JOC Article

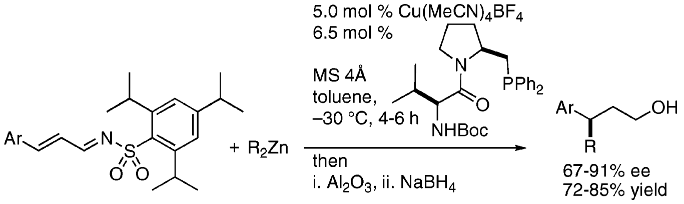
Catalytic Asymmetric Conjugate Addition of Dialkylzinc Reagents to *β*-Aryl-α,*β*-unsaturated *N*-2,4,6-Triisopropylphenylsulfonylaldimines with Use of *N*-Boc-L-Val-Connected Amidophosphane-Copper(I) Catalyst

Takahiro Soeta, Masami Kuriyama, and Kiyoshi Tomioka*

Graduate School of Pharmaceutical Sciences, Kyoto University,
Yoshida, Sakyo-ku, Kyoto 606-8501, Japan

tomioka@pharm.kyoto-u.ac.jp

Received September 8, 2004



Asymmetric conjugate addition of dialkylzinc to α,*β*-unsaturated *N*-2,4,6-triisopropylphenylsulfonylaldimines **9** was catalyzed by 5 mol % *N*-Boc-L-valine-connected amidophosphane **5a**-Cu(MeCN)$_4$BF$_4$ in the presence of 4 Å MS in toluene to afford, after hydrolysis of an imine to an aldehyde through a short alumina column and reduction with sodium borohydride, the corresponding *β*-alkylated alkanols **10** with 67−91% ee in reasonably high yields.

Introduction

Conjugate addition reaction of organometallic reagents with α,*β*-unsaturated aldehydes has maintained a unique position because these acceptors are prone to be more susceptible to 1,2-addtion than α,*β*-unsaturated ketones, esters, amides, and equivalents.[1,2] Complexation of an aldehyde carbonyl group with a bulky aluminum agent has been proven to block a carbonyl group from 1,2-addition permitting the 1,4-conjugate addition of organolithium and Grignard reagents.[3] Chemical modification to chiral[4] and achiral[5] aldimines has been also proven to be effective for the asymmetric conjugate addition of Grignard reagents and organolithiums. We and others have already developed three types of enantioselective 1,2-addition to aldimines; the chiral ether-mediated addition of organolithium reagents to 4-methoxyphenylimines,[6] copper(I)-chiral amidophosphane-catalyzed addition of dialkylzinc reagents to *N*-sulfonylimines,[7,8] and

---

(1) For reviews on enantioselective conjugate addition, see: (a) Tomioka, K.; Nagaoka, Y. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Vol. III, Chapter 31. (b) Tomioka, K. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, 2000; Chapter 12. (c) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346−353. (d) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033−8061. (e) Tomioka, K. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 2004; Supplement to Chapter 31.1, pp 109−124.

(2) For selected works on the covalently bound chiral auxiliary-controlled asymmetric conjugate addition of organometals, see: (a) Tomioka, K.; Suenaga, T.; Koga, K. *Tetrahedron Lett.* **1986**, *27*, 369−372 1986. (b) Oppolzer, W.; Poli, F.; Kingma, A. J.; Starkemann, C.; Bernardinelli, G. *Helv. Chim. Acta* **1987**, *70*, 2201−2214. (c) Basil, L. F.; Meyers, A. I.; Hassner, A. *Tetrahedron* **2002**, *58*, 207−213. (d) Dambacher, J.; Anness, R.; Pollock, P.; Bergdahl, M. *Tetrahedron* **2004**, *60*, 2097−2110.

(3) Maruoka, K.; Imoto, H.; Saito, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 4131−4132.

(4) Kogen, H.; Tomioka, K.; Hashimoto, S.; Koga, K. *Tetrahedron* **1981**, *37*, 3951−3956.

