

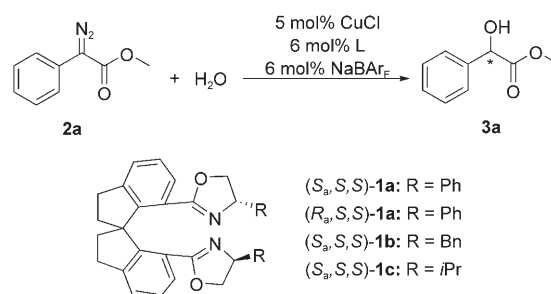
Catalytic Asymmetric Reaction with Water: Enantioselective Synthesis of α -Hydroxyesters by a Copper–Carbenoid O–H Insertion Reaction**

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As one of the most abundant, safe, environmentally benign, and cost-efficient resources, water has been widely used in chemical synthesis and production.^[1] However, catalytic asymmetric transformations using water as a reactant remain a great challenge to chemists, and successful examples are very limited.^[2] Transition-metal-catalyzed asymmetric insertion of α -diazoesters into the O–H bond of water provides an extremely simple approach for the synthesis of chiral α -hydroxyesters in an efficient and atom-economical way.^[3] Although great efforts have been devoted toward the development of efficient catalysts for this important reaction, only two examples of catalytic asymmetric insertions of α -diazoesters into water with low enantioselectivities have been documented.^[4] In 1997, Landais and co-workers^[5] reported the Rh-catalyzed asymmetric insertion of α -diazoester with water in moderate yield (59 %) and very low enantioselectivity (8 % ee). Maier and Fu^[6] also attempted the catalytic asymmetric insertion reaction of methyl α -diazophenylacetate with water using chiral copper/bisazaferrocene complexes as catalysts, and obtained the corresponding α -hydroxyesters in 55 % yield with 15 % ee. We recently demonstrated that the copper complexes of chiral spiro bisoxazoline ligands (spirobox, **1**) are highly efficient catalysts for the asymmetric insertions of α -diazoesters into the N–H bonds of anilines and O–H bonds of phenols.^[7] As a part of our continuing efforts on this compelling research topic, we report herein our investigations on the enantioselective insertion reaction of α -diazoesters with water catalyzed by Cu/spirobox complexes.

The insertion reaction of methyl α -diazophenylacetate (**2a**) with water was performed in dichloromethane at 10 °C with a copper catalyst generated in situ from 5 mol % CuCl, 6 mol % ligand, and 6 mol % NaBAR_F^[8] (Scheme 1). First,

various ligands developed by us and by others were briefly investigated (Table 1). The bisoxazoline ligands such as



Scheme 1.

Table 1: Optimization of the reaction conditions for the asymmetric insertion of methyl α -diazophenylacetate with water.^[a]

Entry	[M]	Ligand	Solvent	T [°C]	Yield [%] ^[b]	ee [%] ^[c]
1	CuCl	(S _a ,S _s)- 1a	CH ₂ Cl ₂	10	76	42
2	CuCl	(R _a ,S _s)- 1a	CH ₂ Cl ₂	10	36	13
3	CuCl	(S _a ,S _s)- 1b	CH ₂ Cl ₂	10	62	20
4	CuCl	(S _a ,S _s)- 1c	CH ₂ Cl ₂	10	53	14
5	CuCl	(S,S)-Ph-box	CH ₂ Cl ₂	10	81	11
6	CuCl	(S,S)- <i>i</i> Pr-pybox	CH ₂ Cl ₂	10	51	0
7	CuCl	(S _a ,S _s)-Ph-bina-box	CH ₂ Cl ₂	10	71	0
8	CuCl	(R _a ,S _s)-Ph-bina-box	CH ₂ Cl ₂	10	69	0
9	CuCl ₂	(S _a ,S _s)- 1a	CH ₂ Cl ₂	10	95	45
10	CuBr ₂	(S _a ,S _s)- 1a	CH ₂ Cl ₂	10	81	49
11	Cu(OTf)	(S _a ,S _s)- 1a	CH ₂ Cl ₂	10	61	44
12	CuPF ₆	(S _a ,S _s)- 1a	CH ₂ Cl ₂	10	95	44
13	Cu(OAc) ₂	(S _a ,S _s)- 1a	CH ₂ Cl ₂	10	66	26
14	CuSO ₄	(S _a ,S _s)- 1a	CH ₂ Cl ₂	10	79	72
15	Ag(OTf) ₂	(S _a ,S _s)- 1a	CH ₂ Cl ₂	30	50	20
16	NiCl ₂	(S _a ,S _s)- 1a	CH ₂ Cl ₂	30	50	54
17	AuCl	(S _a ,S _s)- 1a	CH ₂ Cl ₂	30	44	38
18	CuSO ₄	(S _a ,S _s)- 1a	CHCl ₃	10	85	81
19	CuSO ₄	(S _a ,S _s)- 1a	DCE	10	82	80
20	CuSO ₄	(S _a ,S _s)- 1a	toluene	10	38	19
21	CuSO ₄	(S _a ,S _s)- 1a	THF	10	trace	–
22 ^[d]	CuSO ₄	(S _a ,S _s)- 1a	CHCl ₃	25	90	85
23 ^[e]	CuSO ₄	(S _a ,S _s)- 1a	CHCl ₃	40	91	90
24 ^[f]	CuSO ₄	(S _a ,S _s)- 1a	CHCl ₃	60	67	25

