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Palladium-Catalyzed Direct C−H Bond Alkynylations of Heteroarenes Using *gem*-Dichloroalkenes

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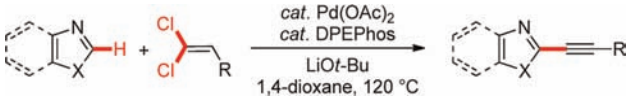
ABSTRACT



Palladium-catalyzed direct alkynylations of heteroarenes were accomplished with inexpensive *gem*-dichloroalkenes as user-friendly electrophiles, which set the stage for a modular, step-economical synthesis of diversely decorated heteroaryl alkynes with ample scope.

Recent years have witnessed significant progress in the direct functionalization of ubiquitous C−H bonds *via* their use as latent functional groups.[1] While a remarkable advance has particularly been made in direct arylations and alkenylations,[2] C−H bond alkylations[3] and alkynylations[4] have unfortunately met thus far with rather limited success. However, the direct alkynylation of heteroarenes gained a considerable impetus by the recent use of 1-bromoalkynes as organic electrophiles (Scheme 1a).[5] Unfortunately, the required 1-haloalkynes are usually relatively unstable, and a significantly more attractive strategy was elegantly developed by Piguel and co-workers, exploiting moisture-stable *gem*-dibromoalkenes[6−8] as alkynylating reagents (Scheme 1b).[9] Yet, while versatile direct arylations have been devised in recent years with aryl chlorides,[10] inexpensive, but challenging, *gem*-dichloroalkenes[11] have, to the best of our knowledge, thus far not been utilized for catalyzed direct alkynylations of unactivated C−H bonds,

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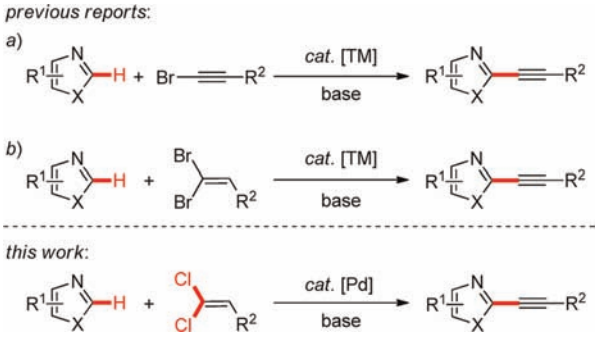
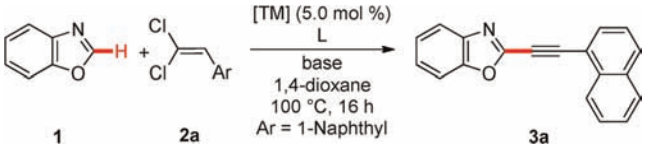
despite their reduced molecular weight as compared to the corresponding *gem*-dibromoalkenes. Within our program on sustainable metal-catalyzed direct C−H bond transformations for an overall streamlining of organic synthesis,[12] we consequently became interested in devising a catalyst for direct alkynylations of heteroarenes with user-friendly *gem*-dichloroalkenes, on which we report herein. Notably, a broadly applicable palladium catalyst furnished diversely substituted (hetero)aryl acetylenes, key structural motifs inter alia in chemical biology and material sciences.[13]

Scheme 1. Direct C−H Bond Alkynylations with Organic Electrophiles



We initiated our studies by probing various reaction conditions for the direct alkynylation of benzoxazole (**1**)[14] with easily accessible *gem*-dichloroalkene **2a** (Table 1). Copper(I) catalysts that were previously utilized for transformations of *gem*-dibromoalkenes unfortunately led only to unsatisfactory yields (entries 1−3). More promising results were, on the contrary, achieved with palladium(II) complexes. Among a variety of phosphine and N-heterocyclic carbene (NHC) ligands, the most efficient catalysis was ensured by bidentate DPEPhos as the ligand (entries

