Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 47 (2006) 4565–4568
Tetrahedron Letters

Catalytic enantioselective electrophilic α-amination of β-ketoesters catalyzed by chiral palladium complexes

Young Ku Kang and Dae Young Kim*

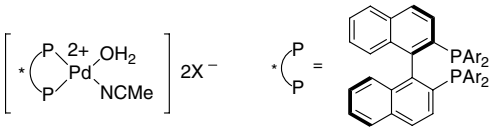
Department of Chemistry, Division of Applied Science, Soonchunhyang University, 644 Eupnae-ri, Shinchang, Asan, Chungnam 336-745, Republic of Korea

Received 27 March 2006; revised 28 April 2006; accepted 1 May 2006
Available online 22 May 2006

Abstract—The catalytic enantioselective electrophilic α-amination promoted chiral palladium complexes is described. Treatment of β-ketoesters with azodicarboxylates as electrophilic amination reagents under mild reaction conditions afforded the corresponding α-amino β-ketoesters with excellent enantiomeric excesses (91–99% ee). Palladium complexes were immobilized in [bmim]PF_6, and their applications to catalytic α-amination of β-ketoesters were successfully demonstrated.

Amino acids are used as pharmaceuticals, agrochemicals, and fundamental synthetic building blocks for preparation of an assortment of biologically valuable molecules.[1] The development of stereoselective synthetic methods for the preparation of natural and non-natural α-amino acid derivatives has attracted considerable attention over the past decades.[2] The most popular methods for the catalytic asymmetric synthesis of α-amino acid are C–C bond formation and include hydrogenation of α-dehydroamino acids,[3] alkylation of a *tert*-butyl glycinate–benzophenone Schiff base[4] and addition to imines using Strecker[5] and Mannich reactions.[6]

The catalytic enantioselective electrophilic amination of carbonyl compounds represents an efficient and the simplest procedures to generate stereogenic carbon center attached to a nitrogen atom.[7] Recently, Jørgensen, Pihko, and Takemoto groups presented the direct enantioselective amination of β-ketoesters catalyzed by chiral copper(II)–bisoxazoline complexes,[8a,b] quinidine-derived alkaloid[8c] and cinchona alkaloid,[8d] and chiral urea[8e] as organocatalysts. As part of the research program related to the development of synthetic methods for the enantioselective construction of stereogenic carbon centers,[9] we report the catalytic enantioselective fluorination and amination of ester derivatives promoted by air- and moisture-stable chiral palladium complexes.[10a,b] In this letter, we wish to report the direct α-amination of cyclic and acyclic β-ketoesters **3** catalyzed by using palladium complexes **1**–**2**[10] with azodicarboxylates **4** as the electrophilic nitrogen source.



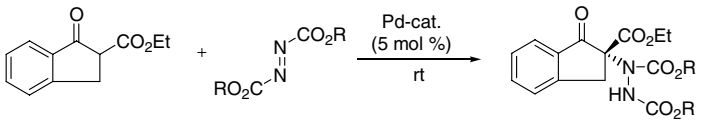
1a: Ar = Ph: (*R*)-BINAP, X = BF_4
1b: Ar = Ph: (*R*)-BINAP, X = SbF_6
1c: Ar = Ph: (*R*)-BINAP, X = OTf
1d: Ar = Ph: (*R*)-BINAP, X = PF_6
2a: Ar = 4-methylphenyl: (*R*)-Tol-BINAP, X = PF_6
2b: Ar = 3,5-dimethylphenyl: (*R*)-Xylyl-BINAP, X = PF_6

To determine suitable reaction conditions for the catalytic enantioselective electrophilic amination of β-ketoesters, we initially investigated the reaction system with indanone carboxylate **3a** using azodicarboxylates **4** as the electrophilic aminating agent in the presence of 5 mol % of catalyst **1a** in MeOH at room temperature. We first examined the impact of the structure of azodicarboxylates **4** on enantioselectivity (Table 1, entries 1–4). The best results have been obtained with *i*-propyl and *t*-butyl ester of azodicarboxylates. Catalysts **1b** and **1d** were more effective than other catalysts (entries 5–7, 9, and 10). The present catalytic system tolerates catalyst loading down to 1.0, 0.1 mol % without compromising either the yield or enantioselectivity (entries 8 and 17). Concerning the solvent, the use of

