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Catalytic Enantioselective O−H Insertion Reactions

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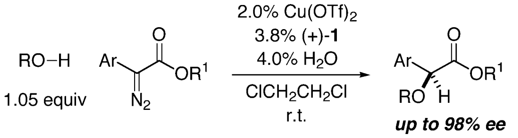
Remarkable advances have been reported in the discovery of methods for catalytic asymmetric insertion into C−H bonds.[1] In contrast, there has been essentially no success in achieving corresponding reactions of O−H bonds (maximum ee: 8%);[2] in fact, there has been only limited progress even with respect to diastereoselective processes.[3,4] In this communication, we describe the first effective catalyst for enantioselective O−H insertions, thereby generating α-alkoxy and α-hydroxy carbonyl compounds in good ee (eq 1).[5,6]



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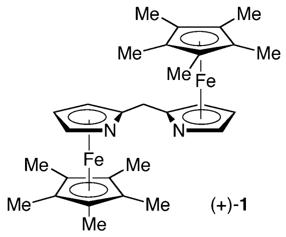
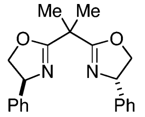


(+)-**1**

Outlined in Table 1 are the effects of a number of reaction parameters on the yield and the ee for the copper-catalyzed coupling of ethanol with methyl α-diazo-α-phenylacetate.[7] A key serendipitous discovery was that the addition of a small amount of water furnishes a much more enantioselective catalyst (entries 1 and 2 versus entry 3).[8] A lower ligand:metal ratio leads to a lower yield and ee (entry 4), as does the use of chiral bisoxazoline, semicorrin, Pybox, DUPHOS, and BINAP ligands (entries 5−9). Under our standard conditions, in the absence of $Cu(OTf)_2$ or in the presence of $CuCl_2$ or CuCl, unsatisfactory yields and essentially no enantioselectivity are observed (entries 10−12). In contrast, $CuPF_6(CH_3CN)_4$ provides an active, but somewhat less stereoselective, catalyst (entry 13 versus entry 1). Insertions conducted in CH_2Cl_2 proceed smoothly with fairly good enantioselectivity, whereas reactions in Et_2O or toluene afford low ee (entries 14−16).[9]



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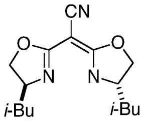

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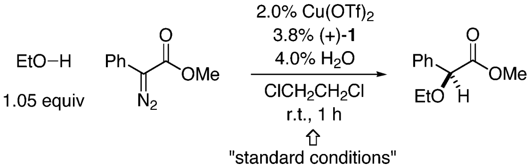
We have examined the impact of the structure of the alcohol on the yield and the ee of copper/bisazaferrocene-catalyzed asymmetric O−H insertion reactions (Table 2). The steric demand of the alkyl group plays an important role, with ethanol furnishing the best results among the four simple alcohols described in entries 1−4. Among ethanol derivatives, dramatically different outcomes are obtained, depending on the substituents on the remote carbon, e.g., 2-trimethylsilylethanol reacts in excellent yield and ee (entry 5), whereas 2,2,2-trifluoroethanol does not undergo insertion (entry 6). 2-Trimethylsilylethanol is a particularly attractive substrate, since the insertion product can be deprotected to provide the α-hydroxy ester in high yield without racemization (eq 2). Reactions of benzyl

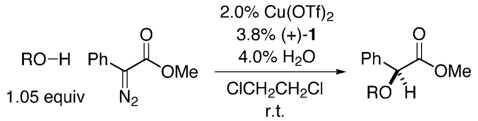
Table 1. Effect of a Range of Reaction Parameters on Catalytic Enantioselective O−H Insertions



entry	change from standard conditions	yield (%)[a,b]	ee (%)[a]
1	none	86	86
2	30% H_2O instead of 4.0% H_2O	98	82
3	no H_2O instead of 4.0% H_2O	93	22
4	2.2% (+)-**1** instead of 3.8% (+)-**1**	50	13
5	3.8% **2** instead of 3.8% (+)-**1**	70	<2
6	3.8% **3** instead of 3.8% (+)-**1** (4 h)	72	40
7	3.8% (*R*)-*i*-Pr-Pybox instead of 3.8% (+)-**1** (20 h)	51	9
8	3.8% (*R*)-Et-DUPHOS instead of 3.8% (+)-**1**	45	<2
9	3.8% (*R*)-BINAP instead of 3.8% (+)-**1** (20 h)	73	<2
10	no $Cu(OTf)_2$ instead of 2.0% $Cu(OTf)_2$ (24 h)	0	−
11	2.0% $CuCl_2$ instead of 2.0% $Cu(OTf)_2$ (20 h)	37	<2
12	2.0% CuCl instead of 2.0% $Cu(OTf)_2$ (20 h)	39	<2
13	2.0% $CuPF_6(CH_3CN)_4$ instead of 2.0% $Cu(OTf)_2$	95	76
14	CH_2Cl_2 instead of $ClCH_2CH_2Cl$	92	72
15	Et_2O instead of $ClCH_2CHCl$ (4 h)	71	7
16	toulene instead of $ClCH_2CH_2Cl$ (4 h)	70	7

[a] Average of two experiments. [b] Determined by GC versus a calibrated internal standard.

