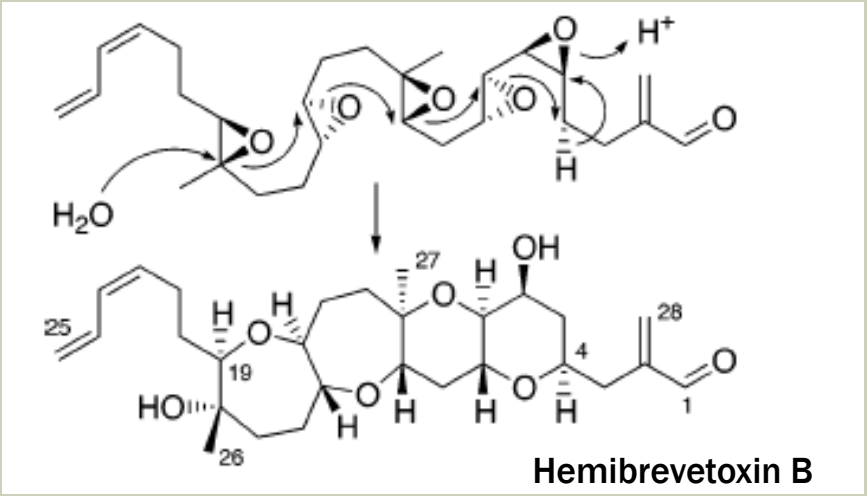
Prof. Armen Zakarian

Methods Applied in Total Synthesis

November 16th 2011

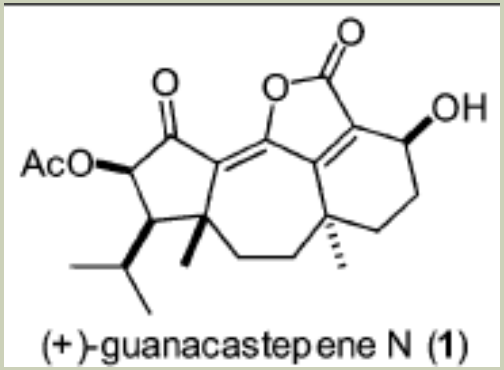
Dr. Armen ZAKARIAN, Florida State University and UCSB

Florida State University (2004-2008)
Prof. Ass. UC Santa Barbara (2008—)



Hemibrevetoxin B

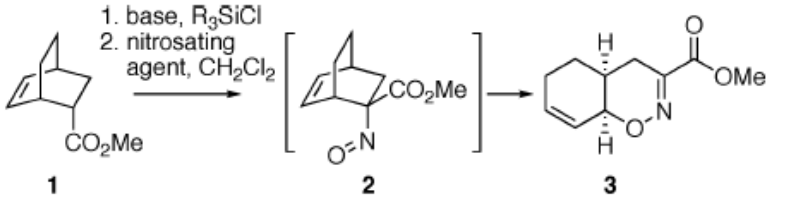
J. Am. Chem. Soc. 2003, 125, 7822 (Holton)



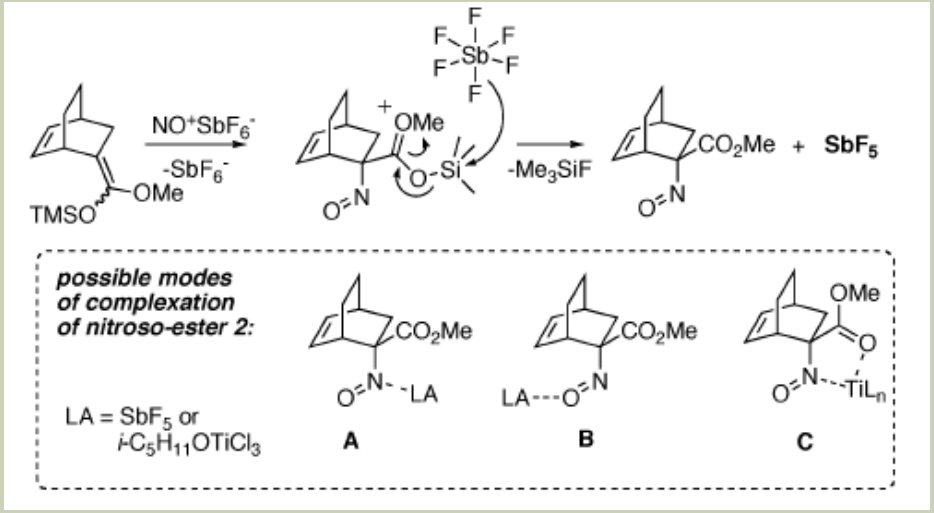
(+)-guanacastepene N (**1**)

