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COMMUNICATION

Dual Ligand-promoted Palladium-catalyzed Nondirected C-H Alkenylation of Aryl Ethers

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Direct C-H functionalization of aryl ethers remains challenging owing to their low reactivity and selectivity. Herein, a novel strategy for nondirected C-H alkenylation of aryl ethers promoted by dual ligand catalyst was demonstrated. This catalytic system readily achieved the highly efficient alkenylation of alkyl aryl ethers (anisole, phenetole, n-propyl phenyl ether, n-butyl phenyl ether and benzyl phenyl ether), cyclic aryl ethers (1,4-benzodioxan, 2,3-dihydrobenzofuran, dibenzofuran), and diphenyl oxides. Moreover, the proposed methodology was successfully employed for the late-stage modification of complex drugs containing the aryl ether motif. Interestingly, the compounds developed herein displayed fluorescent properties, which would facilitate their biological applications.

Transition-metal-catalyzed C-H functionalization can efficiently create C-X bonds and thus offers a highly atom- and step-economic strategy for the construction of complex molecules.[1] Particularly, considering the prevalence of aromatic substructures in natural products and bioactive molecules, the approach of C(sp^2)-H activation of arenes has attracted intense interest. Although great progress has been made during the past decades, selective C–H functionalization of simple arenes can only be achieved for substrates with special functional groups, especially directing groups (DG) whose utility is limited due to additional steps required to introduce/remove DG, resulting in lower yields and limited substrate scope.[2] The C-H activation of simple arenes without DG has developed slowly due to the difficulties arising from electronic and steric effects.[3] To address these challenges, ligands such as pyridines[4], trialkyl phosphide,[5] sulfide,[6] mono-protected amino acids (MPAA)[7] were employed to promote the reaction with higher reaction reactivities and better region-/enantioselectivity.[8] Up to now, various functionalization reactions including borylation,[9] silylation,[10] amination,[11] oxygenation[12] and carbon-heteroatom bond-formation[13] were established elegantly by C-H activation on aromatic ring, implying that ligand promoted selective C-H functionalization has excellent potential to broaden the application of transition-metal catalysed reactions of arenes.

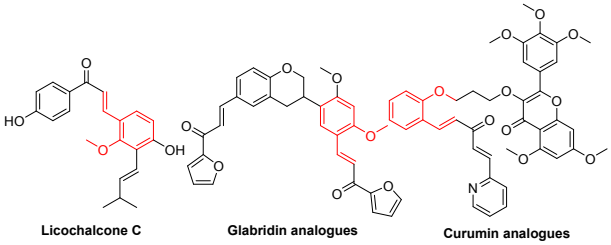
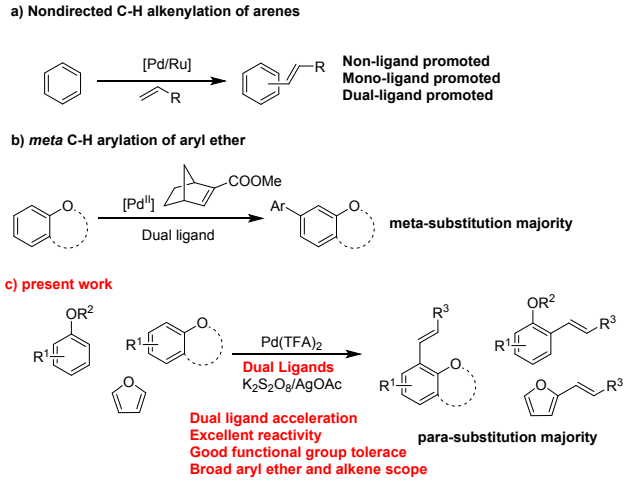


Figure 1. Representative drugs containing alkenylated aryl ethers.

