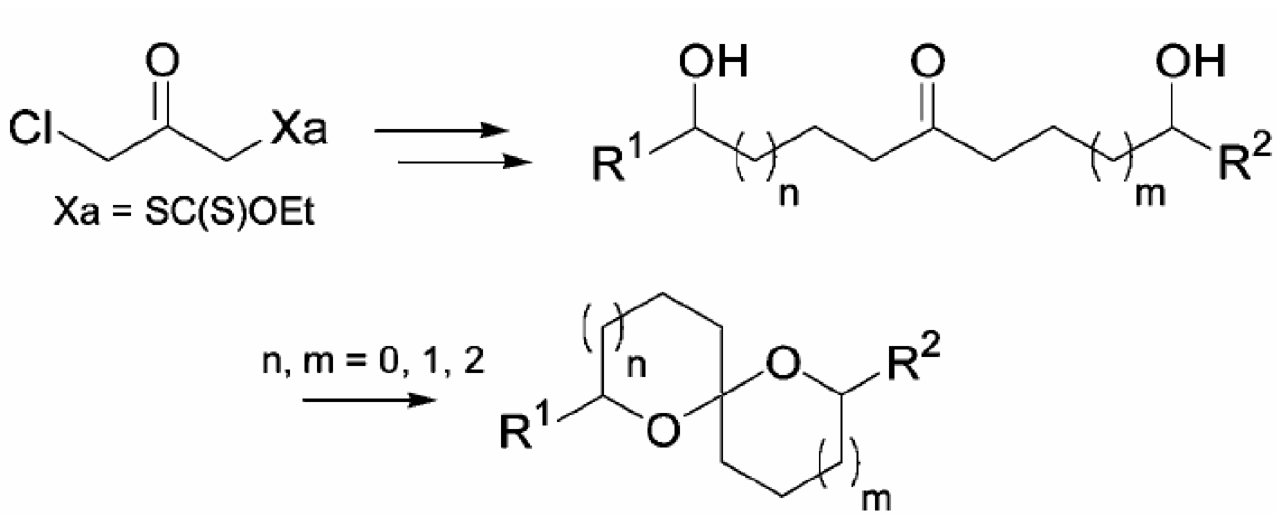
Unified, Radical-Based Approach for the Synthesis of Spiroketals



