ORGANIC
LETTERS

2012
Vol. 14, No. 1
194–197

Enantioselective Carbenoid Insertion into Phenolic O−H Bonds with a Chiral Copper(I) Imidazoindolephosphine Complex

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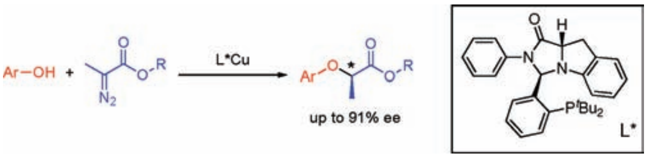
Received November 4, 2011

ABSTRACT



The enantioselective O−H carbenoid insertion reaction with a new chiral copper(I) imidazoindolephosphine complex has been developed. The chiral copper(I) complex catalyzed the insertion of carbenoids derived from α-diazopropionates into the O−H bonds of various phenol derivatives to give the corresponding α-aryloxypropionates with up to 91% ee.

The transition-metal-catalyzed insertion of carbenoid species derived from α-diazocarbonyl compounds into X−H bonds (X = C, O, N, S, Si, etc.) has been widely recognized as a direct and efficient method for the construction of carbon−carbon and carbon−heteroatom bonds.[1,2] In particular, the enantioselective catalytic O−H insertion reaction provides chiral α-alkyloxy or α-aryloxy carbonyl compounds, which are useful synthetic intermediates for the construction of natural products and biologically active molecules.[3] Although various chiral rhodium complexes have been developed to catalyze the carbenoid insertion into C−H bonds with high enantioselectivity,[4] highly enantioselective O−H insertions using chiral transition metal catalysts were not achieved until 2006.[5] In 2006, Fu reported the first example of the highly enantioselective carbenoid insertion into an O−H bond with a chiral copper catalyst. A copper complex of the chiral bisazaferrocene **A** (Figure 1) efficiently catalyzed the highly enantioselective insertion of α-diazo-α-arylacetates into the O−H bonds of alcohols to give the corresponding α-alkyloxy esters with up to 98% ee.[6] Zhou

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(1) For general reviews of the reaction of α-diazocarbonyl compounds, see: (a) Doyle, M. P.; Mckervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley: New York, 1998. (b) Zhang, Z; Wang, J *Tetrahedron* **2008**, *64*, 6577–6605.

(2) (a) For a review of catalytic O−H insertion, see: Miller, D. J.; Moody, C. J. *Tetrahedron* **1995**, *51*, 10811–10843. (b) For a review of catalytic N−H insertion, see: Moody, C. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 9148–9150.

(3) For a recent example, see: Chimichi, S.; Boccalini, M.; Cravotto, G.; Rosati, O. *Tetrahedron Lett*. **2006**, *47*, 2405–2408.

(4) (a) Doyle, M. P.; Duffy, R.; Ratnikov, M.; Zhou, L. *Chem. Rev.* **2010**, *110*, 704–724. (b) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417–424. (c) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev*. **2003**, *103*, 2861–2903.

(5) For an example of the application of a chiral Rh catalyst to an enantioselective O−H insertion, see: (a) Bulugahapitiya, P.; Landais, Y.; Parra-Rapado, L.; Planchenault, D.; Weber, V. *J. Org. Chem.* **1997**, *62*, 1630–1641. For examples of early efforts for diastereoselective O−H insertion, see:(b) Aller, E.; Cox, G. G.; Miller, D. J.; Moody, C. J. *Tetrahedron Lett*. **1994**, *35*, 5949–5952. (c) Aller, E.; Brown, D. S.; Cox, G. G.; Miller, D. J.; Moody, C. J. *J. Org. Chem*. **1995**, *60*, 4449–4460. (d) Miller, D. J.; Moody, C. J.; Morfitt, C. N. *Aust. J. Chem.* **1999**, *52*, 97–108. (e) Jiang, N.; Wang, J.; Chan, A. S. C. *Tetrahedron Lett*. **2001**, *42*, 8511–8513.

(6) Maier, T. C.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 4594–4595.

