



Cite this: *RSC Adv.*, 2019, 9, 18191

Received 1st June 2019
 Accepted 4th June 2019

DOI: 10.1039/c9ra04142g

rsc.li/rsc-advances

Rh(III)-catalyzed C-7 arylation of indolines with arylsilanes *via* C–H activation†

Haiqing Luo,^a Qi Xie, Kai Sun, Jianbo Deng, Lin Xu, Kejun Wang and Xuzhong Luo^{a*}

Site-selective synthesis of C-7 arylated indolines has been achieved *via* oxidative arylation of indolines with arylsilanes under Rh(III)-catalyzed C–H activation of indolines by using CuSO₄ as a co-oxidant. This transformation has been explored for a wide range of substrates under mild conditions.

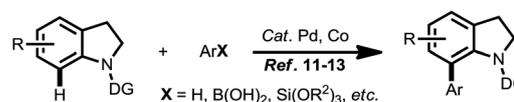
The indole and indoline ring systems represent ubiquitous structural motifs as natural alkaloids and biologically active compounds as well as in functional materials.^{1,2} With the development of C–H bond functionalization,³ a great deal of effort has been devoted to the formation C-2 and C-3 functionalized indoles.⁴ Nevertheless, only a few methods have been explored for the direct C–H bond functionalization of indoles at the C-7 position,⁵ in which the unique work for the direct Pd-catalyzed C–H arylation of indoles with arylboronic acids at the C-7 position was developed by the Shi group using a designed di-*tert*-butylphosphine oxide (TBPO) directing-group.^{5b} In general, the C-7 arylated indolines can be conveniently oxidized to transform into C-7 arylated indoles. So far, transition metals such as Pd,⁶ Rh,⁷ Ru,⁸ Ir,⁹ *etc.*,¹⁰ have been employed as catalysts for the C-7 C–H bond functionalization of indolines, among which the C–H arylation in the C-7 position of indoline was mainly established by using Pd complexes as catalysts (Scheme 1a).¹¹ In 2016, we also reported the Pd-catalyzed C-7 arylation of indolines with arylsilanes *via* C–H bond activation.¹² Recently, the Punniyamurthy group developed the site-selective C-7-arylation of indolines with arylboronic acids by using low-cost and earth-abundant cobalt(II)-PCy₃ as a catalyst.¹³ Even so, in view of the importance of indole and indoline scaffolds, it is still highly desirable to develop more convenient and efficient approaches for the synthesis of C-7 arylated indolines and C-7 arylated indoles.

Meanwhile, recent years have witnessed tremendous developments in the area of Rh(III)-catalyzed C–H bond functionalization,¹⁴ which has allowed effective construction of various C–C bonds. The major advantages of Rh(III) catalysis are (i) high functional-group tolerance, (ii) broad substrate scope, (iii) low catalyst loading, high activity, and high catalytic efficiency.

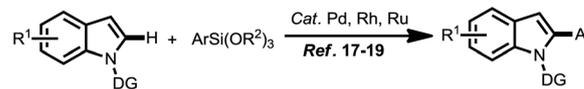
Since the Hiyama cross-coupling reaction had been first reported in 1988,¹⁵ as one of the most useful and reliable synthetic

methods for the construction C–C bonds, the Hiyama cross-coupling reaction has drawn increasing attention.¹⁶ As attractive organometallic coupling partners with many unique advantages such as low toxicity, high stability and environmental benignity, organosilicon reagents were used as coupling partners for the C–H arylation of indoles and indolines (Scheme 1b).¹⁷ Zhang group reported the Pd-catalyzed C-2 arylation of indoles with arylsilanes in acidic medium in 2010. In 2014, Loh group developed the Rh(III) catalyzed C-2 C–H arylation of indoles with arylsilanes in aqueous media.¹⁸ Very recently, Szostak group developed the Ru(II) catalyzed arylation of indoles with arylsilanes *via* C–H activation,¹⁹ it is worth noting that the reaction was carried out in water. However, the methods for the synthesis of C-7 arylated indolines and C-7 arylated indoles are very limited by using arylsilanes as the coupling partners. To the best of our knowledge, the Rh(III) catalyzed C-7 arylation of indolines with arylsilanes has not been achieved. Due to our continuous interest in the arylsilanes-based coupling reaction,^{12,20} we herein would like to report a Rh(III)-catalyzed

