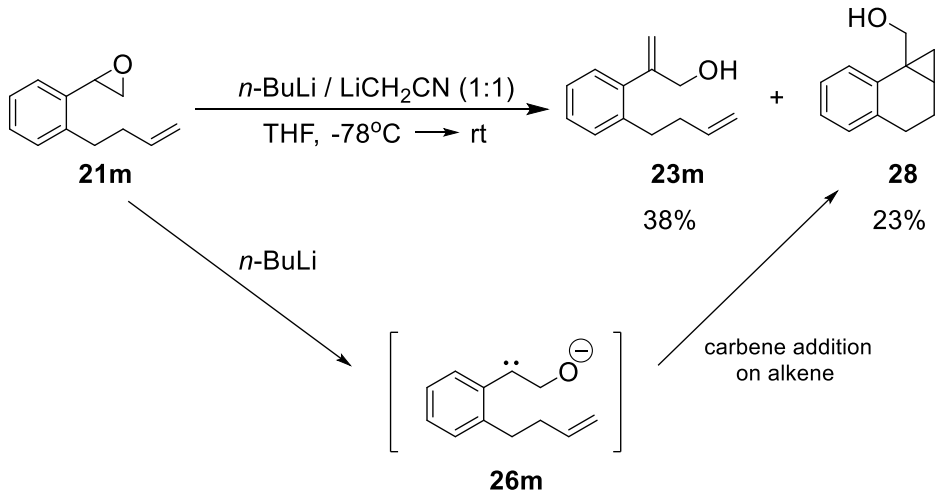
Table 8: Preaparation of 2-arylallyl alcohols from arylepoxide

2.3 Evidence for carbene intermediate mechanism

Since we proposed that the *C1*-homologation reaction involved a carbene intermediate,

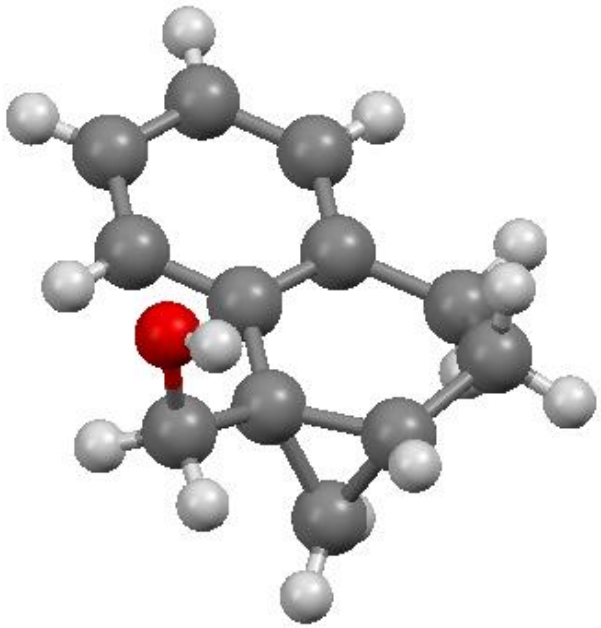
we made several attempts to prove that, but most of them were unsuccessful. We tried to trap the carbene intermediate **26a** based on its common reactivity, that is, addition to a double bond to form a cyclopropyl ring. We made several attempts to trap **26a** with alkenes such as styrene and prop-1-en-1-ylbenzene, but all the attempts were unsuccessful. Later, we added an electron rich alkene, that is, 2,3-dimethyl-2-butene. According to a literature report, if a carbene formed during the reaction pathway, it should form a cyclopropyl intermediate with this alkene. Discouragingly, no target product was seen in the proton NMR, and no isolable amount of any product was observed.

Based on these results, we assumed that the carbene intermediate was very short lived, and the proximity of the double bond to the presumed carbene would play a key role in its addition to the double bond. Finally, we thought of preparing an aryl epoxide including an alkene moiety**, 21m**, which would react intramolecular to yield a cyclopropyl ring in the final product. To our delight, when epoxide **21m** was used **(Scheme 27),** a cyclopropanation adduct **28** (23%) along with **23m** (38%) was isolated. The formation of this adduct strongly indicated the formation of carbene intermediate **26m** and supported our proposed reaction mechanism.



Scheme 27: Evidence for support of carbene mediated mechanism

Additionally, the X-ray crystal structure of **28** was obtained by vapor diffusion method (Hexanes and Methanol solvent system) from the isolated material of **28 (Figure 6).** It further proved the cyclopropanation adduct formation and also provided the geometry of the cyclopropane ring which was cis. The trans geometry of cyclopropane ring in **28** was assumed to be not stable because of the angle strain.



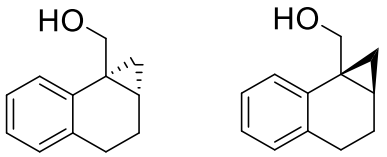
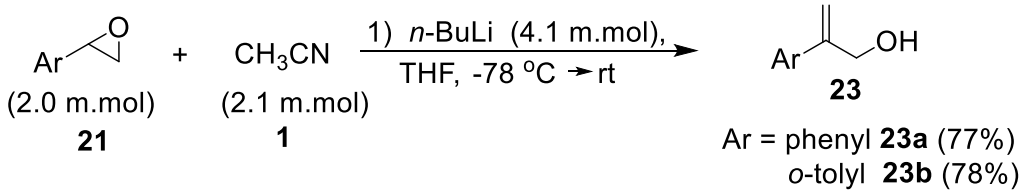


Figure 6: Crystal structure of cyclopropanation adduct

2.4. Modification to the C1-homologation reaction scheme

For operational simplicity, the one pot reaction conditions were slightly changed in that *n*-BuLi was added directly to the solution of **21** and acetonitrile **1** in THF at -78 ^{o}C dropwise. This yielded the respective allyl alcohols **23** after overnight reaction **(Scheme 28).** Encouragingly, the reaction yields were comparable after this modification, with identical results to the earlier procedure **(Scheme 25).**



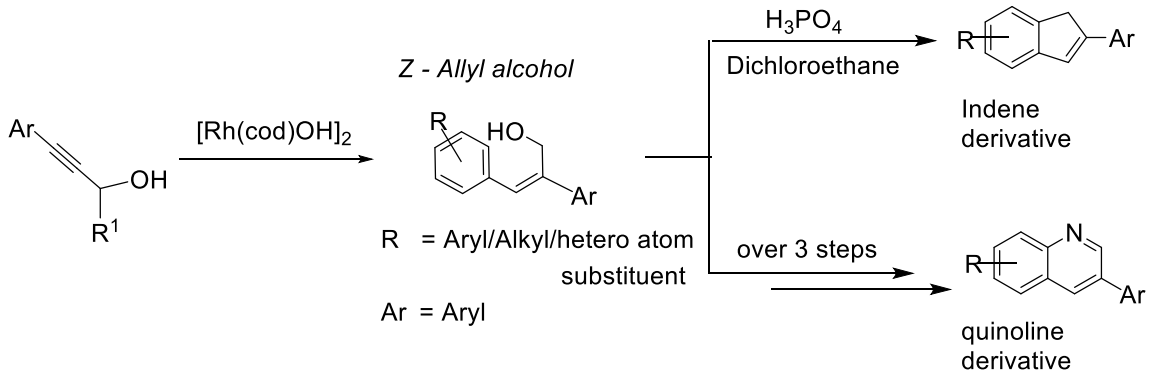
Scheme 28: Modified scheme for *C1*-homologation of arylepoxides

2.5. Conclusion

We made a serendipitous discovery which involved a novel carbene-mediated transformation of aryl epoxides **21** into 2-aryl allyl alcohols **23**. A 1:1 mixture of *n*-butyllithium and lithiated acetonitrile **4** in tetrahydrofuran converted aryl epoxides into one-carbon homologated allyl alcohols in a highly regioselective manner. This work was published in *Organic Letters* in 2013 with the help of my co-worker Toshihide Meijima and Dr. Takashi Tomioka.

2.6. Plan for synthesis of 2,3-diaryl allyl alcohols

Since the idea of *C1*-homologation of aryl epoxides was successful **(Scheme 26)**, we aimed to implement this strategy for the synthesis of more-substituted allyl alcohols, that is, 2,3-diaryl allyl alcohols. The target alcohols are precursors for syntheses of indene and quinoline derivatives. Recently, Lauten et al. reported the synthesis of 2,3-(*Z*)-diaryl allyl alcohols using a rhodium complex, followed by intramolecular cyclization to yield indene and quinolone derivatives **(Scheme 29).**[69] Although there are a few reported methods in the literature to prepare 2,3-diaryl allyl alcohols, those methods were multi-step reaction strategies and used transition metal catalysts (either Rh or Pd complexes) to carry out the reactions. Hence, we proposed the synthesis of 2,3-diaryl allyl alcohols using a *C1*-homologation protocol, as our approach was one-pot and also a transition-metal-free synthesis, which was clearly advantageous over the other available methods in the literature.[69]

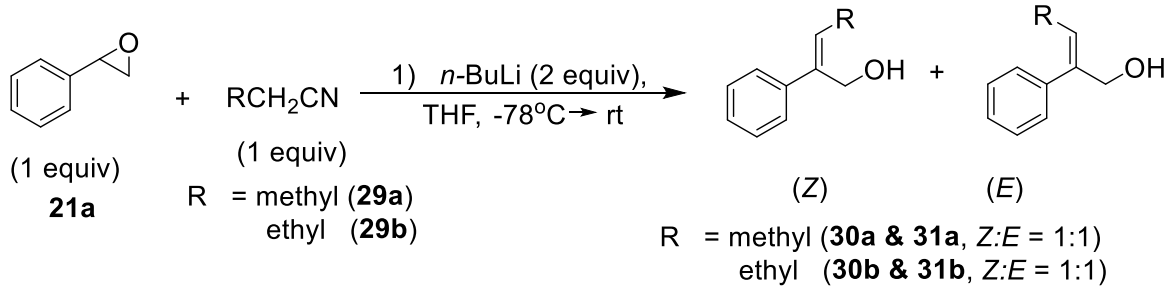


Scheme 29: Lautens' protocol for synthesis indenes and naphthalenes *via* 2,3-diryl allyl alcohols

2.6.1. Results and discussion

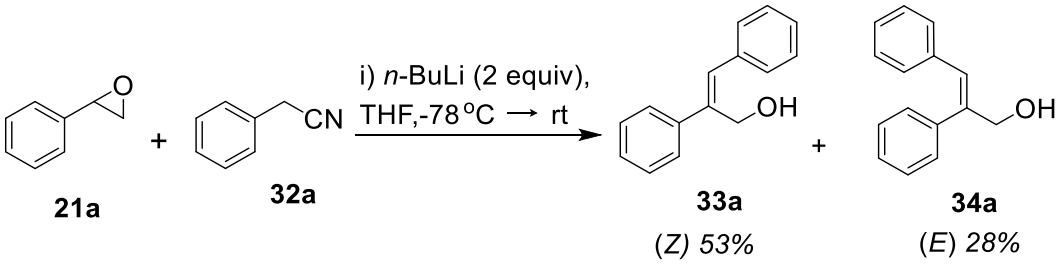
Initially, we tested the compatibility of styrene oxide **21a** under standard conditions with propionitrile **29a (Scheme 30)**. As expected, the reaction gave mixtures of *Z* and *E* allyl alcohols

(**30a** and **31a)** where butyronitrile yielded **30b** *(Z-isomer)* and **31b** *(E-isomer)* respectively as major products. But the reaction was not stereoselective (*Z:E* = 1:1), and seemed to be synthetically less attractive.



