ChemComm
Chemical Communications

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: Y. Gu, X. Sun, B. Wan, Z. Lu and Y. Zhang, *Chem. Commun.*, 2020, DOI: 10.1039/D0CC04602G.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/chemcomm

View Article Online
DOI: 10.1039/D0CC04602G

COMMUNICATION

C(sp^3) –H Activation-Enabled Cross-Coupling of Two Aryl Halides: An Approach to 9,10-Dihydrophenanthrenes

Received 00th January 20xx,
Accepted 00th January 20xx

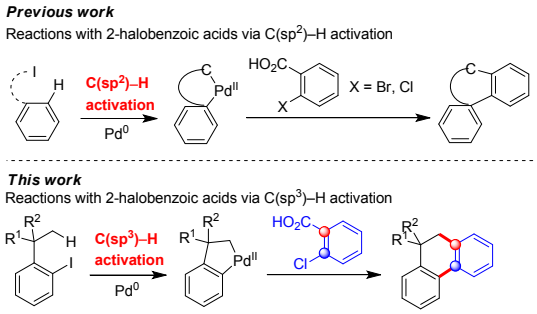
DOI: 10.1039/x0xx00000x

Yichao Gu, Xueliang Sun, Bin Wan, Zhuoer Lu, and Yanghui Zhang*

A palladium-catalyzed cross-coupling reaction of aryl halides with 2-chlorobenzoic acids has been developed. The reaction forms C(sp^3),C(sp^2)-palladacycles through C(sp^3)–H activation. The palladacycles react with 2-chlorobenzoic acids through two successive C–C cross-coupling, and two C–C bonds are formed with high chemoselectivity. The reaction provides an innovative method for the synthesis of 9,10-dihydrophenanthren.

Transition metal-catalysed C–H functionalization has made explosive growth over the past decades and has emerged as a powerful method for organic synthesis.[1] C–H functionalization reactions not only have advantages of high step- and atom-economy, but also afford new strategies for retrosynthetic analysis. Compared to extensively exploited C(sp^2)–H activation, transition metal-catalysed C(sp^3)–H functionalization is more challenging due to the lack of π–orbital interaction, and is still underdeveloped.[2] However, C(sp^3)–H bonds are ubiquitous chemical bonds in organic molecules, and therefore developing C(sp^3)–H functionalization reaction is of paramount significance in organic synthesis and other related fields.

It has been reported that aryl iodides could undergo cross-coupling with 2-halobenzoic acids through Pd-catalyzed C(sp^2)–H activation.[3] In this type of reactions, intramolecular C–H activation forms palladacycles as the intermediates. The palladacycles first react with carbon–halogen bonds of 2-halobenzoic acids and are arylated, and the second C–Pd bonds are then arylated via decarboxylation (**Scheme 1**). The reaction is very intriguing because it represents an innovative reductive cross-coupling reaction. Furthermore, the reaction forms two C–C bonds and provides a facile method for the synthesis of cyclic compounds. All the current reactions of this type were enabled by C(sp^2)–H activation. We were curious if such a cross-coupling could be enabled by C(sp^3)–H activation. Although Pd-catalyzed C(sp^3)–H functionalization reactions of aryl iodides have been reported, most of them are intramolecular cyclization reactions,[4] and intermolecular reactions are still underdeveloped.[5] In almost all the current intermolecular reactions, both of C–Pd bonds reacted with the same atom and formed five-membered compounds. One of the major challenges for developing such intermolecular reactions is that aryl halides tend to undergo homocoupling.[4h,4i] Thus, for the reactions with 2-halobenozic acids, the aryl halide substrates could compete with 2-halobenzoic acids to react with C(sp^2),C(sp^3)-palladacycles formed by C(sp^3)–H activation.



Scheme 1. Reactions of aryl iodides with 2-halobenzoic acids.

