

Catalytic, Enantioselective Alkylation of α -Imino Esters: The Synthesis of Nonnatural α-Amino Acid Derivatives

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Abstract: Methodology for the practical synthesis of nonnatural amino acids has been developed through the catalytic, asymmetric alkylation of α -imino esters and N,O-acetals by enol silanes, ketene acetals, alkenes, and allylsilanes using chiral transition metal-phosphine complexes as catalysts (1-5 mol %). The alkylation products, which are prepared with high enantioselectivity (up to 99% ee) and diastereoselectivity (up to 25:1/anti:syn), are protected nonnatural amino acids that represent potential precursors to natural products and pharmaceuticals. A kinetic analysis of the catalyzed reaction of alkenes with α -imino esters is presented to shed light on the mechanism of this reaction.

Introduction

One of the paramount goals of asymmetric catalysis has been the synthesis of optically pure, nonnatural α -amino acids for use in natural products, peptide, and pharmaceutical chemistry.¹ While a spectrum of methods is available for this purpose, potentially one of the most attractive approaches involves the asymmetric alkylation of imines² and *N*-acetals.³ One very successful imine alkylation strategy that has recently emerged is the catalytic, asymmetric Strecker reaction,⁴ in which a highly oxidized nucleophile such as hydrogen cyanide or its synthetic equivalent is added to imines asymmetrically to produce α -cyanoamine products that can be hydrolyzed to the corresponding optically enriched α -amino acids. An alternative approach, which we employ, involves an imine containing a highly oxidized carboalkoxy substituent, such as an α -imino

ester, first used as precursors to amino acids in groundbreaking work by Weinreb.5

Our recent work has focused on the synthesis of enantioenriched *a*-amino acid derivatives through the catalytic asymmetric alkylation of α -imino esters 1 with a variety of carbonbased nucleophiles using late-transition metal bis(phosphine) complexes as catalysts (eq 1, pathway A).⁶ A complementary system reported by Sodeoka for α -imino ester alkylation using a Pd(II)-based complex that operates through the catalytic generation of enolates is contemporaneous with our work.^{2b} Our catalyst system has also been fruitfully used by others on closely related reactions.⁷ Additionally, we have also developed a practical, preparative scale synthesis of α -amino acid derivatives using hydrolytically stable N,O-acetals 9 (eq 1, pathway B) instead of imines with minimal loss in selectivity or yield.8 Our first contribution concerned the alkylation of α -imino esters by enol silanes (eq 1, pathway A, Nu = 2).⁶ In a related communication, we reported the first example of a catalytic, enantioselective imino ene reaction (eq 1, pathway A, Nu = **11**) to generate enantio-enriched allylic amino acids **4**.^{9,10} Herein

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we summarize the methodology involved in our α -amino acid syntheses and report a new, alternative method to synthesize allylic amino acids via asymmetric allylation of α -imino esters (eq 1, pathway A, Nu = 17).¹¹ Furthermore, we present a kinetic study of the ene reaction of α -imino esters.



Results and Discussion

Enantioselective Alkylation of Imino Esters. For our initial investigations into asymmetric imino alkylations, we chose to examine α -*N*-silvlimino esters **1** with the view that the silvl group would be easily removable in a subsequent deprotection step. However, the reaction of **1a** with enol silane **2a** ($R_1 =$ Ph; $R_2 = H$), catalyzed by a number of phosphine-based metal complexes (3) at -78 °C, led exclusively to racemic products. The nonselectivity in this reaction was attributed to a high background rate and potential cis-trans isomerism about the C=N bond that can interfere with metal binding. Although discouraged, we reasoned that by changing the substituents on the α -imino ester, background rates could be reduced. We then decided to investigate tosyl imine 1b,¹² aware that the substituent modifications in asymmetric catalysis can provide the difference between a successful or an unsuccessful reaction. A notable uncatalyzed reaction rate in THF solution at -50 °C between 1b and 2a was initially a cause for some concern. Generally speaking, reactions that have uncatalyzed rates at temperatures of interest are poor candidates for asymmetric catalysis. However, to our surprise, slow addition of 1.1 equiv of enol silane 2a over the course of 2 h into a solution of the α -imino ester 1b containing 10 mol % (*R*)-BINAP•AgSbF₆ $(3a)^{13}$ at -78 °C gave the protected amino acid 4a (eq 2, R = Ph) in 95% yield and 90% ee, implying that the catalyzed rate must be at least one order of magnitude faster than the background reaction under these conditions (eq 2, Table 1, entry 1). The use of 1 equiv of catalyst 3a led to identical selectivity (90% ee, entry

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Table 1. Enantioselective Alkylation of **1b** with Enolsilanes Catalyzed by Chiral Phosphine Complexes^a

entry ^b	nucleophile	catalyst	T(°C)	% yield	% ee
1	2a : $R = Ph; R' = Me$	3a	-78	95	90
2^c	2a : $R = Ph; R' = Me$	3a	-78	96	90
3	2a : $R = Ph; R' = Me$	3a	-40	97	67
4^d	2a : $R = Ph; R' = Me$	3b	-78	91	80
5	2a : $R = Ph; R' = Me$	3c	-78	95	89
6^e	2a : $R = Ph; R' = Me$	3d	0	95	98
7	2a : $R = Ph; R' = Et$	3d	0	93	96
8	2b : $R = OPh; R' = Me$	3d	-78	83	72
9	2c : $R = 4$ -MeOPh; $R' = Me$	3a	-78	94	86
10	2c : $R = MeOPh; R' = Me$	3d	0	96	98
11	2d : $R = t$ -Bu; $R' = Me$	3a	0	70	75
12	2d : $R = t$ -Bu; $R' = Me$	3d	0	65	90
13	2e : $R = 3$ -NO ₂ Ph; $R' = Me$	3d	0	87	94
14	2f : $R = 3,4$ -Cl ₂ Ph; $R' = Me$	3d	0	92	89

^{*a*} Enantiomeric excesses were determined by a CHIRALCEL OD chiral HPLC column unless otherwise noted. ^{*b*} Reactions were run with 0.4 mmol imine **1b** and 0.04 mmol catalyst (10 mol % metal salt, 10.5 mol % BINAP or Tol-BINAP at the specified temperature for 24 h in THF). ^{*c*} One equivalent of catalyst was used. ^{*d*} Reaction run in CH₂Cl₂. ^{*e*} 2 mol % catalyst was used.

