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Palladium-Catalyzed Cross-Coupling of Aryl Electrophiles with Dimethylalkynylaluminum Reagents

Baomin Wang, Martine Bonin,* and Laurent Micouin*

Laboratoire de Chimie Thérapeutique, UMR 8638 associée au CNRS et à l'Université René Descartes, Faculté des Sciences Pharmaceutiques et Biologiques,
4 av de l'Observatoire, 75270 Paris Cedex 06, France

laurent.micouin@univ-paris5.fr

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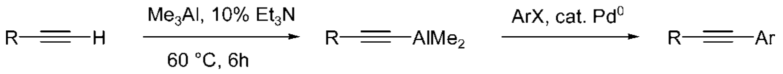
ABSTRACT

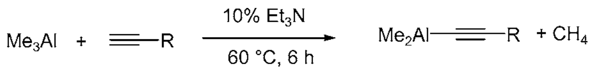


$$R{-}{\equiv}{-}H \xrightarrow[60\ °C,\ 6h]{Me_3Al,\ 10\%\ Et_3N} R{-}{\equiv}{-}AlMe_2 \xrightarrow{ArX,\ cat.\ Pd^0} R{-}{\equiv}{-}Ar$$

Alkynyldimethylaluminum reagents are easily available from terminal akynes and trimethylaluminum via a triethylamine-catalyzed metalation. These compounds can react with various aromatic and heterocyclic halides in the presence of palladium in a fast and efficient way. This catalyzed cross-coupling reaction provides a simple entry to numerous internal alkynes, using a readily available, inexpensive, and nontoxic metalating agent.

The Pd-catalyzed alkynylation[1] is now one of the most general and reliable methods for the synthesis of alkynes, which are known to be useful building blocks for many organic preparations. The Heck and Sonogashira couplings can be performed with terminal alkynes and have found numerous applications.[2] In some cases, however, significant alkyne homodimerization can be encountered, leading to troublesome purifications and low yield of isolated cross-coupled product. The use of preformed metalated alkynes, especially those containing Zn (Negishi coupling),[3] Sn (Stille coupling),[4] and B (Suzuki coupling)[5] can generally overcome this problem. These reactive species are usually prepared via a deprotonation step by a strong base followed by transmetalation of the alkynyllithium or -sodium intermediate. Some examples of the direct preparation of metallic acetylides from terminal alkynes with metals other than alkali have also been reported. In these cases, the metalation generally requires several equivalents of an organic base.[6]

As a part of our work on the use of mixed dialkylalkynylaluminum reagents in stereoselective transformations,[7] we recently reported a straightforward access to these species by a base-catalyzed alumination of terminal alkynes (Figure 1).[8]



$$Me_3Al + {\equiv}{-}R \xrightarrow[60\ °C,\ 6\ h]{10\%\ Et_3N} Me_2Al{-}{\equiv}{-}R + CH_4$$

Figure 1. Triethylamine-catalyzed alumination of terminal alkynes.

This simple procedure does not require strong bases or a transmetalation step and uses widely available, nontoxic trimethylaluminum as a metalating agent.

Although the palladium-catalyzed coupling of alkenylalanes with various electrophiles is a classical procedure for the synthesis of stereodefined olefins,[9] the corresponding

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(1) For recent reviews, see: (a) Negishi, E.-I.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979. (b) Sonogashira, K. *J. Organomet. Chem.* **2002**, *653*, 46. (c) Negishi, E.-I. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., Ed.; Wiley-Interscience: New York, 2002; p 215.

(2) (a) Sonogashira, K. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., Ed.; Wiley-Interscience: New York, 2002; p 493. (b) Sonogashira, K. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; p 203.

(3) Negishi, E.-I. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., Ed.; Wiley-Interscience: New York, 2002; p 229. See also ref 1a.

(4) (a) Kosugi, M.; Fugami, K. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., Ed.; Wiley-Interscience: New York, 2002; p 263. (b) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1.

(5) (a) Suzuki, A. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., Ed.; Wiley-Interscience: New York, 2002; p 249. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

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reaction starting from alkynylalanes has been surprisingly less investigated. Despite one promising example of this reaction reported by Negishi in the early 1980s, the reactivity of aluminum acetylides in cross-coupling reactions has yet to be delineated, as outlined by this author in a recent review.[1,10]

We initially examined the cross-coupling reaction of dimethylheptynylaluminum with phenyl iodide and THF as a cosolvent with different precatalysts (Table 1). Best results were obtained with Pd^0 sources and dppf as a ligand, leading to a full conversion after 24 h (entry 7).

