ChemComm

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

rsc.li/chemcomm

Dynamic Article Links ►
View Article Online
DOI: 10.1039/C7CC01201B

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

Selective mono-alkylation of *N*-methoxybenzamides

Zenghua Chen,[‡a,b,c] Le'an Hu,[‡a,b,c] Fanyun Zeng,[a,b,c] Ranran Zhu,[a,b,c] Shasha Zheng,[a,b,c] Qingzhen Yu[a,b,c] and Jianhui Huang*[a,b,c]

Received (in XXX, XXX) Xth XXXXXXXXX 200X, Accepted Xth XXXXXXXXX 200X
DOI: 10.1039/b000000x

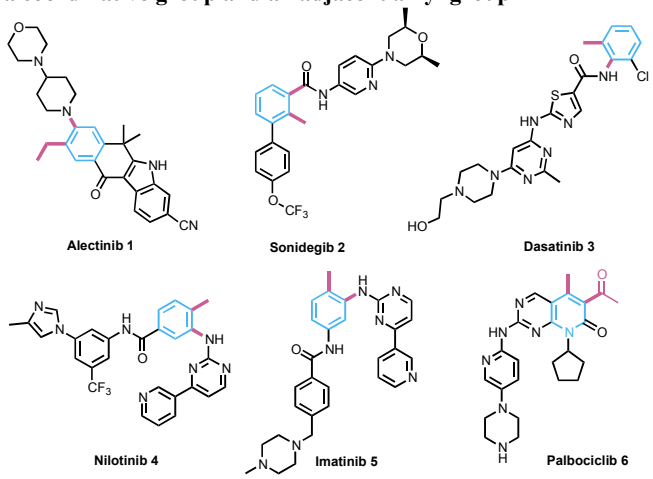
We report our latest discovery of norbornene derivative modulated highly mono-selective *ortho*-C–H activation alkylation reactions on arenes bearing simple mono-dentate coordinating group. Reaction features the employment of readily available benzamides and alkyl halides. During the studies, we have prepared 30 mono-alkylated aryl amides in good yields with good mono-selectivity. We have also demonstrated that structurally rigid alkenes such as norbornene and derivatives are a good class of additives could be used for the future C-H direct functionalizations. The utilization of norbornene type of additives for the assistance of C–H activation processes has opened a new window for the future molecular design using C–H direct functionalization strategies.

Introduction

In organometallic chemistry, the utilization of directing group for the activation and regulation of C–H direct functionalization on the specific position has become one of the most studied areas in the last 10 years. The directed *ortho*-C–H activation of arenes possess coordinative groups for the direct introduction of arenes, alkenes as well as heteroatoms is very well studied.[1-8] More recently, *meta*-C–H activation attracted considerable attention for the access functionalities at the distal position.[9-19] The directed *para*-C–H activation was also beautifully demonstrated by Maiti using nitrile directing groups *via* the D-shaped template.[20]

Arenes bearing potentially coordinative groups with *ortho*-aliphatic groups are often found in drug molecules. A number of selected nib-type of anti-cancer agents **1-6** are shown in **Figure 1**. These molecules are all having a simple mono-dentate directing group with an adjacent alkyl group. Transition-metal mediated *ortho*-C–H activation alkylations have already been very well studied under Pd,[21-25] Ru,[26] Rh,[27,28] Ni,[29,30] Cu,[31] and Fe[32-34] catalysed conditions. Approaches developed so far have been focused on the use of bidentate directing groups[35] as well as the monodentate directing groups[36]. In addition, the selective mono-alkylation over di-alklyation is also a synthetic challenge. Herein, we report our latest discovery on the norbornene derivative modulated highly mono-selective *ortho*-C–H activation alkylation reactions on arenes bearing mono-dentate coordinative group.