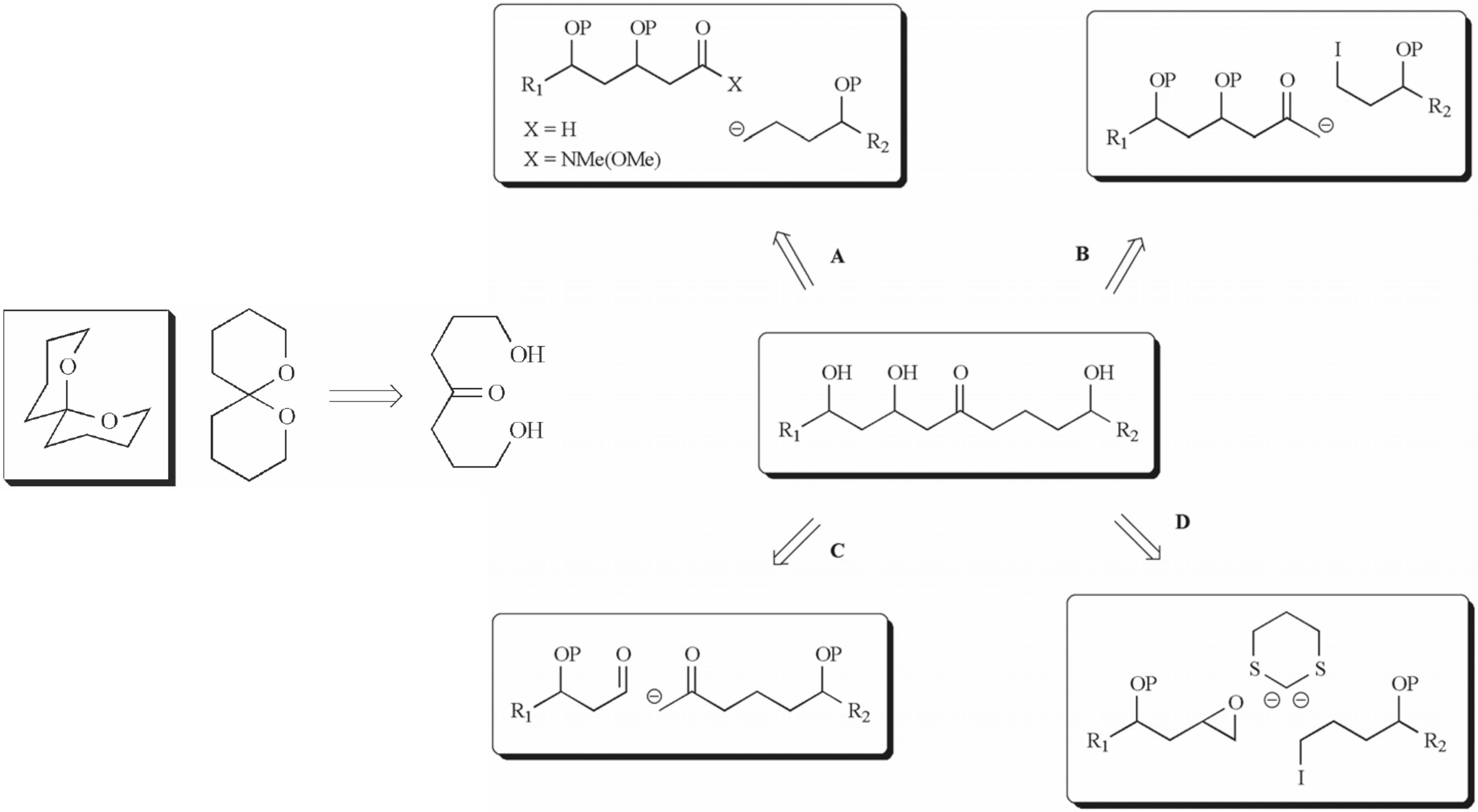
Jennifer Davoren

Current Literature

4/7/2007

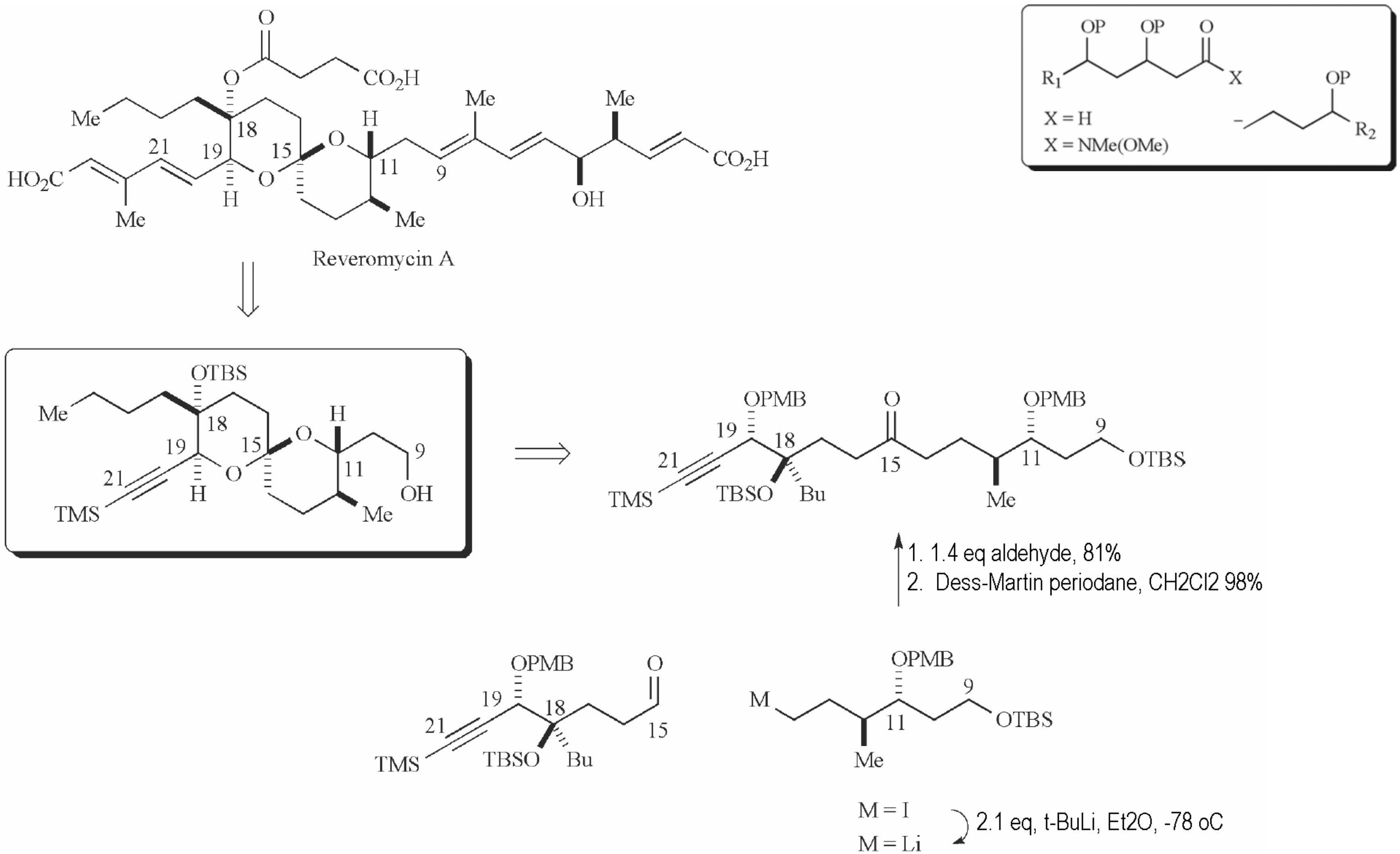
De Greef, M.; Zard, S. Z. *Org. Lett.* **2007**, *9*, 1773-1776.

Commonly Used Strategies for Spiroketal Formation



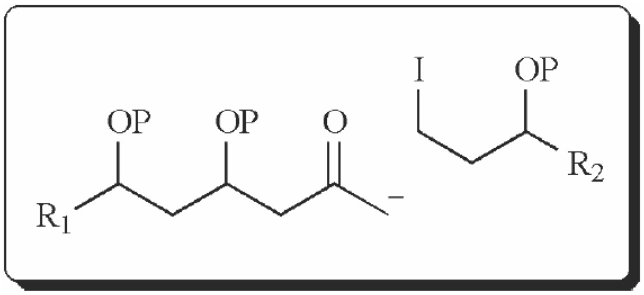
Mead, K. T.; Brewer, B. N. *Curr. Org. Chem.* **2003**, *7*, 227-256

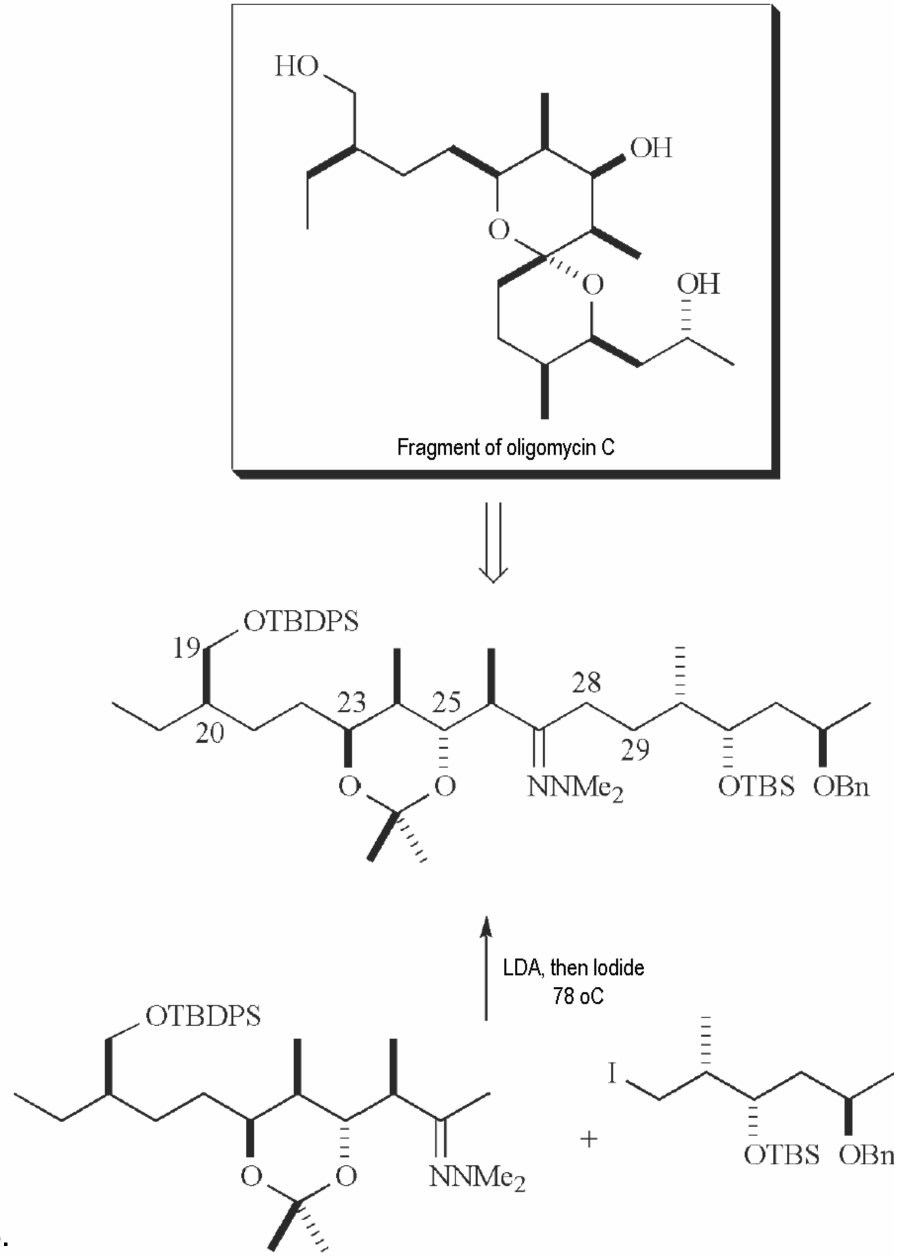
Nucleophilic Attack unto the Spiroketal Carbonyl



Drouet, K. E.; Ling, T.; Tran, H. V.; Theodorakis, E. A. *Org. Lett.* **2000**, *2*, 207-210.

