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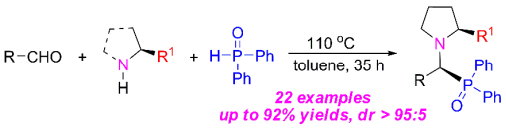
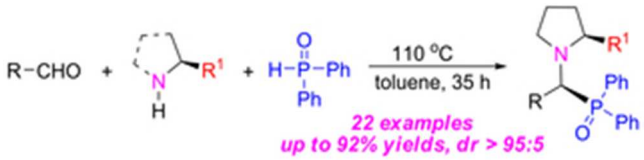


A novel method for high diastereoselective syntheses of chiral α-aminophosphine oxides by a three-component reaction involve a metal-free system was performed.



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Catalyst-Free Three-Component Reaction to Synthesize Chiral α-Amino Phosphine Oxides

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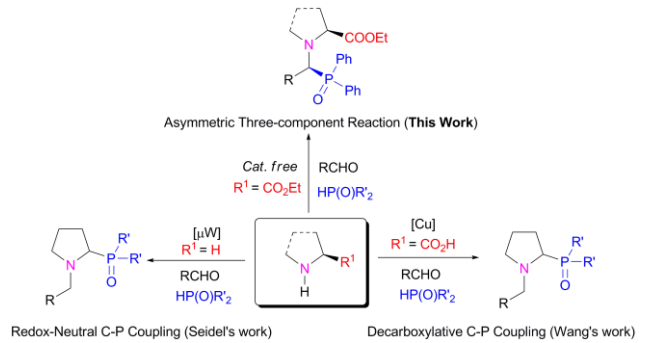
A three-component reaction for high diastereoselective synthesis of chiral α-amino phosphine oxides has been developed and displayed environmentally friendly and atom efficient. The reaction proceeds smoothly without catalysts or additives.

Organic phosphorus compounds feature a variety of biological and pharmacological characteristics prevalent in nucleotides and pharmaceuticals. In particular, α-amino phosphine oxides exhibit antitumor, antibacterial[1], antiviral[2], and enzyme inhibiting[3] activities, which have been widely applied in agrochemistry[4]. Phosphine-containing compounds represent the conventional choice of ligands for transition-metal-catalyzed reactions.[5] As a consequence, researchers in the past decades have expended tremendous effort on building these skeletons[6]; The three-component reaction among amines, carbonyl compounds, and phosphine oxides -- widely known as the Kabachnik-Fields reaction[8] -- for the synthesis of α-aminophosphine oxides in particular has attracted great interest for its step and atom economy[7]. In 2008, Keglevich's group reported the synthesis of corresponding α-aminophosphonate and α-aminophosphine oxide through microwave irradiation in the absence of solvent or catalyst[9]. Recently, Wang and co-workers have disclosed a copper-catalyzed three-component decarboxylative coupling in order to synthesize α-aminophosphine oxides between natural α-amino acids, phosphites, or secondary phosphine oxides and aldehyde[10]. Simultaneously, Seidel's group also reported a three-component reaction in which a simple amine could replace the amino acid[11]. Despite significant advances in this field, methods that involve three-component reaction under catalyst-free conditions for the synthesis of chiral α-aminophosphine oxides still represent formidable challenges[12]. The construction of C-P bond in particular has created major interest in the field as well as an exciting challenge for us.[13] The synthesis of chiral α-aminophosphine also represents an important milestone for us.

Indeed, the development of transition-metal-free processes represents a growing trend in chemical synthesis[14] as well as an attractive and beneficial complement to transition-metal-catalyzed transformations. Our protocol demonstrates great advantages. Herein, we report a new three-component reaction to synthesize chiral α-amino phosphine oxides within a system free of catalysts (Scheme 1). This system exhibits several unique features: (1) the reaction requires no catalyst or additives; (2) the reaction demonstrates high regioselectivity and diastereoselectivity and yields **2a** as the exclusive product; (3) the process is both environmentally friendly and atom efficient.



Scheme 1. Different three-component reactions for the synthesis of α-amino phosphonates or α-amino phosphine oxides.

