Journal Name

COMMUNICATION

Cobalt-catalyzed directed *ortho*-methylation of arenes with methyl tosylate

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

DOI: 10.1039/x0xx00000x

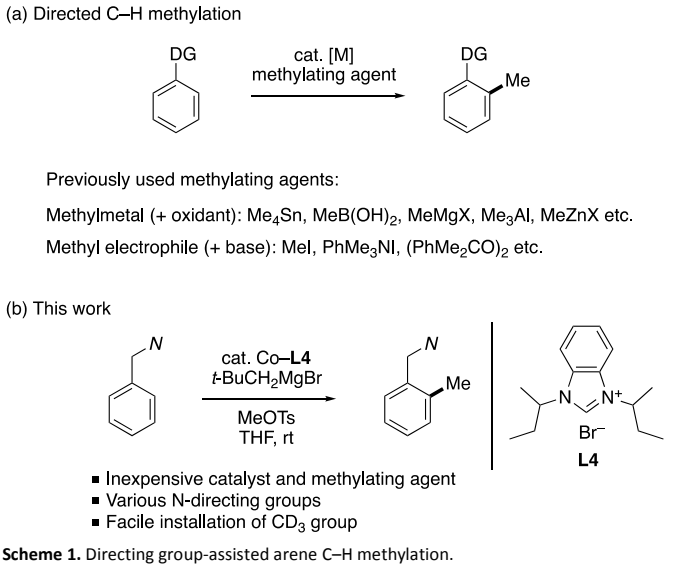
www.rsc.org/

Qiao Sun[a] and Naohiko Yoshikai*[a]

A cobalt-catalyzed directed *ortho* C–H methylation reaction of arenes has been achieved using readily available methyl tosylate as a methylating agent. An in situ-generated cobalt–N-heterocyclic carbene catalyst in combination with neopentylmagnesium bromide promotes the methylation at room temperature. The reaction is applicable to various substrates bearing nitrogen directing groups such as *N*-aryl imine, N–H imine, and 2-pyridyl groups. The present protocol also allows for facile introduction of a trideuteriomethyl group into arenes.

The installation of a methyl group to a drug lead may cause a dramatic improvement of its biological and physical properties.[1] This so-called magic methyl effect calls for the development of efficient catalytic methods for the methylation of organic compounds. Such methylation reactions would also be desired to allow for the introduction of a CD_3 group in light of the growing interest in deuterated drug candidates.[2] While methylation via transition metal-catalyzed cross-coupling has been extensively explored,[3] catalytic methylation of C–H bonds has also gained increasing attention for the atom- and step-economical nature of the process.[1a,4] In this context, a series of transition metal-catalyzed, directing group-assisted C–H methylation reactions have been developed using various methylating agents including methyl electrophiles such as MeI[5] and $PhMe_3NI$,[6] methylmetals such as Me_4Sn,[7] methylboron compounds,[8] MeMgX,[9] Me_3Al,[10] and MeZnX,[11] or other methyl sources such as dicumyl peroxide (Scheme 1a).[12] Nevertheless, some major drawbacks remain in these methylation reactions. Methylmetals are often air- and moisture-sensitive, and their deuterated analogues are not readily available at low cost. The reactions using methyl electrophiles often require precious transition metals such as Pd or high reaction temperature. As such, the development of C–H methylation reactions employing inexpensive earth-abundant metal catalysts[13] and convenient methylating agents continues to be an important task.

Herein, we report on cobalt-catalyzed directed *ortho* C–H methylation of arenes using methyl tosylate as the methylating agent (Scheme 1b).[5f,13c,d,14,15] The reaction is achieved using an in situ-generated cobalt–N-heterocyclic carbene (NHC) catalyst in combination with neopentylmagnesium bromide at room temperature. The reaction is applicable to arenes bearing nitrogen directing groups such as *N*-aryl imine, 2-pyridyl, and N–H imine groups, and allows facile introduction of a CD_3 group using the corresponding tosylate.



