

Principles and Applications of Radical-Radical Coupling



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Literature presentation
Sep. 30, 2022

Outline

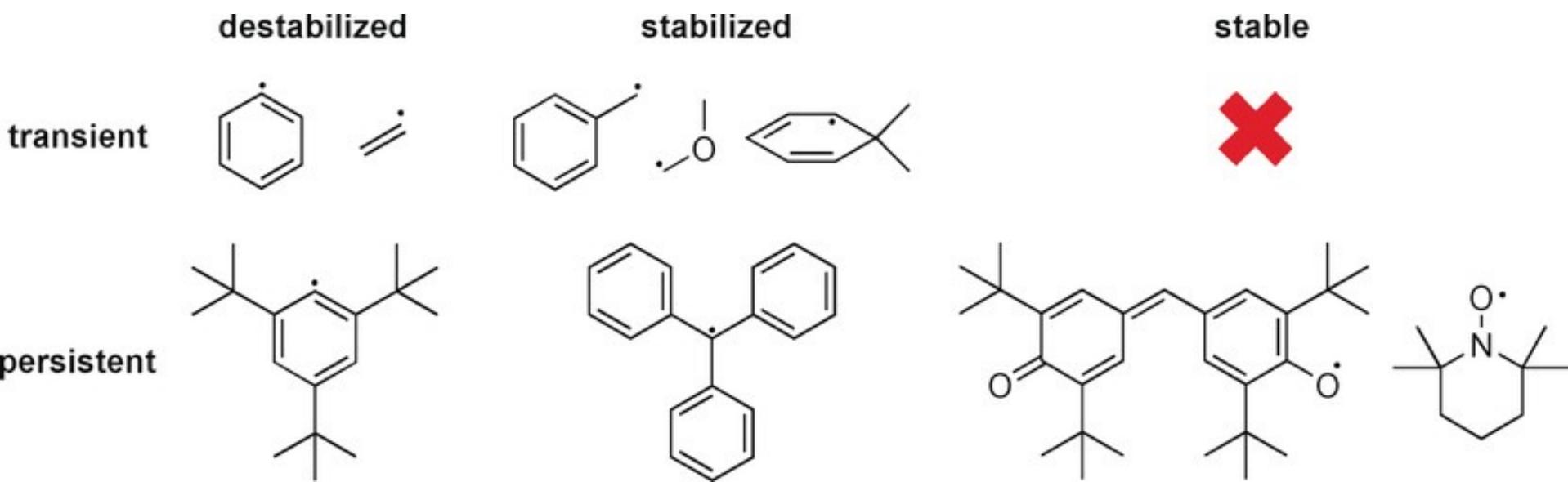
- Principles: persistent radical effect
- How do we generate these radicals?
- How do we mediate the coupling process?
 - Metal catalysts
 - Organic catalysts
- Interesting applications in synthesis

Persistent radical effect

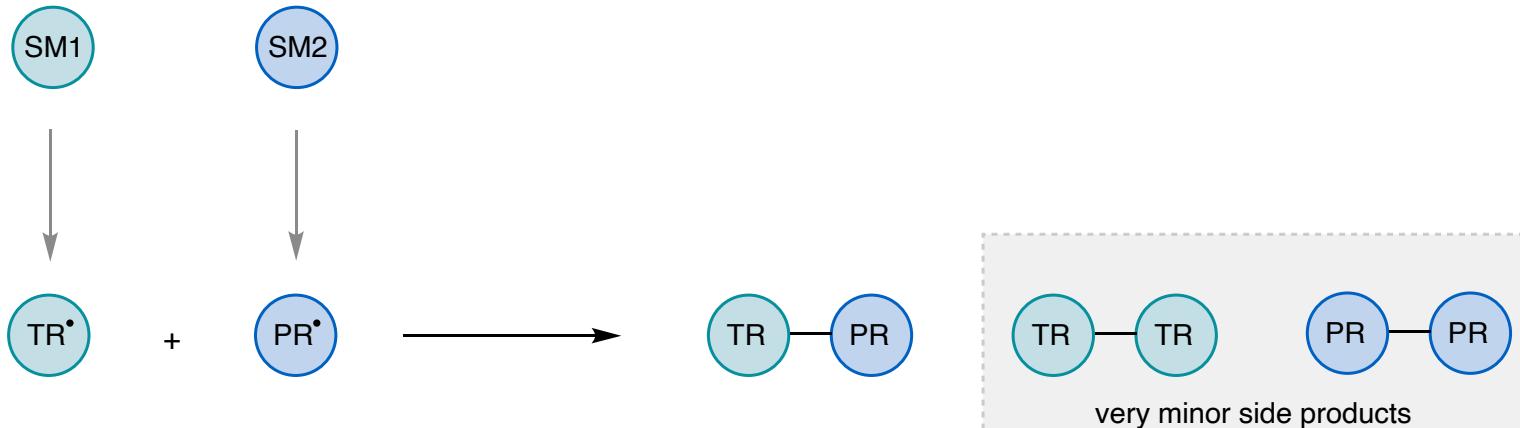
- Persistent: radical lifetime significantly greater than methyl ($\sim 10^3$ s) — kinetic
- Stabilized: corresponding C-H BDE > 104.9 kcal/mol (methane) for C-centered radical — thermodynamic
- Stable: can be handled and stored easily like normal chemical; very persistent

Persistent radical effect

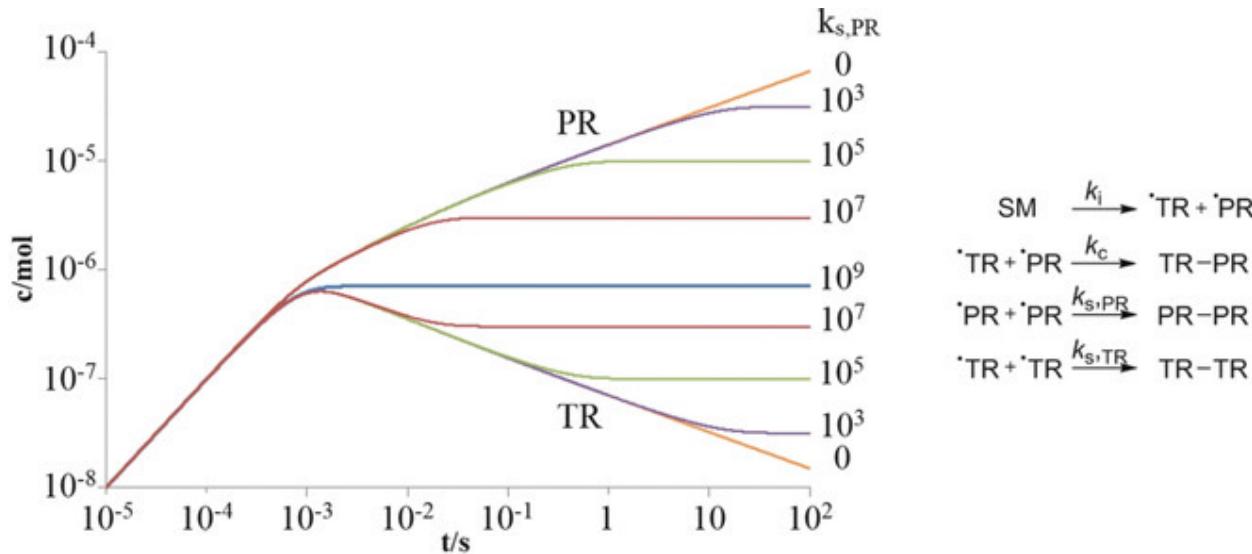
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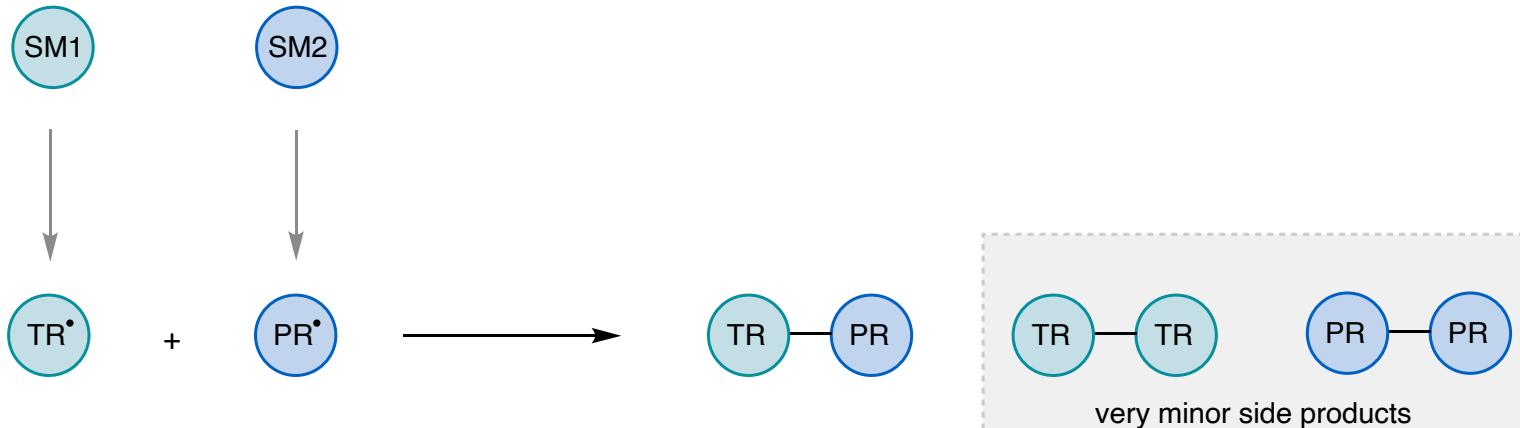
What exactly is PRE?