I. Development of 1,2-Oxaza-Cope Rearrangement

nitroso group

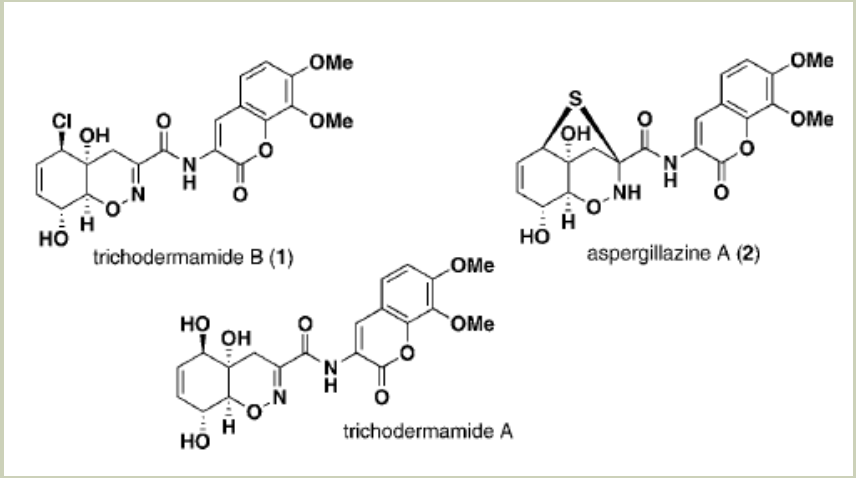


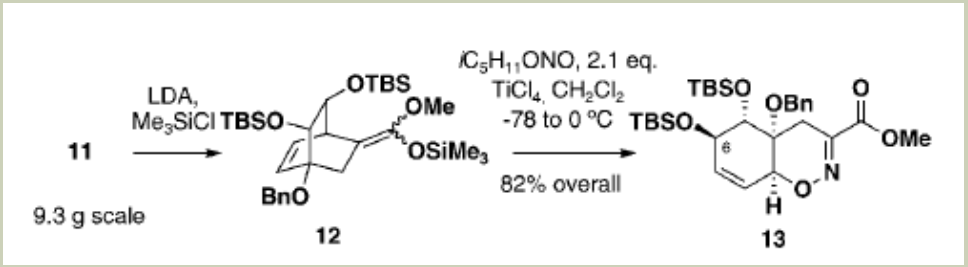
entry	R_3Si	nitrosating agent (equiv)	additive (equiv)	yield[b] (%)
1	TMS	$NOSbF_6/MeNO_2$ (1.2)	none	11
2	TMS	$NOSbF_6/MeNO_2$ (1.2)	Et_3N (2.0)	30
3	TMS	$NOSbF_6/MeNO_2$ (5)	Et_3N (5)	28
4	TBS	$NOSbF_6/MeNO_2$ (1.2)	Et_3N (2.0)	17
5	TBS	$NOSbF_6$/MeCN (1.2)	Et_3N (2.0)	19
6	TBS	$NOSbF_6$/MeCN (1.2)	propylene oxide (5) Et_3N (5)	5
7	TBS	*i*-$C_5H_{11}ONO/TiCl_4$ (1.0)	none	57
8	TBS	*i*-$C_5H_{11}ONO/TiCl_4$ (2.0)	none	50
9	TBS	*i*-$C_5H_{11}ONO/TiCl_4$ (1.0)	Et_3N (0.3)	64
10	TBS	*i*-$C_5H_{11}ONO/TiCl_4$ (1.0)	DBMP[c] (0.3)	68
11	**TMS**	***i*-$C_5H_{11}ONO/TiCl_4$ (1.0)**	**DBMP[c] (0.3)**	**71**
12	TMS	NOCl	DBMP[c] (0.3)	0

