

# Iron-Catalyzed C(sp<sup>2</sup>)–C(sp<sup>3</sup>) Cross-Coupling at Low Catalyst Loading

Elwira Bisz,<sup>a,\*</sup> Marlena Kardela,<sup>a</sup> Aleksandra Piontek<sup>a</sup> and Michal Szostak<sup>a,b,\*</sup>

Received 00th January 20xx,  
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

**The iron-catalyzed C(sp<sup>2</sup>)–C(sp<sup>3</sup>) cross-coupling provides a highly economical route to exceedingly valuable alkylated arenes that are widespread in medicinal chemistry and materials science. Herein, we report an operationally-simple protocol for the selective C(sp<sup>2</sup>)–C(sp<sup>3</sup>) iron-catalyzed cross-coupling of aryl chlorides with Grignard reagents at low catalyst loading. A broad range of electronically-varied aryl and heteroaryl chlorides underwent the cross-coupling using challenging alkyl organometallics possessing β-hydrogens with high efficiency up to 2000 TON. A notable feature of the protocol is the use of environmentally-friendly cyclic urea ligands. A series of guidelines to predict cross-coupling reactivity of aryl electrophiles is provided.**

Spurred by environmental issues, iron-catalyzed cross-couplings have been established as an attractive alternative to precious metals.<sup>1–3</sup> In particular, this type of catalytic cross-coupling technology is of paramount importance in the synthesis of valuable alkylated arenes that are widespread in drug discovery and materials science,<sup>4,5</sup> wherein other metals fail to provide high efficiency in the cross-coupling of challenging alkyl organometallics possessing β-hydrogens due to competing β-hydride elimination, self-coupling and slower transmetallation.<sup>6</sup> High abundance of iron in the Earth's crust notwithstanding, these technologies are extensively utilized in the synthesis of pharmaceuticals at high catalyst loadings,<sup>5</sup> which does not meet current demands of atom-economic and operationally-simple processes.<sup>7</sup>

Following our interest in iron-catalyzed cross-couplings,<sup>8</sup> we recently questioned whether this cross-coupling strategy might be extended to operate at operationally-practical low catalyst loadings. In general, iron-catalyzed C(sp<sup>2</sup>)–C(sp<sup>3</sup>) cross-couplings are performed at high loadings (5 mol% or more),<sup>9,10</sup> with very few reports existing in this area at low catalyst

loadings.<sup>1g,9l</sup>

Herein, we report an efficient and operationally-simple protocol for the selective C(sp<sup>2</sup>)–C(sp<sup>3</sup>) iron-catalyzed cross-coupling of aryl chlorides with Grignard reagents at low catalyst loading. Specifically, a broad range of electronically-varied aryl and heteroaryl chlorides underwent the cross-coupling using challenging alkyl organometallics possessing β-hydrogens with high efficiency up to 2000 TON. A notable feature of the protocol is the use of environmentally-friendly cyclic urea ligands.<sup>11</sup> We provide a series of guidelines to predict cross-coupling reactivity of aryl electrophiles. We fully expect that the findings reported herein will be of high value to practitioners involved in iron catalysis as well as in the synthesis of vital classes of alkylated arenes.

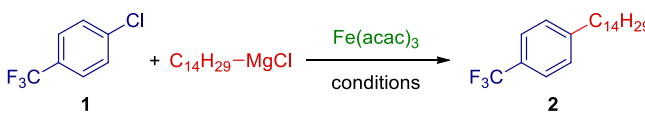
Our investigation began by evaluating of the cross-coupling of a non-coordinating arene, 4-chloro-4-(trifluoromethyl) benzene, with tetradecyl magnesium chloride (Table 1). While our previous studies established that this challenging substrate serves as a competent model system at high iron loading (5 mol%),<sup>8a</sup> from the outset it was unclear whether the coupling would occur at operationally-practical low catalyst loadings. Our initial attempts were thwarted by low conversions and excessive homocoupling of the alkyl Grignard reagent (for example, Table 1, entry 1). A major enhancement of the catalytic efficiency was realized by changing the reaction concentration (Table 1, entry 2). Additional efforts at reaction optimization established that DMI is required for the efficient coupling (entries 3–4). Examination of other additives, such as DMPU (entry 5) and carcinogenic yet the most frequently used in iron-catalyzed cross-couplings, NMP<sup>1g,12</sup> (entry 6) resulted in diminished yields. Interestingly, the use of bioderived 2-MeTHF as a solvent<sup>8b,13</sup> (entry 7) provided a comparable reaction efficiency. Under these conditions, a TON of 1360 was determined at 0.05 mol% loading (entry 8), thus representing a rare example of iron-catalyzed cross-coupling at low loading.

