# *Iron-Catalyzed Carbon-Carbon Cross-Coupling*

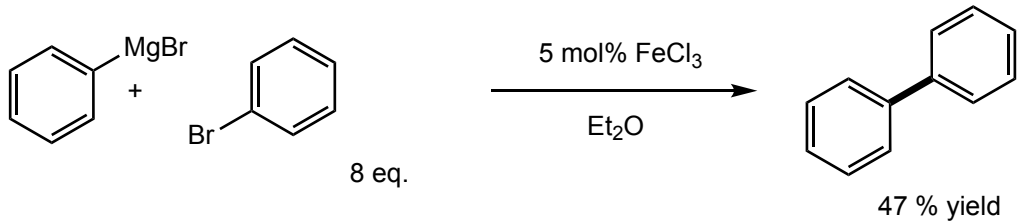
***Adam Bass, Tropical Seminar***
***12/10/2024***





# *Iron-Catalyzed Cross-Coupling: First Examples*

***First report by Karasch and Fields in 1941***

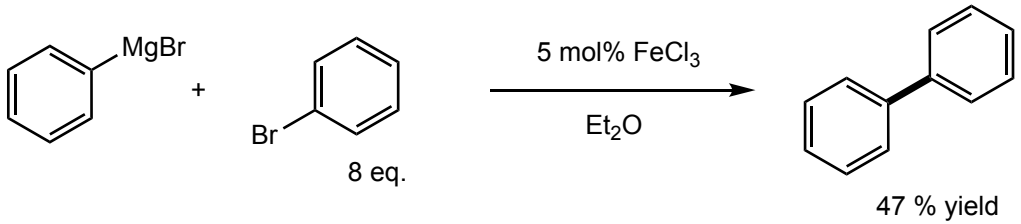



*Reported alongside similar results for many first-row metal salts*

M. S. Kharasch and E. K. Fields *Journal of the American Chemical Society* **1941** *63* (9), 2316-2320

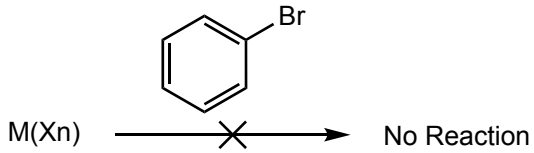
# *Iron-Catalyzed Cross-Coupling: First Examples*

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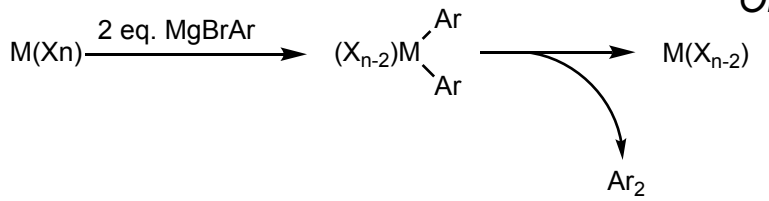



*Reported alongside similar results for many first-row metal salts*

***Reasoned that reduction by nucleophile must generate active species***



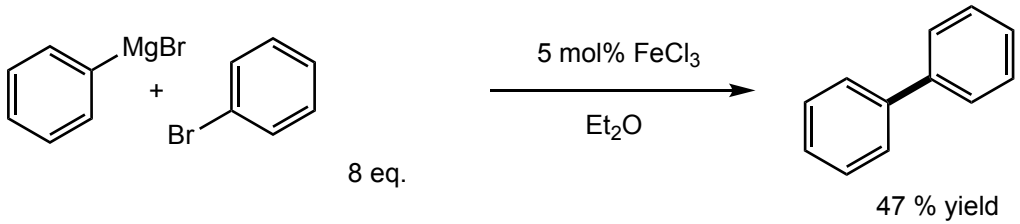

*On-cycle*




M. S. Kharasch and E. K. Fields *Journal of the American Chemical Society* **1941** *63* (9), 2316-2320

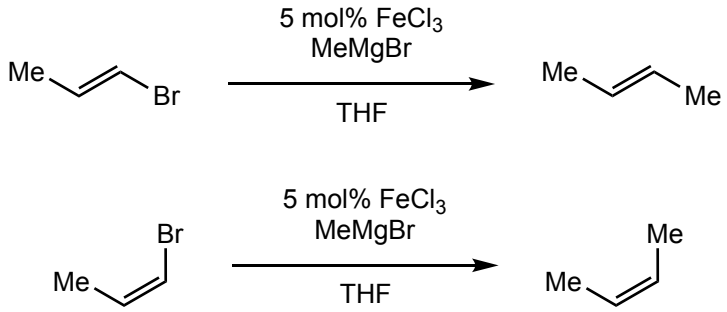
# *Iron-Catalyzed Cross-Coupling: Alkenyl Halides*

## *First report by Karasch in 1941*




*Reported alongside similar results for many first-row metal salts*

## *Followed by Kochi in 1971*

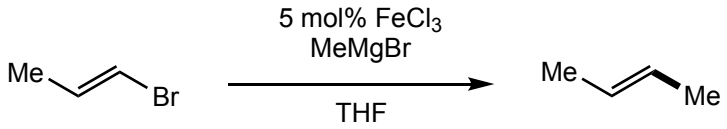


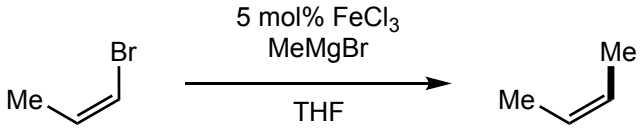

*Trans >15x faster than cis*

M. S. Kharasch and E. K. Fields *Journal of the American Chemical Society* **1941** *63* (9), 2316-2320
Masuhiko Tamura and Jay K. Kochi *Journal of the American Chemical Society* **1971** *93* (6), 1487-1489

# *Iron-Catalyzed Cross-Coupling: Alkenyl Halides*

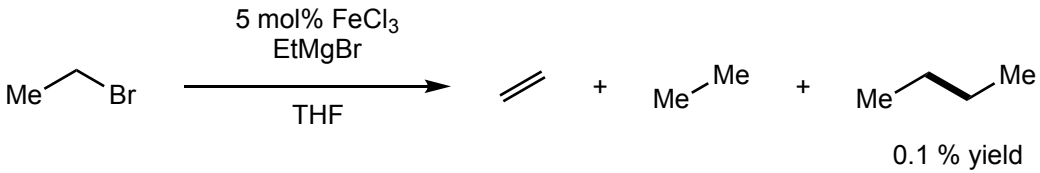
***Followed by Kochi in 1971***




*Trans >15x faster than cis*

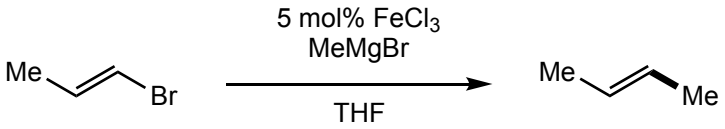
***Observed poor conversion when alkyl electrophile and ethyl nucleophile used***

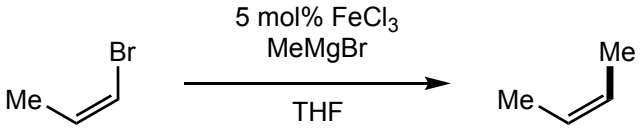



Masuhiko Tamura and Jay K. Kochi *Journal of the American Chemical Society* **1971** *93* (6), 1487-1489

# *Iron-Catalyzed Cross-Coupling: Use of NMP*

***Followed by Kochi in 1971***

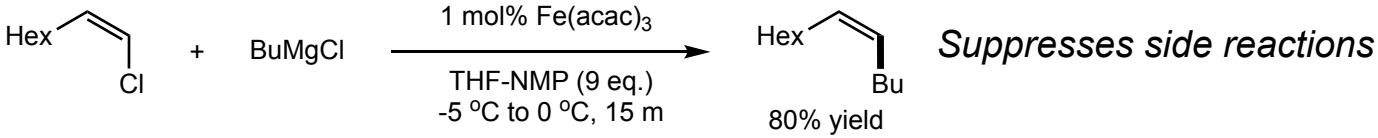



*Trans >15x faster than cis*

***In 1998, Cahiez reports utility of NMP as a cosolvent — first "ligand" innovation in [Fe]-Kumada coupling***

***Generalizing Kochi's coupling***



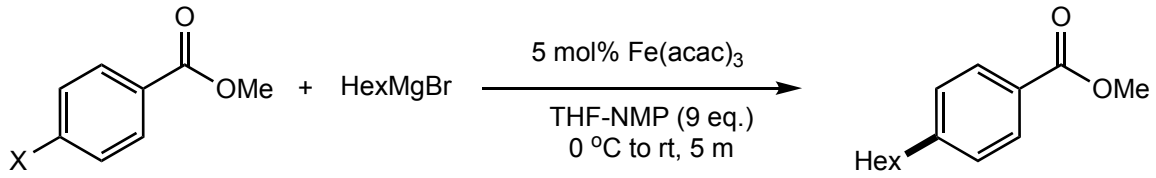

*Suppresses side reactions*


Masuhiko Tamura and Jay K. Kochi *Journal of the American Chemical Society* **1971** *93* (6), 1487-1489

Gérard Cahiez and Hovsep Avedissian *Synthesis* **1998** 1998(8): 1199-1205

# *Iron-Catalyzed Cross-Coupling: Aryl Electrophile*

***First report of aryl cross-coupling by Fürstner in 2002***

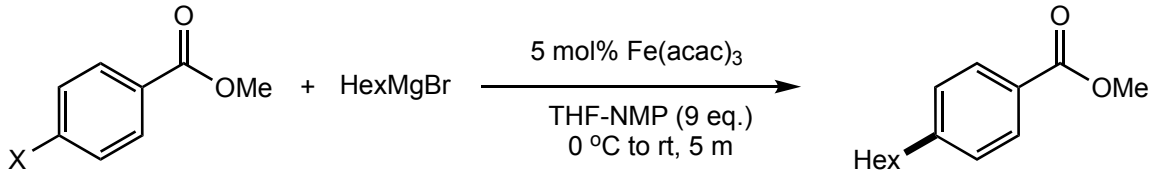



High yields for X = Cl, OTs, OTf
Lower yields and reduction for X = Br, I

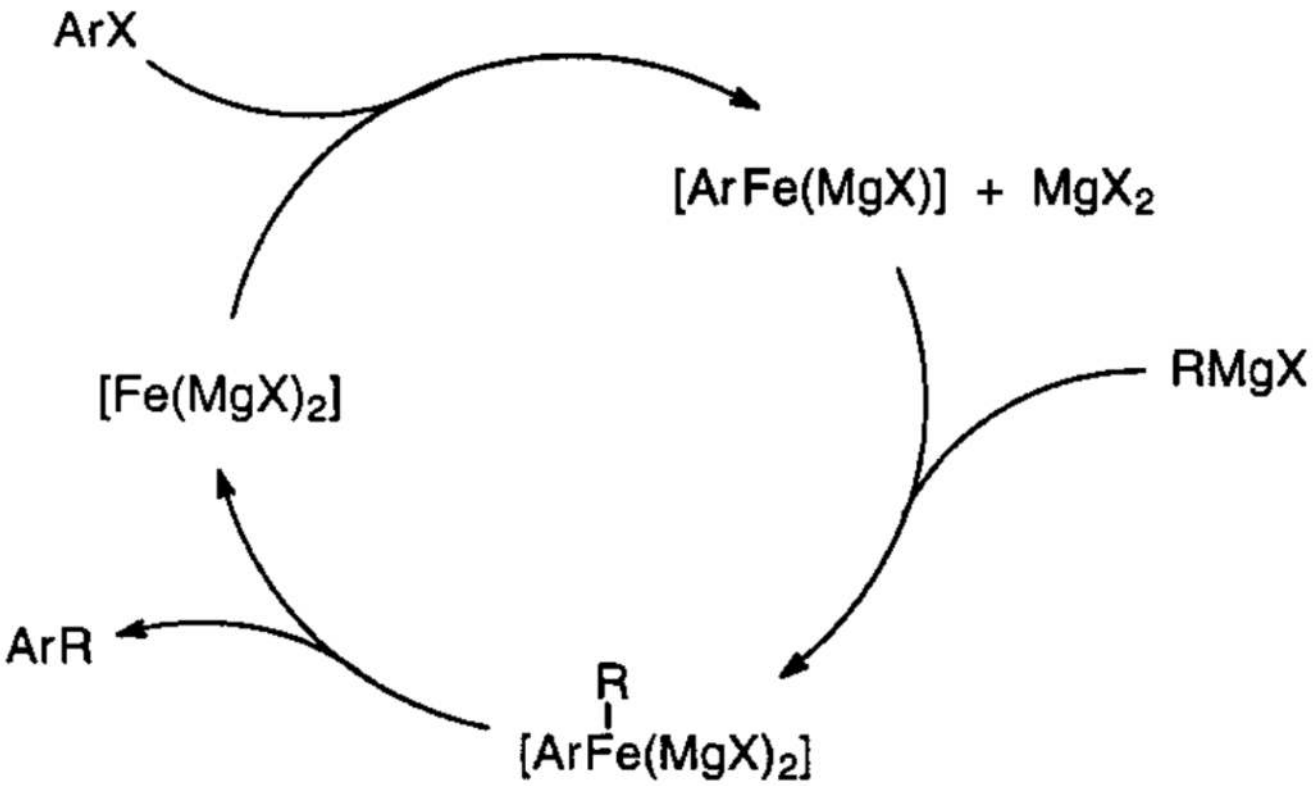
Alois Fürstner and Andreas Leitner *Angew. Chem. Int. Ed.* **2002**, 41, 4, 609-612

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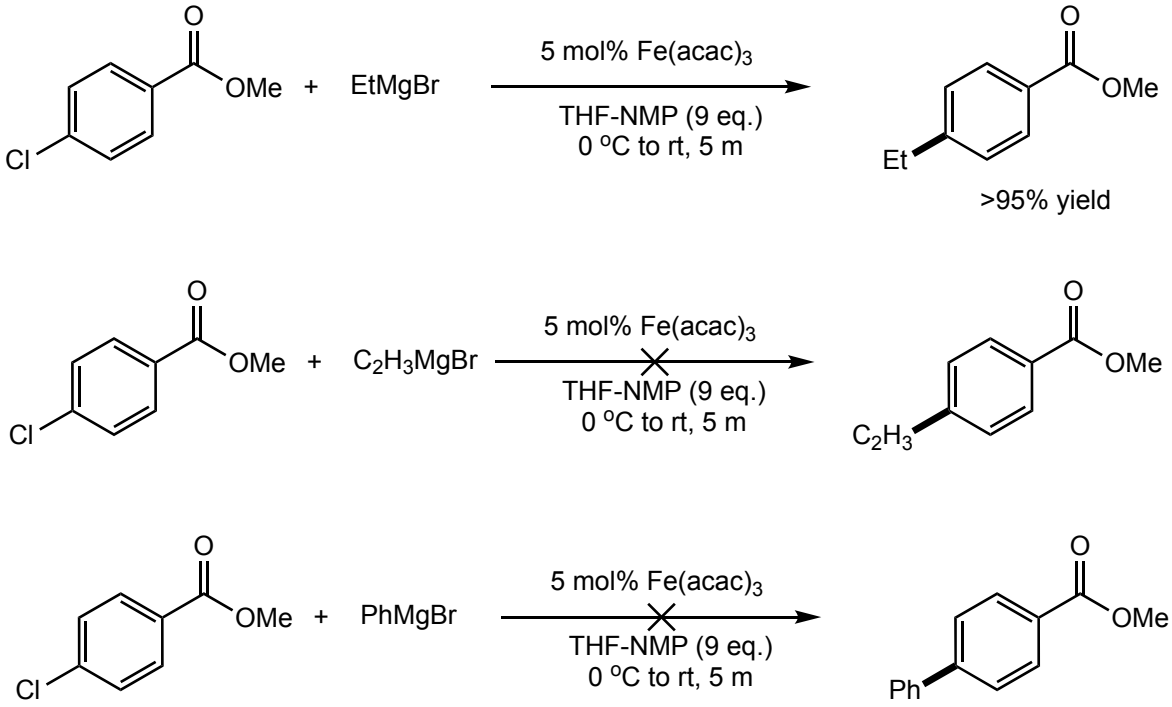



***An $Fe^{2-}$ species is proposed as the on-cycle nucleophile***

Alois Fürstner and Andreas Leitner *Angew. Chem. Int. Ed.* **2002**, 41, 4, 609-612

# *Iron-Catalyzed Cross-Coupling: Aryl Electrophile*

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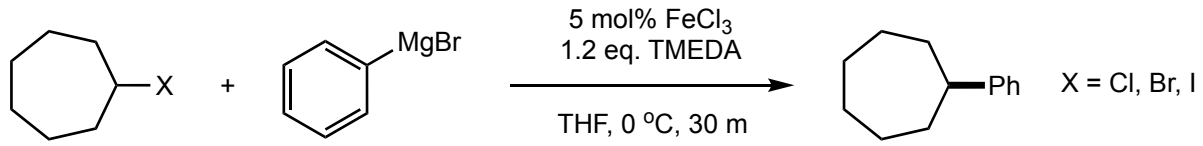



***Poor yields with nucleophiles not containing beta-hydrogens suggests beta-hydrogen elimination is key in catalyst reduction***

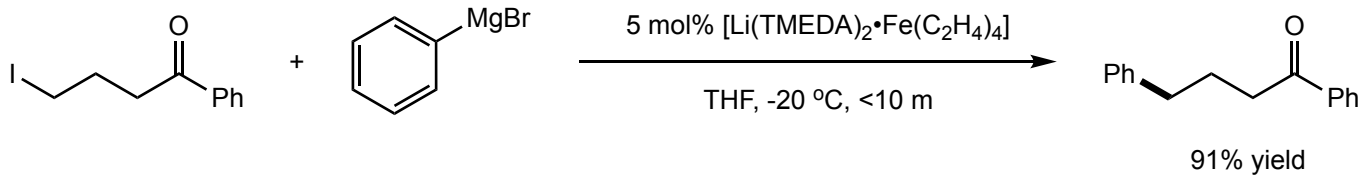
Alois Fürstner and Andreas Leitner *Angew. Chem. Int. Ed.* **2002**, 41, 4, 609-612

# *Iron-Catalyzed Cross-Coupling: Alkyl Halides*

***Nakamura, Fürstner employed now-popular TMEDA ligand in "umpolung" catalysis — continues to be popular in Kumada couplings***




***Fürstner continues to invoke highly-reduced intermediates — but comparable to Fe(III) precatalysts***



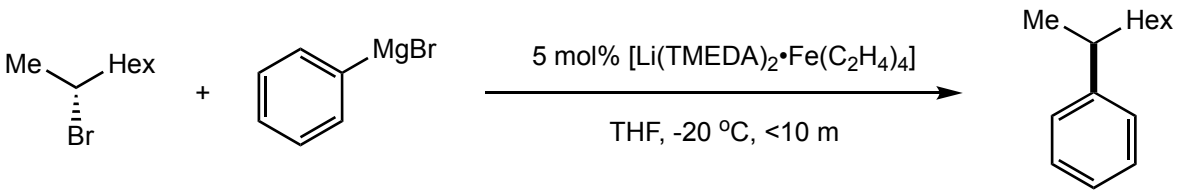

91% yield


Rúben Martin and Alois Fürstner *Angew. Chem. Int. Ed.* **2004**, 43, 3955—3957

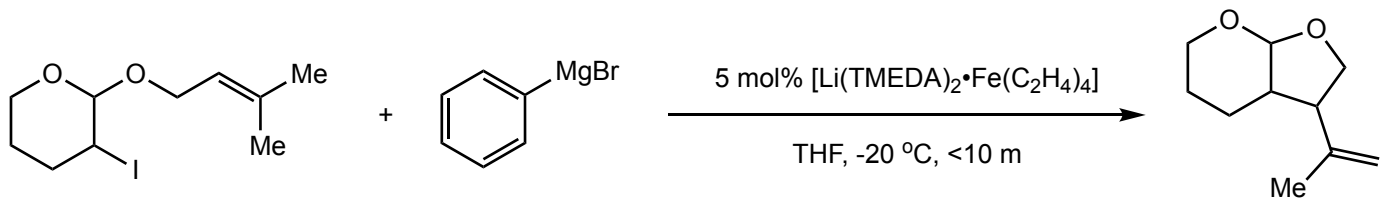
Masaharu Nakamura, Keiko Matsuo, Shingo Ito, and Eiichi Nakamura *Journal of the American Chemical Society* **2004** *126* (12), 3686-3687

# *Iron-Catalyzed Cross-Coupling: Deconvoluting [O]-States*

***Radical-based mechanism is proposed by Fürstner and Nakamura***




94% yield, racemic



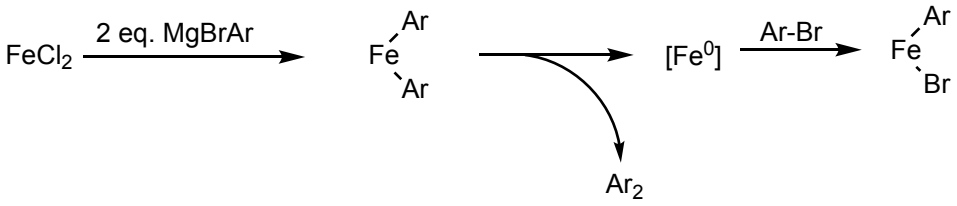

77% yield


Rúben Martin and Alois Fürstner *Angew. Chem. Int. Ed.* **2004**, 43, 3955—3957

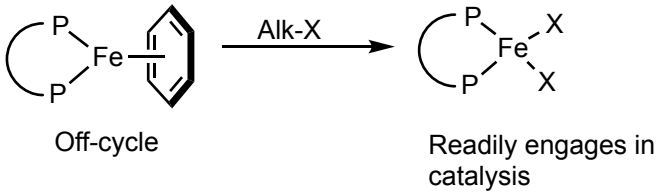
Masaharu Nakamura, Keiko Matsuo, Shingo Ito, and Eiichi Nakamura *Journal of the American Chemical Society* **2004** *126* (12), 3686-3687