[a] Reaction conditions: [M] (0.015 mmol), ligand (0.018 mmol), NaBAR_F (0.018 mmol), and solvent (3 mL) were stirred under argon at room temperature for 2 h to 4 h, then water (1.5 mmol) and methyl α -diazophenylacetate (0.3 mmol) were sequentially introduced, and the reaction mixture was stirred for 2 h to 24 h. [b] Yield of isolated product. [c] Determined on SFC using a Chiralcel OD-H column. [d] Reaction time: 30 min. [e] Reaction time: 15 min. [f] Reaction time: 5 min.

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spirobox **1**, Ph-box,^[9] *i*Pr-pybox,^[10] and Ph-binabox^[11] showed good reactivity in the reaction, but only the spiro bisoxazoline ligand (*S_a,S_s,S_s*)-**1a** gave a moderate level of enantioselectivity (42% *ee*, Table 1, entry 1). Phosphine-containing ligands including binap,^[12] sdP,^[13] phox,^[14] and siphox^[15] were also investigated. The reactions using these ligands require a higher temperature (30 °C) and exhibit no enantioselectivity (data not shown).

To improve the enantioselectivity of the insertion of methyl α -diazophenylacetate (**2a**) with water, the reaction conditions were carefully optimized by using ligand (*S_a,S_s,S_s*)-**1a**. A variety of copper salts were compared as precursors of the catalyst. All tested copper compounds gave O–H insertion products in good yields and moderate enantiomeric excesses, with CuSO₄ showing the highest enantioselectivity (72% *ee*, Table 1, entry 14). In addition to copper, other metals such as Ag, Ni, and Au can also be applied as catalyst precursors for the insertion reaction although the reactivities and enantioselectivities are lower compared to those obtained with CuSO₄ (Table 1, entries 15–17). Variation of the solvent showed that CHCl₃ and 1,2-dichloroethane (DCE) are better solvents, affording insertion products in higher enantiomeric excesses (Table 1, entries 18 and 19). In the coordinating solvent THF, the insertion reaction was prevented (Table 1, entry 21). Further studies revealed that the reaction is sensitive to temperature. Increasing the reaction temperature from 10 °C to 40 °C resulted in improvements in both yield and enantioselectivity (Table 1, entries 22 and 23 vs. entry 18). However, as the reaction temperature was further elevated to 60 °C, both yield and *ee* value of the insertion product dramatically dropped (Table 1, entry 24). The insertion reaction can be carried out in the presence of 2 to 100 equivalents water, giving methyl α -hydroxyphenylacetate in 87–91% yield with 90% *ee*.^[16]

A wide range of α -diazooesters was examined in the insertion reaction with water under optimal reaction conditions, and the results were summarized in Table 2. The ester moiety of the diazo compounds has a slight effect on the reaction, with a smaller R² group being preferable for high yield and enantioselectivity (Table 2, entries 1–3). All tested α -diazophenylacetate substrates having *para* or *meta* substituents on the phenyl rings gave O–H insertion products in high yields (81–92%) and high enantioselectivities (88–94% *ee*) regardless of the electronic properties and steric hindrance of the substituents (Table 2, entries 4–14). In the reaction of *ortho*-substituted α -diazophenylacetates, the situation is very different. The insertion of α -diazo-2-methylphenylacetate (**2o**) with water had an enantioselectivity of 89% *ee* (Table 2, entry 15), which was similar to that in the reaction of α -diazophenylacetate. However, the reactions of α -diazo-2-methoxyphenylacetate (**2p**) and α -diazo-2-chlorophenylacetate (**2q**) gave O–H insertion products in very low enantioselectivities (50% and 36% *ee*, Table 2, entries 16 and 17). Additionally, α -diazo-2-naphthylacetate (**2r**) and α -diazo-3-thienylacetate (**2s**) were also suitable substrates for the O–H insertion reaction with water (Table 2, entries 18 and 19). The benzyl α -diazopropionate (**2t**) smoothly underwent the asymmetric insertion reaction with water to afford

