CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.201002071

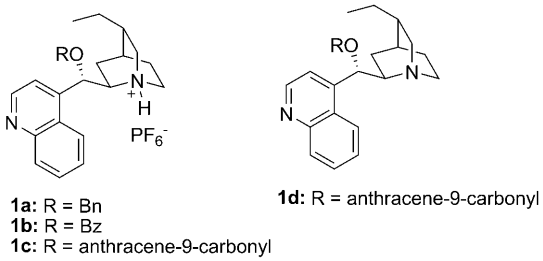
# Enantioselective Radical Addition to Ketimines: A Synthetic Route Towards α,α-Disubstituted α-Amino Acids

**Sang Yoon Kim, Sung Jun Kim, and Doo Ok Jang*[a]**

The addition of organometallic nucleophiles to C=N bonds is one of the most important reactions used for the synthesis of amines, which are valuable synthetic building blocks, as well as biologically active compounds.[1] However, these reactions are limited because they employ highly basic nucleophiles that often cause side reactions. An alternative approach is the use of radical addition reactions to provide neutral reaction conditions and functional-group compatibility. In the past few years, radical addition reactions to aldehyde-derived imine derivatives have been widely investigated.[2] However, studies into addition reactions to ketimines, which have lower reactivity, are rare.[3]

Control of stereochemistry in radical reactions has mainly relied on the utilization of chiral auxiliaries[4] or chiral Lewis acids.[5,6] Recently, there have been reports of the development of organocatalysts for enantioselective radical reactions.[7,8] Offering several advantages, such as low toxicity, low cost, and ease of manipulation, the use of organocatalysts in asymmetric radical reactions is an attractive approach.

Herein, we present a highly enantioselective radical addition reaction to ketimines by using protonated chiral amines (PCAs) under tin-free conditions (Scheme 1). This reaction results in enantioenriched chiral α,α-disubstituted α-amino acids that are difficult to form due to their quaternary stereogenic center, but desirable because of their useful properties.[9] α,α-Disubstituted α-amino acids have received considerable attention because of their stability under physiological conditions, their conformational rigidity, and their biological activity as enzyme inhibitors.[10] The importance of α,α-disubstituted α-amino acids has stimulated research into the development of methodologies for the asymmetric synthesis of these valuable compounds.




**1a:** R = Bn
**1b:** R = Bz
**1c:** R = anthracene-9-carbonyl
**1d:** R = anthracene-9-carbonyl

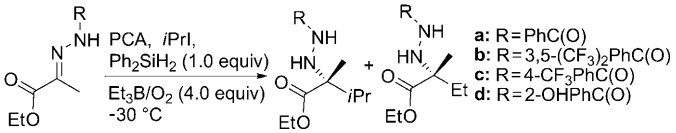
Scheme 1. Structure of some cinchonine-derivatives. Bn = benzyl; Bz = benzoyl.

As a preliminary experiment, an isopropyl radical addition reaction to ethyl pyruvate-derived (*E*)-*N*-benzoylhydrazone **2a** was performed in the presence of a catalytic amount of protonated cinchonine-derivative **1a** at −30 °C. Triethylborane and diphenylsilane were employed as the radical initiator and chain carrier, respectively. After 30 h, the reaction mixture was analyzed, giving adduct **3a** in 42 % yield and 60 % *ee*, along with ethyl-added adduct **3′a** and recovered starting material (Table 1, entry 1). To improve the efficiency and enantioselectivity of the radical addition reaction, ketimines **2b–d** were synthesized and subjected to the reaction conditions, with very similar results to those for **2a** (Table 1, entries 2–4). Next, we modified the structure of the chiral amine. In PCAs **1b** and **c**, the benzyl group of **1a** was replaced by a benzoyl and an anthracene-9-carbonyl substituent, respectively. The increase in steric bulk of the substituent results in a significant improvement in enantioselectivity (Table 1, entries 5–7). Thus, **1c** became the preferred choice of PCA. Further optimization of the reaction conditions was performed by varying the solvent and the ratio of the reagents. The chemical yields were improved by switching the solvent to $ClCH_2CH_2Cl$ (Table 1, entries 1 vs. 5). Interestingly, an increase in the amount of alkyl halide had no effect on the enantioselectivity of the addition adduct, although it provided a higher yield (Table 1, entries 7 vs. 8). The enantioselectivity increased to 96 % *ee* with an increase

[a] S. Y. Kim, S. J. Kim, Prof. Dr. D. O. Jang
Department of Chemistry, Yonsei Universiry
Wonju 220-710 (Korea)
Fax: (+82) 33-760-2182
E-mail: dojang@yonsei.ac.kr

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201002071.

