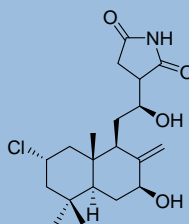


Site-Selective Aliphatic C-H Chlorination Using N-Chloroamides Enables a Synthesis of Chlorolissoclimide

C. D. Vanderwal and E. J. Alexanian et al., *J. Am. Chem. Soc.* **2016**, *138*, 696.

Daniel Meyer
University of Bern

11.03.2016, Journal Club



Outline

- > Autors
- > C-H Chlorination
- > Total Synthesis of Chlorolissoclimide
- > Conclusion

Autors

> Christopher D. Vanderwal (University of California, Irvine)

- Polychlorinated compounds
- Alkaloids from pyridine
- Polycyclic terpenes



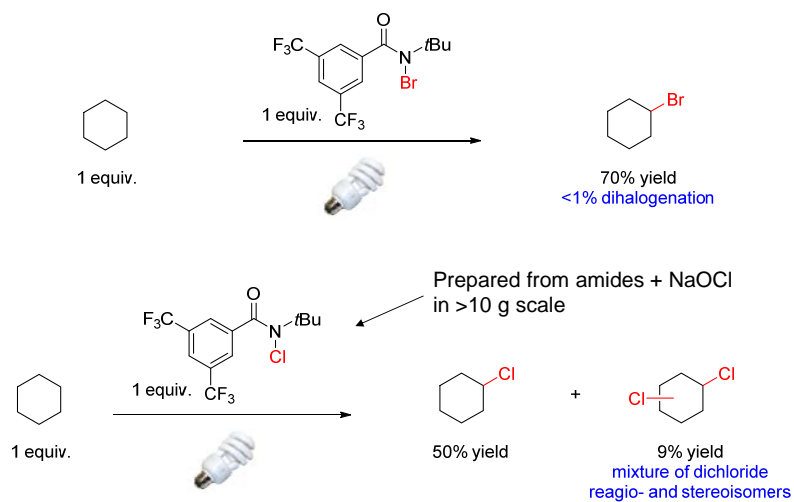
> Erik J. Alexanian (University of North Carolina)

- C–H functionalization using tuned heteroatom-centered radicals
- C–C bond-forming using alkyl electrophiles
- Multicomponent cycloadditions



3

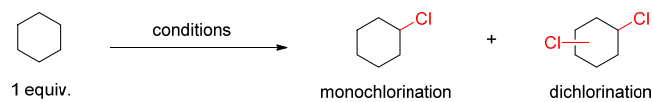
Bromination vs. Chlorination



Alexanian E. J. et al. *J. Am. Chem. Soc.* **2014**, 136, 14389.

4

Chlorination of Cyclohexane

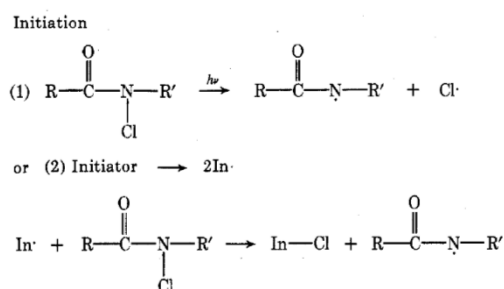


reagents	mono-Cl [%]	di-Cl [%]	conv. [%]
NCS, AIBN, 60 °C, (5 equiv. cyclohexane)	71.1	28.9	-
SOCl ₂ , PBO, 85 °C	71.1	28.9	85.7
Chloroamide, <i>hν</i> , r.t.	86.0	14.0	46.1
Chloroamide, <i>hν</i> , 1 equiv. Cs ₂ CO ₃ , r.t.	90.5	9.5	60.8
Chloroamide, <i>hν</i> , 1 equiv. Cs ₂ CO ₃ , 55 °C	96.9	3.1	71.6