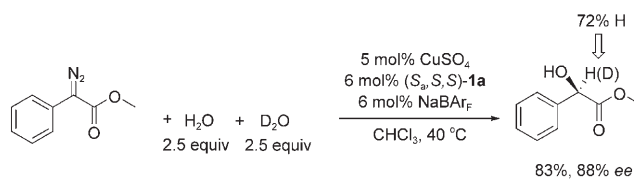
Table 2: Substrate scope for the asymmetric insertion of α -diazooesters with water.^[a]

$\begin{array}{c} \text{R}^1 \\ \\ \text{N}_2 \\ \\ \text{C} \\ \\ \text{O} \\ \\ \text{R}^2 \end{array} + \text{H}_2\text{O} \xrightarrow[\text{30 min}]{\begin{array}{c} 5 \text{ mol\% CuSO}_4 \\ 6 \text{ mol\% (S}_a\text{,S}_s\text{,S}_s\text{)-1a} \\ 6 \text{ mol\% NaBAR}_F \\ \text{CHCl}_3, 40^\circ\text{C} \end{array}} \begin{array}{c} \text{OH} \\ \\ \text{C} \\ \\ \text{O} \\ \\ \text{R}^2 \end{array}$					
Entry	R ¹	R ²	Product	Yield [%]	<i>ee</i> [%]
1	Ph	Me	3a	91	90 (R)
2	Ph	Et	3b	91	88 (R)
3	Ph	<i>i</i> Pr	3c	81	86 (R)
4	4-MeC ₆ H ₄	Me	3d	83	92 (R)
5	4-PhC ₆ H ₄	Me	3e	87	92
6	4-FC ₆ H ₄	Me	3f	90	92 (R)
7	4-ClC ₆ H ₄	Me	3g	83	92 (R)
8	4-BrC ₆ H ₄	Me	3h	86	91 (R)
9	3-MeC ₆ H ₄	Me	3i	87	92
10	3-MeOC ₆ H ₄	Me	3j	89	91 (R)
11	3-FC ₆ H ₄	Me	3k	85	89
12	3-ClC ₆ H ₄	Me	3l	88	88 (R)
13	3-BrC ₆ H ₄	Me	3m	92	88
14	3,4-Cl ₂ C ₆ H ₃	Me	3n	91	94 (R)
15	2-MeC ₆ H ₄	Me	3o	81	89
16	2-MeOC ₆ H ₄	Me	3p	71	50 (R)
17	2-ClC ₆ H ₄	Me	3q	90	36 (R)
18	2-naphthyl	Me	3r	76	90 (R)
19	3-thienyl	Me	3s	70	90
20	Me	Bn	3t	78	78 (R)

[a] The reaction conditions are the same as those in Table 1, entry 23. All reactions were completed within 30 min. For details of operation and analysis, see the Supporting Information.

the corresponding α -hydroxyester in good yield and enantioselectivity (Table 2, entry 20).

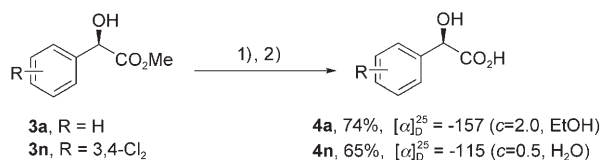
We also conducted a carbenoid insertion with deuterated water. The reaction of α -diazophenylacetate and D₂O gave methyl α -deutero- α -hydroxyphenylacetate in 87% yield with 88% *ee*. Moreover, in a comparative reaction between H₂O and D₂O, a predominant H₂O insertion product (72%) was obtained (Scheme 2), which is similar to the observation by Maier and Fu in the insertion of carbenoids into alcohols.^[6]



Scheme 2.

Optically pure mandelic acid derivatives can be readily prepared by hydrolysis of the insertion products **3**. For example, the hydrolysis of O–H insertion products **3a** and **3n** in aqueous NaOH gave the acids **4a** and **4n** (Scheme 3).^[17] After recrystallization from DCE the optically pure mandelic acids were obtained.

