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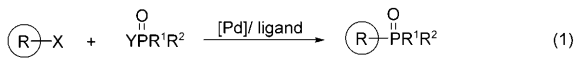
Copper-Catalyzed C–P Coupling through Decarboxylation

Jie Hu, Ning Zhao, Bin Yang, Ge Wang, Li-Na Guo, Yong-Min Liang,* and Shang-Dong Yang*[a]

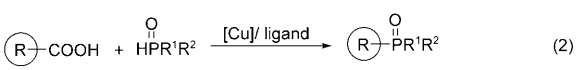
C–P bond construction is highly important in the synthesis of modified nucleosides, nucleotides, and other phosphine-containing ligands.[1] General methods involve transition-metal-catalyzed cross-coupling of aryl halides or triflates with secondary phosphines, or addition of olefin/alkyne by $R_2P(O)M$ (M = Li, Na, K, etc.) reagents [Scheme 1, Eq. (1)].[2] However, in general, only highly reactive aryl iodides can be used as coupling partners or specific and expensive ligands are required to facilitate the high reactivities. In addition, preparation of sensitive and costly phosphine metals is often complicated. As a practical alternative, transition-metal-catalyzed decarboxylative coupling reactions are attractive because: 1) carboxylic acids are cheap, stable, and readily available in various structures; 2) the carboxylic-acid function ensures regioselectivity of the reaction; and 3) only carbon dioxide is produced, instead of metal halides. Pioneering work was reported by Nilsson and Cohen and co-workers, they discovered that copper effectively promotes decarboxylation of aromatic acids.[3] Recently, Gooßen, Myers, and Liu et al. developed a novel protocol for the decarboxylative coupling and widely applied it to C–C bond formation;[4] however, examples of metal-mediated C–P bond formation has yet to be reported.

Traditional coupling



X = Br, I, etc.; Y = Cl, H, K, Na, etc.

Decarboxylative coupling (this work)

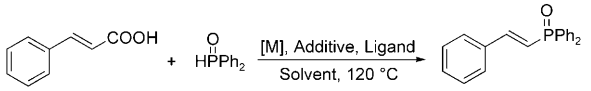


Scheme 1. Copper-catalyzed decarboxylative coupling.

Herein, we describe a versatile method to construct C–P bonds by copper-catalyzed decarboxylative coupling of alkenyl acid, alkyne acid, and *N*-benzylproline, respectively, with $R_2P(O)H$ compounds [Scheme 1, Eq. (2)]. To the best of our knowledge, this report is the first example of copper-catalyzed decarboxylative coupling to construct C–P bonds.

In an initial study, we choose cinnamic acid (**1a**) and $Ph_2P(O)H$ as the model substrates to begin our investigations, because alkenyl di(phenyl)phosphine oxides are key intermediates for the syntheses of various phosphine ligands and present in numerous biologically active products.[5] A general method to build such structure units is the transition-metal-catalyzed addition of $Ph_2P(O)H$ to alkynes, but this transformation always results in a mixture of *E/Z* configurations, and it is difficult to obtain one single product.[6] Another approach is through coupling of alkenyl phosphonates with aryl iodides by Heck-type reactions.[7] However, the preparation of alkenyl phosphonates and the availability of aryl iodides limits the applications. In view of the best regioselectivity and price, alkenyl-acid decarboxylative coupling with $Ph_2P(O)H$ provides a direct and effective method for the synthesis of alkenylphosphine oxides. We did initial tests with CuCl (10 mol%) and 1,10-phenanthroline (10 mol%) as the ligand in *N*-methylpyrrolidone (NMP) at 120 °C (Table 1, entry 1), but did not observe the desired product. When AgOAc (2.0 equiv) was added, the reaction

Table 1. Decarboxylative coupling under different conditions.[a]



