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The first palladium-catalyzed Sonogashira coupling of unactivated secondary alkyl bromides

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Abstract—A palladium-carbene catalyzed Sonogashira coupling of unactivated alkyl bromides with alkyl substituted alkynes is reported. For the first time, unactivated secondary alkyl halides were successfully employed in Sonogashira reactions.
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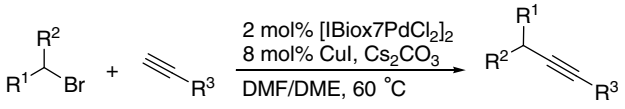
Cross-coupling reactions of aryl halides have become important transformations, significantly altering the way organic molecules are made.[1] For a long time, the corresponding application of non-activated *alkyl* halides remained elusive, due to a generally more difficult oxidative addition step and possible side reactions like β-hydride elimination. In this respect, secondary and tertiary alkyl halides are especially demanding substrates.[2] Recently, catalyst systems have been developed that can oxidatively add to alkyl halides and suppress side reactions and thereby allow the cross-coupling of these substrates.[3,4] In a pioneering effort, Fu et al. developed the first examples of cross-coupling reactions of unactivated *secondary* alkyl halides in 2003.[4a] Later on, other nickel-catalyzed Suzuki, Hiyama and Negishi reactions[4] and an iron-catalyzed Kumada coupling of unactivated secondary alkyl halides were reported.[5]

The Sonogashira coupling[6] of alkynes with organic halides is an efficient method for the synthesis of differently substituted alkynes, versatile synthetic intermediates and also important motifs of biologically active compounds.[7] Traditionally, aromatic halides have been used as the alkyne coupling partner. Fu was the first to efficiently employ unactivated *primary* alkyl bromides and iodides in the Sonogashira reaction using a palladium-carbene catalyst (Scheme 1).[8] However, similar products can be obtained by the prevalent uncatalyzed coupling of deprotonated alkynes with unactivated



Scheme 1. Sonogashira reaction of secondary alkyl halides.

primary or activated alkyl halides. On the contrary, the corresponding uncatalyzed coupling of *secondary* unactivated alkyl halides is troublesome and very low yielding.[9] Therefore, the successful application of more sterically hindered substrates like secondary and tertiary alkyl halides in the Sonogashira reaction would be highly desirable.

Herein we report the first Sonogashira coupling of alkynes with *secondary* alkyl bromides, enabled by the use of palladium-N-heterocyclic carbene complexes (Scheme 1). To the best of our knowledge, this represents the first palladium-catalyzed cross-coupling of unactivated *secondary* alkyl halides.

Our investigation began with the Sonogashira coupling of 1-octyne with cycloheptyl bromide (Table 1). First, using in situ prepared palladium–NHC complexes and the reaction conditions developed by Fu[8] for the coupling of primary alkyl halides, only low amounts of the desired coupling products were formed. A systematic screening of the reaction conditions revealed that increased solvent polarity and elevated temperatures are crucial for the success of this coupling reaction. Cs_2CO_3 was found to be the optimal base. In addition, a variety of NHC ligands were tested under optimized conditions

Keywords: Sonogashira coupling; Cross-coupling; Secondary alkyl halide; Palladium; N-heterocyclic carbene.
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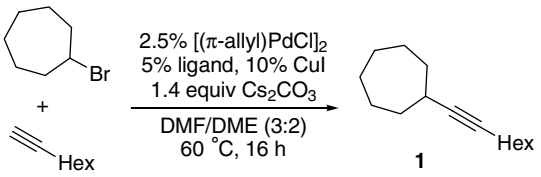
Table 1. Effect of ligand structure on the Sonogashira coupling of cycloheptyl bromide[a]

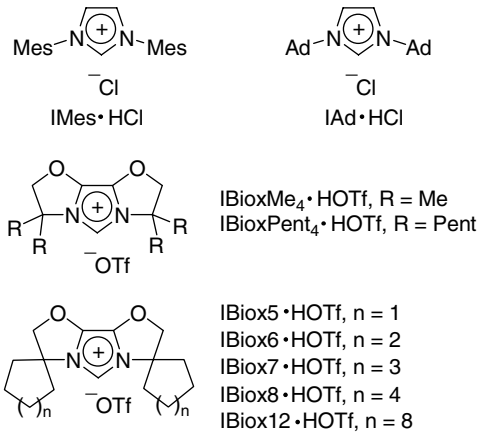


Entry	Ligand	Yield (%)
1	IMes·HCl	51
2	IAd·HCl	41
3	IBioxMe$_4$·HOTf	57
4	IBioxPent$_4$·HOTf	55
5	IBiox6·HOTf	62
6	IBiox7·HOTf	61
7	[IBiox7PdCl$_2$]$_2$[b]	70[c]
8	IBiox8·HOTf	60
9	IBiox12·HOTf	55
10	PPh$_3$	<5
11	PCy$_3$	15

[a] Average yield of two experiments, determined by GC (internal standard).
[b] This preformed Pd complex was used.
[c] Isolated yield.

giving distinctly different results (Table 1). IMes resulted in the formation of a competent catalyst (entry 1). On the other hand, a lower yield was obtained with IAd, the best ligand in Fu's study (entry 2).[8] In both cases, a significant amount of side products like alkyne dimerization products and reductive dimerization products was produced.

