Selective C(sp^2)–H Halogenation of "click" 4-Aryl-1,2,3-triazoles

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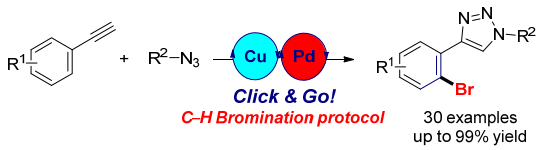
Supporting Information Placeholder

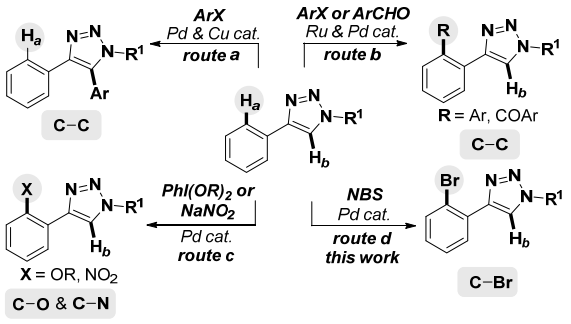
ABSTRACT: Selective bromination reactions of "click compounds" are described. Electron-neutral and electron-deficient arenes selectively undergo unprecedented Pd-catalyzed C–H *ortho*-halogenations assisted by simple triazoles as modular directing groups whereas electron-rich arenes are regioselectively halogenated following an electrophilic aromatic substitution reaction pathway. These C–H halogenation procedures exhibit a wide group tolerance, complement existing bromination procedures and represent versatile synthetic tools of utmost importance for the late-stage diversification of "click compounds". The characterization of a triazole-containing palladacycle and Density Functional Theory (DFT) studies supported the mechanism proposal.



The carbon–halogen bond is undoubtedly a major workhorse within the realm of organic chemistry.[1] In particular, aryl halides are prevalent key motifs in a vast array of natural products and stand out as highly versatile compounds of widespread utility in chemical industry for the assembly of numerous relevant medicinal products and agrochemicals.[2] As a result, the development of novel and practical halogenation procedures is of prime synthetic value in basic and applied chemistry. Classical approaches include electrophilic aromatic substitution (EAS),[3] halogenation of aryldiazonium salts (Sandmeyer reaction)[4] and directed *ortho*-lithiation/halogenation sequence.[5] Despite their common use, those methods suffer from notable drawbacks such as harsh reaction conditions often involving hazardous reagents and mostly lack of regioselectivity across many substrate classes. The last decade has witnessed an increasing interest in the pursuit of selective chelation-directed metal-catalyzed C–H halogenations which are of utmost importance from a sustainability standpoint.[1b] Although a wide variety of directing groups (DGs) have been effectively utilized for the halogenation of C(sp^2)–H bonds,[6,7] expanding the scope to other versatile motifs remains a critical challenge of tremendous impact in the field of C–H functionalization.[8]

1,2,3-Triazole core is a prevalent heterocyclic structure in a wide range of compounds in distinct research areas such as crop protection, medicinal chemistry and material sciences.[9] However, its unique properties have not been fully exploited in the field of metal catalysis.[10] In particular, 4-aryl-1,2,3-triazoles resulting from the atom-economical Cu-catalyzed azide-alkyne [3+2] cycloaddition (CuAAC)[11] represent an ideal platform to design novel C–H functionalization events. If successful, such methods would constitute versatile techniques for the unexplored chemoselective late-stage derivatization of "click compounds".[12] Most of the post-functionalizations of 4-aryl-1,2,3-triazoles involve C–C bond-forming processes such as Pd- or Cu-catalyzed direct arylations selectively occurring at the heterocyclic C–H bond[13] (Scheme 1, *route a*), or triazole-assisted Ru-catalyzed direct arylations and Pd-catalyzed acylations which preferentially proceed at the arene while leaving intact the C5–H site[14] (Scheme 1, *route b*). We and others have recently expanded the latter to Pd-catalyzed C–H oxygenation[15a-b] and nitration reactions[15c] featuring an unconventional role of such simple triazole scaffold as a modular DG in C–heteroatom bond-forming processes (Scheme 1, *route c*). To the best of our knowledge, the parent challenging C–H halogenation event directed by "click triazoles" remains

