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Highly Efficient and Versatile Pd-Catalyzed Direct Alkynylation of Both Azoles and Azolines

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ABSTRACT

A highly efficient and versatile Pd-catalyzed direct alkynylation reaction of heterocycles with 1-bromoalkynes was developed. The substrate scope of the reaction was very broad to include not only azoles but also azolines for the first time, thus offering an important advance in the direct functionalization of heterocycles.

The functionalization of heterocyclic compounds has emerged as one of the most important topics in the field of metal-catalyzed C−H bond activation due to the fact that products are an important synthetic motif in organic synthesis, the pharmaceutical industry, and materials science.[1] Therefore, a vast amount of effort has been made to develop more efficient and versatile methods to functionalize C−H bonds of various heterocycles, thus leading to a range of catalytic systems of Pd, Rh, Cu, or Ni.[2] The recent advances have been directed mainly toward the introduction of aryl, vinyl, or albeit in rare cases, alkyl groups.[3] On the other hand, the installation of an alkynyl moiety at a proper position of heterocycles has been less studied,[4] although Yamaguchi reported an *ortho*-selective alkynylation of benzene derivatives using $GaCl_3$.[5] Recently, Miura[4d] and Piguel[4e] revealed that the C-2 position of azoles was selectively alkynylated using bromoalkynes under Ni and Cu catalysts, respectively. Gevorgyan also reported an elegant protocol of the Pd-catalyzed alkynylation of N-fused heterocycles.[4a] In addition, Tobisu and Chatani developed a Pd-catalyzed *ortho*-alkynylation of aromatic C−H bonds of anilides.[6]

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(2) (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (b) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200. (c) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (d) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013. (e) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074. For relevant works from this laboratory, see: (f) Lee, J. M.; Na, Y.; Han, H.; Chang, S. *Chem. Soc. Rev.* **2004**, *33*, 302. (g) Cho, S. H.; Hwang, S. J.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 9254. (h) Hwang, S. J.; Cho, S. H.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 16158. (i) Cho, S. H.; Kim, J. Y.; Lee, S. Y.; Chang, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 9127. (j) Kim, M.; Kwak, J.; Chang, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 8935.

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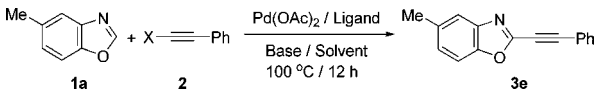
Although these achievements are promising, new catalytic systems are still desired to further improve the reaction efficiency and scope, thus making this approach more attractive. In particular, a similar range of high efficiency is required not only for various azoles which are the most representatively employed substrate type in the precedent catalyst systems[4] but also for other types of partially saturated heterocycles such as azolines which are an important building motif in organic synthesis. Herein, we report a highly efficient Pd-catalyzed direct alkynylation of both azoles and azolines with 1-bromoalkynes.

Optimization of the alkynylation reaction was first tried using 5-methylbenzoxazole (**1a**) and 1-bromophenylacetylene under Pd catalyst systems (Table 1).[7] It was found

Table 1. Optimization of the Pd-Catalyzed Alkynylation of **1a** with 1-Halophenylacetylene[a]



1a 2 3e

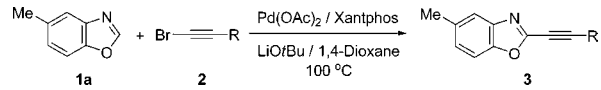
entry	X	ligand	solvent	base	yield[b] (%)
1	Br	SPhos	toluene	K_2CO_3	<5
2	Br	SPhos	toluene	CsOAc	18
3	Br	SPhos	toluene	LiO-*t*-Bu	82
4	Br	none	toluene	LiO-*t*-Bu	17
5	Br	Xantphos	toluene	LiO-*t*-Bu	79
6[c]	Br	Xantphos	1,4-dioxane	LiO-*t*-Bu	99 (99)
7[c]	I	Xantphos	1,4-dioxane	LiO-*t*-Bu	79
8[c]	Cl	Xantphos	1,4-dioxane	LiO-*t*-Bu	16

