Communication
DOI: 10.1002/bkcs.12175 J. Y. Song et al. BULLETIN OF THE KOREAN CHEMICAL SOCIETY

Palladium-catalyzed Aerobic Benzannulation of Pyrazoles with Alkynes

Jae Yeong Song,[†] Jin Hyeok Jang,[†] Shih-Ching Chuang,[‡,*] and Jung Min Joo [†,*]

[†]*Department of Chemistry and Chemistry Institute for Functional Materials, Pusan National University, Busan 46241, Republic of Korea. *E-mail: jmjoo@pusan.ac.kr*
[‡]*Department of Applied Chemistry, National Chiao Tung University, Hsinchu 30010, Taiwan. *E-mail: jscchuang@faculty.nctu.edu.tw*
Received November 28, 2020, Accepted December 2, 2020

Keywords: Pyrazole, Alkyne, Oxygen, Palladium, C─H activation

Pd-catalyzed C─H functionalization of heteroarenes has been established as an important strategy to access heteroarene-containing extended π-systems.[1] In particular, alkynes have been useful building blocks in the development of benzannulated heteroaromatic systems.[2] In these processes, two new C─C bonds are formed by functionalizing two C─H bonds of the heteroarene ring. Thus, it is necessary to employ stoichiometric quantities of oxidants, which are usually expensive and toxic metal oxidants.[3] Alternatively, oxygen has been used as an environmentally friendly oxidant in Pd-catalyzed oxidative transformations.[4] However, the regeneration of Pd(II) species from Pd(0) species in alkyne annulation has mostly been dependent on the use of Ag or Cu salts, presumably because of the inhibitory effect of alkynes strongly coordinated to palladium.[5]

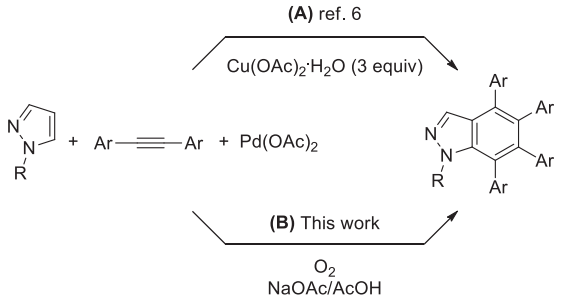
We recently reported Pd-catalyzed benzannulation reactions of pyrazoles with internal alkynes, in which Cu $(OAc)_2{\cdot}H_2O$ was employed as a stoichiometric oxidant Scheme 1(A)).[6] This method was useful for rapidly forming fluorescent tetraaryl indazoles and was later applied to the synthesis of fluorescent polymers.[7] However, the use of stoichiometric quantities of metal oxidants limits their application for synthesizing fluorescent materials because it is difficult to completely remove residual copper, which is likely to coordinate to the nitrogen heterocycles.[8] To eliminate the dependency on metal oxidants, we developed Pd-catalyzed aerobic C─H annulation of pyrazoles using oxygen as the sole oxidant Scheme 1(B)). The difference between the Cu-mediated reactions and this method and its scope are described.

Reaction optimization was performed using *N*-methylpyrazole and diphenylacetylene (Table 1). The initial experiment under an oxygen balloon resulted in low conversion and was significantly less efficient than the original protocol using $Cu(OAc)_2{\cdot}H_2O$ (entries 1 and 2). However, the addition of AcOH and KOAc increased the yield (entries 3 and 4). More importantly, the combination of carboxylic acids and carboxylate salts afforded consistently high yields, among which sodium acetate and acetic acid proved to be optimal (entries 5–7). Presumably, the buffer was beneficial to provide a balance among palladium acetate species throughout the reaction.[9] Solvent screening indicated that DMA was the optimal medium (entries 8–10). Purging with oxygen followed by heating under a closed cap afforded **2a** in a higher yield than using an oxygen balloon (entry 11). The improvement was more evident with relatively unreactive pyrazoles (*e.g.* **2b**: 48% vs. 78% yields). The reaction set up on the benchtop resulted in a slightly reduced yield compared to those performed under an oxygen atmosphere (entry 12).