Substrate 1 M in benzene

5

Mechanism



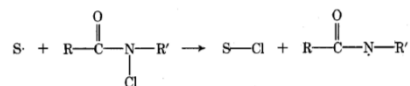
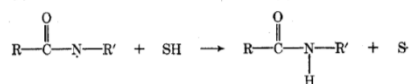
6

Mechanism

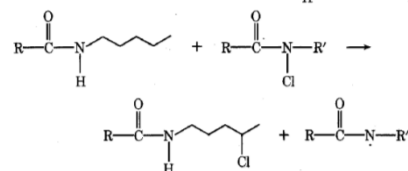
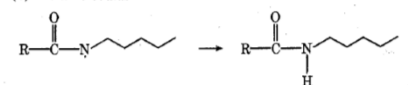
Propagation

(1) Amidyl radical chain

(a) Intermolecular



(b) Intramolecular

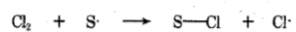
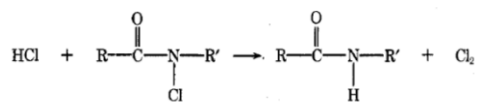


Johnson, R. A.; Green, F. D. *J. Org. Chem.* **1975**, *40*, 2186.

7

Mechanism

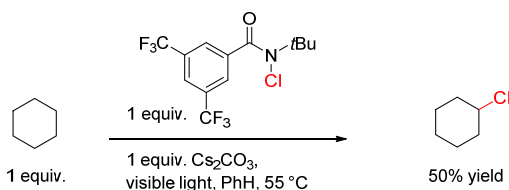
(2) Chlorine atom-HCl chain



Johnson, R. A.; Green, F. D. *J. Org. Chem.* **1975**, *40*, 2186.

8

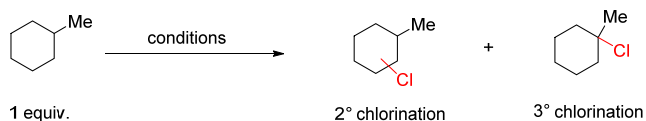
Mechanism



- > *d*₁₂-cyclohexane primary kinetic isotope effect: $k_H/k_D = 4.9$
- > Bromination with N-bromo derivative: $k_H/k_D = 4.9$
- > Consistent with an amidyl radical

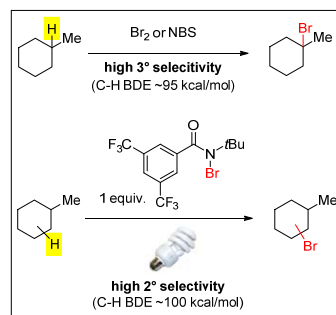
9

Chlorination of Methylcyclohexane



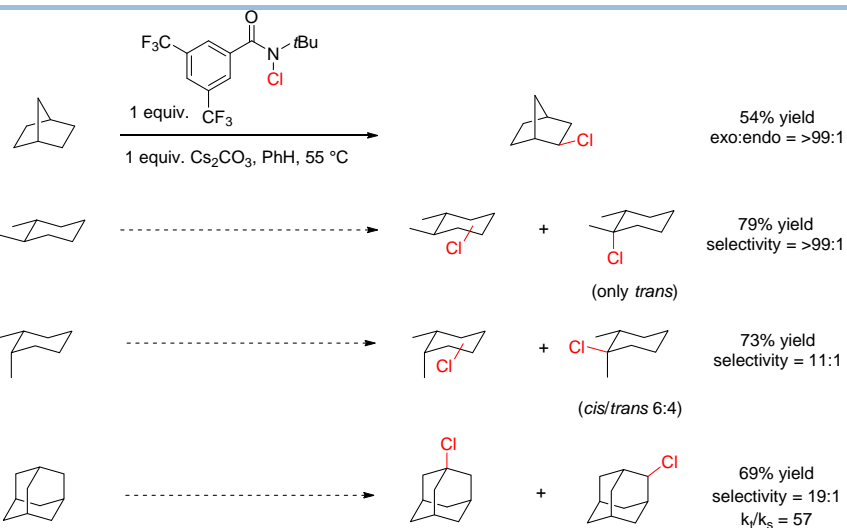
reagents	2° Cl [%]	3° Cl [%]	$k_{\text{secondary}}/k_{\text{tertiary}}$
NCS, AIBN, 60 °C, (neat in methylcyclohex.)	75.9	24.1	0.31
SOCl ₂ , PBO, 85 °C	73.9	26.1	0.28
Chloroamide, <i>h</i> _v , r.t.	74.5	25.5	0.29
Chloroamide, <i>h</i> _v , 1 equiv. Cs ₂ CO ₃ , r.t. (44% yield)	93.3	6.7	1.4
Chloroamide, <i>h</i> _v , 1 equiv. Cs ₂ CO ₃ , 55 °C (74% yield)	98.5	1.5	6.6