Importantly, control reactions established that all reaction components were required for the coupling, *and no reaction was observed in the absence of iron catalyst both in the absence (entry 9) and the presence of DMI (entry 10).*<sup>14</sup>

<sup>a</sup>Department of Chemistry, Opole University, 48 Oleska Street, 45-052 Opole, Poland. E-mail: ebisz@uni.opole.pl.

<sup>b</sup>Department of Chemistry, Rutgers University, 73 Warren Street, Newark, NJ 07102, United States. Fax: (+1)-973-353-1264; Tel: (+1)-973-353-532. E-mail: michal.szostak@rutgers.edu.

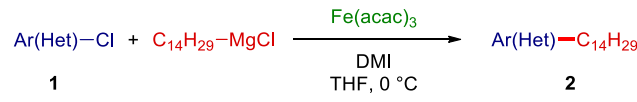
†Electronic Supplementary Information (ESI) available: Experimental details and characterization data. See DOI: 10.1039/x0xx00000x

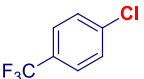
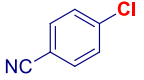
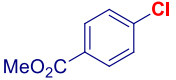
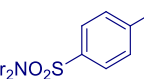
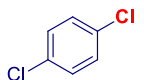
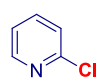
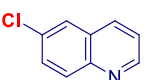
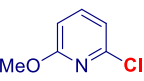
**Table 1.** Optimization of Iron-Catalyzed Cross-Coupling at Low Catalyst Loading<sup>a</sup>


| entry          | Fe(acac) <sub>3</sub> (mol%) | ligand | mol% | time   | yield (%) <sup>b</sup> |
|----------------|------------------------------|--------|------|--------|------------------------|
| 1              | 0.10                         | DMI    | 200  | 10 min | 31                     |
| 2              | 0.10                         | DMI    | 200  | 10 min | 93                     |
| 3              | 0.10                         | DMI    | 100  | 10 min | 67                     |
| 4              | 0.10                         | DMI    | -    | 10 min | 61                     |
| 5              | 0.10                         | DMPU   | 200  | 10 min | 50                     |
| 6              | 0.10                         | NMP    | 200  | 10 min | 64                     |
| 7 <sup>c</sup> | 0.10                         | DMI    | 200  | 10 min | 90                     |
| 8 <sup>d</sup> | 0.05                         | DMI    | 200  | 10 min | 68                     |
| 9              | -                            | -      | -    | 60 min | <2                     |
| 10             | -                            | DMI    | 200  | 60 min | <2                     |

<sup>a</sup>Conditions: ArCl (0.50 mmol), Fe(acac)<sub>3</sub> (x mol%), THF, C<sub>14</sub>H<sub>29</sub>MgCl (1.20 equiv, 1.0 M, THF), 0 °C, 10 min. RMgCl added dropwise over 1–2 s. <sup>b</sup>Determined by <sup>1</sup>H NMR. Entry 1: THF (0.15 M). Entries 2–10: THF (0.50 M). <sup>c</sup>2-MeTHF. <sup>d</sup>THF (0.80 M). DMI = 1,3-dimethyl-2-imidazolidinone. DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone. NMP = N-methyl-2-pyrrolidone.

