

# Chapter 1

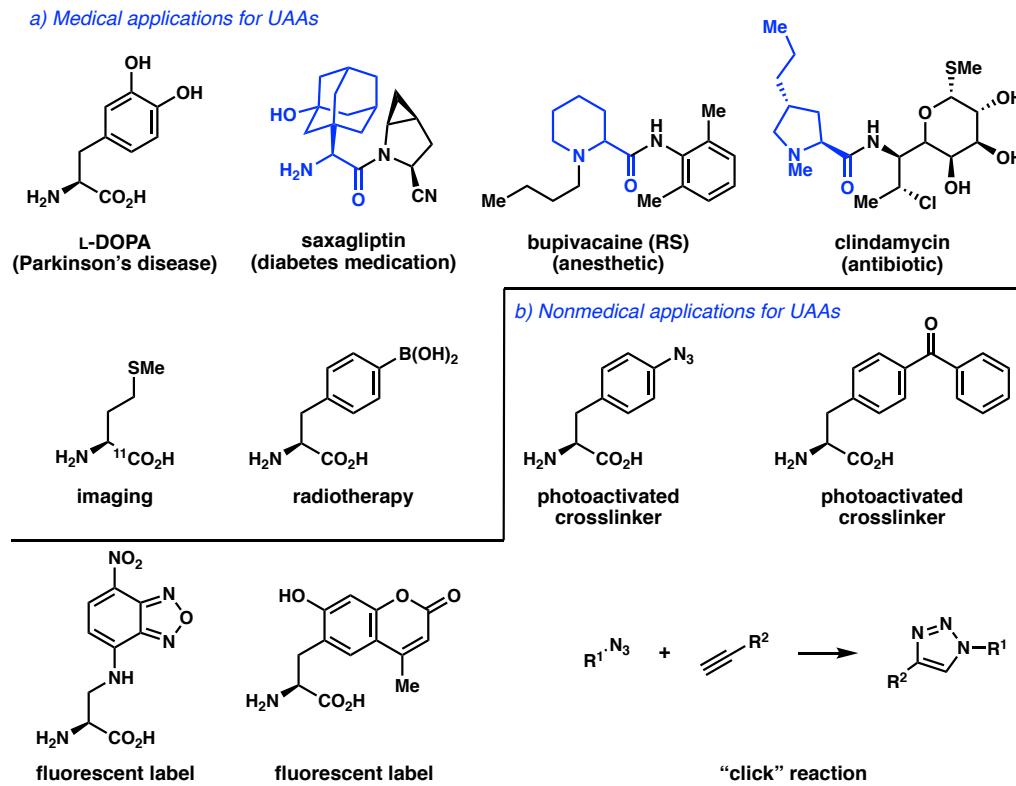
## *Nucleophilic Additions to Oximes, Ketones, and Aldehydes*

### 1.1 INTRODUCTION

Unnatural or unusual amino acids (UAs) are a commonly used tool in many fields, particularly medicinal chemistry, in which they embody potential drugs, building blocks for structure-activity relationship studies, and starting materials for syntheses of complex molecules.<sup>1</sup> These compounds comprise amino acids not included in the twenty most common amino acids found in proteins. They are not coded for in proteins and in most cases are lab-made for a variety of purposes. Medical uses include treatment for various conditions, anesthesia, imaging, and radiotherapy (Figure 1.1, a). Nonmedical uses for UAs include biochemical research, where they can be used as fluorescent labels, photoactivated crosslinkers, or in bioorthogonal reactions. Often in these cases the amino acid is incorporated into a protein where it can be reacted with a marker to allow for later monitoring.<sup>2,3</sup> In these cases, the copper(I)-catalyzed azide-alkyne [3+2] dipolar cycloaddition or click reaction is a useful tool.<sup>3</sup> A UAA bearing either an azide

or alkyne can be incorporated into the desired protein, and the corresponding compound introduced in a click reaction. This allows for monitoring of protein activity or investigation of a particular enzyme active site. The flexibility of incorporating either azide or alkyne as the UAA allows for less disruption of natural enzymatic function.

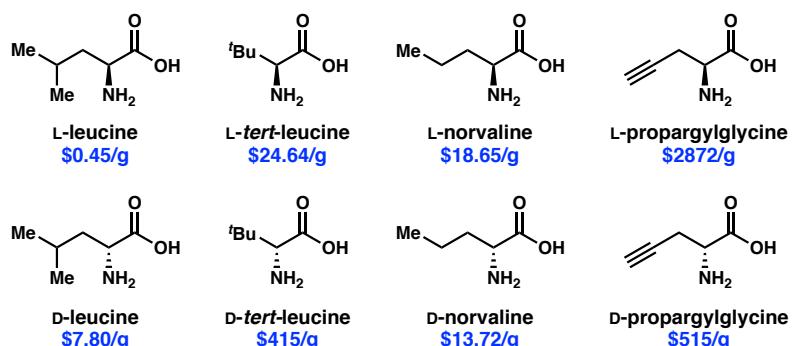
**Figure 1.1.** Uses of unnatural amino acids.<sup>1-4</sup>



However, UAAs are often very expensive or only available as racemates. D isomers are often even more expensive than L isomers due to the lack of existing starting materials that can be sourced from the chiral pool. This pattern is seen even in naturally occurring amino acids, such as leucine, as the L isomers are more common (Figure 1.2). In the case of racemic synthesis, separation is often difficult and time-consuming. For example, on a gram-for-gram basis, D-*tert*-leucine from Sigma-Aldrich is almost seventeen times the price of L-*tert*-leucine (Figure 1.2). Propargylated UAAs are also

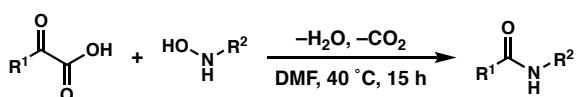
considerably more expensive than their alkyl counterparts. L- and D-propargylglycine are only available in 250 mg and 100 mg sizes, compared to the up to 10 g and 5 g sizes available for their saturated counterparts, L- and D-norvaline. When prices are normalized to per gram, L-propargylglycine costs \$2872 per gram, compared to \$18.65 per gram if L-norvaline is purchased in bulk or \$54 per gram if not. It would therefore be useful to have a way to readily and cheaply access unnatural amino acids

