JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

General and Mild Cobalt-Catalyzed C-Alkylation of Unactivated Amides and Esters with Alcohols

Nicklas Deibl, and Rhett Kempe

J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.6b06448 • Publication Date (Web): 04 Aug 2016

ACS Publications

Journal of the American Chemical Society is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

General and Mild Cobalt-Catalyzed C-Alkylation of Unactivated Amides and Esters with Alcohols

Nicklas Deibl and Rhett Kempe*

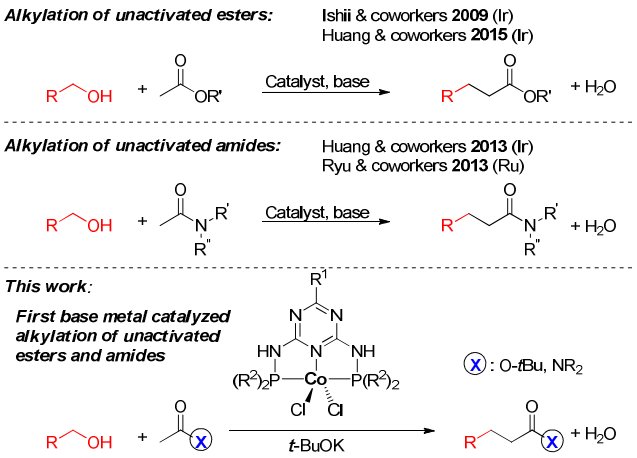
Anorganische Chemie II–Katalysatordesign, Universität Bayreuth, 95440 Bayreuth, Germany

Supporting Information Placeholder

ABSTRACT: The borrowing hydrogen or hydrogen autotransfer methodology is an elegant and sustainable or green concept to construct carbon-carbon bonds. In this concept, alcohols, which can be obtained from barely used and indigestible biomass, such as lignocellulose, are employed as alkylating reagents. An especially challenging alkylation is that of unactivated esters and amides. Only noble metal catalysts based on iridium and ruthenium have been used to accomplish these reactions. Herein, we report on the first base metal catalyzed α-alkylation of unactivated amides and esters by alcohols. Cobalt complexes stabilized with pincer ligands, recently developed in our laboratory, catalyze these reactions very efficiently. The precatalysts can be synthesized easily from commercially available starting materials on a multigram scale and are self-activating under the basic reaction conditions. This Co catalyst class is also able to mediate alkylation reactions of both esters and amides. In addition, we apply the methodology to synthesize ketones and to convert alcohols into aldehydes elongated by two carbon atoms.

α-Alkylation of carbonyl compounds is a fundamental method for the construction of carbon-carbon bonds.[1] In the course of such a transformation, a base is used to deprotonate the carbonyl compound and the anion is trapped with a reactant which bears a leaving group, such as a halide. The borrowing hydrogen (BH) or hydrogen autotransfer (HA) concept is an elegant and operationally easy method for C-C bond formation using alcohols as the electrophile.[2] Alcohols are especially appealing building blocks, since they can be obtained from indigestible, abundantly available and barely used biomass, such as lignocellulose.[3] A transition metal complex is used to oxidize the alcohols to the corresponding carbonyl compound and a subsequent condensation reaction with a CH-acidic compound yields an unsaturated intermediate that is reduced by the catalyst with the hydrogen obtained from the oxidation step. Only water is released in these reactions, rendering them green or sustainable apart from the use of alcohols as an alkylating agent. Derivatives of carboxylic acids, such as esters and amides, are valuable intermediates and products both in industry and academia. An elegant approach to modify ordinary and broadly available amides and esters is the α-alkylation by alcohols. Here, even solvents commonly used and other amides and esters can be converted into more sophisticated and valuable products. However, alkylations of these substrate classes have proved to be challenging. Amides have a comparably low CH-acidic nature due to resonance stabilization and esters can readily undergo side reactions. To date, both α-alkylations of activated[4] and unactivated[5] amides and of activated[6] and unactivated[7] esters with alcohols have only been reported using iridium or ruthenium catalysts (Scheme 1).

