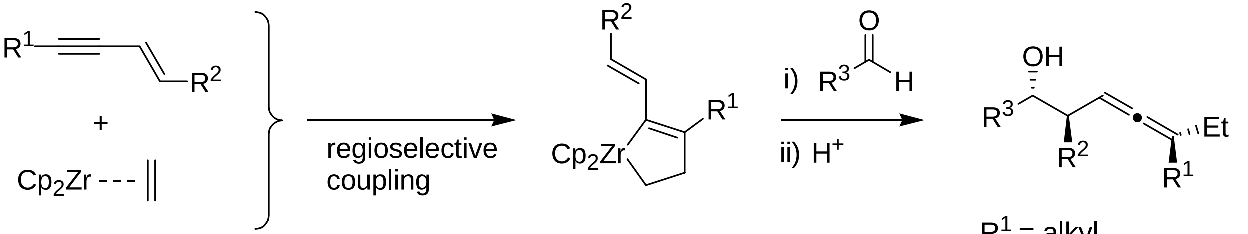
Stereoselective Synthesis of β-Hydroxyallenes with Multiple Contiguous Stereogenic Centers via Aldehyde Addition to α-Alkenyl-Substituted Zirconacyclopentenes

Zhou, Y.; Chen, J.; Zhao, C.; Wang, E.; Liu, Y.; Li, Y. *J. Org. Chem.* **2009**, *74*, 5326-5330.



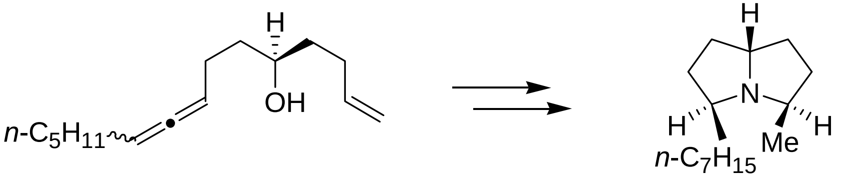
R^1 = alkyl
R^2 = alkyl, aryl
R^3 = alkyl, aryl, heteroaryl

Chad Hopkins

Wipf Group Literature Presentation

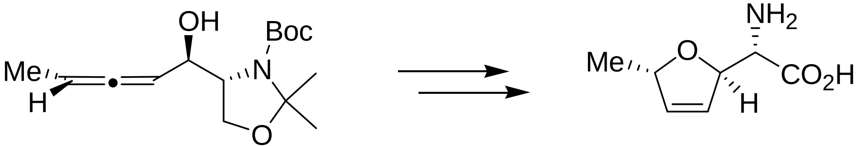
8-15-09

Allenes in Synthesis



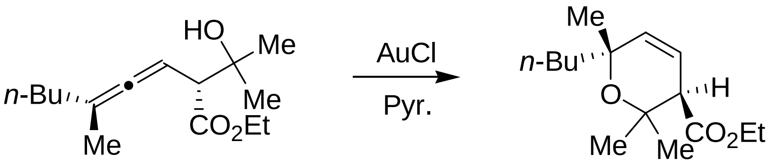
(+)-Xenovenine

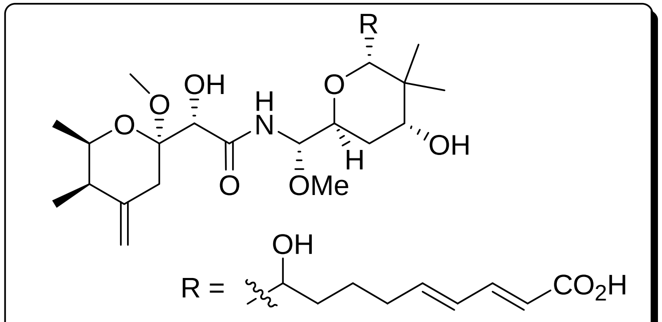
Arredondo, V. M.; Tian, S.; McDonald, F. E.; Marks, T. J. *J. Am. Chem. Soc.* **1999**, *121*, 3633-3639.



Furanomycin

VanBrunt, M. P.; Standaert, R. F. *Org. Lett.* **2009**, *2*, 705-708.

