Cross-Coupling

DOI: 10.1002/anie.201003081

Metal-Mediated Oxidative Cross-Coupling of Terminal Alkynes: A Promising Strategy for Alkyne Synthesis**

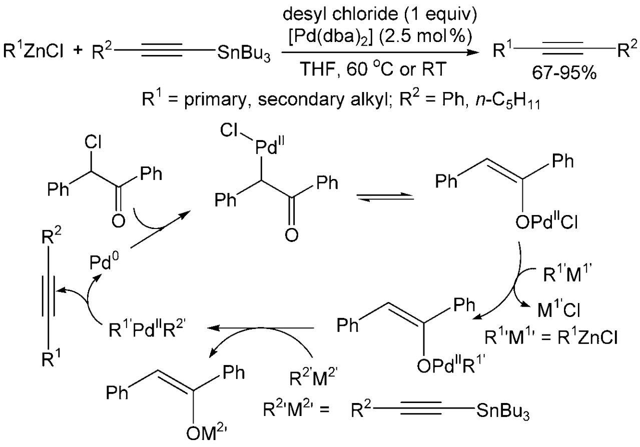
Zhihui Shao and Fangzhi Peng*

alkynes · cross-coupling · homogeneous catalysis · oxidation · synthetic methods

In memory of Keith Fagnou

Alkynes are a recurring functional group in numerous natural products, bioactive compounds, and organic materials as well as versatile intermediates in synthesis.[1] Among the methods for the incorporation of alkynyl functionality into organic molecules, metal-mediated cross-coupling reactions have a prominent role.[2] Arguably, one of the most valuable transformations in this context is the Sonogashira reaction involving terminal alkynes reacting with aryl or vinyl halides, and even alkyl halides as coupling partners.[3] A recent addition to the arsenal of cross-coupling-based synthesis of substituted alkynes is the "inverse Sonogashira coupling" involving metal-catalyzed direct alkynylation of arenes and heterocycles with alkynyl halides.[4] In view of the diverse requirements of C−C bond-forming reactions, the development of a complementary and, especially conceptually innovative strategy would be highly desirable. Recently, metal-mediated oxidative cross-coupling reactions of alkynyl metal reagents or terminal alkynes have emerged as a promising new strategy for access to various alkynes.

The first copper-mediated oxidative acetylenic homocoupling was pioneered by Glaser[5,6] in 1869, however, metal-mediated oxidative cross-coupling reactions of alkynyl metal reagents or terminal alkynes with other nucleophiles remain a significant challenge, largely because of the lack of solutions to overcome the undesired homocoupling under oxidative conditions. In 2006, Lei and co-workers reported a remarkable example of metal-mediated oxidative cross-coupling of alkynyl metal reagents in high yields and selectivity.[7] This protocol is a palladium-catalyzed oxidative cross-coupling of alkynylstannanes with alkyl zinc halides, using 2-chloro-2-phenylacetophenone (desyl chloride) as an oxidant (Scheme 1). Mechanistically, the oxidative addition of desyl chloride to the Pd^0 catalyst and subsequent tautomerization generates an O-bound palladium enolate chloride. This Pd^{II} species undergoes double transmetallation with zinc and tin reagents to produce the C_{sp}−Pd−C_{sp^3} intermediate which undergoes reductive elimination to yield the desired cross-coupling products (Scheme 1). This protocol constitutes a conceptually attractive method for the alkyl–alkynyl cross-coupling. Although two organometallic substrates are used in this protocol, this reaction has the following advantages compared to the Sonogashira coupling[8] of alkyl halides with terminal alkynes: 1) The simple catalyst precursor [Pd(dba)$_2$] (dba = dibenzylideneacetone)without extrogenous ligands showed the best results in this oxidative cross-coupling. However, the exogenous ligands such as N-heterocyclic carbenes[8a,b] and a pincer NN$_2$ ligand[8c] were required in the Sonogashira coupling of alkyl halides. In addition, copper co-catalysis was necessary in the Sonogashira reactions of unactivated alkyl halides;[8] 2) no additional base was required in this oxidative cross-coupling; 3) the aliphatic and aromatic alkynylstannanes with alkylzinc reagents, including β-hydrogen-containing primary and secondary alkylzinc reagents, can be smoothly coupled together in this oxidative cross-coupling. Notably, there is only one example of a Sonogashira coupling of both primary and secondary alkyl halides to date, however, the alkyne substrate scope is rather limited as arylacetylenes are reported to not be suitable substrates.[8b]



Scheme 1. Palladium-catalyzed cross-coupling of alkylzincs and alkynylstannanes. THF = tetrahydrofuran.