1a 1b 2a

	[M]	Ligand[b]	Additives	Solvent	Yield[c][%]
1	CuCl	Phen	–	NMP	<5%
2	CuCl	Phen	AgOAc[d]	NMP	33%
3	CuCl	Phen	AgOAc[e]	NMP	38%
4	CuBr	Phen	AgOAc[e]	NMP	11%
5	CuI	Phen	AgOAc[e]	NMP	37%
6	Cu_2O	Phen	AgOAc[e]	NMP	77%
7	Cu_2O	Phen	KOAc[e]	NMP	33%
8	Cu_2O	Phen	Ag_2CO_3[e]	NMP	88%
9	Cu_2O	Phen	AgO_2[e]	NMP	94%
10	Cu_2O	Phen	AgO_2[d]	NMP	81%
11	Cu_2O	Phen	AgO_2[e]	DMF	38%
12	Cu_2O	Phen	AgO_2[e]	toluene	34%

[a] All the reactions were carried out with [M] (10% mol) in the presence of **1b** (0.2 mmol) in different solvents (2 mL) at 120 °C; [b] Phen = 1,10-phenanthroline (10% mol); [c] Yield of isolated product; [d] 2.0 equivalents; [e] 3.0 equivalents.

[a] J. Hu, N. Zhao, B. Yang, G. Wang, L.-N. Guo, Prof. Y.-M. Liang, S.-D. Yang
State Key Laboratory of Applied Organic Chemistry
Lanzhou University, Lanzhou 730000 (P.R. China)
Fax: (+86) 931-8912859
E-mail: yangshd@lzu.edu.cn

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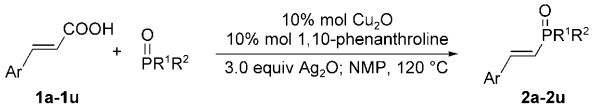
worked and indeed afforded *trans*-alkenylphosphine oxide **2a** in 33% yield after 6 h (Table 1, entry 2). Encouraged by this result, we further optimized the reaction conditions. The AgOAc loading was increased (3.0 equiv), but no distinct change was detected and the yield of **2a** only increased to 38% (Table 1, entry 3). A screening of different Cu salts (Table 1, entries 4–6) revealed Cu_2O as the best catalyst to afford 77% yield of isolated **2a**. Other additives were also evaluated and the results indicated that the use of Ag_2O (3.0 equiv) improved the reaction yield of **2a** to 94%. Solvent screening (Table 1, entries 11–12) showed that NMP was the best choice. The single-crystal structure of *ortho*-methylcinnamic di(phenyl)phosphine oxide (**2d**) confirmed the identity of the product.[8]

Under the optimized reaction conditions (Table 1, entry 9), various cinnamic-acid derivatives were surveyed (Table 2). The corresponding alkenylphosphine oxides were produced with moderate to good yields and high selectivity, regardless if electron-withdrawing or electron-donating groups were introduced on the phenyl ring of the olefinelic acid (Table 2, products **2d–s**). Electronic effects are not evident in this reaction. However, steric hindrance will lead to lower yields. Different $R_2P(O)H$ were also examined and the corresponding products were obtained in moderate yields (Table 2, products **2b–c** and **2t–u**). In addition, we attempted to expand our substrates to vinyl carboxylic acids and benzoic acids, but this failed and the aspired products were not observed. In conclusion, this methodology is regioselective and chemoselective. Compared with previous methods, it is simple and works under relatively mild conditions.

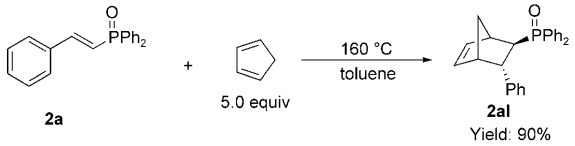
Table 2. Decarboxylative coupling with different substrates.[a,b]



