Organic Syntheses

Discussion Addendum for:

4-Nonylbenzoic Acid

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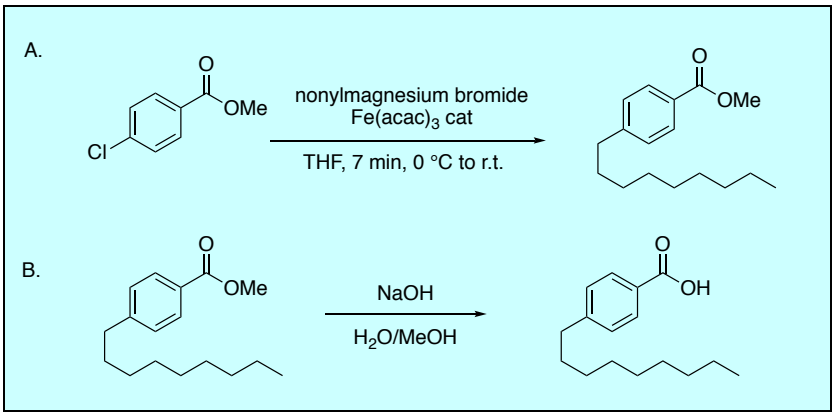

Largely driven by the needs of the life sciences and material chemistry, the demand for ever more efficient procedures for cross coupling does not seem to cease. While palladium-based methods continue to dominate the field at large, the last decade has witnessed the development of a number of innovative new concepts that enrich the portfolio of the practitioner and even challenge organopalladium catalysis in certain ways.

One of these developments relates to the use of early transition metals in lieu of palladium (or other noble metals); actually, this megatrend reaches far beyond cross coupling chemistry.[2] Utilitarian arguments render iron a particularly attractive candidate, because it is cheap, abundant, readily available, environmentally benign and hardly toxic for humans. Moreover, research into homogeneous organoiron catalysis holds the promise of opening entirely new fields of application by leveraging the unique chemical properties of this element in the midst of the periodic table.[2,3]

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Scattered reports on the use of iron catalysts for "cross coupling" date back to the time before this expression had actually been coined. The first deliberate investigation was reported by Kochi and coworkers,[4,5] who showed that simple iron salts are capable of catalyzing the coupling of Grignard reagents with alkenyl halides. Since the yields were variable and the reaction seemed to lack generality, only few applications followed up on this lead finding. It was Cahiez and coworkers who found that the robustness of this process can be largely improved by using aprotic dipolar cosolvents, preferentially N-methylpyrrolidin-2-one (NMP), which seems to stabilize the actual catalyst and/or activates transiently formed organoiron intermediates.[6,7]

Canonical Cross Coupling

Our group showed that the substrate scope reaches far beyond alkenyl halides. In 2002, we reported the first iron-catalyzed cross coupling reactions of aryl- and heteroaryl halides and -sulfonates (Figure 1).[8-12] Shortly thereafter, alkenyl triflates (Figure 2) and acyl chlorides were found to be equally privileged coupling partners.[13] The 2005 *Organic Syntheses* procedures describing the preparation of 4-nonylbenzoic acid, a component of liquid crystalline materials, captures this state of development of iron catalysis well in that it highlights the following notable virtues: (i) high yields with Grignard reagents bearing ß-hydrogen atoms, (ii) exceptionally fast reaction rates at (or below) room temperature, (iii) ready scalability, (iv) convenient ligand-free conditions, and (v) a surprisingly large tolerance vis-à-vis a number of functional groups that are susceptible to uncatalyzed attack by Grignard reagents. Equally important is the fact that electron deficient (hetero)aryl chlorides proved to be more suitable for iron-catalyzed cross coupling than the corresponding bromides or iodides. When working with electron rich (hetero)arenes, however, the corresponding triflates have to be used.[8,9,11] Moreover, it is possible to engage substrates carrying more than one chloride or –sulfonate group either into exhaustive, or site-selective or consecutive one-pot coupling reactions.[9-13]

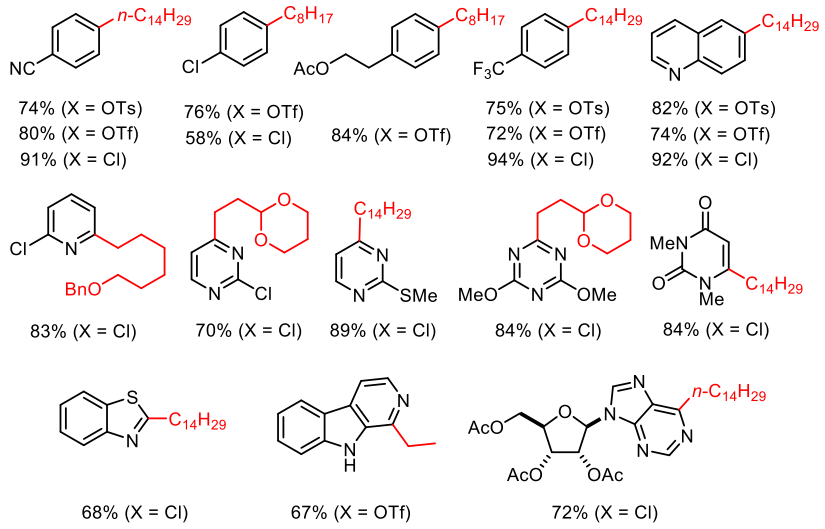


Figure 1. Iron-catalyzed alkyl/(hetero)aryl cross coupling reactions;[9] (throughout this article, the segment derived from the Grignard reagent is shown in red)