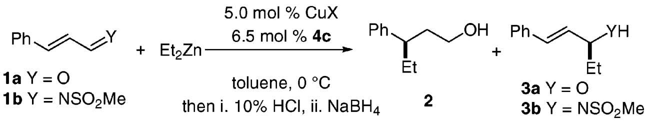
(5) (a) Tomioka, K.; Shindo, M.; Koga, K. *J. Am. Chem. Soc.* **1989**, *111*, 8266−8268. (b) Shindo, M.; Koga, K.; Tomioka, K. *J. Am. Chem. Soc.* **1992**, *114*, 8732−8733. (c) Shindo, M.; Koga, K.; Tomioka, K. *J. Org. Chem.* **1998**, *63*, 9351−9357. (d) Tomioka, K.; Shioya, Y.; Nagaoka, Y.; Yamada, K. *J. Org. Chem.* **2001**, *66*, 7051−7054.

(6) (a) Tomioka, K. *Synthesis* **1990**, 541−549. (b) Tomioka, K.; Inoue, I.; Shindo, M.; Koga, K. *Tetrahedron Lett.* **1990**, *31*, 6681−6684. (c) Fujieda, H.; Kanai, M.; Kambara, T.; Iida, A.; Tomioka, K. *J. Am. Chem. Soc.* **1997**, *119*, 2060−2061. (d) Kambara, T.; Hussein, M. A.; Fujieda, H.; Iida, A.; Tomioka, K. *Tetrahedron Lett.* **1998**, *39*, 9055−9058. (e) Hussein, M. A.; Iida, A.; Tomioka, K. *Tetrahedron* **1999**, *55*, 11219−11228. (f) Kambara, T.; Tomioka, K. *J. Org. Chem.* **1999**, *64*, 9282−9285. (g) Tomioka, K.; Fujieda, H.; Hayashi, S.; Hussein, M. A.; Kambara, T.; Nomura, Y.; Kanai, M.; Koga, K. *Chem. Commun.* **1999**, 715−716. (h) Taniyama, D.; Hasegawa, M.: Tomioka, K. *Tetrahedron Lett.* **2000**, *41*, 5533−5536. (i) Hata, S.; Iguchi, M.; Iwasawa, T.; Yamada, K.; Tomioka, K. *Org. Lett.* **2004**, *6*, 1721−1724. (j) Hata, S.; Iwasawa, T.; Iguchi, M.; Yamada, K.; Tomioka, K. *Synthesis* **2004**, 1471−1475.

(7) (a) Fujihara, H.; Nagai, K.; Tomioka, K. *J. Am. Chem. Soc.* **2000**, *122*, 12055−12056. (b) Nagai, K.; Fujihara, H.; Kuriyama, M.; Yamada, K.; Tomioka, K. *Chem. Lett.* **2002**, 8−9. (c) Soeta, T.; Nagai, K.; Fujihara, H.; Kuriyama, M.; Tomioka, K. *J. Org. Chem.* **2003**, *68*, 9723−9727.

10.1021/jo0484225 CCC: $30.25

SCHEME 1. Copper−Chiral Phosphane-Catalyzed Asymmetric Ethylation of Cinnamaldehyde 1a and Its Aldimine 1b with Diethylzinc Giving 2 and 3



rhodium-chiral amidophosphane-catalyzed addition of arylboroxine reagents to *N*-sulfonylimines.[9,10] As part of our continuing effort to broaden the scope of the copper-chiral amidophosphane-catalyzed addition of dialkylzinc reagents to imines, we are interested in the possibility of controlling 1,4- and 1,2-additions to aldimines of α,β-unsaturated aldehydes, thereby providing an alternative for hitherto difficult asymmetric conjugate addition to α,β-unsaturated aldehydes.[11,12] We describe herein that the combination of $Cu(MeCN)_4BF_4$ and amidophosphane **5a** catalyzes the conjugate addition of dialkylzinc to aldimines **9** of α,β-unsaturated aldehydes to give the corresponding adducts **10** with up to 91% ee in reasonably high yields.