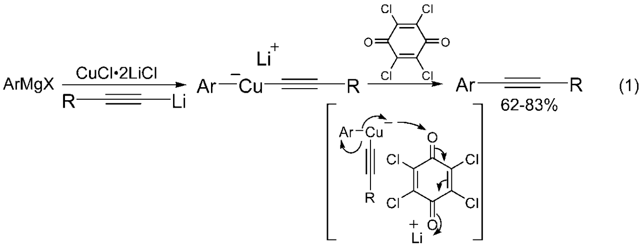
Later, Knochel and co-workers[9] described a novel oxidative cross-coupling from alkynyl lithium and aryl

---

[*] Prof. Dr. Z. Shao, F. Peng
Key Laboratory of Medicinal Chemistry for Natural Resource (Yunnan University), Ministry of Education, School of Chemical Science and Technology, Yunnan University, Kunming (China)
Fax: (+86) 871-503-5538
E-mail: zhihui_shao@hotmail.com

[**] This work was supported by the National Natural Science Foundation of China (20702044, 20962023) and the Program for New Century Excellent Talents in University (NCET-10-0907). We thank the referees for their valuable comments.

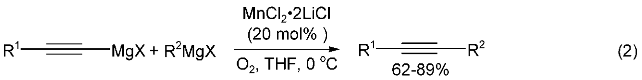
magnesium reagents. This protocol involved the use of stoichiometric amounts of CuI to generate a mixed lithium aryl(alkynyl) cuprate, which was subsequently oxidized by chloranil to give polyfunctional alkynes in good yields [Eq. (1)]. A key feature of this methodology is that halide-containing aryl and heteroaryl magnesium reagents as well as sterically hindered aryl magnesium reagents are all good substrates for this aryl–alkynyl coupling. Generally, the Sonogashira coupling fails for the selective monocoupling of dihaloarenes as well as for the coupling of sterically congested haloarenes.[10]



(1)

A drawback of the work from Knochel and co-workers[9] and from Lei and co-workers involving palladium-catalyzed oxidative cross-coupling of alkynylstannanes,[7] is that the use of chloranil or desyl chloride as the oxidant is not either environmentally or economically advantageous.

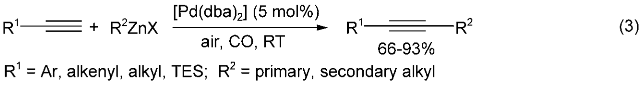
In 2009, an elegant metal-catalyzed oxidative cross-coupling-based synthesis of alkynes by using atmospheric oxygen as an oxidant[11] was disclosed by Cahiez et. al.[12] Various alkynyl and aryl magnesium halides were coupled successfully in the presence of $MnCl_2/O_2$ as a cheap and environmentally friendly catalytic system, providing a variety of arylacetylenes in good yields [Eq. (2)]. Notably, this protocol can also be extended to alkynyl–alkynyl, alkenyl–alkynyl, and aryl–aryl coupling. It was found that the selectivity between hetero- and homocoupling was highly dependent upon the nature of the two Grignard reagents. In most cases, the outcome of the reaction is not statistical and it is possible to obtain preferentially the heterocoupling products by using an excess of either alkynyl or aryl magnesium halides (2.5 equiv).



$$R^1{-}{\equiv}{-}MgX + R^2MgX \xrightarrow[O_2,\ THF,\ 0\ ^\circ C]{MnCl_2{\cdot}2LiCl\ (20\ mol\%)} \underset{62\text{-}89\%}{R^1{-}{\equiv}{-}R^2} \quad (2)$$

A disadvantage of the reactions above is the additional synthetic step needed to preform alkynyl metal reagents. From a practical viewpoint, direct cross-coupling of terminal alkynes and other nucleophiles using atmospheric oxygen or air as the oxidant, which avoids the use of "prefunctionalization" process is highly attractive. More recently, several groups reported the latest development of this methodology.

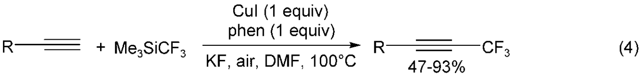
Lei and co-workers employed a palladium catalyst to couple terminal alkynes and alkylzinc reagents under aerobic conditions [Eq. (3); TES = triethylsilyl].[13] It was found that the addition of a certain amount of CO was critical in terms of enhancing the chemical yields and improving the selectivity. When only a dry air or oxygen atmosphere was used, heterocoupling products were produced in lower yields together with polymerization of the alkynes. In this palladium-catalyzed oxidative cross-coupling reaction, CO was speculated to serve as a π-acidic ligand to promote the $C_{sp}{-}C_{sp^3}$ reductive elimination.[14] Thus, various alkylacetylenes were obtained in good yields and excellent selectivity when a 10:1 ratio of air/CO and 3 equivalents of the alkyl zinc reagent were used.



$$R^1{-}{\equiv} + R^2ZnX \xrightarrow[air,\ CO,\ RT]{[Pd(dba)_2]\ (5\ mol\%)} \underset{66\text{-}93\%}{R^1{-}{\equiv}{-}R^2} \quad (3)$$