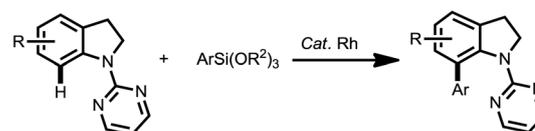
a) C-7 arylation of indolines with various coupling partners



b) C-2 arylation of indoles with arylsilanes



c) **THIS WORK** *via* Rh(III)-catalyzed C–H arylation



Scheme 1 C-2 arylation of indoles with arylsilanes and C-7 arylation of indolines.

Department of Chemistry & Chemical Engineering, Gannan Normal University, Ganzhou 341000, China. E-mail: luohaiqing@sina.com; luoxuzhong@hotmail.com

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c9ra04142g



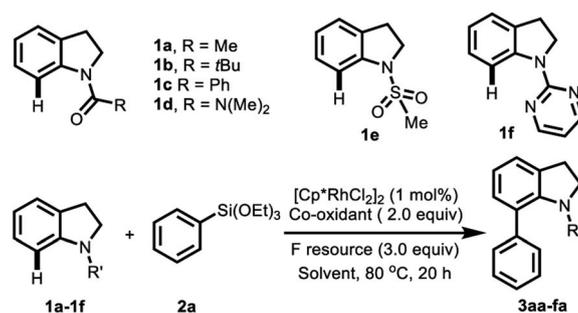
regioselective C-7 arylation of indolines with arylsilanes *via* C–H activation (Scheme 1c), the reaction provides a facile access to C-7 arylated indolines.

At the outset of the investigation, various N-protecting indolines (Table 1, **1a–1f**) were initially used as coupling partners for the direct C-7 C–H arylation with phenyltriethoxysilane **2a** in the presence of 1 mol% of [Cp*RhCl₂]₂ in dioxane at 80 °C, 3.0 equiv. of AgF as the activator for C–Si bond as well as the oxidant, and 2.0 equiv of Cu(OAc)₂ as the co-oxidant. The choice of the N-protecting group was found to be crucial for this arylation, and only pyrimidyl-protected indoline (**1f**) afforded desired arylated product **3fa**. Then, different fluorine sources such as AgF, CsF, KF, and TBAF were examined (Table 1, entries 3–6). Only AgF was found to be effective, thus affording the desired product **3fa**. The reaction can afford the desired product in 72% yield by using no co-oxidant (entry 7). In order to increase the yield, various co-oxidants such as Ag₂CO₃, Ag₂O, Cu(OAc)₂ and CuSO₄ were utilized (entries 8–10), CuSO₄ proved to be the optimal choice. Subsequently, the effect of solvent was then investigated (entries 10–15), and dioxane was found to be suitable for the reaction. To our surprise, this reaction could be performed in aqueous media (dioxane/H₂O = 1/10) in 47% yield

(Table 1, entry 15). Furthermore, in order to gain the milder reaction condition, the reaction temperature was tried to reduce. The results revealed that the reaction carried out at 60 °C offered a relatively low yield in 87% (Table 1, entry 16).

