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Tetrahedron
Tetrahedron 63 (2007) 9581–9597

Tetrahedron report number 811

# Catalytic, asymmetric alkylation of imines

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Received 25 May 2007
Available online 20 June 2007

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## 1. Introduction

Enantioselective catalysis is one of the most efficient methods to conduct the organic synthesis of chiral molecules. The field of catalytic, asymmetric synthesis has thrived and grown since the publication of the first catalytic, asymmetric aldol reaction.[1] While the catalytic, asymmetric alkylation of carbonyl compounds has become commonplace, the analogous catalytic, asymmetric alkylation of imines has primarily evolved over the last decade. In fact,

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0040–4020/$ - see front matter 
doi:10.1016/j.tet.2007.06.043

much of the groundbreaking methodology devised for catalytic, asymmetric alkylation of carbonyl compounds generated the ideas that advanced the catalytic, asymmetric alkylation of imines.

Two main strategies exist for the catalytic, asymmetric alkylation of imines. The first strategy is a chiral Lewis acid approach. This approach employs the use of a transition metal catalyst bound to a chiral ligand. The chiral Lewis acid complex coordinates the imine, forming a chiral ternary complex that directs the nucleophile to the least hindered face of the imine. After the asymmetric carbon–carbon bond forming step, the product is released from the Lewis acid complex so that the cycle can continue. While this approach has been very successful in asymmetric carbonyl alkylations, the methodology is not directly applicable to the analogous imines. The main problem with this approach is the fact that many imines (and the resulting amines) are significantly more Lewis basic than aldehydes or ketones. This Lewis basicity has the effect of inactivating the chiral Lewis acid catalyst. This inactivity can lead to diminished enantioselectivity and/or decreased yields. Despite these issues, many groups have devised methods to alleviate the Lewis basicity of imines by attaching electron-withdrawing groups to the imine nitrogen. Figure 1 outlines common examples of electron-deficient sulfonyl (**1a–c**),[2] phosphoryl (**2a**,**b**),[3] and acyl imines (**3a**,**b**).[4]

The second strategy employed in catalytic, asymmetric alkylation of imines is the chiral nucleophile approach. In this approach, the chiral agent is either directly or indirectly part of the nucleophile before addition to the imine. After alkylation, the chiral moiety is then released for another cycle. This approach has enjoyed success with *N*-silyl imines (**4a**),[5] *N*-aryl imines, and *N*-alkyl imines (**5a–g**) and will be discussed extensively in this review (Fig. 1).

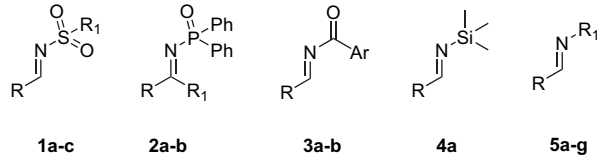


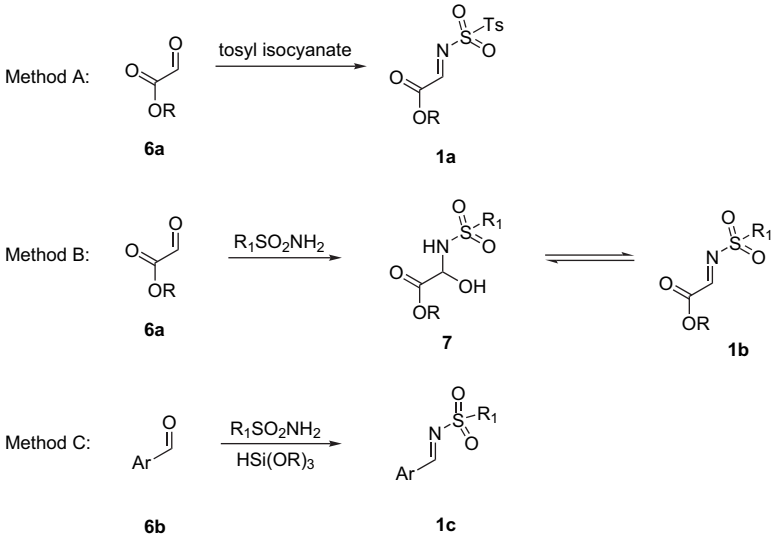

**Figure 1**. Common examples of imines used in catalytic, asymmetric alkylations.

While the majority of the examples presented in this review follow these two approaches, there are other creative methods based on chiral Brønsted acid catalysis,[6] bifunctional catalysis,[7] and enzyme mimics.[8] Indeed, these methods may become commonplace in the future and for this reason they warrant discussion. While this review is by no means comprehensive, the author wishes to provide *all* organic chemists (academic, medicinal, natural product, process, etc.) with useful information regarding catalytic, asymmetric alkylation reactions with imines. Since the field of asymmetric alkylation of imines is already the subject of other reviews,[9] the present report will focus on advances in *catalytic*, asymmetric methodology over the past 7–10 years.

## 2. Imine synthesis and reactivity

### 2.1. Sulfonyl imines

Much of the asymmetric methodologies associated with carbonyl compounds involve Lewis acid catalysis. As mentioned above, one of the major hurdles in the evolution of catalytic iminoalkylation has been the Lewis basicity of the imine nitrogen. Sulfonyl groups can attenuate this basicity and for this reason, sulfonyl imino esters **1a–b** and aryl sulfonyl imines **1c** are both commonly used in catalytic, asymmetric synthesis (vide infra). Scheme 1 outlines the synthesis of α-imino ester **1a**, which is the product of a condensation of tosyl isocyanate and ethyl glyoxylate **6a** in toluene (Method A).[10] Imino ester **1a** is stable under anhydrous conditions for extended periods of time, increasing its utility as a reagent. However, the tosyl protecting group is not ideal for protection purposes due to the required acidic method of deprotection (HBr/HOAc). Other readily removable sulfonyl based protecting groups ($R_1$=$CH_2CH_2TMS$, 4-$NO_2Ph$)[11] can be incorporated into the imino ester via reaction with




**Scheme 1**. General synthesis of *N*-sulfonyl imines.

sulfonamides to form *N*,*O*-acetals **7** (Scheme 1, Method B). These *N*,*O*-acetals are stable, crystalline reagents that generate the desired imine **1b** under certain reaction conditions.[12] Aryl *N*-sulfonyl imines **1c** are commonly synthesized by the condensation of aromatic aldehydes **6b** with sulfonamides in the presence of trialkoxysilanes (Scheme 1, Method C).[13]

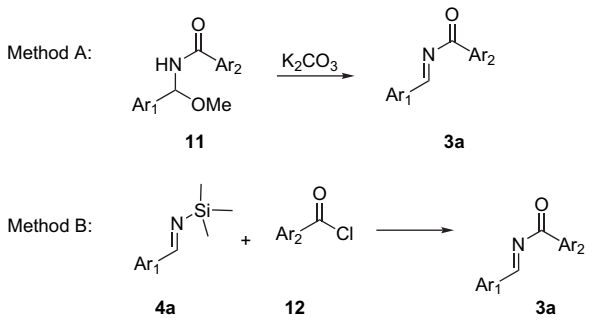
### 2.2. Phosphoryl imines

Phosphoryl imines are useful for Lewis acid catalyzed iminoalkylation for the same reasons as sulfonyl imines. Phosphoryl imines are commonly synthesized by the Stec reaction.[14] Aromatic aldehydes or ketones **6c** ($R_1$=Ar, $R_2$=H, $CH_3$) readily condense with hydroxylamine in high yield (Scheme 2, Method A). Addition of chlorodiphenyl phosphine to the resulting oxime **8** is done at low temperature. In the case of diphenylphosphoryl ketoimines **2a** ($R_2$=$CH_3$), the stability of the imine allows for an aqueous workup and column chromatography to be used for purification. For the more reactive trifluoromethylated ketones **6d**, diphenylphosphonamide **9** condenses in the presence of $Ti(OEt)_4$ to afford the intermediate *N*,*O*-aminal **10**. Similar to the sulfonyl *N*,*O*-acetals **7**, the stable aminal **10** is in equilibrium with the ketoimine **2b** under certain reaction conditions (Scheme 2, Method B).[15]

### 2.3. Acyl imines

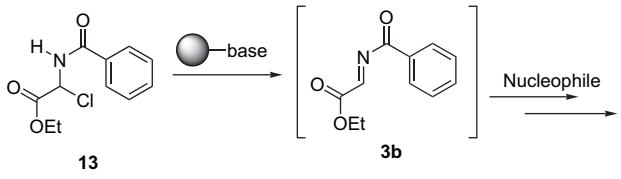
Aromatic acyl imines **3a** can be prepared from heating *N*-(methoxyaryl)benzamides **11** in the presence of base followed by subsequent distillation.[16] A variety of substituted aryl benzylimines were prepared via this method for asymmetric alkylation by Terada et al. (Scheme 3, Method A).[17] Acyl imines can also be prepared from addition of acid chlorides **12** to silyl imines **4a** (Scheme 3, Method B).[18] Imines prepared via Method B may also be purified by recrystallization or distillation.

Due to the limitations associated with high-temperature distillations and hydrolytic instability, acyl imines are not as common as phosphoryl or sulfonyl imines despite sharing the electron-deficient imine nitrogen. In fact, due to their latent instability, they are often synthesized in situ using α-haloglycine.[19] The Lectka group designed a creative and practical method to synthesize acyl imines in situ using polymer-supported bases to eliminate HCl from α-haloamides **13** (Scheme 4).[20] The latent acyl imine **3b** is washed from the polymer-supported base directly into the reaction flask




**Scheme 3**. General synthesis of acyl imines.

containing the desired nucleophile. This method obviates the need for isolation and purification of the acyl imine, increasing the feasibility of acyl imine chemistry.