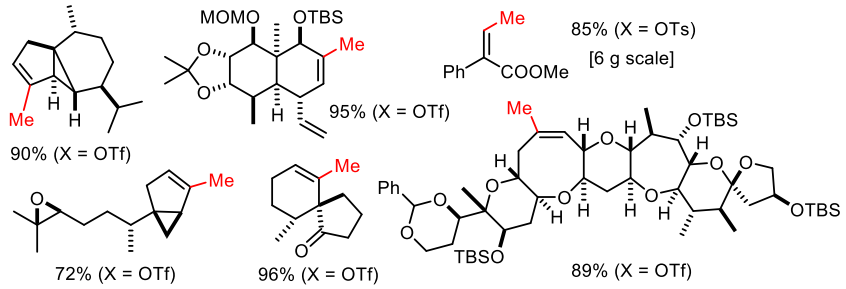


Figure 2. Iron-catalyzed cross coupling of alkenyl sulfonates with MeMg*X*[13,27-31]

In view of these favorable attributes, it may not come as a surprise that this chemistry was rapidly embraced by the academic and industrial community.[14-18] The selected larger scale applications shown in Figure 3 are instructive and illustrate the current state of the art.[19-26]

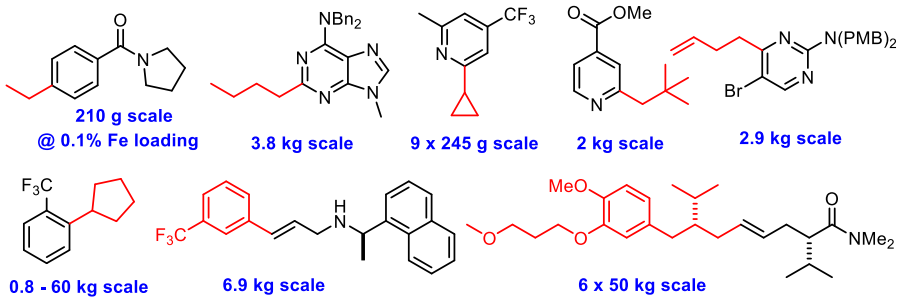


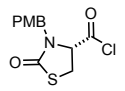
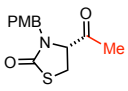
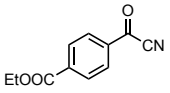
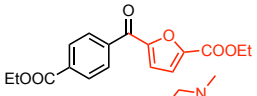
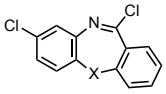
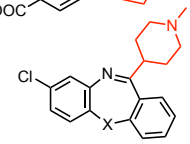
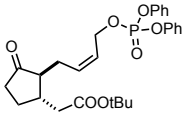
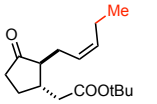
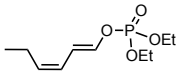
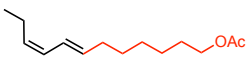
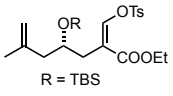
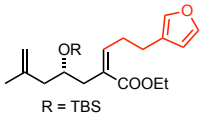
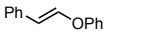
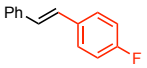
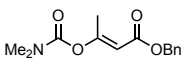
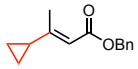
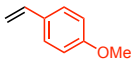
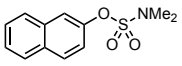
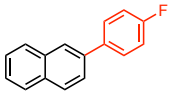
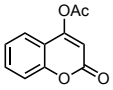
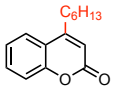
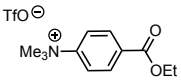
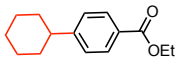
Figure 3. Applications on larger scale[19-26]

Our initial reports had already shown that aryl triflates and even (electron-deficient) aryl tosylates can be cross coupled with alkyl-Grignard reagents in good to excellent yields using $Fe(acac)_3$ as a simple yet efficient precatalyst (cf. Figure 1).[8,9] Alkenyl sulfonates followed shortly thereafter (Figure 2);[13,27,28] a recent *Org. Synth.* procedure further illustrates their utility.[29] Building on these lead discoveries, the scope of the reaction was explored[30-33] and other viable leaving groups were identified, including phosphonates,[23,32,34-37] sulfamates,[32,38,39] carbamates,[38,62] carboxylates,[40,64] trialkyl ammonium salts,[65] and even various (thio) ethers.[61,63] A few selected examples are compiled in Table 1.

Although the cost of the iron salt is hardly a limiting factor, attempts were made to lower the loading; applications using ≤ 1 mol% are not uncommon.[20,41,42] Non-hygroscopic and hence practical $Fe(acac)_3$ is the most popular precatalyst; in certain cases, other salts such as $FeCl_n$ (n = 2, 3), $FeF_3{\cdot}3H_2O$,[38,49] or iron thiolates[43] show better performance. Likewise, numerous iron complexes (formed ex situ or in situ) show good application profiles.