Aryl ether, an important functional moiety in bioactive compounds, is prevalent in natural products, pharmaceuticals, polymer materials, and drug molecules. Its alkenylated-forms often display excellent antitumor and antibacterial bioactivities (Figure 1).[14] Over the last two decades, intensive studies have culminated in the development of C-H alkenylation of non-directed arenes. Notably, Fujiwara[15] and Milstein[16] first developed methods for preparing acrylated arenes catalysed by [Pd]/[Ru]. However, poor reactivity hinders the applications of these methods. Subsequently, mono-ligands such as pyridine or S,O-ligand were demonstrated to effectively accelerate nondirected C-H alkenylation of arenes (Scheme 1a).[17-19] Later, a catalytic system was developed by Gemmeren, which was composed of two complementary ligands, *N*-acetylglycine and pyridine. This new catalytic system significantly increased the reactivity of arenes.[20] However, the above efforts focused mainly on the arenes, and C-H functionalization of aryl ether has been seldom investigated. Yu reported an elegant example for arylation of aryl ether at the *meta*-position using a pyridine derivative as the ligand and norbornene (NBE-CO_2Me) as the transient directing group (Scheme 1b).[21] Nevertheless, the methodologies for C(sp^2)-H functionalization of aryl ethers with broad functional group tolerance remains a major challenge.



Scheme 1. Methods for C-H activation of aryl ethers.

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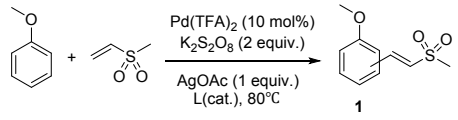
Based on our previous work on regioselective[22] and dual-ligand promoted[20] C-H activation of arene, herein, it is demonstrated that aryl ether can be efficiently alkenylated via Pd/dual ligand catalytic system (Scheme 1c). With the assistance of MPAA and S,O ligand, alkenylation of aryl ethers proceeded smoothly, featuring good yields and broad substrate scope including different aryl ethers (alkyl aryl ethers, cyclic aryl ethers, furan and benzophenone) and alkenes (acrylate styrene, vinylsulfonyl, acrylonitrile, ethyl vinyl ketone and their derivatives).

To implement the alkenylation strategy, the model reaction was performed by treating anisole (2 equiv.) with methyl vinyl sulfone (1 equiv.), $Pd(TFA)_2$ (10 mmol%), $K_2S_2O_8$ (2 equiv.), and AgOAc (1 equiv.) in AcOH at 80 °C (Table 1, Entry 1). The desired product was obtained in 20% yield. Taking into consideration the low reactivity of anisole, various ligands were screened to stabilize Pd (II) intermediate. Trialkyl phosphate and pyridine derivatives, which are well known ligands for C-H activation, did not promote the reaction (Table S7, Entries 2-5). Mono-*N*-protected amino acids were reported to significantly enhance the stabilization of monomeric Pd complexes, thus promoting the C(sp^3/sp^2)-H activation. Subsequently, different *N*-protected leucines were investigated (Table S7, Entries 9-11), and it was found that Ac-Leu-OH (**L1**) achieved the alkenylation of anisole in 52% yield (Table 1, Entry 2). Further optimization studies found that 3-methyl-2-i-propyl-2-(phenylthio)acetic acid (**L2**) gave a slightly improved yield (Table 1, Entry 3). Notably, L1 and L2 as dual ligands accelerated the reaction and the yield increased to 82%. More importantly, the ratio of *ortho*- to *para*- increased to 71:29 (Table 1, Entry 4).

Table 1. Ligand optimization of the alkenylation of anisole



Entry	Ligands	o:p	Yield/%[b]
1	—	27:73	20
2	Ac-Leu-OH (L1)	41:59	52
3	L2	60:40	70
4	**Ac-Leu-OH+L2**	**71:29**	**82**
5	No $Pd(OAc)_2$	-	0

[a]Reaction conditions: anisole (1.2 mmol), methyl vinyl sulfone (1.0 mmol), AcOH (2 mL), $Pd(TFA)_2$ (10 mol%), $K_2S_2O_8$ (2.0 equiv.), AgOAc (1.0 equiv.), L1 (50 mol%), L2 (10 mol%), 80 °C. [b]Isolated yield.