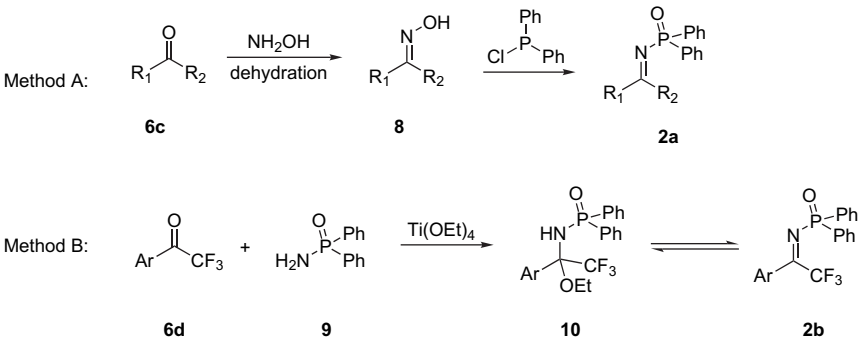



**Scheme 4**. In situ formation of acyl imines.

### 2.4. Silyl imines

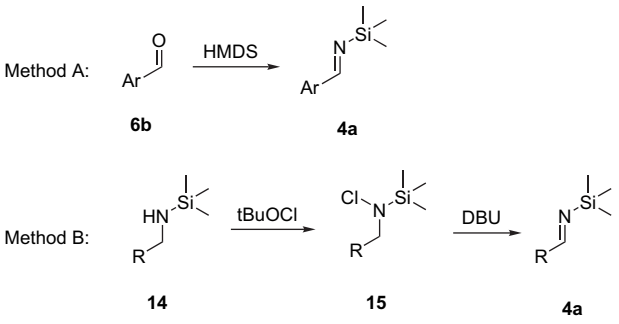
Catalytic, asymmetric iminoalkylations with silyl imines are also attractive due to the ease of deprotection of the silyl group. Silyl imines have been critical in the development of asymmetric synthesis for over 20 years. In particular, they have been used in the synthesis of β-lactams and other useful heterocyclic compounds via cycloaddition reactions.[21] Their use in Lewis acid catalyzed asymmetric alkylations, however, has been rather infrequent, perhaps because of the relative Lewis basicity of the silyl imine nitrogen.[22] Despite this difficulty, the flexibility of silyl protecting groups in synthesis warrants continuing efforts toward catalytic asymmetric iminoalkylations.

Silyl imines are commonly synthesized by the addition of LiHMDS to aldehydes as outlined in Scheme 5 (Method A).[23] This method is simple and high yielding, but suffers from two major drawbacks. The first problem is that the products must be distilled for purification. Complicating this distillation is the fact that some silyl imines polymerize




**Scheme 2**. General synthesis of diphenylphosphoryl aldimines and ketoimines.

at elevated temperatures, making purification difficult. The second limitation is that this method can only be used on aldehydes without an enolizable proton. When using compounds with an enolizable proton, LiHMDS will quantitatively deprotonate the α-proton rather than attack the aldehyde carbon. Alternatively, silyl imines **4a** can be synthesized from the silylated amines **14** by oxidation with *tert*-butylhypochlorite. The silyl imine is formed from HCl elimination of the intermediate *N*-chloride **15** (Scheme 5, Method B).[24]




**Scheme 5**. General synthesis of silyl imines.

## 2.5. *N*-Aryl and *N*-alkyl imines

The *N*-aryl imines (**5a**–**f**), specifically methoxyphenyl (OMP or PMP) imines, are common substrates for asymmetric iminoalkylations. Specifically, these imines are often used with the chiral nucleophile approach. Both the ease of synthesis and the readily removable aryl groups[25] makes *N*-aryl imines ideal substrates for much of the chemistry outlined in this review.

*N*-Aryl imines such as the methoxyphenyl imines **5a**,**b** (PMP and OMP imines), the hydroxyphenyl imine **5c**, and the *N*-benzyl imine **5d** can be synthesized by a simple condensation in the presence of a dehydrating agent or with the use of a Dean–Stark trap (Method A, Scheme 6).[26] The final products still have some latent sensitivity to water, but they are generally crystalline in nature, so purification by recrystallization increases their practical value and utility. Alkyl imines are not as stable and crystalline as their aromatic cousins. Imines with α-protons commonly tautomerize to form enamines **17** rather than imine **5f** (Method B, Scheme 6). Some groups, however, have had success in generating the imines such as **5f** in situ followed by rapid alkylation before tautomerization.[27]

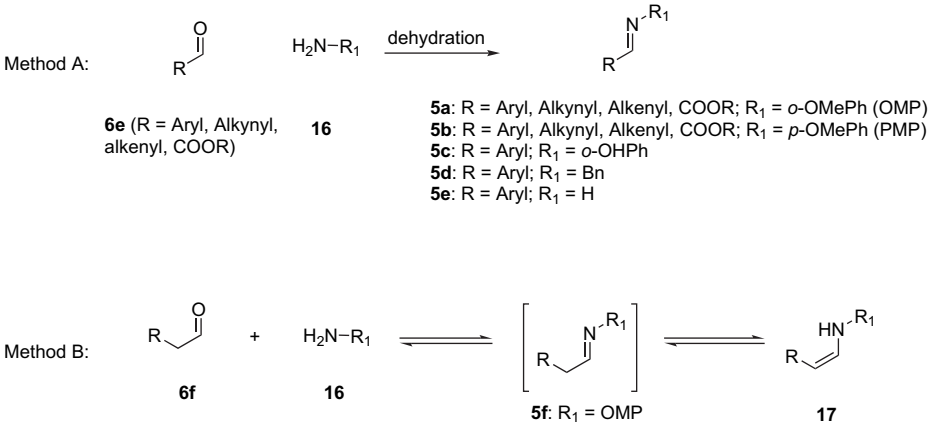
## 3. Nucleophiles for catalytic asymmetric alkylation of imines

Classical nucleophiles such as alkyl lithium reagents and alkyl Grignard reagents have not been studied extensively in this field due to their background reactivity toward imines. The high background reaction rates for these reagents diminish the enantioselectivity and the potential use in catalytic asymmetric reactions.[28] Researchers have preferred to use the less reactive alkyl zinc and alkyl stannanes for catalytic, asymmetric alkylation of imines. Indeed, much of the success in Lewis acid promoted asymmetric iminoalkylations incorporate nucleophiles that have long been used in the analogous asymmetric alkylations of carbonyl compounds (e.g., enol silanes, ketene acetals, olefins, and allyl silanes).

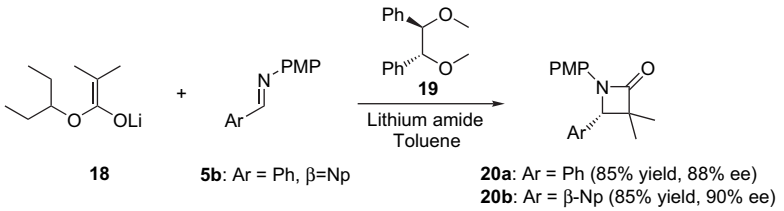
### 3.1. Ketene based nucleophiles

**3.1.1. Ketene enolates.** The earliest report of a catalytic, enantioselective iminoalkylation was published in 1997 by the Tomioka[29] group. The nucleophile of choice for their methodology was a lithium ketene acetal, **18** a well-established carbon nucleophile.[30] Lithium ketene acetal **18** alkylates *N*-PMP aryl imines **5b** in the presence of 20 mol % of diether **19** (Scheme 7). The best results employ lithium cyclohexylisopropylamine (LICA) as the lithium source, and either Ar=phenyl (88% ee) or Ar=β-naphthyl (90% ee) as the PMP imine. The reactions are conducted at low temperature (−50 °C) affording the β-lactams **20a**,**b** in good overall yields (40–95%). While the mechanism for this reaction is not explicitly outlined in the publication, it most likely involves a chiral nucleophilic complex. The likely complex involves the ketene enolate **18** with the lithium chelated by **19**. Despite the apparent lack of substrate flexibility, this work was the first to demonstrate an effective catalytic, enantioselective alkylation of imines using the chiral nucleophile approach.

**3.1.2. Silyl ketene acetals.** Shortly after the Tomioka communication described above, the Kobayashi group




**Scheme 6**. General synthesis of *N*-aryl imines.




**Scheme 7**. Tomioka catalytic, enantioselective alkylation of PMP imines.

performed a catalytic enantioselective Mannich-type reaction with a zirconium based bromo-BINOL complex **22** (Scheme 8).[31] The silyl ketene acetals and thioketene acetals **21a**,**b** react with aryl *o*-hydroxyphenylimines **5c** in the presence of **22** and NMI at −45 °C to afford β-amino esters **23** in good overall yields (56–100%) and selectivities (80–98% ee, $R_1$=Ph, 4-ClPh, α-Np, 2-furyl, cyclohexyl). Consequently, the cyclization of **23** to form a β-lactam does not occur under these reaction conditions. The reason for this is outlined in the proposed reaction mechanism in Figure 2. Initially, the imine **5c** chelates the Zr(IV)$(BrBINOL)_2$ to form the activated chiral Lewis acid ternary complex **24**. The ketene acetals **21a**,**b** react with **24** resulting in carbon–carbon bond formation followed by a silyl transfer to the BrBINOL (complex **25**, Fig. 2). The silyl group is then transferred to the β-amino ester and the catalyst **22** is regenerated. This mechanism is consistent with the best obtained results. For example, naphthyl imines ($R_1$=α-Np) provide the highest selectivity (92% ee with **21a** and 98% ee with **21b**) presumably due to π–π interactions of the naphthyl group with the BrBINOL ligand. Through this publication, the Kobayashi group was the first to demonstrate a successful chiral Lewis acid approach to iminoalkylation.