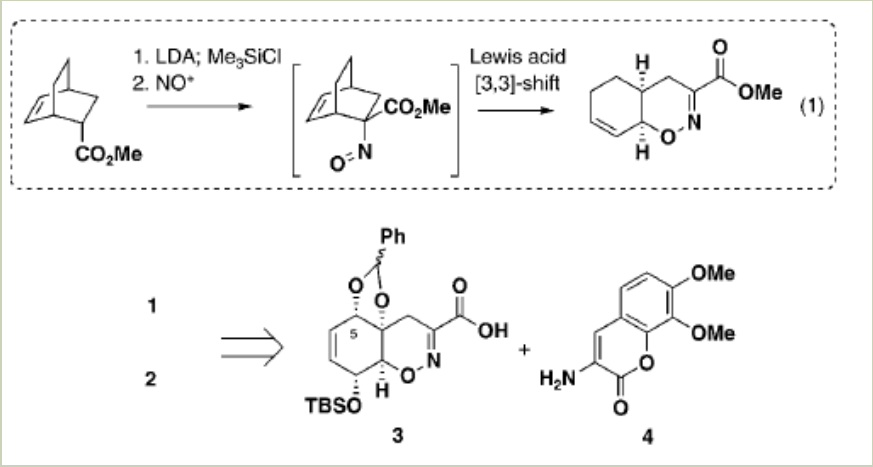


J. Am. Chem. Soc. **2006**, *128*, 5356

I. Total Synthesis
(+/-)-Trichodermamide B

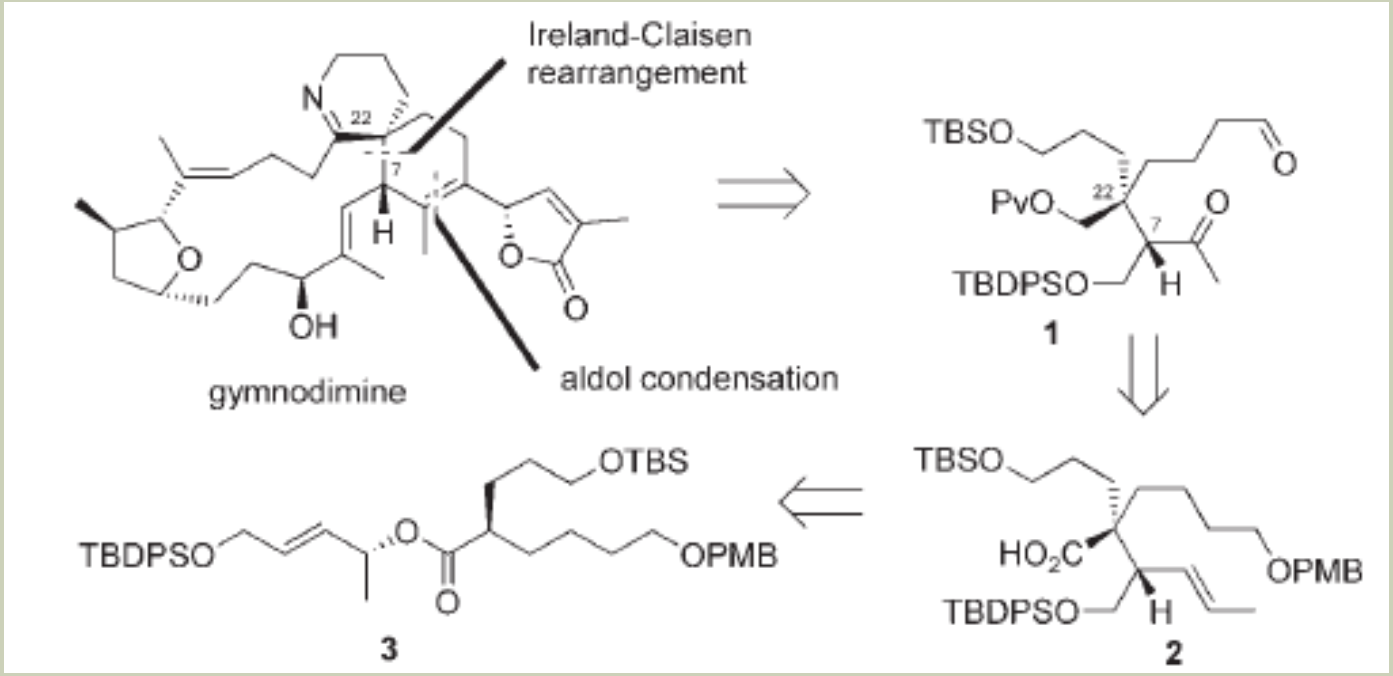






Angew. Chem. Int. Ed. **2008**, *47*, 6829

II. Acyclic Stereocontrol in Ireland–Claisen Rearrangement

