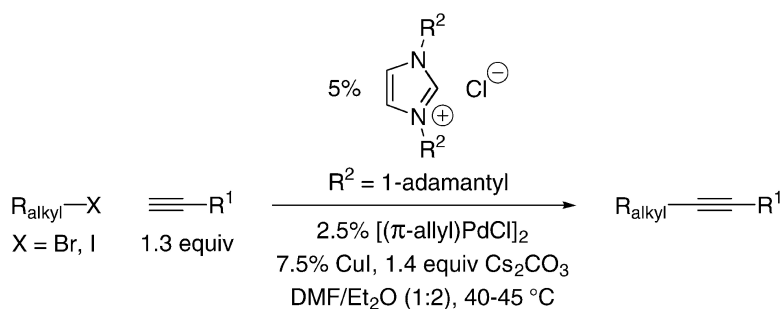


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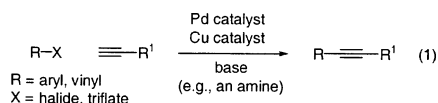
The First Applications of Carbene Ligands in Cross-Couplings of Alkyl Electrophiles: Sonogashira Reactions of Unactivated Alkyl Bromides and Iodides

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Because alkynes are a recurring functional group in a wide range of natural products and other bioactive compounds,¹ as well as versatile intermediates in synthesis,² the development of methods for incorporating them into organic molecules is an important objective. One widely used process is the Sonogashira reaction,³ which typically employs a palladium and a copper catalyst to couple a terminal alkyne with an aryl or vinyl halide or triflate (eq 1). Attractive features of this method include its experimental simplicity and its high atom-economy and functional-group tolerance.



Despite a number of enhancements since its discovery in 1975, the Sonogashira coupling has not yet been shown to be generally applicable to *alkyl* electrophiles (R_{alkyl}-X); indeed, to the best of our knowledge, only activated substrates that lack a β C_{sp}³-H have proved to be suitable reaction partners. Because many of the other methods for coupling alkyl electrophiles with terminal alkynes require a strong base and therefore have limited functional-group compatibility,⁴ the development of an effective catalyst for Sonogashira reactions of alkyl halides would constitute a significant advance for synthetic organic chemistry.

One of the complications that confronts Sonogashira couplings of alkyl electrophiles is the propensity of the intermediate oxidative-addition adduct (Figure 1; A) to undergo β-hydride elimination. This deleterious side reaction is, of course, a general obstacle for palladium- or nickel-catalyzed cross-couplings of alkyl electrophiles. Recently, however, progress has been described in circumventing this difficulty for Suzuki,⁵ Negishi,⁶ Kumada,⁷ Stille,⁸ and Hiyama⁹ reactions.

In contrast to these cross-coupling processes, which employ a *stoichiometric* quantity of an organometallic reagent (organoboron, -zinc, -magnesium, -tin, or -silicon) as the reaction partner, in the Sonogashira coupling, the transmetalating species is generally believed to be a copper acetylide^{3a} that is produced in situ in the presence of a few mol % of a copper catalyst. In light of the need to partition efficiently between transmetalation and β-hydride elimination (Figure 1), the low (substoichiometric) concentration of the copper acetylide renders the development of a catalyst for Sonogashira reactions of alkyl halides a more challenging objective.

In this communication, we describe our progress in addressing this challenge. Specifically, we establish that a Pd/*N*-heterocyclic carbene-based catalyst is effective for Sonogashira reactions of both primary alkyl bromides and iodides under mild conditions (eq 2). By providing the first examples of the utility of *N*-heterocyclic carbene ligands in couplings of alkyl electrophiles, this report suggests new opportunities for developing useful catalysts for reactions of this important family of substrates.

