Catalytic Cascade Reactions by Radical Relay

CH-707 Frontiers in Organic Chemistry I

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H.-M. Huang, M. H. Garduño-Castro, C. Morrill, D. J. Procter,
Chem. Soc. Rev. **2019**, *48*, 4626–4638

Outline

1. Introduction
   - (Radical) Cascade Reactions
   - Radical Relay

2. Examples
   - Intramolecular Radical Relays
   - Radical Relays involving Hydrogen Atom Transfer (HAT)
   - Intermolecular Radical Relays

3. Summary – Strategies for radical formation, relocation and rebound

4. Outlook

Introduction – Cascade Reactions

Cascade/Domino Reactions: a process involving two or more consecutive reactions in which subsequent reactions result as a consequence of the functionality formed by bond formation or fragmentation in the previous step

→ each reaction composing the sequence occurs spontaneously

→ no isolation of intermediates

→ same reaction conditions throughout the consecutive cascade steps

→ no addition of reagents after the initial step

vs

One-pot Reactions: a process in which another reagent, mediator or catalyst is added after the first transformation without isolation of the first formed product

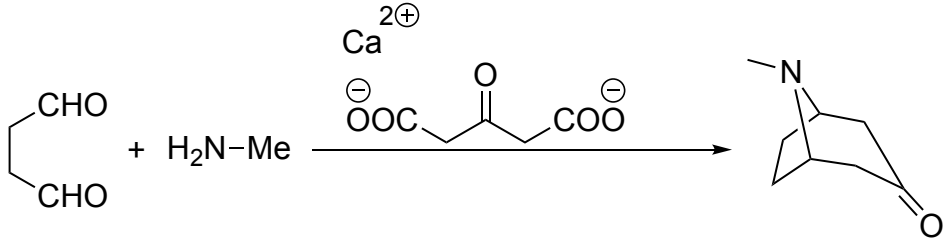
→ **any cascade reaction = one-pot reaction**

→ **any one-pot reaction ≠ cascade reaction**

L. F. Tietze, U. Beifuss, *Angew. Chem. Int. Ed.* **1993**, *32*, 131–163

Introduction – Cascade Reactions

First example: Synthesis of Tropinone (Robinson, 1917)



R. Robinson, *J. Chem. Soc.* **1917**, 762–768

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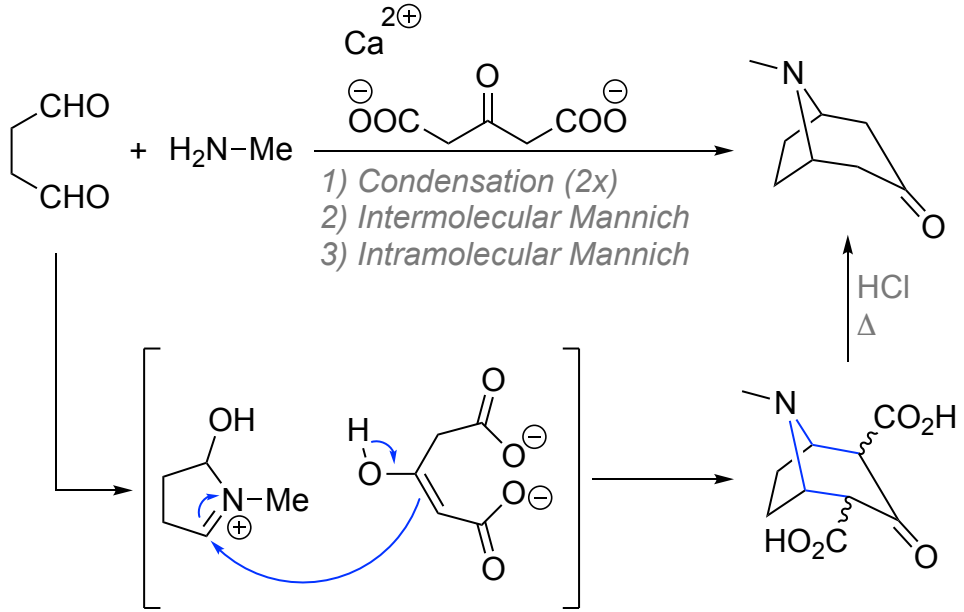

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Introduction – Cascade Reactions

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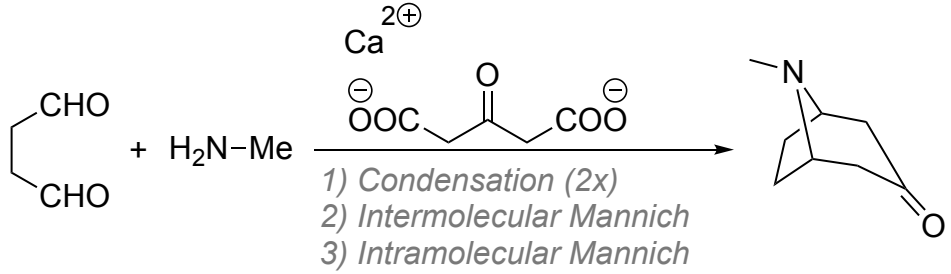
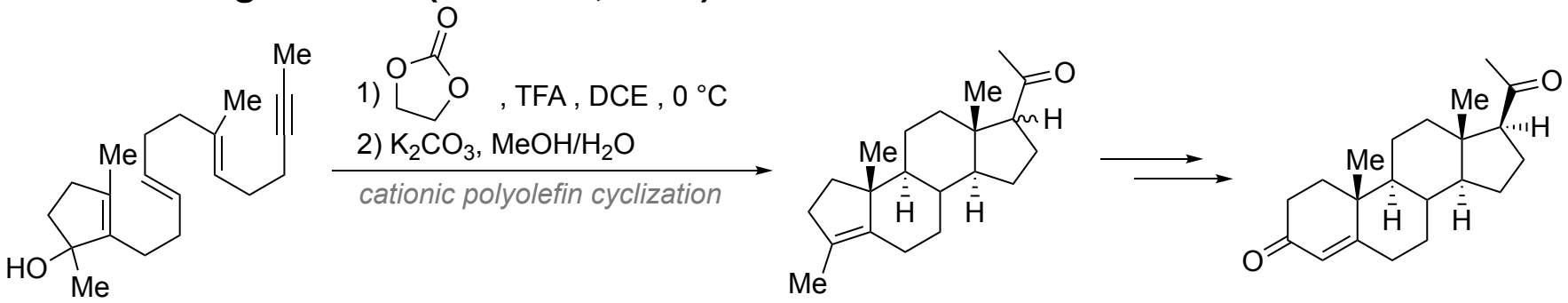


Synthesis of Progesterone (Johnson, 1971)



W. S. Johnson, M. B. Gravestock, B. E. McCarry, *J. Am. Chem. Soc.* **1971**, *93*, 4332–4334

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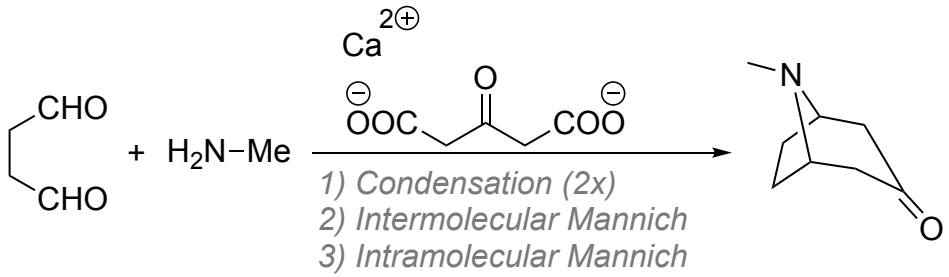