Product	Ar	R^1	R^2	Yield[b][%]
2a	Ph	Ph	Ph	94%
2b	Ph	O*i*Pr	O*i*Pr	50%
2c	Ph	OEt	Ph	76%
2d	*o*-CH_3Ph	Ph	Ph	78%
2e	*m*-CH_3Ph	Ph	Ph	88%
2f	*p*-CH_3Ph	Ph	Ph	60%
2g	*m*-OCH_3Ph	Ph	Ph	92%
2h	*p*-OCH_3Ph	Ph	Ph	70%
2i	3,4-CH_3Ph	Ph	Ph	81%
2j	3,5-OCH_3Ph	Ph	Ph	76%
2k	2,5-OCH_3Ph	Ph	Ph	78%
2l	β-naphthalene	Ph	Ph	90%
2m	3,4-methylenedioxy	Ph	Ph	86%
2n	*p*-ClPh	Ph	Ph	76%
2o	*m*-BrPh	Ph	Ph	60%
2p	*p*-FPh	Ph	Ph	71%
2q	*p*-CNPh	Ph	Ph	63%
2r	2,4-ClPh	Ph	Ph	20%
2s	furan	Ph	Ph	60%
2t	3,4-methylenedioxy	O*i*Pr	O*i*Pr	51%
2u	3,4-methylenedioxy	OEt	Ph	62%

[a] All reactions were carried out under the optimal conditions reported above for 6 h. [b] Yield of isolated product.

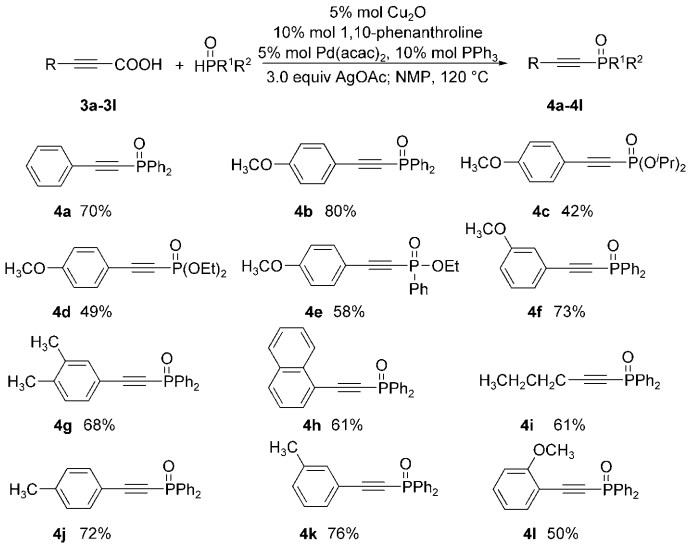
Phosphorus-based ligands are important to many metal-catalyzed organic transformations, including many chiral reactions.[9] Thus, effective and efficient ways to construct these ligands are highly desirable. The alkenyldi(phenyl)phosphine oxides are important skeletons that have been extensively applied to synthesize various phosphorus ligands. We choose product **2a** to react with 1,3-cyclopentadiene through 1,4-cycloaddition to yield phosphorus ligand **2al** in 90% high yield, showing the utility of our chemistry (Scheme 2).



Scheme 2. Phosphorus-ligand synthesis by 1,4-cycloaddition.

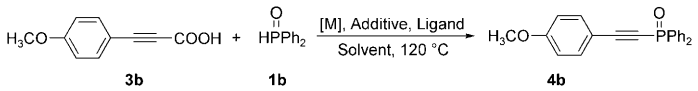
Inspired by these results, we wished to extend this method to the synthesis of alkynyl phosphonates. Alkynyl di(phenyl)phosphine oxides are important precursor to synthesize various (P^O) or (P^N) bidentate ligands.[10] Synthesis of alkynylphosphanes is usually accomplished by treating P^{III}-halides with acetylenides of sodium, lithium, magnesium, or titanium.[11] A significant advance to simplify the process was achieved by Han and co-workers, who developed an efficient copper-catalyzed oxidative coupling of alkynes with $(i\text{PrO})_2P(O)H$. However, under similar reaction conditions, $Ph_2P(O)H$ as substrate did not afford the oxidative-coupling product, because $Ph_2P(O)H$ was oxidized to $Ph_2P(O)OH$.[12] If our assumption of copper-catalyzed decarboxylative coupling of alkyne acid with $Ph_2P(O)H$ for the synthesis of alkynyl di(phenyl)phosphine oxides was achieved, it would be beneficial in general and broadly applicable. At the outset, we examined the reaction of 3-phenylpropiolic acid (**3b**) with $Ph_2P(O)H$ under the decarboxylative reaction conditions. The reaction occurred and the desired product of alkynyl di(phenyl)phosphine oxides (**4b**) was obtained in 23% yield and the structure was confirmed by single-crystal diffraction.[13] To optimize the reaction, we discovered that the Cu/Pd-bimetallic catalysis system was the best choice. When we added $Pd(acac)_2$ (5% mol, acac = acetylacetonate) and PPh_3 (10% mol) to the previously described reaction system, and selected AgOAc as the base, the reaction proceeded smoothly to yield 80% of **4b** (Scheme 3).