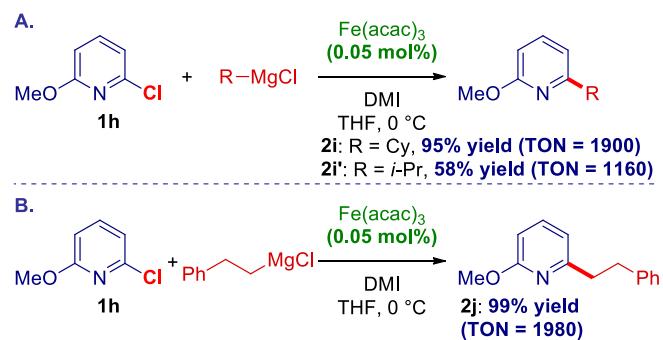
With optimized conditions in hand, we next changed our focus to examine the scope of the reaction (Table 2). In particular, we were interested to determine the scope of electrophilic functional groups on the arene that serve as valuable synthetic handles and are typically not tolerated in other catalytic cross-coupling technologies using cheap and readily available Grignard reagents.<sup>15</sup> Notably, a wide range of electrophilic functional groups was found to be competent substrates in this protocol, providing alkylated arenes with excellent efficiency. First, we tested arenes with carboxylic acid derived functional groups. As mentioned above, our model substrate 4-chloro-4-(trifluoromethyl)benzene could be routinely cross-coupling with TON exceeding 1,000 (Table 2, entries 1–3). Although 4-chlorobenzonitrile proved to be a challenging substrate<sup>16</sup> (entries 4–6), we determined that increasing the amount of the co-solvent delivered the desired coupling product with TON of 740 at 0.10 mol% loading, however, this appears to be the limit under these conditions as a further decrease of the catalyst loading resulted in lower reaction efficiency. Importantly, the cross-coupling could be carried out in the presence of a highly electrophilic ester group (entries 7–9). Extensive optimization established that a combined use of a slow addition protocol (60 min addition) and close to a stoichiometric amount of the Grignard reagent (1.05 equiv) prevented the undesired nucleophilic addition to the ester group,<sup>17</sup> delivering the cross-coupled product in 90% yield at 0.05 mol% loading. However, we note that a further decrease of the catalyst loading was ineffective for this substrate (not shown). Furthermore, as an important synthetic consideration the cross-coupling at 0.50 mol% delivered the product in quantitative yield (not shown); however, the slow addition is required to prevent alcohol formation. Next, a

**Table 2.** Scope of Iron-Catalyzed Cross-Coupling at Low Catalyst Loading<sup>a</sup>


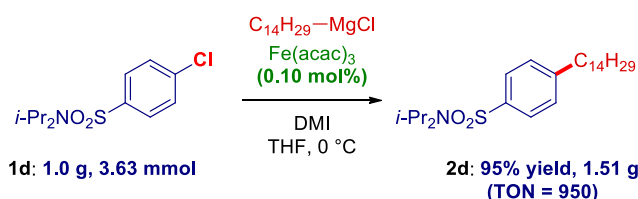
| Entry           | Substrate                                                                            | 2         | Fe(acac) <sub>3</sub> (mol%) | Yield (%) |
|-----------------|--------------------------------------------------------------------------------------|-----------|------------------------------|-----------|
| 1               |    | <b>2a</b> | 0.10                         | 93 (930)  |
| 2               |                                                                                      |           | 0.05                         | 68 (1360) |
| 3               |                                                                                      |           | -                            | <2        |
| 4 <sup>b</sup>  |    | <b>2b</b> | 0.10                         | 74 (740)  |
| 5 <sup>b</sup>  |                                                                                      |           | 0.05                         | 23 (460)  |
| 6 <sup>b</sup>  |                                                                                      |           | -                            | <2        |
| 7 <sup>c</sup>  |    | <b>2c</b> | 0.10                         | 91 (910)  |
| 8 <sup>c</sup>  |                                                                                      |           | 0.05                         | 90 (1800) |
| 9 <sup>c</sup>  |                                                                                      |           | -                            | <2        |
| 10 <sup>d</sup> |    | <b>2d</b> | 0.10                         | 99 (990)  |
| 11 <sup>d</sup> |                                                                                      |           | 0.05                         | 78 (1560) |
| 12 <sup>d</sup> |                                                                                      |           | -                            | <2        |
| 13 <sup>b</sup> |   | <b>2e</b> | 0.50                         | 81 (160)  |
| 14 <sup>b</sup> |                                                                                      |           | 0.10                         | 39 (390)  |
| 15 <sup>b</sup> |                                                                                      |           | -                            | <2        |
| 16 <sup>e</sup> |  | <b>2f</b> | 0.10                         | 78 (780)  |
| 17 <sup>e</sup> |                                                                                      |           | 0.05                         | 50 (1000) |
| 18 <sup>e</sup> |                                                                                      |           | -                            | <2        |
| 19 <sup>f</sup> |  | <b>2g</b> | 0.10                         | 99 (990)  |
| 20 <sup>f</sup> |                                                                                      |           | 0.05                         | 94 (1840) |
| 21 <sup>f</sup> |                                                                                      |           | -                            | 12        |
| 22 <sup>f</sup> |                                                                                      | <b>2h</b> | 0.10                         | 99 (990)  |
| 23 <sup>f</sup> |                                                                                      |           | 0.05                         | 99 (1980) |
| 24 <sup>f</sup> |  |           | 0.01                         | 37 (3300) |
| 25 <sup>f</sup> |                                                                                      |           | -                            | <2        |