Table 2. Catalytic Enantioselective O−H Insertions: Dependence of ee on the Choice of Alcohol



entry	R	yield (%)[a,b]	ee (%)[a]	entry	R	yield (%)[a,b]	ee (%)[a]
1	Me	86	69	6	CH_2CF_3	<2	−
2	Et	85	87	7	Bn	86	77
3	*i*-Pr	76	68	8	*p*-methoxybenzyl	87	82
4	*t*-Bu	<2	−	9	allyl	77	27
5	CH_2CH_2TMS	94	90	10	Ph	56	11[c]

[a] Average of two experiments. [b] Isolated yield. [c] The opposite stereoisomer is produced.

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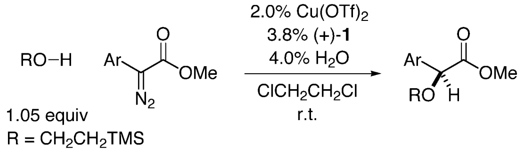
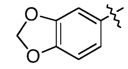
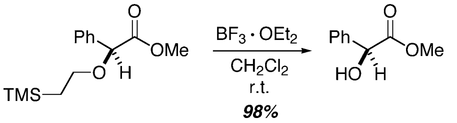
Table 3. Catalytic Enantioselective O−H Insertions: Scope



entry	Ar	yield (%)[a,b]	ee (%)[a]
1	Ph	94	90
2	(2-OMe)C_6H_4	90	96
3[c]	(2-Me)C_6H_4	94	79
4	(2-Cl)C_6H_4	96	96
5	(2-F)C_6H_4	98	98
6[c]	(3-OMe)C_6H_4	96	89
7	(3-Cl)C_6H_4	92	65
8	(4-OMe)C_6H_4	85	86
9	(4-NHAc)C_6H_4	89	87 (99)[d]
10	(4-Ph)C_6H_4	91	86
11[c]	(4-Br)C_6H_4	95	79
12	(4-F)C_6H_4	92	89
13	(4-CF_3)C_6H_4	90	21
14	2-naphthyl	93	84
15		88	89
16	3-thienyl	88	88

[a] Average of two experiments. [b] Isolated yield. [c] Due to ease of synthesis, the ethyl ester was used. [d] Value in parentheses: ee after one recrystallization.

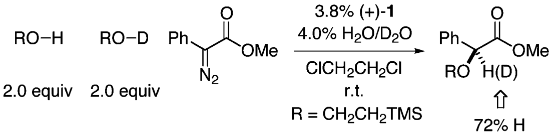
alcohols proceed with fairly good enantioselectivity (entries 7 and 8), although insertions into allyl alcohol and phenol afford unsatisfactory results (entries 9 and 10).[10,11]



(2)

Copper/bisazaferrocene-catalyzed insertions into the O−H bond of 2-trimethylsilylethanol proceed in high yield and generally good enantioselectivity for a range of α-diazo esters (Table 3). Thus, the aromatic ring can be substituted in the ortho (entries 2−5), meta (entries 6 and 7), or para (entries 8−13) positions, and it can be electronically diverse (for an exception, see entry 13). Furthermore, bicyclic substituents are tolerated (entries 14 and 15), as is a heterocycle (entry 16).[12]

Although we have not yet conducted detailed mechanistic studies, we have made two observations worthy of mention. First, product ee correlates linearly with catalyst ee.[13] Second, there is a substantial preference for O−H, rather than O−D, insertion (eq 3).[14]



(3)

In summary, we have developed the first effective method for catalytic enantioselective insertions into O−H bonds. Thus, a copper/bisazaferrocene catalyst couples alcohols such as 2-trimethylsilylethanol with α-aryl-α-diazo esters in high yield and generally good ee. Additional investigations of this and related processes are underway.

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For reviews and leading references, see: (a) Davies, H. M. L.; Long, M. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 3518−3520. (b) Davies, H. M. L. In *Comprehensive Asymmetric Catalysis* (Supplement 1); Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 2004; pp 83−94. (c) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; pp 513−603. (d) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861−2903. (e) Müller, P.; Fuirt, C. *Chem. Rev.* **2003**, *103*, 2905−2919.

(2) Bulugahapitiya, P.; Landais, Y.; Parra-Rapado, L.; Planchenault, D.; Weber, V. *J. Org. Chem.* **1997**, *62*, 1630−1641 (8% ee, 59% yield).