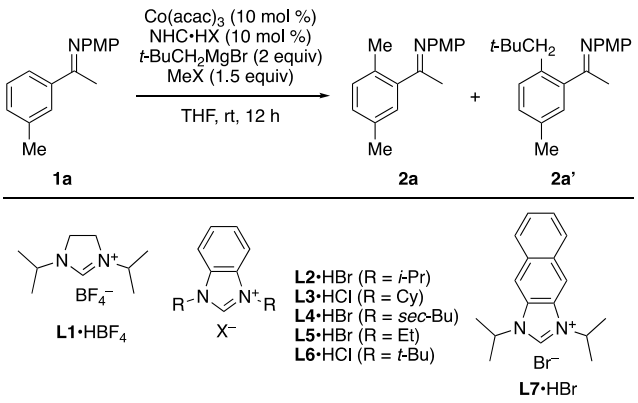
Scheme 1. Directing group-assisted arene C–H methylation.

We explored *ortho*-methylation of imine **1a** derived from 3-methylacetophenone and *p*-anisidine (PMP = *p*-methoxyphenyl) with methyl tosylate (1.5 equiv) in the presence of $Co(acac)_3$ (10 mol %), ligand (10 mol %), and neopentylmagnesium bromide (2 equiv) as a base (Table 1; see also Table S1). N-heterocyclic carbene (NHC) precursors *N*,*N*'-diisopropylimidazolinium tetrafluoroborate (**L1**•HBF_4) and

[a] Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University. E-mail: nyoshikai@ntu.edu.sg
[b] † Footnotes relating to the title and/or authors should appear here.
[c] Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

N,*N*'-diisopropylbenzimidazolium bromide (**L2**•HBr), which proved to be the optimum preligands for the cobalt-catalyzed *ortho*-alkylation with primary and secondary alkyl halides,[14a] promoted methylation of the less hindered *ortho* position to afford the product **2a** in moderate yield along with a small amount of *ortho*-neopentylation product **2a'** (entries 1 and 2). Modification of the *N*-substituents of **L2**•HBr with different secondary alkyl groups such as cyclohexyl (**L3**•HCl) and *sec*-butyl (**L4**•HBr; a 1:1 mixture of diastereomers) improved the reaction further (entries 3 and 4), while analogous ligands bearing primary or tertiary alkyl groups performed poorly (entries 5 and 6). Interestingly, naphtho-fused ligand **L7**•HBr also performed better than **L2**•HBr (entry 7). Other types of ligands such as phosphines and *N*,*N*'-diaryl-substituted NHCs were much less effective for the present methylation (see Table S1). $CoBr_2$ could be used in place of $Co(acac)_3$ (entry 8), while other cobalt salts gave diminished yields. The yield of **2a** could be improved to 80% by increasing the amounts of MeOTs and *t*-$BuCH_2MgBr$ to 2 equiv and 2.7 equiv, respectively (entry 9). Notably, methyl mesylate and trimethyl phosphate also served as viable methylating agents (entries 10 and 11), while methyl iodide afforded **2a** only in a low yield (entry 12).

Table 1. Methylation of imine **1a** with methyl tosylate or related methylating agent.[a]



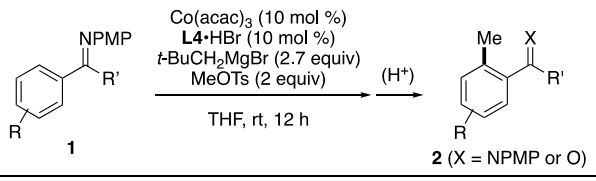
Entry	MeX	NHC•HX	Yield [%][b]	
			2a	**2a'**
1	MeOTs	**L1**•HBF_4	47	4
2	MeOTs	**L2**•HBr	47	1
3	MeOTs	**L3**•HCl	56	3
4	MeOTs	**L4**•HBr	63	2
5	MeOTs	**L5**•HBr	22	2
6	MeOTs	**L6**•HCl	1	0
7	MeOTs	**L7**•HBr	58	1
8[c]	MeOTs	**L4**•HBr	64	2
9[d]	MeOTs	**L4**•HBr	80	2
10	MeOMs	**L4**•HBr	52	1
11	$(MeO)_3P{=}O$	**L4**•HBr	59	3
12	MeI	**L4**•HBr	5	1

[a] The reaction was performed using 0.2 mmol of **1a** (*c* = 0.2 M) and 0.3 mmol of MeX. [b] Determined by GC using *n*-tridecane as an internal standard. [c] $CoBr_2$ was used instead of $Co(acac)_3$. [d] 2 equiv of MeOTs and 2.7 equiv of *t*-$BuCH_2MgBr$ were used.