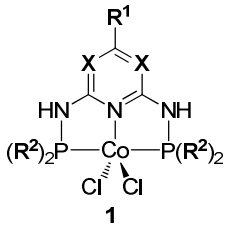
Scheme 1. Recent methods for the alkylation of unactivated amides and esters with alcohols and the work using Co catalysts, stabilized by PN_5P ligands, described herein. R^1 = *i*-Pr, Cyclohexyl; R^2 = 4-CF_3-C_6H_4, NH-C_3H_5, Methyl



The substitution of noble metals by earth-abundant and inexpensive base metals is a key challenge in transition metal-mediated catalysis. Cobalt complexes have recently been reported as catalysts in key reaction steps of the BH/HA concept, such as hydrogenation (olefins,[8] ketones,[9] carboxylic acids,[10] nitriles,[11] esters,[12] CO_2[13]) and dehydrogenation.[14] Our group recently reported C-alkylations based on BH/HA[15] and on the sustainable syntheses of N-heterocycles based on PN_5P-stabilized Ir-complexes.[3c,16] Using the same ligand class, we also reported on the first Co-catalyzed alkylation of aromatic amines by alcohols.[17] Related PN_3P-pincer ligands were introduced by Haupt and coworkers[18] and the broad applicability of this ligand class was demonstrated by Kirchner and coworkers.[19] Herein, we report on the first α-alkylation of unactivated amides and esters by alcohols applying base metal catalysts. Cobalt complexes stabilized with PN_5P-ligands (Scheme 1, bottom) are efficient catalysts for both reactions. The

precatalysts can be synthesized in two steps in almost quantitative yield beginning with commercially available starting materials on a gram scale and become activated under the basic reaction conditions.[9a,17a] In addition, we describe the application of the alkylation of amides to synthesize unsymmetrically substituted ketones and to convert alcohols into aldehydes, which are extended by two carbon atoms.

Table 1. Co complexes used herein to identify the best reaction conditions



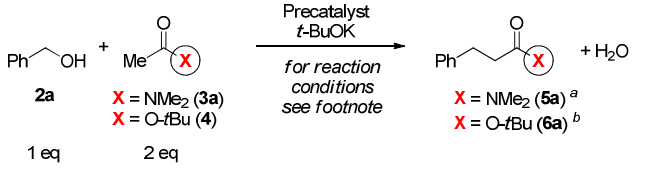
1

Complex	R^1	R^2	X
1a	H	*i*-Pr	N
1b	Me	*i*-Pr	N
1c	Ph	*i*-Pr	N
1d	4-CF_3-C_6H_4	*i*-Pr	N
1e	NH-C_3H_5	*i*-Pr	N
1f	Me	Cy	N
1g	H	*i*-Pr	CH
1h	Me	*i*-Pr	CH
1i	H	Ph	CH

Cy = cyclohexyl.

The reaction between benzyl alcohol (**2a**) and N,N-dimethylacetamide (**3a**) to give **5a** was thoroughly investigated to find broadly applicable reaction conditions for the Co-catalyzed amide alkylation proposed (Tables 1 and 2). Starting with catalyst **1c** (Table 1, 5 mol%), common reaction parameters, such as solvent, base, base amount, substrate ratio and temperature, were investigated (see the Supporting Information [SI] for details). Afterwards, a screening of the Co complexes **1a-1i** (2.5 mol%) was applied in the synthesis of the model compound **5a** (Table 2). While precatalysts **1a-1d** (entries 1-4) gave unsatisfying yields, **1e** and **1f** (entries 5 and 6) gave the highest yield of the alkylation product. Alcohol conversion was quantitative for both precatalysts. Complex **1e** is less expensive (*i*-Pr moieties of the P-atom) and possesses very good solubility in thf or dioxane at RT and is, therefore, very convenient to handle as a stock solution. Thus, **1e** was selected eventually. Most interestingly, **1g-1i**, which are based on a pyridine core, and CoCl2 failed to catalyze the reaction (entries 7-10). In summary, the reaction can be conducted with 2.5 mol% **1e** in thf at 100 °C (closed system) with 1.2 equiv *t*-BuOK as the base and a twofold excess of amide with respect to the alcohol. Notably, these conditions are milder than those for the Ir-catalyzed approach reported by Huang and coworkers (toluene, 120 °C, 2 equiv. base, 2 mol% Ir).[5a] Mechanistic investigations of the model reaction (Table 2) indicate that alcohol oxidation is rate-limiting and reduction of the double bond is comparably fast. The key to a selective reaction is a low concentration of the unsaturated intermediate (N,N-dimethylcinnamamide) since it undergoes multiple side reactions with educts and products (see SI for details). The metal base (metal-to-Co ratio 2 : 1) is used to activate the dichloro complexes via double deprotonation of the ligand and removal of chloro ligands (salt elimination).[9a] The double deprotonation option is a unique feature of the ligand class used herein. Taking note of these optimized conditions, we started to explore the substrate scope of the amide alkylation (Table 3). The screening product **5a** was isolated in 83 % yield. Methyl substituents in the *ortho, meta* and *para*-positions of the phenyl ring furnished **5b-d** in again very good yields (80-85 %, respectively) and application of 1-naphthyl methanol gave **5e** in 78 % yield. Methoxy-substituted benzyl alcohols gave the corresponding products in excellent yields (89 % and 86 % for **5f** and **5g**, respectively). When 4-chlorobenzyl alcohol was subjected to the reaction conditions, partial dechlorination was observed by GC analysis and the products were inseparable by column chromatography. However, the change to *t*-BuONa (instead of *t*-BuOK) under otherwise identical reaction conditions furnished **5h** as the only product in 76 % isolated yield. 3- and 4-pyridine methanol also proved to be challenging alcohols and low conversions were obtained under the standard conditions. However, with the diverse Co-complex library as a toolbox, the application of **1f** with higher catalyst loading (5 mol%) gave the alkylation products **5i** in acceptable 70 % and **5j** in good 81 % yield.

