J|A|C|S
COMMUNICATIONS

Ni-Catalyzed Sonogashira Coupling of Nonactivated Alkyl Halides: Orthogonal Functionalization of Alkyl Iodides, Bromides, and Chlorides

Oleg Vechorkin, Delphine Barmaz, Valérie Proust, and Xile Hu*

Laboratory of Inorganic Synthesis and Catalysis, Institute of Chemical Sciences and Engineering, Ecole Polytechnique Fédérale de Lausanne (EPFL), SB-ISIC-LSCI, BCH 3305, Lausanne CH 1015, Switzerland

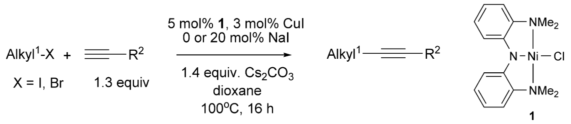
Received July 20, 2009; E-mail: xile.hu@epfl.ch

Substituted alkynes are recurring units in numerous natural products, bioactive molecules, and organic materials.[1] They are also versatile synthetic intermediates.[2] During the last decades, Sonogashira coupling has become one of the most widely used methods for the incorporation of alkynyl functionality into organic compounds.[3] It enables the efficient coupling of an organic halide or pseudohalide with a terminal alkyne, normally using a Pd catalyst and a Cu cocatalyst. The electrophilic coupling partners for Sonogashira reactions, however, are generally limited to aryl and vinyl halides and triflates. Coupling of nonactivated, β-H-containing alkyl halides has been challenging because of their reluctance to undergo oxidative addition and the tendency of metal−alkyl intermediates to undergo unproductive β-H elimination. Moreover, in Sonogashira coupling, the organometallic reagents available for transmetalation are the in situ-generated Cu−alkynyl species. They are present in substoichiometric amounts (a few mol %) with respect to the substrates, which further disfavors the competition between C−C coupling and β-H elimination.[4] Consequently, in contrast to the recent progress of other cross-coupling reactions of nonactivated alkyl halides,[5] there are only two prior reports of successful Sonogashira coupling of such substrates. In their important pioneering studies, Fu et al.[4] and later Glorius et al.[6] demonstrated the coupling of alkyl iodides and bromides, but not chlorides, using Pd(N-heterocyclic carbene) catalysts. Here we describe a Ni-catalyzed Sonogashira coupling of nonactivated alkyl halides that includes chlorides. The difference in reactivities of alkyl−X (X = I, Br, Cl) bonds has allowed us to develop coupling protocols selective for specific C−X bonds, leading to orthogonal functionalization of alkyl halides.

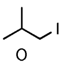
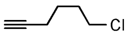
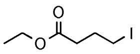
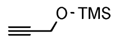
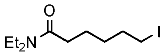
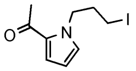
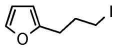
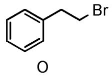
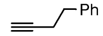
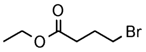
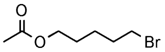
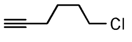
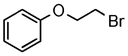
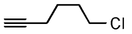
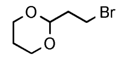
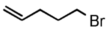
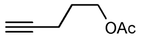
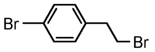
The coupling of octyl iodide with octyne was used as a test reaction. After exploring a wide range of conditions,[7] we found that 7-hexadecyne could be produced in 83% yield in dioxane using a 5 mol % loading of our previously reported Ni^{II} pincer complex $[(^{Me}NN_2)NiCl]$ (**1**)[8,9] as the catalyst, 3 mol % CuI as the cocatalyst, and 1.4 equiv of Cs_2CO_3 as the base (Table 1, entry 1). The best results were obtained at 100 °C. Other combinations of solvents, bases, and cocatalysts led to lower coupling yields.[7] Replacing **1** by $H^{Me}NN_2$, $[(^{Me}NN_2)_2Li_2]$, or $Ni(dme)Cl_2$ (dme = dimethoxyethane) completely shut down the catalysis, confirming the role of complex **1** as the catalyst.[7] The reaction did not occur under metal-free conditions.[7]

The optimized conditions are applicable to the coupling of other alkyl iodides with terminal alkynes (Table 1). Branching at the β-position of the iodide was tolerated (entry 3). Substrates containing reactive functional groups such as ester, amide, aromatic enone, and heterocycle were successfully coupled (entries 4−7). Moreover, an array of terminal alkynes with alkyl, aryl, TMS, OTMS, and alkyl−Cl substituents could be used (entries 1−7). Unfortunately, coupling of secondary alkyl iodides was not successful.

