

Iron-Catalyzed C(sp²)-H Alkylation of Carboxamides with Primary Electrophiles**

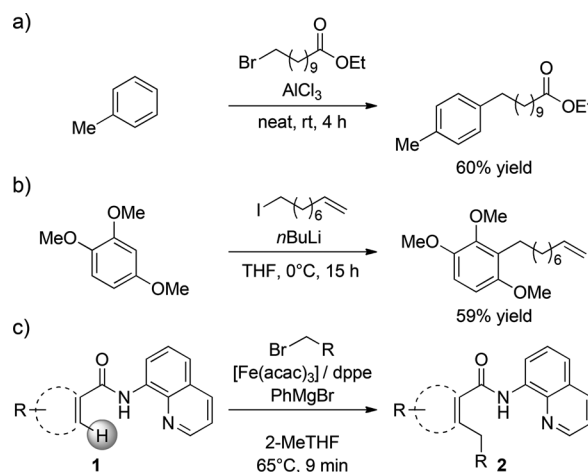
Brendan M. Monks, Erin R. Fruchey, and Silas P. Cook*

Transition-metal-catalyzed cross-coupling reactions have emerged as workhorse reactions in both medicinal chemistry and drug manufacturing.^[1] Although palladium catalysis enables the majority of these transformations, concerns over costs, environmental impact, and human health^[2] have prompted interest in alternative metals. Specifically, cost-effective catalyst systems that enable difficult couplings to take place easily are highly valuable. Moreover, with organic solvents comprising up to 85 % of the waste produced from a drug synthesis,^[3] the ability to efficiently carry out cross-coupling reactions in more environmentally friendly solvents at high concentration^[4] remains an important goal of green chemistry.^[5]

Recently, iron-catalyzed cross-coupling reactions have gained considerable attention because of the low cost, low toxicity, and favorable environmental profile of iron.^[6] This metal also offers impressive reactivity and complementary selectivity relative to the noble metals and nickel.^[7] While iron catalysis works well for a range of traditional nucleophile/electrophile cross-coupling reactions,^[8] the direct coupling of C-H bonds with electrophiles remains largely undeveloped. Consequently, the development of iron-based systems for C-H functionalization reactions represents a critical goal in coupling chemistry.

Currently, few strategies exist for the *ortho* alkylation of carboxylate derivatives. The Friedel-Crafts alkylation offers the potential to use primary halides for aryl alkylations, but poor regioselectivity, carbocation rearrangements, and the requirement for electron-rich aromatics significantly limit this approach (Scheme 1 a).^[9] Alternatively, *ortho* lithiation offers greater selectivity, but the harsh, cryogenic reaction conditions and poor functional-group compatibility restrict its application (Scheme 1 b).^[10] Transition-metal-catalyzed, directed C-H bond functionalization, however, represents a more modern approach to the same bond disconnection.^[11] The currently known C(sp²)-H alkylation examples with unactivated alkyl halides using Pd,^[12] Ru,^[13] Co,^[14] and Ni,^[15]

often suffer from long reaction times, high temperatures, or moderate selectivity. As a result of the pioneering work by Nakamura and co-workers, two classes of electrophiles have been used in iron-catalyzed C-H functionalization, allyl ethers and chloramines.^[16] Consequently, many important electrophiles remain unexplored. Based on our recent experience with the superior performance of iron in a range of transition-metal-catalyzed transformations,^[17] we reasoned that low-valent iron might prove superior for the direct coupling of unactivated alkyl bromides with C-H groups. Considering the need to make industrial processes more environmentally friendly, we explored coupling reactions in 2-methyltetrahydrofuran (2-MeTHF). Here we report the directed *ortho* alkylation of 8-aminoquinoline-based aryl amides **1** to alkylated products **2** using inexpensive and benign iron salts under mild conditions (Scheme 1 c). The reaction does not require a co-oxidant and proceeds in less than 10 min.