- Selective radical cross-coupling is preferred if one radical has significantly longer lifetime



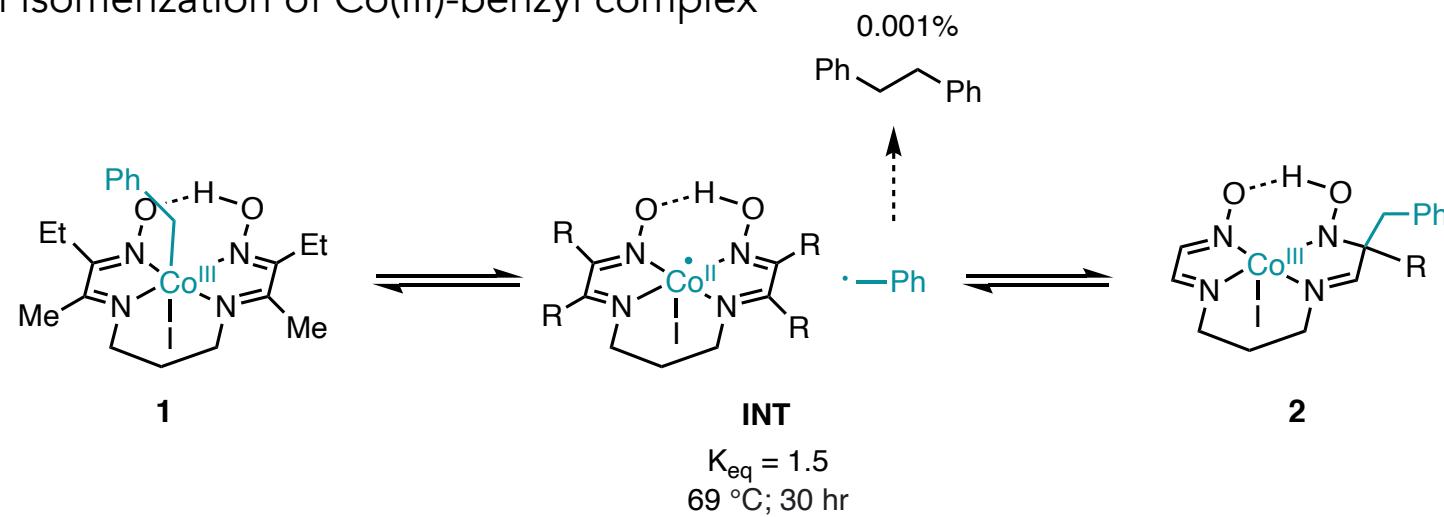
What exactly is PRE?



- Selective radical cross-coupling is preferred if one radical has significantly longer lifetime
- The radicals do not have to be truly “persistent” or “transient”; relative to each other
 - This only works best when two radicals are generated at same/similar rates

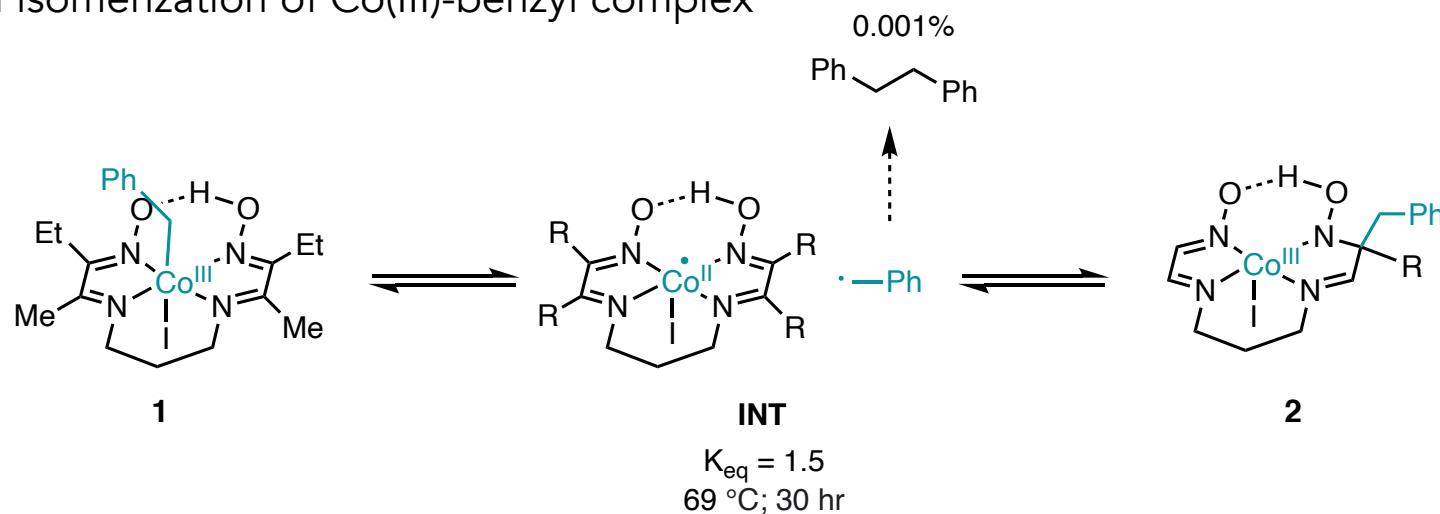
Interesting early examples: isomerization reactions

- Thermal isomerization of Co(III)-benzyl complex

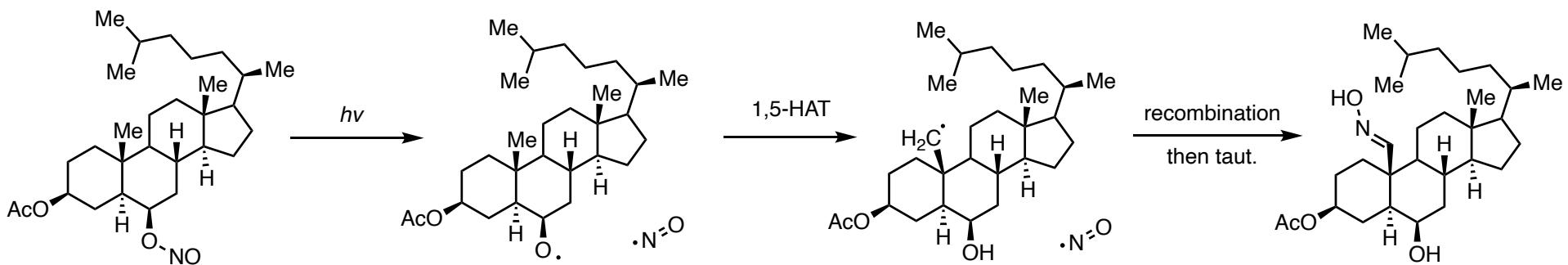


Interesting early examples: isomerization reactions

- Thermal isomerization of Co(III)-benzyl complex



- Barton reaction on a steroid molecule



Daikh, B. E.; Finke, R. G., *J. Am. Chem. Soc.* **1991**, *113*, 4160

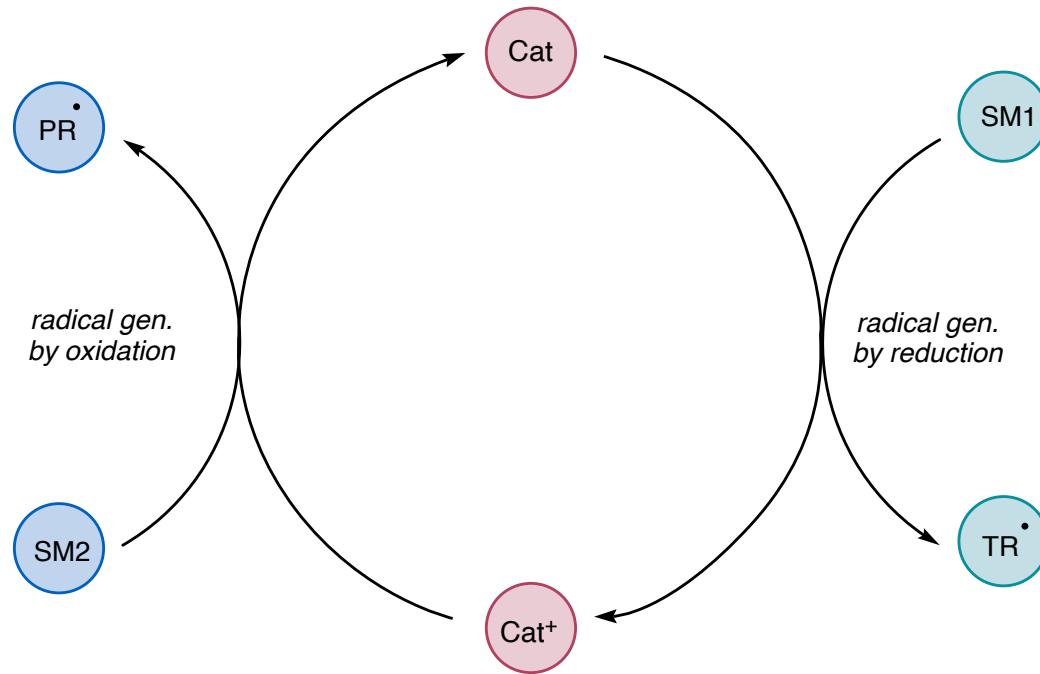
D. H. R. Barton, J. M. Beaton, L. E. Geller, M. M. Pechet, *J. Am. Chem. Soc.* **1960**, *82*, 2640

Why only intramolecular reactions?