<sup>a</sup>1 (0.50 mmol), Fe(acac)<sub>3</sub> (x mol%), DMI (200 mol%), C<sub>14</sub>H<sub>29</sub>MgCl (1.20 equiv, 1.0 M, THF), THF (0.50 M), 0 °C, 10 min. TON is given in brackets. <sup>b</sup>18 h, DMI (600 mol%). <sup>c</sup>C<sub>14</sub>H<sub>29</sub>MgCl (1.05 equiv), slow addition, 60 min. <sup>d</sup>3 h, DMI (200 mol%), <sup>e</sup>C<sub>14</sub>H<sub>29</sub>MgCl (2.0 equiv), 18 h, DMI (600 mol%). <sup>f</sup>18 h, DMI (200 mol%). See ESI for details.

sulfonamide bearing aryl chloride proved to be an exceptionally reactive substrate for the cross-coupling (entries 10–12), affording the product in quantitative yield at 0.10 mol% loading and 78% yield at 0.05 mol% loading. The cleavage of the reactive Ar–SO<sub>2</sub> and SO<sub>2</sub>–N moieties<sup>18</sup> was not observed, consistent with the mild conditions of this protocol. Furthermore, we were pleased to find that a sensitive aryl chloride could be tolerated under the reaction conditions



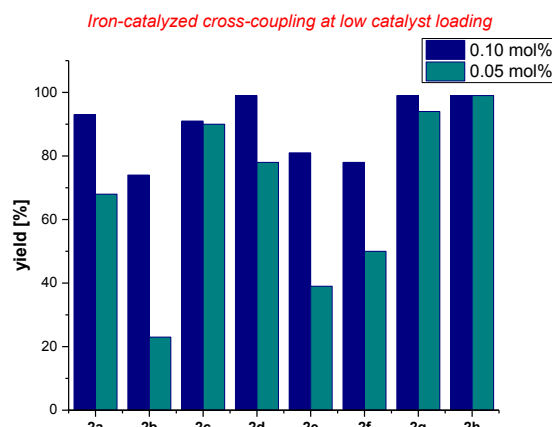
**Scheme 1.** Cross-coupling of Grignard reagents at low catalyst loading.



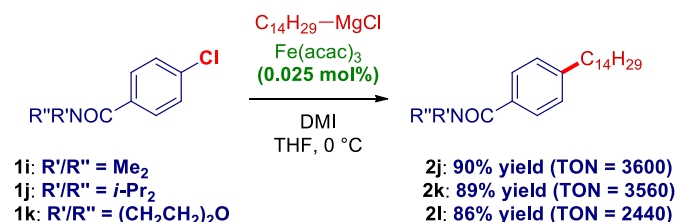
**Scheme 2.** Large scale cross-coupling at low catalyst loading.

(entries 13–15), providing a synthetic handle for subsequent cross-coupling by established methods.<sup>9r</sup> As expected, this substrate proved more challenging, requiring 0.50 mol% loading to achieve synthetically useful conversion. Moreover, this protocol is not limited to aromatic substrates and can also be applied to synthetically valuable heterocycles<sup>19</sup> such as pyridines (entries 16–18) and quinolines (entries 19–21). We determined that cross-coupling of 2-chloropyridine proceeds in 78% yield at 0.10 mol% loading, while further decrease of the loading resulted in an inferior efficiency (entries 16–18). Interestingly, 6-chloroquinoline proved to be much more reactive substrate. In this case, after brief optimization of the reaction conditions, we found that, after extending the reaction time, the cross-coupling afforded the desired alkylated product in 94% yield at 0.05 mol% loading (entries 19–21). Furthermore, we were pleased to find that the cross-coupling of 6-methoxy-2-chloropyridine delivered the biologically-relevant<sup>20</sup> 6-methoxy-2-alkylpyridyl scaffold with excellent efficiency (entries 22–25). Cross-coupling of this system proceeded in quantitative yield at 0.05 mol% loading, while further decrease of catalyst loading resulted in lower conversions.

