Amino Acid Synthesis

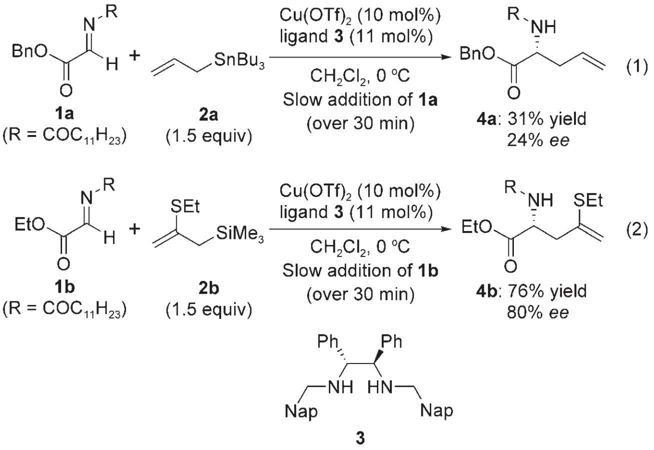
DOI: 10.1002/anie.200504196

# Enantiomerically Enriched Allylglycine Derivatives through the Catalytic Asymmetric Allylation of Iminoesters and Iminophosphonates with Allylsilanes**

*Hiroshi Kiyohara, Yoshitaka Nakamura,*
*Ryosuke Matsubara, and Shū Kobayashi**

The synthesis of α-amino acids is one of the most important topics in modern medicinal chemistry.[1] Among the variety of synthetic methods so far reported, asymmetric carbon–carbon bond-forming reactions of iminoesters provide an efficient route to optically active α-amino acids. While catalytic asymmetric Mannich-type reactions of N-protected iminoesters have already been reported by several groups,[2] few examples of catalytic asymmetric allylations of iminoesters are known despite their utility in organic synthesis.[3] Lectka and co-workers reported that *N*,*O*-acetals react with β-phenylallyltrimethylsilane in the presence of a $Cu^I$/binap (binap = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) complex,[3a] and they also disclosed reactions of *N*-tosyl iminoesters with β-arylallyltrimethylsilanes as well as nonsubstituted allyltrimethylsilane under similar conditions.[3d] However, only β-arylallylsilane gave the desired product with high enantiomeric purity while other allyltrialkylsilanes gave moderate selectivities (up to 72 % *ee*). Jørgensen and co-workers reported highly enantioselective reactions of *N*-tosyl iminoesters with allyltributyltin.[3b,c] They showed that the use of allylsilanes resulted in low yields with low selectivity. Additionally, from a viewpoint of synthetic utility, a sulfonyl group at the nitrogen center is sometimes problematic for deprotection compared to amide or alkoxycarbonyl groups. Hence, the development of environmentally friendlier, efficient, and practical methods is strongly desired. Herein, we report a $Cu^{II}$-catalyzed, highly enantioselective allylation of *N*-acyl and *N*-alkoxycarbonyl iminoesters using environmentally benign allylsilanes as nucleophiles. The first example of catalytic enantioselective allylations of iminophosphonates for the synthesis of α-aminophosphonic acids and their phosphonate esters is also described.

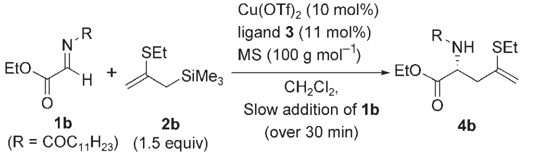
Allylation reactions of *N*-acyliminoester **1** with several allylating reagents were examined in the presence of a copper complex (10 mol %) prepared from $Cu(OTf)_2$ and diamine **3**, which was an efficient catalyst for Mannich-type reactions of iminoesters with silicon enolates.[2f,g] Relatively reactive allyltributylstannane (**2a**) was found to give the desired product, albeit in low yield with low selectivity (Scheme 1, Eq. (1)). On the other hand, when allylsilane **2b**, which bears a sulfur substituent at the β-position to the silicon atom, was employed[4] the allylated product was obtained in high yield with high selectivity [Scheme 1, Eq. (2)].



**Scheme 1.** Allylation reactions of iminoester **1** with several allylating reagents **2** catalyzed by $Cu^{II}$/**3**. Bn = benzyl; Tf = trifluoromethanesulfonyl; Nap = α-naphthyl.

