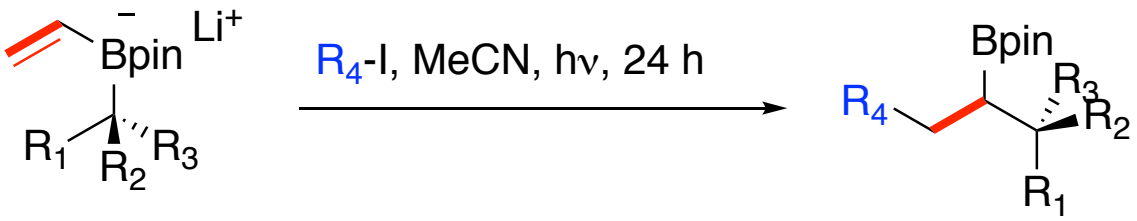
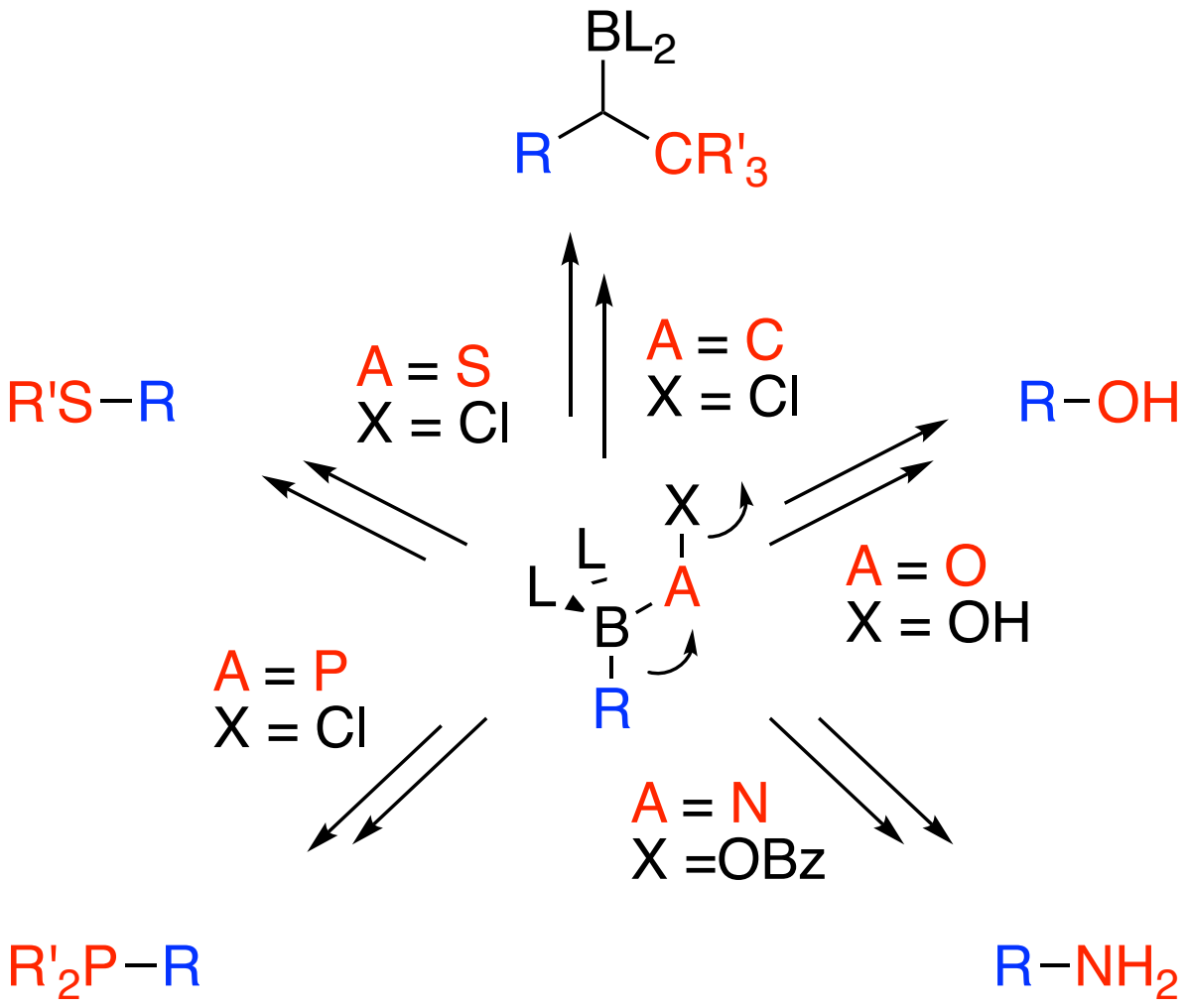
Synthesis of α-Chiral Ketones and Chiral Alkanes Using Radical Polar Crossover Reactions of Vinyl Boron-Ate Complexes