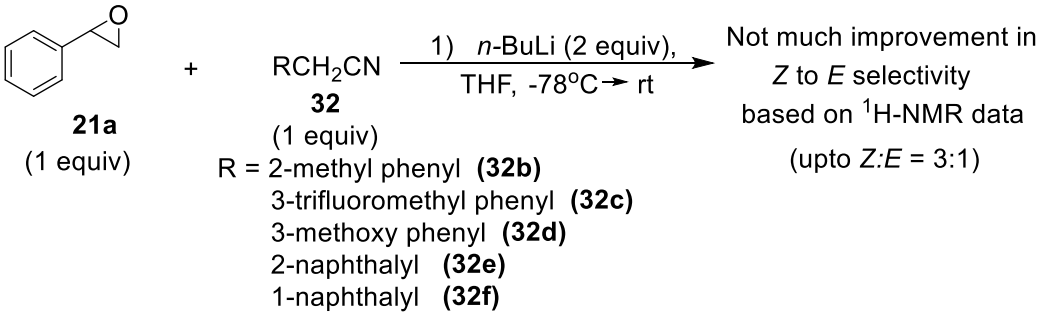
Scheme 30: Initial attempt for synthesis of 2,3-diarylallyl alcohols

Later, we examined the reaction of styrene oxide **21a** with benzyl cyanide **32a** under identical reaction conditions of **Scheme 31** and the reaction successfully yielded the corresponding mixture of allyl alcohols **33a and 34a,** with an overall yield of 85%. To our surprise, unlike propionitrile and butyronitrile, the reaction was stereoselective, and the *Z*-isomer was predominately formed **(57%)** over the *E*-isomer **(28%) (Scheme 31).** Based on these results, we concluded that the selectivity of the *C1*-homologation reaction was directly proportional to the size of the R group, where steric factors were the major criterion for selectivity.



Scheme 31: *C1*-homologation reaction of styrene oxide using benzylcyanide

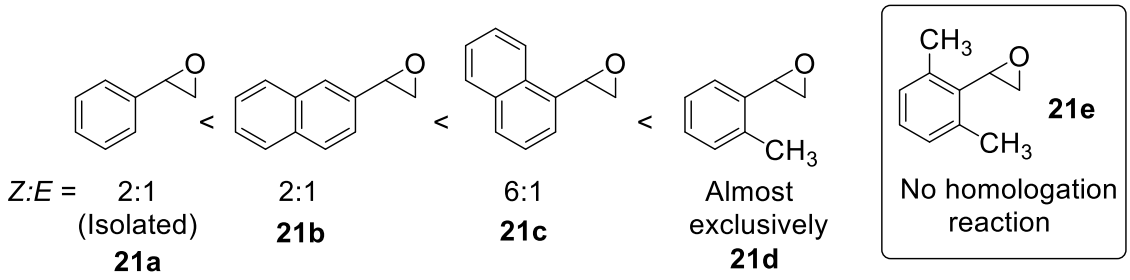
Although the reaction from **Scheme 31** was stereoselective, the selectivity was poor. So, in further optimization of the reaction, we screened a series of aryl acetonitriles **32** to try to enhance the *Z:E* ratio of products by taking advantage of either steric or electronic factors, or both **(Scheme 32).** Aryl acetonitriles with electron rich substituents ($-OCH_3$) and electron deficient substituents ($-CF_3$) were tested against styrene oxide **21a.** Although the selectivity was enhanced (up to *Z:E* = 3:1), it was not that satisfactory. From this scheme it was clear that the effect of electronic factors was minimal on reaction selectivity, since there was no significant difference in either yields or stereoselectivity.



Scheme 32: Optimization of reaction using aryl acetonitriles with styrene oxide

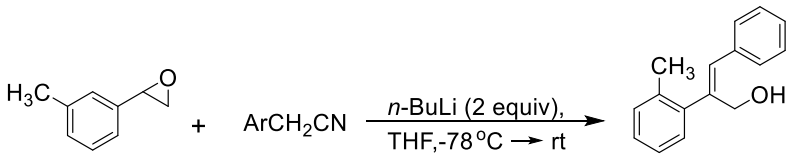
Alternatively, we screened a series of aryl epoxides against benzyl cyanide **(Scheme 33).** The reaction of unsubstituted naphthalene-2-epoxide **21b** with benzyl cyanide **32a** gave an

almost identical *Z:E* selectivity as styrene oxide. Next, naphthalene-1-epoxide **21c** was tested; to our delight, the *Z:E* ratio was enhanced to 6:1. As this was a promising result, we isolated the product. Discouragingly, the isolated yield was low (32%), which may be due steric interference of the bulky naphthyl group. This result encouraged us to screen further with relatively less hindered substituents, such as 2-methyl styrene oxide **21d**. Upon reaction of **21d** with **32a** under standard conditions, the crude proton NMR showed no signs of *E*-isomer formation. This was a really encouraging result and, upon isolation, the reaction obtained 55% yield. Out of curiosity, we then tested 2,6-dimethyl styrene oxide **21e**, but the crude proton NMR revealed that no *Z or E* isomers were formed in the reaction. The reason might be that **21e** possessed too much steric hindrance from the two ortho methyl groups, which limited its deprotonation by *n*-BuLi.

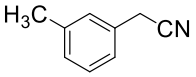
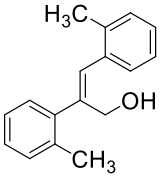
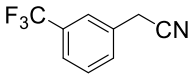
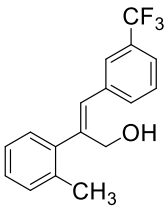
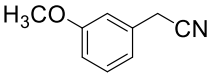
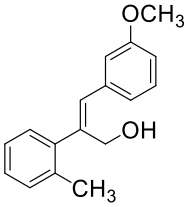
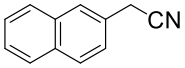
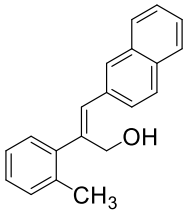
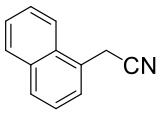
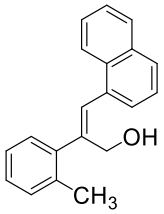
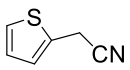
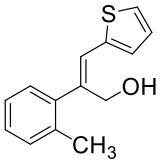


Scheme 33: Optimization of reaction using aryl epoxides with benzylcyanide

With the optimized reaction scheme, a series of aryl acetonitriles were screened against 2-methylstyrene oxide **21d** to obtain the respective 2,3-diaryl allyl alcohols **(Table 9).** Although the reactions yielded exclusively *Z*-isomers, the yields were low (<50%). An additive, TMEDA, was added along with *n*-BuLi to the reaction mixtures to enhance the yield, but it did not help; in fact, it further lowered the yield. Further screening and attempted improvement of yield has been ongoing in our lab.



21d **32** **33a** (*Z*)

Entry	$ArCH_2CN$ (32)	allyl alcohol		yield[a]
1			**33a**	42
2			**33b**	40
3			**33c**	36
4			**33d**	27
5			**33e**	20
6			**33f**	28

[a]isolated yields

Table 9: Preaparation of 2,3-diarylallylalcohols from arylepoxide

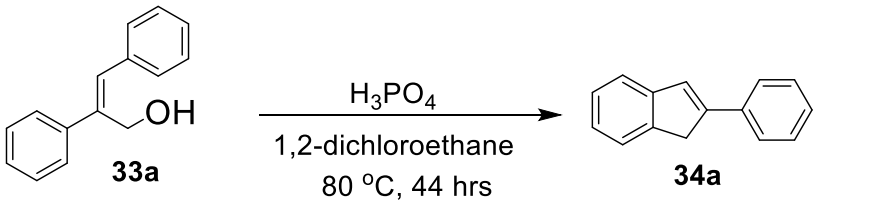
2.7. Applications of C1-homologation reaction

2.7.1. Importance of indene derivatives

Substituted indenes are interesting scaffolds since some of the indene derivatives possess biological activity such as anti-proliferative properties,[70a] conducting materials,[70b] and indenyl metal complexes have been used as catalysts for several reactions.[70c] Due these various applications indene derivatives are always attractive targets in synthetic chemistry.[71]

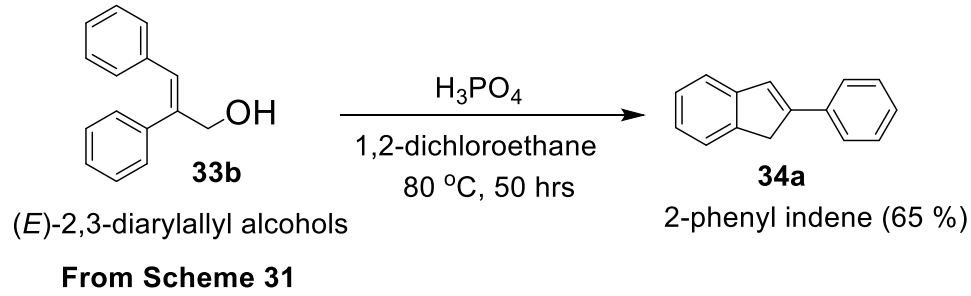
2.7.2. Preparation of indene derivatives

According Lautens' article, indene and naphthalene derivatives were synthesized from (*Z*)-2,3-diaryl allyl alcohols in the presence of orthophosphoric acid (H_3PO_4) in dichloromethane.[69] The reported yields of indene derivatives were moderate to good (up to 91%). Since we successfully synthesized (*Z*)-2,3-diaryl allyl alcohols in a one-pot, transition-metal-free route using our protocol **(Scheme 31)**, we were excited to use the allyl alcohol **33a** for the synthesis of indene. From the reaction of styrene oxide with benzyl cyanide, a mixture of *Z* and *E* isomers was obtained in a 2:1 ratio.[72] The isomers were separated using column chromatography and *Z*-isomer **33a** was used for the indene synthesis. For this intramolecular cyclization reaction, the identical conditions as of Lautens' indene synthesis were applied. As expected, 2-phenylindene was obtained after 44 hrs of reaction at 80 ^oC in dichloroethane **(Scheme 34).**



Scheme 34: Synthesis of 2-phenyl Indene from (*Z*)-2,3-diarylallyl alcohols

Later, out of curiosity, we subjected the *E*-isomer **33b** to intramolecular cyclization under the same conditions as in **Scheme 29**. After 44 hours of reaction at 80 ^{o}C, we could find a TLC spot for the product **34a** along with starting material **33b**; TLC showed that most of the starting material was already consumed**.** After 50 hours of reaction, no evidence of **33b** was seen on the TLC plate, but only the product spot for **34a (Scheme 35).** This was a clear indication that both of the isomers **33a** and **33b** underwent intramolecular cyclization under the Lautens' conditions, although the *E*-isomer cyclized slower than the *Z*-isomer.



33b

(*E*)-2,3-diarylallyl alcohols

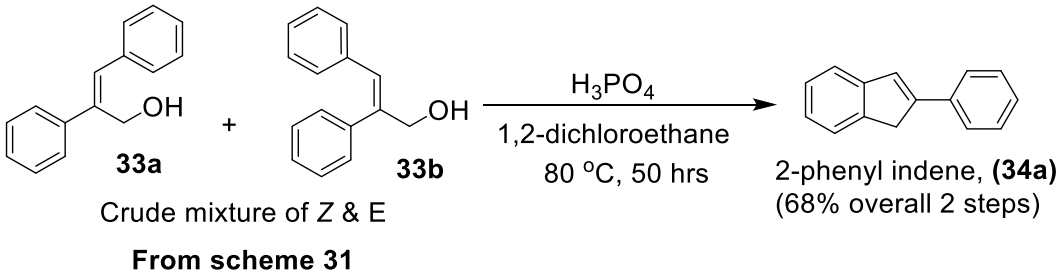
From Scheme 31

34a

2-phenyl indene (65 %)

Scheme 35: Synthesis of 2-phenyl Indene from (*E)*-2,3-diarylallyl alcohols

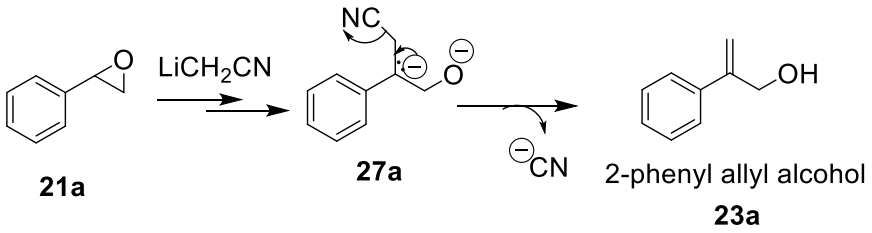
This curious observation lead us to investigate further into the synthesis of indene derivatives from 2,3-diaryl allyl alcohols. Since both *Z* and *E* isomers underwent intramolecular cyclization, we thought of subjecting the crude *Z* and *E* mixture of the products from **Scheme 22**, without isolation, to the Lautens cyclization conditions. To our delight, after 50 hours of reaction, both isomers were consumed, and only the product **34a** TLC spot was observed. Upon isolation, the final target compound **34a** was obtained with an overall yield of 68% **(Scheme 36).**



Scheme 36: Synthesis of 2-phenyl indene with a crude mixture of 2,3-diarylallyl alcohols

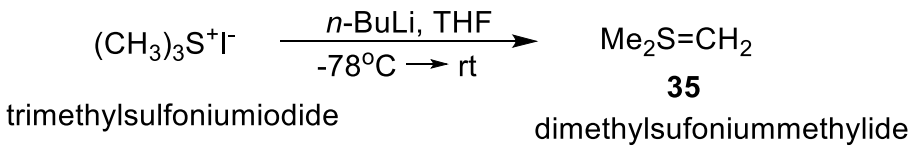
2.8. Cyanide-free reagent for C1-homologation reaction

Although the homologation reaction of styrene oxide using $LiCH_2CN$ was unique and potentially useful for organic synthesis, there was a potential drawback **(Scheme 24).** According to the reaction mechanism, a toxic cyanide ion (^{-}CN) is produced at the end the reaction **(Scheme 37)**.