With the optimized reaction conditions in hand, we then proceeded to explore the scope of the direct C-7 C–H arylation of *N*-(2-pyrimidyl)-indoline with a series of arylsilanes (Table 2). It was found that various phenylsilanes had good compatibility under these reaction conditions. At first, phenyltrimethoxysilane shows good reactivity affording 67% yield. To investigate the steric effect, the phenyltriethoxysilanes bearing methyl group on different positions of the phenyl ring were employed as the substrates (**3fb–3fd**). The results indicate that the phenyltriethoxysilane with *ortho*-methyl substituent was found to afford the desired product for the diminished yield in 33%, which could be due to the steric effect. The direct C–H arylation of *N*-(2-pyrimidyl)-indoline has shown excellent tolerance to both electron-withdrawing and electron-donating groups as aromatic substituents, including alkyl (**3fb–3fe**), alkyloxy (**3ff–3fh**), aryl (**3fi**), fluoro (**3fj**), chloro (**3fk**), and trifluoromethyl groups (**3fl**) in good to excellent yields except the *ortho*-methyl substituent (**3fd**). In addition, the heterocyclic triethoxy(thiophen-2-yl)silane was also used to explore the

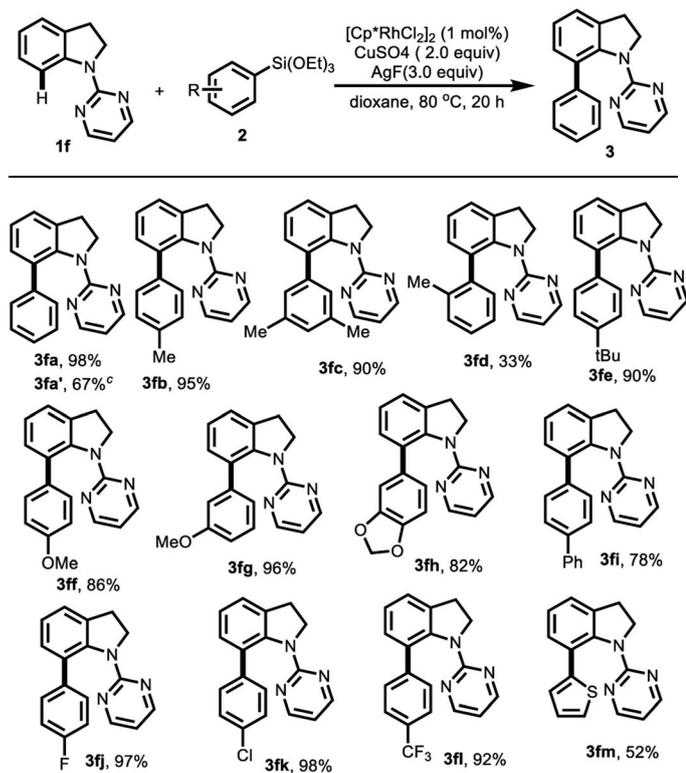
Table 1 Optimization of reaction conditions for the Rh(III)-catalyzed C-7 arylation of indolines with arylsilane^a



Entry	Substrates	Co-oxidant	F source	Solvent	Yield ^b (%)
1	1a–1d	Ag ₂ CO ₃	AgF	Dioxane	0
2	1e	Ag ₂ CO ₃	AgF	Dioxane	0
3	1f	Ag ₂ CO ₃	AgF	Dioxane	81
4	1f	Ag ₂ CO ₃	CsF	Dioxane	0
5	1f	Ag ₂ CO ₃	KF	Dioxane	0
6	1f	Ag ₂ CO ₃	TBAF	Dioxane	0
7	1f	—	AgF	Dioxane	72
8	1f	AgOAc	AgF	Dioxane	89
9	1f	Cu(OAc) ₂	AgF	Dioxane	85
10	1f	CuSO ₄	AgF	Dioxane	98
11	1f	CuSO ₄	AgF	DMF	62
12	1f	CuSO ₄	AgF	DMSO	0
13	1f	CuSO ₄	AgF	iPrOH	81
14	1f	CuSO ₄	AgF	H ₂ O	Messy
15	1f	CuSO ₄	AgF	Dioxane/H ₂ O = 1/10	47
16 ^c	1f	CuSO ₄	AgF	Dioxane	87

^a Unless otherwise noted, the reaction conditions are as follows: **1** (0.3 mmol), **2a** (0.9 mmol), [Cp*Rh(III)Cl₂]₂ (1 mol%), Co-oxidant (0.6 mmol), F resource (0.9 mmol), solvent (3.0 mL). ^b Isolated yield after purification by flash column chromatography on silica gel, n.d.p or trace product was determined by TLC. ^c The reaction temperature was 60 °C.