NMP remains the preferred co-solvent for iron-catalyzed cross coupling reactions (although certain reactions work better in its absence). This compound, however, is potentially repro-toxic. Therefore many attempts were made to avoid its use altogether or substitute NMP by more benign additives, solvents or ligands.[6,29,44,45,54] Among them, cyclic ureas such as N,N-dimethylimidazolidin-2-one (DMI)[55] and various (di)amines, especially TMEDA (N,N,N′,N′-tetramethylethylenediamine),[29,46-48] are most common; their use, however, often mandates slow addition of the Grignard reagent to the reaction mixture. Moreover, numerous reports rely on the use of NHC's or (chelating) (di)phosphines.[49-53]

Table 1. Iron-catalyzed cross coupling: Representative examples

Substrate	Product	Yield	Ref.
		80%	56
		78%	57
		71% (X = O) 82% (X = NH) 86% (X = S)	58
		<87%[a]	59
		83%[b,c]	26
		78%	60
		67%	61
		79%	62
		74%	63
		91%[d]	39
		86%	64
		89%	65

[a] using $Me_3ZnMgBr$ in THF at –78°C; [b] using 0.1 mol% of $Fe(acac)_3$; [c] after acetylation;
[d] using FeF_33H_2O (10 mol%), IPrHCl (20 mol%), THF, reflux

These advances notwithstanding, some important limitations also need to be mentioned. In contrast to palladium-catalyzed cross coupling reactions, which excel when it comes to the formation of $C(sp^2)$–$C(sp^2)$ or $C(sp^2)$–C(sp) bonds, most notably aryl-aryl bonds, iron catalysis is currently much less adequate for this very purpose; competing homo-coupling of the Grignard reagent limits the scope. Although advances have been reported, a general solution that truly rivals palladium (or nickel) catalysts in this particularly important field of applications currently remains elusive.[9,38,39,49,66-68,75]

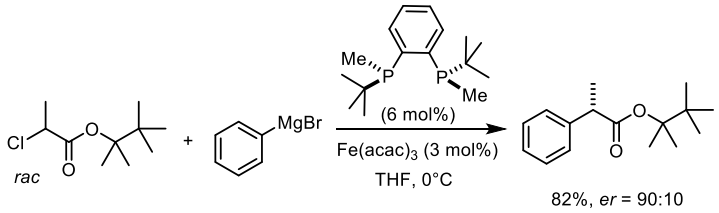
The fact that Grignard reagents are privileged nucleophiles denotes an advantage and a serious limitation at the same time. They are cheap and industrially viable but obviously limited with regard to functional group compatibility. Yet, the exceptional rate of many iron-catalyzed cross coupling reactions partly mitigates this shortcoming: thus, a number of substrates has been successfully engaged, which carry electrophilic substituents that might not subsist in the presence of organomagnesium reagents otherwise. Without claim to be complete, the list includes: alkyl- and aryl halides, amides, carbamates, enoates, epoxides, esters, isocyanates, ketones, nitriles, sulfonates, sulfonamides, thio-carbamates; such kinetic selectivity, however, is potentially case-dependent. Therefore the need persists to enlarge the portfolio of adequate nucleophiles. Encouraging results have been obtained with organomanganese,[69,70] –zinc,[59,71-73] –lithium,[74] –copper,[75] and –boron reagents.[76-80]

In this context, it is pointed out that alkyl/aryl cross coupling can also be effected without preparing a Grignard reagent in a separate step.[81,82] As an example, treatment of a mixture of cyclopentyl bromide and 1-bromo-2-(trifluoromethyl)benzene with magnesium and catalytic amounts of $FeCl_2$ in THF/TMEDA at ambient temperature afforded 1-cyclopentyl-2-(trifluoromethyl)benzene in 67% yield on up to 60 kg scale (Figure 3).[83] As the Grignard reagent transiently formed is directly consumed, large concentrations will not be build-up at any point in time.

Non-Canonical Cross Coupling

The promise that cheap and benign iron catalysts allow palladium to be substituted – at least in certain cross coupling reactions – was (and is) a major incentive.[6,8,9] It soon became clear, however, that this metal is also able to promote cross coupling reactions of substrates that have little or no precedent in the classical canon.

