Catalytic, enantioselective alkylation of alpha-imino esters: the synthesis of nonnatural alpha-amino acid derivatives.

ARTICLE *in* JOURNAL OF THE AMERICAN CHEMICAL SOCIETY · FEBRUARY 2002

Impact Factor: 12.11 · Source: PubMed

8 AUTHORS, INCLUDING:

Dana V Ferraris
McDaniel College
56 PUBLICATIONS **2,622** CITATIONS
SEE PROFILE

Travis Dudding
Brock University
70 PUBLICATIONS **1,849** CITATIONS
SEE PROFILE

Lev Ryzhkov
Towson University
15 PUBLICATIONS **303** CITATIONS
SEE PROFILE

Thomas Lectka
Johns Hopkins University
107 PUBLICATIONS **4,881** CITATIONS
SEE PROFILE

J|A|C|S
ARTICLES
Published on Web 12/04/2001

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

Dana Ferraris, Brandon Young, Christopher Cox, Travis Dudding, William J. Drury, III, Lev Ryzhkov,[#] Andrew E. Taggi, and Thomas Lectka*

Contribution from the Department of Chemistry, Johns Hopkins University, 3400 North Charles Street, Baltimore, Maryland 21218, and Department of Chemistry, Towson University, 8000 York Road, Towson, Maryland 21252

Received August 14, 2001. Revised Manuscript Received October 22, 2001

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 imines[2] 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 enantio-enriched α-amino acid derivatives through the catalytic asymmetric alkylation of α-imino esters **1** with a variety of carbon-based 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

[#] Towson University.

(1) Recent reviews of amino acid synthesis: (a) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407. (b) Williams, R. M. *Synthesis of Optically Active* α*-Amino Acids*; Pergammon: New York, 1989. (c) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539. (d) Hegedus, L. *Acc. Chem. Res.* **1995**, *28*, 299. Synthesis of nonnatural α-amino acids in natural products: (e) Boger, D. L.; Patane, M. A.; Zhou, J. *J. Am. Chem. Soc.* **1994**, *116*, 8544. (f) Boger, D. L.; Yohannes, D. *J. Org. Chem.* **1990**, *55*, 6000.

(2) For representative examples of Lewis acid-catalyzed enantioselective imine alkylations, see: (a) Kobayashi, S.; Ishitiani, H. *Chem. Rev.* **1999**, *99*, 1069. (b) Hagiwara, E.; Fujii, A.; Sodeoka, M. *J. Am. Chem. Soc.* **1998**, *120*, 2474. (c) Kobayashi, S.; Nagayama, S. *J. Am. Chem. Soc.* **1997**, *119*, 10049. (d) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **1997**, *119*, 7153. A proline-catalyzed asymmetric Mannich reaction has recently been reported: (e) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336.

(3) (a) Gomez-Bengoa, E.; Heron, N. M.; Didiuk, M. T.; Luchaco, C. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1998**, *120*, 7649. For reviews of α-amidoalkylation reactions, see: (b) Zaugg, H. E. *Synthesis* **1984**, 85. (c) Zaugg, H. E. *Synthesis* **1984**, 181.

(4) (a) Synopsis: Yet, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 875. (b) Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2000**, *39*, 1279. (c) Porter, J. R.; Wirschun, W. G.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 2657. (d) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901. (e) Kobayashi, S.; Ishitani, H.; Ueno, M. *J. Am. Chem. Soc.* **1998**, *120*, 431. (f) Fujieda, H.; Kanai, M.; Kambara, T.; Iida, A.; Tomioka, K. *J. Am. Chem. Soc.* **1997**, *119*, 2060.

(5) Weinreb, S. M. *Top. Curr. Chem.* **1997**, *190*, 131.

(6) (a) Ferraris, D.; Young, B.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 4548. (b) Ferraris, D.; Young, B.; Cox, C.; Drury, W. J., III; Dudding, T.; Lectka, T. *J. Org. Chem.* **1998**, *63*, 6090.

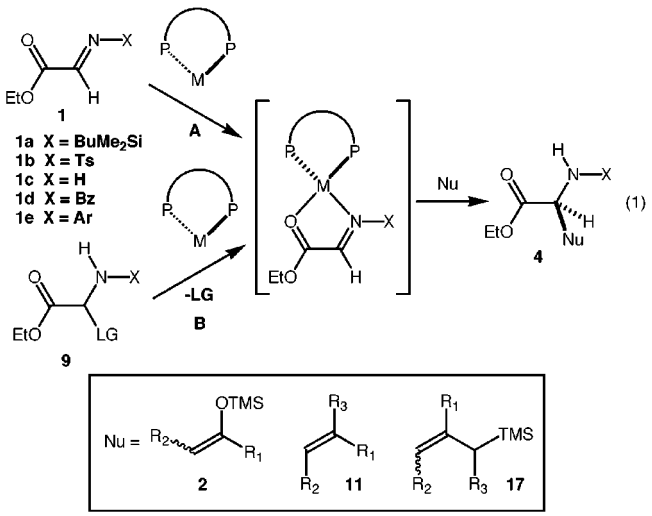
(7) (a) Saaby, S.; Fang, X.; Gathergood, N.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 4114. (b) Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3558. (c) Yao, S.; Saaby, S.; Hazell, R. G.; Jørgensen, K. A. *Chem.-Eur. J.* **2000**, *6*, 2435. (d) Yao, S.; Fang, X.; Jørgensen, K. A. *J. Chem. Soc., Chem. Commun.* **1998**, 2547.

