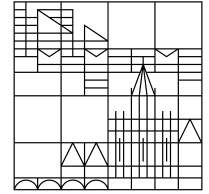


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Dowd-Beckwith ring-enlargement

Philipp Bruttel

Konstanz, 28.09.2022

Outline of the Presentation

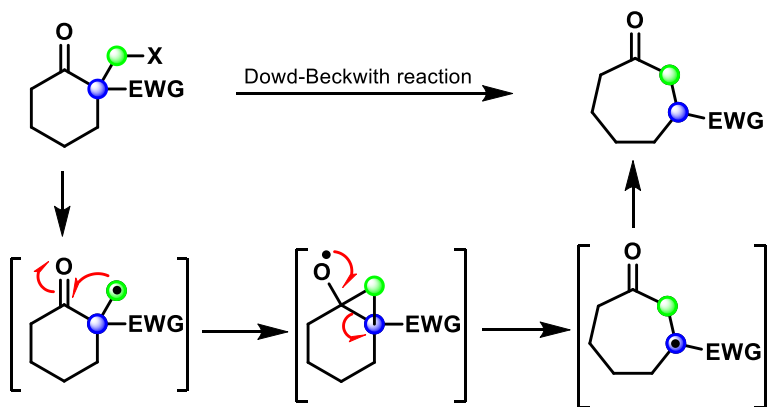
Content

- **General features of the Dowd-Beckwith reaction**
 - **Mechanism, Scope & Limitations**
 - **Main Focus on the synthesis of medium- and large-sized rings**
- **Discussion of methodologies connected to the Dowd-Beckwith reaction**
- **Dowd-Beckwith reaction in radical cascade reactions**
- **Application of the Dowd-Beckwith ring-enlargement in total synthesis**

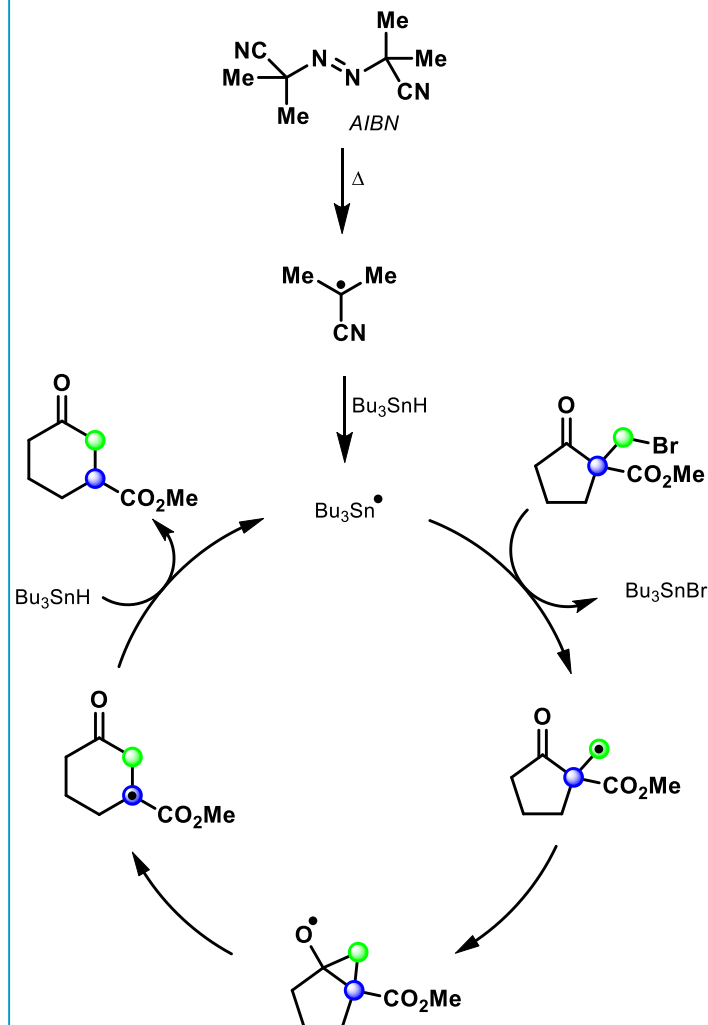
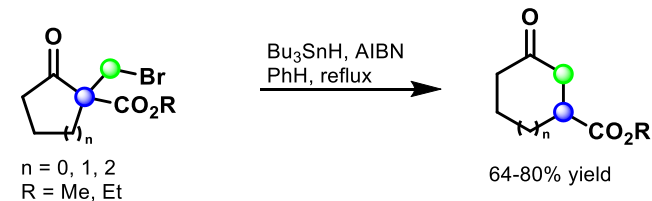
General features of the Dowd-Beckwith ring-enlargement