However, the result was not reproducible (66–76 % yield, 68–80 % *ee*) especially in terms of selectivity. To address this issue, we then examined the addition of dehydrating agents as well as several procedures to add the substrates (Table 1). The addition of 3-Å molecular sieves (3Å MS) and slow addition of the substrates were found to improve the yield, selectivity, and reproducibility (84 % yield, 86 % *ee*; entry 4, Table 1). The 3Å MS were essential for the removal of water, which

**Table 1:** $Cu^{II}$/**3**-catalyzed reactions of iminoester **1b** with allylsilane **2b**.



| Entry | MS | *T* [°C] | Yield [%] | *ee* [%] |
|---|---|---|---|---|
| 1 | – | 0 | 66–76 | 68–80 |
| 2 | 3Å | 0 | 44 | 87 |
| 3 | 3Å | −20 | 56 | 80 |
| 4[a] | 3Å | 0 | 84 | 86 |
| 5[a] | 4Å | 0 | 77 | 80 |
| 6[a] | 5Å | 0 | 70 | 85 |
| 7[a,b] | 3Å | 0 | 76 | 93 |

[a] Allylsilane **2b** (1.36 equiv) was also slowly added (see Supporting Information). [b] Toluene was used as a cosolvent. MS = molecular sieves.

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[*] H. Kiyohara, Y. Nakamura, R. Matsubara, Prof. Dr. S. Kobayashi
Graduate School of Pharmaceutical Sciences
The University of Tokyo
The HFRE Division, ERATO
Japan Science Technology Agency (JST)
Hongo, Bunkyo-ku, Tokyo 113-0033 (Japan)
Fax: (+81) 3-5684-0634
E-mail: skobayas@mol.f.u-tokyo.ac.jp

[**] This work was partially supported by a Grant-in-Aid for Scientific Research from the Japan Society of the Promotion of Sciences (JSPS). H.K. and R.M. thank the JSPS for Fellowships for Japanese Junior Scientists.

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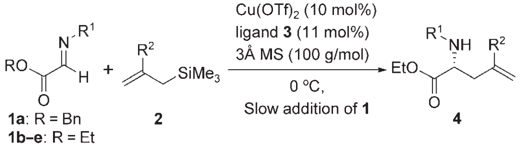
may induce partial hydrolysis of nucleophile **2b** to form a thiol (a potential copper poison). A lower temperature was not beneficial for this reaction (entry 3, Table 1). Slow addition of the substrates suppressed an uncatalyzed background reaction that otherwise furnished racemic product (entry 5, Table 1). Of the molecular sieves tested, 3Å MS were found to be superior to 4Å and 5Å MS. The best enantioselectivity (93% *ee*; entry 7, Table 1) was obtained when toluene was used as a co-solvent in the presence of 3Å MS and when both substrates were simultaneously added to the catalyst solution over 30 min.

Under these optimal conditions, various combinations of electrophiles and nucleophiles were then examined (Table 2). The use of allylsilane **2c** also led to a high yield with high selectivity (entry 2, Table 2). While *N*-acetyl iminoester **1c** gave high selecitivity (entry 3, Table 2), less reactive allylsilane **2d** afforded the desired product in good yield with high selectivity (entry 4, Table 2). Additionally, methallyltrimethylsilane (**2e**) gave a lower yield with high selectivity, and only a trace amount of the desired product was obtained when allyltrimethylsilane (**2f**) was treated with iminoester **1b** under the same conditions. These results, regarding yields, are consistent with a relative reactivity of allylsilane nucleophiles **2b–f** (entries 1–6, Table 2). Allylsilanes **2b** and **2c** also reacted with *N*-Boc iminoesters smoothly to afford the desired adducts in good yields with high selectivities (entries 10 and 11, Table 2).

We presumed the formation of a [4+2]-type self-condensation adduct of iminoester **1b** when less-nucleophilic allylsilanes were employed. We thought at this stage that if less-electrophilic iminoesters were used instead of **1b**, then the self-condensation may be suppressed and even less nucleophilic allylsilanes may react with iminoesters to afford the desired adducts. On the basis of this assumption, we conducted the reaction of *N*-Cbz iminoester **1d** with methallyltrimethylsilane (**2e**). To our delight, the reaction proceeded smoothly to afford the desired allylated adduct in excellent yield and with moderate selectivity. After optimization, the selectivity was improved to 88% *ee* (entry 8, Table 2). These optimal conditions were found to be applicable to the reaction with allyltrimethylsilane **2f** (entry 9, Table 2).[5]

*Table 2:* Substrate scope for $Cu^{II}$/**3**-catalyzed reactions of iminoesters **1** with allylsilanes **2**.