2) and also suggested that the uncatalyzed reaction plays a minor role in affecting asymmetric induction under these conditions. When we conducted this reaction at -40 °C, the selectivity decreased to 67% ee (entry 3). The complex (*R*)-BINAP•Pd(ClO₄)₂•(CH₃CN)₂ (**3b**) afforded somewhat lower ee (80%, entry 4). A mechanistically distinct version of this catalyst system was employed by Sodeoka and co-workers in their studies.^{2b}



The straw-yellow complex (*R*)-BINAP•CuClO₄•(CH₃CN)₂ (**3c**)¹⁴ performed as well as **3a** (entry 5), whereas (*R*)-Tol-BINAP•CuClO₄•(CH₃CN)₂ (**3d**) provided the best results, giving high yield (95%) and selectivity even when this reaction was conducted at 0 °C in the presence of only 2 mol % catalyst (98% ee, entry 6). This increase in selectivity when using (*R*)-Tol-BINAP in preference to (*R*)-BINAP was also noted in the recent findings of Carreira in a Cu(II)-phosphine catalyzed asymmetric aldol reaction.¹⁵ Interestingly, a bulkier triethylsilyl (TES) group on the enol silane does not adversely affect the rate or the enantioselectivity of the reaction (entry 7). A noteworthy feature of the reaction is that enol silanes react with good selectivity, whereas silyl ketene acetals, classic substrates

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Figure 1. Reactive complexes for enantioselective reaction.

of aldol methodology, appear to possess high uncatalyzed rates at the temperatures we screened, leading to lower selectivity (entry 8).

We also determined that the use of slightly more reactive enol silane 2c led to 86% ee at -78 °C with 10 mol % Ag(I)based catalyst 3a (eq 2, Table 1, entry 9) and 98% ee with Cu(I)based catalyst 3d (entry 10). Other enol silanes 2d-f (Table 1) were also examined. For example, the enol silane 2d derived from pinacolone gave much lower yield and reduced ee with catalysts 3a and 3d (entries 11, 12). In general, aliphatic enol silanes gave slightly lower ee's. Competition experiments, in the presence of 10 mol % catalyst **3d**, showed that nucleophile 2c reacted the fastest, whereas nucleophiles 2e and 2f reacted slower, correlating well with the relative nucleophilicity of the enol silanes. The use of enol silanes 2e and 2f led to compounds 4e and 4f, precursors to γ -oxo- α -amino acids which are currently of interest as inhibitors of kynurenine-3-hydroxylase (entries 13 and 14).¹⁶These synthetic precursors are often crystalline, and one recrystallization from ether/hexane afforded enantiomerically pure materials (>99% ee). The tosyl group can be removed from the products 4 by treatment with phenol in a refluxing solution of HBr/AcOH, followed by addition of water. For example, product 4a led to the corresponding amino acid in 75% chemical yield with no detectable racemization (eq 3).¹⁷ Many acid-sensitive functional groups are not stable to these strongly acidic conditions, and a practical synthesis of γ -oxo- α -amino acids 5 using easily removable sulfonamido groups is discussed below.



Structure of Catalyst 3c. Interesting reports on the intermediacy of Pd(II)- and Cu(II)-based enolates in catalytic asymmetric imine additions and aldol reactions appeared at the time of our first submissions in this area and prompted us to examine whether they might be involved in our system. As postulated above, we believe that chiral Lewis acid complexes 3 chelate imino esters 1, activating them for enantioselective addition (Figure 1, structure A).

While our initial report was under review, Sodeoka et al. described the use of binuclear Pd(II) catalysts for the enantioselective alkylation of *N*-aryl α -imino esters **1e** with enol silanes in enantiomeric excesses as high as 93%. Exhaustive physical studies (NMR and MS) identified bimetallic complex structure B (Figure 1), containing a metal-based enolate, as a likely reactive intermediate.¹⁸ After noting our use of related anhydrous dicationic Pd(II) catalyst 3b in reactions of 1b, they attempted to apply their chiral enolate procedure of Pd(II)-aquo complexes using N-tosyl imino ester 1b and were surprised to discover that no asymmetric induction was observed in the reaction products over a range of temperatures and changes in solvent.¹⁸ They ascertained that these Pd(II)-aquo complexes, with their acidic protons, were nonselectively catalyzing the addition reaction of 1b with enol silanes and that exclusion of water to form a dicationic Pd(II) complex was necessary to attain selectivity with imino ester 1b, per our results. In subsequent experiments, Sodeoka et al. reported that N-aryl imino esters 1e proved to be poor substrates for activation with catalyst 3b,¹⁸ a result independently confirmed in our laboratories. Their NMR investigation of this reaction showed peak broadening in the signals attributed to N-aryl imino esters when combined with catalyst 3b, an effect ascribed to strong coordination between the imine and palladium center (but evidently not fulfilling the requirements for asymmetric induction). Without question, the substituent on the imine-N plays a critical role in controlling both the selectivity and the reaction mechanism.

Carreira et al. have postulated that both Cu(I) and Cu(II) enolates add enantioselectively (with ee's up to 94%) to aldehydes employing a complex derived from Tol-BINAP and Cu(I) and Cu(II) fluorides formed in situ (Figure 1, structure C).15 A subsequent detailed mechanistic study employing React IR documented the involvement of Cu-based enolates in Carreira's system.^{15a} For our part, several experiments were performed to discern whether a Cu(I) enolate played a role as an active nucleophile in our reaction. Treatment of a 1 mM solution of enol silane 2a in CD_2Cl_2 with 1 equiv of catalyst 3d produced no discernible change in the ¹³C or ¹H NMR spectra of the enolate over the course of 1 week. Keeping in mind that we had demonstrated a chelate-based interaction between imino ester 1b and the catalyst 3c by IR spectroscopy (see below),^{6a} our results are consistent with catalysts 3 working as classical Lewis acids. Nevertheless, this result does not rule out the possibility of a small, but kinetically significant, quantity of metal enolate in our reaction. To force the issue, a putative copper enolate was formed by adding 1 equiv of KH to acetophenone in THF, followed by metal metathesis with (PPh₃)₂•CuClO₄•(CH₃CN)₂ and precipitation of KClO₄. This brown mixture was then added to a solution of the imine 1b in THF at low temperature and allowed to warm. After several hours of stirring, no product formation occurred. Upon quenching, only acetophenone and a polar, unidentified polymeric solid were isolated. These results led us to conclude that a Cu(I) enolate was probably not the active species in the alkylation of imino ester 1b.

