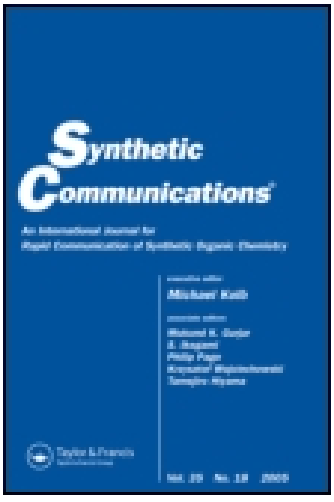

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Copper- and Amine-Free Sonogashira Reaction of *N,N*-Disubstituted Propargylamine: Synthesis of Substituted Aryl Propargylamine

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Abstract: A copper- and amine-free Sonogashira reaction of *N,N*-disubstituted propargylamine (DEP) is reported. The procedure was mild and tolerated a series of aryl bromides, affording the substituted aryl propargylic amines in good to excellent yield.

Keywords: Aryl bromide, copper free, palladium, propargylamine, Sonogashira reaction

Palladium-catalyzed coupling of terminal alkynes with aryl or alkenyl iodides, which was described for the first time by Sonogashira et al. in 1975, is one of the most straightforward methods for the preparation of aryl alkynes and conjugated enynes.[1] Usually the Sonogashira coupling is carried out in the presence of catalytic amounts of a palladium complex as well as copper iodide in an amine as solvent to obtain good yield.[2]

Propargyl amines are not only synthetically important intermediates for preparation of various nitrogen compounds such as (*E*)-allylamines, pyrroles, β-lactams, and pyrrolidines[3] but are also biologically important.[4] Substituted aryl propargylic amines bearing various substituents in the aromatic ring display strong inhibitory activities toward several enzymes. There are some routes to propargylamine, including amination of propargylic electrophiles,[5] $TiCl_4$-mediated amination of propargyl ester,[6] addition of 1-alkynes to preformed imines,[7] or Sonogashira reaction of aryl halides with propargylamine.[8]

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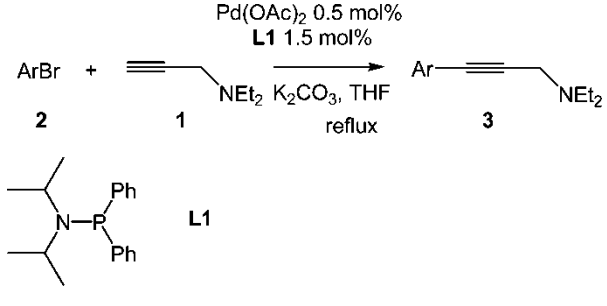
However, the copper-free Sonogashira reaction of propargylamine was rarely reported. The Cu(I) acetylides formed in situ could undergo oxidative dimerization to give diaryldiacetylenes when they are exposed to air or an oxidant (a reaction known as the Glaser coupling).[9] These by-products are generally difficult to separate from the desired products. Moreover, only a few results were reported using less reactive aryl bromides.[10]

Cheng et al. reported that aminophosphine **L1**, which is air-stable and facile to prepare was a highly efficient ligand in the Suzuki cross-coupling reaction and Sonogashira reaction.[11] Accordingly, we envisioned enlarging the application scope of the ligand in the Sonogashira reaction. Herein, we report a copper- and amine-free Sonogashira reaction between aryl bromides and *N,N*-diethyl propargylamine (DEP) employing aminophosphine ligands (Scheme 1).

For the study, based on Zhang's results,[11] THF was chosen as the solvent and potassium carbonate as the base. The reaction was run at 65°C under nitrogen in the presence of a combination of $Pd(OAc)_2$ and **L1** as catalyst.

Treatment of a mixture of **1** (334 mg, 3 mmol), 4-bromoanisole **2a** (374 mg, 2 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), and L1 (8.6 mg, 0.03 mmol) in dry THF (5 mL) at 65°C under an inert atmosphere for 8 h produced the desired product **3a** in 86% yield. This is a promising result, because no copper salt and amine was required. Then a series of aryl bromides were tested in the reaction conditions. Results are summarized in Table 1.

All of the aryl bromides substrates processing electron-donating and electron-withdrawing groups worked well under the reaction conditions in the absence of CuI or amine. For example, the aryl bromides, which contain electron-donating substituents, were considered reluctant to oxidative addition to Pd(0); however, 86% and 90% of isolated product (**3a**, **3b**) were obtained for the coupling reaction, respectively (Table 1, entries 1, 2). The *ortho* group in the aryl bromide had some effect in the reaction, although the yield slightly decreased to 81% for 2-bromo-*m*-xylene (**2h**) (Table 1, entry 8), the reaction became sluggish, and more catalyst load was required. For the 1-bromonaphthalene (**2d**), which is electron rich and a hindrance in the *ortho* position, the yield reached 78% (Table 1, entry 4). The 4-bromobenzaldehyde (**2f**) and 3-bromobenzaldehyde (**2g**) were not



Scheme 1.