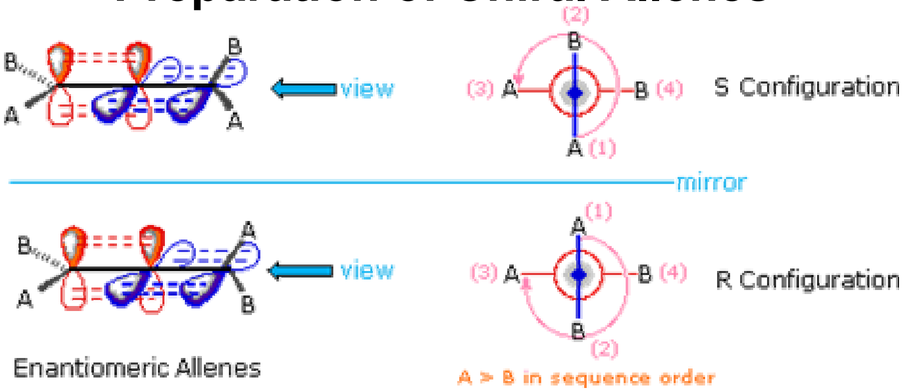




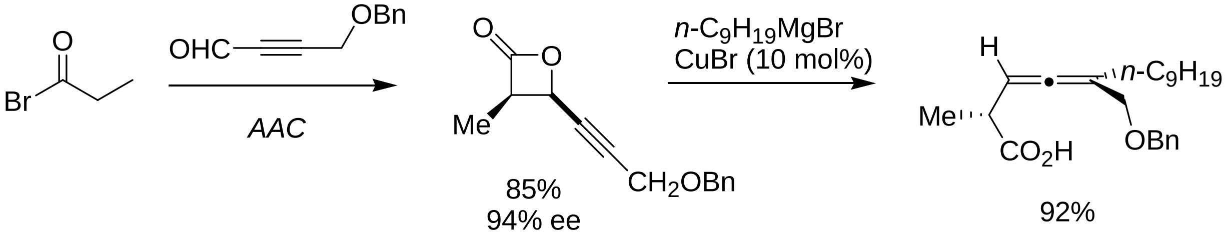
Onnamide F (antifungal)

Gockel, B.; Krause, N. *Org. Lett.* **2006**, *8*, 4485-4488.

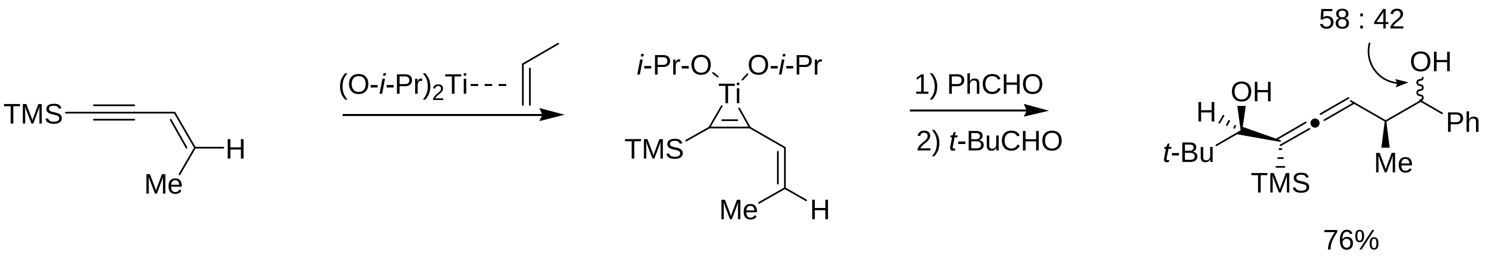
Preparation of Chiral Allenes



http://www.cem.msu.edu/~reusch/VirtualText/special1.htm



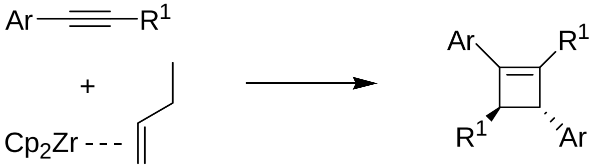
Wan, Z.; Nelson, S. G. *J. Am. Chem. Soc.* **2000**, *122*, 10470-10471.



Hamada, T.; Mizojiri, R.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **2000**, *122*, 7138-7139.

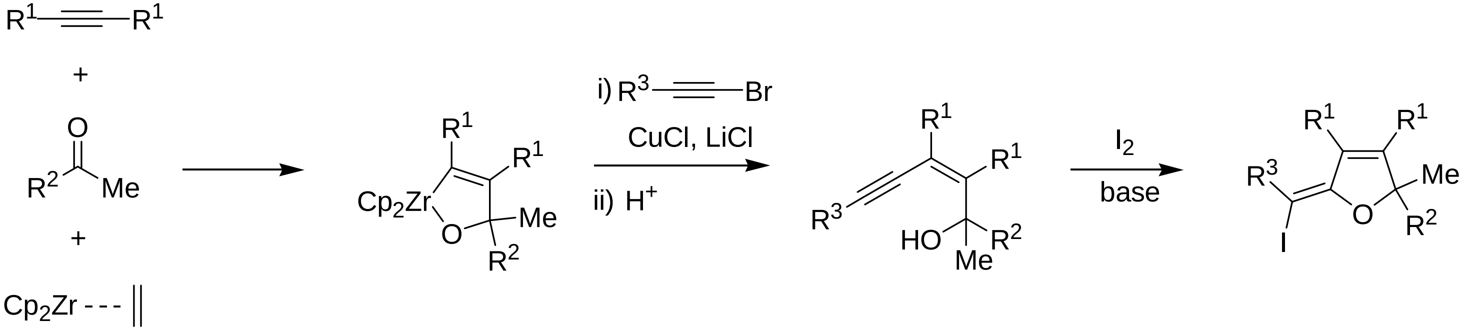
For additional reading pertaining to synthesis of allenes and their use, see: *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, Germany, 2004 and *Allenes in Organic Synthesis*; Schuster, H. F., Coppola, G. M., Eds.; John Wiley & Sons: New York, 1984.

