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Communication

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Cobalt-Catalyzed *ortho*-Alkylation of Aromatic Imines with Primary and Secondary Alkyl Halides

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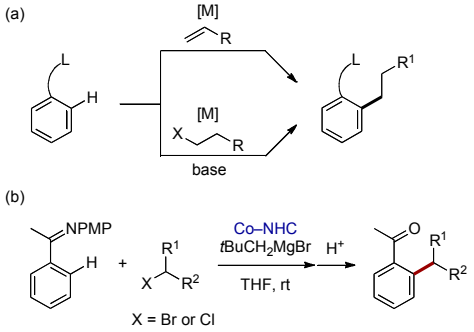
Supporting Information Placeholder

ABSTRACT: We report here cobalt–*N*-heterocyclic carbene catalytic systems for the *ortho*-alkylation of aromatic imines with alkyl chlorides and bromides, which allows introduction of a variety of primary and secondary alkyl groups at room temperature. Stereochemical outcomes of the reaction of secondary alkyl halides suggest that the present reaction involves single-electron transfer from a cobalt species to the alkyl halide to generate the corresponding alkyl radical. A cycloalkylated product obtained by this method can be transformed into unique spirocycles through manipulation of the directing and the cycloalkyl groups.

The discovery of the ruthenium-catalyzed *ortho*-alkylation of aromatic ketones with olefins by Murai et al. in 1993 brought about a new paradigm in regioselective aromatic alkylations (Scheme 1a, top).[1] Since then, a series of catalytic systems have been developed for the chelation-assisted alkylation using terminal olefins.[2,3] However, this strategy has been less successful in the introduction of a secondary alkyl group for various reasons, such as *anti*-Markovnikov selectivity with terminal olefins, low reactivity of internal olefins, and isomerization of internal acyclic olefins, with limited exceptions.[4,5] More recently, *ortho*-alkylation employing alkyl halides as alkylating agents has emerged as an alternative strategy (Scheme 1a, bottom).[6,7] Nevertheless, while successful for primary alkyl halides, this strategy has been practiced with only a handful of secondary alkyl halides.[7a,d,f,8-10] Here, we report a significant expansion of the scope of the latter strategy achieved with a cobalt–*N*-heterocyclic carbene (NHC) catalyst system, which allows *ortho*-alkylation of aromatic imines using a variety of primary and secondary alkyl halides under room-temperature conditions (Scheme 1b). The activation of the alkyl halide is proposed to occur through single-electron transfer from a cobalt species, generating the corresponding alkyl radical.

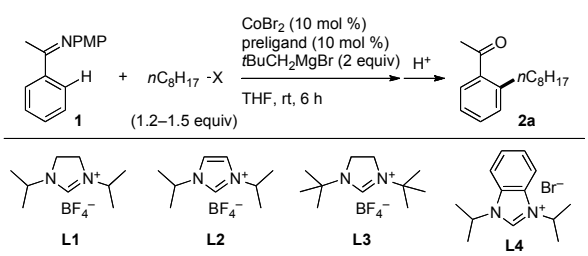
Scheme 1. *ortho*-Alkylation of Arenes with Olefins or Alkyl Halides



With our recent development of cobalt/NHC/Grignard catalytic systems for *ortho* C–H functionalization using aldimine[11] and aryl chloride[12] as electrophiles, we conceived that a similar system would allow *ortho*-alkylation with alkyl halides, and thus commenced the present study with the reaction of acetophenone imine **1** with *n*-octyl chloride (Table 1). The catalytic system consisting of $CoBr_2$ (10 mol %), IMes•HCl (10 mol %), and *t*$BuCH_2MgBr$ (2 equiv), which we employed for the *ortho*-arylation,[12a] was only modestly effective, affording the alkylation product **2a** in 38% yield (entry 1). Other popular bulky NHC preligands, such as IPr•HCl and SIMes•HCl, exhibited poorer performances (entries 2 and 3). Upon further screening, we found that a simple *N*,*N*'-diisopropylimidazolinium salt **L1** improved the yield to 64% (entry 4). While the unsaturated analogue **L2** and *t*-butyl analogue **L3** were less effective (entries 5 and 6), the benzo-fused analogue **L4** further improved the yield to 82% (entry 7). As was the case in our previous studies,[11,12a] *t*$BuCH_2MgBr$ performed best among a series of alkyl Grignard reagents (primary, secondary, and those without β-hydrogen), causing *ortho*-neopentylation to only a small extent (< 2% for most cases).