Substrate 1 M in benzene



10

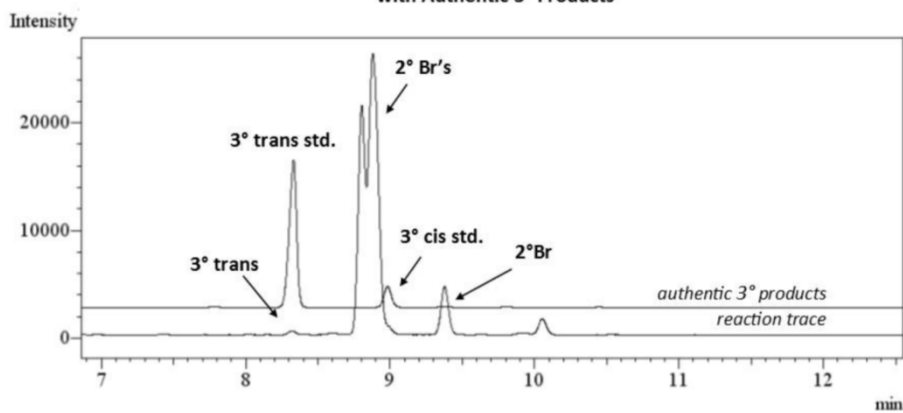
Chlorination alkenes



11

Bromination *trans*-1,2-Dimethylcyclohexane

Overlaid Chromatogram: Bromination of *trans*-1,2-Dimethylcyclohexane
with Authentic 3° Products

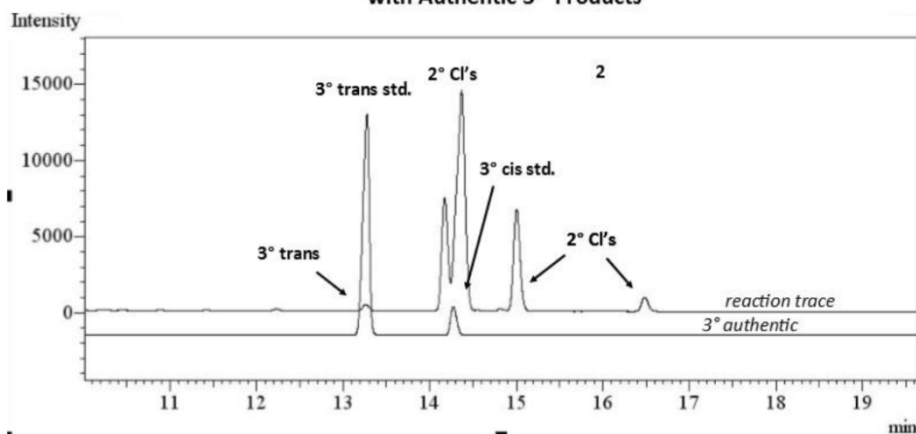


J. Am. Chem. Soc. 2008, 130, 8172.

12

Chlorination *trans*-1,2-Dimethylcyclohexane

Overlaid Chromatogram: Chlorination of 1,2 *trans* dimethylcyclohexane with Authentic 3° Products