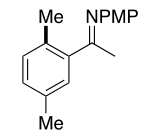
With the Co/**L4** catalytic system in hand, we explored methylation of a series of aryl *N*-PMP imines (Table 2).[16] The reaction of *meta*-substituted imines took place at the less-hindered *ortho* positions to afford the corresponding methylation products **2a**–**2e** in good yields. Likewise, 2-naphthylimine underwent regioselective methylation at the 3-position (see the product **2f**). Imines derived from 1-tetralone or 4-chromanone derivatives were also methylated to afford the products **2g**–**2j** in moderate to good yields. The scalability of the present reaction was demonstrated for tetralone derivative **1h** on a 5 mmol scale, which afforded **2h** in a good yield of 84%. Using 1.5 equiv of MeOTs and 2 equiv of *t*-$BuCH_2MgBr$, *para*-phenyl or methoxy-substituted imines afforded monomethylation products **2k** or **2l**, respectively, as the major product along with nonnegligible amount of the dimethylation product. Imines derived from propiophenone and butyrophenone preferentially afforded the monomethylation products **2m** and **2n**, respectively. N-methylindoles underwent C2-methylation with the assistance of ketimine or aldimine directing group on the C3 position (see the products **2o** and **2p**).

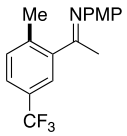
Using large excess MeOTs (4 equiv) and *t*-$BuCH_2MgBr$ (5.3 equiv), *para*-phenyl-substituted imine afforded the dimethylation product **2k'** as the major product. Imines bearing *para*- or *meta*-fluorine substituents were found to show greater preference toward dimethylation, affording the products **2q**–**2s** as the major products. Among them, the 3,5-difluoro-substituted imine was particularly reactive, and smoothly underwent dimethylation using only 2.5 equiv of MeOTs. Thus, unlike other *meta*-substituents (cf. products **2a**–**2e**), the *meta*-fluorine substituent does not act as a steric hindrance but rather promotes methylation at its proximity. The propensity of these fluorinated substrates toward dimethylation may be ascribed to the effect of fluorine to facilitate C–H activation of its proximal (especially *ortho*) positions.[17,18]

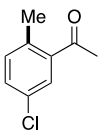
Table 2. Scope of Aryl N-PMP imines[a]

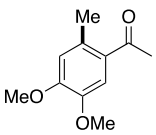


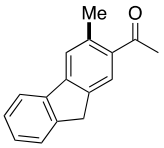
monomethylation

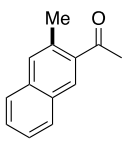

2a, 81%

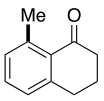

2b, 68%[b]

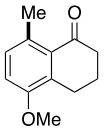

2c, 56%

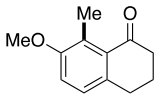

2d, 72%

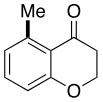

2e, 74%

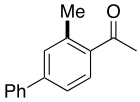

2f, 81%[c]

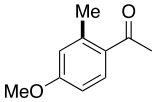

2g, 67%[d]

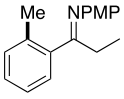

2h, 83%
84% (5 mmol scale)

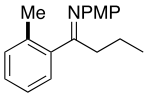

2i, 55%

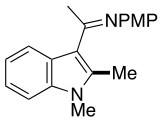

2j, 62%

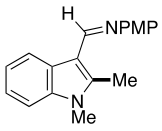

2k, 49% (13%)[d,e]


2l, 42% (11%)[d,e]

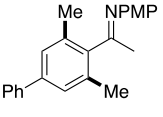

2m, 66% (11%)[e]

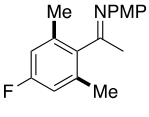

2n, 65% (3%)[e]

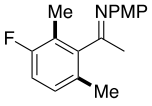

2o, 57%

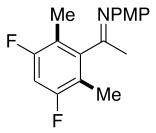

2p, 59%

dimethylation


2k', 50%[f]


2q, 85%[b]

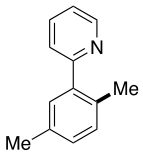

2r, 67%[f]

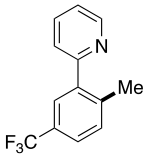

2s, 74%[g]