The potential ease of interconversion between Cu(I) and Cu(II) must also be taken into account.¹⁹ To our surprise, a similar, although somewhat less effective, catalyst could also be generated by mixing Cu(ClO₄)₂ with (R)- or (S)-BINAP in

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Scheme 1. Proposed Catalytic Cycle for Enantioselective α -Imino Ester Alkylation



THF. This catalyst afforded product 4a in 85% ee under the conditions of our screen (versus 89% ee with 3c). In addition, major ligand-based byproducts of this reaction were identified as the mono- and bis(phosphine) oxide of BINAP (BINAPO).²⁰ To determine the source of oxygen in this phosphine oxidation, $Cu(ClO_4)_2$ was added to (S)-BINAP in a THF solution to which a slight excess of water enriched in H218O had been added. Workup and MS analysis of the BINAPO byproduct showed a corresponding isotopic incorporation of ¹⁸O into the phosphine oxide moiety,²¹ implying that a small amount of adventitious water is the oxygen source when BINAP is oxidized by Cu(ClO₄)₂.²² We are aware that bisphosphine monoxides can act as ligands in Lewis acid-catalyzed reactions,23 and for this reason, we employed both Cu(I)• and Cu(II)•BINAPO complexes in the alkylation of 1b. These catalysts led to racemic products 4, implying that only Cu(I)•BINAP is the active catalyst in our system, albeit present in small amounts when a Cu(II) salt is employed as a starting material. Remarkably, the other contaminants, and potentially competing catalysts, do not interfere with selectivity to an appreciable extent.

Additionally, the UV spectra of catalysts **3c** and **3d** derived from either Cu(I) or Cu(II) salts appeared virtually identical, with features characteristic of Cu(I) (including the lack of d–d absorption bands indicative of Cu(II)). Similarly, NMR spectra showed none of the expected paramagnetic broadening associated with the use of Cu(II), even when Cu(ClO₄)₂ was the starting copper salt. The structure of **3c** was finally determined by X-ray crystallography, as reported in our earlier communication.^{6b} When single crystals of catalyst **3c** were redissolved

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Figure 2. Theoretical calculations of model imine 1c.

in THF or CH_2Cl_2 , a fully competent catalyst solution was formed. We also found that the catalyst could be stored in the solid state under argon indefinitely for ease of use.

Mechanism of Catalytic Enol Silane Imino Alkylation. A proposed catalytic cycle for our reaction is depicted below in Scheme 1. The first step is the formation of an activated imine/ Cu(I) complex 6b (five-membered chelate) which rigidifies the system, minimizing the degrees of freedom of the imine. Evidence for chelate formation in the catalyzed reaction (eqs 1, 4) was obtained by FTIR spectroscopy. Upon the addition of 1 equiv of catalyst 3c, the ester carbonyl band of 1b at 1735 cm⁻¹ shifted by -38 cm⁻¹ to 1697 cm⁻¹, and the C=N absorption shifted from 1630 to 1618 cm^{-1} (-12 cm^{-1}). The carbonyl band underwent the greater frequency shift, as would be expected for chelate formation.²⁴ Theoretical calculations of model imine 1c and Cu(I) complex 6a fully optimized at the B3LYP/6-31G* level²⁵using Gaussian 98 indicated that in the ground-state geometry of 1c the π -system of the imino group lies perpendicular to that of the carbonyl group (Figure 2). The activated complex 6a is calculated to be tetrahedral, consistent with other complexes of Cu(I).²⁶ A vibrational analysis of **6a** indicates a greater shift (-45 cm^{-1}) for the carbonyl group than for the imino group (-5 cm^{-1}) relative to precursor 1c, consistent with our experimental observations.²⁷ Without this chelate interaction, much of the selectivity is lost as illustrated by the use of simple imines, which react sluggishly and produce products with poor optical induction.²⁸ The next steps include stereochemistry-determining addition (re attack) and transilylation, which occurs from the carbonyl oxygen to the sulfonamido nitrogen yielding the silvlated product N-TMS-4 and regenerating the active catalyst 3c. The silvlated product N-TMS-4 can usually be seen by TLC and NMR, and desilylation only takes place after acidic workup, quenching with a fluoride source, or column chromatography. Adding t-BuOH (1 equiv) as a proton source in the reaction can intercept the transilylation step, producing desilylated products directly and a silvl ether as a byproduct with only a modest decrease in the rate of reaction.

Enantio- and Diastereoselective Imine Alkylation. We recently noted that excellent anti diastereoselectivity (up to 25: 1) as well as enantioselectivity (up to 99% ee) can be obtained

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Table 2. Diastereoselective Alkylations of α-Imino Ester 1b



1	2g: R = Me	3c	80	92	10/1
2	2g: R = Me	3d	86	98	25/1
3	2g: R = Me	3e	86		1.3/1
4	$2\mathbf{g}$: $\mathbf{R} = \mathbf{E}\mathbf{t}$	3c	77	95	14/1
5	2g : $R = Me(Ph)_2$	3c	78	95	16/1
6	2g: R = Me	3b	81	38	1/4
7	2h	3d	82	>99	20/1
8^b	2i	3d	75	99	15/1
9^b	2j	3c	75	78	7/1
10^{b}	2j	3d	71	88	11/1
11^{b}	2k	3c	71	91	17/1

^a Reactions were carried out at 0 °C to room temperature. ^b Reaction carried out at -78 °C. c Enantiomeric excesses were determined by a CHIRALCEL OD chiral HPLC column.

when substituted enol silanes are employed in the alkylation reaction (eq 4) regardless of the geometry of the enol silane.^{6,29} We also observed that the nature of the phosphine ligands we employed (PPh₃, BINAP, Tol-BINAP) is directly responsible for the diastereoselectivity of the products.



Initial screening focused on the reaction of Z-enol silane $2g^{30}$ with α -imino ester 1b. As part of our standard procedure, slow addition of a CH₂Cl₂ solution of 1.1 equiv of 2g over 1 h to a mixture of catalyst (1-10 mol % 3c) and imine (1b) at 0 °C afforded product 4g with good yield (80%) and excellent ee (92%) and diastereoselection (anti/syn = 10/1; Table 2, entry 1). Once again, the yield, enantioselectivity, and diastereoselectivity all increased noticeably with the use of (S)-Tol-BINAP•CuClO₄•(CH₃CN)₂ (3d) (entry 2), while the diastereoselectivity all but vanished with the use of achiral catalyst $CuClO_4 \bullet (PPh_3)_2 \bullet (CH_3CN)_2$ (**3e**)³¹ (anti/syn = 1.3/1; entry 3). As noted in the previous section, the size of the silane substituent did not appreciably affect the enantioselectivity; however, the diastereoselectivity noticeably improved. For example, increasing the size of the silane group (e.g., triethylsilyl TES-2g and diphenylmethylsilyl DPMS-2g) led to anti/syn ratios of 14:1 and 16:1, respectively, with catalyst 3c (entries 4, 5). An interesting reversal of diastereoselectivity was noted when the putative square planar complex (R)-BINAP•Pd(ClO₄)₂ (**3b**) was employed in the same reaction to afford the desired product in a 1/4 anti/syn ratio with modest enantioselectivity (entry 6).

