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

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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 CD₃ 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 MeI⁵ and PhMe₃NI,⁶ methylmetals such as Me₄Sn,⁷ methylboron compounds,⁸ MeMgX,⁹ Me₃Al,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 catalysts¹³ 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 CD₃ group using the corresponding tosylate.

(a) Directed C–H methylation

Previously used methylating agents:

Methylmetal (+ oxidant): Me₄Sn, MeB(OH)₂, MeMgX, Me₃Al, MeZnX etc.

Methyl electrophile (+ base): MeI, PhMe₃NI, (PhMe₂CO)₂ etc.

(b) This work

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'*-diisopropylimidazolium tetrafluoroborate (**L1**•HBF₄) and

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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). CoBr₂ 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*-BuCH₂MgBr 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

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*-BuCH₂MgBr, *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*-BuCH₂MgBr (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}

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) ₃ P=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 CoBr₂ was used instead of Co(acac)₃. ^d 2 equiv of MeOTs and 2.7 equiv of *t*-BuCH₂MgBr 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

Table 4. Trideuteriomethylation of selected arene substrates.^a

2a-d₃ , 81%	2d-d₃ , 64%	2h-d₃ , 81%
2p-d₃ , 53%	4a-d₃ , 68%	4k-d₃ , 64%

^a The reaction was performed under the conditions shown in Table 2 using CD₃OTs 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*-BuCH₂MgBr 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*-BuCH₂MgBr 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.

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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.

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etc.

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