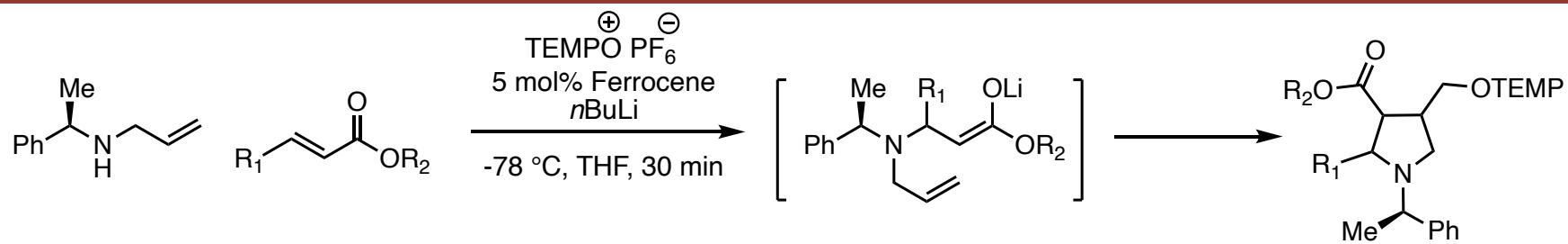
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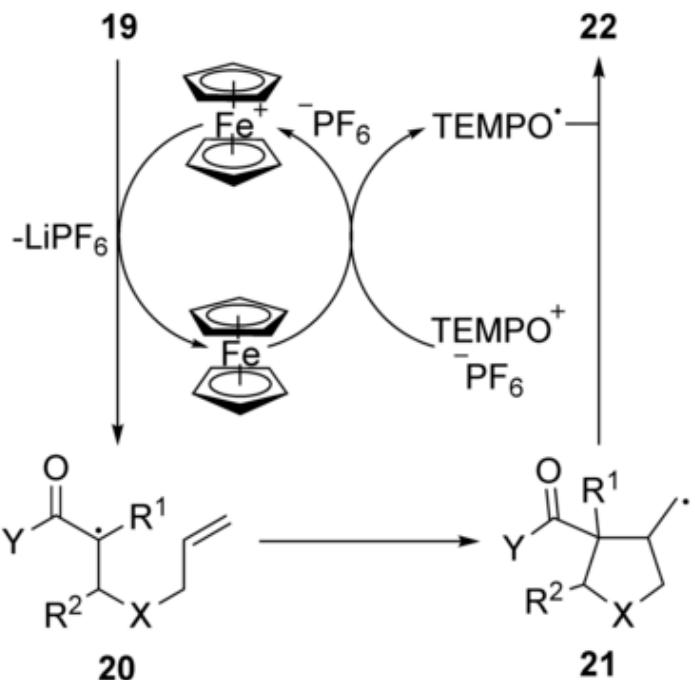
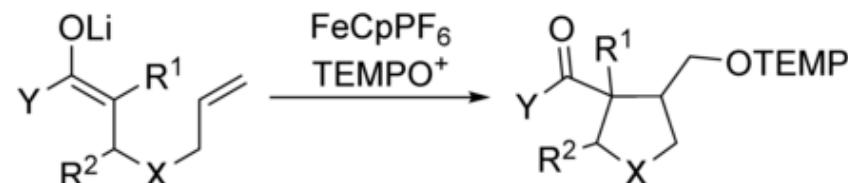
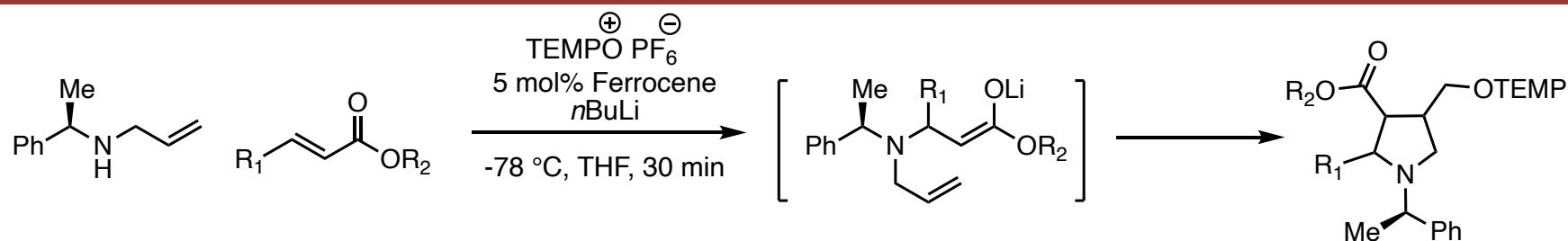
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Redox catalytic cycle for radical generation

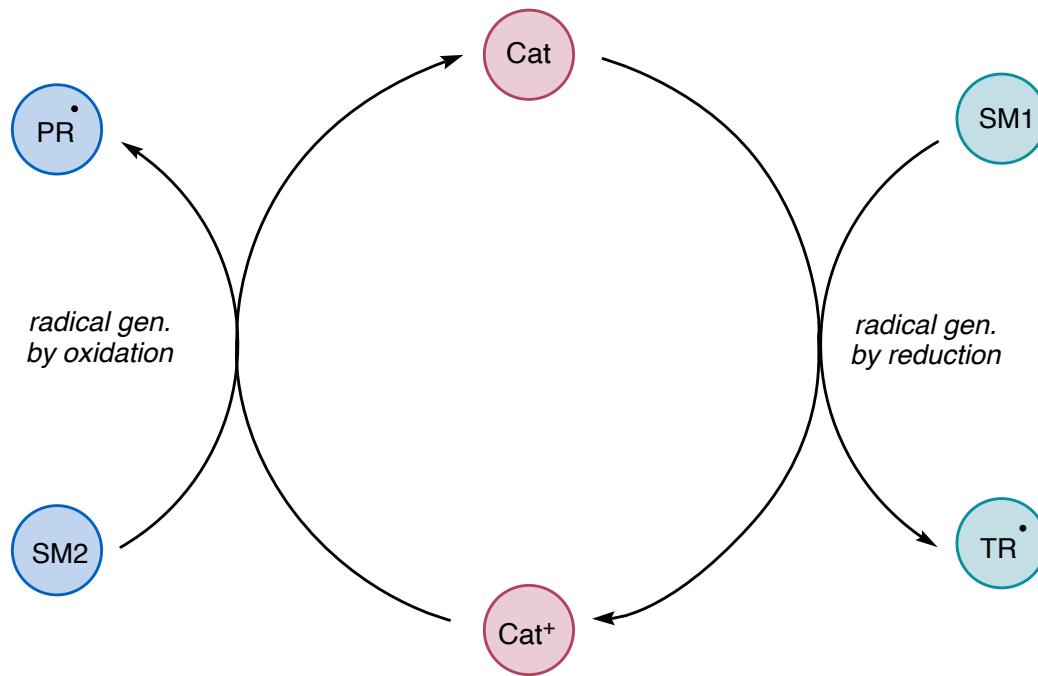


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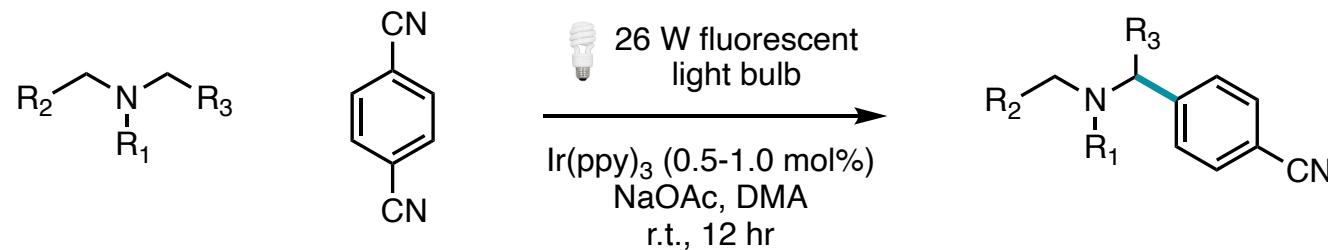
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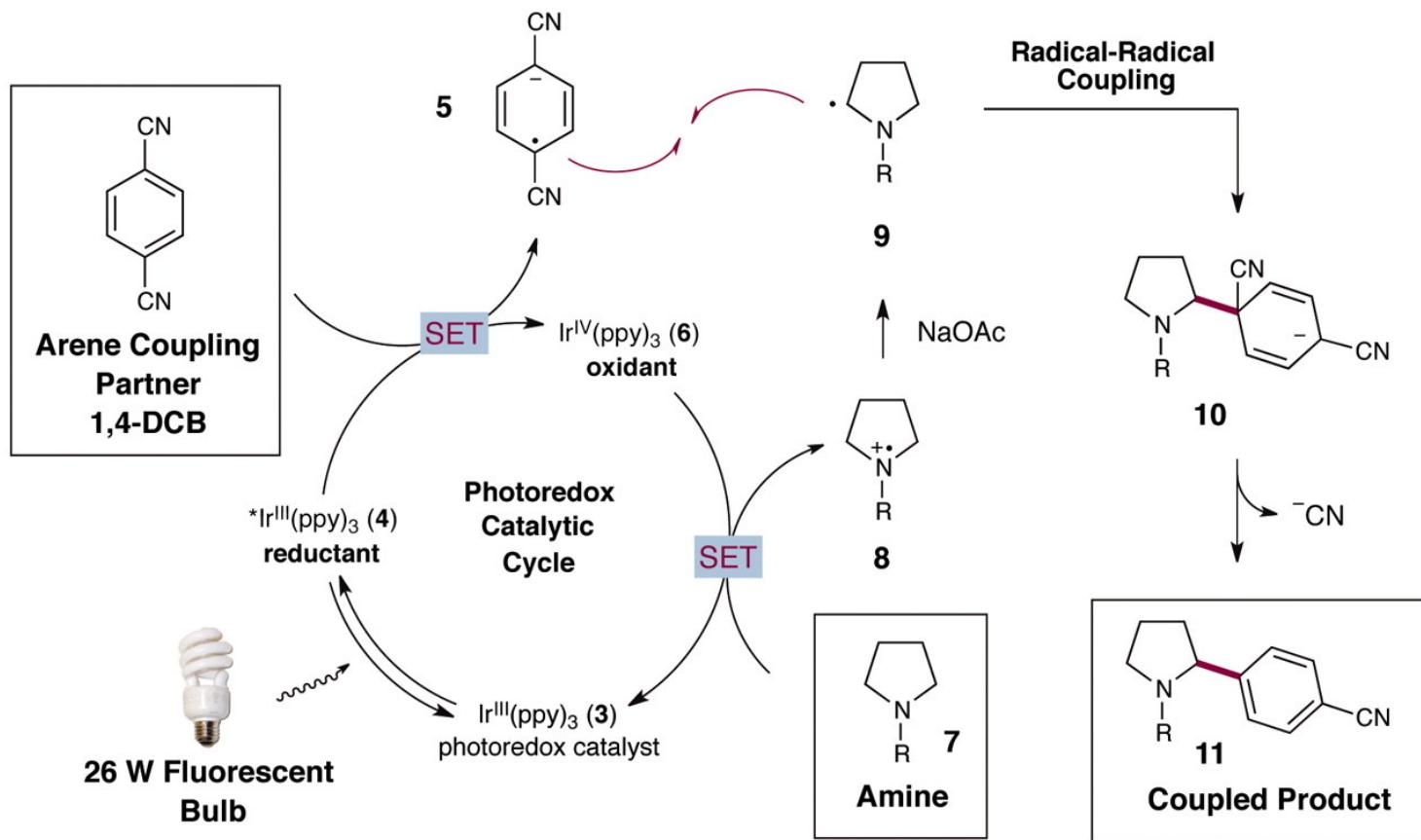
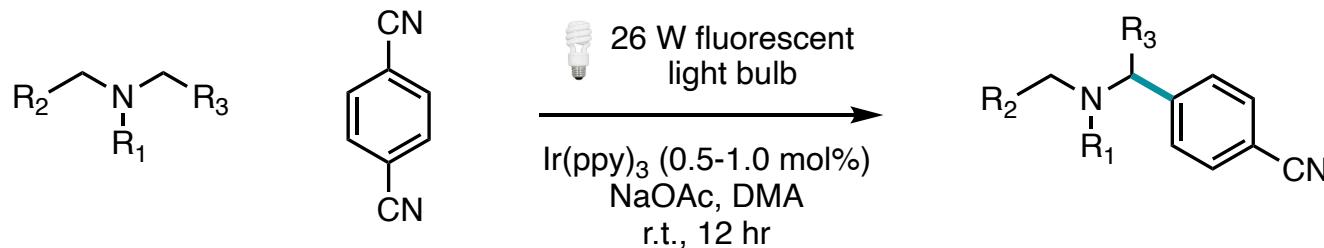


- What if this is incorporated in a photocatalytic cycle?

