

Palladium-Catalyzed Oxidative Alkynylation of Heterocycles with Terminal Alkynes under Air Conditions

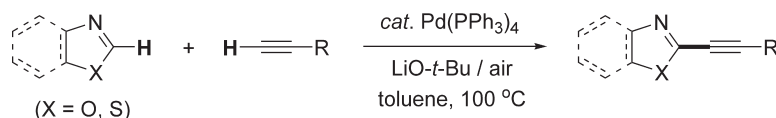
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ABSTRACT



Pd-Catalyzed oxidative alkynylation of azoles with terminal alkynes was developed via simultaneous activation of both heterocyclic sp^2 C–H and alkynyl sp C–H bonds. The choice of palladium catalyst source and external base resulted in being important factors for performing the reaction with high efficiency and selectivity, and air was successfully utilized as an environmental oxidant in the present alkynylation procedure.

In recent years, a promising strategy of C–H bond activation has been extensively utilized for C–C bond formation which is one of the most important topics in organic chemistry.¹ This direction of research has been stimulated mainly due to the advantage of enabling a more straightforward access to target molecules without requiring prefunctionalization of starting molecules, thus minimizing side products in fewer steps. Therefore, although the C–H bond functionalization often requires relatively harsh reaction conditions, it is considered as an attractive alternative to the conventional coupling approaches, in which both reactants are preactivated (Scheme 1, path I).² With regard to this aspect, highly efficient C–C bond forming protocols

have been developed from the direct reaction of heteroarenes with aryl- or vinyl-(pseudo)halides (path II).³

More recently, a more challenging route to the C–C bond formation has been scrutinized using *two nonactivated reactants* (path III). Indeed, the oxidative C–C bond formation via the activation of $\text{C}(\text{sp}^2)$ –H or $\text{C}(\text{sp}^3)$ –H bonds has been extensively studied using various metal catalysts.^{4,5} On the other hand, while the activation of $\text{C}(\text{sp})$ –H bonds has been examined for the oxidative couplings,⁶ synthetic applications of the strategy still remain largely unexplored mainly because of the undesired homocoupling of terminal alkynes under the conditions. Although Sonogashira reaction is a powerful tool for

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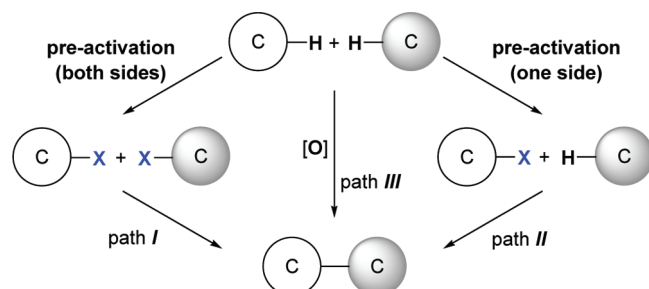
(3) (a) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (b) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013. (c) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074.

(4) For recent examples of C–C bond formation via $\text{C}(\text{sp}^2)$ –H bond activation, see: (a) Boele, M. D. K.; van Strijdonck, G. P. F.; de Vries, A. H. M.; Kamer, P. C. J.; de Vries, J. G.; van Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2002**, *124*, 1586. (b) Dwight, T. A.; Rue, N. R.; Charyk, D.; Josselyn, R.; DeBoef, B. *Org. Lett.* **2007**, *9*, 3137. (c) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 11904. (d) Stuart, D. R.; Villemure, E.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 12072. (e) Cho, S. H.; Hwang, S. J.; Chang, S. J. *Am. Chem. Soc.* **2008**, *130*, 9254. (f) Egami, H.; Katsuki, T. *J. Am. Chem. Soc.* **2009**, *131*, 6082. (g) Kwon, K.-H.; Lee, D. W.; Yi, C. S. *Organometallics* **2010**, *29*, 5748. (h) Morimoto, K.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2010**, *12*, 2068. (i) Wei, Y.; Su, W. J. *Am. Chem. Soc.* **2010**, *132*, 16377.

