Enantioselective Copper-Catalyzed O–H Insertion of α-Diazo Phosphonates

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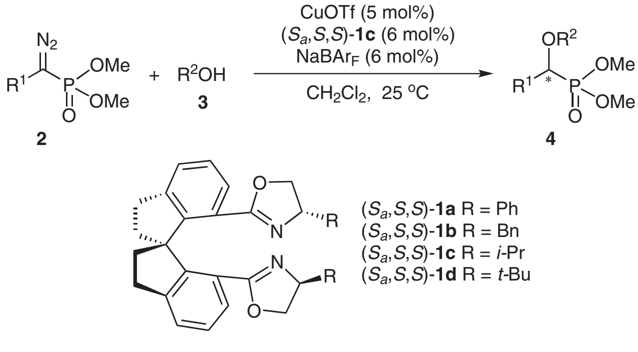
Abstract: A copper-catalyzed asymmetric O–H insertion of α-diazo phosphonates with alcohols by using chiral spiro bisoxazoline ligands was developed. The insertion reaction exhibited good yields (up to 89%) with high enantioselectivities (up to 98% ee) and provided an efficient approach for synthesis of enantiomerically enriched α-alkoxy and hydroxy phosphonate derivatives starting from readily available materials.

Key words: asymmetric O–H insertion, chiral spiro ligands, copper catalysts, α-diazo phosphonates, α-alkoxy phosphonates

Enantiomerically enriched α-functionalized phosphonate derivatives are important building blocks for biologically active compounds, particular for pharmaceuticals. The development of efficient and enantioselective methods for preparation of α-functionalized phosphonates is of high value and has drawn increasing attention.[1] Transition-metal-catalyzed asymmetric O–H bond insertion reaction of α-diazo phosphonates provides an convenient approach to chiral α-alkoxy and hydroxy phosphonate derivatives.[2] Although the copper- and iron-catalyzed asymmetric O–H insertions of α-diazo esters with alcohols, phenols, and even water have been accomplished with excellent enantioselectivities by Fu's group[3] and our group,[4] the enantioselective O–H insertions of α-diazo phosphonates have not been explored yet,[5] partially due to high stability of α-diazo phosphonates.[6] As a part of our continuous efforts on the transition-metal-catalyzed asymmetric hetero-atom–hydrogen bond (X–H, X = N, O, S, Si, etc.) insertion reactions,[7] we here report a copper-catalyzed asymmetric O–H insertion of α-diazo phosphonates with alcohols by using chiral spiro bisoxazoline ligands **1** (Scheme 1). The O–H insertion reaction exhibited good yields (up to 89%) with high enantioselectivities (up to 98% ee). To the best of our knowledge, this is the first enantioselective X–H insertion reaction of α-diazo phosphonates.

In the initial study, the insertion reaction of dimethyl diazo(phenyl)methylphosphonate (**2a**) with *n*-butanol (**3a**) was performed in dichloromethane at 25 °C in the presence of 5 mol% catalyst generated in situ from CuCl, (S_a,*S*,*S*)-**1a**, and $NaBAr_F$[8] (Table 1). To our delight, the reaction ran smoothly and afforded the desired O–H insertion product, dimethyl butoxy(phenyl)methylphosphonate (**4aa**) in 76% yield with 73% ee (Table 1, entry 1).