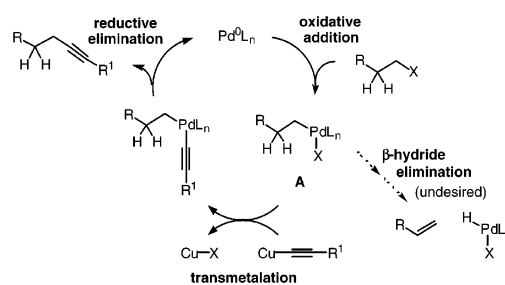
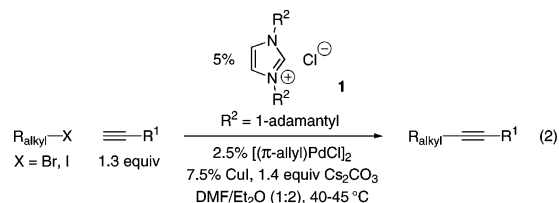









Figure 1. Possible pathway for a Sonogashira reaction.



To date, all of the palladium catalysts that have proved to be effective for coupling unactivated, β-hydrogen-containing alkyl electrophiles have employed phosphines as ligands (PPh₃, trialkylphosphines, and alkyldiaminophosphines).^{5,6c,7b,8,9} Unfortunately, our attempts to achieve a Sonogashira reaction between *n*-nonyl bromide and 1-octyne in the presence of PPh₃, PCy₃, P(*t*-Bu)₂Me, or PCy-(1-pyrrolidinyl)₂ and palladium and copper complexes were ineffective (<5% yield; Table 1, entries 1–4). Consequently, we turned our attention to other families of ligands, and we were pleased to discover promising reactivity in the presence of *N*-heterocyclic carbenes.^{10,11} Although an *N*-mesityl-substituted dihydroimidazole-derived ligand was ineffective (<5% yield; entry 5), an increase in the steric demand of the aryl group led to a fairly efficient process (58% yield; entry 6). Use of an analogous, unsaturated ligand resulted in a further enhancement in yield (67%; entry 7) as did replacement of the 2,6-(*i*-Pr)₂Ph groups with *tert*-alkyl substituents (~80%; entries 8 and 9). Both the palladium (entry 10) and the copper (entry 11) complexes are essential for achieving the desired Sonogashira reaction.¹²

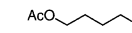
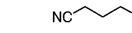
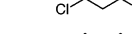
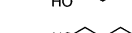
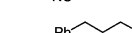
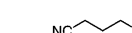
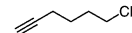
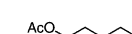
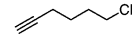
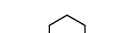
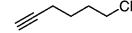

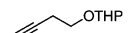

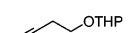
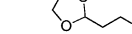
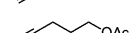
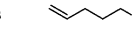
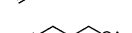
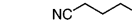
The optimized coupling conditions can be applied to unactivated alkyl bromides that contain a wide range of functional groups, including esters, nitriles, olefins, acetals, and unprotected alcohols (Table 2). Furthermore, alkyl bromides react selectively in the presence of alkyl chlorides (entries 4, 7–9). The efficiency of the Sonogashira coupling is somewhat sensitive to the structure of the alkyne. Unfunctionalized (entries 1–6), including sterically demanding (entry 6), alkynes react in moderate-to-good yield, as do chloride- and acetal-bearing substrates (entries 7–11). However, for Sonogashira couplings of certain other alkynes, slight alterations in the conditions (e.g., temperature or catalyst loading) are necessary to obtain reasonable yields of the desired product (entries 12–14).¹³

Table 1. Effect of Ligand Structure on the Sonogashira Coupling of an Unactivated Alkyl Bromide

entry	ligand	yield (%) ^a	
1	10% PPh ₃	<5	
2	10% PCy ₃	<5	
3	10% P(<i>t</i> -Bu) ₂ Me	<5	
4	10% PCy(1-pyrrolidinyl) ₂	<5	
5		R = mesityl (5%) R = 2,6-(<i>i</i> -Pr) ₂ Ph (5%)	<5
6		R = 2,6-(<i>i</i> -Pr) ₂ Ph (5%) R = <i>t</i> -Bu (5%)	58
7		R = 1-adamantyl (5%)	67
8		R = 1-adamantyl (5%) ^b	81
9		R = 1-adamantyl (5%) ^c	80
10		R = 1-adamantyl (5%) ^b	<5
11		R = 1-adamantyl (5%) ^c	<5

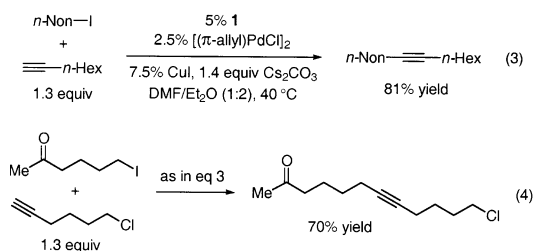
^a Determined by GC versus a calibrated internal standard (average of at least two runs). ^b Reaction was conducted without [(π -allyl)PdCl]₂. ^c Reaction was conducted without CuI.