The readiness with which primary and secondary alkyl halides participate in iron-catalyzed cross coupling with arylmagnesium halides and other nucleophiles illustrates the point.[47,48,50,51,84-91] The functional group tolerance is remarkable and even sterically hindered alkyl halides usually react well (Table 2). Moreover, exploratory studies showed that asymmetric enantioconvergent cross coupling of racemic secondary alkyl halides is possible with iron catalysts bearing chelating diphosphine ligands that are chiral at phosphorus (Scheme 1).[92]

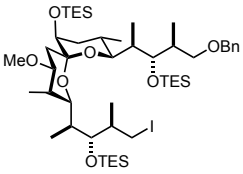
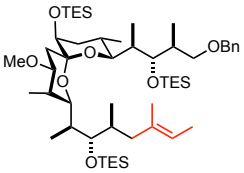
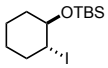
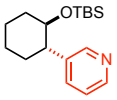
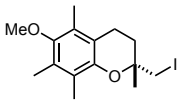
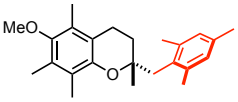
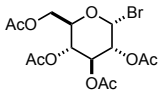
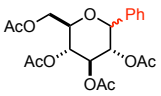
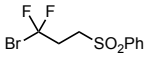
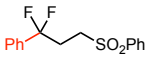
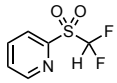
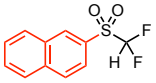
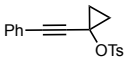
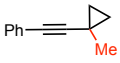
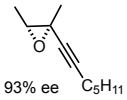
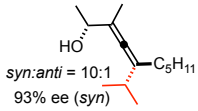
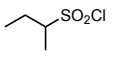
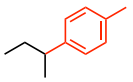
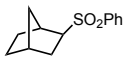
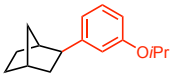


Scheme 1. Pioneering study into asymmetric iron-catalyzed aryl/alkyl cross coupling[92]

Even less conventional substrates work well (Table 2). 1-Alkynylcyclopropyl tosylates, for example, react with Grignard reagents in the presence of $Fe(acac)_3$ cat. under net propargylic substitution;[112] this striking result illustrates that even tertiary alkyl electrophiles can be successfully engaged in iron-catalyzed cross coupling.[52,112] Yet, this pattern contrasts the behavior of most other propargylic compounds, which usually afford allenes by S_N2' type substitution reactions (except for some propargyl bromides).[93-97,113] For propargylic epoxides it was shown that the RMgX reagent approaches *syn* to the O-atom, whereas organocopper reagents deliver the R-substituent *anti* to the leaving group.[95,113]

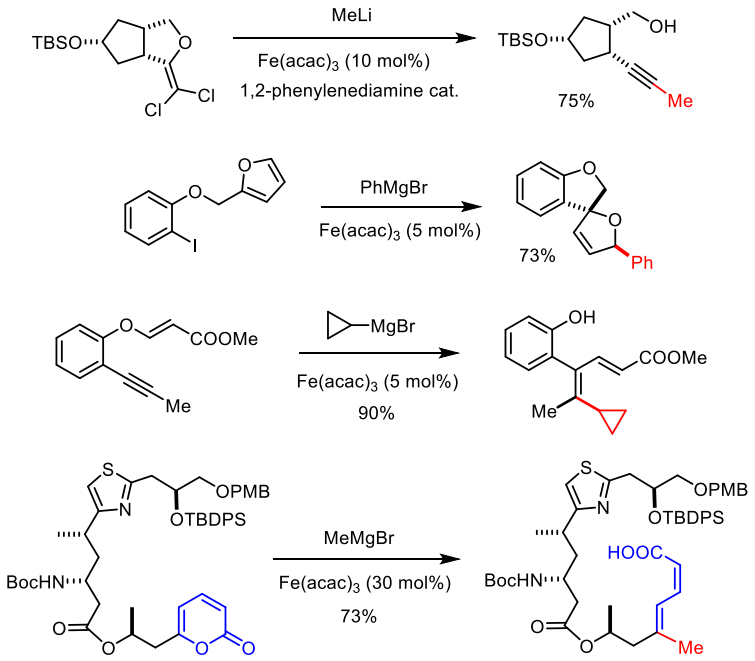
An unconventional cross coupling reaction is manifest in the conversion of lactone-derived *gem*-dichloroalkenes into non-terminal alkynes (Scheme 2).[98-100] Note that the R-group of the organolithium reagent is incorporated into the product as the substituent capping the alkyne; this transformation likely proceeds via carbenoid intermediates. Even more involved cross coupling "cascades" are known in the literature (Scheme 2).[101,102]

Table 2. Iron-catalyzed cross coupling of unorthodox electrophiles

Substrate	Product	Yield	Ref.
		84%	103
		80%	104
		67% {R = $CHPh_2$) 64% (R = Cbz)	105,106
		77%[a]	107
		96%[a,b]	108,109
		62%	110
		81%[b]	111
		70%	112
		94%	113
		64%	114
		62%	115

[a] using an iron diphosophine complex as precatalyst; [b] using Ar_2Zn

 DOI: 10.15227/orgsyn.096.0001



Scheme 2. Some unorthodox iron-catalyzed "cross coupling" reactions[99,101,102,118]

The iron-catalyzed ring opening/cross coupling of 2-pyrone derivatives is fairly unique.[116] In a formal sense, the enol ester moiety embedded into the heterocyclic ring serves as a leaving group. The available mechanistic evidence, however, suggests that the iron catalyst formed in situ does not insert into the C–O bond; rather, coordination to the pyrone π-system is thought to trigger a 1,6-addition/ring opening cascade. Whether the ring opening step itself is an electrocyclic process or follows an ionic mechanism remains to be firmly established. In any case, this chemistry is compatible with functional groups and various donor sites; it gives access to non-thermodynamic dienoates that are difficult to make in isomerically pure form otherwise. A late-stage application during the total synthesis of the potent anticancer agent pateamine A illustrates this aspect (Scheme 2). [117,118]