C. Gerleve, M. Kischkewitz, A. Studer

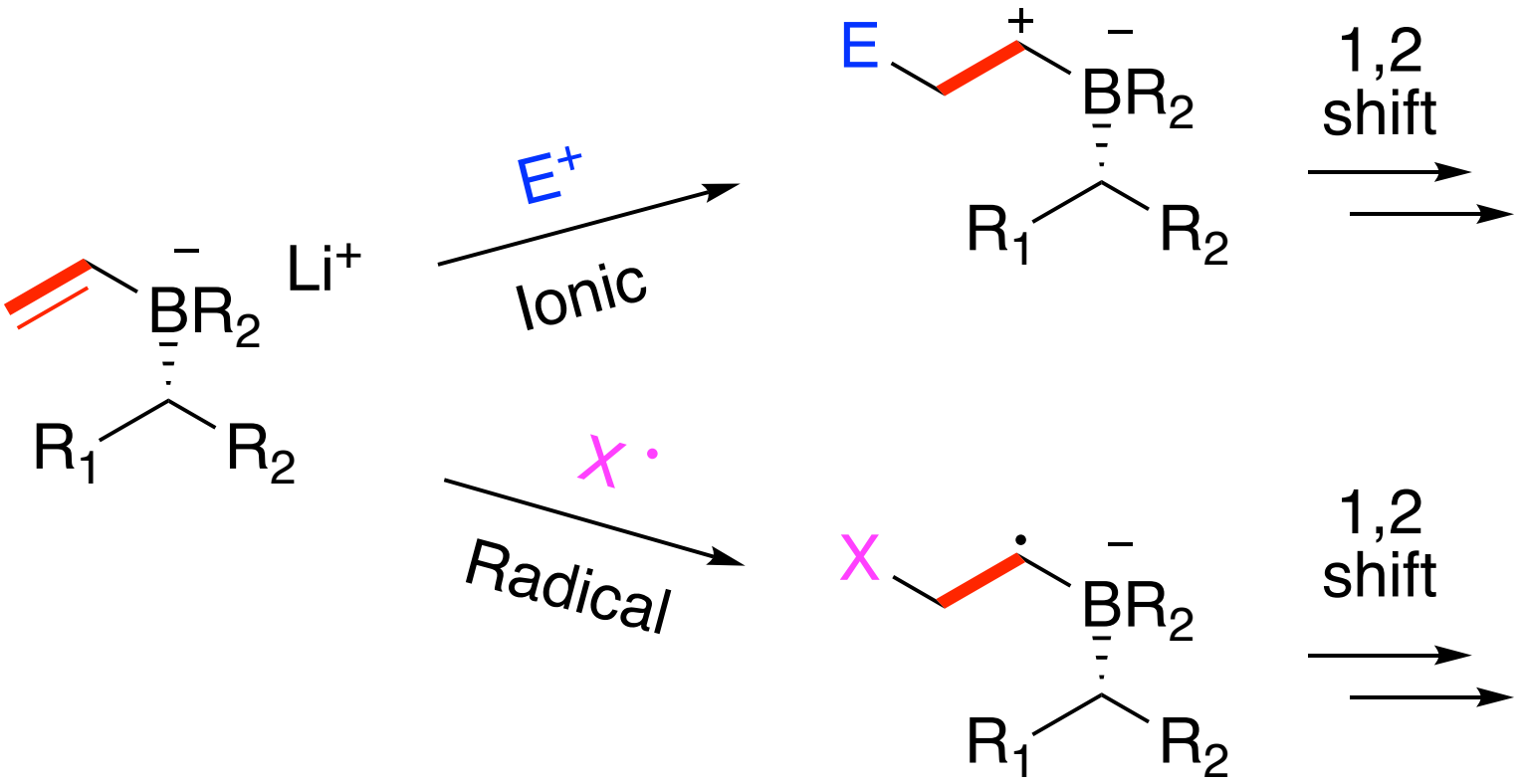
Angew. Chem. Int. Ed. **2018**, *ASAP*, DOI: 10.1002/anie.201711390.



1,2-Metallate Shifts with Boron



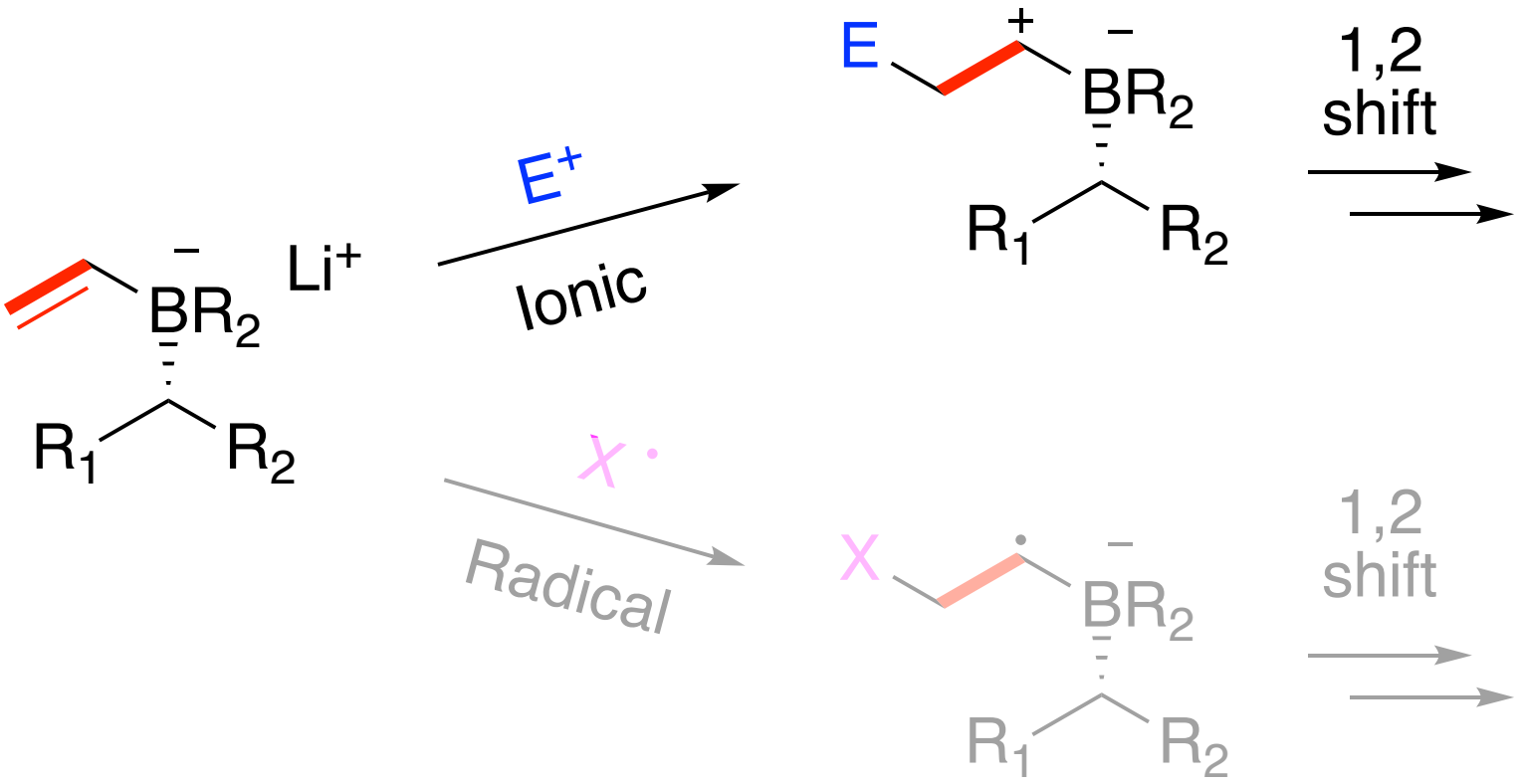
Two Pathways for Promoting Migration



- Ionic: Zweifel olefination, Pd conjunctive cross-coupling
- Radical: Et_3B/O_2,photochemical,