Author’s Previous Work

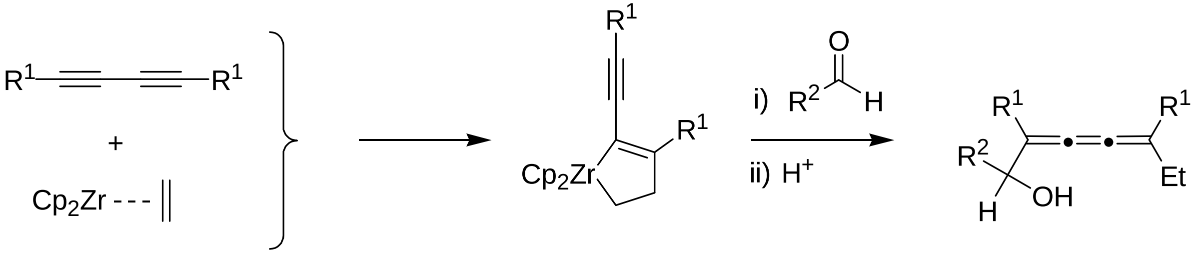


R^1 = alkyl, aryl, TMS

Liu, Y.; Liu, M.; Song, Z. *J. Am. Chem. Soc.* **2005**, *127*, 3662-3663.



Liu, Y.; Song, F.; Cong, L. *J. Org. Chem.* **2005**, *70*, 6999-7002.

