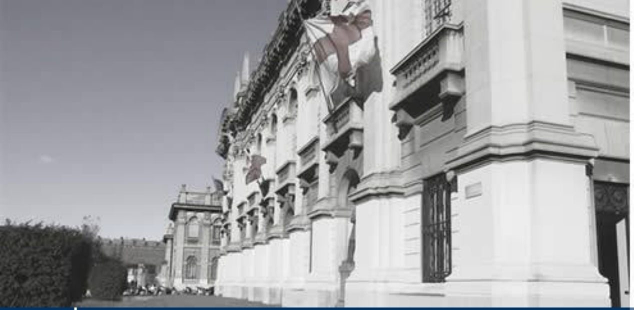


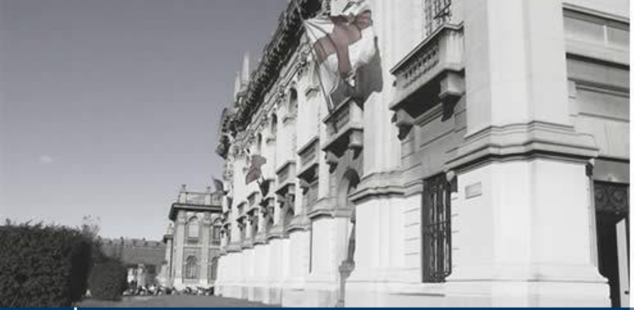
Department CMIC
Lecture 5d – FR5d

POLITECNICO DI MILANO

Free-Radicals:
Chemistry and Biology

Prof. Attilio Citterio
Dipartimento CMIC “Giulio Natta”
http://iscamap.chem.polimi.it/citterio/education/free-radical-chemistry/

Content



POLITECNICO DI MILANO





Radical Oxidation and Reduction
(H-Abstraction and SET Processes)

Prof. Attilio Citterio
Dipartimento CMIC “Giulio Natta”

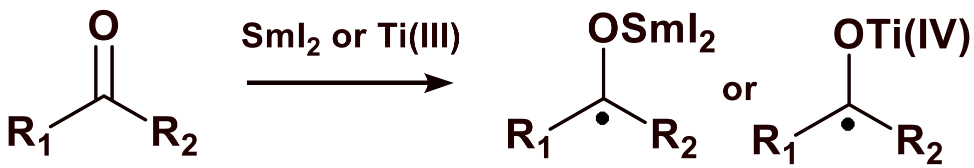
Transition Metals Induced SET Processes

- SmI_2 and Titanocene(III)-mediated radical addition
- Co(I)-catalyzed cross-coupling reaction
- Ti(III)-catalyzed reductive addition and dimerization
- Cu(I)-catalyzed atom transfer reaction
- Mn(III) and Fe(III)-promoted oxidative radical reaction
- Ce(IV)-promoted oxidative radical reaction

Generation of the Radical by SET Process

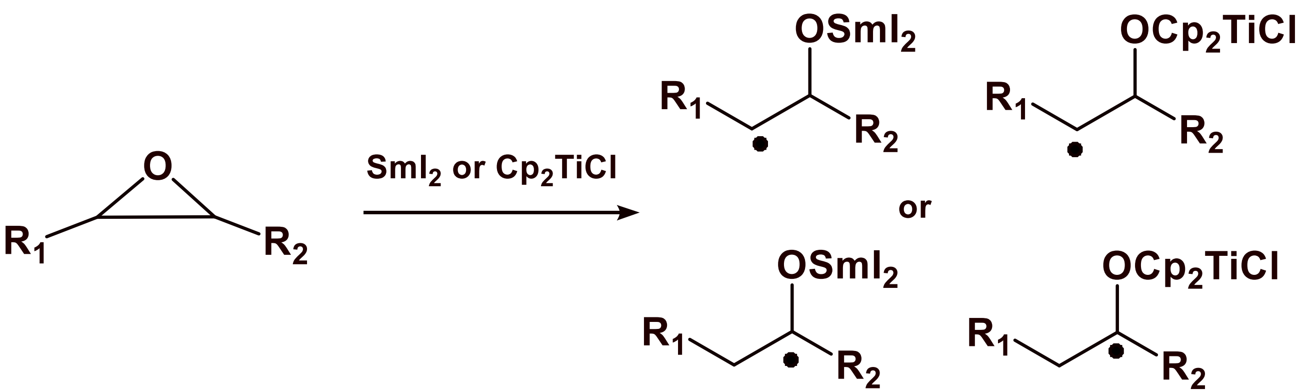
- $R^1\text{-}X + Sm(II) \text{ or } Ti(III) \rightarrow R^{1\bullet} + Sm(III)X^{2+} \text{ or } Ti(IV)X^{3+}$

1. Ketyl Radical Generated from Carbonyl Group



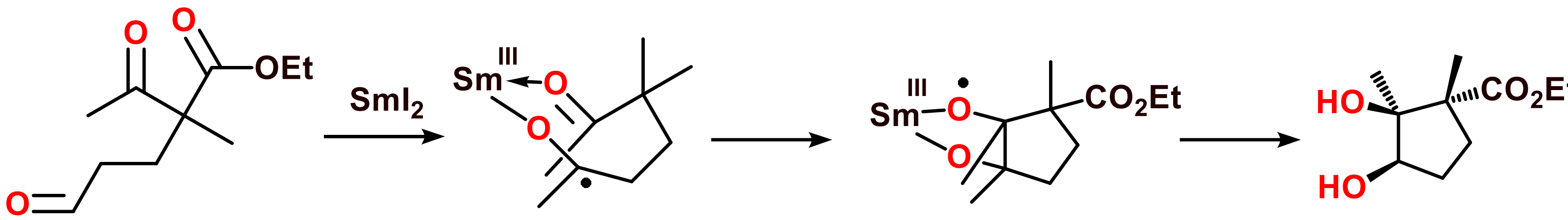
Ketyl Radical

2. β-Radical Generated from Epoxide



Ketyl Radical Generated from Carbonyl Group

- ***SmI_2 Mediated Pinacol Coupling***

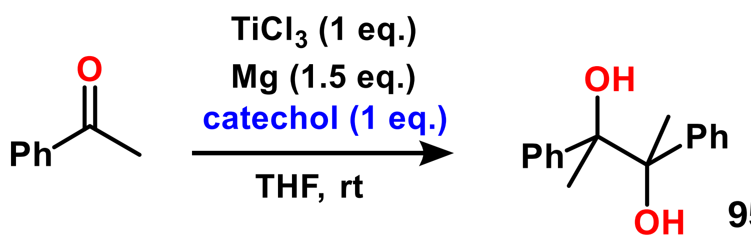


77%. dr 200:1

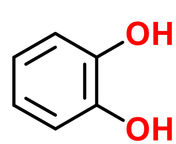
Procter, D. J.; Edmonds, D. J.; Johnston, D.; Chem. Rev. 2004, 104, 3371

- ***Ti Mediated Pinacol Coupling***

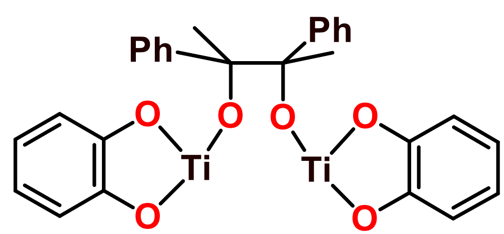
McMurry Reaction



95%

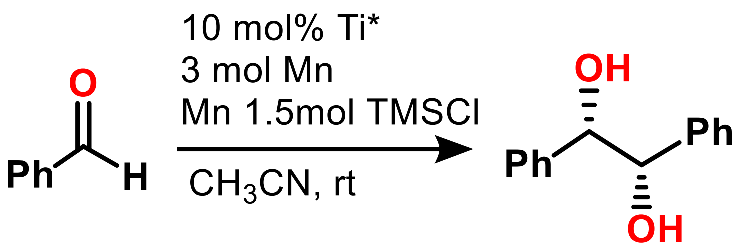


catechol

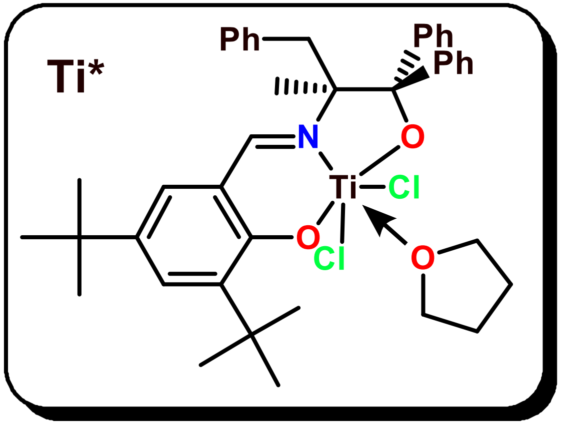


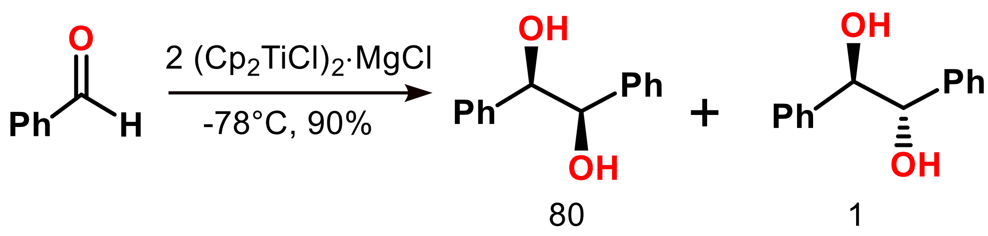
Banerji, A.; Balu, N.; Nayak, S. K.; *J. Am. Chem. Soc.* **1996**, *118,* 5932

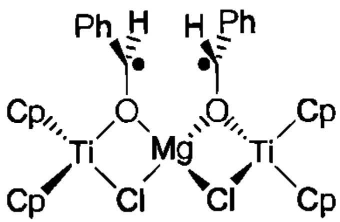
Titanocene(III)-Catalyzed Enantioselective Pinacol Coupling



(S,S) 94%, *dl:meso* = 96:4, ee 63%







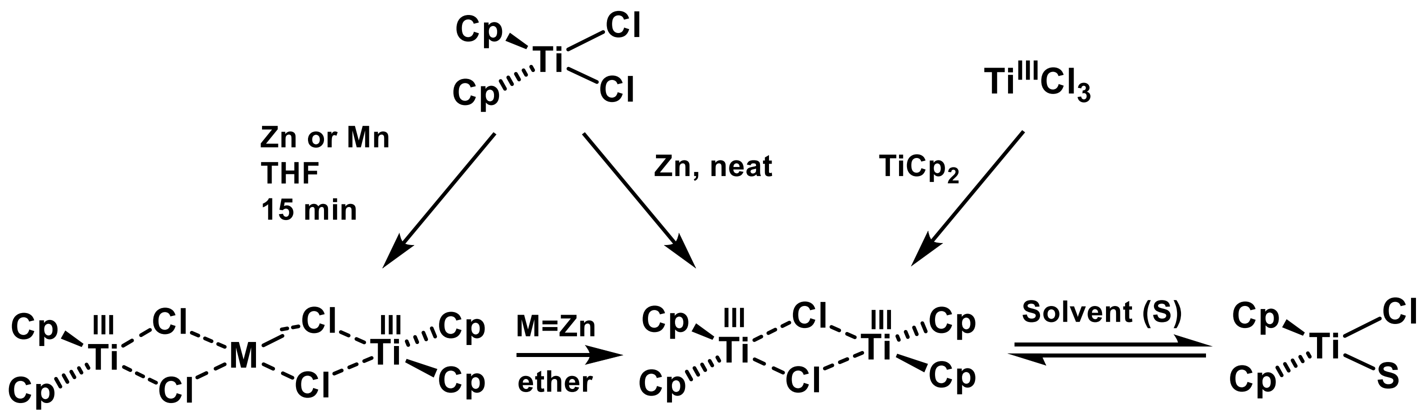
Proposed intermediate leading to high diastereoselectivity.

X-ArCHO, RCH=CHCHO, furyl-CHO

Riant, O.; Bensari, A.; Renaud, J.-L.; *Org. Lett.* **2003**, *5*, 3395

Y. Handa, J. Inanaga, *Tetrahedron Lett*. **1987**, *28*, 5717.

Preparation of Cp_2TiCl

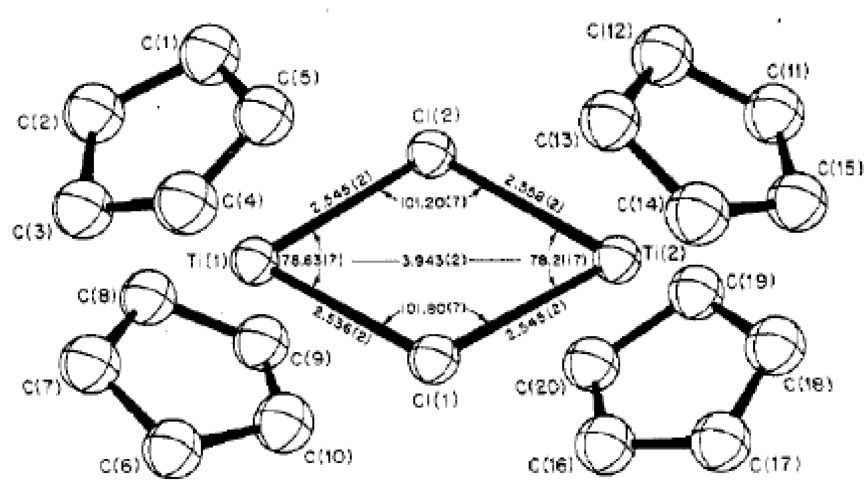


Ti(III): [Ar] $3d^1$

Cp_2TiCl generated by *in situ* reduction with Mn or Zn.

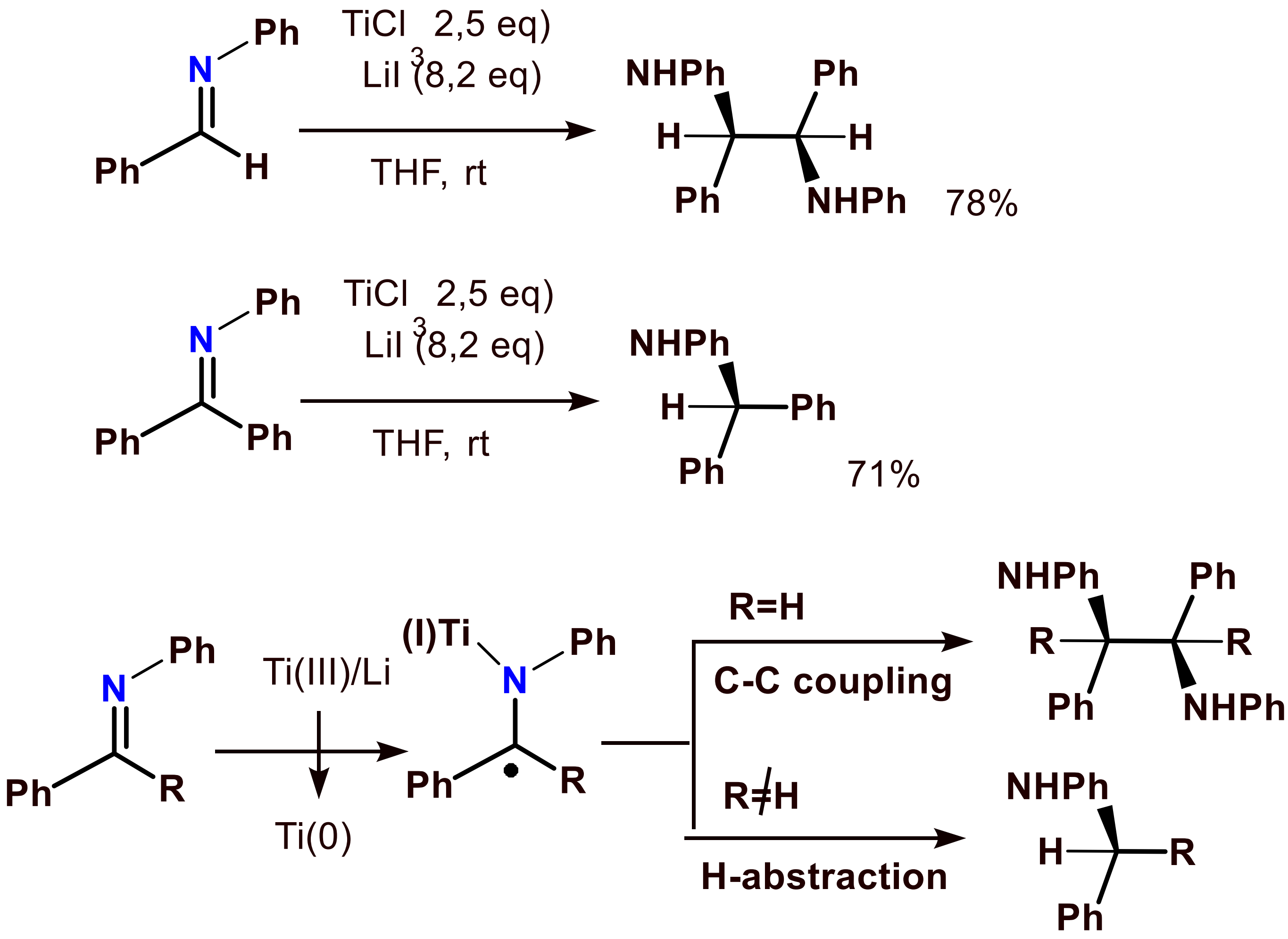
Both dimer and trimer work equally well in most cases.