Keywords: Chiral palladium complexes; Amination; Asymmetric reactions; Ionic liquids.
* Corresponding author. Tel.: +82 41 530 1244; fax: +82 41 530 1247; e-mail: dyoung@sch.ac.kr

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.05.003

Table 1. Optimization of the reaction conditions



3a **4a-d** **5aa-ad**

Entry	4, R	Cat.	Solvent	Time (h)	Yield[a] (%)	ee[b] (%)
1	**4a**, Et	**1a**	MeOH	0.5	**5aa**, 83	80
2	**4b**, *i*-Pr	**1a**	MeOH	0.5	**5ab**, 86	86
3	**4c**, *t*-Bu	**1a**	MeOH	7	**5ac**, 97	87
4	**4d**, Bn	**1a**	MeOH	27	**5ad**, 64	69
5	**4b**, *i*-Pr	**1b**	MeOH	0.5	**5ab**, 98	97
6	**4b**, *i*-Pr	**1c**	MeOH	0.5	**5ab**, 96	93
7	**4b**, *i*-Pr	**1d**	MeOH	0.5	**5ab**, 98	97
8[c]	**4b**, *i*-Pr	**1d**	MeOH	18	**5ab**, 96	96
9	**4b**, *i*-Pr	**2a**	MeOH	0.5	**5ab**, 95	45
10	**4b**, *i*-Pr	**2b**	MeOH	0.5	**5ab**, 95	73
11	**4b**, *i*-Pr	**1d**	EtOH	1	**5ab**, 89	81
12	**4b**, *i*-Pr	**1d**	THF	21	**5ab**, 70	91
13	**4b**, *i*-Pr	**1d**	CH_2Cl_2	18	**5ab**, 84	85
14	**4b**, *i*-Pr	**1d**	Toluene	18	**5ab**, 65	47
15	**4b**, *i*-Pr	**1d**	Acetonitrile	18	**5ab**, 95	63
16	**4b**, *i*-Pr	**1d**	Acetone	20	**5ab**, 97	97
17[d]	**4b**, *i*-Pr	**1d**	Acetone	70	**5ab**, 96	97
18	**4b**, *i*-Pr	**1b**	[bmim]PF_6	12	**5ab**, 96	91
19	**4b**, *i*-Pr	**1d**	[bmim]PF_6	18	**5ab**, 81	71
20	**4b**, *i*-Pr	**1b**	[bmim]SbF_6	12	**5ab**, 92	89
21	**4a**, Et	**1a**	[bmim]BF_4	0.5	**5aa**, 88	0
22	**4a**, Et	**1d**	[bmim]BF_4	1	**5aa**, 90	0
23	**4a**, Et	**1b**	[bmim]SbF_6	0.5	**5aa**, 91	87
24	**4a**, Et	**1d**	[bmim]SbF_6	1	**5aa**, 89	79
25	**4a**, Et	**1b**	[bmim]PF_6	1	**5aa**, 96	97
26	**4a**, Et	**1d**	[bmim]PF_6	1	**5aa**, 93	85

[a] Yield of isolated product.
[b] Enantiopurity of **5** was determined by HPLC analysis with Chiralpak AD (for **5aa**–**ac**) and AS (for **5ad**) columns.
[c] Reaction carried out using 1.0 mol % of catalyst.
[d] Reaction carried out using 0.1 mol % of catalyst.

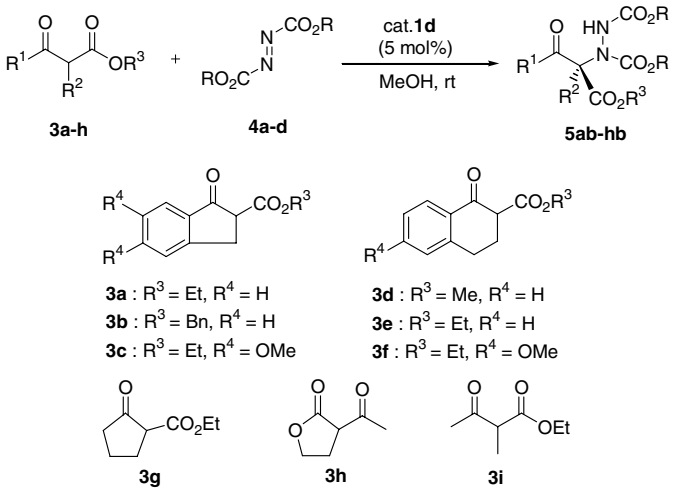
MeOH gave the best results in the yield and the enantiomeric excess (entry 7). Acetone also provided good enantioselectivity, but longer reaction time was necessary for the completion of the reaction (entry 16). Interestingly, ionic liquid [bmim]PF_6 is also a suitable solvent for this reaction, providing the desired amination product with excellent enantiomeric excess. Ionic liquids such as [bmim]PF_6 and [bmim]SbF_6 showed over 70% ee, but [bmim]BF_4 gave racemic product. Catalyst **1b** was more effective than other catalysts in ionic liquid [bmim]PF_6 (Table 1, entries 25–26).