Scheme 1. Select examples of aryl C-H functionalization methods.

a) Friedel-Crafts reaction;^[9a] b) *ortho* lithiation/alkylation;^[10d] c) Fe-catalyzed alkylation (this work).

The iron-catalyzed *ortho* alkylation of aryl amides was optimized through the systematic evaluation of the pertinent reaction parameters (see the Supporting Information). Among several well-known directing groups, few provided any product at all, and Daugulis' 8-aminoquinoline^[18] proved to be significantly better (68 % yield) than either 2-methylaminopyridine^[19] (19 % yield) or 2-thiomethylaniline^[12d] (3 % yield). We optimized the reaction to use inexpensive and widely available 1,2-bis(diphenylphosphino)ethane (dppe) as the requisite ligand. Although several Grignard reagents were

[*] B. M. Monks,^[‡] E. R. Fruchey,^[‡] Prof. S. P. Cook
Department of Chemistry, Indiana University
800 East Kirkwood Avenue, Bloomington, IN 47405 (USA)
E-mail: sicook@indiana.edu
Homepage: <http://www.indiana.edu/~cooklab/>

[‡] These authors contributed equally to this work.

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viable in the reaction, phenylmagnesium bromide offered the highest conversion to product, while minimizing the direct coupling of Grignard and benzamide substrate.^[20] The rate of Grignard addition was critical to the success of the reaction (i.e., dropwise additions over less than nine minutes compromised the yield of the reaction). With these observations taken into account, the reaction is performed by combining [Fe(acac)₃] (10 mol %), dppe (15 mol %), and primary bromide (3 equiv) in reagent-grade 2-MeTHF (1M) at 65 °C, followed by the slow addition of Grignard (9 min).

With a robust set of reaction conditions available for the *ortho* alkylation of aryl amides, a variety of substrates were evaluated (Table 1). In contrast to Pd-,^[12a,b,d,e] Co-,^[14a] and Ni-catalyzed^[15a,b] C–H alkylations, the reaction provides exclusively the monosubstituted products without any detectable bis(alkylation) (entries 1–12, 14, and 15, Table 1). Moreover, the presence of a *meta* substituent provided very high levels of regioselectivity, favoring the less-hindered position (entries 1–7, 14, and 15, Table 1). Remarkably, even *m*-fluorobenzamide **7** provided product **27** with more than 20:1 regioselectivity (entry 5, Table 1). As would be expected, this high monoselectivity precludes the use of *ortho*-substituted benzamides (see the Supporting Information), except for the relatively small *o*-fluorobenzamide **18** (entry 16, Table 1). Finally, the reaction proceeds well on gram scale, providing **24** in 80% yield with 88% conversion (entry 2, Table 1).

Next, various alkyl bromide derivatives were evaluated in the reaction (Table 2). Interestingly, the transformation tolerated sterically hindered electrophiles (entries 4, 5, 9, and 10, Table 2). Even neopentyl bromide, a generally recalcitrant electrophile under other conditions,^[13,14b] provided synthetically useful yields of **52** (entry 10, Table 2). One major concern with the use of phenylmagnesium bromide as the base and reductant in this chemistry is the potential for cross-reactivity. Fortunately, the phenylmagnesium bromide reacts with sufficient rate as to allow the use of esters in the reaction with no evidence of Grignard addition into the product ester (entry 8, Table 2). Unfortunately, the use of unactivated primary chlorides and unactivated C–O-based electrophiles, such as tosylates and phosphinates, failed under these reaction conditions. Primary iodides, however, proved competent in the transformation, albeit in diminished yield (entry 14, Table 2). Attempts to employ secondary electrophiles in this reaction resulted in complex reaction mixtures containing polyalkylated products.