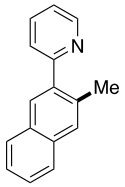
[a] The methylated products were isolated in the form of imine or ketone (after hydrolysis). The imine products existed as *E*/*Z* mixtures. See the Supplementary Information for details. [b] 3 equiv of MeOTs and 4 equiv of *t*-$BuCH_2MgBr$ were used. [c] The regioselectivity was 94:6 (major isomer shown). [d] 1.5 equiv of MeOTs and 2 equiv of *t*-$BuCH_2MgBr$ were used. [e] The yield of *ortho*-dimethylation product (GC) is shown in the parentheses. [f] 4 equiv of MeOTs and 5.3 equiv of *t*-$BuCH_2MgBr$ were used. [g] 2.5 equiv of MeOTs and 3.3 equiv of *t*-$BuCH_2MgBr$ were used.

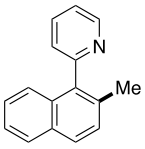
Next, we explored *ortho* C–H methylation of arenes bearing other directing groups (Table 3). 2-Arylpyridines bearing sterically distinct *ortho*-positions underwent selective methylation at the less hindered positions (see the products **4a**–**4c**). Under the standard conditions, parent 2-phenylpyridine afforded a ca. 1:1 mixture of mono- and di-methylation products **4e** and **4f**, and the reaction using the former as the starting material afforded **4f** in moderate yield. Attempts to improve the selectivity toward **4e** or **4f** met with partial success. The reaction using 1.5 equiv MeOTs and 2 equiv *t*-$BuCH_2MgBr$ afforded **4e** in 47% yield (along with **4f** in 19%), while the one using 4 equiv MeOTs and 5.3 equiv *t*-$BuCH_2MgBr$ afforded **4f** in 55% yield (along with **4e** in 12%). As was observed for the imine-directed methylation (Table 2, the product **2r**), 2-arylpyridine with a *meta*-fluorine atom underwent facile dimethylation to give **4g** as the major product. The presence of a 3-methyl group on the pyridine ring assisted exclusive monomethylation (see **4h**). In contrast to 2-phenylpyridine, 2-phenylpyrimidine afforded dimethylation product **4i** as the major product (59%) along with minor monomethylation product (9%). With increased amounts of MeOTs (4 equiv) and *t*-$BuCH_2MgBr$ (5.3 equiv), **4i** was obtained in 75% yield. The pyridine directing group also assisted C–H methylation of thiophene and indole (see the products **4j** and **4k**). Lastly, pivaloyl N–H imine also proved to serve as a viable directing group for the present C–H methylation (see the product **4l**).[14d,19]

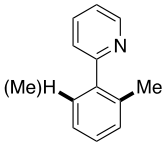
Table 3. Methylation of other arene substrates.[a]

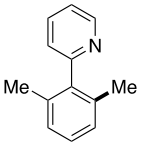

4a, 78%

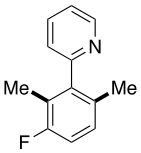

4b, 33%

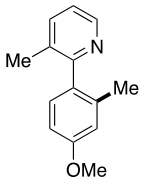

4c, 64%

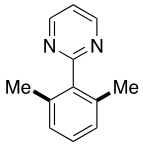

4d, 62%

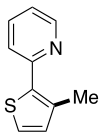

4e (mono), 37%
4f (di), 33%

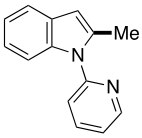

4f, 60%

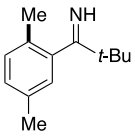

4g, 57%


4h, 60%


4i, 75%[b]


4j, 30%[b]

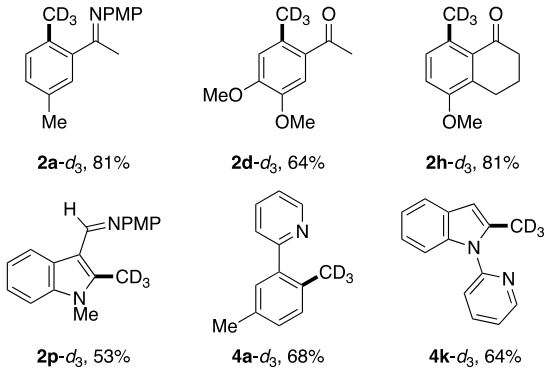

4k, 68%


4l, 54%

[a] Unless otherwise noted, the reaction was performed under the conditions shown in Table 2. [b] 4 equiv of MeOTs and 5.3 equiv of *t*-$BuCH_2MgBr$ were used.