J. Am. Chem. Soc. **2008**, *130*, 8172.

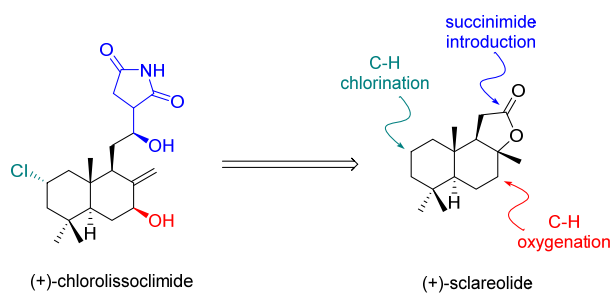
13

Aliphatic C-H Chlorination

substrate (1 equiv.)	selective chlorination [%]					combined yield [%]
	α	β	γ	δ	ω	
<chem>COCC(=O)CCCC</chem> with SOCl ₂ , BPO, 85 °C <chem>COCC(=O)CCCC</chem>	-	12	38	42	8	-
<chem>ClCCCCC</chem>	4	5	20	58	14	83
<chem>CC(=O)CCCC</chem>	9	6	15	57	13	74
<chem>CC(=O)OCCCC</chem>	-	9	20	57	14	89
<chem>C1=CC=C(NC1)CCCC</chem>	-	-	5	81	14	80
<chem>C1=CC=C(NC1)CC(C)CC</chem>	-	2	8	64	27	69
<chem>COCC(C)C=C</chem> 	-	-	-	-	-	65 (isolated yield)