Interestingly, the use of cyclopropylmethyl bromide provides homoallyl product **49** in 75% yield, and the addition of free-radical inhibitor butylhydroxytoluene (BHT) compromised the yield somewhat (Scheme 2a). Additionally, subjecting 6-bromo-1-hexene to the optimized reaction conditions produced a mixture of linear product **56** and cyclized product **57** in 60% combined yield and 1.0:4.9 ratio of **56**:**57** (Scheme 2b). The addition of BHT both increased the yield slightly and caused a detectable reduction in the formation of cyclized product **57** (Scheme 2b). While consistent with primary radical formation,^[21] these results can also be explained by organometallic β -carbon elimination (in Scheme 2a) and migratory insertion (in Scheme 2b).^[22]

Table 1: The C(sp²)–H alkylation of carboxamides with *n*-butyl bromide.

$ \begin{array}{c} \text{R}-\text{C}_6\text{H}_4-\text{C}(=\text{O})\text{NH-Q} \\ \text{3-22} \end{array} \xrightarrow[\text{2-MeTHF (1 M), 65}^\circ\text{C, 9 min}]{\begin{array}{c} n\text{BuBr (3.0 equiv)} \\ \text{PhMgBr (3.45 equiv)} \\ [\text{Fe}(\text{acac})_3] \text{ (10 mol \%)} \\ \text{dppe (15 mol \%)} \end{array}} \begin{array}{c} \text{R}-\text{C}_6\text{H}_4-\text{C}(=\text{O})\text{NH-Q} \\ \text{23-42} \end{array} $				
Entry	Product	Yield (Conv.) [%] ^[a]		
1	R = H	23	86 (98)	
2	Me	24	83 (90) ^[b]	
3	Cl	25	79 (98)	
4	Br	26	37 (93)	
5	F	27	81 (100)	
6	CF ₃	28	47 (100) ^[c]	
7	OMe	29	87 (96)	
8	R = OMe	30	63 (100)	
9	CF ₃	31	73 (89) ^[c]	
10	SMe	32	53 (100)	
11	<i>t</i> Bu	33	75 (100)	
12	NMe ₂	34	64 (73)	
13		35	66 (100)	
14		36	69 (81)	
15		37	80 (95)	
16		38	63 (82) ^[c]	
17		39	74 (91) ^[c]	
18		40	59 (71) ^[c]	
19		41	63 (91) ^[c]	
20		42	79 (95) ^[c]	

[a] Yields of isolated products after column chromatography on silica gel. [b] Reaction run on 1.0 g scale of **4** gave **24** in 80% yield (977 mg, 88% conversion). [c] PhMgBr (4.44 equiv), [Fe(acac)₃] (20 mol %), dppe (30 mol %), *n*BuBr (3.5 equiv). Q = 8-quinolyl.

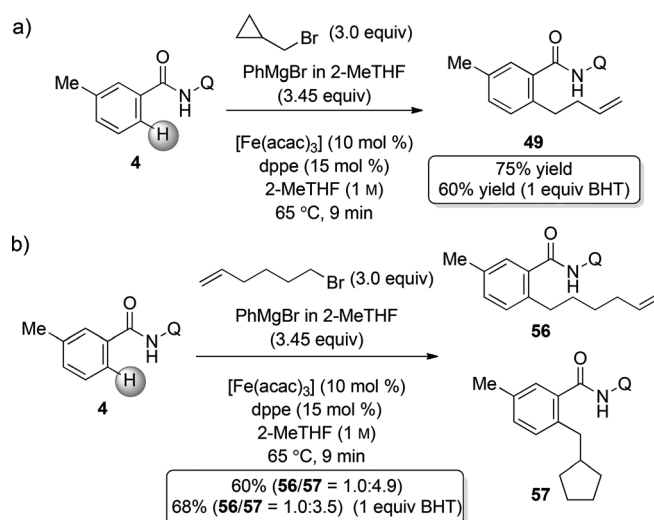
An intermolecular competition experiment between **3** and [D₃]-**3** provided a kinetic isotope effect (KIE) of 1.5 (Scheme 3a). While higher than other reported isotope effects for C–H alkylation reactions,^[12f,16a] this value is lower than the expected 1.8 to 3.4 for a primary KIE.^[20e,j] An intramolecular KIE experiment with monodeuterated [D₁]-**3** provided a significant primary KIE of 2.9 (Scheme 3b).