In an effort to improve the work of Sodeoka and Kobayashi, the Hoveyda group later reported a catalytic, asymmetric Mannich-type reaction.[32] Silver acetate and ligand **27** catalyze the addition of **26** to alkynyl OMP imines **5a** ($R_1$=substituted alkynyl). The β-amino esters **28** are isolated in 61–91% isolated yields and 84–94% ee (Scheme 9). This work expanded the substrate flexibility of this type of iminoalkylation and provided a convenient route to olefinic and aliphatic β-amino esters via reduction of the alkyne.

**3.1.3. Ketene Zwitterionic enolates.** The Lectka group elegantly devised catalytic, asymmetric methodology to synthesize β-lactams from ketene enolates and imines.[33] Classically, the nucleophilic nitrogen on an imine reacts with the electrophilic ketene carbon to form a β-lactam (Staudinger reaction). The Lectka approach affords the β-lactam via an umpolung of the ketene and imine (i.e., the nucleophilic Zwitterionic ketene enolate reacts with an electrophilic activated imine). This chiral nucleophile approach uses a benzoylquinine catalyst (**30**, BQ) to form the ketene enolate **32** (Fig. 3). This Zwitterionic enolate alkylates imino ester **1a** in a highly enantioselective and diastereoselective manner to form the *cis*-β-lactams **31** (R=Ph, Bn, Et, vinyl, Br, $N_3$, OAc). The catalyst **30** is regenerated by using a general base (e.g., the proton sponge). This methodology has led to the catalytic, asymmetric synthesis of substituted *cis*-β-lactams **31** in good yields (45–65%) and selectivities (95–99% ee and 25–99:1 dr) (Scheme 10).

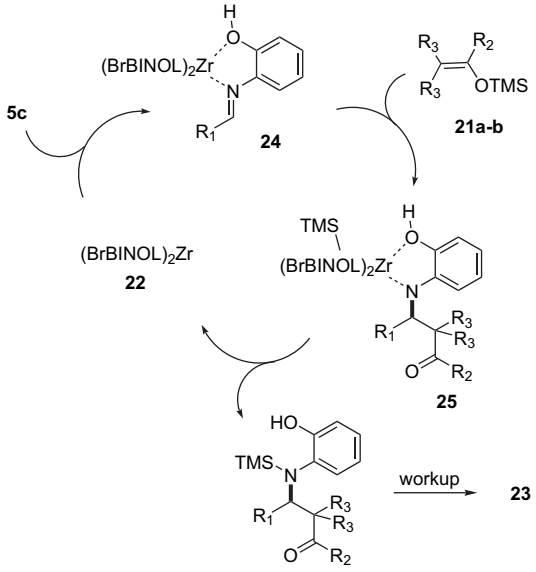
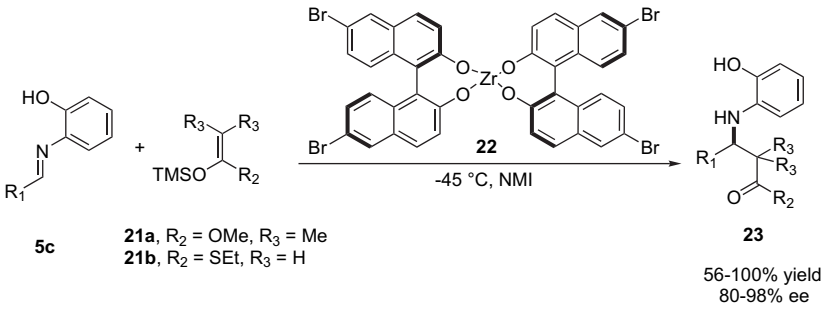
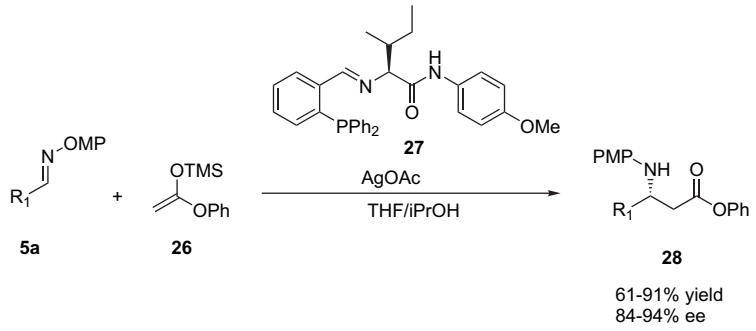



**Figure 2**. Proposed catalytic cycle for Zr-BINOL-catalyzed Mannich-type reaction.




**Scheme 8**. Kobayashi zirconium-catalyzed Mannich-type reaction.




**Scheme 9**. Hoveyda catalytic, asymmetric Mannich-type reaction.

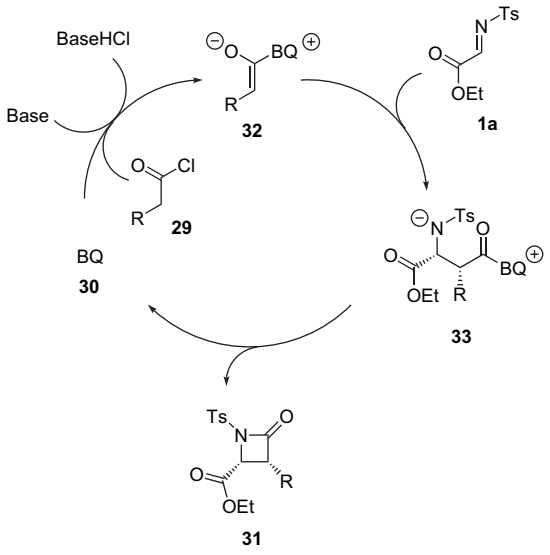
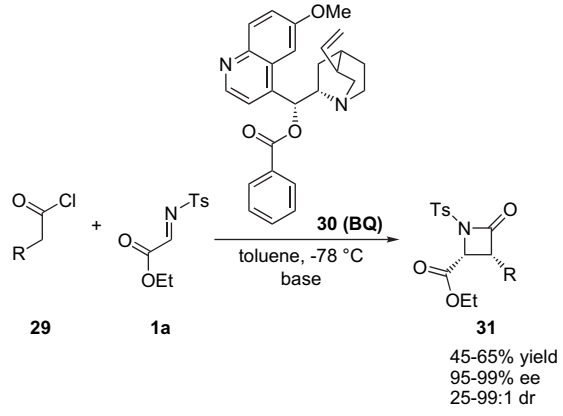



**Figure 3**. Proposed catalytic cycle of Lectka asymmetric β-lactam synthesis.




**Scheme 10**. Lectka catalytic, asymmetric synthesis of β-lactams.

The proposed mechanism for this β-lactam synthesis is outlined in Figure 3. Chiral Zwitterion **32** is generated from acid chloride **29** in one of the two ways depending on the nature of the base. Kinetic experiments have established that when using the proton sponge as a base, the BQ (**30**) is acylated by the acid chloride **29** followed by tautomerization to **32**. With other bases such as $K_2CO_3$ and NaH, the ketene is formed from **29** first, followed by acylation by BQ.[4] Chiral enolate **32** rapidly reacts with the activated imino ester **1a** to form the Zwitterionic β-keto amino ester **33**. Upon cyclization, the β-lactam is formed and the BQ **30** is regenerated.

Further improvements of this methodology were accomplished by modifying the BQ base **30** with a chelating group to bind $In(OTf)_3$ and create a bifunctional catalyst.[7] Attempting to mimic the polyfunctional nature of metalloenzymes, the Lectka group designed catalyst **34** with a Lewis acid (indium) and Lewis base (quinuclidine) in close proximity. This system was optimized to minimize the 'head-to-tail' interaction that may occur when a Lewis acid and Lewis base are in the same molecule. The proposed mechanism with this catalyst is outlined in Figure 4. The quinuclidine portion of catalyst **34** forms the ketene enolate **35**. Concomitantly, the indium complexes imino ester **1a** activating it for nucleophilic substitution (complex **36**). Intramolecular alkylation and cyclization of the β-amino ester (Fig. 3) lead to the *cis*-β-lactams in 91–98% yields, 96–98% ee, and 9:1 to 60:1 cis selectivity. This is a notable improvement in yield from the previous methodology using BQ **30** alone (45–65%).

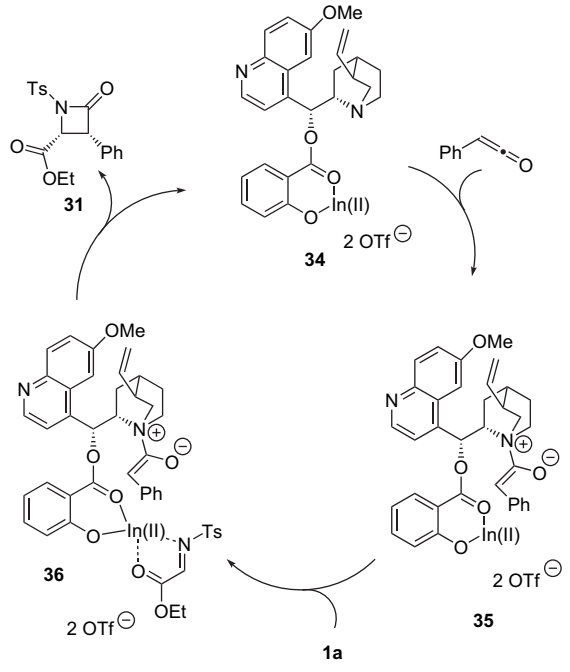
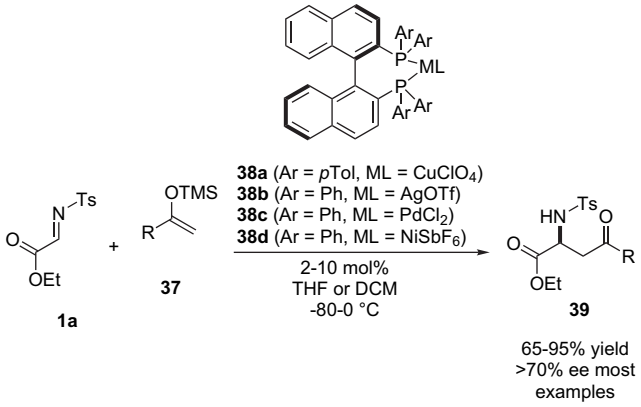