**Figure 1.2.** Price per gram comparison of select amino acids.



Bode *et al.* have shown that C-terminal  $\alpha$ -keto carboxylic acids can be condensed with hydroxylamines to give peptide bonds, allowing quick use of a hydroxylamine as an unnatural amino acid (Scheme 1.1).<sup>5</sup> Similarly, the hydroxylamine could readily be reduced to the free amine, providing the same result. It was therefore desired to design a new reaction framework by which an oxime ester could be nucleophilically substituted with a propargyl group to form a propargylated hydroxylamine, which could be useful as a UAA as well as handles for “click” chemistry.<sup>3</sup>

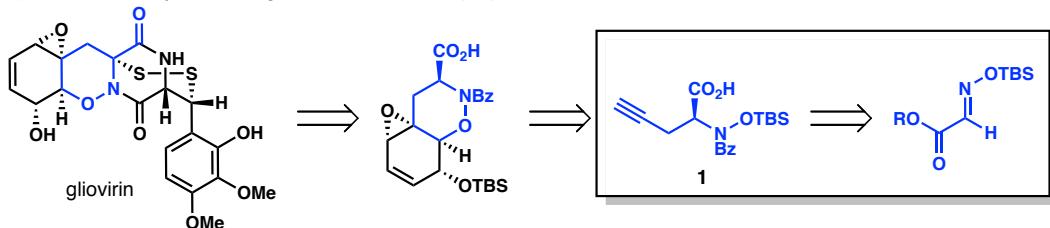
**Scheme 1.1.** Formation of peptide bonds via condensation of hydroxylamines with  $\alpha$ -ketoacids.



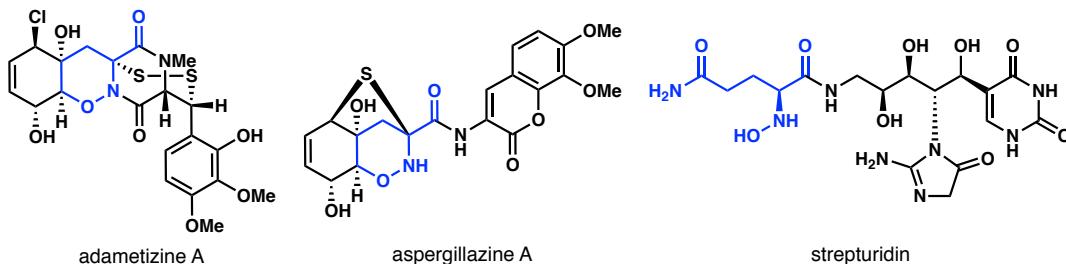
In addition to providing potential UAAs, the desired methodology could prove useful in synthesis. Our lab intended to use the product in the total synthesis of gliovirin, a natural product. A potential retrosynthesis can be seen in Figure 1.3, a. Other natural products that might be made from the desired product (**1**) include adametizine A, aspergillazine A, and strepturidin.

**Figure 1.3.** Examples of natural products which could be made using the proposed method.<sup>6,7</sup>

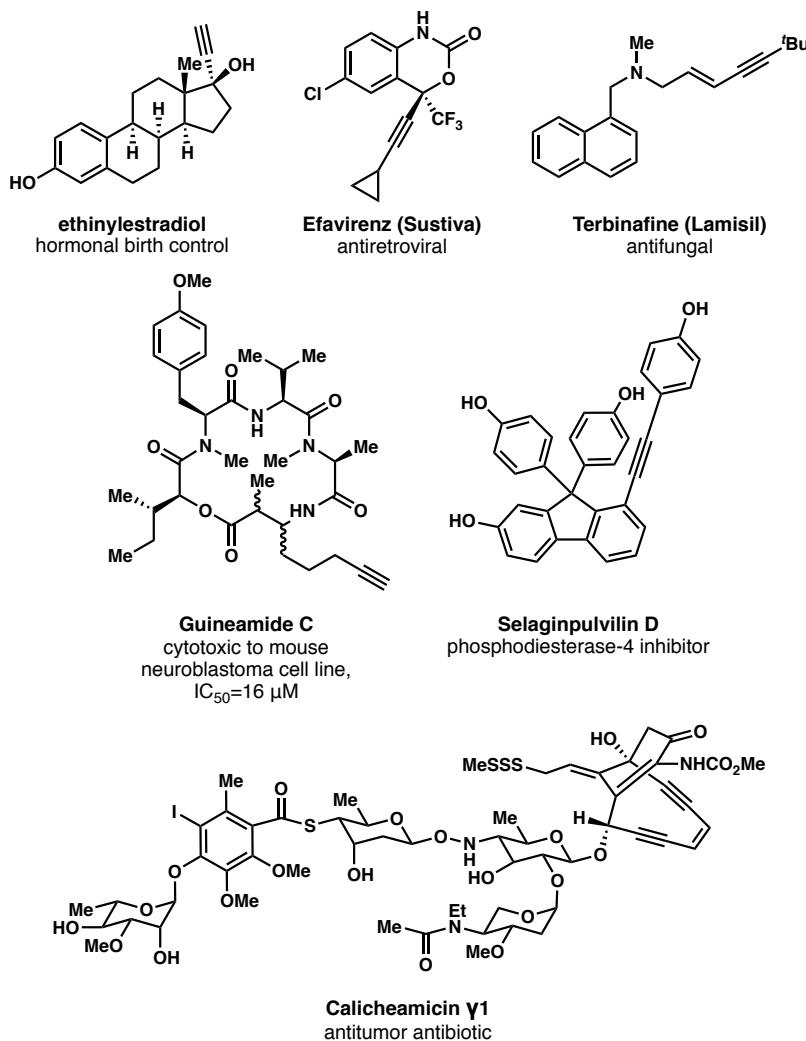
a) Potential retrosynthesis of gliovirin based on our proposed method.



b) Other molecules that could be made from 1.



Alkyne **1** is useful in chemical synthesis where it provides a convenient source of acetylenic groups, which can then be used as a functional handle to access a wide variety of structural motifs. Additionally, alkynes are a significant motif in natural products and pharmaceutical design (Figure 1.4).