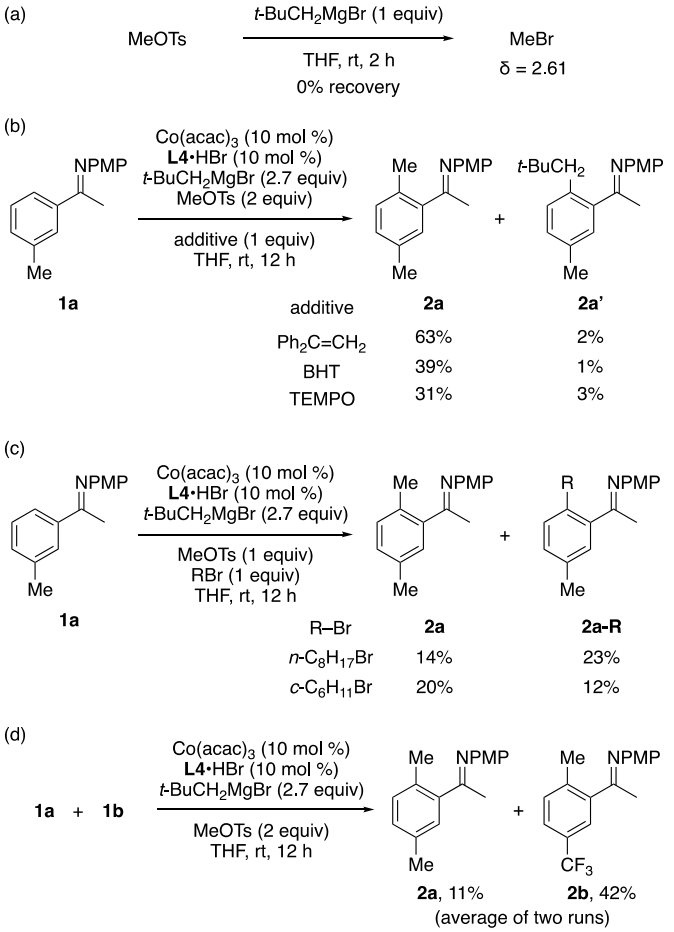
Given the affordability of deuterated methanol and facile preparation of the corresponding tosylate, the present reaction would serve as a convenient method for the installation of a CD_3 group into arenes. To illustrate this point, selected arene substrates were subjected to the reaction using CD_3OTs instead of MeOTs, thus affording the corresponding trideuteriomethylation products in yields comparable to that obtained using parent methyl tosylate (Table 4).

Table 4. Trideuteriomethylation of selected arene substrates.[a]



[a] The reaction was performed under the conditions shown in Table 2 using CD_3OTs instead of MeOTs.

To gain mechanistic insight into the present reaction, several control experiments were performed. First, exposure of MeOTs to a THF solution of *t*-$BuCH_2MgBr$ resulted in complete decomposition of MeOTs within 2 h and formation of MeBr as confirmed by ^1H NMR analysis (δ = 2.61; Scheme 2a). The same was observed for MeOMs and $(MeO)_3PO$. Thus, MeBr is likely to serve as the actual methylating agent in the present methylation. Second, the methylation of **1a** was not apparently affected by the addition of 1,1-diphenylethylene but was significantly inhibited in the presence of 2,6-di-*tert*-butyl-4-methylphenol (BHT) or (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) (Scheme 2b). This may suggest single electron transfer (SET) mechanism for the activation of MeBr.[14] Third, the reaction of **1a** with a mixture of MeOTs and *n*-octyl bromide or cyclohexyl bromide did not show significant chemoselectivity (Scheme 2c), which would also suggest that SET rather than inner-sphere oxidative addition is more likely to operate in the C–Br cleavage. Finally, a competition between the imines **1a** and **1b** resulted in preferential methylation of the latter (Scheme 2d), pointing to preferential cyclometalation of the electron-poor arene C–H bond. Note that the lower yield of **2b** (68%, under more forcing conditions) than that of **2a** (81%) in Table 2 was due to unidentified competitive decomposition of **1b** under the methylation conditions. Such decomposition was also observed in the reaction of trifluoromethyl-substituted 2-phenylpyridine, thus diminishing the yield of **4b** (see Table 3). In a competition experiment, **4b** was obtained in preference to **4a** (30% vs 12%), again suggesting higher propensity of the electron-poor arene C–H bond toward cyclometalation.