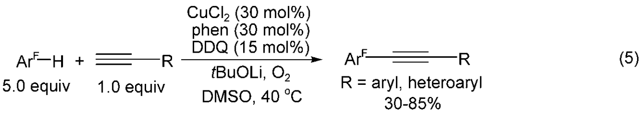
R^1 = Ar, alkenyl, alkyl, TES; R^2 = primary, secondary alkyl

The trifluoromethylation of terminal alkynes reported by Qing and co-workers[15] involved copper-mediated aerobic oxidative cross-coupling of terminal alkynes with $CuCF_3$ generated in situ from Me_3SiCF_3, KF, and CuI [Eq. (4); DMF = *N,N'*-dimethylformamide, phen = 1,10-phenanthroline]. This protocol provides a general, straightforward, and practically useful method for the preparation of trifluoromethylated acetylenes, which are versatile building blocks, in medicinal, agrochemical, and material science.



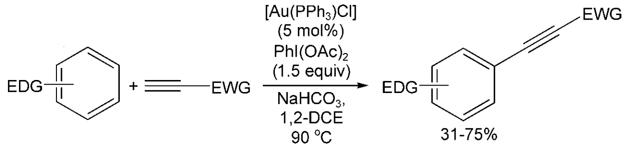
$$R{-}{\equiv} + Me_3SiCF_3 \xrightarrow[KF,\ air,\ DMF,\ 100^\circ C]{CuI\ (1\ equiv),\ phen\ (1\ equiv)} \underset{47\text{-}93\%}{R{-}{\equiv}{-}CF_3} \quad (4)$$

Another elegant example of metal-catalyzed oxidative cross-coupling for the synthesis of fluorinated alkynes through $C_{sp}{-}C_{sp^2}$ bond-forming reactions was recently reported by Su and co-workers.[16] This protocol involved copper-catalyzed aerobic oxidative cross-coupling of terminal alkynes with electron-deficient polyfluoroarenes (activated arenes) under strong basic conditions [Eq. (5); DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DMSO = dimethylsulfoxide]. Although this direct alkynylation of an aromatic C–H bond with terminal alkynes appears quite attractive, the reaction has only two or so turnover numbers based on Cu—that is barely catalytic. Fortunately, the catalyst used in this reaction is $CuCl_2$, which is inexpensive.



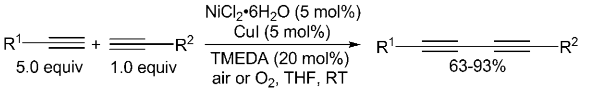
$$\underset{5.0\ equiv}{Ar^F{-}H} + \underset{1.0\ equiv}{{\equiv}{-}R} \xrightarrow[tBuOLi,\ O_2,\ DMSO,\ 40\ ^\circ C]{CuCl_2\ (30\ mol\%),\ phen\ (30\ mol\%),\ DDQ\ (15\ mol\%)} \underset{\substack{R\ =\ aryl,\ heteroaryl \\ 30\text{-}85\%}}{Ar^F{-}{\equiv}{-}R} \quad (5)$$

Almost simultaneously, Nevado and co-workers reported an unusual gold-catalyzed direct alkynylation of arenes with terminal alkynes by using $PhI(OAc)_2$ as an oxidant.[17] The most remarkable feature of this protocol is that the use of "deactivated" electron-deficient alkynes and electron-rich arenes as coupling partners [Eq. (6); DCE = dichloroethane].



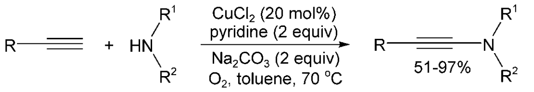
(6)

Recently, a metal-catalyzed oxidative heterocoupling of two different terminal alkynes was reported by Lei and coworkers [Eq. (7); TMEDA = *N,N,N′,N′*-tetramethyl-1,2-ethanediamine].[18] They employed $NiCl_2{\cdot}6H_2O/CuI$ as the catalyst, and used air or O_2 as the oxidant. By using an excess of one of the terminal alkyne substrates, a variety of unsymmetric conjugated diynes can be obtained in good yields. However, the use of 5 equivalents of one of the terminal alkynes would inevitably result in the formation of a considerable amount of homocoupled products.



(7)

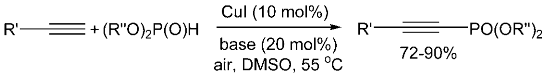
Metal-catalyzed oxidative coupling of terminal alkynes with heteroatom nucleophiles has also been developed. Two recent examples are highlighted here [Eq. (8)].[19] In the protocol reported by Stahl and co-workers,[19a] various nitrogen nucleophiles including cyclic carbamates, amides, and ureas as well as 4-substituted-*N*-alkyl benzenesulfonamides were smoothly coupled with terminal alkynes to give ynamides, which are of importance in organic synthesis.



