Catalytic Approach for the Formation of Optically Active Allyl α-Amino Acids by Addition of Allylic Metal Compounds to α-Imino Esters

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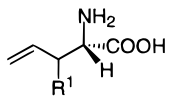
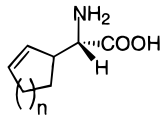
A new catalytic enantioselective approach for the formation of allyl α-amino acid derivatives by reaction of *N*-tosyl α-imino esters with allyl stannanes and silanes catalyzed by chiral copper(I) complexes has been developed. A series of different BINAP and phosphine−oxazoline (P,N) ligands have, in combination with various Lewis acids, been tested as chiral catalysts for allylation of *N*-tosyl α-imino esters. It has been found that both type of ligands, in combination with copper(I) salts, give highly valuable unsaturated α-amino acid derivatives. The reaction has been investigated for different allyl stannanes and silanes, and it has been found that tri-*n*-butyl allyl stannane gives the best results of the simple allyl compounds tested, leading to *γ*,*δ*-unsaturated α-amino acid derivatives in up to 94% yield and with up to 83% ee, which can be improved to be >95% ee by recrystallization. The reaction has also been investigated using different acyclic and cyclic allyl stannanes leading to various types of unsaturated α-amino acid derivatives in very high yield (up to 95%) and with up to 98% ee. The stereochemistry and absolute configurations of the allyl α-amino acid derivatives have been determined by X-ray analysis, and it is suggested that the reaction takes place as an ene-like reaction.

Introduction

Optically active α-amino acids are highly valuable compounds in science and technology. They serve, for example, as precursors for new and interesting peptides and proteins, complex chiral molecules, and combinatorial libraries.[1,2] Effective procedures to prepare optically active α-amino acids are therefore highly desirable, and not surprisingly, a great deal of work has been devoted to the asymmetric synthesis of α-amino acids.[3] One of the most direct ways to obtain α-amino acids is the nucleophilic addition to glyoxylate imines, and previous work in this field has mainly been conducted by employing various chiral auxiliaries.[3h−m] Allylic α-amino acids such as **1a** and **1b** are of particular importance as building blocks for organic synthesis because the *γ*,*δ*-double bond can easily be converted into many different functional groups.[2]



1a



1b

Recently, the first catalytic enantioselective ene reaction of the *N*-tosyl imino ester **2** with alkenes, which provided a highly efficient route to the formation of optically active allylic α-amino acids, has been reported independently by Lectka's group and by us.[4] Unfortunately, the simple *γ*-unsubstituted allylic α-amino acid, such as **1a**, could not be obtained using this asymmetric catalytic ene reaction, as monosubstituted alkenes did not react. We have thus turned our attention to the development of a catalytic enantioselective addition reaction that can lead to the class of allylic α-amino acid derivatives **1a** and **1b**. This paper presents the development of the catalytic enantioselective allylic addition[5] of allylic metal compounds, such as **3a**,**b** and **4a**−**d**, to the *N*-tosyl glyoxylate imino ester **2**, catalyzed by chiral Lewis acid complexes and leading to the highly valuable *γ*,*δ*-unsaturated α-amino acid derivatives **5** (eq 1). Furthermore, reactions of both cyclic and other acyclic allyl

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(1) See, for example: Bloch, R. *Chem. Rev.* **1998**, *98*, 1407.
(2) See, for example: (a) Bolton, G. L.; Hodges, J. C.; Rubin, J. R. *Tetrahedron* **1997**, *53*, 6611. (b) Miller, S. J.; Blackwell, H. E.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 9606. (c) Pernerstorfer, J.; Schuster, M.; Blechert, S. *J. Chem. Soc., Chem. Commun.* **1997**, 1949. (d) Broxterman, Q. B.; Kaptein, B.; Kamphuis, J.; Schoemaker, H. E. *J. Org. Chem.* **1992**, *57*, 6286. (e) Kurokawa, N.; Ohfune, Y. *J. Am. Chem. Soc.* **1986**, *108*, 6041. (f) Schmidt, U.; Schmidt, J. *Synthesis* **1994**, 300. (g) Schneider, H.; Sigmund, G.; Schricker, B.; Thirring, K.; Berner, H. *J. Org. Chem.* **1993**, *58*, 683.
(3) See, for example: (a) Cintas, P. *Tetrahedron* **1991**, *47*, 6079. (b) Williams, R. M.; Im, M.-N. *J. Am. Chem. Soc.* **1991**, *113*, 9276. (c) Williams, R. M.; Im, M.- N. *Tetrahedron Lett.* **1988**, *29*, 6075. (d) Ikegami, S.; Uchiyama, H.; Hayama, T.; Katsuki, T.; Yamaguchi, M. *Tetrahedron* **1988**, *44*, 5333. (e) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539. (f) Myers, A. G.; Gleason, J. L.; Yoon T.; Kung, D. W. *J. Am. Chem. Soc.* **1997**, *119*, 656. (g) Tanaka, K.; Ahn, M.; Watanabe, Y.; Fuji, K. *Tetrahedron: Asymmetry* **1996**, *7*, 1771. (h) Yamamoto, Y.; Ito, W.; Maruyama, K. *J. Chem. Soc., Chem. Commun.* **1985**, 1131. (i) Yamamoto, Y.; Ito, W. *Tetrahedron* **1988**, *44*, 5415. (j) Yamamoto, Y.; Nishii, S.; Maruyama, K.; Komatsu, T.; Ito, W. *J Am. Chem. Soc.* **1986**, *108*, 7778. (k) Hanessian, S.; Yang, R.-Y. *Tetrahedron Lett.* **1996**, *37*, 5273. (l) Kazmaier, U.; Krebs, A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2012. (m) Hallett, D. J.; Thomas, E. J. *J. Chem. Soc., Chem. Commun.* **1995**, 657. (n) Yeh, T.-L.; Liao, C.-C.; Uang, B.-J. *Tetrahedron* **1997**, *53*, 11141. (o) Hagiwara, E.; Fujii, A.; Sodeoka, M. *J. Am. Chem. Soc.* **1998**, *120*, 2474.
(4) (a) Drury, W. J., III; Ferraris, D.; Cox, C.; Young, B.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 11006. (b) Yao, S.; Fang, X.; Jørgensen, K. A. *J. Chem. Soc., Chem. Commun.* **1998**, 2547.