**Figure 1.4.** Alkyne-containing drugs and natural products.<sup>8-10</sup>

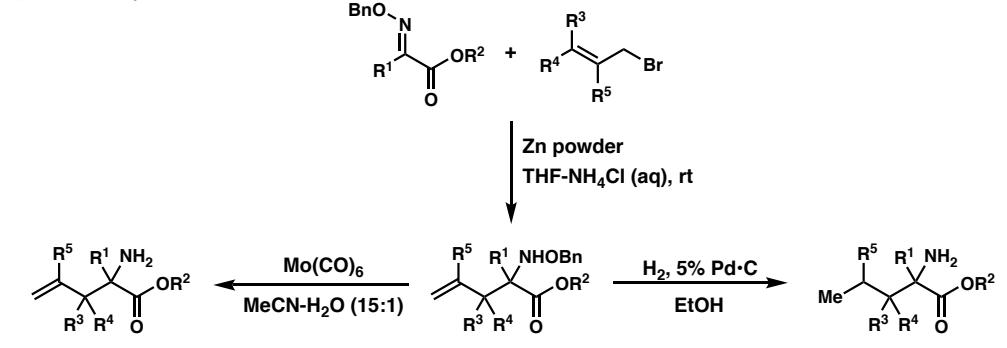
## 1.2 REACTIONS OF OXIMES

In 1996, Hanessian *et al.* designed the asymmetric allylation of oxime esters via a stoichiometric zinc nucleophile. Initially, they developed the racemic reaction using stoichiometric zinc powder, an allyl bromide, and a glyoxylic oxime ester to provide the corresponding allylated hydroxylamine, which could either be reduced to a homoallylic amine using  $Mo(CO)_6$  or fully reduced to the alkyl amine using  $H_2/Pd-C$  (Scheme 1.2, a).<sup>11</sup> They then showed that by using Oppolzer's camphorsultam chiral auxiliary, the

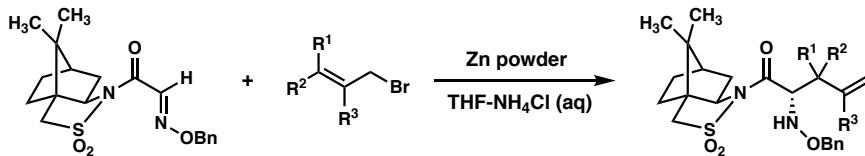
corresponding oxime amide could be reacted enantiospecifically with an allyl bromide, zinc powder, and THF-NH<sub>4</sub>Cl to form an allylated hydroxylamine in excellent yield and moderate to good diastereoselectivity (Scheme 1.2, b).<sup>11</sup>

**Scheme 1.2.** Racemic and enantiospecific allylation of oximes.

a) Racemic allylation of oximes

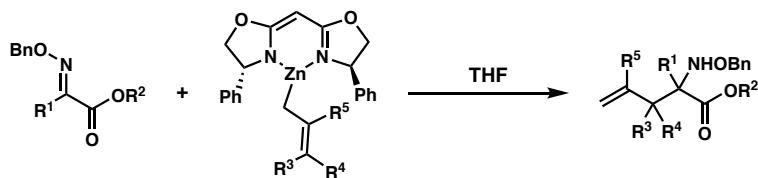


b) Enantiospecific allylation of chiral oxime amide



Later that year, Hanessian *et al.* developed a second allylation that used an external ligand to form a chiral allylic zinc bromide and allylate  $\alpha$ -ketoester oximes (Scheme 1.3). By using phenyl bis(oxazoline) (PhBOX), they achieved allylation of their oximes in good yield and high e.e. Additionally, the ligand could be recovered without loss of optical activity.<sup>12</sup>

**Scheme 1.3.** Asymmetric allylation with an external ligand.



Building from Hanessian's successful allylation of oximes, Ritson *et al.* developed a one-pot procedure for the allylation of various oximes.<sup>13</sup> They initially

tested Hanessian's aqueous conditions against compounds **2** and **3** but found that while **2** gave the expected hydroxylamine **4** in 92% yield, the more electrophilic **3** only gave a 38% yield of **5** (Table 1.1, entries 1 and 2). They next found that **3** was unreactive toward allyltrimethylsilane in the presence of  $\text{BF}_3\text{-OEt}_2$  (Table 1.1, entry 3).

**Table 1.1.** Allylation of oximes using allylindium reagents.

**2** R = Bn  
**3** R =  $\text{COCH}_2\text{CH=CH}_2$

**4** R = Bn  
**5** R =  $\text{COCH}_2\text{CH=CH}_2$

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Entry	Oxime	Conditions	Product	Yield
1	<b>2</b>	$\text{CH}_2=\text{CHCH}_2\text{Br}$ , Zn $\text{NH}_4\text{Cl}$ (aq.)	<b>4</b>	92%
2	<b>3</b>	$\text{CH}_2=\text{CHCH}_2\text{Br}$ , Zn $\text{NH}_4\text{Cl}$ (aq.)	<b>5</b>	38%
3	<b>3</b>	$\text{TMSCH}_2\text{CH=CH}_2$ $\text{BF}_3\text{-OEt}_2$ , $\text{CH}_2\text{Cl}_2$	nr	nr
4	<b>3</b>	$\text{CH}_2=\text{CHCH}_2\text{MgBr}$ , $\text{Et}_2\text{O}$	<b>6, 7</b>	—
5	<b>3</b>	$\text{In}^0$ , $\text{CH}_2=\text{CHCH}_2\text{Br}$ , DMF	<b>5</b>	56%
6	<b>2</b>	$\text{In}^0$ , $\text{CH}_2=\text{CHCH}_2\text{Br}$ , DMF	<b>4</b>	>80%
7	<b>2</b>	$\text{In}^0$ , $\text{CH}_2=\text{CHCH}_2\text{Br}$ THF—DMF, 15 min	<b>4, 8</b>	24%

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**6**

**7**

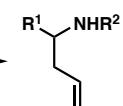
**8**

Treatment of **3** with allylmagnesium bromide produced the deprotected oxime **6** and the bisallyl ketone **7** instead of the desired allylated compound (entry 4). Ritson *et al.* then “reasoned that the electron-withdrawn oxime glyoxylates such as **[3]** and **[2]** might react with allylindium reagents.” Therefore, they added indium powder to allyl bromide and subsequently added **3**, which was converted to **5** in 56% yield (entry 5). Subjecting oxime **2** to the same conditions gave compound **4** in >80% yield (entry 6). In order to optimize the reaction, the authors increased the concentration of the reagents. Analysis of

the reaction mixture showed that, in fifteen minutes, **2** was converted to product **4** (24%), dimers such as **8** (19%) and polymers (entry 7). The authors added acetic anhydride in order to eliminate dimerization, and subsequently triethylamine to force full reaction with the acetic anhydride. They were able to expand the reaction to encompass substrates containing different esters, as well as both benzoyl- and benzyl-protected oximes. Additional viable substrates included crotyl bromide, one ketoxime, and one nitrile.

