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Transition-Metal-Free Alkynylation of Aryl Chlorides

Thanh Truong and Olafs Daugulis*

Department of Chemistry, University of Houston, Houston, Texas 77204-5003, United States

olafs@uh.edu

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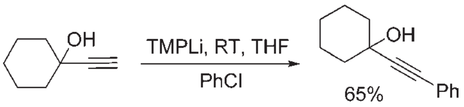
ABSTRACT



Two sets of conditions have been developed for a base-mediated, transition-metal-free alkynylation of aryl chlorides that proceeds via benzyne intermediates. The first set of conditions involves the use of TMPLi base in a pentane/THF mixture at 25 °C. The second set involves use of a metal alkoxide base in dioxane at elevated temperature. Reasonable functional group tolerance has been observed. Fluoro, trifluoromethyl, silyl, cyano, and alcohol functionalities are compatible with the reaction conditions.

Transition-metal-catalyzed formation of carbon–carbon bonds has become an indispensable tool in organic synthesis.[1] Specifically, the Sonogashira reaction, palladium- and copper-cocatalyzed formation of sp^2–sp carbon–carbon bonds between aryl halides and terminal alkynes, is one of the most important methods for the synthesis of substituted acetylenes.[2] However, trace residues of transition metals are often difficult to remove from final products that are used for pharmaceutical applications.[3] Consequently, it is advantageous to develop transition-metal-free cross-coupling reactions.[4] Several examples of such sp^2–sp carbon–carbon bond formation reactions have been described in the literature.[5] In most cases, however, either photochemical activation, preformed Grignard reagents, or activated aryl halides are required.

A few examples of benzyne reactions with alkynes have been reported. A mechanistically distinct publication describes an ene reaction of arynes with alkynes affording allenes.[6] The arynes are generated from 2-(trimethylsilyl)aryl triflates, and only alkynes possessing propargylic hydrogen substituents are reactive. Benzyne cycloadditions with alkynes have also been reported.[7] In an early mechanistic work, Roberts has investigated benzyne reactivity with a variety of nucleophiles such as fluorenyl, anilide, acetophenone enolate, and phenylacetylide.[8] Copper- and other transition-metal-catalyzed reactions of alkynes with arynes have been described.[9] However, a

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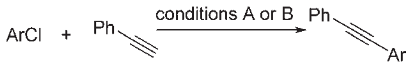
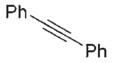
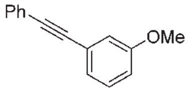
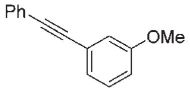
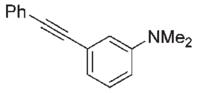
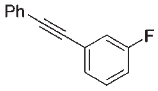
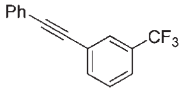
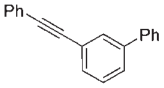
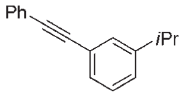
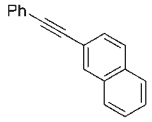
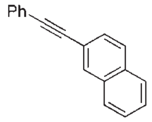
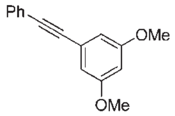
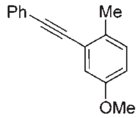
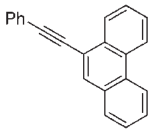
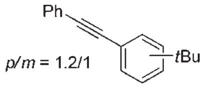
10.1021/ol2014736

Table 1. Alkynylation Scope with Respect to Aryl Chlorides[a]



entry	ArCl/conditions	product	yield, %
1	PhCl, A A B		91 61[b] 77
2	2-ClC$_6$H$_4$OMe A		75
3	3-ClC$_6$H$_4$OMe B		86
4	3-ClC$_6$H$_4$NMe$_2$ A		85
5	3-ClC$_6$H$_4$F B		82
6	3-ClC$_6$H$_4$CF$_3$, A B		70 74
7	(a) 2-BrC$_6$H$_4$Ph A (b) 2-FC$_6$H$_4$Ph, A		78 70
8	2-ClC$_6$H$_4$*i*Pr A		85
9	2-naphthyl chloride A		81
10	1-naphthyl chloride A		60
11	3,5-(MeO)$_2$C$_6$H$_3$Cl B		81
12	2-MeO-5-MeC$_6$H$_3$Cl A		75
13	9-chlorophenanthrene A		86
14[c]	4-*t*BuC$_6$H$_4$Cl A		90