The cross-reactions of different $R_2P(O)H$ compounds was investigated and the corresponding alkynylphosphonates were produced in moderate to good yields (Table 3, entries 6–20). Notably, di(phenyl)phosphine oxide exhibited higher activity than others. Different alkyne acids were also screened and the results illustrate that electronic effects and steric hindrance play the key roles in this reaction; electron



Scheme 3. Decarboxylative coupling with different alkynes. The reactions were carried out under the optimal reaction conditions reported above for 6 h. Isolated yields are given for each compound.

Table 3. Decarboxylative coupling with alkynyl acid under different conditions.[a]

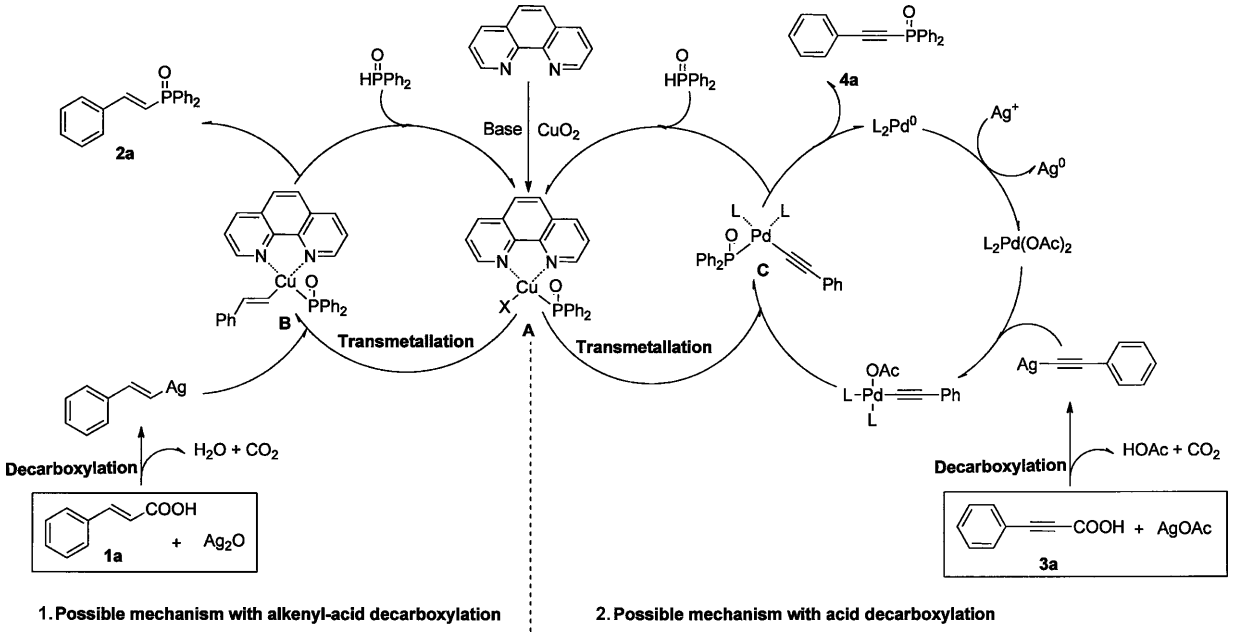


	Cu/L[b]	Pd/L[c]	Additives[d]	Solvent	Yield[e][%]
1	Cu_2O/Phen	–	Ag_2O	NMP	23%
2	Cu_2O/Phen	–	AgOAc	NMP	41%
3	Cu_2O/Phen	–	Ag_2CO_3	NMP	43%
4	Cu_2O/Phen	–	K_2CO_3	NMP	n.r.[f]
5	Cu_2O/Phen	$Pd(acac)_2$	Ag_2CO_3	NMP	48%
6	Cu_2O/Phen	$Pd(acac)_2$/P(*o*-$CH_3Ph)_3$	Ag_2CO_3	NMP	56%
7	Cu_2O/Phen	$Pd(acac)_2$/P(*o*-$CH_3Ph)_3$	K_2CO_3	NMP	15%
8	Cu_2O/Phen	$Pd(acac)_2$/P(*o*-$CH_3Ph)_3$	AgOAc	NMP	75%