(5) For recent examples of C–C bond formation via $\text{C}(\text{sp}^3)$ –H activation, see: (a) Lin, S.; Song, C. X.; Cai, G. X.; Wang, W.-H.; Shi, Z.-J. *J. Am. Chem. Soc.* **2008**, *130*, 12901. (b) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335. (c) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (d) Urkalan, K. B.; Sigman, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 18042.

introducing organic groups at the terminal alkynyl carbon, a recent advance in the direct alkynylation of C(sp²)–H bonds appears as a promising alternative to the conventional Sonogashira procedure, in which aryl or vinyl halides are employed.⁷

Scheme 1. Strategies of C–C Bond Formation

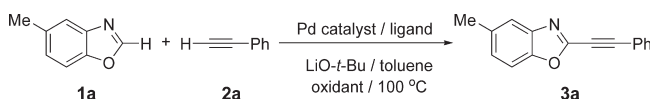


Recently, our group has disclosed a Pd-catalyzed alkynylation of azoles using *1-haloalkynes*, and its efficiency was observed to be dependent on the ease of C(sp²)–H bond activation.⁸ During the course of this study, we found that a *terminal alkyne itself* was able to be coupled with azoles under oxidative catalytic conditions. In fact, oxidative alkynylation of arenes with 1-alkynes was developed using Au^{6h} or Cu⁶ⁱ catalytic systems. In addition, Miura revealed an elegant protocol of oxidative alkynylation of azoles using a Ni catalyst.^{6m} Despite these developments, plenty of room for improvement still remains with regard to reaction efficiency and substrate scope. We herein describe a new procedure for the oxidative alkynylation of azoles using terminal alkynes under Pd-catalyzed conditions.

5-Methylbenzoxazole (**1a**) and phenylacetylene (**2a**) were chosen as model substrates in order to optimize the oxidative alkynylation conditions (Table 1).⁹ We were pleased to observe that a desired product (**3a**) was obtained albeit in moderate yield when a Pd(OAc)₂ catalyst was used in the presence of a 2,2'-bipyridine (bipyridyl) ligand under an O₂ atmosphere (entry 1). The reaction efficiency was highly sensitive to the choice of bases, and LiO-*t*-Bu provided the best results among the various bases examined

(e.g., entry 2). Use of other oxidants such as iodobenzene diacetate or *tert*-butyl hydroperoxide resulted in much lower product yields (entries 3 and 4, respectively). While Pd(PPh₃)₄ alone displayed similar catalytic activity compared to that from combined use of Pd(OAc)₂/bipyridyl (entry 5), a higher product yield was obtained when the reaction was carried out open to air, a weaker oxidant for oxidizing the phosphine ligand, than under an O₂ atmosphere (compare entries 5 and 6).

Table 1. Optimization of the Pd-Catalyzed Alkynylation^a



entry	catalyst/ligand	oxidant	solvent	temp (°C)	yield (%) ^b
1	Pd(OAc) ₂ /bipyridyl	O ₂	toluene	100	30
2 ^c	Pd(OAc) ₂ /bipyridyl	O ₂	toluene	100	N.R.
3	Pd(OAc) ₂ /bipyridyl	PhI(OAc) ₂	toluene	100	N.R.
4	Pd(OAc) ₂ /bipyridyl	<i>t</i> -BuOOH	toluene	100	<5
5	Pd(PPh ₃) ₄	O ₂	toluene	100	38
6	Pd(PPh ₃) ₄	air	toluene	100	50
7 ^d	Pd(PPh ₃) ₄	air	toluene	100	67 ^f
8 ^e	Pd(PPh ₃) ₄	air	toluene	100	74 ^f
9	none	air	toluene	100	N.R.
10	Pd ₂ (dba) ₃	air	toluene	100	<5
11	Pd(dba) ₃ /PPh ₃	air	toluene	100	44
12	Pd(PPh ₃) ₄	air	toluene	80	15
13	Pd(PPh ₃) ₄	air	xylylene	130	<5

^a **1a** (1.5 equiv), **2a** (0.5 mmol), palladium catalyst (5 mol %), ligand (bidentate: 5.5 mol %; monodentate: 11 mol %), base (2 equiv), oxidant (O₂ and air: 1 atm, others: 2 equiv), solvent (3 mL) for 12 h. ^b NMR yield. N.R. indicates no reaction. ^c KO-*t*-Bu (2 equiv) was used instead of LiO-*t*-Bu. ^d **1a** (2 equiv) and base (3 equiv). ^e **1a** (3 equiv) and base (4 equiv). ^f Isolated yield.

