Tetrahedron Letters 56 (2015) 3754–3757

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Rhodium-catalyzed regioselective direct C–H arylation of indoles with aryl boronic acids

Liang Wang [a,b,*], Xing Qu [a], Zhan Li [a], Wang-Ming Peng [a,*]

[a] Key Laboratory of Optoelectronic Chemical Materials and Devices, Ministry of Education, Jianghan University, 8 Sanjiaohu Road, Wuhan, Hubei 430056, China
[b] School of Chemical and Enviromental Engineering, Jianghan University, 8 Sanjiaohu Road, Wuhan, Hubei 430056, China

ARTICLE INFO

Article history:
Received 2 March 2015
Revised 2 April 2015
Accepted 6 April 2015
Available online 29 April 2015

Keywords:
C–H arylation
Indoles
Aryl boronic acids
Rhodium-catalysis

ABSTRACT

A highly efficient Rh(III)-catalyzed direct C–H arylation of indoles with aryl boronic acids under mild conditions has been developed. The methodology features wide substrate scope and excellent functional group compatibility (34 examples, up to 99% yield). The arylated products can also be conveniently transformed into biologically active polycyclic indole derivatives.

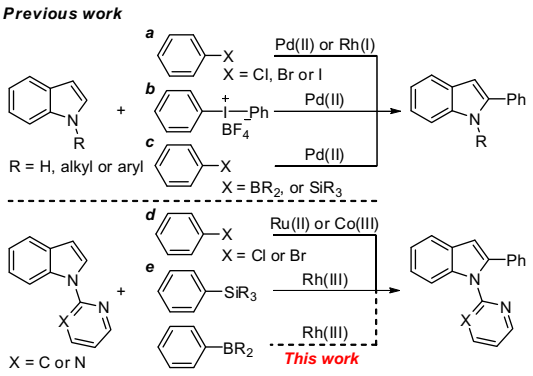
Arylated indoles and their derivatives are common structural motifs in a series of natural products, pharmaceuticals, and biologically active compounds.[1] Therefore, enormous efforts have been devoted to the construction of arylated indole scaffolds over last several decades.[2] The majority has always been based on the traditional cross-coupling reaction, which requires preactivation of both aryl coupling partners.[3] Recently, transition-metal-catalyzed C–H activation has emerged as one of the most powerful tools for functionalization of indoles and other bioactive heterocycles due to its step- and atom-economical features.[4] In this context, various coupling species had been employed in the field of direct C–H arylation of indoles.[5] Pioneering works on C–H arylation of indoles using aryl halides have been reported by Sames' and Larrosa's groups, respectively (Scheme 1a).[6] Shortly after, Sanford reported on the direct C–H arylation of indoles with hypervalent iodine reagents via a $Pd^{(II)/(IV)}$ catalytic cycle in the presence of HOAc (Scheme 1b).[7] Shi and Zhang also independently disclosed that both aryl boronic acids and arylsiloxanes proved to be good coupling partners in the oxidative arylation of indoles under acidic conditions (Scheme 1c).[8] Despite significant advances, there are still some limitations with these methods, such as the use of high catalyst loading, acidic medium, long reaction time, or lower efficiency. Therefore, it is still highly desirable to develop more efficient methods for regioselective direct C–H arylation of indoles under mild conditions.

The last several years have witnessed remarkable progress in the selective activation of C2–H bond of indoles through installation of removable directing groups at the N1-position of indoles.[9,10] For instance, Ackermann had documented the first example of direct C–H arylation of indoles using the readily installable and removable pyrimidyl group (Scheme 1d).[11] Quite recently, Xu and Loh developed an elegant Rh(III)-catalyzed C–H arylation of *N*-pyrimidyl indoles with arylsilanes in aqueous media (Scheme 1e).[12] Compared with arylhalides and organosilicon, aryl boronic acids have several unique advantages, including nontoxicity, high stability, environmental benignity, and readily availability.[13] Very recently, Cui and co-workers had achieved carboxamide group-assisted coupling of indoles and aryl boronic acids using Rh(III)/Cu(II) catalytic system.[14] Encouraged by these excellent works, herein, we developed a Rh(III)-catalyzed highly efficient and regioselective C–H arylation of indoles with arylboronic acids under mild conditions.