To examine the generality of the catalytic enantioselective amination of β-ketoesters **3** by using chiral palladium complexes **1**, we studied the amination of various β-ketoesters **3a**–**i**.[11] As it can be seen from the results summarized in Table 2, the corresponding α-aminated β-ketoesters **5ab**–**id** were obtained in moderate to excellent yields and excellent enantioselectivities. The cyclic β-ketoesters **3a**–**h**, with cyclic aromatic ketones **3a**–**f**, cyclic aliphatic ketone **3g**, and cyclic ester group **3h**, reacted with azodicarboxylates **4** to give the corresponding α-aminated β-ketoesters **5ab**–**hb** in 56–99% yields and 91–99% ee (Table 2, entries 1–11). Acyclic β-ketoesters **3i** reacted with dibenzyl azodicarboxylate (**4d**) to afford the α-aminated β-ketoesters **5id** with 95% ee (Table 2, entry 12).

The employment of ionic liquids as solvents for chemical reactions has been receiving increased attention because they have essentially no vapor pressure and provide high solubility for a wide range of organic and organometallic compounds.[12] These solvents are reusable, simplify product isolation and allow for catalysts recycling.[13] From the results of the amination of β-ketoesters **3a** in ionic liquids (Table 1, entries 18–26), we also tested recycling of catalyst **1b** (Scheme 1).[14] The reaction was performed five times without affecting the yield and selectivity. The pale brown color [bmim]PF_6 layer and colorless ether layer indicated that chiral palladium catalyst was retained in ionic liquid layer. In the second recycling experiment, the desired product was obtained in 95% yield and 97% ee. Further, the catalyst recycled up to five times, maintaining the excellent yield and enantioselectivity. The complete reproducibility in this amination is a proof for the negligible leaching of the palladium catalyst.

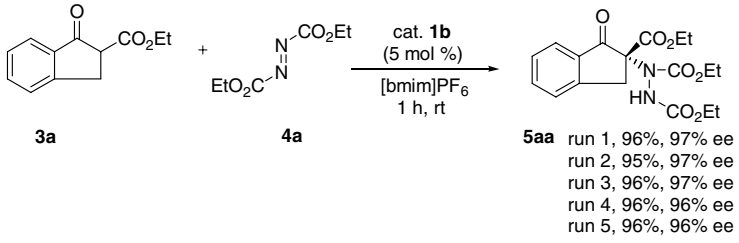
In conclusion, we have developed a highly efficient catalytic enantioselective α-amination of cyclic and acyclic

Table 2. Catalytic enantioselective amination of β-ketoesters



Entry	3	4, R	Time (h)	Yield (%)	ee[a] (%)
1	**3a**	**4b**, *i*-Pr	0.5	**5ab**, 98	97
2	**3a**	**4a**, Et	0.5	**5aa**, 94	99
3	**3b**	**4b**, *i*-Pr	0.5	**5bb**, 99	94
4	**3c**	**4b**, *i*-Pr	120	**5cb**, 64	93
5[b]	**3c**	**4b**, *i*-Pr	170	**5cb**, 71	95
6[c]	**3d**	**4c**, *t*-Bu	106	**5dc**, 56	95
7	**3e**	**4a**, Et	1	**5ea**, 75	91
8[d]	**3f**	**4c**, *t*-Bu	144	**5fc**, 66	91
9	**3g**	**4b**, *i*-Pr	31	**5gb**, 89	97
10	**3g**	**4d**, Bn	1	**5gd**, 73	93 (*R*)[e]
11[c]	**3h**	**4b**, *i*-Pr	9	**5hb**, 93	93
12	**3i**	**4d**, Bn	62	**5id**, 57	95 (*R*)[e]