Table 2: The *ortho* C–H functionalization of *m*-tolylbenzamide **4** with alkyl bromide derivatives.

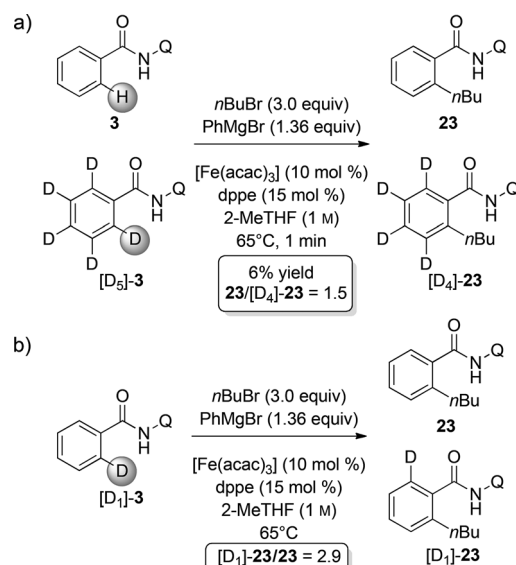
Entry	Alkyl halide	Product	Yield (Conv.) [%] ^[a]
1			43 82 (87)
2			R' = Me 44 74 (94)
3			Bn 45 58 (83)
4			R' = Me 46 68 (88)
5			Ph 47 70 (88)
6			48 74 (86)
7			49 76 (100) ^[b]
8			50 53 (62) ^[b]
9			51 31 (74) ^[b]
10			52 47 (52) ^[b]
11			53 90 (98)
12			Ar = Ph 54 72 (84)
13			4-(MeO)C ₆ H ₄ 55 47 (69)
14			4-(MeO)C ₆ H ₄ 55 31 (36) ^[b]

[a] Yields of isolated products after column chromatography on silica gel. [b] PhMgBr (4.44 equiv) [Fe(acac)₃] (20 mol %), dppe (30 mol %), alkyl halide (3.5 equiv). [c] Yields based on ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. Q = 8-quinoliny.

The observed difference in the KIE for the inter- and intramolecular reactions indicates that C–H cleavage is not the sole contributor to product selectivity in the intermolec-



Scheme 2. Formation of rearranged products. Q = 8-quinoliny.



Scheme 3. Experiments on a) intermolecular and b) intramolecular kinetic isotope effects. Q = 8-quinoliny.

ular competition reaction (Scheme 3a). The small intermolecular KIE ($k_H/k_D = 1.5$) suggests that the product-determining step(s) occurs prior to C–H cleavage, producing the observed minimal isotopic selectivity. The significant intramolecular KIE ($k_H/k_D = 2.9$) indicates that C–H cleavage is involved in the product-determining step for the intramolecular case. Together, the small intermolecular KIE and the large intramolecular KIE imply that substrate coordination is irreversible and occurs prior to C–H cleavage.^[23] A plausible explanation would be turnover-limiting binding of the substrate to iron, followed by rapid, irreversible C–H cleavage.

During the exploration of this reaction, we noticed that aryl amides with electron-withdrawing groups appeared to react at slower rates or with lower conversions per time unit. To examine the electronic effects of the ring more closely, we performed a series of competition experiments (Table 3). In

Table 3: Reactivity effects for electron-donating and electron-withdrawing substituents.