(8) Ferraris, D.; Dudding, T.; Young, B.; Drury, W. J., III; Lectka, T. *J. Org. Chem.* **1999**, *64*, 2168.

(9) Drury, W. J., III; Ferraris, D.; Cox, C.; Young, B.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 11006.

(10) (a) For a review of imino ene reactions, see: Borzilleri, R. B.; Weinreb, S. M. *Synthesis* **1995**, 347. (b) For a review of asymmetric ene reactions, see: Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021. For two notable examples of asymmetric ene reactions, see: (c) Evans, D. A.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T.; Tregay, S. W. *J. Am. Chem. Soc.* **1998**, *120*, 5824. (d) Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1989**, *111*, 1940.

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.



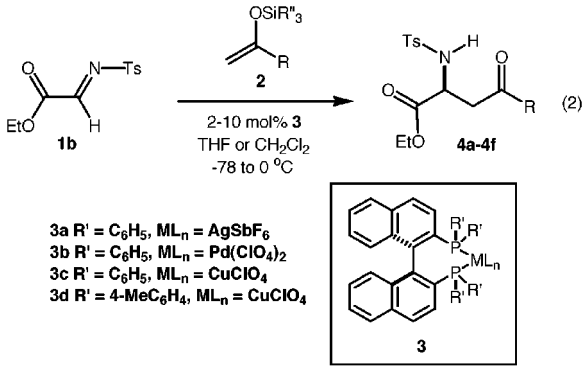
Results and Discussion

Enantioselective Alkylation of Imino Esters. For our initial investigations into asymmetric imino alkylations, we chose to examine α-*N*-silylimino esters **1** with the view that the silyl 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•$AgSbF_6$ (**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 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•$Pd(ClO_4)_2$•$(CH_3CN)_2$ (**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]

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_2Ph; R' = Me	**3d**	0	87	94
14	**2f**: R = 3,4-Cl_2Ph; 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 CH_2Cl_2. [e] 2 mol % catalyst was used.



The straw-yellow complex (*R*)-BINAP•$CuClO_4$•$(CH_3CN)_2$ (**3c**)[14] performed as well as **3a** (entry 5), whereas (*R*)-Tol-BINAP•$CuClO_4$•$(CH_3CN)_2$ (**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

(11) For recent examples of catalytic, asymmetric allylations, see: (a) Chen, G.-M.; Ramachandran, P. V.; Brown, H. C. *Angew. Chem., Int. Ed.* **1999**, *38*, 825. (b) Nakamura, H.; Nakamura, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 4242. (c) Yanagisawa, A.; Nakashima, H.; Ishiba, A.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 4723. (d) Fang, X.; Johannsen, M.; Yao, S.; Gathergood, N.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1999**, *64*, 4844.

(12) α-Imino ester **1b** was first used by Weinreb: Tschaen, D. H.; Turos, E.; Weinreb, S. M. *J. Org. Chem.* **1984**, *49*, 5058.

(13) Yanagisawa, A.; Nakashima, H.; Ishiba, A.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 4723.

(14) For the preparation of $Cu(ClO_4)$•$(MeCN)_4$ see: Kubas, G. J. In *Inorganic Synthesis*; Shriver, D. F., Ed.; Plenum: New York, 1979; Vol. 19, p 90.

(15) (a) Pagenkopf, B. L.; Krüger, J.; Stojanovic, A.; Carreira, E. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 3124. (b) Kruger, J.; Carreira, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 837.

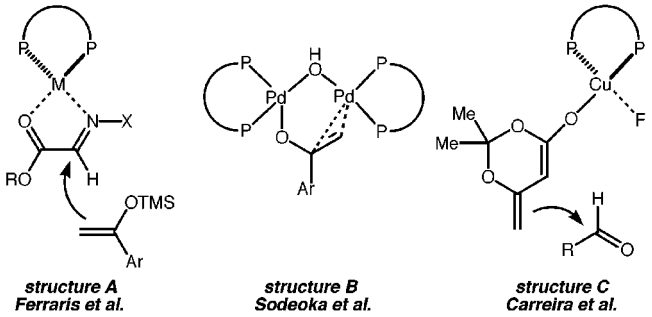
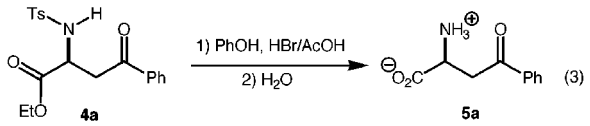


Figure 1. Reactive complexes for enantioselective reaction.

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).[16]These 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 ^{13}C or ^{1}H 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 $(PPh_3)_2{\bullet}CuClO_4{\bullet}(CH_3CN)_2$ and precipitation of $KClO_4$. 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**.

