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Chiral *N,N′*-dioxide-iron(II) complexes catalyzed enantioselective oxa-Michael addition of α,β-unsaturated aldehydes

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ABSTRACT

The enantioselective oxa-Michael addition reaction of 1-(4-methoxyphenyl) ethanone oxime to various α,β-unsaturated aldehydes was accomplished by using chiral *N,N′*-dioxide-$FeSO_4{\cdot}7H_2O$ (1:1) complex. Aromatic acid was employed as additive to increase the yield of the reaction. The corresponding adducts were obtained in moderate yields with up to 76% ee under mild conditions.

Chiral β-hydroxy carbonyl compounds and 1,3-diols are important building blocks in natural products and valuable skeleton for organic synthesis. The most efficient strategy for their preparation is asymmetric oxa-Michael addition reaction and great efforts have been devoted to this area.[1,2] However, when the substrate concerned α,β-unsaturated aldehydes, there were only two efficient methods[3] with the exception of salicyl aldehyde derivatives.[4] The first highly chemo- and stereoselective oxa-Michael addition of α,β-unsaturated aldehydes was reported by Jørgensen's group[3a] using diarylprolinol silyl ether. Subsequently, Maruoka[3b] developed an axially chiral organocatalyst. Thus, the catalytic asymmetric oxa-Michael addition of α,β-unsaturated aldehydes remained one of the most challenging and interesting topics to be further explored.

Chiral Lewis acids are powerful catalysts for many enantioselective reactions.[5] Particularly, the environmentally benign biometals, such as zinc, iron, and copper, have drawn more and more attention. Iron, as one of the most abundant elements on the earth, is nontoxic, inexpensive, and readily available, and consequently becomes the ideal candidate. During the past decade, iron salts were demonstrated to be efficient for many organic processes.[6] However, it is relatively underrepresented compared to other transition metals (e.g., Ru, Rh, Pd, Ir etc.), especially in the field of asymmetric catalysis.[7] On the other hand, chiral *N*-oxide compounds and their complexes with different metals are emerging as a class of efficient catalysts in the asymmetric catalysis.[8,9] Herein, we report an enantioselective oxa-Michael addition of α,β-unsaturated aldehydes catalyzed by chiral *N,N′*-dioxide-$FeSO_4{\cdot}7H_2O$ complex under mild conditions.

In view of the poor nucleophilicity of the hard (HSAB) oxygen reagent, the study was initiated from 1-(4-methoxyphenyl) ethanone oxime **5** as nucleophile which contained an electron-donating group on the aromatic ring. The asymmetric addition of **5** to crotylaldehyde (**4a**) was carried out using different metals complexed with ligand **1**. It was found that the metals[10] which worked well in our previous studies failed to have any mentionable stereoselective control. Although L**1**-$Fe(ClO_4)_2{\cdot}6H_2O$ complex induced the reaction with poor ee (Table 1, entry 1), it showed the potential of iron(II) to catalyze this asymmetric conjugate addition. Therefore, some other iron(II) salts were screened (Table 1, entries 2–6), and $FeSO_4{\cdot}7H_2O$ gave the desired product in 24% yield and 63% ee (Table 1, entry 2). Changing iron(II) to iron(III) maintained the enantioselectivity well, but decreased the yield (Table 1, entry 2 vs entry 7). Iron(0) powder exhibited poor performance (Table 1, entry 8). It was worth noting that the reaction could tolerate air and moisture due to the stability of $FeSO_4{\cdot}7H_2O$.