# *Iron-Catalyzed Cross-Coupling: Deconvoluting [O]-States*

***C(sp$^2$)—X activation may require low-valent species (Fe$^n$, n<2)***



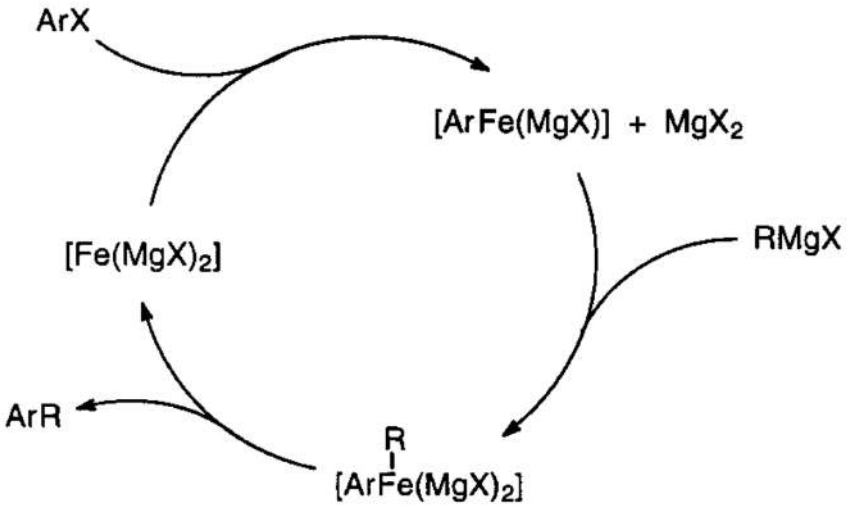

***Low-valent [Fe] reacts quickly with C(sp$^3$)—X, forming on-cycle Fe(II) species***



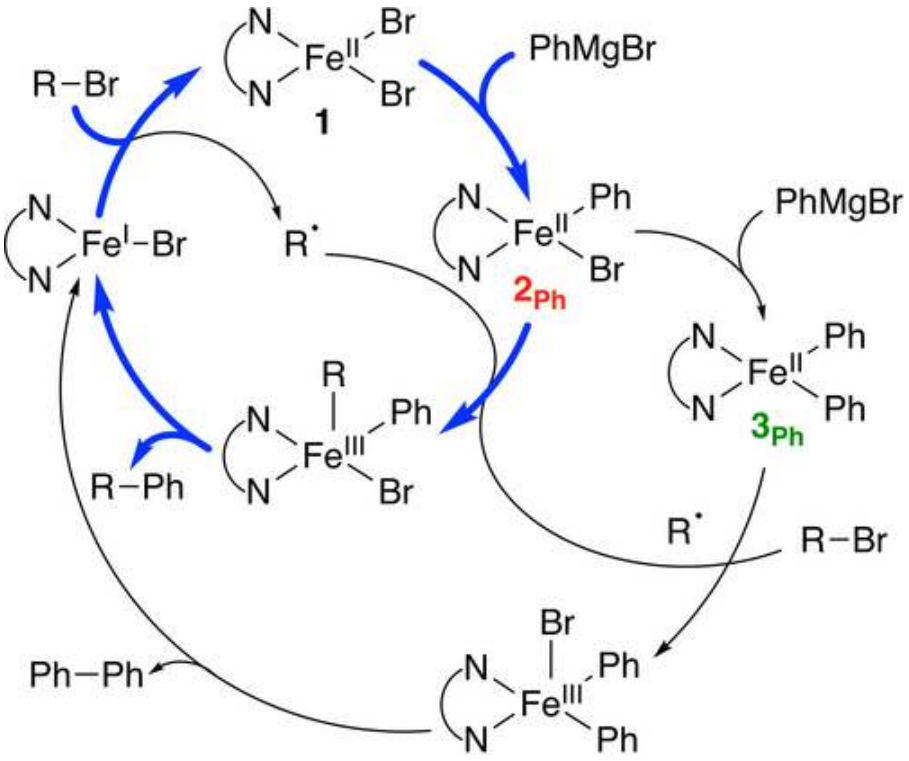

***Reactivity toward C(sp$^2$)—X more likely from low-valent iron species, C(sp$^3$)—X activation possible from Fe(II)***

# *Iron-Catalyzed Cross-Coupling: Mechanisms of C($sp^2$)—C($sp^3$) Kumada Coupling*

**For Ar—X electrophile: ate-complex activation**




**For Alk—X electrophile: radical chain**



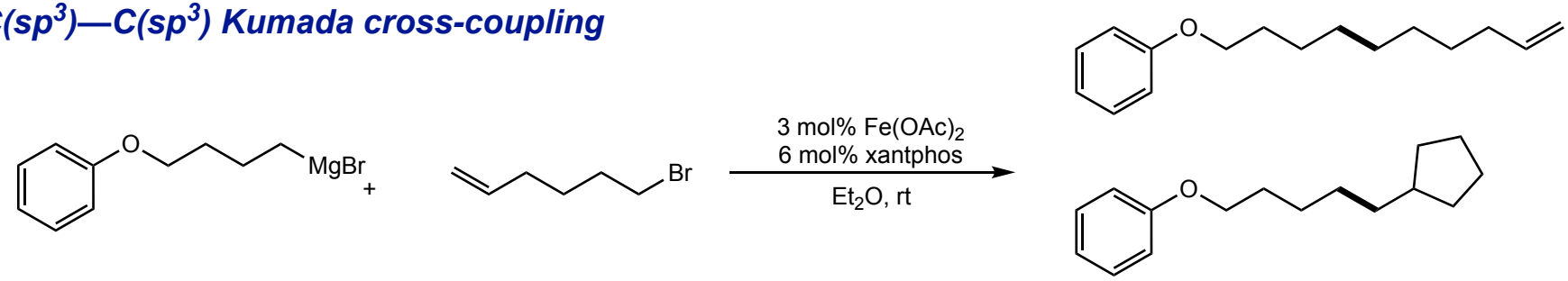


Nikki J. Bakas, Jeffrey D. Sears, William W. Brennessel, and Michael L. Neidig *Angew. Chem. Int. Ed.* **2022**, 61, e202114986

Alois Fürstner and Andreas Leitner *Angew. Chem. Int. Ed.* **2002**, 41, 4, 609-612

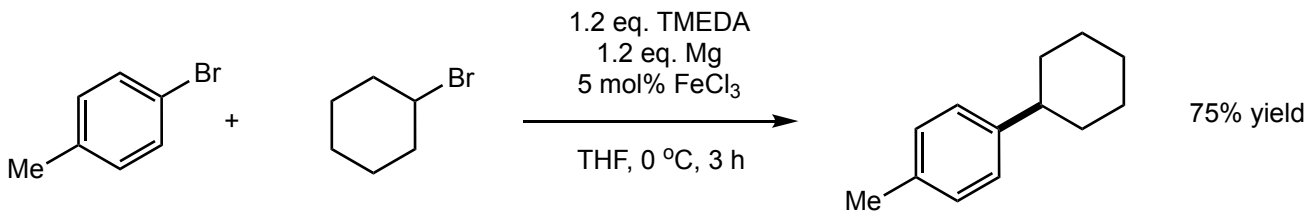
# *Iron-Catalyzed Cross-Coupling: Expanding Beyond C($sp^2$)—C($sp^3$) Kumada Coupling*

## *C($sp^3$)—C($sp^3$) Kumada cross-coupling*



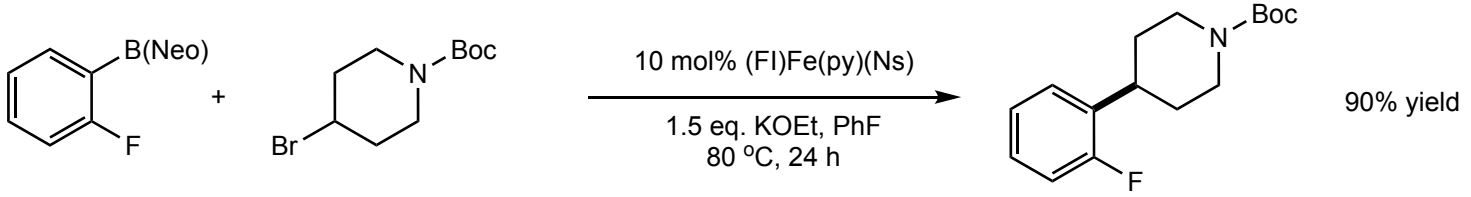

51% yield, 95:5 cyclized:linear

## *Cross-electrophile coupling*




75% yield

## *Milder nucleophiles: Negishi and Suzuki*




90% yield

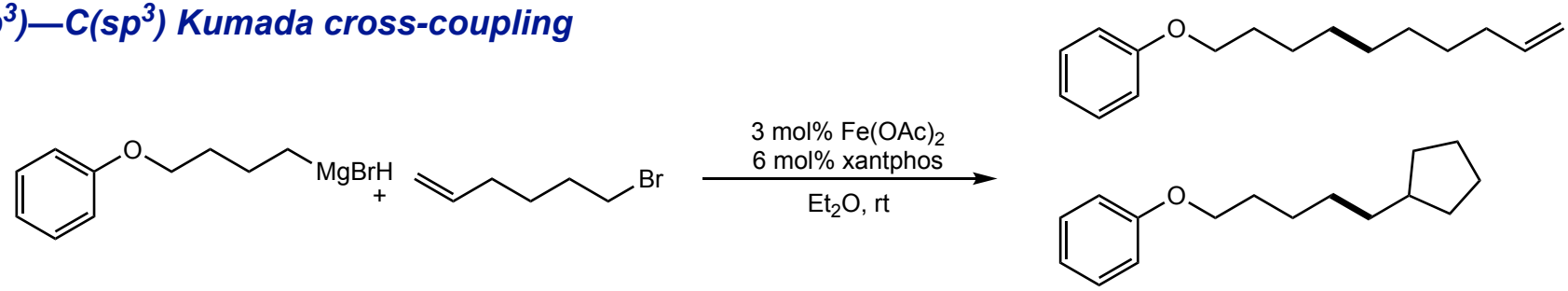

K. G. Dongol, H. Koh, M. Sau, C. L. L. Chai *Adv. Synth. Catal.* **2007**, 349: 1015-1018

Waldemar Maximilian Czaplik, Matthias Mayer, Axel Jacobi von Wangelin *Angew. Chem. Int. Ed.* **2009**, 48, 607 –610

Paul O. Peterson, Matthew V. Joannou, Eric M. Simmons, Steven R. Wisniewski, Junho Kim, and Paul J. Chirik *ACS Catalysis* **2023** 13 (4), 2443-2448

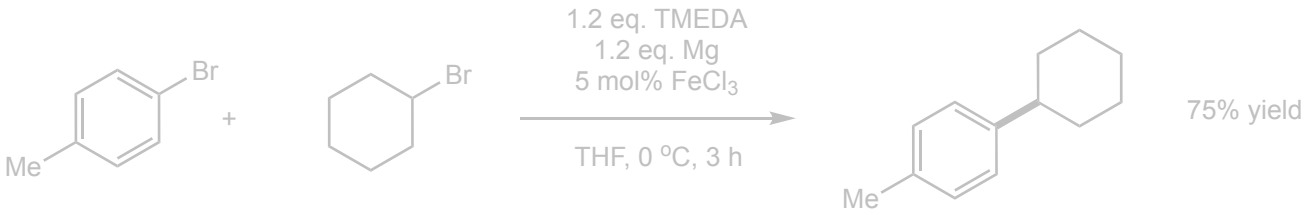
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## *C($sp^3$)—C($sp^3$) Kumada cross-coupling*



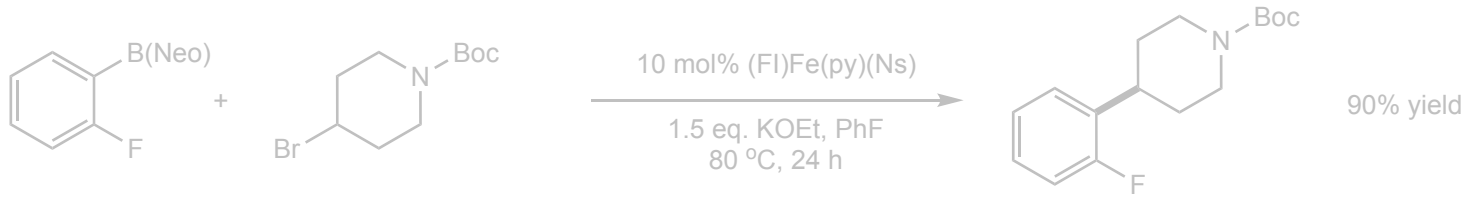

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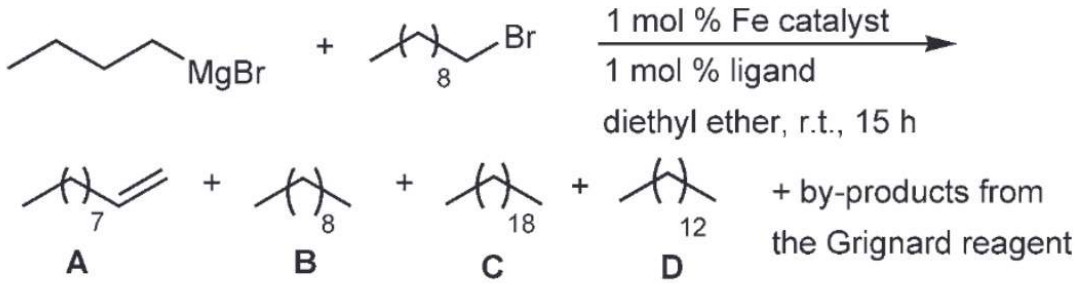

K. G. Dongol, H. Koh, M. Sau, C. L. L. Chai *Adv. Synth. Catal.* **2007**, 349: 1015-1018

Waldemar Maximilian Czaplik, Matthias Mayer, Axel Jacobi von Wangelin *Angew. Chem. Int. Ed.* **2009**, 48, 607 –610

Paul O. Peterson, Matthew V. Joannou, Eric M. Simmons, Steven R. Wisniewski, Junho Kim, and Paul J. Chirik *ACS Catalysis* **2023** 13 (4), 2443-2448

# *Iron-Catalyzed Cross-Coupling: $C(sp^3)$—$C(sp^3)$ Kumada Coupling*

## *$C(sp^3)$—$C(sp^3)$ Kumada cross-coupling by Chai*



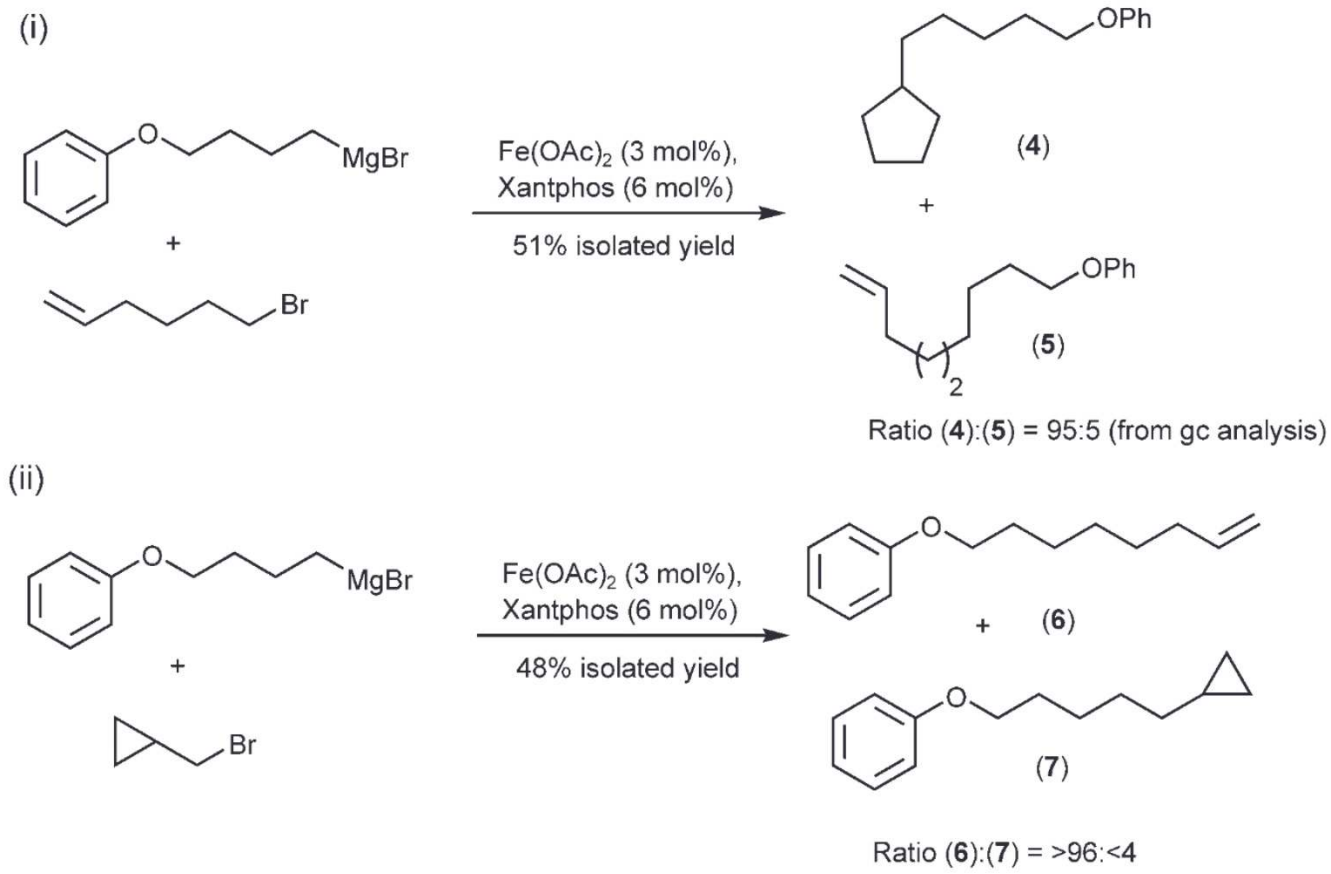

| Ligands | **A** (%) | **B** (%) | **C** (%) | **D** (%) |
|---|---|---|---|---|
| No ligand | 15 | 58 | 16 | 3 |
| Triphenylphosphine, $PPh_3$ | 7 | 50 | 7 | 15 |
| Tricyclohexylphosphine | 18 | 57 | 0 | 2 |
| 2-(Di-*tert*-butylphosphino)biphenyl | 11 | 62 | 12 | 4 |
| 2-(Dicyclohexylphosphino)-2′,6′-dimethoxybiphenyl | 15 | 51 | 16 | 8 |
| 1,2-Bis(dipentafluorophenylphosphino)ethane | 10 | 64 | 6 | 5 |
| 1,2-Bis(diphenylphosphino)ethane | 14 | 58 | 7 | 5 |
| 2,2-Bis(diphenylphosphino)-1,1-binaphthyl | 10 | 43 | 11 | 18 |
| 9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene (**1**) | 2 | 31 | 10 | 51 |
| Bis(2-diphenylphosphinophenyl) ether (**2**) | 10 | 62 | 13 | 5 |
| 9,9-Dimethyl-4,5-bis(di-*tert*-butylphosphino)xanthene (**3**) | 9 | 44 | 6 | 11 |
| Tri-*n*-butyl phosphite | 12 | 38 | 9 | 14 |
| Tris(2,2,2-trifluoroethyl) phosphite | 11 | 56 | 11 | 2 |