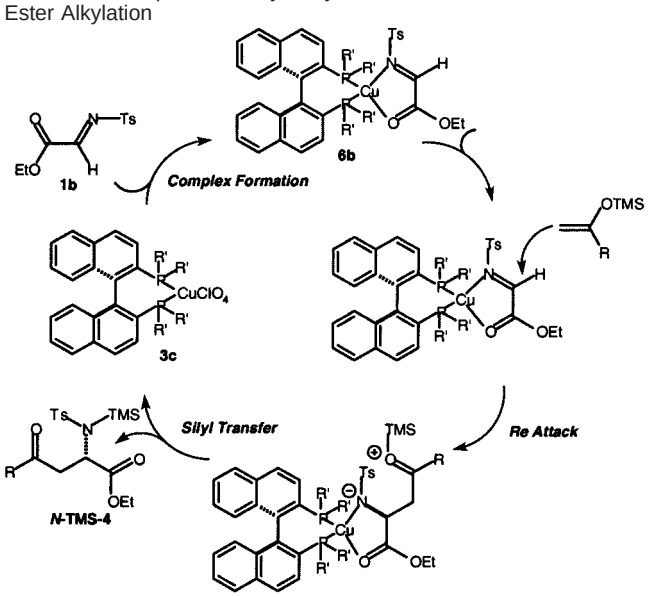
The potential ease of interconversion between Cu(I) and Cu(II) must also be taken into account.[19] To our surprise, a similar, although somewhat less effective, catalyst could also be generated by mixing $Cu(ClO_4)_2$ with (*R*)- or (*S*)-BINAP in

(16) (a) Rover, S.; Cesura, A. M.; Huguenin, P.; Kettler, R.; Szente, A. *J. Med. Chem.* **1997**, *40*, 4378. (b) Golubev, A. S.; Sewald, N.; Burger, K. *Tetrahedron* **1996**, *52*, 14757. (c) Berrée, F.; Chang, K.; Cobas, A.; Rapoport, H. *J. Org. Chem.* **1996**, *61*, 715. (d) Botting, N. P. *Chem. Soc. Rev.* **1995**, 401. (e) Pellicciari, R.; Natalini, B.; Constantino, G. *J. Med. Chem.* **1994**, *37*, 647.

(17) Li, G.; Sharpless, K. B. *Acta Chem. Scand.* **1996**, *50*, 649.

(18) Fujii, A.; Hagiwara, E.; Sodeoka, M. *J. Am. Chem. Soc.* **1999**, *121*, 5450.

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 $H_2{}^{18}O$ had been added. Workup and MS analysis of the BINAPO byproduct showed a corresponding isotopic incorporation of ^{18}O into the phosphine oxide moiety,[21] implying that a small amount of adventitious water is the oxygen source when BINAP is oxidized by $Cu(ClO_4)_2$.[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 $Cu(ClO_4)_2$ 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 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.

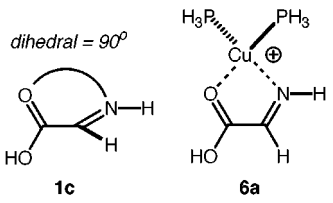


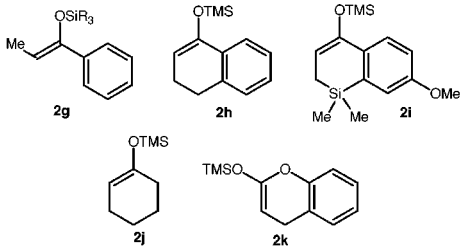
Figure 2. Theoretical calculations of model imine **1c**.

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* level[25]using 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 silylated product *N*-TMS-**4** and regenerating the active catalyst **3c**. The silylated 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 silyl 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

(19) Hathaway, B. J. In *Comprehensive Coordination Chemistry*; Wilkinson, G., Fillard, R. D., McCleverty, J. A., Eds.; Pergamon: New York, 1987; Vol. 5.
(20) The synthesis and characterization of BINAPO has been described: (a) Tayaka, H.; Mashima, K.; Koyano, K.; Yagi, M.; Kumobayashi, H.; Taketomi, T.; Akutagawa, S.; Noyori, R. *J. Org. Chem.* **1986**, *51*, 629.
(21) Mass spectral analysis indicated an isotopic enrichment at the M + 2 and M + 4 peaks of BINAPO.
(22) Phosphine oxidation by $Cu(SO_4)_2$ is precedented: Berners-Price, S. J.; Johnson, R. K.; Mirabelli, C. K.; Faucette, L. F.; McCabe, F. L.; Sadler, P. J. *Inorg. Chem.* **1987**, *26*, 3383.
(23) (a) Abu-Gnim, C.; Amer, I. *J. Organomet. Chem.* **1996**, *516*, 235. (b) Wegman, R. W.; Abatjoglou, A. G.; Harrison, A. M. *J. Chem. Soc., Chem. Commun.* **1987**, 1891.
(24) Structural evidence exists for the chelate binding of α-imino esters and Zn(II): Van Vliet, R. P.; Van Koten, G.; Modder, J. F.; Van Beek, J. A. M.; Klaver, W. J. *J. Organomet. Chem.* **1987**, *319*, 285. Chelate formation is expected to enhance selectivity by restricting rotation about the bond between nitrogen and the metal in the activated complex.
(25) Hybrid density functional theory/Hartree-Fock (DFT/HF) theory is a promising emerging method for the modeling of transition metal-based complexes: (a) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B: Condens. Matter* **1988**, *37*, 785. (b) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (c) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 1372.
(26) Cotton, F. A.; Wilkinson, G. *Advanced Inorganic Chemistry*; Wiley-Interscience: New York, 1988; p 756.
(27) Calculated frequencies for **1c** are 1565 cm^{-1} for the imino group and 1735 cm^{-1} for the carbonyl group; for **6b** they are 1560 cm^{-1} for the imino group and 1690 cm^{-1} for the carbonyl group.
(28) Unpublished results from our laboratories.

