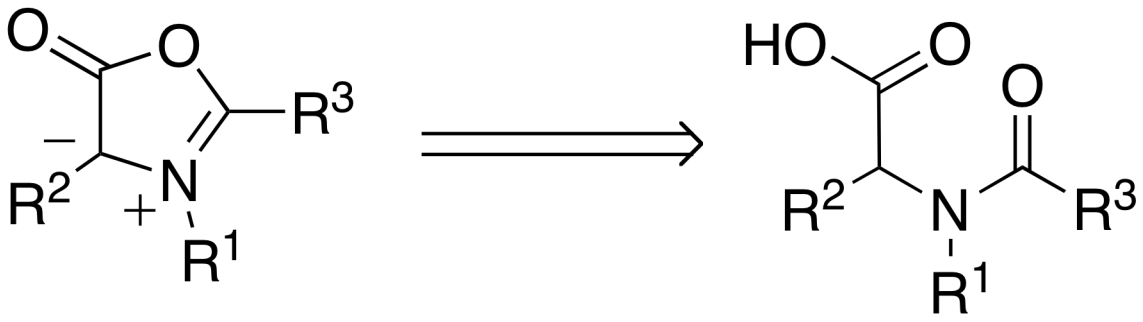
Effect of Substitution on the Intramolecular 1,3-Dipolar Cycloaddition of Alkene Tethered Münchnones

Guillaume Belanger, Myriam April, Etienne Dauphin, and Stephanie Roy

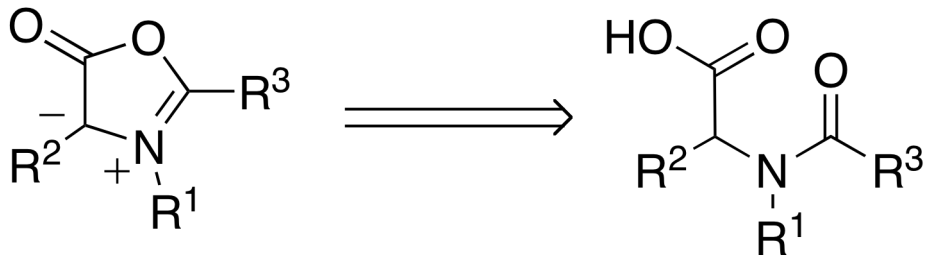
J. Org. Chem. **2007,** *72*, 1104



John Maciejewski
Current Literature

March 3, 2007

The Münchnone



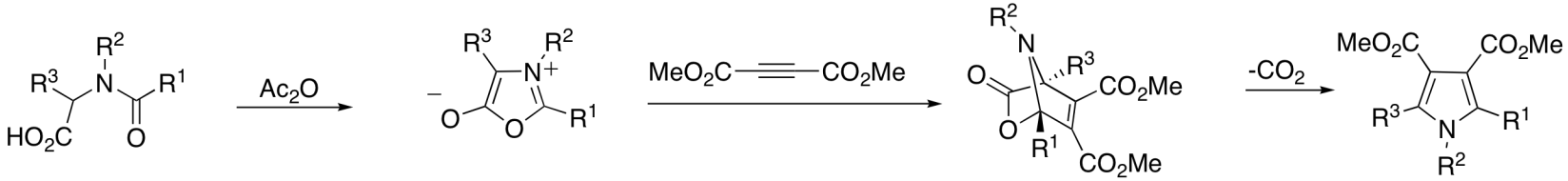
Münchnone (1,3-oxazolium-5-olate)

- 1,3-dipolar species
- Prepared from amido acids (activated by Ac_2O, DCC or Mukaiyama's salt)
- May react inter- or intramolecularly with dipolarophiles (alkenes or alkynes)
- Three sites to tether a dipolarophile (R^1, R^2, R^3) for intramolecular reactions