At the outset of our study, we examined the C–H arylation of *N*-pyrimidyl indole **1a** with phenylboronic acid **2a** using the $[RhCp^*Cl_2]_2$ in MeOH at 60 °C (Table 1). Fortunately, the product **3a** was isolated in moderate yield in the presence of Ag_2O or $Cu(OAc)_2$ as the oxidant. Much to our delight, the yield was drastically increased to 91% when we change the oxidant to AgOAc (Table 1, entry 3). Encouraged by this result, a variety of silver salts had been tested in this catalytic system. Gratifyingly, the yield was

* Corresponding authors. Tel./fax: +86 27 84225308.
E-mail addresses: wangliang@mail.jhun.edu.cn (L. Wang), pwm_jhun@163.com (W.-M. Peng).

http://dx.doi.org/10.1016/j.tetlet.2015.04.015
0040-4039/

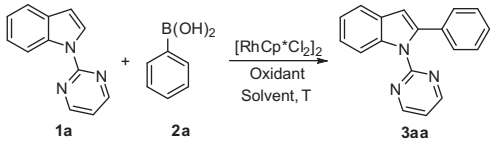


Scheme 1. Direct C–H arylation of indoles.

further improved to 98% and the reaction time could be shortened to 6 h when $AgOOCCF_3$ was used in this C–H arylation process (Table 1, entry 5). It was worthy to note that high reaction activity could be also maintained even at lower reaction temperature (Table 1, entry 8). Next, a survey of the reaction media revealed that protic solvents such as EtOH and *i*-PrOH were effective reaction medium. Other solvents, such as toluene, CH_3CN or DMF were almost ineffective for this transformation (Table 1, entries 12–16). The control experiment confirmed that the transformation did not occur in the absence of the catalyst.

With the optimal conditions in hand, we subsequently investigated its scope in the C2-selective arylation of diverse *N*-pyrimidyl indoles. As shown in Table 2, *N*-pyrimidyl indoles containing electron-donating and electron-withdrawing groups from C3 to C7 position proceeded smoothly to give the desired products in good to excellent yields in short reaction time. A number of alkyl and alkyoxyl substituents (**3ba**, **3da**–**3fa**, **3ka**, and **3na**) can be incorporated on the indole ring at various positions without significant

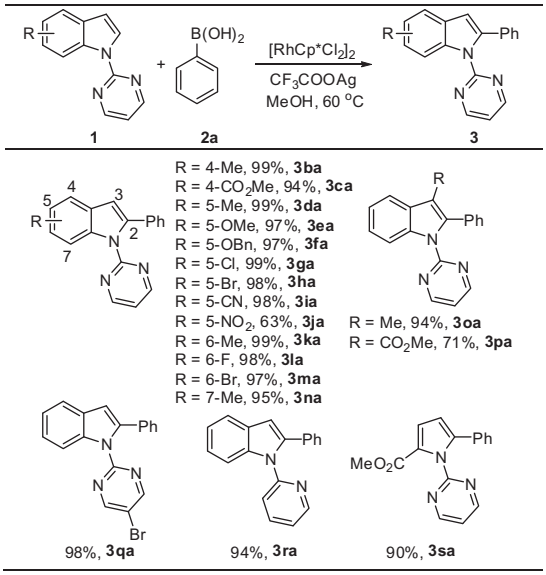
Table 1
Optimization of reaction conditions