We were interested in whether an *E*-enol silane could reverse the stereochemistry at the β -carbon leading to the syn product. In many cases, simple *E*-enol silanes are difficult to synthesize isomerically pure without laborious purification. One way to approach the problem of diastereoselective enolization is to enforce E-geometry by using a cyclic framework. Contrary to our presumptions, the cyclic enol silane 2h affords a 20/1 anti/ syn ratio of product **4h** in >99% ee with catalyst **3d** (Table 2, entry 7). Enol silane 2i, derived from the corresponding known ketone,³² can be viewed as a masked equivalent of an *E*-enol silane. This silvl tetralone 2i afforded the product 4i with anti stereochemistry in 99% ee at -78 °C (15/1 anti/syn, entry 8).33 We found that higher reaction temperatures drastically eroded the enantio- and diastereoselectivity of 4i due to an appreciable nonselective background rate between 1b and 2i. The enol silane 2j derived from cyclohexanone affords product 4j in 71% yield (88% ee, 11:1 anti/syn, entry 10) with catalyst 3d. Once again, both the enantioselectivity and diastereoselectivity diminished slightly with the use of catalyst 3c (78% ee, 7/1 anti/syn, entry 9). Ketene acetal 2k, derived from coumarinone, yielded the protected amino acid 4k in 91% ee and 71% yield with excellent anti diastereoselectivity (entry 11). Compound 2k is the only ketene acetal that we found to work well in the reaction. Its "flat" geometry and the presence of an aromatic ring seem to favor enhanced selectivity, as well as the reduced background rate due to α -substitution.



The absolute and relative stereochemistry of 4g were determined by a diastereoselective reduction/cyclization sequence to yield the lactone 7, followed by removal of the tosyl group. BOC-protection of the amino group then led to the known compound 8 (eq 5).³⁴ This methodology thus provides a convenient way to synthesize asymmetrically trisubstituted lactones that are building blocks for many natural products.³⁵ Similarly, syn-4c is a potential precursor to the nonnatural amino acid segment of the nikkomycin family of antibiotics (eq 6).³⁶ The absolute and relative stereochemistry of 4h was determined from the crystal structure of (1'R, 2S)-4h.³⁷ Stereoregularity was then inferred for the cyclic products 4i, 4j, and 4k.

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 Ruthkosky, M.; Kelly, C. A.; Zaros, M. C.; Meyer, G. J. J. Am. Chem. Soc. 1997, 119, 12004.

⁽³²⁾ Barcza, S.; Hoffman, C. W. Tetrahedron 1975, 31, 2363.

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^{(35) (}a) Jackson, R. F. W.; Rettie, A. B.; Wood, A.; Wythes, M. J. J. Chem. Soc., Perkin Trans. 1 1994, 1719. (b) Raffauf, R. F.; Zennie, T. M.; Onan, K. D.; LeQuesne, P. W. J. Org. Chem. 1984, 49, 2714.

Table 3. Asymmetric Alkylations of 1d and Acetals Using Catalyst $\mathbf{3d}^a$

entry	acetal	nucleophile	% yield	% ee	product
1	1d	2a	84	62	10a
2	9a (X = Bz; LG = Br)	2a	86	60	10a
3	9b (X = p -An; R = Br)	2a	89	56	10b
4^b	9c (X = Ac; R = OH)	2a	96	50	10c
5	9d (X = Ts; R = OH)	2a	93	95	4a
6	9e (X = Ns; R = Br)	2e	86	87	10d
7^c	9f ($X = SES; R = OH$)	2a	78	98	10e
8	9g (X = Ms; R = OH)	2a	89	85	10f

^{*a*} Abbreviations: Bz, benzoyl; *p*-An, 4-methoxybenzoyl; Ac, acetyl; Ts, *p*-toluenesulfonyl; Ms, methanesulfonyl; Ns, *p*-nitrobenzenesulfonyl; SES, trimethylsilyl-ethanesulfonyl. Enantiomeric excesses were determined by a CHIRALCEL OD chiral HPLC column. ^{*b*} Reaction carried out in refluxing CH₂Cl₂. ^{*c*} Enantiomeric excesses were determined by ¹H NMR in the presence of (+)-Pr(hfc)₃ chiral shift reagent.

Synthesis of γ -Oxo- α -Amino Acids from Acetals. With the optimization of enantio- and diastereoselective imino alkylation in hand, we decided to address practical issues of our methodology, namely product deprotection and the hydrolytic stability of the starting material. We reported the synthesis of γ -oxo- α -amino acids from easy-to-synthesize *N*,*O*-acetals **9** using 5 mol % catalyst **3d**.⁸ Initially, we screened amides **9a**–**c**, which are easily prepared from glycine ethyl ester in two steps.^{38,39} If the catalyst could promote the elimination of the leaving group, the corresponding α -imino esters **1** would then serve as the activated intermediate, and enantioselective alkylation would afford acylated amino acid derivatives **10** (eq 7).



In entries 2–4 (**9a**–c, Table 3) which we investigated, the X-substituent on the *N*,*O*-acetal was either an acyl or an aryl group. The reaction between amides **9a**–c and enol silane **2a** did not proceed to any appreciable extent in the absence of catalyst **3d**. However, as shown in Table 3, the maximum enantiomeric excess was only 60% using 5 mol % catalyst **3d** (Table 3, entry 2). We realized that, not surprisingly, sulfon-amido *N*,*O*-acetals proved to be the most useful acetal substrates.⁴⁰

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- (38) (a) Münster, P.; Steglich, W. Synthesis 1987, 223. (b) Kober, R.; Steglich, W. Liebigs Ann. Chem. 1983, 599.
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 (40) Metargende R. Chiral and Chiral actions (2014)
- (40) Matuszczak, B. Monatsh. Chem. 1996, 127, 1291

In fact, the selectivity increased as a solution of **9d** and catalyst **3d** (5 mol %) was mixed at 0 °C with 2 equiv of enol silane **2a** for 5 h, leading to compound **4a** in 93% yield and 95% ee (Table 3, entry 5). Although substrate **9d** is a highly crystalline and stable starting material, removal of the tosyl group in a subsequent step requires long reaction times and highly acidic conditions. We envisaged that other more easily removable sulfonamido protecting groups could be substituted for the tosyl group to provide complementary deprotection procedures.⁴¹ As noted in a previous communication,^{6a} the sulfonyl groups are interchangeable, but variations in selectivity and yield occur (Table 3, entries 6, 7). For example, when mesyl *N*,*O*-acetal **9g** reacts with enol silane **2a** in the presence of catalyst **3d**, compound **10g** is produced with only 87% ee (entry 8).