This Discussion Addendum cannot provide a comprehensive treatise of iron-catalyzed cross coupling, broadly defined;[14-18] rather, the chosen examples are meant to illustrate the tremendous advances in the field since

the original *Org. Synth.* procedure was published in 2005. Although further growth can be safely anticipated, iron catalysis at large awaits better mechanistic understanding.[2] The massive analytical challenges notwithstanding, substantial recent progress provides an encouraging outlook.[119,120]

References

1. Max-Planck-Institut für Kohlenforschung, 45470 Mülheim/Ruhr, Germany. Email address: fuerstner@kofo.mpg.de.
2. Fürstner, A. *ACS Centr. Sci.* **2016**, *2*, 778–789.
3. Nakamura, E.; Yoshikai, N. *J. Org. Chem.* **2010**, *75*, 6061–6067.
4. Tamura, M.; Kochi, J. K. *J. Am. Chem. Soc.* **1971**, *93*, 1487–1489.
5. Kochi, J. K. *J. Organomet. Chem.* **2002**, *653*, 11–19.
6. Cahiez, G.; Avedissian, H. *Synthesis* **1998**, 1199–1205.
7. Munoz, S. B.; Daifuku, S. L.; Sears, J. D.; Baker, T. M.; Carpenter, S. H.; Brennessel, W. W.; Neidig, M. L. *Angew. Chem. Int. Ed.* **2018**, *57*, 6496–6500.
8. Fürstner, A.; Leitner, A. *Angew. Chem. Int. Ed.* **2002**, *41*, 609–612.
9. Fürstner, A.; Leitner, A.; Méndez, M.; Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856–13863.
10. Fürstner, A.; Leitner, A. *Angew. Chem. Int. Ed.* **2003**, *42*, 308–311.
11. Seidel, G.; Laurich, D.; Fürstner, A. *J. Org. Chem.* **2004**, *69*, 3950–3952.
12. Scheiper, B.; Glorius, F.; Leitner, A.; Fürstner, A. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 11960–11965.
13. Scheiper, B.; Bonnekessel, M.; Krause, H.; Fürstner, A. *J. Org. Chem.* **2004**, *69*, 3943–3949.
14. Sherry, B. D.; Fürstner, A. *Acc. Chem. Res.* **2008**, *41*, 1500–1511.
15. Nakamura, E.; Hatakeyama, T.; Ito, S.; Ishizuka, K.; Ilies, L.; Nakamura, M. *Org. React.* **2014**, *83*, 1–209.
16. Bauer, I.; Knölker, H.-J. *Chem. Rev.* **2015**, *115*, 3170–3387.
17. Cahiez, G.; Moyeux, A.; Cossy, J. *Adv. Synth. Catal.* **2015**, *357*, 1983–1989.
18. Piontek, A.; Bisz, E.; Szostak, M. *Angew. Chem. Int. Ed.* **2018**, *57*, 11116–11128.
19. Tewari, N.; Maheshwari, N.; Medhane, R.; Nizar, H.; Prasad, M. *Org. Process Res. Dev.* **2012**, *16*, 1566–1568.
20. Rushworth, P. J.; Hulcoop, D. G.; Fox, D. J. *J. Org. Chem.* **2013**, *78*, 9517–9521.