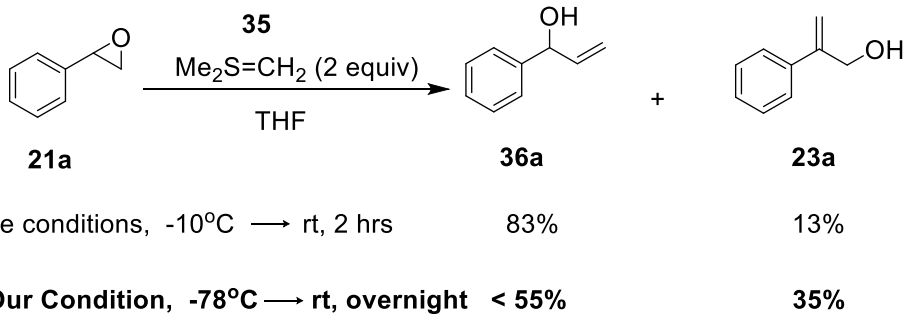
Scheme 37: Generation of $-CN^-$ as side product in C1-homologation reaction

In order to avoid the formation of the cyanide ion in the *C1*-homologation reaction, an alternative "cyanide-free" reagent was sought. Dimethylsulfonium methylide, $Me_2S{=}CH_2$ **(35)**, is a well-known homologating reagent[73-83], and the expected by-product was non-toxic dimethyl sulfide (Me_2S). Methylide reagent **35** can be readily prepared by treating trimethylsulfonium iodide ($Me3S^+I^-$) with *n*-BuLi in THF solvent at low temperatures, such as -78 °C **(Scheme 38).**



Scheme 38: Preparation of dimethylsulfonium methylide reagent

According to a literature report,[84] styrene oxide (**21a)** undergoes a ring opening reaction with **35** at -10 °C and produces allyl alcohol **36a** along with **23a**, a side product in the reaction. So we tested the reaction with similar conditions, but applied a lower temperature (-78 °C). Excitedly, the reaction yield of **23a** improved from 13% to 35% **(Scheme 39).**



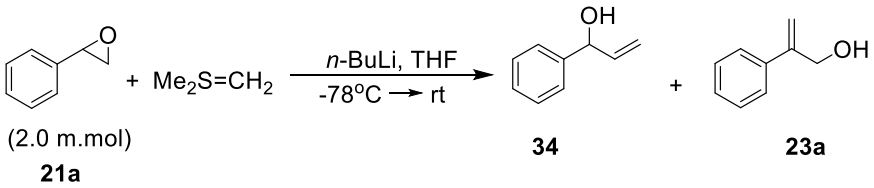
Scheme 39: α-Methylenation of styreneoxide using dimethylsulfonium methylide reagent

In **Scheme 39**, dimethylsulfonium methylide **35** was acting as a base as well as a nucleophile. Since methylide reagent was not a strong enough base to deprotonate the benzylic proton efficiently, as other, stronger bases like *n*-BuLi can, the yields were low. So we used a mixture of *n*-BuLi (as a base) and $Me_2S=CH_2$ (as a nucleophile) at -78 °C to improve the yield of **23a.**

2.9. Optimization of methylenation reaction using methylide reagent

We optimized the reaction by changing the concentrations of both *n*-BuLi and methylide

reagent **35 (Table 10).** Interestingly, when 2 equiv of methylide reagent **35** were used, the reaction yield of **23a** went up to 55% **(entry 3, Table 10)**. A further increase of the amount of methylide resulted in lower yields **(entry 4, Table 10).** When TMEDA was used in the reaction, surprisingly, neither of the products was observed **(entry 5, Table 10)**, hence this additive was ineffective in improving the reaction yield. Besides methylide reagent, another well-known homologating reagent, CH_2I_2, was tested. Discouragingly, no isolable product was seen, but to our surprise, a significant amount of styrene oxide was recovered even after 24 hours of reaction **(entries 7 & 8, Table 10).**



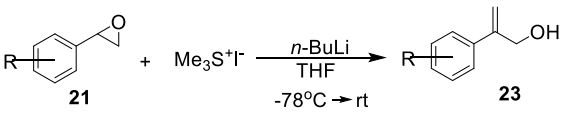
Scheme 40: Optimization of homologation reaction with methylide reagent

Entry	$Me_3S^+I^-$ (m.mol)	*n*-BuLi (m.mol)	**23a** (%)[a]	**34** (%)[a]
1	2.1	4.2	28	19
2	3.1	4.2	36	24
3	4.1	6.2	55	12
4	5.1	7.2	53	8
5[b]	4.1	6.2	0	0
6	4.0	4.0	29	52
	CH_2I_2 (m.mol)			
7	2.1	4.1	N/A[c]	
8	4.1	6.1	N/A[c]	

[a] By NMR (internal standard). [b] Used TMEDA.
[c] Styrene oxide mostly recovered, along with minor side-products.

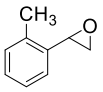
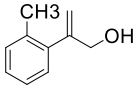
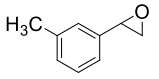
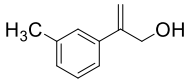
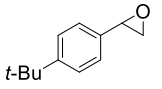
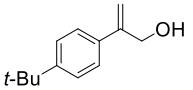
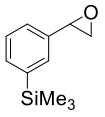
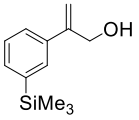
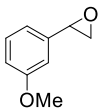
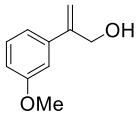
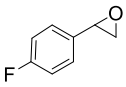
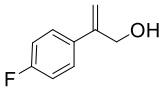
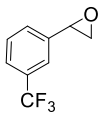
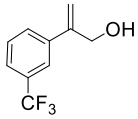
Table 10: Optimization of homologation reaction with *n*-BuLi/methylide reagent

Once the reaction conditions were optimized, the scope and generality of the methylenation reaction were subsequently investigated **(Table 11).** Aryl epoxides with alkyl substitutions on ortho, meta, or para positions **(entries 1–3)** provided their respective allyl alcohols in fair yields (up to 51%). Aryl epoxides containing both electron-donating and electron-withdrawing functional groups gave a moderate yield upon methylenation **(entries 4–7).** When compared to the *n*-BuLi–$LiCH_2CN$ system **(Table 8),** the yields of the methylenation reaction were inferior by 10–30%, presumably due to the lower solubility of the reagent $Me_3S^+I^-$. In spite of this, the *n*-BuLi–$Me_2S{=}CH_2$ system works as a useful alternative system while large scale practical investigations and also to avoid harmful cyanide ion generation.



21 23

Scheme 41: Methylenation of styrene oxide by methylide reagent

Entry	Aryl Oxide (21)	allyl alcohol (23)		yield[a]
1			**23b**	51
2			**23c**	50
3			**23d**	40
4			**23n**	53
5			**23k**	51
6			**23o**	39
7			**23p**	36

[a]isolated yield

Table 11: Methylination reaction of styrene oxide using methylide reagent

2.10. Conclusion

The use of an *in situ* generated sulfur-based ylide, $Me_2S{=}CH_2$, successfully converted a series of aryl epoxides into conjugated allyl alcohols in the presence of *n*-BuLi in an unusual regioselective manner. This 'cyanide-free' protocol also overcame the previous major issues encountered in the *n*-BuLi–$LiCH_2CN$ system. We published this work in *Tetrahedron Letters* in 2014 with the help of my co-worker Amber James and Dr. Takashi Tomioka.

CHAPTER III

GENERAL METHODS OF PREPARATION AND CHARACTERIZATION DATA

CHAPTER I

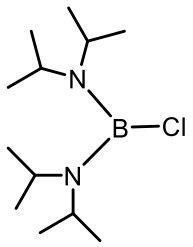
General Methods:

All the moisture sensitive experiments were performed in flame dried glassware fitted with rubber septa under argon atmosphere. Tetrahydrofuran (THF) was distilled over sodium/benzophenone ketyl. Tetramethylethylenediamine (TMEDA) was distilled over calcium hydride. Bis(diisopropylamino)chloroborane was prepared in accordance with the literature procedure. Unless otherwise noted, all other reagents were obtained from commercial sources and used as received. ^{1}H nuclear magnetic resonance (NMR) spectra were recorded on Bruker Avance DRX 300 (300 MHZ) or DRX 500 (500 MHz) spectrometers. NMR data are presented as follows:

chemical shift (in ppm on the δ scale relative to δH 7.26 for the residual protons in $CDCl_3$), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant (J/Hz), integration. Coupling constants were taken directly from the spectra and are uncorrected. ^{13}C NMR spectra were recorded at 75 or 125 MHz, and all chemical shift values are reported in ppm on the δ scale, with an internal reference of δC 77.0 for $CDCl_3$. Analytical TLC was performed on silica gel plates using UV light and/or potassium permanganate stain followed by heating. Flash column chromatography was performed on silica gel 60A (32-63D). High-resolution mass spectra (HR-MS) were recorded using a Waters SYNAPT HDMS quadrupole time of flight (Q-TOF) mass spectrometer. All the HR-MS experiments were conducted at the hands of the graduate students of Dr. Amala Dass research group at the University of Mississippi.

1-Chloro-*N*,*N*,*N*',*N*'-tetraisopropylboranediamine: (7)

This starting material was prepared according to the procedure in the reported literature.[31]

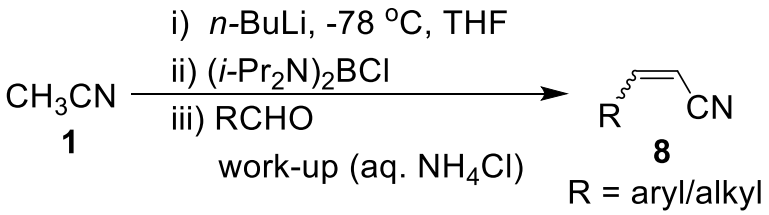


A 1000 mL, three necked, round-bottomed flask was flame dried and purged with argon and equipped with a magnetic stir bar, rubber septum, and a reflux condenser connected to an argon inlet adapter was assembled. Dry toluene (200 mL) was added to the flask followed by the addition of diisopropylamine (115 mL, 820 mmol) were added to the flask *via* a syringe. The flask was cooled in an ice-water bath and solution of trichloroboron (200 mL, 1 M in DCM, 200 mmol) was added dropwise. The solution was stirred for 30 min at 0 °C. The cooling bath was then removed and the reaction mixture was stirred at room temperature for an additional 30 min. The rubber septum was replaced with a glass stopper under argon flow, and all glass joints were secured with Keck clips. The reaction mixture was set under reflux for two days. After cooling to room temperature, the resulting mixture was filtered. Since the product was highly sensitive to moisture, any contact with air was avoided/minimized. The resulting salt was washed with dry hexanes, and the combined filtrates were concentrated *in vacuo*. The residue was distilled under reduced pressure (65~80 °C, 0.1 mmHg) to get 42.8 g of a clear oil. This product released fumes upon exposure to atmosphere.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (d, J = 6.6 Hz, 24H), 3.46 (sep, J = 6.6 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 47.0, 23.4; this product spectroscopically matched that of the known compound.[31]

One-pot synthesis of *β*-monosubstitued (*Z*)-acrylonitriles (Scheme 8): [29]

This procedure was conducted by Yusuke Takahashi, Trey G. Vaughan, Takayoshi Yanase.