A higher product yield was obtained with the larger equivalent of oxazole and base (entries 7–8). While no reaction was observed in the absence of the Pd(PPh₃)₄ species (entry 9), other Pd sources showed lower activity even in the presence of the PPh₃ ligand (entries 10–11). The reaction proceeded slowly at lower temperature while decomposition of azole was dominant at higher temperatures (entries 12–13).

Various terminal alkynes were next applied to the optimized conditions in the reaction with **1a** (Table 2). Phenylacetylenes bearing a range of substituents were coupled at the 2-position of **1a** to afford the desired products in good yields (entries 1–8). Steric bulkiness at the aryl part did not diminish the reaction efficiency as demonstrated in entry 2.¹⁰ While the reaction of phenylacetylenes substituted with electron-donating groups readily took place to provide high product yields, electron-withdrawing substituents resulted in slightly lower yields mainly due to dimerization of the alkynes (entries 6–8). 1-Naphthylacetylene and conjugated enyne readily reacted with **1a** under the optimized conditions

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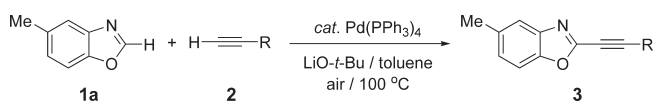
(7) Dudnik, A. S.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2010**, *49*, 2096.

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(9) For details, see the Supporting Information.

(10) This tendency was observed in the previous Ni-catalyzed reaction (ref 6m).

Table 2. Pd-Catalyzed Oxidative Alkynylation of **1a** with Various Terminal Alkynes^a



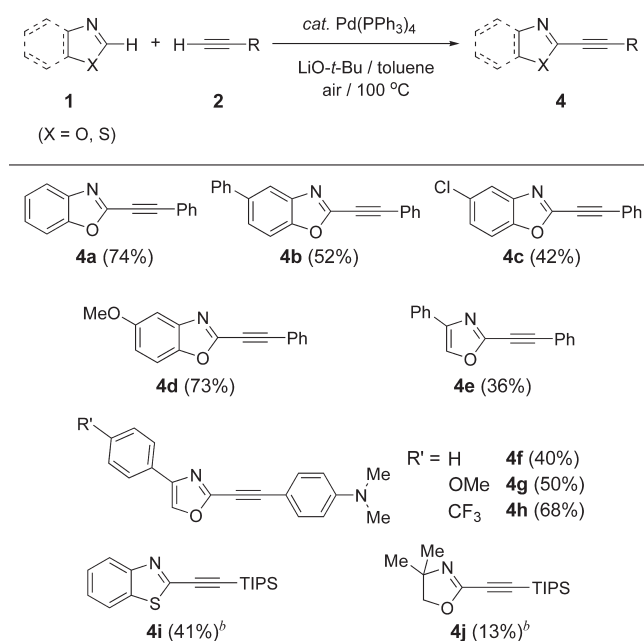
entry	R	product	yield (%) ^b
1	(4-Me)C ₆ H ₄	3b	75
2	(2-Me)C ₆ H ₄	3c	88
3	(4-MeO)C ₆ H ₄	3d	67
4	(4-PhO)C ₆ H ₄	3e	73
5	(4-Me ₂ N)C ₆ H ₄	3f	82
6 ^c	(4-CF ₃)C ₆ H ₄	3g	50
7	(4-Cl)C ₆ H ₄	3h	64
8	(4-F)C ₆ H ₄	3i	52
9	1-Naphthyl	3j	63
10	1-Cyclohexenyl	3k	67
11	3-Thiophene	3l	75
12	3-Pyridyl	3m	36
13 ^d	Cyclohexyl	3n	41
14 ^d	Triisopropylsilyl	3o	31

^a **1a** (3 equiv), **2** (0.5 mmol), Pd(PPh₃)₄ (5 mol %), LiO-*t*-Bu (4 equiv), toluene (3 mL) for 12 h. ^b Isolation yield. ^c Alkyne was slowly added. ^d The reaction was performed at 130 °C in xylene (3 mL) solvent.