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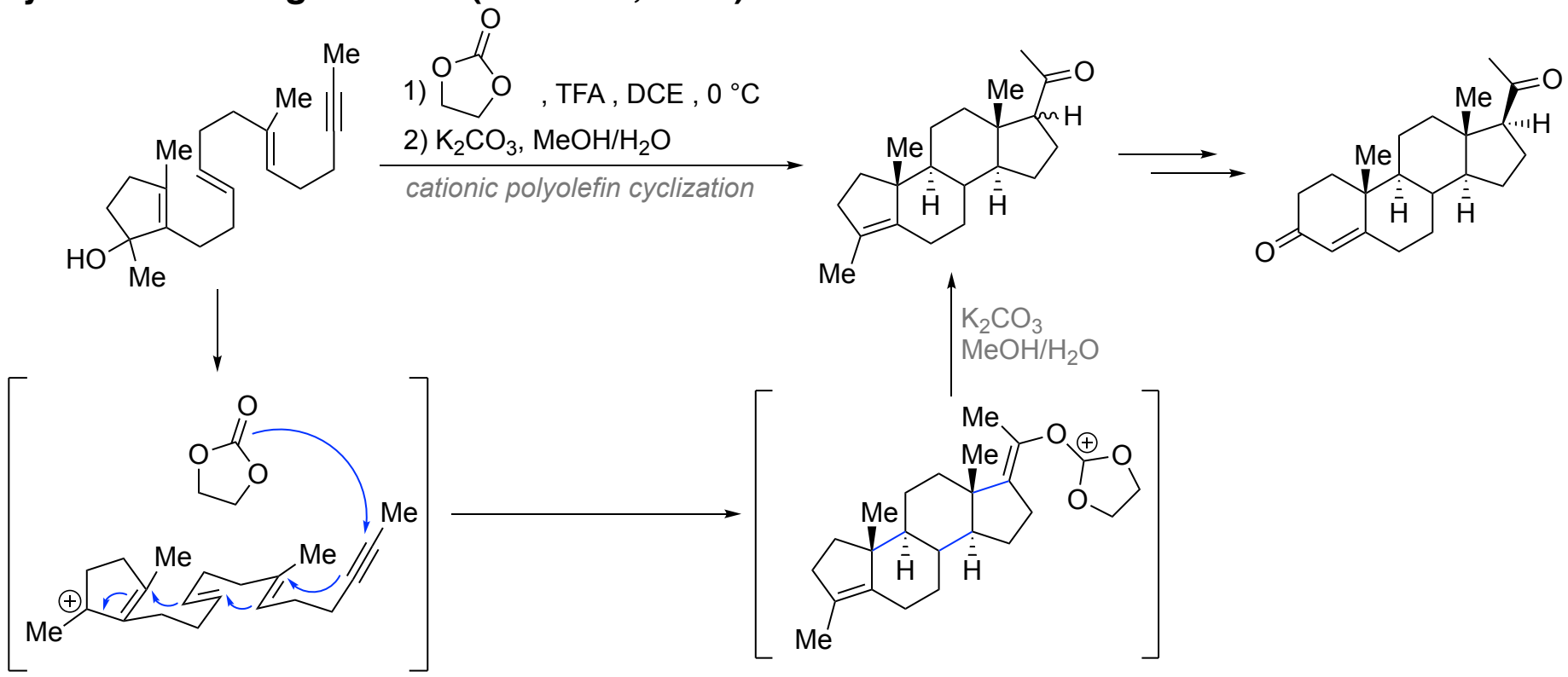

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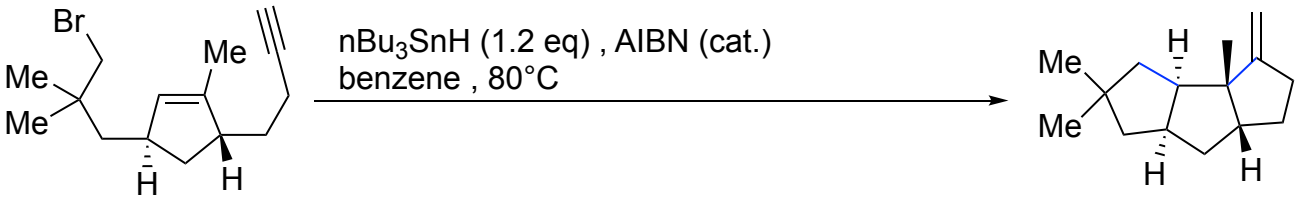
Introduction – Radical Cascade Reactions

Total synthesis of (+/–)-Hirsutene (Curran, 1985) – Key step constitutes a radical



D. P. Curran, M.-H. Chen, *Tetrahedron Lett.* **1985**, *26,* 4991–4994

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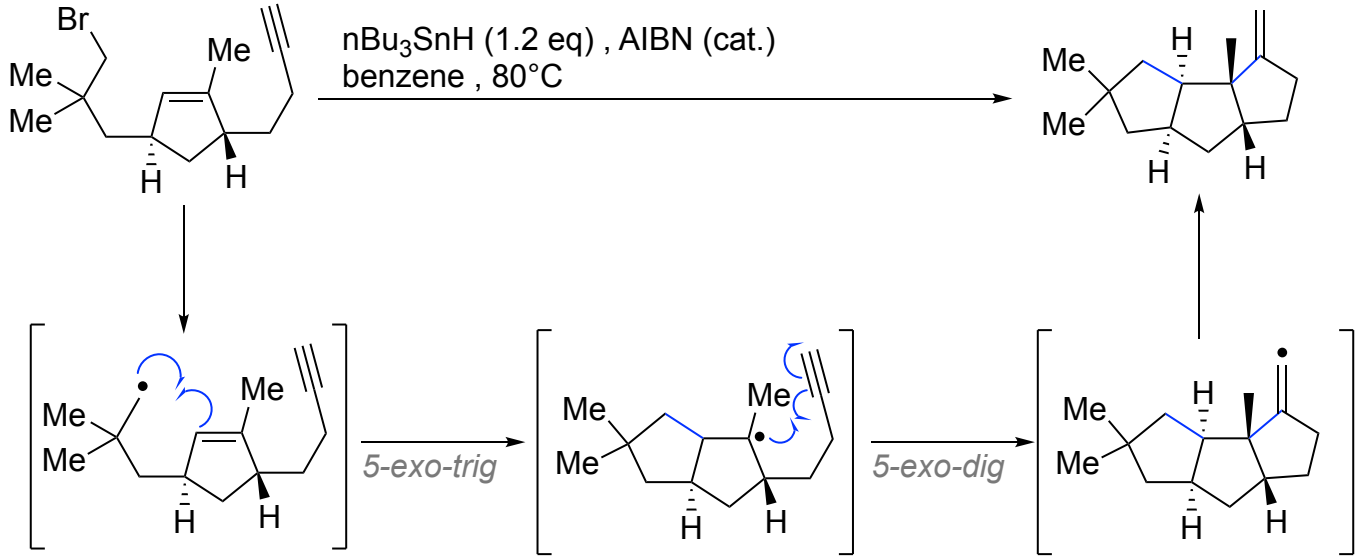
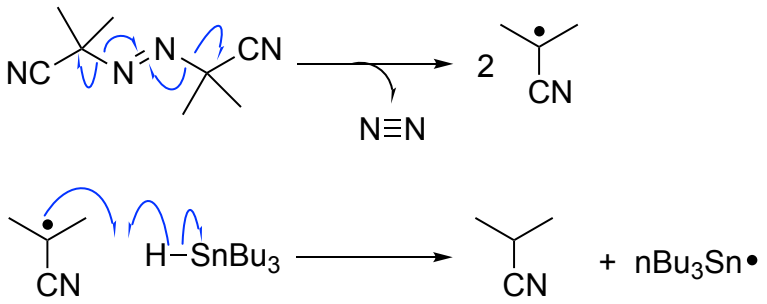


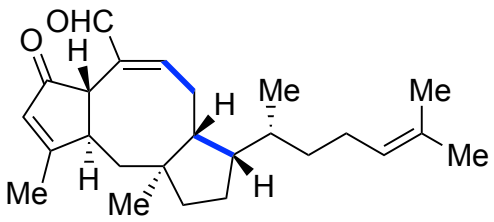
Initiation:



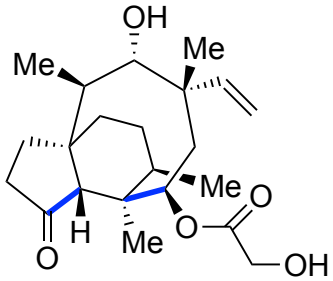
D. P. Curran, M.-H. Chen, *Tetrahedron Lett.* **1985**, *26,* 4991–4994

Introduction – Radical Cascade Reactions

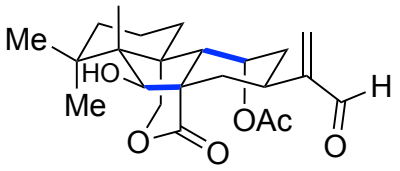
Achieving rapid complexity in total syntheses of natural products and complex materials:



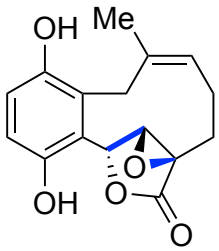
(–)-6-epi-ophiobolin N



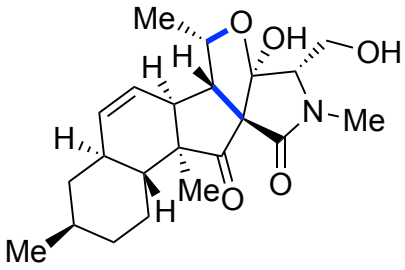
(+)-pleuromutilin



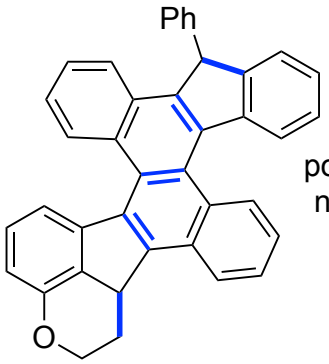
(–)-maoecrystal Z



(+/–)-clavilactone



(+)-fusarisetin



polyaromatic nanoribbon

⛔ stoichiometric amounts of reagents and/or additives required to mediate these strategies

M. Yan, J. C. Lo, J. T. Edwards, P. S. Baran, *J. Am. Chem. Soc.* **2016**, *138,* 12692–12714

Introduction – Radical Relay

Definition: redox-neutral process in which radical character is re-generated and thus

(by Procter) only a catalytic amount of radical-generating reagent is required

3 key stages:

1) Radical Formation: Radical character is generated by SET or addition of radical

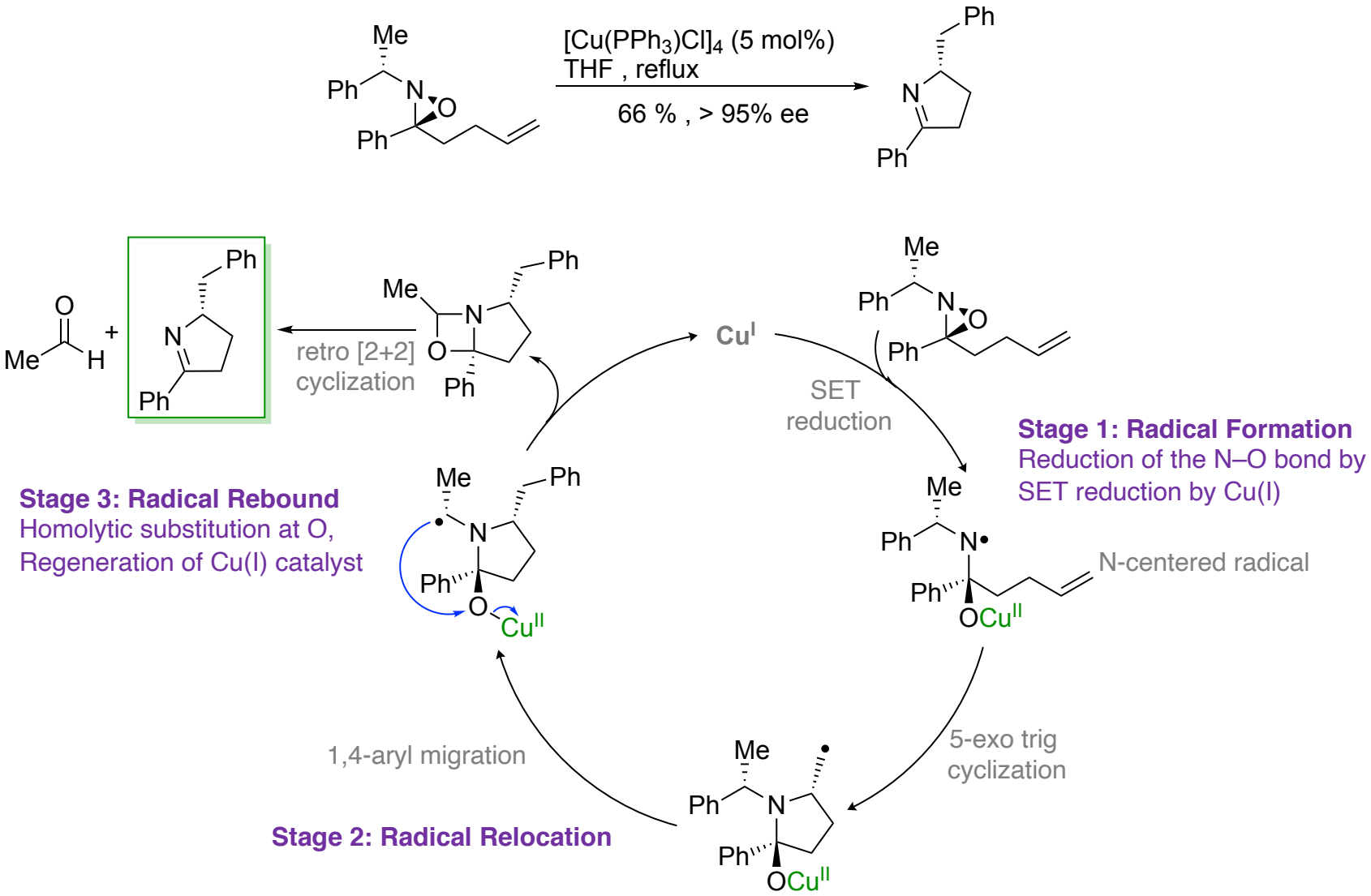
2) Radical Relocation: Radical character is propagated during a bond-forming / breaking sequence

3) Radical Rebound: Radical character is recycled, typically by SET back to metal catalyst or expulsion of a radical that acts as a catalyst

H.-M. Huang, M. H. Garduño-Castro, C. Morrill, D. J. Procter, *Chem. Soc. Rev.* **2019**, *48*, 4626–4638

Examples – Intramolecular Radical Relays

Cu(I)-catalyzed cascade synthesis of pyrrolines (Aubé 1992)



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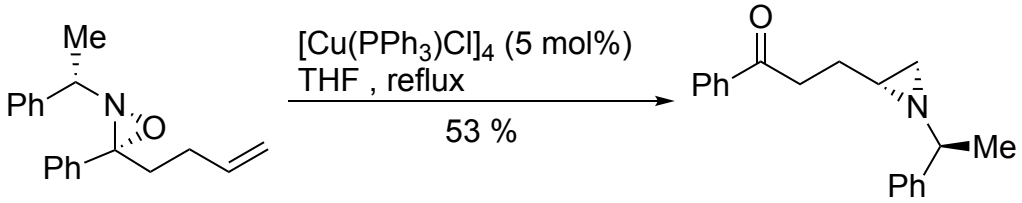

QUESTION: Why does the diastereoisomeric oxaziridine lead to an azirine instead of the pyrroline?