(7) Asymmetric O−H insertion with a copper complex: (a) Chen, C.; Zhu, S.-F.; Liu, B.; Wang, L.-X.; Zhou, Q.-L. *J. Am. Chem. Soc*. **2007**, *129*, 12616–12617. (b) Zhu, S.-F.; Chen, C.; Cai, Y.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2008**, *47*, 932–934. (c) Zhu, S.-F.; Chen, W.-Q.; Zhang, Q.-Q.; Mao, H.-X.; Zhou, Q.-L. *Synlett* **2011**, 919–922. (d) Zhu, S.-F.; Song, X.-G.; Li, Y.; Cai, Y.; Zhou, Q.-L *J. Am. Chem. Soc.* **2010** *132*, 16374–16376. Asymmetric O−H insertion with an iron complex: (e) Zhu, S.-F.; Cai, Y.; Mao, H.-X.; Xie, J.-H.; Zhou, Q.-L. *Nat. Chem.* **2010**, *2*, 546–551.

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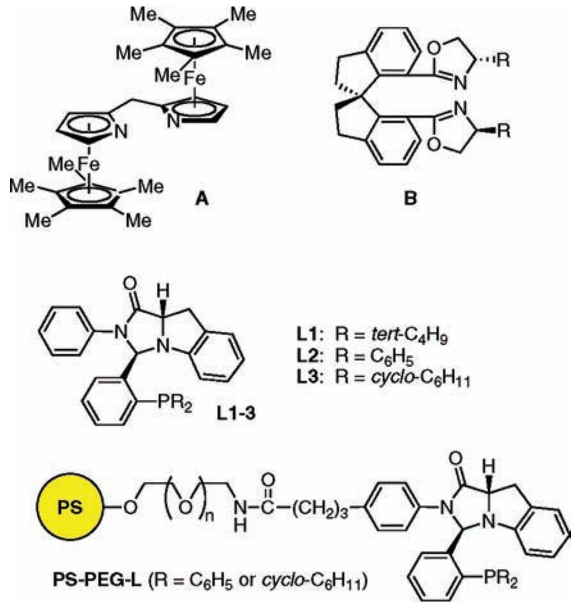


Figure 1. Structure of chiral ligands.

also has found that copper and iron complexes of the chiral spiro bisoxazoline ligands **B** (Figure 1) are effective for asymmetric carbenoid insertion into O−H bonds of phenols, water, alcohols, and ω-hydroxy-α-diazoesters to provide the corresponding O−H inserted products with high enantioselectivity.[7] Although a recent theoretical study has suggested that chiral copper(I) complexes are superior to chiral dirhodium(II) complexes for catalytic carbenoid insertion into O−H bonds with high enantioselectivity,[8] to date only two ligand systems (**A** and **B**; *vide supra*) are available to achieve high stereoselectivity. Thus, while these pioneering strides have been made, additional studies on catalyst systems to achieve highly enantioselective carbenoid insertion into O−H bond are still warranted.

On the other hand, we have developed the chiral imidazoindolephosphine ligands (**L1**−**3** and **PS-PEG-L**), which are very effective for various Pd-catalyzed asymmetric organic transformations in organic as well as aqueous media.[9] As part of our effort to demonstrate the wide utility of this chiral imidazoindolephosphine, we envisioned these ligands being used for asymmetric copper-catalyzed organic transformations, such as the O−H insertion of carbenoids. We report herein a new chiral copper(I) catalyst for enantioselective phenolic O−H insertion. The copper(I) complex of the chiral imidazoindolephosphine ligand **L1** catalyzed the O−H insertion of carbenoids derived from α-diazopropionates into phenols to give the corresponding α-aryloxy products with up to 91% ee.