The scope of the aerobic benzannulation method was studied by varying the pyrazole substituents (Table 2). Various alkyl groups at the nitrogen atom of the pyrazole ring, including the SEM protecting group, were tolerated (entries 1–5). However, *N*-phenyl pyrazole did not undergo a benzannulation reaction, presumably because of the formation of a palladacycle through the *ortho*-position of the phenyl ring (entry 6).[10] Both C3-methyl- and trifluoromethyl-substituted pyrazoles were converted to the corresponding benzannulation products in good yields (entries 7 and 8). Diarylacetylenes with electronically different *para*-substituents were also coupled with *N*-methylpyrazole under aerobic conditions (entries 9–11). However, reactions with alkyl alkynes yielded only trace amounts of the desired products. This suggests a limitation of the aerobic method compared to the Cu-mediated reaction, which afforded moderate yield (not shown).[6]

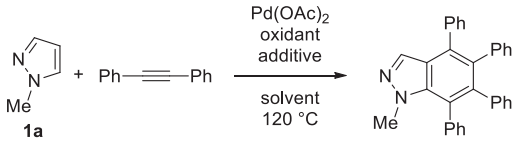
To further compare the aerobic and Cu-mediated methods, 1:1 annulation reactions of phenylpyrazoles with an alkyne were performed (Scheme 2). The general reactivity of pyrazoles indicates that electrophilic substitution occurs at the C4 position, whereas deprotonation with a strong base favors the C5 position.[11] The aerobic method was superior to the Cu method for C─H annulation at the pyrazole C5 position, as the added carboxylate-assisted metalation of the acidic C─H bond Scheme 2(A)).[12] However, these two methods did not produce significantly different results for the annulation at the C4 position Scheme 2(B)). Interestingly, the least reactive C3 position was functionalized, preferentially generating the corresponding 1:2 annulation product (**4c**) over the 1:1 annulation product (**4b**). This result suggests that after the first

BULLETIN OF THE
KOREAN CHEMICAL SOCIETY



Scheme 1. Benzannulation of pyrazoles using oxidants.

Table 1. C–H annulation of *N*-methylpyrazole.[a]



Entry	Oxidant	Additive	Solvent	Yield (%)
1[b]	Cu $(OAc)_2·H_2O$	–	DMA	63
2	O_2	–	DMA	29
3	O_2	AcOH	DMA	43
4	O_2	KOAc	DMA	64
5[c]	O_2	KOAc/AcOH	DMA	68
6[c]	O_2	NaOAc/AcOH	DMA	76(75)[d]
7[c]	O_2	NaOPiv/PivOH	DMA	68
8[c]	O_2	NaOAc/AcOH	DMSO	21
9[c]	O_2	NaOAc/AcOH	PhCl	38
10[c]	O_2	NaOAc/AcOH	DMF	64
11[c,e]	O_2	NaOAc/AcOH	DMA	78(77)[d]
12[c,f]	Air	NaOAc/AcOH	DMA	72

[a] Reaction conditions: *N*-methylpyrazole (0.20 mmol), diphenylacetylene (0.60 mmol), $Pd(OAc)_2$ (0.010 mmol), additive (0.40 mmol), solvent (0.20 M), 120°C, 16 h, O_2 balloon. Yield determined by ^{1}H NMR.

[b] With $Cu(OAc)_2·H_2O$ (0.60 mmol).

[c] With a carboxylate and carboxylic acid (0.20 mmol, each).

[d] Isolated yield.