J. Aubé, X. Ping, Y. Wang, F. Takusagawa, *J. Am. Chem. Soc.* **1992**,*114,* 5466–5467

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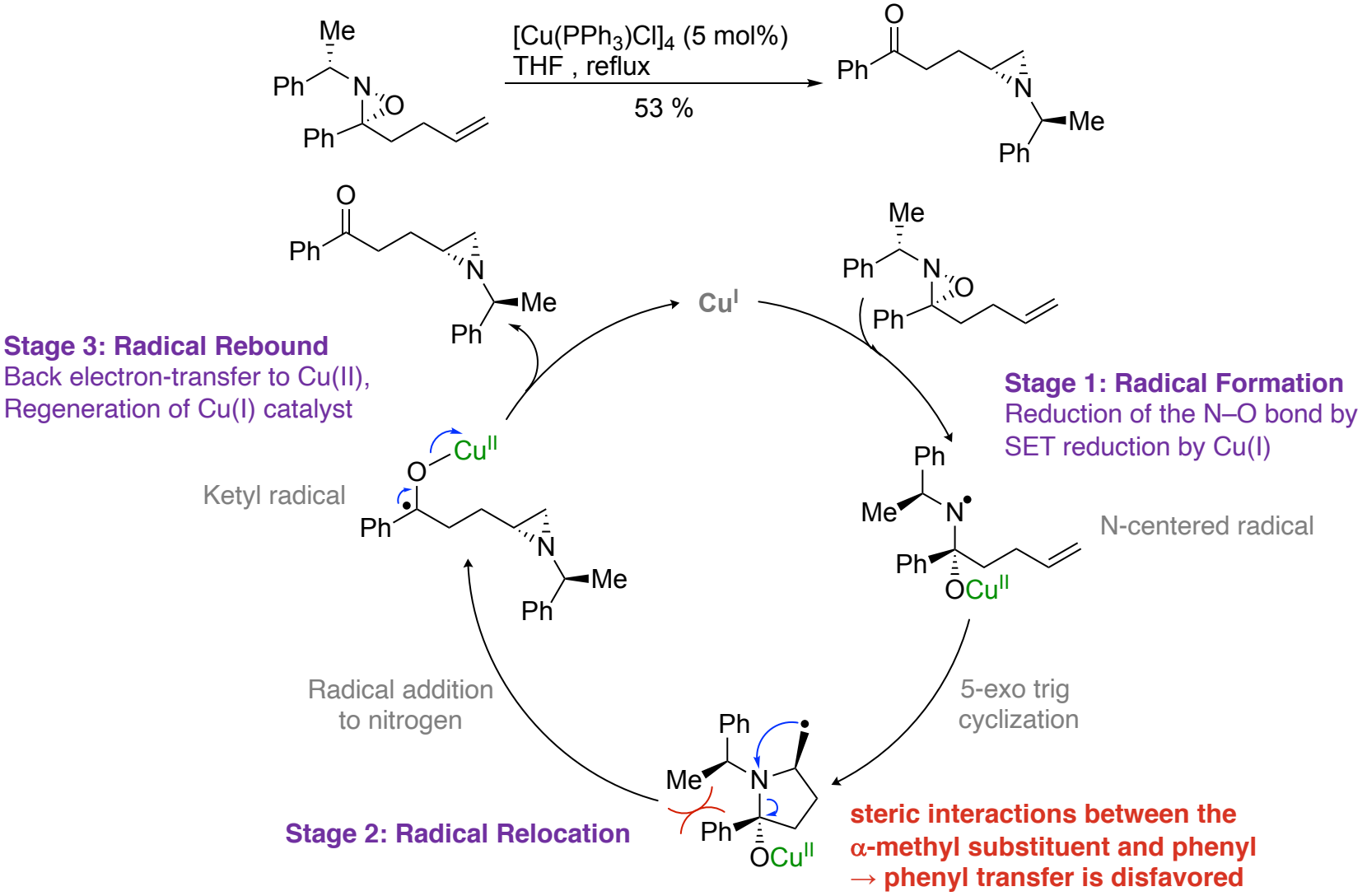

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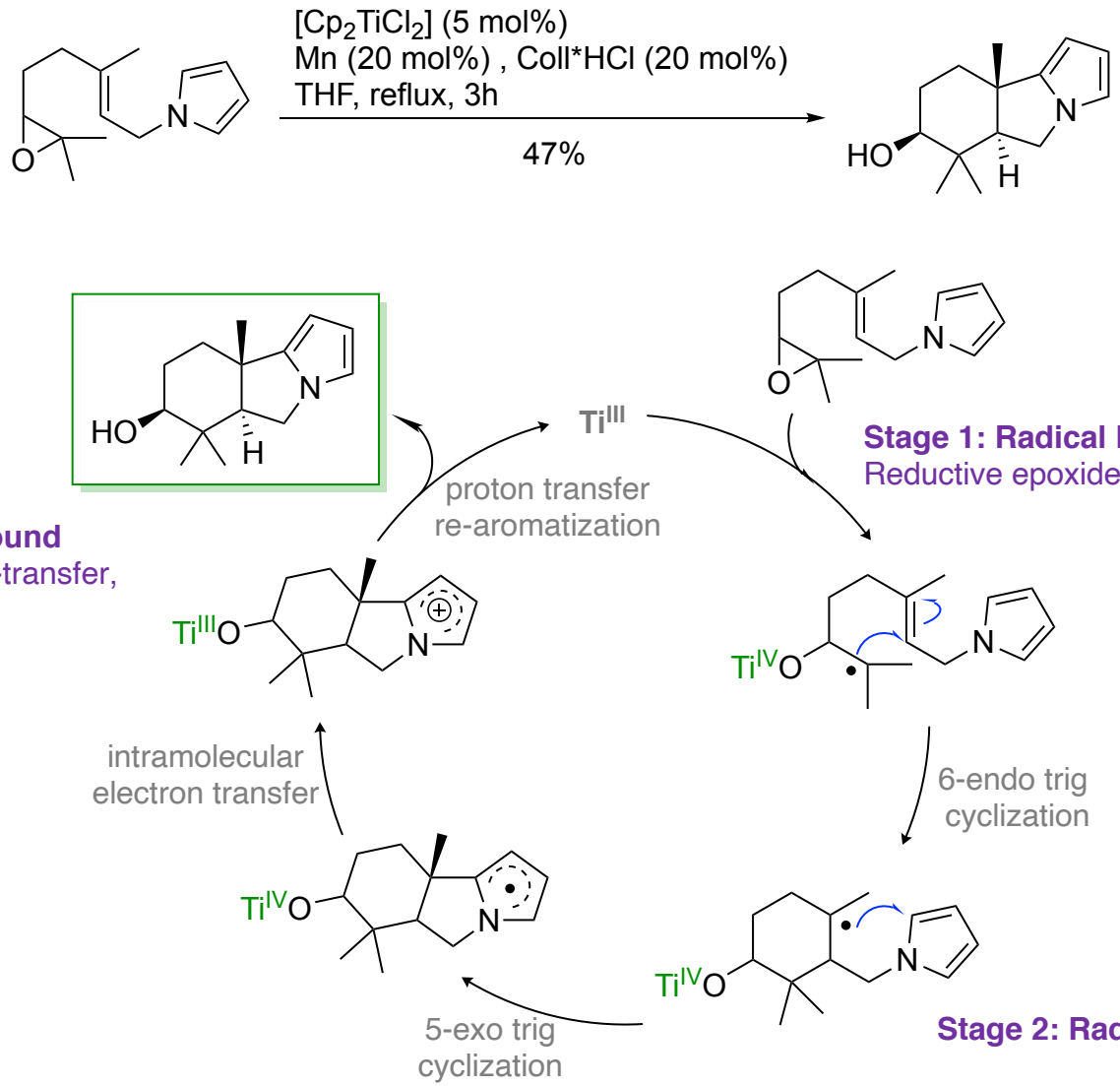
Examples – Intramolecular Radical Relays