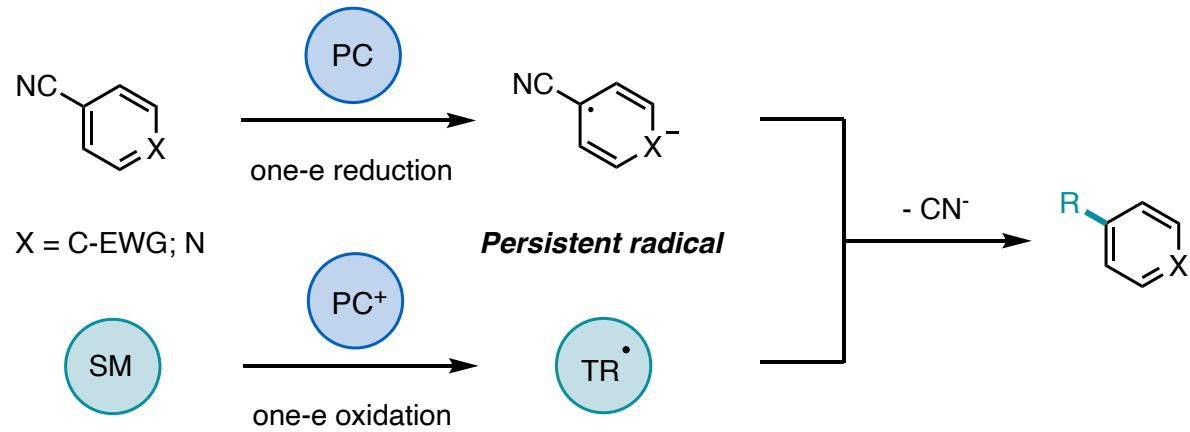
A “serendipitous” discovery



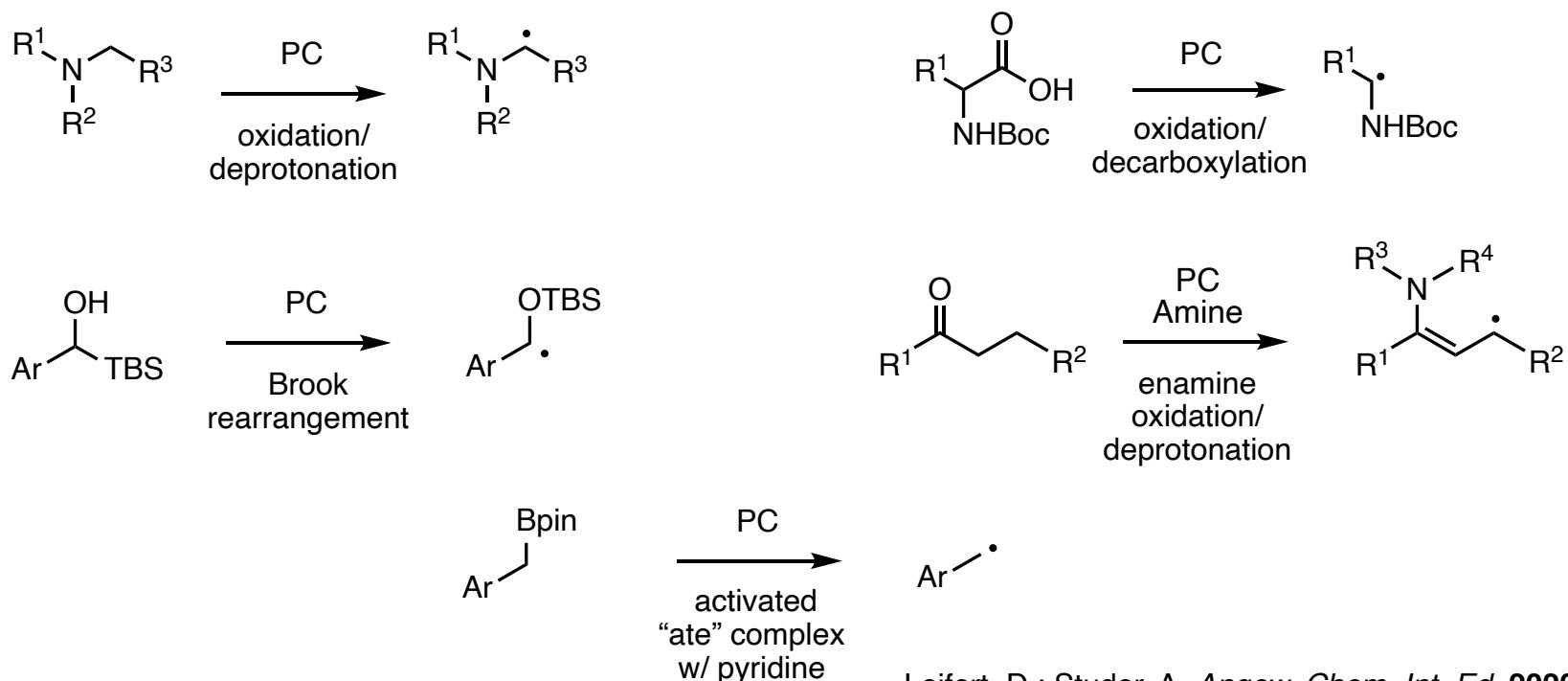
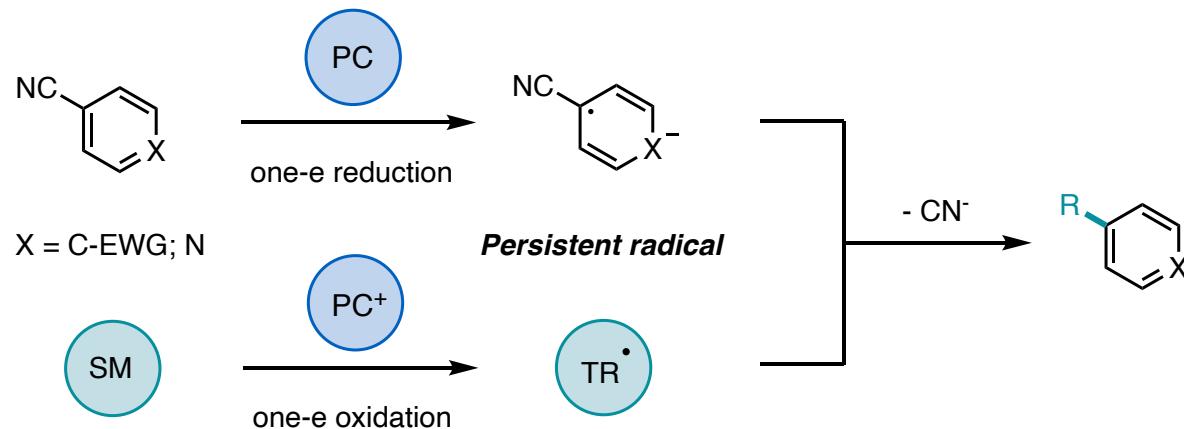
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Breaking down the process: cyanoarenes-derived persistent radicals



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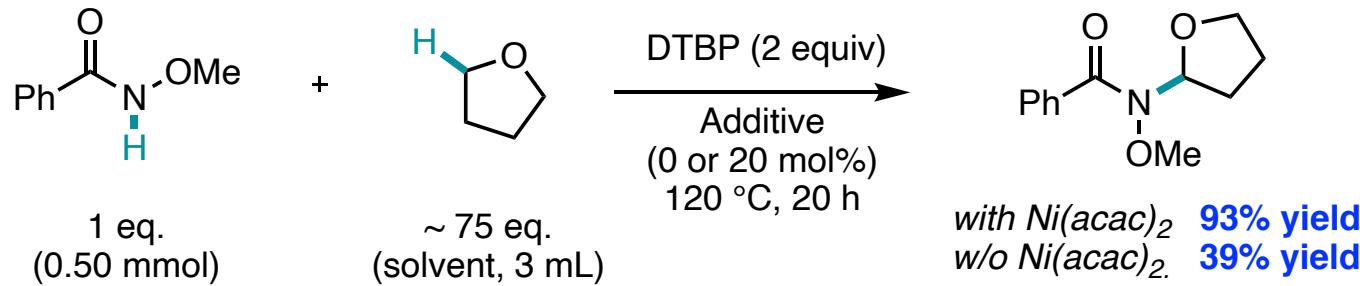


Moving along: what if we only have transient radicals?