Entry[a]	Oxidant	Temp (°C)	Solvent	*t* (h)	Yield (%)[b]
1	Ag_2O	60	MeOH	24	55
2	$Cu(OAc)_2$	60	MeOH	24	53
3	AgOAc	60	MeOH	24	91
4	Ag_2CO_3	60	MeOH	24	59
5[c]	$AgOOCCF_3$	60	MeOH	6	98(98)
6	$AgBF_4$	60	MeOH	24	23
7	$AgSO_3CF_3$	60	MeOH	24	18
8	$AgOOCCF_3$	40	MeOH	24	94
9	$AgOOCCF_3$	25	MeOH	24	55
10	$AgOOCCF_3$	60	EtOH	24	95
11	$AgOOCCF_3$	60	*i*-PrOH	24	72
12	$AgOOCCF_3$	60	*t*-BuOH	24	10
13	$AgOOCCF_3$	60	THF	24	21
14	$AgOOCCF_3$	60	Toluene	24	5
15	$AgOOCCF_3$	60	CH_3CN	24	8
16	$AgOOCCF_3$	60	DMF	24	14
17[d]	$AgOOCCF_3$	60	MeOH	24	—

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), $[RhCp^*Cl_2]_2$ (1.0 mol %), oxidant (0.8 mmol) and solvent (1.0 mL) under Ar.
[b] Isolated yields.
[c] Yield in parentheses without any particular precautions to extrude oxygen or moisture.
[d] Without catalyst.

Table 2
Substrate scope of C–H arylation[a,b]



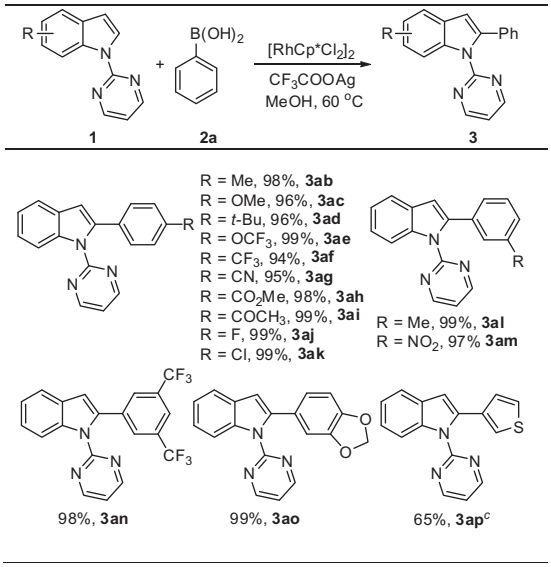
[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), $[RhCp^*Cl_2]_2$ (1.0 mol %), $AgOOCCF_3$ (0.8 mmol) and MeOH (1.0 mL), 60 °C, 4–6 h under Ar.
[b] Isolated yields.

loss in reaction efficiency. The reaction showed good functional group compatibility. The reaction of indoles with electron-withdrawing groups, such as a fluoro, chloro, bromo, cyano, and ester groups, worked efficiently and generated the corresponding products **3la**, **3ga**, **3ha**, **3ma**, **3ia**, and **3ca** in excellent yields. These functional groups could be used for further functionalization and applications in organic synthesis. Tolerance to strongly electron-deficient NO_2-group, which was less explored in C–H functionlization of indole core, was especially noteworthy since it was a useful functional handle for further amination. Perhaps more importantly, substituents at the C3- and C7-position of indole (**3oa**, **3pa**, and **3na**) not only demonstrate that steric interactions were well tolerated, but also excellent regioselectivity was observed in our catalytic system. Besides the pyrimidine group, substrate with pyridine as a directing group also worked well with 94% yield (**3ra**). Importantly, this protocol could also be successfully applied to pyrrole substrate to provide 90% yield of the corresponding product **3sa**.