Scheme 2. Control experiments.

Conclusions

In summary, we have developed a cobalt-catalyzed directed *ortho* C–H methylation reaction of arenes using methyl tosylate. A catalytic system comprised of $Co(acac)_3$, *N,N'*-di(2-butyl)benzimidazolium bromide, and *t*-$BuCH_2MgBr$ promotes the reaction at room temperature, where the Grignard reagent acts not only as a base to remove the *ortho*-hydrogen but also as a bromide donor to convert methyl tosylate into the actual methylating agent, i.e., methyl bromide. The present reaction is applicable to different nitrogen directing groups, features inexpensive methylating agent and catalyst, and allows facile installation of trideuteriomethyl group. Further studies on cobalt-catalyzed C–H/electrophile coupling are underway in our laboratory.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

This work was supported by the Ministry of Education (Singapore) and Nanyang Technological University (RG114/15 and MOE2016-T2-2-043).

Notes and references

‡ Footnotes relating to the main text should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.
§
§§
etc.

1 (a) H. Schonherr and T. Cernak, *Angew. Chem. Int. Ed.*, 2013, **52**, 12256; (b) E. J. Barreiro, A. E. Kummerle and C. A. M. Fraga, *Chem. Rev.*, 2011, **111**, 5215; (c) C. S. Leung, S. S. F. Leung, J. Tirado-Rives and W. L. Jorgensen, *J. Med. Chem.*, 2012, **55**, 4489.

2 (a) A. Katsnelson, *Nat. Med.*, 2013, **19**, 656; (b) A. Mullard, *Nat. Rev. Drug Discov.*, 2016, **15**, 219.

3 (a) L. Hu, X. Liu and X. Liao, *Angew. Chem. Int. Ed.*, 2016, **55**, 9743; (b) D. Heijnen, F. Tosi, C. Vila, M. C. A. Stuart, P. H. Elsinga, W. Szymanski and B. Feringa, *Angew. Chem. Int. Ed.*, 2017, **56**, 3354.

4 G. Yan, A. J. Borah, L. Wang and M. Yang, *Adv. Synth. Catal.*, 2015, **357**, 1333.

5 (a) D. Shabashov and O. Daugulis, *J. Am. Chem. Soc.*, 2010, **132**, 3965; (b) Y. Zhao and G. Chen, *Org. Lett.*, 2011, **13**, 4850; (c) S.-Y. Zhang, G. He, W. A. Nack, Y. Zhao, Q. Li and G. Chen, *J. Am. Chem. Soc.*, 2013, **135**, 2124; (d) S.-Y. Zhang, Q. Li, G. He, W. A. Nack and G. Chen, *J. Am. Chem. Soc.*, 2013, **135**, 12135; (e) R.-Y. Zhu, J. He, X.-C. Wang and J.-Q. Yu, *J. Am. Chem. Soc.*, 2014, **136**, 13194; (f) Y. Aihara, J. Wuelbern and N. Chatani, *Bull. Chem. Soc. Jpn.*, 2015, **88**, 438; (g) S. J. Tremont and H. U. Rahman, *J. Am. Chem. Soc.*, 1984, **106**, 5759; (h) B. Wang, X. Wu, R. Jiao, S.-Y. Zhang, W. A. Nack, G. He and G. Chen, *Org. Chem. Front.*, 2015, **2**, 1318; (i) M. J. Jang and S. W. Youn, *Bull. Korean Chem. Soc.*, 2011, **32**, 2865.

