A Novel Synthesis of α-Amino Acid Derivatives through Catalytic, Enantioselective Ene Reactions of α-Imino Esters

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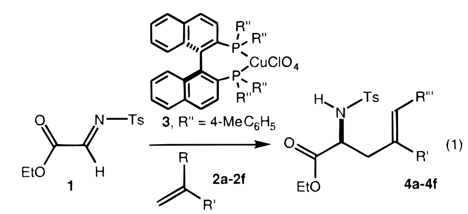
Received June 29, 1998

The Lewis acid-catalyzed ene reaction of carbonyl compounds with alkenes represents a powerful method for selective C−C bond formation,[1] and two notable catalytic, enantioselective variants are known.[2] However, the corresponding catalytic, enantioselective ene reaction between alkenes and imines has not been reported even though the allylic amines that would be generated are useful synthetic intermediates.[3] The diastereoselective version of the imino ene reaction is nevertheless well-precedented[4] and has been elegantly applied in the total synthesis of members of the methanomorphanthridine class of natural products[5] as well as (−)-perhydrohistrionicotoxin.[6] Lewis acid catalysis of the imino ene reaction is also well-known although, in many cases, stoichiometric quantities of promoter are employed.[4a−e] From our standpoint, the use of catalytic amounts of a chiral Lewis acid catalyst in combination with α-imino esters[4e−g,5] as enophiles would unveil a novel route to a variety of enantiopure nonnatural α-amino acids. In previous work, we demonstrated catalytic, enantioselective alkylation of chelating α-imino ester **1** with enolsilane nucleophiles through the use of the versatile Lewis acid catalysts (*R*)- or (*S*)-Tol-BINAP-$CuClO_4\cdot(CH_3CN)_2$ (**3**).[7] In this paper, we report an operationally convenient and efficient, catalytic, enantioselective imino ene reaction of α-imino ester **1** with alkenes **2a**−**f** catalyzed by Lewis acid complex **3** and show this reaction to be a useful new pathway to α-amino acid derivatives **4a**−**f** (eq 1).



We initiated our study with the reaction between **1** and α-methylstyrene **2a**.[8] This ene substrate was chosen on the basis of the known stabilization that an aromatic substituent at C-2 has upon the electrocyclic transition state.[9] Reaction of 1 equiv each of **1** and **2a** catalyzed by 5 mol % (*R*)-Tol-BINAP-$CuClO_4\bullet(CH_3CN)_2$ (**3**) in THF at room temperature is clean and enantioselective (87% ee) but slow and low yielding (35%, Table 1, entry 1). Performing the reaction in CH_2Cl_2 moderately improved the enantioselectivity but did not greatly increase the yield, whereas refluxing the reaction mixture improved yield but eroded enantioselectivity (entries 2−4). We were intrigued by the proposal that aromatic solvents can increase the rates of certain formally electrocyclic reactions;[10] however, Lewis acid complex **3** is not soluble in nonpolar aromatic solvents such as toluene or benzene. Encouraged by a recent report detailing the similar polarity characteristics of CH_2Cl_2 and benzotrifluoride (BTF),[11] we tested this aromatic solvent in our reaction. Catalyst **3** is soluble in BTF, and this led to a marked increase in selectivity (99% ee) although the yield after 18 h remained low (entry 5). Screening several other polar aromatic solvents demonstrated similarly high selectivity but modest yields (entries 6−8). We discovered that if we simply doubled the concentration of alkene, the reaction reached completion after 18 h while excellent ee (99%, entry 9)[12] was maintained. Several other transition-metal (*R*)-BINAP complexes were screened for catalytic activity and enantioselectivity, as shown in Table 2. However, our original system proved superior to these alternatives in each case. Additionally, although our standard screening protocol employed 5 mol % catalyst, we found that a multigram scale reaction between **1** and **2a** could be conducted with 2 mol % catalyst, affording product in 90% yield and 99% ee.

With optimal conditions for α-methylstyrene (**2a**) in hand,[13] several other alkenes were investigated, all affording good to excellent yield and enantioselectivity (Table 3).[14] For example, tetralene **2b** provided **4b** in 94% yield and 99% ee, and an aliphatic ene, methylenecyclohexane **2c**, similarly led to product in 85% yield and 95% ee. Heteroatom-containing ene substrates are also compatible with our reaction conditions, demonstrating that the catalyst is tolerant of various functional groups and Lewis basic sites on the alkene. For example, vinyl sulfide **2d** (entry 4) is an excellent substrate, affording product in 85% yield and 98% ee. The transformation on an amino-containing ene allows the construction of tryptophan derivative **4e** (entry 5, 90% yield and 85% ee). This is interesting because there currently exists no general synthetic method for the construction of tryptophan analogues in optically active form through catalytic methodology.[15] Finally, an oxygen-containing ene provided fufurylalanine **4f** in 85% yield and 89% ee (entry 6). It is noteworthy that most of the products (**4a,b,d,f**) can be obtained in optically pure form

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(3) For a review of imino ene reactions, see: (a) Weinreb, S. M. *Top. Curr. Chem.* **1997**, *190*, 131. (b) Borzilleri, R. B.; Weinreb, S. M. *Synthesis* **1995**, 347.