Table 2. Catalyst screening for amide and ester alkylation



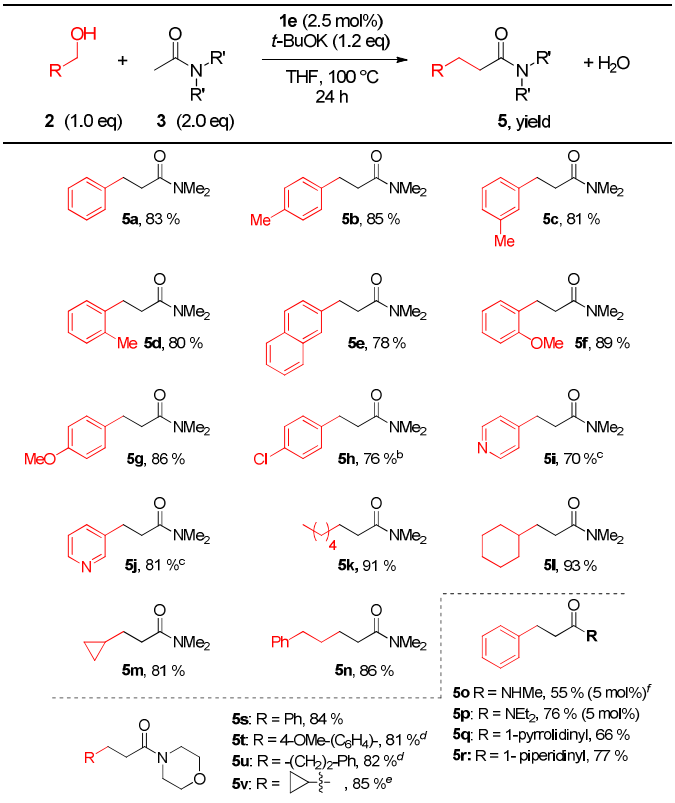
Entry	[Co] Precatalyst	Yield [%][c] 5a	6a
1	**1a**	7	13
2	**1b**	49	43
3	**1c**	25	50
4	**1d**	41	60
5	**1e**	69	42
6	**1f**	74	45
7	**1g**	0	31
8	**1h**	0	24
9	**1i**	0	0
10	$CoCl_2$	0	0

Reaction conditions: [a] Benzyl alcohol (1 mmol), N,N-dimethylacetamide (2 mmol), *t*-BuOK (1.2 mmol), THF (4 mL), [Co] (0.025 mmol), 20 h at 100 °C (oil bath temperature); [b] Benzyl alcohol (1 mmol), *tert*-butyl acetate (2 mmol), toluene (1 mL), [Co] (0.02 mmol), 20 h at 70 °C (oil bath temperature) [c] Determined by GC with dodecane as an internal standard.