Having identified **L1** and **L4** as promising preligands, we examined the effect of the leaving group. The reaction of *n*-octyl bromide took place smoothly with both **L1** and **L4** (entries 8 and 9), while *n*-octyl iodide underwent substantial dehydrohalogenation (as judged by GC analysis), and thus produced **2a** in only low yield (entries 10 and 11). *n*-Octyl tosylate participated in the reaction at an elevated temperature of 60 °C to afford **2a** in moderate yields (entries 12 and 13). However, control experiments showed that *n*-octyl tosylate and *t*$BuCH_2MgBr$ undergo substantial displacement of the tosyloxy group with the bromide anion at room temperature in the absence of the cobalt catalyst and **1**, thus suggesting that this alkylation reaction does not occur directly from *n*-octyl tosylate but goes through *n*-octyl bromide.

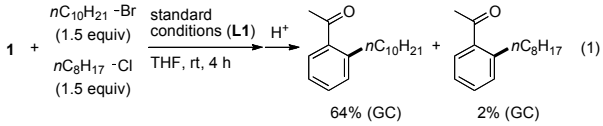
Table 1. Screening of Reaction Conditions[a]



entry	X	preligand	yield (%)[b]
1	Cl	IMes•HCl	38
2	Cl	IPr•HCl	13
3	Cl	SIMes•HCl	20
4	Cl	**L1**	64
5	Cl	**L2**	38
6	Cl	**L3**	14
7	Cl	**L4**	82[c]
8	Br	**L1**	79[c]
9	Br	**L4**	57
10	I	**L1**	14
11	I	**L4**	6
12[d]	OTs	**L1**	64[c]
13[d]	OTs	**L4**	49[c]

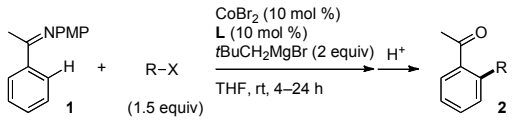
[a] Reaction was performed on a 0.3 mmol scale. PMP = *p*-methoxyphenyl. [b] Determined by GC using *n*-tridecane as an internal standard. [c] Isolated yield. [d] Performed at 60 °C.

The present catalytic systems were applicable to *ortho*-alkylation of **1** with a variety of primary alkyl chlorides and bromides (Table 2). The reaction of *n*-hexyl bromide could be performed on a 10 mmol scale in 77% yield (entry 1). 5-Bromo-1-pentene and 6-bromo-1-hexene afforded the expected alkylation products along with small amounts of minor isomers arising from terminal-to-internal olefin isomerization (entries 4 and 5).[13] The C–F and C–Cl bonds remained intact in the reaction of 1-bromo-4-fluorobutane and 1-bromo-4-chlorobutane, respectively (entries 6 and 7). The chemoselectivity in the latter case was consistent with an intermolecular competition reaction of *n*-bromodecane and *n*-chlorooctane with **1**, which predominantly afforded the *n*-decylation product (eq 1). On the other hand, the reaction of 6-bromohexyl tosylate was accompanied by a minor product **2h'** with a C–Br bond at the alkyl terminus, which presumably formed through displacement of the tosyloxy group of the major product **2h** by the bromide anion (entry 8; vide supra). Chemoselective activation of alkyl chloride was achieved in the presence of an aryl fluoride or chloride moiety (entries 9 and 10).



