Organic LETTERS

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Palladium-Catalyzed Aerobic Oxidative C–H Olefination with Removable 1,2,3-Triazole Directing Group

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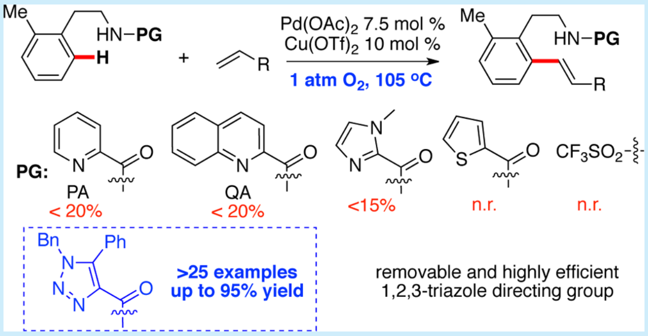
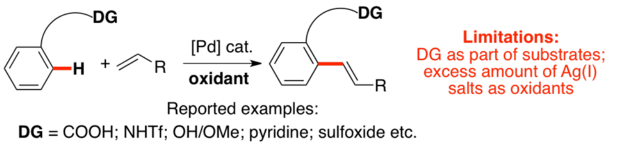
Supporting Information

ABSTRACT: *Ortho*-olefination of arenes was achieved with removable 1,2,3-triazole auxiliary through Pd-catalyzed C–H activation. Excellent yields were received even when molecular O_2 (1 atm) was used as the terminal oxidant. Other heterocyclic directing groups, such as pyridine and quinoline, gave poor reactivity under this aerobic oxidative condition, which highlighted the unique reactivity of triazole in promoting directed C–H activation.



During the past decade, transition metal catalyzed C–H functionalization has been utilized as an efficient approach in complex molecule synthesis.[1] The Pd-mediated C–H olefination of arenes has been reported since 1960s (Fujiwara-Moritani oxidative Heck reaction).[2] However, poor selectivity remains a challenge for this transformation, since selectivity usually relies on the reactivity of different C–H bonds for given substrates.[3] To achieve selective C–H functionalization, various directing groups (DGs), such as OR, COOH and pyridine, have been developed (Scheme 1).[4,5]

Scheme 1. Selective C–H Olefination Using Directing Groups



As amine is usually not an effective directing group, one interesting approach is the removable amide protecting group as chelating directing group.[6] Among literature reported examples, picolinic acid (PA) and quinaldic acid (QA) moieties were the most successful precursors.[7] Interestingly, neither compound has been used as a viable directing group for C–H olefination under oxidative heck conditions.[8] In fact, our later studies (*vide infra*) confirmed that PA and QA could not promote effective C–H olefination due to the rapid Pd decomposition (formation of palladium black). The only successful example of C–H olefination using the removable DG strategy was the -NHTf system reported by Yu and co-workers.[9] However, in that case, excess silver salts (2.5 equiv) were required as the oxidant to facilitate the reaction. Herein, we report the 1,2,3-triazole-4-carboxylic acid as the removable directing group (formation of triazole amide) in promoting selective C–H olefination. This new triazole DG not only gives the desired products in excellent yields (up to 95%), but also allows molecular oxygen (1 atm) to be used as terminal oxidant under "open-flask" conditions, emphasizing the high efficiency of this new triazole DG in promoting inactive C–H functionalization.

During the last several years, our group has been working on triazole ligand promoted transition metal catalysis.[10] Recently, we reported 1,2,3-triazole (TA) as a new versatile removable directing group in promoting sp^2 and sp^3 C–H activation using $PhI(OAc)_2$ as the oxidant.[11] Impressively, the triazole DGs indicated excellent chemoselectivity, achieving selective C–N reductive elimination (cyclization) or C–O reductive elimination (substitution) through alternating the triazole DG coordination patterns (TA(Bn) vs TA-Py, Figure 1A). Encouraged by the result that TA-Py DG successfully avoided cyclization, we put our attention on directed C–H activation, namely, C–H olefination. This is because A) as mentioned above, directed C–H olefination is a very useful transformation with few economic methods available in literature, and B) this Heck-type transformations will not only provide a good platform to evaluate the performance of TA-directing group under Pd(0)–Pd(II) conditions, but also create the possibility of using molecular O_2 as the oxidant to substitute the expensive $PhI(OAc)_2$. The TA-Py modified amide **1** was then prepared to react with *n*-butyl acrylate (Figure 1B).

