Title	Palladium-catalyzed para-selective alkylation of electron-deficient arenes
Author(s)	Jiao, Zhiwei; Lim, Li Hui; Hirao, Hajime; Zhou, Steve Jianrong
Citation	Jiao, Z., Lim, L. H., Hirao, H., & Zhou, S. J. (2018). Palladium-catalyzed para-selective alkylation of electron-deficient arenes. Angewandte Chemie International Edition, 57(21), 6294-6298. doi:10.1002/anie.201801967
Date	2018
URL	http://hdl.handle.net/10220/48297
Rights	© 2018 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim. This is the peer reviewed version of the following article: Jiao, Z., Lim, L. H., Hirao, H., & Zhou, S. J. (2018). Palladium-catalyzed para-selective alkylation of electron-deficient arenes. Angewandte Chemie International Edition, 57(21), 6294-6298, which has been published in final form at http://dx.doi.org/10.1002/anie.201801967. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Use of Self-Archived Versions.

Palladium-Catalyzed *Para*-Selective Alkylation of Electron-Deficient Arenes

Zhiwei Jiao, Li Hui Lim, Hajime Hirao and Jianrong Steve Zhou*

Abstract: Intermolecular alkylation of electron-deficient arenes proceeds with good para selectivity. Palladium catalysts are used to generate nucleophilic alkyl radicals from alkyl halides, which then add onto arenes directly. Its scope of arenes and site of alkylation of are opposite to those of classical Friedel-Crafts alkylation, which prefers electron-rich rings.

Arenes are ubiquitous in many bioactive natural products, drugs and function materials. [1] For example, in the FDA Orange Book, arenes are the most frequently used skeletons in small molecule drugs.[1b] In research of functionalization of arenes, site-selective alkylation is an important topic.[2] Friedel-Crafts alkylation occurs via electrophilic aromatic substitution and is usually the reaction of choice owing to easy availability of alkylating reagents. The reaction works well with electron-neutral and rich rings such as phenols and anilines, but the products are often accompanied with over-alkylation and isomerization of primary alkyl groups.[3] Furthermore, the reaction does not work with electron-poor arenes.

In recent years, transition metal-catalyzed *ortho*-alkylation of arenes has made great progress by employing directing groups, but examples for alkylation on remote sites of arenes remain very rare. For example, Ackermann and Frost separately disclosed Ru-catalyzed *meta*-alkylation of 2-arylpyridines and aniline derivatives, via a pathway of radical alkylation of metallacycle intermediates.[4] Yu *et al.* also published *meta*-selective alkylation of α-arylacetamides via dual catalysis of palladium and norbornene to introduce primary alkyl chains.[5] Similarly, metal-catalyzed *para*-alkylation of arenes to introduce unactivated alkyl groups is also very rare. Only recently Nakao *et al.* reported nickel-catalyzed *para*-alkylation of benzamides, diaryl ketones and aryl sulfones in the presence of a bulky aluminum complex,[6] but only primary alkyl and norbornyl groups were introduced from olefins (Figure 1a). Herein, we report the first examples of intermolecular alkylation of *electron-deficient* benzene and naphthalene derivatives, using palladium catalysts and alkyl halides (Figure 1b). Importantly, the alkylation preferentially occurs *para* to electron-withdrawing groups on arenes.

In recent years, there has been emerging interest in palladium radical catalysis which provides products and selectivity that were previously unattainable.[7] Thus, selective alkylation has been reported for unsaturated systems such as olefins,[8] alkynes[9] NH-imines,[10] CO (carbonylation)[11] and unsaturated heterocycles.[12] Recently, Alexania *et al*. applied this type of palladium catalysis to intramolecular alkylative cyclization of arenes that formed benzofused 5- and 6-membered rings.[13] This kind of cyclization on arenes is intrinsically fast, regardless of electronic properties of radicals and arenes; moreover, no regioselectivity issue is a concern.[14]