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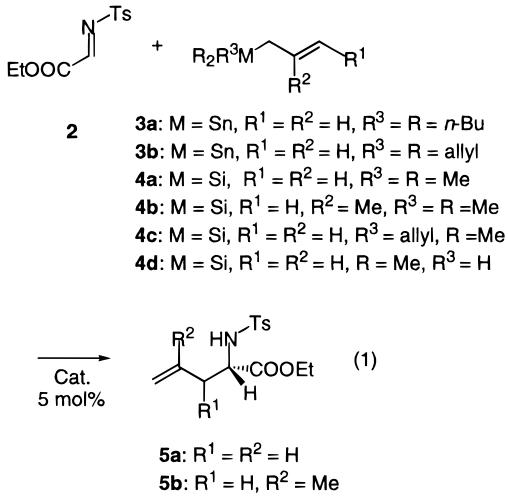
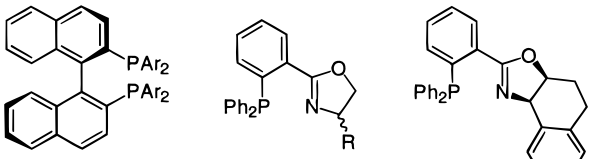
stannanes leading to attractive α-amino acid derivatives are also presented.



Results and Discussion

The chiral complexes prepared from the chiral P,P-ligands BINAP **6a**,**b** and copper(I) salts have been proven efficient for catalytic enantioselective alkylation with enol silanes and hetero-Diels–Alder reactions of the *N*-tosyl imino ester **2**.[6] Phosphine–oxazoline ligands (P,N-ligands) have been shown useful in various catalytic asymmetric reactions, such as π-allyl addition and Heck reactions.[7] Thus, we have studied the present allylic addition to **2**, applying both the BINAP **6a**,**b** and P,N-ligands[8] **7a**–**d** as chiral auxiliaries.



The allyl stannanes **3a**,**b** and silanes **4a**–**d** have been tested for the reaction with the *N*-tosyl imino ester **2** in the presence of 5 mol % (*S*)-Tol-BINAP **6b**-$CuPF_6$ as catalyst in CH_2Cl_2 (eq 1) (for experimental procedure, see Experimental Section). Generally, the reaction of allyl stannanes **3a**,**b** with **2** proceeds well at −78 °C, and full conversion was observed after stirring overnight. Silanes **4a**–**d** were less reactive toward **2** and higher reaction temperatures of −20 to 25 °C were required. The results are given in Table 1.

Table 1. Reaction of *N*-Tosyl α-Imino Ester 2 with Allyl Stannanes 3a,b and Silanes 4a–d in the Presence of (*S*)-Tol-BINAP 6b-$CuPF_6$ (5 mol %) in CH_2Cl_2 (eq 1)

Entry	Allyl-metal compound		Yield[a] / %	ee[b] / %
1	$(n\text{-Bu})_3Sn$	**3a**	**5a** - 88	23 (*R*)[c]
2	$(allyl)_3Sn$	**3b**	**5a** - 85	21 (*R*)[c]
3	Me_3Si	**4a**	**5a** - 34	58 (*R*)[c]
4	Me_3Si, Me	**4b**	**5b** - 47	64 (*R*)[d]
5	$Me_2Si(\ )_2$	**4c**	**5a** - 34	57 (*R*)[c]
6	H, Me_2Si	**4d**	**5a** - 40	58 (*R*)[c]

[a] Isolated yield. [b] Determined by HPLC on Chiralcel OD column. [c] Absolute configuration was assigned by X-ray analysis. [d] Absolute configuration was assigned by comparing HPLC results with a reference compound.

The results in Table 1 show that the allyl stannanes **3a**,**b** give the highest yield but low ee of the allyl α-amino acid derivative **5a** by reaction with the *N*-tosyl imino ester **2** (entries 1 and 2). The allyl silanes **4a**,**c**,**d** also react with **2** using (*S*)-Tol-BINAP-**6b**-$CuPF_6$ as the catalyst, but the yield of **5** is lower compared with that from **3a**,**b**, whereas an improvement of the ee to 58% is observed (entries 3, 5, and 6). Using the allyl silane **4b** gives the allyl α-amino acid derivative **5b** in 47% yield with an ee of 64% (entry 4).