Ni conjunctive cross-coupling

Two Pathways for Promoting Migration



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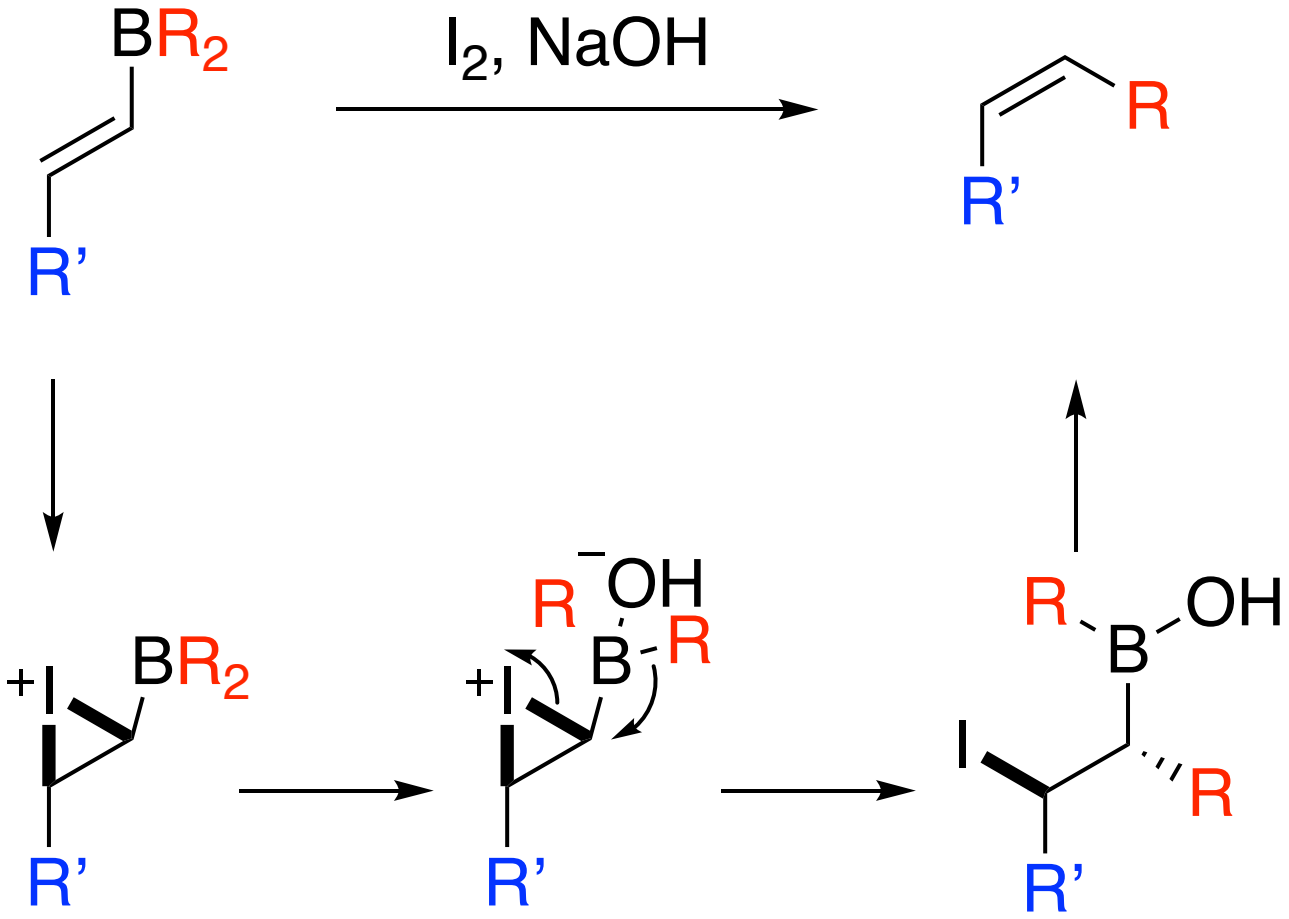
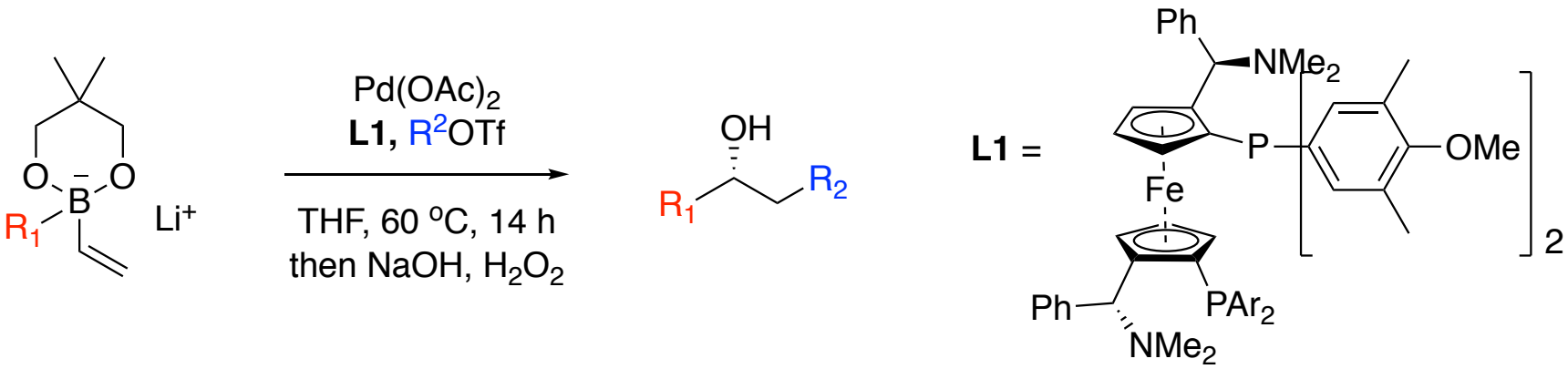
Zweifel Olefination