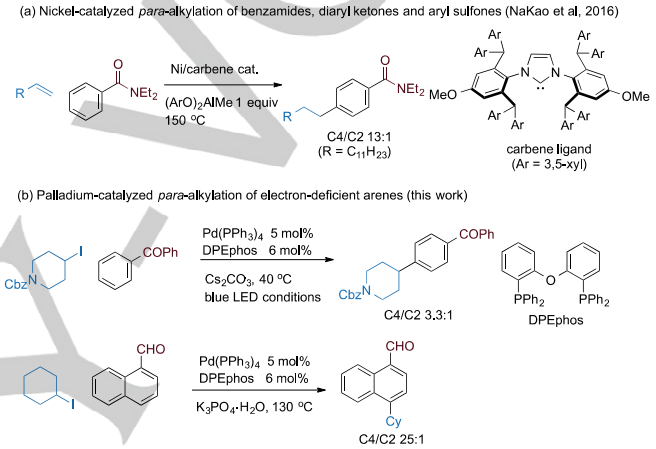


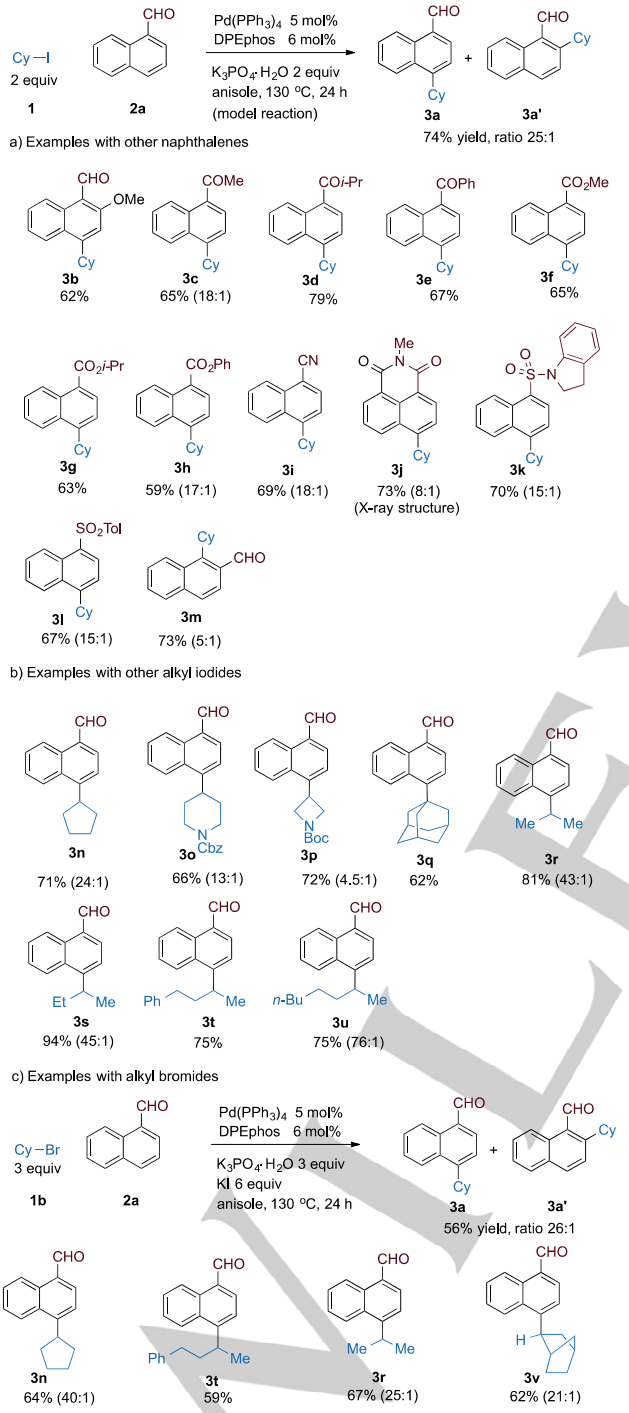
Figure 1. Recent examples of intermolecular *para*-selective alkylation of electron-decificent arenes

We initially attempted a model reaction between iodocyclohexane and 1-formylnaphthalene in the presence of palladium catalysts (Scheme 1a). We found that a combination of $Pd(PPh_3)_4$ and DPEphos was sufficient to promote C4-selective alkylation in 74% yield. The major byproduct from cyclohexyl iodide is elimination to cyclohexene and byproducts from 1-formylnaphthlene **2a** included naphthalene, momo- and dialkylated naphthlenes in small amounts after decarbonylation. Other ancillary ligands such as triarylphosphines, trialkyphosphines, bisphosphines and *N*-heterocyclic carbenes did not lead to better yields or selectivity (see the Supporting Information). In the model reaction, judicious choice of $K_3PO_4{\cdot}H_2O$ base and an aromatic solvent, anisole helped to minimize side reactions such as elimination of alkyl iodides to alkenes and over-alkylation of arenes. Similar alkylation reactions didn't proceed in the presence of nickel and copper catalysts in our hands.

