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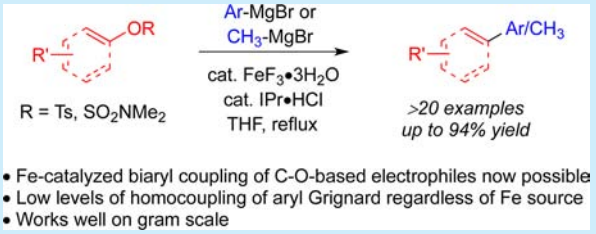
Iron-Catalyzed Coupling of Aryl Sulfamates and Aryl/Vinyl Tosylates with Aryl Grignards

Toolika Agrawal and Silas P. Cook*

Department of Chemistry, Indiana University, 800 East Kirkwood Avenue, Bloomington, Indiana 47405-7102, United States

Supporting Information

ABSTRACT: The iron-catalyzed coupling of aryl sulfamates and tosylates with aryl Grignard reagents is reported for the first time. The methodology employs air-stable, low-cost $FeF_3{\cdot}3H_2O$ and the N-heterocyclic carbene ligand IPr·HCl as the preligand to form a long-lived catalyst upon treatment with aryl Grignards. The reaction provides a range of cross-coupled products in good-to-excellent yields. In contrast to previous reports with aryl chlorides, these reactions proceed with low levels of Grignard homocoupling regardless of the iron source.

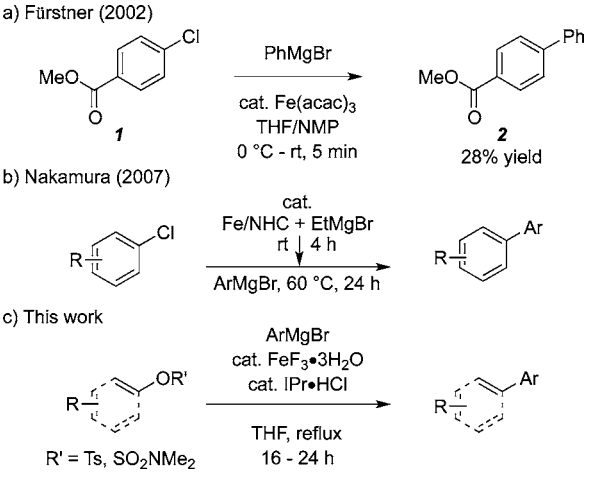


Traditionally, cross-coupling reactions to form biaryls have overwhelmingly depended on palladium catalysis, but increasing costs and the concern of residual contamination have prompted the investigation of alternative metals.[1] Iron, one of the earliest catalysts reported in cross-coupling reactions,[2] offers an appealing alternative to palladium due to its low cost, broad availability, and low toxicity.[3] More importantly, iron possesses significantly different reactivity than Pd, Ni, or Cu, thereby offering the potential to fill the reactivity gaps of known methods.

Alkenyl or aryl halides are frequently used as the electrophiles in Pd-, Ni-, and Cu-catalyzed cross-coupling reactions due to their relatively high reactivity. However, the disadvantages associated with the preparation, handling, and disposal of organohalides raise environmental and regulatory concerns for the pharmaceutical industry.[4] Thus, much effort has been directed to the search for alternatives to organohalides.[5] Among these, C−O-based electrophiles are particularly attractive due to the unparalleled natural abundance and low cost of carbonyl and phenol compounds.[6] Since nontriflate, C−O-based electrophiles offer significant benefits over triflate electrophiles,[7] extensive efforts with Ni[7,8] and, to a lesser extent, Pd[9] have focused on activating Csp^2−O bonds. Although iron-catalyzed cross-coupling reactions generally perform better with aryl triflates and tosylates than with iodides and bromides,[10] few reports on the use of alternate C−O electrophiles exist.[11]