The high yield of the allyl α-amino acid derivative **5a** by reaction of the allyl stannane **3a** with the *N*-tosyl imino ester **2** catalyzed by (*S*)-Tol-BINAP **6b**-$CuPF_6$ leads us to study this reaction further. Performing this catalytic reaction in THF led to a significant improvement of the ee of **5a**, as 80% ee was obtained. Thus, the reaction of **2** with **3a** catalyzed by (*R*)-Tol-BINAP **6b**-$CuPF_6$ was investigated in various solvents, as well as for different anions of copper(I) salts. The results are presented in Table 2.

It appears from Table 2 that the isolated yields of the allyl α-amino acid derivative **5a** are very high for all solvents and anions investigated, as up to 96% yield is obtained in acetonitrile. The ee of **5a** is very dependent on the solvents used. In THF and toluene, the ee is improved to 80% and 83%, respectively (entries 2 and 5), whereas in acetonitrile and *N*-methyl-2-pyrrolidinone, a racemic mixture is formed (entries 6 and 7). In contrast to the solvent dependence, the ee is nearly independent of the anions used (entries 2, 8, and 9).

The different chiral P,P-ligands **6a**,**b** and P,N-ligands **7a**–**d** have in combination with $CuPF_6$ as the Lewis acid

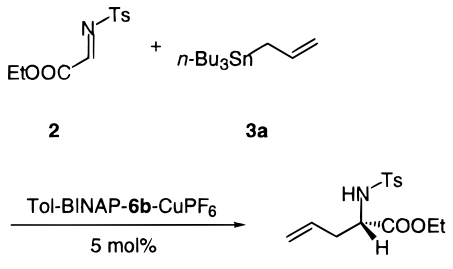
(5) For the first asymmetric catalytic allylation of imines, see: (a) Nakamura, H.; Nakamura, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 4242. For asymmetric addition of organometalic reagents to imines using substoichiometric to catalytic amounts of external chiral ligands, see: (b) Denmark, S.-E.; Nicaise, O. J.-C. *J. Chem. Soc., Chem. Commun.* **1996**, 999 and the references therein. For asymmetric, catalytic Mannich-type reactions and Strecker reactions using chiral zirconium catalysts, see: (c) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **1997**, *119*, 7153. (d) Ishitani, H.; Komiyama, S.; Kobayashi, S. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3186.

(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. (c) Yao, S.; Johannsen, M.; Hazell R. G.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **1998**, *37*, 3121.

(7) (a) LIoyd-Jones, G. C.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 462. (b) Sprinz, J.; Helmchen, G. *Tetrahedron Lett.* **1993**, *34*, 1769. (c) Dawson, G. J.; Frost, C. G.; Williams, J. M. J.; Coote, S. J. *Tetrahedron Lett.* **1993**, *34*, 3149. (d) Loiseleur, O.; Meier, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 200. (e) Wiese, B.; Helmchen, G. *Tetrahedron Lett.* **1998**, *39*, 5727.

(8) For the preparation of P,N-ligands, see: (a) Peer, M.; de Jong, J. C.; Kiefer, M.; Langer, T.; Rieck, H.; Schell, H.; Sennhenn, P.; Sprinz, J.; Steinhagen, H.; Wiese, B.; Helmchen, G. *Tetrahedron* **1996**, *52*, 7547. (b) Koch, G.; Lloyd-Jones, G. C.; Loiseleur, O.; Pfaltz, A.; Prétôt, R.; Schaffner, S.; Schnider, P.; von Matt, P. *Recl. Trav. Chim. Pays-Bas* **1995**, *114*, 206.

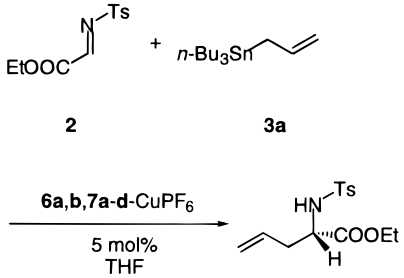
Table 2. Reaction of *N*-Tosyl α-Imino Ester 2 with Tri-*n*-butyl Allyl Stannane 3a Catalyzed by Tol-BINAP 6b-CuX (X = PF_6, ClO_4, and OTf) in Various Solvents



entry	catalyst	solvent	*T* (°C)	yield **5a**[a] (%)	ee[b] (%)
1	(*S*)-**6b**-$CuPF_6$	CH_2Cl_2	−78	88	23 (*R*)
2	(*R*)-**6b**-$CuPF_6$	THF	−78	87	80 (*S*)
3	(*R*)-**6b**-$CuPF_6$	F_3C-Ph	−20	92	71 (*S*)
4	(*R*)-**6b**-$CuPF_6$	Et_2O	−78	90	75 (*S*)
5	(*R*)-**6b**-$CuPF_6$	toluene	−78	91	83 (*S*)
6	(*R*)-**6b**-$CuPF_6$	MeCN	−40	96	rac
7	(*R*)-**6b**-$CuPF_6$	M-Pyr[c]	−20	83	rac
8	(*R*)-**6b**-$CuClO_4$	THF	−78	92	76 (*S*)
9	(*R*)-**6b**-CuOTf	THF	−78	91	73 (*S*)

[a] Isolated yield. [b] Determined by HPLC on Chiralcel OD column. [c] M-Pyr: *N*-methyl-2-pyrrolidinone.