9,10-Dihydrophenanthrenes are essential structural motifs widely present in bioactive natural products.[6] Of note, many bioactive 9,10-dihydrophenanthrene compounds bear substituents on the methylene groups and the benzene rings.[7] Therefore, 9,10-dihydrophenanthrenes, in particular multisubstituted derivatives, have been the intriguing synthetic targets, and developing new reactions for the construction of the 9,10-dihydrophenanthrene skeleton has been the subject of intensive research.[8] Notably, transition metal-catalyzed C–H functionalization has been successfully exploited to develop innovative synthetic methods for 9,10-dihydrophenanthrene and its derivatives.[9] The current reactions are limited to intramolecular cyclization through C(sp^2)–H activation and require the preparation of complex

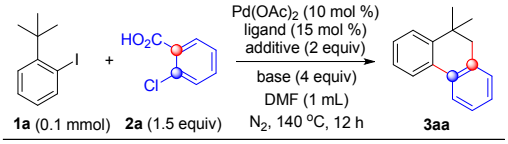
* Y. Gu, X. Sun, B. Wan, Z. Lu, Prof. Dr. Y. Zhang
School of Chemical Science and Engineering, Shanghai Key Laboratory of Chemical Assessment and Sustainability, Tongji University
1239 Siping Road, Shanghai 200092, China
E-mail: zhangyanghui@tongji.edu.cn

† Electronic Supplementary Information (ESI) available: full experimental details and characterisation. See DOI: 10.1039/x0xx00000x

substrates. It is still highly desirable to develop concise C–H functionalization reactions to allow easy access to 9,10-dihydrophenanthrene derivatives. Herein, we report the cross-coupling reaction of aryl iodides with 2-halobenzoic acids via C(sp^3)–H activation. The reaction involves dual C-C bond formation and represents an innovative method for the construction of 9,10-dihydrophenanthrene structures.

We commenced our studies by choosing 1-(*tert*-butyl)-2-iodobenzene (**1a**) and 2-chlorobenzoic acid as the model substrates. As shown in **Table 1**, **1a** coupled with **2a** to yield 9,9-dimethyl-9,10-dihydrophenanthrene **3aa** in 26% yield in the presence of catalyst $Pd(OAc)_2$ and base K_2CO_3 (entry 1). The yield was improved dramatically by adding a tetrabutylammonium salt (entries 2 and 3).[10] To further enhance the yield, a range of phosphine ligands were surveyed. P(*p*-tol)$_3$ proved to be optimal, and the yield increased to 88% (entries 4-8). Other inorganic bases were also examined. While Na_2CO_3 and K_3PO_4 gave similar yields, Cs_2CO_3 and KOAc are much less efficient than K_2CO_3 (entries 9-12). 2-Bromo-*tert*-butylbenzene was also able to undergo the coupling reaction, and **3aa** was formed in 86% yield (entry 13). Although 2-bromobenzoic acid was also suitable, the reaction was much less efficient (entry 14). Notably, a yield of 69% was still obtained when the catalyst loading was lowered to 5 mol% (entry 15).

