Organic LETTERS

Letter

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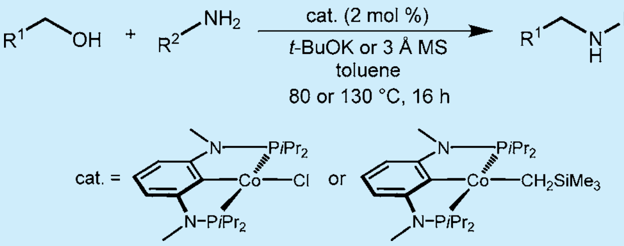
Co(II) PCP Pincer Complexes as Catalysts for the Alkylation of Aromatic Amines with Primary Alcohols

Matthias Mastalir,[†] Gerald Tomsu,[†] Ernst Pittenauer,[‡] Günter Allmaier,[‡] and Karl Kirchner*[,†]

[†]Institute of Applied Synthetic Chemistry and [‡]Institute of Chemical Technologies and Analytics, Vienna University of Technology, Getreidemarkt 9/163-AC, A-1060 Wien, Austria

Supporting Information

ABSTRACT: Efficient alkylations of amines by alcohols catalyzed by well-defined Co(II) complexes are described that are stabilized by a PCP ligand (*N*,*N*′-bis(diisopropylphosphino)-*N*,*N*′-dimethyl-1,3-diaminobenzene) based on the 1,3-diaminobenzene scaffold. This reaction is an environmentally benign process implementing inexpensive, earth-abundant nonprecious metal catalysts and is based on the acceptorless alcohol dehydrogenation concept. A range of primary alcohols and aromatic amines were efficiently converted into mono-*N*-alkylated amines in good to excellent isolated yields.



The catalytic alkylation of amines with alcohols represents an environmentally benign and atom-economic pathway for the synthesis of substituted imines or amines that have important synthetic applications in the synthesis of dyes, fragrances, fungicides, pharmaceuticals, and agricultural chemicals.[1−3] In terms of sustainability, the choice of alcohols as substrates is highly desirable as they are readily available by a variety of industrial processes and can be obtained renewably via fermentation or catalytic conversion of lignocellulosic biomass.[4] The catalytic cycle involves two or three successive steps: (i) acceptorless dehydrogenation (AD) of alcohols,[5] (ii) imine formation, and (iii) in situ hydrogenation of imines (borrowing hydrogen methodology). Key features are that the process is hydrogen neutral and that the only stoichiometric byproduct is water.

Despite the significance of such coupling reactions, homogeneous catalysts mostly employ precious metals such as Ru,[6] Rh,[7] Ir,[8] and Os.[9] In comparison, the same reaction with catalysts that utilize nonprecious, earth-abundant metals[10] is much less developed, although base metals were found to readily oxidize alcohols via AD.[11,12] Kempe and co-workers described for the first time new Co PNP pincer catalysts based on a triazine backbone that was highly active for the alkylation of aromatic amines (Figure 1).[13] This compound was particularly interesting since in the course of the catalytic reaction species with deprotonated, i.e., anionic, triazines seem to play a key role. Hanson[14a] and Zhang[14b] reported a Co catalyst, stabilized by a bis(phosphino)amine (PNP) ligand (Figure 1), which is able to afford imines and/or amines depending on the reaction conditions. The groups of Feringa and Barta,[15a] Wills,[15b] and Zhao[15c] reported the alkylation of amines with alcohols to give amines by utilizing Fe catalysts featuring functionalized cyclopentadienone or hydroxy cyclopentadienyl ligands based upon Knölker's complex or derivatives thereof.[16]

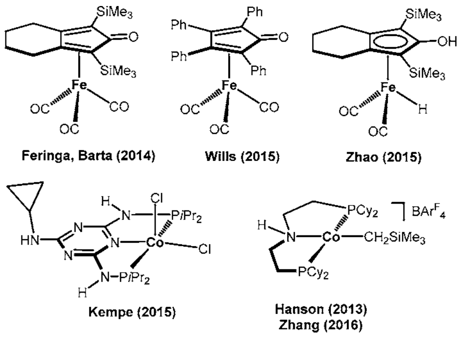


Figure 1. Efficient base metal catalysts for the alkylation of amines with alcohols.