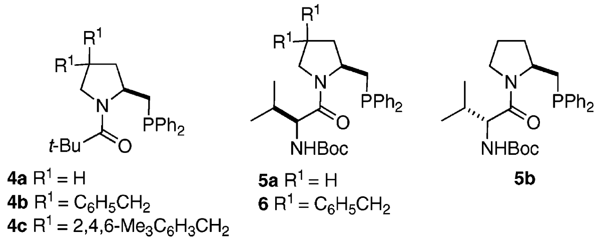


FIGURE 1. Chiral amidophosphanes **4**−**6**.

Reaction of Diethylzinc with Cinnamaldehyde and its *N*-Methanesulfonylimine. We began our studies with the reaction of cinnamaldehyde **1a** with diethylzinc in the presence of 5 mol % copper(II) triflate and 6.5 mol % chiral amidophosphane **4c** in toluene at 0 °C, the conditions established in the 1,2-addition[7c] (Scheme 1, Figure 1). Although **1a** was consumed within 5 h, a mixture of comparable amounts of 1,4- and 1,2-addition alcohols (−)-**2**[13] with 7% ee and **3a**[14] with 13% ee was obtained in 55% combined yield after sodium borohydride reduction of an aldehyde (Table 1, entry 1). We then examined the reaction of the corresponding aldimines **1** with respect to regio- and enantioselectivity. *N*-Methanesulfonylimine **1b**[15] was treated with diethylzinc under the same catalysis conditions as the reaction of **1a**, followed by imine-hydrolysis with 10% HCl and then sodium borohydride reduction, to give a mixture of comparable amounts of **2** with 32% ee in 41% yield and **3b** with 68% ee in 32% yield (entry 2). The source of copper was found to be influential to the 1,4-/1,2-selectivity as well as enantioselectivity. Copper(I) triflate benzene complex gave the slightly improved level of selectivity with copper(II) triflate (entry 3). Although naphthenate,[16] acetate, bromide and iodide dimethyl sulfide complexes were 1,4-selective copper sources excepting cyanide and free iodide,[17] enantioselectivity was generally unsatisfactory (entries 4−9).

Copper(I)-L-Val-Connected Phosphane-Catalyzed Reaction with Sterically Tuned *N*-Sulfonylimine. *N*-Tosylimine **1c**[15] was also not a good acceptor to give a mixture of **2** (16% ee) and **3c** (83% ee) in a similar product valance with **1b** (Table 2, entry 1). Fortunately, aldimine **1d** bearing a bulky 2,4,6-triisopropylbenzenesulfonyl group was found to be more 1,4-selectively converted to **2** with 47% ee in 66% yield and **3d** (1% ee) in 12% yield (entry 2). We also examined the effects of copper and amidophosphane on the reaction of **1d** with diethylzinc. Without both copper(II) triflate and phosphane **4c**, the reaction was very sluggish at 0 °C for 19 h to give **2** in 32% yield (entry 3). Without **4c** the copper-catalyzed reaction was also sluggish, at 0 °C for 20 h, giving **2** in 43% yield and **3d** in 14% yield (entry 4). These two results apparently indicated the high potentiality of a copper−phosphane combination as a catalyst. We then examined the effects of chiral phosphanes **4**−**6** on the 1,4-selectivity and enantioselectivity of the reaction with **1d**. Unfortunately, the less bulky amidophosphane **4a**[18] gave a mixture of **2** with 20% ee in 57% yield and **3d** with 67% ee in 18% yield (entry 5). Interestingly, a chiral amidophosphane **4b**[7c] bearing two benzyl groups on a pyrrolidine ring efficiently suppressed the 1,2-addition of diethylzinc to **1d** at 0 °C for 2 h, giving the corresponding 1,4-product **2** with 57% ee in 74% yield, after hydrolysis of an imine to an aldehyde through a short alumina column and subsequent reduction of an aldehyde with sodium borohydride (entry 6). It was fortunate to find that valine-connected amidophosphanes **5** and **6** gave the conjugate addition product **2** as the sole product. *N*-Boc-L-Valine-connected amidophosphane **5a**[9] gave **2** with 61% ee in 77% yield (Table 2, entry 7). However, the use of **6** bearing two benzyl groups on the pyrrolidine ring gave **2** with a decreased 24% ee in 72% yield (entry 9). D-Valine-connected phosphane **5b** was not the better ligand, giving **2** with 43% ee in 75% yield (entry 8).