Table 1. Survey of the Reaction Conditions

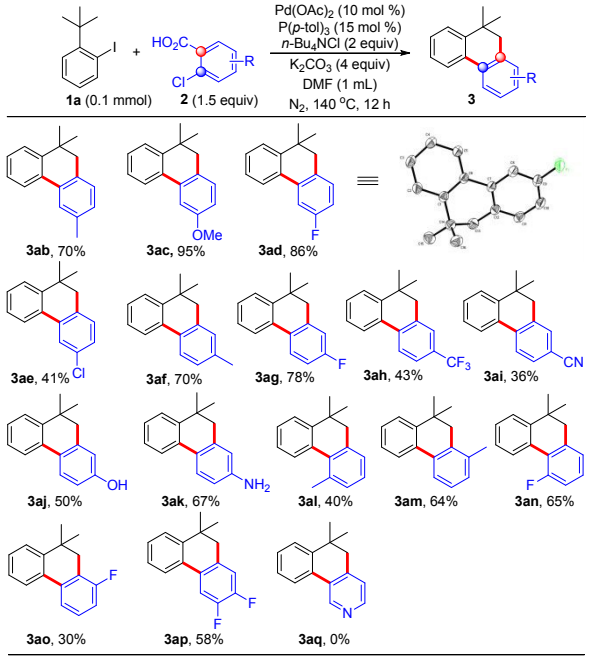


entry	base	additive	ligand	yield (%)[a]
1	K_2CO_3	/	/	26
2	K_2CO_3	*n*-Bu_4NBr	/	62
3	K_2CO_3	*n*-Bu_4NCl	/	68
4	K_2CO_3	*n*-Bu_4NCl	PPh_3	70
5	K_2CO_3	*n*-Bu_4NCl	P(*p*-tol)$_3$	88 (85)[b]
6	K_2CO_3	*n*-Bu_4NCl	P(*o*-tol)$_3$	79
7	K_2CO_3	*n*-Bu_4NCl	P(*p*-F-Ph)$_3$	71
8	K_2CO_3	*n*-Bu_4NCl	PCy_3	59
9	Na_2CO_3	*n*-Bu_4NCl	P(*p*-tol)$_3$	86
10	Cs_2CO_3	*n*-Bu_4NCl	P(*p*-tol)$_3$	40
11	KOAc	*n*-Bu_4NCl	P(*p*-tol)$_3$	62
12	K_3PO_4	*n*-Bu_4NCl	P(*p*-tol)$_3$	82
13	K_2CO_3	*n*-Bu_4NCl	P(*p*-tol)$_3$	86[c]
14	K_2CO_3	*n*-Bu_4NCl	P(*p*-tol)$_3$	33[d]
15	K_2CO_3	*n*-Bu_4NCl	P(*p*-tol)$_3$	69[e]

[a] The yields were determined by ^{1}H NMR analysis of the crude reaction mixture using $CHCl_2CHCl_2$ as the internal standard. [b] Isolated yield. [c] 2-bromo-*tert*-butylbenzene. [d] 2-bromobenzoic acid. [e] 5 mol % of $Pd(OAc)_2$, 7.5 mol % of ligand.

Having identified the optimal conditions for the cross-coupling of two different aryl halides, we investigated the substrate scope of the reaction. The performance of various 2-chlorobenzoic acid derivatives was first probed. Substrates bearing a methyl, methoxy, or fluoro group at the 4 position could couple with **1a** efficiently, and the corresponding products were formed in high yields (**3ab-3ae**). The structure of **3ad** was identified by single-crystal X-ray crystallography.[11] Notably, the iodo-carbon coupled with the chloro-carbon of 2-chlorobenzoic acid selectively, and the methyl carbon reacted with the carbon attached by the carboxyl group. It should be mentioned that a chloro group was tolerated (**3ae**). The suitability of 5-substituted 2-chlorobenzoic acids was then investigated. Whereas methyl or fluoro-substituted substrates exhibited high reactivity, a trifluoromethyl or cyano group gave a low yield (**3af-3ai**). Notably, a free hydroxyl and amino group were compatible, which allows for the further transformation of the products (**3aj** and **3ak**). The impact of *ortho*-substituents on the reaction was also examined. The yield decreased to 40% for 3-methyl-substituted substrate, which should result from the steric hindrance imposed by the methyl group (**3al**). A yield of 64% was still obtained for the substrate bearing a methyl group *ortho* to the carboxyl group (**3am**). Whereas 3-fluoro-substituted benzoic acid gave a yield of 65%, the presence of a 6-fluoro group led to a sharp decrease in the yield (**3an** and **3ao**). Difluoro-substituted substrates was also suitable, and 3-chloroisonicotinic acid failed to form the desired product (**3ap** and **3aq**).

