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3-(Diphenylphosphino)propanoic acid: an efficient ligand for the Pd/Cu-catalyzed homo-coupling of terminal alkynes in the presence of oxygen at room temperature

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A simple, yet efficient system for $PdCl_2$/CuI to catalyze the homo-coupling reactions of various terminal alkynes has been developed using 3-(diphenylphosphino)propanoic acid as ligand in the presence of oxygen. The alkynes, including aromatic, heteroaromatic and aliphatic alkynes, were transformed at room temperature into the corresponding 1,3-diynes in moderate to excellent yields. The turnover number was up to 1.04×10^3.

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Keywords: 1,3-diynes; palladium; P,O ligand; terminal alkyne; homo-coupling

Introduction

As important structural motifs, 1,3-diynes are frequently found in natural products, pharmaceuticals and other bioactive compounds demonstrating diverse biological and antibacterial properties.[1] Moreover, conjugated diynes play an integral role in the design of macrocyclic annulenes, organic conductors, supramolecular switches and carbon-rich materials.[2–4] As a result, much attention has been devoted to the development of highly efficient catalytic systems for the synthesis of diynes.[5] In general, the homo-coupling of terminal alkynes, catalyzed by a combination of palladium and copper salts, proves to be the most attractive technique providing superior efficacy in combination with mild reaction conditions.[6] Copper- or silver-mediated alkyne homo-coupling reaction without the use of palladium has also been reported recently; however, high copper or silver catalyst loadings are still required.[7,8] Increasing economic and environmental interests offer an incentive to develop advanced strategies for the efficient homo-coupling of terminal alkynes.

P,O bidentate derivatives are well-known ligands for transition metal-catalyzed organic reactions with suitable electron environments and advantageous steric interactions for the phosphorus atom. In general, the P,O moieties can provide an additional coordination site for the catalytically active metal center and therefore may enhance its potency. Since Keim first reported that Ni(II)/P,O chelating ligands were highly active in oligomerization and polymerization reactions of ethylene,[9] this particular ligand class has become the main synthetic target of interest. A variety of analogous P,O chelating ligands have been successively synthesized and applied in the development of novel homogeneous catalysts.[10] For example, Pd- and Ni-catalyzed coupling reactions for C–C bond formation could be achieved in the presence of P,O chelating ligands.[11–13] However, studies of Pd-catalyzed homo-coupling reactions of terminal alkynes in the presence of P,O chelating ligands have been rarely reported.

Herein, we describe a simple yet practical synthetic approach to obtain 1,3-diynes through a combination of 0.1 mol% $PdCl_2$- and 2 mol% CuI-catalyzed homo-coupling reactions of terminal alkynes at room temperature using 3-(diphenylphosphino)propanoic acid as a ligand in the presence of oxygen.

Experimental

Materials and instrumentation

All reactions were carried out under air using magnetic stirring unless otherwise noted. ^{1}H NMR spectral data were recorded with a Bruker DPX-400 spectrometer using tetramethylsilane as internal standard and $CDCl_3$ as solvent. Mass spectra were recorded with a GC-MS (Agilent 7890A/5975C) instrument under EI model. Column chromatography was performed with silica gel (200–300 mesh) purchased from Qingdao Haiyang Chemical Co. Ltd. All other reagents were of analytical grade quality, purchased from Adamas-beta Pharmaceuticals Inc. and used as received. Ligands **1** and **2** (Scheme 1) were synthesized using a literature method.[14]

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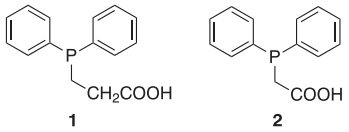


Scheme 1. Ligands used in the study.

General procedure for Pd/Cu-catalyzed homo-coupling reaction of terminal alkynes

A Schlenk tube (25 ml) equipped with a stir bar was charged with $PdCl_2$ (0.1 mol%), $Ph_2PCH_2CH_2COOH$ (0.2 mol%), CuI (2 mol%), NEt_3 (1 mmol), phenylacetylene (1.0 mmol) and dimethylformamide (DMF; 1.0 ml), and the mixture was stirred at room temperature under oxygen balloon for 24 h. The solution was quenched with water and extracted with EtOAc (3 × 10 ml). The combined EtOAc extracts were dried over anhydrous Na_2SO_4 and filtered and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel with polyethylene and EtOAc as the eluent to obtain the desired products.