Next, the scope of anisole was diversified by reacting with methyl vinyl sulfone under the above optimized conditions (Table 2). The aryl ether derivatives functionalized with methyl, tert-butyl, chloride, bromide, iodide, cyano, nitro, or ester groups all yielded the desired product (62-90%), indicating that the presence of electron-donating/electron-withdrawing groups did not decrease the efficiency of the reaction (**2**-**13**). Notably, *para*-functionalized anisole was converted into a single corresponding product (**4**, **10**-**13**). Furthermore, anisole and *ortho* substituted substrates provided excellent *ortho*-selective products (**2**, **5**-**7**). Substrates with *meta*-substituted functional groups did not display preference over the three positions (**3**, **8**, **9**). Intriguingly, methoxynaphthalenes underwent alkenylation with methyl vinyl sulfone in good yields; both 1-methoxynaphthalene and 2-methoxynaphthalene gave two alkenylated products at a and b position in 1:1 ratio (**14**, **15**). 7-Methoxyl coumarin was alkenylated under the standard conditions in moderate yield (**16**, 43%), providing a direct and efficient alkenylation method to explore new coumarin-based fluorescent dyes and for drug modification.

Table 2. Substrate scope study with anisoles

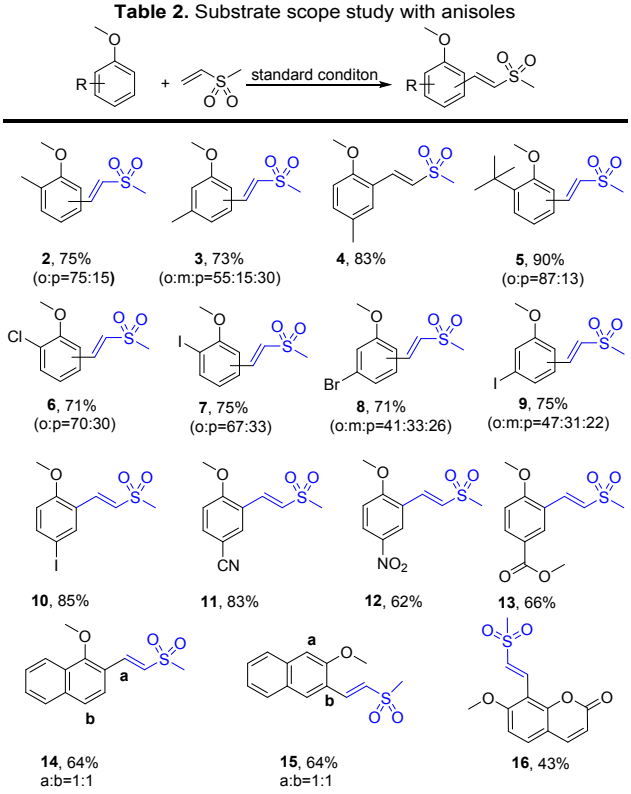
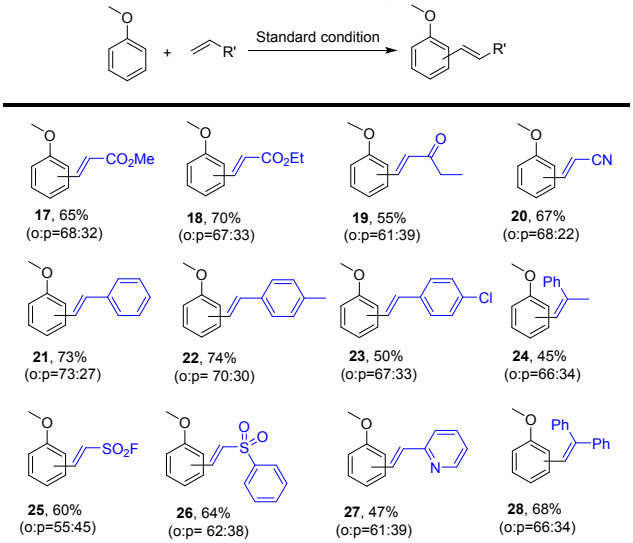