Table 1. Precatalyst Screen in the Cross-Coupling of Dimethylheptynylaluminum with Phenyl Iodide

$$\mathrm{PhI} + \mathrm{Pent{-}{\equiv}{-}AlMe_2} \xrightarrow[\text{THF, rt, 24 h}]{5\ \%\ \mathrm{Pd^0},\ \text{ligand}} \mathrm{Pent{-}{\equiv}{-}Ph}$$

entry	Pd^0, ligand	conversion (%)[a]
1	$Pd(PPh_3)_4$	<10
2	$Pd(PPh_3)_2Cl_2 + 2PPh_3$	10
3	$Pd(OAc)_2 + 4PPh_3$	13
4	$Pd_2(dba)_3{\cdot}CHCl_3$	40
5	$Pd_2(dba)_3{\cdot}CHCl_3 + 4PPh_3$	<10
6	$Pd_2(dba)_3{\cdot}CHCl_3 + 2dppb$	10
7	$Pd_2(dba)_3{\cdot}CHCl_3 + 2dppf$	100

[a] Estimated by GC after 24 h.

The introduction of a cosolvent proved to have a dramatic influence on the rate of cross-coupling, as depicted in Table 2. Low conversion was observed in toluene, CH_2Cl_2, or DMF (entries 1−3), whereas a significant rate enhancement could be obtained with DME (entry 5) and, to a lesser extent, THF (entry 4).

Table 2. Cosolvent Influence in the Cross-Coupling of Dimethylheptynylaluminum with Phenyl Iodide

$$\mathrm{PhI} + \mathrm{Pent{-}{\equiv}{-}AlMe_2} \xrightarrow[5\ \%\ \text{dppf, heptane/}\textbf{solvent}]{2.5\ \%\ \mathrm{Pd_2(dba)_3.CHCl_3}} \mathrm{Pent{-}{\equiv}{-}Ph}$$

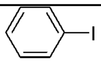
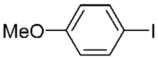
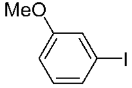
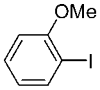
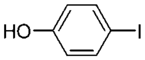
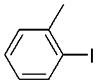
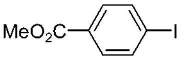
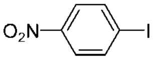
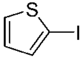
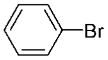
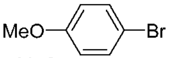
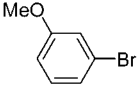
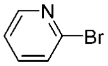
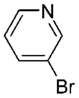
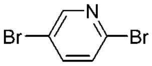
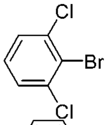
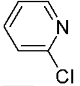
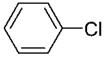
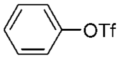
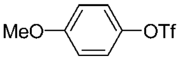
entry	cosolvent	time (h)	conversion (%)[a]
1	toluene	24	40
2	CH_2Cl_2	24	40
3	DMF	24	30
4	THF	8	100
5	DME	4.5	100

[a] Estimated by GC.

These optimized conditions were then used for a comparative study of different electrophiles (Table 3). With iodinated

Table 3. Electrophile Variation in the Cross-Coupling Reaction

$$\mathrm{ArX} + \mathrm{Pent{-}{\equiv}{-}AlMe_2} \xrightarrow[5\ \%\ \text{dppf, heptane/DME}]{2.5\ \%\ \mathrm{Pd_2(dba)_3.CHCl_3}} \mathrm{Pent{-}{\equiv}{-}Ar}$$

entry[a]	ArX	*T* (°C)/ time (h)	yield (%)[b]
1		20/ 4.5	100
2		20/ 2	99
3		20/ 3	100
4		85/ 1	100
5		20/ 3	95[c]
6		85/ 3	100
7		20/ 4	90
8		20/ 3	See text[d]
9		20/ 3	100
10		85/ 5	87
11		85/ 4	90
12		85/ 4	89
13		85/ 0.5	100
14		85/ 1	100
15		85/ 1	100[c]
16		85/ 24	60[e]
17		85/ 5	70
18		85/ 7	0
19		85/ 3	62
20		85/ 3	58

[a] Reaction conditions: ArX (1 equiv), Pent−≡AlMe$_2$ (1.5 equiv). [b] Isolated yield based on ArX. [c] Performed with 2 equiv of alanes. [d] Pent−≡−≡−Pent was obtained in 75% yield (based on Pent≡AlMe$_2$). [e] Conversion = 75%.