Mechanistic considerations

- radical addition/fragmentation sequence
- ring enlargement by incorporation of side chain
- one and three carbon atoms incorporation most feasible due to radical kinetics
- competing side reactions (direct defunctionalization, 1,5-HAT processes)



Dowd et al., *J. Am. Chem. Soc.* **1987**, 109, 3493-3494;
Beckwith et al., *J. Chem. Soc. Chem. Commun.* **1987**, 666-667;
Dowd et al., *Chem. Rev.* **1993**, 93, 2091-2115.

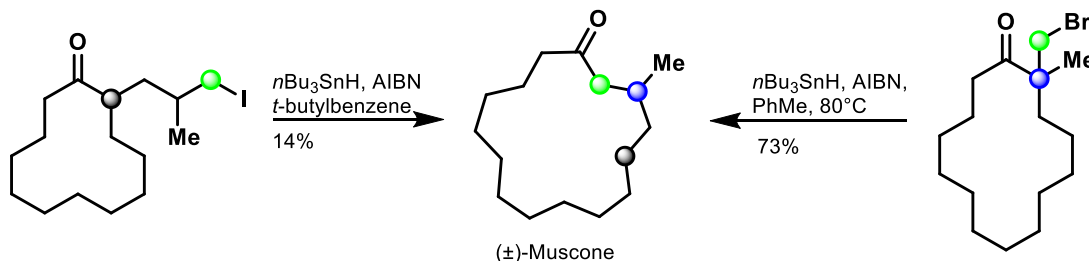


General features of the Dowd-Beckwith ring-enlargement

Synthesis of medium- and large-sized carbocycles

- Synthesis of medium-sized rings (8- to 12-membered rings) is difficult *via* end-to-end cyclizations due to disfavoured enthalpic and entropic effects
- Dowd-Beckwith reaction circumvents this by an addition/fragmentation approach
- combination of a Dowd-Beckwith reaction and an initial/ a follow-up radical reaction can lead to potent and fast establishment of complex polycyclic molecules