The steric hindrance of neopentyl bromide and trimethylsilylmethyl chloride did not interfere with the reaction (entries 11 and 12). Acetal protection was necessary for introducing an alkyl chain with a ketone moiety (entry 13), while secondary amide was tolerable albeit with a modest reaction efficiency (entry 14). A pyridyl moiety in the alkyl chloride made the reaction rather sluggish (entry 15).[14] The reaction of cyclopropylmethyl bromide resulted in a complex mixture (entry 16); we failed to detect either of the possible products arising from simple alkylation (i.e., cyclopropylmethylation) and ring opening followed by alkylation (i.e., homoallylation). The results in entries 5 and 16 will be discussed again later in a mechanistic context.

Table 2. Alkylation of **1** with Primary Alkyl Halides[a]



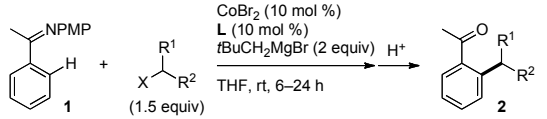
entry	R–X	L	yield (product)[b]
1[c]	nC_6H_{13} -Br	**L1**	77% (**2b**)
2	Ph–Cl	**L4**	73% (**2c**)
3	Ph–Br	**L1**	82% (**2c**)
4	Br	**L1**	66% (**2d**, R = -$(CH_2)_3$CH=CH_2) 6% (**2d'**, R = -$(CH_2)_2$CH=$CHCH_3$)[d]
5	Br	**L1**	85% (**2e**, R = -$(CH_2)_4$CH=CH_2) 12% (**2e'**, R = -$(CH_2)_3$CH=$CHCH_3$)[d]
6	F, Br	**L1**	73% (**2f**, R = -$(CH_2)_4$F)
7	Cl, Br	**L1**	80% (**2g**, R = -$(CH_2)_4$Cl)
8	TsO, Br	**L1**	71% (**2h**, R = -$(CH_2)_6$OTs) 18% (**2h'**, R = -$(CH_2)_6$Br)
9	X, Cl	**L4**	77% (**2i**, X = F)
10	X, Cl	**L4**	61% (**2j**, X = Cl)
11	*t*Bu–Br	**L1**	86% (**2k**)
12	Me_3Si–Cl	**L1**	65% (**2l**)
13	O,O, Br	**L4**	69% (**2m**, R = -$(CH_2)_3$C(=O)CH_3)
14[e]	N, O, Br	**L1**	41% (**2n**)[f]
15	N, Cl	**L4**	19% (**2o**)[g]
16	Br	**L1/L4**	complex mixture

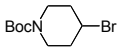
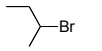
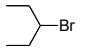
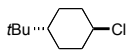
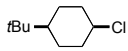
[a] Unless otherwise noted, the reaction was performed on a 0.3 mmol scale. [b] Isolated yield. [c] 10 mmol scale. [d] Obtained as a mixture, and the ratio was determined by ^{1}H NMR. [e] 2 equiv of alkyl bromide was used, and an additional 1 equiv of *t*$BuCH_2MgBr$ was added at the reaction time of 2 h. [f] Obtained as a mixture with the alkyl bromide and its β-elimination product. [g] Obtained as a mixture with *p*-anisidine.

Gratifyingly, the present reaction was also applicable to a variety of secondary alkyl chlorides and bromides (Table 3). Cycloalkyl halides with different ring size (4 to 12) afforded the corresponding alkylation products in moderate to good yields (entries 1–7). The reaction also allowed alkylation with Boc-protected 4-bromopiperidine (entry 8). Linear secondary alkyl halides were also amenable to the reaction. With the Co–**L1** catalyst, isopropyl chloride, bromide, and *sec*-butyl bromide afforded the corresponding alkylation products with only a small degree of secondary-to-primary isomerization (entries 9–11). The use of the Co–**L4** catalyst improved the yields by 10–20% but reduced the regioselectivity (*i*:*n* = 8:2 to 7:3). The reaction of 3-bromopentane exclusively afforded the 3-pentylation product (entry 12). The reaction of *exo*-2-norbornane took place smoothly with an *exo*/*endo* ratio of 90:10 (entry 13). *Trans*- and *cis*-isomers of 1-chloro-4-*tert*-