[a] Enantiopurity of **5** was determined by HPLC analysis with Chiralpak AD (for **5ab**, **5bb**, **5cb**, **5fc**, **5gb**, and **5id**), AS (for **5gd** and **5hb**), and Chiralcel OD-H (for **5ea** and **5dc**) columns.
[b] Reaction carried out in acetone.
[c] Reaction carried out using catalyst **1a**.
[d] Reaction carried out using catalyst **1b**.
[e] Absolute configuration was determined by comparison of the optical rotation and the HPLC retention time of the corresponding ester with literature value.[8a]



Scheme 1. Catalyst recycling studies.

β-ketoesters using air- and moisture-stable chiral palladium complexes. The desired α-aminated products were obtained in good to high yields, and excellent enantioselectivities (91–99% ee) were observed for all the substrates examined in this work. It should be noted that this reaction proceeds well in environmentally benign alcoholic solvent and ionic liquid. Chiral palladium complex **1b** was efficiently immobilized in ionic liquid and reused five times in this amination with excellent enantioselectivity. This catalytic enantioselective amination in MeOH or ionic liquid has been shown to be practical from environmental and economical points of view. We believe that this report provides a practical method for the preparation of chiral α-amino acid derivatives, and the availability of these compounds should facilitate medicinal chemical studies in various fields. Further details and application of this amination will be presented in due course.

Acknowledgements

This research was supported by Korea Research Foundation Grant founded by the Korean Government

(MOEHRD, Basic Research Promotion Fund) (R05-2004-000-10431-0).