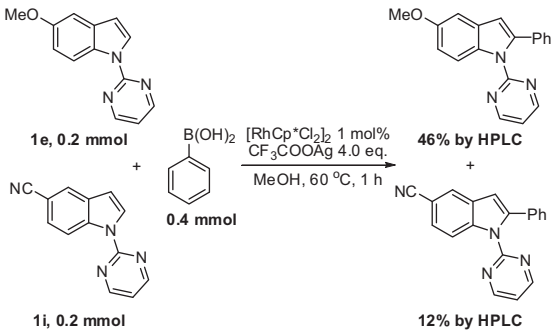
Encouraged by those excellent results, the scope of the C–H arylation reaction was further extended to different functionalized arylboronic acids (Table 3). A large variety of arylboronic acids bearing electron-donating (Me, OMe, *t*-Bu, and OCF_3) and electron-withdrawing (CF_3, CN, CO_2Me, Cl, and F,) groups proceeded efficiently to produce the arylated products (**3ab**–**3al**) in excellent yields. These results clearly indicated that there was no obvious correlation between the yield and the electronic effect of the substituent. Particularly, substrate with a strongly electron-withdrawing NO_2-group could also successfully participate in this catalytic transformation, affording the corresponding product (**3am**) with 97% yield. Notably, the acetyl group on the aryl ring was compatible in this catalytic process and the desired product **3ai** was obtained in a nearly quantitative yield. The current catalytic system was not restricted to the use of monosubstituted substrate, but also allowed for different disubstituted arylboronic acids (**3an**–**3ao**). Additionally, the thiopheneboronic acid was also found to be a good coupling-partner (**3ap**).

In order to gain an understanding of more details on the reaction, the competition experiments between different substituted indoles indicated that electron-rich indole **1e** was preferentially

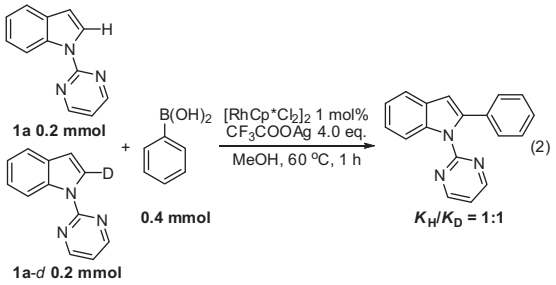
Table 3
Substrate scope of C–H arylation[a,b]



[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), $[RhCp^*Cl_2]_2$ (1.0 mol %), $AgOOCCF_3$ (0.8 mmol) and MeOH (1.0 mL), 60 °C, 4–6 h under Ar.
[b] Isolated yields.
[c] $[RhCp^*Cl_2]_2$ (2.0 mol %), 100 °C.



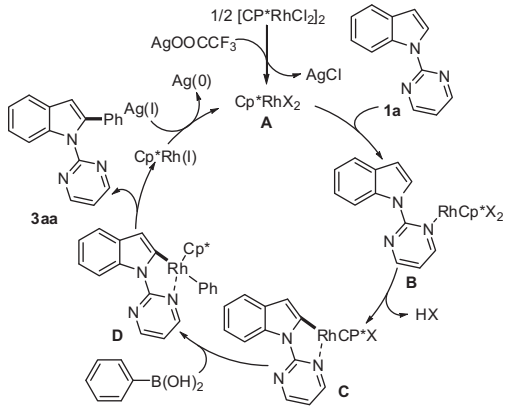
Scheme 2. Intermolecular competition experiment.



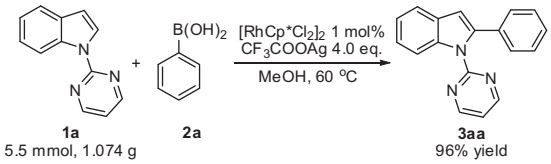
Scheme 3. Kinetic isotope effect.

converted, suggesting they were better substrates than electron-poor indoles (Scheme 2).