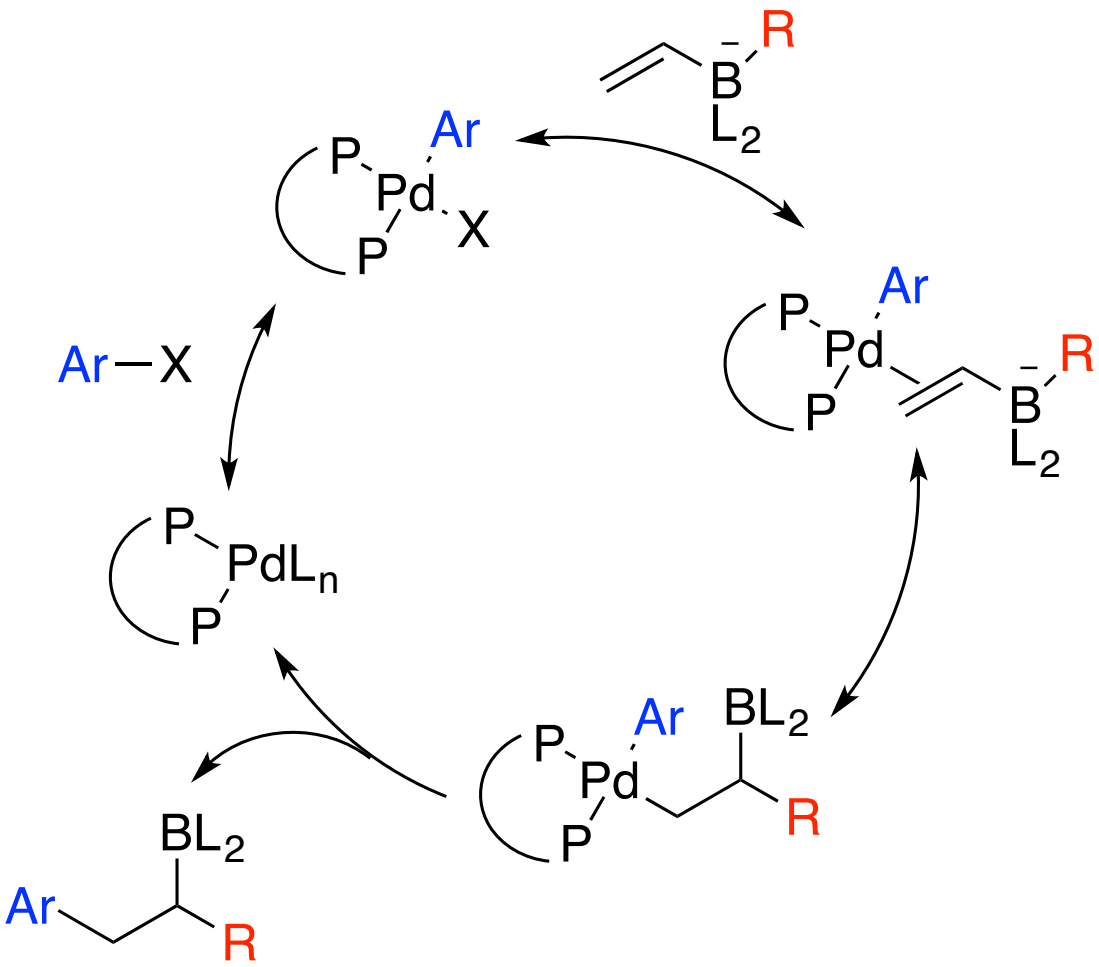
J. Am. Chem. Soc. **1967**, *89*, 3652.
Synthesis. **2017,** *49,* 3323-3336.

Pd-Cat. Conjunctive Cross-Coupling



- 1-2 mol% halide ion detrimental
  - Solution: "…lithium-halogen exchange with *n*-BuLi followed by low temperature crystallization of vinyl lithium."
- Alternatives
  - Increase catalyst loading by 2.5x
  - Li-Sn exchange

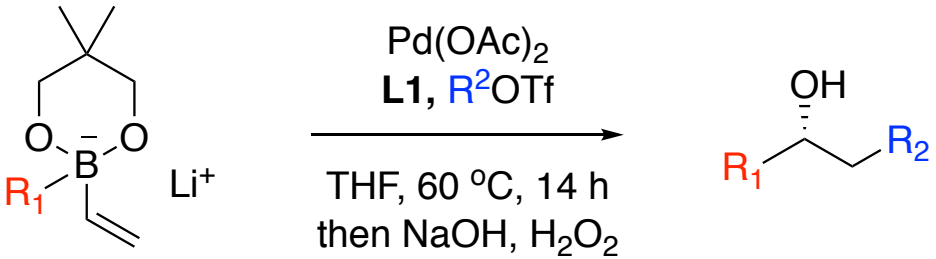
Proposed Catalytic Cycle

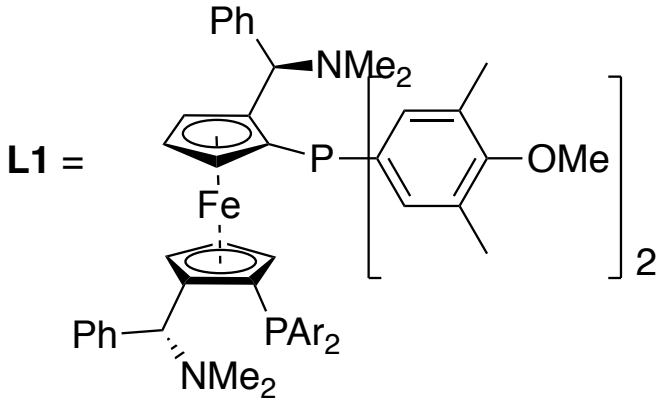


Science. **2016,** *351,* 70-74.