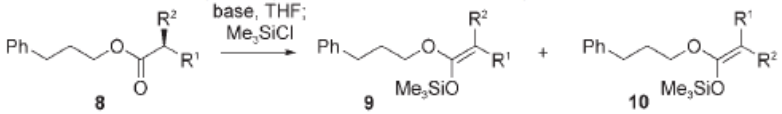


Once Again [3,3] !!!

Angew. Chem. Int. Ed. **2007**, *46*, 7466

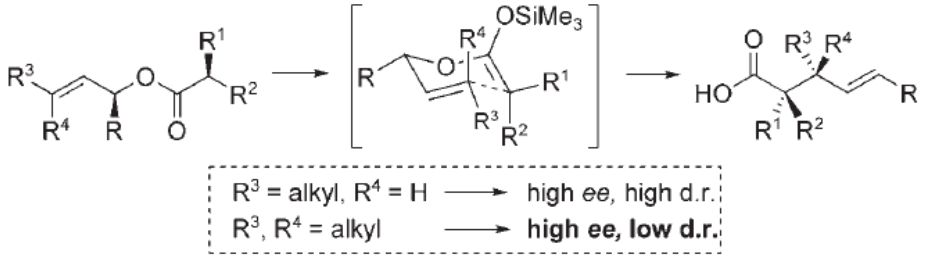
II. Acyclic Stereocontrol in Ireland–Claisen Rearrangement

Table 1: Preliminary study of the stereoselectivity of enolization.