Our method afforded alkylation of naphthalene derivatives bearing electron-withdrawing groups at C1 positions with good C4 selectivity (Scheme 1a). The electron-withdrawing groups at C1 position can be aldehydes (**3a** and **3b**), ketones (**3c**-**3e**), esters (**3f-3h**), a nitrile (**3i**), a sulfonamide (**3k**) and a sulfone (**3l**). From an imide derivative, the major isomer **3j** was alkylated at C4 position, too, as confirmed by X-ray diffraction.[18] However, we found that the presence of a nitro group led to a complex mixture. When a 2-formyl derivative was used, alkylation mainly took place at C1 position instead (**3m**). Under Friedel-Crafts conditions, α– or β– alkylation of unactivated naphthalenes can

[*] Dr. Z. Jiao, Dr. L. H. Lim. Prof. Dr. H. Hirao, Prof. Dr. J. S. Zhou
Division of Chemistry and Biological Chemistry
School of Physical and Mathematical Sciences
Nanyang Technological University, 21 Nanyang Link, SPMS-CBC-06-03, Singapore 637371
E-mail: jrzhou@ntu.edu.sg
Prof. Dr. H. Hirao
Department of Chemistry, City University of Hong Kong
Tat Chee Avenue, Kowloon, Hong Kong (China)
Supporting information for this article is given via a link at the end of the document.

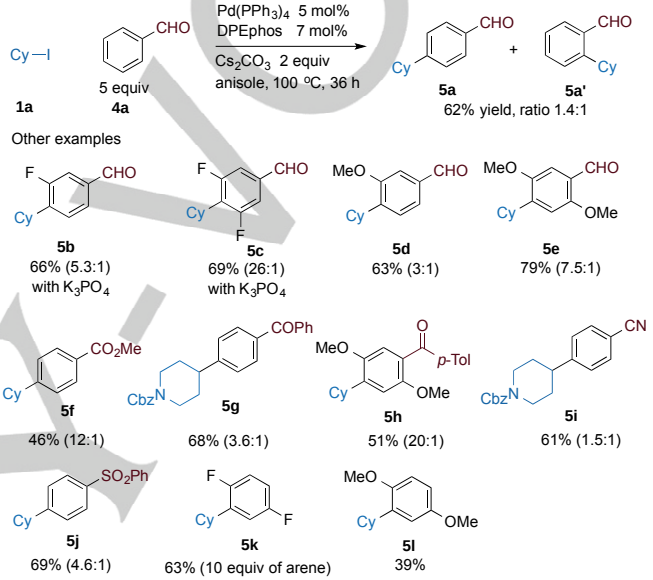
be achieved under either kinetic or thermodynamic control.[15] Recently, Rodríguez *et al.* reported that radical alkylation of electron-neutral naphthalenes resulted in 8:1 β selectivity, using alkylboronic acids and $Mn(OAc)_3$.[16] However, alkylation of electron-poor naphthalenes was not reported under those conditions.



Scheme 1. Examples of alkylation of naphthalene derivatives.

We also tested other alkyl iodides with the model arene **2a** (Scheme 1b). Both cyclic (**3n**-**3p**) and acyclic *sec*-alkyl iodides (**3r**-**3u**) gave good results. Notably, 1-adamantyl iodide, a *tert*-alkyl electrophile also gave the desired product **3q** in 62% yield, but *t*-butyl iodide gave very low yield unfortunately (<10%).

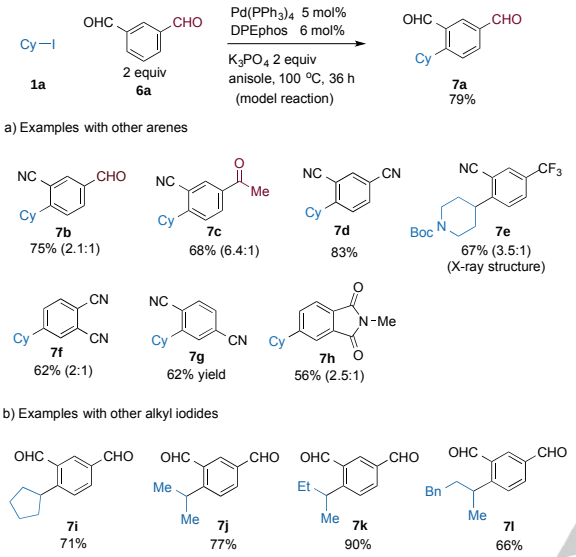
Some *sec*-alkyl bromides were also amendable for alkylation when KI was added (Scheme 1c). Notably, rigid *exo*-2-bromonorbornane afforded the coupling product **3v** with good exo-selectivity (**3v**). Unfortunately, simple linear alkyl halides such as *n*-dodecyl iodide didn't afford desired alkylation products due to base-caused HI elimination to produce alkenes. Moreover, when ethyl 2,2,2-bromodifluoroacetate or 1,1,1-trifluoro-2-iodoethane was used as alkylation reagent, the desired product was formed in low yield (<10%).