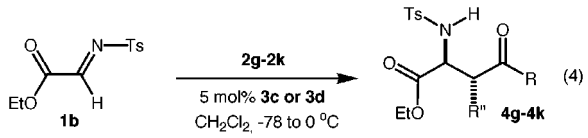
Table 2. Diastereoselective Alkylations of α-Imino Ester **1b**



entry[a]	nucleophile	catalyst	yield	ee %[c]	anti/syn
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	**2g**: R = Et	**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

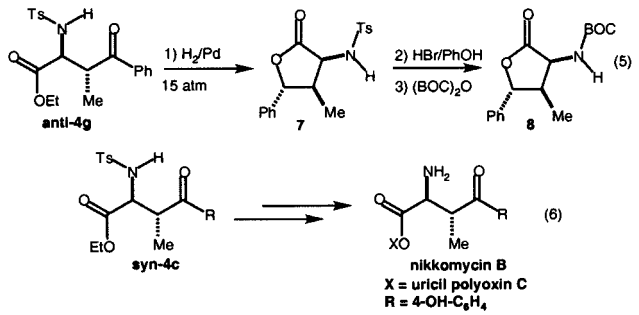
[a] Reactions were carried out at 0 °C to room temperature. [b] Reaction carried out at −78 °C. [c] Enantiomeric excesses were determined by a CHIRALCEL OD chiral HPLC column.

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 (PPh_3, 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 CH_2Cl_2 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•$CuClO_4$•$(CH_3CN)_2$ (**3d**) (entry 2), while the diastereoselectivity all but vanished with the use of achiral catalyst $CuClO_4$•$(PPh_3)_2$•$(CH_3CN)_2$ (**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•$Pd(ClO_4)_2$ (**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 silyl 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*,2*S*)-**4h**.[37] Stereoregularity was then inferred for the cyclic products **4i**, **4j**, and **4k**.

(29) Mukaiyama and co-workers also note predominant anti addition to aldehydes regardless of double bond geometry in the presence of a Lewis acid catalyst: (a) Mukayama, T.; Kobayashi, S.; Tamura, M.; Sagawa, Y. *Chem. Lett.* **1987**, 491. (b) Mukaiyama, T.; Kobayashi, S.; Murakami, M. *Chem. Lett.* **1985**, 447.

(30) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066.

(31) 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.

(33) Desilylation of **4i** can be performed in a number of ways, see: (a) Hayes, M. A. In *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Pergamon: New York, 1995; Vol. 1, p 447. (b) Mukai, C.; Miyakawa, M.; Mihira, A.; Hanaoka, M. *J. Org. Chem.* **1992**, *57*, 2034. (c) Mukai, C.; Cho, W.-J.; Kim, I. J.; Hanaoka, M. *Tetrahedron* **1991**, *47*, 3007.

(34) (a) Gair, S.; Jackson, R. F. W.; Brown, P. A. *Tetrahedron Lett.* **1997**, *38*, 3059. (b) Barluenga, J.; Viado, A. L.; Aguilar, E.; Fustero, S.; Olano, B. *J. Org. Chem.* **1993**, *58*, 5972.

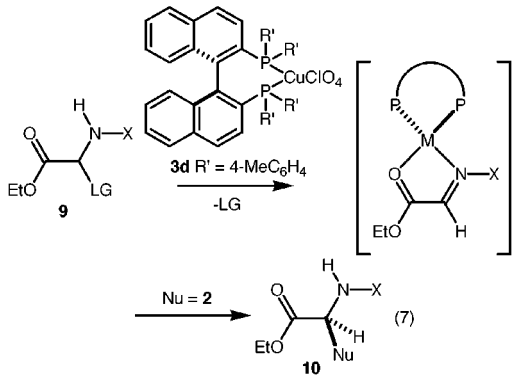
(35) (a) Jackson, R. F. W.; Rettie, A. B.; Wood, A.; Wythes, M. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1719. (b) Raffauf, R. F.; Zennie, T. M.; Onan, K. D.; LeQuesne, P. W. *J. Org. Chem.* **1984**, *49*, 2714.

Table 3. Asymmetric Alkylations of **1d** and Acetals Using Catalyst **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

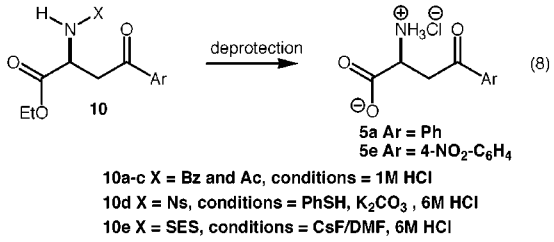
[a] Abbreviations: Bz, benzoyl; *p*-An, 4-methoxybenzoyl; Ac, acetyl; Ts, *p*-toluenesulfonyl; Ms, methanesulfonyl; Ns, *p*-nitrobenzenesulfonyl; SES, trimethylsilyl-ethanesulfonyl. Enantiomeric excesses were determined by a CHIRALCEL OD chiral HPLC column. [b] Reaction carried out in refluxing CH_2Cl_2. [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, sulfonamido *N*,*O*-acetals proved to be the most useful acetal substrates.[40]

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).