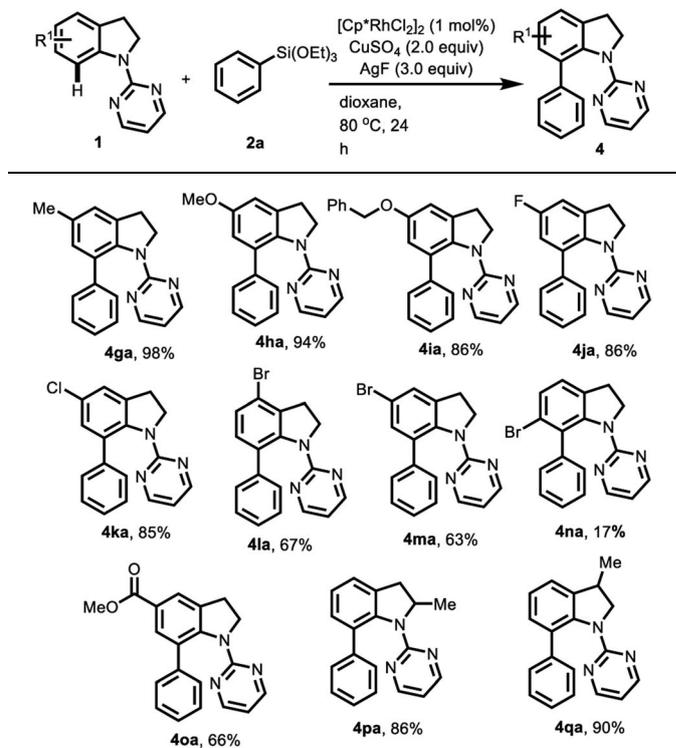
Table 2 Rh(III)-catalyzed the direct C-7 arylation of indoline **1f** with various phenyltriethoxysilane **2**^{a,b}

^a Unless otherwise noted, the reaction conditions are as follows: **1f** (0.3 mmol), **2** (0.9 mmol), dioxane (3.0 mL). ^b All the yields refer to isolated yields. ^c Phenyltrimethoxysilane was used.

possibility of the C-H arylation. To our delight, the reaction also afforded the corresponding product in moderate yield (**3fm**).

To further evaluate the substrate scope, various substituted *N*-(2-pyrimidyl)-indolines were used to test the reaction with the phenyltriethoxysilane **2a** under the optimized reaction conditions. The results are summarized in Table 3. In general, the (2-pyrimidyl)-indolines bearing electron-donating groups on the aromatic ring such as 5-methyl and 5-alkoxy group react smoothly to afford the corresponding arylated products in excellent yields (**4ga–4ha**). In addition, the reactions with the (2-pyrimidyl)-indolines bearing electron-withdrawing group on the aromatic ring also afford moderate to good yield (**4ja–4oa**), except the substrate **1n** with 6-bromo group showed low activity affording 17% yield, which may be attributed to the steric hindrance of the bromo functionality. Furthermore, the substrates with C-2 or C-3 methyl substituted group on the indoline ring also show excellent compatibility with the reaction condition in 86% (**4pa**) and 90% yield (**4qa**), respectively.

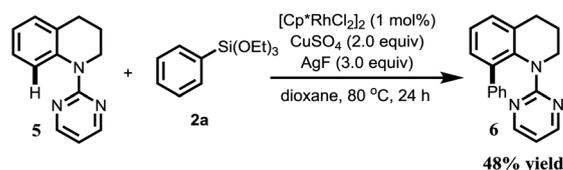
To explore the utility of this transformation, we tried to explore direct C-8 C-H arylation with *N*-(2-pyrimidyl)-tetrahydroquinoline **5** and phenyltriethoxy-silane **2a** under the standard condition, to our delight, the desired C-8 C-H arylated product was obtained in 48% yield (Scheme 2).