Recently, we have reported on the synthesis and application of a new family of bioxazoline-derived NHC (IBiox) (Scheme 2).[10] These electron-rich donor ligands are sterically demanding but exhibit a certain degree of flexibility.[11] In addition, this family of ligands has very similar electronic properties but different steric demand rendering the IBiox ligands well suited for the systematic optimization of a metal–NHC complex catalyzed reaction. This was showcased by employing a series of different IBiox ligands in this study. IBiox6 and IBiox7 were the best ligands resulting in yields of above 60% and the formation of significantly less side products (entries 5 and 6).[12] The use of the preformed complex [IBiox7PdCl$_2$]$_2$ led to an additionally increased yield of 70%. Phosphine ligands were not suitable as ligands in this reaction under the conditions employed (entries 10 and 11).

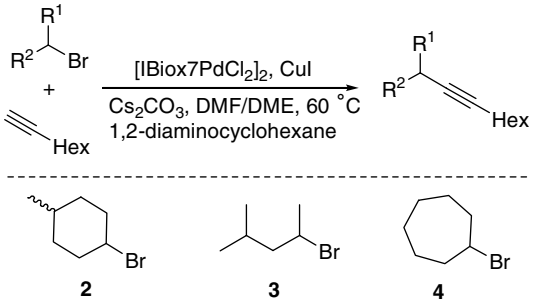


Scheme 2. NHC ligand precursor.

A variety of differently substituted alkyl and cycloalkyl bromides can be successfully coupled with 1-octyne using this new catalyst system. Interestingly, the additional use of catalytic amounts of 1,2-diaminocyclohexane was found to be beneficial in some cases (Table 2). Under standard conditions, the coupling of 1-octyne with a cis/trans-mixture of 4-methylcyclohexyl bromide gave only a low yield of the desired coupling products. The addition of 1,2-diaminocyclohexane led to an improved yield and the formation of less side products (entries 1 and 2). The Sonogashira coupling of the acyclic bromide **3** also benefited from this additive (entries 3 and 4). However, in other cases the additive did not effect the yield or had a deleterious effect. In the case of cycloheptyl bromide, only a minor improvement was observed (entries 5–7). Interestingly, related amine additives like *n*-hexyl amine gave comparable results.[13]

Table 3 summarizes the results of the Sonogashira coupling of secondary alkyl bromides.[14,15] Cyclopentyl, -hexyl, -heptyl and -octyl bromide were successfully coupled under these conditions. The use of the corresponding iodide often gave a significantly reduced yield (entries 2 and 5). The more challenging secondary *acyclic* alkyl bromides can also be coupled. Since the reaction conditions are rather mild, a variety of functional groups is tolerated on the alkyl bromide chain. Acetyl

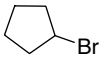
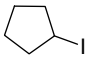
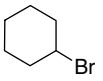
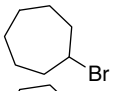
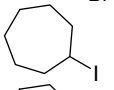
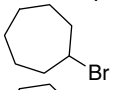
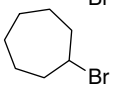
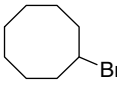
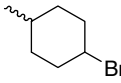
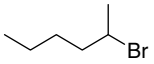
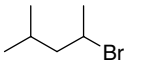
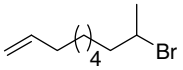
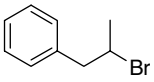
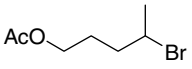
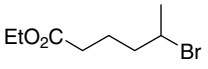
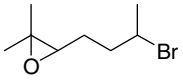
Table 2. Additive effect of 1,2-diaminocyclohexane on the Sonogashira coupling of different substrates[a]



Entry	Bromide	1,2-Diamino-cyclohexane [mol%]	Product	Yield [%]
1	**2**	0	**5**	24
2	**2**	20	**5**	56
3	**3**	0	**6**	33
4	**3**	20	**6**	62
5	**4**	0	**1**	70
6	**4**	8	**1**	76
7	**4**	20	**1**	71

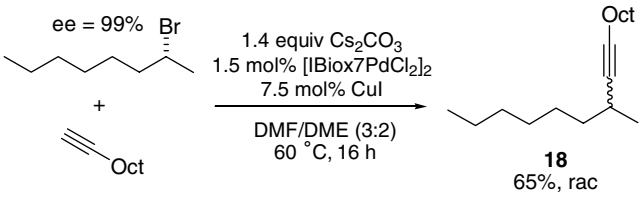
[a] Reaction conditions: [IBiox7PdCl$_2$]$_2$ (2 mol %), CuI (8 mol %), Cs$_2$CO$_3$ (1.45 equiv), alkyne (1.45 equiv), DMF/DME (3:2), 60 °C, 16–18 h, isolated yield.