When aliphatic (branched and linear) alcohols were used in this reaction (products **5k-n**), the highest yields of up to 93 % were obtained. In order to C-alkylate a secondary amide the reaction conditions had to be adjusted and **5o** was obtained in 55 % yield when the reaction was run in 1,4-dioxane at 120 °C with 1.5 equiv *t*-BuOK and 5 mol% **1e**. Further variation of the amide moiety gave **5p-r** in good yields (66-77 %, respectively) and the very interesting N-morpholino amides **5s-v** (*vide infra*) in very good yields, even on a higher scale (10 mmol, > 2 gram for **5t,u**). The latter compounds exhibit a similar reactivity to Weinreb amides

(R-CO-N(Me)OMe) which failed to react. Taking note of the good performance of the Co catalysts for the amide alkylation, we focused on acetates as the coupling partner (Table 4, top).

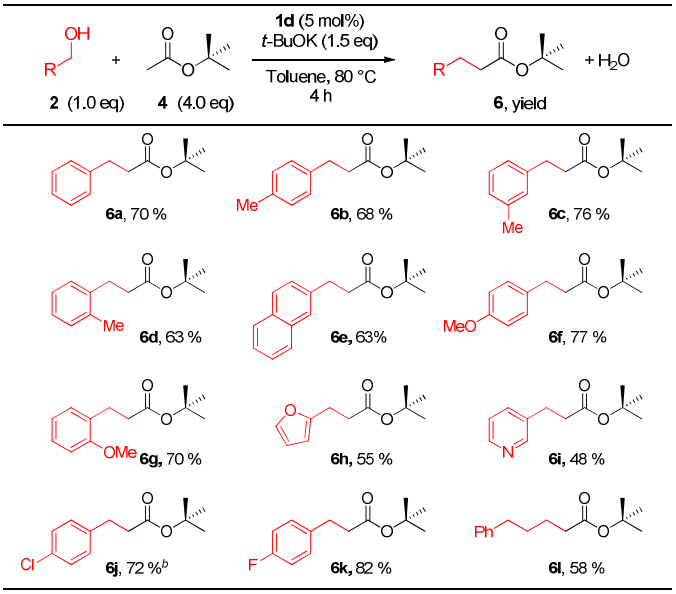
Table 3. Product scope for amide alkylation[a]



[a] *Reaction conditions*: Alcohol (1 mmol), amide (2 mmol), *t*-BuOK (1.2 mmol), **1e** (0.025 mmol) and THF (4 mL) were heated for 24 h at 100 °C (oil bath) in a closed system. Yields are of isolated products. [b] *t*-BuONa was used as a base. [c] **1f** (5 mol%) was used. [d] 10 mmol scale. [e] 5 mmol scale. [f] 1,4-dioxane, 120 °C, 1.5 eq *t*-BuOK.

The reaction between benzyl alcohol and *tert*-butyl acetate was investigated to find suitable reaction conditions (Table 1, synthesis of **6a**; see the SI for details). A catalyst screening identified precatalyst **1d** (entry 4) to be the most active for this transformation. The peak of product yield was obtained when the amount of *tert*-butyl acetate (**4**) was increased to four equiv. When the reaction was conducted in neat *tert*-butyl acetate, the yield dropped. In summary, the reaction should be run in toluene at 80 °C with 1.5 equiv. of *t*-BuOK, four equiv. of *tert*-butyl acetate and complex **1d** (5 mol%). *tert*-Butyl acetate undergoes fast transersterification and the equilibrium is shifted to the alkylated *tert*-butyl esters **6** with the consumption of the primary alcohol (see SI for details). Having pinpointed the reaction conditions, we explored the substrate scope of this reaction (Table 4). The application of benzyl and methylbenzyl alcohols and 1-naphthyl methanol gave the ester alkylation products **6a-e** in 63-76 % isolated yields, respectively. The use of electron-rich methoxybenzyl alcohols furnished the corresponding products in good yields as well (77 and 70% for **6f**,**g**, respectively). The application of methanol bearing heteroaromatic substituents (furyl, pyridyl) also gave the C-alkylation products, albeit in lower yields (55 % for **6h** and 48 % for **6i**). In order to obtain the chlorine-substituted product **6j** free of side products (72 % yield), *t*-BuONa had to be used as the base (*t*-BuOK: 48 % isolated yield).