***Wide bite-angle, rigid, xantphos gave highest yield and suppressed side-product formation***

K. G. Dongol, H. Koh, M. Sau, C. L. L. Chai *Adv. Synth. Catal.* **2007**, 349: 1015-1018

# *Iron-Catalyzed Cross-Coupling: C($sp^3$)—C($sp^3$) Kumada Coupling*

***Radical clocks give evidence for cage-escape radicals***

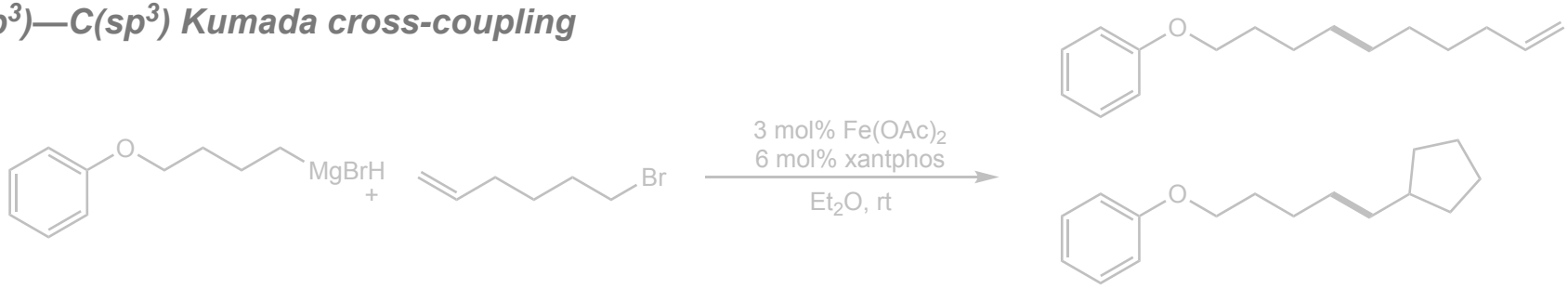



**Scheme 3.** Probing the mechanism of $sp^3$–$sp^3$ iron-catalysed cross-coupling reactions.

K. G. Dongol, H. Koh, M. Sau, C. L. L. Chai *Adv. Synth. Catal.* **2007**, 349: 1015-1018

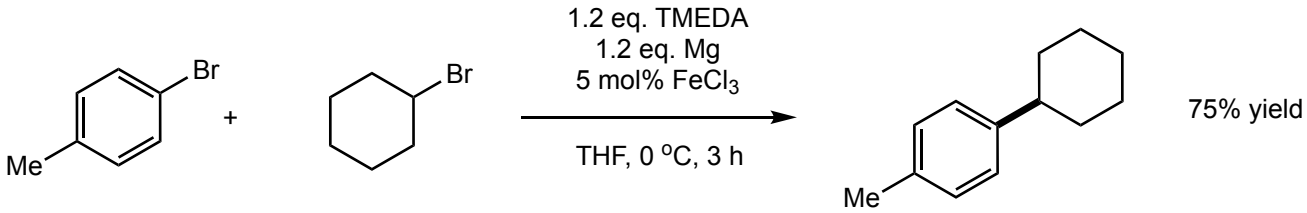
# *Iron-Catalyzed Cross-Coupling: Expanding Beyond C($sp^2$)—C($sp^3$) Kumada Coupling*

## *C($sp^3$)—C($sp^3$) Kumada cross-coupling*



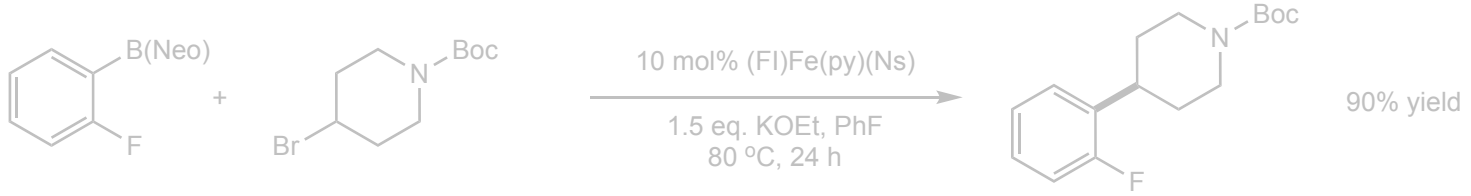

51% yield, 95:5 cyclized:linear

## *Cross-electrophile coupling*




75% yield

## *Milder nucleophiles: Negishi and Suzuki*




90% yield

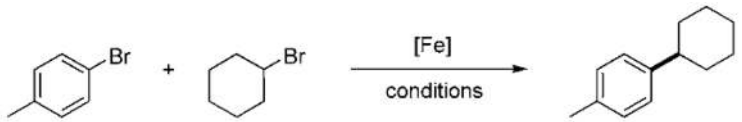

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Waldemar Maximilian Czaplik, Matthias Mayer, Axel Jacobi von Wangelin *Angew. Chem. Int. Ed.* **2009**, 48, 607 –610

Paul O. Peterson, Matthew V. Joannou, Eric M. Simmons, Steven R. Wisniewski, Junho Kim, and Paul J. Chirik *ACS Catalysis* **2023** 13 (4), 2443-2448

# *Iron-Catalyzed Cross-Coupling: Cross-Electrophile Coupling*

## *Cross-electrophile coupling*




**1a** **2a** **3a**

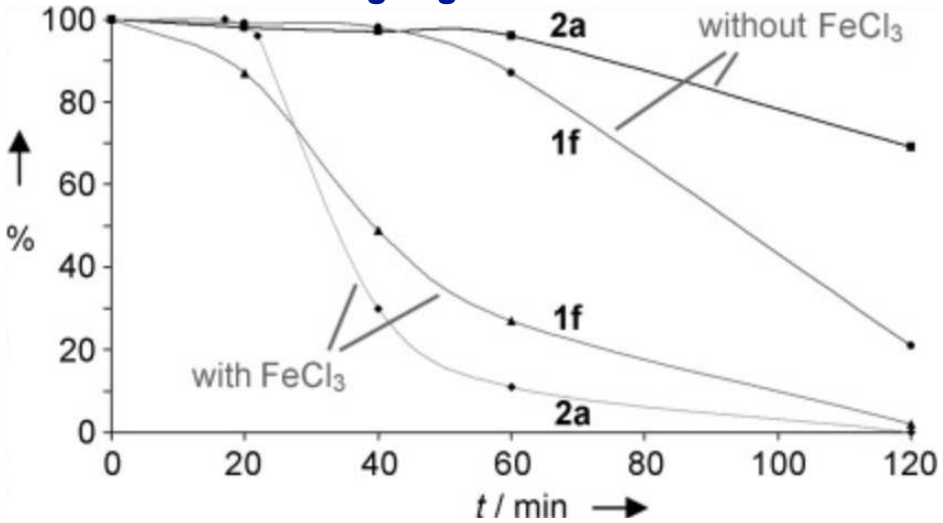
| *T* [°C] | Solvent | Additive[a] | $FeCl_3$ [mol%] | **1a/2a** | Yield [%][b] |
|---|---|---|---|---|---|
| 20 | $Et_2O$ | TMEDA | 5 | 1:1.2 | 0 (0) |
| | MTBE | | | | 0 (0) |
| | dioxane | | | | <10 (0) |
| | *c*-$C_6H_{12}$ | | | | 0 (0) |
| | THF | | | | 65 (9) |
| | 2-Me-THF | | | | 65 (6) |
| 0 | THF | TMEDA | 5 | 1:1.2 | 70 (9) |
| 45 | | | | | 53 (10) |
| 0 | THF | TMEDA | 7.5 | 1:1.2 | 72 (14) |
| | | | 10 | | 75 (14) |
| | | | 15 | | 69 (14) |
| 0 | THF | – | 5 | 1:1.3 | 27 (8) |
| | | py | | | 0 (0) |
| | | phen | | | 0 (0) |
| | | DMA | | | 31 (9) |
| | | $NEt_3$ | | | 32 (15) |
| | | DACH | | | 0 (0) |
| | | $Me_4$-DACH | | | 38 (12) |
| | | NMP[c] | | | <5 (0) |

***Optimized conditions very similar to classic C($sp^2$)—C($sp^3$) Kumada***

Waldemar Maximilian Czaplik, Matthias Mayer, Axel Jacobi von Wangelin *Angew. Chem. Int. Ed.* **2009**, 48, 607 –610

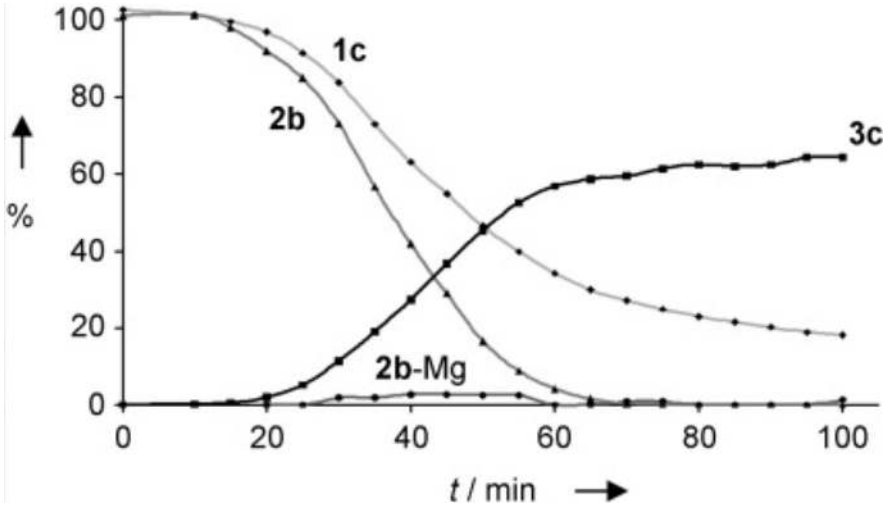
# *Iron-Catalyzed Cross-Coupling: Cross-Electrophile Coupling*

***Fe-cat gringard formation***




***2a/1f are aryl and alkyl electrophiles***

***Evidence for mixed-gringard species***

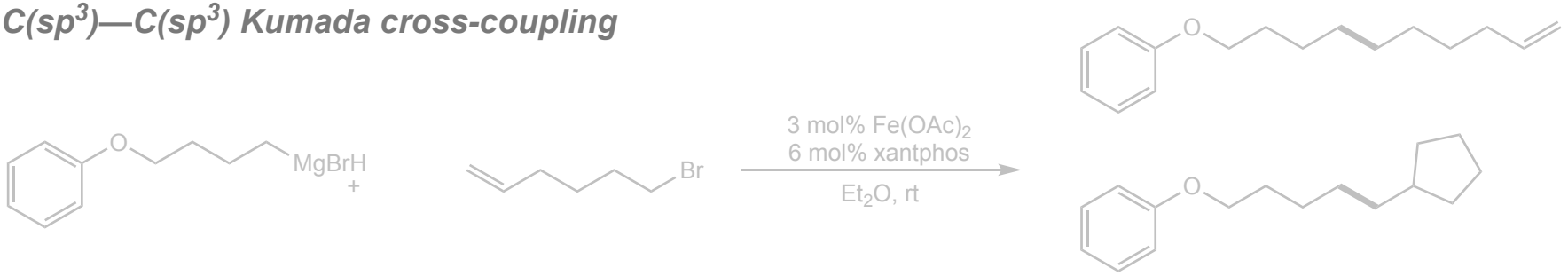



***2b is alkyl electrophile***

Waldemar Maximilian Czaplik, Matthias Mayer, Axel Jacobi von Wangelin *Angew. Chem. Int. Ed.* **2009**, 48, 607 –610

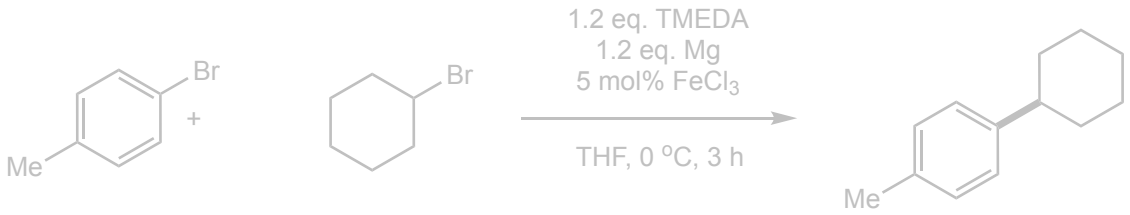
# *Iron-Catalyzed Cross-Coupling: Expanding Beyond C($sp^2$)—C($sp^3$) Kumada Coupling*

## *C($sp^3$)—C($sp^3$) Kumada cross-coupling*



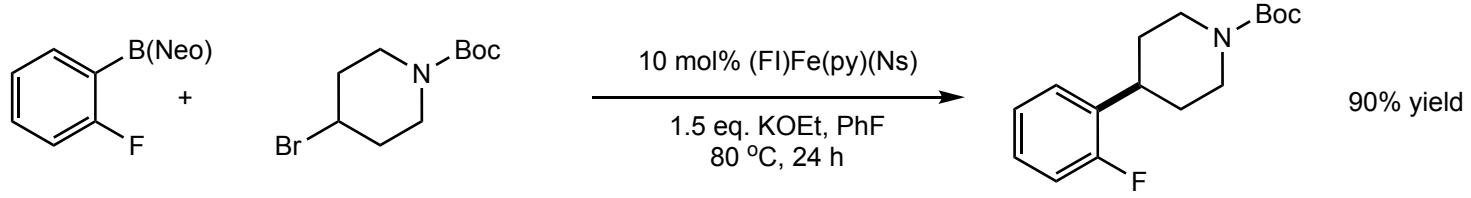

51% yield, 95:5 cyclized:linear

## *Cross-electrophile coupling*




75% yield

## *Milder nucleophiles: Negishi and Suzuki*




90% yield

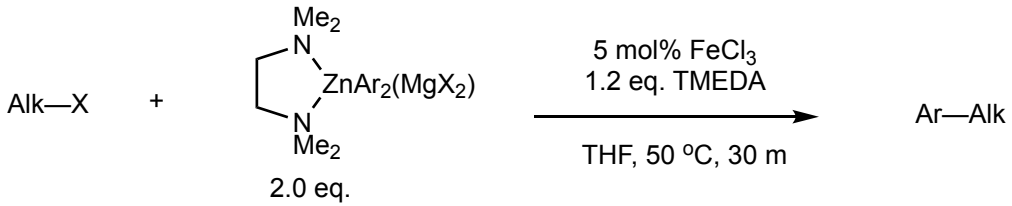

K. G. Dongol, H. Koh, M. Sau, C. L. L. Chai *Adv. Synth. Catal.* **2007**, 349: 1015-1018

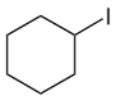
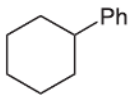
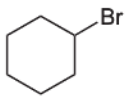
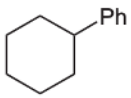
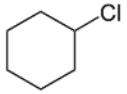
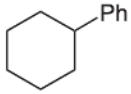
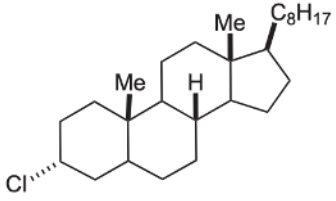
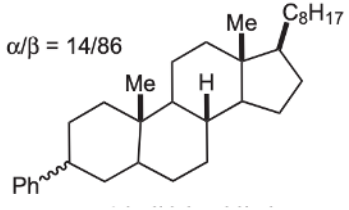
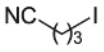
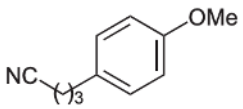
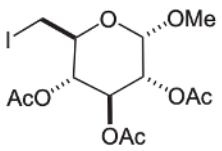
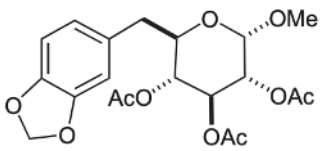
Waldemar Maximilian Czaplik, Matthias Mayer, Axel Jacobi von Wangelin *Angew. Chem. Int. Ed.* **2009**, 48, 607 –610

Paul O. Peterson, Matthew V. Joannou, Eric M. Simmons, Steven R. Wisniewski, Junho Kim, and Paul J. Chirik *ACS Catalysis* **2023** 13 (4), 2443-2448

# *Iron-Catalyzed Cross-Coupling: Toward Synthetic Utility*

***For Negishi, conditions similar to Kumada, but less active nucleophile demands heating — magnesium salt required for cross-coupling to proceed***

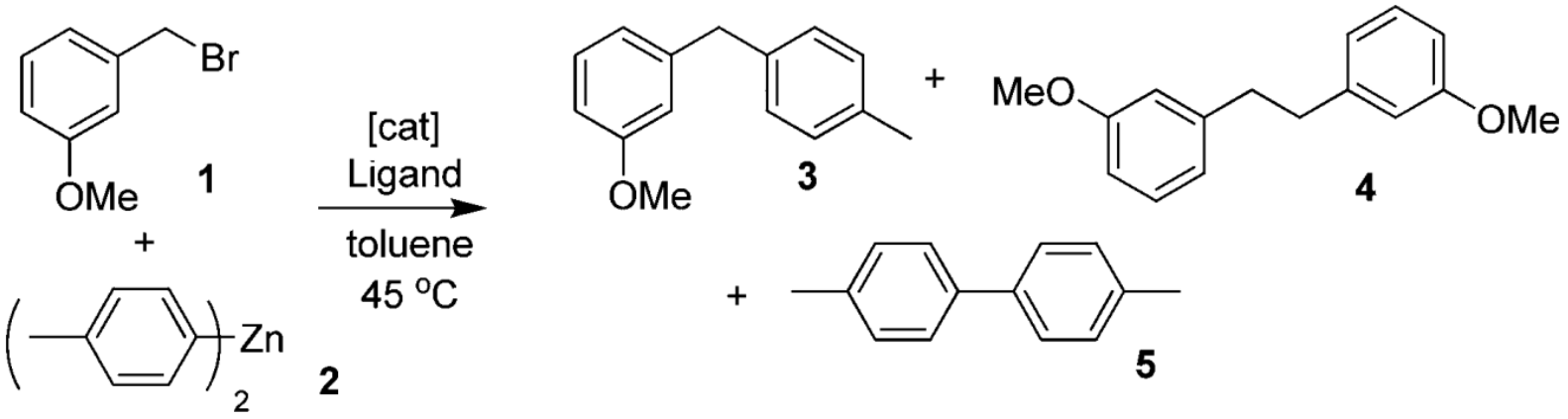



| Entry | $(FG)R_{alkyl}$–X | Arylzinc[b] | Product | Yield (%)[c] |
|---|---|---|---|---|
| 1 |  | **5** |  | 98 |
| 2 |  | **5** |  | 97 |
| 3[d] |  | **5** |  | 88 |
| 4[e] |  | **5** |  | 89 |
| 10 |  | **8** |  | 86 |
| 11[f] |  | **9** |  | 90 |

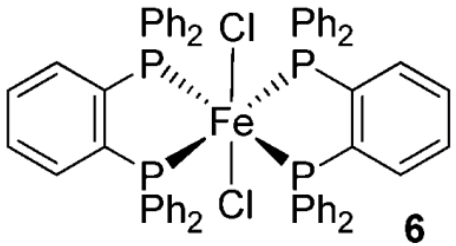
Masaharu Nakamura, Shingo Itob, Keiko Matsuob, and Eiichi Nakamura *Synlett* **2005**, 11, 1794-1798

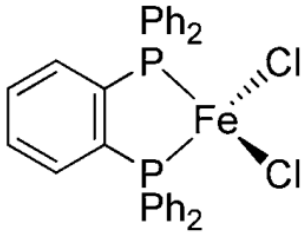
# *Iron-Catalyzed Cross-Coupling: Phosphine Precatalysts*

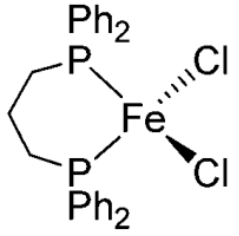
***Bedford invokes phosphine precatalysts for Negishi coupling — operates on benzyl halides — similarly requires residual magnesium salt***




[cat] =



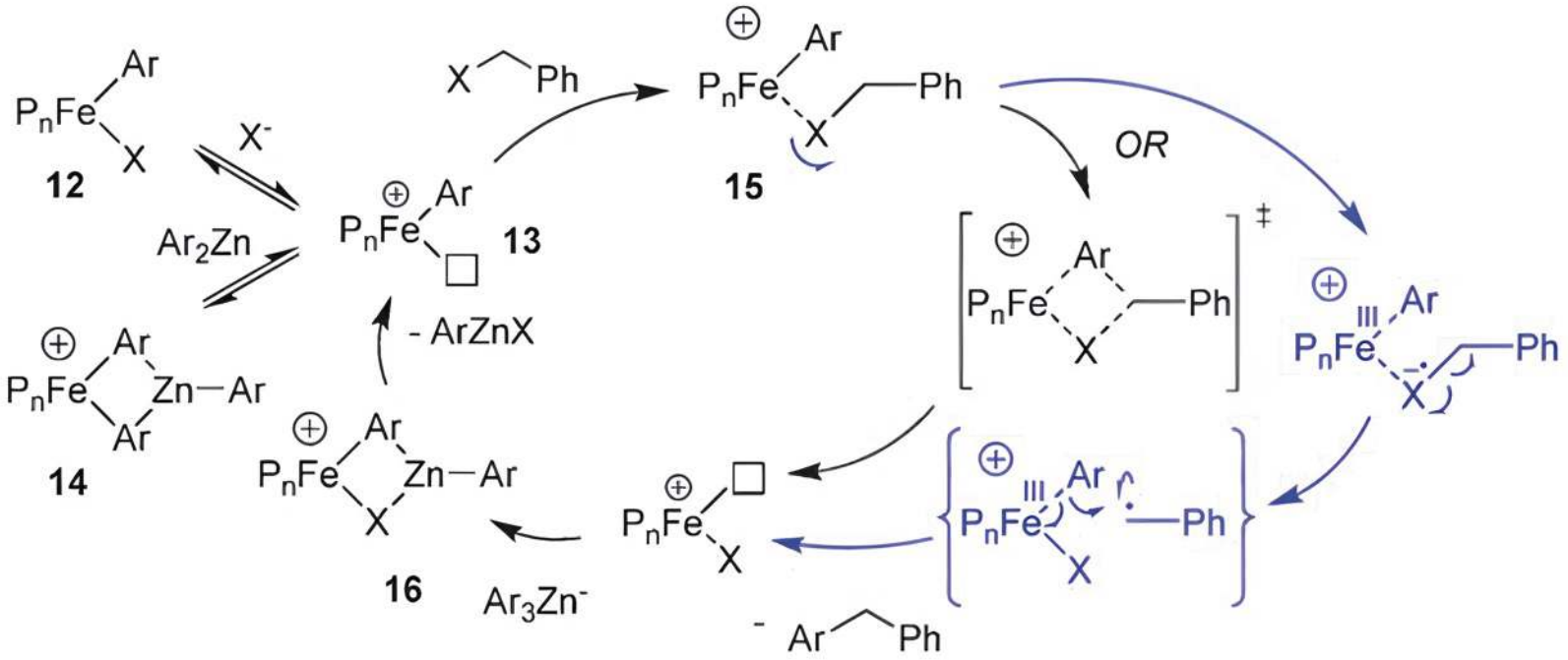

*Catalytic activity:*[a]

| Complex | **3** | **4** | **5** (%)[b] |
|---|---|---|---|
| **6** | 94 | - | 3 |
| **6**[d] | 71 | - | 6 |
| **7** | 80 | <1 | 2 |
| **7**[c] | 86 | 4 | 4 |
| **8** | 71 | 3 | 3 |
| **8**[c] | 90 | 3 | 3 |

