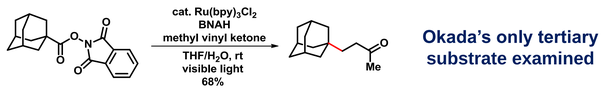
Forming Quaternary Carbons Using Photoredox Catalysis and Applications to the Total Synthesis of Terpene Natural Products

Gregory L. Lackner, Kyle W. Quasdorf, Gerald Pratsch, Daniel S. Müller, Nicholas L. Untiedt, André P. Dieskau and Larry E. Overman

Department of Chemistry, University of California, Irvine.

Background and Previous Work

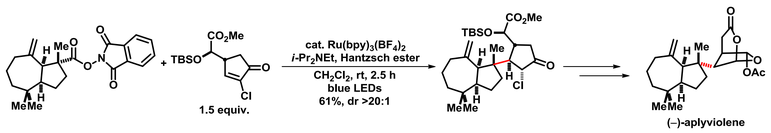
Constructing quaternary carbons via tertiary radical intermediates is an effective but underutilized synthetic strategy.



Okada's only tertiary substrate examined

Okada, K.; Okamoto, K.; Morita, N.; Okubo, K.; Oda, M. *J. Am. Chem. Soc.* **1991**, *113*, 9401–9402.

- **Key radical coupling step in the total synthesis of (–)-aplyviolene:**

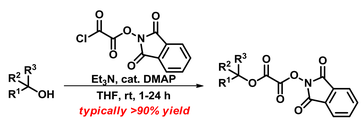


Schnermann, M. J.; Overman, L. E. *Angew. Chem., Int. Ed.* **2012**, *51*, 9576–9580.

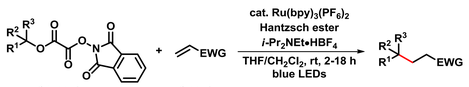
Generating radicals from carboxylic acid derivatives requires incorporating a sacrificial C-C bond.

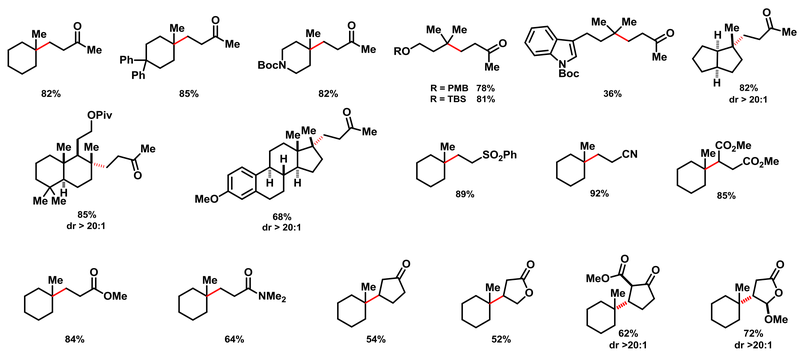
Can we design a similar tertiary alcohol-derived radical precursor?

Forming Quaternary Carbons From Alcohol Derivatives



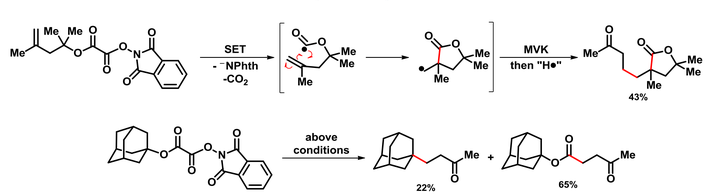
- **Purified by trituration with 25:1 hexanes:CH_2Cl_2**
  - **Stable indefinitely when stored at –20 °C**





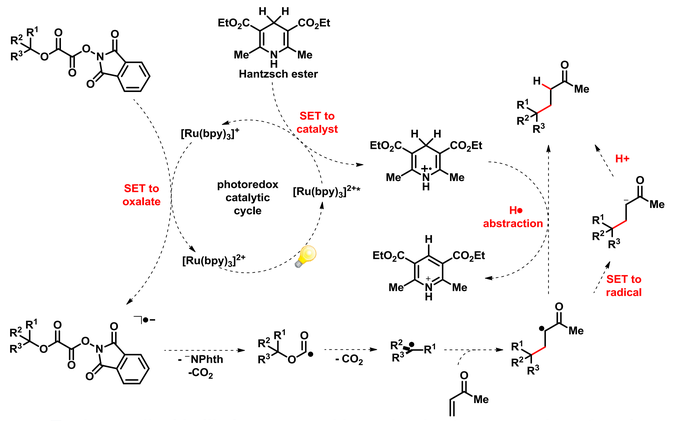
- **Electron-deficiency of the acceptor is critical for successful coupling**