In situ regeneration of Ti(III) possible allowing it to function catalytically.



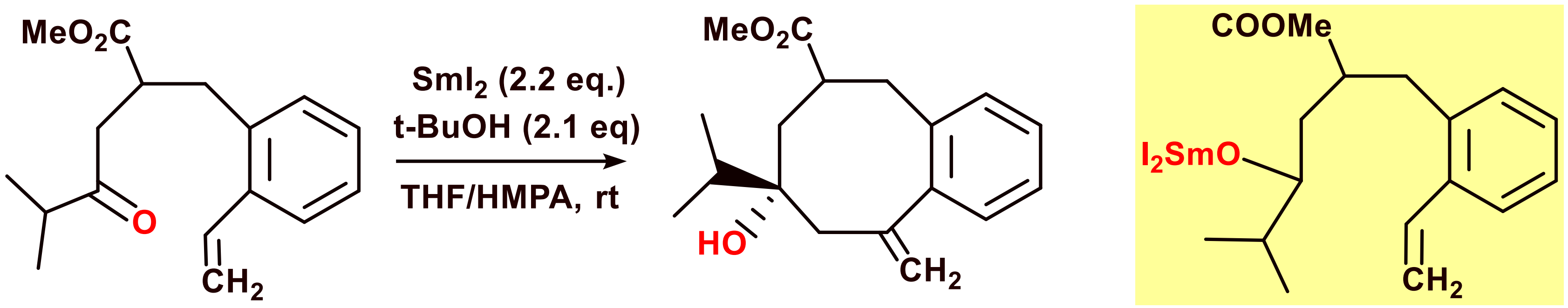
R. Jungst; D. Sekutiwski; J. Davis; M. Luly; G. Stucky, *Inorg. Chem*. **1977**, *16*, 1645.

Titanocene Mediated Imino-Pinacol Coupling

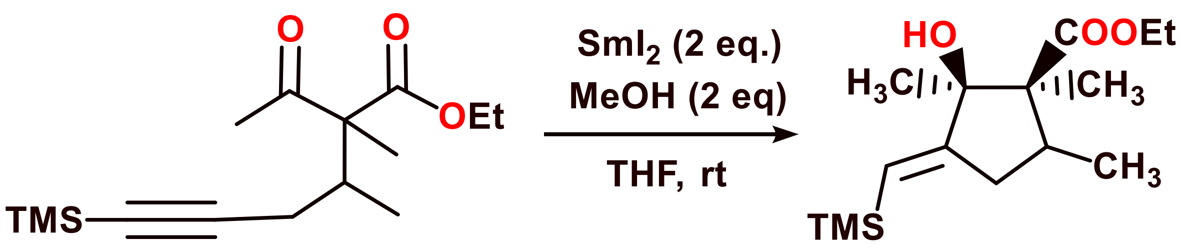


Banerji, A.; Talukdar, S.; *J. Org. Chem.* **1998,** *63,* 3468

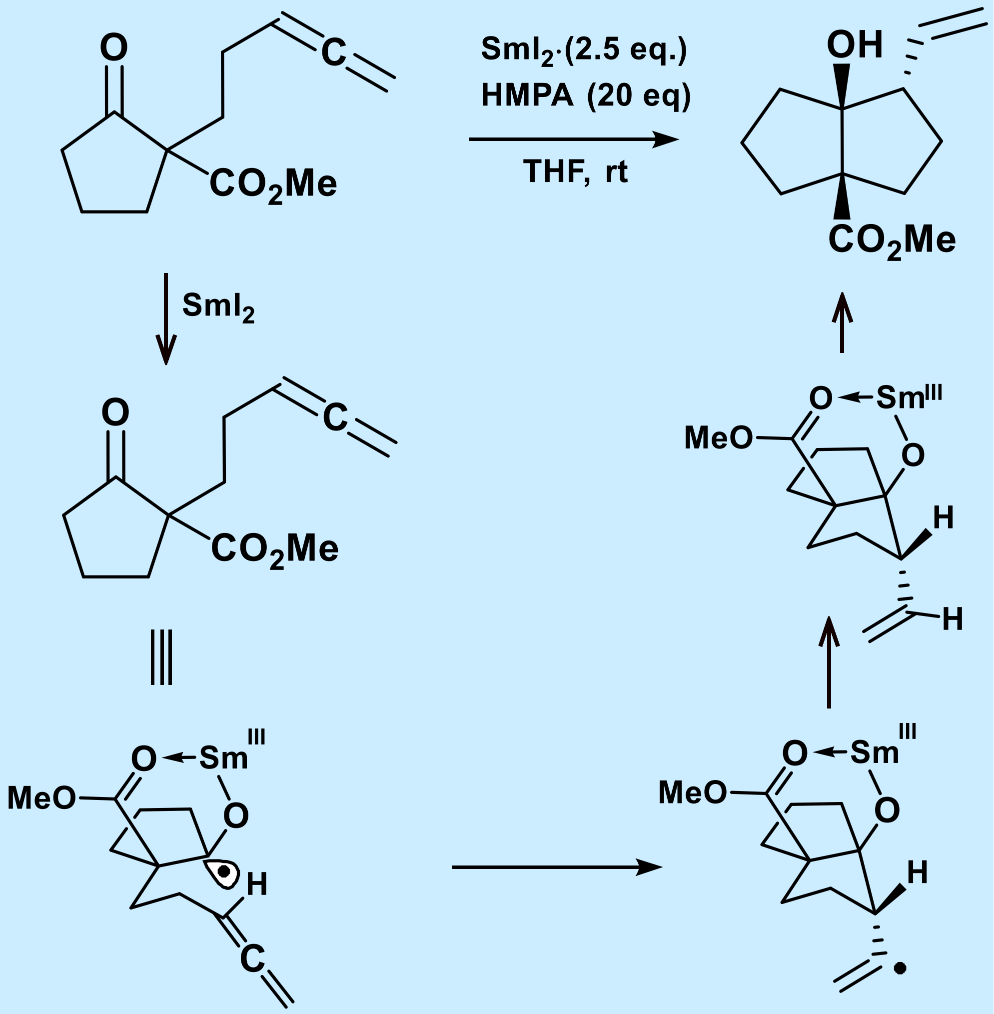
Ketyl Reductive Coupling with Alkene, Alkyne



Reissig, H.-U.; Dinesh, C. U.; *Angew. Chem. Int. Ed.* **1999**, *38*, 789



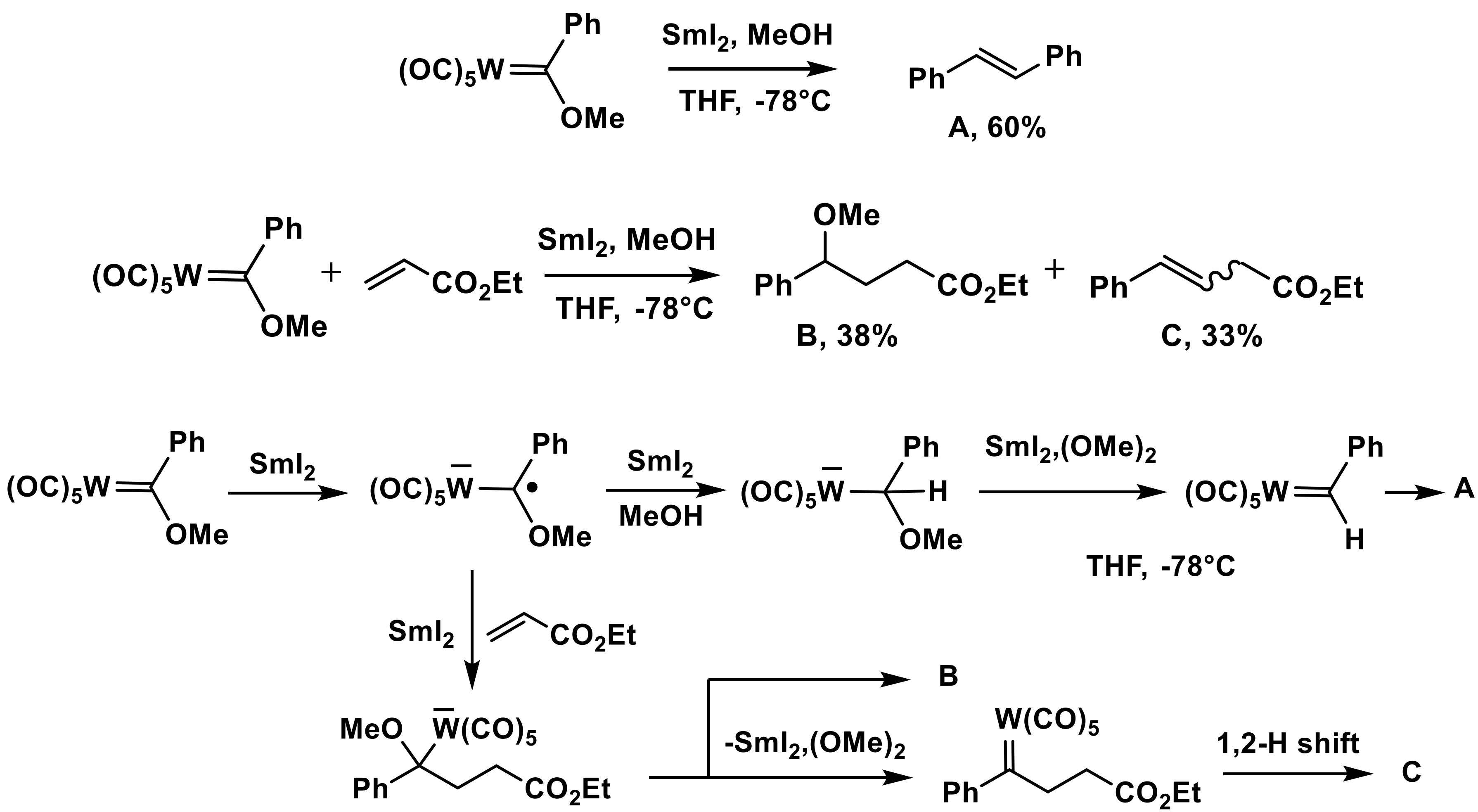
Molander, G. A.; Kenny, G.; *J. Am. Chem. Soc.* **1989**, *111*, 8236



68%, dr > 95:5

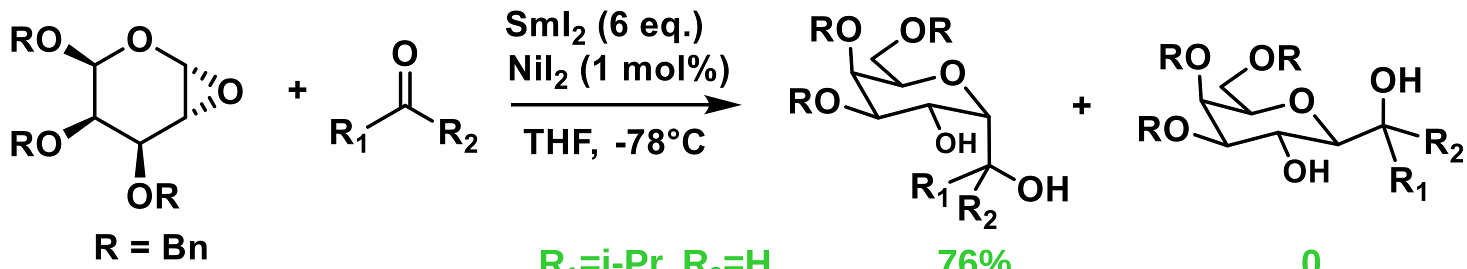
Molander, G. A.; Cormier, E. P.;
J. Org. Chem. **2005**, *70*, 2622

One-Electron Reduction of Fischer-Type Carbene

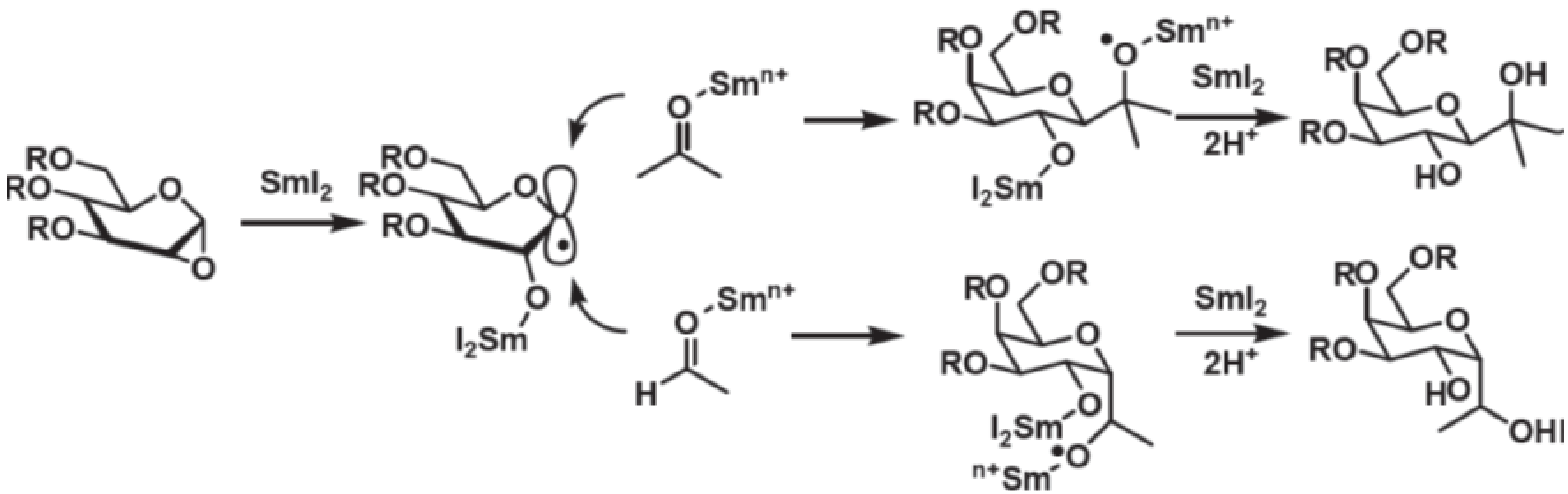


Iwasawa, N.; Fuchibe, K.; *Org. Lett.* **2000**, *2*, 3297

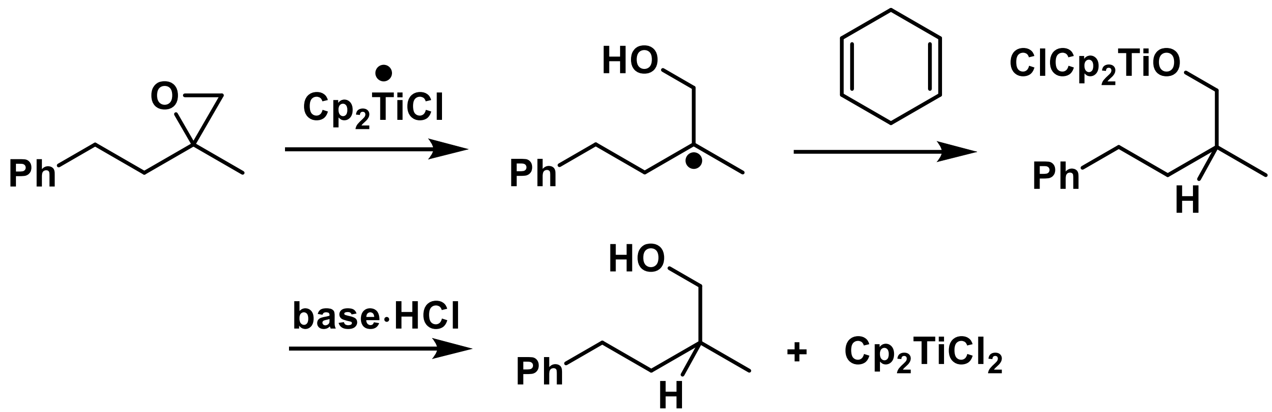
Coupling of Epoxide and Carbonyl Compounds