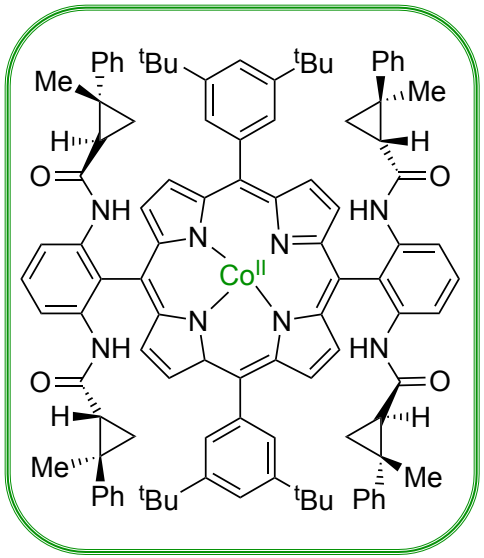
Ti(III)-catalyzed cascade synthesis of dihydropyrrolizine scaffolds (Gansäuer 2016)

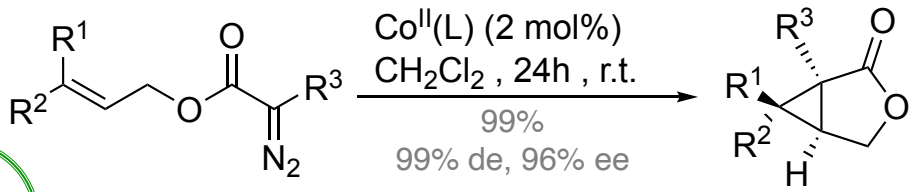


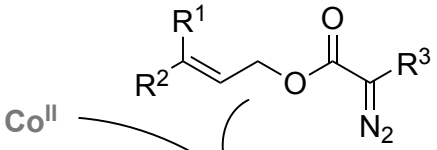
S. Hildebrandt, A. Gansäuer, *Angew. Chem. Int. Ed.* **2016**, *55,* 9719–9722

Examples – Intramolecular Radical Relays

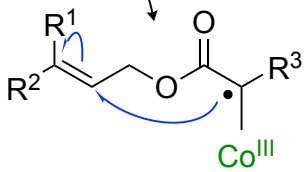
Co(II)-catalyzed enantioselective cascade synthesis of cyclopropanes (Zhang 2011)







Stage 1: Radical Formation
Decomposition of diazoacetate,
Capture of carbene by Co(II)



Alkyl radical

X. Xu, H. Lu *et al.*, *J. Am. Chem. Soc.* **2011**,*133,* 15292–15295

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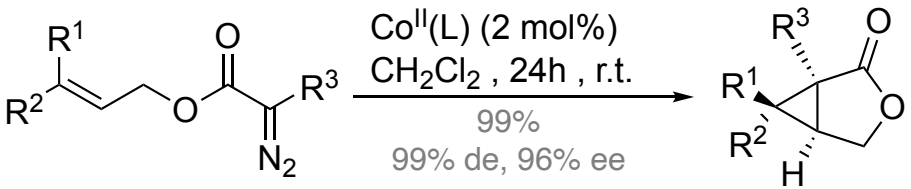