Table 3. Sonogashira coupling of secondary alkyl halides with 1-octyne[a]

Entry	Alkyl halide	Product	Yield [%]
1		**7**	65
2[b]		**7**	45
3		**8**	71
4[c]		**1**	76
5[b]		**1**	49
6[d]		**9**	71
7[e]		**10**	77
8		**11**	54
9[b]		**5**	56
10[b]		**12**	77
11[b]		**6**	62
12		**13**	67
13[b]		**14**	39
14		**15**	63
15		**16**	76
16		**17**	57

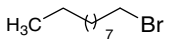
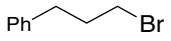
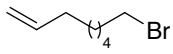
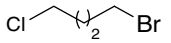
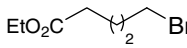
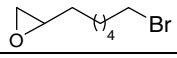
[a] Reaction conditions: $[IBiox7PdCl_2]_2$ (2 mol %), CuI (8 mol %), Cs_2CO_3 (1.4 equiv), alkyne (1.45 equiv), DMF/DME (3:2), 60 °C, 16–18 h, isolated yield.
[b] 20 mol % 1,2-diaminocyclohexane used as an additive.
[c] 8 mol % 1,2-diaminocyclohexane used as an additive.
[d] 1-decyne was used instead of 1-octyne.
[e] 1-dodecyne was used instead of 1-octyne.

protected alcohols, ester groups, epoxides, olefines and aromatics are well tolerated. In addition, the chain length of the alkyne can be varied (entries 6 and 7). However, it has to be noted that the alkyne substrate scope is rather limited. We have been surprised that a variety of other alkynes like phenylacetylene or propargyl alcohol failed to give the desired products in this coupling reaction.



Scheme 3. Sonogashira coupling of an enantiomerically pure secondary alkyl bromide.

Table 4. Sonogashira coupling of primary alkyl bromides with 1-octyne

Entry	Alkyl halide	Product	Yield [%]
1		**19**	77
2		**20**	66
3		**21**	61
4		**22**	60
5		**23**	78
6		**24**	62

An interesting aspect of this coupling reaction is the possible creation of a stereocenter. In order to investigate the stereochemical nature of this process, we submitted an enantiomerically pure substrate, (*R*)-2-bromo octane, to the Sonogashira reaction conditions (Scheme 3). Interestingly, this reaction resulted in a complete loss of the stereochemical information and in the formation of *racemic* product.

In addition to secondary alkyl bromides, primary alkyl bromides are also suitable substrates for the Sonogashira coupling under the conditions developed in this study (Table 4). Once again, multiple functional groups like chloride, ester or epoxide groups are well tolerated. The yields obtained for these primary substrates are comparable to the results obtained by Fu.[8]

In conclusion, a palladium-IBiox-based catalyst system allows the Sonogashira coupling of some alkynes with primary and secondary alkyl bromides, tolerating many functional groups in the alkyl bromide component.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet-

let.2006.02.111. It contains experimental procedures for the synthesis of $[(IBiox7)PdCl_2]_2$ and for the Sonogashira reactions as well as characterization data for all coupling products.

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11. The flexibility of ligands is an important property and its beneficial effects are increasingly recognized. For examples, see: (a) Lavallo, V.; Canac, Y.; Prasang, C.; Donnadieu, B.; Bertrand, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 5705; (b) Lavallo, V.; Canac, Y.; DeHope, A.; Donnadieu, B.; Bertrand, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 7236; (c) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685.
12. This is in contrast to our results in the Suzuki–Miyaura reaction, where IBiox12 was the optimal ligand system: Ref. 10b.
13. The beneficial effect of diamine ligands on copper-catalyzed reactions has recently been explored by Buchwald: (a) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421, and references cited therein; See also: (b) Wang, L.; Yan, J.; Li, P. H.; Wang, M.; Su, C. N. *J. Chem. Res. Synop.* **2005**, 112, and (c) Ref. 1a.
14. Due to the low polarity of the products, purification was rather tedious and in several cases multiple chromatographic steps were needed.
15. General procedure for the Sonogashira reaction using alkyl halides: $[IBiox7PdCl_2]_2$ (10 mg, 0.01 mmol), Cs_2CO_3 (228 mg, 0.7 mmol) and CuI (8 mg, 0.04 mmol) were stirred with dry DMF (1.2 mL) and dry DME (0.8 mL) at room temperature for 20 min. After addition of the alkyl bromide (0.5 mmol, 1.0 eq), alkyne (0.73 mmol, 1.45 equiv) and amine-additive the reaction mixture was stirred at 60 °C for 16–18 h. The reaction mixture was allowed to cool to room temperature and was quenched by either filtering through a short silica column (eluent: hexane or dichloromethane) or by extraction with pentane or diethyl ether (3–4 times, 15 mL) and water (15 mL, with a few drops of TMEDA). The organic phase was washed with brine (20 mL), dried over Na_2SO_4 (20 mL) and concentrated under reduced pressure. After purification by flash chromatography (eluent: hexane or pentane/diethylether) the products were obtained as pale-yellow liquids.