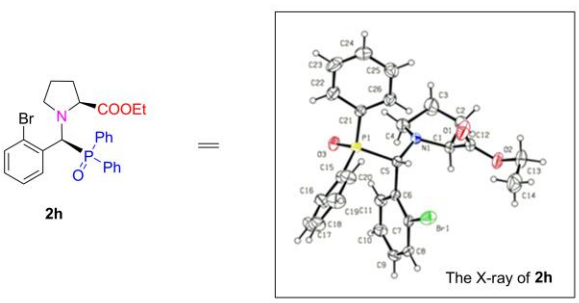


Figure 1. The absolute configuration determined by the X-ray of **2h.**

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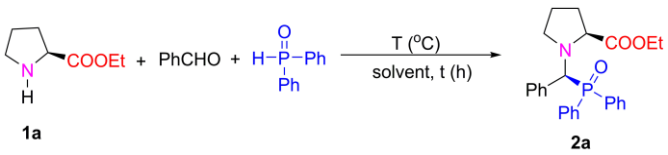
We set up our research by evaluating the reaction between 1.5 equiv of (*S*)-ethyl pyrrolidine-2-carboxylate, 1.5 equiv of benzaldehyde, and 1.0 equiv of diphenylphosphine oxide (Table 1). A screening of different solvents showed that toluene was the best choice and the desired product **2a** was obtained in 58% yield (Table 1, entry 3). The reaction could be also performed in DCE, DMF, THF, and dioxane respectively; lower yields were observed. Encouraged by these results, we selected toluene as the reaction solvent and further investigated the reaction temperature; results indicated that 110 ℃ was a more suitable parameter to this reaction (Table 1, entries 6-11). A screening of the additives revealed that the presence of $MgSO_4$, Na_2SO_4, or 4 Å MS especially decreased the yields of the desired product (Table 1, entries 12-14), and Cs_2CO_3 shut down the reaction entirely (Table 1, entry 12-15). We have also screened the reaction concentration and the ratio of starting materials and found that the reaction concentration of 0.3 mol/L and the ratio of **1a**: E: $H(O)PPh_2$ = 1.5:1.5:1 were the best choice. Through further study we defined optimal reaction conditions by as the use of **1a** (1.5 equiv), diphenylphosphine oxide (1.0 equiv), (*S*)-ethyl pyrrolidine-2-carboxylate (1.5 equiv) in toluene at 110 ℃ under an argon atmosphere.

Table 1. Optimization of reaction conditions.[a]



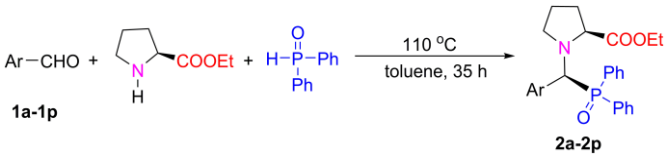
1a **2a**

Entry	Solvent	T (℃)	Additive (eq.)	Yield (%)[b]
1	DCE	80		39
2	DMF	80		31
3	toluene	80		58
4	THF	80		49
5	dioxane	80		36
6	toluene	60		43
7	toluene	70		52
8	toluene	90		63
9	toluene	100		68
10	toluene	110		78
11	toluene	120		65
12	toluene	110	Na_2SO_4 (0.5)	64
13	toluene	110	$MgSO_4$ (0.5)	68
14	toluene	110	4Å MS (0.5)	59
15	toluene	110	Cs_2CO_3 (0.5)	0

[a] Reaction conditions: **1a** (0.45 mmol, 46 μL), (*L*)-ethyl pyrrolidine-2-carboxylate (0.45 mmol, 64 mg), diphenylphosphine oxide (0.3 mmol, 60.6 mg), solvent (2.0 mL), additive (50 mol %), at 80 °C (oil-bath temperature), under argon atmosphere for 30 h. [b] Isolated yield. DCE = 1,1-dichloroethane, DMF = *N*, *N*-dimethylformamide, THF = Tetrahydrofuran

With optimized reaction conditions in hand, we explored different substituted benzaldehydes in order to examine the scope of the substrates. Table 2 lists the results. Reactions proceeded in moderate-to-excellent yields with aromatic aldehydes and tolerated a variety of functional groups (Table 2, entries **2a**-**2p**). Gratifyingly, when we attempted to use benzaldehyde derivatives with both electron-donating and electron-withdrawing groups, all could afford the desired products in good yields with excellent diastereo-selectivity. In particular, when 4-methylbenzaldehyde was used as the reaction partner, the product **2d** was obtained in 95% yield with a 95:5 dr value. We were delighted to note that the Cl and Br substituent could also be tolerated in optimized reaction conditions. Substrates with a *para*-substituted Me, Cl, and Br could afford corresponding products in good to excellent yields. However, no desired product was observed with 2-nitrobenzaldehyde (Table 2, entry **2m**).

Table 2. The effect of substituents on the benzaldehyde moiety[a]



1a-1p **2a-2p**

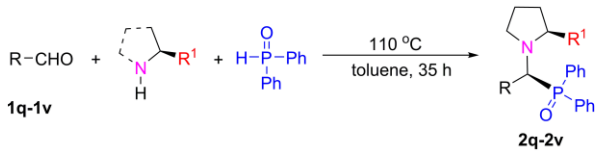
Entry	Ar	Yield (%)[b]	dr (%)[c]
2a	Ph	78	> 95:5
2b	2-MePh	80	> 95:5
2c	3-MePh	78	> 95:5
2d	4-MePh	95	> 95:5
2e	2-ClPh	66	> 95:5
2f	3-ClPh	76	> 95:5
2g	4-ClPh	81	> 95:5
2h	2-BrPh	78	> 95:5
2i	3-BrPh	83	> 95:5
2j	4-BrPh	69	> 95:5
2k	2-OMePh	84	> 95:5
2l	4-OMePh	77	> 95:5
2m	2-NO_2Ph	0	
2n	3-NO_2Ph	75	> 95:5
2o	4-CNPh	68	> 95:5
2p	3,5-*di*-OMePh	72	> 95:5