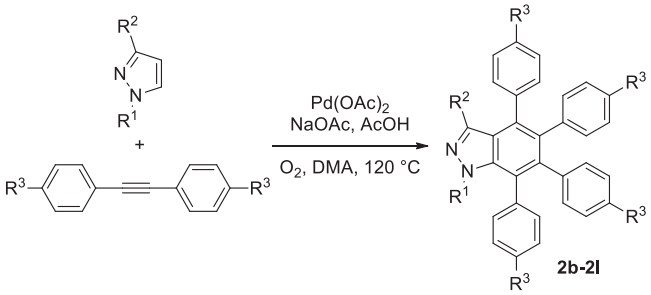
[e] Purged with O_2 and heated under a closed cap.

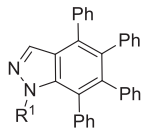
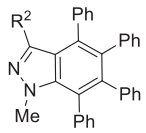
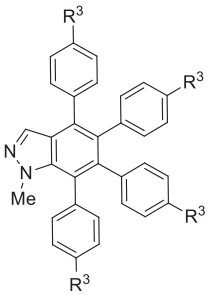
[f] Prepared on the benchtop and heated under a closed cap.

addition of the alkyne, the second addition was more facile than ring closure with the phenyl group. In addition, this represents the first example of C3,C4-benzannulation of a pyrazole to provide a (*2H*)-indazole.

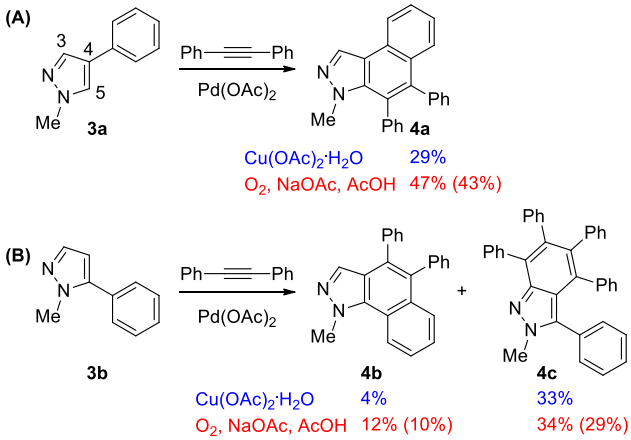
In conclusion, we developed Pd-catalyzed aerobic annulation reactions of pyrazoles. Using oxygen as an oxidant, 1:2 and 1:1 annulation reactions of pyrazoles with alkynes

Table 2. Substrate scope of C–H annulation.[a]



Entry	Product		Yield (%)
1		R^1 = *n*Bu	**2b** (78%)
2		*n*Hex	**2c** (68%)
3		$(CH_2)_2Ph$	**2d** (45%)
4		SEM	**2e** (59%)
5		$(CH_2)_2CO_2nBu$	**2f** (30%)
6		Ph	**2g** (0%)
7		R^2 = Me	**2h** (65%)
8		CF_3	**2i** (63%)
9		R^3 = Me	**2j** (65%)
10		MeO	**2k** (60%)
11		F	**2l** (48%)

[a] Reaction conditions: a pyrazole (0.20 mmol), diarylacetylene (0.60 mmol), $Pd(OAc)_2$ (0.010 mmol), NaOAc (0.20 mmol), AcOH (0.20 mmol), DMA (0.20 M), 120°C, 16 h, under O_2. Isolated yields.



Scheme 2. 1:1 Annulation of phenylpyrazoles. ^{1}H NMR yield. Isolated yield in parentheses.

were achieved. Complementary to the Pd-catalyzed, Cu-mediated annulation reaction of pyrazoles, this aerobic approach will be useful in providing various indazoles

without Cu salt contamination. The application of this aerobic method for the preparation of other heterocycles is under investigation and will be reported in due course.

Acknowledgments. This work was funded by the National Research Foundation of Korea (NRF-2019R1A2C1007852 and NRF-2019R1A4A1028007. Supporting Information. Additional supporting information may be found online in the Supporting Information section at the end of the article. The corrected version Supporting Information. Experimental procedures,compound characterization data, and NMR spectra can be found online in the Supporting Information section at the end of the article.