butylcyclohexane both afforded the product **2v** with the same *trans*/*cis* ratio of 79:21 (entries 14 and 15).[14] *tert*-Butyl bromide and chloride decomposed under the reaction conditions, and afforded neither the *tert*-butylation nor the isobutylation products.

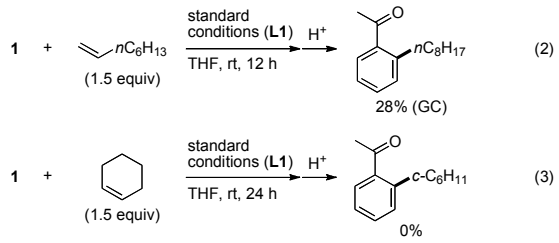
Table 3. Alkylation of **1** with Secondary Alkyl Halides[a]



entry	R–X	L	yield (product)[b]
1	*c*-C_4H_7 -Cl	**L4**	51% (**2p**)
2	*c*-C_4H_7 -Br	**L1**	75% (**2p**)
3[c]	*c*-C_5H_9 -Cl	**L1**	78% (**2q**)
4	*c*-C_6H_{11} -Cl	**L4**	73% (**2r**)
5	*c*-C_6H_{11} -Br	**L1**	90% (**2r**)
6	*c*-C_7H_{13} -Cl	**L4**	84% (**2s**)
7[c,d]	*c*-$C_{12}H_{23}$ -Cl	**L1**	65% (**2t**)
8[c,d]		**L1**	42% (**2u**)
9	*i*-C_3H_7 -Cl	**L1**	65% (**2v**, *i*:*n* = 99:1)[e]
10	*i*-C_3H_7 –Br	**L1**	68% (**2v**, *i*:*n* = 93:7)[e]
11		**L1**	56% (**2w**, *i*:*n* = 94:6)[e]
12		**L1**	63% (**2x**)
13		**L1**	82% (**2y**, *exo*:*endo* = 90:10)[e]
14	 (*trans*:*cis* = 91:9)	**L4**	31% (**2z**, *trans*:*cis* = 79:21)[f]
15	 (*trans*:*cis* = 4:96)	**L4**	30% (**2z**, *trans*:*cis* = 79:21)[f]

[a] The reaction was performed on a 0.3 mmol scale. [b] Isolated yield. [c] An additional 1 equiv of *t*$BuCH_2MgBr$ was added at the reaction time of 2 h or 5 h. [d] 2 equiv of alkyl halide was used. [e] *i*:*n* refers to the ratio of the secondary and primary alkylation products, which was determined by ^1H NMR. [f] The ratio was determined by GC.