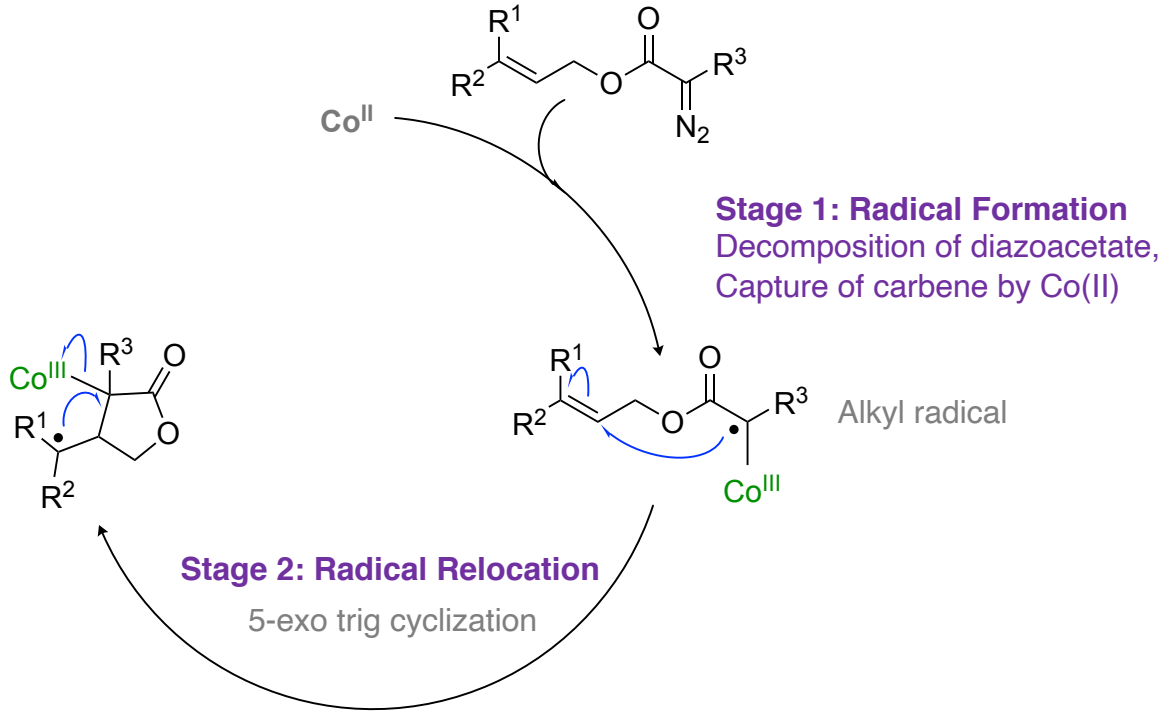

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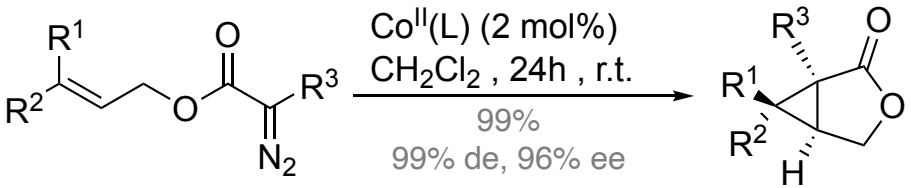
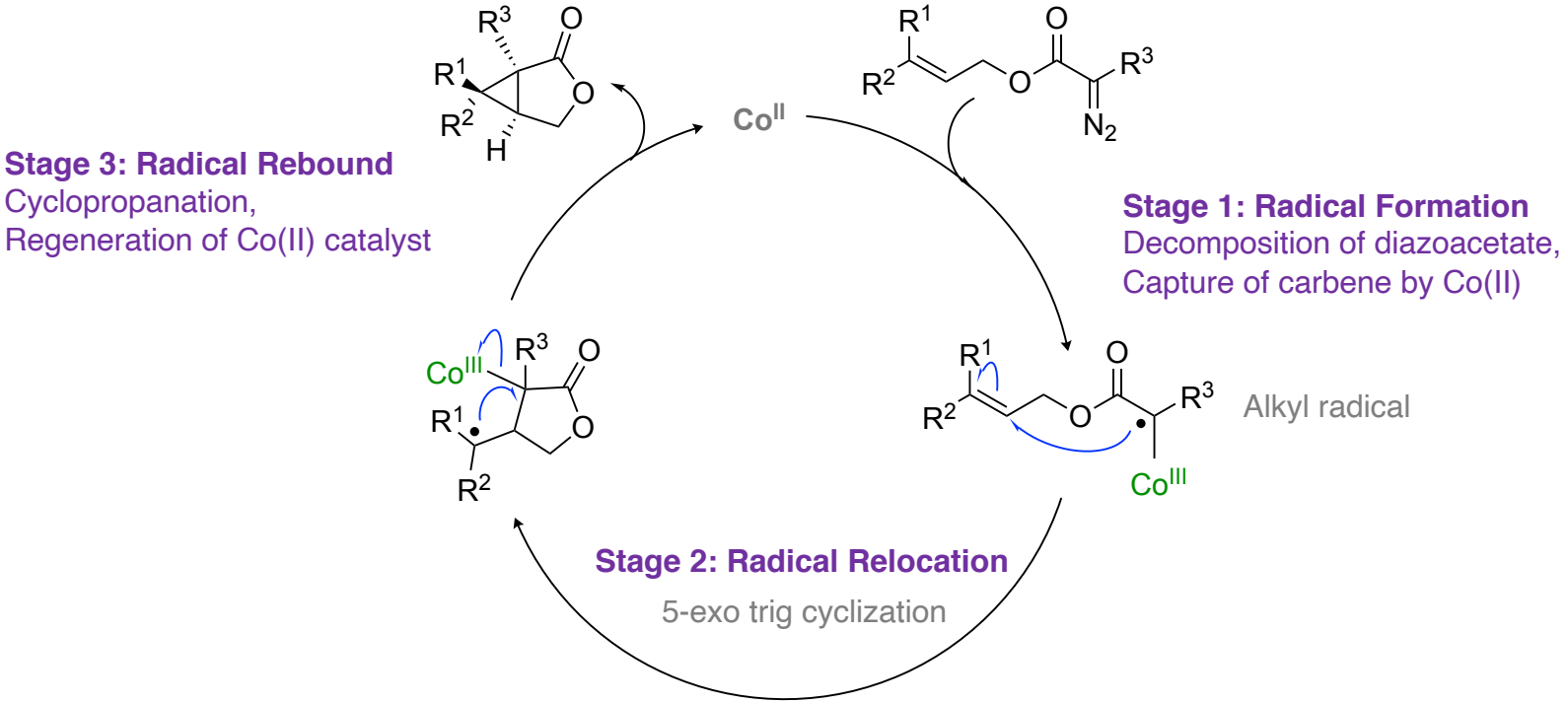
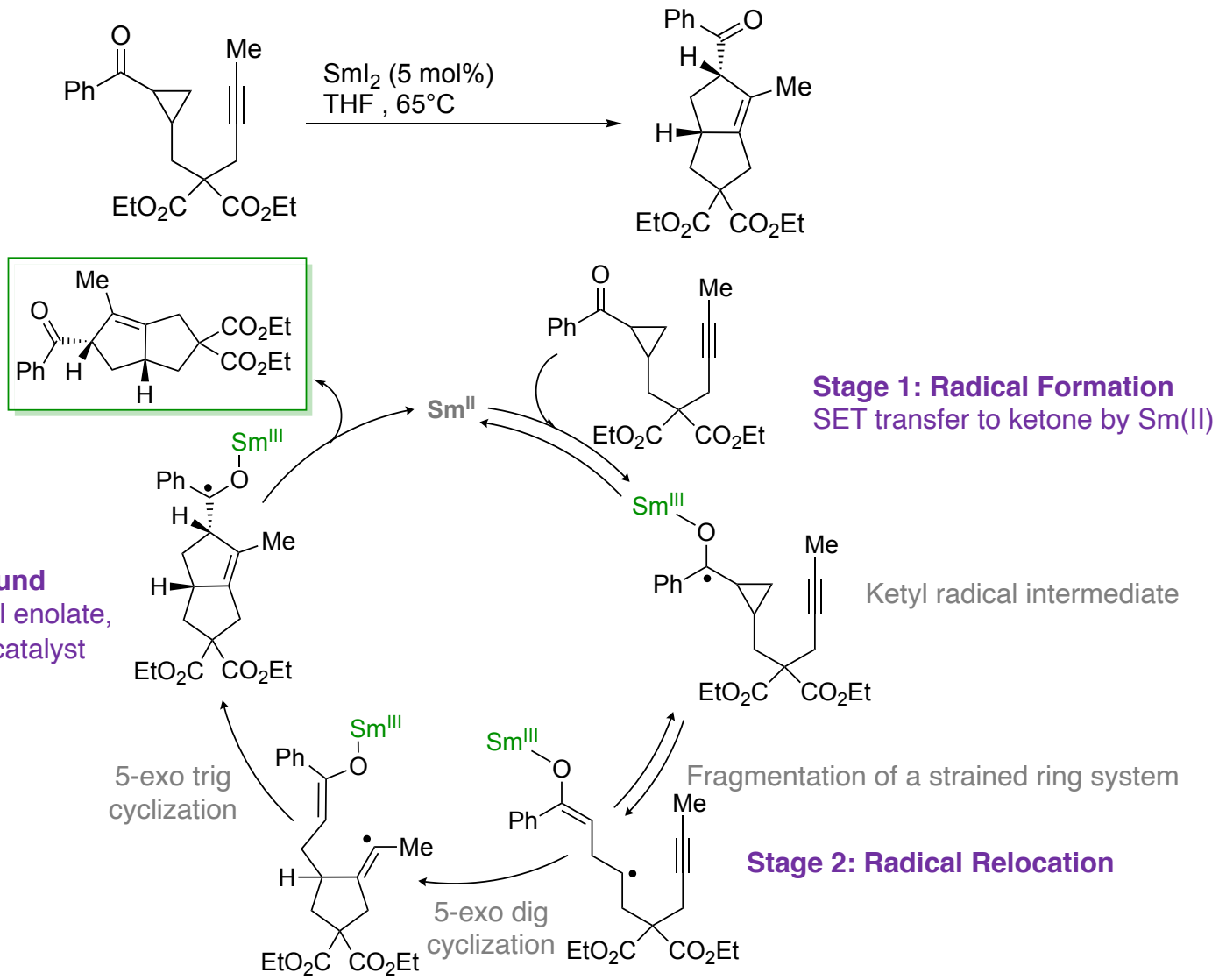




X. Xu, H. Lu *et al.*, *J. Am. Chem. Soc.* **2011**,*133,* 15292–15295

Examples – Intramolecular Radical Relays

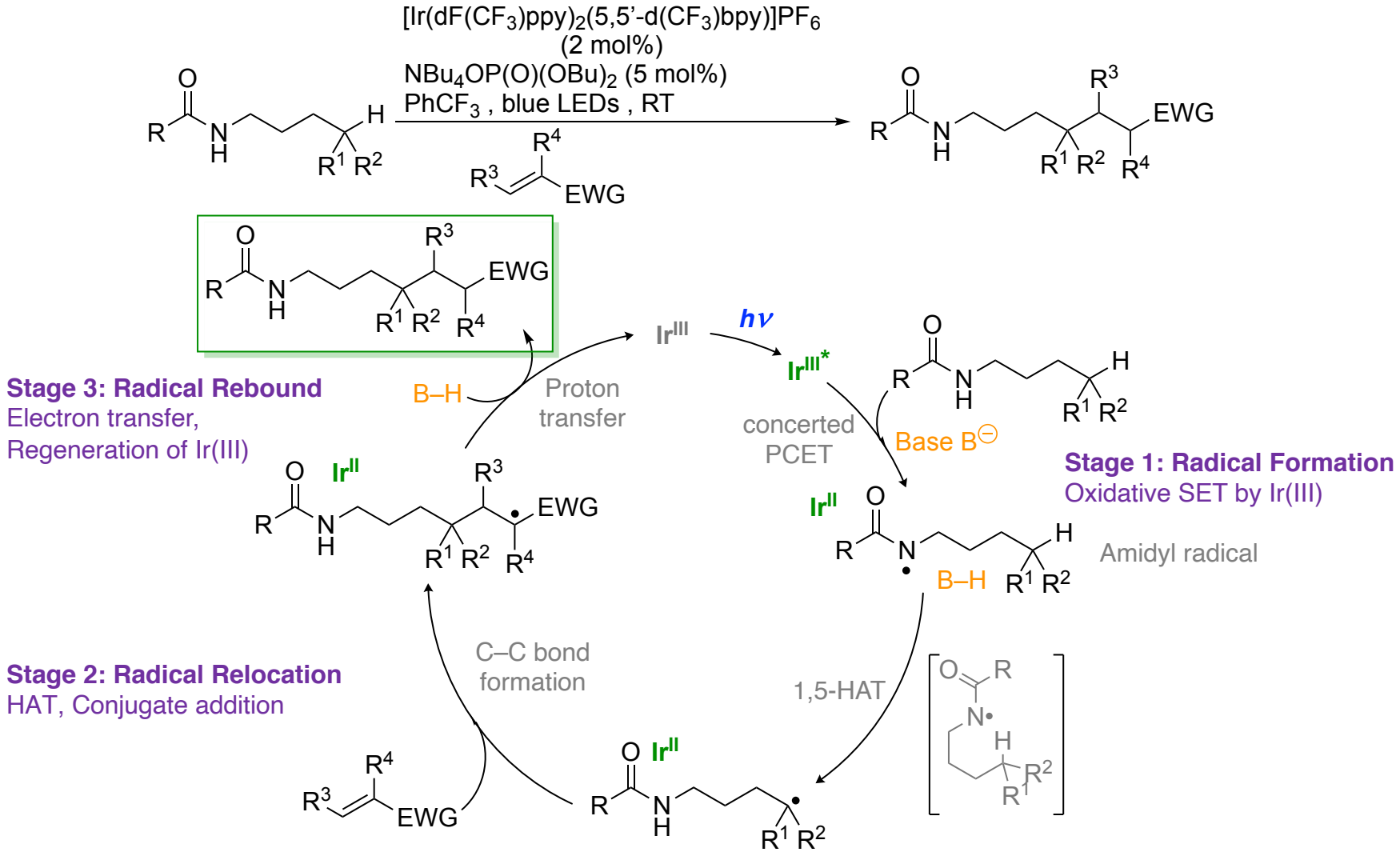
Sm(II)-catalyzed cyclization cascade (Procter 2019)



