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Redox-Neutral α -C–H Bond Functionalization of Secondary Amines with Concurrent C–P Bond Formation/*N*-Alkylation

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Abstract

Redox-neutral formation of C–P bonds in the α -position of amines was achieved via a process that features a combination of an oxidative α -C–H bond functionalization and a reductive *N*-alkylation. Benzoic acid functions as an efficient catalyst in this three-component reaction of cyclic secondary amines, aldehydes and phosphine oxides to provide rapid access to α -amino phosphine oxides not easily accessible by classic Kabachnik-Fields reactions.

α -Aminophosphonic acids and their phosphonate derivatives have received considerable attention as surrogates of both natural and unnatural α -amino acids.¹ These compounds are known to exhibit antitumor, antibiotic, pharmacogenetic and pharmacological properties, and are widely applied in agrochemistry.² Not surprisingly, much effort has been devoted to the efficient synthesis of α -aminophosphonates and their related α -amino phosphine oxides.³ The three-component reaction between amines, carbonyl compounds and phosphonates, widely known as the Kabachnik-Fields reaction,⁴ is one of the most useful methods for the synthesis of such compounds (eq 1).⁵ An alternate strategy, namely the direct α -phosphonation of tertiary amines, has been realized by oxidative C–H functionalization,^{6,7} including photoredox catalysis (eq 2).⁸ Apart from the requirement for an oxidant, such processes are often limited to *N*-aryl tetrahydroisoquinolines and *N,N*-dialkylanilines. A copper-catalyzed decarboxylative three-component, coupling approach to ring-substituted α -aminophosphonates was reported by Wang and coworkers (eq 3).^{9,10,11} We envisioned an alternate three-component reaction in which the amino acid would be replaced with a simple amine, removing the requirement for a prefunctionalized substrate (eq. 4). This would result in a method for C–P bond formation via functionalization of relatively unreactive C–H bonds. Here we report the first examples of such a process.

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Supporting Information Available. Experimental procedures and characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

Typical Kabachnik-Fields Reaction:

(1)

Oxidative C–P Bond Formation:

(2)

Decarboxylative C–P Bond Formation:

(3)

Redox-Neutral C–P Bond Formation (This Work):

(4)

As part of our efforts to develop new amine C–H bond functionalization reactions,^{12,13} we recently reported amine C–cyanations^{12m} and C–alkynylations.¹²ⁿ These redox-neutral¹⁴ transformations combine a reductive *N*-alkylation with an oxidative C–functionalization and feature azomethine ylides as reactive intermediates (Figure 1). Water is produced as the only byproduct. The obvious challenge in the development of such reactions is that they compete with classic organic reactions (e.g., Strecker reaction), namely the addition of the nucleophile to the initially formed iminium ion. An indirect solution to this problem was developed in the case of the C–cyanation; we have shown that C–aminonitriles corresponding to **8** can equilibrate to the thermodynamically more stable regioisomers **7**.^{12m} In the C–alkynylation, only minimal isomerization was observed between the propargylic amines corresponding to **7** and **8**.¹²ⁿ Here, good to excellent ratios of **7/8** were obtained by using relatively bulky and/or electron-deficient aromatic aldehydes (e.g., 2,6-dichlorobenzaldehyde, mesitaldehyde). The use of these aldehydes in combination with an appropriate catalyst (e.g., a carboxylic acid) apparently accelerates the iminium isomerization pathway and/or decreases the rate of the classic three-component coupling reaction.

With the above considerations in mind, we chose 2,6-dichlorobenzaldehyde as the reaction partner to evaluate the proposed reaction of pyrrolidine and different phosphites/phosphine oxides (Table 1). Based on previous success, benzoic acid was selected as the catalyst. Reactions proceeded smoothly under microwave irradiation at 200 °C and the desired regioisomer **9** was consistently isolated as the major product. When diethyl phosphite (1.5

equiv) was allowed to react with pyrrolidine (1.2 equiv) and 2,6-dichlorobenzaldehyde in toluene for 15 min, the desired product **9a** was formed in 54% yield (entry 1). In addition, compound **11**, the apparent product of a reductive amination, was also isolated in 13% yield.^{15,16} The corresponding reaction with dibenzyl phosphite led to the formation of **9b** in 44% yield, accompanied by simultaneous formation of **11** in 30% yield (entry 2). Gratifyingly, with diphenylphosphine oxide (1.5 equiv) as the reaction partner, product **9c** was obtained exclusively in 86% yield (entry 3). Lowering the amount of diphenylphosphine oxide to 1.2 equiv did have no adverse effect on the outcome of the reaction (entry 4). A reduction in catalyst loading to 10 mol% led to a slight decrease in yield (entry 5). The use of 2-ethylhexanoic acid in place of benzoic acid resulted in the exclusive formation of **9c** in 84% yield (entry 6). Interestingly, the reaction of 2,6-dichlorobenzaldehyde, pyrrolidine and diphenylphosphine oxide also proceeded without the addition of any catalyst to furnish the desired product **9c** in good yield (entry 7). No product formation was observed with copper(II) 2-ethylhexanoate, the catalyst that had proved optimal in the amine – alkynylation (entry 8).¹²ⁿ