Next, we turned our attention to demonstrate the cross-coupling of challenging alkyl Grignard reagents under low catalyst loading conditions (Scheme 1). As demonstrated in Scheme 1, these conditions are amenable to the cross-coupling of secondary Grignard reagents prone to  $\beta$ -hydride elimination, such as cyclohexyl Grignard as well as the more challenging isopropylmagnesium bromide. It is noteworthy that under these low loading conditions, isomerization was not observed (b:l >20:1). Moreover, the cross-coupling of 2-phenethyl Grignard, which is susceptible to styrene formation, proceeded without any modification of the reaction conditions, attesting to the generality of this protocol.



**Fig 1.** Graphical representation of iron-catalyzed cross-coupling at low catalyst loading. **2e:** columns correspond to 0.50 and 0.10 mol% loading, respectively.



**Scheme 3.** Cross-coupling of 4-chlorobenzamides at low catalyst loading.

To demonstrate the synthetic utility of this cross-coupling protocol at low catalyst loading, a gram scale reaction was performed at 0.10 mol% loading (Scheme 2). The alkylated benzenesulfonamide was obtained in excellent yield after direct recrystallization, highlighting the synthetic potential of this operationally-simple protocol. Alkylated benzenesulfonamides represent key pharmacophores in medicinal chemistry due to their diverse biological properties.<sup>21</sup>

To further expand the scope of the cross-coupling at low catalyst loading, we examined the reactivity of representative 4-chlorobenzamides (Scheme 3). The iron catalyzed cross-coupling of these substrates provides access to alkylated benzamides and related functional groups, which have found wide applications as bioactive compounds and functional materials.<sup>8d</sup> We were pleased to find that the coupling of three representative 4-chlorobenzamides, including a model *N,N*-Me<sub>2</sub> amide, a sterically-hindered *N,N*-*i*-Pr<sub>2</sub> amide and a chelating, modifiable *N*-morpholinyl amide proceed in 86–90% yields at 0.025 mol% loading, which to our knowledge is the highest TON recorded in iron-catalyzed cross-coupling to date.

While the present catalytic manifold is distinguished by its superb functional group tolerance to electrophilic functional groups, which are not compatible with other iron-catalyst systems, a short discussion of limitations is in order. It is established that nitro, ketones and imines are not tolerated by the system. Ethers are tolerated, however, cannot be used as activating groups in this catalytic manifold. For example,

experiments with 4-PhO-C<sub>6</sub>H<sub>4</sub>-Cl under high catalyst loading resulted in <10% conversion. However, our preliminary studies indicate that even highly unstable OPh groups are tolerated by the system. For example, the cross-coupling of an activated phenolic ester, 4-Cl-C<sub>6</sub>H<sub>4</sub>-C(O)-OPh, proceeds in an unoptimized 54% yield at 0.10 mol% loading. Furthermore, electron-rich heterocycles are not compatible with the system. However, electron-deficient heterocycles are compatible and highly active. Our preliminary studies indicate that the reaction efficiency can be correlated with stabilization of the negative charge. Studies to expand the scope and even further improve catalytic performance are ongoing. All substrates selected for the study were used on purpose to cover the range of electrophilic functional groups and allow benchmarking against other conditions for iron-catalyzed cross-coupling.

It is also important to emphasize the role of DMI (1,3-dimethyl-2-imidazolidinone) as an efficient ligand to iron. Cyclic ureas are vastly preferred due to lack of toxicity associated with NMP. Furthermore, cyclic ureas are more strongly O-donating due to Nlp to C=O conjugation from both nitrogen atoms. Ongoing studies are focused on further ligand optimization and development of improved understanding of this cross-coupling manifold.