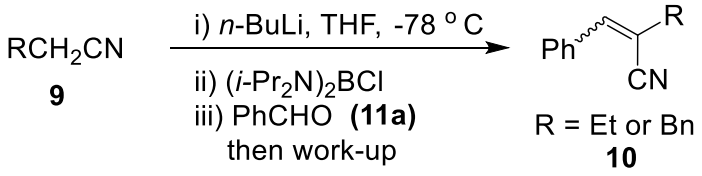


General procedure:

Into a flame-dried 25 mL round-bottomed flask was added dry THF (8.0 mL) under an argon atmosphere. After cooling to -78 ºC (acetone/dry-ice bath), *n*-BuLi (880 µL, 2.5 M in hexane, 2.2 mmol) and dry CH_3CN (172 µL, 3.3 mmol) were added dropwise, respectively. After stirring for 20 min, (*i*- $Pr_2N)_2BCl$ (271 mg, 1.1 mmol) was then slowly added. After stirring for 1hour, benzaldehyde (102 µL, 1.0 mmol) was added. The reaction mixture was stirred for an additional hour at -78 ºC and quenched with half saturated NH_4Cl (5 mL) (-78ºC to r.t. over 30 min). After the phase separation, the aqueous layer was extracted with Et_2O (x2).

The combined organics were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by SiO_2 column chromatography with Hex/EtOAc system to the target acrylonitriles.

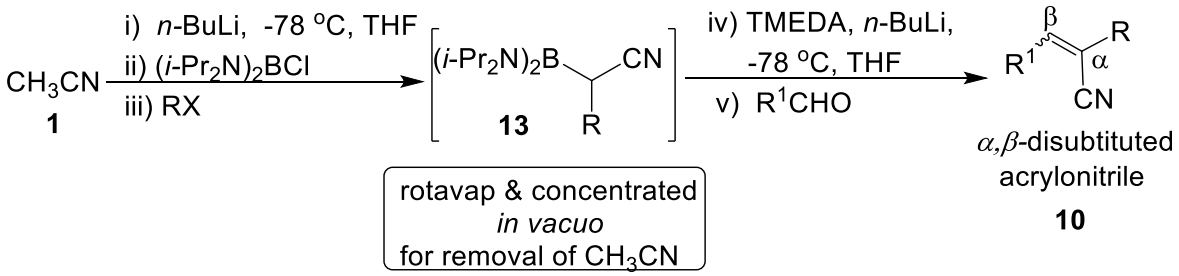
Linear Approach for Preparation for α,β- disubstituted Acrylonitriles (Scheme 11):



General Procedure for Linear Approach:

Into a flame-dried round-bottomed flask was added dry THF (8.0 mL) under an argon atmosphere. After the mixture was cooled to -78 ^{o}C (acetone/dry ice bath), *n*-BuLi (880 μL, 2.5M in hexane, 2.2mmol) and a nitrile (3.3 mmol) were added dropwise, respectively. After the mixture was stirred for 5 min, (*i*-$Pr_2N)_2BCl$ (300 μL, 1.1 mmol) was then slowly added. After another 1 hour of stirring, an aldehyde (1.0 mmol) was added. The reaction mixture was stirred for an additional 1 hour at -78^{o}C and quenched with half-saturated NH_4Cl (5 mL) (-78 ^{o}C to rt over 30 min). After the phase separation, the aqueous layer was extracted with Et_2O (x2). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. *E/Z* ratio was determined by ^{1}H NMR of the crude reaction mixture. The crude product was purified by SiO_2 column chromatography (hexane/EtOAc eluent system) to afford the corresponding acrylonitrile as a mixture of *E/Z* isomers.

Divergent Approach for Preparation for *α,β*- disubstituted Acrylonitriles (Scheme 15):



General Procedure for Divergent Approach:

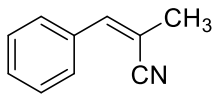
Into a flame dried round-bottomed flask was added dry THF (8.0 mL) under an argon atmosphere. After the mixture was cooled to -78 ^{o}C (acetone/dry ice bath), *n*-BuLi (1.0 mL, 2.5 M in hexane, 2.5 mmol) and dry CH_3CN (195 μL, 3.75 mmol) were added dropwise,

respectively. After the mixture was stirred for 20 min, (i-$Pr_2N)_2BCl$ (342 μL, 1.25 mmol) was then slowly added. After another 1 hour of stirring, alkyl halide (1.25 mmol) was added. The reaction mixture was stirred for an additional 1 hour at 0 ^oC and then concentrated under reduced pressure. Subsequently, dry THF (6.0 mL) was added into the crude mixture under an argon atmosphere. After the mixture was cooled to -78 ^oC (acetone/dry ice bath), tetramethylethylenediamine (188 μL, 1.25 mmol) and *n*-BuLi (500 μL, 2.5 M in hexane, 1.25 mmol) were added dropwise. After the mixture was stirred for 1 hour, an aldehyde (1.0 mmol) was slowly added, and the resulting mixture was stirred for 1.5 hour at the same temperature. The reaction mixture was then quenched with half saturated NH_4Cl (6 mL) (-78 ^oC to rt over 30 min). After the phase separation, the aqueous layer was extracted with Et_2O (x2). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. *E/Z* ratio was determined by ^1H NMR of the crude reaction mixture. The crude product was purified by SiO_2 column chromatography (hexane/EtOAc eluent system) to afford the corresponding acrylonitrile as a mixture of *E/Z* isomers. The *E/Z* mixture was subsequently separated for characterization purpose. The use of toluene as an eluent for SiO_2 column chromatography allowed for isolation of each isomer. The *E/Z* configurations were determined, based on the fact that, in ^{13}C NMR spectra, the allylic carbon (on the α-carbon) of an α,β-disubstituted (*E*)-acrylonitrile appears at higher field than the same carbon of the (*Z*)-isomer,[51] and in ^1H NMR spectra, the vinylic proton on the β-carbon of (*Z*)-isomer appears at higher field than the same proton of the *E*-isomer.[43]

2-Methyl-3-phenylacrylonitrile (10a):

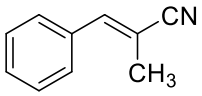
Column chromatography (Hex/EtOAc = 99/1) yielded **10a** (118 mg, 83%, *Z/E* = 70:30)

(*Z*)-isomer (major): R_f 0.81 (toluene)



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 – 7.68 (m, 2H), 7.44 – 7.36 (m, 3H), 6.94 (apparent s, 1H), 2.16 (d, J = 1.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.0, 133.8, 129.8, 128.8, 128.4, 119.2, 106.1, 22.2. This product spectroscopically matched that of the known compound.[85]

***(E)*-Isomer (minor): R_f 0.76 (toluene)**

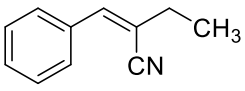


^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 – 7.31 (m, 5H), 7.21 (apparent s, 1H), 2.15 (d, J = 1.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.2, 134.0, 129.27, 129.24, 128.6, 121.2, 109.6, 16.7. This product spectroscopically matched that of the known compound.[86]

2-Benzylidenebutanenitrile (10b):

Column chromatography (Hex/EtOAc = 99/1) yielded **10b** (111 mg, 71%, Z/E = 70:30).

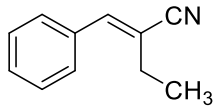
***Z*-Isomer (major): R_f 0.86 (toluene)**



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 – 7.70 (m, 2H), 7.45 – 7.36 (m, 3H), 6.94 (apparent s, 1H), 2.44 (qd, J = 7.5, 1.2 Hz, 2H), 1.26 (t, J = 7.5Hz, 3H); ^{13}C NMR (75MHz, $CDCl_3$) δ 142.4,

133.8, 129.8, 128.7, 128.5, 118.7, 112.9, 29.6, 13.0; HRMS (TOF MS ES$^+$) calcd for $C_{11}H_{11}NNa$ 180.0789 $[M + Na]^+$, found 180.0818.

***E*-Isomer (minor): R_f 0.83 (toluene)**

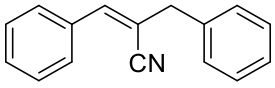


^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 – 7.20 (m, 6H), 2.54 – 2.47 (m, 2H), 1.26 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6, 134.1, 129.2, 129.1, 128.7, 120.2, 117.2, 22.9, 12.8; HRMS (TOF MS ES+) calcd for $C_{11}H_{11}NNa$ 180.0789 $[M + Na]^+$, found 180.0787.

2-Benzyl-3-phenylacrylonitrile (10c):

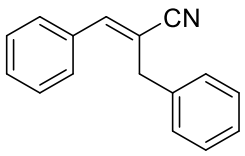
Column chromatography (Hex/EtOAc = 99/1) yielded **10c** (185 mg, 84%, Z/E = 86:14).

***Z*-Isomer (major): R_f 0.92 (toluene)**



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 – 7.73 (m, 2H), 7.42 – 7.29 (m, 8H), 6.98 (s, 1H), 3.72 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.0, 136.4, 133.5, 130.1, 128.89, 128.87, 128.8, 128.7, 127.3, 118.7, 110.8, 42.2. This product spectroscopically matched that of the known compound.[87]

***E*-Isomer (minor): R_f 0.86 (toluene)**

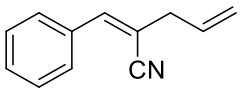


^{1}H NMR (500 MHz, $CDCl_3$**)** δ 7.41 – 7.24 (m, 11H), 3.82 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.2, 136.4, 133.7, 129.5, 129.0, 128.9, 128.8, 128.3, 127.2, 120.2, 114.1, 35.5; HRMS (TOF MS ES$^+$) calcd for $C_{16}H_{13}NNa$ 242.0946 $[M + Na]^+$, found 242.0941.

2-Benzylidenepent-4-enenitrile (10d):

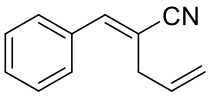
Column chromatography (Hex/EtOAc = 99/1) yielded **10d** (140 mg, 83%, Z/E = 70:30).

***Z*-Isomer (major): R_f 0.88 (toluene)**



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (apparent d, J = 7.0 Hz, 2H), 7.42 – 7.40 (m, 3H), 6.96 (s, 1H), 5.93 – 5.87 (m, 1H), 5.29 – 5.25 (m, 2H), 3.14 (d, J = 6.5 Hz, 2H); ^{13}CNMR (125 MHz, $CDCl_3$) δ 143.9, 133.6, 132.8, 130.1, 128.8, 128.6, 118.8, 118.6, 109.5, 40.0. This product spectroscopically matched that of the known compound.[88]

***E*-Isomer (minor): R_f 0.84 (toluene)**

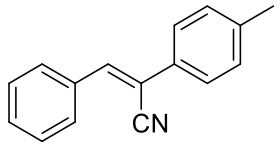


^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.30 (m, 6H), 5.97 – 5.90 (m, 1H), 5.30 – 5.26 (m, 2H), 3.21 (d, J = 5.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.1, 133.7 132.4, 129.5, 129.0, 128.7, 120.2, 118.2, 113.0, 33.9; HRMS (TOF MS ES^{+}) calcd for $C_{12}H_{11}NNa$ 192.0789 $[M + Na]^{+}$, found 192.0786.

2-(4-Methylbenzyl)-3-phenylacrylonitrile (10e):

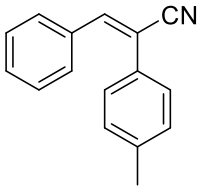
Column chromatography (Hex/EtOAc = 99/1) yielded **10e** (208 mg, 89%, Z/E = 88:12).