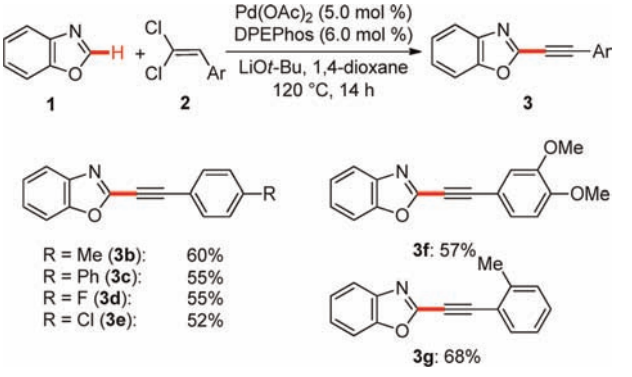
Table 1. Optimization of Direct Alkynylation of Benzoxazole (**1**)[a]



entry	[TM]	L (mol %)[15]	base	yield (%)
1	CuI	XantPhos (5.0)	LiO*t*-Bu	13
2	$CuBr•SMe_2$	XantPhos (5.0)	LiO*t*-Bu	13
3	$CuBr•SMe_2$	DPEPhos (5.0)	LiO*t*-Bu	17
4	$Pd(OAc)_2$	XantPhos (5.0)	LiO*t*-Bu	46
5	$Pd(OAc)_2$	PPh_3 (10)	LiO*t*-Bu	38
6	$Pd(OAc)_2$	PCy_3 (10)	LiO*t*-Bu	20
7	$Pd(OAc)_2$	JohnPhos (10)	LiO*t*-Bu	40
8	$Pd(OAc)_2$	DavePhos (10)	LiO*t*-Bu	40
9	$Pd(OAc)_2$	HIPrCl (10)	LiO*t*-Bu	19
10	$Pd(OAc)_2$	dppp (5.0)	LiO*t*-Bu	39
11	$Pd(OAc)_2$	dppf (5.0)	LiO*t*-Bu	56
12	$Pd(OAc)_2$	dppe (5.0)	LiO*t*-Bu	62
13	$Pd(OAc)_2$	DPEPhos (5.0)	LiO*t*-Bu	68
14	–	DPEPhos (5.0)	LiO*t*-Bu	–
15	$Pd(OAc)_2$	DPEPhos (5.0)	KO*t*-Bu	–
16	$Pd(OAc)_2$	DPEPhos (5.0)	K_3PO_4	–
17	$Pd(OAc)_2$	DPEPhos (5.0)	Cs_2CO_3	–
18	$Pd(OAc)_2$	DPEPhos (6.0)	LiO*t*-Bu	75[b]

[a] Reaction conditions: **1** (0.50 mmol), **2a** (0.75 mmol), [TM] (5.0 mol %), L (5.0−10 mol %), base (2.50 mmol), 1,4-dioxane (2.0 mL), 100 °C, 16 h. [b] 120 °C, 13 h; yields of isolated products.