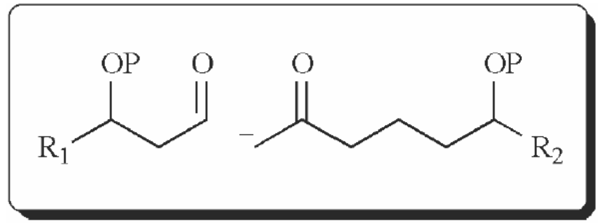
Alpha alkylation of the Spiroketal Carbonyl

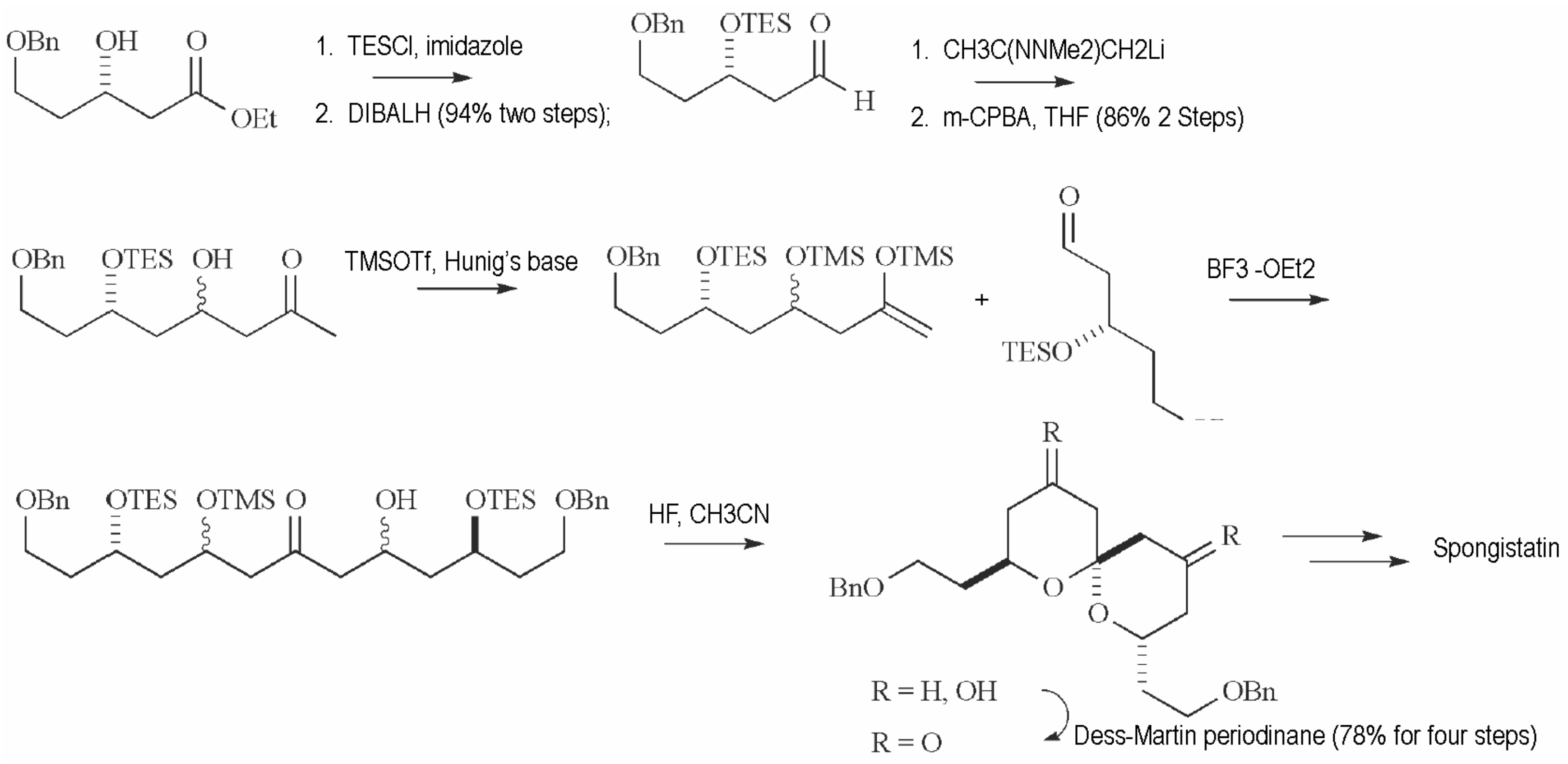




Panek, J. S.; Jain, N. F. *J. Org. Chem.* **2001**, *66*, 2747-2756.

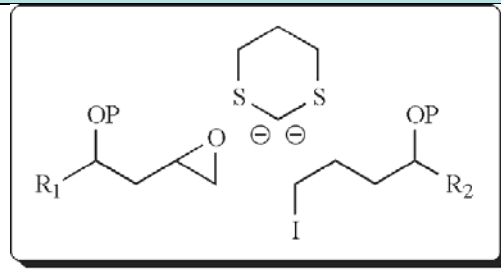
Aldol Reaction Using the Spiroketal Carbonyl as an Enolate

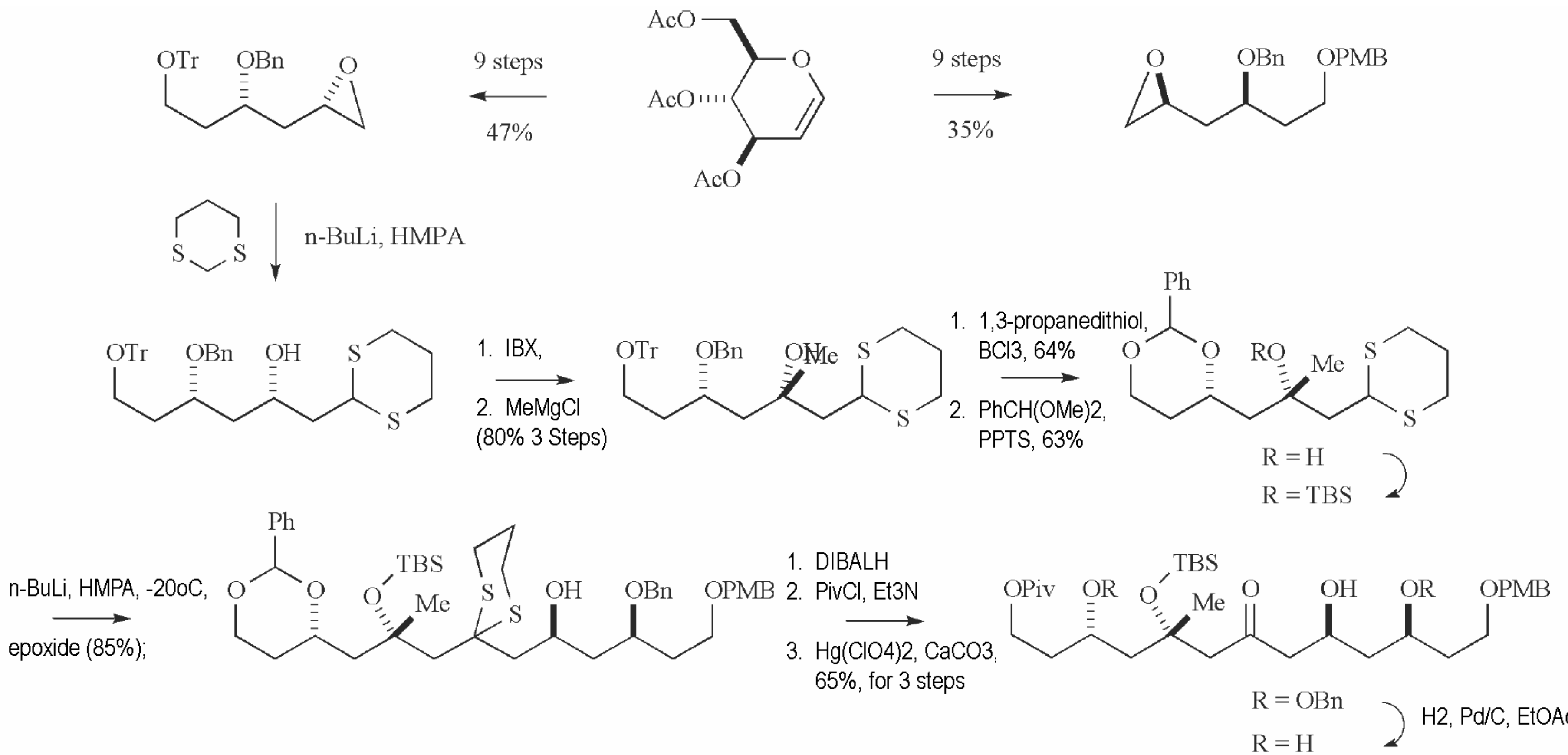




Claffey, M. M.; Hayes, C. J.; Heathcock, C. H. *J. Org. Chem.* **1999**, *64*, 8267-8274.