[a] Method A: aryl halide (1.5–2.5 equiv), phenylacetylene (1 equiv), TMPLi (3–4 equiv), pentane/THF, 25 °C. Method B: aryl halide (2.6–3 equiv), phenylacetylene (1 equiv), *t*BuONa or *t*BuOK (7 equiv), dioxane, 106–135 °C. Yields are isolated yields of a pure major isomer unless otherwise noted, and reactions were run on a 0.5 mmol scale. See Supporting Information for details. [b] 1:1 ratio of PhCl and alkyne. [c] Isomer mixture; *m*/*p* ratio 1/1.2.

general procedure for aryl chloride alkynylation that proceeds via a benzyne mechanism has not been developed.

We have recently reported a direct transition-metal-free, base-mediated intermolecular arylation of heterocycles and arenes by aryl halides.[10] By employing hindered lithium amide bases in pentane/THF mixtures, thiophenes, furans, imidazoles, indoles, pyrroles, pyrazines, pyridines, and methoxybenzene derivatives can be arylated by aryl chlorides and fluorides. The reactions proceed via benzyne intermediates and are highly regioselective with respect to an arene coupling component. In this report, we expand the methodology to base-mediated alkynylation of aryl chlorides that can be thought of as a transition-metal-free Sonogashira coupling.

Two sets of reaction conditions were developed for the aryl chloride alkynylation. The first one employs a lithium 2,2,6,6-tetramethylpiperidide (LiTMP) base[11] in a pentane/THF mixture. Use of hindered LiTMP retards the reaction of benzyne with a base. The relative reactivity of the base and alkynyl anion with benzyne is modulated by employing a solvent where the amide base is sparingly soluble. This set of conditions is based on an earlier report for heterocycle arylation by aryl halides.[10] The second set of conditions involves heating a reaction mixture in dioxane in the presence of an alkoxide base and is based on a previously published intramolecular arylation of phenol derivatives proceeding via benzyne intermediates.[12] For most of the examples, both sets of conditions afford comparable yields.

The reaction scope with respect to aryl chlorides is presented in Table 1. Arylation of phenylacetylene by 2- and 3-chloroanisole affords 3-methoxydiphenylacetylene (entries 2 and 3). Both of the isomeric aryl chlorides form

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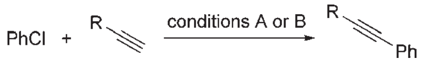
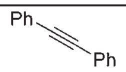
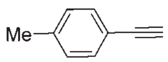
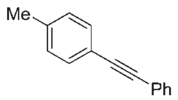
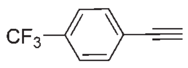
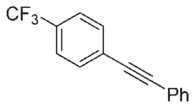
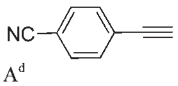
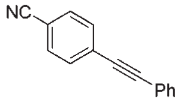
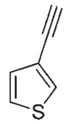
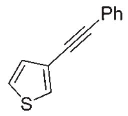
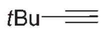
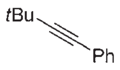
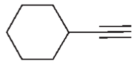
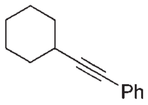
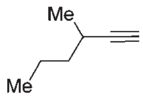
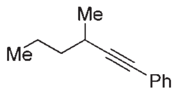
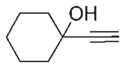
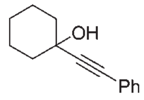
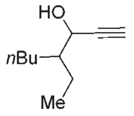
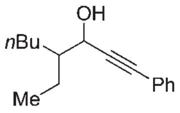
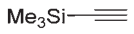
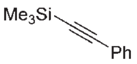
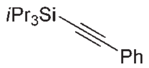
3-methoxybenzyne.[13] The following regioselective nucleophile addition to benzyne is explained in terms of ground-state polarization of the aryne by electron-withdrawing substituents and the energy that is required to distort the aryne into two possible transition states.[14] 3-Chlorodimethylaniline and 3-chlorobenzotrifluoride are reactive, and products are obtained in good yields (entries 4 and 6). For the latter substrate, both reaction conditions afford good yields. Interestingly, by employing the *t*BuONa base, it is possible to selectively substitute chloride in 3-fluorochlorobenzene (entry 5). For this substrate, use of the TMPLi base was not successful. In several cases, isomer mixtures are obtained. For 2-chlorocumene (entry 8), a 12/1 isomer mixture was obtained with the 3-isomer as a major product. The alkynylation of 1- and 2-chloronaphthalenes affords product as 5.4/1 and 11.6/1 isomer mixtures, with the 2-isomer of the product predominating (entries 9 and 10). The reported yields are those of a pure major isomer after purification by HPLC. 3,5-Dimethoxychlorobenzene, 3-chloro-4-methoxytoluene, and 9-chlorophenanthrene are reactive, and products are obtained in good yields (entries 11–13). If 4-chloro-*tert*-butylbenzene is used, a nearly 1/1 mixture of alkynylation product isomers is obtained (entry 14).