Scheme 2. Direct Alkynylation with Substituted *gem*-Dichloroalkenes **2**



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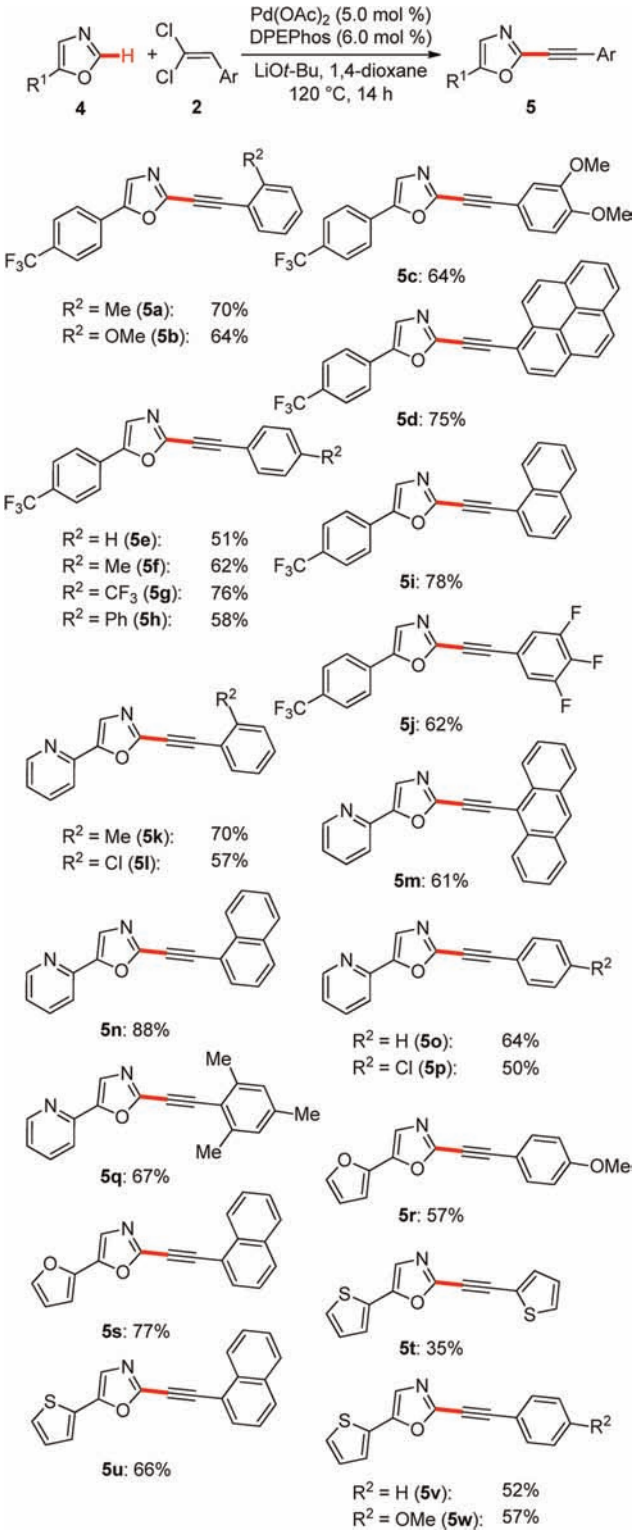
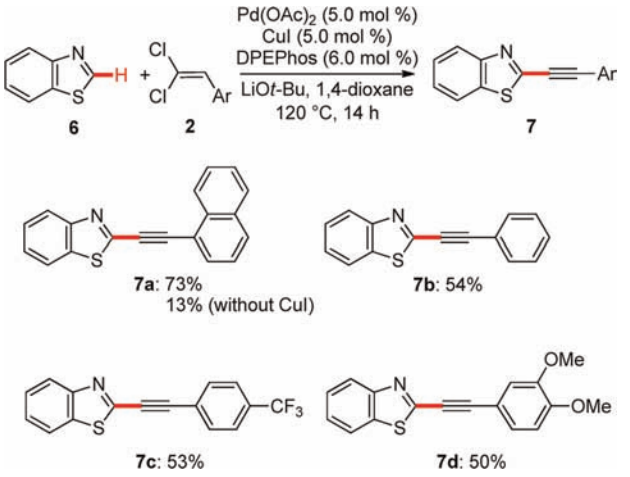
(15) Acronyms and abbreviations of (pre)ligands: XantPhos = 4,5-(diphenylphosphino)-9,9-dimethylxanthene; JohnPhos = 2-(dicyclohexylphosphino)biphenyl; DavePhos = 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl; HIPr = *N*,*N*′-bis(2,6-diisopropylphenyl)imidazolium; DPEPhos = oxybis(2,1-phenylene)bis(diphenylphosphine).

Scheme 3. C−H Bond Alkynylation Using Oxazoles **4**



Scheme 4. C−H Bond Alkynylation on Benzothiazole (**6**)



With an optimized catalytic system in hand, we explored its scope in the direct alkynylation of benzoxazole (**1**) using differently substituted *gem*-dichloroalkenes **2** (Scheme 2). Thereby, substituted alkynes **3** were obtained bearing electron-withdrawing or -donating substituents on the arenes, even when employing sterically congested, *ortho*-substituted starting materials **2**.

The optimized palladium catalyst was not restricted to benzoxazoles **1** as the substrates. Indeed, the direct functionalization of oxazoles **4** occurred with remarkably high catalytic efficacy as well, which allowed for the modular assembly of different heteroaryl alkynes **5** (Scheme 3). Here, a variety of useful functional groups was well tolerated, thereby also setting the stage for the preparation of alkynes **5** being decorated with valuable heteroarenes, such as pyridines (**5k**−**5q**), furans (**5r** and **5s**), or thiophenes (**5t**−**5w**).

Finally, the catalytic direct C−H bond alkynylation of benzothiazole (**6**) with *gem*-dichloroalkenes **2** was found to be possible as well, provided that cocatalytic amounts of CuI were employed as an additive (Scheme 4).

In summary, we have reported on the first C−H bond alkynylations with user-friendly, inexpensive *gem*-dichloroalkenes as electrophiles, which enabled step-economical, thus environmentally benign, direct functionalizations of various heteroarenes with ample scope.

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Supporting Information Available. Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

4−13), while LiO*t*-Bu resulted in being the base of choice (entries 14−18). As to the solvent, 1,4-dioxane (75%, entry 18) proved superior when being compared to DMA (< 2%), NMP (< 2%), *meta*-xylene (39%), or toluene (62%) under otherwise identical reaction conditions.