Table 2. Sonogashira Couplings of Unactivated Alkyl Bromides (eq 2)

entry	R-Br	\equiv -R ¹	yield (%) ^a
1	<i>n</i> -Non-Br	\equiv - <i>n</i> -Hex	77
2	AcO-  -Br	\equiv - <i>n</i> -Hex	71
3	NC-  -Br	\equiv - <i>n</i> -Hex	79
4	Cl-  -Br	\equiv - <i>n</i> -Dec	50
5	HO-  -Br	\equiv - <i>n</i> -Bu	59
6	NC-  -Br	\equiv - <i>t</i> -Bu	70
7	Ph-  -Br	\equiv -  -Cl	74
8	NC-  -Br	\equiv -  -Cl	74
9	AcO-  -Br	\equiv -  -Cl	73
10	 -Br	\equiv -  -OTHP	67
11	 -Br	\equiv -  -OTHP	69
12	 -Br	\equiv -  -OAc	58 ^b
13	 -Br	\equiv -  -OAc	51 ^b
14	NC-  -Br	\equiv -Ph	61 ^c

^a Isolated yield, average of two runs. ^b Reaction was conducted at 60 °C. ^c 7.5% [(π -allyl)PdCl]₂, 22.5% CuI, and 15% ligand were employed.

The standard catalyst system for Sonogashira reactions of alkyl bromides can be applied without modification to alkyl iodides (eqs 3 and 4). Thus, couplings of unfunctionalized and functionalized substrates proceed with useful efficiency.



In conclusion, we have developed a Pd/*N*-heterocyclic carbene-based catalyst that achieves the Sonogashira coupling of an array

of functionalized, unactivated, β -hydrogen-containing alkyl bromides and iodides under mild conditions. Because the transmetalating agent in the Sonogashira reaction is generated in situ in low concentration, we anticipate that the development of an effective catalyst (that avoids β -hydride elimination) for this coupling process may be of particular interest. In addition, this study furnishes the first example of a nonphosphine-based palladium catalyst for cross-coupling unactivated alkyl electrophiles, thereby providing an impetus for future efforts at catalyst development that extend beyond phosphine ligands.

Acknowledgment. M.E. is indebted to Boehringer Ingelheim for providing the opportunity and means for this scientific venture. Support has been provided by the NIH (R01-GM62871), Merck, and Novartis.

Supporting Information Available: Experimental procedures and compound characterization data (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (12) Notes: (a) Reactions in toluene, Et₂O, MTBE, EtOAc, THF, and DME proceed in relatively poor yield. Couplings in DMF, NMP, *N,N*-dimethylacetamide, and MeCN furnish moderate-to-good yields for unfunctionalized, but relatively poor yields for functionalized, substrates. (b) Use of a 3:1 or 1:1 Cu: Pd ratio leads to a significant deterioration in yield. (c) The coupling also proceeds well at room temperature, but a longer reaction time is required. (d) Use of K₂CO₃, CsOH, or K₃PO₄·H₂O, rather than Cs₂CO₃, leads to a somewhat poorer yield, whereas NEt₃, Cy₂NMe, and KO^{*t*}-Bu are ineffective. (e) Replacement of CuI with CuCl, CuBr, or (CuOTf)₂ results in a modest yield of the desired product. AgI is ineffective.
- (13) (a) For Table 2, the olefin that is derived from the loss of HBr from the alkyl bromide is the predominant identifiable side product. (b) For Table 2, entries 12–14, at lower temperature or with less catalyst, more of the olefin side product is observed. (c) In preliminary experiments, reactions of (trimethylsilyl)acetylene and 5-hexynitrile have also required a higher catalyst loading.

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