Unfortunately, under previous standard conditions ($PhI(OAc)_2$ as the oxidant, 100 °C), no C–H olefination was observed, though the undesired cyclization was successfully prevented (complete recovery of starting material). Interest-

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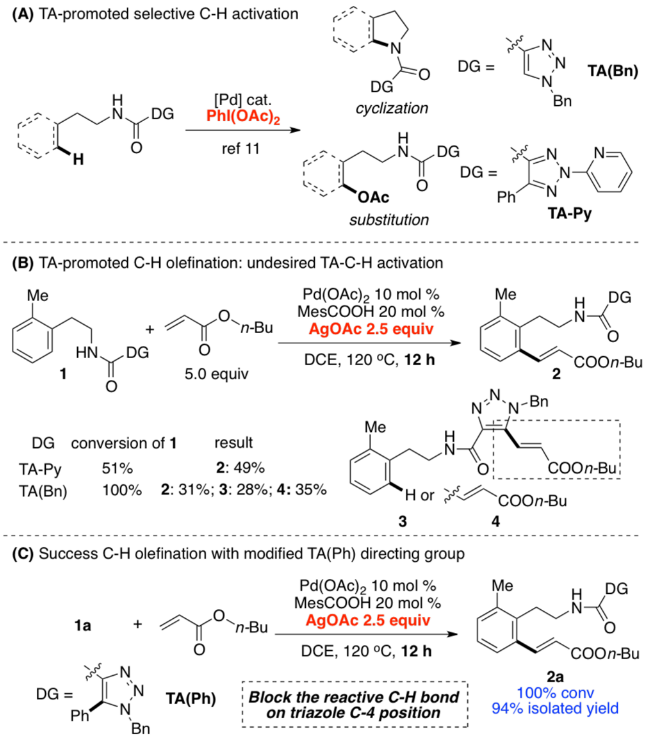


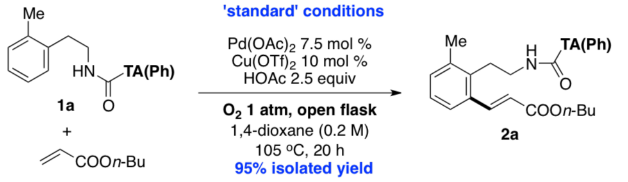
Figure 1. Triazole group directed C−H activation.

ingly, a brief screening revealed AgOAc (2.5 equiv) as effective oxidant to promote this C−H olefination, giving the desired alkene **2** in good yield (51% conversion and 49% yield). Moreover, cyclization product was not observed even with the bidentate TA(Bn) as the directing group under this new conditions (AgOAc as oxidant). In fact, the desired C−H olefination product **2** was obtained in 31% yield along with olefination on the triazole C−H bond (**4**, 35% yield). Thus, Pd-catalyzed direct triazole C−H activation, which has been reported by Ackermann, Jiang and others[12] is the main problem for achieving C−H olefination with good selectivity. We then postulated that the 4,5-disubsituted triazoles TA(Ph) shown in Figure 1C, should be of effective DG to promote this C−H olefination by blocking the reactive triazole C−H bond. As expected, reaction of TA(Ph) modified **1a** under the standard condition gave the desired C−H olefination product **2a** in excellent yield (94%, Figure 1C).

This result was crucial since it confirmed the possibility of using triazole DG to promote C−H activation under Pd(0)−Pd(II) conditions. Considering the low redox potential between Pd(0) and Pd(II), we put our effort into exploring the feasibility of using molecular O_2 as the terminal oxidant.[13,14] The screening of conditions is summarized in Table 1.