Scheme 1. Metal-Catalyzed C–H Functionalization Processes using "Click" 4-Aryl-1,2,3-triazoles

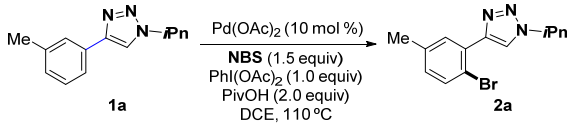


unexplored (Scheme 1, *route d*). If developed, this methodology would complement existing C–H halogenations of arenes and clearly provide straightforward access to a variety of densely substituted heterocyclic units in which the introduced halide motif could behave as a temporary functional group allowing even further structural diversification. As part of our interest in heterocyclic chemistry,[15,16] we describe herein selective C(sp^2)–H halogenation methods using 4-aryl-1,2,3-triazoles, which feature a unique tool to enable the build-up of molecular diversity combined with a rapid assembly of the required heterocyclic substrates via "click chemistry".

We first prepared triazole **1a** upon CuAAC and study its bromination as the model reaction.[17] After careful optimization, we found that the desired transformation was possible and *ortho*-bromo derivative **2a** was obtained in 70% yield when using a combination of $Pd(OAc)_2$ as catalyst, *N*-bromosuccinimide (NBS) as brominating agent, (diacetoxyiodo)benzene as co-oxidant and pivalic acid as additive (Table 1, entry 1). Notably, monobromination of **1a** preferentially took place in the less hindered *ortho*-position while competitive *ortho*-acetoxylation of the arene ring was just detected in trace amounts. Control experiments evidenced the crucial impact on reactivity of all the variables: the reaction did not occur in the absence of palladium catalyst (entry 2), the addition of an external oxidant was determinant to obtain high yields (entry 3),[18] the presence of a protic acid clearly enhanced the target C–H halogenation (entry 4) and the parent *ortho*-acetoxylation of **1a** took place in the absence of

NBS, albeit in low yields (entry 5). The use of other Pd sources (entries 8-10), oxidants (entry 7), brominating agents (entry 11) or protic acids (entry 12) afforded substantially lower yields of **2a**. Likewise, the performance of the process at distinct temperatures did not improve the reaction outcome.[19]

Table 1. Pd-Catalyzed C(sp^2)−H Bromination of 1a[a]



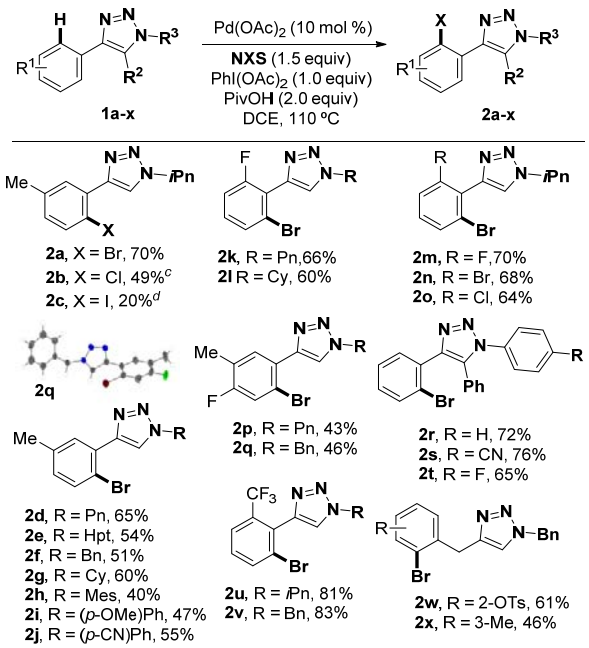
entry	change from standard conditions	yield (%)[b]
1	none	70
2	without $Pd(OAc)_2$	0
3	without $PhI(OAc)_2$	27
4	without PivOH	50
5	without NBS	25[c]
6	under air	55
7	$K_2S_2O_8$ instead of $PhI(OAc)_2$	traces
8	$PdCl_2(MeCN)_2$ instead of $Pd(OAc)_2$	61
9	$Pd(TFA)_2$ instead of $Pd(OAc)_2$	48
10	$Pd(dba)_2$ instead of $Pd(OAc)_2$	42
11	$CuBr_2$ instead of NBS	0
12	$AdCO_2H$ instead of PivOH	47