Table 3. Reaction of *N*-Tosyl α-Imino Ester 2 with Tri-*n*-butyl Allyl Stannane 3a in the Presence of Different Chiral P,P- (6a,b) and P,N-Ligands (7a−d)[a]



entry	ligand-$CuPF_6$	mol %	yield **5a**[b] (%)	ee[c] (%, config)
1	(*R*)-**6a**-$CuPF_6$	5	83	72 (*S*)
2	(*R*)-**6b**-$CuPF_6$	5	87	80 (*S*)
3	(*R*)-**6b**-$CuPF_6$	10	85	80 (*S*)
4	(*R*)-**6b**-$CuPF_6$	1	74	73 (*S*)
5	(*R*)-**7a**-$CuPF_6$	10	88	26 (*R*)
6	(*R*)-**7b**-$CuPF_6$	10	94	41 (*S*)
7	(*S*)-**7c**-$CuPF_6$	10	94	73 (*S*)
8	(3a*S*,9b*R*)-**7d**-$CuPF_6$	10	94	38 (*R*)

[a] At −78 °C in THF. [b] Isolated yield. [c] Determined by HPLC on Chiralcel OD column.

been tested for catalytic and enantioselective properties for the reaction of the *N*-tosyl α-imino ester **2** with tri-*n*-butyl allyl stannane **3a** in THF. The results are presented in Table 3.

The complex of $CuPF_6$ salt with (*R*)-Tol-BINAP **6b** induces the highest ee, 80%, of the allyl α-amino acid derivative **5a** among the various P,P- and P,N-ligands tested (entry 2). Increasing the catalyst loading to 10 mol % does not improve the yield and ee of **5a** (entry 3), while it is of practical importance that the reaction proceeds with good yield and ee using only 1 mol % of (*R*)-**6b**-$CuPF_6$ as the catalyst (entry 4). The P,N-ligands **7a**−**d**, which in other reactions have been found to give high ee's,[7] lead to a high isolated yield of **5a**, up to 94% (entries 6−8); however, only moderate ee's are obtained, except in the case where (*S*)-**7c**-$CuPF_6$ is applied as the catalyst and leads to 73% ee (entry 7).

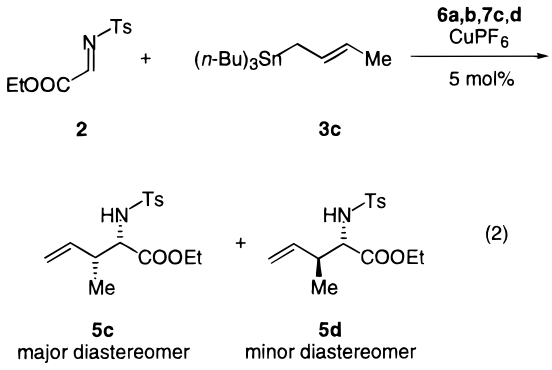
Table 4. Reaction of *N*-Tosyl α-Imino Ester 2 with Tri-*n*-butyl *trans*-2-Butene Stannane 3c in the Presence of Different Chiral P,P- (6a,b) and P,N-Ligands (7c) (eq 2)[a]

entry	ligand-$CuPF_6$	solvent	mol %	yield[b] (%)	**5c**:**5d** ratio	ee[c] **5c**/**5d** (%)
1	(*R*)-**6a**-$CuPF_6$	THF	10	91	7:1	86/87
2	(*R*)-**6b**-$CuPF_6$	THF	5	88	8:1	84/81
3	(*R*)-**6b**-$CuPF_6$	toluene	10	88	7:1	87/89
4	(*R*)-**6b**-$CuPF_6$	CH_2Cl_2	10	87	6:1	43/40
5	(*S*)-**7c**-$CuPF_6$	THF	10	91	10:1	74/81
6	(3a*S*,9b*R*)-**7d**-$CuPF_6$	THF	10	94	7:1	rac/68

[a] At −78 °C in various solvents. [b] Isolated yield. [c] Determined by HPLC on Chiralcel OD column.

The absolute configuration of the allyl α-amino acid derivative **5a** obtained in the reaction of the *N*-tosyl α-imino ester **2** with tri-*n*-butyl allyl stannane **3a** catalyzed by (*R*)-Tol-BINAP **6b**-$CuPF_6$ was assigned as *S* by X-ray analysis (See Supporting Information). Furthermore, the absolute configuration of product **5b** obtained by using (*S*)-Tol-BINAP **6b**-$CuPF_6$ as the catalyst has been assigned as *R* by comparing HPLC results and rotation with a reference compound.[4b] It should also be noted that the absolute configuration of the products formed is independent of the allylic metal compounds used (Table 1).