Table 1. Sonogashira Coupling of Alkyl Iodides and Bromides[a]



1

Entry	Alkyl^1-X	$\equiv$—R^2	Yield (%)[b]
1	Octyl-I	$\equiv$—n-C_6H_{13}	83
2	Octyl-I	$\equiv$—TMS	74[c]
3			84
4			73[c]
5		$\equiv$—n-C_6H_{13}	68
6		$\equiv$—n-C_6H_{13}	61
7		$\equiv$—Ph	84
8			89
9		$\equiv$—n-C_6H_{13}	73
10			70
11			79
12		$\equiv$—n-C_4H_9	76
13			59
14		$\equiv$—n-C_6H_{13}	69

[a] For coupling of iodides, no NaI was added; for coupling of bromides, 20 mol % NaI was added. [b] Isolated yields relative to the alkyl halide. [c] Using 1.5 equiv of alkyne.

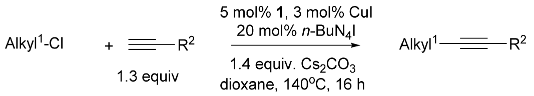
The coupling of alkyl bromides under these conditions is also possible but requires an iodide salt as an additive. The best results were obtained using 20 mol % NaI.[7] The coupling presumably occurs after the alkyl bromides are converted into their corresponding iodides in situ by Br/I exchange. Alkyl bromides containing ester, ether, acetal, and olefin groups were readily converted into substituted alkynes (Table 1, entries 9−13). Coupling of alkyl−Br is selective in the presence of Ar−Br bonds (entry 14).

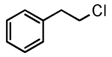
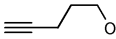
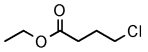
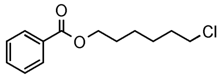
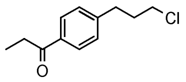
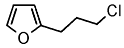
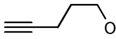
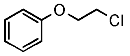
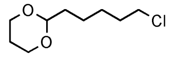
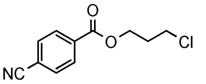
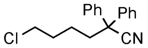
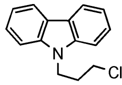
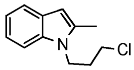
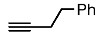
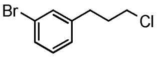
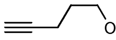
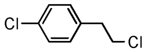
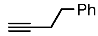
Compared with alkyl bromides and iodides, alkyl chlorides are even more challenging substrates. In fact, we are not aware of any prior example of Sonogashira coupling of nonactivated

10.1021/ja906040t CCC: $40.75

alkyl chlorides. Gratifyingly, in combination with an in situ catalytic Cl/I exchange process, complex **1** also catalyzes the coupling of alkyl chlorides (Table 2). n-Bu$_4$NI (20 mol %) was used as an additive, and the reactions were conducted at 140 °C (entry 1). The reaction gave only 4.1% yield under metal-free conditions.[7] Even at such a relatively elevated temperature, functional groups such as ester, keto, furan, ether, acetal, nitrile, and heterocycle were tolerated (entries 3−12). The coupling of alkyl−Cl bonds is selective over aryl−Cl/Br bonds (entries 13 and 14). Alkynes containing alkyl, aryl, Si(i-Pr)$_3$, and acetate groups were all viable coupling partners.

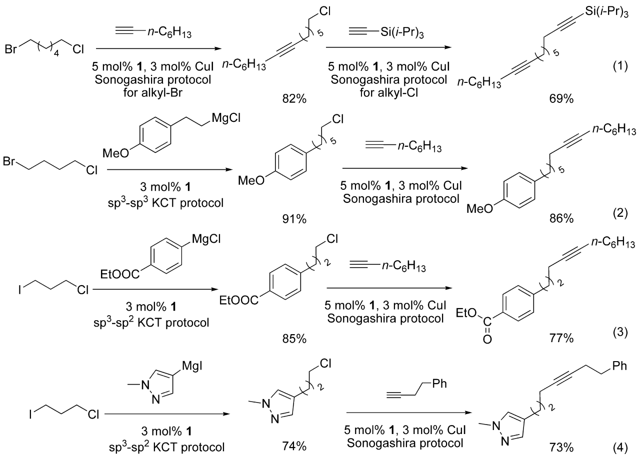
Table 2. Sonogashira Coupling of Alkyl Chlorides



Entry	Alkyl^1-Cl	$\equiv$—R^2	Yield (%)[a]
1	Octyl-Cl	$\equiv$—n-C$_6$H$_{13}$	89
2			66
3		$\equiv$—Si(i-Pr)$_3$	62
4		$\equiv$—n-C$_6$H$_{13}$	70
5		$\equiv$—n-C$_6$H$_{13}$	57
6			64
7		$\equiv$—n-C$_6$H$_{13}$	88
8		$\equiv$—n-C$_6$H$_{13}$	73
9		$\equiv$—n-C$_6$H$_{13}$	63
10		$\equiv$—n-C$_6$H$_{13}$	66
11		$\equiv$—n-C$_6$H$_{13}$	85
12			75
13			58
14			72

[a] Isolated yields relative to alkyl chloride.