First, the TA(Ph) amide alone could give the desired C−H olefination with O_2 as oxidant (entry 2), though in low yield (22%). Addition of HOAc (2.5 equiv) slightly improved the reaction performance (entry 3) with a significant amount of **1a** leftover. Finally, addition of $Cu(OTf)_2$ cocatalyst (10 mol %) led to complete **1a** conversion, giving the desired C−H olefination product **2a** in excellent isolated yield (95%).[15] To the best of our knowledge, this is the first successful example of removable directing group promoted C−H olefination using O_2 as the terminal oxidant.[16]

Table 1. Selected Optimization of Reaction Conditions[a,b]



entry	variations from the “standard” conditions	conversion of **1a** (%)	yield of **2a** (%)
1	w/o $Pd(OAc)_2$	0	0
2	w/o HOAc and $Cu(OTf)_2$	24	22
3	w/o $Cu(OTf)_2$	30	28
4	w/o HOAc	50	48
5	$CuCl_2$ instead of $Cu(OTf)_2$	<5	<5
6	$Cu(OAc)_2$ instead of $Cu(OTf)_2$	65	61
7	HOAc as solvent	33	31
8	toluene as solvent	78	75
9	$PdCl_2$ instead of $Pd(OAc)_2$	<10	<10
10	air	75	60
11	no O_2 (Ar protection)	trace	trace

[a]Reaction conditions: 1(0.1 mmol), *n*-butyl acrylate (0.4 mmol), catalyst, additives, and solvent (0.2 M) in a 20 mL Schlenk tube with O_2 balloon. [b]Determined by ^1H NMR using 1,3,5 trimethoxybenzene as internal standard;

Substrates containing other common directing groups were also prepared and evaluated under the same conditions. As shown in Figure 2, poor yields were obtained in all tested cases, including PA- and QA-modified substrates. These results highlighted the unique reactivity of 1,2,3-triazole directing groups in promoting C−H activation. Triazole ester and *N*-methyltriazole amide gave no reactions, which was consistent with the chelation model (for successful C−H activation) as reported in other similar systems. To evaluate the reaction scope, various TA(Ph)-modified substrates were prepared and treated under the optimal conditions.

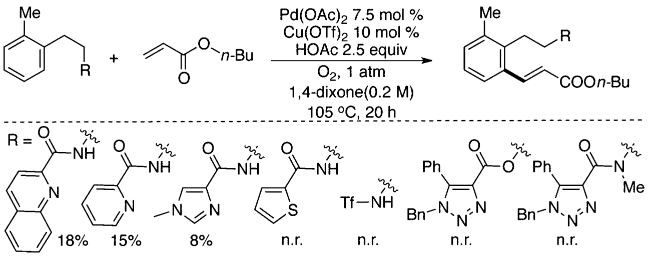


Figure 2. Evaluation of other directing groups.

As shown in Figure 3, this new TA-directing group tolerated a large number of substrates, furnishing the corresponding olefination in good to excellent yields. Both EDG (**2b**) and EWG (**2c**) modified arenes were suitable for this reaction. Notably, substrates with *ortho*-halides (**2c**, **2d**) could survive the reaction, giving the desired C−H activation (over oxidative addition) in good yields. Good regioselectivity was obtained for the *meta*-substituted benzenes, with substitution occurring primarily at the less hindered *ortho*-carbons position (**2e−g**). Typically, the selectivity of mono- and diolefination would be poor when both *ortho*-C−H’s were present (**2j** and **2k**). This problem was overcome by increasing the steric bulkiness at the benzylic position. As shown in **2l**, incorporation of a methyl group effectively improved the m:d selectivity to >20:1. Meanwhile, use of an excess amount of alkene (12 equiv) gave the diolefination in good yields (**2m**,**o**). The scope of