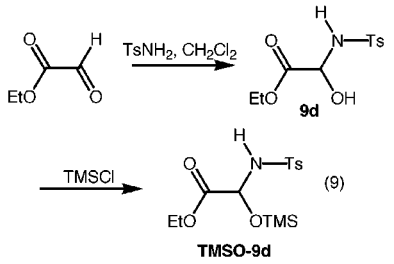


Once again, a variety of protecting groups including 2-trimethylsilylethylenesulfonyl (SES), benzoyl (Bz), and nosyl (Ns) were demonstrated to be effective under the reaction conditions producing products **10** in moderate to excellent enantioselectivity. In the deprotection step, compounds **10a**−**e** 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*,*O*-acetal 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*,*O*-acetal **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 silyl ketene acetals can be quenched through silyl 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 CD_2Cl_2 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

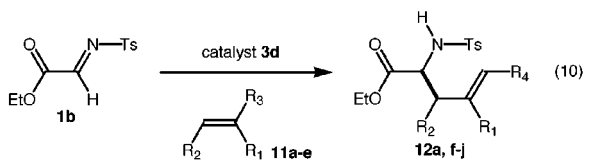
(36) (a) Barrett, A. G. M.; Dhanak, D.; Lebold, S.; Russell, M. A. *J. Org. Chem.* **1991**, *56*, 1894. (b) Helms, G. L.; Moore, R. E.; Niemczura, W. P.; Patterson, G. M. L.; Tomer, K. B.; Gross, M. L. *J. Org. Chem.* **1988**, *53*, 1298.
(37) A sample of compound **4h** was donated to the National Cancer Institute as a potential antiproliferative agent as part of their study to identify new classes of anticancer drugs.
(38) (a) Münster, P.; Steglich, W. *Synthesis* **1987**, 223. (b) Kober, R.; Steglich, W. *Liebigs Ann. Chem.* **1983**, 599.
(39) For glycine derived *N*-acetals used for the chiral auxiliary-based asymmetric synthesis of α-amino acids see: Williams, R. M.; Sinclair, P. J.; Zhai, D.; Chen, D. *J. Am. Chem. Soc.* **1988**, *110*, 1547.
(40) Matuszczak, B. *Monatsh. Chem.* **1996**, *127*, 1291.
(41) (a) Bowman, W. R.; Coghlan, D. R. *Tetrahedron* **1997**, *53*, 15787. (b) Garigipati, R. S.; Tschaen, D. M.; Weinreb, S. M. *J. Am. Chem. Soc.* **1990**, *112*, 3475. (c) Weinreb, S. M.; Demko, D. M.; Lessen, T. A. *Tetrahedron Lett.* **1986**, *42*, 2099.
(42) (a) Kosikowski, A. P.; Adamczyk, M. *J. Org. Chem.* **1983**, *48*, 366. (b) Salituro, F.; Tomlinson, R. C.; Baron, B. M.; Palfreyman, M. G.; McDonald, I. A. *J. Med. Chem.* **1994**, *37*, 334.

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 ^{1}H NMR or TLC. This finding leads us to suggest that adventitious water, silanol, or an $L_nCu\bullet ROH$ 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.



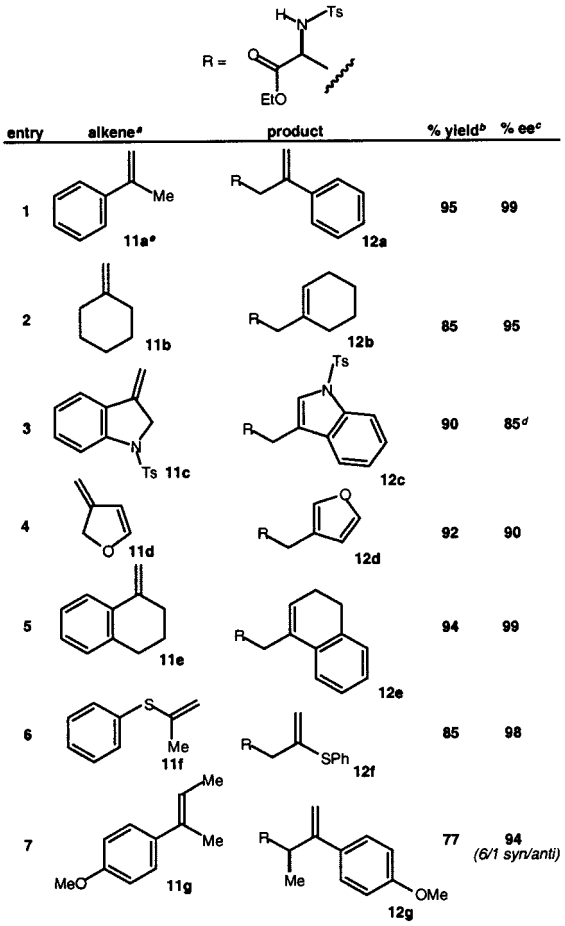
We have used this mechanistic information to optimize the reaction further in the form of a one-pot procedure. By using 1 equiv of TMSCl, acetal **9d** (which is formed in situ from ethyl glyoxylate and $TsNH_2$) can be silylated in the pot to form the putative silylacetal TMSO-**9d**, thus obviating 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 CH_2Cl_2 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 ^{1}H NMR in the presence of (+)-Pr(hfc)$_3$ chiral shift reagent. [e] Reaction performed on 5 mmol scale.