Robin B. Bedford, Michael Huwea and Mark C. Wilkinson *Chem. Commun.*, **2009**, 600–602

# *Iron-Catalyzed Cross-Coupling: Phosphine Precatalysts*

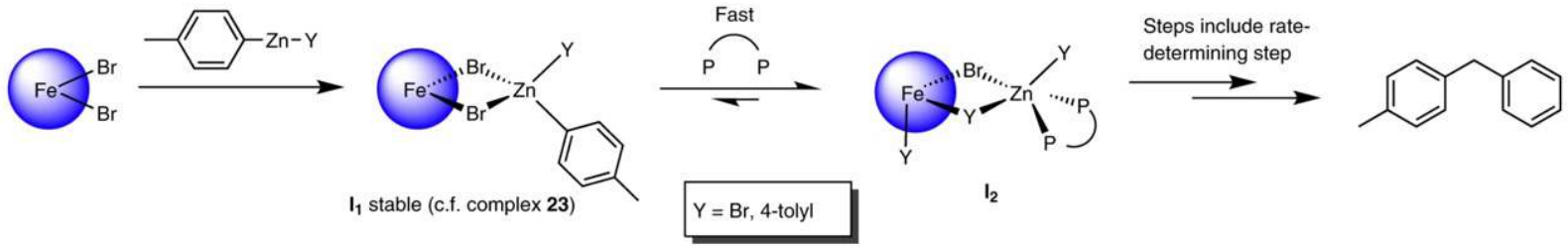
***Proposes cationic intermediate, two possibilities for C—C bond formation***




Robin B. Bedford, Michael Huwea and Mark C. Wilkinson *Chem. Commun.*, **2009**, 600–602

# *Iron-Catalyzed Cross-Coupling: Fe-Ferrates*

***Follow-up studies countered earlier claim: no evidence of phosphine binding during catalysis on NMR or time-resolved XAFS***




In the proposed mechanism, the inactive intermediate $\mathbf{I_1}$, closely related to the isolated complex **23**, reacts with a chelating diphosphine (P-P) to give active intermediate $\mathbf{I_2}$. The rate-determining step occurs subsequently, after reaction of $\mathbf{I_2}$ with a separate iron–benzyl species.

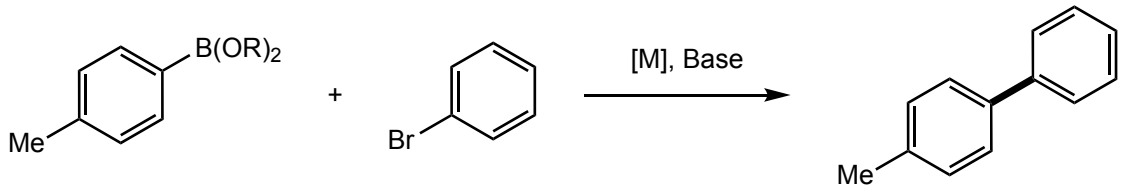
***Main [Fe] species are bromoferrates***

***Phosphines are chelated to zinc and assist with TM***


Antonis M. Messinis, Stephen L. J. Luckham, Peter P. Wells, Diego Gianolio, Emma K. Gibson, Harry M. O'Brien, Hazel A. Sparkes, Sean A. Davis, June Callison, David Elorriaga, Oscar Hernandez-Fajardo, and Robin B. Bedford *Nature Catalysis* **2019** 2 123–133

# *Iron-Catalyzed Cross-Coupling: Suzuki—Miyaura*

***More mild than even Negishi conditions, promises an efficient, modular coupling system for forming carbon-carbon bonds***




***After amide coupling, it is the most common reaction in pharma***

***The iron-catalysed Suzuki reaction… …represents something of a 'holy grail' in coupling chemistry — Bedford, Nakamura***


Robin B. Bedford, Masaharu Nakamura, Nicholas J. Gower, Mairi F. Haddow, Mark A. Hall, Michael Huwe, Tohru Hashimoto, Rukeme A. Okopie *Tetrahedron Letters* **2009** 50(45) 6110-6111

Brown, D. G.; Boström, J. *J. Med. Chem.* **2016**, 59, 4443−4458

# *Iron-Catalyzed Cross-Coupling: Suzuki—Miyaura, the Importance of Base*

***Lots of factors go into the usability of a base in pharma!***

| Carbonates | CAS number | EHS | Clean chemistry | Greenness | $pK_a^w$ ($BH^+$) | GRAS[b] | Comment |
|---|---|---|---|---|---|---|---|
| Sodium bicarbonate | 144-55-8 | 10 | 9 | 9.3 | 5.95[17] | YES | |
| Potassium bicarbonate | 298-14-6 | 10 | 9 | 9.3 | 5.95[17] | YES | |
| Sodium carbonate | 497-19-8 | 10 | 9 | 9.3 | 9.1[17] | YES | |
| Potassium carbonate | 584-08-7 | 9 | 9 | 8.8 | 9.1[17] | NO | |
| Cesium carbonate | 534-17-8 | 10 | 5 | 7.4 | 9.1[17] | NO | |

| Phosphates | CAS number | EHS | Clean chemistry | Greenness | $pK_a^w$ ($BH^+$) | GRAS[b] | Comment |
|---|---|---|---|---|---|---|---|
| Trisodium phosphate (anh.) | 7601-54-9 | 10 | 8 | 9.0 | 11.74[18] | YES | |
| Tripotassium phosphate (anh.) | 7778-53-2 | 7 | 7 | 7.3 | 11.74[18] | YES | |

| Hydroxides | CAS number | EHS | Clean chemistry | Greenness | $pK_a^w$ ($BH^+$) | GRAS[b] | Comment |
|---|---|---|---|---|---|---|---|
| Potassium hydroxide | 1310-58-3 | 7 | 9 | 8.0 | 15.74[19] | YES | Causes severe burns (R35). |
| Sodium hydroxide | 1310-73-2 | 7 | 9 | 8.0 | 15.74[19] | YES | Causes severe burns (R35). |
| Calcium hydroxide | 1305-62-0 | 7 | 9 | 8.0 | 15.74[19] | YES | |
| Barium hydroxide | 17194-00-2 | 7 | 8 | 7.7 | 15.74[19] | NO | |
| Lithium hydroxide | 1310-65-2 | 4 | 8 | 5.7 | 15.74[19] | NO | |

| Hydrides | CAS number | EHS | Clean chemistry | Greenness | $pK_a^w$ ($BH^+$) | GRAS[b] | Comment |
|---|---|---|---|---|---|---|---|
| Sodium hydride | 7646-69-7 | 5 | 5 | 5.0 | *35.0*[20] | NO | May cause runaway reaction with certain solvents, such as DMF, DMA. Highly flammable gaseous by-product (hydrogen) needs abating. Use of mineral oil dispersions greatly reduces fire hazard. |
| Potassium hydride | 7693-26-7 | 5 | 5 | 5.0 | *35.0*[20] | NO | May cause runaway reaction with certain solvents, such as DMF, DMA. Highly flammable gaseous by-product (hydrogen) needs abating. Use of mineral oil dispersions greatly reduces fire hazard. |

| Acetates | CAS number | EHS | Clean chemistry | Greenness | $pK_a^w$ ($BH^+$) | GRAS[b] | Comment |
|---|---|---|---|---|---|---|---|
| Potassium acetate | 127-08-2 | 10 | 9 | 9.3 | 4.76[21] | NO | |
| Sodium acetate | 127-09-3 | 10 | 9 | 9.3 | 4.76[21] | YES | |

| Alkoxides | CAS number | EHS | Clean chemistry | Greenness | $pK_a^w$ ($BH^+$) | GRAS[b] | Comment |
|---|---|---|---|---|---|---|---|
| Sodium methoxide | 124-41-4 | 5 | 9 | 6.9 | 15.1[22] | NO | Highly flammable (R11). Toxic (R23/24/25). |
| Sodium ethoxide | 141-52-6 | 5 | 9 | 6.9 | 15.93[22] | NO | Highly flammable (R11). |
| Sodium *tert*-butoxide | 865-48-5 | 5 | 9 | 6.9 | 19.2[22] | NO | Highly flammable (R11). Causes severe burns (R35). |
| Potassium *tert*-butoxide | 865-47-4 | 5 | 9 | 6.9 | 19.2[22] | NO | Highly flammable (R11). Causes severe burns (R35). |
| Lithium methoxide | 865-34-9 | 4 | 8 | 5.7 | 15.1[22] | NO | Highly flammable (R11). Toxic (R23/24/25). |
| Lithium ethoxide | 2388-07-0 | 4 | 8 | 5.7 | 15.93[22] | NO | Highly flammable (R11). |
| Lithium *tert*-butoxide | 1907-33-1 | 4 | 8 | 5.7 | 19.2[22] | NO | Highly flammable (R11). |

| Phosphazanes | CAS number | EHS | Clean chemistry | Greenness | $pK_a^w$ ($BH^+$) | GRAS[b] | Comment |
|---|---|---|---|---|---|---|---|
| Phosphazane BEMP | 98015-45-3 | 7 | 5 | 6.0 | 27.58[23] | NO | |
| Phosphazane P2-Et | 165535-45-5 | 7 | 5 | 6.0 | 32.66[23] | NO | |

| Amines | CAS number | EHS | Clean chemistry | Greenness | $pK_a^w$ ($BH^+$) | GRAS[b] | Comment |
|---|---|---|---|---|---|---|---|
| 2-Methylpyridine | 109-06-8 | 8 | 9 | 8.3 | 5.97[24] | NO | |
| 2,6-Lutidine | 108-48-5 | 8 | 9 | 8.3 | 6.75[24] | NO | |
| DBN | 3001-72-7 | 7 | 9 | 8.0 | *13.5*[25] | NO | |
| Pyridine | 110-86-1 | 7 | 9 | 7.5 | 5.17[24] | NO | Highly flammable (R11). |

| Amines | CAS number | EHS | Clean chemistry | Greenness | $pK_a^a$ ($BH^+$) | GRAS[b] | Comment |
|---|---|---|---|---|---|---|---|
| 4-Methylpyridine | 108-89-4 | 7 | 9 | 7.5 | 6.02[24] | NO | Toxic (R24). |
| Morpholine | 110-91-8 | 7 | 9 | 7.5 | 8.49[26] | NO | |
| Diethylaminopropylamine | 104-78-9 | 7 | 9 | 7.5 | *10.48*[27] | NO | |
| Tetramethylguanidine | 80-70-6 | 7 | 9 | 7.5 | 13.6[28] | NO | |
| DBU | 6674-22-2 | 7 | 8 | 7.3 | *12.5*[25] | NO | Causes severe burns (R35). |
| 2,2,6,6-Tetramethylpiperidine | 768-66-1 | 7 | 8 | 7.3 | 11.1[29] | NO | |
| Triethylamine | 121-44-8 | 5 | 9 | 6.9 | 10.77[30] | NO | Highly flammable (R11). Toxic (R23/24). Causes severe burns (R35). |
| Diisopropylamine | 108-18-9 | 5 | 9 | 6.9 | 11.05[56] | NO | Highly flammable (R11). |
| Piperidine | 110-89-4 | 5 | 9 | 6.9 | 11.22[31] | NO | Highly flammable (R11). Toxic (R23/24). |
| Dimethylethylamine | 598-56-1 | 5 | 9 | 6.9 | 10.16[32] | NO | Highly flammable (R11). |
| Dipropylamine | 142-84-7 | 5 | 9 | 6.9 | 10.91[28] | NO | Highly flammable (R11). Causes severe burns (R35). |
| *N*-Methylmorpholine | 109-02-4 | 5 | 9 | 6.9 | 7.41[29] | NO | Highly flammable (R11). |
| *n*-Butylamine | 109-73-9 | 5 | 9 | 6.9 | 10.61[33] | NO | Highly flammable (R11). Causes severe burns (R35). |
| Diethylamine | 109-89-7 | 5 | 9 | 6.9 | 10.98[56] | NO | Highly flammable (R11). Causes severe burns (R35). |
| Ammonia | 7664-41-7 | 5 | 9 | 6.5 | 9.21[34] | NO | Toxic (R23). |
| Diisopropylethylamine | 7087-68-5 | 5 | 9 | 6.5 | *10.75*[35] | NO | Highly flammable (R11). |
| *tert*-Butylamine | 75-64-9 | 5 | 9 | 6.5 | 10.63[30] | NO | Highly flammable (R11). Toxic (R25). Causes severe burns (R35). |
| DABCO® | 280-57-9 | 5 | 9 | 6.5 | *8.4*[25] | NO | Highly flammable (R11). |
| Cyclohexylamine | 108-91-8 | 5 | 9 | 6.5 | 10.62[56] | NO | |
| Tributylamine | 102-82-9 | 5 | 7 | 6.3 | 9.93[37] | NO | Toxic (R23/24/25). |
| 4-(Dimethylamino)pyridine | 1122-58-3 | 3 | 9 | 5.2 | 9.60[38] | NO | Toxic (R25/27). |
| Dicyclohexylamine | 101-83-7 | 3 | 7 | 4.3 | 11.25[39] | NO | Toxic (R24/25). |
| Imidazole | 288-32-4 | 2 | 9 | 3.9 | 6.99[39] | NO | Toxic (R61). |

| Disilazides | CAS number | EHS | Clean chemistry | Greenness | $pK_a^a$ ($BH^+$) | GRAS[b] | Comment |
|---|---|---|---|---|---|---|---|
| KHMDS | 40949-94-8 | 5 | 7 | 5.9 | 29.5[40] | NO | Highly flammable (R11). |
| NaHMDS | 1070-89-9 | 5 | 7 | 5.9 | 29.5[40] | NO | Highly flammable (R11). |
| LiHMDS | 4039-32-1 | 4 | 8 | 5.5 | 29.5[40] | NO | Highly flammable (R11). |

| Amides | CAS number | EHS | Clean chemistry | Greenness | $pK_a^a$ ($BH^+$) | GRAS[b] | Comment |
|---|---|---|---|---|---|---|---|
| LiTMP | 38227-87-1 | 4 | 8 | 5.5 | 37.3[40] | NO | |
| LDA | 4111-54-0 | 3 | 8 | 4.5 | 35.7[40] | NO | Highly flammable (R11). |
| Sodium amide | 7782-92-5 | 4 | 3 | 3.7 | *35.0*[20] | NO | Forms peroxide. Toxic and flammable gaseous by-product (ammonia) needs abating. |
| Lithium amide | 7782-89-0 | 4 | 3 | 3.7 | *35.0*[20] | NO | Forms peroxide. Toxic and flammable gaseous by-product (ammonia) needs abating. |

| Alkyllithiums | CAS number | EHS | Clean chemistry | Greenness | $pK_a^a$ ($BH^+$) | GRAS[b] | Comment |
|---|---|---|---|---|---|---|---|
| 6-Hexyllithium | 21369-64-2 | 2 | 8 | 4.0 | *40.0*[41] | NO | Highly flammable (R11). Causes severe burns (R35). |
| *n*-Butyllithium | 109-72-8 | 1 | 7 | 3.1 | *50.0*[41] | NO | Highly flammable (R11). Highly flammable gaseous by-product (butane) needs abating. |
| *sec*-Butyllithium | 598-30-1 | 1 | 7 | 3.1 | *51.0*[41] | NO | Highly flammable (R11). Causes severe burns (R35). Highly flammable gaseous by-product (butane) needs abating. |
| *tert*-Butyllithium | 594-19-4 | 1 | 7 | 3.1 | *53.0*[41] | NO | Highly flammable (R11). Highly flammable gaseous by-product (isobutane) needs abating. |

Richard K. Henderson, Alan P. Hill, Anikó M. Redman and Helen F. Sneddon *Green Chem.,* **2015**, 17, 945

# *Iron-Catalyzed Cross-Coupling: Suzuki—Miyaura, the Importance of Base*

***Bases in these categories are less dangerous and broadly FG-compatible***

| Carbonates | CAS number | EHS | Clean chemistry | Greenness | $pK_a^a$ ($BH^+$) | GRAS[b] |
|---|---|---|---|---|---|---|
| Sodium bicarbonate | 144-55-8 | 10 | 9 | 9.3 | 5.95[17] | YES |
| Potassium bicarbonate | 298-14-6 | 10 | 9 | 9.3 | 5.95[17] | YES |
| Sodium carbonate | 497-19-8 | 10 | 9 | 9.3 | 9.1[17] | YES |
| Potassium carbonate | 584-08-7 | 9 | 9 | 8.8 | 9.1[17] | NO |
| Cesium carbonate | 534-17-8 | 10 | 5 | 7.4 | 9.1[17] | NO |

| Alkoxides | CAS number | EHS | Clean chemistry | Greenness | $pK_a^a$ ($BH^+$) | GRAS[b] |
|---|---|---|---|---|---|---|
| Sodium methoxide | 124-41-4 | 5 | 9 | 6.9 | 15.1[22] | NO |
| Sodium ethoxide | 141-52-6 | 5 | 9 | 6.9 | 15.93[22] | NO |
| Sodium *tert*-butoxide | 865-48-5 | 5 | 9 | 6.9 | 19.2[22] | NO |
| Potassium *tert*-butoxide | 865-47-4 | 5 | 9 | 6.9 | 19.2[22] | NO |
| Lithium methoxide | 865-34-9 | 4 | 8 | 5.7 | 15.1[22] | NO |
| Lithium ethoxide | 2388-07-0 | 4 | 8 | 5.7 | 15.93[22] | NO |
| Lithium *tert*-butoxide | 1907-33-1 | 4 | 8 | 5.7 | 19.2[22] | NO |

Richard K. Henderson, Alan P. Hill, Anikó M. Redman and Helen F. Sneddon *Green Chem.,* **2015**, 17, 945

# *Iron-Catalyzed Cross-Coupling: Suzuki—Miyaura, the Importance of Base*

***These bases are very difficult to scale and are dangerous, not FG-compatible, or both***

| Amides | CAS number | EHS | chemistry | Greenness | $(BH^+)$ | GRAS[b] |
|---|---|---|---|---|---|---|
| LiTMP | 38227-87-1 | 4 | 8 | 5.5 | $37.3^{40}$ | NO |
| LDA | 4111-54-0 | 3 | 8 | 4.5 | $35.7^{40}$ | NO |
| Sodium amide | 7782-92-5 | 4 | 3 | 3.7 | $35.0^{20}$ | NO |
| Lithium amide | 7782-89-0 | 4 | 3 | 3.7 | $35.0^{20}$ | NO |

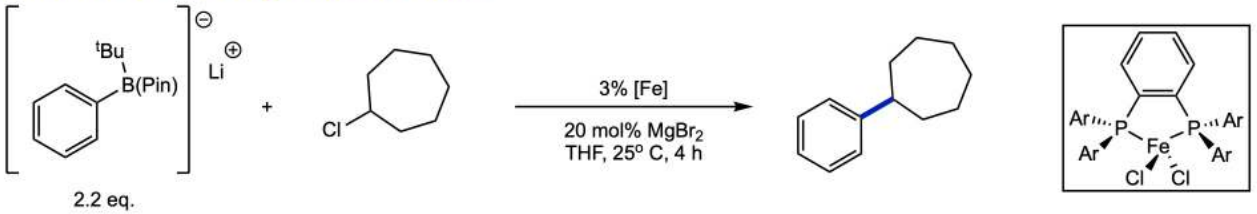
| Alkyllithiums | CAS number | EHS | Clean chemistry | Greenness | $pK_a$[a] $(BH^+)$ | GRAS[b] |
|---|---|---|---|---|---|---|
| *n*-Hexyllithium | 21369-64-2 | 2 | 8 | 4.0 | $40.0^{41}$ | NO |
| *n*-Butyllithium | 109-72-8 | 1 | 7 | 3.1 | $50.0^{41}$ | NO |
| *sec*-Butyllithium | 598-30-1 | 1 | 7 | 3.1 | $51.0^{41}$ | NO |
| *tert*-Butyllithium | 594-19-4 | 1 | 7 | 3.1 | $53.0^{41}$ | NO |

Richard K. Henderson, Alan P. Hill, Anikó M. Redman and Helen F. Sneddon *Green Chem.,* **2015**, 17, 945