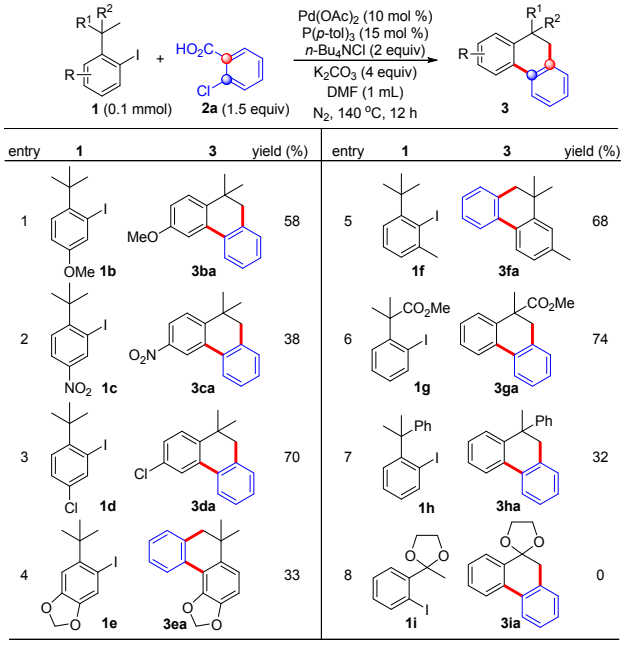
Table 2. Substrate Scope with the Respect to 2-Chlorobenzoic Acids



The 2-iodo-*tert*-butylbenzene scope was then investigated. The substrate bearing an electron-donating methoxy group gave 9,10-dihydrophenanthrene **3aa** in 58% yield, and the presence of an electron-withdrawing nitro group led to a low yield (**3ba** and **3ca**). The chloro group was well-tolerated (**3da**). For substrate **1e**, the C–H bond *ortho* to the *tert*-butyl group was phenylated and migrated product **3ea** was obtained (**3ea**). The reaction of **1f** also involved a migration process, affording product **3fa** in 68% yield. The reactions of iodobenzenes bearing a derivatized *tert*-butyl group were also studied. The isopropyl groups substituted by an ester or phenyl group could participate in the dual cross-coupling reaction (**3ga** and **3ha**). However, **1i**, which contains a

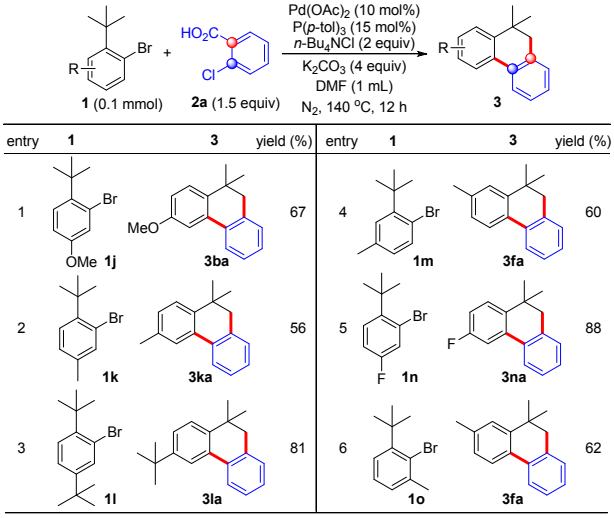
single methyl group, failed to give product **3ia**.

Table 3. Substrate Scope with the Respect to Iodobenzenes

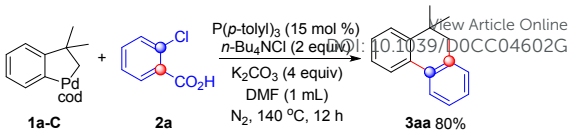


We also examined the reactions of various 2-bromo-*tert*-butylbenzenes. As outlined in **Table 4**, a range of 2-bromo-*tert*-butylbenzenes, substituted by a methoxy, methyl, *tert*-butyl, or fluoro group reacted with **2a** efficiently, and the corresponding products were obtained in moderate or high yields (**3ja**-**3na**). Just as **1f**, *ortho*-methyl-substituted substrate **1o** also formed migrated product **3fa**.