Table 1. Sonogashira reaction of *N,N*-disubstituted propargylamine

Entry	Aryl bromide	Yield (%)[a]
1	4-Bromoanisole	86
	2a	**3a**
2	3-Bromoanisole	90
	2b	**3b**
3	Bromobenzene	88
	2c	**3c**
4	1-Bromonaphthalene	78[b]
	2d	**3d**
5	4-Bromotoluene	76
	2e	**3e**
6	4-Bromobenzaldehyde	89
	2f	**3f**
7	3-Bromobenzaldehyde	86
	2g	**3g**
8	2-Bromo-*m*-xylene	81[b]
	2h	**3h**
9	2-Bromomesitylene	63[b]
	2i	**3i**
10	2-Bromopyridine	59[b]
	2j	**3j**

[a]Isolated yield, all reactions were run with aryl bromide (2 mmol), DEP (3 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), K_2CO_3 (828 mg, 6 mmol), and **L1** (8.6 mg, 0.03 mmol) in 5 ml of THF at 65°C for 8 h.

[b]$Pd(OAc)_2$ (11.2 mg, 0.05 mmol) and **L1** (43.1 mg, 0.15 mmol).

sensitive in the reaction conditions, affording the desired products in 89% and 86% yield, respectively (Table 1, entries 6, 7).

In conclusion, we developed a copper- and amine-free Sonogashira reaction of *N,N*-disubstituted propargylamine. It is a facile and mild way to synthesis substituted aryl propargylamine. Aminophosphine was used as the ligands. The ligand is facile to be prepared from commercial available material and is air stable.

EXPERIMENTAL

General

All reactions and manipulations were conducted under a nitrogen atmosphere using standard Schlenk techniques. Column chromatography was performed

using EM silica gel 60 (300–400 mesh) or Al_2O_3; ^1H NMR, and ^{13}C NMR were recorded on a 300 MHz spectrometer. Chemical shifts were reported in ppm downfield from tetramethylsilane with the solvent resonance as the internal standard.

Materials

THF was distilled from sodium-diphenylacetone prior to use. K_2CO_3, aryl bromides, and DEP were used directly as obtained commercially unless otherwise noted.

General Procedure for the Sonogashira Reaction

Under a nitrogen atmosphere, a Schlenk reaction tube was charged with DEP (334 mg, 3 mmol), aryl bromide (2 mmol), K_2CO_3 (828 mg, 6 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), L1 (8.6 mg, 0.15 mmol), and THF (5 mL). The reaction tube was purged with N_2 under a dry ice bath. After the mixture was heated at 65°C for 8 h, the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on a silica gel (pre-eluted with 5% trimethylamine in petroleum) to give the product **3**.

Data

3a 1-(*p*-Anisyl)-3-(diethylamino)propyne[10a]

^1H NMR (300 MHz, $CDCl_3$) δ 7.33 (d, $J = 8.7$ Hz, 2H), 6.78 (d, $J = 8.7$ Hz, 2H), 3.76 (s, 3H), 3.59 (s, 2H), 2.58 (q, $J = 7.2$ Hz, 4H), 1.08 (t, $J = 7.2$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.2, 133.3, 115.4, 113.7, 84.6, 82.7, 55.1, 47.1, 41.4, 23.0.

3b 1-(*m*-Anisyl)-3-(diethylamino)propyne

^1H NMR (300 MHz, $CDCl_3$) δ 7.25–7.21 (m, 1H), 7.19–7.16 (m, 1H), 7.02–6.99 (m, 1H), 6.95–6.83 (m, 1H), 3.76 (s, 3H), 3.62 (s, 2H), 2.62 (q, $J = 7.2$ Hz, 4H), 1.11 (t, $J = 7.2$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.2, 129.2, 124.2, 120.1, 116.7, 114.6, 84.8, 82.3, 55.1, 47.1, 41.7, 12.5. MS (EI): m/z 217 (M^+), IR (neat, cm^{-1}): 3067 (w), 2967 (s), 2823 (s), 2358 (m), 1590 (s), 1474 (s), 1120 (m), 1124 (s), 1094 (s). Anal. calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.14; H, 8.66; N, 6.64.