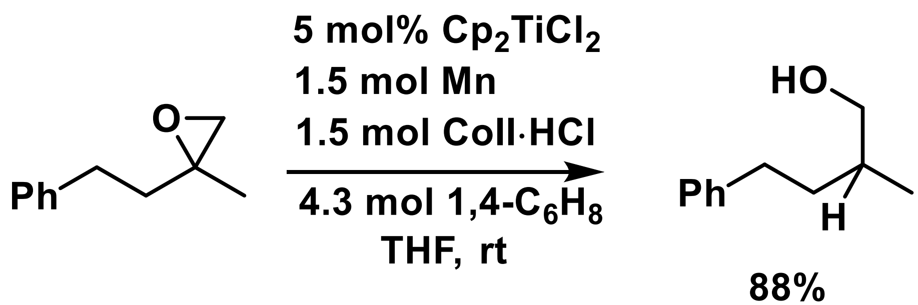


R_1=i-Pr, R_2=H,	76%	0
R_1=R_2=Me	0	70%



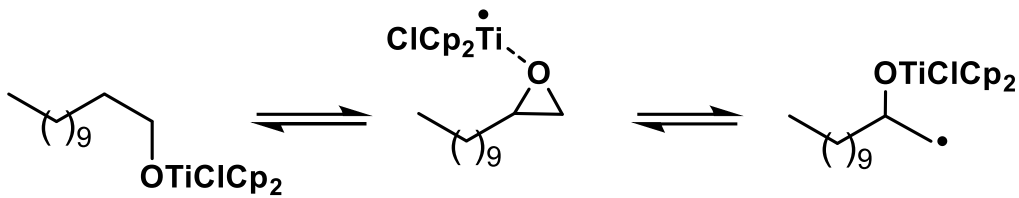
Chiara, J. L.; Sesmilo, E.; *Angew. Chem., Int. Ed.* **2002**, *41*, 3242

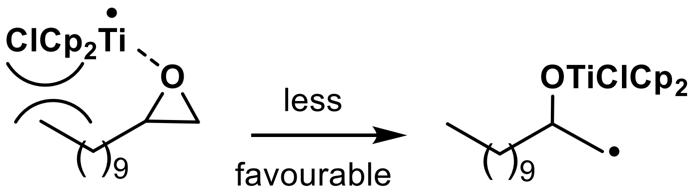




Gansäuer, A.; Bluhm, H.; Pierobon, M.; *J. Am. Chem. Soc.* **1998,** *120,* 12849

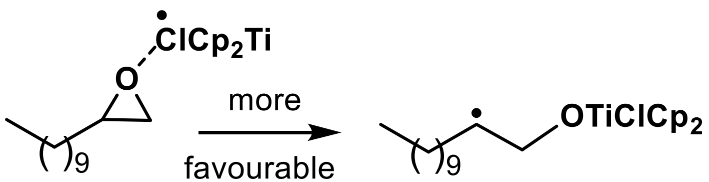
Mechanism of Epoxide Opening

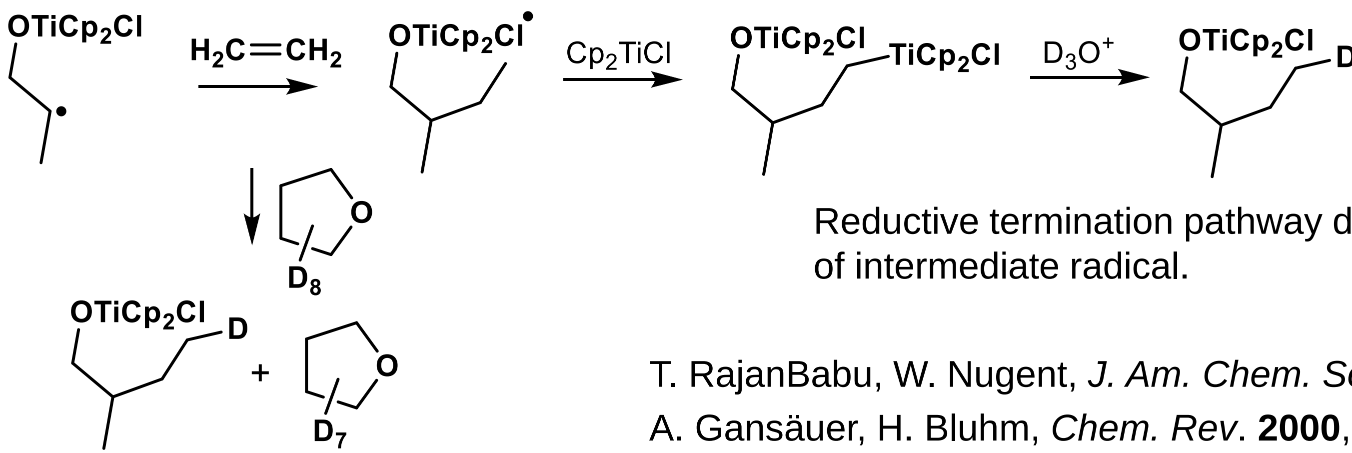




Product ratios show higher substituted radical formed.

Titanium attached to radical it created--reagent control.



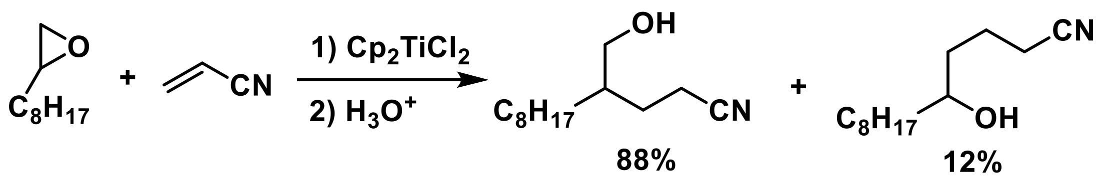


Reductive termination pathway depends on reactivity of intermediate radical.

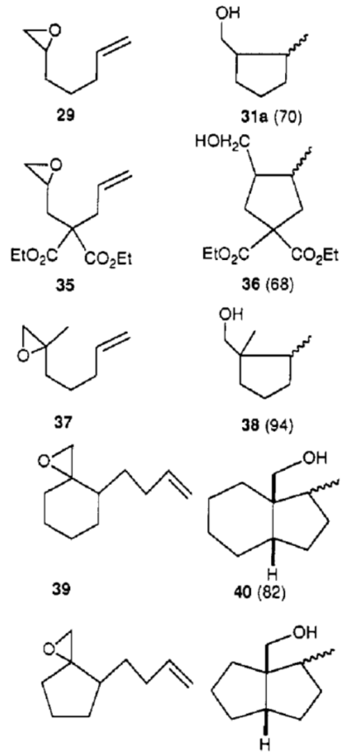
T. RajanBabu, W. Nugent, *J. Am. Chem. Soc*. 1994, 116, 986.

A. Gansäuer, H. Bluhm, *Chem. Rev*. **2000**, *100*, 2771.

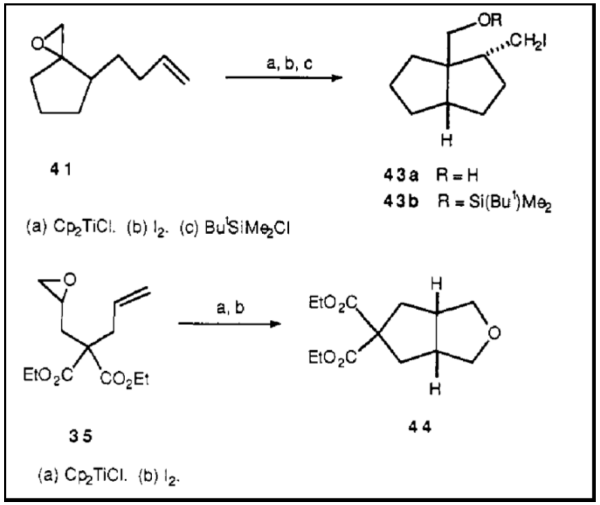
Epoxide Opening and Trapping



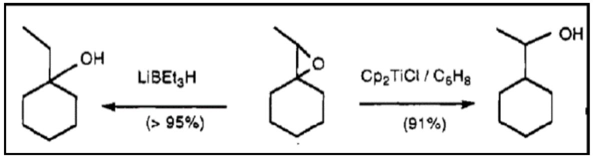
Radical formation at the higher substituted carbon.



entry	epoxide	product (% yield)	isomer ratio
1	29	31a (70)	cis/trans 2:1
2	35	36 (68)	cis/trans 85:15
3	37	38 (94)	cis/trans 1:1
4	39	40 (82)	endo/exo 55:45
5	41	42 (88)	endo/exo 90:10



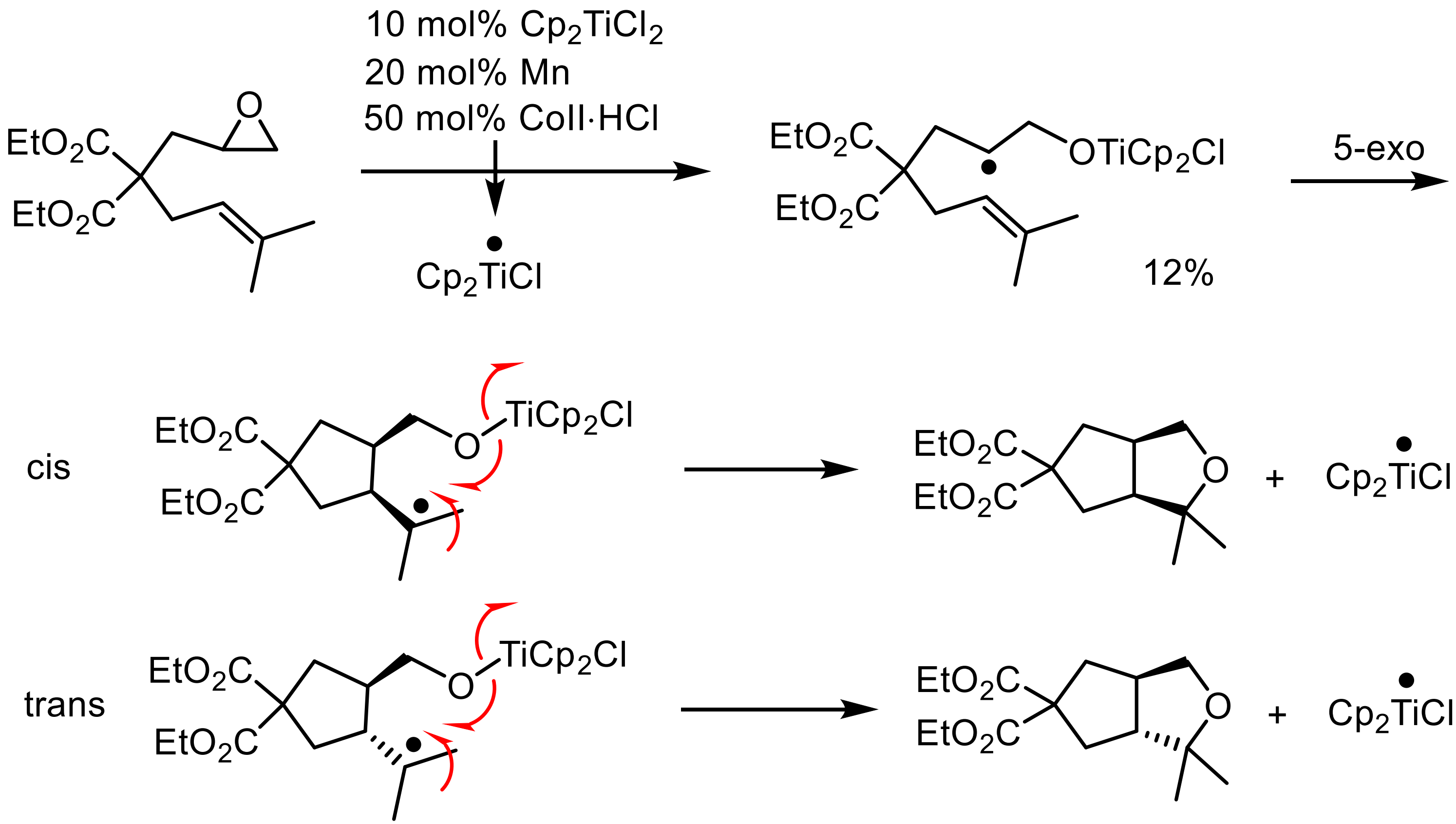
Electrophilic workup



Complementary to nucleophilic epoxide opening

T. RajanBabu, W. Nugent, *J. Am. Chem. Soc*. **1994**, *116*, 986.

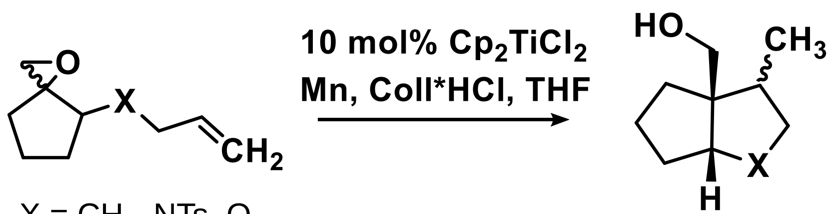
Cp_2TiCl Tandem Reaction with Homolytic Cleavage of a Ti-O Bond



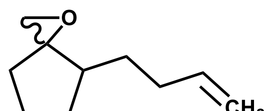
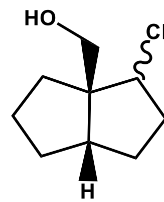
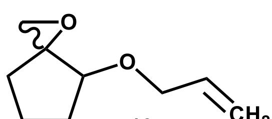
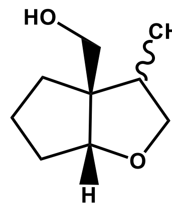
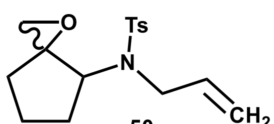
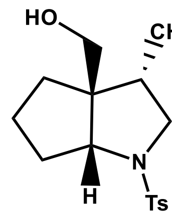
y: 66% *cis:trans*=100:0

Gansäuer, A.; Rinker, B.; Pierobon, M. N.; *Angew. Chem., Int. Ed.* **2003**, *42*, 3687

Diastereoselectivity in 5-Member Ring Formation

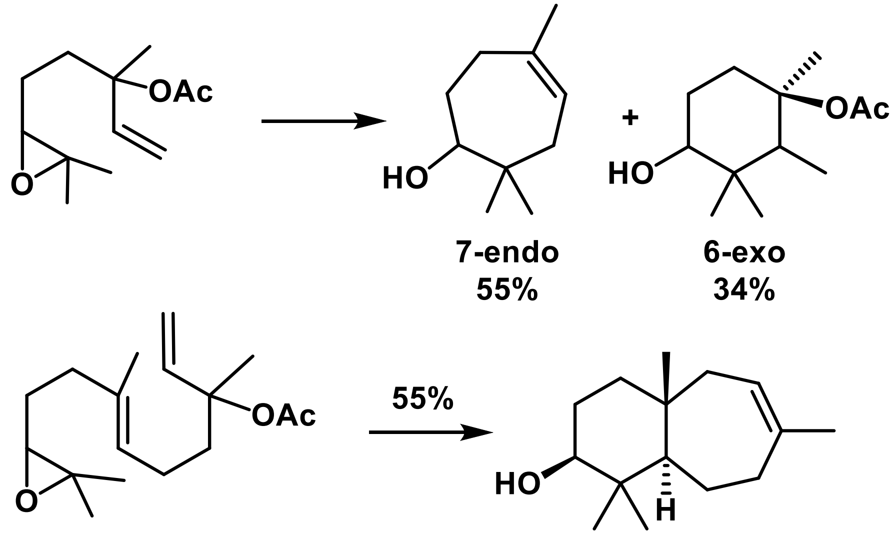


X = CH_2, NTs, O

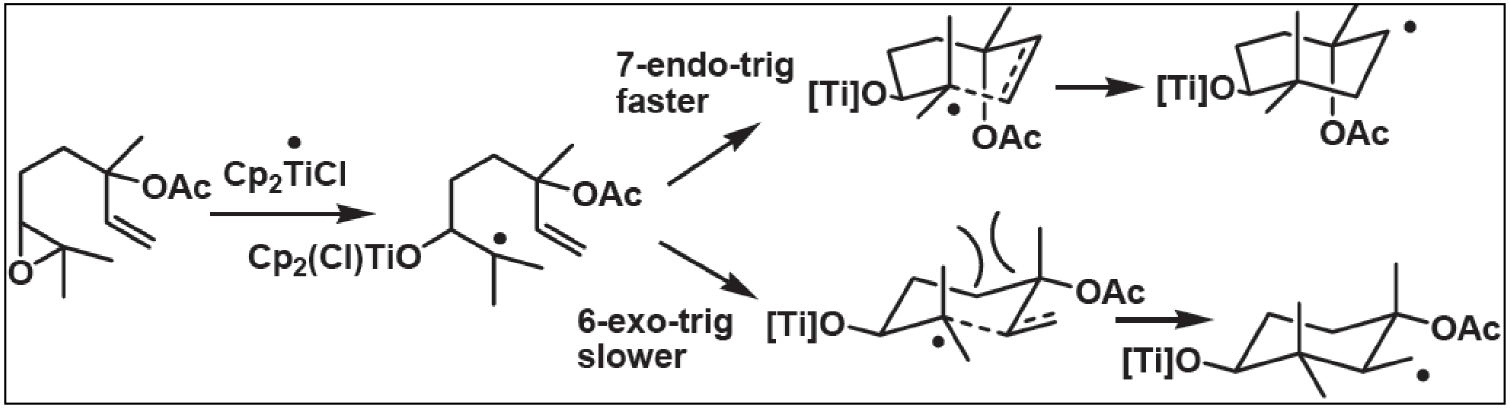
Substrate	Product	Yield %	dr
 1 dr 75:25	 56	66	>98.2
 19 dr >97:3	 65	68	54.42
 50	 77	62	86.14