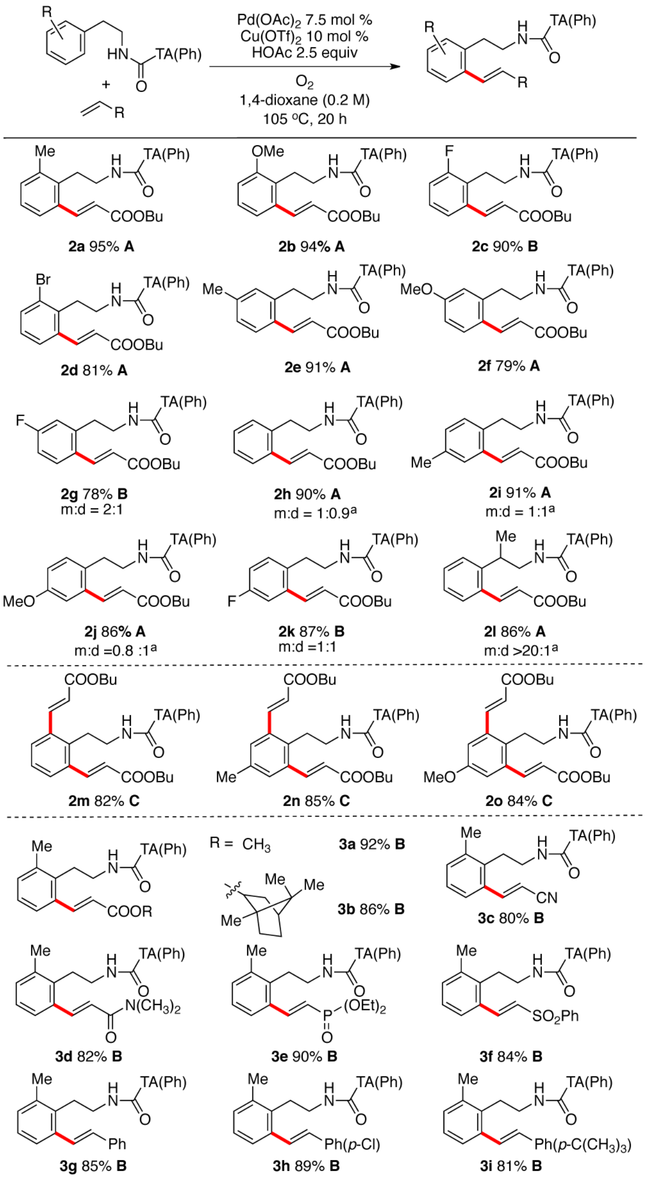


Figure 3. Substrate scope. General reaction conditions: **1** (0.2 mmol), alkene (0.8 mmol), HOAc (5.0 mmol), and catalyst in 1,4-dioxane (1.0 mL). Conditions A: 7.5 mol % of $Pd(OAc)_2$ and 10 mol % of $Cu(OTf)_2$, O_2 balloon, 105 °C, 20 h. Conditions B: 10 mol % of $Pd(OAc)_2$ and 10 mol % of $Cu(OTf)_2$, 1 atm of O_2 charged in sealed tube, 115 °C, 20 h. Conditions C: 15 mol % of $Pd(OAc)_2$ and 10 mol % of $Cu(OTf)_2$, 2.4 mmol of *n*-butyl acrylate, 1 atm of O_2 charged in sealed tube, 115 °C, 20 h. Isolated yield. [a]The ratio of mono and di substitution was determined by ^{1}HNMR.

alkene was also evaluated. Besides acrylate, most of other activated alkenes, such as acrylonitrile (**3c**), acrylamide (**3d**), vinyl phosphate (**3e**), and vinyl sulfone (**3f**), are suitable for this transformation, giving the desired olefins in excellent yields. Impressively, nonactive olefins, such as styrene derivatives, could also undergo this transformation with good to excellent yields (**3g−i**). However, similar to other reported Heck-type reactions, α- or β-substituted alkenes failed to give the desired products due to steric hindrance on either alkene insertion or β-hydride elimination steps. Nevertheless, the broad substrate scope, simple reaction conditions and use of oxygen as the oxidant highlighted the advantages of this new triazole-directing group in promoting selective C−H olefination.