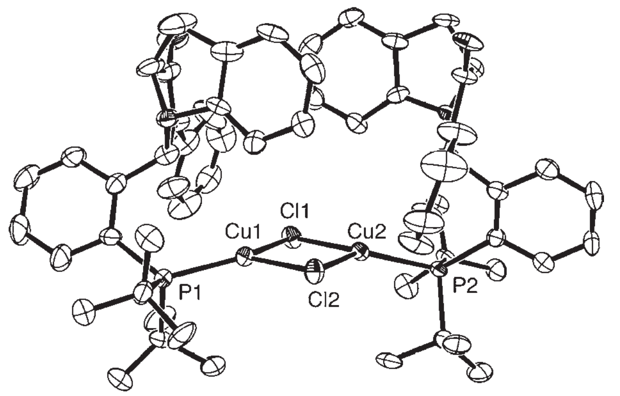
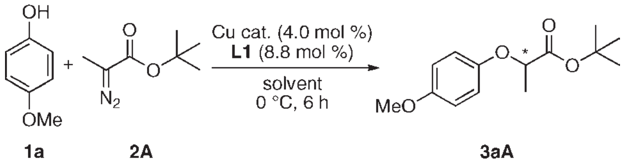


Figure 2. ORTEP drawing of the crystal structure of **CuCl(L1)**. The hydrogen atoms and the solvent molecule (Et$_2$O) have been omitted for clarity.

As our initial study, we treated the chiral imidazoindolephosphine ligand **L1** with CuCl in CH$_2$Cl$_2$, which gave the copper(I) complex **CuCl(L1)** in 72% yield. The X-ray crystallographic analysis revealed that the structure of the copper(I) complex (**CuCl(L1)**) exhibited a dimeric form consisting of two trigonal planar copper centers (Figure 2).[10]

Table 1. Condition Screening for the Reaction of 4-Methoxyphenol (**1a**) with *tert*-Butyl α-Diazopropionate (**2A**) in the Presence of Copper Catalysts[a]



entry	copper source	solvent	yield (%)[b]	ee (%)[c]
1[d]	CuCl	CH$_2$Cl$_2$	0	–
2	CuI	CH$_2$Cl$_2$	0	–
3	CuOAc	CH$_2$Cl$_2$	1	58
4	[Cu(CH$_3$CN)$_4$]PF$_6$	CH$_2$Cl$_2$	15	71
5	CuCl and NaBARF	CH$_2$Cl$_2$	57	20
6	CuOTf•(C$_6$H$_6$)$_{0.5}$	CH$_2$Cl$_2$	51	77
7	Cu(OTf)$_2$	CH$_2$Cl$_2$	16	19
8	CuOTf•(C$_6$H$_6$)$_{0.5}$	DMF	0	–
9	CuOTf•(C$_6$H$_6$)$_{0.5}$	THF	4	58
10	CuOTf•(C$_6$H$_6$)$_{0.5}$	toluene	38	58

[a] Conditions: **1a** (0.25 mmol), **2A** (0.125 mmol), copper source (4.0 mol %), **L1** (8.8 mol %), CH$_2$Cl$_2$ (500 μL), 0 °C, 6 h. [b] Determined by GC with an internal standard (mesitylene). [c] Determined by GC equipped with a CP-Chirasil-Dex CB column. [d] 4.0 mol % of **CuCl(L1)** was used.

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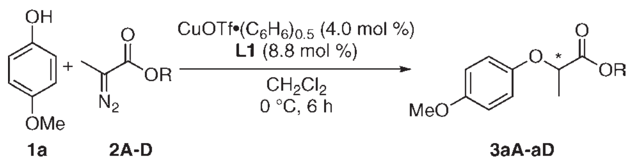
(8) Liang, Y.; Zhou, H.; Yu, Z.-X. *J. Am. Chem. Soc.* **2009**, *131*, 17783–17785.

(9) (a) Shibatomi, K.; Uozumi, Y. *Tetrahedron: Asymmetry* **2002**, *13*, 1769–1772. (b) Uozumi, Y.; Shibatomi, K. *J. Am. Chem. Soc.* **2001**, *123*, 2919–2920. (c) Uozumi, Y.; Tanaka, H.; Shibatomi, K. *Org. Lett.* **2004**, *6*, 281–283. (d) Nakai, Y.; Uozumi, Y. *Org. Lett.* **2005**, *7*, 291–293. (e) Uozumi, Y.; Kimura, M. *Tetrahedron: Asymmetry* **2006**, *17*, 161–166. (f) Uozumi, Y.; Suzuka, T. *J. Org. Chem.* **2006**, *71*, 8644–8646. (g) Uozumi, Y.; Takenaka, H.; Suzuka, T. *Synlett* **2008**, 1557–1561. (h) Uozumi, Y.; Suzuka, T. *Synthesis* **2008**, 1960–1964. (i) Uozumi, Y.; Matsuura, Y.; Arakawa, T.; Yamada, Y. M. A. *Angew. Chem., Int. Ed.* **2009**, *48*, 2708–2710.