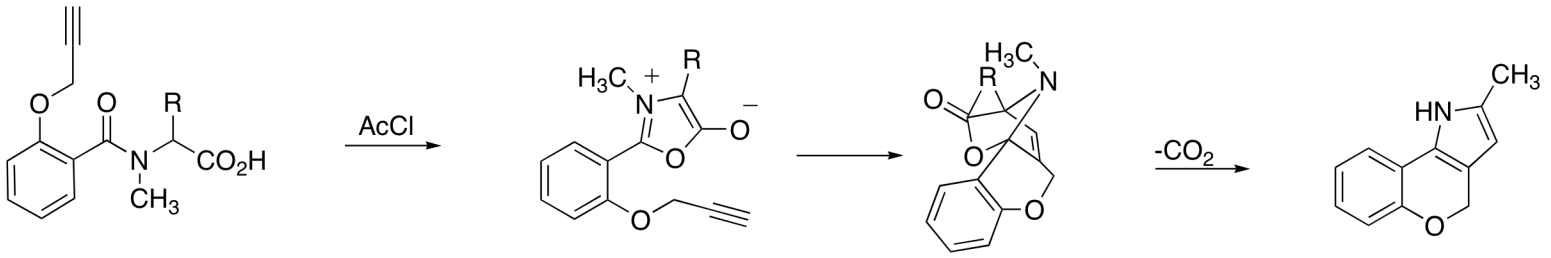
Huisgen, R. *J. Org. Chem.* **1976,** *41,* 403.

Gribble, G. W. In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products;* Padwa, A., Pearson, W. S., Eds; John Wiley & Sons: Hoboken, NJ, 2003; pp 681-755.

1,3-Dipolar Cycloadditions



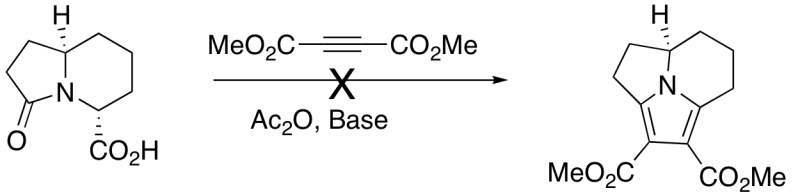
Padwa, A.; Lim, R.; MacDonald, J.G. *J. Org. Chem.* **1985,** *50*, 3816



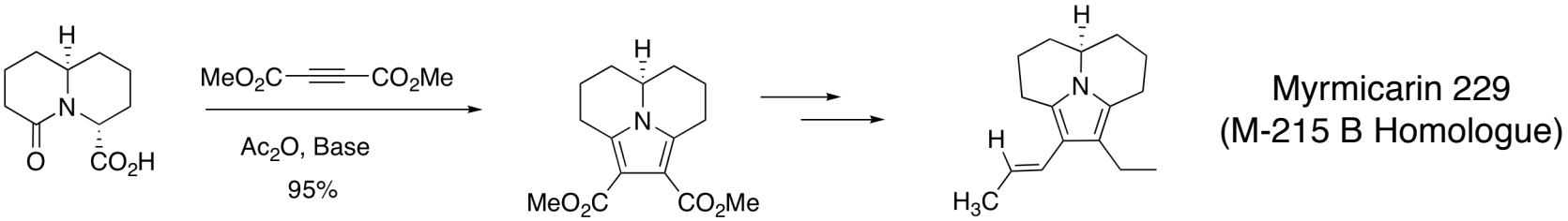
Kato, H.; Wang, S-F.; Nakano, H. *J. Chem. Soc., Perkin Trans. 1* **1989,** 361