**Figure 4**. Lectka bifunctional catalysis in β-lactam synthesis.

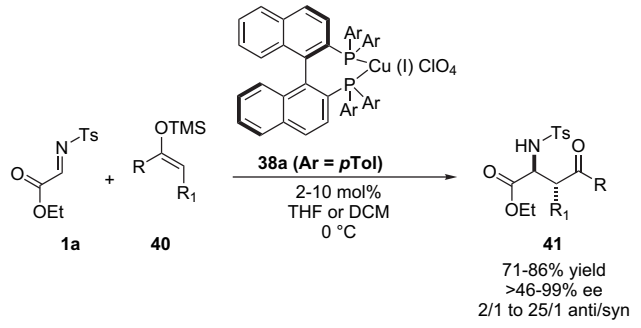
### 3.2. Enol silanes

The earliest report of catalytic iminoalkylation with enol silanes was published by the Lectka group in 1998.[34] Aromatic and aliphatic enol silanes **37** (R=Ph, substituted Ph, *t*-Bu, β-Np) alkylate **1a** in the presence of BINAP derived metal complexes of Ag(I), Cu(I), Pd (II), and Ni (II) (**38a–d**, Scheme 11). The Cu(I) and Ag(I) based catalysts **38a** or **38b** provide the best results with enantioselectivities >90% and yields >70%. The enantioselectivities decline upon use of nickel or palladium based BINAP catalysts **38c** and **38d** (30–80% ee).




**Scheme 11**. Lectka catalytic, asymmetric alkylation of imino esters with enol silanes.

A diastereoselective version of this reaction was also achieved by this group later in 1998.[35] As outlined in Scheme 12, both cyclic (*E*) and acyclic (*Z*) enol silanes afford tosyl-protected amino keto esters **41** in >70% yield and 46–99% ee. Diastereomeric ratios range from 3:1 (*anti*/*syn*, R=Et, $R_1$=Me) to 25:1 (*anti*/*syn*, R=Ph, $R_1$=Me).




**Scheme 12**. Lectka catalytic, diastereoselective iminoalkylation with enol silanes.

The proposed mechanism of action for the copper-catalyzed addition of enol silanes is outlined in Figure 5. The Cu(I)-tol-BINAP complex binds the imino ester **1a**, leading to complex **42**. The ligand selectively promotes alkylation with **32** on one face of the imine to form complex **43**. After silyl transfer, the amino ester **44** dissociates from the complex and the catalyst **38a** is regenerated for another cycle. This methodology was further improved to include more practical and readily removable protecting groups for the imine nitrogen such as SES and Ns from the *N*,*O*-acetals **7**.[36]

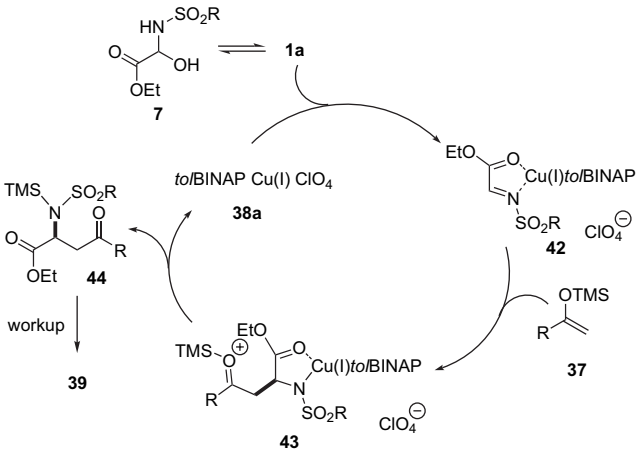


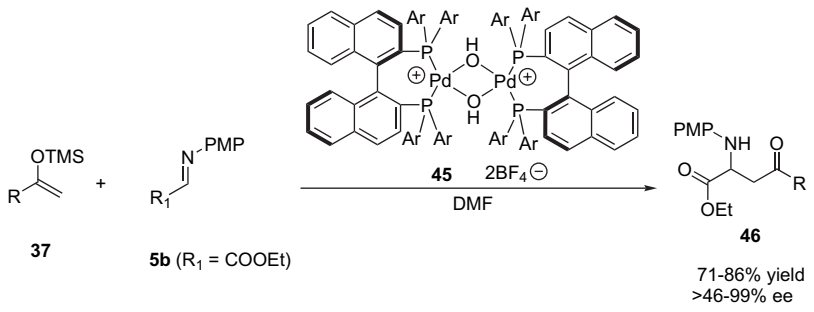

**Figure 5**. Catalytic cycle of Lectka iminoalkylation with enol silanes.

The Sodeoka group later reported similar results with a binuclear $[\{Pd(R)\text{-tol-BINAP})\text{-}(\mu\text{-OH})\}_2]^{2+}(BF_4^-)_2$ complex **45** and the PMP imino ester **5b** ($R_1$=COOEt, Scheme 13).[37] Initial attempts at this reaction generated $HBF_4$ in situ from the catalyst and enol silane. This $HBF_4$ catalyzes the alkylation of **5b** in a racemic fashion. Thus, removal of the water from the catalyst with molecular sieves affords the hydroxyl-bridged catalyst **45** and limits the formation of $HBF_4$. The yields and enantioselectivities are similar to that reported by Lectka[34] (45–95%, 53–90% ee, R=Ph, β-Np, $CH_3$, substituted Ph), however, the proposed catalytic mechanism is notably different. Sodeoka's proposed catalytic cycle incorporates a palladium enolate as the key intermediate (chiral nucleophile approach) similar to that proposed by Tomioka.[29] The Lectka approach, however, employs a chiral Lewis acid approach similar to Kobayashi[31] (Figs. 2 and 5). While both approaches are effective, the lack of substrate flexibility (i.e., R=aryl groups) is still a limitation of these methodologies.

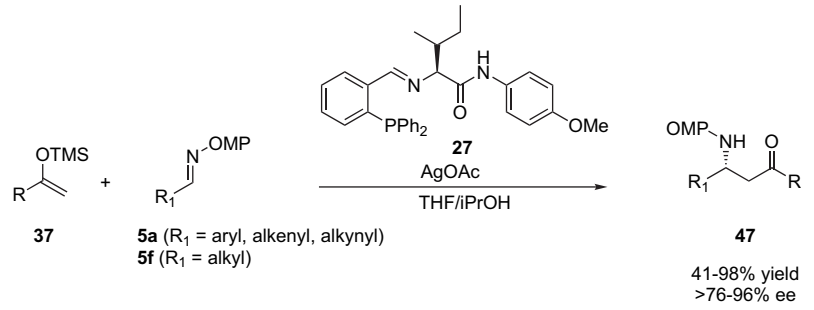
The Hoveyda group later improved the applicability of catalytic iminoalkylations with enol silanes.[27] Both methyl and phenyl enol silanes (**37**, R=Me or Ph) alkylate aryl and aliphatic OMP imines **5a** and **5f** in high overall yields and selectivity using the silver catalyst **27** (Scheme 14). This methodology affords aryl amines **47** ($R_1$=aryl, heteroaryl) in moderate yields (54–96%) with good enantioselectivity (76–98% ee) depending on the nature and substitution pattern of the aryl group. This methodology also applies to alkenyl imines as well as alkynyl imines ($R_1$=alkenyl, alkynyl, 47–98% yield, 88–92% ee). Most remarkably, the *aliphatic* amino ketones ($R_1$=alkyl) are obtained in yields of 41–60% (92–94% ee) despite the tautomerization side reaction (Scheme 6). This group also used this methodology with the Danishefsky diene to synthesize substituted piperidines in an asymmetric fashion.[38] The Hoveyda methodology stands as one of the most practical and versatile methods for catalytic enantioselective addition of enol silanes to imines.

### 3.3. Alkyl zinc reagents

Alkyl zinc reagents are one of the most common nucleophiles for alkylation of aldehydes.[39] While not as readily




**Scheme 13**. Sodeoka catalytic, enantioselective alkylation of imines with enol silanes.

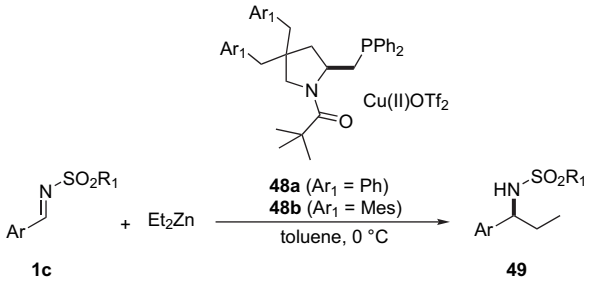



**Scheme 14**. Hoveyda Ag-catalyzed asymmetric Mannich reactions with enol silanes.

available as Grignard reagents or alkyl lithium reagents, several groups have successfully contributed to the catalytic, asymmetric addition of dialkyl zinc reagent to imines.