The reaction of the *N*-tosyl α-imino ester **2** with allyl stannanes has also been studied for allyl stannanes other than **3a**,**b** in an attempt to extend the scope of the reactions. The results for the reaction of **2** with tri-*n*-butyl *trans*-2-butene stannane **3c** (eq 2) in the presence of various chiral copper(I) catalysts in different solvents are presented in Table 4.



The reaction of the *N*-tosyl α-imino ester **2** with tri-*n*-butyl *trans*-2-butene stannane **3c** catalyzed by the various chiral copper(I) catalysts gives a mixture of the two diastereomers **5c** and **5d**. It was not possible to assign the diastereochemistry of **5c** and **5d** on the basis of NMR spectroscopy; however, the structure of the major product **5c** was solved by X-ray analysis and is shown in Figure 1. Thus, the major product **5c** obtained by using (*R*)-Tol-BINAP **6b**-$CuPF_6$ has the absolute configuration as 2*S*,3*R* (Figure 1) and is the *syn* diastereomer.

The ratio of the *syn*:*anti* diastereomers is not very dependent on the chiral ligands; the highest *syn*:*anti* ratio is obtained when the P,N-ligand (*R*)-**7c** is used, leading

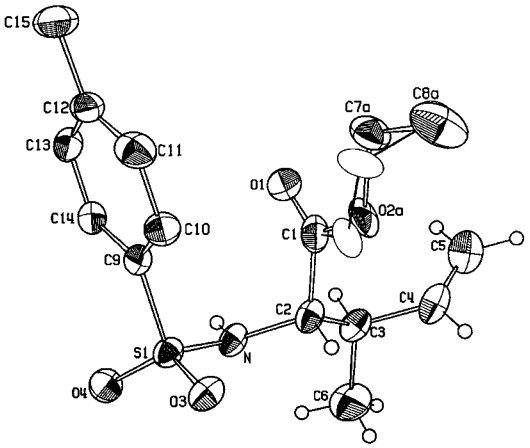
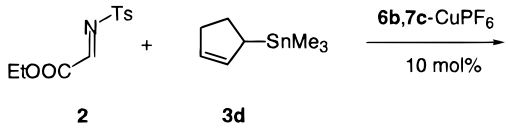


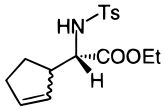
Figure 1. Molecular structure of **5c** for the assignment of diastereochemistry (*syn*) and the absolute configuration, *S* at C2 and *R* at C3. Most hydrogen atoms are omitted. Some disorder of the ethyl group (30%) is indicated in thin line.

to a 10:1 ratio of **5c**:**5d**, whereas the BINAP ligands (*R*)-**6a** and (*R*)-**6b** give a *syn*:*anti* ratio of 6−8:1 in the various solvents studied and up to 87% ee of the *syn* diastereomer. The ee of the *syn* diastereomer **5c** in the reaction catalyzed by (*R*)-Tol-BINAP **6b** (entry 2, Table 4) can be improved to >93% by recrystallization, and the X-ray structure (Figure 1) was solved using this product. It is also notable that the *anti* diastereomer **5d** is obtained with 89% ee in the reaction catalyzed by (*R*)-**6b** in toluene (entry 3). The ee of the *syn*:*anti* diastereomers **5c** and **5d** is about 85% for each using the (*R*)-Tol-BINAP **6b** ligand with THF and toluene as the solvents (entries 2 and 3), whereas lower ee's of the *syn* diastereomer are obtained for the P,N-ligands (entries 5 and 6).

The catalytic enantioselective reaction of the *N*-tosyl α-imino ester **2** has further been studied for the cyclic allyl stannane trimethyl-cyclopent-2-enyl-stannane **3d** (eq 3). This reaction also gives two diastereomers **5e**; the



2 **3d**



5e (3)

syn:*anti* relationship of **5e** could not be assigned. The results for the reaction of **2** with **3d** catalyzed by (*R*)-Tol-BINAP **6b**, (*S*)-Tol-BINAP **6b**, and the P,N-ligand **7c** in combination with $CuPF_6$ in THF are presented in Table 5.

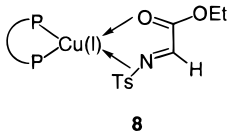
The results in Table 5 show that the two diastereomers of **5e** are formed in high yields but with a relatively low diastereoselectivity. For (*R*)-**6b**-$CuPF_6$ as the catalyst, the two diastereomers are formed in a 1:2 ratio with a very high ee (97%) of the minor diastereomer, while the major diastereomer is formed in 70% ee (Table 5, entry 1). The diastereoselectivity is independent of the absolute configuration of the ligand. The use of (*S*)-**6b**-$CuPF_6$ as the catalyst for the reaction of *N*-tosyl α-imino ester **2** with

Table 5. Reaction of *N*-Tosyl α-Imino Ester 2 with Trimethyl-cyclopent-2-enyl-stannane 3d in the Presence of Different Chiral P,P- (6a) and P,N-Ligands (7c,d) (eq 3)[a]

entry	ligand-$CuPF_6$	yield[b] (%)	diast[c] ratio	ee[d] (%)
1	(*R*)-**6b**-$CuPF_6$	95	1:2	97/70
2	(*S*)-**6b**-$CuPF_6$	95	1:2	98/71
3	(*S*)-**7c**-$CuPF_6$	86	2:1	84/68

[a] At −78 °C in THF. [b] Isolated yield. [c] Ratio of the two diastereomers. [d] Determined by HPLC on Chiralcel OJ column.

