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Cobalt-Catalyzed Directed Alkylation of Olefinic C–H Bond with Primary and Secondary Alkyl Chlorides

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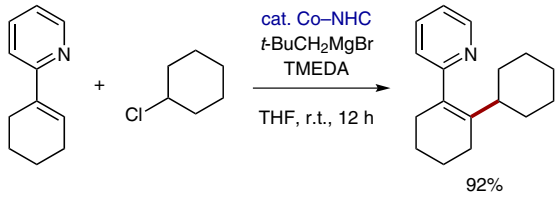

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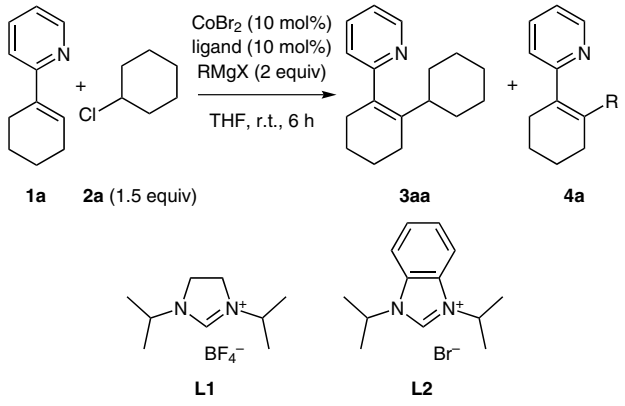
Abstract A cobalt–N-heterocyclic carbene catalytic system promotes pyridine-directed olefinic C–H alkylation reactions using a variety of primary and secondary alkyl chlorides under mild conditions. Radical clock experiments suggest that the reaction involves single-electron transfer from the cobalt intermediate to the alkyl chloride.

Key words cobalt, C–H activation, alkylations, alkyl halides, alkenes

Transition-metal-catalyzed, directing-group-assisted alkylation of aromatic compounds with alkyl halides allows the introduction of a variety of alkyl groups into the aromatic ring with predictable regioselectivity,[1] and thus serves as a complementary tool to the classical Friedel–Crafts alkylation as well as transition-metal-catalyzed C–H alkylation through hydroarylation of alkenes.[2] Over the past several years, a significant progress has been made for this type of reaction with the development of catalytic systems based on ruthenium,[3] palladium,[4] nickel,[5] cobalt,[6] and iron.[7] Analogous alkylation on an olefinic substrate is also conceivable and appears attractive for the stereoselective synthesis of multisubstituted olefins. Thus far, such reactions have been achieved only for acrylamide derivatives bearing a bidentate 8-aminoquinoline directing group under nickel or iron catalysis.[5a,7a,c] As a part of our continuing research on cobalt-catalyzed C–H functionalization reactions,[8] we report here that olefinic C–H alkylation of a 2-alkenylpyridine derivative can be achieved using primary and secondary alkyl chlorides with the aid of a cobalt–N-heterocyclic carbene (NHC) catalyst and a neopentyl Grignard reagent.[9,10]

We recently developed cobalt–NHC catalytic systems that allow *ortho*-alkylation of aryl imines and 2-arylpyridines with primary and secondary alkyl halides, identifying 1,3-diisopropyl-2,5-dihydro-1*H*-imidazol-3-ium tetrafluoroborate (**L1**) and its benzo-fused analogue **L2** as effective NHC preligands.[6a,c] The present study began with an attempt to apply these catalytic systems to the reaction of 2-(cyclohex-1-en-1-yl)pyridine (**1a**) and chlorocyclohexane (**2a**). The catalytic system consisting of $CoBr_2$ (10 mol%), **L1** (10 mol%), and neopentylmagnesium bromide (2 equiv) promoted the desired reaction to afford the cyclohexylation product **3aa** in a moderate yield of 63%, along with a small amount of a byproduct **4a** arising from vinylic C–H alkylation with the Grignard reagent (Table 1, entry 1). The use of **L2** instead of **L1** gave a comparable result, while the formation of **4a** was slightly suppressed (Table 1, entry 2). Popular NHC precursors such as 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride (IMes·HCl) and 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (IPr·HCl) exhibited much poorer performances (Table 1, entries 3 and 4).