H.-M. Huang, J. J. W. McDouall, D. J. Procter, *Nat. Catal.* **2019**, *2,* 211–218

Examples – Radical Relays involving HAT

Ir(III)-catalyzed cascade reaction (Knowles and Rovis, 2016)

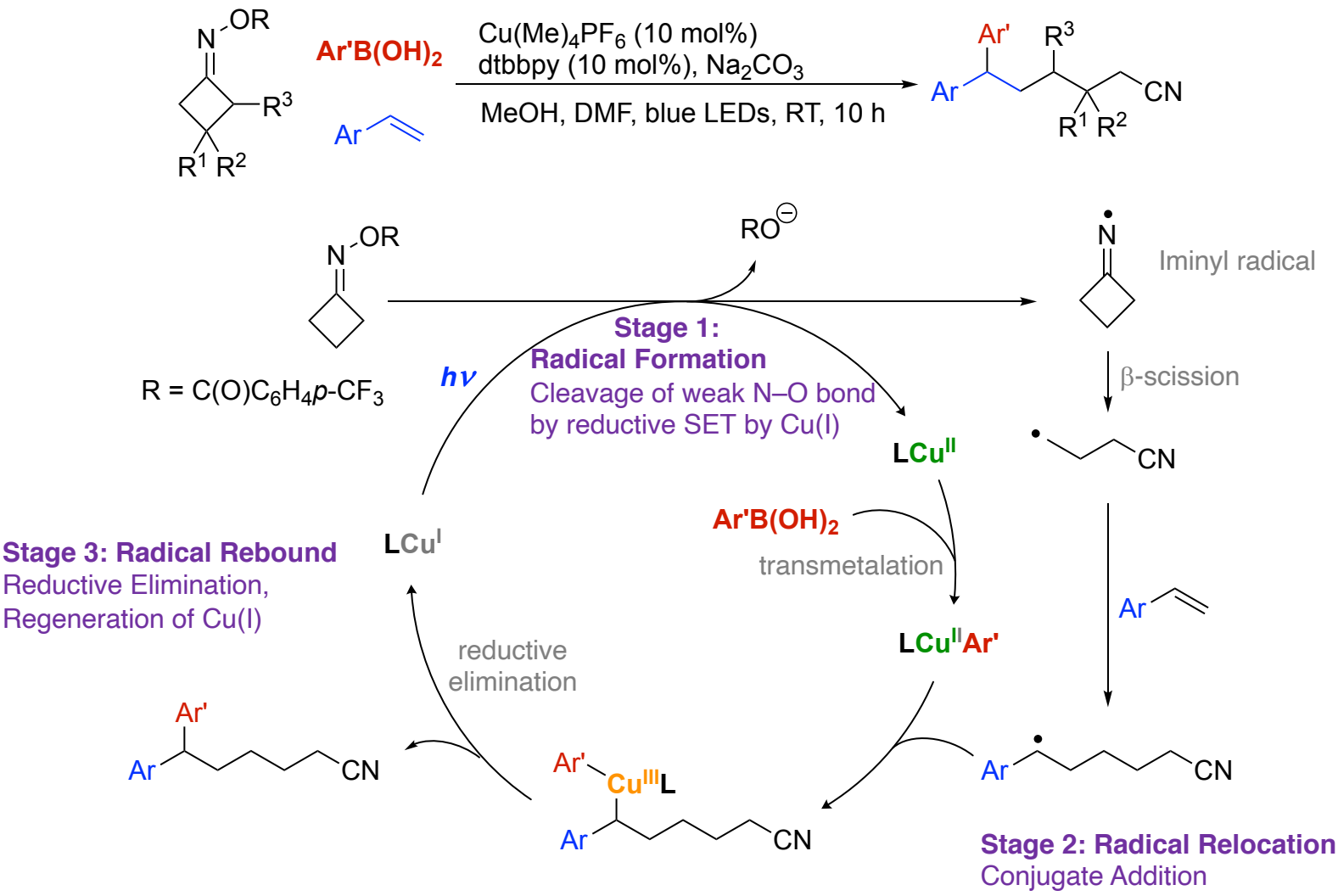


G. J. Choi, Q. Zhu, D. C. Miller, C. J. Gu, R. R. Knowles, *Nature* **2016**, *539,* 268–271

J. C. K. Chu, T. Rovis, *Nature* **2016**, *539,* 272–275

Examples – Intermolecular Radical Relays

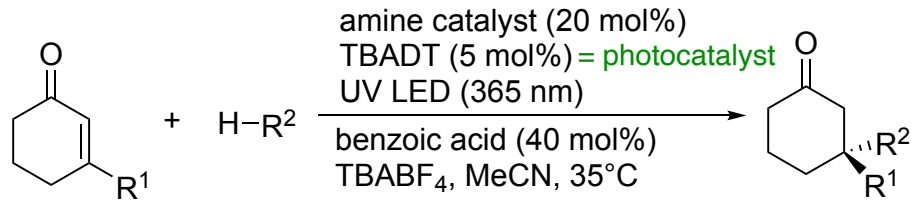
Cu(I)-catalyzed multicomponent coupling (Xiao and Chen, 2018)