Use of Dithiane as an Acyl Anion Equivalent

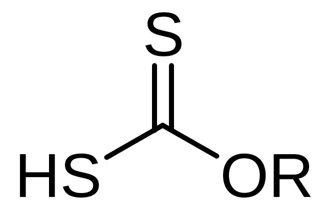




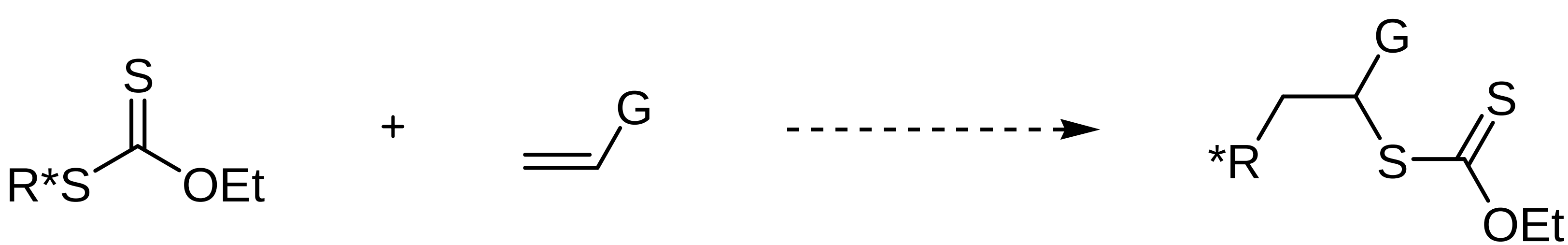
Terauchi, T.; Nakata, M. *Tetrahedron Lett.* **1998**, *39*, 3795-3798.

Radical Addition of Xanthates to Olefins

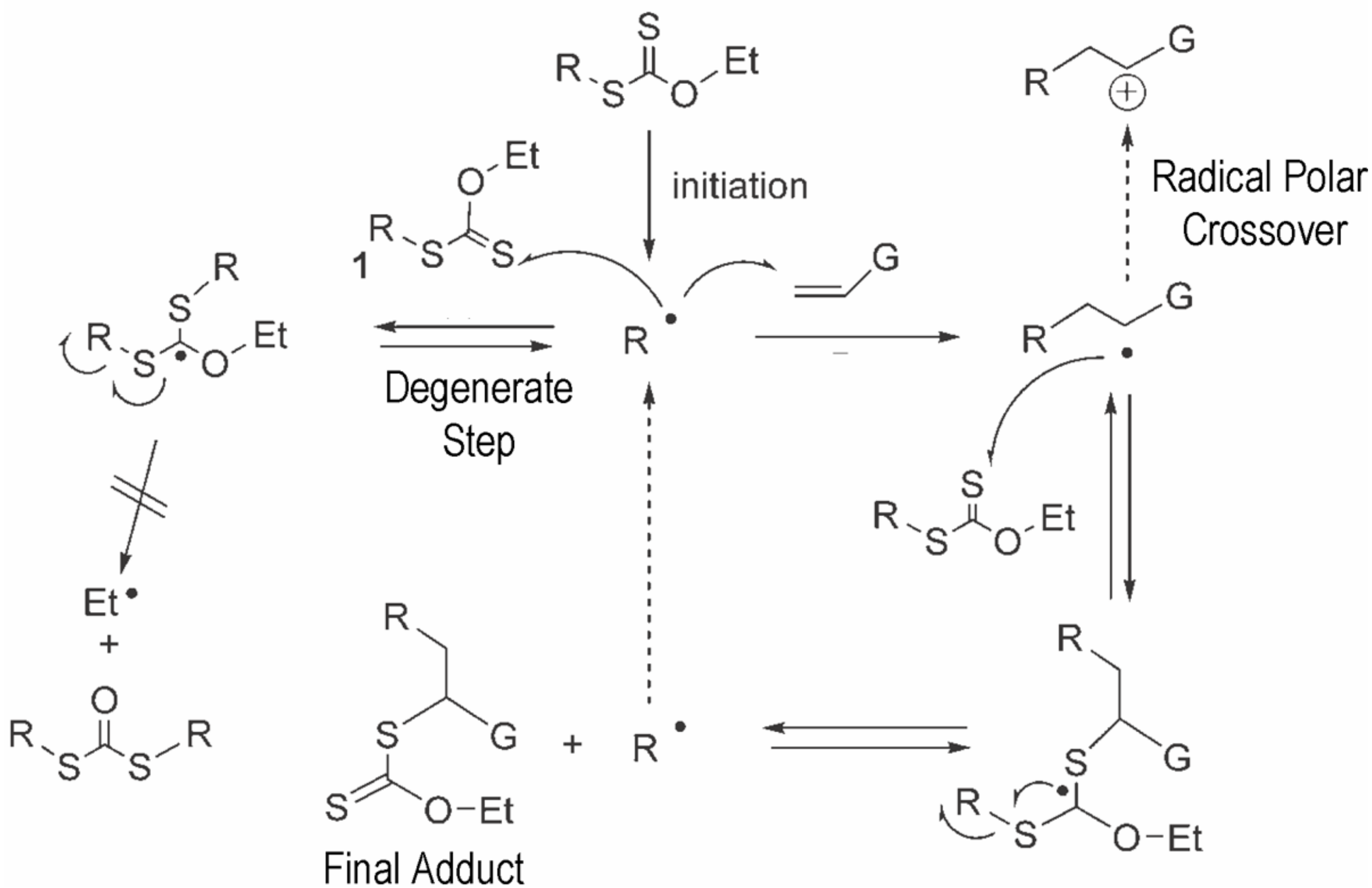
- **Xanthates** are the salts and esters of a xanthic acid, ROC(=S)SH or O-esters of dithiocarbonic acid where R is any organic residue. The ethyl ester $CH_3CH_2OC(=S)SH$ is also the parent compound xanthic acid. Many xanthates have a yellow color, which gives the compound its name derived from *xanthous*, meaning yellow- *Wikipedia*