[a] Reaction conditions: **1a** (0.25 mmol), $Pd(OAc)_2$ (10 mol %), NBS (1.5 equiv), $PhI(OAc)_2$ (1.0 equiv), PivOH (2.0 equiv), DCE (0.25 M) at 110 ºC for 24 h under Ar. [b] Yield of isolated product after column chromatography. [c] *ortho*-acetoxylated triazole derivative was obtained.

Having established an optimal system for the selective Pd-catalyzed *ortho*-halogenation of "click compounds", we next evaluated its generality utilizing a variety of substituted 4-aryl-1,2,3-triazoles easily obtained by CuAAC of the corresponding alkynes and azides. Importantly, the electronic nature of the arene had a tremendous impact on the halogenation process. The Pd-catalyzed *ortho*-bromination of triazole derivatives bearing either electron-neutral or electron-withdrawing substituents smoothly proceeded to selectively afford the corresponding monobrominated arenes in moderate to good yields (Scheme 2). When using the parent *N*-chloro and *N*-iodosuccinimide the corresponding chlorinated and iodinated products, **2b** and **2c** respectively, were obtained, albeit in comparatively lower yields. Importantly, *meta*-substituted arenes demonstrated excellent site selectivity in the process, providing monohalogenated compounds as sole regioisomers (**2a-2j**, **2p-2q**) as verified by X-ray analysis of **2q**. The efficiency of the reaction was not impeded by *ortho* substituents on the aryl ring (**2k-2o**, **2u-2v**). Of remarkable importance are examples **2r-2t** where arenes with various accessible C(sp^2)−H bonds selectively underwent the monobromination event and not even traces of dihalogenated product were detected. Notably, several functional groups were perfectly accommodated such as ethers (**2i**), halides (**2k-q**, **2t-v**), cyano (**2j, 2s**) and tosylate (**2w**). Our process was also applicable to 4-benzyl-1,2,3-triazoles **1w-x** proceeding in those cases through the presumable formation of a six-membered palladacycle.

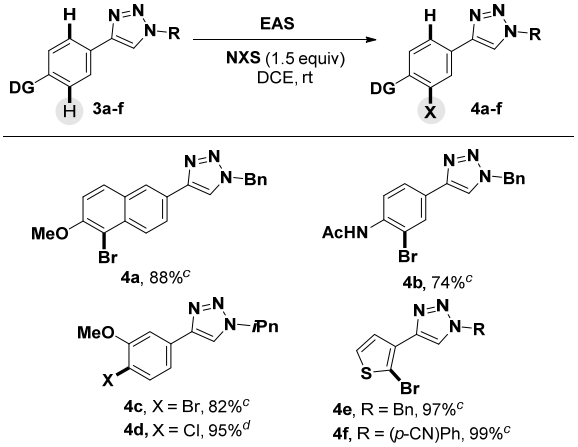
In striking contrast, when submitting the electron-rich substrate **3a** to the standard conditions the projected triazole- directed *ortho*-bromination did not occur in the presence or absence of palladium catalyst, and instead the bromination selectively took place in the 5 position of naphthyl ring (Scheme 3). After slight modifications of the reaction conditions, we observed that just mixing the substrate with NBS at room temperature furnished brominated product **4a** in 88% yield. Interestingly, other electron-rich substrates followed the same trend and uncatalyzed EAS predominated over the Pd-catalyzed *ortho*-functionalization process. In this respect, triazoles bearing acetanilide and anisole units (**3b-c**) as well as thiophenes (**3e-f**) were efficiently brominated following an EAS mechanism.[20] Importantly, the alternative employment of *N*-clorosuccinimide led to the corresponding chlorinated product **4d** in excellent yield.