Evidence for an alkoxycarbonyl radical intermediate:



Lackner, G. L.; Quasdorf, K. W.; Overman, L. E. *J. Am. Chem. Soc.* **2013,** *135*, 15342–15345.

Proposed Photoredox-Catalyzed Radical Coupling Mechanism

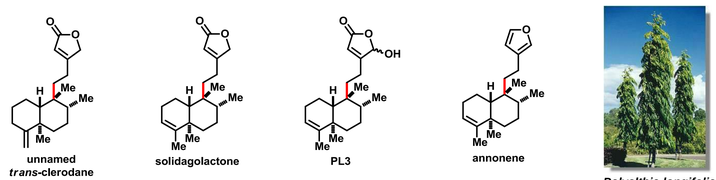


Two potential termination pathways

- **Tertiary radical is likely generated by reductive fragmentation of oxalate substrates**
  - **Termination may occur via H-atom abstraction or SET/protonation**

Lackner, G. L.; Quasdorf, K. W.; Overman, L. E. *J. Am. Chem. Soc.* **2013,** *135*, 15342–15345.
Additional reactivity and mechanism studies: Lackner, G. L.; Quasdorf, K. W.; Pratsch, G.; Overman, L. E. *J. Org. Chem.* **2015**, *80*, 6012–6024.
Pratsch, G.; Lackner, G. L.; Overman, L. E. *J. Org. Chem.* **2015**, *80*, 6025–6036.

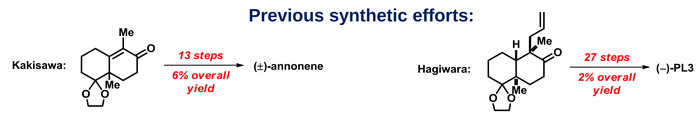
Synthetic Applications: *trans*-Clerodane Diterpenes



Polyalthia longifolia

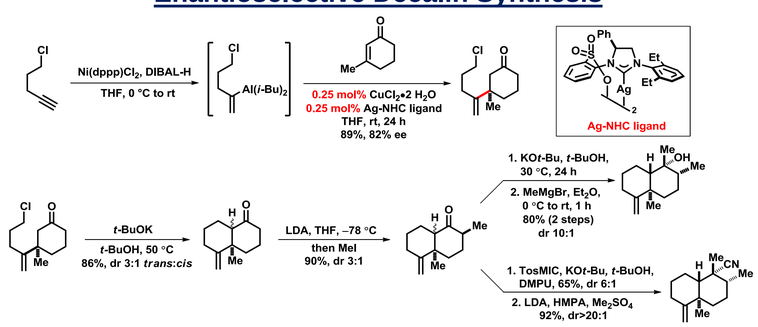
- **Isolated from *Polyalthia longifolia* and other plant sources**
- **Most *trans*-clerodanes exhibit antifeedant activity; PL3 also has antibacterial, antileishmanial, lipid lowering, and antitumor activity.**

Previous synthetic efforts:



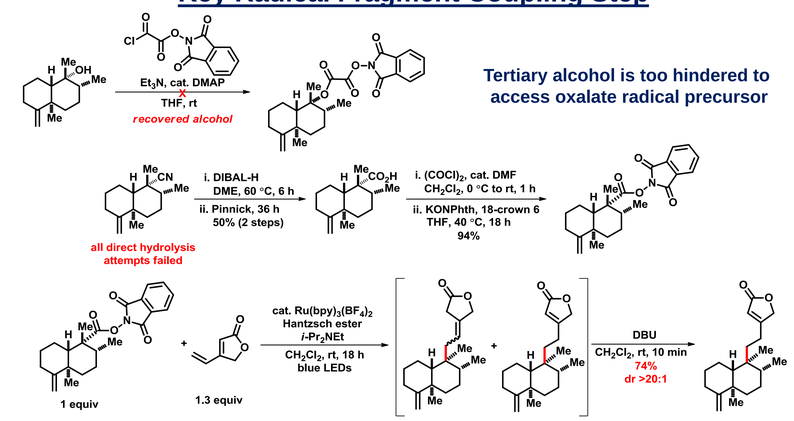
Bohlman, F.; Ahmed, M.; Jakupovic, J.; King, J. M.; Robinson, H. *Rev. Latinoam. Quim.* **1984**, *15*, 16−18.
Takahashi, S.; Kusumi, T.; Kakisawa, H. *Chem. Lett.* **1979**, 515−518.
Hagiwara, H.; Inome, K.; Uda, H. *Tetrahedron Lett.* **1994**, *35*, 8189−8192.