Table 1. Optimization of the enantioselective radical addition reaction to ketimine C=N bonds.




**2a-d** **3a-d** **3'a-d**

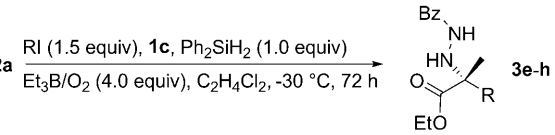
| Entry | **2** | PCA ([equiv]) | *i*PrI [equiv] | Solvent | *t* [h] | Yield of **3** [%][a] | *ee* of **3** [%][b] |
|---|---|---|---|---|---|---|---|
| 1 | **2a** | **1a** (0.30) | 1.5 | $CH_2Cl_2$ | 30 | 42 (13) | 60 |
| 2 | **2b** | **1a** (0.30) | 1.5 | $CH_2Cl_2$ | 30 | 43 (12) | 60 |
| 3 | **2c** | **1a** (0.30) | 1.5 | $CH_2Cl_2$ | 30 | 44 (13) | 60 |
| 4 | **2d** | **1a** (0.30) | 1.5 | $CH_2Cl_2$ | 30 | 40 (13) | 40 |
| 5 | **2a** | **1a** (0.30) | 1.5 | $C_2H_4Cl_2$ | 30 | 60 (14) | 60 |
| 6 | **2a** | **1b** (0.30) | 1.5 | $C_2H_4Cl_2$ | 30 | 60 (12) | 64 |
| 7 | **2a** | **1c** (0.30) | 1.5 | $C_2H_4Cl_2$ | 30 | 61 (14) | 78 |
| 8 | **2a** | **1c** (0.30) | 5.0 | $C_2H_4Cl_2$ | 72 | 76 (14) | 78 |
| 9 | **2a** | **1c** (0.75) | 5.0 | $C_2H_4Cl_2$ | 72 | 78 (14) | 86 |
| 10 | **2a** | **1c** (1.0) | 1.5 | $C_2H_4Cl_2$ | 72 | 79 (13) | 96 |
| 11 | **2a** | **1d** (1.0) | 1.5 | $C_2H_4Cl_2$ | 72 | 70 (19) | 0 |

[a] Isolated yield. The yield in parentheses is for **3′**. [b] Determined by chiral HPLC analysis and compared with the authentic racemic material.

in the amount of **1c** used in the reaction, showing the catalytic nature of PCA **1c** (Table 1, entries 9 and 10). A control experiment was performed with unprotonated cinchonine-derivative **1d**, gaving a racemic mixture (Table 1, entry 11). It is notable that only 1.5 equivalents of alkyl halide were used; generally, intermolecular radical addition reactions require a large excess of either an alkyl halide or a radical acceptor to obtain a high yield of the addition product.[11]

Subsequently, we investigated the effect of radical precursors on the yield and enantioselectivity of the reaction (Table 2). The addition reaction with a secondary radical produced a high yield with a high enantioselectivity (Table 2, entry 1). With tertiary alkyl halides, the addition reactions turned out to be extremely enantioselective, even with a substoichiometric amount of **1c** (Table 2, entries 2–5). The reaction with a primary iodide afforded moderate enantioselectivity (Table 2, entry 6). When the reaction was run with ethyl iodide, the sole product **3′a** was obtained in 91% yield and 80% *ee* (Table 2, entry 7).

Table 2. Various alkyl radical addition reactions to **2a** in the presence of **1c**.

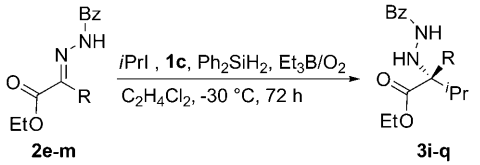



| Entry | R | Product | **1c** [equiv] | Yield of **3** [%][a] | *ee* of **3** [%][b] |
|---|---|---|---|---|---|
| 1 | cyclohexyl | **3e** | 1.0 | 74 (16) | 96 |
| 2 | *t*Bu | **3f** | 0.75 | 71 (19) | 98 |
| 3 | *t*Bu | **3f** | 1.0 | 73 (19) | 99 |
| 4 | 1-adamantyl | **3g** | 0.75 | 70 (21) | 98 |
| 5 | 1-adamantyl | **3g** | 1.0 | 71 (23) | 99 |
| 6 | *n*-octyl | **3h** | 1.0 | 54 (23) | 76 |
| 7 | Et | **3′a** | 1.0 | – (91) | 80 |

[a] Isolated yield. The yield in parenthesis is for **3′a**. [b] Determined by chiral HPLC analysis and compared with the authentic racemic material.