***Z*-Isomer (major): R_f 0.90 (toluene)**



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (apparent d, J = 6.0 Hz, 2H), 7.41 – 7.39 (m, 3H), 7.18 (s, 4H), 6.95 (s, 1H), 3.67 (s, 2H), 2.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.8, 137.0, 133.6, 133.3, 130.0, 129.6, 128.80, 128.77, 128.65, 118.7, 111.1, 41.8, 21.1. This product spectroscopically matched that of the known compound.[89]

***E*-Isomer (minor): R_f 0.85 (toluene)**



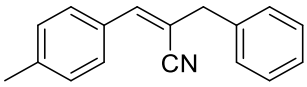
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.36 (m, 6H), 7.15 (s, 4H), 3.78 (s, 2H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.0, 136.9, 133.8, 133.3, 129.6, 129.5, 129.0, 128.8, 128.2, 120.3,

114.3, 35.1, 21.1; HRMS (TOF MS ES$^+$) calcd for $C_{17}H_{15}NNa$ 256.1102 $[M + Na]^+$, found 256.1097.

2-Benzyl-3-(p-tolyl)acrylonitrile (10f):

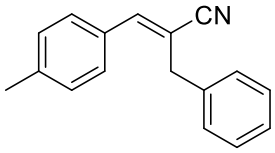
Column chromatography (Hex/EtOAc = 99/1) yielded **10f** (224 mg, 96%, Z/E = 88:12).

***Z*-Isomer (major): R_f 0.87 (toluene)**



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, J = 8.0 Hz, 2H), 7.40 – 7.28 (m, 5H), 7.20 (d, J = 8.0 Hz, 2H), 6.93 (s, 1H), 3.70 (s, 2H), 2.38 (s, 3H); ^{13}C NMR(125 MHz, $CDCl_3$) δ 144.0, 140.5, 136.6, 130.8, 129.5, 128.89, 128.85, 128.7, 127.3, 118.9, 109.4, 42.2, 21.4. This product spectroscopically matched that of the known compound.[90]

***E*-Isomer (minor): R_f 0.80 (toluene)**

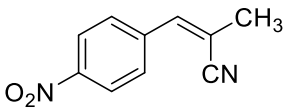


^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.19 (m, 10H), 3.83 (s, 2H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.3, 139.9, 136.5, 130.9, 129.5, 129.0, 128.9, 128.3, 127.2, 120.5, 112.9, 35.5, 21.4; HRMS (TOF MS ES$^+$) calcd for $C_{17}H_{15}NNa$ 256.1102 $[M + Na]^+$, found 256.1096.

2-Methyl-3-(4-nitrophenyl)acrylonitrile (10g)

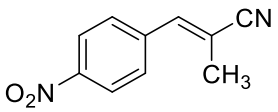
Column chromatography (Hex/EtOAc = 99/1) yielded **10g** (151 mg, 80%, *Z/E* = 81:19).

***Z*-Isomer (major): R_f 0.79 (toluene)**



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (d, J = 8.7 Hz, 2H), 7.84 (d, J = 8.7 Hz, 2H), 7.01 (apparent s, 1H), 2.23 (d, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.1, 141.3, 139.7, 129.2, 124.0, 118.1, 111.1, 22.3. This product spectroscopically matched that of the known compound.[85]

***E*-Isomer (minor): R_f 0.75 (toluene)**

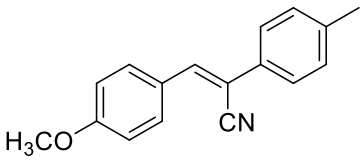


^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (d, J = 8.7 Hz, 2H), 7.49 (d, J = 8.7 Hz, 2H), 7.26 (apparent s, 1H), 2.17 (d, J = 1.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.7, 141.8, 140.0, 130.0, 123.9, 120.1, 113.7, 17.0; HRMS (TOF MS ES$^+$) calcd for $C_{10}H_8N_2O_2Na$ 211.0483 $[M + Na]^+$, found 211.0476.

3-(4-Methoxyphenyl)-2-(4-methylbenzyl)acrylonitrile (10h):

Column chromatography (toluene) yielded **10h** (190 mg, 72%, Z-isomer only).

***Z*-Isomer (major): R_f 0.86 (toluene**)

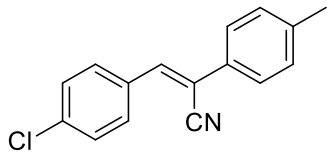


^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.18 (s, 4H), 6.92 (d, J = 8.7 Hz, 2H), 6.89 (s, 1H), 3.84 (s, 3H), 3.64 (s, 2H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.9, 143.3, 136.8, 133.7, 130.4, 129.5, 128.7, 126.3, 119.3, 114.1, 107.9, 55.3, 41.7, 21.1. This product spectroscopically matched that of the known compound.[89]

3-(4-Chlorophenyl)-2-(4-methylbenzyl)acrylonitrile (10i):

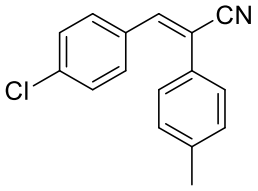
Column chromatography (Hex/EtOAc = 99/1) yielded **10i** (240 mg, 90%, Z/E = 86:14).

***Z*-Isomer (major): R_f 0.94 (toluene)**



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, J = 8.5 Hz, 2H), 7.36 (d, J = 8.5 Hz, 2H), 7.18 (s, 4H), 6.89 (s, 1H), 3.67 (s, 2H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.2, 137.0, 135.8, 133.0, 132.0, 129.9, 129.6, 129.0, 128.8, 118.4, 111.7, 41.7, 21.0. This product spectroscopically matched that of the known compound.[89]

***E*-Isomer (minor): R_f 0.89 (toluene)**

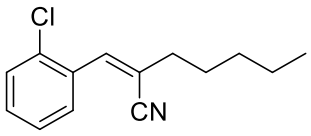


^{1}HNMR (300 MHz, $CDCl_3$) δ 7.39 – 7.10 (m, 9H), 3.75 (s, 2H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6, 137.0, 135.6, 132.9, 132.1, 130.3, 129.7, 129.1, 128.1, 120.1, 114.9, 35.1, 21.1; HRMS (TOF MS ES+) calcd for $C_{17}H_{14}ClNNa$ 290.0713 $[M + Na]^+$, found 290.0713.

2-(2-Chlorobenzylidene)hexanenitrile (10j):

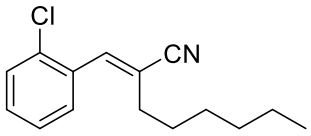
Column chromatography (Hex/EtOAc = 99/1) yielded **10j** (168 mg, 72%, Z/E = 85:15).

***Z*-Isomer (major): R_f 0.93 (toluene)**



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 – 7.90 (m, 1H), 7.44 – 7.26 (m, 4H), 2.45 (t, J = 7.2 Hz, 2H), 1.71 – 1.65 (m, 2H), 1.41 – 1.35 (m, 4H), 0.93 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.9, 133.8, 132.3, 130.7, 129.6, 129.2, 127.1, 118.2, 115.1, 35.9, 30.8, 27.7, 22.3, 14.0. This product spectroscopically matched that of the known compound.[91]

***E*-Isomer (minor): R_f 0.91 (toluene)**

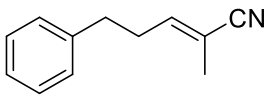


^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 – 7.21 (m, 5H), 2.35 – 2.30 (m, 2H), 1.65 – 1.60 (m, 2H), 1.29 – 1.26 (m, 4H), 0.87 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.2, 133.9, 132.5, 130.3, 130.0, 129.9, 126.6, 119.7, 118.1, 30.9, 29.3, 27.6, 22.2, 13.9; HRMS (TOF MS ES+) calcd for $C_{14}H_{16}ClNNa$ 256.0869 $[M + Na]^+$, found 256.0864.

2-Methyl-5-phenylpent-2-enenitrile (10k):

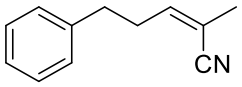
Column chromatography (Hex/EtOAc = 20/1) yielded **10k** (149 mg, 87%, Z/E = 11:89).

***E*-Isomer (major): R_f 0.81 (toluene)**



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 – 7.12 (m, 5H), 6.32 (dt, J = 7.5, 0.8 Hz, 1H), 2.71 (t, J = 7.5 Hz, 2H), 2.45 (dt, J = 7.5, 7.5 Hz, 2H), 1.72 (d, 0.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.9, 140.1, 128.4, 128.2, 126.2, 120.4, 109.8, 34.0, 30.1, 14.6; HRMS (TOF MS ES+) calcd for $C_{12}H_{13}NNa$ 194.0946 $[M + Na]^+$, found 194.0940.

***Z*-Isomer (minor): R_f 0.85 (toluene)**

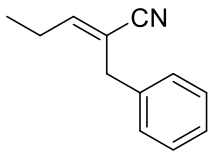


^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 – 7.17 (m, 5H), 6.14 (t, J = 7.1 Hz, 1H), 2.75 – 2.65 (m, 4H), 1.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.0, 140.2, 128.5, 128.3, 126.2, 117.9, 109.8, 34.7, 33.0, 20.0; HRMS (TOF MS ES^+) calcd for $C_{12}H_{13}NNa$ 194.0946 $[M + Na]^+$, found 194.0941.

2-Benzylpent-2-enenitrile (10l):

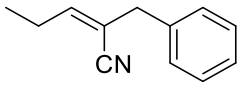
Column chromatography (Hex/EtOAc = 98/2) yielded **10l** (169 mg, 99%, Z/E = 16:84).

***E*-Isomer (major): R_f 0.82 (toluene)**



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.22 (m, 5H), 6.46 (t, J = 7.5 Hz, 1H), 3.56 (s, 2H), 2.33 (dq, J = 7.5, 7.5 Hz, 2H), 1.09 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.1, 136.7, 128.8, 128.3, 127.0, 119.9, 113.4, 34.6, 22.1, 12.9; HRMS (TOF MS ES+) calcd for $C_{12}H_{13}NNa$ 194.0946 $[M + Na]^+$, found 194.0940.

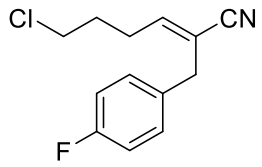
***Z*-Isomer (minor): R_f 0.86 (toluene)**



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 – 7.19 (m, 5H), 6.18 (t, J = 7.5 Hz, 1H), 3.50 (s, 2H), 2.39 (dq, J = 7.5, 7.5 Hz, 2H), 1.06 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.0, 136.6, 128.77, 128.73, 127.1, 117.4, 113.6, 40.2, 25.0, 13.1; HRMS (TOF MS ES^+) calcd for $C_{12}H_{13}NNa$ 194.0946 $[M + Na]^+$, found 194.0941.

6-Chloro-2-(4-fluorobenzyl)hex-2-enenitrile (10m)

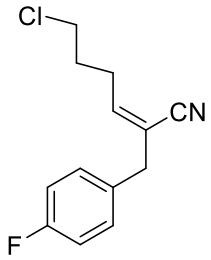
Column chromatography (Hex/EtOAc = 20/1) yielded **10m** (181 mg, 76%, Z/E =12:88).



***E*-Isomer (major): R_f 0.83 (toluene)**

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 – 7.17 (m, 2H), 7.06 – 6.99 (m, 2H), 6.41 (t, J = 7.5 Hz, 1H), 3.59 – 3.55 (m, 4H), 2.50 (apparent q, J = 7.5 Hz, 2H), 1.99 – 1.89 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.0 (d, $^1J_{CF}$ = 244.2 Hz), 146.5, 132.1 (d, $^4J_{CF}$ = 3.3 Hz), 130.0 (d, $^3J_{CF}$ = 8.0 Hz), 119.4, 115.8 (d, $^2J_{CF}$ = 21.5 Hz), 115.4, 43.8, 33.9, 30.8, 25.7; HRMS (TOF MS ES$^+$) calcd for $C_{14}H_{12}ClFNNa$ 260.0618 $[M + Na]^+$, found 260.0609.

***Z*-Isomer (minor): R_f 0.88 (toluene)**

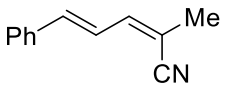


^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 – 7.14 (m, 2H), 7.06 – 7.00 (m, 2H), 6.18 (t, J = 7.5 Hz, 1H), 3.54 (t, 6.5, 2H), 3.50 (s, 2H), 2.55 (apparent q, 7.5 Hz, 2H) 1.93 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.0 (d, $^1J_{CF}$ = 244.4 Hz), 146.4, 131.9 (d, $^4J_{CF}$ = 3.0 Hz), 130.2 (d, $^3J_{CF}$ = 8.0 Hz), 117.0, 115.7 (d, $^2J_{CF}$ = 21.3 Hz), 115.6, 43.8, 39.6, 31.3, 28.9; HRMS (TOF MS ES$^+$) calcd for $C_{14}H_{12}ClFNNa$ 260.0618 $[M + Na]^+$, found 260.0632.