Scheme 2. Pd-Catalyzed C(sp^2)−H *ortho*-Halogenation of Arenes 1a-y[a,b]



[a] As for Table 1, entry 1. [b] Yield of isolated product after column chromatography, average of at least two independent runs. [c] *N*-chlorosuccinimide (2.0 equiv) was used. [d] *N*-iodosuccinimide was used.

Scheme 3. Regioselective EAS of Arenes 3a-f [a,b]

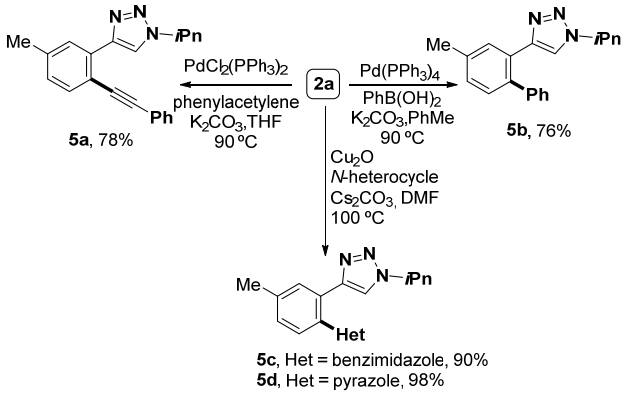


[a] Reaction conditions: **3** (0.25 mmol), NXS (1.5 equiv), DCE (0.25 M) at rt for 24 h under Ar. [b] Yield of isolated product after column chromatography, average of at least two independent runs. [c] Using *N*-bromosuccinimide. [d] Using *N*-chlorosuccinimide.

The usefulness of the developed method is highlighted by the synthetically practical transformations that the prepared triazoles can undergo at the C−Br site through metal-catalyzed C−C and C−N bond-forming processes. As depicted on Scheme 4, Pd-

catalyzed Sonogashira and Suzuki couplings provided **5a** and **5b** in good yields; the latter can be also obtained upon nickel catalysis albeit in moderate yields (see the *Supporting Information*). Noteworthy, common scaffolds in medicinally relevant targets such as heterocyclic arenes were successfully introduced by Cu-catalyzed *N*-arylations that furnished **5c** and **5d** in excellent yields.

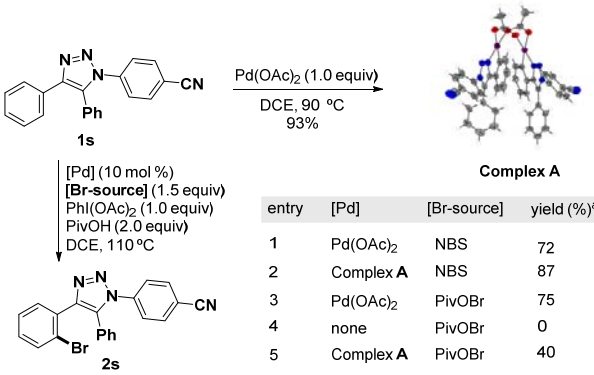
Scheme 4. Versatility of Brominated Triazoles