Table 1 Optimization of Reaction Conditions[a]



Entry	Ligand	RMgX	**3aa** (%)[b]	**4a** (%)[b]
1	**L1**	*t*-BuCH$_2$MgBr	63	6
2	**L2**	*t*-BuCH$_2$MgBr	65	2
3	IMes·HCl	*t*-BuCH$_2$MgBr	12	2
4	IPr·HCl	*t*-BuCH$_2$MgBr	23	9
5	**L2**	Me$_3$SiCH$_2$MgCl	14	9
6	**L2**	*n*-BuMgBr	21	26

Table 1 (continued)

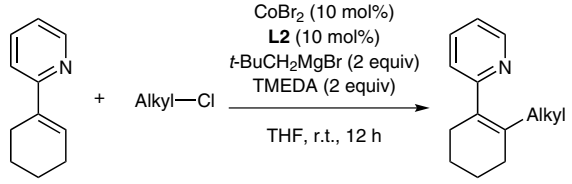
Entry	Ligand	RMgX	**3aa** (%)[b]	**4a** (%)[b]
7	**L2**	*i*-PrMgBr	1	29
8	**L2**	CyMgCl	1	–
9[c]	**L2**	*t*-BuCH$_2$MgBr	85	4
10[c,d]	**L2**	*t*-BuCH$_2$MgBr	73	4
11[c,e]	**L2**	*t*-BuCH$_2$MgBr	7	1
12[c,f]	**L2**	*t*-BuCH$_2$MgBr	39	2

[a] The reaction was performed on a 0.3 mmol scale.
[b] Determined by GC using *n*-tridecane as an internal standard.
[c] TMEDA (2 equiv) was added.
[d] The loadings of CoBr$_2$ and **L2** were reduced to 5 mol%.
[e] The reaction was performed at 0 °C.
[f] Bromocyclohexane was used instead of **2a**.

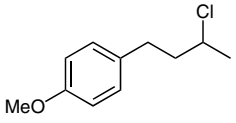
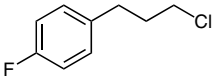
Using **L2**, we further examined other reaction parameters. Replacement of neopentylmagnesium bromide with other primary or secondary Grignard reagent resulted in a diminished yield of **3aa** (Table 1, entries 5–8), while in some cases substantial formation of the undesirable alkylation product **4a** was observed (Table 1, entries 6 and 7). The addition of TMEDA (2 equiv) considerably improved the efficiency of the reaction, thus affording **3aa** in 85% yield (Table 1, entry 9).[11] With TMEDA as the additive, the catalyst loading could be reduced to 5 mol% albeit with a decrease in the product yield by ca. 10% (Table 1, entry 10), while the reaction became markedly sluggish at 0 °C (Table 1, entry 11). Note that the use of bromocyclohexane instead of **2a** afforded **3aa** in only 39% yield (Table 1, entry 12).

With the optimized conditions (Table 1, entry 9) in hand, we explored the scope of the vinylic C–H alkylation reaction. We first examined the reaction of **1a** with various alkyl chlorides (Table 2). Cycloalkyl chlorides of various ring sizes smoothly participated in the reaction to afford the corresponding products **3aa**–**3ad** in good to excellent yields (entries 1–4). The reaction of isopropyl chloride was efficiently achieved at 40 °C with a high ratio of the isopropylation product to the *n*-propylation product (entry 5). A (3-chlorobutyl)benzene derivative **2f** was also amenable to the present reaction, while the ratio of the secondary to primary isomers degraded slightly (entry 6). The reactions using primary alkyl chlorides such as *n*-butyl, *n*-octyl, and phenethyl chlorides proceeded at room temperature to afford the desired products **3ag**–**3aj** in moderate to good yields (entries 7–10). Note that the reaction of phenethyl chloride was accompanied by the formation of a minor amount of the branched isomer (entry 9). The reaction of neopentyl chloride required an elevated temperature of 60 °C, presumably due to the steric hindrance at the β-position (entry 11).