To evaluate the generality and scope of the reaction, a wide range of ketimines were subjected to the optimized conditions, providing a diverse range of enantioenriched *tert*-alkyl amines that are not readily prepared by using organometallic nucleophiles (Table 3). The ketimines examined gave very high yields and extremely high enantioselectivities (Table 3, entries 1–3 and 5–9) with the exception of **2h**, which contains a bulky substituent (R = *t*Bu; Table 3, entry 4). It is notable that radical addition to phenylglyoxylate-derived imine **2n** did not proceed under the reaction conditions. Remarkably, functional groups such as phenols, esters, and nitro groups were tolerated under these conditions.

Table 3. Scope of the isopropyl radical addition reactions to ketimines.




**2e-m** **3i-q**

| Entry | | R | Product | Yield [%][a] | *ee* [%][b] |
|---|---|---|---|---|---|
| 1 | **2e** | Et | **3i** | 77 | 97 |
| 2 | **2f** | $CF_3$ | **3j** | 81 | 96 |
| 3[c] | **2g** | *i*Bu | **3k** | 76 | 96 |
| 4 | **2h** | *t*Bu | **3l** | 62 | 40 |
| 5[c] | **2i** | $Ph(CH_2)_2$ | **3m** | 76 | 97 |
| 6 | **2j** | 2-$NO_2PhCH_2$ | **3n** | 80 | 97 |
| 7 | **2k** | 4-$OHPhCH_2$ | **3o** | 75 | 95 |
| 8 | **2l** | $EtOC(O)CH_2$ | **3p** | 77 | 96 |
| 9[c] | **2m** | $EtOC(O)(CH_2)_2$ | **3q** | 78 | 96 |
| 10 | **2n** | Ph | – | – | – |

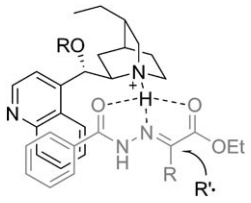
[a] Isolated yield. [b] Determined by chiral HPLC analysis and compared with the authentic racemic material. [c] *Z*-isomer. The other ketimines are the *E*-isomers.

Even though various chiral phase-transfer catalysts (PTC) have been developed for the synthesis of α,α-disubstituted amino acids, only the copper(II)-salen complex[12] and Maruoka's catalyst[13] provide α,α-disubstituted amino acids with two primary alkyl substituents at the α-position. However, even those PTCs do not satisfactorily synthesize α,α-disubstituted amino acids possessing at least one branched substituent at the α-position. Our method affords α,α-disubstituted amino acids even with a sterically hindered substituent. Moreover, the synthesis of α,α-disubstituted amino acids containing two branched α-substituents is possible with a high enantioselectivity. From this point of view, the present catalyst system is superior to previously reported chiral PTCs.

Sequential treatment of isopropyl adduct **3a** with $SmI_2$/MeOH[14] and aqueous NaOH to cleave the N–N bond and hydrolyze the ester group produced the known compound (*R*)-2-amino-2,3-dimethylbutanoic acid, confirming the assignment of the configuration.[15] Similar treatment of **3q** afforded 2-(*R*)-isopropylglutamic acid,[16] showing that both *E* and *Z* isomers provide addition products with *R* absolute configuration.

We hypothesize that the $N^+$–H proton in a PCA interacts with a ketimine through hydrogen bonding, along with π–π stacking of the aromatic rings of the substrate and the PCA. These two factors provide a chiral environment that leads to the *R* configuration of the addition adduct. The formation of substrate–PCA complexes through hydrogen bonding and π–π interactions is supported by $^1$H NMR spectroscopy experiments (see the Supporting Information). Upon addition of **2a** to a solution of **1c** in $CDCl_3$, an upfield shift of $\Delta\delta =$ 0.73 ppm was observed for the $N^+$–H hydrogen atom in **1c**.[17] Furthermore, changes in the chemical shifts ($\Delta\delta = 0$–~0.09 ppm) of the benzene rings in **2a** and **1c** were observed.