A. Gansäuer, M. Pierobon, H. Bluhm, *Synthesis* **2001**, 2500

Titanocene(III)-Catalyzed 7-endo Radical Cyclizations

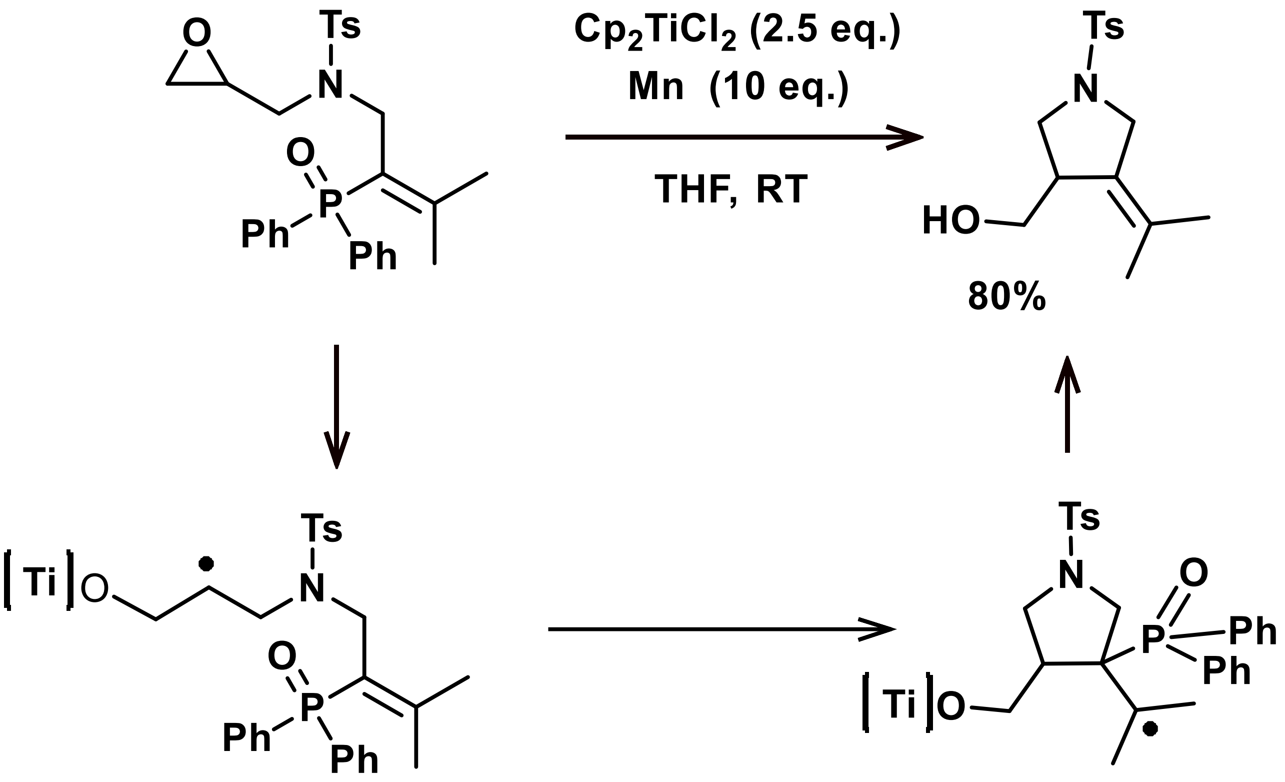


Condition: 10 mol% Cp_2TiCl_2, 20 mol Mn, 20 mol Coll HCl, 10 mol TMSCl, in THF at room temperature



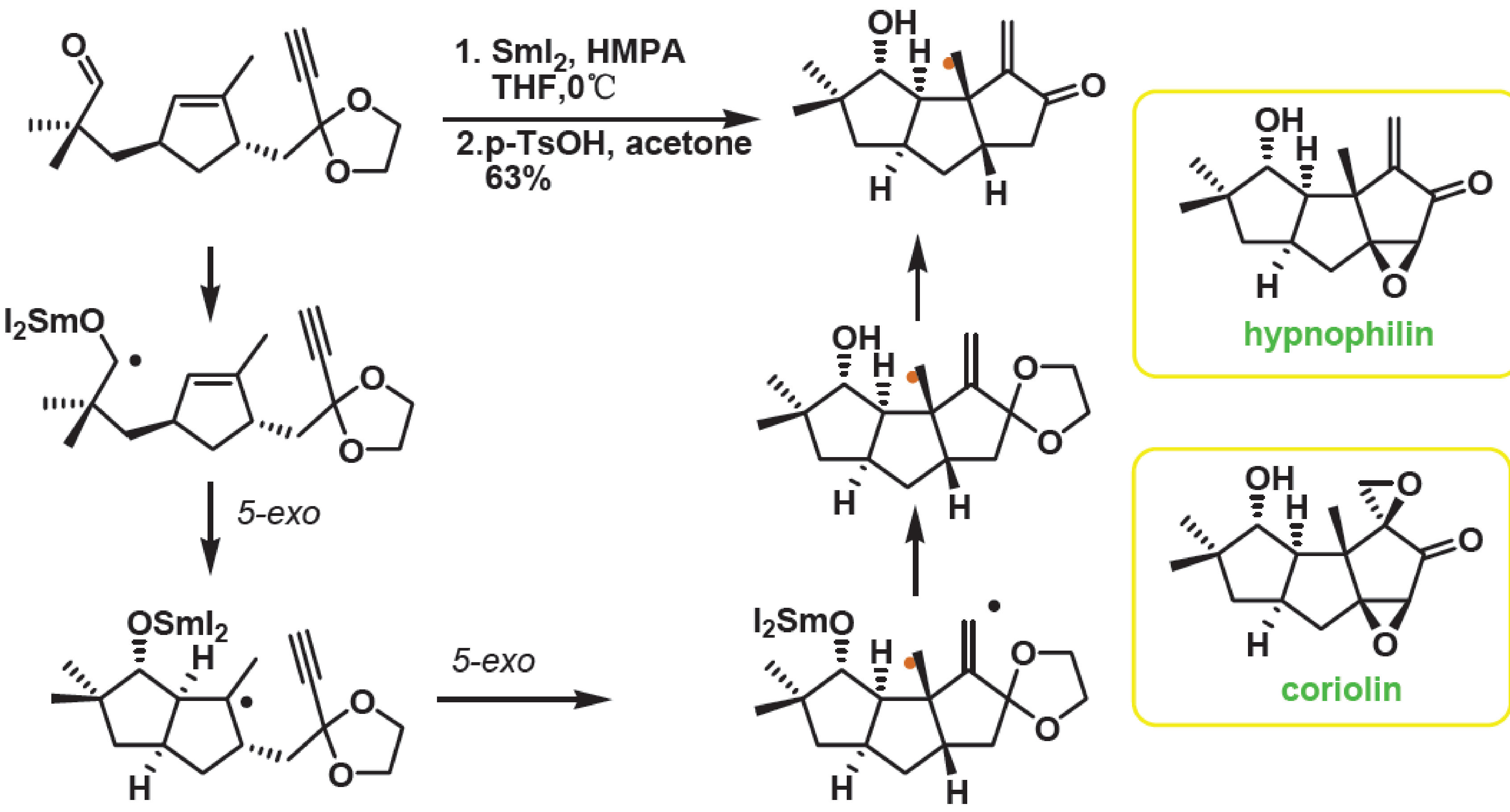
Oltra, J. E.; Justicia, J.; Oller-López, J. L.; *J. Am. Chem. Soc.* **2005**, *127*, 14911

Domino Radical Cyclization/β-Elimination of Phosphine Oxide



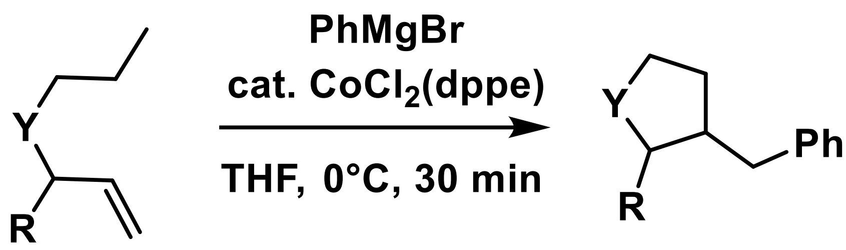
Fensterbank, L.; Leca, D.; *Angew. Chem., Int. Ed.* **2004**, *43*, 4220

Cyclizations in Natural Product Synthesis

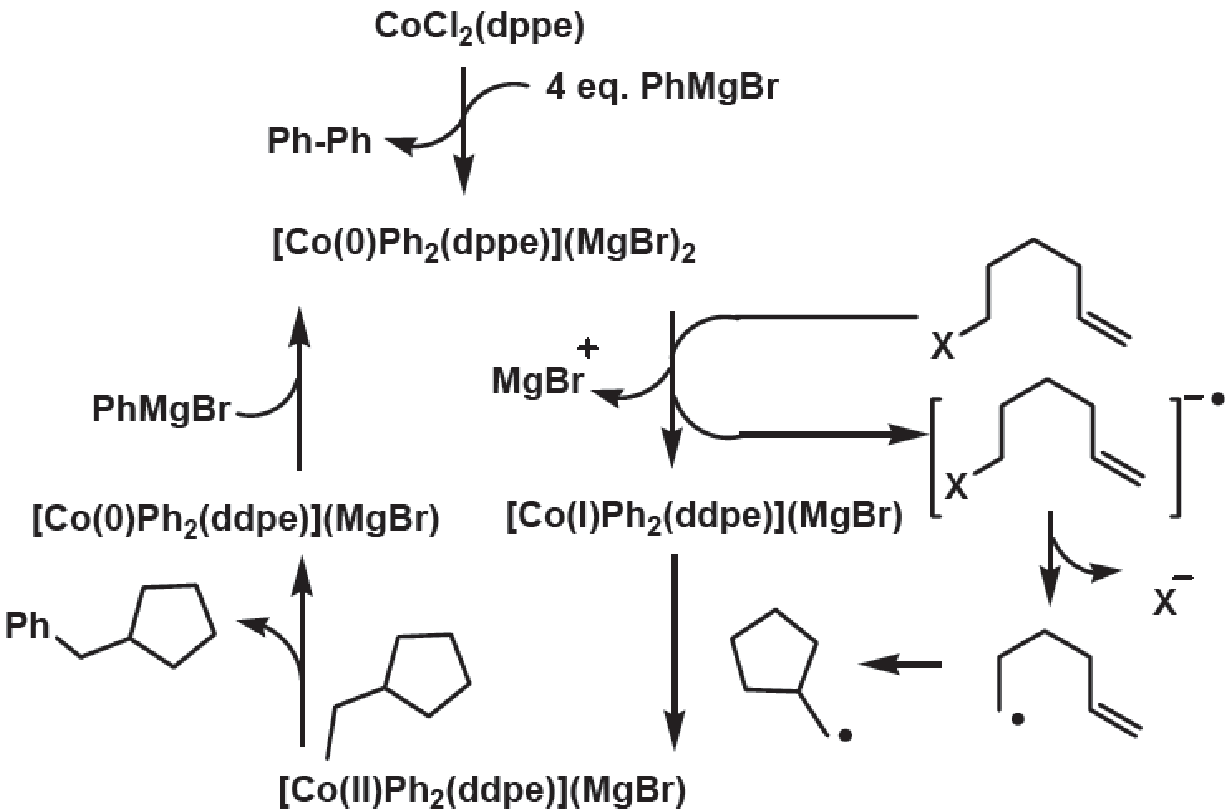


Curran, D. P.; Fevig, T. L.; Elliott, R. L.; *J. Am. Chem. Soc*. **1988**, *110*, 5064

Cobalt-Catalyzed Tandem Radical Cyclization and Cross-Coupling Reaction

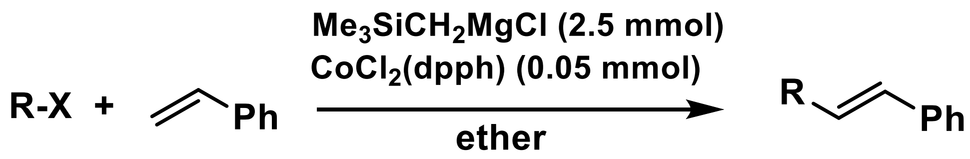


R=H, X= I, Y=4-Me-C_6H_4N 81%
R=n-C_5H_{11}, X=Br, Y= O 59%

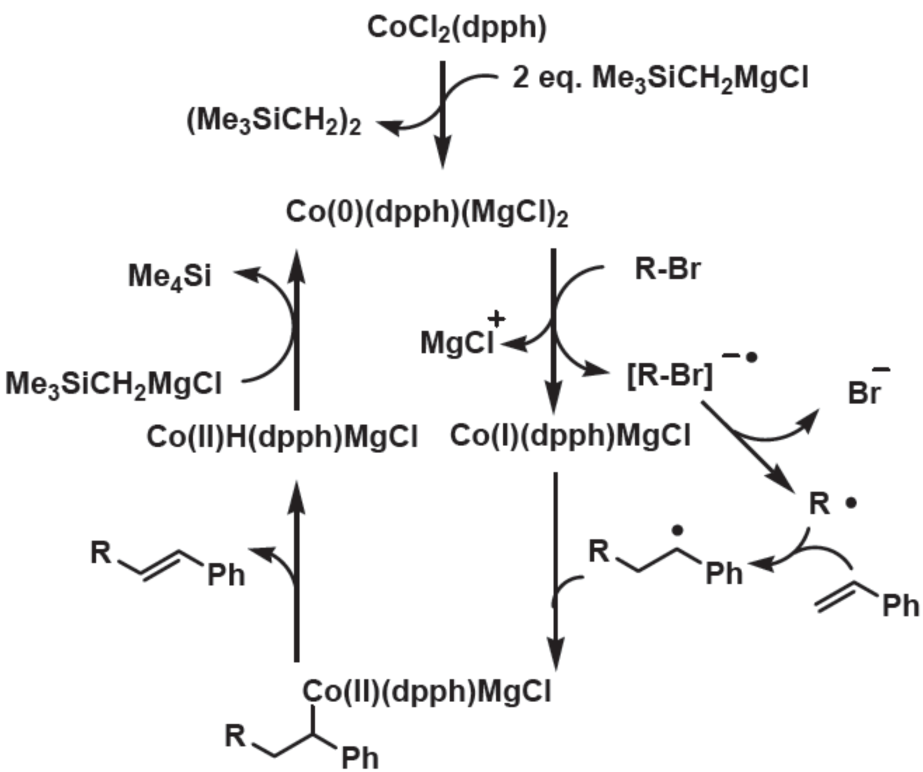


Oshima, K.; Wakabayashi, K.; Yorimitsu, H.; *J. Am Chem. Soc.* **2001**, *123*, 5374**.**

Cobalt-Catalyzed Heck-Type Reaction

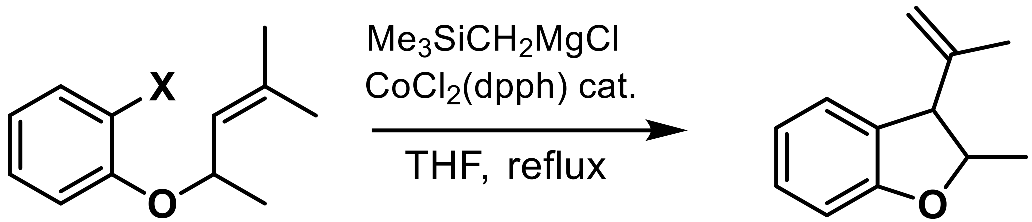


n-$C_6H_{13}CH(CH_3)Br$	20	73%
n-$C_{12}H_{25}Br$	20	76%
Ad-Br	20	87%
t-Bu-Br	35	67%
n-$C_{12}H_{25}I$	35	57%
n-$C_{12}H_{25}Cl$	35	74%



Oshima, K.; Ikeda, Y.; Nakamura, Y.; *J. Am Chem. Soc*. **2002**, *124*, 6514

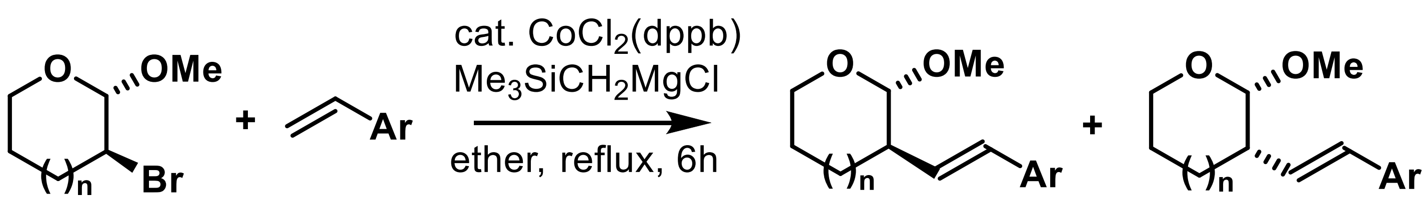
Cobalt-Catalyzed Intramolecular Heck-Type Reaction