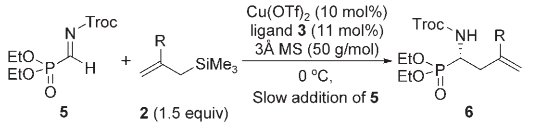


| Entry | 1 | 2 | Addition of 2[a] | Product | Yield [%] | *ee* [%] |
|---|---|---|---|---|---|---|
| 1[b,c] | **1b**: $R^1=C_{11}H_{23}CO$ | **2b**: $R^2=SEt$ | 0.14+1.36 | **4b** | 76 | 93 |
| 2[b,c] | **1b**: $R^1=C_{11}H_{23}CO$ | **2c**: $R^2=SPh$ | 0.14+1.36 | **4c** | 84 | 92 |
| 3[c,d] | **1c**: $R^1=CH_3CO$ | **2b**: $R^2=SEt$ | 0.14+1.36 | **4d** | 75 | 90 |
| 4[c,d] | **1b**: $R^1=C_{11}H_{23}CO$ | **2d**: $R^2=Ph$ | 0.5+1.0 | **4e** | 68 | 91 |
| 5[d] | **1a**: $R^1=C_{11}H_{23}CO$ | **2e**: $R^2=CH_3$ | 3.0+0 | **4f** | 33 | 90 |
| 6[d] | **1a**: $R^1=C_{11}H_{23}CO$ | **2f**: $R^2=H$ | 3.0+0 | **4g** | trace | – |
| 7[d] | **1d**: $R^1=Cbz$ | **2e**: $R^2=CH_3$ | 3.0+0 | **4h** | 94 | 63 |
| 8[e] | **1d**: $R^1=Cbz$ | **2e**: $R^2=CH_3$ | 3.0+0 | **4h** | 99 | 88 |
| 9[e] | **1d**: $R^1=Cbz$ | **2f**: $R^2=H$ | 3.0+0 | **4i** | 73 | 88 |
| 10[b,c] | **1e**: $R^1=Boc$ | **2b**: $R^2=SEt$ | 0.14+1.36 | **4j** | 84 | 86 |
| 11[b,c] | **1e**: $R^1=Boc$ | **2c**: $R^2=SPh$ | 0.14+1.36 | **4k** | 71 | 86 |

[a] For example, for entry 1, 0.14 equiv of **2b** was added initially, followed by the slow addition of a further 1.36 equiv of **2b** simultaneously with **1** (see Supporting Information for details). [b] $CH_2Cl_2$/toluene. [c] Simultaneous slow addition of **2**. [d] $CH_2Cl_2$ as the solvent. [e] $CH_2Cl_2$/THF. Cbz = benzyloxycarbonyl; Boc = *tert*-butoxycarbonyl.

Furthermore, we were pleased to find that this catalyst system could be successfully applied to allylations of iminophosphonate **5** (Table 3). As reported previously,[6] the catalyst turnover frequency was lower in reactions of iminophosphonates than in those of iminoesters. Therefore, slow addition of the electrophile was also essential in this allylation reaction. Note that even less reactive allylsilanes such as **2e** and **2f** afforded the desired products in good yields and with high enantioselectivities, and that highly enantioselective allylation of an iminophosphonate was attained for the first time.

*Table 3:* $Cu^{II}$/**3a**-catalyzed reactions of iminophosphonate **5** with allylsilanes **2**.



| Entry | 2 | Addition of 2 | Product | Yield [%] | *ee* [%] |
|---|---|---|---|---|---|
| 1[a,b] | **2b**: R = SEt | 0.14+1.36 | **6a** | 80 | 82 |
| 2[a,b] | **2c**: R = SPh | 0.14+1.36 | **6b** | 86 | 79 |
| 3[c] | **2d**: R = Ph | 1.5+0 | **6c** | 71 | 85 |
| 4[c] | **2e**: $R=CH_3$ | 1.5+0 | **6d** | 73 | 89 |
| 5[c] | **2f**: R = H | 1.5+0 | **6e** | 66 | 80 |

[a] $CH_2Cl_2$ as the solvent. [b] Simultaneous slow addition of **2**. [c] $CH_2Cl_2$/THF. Troc = trichloroethyloxycarbonyl.

In summary, highly enantioselective and efficient allylation reactions of iminoesters and an iminophosphonate using various allylsilanes, catalyzed by a copper complex prepared from $Cu(OTf)_2$ and chiral diamine **3**, have been developed. Whereas the study of catalytic asymmetric allylations with iminoesters was relatively neglected in relation to the corresponding Mannich-type reactions, this study provides a useful method for the preparation of a variety of amino acids as well as aminophosphonic acids based on the allylation protocol. Further investigations to improve the yields and enantioselectivity by optimization of the ligand are currently in progress.

Received: November 24, 2005

**Keywords:** allylation · amino acids · asymmetric catalysis · iminoesters · synthetic methods

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