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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}



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 CuCl₂ or CuCl, unsatisfactory yields and essentially no enantioselectivity are observed (entries 10–12). In contrast, CuPF₆(CH₃-CN)₄ provides an active, but somewhat less stereoselective, catalyst (entry 13 versus entry 1). Insertions conducted in CH₂Cl₂ proceed smoothly with fairly good enantioselectivity, whereas reactions in Et₂O or toluene afford low ee (entries 14–16).⁹

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., $\ensuremath{\textit{Table 1.}}$ 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 ₂ O instead of 4.0% H ₂ O	98	82	
3	no H ₂ O instead of 4.0% H ₂ O	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% (<i>R</i>)- <i>i</i> -Pr-Pybox	51	9	
	instead of 3.8% (+)-1 (20 h)			
8	3.8% (R)-Et-DUPHOS	45	<2	
	instead of 3.8% (+)-1			
9	3.8% (R)-BINAP instead of	73	<2	
	3.8% (+)-1 (20 h)			
10	no Cu(OTf) ₂ instead of	0	_	
	2.0% Cu(OTf) ₂ (24 h)			
11	2.0% CuCl ₂ instead of	37	<2	
	2.0% Cu(OTf) ₂ (20 h)			
12	2.0% CuCl instead of	39	<2	
	2.0% Cu(OTf) ₂ (20 h)			
13	2.0% CuPF ₆ (CH ₃ CN) ₄ instead	95	76	
	of 2.0% Cu(OTf) ₂			
14	CH ₂ Cl ₂ instead of ClCH ₂ CH ₂ Cl	92	72	
15	Et ₂ O instead of ClCH ₂ CHCl (4 h)	71	7	
16	toulene instead of ClCH ₂ CH ₂ Cl (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

	RO-H P 1.05 equiv	h N ₂	`OMe	2.0% Cu(0 3.8% (+ 4.0% H CICH ₂ CH r.t.	$\begin{array}{ccc} DT(f)_2 \\)-1 & O \\ p_2 O \\ p_2 Cl & Ph \\ RO & H \end{array}$	Лe	
entry	R	yield (%) ^{a,b}	ee (%) ^a	entry	R	yield (%) ^{a,b}	ee (%) ^a
1	Me	86	69	6	CH ₂ CF ₃	<2	_
2	Et	85	87	7	Bn	86	77
3	<i>i</i> -Pr	76	68	8	p-methoxybenzyl	87	82
4	t-Bu	<2	_	9	allyl	77	27
5	CH ₂ CH ₂ TMS	94	90	10	Ph	56	11 ^c

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

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 3. Catalytic Enantioselective O-H Insertions: Scope



^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



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



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.

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- We do not yet understand the role that water is playing in these reactions. 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 (\sim 55%) and low ee (\sim 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 (a-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)
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- (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 + TMSCH₂CH₂OD: 94% yield, 78% ee).

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