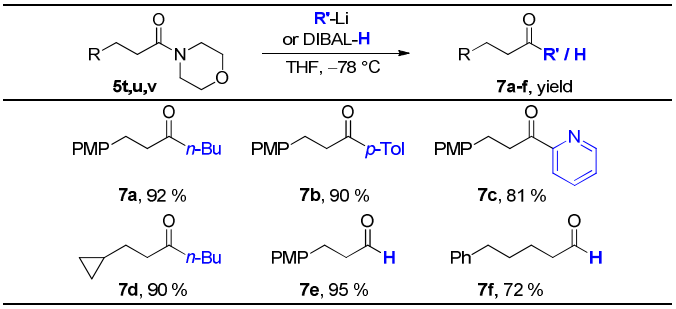
Table 4. Product scope for ester alkylation[a]



[a] *Reaction conditions*: Alcohol (1 mmol), *tert*-butyl acetate (4 mmol), *t*-BuOK (1.5 mmol), toluene (1 mL), **1d** (5 mol%), 4 h at 80 °C (oil bath). Yields are of isolated products. [b] *t*-BuONa was used as a base.

The use of 4-fluorobenzyl alcohol gave an excellent yield (**6k**, 82 %). Ester **6l** could be obtained in 58 % yield using 3-phenyl-1-propanol.

Table 5. Derivatization of amide substrates[a]



[a] *Reaction conditions*: THF, –78 °C, R'-Li (2.5-3 eq) or diisopropylaluminum hydride (DIBAL-H, 1.15-1.30 eq), 1 h reaction time. Yields are of isolated products. PMP = *para*-methoxyphenyl, *p*-Tol = *para*-tolyl, Bu = butyl.

Finally, we became interested in exploring the applicability of amide alkylation products synthesized via Co catalysis to expand the scope of the BA/HA methodology[16a,20] (Table 5). N-morpholino amides **5t-v** were converted into the corresponding ketones **7a-d** using alkyl and aryl Li reagents and only mono-addition was observed (as opposed to esters). The reaction of **5t** and **5u** with diisobutyl aluminumhydride (DIBAL-H) at –78 °C gave aldehydes **7e** and **7f** in 95 and 73 % yield, respectively.

In summary, we report on the first base metal catalyzed C-alkylation of unactivated amides and esters by alcohols. The reaction is catalyzed most efficiently by PN_5P-stabilized Co-complexes developed in our laboratory. These catalysts are

easy to synthesize on a large scale from commercially available starting materials. The catalysts are self-activating under the reaction conditions needed to accomplish the alkylations. The method is characterized by mild reaction conditions and good functional group tolerance. A key to a broad substrate scope is also the library of easily accessible PN_5P-Co catalysts. Amide alkylation products were obtained in up to 93 % isolated yields with catalyst loadings nearly the same as those reported for Ir, but under milder reaction conditions and applying less base. The demanding ester alkylation reaction gave the corresponding products in moderate to good yields. So far, different catalyst classes have been applied to α-alkylate amides and esters. Finally, further transformations of the amide alkylation products into compounds with other functional groups (ketone, aldehyde) showcase the value of the products obtained by this method. Eight novel compounds out of 40 examples have been synthesized.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

kempe@uni-bayreuth.de

Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

We thank the Deutsche Forschungsgemeinschaft, DFG, KE 756/23-2 28-1, for financial support.

REFERENCES

(1) Clayden, J.; Greeves, N.; Warren, S.; Wothers, P. *Organic Chemistry*; Oxford University Press: Oxford, **2001**.

(2) For selected reviews on C-alkylation by alcohols, see: (a) Huang, F.; Liu, Z.; Yu, Z. *Angew. Chem. Int. Ed.* **2016**, 55, 862-875. (b) Nandakumar, A.; Midya, S. P.; Landge, V. G.; Balaraman, E. *Angew. Chem. Int. Ed.* **2015**, *54*, 11022-11034. (c) Shimizu, K.-I. *Catal. Sci. Technol.* **2015**, *5*, 1412-1427. (d) Obora, Y. *ACS Catal.* **2014**, *4*, 3972-3981. (e) Gunanathan, C.; Milstein, D. *Science* **2013**, *341*, 1229712. (f) Alonso, F.; Riente, P.; Yus, M. *Acc. Chem. Res.* **2011**, 44, 379-391. (g) Suzuki, T. *Chem. Rev.* **2011**, *111*, 1825-1845. (h) Dobereiner, G. E.; Crabtree, R. H. *Chem. Rev.* **2010**, *110*, 681-703. (i) Yamaguchi, R.; Fujita, K.-I.; Zhu, M. *Heterocycles* **2010**, *81*, 1093-1140. (j) Ishii, Y.; Obora, Y. *Synlett* **2010**, *2011*, 30-51. (k) Nixon, T. D.; Whittlesey, M. K.; Williams, J. M. *Dalton Trans.* **2009**, *7*, 753-762. (l) Guillena, G.; Ramon, D. J.; Yus, M. *Angew. Chem. Int. Ed.* **2007**, *46*, 2358-2364. (m) Hamid, M. H. S. A.; Slatford, P. A.; Williams, J. M. J. *Adv. Synth. Catal.* **2007**, *349*, 1555-1575.