References and notes

1. For reviews on the synthesis of α-amino acids, see: (a) Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon: Oxford, 1989; (b) Hanessian, S.; McNaughton-Smith, G.; Lombart, H.-G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789; (c) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. In *Comprehensive Asymmetric Catalysis*; Springer: Berlin, 1999; Vols. 1–3; (d) Kotha, S. *Acc. Chem. Res.* **2003**, *36*, 342; (e) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013.
2. (a) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539; (b) Arend, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 2873.
3. (a) Okuma, T.; Kitamura, M.; Noyori, R. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: New York, 2000; pp 1–110; (b) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029.
4. (a) Corey, E. J.; Now, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414; (b) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1997**, *38*, 8595.
5. See, for example: (a) Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2000**, *39*, 1279; (b) Takamura, M.; Hamashima, Y.; Usuda, H.; Kanai, M.; Shibassaki, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 1650; (c) Corey, E. J.; Grogan, M. J. *Org. Lett.* **1999**, *1*, 157; (d) Ishitani, H.; Komiyama, S.; Hasegawa, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 762.
6. See, for example: (a) Kobayashi, S.; Hamada, T.; Manabe, K. *J. Am. Chem. Soc.* **2002**, *154*, 5640; (b) Ferassis, D.; Young, B.; Cox, C.; Dudding, T.; Drury, W. J.; Ryzhkov, L.; Taggi, A. E.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 67; (c) Cordova, A.; Watanabe, S. I.; Tanaka, F.; Notz, W.; Barbas, C. F. *J. Am. Chem. Soc.* **2002**, *124*, 1842; (d) Cordova, A.; Notz, W.; Zhong, G.; Betancort, J. M.; Barbas, C. F. *J. Am. Chem. Soc.* **2002**, *124*, 1866; (e) List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827; (f) Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 112964; (g) Juhl, K.; Gathergood, N.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 2995.
7. For reviews on asymmetric α-amination reactions, see: (a) Genet, J.-P.; Creck, C.; Lavergne, D. In *Modern Amination Methods*; Ricci, A., Ed.; Wiley-VCH: Weinheim, 2000, Chapter 3; (b) Greck, C.; Drouillat, B.; Thomassigng, C. *Eur. J. Org. Chem.* **2004**, 1377; (c) Erdik, E. *Tetrahedron* **2004**, *60*, 8742; (d) Janey, J. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4292.
8. (a) Marigo, M.; Juhl, K.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1367; (b) Ma, S.; Jiao, N.; Zheng, Z.; Ma, Z.; Lu, Z.; Ye, L.; Deng, Y.; Chen, G. *Org. Lett.* **2004**, *6*, 2193; (c) Saaby, S.; Bella, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 8120; (d) Pihko, P. M.; Pohjakallio, A. *Synlett* **2004**, 2115; (e) Xu, X.; Yabuta, T.; Yuan, P.; Takemoto, Y. *Synlett* **2006**, 137.
9. (a) Kim, D. Y.; Park, E. J. *Org. Lett.* **2002**, *4*, 545; (b) Kim, D. Y.; Choi, Y. J.; Park, H. Y.; Joung, C. U.; Koh, K. O.; Mang, J. Y.; Jung, K.-Y. *Synth. Commun.* **2003**, *33*, 435; (c) Park, E. J.; Kim, M. H.; Kim, D. Y. *J. Org. Chem.* **2004**, *69*, 6897; (d) Park, E. J.; Kim, H. R.; Joung, C. W.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2004**, *25*, 1451; (e) Kim, D. Y.; Huh, S. C. *Bull. Korean Chem. Soc.* **2004**, *25*, 347.
10. (a) Kim, S. M.; Kim, H. R.; Kim, D. Y. *Org. Lett.* **2005**, *7*, 2309; (b) Kim, H. R.; Kim, D. Y. *Tetrahedron Lett.* **2005**, *46*, 3115; (c) Kim, S. M.; Kang, Y. K.; Lee, K.; Mang, J. Y.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2006**, *27*, 423; (d) Li, K.; Hii, K. K. *Chem. Commun.* **2003**, 1132; (e) Li, K.; Horton, P. N.; Hursthouse, M. B.; Hii, K. K. *J. Organomet. Chem.* **2003**, *665*, 250; (f) Hamashima, Y.; Yagi, K.; Takano, H.; Tamas, L.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 14530; (g) Fujii, A.; Hagiwara, E.; Sodeoka, M. *J. Am. Chem. Soc.* **1999**, *121*, 5450; For a aquapalladium complex, see (h) Shimada, T.; Bajracharya, G. B.; Yamamoto, Y. *Eur. J. Org. Chem.* **2005**, 59, and references cited therein; (i) Vicente, J.; Arcas, A. *Coord. Chem. Rev.* **2005**, *249*, 1135; For Pd(II) chemistry, see (j) Tsuji, J. *Palladium Reagents and Catalysts: New Perspectives for 21st Century*; John Willey & Son: Chichester, 2004.
11. *General procedure for the amination of* β-*ketoesters*: To a stirred solution of β-ketoester **3** (0.3 mmol) and catalyst **1d** (16.1 mg, 0.015 mmol) in MeOH (3 mL) was added azodicarboxylate **4** (0.45 mmol) at room temperature. The reaction mixture was stirred for 0.5–170 h at room temperature. The mixture was diluted with saturated NH_4Cl solution (30 mL) and extracted with ethyl ether (2×30 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated, and purified by flash chromatography to afford the α-aminated β-ketoester.
12. (a) Dupont, J.; de Souza, R. F.; Saurez, P. A. Z. *Chem. Rev.* **2002**, *102*, 3667; (b) Seddon, R. *Chem. Commum.* **2001**, 2399; (c) Wasserscheid, P.; Kein, W. *Angew. Chem., Int. Ed.* **2000**, *39*, 3772; (d) Welton, T. *Chem. Rev.* **1999**, *99*, 2071.
13. (a) Song, C. E. *Chem. Commun.* **2004**, 1033; (b) Baudequin, C.; Baudoux, J.; Levillain, J.; Cahard, D.; Gaumont, A.-C.; Plaquevent, J.-C. *Tetrahedron: Asymmetry* **2003**, *14*, 3081; (c) Davis, J. H., Jr.; Fox, P. A. *Chem. Commun.* **2003**, 1209.
14. *Typical procedure for the amination of* β-*ketoester in ionic liquid*: To a stirred solution of ethyl indanone-2-carboxylate (**3a**, 61.3 mg, 0.3 mmol) and catalyst **1b** (18.9 mg, 0.015 mmol) in [bmim]PF_6 (0.5 mL) was added diethyl azodicarboxylate (**4a**, 78.3 mg, 0.45 mmol) at room temperature. The reaction mixture was stirred for 1 h at room temperature. Diethyl ether (5×5 mL) was added for extraction. Ether was decanted with a syringe and the combined ether layers were concentrated and purified by flash chromatography to afford the α-aminated β-ketoester **5aa**. The separated [bmim]PF_6 layer containing catalyst **1b** was reused in the next cycle.