Miyabe *et al.* previously “reported the palladium-indium iodide-mediated regioselective allylation of glyoxylic oxime ether.” They noted that in anhydrous THF  $\alpha$ -adducts were selectively formed, whereas in the presence of water  $\gamma$ -adducts were formed.<sup>14</sup> Therefore, they next examined the reactivity of glyoxylic oximes and hydrazones toward an allylindium reagent and the effects of water on this reaction.<sup>15</sup> Initially, they tested the reactivity of different oximes and hydrazones toward allyl acetate in the presence of  $\text{Pd}(\text{PPh}_3)_4$  and indium(I) iodide in THF. They found that **9a** could be allylated in one hour in 92% yield (Table 1.2, entry 1). However, **9b** did not react, and

**Table 1.2.** Palladium- and indium-catalyzed allylation of oximes and hydrazones with allyl acetate.

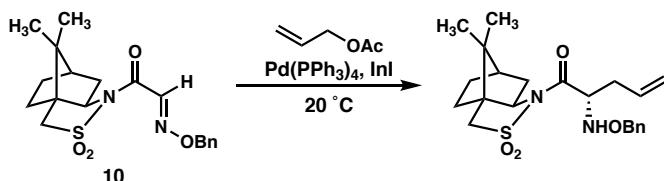
		<b>9a-d</b>		$\xrightarrow[\text{THF, 20 } ^\circ\text{C}]{\text{InI, Pd}(\text{PPh}_3)_4}$	
Entry	Imine	R <sup>1</sup>	R <sup>2</sup>	Time (h)	Yield (%)
1	<b>9a</b>	CO <sub>2</sub> Me	OBn	1	92
2	<b>9b</b>	Ph	OBn	10	nr
3	<b>9c</b>	CO <sub>2</sub> Me	NHBz	1	82
4	<b>9d</b>	CO <sub>2</sub> Me	NPh <sub>2</sub>	10	nr

they recovered 97% of the starting material (entry 2). **9c** also afforded the desired allylated product in 82% yield, whereas **9d** did not react (entries 3-4). They suggest that

the results are consistent with a six-membered ring transition state being important for successful allylation.

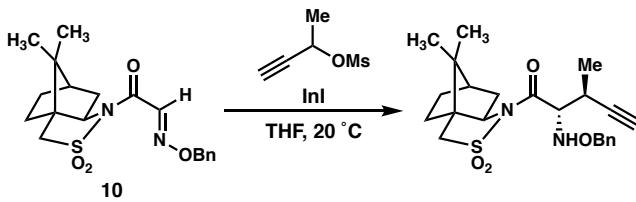
They next examined the reaction of **10**, which showed low diastereomer excess in anhydrous THF and marked improvement when running in 10:1 THF–H<sub>2</sub>O (Table 1.3, entries 1 and 3). They suggest this effect would be due to the reversibility of the allylation reaction. Although in anhydrous THF longer reaction times led to lower diastereoselectivity (Table 1.3, entries 1-2), this was not found to be the case in 10:1 THF–H<sub>2</sub>O (entries 3-4).

**Table 1.3.** Effects of solvent on the allylation of oxime **10**.



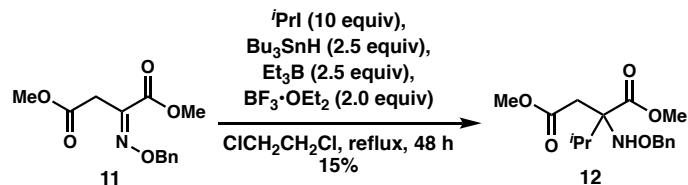
Entry	Solvent	Time (h)	Yield (%)	de (%)
1	THF	0.25	89	62
2	THF	3	91	20
3	THF–H <sub>2</sub> O (10:1)	0.25	88	92
4	THF–H <sub>2</sub> O (10:1)	20	95	91

Finally, they tested the propargylation of oxime **10** in anhydrous THF (Table 1.4). It was found that the reaction proceeded in good yield with LiBr or LiCl and a palladium catalyst (Table 1.4, entries 3-5). Although they could not determine the exact diastereoselectivity by <sup>1</sup>H NMR, they state that “the combined yields of other diastereoisomers were less than 7%.”

**Table 1.4.** Propargylation of **10** in anhydrous THF.

Entry	Catalyst	Additive	Time (h)	Yield (%)
1	none	none	20	nr
2	Pd(PPh <sub>3</sub> ) <sub>4</sub>	none	50	67
3	Pd(PPh <sub>3</sub> ) <sub>4</sub>	LiBr	25	75
4	Pd(OAc) <sub>2</sub> •PPh <sub>3</sub>	LiBr	15	78
5	Pd(dppf)Cl <sub>2</sub>	LiCl	15	72

Mitani *et al.* developed a method for the preparation of  $\alpha,\alpha$ -disubstituted amino acid derivatives by the reaction of  $\alpha$ -oxime esters with alkylzinc reagents.<sup>16</sup> Initially, they examined the radical alkylation of **11** using isopropyl iodide, Bu<sub>3</sub>SnH, and Et<sub>3</sub>B. After trying a variety of reaction conditions, the best result was formation of **12** in 15% yield (Scheme 1.4).

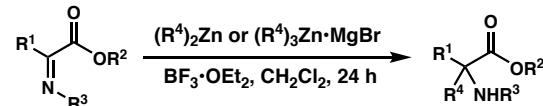
**Scheme 1.4.** Alkylation of **11** via radical pathway.

They next began examining reactivity of **11** with various alkylzinc reagents, finding 76% yield when **11** was reacted with two equivalences of diethylzinc in the presence of BF<sub>3</sub>•OEt<sub>2</sub> in CH<sub>2</sub>Cl<sub>2</sub> at reflux (Table 1.5, entry 2). Mitani *et al.* then attempted to enhance the nucleophilicity of the organozinc species by using the zincate complex (e.g. Et<sub>3</sub>Zn•MgBr) as well as by trying a different Lewis acid, Ti(O-*i*-Pr)<sub>4</sub> (Table 1.5, entry 3). Using BF<sub>3</sub>•OEt<sub>2</sub> and two equivalences of Et<sub>3</sub>Zn•MgBr, they were able to achieve a maximum yield of 82% (entry 4).