Once again, a variety of protecting groups including 2-trimethylsilylethylenesulfonyl (SES), benzoyl (Bz), and nosyl (Ns) were demonstrated to be effective under the reaction conditions producing products **10** in moderate to excellent enantioselectivity. In the deprotection step, compounds **10a**-e can be converted to amino acids **5** in yields ranging from 60 to 87% with no detectable racemization (eq 8). In fact, we used this methodology for the multigram synthesis of (*L*)-3-nitrobenzoylalanine (**5e**) in 48% overall yield from acetal **9e** (Table 3, entry 6) using only 1 mol % **3d**. This compound is currently one of the best inhibitors of kynurenine-3-hydroxylase and kynureninase. Our methodology affords this amino acid in higher enantioselectivities and yield than any of the previously reported syntheses.⁴²

With the issues of practicality and flexibility addressed, we turned our attention to a curious mechanistic aspect of the N,Oacetal reaction, which differs from imino ester alkylation reactions by the necessity of generating the imine in situ. One manifestation of this difference is the requirement for 2 equiv of enol silane 2a for the acetal alkylation to go to completion. To our surprise, the use of 1 equiv of enol silane 2a with N,Oacetal 9d did not lead to product 4a with 5 mol % 3d; however, when 2 equiv were used, product 4a was formed in good yield. Although silvl ketene acetals can be guenched through silvl transfer reactions with alcohols, enol silanes are also known to act as silylating reagents.43 This anomaly prompted us to examine the enol silane reaction through ¹H NMR experiments. For example, when acetal 9d was dissolved in CD₂Cl₂ along with 1 equiv of enol silane 2a, an immediate change in the ¹H NMR spectrum occurred. The enol silane resonances disappeared, and those characteristic of acetophenone and silylacetal

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TMSO-9d developed. A second equivalent of enol silane 2a was then added to the mixture, and the reaction was monitored; no product formation was noted even after extended periods of time. After addition of the catalyst 3d, however, resonances due to product began to appear. Interestingly, peaks due to the intermediate imine 1b were not observed, nor were those for the *N*-trimethylsilylated product *N*-TMS-4 (Scheme 1). In the reaction of *N*,*O*-acetal 9d with enol silane 2a, no silylated product is observed by ¹H NMR or TLC. This finding leads us to suggest that adventitious water, silanol, or an L_nCu•ROH species is protonating the product immediately after alkylation.⁴⁴ Not surprisingly, only 1 equiv of enol silane 2 is needed to alkylate *N*,*O*-acetal 9a, 9b, and 9e, reactions in which *O*-silylation cannot take place.



We have used this mechanistic information to optimize the reaction further in the form of a one-pot procedure. By using 1 equiv of TMSCl, acetal **9d** (which is formed in situ from ethyl glyoxylate and TsNH₂) can be silylated in the pot to form the putative silylacetal TMSO-**9d**, thus obviating the need to sacrifice an additional equivalent of enol silane in the reaction of **9** and **2**. TMSCl is added to the reaction after the acetal has been added to the catalyst solution, and the reaction is stirred for 15 min (eq 9). The solution is then cooled to 0 °C and submitted to the standard reaction with enol silanes **2**.

Catalytic, Enantioselective Imino Ene Reaction. In an initial report,⁹ we demonstrated the first effective example of a catalytic, enantioselective imino ene reaction (eq 10) to form α -amino acid derivatives.⁴⁵ Through this effort, optimal conditions for the reaction in terms of solvent, temperature, and reaction times were achieved. Benzotrifluoride (BTF) was found to be the ideal solvent for all reactions; it combines solubilizing power with an aromatic nature that seems to be beneficial to selectivity. The olefins we investigated were subjected to the standard reaction conditions (BTF solvent, room temperature, 5 mol % catalyst, and a 2:1 olefin:imino ester stoichiometry), affording products in excellent yield and enantioselectivity (Table 4, and eq 10).⁴⁶



Our test olefinic substrate α -methylstyrene **11a** was subjected to the reaction conditions (BTF, room temperature, 12 h) to afford the protected amino acid **12a** in 95% yield and 99% ee using 5 mol % catalyst (Table 4, entry 1). When the reaction

Table 4. Ene Reactions of 11a-e with 1b Catalyzed by 3d



^{*a*} Reactions were conducted under standard conditions in BTF or CH₂Cl₂ at room temperature unless otherwise noted. ^{*b*} Isolated yield after chromatography. ^{*c*} Enantiomeric excesses before crystallization were determined by CHIRALCEL OD chiral HPLC column. ^{*d*} Enantiomeric excesses were determined by ¹H NMR in the presence of (+)-Pr(hfc)₃ chiral shift reagent. ^{*e*} Reaction performed on 5 mmol scale.

was conducted on a gram scale with 1 mol % **3d**, both the selectivity and yield were maintained. Aliphatic olefins worked well under the reaction conditions as methylenecyclohexane **11b** led to product **12b** in 85% yield and 95% ee (entry 2). Heteroatom-containing ene substrates are also compatible with our reaction conditions, demonstrating that the catalyst is tolerant of various functional groups and moderately Lewis basic sites on the alkene. For example, tryptophan derivatives can be synthesized by the alkylation of **1b** with **11c** forming **12c** in 90% yield and 85% ee (entry 3). This reaction is important because no general synthetic method for the construction of tryptophan analogues in optically active form through catalytic methodology exists.⁴⁷ Rich et al. have used this process to synthesize a substituted tryptophan intermediate in high yield

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- (46) Conversion of 12a into compound 5a established the sense of induction as (S). Stereoregularity was inferred for products 12b-j.



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and ee toward the total synthesis of complestatin.⁴⁸ The oxygencontaining ene⁴⁹ **11d** provided the protected fufurylalanine **12d** in 92% yield and 90% ee (entry 4). Other substrates with aromatic rings, such as 11e, work well (entry 5). Additonally, the more nucleophilic enol sulfide 11f is a superior substrate (entry 6). It is noteworthy that most of the products (12a-g)can be obtained in analytically pure form without chromatography by straightforward crystallization of the organic concentrate (EtOAc/hexanes) after aqueous workup.



Development of a Syn-Selective Ene Reaction. One of our goals was to devise a syn-selective, β -alkyl- α -amino acid synthesis as a prelude to the total synthesis of the nikkomycin class of antifungals. For example, on the basis of kinetic isotope effect studies, we believe that the reaction proceeds through a classical, closed six-membered transition state for relatively nonpolar olefins such as α -methylstyrene. Proposed transition state models are illustrated in Figure 3. Weinreb et al. have postulated that endo transition states for imino ene reactions are energetically more favorable than are the exo due to the complementary charge attraction of the nitrogen lone pair and the positive charge that develops on the central carbon in the ene during the course of a concerted, but nevertheless asynchronous, transition state.^{50a} However, in our system, the steric interaction between the large tetrahedral metal ligand complex and the ene nucleophile means that the reaction is less likely to go through an endo transition state (Figure 3). For this reason, the more plausible transition states for the catalyzed imino ene reaction are exo. Consequently, syn diastereoselectivity should result from the exo-E transition state and an appropriately substituted E-olefin (Figure 3).