Synthesis of (\pm)-Muscone via Dowd-Beckwith ring-enlargement

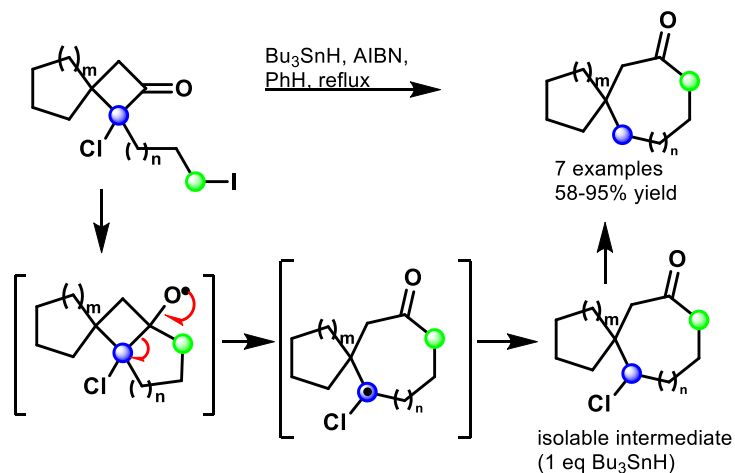


Dowd et al. , *Tet. Lett.* **1992**, 48, 4773-4792

Yeung et al. , *Org. Lett.* **2017**, 19, 1422-1425

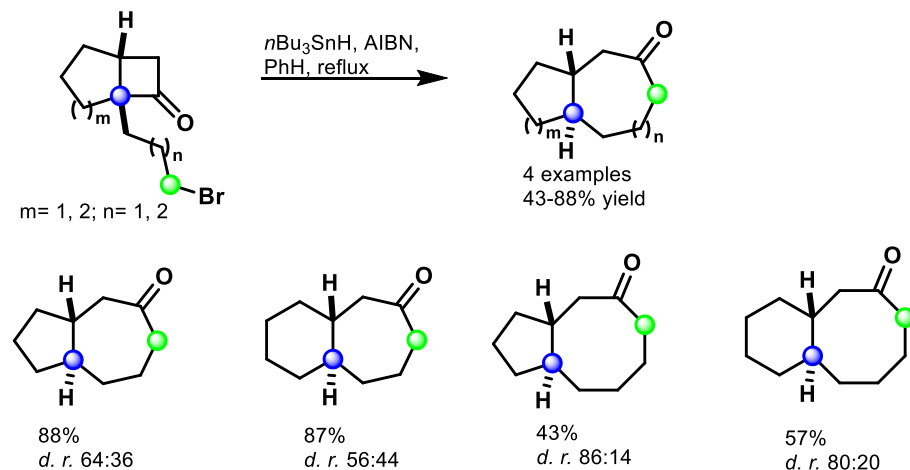
Methodology utilizing Dowd-Beckwith reaction sequences