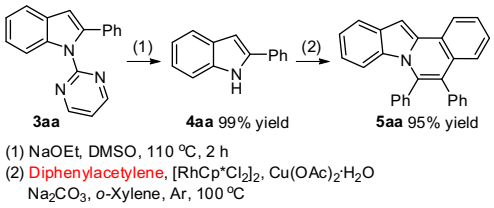
Intermolecular kinetic isotope effect was readily achieved through a competition experiment between *N*-pyrimidyl indole **1a** and its deuterated analogue **1a**-*d* (H/D = 1) (Scheme 3). It was observed that the reaction did not exhibit kinetic isotope effect (k_H/k_D = 1.0), which may imply that the C–H bond cleavage at the C2 position of indole was not involved in the rate-determining step in the overall catalytic process.



Scheme 4. Proposed mechanism.



Scheme 5. Gram-scale experiment.



Scheme 6. Synthesis of polycyclic indoles.

Based on the above preliminary results and precedent reports, a plausible mechanism is proposed in Scheme 4.[13] The Rh complex would be activated by $AgOOCCF_3$ to generate the electrophilic cationic complex **A**. Then, coordination of the pyrimidyl group of indole **1a** and the subsequent regioselective C–H activation provide the rhodacycle species **C**. Subsequently, The five-membered rhodacycle **C** reacts with boronic acid to afford the new Rh(III) intermediate **D**, reductive elimination gives the final product **3aa** and Rh(I) species, which is oxidized to regenerate Rh(III) to complete the catalytic cycle.

To demonstrate the synthetic potential of this methodology, the C–H arylation of *N*-pyrimidyl indoles **1a** was performed on a gram scale under the optimized conditions without a significant decrease in the product yield (Scheme 5).

In addition, we removed the pyrimidyl group in compound **3aa** according to the reported method to afford *N*-free phenylindole in excellent yields.[10] Then, oxidative coupling *N*-free phenylindole **4aa** with alkynes using Miura's method provided the polycyclic indole derivative **5aa**, which has been well documented as the privileged core structural motif in many bioactive alkaloids and pharmaceuticals (Scheme 6).[15]

In summary, we have developed a highly efficient Rh(III)-catalyzed direct C–H arylation of indole with arylboronic acids under mild conditions. A wide range of functionalized substrates were suitable for this reaction, furnishing the corresponding products with excellent yields and regioselectivity. A plausible reaction mechanism was proposed based on several competition and kinetic isotope experiments. Moreover, the method may find applications in the synthesis of polycyclic indole derivatives.

Acknowledgement

We are grateful to the National Science Foundation of China (No. 21302064) for support of this research.

Supplementary data

Supplementary data (detailed experimental procedures, IR, ^{1}H NMR and ^{13}C NMR for **3**, **4aa**, **5aa**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.04.015. These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