(entries 9 and 10, respectively). While alkynylation of **1a** with thiophenacetylene occurred with high efficiency (entry 11), the presence of a pyridyl moiety decreased the product yield (entry 12). Importantly, an aliphatic alkyne was introduced under the conditions albeit in a rather moderate yield (entry 13). However, the reaction with linear derivatives such as 1-octyne was very sluggish only affording less than 5% product yield under the applied conditions. A silyl protected acetylene was alkynylated at the 2-position of **1a** to afford the corresponding product **3o** which would be a precursor of terminal acetylene upon desilylation (entry 14).

Alkynylation of various heterocycles was subsequently investigated under the optimized conditions (Scheme 2). Unsubstituted benzoxazole smoothly underwent the alkynylation reaction with phenylacetylene to afford **4a** in 74% yield. While the reaction of 5-substituted benzoxazoles²¹ produced the corresponding products in moderate to good yields (**4b–4d**), higher reactivity was observed with substrates bearing electron-donating groups (e.g., **4d**). Importantly, oxazoles in addition to benzoxazoles were also alkynylated selectively at the 2-position. For instance, the reaction of 4-phenyloxazole with phenylacetylene proceeded to give 2-alkynyl-4-phenyloxazole (**4e**) albeit in lower yield. Interestingly, electronic effects of substituents were observed in the reaction of 4-aryloxazoles.¹¹ Electron-withdrawing substituents on those substrates provided higher product yields (compare **4h** and **4g**). On the other hand, benzothiazole underwent the alkynylation in rather modest efficiency, and a moderate

Scheme 2. Pd-Catalyzed Oxidative Alkynylation of Heterocycles with Terminal Alkynes^a

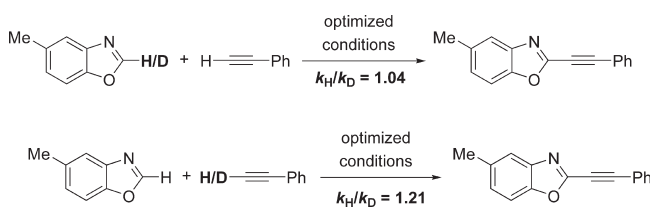


^a Conditions: **1** (3 equiv), **2** (0.5 mmol), Pd(PPh₃)₄ (5 mol %), LiO-*t*-Bu (4 equiv), toluene (3 mL) for 12 h (yield of isolated products). ^b CoCl₂ (5 mol %) was used as an additive. TIPS indicates triisopropylsilyl.

product yield was obtained in the presence of a cobalt salt while the desired product (**4i**) was formed in low yield (< 5%) in the absence of the cobalt additive.^{12,13} However, only a poor product yield (**4j**) resulted from the reaction of a partially saturated oxazoline.

In order to gain insight into the present oxidative alkynylation reaction, kinetic isotope effects (KIE) were studied with regard to the C–H/D bonds of 5-methylbenzoxazole and phenylacetylene (Scheme 3). No significant KIE values were observed in both cases, thereby indicating that the C–H bond breaking is not involved in the rate-determining step in the present alkynylation reaction.^{14,15}