The source of copper was also influential on the enantioselectivity of the reaction of **1d** with a copper-**5a**

---

(8) (a) Porter, J. R.; Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 10409−10410. (b) Boezio, A. A.; Pytkowicz, J.; Côté, A.; Charette, A. B. *J. Am. Chem. Soc.* **2003**, *125*, 14260−14261. (c) Côté, A.; Boezio, A. A.; Charette, A. B. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5405−5410.

(9) Kuriyama, M.; Soeta, T.; Hao, X.; Chen, Q.; Tomioka, K. *J. Am. Chem. Soc.* **2004**, *126*, 8128−8129.

(10) (a) Review: Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103,* 2829−2844. (b) Hayashi, T.; Ishigetani, M. *J. Am. Chem. Soc.* **2000**, *122*, 976−977. (c) Hayashi, T.; Ishigetani, M. *Tetrahedron* **2001**, *57*, 2589−2595. (d) Hermanns, N.; Dahmen, S.; Bolm, C.; Bräse, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 3692−3694.

(11) Rhodium-catalyzed conjugate addition and reduction of cinnamaldehyde with arylboronic acid have been reported. (a) Itooka, R.; Iguchi, Y.; Miyaura, N. *J. Org. Chem.* **2003**, *68*, 6000−6004. (b) Wang, Z.; Zou, G.; Tang, J. *Chem. Commun.* **2004**, 1192−1193.

(12) Asymmetric Michael reactions to enals have been reported. (a) Brown, S. P.; Goodwin, N. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 1192−1194. (b) Ooi, T.; Doda, K.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 9022−9023.

(13) Absolute configuration of (−)-**2** was determined by comparison of the specific rotation with the reported value. Pridgen, N.; Mokhallalati, M. K.; Wu, M.-J. *J. Org. Chem.* **1992**, *57*, 1237−1241. The ee was determined by chiral stationary phase HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 50/1, 1.0 mL/min, 254 nm, major 16.0 min and minor 19.4 min).

(14) Okamoto, T.; Oka, S. *J. Org. Chem.* **1983**, *49*, 1589−1594.

(15) Georg, G. L.; Harriman, G. C. B.; Peterson, S. A. *J. Org. Chem.* **1995**, *60*, 7366−7368.

(16) Alexakis, A.; Benhaim, C.; Rosset, S.; Humam, M. *J. Am. Chem. Soc.* **2002**, *124*, 5262−5263.

(17) Kanai, M.; Nakagawa, Y.; Tomioka, K. *Tetrahedron* **1999**, *55*, 3843−3854.

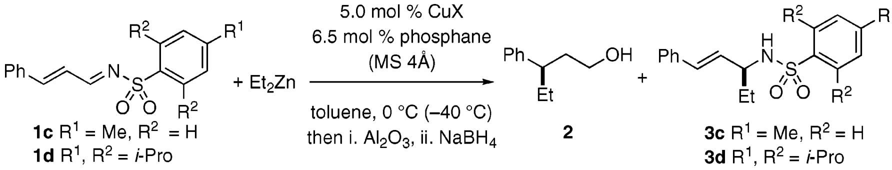
(18) Kanai, M.; Tomioka, K. *Tetrahedron Lett.* **1995**, *36*, 4275−4278.