Figure 1. Anti-cancer agents containing arene skeletons with a coordinative group and an adjacent alkyl group



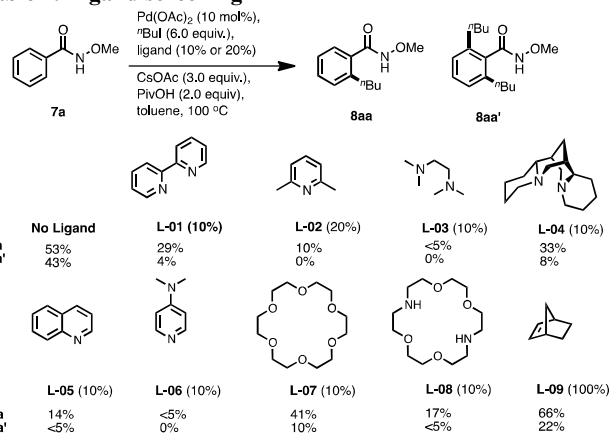
Using easily available benzamide **7a**, a common mono-dentate directing group developed by Yu,[37] we started screening sets of conditions for the reaction. The reaction of benzamide **7a** in the presence of 10% of $Pd(OAc)_2$ as the catalyst, with no additives did not give any of our desired mono-alkylated product **8aa** nor di-alkylated benzamide **8aa'**. A range of inorganic bases such as KOAc, K_2HPO_4 and K_2CO_3 as the additives were examined, the reactions were not very successful, no desired products were observed (*supporting information Table 1*). When CsOAc was utilized, the desired mono-alkylated product **8aa** was isolated in 25% yield together with 5% of di-alkylated product **8aa'**. Interestingly, inspired by Dong's 'acetate cocktail' idea,[18] the addition of acetic acid together with CsOAc gave the desired mono-alkylated product **8aa** in 34% together with 15% of di-alkylated product **8aa'**. A total 96% conversion was observed while 2.0 equivalents of PivOH was employed and the mono-alkylated product **8aa** was isolated in 53% yield together with 43% of dialkylated benzamide **8aa'**. Under Chen's conditions[25] on the corresponding bidentate quinolyl amides, only a trace amount of desired product was formed; the reaction conversion was very low.

With the good conditions for high starting material conversion in hand, we have examined the relatively weak ligand for the increase of steric of Pd catalyst. A number of ligands **L-01-L-09** were tested. These ligands include pyridine type of ligands,

View Article Online
DOI: 10.1039/C7CC01201B

amine ligands, crown ether, diaza crown ether and norbornene. The corresponding results are listed in **Table 2**. The reaction using 1.0 equivalent of bispyridine **L-01** did not provide any of our desired products, the use of 10% of ligand **L-01** gave our desired product **8aa** in 29% yield together with 4% of di-alkylated arene **8aa'**. The selectivity was very good, however, the reaction conversion was rather low. Similar results were also obtained on other cases when ligands having heteratom lone pairs available. The use of less eletrondonating additive such as norborene[37] did not affect the reactivity much. More interestingly, when increasing the amount of norbornene used to 1.0 equivalent, the reaction resulted in good conversion with potential mono-selectivity.

Table 1. Ligand screening



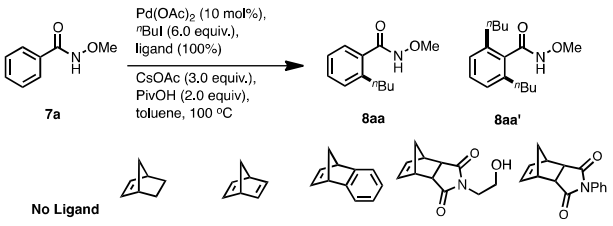
	No Ligand	L-01 (10%)	L-02 (20%)	L-03 (10%)	L-04 (10%)
8aa	53%	29%	10%	<5%	33%
8aa'	43%	4%	0%	0%	8%

	L-05 (10%)	L-06 (10%)	L-07 (10%)	L-08 (10%)	L-09 (100%)
8aa	14%	<5%	41%	17%	66%
8aa'	<5%	0%	10%	<5%	22%