While iron-catalyzed cross-coupling reactions represent something of the "holy grail" of coupling chemistry, iron-catalyzed biaryl couplings remain rare.[10b,12] While reports of iron-catalyzed Suzuki couplings provided ample excitement,[13] residual palladium proved to be the true catalyst.[14] The direct coupling of aryl halides and aryl Grignard reagents in the presence of ferric or ferrous precatalysts is low yielding (Scheme 1a).[10a] This has generally been ascribed to the weak reducing properties of aryl Grignards relative to alkyl Grignards[15] and extensive homocoupling of aryl Grignards.[16]

Scheme 1. Iron-Catalyzed Biaryl Couplings[a]



[a](a) A single example of electron-deficient aryl chloride coupling led to significant homocoupling of the phenyl Grignard.[10a] (b) Excess phenylmagnesium bromide or sacrificial ethylmagnesium bromide can affect the coupling of aryl chlorides with aryl Grignard reagents.[17] (c) The direct coupling of C−O-based electrophiles and aryl Grignard reagents is reported here.

Nakamura overcomes the reduction problem by using sacrificial alkyl Grignard to produce low-valent iron species capable of entering the catalytic cycle for coupling (Scheme 1b).[17] The importance of C−O-based electrophiles combined with the complete lack of iron-catalyzed examples prompted us to investigate this possibility (Scheme 1c).

Based on Nakamura's use of sacrificial alkyl Grignard,[12b,17] we investigated his conditions in the context of C−O-based electrophiles and aryl Grignards. Unfortunately, these con-

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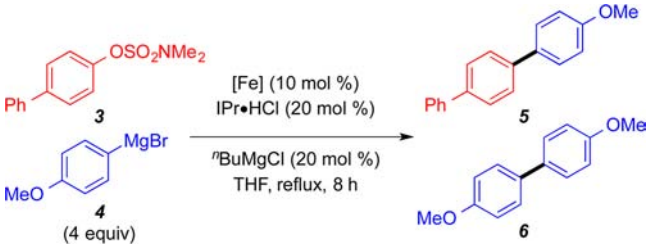
ditions produced no detectable biaryl formation. On reducing the time for iron reduction from 4 h to 2 min, biaryl coupling was observed along with extensive coupling of the sacrificial alkyl Grignard reagent with aryl sulfamate, thereby demonstrating the significant reactivity difference of aryl sulfamates compared to aryl chlorides (see the Supporting Information). Reducing the equivalents of sacrificial alkyl Grignard relative to iron suppressed the alkyl-coupling side reaction and provided high yield (92%) of biaryl product (Table 1, entry 9).

Table 1. Evaluation of Iron Precatalysts in the Coupling of Aryl Sulfamate 3 and 4-(Methoxyphenyl)magnesium Bromide in the Presence of Sacrificial *n*-Butylmagnesium Chloride as the Reductant



entry	[Fe]	SM (*3*) yield[a] (%)	*5* yield[a] (%)	*6* yield[a] (%)
1	$FeCl_3$	65	28	6
2	$FeCl_2$	70	19	7
3	$Fe(OTf)_2$	58	29	4
4	$Fe(OAc)_2$	68	26	9
5	$FeBr_2$	71	20	8
6	$FeCl_3•6H_2O$	56	34	9
7	$Fe(BF_4)_2•6H_2O$	67	22	6
8	$Fe(acac)_3$	53	29	9
9	$FeF_3•3H_2O$	7	92	5