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(7) (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. (c) Carreira et al. have employed a Tol-BINAP-CuF_2 complex as an effective catalyst for the asymmetric aldol reaction, see: Kruger, J.; Carreira, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 837.

(8) The rate of reaction between **1** and **2a** at ambient temperature and pressure is slow. No product is noted after 5 days regardless of solvent used.

(9) Thomas, B. E.; Houk, K. N. *J. Am. Chem. Soc.* **1993**, *115*, 790.

(10) Sauer, J.; Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 779.

(11) Ogawa, A.; Curran, D. P. *J. Org. Chem.* **1997**, *62*, 450.

(12) It is well-known that the ene reaction has a negative entropy of activation (Franzus, B. *J. Org. Chem.* **1963**, *28*, 2954) and is believed to have a negative volume of activation (Matsumoto, K.; Sera, A. *Synthesis* **1985**, 999). We expected high-pressure conditions to produce a rate enhancement. As expected, impression of 12 kbar upon the reaction in BTF gave a quantitative yield of **4a** even without a catalyst present. However, under these high pressure conditions the reaction proceeds by a nonselective pathway, leading only to racemic **4a**.

(13) A general procedure for the conduction of imino ene reactions consists of the following: All manipulations prior to workup were performed under N_2, either in a drybox or by syringe techniques. To 0.5 mmol of α-imino ester **1** stirring in 1 mL of BTF was added 0.025 mmol of catalyst **3** (formed by stirring 0.025 mmol $Cu(MeCN)_4ClO_4$ and 0.026 mmol (*R*)-Tol-BINAP in 1 mL of BTF for 1 h) followed by addition of 1 mmol of ene substrate **2**. The reaction was then stirred until TLC indicated complete conversion of the starting material. The mixture was quenched by the addition of H_2O and extracted with CH_2Cl_2. Combination of the organic extracts, drying with Na_2SO_4, concentration by rotary evaporation, and finally purification by flash column chromatography with EtOAc/hexanes as eluent provided analytically pure **4**.

(14) See Supporting Information for proof of absolute stereochemistry.

10.1021/ja982257r CCC: $15.00
Published on Web 10/09/1998

Table 1. Solvent Effects on Ene Reactions between **1** and **2a**

entry	conditions[a]	% yield[b]	% ee[c]	entry	conditions[a]	% yield[b]	% ee[c]
1	THF, rt	35	87	6	*o*-dichlorobenzene, rt	35	90
2	CH_2Cl_2, rt	30	93	7	nitrobenzene, rt	28	90
3	THF, reflux	57	79	8	anisole, rt	52	96
4	CH_2Cl_2, reflux	61	87	9	BTF, rt, 2 equiv **2a**	92	99
5	BTF, rt	55	99				

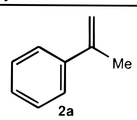
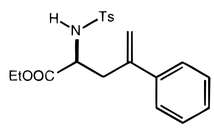
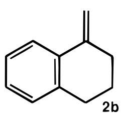
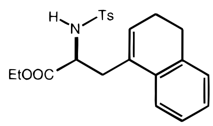
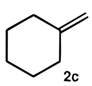
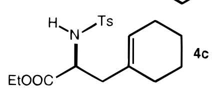
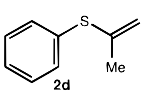
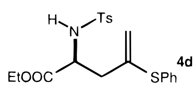
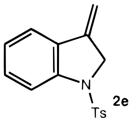
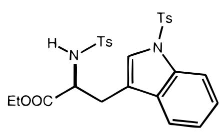
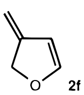
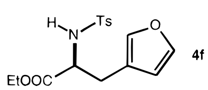
[a] Unless otherwise noted, reactions were run with 0.5 mmol of imine **1a**, 0.5 mmol of **2a**, and 0.025 mmol of catalyst **3** at the specified temperature for 18 h. [b] Isolated yield of **4a** after chromatography. [c] Enantiomeric excess of **4a** before recrystallization; determined by HPLC on chiral support.