To further increase the enantioselectivity, a series of *N,N′*-dioxides **2** and **3** were synthesized and evaluated (Fig. 1). As shown in Table 2, shortening the linkage between the two chiral backbones caused a slight increase in the yield (Table 2, entry 1 vs entry 2). In addition, the amide moiety of the ligand had significant influence on the reaction (Table 2, entries 2–6). Ligands derived from aliphatic amine generally worked better than those derived from aromatic amine. The remarkable improvement of ee was achieved when ligand **2b** containing *tert*-butyl group was employed (Table 2, entry 3). Furthermore, the results were greatly dependent on the amino acid fragment (Table 2, entries 7–9). Ligand **3b** and **3c**

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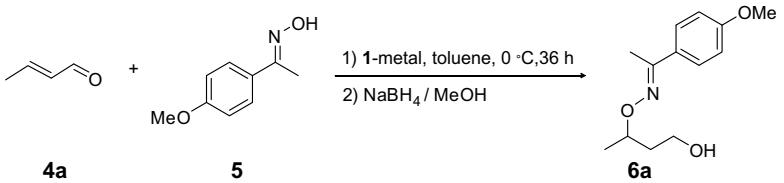
Table 1
Optimization of iron(II) salts



4a 5 6a

Entry[a]	Metal	Yield[b] (%)	ee[c] (%)
1	$Fe(ClO_4)_2{\cdot}6H_2O$	16	19
2	$FeSO_4{\cdot}7H_2O$	24	63
3	$Fe(BF_4)_2{\cdot}6H_2O$	20	12
4	$Fe(OCH_3)_2$	5	16
5	$Fe(acac)_2$	7	14
6	$Fe(OAc)_2$	54	46
7	$Fe_2(SO_4)_3{\cdot}H_2O$	17	63
8	Fe powder	8	30

[a] Performed with **4a** (0.375 mmol), **5** (0.25 mmol), metal:**1** = 1:1 (0.025 mmol) in toluene (0.5 mL).
[b] Isolated yield after reduction by $NaBH_4$/MeOH.
[c] Determined by chiral HPLC.

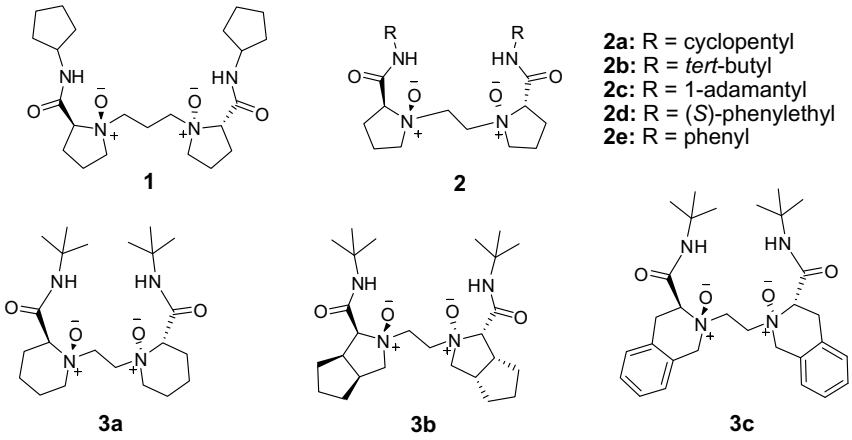
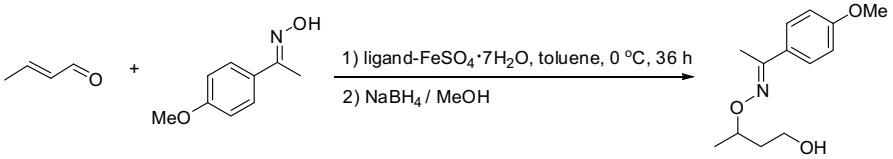


Figure 1. The ligands evaluated.

Table 2
The screening of the ligands using $FeSO_4{\cdot}7H_2O$

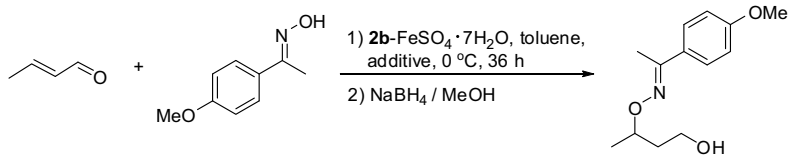


4a 5 6a

Entry[a]	Ligand	Yield[b] (%)	ee[c] (%)
1	**1**	24	63
2	**2a**	32	64
3	**2b**	12	75
4	**2c**	6	67
5	**2d**	23	41
6	**2e**	8	35
7	**3a**	4	48
8	**3b**	Trace	ND[d]
9	**3c**	Trace	ND[d]

[a] Performed with **4a** (0.375 mmol), **5** (0.25 mmol), ligand: metal = 1:1 (0.025 mmol) in toluene (0.5 mL).
[b] Isolated yield after reduction by $NaBH_4$/MeOH.
[c] Determined by chiral HPLC.
[d] Not determined.