9	Cu_2O/Phen	$Pd(acac)_2$/P(*o*-$CH_3Ph)_3$	Ag_2O	NMP	36%
10	–	$Pd(acac)_2$/P(*o*-$CH_3Ph)_3$	AgOAc	NMP	14%
11	CuBr/Phen	$Pd(acac)_2$/P(*o*-$CH_3Ph)_3$	AgOAc	NMP	69%
12	CuI/Phen	$Pd(acac)_2$/P(*o*-$CH_3Ph)_3$	AgOAc	NMP	27%
13	Cu_2O/Phen	$Pd(acac)_2$/P(*p*-$CH_3Ph)_3$	AgOAc	NMP	67%
14	Cu_2O/Phen	$Pd(acac)_2$/PPh_3	AgOAc	NMP	80%
15	Cu_2O/Phen	$Pd(acac)_2$/dppp[g]	AgOAc	NMP	71%
16	Cu_2O/Phen	$Pd_2(dba)_3$/PPh_3	AgOAc	NMP	70%
17	Cu_2O/Phen	$Pd(OAc)_2$/PPh_3	AgOAc	NMP	12%
18	Cu_2O/Phen	$Pd(acac)_2$/PPh_3	AgOAc	Toluene	8%
19	Cu_2O/Phen	$Pd(acac)_2$/PPh_3	AgOAc	DMF	6%
20	Cu_2O/Phen	$Pd(acac)_2$/PPh_3	AgOAc	DMSO	52%

[a] All the reactions were carried out in the presence of **1b** (0.2 mmol) in different solvents (2 mL) at 120 °C; [b] Cu/L 5:10% mol; [c] Pd/L 5:10% mol; [d] 3.0 equivalents; [e] Yield of isolated product; [f] n.r. = no reaction; [g] dppp = diphenyl-1-pyrenylphosphine.

donors, such as methoxyl located in *para* position, will improve the yield effectively, whereas in the *ortho* position they will decrease the yield. Note that fatty alkyne acid also worked smoothly in this transformation.