The study reported herein not only establishes a low-loading, operationally-simple technology for C(sp<sup>2</sup>)-C(sp<sup>3</sup>) cross-coupling, but also provides valuable data into the order of reactivity of aryl electrophiles in iron catalyzed cross-coupling (Fig. 1).<sup>9a,b</sup> On the basis of our data, the following order of reactivity of activating groups is established: Cl < CN < CF<sub>3</sub> < CO<sub>2</sub>R ≈ SO<sub>2</sub>R<sub>2</sub> < pyridine < quinoline. We believe that the guidelines to predict cross-coupling reactivity of aryl electrophiles will contribute to improving the practicality of iron catalyzed cross-coupling technologies in organic synthesis using challenging alkyl organometallics.<sup>4–6</sup>

In conclusion, we have reported an efficient protocol for selective C(sp<sup>2</sup>)-C(sp<sup>3</sup>) iron-catalyzed cross-coupling of aryl chlorides with Grignard reagents at low catalyst loading. The reaction demonstrates a broad substrate scope with respect to electrophilic functional groups that can be used as handles for further functionalization and are typically not tolerated using other cross-coupling technologies. The study gave valuable insight into the order for reactivity of activating groups in iron-catalyzed cross-coupling. We believe that the compatibility of iron-catalyzed cross-coupling with operationally-practical low catalyst loading could lead to the development of improved methods of high value to practitioners involved in iron catalysis as well as in the synthesis of various classes of alkylated arenes. Studies to establish better understanding of the mechanistic details and on related cross-coupling protocols are currently underway and will be reported in due course.

We gratefully acknowledge Narodowe Centrum Nauki (grant no. 2014/15/D/ST5/02731), Rutgers University and the NSF (CAREER CHE-1650766) for generous financial support.