X= I: 90% X=Br 77% X= Cl 26%

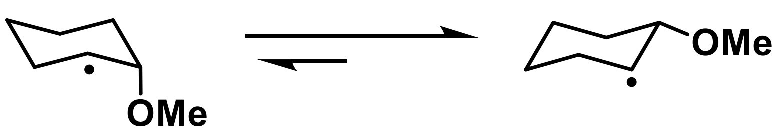
Oshima, K.; Fujioka, T.; Nakamura, T.; *Org. Lett.* **2002**, *4*, 2257

Diastereoselectivity in the Styrylation Reaction



Ar = p-MeOC_6H_4

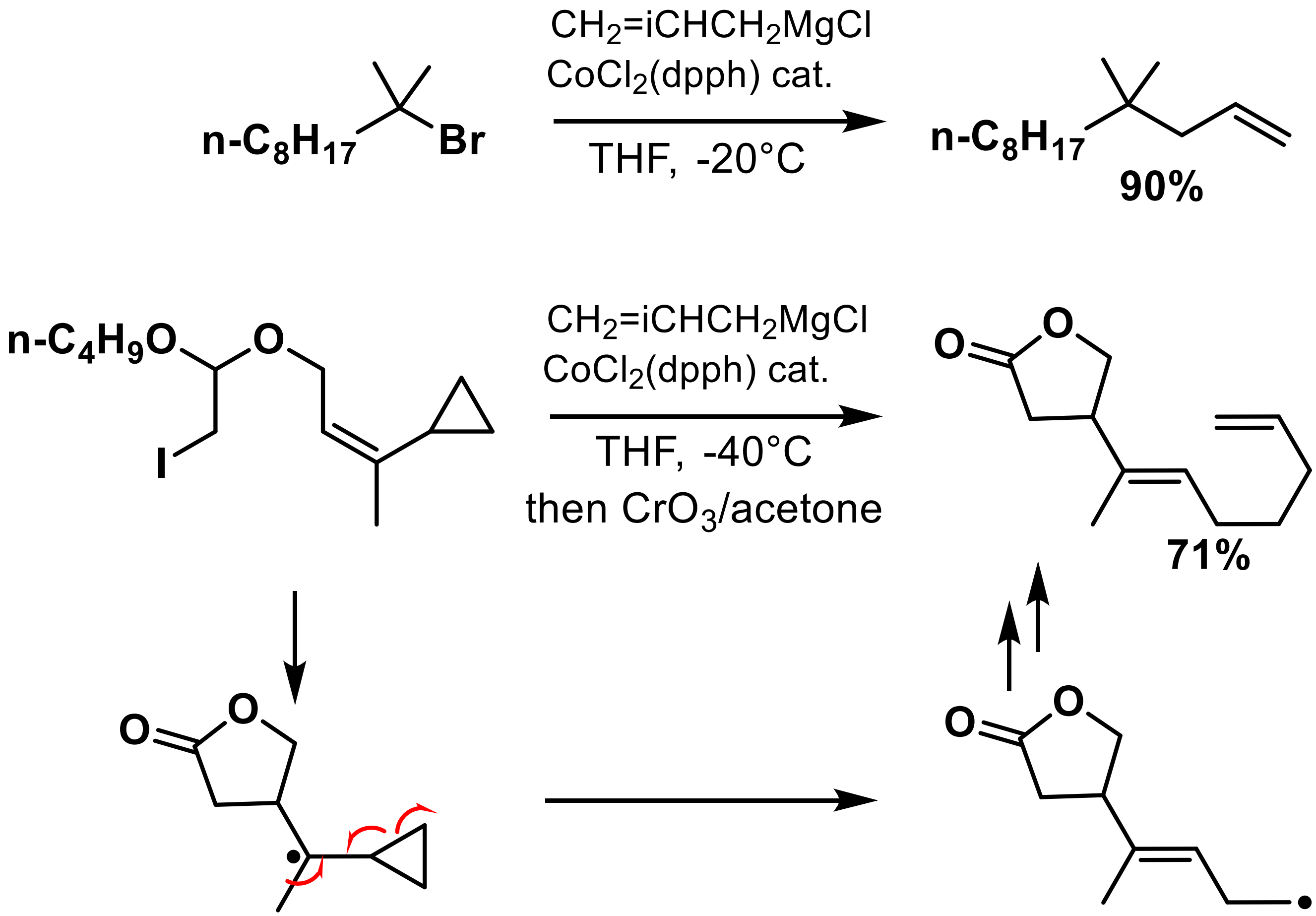
n=1 69% *trans*:*cis*=61: 39n=0 54% *trans*:*cis*=91: 9



rather flexible nature of six-membered ring

Oshima, K.; Affo, W.; Ohmiya, H.; *J. Am Chem. Soc.* **2006**, *128*, 8068

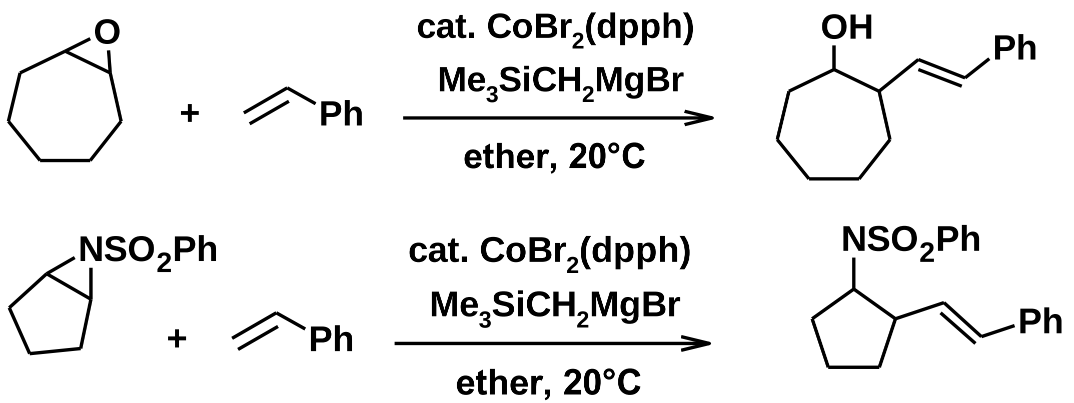
Alkyl Halides with Allylic Grignard Reagents



Oshima, K.; Tsuji, T.; Yorimitsu, K.; *Angew. Chem., Int. Ed.* **2002**, *41*, 4137

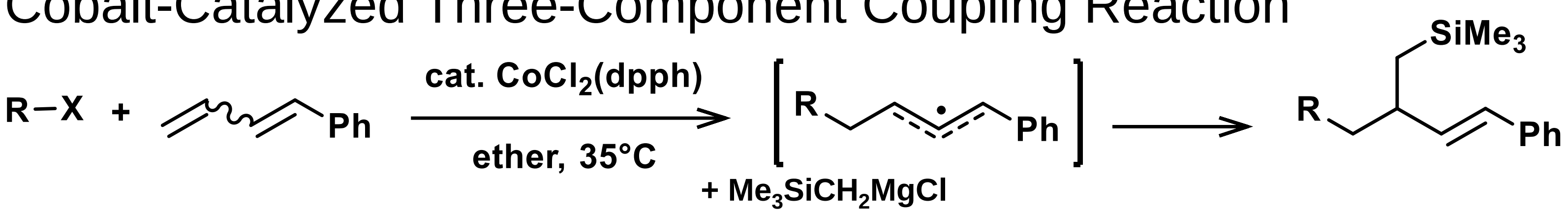
Other Cobalt(I) Catalized Reactions

- Heck-Type Reactions of Epoxide and Aziridine with Styrene



Oshima, K.; Ikeda, Y.; Yorimitsu, H.; *Adv. Synth. Catal.* **2004**, *346*, 1631

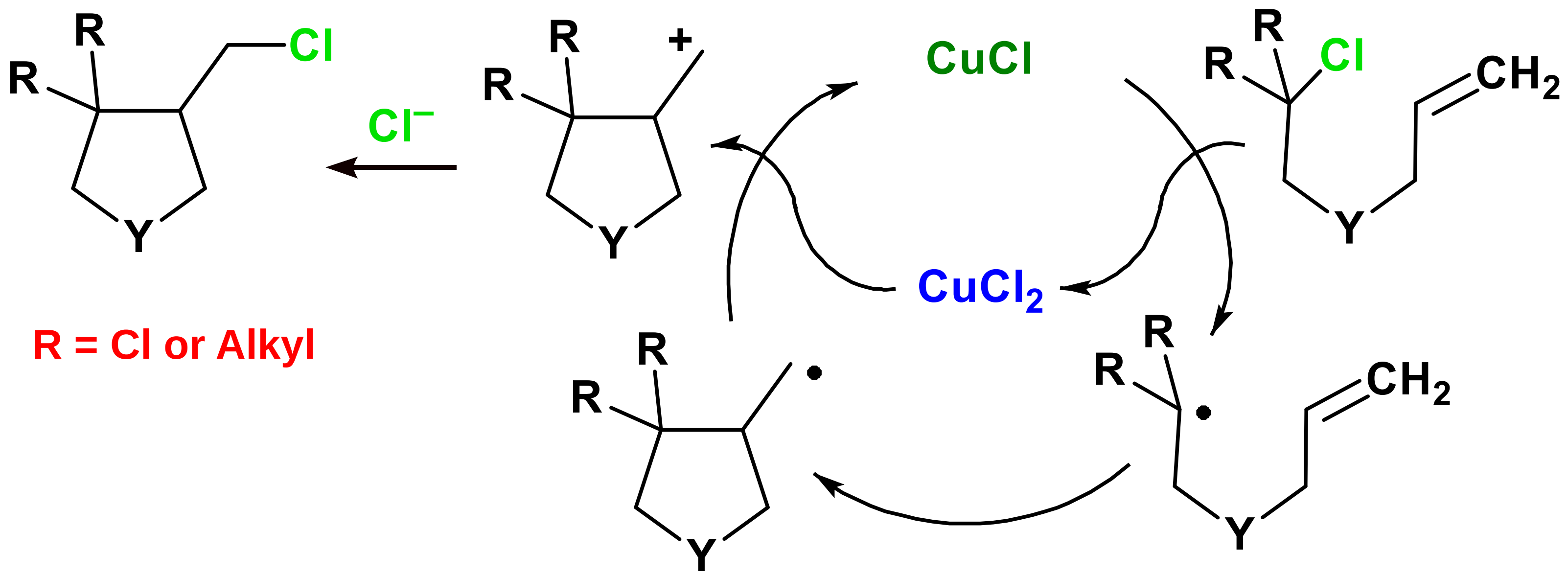
- Cobalt-Catalyzed Three-Component Coupling Reaction



R-X: n-C_9H_{19}Br 84%
t-BuBr 87%
c-C_6H_{11}I 60%

Oshima, K.; Mizutani, K.; Shinokubo, H.; *Org. Lett.* **2003**, *5*, 3959

General Process for the Atom Transfer Reaction



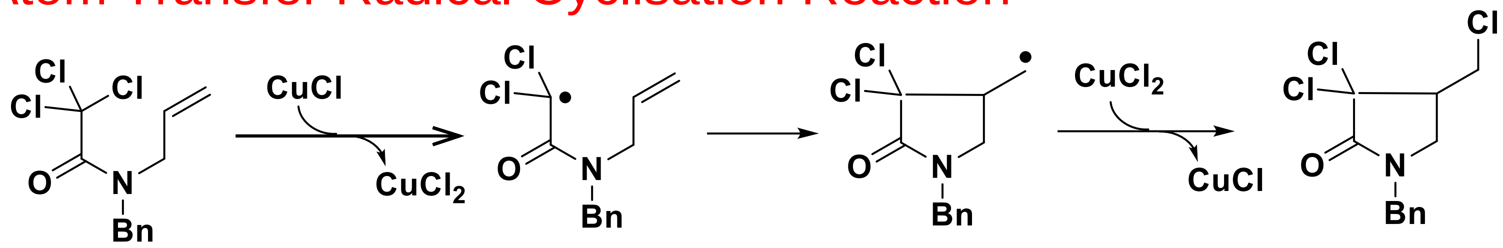
(a) the low cost of copper halides

(b) the ease of work-up of the reactions

(c) the catalytic nature of the process

Cu(I)-Mediated Radical Reaction

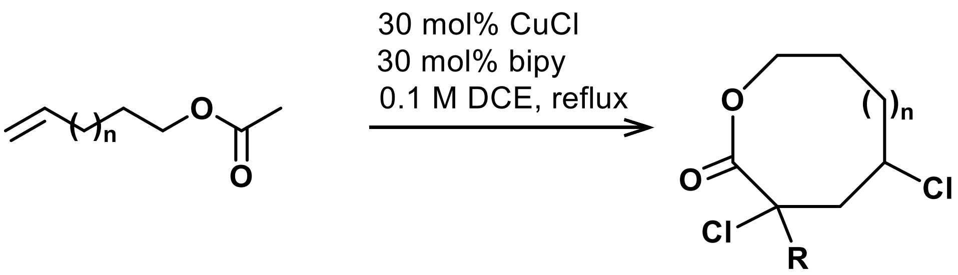
- Atom Transfer Radical Cyclisation Reaction



Catalyst (mol%)	Solvent			
CuCl (30)	MeCN	80℃	18h	68%
CuCl -bipy (30)	CH_2Cl_2	rt	1h	98%

Itoh, K.; Nagashim, H.; N. Ozaki, N.; *J. Org. Chem*., **1993**, *58*, 464

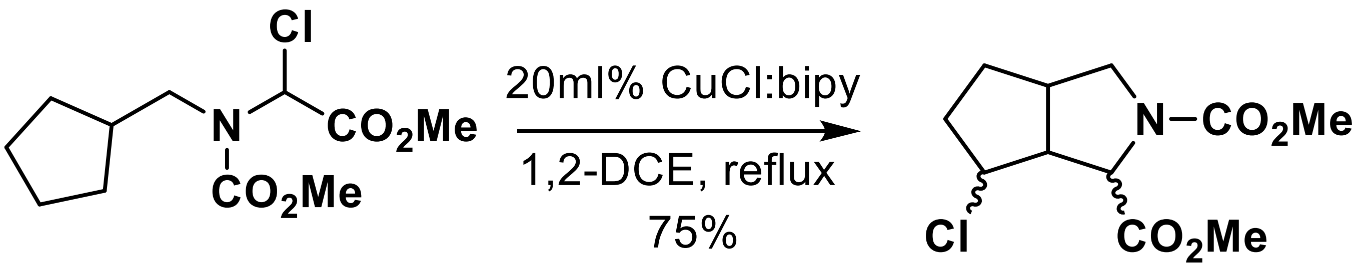
- Synthesis of Medium Ring Lactone



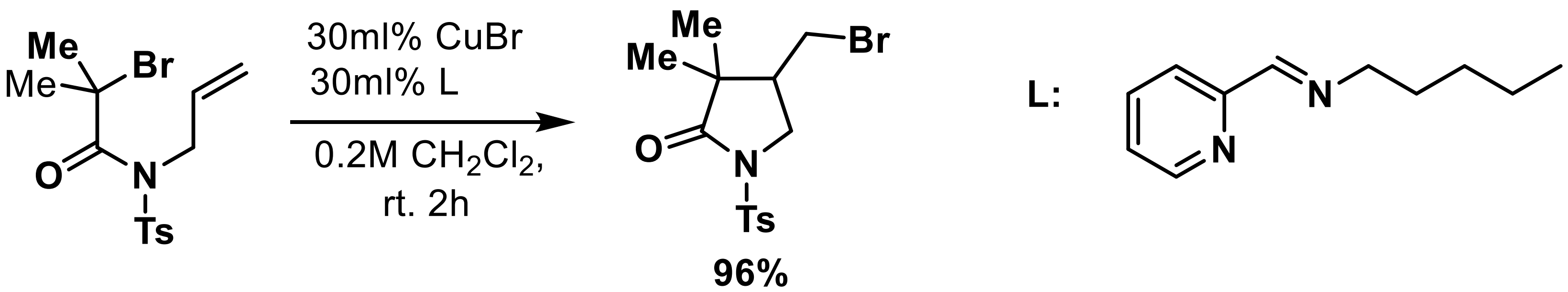
R=Cl, n=1, 60%
R=Cl, n=2, 59%
R=H, n=1, 75%