- Metal catalysts are able to mediate the coupling process

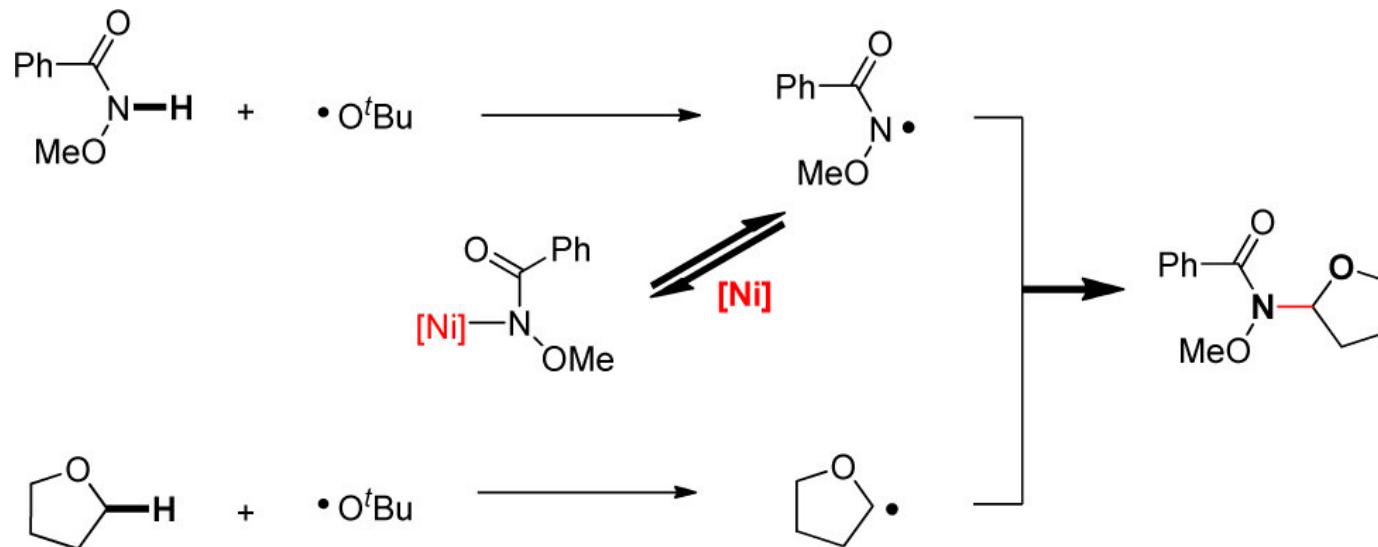
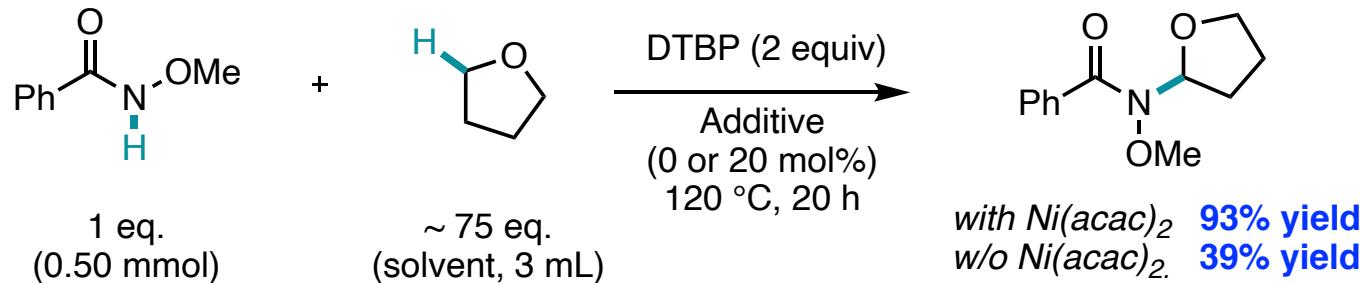
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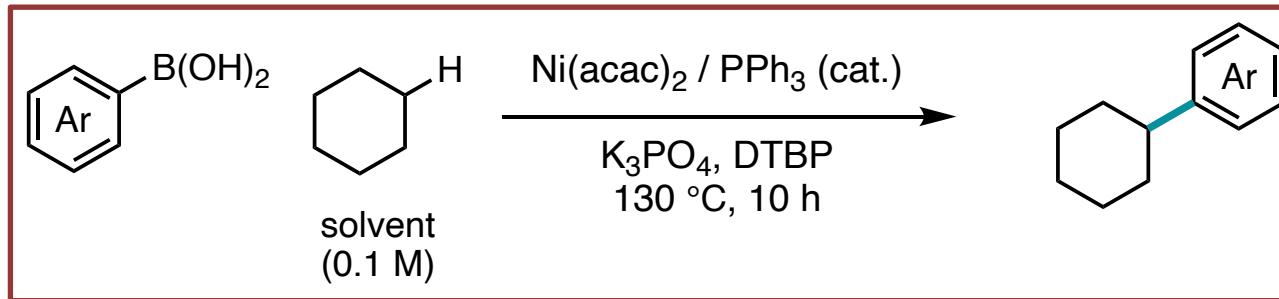
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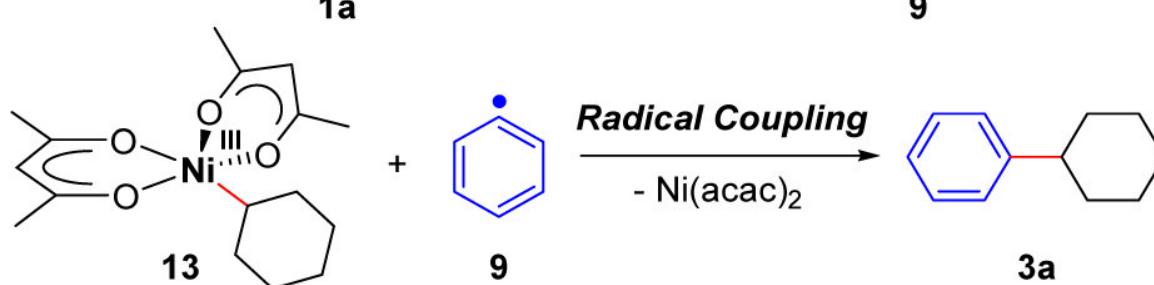
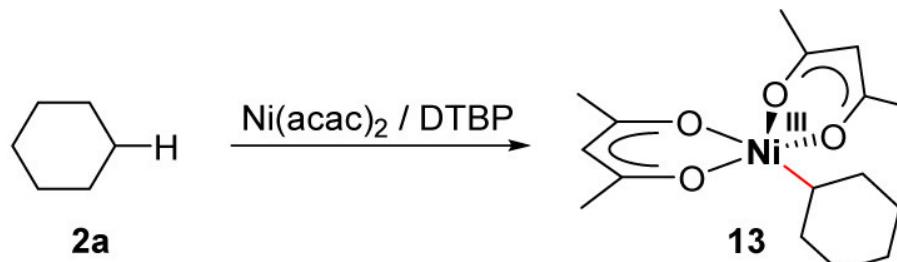
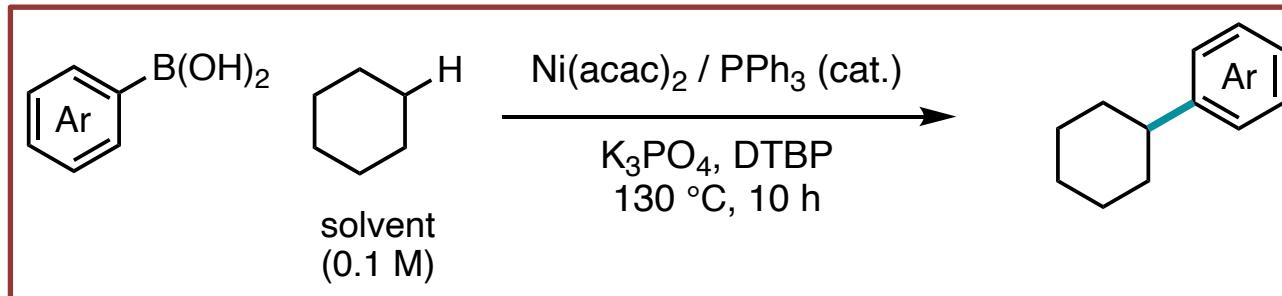
A similar reaction with carbon fragments

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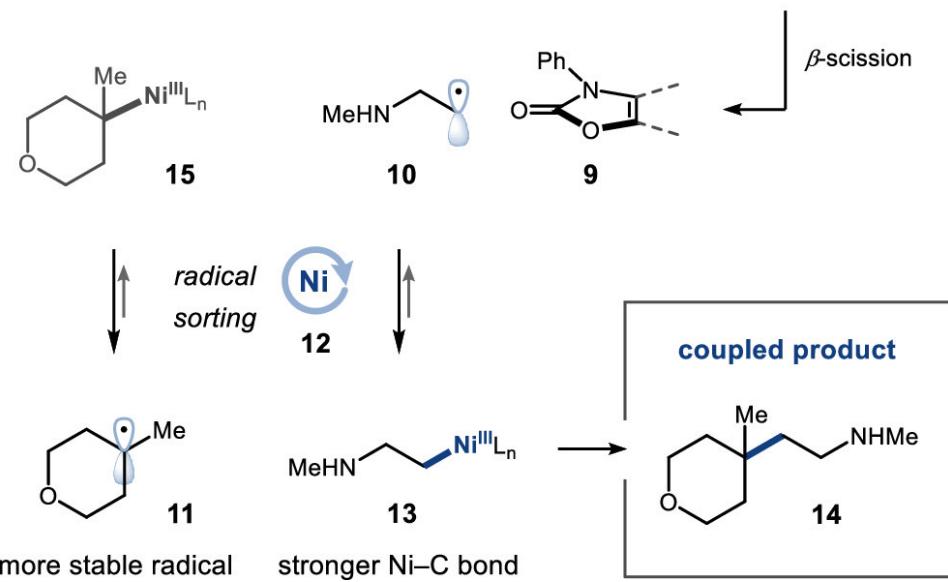
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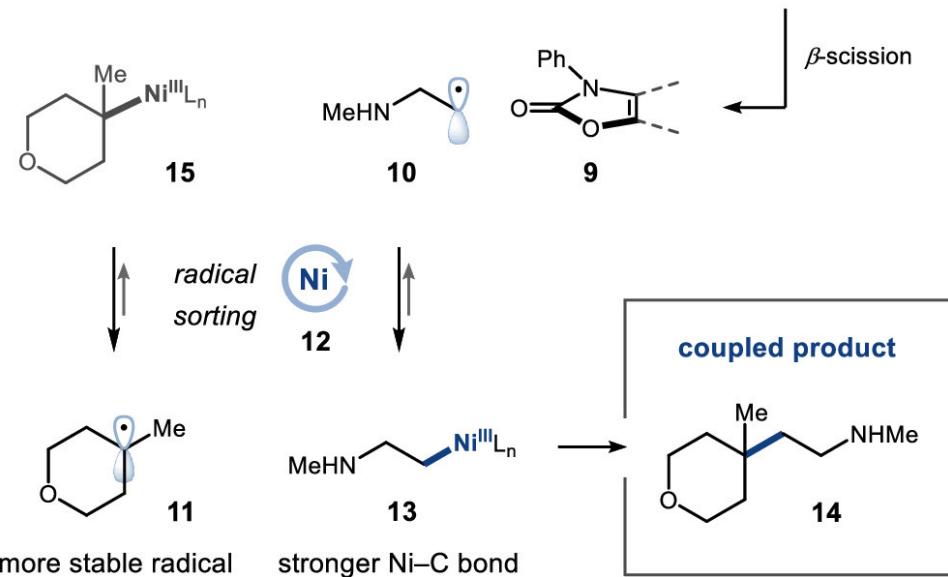
More discussions in the role of metal