(3) (a) Vispute, T. P.; Zhang, H.; Sanna, A.; Xiao, R.; Huber, G. W. *Science* **2010**, *330*, 1222-1227. (b) Tuck, C. O.; Perez, E.; Horvath, I. T.; Sheldon, R. A.; Poliakoff, M. *Science* **2012**, *337*, 695-699. (c) Michlik, S.; Kempe, R. *Nat. Chem.* **2013**, 5, 140-144.

(4) (a) Jensen, T.; Madsen, R. *J. Org. Chem.* **2009**, *74*, 3990-3992. (b) Grigg, R.; Whitney, S.; Sridharan, V.; Keep, A.; Derrick, A. *Tetrahedron* **2009**, *65*, 7468-7473.

(5) (a) Guo, L.; Liu, Y.; Yao, W.; Leng, X.; Huang, Z. *Org. Lett.* **2013**, *15*, 1144-1147. (b) Kuwahara, T.; Fukuyama, T.; Ryu, I. *RSC Adv.* **2013**, *3*, 13702-13704.

(6) (a) Grigg, R.; Whitney, S.; Sridharan, V.; Keep, A.; Derrick, A. *Tetrahedron* **2009**, *65*, 7468-7473. (b) Ledger, A. E. W.; Slatford, P. A.; Lowe, J. P.; Mahon, M. F.; Whittlesey, M. K.; Williams, J. M. J. *Dalton Trans.* **2009**, *7*, 716-722. (c) Morita, M.; Obora, Y.; Ishii, Y. *Chem. Commun.* **2007**, *7*, 2850-2852.

(7) (a) Guo, L.; Ma, X.; Fang, H.; Jia, X.; Huang, Z. *Angew. Chem. Int. Ed.* **2015**, *54*, 4023-4027. (b) Iuchi, Y.; Obora, Y.; Ishii, Y. *J. Am. Chem. Soc.* **2010**, *132*, 2536-2537.

(8) (a) Friedfeld, M. R.; Shevlin, M.; Margulieux, G. W.; Campeau, L. C.; Chirik, P. J. *J. Am. Chem. Soc.* **2016**, *138*, 3314-3324. (b) Chirik, P. J. *Acc. Chem. Res.* **2015**, *48*, 1687-1695. (c) Friedfeld, M. R.; Margulieux, G. W.; Schaefer, B. A.; Chirik, P. J. *J. Am. Chem. Soc.* **2014**, *136*, 13178-13181. (d) Lin, T. P.; Peters, J. C. *J. Am. Chem. Soc.* **2014**, *136*, 13672-13683. (e) Lin, T. P.; Peters, J. C. *J. Am. Chem. Soc.* **2013**, *135*, 15310-15313. (f) Monfette, S.; Turner, Z. R.; Semproni, S. P.; Chirik, P. J. *J. Am. Chem. Soc.* **2012**, *134*, 4561-4564. (g) Knijnenburg, Q.; Horton, A. D.; Heijden, H. v. d.; Kooistra, T. M.; Hetterscheid, D. G. H.; Smits, J. M. M.; Bruin, B. d.; Budzelaar, P. H. M.; Gal, A. W. *J. Mol. Catal. A: Chem.* **2005**, *232*, 151-159.

(9) (a) Rösler, S.; Obenauf, J.; Kempe, R. *J. Am. Chem. Soc.* **2015**, *137*, 7998-8001. (b) Gartner, D.; Welther, A.; Rad, B. R.; Wolf, R.; Jacobi von Wangelin, A. *Angew. Chem. Int. Ed.* **2014**, 53, 3722-3726. (c) Zhang, G.; Vasudevan, K. V.; Scott, B. L.; Hanson, S. K. *J. Am. Chem. Soc.* **2013**, *135*, 8668-8681. (d) Zhang, G.; Hanson, S. K. *Chem. Commun.* **2013**, *49*, 10151-10153. (e) Zhang, G.; Scott, B. L.; Hanson, S. K. *Angew. Chem. Int. Ed.* **2012**, *51*, 12102-12106.