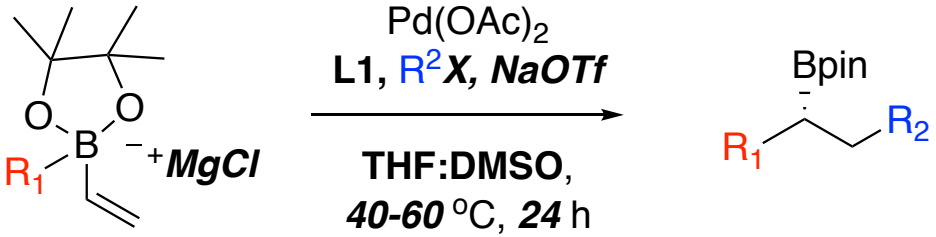
Advancements in Conjunctive Cross-Coupling

Morken 2016





Morken 2017

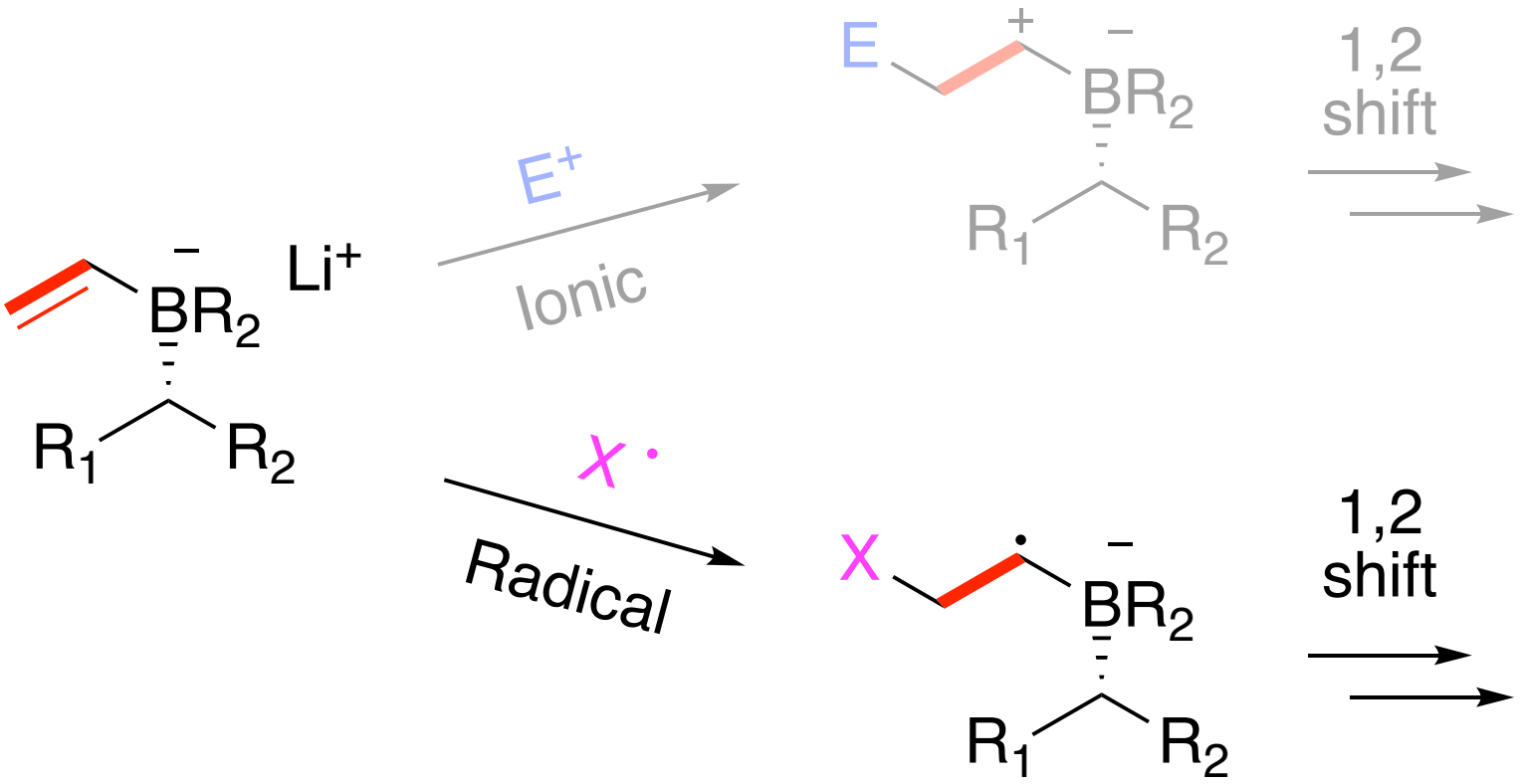


Improvements:

- Halide ion tolerance
- Electron-deficient aromatics
- More effective for R_1 = alkyl
- X = OTf or Br

Science. **2016,** *351,* 70-74.
J. Am. Chem. Soc. **2017**, *139*, 3153-3160.

Two Pathways for Promoting Migration

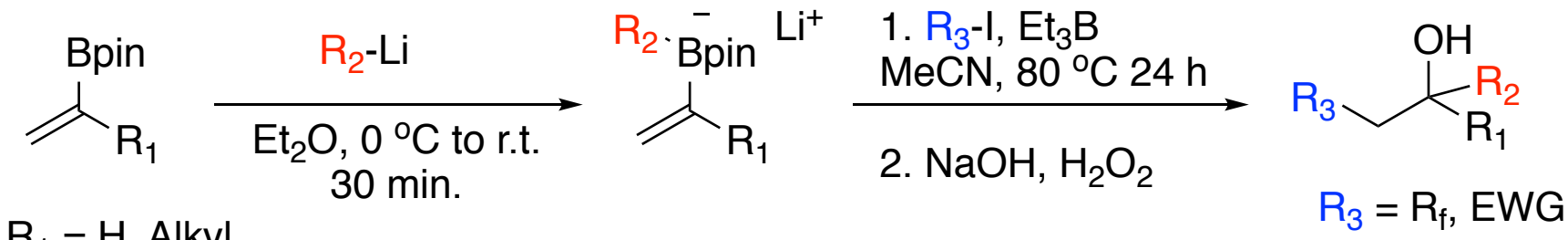


- Ionic: Zweifel olefination, Pd conjunctive cross-coupling
- Radical: Et_3B/O_2,photochemical,

Ni conjunctive cross-coupling

Studer's Original Radical-Promoted 1,2-Migration

Studer 2017



R_1 = H, Alkyl

R_2 = Ph, Alkyl

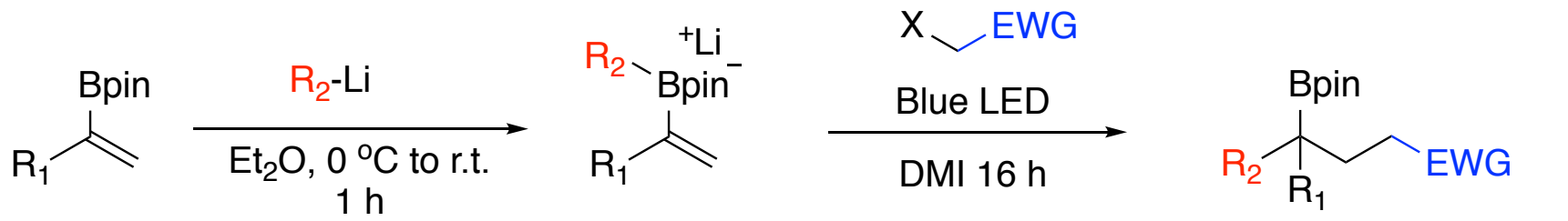
R_3 = R_f, EWG

- First radical-promoted 1,2-migration of boron-ate complex
- Complimentary to Morken's work (β-alkylation vs. β-arylation)
- Uses 5 eq. R_3-I

Science. **2017,** *355,* 936-938.