[a] Reaction conditions: **1a** (1.5 equiv), **2** (0.5 mmol), $Pd(OAc)_2$ (5 mol %), ligand (11 mol % for SPhos, 5.5 mol % for Xantphos), base (2 equiv). [b] NMR yield and the number in parentheses is the isolated yield. [c] **1a** (1.2 equiv), $Pd(OAc)_2$ (2.5 mol %), and ligand (2.8 mol %) were used for 2 h.

that alkynylation at the C-2 position of benzoxazole took place with low efficiency when $Pd(OAc)_2$ was used with 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (SPhos) and CsOAc (entry 2). In this case, most of the bromoalkyne was transformed to 1,4-diphenylbutadiyne (40%), implying that dimerization is a major side reaction competing with the desired reaction. As observed in the previous examples of the azole couplings,[3j,8] the reaction efficiency was significantly improved when LiO-*t*-Bu was employed as a base (entry 3). While only poor yield was obtained in the absence of the ligand (entry 4), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos) turned out to be the most effective ligand in 1,4-dioxane at 100 °C(entry 6). It should be noted that the homocoupling of 1-bromoalkyne was completely inhibited under these conditions.[9] On the other hand, while the reaction of 1-iodophenylacetylene[10] resulted in a slight decrease of product yield (entry 7), that of the 1-chloro derivative[11] was much more sluggish (entry 8).

The above optimized conditions were subsequently applied to a range of 1-bromoalkynes in the reaction with **1a**, and the reaction proceeded well with various substrates including previously reported ones[4d,e] (Table 2).[12] Linear or cyclic

Table 2. Direct Alkynylation of **1a** with 1-Bromoalkynes[a]



1a 2 3

entry	bromoalkyne (R)	time (h)	product	yield[b] (%)
1	$CH_3(CH_2)_4CH_2$	4	**3a**	75
2	cyclohexyl	2	**3b**	85
3	$Cl(CH_2)_3CH_2$	2	**3c**	69
4	1-cyclohexenyl	4	**3d**	97
5	Ph	2	**3e**	99
6	$(4\text{-Me})C_6H_4$	4	**3f**	92
7	$(4\text{-Cl})C_6H_4$	4	**3g**	95
8	$(4\text{-Br})C_6H_4$	4	**3h**	80
9	$(2\text{-Br})C_6H_4$	2	**3i**	87
10	$(4\text{-CF}_3)C_6H_4$	4	**3j**	80
11	$(4\text{-MeO})C_6H_4$	4	**3k**	89
12	Si(*i*-Pr)$_3$	2	**3l**	79

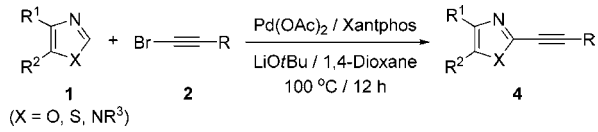
[a] Reaction conditions: **1a** (1.2 equiv), **2** (0.5 mmol), $Pd(OAc)_2$ (2.5 mol %), Xantphos (2.8 mol %) and LiO*t*Bu (2 equiv) in 1,4-dioxane under 100 °C. [b] Isolated yield.

aliphatic 1-bromoalkynes (entries 1 and 2) or that bearing a functional group (entry 3) were readily alkynylated at the C-2 position of **1a**. A bromoalkyne conjugated to the vinyl group was also easily reacted under the conditions (entry 4). Arylacetylenes bearing various substituents were smoothly installed at the C-2 position of **1a** to afford the corresponding 2-alkynylheteroarenes in good to excellent yields (entries 5−11). It should be noted that the electronic and/or steric variation on the phenyl substituents displayed negligible effects on the reaction efficiency. In addition, the reaction was completely chemoselective in that the bromo substituent on the arylacetylenes was completely intact (entries 8 and 9). Significantly, bromosilylacetylene, a precursor of terminal alkyne, was also readily reacted to afford the corresponding silyl group-protected alkynylbenzoxazole (**3l**) in 79% yield (entry 12).