Scheme 1

The change of ligand (S_a,*S*,*S*)-**1a** to (R_a,*S*,*S*)-**1a** slowed the reaction down and markedly decreased the yield and enantioselectivity (entry 2), indicating that the ligand (S_a,*S*,*S*)-**1a** has matched chiralities, which is consistent with our previous findings in the O–H and N–H insertion reactions of α-diazo esters. The further studies on the substituent effects of oxazoline rings of ligand **1** revealed that the alkyl substituents, such as benzyl and isopropyl, were beneficial for gaining high enantioselectivity (Table 1, entries 3 and 4). The ligand (S_a,*S*,*S*)-**1c** with isopropyl groups exhibited best chiral induction (Table 1, entry 4). Increasing the steric hindrance of the substituent on oxazoline rings of ligand to *tert*-butyl (**1d**) had a negative effect on the reactivity as well as enantioselectivity (Table 1, entry 5). The solvent impacted on the reactivity and enantioselectivity of reaction. Similar with other copper-catalyzed carbene transfer reactions, the O–H insertion of α-diazo phosphonates performed well in chlorinated solvents, giving good yields and high ee values (Table 1, entries 4, 6, and 7). The less polar solvent toluene slowed down the reaction significantly and afforded only moderate enantioselectivity (Table 1, entry 8). The reaction was fully prohibited when performed in THF, a strong coordinating solvent (Table 1, entry 9). All the tested copper salts including Cu(I) and Cu(II) were suitable catalyst precursors for the insertion reaction. However, Cu(I) precursors such as CuCl, $CuPF_6$, and CuOTf afforded higher yields and enantioselectivities comparing to Cu(II) precursor $CuCl_2$ (Table 1, entries 4, 10–12). Among the copper precursors studied, CuOTf showed the best reactivity and enantioselectivity (Table 1, entry 11). The additive $NaBAr_F$ played an important role

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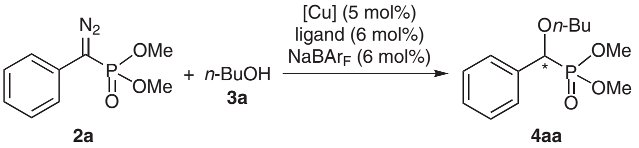
Table 1 Copper-Catalyzed Asymmetric Insertion of Dimethyl Diazo(phenyl)methylphosphonate (**2a**) into O–H Bonds of *n*-Butanol: Optimization of Reaction Conditions[a]



Entry	[Cu]	Ligand	Solvent	Time (h)	Yield (%)[b]	ee (%)[c]
1	CuCl	(S_a,S,S)-**1a**	CH_2Cl_2	1.5	76	73
2	CuCl	(R_a,S,S)-**1a**	CH_2Cl_2	4	31	9
3	CuCl	(S_a,S,S)-**1b**	CH_2Cl_2	1	77	87
4	CuCl	(S_a,S,S)-**1c**	CH_2Cl_2	3	88	90
5	CuCl	(S_a,S,S)-**1d**	CH_2Cl_2	12	70	19
6	CuCl	(S_a,S,S)-**1c**	$CHCl_3$	3	84	90
7	CuCl	(S_a,S,S)-**1c**	DCE	6	85	83
8	CuCl	(S_a,S,S)-**1c**	toluene	12	65	40
9	CuCl	(S_a,S,S)-**1c**	THF	n.r.[d]	–	–
10	$CuPF_6(MeCN)_4$	(S_a,S,S)-**1c**	CH_2Cl_2	3	86	91
11	$(CuOTf)_2$·toluene	(S_a,S,S)-**1c**	CH_2Cl_2	1	89	91
12	$CuCl_2$	(S_a,S,S)-**1c**	CH_2Cl_2	3	79	74
13[e]	$(CuOTf)_2$·toluene	(S_a,S,S)-**1c**	CH_2Cl_2	5	77	48
14[f]	$(CuOTf)_2$·toluene	(S_a,S,S)-**1c**	CH_2Cl_2	1	63	87
15	$(CuOTf)_2$·toluene	(S,S)-Box	CH_2Cl_2	1	88	10
16	$(CuOTf)_2$·toluene	(S,S)-Pybox	CH_2Cl_2	3	n.p.[g]	–
17	$FeCl_2·4H_2O$	(S_a,S,S)-**1c**	CH_2Cl_2	48	57	*rac*

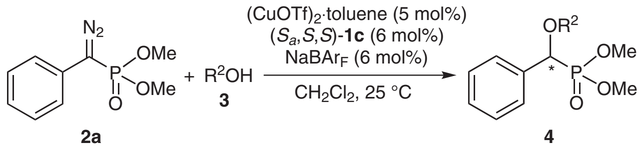
[a] Reaction conditions: [Cu]/ligand/$NaBAr_F$/**2a**/**3a** = 0.02:0.024:0.024:0.4:2.0 (mmol), in 4 mL solvent at 25 °C.
[b] Isolated yield.
[c] Determined by HPLC using a Chiralcel OJ-H column.
[d] No reaction.
[e] Without $NaBAr_F$.
[f] Using 2 equiv of *n*-BuOH.
[g] No desired product.