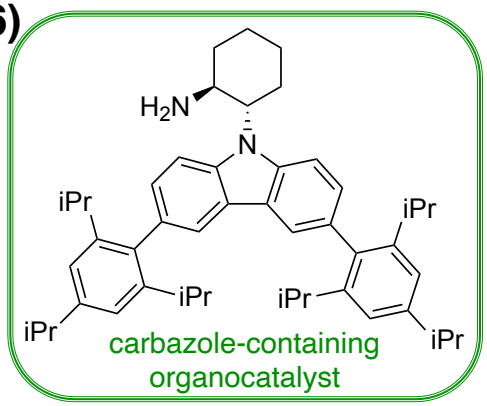


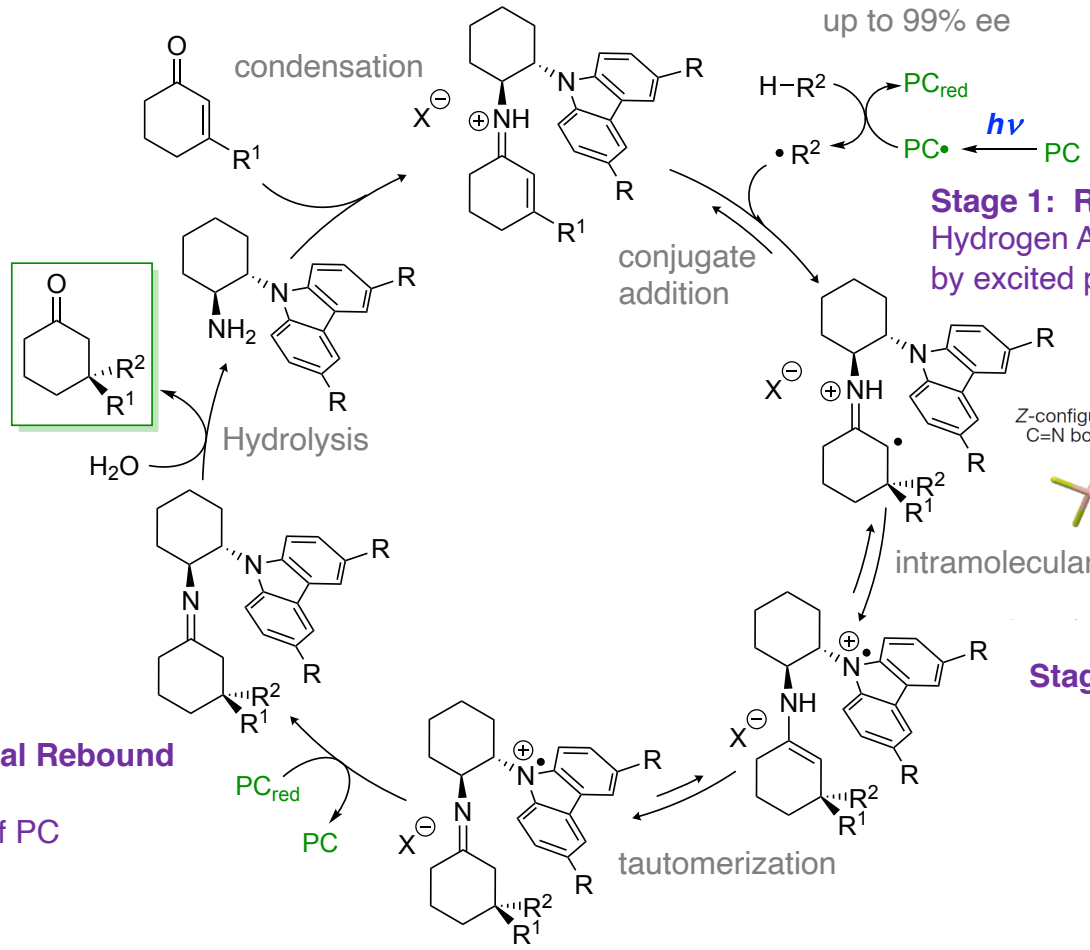
X. Y. Yu, Q. Q. Zhao, J. Chen, J. R. Chen, W. J Xiao, *Angew. Chem. Int. Ed.* **2018**, *57,* 15505–15509

Examples – Intermolecular Radical Relays

Merging organocatalysis and photoredox catalysis (Melchiorre, 2016)







J. J. Murphy D. Bastida, S. Paria, M. Fagnoni, P. Melchiorre, *Nature* **2016**, *532,* 218–222

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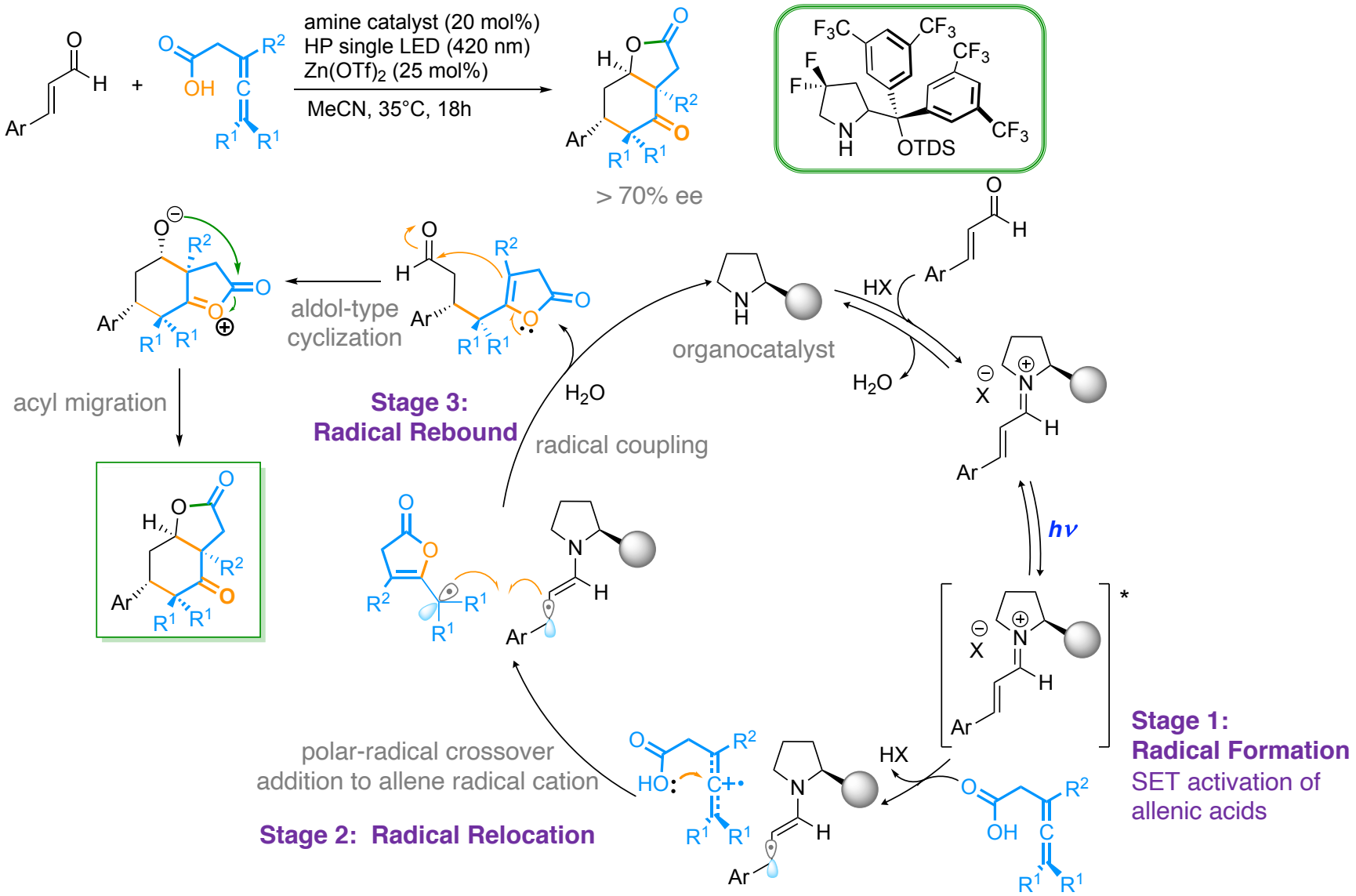

L. A. Perego, P. Bonilla, P. Melchiorre, *Adv. Synth. Catal.* **2020**, *362,* 302–307

Summary – Cascade Reactions by Radical Relay

Strategies for radical formation:

1. Cleavage of a weak bond by reductive SET from a low valent metal
2. Fragmentation of a strained ring system
3. Capture of a carbene by a low valent metal catalyst
4. Fragmentation promoted by visible light

Strategies for radical relocation:

1. Driven by release of ring strain
2. Hydrogen Atom Transfer (HAT)
3. Conjugate Addition

Following the Baldwin Rules

Strategies for radical rebound:

1. Homolytic substitution (at oxygen)
2. Intramolecular electron-transfer to regenerate the catalyst
3. Radical addition to a metal enolate

Enantioselective Radical Relays

Metal-free Radical Relays using organocatalysts

Outlook

- (radical) cascades as versatile tools for the construction of complex, molecular architectures
- high sustainability: atom-economic
  energy-efficient
  waste minimization (only catalytic amounts)

- challenging starting materials – strained ring systems, diazo-compounds etc.

Can more general starting materials serve as an input?

Can general design principles be developed to upgrade any radical process to a catalytic relay process?

Thank you very much for your attention!