The Tomioka group was one of the first to successfully employ a chiral catalyst in the addition of a dialkyl zinc reagent to aryl sulfonyl imines **1c** (Ar=substituted Ph, α-Np, β-Np, 2-furyl).[40] Copper(II) triflate complexed with ligand **48a** catalyzes the addition of diethyl zinc to phenyl *N*-aryl sulfonyl imines **1c**. The enantioselectivity and yields depend on the electronic nature of the sulfonyl group ($R_1$). Electron-donating groups afford phenyl ethyl sulfonyl amines **49** in 94–95% yield and 89–94% ee. Electron-withdrawing groups (e.g., $R_1$=4-$NO_2$Ph), however, dramatically lower the yields to 22–67% and diminish the enantioselectivities as well (<70% ee). Tomioka attributed this loss in selectivity to the diminished binding potential of the sulfonyl nitrogen with the Cu(II) complex. Interestingly, other common chiral bisphosphine ligands such as BINAP and DIOP are completely ineffective at inducing chirality in this system. Tomioka further optimized this catalytic methodology in several ways: (1) manipulation of the ligand **48a** to mesityl ligand **48b**, (2) introduction of a readily cleavable SES group on the imine nitrogen ($R_1$=$CH_2CH_2TMS$), (3) changing the copper, and (4) changing the solvent.[41] The best results are outlined in Scheme 15, the mesityl ligand **48b** ($Ar_1$=2,4,6-trimethylphenyl) with $Cu(OTf)_2$ in toluene affords the ethyl aryl sulfonyl amines in 69–97% yield and 86–96% ee (Ar=substituted Ph, Np, furyl).

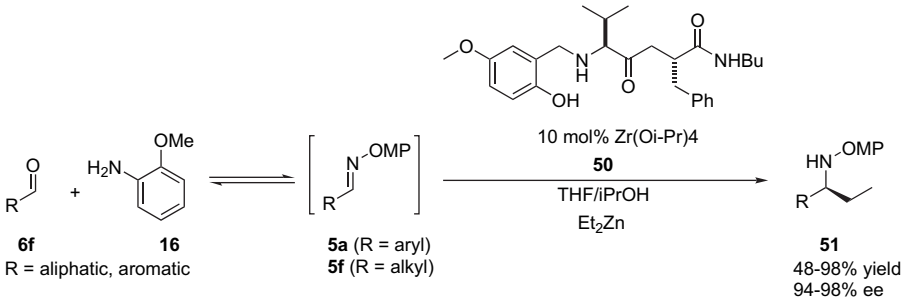
The Hoveyda group further improved upon the work of Tomioka by employing the use of a zirconium derived chiral catalyst **50**.[42] $Et_2Zn$, $Me_2Zn$, $Oct_2Zn$, or alkynylzinc selectively alkylate several aryl and heteroaryl OMP imines **5a** and **5f**[43] in the presence of catalyst **50**. Furthermore, catalyst



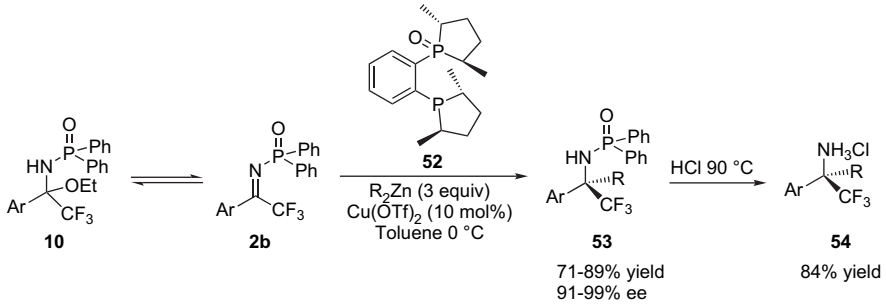

**Scheme 15**. Tomioka catalytic, asymmetric iminoalkylations with organozinc reagents.

**50** promotes the addition of dialkyl zinc reagents to *aliphatic* imines **5f**, generated in situ from alkyl aldehyde **6f** (R=propyl, pentyl, Bn, cyclopropyl, OH) and *o*-anisidine. The OMP-protected amines **51** are obtained in good yields (48–98%) and enantioselectivities (>90% ee) based on the nature of the R group.[44] Generally, aliphatic imines with an acidic α-proton suffer from the problem of enamine formation and subsequent addition to the electrophilic aldehyde or imine (i.e., Mannich or aldol type reactions, Scheme 16). Interestingly, limited side products (<2%) resulting from the addition of the enamine to either the aldehyde or the imine are detected. This work marks one of the few methods to asymmetrically alkylate aliphatic imines in good yields and enantioselectivity.

Much of the imine substrates for asymmetric dialkyl zinc reactions are aldimines. The Charette group recently reported a method to alkylate trifluoromethyl ketoimines **2b** with the copper(II) BozPhos catalyst **52**.[45] Both $Et_2Zn$ and $Me_2Zn$ alkylate the hemiaminals **10** in 71–85% yields and >90% ee (Scheme 17) in the presence of catalyst **52**. The cleavage of the resulting phosphonamide **53** is accomplished with




**Scheme 16**. Hoveyda catalytic, asymmetric iminoalkylations with organozinc reagents.



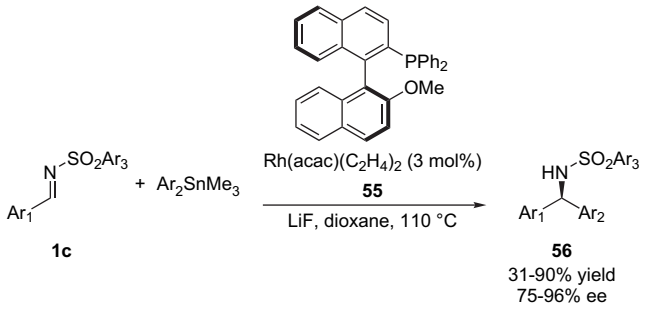

**Scheme 17**. Charette copper-catalyzed asymmetric addition of organozinc reagents to ketoimines.

concentrated HCl to afford the stereospecific trifluoromethyl amines **54** in good yield without racemization.

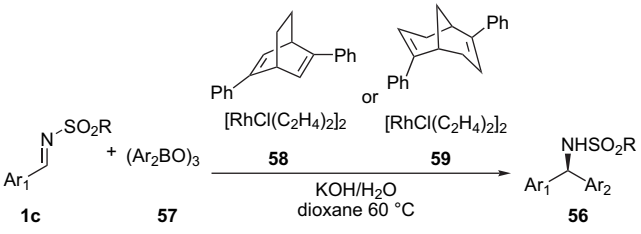
### 3.4. Nucleophilic arylations

**3.4.1. Aryl stannanes.** The most successful use of aryl stannanes in asymmetric iminoalkylation was performed by the Hayashi group.[46] A wide variety of trimethyl aryl stannanes react with the sulfonyl imine **1c** in the presence of catalyst **55** in 31–90% yield and 75–96% ee (Scheme 18). Slight improvements in enantioselectivity occur upon substitution of the methoxy group of the ligand with a 3,5-dimethyl-4-methoxyphenyl group. Despite the impractical nature of alkyl stannanes, the Hayashi group designed one of the first efficient syntheses of protected diaryl amines **56** using chiral catalysis. The usefulness and biological relevance of enantiopure, diaryl amines is well precedented.[47] The use of aryl boronic acid equivalents instead of aryl stannanes further improved this methodology.

While aryl boronic acids have been used extensively in Suzuki coupling reactions and other arylations,[48] only recently have they been used to alkylate imines. The Hayashi group was the first to enantioselectively arylate imines with boronic acid equivalents using chiral diene rhodium complexes such as **58** and **59**. Scheme 19 outlines the arylation conditions with **1c** affording diarylsulfonyl amines **56** in excellent yields (>90%) and enantioselectivities (>95%).[49] A further extension of this work exemplifies the practicality of this methodology as the easily removable nitrophenylsulfonyl group (R=4-$NO_2$Ph) replaces the ubiquitous toluenesulfonyl group (R=4-$CH_3$Ph). By altering the chiral ligand from **58** to **59**, the asymmetric alkylation of the nosyl imines results in >94% yield and >95% ee.[50] In addition, the deprotection of the Ns group is facile and high yielding (>95%) affording mixed diarylmethylamines in excellent yield over two steps.




**Scheme 18**. Hayashi catalytic, asymmetric arylation of imines with stannanes.




**Scheme 19**. Hayashi catalytic, asymmetric arylation of imines.

A reasonable explanation for the induction of chirality is offered by Hayashi as outlined in Figure 6. The aryl boroxines add to the chiral rhodium complex (**60**) followed by coordination of the aryl sulfonyl imine (complex **61**). The authors propose that the imine coordinates the rhodium in a fashion that minimizes the steric aryl/aryl interaction between the ligand and the aryl groups on the imine. After complexing the imine, the $Ar_2$ group alkylates the imine affording the Ns-(*S*)-diarylmethylamine **56** and catalyst **58**.