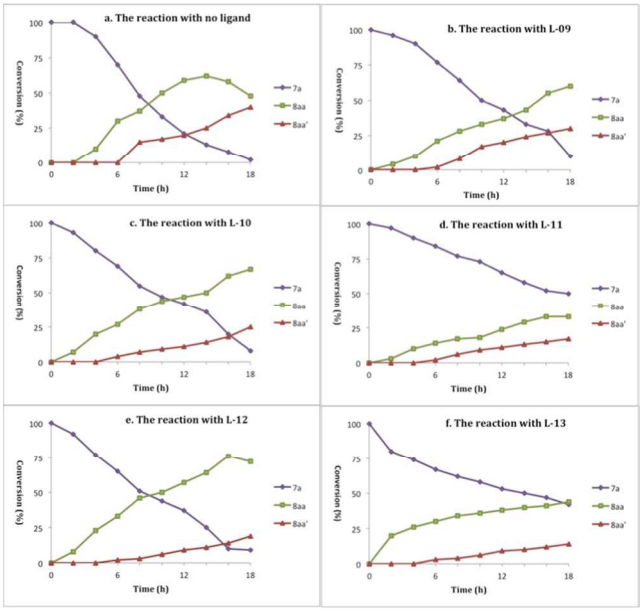
The further detailed process monitoring was proceeded on a series of norbornene derivatives. The conversion of mono-alkylated product **8aa** and di-alkylated benzamide **8aa'** as well as the consumption of starting benzamide were showing in graphs **a-f Figure 2**.

From the six figures, we could clearly see that in the absence of external additive the formation di-alkylated benzamide **8aa'** started after 6 hours, and the ratio of mono- and dialkylated product was nearly 1:1 after 18 hours. The reaction with **L-10** seems very promising as we could see the selective formation of monoalkylated **8aa** during the processes. The utilization of **L-11** was less effient as the reaction went slow with poor selectivity. Encouragingly, the reaction with **L-12** provide our desired product in a much better selectivity over di-alkylated product **8aa'** comparing to the reactions with other norbornene additives.

Figure 2. Additive screening on norbornene derivatives[a]



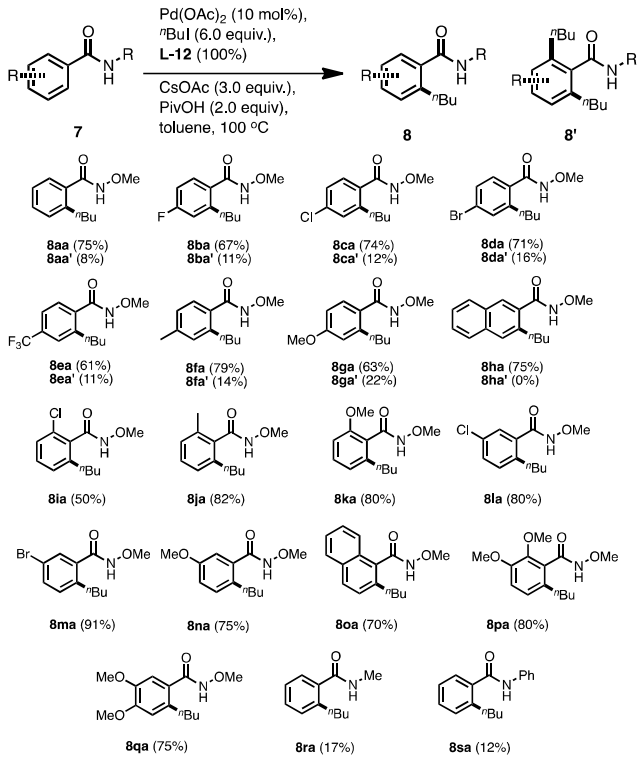
	No Ligand	L-09	L-10	L-11	L-12	L-13
8aa	53%	66%	68%	44%	75%	45%
8aa'	43%	22%	12%	19%	8%	4%



[a]The conversions of **7a** to **8aa** and **8aa'** within a period of 18 h.

With the optimal conditions in hand, we have evaluated the scope and limitations of this reaction. Using iodobutane as the alkylating reagent, a broad range of substrates with both electron rich and electron deficient substituents on *para*-, *meta*- and *ortho*-positions were examined. For the examples with no substituent or substituents on *para*-positions, the reaction are all working smoothly with good mono-selectivity. (**Table 2**)