Table 3
Optimization of the additives



4a **5** **6a**

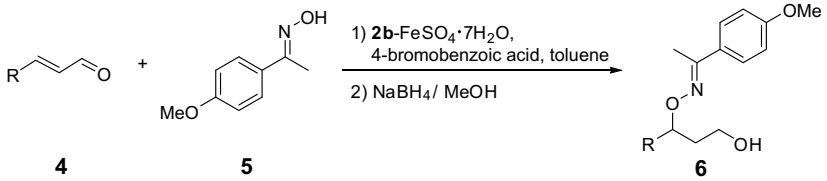
Entry[a]	Additive	Additive loading (mol %)	Yield[b] (%)	ee[c] (%)
1	—	—	12	75
2	H_2O	10	30	77
3	MeOH	10	23	74
4	4-Bromophenol	10	17	68
5	(*R*)-2-hydroxy-2-phenylacetic acid	10	61	44
6	(*S*)-2-Hydroxy-2-phenylacetic acid	10	65	39
7	TsOH	10	23	23
8	4-Methoxybenzoic acid	10	44	73
9	Benzoic acid	10	53	71
10	4-Bromobenzoic acid	10	65	68
11	2-Nitrobenzoic acid	10	70	29
12	4-Bromobenzoic acid	5	40	74
13	4-Bromobenzoic acid	20	64	66
14[d]	4-Bromobenzoic acid	10	45	78
15[d,e]	4-Bromobenzoic acid	10	62	75

[a] Performed with **4a** (0.375 mmol), **5** (0.25 mmol), **2b** (0.025 mmol), $FeSO_4·7H_2O$ (0.025 mmol), and additive in toluene (0.5 mL).
[b] Isolated yield after reduction by $NaBH_4$/MeOH.
[c] Determined by chiral HPLC.
[d] Performed in 1.0 mL toluene.
[e] t = 61 h.

only provided trace product, which might be ascribed to their much stronger rigidity (Table 2, entries 8 and 9).

The oxa-Michael addition of α,β-unsaturated aldehydes generally suffered from low yield, which could be ascribed to the reaction reversibility coupled with the competitive formation of acetal.[3a] In order to improve the yield, protonic additives[11] were introduced to the reaction. As shown in Table 3, the yield could be increased to various extents in the presence of protonic additives. It seemed that proper acidity was necessary. The addition of water, alcohol, or phenol could not lead to obvious improvement (Table 3, entries 2–4). The yield was sharply increased to 61% by employing (*R*)-2-hydroxy-2-phenylacetic acid, albeit with serious erosion of enantioselectivity (Table 3, entry 5). The configuration of the additive has little effect on the selectivity (Table 3, entry 5 vs entry 6). To our delight, screening of substituted benzoic acid series (Table 3, entries 8–11) indicated that 4-bromobenzoic acid was favorable in terms of yield and enantioselectivity (Table 3, entry 10). A remarkable increase in enantiomeric excess, from 69% to 78%, was achieved when the reaction concentration was lessened to 0.25 M (Table 3, entry 14). Accordingly, extensive screening has shown that the optimized catalytic reaction conditions are 1.5 equiv **4a**, 0.25 mmol **5**, 10 mol % **2b**, 10 mol % $FeSO_4·7H_2O$, 10 mol % 4-bromobenzoic acid in toluene (1.0 mL) at 0 °C. The yield could be further increased by prolonging reaction time (Table 3, entry 15).