In order to gain some insights into the reaction mechanism, several control experiments as well as DFT studies were performed. To support the intermediacy of a triazole-containing palladacycle, a stoichiometric reaction of triazole **1s** with $Pd(OAc)_2$ in DCE was performed and the bimetallic complex **A** was pleasingly obtained in 93% yield. Such dinuclear complex was characterized by NMR spectroscopy and by X-ray crystallography; to the best of our knowledge, *it represents the first palladallacycle involving a "click" 1,2,3-triazole as chelating group.* Importantly, complex **A** efficiently catalyzed the formation of **2s** from **1s** in 87% isolated yield, which indicates that it is likely an active species within the catalytic cycle (Table 2, entry 2). In related metal-catalyzed halogenations the crucial role of the acid as additive has been described as either to protonate the carbonyl group of the *N*-halosuccinimide thus rendering a more effective halonium source[6f] or to *in situ* produce the corresponding acyl hypohalite by combination with NXS.[7d] Accordingly, we prepared a solution of pivaloyl hypobromite (PivOBr) following a reported procedure[21] and it was found to be a powerful halogenating agent providing the brominated arene **2s** in similar yields to the standard conditions (Table 2, entry 3) or in moderate yield when using complex **A** as Pd source (Table 2, entry 5).

While further studies are clearly required to confirm the mechanistic scenario, a plausible mechanism is proposed in Scheme 5. The reaction would start by a cyclopalladation process to furnish a bimetallic species $\mathbf{I_B}$ which has been confirmed by DFT studies to be more stable than its monomeric species $\mathbf{I_A}$.[22] Therefore, a dissociation prior to the oxidation step seems a rather feasible reaction pathway. Likewise, in accordance with experiments depicted on Table 2, DFT studies revealed that the oxidation step is energetically more favorable assisted by *in situ* generated PivOBr (*path a*) than NBS (*path b*).[22,23] Finally, C−Br bond-forming reductive elimination[24] from the monometallic Pd-intermediate **II** would afford the desired product and regenerate the active Pd catalyst.[18]

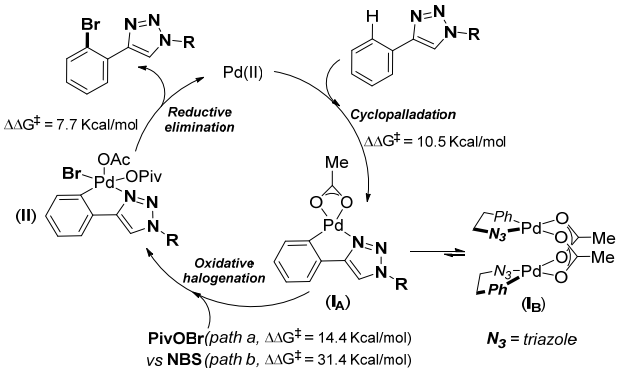
Table 2. Control Experiments with Triazole 1s[a]



entry	[Pd]	[Br-source]	yield (%)[a,b]
1	$Pd(OAc)_2$	NBS	72
2	Complex **A**	NBS	87
3	$Pd(OAc)_2$	PivOBr	75
4	none	PivOBr	0
5	Complex **A**	PivOBr	40

[a] As for Table 1, entry 1. [b] Yield of isolated product after column chromatography, average of at least two independent runs.

Scheme 5. Proposed Reaction Mechanism



In summary, we have disclosed unprecedented $C(sp^2)$−H halogenations events upon "click" triazoles, which represent practical late-stage diversification strategies toward molecular complexity. The electronic nature of the arene is pivotal in selectively boosting the reaction mechanism either by a triazole-directed Pd-catalyzed *ortho*-functionalization or by an EAS reaction. Importantly, a triazole-containing palladacycle was identified as a competent intermediate along the catalytic cycle and DFT studies supported the role of *in situ* generated PivOBr as the more plausible halogenating agent. Further mechanistic investigations are currently underway in our laboratories.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, DFT calculation data, X-ray crystallographic data for compound **2q** and complex **A** and spectral 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 interests.

ACKNOWLEDGMENT

We thank for technical and human support provided by SGIker of UPV/EHU and European funding (ERDF and ESF). We are grateful to Gobierno Vasco (ELKARTEK_KK-2015/0000101; IT_1033-16) and UPV/EHU (GIU15/31) for financial support. A. C. thanks MINECO for a Ramón y Cajal research contract (RYC-2012-09873). Cost-CHAOS action is also acknowledged.