Table 2. Synthesis of monoalkylated aryl amides



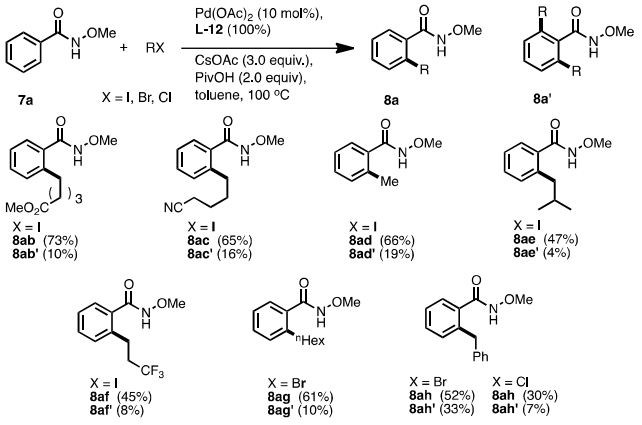
All the *para*-substituted benzamides were successfully alkylated in a mono-selective fashion and the corresponding butyl substituted arenes **8aa**-**8ga** were obtained in good yields with good selectivity. Benzamides with *ortho*-substituents could also be converted to the corresponding alkylated products under our

View Article Online
DOI: 10.1039/C7CC01201B

conditions. The reactions with *meta*-substituted aryl amides did not give the alkyl group in a position between the two substituents due to the steric reasons and products **8la**, **8ma** and **8na** were isolated in good to excellent yields. In addition, reactions on benzamides with other protecting groups such as methyl and phenyl were also examined and the desired products **8ra** and **8sa** were also isolated in 17% and 12% yields due to the low reaction conversion.

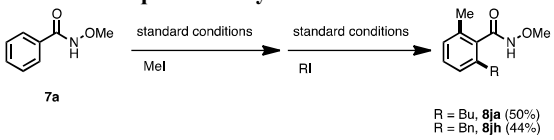
Under our standard conditions, reactions with a number of alkyl halides were also evaluated. The corresponding alkylated products with alkyl iodides were all successfully obtained in good yields. (**Table 3**) The utilization of alkyl bromides and chloride were also studied. It seemed that the reactions with alkyl bromides gave similar results as the ones using alkyl iodides, however, reaction with alkyl chloride was less efficient due to the low conversion.

Table 3. Reactions with various alkyl halides



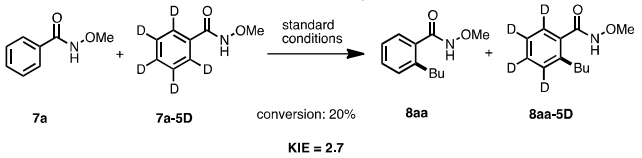
The sequential alkylation reactions with different alkyl halides were also demonstrated. (**Scheme 1**) Benzamides **8ja** and **8jh** were successfully prepared after two separate alkylation steps. The one-pot reaction only provided the desired products in low yields.

Scheme 1. Sequential alkylation reaction



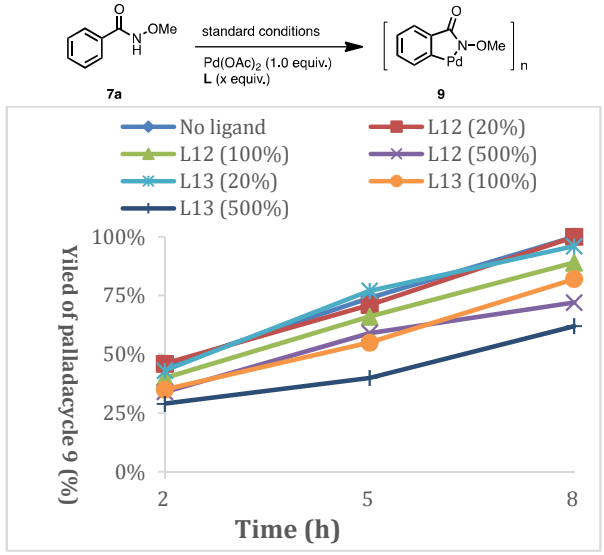
To help us understand this reaction better, the KIE studies were carried out. A mixture of **7a** and **7a-5D** was treated with $Pd(OAc)_2$ under the standard conditions, the reaction was stopped at 20% conversion. A KIE value of 2.7 was then obtained. These results suggested that the initial CMD processes could be the rate limiting step during the catalytic system.[38,39]