1,3-Dipolar Cycloadditions

Indolizidine-derived myrmicarin alkaloids



Indolizidine münchnone too strained

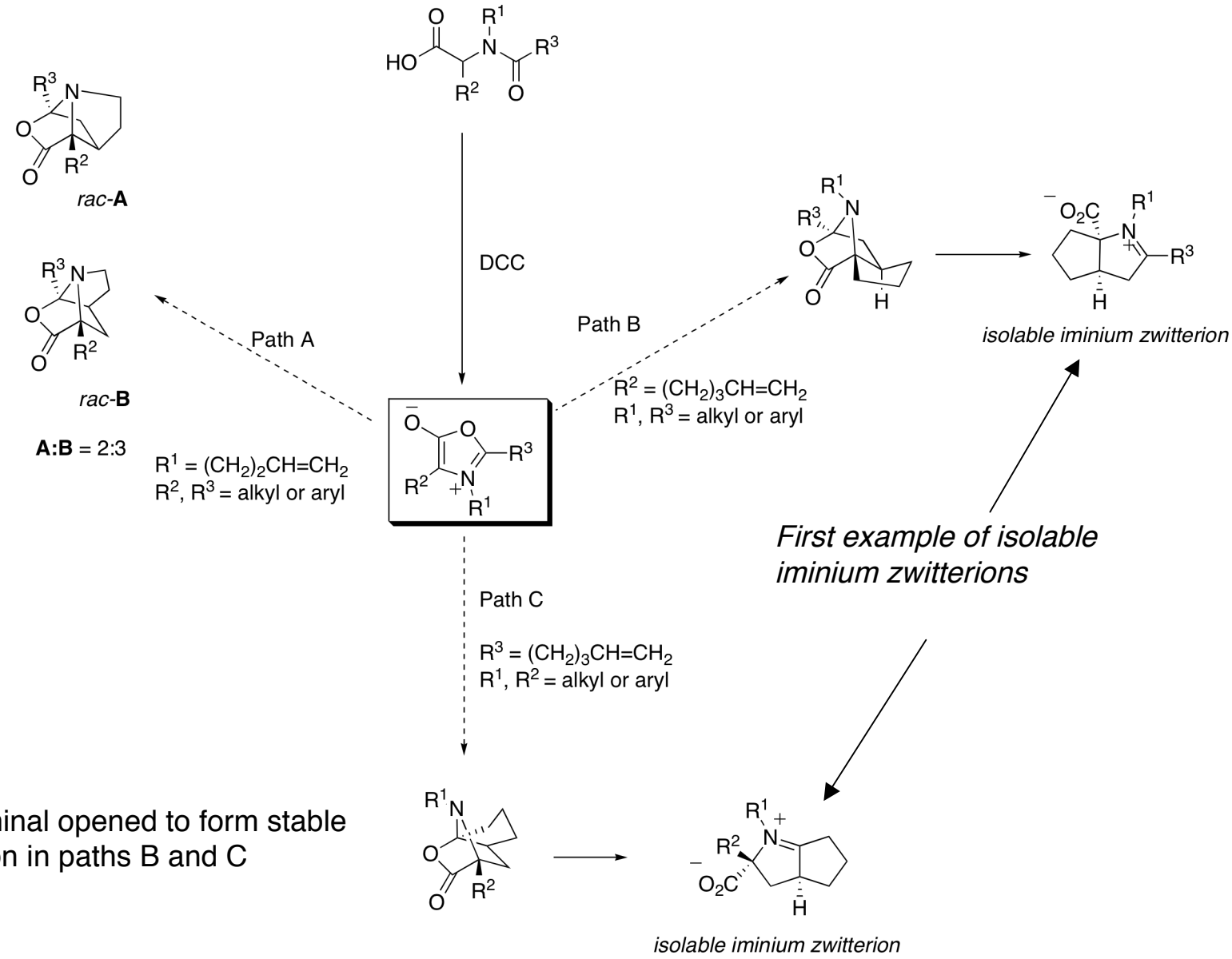


Myrmicarin 229
(M-215 B Homologue)