Table 4
The scope of the substrates



4 **5** **6**

Entry[a]	Substrate	R	Time (h)	Product	Yield[b] (%)	ee[c] (%)
1	**4a**	Me	61	**6a**	62	75
2	**4b**	Et	61	**6b**[d]	47	72 (*R*)
3	**4c**	Pr	61	**6c**	50	75
4	**4d**	Bu	75	**6d**	56	73
5[e]	**4e**	Hep	61	**6e**	52	76
6[f]	**4f**	*i*-Pr	61	**6f**	30	74

[a] Performed with **4** (0.375 mmol), **5** (0.25 mmol), **2b** (0.025 mmol), $FeSO_4·7H_2O$ (0.025 mmol), and 4-bromobenzoic acid (0.025 mmol) in 1.0 mL toluene at 0 °C.
[b] Isolated yield after reduction by $NaBH_4$/MeOH.
[c] Determined by chiral HPLC.
[d] See Ref. 14.
[e] 0.0375 mmol Isophthalic acid as additive.
[f] 0.025 mmol 4-Methoxybenzoic acid as additive.

Under the optimized reaction conditions, various α,β-unsaturated aldehydes were tested in the asymmetric oxa-Michael addition. As shown in Table 4, most substrates reacted smoothly with **5** to afford the addition product **6** in good yields[12] with up to 76% ee. In terms of the stereochemical outcoming, variation of the substituents at β-position has little impact. Both the primary and secondary alkyl groups could be well tolerated (Table 4, entries 1–6). When the primary alkyl substituents ranged in size from methyl to *n*-heptyl, the adducts **6** were obtained in good yields (Table 4, entries 1–5). However, switching R to isopropyl diminished the yield to 30%, which probably attributed to the steric hindrance of the branch (Table 4, entry 6).

In summary, we have developed an asymmetric oxa-Michael addition catalyzed by a chiral *N*,*N*′-dioxide-$FeSO_4{\cdot}7H_2O$ complex with acid as additive. The reaction underwent smoothly to give the corresponding adducts in moderate yields and good enantioselectivities (up to 76% ee). It should be noted that a nontoxic, inexpensive, and environmentally friendly biometal was employed in the process. The simple procedure[13] made the method more practical. Further effort aimed at the mechanism and the improvement of enantioselectivity is currently underway.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.09.041.