Table 4 Substrate Scope with the Respect to Bromobenzenes



Mechanistic studies were then conducted. First, palladacycle **1a-C** was prepared and was allowed to react with **2a**. Product **3a** was obtained in 80% yield (**Scheme 2**), which implies that a palladacycle could act as the intermediate in the cross-coupling reaction. Time-course of the yields was studied. As shown in **Fig. 1**, the reaction was initiated quickly, and product **3aa** was formed in 37% yield in five minutes. The reaction also proceeded at a high rate, and the optimal yield was almost obtained in 110 minutes in the reaction of **1a**.



Scheme 2. Mechanistic Studies.

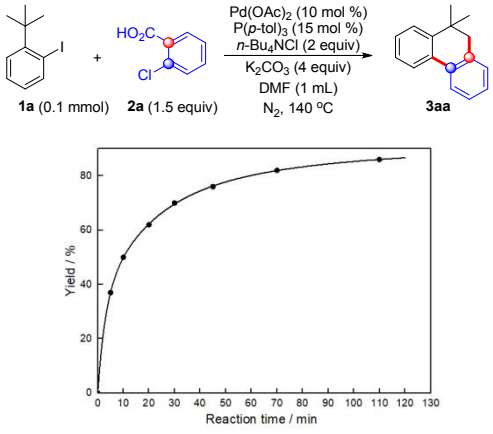
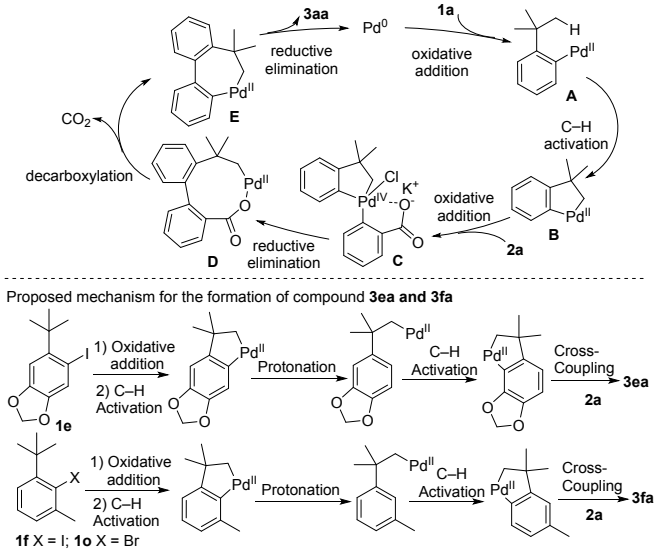


Fig. 1 Time-course of yields for the formation of **3aa**.

On the basis of **th**e mechanistic studies and previous reports[3b], [5], we proposed a mechanism for the 9,10-dihydrophenanthrene-forming reaction (**Scheme 3**). The catalytic cycle is initiated by the oxidative addition to yield Pd^{II} species **A**. The subsequent C(sp^3)–H activation forms palladacycle **B**. A second oxidative addition of 2-chlorobenzoic acid to the palladacycle affords Pd^{IV} species **C**. The first C-C bond is formed via reductive elimination, which is followed by decarboxylation to give seven-membered palladacycle **E**. A second reductive elimination yields final product **3aa**.

Scheme 3. Proposed Mechanism.



For the formation of **3ea**, the palladacycle decomposes to give an alkylpalladium(II) species. The alkylpalladium(II) species then activates *ortho*-C–H bond to generate a second palladacycle, which may be stabilized by the binding of the oxygen atom. The second palladacycle then undergoes coupling reaction with 2-chlorobenzoic acid to form product

3ea. **3fa** is formed in a similar migration process. The driving force for the migration should be the steric hindrance imposed by the methyl group, which impedes the reaction of the palladacycle with 2-chlorobenzoic acid.

In conclusion, we have developed a Pd-catalyzed cross-coupling reaction of aryl iodides with 2-chlorobenzoic acids. Mechanistic studies support that C(sp^3), C(sp^2)-palladacycles were generated through C(sp^3)–H activation and acted as the intermediates. The reaction formed two C–C bonds and afforded six-membered products. A range of 2-chlorobenozic acids and iodobenzenes bearing an *ortho*-alkyl group underwent the cross-coupling reaction, and the reaction provides an innovative method for the synthesis of 9,10-dihydrophenanthrenes. The reaction also represents the first example of Pd-catalyzed C(sp^3)–H arylation of iodobenzenes with 2-chlorobenzoic acids.