Table 2 Alkylation of **1a** with Various Alkyl Chlorides[a]



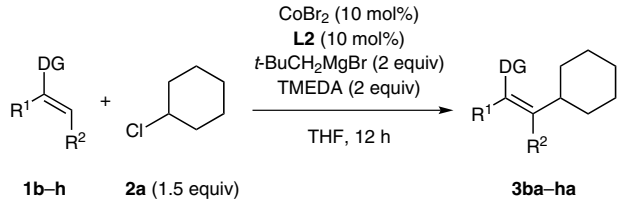
1a **2a–k** (1.5 equiv) **3aa–ak**

Entry	Alkyl chloride		Product	Yield (%)[b]
1	**2a**	*c*-C$_6$H$_{11}$Cl	**3aa**	92
2	**2b**	*c*-C$_4$H$_7$Cl	**3ab**	76
3	**2c**	*c*-C$_5$H$_9$Cl	**3ac**	90
4[c]	**2d**	*c*-C$_7$H$_{13}$Cl	**3ad**	93
5[d]	**2e**	*i*-C$_3$H$_7$Cl	**3ae** (*i*/*n* = 97:3)[e]	85
6	**2f**		**3af** (*i*/*n* = 91:9)[e]	86
7	**2g**	*n*-C$_4$H$_9$Cl	**3ag**	81
8	**2h**	*n*-C$_8$H$_{17}$Cl	**3ah**	85
9	**2i**	Ph(CH$_2$)$_2$Cl	**3ai** (*i*/*n* = 5:95)[e]	70
10	**2j**		**3aj**	65
11[f]	**2k**	*t*-BuCH$_2$Cl	**3ak**	72

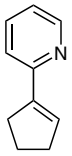
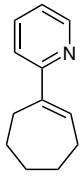
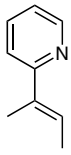
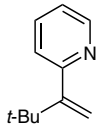
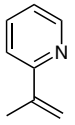
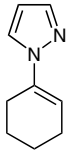
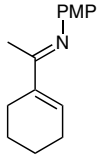
[a] The reaction was performed on a 0.3 mmol scale.
[b] Isolated yield.
[c] Alkyl chloride (2 equiv) and *t*-BuCH$_2$MgBr (2.5 equiv) were used.
[d] The reaction was performed at 40 °C.
[e] The ratio of the secondary and primary alkylation products.
[f] The reaction was performed at 60 °C.

Next, different olefinic substrates were subjected to the reaction with **2a** (Table 3). Five- and seven-membered cyclic 2-alkenylpyridines **1b** and **1c** afforded the corresponding tetrasubstituted olefins **3ba** and **3ca**, respectively, in good yields (entries 1 and 2). Analogous acyclic 2-alkenylpyridine **1d** also participated in the reaction to afford the product **3da** in a modest yield of 41% (entry 3). The reaction of 2-alkenylpyridine **1e** bearing a *tert*-butyl group at the α-position took place at 60 °C with moderate efficiency (entry 4). With a methyl group instead of the *tert*-butyl group at the α-position, the reaction became complicated and afforded an intractable mixture, in which the desired product was not detected (entry 5). A pyrazolyl group proved to serve as a directing group for the present reaction, albeit with low efficiency (entry 6). Unfortunately, α,β-unsaturated imines, even with a geometrically favorable cyclohexenyl skeleton (**1h**), failed to participate in the reaction (entry 7).