Scheme 2. Examples of alkylation of benzene derivatives containing a single electron-withdrawing group. Only structures of major isomers were shown.

Monocyclic arenes with a single electron-withdrawing group are much less reactive than naphthalene derivatives. Thus, a higher concentration of the arenes was needed to intercept the putative alkyl radicals. After many experiments, we were gratified to find that when 5 equivalents of arenes were used together with Cs_2CO_3 base, the coupling products were formed in moderate to good yields (Scheme 2). After reaction, most of the excess arenes remained. The use of K_3PO_4 led to very low yields in most cases. However, in reactions of two fluorinated benzaldehydes (**5b** and **5c**), the use of K_3PO_4 improved the ratio of regioisomers. Common arenes such as benzaldehyde (**5a**), methyl benzoate (**5f**), benzophenone (**5g**), benzonitrile (**5i**) and diphenyl sulfone (**5j**) were all suitable substrates and alkyl groups were mainly added at *para* positions. Cyclohexyl radical also added to benzophenone efficiently, but the resulting isomers were difficult to separate on silica. Thus, a piperidine-derived iodide was used to afford **5g** and its ortho isomer. Notably, acetophenone didn't react at all. Moreover, we found that F substitution (**5b** and **5c**) and electron-releasing OMe groups on benzaldehyde (**5d** and **5e**) didn't pose a problem in the alkylation. At last, both *p*-difluorobenzene and highly electron-rich *p*-dimethoxybenzene were sufficiently reactive to trap cyclohexyl radical to give products **5k** and **5l** in moderate yields. In the case of **5k**, 10 equiv of difluorobenzene was used

while no anisole solvent was added. Under the optimized conditions, the reaction of fluorobenzene (10 equiv as solvent) and cyclohexyl iodide gave 40% yield of two alkylation isomers with a ratio of 1.5:1. Chlorobenzene also afforded about 40% yield of two main isomers (2.6:1). Unfortunately, when phenyl bromide and phenyl iodide were used, we didn't detect any alkylation product and most of starting material remained after reaction.

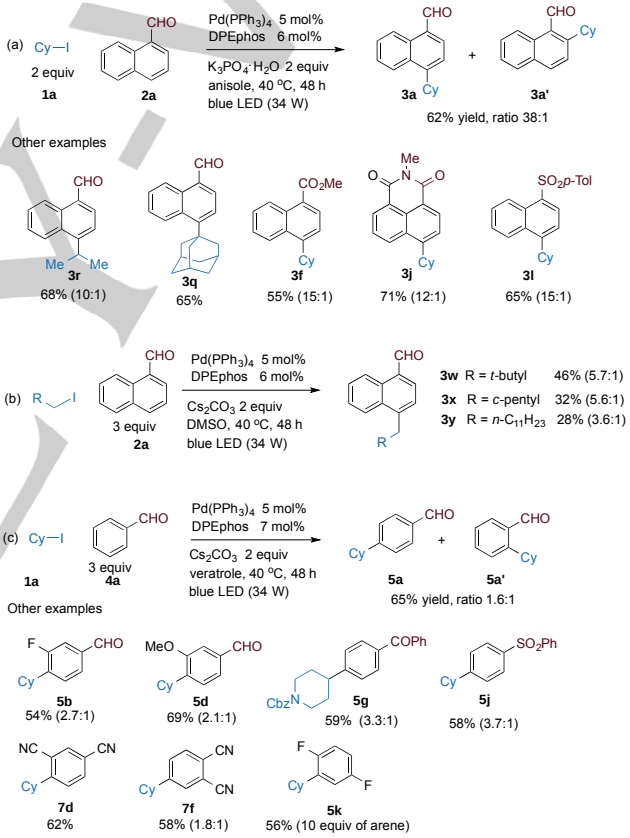


Scheme 3. Examples of alkylation of benzene derivatives activated by two electron-withdrawing groups. Only structures of major isomers were shown.

