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Cross-coupling of arylboronic acids with terminal alkynes in air

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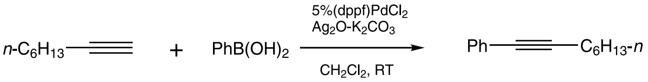
Abstract—A new procedure has been developed for constructing arylalkynes through cross-coupling of terminal alkynes with arylboronic acids catalyzed by a palladium–silver system under mild conditions.

Alkyne moieties are widely found in natural products and artificial organic materials.[1] Sonogashira cross-coupling has dominated the methodologies for construction of aryl alkynes.[2] There are some drawbacks with the traditional Sonogashira coupling procedure. For example, it does not work well for electron-deficient alkynes. So, many efforts have been devoted to develop modifications or alternatives.[3] Recently, an umpolung complement to Sonogashira procedure has been reported using thioalkynes and boronic acids under non-basic condition.[4] However, thioalkynes have to be prepared separately. We report here a palladium-catalyzed, silver-assisted procedure for constructing arylalkynes by direct cross-coupling of boronic acids with terminal alkynes in air.

Silver(I) oxide has been known to activate C–B bond, thus accelerating the transmetalation between $RB(OH)_2$ and palladium species.[5] When octyne and $PhB(OH)_2$ were subjected to treatment with Ag_2O-Pd(dppf)Cl_2 in the presence of excess of K_2CO_3 in CH_2Cl_2 or toluene under N_2 the desired cross-coupling proceeded smoothly. In fact, the above cross-coupling tolerated air and water although protodeborylation of boronic acids happened in some cases.



An initiation period was observed for the cross-coupling, so no product was detected before a reddish–brown color appeared. Oxidative silver salts and bases were crucial for the success of the cross-coupling. Thus AgOAc failed to work without excess K_2CO_3, while $AgNO_3$ promoted only homo-coupling of $PhB(OH)_2$. However, in the presence of excess of K_2CO_3 both these silver salts gave results similar to that obtainable from Ag_2O (Table 1, entries 2, 7 and 8). Non-oxidative silver salt, such as Ag_3PO_4, displayed no activity regardless whether there was K_2CO_3 or not. Ag_2CO_3 worked only at elevated temperature (Table 1, entry 5). Ag_2O (1 equiv.) with excess K_2CO_3 required much longer reaction time and other metal oxides showed no reactivity (Cu_2O) or less efficiency (HgO). Palladium sources such as $(PPh_3)_2PdCl_2$ and $PdCl_2(Bmim)_2$ (Bmim = *N*-methyl-*N′*-butylimidazol-2-ylidene) were also tested as catalysts. The former was less efficient and the later decomposed when exposed to Ag(I) salts. After much experimentation, a combination of 5% equiv. Pd(dppf)Cl_2, 2 equiv. Ag_2O and 5 equiv. K_2CO_3 was found to gave the best performance.[6]

Table 1. Cross-coupling of octyne with phenylboronic acid[a]

Entry	Catalyst	Additive	Solvent	Yield (%)[b]
1	$(PPh_3)_2PdCl_2$	Ag_2O	CH_2Cl_2	56
2	(dppf)$PdCl_2$	Ag_2O	CH_2Cl_2	89
3	(dppf)$PdCl_2$	Ag_2O	THF	60
4	(dppf)$PdCl_2$	Ag_2O	Toluene	87
5	(dppf)$PdCl_2$	Ag_2CO_3[c]	Toluene	70
6	(dppf)$PdCl_2$	HgO[c]	Toluene	49
7	(dppf)$PdCl_2$	AgOAc[d]	CH_2Cl_2	80
8	(dppf)$PdCl_2$	$AgNO_3$[d]	CH_2Cl_2	85
9	(dppf)$PdCl_2$	Ag_3PO_4	CH_2Cl_2	Trace

[a] Reactions were run with 1.1 equiv. $PhB(OH)_2$ for 20–30 h in air and at 25°C.

[b] Isolated yields.

[c] Heated at 60°C.

[d] No cross-coupling without K_2CO_3.

Keywords: cross-coupling; alkyne; arylboronic acid; palladium; silver.

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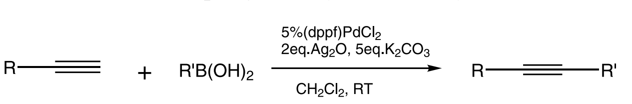
Table 2. Cross-coupling of alkynes with arylboronic acids



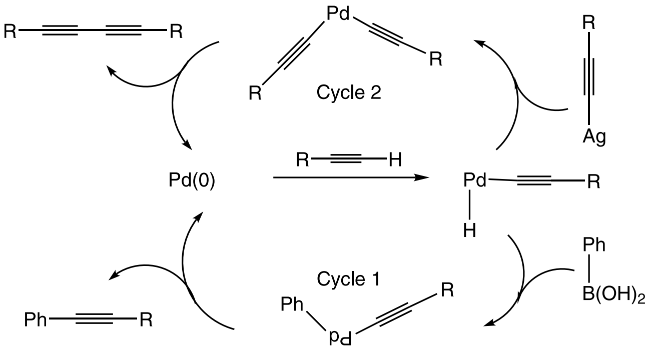
1a-1h

Entry	RC≡CH	R′-B(OH)$_2$	Product	Yield (%)[a]
1	n-C$_6$H$_{13}$	Ph	**1a**	90
2	n-C$_6$H$_{13}$	p-EtO$_2$CC$_6$H$_4$	**1b**	81
3	n-C$_6$H$_{13}$	p-MeOC$_6$H$_4$	**1c**	87
4	CH$_2$OBn	Ph	**1d**	87
5	EtO$_2$C	Ph	**1e**	86
6	EtO$_2$C	p-EtO$_2$CC$_6$H$_4$	**1f**	78
7	Ph	Ph	**1g**	30[b]
8	n-C$_6$H$_{13}$	n-C$_4$H$_9$	**1h**	0[c]

[a] Isolated yields.