Pirrung, F. O. H.; Steeman, W. J. M.; *Tetrahedron Lett*., **1992**, *33*, 5141

Cu(I)-Mediated Cyclisation of mono-Halo Substrates

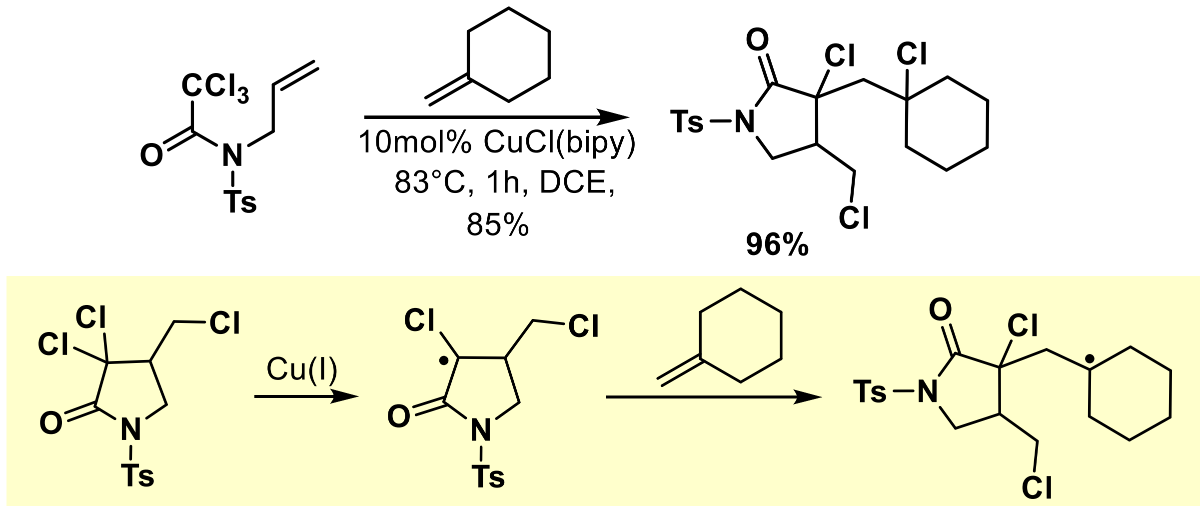


Speckamp, W. N.; Udding, J. H.; Tuijp, C. J. M.; *Tetrahedron*, **1994**, *50*, 1907

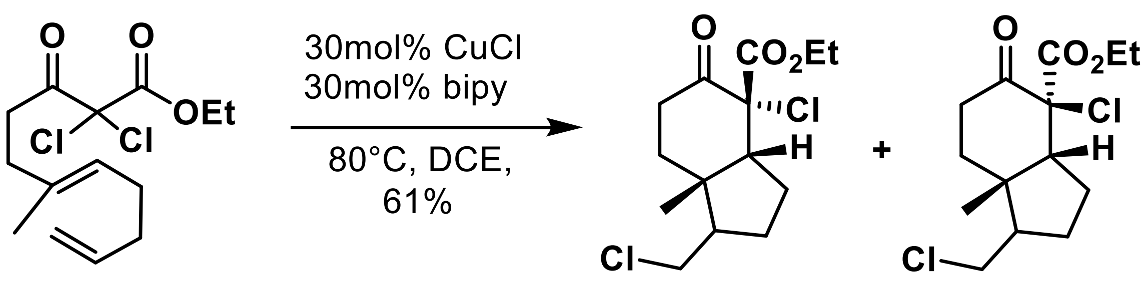


Clark, A. J.; Battle, G. M.; Heming, A. M.; *Tetrahedron Lett.*, **2001**, *42*, 2003

Copper Catalyzed Tandem Reactions

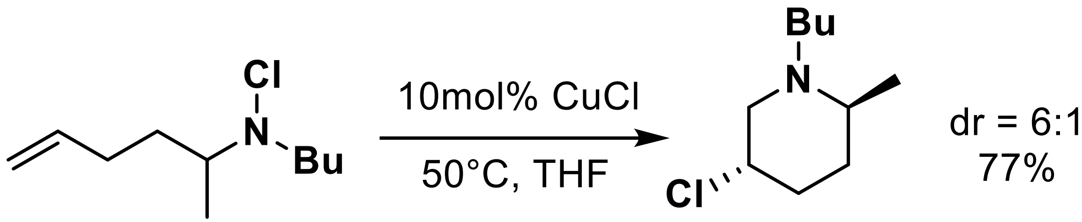


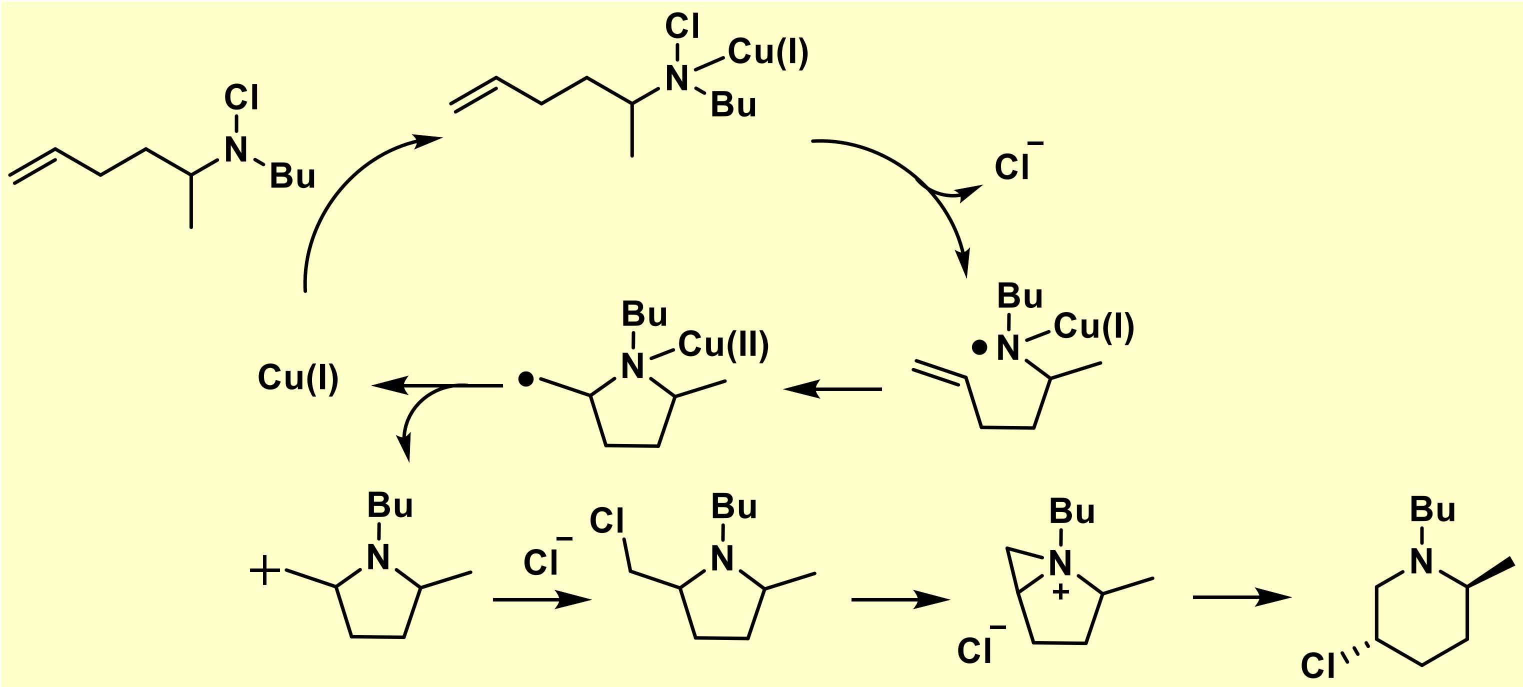
Nagashima,H.; Iwamatsu, S.; Kondo, H.; *Tetrahedron*, **1999**, *55*, 1687



Yang, D.; Yan, Y. L.; Zheng, B. F.; *Org. Lett*. **2006**, *8*, 5757

Copper Catalyzed Diastereoselective Addition of N-Chloroamineto Double Bond

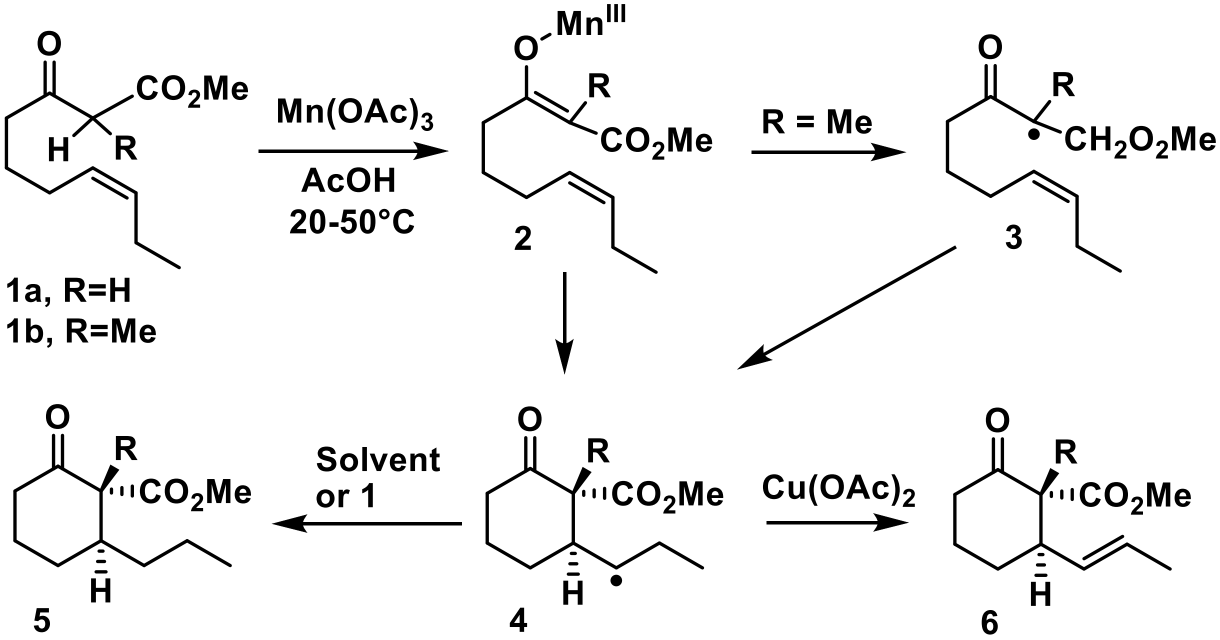




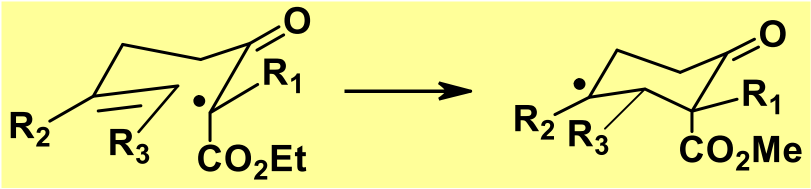
Göttlich, R.; Heuger, G.; Kalsow, S.; Eur. *J. Org. Chem*. **2002**, 1848