xanthic acid



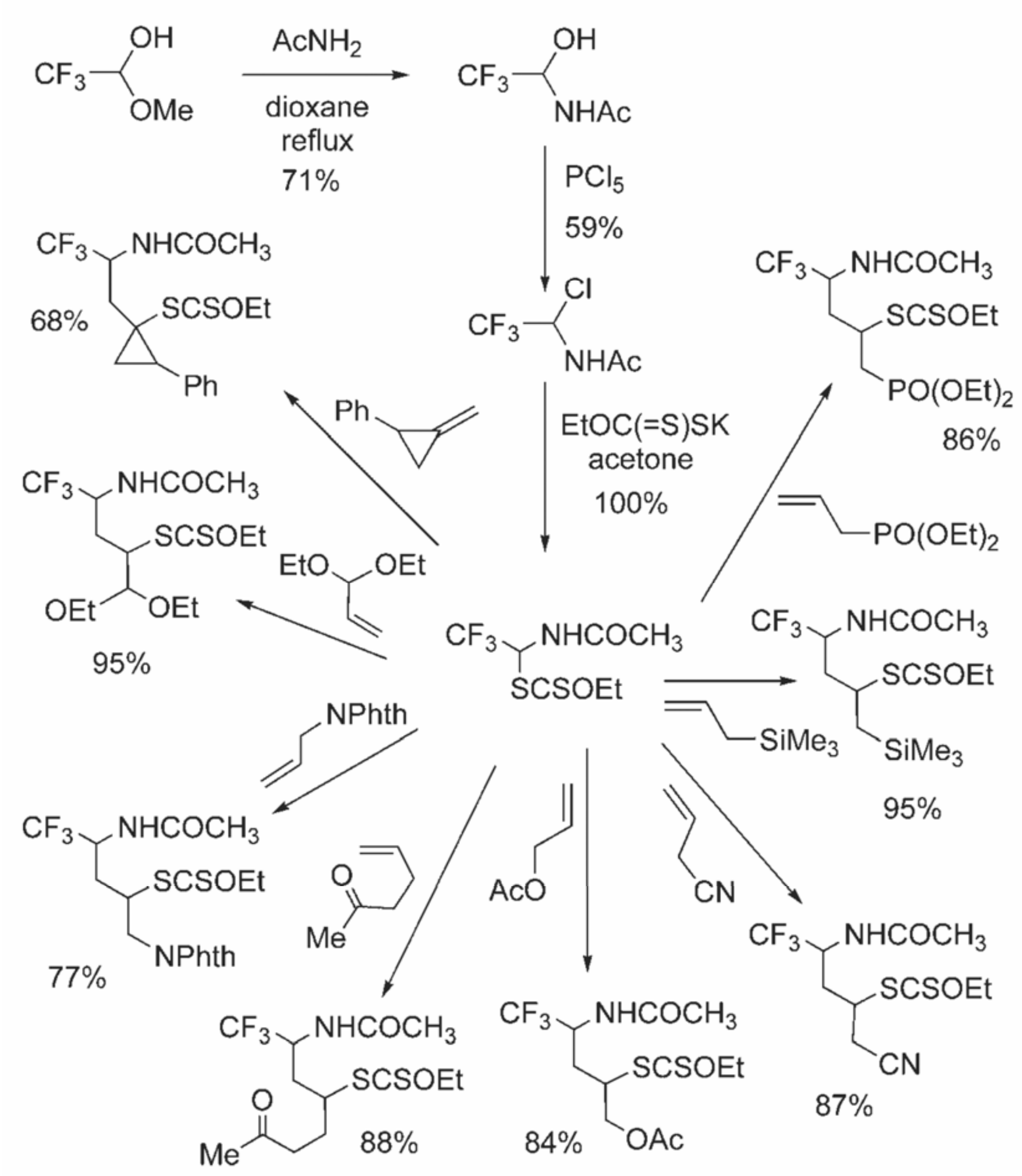
Reaction Manifold for the Addition of Xanthates to Olefins

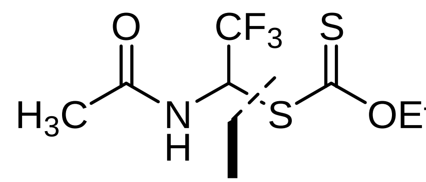


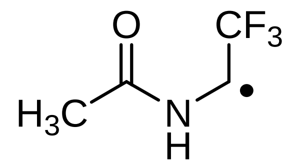
The Xanthate group exerts a powerful regulating influence on the concentration of the various radicals in the medium, scavenging reactive radicals and releasing stabilized radicals

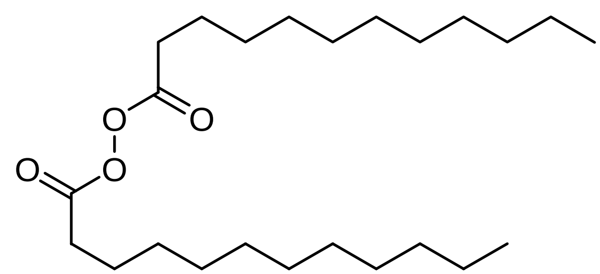
Quiclet-Sire, B.; Zard, S. Z. *Chem. Eur. J.* **2006**, *12*, 6002-6016.