Enantioselective Decalin Synthesis



Müller, D. S.; Untiedt, N. L.; Dieskau, A. P.; Lackner, G. L.; Overman, L. E. *J. Am. Chem. Soc.* **2015**, *137*, 660–663.
May, T. L.; Dabrowski, J. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011**, *133*, 736−739.
Piers, E.; Wai, J. S. M. *Can. J. Chem.* **1994**, *72*, 146–157.

Key Radical Fragment Coupling Step

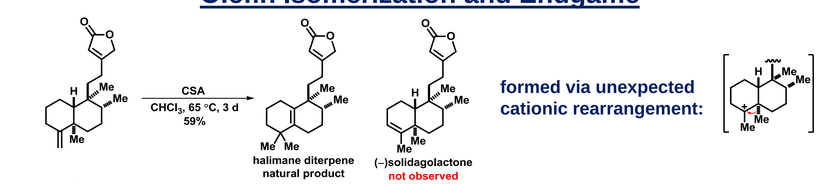


Tertiary alcohol is too hindered to access oxalate radical precursor

High dilution and excess Hantzsch ester required to prevent allylic radical dimerization

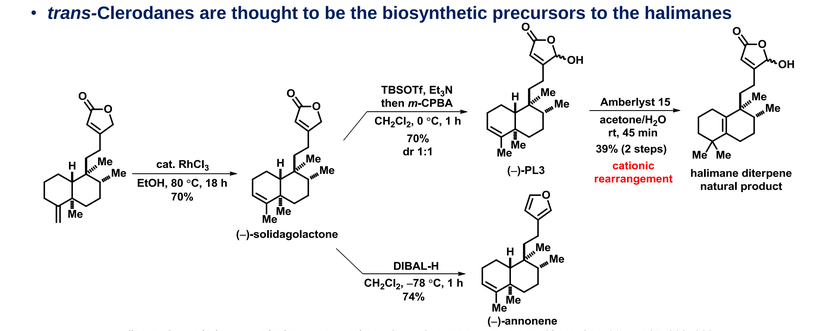
Müller, D. S.; Untiedt, N. L.; Dieskau, A. P.; Lackner, G. L.; Overman, L. E. *J. Am. Chem. Soc.* **2015**, *137*, 660–663.

Olefin Isomerization and Endgame



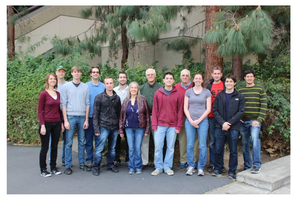
formed via unexpected cationic rearrangement:

- **Halimanes and *trans*-clerodanes are isolated from common biological sources**
- ***trans*-Clerodanes are thought to be the biosynthetic precursors to the halimanes**



Müller, D. S.; Untiedt, N. L.; Dieskau, A. P.; Lackner, G. L.; Overman, L. E. *J. Am. Chem. Soc.* **2015**, *137*, 660–663.
Zhou, M.; Geng, H.-C.; Zhang, H.-B.; Dong, K.; Wang, W.-G.; Du, X.; Li, X.- N.; He, F.; Qin, H.-B.; Li, Y.; Pu, J.-X.; Sun, H.-D. *Org. Lett.* **2013**, *15*, 314–317.
: Utkina, N.; Denisenko, V. A.; Scholokova, O. V.; Makarchenko, A. E. *J. Nat. Prod.* **2003**, *66*, 1263–1265.

Acknowledgements



Professor Larry E. Overman
Carol Schwartz

UC Irvine
Facilities & Staff

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