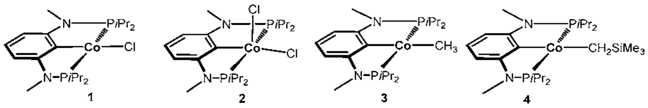


Figure 2. Co(II) and Co(III) PCP pincer complexes tested as catalysts.

Inspired by recent discoveries, we describe here the efficient alkylation of amines with alcohols catalyzed by Co(II) complexes which are stabilized by an anionic PCP ligand based on the 1,3-diaminobenzene scaffold (Figure 2).[17] It has to be noted that Co PCP complexes have as yet not been applied in catalysis.[18]

Co complexes **1** and **2** were screened for the alkylation of aniline with benzyl alcohol (1.4 equiv) in toluene (4 mL) at 80 °C with *t*-BuOK (1.3 equiv) as the additive. Complexes **3** and **4**

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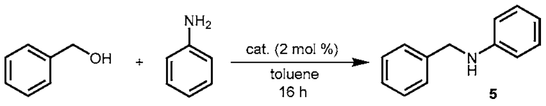
Table 1. Catalyst Screening of the Alkylation of Aniline with Benzyl Alcohol



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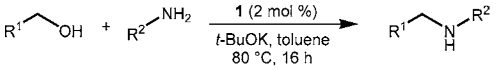
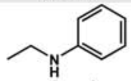
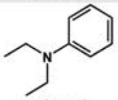
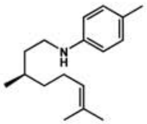
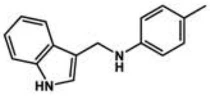
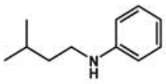
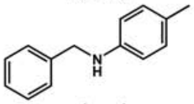
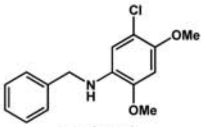
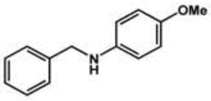
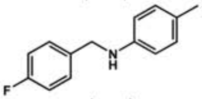
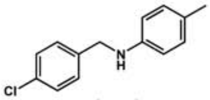
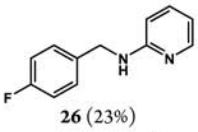
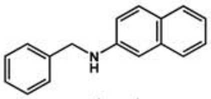
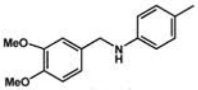
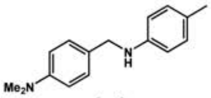
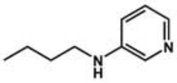
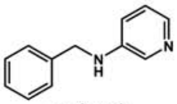
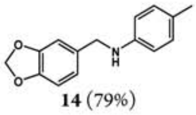
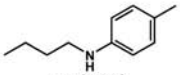
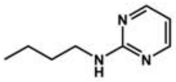
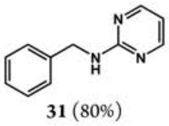
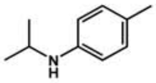
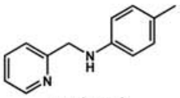
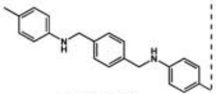
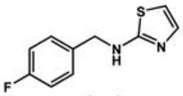
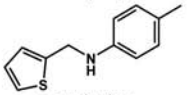
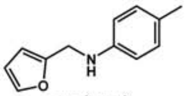
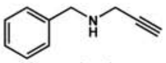
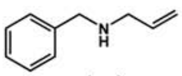
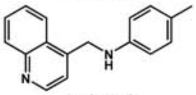
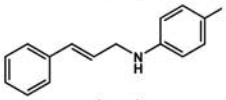
entry	cat.	temp (°C)	additive	yield[a] (%)
1	**1**	80	*t*-BuOK	93
2	**1**[b]	80	*t*-BuOK	84
3[c]	**1**	80	*t*-BuOK	79
4[d]	**1**	80	*t*-BuOK	65
5	**2**	80	*t*-BuOK	30[e]
6	**3**	130	3 Å MS	74
7	**3**	130	none	15
8	**4**	130	3 Å MS	94
9	**4**	130	none	22