The work was supported by the National Natural Science Foundation of China (No. 21971196 and 21672162).

Conflicts of interest

The authors declare no conflict of interest.

Notes and references

1 a) *C–H Activation* (Eds.: J.-Q. Yu, Z. Shi), Springer, Heidelberg, 2010; b) "Carbon-Carbon-Bond Formation via C–H Bond Functionalization": Y.-H. Zhang, G.-F. Shi and J.-Q. Yu in *Comprehensive Organic Synthesis*, 2nd ed., Vol. 3 (Eds.: G. Molander, P. Knochel), Elsevier, Oxford, 2014, pp. 1101–1209; c) C. Liu, J.-W. Yuan, M. Gao, S. Tang, W. Li, R.-Y. Shi and A.-W. Lei, *Chem. Rev.*, 2015, **115**, 12138; d) T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147; e) O. Daugulis, J. Roane and L. D. Tran, *Acc. Chem. Res.*, 2015, **48**, 1053; f) J. Miao and H. Ge, *Eur. J. Org. Chem.*, 2015, **2015**, 7859; g) T. Gensch, M. N. Hopkinson, F. Glorius and J. Wencel-Delord, *Chem. Soc. Rev.*, 2016, **45**, 2900; h) M. Moselage, J. Li and L. Ackermann, *ACS Catal.*, 2016, **6**, 498; i) S. Rej, Y. Ano and N. Chatani, *Chem. Rev.*, 2020, **120**, 1788.

2 For reviews on C(sp^3)-H functionalization: a) J. He, M. Wasa, K. S. L. Chan, Q. Shao and J.-Q. Yu, *Chem. Rev.*, 2017, **117**, 8754; b) Y. Xu and G. Dong, *Chem. Sci.*, 2018, **9**, 1424; c) Z. Chen, M.-Y. Rong, J. Nie, X.-F. Zhu, B.-F. Shi and J.-A. Ma, *Chem. Soc. Rev.*, 2019, **48**, 4921; d) B.-J. Li and Z.-J. Shi *Chem. Soc. Rev.*, 2012, **41**, 5588; e) J. C. K. Chu and T. Rovis, *Angew. Chem., Int. Ed.*, 2018, **57**, 62; f) R. Jazzar, J. Hitce, A. Renaudat, J. Sofack-Kreutzer and O. Baudoin, *Chem. Eur. J.*, 2010, **16**, 2654.

3 a) W.-C. Fu, Z. Wang, W. T. K. Chan, Z. Y. Lin and F. Y. Kwong, *Angew. Chem., Int. Ed.*, 2017, **56**, 7166; b) Q.-Y. Zhao, W.-C. Fu and F. Y. Kwong, *Angew. Chem., Int. Ed.* 2018, **57**, 3381; c) Y.-Z. Yang, B. Zhou, X.-M. Zhu, G.-B. Deng, Y. Liang and Y. Yang, *Org. Lett.*, 2018, **20**, 5402; d) X.-M. Yang, H.-Y. Lu, X.-M. Zhu, L.-W. Zhou, G.-B. Deng, Y. Yang and Y. Liang. *Org. Lett.*, 2019, **21**, 7284; e) X.-A. Luo, L.-W. Zhou, H.-Y. Lu, G.-B. Deng, Y. Liang, C.-M. Yang and Y. Yang, *Org. Lett.*, 2019, **21**, 9960.