Synthesis of spiroannulated ring systems



Dowd et al., *Tet. Lett.* **1992**, 33, 3285-3288

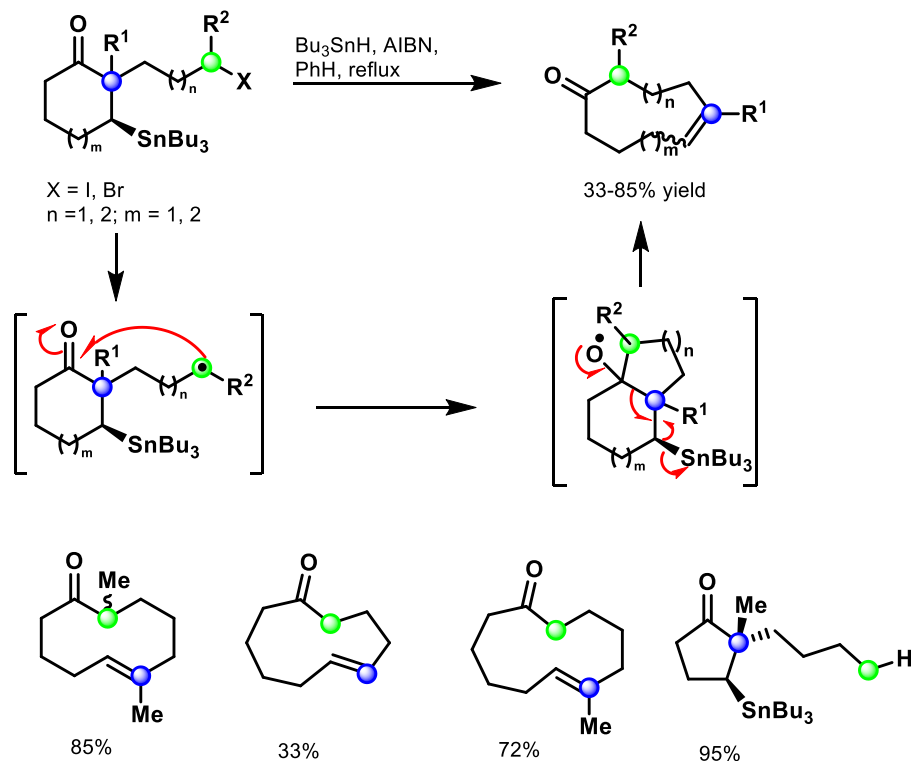
Synthesis of annelated ring systems



Dowd et al., *Tet. Lett.* **1995**, 36, 2729-2732

Methodology utilizing Dowd-Beckwith reaction sequences

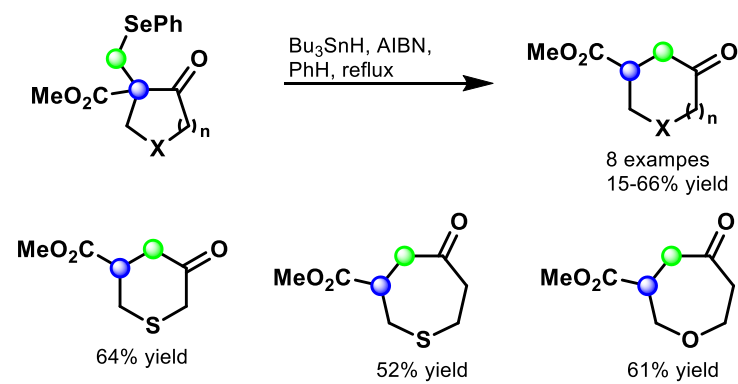
Synthesis of substituted lactons rings



Baldwin et al., *J. Chem. Soc. Chem. Commun.* **1988**, 1404-1406;

Baldwin et al., *Tetrahedron* **1991**, 47, 6795-6812.

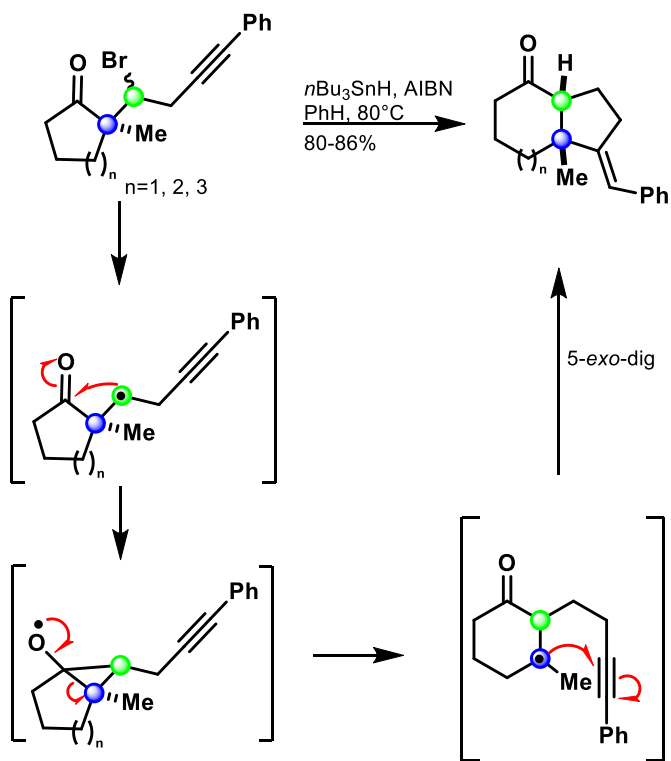
Ring-expansion on heterocycles



Dowd et al., *Tet. Lett.* **1989**, 30, 6129-6132

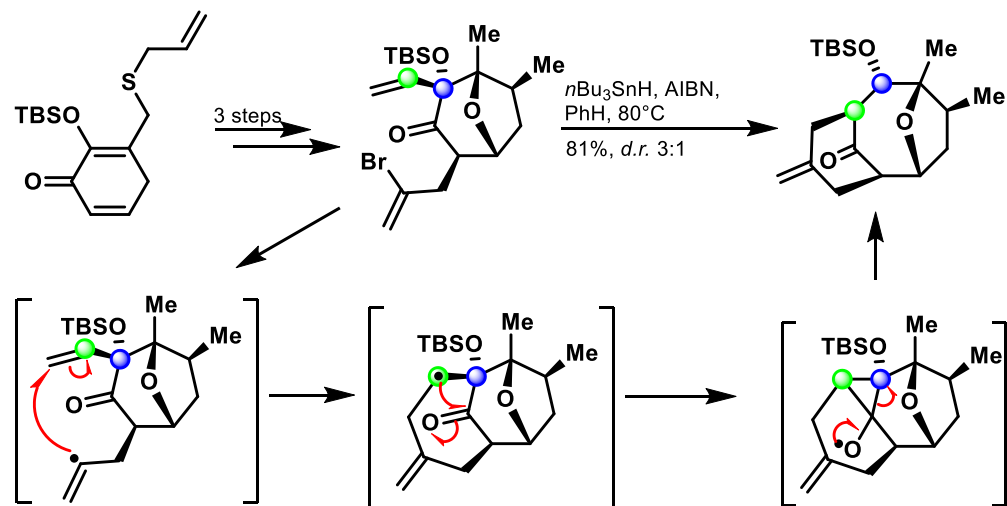
Dowd-Beckwith reaction in radical cascade reactions