21. Risatti, C.; Natalie Jr., K. J.; Shi, Z.; Conlon, D. A. *Org. Process Res. Dev*. **2013**, *17*, 257–264.
22. Bartoccini, F.; Piersanti, G.; Armaroli, S.; Cerri, A.; Cabri, W. *Tetrahedron Lett*. **2014**, *55*, 1376–1378.
23. Andersen, S. M.; Bollmark, M.; Berg, R.; Fredriksson, C.; Karlsson, S.; Liljeholm, C.; Sörensen, H. *Org. Process Res. Dev*. **2014**, *18*, 952–959.
24. Gangula, S.; Neelam, U. K.; Baddam, S. R.; Dahanukar, V. H.; Bandichhor, R. *Org. Process Res. Dev*. **2015**, *19*, 470–475.
25. Mullens, P.; Cleator, E.; McLaughlin, M.; Bishop, B.; Edwards, J.; Goodyear, A.; Andreani, T.; Jin, Y.; Kong, J.; Li, H.; Williams, M.; Zacuto, M. *Org. Process Res. Dev*. **2016**, *20*, 1075–1087.
26. Cahiez, G.; Guerret, O.; Moyeux, A.; Dufour, S.; Lefevre, N. *Org. Process Res. Dev*. **2017**, *21*, 1542–1546.
27. Fürstner, A.; Hannen, P. *Chem. Eur. J*. **2006**, *12*, 3006–3019.
28. Fürstner, A.; Schlecker, A. *Chem. Eur. J*. **2008**, *14*, 9181–9191.
29. Tsutsumi, T.; Ashida, Y.; Nishikado, H.; Tanabe, Y. *Org. Synth*. **2018**, *95*, 403–424.
30. (a) Hamajima, A.; Isobe, M. *Org. Lett*. **2006**, *8*, 1205–1208. (b) Maulide, N.; Marko, I. *Synlett* **2005**, 2195–2198.
31. Liu, Q.; Deng, Y.; Smith, A. B. *J. Am. Chem. Soc*. **2017**, *139*, 13668–13671.
32. Gogsig, T. M.; Lindhardt, A. T.; Skrydstrup, T. *Org. Lett*. **2009**, *11*, 4886–4888.
33. Agrawal. T.; Cook, S. P. *Org. Lett*. **2013**, *15*, 96–99.
34. Larsen, U. S.; Martiny, L.; Begtrup, M. *Tetrahedron Lett*. **2005**, *46*, 4261–4263.
35. Cahiez, G.; Gager, O.; Habiak, V. *Synthesis* **2008**, 2636-2644.
36. Li, Z.; Liu, L.; Sun, H.; Shen, Q.; Zhang, Y. *Dalton Trans*. **2016**, *45*, 17739–17747.
37. Xing, T.; Zhang, Z.; Da, Y.-X.; Quan, Z.-J.; Wang, X.-C. *Asian J. Org. Chem*. **2015**, *4*, 538–544.
38. Silberstein, A. L.; Ramgren, S. D.; Garg, N. K. *Org. Lett*. **2012**, *14*, 3796–3799.
39. Agrawal. T.; Cook, S. P. *Org. Lett*. **2014**, *16*, 5080–5083.
40. Li, B.-J.; Wu, Z.-H.; Guan, B.-T.; Sun, C.-L.; Wang, B.-Q.; Shi, Z.-J. *J. Am. Chem. Soc*. **2009**, *131*, 14656–14657.
41. Bisz, E.; Szostak, M. *Adv. Synth. Catal*. (DOI: 10.1002/adsc.201800849).
42. Buono, F. G.; Zhang, Y.; Tan, Z.; Brusoe, A.; Yang, B.-S.; Lorenz, J. C.; Giovannini, R.; Song, J. J.; Yee, N. K.; Senanayake, C. H. *Eur. J. Org. Chem*. **2016**, 2599–2602.

43. Cahiez, G.; Gager, O.; Buendia, J.; Patrinote, C. *Chem. Eur. J.* **2012**, *18*, 5860–5863.
44. Sova, M.; Frlan, R.; Gobec, S.; Stavber, G.; Casar, Z. *Appl. Organomet. Chem*. **2015**, *29*, 528–535.
45. Kuzmina, O. M.; Steib, A. K.; Markiewicz, J. T.; Flubacher, D.; Knochel, P. *Angew. Chem. Int. Ed*. **2013**, *52*, 4945–4949.
46. Noda, D.; Sunada, Y.; Hatakeyama, T.; Nakamura, M.; Nagashima, H. *J. Am. Chem. Soc*. **2009**, *131*, 6078–6079.
47. Cahiez, G.; Habiak, V.; Duplais, C.; Moyeux, A. *Angew. Chem. Int. Ed*. **2007**, *46*, 4364–4366.
48. Bedford, R. B.; Bruce, D. W.; Frost, R. M.; Hird, M. *Chem. Commun*. **2005**, 4161–4163.
49. Hatakeyama, T.; Hashimoto, S.; Ishizuka, K.; Nakamura, M. *J. Am. Chem. Soc*. **2009**, *131*, 11949–11963.
50. Bica, K.; Gaertner, P. *Org. Lett*. **2006**, *8*, 733–735.
51. Bedford, R. B.; Betham, M.; Bruce, D. W.; Danopoulos, A. A.; Frost, R. M.; Hird, M. *J. Org. Chem*. **2006**, *71*, 1104–1110.
52. Ghorai, S. K.; Jin, M.; Hatakeyama, T.; Nakamura, M. *Org. Lett*. **2012**, *14*, 1066–1069.
53. Perry, M. C.; Gillett, A. N.; Law, T. C. *Tetrahedron Lett*. **2012**, *53*, 4436–4439.
54. Kuzmina, O. M.; Steib, A. K.; Flubacher, D.; Knochel, P. *Org. Lett*. **2012**, *14*, 4818–4821.
55. Bisz, E.; Szostak, M. *Green Chem*. **2017**, *19*, 5361–5366.
56. Fürstner, A.; De Souza, D.; Parra-Rapado, L.; Jensen, J. *Angew. Chem. Int. Ed*. **2003**, *42*, 5358–5360.
57. Duplais, C.; Bures, F.; Sapountzis, I.; Korn, T. J.; Cahiez, G.; Knochel, P. *Angew. Chem. Int. Ed*. **2004**, *43*, 2968–2970.
58. Ottesen, L. K.; Ek, R.; Olsson, R. *Org. Lett*. **2006**, *8*, 1771–1773.
59. Saito, S.; Yamazaki, S.; Yamamoto, H. *Angew. Chem. Int. Ed*. **2001**, *40*, 3613–3617.
60. Deng, H.; Cao, W.; Liu, R.; Zhang, Y.; Liu, B. *Angew. Chem. Int. Ed.* **2017**, *56*, 5849–5852.
61. Iwasaki, T.; Akimoto, R.; Kuniyasu, H.; Kambe, N. *Chem. Asian J*. **2016**, *11*, 2834–2837.
62. Parra Rivera, A. C.; Still, R.; Frantz, D. E. *Angew. Chem. Int. Ed*. **2016**, *55*, 6689–6693.
63. Itami, K.; Higashi, S.; Mineo, M.; Yoshida, J.-I. *Org. Lett*. **2005**, *7*, 1219–1222.