**Table 1.5.** Optimization of the alkylation of **11**.

Entry	Alkylzinc (equiv)	Lewis acid	Temp	Yield (%)
1	Et <sub>2</sub> Zn (1)	BF <sub>3</sub> ·OEt <sub>2</sub>	reflux	55
2	Et <sub>3</sub> Zn (2)	BF <sub>3</sub> ·OEt <sub>2</sub>	reflux	76
3	Et <sub>3</sub> Zn·MgBr (2)	Ti(O- <i>i</i> -Pr) <sub>4</sub>	0 °C	65
4	Et <sub>3</sub> Zn·MgBr (2)	BF <sub>3</sub> ·OEt <sub>2</sub>	0 °C	82

With these conditions in hand, the authors set out to expand the scope of their reaction. They first tested the alkylation of methyl pyruvate oxime, **14a**. Unbranched alkylzincate reagents gave the corresponding product in good yield (Table 1.6, entry 1). Reaction with *i*Pr<sub>3</sub>Zn·MgBr resulted in a low yield, which was improved by increasing the equivalence of alkylzinc (entries 2-3). Allylation of **14a** occurred in low yield (23-41% yield), but this was increased to 68% by increasing the reaction temperature to

**Table 1.6.** Alkylation of glyoxyl oximes and imine with organozinc reagents.

**14a** R<sup>1</sup> = Me, R<sup>2</sup> = Me, R<sup>3</sup> = OBn

**14b** R<sup>1</sup> = *t*Bu, R<sup>2</sup> = Et, R<sup>3</sup> = OBn

**14c** R<sup>1</sup> = *i*Pr, R<sup>2</sup> = Et, R<sup>3</sup> = OBn

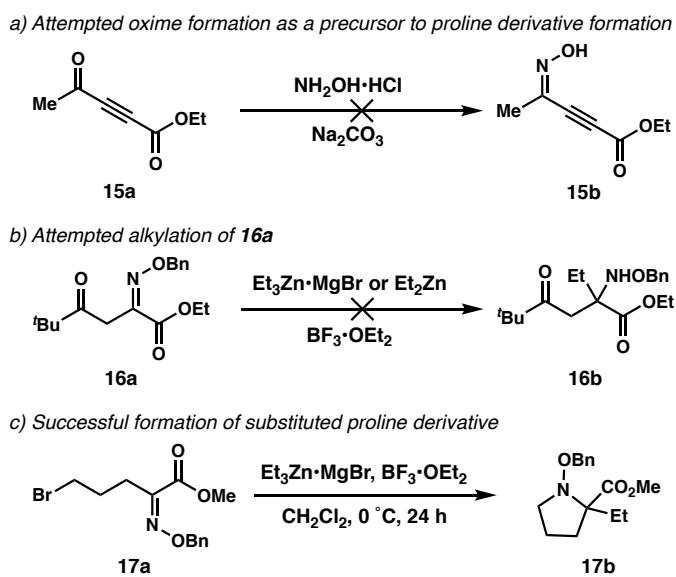
**14d** R<sup>1</sup> = Me, R<sup>2</sup> = Me, R<sup>3</sup> = Bn

Entry	Starting Material	Conditions	Yield (%)
1	14a	Et <sub>2</sub> Zn (2 equiv), 0 °C	85
2	14a	<i>i</i> Pr <sub>3</sub> Zn·MgBr (2 equiv, 0 °C)	31
3	14a	<i>i</i> Pr <sub>3</sub> Zn·MgBr (3 equiv, 0 °C)	64
4	14a	(CH <sub>2</sub> =CHCH <sub>2</sub> ) <sub>3</sub> Zn·MgBr (2 equiv), 0 °C	23
5	14a	(CH <sub>2</sub> =CHCH <sub>2</sub> ) <sub>3</sub> Zn·MgBr (2 equiv), reflux	68
6	14b	Bu <sub>3</sub> Zn·MgBr (4 equiv), reflux	74
7	14b	Et <sub>3</sub> Zn·MgBr (4 equiv), r.t.	67
8	14b	<i>i</i> Pr <sub>3</sub> Zn·MgBr (4 equiv), r.t.	69
9	14b	(CH <sub>2</sub> =CHCH <sub>2</sub> ) <sub>3</sub> Zn·MgBr (2 equiv), r.t.	72
10	14c	(CH <sub>2</sub> =CHCH <sub>2</sub> ) <sub>3</sub> Zn·MgBr (2 equiv), r.t.	66
11	14d	(CH <sub>2</sub> =CHCH <sub>2</sub> ) <sub>3</sub> Zn·MgBr, 0 °C	19
12	14d	(CH <sub>2</sub> =CHCH <sub>2</sub> ) <sub>2</sub> Zn, 0 °C	9

reflux (entries 4-5). Additionally, the authors tested their conditions against oximes **14b** and **14c**, with good yield (entries 6-10). They attempted the allylation of an imine (**14d**) using this reaction scaffold, which gave low yields (entries 11-12).

Finally, they turned their attention to synthesis of amino acid derivatives. However, they initially were unable to form the desired oxime ester **15b** (Scheme 1.5, a), and subsequently found that treatment of **16a** resulted in complete consumption of the starting material with no desired product formed (Scheme 1.5, b). Finally, they found that under their reaction conditions, **17a** could be used to form  $\alpha$ -substituted proline derivatives (Scheme 1.5, c).

**Scheme 1.5.** Attempted formation of  $\alpha$ -substituted proline derivatives.



### 1.3 PROPARGYLATION REACTIONS

In 2001, Evans *et al.* showed the selective propargylation of ethyl glyoxylate using scandium triflate and TMS-allenyl compounds as the nucleophile.<sup>17</sup> They found that  $\text{Sc}(\text{OTf})_3$  and Ph-PyBOX (**18**) promoted the addition of 1-methyl-1-(trimethylsilyl)allene

to ethyl glyoxylate in high enantioselectivity and yield. Adding hexafluoro-2-propanol (HFIP) was found to slightly improve yields by suppressing formation of oligomeric byproducts. Ethyl glyoxylate was propargylated in good to excellent enantioselectivity and yield using allenyl silanes with both linear and branched alkyl substituents (Table 1.7). It was discovered that [3+2] cycloaddition products could be formed by increasing the steric bulk of the silane substituents.