Table 2. Results of Other Metal (R)-BINAP Complexes on the Imino Ene Reaction

entry	metal[a]	% ee	entry	metal[a]	% ee
1	$AgSbF_6$	71	4	$Ni(ClO_4)_2$	0
2	$Pd(SbF_6)_2$	35	5	$Co(SbF_6)_2$	0
3	$Rh(COD)ClO_4$	0	6	$Sn(OTf)_2$	***b***

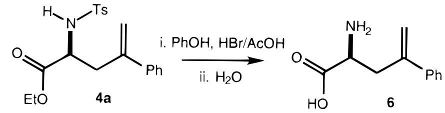
[a] Screen performed with 5 mol % metal and 5.5 mol % *(R)*-BINAP. [b] Reaction returned only starting materials.

Table 3. Ene Reactions of **2a**−**f** with **1** Catalyzed by **3**

entry	alkene	product	% yield[b]	% ee[c]
1		 4a	92	99
2		 4b	94	99
3		 4c	85	95
4		 4d	85	98
5		 4e	90	85[d]
6		 4f	85	89

[a] Reactions were conducted under standard conditions in BTF solvent at room temperature,[13] unless otherwise noted. [b] Isolated yield of **4** after chromatography. [c] Enantiomeric excess before crystallization; determined by HPLC on chiral support. [d] Enantioselectivity determined by NMR in the presence of a chiral shift reagent.

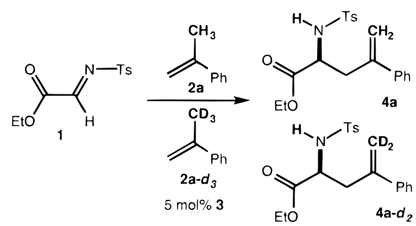
without chromatography by straightforward crystallization of the organic concentrate (EtOAc/hexanes) after aqueous workup. Removal of the tosyl group from product **4a** was accomplished by treatment with HBr/phenol[16] to provide α-amino acid **6** in 75% yield (eq 2). These reaction conditions are strenuous, as are all of the alternatives (sodium naphthalenide, Li/NH_3, $h\nu$);[17] however,



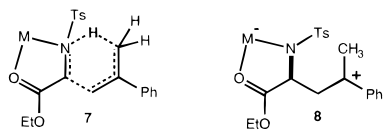
(2)

the deprotection proceeds in respectable yield without racemization in our system,[14] although milder deprotection alternatives are under investigation.

Prototype ene reactions have been proposed to proceed through a concerted, nonpolar transition state.[18] 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 **2a** and **2a-*d*$_3$** was subjected to our standard reaction conditions in both BTF and THF solvent in the presence of **1** and 5 mol % **3** (eq 3). Analysis of the reaction mixture at 5% conversion indicated



(3)



a phenomenological KIE (k_H/k_{D3}) of 4.4 in THF and BTF.[19] The observed KIE is a superposition of normal primary and α-secondary KIEs, and as a consequence, the primary KIE should account for about ~80% of the observed value.[20] 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 **7**). Were the reaction to proceed stepwise through the cationic intermediate **8**, an observed *β*-secondary KIE in the neighborhood of 1.9 (or lower) would be expected. Whether the reaction proceeds through a concerted pathway for other more polar substrates is under current investigation.

In conclusion, we have demonstrated the first catalytic, enantioselective imino ene reaction that provides direct access to nonnatural α-amino acids of high optical purity. Application of this methodology to the production of complex α-amino acid derivatives, natural products, and enzyme inhibitors is underway and will be reported in due course.

Acknowledgment. The authors sincerely thank Professor John Toscano for access to his FTIR spectrometer and Professor Gary Posner for use of his high pressure reaction apparatus. For support, T.L. thanks Eli Lilly for a Young Faculty Grantee Award, the American Cancer Society, and the Petroleum Research Fund. D.F. thanks JHU for a Marks Fellowship and C.C. thanks the Organic Division of the American Chemical Society for a Graduate Fellowship (sponsored by Organic Reactions, Inc.).

Supporting Information Available: General procedures for the conduct of catalytic reactions, spectroscopic details for all new compounds, and proof of absolute configuration are included (5 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

JA982257R

(15) To date the syntheses of optically active tryptophan derivatives have centered on transfer of chirality (Tabushi, I.; Kuroda, Y.; Yamada, M. Higashimura, H. *J. Am. Chem. Soc.* **1985**, *107*, 5545), enzymatic resolution (Gebler, J.; Woodside, A. B.; Poulter, C. D. *J. Am. Chem. Soc.* **1992**, *114*, 7354 and Gerig, J. T.; Klinkenborg, J. C. *J. Am. Chem. Soc.* **1980**, *102*, 4267), and preparatory chiral HPLC separations (Sakagami, Y.; Manabe, K.; Aitani, T.; Thiruvikraman, S. V.; Marumo, S. *Tetrahedron Lett.* **1993**, *34*, 1057.

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(19) 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 **2a** and **2a-*d*$_3$**. See the Supporting Information for details.

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