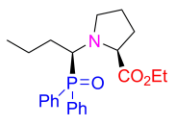
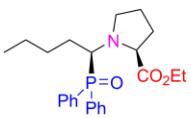
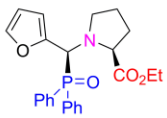
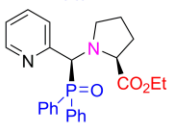
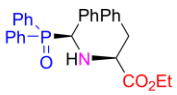
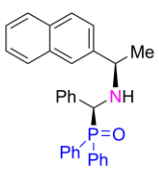
[a] Reaction condition: **1a** (0.45 mmol, 46 μL), (*S*)-ethyl pyrrolidine-2-carboxylate (0.45 mmol, 64 mg), diphenylphosphine oxide (0.3 mmol, 60.6 mg) solvent (2.0 mL), at 110 °C (oil-bath temperature), under argon atmosphere for 35 h. [b] Isolated yield. [c] Determined by ^{1}H NMR or ^{31}P NMR.

In order to further expand the scope of substrates, we tested aliphatic aldehydes. Lower yields and dr values were achieved as a result (Table 3). For example, **2q** was obtained in 68% yield with 51:49 dr value and **2r** was formed in 57% yield with 53:47 dr value. Aromatic heterocyclic aldehydes could also give the desired

products in moderate yields with good dr values (**2s**, **2t**). Diverse chiral amino acid ester and amines were also readily converted into the desired products in good yields with moderate dr values (**2u**, **2v**). Results indicate that lower dr values were obtained when aliphatic aldehydes were used, and the ratios of two products' configurations were close to 1:1. The results shown in Table 2 and Table 3 suggest that the diastereoselectivity of the products mainly depend on the steric hindrance that occurs between the chiral ethyl ester of (*S*)-ethyl pyrrolidine-2-carboxylate and various substituted aromatic aldehydes.

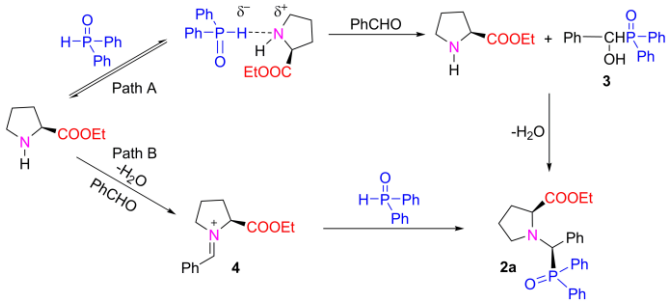
Table 3 The effect of aliphatic aldehydes, aromatic heterocyclic aldehydes, and other chiral amino acid esters or amines.[a]



Entry	Product	Yield (%)[b]	dr (%)[c]
2q		68	51:49
2r		57	53:47
2s		60	> 95:5
2t		76	79:21
2u		74	65:35
2v		92	74:26

[a] Reaction condition: **1a** (0.45 mmol, 46 μL), (*S*)-ethyl pyrrolidine-2-carboxylate (0.45 mmol, 64 mg), Diphenylphosphine oxide (0.3 mmol, 60.6 mg) solvent (2 mL), additive (50 mol %), at 110 °C (oil-bath temperature), under argon atmosphere for 35 h. [b] Isolated yield. [c] Determined by ^{1}H NMR or ^{31}P NMR.

The reaction may proceed *via* two pathways at the same time. Path A revealed that prior to the condensation of benzaldehyde and diphenylphosphine oxide, diphenylphosphine oxide was activated by forming a weak H-bond between the N atom of (*S*)-ethyl pyrrolidine-2-carboxylate and O=P-H function[8, 15] which leads to the formation of *α*-hydroxyphosphine oxide **3**. Compound **3** was isolated and identified by using NMR (ESI). In addition, we observed by TLC an obvious decrease in the concentration of compound **3** during the reaction process. Finally, the reaction of *α*-hydroxyphosphine oxide moiety **3** between (*S*)-ethyl pyrrolidine-2-carboxylate resulted in dehydration to form the target compound **2a**. The other pathway involves the reaction of benzaldehyde and (*S*)-ethyl pyrrolidine-2-carboxylate (secondary amine), which forms the imine intermediate **4**, which then attacked by diphenylphosphine oxide to afford **2a**.



Scheme 2. The proposed possible mechanism for the reaction.

Conclusions

In summary, we have developed a novel method for high diastereoselective syntheses of chiral α-aminophosphine oxides by a three-component reaction in a metal-free system. This reaction could be widely used to prepare a series of chiral *α*-aminophosphine oxides from chiral amino acid esters or even chiral amines.

Acknowledgements

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