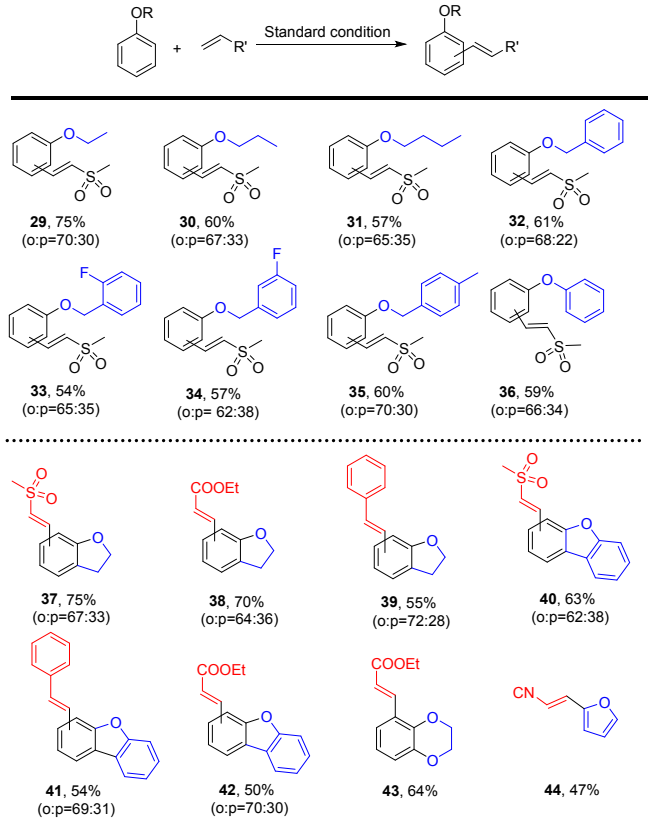
Table 3. Substrate scope study with alkenes



Next, various types of olefins were examined in the catalytic system (Table 3). First, acrylate alkenylations were assessed and the desired products were obtained in good yields (**17**, 65%; **18**, 70%). Vinyl ketone and alkyl acrylonitrile produced **19** and **20** with yields of 55% and 67%, respectively. Next, aryl ethylenes were examined and their corresponding products (**21**, **22**, **23**, **24**, **28**) were formed in 45–74% yields. Interestingly, this

reaction could be successfully applied to non-terminal olefins such as 2-phenyl-1-propene, leading to the compound **24** after cis-transformation. Phenyl vinyl sulfone and vinyl pyridine effectively generated compounds **26** and **27** in yields of 64% and 47%. Sulfonyl fluoride is easily coupled to hydroxyl and amino groups and widely applied to protein labelling and high throughput drug screening. However, it was difficult to insert sulfonyl fluoride into anisole directly using the reported method. To overcome this issue, it was innovatively introduced in the aryl ether in good yield under the optimized conditions (**25**, 60%).

Table 4. Substrate scope study with aryl ethers



Based on these results, the application of the methodology to more aryl ethers was further explored, including cyclic aryl ethers and diphenyl oxides. As shown in Table 4, the alkyl (more than one carbon) aryl ethers were efficiently converted to the corresponding products. The yields of aryl ethers with long aryl chains slightly decreased (**29–31**, 57–75%). Aryl ethers containing an aryl group were well tolerated for the reaction (**32–35**, 54–61%). Surprisingly, the direct vinyl sulfonation of diphenyl ether led to the formation of compound **36** in 59% yield. Aryl cyclic ethers, a special class of ethers found in nature, are often overlooked in studies of C-H activation. Herein, aryl cyclic ethers were tested in the reaction under the standard conditions (**37–44**). 2,3-Dihydrobenzofuran was investigated and the corresponding alkenylated products, including methyl vinyl sulfone, styrene, and ethyl acrylate were obtained in good yields (**37**, **38**, **39**). Similarly, methyl vinyl sulfonated, styrenated, and ethyl acrylated dibenzofurans (**40–42**) were obtained in yields of 50–63%. 2,3-Dihydrobenzofuran and dibenzofuran are "parents" of many organic compounds with various biological activities, including anti-bacterial, anti-tumour and anti-inflammatory activities. Therefore, the alkenylation modification of benzofuran derivatives has potential in the development of new drugs. Herein, the desired alkenylated derivatives **43** were obtained in yields of 64%. Similarly, furan gave the corresponding alkenylated product **44** in 47% yield, indicating the possibility of modification in complex five-membered heterocyclic ring compounds. It is worth noting that the above functionalization mainly occurred at *ortho*-position, while **43** was obtained as the sole products. Thus, alkenes could be directly introduced into benzodioxan, 2,3-dihydrobenzofuran, dibenzofuran, and diphenyl oxides via Pd-catalysed C-H activation, demonstrating their potential for modification of aryl cyclic ethers.