The reaction scope with respect to alkynes is presented in Table 2. Sodium acetylide can be used under both reaction conditions to form disubstitution products (entry 1). Substituted phenylacetylenes are reactive (entries 2–3). Cyano group is tolerated (entry 4). 3-Ethynylthiophene affords the product in good yield (entry 5). Many aliphatic alkynes can be used as coupling partners. *t*-Butylacetylene, cyclohexylacetylene, and 3-methyl-1-hexyne are reactive and couplings proceed in good yields (entries 6–8). However, for alkynes possessing propargylic hydrogens, careful temperature optimization is required to prevent base-mediated conversion to allene and method B could not be used due to high reaction temperature. Primary alkylacetylenes suffer extensive isomerization to allenes and acceptable yields could not be obtained. Tertiary and hindered secondary hydroxyl groups are tolerated (entries 9 and 10). Silyl group-containing alkynes are arylated in good yields and cleavage of the silyl substituent is not observed if TMPLi base is employed (entries 11 and 12).

Preliminary mechanistic investigations were performed. Thus, 3-chloroanisole and 4-methoxyphenylacetylene were heated in dioxane at 110 °C in the presence of 6 equiv of *t*BuOK and 6.5 equiv of *t*BuOD (Scheme 1). The H/D exchange conditions were chosen to mimic conditions B. Workup and isolation afforded the coupling product in 31% yield. Unreacted 3-chloroanisole was recovered in 25% yield. Analysis by ^{1}H NMR showed extensive incorporation of the deuterium label adjacent to methoxy and chloro substituents arising from the metalation–deuteration sequence in recovered chloroarene and the coupling product. Similar results were obtained in the reaction of 2-chloroanisole with 4-methoxyacetylene. Interestingly, *t*-BuOK is able to *ortho*-metalate nonactivated methoxyarenes as evidenced by deuteration of the *p*-methoxyphenyl group.

Table 2. Alkynylation Scope with Respect to Alkynes[a]



entry	alkyne/conditions	product	yield, %
1	Na acetylide (NaCCH) A[b] B[c]		 86 78
2	 A B		 87 75
3	 A B		 90 78
4	 A[d]		50
5	 B		73
6	 A B		 93 78
7[c]	 A		67
8[c]	 A		76
9	 A		65
10	 A		62
11	 A		85
12	 A		93

[a] Method A: PhCl (1.8–2 equiv), alkyne (1 equiv), TMPLi (3.2–4.4 equiv), pentane/THF, THF, or diethyl ether solvent, 25 °C. Method B: chlorobenzene (3.0 equiv), alkyne (1.0 equiv), *t*BuOK (7 equiv), dioxane, 106 °C. Yields are isolated yields, and reactions were run on a 0.5 mmol scale. See Supporting Information for details. [b] PhCl (4 equiv), TMPLi (5.6 equiv). [c] PhCl (5 equiv), *t*BuOK (8 equiv). [d] Reaction at −55 °C. [e] Reaction at −63 °C.