3c 1-Phenyl-3-(diethylamino)propyne[10a]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43–7.40 (m, 2H), 7.29–7.25 (m, 3H), 3.64 (s, 2H), 2.63 (q, $J = 7.2$ Hz, 4H), 1.11 (t, $J = 7.2$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 131.7, 128.2, 127.9, 123.4, 84.9, 84.5, 47.3, 41.5, 12.6.

3d 1-Naphthalenyl-3-(diethylamino)propyne[10a]

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.34 (d, $J = 8.1$ Hz, 1H), 7.85–7.81 (m, 2H), 7.67–7.65 (m, 1H), 7.57–7.50 (m, 2H), 7.43–7.40 (m, 1H), 3.82 (s, 2H), 2.73 (q, $J = 7.2$ Hz, 4H), 1.18 (t, $J = 7.2$ Hz, 6H);. ^{13}C NMR (75 MHz, $CDCl_3$): δ 133.3, 133.1, 130.5, 128.3, 128.2, 126.6, 126.3, 126.2, 125.1, 89.3, 83.1, 47.5, 41.7, 12.7.

3e 3-(Diethylamino)-1-(*p*-tolyl)propyne[10a]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, $J = 8.1$ Hz, 2H), 7.08 (d, $J = 8.1$ Hz, 2H), 3.63 (s, 2H), 2.63 (q, $J = 7.2$ Hz, 4H), 2.33 (s, 3H), 1.11 (t, $J = 7.2$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.9, 131.6, 128.9, 120.3, 85.0, 83.6, 47.3, 41.5, 21.4, 12.6.

3f 4-(3-(Diethylamino)prop-1-ynyl)benzaldehyde[10a]

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.97 (s, 1H), 7.79 (d, $J = 8.3$ Hz, 2H), 7.53 (d, $J = 8.3$ Hz, 2H), 3.65 (s, 2H), 2.61 (q, $J = 7.2$ Hz, 4H), 1.11 (t, $J = 7.2$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.3, 135.3, 132.2, 129.7, 129.4, 89.2, 84.3, 47.3, 41.6, 12.5.

3g 3-(3-(Diethylamino)prop-1-ynyl)benzaldehyde

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.98 (s, 1H), 7.91 (s, 1H), 7.80–7.78 (m, 1H), 7.67–7.64 (m, 1H), 7.49–7.46 (m, 1H), 3.65 (s, 2H), 2.64 (q, $J = 7.2$ Hz, 4H), 1.12 (t, $J = 7.2$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.5, 137.2, 136.4, 132.9, 128.9, 128.7, 124.6, 91.3, 83.4, 47.3, 41.4, 12.5. MS (EI): m/z 215 (M^+), IR (neat, cm^{-1}): 3067 (w), 2971 (m), 2819 (m), 2357 (m), 1707 (s), 785 (s). Anal. calcd for $C_{14}H_{17}NO$: C, 77.10; H, 7.96; N, 6.51. Found: C, 77.02; H, 7.74; N, 6.57.

3h 3-(2,6-Dimethylphenyl)-*N,N*-diethylprop-2-yn-1-amine

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06–7.03 (m, 3H), 3.77 (s, 2H), 2.66 (q, $J = 7.2$ Hz, 4H), 2.43 (s, 6H), 1.14 (t, $J = 7.2$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.1, 127.3, 126.6, 123.2, 92.5, 82.5, 47.4, 41.4, 21.3, 12.7. MS (EI): m/z 215 (M^+), IR (neat, cm^{-1}): 3064 (w), 2966 (s), 2819

(m), 2926 (m), 2357 (s), 1677 (m), 1460 (s). Anal. calcd for $C_{15}H_{21}NO$: C, 83.67; H, 9.83; N, 6.50. Found: C, 83.51; H, 9.62; N, 6.64.

3i *N,N*-Diethyl-3-mesitylprop-2-yn-1-amine[10a]

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.85 (s, 2H), 3.75 (s, 2H), 2.63 (q, $J = 7.2$ Hz, 4H), 2.39 (s, 6H), 2.27 (s, 3H), 1.13 (t, $J = 7.2$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.0, 137.2, 127.5, 120.2, 91.6, 82.6, 47.4, 41.4, 21.2, 21.1, 12.8.

3j *N,N*-Diethyl-3-(pyridin-2-yl)prop-2-yn-1-amine[10a]

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54–8.52 (m, 1H), 7.59–7.57 (m, 1H), 7.39–7.36 (m, 1H), 7.19–7.15 (m, 1H), 3.65 (s, 2H), 2.62 (q, $J = 7.2$ Hz, 4H), 1.14 (t, $J = 7.2$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.8, 143.3, 136.0, 127.1, 122.6, 84.9, 84.6, 47.4, 41.3, 12.6.

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