In conclusion, we have developed a highly enantioselective radical addition reaction to the C=N of ketimines under metal-free conditions. The method provides a general route for the synthesis of a diverse range of enantioenriched α,α-disubstituted α-amino acids. The mechanistic studies prove that a PCA interacts with a ketimine through hydrogen bonding and π–π stacking, providing a chiral environment to attain the high enantioselectivity.

## Experimental Section

**General procedure for the enantioselective radical addition to ketimines**: A mixture of **1c** (0.4 mmol) and a ketimine (0.4 mmol) in $ClCH_2CH_2Cl$ (4 mL) was stirred at room temperature under argon for 10 min. Diphenylsilane (0.4 mmol) and an alkyl halide (0.6 mmol) were then added, followed by triethylborane (1.6 mmol, 1 M solution in hexane). Air (110 mL) was added into the solution through a needle by using a syringe pump at −30 °C, over 72 h. After completion of the reaction, the reaction mixture was allowed to warm to room temperature and then washed with water. Then, after evaporation of the solvent, the residue was purified by flash column chromatography on silica gel, giving the corresponding addition product. Enantiomeric excesses were determined by chiral HPLC analysis (Daicel Chiralpak IA) through comparison with authentic racemic material.

## Acknowledgements

This work was supported by a Korea Research Foundation Grant, which is funded by the Korean Government (KRF-2008-521-C00153).