Table 3 Reaction of Different Olefins with **2a**[a]

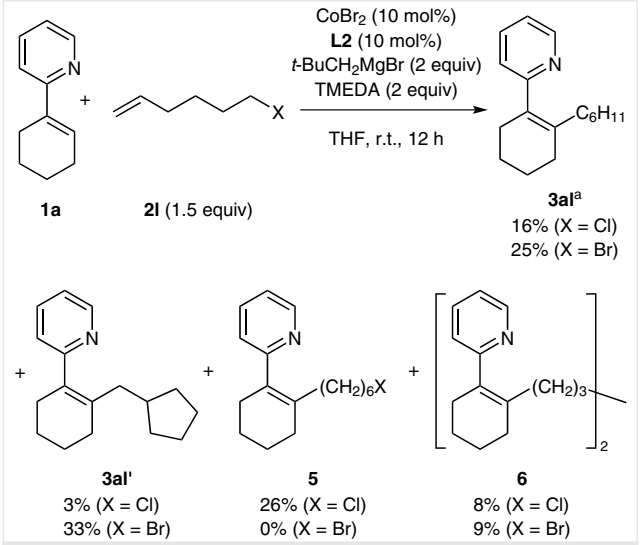


1b–h **2a** (1.5 equiv) **3ba–ha**

Entry	Olefin	Temp (°C)	Product	Yield (%)[b]
1	**1b** 	40	**3ba**	77[c]
2	**1c** 	40	**3ca**	68[c]
3	**1d** 	r.t.	**3da**	41[c]
4	**1e** 	60	**3ea**	46
5	**1f** 	r.t.	**3fa**	N.D.
6[d]	**1g** 	60	**3ga**	7
7	**1h** 	60	**3ha**	N.D.

[a] The reaction was performed on a 0.3 mmol scale.
[b] Isolated yield.
[c] The product was obtained as a mixture with the C–H neopentylation product.
[d] With 4.5 equiv of **2a** and 5 equiv of *t*-BuCH$_2$MgBr.

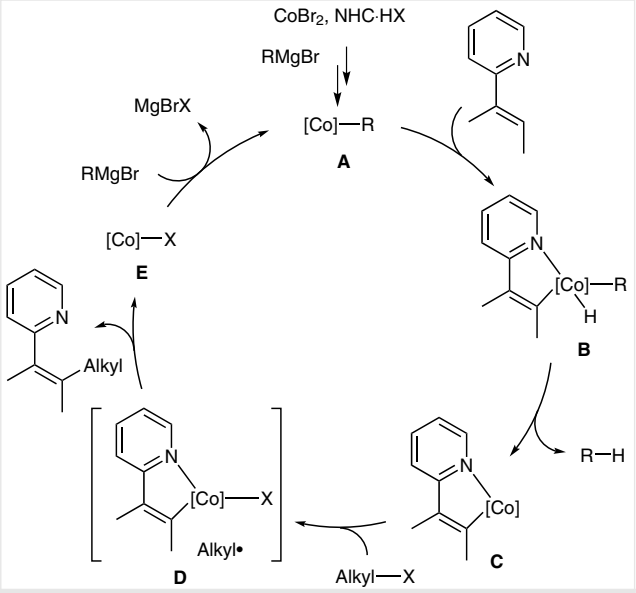
With several lines of evidence, including results of radical clock experiments, we previously proposed that the cobalt–NHC-catalyzed *ortho*-alkylation of an aryl imine with an alkyl halide involves single-electron transfer from the cobalt center to the alkyl halide to generate the alkyl radical.[6a,c] To examine whether the present reaction also proceeds through a similar process, we performed radical clock experiments using **1a** and 6-halohex-1-ene (**2l**) as the substrates (Scheme 1). The reaction of **1a** with 6-chlorohex-1-ene afforded the expected direct alkylation product **3al** and the ring-closing alkylation product **3al′** in 16% and 3% yields, respectively, along with another two alkylation products **5** (26%) and **6** (9%). The product **5** appears to have been formed through the insertion of the C=C double bond of **2l** into the vinylic C–H bond of **1a**, with the C–Cl bond untouched. Participation of both the C–Cl and C=C bond of **2l** in the vinylic C–H functionalization should have resulted in the dimeric product **6**. The distribution of the four products was very different when 6-bromohex-1-ene was used instead of the corresponding chloride. The reaction afforded a near equimolar mixture of **3al** and **3al′** in an overall yield of 58%. The olefin insertion product **5** was not detected, while the formation of a minor amount of the double alkylation product **6** was observed.