**Table 1.7.** Propargylation of ethyl glyoxylate.

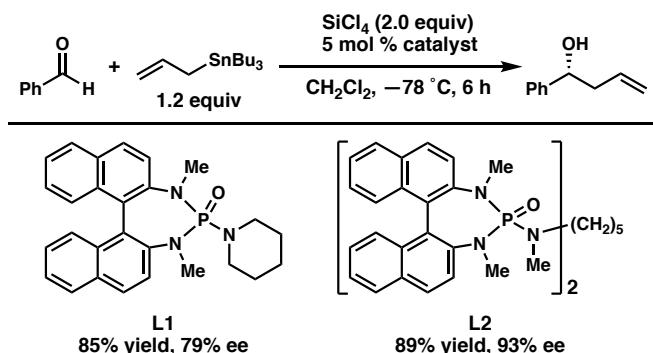
Entry	R	Yield (%)	ee (%)
1	Me	95	98
2	Cy	95	90
3	(CH <sub>2</sub> ) <sub>3</sub> OTBS	75	93
4	<i>i</i> Pr	96	93

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Denmark *et al.* utilized a Lewis base-activated Lewis acid to catalyze the enantioselective allylation and propargylation of aldehydes.<sup>18</sup> By activating a weak, achiral Lewis acid with a chiral Lewis base, they avoided some of the complications of Lewis acids including a competing achiral background reaction. Proof-of-concept studies showed that  $\text{SiCl}_4$  and HMPA could promote the allylation of benzaldehyde with allyltributylstannane without background reactions. They next began developing the asymmetric reaction and found that a BINAP-based phosphoramido ligand **L1** could catalyze this reaction in high yield and enantioselectivity (Figure 1.5). Initial optimization showed that linked phosphoramido **L2** gave the highest enantioselectivity (Figure 1.5),

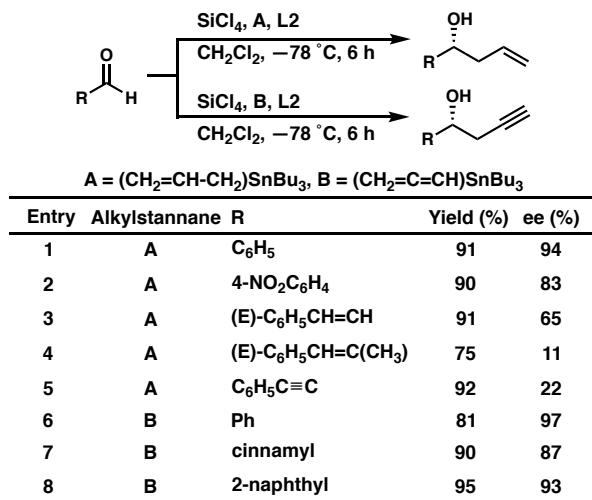
and further investigations showed that silicon tetrachloride was the optimal silicon source.

**Figure 1.5.** Optimization of the phosphoramido ligand for allylation of benzaldehyde.



Investigation into the reaction showed that it gave good yields for a variety of aldehydes but enantioselectivity was highly dependent on the structure of the substrate (Table 1.8, entries 1-5). The authors were also able to use allenyltributylstannane to propargylate compounds in high yield and enantioselectivity without detecting the isomeric allenyl compound (Table 1.8, entries 6-8).

**Table 1.8.** Activated Lewis acid-catalyzed allylation and propargylation of aldehydes.



Hernandez *et al.* reported the use of two borabicyclodecanes, *B*-allenyl-10-Ph-9-BBD (**19**) and  $\gamma$ -trimethylsilyl-propargyl-10-Ph-9-BBD (**20**) for propargylation and allenylation of ketones.<sup>19</sup> These reagents are air-stable and readily prepared in optically pure forms. Initially, the authors examined the asymmetric propargylation of various ketones using **19** (Table 1.9, entries 1-5). The resulting tertiary alcohols were obtained in good yield (62-85%) and good to high enantioselectivity (61-93%). They note that the addition to propiophenone was much slower, requiring two days at 25 °C (Table 1.9,

**Table 1.9.** Propargylation and allenylation of ketones using borabicyclodecanes.

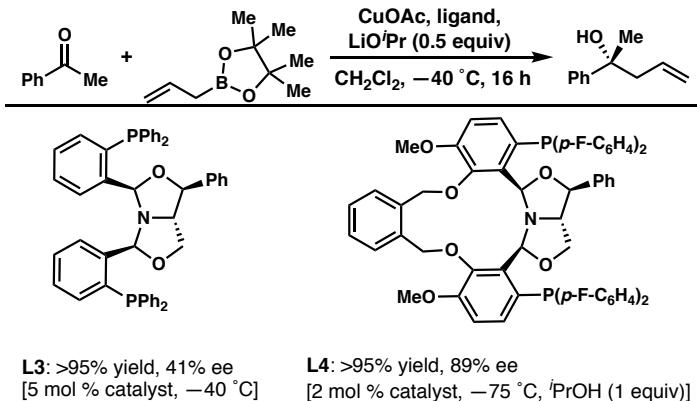
Entry	R <sup>1</sup>	R <sup>2</sup>	19 or 20	Yield (%)	% ee
1	Ph	Me	19	85	93
2	Ph	Et	19	65	76
3	Et	Me	19	71	74
4	TMS	Me	19	62	90
5	CH <sub>2</sub> =CH	Me	19	64	61
6	Bu	Me	20	62	84
7	p-MeOC <sub>6</sub> H <sub>4</sub>	Me	20	95	92
8	p-BrC <sub>6</sub> H <sub>4</sub>	Me	20	80	98
9	2-C <sub>4</sub> H <sub>2</sub> S	Me	20	71	78
10	Ph	Et	20	63	64

entry 2). However, even this and other challenging substrates such as 2-butanone and methyl vinyl ketone were obtained with good selectivities (76%, 74%, and 61% respectively). Hernandez *et al.* found that the allenylation of various ketones using **20** proceeded in good to excellent yield (62-95%) and good to excellent enantioselectivity (78-98%) with the exception of propiophenone, which gave 64% ee (Table 1.9, entries 6-

10). The recyclable nature of the 9-BBD reagent and fairly wide variety of ketones make this a suitable addition to the propargylation toolbox.