Formation of α-Trifluoromethyl Amines





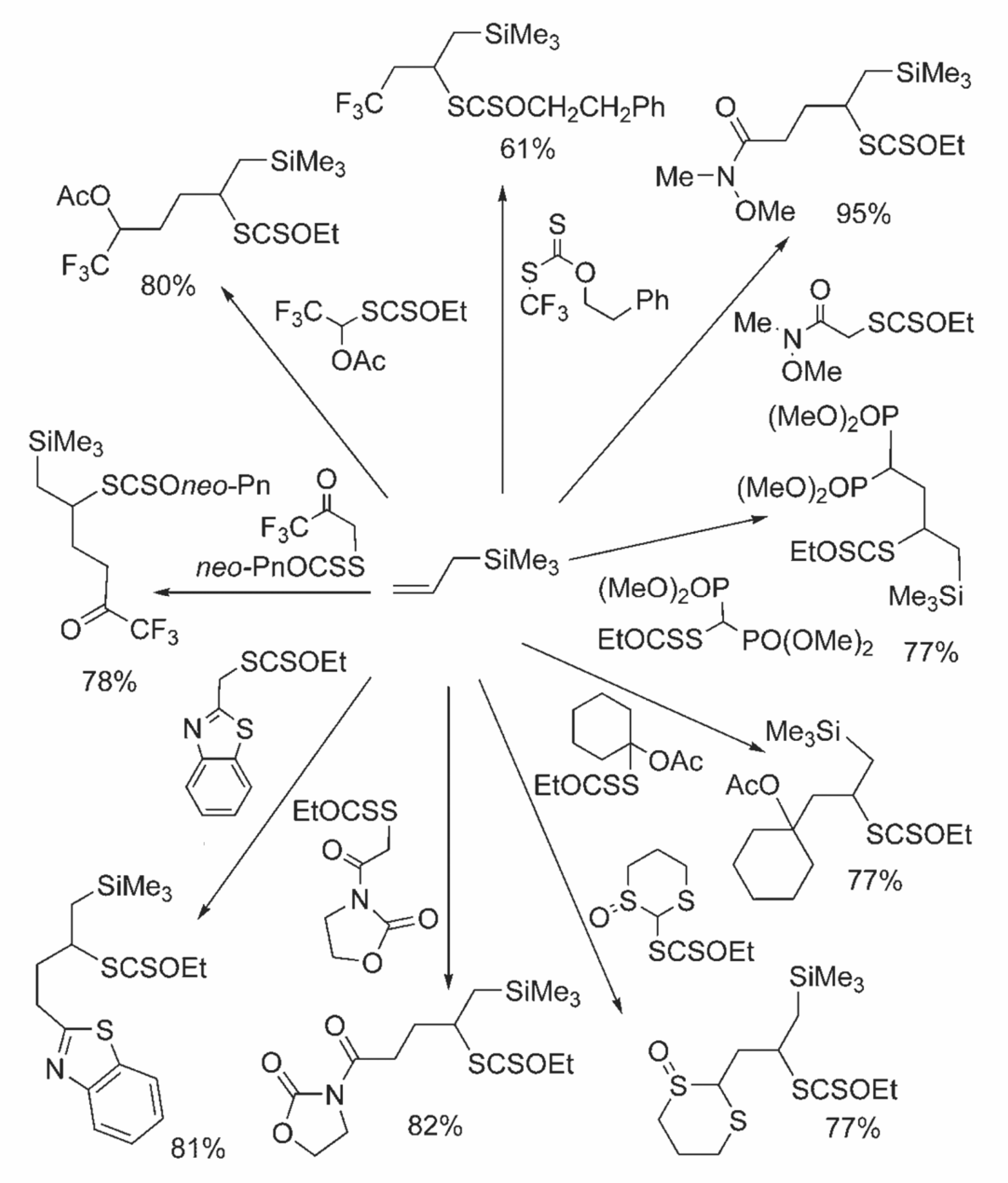
R= 



Conditions:
lauroyl peroxide (2-10 mol%),
$ClCH_2CH_2Cl$, reflux

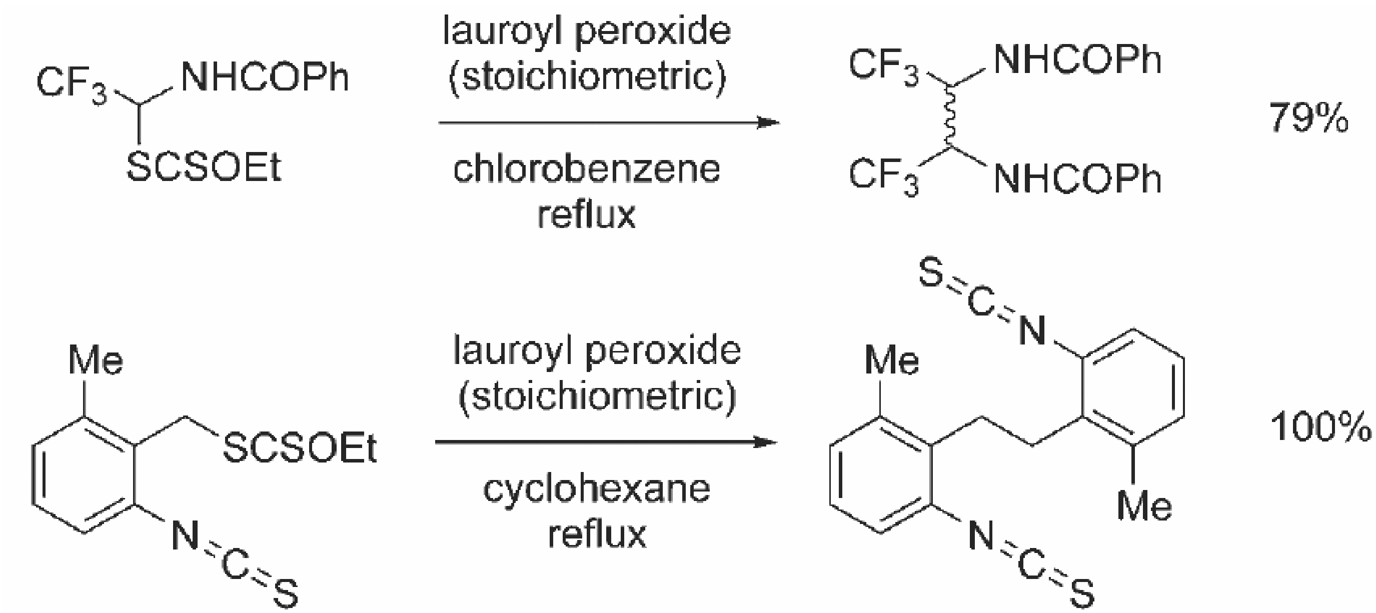
Gagosz, F.; Zard, S. Z. *Org. Lett.* **2003**, *5*, 2655-2657

Radical Additions to Allyl Trimethylsilane



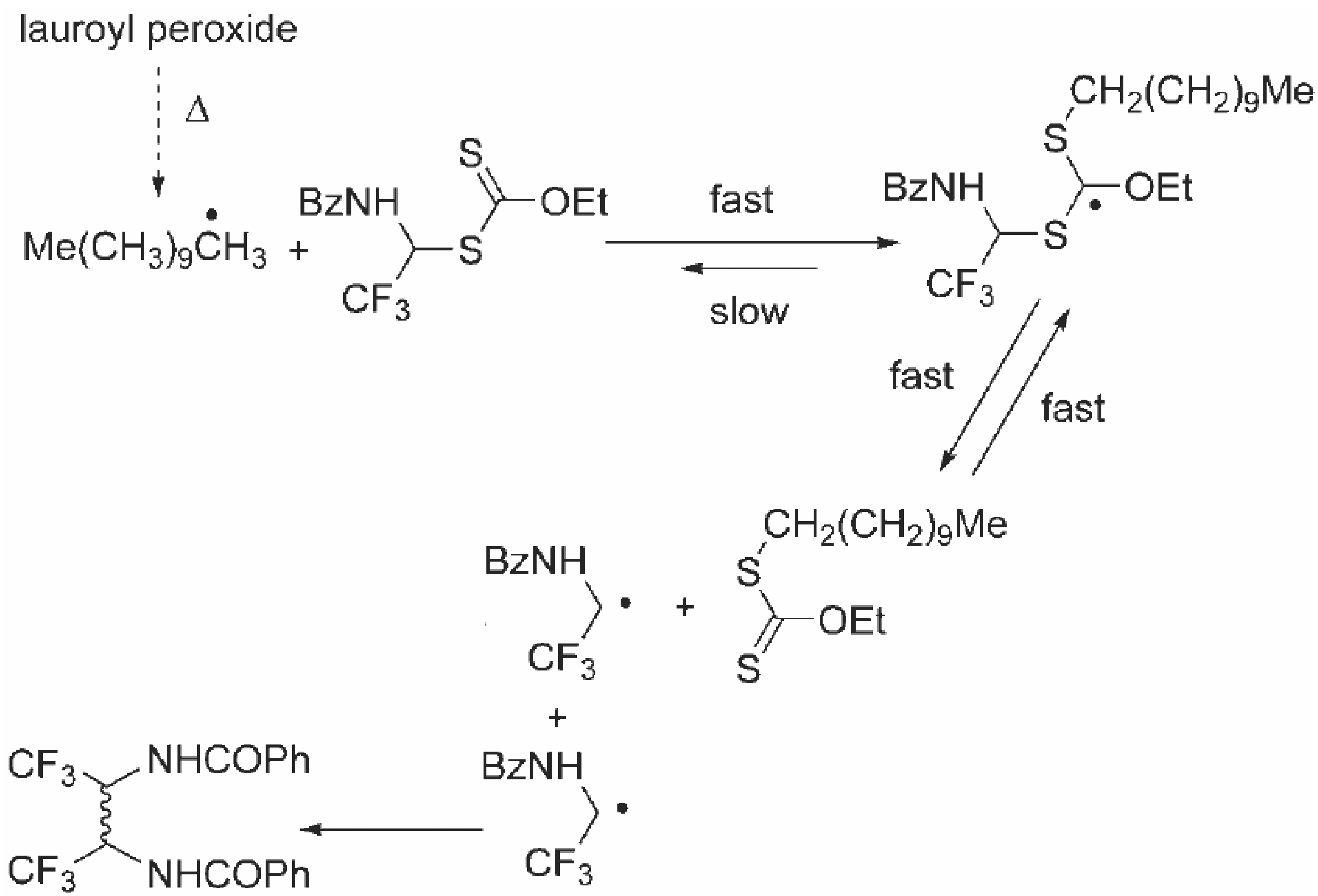
- Reagents are cheap, stable, and readily available
- Convergent and atom economical process
- No heavy metals are involved
- Can be run under high concentrations
- DCE is the most commonly used solvent, but water can also be used
- Peroxides are the most commonly used initiators
- Tolerance of a wide variety of functional groups