Quinolizidine münchnone intermediate allows cycloaddition to occur

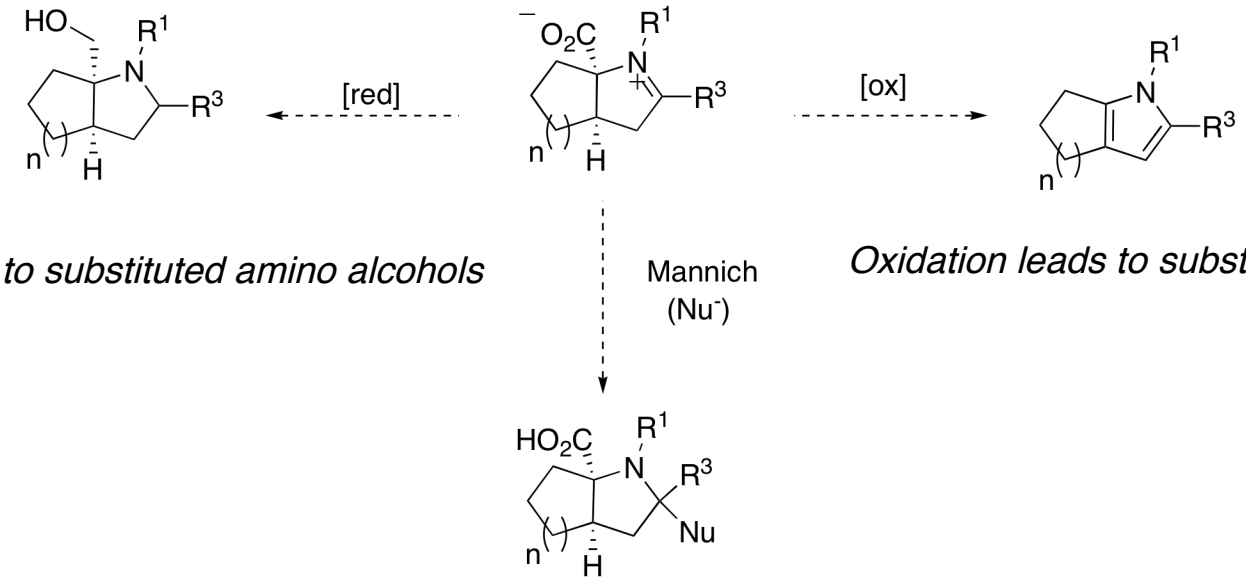
Angle, S. R. *J. Org. Chem.* ASAP (2/22/07)

Scope of Featured Article



Hemiaminal opened to form stable zwitterion in paths B and C

Synthetic Utility of Novel Intermediates



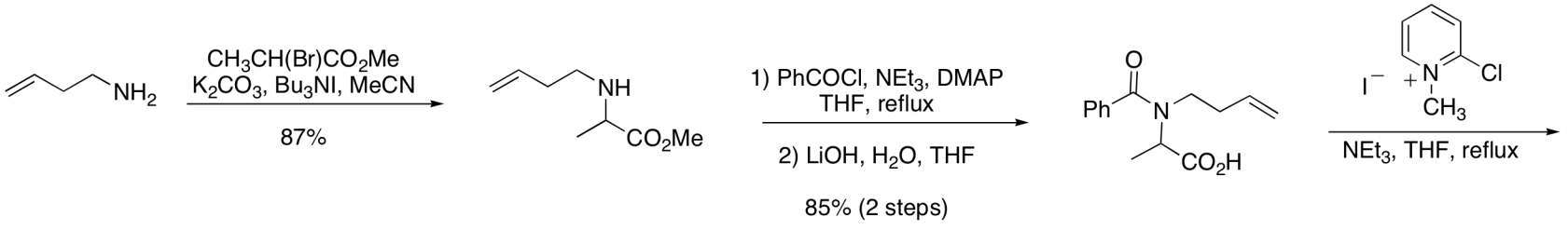
Reduction leads to substituted amino alcohols

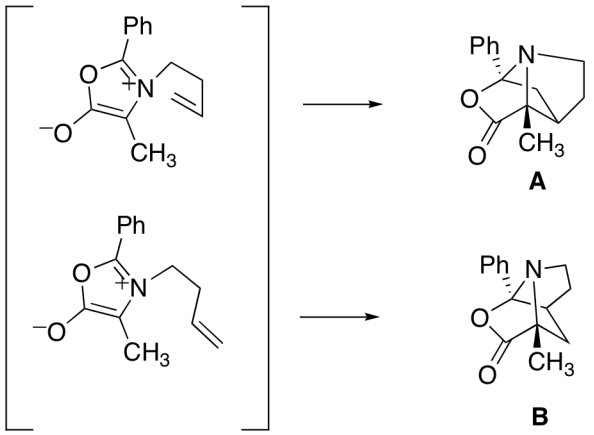
Oxidation leads to substituted pyrroles

Addition to imine by internal or external nucleophile

Methodology may be used in pyrrole, pyrrolidine (n=1) or hydroindole scaffolds (n=2)