Scheme 2. KIE studies of mono-alkylation of benzamide



We have further studied the effects of norbornene additives on the the formation of palladacycle **9**. Similar to Catellani reaction,[40] the palladacycle **9** we isolated has no norbornene associated in the complex. Under our standard reaction conditions, when stoichiometric amount of $Pd(OAc)_2$ was used, the results of reactions in the presence of various amount of additives are shown in **Figure 3**. From the graph we could see that the relatively slow C–H activation processes led to better nomo-alkylation selectivity, however, if the C–H activation is too slow, then the reaction would then result in low conversion (blue line with 500% of **L-13**).

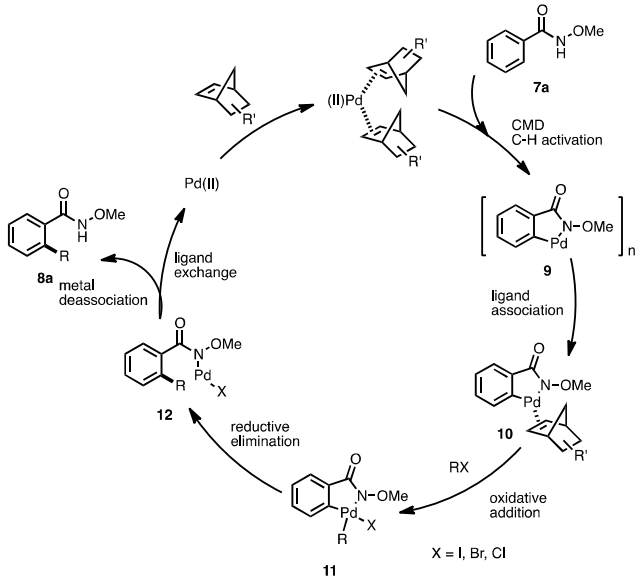
Figure 3. Conversion for the preparation of the palladacycle 9



Conditions: Benzamide **7a** (0.01 mmol), $Pd(OAc)_2$ (0.01 mmol), PivOH (0.02 mmol), toluene (1 mL), 100°C by using **L-12** or **L-13**.

Based on these results, we have proposed a reaction mechanism. Under standard CMD processes, starting from benzamide **7a**, a low energy palladacycle **9** could be formed followed by a possible ligand/additive assisted monomer formation to give a more active species **10**.

Figure 4. Plausible reaction mechanism



The use of additive may slow down the CMD processes while the addition of norbornene additive would at the same time speed up the ligand association processes. The use of additive would also slow down the second C–H activation processes due to the steric reasons. Therefore, the choose of appropriate amount of

View Article Online
DOI: 10.1039/C7CC01201B

additive is crucial for both reactivity and mono-selectivity. An oxidative addition of Pd(II) onto the alkyl halide to give a Pd(IV) intermediate **11** which could then undergo a reductive elimination gives rise to the alkylated Pd(II) complex **12** and further metal deassociation to provide our desired product **8a** together with Pd(II). The Pd(II) catalyst could be then used for the next catalytic cycle.

In conclusion, we have reported a novel norbornene-assisted Pd catalyzed mono-selective alkylation reaction using aryl amide with readily available alkyl halides. During the studies, we have prepared 30 mono-alkylated aryl amides in good yields with good selectivity. In addition, we have also studied the efficiency of various additives for the reaction kinetics as well as the mono-selectivity. The utilization of norbornene type of additives for the assistance of C–H activation processes has opened a new window for the future molecular designing using C–H direct functionalization strategies.

Acknowledgements

The financial support from the "973" Program (2015CB856500), the NSFC (Grant No. 21302136, 21672159) and Tianjin Natural Science Foundation (Grant No. 13JCQNJC04800) are gratefully acknowledged.