Later, we found that doubly activated benzene derivatives were much more reactive than benzaldehyde. Hence, 2 equiv of 1,3-diformylbenzene was enough to give good yield of alkylation product **7a** and helped to prevent second alkylation (Scheme 3a). After reaction, most of the unreacted arenes still remained. In terms of regioselectivity, the addition took place predominantly *para* to aldehyde (**7b**) and ketone groups (**7c**) in competition with a nitrile group in the same molecule. The alkylation was also sensitive to steric effect, resulting in less alkylation occurring ortho to the ketone group (**7c**) than the more electron-poor aldehyde (**7b**). However, we found that in **7e** the major site of alkylation was ortho to the nitrile group, likely due to steric effect of the CF_3 group. The reaction also proceeded well with *o*-phthalonitrile (**7f**), terephthalonitrile (**7g**) and *N*-methylphthalimide (**7h**). However, similar reactions of *o*-phthalaldehyde gave a complex mixture. Some other *sec*-alkyl iodides were also subjected to the reaction with 1,3-diformylbenzene, which provided the desired products **7i-7l** with moderate to good yields (Scheme 3b).

Recently, Gevorgyan, Fu and Yu groups reported that blue LED light helped to promote Pd-catalyzed radical alkylation of vinyl arenes and heteroarenes at room temperature.[17] In order to minimize base–caused elimination of alkyl halides and other side reactions at high reaction temperature, we explored a model reaction between iodocyclohexane and 1-formylnaphthalene **1a** under irradiation of blue LED light (Scheme 4a). After many trials, we were delighted to receive products **3a** in satisfactory yields at 40 °C in the presence of $K_3PO_4{\cdot}H_2O$ as base. The reaction was devoid of many byproducts under conventional heating conditions. The blue LED conditions were successfully applied to other naphthalene derivatives that were activated with a single electron-withdrawing group.

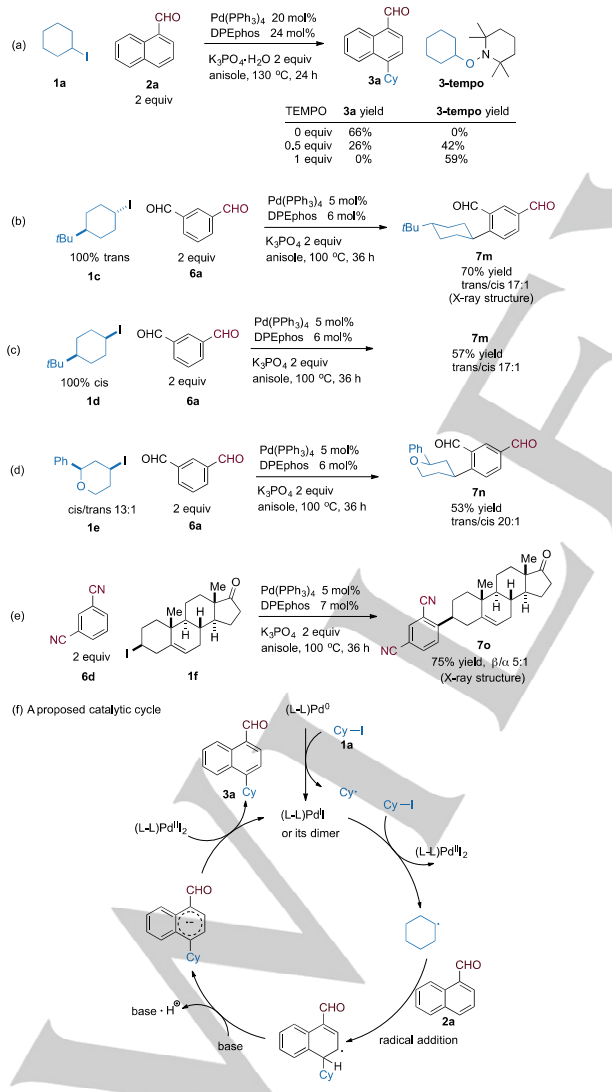
Notably, we discovered that alkylation of **2a** (3 equiv) with primary alkyl iodides can be achieved, albeit in moderate yields, when cesium carbonate was used as base in DMSO (Scheme 4b). In comparison, the products **3w-y** were not formed under conventional heating as described in Scheme 1. In the reaction of **3y**, we detected that some *n*-dodecyl iodide gave rise to byproducts dodecene (34%) and dodecane (5%). The blue LED conditions also allowed us to reduce the stoichiometry of challenging substrates, benzene derivatives with one EWG, to 3 equiv in alkylation (**5b**, **5d**, **5g** and **5j** in Scheme 4c). The optimal solvent was veratrole and the best base was Cs_2CO_3.