(3) For examples of diastereoselective O−H insertion reactions, see: (a) Aller, E.; Cox, G. G.; Miller, D. J.; Moody, C. J. *Tetrahedron Lett.* **1994**, *35*, 5949−5952. (b) Aller, E.; Brown, D. S.; Cox, G. G.; Miller, D. J.; Moody, C. J. *J. Org. Chem.* **1995**, *60*, 4449−4460. (c) Shi, G.-q.; Cao, Z.-y.; Cai, W.-l. *Tetrahedron* **1995**, *51*, 5011−5018. (d) Bulugahapitiya, P.; Landais, Y.; Parra-Rapado, L.; Planchenault, D.; Weber, V. *J. Org. Chem.* **1997**, *62*, 1630−1641. (e) Miller, D. J.; Moody, C. J.; Morfitt, C. N. *Aust. J. Chem.* **1999**, *52*, 97−107. (f) Pansare, S. V.; Jain, R. P.; Bhattacharyya, A. *Tetrahedron Lett.* **1999**, *40*, 5255−5258. (g) Moody, C. J.; Morfitt, C. N.; Slawin, A. M. Z. *Tetrahedron: Asymmetry* **2001**, *12*, 1657−1661. (h) Jiang, N.; Wang, J.; Chan, A. S. C. *Tetrahedron Lett.* **2001**, *42*, 8511−8513. (i) Doyle, M. P.; Yan, M. *Tetrahedron Lett.* **2002**, *43*, 5929−5931. (j) Im, C. Y.; Okuyama, T.; Sugimura, T. *Chem. Lett.* **2005**, 1328−1329. (k) Bolm, C.; Saladin, S.; Classen, A.; Kasyan, A.; Veri, E.; Raabe, G. *Synlett* **2005**, 461−464.

(4) For reviews of catalyzed insertions of diazo compounds into O−H bonds, see: (a) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley: New York, 1998; Chapters 8.3 and 8.4. (b) Miller, D. J.; Moody, C. J. *Tetrahedron* **1995**, *50*, 10811−10843.

(5) For leading references to the synthesis and the utility of α-hydroxycarbonyl compounds, see: (a) Janey, J. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4292−4300. (b) Chen, B.-C.; Zhou, P.; Davis, F. A.; Ciganek, E. *Org. React.* **2003**, *62*, 1−356.

(6) For previous applications of bisazaferrocene ligands in asymmetric catalysis, see: (a) Lo, M. M.-C.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 10270−10271. (b) Lo, M. M.-C.; Fu, G. C. *Tetrahedron* **2001**, *57*, 2621−2634. (c) Lo, M. M.-C.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 4572−4573.

(7) For transition metal-catalyzed insertions of diazo compounds into O−H bonds, rhodium, not copper, complexes have generally been the catalysts of choice (see ref 4). For a recent report of an effective copper-based catalyst, see: Morilla, M. E.; Molina, M. J.; Diaz-Requejo, M. M.; Belderrain, T. R.; Nicasio, M. C.; Trofimenko, S.; Perez, P. J. *Organometallics* **2003**, *22*, 2914−2918.

(8) We do not yet understand the role that water is playing in these reactions.

(9) Reactions of α-diazo esters derived from primary alcohols (rather than secondary alcohols, tertiary alcohols, or phenols) proceed with the highest yield and enantioselectivity. Insertions by α-diazo ketones and amides furnish low ee.

(10) For the reaction of allyl alcohol, we observe no cyclopropanation of the olefin (see also ref 7).

(11) Under our standard conditions, when water is employed as a substrate, O−H insertion occurs in moderate yield (∼55%) and low ee (∼15% ee). Triphenylsilanol and triethylsilanol are unreactive.

(12) Notes: (a) Highly electron-rich α-aryl-α-diazo carbonyl compounds are relatively unstable, and they are not suitable substrates under our standard conditions. Insertions of α-pyridyl-α-diazo esters proceed in low ee. (b) Reaction of an alkenyl-substituted (α-styryl) diazoacetate leads to the formation of the desired product in 27% yield and 13% ee. We have not yet attempted to optimize this process. (c) Under our standard conditions, α-alkyl-α-diazoacetates undergo a 1,2-H shift to furnish α,β-unsaturated esters. (d) For the insertion depicted in entry 1 of Table 3, decreasing the catalyst loading to 0.5% $Cu(OTf)_2$/0.95% **1** leads to a drop in ee (76% ee, 96% yield).

(13) For a review of nonlinear effects in asymmetric catalysis, see: Kagan, H. B.; Luukas, T. O. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Chapter 4.1.

(14) Insertions into the O−D bond of deuterated alcohols furnish a route to enantioenriched α-deuterio-α-hydroxy esters (e.g., methyl α-diazo-α-phenylacetate + $TMSCH_2CH_2OD$: 94% yield, 78% ee).

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