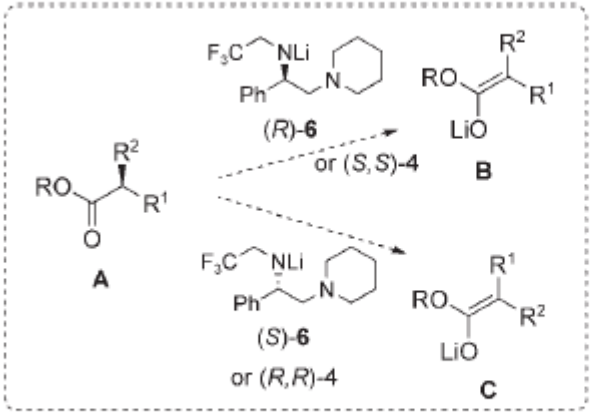
Entry	Ester	R^1	R^2	Base[a]	Z/E[b]
1	**8a**	CH_2CH_3	CH_3	LDA	67:33
2	**8a**	CH_2CH_3	CH_3	(*S*,*S*)-**4**	**95:5**
3	**8a**	CH_2CH_3	CH_3	(*R*,*R*)-**4**	21:79
4	**8a**	CH_2CH_3	CH_3	(*S*)-**5**	24:76
5	**8a**	CH_2CH_3	CH_3	(*R*)-**5**	92:8
6	**8a**	CH_2CH_3	CH_3	(*S*)-**6**	**8:92**
7	**8a**	CH_2CH_3	CH_3	(*R*)-**6**	92:8
8	**8b**	CH_3	CH_2CH_3	(*S*)-**6**	91:9
9	**8b**	CH_3	CH_2CH_3	(*R*)-**6**	8:92
10	**8c**	$(CH_2)_4OPMB$	$CH_2CH(CH_3)_2$	LDE	50:50
11	**8c**	$(CH_2)_4OPMB$	$CH_2CH(CH_3)_2$	LDA	82:18
12	**8c**	$(CH_2)_4OPMB$	$CH_2CH(CH_3)_2$	(*R*,*R*)-**4**	98:2
13	**8c**	$(CH_2)_4OPMB$	$CH_2CH(CH_3)_2$	(*S*,*S*)-**4**	75:25
14	**8c**	$(CH_2)_4OPMB$	$CH_2CH(CH_3)_2$	(*R*)-**5**	50:50
15	**8c**	$(CH_2)_4OPMB$	$CH_2CH(CH_3)_2$	(*S*)-**5**	>95:5
16	**8c**	$(CH_2)_4OPMB$	$CH_2CH(CH_3)_2$	(*R*)-**6**	**29:71**
17	**8c**	$(CH_2)_4OPMB$	$CH_2CH(CH_3)_2$	(*S*)-**6**	**>98:2**
18	**8d**	CH_2CH_3	CH_2Ph	LDA	65:35
19	**8d**	CH_2CH_3	CH_2Ph	(*R*,*R*)-**4**	**>98:2**

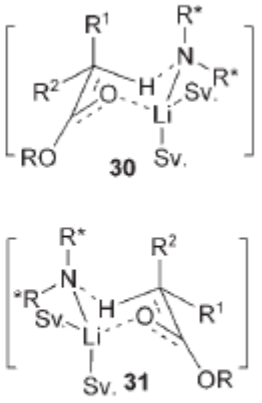
[a] LDA = lithium diisopropylamide, LDE = lithium diethylamide. [b] The ratio of isomers was determined by ^{1}H NMR spectroscopy at 500 MHz of the crude mixture of products. The configuration was established by NOE experiments.



Problem Identification

E/Z enolate

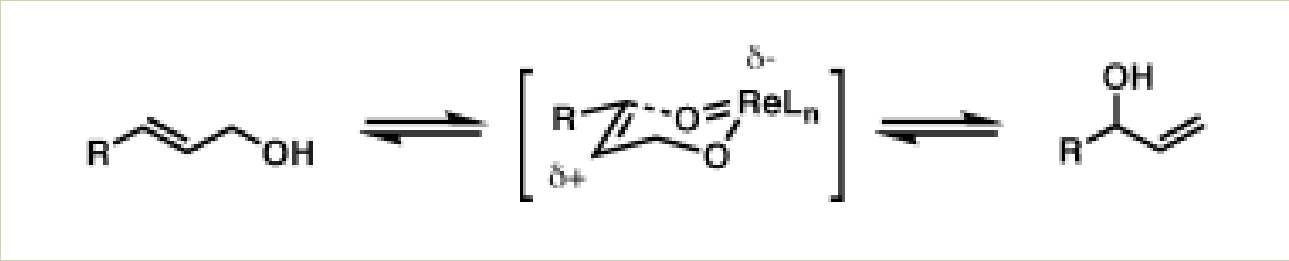




Scheme 5. An empirical predictive model for the stereoselective enolization. Sv. = solvent molecule.