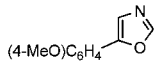
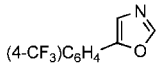
Next, we investigated the scope of azole heterocycles under the reaction conditions (Table 3). The C-2 position of parent oxazole was selectively alkynylated in high yields (entries 1−2). Reactions of oxazoles bearing electronically different aryl groups at the C-5 position took place with high

(6) Tobisu, M.; Ano, Y.; Chatani, N. *Org. Lett.* **2009**, *11*, 3250.
(7) For details, see the Supporting Information.
(8) Canivet, J.; Yamaguchi, J.; Ban, I.; Itami, K. *Org. Lett.* **2009**, *11*, 1733.
(9) For an example of increased product yield by decreasing the amount of catalyst, see: Lane, B. S.; Sames, D. *Org. Lett.* **2004**, *6*, 2897.
(10) For the preparation of 1-iodophenylacetylene, see: Xu, W.; Chen, Q.-Y. *J. Org. Chem.* **2002**, *67*, 9421.
(11) For the preparation of 1-chlorophenylacetylene, see: Sud, D.; Wigglesworth, T. J.; Branda, N. R. *Angew. Chem., Int. Ed.* **2007**, *46*, 8017.
(12) For the preparation of 1-bromoalkynes, see: (a) Li, L.-S.; Wu, Y.-L. *Tetrahedron Lett.* **2002**, *43*, 2427. (b) Abou, A.; Foubelo, F.; Yus, M. *Tetrahedron* **2007**, *63*, 6625. (c) Kim, J. Y.; Kim, S. H.; Chang, S. *Tetrahedron Lett.* **2008**, *49*, 1745.

Table 3. Direct Alkynylation of Azoles with 1-Bromoalkynes[a]



1 (X = O, S, NR3) 2 4

entry	heterocycle	R	product	yield (%)[b]
1[c]		Ph	**4a**	93
2[c]		Si(*i*-Pr)$_3$	**4b**	71
3		Ph	**4c**	99
4		Si(*i*-Pr)$_3$	**4d**	78
5		Ph	**4e**	98
6		Si(*i*-Pr)$_3$	**4f**	77
7		Ph	**4g**	94
8		Si(*i*-Pr)$_3$	**4h**	78
9[d,e]		Ph	**4i**	59 (10%)[f]
10[d]		Si(*i*-Pr)$_3$	**4j**	68
11[d]		Si(*i*-Pr)$_3$	**4k**	53
12[d]		Si(*i*-Pr)$_3$	**4l**	63

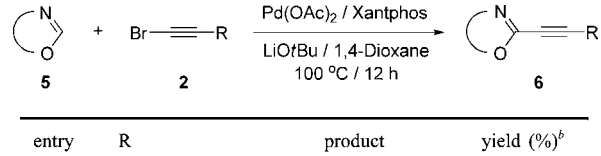
[a] Reaction conditions: **1** (1.2 equiv), **2** (0.5 mmol), $Pd(OAc)_2$ (2.5 mol %), Xantphos (2.8 mol %) and LiO-*t*-Bu (2 equiv) in 1,4-dioxane at 100 °C. [b] Isolated yield. [c] **1** (1.5 equiv) was used. [d] **1** (1.5 equiv), $Pd(OAc)_2$ (5 mol %), and Xantphos (5.5 mol %) were used. [e] CuI (5 mol %) was used as an additive. [f] GC yield of the product without CuI.

efficiency to give the corresponding 2-alkynyloxazoles (entries 3−8).