Ring-expansion/5-exo-dig cyclization cascade



Boger et al., *J. Org. Chem.* **1990**, *55*, 5442-5444

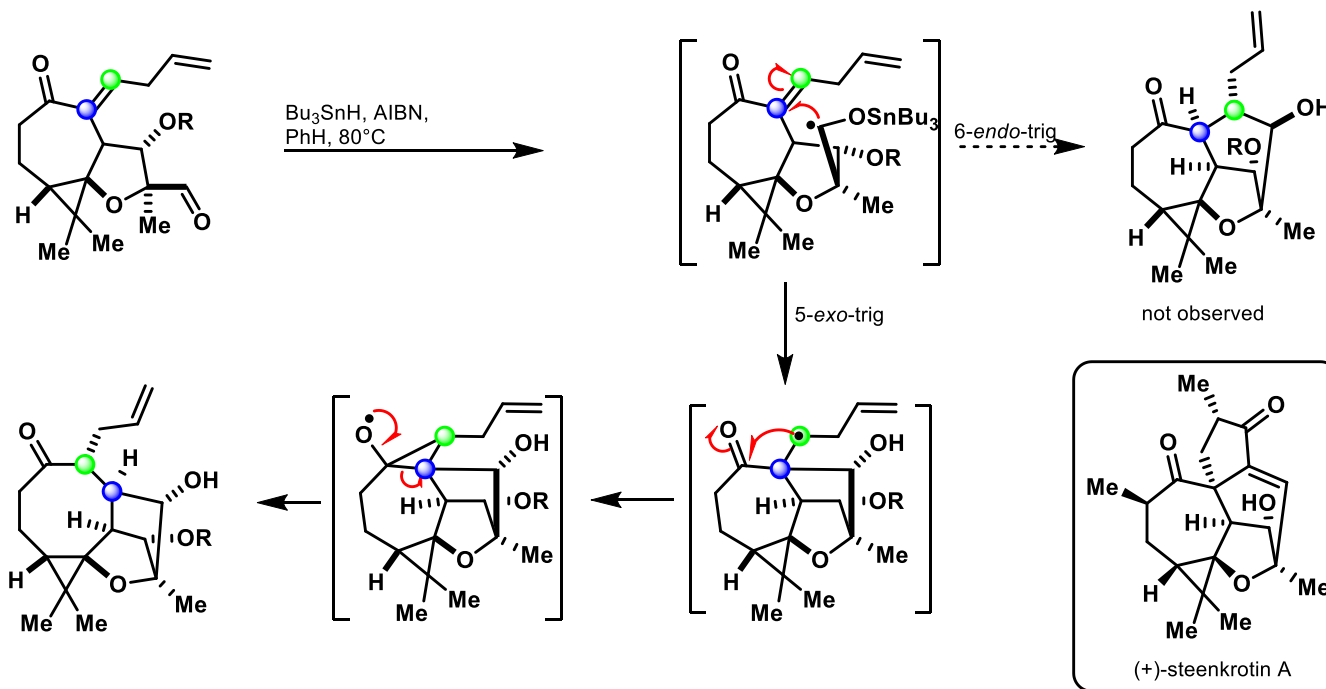
Radical cyclization/ Ring-expansion cascade to access bridged polycyclic systems