REFERENCES

1. (a) Saikia, I.; Borah, A. J.; Phukan, P. *Chem. Rev.* **2016**, *116*, 6837. (b) Petrone, D. A.; Ye, J.; Lautens, M. *Chem. Rev.* **2016**, *116*, 8003.
2. Ruiz-Castillo, P.; Buchwald, S. L. *Chem Rev.* **2016**, *116*, 12564 and references cited therein.
3. De la Mare, P. B. *Electrophilic halogenations*; Cambridge University Press: Cambridge, 1976, chapter 5.
4. Hodgson, H. H. *Chem. Rev.* **1947**, *40*, 251.
5. (a) Florio, S.; Salomone, A. *Synthesis* **2016**, *48*, 1993. (b) Hartung, C. G.; Snieckus, V. in Modern Arene Chemistry (Ed.: D. Astruc), Wiley-VCH, Weinheim, **2002**, pp. 330.
6. For selected Pd-catalyzed C(sp^2)−H halogenations, see: (a) Sun, X.; Yao, X.; Zhang, C.; Rao, Y. *Chem. Commun.* **2015**, *51*, 10014. (b) Sarkar, D.; Melkonyan, F. S.; Gulevich, A. V.; Gevorgyan, V. *Angew. Chem. Int. Ed.* **2013**, *52*, 10800. (c) Sun, X.; Shan, G.; Sun, Y.; Rao, Y. *Angew. Chem. Int. Ed.* **2013**, *52*, 4440. (d) Wang, X.-C.; Hu, Y.; Bonacorsi, S.; Hong, Y.; Burrell, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 10326. (e) Du, B.; Jiang, X.; Sun, P. *J. Org. Chem.* **2013**, *78*, 2786. (f) Huang, C.; Chernyak, N.; Dudnik, A. S.; Gevorgyan, V. *Adv. Synth. Catal.* **2011**, *353*, 1285. (g) Bedford, R. B.: Haddow, M. F.; Mitchell, C. J.; Webster, R. L. *Angew. Chem. Int. Ed.* **2011**, *50*, 5524. (h) Mei, T.-S.; Giri, R.; Maugel, N. Yu, J.-Q. *Angew. Chem. Int. Ed.* **2008**, *47*, 5215. (i) Wan, X.; Ma, Z.; Li, B.; Zhang, K.; Cao, S.; Zhang, S.; Shi, Z. *J. Am. Chem. Soc.* **2006**, *128*, 7416. (j) Kalyani, D.; Dick, A. R.; Anani, W. Q.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 2523.
7. For selected C(sp^2)−H halogenations using other transition metal-catalysts, see: (a) Zhan, B.-B.; Liu, Y.-H.; Hu, F.; Shi, B.-F. *Chem. Commun.* **2016**, *52*, 4934. (b) Li, B.; Liu, B.; Shi, B.-F. *Chem. Commun.* **2015**, *51*, 5093. (c) Urones, B.; Martínez, A. M.; Rodríguez, N.; Arrayás, R. G.; Carretero, J. C. *Chem. Commun.* **2013**, *49*, 11044. (d) Du, Z.-J.; Gao, L.-X.; Lin, Y.-J.; Han, F.-S. *ChemCatChem* **2014**, *6*, 123.
8. For selected reviews on chelation-assisted C−H functionalizations, see: (a) Zhu, R.-Y.; Farmer, M. E.; Chen, Y.-Q.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2016**, *55*, 10578. (b) Liu, J.; Chen, G.; Tan, Z. *Adv. Synth. Catal.* **2016**, *358*, 1174. (c) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2015**, *112*, 5879. (d) Daugulis, O.; Roane, J.; Tran, L. D. *Acc. Chem. Res.* **2015**, *48*, 1053. (e) Rouquet, G.; Chatani, N. *Angew. Chem. Int. Ed.* **2013**, *52*, 11726. (f) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315. (g) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147.