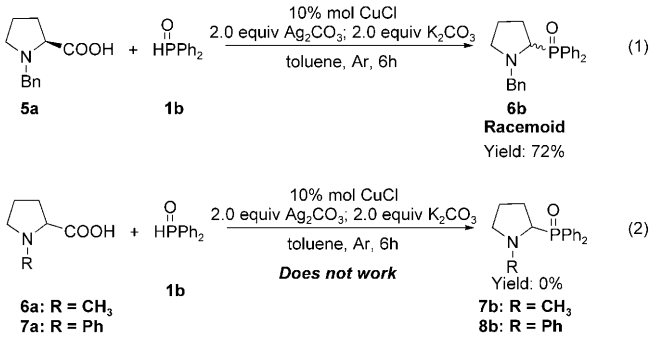
In general, copper-catalyzed C–P bond formation mainly has two distinct pathways; one proposed mechanism is Cu-catalyzed phosphination of aryl halides and may proceed through Cu^I/Cu^{III} cycles. In the initial step, Cu^I first reacts with $Ph_2P(O)H$ and forms the $[Cu^IPPh_2]$ complex in the presence of a base, then oxidative addition with an aromatic halide produces the $[ArCu^{III}XPPh_2]$ intermediate, after which reductive elimination occurs to obtain the product; this realizes the catalytic cycle.[14] The other pathway involves alkylation of a secondary phosphine and the valence of copper is not changed in the transformation. This pathway proceeds through phosphido intermediates and C–P bond formation occurs by a nucleophilic attack of the $[M–PR_2]$ groups at alkylhalide electrophiles. Ligand substitution and proton transfer to a base then yield the product and regenerate the catalyst.[15] This proposed mechanism is related to those suggested for catalytic C–X (X = N, O, S) bond formations mediated by nucleophilic Cu^I amides, alkoxides, or thiolate complexes.[16] In contrast to the above-mentioned mechanisms, Cu-catalyzed decarboxylative C–P cross-coupling reactions are significantly different in the catalytic process. Considering that the pentavalent phosphine is involved in this transformation, we have outlined a possible mechanistic pathway for formation the C–P bonds by decarboxylation of alkenyl and alkynyl acids in Scheme 4. In the presence of silver salts, the reaction of $Ph_2P(O)H$ with the copper/Phen catalyst is expected to yield the Cu^{II}–phosphine-complex **A**. In parallel, the carboxylic acids should be converted into alkenyl and alkynyl–silver species by decarboxylation through a stoichiometric amount of silver that coordinates to the carboxylate oxygen and is inserted into the C–C(O) bond under extrusion of CO_2. In path 1, alkenyl silver would then transfer the alkenyl group to copper under formation of silver derivates by transmetallation to give the organocopper-intermediate **B**. Finally, the desired product **2a** would be released, regenerating the initial copper species and resuming the catalytic cycle. In path 2, because the alkynyl–silver species is more stable than alkenyl silver, direct transmetallation with copper-complex **A** would be relatively difficult. A Pd^0 species is added to the reaction system; this accelerates the transmetallation. Firstly, Pd^0 is oxidized to Pd^{II} with silver salt, and then the Pd^{II} complex is transmetallated with alkynyl silver to form the alkynyl–palladium intermediate. This highly active alkynyl–palladium species transmetallated with Cu^{II}-complex **A** gives intermediate **C**, after which product **4a** is obtained by reductive



Scheme 4. Proposed mechanisms of decarboxylation with alkenyl and alkynyl acid.

elimination and the metal is released to reinitiate the catalytic cycle. In addition, the experimental data showed that the copper catalyst is crucial in the C–P decarboxylative coupling, which proceed through Cu^{I}/Cu^{II} cycles.

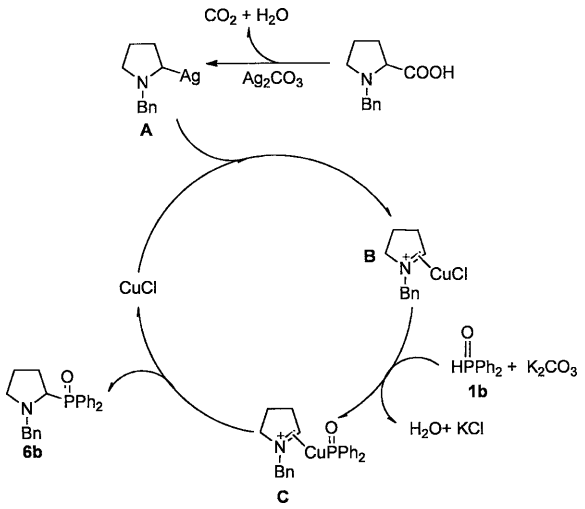
Recently, Li and Sames with co-workers performed the Cu- or Ru-catalyzed decarboxylative coupling of sp^3-hybridized carbons of amino acids.[17] This finding offers a novel and potential pathway for the synthesis of different phosphorus ligands in one step by the decarboxylative coupling with $Ph_2P(O)H$. We choose the natural *N*-benzyl-L-proline to begin our attempts [Scheme 5, Eq. (1)]. To our delight, the reaction proceeded in the presence CuCl (10% mol), Ag_2CO_3 (2.0 equiv), and K_2CO_3, as base, in toluene at 120 °C to afford the potential phosphorus ligand of *N*-benzyl-2-(di(phenyl)phosphoryl)pyrrolidine (**6b**) in 72% yield. This reaction also provides the possibility to synthesize a chiral ligand. Therefore, the *ee* value of **6b** was also investigated, but unfortunately the results indicated that only a racemic product was obtained.



