Propylene Oxide Assisted Sonogashira Coupling Reaction

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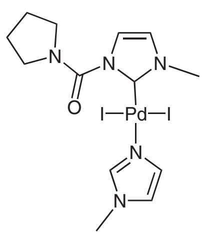
Abstract: A propylene oxide assisted base-free Sonogashira cross-coupling reaction has been developed. The unique feature of the current protocol has extended the scope of Sonogashira reaction to some base-sensitive substrates.

Key words: base-free, propylene oxide, Sonogashira reaction

Sonogashira coupling reaction, first emerged in 1975,[1] involved cross-coupling of a terminal alkyne with an aryl or alkenyl halide.[2,3] The reaction has been most frequently conducted in the presence of a catalytic amount of palladium complex and copper(I) iodide. Natural products chemistry and material science have witnessed the extensive applications of this useful type of transformation to constructing various interesting substituted and conjugated alkynes.[2]

The original Sonogashira reaction and most of the modified versions[1–3] require the use of an organic or inorganic base, which unavoidably causes problems in the case of base-sensitive substrates. Since propylene oxide (PO) is a well-known acid scavenger widely used in amino acid and peptide chemistry, we envisioned that the commercially available and inexpensive PO[4] might be able to assist a base-free Sonogashira reaction.

N-Carbamoyl-substituted heterocyclic carbene complex of palladium(II) (**1**; Figure 1), developed by Batey and coworkers in 2002, is of good thermal and hydrolytic stability and can efficiently catalyze Sonogashira cross-coupling of various aryl halides with terminal alkynes.[3b]

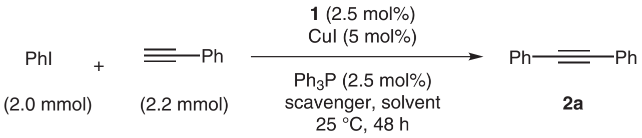


Batey Pd-carbene complex (**1**)

Figure 1

The feasibility of base-free Sonogashira coupling was first tested on iodobenzene and phenylacetylene, with the Batey Pd-carbene complex **1** (2.5 mol%), PPh_3 (2.5 mol%) and CuI (5 mol%) as the catalysts. Reaction of the above components in DMF in the presence of Et_3N[5a] (3.6 equiv) at 25 °C for 48 hours afforded diphenylacetylene (**2a**) in excellent yield (Table 1, entry 1), which proved the activity of the catalysts. Replacement of Et_3N with PO (0, 3, 5,[5b] and 10 equiv) gave **2a** in 2.8%, 74%, 84%, and 81% yields, respectively (entries 2–5), suggesting that five equivalents of PO should be sufficient. In addition, lower yield was obtained in THF or MeCN as the solvent, presumably due to relatively poorer solubility of the Pd catalyst **1** (entries 6 and 7).

Table 1 Sonogashira Coupling of Iodobenzene with Phenylacetylene under Different Conditions



Entry	Solvent	Scavenger	Yield (%)[a]
1	DMF	Et_3N (3.6 equiv)	93
2	DMF	PO (0 equiv)	2.8
3	DMF	PO (3 equiv)	74
4	DMF	PO (5 equiv)	84
5	DMF	PO (10 equiv)	81
6	THF	PO (5 equiv)	63
7	MeCN	PO (5 equiv)	64

[a] Isolated yield.

After the initial success of base-free coupling of iodobenzene and phenylacetylene, additional substrates were inspected under the above reaction conditions [**1** (2.5 mol%), CuI (5 mol%), PPh_3 (2.5 mol%), PO (5 equiv), DMF, 25 °C]. As shown in Table 2, iodobenzene reacted in high yields with various terminal alkynes such as 1-hexyne, propargyl alcohol, and 2-methyl-3-butyn-2-ol in 80–90% yields (entries 2–4). The coupling products of substituted iodobenzenes (*p*-Me, *p*-MeO, and *m*-NO_2)

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Table 2 PO-Assisted Sonogashira Coupling of Aryl Iodides with Terminal Alkynes[a]

$$\text{ArI} + \equiv\!\!-\text{R} \xrightarrow[\text{DMF, 25 °C, 48 h}]{\mathbf{1}\text{, CuI, Ph}_3\text{P, PO}} \text{Ar}-\!\!\equiv\!\!-\text{R}$$