for the insertion reaction, because the absence of additive lowered the yield as well as enantioselectivity (Table 1, entry 13). The sufficient excess of *n*-butanol was necessary for obtaining high yield. Decreasing the amount of *n*-butanol to two equivalents compromised the reactivity of reaction (Table 1, entry 14). Under the standard reaction conditions, chiral bisoxazoline ligand (S,S)-Box[9] only afforded the O–H insertion product in 10% ee albeit with good yield (Table 1, entry 15). Although the copper complex of (S,S)-Pybox[10] promoted the decomposition of diazo compound **2a** easily, no desired O–H insertion product was determined (Table 1, entry 16). These results clearly demonstrated that the spirobiindane backbone of the ligands **1** plays a key role in tuning both reactivity and enantioselectivity of the catalysts. Although the iron was found to be superior catalyst for O–H insertion of α-diazo esters,[4c] it was proven to be less efficient for the present insertion reaction (Table 1, entry 17).

Under the optimal reaction conditions, the insertion reactions between dimethyl diazo(phenyl)methylphosphonate (**2a**) with various alcohols were carried out. As shown in Table 2, all the tested saturated primary alcohols accomplished the insertion reaction within one hour, yielding the corresponding products 2-alkoxy phosphonates in good yields (74–89%) with high enantioselectivities (84–92% ee) (Table 2, entries 1–8). In contrast, the secondary alcohol, isopropanol afforded insertion product in only 19% yield, but with 89% ee (Table 2, entry 9). Besides, the prop-2-en-1-ol (**3j**) can also complete the transformation albeit a longer reaction time was required for full conversion and only moderate enantioselectivity (38% ee) was obtained (Table 2, entry 10). Interestingly, introducing a 2-methyl group to the allylic alcohol, the reaction became faster and the enantioselectivity was significantly increased to 85% ee (Table 2, entry 11). The benzyl alcohol (**3l**) was also suitable substrate for O–H insertion with **2a**, giving acceptable yield (69%) and good enantioselectivity (87% ee) under the standard reaction conditions (Table 2, entry 12).

We then explored the scope of 2-diazo phosphonate substrates **2** in the O–H insertion with *n*-butanol (Table 3). The impact of substituent groups on phenyl of dimethyl

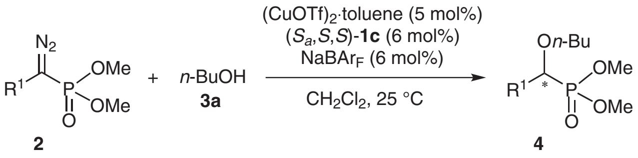
Table 2 Copper-Catalyzed Asymmetric Insertion of Dimethyl Diazo(phenyl)methylphosphonate (**2a**) into the O–H Bond of Alcohols[a]



Entry	R^2	Product	Time (h)	Yield (%)	ee (%)
1	*n*-Bu	**4aa**	1	89	91
2	Me	**4ab**	1	87	84
3	Et	**4ac**	1	82	91
4	*n*-C_8H_{17}	**4ad**	1	82	87
5	*n*-$C_{10}H_{21}$	**4ae**	1	84	88
6	$TMSCH_2CH_2$	**4af**	1	87	90
7	*i*-Bu	**4ag**	1	74	92
8	*i*-Arm	**4ah**	1	83	92
9	*i*-Pr	**4ai**	1	19	89
10	$CH=CHCH_2$	**4aj**	12	81	38
11	$CH=C(CH_3)CH_2$	**4ak**	3	70	85
12	Bn	**4al**	3	69	87

[a] The reaction conditions were the same as those in Table 1, entry 11. For analyses of products, see Supporting Information.