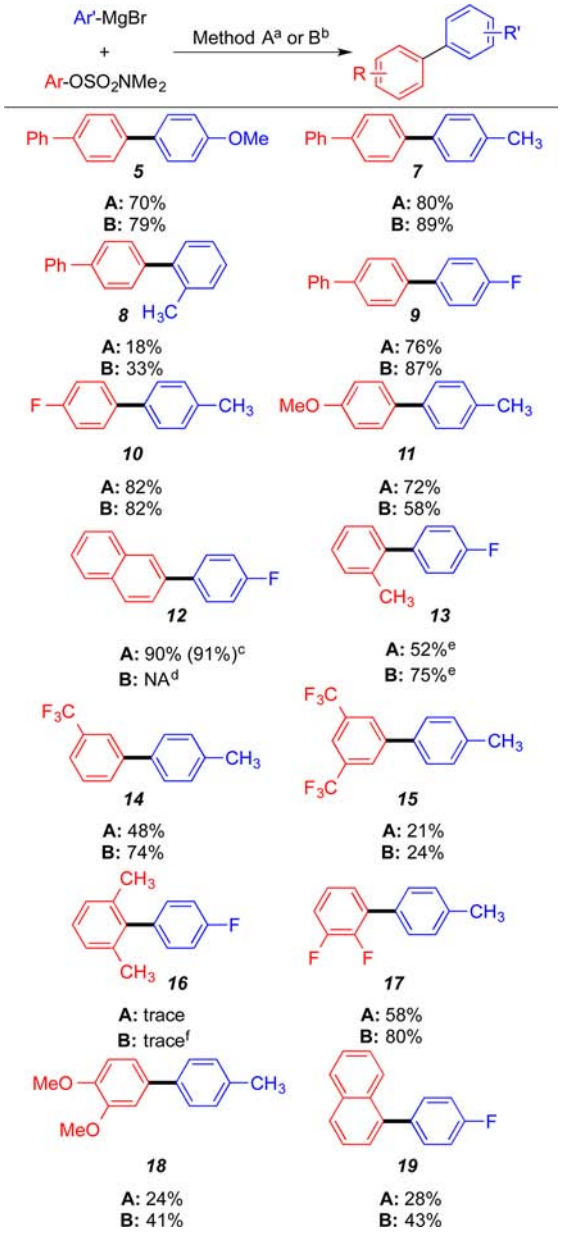
[a]Isolated yields after silica chromatography.

For the biaryl coupling of aryl chlorides, metal fluorides (Fe, Co, Ni) have been documented to overcome the undesired homocoupling of aryl Grignard nucleophiles.[12b,17] Interestingly, aryl sulfamates react with a wide range of iron precatalysts without appreciable homocoupling side-product formation, thereby demonstrating the enhanced rate of aryl sulfamate coupling relative to aryl chlorides under these conditions. While the homocoupling of aryl Grignard proved a nonissue, iron precatalysts other than FeF_3 proved inferior in terms of conversion to product (Table 1). The superior performance of FeF_3 stems from the longer catalyst lifetime of the active catalyst derived from FeF_3, demonstrating an important role of fluoride ions in stabilizing the active iron species.

With these optimized conditions in hand, the exploration of substrate scope could commence. Disappointingly, these optimized conditions provided poor yields for all substrates beyond *p*-phenylphenyl sulfamate (**3**, Supporting Information). While exploring the source of this underperformance, we determined that removing the sacrificial alkyl Grignard from the reaction generally led to significant improvement in yields (Scheme 2).

In the coupling reaction without sacrificial alkyl Grignard, both electron-rich (Scheme 2, **5** and **7**) and electron-deficient (Scheme 2, **9**) aryl Grignard reagents proceeded well. However, the reaction was found to be sensitive to sterics as *ortho*-substituted aryl Grignard reagent (Scheme 2, **8**) led to a poor yield of the coupled product. Although electron-deficient sulfamates (Scheme 2, **10**, **14**, and **17**) were found to be

Scheme 2. Aryl Sulfamate Cross-Coupling with Aryl Grignard Reagents



[a]$FeF_3·3H_2O$ (10 mol %), IPr·HCl (20 mol %), ArMgBr (3 equiv), THF (0.1 M), reflux, 16 h. [b]$FeF_3·3H_2O$ (10 mol %), IPr·HCl (20 mol %), ArMgBr (4 equiv), THF (0.1 M), reflux, 24 h. [c]Yield in parentheses refer to reactions run at 1g scale. [d]No starting material left after 16 h. [e]NMR yield using 1,3,5-trimethoxybenzene as an internal standard. [f]Reaction run for 48 h.