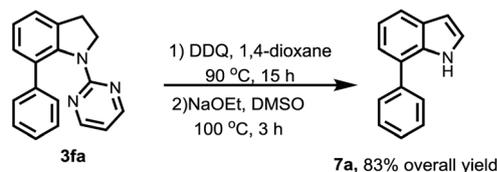
Table 3 Rh(III)-catalyzed the direct C-7 arylation of various indolines **1** with phenyltriethoxysilane **2a**^{a,b}

^a Unless otherwise noted, the reaction conditions are as follows: **1** (0.3 mmol), **2a** (0.9 mmol), dioxane (3.0 mL). ^b All the yields refer to isolated yields.

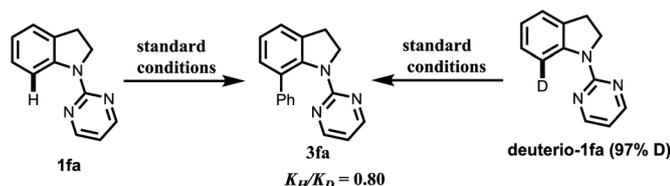
To further demonstrate the synthetic utility of the method, the transformation of C-7 arylated indoline into C-7 arylated indole was studied.^{13,21} As shown in Scheme 3, the transformation was begun with the oxidation of C-7 arylated *N*-(2-pyrimidyl)-indoline **3fa** by the use of DDQ (2,3-dicyano-5,6-dichlorobenzoquinone), followed by removing pyrimidyl group in the present of base. Finally, 83% yield of the C-7 arylated indole product **7a** was successfully obtained.

To gain some preliminary mechanistic insights, kinetic isotope experiments were conducted. The parallel reactions of **1f** and **deuterio-1f** with **2a** resulted $k_{\text{H}}/k_{\text{D}} = 0.80$ (Scheme 4), which suggested that the C-H cleavage was not the rate-determining step in the catalytic cycle. On the basis of previous literatures,^{18,22,23} a plausible mechanism is proposed as shown Scheme 5. The process is likely to be initiated by the

**Scheme 2** Rh(III)-catalyzed the direct C-8 arylation of *N*-(2-pyrimidyl)-tetrahydroquinoline **5** with phenyltriethoxysilane **2a**.



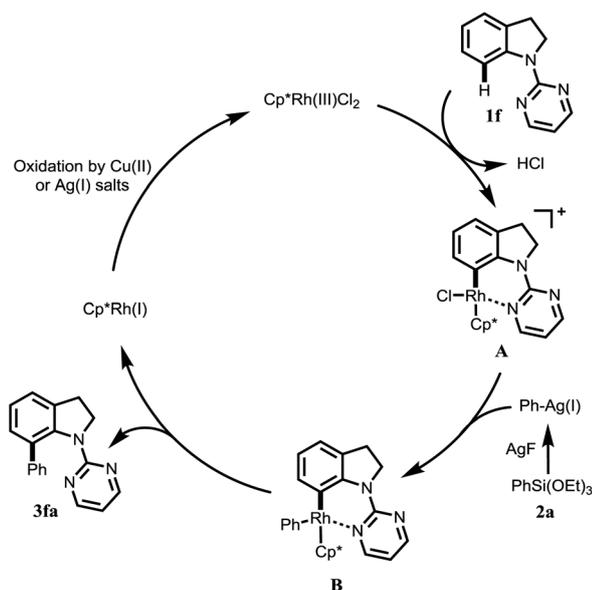
Scheme 3 Transformation of C-7-arylated indoline **3fa** to the corresponding indole **7a**.