Entry	Product ratios		Yield [%] ^[a]
1	<i>m</i> -MeO/ <i>m</i> -CF ₃	3.0:1.0	19
2	<i>p</i> -MeO/ <i>p</i> -CF ₃	1.0:1.0	26
3	<i>m</i> -MeO/ <i>p</i> -MeO	1.1:1.0	68
4	<i>m</i> -CF ₃ / <i>p</i> -CF ₃	1.0:1.4	17

[a] Yields based on ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. Q = 8-quinolinyl.

these experiments, a methoxy or trifluoromethyl group was installed either in *para* position to the amide or the C–H bond to be coupled. Interestingly, an electron-rich group (OMe) in *meta* position to the amide (*para* to the C–H bond) results in significantly more alkylation than the CF₃ group in the same position (entry 1, Table 3). Meanwhile, having either a methoxy or trifluoromethyl group in *para* position to the amide has no effect on the product ratio (entry 2, Table 3). Comparing the methoxy group at either the *meta* or *para* positions shows a slight preference for product formation in the case where the electron-donating group is in *meta* position to the amide (*para* to the C–H; entry 3, Table 3). Moreover, methoxy groups at either position result in significantly higher conversion. Finally, placing the trifluoromethyl group in *meta* position to the amide (*para* to the C–H) inhibits product formation more than placement in the *para* position to the amide (entry 4, Table 3). In conjunction with the KIE data, these results indicate that electron-donating substrates lower the energy for substrate coordination, thereby leading to a higher conversion to the product. In contrast, electron-withdrawing substrates increase the energy for substrate coordination and, therefore, inhibit conversion relative to the electron-rich substrates.

In summary, we have developed a robust iron-catalyzed *ortho* alkylation of aryl amides. The reaction generally proceeds in high yields with exceptional regioselectivity. The reaction is complete in less than 10 min and can be performed in bio-derived 2-methyltetrahydrofuran as solvent on gram scale. The reactivity and selectivity provides a reaction profile unique among the reported C–H functionalization reactions, thereby complementing current strategies. The low cost and toxicity of the reagents should simplify the large-scale implementation of this C–H functionalization. Moreover, mechanistic experiments indicate that substrate coordination is irreversible and occurs prior to C–H cleavage. Further efforts will be directed toward mechanistic understanding and expanding the scope of this interesting transformation.

Experimental Section

General procedure for the alkylation reaction: An oven-dried 8 mL screw thread culture tube (Kimberly-Chase) was purged with N₂, then charged with [Fe(acac)₃] (0.1 equiv), dppe (0.15 equiv), and the benzamide (1.0 equiv). Subsequently the solids were dissolved by the addition of reagent-grade 2-MeTHF (1M) and alkyl electrophile (3.0 equiv) under N₂. The mixture was then placed in an oil bath at 65°C and PhMgBr in 2-MeTHF (1.1 equiv) was added in a single portion. Following the first addition of Grignard, an additional portion of PhMgBr in 2-MeTHF (2.35 equiv) was added dropwise to the reaction at 65°C over 9 min. Upon completion of Grignard addition, the reaction was stirred at 65°C for 1 min, brought to RT, and allowed to cool for an additional 2 min. Subsequently the reaction was quenched with saturated ammonium chloride (0.02M) and extracted with DCM (3 × 0.1M). The combined organic extracts were dried (MgSO₄), filtered, and concentrated to give a residue. The residue was purified by flash chromatography on silica gel using hexanes and ethyl acetate in appropriate combination based on the R_f of the desired product.