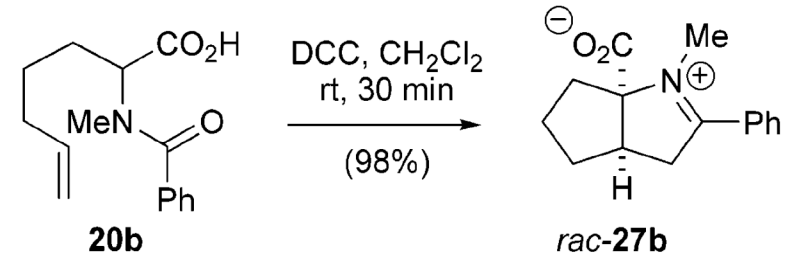
Path A: Dipolarophiles Tethered at Nitrogen

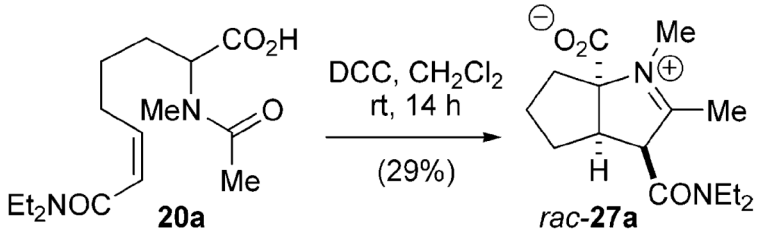


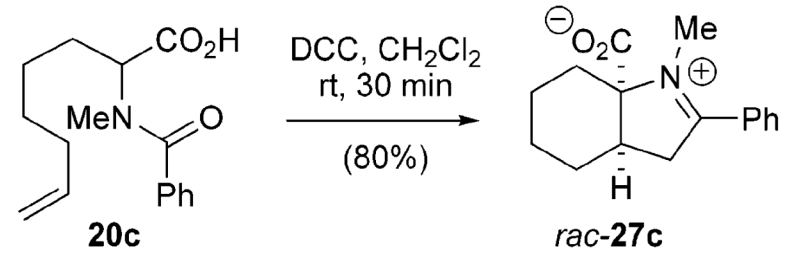


Intramolecular 1,3-dipolar cycloaddition using aliphatic nitrogen tether

Path B: Dipolarophiles Tethered at α-Amino Position

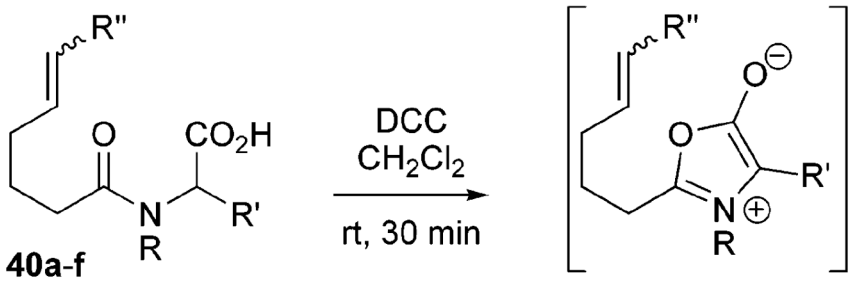






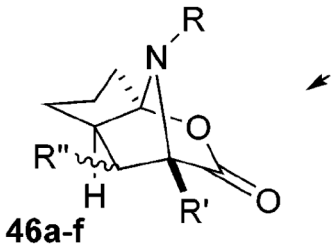
First reported isolation of iminium zwitterionic products