Scheme 4 Parallel kinetic isotope experiment.

coordination of the nitrogen atom of 2-pyrimidyl group of **1f** to the rhodium catalyst, leading directly to cyclometalation process *via* C–H bond activation to afford the five-membered rhodacycle **A**.²⁴ The Ph–Ag species can be generated *via* the C–Si activation by the nucleophilic attack of a fluoride ion on silicon,^{20c,25} followed by the transmetalation with intermediate **A** to afford the Rh(III) intermediate **B**, from which reductive elimination would provide C-7 arylated indolines **3fa** and regenerate the Rh(I) catalyst, which is reoxidized to Rh(III) species by Ag(I) or Cu(II) salts to complete the catalytic cycle.

In summary, we have demonstrated a Rh(III)-catalyzed oxidative arylation of indolines with arylsilanes *via* C–H activation by using CuSO₄ as an co-oxidant. This general transformation exhibits excellent reactivity and broad substrate



Scheme 5 Plausible catalytic cycle for Rh(III)-catalyzed the direct C-7 arylation of indolines with phenyltriethoxysilane.

scopes, various functional groups are well tolerated under the mild reaction conditions. This reaction constitutes a complement method for the synthesis the desired C-7 arylated indolines up to excellent yields, which can be conveniently transformed into C-7 arylated indoles.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The project was supported by the National Natural Science Foundation of China (No. 21762002, 21562003) and Undergraduate Training Programs for Innovation and Entrepreneurship of Gannan Normal University (CX170049).

Notes and references

- (a) J. S. Mason, I. Morize, P. R. Menard, D. L. Cheney, C. Hulme and R. F. Labaudiniere, *J. Med. Chem.*, 1999, **42**, 3251; (b) K. C. Nicolaou, J. A. Pfefferkorn, A. J. Roecker, G. Cao, S. Barluenga and H. J. Mitchell, *J. Am. Chem. Soc.*, 2000, **122**, 9939; (c) J. D. Podoll, Y. Liu, L. Chang, S. Walls, W. Wang and X. Wang, *Proc. Natl. Acad. Sci. U. S. A.*, 2013, **110**, 15573.
- (a) U. Pindur and T. Lemster, *Curr. Med. Chem.*, 2001, **8**, 1681; (b) H. Knçlker and K. R. Reddy, *Chem. Rev.*, 2002, **102**, 4303; (c) D. A. Horton, G. T. Bourne and M. L. Smythe, *Chem. Rev.*, 2003, **103**, 893; (d) A. J. Kochanowska-Karamyan and M. T. Hamann, *Chem. Rev.*, 2010, **110**, 4489; (e) M. G. Bell, D. L. Gernert, T. A. Grese, M. D. Belvo, P. S. Borromeo, S. A. Kelley, J. H. Kennedy, S. P. Kolis, P. A. Lander and R. Richey, *J. Med. Chem.*, 2007, **50**, 6443; (f) T. Owa, A. Yokoi, K. Yamazaki, K. Yoshimatsu, T. Yamori and T. Nagasu, *J. Med. Chem.*, 2002, **45**, 4913.
- For selected reviews on C–H bond functionalization, see:(a) C. Sambigiagio, D. Schönbauer, R. Blicke, T. Dao-Huy, G. Pototschnig, P. Schaaf, T. Wiesinger, M. F. Zia, J. Wencel-Delord, T. Besset, B. U. W. Maesa and M. Schnürch, *Chem. Soc. Rev.*, 2018, **47**, 6603; (b) J. He, M. Wasa, K. S. L. Chan, Q. Shao and J.-Q. Yu, *Chem. Rev.*, 2017, **117**, 8754; (c) Y. Wei, P. Hu, M. Zhang and W. Su, *Chem. Rev.*, 2017, **117**, 8864; (d) J. Wencel-Delord, T. Drçge, F. Kiu and F. Glorius, *Chem. Soc. Rev.*, 2011, **40**, 4740; (e) N. Kuhl, M. N. Hopkinson, J. Wencel-Delord and F. Glorius, *Angew. Chem.*, 2012, **124**, 10382; *Angew. Chem., Int. Ed.*, 2012, **51**, 10236; (f) J. J. Mousseau and A. B. Charette, *Acc. Chem. Res.*, 2013, **46**, 412.
- For selected reviews, see:(a) I. V. Seregin and V. Gevorgyan, *Chem. Soc. Rev.*, 2007, **36**, 1173; (b) L. Joucla and L. Djakovitch, *Adv. Synth. Catal.*, 2009, **351**, 673; (c) E. M. Beck and M. J. Gaunt, *Top. Curr. Chem.*, 2010, **292**, 85; (d) S. Cacchi and G. Fabrizi, *Chem. Rev.*, 2011, **111**, PR215.
- (a) D. W. Robbins, T. A. Boebel and J. F. Hartwig, *J. Am. Chem. Soc.*, 2010, **132**, 4068; (b) Y. Yang, X. Qiu, Y. Zhao, Y. Mu and