The diastereoselective version of the prototype imino ene reaction is well precedented⁵⁰ and has been elegantly applied in the total synthesis of members of the methanomorphanthridine

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Figure 3. Proposed closed transition state model for the diastereoselective imino ene reaction

class of natural products,⁵¹ as well as (-)-perhydrohistrionicotoxin.⁵² We first subjected substrate **11g** (entry 7, Table 4) to standard conditions at room temperature in BTF solvent over the course of 3 days. The major product of this reaction is indeed **12g** (77% yield and 94% ee for the syn isomer; crude anti/syn 1/6), albeit formed sluggishly in moderate diastereoselectivity. Upon ozonolysis syn-12g would be a precursor to the amino acid segment of nikkomycin B.

Recently Gagné et al. reported that the addition of excess *p*-trifluoromethylphenol to glyoxylate ene reactions provides a notable rate enhancement.53 Gagné postulated that the acidic phenol promotes counterion dissociation through hydrogen bonding. Following this lead, we tried *p*-trifluoromethylphenol in the ene reaction of trisubstituted alkene 11g with imino ester 1b and found that the rate of reaction increases by a substantial amount (eq 11). This allowed us to conduct the reaction at 0 °C in BTF over the course of 10 h, although unfortunately the diastereoselectivity is eroded somewhat (anti/syn 1/3), although the ee (94%) is maintained. We believe, though, that this rate acceleration will prove to be general for a variety of substrates.



Kinetics of the Catalyzed Imino Ene Reaction. One advantage to slow reactions is that they can be very amenable to kinetic studies. Along those lines, we sought to study the

mechanism of the imino ene reaction (which proceeds smoothly at 0 °C over the course of hours) in greater detail. Prototype ene reactions have been proposed to proceed through a concerted, nonpolar transition state.54 During the course of our studies, we noted a general insensitivity to solvent polarity in the rate of reaction of 1b with 11a, consistent with a concerted reaction pathway. However, the possibility of a stepwise reaction does exist, particularly when an aryl group is available to stabilize a transient carbocation. To shed light on this mechanistic question, we investigated the reaction through kinetic isotope effect (KIE) studies. A 1:1 mixture of alkenes 11a and **11a**- d_3 was subjected to our standard reaction conditions in both BTF and THF solvents in the presence of 1b and 5 mol % 3d (eq 12). Analysis of the reaction mixture at 5% conversion indicated a KIE $k_{\rm H}/k_{\rm D3}$ of 4.4 in THF and BTF.⁵⁵ The observed KIE is a superposition of normal primary and α -secondary KIE's, and as a consequence, the primary KIE should account for $\sim 80\%$ of the observed value.⁵⁶ The result is nevertheless consistent with a large degree of rate-determining transfer of H(D) in the transition state, in line with a concerted mechanism (structure 13). If the reaction were to proceed stepwise through the cationic intermediate 14, an observed β -secondary KIE in the neighborhood of 1.9 (or lower) would be expected. Whether the reaction would be concerted for more polar alkenes is questionable.

These KIE studies established that the alkene plays a role in the rate-determining step of the imino ene reaction. We also found that by doubling the concentration of alkene, the rate of reaction was doubled. Similarly, a 4-fold increase in alkene concentration brought about a 4-fold rate increase. These results prompted us to examine, in more detail, the kinetic order of the catalyst and other reagents in the rate equation. The rate of the imino ene reaction between 1b and 11a is documented to be moderate at room-temperature, making it optimal to study for kinetic experiments.¹⁰ Solutions of α-methylstyrene 11a (psuedo first-order, 5 M) and imine 1b (0.2 M) were subjected to 2.5 mol % 3d at 0 °C in CH₂Cl₂. Aliquots of the reaction mixture were assayed over a 5 h period to determine the rate of product formation with respect to an internal standard of biphenyl. This rate correlated well with the rate of consumption of imine 1b. Under these conditions, the reaction followed firstorder kinetics as indicated by a log plot (Figure 4).

To determine the effect of catalyst loading on this reaction, the concentrations of imine **1b** and α -methylstyrene **11a** in CH₂Cl₂ were kept constant (0.2 M), and depletion of imine **1b** was measured over a 5 h period varying only the concentration of catalyst **3d**. Once again, at low conversion, the reactions followed pseudo first-order kinetics. A rate enhancement was observed as the concentration of catalyst increased, as shown in Figure 5. Doubling the concentration of the catalyst from 2.5 to 5 mol % doubled the rate of reaction at 0 °C, and subsequent doubling of the catalyst concentration to 10 mol % led to a further 2-fold increase in rate, indicating that the reaction is first-order in catalyst. Consequently, the kinetic data allow



Figure 4. Pseudo first-order behavior of catalytic imino ene reaction.



Figure 5. Effect of catalyst loading on rate of imino ene reaction.

us to propose a rate equation for the reaction (eq 13). The observed rate constant k' was determined to be $6.8 \times 10^{-3} \text{ min}^{-1}$ as derived from eq 13. Factoring out the concentrations of α -methylstyrene **11a** and catalyst **3e**, the rate constant k was found to be $3.4 \times 10^{-2} \text{ min}^{-1} \text{ M}^{-2}$.

rate
$$=\frac{-d[\mathbf{1b}]}{dt} = \frac{d[\mathbf{12a}]}{dt} = k'[\mathbf{1b}] = k[\mathbf{11a}][\mathbf{3d}][\mathbf{1b}]$$
 (13)

In each of the log plots, one can discern a very slight downward curvature that may be indicative of product inhibition. As noted previously, the imine **1b** could be an effective bidentate ligand for the catalyst 3d. The product 12a, however, could also serve as a modest inhibitor of the catalyst 3d at higher concentrations through a similar chelate structure. To determine the effect of product inhibition on the imino ene reaction, three experiments were performed simultaneously.57 In all three reactions, concentrations of α -methylstyrene 11a (0.2 M) and imine 1b (0.2 M) were kept constant. In the second reaction, a 0.1 M solution of product (S)-12a was added to the imine/styrene mixture. Likewise, a 0.1 M solution of product (R)-12a was added to the third reaction. All three reactions were initiated at 0 °C by addition of catalyst 3d. The reaction rates were measured over a 2 h period by GC analysis of the reaction mixture, using a constant amount of biphenyl as an internal standard. For the second and third reaction, an approximate 50% reduction in rate was observed, presumably due to the nonproductive, nonenantioselective binding of the catalyst to the product.