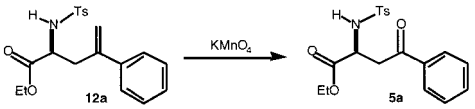
was conducted on a gram scale with 1 mol % **3d**, both the selectivity and yield were maintained. Aliphatic olefins worked well under the reaction conditions as methylenecyclohexane **11b** led to product **12b** in 85% yield and 95% ee (entry 2). Heteroatom-containing ene substrates are also compatible 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

(43) (a) Kita, Y.; Shibata, N.; Miki, T.; Takemura, Y.; Tamura, O. *Chem. Pharm. Bull.* **1992**, *40*, 12. (b) Onaka, M.; Ohno, R.; Izumi, Y. *Tetrahedron Lett.* **1989**, *30*, 747.

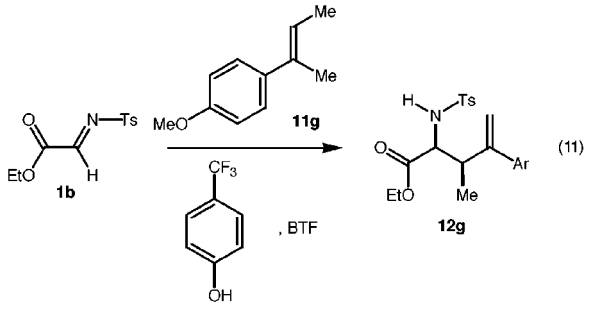
(44) For acid-catalyzed siloxane formation, see: Grubb, W. T. *J. Am. Chem. Soc.* **1954**, *76*, 3408.

(45) Subsequent to our report, Jørgensen published an imino ene reaction using catalyst **3d**: Yao, S.; Fang, X.; Jørgensen, K. A. *J. Chem. Soc., Chem. Commun.* **1998**, 2547.

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



and ee toward the total synthesis of complestatin.[48] The oxygen-containing ene[49] **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 precedented[50] and has been elegantly applied in the total synthesis of members of the methanomorphanthridine

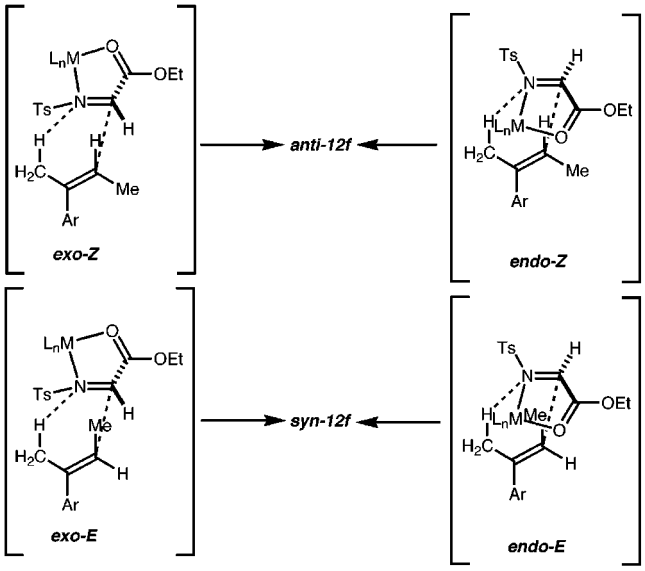
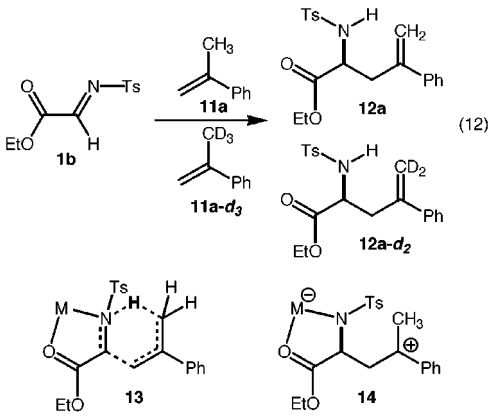


Figure 3. Proposed closed transition state model for the diastereoselective imino ene reaction.