Moreover two μ-chloride anions and one phosphine atom of the ligand coordinate to the copper center.

With the chiral copper(I) complex in hand, we next investigated the carbenoid insertion into O–H bonds. The reaction of 2 equiv of 4-methoxyphenol (**1a**) with 1 equiv of *tert*-butyl α-diazopropionate (**2A**) in the presence of 4.0 mol % of **CuCl(L1)** in CH_2Cl_2 was carried out at 0 °C for 6 h. However the desired O–H insertion product was not obtained (Table 1, entry 1). We speculated that the strong coordination of the chloride anions to the copper center might have inhibited formation of the copper-carbenoid intermediate derived from the α-diazocarbonyl compounds. Therefore we tested a series of copper sources having various counteranions for the O–H insertion (Table 1, entries 2–7).

Table 2. Scope for α-Diazopropionates (**2**) in the Asymmetric Copper-Catalyzed Carbenoid Insertion into 4-Methoxyphenol (**1a**)[a]



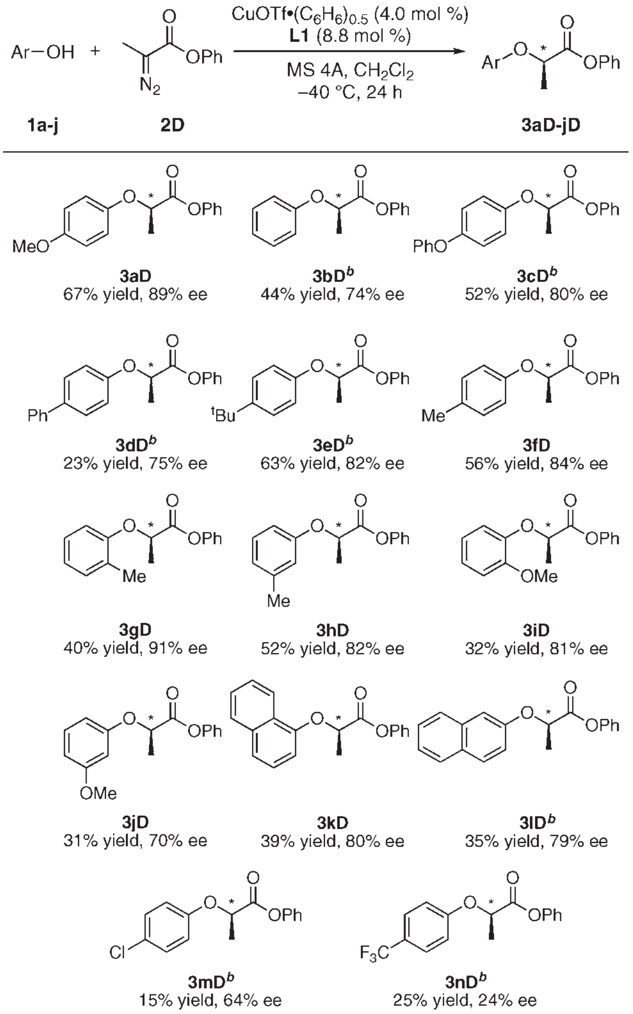
entry	2	R	additive[b]	3	yield (%)[c]	ee (%)[d]
1	**2A**	*t*-Bu	–	**3aA**	51[e]	77
2	**2B**	benzyl	–	**3aB**	40	33
3	**2C**	thexyl[f]	–	**3aC**	42	76
4	**2D**	Ph	–	**3aD**	68	84
5	**2D**	Ph	MS 4A	**3aD**	55	86
6[g]	**2D**	Ph	MS 4A	**3aD**	50	89
7[h]	**2D**	Ph	MS 4A	**3aD**	67	89