One of the useful features in this Ni-catalyzed Sonogashira coupling is that it can be selective among alkyl halides, depending on the reaction conditions (additive and temperature). It is therefore possible to carry out sequential coupling reactions on substrates containing more than one type of alkyl−X bond (eq 1). Furthermore, the current protocol for Sonogashira coupling of alkyl chlorides can be combined with our Kumada−Corriu−Tamao (KCT) coupling protocols for alkyl bromides and iodides,[9] leading to the multiple functionalization of substrates with both alkyl−Cl and alkyl−Br or alkyl−I units (eqs 2−4).



While the mechanism of these reactions is still under investigation, we propose that a (^{Me}NN$_2$)Ni^{II}−alkynyl complex is the key intermediate. This complex reacts with alkyl halide to form the coupling product via sequential oxidative addition and reductive elimination, similar to the KCT coupling catalyzed by the same complex.[7,9]

In summary, we have developed the first Ni-based methods for Sonogashira coupling of nonactivated, β-H-containing alkyl halides. This also appears to be the first time that alkyl chlorides have been used in Sonogashira reactions. The coupling tolerates a wide range of functional groups in both coupling partners. Substituted alkynes could also be prepared in comparable yields by reactions of alkyl halides with alkynyl anions in liquid ammonia solutions.[10] However, the latter methods require a strong base and thus have limited functional-group tolerance for both alkyl halides and terminal alkynes. Therefore, the current Sonogashira protocols are advantageous for the preparation of highly functionalized alkynes. By judicious choices of coupling conditions, different alkyl−X bonds can be differentiated, leading to orthogonal functionalization of alkyl iodides, bromides, and chlorides.

Acknowledgment. We thank the EPFL for financial support.

Supporting Information Available: Experimental details, additional entries, and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) *Chemistry of Triple-Bonded Functional Groups*; Patai, S., Ed.; Wiley: New York, 1994.

(2) *Modern Acetylene Chemistry*; Stang, P. J., Diederich, F., Eds.; VCH: Weinheim, Germany, 1995.

(3) (a) Sonogashira, K. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002; pp 493−529. (b) Negishi, E.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979. (c) Tykwinski, R. R. *Angew. Chem., Int. Ed.* **2003**, *42*, 1566. (d) Marsden, J. A.; Haley, M. M. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; De Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004. (e) Plenio, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 6954.

(4) Eckhardt, M.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 13642.

(5) Recent reviews and hightlights: (a) Netherton, M. R.; Fu, G. C. *Adv. Synth. Catal.* **2004**, *346*, 1525. (b) Frisch, A. C.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 674. (c) Cardenas, D. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 384. (d) Terao, J.; Kambe, N. *Acc. Chem. Res.* **2008**, *41*, 1545. (e) Glorius, F. *Angew. Chem., Int. Ed.* **2008**, *47*, 8347. (f) Rudolph, A.; Lautens, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2656. (g) Giovannini, R.; Studemann, T.; Dussin, G.; Knochel, P. *Angew. Chem., Int. Ed.* **1998**, *37*, 2387.

(6) Altenhoff, G.; Wurtz, S.; Glorius, F. *Tetrahedron Lett.* **2006**, *47*, 2925.

(7) See the Supporting Information.

(8) Csok, Z.; Vechorkin, O.; Harkins, S. B.; Scopelliti, R.; Hu, X. L. *J. Am. Chem. Soc.* **2008**, *130*, 8156.

(9) (a) Vechorkin, O.; Csok, Z.; Scopelliti, R.; Hu, X. L. *Chem.*—*Eur. J.* **2009**, *15*, 3889. (b) Vechorkin, O.; Hu, X. L. *Angew. Chem., Int. Ed.* **2009**, *48*, 2937. (c) Vechorkin, O.; Proust, V.; Hu, X. L. *J. Am. Chem. Soc.* **2009**, *131*, 9756.

(10) (a) Shepherd, J. N.; Stenzel, J. R. *J. Chem. Educ.* **2006**, *83*, 425. (b) Vaughn, T. H.; Hennion, G. F.; Vogt, R. R.; Nieuwland, J. A. *J. Org. Chem.* **1937**, *2*, 1.

JA906040T