Mn(III)-Mediated Radical Reaction

Mechanism of Oxidation of Carbonyl Substrate

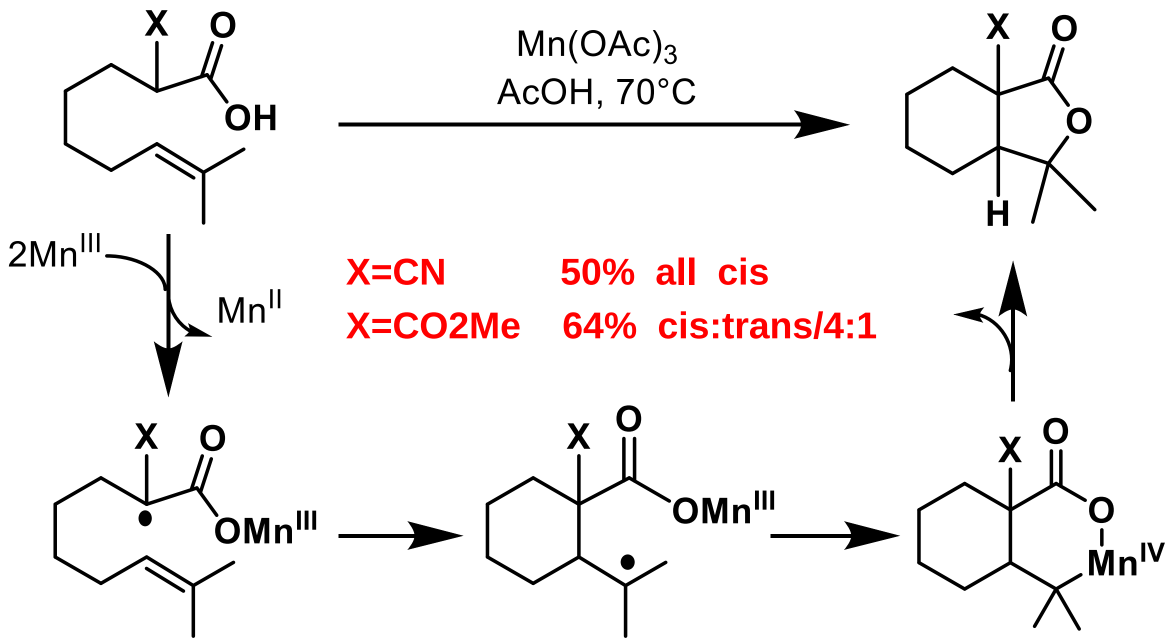


Stereochemistry of Cyclization



Snider, B.; B.; *Chem. Rev*. **1996**, *96*, 339

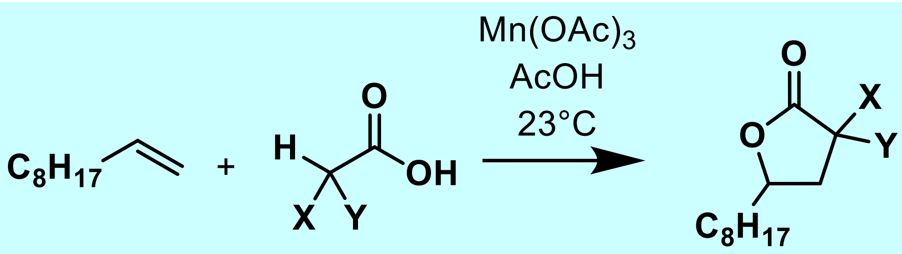
Radicals Derived from Acids



X=CN 50% all cis

X=CO2Me 64% cis:trans/4:1

Fristad, W. E.; Ernst, A. B.; *Tetrahedron Lett.* **1985**, *26*, 3761



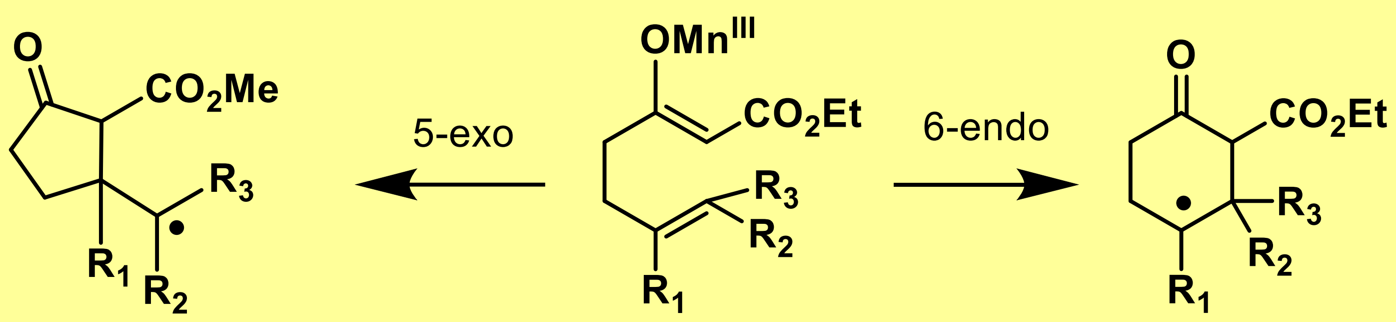
$X=CN, Y=H$ 85%

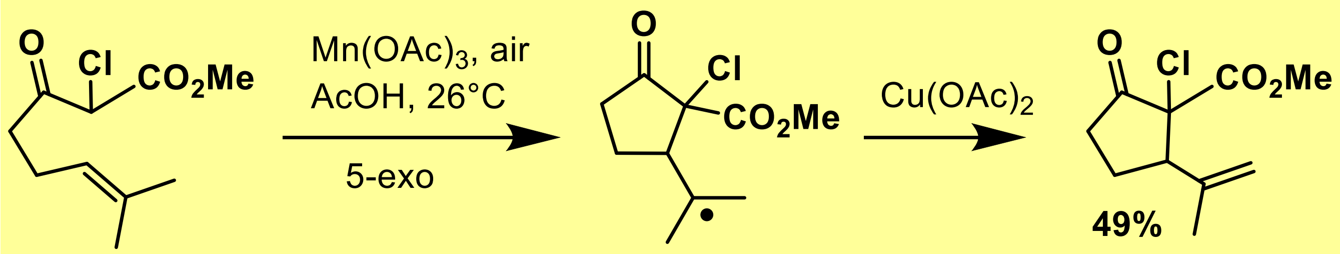
$X=CO_2Et, Y=H$ 74%

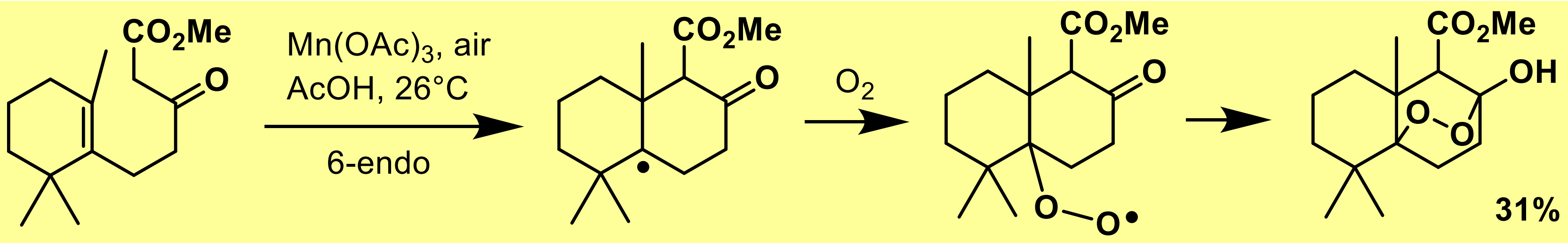
$X=CO_2Et, Y=Cl$ 73%

Fristad, W. E.; Peterson, J. R.; *J. Org. Chem.* **1985**, *50*, 3143

Oxidative Cyclizationsof β-KetoEsters





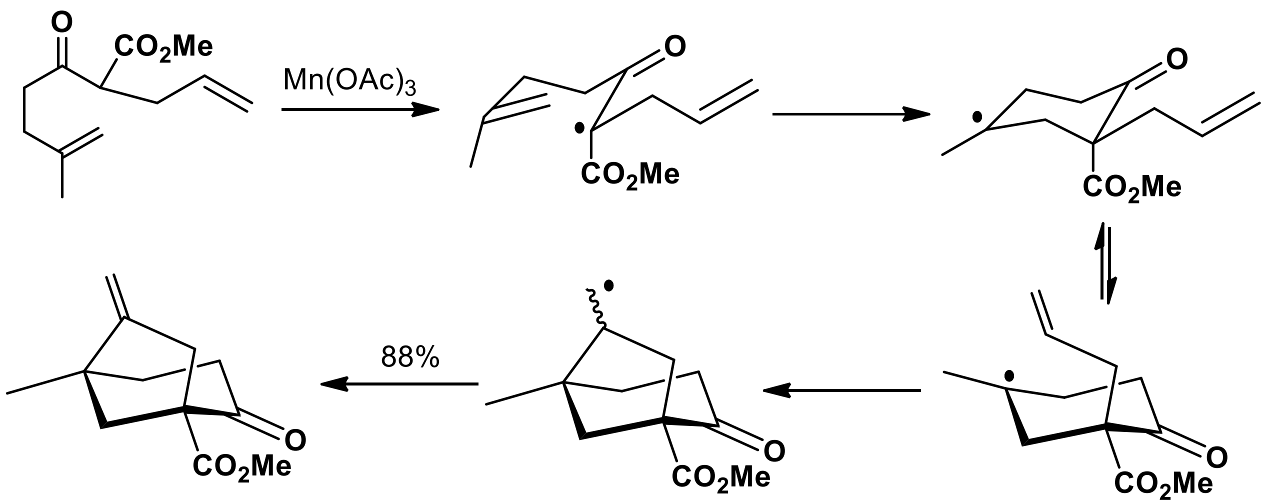


Snider, B. B.; Patricia, J. J.; Kates, S. A. *J. Org. Chem*. **1988**, *53*, 2137

Colombo, M. I.; Signorella, S.; Mischne, M. P.; *Tetrahedron* **1990**, *46*, 4149

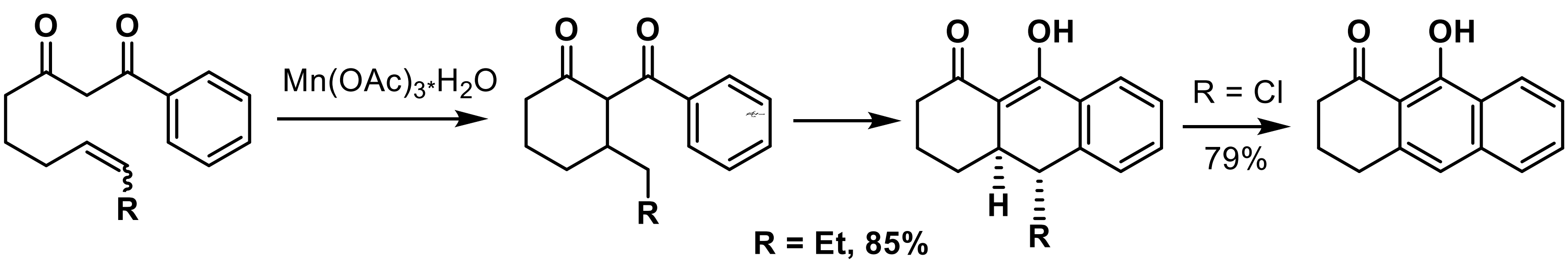
Tandem Oxidative Intramolecular Cyclizations

Additions of Radical to Two Double Bond



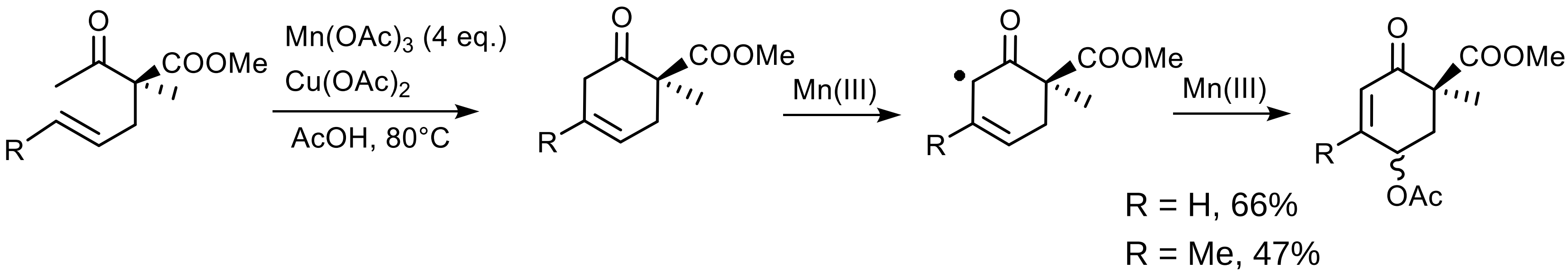
Snider, B. B.; Dombroski, M. A.; Kates, S. A.; *J. Am. Chem. Soc*. **1990**, *112*, 2759

Additions of Radical to Aromatic Ring



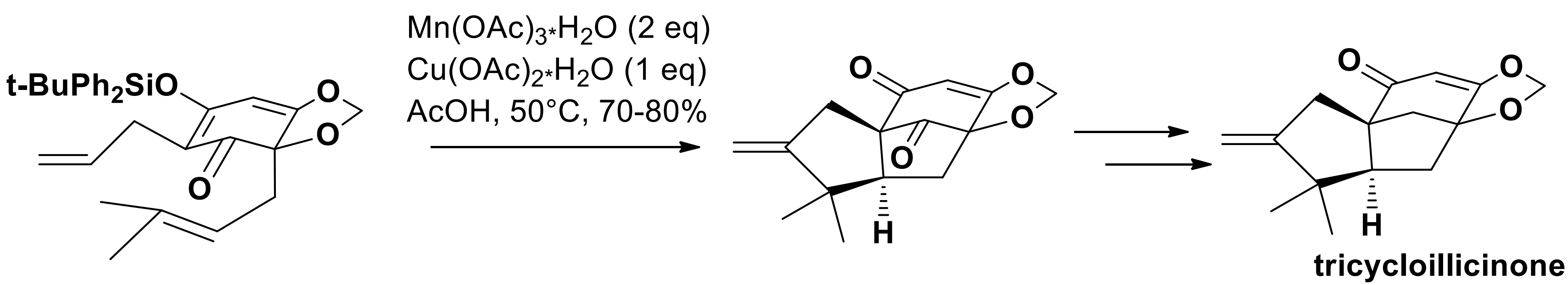
Snider, B. B.; Zhang, Q. *J. Org. Chem*. **1992**, *57*, 4195

Radicals Derived from Oxidation of Ketone



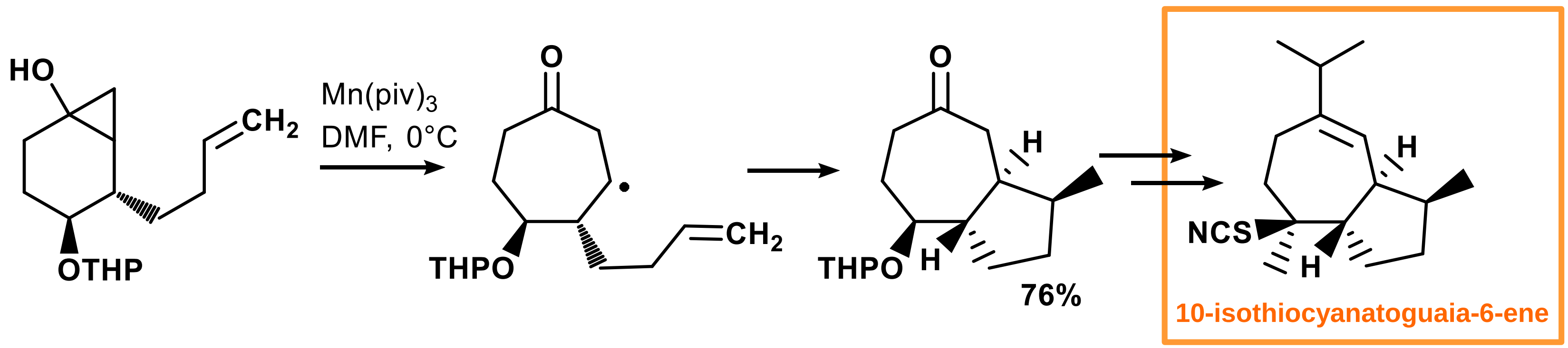
Breuilles, P.; Uguen, D. *Bull. Chim. Soc. Fr*. **1988**, 705.

Radicals Derived from Oxidation Enol Ether

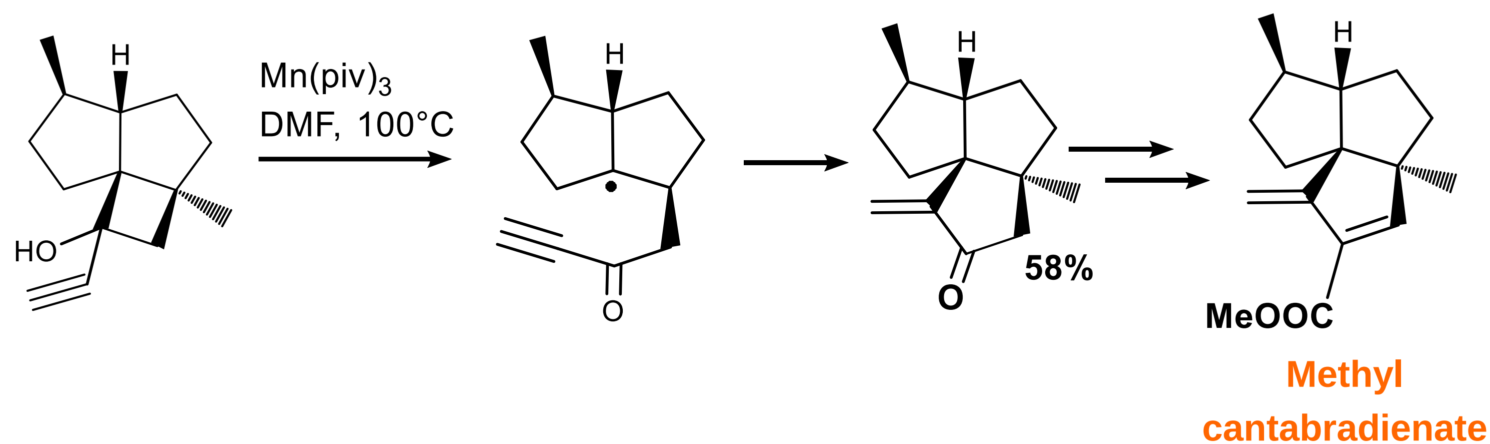


Pettus, T. R. R.; Chen, X. T.; *J. Am. Chem. Soc*. **1998**, *120*, 12684

Mn(III) Mediated Tandem Fragmentation-Cyclizations

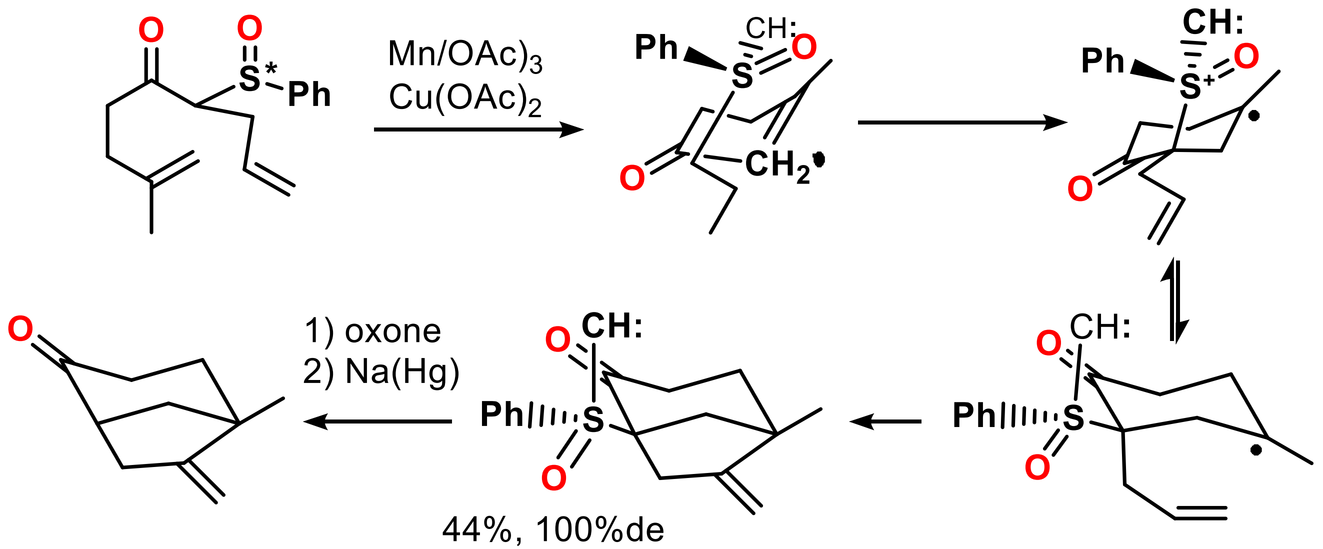


Iwasawa, N.; Funahashi, M.; Bull. *Chem. Soc. Jpn*. **1999**, *72*, 85

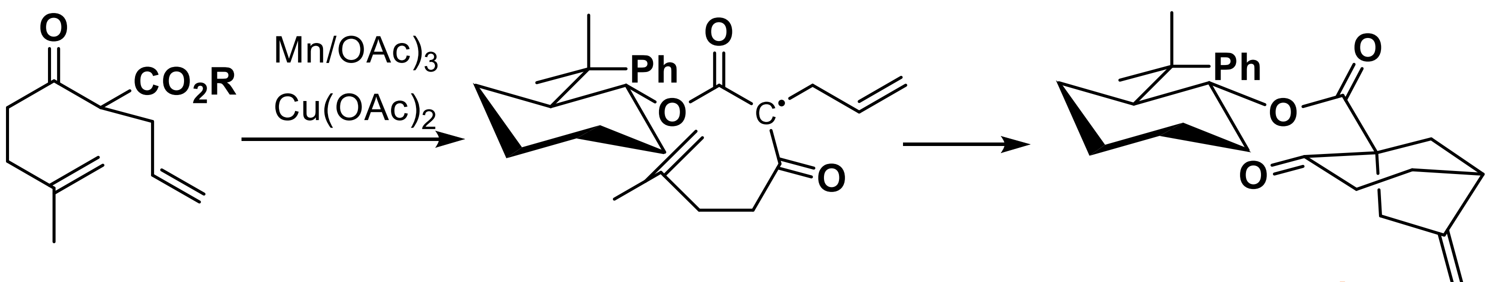


Snider, B. B. J.;Vo, N. H.; *J.Org. Chem.* **1994**, **59**, 5419

Asymmetric Free-Radical Cyclization



Snider, B. B.; Wan, B. Y. F.; Buckman, B. O.; *J. Org. Chem*. **1991**, *56*, 328