4 a) O. Baudoin, *Acc. Chem. Res*., 2017, **50**, 1114; b) O. Baudoin, A. Herrbach and F. Guéritte, *Angew. Chem., Int. Ed.*, 2003, **42**, 5736; c) H. Ren and P. Knochel, *Angew. Chem., Int. Ed.*, 2006, **45**, 34625; d) C.-G. Dong and Q.-S. Hu, *Angew. Chem., Int. Ed.*, 2006, **45**, 2289; e) M. Lafrance, S. I. Gorelsky and K. Fagnou, *J. Am. Chem. Soc.*, 2007, **129**, 14570; f) M. Chaumontet, R. Piccardi, N. Audic, J. Hitce, J. L. Peglion, E. Clot and O. Baudoin, *J. Am. Chem. Soc.*, 2008, **130**, 15157; g) S.Rousseaux, M. Davi, J. Sofack-Kreutzer, C. Pierre, C. E.Kefalidis, E. Clot, K. Fagnou and O. Baudoin, *J. Am. Chem. Soc.*, 2010, **132**, 10706; h) J.-X. Yan, H. Li, X.-W. Liu, J.-L. Shi, X. Wang and Z.-J. Shi, *Angew. Chem., Int. Ed.*, 2014, **126**, 5045; i) M. Wang, X. Zhang, Y.-X. Zhuang, Y.-H. Xu and T.-P. Loh, *J. Am. Chem. Soc.*, 2015, **137**, 1341; j) L. Yang, R. Melot, M. Neuburger and O. Baudoin, *Chem. Sci.*, 2017, **8**, 1344.

5 a) S.-L. Cai, Y. Li, C. Yang, J. Sheng and X.-S. Wang, *ACS Catal.*, 2019, **9**, 10299; b) A. Gutiérrez-Bonet, F. Juliá-Hernández, B. de Luis and R. Martin, *J. Am. Chem. Soc.* 2016, **138**, 6384; c) Z. Wu, D. Ma, B. Zhou, X.-M. Ji, X.-T. Ma, X.-L. Wang and Y.-H. Zhang, *Angew. Chem. Int. Ed.*, 2017, **129**, 12456; d) A.-L. Lu, X.-M. Ji, B. Zhou, Z. Wu and Y.-H. Zhang, *Angew. Chem., Int. Ed.*, 2018, **57**, 3233. e) B.-J. Tan, L. Bai, P. Ding, J.-J. Liu, Y.-Y. Wang and X.-J. Luan, *Angew. Chem. Int. Ed.*, 2019, **58**, 1474; f) X.-L. Sun, Z. Wu, W.-X. Qi, X.-M. Ji, C. Cheng and Y.-H. Zhang. *Org. Lett.*, 2019, **21**, 6508; g) T. E. Barder, S. D. Walker, J. R. Martinelli and S. L. Buchwald, *J. Am. Chem. Soc.*, 2005, **127**, 4685; h) G. Dyker, *Angew. Chem., Int. Ed.*, 1992, **31**, 1023; i) G. Dyker, *Angew. Chem., Int. Ed.*, 1994, **33**, 103.

6 a) D. H. Miles, J. Bhattacharyya, N. V. Mody, J. L. Atwood, S. Black and P. A. Hedin, *J. Am. Chem. Soc.*, 1977, **99**, 618; b) D. L. Boger, L. A. Mitscher, M. D. Mullican, S. D. Drake and P. Kitos, *J. Med. Chem.*, 1985, **28**, 1543; c) X.-Y. Wang, C.-Q. Ke, C.-P. Tang, D. Yuan and Y. Ye, *J. Nat. Prod.*, 2009, **72**, 1209; d) C.-L. Lee, F.-R. Chang, M.-H Yen, D. Yu, Y.-N. Liu, K. F. Bastow, S. L. Morris-Natschke, Y.-C. Wu and K.-H. Lee, *J. Nat. Prod.*, 2009, **72**, 210; e) F. Delle Monache, G. Delle Monache, J. F. Cavalcanti and R. M. Pinheiro, *Tetrahedron Lett.*, 1987, **28**, 563.