(8)

The protocol from Han and co-workers[19b] provides a straightforward entry into synthetically and biologically important alkynylphosphonates employing terminal alkynes with H-phosphonates as coupling partners [Eq. (9)].

As a promising new strategy for the synthesis of alkynes, metal-mediated oxidative cross-coupling reactions of alkynyl metal reagents or terminal alkynes has shown remarkable advantages and enormous potentials in the construction of $C_{sp}-C_{sp^3}$, $C_{sp}-C_{sp^2}$, $C_{sp}-C_{sp}$, and C_{sp}–heteroatom bonds. Although some mechanistic details are still unexplored, the current advances promise continuing interest in and broad application of this method in modern synthesis.



(9)

Received: May 21, 2010
Revised: July 5, 2010

---

[1] *Acetylene Chemistry: Chemistry, Biology, and Material Science* (Eds.: F. Diederich, P. J. Stang, R. R. Tykwinski), Wiley-VCH, Weinheim, **2005**.
[2] *Metal-Catalyzed Cross-Coupling Reactions, Vol. 1 & 2* (Eds.: A. de Meijere, F. Diederich), 2nd ed., Wiley-VCH, Weinheim, **2004**.
[3] For a recent review, see: R. Chinchilla, C. Najera, *Chem. Rev.* **2007**, *107*, 874.
[4] For a recent highlight, see: A. S. Dudnik, V. Gevorgyan, *Angew. Chem.* **2010**, *122*, 2140; *Angew. Chem. Int. Ed.* **2010**, *49*, 2096.
[5] a) C. Glaser, *Ber. Dtsch. Chem. Ges.* **1869**, *2*, 422; b) C. Glaser, *Ann. Chem. Pharm.* **1870**, *154*, 137.
[6] For a review on acetylenic coupling, see: P. Siemsen, R. C. Livingston, F. Diederich, *Angew. Chem.* **2000**, *112*, 2740; *Angew. Chem. Int. Ed.* **2000**, *39*, 2632.
[7] a) Y. Zhao, H. Wang, X. Hou, Y. Hu, A. Lei, H. Zhang, L. Zhu, *J. Am. Chem. Soc.* **2006**, *128*, 15048; b) L. Jin, Y. Zhao, H. Wang, A. Lei, *Synthesis* **2008**, 649.
[8] a) E. Eckhardt, G. Fu, *J. Am. Chem. Soc.* **2003**, *125*, 13642; b) G. Altenhoff, S. Wurtz, F. Glorius, *Tetrahedron Lett.* **2006**, *47*, 2925; c) O. Vechorkin, D. Barmaz, V. Proust, X. Hu, *J. Am. Chem. Soc.* **2009**, *131*, 12078.
[9] S. R. Dubbaka, M. Kienle, H. Mayr, P. Knochel, *Angew. Chem.* **2007**, *119*, 9251; *Angew. Chem. Int. Ed.* **2007**, *46*, 9093.
[10] H. Doucet, J.-C. Hierso, *Angew. Chem.* **2007**, *119*, 850; *Angew. Chem. Int. Ed.* **2007**, *46*, 834.
[11] For a recent perspective on metal-catalyzed oxidation of organic chemicals with O_2, see: S. S. Stahl, *Science* **2005**, *309*, 1824.
[12] G. Cahiez, C. Duplais, J. Buendia, *Angew. Chem.* **2009**, *121*, 6859; *Angew. Chem. Int. Ed.* **2009**, *48*, 6731.
[13] M. Chen, X. Zheng, W. Li, J. He, A. Lei, *J. Am. Chem. Soc.* **2010**, *132*, 4101.
[14] T.-Y. Luh, M.-K. Leung, K.-T. Wong, *Chem. Rev.* **2000**, *100*, 3187.
[15] L. Chu, F. Qing, *J. Am. Chem. Soc.* **2010**, *132*, 7262.
[16] Y. Wei, H. Zhao, J. Kan, W. Su, M. Hong, *J. Am. Chem. Soc.* **2010**, *132*, 2522.
[17] T. de Haro, C. Nevado, *J. Am. Chem. Soc.* **2010**, *132*, 1512.
[18] W. Yin, C. He, M. Chen, H. Zhang, A. Lei, *Org. Lett.* **2009**, *11*, 709.
[19] a) T. Hamada, X. Ye, S. S. Stahl, *J. Am. Chem. Soc.* **2008**, *130*, 833; b) Y. Gao, G. Wang, L. Chen, P. Xu, Y. Zhao, Y. Zhou, L.-B. Han, *J. Am. Chem. Soc.* **2009**, *131*, 795.