Scheme 1



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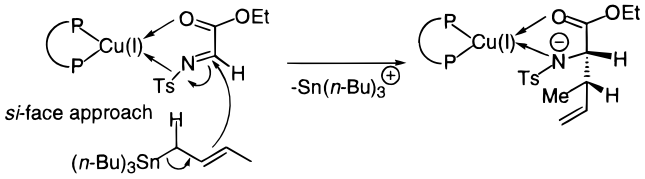

9 **10**

trimethyl-cyclopent-2-enyl-stannane **3d** gives the same major diastereomer with the same ratio and high ee (but opposite enantiomer) (entry 2) as the use of the opposite enantiomer of the ligand. The application of the P,N-ligand **7c** in combination with $CuPF_6$ as the catalyst reverses the diastereomeric ratio relative to the BINAP−$CuPF_6$ catalyst, and the major diastereomer is formed with high (84%) enantiomeric excess (entry 3).

The products **5c**,**d** obtained by the reaction of the *N*-tosyl α-imino ester **2** with tri-*n*-butyl *trans*-2-butene stannane **3c** catalyzed by the various chiral copper(I) catalysts give important information about the reaction mechanism. The formation of **5c** and **5d** with a methyl substituent on C-3 by this reaction points to an ene-like reaction, and a tentative mechanism is outlined in Scheme 1. It is proposed that the first step is a coordination of **2** to the chiral Lewis acid catalyst, leading to intermediate **8**. Previous investigations of catalytic enantioselective hetero-Diels−Alder reactions with various imines using the BINAP−Cu(I) catalytic system have shown that both the ester and tosyl substituents of the imine are necessary for obtaining the high ee.[6c] At the present stage of investigations, we are not able to account for the exact coordination of **2** to the catalyst, and therefore the coordination mode for the imine fragment of **2** is tentatively shown between the nitrogen atom and the tosyl substituent in **8** in Scheme 1. In the next step, the allyl stannane (compound **3c** in Scheme 1) approaches the carbon−nitrogen double bond in an ene-like fashion (**9**). To account for the absolute configuration of the product formed, the alkene has to approach the imine from the *si* face.

A catalytic enantioselective approach for the formation of highly valuable unsaturated α-amino acid derivatives by reaction of *N*-tosyl α-imino esters with mainly allyl stannanes catalyzed by chiral BINAP and phosphine−oxazoline (P,N) copper(I) complexes has been developed. Simple γ,δ-unsaturated α-amino acid derivatives are formed in up to 94% yield and with up to 83% ee, which

can be improved to be >95% ee by recrystallization. Other acyclic and cyclic allyl stannanes give, in an ene-like reaction fashion, the related unsaturated α-amino acid derivatives in high yield with good to moderate diastereoselectivity and with up to 98% ee. It has been found that the BINAP ligands induce higher enantioselectivity in the reactions studied compared to the P,N-ligands. On the basis of the absolute configuration of the products, it is proposed that the allyl stannane approaches the *si* face of the imine when (*R*)-Tol-BINAP-Cu(I) is applied as the catalyst.

Experimental Section

General Methods. All reactions were carried out using anhydrous solvents under N_2 in flame-dried Schlenk tubes. Solvents were dried according to standard procedures and distilled prior to use. TLC was performed on Merck analytical silica gel 60 F_{254} plates and visualized with basic $KMnO_4$ solution. Merck silica gel (230−400 mesh) was used for flash chromatography (FC). Enantiomeric excess (ee) was determined by HPLC using a 4.6 mm × 25 cm Daicel Chiracel OD or OJ column.

Materials. (*R*)-(+)-2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl ((*R*)-BINAP, **6a**) and (*R*)-(+)-2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl ((*R*)-Tol-BINAP, **6b**) were purchased from Strem. (−)-(4*R*)-4,5-Dihydro-2-[2′-(diphenylphosphino)-phenyl]-4-phenyloxazole (**7a**), (+)-(4*R*)-4-*tert*-butyl-4,5-dihydro-2-[2′-(diphenylphosphino)phenyl]oxazole (**7b**), (−)-(4*S*)-4,5-dihydro-2-[2′-(diphenylphosphino)phenyl]-4-isopropyloxazole (**7c**), and (3a*S*,9b*R*)-2-[2′-(diphenylphosphino)phenyl]-3a,4,5,9b-tetrahydro-naphtho[1,2-*d*]-oxazole (**7d**) were prepared according to the literature procedures.[8] $CuPF_6$·4MeCN and $CuClO_4$·4MeCN were prepared according to the literature procedure.[9] $(CuOTf)_2$·C_6H_6 was purchased from Aldrich. Allyltributylstannane, allyltrimethylsilane, diallyldimethylsilane, and allyldimethylsilane were purchased from Lancaster and were used as received. Tetraallylstannane and (2-methyl-propenyl)trimethylsilane were purchased from ABCR. Tri-*n*-butyl-but-2-enyl-stannane and trimethyl-cyclopent-2-enyl-stannane were prepared according to literature procedure.[10] *N*-Tosyl α-imino ester **2** was prepared from ethyl glyoxlate and *p*-toluenesulfonyl isocyanate by literature procedure.[11]