(10) Korstanje, T. J.; van der Vlugt, J. I.; Elsevier, C. J.; de Bruin, B. *Science* **2015**, 350, 298-302.

(11) Mukherjee, A.; Srimani, D.; Chakraborty, S.; Ben-David, Y.; Milstein, D. *J. Am. Chem. Soc.* **2015**, *137*, 8888-8891.

(12) Srimani, D.; Mukherjee, A.; Goldberg, A. F.; Leitus, G.; Diskin-Posner, Y.; Shimon, L. J.; Ben David, Y.; Milstein, D. *Angew. Chem. Int. Ed.* **2015**, 54, 12357-12360.

(13) (a) Federsel, C.; Ziebart, C.; Jackstell, R.; Baumann, W.; Beller, M. *Chem. Eur. J.* **2012**, *18*, 72-75. (b) Jeletic, M. S.; Mock, M. T.; Appel, A. M.; Linehan, J. C. *J. Am. Chem. Soc.* **2013**, *135*, 11533-11536.

(14) Zhang, G.; Hanson, S. K. *Org. Lett.* **2013**, *15*, 650-653.

(15) Blank, B.; Kempe, R. *J. Am. Chem. Soc.* **2010**, *132*, 924-925.

(16) (a) Deibl, N.; Ament, K.; Kempe, R. *J. Am. Chem. Soc.* **2015**, *137*, 12804-12807. (b) Hille, T.; Irrgang, T.; Kempe, R. *Chem. Eur. J.* **2014**, *20*, 5569-5572. (c) Michlik, S.; Kempe, R. *Angew. Chem. Int. Ed.* **2013**, 52, 6326-6329.

(17) (a) Rösler, S.; Ertl, M.; Irrgang, T.; Kempe, R. *Angew. Chem. Int. Ed.* **2015**, *54*, 15046-15050. Nearly parallel, Zhang and coworkers introduced a different Co catalyst which was able to alkylate aliphatic and aromatic amines: (b) Zhang, G.; Yin, Z.; Zheng, S. *Org. Lett.* **2016**, *18*, 300-303.

(18) (a) Schirmer, W.; Flörke, U.; Haupt, H. J. *Z. Anorg. Allg. Chem.* **1987**, 545, 83-97. (b) Li, H.; Zheng, B.; Huang, K.-W. *Coord. Chem. Rev.* **2015**, *293-294*, 116-138.

(19) Selected examples of recent publications: (a) Murugesan, S.; Stoger, B.; Pittenauer, E.; Allmaier, G.; Veiros, L. F.; Kirchner, K. *Angew. Chem. Int. Ed.* **2016**, 55, 3045-3048. (b) Bertini, F.; Gorgas, N.; Stöger, B.; Peruzzini, M.; Veiros, L. F.; Kirchner, K.; Gonsalvi, L. *ACS Catal.* **2016**, *6*, 2889-2893. (c) Gorgas, N.; Stöger, B.; Veiros, L. F.; Kirchner, K. *ACS Catal.* **2016**, *6*, 2664-2672. (d) Gorgas, N.; Stöger, B.; Veiros, L. F.; Pittenauer, E.; Allmaier, G.; Kirchner, K. *Organometallics* **2014**, *33*, 6905-6914. (e) Murugesan, S.; Stöger, B.; Carvalho, M. D.; Ferreira, L. P.; Pittenauer, E.; Allmaier, G.; Veiros, L. F.; Kirchner, K. *Organometallics* **2014**, *33*, 6132-6140. (f) de Aguiar, S. R.; Stoger, B.; Pittenauer, E.; Puchberger, M.; Allmaier, G.; Veiros, L. F.; Kirchner, K. *J. Organomet. Chem.* **2014**, *760*, 74-83.

(20) Frost, J. R.; Cheong, C. B.; Akhtar, W. M.; Caputo, D. F.; Stevenson, N. G.; Donohoe, T. J. *J. Am. Chem. Soc.* **2015**, *137*, 15664-15667.

Insert Table of Contents artwork here