## Notes and references

- For selected reviews on iron-catalysis, see: (a) A. Fürstner and R. Martin, *Chem. Lett.*, 2005, **34**, 624; (b) B. D. Sherry and A. Fürstner, *Acc. Chem. Res.*, 2008, **41**, 1500; (c) W. M. Czaplik, M. Mayer, J. Cvengros and A. Jacobi von Wangelin, *ChemSusChem*, 2009, **2**, 396; (d) B. Plietker, *Top. Organomet. Chem.*, Vol. 33, Springer, 2011; (e) E. B. Bauer, *Top. Organomet. Chem.*, Vol. 50, Springer, 2015; (f) I. Marek and Z. Rappoport, *The Chemistry of Organoirron Compounds*, Wiley, 2014; (g) I. Bauer and H. J. Knölker, *Chem. Rev.*, 2015, **115**, 3170; For a review on iron catalysis in natural product synthesis, see: (h) J. Legros and B. Fidegarde, *Nat. Prod. Rep.*, 2015, **32**, 1541; (i) For a review on iron-catalyzed cross-couplings of C–O electrophiles, see: E. Bisz and M. Szostak, *ChemSusChem*, 2017, **10**, 3964.
- For a leading perspective on homogeneous iron catalysis, see: A. Fürstner, *ACS Cent. Sci.*, 2016, **2**, 778.
- For reviews on base-metal catalysis, see: (a) G. Cahiez and A. Moyeux, *Chem. Rev.*, 2010, **110**, 1435; (b) B. M. Rosen, K. W. Quasdorf, D. A. Wilson, N. Zhang, A. M. Resmerita, N. K. Garg and V. Percec, *Chem. Rev.*, 2011, **111**, 1346; (c) J. Miao and H. Ge, *Eur. J. Org. Chem.*, 2015, 7859; For leading reviews on sustainable catalysis, see: (d) E. Nakamura and K. Sato *Nat. Mater.*, 2011, **10**, 158; (e) A. Fürstner, *Adv. Synth. Catal.*, 2016, **358**, 2362; (f) J. R. Ludwig and C. S. Schindler, *Chem.*, 2017, **2**, 313; For studies on metal toxicity, see: (g) K. S. Egorowa and V. P. Ananikov, *Angew. Chem. Int. Ed.*, 2016, **55**, 12150; (h) P. A. Frey and G. H. Reed, *ACS Chem. Biol.*, 2012, **7**, 1477. (i) See ref. 2, and references cited therein.
- (a) T. J. Colacot, *New Trends in Cross-Coupling*, The Royal Society of Chemistry, 2015; (b) J. Magano and J. R. Dunetz, *Chem. Rev.*, 2011, **111**, 2177; (c) C. Torborg and M. Beller, *Adv. Synth. Catal.*, 2009, **351**, 3027.
- A. Piontek, E. Bisz and M. Szostak, *M. Angew. Chem. Int. Ed.*, 2018, **57**, 11116.
- (a) R. Jana, T. P. Pathak and M. S. Sigman, *Chem. Rev.*, 2011, **111**, 1417; (b) R. Giri, S. Thapa and A. Kafle, *Adv. Synth. Catal.*, 2014, **356**, 1395.
- (a) C. C. C. Johansson-Seechurn, M. O. Kitching, T. J. Colacot and V. Snieckus, *Angew. Chem. Int. Ed.*, 2012, **51**, 5062; (b) M. L. Crawley and B. M. Trost, *Applications of Transition Metal Catalysis in Drug Discovery and Development: An Industrial Perspective*, Wiley, 2012; (c) A. Molnar, *Palladium-Catalyzed Coupling Reactions: Practical Aspects and Future Developments*, Wiley, 2013; (d) J. C. Hierso, M. Beauperin and P. Meunier, *Eur. J. Inorg. Chem.*, 2007, 3767.
- For selected studies from our group, see: (a) E. Bisz and M. Szostak, *Green Chem.*, 2017, **19**, 5361; (b) E. Bisz and M. Szostak, *ChemSusChem*, 2018, **11**, 1290; See, also: (c) A. Piontek and M. Szostak, *Eur. J. Org. Chem.*, 2017, **48**, 7271; (d) E. Bisz and M. Szostak, *Adv. Synth. Catal.*, 2018, DOI: 10.1002/adsc.201800849.
- For select leading studies on iron-catalyzed cross-couplings, see: (a) A. Fürstner and A. Leitner, *Angew. Chem. Int. Ed.*, 2002, **41**, 609; (b) A. Fürstner, A. Leitner, M. Mendez and H. Krause, *J. Am. Chem. Soc.*, 2002, **124**, 13856; (c) A. Fürstner and A. Leitner, *Angew. Chem. Int. Ed.*, 2003, **42**, 308; (d) A. Fürstner, D. De Souza, L. Parra-Rapado and J. T. Jensen, *Angew. Chem. Int. Ed.*, 2003, **42**, 5358; (e) G. Seidel, M. Laurich and A. Fürstner, *J. Org. Chem.*, 2004, **69**, 3950; (f) A. Fürstner and L. Turet, *Angew. Chem. Int. Ed.*, 2005, **44**, 3462; (g) A. Fürstner and R. Martin, *Angew. Chem. Int. Ed.*, 2004, **43**, 3955; (h) R. B. Bedford, D. W. Bruce, R. M. Frost, J. W. Goodby and M. Hird, *Chem. Commun.*, 2004, 2822; (i) R. B. Bedford, D. W. Bruce, R. M. Frost and M. Hird, *Chem. Commun.*, 2005, 4161; (j) W. M. Czaplik, M. Mayer and A. Jacobi von Wangelin, *Angew. Chem. Int. Ed.*, 2009, **48**, 607; (k) S. Gülak and A. Jacobi von Wangelin, *Angew. Chem. Int. Ed.*, 2012, **51**, 1357; (l) D. Gärtner, A. L. Stein, S. Grupe, J. Arp and A. Jacobi von Wangelin, *Angew. Chem. Int. Ed.*, 2015, **54**, 10545; (m) G. Cahiez, V. Habiak, C. Duplais and A. Moyeux, *Angew. Chem. Int. Ed.*, 2007, **46**, 4364; (n) A. Guerinot, S.