Notes and references

[a]*School of Pharmaceutical Science and Technology, Tianjin University, Tianjin 300072, China. Fax: 0086-22-27404031; Tel: 0086-22-27409894; E-mail: jhuang@tju.edu.cn*
[b]*Collaborative Innovation Center of Chemical Science and Engineering (Tianjin)*
[c]*Tianjin Key Laboratory for Modern Drug Delivery & High-Efficiency,*
‡These authors contributed equally.
† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/
Email: jhuang@tju.edu.cn

1 B. K. Singh, R. Jana, *J. Org. Chem.* **2016**, *81*, 831.
2 S. Zhao, Y.-J. Liu, S.-Y. Yan, F.-J. Chen, Z.-Z. Zhang, B.-F. Shi, *Org. Lett.* **2015**, *17,* 3338.
3 N. Hasegawa, V. Charra, S. Inou, Y. Fukumoto, N. Chatani, *J. Am. Chem. Soc.* **2011,** *133,* 8070.
4 A. M. Suess, M. Z. Ertem, C. J. Cramer, S. S. Stahl, *J. Am. Chem. Soc.* **2013,** *135,* 9797.
5 J. Xu, Z.-Z. Zhang, W. Rao, B.-F. Shi, *J. Am. Chem. Soc.* **2016,** *138,* 10750.
6 Z. Liu, J. Derosa, K. M. Engle, *J. Am. Chem. Soc.* **2016,** *138,* 13076.
7 L.-S. Zhang, G.-H. Chen, X. Wang, Q.-Y. Guo, X.-S. Zhang, F. Pan, K. Chen, Z.-J. Shi, *Angew. Chem. Int. Ed.* **2014,** *53,* 3899.
8 J.-T. Zhang, H. Chen, C. Lin, Z.-X. Liu, C. Wang, Y.-H. Zhang, *J. Am. Chem. Soc*. **2015**, *137*, 12990.
9 R. J. Phipps, M. J. Gaunt, *Science* **2009***, 323,* 1593.
10 H A. Duong, R. E. Gilligan, M. L. Cooke, R. J. Phipps, M. J. Gaunt, *Angew. Chem. Int. Ed.* **2011,** *50*, 463.
11 O. Saidi, J. Marafie, A. E. W. Ledger, P. M. Liu, M. F. Mahon, G. K. Kohn, M. K. Whittlesey, C. G. Frost, *J. Am. Chem. Soc.* **2011,** *133,* 19298.
12 N. Hofmann, L. Ackermann, *J. Am. Chem. Soc.* **2013**, *135*, 5877.
13 Q. Yu, L. Hu, Y. Wang, S. Zheng, J. Huang, *Angew. Chem. Int. Ed.* **2015**, *54*, 15284.
14 C. J. Teskey, Y. W. Lui, M. F. Greaney, *Angew. Chem. Int. Ed.* **2015**, *54*, 11677.
15 D. Leow, G. Li, T-S. Mei, J.-Q. Yu, *Nature* **2012**, *486*, 518.
16 Y.-F. Yang, G.-J. Cheng, P. Liu, D. Leow, T.-Y. Sun, P. Chen, X. Zhang, J.-Q. Yu, Y.-D. Wu, K. N. Houk. *J. Am. Chem. Soc.* **2014,** *136,* 344.
17 L. Wan, N. Dastbaravardeh, G. Li, J.-Q. Yu, *J. Am. Chem. Soc.* **2013**, *135*, 18056.
18 Z. Dong, J. Wang, G. Dong, *J. Am. Chem. Soc.* **2015**, *137*, 5887.
19 X.-C. Wang, W. Gong, L.-Z. Fang, R.-Y. Zhu, S. Li, K. M. Engle, J.-Q. Yu, *Nature* **2015***, 519,* 334.
20 S. Bag, T. Patra, A. Modak, A. Deb, S. Maity, U. Dutta, A. Dey, R. Kancherla, A. Maji, A. Hazra, M Bera, D. Maiti, *J. Am. Chem. Soc.* **2015**, *137*, 11888.
21 X. Chen, J. Li, X. Hao, C. E. Goodhue, J.-Q. Yu, *J. Am. Chem. Soc.* **2006**, *128*, 78.
22 X. Chen, C. E. Goodhue, J.-Q. Yu, *J. Am. Chem. Soc.* **2006**, *128*, 12634.
23 D. Shabashov, O. Daugulis, *J. Am. Chem. Soc*. **2010**, *132*, 3965.