Scheme 1 Radical clock experiments. The yields were estimated by GC using *n*-tridecane as an internal standard. The reaction also afforded C–H neopentylation product (9%). [a] Obtained as a mixture of four or five different isomers. The position of the double bond of each isomer was not determined.

With the above observations, we suggest that the present reaction features a catalytic cycle similar to that proposed for the *ortho*-alkylation (Scheme 2). An organocobalt species **A** generated from the cobalt precatalyst and the Grignard reagent undergoes cyclometalation of 2-alkenyl-

pyridine through vinylic C–H oxidative addition and reductive elimination of alkane R–H to give a cobaltacycle **C**.[12] Single-electron transfer from the intermediate **C** to the alkyl halide is followed by the coupling of the resulting alkenylcobalt species and alkyl radical (**D**),[13] thus affording the alkylation product.[14,15] Transmetalation of the cobalt halide **E** and the Grignard reagent regenerates the initial species **A**. In light of the ratio of **3al** and **3al′** (Scheme 1), the C–C bond formation would occur at a relatively fast rate. The putative C–H oxidative addition intermediate **B** may be responsible for the formation of the olefin insertion products **5** and **6**.



Scheme 2 Proposed catalytic cycle

In summary, we have demonstrated that the cobalt–NHC catalytic system is capable of promoting olefinic C–H alkylation with primary and secondary alkyl chlorides, presumably through single-electron transfer as one of the key steps.[16] The present study has also indicated the potential of cobalt catalysis for olefinic C–H alkylation through the insertion of simple olefins.[17]

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1379247.