2-Methyl-5-phenylpenta-2,4-dienenitrile (10n)

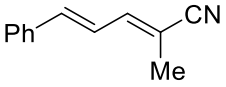
Column chromatography (Hex/EtOAc = 25/1) yielded **10n** (139 mg, 82%, Z/E = 69:31).

Z-Isomer (major): R_f 0.85 (toluene)



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (apparent d, J = 6.9 Hz, 2H), 7.40 – 7.30 (m, 3H), 7.14 (dd, J = 15.5, 11.3 Hz, 1H), 6.81 – 6.72 (m, 2H), 2.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.9, 138.6, 135.8, 129.1, 128.8, 127.2, 124.6, 118.5, 107.8, 20.2; HRMS (TOF MS ES$^+$) calcd for $C_{12}H_{11}NNa$ 192.0789 $[M + Na]^+$, found 192.0767.

***E*-Isomer (minor): R_f 0.79 (toluene)**

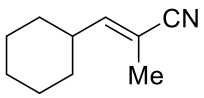


^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (apparent d, J = 6.6 Hz, 2H), 7.40 – 7.32 (m, 3H), 6.97 (dd, J = 14.7, 10.8 Hz, 1H), 6.91 – 6.79 (m, 2H), 2.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.7, 139.8, 135.8, 129.3, 128.9, 127.2, 121.9, 107.4, 15.3; HRMS (TOF MS ES$^+$) calcd for $C_{12}H_{11}NNa$ 192.0789 $[M + Na]^+$, found 192.0785.

3-Cyclohexyl-2-methylacrylonitirle (10o)

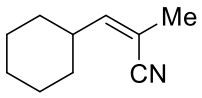
Column chromatography (Hex/EtOAc = 20/1) yielded **10o** (125 mg, 84%, Z/E = 24:76).

***E*-Isomer (major): R_f 0.77 (toluene)**



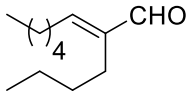
^{1}H NMR (300 MHz, CDCl3) δ 6.17 (qd, J = 1.5, 9.6 Hz, 1H), 2.38 – 2.24 (m, 1H), 1.86 (d, J = 1.5 Hz, 1H), 1.76 – 1.59 (m, 5H), 1.36_1.06 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.4, 120.9, 107.3, 37.6, 31.5, 25.6, 25.3, 14.8; HRMS (TOF MS ES+) calcd for $C_{10}H_{15}NNa$ 172.1102 $[M + Na]^+$, found 172.1096.

***Z*-Isomer (minor): R_f 0.85 (toluene)**



^{1}H NMR (300 MHz, $CDCl_3$) δ 5.96 (qd, J = 1.5, 9.9 Hz, 1H), 2.57 – 2.43 (m, 1H), 1.90 (d, J = 1.5 Hz, 3H), 1.76 – 1.62 (m, 5H), 1.41_1.02 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.7, 118.3, 106.8, 40.8, 32.1, 25.6, 25.2, 20.1; HRMS (TOF MS ES^+) calcd for $C_{10}H_{15}NNa$ 172.1102 $[M + Na]^+$, found 172.1094.

Synthesis of (*E*)-2-Butyl-2-octenal (16):

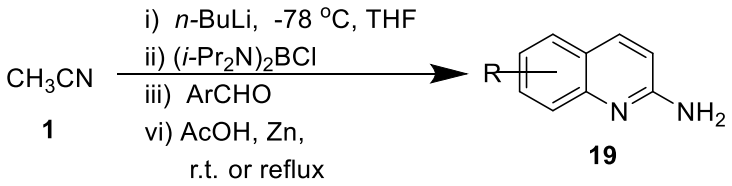


Into a flame-dried round bottomed flask was added dry THF (15 mL) under an argon atmosphere. After the mixture was cooled to 78 ^{o}C (acetone/dry ice bath), *n*-BuLi (2.0 mL, 2.5M solution in hexanes, 5.0 mmol) and dry CH_3CN (0.390 mL, 7.5 mmol) were added dropwise, respectively. After the mixture was stirred for 20 min, $(i\text{-}Pr_2N)_2BCl$ (0.684 mL, 2.5 mmol) was then slowly added. After another 1 hour of stirring, 1-iodobutane (0.285 mL, 2.5 mmol) was

added. The reaction mixture was stirred for an additional 1 hour at 0 ^{o}C and then concentrated under reduced pressure. Dry THF (15 mL) was subsequently added into the crude mixture under an argon atmosphere. After the mixture was cooled to 78 ^{o}C (acetone/dry ice bath), tetramethylethylenediamine (0.376 mL, 2.5 mmol) and *n*-BuLi (1.0 mL, 2.5 M solution in hexane, 2.5 mmol) were added dropwise. After the mixture was stirred for 1 hour, hexanal (0.246 mL, 2.0mmol) was slowly added, and the resulting mixture was stirred for 1.5 hour at the same temperature. The reaction mixture was then quenched with half-saturated NH_4Cl (12 mL) (78 ^{o}C to rt over 30 min). After the phase separation, the aqueous layer was extracted with Et_2O, and the combined organics were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The obtained crude product **14q** (E/Z = 86:14) was directly used for the next reaction. Into a solution of **14q** (236 mg, 1.31 mmol) in dry toluene (14 mL) under argon atmosphere was added DIBAL (3.29 mL, 1.0 M solution in hexane, 3.29 mmol) slowly at 78 ^{o}C. After being stirred for 1.5 hour at the same temperature, the reaction mixture was quenched with methanol (1.0 mL) and was then warmed to room temperature. The resulting mixture was diluted with CH_2Cl_2, filtered through a Celite pad, and concentrated under reduced pressure. The crude product was purified by SiO_2 column chromatography (toluene as eluent) to afford **16** (186 mg, 51% over two steps) as a colorless oil: ^{1}H NMR (300MHz, $CDCl_3$) δ 9.36 (s, 1H), 6.44 (t, J = 7.5 Hz, 1H), 2.34 – 2.20 (m, 4H), 1.52 – 1.29 (m, 10H), 0.94 – 0.87 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.4, 155.4, 143.8, 31.5, 30.9, 28.9, 28.4, 23.8, 22.8, 22.5, 14.0, 13.9. This product spectroscopically matched that of the known compound.[91]

Synthesis of 2-aminoquinolines 18 (19a–19g)

This procedure was conducted by Yusuke Takahashi, Toshihide Maejima.[33]

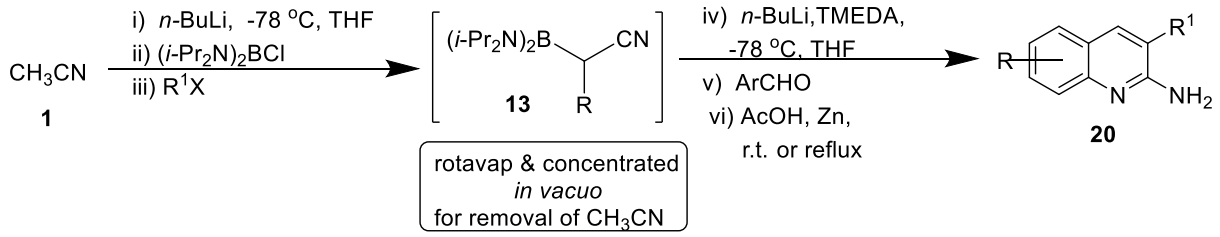


General procedure for Scheme 18:

Into a solution of *n*-BuLi (2.5 M in hexanes; 0.88 mL, 2.2 mmol) in THF (6 mL) at −78 °C was added acetonitrile (172 μL, 3.3 mmol) dropwise with stirring. After 20 min, (*i*-$Pr_2N)_2BCl$ (301 μL, 1.1 mmol) was added dropwise with stirring at −78 °C. After 1 h, an aldehyde (1.0 mmol) was added slowly with stirring at −78 °C and the mixture was stirred for another hour. The reaction was then quenched with acetic acid (1.0 mL, 17.5 mmol) and allowed to warm up to room temperature. The reaction mixture was treated with zinc powder (0.33 g, 5.0 mmol) and stirred overnight at room temperature (for entries 1 and 2) or refluxed overnight (for entries 3–6). The mixture was basified with excess ammonium hydroxide (~15 mL) to pH 9–10. After stirring for 30 min, the aqueous layer was extracted three times with EtOAc (5 mL each). The combined organic extracts were dried over $MgSO_4$, concentrated, and chromatographed ($CHCl_3$–MeOH eluent system) to give a 2-aminoquinoline derivative **19.**

Synthesis of 3-substituted-2-aminoquinolines 19 (20a–20i):

This procedure was conducted by Yusuke Takahashi, Toshihide Maejima.[29]

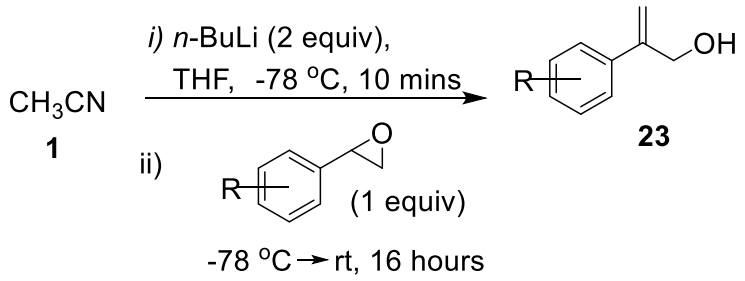


General procedure for Scheme 19:

Into a solution of *n*-BuLi (2.5 M in hexanes; 0.88 mL, 2.2 mmol) in THF (6 mL) at −78 °C was added acetonitrile (172 μL, 3.3 mmol) dropwise with stirring. After 20 min, $(i\text{-}Pr_2N)_2BCl$ (301 μL, 1.1 mmol) was added dropwise with stirring at −78 °C. After 1 hour, an alkylhalide (1.1 mmol) was added slowly with stirring at −78 °C and the mixture was stirred for another hour. After the reaction mixture was allowed to warm up to room temperature, THF and acetonitrile were removed by rotary evaporation. Another portion of THF (6.0 mL) was added to the reaction pot and the mixture was cooled to −78 °C. TMEDA (165 μL, 1.1 mmol) and *n*-BuLi in hexanes (2.5 M; 0.44 mL, 1.1 mmol) were then added dropwise with stirring in this order at −78 °C. After 1 h, an aldehyde (1 mmol) was added slowly at −78 °C and the mixture was stirred for another hour. The reaction was then quenched with acetic acid (1 mL, 17.5 mmol) and allowed to warm up to room temperature. The reaction mixture was treated with zinc powder (0.33 g, 5.0 mmol) and stirred overnight at room temperature. The mixture was basified with excess ammonium hydroxide (~15 mL) to pH 9–10. After stirring for 30 min, the aqueous layer was extracted three times with EtOAc (5 mL each). The combined organic extracts were dried ($MgSO_4$), concentrated, and chromatographed to give a 3-substituted-2-aminoquinoline **20**.

CHAPTER II

Synthesis of 2-arylallyl alcohols from aryl epoxides (Scheme 26):



All aryl epoxides except styrene oxide and 2-methyl-3-phenyloxirane were prepared in accordance with literature procedure.[95]

General experimental Procedure:

Into a flame-dried 10 mL round-bottomed flask was added dry THF (3.0 mL) under an argon atmosphere. After cooling to -78 ^{o}C (acetone/dry-ice bath), *n*-BuLi (1.64 mL, 2.5 M in hexane, 4.1 mmol) and dry CH_3CN (110 μL, 2.1 mmol) were slowly added respectively. After stirring for 15.20 min, aryl epoxide (2.0 mmol) was added. The reaction mixture was gradually warmed up to room temperature overnight and quenched with saturated $NaHCO_3$ (3 mL). After the phase separation, the aqueous layer was extracted with Et_2O (x2). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by SiO_2 column chromatography (Hex/EtOAc = 7/3).