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- [1] S. D. Roughley, A. M. Jordan, *J. Med. Chem.* **2011**, 54, 3451–3479.
- [2] C. E. Garrett, K. Prasad, *Adv. Synth. Catal.* **2004**, 346, 889–900.
- [3] J. M. Fortunak, *Future Med. Chem.* **2009**, 1, 571–575.
- [4] R. K. Henderson, C. Jiménez-González, D. J. C. Constable, S. R. Alston, G. G. A. Inglis, G. Fisher, J. Sherwood, S. P. Binks, A. D. Curzons, *Green Chem.* **2011**, 13, 854–862.
- [5] a) P. T. Anastas, J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, New York, **1998**; b) D. J. C. Constable, P. J. Dunn, J. D. Hayler, G. R. Humphrey, J. L. Leazer, Jr., R. J. Linderman, K. Lorenz, J. Manley, B. A. Pearlman, A. Wells, A. Zaks, T. Y. Zhang, *Green Chem.* **2007**, 9, 411–420.
- [6] C. Bolm, *Nat. Chem.* **2009**, 1, 420–421.
- [7] A. Kulkarni, O. Daugulis, *Synthesis* **2009**, 4087–4109.
- [8] a) B. D. Sherry, A. Fürstner, *Acc. Chem. Res.* **2008**, 41, 1500–1511; b) W. M. Czaplik, M. Mayer, J. Cvengroš, A. von Wangelin, *ChemSusChem* **2009**, 2, 396–417.
- [9] a) S. Bhattacharya, M. Subramanian, *Tetrahedron Lett.* **2002**, 43, 4203–4206; b) M. Bandini, M. Tragni, *Org. Biomol. Chem.* **2009**, 7, 1501–1507.
- [10] a) H. Gilman, R. L. Bebb, *J. Am. Chem. Soc.* **1939**, 61, 109–112; b) G. Wittig, G. Fuhrmann, *Chem. Ber.* **1940**, 73, 1197–1218; c) V. Snieckus, *Chem. Rev.* **1990**, 90, 879–933; d) T. Bach, A. Lemarchand, *Synlett* **2002**, 1302–1304.
- [11] L. Ackermann, *Chem. Commun.* **2010**, 46, 4866–4877.
- [12] a) S. J. Tremont, H. U. Rahman, *J. Am. Chem. Soc.* **1984**, 106, 5760–5762; b) J. S. McCallum, J. R. Gasdaska, L. S. Liebeskind, S. J. Tremont, *Tetrahedron Lett.* **1989**, 30, 4085–4088; c) Y.-H. Zhang, B.-F. Shi, J.-Q. Yu, *Angew. Chem.* **2009**, 121, 6213–6216; *Angew. Chem. Int. Ed.* **2009**, 48, 6097–6100; d) D. Shabashov, O. Daugulis, *J. Am. Chem. Soc.* **2010**, 132, 3965–3972; e) Y. Zhao, G. Chen, *Org. Lett.* **2011**, 13, 4850–4853; f) B. Xiao, Z.-J. Liu, L. Liu, Y. Fu, *J. Am. Chem. Soc.* **2013**, 135, 616–619; g) E. T. Nades, G. I. F. Santos, D. Shabashov, O. Daugulis, *J. Org. Chem.* **2013**, 78, 9689–9714.
- [13] L. Ackermann, P. Novák, R. Vicente, N. Hofmann, *Angew. Chem.* **2009**, 121, 6161–6164; *Angew. Chem. Int. Ed.* **2009**, 48,