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(6) For a review on σ-metal alkynyl complexes, see: (a) Long, N. J.; Williams, C. K. *Angew. Chem., Int. Ed.* **2003**, *42*, 2586. For recent examples of Negishi coupling with in-situ-generated alkynylzinc derivatives, see: (b) Negishi, E.-I. Qian, M.; Zeng, F.; Anastasia, L.; Babisnski, D. *Org. Lett.* **2003**, *5*, 1597. (c) Anastasia, L.; Negishi, E.-I. *Org. Lett.* **2001**, *3*, 3113.

electrophiles, the expected coupling products were obtained in a few hours at room temperature in almost quantitative yields, with only traces of homocoupling product. A lower rate was observed with ortho-substituted iodides (entries 4 and 6), but this problem was overcome by performing the reaction at a higher temperature. Electron-donating (entries 2−4) as well as electron-withdrawing (entry 7) groups were well tolerated, and unprotected *p*-iodophenol could also be coupled if 2 equiv of alkynylalane were used (entry 5). Surprisingly, *p*-nitro iodobenzene did not lead to the expected product but cocatalyzed the alkyne homodimerization.[11]

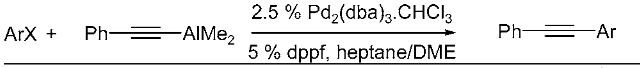
Bromo-derivatives could also react when performing the reaction at 85 °C and led to the corresponding cross-coupling products in a few hours and fairly good yields (entries 10−12).

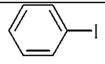
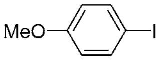
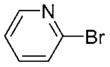
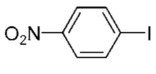
2-Substituted pyridine proved to be more reactive than its 3-substituted counterpart (entries 13 and 14), but 2,5-dibromopyridine could be quantitatively fully alkynylated using 2 equiv of alanes. Once again, steric hindrance led to lower reaction rates (entry 16), and no conversion could be observed when using aromatic chlorides (entry 18), except for the more reactive 2-chloropyridine (entry 17). Triflate seems to be a less efficient leaving group than bromide (entries 19 and 20).

Interestingly, despite the known Lewis acidity of aluminum, the presence of various basic sites (S, N, O, CO group) on the electrophiles did not significantly influence the scope of the coupling process.

Since the reactivity of aromatic alkynes could differ from the behavior of alkynes bearing aliphatic groups, the coupling reaction was then investigated with dimethylphenylacetylidealuminum (Table 4).

Table 4. Electrophile Variation in the Cross-Coupling Reaction with Dimethylphenylacetylidealuminum



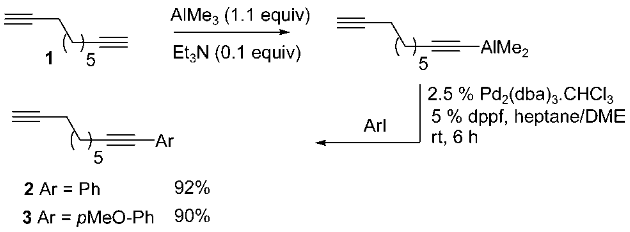
entry[a]	ArX	*T* (°C)/ time (h)	yield (%)[b]
1		20/ 6	100
2		20/ 5	99
3		85/ 1	92
4		20/ 4	See text[c]

[a] Reaction conditions: ArX (1 equiv), Pent$-\equiv$AlMe$_2$ (1.5 equiv). [b] Isolated yield based on ArX. [c] Ph$-\equiv-\equiv-$Ph was obtained in 70% yield (based on Ph$\equiv$AlMe$_2$).

Although slightly less reactive, this alkynylalane led to the corresponding alkyne in excellent yields (entries 1−3), except with *p*-nitro iodobenzene, which cocatalyzed the alkyne homodimerization.