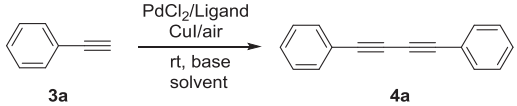
Results and discussion

Initially, we chose the homo-coupling of phenylacetylene as a model reaction catalyzed by Na_2PdCl_4 (2 mol%) in combination with ligands **1** and **2** (4 mol%) in the presence of CuI (2 mol%), CH_3CN (4 ml) as solvent and NaOH (3.0 mmol) as base at room temperature in air. As evident from Table 1, when CuI is used as sole catalyst, no homo-coupling product is observed (Table 1, entry 1). Similarly, this reaction is unlikely to progress in the absence of $PdCl_2$ or CuI (Table 1, entries 2 and 3). However, when $PdCl_2$ and CuI are used as the catalysts without ligand **1**, the coupling product is obtained in very low yield (Table 1, entry 4). Although addition of ligand **1** improves the reactivity, a yield of only 32% is obtained (Table 1, entry 5). Experiments using a variety of different bases show Et_3N to be the most suitable base for the formation of the desired product in 71% yield (Table 1, entry 10). The use of other bases, such as CH_3CO_2Na, Cs_2CO_3, $K_3PO_4 \cdot H_2O$ and Na_2CO_3, results in very low yields (Table 1, entries 6–9). The selection of an appropriate solvent is another key factor for the success of the catalytic reaction. DMF and 1,4-dioxane prove to be the preferred reaction solvents compared to H_2O, CH_3OH and dimethylsulfoxide (DMSO), resulting in the formation of the desired product in 83 and 81% yields, respectively (Table 1, entries 11–15). However, when ligand **2** is used as the ligand and DMF as the solvent, a yield of only 60% is obtained (Table 1, entry 16).

In light of these intriguing results, we continued our studies by comparing different reaction conditions, focusing on catalyst loadings, ligands, solvents and bases in the presence of 1 atm neat oxygen (Table 2). Interestingly, upon decreasing the $PdCl_2$/ligand loading from 2 mol%/4 mol% to 0.1 mol%/0.2 mol%, the product yield still remains constant at 96–98% (Table 2, entries 1–4). Although the product yield declines upon further decreasing the $PdCl_2$ or CuI loading, the turnover number increases up to 1.04×10^3 (Table 2, entries 5 and 6). Worth noting in this context is the fact that 1 ml of DMF and 1 mmol of Et_3N in the presence of 1 atm O_2 as an oxidant prove to be sufficient for this transformation (Table 2, entries 7 and 8). However, the reaction time is significantly reduced to 12 h and the yield of the product **4a** decreases to 55% (Table 1, entry 9). Finally, a combination of $PdCl_2$ (0.1 mol%), ligand **1** (0.2 mol%), CuI (2 mol%) and Et_3N (1 equiv.) at room temperature in DMF (1 ml) is found to be the most optimal reaction conditions for the homo-coupling of terminal alkynes.

As a result of these optimization assays, we investigated the substrate range of this particular homo-coupling reaction. The results are listed in Table 3. First, the homo-coupling reaction of *meta*-substituted terminal alkynes was investigated. It is found that neither the electronic properties nor the steric hindrance of the substrates have any obvious effects on the coupling reaction. Most reactions afford the desired products **4b–4e** in good yields (Table 3, entries 1–4). However, using alkyne **3f** bearing an amino group

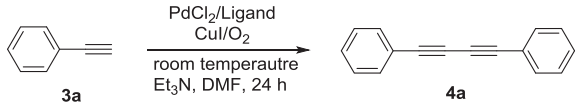
Table 1. Optimization of reaction conditions under air[a]



Entry	$PdCl_2$ (%)	Ligand/amount (%)	CuI (%)	Solvent	Base	Yield (%)[b]
1	—	—	2	CH_3CN	NaOH	0
2	—	**1**/4	2	CH_3CN	NaOH	0
3	2	**1**/4	—	CH_3CN	NaOH	0
4	2	0	2	CH_3CN	NaOH	15
5	2	**1**/4	2	CH_3CN	NaOH	32
6	2	**1**/4	2	CH_3CN	CH_3CO_2Na	25
7	2	**1**/4	2	CH_3CN	Cs_2CO_3	27
8	2	**1**/4	2	CH_3CN	$K_3PO_4 \cdot H_2O$	50
9	2	**1**/4	2	CH_3CN	Na_2CO_3	23
10	2	**1**/4	2	CH_3CN	NEt_3	71
11	2	**1**/4	2	H_2O	NEt_3	21
12	2	**1**/4	2	CH_3OH	NEt_3	47
13	2	**1**/4	2	DMSO	NEt_3	59
14	2	**1**/4	2	DMF	NEt_3	83
15	2	**1**/4	2	Dioxane	NEt_3	81
16	2	**2**/4	2	DMF	NEt_3	60

[a]Reaction conditions: phenylacetylene, 1.0 mmol; base, 3.0 mmol; solvent, 4 ml; room temperature; 24 h; air balloon.
[b]Isolated yield.