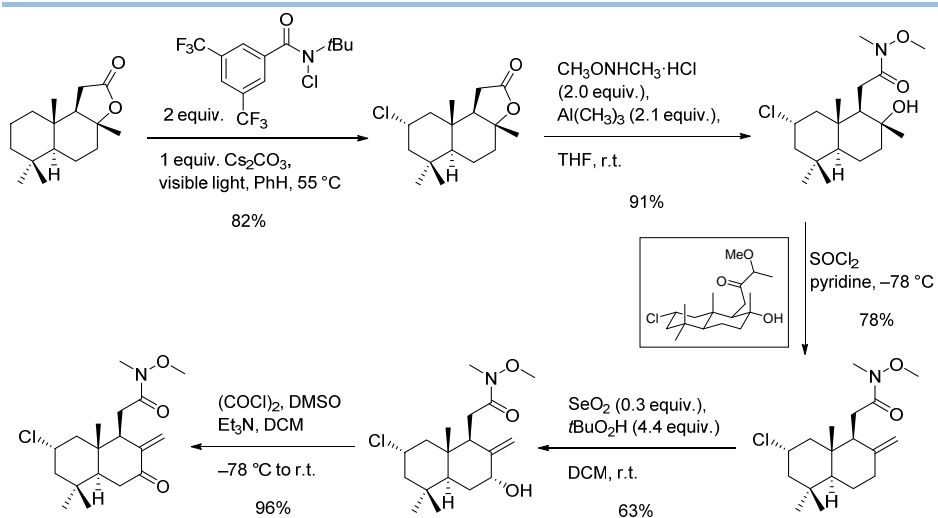
14

Retrosynthetic Analysis



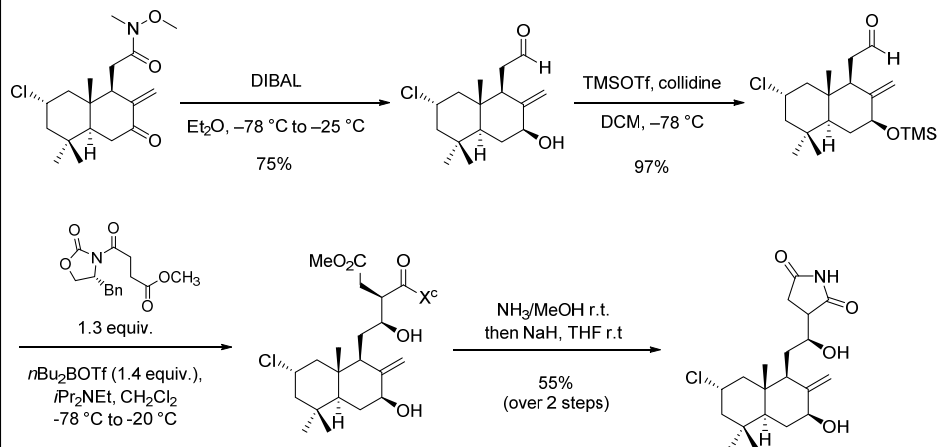
15

Forward Synthesis



16

Forward Synthesis



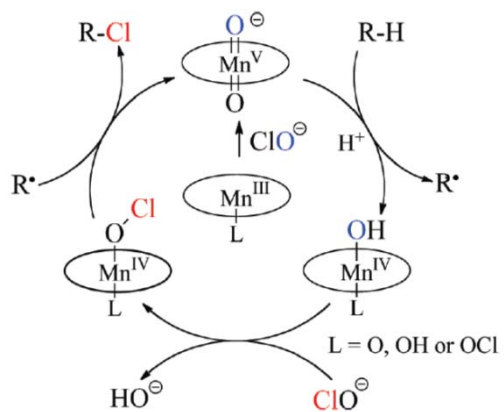
17

Conclusion

- > Site-selective approach to aliphatic C-H chlorination
— electronical and sterical influence of substrate
- > First total synthesis of (+)-chlorolissoclimide
- > 14% yield over nine steps

18

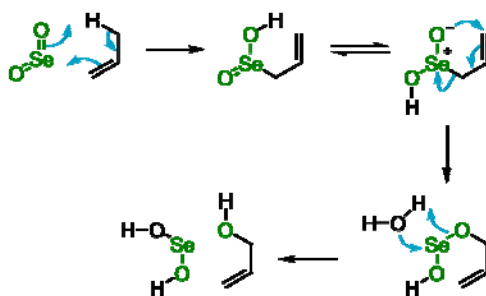
Manganes Porphyrins



J. Am. Chem. Soc. **2006**, 128, 15552.

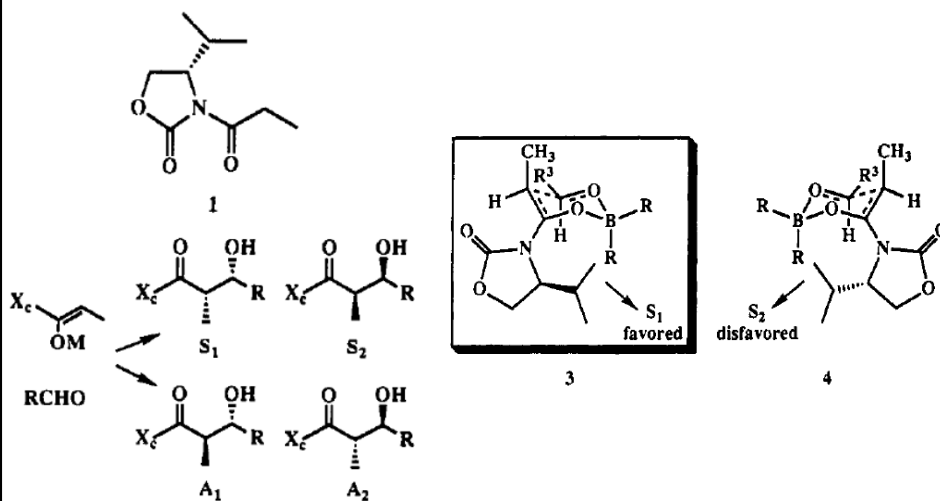
19

Selenium Dioxide Oxidation



20

Syn-Aldol Addition



Nerz-Stormes, M.; Thornton, E. R. J. Org. Chem. 1991, 56, 2489.

21