[a] Isolated yields. [b] 1 mol % of catalyst. [c] 8 h. [d] 4 h. [e] 59% imine.

bearing the strongly basic coligands Me and CH_2SiMe_3 were studied under base-free conditions with the same substrates but with added 3 Å (0.2 g) molecular sieves (MS) in toluene (4 mL). For this methodology, higher reaction temperatures (130 °C) were required. All reactions were performed in a closed vial. The results are summarized in Table 1. The products were analyzed by ^{1}H and $^{13}C\{^{1}H\}$ NMR and ESI MS and identified by comparison with authentic samples. All new products were additionally analyzed by HRMS. In general, isolated yields after purification by column chromatography are reported. When **1** (2.0 mol % based on alcohol) was used as precatalyst, *N*-benzylaniline was isolated selectively after 16 h in 93% yield (Table 1, entry 1). Lower catalyst loading (1 mol %) or shorter reaction times (8 and 4 h) resulted in slightly lower yields (Table 1, entries 2–4). Co(III) precatalyst **2** exhibited poor catalytic activity and an in addition to amine formation, large amounts of the corresponding *N*-phenylmethylene benzeneimine were obtained (Table 1, entry 5). With **3** and **4**, in both cases *N*-benzylaniline was formed selectively, but the yield was

Table 2. Coupling of Primary Alcohols and Amines Catalyzed by 1[a]



entry	product (yield)	entry	product (yield)	entry	product (yield)	entry	product (yield)
1	 **6** (92%)	2	 **7** (10%)	17	 **22** (91%)	18	 **23** (79%)
3	 **8** (85%)	4	 **9** (94%)	19	 **24** (72%)	20	 **25** (90%)
5	 **10** (92%)	6	 **11** (72%)	21	 **26** (23%)	22	 **27** (93%)
7	 **12** (75%)	8	 **13** (87)%	23	 **28** (78%)	24	 **29** (84%)
9	 **14** (79%)	10	 **15** (89%)	25	 **30** (75%)	26	 **31** (80%)
11	 **16** (0%)	12	 **17** (17%)	27	 **32** (78%)	28	 **33** (0%)
13	 **18** (59)%	14	 **19** (67%)	29	 **34** (0%)	30	 **35** (0%)
15	 **20** (81%)	16	 **21** (91%)				

[a] Isolated yields.

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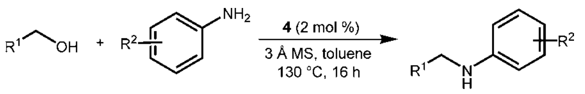
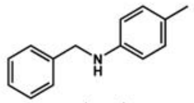
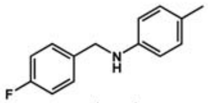
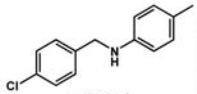
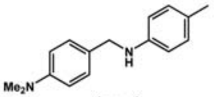
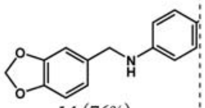
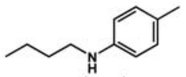
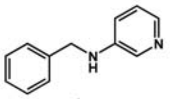
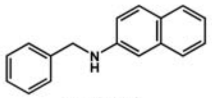
Table 3. Coupling of Primary Alcohols and Anilines Catalyzed by 4[a]



entry	product (yield)	entry	product (yield)
1	 **9** (90%)	2	 **10** (78%)
3	 **11** (66%)	4	 **13** (80%)
5	 **14** (76%)	6	 **15** (89%)
7	 **29** (73)%	8	 **27** (91%)

[a]Isolated yields.

significantly higher in the case of the latter (94%) (Table 1, entries 6 and 8). In the absence of MS, the yields were considerably lower (Table 1, entries 7 and 9).