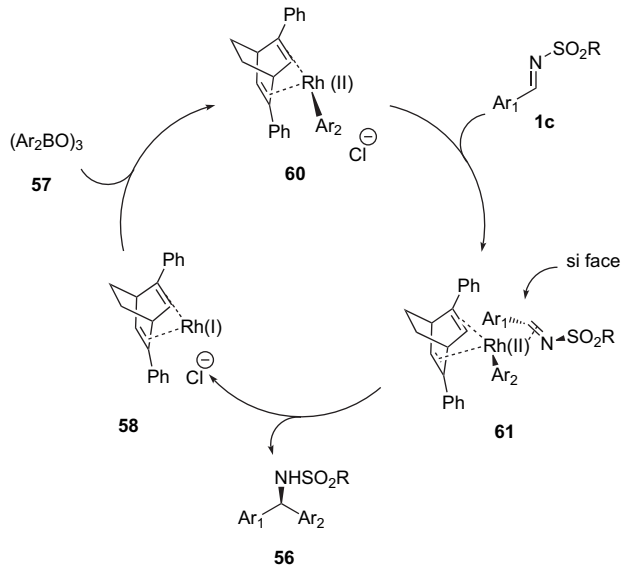



**Figure 6**. Catalytic cycle of Hayashi asymmetric arylation of imines.

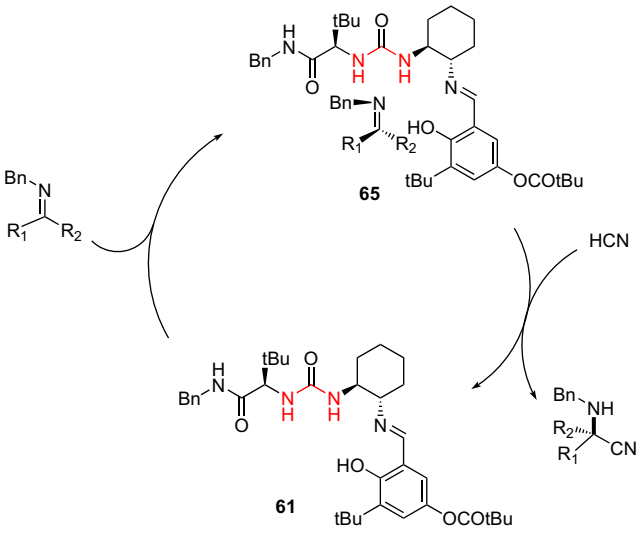



**Figure 7**. Proposed catalytic cycle of Jacobsen asymmetric Strecker reaction.

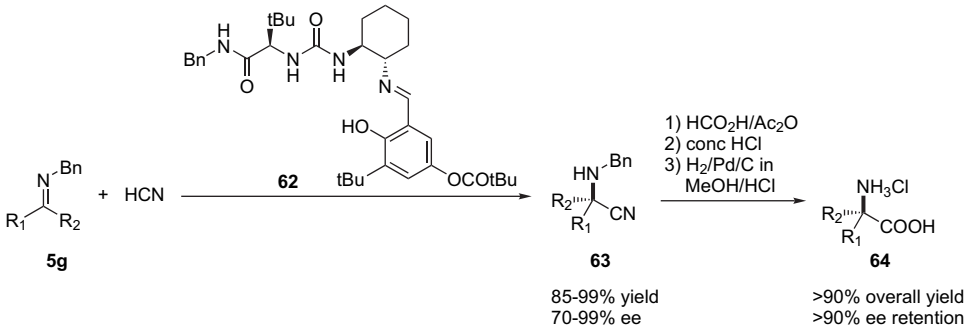
### 3.5. Cyanide based nucleophiles (Strecker reaction)

The Strecker reaction is perhaps the most classical and efficient method to synthesize natural and unnatural amino acids from imines.[51] The Jacobsen group designed one of the first catalytic, asymmetric versions of this reaction.[8] Through structure based optimization, Jacobsen designed Schiff base **62** as a chiral catalyst for the hydrocyanation of alkyl and aryl aldimines and ketoimines **5g** (Scheme 20). Interestingly, catalyst **62** is neither Lewis acid based, nor does it directly interact with the nucleophile indicating that the reaction mechanism lies outside most of the conventional catalytic cycles outlined in this review. Kinetic studies indicate that the reaction is first order with respect to catalyst and HCN and saturation dependent with respect to the imine. This result implies that a reversible imine-catalyst complex, presumably via H-bonding, is most likely responsible for induction of chirality. Deletion studies indicate that the catalyst **62** binds both aldimines ($R_2$=H) and ketoimines ($R_2$=$CH_3$) via the two urea hydrogen atoms (in red, Fig. 7). These hydrogen bonds lock the imine in a *Z* conformation where both the imine *N*-benzyl group and the alkyl/aryl groups ($R_1$) are directed away from the catalyst (complex **65**, Fig. 7). In addition, the unhindered side of the imine is available for attack by HCN. The catalyst promotes the alkylation of both aldimines and ketoimines in excellent yields (mostly >90%) and enantioselectivities (>90% in most cases). Despite reports of instability of nitrile **63**, the subsequent hydrolysis and deprotection of the benzyl group are achieved without epimerization at the α-center of the amino acid **64** (Scheme 20).

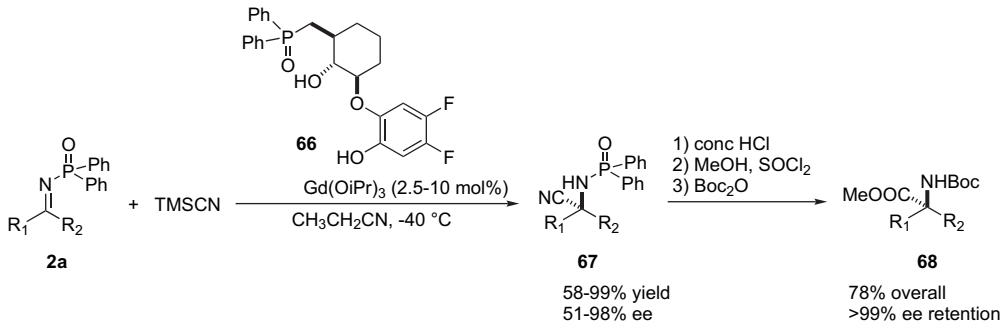
A more conventional chiral Lewis acid approach was employed by the Shibasaki group as they reported a lanthanide based catalyst **66** in an asymmetric Strecker reaction (Scheme 21).[52] Some benefits of this methodology are the improved stability of the nitrile **67** as well as wide substrate variability ($R_1$=Ph, Np, pentyl, $^i$Pr, cinamoyl; $R_2$=Me, Et). Aliphatic, aromatic, and olefinic ketoimines **2a** are alkylated with TMSCN in good yields (58–99%) and enantioselectivities (>88% most cases). Conversion of the Strecker adducts to protected amino acids is achieved in high yields affording *N*-Boc methyl esters **68** in 78% overall yield with complete retention of stereochemistry (Scheme 21).

### 3.6. Nucleophilic allylation

Several successful methods have been developed for catalytic, asymmetric allylation of imines. Consequently, each method has a unique catalytic mechanism with equally effective results. One of the first successful attempts at

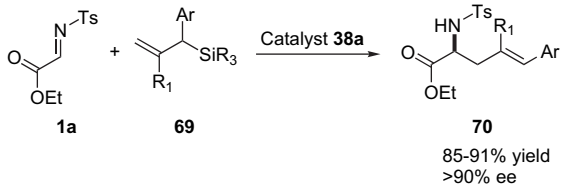



**Scheme 20**. Jacobsen catalytic, asymmetric Strecker reaction.




**Scheme 21**. Shibasaki catalytic, asymmetric Strecker reaction.

catalytic, asymmetric allylation of imines was accomplished by the Lectka group using arylallyl silanes **69**.[36] This chiral Lewis acid approach utilizes catalyst **38a** to obtain olefinic amino esters **70** in good yields (85–91%), but only allyl silanes with aromatic groups ($R_2$=Ar) provide good enantioselectivity (>90% ee) (Scheme 22).




**Scheme 22**. Lectka catalytic, asymmetric allylation of imines.

The Morken group discovered a creative chiral nucleophile approach for catalytic asymmetric allylation of imines. The chiral diborane **72**, generated in a catalytic, asymmetric fashion, alkylates silyl imine **4a** ($R_1$=Ph) or the unsubstituted imine **5e** (Scheme 23).[22] The diborane is generated by a catalytic asymmetric diboration of substituted allenes using 2.5 mol % of the $Pd_2(dba)_3$ and 6 mol % phosphonamide **71** as the chiral catalyst. The diborane **72** reacts with aromatic or olefinic imines **4a** and **5e** stereospecifically ($R_1$=aryl, alkyl, alkenyl). Through acetylation and oxidation, β-amino ketones **73** are obtained in 30–70% yields and >87% ee.

The proposed transition states for this asymmetric allylation are displayed in Figure 8. The unsubstituted imine **5e**, generated in situ from the aldehyde and $NH_4OAc$, presumably reacts in the transition state A to afford the (*R*) configured amino ketone **74**. In fact, an X-ray crystal structure of aminoborane **74** further supports transition state A as the predominant pathway for the asymmetric allylation. Due to steric, diaxial interactions, the product from transition state B (**75**) is not observed to any appreciable extent under the reaction conditions.

The Yamamoto group also recently devised catalytic, asymmetric allylation methodology utilizing a chiral nucleophile approach.[53] Tetraallylsilane alkylates aldimines **5a**,**b**,**d** under mild conditions in the presence of a bis π-allylpalladium catalyst **76** at 0 °C. A variety of *N*-benzyl, OMP, and PMP imines are allylated in high yields (68–98%) and enantioselectivities (52–94% ee) as outlined in Scheme 24. The catalytic cycle for these allylations is outlined in Figure 9. The Lewis acid (Pd in this case) coordinates the allyl group upon activation by TBAF. This Pd–allyl complex **78** is the chiral nucleophile that coordinates and reacts with the imine in an enantioselective manner (complexes **79** and **80**, Fig. 9).