Photochemically-Induced 1,2-Migration

Aggarwal 2017



R_1 = H, Alkyl

R_2 = Ar, Alkyl

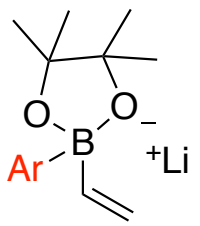
X = I, Br (+NaI), Cl (+NaI)

- Difficult substrates require $Ru(bpy)_3Cl_2{\cdot}2H_20$
- Uses 1.5 eq. halide
- Direct comparison with yields from Studer's method are difficult

J. Am. Chem. Soc.. **2017,** *139,* 5736-5739.

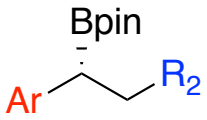
Ni-Cat. Conjunctive Cross-Coupling

Morken 2017



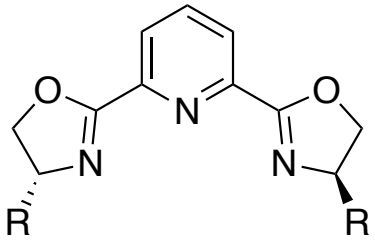
[[methallyl]NiCl]$_2$
L, R^2X

THF 60 °C, 15 h

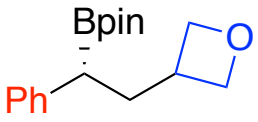


R_2 = Alkyl
X = I, Br (+NaI)

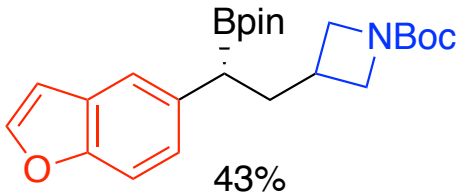
L =



R = Ph: $189/500mg
R = *m*-xylyl: not commercial



49%
er 98:2



43%
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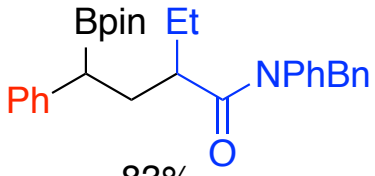
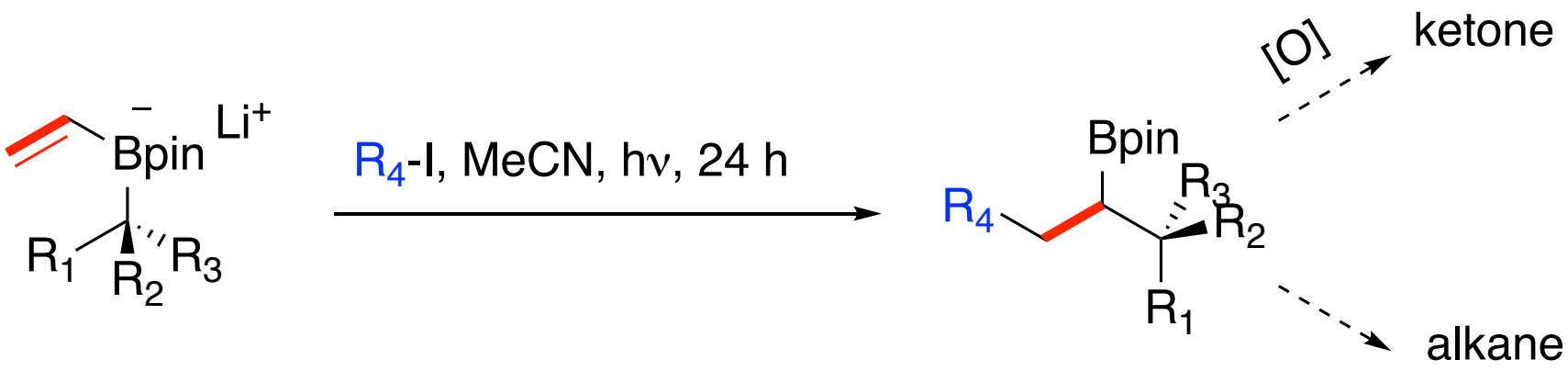


83%
er 51:49
dr 1.6:1

- More interesting substrate scope
- Enantioselective reactions possible
- Uses 1.2 eq. R_3-X
- Less expensive metal, ligand (some cases)

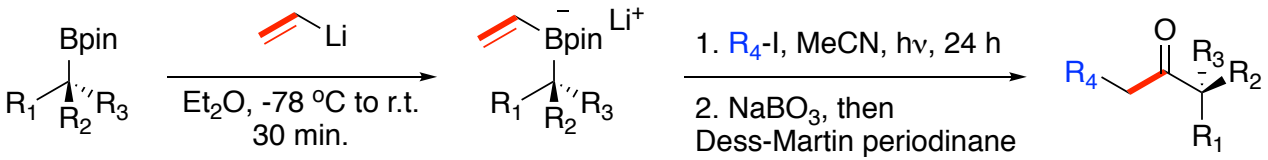
J. Am. Chem. Soc.. **2017,** *139,* 17293-17296.