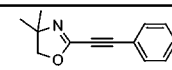
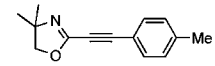
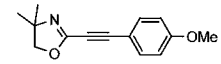
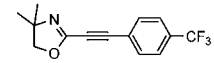
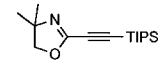
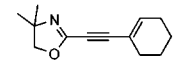
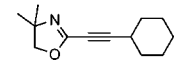
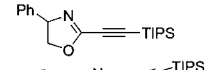
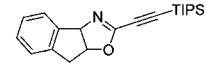
It is highly noteworthy that the present alkynylation protocol can also be applied to other types of heteroarenes, although with slightly lower efficiency when compared to (benz)oxazoles. For instance, derivatives of benzothiazole (entries 9 and 10), benzimidazole (entry 11), or imidazole (entry 12) were found to be included as reactive substrates to afford the corresponding C-2 alkynylazoles. Interestingly, the product yield was significantly improved by the addition of catalytic amount of CuI in the reaction of benzothiazole with 1-bromophenylacetylene, presumably due to the beneficial effects of the copper additive.[4e,13]

Gratifyingly, it was found that the alkynylation reaction was readily extended for the first time, to the best of our knowledge, to partially saturated oxazolines and their analogues under the optimal conditions (Table 4). Since oxazoline moieties are highly versatile building blocks in

Table 4. Direct Alkynylation of Oxazolines[a]



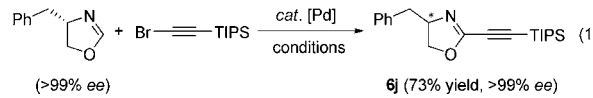
5 2 6

entry	R	product	yield (%)[b]
1	Ph	 **6a**	91
2	(4-Me)C$_6$H$_4$	 **6b**	82
3	(4-MeO)C$_6$H$_4$	 **6c**	82
4	(4-CF$_3$)C$_6$H$_4$	 **6d**	65
5	Si(*i*-Pr)$_3$	 **6e**	99
6	1-Cyclohexenyl	 **6f**	71
7	Cyclohexyl	 **6g**	48
8[c]	Si(*i*-Pr)$_3$	 **6h**	78
9	Si(*i*-Pr)$_3$	 **6i**	61

[a] Reaction conditions: **5** (1.5 equiv), **2** (0.5 mmol), $Pd(OAc)_2$ (2.5 mol %), Xantphos (2.8 mol %), and LiO-*t*-Bu (2 equiv) in 1,4-dioxane at 100 °C. TIPS indicates triisopropylsilyl. [b] Isolated yield. [c] Reaction was run for 16 h.

organic synthesis,[14] the application of the direct alkynylation protocol to oxazolines would draw intense interests for the derivatization of those heterocyclic compounds.

Using 4,4-dimethyloxazoline as a test substrate, it was observed that the alkynylation reaction proceeded smoothly to afford the desired products in high yields (entries 1−4). Notably, bromoalkynes substituted with silyl, conjugated alkenyl, and alkyl groups were readily reacted with 4,4-dimethyloxazoline (entries 5, 6, and 7, respectively), although the last reaction provided just a moderate yield.[15] The fact that 4-phenyloxazoline was alkynylated only at the C-2 position in good yield demonstrates again that the reaction is highly regioselective (entry 8). When 4,5-indanediyloxazoline, prepared according to the Meyers' procedure,[16] was subjected to the present conditions, the desired product was obtained in synthetically acceptable yield (entry 9).



(>99% *ee*) **6j** (73% yield, >99% *ee*)

Meanwhile, it was observed that no racemization took place during the course of the alkynylation reaction with the

(13) For examples of CuI additive effects on the Pd-catalyzed direct arylation of azoles, see: (a) Satoh, T.; Kokubo, K.; Miura, M.; Nomura, M. *Organometallics* **1994**, *13*, 4431. (b) Pivsa-Art, S.; Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 467.