[b] Biphenylbutadinye **2a** (60%) and biphenyl (10%) were obtained.

[c] 7,9-Hexadecyldiyne **2b** was isolated in 95% yield.



Scheme 1. A plausible mechanism for the Pd–Ag catalyzed cross-coupling of arylboronic acids with alkynes.

Typical electron donor (MeO) or withdrawing groups (CO$_2$Me) on the arylboronic acid component showed little effect on the cross-coupling reaction (Table 2, entries 2 and 3). It is noteworthy that the electron-deficient alkyne, ethyl propiolate, also gave the desired cross-coupling product in good yield since the traditional Sonogashira coupling procedure leads to low yields for electron-deficient alkynes. However, PhC≡CH tended to self-couple during cross-coupling with PhB(OH)$_2$ (Table 2, entry 7). Alkylboronic acid, such as BuB(OH)$_2$, was inert under the condition. So only homocoupling of the alkyne occurred for 1-octyne and BuB(OH)$_2$ (Table 2, entry 8).[7]

A plausible mechanism for the cross-coupling is shown in Scheme 1. The precursor of catalytic species, palladium(II) was first reduced to palladium(0) by arylboronic acid or alkynylsilver (I) formed in situ. The key role of Ag$_2$O in the mechanism is probably to activate the alkynylpalladium complex, thus facilitating the transmetalation of aryl group from arylboronic acid. Through the mechanism, cycle 1 provides cross-coupling products while homo-coupling of alkynes takes place through cycle 2. Both cycles 1 and 2 begin with C–H oxidative addition of terminal alkyne to Pd(0) species,[8] followed by transmetalation from boron or alkyne respectively, so they should be competitive. When transmetalation from boron was much slower than from alkyne, such as in the case of BuB(OH)$_2$, homo-coupling of the alkyne would occur. If they were comparable the selectivity of both cross- and homo-coupling would be low and a mixture of homo- and cross-coupling products would be produced, such as in the case of PhC≡CH with PhB(OH)$_2$.

In conclusion, an unprecedented generally efficient procedure catalyzed by a palladium–silver system for cross-coupling of arylboronic acids with alkynes under mild conditions has been developed. The umpolung procedure to the traditional Sonogashira coupling worked well for both electron-rich and -deficient alkynes. Investigation of the scope and utility of the procedure in synthesis is in progress in our laboratory.

Acknowledgements

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6. *Representative procedure for the cross-coupling*: To a solution of alkyne (1.0 mmol) and boronic acid (1.1 mmol) in 10 mL CH$_2$Cl$_2$ was added 0.05 equiv. (dppf)PdCl$_2$ (35 mg, 0.05 mmol) followed by 5 equiv. K$_2$CO$_3$ (0.7 g, 5.0 mmol) and 2.5 equiv. Ag$_2$O (0.6 g, 2.5 mmol,). After the mixture was stirred for 3–5 min a reddish–brown color developed. The resulting deep brown mixture was stirred at room temperature (25°C) until no starting material was detected (20–30 h). Then the mixture was filtered and filtrate was evaporated under reduced pressure. The crude products were purified by flash chromatography or PTLC. All known compounds were identified by comparing their ^{1}H

NMR with those reported in the literature. The analytical data for new compounds are as follows:

1c: ^{1}H NMR (500 MHz, CDCl$_3$, 25°C) ppm: 7.30 (d, 2H, J=4.5 Hz); 6.80 (d, 2H, J=4.0 Hz,); 3.78 (s, 3H, OCH$_3$), 2.45 (t, 2H, J=3.5 Hz, CH$_2$); 1.60–1.70 (m, 2H); 1.45–1.50 (m, 2H), 1.30–1.40 (m, 4H), 0.95 (t, J= 3.5 Hz, 3H, CH$_3$). ^{13}C NMR: 159.7, 133.5, 117.1, 114.5, 89.4, 81.0, 55.9, 32.1, 29.6, 29.3, 23.2, 20.1, 14.7. EI-MS, *m*/*z* (relative, %): 216 (65.0) [M$^+$], 187 (26.0) [M−29]$^+$, 173 (48.0), 145 (100.0). Elemental analyses for $C_{15}H_{20}O$: Found: C, 83.60; H, 9.18. Required: C, 83.29; H, 9.32.

1d: ^{1}H NMR (300 MHz, CDCl$_3$, 25°C) ppm: 7.30–7.50 (m, 10H, Ph); 4.71 (s, 2H, OCH$_2$), 4.41 (s, 2H, OCH$_2$). ^{13}CNMR: 137.5, 131.7, 128.4, 128.2, 128.0, 127.8, 122.6, 86.4, 85.1, 71.6, 57.8. EI-MS, *m*/*z* (relative, %): 222 (2.0) [M$^+$], 221 (5.0) [M−1] $^+$, 193 (29.0), 115 (100.0), 91 (39.0). Elemental analyses for $C_{16}H_{14}O$: Found: C, 86.13; H, 6.27. Required: C, 86.45; H, 6.35.

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