Rodriguez et al., *Org. Lett.* **2001**, *3*, 1181-1183

Dowd-Beckwith reaction in radical cascade reactions

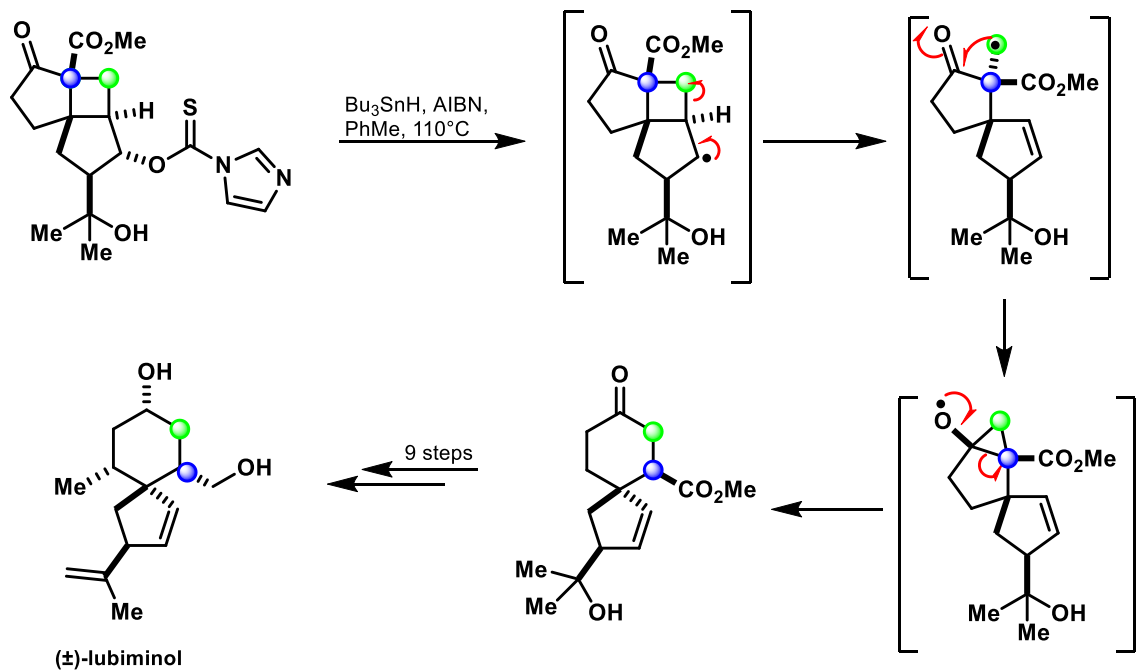
Unexpected/Unwanted radical cyclization/ ring-expansion cascade