References and notes

1. (a) Stewart, I. C.; Bergman, R. G.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 8696; (b) Wabnitz, T. C.; Spencer, J. B. *Org. Lett.* **2003**, *5*, 2141; (c) Bhuniya, D.; Mohan, S.; Narayanan, S. *Synthesis* **2003**, *7*, 1018; (d) Lesch, B.; Bräse, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 115; (e) Farnworth, M. V.; Cross, M. J.; Louie, J. *Tetrahedron Lett.* **2004**, *45*, 7441; (f) Murtagh, J. E.; McCooey, S. H.; Connon, S. J. *Chem. Commun.* **2005**, 227; (g) Avery, T. D.; Caiazza, D.; Culbert, J. A.; Taylor, D. K.; Tiekink, E. R. T. *J. Org. Chem.* **2005**, *70*, 8344; (h) Tinarelli, A.; Paolucci, C. *J. Org. Chem.* **2006**, *71*, 6630.
2. (a) Almaşi, D.; Alonso, D. A.; Nájera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 299; (b) van Lingen, H. L.; Zhuang, W.; Hansen, T.; Rutjes, F. P. J. T.; Jørgensen, K. A. *Org. Biomol. Chem.* **2003**, *1*, 1953; (c) Vanderwal, C. D.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 14724; (d) Ramachary, D. B.; Mondal, R. *Tetrahedron Lett.* **2006**, *47*, 7689; (e) Dinér, P.; Nielsen, M.; Bertelsen, S.; Niess, B.; Jørgensen, K. A. *Chem. Commun.* **2007**, 3646; (f) Carlone, A.; Bartoli, G.; Bosco, M.; Pesciaioli, F.; Ricci, P.; Sambri, L.; Melchiorre, P. *Eur. J. Org. Chem.* **2007**, 5492; (g) Rios, R.; Sundén, H.; Ibrahem, I.; Córdova, A. *Tetrahedron Lett.* **2007**, *48*, 2181; (h) Biddle, M. M.; Lin, M.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 3830; (i) Li, D. R.; Murugan, A.; Falck, J. R. *J. Am. Chem. Soc.* **2008**, *130*, 46; (j) Xiong, X.; Ovens, C.; Pilling, A. W.; Ward, J. W.; Dixon, D. J. *Org. Lett.* **2008**, *10*, 565.
3. (a) Bertelsen, S.; Dinér, P.; Johansen, R. L.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 1536; (b) Kano, T.; Tanaka, Y.; Maruoka, K. *Tetrahedron* **2007**, *63*, 8658.
4. (a) Govender, T.; Hojabri, L.; Moghaddam, F. M.; Arvidsson, P. I. *Tetrahedron: Asymmetry* **2006**, *17*, 1763; (b) Sundén, H.; Ibrahem, I.; Zhao, G.-L.; Eriksson, L.; Córdova, A. *Chem. Eur. J.* **2007**, *13*, 574; (c) Li, H.; Wang, J.; E-Nunu, T.; Zu, L.; Jiang, W.; Wei, S.; Wang, W. *Chem. Commun.* **2007**, 507.
5. *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH: Weinheim, 2008.
6. (a) Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217. and references therein; A New Monograph on the Use of Iron in Organic Synthesis: (b) *Iron Catalysis*; Plietker, B., Ed., Wiley-VCH: Weinheim, 2008.
7. Some selected reports of Iron in asymmetric catalysis: (a) Corey, E. J.; Imai, N.; Zhang, H.-Y. *J. Am. Chem. Soc.* **1991**, *113*, 728; (b) Nakamura, M.; Hirai, A.; Nakamura, E. *J. Am. Chem. Soc.* **2000**, *122*, 978; (c) Matsukawa, S.; Sugama, H.; Imamoto, T. *Tetrahedron Lett.* **2000**, *41*, 6461; (d) Yamashita, Y.; Ueno, M.; Kuriyama, Y.; Kobayashi, S. *Adv. Synth. Catal.* **2002**, *344*, 929; (e) Viton, F.; Bernardinelli, G.; Kündig, E. P. *J. Am. Chem. Soc.* **2002**, *124*, 4968; (f) Sturm, T.; Weissensteiner, W.; Spindler, F.; Mereiter, K.; López-Agenjo, A. M.; Manzano, B. R.; Jalón, F. A. *Organometallics* **2002**, *21*, 1766; (g) Du, G.; Andrioletti, B.; Rose, E.; Woo, L. K. *Organometallics* **2002**, *21*, 4490; (h) Itoh, T.; Kawai, K.; Hayase, S.; Ohara, H. *Tetrahedron Lett.* **2003**, *44*, 4081; (i) Redlich, M.; Hossain, M. M. *Tetrahedron Lett.* **2004**, *45*, 8987; (j) Schaefer, C.; Fu, G. C. *Angew. Chem., Int. Ed.* **2005**, *44*, 4606; (k) Jankowska, J.; Paradowska, J.; Rakiel, B.; Mlynarski, J. *J. Org. Chem.* **2007**, *72*, 2228; (l) Sui-Seng, C.; Freutel, F.; Lough, A. J.; Morris, R. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 940; (m) Suzuki, K.; Oldenburg, P. D.; Que, L., Jr. *Angew. Chem., Int. Ed.* **2008**, *47*, 1887; (n) Shaikh, N. S.; Enthaler, S.; Junge, K.; Beller, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 2497; (o) Kawatsura, M.; Komatsu, Y.; Yamamoto, M.; Hayase, S.; Itoh, T. *Tetrahedron* **2008**, *64*, 3488.