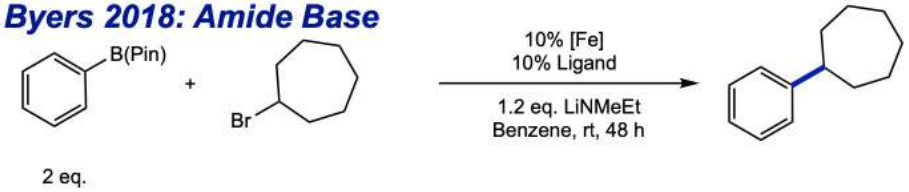
# *Iron-Catalyzed Cross-Coupling: Suzuki—Miyaura, the Importance of Base*

***A benchmark for Suzuki reaction development is by base-compatbility***

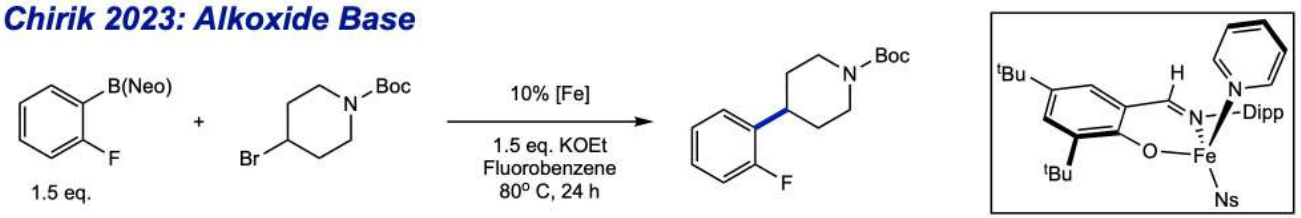
### *Nakamura 2010: Alkyllithium Base*




### *Byers 2018: Amide Base*

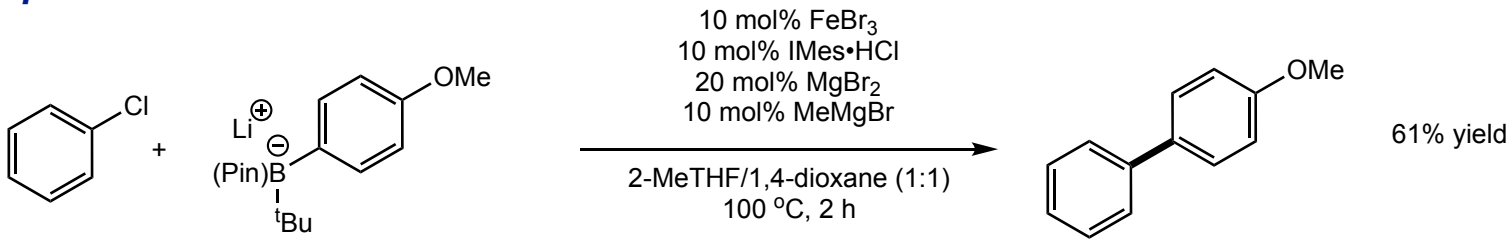



### *Chirik 2023: Alkoxide Base*



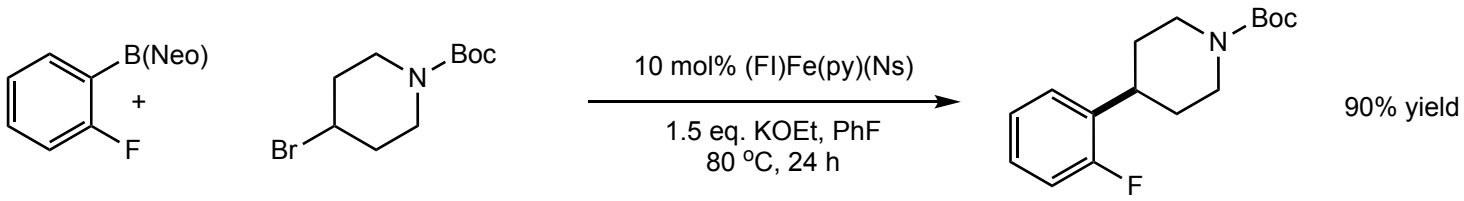
# *Iron-Catalyzed Cross-Coupling: Suzuki—Miyaura, two Subfields*

## *Aryl electrophiles*




61% yield

## *Alkyl electrophiles*



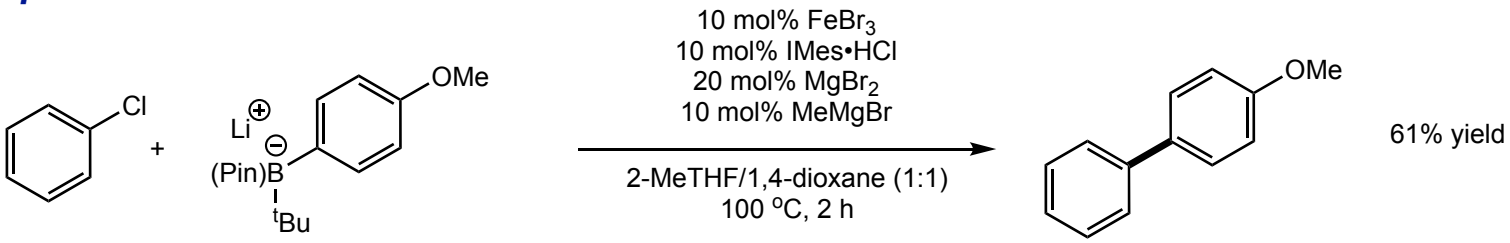

90% yield


Benjamin J. S. Rowsell, Harry M. O'Brien, Gayathri Athavan, Patrick R. Daley-Dee, Johannes Krieger, Emma Richards, Karl Heaton, Ian J. S. Fairlamb and Robin B. Bedford *Nature Catalysis* **2024** 7 1186–1198

Paul O. Peterson, Matthew V. Joannou, Eric M. Simmons, Steven R. Wisniewski, Junho Kim, and Paul J. Chirik *ACS Catalysis* **2023** 13 (4), 2443-2448

# *Iron-Catalyzed Cross-Coupling: Suzuki—Miyaura, two Subfields*

## *Aryl electrophiles*




## *Alkyl electrophiles*



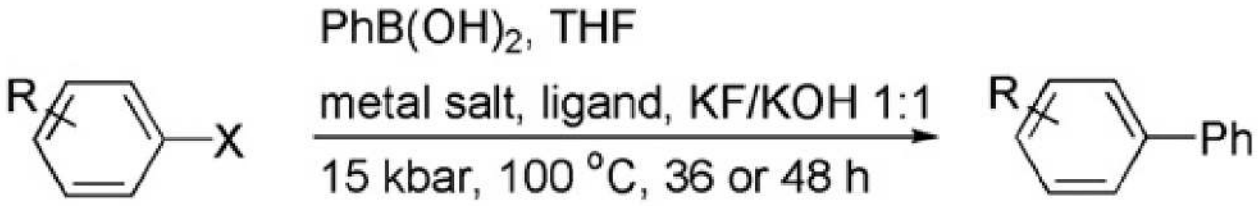


Benjamin J. S. Rowsell, Harry M. O'Brien, Gayathri Athavan, Patrick R. Daley-Dee, Johannes Krieger, Emma Richards, Karl Heaton, Ian J. S. Fairlamb and Robin B. Bedford *Nature Catalysis* **2024** 7 1186–1198

Paul O. Peterson, Matthew V. Joannou, Eric M. Simmons, Steven R. Wisniewski, Junho Kim, and Paul J. Chirik *ACS Catalysis* **2023** 13 (4), 2443-2448

# *Iron-Catalyzed Cross-Coupling: Aryl Electrophile SMC*

***First report of [Fe] SMC is at elevated pressures***




**a**, R = H
**b**, R = 4-$NO_2$
**c**, R = 4-Me
**d**, R = 4-OMe
**e**, R = 4-CN

**1**, X = Cl
**2**, X = Br

**3**

Suzuki–Miyaura cross-coupling at elevated pressure

| Entry | Aryl halide[a] | Metal salt[b] | Ligand[c] | Pressure (bar) | Conv.[d] (%) |
|---|---|---|---|---|---|
| 1 | **1b** | $Pd(OAc)_2$ | $PPh_3$ | 1 | 66 |
| 2 | **1b** | $Pd(OAc)_2$ | $PPh_3$ | 15,000 | 83 |
| 3 | **1b** | $Pd(OAc)_2$ | dppy | 15,000 | ⩾99 |
| 4 | **1b** | $NiCl_2$(10%) | $PPh_3$ | 1 | ⩽1 |
| 5 | **1b** | $NiCl_2$ | $PPh_3$ | 15,000 | 54 |
| 6 | **1b** | $CoCl_2$ | $PPh_3$ | 1 | ⩽1 |
| 7 | **2a** | $NiCl_2$ | dppy | 15,000 | ⩾99 |
| 8 | **2a** | $CoCl_2$ | dppy | 15,000 | ⩾99 |
| 9 | **2a** | $FeCl_3$ | dppy | 15,000 | 97 |
| 10 | **2c** | $CoCl_2$ | dppy | 15,000 | 60 |
| 11 | **2c** | $FeCl_3$ | dppy | 15,000 | 67 |
| 12 | **2c** | $FeCl_3$ | dppy | 1 | ⩽1 |
| 13 | **2d** | $PdCl_2$ | dppy | 15,000 | 84 |
| 14 | **2e** | $PdCl_2$ | dppy | 15,000 | ⩾99 |

Guo, Y.; Young, D. J.; Hor, T. S. A. *Tetrahedron Lett.* **2008**, 49, 5620.

# *Iron-Catalyzed Cross-Coupling: Aryl Electrophile SMC*

***Subsequent reports at ambient pressures demonstrate reproductibility issues…***

Retraction notice

## Retraction notice to "*trans*-Tetrakis(pyridine)dichloroiron(II) as catalyst for Suzuki cross-coupling in ethanol and water" [Tetrahedron Lett. 49 (2008) 6679]

## Retraction: Iron-Catalyzed Suzuki–Miyaura Cross-Coupling Reaction

Retraction(s) for this article

# *Iron-Catalyzed Cross-Coupling: Aryl Electrophile SMC*

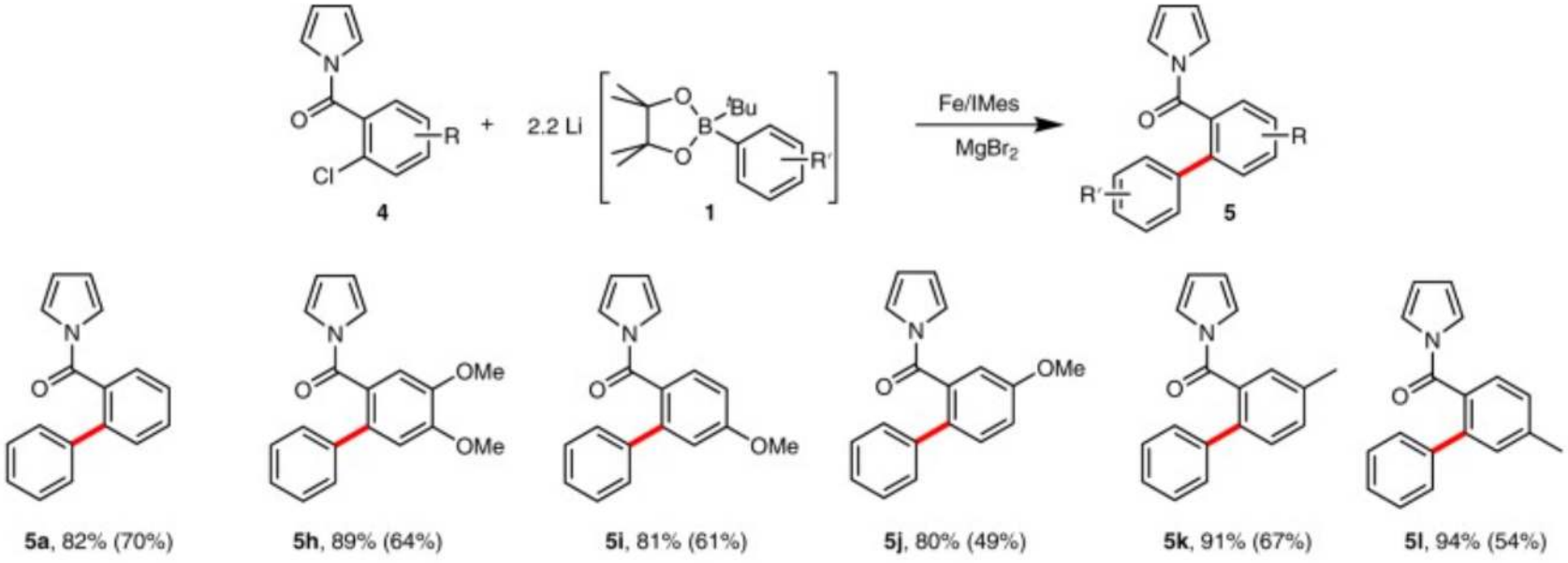
***Bedford and Nakamura prove that PPB Pd can catalyze the reaction in high-yields***

In our hands, Fe(II) or (III) pyridine complexes show no activity in Suzuki biaryl cross-coupling reactions, except in one irreproducible instance when complete conversion was observed. A comparison with palladium acetate under the same conditions showed that complete conversion can be obtained in a S:C ratio of 1,000,000:1 and therefore extreme caution must be exercised to prevent 'false-positives' arising from trace Pd-contaminants.

Robin B. Bedford, Masaharu Nakamura, Nicholas J. Gower, Mairi F. Haddow, Mark A. Hall, Michael Huwe, Tohru Hashimoto, Rukeme A. Okopie *Tetrahedron Letters* **2009** 50(45) 6110-6111

# *Iron-Catalyzed Cross-Coupling: Aryl Electrophile SMC*

***Early example of [Fe]-cat. SMC with aryl electrophile—requires $^{t}$BuLi base***

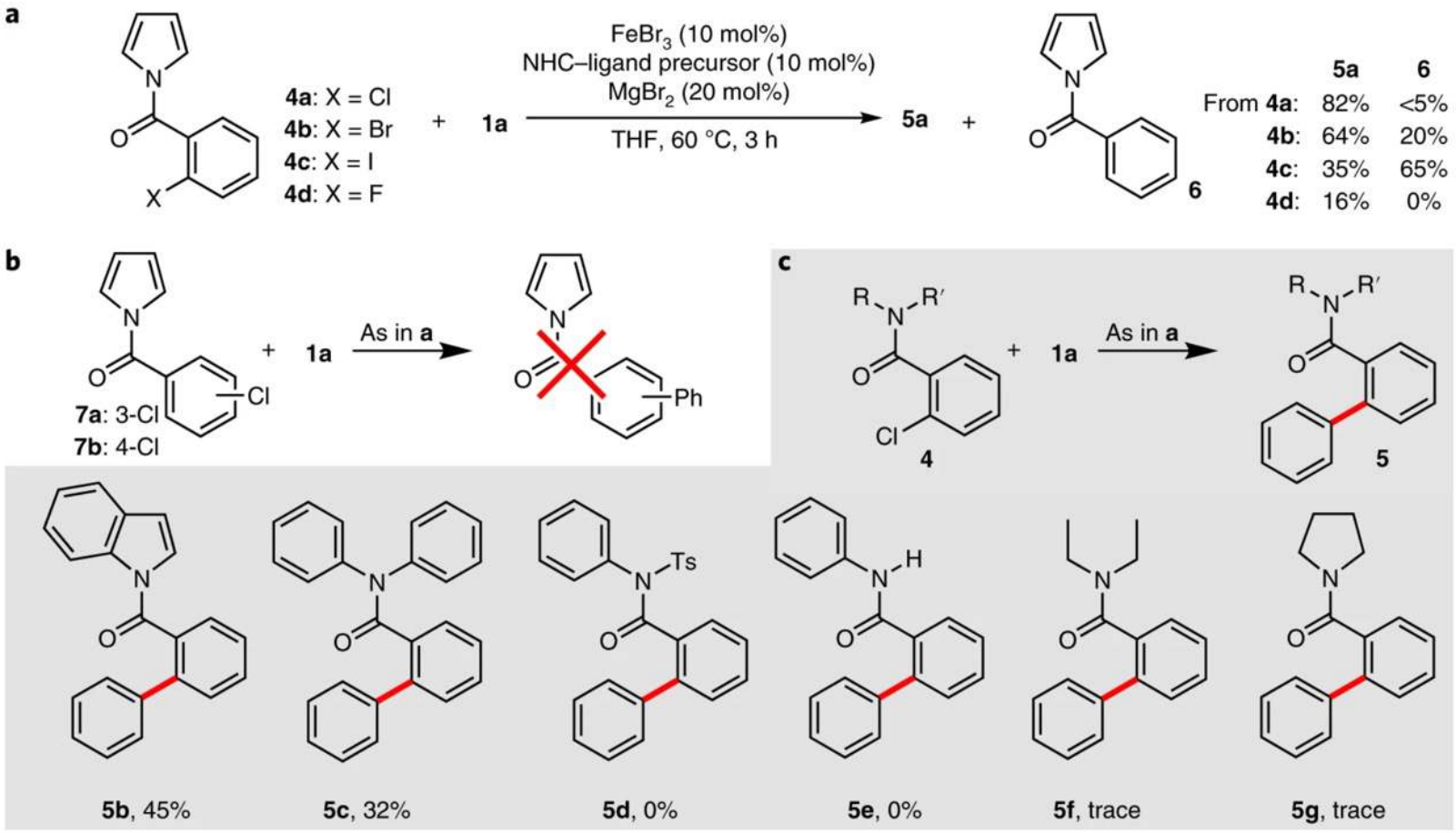



**5a**, 82% (70%) **5h**, 89% (64%) **5i**, 81% (61%) **5j**, 80% (49%) **5k**, 91% (67%) **5l**, 94% (54%)

Harry M. O'Brien, Mattia Manzotti, Roman D. Abrams, David Elorriaga, Hazel A. Sparkes, Sean A. Davis and Robin B. Bedford *Nature Catalysis* **2018** 1 429–437

# *Iron-Catalyzed Cross-Coupling: Aryl Electrophile SMC*

***Early example of [Fe]-cat. SMC with aryl electrophile, highly limited scope***

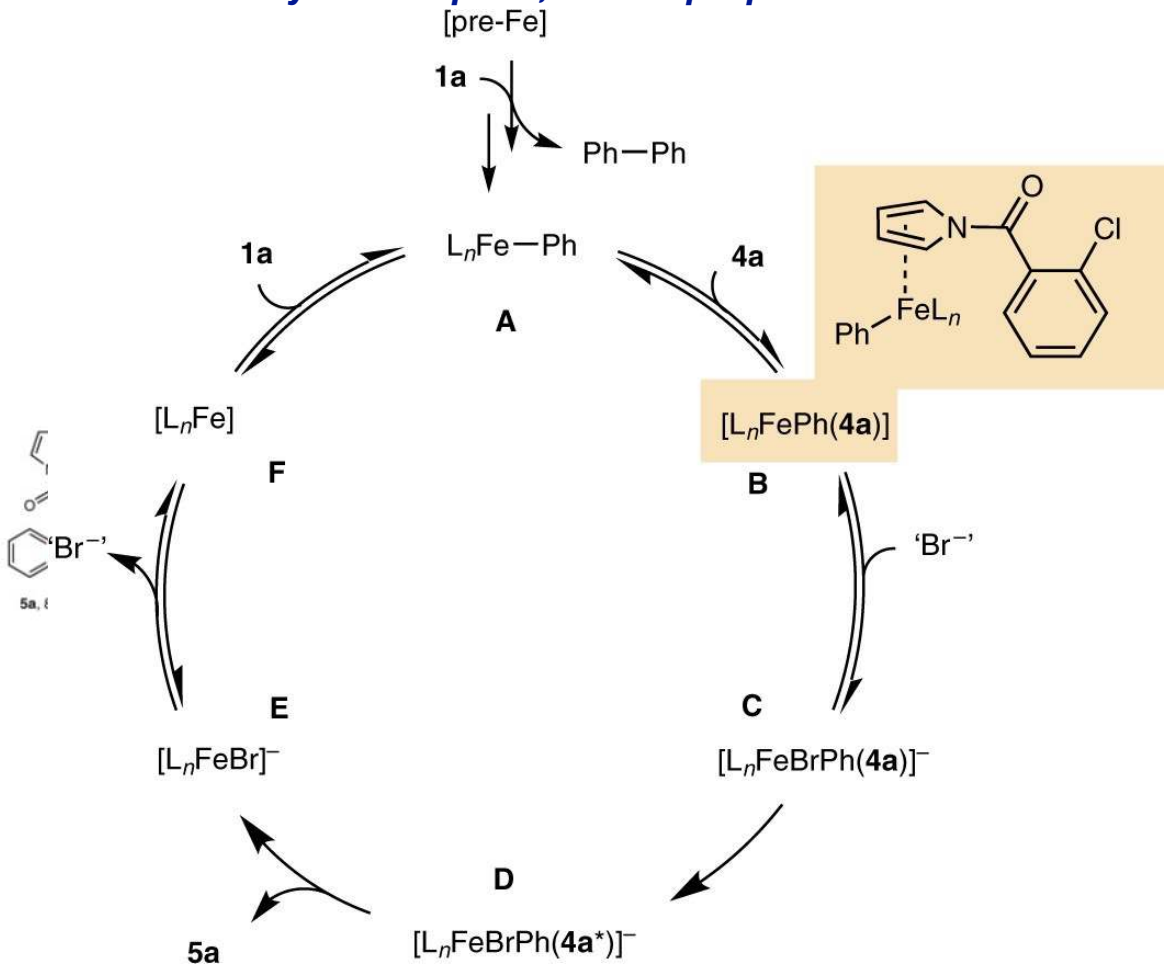



*IMes(HCl) is ligand precursor

Harry M. O'Brien, Mattia Manzotti, Roman D. Abrams, David Elorriaga, Hazel A. Sparkes, Sean A. Davis and Robin B. Bedford *Nature Catalysis* **2018** 1 429–437