Catalytic, Enantioselective Allylations of α -Imino Esters. Complementary to our work with enol silane and alkene

⁽⁵⁵⁾ The k_H/k_D was determined by mass spectral analysis of the products resulting from the competition reaction carried out on a 1: 1 mixture of **11a** and **11a-d_3**. This observed primary kinetic isotope effect is in line with previous observations on prototype ene systems, see: (a) Achmatowicz, O., Jr.; Szymoniak, J. J. Org. Chem. **1980**, 45, 4. (b) Kwart, H.; Brechbiel, M. W. J. Org. Chem. **1982**, 47, 3355. (c) Dai, S.-H.; Dolbier, W. R., Jr. J. Am. Chem. Soc. **1972**, 94, 3953.

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nucleophiles, we have also developed a catalytic, enantio- and diastereoselective procedure for the addition of allylsilanes 17a-h to α -imino ester 1b catalyzed by complex 3d, demonstrating the utility of this reaction as an alternative means to homoallylic α -amino acid derivatives 12 (eq 14).⁵⁸ Jørgensen et al. have also reported an allylation method using catalyst 3d affording products in moderate to good ee's.^{11d} Generally speaking, allylsilanes are intermediate in nucleophilicity between simple alkenes and enol silanes. They are often postulated to react through open, or Mukaiyama-type, transition states such as enol silanes. Consequently, anti-diastereoselectivity could analogously be expected in their catalyzed reactions with α -imino ester 1b.



Using our previous work as a model, we subjected α -imino ester 1b to allyltrimethylsilane 17a (R_2 , $R_3 = H$, $R_1 = H$) catalyzed by 5 mol % (R)-Tol-BINAP•CuClO₄•(CH₃CN)₂ (3d) in CH_2Cl_2 at -78 °C. The reaction proceeded smoothly, affording the expected allylated product 12h in good yield (87%) with modest enantioselectivity (64%, Table 5, entry 1). In an effort to improve the selectivity, we screened a number of solvents including THF and BTF, obtaining product 12h in 56% ee and 57% ee, respectively, and in comparable yield. A minimal solvent effect on selectivity seems to operate in this process, affording us little room for optimization. This led us to explore how the nature of the silane affected the reaction. The slightly more reactive triethylallylsilane 17b gave 12h in 88% yield and 72% ee, whereas the bulkier tri-n-butylsilane of 17c (R₁, R₂, $R_3 = H, R = n$ -Bu) afforded **12h** in 89% yield and 51% ee in CH₂Cl₂. Clearly, a delicate balance exists between the size of the silane substituents and the selectivity of the reaction.

The "Aromatic" Effect. In an attempt to improve selectivity in the allylation reaction, we found that aromatic substituents on the allyl group could dramatically improve the enantioselectivity of the reaction (Table 5). For example, phenylsubstituted allylsilane 17d provided 12a in 91% yield and 94% ee using catalyst 3d (entry 4). As a general trend in several classes of reactions, we have found that placement of aromatic substituents on the reacting nucleophiles increases the enantioselectivity significantly. As to whether this indicates the presence of possible beneficial π -stacking interactions with the catalyst, we can only speculate. To emphasize the practicality of these allylations, silane 17d also alkylated hydrolytically stable acetal 9e in 90% ee and 85% yield under these conditions (entry 5). Allylsilane 17e led to product 12i in 85% yield and 75% ee (entry 6). Compound 12i is a precursor to styrylalanine, a nonnatural amino acid with great importance in the pharmaceutical industry.⁵⁹ Interestingly, the presence of an aryl group on the allylsilane improves the enantioselectivity in an analogous Table 5. Allylation Reactions of 1b with 17a-h Catalyzed by 3d



^{*a*} Reactions run at -78 °C in CH₂Cl₂, ^{*b*} Enantiomeric excess was determined by CHIRALCEL OD chiral HPLC column. ^{*c*} dr represents the (anti/syn) ratio. ^{*d*} Reaction run with acetal **9e** rather than imine **1b**.

manner to the enol silane as illustrated by the naphthyl allylsilane **17f** that afforded product **12j** in 93% ee (entry 7). Next, we explored the diastereoselectivity of the imino allylations. Using **17g** as a control, we determined the effect of alkene geometry on the diastereoselectivity of product formation. The *Z*-allylsilane **17g** was readily available from Ni-catalyzed cross coupling of (trimethylsilylmethyl)magnesium chloride with the corresponding enolsilane **2g**.⁶⁰ Allylation of **1b** by **17g** under the standard reaction conditions afforded **12k** in excellent enantio- and anti-diastereoselectivity, presumably through an open transition state (entry 8).⁶¹ Next, the tetralone derivative **17h** was prepared to establish how the alternate *E*-allylsilane geometry would effect the outcome of the reaction. Product **12l** was isolated in 88% yield, possessing excellent de (10:1 anti: syn) and ee (anti **12l** = 87%, entry 9).

Summary

We have developed a broadly based methodology for the practical synthesis of nonnatural α -amino acids by catalytic enantioselective alkylation of α -imino esters and acetals with enol silanes, allylsilanes, and olefins. The most effective catalysts for these alkylations are derived from chiral Cu(I)-phosphine complexes. Using these catalysts, imino alkylations lead to direct precursors of natural products and pharmaceuticals with high enantioselectivities (up to 99% ee) and anti-dia-

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⁽⁶¹⁾ The absolute stereochemistry of the products 12i was determined by a simple oxidative cleavage of the alkene as reported in Viski, P.; Szeverényi, Z.; Simándi, L. J. Org. Chem. 1986, 51, 3213.

stereoselectivities (up to 25:1/anti:syn). The kinetic data for the imino ene reaction, including isotope effects and rate studies, provide detailed evidence for the presence of a concerted, closed transition state and classical Lewis acidic activation of the imino ester substrate.

Experimental Section

General Alkylation Procedure using Ag(I) and Cu(I) Complexes. The metal BINAP complexes were formed by dissolving (R)-BINAP (25 mg, 0.04 mmol) or (R)-Tol-BINAP (with Cu(I) or Ag(I)) perchlorate or hexafluoroantimonate (0.035 mmol) in THF (1-2 mL) and were stirred at room temperature under nitrogen for 30 min. The α -imino ester 1b (100 mg, 0.40 mmol) was then added to the metal complex solution. The mixture was then cooled to -78 °C using a MeOH cryogenic bath (FTS Systems). A solution of the enol silane 2a (83 mg, 0.43 mmol) in THF (0.5 mL) was added to the reaction mixture dropwise over 2 h. The reaction was stirred overnight at -78 °C to ensure complete reaction and was then quenched dropwise with MeOH (5 mL). Upon warming the quenched reaction to room temperature, it was diluted with water (10 mL) and extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with saturated NaHCO3 (5 mL) and brine (5 mL). The organic layer was dried over Na₂SO₄, filtered, and the solvent was removed under reduced pressure. The crude residue (175 mg) was subject to column chromatography (20% EtOAc/ hexanes) on a small silica gel plug yielding 138 mg of 4a (95% yield). Recrystallization from ether/hexane afforded the product in >99% ee.