6 T. Uemura, M. Yamaguchi and N. Chatani, *Angew. Chem. Int. Ed.*, 2016, **55**, 3162.

7 X. Chen, J.-J. Li, X.-S. Hao, C. E. Goodhue and J.-Q. Yu, *J. Am. Chem. Soc.*, 2006, **128**, 78.

8 (a) R. Giri, N. Maugel, J.-J. Li, D.-H. Wang, S. P. Breazzano, L. B. Saunders and J.-Q. Yu, *J. Am. Chem. Soc.*, 2007, **129**, 3510; (b) H.-X. Dai, A. F. Stepan, M. S. Plummer, Y.-H. Zhang and J.-Q. Yu, *J. Am. Chem. Soc.*, 2011, **133**, 7222; (c) J. A. Romero-Revilla, A. Garcia-Rubia, R. G. Arrayas, M. A. Fernandez-Ibanez and J. C. Carretero, *J. Org. Chem.*, 2011, **76**, 9525; (d) S. R. Neufeldt, C. K. Seigerman and M. S. Sanford, *Org. Lett.*, 2013, **15**, 2302.

9 Q. Chen, L. Ilies, N. Yoshikai and E. Nakamura, *Org. Lett.*, 2011, **13**, 3232; (b) K. Graczyk, T. Haven and L. Ackermann, *Chem. Eur. J.*, 2015, **21**, 8812; (c) T. Sato, T. Yoshida, H. H. Al Mamari, L. Ilies and E. Nakamura, *Org. Lett.*, 2017, **19**, 5458.

10 (a) R. Shang, L. Ilies and E. Nakamura, *J. Am. Chem. Soc.*, 2015, **137**, 7660; (b) R. Shang, L. Ilies and E. Nakamura, *J. Am. Chem. Soc.*, 2016, **138**, 10132; (c) H. Wang, S. Zhang, Z. Wang, M. He and K. Xu, *Org. Lett.*, 2016, **18**, 5628.

11 L. Ilies, S. Ichikawa, S. Asako, T. Matsubara and E. Nakamura, *Adv. Synth. Catal.*, 2015, **357**, 2175.

12 (a) Y. Zhang, J. Feng and C. J. Li, *J. Am. Chem. Soc.*, 2008, **130**, 2900; (b) T. Kubo and N. Chatani, *Org. Lett.*, 2016, **18**, 1698; (c) Q. Li, Y. Li, W. Hu, R. Hu, G. Li and H. Lu, *Chem. Eur. J.*, 2016, **22**, 12286.

13 (a) R. Shang, L. Ilies and E. Nakamura, *Chem. Rev.*, 2017, **117**, 9086; (b) W. Liu and L. Ackermann, *ACS Catal.*, 2016, **6**, 3743; (c) K. Gao and N. Yoshikai, *Acc. Chem. Res.*, 2014, **47**, 1208; (d) M. Moselage, J. Li and L. Ackermann, *ACS Catal.*, 2016, **6**, 498; (e) G. Pototschnig, N. Maulide and M. Schnürch, *Chem. Eur. J.*, 2017, **23**, 9206.

14 (a) K. Gao and N. Yoshikai, *J. Am. Chem. Soc.*, 2013, **135**, 9279; (b) B. Punji, W. Song, G. A. Shevchenko and L. Ackermann, *Chem. Eur. J.*, 2013, **19**, 10605; (c) K. Gao, T. Yamakawa and N. Yoshikai, *Synthesis*, 2014, **46**, 2024; (d) W. Xu and N. Yoshikai, *Chem. Sci.*, 2017, **8**, 5299.

15 Chatani and coworkers reported a combined use of MeOTs and NaI for Ni-catalyzed, bidentate amide-directed C–H methylation, where in situ-generated MeI was assumed to serve as the methylating agent (see ref 5f).

16 Acidic hydrolysis (3 N aq. HCl, room temperature for 1 h) of some methylation products led to substantial decrease (> 10%) in the yield (for the mono-methylated products such as **2a** and **2b**) or was rather sluggish (for the di-methylated products such as **2q**–**2s**). For such cases, we did not optimize hydrolysis conditions but isolated the products in the form of imine.

17 O. Eisenstein, J. Milani and R. N. Perutz, *Chem. Rev.*, 2017, **117**, 8710.

18 For the reaction of *meta*-fluorinated imine, we are not sure which *ortho*-position is initially methylated to eventually afford the dimethylation product **2r**, while we suspect that the position proximal to fluorine is more reactive. The monomethylated product could not be isolated in a pure form even using a limited amount of MeOTs.

19 W. Xu and N. Yoshikai, *Angew. Chem., Int. Ed.*, 2016, **55**, 12731.