**Keywords:** amino acids · asymmetric synthesis · enantioselectivity · organocatalysis · radical reactions

[1] G. K. Friestad, A. K. Mathies, *Tetrahedron* **2007**, *63*, 2541–2569.
[2] a) G. K. Friestad, J.-C. Marie, Y. Suh, J. Qin, *J. Org. Chem.* **2006**, *71*, 7016–7027; b) G. K. Friestad, C. Draghici, M. Soukri, J. Qin, *J. Org. Chem.* **2005**, *70*, 6330–6338; c) H. Miyabe, M. Ueda, T. Naito, *Synlett* **2004**, 1140–1157; d) K. Yamada, Y. Yamamoto, M. Maekawa, K. Tomioka, *J. Org. Chem.* **2004**, *69*, 1531–1534; e) G. K. Friestad, Y. Shen, E. L. Ruggles, *Angew. Chem.* **2003**, *115*, 5215–5217; *Angew. Chem. Int. Ed.* **2003**, *42*, 5061–5068; f) M. Fernández, R. Alonso, *Org. Lett.* **2003**, *5*, 2461–2464; g) G. K. Friestad, J. Qin, *J. Am. Chem. Soc.* **2001**, *123*, 9922–9923.
[3] a) G. K. Friestad, A. Ji, *Org. Lett.* **2008**, *10*, 2311–2313; b) H. Miyabe, Y. Yamaoka, Y. Takemoto, *Synlett* **2004**, 2597–2599.
[4] a) G. Bar, A. Parsons, *Chem. Soc. Rev.* **2003**, *32*, 251–263; b) B. Guérin, W. W. Ogilvie, Y. Guindon in *Radicals in Organic Synthesis, Vol. 1* (Eds.: P. Renaud, M. P. Sibi), Wiley-VCH, Weinheim, **2001**; c) L. Feray, M. P. Bertrand, *Eur. J. Org. Chem.* **2008**, 3164–3170; d) F. Denes, F. Chemla, J. F. Normant, *Angew. Chem.* **2003**, *115*, 4177–4180; *Angew. Chem. Int. Ed.* **2003**, *42*, 4043–4096.
[5] For reviews, see: a) M. P. Sibi, S. Manyem, J. Zimmerman, *Chem. Rev.* **2003**, *103*, 3263–3296; b) M. P. Sibi, N. A. Porter, *Acc. Chem. Res.* **1999**, *32*, 163–171; c) P. Renaud, M. Gerster, *Angew. Chem.* **1998**, *110*, 2704–2722; *Angew. Chem. Int. Ed.* **1998**, *37*, 2562–2579.
[6] a) D. Yang, B.-F. Zheng, Q. Gao, S. Gu, N.-Y. Zhu, *Angew. Chem.* **2006**, *118*, 261–264; *Angew. Chem. Int. Ed.* **2006**, *45*, 255–258; b) J. E. Hein, J. Zimmerman, M. P. Sibi, P. G. Hultin, *Org. Lett.* **2005**, *7*, 2755–2758; c) M. P. Sibi, K. Patil, *Org. Lett.* **2005**, *7*, 1453–1456; d) L. He, G. S. C. Srikanth, S. L. Castle, *J. Org. Chem.* **2005**, *70*, 8140–8147; e) M. P. Sibi, G. Petrovic, J. Zimmerman, *J. Am. Chem. Soc.* **2005**, *127*, 2390–2391.
[7] a) D. O. Jang, S. Y. Kim, *J. Am. Chem. Soc.* **2008**, *130*, 16152–16153; b) M. P. Sibi, M. Hasegawa, *J. Am. Chem. Soc.* **2007**, *129*, 4124–4125; c) S. Bertelsen, M. Nielsen, K. A. Jørgensen, *Angew. Chem.* **2007**, *119*, 7500–7503; *Angew. Chem. Int. Ed.* **2007**, *46*, 7356–7359; d) S. Mukherjee, B. List, *Nature* **2007**, *447*, 152–153; e) D. H. Cho, D. O. Jang, *Chem. Commun.* **2006**, 5045–5047; f) P. Wessig, *Angew. Chem.* **2006**, *118*, 2224–2227; *Angew. Chem. Int. Ed.* **2006**, *45*, 2168–2171; g) A. Bauer, F. Westkömper, S. Grimme, T. Bach, *Nature* **2005**, *436*, 1139–1140; h) T. Aechtner, M. Dressel, T. Bach, *Angew. Chem.* **2004**, *116*, 5974–5976; *Angew. Chem. Int. Ed.* **2004**, *43*, 5849–5851.
[8] For protonated chiral catalysts, see: a) A. Singh, J. N. Johnston, *J. Am. Chem. Soc.* **2008**, *130*, 5866–5867; b) J. C. Wilt, R. M. Pink, J. N. Johnston, *Chem. Commun.* **2008**, 4177–4179; c) C. Bolm, T. Rantanen, I. Schiffers, L. Zani, *Angew. Chem.* **2005**, *117*, 1788–1793; *Angew. Chem. Int. Ed.* **2005**, *44*, 1758–1763; d) N. A. Paras, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2001**, *123*, 4370–4371; e) K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243–4244.
[9] For reviews on the synthesis of α,α-disubstituted α-amino acids, see: a) S. Cabrera, E. Reyes, J. Alemán, M. Milelli, S. Kobbelgaard, K. A. Jørgensen, *J. Am. Chem. Soc.* **2008**, *130*, 12031–12037; b) H. Vogt, S. Bräse, *Org. Biomol. Chem.* **2007**, *5*, 406–430; c) Y. Ohfune, T. Shinada, *Eur. J. Org. Chem.* **2005**, 5127–5143; d) C. Cativiela, M. D. Díaz-de-Villegas, *Tetrahedron: Asymmetry* **2000**, *11*, 645–732.
[10] a) P. Maity, B. Konig, *Biopolymers* **2008**, *90*, 8–27; b) M. Tanaka, *Chem. Pharm. Bull.* **2007**, *55*, 349–358; c) S. Sagan, P. Karoyan, O. Lequin, G. Chassaing, S. Lavielle, *Curr. Med. Chem.* **2004**, *11*, 2799–2822; d) V. J. Hruby, *Acc. Chem. Res.* **2001**, *34*, 389–397.
[11] H. Miyabe, Y. Yamaoka, Y. Takemoto, *J. Org. Chem.* **2005**, *70*, 3324–3327.
[12] Y. N. Belokon, D. Bhave, D. D'Addario, E. Groaz, V. Maleev, M. North, A. Pertrosyan, *Tetrahedron Lett.* **2003**, *44*, 2045–2048.
[13] T. Ooi, M. Takeuchi, M. Kameda, K. Maruoka, *J. Am. Chem. Soc.* **2000**, *122*, 5228–5229.
[14] R. Hirabayashi, C. Ogawa, M. Sugiyra, S. Kobayashi, *J. Am. Chem. Soc.* **2001**, *123*, 9493–9499.
[15] X. Dai, T. Nakai, J. A. C. Romero, G. C. Fu, *Angew. Chem.* **2007**, *119*, 4445–4447; *Angew. Chem. Int. Ed.* **2007**, *46*, 4367–4369.
[16] L. M. Harwood, S. N. G. Tyler, M. G. B. Drew, A. Jahans, I. D. MacGilp, *ARKIVOC* **2000**, 820–831.
[17] O. P. Kryatova, I. V. Korendovych, E. V. Rybak-Akimova, *Tetrahedron* **2004**, *60*, 4579–4588: The proton of $^+$N–H might be located in the core of aromatic rings.

Received: July 21, 2010
Published online: October 11, 2010