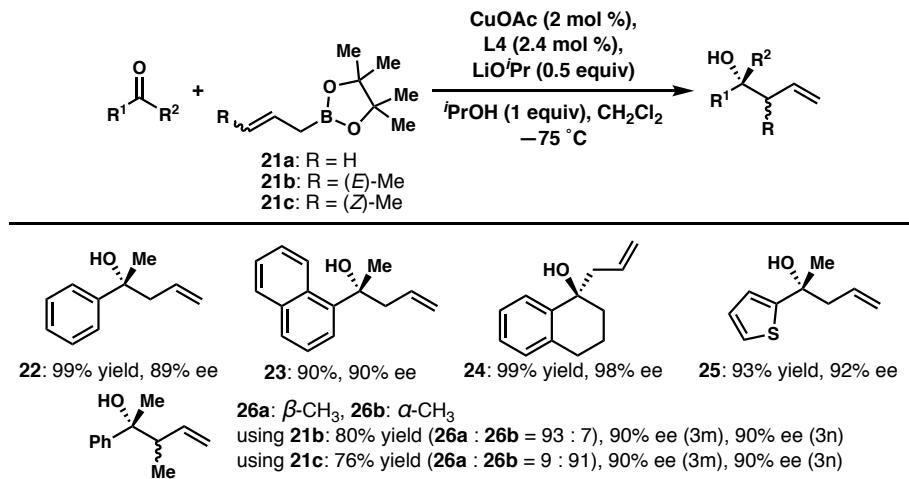
Shi *et al.* sought to develop a modular approach to chiral phosphine development, which they applied to discovery of a catalyst for the Cu(I)-catalyzed asymmetric allylation and propargylation of ketones.<sup>20</sup> They first examined diphosphine **L3** in the Cu-catalyzed asymmetric allylation of acetophenone (Figure 1.6). The product was obtained in quantitative yield and 41% ee. In order to improve the enantioselectivity of the reaction, they designed the next ligands with a constrained macrocycle, which eventually increased enantioselectivity to 89% ee using **L4** (Figure 1.6).

**Figure 1.6.** Ligand optimization for the copper-catalyzed allylation of acetophenone.



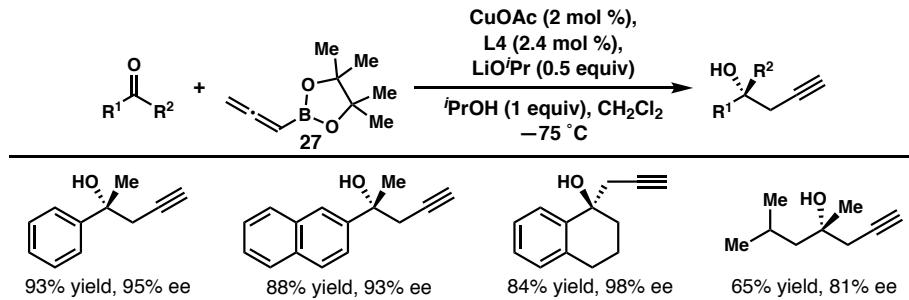
Using **L4** and the tetramethyl dioxaborolane **21a**, the authors were able to allylate a variety of ketones in good to excellent yield and enantioselectivity (Figure 1.7, 22-25). They also found that crotylation using **L4** and **21a** or **21b** “also proceeded with improved diastereo- and enantioselectivity” relative to their previous reaction using *i*Pr-DuPHOS (Figure 1.7, 26a-26b). However, they note that their enantio- and diastereoselectivity were slightly inferior to that reported by Schaus.<sup>21</sup>

**Figure 1.7.** Copper-catalyzed allylation and crotylation using tetramethyl dioxaborolanes.



They also were able to use this reaction with allenyl dioxaborolane **27** to propargylate a range of ketones in good to excellent yield and enantioselectivity (Figure 1.8).

**Figure 1.8.** Copper-catalyzed propargylation using allenyl tetramethyl dioxaborolane.



Schaus and Barnett demonstrated the enantioselective propargylation of ketones using 1,3-dioxaborolanes with a BINOL catalyst.<sup>22</sup> They initially investigated the reactions of **28** with acetophenone with **L5** as the catalyst. They found that no reaction occurred at room temperature. However, with heating to 65 °C, they obtained alcohol **30** in 80% yield and an enantiomeric ratio of 93:7 after only 15 hours (Table 1.10, entry 1).

They were able to reduce the reaction time by the use of microwave irradiation (entry 2).

Next, they investigated the use of allenylidioxaborolane **29**, hypothesizing that the greater ring strain in the boronate would result in a faster reaction. They found that this was the case, and in addition saw an increase in reactivity at room temperature (Table 1.10, entries 3-4). Ultimately it was determined that reaction with **29** under microwave conditions gave the greatest yield (85%) and enantioselectivity (97:3 er).

**Table 1.10.** Chiral biphenol-catalyzed propargylation of acetophenone.

28 n = 2  
29 n = 1

30

Entry	Boronate	Method <sup>a</sup>	Temp (°C)	Time (h)	Yield (%)	er
1	28	a	65	15	80	93:7
2	28	b	105	1	77	93:7
3	29	a	65	15	80	97:3
4	29	b	60	1	85	97:3

<sup>a</sup> Catalyst was dissolved in boronate and then ketone added.  
Heated using the following methods: (a) conventional heating  
(b) microwave reactor held at 10 W

The substrate scope of the reaction was found to encompass ketones with varied steric and electronic properties, and the authors found that in the case of ketones with lowered steric hindrance they could use 3,3'-Mes<sub>2</sub>-BINOL (**L6**) or 3,3'-anthracyl-BINOL to improve the selectivity (Table 1.11, entries 2 and 5).

**Table 1.11.** Substrate scope of biphenol-catalyzed propargylation.

L5 (10 mol %)  
μwave

Entry	R <sup>1</sup>	R <sup>2</sup>	Yield (%)	er
1	Ph	CH <sub>3</sub>	85	97:3
2 <sup>a</sup>	Ph(CH <sub>2</sub> ) <sub>2</sub>	CH <sub>3</sub>	86	79:21
3	Ph	CH <sub>2</sub> Ph	98	98:2
4	naphthyl	CH <sub>3</sub>	86	97:3
5 <sup>a</sup>	PhCHCH	CH <sub>3</sub>	91	95:5
6	1-cyclohexenyl	CH <sub>3</sub>	68	96:4