Kinetic isotope studies were also performed to probe the reaction mechanism. A primary KIE was observed (K_H/K_D = 2.1) as shown in Figure 4A, suggesting a C−H activation over a Lewis acid catalyzed Friedel−Crafts-type mechanism. Removal of TA directing group was demonstrated in Figure 4B using the general protocol reported by Chen.[16a] The Boc protected alkene−amine was obtained in excellent yield. Finally, treating the resulting acrylate−amide product (**3a**) with NaH gave the tetrahydroisoquinoine in excellent yield (Figure 4C), further highlighting the efficiency and potential application of this method in complex molecules synthesis.

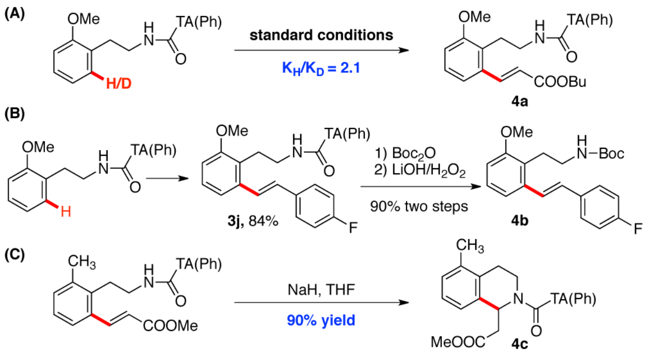


Figure 4. Kinetic Isotope effect and derivatization.

In conclusion, we have unveiled 1,2,3-triazole as an effective directing group in promoting aerobic C−H oxidative olefination. This study not only revealed a new efficient and economic approach (using 1 atm of O_2 as the terminal oxidant) in achieving selective C−H olefination but also confirmed the versatile reactivity of 1,2,3-triazole in promoting metal catalyzed C−H activation. Other synthetic applications using this new TA-directed C−H activation strategy are currently under investigation.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507. (b) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077. (c) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. (d) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417. (e) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem. Int. Ed.* **2009**, *48*, 9792. (f) Giri, R.; Shi, B.-F.; Engle, K. M.; Maugel, N.; Yu, J.-Q. *Chem. Soc. Rev.* **2009**, *38*, 3242. (g) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068. (h) Wencel-Delord, J.; Droege, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740. (i) Yeung, C. S.; Dong, V. M. *Chem. Rev.*

2011, *111*, 1215. (j) Song, G.; Wang, F.; Li, X. *Chem. Soc. Rev.* **2012**, *41*, 3651.

(2) (a) Moritani, I.; Fujiwara, Y. *Tetrahedron Lett.* **1967**, 1119. (b) Le Bras, J.; Muzart, J. *Chem. Rev.* **2011**, *111*, 1170.

(3) For recent examples of transition metal catalyzed nondirected C-H olefination of arene, see: (a) Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 5072. (b) Kubota, A.; Emmert, M. H.; Sanford, M. S. *Org. Lett.* **2012**, *14*, 1760. (c) Ying, C.-H.; Yan, S.-B.; Duan, W.-L. *Org. Lett.* **2014**, *16*, 500. (d) Vora, H. U.; Silvestri, A. P.; Engelin, C. J.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2014**, *53*, 2683.

(4) For recent examples of Pd-catalyzed directing C-H olefination, see: (a) Wang, D.-H.; Engle, K. M.; Shi, B.-F.; Yu, J.-Q. *Science* **2010**, *327*, 315. (b) Lu, Y.; Wang, D.-H.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 5916. (c) Garcia-Rubia, A.; Angeles Fernandez-Ibanez, M.; Gomez Arrayas, R.; Carlos Carretero, J. *Chem.—Eur. J.* **2011**, *17*, 3567. (d) Wang, C.; Ge, H. *Chem.—Eur. J.* **2011**, *17*, 14371. (e) Yu, M.; Xie, Y.; Xie, C.; Zhang, Y. *Org. Lett.* **2012**, *14*, 2164. (f) Gandeepan, P.; Cheng, C.-H. *J. Am. Chem. Soc.* **2012**, *134*, 5738. (g) Meng, X.; Kim, S. *Org. Lett.* **2013**, *15*, 1910. (h) Wang, B.; Shen, C.; Yao, J.; Yin, H.; Zhang, Y. *Org. Lett.* **2013**, *16*, 46. (i) Dai, H.-X.; Li, G.; Zhang, X.-G.; Stepan, A. F.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 7567. (j) Tang, R.-Y.; Li, G.; Yu, J.-Q. *Nature* **2014**, *507*, 215.