TABLE 1. Copper−Amidophosphane 4c-Catalyzed Asymmetric Reaction of Cinnamaldehyde 1a and Its *N*-Methanesulfonylimine 1b with Diethylzinc

entry	**1**	CuX	time (h)	yield of **2** (%)	ee of **2** (%)[a]	yield of **3** (%)	ee of **3** (%)[a]
1	**1a**	$Cu(OTf)_2$	5	25	7	30	13
2	**1b**	$Cu(OTf)_2$	1	41	32	32	68
3	**1b**	$(CuOTf)_2-PhH$	1	54	34	21	63
4	**1b**	Cu(naphthenate)$_2$	1	68	4	4	3
5	**1b**	$Cu(OAc)_2-H_2O$	1	60	1	2	8
6	**1b**	CuCN	6	1	nd	1	nd
7	**1b**	$CuBr-SMe_2$	1	62	4	3	3
8	**1b**	$CuI-SMe_2$	2	58	10	2	22
9	**1b**	CuI	5	7	1	1	nd

[a] nd: Not determined.

TABLE 2. CuX−Amidophosphane-Catalyzed Asymmetric Reaction of *N*-Arylsulfonylimine with Diethylzinc

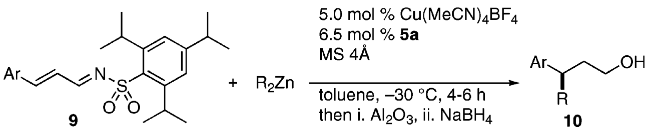


entry	**1**	CuX	ligand	4 Å MS	time (h)	yield of **2** (%)	ee of **2** (%)	yield of **3** (%)	ee of **3** (%)[b]
1[a]	**1c**	$Cu(OTf)_2$	**4c**	none	5	40	16	32	83
2	**1d**	$Cu(OTf)_2$	**4c**	none	3	60	47	14	1
3	**1d**	none	none	none	19	32	0	0	0
4	**1d**	$Cu(OTf)_2$	none	none	20	43	0	14	0
5	**1d**	$Cu(OTf)_2$	**4a**	none	3	57	20	18	67
6	**1d**	$Cu(OTf)_2$	**4b**	none	2	74	57	0	nd
7	**1d**	$Cu(OTf)_2$	**5a**	none	3	77	61	0	nd
8	**1d**	$Cu(OTf)_2$	**5b**	none	3	75	43	0	nd
9	**1d**	$Cu(OTf)_2$	**6**	none	3	73	24	0	nd
10	**1d**	$Cu(MeCN)_4BF_4$	**5a**	none	3	79	65	0	nd
11	**1d**	$Cu(MeCN)_4BF_4$	**5a**	4 Å MS	3	80	68	0	nd
12[a]	**1d**	$Cu(MeCN)_4BF_4$	**5a**	4 Å MS	5	77	80	0	nd
13	**1c**	$Cu(MeCN)_4BF_4$	**4c**	none	5	65	5	18	56

[a] Conducted at −40 °C. [b] nd: Not determined.

catalyst, giving **2** with 65% ee in 79% yield by the use of $Cu(MeCN)_4BF_4$[19] (Table 2, entry 10). Use of 4 Å molecular sieves[20] was beneficial to the reaction, improving the enantioselectivity to 68% ee (entry 11).[21] Finally, improvement in enantioselectivity was observed by conducting the reaction with 5 mol % $Cu(MeCN)_4BF_4$-**5a** as a catalyst in the presence of 4 Å MS at −40 °C for 4 h to afford (−)-**2** with 80% ee in 77% yield (entry 12). It is important to note that a major factor in controlling 1,4-/1,2-selectivity seems to be the structure of phosphane **5a**, not the source of copper, because $Cu(MeCN)_4BF_4$-**4c** converted **1c** to a mixture of **2** with 5% ee in 65% yield and **3c** with 56% ee in 18% yield (entry 13).

TABLE 3. $Cu(MeCN)_4BF_4$-5a Catalyzed Asymmetric Alkylation of 9 Giving 10[25]



entry	imine	Ar	time (h)	R	alcohols	yield (%)	ee (%)[b]
1[a]	**1d**	Ph	4	Et	**2**	80	80
2	**9e**	2-MeC_6H_4	4	Et	**10e**	84	83
3	**9f**	3-MeC_6H_4	4	Et	**10f**	80	81
4	**9g**	2-$MeOC_6H_4$	4	Et	**10g**	75	75
5	**9h**	4-$MeOC_6H_4$	5	Et	**10h**	78	79
6	**9i**	2-ClC_6H_4	4	Et	**10i**	79	82
7	**9j**	4-ClC_6H_4	4	Et	**10j**	78	78
8	**9k**	1-naphthyl	5	Et	**10k**	82	91
9	**9l**	2-naphthyl	5	Et	**10l**	85	75
10	**9m**	2-furyl	6	Et	**10m**	72	67[c]
11	**9k**	1-naphthyl	4	*i*-Pr	**10n**	77	78