Selective Formation of Homodimers

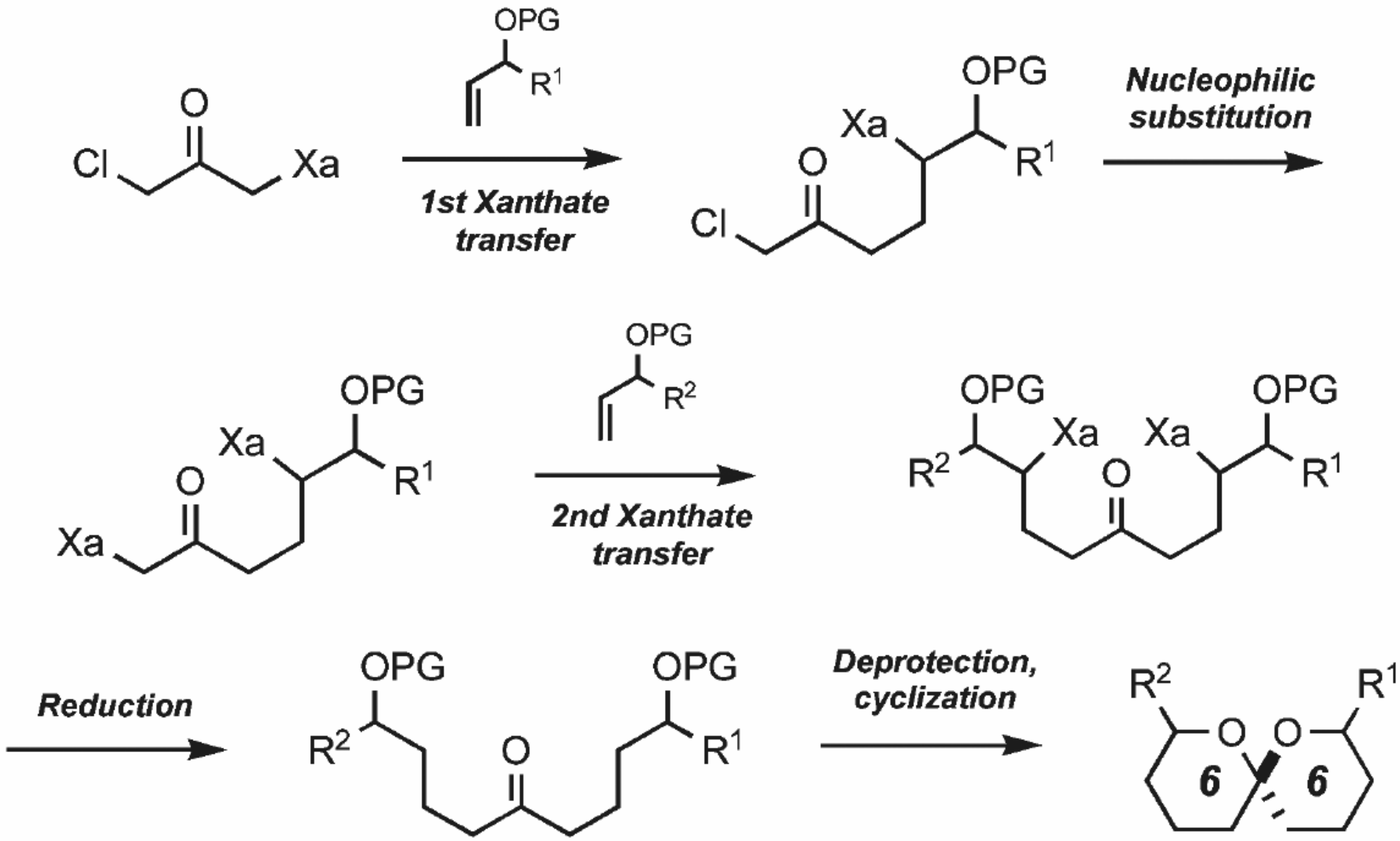


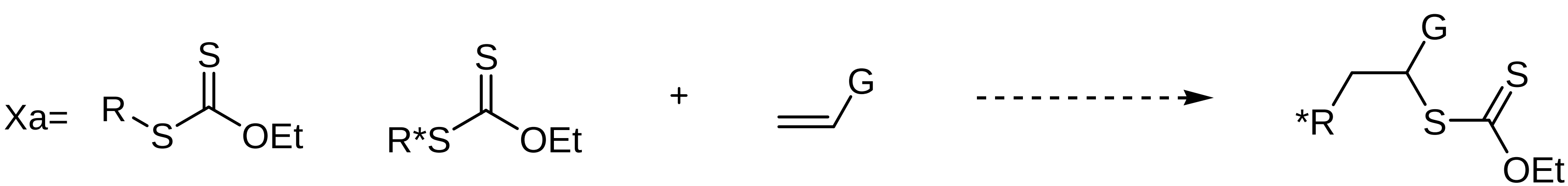
Gagosz, F.; Zard, S. Z. *Org. Lett.* **2003**, *5*, 2655-2657
Alajarin, M.; Vidal, A.; Ortin, M.-M. *Org. Biomol. Chem.* **2003**, *1*, 4282-4292.

Mechanism for the Formation of Homodimers



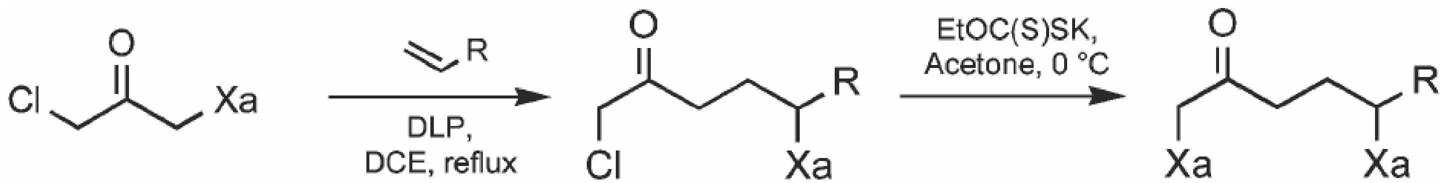
Synthetic Route to Spiroketals

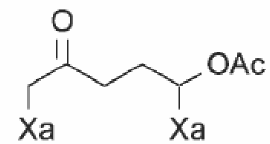
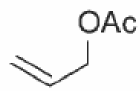
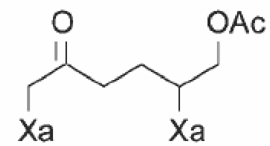
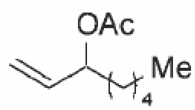
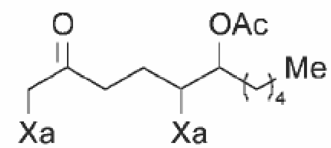
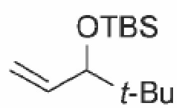
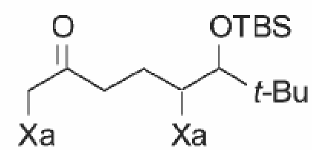
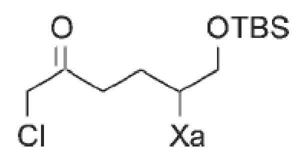




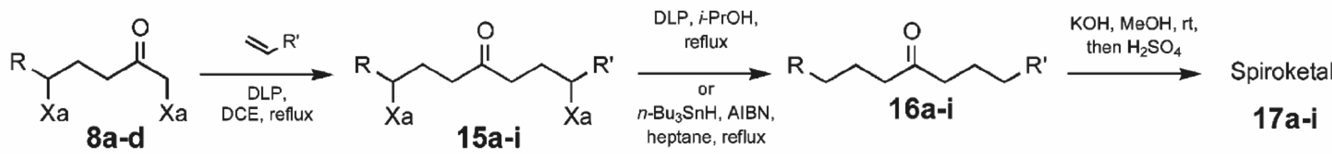
De Greef, M.; Zard, S. Z. *Org. Lett.* **2007**, *9*, 1773-1776.