(5) For recent examples of other metal catalyzed directing C-H olefination: see: (a) Kwon, K.-H.; Lee, D. W.; Yi, C. S. *Organometallics* **2010**, *29*, 5748. (b) Feng, C.; Loh, T.-P. *Chem. Commun.* **2011**, *47*, 10458. (c) Garcia-Rubia, A.; Angeles Fernandez-Ibanez, M.; Gomez Arrayas, R.; Carlos Carretero, J. *Chem.—Eur. J.* **2011**, *17*, 3567. (d) Padala, K.; Jeganmohan, M. *Org. Lett.* **2011**, *13*, 6144. (e) Patureau, F. W.; Besset, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 1064.

(6) For examples of other amide as directing group for Pd catalyzed C-H functionalization of acid derivatives, see: (a) Yoo, E. J.; Wasa, M.; Yu, J.-Q *J. Am. Chem. Soc.* **2010**, *132*, 17378. (b) Ano, Y.; Tobisu, M.; Chatani, N. *Org. Lett.* **2011**, *14*, 354. (c) Ano, Y.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 12984. (d) Dai, H.-X; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *134*, 134. (e) Wasa, M.; Chan, K. S. L; Zhang, X.-G; He, J.; Miura, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2012**, *134*, 18570−18572. (f) Zhang, X.-G; Zhang, H.-X.; Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2012**, *134*, 11948−11951. (g) Tran, L. D.; Daugulis, O. *Angew. Chem., Int. Ed.* **2012**, *51*, 5188−5191. (h) Chen, F.-J.; Zhao, S.; Hu, F.; Chen, K.; Zhang, Q.; Zhang, S.-Q.; Shi, B.-F. *Chem. Sci.* **2013**, *4*, 4187. (i) Zhang, Q.; Chen, K.; Rao, W.; Zhang, Y.; Chen, F.-J.; Shi, B.-F. *Angew. Chem., Int. Ed.* **2013**, *52*, 13588.

(7) For examples of picolinic amide as directing group, see: (a) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154. (b) Nadres, E. T.; Daugulis, O. *J. Am. Chem. Soc.* **2011**, *134*, 7. (c) Zhang, S.-Y.; He, G.; Zhao, Y.; Wright, K.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2012**, *134*, 7313. (d) Zhang, S.-Y.; He, G.; Nack, W. A.; Zhao, Y.; Li, Q.; Chen, G. *J. Am. Chem. Soc.* **2013**, *135*, 2124.

(8) For examples of picolinic amide as directing group for C-H olefination using vinyl iodides., see: (a) He, G.; Chen, G. *Angew. Chem., Int. Ed.* **2011**, *50*, 5192. (b) Zhao, Y.; He, D.; Nack, W. A.; Chen, G. *Org. Lett.* **2012**, *14*, 2948.

(9) (a) Li, J.-J.; Mei, T.-S.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 6452. (b) Liu, Q.; Li, Q.; Ma, Y.; Jia, Y. *Org. Lett.* **2013**, *15*, 4528.