Ding et al., Chem. Eur. J. **2016**, 22, 959-970

Application in Total Synthesis

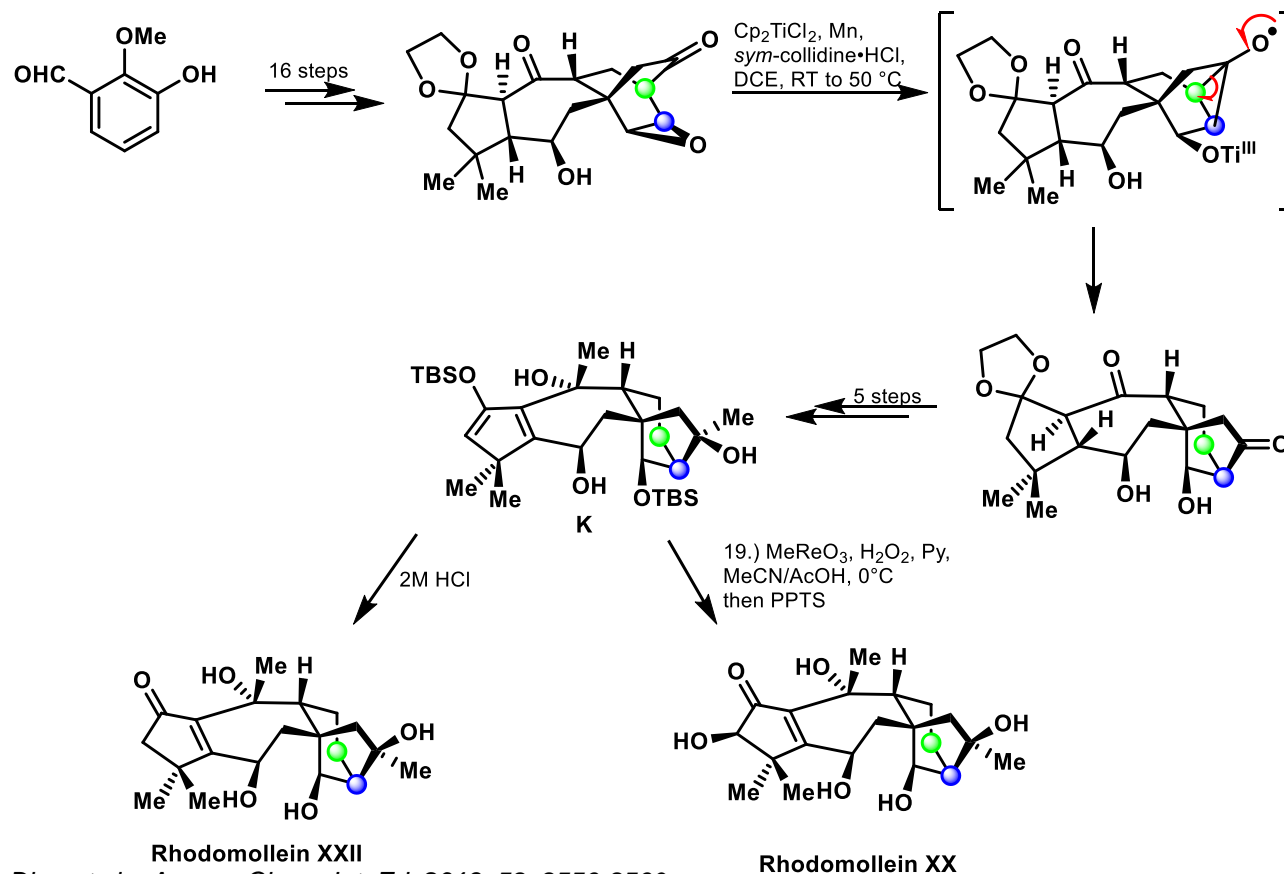
Total Synthesis of (±)-Lubiminol by Crimmins group



Crimmins, *J. Am. Chem. Soc.* **1998**, *120*, 1747-1758

Application in Total Synthesis

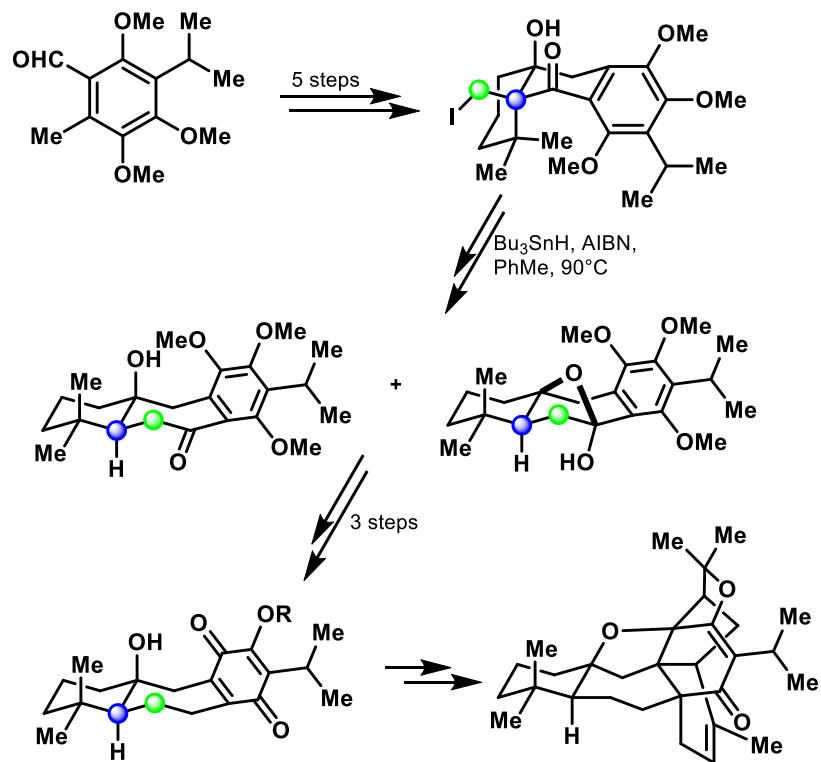
Total Synthesis of Rhodomollein XX and XXII by Ding group