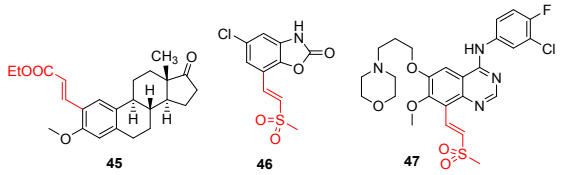


Figure 2. Late-stage functionalization of antitumor drug-loaded aryl ethers.

Late-stage functionalization of highly active compounds or drugs has been a major research topic in recent years. Therefore, the late-stage alkenylation of drugs containing aryl ethers was investigated. The three investigated drugs, estrone, chlorzoxazone, and gefitinib, produced the corresponding *ortho*-alkenylated products **45–47** in yields of 42%, 37%, and 30%, respectively (Figure 2). Thereafter, **47**, a derivative of anti-cancer drug gefitinib, was subjected to an antitumor activity study, and found to display similar activity as gefitinib (Figure S2).

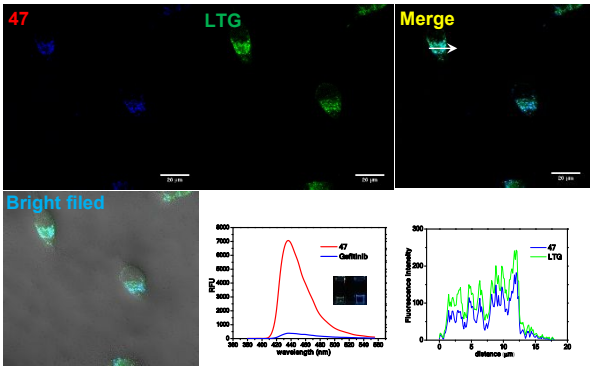


Figure 3. Co-localization experiments in HeLa cells. Cells were pre-treated with LTG (Lyso-Tracker Green, 0.25 μM) for 25 min and then incubated with **47** (10 μM) for 15 min; LTG channel, λ_{ex}=504 nm, λ_{em}=520-570 nm; **47** channel, λ_{ex}=405 nm, λ_{em}=420-460 nm; Intensity correlation plot of **47** and LTG channel; Intensity profiles of ROI (region of interest) across the cell. Scale bar: 20μm.

Interestingly, it was also found that the modified drug displayed improved fluorescent properties (Figure S3), with a maximum fluorescence at 455 nm when excited at 370 nm. Thus, the modified drug was further employed for cell imaging with HeLa cells. After 3 h of incubation with **47**, the drug was observed to exhibit blue fluorescence and the cell morphology was dramatically changed due to the high cytotoxicity of **47** towards HeLa cells (Figure S4). Additionally, localization of the compound was demonstrated by a colocalization assay using Lyso Tracker Green (LTG, a commercial mitochondrial tracker). The green fluorescence from LTG overlapped well with that of **47** (Figure 3). The changes in the intensity profile of the linear regions of interest (ROI) demonstrated the lysosome-targeting property of **47** due to its morpholine motif. Thus, these results

further support the potential application of this strategy in chemical biology.