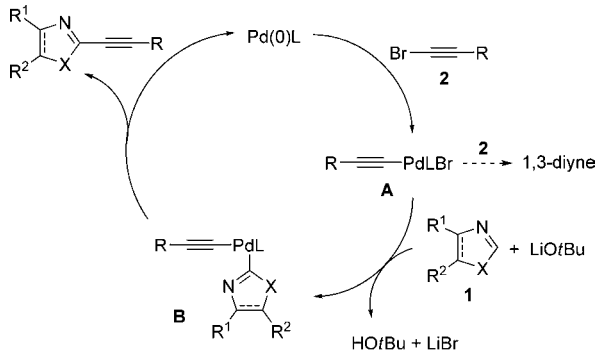
(14) (a) Meyers, A. I.; Temple, D. L., Jr. *J. Am. Chem. Soc.* **1970**, *92*, 6644. (b) Reuman, M.; Meyers, A. I. *Tetrahedron* **1985**, *41*, 837.

(15) For examples of the possible side reactions of initially produced 2-alkyloxazolines, see: (a) *The Chemistry of Heterocycles*; Eicher, T., Hauptmann, S., Eds.; Wiley-VCH: Weinheim, 2003. (b) Capriati, V.; Degennaro, L.; Florio, S.; Luisi, R. *Tetrahedron Lett.* **2007**, *48*, 8651.

use of an optically active 4-benzyloxazoline (eq 1). Since chiral oxazolines have been widely used as ligands or versatile precursors in asymmetric synthesis,[17] a direct alkynylation of chiral oxazolines would offer a new and convenient opportunity for the functionalization of those compounds.

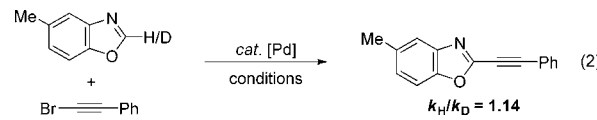
While a precise description of the reaction paths of the present Pd-catalyzed direct alkynylation of heterocycles still requires comprehensive mechanistic studies, a proposal is presented in Scheme 1 on the basis of preliminarily obtained

Scheme 1. Plausible Mechanism of the Pd-Catalyzed Direct Alkynylation of Heterocycles



kinetic data and precedent reports on the relevant arylation reactions.[3d,18]

An oxidative addition of 1-bromoalkyne (**2**) to a zerovalent Pd species is envisioned to take place as an initial step leading to a Pd−acetylide intermediate (**A**). In fact, it was observed that $Pd(PPh_3)_4$ also catalyzed the alkynylation with a comparable yield under otherwise identical conditions.[19] It is then presumed that the employed base (LiO-*t*-Bu) abstracts a proton at the C-2 position of heterocycles employed, and a transmetalation process of thus-formed lithiated heterocyclic species with the Pd−acetylide complex **A** would occur to generate a heterocyclic alkynylpalladium intermediate (**B**).[20] As the final step of the catalytic cycle, reductive elimination of **B** produces 2-alkynyl heterocycles upon the regeneration of Pd(0) species.



The negligible primary kinetic isotope effect (KIE) observed in the alkynylation of *d*-labeled 5-methylbenzoxazole (eq 2)[21] may support that the transmetalation step does not proceed via the C−H bond activation pathway.[22] However, since the KIE value is in the range of those for the arylation of heterocycles via an electrophilic pathway,[4a] an alternative route involving an electrophilic addition of deprotonated heterocycles to the Pd−acetylide complex **A** can also be considered. In addition, although a palladacyclic species was suggested by Chatani as a plausible intermediate in the coupling reaction of 1-bromoalkynes with aromatic C−H bonds in anilides,[6] this can be ruled out herein since 1,3-diynes were detected as side products albeit in trace amounts in all cases examined.

In summary, we have developed a highly efficient and versatile Pd-catalyzed direct alkynylation reaction of heterocycles with 1-bromoalkynes to afford 2-alkynylheterocycles. The substrate scope of the reaction turned out to be very broad to include not only azoles but also partially saturated azolines for the first time, thus offering an important advance in the direct functionalization of heterocycles.

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

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