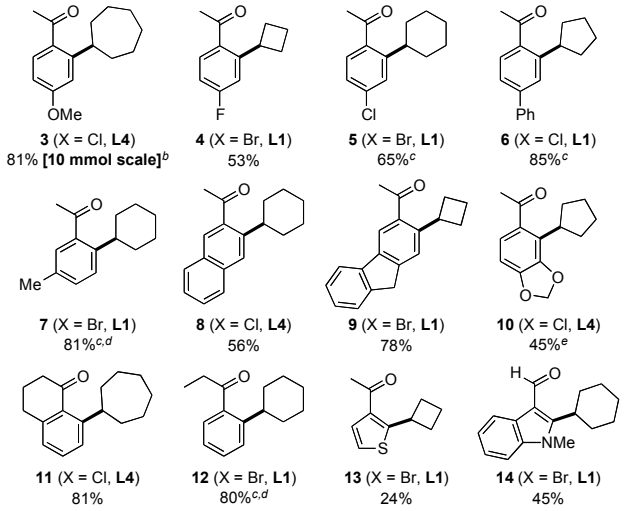
With some of the results in Tables 2 and 3, we speculate that a radical-type mechanism operates in the present reaction (see Scheme S1 for a possible catalytic cycle). The stereochemical outcomes in Table 3, entries 13–15 suggest that the reaction involves, as has been proposed for the cobalt-catalyzed cross-coupling reaction of alkyl halides,[15,16] formation of a secondary alkyl radical through single-electron transfer from a cobalt species followed by recombination of the cobalt and the radical centers. The resulting alkylcobalt species may undergo β-hydride elimination/re-insertion prior to C–C bond formation, which would have caused partial isomerization of the acyclic secondary alkyl groups to the primary alkyl groups (Table 3, entries 9–11). While the present catalytic system caused formation of olefin byproducts via β-elimination of the alkyl halide (e.g., 1-octene and its isomers from *n*-octyl halide), control experiments showed that a terminal olefin is much less reactive than a primary alkyl halide (eq 2), and that a cyclic olefin is entirely unreactive (eq 3). Thus, olefins would not be involved in the major productive pathway of the present reaction.



The absence of cyclopentylmethylated product in the reaction of 6-bromo-1-hexene (Table 2, entry 5) may be interpreted as a consequence of faster recombination of the 5-hexenyl radical with the cobalt center than its 5-*exo*-*trig* cyclization.[17] The failure of cyclopropylmethylation (Table 2, entry 16) may be explained by rapid ring opening of a cyclopropylmethyl radical (which is much faster than cyclization of the 5-hexenyl radical),[18] while the reason for the further complication of the reaction (i.e., absence of homoallylation product) is not clear at present.

The scope of aromatic imines was explored using cycloalkyl chloride or bromide as the alkylating agent (Table 4). Imines bearing methoxy, fluoro, chloro, and phenyl substituents at the *para*-position afforded the products **3**–**6** in moderate to good yields, while a bromo-substituted analogue afforded a complex mixture of products arising from *ortho*-alkylation and cross-coupling on the C–Br bond. Alkylation of *meta*-tolyl, 2-naphthyl, and 3-fluorenyl imines took place exclusively at the less hindered position (see products **7**–**9**), with tolerance of the acidic C9-H site in the latter case. On the other hand, a methylenedioxy group at the 3,4-position directed the reaction to take place preferentially at the proximal position, affording the product **10** and its regioisomer **10'** in a ratio of 84:16. Imines derived from tetralone and propiophenone afforded the products **11** and **12** in good yields. Cyclohexylation of the C2 position of thiophene and indole rings was also achieved, albeit in modest yields (see products **13** and **14**).

Table 4. Products of Cycloalkylation of Different Imines[a]

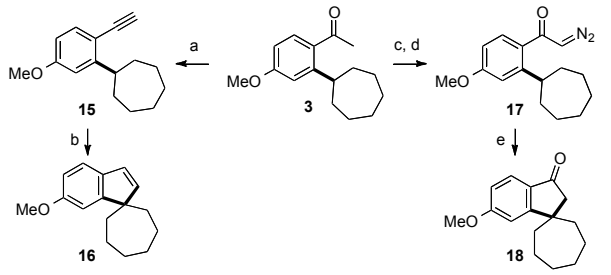


[a] The product was obtained after acidic hydrolysis of the reaction of PMP imine (0.3 mmol) under the standard conditions for 24 h. The leaving group and the ligand used are indicated for each case. [b] The reaction time was 6 h. [c] An additional 1 equiv of *t*$BuCH_2MgBr$ was added at the reaction time of 2, 4, or 5 h. [d] 2

equiv of alkyl halide was used. [e] Obtained as a mixture with a regioisomer **10'** in a ratio of 84:16.