(10) (a) Duan, H. F.; Sengupta, S.; Petersen, J. L.; Akhmedov, N. G.; Shi, X. D. *J. Am. Chem. Soc.* **2009**, *131*, 12100. (b) Duan, H. F.; Sengupta, S.; Petersen, J. L.; Shi, X. D. *Organometallics* **2009**, *28*, 2352. (c) Liao, W. Y.; Chen, Y. F.; Liu, Y. X.; Duan, H. F.; Petersen, J. L.; Shi, X. D. *Chem. Commun.* **2009**, 6436. (d) Chen, Y. F.; Yan, W. M.; Akhmedov, N. G.; Shi, X. D. *Org. Lett.* **2010**, *12*, 344. (e) Wang, D. W.; Ye, X. H.; Shi, X. D. *Org. Lett.* **2010**, *12*, 2088. (f) Yan, W. M.; Ye, X. H.; Akhmedov, N. G.; Petersen, J. L.; Shi, X. D. *Org. Lett.* **2012**, *14*, 2358. (g) Yan, W. M.; Ye, X. H.; Weise, K.; Petersen, J. L.; Shi, X. D. *Chem. Commun.* **2012**, *48*, 3521. (h) Xi, Y. M.; Wang, D. W.; Ye, X. H.; Akhmedov, N. G.; Petersen, J. L.; Shi, X. D. *Org. Lett.* **2014**, *16*, 306. (i) Xi, Y. M.; Dong, B. L.; McClain, E. J.; Wang, Q. Y.; Gregg, T. L.; Akhmedov, N. G.; Petersen, J. L.; Shi, X. D. *Angew. Chem., Int. Ed.* **2014**, *53*, 4657. (j) Wang, Q. Y.; Motika, S. E.; Akhmedov, N. G.; Petersen, J. L.; Shi, X. D. *Angew. Chem., Int. Ed.* **2014**, *53*, 5418.

(11) Ye, X. H.; He, Z. R.; Ahmed, T.; Weise, K.; Akhmedov, N. G.; Petersen, J. L.; Shi, X. D. *Chem. Sci.* **2013**, *4*, 3712.

(12) For recent examples of C-H funcationization on C-4 of 1,2,3-triazole, see: (a) Chuprakov, S.; Chernyak, N.; Dudnik, A. S.; Gevorgyan, V. *Org. Lett.* **2007**, *9*, 2333. (b) Iwasaki, M.; Yorimitsu, H.; Oshima, K. *Chem. Asian. J.* **2007**, *2*, 1430. (c) Ackermann, L.; Vicente, R.; Born, R. *Adv. Synth. Catal.* **2008**, *350*, 741. (d) Jiang, H.; Feng, Z.; Wang, A.; Liu, X.; Chen, Z. *Eur. J. Org. Chem.* **2010**, *2010*, 1227. (e) Liu, W.; Li, Y.; Xu, B.; Kuang, C. *Org. Lett.* **2013**, *15*, 2342.

(13) (a) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400. (b) Campbell, A. N.; Stahl, S. S. *Acc. Chem. Res.* **2012**, *45*, 851. (c) Shi, Z.; Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3381.

(14) For examples of Pd-catalzyed C-H olefination using O_2 as terminal oxidant, see: (a) Beck, E. M.; Grimster, N. P.; Hatley, R.; Gaunt, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 2528. (b) Wang, J.-R.; Yang, C.-T.; Liu, L.; Guo, Q.-X. *Tetrahedron Lett.* **2007**, *48*, 5449. (c) Cong, X.; You, J.; Gao, G.; Lan, J. *Chem. Commun.* **2013**, *49*, 662. (d) Liu, B.; Jiang, H.-Z.; Shi, B.-F. *J. Org. Chem.* **2014**, *79*, 1521.

(15) (a) Werner, E. W.; Sigman, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 13981. (b) Mei, T.-S.; Werner, E. W.; Burckle, A. J.; Sigman, M. S. *J. Am. Chem. Soc.* **2013**, *135*, 6830.

(16) For other two examples of PA auxiliary directing C-H functionlization using O_2 as terminal oxidant, see: (a) Zhao, Y.; Chen, G. *Org. Lett.* **2011**, *13*, 4850. (b) Zhang, L.-S.; Chen, G.; Wang, X.; Guo, Q.-Y.; Zhang, X.-S.; Pan, F.; Chen, K.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2014**, *53*, 3899.