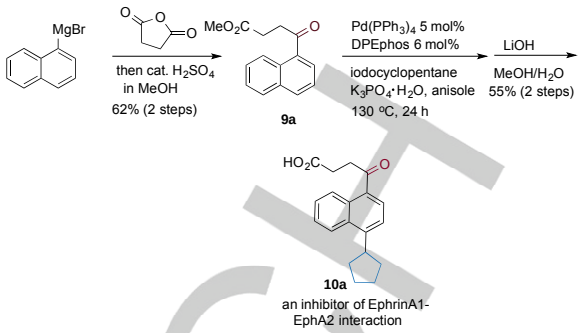
Scheme 4. Examples of alkylation of arenes under irradiation of blue LED light. Only structures of major isomers were shown.

To gain some mechanistic insight on the alkyl radicals, we added 1 equiv TEMPO to the model reaction of **2a**, which led to complete inhibition of the alkylation reaction and TEMPO-trapped byproduct in 59% yield (Scheme 5a); when only 0.5 equiv of TEMPO was added, the TEMPO-trapped byproduct was formed in 42% yield along with alkylation product **3a** in 26% yield. Moreover, the reaction of **6a** with either cis or trans isomer of a 4-substituted cyclohexyl iodide **1c** or **1d** gave the *trans*-isomer **7m** selectively and in the same trans/cis ratio (17:1) (Scheme 5b-c). The configuration of **7m** was confirmed by X-ray crystallography.[18] In the second example, the cis isomer of a

tetrahydrapyranyl iodide **1e** reacted to afford selectively cis-isomer **7n** (Scheme 5d). In the third example, the reaction of **6d** with dehydroandrosterone derivative **1f** gave product **7o** in 5:1 β/α selectivity (Scheme 5e). The stereochemistry of the major isomer was also determined by X-ray diffractional analysis.[18] Thus, in all three cases, the new C-C bonds were formed selectively at the equatorial positions of the substituted six-membered rings, which is consistent with alkyl radical addition to heteroarenes.[12b] We also used DFT calculation to model the key step of cyclohexyl radical addition to arenes, including 1-formylnaphthalene **2a**, benzaldehyde **4a** and diphenylsulfone **4j**. The energy gap of two transition states leading to two regioisomers correlated qualitatively well with experimentally observed isomeric ratio (see the Supporting information). Therefore, we propose a tentative catalytic cycle featuring a key step of alkyl radical addition to arenes (Scheme 5f). After the addition, the base removes a proton from the arene-centered radical to produce a radical anion, which is stabilized by the electron-withdrawing group. At present, we cannot differentiate a shuttle of Pd(I)/(II) versus that of Pd(0)/(I).



Scheme 5. Mechanistic studies



Scheme 6. Synthetic application

1,4-Disubstituted naphthalenes are present as core motifs in some antimicrobial and anticancer agents and also in some function materials.[19] For example, **10a** is a novel inhibitor of Ephrine A1–EphA2 interaction. This kind of interaction was explored recently as a new target for cancer treatment.[20] Under our alkylation conditions, **10a** can be easily obtained by treating **9a** with cyclopentyl iodide (Scheme 6).

In summary, we report a new para-selective alkylation method for electron-deficient arenes. The type of arenes and sites of alkylation are opposite to those of classical Friedel-Crafts reaction. The latter works better with electron-rich aromatic rings, and the more electron-rich positions on the rings are more reactive.

Acknowledgements

We thank Singapore Ministry of Education Academic Research Fund Tier 1 grants (MOE2015-T1-001-166 and RG112/16) and Nanyang Technological University for financial support.

Keywords: palladium catalysis • alkylation • alkyl radicals • arenes• synthetic method