- Z. Shi, *J. Am. Chem. Soc.*, 2016, **138**, 495; (c) L. Xu, C. Zhang, Y. He, L. Tan and D. Ma, *Angew. Chem., Int. Ed.*, 2016, **55**, 321.
- 6 (a) L.-Y. Jiao and M. Oestreich, *Org. Lett.*, 2013, **15**, 5374; (b) D. Yang, S. Mao, Y.-R. Gao, D.-D. Guo, S.-H. Guo, B. Li and Y.-Q. Wang, *RSC Adv.*, 2015, **5**, 23727; (c) M. Kim, N. K. Mishra, J. Park, S. Han, Y. Shin, S. Sharma, Y. Lee, E.-K. Lee, J. H. Kwak and I. S. Kim, *Chem. Commun.*, 2014, **50**, 14249.
- 7 (a) X.-F. Yang, X.-H. Hu, C. Feng and T.-P. Loh, *Chem. Commun.*, 2015, **51**, 2532; (b) X.-F. Yang, X.-H. Hu and T.-P. Loh, *Org. Lett.*, 2015, **17**, 1481; (c) S. H. Han, M. Choi, T. Jeong, S. Sharma, N. K. Mishra, J. Park, J. S. Oh, W. J. Kim, J. S. Lee and I. S. Kim, *J. Org. Chem.*, 2015, **80**, 11092; (d) M. Jeon, N. K. Mishra, U. De, S. Sharma, Y. Oh, M. Choi, H. Jo, R. Sachan, H. S. Kim and I. S. Kim, *J. Org. Chem.*, 2016, **81**, 9878; (e) N. K. Mishra, M. Jeon, Y. Oh, H. Jo, J. Park, S. Han, S. Sharma, S. H. Han, Y. H. Jung and I. S. Kim, *Org. Chem. Front.*, 2017, **4**, 241.
- 8 (a) C. S. Yi, S. Y. Yunand and I. A. Guzei, *J. Am. Chem. Soc.*, 2005, **127**, 5782; (b) A. Mishra, T. K. Vats, M. P. Nair, A. Das and I. Deb, *J. Org. Chem.*, 2017, **82**, 12406; (c) P. B. De, S. Banerjee, S. Pradhan and T. Punniyamurthy, *Org. Biomol. Chem.*, 2018, **16**, 5889; (d) C. Pan, A. Abdulkader, J. Hang, Y. Cheng and C. Zhu, *Chem. –Eur. J.*, 2014, **20**, 3606.
- 9 (a) S. Pan, T. Wakaki, N. Ryu and T. Shibata, *Chem. –Asian J.*, 2014, **9**, 1257; (b) Y. Kim, J. Park and S. Chang, *Org. Lett.*, 2016, **18**, 1892; (c) Y. Wu, Y. Yang, B. Zhou and Y. Li, *J. Org. Chem.*, 2015, **80**, 1946.
- 10 See review: A. S. Tariq, P. B. De, S. Pradhan and T. Punniyamurthy, *Chem. Commun.*, 2019, **55**, 572, and references cited therein.
- 11 (a) D. Kalyani, N. R. Deprez, L. V. Desai and M. S. Sanford, *J. Am. Chem. Soc.*, 2005, **127**, 7330; (b) Z. Shi, B. Li, X. Wan, J. Cheng, Z. Fang, B. Cao, C. Qin and Y. Wang, *Angew. Chem., Int. Ed.*, 2007, **46**, 5554; (c) T. Nishikata, A. R. Abela, S. Huang and B. H. Lipshutz, *J. Am. Chem. Soc.*, 2010, **132**, 4978; (d) L. Y. Jiao and M. Oestreich, *Eur. J. Org. Chem.*, 2013, **19**, 10845; (e) L. Y. Jiao, P. Smirnov and M. Oestreich, *Org. Lett.*, 2014, **16**, 6020.