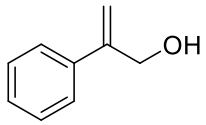
Caution: Due to the generation of cyanide ion during the course of the reaction, all operations, including work-up, should be carried out in a fume hood and the cyanide-containing waste should be properly handled and disposed.

A modified, concise method for synthesis of 2-arylallyl alcohols from aryl epoxides (Scheme 28)

Into a flame-dried 10 mL round-bottomed flask were added aryl epoxide (2.0 mmol), dry CH_3CN (110 μL, 2.1 mmol), and dry THF (3.0 mL) under an argon atmosphere. After cooling to -78 ^{o}C (acetone/dry-ice bath), *n*-BuLi (1.64 mL, 2.5 M in hexane, 4.1 mmol) was added dropwise. The reaction mixture was then gradually warmed up to room temperature overnight and quenched with saturated $NaHCO_3$ (3 mL). After the phase separation, the aqueous layer was extracted with Et_2O (x2). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by SiO_2 column chromatography

Caution: Due to the generation of cyanide ion during the course of the reaction, all operations, including work-up, should be carried out in a fume hood and the cyanide-containing waste should be properly handled and disposed.

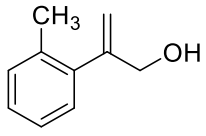
2-Phenylprop-2-en-1-ol (23a):



Column chromatography yielded **23a** as a colorless liquid (215 mg, 80%). R_f 0.30 (Hex/EtOAc = 7/3).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 – 7.44 (m, 2H), 7.39 – 7.29 (m, 3H), 5.48 (s, 1H), 5.36 (d, J = 1.2 Hz, 1H), 4.56 (d, J = 6.0 Hz, 2H), 1.55 (t, J = 6.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.2. 138.5, 128.5, 127.9, 126.0, 112.5, 64.9; HRMS (TOF MS ES$^+$) calcd for $C_9H_{11}O$ 135.0810 $[M + H]^+$, found 135.0781. This product spectroscopically matched that of the known compound.[93]

2-(o-Tolyl)prop-2-en-1-ol (23b):

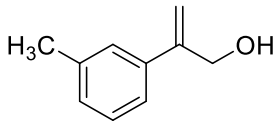


Column chromatography yielded 2b as a colorless liquid (240 mg, 81%). R_f 0.37 (Hex/EtOAc = 7/3).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 – 7.10 (m, 4H), 5.49 (d, J = 1.5 Hz, 1H), 5.06 (d, J = 1.2 Hz,

1H), 4.31 (d, J = 6.3 Hz, 2H), 2.32 (s, 3H), 1.75 (t, J = 6.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.0, 139.6, 135.4, 130.2, 128.7, 127.5, 125.6, 113.2, 66.1, 19.7; HRMS (TOF MS ES$^+$) calcd for $C_{10}H_{13}O$ 149.0966 $[M + H]^+$, found 149.0957.

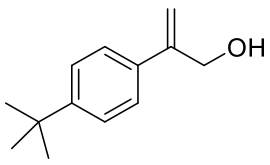
2-(m-Tolyl)prop-2-en-1-ol (23c):



Column chromatography yielded **23c** as a colorless liquid (213 mg, 72%). R_f 0.32 (Hex/EtOAc = 7/3).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 – 7.23 (m, 3H), 7.15 – 7.11 (m, 1H), 5.45 (s, 1H), 5.33 (d, J = 1.0 Hz, 1H), 4.54 (d, J = 5.5 Hz, 2H), 2.37 (s, 3H), 1.64 (t, J = 5.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.4, 138.5, 138.1, 128.7, 128.4, 126.8, 123.2, 112.4, 65.1, 21.5; HRMS (TOF MS ES+) calcd for $C_{10}H_{13}O$ 149.0966 $[M + H]^+$, found 149.0940.

2-(4-(tert-Butyl)phenyl)prop-2-en-1-ol (23d):

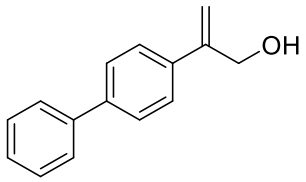


Column chromatography yielded **23d** as a colorless liquid (194 mg, 51%). R_f 0.36 (Hex/EtOAc = 7/3).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.36 (m, 4H), 5.46 (s, 1H), 5.31 (d, J = 1.2 Hz, 1H), 4.55 (d, J = 6.0 Hz, 2H), 1.54 (t, J = 6.0 Hz, 1H), 1.33 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.0,

147.0, 135.5, 125.7, 125.4, 111.9, 65.1, 34.5, 31.3. This product spectroscopically matched that of the known compound.[94]

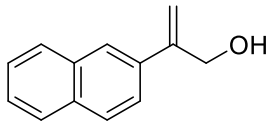
2-([1,1'-Biphenyl]-4-yl)prop-2-en-1-ol (23e):



Column chromatography yielded **23e** as a yellow solid (269 mg, 64%). R_f 0.24 (Hex/EtOAc = 7/3).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 – 7.30 (m, 9H), 5.54 (s, 1H), 5.39 (d, J = 1.0 Hz, 1H), 4.60 (d, J = 6.5 Hz, 2H), 1.56 (t, J = 6.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.8, 140.8, 140.6, 137.3, 128.8, 127.4, 127.2, 127.0, 126.5, 112.7, 65.1. The spectral data matched those reported previously.[95]

2-(Naphthalen-2-yl)prop-2-en-1-ol (23f):

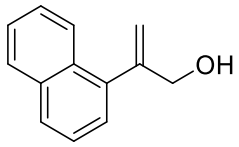


Column chromatography yielded **23f** as a white solid (261 mg, 71%). R_f 0.28 (Hex/EtOAc = 7/3).

^{1}H NMR (300MHz, $CDCl_3$) δ 7.90 – 7.80 (m, 4H), 7.64 – 7.60 (m, 1H), 7.51 – 7.45 (m, 2H), 5.63 (s, 1H), 5.47 (d, J = 0.9 Hz, 1H), 4.68 (d, J = 5.1 Hz, 2H), 1.55 (t, J = 5.7 Hz, 1H); ^{13}C NMR

(75 MHz, $CDCl_3$) δ 147.1, 135.7, 133.4, 133.0, 128.2, 128.1, 127.6, 126.3, 126.1, 124.8, 124.3, 113.2, 65.2. The spectral data matched those reported previously.[96]

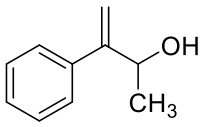
2-(Naphthalen-1-yl)prop-2-en-1-ol (23g):



Column chromatography yielded **23g** as a colorless liquid (284 mg, 77%). R_f 0.30 (Hex/EtOAc = 7/3).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05 – 8.01 (m, 1H), 7.89 – 7.79 (m, 2H), 7.52 – 7.31 (m, 4H), 5.71 (d, J = 1.5 Hz, 1H), 5.27 (d, J = 1.5 Hz, 1H), 4.48 (d, J = 6.0 Hz, 2H), 1.67 (t, J = 6.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.8, 137.9, 133.7, 131.5, 128.3, 127.8, 126.1, 125.8, 125.7, 125.4, 125.2, 114.8, 66.7. The spectral data matched those reported previously.[97]

3-Phenylbut-3-en-2-ol (23h):

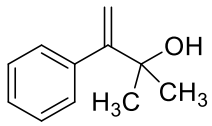


Column chromatography yielded **23h** as a colorless liquid (193 mg, 65%). R_f 0.36 (Hex/EtOAc = 7/3).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.30 (m, 5 H), 5.37 (s, 1 H), 5.28 (s, 1H), 4.85 – 4.78 (m, 1H), 1.68 (d, J = 3.5 Hz, 1H), 1.33 (d, J = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.1, 139.9, 128.4, 127.6, 126.8, 111.6, 69.5, 22.6. The spectral data matched those reported

previously.[98]

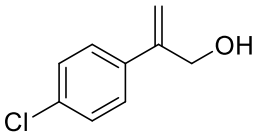
2-Methyl-3-phenylbut-3-en-2-ol (23i):



Column chromatography yielded **23i** as a white solid (211 mg, 65%). R_f 0.42 (Hex/EtOAc = 7/3).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 5H), 5.43 (d, J = 1.2 Hz, 1H), 4.97 (d, J = 0.9 Hz, 1H), 1.56 (s, 1H), 1.42 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1, 141.5, 128.8, 127.8, 127.0, 112.5, 73.0, 29.7; HRMS (TOF MS ES$^-$) calcd for $C_{11}H_{13}O$ 161.0966 $[M - H]^-$, found 161.0945.

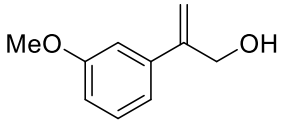
2-(4-Chlorophenyl)prop-2-en-1-ol (23j):



Column chromatography yielded **23j** as a light yellow liquid (148 mg, 44%). R_f 0.25 (Hex/EtOAc = 7/3).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.30 (m, 4H), 5.47 (d, J = 0.9, 1H), 5.37 (d, J = 0.9, 1H), 4.52 (d, J = 4.8 Hz, 2H), 1.55 (t, J = 5.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.2, 136.9, 133.8, 128.7, 127.4, 113.3, 65.0. The spectral data matched those reported previously.[99]

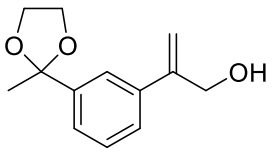
2-(3-Methoxyphenyl)prop-2-en-1-ol (23k):



Column chromatography yielded **23k** as a colorless liquid (197 mg, 60%). R_f 0.24 (Hex/EtOAc = 7/3).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 – 7.25 (m, 1H), 7.06 – 6.98 (m, 2H), 6.88 – 6.84 (m, 1H), 5.47 (d, J = 0.9 Hz, 1H), 5.36 (d, J = 1.2 Hz, 1H), 4.53 (d, J = 6.0 Hz, 2H), 3.83 (s, 3H), 1.60 (t, J = 6.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7, 147.2, 140.0, 129.5, 118.6, 113.2, 112.8, 112.1, 65.1, 55.2; HRMS (TOF MS ES$^-$) calcd for $C_{10}H_{11}O_2$ 163.0759 $[M - H]^-$, found 163.0788.

2-(3-(2-Methyl-1,3-dioxolan-2-yl)phenyl)prop-2-en-1-ol (23l):

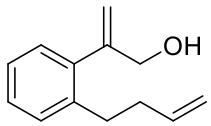


Column chromatography yielded **23l** as a colorless liquid (287 mg, 65%). R_f 0.17 (Hex/EtOAc = 7/3).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (s, 1H), 7.45 – 7.31 (m, 3H), 5.50 (s, 1H), 5.37 (s, 1H), 4.56 (d, J = 6.0 Hz, 2H), 4.05 (t, J = 7.0 Hz, 2H), 3.79 (t, J = 7.0 Hz, 2H), 1.67 (s, 3H), 1.55 (t, J = 6.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.3, 143.7, 138.5, 128.4, 125.6, 124.9, 122.9, 112.8, 108.8, 65.0, 64.5, 27.7; HRMS (TOF MS ES$^+$) calcd for $C_{13}H_{17}O_3$ 221.1178 [M +

H]$^+$, found 221.1151.

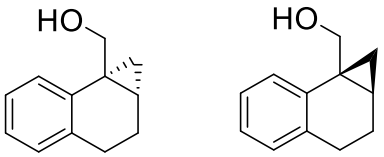
2-(2-(But-3-en-1-yl)phenyl)prop-2-en-1-ol (23m):



Column chromatography yielded **23m** as a light orange liquid (149 mg, 40%). R_f 0.31 (Hex/EtOAc = 9/1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 – 7.09 (m, 4H), 5.86 (ddt, J = 16.8, 10.2, 6.6 Hz, 1H), 5.49 (d, J = 0.9 Hz, 1H), 5.10 – 4.95 (m, 3H), 4.31 (s, 2H), 2.72 (t, 7.8 Hz, 2H), 2.34 (apparent q, J = 7.5 Hz, 2H), 1.72 (bs,1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.7, 139.4, 139.3, 138.1, 129.2, 129.0, 127.6, 125.7, 114.8, 113.2, 66.6, 35.7, 32.3; HRMS (TOF MS ES$^+$) calcd for C13H17O 189.1279 [M + H]$^+$, found 189.1260.