[a] Reaction was conducted at −40 °C. Data taken from Table 2, entry 12. [b] Unless otherwise noted, the ee was determined by a chiral stationary phase HPLC. [c] Ee was determined by the ^{19}F NMR of the corresponding Mosher ester.

The reaction of a variety of α,*β*-unsaturated aldimines **9** has been examined with $Cu(MeCN)_4BF_4$-**5a** as a catalyst in the presence of 4 Å MS at −30 °C in toluene (Table 3). *N*-Sulfonylimines **9** were prepared in good yields by condensing the corresponding aldehydes **7**[22] with sulfonylamide **8**[23] in tetraethoxysilane[24] at 160 °C (Scheme 2). The reactions of **9e** and **9f**, having 2- and 3-methylphenyl groups, gave **10e** with 83% ee in 84% yield and **10f** with 80% ee in 81% yield (entries 2 and 3). The reaction of **9g** and **9h**, having electron-donating 2-

---

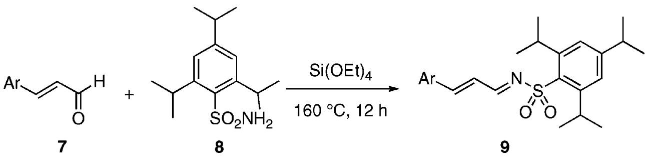
[19] Liang, Y.; Gao, S.; Wan, H.; Hu, Y.; Chen, H.; Zheng, Z.; Hu, X. *Tetrahedron: Asymmetry* **2003**, *14*, 3211−3217.

[20] Molecular sieves 4 Å were crashed and heated three times for 1 min by microwave before use. Ohgushi, T.; Nagae, M. *J. Porous Mater.* **2003**, *10*, 139−143.

[21] Reaction using **5a**-$Cu(OTf)_2$ and 4 Å MS afforded **2** with 62% ee in 76% yield.

[22] Battistuzzi, G.; Cacchi, S.; Fabrizi, G. *Org. Lett.* **2003**, *5*, 777−780.

SCHEME 2. Synthesis of 9 from 7 and 8



and 4-methoxyphenyl groups, gave **10g** with 75% ee in 75% yield and **10h** with 79% ee in 78% yield (entries 4 and 5). The reaction of **9i** and **9j**, having electron-withdrawing 2- and 4-chlorophenyl groups, gave **10i** with 82% ee in 79% yield and **10j** with 78% ee in 78% yield (entries 6 and 7). The reaction of 3-(naphthalen-1-yl)-acrylaldehyde imine **9k** gave **10k** with 91% ee in 82% yield (entry 8). The reaction of **9l** gave **10l** with 75% ee in 85% yield (entry 9). The reaction of **9m**, having a heterocyclic 2-furyl group, gave **10m** with 67% ee in 72% yield (entry 10). A propyl group was also introduced into **9k** with dipropylzinc to give **10n** with 78% ee in 87% yield (entry 11).

In conclusion, a catalytic asymmetric conjugate addition of dialkylzinc to sterically tuned, unsaturated sulfonylaldimines was achieved with high 1,4-selectivity and enantioselectivity using the *N*-Boc-L-valine-connected amidophosphane−copper(I) catalyst. The combination of an appropriate amidophosphane and copper(I) is key to the success. Further studies will be focused on the examination of various natural amino acid-connected amidophosphanes.