Radical shuffling: Ni(II) catalyst and alkyl radicals

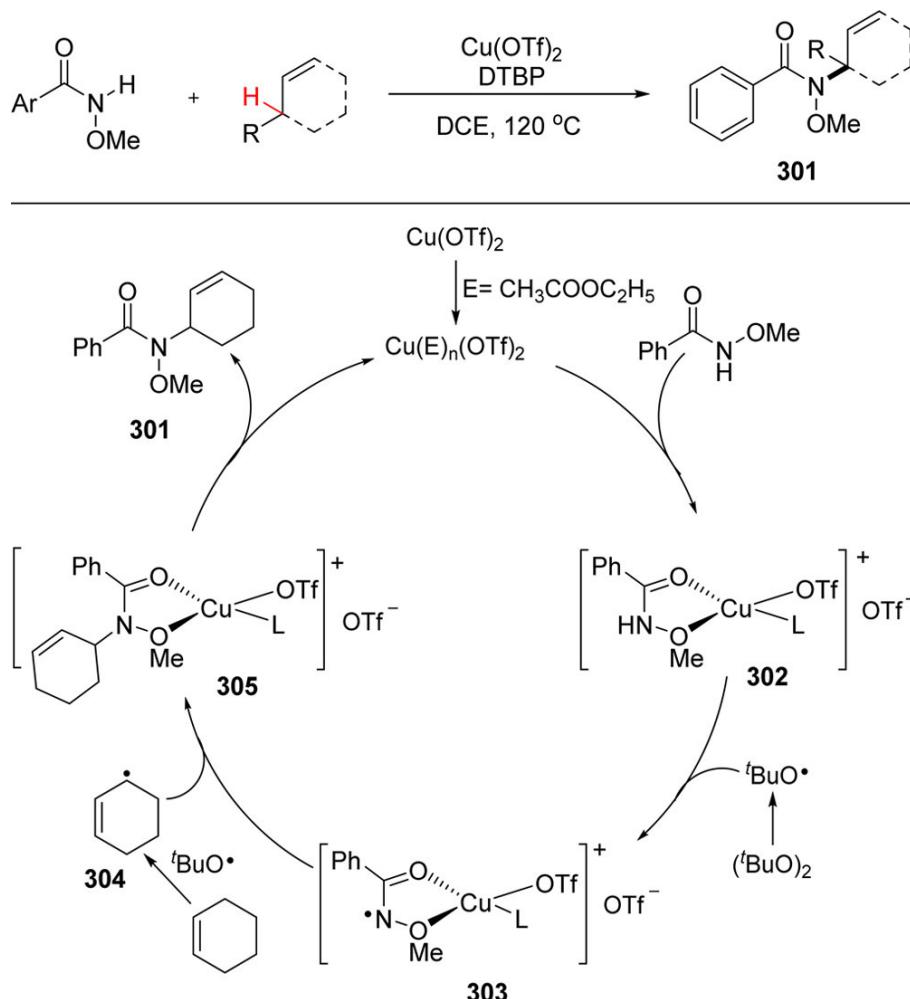


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Radical shuffling: Ni(II) catalyst and alkyl radicals



Different activation mode: 'ligand-centered radical'

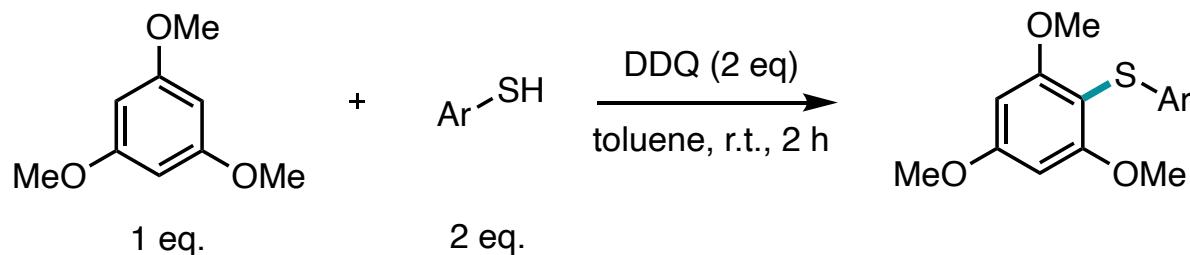


What about organocatalysts?

- Aid in generation of the radical species
- Also help in stabilization of one radical species relative to the other