24 S. Zhang, G. He, G. Chen, *J. Am. Chem. Soc*. **2013**, *135*, 2124.
25 S. Zhang, Q. Li, G. He, W. A. Nack, G. Chen, *J. Am. Chem. Soc*. **2015**, *137*, 531.
26 L. Ackermann, P. Novák, R. Vicente, N. Hofmann, *Angew. Chem. Int. Ed.* **2009**, *48*, 6045
27 H. Wang, S. Yu, Z. Qi, X. Li, *Org. Lett.* **2015,** *17,* 2812.
28 K. Shibata, T. Yamaguchi, N. Chatani. *Org. Lett.* **2015**, *17*, 3584.
29 (a) W. Song, S. Lackner, L. Ackermann, *Angew. Chem. Int. Ed.* **2014**, *53*, 2477. (b) Z. Ruan, S. Lackner, L. Ackermann, *Angew. Chem. Int. Ed.* **2016**, *55*, 3153
30 T. Kubo, N. Chatani. *Org. Lett.* **2016**, *18*, 1698.
31 X. Chen, Z. Tan, Q. Gui, L. Hu, G. Wang, *Chem. Eur. J.* **2016**, *22*, 6218.
32 (a) S. Asako, L. Ilies, E. Nakamura, *J. Am. Chem. Soc.* **2013**, *135*, 17755; (b) L. Ilies, T. Matsubara, S. Ichikawa, S. Asako, E. Nakamura, *J. Am. Chem. Soc.* **2014**, *136*, 13126.
33 (a) R. Shang, L. Ilies, E. Nakamura, *J. Am. Chem. Soc.* **2015**, *137*, 7660; (b) E. R. Fruchey, B. M. Monks, S. P. Cook, *J. Am. Chem. Soc.* **2014**, *136*, 13130.
34 G. Cera, T. Haven, L. Ackermann, *Angew. Chem. Int. Ed.* **2016**, *55*, 1484
35 For pioneering work of the use of bidentate auxiliary, see: V. G. Zaitsev, D. Shabashov and O. Daugulis, *J. Am. Chem. Soc.* **2005**, *127*, 13154.
36 (a) Y.-H. Zhang, B.-F. Shi, J.-Q, Yu, *Angew. Chem. Int. Ed*. **2009**, *48*, 6097; (b) Q. Chen, L. Ilies, E. Nakamura, *J. Am. Chem. Soc*. **2011**, *133*, 428; (c) K. Gao, N. Yoshikai, *J. Am. Chem. Soc*. **2013**, *135*, 9279; (d) L. Ackermann, N. Hofmann, R. Vicente, *Org. Lett.* **2011**, *13*, 1875; (e) L. Ackermann, *Chem. Commun.* **2014**, *50*, 13825.
37 (a) M. Green, J. A. K. Howard, J. L. Spencer, F. G. A. Stone, *J. Chem. Soc., Dalton Trans.* **1977**, 271; (b) M. Schwalbe, D. Walther, H. Schreer, J. Langer, H. Görls, *J. Organomet. Chem*. **2006**, *691*, 4868; (c) D. B. Dell'Amico, L. Labella, F. Marchetti, S. Samaritani, *J. Organomet. Chem.* **2011**, *696*, 1349.
38 D.-H. Wang, M. Wasa, R. Giri, J.-Q. Yu, *J. Am. Chem. Soc*. **2008**, *123*, 7190.
39 E. M. Simmons, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2012**, *51*, 3066.
40 (a) Q. Yu, N. Zhang, J. Huang, S. Lu, Y. Zhu, X. Yu, K. Zhao, *Chem. Eur. J.* **2013**, *19*, 11184; (b) W. Liu, Q. Yu, L. Hu, Z. Chen, J. Huang, *Chem. Sci.* **2015**, *6*, 5768.
41 (a) M. Catellani, F. Frignani, A. Rangoni, Angew. Chem. Int. Ed. **1997**, *36*, 119; (b) M. Catellani, C. Mealli, E. Motti, P. Paoli, E. Perez-Carreno, P. S. Pregosin, *J. Am. Chem. Soc.* **2002**, *124*, 4336; (c) N. Dell Ca', M. Fontana, E. Motti, M. Catellani, *Acc. Chem. Res.* **2016**, *49*, 1389.