# *Iron-Catalyzed Cross-Coupling: Aryl Electrophile SMC*

***Early example of [Fe]-cat. SMC with aryl electrophile, ferrate proposed to be on-cylce***

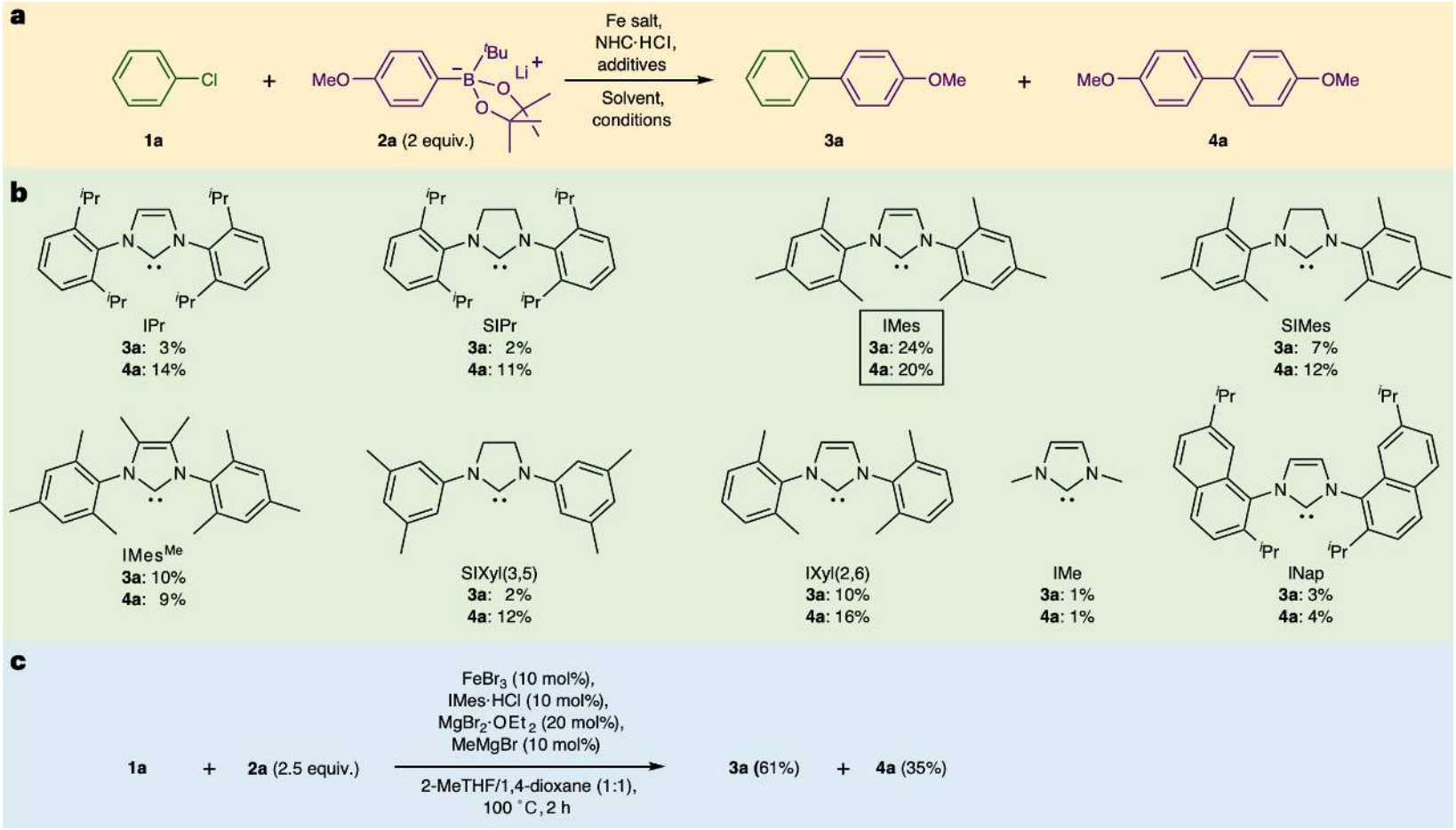



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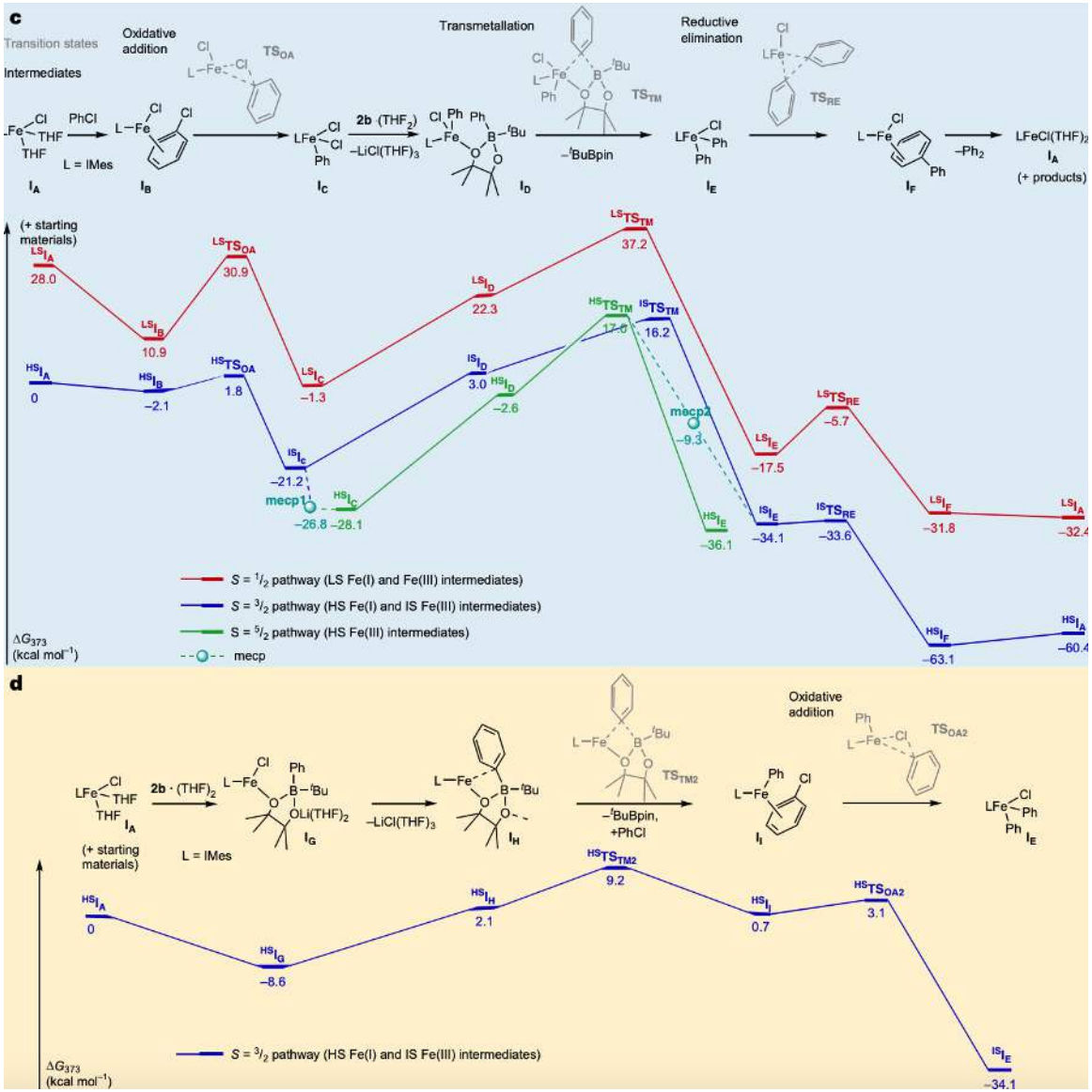
# *Iron-Catalyzed Cross-Coupling: Aryl Electrophile SMC*

***Requires $^{t}$BuLi, but first report with simple aryl chlorides***




Benjamin J. S. Rowsell, Harry M. O'Brien, Gayathri Athavan, Patrick R. Daley-Dee, Johannes Krieger, Emma Richards, Karl Heaton, Ian J. S. Fairlamb and Robin B. Bedford *Nature Catalysis* **2024** 7 1186–1198

# *Iron-Catalyzed Cross-Coupling: Aryl Electrophile SMC*

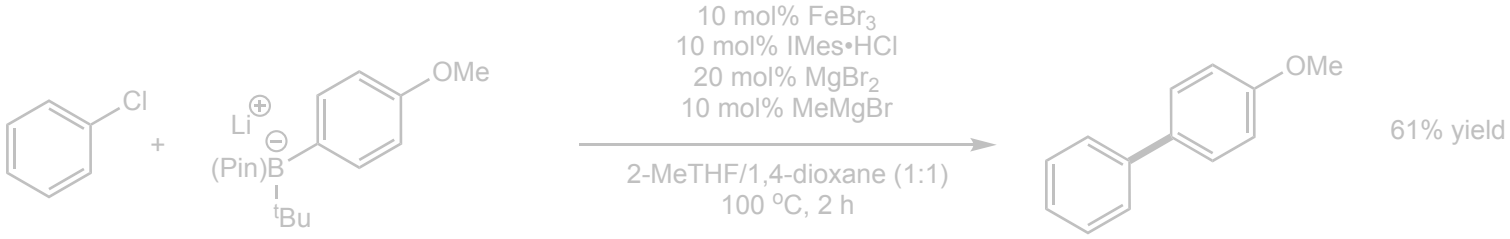



***DFT studies indicate an Fe(I)/(III) pathway with transmetalation preceding O.A.***

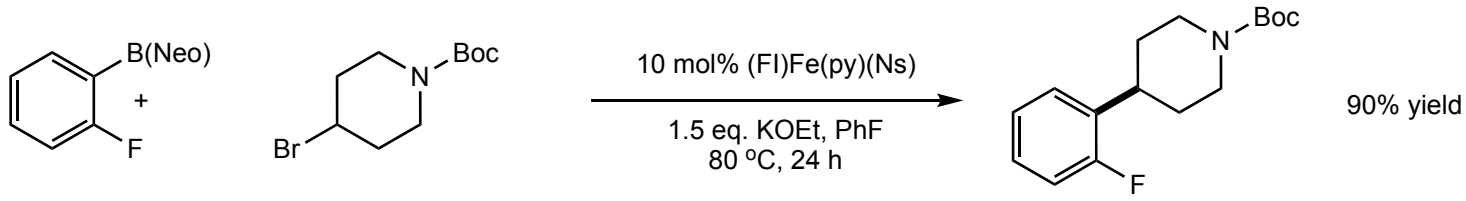
Benjamin J. S. Rowsell, Harry M. O'Brien, Gayathri Athavan, Patrick R. Daley-Dee, Johannes Krieger, Emma Richards, Karl Heaton, Ian J. S. Fairlamb and Robin B. Bedford *Nature Catalysis* **2024** 7 1186–1198

# *Iron-Catalyzed Cross-Coupling: Suzuki—Miyaura, two Subfields*

## *Aryl electrophiles*



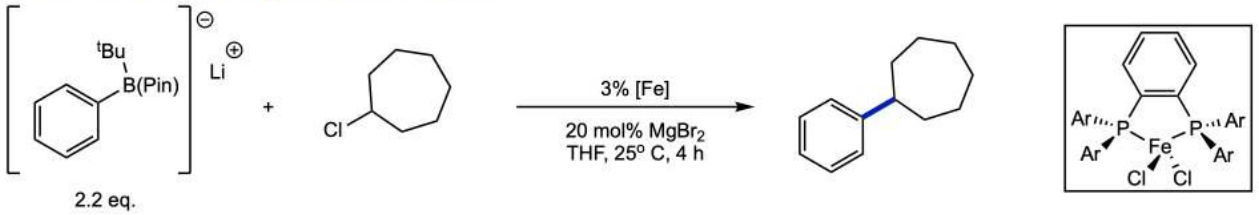

## *Alkyl electrophiles*



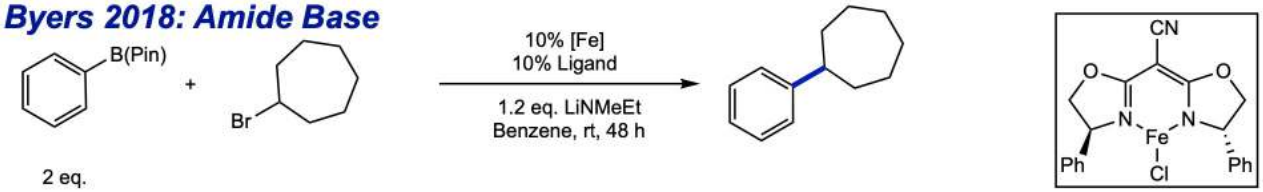

Paul O. Peterson, Matthew V. Joannou, Eric M. Simmons, Steven R. Wisniewski, Junho Kim, and Paul J. Chirik *ACS Catalysis* **2023** 13 (4), 2443-2448

# *Iron-Catalyzed Cross-Coupling: Alkyl Electrophile SMC*

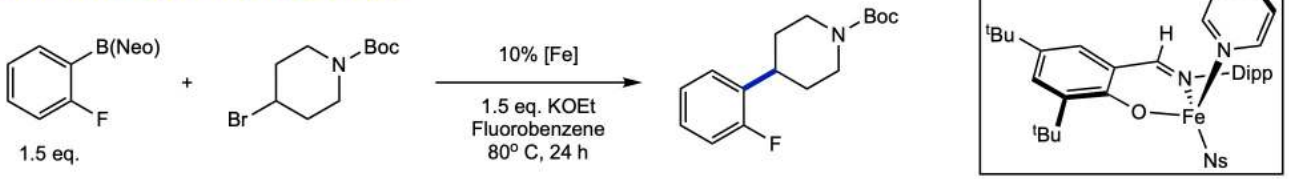
## *Nakamura 2010: Alkyllithium Base*




## *Byers 2018: Amide Base*

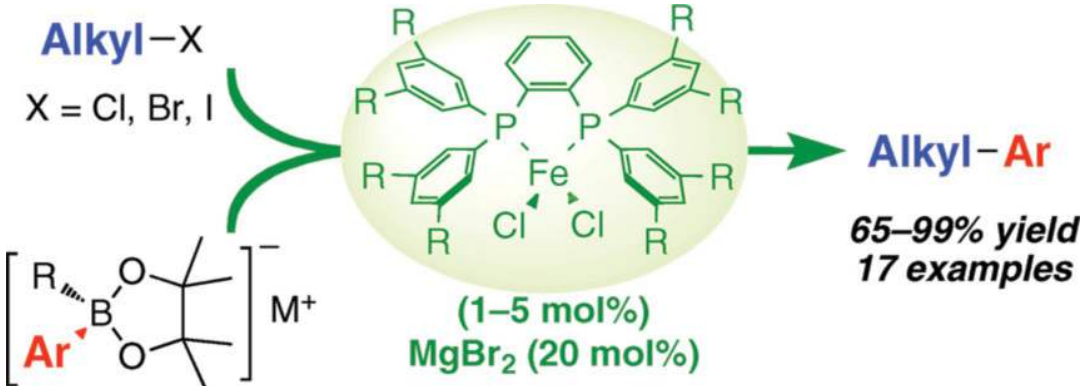



## *Chirik 2023: Alkoxide Base*



# *Iron-Catalyzed Cross-Coupling: Alkyl Electrophile SMC*

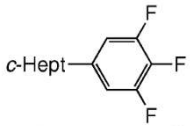
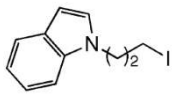
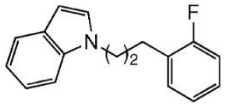
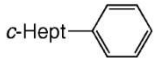
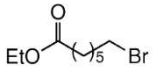
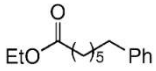
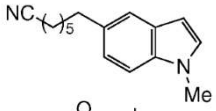
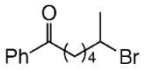
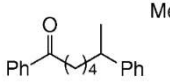
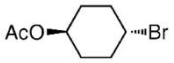
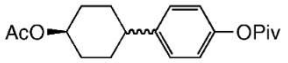
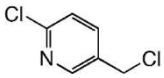
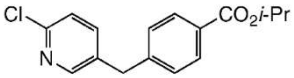
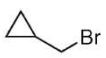
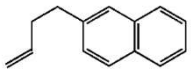
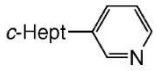
***Nakamura is credited with the first iron-catalyzed C($sp^2$)—C($sp^3$) SMC***




Takuji Hatakeyama, Toru Hashimoto, Yoshiyuki Kondo, Yuichi Fujiwara, Hirofumi Seike, Hikaru Takaya, Yoshinori Tamada, Teruo Ono, and Masaharu Nakamura
*Journal of the American Chemical Society* **2010** 132 (31), 10674-10676

# *Iron-Catalyzed Cross-Coupling: Alkyl Electrophile SMC*

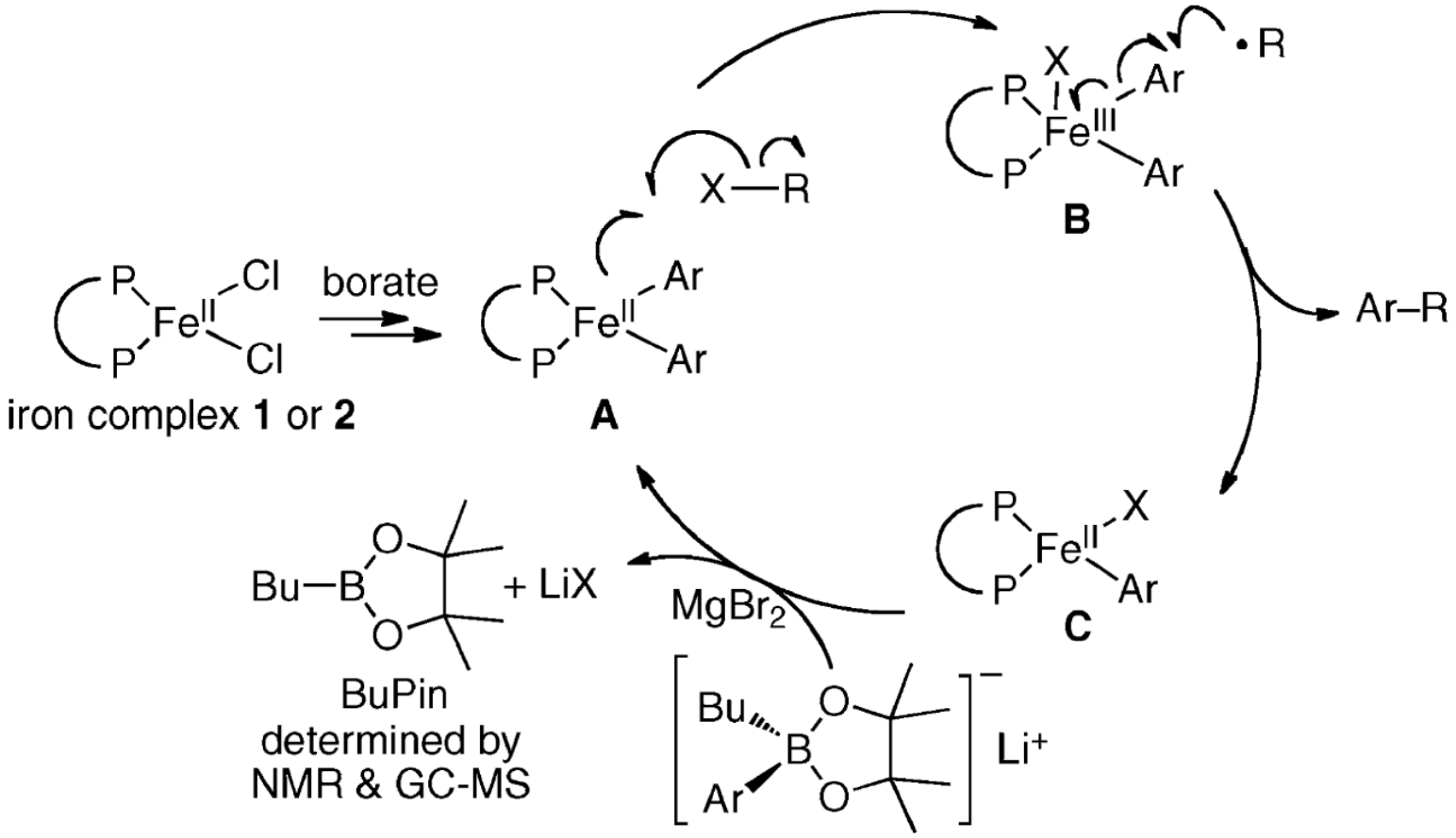
## *Fairly diverse functional-group tolerance given conditions*

| entry[a] | Alkyl–X | coupling product | yield (%)[b] |
|---|---|---|---|
| 1[c] | | | 99 (R" = H) |
| 2 | | | 98 (R" = OMe) |
| 3 | | | 94 (R" = $NMe_2$) |
| 4 | *c*-Hept–Br | *c*-Hept–R" | 77 (R" = Cl) |
| 5[d,e,f] | | | 90 (R" = $CO_2Me$) |
| 6[d,e,f] | | | 81 (R" = $CO_2Et$) |
| 7[d,e,f] | | | 74 (R" = $CO_2i$-Pr) |
| 8 | |  | 83 |
| 9 |  |  | 79 |
| 10[f,g] | *c*-Hept–Cl |  | 93[h] |
| 11 |  |  | 90 |
| 12[g] |  |  | 96 |
| 13[e] |  |  | 65 |
| 14[d,e] |  |  | 83[i] |
| 15[d,f] |  |  | 86 |
| 16 |  |  | 99[j] |
| 17[d] | *c*-Hept–Br |  | 73 |