Path C: Dipolarophiles Tethered at Amido Position

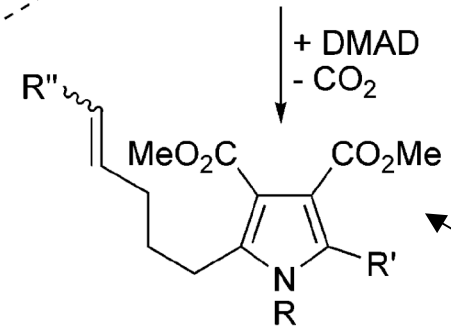


40a-f

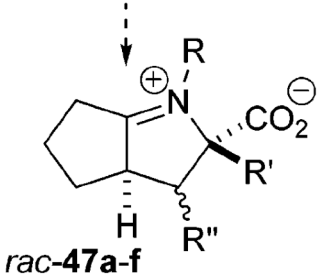
45a-f



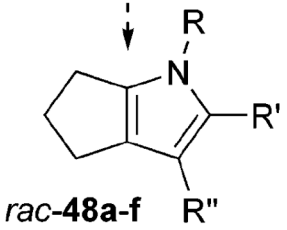
46a-f



49a (99%) **49d** (99%)
49b (83%) **49e** (88%)
49c (99%) **49f** (54%)



rac-**47a-f**



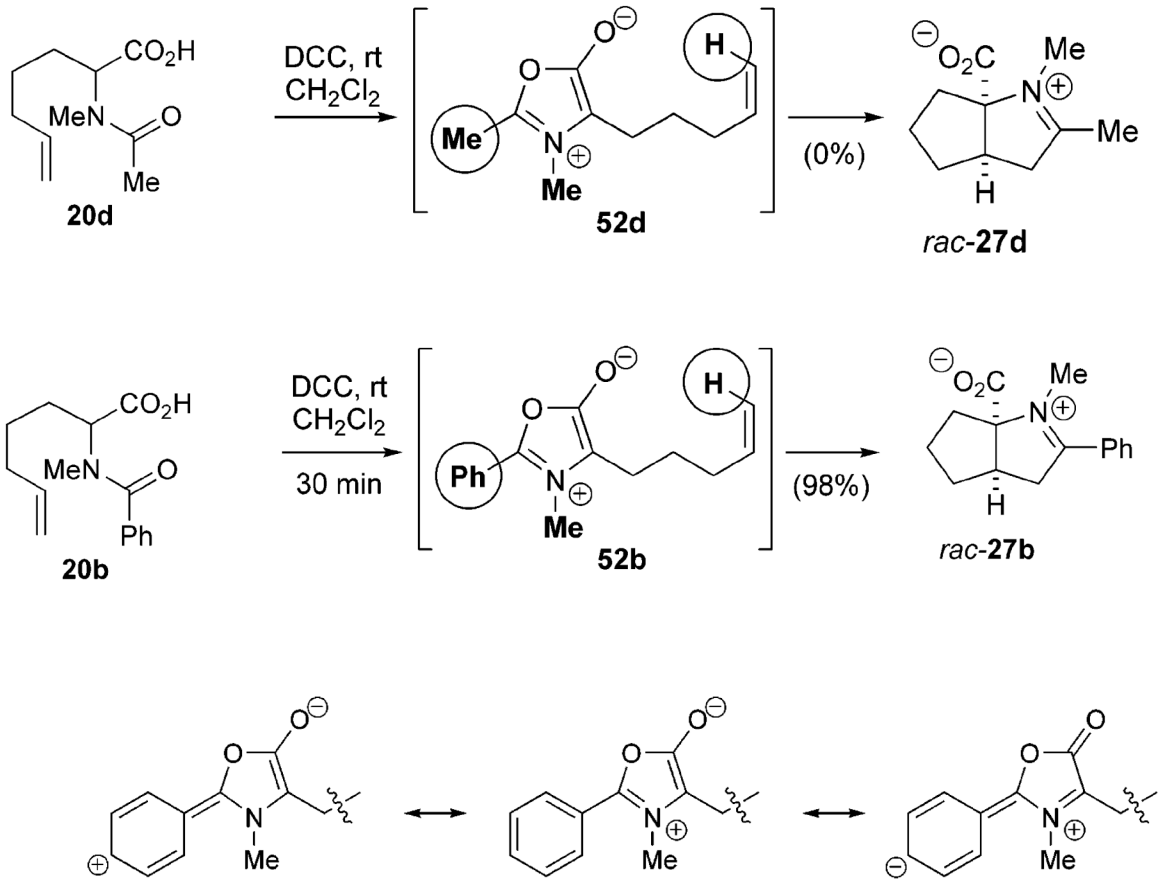
rac-**48a-f**

	R	R'	R"
a	Me	Ph	H
b	Ph	Me	H
c	Ph	Ph	H
d	4-$MeOC_6H_4$	Me	H
e	Ph	Me	Cl
f	Ph	Me	OMe