[a] Conditions: **1a** (0.25 mmol), **2** (0.125 mmol), CuOTf•$(C_6H_6)_{0.5}$ (4.0 mol %), **L1** (8.8 mol %), CH_2Cl_2 (500 μL), 0 °C, 6 h. [b] 60 mg of MS 4A were added. [c] Isolated yield unless otherwise mentioned. [d] Determined by GC equipped with a CP-Chirasil-Dex CB column (for **3aA**) or HPLC equipped with chiral stationary column (for **3aB**-**3aD**). [e] GC yield. [f] Thexyl = 2,3-dimethylbutan-2-yl. [g] The reaction was performed at –40 °C for 24 h. [h] The reaction was performed at –40 °C for 24 h. **1a** (0.75 mmol) was used.

The O–H insertion using 4.0 mol % of CuI in the presence of 8.8 mol % of **L1** did not afford the desired O–H inserted product (entry 2). When CuOAc and $[Cu(CH_3CN)_4]PF_6$ were used as the copper sources, *tert*-butyl α-aryloxypropionate **3aA** was obtained in 1% and 15% yield with 58% and 71% ee, respectively (entries 3 and 4). The combination of CuCl and NaBARF[11] increased the yield of **3aA** to 57%, although the enantioselectivity was low (20% ee, entry 5). The use of CuOTf•$(C_6H_6)_{0.5}$ increased both the yield and enantioselectivity, providing **3aA** in 51% yield and 77% ee (entry 6).[12] The O–H insertion in the presence of $Cu(OTf)_2$ gave the product in 16% yield with 19% ee (entry 7). The reaction of **1a** with **2A** in the presence of CuOTf•$(C_6H_6)_{0.5}$ and **L1** was also conducted in various solvents such as DMF, THF, and toluene (entries 8–10). However neither the yield nor ee were improved under these conditions.

For further optimization of the reaction conditions, α-diazopropionates bearing various substituents on the ester were examined for the copper-catalyzed O–H insertion (Table 2).[13] The reaction with benzyl and thexyl α-diazopropionates (**2B** and **2C**, thexyl = 2,3-dimethylbutan-2-yl) afforded the corresponding α-aryloxypropionates **3aB** and **3aC** in 40% and 42% yield with 38% and 76% ee, respectively (entries 2 and 3). The use of phenyl α-diazopropionate

Scheme 1. Scope of Phenols (**1**) in the Asymmetric Copper-Catalyzed Carbenoid Insertion with **2D**[a]



[a] Conditions: **1** (0.25 mmol), **2D** (0.125 mmol), CuOTf•$(C_6H_6)_{0.5}$ (4.0 mol %), **L1** (8.8 mol %), MS 4A (60 mg), CH_2Cl_2 (500 μL), –40 °C, 24 h. The yields are of isolated products. The ee values were determined by HPLC equipped with chiral stationary columns. The absolute configuration of **3bD** was determined to be *R* (see Scheme 2), and those of **3aD** and **3cD**–**nD** were tentatively assigned on the basis of the mechanistic similarity of the asymmetric induction. [b] CuOTf•$(C_6H_6)_{0.5}$ (8.0 mol %) and **L1** (17.6 mol %) were used.

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(10) See the Supporting Information for details of the X-ray crystallographic analysis.

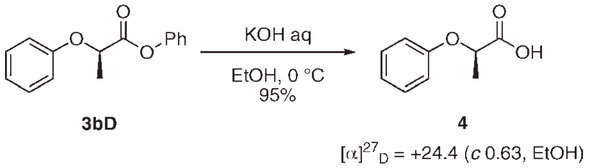
(11) $BARF^-$ = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate. Zhou and co-workers used the combination of CuCl and NaBARF as the optimal conditons in ref 7a–7d.

(**2D**) increased both the yield and enantioselectivity, providing the product **3aD** in 68% yield with 84% ee (entry 4). Addition of molecular sieves 4A improved the enantioselectivity from 84% to 86% ee (entry 5). When the reaction was carried out at −40 °C for 24 h, further improvement of the ee value was observed (entry 6, 89% ee). When 3 equiv of phenyl α-diazopropionate **2D** were used, the yield of **3aD** was increased to 67% with the same enantioselectivity (entry 7).