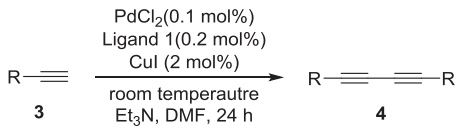
Table 2. Optimization of reaction conditions under O_2[a]



Entry	$PdCl_2$ (%)/ ligand **1** (%)	CuI (%)	DMF (ml)	NEt_3 (mmol)	Yield (%)[b]
1	2/4	2	4	3	96
2	1/2	2	4	3	96
3	0.5/1	2	4	3	97
4	0.1/0.2	2	4	3	98
5	0.05/0.1	2	4	3	52
6	0.1/0.2	1	4	3	50
7	0.1/0.2	2	1	3	96
8	0.1/0.2	2	1	1	97
9[c]	0.1/0.2	2	1	1	55

[a]Reaction conditions: phenylacetylene, 1.0 mmol; ligand **1**; room temperature; 24 h; oxygen balloon.
[b]Isolated yield.
[c]Reaction time: 12 h.

Table 3. Homo-coupling of terminal alkyne catalyzed by $PdCl_2$/**1**[a]



Entry	R/**3**	Product	Yield (%)[b]
1	3-FC_6H_4/**3b**	**4b**	99
2	3-ClC_6H_4/**3c**	**4c**	89
3	3-MeC_6H_4/**3d**	**4d**	98
4	3-$MeOC_6H_4$/**3e**	**4e**	85
5	3-$NH_2C_6H_4$/**3f**	**4f**	65
6	4-FC_6H_4/**3g**	**4g**	86
7	4-ClC_6H_4/**3h**	**4h**	87
8	4-MeC_6H_4/**3i**	**4i**	99
9	4-$MeOC_6H_4$/**3j**	**4j**	98
10	4-$CH_2CNC_6H_4$/**3k**	**4 k**	83
11	4-$C_5H_{11}C_6H_4$/**3l**	**4l**	70
12	4-PhC_6H_4/**3m**	**4m**	95
13	3-Thiophyl/**3n**	**4n**	95
14	Cyclopropyl/**3o**	**4o**	95
15	Cyclohexyl/**3p**	**4p**	68
16	Pentyl/**3q**	**4q**	47

[a]Reaction conditions: alkyne, 1.0 mmol; $PdCl_2$, 0.1 mol%; ligand **1**, 0.2 mol%; CuI, 2 mol%; NEt_3, 1 mmol; DMF, 1 ml; room temperature; 24 h; oxygen balloon.

[b]Isolated yield.

results in the formation of the corresponding product **4f** in merely 65% yield under similar reaction conditions (Table 3, entry 5). Use of *para*-substituted terminal alkynes with electron-donating as well as electron-withdrawing substituents results in efficient homo-coupling reactions and the corresponding products **3g–3m** are obtained in moderate to excellent yields (Table 3, entries 6–12). The heteroaromatic alkyne species **3n** proves to be another suitable substrate and affords the desired product **4n** in 95% yield (Table 3, entry 13). Subsequently, the catalytic system was applied to aliphatic terminal alkynes. Ethynylcyclopropane (**3o**) and ethynylcyclohexane (**3p**) are converted into the corresponding 1,4-dialkyl-1,3-diynes (**4o** and **4p**) in 95 and 68% yields, respectively (Table 3, entries 14 and 15). In contrast, hept-1-yne (**3q**) proves to be less reactive, most notably due to the weaker acidity of the acetylenic proton. The corresponding product **4q** is obtained in 47% yield (Table 3, entry 16).

Conclusions

In summary, we have established a simple, yet efficient approach for the $PdCl_2$/3-(diphenylphosphino)propanoic acid/CuI-catalyzed oxidative homo-coupling of terminal alkynes at room temperature in the presence of oxygen. The transformation proves to be efficient and widely applicable using a variety of aromatic, heteroaromatic and aliphatic alkynes. The desired symmetric 1,3-diynes are obtained in moderate to excellent yields.

Acknowledgments

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