Activated alkenes do not work well as dipolarophiles when tethered at amido position

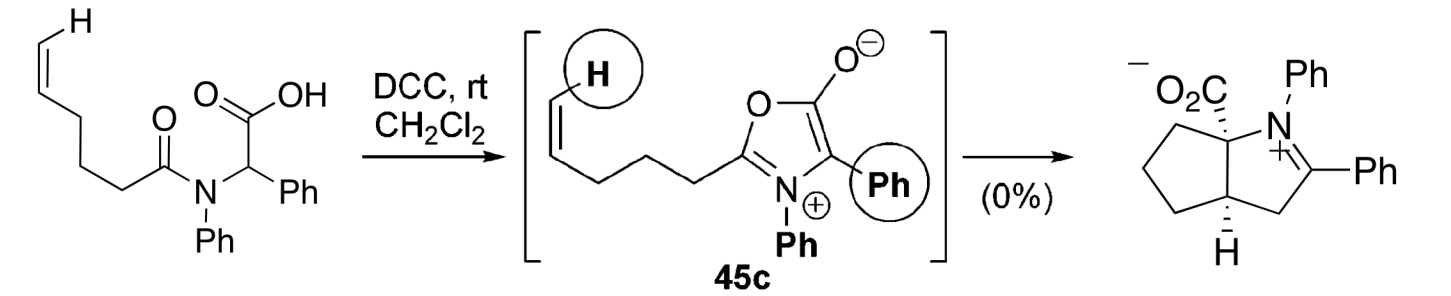
Münchnone formation confirmed by trapping intermediate with DMAD to form pyrrole

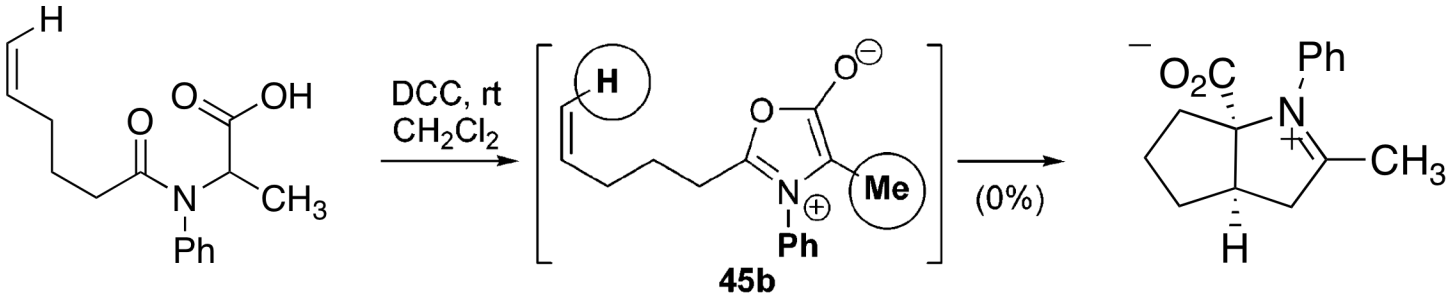
Effects of Substitution on Münchnone



Using phenyl substituent increases reactivity and thermal stability of münchnone

Effects of Substitution on Münchnone





Substituent has little impact on reactivity

Summary/Conclusions

- Two new reaction sequences have been developed that produce novel zwitterionic intermediates
- Münchnones are both activated and stabilized by conjugated substituents
- Starting materials can be easily prepared/purchased, making these convergent reaction sequences useful in specialized synthetic applications