References and Notes

(1) Ackermann, L. *Chem. Commun.* **2010**, *46*, 4866.
(2) For selected 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) Ackermann, L.; Novák, P.; Vicente, R.; Hofmann, N. *Angew. Chem. Int. Ed.* **2009**, *48*, 6045.
(4) (a) Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2009**, *48*, 6097. (b) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965. (c) Zhao, Y.-S.; Chen, G. *Org. Lett.* **2011**, *13*, 4850.
(5) (a) Aihara, Y.; Chatani, N. *J. Am. Chem. Soc.* **2013**, *135*, 5308. (b) Song, W.; Lackner, S.; Ackermann, L. *Angew. Chem. Int. Ed.* **2014**, *53*, 2477.
(6) (a) Gao, K.; Yoshikai, N. *J. Am. Chem. Soc.* **2013**, *135*, 9279. (b) Punji, B.; Song, W. F.; Shevchenko, G. A.; Ackermann, L. *Chem. Eur. J.* **2013**, *19*, 10605. (c) Gao, K.; Yamakawa, T.; Yoshikai, N. *Synthesis* **2014**, *46*, 2024.
(7) (a) Ilies, L.; Matsubara, T.; Ichikawa, S.; Asako, S.; Nakamura, E. *J. Am. Chem. Soc.* **2014**, *136*, 13126. (b) Fruchey, E. R.; Monks, B. M.; Cook, S. P. *J. Am. Chem. Soc.* **2014**, *136*, 13130. (c) Monks, B. M.; Fruchey, E. R.; Cook, S. P. *Angew. Chem. Int. Ed.* **2014**, *53*, 11065.
(8) Gao, K.; Yoshikai, N. *Acc. Chem. Res.* **2014**, *47*, 1208.
(9) For an example of cobalt-catalyzed olefinic C–H functionalization, see: Yamakawa, T.; Yoshikai, N. *Org. Lett.* **2013**, *15*, 196.
(10) For examples of other types of olefinic C–H functionalization of 2-alkenylpyridines, see: (a) Oi, S.; Sakai, K.; Inoue, Y. *Org. Lett.* **2005**, *7*, 4009. (b) Ackermann, L.; Born, R.; Alvarez-Bercedo, P. *Angew. Chem. Int. Ed.* **2007**, *46*, 6364. (c) Kuninobu, Y.; Fujii, Y.; Matsuki, T.; Nishina, Y.; Takai, K. *Org. Lett.* **2009**, *11*, 2711. (d) Ilies, L.; Asako, S.; Nakamura, E. *J. Am. Chem. Soc.* **2011**, *133*, 7672. (e) Li, Y.; Zhang, X.-S.; Zhu, Q.-L.; Shi, Z.-J. *Org. Lett.* **2012**, *14*, 4498.
(11) (a) Li, B.; Wu, Z.-H.; Gu, Y.-F.; Sun, C.-L.; Wang, B.-Q.; Shi, Z.-J. *Angew. Chem. Int. Ed.* **2011**, *50*, 1109. (b) Yamakawa, T.; Yoshikai, N. *Chem. Asian J.* **2014**, *9*, 1242.
(12) Klein, H.-F.; Camadanli, S.; Beck, R.; Leukel, D.; Flörke, U. *Angew. Chem. Int. Ed.* **2005**, *44*, 975.
(13) Wakabayashi, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2001**, *123*, 5374.
(14) (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. (c) Cahiez, G.; Chaboche, C.; Duplais, C.; Moyeux, A. *Org. Lett.* **2009**, *11*, 277.
(15) For reviews on cobalt-catalyzed cross-coupling reactions, see: (a) Cahiez, G.; Moyeux, A. *Chem. Rev.* **2010**, *110*, 1435. (b) Hess, W.; Treutwein, J.; Hilt, G. *Synthesis* **2008**, 3537. (c) Gosmini, C.; Begouin, J. M.; Moncomble, A. *Chem. Commun.* **2008**, 3221. (d) Yorimitsu, H.; Oshima, K. *Pure Appl. Chem.* **2006**, *78*, 441.
(16) **General Procedure for 2-{[1,1′-Bi(cyclohexan)]-1-en-2-yl}pyridine (3aa)**: In a 10-mL Schlenk tube were placed $CoBr_2$ (0.3 M in THF, 0.10 mL, 0.030 mmol), 1,3-diisopropylbenzimidazolium bromide (**L2**; 8.5 mg, 0.030 mmol), 2-(cyclohex-1-en-1-yl)pyridine (**1a**; 47.8 mg, 0.30 mmol), chlorocyclohexane (**2a**; 53.6 µL, 0.45 mmol), TMEDA (90 µL, 0.60 mmol) and THF (0.28 mL). To the mixture was added a THF solution of *t*-BuCH_2MgBr (0.96 M, 0.63 mL, 0.60 mmol) dropwise at 0 °C. The reaction mixture was stirred at r.t. for 6 h, and then quenched by the addition H_2O (1.0 mL). The resulting mixture was extracted with EtOAc (3 × 3 mL). The combined organic layer was dried

over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (eluent: hexane–EtOAc, 100:12) to afford a mixture of **3aa** and 2-(2-neopentylcyclohex-1-en-1-yl)pyridine in a ratio of 30:1 (determined by ^{1}H NMR) as a yellow solid (69.2 mg, 92% yield for **3aa**). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.00–1.09 (m, 3 H), 1.27–1.37 (m, 2 H), 1.48–1.55 (m, 3 H), 1.62–1.74 (m, 6 H), 2.05–2.12 (m, 3 H), 2.30–2.33 (m, 2 H), 7.09–7.11 (m, 2 H), 7.58–7.63 (m, 1 H), 8.56–8.60 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.2, 23.3, 24.5, 26.3, 26.6 (2 × C), 31.0, 31.2 (2 × C), 42.1, 121.0, 123.4, 131.2, 136.0, 140.0, 149.5, 162.9. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{24}N$: 242.1909; found: 242.1908.

(17) (a) Ilies, L.; Chen, Q.; Zeng, X.; Nakamura, E. *J. Am. Chem. Soc.* **2011**, *133*, 5221. (b) Gao, K.; Yoshikai, N. *J. Am. Chem. Soc.* **2011**, *133*, 400. (c) Gao, K.; Yoshikai, N. *Angew. Chem. Int. Ed.* **2011**, *50*, 6888. (d) Lee, P.-S.; Yoshikai, N. *Angew. Chem. Int. Ed.* **2013**, *52*, 1240.

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