Finally, the selective mono-cross-coupling of a terminal diyne was attempted. Thus, the metalation of 1,9-decadiyne **1** in the presence of 1.1 equiv of trimethylaluminum, followed by Pd-catalyzed coupling with aromatic halides, led to the terminal alkynes **2** and **3** in 92 and 90% yields, respectively (Scheme 1).

Scheme 1. Selective Mono-Cross-Coupling of Terminal Diyne **1**



In conclusion, the scope of the Pd-catalyzed alkynylation of aromatic and heteroaromatic electrophiles with mixed dimethylalkynylaluminum reagents appears to be broad. The preparation of reactive acetylides, using inexpensive, widely available, and nontoxic trimethylaluminum as a metal source via a triethylamine-catalyzed terminal metalation can provide a valuable alternative route to reactive acetylides in metal-catalyzed cross-coupling reactions. Efforts are currently being made to explore the scope of this reaction with functional alkynes as well as the exact mechanism of this palladium cross-coupling reaction.[12]

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(7) (a) Blanchet, J.; Bonin, M.; Chiaroni, A.; Micouin, L.; Riche, C.; Husson, H.-P. *Tetrahedron Lett.* **1999**, *40*, 2935. (b) Blanchet, J.; Bonin, M.; Micouin, L.; Husson, H.-P. *J. Org. Chem.* **2000**, *65*, 6423. (c) Blanchet, J.; Bonin, M.; Micouin, L.; Husson, H.-P. *Tetrahedron Lett.* **2001**, *42*, 3171. (d) Blanchet, J.; Bonin, M.; Micouin, L.; Husson, H.-P. *Eur. J. Org. Chem.* **2002**, 2598.

(8) Feuvrie, C.; Blanchet, J.; Bonin, M.; Micouin, L. *Org. Lett.* **2004**, *6*, 2333.

(9) Huo, S.; Negishi, E.-I. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., Ed.; Wiley-Interscience: New York, 2002; p 335.

(10) (a) Negishi, E.-I. *Acc. Chem. Res.* **1982**, *15*, 340. (b) Negishi, E.-I. *J. Organomet. Chem.* **2002**, *653*, 34. For the use of tetraalkynylaluminates in palladium-catalyzed cross-coupling with aryl bromides, see: (c) Gelman, D.; Tsvelikhovsky, D.; Molander, G. A.; Blum, J. *J. Org. Chem.* **2002**, *67*, 6287. For the use of mixed alkynylaluminum reagents in palladium-catalyzed cross-coupling with acyl chlorides, see: (d) Wakamatsu, K.; Okuda, Y.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2425.

(11) In this case, *p*-nitro iodobenzene probably behaves as an oxidant in a palladium-catalyzed Glaser-type homocoupling. This coupling does not occur without palladium catalyst. For a recent review on acetylenic homo- and cross-coupling reactions, see: Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2003**, *39*, 2632.

(12) **Typical Procedure.** The preparation of hept-1-ynyl-benzene (entry 1) is representative. Alane solution preparation: A dry and argon-flushed flask equipped with a magnetic stirrer and condenser was charged with a commercial trimethylaluminum solution (10 mL, 2 M in heptane) (CAUTION: trimethylaluminum is flammable), and triethylamine (0.28 mL, 2 mmol) was then added dropwise via a syringe. 1-Heptyne (2.36 mL, 18 mmol) was dropwise added 5 min later, and the reaction mixture was stirred at 60 °C for 6 h, until the gas evolution ceased. The prepared alane solution can be stored under argon in the dark for several days. Coupling reaction: Pd$_2$(dba)$_3$·CHCl$_3$ (11.9 mg, 0.0115 mmol), dppf (12.8 mg, 0.023 mmol), and the alane solution (0.5 mL, 0.70 mmol) were added sequentially to a dry Schlenk tube charged with PhI (51 μL, 0.46 mmol) and freshly distilled dry DME (3 mL). The reaction mixture was stirred at room temperature and monitored by GC. After completion, Et$_2$O (3 mL) and a 2 M aqueous solution of Rochelle's salt (3 mL) were added. After the solution was stirred for 10 min, the organic phase was separated, washed with water and brine, and dried over anhydrous magnesium sulfate, and the solvent was evaporated. Chromatographic purification on silica gel (eluent: cyclohexane) afforded 79.1 mg of hept-1-ynyl-benzene.

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Supporting Information Available: Analytical data for all new compounds and NMR spectra of all synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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