Cyclopropane (28):

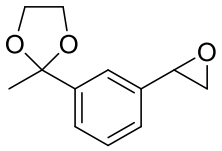


The initial column chromatography (Hex/EtOAc = 9/1) separated **23m** and **28**, but **28** was still impure. The second column chromatography (CHCl3/EtOAc = 3/1) yielded pure **28** as a white solid (94 mg, 27%). R_f 0.21 (Hex/EtOAc = 9/1), R_f 0.64 ($CHCl_3$/EtOAc = 3/1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, J = 7.8 Hz, 1H), 7.22 – 7.14 (m, 1H), 7.11 – 7.00 (m, 2H), 4.07 (d, J = 11.7 Hz, 1H), 3.57 (d, J = 11.7 Hz, 1H), 2.63 (ddd, J = 15.9, 5.1, 2.4 Hz, 1H),

2.47 (ddd, J = 15.9, 12.6, 6.0 Hz, 1H), 2.15.1.98 (m, 2H), 1.86.1.72 (m, 1H), 1.52.1.43 (m, 1H), 0.95 (apparent t, J = 5.1 Hz, 1H), 0.79 (dd, J = 8.4, 5.1 Hz, 1H); $_{13}$C NMR (75 MHz, $CDCl_3$) δ 138.2, 135.0, 128.8, 126.3, 126.0, 125.0, 69.0, 26.4, 24.3, 21.5, 19.7, 13.1; HRMS (TOF MS ES^+) calcd for C12H15O 175.1123 $[M + H]^+$, found 175.1114.

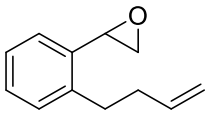
2-methyl-2-(3-(oxiran-2-yl)phenyl)-1,3-dioxolane 21l (entry 11 in Table 9):



The epoxide **21l** was prepared from 3-(2-methyl-1,3-dioxolan- 2-yl)benzaldehyde and was obtained as a colorless liquid. R_f 0.21 (Hex/EtOAc = 99:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.41 (m, 2H), 7.36 – 7.29 (m, 1H), 7.22 – 7.18 (m, 1H), 4.08 – 4.00 (m, 2H), 3.89 – 3.85 (m, 1H), 3.81 – 3.74 (m, 2H), 3.15 (dd, J = 5.4, 4.2 Hz, 1H), 2.83 (dd, J = 5.4, 2.7 Hz, 1H), 1.65 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.9, 137.7, 128.5, 125.2, 124.9, 122.7, 108.7, 64.5, 64.4, 52.4, 51.1, 27.6; HRMS (TOF MS ES^+) calcd for $C_{12}H_{15}O_3$ 207.1021 $[M + H]^+$, found 207.0993.

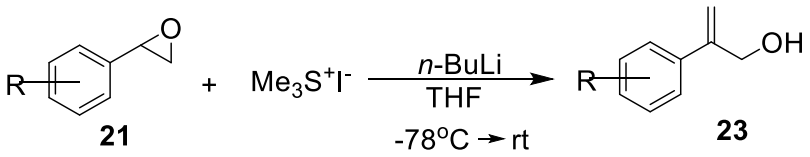
2-(2-(but-3-en-1-yl)phenyl)oxirane (21m):



The epoxide **21m** was prepared from 2-(but-3-en-1-yl)benzaldehyde and was obtained as a colorless liquid. R_f 0.64 (toluene).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 – 7.19 (m, 4H), 5.92 (ddt, J = 17.1, 10.2, 6.6 Hz, 1H), 5.14 – 5.02 (m, 2H), 4.07 (dd, J = 3.9, 2.7 Hz, 1H), 3.17 (dd, J = 5.7, 4.2 Hz, 1H), 2.92 – 2.85 (m, 2H), 2.72 (dd, J = 5.7, 2.7 Hz, 1H), 2.48 – 2.38 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.0, 137.6, 135.4, 128.9, 127.6, 126.3, 124.1, 115.1, 50.3, 50.0, 35.0, 32.0; HRMS (TOF MS ES^+) calcd for $C_{12}H_{15}O$ 175.1123 $[M + H]^+$, found 175.1096.

Methylenation of styrene oxide by methylide reagent (Scheme 41):

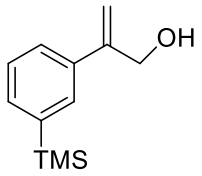


General Procedure:

Into a flame dried 10.0 mL round-bottomed flask was added trimethylsulfonium iodide (4.1 m.mol, 836 mg), which was then dried under *vacuuo* for 10 min and purged with argon (x3 times). Dry THF was added (3.0 mL) followed by the addition of the respective aryloxirane (2.0 m.mol) to the flask under an argon atmosphere. After the mixture was cooled to -78 ^{o}C (acetone/dry ice bath), *n*-BuLi (2.48 mL, 2.5 M in hexane, 6.2 m.mol) was added dropwise. After that the Dewar cooling bath was filled with dry ice and acetone and the reaction mixture was left for stirring overnight, whereupon the reaction temperature was slowly increased to room temperature. The reaction mixture was then quenched with saturated $NaHCO_3$ (3.0 mL) at room temperature. After phase separation, the aqueous layer was extracted with Et_2O (X2). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was then purified by SiO_2 column chromatography (Hex/EtOAc = 7:3) to afford the corresponding aryl substituted allyl alcohol.

Note: The aryloxirane can be added to the flask either before or after *n*-BuLi. If *n*-BuLi is added to the flask after the addition of aryloxirane, it should be added very slowly (dropwise) since the manner of addition affects the regioselectivity as well as %yield of the reaction.

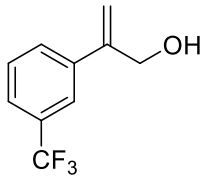
2-(3-(Trimethylsilyl)phenyl)prop-2-en-1-ol (23n):



The alcohol was synthesized from trimethyl(3-(oxiran-2-yl)phenyl)silane and was obtained as a light yellowish liquid (0.218g, 53%). R_f 0.46 (Hex/EtOAc = 7:3).

^{1}H NMR (300MHz, $CDCl_3$) δ 7.61 – 7.59 (m, 1H), 7.50 – 7.28 (m, 3H), 5.47 (d, *J* = 0.9 Hz, 1H), 5.38 (d, *J* = 1.2 Hz, 1H), 4.58 (d, *J* = 5.7 Hz, 2H), 1.55 (t, *J* = 6.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.8, 140.8, 137.9, 132.9, 130.9, 127.8, 126.6, 112.5, 65.1, 0.0; HRMS (TOF MS ES^+) calcd for $C_{12}H_{18}OSi$ 206.1127 $[M]^+$, found 206.1109.

2-(3-(Trifluoromethyl)phenyl)prop-2-en-1-ol (23p):



The alcohol was synthesized from 2-(3-(trifluoromethyl)phenyl)oxirane and was obtained as a colorless liquid (0.150g, 37%). R_f 0.28 (Hex/EtOAc = 7:3).

^{1}H NMR (300MHz, $CDCl_3$) δ 7.71 – 7.69 (m, 1H), 7.65 – 7.45 (m, 3H), 5.54 (d, *J* = 0.9 Hz, 1H),

5.46 (d, *J* = 0.9 Hz, 1H), 4.57 (d, *J* = 5.4 Hz, 2H), 1.55 (t, *J* = 6.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.1, 139.4, 130.8 (q, *J* = 31.8 Hz), 129.4, 128.9, 124.5 (q, *J* = 3.7 Hz), 124.1 (q, *J* = 270.6 Hz), 122.8 (q, *J* = 3.8 Hz), 114.3, 64.7; HRMS (TOF MS ES$^+$) calcd for $C_{10}H_9F_3O$ 201.0527 $[M - H]^+$, found 201.0520.

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VITA

Rambabu Sankranti was born in Nalgonda, Telangana, India on May 10th, 198. After graduating from AVM College, Nakrekal, Nalgonda, Telangana, India in April 1996, he pursued his Bachelor's degree in Chemistry in Noble Degree College, Hyderabad, Telangana, India. After that, he succeeded with a 33rd rank among 17000 applicants to get an admission into Master of Science in Osmania University, Hyderabad, India. He successfully graduated with Master of Science in Organic Chemistry in 2006. Then he worked as a lecturer in Osmania University where he taught organic chemistry classes to both undergraduate and graduate students from June 2006 to December 2008. He then joined in Department of Chemistry and Biochemistry, Jackson State University in January 2009 for Ph.D. in Chemistry and worked as a teaching assistant for sophomore undergraduate students in the semester of spring 2009. Later, he moved to University of Mississippi and joined Dr. Takashi Tomioka's group in Department of Chemistry and Biochemistry with a research focus on synthetic organic chemistry. During his graduation, he published the research work in peer reviewed journals and presented the group's research in various national and regional conferences. He did a 6-month internship in GlaxoSmithKline pharmaceuticals, King of Prussia from July 2014 – February 2015 in Respiratory DPU where he was exposed to synthetic and analytical techniques in the real time drug discovery process. After graduation he will be working with Tergus pharma, Durham, NC, USA as a Research Scientist.

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EDUCATION

M.Sc., Organic Chemistry, Osmania University, May 2006

B.Sc., Chemistry, Osmania University, May 2001

TEACHING EXPERIENCE

Teaching Assistant, Fall 2009 – Fall 2013

University of Mississippi

Courses: CHEM 225 Elementary Organic Chemistry Laboratory I, CHEM 226

Elementary Organic Chemistry Laboratory II, CHEM 423 Organic Analysis

Teaching Assistant, Spring 2009

Jackson State University

Courses: CHM 241 Elementary Organic Chemistry Laboratory

Teaching Assistant, Fall 2006 – Fall 2008

Osmania University

Courses: Reaction Mechanism, Asymmetric Synthesis

HONORS and FELLOWSHIPS

ACS Graduate Research Award for the Year 2014-2015, 2015

Department of Chemistry, University Mississippi.

ACS Graduate Research Award for the Year 2013-2014, 2014

Department of Chemistry, University Mississippi.

Best Graduate Poster Award, 2011

National Center for Natural Products Research, University Mississippi.

PUBLICATIONS and PRESENTATIONS

Takashi Tomioka*, Rambabu Sankranti, Amber James, Daniell Mattern. "Regioselective ring-opening *α*-methylenation of aryl epoxides to conjugated allyl alcohols utilizing *n*-BuLi and $Me_2S{=}CH_2$ reagents". *Tetrahedron Letters*, **2014**, 55 (23), 3443.

Research Poster Presentation at 247th ACS National Conference, Dallas, TX. (March **2014**)

Poster Title: A Novel approach for the synthesis of 2,3-diaryl allyl alcohols from aryl epoxides: synthons for indene and quinoline derivatives.

Research Oral Presentation at 39th ACS North East Regional Meeting, New Haven, CT. (October **2013**)

Presentation Title: "*n*-BuLi/$Me_2S{=}CH_2$ -mediated novel transformation of aryl epoxides into conjugated allyl alcohols".

Takashi Tomioka*, Rambabu Sankranti, Tsuyoshi Yamada, and Courtney Clark. "*n*-BuLi/$LiCH_2CN$-Mediated One-Carbon Homologation of Aryl Epoxides into Conjugated Allyl Alcohols". *Organic Letters*, **2013**, 15 (19), 5099.

Highlighted in *Synfacts* **2013**, 9 (12), 1333.

Research Poster Presentation at National Center for Natural Products Research, University of Mississippi, University, MS. (November **2012**)

Poster Title: *n*-BuLi –$LiCH_2CN$ mediated regioselective transformation of aryl/vinyl epoxides into conjugated allyl alcohols.

Takashi Tomioka*, Rambabu Sankranti, Trey G. Vaughan, Toshihide Maejima, Takayoshi Yanase. "An α-Diaminoboryl Carbanion Assisted Stereoselective Single-Pot Preparation of α,β -Disubstituted Acrylonitriles". *Journal of Organic Chemistry*, **2011**, 76 (19), 8053.

Research Poster Presentation at National Center for Natural Products Research, University of Mississippi, University, MS. (October **2011**)

Poster Title: A Single-pot, α-Diaminoboryl Carbanion Mediated Stereoselective Preparation of α,β-Disubstituted Acrylonitriles.