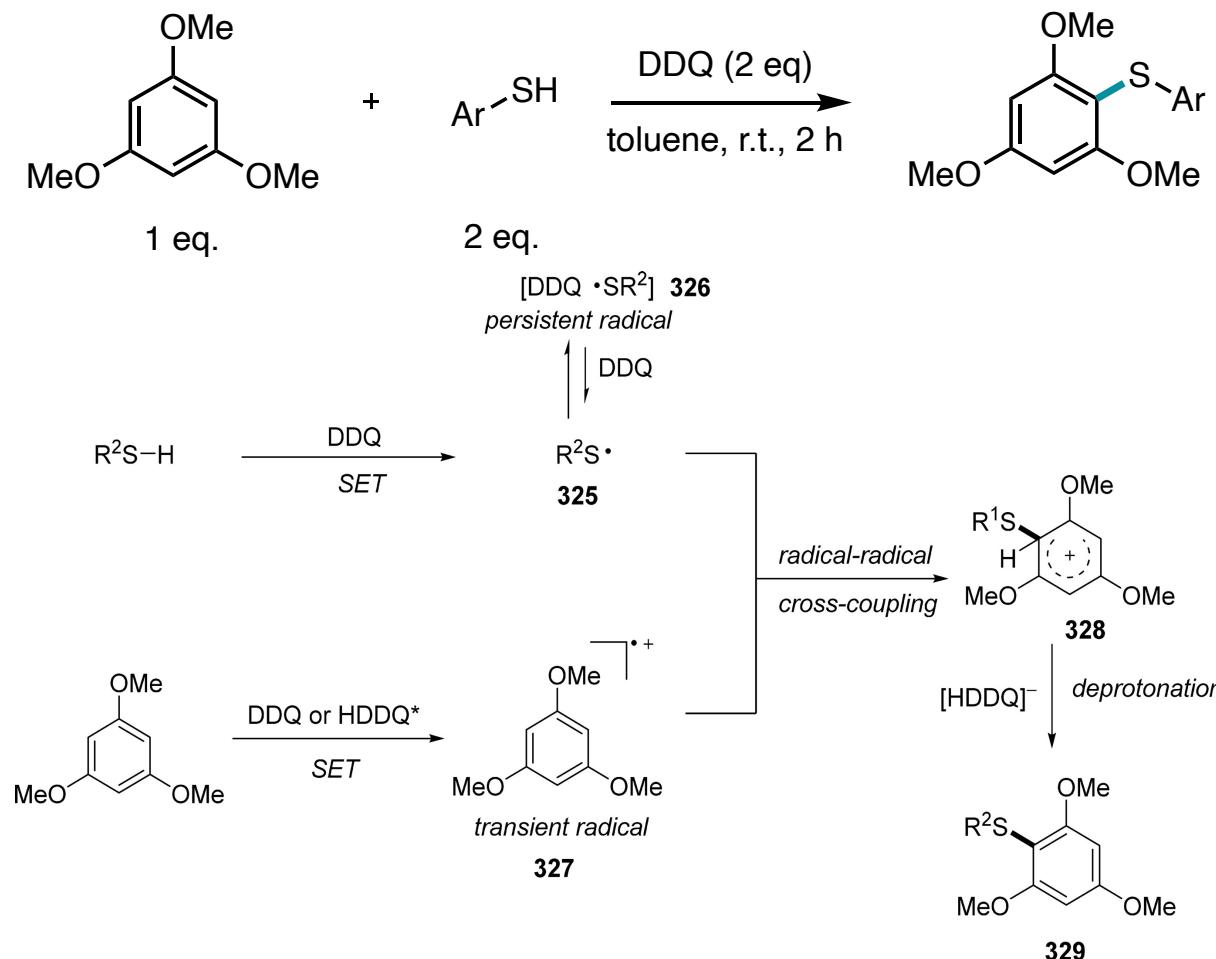
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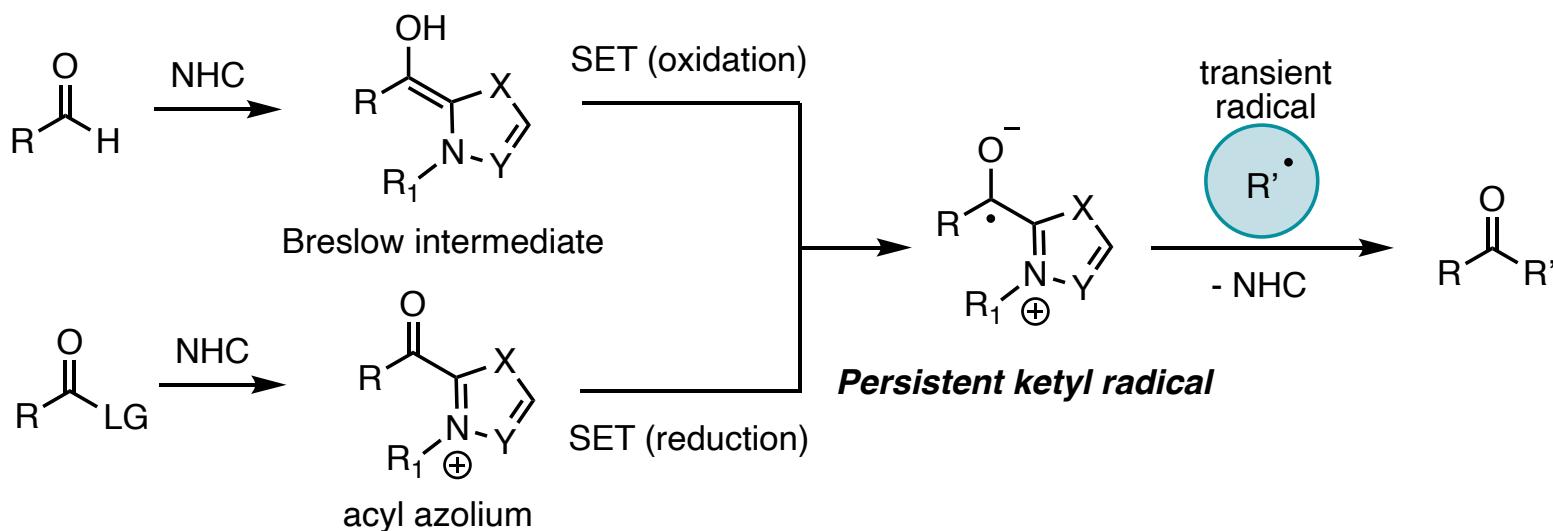
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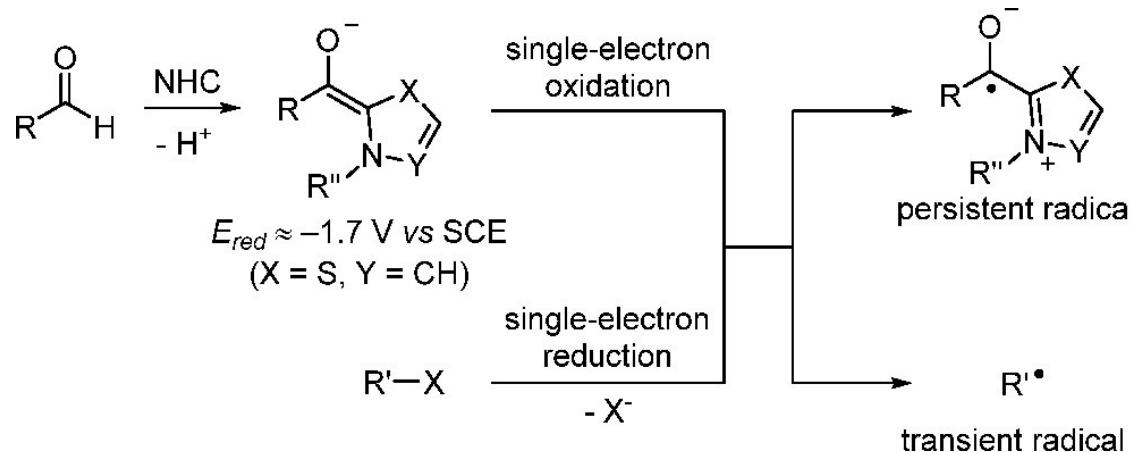
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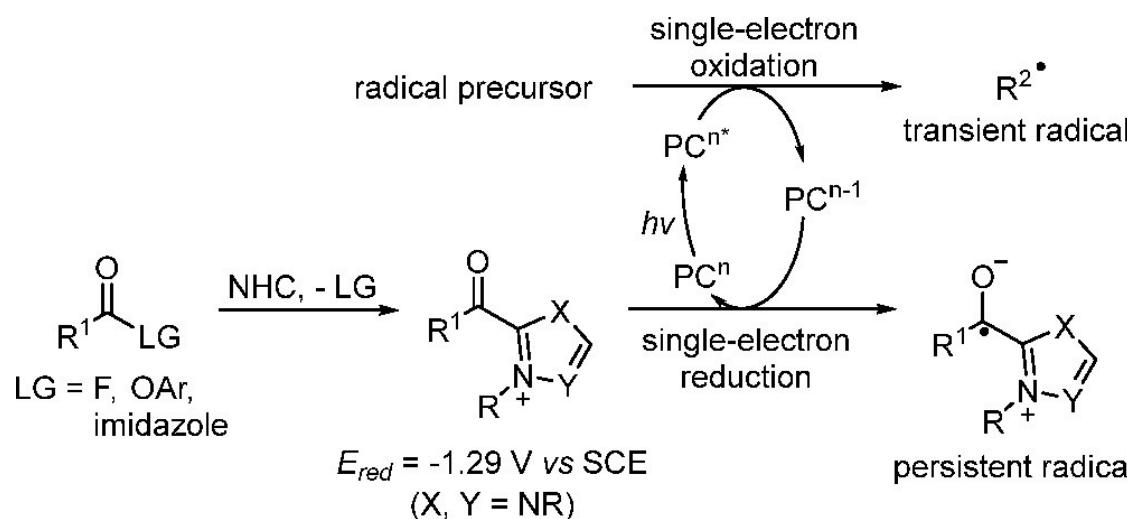
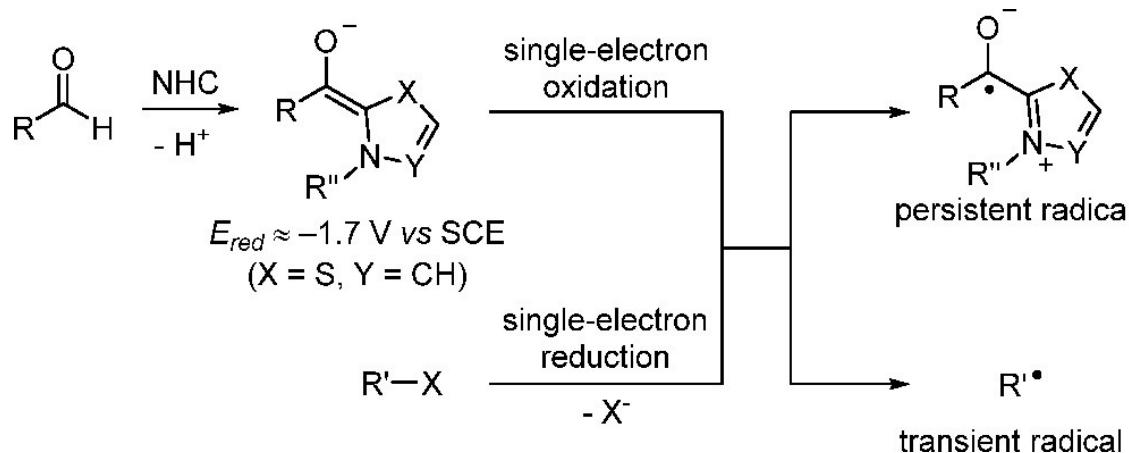
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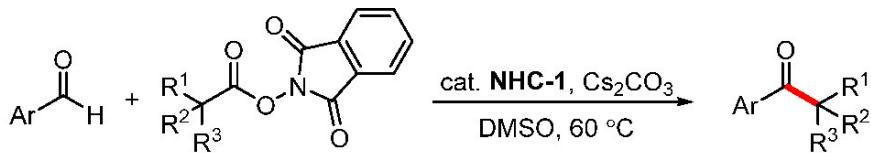
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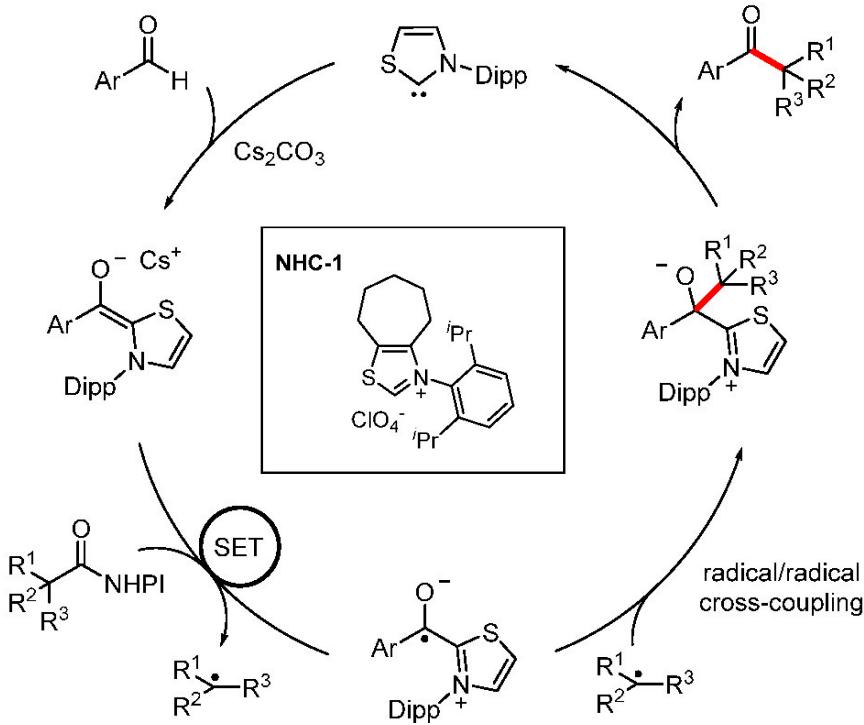


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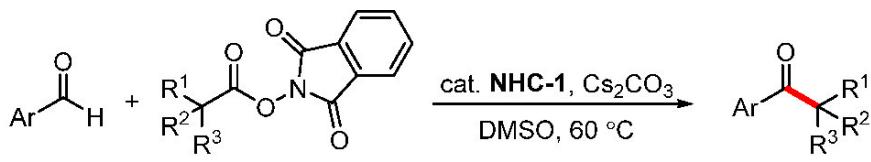


Proposed mechanism:

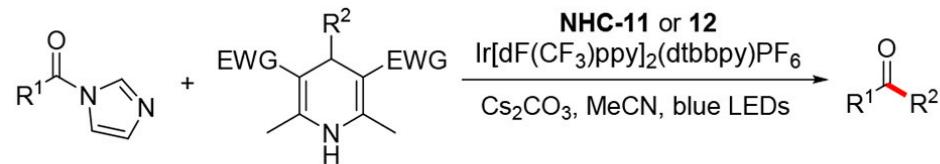
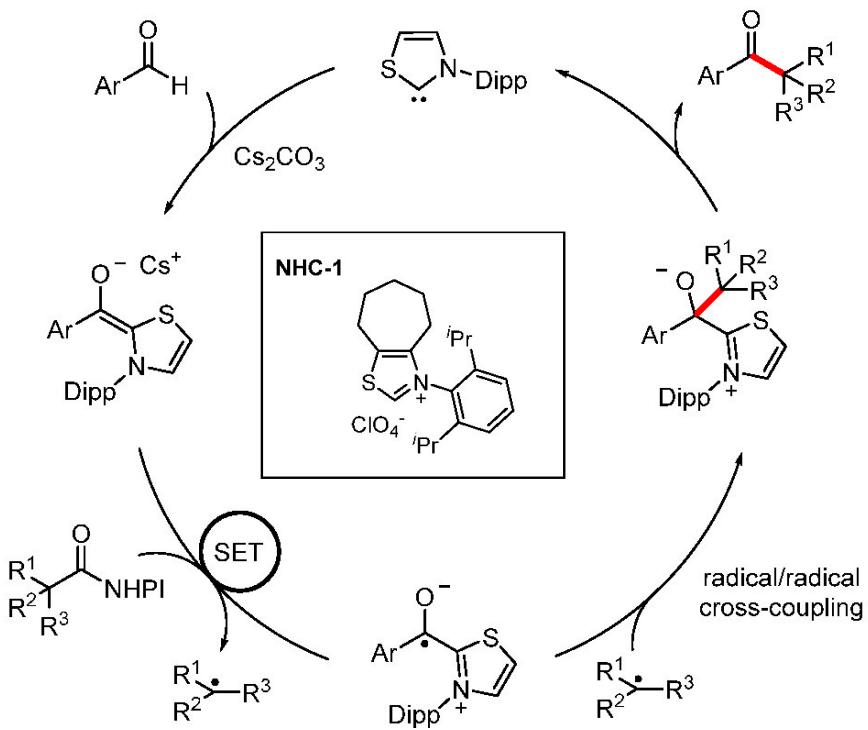


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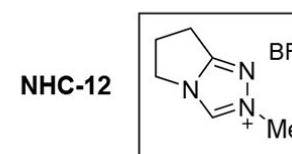
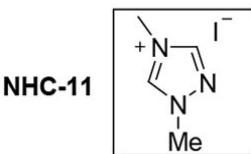
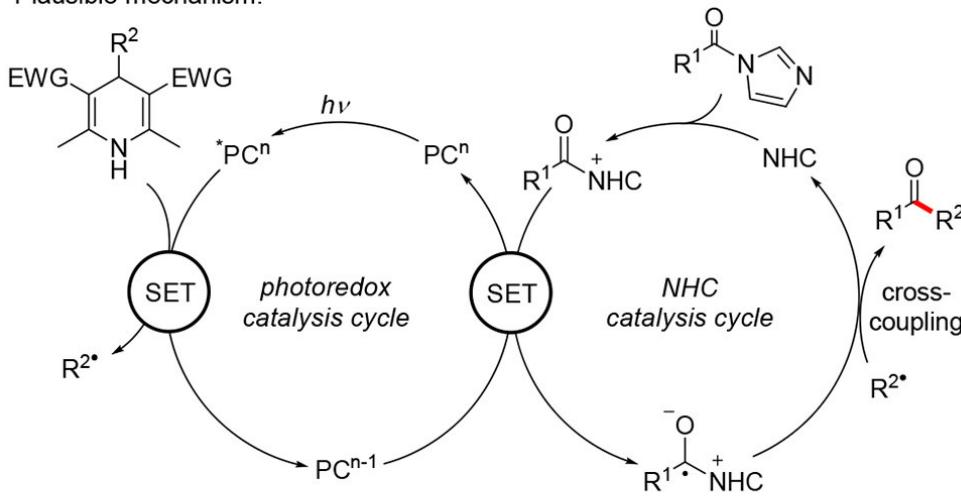
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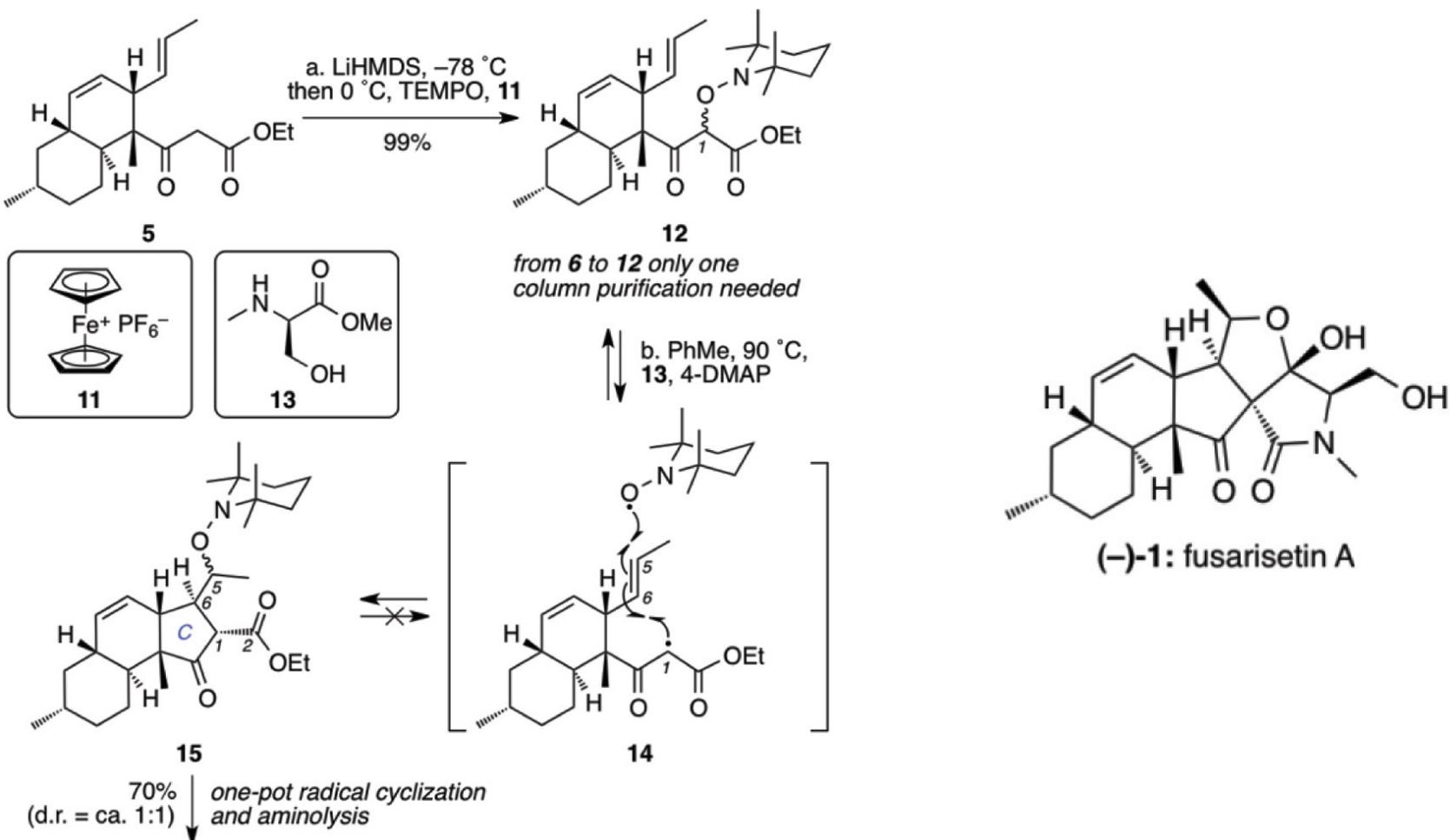
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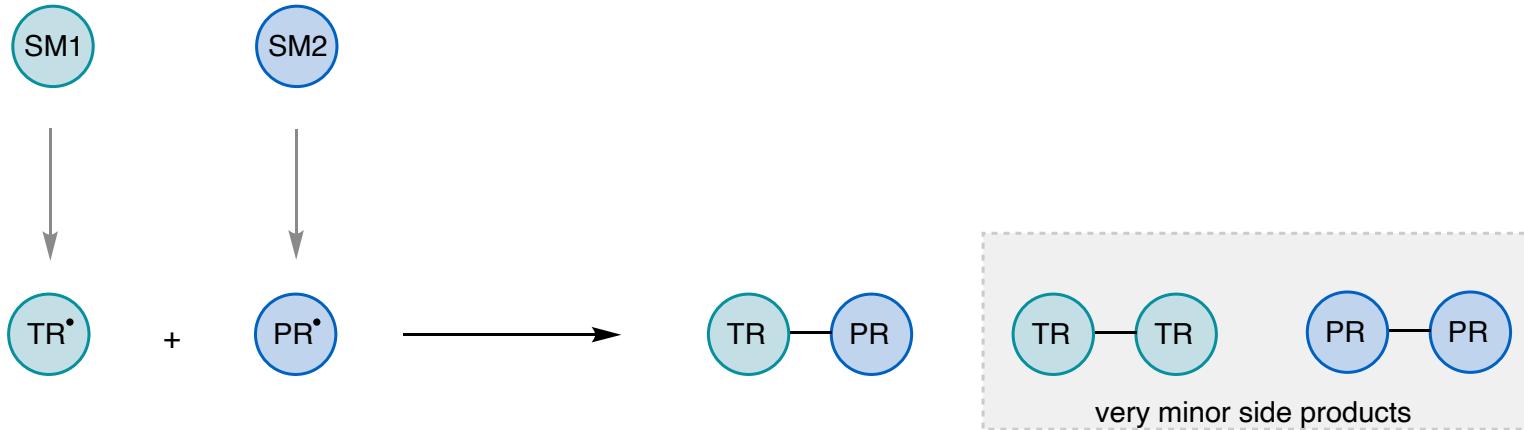
Plausible mechanism:



Last but not least: cool synthesis applications



Conclusion



- Selective radical cross-coupling is possible through tuning of multiple governing effects
 - Alternative pathways achieving existing reactivity
 - Expansion of the scope of molecular building blocks
 - Chemists still have a lot more to learn!