slightly better than electron-rich sulfamates (Scheme 2, **11** and **18**), 3,5-bis(trifluoromethyl)phenol sulfamate (Scheme 2, **15**) proved to be an exception. While *o*-cresol sulfamate (Scheme 2, **13**) coupled in good yield, 2,6-xylenyl sulfamate (Scheme 2, **16**) does not react under these conditions. Surprisingly, 2-naphthyl sulfamate (Scheme 2, **12**) reacts significantly better than 1-naphthyl sulfamate (Scheme 2, **19**). Overall, the reactions proceed cleanly with no observable side products (unreacted starting sulfamate is observed in the case of <50% yield substrates) and less than 5% Grignard homocoupling in each case. Moreover, the reaction is scalable with comparable

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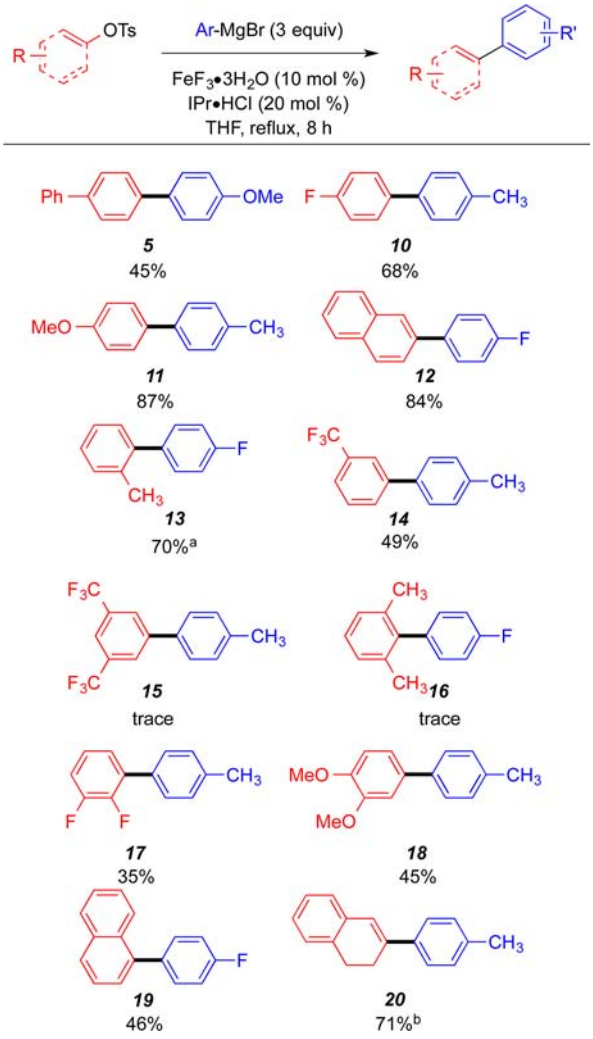
yields obtained when the reaction is performed on a 1-g scale (Scheme 2, **12**). Since aryl tosylates represent synthetically attractive C−O-based electrophiles, we evaluated the coupling conditions in the context of these electrophiles. While tosylates reacted much faster than the corresponding sulfamates, extensive phenol formation was observed along with lower overall conversion (Scheme 3). Moreover, a conjugated vinyl tosylate also proved competent in the reaction to form compound **20**.[18]

Scheme 3. Aryl Tosylate Cross Coupling with Aryl Grignard Reagents



[a]Yield determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. [b]12% homocoupling of the Grginard reagent observed.

The original Kochi coupling combined vinyl bromide with methylmagnesium bromide.[2] Iron catalysis has also been used to couple methyl Grignard reagents with alkenyl triflates,[10e,19] heteroaryl chlorides,[10e] acid chlorides,[10e] 4-pyrones,[20] and vinyl cyclopropanes.[21] However, examples of iron-catalyzed methyl Grignard coupling with phenyl electrophiles remain rare. New methyl installation technologies are critically needed to address the dearth of methyl coupling methodologies[22] and allow exploration of the "magic" methyl effect in medicinal chemistry.[23] Bolstered by the ability of this system to couple C−O-based electrophiles and aryl Grignard reagents without sacrificial alkyl Grignard reductant, we evaluated other Grignard nucleophiles lacking β-hydrogens. We were pleased to find that methylmagnesium bromide couples well under our conditions (94% yield, Scheme 4). Strangely, allylmagnesium bromide and benzylmagnesium bromide do not couple and remain under investigation.