In summary, a dual ligand direct alkenylation of aryl ethers catalysed by Pd was demonstrated in this study. The reaction was accelerated by leucine and S,O ligand and showed wide substrate scope, including alkyl aryl ethers and cyclic aryl ethers. Considering the ubiquity of these aryl ethers in natural products and pharmaceuticals, the proposed strategy was also applied for successful late-stage modification of complex molecules, demonstrating its potential application in the development of new drugs. Moreover, the alkenylated modified anti-tumour drugs exhibited excellent fluorescent properties. Taken together, the proposed methodology has great potential in the development of novel pharmaceuticals, advanced materials, and new fluorescent dyes.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

There are no conflicts to declare

Notes and references

1 a) J. Yamaguchi, A. D. Yamaguchi, *Angew. Chem. Int. Ed.* **2012**, 51, 8960; b) T. Newhouse, P. S. Baran, *Angew. Chem. Int. Ed.* **2011**, 50, 3362.

2 a) T. K. Achar, J. P. Biswas, S. Porey, T. Pal, K. Ramakrishna, S. Maiti, D. Mait, *J. Org. Chem.* **2019**, 84, 8315; b) A. Modak, A. Mondal, R. Watile, S. Mukherjee, D. Maiti, *Chem. Commun*. **2016**, 52, 13916; c) T. Patra, R. Watile, S. Agasti, T. Naveen, D. Maiti, *Chem. Commun.* **2016**, 52, 2027; d) S. Maity, E. Hoque, U. Dhawa, D. Maiti, *Chem. Commun.* **2016**, 52, 14003; e) T. K. Achar, X.-L. Zhang, R. Mondal, M. S. Shanavas, S. Maiti, S. Maity, N. Pal, R. S. Paton, D. Maiti, *Angew. Chem. Int. Ed.* **2019**, 58, 10353; f) M. Bera, A. Maji, S. K. Sahoo, D. Maiti, *Angew. Chem. Int. Ed.* **2015**, 54, 8515; g) M. Bera, A. Modak, T. Patra, A. Maji, D. Maiti, *Org. Lett.* **2014**, 16, 5760; h) U. Dutta, S. Maiti, S. Pimparkar, S. Maiti, L. R. Gahan, E. H. Krenske, D. W. Lupton, D. Maiti, *Chem. Sci.* **2019**, 10, 7426; i) M. Brochetta, T. Borsari, S. Bag, S. Jana, S. Maiti, A. Porta, D. B. Werz, G. Zanoni, D. Maiti, *Chem. Eur. J.* **2019**, 25, 10323; j) S. Agasti, B. Mondal, T. K. Achar, S. K. Sinha, A. S. Suseelan, K. J. Szabo, F. Schoenebeck, D. Maiti, *ACS Catal.* **2019**, 9, 9606; k) K. Seth, M. Bera, M. Brochetta, S. Agasti, A. Das, A. Gandini, A. Porta, G. Zanoni, D. Maiti, *ACS Catal.* **2017**, 7, 7732; l) S. Maity, P. Dolui, R. Kancherla, D. Maiti, *Chem. Sci.* **2017**, 8, 5181; m) A. Deb, A. Hazra, Q. Peng, R. S. Paton, D. Maiti, *J. Am. Chem. Soc.* **2017**, 139, 763; n) S. Bag, D. Maiti, *synthesis*, **2016**, 48, 804; o) U. Dutta, S. Maiti, S. Pimparkar, S. Maiti, L. R. Gahan, E. H. Krenske, D. W. Lupton, D. Maiti, *Chem. Sci.* **2019**, 10, 7426; p) S. Agasti, U. Sharma, T. Naveen, D. Maiti, *Chem. Commun.* **2015**, 51, 5375; q) A. Deb, D. Maiti, *Eur. J. Org. Chem.* **2017**, 9, 1239; r) Q. Zhang, K. Chen, W. Rao, Y. Zhang, F.-J. Chen, B.-F. Shi, *Angew. Chem. Int. Ed.* **2013**, 52, 13588.