Having established **1** and **4** as efficient catalysts, the two methodologies were applied to other substrates including substituted benzyl alcohols, aliphatic alcohols such as (*R*)-citronellol, EtOH, and *n*-BuOH as well as aromatic amines. These results are shown in Tables 2 and 3. In most cases, the resulting mono-*N*-alkylated amines were isolated in good to excellent yields. Exceptions are the reactions of 2-propanol with *p*-toluidine (Table 2, entry 7), *p*-fluorobenzylacohol with thiazol-2-amine (Table 2, entry 28), as well as benzyl acohol with allyl- and propargylamine (Table 2, entries 29 and 30) where no product was obtained at all. In the case of the latter, the low yield may be due to polymerization of the amines under these reaction conditions. With 2-pyridinemethanol and *p*-toluidine only 17% of product could be isolated (Table 2, entry 14). It has to be noted that in general dialkylated amines were not formed. This has been tested with EtOH (2.2 mmol), *t*-BuOK (2.6 mmol), and aniline (1.0 mmol) affording only 10% of the dialkylated aniline; the major product is the monoalkylated amine **6** (Table 2, entry 2).

In conclusion, we have reported two examples of efficient alkylations of amines with alcohols catalyzed by well-defined Co(II) complexes which are stabilized by an anionic PCP ligand based on the 1,3-diaminobenzene scaffold. The precatalysts are easily prepared from commercially available reagents in either one- or two-step procedures in high yields. These alkylation reactions are environmentally benign processes, implement inexpensive, earth-abundant nonprecious metal catalysts, and are based on the acceptorless alcohol dehydrogenation concept. A range of substituted benzyl alcohols and aliphatic alcohols ((*R*)-citronellol, EtOH, and *n*-BuOH) and aromatic amines were efficiently converted into mono-*N*-alkylated amines in good to excellent isolated yields. We believe that this work may contribute to the development of waste-free sustainable base metal catalysis.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01647.

Synthetic procedures; ^{1}H and ^{13}C{^{1}H} NMR spectra for all organic products (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: kkirch@mail.tuwien.ac.at.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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■ REFERENCES

(1) Guillena, G.; Ramon, D. J.; Yus, M. *Chem. Rev.* **2010**, *110*, 1611−1641.

(2) (a) *Pharmaceuticals: Classes, Therapeutic Agents, Areas of Application*; McGuire, J. L., Ed.; Wiley−VCH, 2000; Vols. *1*−*4*. (b) Rappoport, Z. J.; Liebman, F. *The Chemistry of Hydroxylamines, Oximes and Hydroxamic Acids*; Wiley: New York, 2009; p 609.

(3) (a) Lawrence, S. A. *Amine: Synthesis Properties and Applications*; Cambridge University: Cambridge, 2004. (b) Brown, B. R. *The Organic Chemistry of Aliphatic Nitrogen Compounds*; Cambridge University: Cambridge, 2004.

(4) Barta, K.; Ford, P. C. *Acc. Chem. Res.* **2014**, *47*, 1503−1512.

(5) (a) Yang, Q.; Wang, Q.; Yu, Z. *Chem. Soc. Rev.* **2015**, *44*, 2305−2329. (b) Zell, T.; Milstein, D. *Acc. Chem. Res.* **2015**, *48*, 1979−1994. (c) Obora, Y. *ACS Catal.* **2014**, *4*, 3972−3981. (d) Nandakumar, A.; Midya, S. P.; Landge, V. G.; Balaraman, E. *Angew. Chem., Int. Ed.* **2015**, *54*, 11022−11034. (e) Ketcham, J. M.; Shin, I.; Montgomery, T. P.; Krische, M. J. *Angew. Chem., Int. Ed.* **2014**, *53*, 9142−9150. (f) Gunanathan, C.; Milstein, D. *Science* **2013**, *341*, 249−260. (g) Pan, S.; Shibata, T. *ACS Catal.* **2013**, *3*, 704−712. (h) Bähn, S.; Imm, S.; Neubert, L.; Zhang, M.; Neumann, H.; Beller, M. *ChemCatChem* **2011**, *3*, 1853−1864. (i) Watson, A. J. A.; Williams, J. M. J. *Science* **2010**, *329*, 635−636. (j) Guillena, G.; Ramón, D. J.; Yus, M. *Chem. Rev.* **2010**, *110*, 1611−1641. (k) Dobereiner, G. E.; Crabtree, R. H. *Chem. Rev.* **2010**, *110*, 681−703. (l) Hamid, M. H. S. A.; Slatford, P. A.; Williams, J. M. J. *Adv. Synth. Catal.* **2007**, *349*, 1555−1575.