8. For reviews on chiral *N*-oxides in asymmetric catalysis, see: (a) Chelucci, G.; Murineddu, G.; Pinna, G. A. *Tetrahedron: Asymmetry* **2004**, *15*, 1373; (b) Malkov, A. V.; Kočovský, P. *Eur. J. Org. Chem.* **2007**, 29.
9. For examples of our previous work: (a) Huang, X.; Huang, J. L.; Wen, Y. H.; Feng, X. M. *Adv. Synth. Catal.* **2006**, *348*, 2579; (b) Qin, B.; Xiao, X.; Liu, X. H.; Huang, J. L.; Wen, Y. H.; Feng, X. M. *J. Org. Chem.* **2007**, *72*, 9323; (c) Shang, D. J.; Xin, J. G.; Liu, Y. L.; Zhou, X.; Liu, X. H.; Feng, X. M. *J. Org. Chem.* **2008**, *73*, 630; (d) Yu, Z. P.; Liu, X. H.; Dong, Z. H.; Xie, M. S.; Feng, X. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 1308; (e) Yang, X.; Zhou, X.; Lin, L. L.; Chang, L.; Liu, X. H.; Feng, X. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 7079.
10. The metals included Cu(I), Sc(III), In(III), and La(III). See Refs. 9b–e.
11. Wabnitz, T. C.; Yu, J.-Q.; Spencer, J. B. *Chem. Eur. J.* **2004**, *10*, 484.
12. Though the yields seemed to be moderate, the results should be acceptable in the asymmetric oxa-Michael addition due to the poor nucleophilicity of oxygen nucleophiles.
13. *General procedure for the asymmetric oxa-Michael addition*: Compound **2b** (0.025 mmol), $FeSO_4{\cdot}7H_2O$ (0.025 mmol), **5** (0.25 mmol), and acidic additives (0.025 mmol) were dissolved in 0.4 mL toluene. After the mixture was cooled down to 0 °C, α,β-unsaturated aldehyde (0.375 mmol) was added, which was followed by the addition of 0.6 mL toluene. The contents were stirred at 0 °C for the indicated time as shown in Table 4. $NaBH_4$ (10 mg) and instantaneously MeOH (0.5 mL) was added. The reduction reaction was quenched with sat. NH_4Cl (aq) and extracted with CH_2Cl_2 (10 mL × 3). Evaporation of the solvent and column chromatography (Et_2O/petroleum oil, 2:3 v/v) afforded the pure products. Product **6a**: Pale yellow liquid, $[\alpha]_D^{26} + 5.8$ (*c* 0.208, CH_2Cl_2) (75% ee). HPLC (OJ-H column, 2-propanol/hexane, 10/90, flow 1.0 mL/min, detection at 254 nm). t_R (minor) = 15.71 min, t_R (major) = 17.27 min. ^1H NMR (400 MHz, $CDCl_3$): δ 1.33 (d, 3H, *J* = 6.4 Hz), 1.86–1.90 (m, 2H), 2.20 (s, 3H), 2.62 (s, 1H), 3.73–3.83 (m, 2H), 3.81 (s, 3H), 4.49–4.53 (m, 1H), 6.86–6.90 (m, 2H), 7.55–7.59 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.80, 20.47, 39.07, 55.30, 60.11, 77.60, 113.82, 127.32, 129.19, 154.12, 160.39 ppm; ESI-HRMS calcd for ($C_{13}H_{19}NO_3$+Na^+) 260.1257, found: 260.1254.
14. The product **6b** (4-methoxyacetophenone-*O*-1-hydroxypentan-3-yl oxime) was transformed to the corresponding benzaldehyde-*O*-1-hydroxypentan-3-yl oxime: ^1H NMR (400 MHz, $CDCl_3$): δ 0.98 (t, 3H, *J* = 7.2 Hz), 1.61–1.68 (m, 1H), 1.73–1.83 (m, 1H), 1.86–1.95 (m, 2H), 3.77–3.85 (m, 2H), 4.30–4.35 (m, 1H), 7.36–7.38 (m, 3H), 7.55–7.58 (m, 2H), 8.09 (s, 1H). $[\alpha]_D^{26}$ +17.5 (*c* 0.126, CH_2Cl_2) (60% ee). Lit[3a]: $[\alpha]_D^{26}$ +22.9 (*c* 1.06, CH_2Cl_2) (95% ee).