Further manipulation of the directing group and the newly introduced cycloalkyl group allows construction of unique benzo-fused spirocycles (Scheme 2). Conversion of the acetyl group of **3** to an ethynyl group was followed by platinum-catalyzed carbocyclization[19] to afford indene **16** in a moderate yield. In another example, diazo transfer to the acetyl group of **3** and subsequent rhodium-catalyzed intramolecular C–H insertion furnished indenone **18** in 27% overall yield (unoptimized).

Scheme 2. Transformation of *ortho*-Cycloalkylation Product to Spirocycles[a]



[a] Reaction conditions: a) LDA, $ClP(O)(OEt)_2$, THF, –78 °C to rt, then LDA, –78 °C to rt, 56%; b) $PtCl_2$, CuBr, toluene, 100 °C, 77%; c) LiHMDS, THF, –78 °C, then $CF_3CO_2CH_2CF_3$, –78 °C to rt; d) 4-acetamidobenzenesulfonyl azide, H_2O, Et_3N, MeCN, rt, 75% (two steps); e) $Rh_2(OAc)_4$, CH_2Cl_2, rt, 36%.

In summary, we have developed a cobalt–NHC-catalyzed *ortho*-alkylation reaction of aromatic imines with a broad range of primary and secondary alkyl chlorides and bromides under mild room-temperature conditions. It may be noted that the present reaction and the cobalt-catalyzed aryl–alkyl cross-coupling reaction are markedly different with respect to the scope of alkyl halides, the latter being applicable to alkyl iodides and bromides but not to alkyl chlorides,[15,16] while these reactions appear to share the feature of a single-electron transfer from a cobalt species to alkyl halide. The proposed radical process will be further investigated from mechanistic and synthetic points of view.

ASSOCIATED CONTENT

Supporting Information. Detailed experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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REFERENCES

(1) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529.

(2) For recent reviews, see: (a) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013. (b) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (c) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315. (d) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879.

(3) For recent examples, see: (a) Kakiuchi, F.; Kochi, T.; Mizushima, E.; Murai, S. *J. Am. Chem. Soc.* **2010**, *132*, 17741. (b) Ilies, L.; Chen, Q.; Zeng, X.; Nakamura, E. *J. Am. Chem. Soc.* **2011**, *133*, 5221. (c) Gao, K.; Yoshikai, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 6888. (d) Schinkel, M.; Marek, I.; Ackermann, L. *Angew. Chem., Int. Ed.* **2013**, *52*, 3977. (e) Rouquet, G.; Chatani, N. *Chem. Sci.* **2013**, *4*, 2201.

(4) Branched-selective reaction with styrene derivatives: (a) Uchimaru, Y. *Chem. Commun.* **1999**, 1133. (b) Gao, K.; Yoshikai, N. *J. Am. Chem. Soc.* **2011**, *133*, 400. (c) Pan, S.; Ryu, N.; Shibata, T. *J. Am. Chem. Soc.* **2012**, *134*, 17474. (d) Lee, P.-S.; Yoshikai, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 1240.

(5) Reaction of phenol and anisole derivatives with alkyl olefins: (a) Lewis, L. N.; Smith, J. F. *J. Am. Chem. Soc.* **1986**, *108*, 2728. (b) Dorta, R.; Togni, A. *Chem. Commun.* **2003**, 760. (c) Kuninobu, Y.; Matsuki, T.; Takai, K. *J. Am. Chem. Soc.* **2009**, *131*, 9914. (d) Oyamada, J.; Hou, Z. *Angew. Chem., Int. Ed.* **2012**, *51*, 12828.

(6) Ackermann, L. *Chem. Commun.* **2010**, *46*, 4866.