Scheme 5. Decarboxylative coupling with *N*-benzyl-protected proline.

To obtain more information about the mechanistic pathway, reactions with *N*-methylproline (**6a**) and *N*-phenylproline (**7a**) were carried out under the same reaction conditions [Scheme 5, Eq. (2)]. Not surprisingly, this reaction did not work and the direct-coupling products **7b** and **8b** were not observed. Based on these results, we can concluded that the mechanism of the C–P bond formation by decarboxylation should be the same as Li reported for the CuBr-catalyzed oxidative decarboxylation of α-amino acids for C–C bond formation, for which an imine-copper complex is considered to be the key intermediate. The proposed mechanism for the C–P coupling by decarboxylation illustrated in Scheme 6. *N*-benzylproline decarboxylation by Ag_2CO_3 gives silver-complex **A**; this activated species, prompted by CuCl, quickly forms the copper–imine-intermediate **B**. The coupling of **B** with $Ph_2P(O)H$ in the presence of the base affords the desired product **6b** and regenerates the copper catalyst.

In summary, we have developed a protocol for preparation of various di(phenyl)phosphoryl compounds through a copper-catalyzed decarboxylative coupling reaction of $Ph_2P(O)H$ with alkenyl acids, alkynyl acids, and *N*-benzylproline. Notably, this process exhibits the following, very attractive features: the best regio- and chemoselectivity reported so far for C–P coupling, good functional-group tolerance, and good scale-up possibilities. Further applications of this approach to the synthesis of chiral ligands are ongoing.



Scheme 6. Decarboxylative coupling with *N*-benzylproline.

Experimental Section

Preparation of 2a–u: $R_2P(O)H$ (0.2 mmol) Cu_2O (10 mol%), 1,10-phenanthroline (10 mol%), and Ag_2O (3.0 equiv) were added to a solution of **1** (0.30 mmol) in NMP (2.0 mL) in a vial (10 mL), which was charged with Ar three times. The mixture was allowed to stir at room temperature for 1 min and then heated to 120°C for 6 h. Then the reaction was cooled to room temperature and the suspension was filtered through a Celite pad and extracted with EtOAc three times. The combined organic extracts were washed with water and saturated brine. The organic layers were dried over filtered Na_2SO_4. Solvents were evaporated under reduced pressure. The desired products **2a–u** were obtained in the corresponding yields after purification by chromatography on silica gel.

Preparation of 4a–l: $R_2P(O)H$ (0.2 mmol) Cu_2O (5 mol%), 1,10-phenanthroline (10 mol%), $Pd(acac)_2$ (5 mol%), PPh_3 (10 mol%), and AgOAc (3.0 equiv) were added to a solution of arylpropiolic acid (0.30 mmol) in NMP (2.0 mL) in a vial (10 mL), which was charged with Ar three times. The mixture was allowed to stir at room temperature for 1 min and then heated to 120°C for 6 h. Then the reaction was cooled to room temperature and the suspension was filtered through a Celite pad and extracted with EtOAc three times. The combined organic extracts were washed with water and saturated brine. The organic layers were dried over filtered Na_2SO_4. Solvents were evaporated under reduced pressure. The desired products **4a–l** were obtained in the corresponding yields after purification by chromatography on silica gel.

Preparation of 6b: $Ph_2P(O)H$ (0.2 mmol), CuCl (10 mol%), K_2CO_3 (2.0 equiv), and Ag_2CO_3 (2.0 equiv) were added to a solution of **5a** (0.30 mmol) in toluene (2.0 mL) in a vial (10 mL), which was charged with Ar three times. The mixture was allowed to stir at room temperature for 1 min and then heated to 120°C for 6 h. Then the reaction was cooled to room temperature and the suspension was filtered through a Celite pad and extracted with EtOAc three times. The combined organic extracts were washed with water and saturated brine. The organic layers were dried over filtered Na_2SO_4. Solvents were evaporated under reduced pressure. The desired product **6b** was obtained in the corresponding yield after purification by chromatography on silica gel.

Acknowledgements

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Keywords: catalysis · copper · C–P coupling · decarboxylation · phosphorus

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