Scheme 4. Coupling of Aryl Sulfamate 3 with Methylmagnesium Bromide

It should be noted that significant differences exist between reactions performed in the presence of sacrificial alkyl Grignard and reactions performed without. While it is too early to speculate about the mechanistic implications, reduction of the precatalyst system with sacrificial alkyl Grignard produced a shorter-lived catalyst that ceased turnover after approximately 6−8 h, whereas by simply relying on the aryl Grignard coupling partner for reducing equivalents, the resulting catalyst system continued operating past 24 h. Such behavior may be related to the low-valent oxidation state of iron produced by alkyl Grignard reduction[15,24] versus aryl Grignard reduction.[25]

In summary, we have developed the first iron-catalyzed direct coupling of aryl sulfamates and tosylates with aryl Grignard reagents. Although the reaction was shown to tolerate a number of iron precatalysts with no significant homocoupling of aryl Grignard, fluoride counterions were found to be necessary to achieve high yields of the desired cross-coupled product. Moreover, reactions performed without prereduction of FeF_3 work better in almost all cases. Further efforts will be directed toward understanding the reaction mechanism and expanding the scope of this interesting transformation.

■ ASSOCIATED CONTENT

Supporting Information

Description of procedures and spectral data for all new compounds is described. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: sicook@indiana.edu.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Garrett, C. E.; Prasad, K. *Adv. Synth. Catal.* **2004**, *346*, 889.