64. Gärtner, D.; Stein, A. L.; Gruppe, S.; Arp, J.; Jacobi von Wangelin, A. *Angew. Chem. Int. Ed*. **2015**, *54*, 10545–10549.
65. Guo, W.-J.; Wang, Z.-X. *Tetrahedron* **2013**, *69*, 9580–9585.
66. Chua, Y.-Y.; Duong, H. A. *Chem. Commun*. **2016**, *52*, 1466–1469.
67. Teng, Q.; Wu, W.; Duong, H. A.; Huynh, H. V. *Chem. Commun*. **2018**, 54, 6044–6057.
68. Zhang, R.; Zhao, Y.; Liu, K.-M.; Duan, X.-F. *Org. Lett*. **2018**, *20*, 7942–7946.
69. Hofmayer, M. S.; Hammann, J. M.; Cahiez, G.; Knochel, P. *Synlett* **2018**, *29*, 65–70.
70. Fürstner, A.; Brunner, H. *Tetrahedron Lett*. **1996**, *37*, 7009–7012.
71. Nakamura, M.; Ito, S.; Matsuo, K.; Nakamura, E. *Synlett* **2005**, 1794–1798.
72. Ito, S.; Fujiwara, Y.-I.; Nakamura, E.; Nakamura, M. *Org. Lett*. **2009**, *11*, 4306–4309.
73. Benischke, A. D.; Leroux, M.; Knoll, I.; Knochel, P. *Org. Lett*. **2016**, *18*, 3636–3629.
74. Liu, Q.; Wang, Z.-Y.; Peng, X.-S.; Wong, H. N. C. *J. Org. Chem*. **2018**, *83*, 6325–6333.
75. Sapounzis, I.; Lin, W.; Kofink, C. C.; Despotopoulou, C.; Knochel, P. *Angew. Chem. Int. Ed*. **2004**, *43*, 1454–1458.
76. Hatakeyama, T.; Hashimoto, T.; Kondo, Y.; Fujiwara, Y.; Seike, H.; Takaya, H.; Tamada, Y.; Ono, T.; Nakamura, M. *J. Am. Chem. Soc*. **2010**, *132*, 10674–10676.
77. Hatakeyama, T.; Hashimoto, T.; Nakamura, M. *J. Org. Chem*. **2012**, *77*, 1168–1172.
78. Nakawaga, N.; Hatakeyama, T.; Nakamura, M. *Chem. Lett*. **2015**, *44*, 486–488.
79. Bedford, R. B.; Brenner, P. B.; Carter, E.; Carvell, T. W.; Cogswell, P. M.; Gallagher, T.; Harvey, J. N.; Murphy, D. M.; Neeve, E. C.; Nunn, J.; Pye, D. R. *Chem. Eur. J*. **2014**, *20*, 7935–7938.
80. O'Brien, H. M.; Manzotti, M.; Abrams, R. D.; Elorriaga, D.; Sparkes, H. A.; Davis, S.A.; Bedford, R. B. *Nature Catal*. **2018**, *1*, 429–437.
81. Czaplik, W. M.; Mayer, M.; Jacobi von Wangelin, A. *Angew. Chem. Int. Ed*. **2009**, *48*, 607–-610.
82. Fürstner, A. *Angew. Chem. Int. Ed*. **2009**, *48*, 1364–367.
83. Sengupta, D.; Gharnaoui, T.; Krishnan, A.; Buzard, D. J.; Jones, R. M.; Ma, Y.-A.; Burda, R.; Montalban, A. G.; Semple, G. *Org. Proc. Res. Dev*. **2015**, *19*, 618–623.

84. Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, E. *J. Am. Chem. Soc*. **2004**, *126*, 3686–3687.
85. Nagano, T.; Hayashi, T. *Org. Lett*. **2004**, *6*, 1297–1299.
86. Martin, R.; Fürstner, A. *Angew. Chem. Int. Ed*. **2004**, *43*, 3955–3957.
87. Fürstner, A.; Martin, R.; Krause, H.; Seidel, G.; Goddard, R.; Lehmann, C. W. *J. Am. Chem. Soc*. **2008**, *130*, 8773–8787.
88. Chowdhury, R. R.; Crane, A. K.; Fowler, C.; Kwong, P.; Kozak, C. M. *Chem. Commun*. **2008**, 94–96.
89. Guérinot, A.; Reymond, S.; Cossy, J. *Angew. Chem. Int. Ed*. **2007**, *46*, 6521–6524.
90. Bauer, G.; Cheung, C. W.; Hu, X. *Synthesis* **2015**, *47*, 1726–1732.
91. Dongul, K. G.; Koh, H.; Sau, M.; Chai, C. L. L. *Adv. Synth. Catal*. **2007**, *349*, 1015–1018.
92. Jin, M.; Adak, L.; Nakamura, M. *J. Am. Chem. Soc*. **2015**, *137*, 7128–7134.
93. Pasto, D. J.; Chou, S. K.; Waterhouse, A.; Shults, R. H.; Hennion, G. F. *J. Org. Chem*. **1978**, *43*, 1385–1388.
94. Domingo-Legards, P.; Soler-Yanes, R.; Quiros-López, M. T.; Bunuel, E.; Cárdenas, D. J. *Eur. J. Org. Chem*. **2018**, 4900–4904.
95. Fürstner, A.; Kattnig, E.; Lepage, O. *J. Am. Chem. Soc*. **2006**, *128*, 9194–9204.
96. Kang, T.; Song, S. B.; Kim, W.-Y.; Kim, B. G.; Lee, H.-Y. *J. Am. Chem. Soc.* **2014**, *136*, 10274–10276.
97. Kessler, S. N.; Bäckvall, J. E. *Angew. Chem. Int. Ed*. **2016**, *55*, 3734–3738.
98. Lehr, K.; Schulthoff, S.; Ueda, Y.; Mariz, R.; Leseurre, L.; Gabor, B.; Fürstner, A. *Chem. Eur. J*. **2015**, *21*, 219–227.
99. Fuchs, M.; Fürstner, A. *Angew. Chem. Int. Ed*. **2015**, *54*, 3978–3982.
100. Mata, G.; Wölfl, B.; Fürstner, A. *Chem. Eur. J*. **2019**, *25*, 246–254.
101. Adams, K.; Ball, A. K.; Birkett, J.; Brown, L.; Chappell, B.; Gill, D. M.; Lo, P. K. T.; Patmore, N. J.; Rice, C. R.; Ryan, J.; Raubo, P.; Sweeney, J. B. *Nature Chem*. **2016**, *9*, 396–401.
102. Echeverria, P.-G.; Fürstner, A. *Angew. Chem. Int. Ed*. **2016**, *55*, 11188–11192.
103. Gregg, C.; Gunawan, C.; Ng, A. W. Y.; Wimala, S.; Wickremasinghe, S.; Rizzacasa, M. A. *Org. Lett*. **2013**, *15*, 516–519.
104. Steib, A. K.; Thaler, T.; Komeyama, K.; Mayer, P.; Knochel, P. *Angew. Chem. Int. Ed*. **2011**, *50*, 3303–3307.
105. Parmar, D.; Henkel, L.; Dib, J.; Rueping, M. *Chem. Commun*. **2015**, *51*, 2111–2113.

106. Barré, B.; Gonnard, L.; Campagne, R.; Reymond, S.; Marin, J.; Ciapetti, P.; Brellier, M.; Guérinot, A.; Cossy, J. *Org. Lett*. **2014**, *16*, 6160–6163.
107. Sun, C.-L.; Krause, H.; Fürstner, A. *Adv. Synth. Catal*. **2014**, *356*, 1281–1291.
108. Adak, L.; Kawamura, S.; Toma, G.; Takenaka, T.; Isozaki, K.; Takaya, H.; Orita, A.; Li, H. C.; Shing, T. K. M.; Nakamura, M. *J. Am. Chem. Soc*. **2017**, *139*, 10693–10701.
109. Nicolas, L.; Angibaud, P.; Stansfield, I.; Bonnet, P.; Meerpoel, L.; Reymond, S.; Cossy, J. *Angew. Chem. Int. Ed*. **2012**, *51*, 11101–11104.
110. An, L.; Xiao, Y.-L. ; Zhang, S.; Zhang, X. *Angew. Chem. Int. Ed*. **2018**, *57*, 6921–6925.
111. Miao, W.; Zhao, Y.; Ni, C.; Gao, B.; Zhang, W.; Hu, J. *J. Am. Chem. Soc*. **2018**, *140*, 880–883.
112. Tindall, D. J. ; Krause, H. ; Fürstner, A. *Adv. Synth. Catal*. **2016**, *358*, 2398–2403.
113. Fürstner, A.; Méndez, M. *Angew. Chem. Int. Ed*. **2003**, *42*, 5355–5357.
114. Rao Volla, C. M.; Vogel, P. *Angew. Chem. Int. Ed*. **2008**, *47*, 1305–1307.
115. Denmark, S. E.; Cresswell, A. J. *J. Org. Chem*. **2013**, *78*, 12593–12628.
116. Sun, C.-L.; Fürstner, A. *Angew. Chem. Int. Ed*. **2013**, *52*, 13071–13075.
117. Zhuo, C.-X.; Fürstner, A. *Angew. Chem. Int. Ed*. **2016**, *55*, 6051–6056.
118. Zhuo, C.-X.; Fürstner, A. *J. Am. Chem. Soc*. **2018**, *140*, 10514–10523.
119. Casitas, A.; Krause, H.; Goddard, R.; Fürstner, A. *Angew. Chem. Int. Ed*. **2015**, *54*, 1521–1526.
120. Sears, J. D.; Neate, P. G. N.; Neidig, M. L. *J. Am. Chem. Soc*. **2018**, *140*, 11872–11883.

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