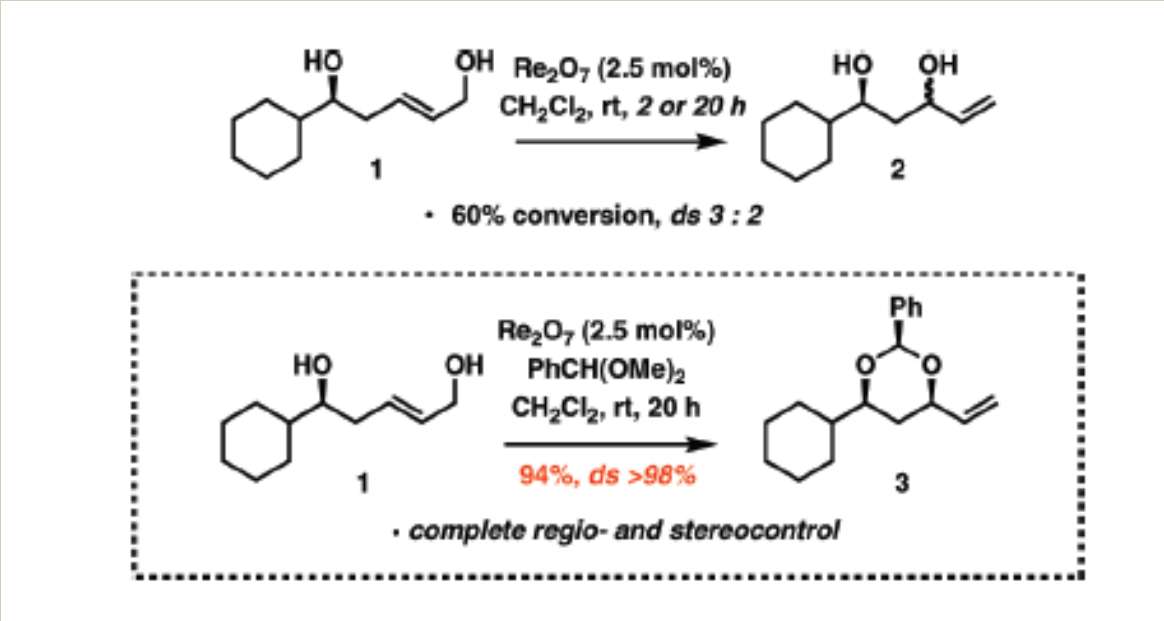
Angew. Chem. Int. Ed. 2007, 46, 7466

III. Regio- and Stereocontrol in Rhenium-Catalyzed Transposition of Allylic Alcohols



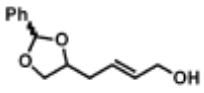
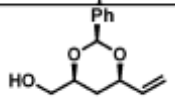
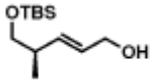
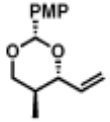
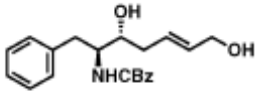
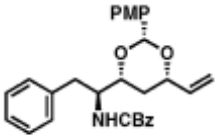
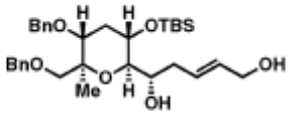
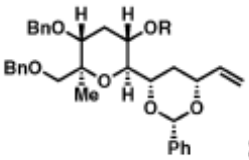
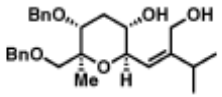
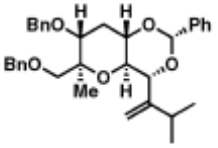
J. Am. Chem. Soc. **2010**, *132*, 5962

III. Regio- and Stereocontrol in Rhenium-Catalyzed Transposition of Allylic Alcohols



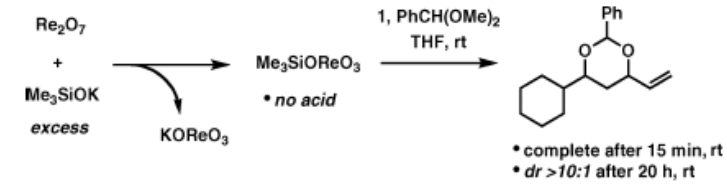
J. Am. Chem. Soc. **2010**, *132*, 5962

III. Regio- and Stereocontrol in Rhenium-Catalyzed Transposition of Allylic Alcohols

entry	substrate	product (yield, dr)
1		 80%, 96:4
2		 84%, 85:15
3		 65%, >98:2
10		 82%,[c] >98:2
11		 97%, >98:2