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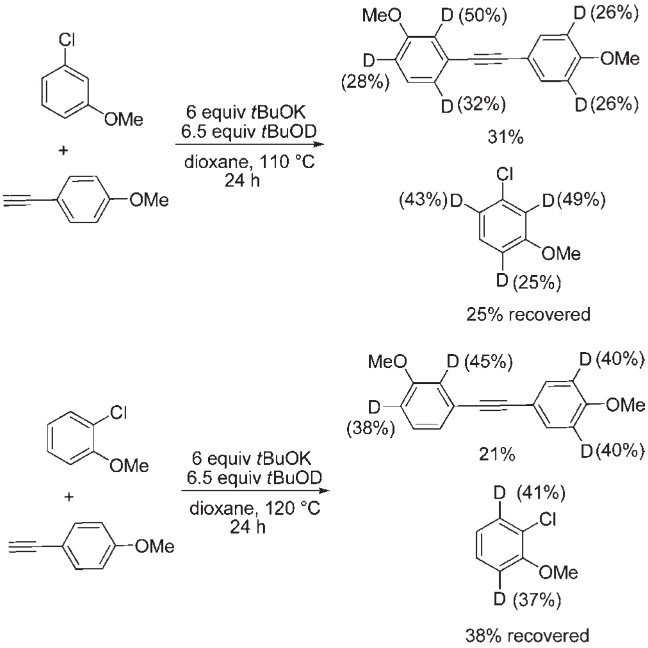
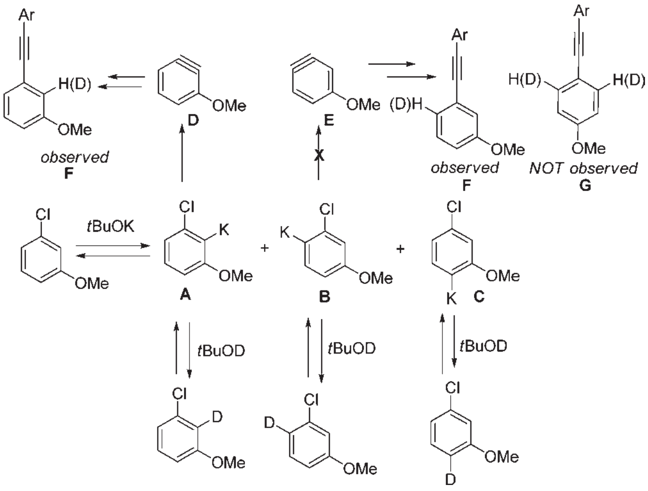
Scheme 1. Deuteration Experiments



Deuterium incorporation at 2- and 4-positions of recovered 3-chloroanisole is noteworthy. Deuterium incorporation in recovered 3-chloroanisole can be explained by the intermediacy of three isomers of the arylpotassium species: A, B, and C (Scheme 2). *ortho*-Aryne cannot be formed from C. Compound A can form only 3-methoxybenzyne D that regioselectively[14] reacts with an alkyne anion to form the observed product F. On the other hand, arylpotassium B could form 4-methoxybenzyne E that would react to afford two product isomers F and G in nearly equal amounts. Since compound G is not observed, and the deuteration experiment suggests that B is present in the reaction mixture, it must be concluded that aryne formation from A is more facile than aryne formation from B.[15] Collum and co-workers have measured the rate constants for benzyne formation from substituted aryllithiums and concluded that haloanisoles are especially reactive toward LiX elimination.[15d]

Scheme 2. Metalation–Benzyne Formation Sequence



In conclusion, two sets of conditions for base-mediated, transition-metal-free alkynylation of aryl chlorides have been developed. The first set of conditions involves the use of the hindered TMPLi base in a pentane/THF mixture at room temperature. The second set involves use of a metal alkoxide base in dioxane at elevated temperature. The method tolerates functional groups such as fluoro, trifluoromethyl, silyl, and cyano. Tertiary and secondary alcohols are also compatible with the reaction conditions.

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Supporting Information Available. Experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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