3 J. L. Bras, J. Muzart, *Chem. Rev.* **2011**, 111, 1170.

4 a) Y.-H. Zhang, B.-F. Shi, J.-Q. Yu, *J. Am. Chem. Soc*. **2009**, 131, 5072; b) A. Kubota, M. H. Emmert, M. S. Sanford, *Org. Lett.* **2012**, 14, 1760.

5 a) J.-Y. Cho, M. K. Tse, D. Holmes, R. E. Maleczka, M. R. Smith, *Science.* **2002**, 295, 305; b) Y. Saito, Y. Segawa, K. Itami, *J. Am.Chem. Soc.* **2015**, 137, 5193.

6 K. Naksomboon, Y. Álvarez-Casao, M. Uiterweerd, N. Westerveld, B. Maciá, M. Á. Fernández-Ibáñez, *Tetrahedron Letters*, **2018**, 59, 379.

7 a) G.-J. Cheng, Y.-F. Yang, P. Liu, P. Chen, T.-Y. Sun, G. Li, X.-H. Zhang, K. N. Houk, J.-Q. Yu, Y.-D. Wu, *J. Am. Chem. Soc*. **2014**, 136, 894; b) Y.-S. Kang, P. Zhang, M.-Y. Li, Y.-K. Chen, H.-J. Xu, J. Zhao, W.-Y. Sun, J.-Q. Yu, Y. Lu, *Angew. Chem. Int. Ed.* **2019**, 58, 9099; c) Y.-H. L, P.-X. Li, Q.-J. Y, Z.-Z. Zhang, D.-Y. Huang, M. D. Le, H. Song, L. Liu, B.-F. Shi, *Org. Lett.* **2019**, 21, 1895; d) B. E. Haines, D, G. Musaev, *ACS Catal.* **2015**, 5, 830; e) R. E. Plata, D. E. Hill, B. E. Haines, D. G. Musaev, L. Chu, D. P. Hickey, M. S. Sigman, J.-Q. Yu, D. G. Blackmond, *J. Am. Chem. Soc.* **2017**, 139, 9238; f) S. Kathiravan, I. Nicholls, *Chem. Eur. J.* **2017**, 23, 7031; g) A. Mishra, U. Mukherjee, T. K. Vats, I. Deb, *J. Org. Chem.* **2018**, 83, 3756; h) J. J. Gair, B. E. Haines, A. S. Filatov, D. G. Musaev, J. C. Lewis, *Chem. Sci.* **2017**, 8, 5746; i) Y.-Z. Ding, S. Fan, X.-X. Chen, Y.-Z. Gao, S.-D. Li, G. Li, *Org. Lett.* **2019**, 21, 4224; j) Y.-J. Liu, Z.-X. Zhou, D. Xie, X.-P. Luo, H. Wang, B. Liu, M.-Z. Zeng, *Org. Lett.* **2018**, 20, 7274; k) H.-L. Wang, R.-B. Hu, H. Zhang, A.-X. Zhou, S.-D. Yang, *Org. Lett.* **2013**, 15, 5302; l) S. Kathiravan, I. A. Nicholls, *Chem. Eur. J.* **2017**, 23, 7153; m) L. Jin, Q.-J. Yao, P.-P. Xie, Y. Li, B.-B. Zhan, Y.-Q. Han, X. Hong, B.-F. Shi, *Chem*. **2020**, DOI: 10.1016/j.chempr.2019.12.011; n) L. Liu, Y.-H. Liu, B.-F. Shi, *Chem. Sci*. **2020**, 11, 290; o) D.-H. Wang, K. M. Engle, B.-F. Shi, *Science*. 2010, 327, 315; p) B.-F. Shi, N. Maugel, Y.-H. Zhang, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2008**, 47, 4882.