[1] Examples: a) J. L. Segura, N. Martin, *J. Mater. Chem.* **2000**, *10*, 2403; b) R. D. Taylor, M. MacCoss, A. D. Lawson, *J. Med. Chem.* **2014**, *57*, 5845.
[2] Example: A. S. S. Wilson, M. S. Hill, M. F. Mahon, C. Dinoi, L. Maron, *Science* **2017**, *358*, 1168.
[3] a) S.-L. You, Q. Cai, M. Zeng, *Chem. Soc. Rev.* **2009**, *38*, 2190; e) M. Rueping, B. J. Nachtsheim, *Beilstein J Org Chem* **2010**, *6*, 6; f) R. R. Naredla, D. A. Klumpp, *Chem. Rev.* **2013**, *113*, 6905; g) D. A. Klumpp, "Electrophilic Aromatic Substitution" in *Arene Chemistry*, John Wiley & Sons, Inc, **2015**, pp. 1.
[4] Examples: a) N. Hofmann, L. Ackermann, *J. Am. Chem. Soc.* **2013**, *135*, 5877; b) J. Li, S. Warratz, D. Zell, S. De Sarkar, E. E. Ishikawa, L. Ackermann, *J. Am. Chem. Soc.* **2015**, *137*, 13894; c) A. J. Paterson, S. St John-Campbell, M. F. Mahon, N. J. Press, C. G. Frost, *Chem. Commun.* **2015**, *51*, 12807.
[5] Examples: a) P.-X. Shen, X.-C. Wang, P. Wang, R.-Y. Zhu, J.-Q. Yu, *J. Am. Chem. Soc.* **2015**, *137*, 11574; b) X.-C. Wang, W. Gong, L.-Z. Fang, R.-Y. Zhu, S. Li, K. M. Engle, J.-Q. Yu, *Nature* **2015**, *519*, 334.
[6] a) S. Okumura, S. Tang, T. Saito, K. Semba, S. Sakaki, Y. Nakao, *J. Am. Chem. Soc.* **2016**, *138*, 14699; b) S. Okumura, Y. Nakao, *Org. Lett.* **2017**, *19*, 584.
[7] Review: Q. Liu, X. Dong, J. Li, J. Xiao, Y. Dong, H. Liu, *ACS Catal.* **2015**, *5*, 6111.
[8] Examples: a) S. Bräse, B. Waegell, A. de Meijere, *Synthesis* **1998**, 148; b) K. S. Bloome, E. J. Alexanian, *J. Am. Chem. Soc.* **2010**, *132*, 12823; c) K. S. Bloome, R. L. McMahen, E. J. Alexanian, *J. Am. Chem. Soc.* **2011**, *133*, 20146; d) C. M. McMahon, E. J. Alexanian, *Angew. Chem.* **2014**,*126*, 6084; *Angew. Chem. Int. Ed.* **2014**, *53*, 5974; e) Y. Zou, J. Zhou, *Chem. Commun.* **2014**, *50*, 3725; f) M. Parasram, V. O. Iaroshenko, V. Gevorgyan, *J. Am. Chem. Soc.* **2014**, *136*, 17926; (g) X. Dong, Y. Han, F. Yan, Q. Liu, P. Wang, K. Chen, Y. Li, Z. Zhao, Y. Dong,

H. Liu, *Org. Lett.* **2016**, *18*, 3774; h) S. Sumino, I. Ryu, *Org. Lett.* **2016**, *18*, 52; (i) A. R. O. Venning, M. R. Kwiatkowski, J. E. Roque Peña, B. C. Lainhart, A. A. Guruparan, E. J. Alexanian, *J. Am. Chem. Soc.* **2017**, *139*, 11595.

[9] a) B. M. Monks, S. P. Cook, *J. Am. Chem. Soc.* **2012**, *134*, 15297; b) B. M. Monks, S. P. Cook, *Angew. Chem.* **2013**,*125*, 14464; *Angew. Chem. Int. Ed.* **2013**, *52*, 14214.

[10] D. M. Peacock, C. B. Roos, J. F. Hartwig, *ACS Centr. Sci.* **2016**, *2*, 647.

[11] Examples: a) T. Ishiyama, N. Miyaura, A. Suzuki, *Tetrahedron Lett.* **1991**, *32*, 6923; b) I. Ryu, S. Kreimerman, F. Araki, S. Nishitani, Y. Oderaotoshi, S. Minakata, M. Komatsu, *J. Am. Chem. Soc.* **2002**, *124*, 3812; c) S. Sumino, A. Fusano, T. Fukuyama, I. Ryu, *Acc. Chem. Res.* **2014**, *47*, 1563; d) S. Sumino, T. Ui, Y. Hamada, T. Fukuyama, I. Ryu, *Org. Lett.* **2015**, *17*, 4952; e) B. T. Sargent, E. J. Alexanian, *J. Am. Chem. Soc.* **2016**, *138*, 7520.

[12] a) B. Xiao, Z.-J. Liu, L. Liu, Y. Fu, *J. Am. Chem. Soc.* **2013**, *135*, 616; b) X. Wu, J. W. T. See, K. Xu, H. Hirao, J. Roger, J.-C. Hierso, J. Zhou, *Angew. Chem.* **2014**,*126*, 13791; *Angew. Chem. Int. Ed.* **2014**, *53*, 13573.