Additions of Chloroketone Xanthate



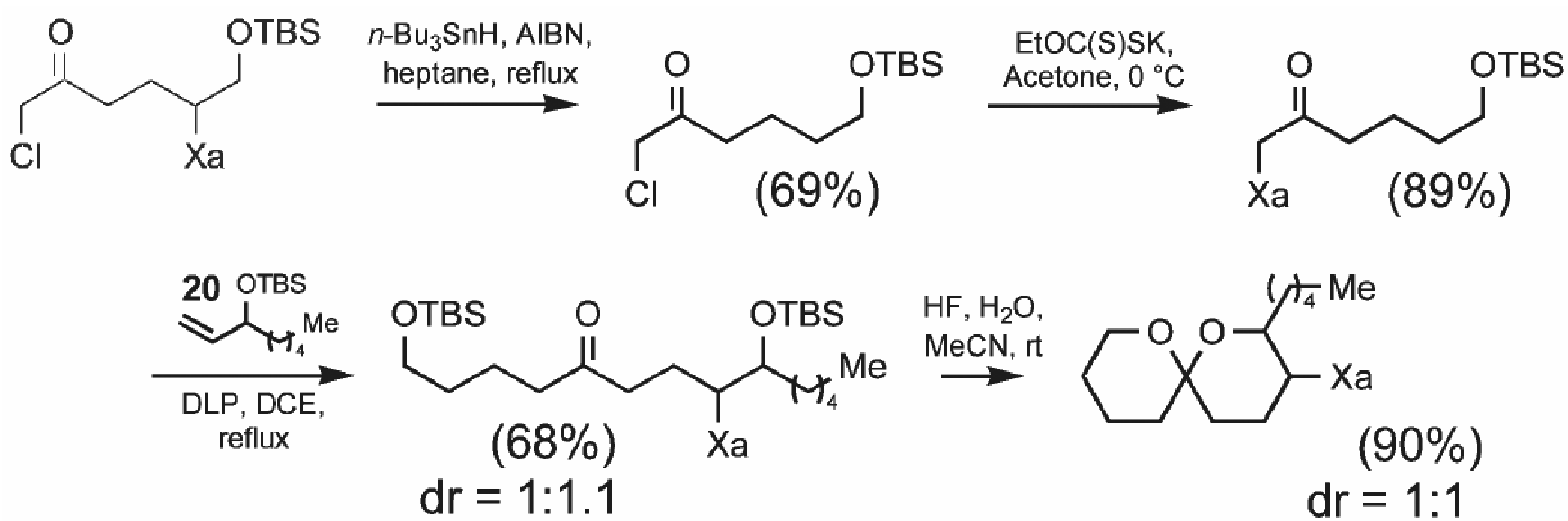
entry	*olefin*	*Product*	*yield (%)*
a			(52%)
b			(80%)
c			(80%) dr = 1:1
d			(54%) dr = 1:3
e			(72%)

Formation of Spiroketals

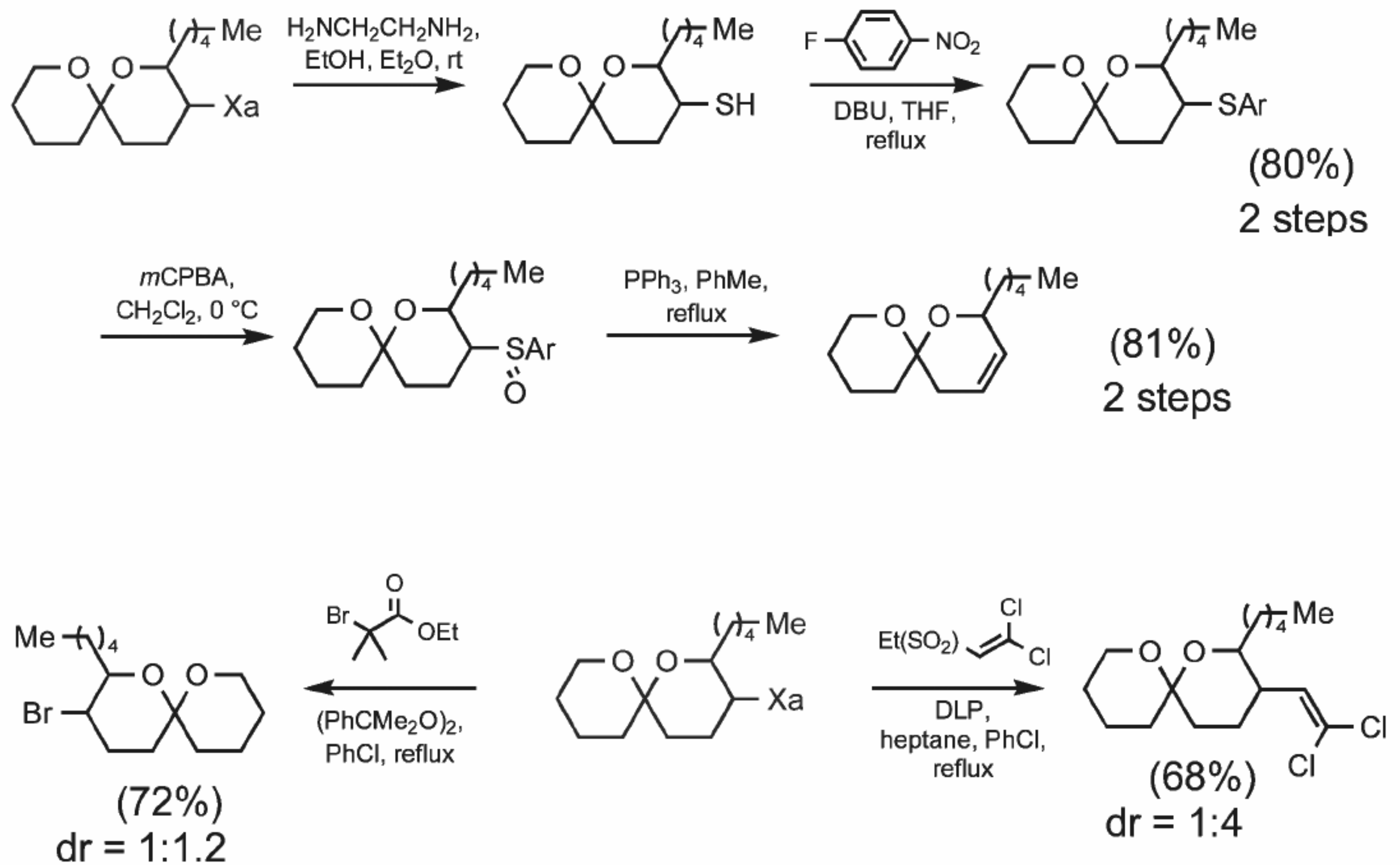


entry	di-xanthate	olefin	15a-i yield (%)[a]	16a-i yield (%)	17a-i yield (%)[b]
a	8b	4	15a (88%)	16a (79%)	17a (71%)
b	8b	9	15b (70%)	16b[c] (R=Ac, 60%) + 16b' (R=H, 25%)	17b (75%)
c	8b	10	15c (82%)	16c[c] (R=Ac, 75%) + 16c' (R=H, 15%)	17c (74%)
d	8b	11	15d (69%)	16d (76%)	17d[d] (61%)
e	8b	12	15e (78%)	16e (84%)	17e (72%)
f	8c	13	15f[e]	16f[f] (58%)	17f (75%)
g	8c	2	15g[e]	16g[f] (50%)	17g (68%)
h	8a	12	15h (57%)	16h (57%)	17h (92%)
i	8d	14	15i (56%)	16i[c] (85%)	17i[f,g] (57%)

Synthesis of a Xanthate Containing Spiroketal



Modification of the Xanthate Group



Conclusions

- A novel route to dihydroxy ketones and hence to spiroketals, which takes advantage of the xanthate transfer reaction
- Synthesis is modular and tolerant of many of the functional groups commonly encountered in modern synthesis
- Allows the concise assembly of spiroketals with various combinations of ring sizes
- Yields are generally good