8 a) B.-B. Zhan, L. Wang, J. Luo, X.-F. Lin, B.-F. Shi, *Angew. Chem. Int. Ed.* 2020, DOI: 10.1002/anie.201915674; b) J. Luo, T. Zhang, L. Wang, G. Liao, Q.-J. Yao, Y.-J. Wu, B.-B. Zhan, Y. Lan, X.-F. Lin, B.-F. Shi, *Angew. Chem. Int. Ed.* **2019**, 58, 6708; c) S.-Y. Yan, Y.-Q. Han, Q.-J. Yao, X.-L. Nie, L. Liu, B.-F. Shi, *Angew. Chem. Int. Ed.* **2018**, 57, 9093; d) T. Zhou, M.-X. Jiang, X. Y, Q. Yue, Y.-Q. Han, Y. Ding, B.-F. Shi, *Chin. J. Chem.* **2020**, 38, 242; e) Q. Zhang, B.-F. Shi, *Chin. J. Chem.* **2019**, 37, 647; f) Y.-Q. Han, Y. Ding, T. Zhou, S.-Y. Yan, H. Song, B.-F. Shi, *J. Am. Chem. Soc*. **2019**, 141, 4558.

9 I. A. I. Mkhalid, J. H. Barnard, T. B. Marder, J. M. Murphy, J. F. Hartwig, *Chem. Rev.* **2010**, 110, 890.

10 C. Cheng, J. F. Hartwig, *Science*. **2014**, 343, 853.

11 R. Shrestha, P. Mukherjee, Y. Tan, Z. C. Litman, J. F. Hartwig, *J. Am. Chem. Soc*. **2013**, 135, 8480.

12 A. K. Cook, M. S. Sanford, *J. Am. Chem. Soc.* **2015**, 137, 3109.

13 E. M. Beck, R. Hatley, M. J. Gaunt, *Angew. Chem. Int. Ed.* **2008**, 47, 3004; *Angew. Chem.* **2008**, 120, 3046.

14 a) J. Pospíšil, I. E. Markó, *Tetrahedron Lett*. **2008,** 49, 1523; b) A. Porta, S. Re, G. Zanoni, G. Vidari, *Tetrahedron*. **2007**, 63, 3989; c) Y. H. Jiang, J. Hong, S. D. Burke, *Org. Lett.* **2004**, 6, 1445.

15 Y. Fujiwara, I. Moritani, S. Danno, R. Asano, S. Teranishi, *J. Am. Chem. Soc.* **1969**, 91, 7166.

16 H. Weissman, X. Song, X.; Milstein, D. *J. Am. Chem. Soc.* **2001**, 123, 337.

17 P. Wang, P. Verma, G-Q. X, J. Shi, J. X. Qiao, S.-W. T, P. T. Cheng, M. A. Poss, M. E. Farmer, K.-S. Yeung, J.-Q. Yu, *Nature*, **2017**, 551, 489.

18 A. Kubota, M. H. Emmert, M. S. Sanford, *Org. Lett.* **2012**. 14, 1760.

19 K. Naksomboon, C. Valderas, M. Gómez-Martínez, Y. Álvarez-Casao, M. Á. Fernández-Ibáñez, *ACS Catal*. **2017**, 7, 6342.

20 H. Chen, P. Wedi, T. Meyer, G. Tavakoli, M. van Gemmeren, *Angew. Chem. Int. Ed.* **2018**, 57, 2497.

21 L. Y. Liu, J. X. Qiao, K. S. Yeung, W. R. Ewing, J. Q. Yu, *J. Am. Chem. Soc.* **2019**, 141, 14870.

22 Y.-D. Dou, Kenry, J. Liu, J.-J. Z, *Chem. Eur. J.* **2019**, 25, 6896.

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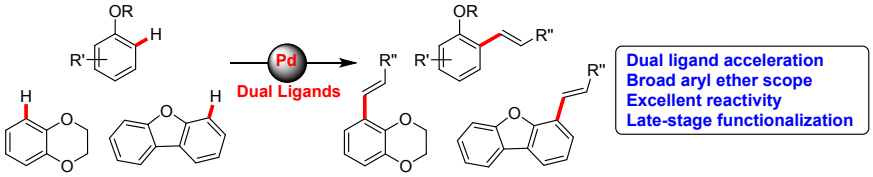

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