1. (a) Bandini, M.; Eichholzer, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9608; (b) Kochanowska-Karamyan, A. J.; Hamann, M. T. *Chem. Rev.* **2010**, *110*, 4489.
2. (a) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873; (b) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172; (c) Stuart, D. R.; Villemure, E.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 12072; (d) Gong, X.; Song, G.; Zhang, H.; Li, X. *Org. Lett.* **2011**, *13*, 1766; (e) Nishino, M.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 6993.
3. Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2011**, *111*, 5.
4. For selected reviews, see: (a) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826; (b) Campeau, L.-C.; Fagnou, K. *Chem. Soc. Rev.* **2007**, *1058*, 36; (c) Giri, R.; Shi, B. F.; Engle, K. M.; Maugel, N.; Yu, J.-Q. *Chem. Soc. Rev.* **2009**, *38*, 3242; (d) Daugulis, O.; Do, H. Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *1074*, 42; (e) Colby, D. A.; Berman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624; (f) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147; (g) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740; (h) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068; (i) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215; (j) McMurray, L.; OHara, F.; Gaunt, M. J. *Chem. Soc. Rev.* **1885**, *2011*, 40; (k) Song, G.; Wang, F.; Li, X. *Chem. Soc. Rev.* **2012**, *41*, 3651; (l) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879; (m) Ackermann, L. *Acc. Chem. Res.* **2014**, *47*, 281.
5. For selected reviews, see: (a) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173; (b) Joucla, L.; Djakovitch, L. *Adv. Synth. Catal.* **2009**, *351*, 673; For selected examples, see: (c) Wang, L.; Yi, W. B.; Cai, C. *Chem. Commun.* **2011**, 806; (d) Pintori, D. G.; Greaney, M. F. *J. Am. Chem. Soc.* **2011**, *133*, 1209; (e) Huang, Y.; Lin, Z.; Cao, R. *Chem. Eur. J.* **2011**, *17*, 12706; (f) Nandi, D.; Jhou, Y. M.; Lee, J. Y.; Kuo, B. C.; Liu, C. Y.; Huang, P. W.; Lee, H. M. *J. Org. Chem.* **2012**, *77*, 9384; (g) Wu, M.; Luo, J.; Xiao, F.; Zhang, S.; Deng, G.-J.; Luo, H.-A. *Adv. Synth. Catal.* **2012**, *354*, 335; (h) Song, W.; Ackermann, L. *Angew. Chem., Int. Ed.* **2012**, *51*, 8251; (i) Chen, S.; Liao, Y.; Zhao, F.; Qi, H.; Liu, S.; Deng, G.-J. *Org. Lett.* **2014**, *16*, 1618; (j) Zhang, L.; Xue, X.; Xu, C.; Pan, Y.; Zhang, G.; Xu, L.; Li, H.; Shi, Z. *ChemCatChem* **2014**, *6*, 3069.
6. (a) Wang, X.; Lane, B. S.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 4996; (b) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050; (c) Bressy, C.; Alberico, D.; Lautens, M. *J. Am. Chem. Soc.* **2005**, *127*, 13148; (d) Lebrasseur, N.; Larrosa, I. *J. Am. Chem. Soc.* **2008**, *130*, 2926; (e) Islam, S.; Larrosa, I. *Chem. Eur. J.* **2013**, *19*, 15093.
7. Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 4972.
8. (a) Yang, S.-D.; Sun, C.-L.; Fang, Z.; Li, B.-J.; Li, Y.-Z.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1473; (b) Zhao, J.; Zhang, Y.; Cheng, K. *J. Org. Chem.* **2008**, *73*, 7428; (c) Liang, Z.; Yao, B.; Zhang, Y. *Org. Lett.* **2010**, *12*, 3185; (d) Williams, T. J.; Reay, A. J.; Whitwood, A. C.; Fairlamb, I. J. S. *Chem. Commun.* **2014**, 3052.