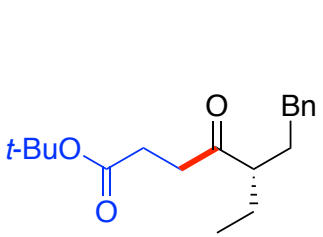
Title Paper



- Uses 400 W lamp
- Same scales as Aggarwal paper (0.3 mmol)

Title Paper: Ketone Scope





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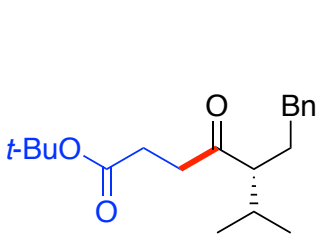

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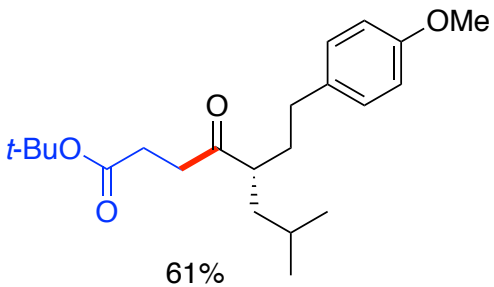

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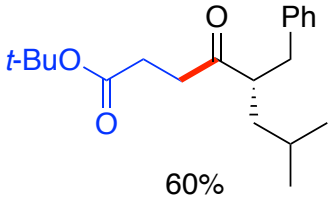

60%
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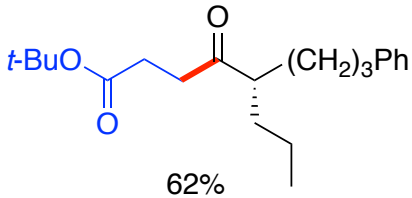

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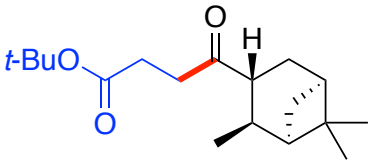

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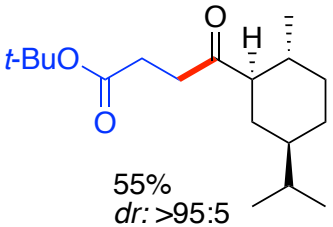

55%
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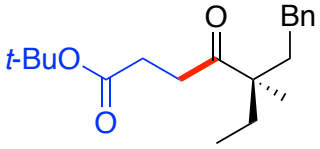
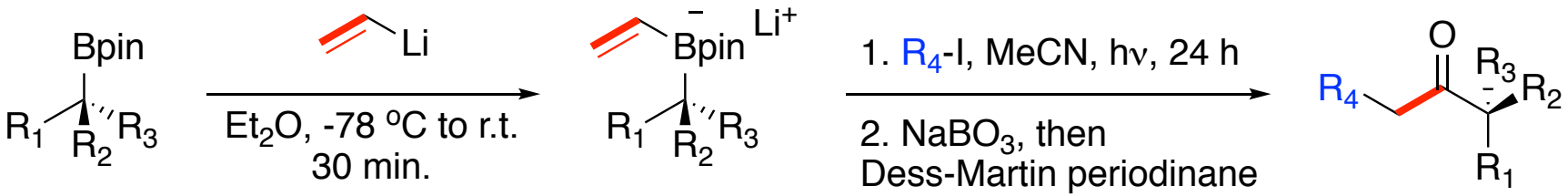
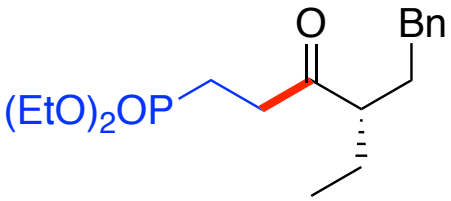


20%
er: >99:1

Angew. Chem. Int. Ed. **2018**, *ASAP*,
DOI: 10.1002/anie.201811390
6/28/2018

Title Paper: Other Iodides





40%,
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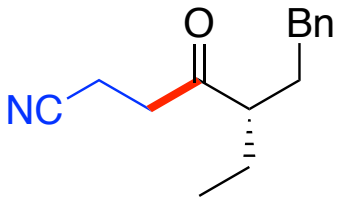

38%,
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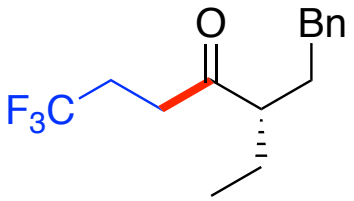
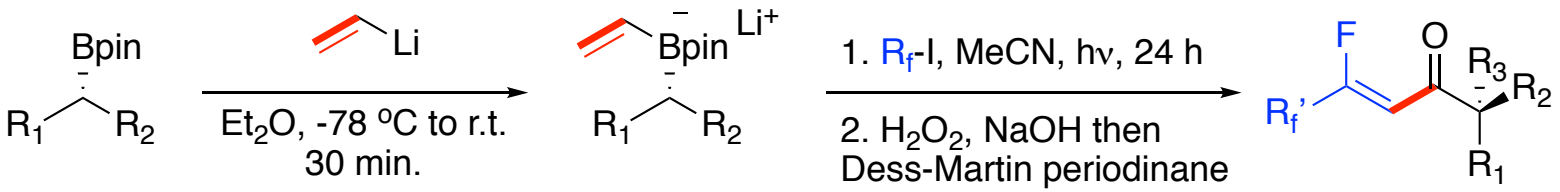
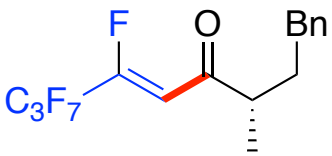


27%,
er: 98:2

Angew. Chem. Int. Ed. **2018**, *ASAP*,
DOI: 10.1002/anie.201811390
6/28/2018

Title Paper: Use of Perfluoroalkyl Iodides





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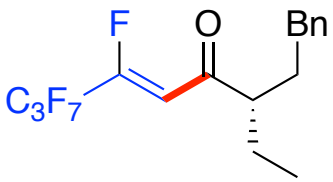

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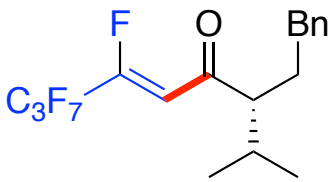

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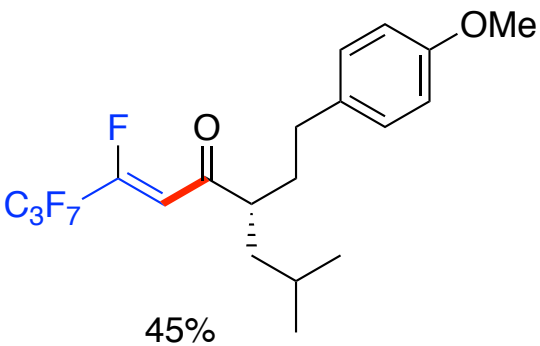