General Procedure. To a flame-dried Schlenk tube was added $CuPF_6$·4MeCN (7.5 mg, 0.02 mmol) and (*R*)-Tol-BINAP (15 mg, 0.022 mmol) under N_2. The mixture was stirred for 1 h under vacuum, freshly distilled anhydrous solvent (1.5 mL) was added with a syringe under N_2, and the light yellow solution was stirred for 0.5−1 h. *N*-Tosyl α-imino ester **2** (0.4 mmol) was added at room temperature, and the solution was placed at the desired reaction temperature before the allylic metal compound (0.48 mmol) was added. Then the reaction temperature was maintained for 12−24 h. After evaporation of the solvent, the crude product was purified by flash chromatography (20% EtOAc in pentane) to give the allyl α-amino acid derivative **5a** as a colorless solid. Enantiomeric excess was detected by chiral HPLC using Chiralcel OD or OJ column (hexane/*i*-PrOH 99.7:0.3, 0.7 mL/min).

Preparation of (*S*)-2-(*N*-Tosyl)-amino-pent-4-enoic Acid Ethyl Ester (5a) using 5 mol % (*R*)-Tol-BINAP−$CuPF_6$·4MeCN. According to general procedure, reaction of *N*-tosyl imino ester **2** (105 mg, 0.4 mmol) and allyltributylstannane **3a** (148 μL, 0.48 mmol) in toluene using 5 mol % complex of (*R*)-Tol-BINAP **6b** and $CuPF_6$·4MeCN as the catalyst afforded, after purification by FC (20% EtOAc in pentane), product **5a** (108 mg, 91%) as a colorless solid with 83% ee detected by chiral HPLC using Chiralcel OD column (hexane/*i*-PrOH 99.7: 0.3, 0.7 mL/min), $[\alpha]^{rt}_D = +16.5$ [*c* 1.1, $CHCl_3$]. The absolute configuration was assigned to be *S* by X-ray analysis (vide infra). Reaction of *N*-tosyl α-imino ester **2** with allyl stannane **3b** and silanes **4a**,**c**,**d** provided the same product **5a**. ^{1}H NMR δ 7.71 (d, J = 8.2 Hz, 2H), 7.28 (d, J = 8.2 Hz, 2H), 5.63 (ddt, J = 17.4, 10.4, 7.0 Hz, 1H), 5.16 (d, J = 8.8 Hz, 1H), 5.10 (dd, J = 10.4, 1.5, Hz, 1H), 5.08 (dd, J = 17.4, 1.5 Hz, 1H), 3.99 (dt, J = 8.8, 7.0 Hz, 1H), 3.96 (q, J = 7.1 Hz, 2H), 2.46 (dd, J = 7.0, 7.0 Hz, 2H), 2.41 (s, 3H), 1.11 (t, J = 7.1 Hz, 3H). ^{13}C NMR δ 170.83, 143.63, 136.80, 131.28, 129.60, 127.25, 119.70, 61.69, 55.17, 37.65, 21.50, 13.96.

Preparation of (*R*)-2-(*N*-Tosyl)-amino-4-methyl-pent-4-enoic Acid Ethyl Ester (5b) using 5 mol % (*S*)-Tol-BINAP−$CuPF_6$·4MeCN. Product **5b** was obtained from the reaction of *N*-tosyl α-imino ester **2** with (2-methyl-propenyl)-trimethylsilane **4b**. The crude product was purified by FC (20% EtOAc in pentane) to provide the title product as a colorless solid in 47% yield with 64% ee according to chiral HPLC using Chiralcel OD column (hexane/*i*-PrOH 99.7:0.3, 0.3 mL/min). The absolute configuration was assigned to be *R* by comparing the results of HPLC of product **5b** obtained using (*S*)-tol-BINAP with that of a reference compound from ene reaction of *N*-tosyl imino ester **2** with isobutylene.[4b] ^{1}H NMR δ 7.72 (d, J = 8.3 Hz, 2H), 7.27 (d, J = 8.3 Hz, 2H) 5.05 (d, J = 8.8 Hz, 1H), 4.82 (d, = 1.1 Hz, 1H), 4.71 (d, J = 1.1 Hz, 1H), 4.03 (ddd, J = 8.8, 7.7, 6.0 Hz, 1H), 3.95 (q, J = 7.3 Hz, 2H), 2.41 (s, 3H), 2.42 (dd, J = 13.8, 6.0 Hz, 1H), 2.34 (dd, J = 13.8, 7.7 Hz, 1H), 1.65 (s, 3H), 1.10 (t, J = 7.3 Hz, 3H). ^{13}C NMR δ 171.36, 143.58, 139.53, 136.75, 129.50, 127.26, 115.19, 61.50, 54.23, 41.61, 21.75, 21.46, 13.86.