(6) For selected examples of Ru-catalyzed aminations of alcohols, see: (a) Hollmann, D.; Tillack, A.; Michalik, D.; Jackstell, R.; Beller, M. *Chem. - Asian J.* **2007**, *2*, 403−410. (b) Tillack, A.; Hollmann, D.; Mevius, K.; Michalik, D.; Bahn, S.; Beller, M. *Eur. J. Org. Chem.* **2008**, *2008*, 4745−4750. (c) Imm, S.; Bähn, S.; Neubert, L.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 8126−8129. (d) Zhang, M.; Imm, S.; Bähn, S.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 11197−11201. (e) Hamid, M. H. S. A.; Williams, J. M. J. *Chem. Commun.* **2007**, 725−727. (f) Hamid, M. H. S. A.; Williams, J. M. J. *Tetrahedron Lett.* **2007**, *48*, 8263−8265. (g) Hamid, M. H. S. A.; Allen, C. L.; Lamb, G. W.; Maxwell, A. C.; Maytum, H. C.; Watson, A. J. A.; Williams, J. M. J. *J. Am. Chem. Soc.* **2009**, *131*, 1766−1774. (h) Gunanathan, C.; Milstein, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 8661−8664. (i) Yamaguchi, K.; He, J.; Oishi, T.; Mizuno, N. *Chem. - Eur. J.* **2010**, *16*, 7199−7207. (j) Monrad, R. N.; Madsen, R. *Org.*

Biomol. Chem. **2011**, *9*, 610−615. (k) Marichev, K. O.; Takacs, J. M. *ACS Catal.* **2016**, *6*, 2205−2210.

(7) (a) Morton, D.; Cole-Hamilton, D. J. *J. Chem. Soc., Chem. Commun.* **1987**, *0*, 248−249. (b) Zweifel, T.; Naubron, J.-V.; Grützmacher, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 559−563.

(8) For selected examples of Ir-catalyzed aminations of alcohols, see: (a) Kawahara, R.; Fujita, K.; Yamaguchi, R. *J. Am. Chem. Soc.* **2010**, *132*, 15108−15111. (b) Kawahara, R.; Fujita, K.; Yamaguchi, R. *Adv. Synth. Catal.* **2011**, *353*, 1161−1168. (c) Prades, A.; Corberan, R.; Poyatos, M.; Peris, R. *Chem. - Eur. J.* **2008**, *14*, 11474−11479. (d) Blank, B.; Madalska, M.; Kempe, R. *Adv. Synth. Catal.* **2008**, *350*, 749−758. (e) Blank, B.; Michlik, S.; Kempe, R. *Adv. Synth. Catal.* **2009**, *351*, 2903−2911. (f) Blank, B.; Michlik, S.; Kempe, R. *Chem. - Eur. J.* **2009**, *15*, 3790−3799. (g) Michlik, S.; Kempe, R. *Chem. - Eur. J.* **2010**, *16*, 13193−13198. (h) Michlik, S.; Hille, T.; Kempe, R. *Adv. Synth. Catal.* **2012**, *354*, 847−862. (i) Gnanamgari, D.; Sauer, E. L. O.; Schley, N. D.; Butler, C.; Incarvito, C. D.; Crabtree, R. H. *Organometallics* **2009**, *28*, 321−325. (j) Saidi, O.; Blacker, A. J.; Farah, M. M.; Marsden, S. P.; Williams, J. M. J. *Chem. Commun.* **2010**, *46*, 1541−1543. (k) Cumpstey, I.; Agrawal, S.; Borbas, E. K.; Martin-Matute, B. *Chem. Commun.* **2011**, *47*, 7827−7829. (l) Agrawal, S.; Lenormand, M.; Martin-Matute, B. *Org. Lett.* **2012**, *14*, 1456−1459. (m) Bartoszewicz, A.; Marcos, R.; Sahoo, S.; Inge, A. K.; Zou, X.; Martin-Matute, B. *Chem. - Eur. J.* **2012**, *18*, 14510−14519. (n) Li, J.-Q.; Andersson, P. G. *Chem. Commun.* **2013**, *49*, 6131−6133. (o) Balcells, D.; Nova, A.; Clot, E.; Gnanamgari, D.; Crabtree, R. H.; Eisenstein, O. *Organometallics* **2008**, *27*, 2529−2535.