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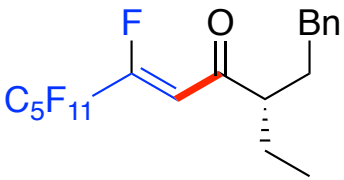

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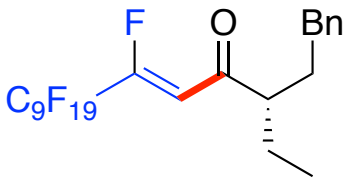

50%
er: 99:1

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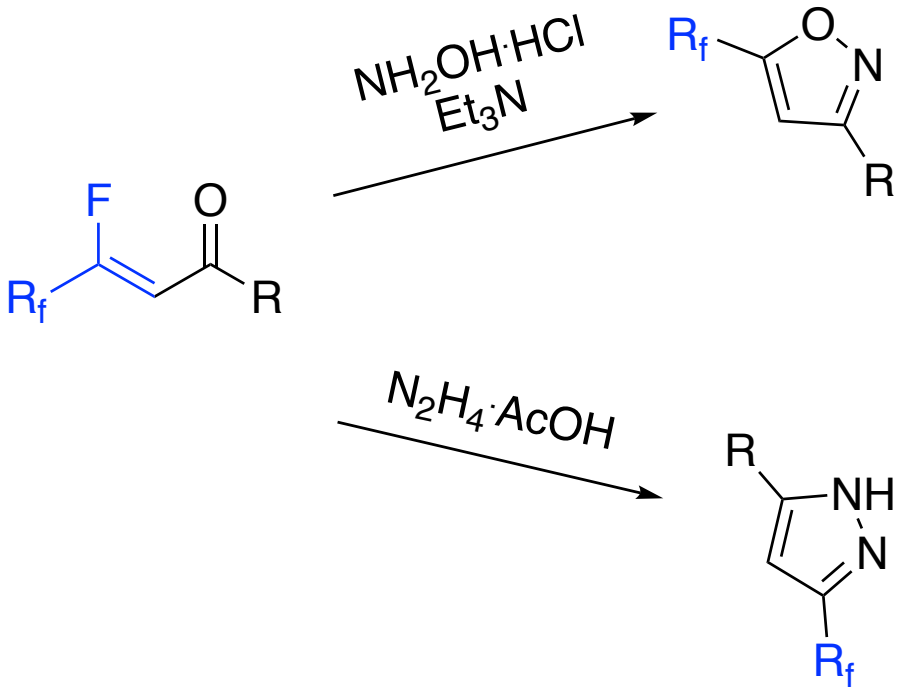
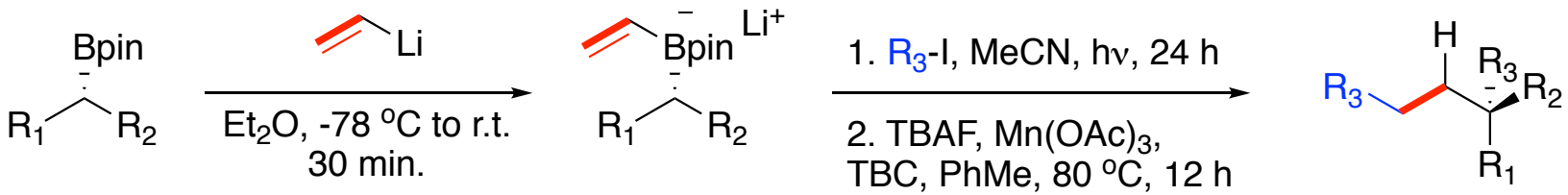
6/28/2018

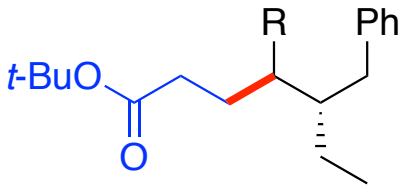
Application of Fluorinated Ketones



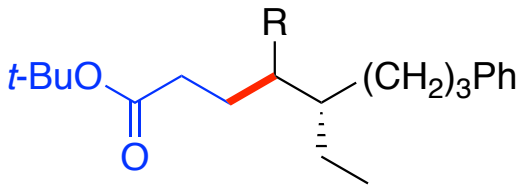
Bull. Chem. Soc. Jpn.. **2002,** *75,* 1833-1842.

Title Paper: δ-Chiral Esters

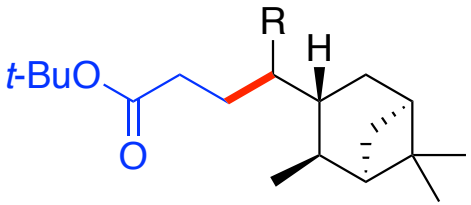




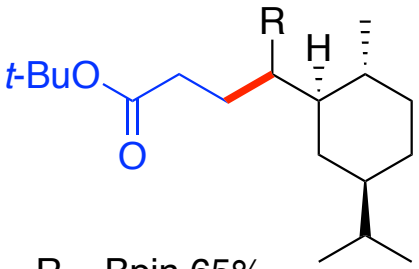
R = Bpin 75%
R = H 76% *er*:>99:1



R = Bpin 70%
R = H 65% *er*:98:2



R = Bpin 66%
R = H 79% *dr*:>95:5



R = Bpin 65%
R = H 85% *dr*:>95:5

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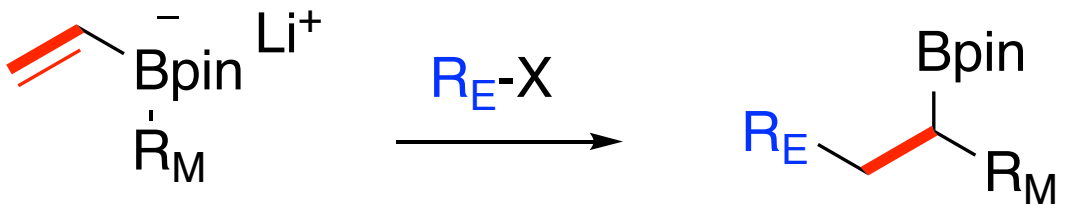
DOI: 10.1002/anie.201711390

Summary



	R_M Alkyl	R_M Aryl	R_E Alkyl	R_E Aryl	Enantiosel.?
Morken Pd					
Morken Ni					
Studer hv					
Aggarwal hv					
Studer new					

- Green = Yes
- Yellow = Partial
- Red = No