Preparation of 2-(*N*-Tosyl)-amino-3-methyl-pent-4-enoic Acid Ethyl Ester (5c) using 10 mol % (*R*)-Tol-BINAP−$CuPF_6$·4MeCN. According to general procedure, reaction of *N*-tosyl imino ester **2** (105 mg, 0.4 mmol) and tri-*n*-butyl-but-2-enyl-stannane **3c** (248 μL, 0.8 mmol) in toluene using 10 mol % complex of (*R*)-Tol-BINAP **6b** and $CuPF_6$·4MeCN as the catalyst afforded, after purification by FC (15% EtOAc in pentane), a diastereomeric mixture of **5c** and **5d** as a colorless solid (107 mg, 88% yield). The **5c**:**5d** ratio was 7:1 according to HPLC. The ee of the major product **5c** and the minor product **5d** was 87% and 89%, respectively, based on chiral HPLC using Chiralcel OD column (hexane/*i*-PrOH 99.0: 1.0, 0.35 mL/min). ^{1}H NMR δ 7.70 (d, J = 8.3 Hz, 2H), 7.27 (d, J = 8.3 Hz, 2H), 5.63 (ddd, J = 17.1, 10.0, 8.3 Hz, 1H), 5.07 (d, J = 7.7 Hz, 1H), 5.06 (d, J = 10.0 Hz, 1H), 5.04 (d, J = 17.1 Hz, 1H), 3.92−3.77 (m, 3H), 2.50 (dqd, J = 8.3, 7.2, 6.0 Hz, 1H), 2.40 (s, 3H), 1.07 (t, J = 7.2 Hz, $3H_3$), 1.03 (d, J = 7.2 Hz, 3H). ^{13}C NMR δ 170.56, 143.62, 137.95, 129.54, 127.36, 127.30, 116.81, 61.36, 59.83, 41.69, 21.51, 15.85, 13.94.

Preparation of Cyclopent-2-enyl-tosylamino-acetic Acid Ethyl Ester (5e) using 10 mol % (*S*)-Tol-BINAP−$CuPF_6$·4MeCN. According to general procedure, reaction of *N*-tosyl imino ester **2** (105 mg, 0.4 mmol) and trimethyl-cyclopent-2-enyl-stannane **3d** (180 μL, 0.8 mmol) in toluene using 10 mol % complex of (*S*)-Tol-BINAP **6b** and $CuPF_6$·4MeCN as the catalyst afforded, after purification by FC (15% EtOAc in pentane), a diastereomeric mixture as a colorless solid (125 mg, 94% yield). The ratio of two diastereomers was 2:1 according to HPLC. The ee of the major product was 71%, and the ee of the minor product was 98% according to chiral HPLC using Chiralcel OJ column (hexane/*i*-PrOH 99.0:1.0, 0.3 mL/min). ^{1}H NMR δ 7.63 (d, J = 8.2 Hz, 2H), 7.21 (d, J = 8.2 Hz, 2H), 5.87 (m, 1H) (minor), 5.78 (m, 1H) (major), 5.40 (m, 1H) (major), 5.36 (m, 1H) (minor), 5.04 (d, J = 9.9 Hz, 1H) (major), 4.90 (d, J = 10.4 Hz, 1H) (minor), 3.88−3.74 (m, 3H,), 3.10−3.02 (m, 1H) (minor), 3.00−2.95 (m, 1H,) (major), 2.34 (s, 3H), 2.45−1.58 (m, 4H), 1.03 (t, J = 7.2 Hz, 3H) (major), 1.01 (t, J = 7.2 Hz, 3H) (minor). ^{13}C NMR δ 171.12, 170.90 (minor), 143.53, 143.49 (minor), 136.81, 136.04, 134.15, 129.50, 129.36 (minor), 127.50 (minor), 127.32, 61.44, 61.33 (minor), 58.97, 58.80 (minor), 49.25, 48.41 (minor), 32.46 (minor), 31.81, 25.91 (minor), 25.47, 21.49, 13.92.

X-ray Determinations. Compound 5a. Data were collected from a needle-shaped crystal of **5a** on a SMART

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diffractometer using Mo Kα radiation (λ = 0.710 73 Å). **5a** is monoclinic, space group $P2_1$, a = 17.7540(9) Å, b = 5.1188(2) Å, c = 17.9060(9) Å. A total of 24108 reflections were measured, 7642 unique, internal agreement 0.043. The structure was solved by direct methods (SIR97)[12a] and refined by least squares to R = 0.042, R_w = 0.047 for 472 parameters. The absolute configuration was determined from the anomalous scattering contribution of sulfur by least-squares refinement of the Rogers parameter,[12b] giving a value of 0.91(11); 2261 Friedel pairs were included in the refinement.

Compound 5c. Data were collected from a needle-shaped crystal of **5c** on a SMART diffractometer using Mo Kα radiation (λ = 0.710 73 Å). **5c** is monoclinic, space group $P2_12_12_1$; a = 5.3398(4) Å, b = 12.5673(8) Å, c = 24.295(2) Å. A total of 24662 reflections were measured, 4861 unique, internal agreement 0.040. The structure was solved as above and refined by least squares to R = 0.042, R_w = 0.044 for 222 parameters. The absolute configuration was determined from the anomalous scattering contribution of sulfur by least-squares refinement of the Rogers parameter,[12b] giving a value of 103(17); 1096 Friedel pairs were included in the refinement.

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Supporting Information Available: NMR, HPLC (for assignment of the absolute configuration of **5b**), and X-ray structure of **5a** and X-ray data for **5a** and **5c**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO990238+

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