Scheme 3. Kinetic Isotope Effect Study



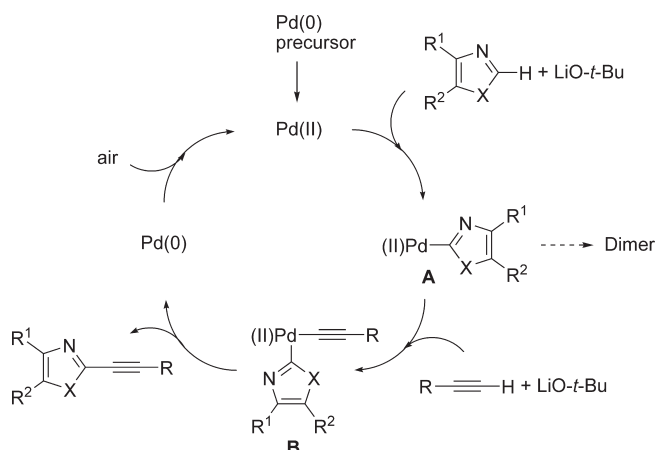
Although more comprehensive studies are required to describe the mechanistic details, a plausible pathway of the

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(12) When CoCl₂ (5 mol %) was applied without palladium, 5% (GC yield) of the desired product was formed.

(13) For a review on cooperative effects of multicatalytic systems, see: Lee, J. M.; Na, Y.; Han, H.; Chang, S. *Chem. Soc. Rev.* **2004**, 33, 302.

Scheme 4. Proposed Mechanism for the Pd-Catalyzed Oxidative Alkynylation of Heterocycle



oxidative alkynylation of azoles is shown in Scheme 4 based on the above KIE results and precedent literature.⁶ⁱ It is postulated that an initial deprotonation of an azole C(2)–H bond takes place by the action of an alkoxide base leading to a lithium azolate that is subsequently transmetalated into an *in situ* generated Pd(II) species to afford an azolyl complex of palladium(II) (**A**).¹⁶ At this stage, a dimerization pathway of azoles is envisioned to be minimized since the formation of a palladium acetylide species **B** will be highly facile. Reductive elimination of the key intermediate (**B**) is assumed to subsequently occur to give

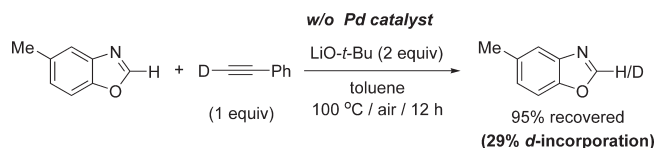
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(15) For the oxidative addition of a terminal alkyne to an iridium complex, see: Chin, C. S.; Yoon, J.; Song, J. *Inorg. Chem.* **1993**, *32*, 5901.

(16) (a) L'Helgoual'ch, J.-M.; Seggio, A.; Chevallier, F.; Yonehara, M.; Jeanneau, E.; Uchiyama, M.; Mongin, F. *J. Org. Chem.* **2008**, *73*, 177. (b) Do, H.-Q.; Khan, R. M. K.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 15185. (c) Canivet, J.; Yamaguchi, J.; Ban, I.; Itami, K. *Org. Lett.* **2009**, *11*, 1733.

the 2-alkynylazole product and Pd(0) species which is reoxidized under the aerobic conditions in accordance with the precedent literature.¹⁷

Scheme 5. Proton and Deuterium Exchange Experiment in the Absence of Palladium Species



However, the order of transmetalation into a palladium-(II) species between two lithiated substrates of azoles and 1-alkynes is not clear at the moment. In fact, a noticeable degree of proton/deuterium exchange takes place between 5-methylbenzoxazole and deuterated phenylacetylene in the absence of a palladium species (Scheme 5).

In conclusion, we have described the first example of a palladium-catalyzed oxidative alkynylation of azole heterocycles. Terminal alkynes are directly employed under aerobic conditions to afford 2-alkynylazoles in moderate to good yields. Detailed mechanistic studies and synthetic applications are currently ongoing.

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

(17) For representative references regarding the *in situ* aerobic oxidation of Pd(0) to Pd(II) species, see: (a) Schott, G. W. H.; Heimbach, P. *Angew. Chem., Int. Ed.* **1967**, *6*, 92. (b) Popp, B. V.; Stahl, S. S. *Chem.—Eur. J.* **2009**, *15*, 2915. (c) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400. (d) Adamo, C.; Amatore, C.; Ciofin, I.; Jutand, A.; Lakmini, H. *J. Am. Chem. Soc.* **2006**, *128*, 6829.