(2) (a) Tamura, M.; Kochi, J. *J. Organomet. Chem.* **1971**, *31*, 289. (b) Tamura, M.; Kochi, J. K. *J. Am. Chem. Soc.* **1971**, *93*, 1487. (c) Neumann, S. M.; Kochi, J. K. *J. Org. Chem.* **1975**, *40*, 599. (d) Smith, R. S.; Kochi, J. K. *J. Org. Chem.* **1976**, *41*, 502.
(3) (a) Sherry, B. D.; Fürstner, A. *Acc. Chem. Res.* **2008**, *41*, 1500. (b) Nakamura, E.; Yoshikai, N. *J. Org. Chem.* **2010**, *75*, 6061.
(4) Constable, D. J. C.; Dunn, P. J.; Hayler, J. D.; Humphrey, G. R.; Leazer, J. J. L.; Linderman, R. J.; Lorenz, K.; Manley, J.; Pearlman, B. A.; Wells, A.; Zaks, A.; Zhang, T. Y. *Green Chem.* **2007**, *9*, 411.
(5) Zapf, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 5394.
(6) Corma, A.; Iborra, S.; Velty, A. *Chem. Rev.* **2007**, *107*, 2411.
(7) Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A.-M.; Garg, N. K.; Percec, V. *Chem. Rev.* **2011**, *111*, 1346.
(8) (a) Antoft-Finch, A.; Blackburn, T.; Snieckus, V. *J. Am. Chem. Soc.* **2009**, *131*, 17750. (b) Guan, B.-T.; Wang, Y.; Li, B.-J.; Yu, D.-G.; Shi, Z.-J. *J. Am. Chem. Soc.* **2008**, *130*, 14468. (c) Guan, B.-T.; Xiang, S.-K.; Wu, T.; Sun, Z.-P.; Wang, B.-Q.; Zhao, K.-Q.; Shi, Z.-J. *Chem. Commun.* **2008**, 1437. (d) Xu, L.; Li, B.-J.; Wu, Z.-H.; Lu, X.-Y.; Guan, B.-T.; Wang, B.-Q.; Zhao, K.-Q.; Shi, Z.-J. *Org. Lett.* **2010**, *12*, 884. (e) Quasdorf, K. W.; Riener, M.; Petrova, K. V.; Garg, N. K. *J. Am. Chem. Soc.* **2009**, *131*, 17748. (f) Quasdorf, K. W.; Tian, X.; Garg, N. K. *J. Am. Chem. Soc.* **2008**, *130*, 14422. (g) Ramgren, S. D.; Silberstein, A. L.; Yang, Y.; Garg, N. K. *Angew. Chem., Int. Ed.* **2011**, *50*, 2171. (h) Mesganaw, T.; Silberstein, A. L.; Ramgren, S. D.; Nathel, N. F. F.; Hong, X.; Liu, P.; Garg, N. K. *Chem. Sci.* **2011**, *2*, 1766. (i) Hie, L.; Ramgren, S. D.; Mesganaw, T.; Garg, N. K. *Org. Lett.* **2012**, *14*, 4182. (j) Mesganaw, T.; Fine Nathel, N. F.; Garg, N. K. *Org. Lett.* **2012**, *14*, 2918. (k) Taylor, B. L. H.; Swift, E. C.; Waetzig, J. D.; Jarvo, E. R. *J. Am. Chem. Soc.* **2010**, *133*, 389. (l) Taylor, B. L. H.; Harris, M. R.; Jarvo, E. R. *Angew. Chem., Int. Ed.* **2012**, *51*, 7790. (m) Ehle, A. R.; Zhou, Q.; Watson, M. P. *Org. Lett.* **2012**, *14*, 1202. (n) Greene, M. A.; Yonova, I. M.; Williams, F. J.; Jarvo, E. R. *Org. Lett.* **2012**, *14*, 4293. (o) Taylor, B. L. H.; Jarvo, E. R. *Synlett* **2011**, *2011*, 2761. (p) Sengupta, S.; Leite, M.; Raslan, D. S.; Quesnelle, C.; Snieckus, V. *J. Org. Chem.* **1992**, *57*, 4066. (q) Macklin, T. K.; Snieckus, V. *Org. Lett.* **2005**, *7*, 2519. (r) Wehn, P. M.; Du Bois, J. *Org. Lett.* **2005**, *7*, 4685.
(9) (a) Roy, A. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 8704. (b) Nguyen, H. N.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11818. (c) Scott, W. J.; Crisp, G. T.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4630. (d) Hansen, A. L.; Ebran, J.-P.; Ahlquist, M.; Norrby, P.-O.; Skrydstrup, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3349. (e) Munday, R. H.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 2754. (f) Zhang, L.; Wu, J. *J. Am. Chem. Soc.* **2008**, *130*, 12250. (g) So, C. M.; Zhou, Z.; Lau, C. P.; Kwong, F. Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 6402.