Experimental Section

Asymmetric Ethylation of 9k with Diethylzinc Catalyzed by 5a-Copper(I) Giving 10k (Table 3, Entry 8). Under an Ar atmosphere, a solution of amidophosphane **5a** (30.5 mg, 0.065 mmol) in 4 mL of toluene was added to a suspension of $Cu(MeCN)_4BF_4$ (15.1 mg, 0.050 mmol) and 4 Å MS (750 mg) in 14.5 mL of toluene. The resulting solution was stirred for 1 h at room temperature. A solution of aldimine **10k** (447 mg, 1.0 mmol) in 13 mL toluene was added at room temperature. After stirring at room temperature for 10 min, the reaction mixture was cooled to −30 °C over 0.5 h and then stirred at −30 °C for 0.5 h. A hexane solution of diethylzinc (1.2 mL, 1.2 mmol) was added at −30 °C, and the whole was stirred at −30 °C for 2 h. Then, a hexane solution of diethylzinc (1.2 mL, 1.2 mmol)[26] was added and the whole was stirred at −30 °C for an additional 3 h. The reaction was quenched with saturated NH_4Cl and stirred at room temperature for 0.5 h. After filtration through Celite, the organic layer was separated and the water layer was extracted with ethyl acetate. The combined organic layers were washed with saturated $NaHCO_3$ and brine and then dried over Na_2SO_4. Concentration gave a pale yellow oil (513 mg), which was filtered through aluminum oxide 90 standardized (Merck, 20 g) using ethyl acetate (300 mL) as an eluate. Concentration gave a pale yellow oil, which was treated with $NaBH_4$ (37 mg, 1.0 mmol) in methanol (4.0 mL) for 0.5 h at 0 °C. After addition of water and ethyl acetate, the organic layer was separated. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with saturated $NaHCO_3$ and brine and then dried over Na_2SO_4. Concentration and purification by silica gel column chromatography (hexane/ethyl acetate = 20/1) gave **10k** (175 mg, 82% yield) as a pale yellow oil of $[\alpha]^{25}_{D}$ −4.01 (*c* 1.27, $CHCl_3$). The ee was determined to be 91% by HPLC (Daicel Chiralcel AD-H, hexane/*i*-PrOH = 50/1, 1.0 mL/min, 254 nm, major 19.9 min and minor 21.9 min). ^1H NMR δ: 0.82 (3H, t, J = 7.3 Hz), 1.14 (1H, brs), 1.85 (2H, m), 2.01−2.13 (2H, m), 3.45−3.63 (3H, m), 7.41−8.23 (7H, m). ^{13}C NMR δ: 11.8, 29.4, 38.7, 60.9, 123.2, 125.3, 125.5, 125.7, 126.4, 128.9, 132.6, 133.9, 141.3. IR (neat): 3350 cm^{-1}. EIMS *m/z*: 214 (M^+). HRMS (EI) Calcd for $C_{15}H_{18}O$: 214.1357. Found: 214.1352.

Acknowledgment. This research was supported by the 21st Century Center of Excellence Program “Knowledge Information Infrastructure for Genome Science” and a Grant-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology, Japan. M.K. is thankful for the receipt of a JSPS fellowship.

Supporting Information Available: Experimental procedure, characterization data, NMR spectra, and HPLC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0484225

---

[23] (a) Pal, M.; Madan, M.; Padakanti, S.; Pattabiraman, V. R.; Kalleda, S.; Vanguri, A.; Mullangi, R.; Mamidi, N. V. S. R.; Casturi, S. R.; Malde, A.; Gopalakrishnan, B.; Yeleswarapu, K. R. *J. Med. Chem.* **2003**, *46*, 3975−3981. (b) Wan, Y.; Wu, X.; Kannan, M. A.; Alterman, M. *Tetrahedron Lett.* **2003**, *44*, 4523−4525.

[24] Love, B. E.; Raje, P. S.; Williams, T. C., II. *Synlett* **1994**, 493−494.

[25] Absolute configuration of **10** was tentatively assigned on the basis of the absolute configuration determined for **2** (**10** Ar = Ph).

[26] Addition of 2.0 equiv of Et_2Zn in one portion gave **2** with 56% ee, slightly lower ee compared with 57% ee (Table 2, entry 6).