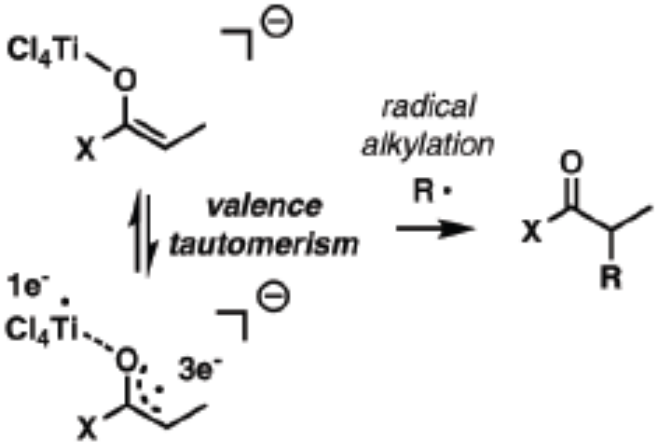
[a] Reactions were performed in CH_2Cl_2 (~0.2 M) with 2.5 mol % of Re_2O_7 and 2.0 equiv of $PhCH(OMe)_2$ or 4-MeOPhCH(OMe)$_2$; dr is determined by 500 MHz ^1H NMR.[b] Overall yield after treatment with TBAF.[c] R=H/R=TBS 5.3:1.

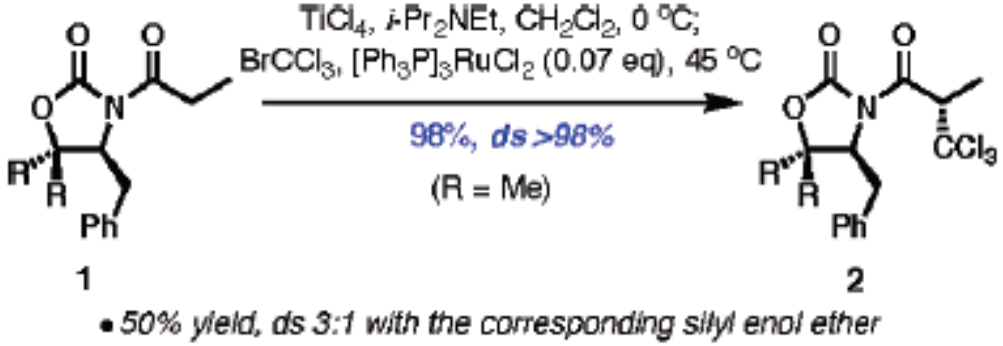
Scheme 3. Reactivity in the Absence of a Brønsted Acid