Ding et al., *Angew. Chem. Int. Ed.* **2019**, 58, 8556-8560

Application in Total Synthesis

Total Synthesis of perovskone A-C by Gao group



R = H: perovskatone D

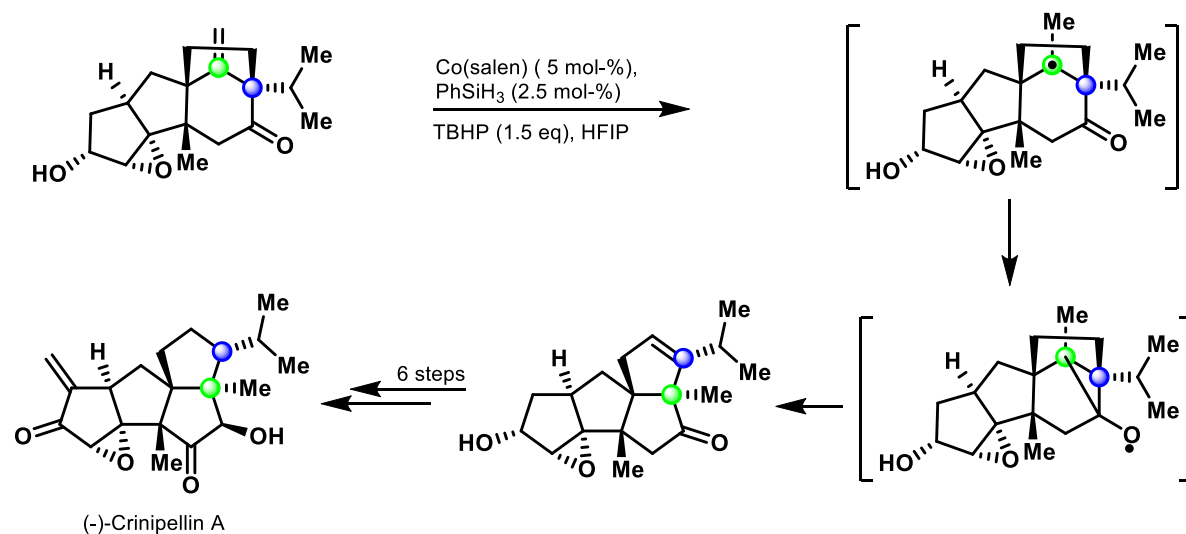
R = Me: methyl-perovskatone D

perovskone

Gao et al., *J. Am. Chem. Soc.* **2021**, *143*, 6370-6375

Application in Total Synthesis

Total Synthesis of (-)-Crinipellin A by Ding group



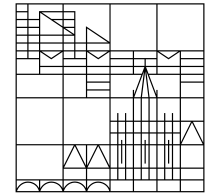
Ding et al., *J. Am. Chem. Soc.* **2022**, 144, 2495-2500

Conclusion

Advantages and Drawbacks of the Dowd-Beckwith ring-enlargement

- **feasible for the synthesise of medium-sized rings**
- **impressive/efficient as part of a radical cascade reaction**
- **mainly applications with carbon centered radicals**
- **bad atom efficiency and risks for the environment**
 - high dilution, elevated reaction temperature necessary
 - usage of tributyltin hydride and halogenated compounds
- **limited scope due to competing side reactions**
- **predictabiliy of stereochemical outcome**

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**Thank you for your
attention!**

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- [4] Dowd et al. , *Tet. Lett.* **1992**, 48, 4773-4792
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- [16] Gao et al. , *J. Am. Chem. Soc.* **2021**, 143, 6370-6375
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