General Alkylation Procedure for Pd(II) Complexes. The metal ligand complex was made by mixing (*R*)-BINAP•PdCl₂ (Aldrich, 31 mg, 0.04 mmol) and AgClO₄ (15 mg, 0.076 mmol) in acetonitrile. The fluffy white precipitate (AgCl) was filtered off, and the resulting acetonitrile solution was concentrated in vacuo leaving the (*R*)-BINAP•Pd(ClO₄)₂ as a yellow crystalline solid. The solid was dissolved in CH₂Cl₂ and used in an analogous manner to the aforementioned procedure.

Representative Alkylation of 1b with Cu(ClO₄)₂ and (*S***)-BINAP**. A solution of (*S*)-BINAP (25 mg, 0.04 mmol) and Cu(ClO₄)₂ (10 mg, 0.04 mmol) in THF (1 mL) was stirred for 30 min in a drybox. The greenish color of the solution eventually faded, and the mixture turned pale yellow. This catalyst was added to a solution of imino ester **1b** (100 mg, 0.40 mmol) in THF (1 mL). The mixture was cooled to 0 °C, and a solution of **2a** (R' = H) (84 mg, 0.44 mmol) in 0.5 mL of THF was added to the catalyst/imine solution over a 1 h period. After 12 h of stirring, the mixture was quenched with MeOH and washed with H₂O/CH₂Cl₂ (10 mL). The organic layer was partitioned, and the aqueous layer was extracted with CH₂Cl₂ (2 × 5 mL). The combined organics were dried, concentrated, and purified by flash chromatography to yield 85% of the product amino ester in 85% ee.

Representative Diastereoselective Alkylation Procedure. The Cu(I) phosphine complexes were formed by dissolving (R) or (S)-BINAP (13 mg, 0.02 mmol) or (R) or (S)-Tol-BINAP with $CuClO_4$ • $(CH_3CN)_4$ (6.2 mg, 0.019 mmol) in THF or CH_2Cl_2 (1 mL) and by stirring at room temperature for 30 min. Then 100 mg (0.40 mmol) of 1b was added to the metal complex solution. The mixture was placed under nitrogen at 0 °C, and a solution of the enol silane 2g (90 mg, 0.44 mmol) in CH₂Cl₂ (0.5 mL) was added to the reaction mixture dropwise over 1 h. The reaction was gradually warmed to room temerature overnight to ensure complete reaction and was then quenched dropwise with MeOH (2 mL). Upon warming the quenched reaction to room temperature, it was diluted with water (5 mL) and extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were washed with brine (5 mL) and aqueous 10% KF (5 mL). The organic layer was dried over Na₂SO₄, and the solvent was removed under reduced pressure. The crude residue (200 mg) was subject to column chromatography (20% EtOAc/hexanes) on a small silica gel plug yielding 135 mg of 4g (86% yield).

Representative Alkylation Procedure of Acetals 9. The catalyst **3d** was made by dissolving (*R*)-Tol-BINAP (15 mg, 0.022 mmol) and $CuClO_4 \cdot (CH_3CN)_2$ (7 mg, 0.021 mmol) in CH_2Cl_2 (1 mL). To the tosyl acetal **1b** (100 mg, 0.37 mmol) in CH_2Cl_2 (2 mL) was added the solution of catalyst **3d**. This reaction mixture was cooled to 0 °C, and the enol silane **2a** (142 mg, 0.74 mmol) was added to the reaction mixture over a period of 30 min. The reaction was stirred at room temperature or heated to reflux until completion as shown by TLC (30% EtOAc/hexanes). The reaction was partitioned with water (3 mL) and CH_2Cl_2 (3 mL). The organic layer was dried with MgSO₄, and the solvent was removed in vacuo. The crude residue (200 mg) was subject to column chromatography on silica gel to yield 128 mg of the final product (93% yield, 95% ee).

Representative Ene Alkylation Procedure. The Cu(I) phosphine complexes were formed by dissolving (*R*)-Tol-BINAP (20.4 mg, 0.030 mmol) with CuClO₄•(CH₃CN)₄ (8.2 mg, 0.025 mmol) in benzotrifluoride (1 mL) or CH₂Cl₂ and by stirring at room temperature for 30 min to give a pale yellow solution. The α -imino ester **1b** (128 mg, 0.50 mmol) was added to the metal complex solution. The mixture was placed under nitrogen at room temperature, and a solution of the olefin **11a** (R = Me, R' = Ph) (118 mg, 1.00 mmol) in BTF (0.5 mL) was added to the reaction mixture. The reaction was allowed to stir for 18 h at room temperature to ensure completion. The reaction was quenched with water (5 mL) and extracted with CH₂Cl₂ (2 × 5 mL). The combined organic layers were dried over MgSO₄, and the solvent was removed under reduced pressure. The crude residue was subjected to column chomatography (5–20% EtOAc/hexanes) on a small silica gel plug (2.5 × 3 cm) yielding 176.5 mg of **12a** (95% yield).

Representative Allylation Procedure. The Cu(I) phosphine complexes were formed by dissolving (R)-Tol-BINAP (15 mg, 0.022 mmol) with CuClO₄•(CH₃CN)₄ (7 mg, 0.021 mmol) in CH₂Cl₂ (1 mL) with stirring at room temperature for 30 min to give a pale yellow solution. The α -imino ester **1b** (128 mg, 0.50 mmol) was added to the metal complex solution. The mixture was removed from the glovebox and placed under nitrogen and cooled to -78 °C. A solution of the allylsilane 17d (95 mg, 0.5 mmol) in CH₂Cl₂ (0.5 mL) was added to the reaction mixture dropwise over 1 h. The reaction was stirred for 12 h and allowed to gradually warm to room temperature. The reaction was quenched with water (5 mL) and extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were dried over MgSO₄, and the solvent was removed under reduced pressure. The crude residue was subjected to column chromatography (5-20% EtOAc/hexanes) on a small silica gel plug (2.5×3 cm) yielding 170 mg of 12a (94% ee, 91% yield).

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Supporting Information Available: Experimental details and characterization data for 1a, 4a–j, 5e, 7, 9d–g, 10c, 10e, 12a–e, 12h–l, 17d, 17e. This material is available free of charge via the Internet at http://pubs.acs.org.

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