Basic conditions still produce the desired 1,3-syn ketal

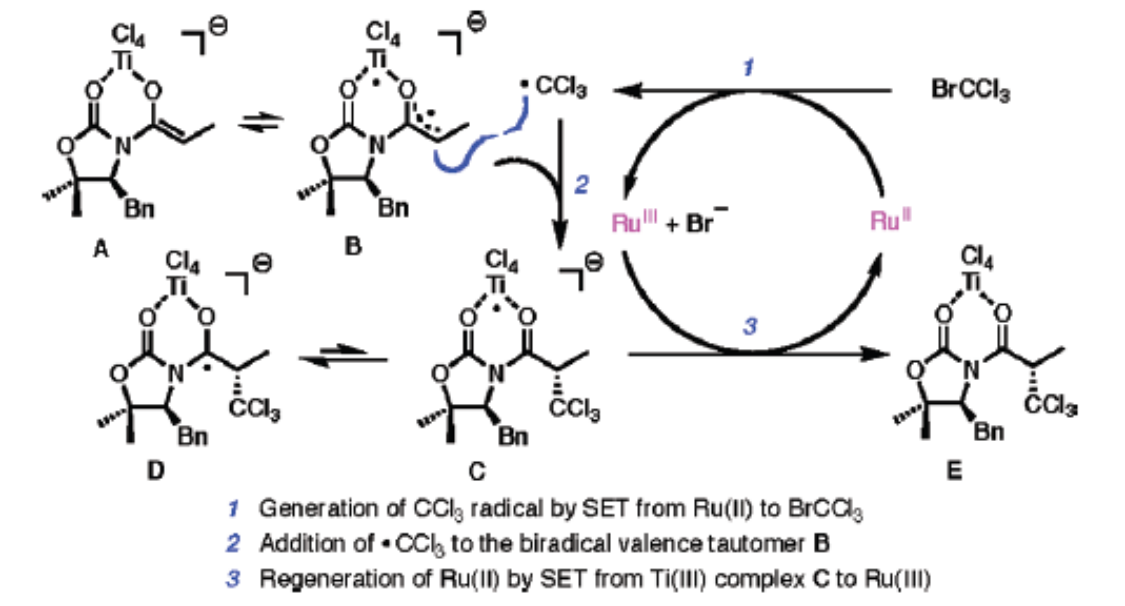
IV. Redox Catalysis For Radical Alkylation Alcohols





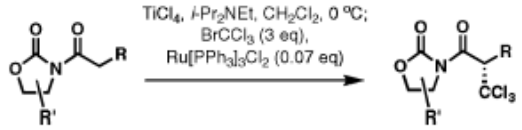
Science **1945**, *102*, 128 (Kharasch)

IV. Total Synthesis
Neodysidenin



J. Am. Chem. Soc. **2010**, *132*, 1482

IV. Total Synthesis
Neodysidenin



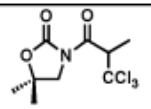
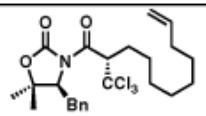
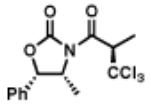
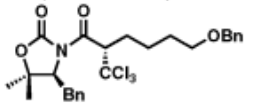
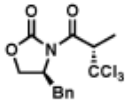
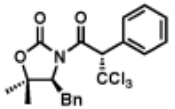
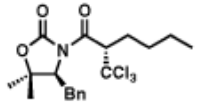
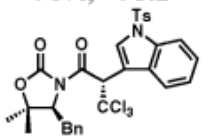
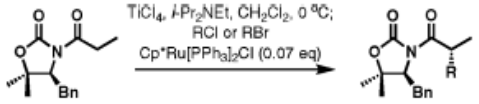
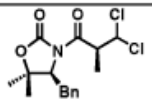
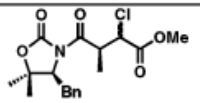
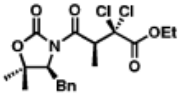
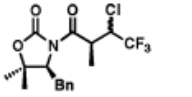
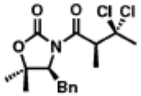
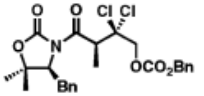
entry	product (dr, yield)[b]	entry	product (dr, yield)[b]
1	 95%	5	 63% (91% brsm), >98:2 [c]
2	 89%, >98:2	6	 87%, >98:2
3	 86%, >98:2	7	 91%, >98:2
4	 99%, >98:2	8	 61%, >98:2

Table 2. Radical Haloalkylation: Haloalkylating Agent Scope



entry	product	yield dr[a]	entry	product	yield dr[a]
1		64% >98:2	4		75% 1.3:1[b]
2		83% >98:2	5		71% 1.6:1[b]
3		71% >98:2	6		76% >98:2

[a] All reported yields are of isolated products; dr was determined by 500 MHz ^{1}H NMR. [b] At the indicated stereocenter.

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