7 a) K. Baba, T. Kido, M. Taniguchi and M. Kozawa, *Phytochemistry,* 1994, **36**, 1509; b) K. Ezaki, M. Satake, T. Kusumi and H. Kakisawa, *Tetrahedron Lett.*, 1991, **32**, 2793; c) F. Delle Monache, G. Delle Monache, B. Botta and E. Gacs-Baitz, *Heterocycles*, 2002, **56**, 589; d) A. Ericsson, A. Marinier and F. C. Zusi, *PCT Int. Appl.* 2002, WO 2002065984 A2 20020829.

8 a) Y. Suzuki, T. Nemoto, K. Kakugawa, A. Hamajima and Y. Hamada, *Org. Lett.,* 2012, **14**, 2350; b) S. Ueno, S. Komiya, T. Tanaka and R. Kuwano, *Org. Lett.*, 2012, **14**, 338; c) D. S. Roman, Y. Takahashi and A. B. Charette, *Org. Lett.*, 2011, **13**, 3242; d) R. Jana, I. Chatterjee, S. Samanta and J. K. Ray, *Org. Lett.*, 2008, **10**, 4795; e) C. Zhu, Y. Shi, M.-H. Xu and G.-Q. Lin, *Org. Lett.*, 2008, **10**, 1243; f) R. Pratap and V. J. Ram, *J. Org. Chem.*, 2007, **72**, 7402; g) N. Saito, K. Shiotani, A. Kinbara and Y. Sato, *Chem. Commun.*, 2009, 4284; h) S. Bhuvaneswari, M. Jeganmohan and C.-H. Cheng, *Org. Lett.*, 2006, **8**, 5581; i) I. Quintana, A. J. Boersma, D. Peña, D. Pérez and E. Guitián, *Org. Lett*., 2006, **8**, 3347; j) S. S. Bhojgude, A. Bhunia, R. G. Gonnade and A. T. Biju, *Org. Lett.*, 2014, **16**, 676.

9 a) L.-C. Campeau, M. Parisien, M. Leblanc and K. Fagnou, *J. Am. Chem. Soc.*, 2004, **126**, 9186; b) T. J. Corrie, L. T. Ball, C. A. Russell and G. C. Lloyd-Jones, *J. Am. Chem. Soc.*, 2017, **139**, 245; c) L.-C. Campeau, P. Thansandote and K. Fagnou, *Org. Lett*., 2005, **7**, 1857.

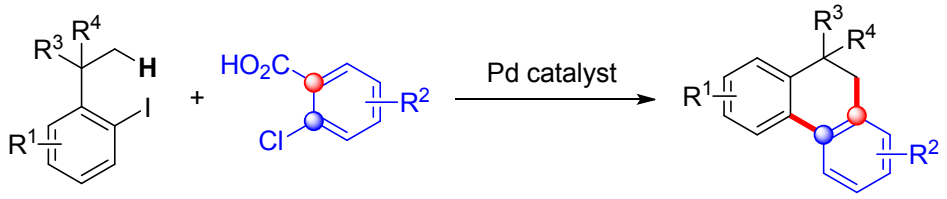
10 For the role of tetrabutylammonium salt in promoting Pd(0)-catalyzed reaction of aryl halides. See: a) C. Amatore, M. Azzabi and A. Jutand, *J. Am. Chem. Soc.*, 1991, **113**, 8375; b) M. Piber, A. E. Jensen, M. Rottländer and P. Knochel, *Org. Lett.*, 1999, **1**, 1323.

11 CCDC 2013468 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

DOI: 10.1039/D0CC04602G

C(sp³)–H Activation-Enabled Cross-Coupling of Two Aryl Halides: An Approach to 9,10-Dihydrophenanthrenes

Yichao Gu, Xueliang Sun, Bin Wan, Zhuoer Lu, and Yanghui Zhang*



C(sp³)-H activation **Cross-coupling of two aryl halides** **An innovative approach to 9,10-dihydrophenanthrenes**

A palladium-catalyzed cross-coupling reaction of aryl halides with 2-chlorobenzoic acids has been developed through C(sp³)–H activation, which provides an innovative method for the synthesis of 9,10-dihydrophenanthren.