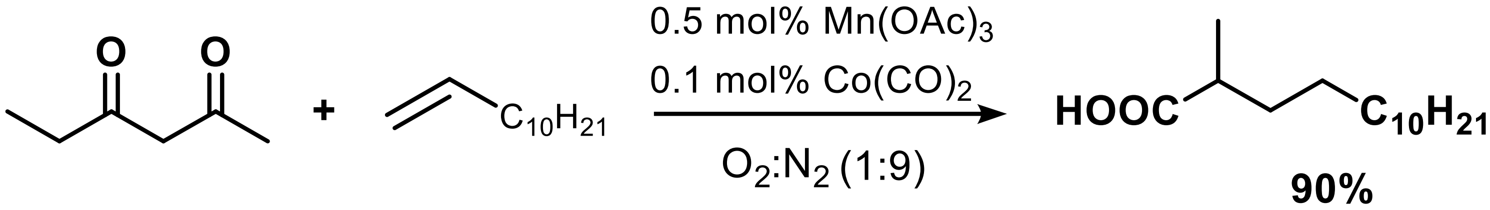


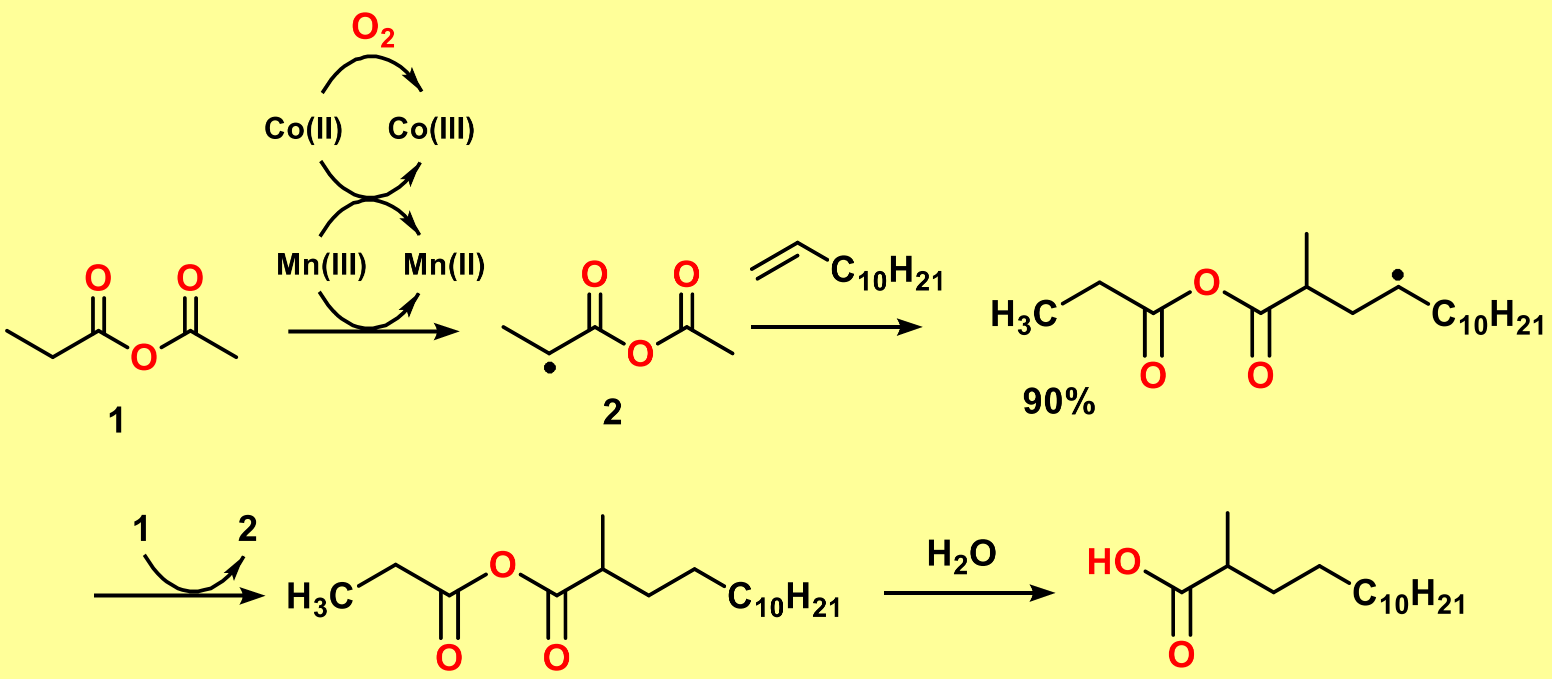
R = (-)-Phenylmenthyl

90%, 86%de

Snider, B. B.; Zhang, Q.; Mohan, R. M.; *J.Org. Chem*. **1993**, *58*, 7640

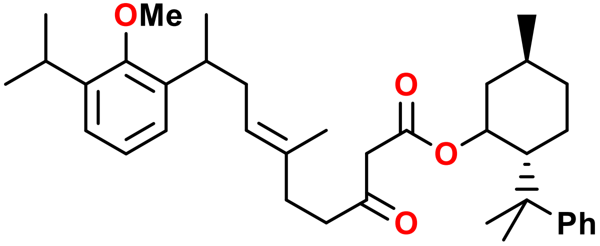
Addition of Carboxyalkyl Radical to Alkene





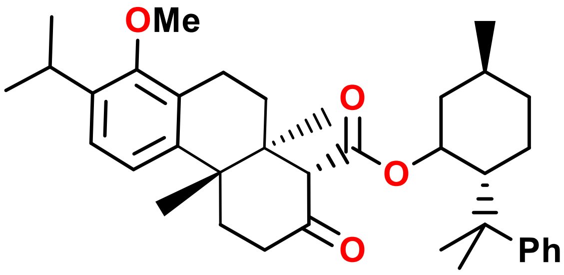
shii, Y.; Hirase, K.; Sakaguchi, S.; *J. Org. Chem*. **2003**, *68*, 5974

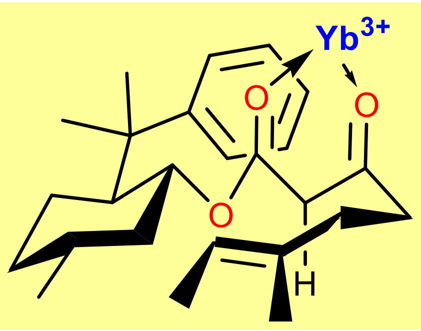
Enantioselective Synthesis of (-)-Triptolide

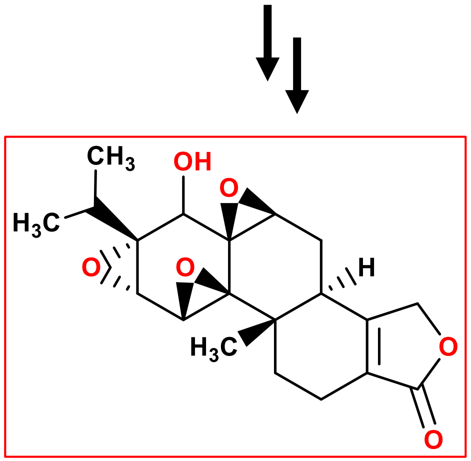


Mn(OAc)$_3$ 2H$_2$O(2.2equiv)
Yb(OTf)$_3$ H$_2$O (1.0 equiv)
CF$_3$CH$_2$OH, -5 °C

77%, dr 38:1



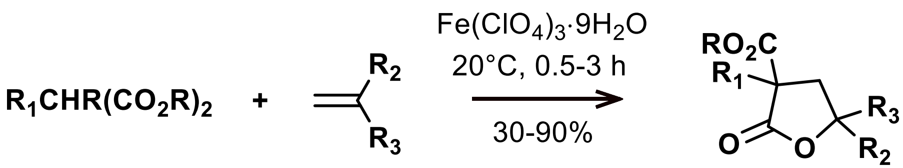




(-)-triptolide

Yang, D.; Ye, Y. X.; Gu, S.; *J. Am. Chem. Soc*. **1999**, *121*, 5579
Ibid, **2000**, *122*, 1658.

Iron(III) Oxidation of Carbonyl Compounds in the Presence of Olefins



1 2 3

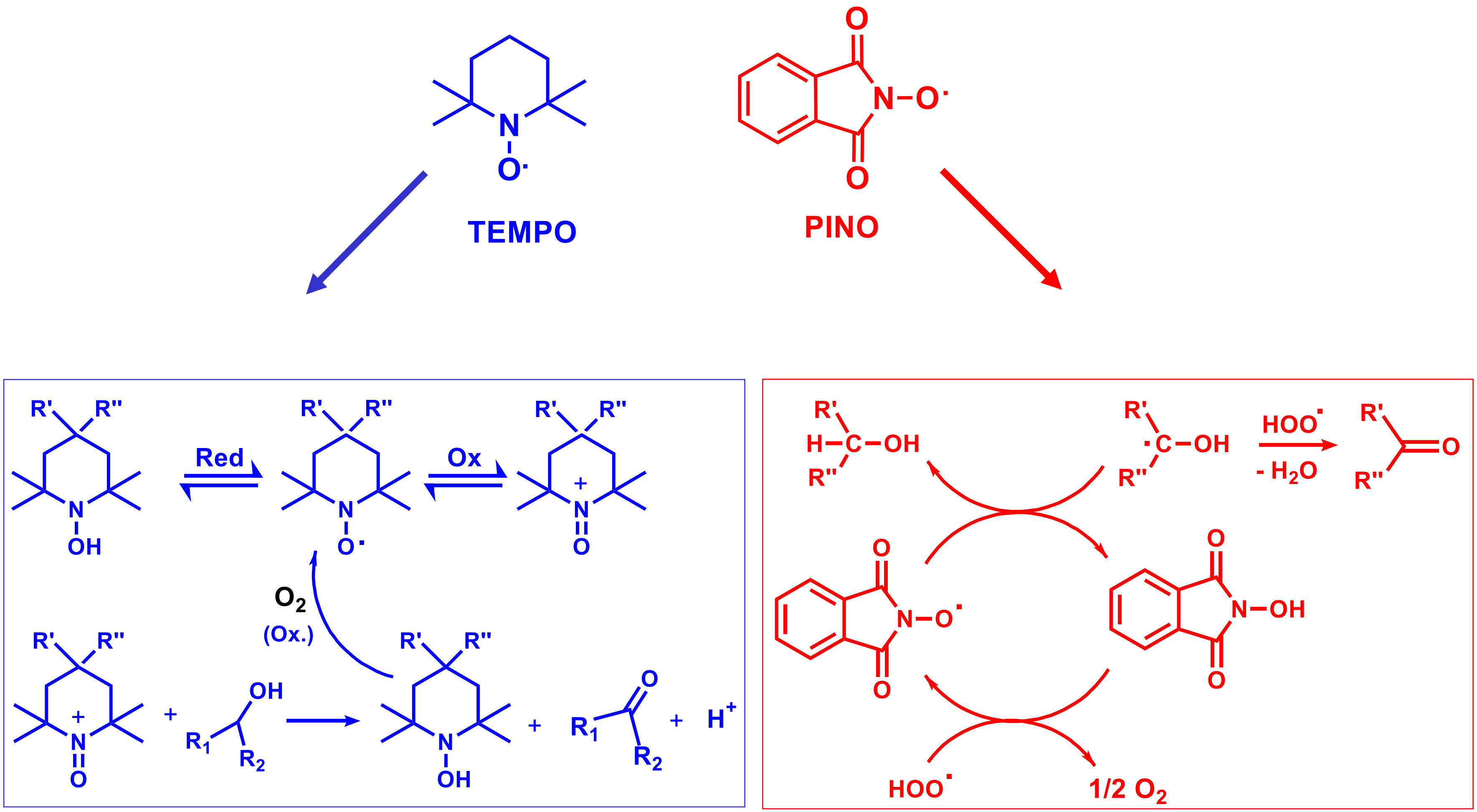
1a-g		2a-h	
1a R=Et	R_1=Me	2a R^2 = H	R^3 = Ph
1b R=Et	R_1=4-Cl-C_6H_4-CH_2	2b R^2=H	R^3=4-MeO-C_6H_4-
1c R=$PhCH_2$	R_1=Me	2c R^2=H	R1=4-Cl-C_6H_4
1d R=Et	R_1=H	2d R^2=Me	R^3=C(Me)=CH_2-
1e R=Et	R_1 = Ph$(CH_2)_3$	2e R^2=H	R^3=CH=CH_2
1f R=Et	R_1=$PhCH_2$	2f R^2=H	R^3=c-C_6H_{13}
1g R=Et	R_1=n-Bu	2g R^2=Me	R^3=t-Bu
		2h R^2=Ph	R^3=$(CH_2)_3CH(CO_2Et)_2$

Table. γ-Lactones by FEP oxidation of dialkyl malonates 1 in the presence of olefins 2. {FEP:1:2) molar ratio = 2:1:1.2, MeCN, 20'C).

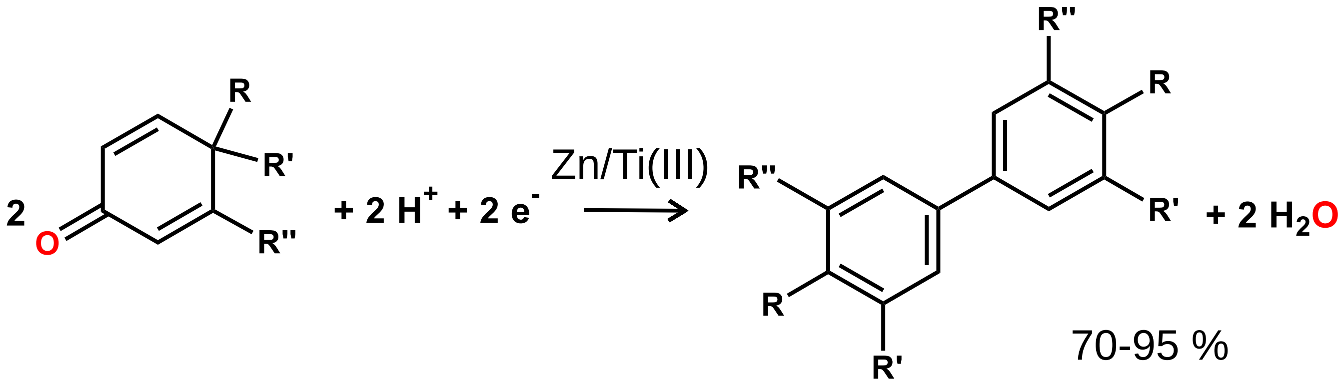
Entry	1	2	2(conv.%)[a]	3(Yletd %)[b,c]
1	1a	2a	95	90
2	1b	2a	92	89
3	1c	2a	100	91
4	1d	2a	50	65[d]
5	1e	2a	95	90
6	1a	2b	84	78
7	1f	2c	87	80
8	1b	2d	94	89
9	1b	2e	90	52[e]
10	1g	2e	82	75
11	1a	2f	90	38[f]
12	1g	2g	92	58
13	--	2h	91	80[g]
14	1g	2a	95	90

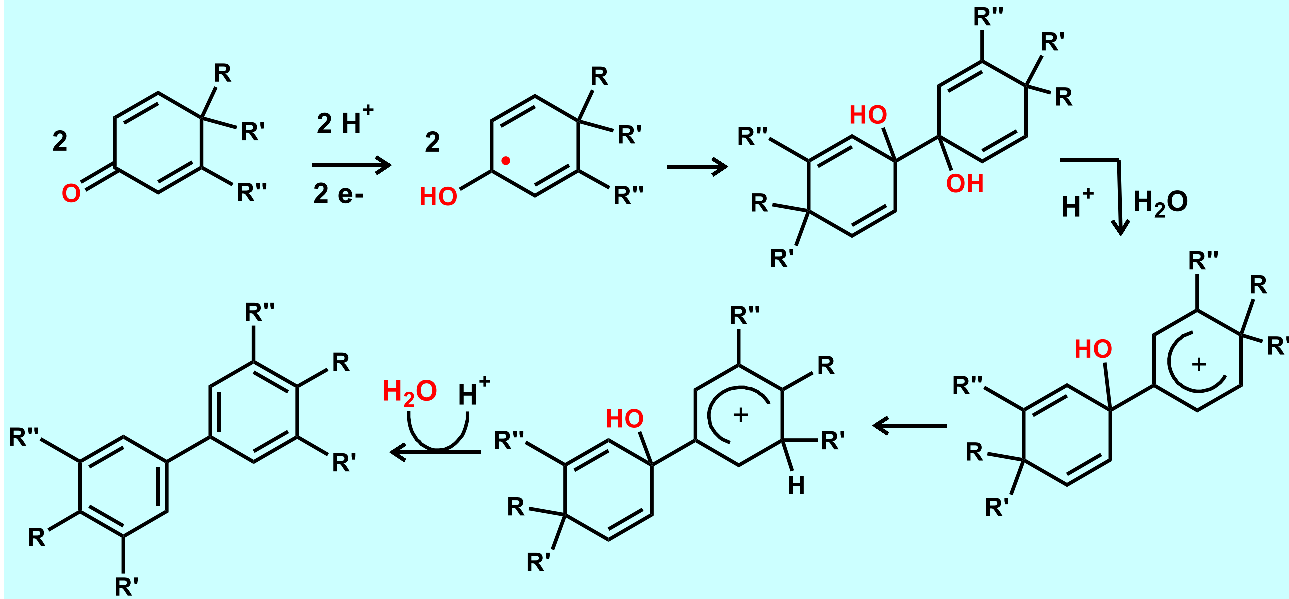
Citterio, A.; Sebastiano, R.; Nicolini, M.; Santi, R. **Synlett**, 1, pp. 42-3 (1990)

Nitroxide Radical Promoted Alcohol Oxidation



Homolytic Reduction of 4,4-Cycloesadienones and Ionic Rearrangement to Biaryls





Citterio, Barra Thesis 1997