9. For selected reviews, see: (a) Kacprzak, K.; Skiera, I.; Piasecka, M.; Paryzek, Z. *Chem. Rev.* **2016**, *116*, 5689. (b) Tiwari, V. K.; Mishra, B. B.; Mishra, K. B.; Mishra, N.; Singh, A. S.; Chen, X. *Chem. Rev.* **2016**, *116*, 3086. (c) Thirumurugan, P.; Matosiuk, D.; Jozwiak, K. *Chem Rev.* **2013**, *113*, 4905.
10. (a) Cera, G.; Ackermann, L. *Top. Curr. Chem.* **2016**, DOI 10.1007/s41061-016-0059-6. (b) Ye, X.; Xu, C.; Wojtas, L.; Akhmedov, N. G.; Chen, H.; Shi, X. *Org. Lett.* **2016**, *18*, 2970. (c) Cera, G.; Haven, T.; Ackermann, L. *Angew. Chem. Int. Ed.* **2016**, *55*, 1484. (d) Al Mamari, H. H.; Diers, E.; Ackermann, L. *Chem. Eur. J.* **2014**, *20*, 9739. (e) Gu, Q.; Al Mamari, H. H.; Grazyk, K.; Diers, E.; Ackermann, L. *Angew. Chem. Int. Ed.* **2014**, *53*, 3868. (f) Ye, X.; Shi, X. *Org. Lett.* **2014**, *16*, 4448. (g) Ye, X.; He, Z.; Ahmed, T.; Weise, K.; Akhmedov, N. G.; Petersen, J. L.; Shi, X. *Chem. Sci.* **2013**, *4*, 3712.
11. For reviews, see: (a) Wei, F.; Wang, W.; Ma, Y.; Tunga, C.-H.; Xu, Z. *Chem. Commun.* **2016**, *52*, 14188. (b) Haldón, E.; Nicasio, M. C.; Pérez, P. J. *Org. Biomol. Chem.* **2015**, *13*, 9528. (c) Ackermann, L.; Potukuchi, H. K. *Org. Biomol. Chem.* **2010**, *8*, 4503. (d) Meldal, M.; Tornøe, C. W. *Chem. Rev.* **2008**, *108*, 2952. For early reports, see: (e) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2596. (f) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *57*, 3057.
12. Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2001**, *40*, 2004.
13. For selected examples, see: (a) Qureshi, Z.; Kim, J. Y.; Bruun, T.; Lam, H.; Lautens, M. *ACS Catal.* **2016**, *6*, 4946. (b) Tian, X.; Yang, F.; Rasina, D.; Bauer, M.; Warratz, S.; Ferlin, F.; Vaccaro, L.; Ackermann, L. *Chem. Commun.* **2016**, *52*, 9777. (c) Ackermann, L.; Althammer, A.; Fenner, S. *Angew. Chem. Int. Ed.* **2009**, *48*, 201. (d) Ackermann, L.; Vicente, R.; Born, R. *Adv. Synth. Catal.* **2008**, *350*, 741. (e) Chuprakov, S.; Chernyak, N.; Dudnik, A. S.; Gevorgyan, V. *Org. Lett.* **2007**, *9*, 2333. (f) Iwasaki, M.; Yorimitsu, H.; Oshima, K. *Chem. Asian. J.* **2007**, *2*, 1430.
14. (a) Jiang, Y.; Ma, X.; Zhao, F.; Han, C. *Synlett* **2017**, DOI: 10.1055/s-0036-1588123. (b) Ackermann, L.; Novák, P.; Vicente, R.; Pirovano, V.; Potukuchi, H. *Synthesis* **2010**, 2245. (c) Ackermann, L.; Vicente, R.; Althammer, A. *Org. Lett.* **2008**, *10*, 2299. (d) Ackermann, L.; Born, R.; Vicente, R. *ChemSusChem* **2009**, *2*, 546. For related alkenylations, see: (d) Tirler, C.; Ackermann, L. *Tetrahedron* **2015**, *71*, 4543. (f) Li, X. G.; Liu, K.; Zou, G.; Liu, P. N. *Eur. J. Org. Chem.* **2014**, 7878.