The copper-catalyzed asymmetric insertion of the carbenoid derived from phenyl α-diazopropionates into the O−H bonds of various phenol derivatives was investigated under the above-described optimal conditions (Scheme 1). The reaction of phenol **1b** with phenyl α-diazopropionate **2D** at −40 °C for 24 h gave the product **3bD** in 44% yield with 74% ee. *Para*-substituted phenols bearing electron-donating groups such as phenoxyl, phenyl, *tert*-butyl, and methyl groups (**1c**−**1f**) underwent the O−H insertion to afford the corresponding α-aryloxycarbonyl compounds **3cD**−**3fD** in 23−63% yield with 75−84% ee. *Ortho*- and *meta*-substituted phenols (**1g**−**1j**) were tolerated for the reaction. In particular, when *o*-cresol (**1g**) was used as the phenol substrate, the highest enantioselectivity (91% ee) was observed. The reaction of 1- and 2-naphthols (**1k** and **1l**) also proceeded to provide the products **3kD** and **3lD** with 80% and 79% ee, respectively. When phenols bearing *p*-chloro and *p*-trifluoro groups (**1m** and **1n**) were used, the products **3mD** and **3nD** were obtained in low yield with low enantioselectivity.

The absolute stereochemistry of **3bD** was determined to be (+)-*R* by correlation with the known 2-phenoxypropionate **4** formed by alkaline hydrolysis. Thus, the O−H inserted product phenyl 2-phenoxypropionate **3bD** was treated with aqueous KOH in EtOH at 0 °C to give (*R*)-2-phenoxypropionate **4** ($[\alpha]^{27}_D$ = +24.4 (*c* 0.63, EtOH)) in 95% yield (Scheme 2).[14]

Scheme 2. Hydrolysis of **3bD**



In conclusion, we have developed a new chiral copper catalyst to promote the highly enantioselective insertion of carbenoids derived from α-diazopropionates into phenolic O−H bonds. The copper(I) complex of imidazoindolephoshine **L1** catalyzed the reaction of phenols with α-diazopropionates to give the corresponding α-aryloxypropionates in up to 67% yield with up to 91% ee. Additional investigations into the substrate scope and the reaction mechanism are underway in our laboratory.

Acknowledgment. This work was supported financially by a JSPS Grant-in-Aid for young scientists (B), No. 22750141. We also acknowledge partial financial support from JSPS (Grant-in-Aid for Scientific Research, No. 20655035), MEXT (Science Research on Priority Area, No. 460), and METI/NEDO (Green-Sustainable Chemical Process project) and JASSO-JENESYS programs.

Supporting Information Available. General procedures; ^{1}H, ^{13}C, and ^{31}P NMR spectra; GC or HPLC charts for the determination of the ee values; the CIF file for the crystal structure of CuCl(L1). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) When 4.4 mol % of L1 was used in the reaction of **1a** and **2A**, the product **3aA** was obtained with 50% ee. Therefore the possibility that the copper complex with the ratio Cu/L1 = 1:2 (CuOTf(L1)$_2$) acts as the active catalyst cannot be excluded, although the crystal structure of CuCl(L1) with the ratio Cu/L1 = 1:1 was obtained. A detailed mechanistic investigation is underway.

(13) We also tested the O−H insertion of *p*-methoxylphenol with ethyl α-diazo-α-phenylacetate under similar conditions. Unfortunately, low enantioselectivity was observed (7% ee).

(14) For the specific rotation value of (*R*)-(+)-2-phenoxypropionate, see: (a) Perron, Y. G.; Minor, W. F.; Holdrege, C. T.; Gottstein, W. J.; Godfrey, J. C.; Crast, L. B.; Babel, R. B.; Cheney, L. C. *J. Am. Chem. Soc.* **1960**, *82*, 3934–3938 ($[\alpha]^{25}_D$ = +39.8 (*c* 1.0, EtOH)). (b) Reference 7a ($[\alpha]^{19}_D$ = +38.9 (*c* 1.3, EtOH)).