(7) (a) Ackermann, L.; Novak, P.; Vicente, R.; Hofmann, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 6045. (b) Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 6097. (c) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965. (d) Chen, Q.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2011**, *133*, 428. (e) Ackermann, L.; Hofmann, N.; Vicente, R. *Org. Lett.* **2011**, *13*, 1875. (f) Zhao, Y. S.; Chen, G. *Org. Lett.* **2011**, *13*, 4850. (g) Aihara, Y.; Chatani, N. *J. Am. Chem. Soc.* **2013**, *135*, 5308.

(8) For examples of non-directed alkylation of heteroarenes with secondary alkyl halides, see: (a) Xiao, B.; Liu, Z.-J.; Liu, L.; Fu, Y. *J. Am. Chem. Soc.* **2013**, *135*, 616. (b) Ren, P.; Salihu, I.; Scopelliti, R.; Hu, X. *Org. Lett.* **2012**, *14*, 1748.

(9) For *meta*-selective alkylation with secondary alkyl halides through cyclometalation process: Hofmann, N.; Ackermann, L. *J. Am. Chem. Soc.* **2013**, *135*, 5877.

(10) For *ortho*-alkylations using different sources of secondary alkyl groups, see: (a) Lee, D. H.; Kwon, K. H.; Yi, C. S. *J. Am. Chem. Soc.* **2012**, *134*, 7325. (b) Deng, G. J.; Zhao, L.; Li, C. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 6278.

(11) Gao, K.; Yoshikai, N. *Chem. Commun.* **2012**, *48*, 4305.

(12) (a) Gao, K.; Lee, P. S.; Long, C.; Yoshikai, N. *Org. Lett.* **2012**, *14*, 4234. See also: (b) Song, W.; Ackermann, L. *Angew. Chem., Int. Ed.* **2012**, *51*, 8251.

(13) Kobayashi, T.; Yorimitsu, H.; Oshima, K. *Chem. Asian J.* **2009**, *4*, 1078.

(14) When the yield was poor, we typically observed recovery of a large part of the imine and decomposition of the alkyl halide to olefins.

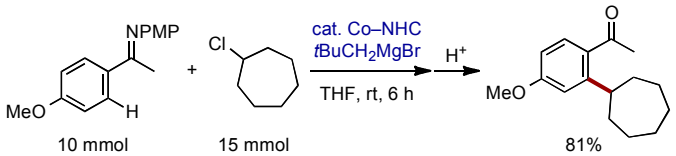
(15) (a) Ohmiya, H.; Wakabayashi, K.; Yorimitsu, H.; Oshima, K. *Tetrahedron* **2006**, *62*, 2207. (b) Ohmiya, H.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2006**, *128*, 1886.

(16) Cahiez, G.; Moyeux, A. *Chem. Rev.* **2010**, *110*, 1435.

(17) Even in cross-coupling reactions proposed to involve radical mechanisms, the fate of this radical probe depends on each case. For examples, see: (a) Wakabayashi, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2001**, *123*, 5374. (b) Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 3686. (c) Bedford, R. B.; Bruce, D. W.; Frost, R. M.; Hird, M. *Chem. Commun.* **2005**, 4161. (d) Bedford, R. B.; Betham, M.; Bruce, D. W.; Davis, S. A.; Frost, R. M.; Hird, M. *Chem. Commun.* **2006**, 1398. (e) Yasuda, S.; Yorimitsu, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 287. (f) Vechorkin, O.; Proust, V.; Hu, X. *J. Am. Chem. Soc.* **2009**, *131*, 9756.

(18) For examples of cross-couplings involving ring opening of this probe, see ref 17c,d,f and the following: Fürstner, A.; Martin, R.; Krause, H.; Seidel, G.; Goddard, R.; Lehmann, C. W. *J. Am. Chem. Soc.* **2008**, *130*, 8773.

(19) Yang, S.; Li, Z.; Han, X.; He, C. *Angew. Chem., Int. Ed.* **2009**, *48*, 3999.


NPMP
MeO
H
Cl
cat. Co–NHC
tBuCH2MgBr
THF, rt, 6 h
H+
O
MeO
10 mmol
15 mmol
81%