9. For representative examples on C2–H functionalization of indoles, see: *C2-alkenylation* (a) García-Rubia, A.; Arrayás, R. G.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 6511; (b) Garca-Rubia, A.; Urones, B.; GmezArrays, R.; Carretero, J. C. *Chem. Eur. J.* **2010**, *16*, 9676; (c) Yang, L.; Zhang, G.; Huang, H. *Adv. Synth. Catal.* **2014**, *356*, 1509; (d) Gong, B.-W.; Shi, J.-J.; Wang, X.-W.; Yan, Y.-N.; Li, Q.; Meng, Y.-Q.; Xu, H. E.; Yi, W. *Adv. Synth. Catal.* **2014**, *356*, 137; *C2-alkylation:* (e) Chan, W.-W.; Yeung, S. H.; Zhou, Z.-Y.; Chan, A. S. C.; Yu, W.-Y. *Org. Lett.* **2010**, *12*, 604; (f) Jiao, L.; Bach, T. *J. Am. Chem. Soc.* **2011**, *133*, 12990; (g) Pan, S.; Ryu, N.; Shibata, T. *J. Am. Chem. Soc.* **2012**, *134*, 17474; (h) Jiao, L.; Herdtweck, E.; Bach, T. *J. Am. Chem. Soc.* **2012**, *134*, 14563; (i) Wang, H.; Schröder, N.; Glorius, F. *Angew. Chem., Int. Ed.* **2013**, *52*, 5386; (j) Shi, J.; Yan, Y.; Li, Q.; Xu, H. E.; Yi, W. *Chem. Commun.* **2014**, 6483; (k) Zhang, Y.; Zheng, J.; Cui, S. *J. Org. Chem.* **2014**, *79*, 6490; *C2-alkynylation:* (l) Tolnai, G. L.; Ganss, S.; Brand, J. P.; Waser, J. *Org. Lett.* **2013**, *15*, 112; (m) Xie, F.; Qi, Z.; Yu, S.; Li, X. *J. Am. Chem. Soc.* **2014**, *136*, 4780; *C2-Cyanation:* (n) Kou, X.; Zhao, M.; Qiao, X.; Zhu, Y.; Tong, X.; Shen, Z. *Chem. Eur. J.* **2013**, *19*, 16880; (o) Pan, C.; Jin, H.; Xu, P.; Liu, X.; Cheng, Y.; Zhu, C. *J. Org. Chem.* **2013**, *78*, 9494; (p) Hong, X.; Wang, H.; Qian, G.; Tan, Q.; Xu, B. *J. Org. Chem.* **2014**, *79*, 3228; *C2-acylation:* (q) Zhou, B.; Yang, Y.; Li, Y. *Chem. Commun.* **2012**, 5163; (r) Pan, C.; Jin, H.; Liu, X.; Cheng, Y.; Zhu, C. *Chem. Commun.* **2013**, 2933; (s) Ma, Y.; You, J.; Song, F. *Chem. Eur. J.* **2013**, *19*, 1189; (t) Zhou, W.; Li, P.; Zhang, Y.; Wang, L. *Adv. Synth. Catal.* **2013**, *355*, 2343.
10. (a) Wang, Z.; Song, F.; Zhao, Y.; Huang, Y.; Yang, L.; Zhao, D.; Lan, J.; You, J. *Chem. Eur. J.* **2012**, *18*, 16616; (b) Ding, Z.; Yoshikai, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 4698; (c) Shi, Z.; Boultadakis-Arapinis, M.; Glorius, F. *Chem. Commun.* **2013**, 6489; (d) Yoshino, T.; Ikemoto, H.; Matsunaga, S.; Kanai, M. *Chem. Eur. J.* **2013**, *19*, 9142; (e) Sun, B.; Yoshino, T.; Matsunaga, S.; Kanaia, M. *Adv. Synth. Catal.* **2014**, *356*, 1491; (f) Xu, H.; Qiao, X.; Yang, S.; Shen, Z. *J. Org. Chem.* **2014**, *79*, 4414; (g) Yu, S.; Li, X. *Org. Lett.* **2014**, *16*, 1200.
11. (a) Ackermann, L.; Lygin, A. V. *Org. Lett.* **2011**, *13*, 3332; (b) Punji, B.; Song, W.; Shevchenko, G. A.; Ackermann, L. *Chem. Eur. J.* **2013**, *19*, 10605.
12. Lu, M.-Z.; Lu, P.; Xu, Y.-H.; Loh, T.-P. *Org. Lett.* **2014**, *16*, 2614.
13. (a) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359; (b) Chen, X.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 12634; (c) Wang, D.-H.; Wasa, M.; Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 7190; (d) Kirchberg, S.; Frohlich, R.; Studer, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 4235; (e) Yoshikai, N.; Asako, S.; Yamakawa, T.; Ilies, L.; Nakamura, E. *Chem. Asian J.* **2011**, *6*, 3059; (f) Karthikeyan, J.; Haridharan, R.; Cheng, C.-H. *Angew. Chem., Int. Ed.* **2012**, *51*, 12343; (g) Nimje, R. Y.; Leskinen, M. V.; Pihko, P. M. *Angew. Chem., Int. Ed.* **2013**, *52*, 4818.
14. Zheng, J.; Zhang, Y.; Cui, S. *Org. Lett.* **2014**, *16*, 3560.
15. Morimoto, K.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2010**, *12*, 2068.