<sup>a</sup> Reaction run with 10 mol % **L6** instead of **L5**

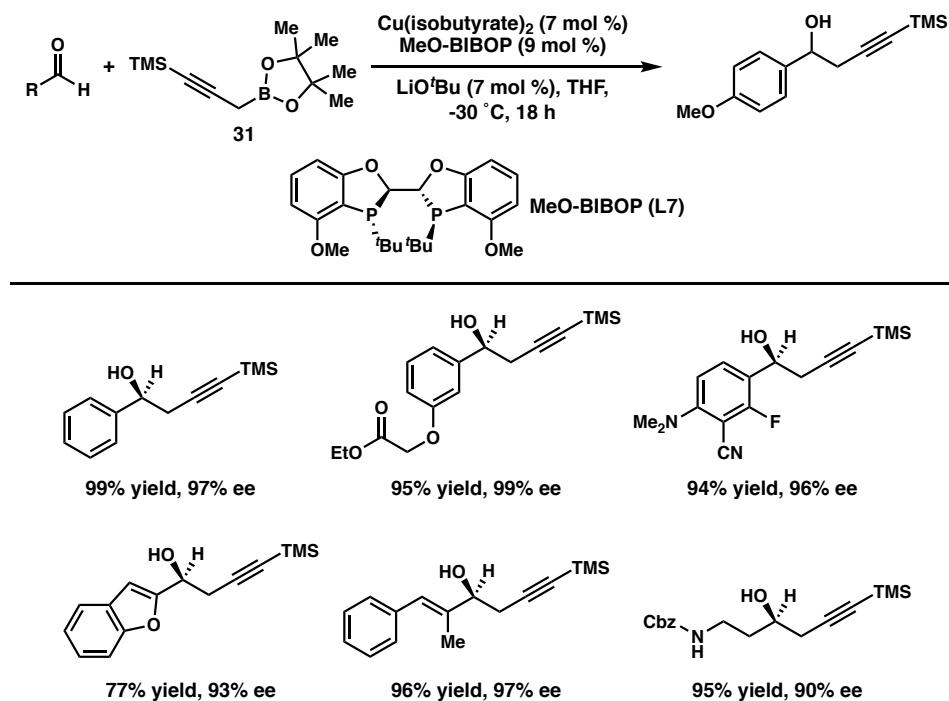
L6  
Ar = 2,4,6-(CH<sub>3</sub>)<sub>3</sub>C<sub>6</sub>H<sub>2</sub>

They also investigated whether the reaction could be used for diastereoselective propargylations using a racemic boronate. They found that the methyl allenyl borolane gave the *syn*-methylpropargyl product in 93% yield and in 86:14 diasteromeric ratio (Table 1.12, entry 1). By using allenes with larger substituents at the  $\gamma$ -position, the authors were able to improve the diastereoselectivity of the reaction even to the point of obtaining the product in >25:1 dr and 94:6 er from the isopropyl allenyl borolane (Table 1.12, entry 2).

**Table 1.12.** Diastereoselective biphenol-catalyzed propargylation.

Entry	R	Yield (%)	er	dr
1	Me	93	92:8 (major) 98:2 (minor)	86:14
2	<i>i</i> Pr	82	94:6 (major)	>25:1
3	Ph	98	94:6 (major) 96:4 (minor)	87:13

Similarly, in 2010 Fandrick *et al.* used a dioxaborolane compound (**31**) with a BIBOP catalyst to perform enantioselective propargylation of aldehydes.<sup>23</sup> During their initial optimization, they noted a slow background reaction with or without a copper catalyst. They found that phosphine ligands greatly increased the selectivity for the alkynyl product rather than the allene; the highest enantioselectivity came from the methoxy derivative of their parent BIBOP ligand (MeO-BIBOP, **L7**). Their reaction conditions gave high enantioselectivities and yields for a variety of aromatic substrates with a slight decrease in enantioselectivity for the one aliphatic substrate (Figure 1.9). Their conditions also allowed them, in at least one case, to selectively propargylate an aromatic ketone rather than an ester (Figure 1.9).

**Figure 1.9.** Copper(II) isobutyrate-catalyzed propargylation substrate scope.

A 2011 study by Fandrick *et al.* focused on the copper-catalyzed, enantioselective propargylation of ketones.<sup>24</sup> They initially focused on methyl ethyl ketone (MEK) for the challenges it represents in enantiocontrol. Initial attempts employing their previous copper(II) isobutyrate—MeO-BIBOP system yielded the homopropargylated alcohol **32** with an ee of 69% (Table 1.13, entry 1). After “an intensive ligand, solvent, and catalyst survey,” they found that using Xyl-BINAP (**L9**) raised the enantioselectivity to 83% and unsubstituted BINAP raised enantioselectivity to 90% (Table 1.13, entries 2-3). Decreasing the reaction temperature to  $-83^\circ\text{C}$  provided **32** in 83% yield and 95% ee (entry 4).

Subsequently, the authors investigated the scope of the reaction, finding it to be efficient over a variety of compounds with uniformly high enantioselectivity and good to excellent yield (Table 1.14). However, benzofuran methyl ketone required increased

catalyst loading and 35 hours reaction time to go to completion and showed an ee of only 84% (Table 1.14, entry 5).

**Table 1.13.** Ligand optimization for copper-catalyzed propargylation of ketones.

Entry	Ligand	Temp (°C)	Conversion (Isolated Yield)	ee (%)
1	MeO-BIBOP	-25	99%	69%
2	Xyl-BINAP	-25	99%	83%
3	BINAP	-62	99% (81%)	90%
4	BINAP	-83	99% (83%)	95%

**Table 1.14.** Substrate scope of the Cu-BINAP asymmetric propargylation.

Entry	R <sup>1</sup>	R <sup>2</sup>	Yield (%)	ee (%)
1	Et	Me	81	90
2	cPr	Me	96	98
3	CH <sub>2</sub> CH <sub>2</sub> Ph	Me	77	90
4	p-NO <sub>2</sub> Ph	Me	85	93
5 <sup>a</sup>	Benzofuran	Me	80	84

<sup>a</sup> 10 mol % catalyst, 35 h

## 1.4 CONCLUDING REMARKS

As this chapter encompasses, transition metal catalysis readily enables the allylation and propargylation of ketones and aldehydes, as well as the allylation of oximes in high yield and enantioselectivity. The propargylation of oximes, however, is a less explored field. Enantioselective reactions often require expensive metals such as palladium or indium, or a chiral auxiliary, which can increase steps in a synthesis and is often simply unwieldy. There remains to be seen a straightforward oxime propargylation which proceeds catalytically over a wide substrate scope. This would fill a gap in the synthetic toolbox as well as provide a method of access to various unnatural amino acids or synthetic precursors.