Takuji Hatakeyama, Toru Hashimoto, Yoshiyuki Kondo, Yuichi Fujiwara, Hirofumi Seike, Hikaru Takaya, Yoshinori Tamada, Teruo Ono, and Masaharu Nakamura
*Journal of the American Chemical Society* **2010** 132 (31), 10674-10676

# *Iron-Catalyzed Cross-Coupling: Alkyl Electrophile SMC*

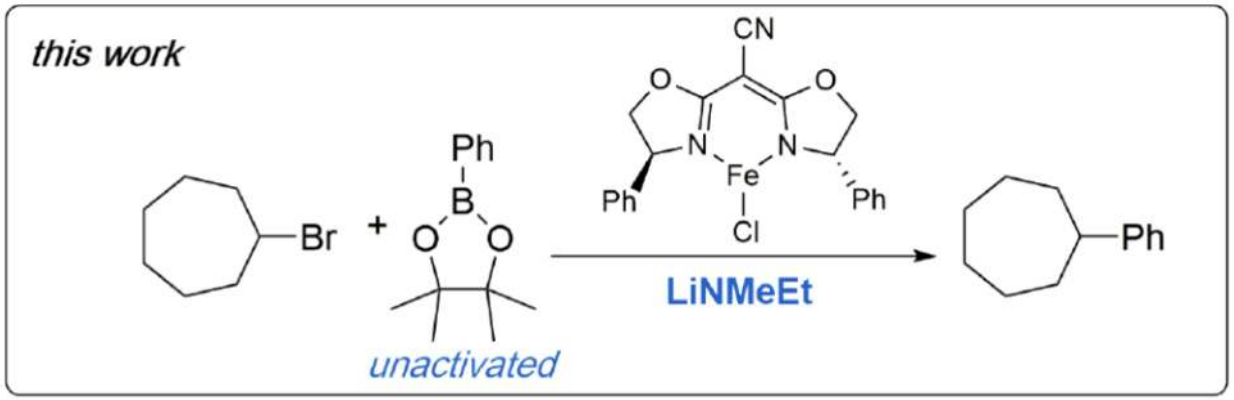
***Proposed mechanism is similar to other alkyl-electrophile systems, but with no cage escape***

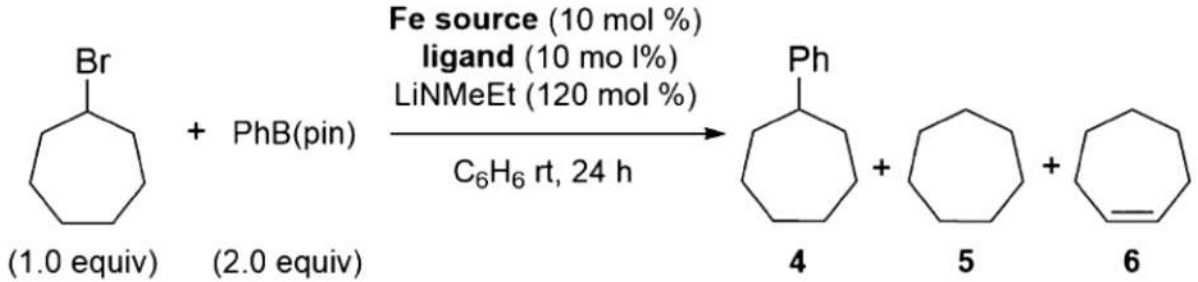


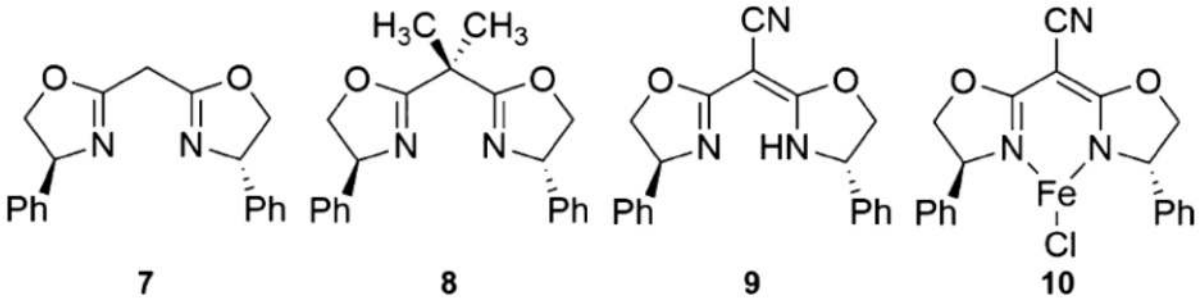

Takuji Hatakeyama, Toru Hashimoto, Yoshiyuki Kondo, Yuichi Fujiwara, Hirofumi Seike, Hikaru Takaya, Yoshinori Tamada, Teruo Ono, and Masaharu Nakamura
*Journal of the American Chemical Society* **2010** 132 (31), 10674-10676

# *Iron-Catalyzed Cross-Coupling: Alkyl Electrophile SMC*

***Next major advance is with amide base, Byers also uses L,X ligand***



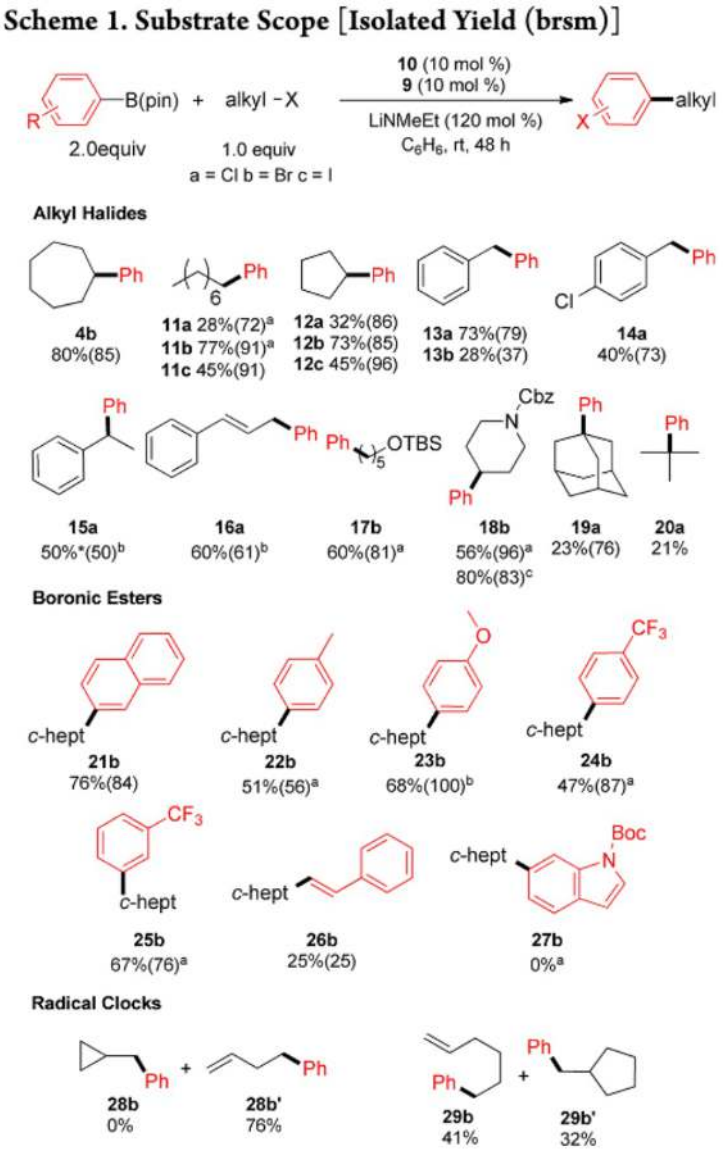




Michael P. Crockett, Chet C. Tyrol, Alexander S. Wong, Bo Li, and Jeffery A. Byers *Organic Letters* **2018** *20* (17), 5233-5237

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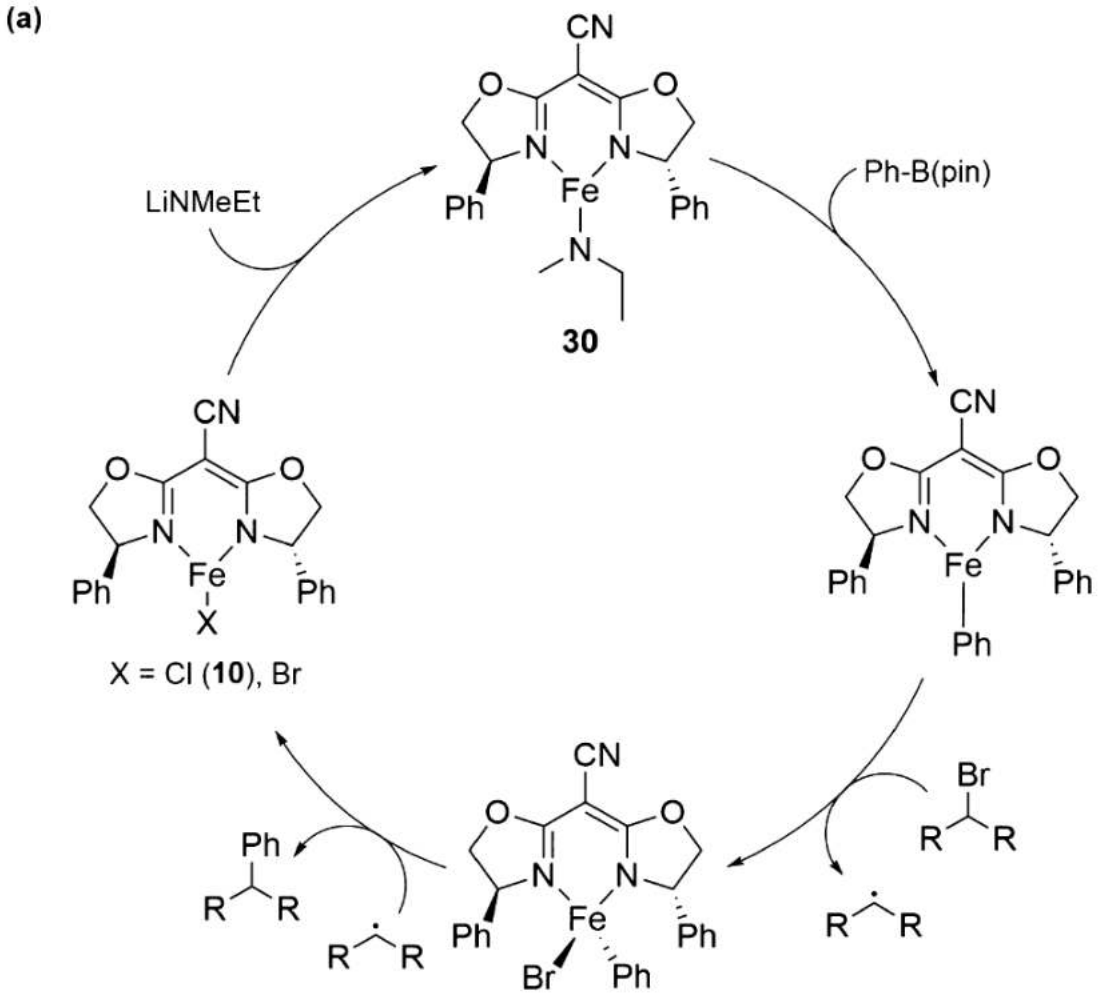
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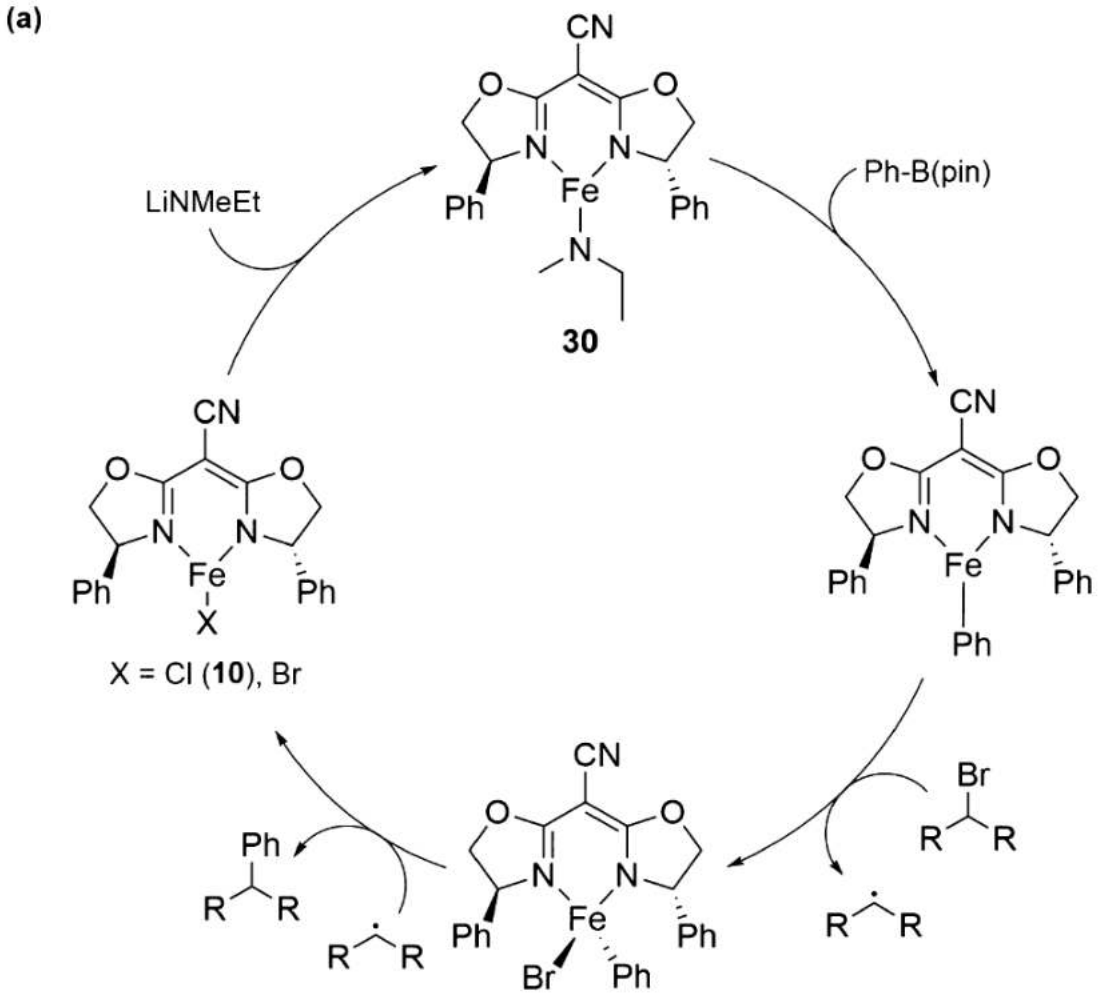
***Proposed mechanism is similar to Nakamura's***




Michael P. Crockett, Chet C. Tyrol, Alexander S. Wong, Bo Li, and Jeffery A. Byers *Organic Letters* **2018** *20* (17), 5233-5237

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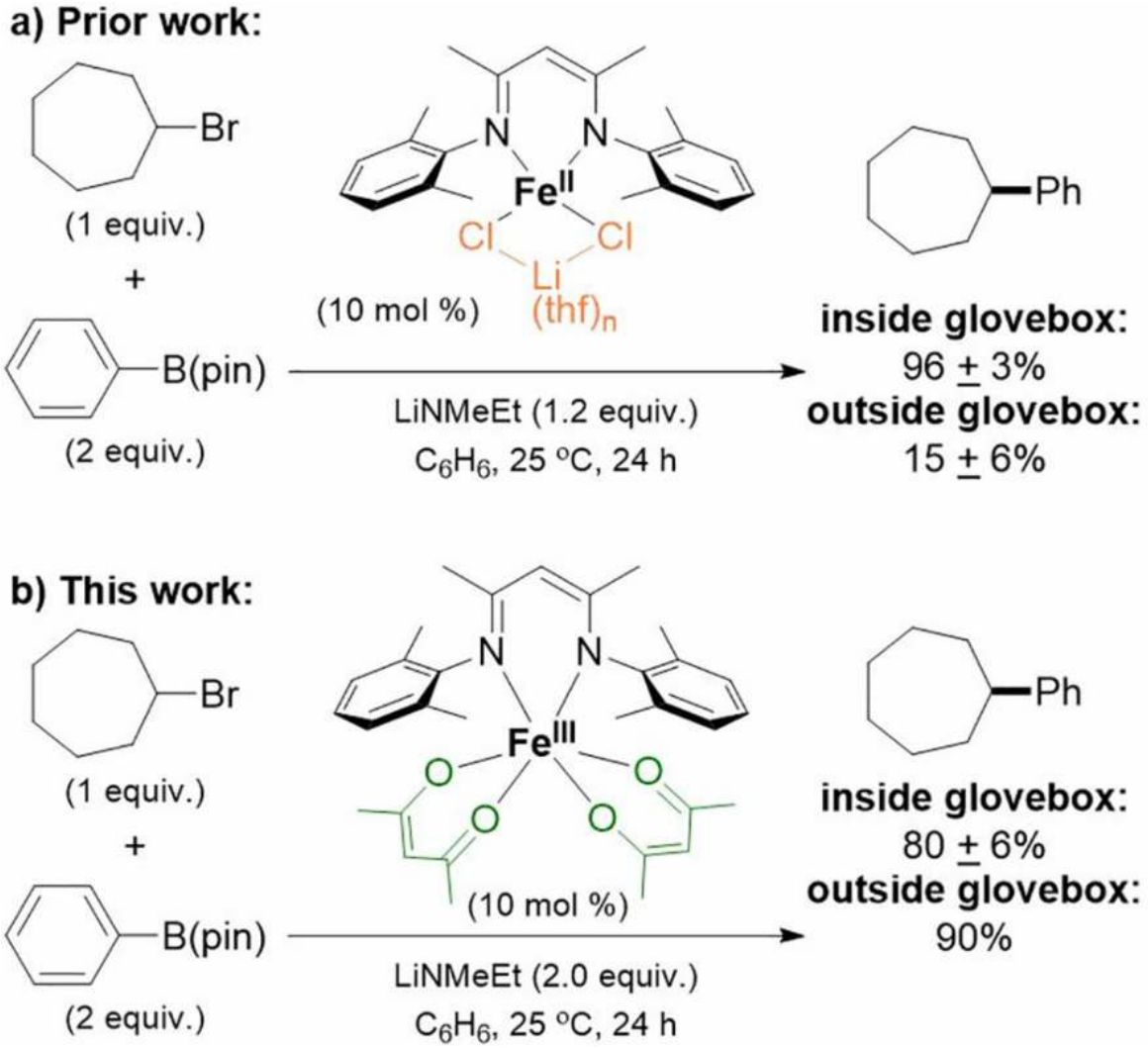
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Michael P. Crockett, Chet C. Tyrol, Alexander S. Wong, Bo Li, and Jeffery A. Byers *Organic Letters* **2018** *20* (17), 5233-5237

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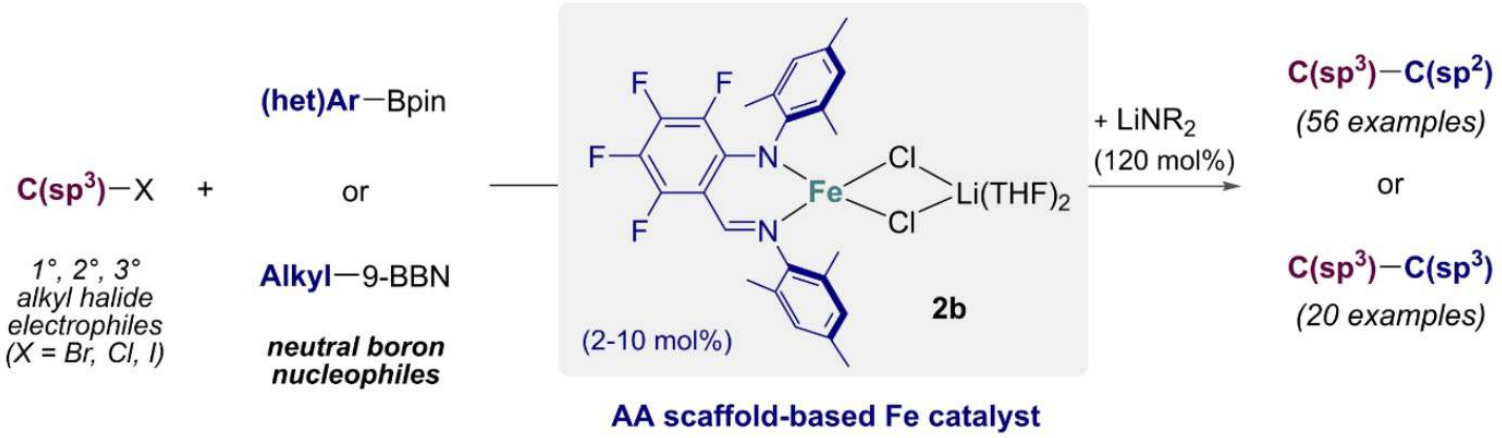
***Byer's group also developed an extremely rare example of an air-stable [Fe] cross-coupling precatalyst***