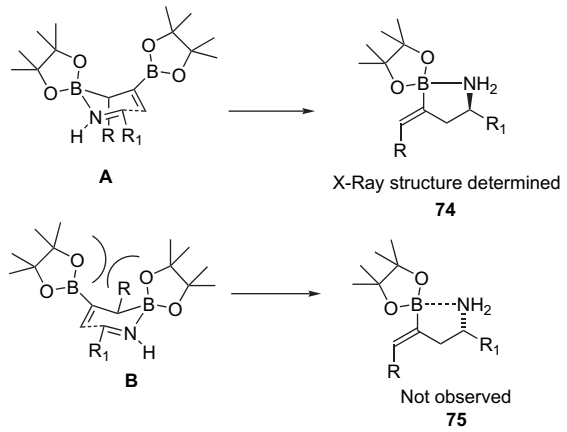
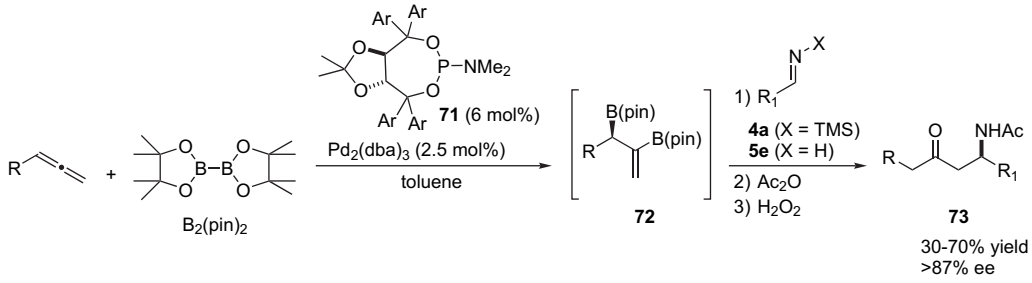
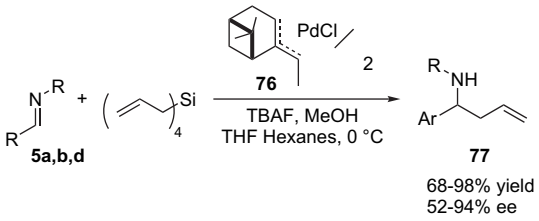



**Figure 8**. Proposed transition state for Morken allylation of imines.




**Scheme 23**. Morken catalytic, enantioselective diboration and allylation of imines.




**Scheme 24**. Yamamoto catalytic, asymmetric allylation of imines.

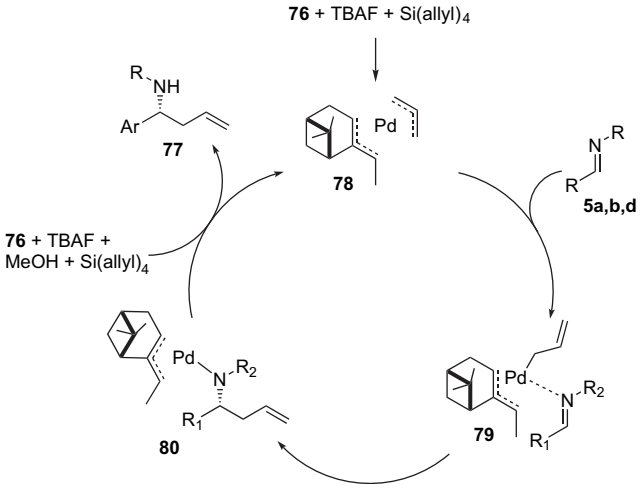
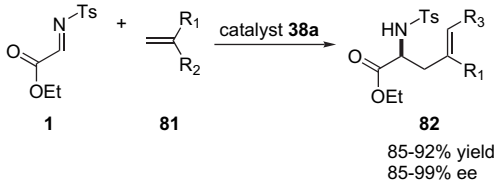



**Figure 9**. Yamamoto proposed allylation catalytic cycle.

Reductive elimination of the amine **77** from complex **80** occurs followed by addition of another equivalent of the allyl group for another cycle.

### 3.7. Miscellaneous nucleophiles

**3.7.1. Olefins (imino ene reaction).** Few examples of catalytic asymmetric ene reactions exist in the literature.[54] In 1998, the Lectka group developed methodology that stands as one of the few examples of a catalytic enantioselective imino ene reaction.[55] Aliphatic, aromatic, and heteroaromatic olefins alkylate imino ester **1a** in the presence of Cu(I)tol-BINAP complex **38a** in 85–92% yield and 85–99% ee (Scheme 25). In addition, a diastereoselective version of this reaction as well as mechanistic insight into this reaction were reported in a later publication.[36] This methodology resulted in the synthesis of several unnatural amino acid derivatives as well as the first catalytic, enantioselective synthesis of several tryptophan derivatives.




**Scheme 25**. Lectka catalytic, enantioselective imino ene reaction.

**3.7.2. Aldehyde couplings.** In an elegant case, the Miller group devised methodology to alkylate acyl imines with the *aldehydic* carbon of arylbenzaldehydes. In the presence of base, the aldehyde **6b** reacts with the catalyst **84** to form the Zwitterionic intermediate **86** (Fig. 10). This intermediate alkylates the acyl imine **3a** ($Ar_1$ and $Ar_2$=Ph) affording keto-amides **85** (Scheme 26). This methodology generates biaryl keto-amides **85** in high yield (57–100%) and high enantioselectivity (75–83% ee and >98% ee upon recrystallization).[56] The presumed mechanism of this reaction falls under the chiral nucleophile approach as shown in Figure 10. The presence of base leads to the formation of the Zwitterionic species **86** by addition of the aldehyde to the thiazole ring. This Zwitterion then coordinates the acyl imine prior to alkylation. Upon alkylation, the intermediate **86** collapses and the catalyst is regenerated. While there was no mention of substrate constraints, the modular design of the ligand lends itself to further optimization of this methodology.

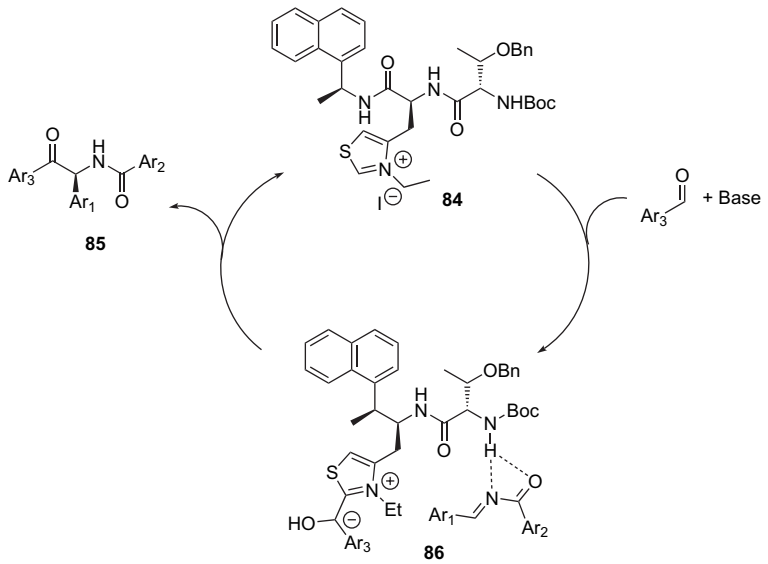
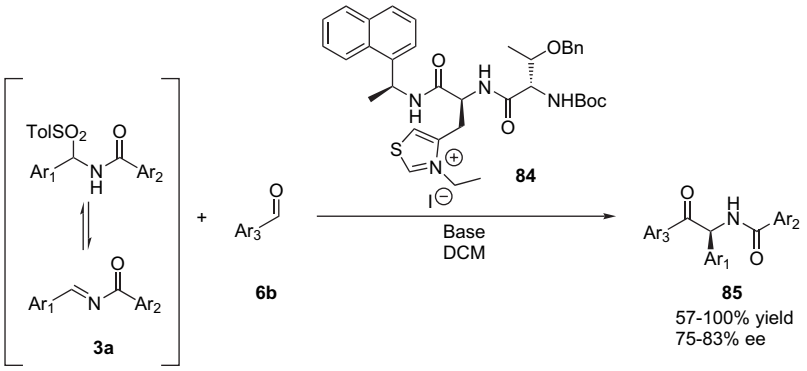
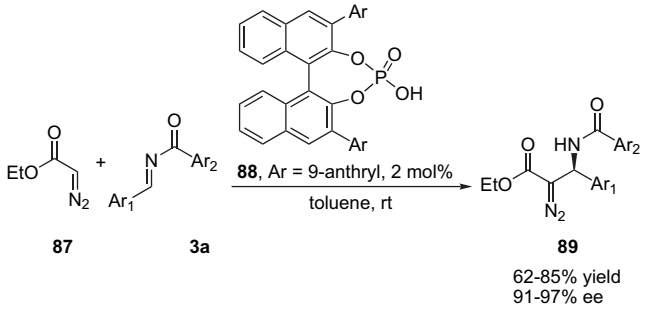



**Figure 10**. Proposed catalytic mechanism for Miller aldehyde–imine cross-coupling.




**Scheme 26**. Miller catalytic, enantioselective aldehyde–imine cross-couplings.

**3.7.3. α-Diazoesters.** The Terada group devised a unique method to synthesize β-amino esters using a phosphate-catalyzed Friedel–Crafts type addition of α-diazoesters **87** to acyl imines **3a**. The general reaction is outlined in Scheme 27. The chiral phosphonate **88** is clearly responsible for induction of chirality, but the mechanism for this reaction is still under investigation. The authors propose a chiral Brønsted acid catalyzed reaction, a unique approach utilized infrequently in iminoalkylations.[6] This methodology provides the means to make α-diazoesters **89** in 62–85% yield and 91–97% ee.




**Scheme 27**. Terada catalytic, asymmetric alkylation of acyl imines with α-diazoester.

## 4. Applications for catalytic, asymmetric alkylation of imines

Ultimately, the methodologies discussed in this review are merely academic if they cannot be applied to the fields of medicinal chemistry, process chemistry, or natural product synthesis. Consequently, catalytic, asymmetric alkylations have shown utility in the synthesis of biologically active molecules as well as natural products. A few examples will be discussed in the sections below.

### 4.1. Diarylmethylamines

The diarylmethylamine moiety (in red, Fig. 11) is a common pharmacophore for multiple drug classes such as antidepressants, calcium channel blockers, and $H_1$ receptor antagonists. Much of the drugs incorporating this moiety such as cetirizine (Zyrtec®), tianeptine, and lomerizine either have two identical aryl groups or a racemic center (Fig. 11). These popular medications were developed as racemates because at the time the technology did not permit a feasible, scalable synthesis of the pure enantiomers. The discriminatory nature of all enzymes would lead one to believe that enantiopure versions of these drugs may be more potent than the racemates. With the development of the Hayashi method of catalytic, asymmetric iminoarylation,[49,50] the diaryl portion of cetirizine and tianeptine can be synthesized enantioselectively in high yield. Scheme 28 outlines the efficient synthesis of the 4-chlorophenyl phenylmethylamine moiety via catalytic, enantioselective arylation of the nosyl imine **1c** ($Ar_1$=4-chlorophenyl) using catalyst **59**. Deprotection of the nosyl group with thiophenol and $K_2CO_3$ in DMF results in a 96% yield of (*S*)-phenyl (4-chlorophenyl)-methylamine **91** without any epimerization of the chiral center (98% ee).