- Reymond and J. Cossy, *Angew. Chem. Int. Ed.*, 2007, **46**, 6521; (o) T. Hatakeyama and M. Nakamura, *J. Am. Chem. Soc.*, 2007, **129**, 9844; (p) O. M. Kuzmina, A. K. Steib, J. T. Markiewicz, D. Flubacher and P. Knochel, *Angew. Chem. Int. Ed.*, 2013, **52**, 4945; (q) M. Jin, L. Adak and M. Nakamura, *J. Am. Chem. Soc.*, 2015, **137**, 7128; For the selective iron-catalyzed cross-coupling of 1,4-dichlorobenzene and related substrates, see: (r) B. Scheiper, M. Bonnekessel, H. Krause and A. Fürstner, *J. Org. Chem.*, 2004, **69**, 3943; For recent studies showing the intricacy of the catalytic system, see: (s) A. Casitas, H. Krause, R. Goddard and A. Fürstner, *Angew. Chem. Int. Ed.*, 2015, **54**, 1521; (t) A. Casitas, J. A. Rees, R. Goddard, E. Bill, D. DeBeer and A. Fürstner, *Angew. Chem. Int. Ed.*, 2017, **56**, 10108.
- 10 For select mechanistic studies, see: (a) A. Fürstner, R. Martin, H. Krause, G. Seidel, R. Goddard and C. W. Lehmann, *J. Am. Chem. Soc.*, 2008, **130**, 8773; (b) C. Cassani, Bergonzini and C. J. Wallentin, *ACS Catal.*, 2016, **6**, 1640; (c) T. L. Mako and J. A. Byers, *Inorg. Chem. Front.*, 2016, **3**, 766; (d) See, ref. 2.
- 11 For the seminal report on using cyclic ureas as HMPA replacement, see: (a) T. Mukhopadhyay and D. Seebach, *Helv. Chim. Acta*, 1982, **65**, 385. For selected pertinent studies, see: (b) P. G. Jesso, *Green Chem.*, 2011, **13**, 1391; (c) T. Welton, *Proc. R. Soc. A*, 2015, **471**, 502; (d) F. P. Byrne, S. Jin, G. Paggiola, T. H. M. Petchey, J. H. Clark, T. J. Farmer, A. J. Hunt, C. R. McElroy, and J. Sherwood, *Sustain. Chem. Process*, 2016, **4**, 7.
- 12 For a WHO report on reprotoxicity of NMP, see: (a) B. Åkesson, *N-Methyl-2-Pyrrolidone*; WHO: Geneva, 2001; (b) NMP is classified as a chemical of very high concern and a proposal has been put forward to restrict the use of NMP in Europe: <https://echa.europa.eu/candidate-list-table>.
- 13 For leading reviews on 2-MeTHF, see: (a) D. F. Aycok, *Org. Process Res. Dev.*, 2007, **11**, 156; (b) V. Pace, P. Hoyos, L. Castoldi, P. D. de Maria and A. R. Alcantara, *ChemSusChem*, 2012, **5**, 1369; (c) S. Monticelli, L. Castoldi, I. Murgia, R. Senatore, E. Mazzeo, J. Wackerlig, E. Urban, T. Langer and V. Pace, *Monatsh. Chem.*, 2017, **148**, 37.
- 14 For a pertinent discussion, see: S. L. Buchwald and C. Bolm, *Angew. Chem. Int. Ed.* **2009**, **48**, 5586.
- 15 For a leading review on Pd-catalyzed cross-couplings with Grignard reagents, see: (a) C. E. I. Knappe and A. Jacobi von Wangelin, *Chem. Soc. Rev.*, 2011, **40**, 4948; For additional examples, see: (b) G. A. Molander, J. P. Wolfe and M. Larhed, *Science of Synthesis: Cross-Coupling and Heck-Type Reactions*, Thieme, 2013; (c) A. de Meijere, S. Bräse and M. Oestreich, *Metal-Catalyzed Cross-Coupling Reactions and More*, Wiley, 2014.
- 16 For nucleophilic addition of Grignard reagents to aryl nitriles, see: G. Dilauor, M. Dell'Aera, P. Vitale, V. Capriati and F. M. Pena, *Angew. Chem. Int. Ed.*, 2017, **129**, 10334, and references cited therein.
- 17 For a recent elegant example of organometallic addition to an ester group, see: (a) A. Link and C. Sparr, *Angew. Chem. Int. Ed.*, 2018, **57**, 7136; For a review, see: (b) M. J. Pedersen, S. Born, U. Neuenschwander, T. Skovby, M. J. Mealy, S. Kiil, K. Dam-Johansen and K. F. Jensen, *Ind. Eng. Chem. Res.*, 2018, **57**, 4859.
- 18 (a) F. Schoenebeck, J. A. Murphy, S. Zhou, Y. Uenoyama, Y. Miclo and T. Tuttle, *J. Am. Chem. Soc.*, 2007, **129**, 13368. (b) C. H. Cho, H. S. Yun and K. Park, *J. Org. Chem.*, 2003, **69**, 3017.
- 19 J. A. Joule and K. Mills, *Heterocyclic Chemistry*, Wiley, 2010.
- 20 J. A. Bull, J. J. Mousseau, G. Pelletier and A. B. Charette, *Chem. Rev.*, 2012, **112**, 2642.
- 21 Drews, J. *Science*, 2000, **287**, 1960.

#### Iron-catalyzed C(sp<sup>2</sup>)-C(sp<sup>3</sup>) cross-coupling at low catalyst loading