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

(47) To date the syntheses of optically active tryptophan derivatives have centered on transfer of chirality: (a) Tabushi, I.; Kuroda, Y.; Yamada, M.; Higashimura, H. *J. Am. Chem. Soc.* **1985**, *107*, 5545. Enzymatic resolution: (b) Gebler, J.; Woodside, A. B.; Poulter, C. D. *J. Am. Chem. Soc.* **1992**, *114*, 7354. (c) Gerig, J. T.; Klinkenborg, J. C. *J. Am. Chem. Soc.* **1980**, *102*, 4267. Preparatory chiral HPLC separations: (d) Sakagami, Y.; Manabe, K.; Aitani, T.; Thiruvikraman, S. V.; Marumo, S. *Tetrahedron Lett.* **1993**, *34*, 1057.
(48) Elder, A. M.; Rich, D. H. *Org. Lett.* **1999**, *1*, 1443.
(49) Miles, W. H.; Berreth, C. L.; Smiley, P. M. *Tetrahedron Lett.* **1993**, *34*, 5221.
(50) (a) Weinreb, S. M.; Smith, D. T.; Jin, J. *Synthesis* **1998**, *61*, 509. (b) Laschat, S.; Fröhlich, R.; Wibbeling, B. *J. Org. Chem.* **1996**, *61*, 9. (c) Laschat, S.; Grehl, M. *Chem. Ber.* **1994**, *127*, 2023. (d) Laschat, S.; Grehl, M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 458. (e) Mikami, K.; Kaneko, M.; Yajima, T. *Tetrahedron Lett.* **1993**, *34*, 4841. (f) Tschaen, D. M.; Turos, E.; Weinreb, S. M. *J. Org. Chem.* **1984**, *49*, 5058. (g) Tschaen, D. M.; Weinreb, S. M. *Tetrahedron Lett.* **1982**, *23*, 3015.
(51) Jin, J.; Weinreb, S. M. *J. Am. Chem. Soc.* **1997**, *119*, 5774.
(52) Tanner, D.; Hagberg, L. *Tetrahedron* **1998**, *54*, 7907.
(53) Koh, J. H.; Larsen, A. O.; Gagné, M. R. *Org. Lett.* **2001**, *3*, 1233.
(54) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed.; VCH: Weinheim, 1988; pp 164−165.

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_H/k_{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 ~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 CH_2Cl_2. 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 first-order 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 CH_2Cl_2 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

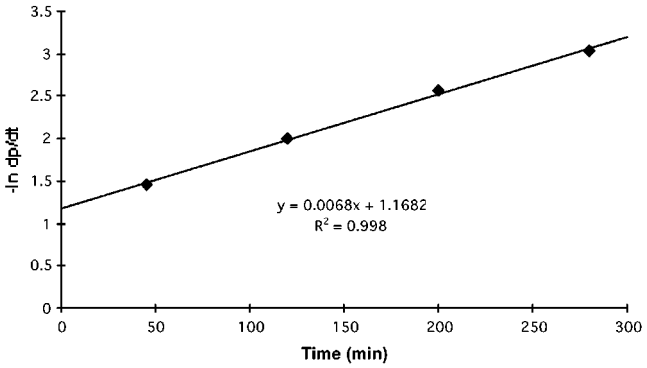


Figure 4. Pseudo first-order behavior of catalytic imino ene reaction.

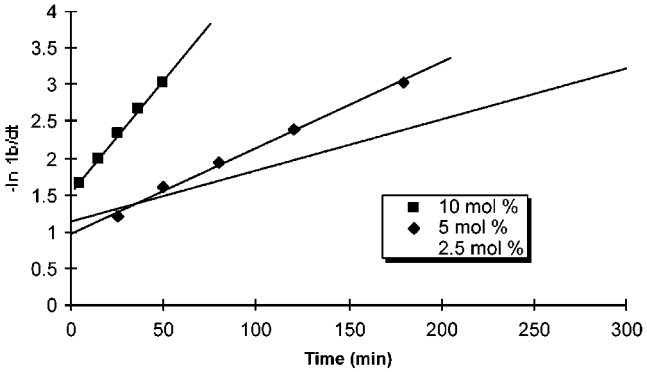


Figure 5. Effect of catalyst loading on rate of imino ene reaction.

us to propose a rate equation for the reaction (eq 13). The observed rate constant k' was determined to be 6.8×10^{-3} 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 3.4×10^{-2} min^{-1} M^{-2}.

$$\text{rate} = \frac{-\text{d}[\mathbf{1b}]}{\text{d}t} = \frac{\text{d}[\mathbf{12a}]}{\text{d}t} = k'[\mathbf{1b}] = k[\mathbf{11a}][\mathbf{3d}][\mathbf{1b}] \quad (13)$$

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.

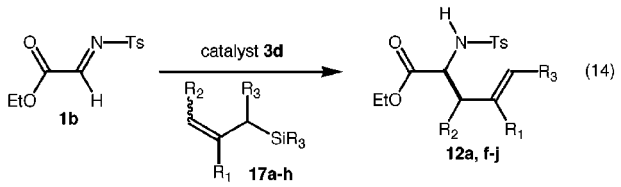
Catalytic, Enantioselective Allylations of α-Imino Esters. Complementary to our work with enol silane and alkene

(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.

(56) Carpenter, B. K. *Determination of Organic Reaction Mechanisms*; Wiley: New York, 1984; pp 83−111.

(57) (a) Laidler, K. J. *Chemical Kinetics*; Harper and Row: New York, 1987. (b) Kobayashi, S.; Ishitani, H. *J. Am. Chem. Soc.* **1994**, *116*, 4083.