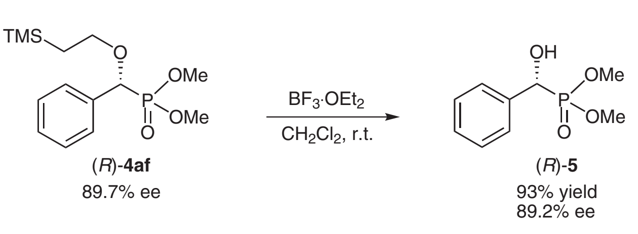
Table 3 Copper-Catalyzed Asymmetric Insertion of Diazo Phosphonate into O–H Bonds of *n*-Butanol[a]



Entry	R^1	Product	Time (h)	Yield (%)	ee (%)
1	Ph	**4aa**	1	89	91
2	2-FC_6H_4	**4ba**	1	82	90
3	2-$MeOC_6H_4$	**4ca**	1	45	98
4	3-ClC_6H_4	**4da**	1	86	87
5	3-$MeOC_6H_4$	**4ea**	1	80	88
6	4-ClC_6H_4	**4fa**	1	83	84
7	4-MeC_6H_4	**4ga**	1	70	92
8	2-naphthyl	**4ha**	1	80	88
9	Me	**4ia**	8	<10%	n.d.

[a] The reaction conditions were the same as those of Table 1, entry 11. For analyses of products, see Supporting Information.

diazo(aryl)methylphosphonates was evaluated. All the tested diazo phosphonates with different substituents on the phenyl group afforded high level of enantioselectivity (84–98% ee, Table 3, entries 2–7). The substrates with an electron-donating group, such as methyl or methoxy group, at 2- or 4-position showed higher enantioselectivity, with the diazo compound **2c** with a 2-methoxy group being the highest enantioselective (98% ee) (Table 3, entry 3). Besides phenyl group, 2-naphthyl-substituted diazo phosphonates **2h** also exhibited high yield with good enantioselectivity (Table 3, entry 8). The substrate **2i**, containing an alkyl group at α-position of diazo phosphonate, was also examined in the O–H insertion reaction, however, the desired insertion product was isolated in very low yield (Table 3, entry 9).



Scheme 2 Deprotection of (*R*)-**4af**

α-Alkoxy phosphonates have potential utilities in pharmaceutical chemistry. For instance, α-alkoxynaphthylmethylphosphonic acid has been developed as a highly active purple acid phosphatases (PAPs) inhibitor.[11] Moreover, α-alkoxy phosphonates can be easily transformed to α-hydroxy phosphonates or α-hydroxy phosphonic acids, which are also biologically important compounds.[1c] As an example, the compound (*R*)-**4af** was converted into α-hydroxy phosphonate (*R*)-**5** in the presence of trifluoroborane in high yield and with conservation of the enantiomeric excess (Scheme 2).

The studies on the mechanism of the O–H insertion of α-diazo phosphonates are in progress in this laboratory. At this stage, we performed a kinetic isotopic experiment. As shown in Scheme 3, the O–H insertion of α-diazo phosphonate **2a** with methanol had a secondary kinetic isotopic effect ($k_H/k_D = 1.5$). This quotient is significantly lower than those of copper-catalyzed O–H insertion reaction of α-diazo esters ($k_H/k_D = 2.6$)[3] and implies that the metal carbene formation, rather than the proton migration, is most likely the rate-determining step.[12]

In summary, asymmetric copper-catalyzed O–H insertion reaction of α-diazo phosphonates with alcohols was developed. The copper complexes of chiral spiro bisoxazoline ligands were proven to be efficient catalysts, producing α-alkoxy and hydroxy phosphonates in good yields and high enantioselectivities.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

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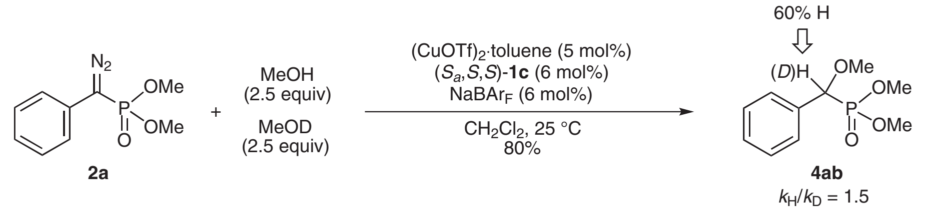

Scheme 3 Kinetic isotopic experiment

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(8) $NaBAr_F$ = sodium tetrakis[3,5-bis(trifluoromethyl)-phenyl]borate.

(9) Box = 2,2′-(1-methylethyliene)bis(4,5-dihydro-4-*tert*-butyloxazole).

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