- 12 H. Luo, H. Liu, Z. Zhang, Y. Xiao, S. Wang, X. Luo and K. Wang, *RSC Adv.*, 2016, **6**, 39292.
- 13 P. B. De, S. Pradhan, S. Banerjee and T. Punniyamurthy, *Chem. Commun.*, 2018, **54**, 2494.
- 14 For reviews on Rh(III)-catalyzed C–H activation, see: (a) G. Song and X. Li, *Acc. Chem. Res.*, 2015, **48**, 1007; (b) G. Song, F. Wang and X. Li, *Chem. Soc. Rev.*, 2012, **41**, 3651; (c) F. W. Patureau, J. Wencel-Delord and F. Glorius, *Aldrichimica Acta*, 2012, **45**, 31; (d) T. Satoh and M. Miura, *Chem. –Eur. J.*, 2010, **16**, 11212; (e) D. A. Colby, A. S. Tsai, R. G. Bergman and J. A. Ellman, *Acc. Chem. Res.*, 2012, **45**, 814; (f) C. Dutta and J. Choudhury, *RSC Adv.*, 2018, **8**, 27881.
- 15 Y. Hatanaka and T. Hiyama, *J. Org. Chem.*, 1988, **53**, 918.
- 16 (a) T. Komiyama, Y. Minami and T. Hiyama, *ACS Catal.*, 2017, **7**, 631; (b) S. E. Denmark and A. Ambrosi, *Org. Process Res. Dev.*, 2015, **19**, 982; (c) Y. Nakao and T. Hiyama, *Chem. Soc. Rev.*, 2011, **40**, 4893; (d) S. E. Denmark and C. S. Regens, *Acc. Chem. Res.*, 2008, **41**, 1486.
- 17 Z. J. Liang, B. B. Yao and Y. H. Zhang, *Org. Lett.*, 2010, **12**, 3185.
- 18 M. Z. Lu, P. Lu, Y. H. Xu and T. P. Loh, *Org. Lett.*, 2014, **16**, 2614.
- 19 P. Nareddy, F. Jordan and M. Szostak, *Org. Lett.*, 2018, **20**, 341.
- 20 (a) H. Luo, Z. Zhang, H. Liu and H. Liu, *Chin. J. Org. Chem.*, 2015, **35**, 802; (b) H. Luo, H. Liu, X. Chen, K. Wang, X. Luo and K. Wang, *Chem. Commun.*, 2017, **53**, 956; (c) H. Luo and W. Dong, *Synth. Commun.*, 2013, **43**, 2733.
- 21 P. Gandeepan, J. Koeller and L. Ackermann, *ACS Catal.*, 2017, **7**, 1030.
- 22 K. Cheng, H. Li, Y. Li, X.-S. Zhang, Z.-Q. Lei and Z.-J. Shi, *Chem. Sci.*, 2012, **3**, 1645.
- 23 S. D. Yang, B. J. Li, X. B. Wan and Z. J. Shi, *J. Am. Chem. Soc.*, 2007, **129**, 6066.
- 24 H. Li, J. Jie, S. Wu, X. Yang and H. Xu, *Org. Chem. Front.*, 2017, **4**, 250.
- 25 A. Sugiyama, Y. Ohnishi, M. Nakaoka, Y. Nakao, H. Sato, S. Sakaki, Y. Nakao and T. Hiyama, *J. Am. Chem. Soc.*, 2008, **130**, 12975.