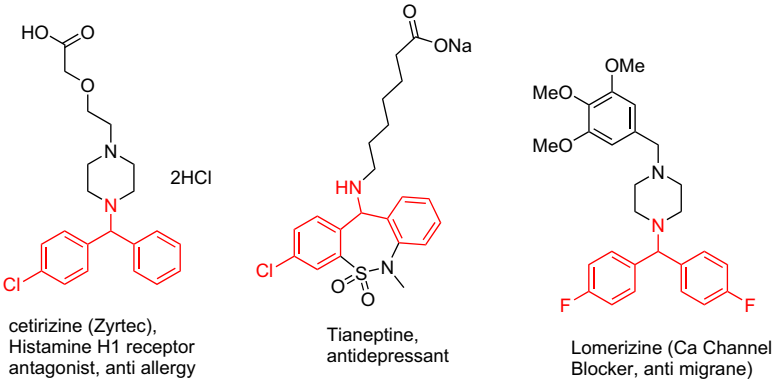
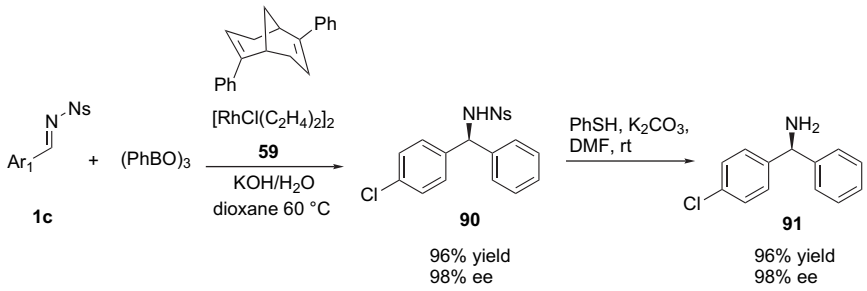



**Figure 11**. Drugs with diarylmethylamine moiety.



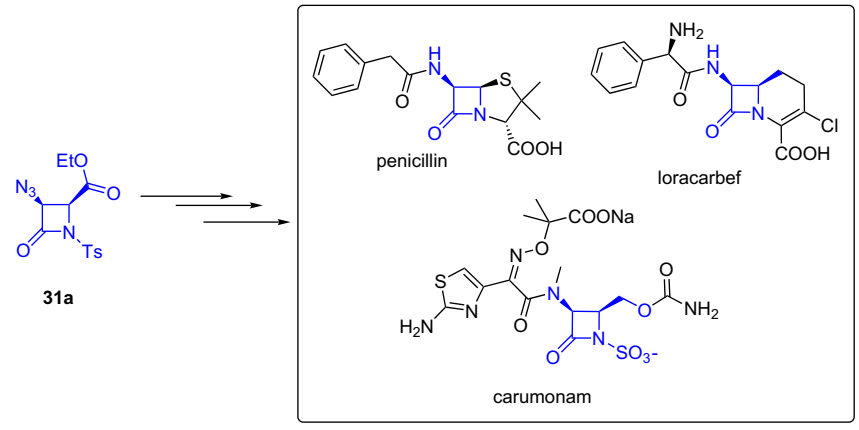

**Scheme 28**. Enantioselective synthesis of diarylmethylamine **91**.

## 4.2. β-Lactams

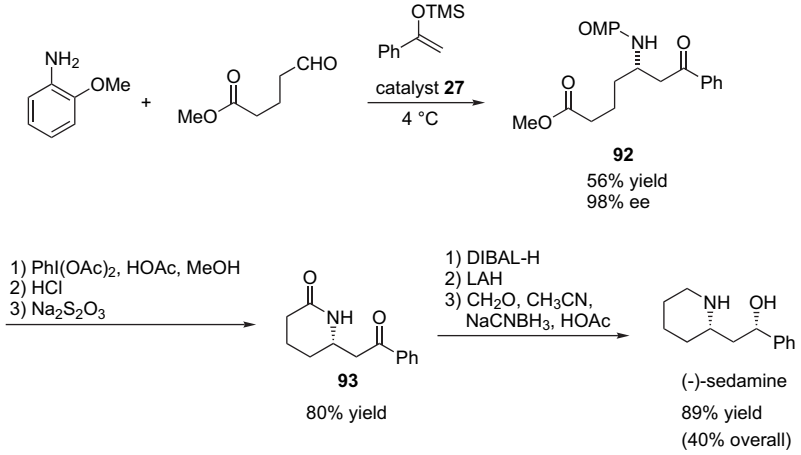
The biological relevance and historical significance of β-lactams as antibiotics is indisputable.[57] Due to the ever increasing number of cases of bacterial resistance,[58] the need for new antibiotics is more than warranted. Since the discovery of the basic structural pharmacophore of penicillin, hundreds of groups have contributed to the synthesis of β-lactams. Despite this dramatic effort, however, very few catalytic, enantioselective methods exist for β-lactam synthesis. The Lectka methodology outlined in Section 3.1.3 affords a practical means to synthesize β-lactams with medicinal properties. The Lectka asymmetric β-lactam synthesis affords compound **31a** (R=$N_3$) in 47% yield, 98% ee, and 25:1 dr from readily available starting materials.[33] One can clearly see the utility of **31a** (in blue, Scheme 29) as an intermediate in the synthesis of antibiotics such as penicillin and other carbapenem derivatives (i.e., loracarbef and carumonam).

## 4.3. (−)-Sedamine

The piperidine derivative (−)-sedamine is a member of the *Lobelia* genus of plant alkaloids. Over time, the lobelia extracts have been used to treat wide variety of respiratory ailments.[59] Several groups have contributed to the synthesis of sedamine in overall yields below 20%.[60,59] Using catalytic asymmetric iminoalkylation, the Hoveyda group synthesized sedamine in three steps with a 40% overall yield (Scheme 30). The key step is the silver-catalyzed alkylation




**Scheme 29**. β-Lactam based antibiotics.




**Scheme 30**. Hoveyda total synthesis of sedamine.

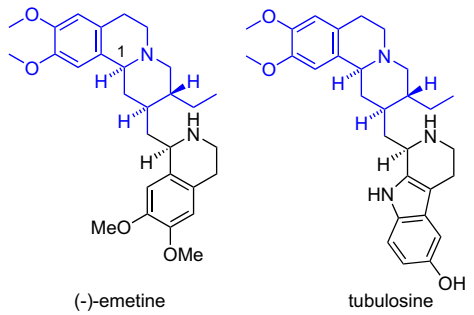
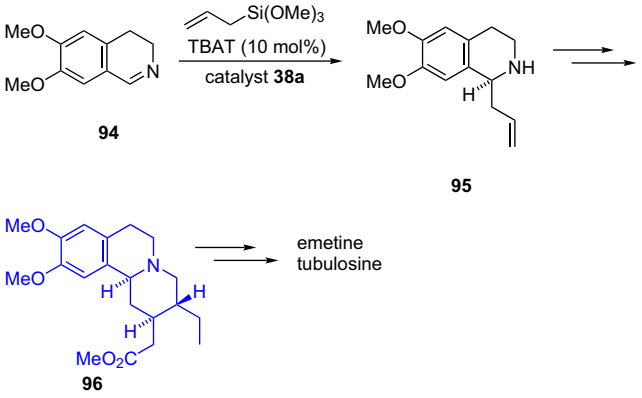



**Figure 12**. Natural products (−)-emetine and tubulosine.

of an aliphatic imine (generated in situ from *o*-anisidine and 5-oxo-pentanoic acid methyl ester) with enol silane **37a** (R=Ph) affording β-amino ketone **92** in >98% ee and 56% yield. Concomitant removal of the OMP and intramolecular cyclization affords compound **93** in 80% yield. Reduction of the amide and ketone affords the enantiomerically pure (−)-sedamine in 40% overall yield.[27]

### 4.4. (−)-Emetine and tubulosine

The isoquinoline alkaloids (−)-emetine and tubulosine (Fig. 12) have shown biological activity against several cancer cell lines[61] as well as antiprotozoic activity.[62] The Itoh group devised methodology to synthesize a key intermediate in the synthesis of these alkaloids using a critical catalytic asymmetric allylation reaction. Imine **94** is selectively allylated with allyl trimethoxysilane in the presence of Cu(I)tol-BINAP **38a** as the catalyst. The stereocenter at the C-1 of the isoquinoline ring is formed in 67% yield and 97% ee (compound **95**, Scheme 31).[63] After several steps, intermediate **96**, a precursor to both emetine and tubulosine (in blue, Fig. 12), is synthesized in 22% overall yield. Prior to this publication, compound **96** could only be synthesized in 3% yield over 12 steps.[64]




**Scheme 31**. Synthesis of key intermediate toward (−)-emetine and tubulosine.

## 5. Conclusions

Enantioselective catalysis is one of the most efficient methods to conduct the organic synthesis of chiral molecules. The past decade has witnessed remarkable developments in the field of catalytic, asymmetric iminoalkylation. Contributions from many academic groups have led to dramatic improvements in the synthesis of natural and unnatural α-amino acids, β-ketoamines, β-lactams, select natural products, and chiral amines. With improvements in practicality and an eye toward biological relevance, these groups will undoubtedly continue to advance the field in a direction that benefits academic chemists, natural product chemists, process chemists and medicinal chemists alike.

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