- 6045–6048; b) L. Ackermann, N. Hofmann, R. Vicente, *Org. Lett.* **2011**, *13*, 1875–1877.
- [14] a) Q. Chen, L. Ilies, E. Nakamura, *J. Am. Chem. Soc.* **2011**, *133*, 428–429; b) K. Gao, N. Yoshikai, *J. Am. Chem. Soc.* **2013**, *135*, 9279–9282; c) B. Punji, W. Song, G. A. Shevchenko, L. Ackermann, *Chem. Eur. J.* **2013**, *19*, 10605–10610.
- [15] a) Y. Aihara, N. Chatani, *J. Am. Chem. Soc.* **2013**, *135*, 5308–5311; b) X. Wu, Y. Zhao, H. Ge, *J. Am. Chem. Soc.* **2014**, *136*, 1789–1792; c) W. Song, S. Lackner, L. Ackermann, *Angew. Chem.* **2014**, *126*, 2510–2513; *Angew. Chem. Int. Ed.* **2014**, *53*, 2477–2480.
- [16] a) S. Asako, L. Ilies, E. Nakamura, *J. Am. Chem. Soc.* **2013**, *135*, 17755–17757; b) T. Matsubara, S. Asako, L. Ilies, E. Nakamura, *J. Am. Chem. Soc.* **2014**, *136*, 646–649; c) S. Asako, J. Norinder, L. Ilies, N. Yoshikai, E. Nakamura, *Adv. Synth. Catal.* **2014**, *356*, 1481–1485.
- [17] a) G. K. Jarugumilli, S. P. Cook, *Org. Lett.* **2011**, *13*, 1904–1907; b) T. Agrawal, S. P. Cook, *Org. Lett.* **2013**, *15*, 96–99; c) L. R. Jefferies, S. P. Cook, *Org. Lett.* **2014**, *16*, 2026–2029; d) L. R. Jefferies, S. P. Cook, *Tetrahedron* **2014**, *70*, 4204–4207; e) T. C. Attack, R. M. Lecker, S. P. Cook, *J. Am. Chem. Soc.* **2014**, *136*, 9521–9523.
- [18] V. G. Zaitsev, D. Shabashov, O. Daugulis, *J. Am. Chem. Soc.* **2005**, *127*, 13154–13155.
- [19] S. Inoue, H. Shiota, Y. Fukumoto, N. Chatani, *J. Am. Chem. Soc.* **2009**, *131*, 6898–6899.
- [20] a) J. Norinder, A. Matsumoto, N. Yoshikai, E. Nakamura, *J. Am. Chem. Soc.* **2008**, *130*, 5858–5859; b) N. Yoshikai, A. Matsumoto, J. Norinder, E. Nakamura, *Angew. Chem.* **2009**, *121*, 2969–2972; *Angew. Chem. Int. Ed.* **2009**, *48*, 2925–2928; c) N. Yoshikai, A. Matsumoto, J. Norinder, E. Nakamura, *Synlett* **2010**, 313–316; d) L. Ilies, S. Asako, E. Nakamura, *J. Am. Chem. Soc.* **2011**, *133*, 7672–7675; e) N. Yoshikai, S. Asako, T. Yamakawa, L. Ilies, E. Nakamura, *Asian J. Chem.* **2011**, *6*, 3059–3065; f) L. Ilies, M. Kobayashi, A. Matsumoto, N. Yoshikai, E. Nakamura, *Adv. Synth. Catal.* **2012**, *354*, 593–596; g) L. Ilies, E. Konno, Q. Chen, E. Nakamura, *Asian J. Org. Chem.* **2012**, *1*, 142–145; h) R. Shang, L. Ilies, A. Matsumoto, E. Nakamura, *J. Am. Chem. Soc.* **2013**, *135*, 6030–6032; i) J. J. Sirois, R. Davis, B. DeBoef, *Org. Lett.* **2014**, *16*, 868–871; j) Q. Gu, H. H. Al Mamari, H. H. Al, K. Graczyk, E. Diers, L. Ackermann, *Angew. Chem.* **2014**, *126*, 3949–3952; *Angew. Chem. Int. Ed.* **2014**, *53*, 3868–3871.
- [21] D. Noda, Y. Sunada, T. Hatakeyama, M. Nakamura, H. Nagashima, *J. Am. Chem. Soc.* **2009**, *131*, 6078–6079.
- [22] For an example of a Ru-catalyzed organometallic β -carbon elimination, see: X. Hong, B. M. Trost, K. N. Houk, *J. Am. Chem. Soc.* **2013**, *135*, 6588–6600. For an analogous example catalyzed by Fe, see: A. Fürstner, K. Majima, R. Martin, H. Krause, E. Kattnig, R. Goddard, C. W. Lehmann, *J. Am. Chem. Soc.* **2008**, *130*, 1992–2004.
- [23] E. M. Simmons, J. F. Hartwig, *Angew. Chem.* **2012**, *124*, 3120–3126; *Angew. Chem. Int. Ed.* **2012**, *51*, 3066–3072.