Supporting Information. Additional supporting information may be found online in the Supporting Information section at the end of the article.

References

1. (a) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174. (b) L. Ackermann, R. Vicente, A. R. Kapdi, *Angew. Chem. Int. Ed.* **2009**, *48*, 9792. (c) S. H. Cho, J. Y. Kim, J. Kwak, S. Chang, *Chem. Soc. Rev.* **2011**, *40*, 5068. (d) Y. Segawa, T. Maekawa, K. Itami, *Angew. Chem. Int. Ed.* **2015**, *54*, 66. (e) H. Ito, K. Ozaki, K. Itami, *Angew. Chem. Int. Ed.* **2017**, *56*, 11144. (f) C. B. Bheeter, L. Chen, J.-F. Soule, H. Doucet, *Catal. Sci. Technol.* **2016**, *6*, 2005. (g) Y. Yang, J. Lan, J. You, *Chem. Rev.* **2017**, *117*, 8787. (h) P. Y. Choy, S. M. Wong, A. Kapdi, F. Y. Kwong, *Org. Chem. Front.* **2018**, *5*, 288.
2. (a) T. Satoh, M. Miura, *Chem.–Eur. J.* **2010**, *16*, 11212. (b) J. Le Bras, J. Muzart, *Synthesis* **2014**, *46*, 1555. (c) A. Park, S. M. Choi, T. S. Kim, E. K. Yum, *Bull. Kor. Chem. Soc.* **2019**, *40*, 1134. (d) J.-Y. Son, C. Maeng, P. H. Lee, *Bull. Kor. Chem. Soc.* **2020**, *41*, 388.
3. (a) M. Yamashita, H. Horiguchi, K. Hirano, T. Satoh, M. Miura, *J. Org. Chem.* **2009**, *74*, 7481. (b) K. Fukuzumi, Y. Unoh, Y. Nishii, T. Satoh, K. Hirano, M. Miura, *J. Org. Chem.* **2016**, *81*, 2474. (c) X. Yang, L. Jiang, M. Yang, H. Zhang, J. Lan, F. Zhou, X. Chen, D. Wu, J. You, *J. Org. Chem.* **2018**, *83*, 9538. (d) S. Wu, Z. Wang, D. Ma, C. Chen, B. Zhu, *Org. Chem. Front.* **2020**, *7*, 1158.
4. D. Wang, A. B. Weinstein, P. B. White, S. S. Stahl, *Chem. Rev.* **2018**, *118*, 2636.
5. A. Jutand, *Chem. Rev.* **2008**, *108*, 2300.
6. O. S. Kim, J. H. Jang, H. T. Kim, S. J. Han, G. C. Tsui, J. M. Joo, *Org. Lett.* **2017**, *19*, 1450.
7. Q. Gao, T. Han, Z. Qiu, R. Zhang, J. Zhang, R. T. K. Kwok, J. W. Y. Lam, B. Z. Tang, *Polym. Chem.* **2019**, *10*, 5296.
8. A. Tigreros, J. Portilla, *RSC Adv.* **2020**, *10*, 19693.
9. J. Váňa, J. Bartáček, J. Hanusek, J. Roithová, M. Sedlák, *J. Org. Chem.* **2019**, *84*, 12746.
10. (a) N. Umeda, H. Tsurugi, T. Satoh, M. Miura, *Angew. Chem. Int. Ed.* **2008**, *47*, 4019. (b) N. Umeda, K. Hirano, T. Satoh, N. Shibata, H. Sato, M. Miura, *J. Org. Chem.* **2011**, *76*, 13.
11. (a) R. Goikhman, T. L. Jacques, D. Sames, *J. Am. Chem. Soc.* **2009**, *131*, 3042. (b) E. Kang, H. T. Kim, J. M. Joo, *Org. Biomol. Chem.* **2020**, *18*, 6192.
12. L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315.