(9) Bertoli, M.; Choualeb, A.; Lough, A. J.; Moore, B.; Spasyuk, D.; Gusev, D. G. *Organometallics* **2011**, *30*, 3479−3482.

(10) Bullock, R. M. *Catalysis without Precious Metals*; Wiley−VCH: Weinheim, 2010.

(11) (a) Alberico, E.; Sponholz, P.; Cordes, C.; Nielsen, M.; Drexler, H.-J.; Baumann, W.; Junge, H.; Beller, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 14162−14166. (b) Koehne, I.; Schmeier, T. J.; Bielinski, E. A.; Pan, C. J.; Lagaditis, P. O.; Bernskoetter, W. H.; Takase, M. K.; Würtele, C.; Hazari, N.; Schneider, S. *Inorg. Chem.* **2014**, *53*, 2133−2143. (c) Bielinski, E. A.; Lagaditis, P. O.; Zhang, Y.; Mercado, B. Q.; Würtele, C.; Bernskoetter, W. H.; Hazari, N.; Schneider, S. *J. Am. Chem. Soc.* **2014**, *136*, 10234−10237. (d) Chakraborty, S.; Dai, H.; Bhattacharya, P.; Fairweather, N. T.; Gibson, M. S.; Krause, J. A.; Guan, H. *J. Am. Chem. Soc.* **2014**, *136*, 7869−7872. (e) Werkmeister, S.; Junge, K.; Wendt, B.; Alberico, E.; Jiao, H.; Baumann, W.; Junge, H.; Gallou, F.; Beller, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 8722−8726. (f) Chakraborty, S.; Brennessel, W. W.; Jones, W. D. *J. Am. Chem. Soc.* **2014**, *136*, 8564−8567. (g) Chakraborty, S.; Lagaditis, P. O.; Förster, M.; Bielinski, E. A.; Hazari, N.; Holthausen, M. C.; Jones, W. D.; Schneider, S. *ACS Catal.* **2014**, *4*, 3994−4003. (h) Bonitatibus, P. J., Jr; Chakraborty, S.; Doherty, M. D.; Siclovan, O.; Jones, W. D.; Soloveichik, G. L. *Proc. Natl. Acad. Sci. U. S. A.* **2015**, *112*, 1687−1692.

(12) Chakraborty, S.; Piszel, P. E.; Brennessel, W. W.; Jones, W. D. *Organometallics* **2015**, *34*, 5203−5206.

(13) Rösler, S.; Ertl, M.; Irrgang, T.; Kempe, R. *Angew. Chem., Int. Ed.* **2015**, *54*, 15046−15050.

(14) (a) Zhang, G.; Hanson, S. K. *Org. Lett.* **2013**, *15*, 650−653. (b) Zhang, G.; Yin, Z.; Zheng, S. *Org. Lett.* **2016**, *18*, 300−303.

(15) (a) Yan, T.; Feringa, B. L.T.; Barta, K. *Nat. Commun.* **2014**, *5*, 5602−5609. (b) Rawlings, A. J.; Diorazio, L. J.; Wills, M. *Org. Lett.* **2015**, *17*, 1086−1089. (c) Pan, H.-J.; Ng, T. W.; Zhao, Y. *Chem. Commun.* **2015**, *51*, 11907−11910.

(16) Knölker, H. J.; Baum, E.; Goesmann, H.; Klauss, R. *Angew. Chem., Int. Ed.* **1999**, *38*, 2064−2066.

(17) Murugesan, S.; Stöger, B.; Carvalho, M. D.; Ferreira, L. P.; Pittenauer, E.; Allmaier, G.; Veiros, L. F.; Kirchner, K. *Organometallics* **2014**, *33*, 6132−6140.

(18) Murugesan, S.; Kirchner, K. *Dalton Trans.* **2016**, *45*, 416−439.

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