Asymmetric Catalysis

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

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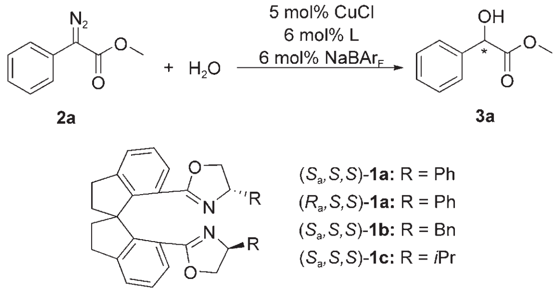
As one of the most abundant, safe, environmentally benign, and cost-efficient resources, water has been widely used in chemical synthesis and production.[1] However, catalytic asymmetric transformations using water as a reactant remain a great challenge to chemists, and successful examples are very limited.[2] 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_2Cl_2	10	76	42
2	CuCl	(R_a,S,S)-**1a**	CH_2Cl_2	10	36	13
3	CuCl	(S_a,S,S)-**1b**	CH_2Cl_2	10	62	20
4	CuCl	(S_a,S,S)-**1c**	CH_2Cl_2	10	53	14
5	CuCl	(S,S)-Ph-box	CH_2Cl_2	10	81	11
6	CuCl	(S,S)-*i*Pr-pybox	CH_2Cl_2	10	51	0
7	CuCl	(S_a,S,S)-Ph-bina-box	CH_2Cl_2	10	71	0
8	CuCl	(R_a,S,S)-Ph-bina-box	CH_2Cl_2	10	69	0
9	$CuCl_2$	(S_a,S,S)-**1a**	CH_2Cl_2	10	95	45
10	$CuBr_2$	(S_a,S,S)-**1a**	CH_2Cl_2	10	81	49
11	Cu(OTf)	(S_a,S,S)-**1a**	CH_2Cl_2	10	61	44
12	$CuPF_6$	(S_a,S,S)-**1a**	CH_2Cl_2	10	95	44
13	$Cu(OAc)_2$	(S_a,S,S)-**1a**	CH_2Cl_2	10	66	26
14	$CuSO_4$	(S_a,S,S)-**1a**	CH_2Cl_2	10	79	72
15	$Ag(OTf)_2$	(S_a,S,S)-**1a**	CH_2Cl_2	30	50	20
16	$NiCl_2$	(S_a,S,S)-**1a**	CH_2Cl_2	30	50	54
17	AuCl	(S_a,S,S)-**1a**	CH_2Cl_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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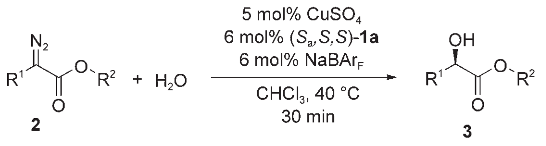
spirobox **1**, Ph-box,[9] *i*Pr-pybox,[10] and Ph-binabox[11] showed good reactivity in the reaction, but only the spiro bisoxazoline ligand (S_a,*S*,*S*)-**1a** gave a moderate level of enantioselectivity (42% *ee*, Table 1, entry 1). Phosphine-containing ligands including binap,[12] sdp,[13] phox,[14] 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*)-**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 $CuSO_4$ 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 $CuSO_4$ (Table 1, entries 15–17). Variation of the solvent showed that $CHCl_3$ 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-diazoesters 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 R^2 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 the corresponding α-hydroxyester in good yield and enantioselectivity (Table 2, entry 20).

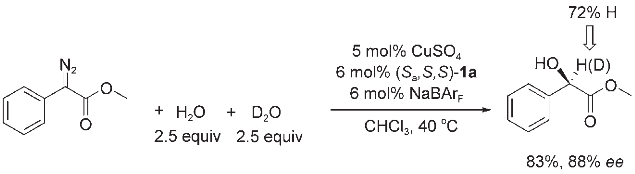
Table 2: Substrate scope for the asymmetric insertion of α-diazoesters with water.[a]



Entry	R^1	R^2	Product	Yield [%]	*ee* [%]
1	Ph	Me	**3a**	91	90 (*R*)
2	Ph	Et	**3b**	91	88 (*R*)
3	Ph	*i*Pr	**3c**	81	86 (*R*)
4	4-MeC_6H_4	Me	**3d**	83	92 (*R*)
5	4-PhC_6H_4	Me	**3e**	87	92
6	4-FC_6H_4	Me	**3f**	90	92 (*R*)
7	4-ClC_6H_4	Me	**3g**	83	92 (*R*)
8	4-BrC_6H_4	Me	**3h**	86	91 (*R*)
9	3-MeC_6H_4	Me	**3i**	87	92
10	3-$MeOC_6H_4$	Me	**3j**	89	91 (*R*)
11	3-FC_6H_4	Me	**3k**	85	89
12	3-ClC_6H_4	Me	**3l**	88	88 (*R*)
13	3-BrC_6H_4	Me	**3m**	92	88
14	3,4-$Cl_2C_6H_3$	Me	**3n**	91	94 (*R*)
15	2-MeC_6H_4	Me	**3o**	81	89
16	2-$MeOC_6H_4$	Me	**3p**	71	50 (*R*)
17	2-ClC_6H_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.

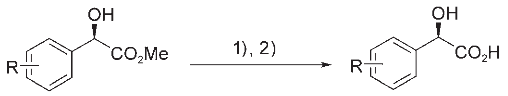
We also conducted a carbenoid insertion with deuterated water. The reaction of α-diazophenylacetate and D_2O gave methyl α-deutero-α-hydroxyphenylacetate in 87% yield with 88% *ee*. Moreover, in a comparative reaction between H_2O and D_2O, a predominant H_2O insertion product (72%) was obtained (Scheme 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



3a, R = H
3n, R = 3,4-Cl$_2$

4a, 74%, $[\alpha]_D^{25}$ = -157 (c=2.0, EtOH)
4n, 65%, $[\alpha]_D^{25}$ = -115 (c=0.5, H$_2$O)

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 cm^3 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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[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] *i*Pr-pybox = 2,6-bis(4,5-dihydro-4-isopropyloxazol-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-isopropyloxazole.

[15] siphox = 7-diphenylphosphino-7′-(4,5-dihydro-4-phenyloxazol-2-yl)-1,1′-spirobiinane.

[16] Because the reaction is biphasic, the amount of water used has a negligible influence on the yield and enantioselectivity.

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