To establish the influence that the nature of the aldehyde exerts on product ratios, the three-component reaction was performed with unsubstituted benzaldehyde (Table 2). A favorable product ratio for **9d/10d** of 4.4:1 was observed after a short reaction time of just 5 min (Table 2, entry 1). An increase in reaction time favorably affected product ratios (entries 1–3) and at a reaction time of 30 min, products **9d/10d** were obtained in a 21:1 ratio and 87% combined yield. In the absence of any catalyst, the reaction yielded predominantly the undesired regioisomer **10d** (entries 4–6), showing that the good product ratio in the uncatalyzed reaction of 2,6-dichlorobenzaldehyde is specific to that particular aldehyde (see Table 1, entry 7). No further improvement could be achieved with 2-ethylhexanoic acid as the catalyst (entries 7, 8). Trifluoroacetic acid proved to be an inferior catalyst (entry 9). This observation is consistent with the previously established requirement for a weakly acidic carboxylic acid catalyst.^{12m}

The results shown in Table 2 suggest that the equilibration of regioisomeric products is an important factor that affects the observed product ratios. To unambiguously establish that product isomerization does indeed occur, compound **10c** was exposed to the previously established reaction conditions (eq 7). In the event, **9c** was obtained in 86% yield as the only detectable regioisomer. In the otherwise identical experiment with **10d**, products **9d/10d** were obtained as an 11:1 regioisomeric mixture in 84% yield (eq 8). While this result nicely matches the second entry in Table 2, the product ratio suggests that the thermodynamic equilibrium ratio is not reached after 15 min. Importantly, no isomerization was observed upon exposing **9c** or **9d** to the reaction conditions.

(7)

(8)

The scope of the three-component reaction was explored under the optimized conditions (Figure 2). Reactions of pyrrolidine and diphenylphosphine oxide with various aromatic aldehydes consistently led to the formation of the desired α -amino phosphine oxides **9** as the major or nearly exclusive products. Electron-donating and electron-withdrawing groups at different ring positions were well tolerated. Heterocyclic aldehydes were also viable substrates. Benzophenone led to the exclusive formation of ring-substituted product. It was further shown that dibenzylphosphine oxide gives favorable results which are comparable to those of diphenylphosphine oxide. The use of hydrocinnamaldehyde as the substrate gave only the undesired regioisomer. This outcome is similar to what was observed in the corresponding cyanation reaction.^{12m} Upon exposing piperidine to the reaction conditions with diphenylphosphine oxide and 2,6-dichlorobenzaldehyde, the corresponding product was obtained in a 1:1 regioisomeric ratio, albeit in low yield. Azepane provided an even less favorable product ratio and morpholine gave only the regular Kabachnik-Fields reaction product.

(9)

In summary, we have developed a convenient approach for C–P bond formation in the α -position of amines by replacing existing C–H bonds. The oxidative α -functionalization is coupled to a reductive *N*-alkylation, rendering the overall process redox-neutral. Further applications of this general concept are currently being developed in our laboratory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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16. The competing reduction process in the reaction with diethyl phosphite was also observed with other aldehydes. For instance, mesitaldehyde provided the desired α -functionalized product in a >25:1 ratio and 36% yield, accompanied by 18% of the product resulting from reductive amination. With benzaldehyde, α -functionalized product was obtained in a >25:1 ratio and 47% yield, accompanied by 25% of *N*-benzyl pyrrolidine.

Figure 1.
Competing reaction pathways in the α -C-H bond functionalization of amines.

Figure 2.
Scope of the three-component reaction.

Table 1

Evaluation of Reaction Parameters^a

a: R = OEt; b: R = OBn; c: R = Ph

entry	HPOR ₂ (equiv)	catalyst (mol %)	ratio 9/10	yield 9+10(%)	yield 11(%)
1	HPO(OEt) ₂ (1.5)	PhCOOH (20)	>25:1	54	13
2	HPO(OBn) ₂ (1.5)	PhCOOH (20)	>25:1	44	30
3	HPOPh ₂ (1.5)	PhCOOH (20)	>25:1	86	N/A
4	HPOPh ₂ (1.2)	PhCOOH (20)	>25:1	86	N/A
5	HPOPh ₂ (1.2)	PhCOOH (10)	>25:1	80	N/A
6	HPOPh ₂ (1.2)	2-EHA (20)	>25:1	84	N/A
7	HPOPh ₂ (1.2)	--	>25:1	86	N/A

Table 2Dependence of Product Ratios on Catalyst and Reaction Time^a

entry	catalyst	time (min)	ratio 9d/10d	yield 9d+10d(%)
1	PhCOOH	5	4.4:1	86
2	PhCOOH	15	10:1	87
3	PhCOOH	30	21:1	87
4	--	5	1:6	83
5	--	30	1:3	86
6	--	60	1:1	81
7	2-Ethylhexanoic acid	5	1.2:1	92
8	2-Ethylhexanoic acid	30	13:1	83
9	TFA	30	1:1	66

^aReactions were performed on a 0.5 mmol scale