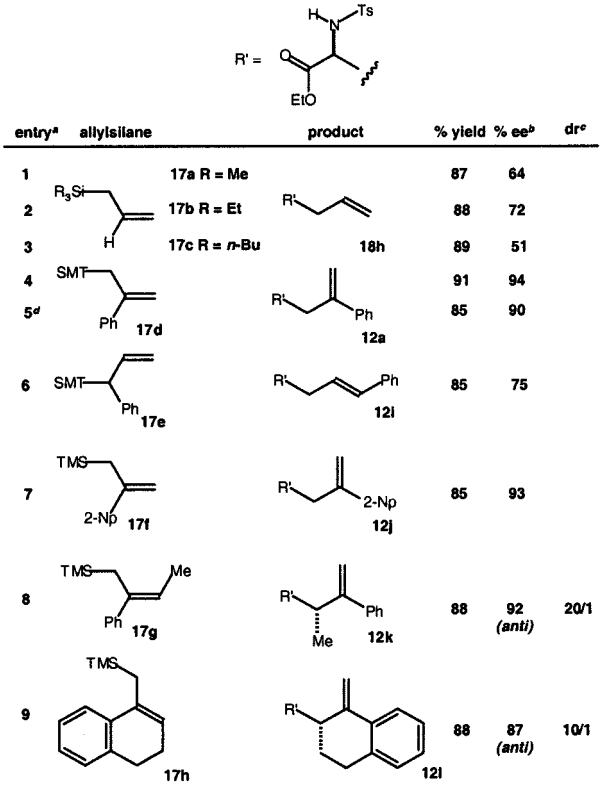
nucleophiles, we have also developed a catalytic, enantio- and diastereoselective procedure for the addition of allylsilanes **17a**−**h** to α-imino ester **1b** catalyzed by complex **3d**, demonstrating the utility of this reaction as an alternative means to homoallylic α-amino acid derivatives **12** (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•$CuClO_4$•$(CH_3CN)_2$ (**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** (R_1, R_2, R_3 = H, R = *n*-Bu) afforded **12h** in 89% yield and 51% ee in CH_2Cl_2. 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, phenyl-substituted 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 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).

Table 5. Allylation Reactions of **1b** with **17a**−**h** Catalyzed by **3d**



[a] Reactions run at −78 °C in CH_2Cl_2. [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**.

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-

(58) (a) Chen, G.-M.; Ramachandran, P. V.; Brown, H. C. *Angew. Chem., Int. Ed.* **1999**, *38*, 825. (b) Nakamura, H.; Nakamura, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 4242. (c) Nakamura, K.; Nakamura, H.; Yamamoto, Y. *J. Org. Chem.* **1998**, *64*, 2614. (d) Yanagisawa, A.; Nakashima, H.; Ishiba, A.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 4723.

(59) Burk, M. J.; Bedingfield, K. M.; Kiesman, W. F. *Tetrahedron Lett.* **1999**, *40*, 3093.

(60) Hayashi, T.; Katsuro, Y.; Kumada, M. *Tetrahedron Lett.* **1980**, *21*, 3915.

(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 $NaHCO_3$ (5 mL) and brine (5 mL). The organic layer was dried over Na_2SO_4, 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•$PdCl_2$ (Aldrich, 31 mg, 0.04 mmol) and $AgClO_4$ (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•$Pd(ClO_4)_2$ as a yellow crystalline solid. The solid was dissolved in CH_2Cl_2 and used in an analogous manner to the aforementioned procedure.

Representative Alkylation of 1b with $Cu(ClO_4)_2$ and (*S*)-BINAP. A solution of (*S*)-BINAP (25 mg, 0.04 mmol) and $Cu(ClO_4)_2$ (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 H_2O/CH_2Cl_2 (10 mL). The organic layer was partitioned, and the aqueous layer was extracted with CH_2Cl_2 (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 CH_2Cl_2 (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 Na_2SO_4, 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 $CuClO_4$•$(CH_3CN)_2$ (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 $MgSO_4$, 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 $CuClO_4$•$(CH_3CN)_4$ (8.2 mg, 0.025 mmol) in benzotrifluoride (1 mL) or CH_2Cl_2 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 CH_2Cl_2 (2 × 5 mL). The combined organic layers were dried over $MgSO_4$, 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 $CuClO_4$•$(CH_3CN)_4$ (7 mg, 0.021 mmol) in CH_2Cl_2 (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 CH_2Cl_2 (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 $MgSO_4$, 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).

Acknowledgment. The authors thank Professors Kenneth Karlin for a supply of the $Cu(ClO_4)$•$(MeCN)_4$ complex and John Toscano for use of his FTIR spectrometer. For financial support T.L. thanks the NSF Career Program, Eli Lilly, DuPont, the Dreyfus Foundation, and the Sloan Foundation. C.C. and A.T. thank the Organic Division of the American Chemical Society for Graduate Fellowships sponsored by Organic Reactions, Inc. (1997−1998 and 2001−2002, respectively). The authors thank Dr. Victor G. Young, Jr., director of the X-ray Crystallographic Laboratory at the University of Minnesota, for obtaining the crystal structures of **4h** and **3c**.

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.

JA016838J