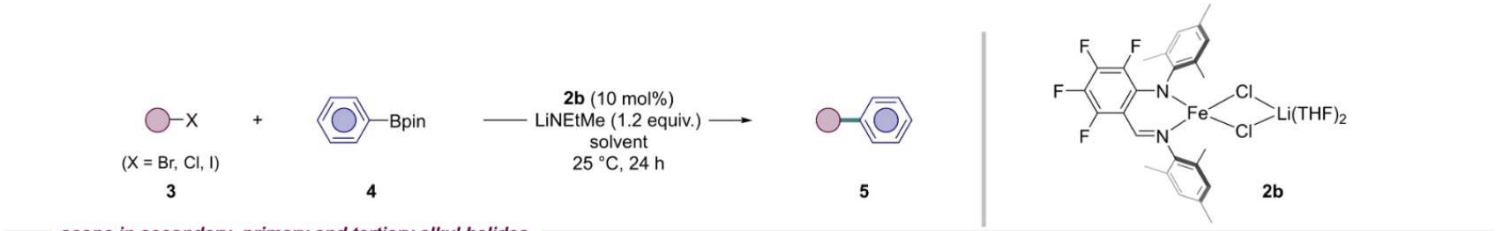


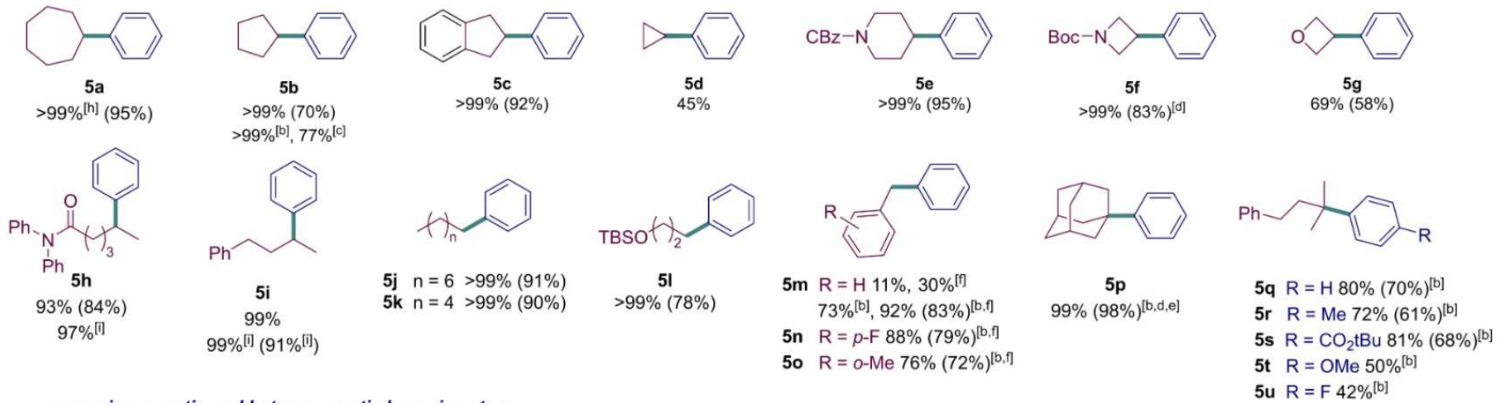

Alexander S. Wong, Bufan Zhang, Bo Li, Michael L. Neidig, and Jeffery A. Byers *Organic Process Research & Development* **2021** 25 (11), 2461-2472

# *Iron-Catalyzed Cross-Coupling: Alkyl Electrophile SMC*

## *C(sp³)—C(sp³) reported this year*



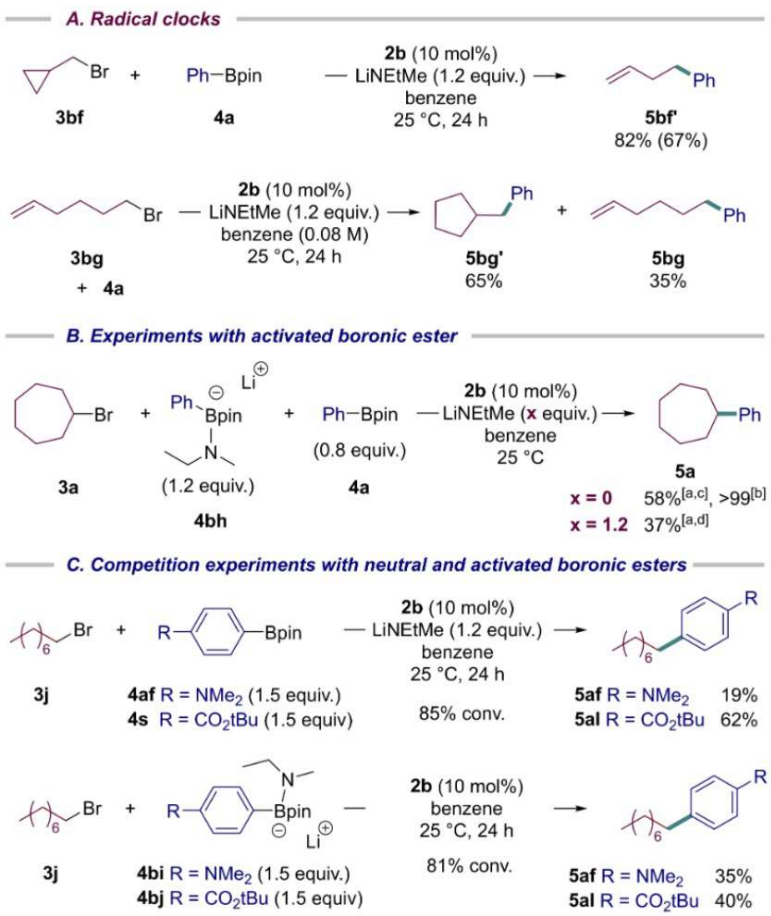



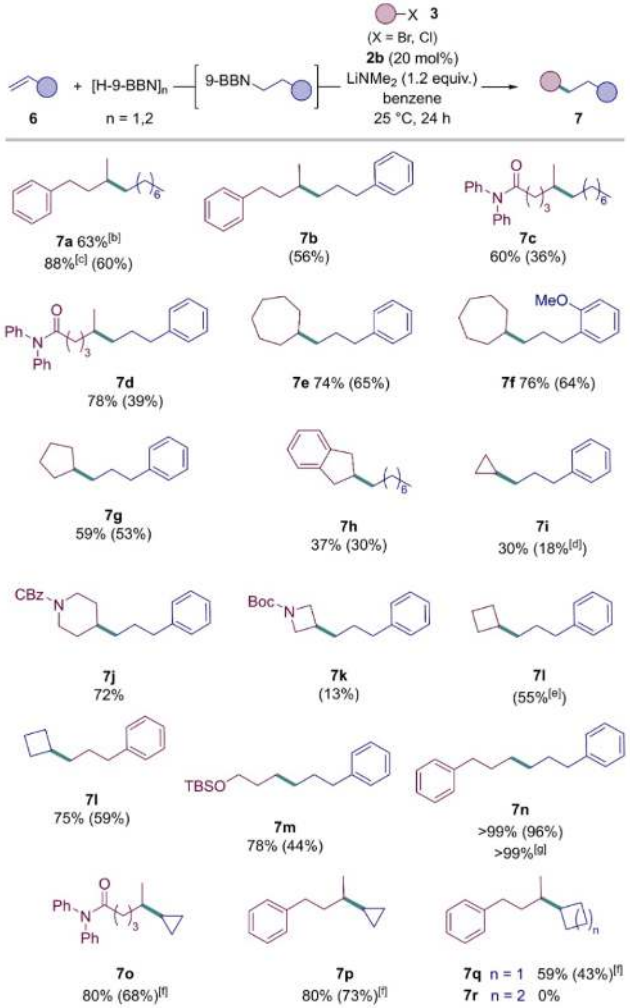

Donghuang Chen, Clément Lepori, Régis Guillot, Richard Gil, Sophie Bezzenine, and Jérôme Hannedouche *Angew. Chem. Int. Ed*. **2024**, 63, e202408419

# *Iron-Catalyzed Cross-Coupling: Alkyl Electrophile SMC*

## *Mechanistic studies had near-identical findings to Byers*




## *Broad alkyl-alkyl scope*

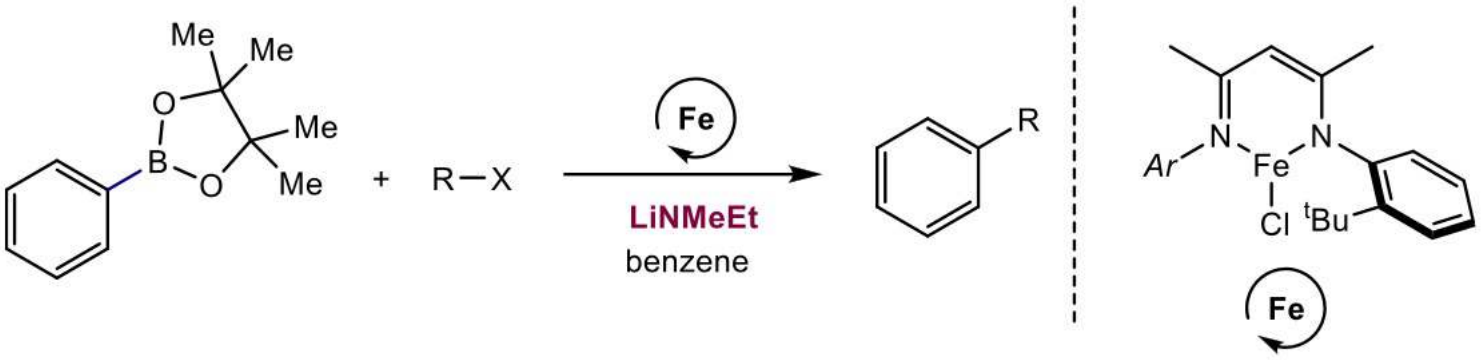



Donghuang Chen, Clément Lepori, Régis Guillot, Richard Gil, Sophie Bezzenine, and Jérôme Hannedouche *Angew. Chem. Int. Ed*. **2024**, 63, e202408419

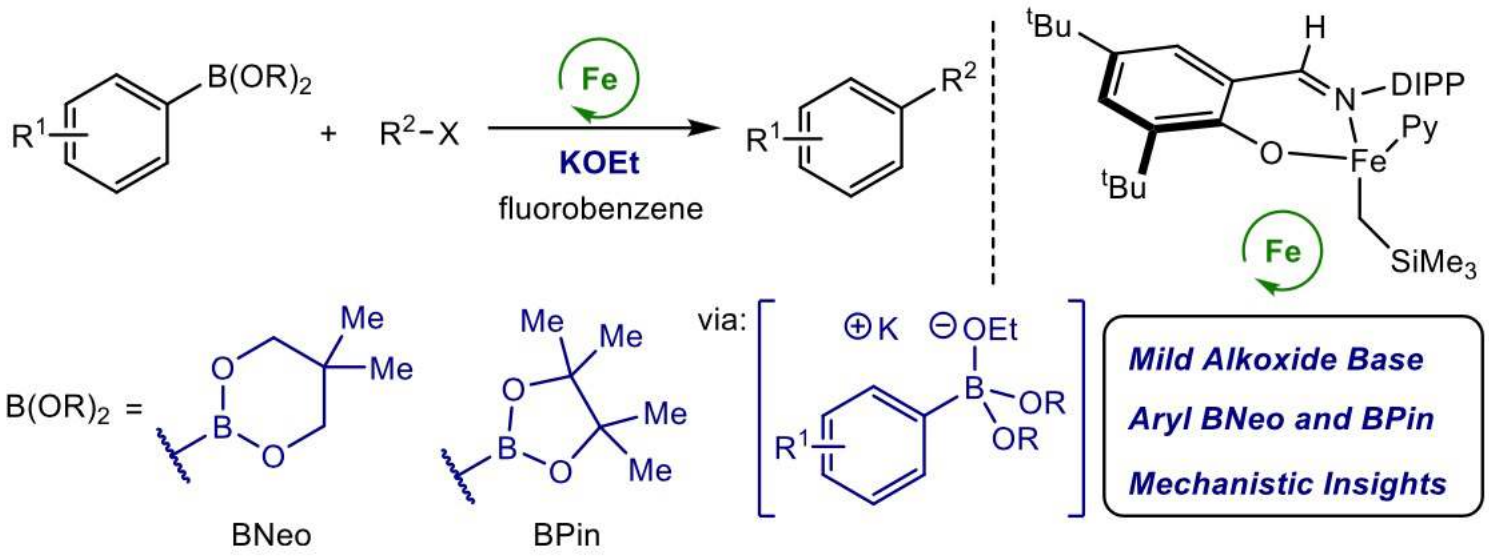
# *Iron-Catalyzed Cross-Coupling: Alkyl Electrophile SMC*

***Paul Peterson first to report with alkoxide base***

***A. Iron-Catalyzed Cross-Coupling using an Amide Base (Byers 2020)***



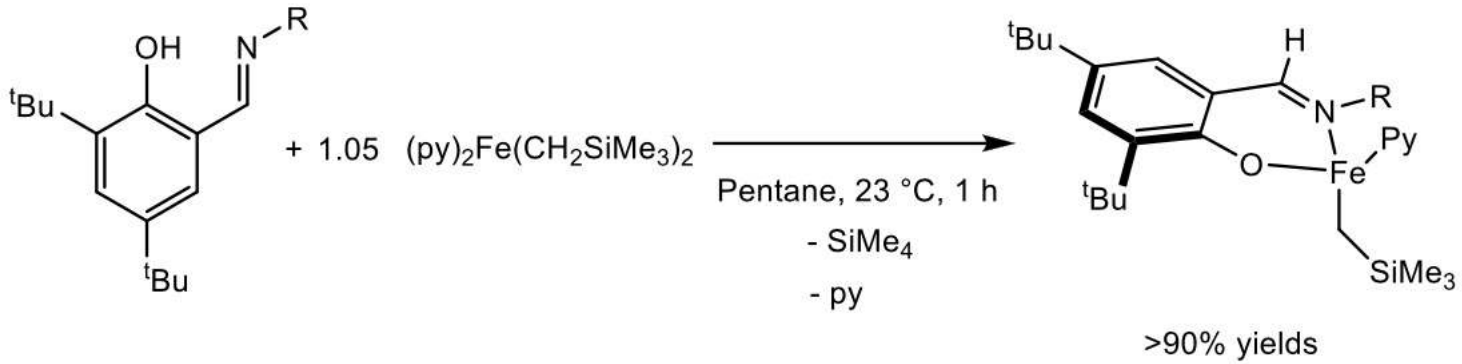

***B. This Work: Iron-Catalyzed Cross-Coupling using an Alkoxide Base***



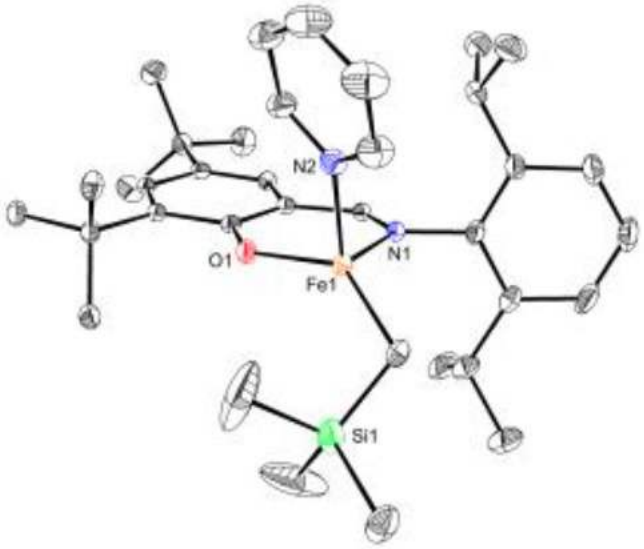

Paul O. Peterson, Matthew V. Joannou, Eric M. Simmons, Steven R. Wisniewski, Junho Kim, and Paul J. Chirik *ACS Catalysis* **2023** 13 (4), 2443-2448

# *Iron-Catalyzed Cross-Coupling: Alkyl Electrophile SMC*

***Well-defined precatalyst, helps solidify L,X ligands for C($sp^2$)—C($sp^3$) SMC***




>90% yields

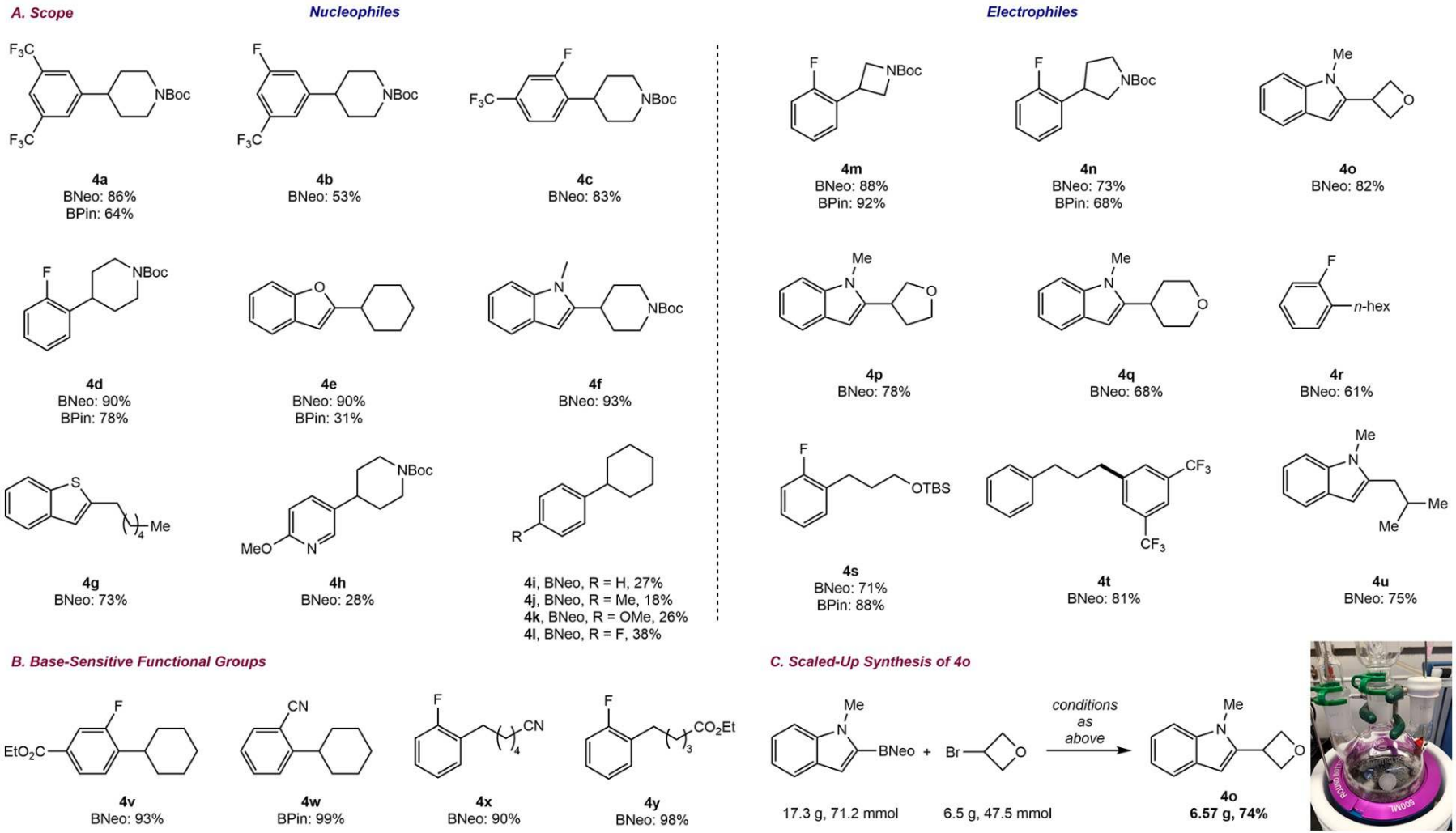



| Compound | R |
|---|---|
| **1a** | DIPP |
| **1b** | Mes |
| **1c** | 4-MeO-Ph |
| **1d** | Cy |
| **1e** | iPr |
| **1f** | tBu |

Paul O. Peterson, Matthew V. Joannou, Eric M. Simmons, Steven R. Wisniewski, Junho Kim, and Paul J. Chirik *ACS Catalysis* **2023** 13 (4), 2443-2448

# *Iron-Catalyzed Cross-Coupling: Alkyl Electrophile SMC*

## *Scope is highly limited to electronically-activated nucleophiles*




[a]Reactions performed on 0.2–0.5 mmol scale; yields are isolated. For unsuccessful substrates, see Supporting Information.

Paul O. Peterson, Matthew V. Joannou, Eric M. Simmons, Steven R. Wisniewski, Junho Kim, and Paul J. Chirik *ACS Catalysis* **2023** 13 (4), 2443-2448