In summary, the first highly enantioselective carbenoid insertion into water has been realized with Cu/spirobox



Scheme 3. Reaction conditions: 1) 1.25 M NaOH, EtOH, 0°C to RT, 2 h. 2) Recrystallization from DCE. Optical rotation is shown in deg cm³ g⁻¹ dm⁻¹ and concentration in g cm⁻³.

complexes as catalysts. This reaction represents one of few catalytic asymmetric procedures using water as a reactant and provides an efficient method for preparing chiral α -hydroxyesters and acids starting from readily available materials under mild reaction conditions.

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- [1] For general reviews, see: a) "Special Issue: Water", *Chem. Rev.* **2002**, 102, 2625; b) G. W. Robinson, S. B. Zhu, S. Singh, M. W. Evans, *Water in Biology, Chemistry, and Physics*, World Scientific, Singapore, **1996**; c) C.-J. Li, T.-H. Chen, *Organic Reactions in Aqueous Media*, Kluwer Academic Publisher, Dordrecht, **1997**.
- [2] For a review, see: a) *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Heidelberg, **1999**, chap. 11 and 35; for examples, see: b) H. Alper, N. Hamel, *J. Am. Chem. Soc.* **1990**, 112, 2803; c) M. Tokunaga, J. F. Larrow, F. Kakiuchi, E. N. Jacobsen, *Science* **1997**, 277, 936; d) A. El-Qisairi, O. Hamed, P. M. Henry, *J. Org. Chem.* **1998**, 63, 2790.
- [3] For reviews on non-asymmetric catalytic insertion of α -diazoesters with water, see: a) M. P. Doyle, M. A. McKerver, T. Ye, *Modern Catalytic Methods for Organic Synthesis with Diazo compounds*, Wiley, New York, **1998**, chap. 8; b) T. Ye, M. A. McKerver, *Chem. Rev.* **1994**, 94, 1091; c) D. J. Miller, C. J. Moody, *Tetrahedron* **1995**, 51, 10811.
- [4] For diastereoselective carbenoid insertion into water, see: a) Y. Landais, D. Planchenault, V. Weber, *Tetrahedron Lett.* **1994**, 35, 9549; b) E. Aller, D. S. Brown, G. G. Cox, D. J. Miller, C. J. Moody, *J. Org. Chem.* **1995**, 60, 4449; c) M. P. Doyle, M. Yan, *Tetrahedron Lett.* **2002**, 43, 5929.
- [5] P. Bulugahapitiya, Y. Landais, L. Parra-Rapado, D. Planchenault, V. Weber, *J. Org. Chem.* **1997**, 62, 1630.
- [6] T. C. Maier, G. C. Fu, *J. Am. Chem. Soc.* **2006**, 128, 4594.
- [7] a) B. Liu, S.-F. Zhu, W. Zhang, C. Chen, Q.-L. Zhou, *J. Am. Chem. Soc.* **2007**, 129, 5834; b) C. Chao, S.-F. Zhu, B. Liu, L.-X. Wang, Q.-L. Zhou, *J. Am. Chem. Soc.* **2007**, 129, 12616.
- [8] BAr_F⁻ = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate.
- [9] Ph-box = 2,2'-bis(4,5-dihydro-4-phenyloxazol-2-yl)propane.
- [10] iPr-pybox = 2,6-bis(4,5-dihydro-4-isopropoxyloxazol-2-yl)pyridine.
- [11] Ph-binabox = 2,2'-bis(4,5-dihydro-4-phenyloxazol-2-yl)-1,1'-binaphthyl.
- [12] binap = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl.
- [13] sdp = 7,7'-bis(diphenylphosphino)-1,1'-spirobiindane.
- [14] phox = 2-(2-diphenylphosphinophenyl)-4,5-dihydro-4-isopropoxyloxazole.
- [15] siphox = 7-diphenylphosphino-7'-(4,5-dihydro-4-phenyloxazol-2-yl)-1,1'-spirobiindane.
- [16] Because the reaction is biphasic, the amount of water used has a negligible influence on the yield and enantioselectivity.
- [17] a) U. Felfer, U. T. Strauss, W. Kroutil, W. M. F. Fabian, K. Faber, *J. Mol. Catal. B* **2001**, 15, 213; b) Y. Sun, X. Wang, J. Wang, Q. Meng, H. Zhang, L. Jiang, Z. Zhang, *Org. Lett.* **2005**, 7, 5425.