Entry	Ar	R	Product	Yield (%)[b]
1	Ph	Ph	**2a**[3c]	84
2	Ph	*n*-Bu	**2b**[3b]	80
3	Ph	CH_2OH	**2c**[3b]	90
4	Ph	$C(Me)_2OH$	**2d**[3c]	86
5	*p*-MeC_6H_4	Ph	**2e**[6]	78
6	*p*-$MeOC_6H_4$	Ph	**2f**[3c]	83[c]
7	*m*-$O_2NC_6H_4$	Ph	**2g**[7]	97

[a] The reaction of aryl iodide (2 mmol) and alkyne (110 mol%) was carried out in degassed DMF with **1** (2.5 mol%), CuI (5 mol%), PPh_3 (2.5 mol%), and PO (5 equiv) at 25 °C for 48 h.
[b] Isolated yield.
[c] The reaction was carried out at 50 °C.

with phenylacetylene were formed in 78–97% yields (entries 5–7).

Next, PO-assisted Sonogashira coupling of aryl bromides with 1-alkynes was investigated (Table 3). The cross-coupling of bromobenzene with phenylacetylene was rather sluggish at 25 or 50 °C. However, the reaction was remarkably accelerated at 80 °C and diphenylacetylene was furnished in 81% yield (entry 1). This protocol was then applied to a series of other aryl bromides and terminal alkynes. For instance, bromobenzene coupled efficiently with 1-hexyne, propargyl alcohol, and 2-methyl-3-butyn-2-ol in good yields (82–85%) at 80 °C in the presence of PO (entries 2–4). Moreover, the cross-coupling reaction of phenylacetylene with several aryl bromides other than bromobenzene was scrutinized. For the bromobenzenes with an electron-withdrawing group (such as formyl, acetyl, and nitro) at the *para* position, the transformation proceeded cleanly and gave rise to the internal alkynes in 91–94% yields (entries 5–7). Reaction of phenylacetylene with bromobenzenes bearing a *para* substituent of phenyl or methyl generated the corresponding products in 78% and 84% yields, respectively (entries 8 and 9). Finally, 3-quinolinyl bromide, a weak base itself, reacted very little with phenylacetylene without the aid of PO (or other bases). In the presence of five equivalents of PO, the reaction proceeded smoothly (entry 10).

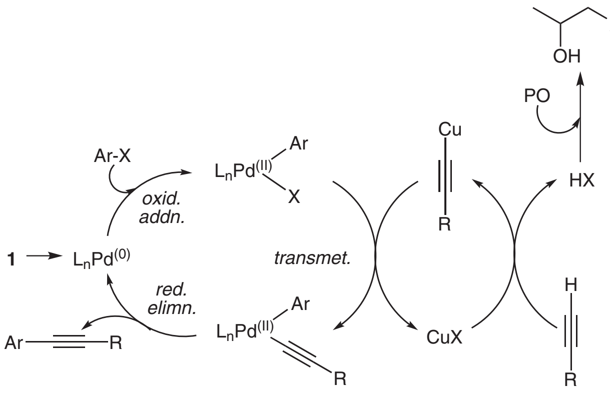
A plausible mechanism for the base-free Sonogashira coupling reaction has been proposed, which follows the expected oxidative addition, transmetallation, and reductive elimination pathway (Scheme 1). Here, the striking feature lies in the fact that the Bronsted acid (HX), produced in the reaction, was scavenged by PO instead of Et_3N or other bases. The release of a halohydrin provides a driving force for the catalytic cycle.

Table 3 PO-Assisted Sonogashira Coupling of Aryl Bromides with Terminal Alkynes[a]

$$\text{ArBr} + \equiv\!\!-\text{R} \xrightarrow[\text{DMF, 80 °C, 48 h}]{\mathbf{1}\text{, CuI, Ph}_3\text{P, PO}} \text{Ar}-\!\!\equiv\!\!-\text{R}$$