[13] A. R. O. Venning, P. T. Bohan, E. J. Alexanian, *J. Am. Chem. Soc.* **2015**, *137*, 3731.

[14] A. Studer, D. P. Curran, *Angew. Chem.* **2016**,*128*, 58; *Angew. Chem. Int. Ed.* **2016**, *55*, 58.

[15] G. A. Olah, J. A. Olah, *J. Am. Chem. Soc.* **1976**, *98*, 1839.

[16] S. Castro, J. J. Fernández, F. J. Fañanás, R. Vicente, F. Rodríguez, *Chem.-Eur. J.* **2016**, *22*, 9068.

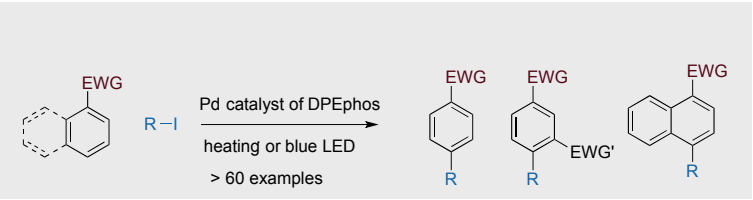
[17] a) D. Kurandina, M. Parasram, V. Gevorgyan, *Angew. Chem.* **2017**,*129*, 14400; *Angew. Chem. Int. Ed.* **2017**, *56*, 14212; b) M. Parasram, V. Gevorgyan, *Chem. Soc. Rev.* **2017**, *46*, 6227; c) G. Z. Wang, R. Shang, W. M. Cheng, Y. Fu, *J. Am. Chem. Soc.* **2017**, *139*, 18307; d) W. J. Zhou, G. M. Cao, G. Shen, X. Y. Zhu, Y. Y. Gui, J. H. Ye, L. Sun, L. L. Liao, J. Li, D. G. Yu, *Angew. Chem.* **2017**,*129*, 15889; *Angew. Chem., Int. Ed.* **2017**, *56*, 15683; e) G. Z. Wang, R. Shang, Y. Fu, *Org. Lett.* **2018**, *20*, 888.

[18] CCDC 1823220-1823223 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk /data_request/cif.

[19] a) J. Wei, D. L. Vander Jagt, R. E. Royer, L. M. Deck, *Tetrahedron Lett.* **2010**, *51*, 5757; b) L. Bouche, C. D. Christ, S. Siegel, A. E. Fernandez-Montalvan, S. J. Holton, O. Fedorov, A. Ter Laak, T. Sugawara, D. Stockigt, C. Tallant, J. Bennett, O. Monteiro, L. Diaz-Saez, P. Siejka, J. Meier, V. Putter, J. Weiske, S. Muller, K. V. M. Huber, I. V. Hartung, B. Haendler, *J. Med. Chem.* **2017**, *60*, 4002; c) Z. H. Wu, Z. T. Huang, R. X. Guo, C. L. Sun, L. C. Chen, B. Sun, Z. F. Shi, X. Shao, H. Li, H. L. Zhang, *Angew. Chem.* **2017**,*129*, 13211; *Angew. Chem. Int. Ed.* **2017**, *56*, 13031; d) J. Yin, M. Tan, D. Wu, R. Jiang, C. Li, J. You, *Angew. Chem.* **2017**,*129*, 13274; *Angew. Chem. Int. Ed.* **2017**, *56*, 13094.

[20] a) J. Wykosky, W. Debinski, *Mol. Cancer Res.* **2008**, *6*, 1795; b) D. Pala, R. Castelli, M. Incerti, S. Russo, M. Tognolini, C. Giorgio, I. Hassan-Mohamed, I. Zanotti, F. Vacondio, S. Rivara, M. Mor, A. Lodola, *J. Chem. Inf. Model.* **2014**, *54*, 2621; c) D. Callegari, D. Pala, L. Scalvini, M. Tognolini, M. Incerti, S. Rivara, M. Mor, A. Lodola, *Molecules* **2015**, *20*, 17132.

COMMUNICATION



Intermolecular radical alkylation of electron-deficient arenes proceeds with *para* selectivity, via palladium radical catalysis. The type of arenes and site of addition on arenes are opposite to those of classical Friedel-Crafts alkylation.

*Zhiwei Jiao, Li Hui Lim, Hajime Hirao and Jianrong Steve Zhou **

Page No. – Page No.

Palladium-Catalyzed *Para*-Selective Alkylation of Electron-Deficient Arenes