(10) (a) Fürstner, A.; Leitner, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 609. (b) Fürstner, A.; Leitner, A.; Méndez, M.; Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856. (c) Fürstner, A.; Leitner, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 308. (d) Seidel, G.; Laurich, D.; Fürstner, A. *J. Org. Chem.* **2004**, *69*, 3950. (e) Scheiper, B.; Bonnekessel, M.; Krause, H.; Fürstner, A. *J. Org. Chem.* **2004**, *69*, 3943.
(11) (a) Cahiez, G.; Gager, O.; Habiak, V. *Synthesis* **2008**, *2008*, 2636. (b) Hayashi, N.; Nakada, M. *Tetrahedron Lett.* **2009**, *50*, 232. (c) Li, B.-J.; Xu, L.; Wu, Z.-H.; Guan, B.-T.; Sun, C.-L.; Wang, B.-Q.; Shi, Z.-J. *J. Am. Chem. Soc.* **2009**, *131*, 14656. (d) Agrawal, T.; Cook, S. P. *Org. Lett.* **2012**, *15*, 96. (e) Silberstein, A. L.; Ramgren, S. D.; Garg, N. K. *Org. Lett.* **2012**, *14*, 3796.
(12) (a) Sapountzis, I.; Lin, W.; Kofink, C. C.; Despotopoulou, C.; Knochel, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 1654. (b) Hatakeyama, T.; Hashimoto, S.; Ishizuka, K.; Nakamura, M. *J. Am. Chem. Soc.* **2009**, *131*, 11949. (c) Gülak, S.; Jacobivon Wangelin, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 1357. (d) Kuzmina, O. M.; Steib, A. K.; Flubacher, D.; Knochel, P. *Org. Lett.* **2012**, *14*, 4818. (e) Kuzmina, O. M.; Steib, A. K.; Markiewicz, J. T.; Flubacher, D.; Knochel, P. *Angew. Chem., Int. Ed.* **2013**, *52*, 4945. (f) Chua, Y. Y.; Duong, H. A. *Chem. Commun.* **2014**, *50*, 8424.
(13) (a) Kylmälä, T.; Valkonen, A.; Rissanen, K.; Xu, Y.; Franzén, R. *Tetrahedron Lett.* **2008**, *49*, 6679. (b) Bézier, D.; Darcel, C. *Adv. Synth. Catal.* **2009**, *351*, 1732.
(14) (a) Kylmälä, T.; Valkonen, A.; Rissanen, K.; Xu, Y.; Franzén, R. *Tetrahedron Lett.* **2009**, *50*, 5692. (b) Bedford, R. B.; Nakamura, M.; Gower, N. J.; Haddow, M. F.; Hall, M. A.; Huwe, M.; Hashimoto, T.; Okopie, R. A. *Tetrahedron Lett.* **2009**, *50*, 6110. (c) Bézier, D.; Darcel, C. *Adv. Synth. Catal.* **2010**, *352*, 1081.
(15) Fürstner, A.; Martin, R.; Krause, H.; Seidel, G.; Goddard, R.; Lehmann, C. W. *J. Am. Chem. Soc.* **2008**, *130*, 8773.
(16) (a) Kharasch, M. S.; Fields, E. K. *J. Am. Chem. Soc.* **1941**, *63*, 2316. (b) Nagano, T.; Hayashi, T. *Org. Lett.* **2005**, *7*, 491. (c) Cahiez, G.; Chaboche, C.; Mahuteau-Betzer, F.; Ahr, M. *Org. Lett.* **2005**, *7*, 1943. (d) Cahiez, G.; Moyeux, A.; Buendia, J.; Duplais, C. *J. Am. Chem. Soc.* **2007**, *129*, 13788.
(17) Hatakeyama, T.; Nakamura, M. *J. Am. Chem. Soc.* **2007**, *129*, 9844.
(18) Dunet, G.; Knochel, P. *Synlett* **2006**, 407.
(19) (a) Furstner, A.; Hannen, P. *Chem.—Eur. J.* **2006**, *12*, 3006. (b) Furstner, A.; Krause, H.; Lehmann, C. W. *Angew. Chem., Int. Ed.* **2006**, *45*, 440. (c) Hamajima, A.; Isobe, M. *Org. Lett.* **2006**, *8*, 1205.
(20) Sun, C. L.; Furstner, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 13071.
(21) Sherry, B. D.; Furstner, A. *Chem. Commun.* **2009**, 7116.
(22) Molander, G. A.; Yun, C.-S.; Ribagorda, M.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 5534.
(23) (a) Schönherr, H.; Cernak, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 12256. (b) Barreiro, E. J.; Kümmerle, A. E.; Fraga, C. A. M. *Chem. Rev.* **2011**, *111*, 5215.
(24) Bogdanovic, B.; Schwickardi, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4610.
(25) Bedford, R. B.; Brenner, P. B.; Carter, E.; Cogswell, P. M.; Haddow, M. F.; Harvey, J. N.; Murphy, D. M.; Nunn, J.; Woodall, C. H. *Angew. Chem., Int. Ed.* **2014**, *53*, 1804.