Entry	Ar	R	Product	Yield (%)[b]
1	Ph	Ph	**2a**[3c]	81
2	Ph	*n*-Bu	**2b**[3b]	84
3	Ph	CH_2OH	**2c**[3b]	82
4	Ph	$C(Me)_2OH$	**2d**[3c]	85
5	*p*-$OHCC_6H_4$	Ph	**2h**[7]	91
6	*p*-AcC_6H_4	Ph	**2i**[3b]	94
7	*p*-$O_2NC_6H_4$	Ph	**2j**[3b]	94
8	*p*-PhC_6H_4	Ph	**2k**[7]	78
9	*p*-MeC_6H_4	Ph	**2e**[6]	84
10	3-quinolinyl	Ph	**2l**[8]	81

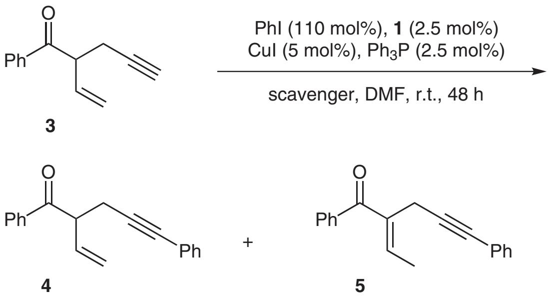
[a] The reaction of aryl bromide (2 mmol) and alkyne (110 mol%) was carried out in degassed DMF with **1** (2.5 mol%), CuI (5 mol%), PPh_3 (2.5 mol%), and PO (5 equiv) at 80 °C for 48 h.
[b] Isolated yield.



Scheme 1 Mechanism of the coupling reaction

To demonstrate the advantage of the current protocol, Sonogashira reaction of a terminal alkyne having a deconjugated enone unit (**3**) with iodobenzene was explored in the presence of PO and Et_3N as scavengers, respectively (Table 4). After the reaction proceeded for 48 hours with PO as the scavenger, both **4** and **5** were formed (80% combined yield, **4**/**5** = 69:31), where **4** was the regular coupling product and **5** resulted from both Sonogashira coupling and carbon–carbon double bond shift (entry 2). At shortened reaction time (24 h), the ratio of **4**/**5** was improved to 94:6 while the combined yield dropped to 57% (entry 1). In contrast, when reaction was run in Et_3N–DMF (1:1), conjugated enone **5** was obtained as the sole product (entry 3). Even though in this case the double bond shift could not be avoided completely with PO used

Table 4 PO-Assisted Sonogashira Coupling of Alkyne **3** with Iodobenzene



Entry	Scavenger	Time (h)	**4**/**5**	Yield [**4** + **5** (%)][a]
1	PO (5 equiv)	24	94:6	57
2	PO (5 equiv)	48	69:31	80
3	Et_3N (excess)	24	0:100	88

[a] Isolated yield.

as the scavenger, our protocol should in general be a better choice for base-sensitive substrates.

In conclusion, a PO-assisted Sonogashira cross-coupling reaction has been developed. The unique base-free feature of the current protocol has extended the scope of Sonogashira reaction to some base-sensitive substrates. Other related transition-metal-catalyzed cross-coupling reactions might also benefit from the current PO strategy. The research results along these lines will be reported in due course.

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

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(5) (a) For an example of Sonogashira reaction with Et_3N as both the solvent and the base in preparing diphenylacetylene, see: Perner, R. J.; Gu, Y.-G.; Lee, C.-H.; Bayburt, E. K.; McKie, J.; Alexander, K. M.; Kohlhaas, K. L.; Wismer, C. T.; Mikusa, J.; Jarvis, M. F.; Kowaluk, E. A.; Bhagwat, S. S. *J. Med. Chem.* **2003**, *46*, 5249. (b) **General Procedure**: The Batey Pd-carbene complex **1** (2.5 mol%), CuI (5 mol%), Ph_3P (2.5 mol%) and DMF (2 mL) were added to a dry 10-mL septum-capped round-bottomed flask under a nitrogen atmosphere. Aryl iodide (2 mmol), alkyne (110 mol%), and PO (5 equiv) were then added to the above mixture. While the mixture was stirred, the flask was cooled to –78 °C, vacuumed, and charged with nitrogen. This process was repeated for three times. After the mixture was warmed to 25 °C, stirring was continued at that temperature for 48 h. The mixture was diluted with H_2O and extracted with E_2O. The organic extracts were combined, washed with brine, dried ($MgSO_4$), filtered, and concentrated to give a residue, which was purified by flash column chromatography on silica gel.

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