15. (a) Irastorza, A.; Aizpurua, J. M.; Correa, A. *Org. Lett.* **2016**, *18*, 1080. (b) Zhao, F.; Chen, Z.; Ma, X.; Huang, S.; Jiang, Y. *Tetrahedron Lett.* **2017**, *58*, 614. (c) Zhao, F.; Chen, Z.; Huang, S.; Jiang, Y. *Synthesis* **2016**, *48*, 2105.
16. Correa, A.; Fiser, B.; Gómez-Bengoa, E. *Chem. Commun.* **2015**, *51*, 13365.
17. For halogenations of 2-aryl-1,2,3-triazoles, see: Tian, Q.; Chen, X.; Liu, W.; Wang, Z.; Shi, S.; Kuang, C. *Org. Biomol. Chem.* **2013**, *11*, 7830. The bromination of related 1-aryl-1,2,3-triazoles was reported unsuccessful. Remarkably, our model substrate **1a** remained unreactive too under those conditions, thus evidencing the crucial impact of the triazole substitution pattern in its metal-coordinating ability and the subtleties of "click triazoles".
18. Although the exact role of $PhI(OAc)_2$ is currently unclear, it presumably helps to maintain the reactive Pd species. See ref 6b and 6c. At this stage, the *in situ* formation of highly electrophilic $PhIBr_2$ upon ligand exchange with NBS cannot be entirely ruled out. Karade, N. N.; Shirodkar, S. G.; Dhoot, B. M.; Waghmare, P. B. *J. Chem. Res.* **2005**, *4*, 274.
19. The addition of diamines or protected amino acids as supporting ligands did not improve the yields. See for example: Engle, K. A. *Pure Appl. Chem.* **2016**, *88*, 119.
20. For selected electrophilic halogenations of electron-rich arenes, see: (a) Maddox, S. M.; Dinh, A. N.; Armenta, F.; Um, J.; Gustafson, J. L. *Org. Lett.* **2016**, *18*, 5476. (b) Prakash, G. K. S.; Mathew, T.; Hoole, D.; Esteves, P. M.; Wang, Q.; Rasul, G.; Olah, G. A. *J. Am. Chem. Soc.* **2004**, *126*, 15770. (c) Yang, L.; Lu, Z.; Stahl, S. S. *Chem. Commun.* **2009**, 6460. (d) Bedford, R. B.; Mitchell, C. J.; Webster, R. L. *Chem. Commun.* **2010**, *46*, 3095. (e) Bedford, R. B.; Engelhart, J. U.; Haddow, M. F.; Mitchell, C. J.; Webster, R. L. *Dalton Trans.* **2010**, *39*, 10464.
21. (a) Chen, K.; Baran, P. S. *Nature* **2009**, *459*, 824. (b) Skell, P. S.; May, D. D. *J. Am. Chem. Soc.* **1983**, *105*, 3999.
22. For a full discussion based on DFT studies, see the *Supporting Information*.
23. For reviews, see: (a) Topczewski, J. J.; Sanford, M. S. *Chem. Sci.* **2015**, *6*, 70. (b) Powers, D. C.; Ritter, T. *Acc. Chem. Res.* **2012**, *45*, 840. (c) Hickman, A. J.; Sanford, M. S. *Nature* **2012**, *484*, 177. (d) Muñiz, K. *Angew. Chem. Int. Ed.* **2009**, *48*, 9412.
24. (a) Racowski, J. M.; Sanford, M. S. *Top. Organomet. Chem.* **2011**, *35*, 61. (b) Powers, D. C.; Benitez, D.; Tkatchouk, E.; Goddard III, W. A.; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 14092.