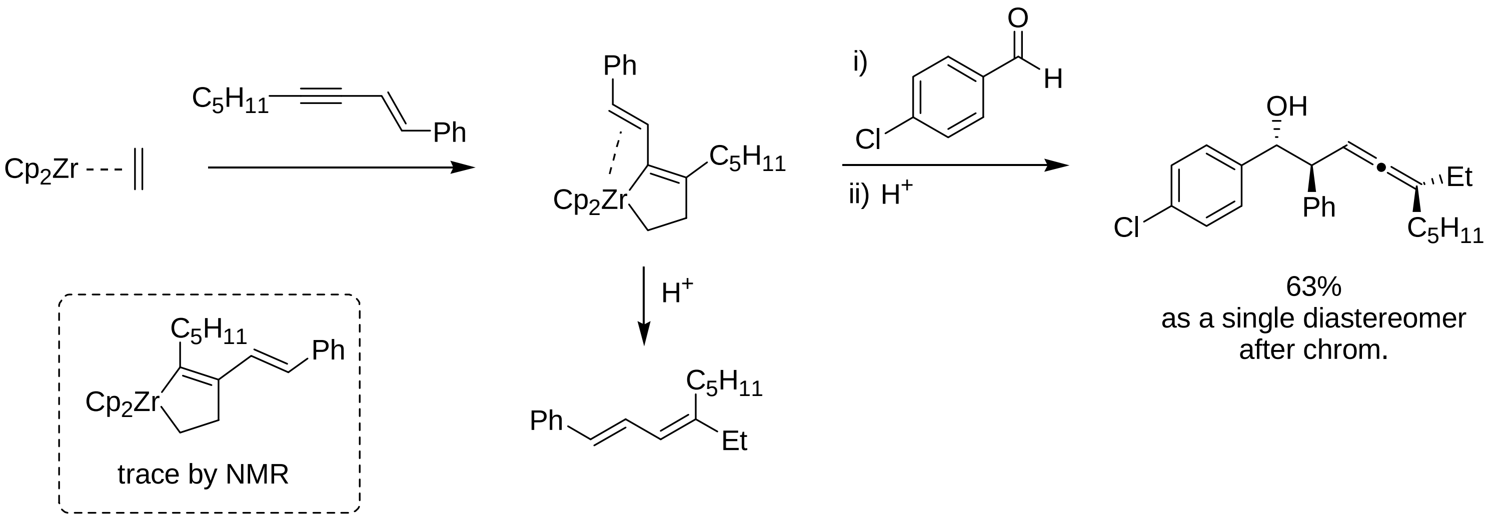


R^1 = alkyl, aryl, heteroaryl, TMS

R^2 = alkyl, aryl, heteroaryl

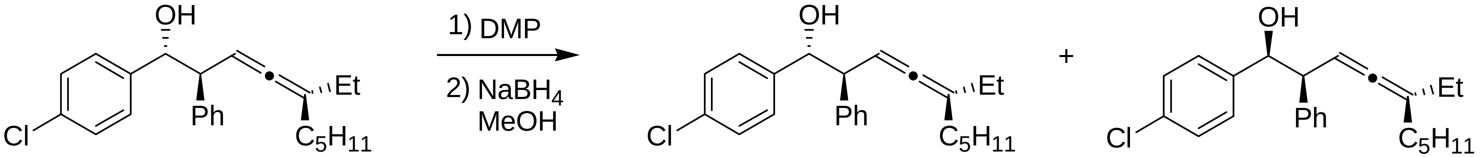
Liu, Y.; Gao, H.; Zhou, S. *Angew. Chem. Int. Ed.* **2006**, *45*, 4163-4167.

New Synthetic Potential



63%
as a single diastereomer
after chrom.

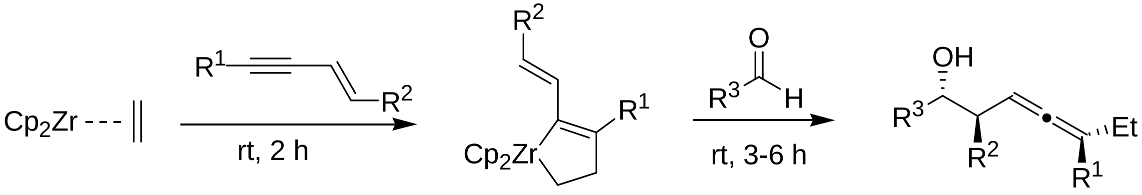
trace by NMR

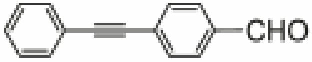


25%
(1*R*, 2*S*, *R*$_a$)

58%
(1*S*, 2*S*, *R*$_a$)
(*x-ray*)

Reaction Scope

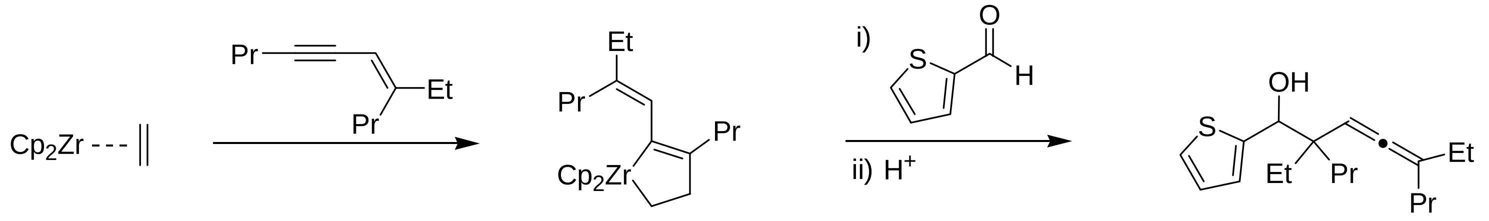


entry	R^1	R^2	R^3CHO	product	yield(%)^a
1	n-C_5H_{11}	Ph	p-ClC_6H_4CHO	**5a**	63 (93:7)
2	n-Pr	Ph	3,4,5-$(MeO)_3C_6H_2CHO$	**5b**	68 (93:7)
3	n-C_5H_{11}	Ph	p-$CH_3C_6H_4CHO$	**5c**	68 (97:3)
4	n-C_5H_{11}	Ph	p-$NMe_2C_6H_4CHO$	**5d**	72^b (93:7)
5	n-C_5H_{11}	Ph	PhCHO	**5e**	58 (97:3)
6	n-C_5H_{11}	Ph	p-$NO_2C_6H_4CHO$	**5f**	67 (88:12)
7	n-C_5H_{11}	Ph		**5g**	53 (96:4)
8	n-C_5H_{11}	Ph	^nPrCHO	**5h**	63 (98:2)
9	n-Pr	Ph	1-naphthaldehyde	**5i**	65 (96:4)
10	n-Pr	Ph	p-$NO_2C_6H_4CHO$	**5j**	71 (89:11)
11	n-Pr	Ph		**5k**	65 (96:4)
12	n-Bu	n-Bu	^nPrCHO	**5l**	63^c

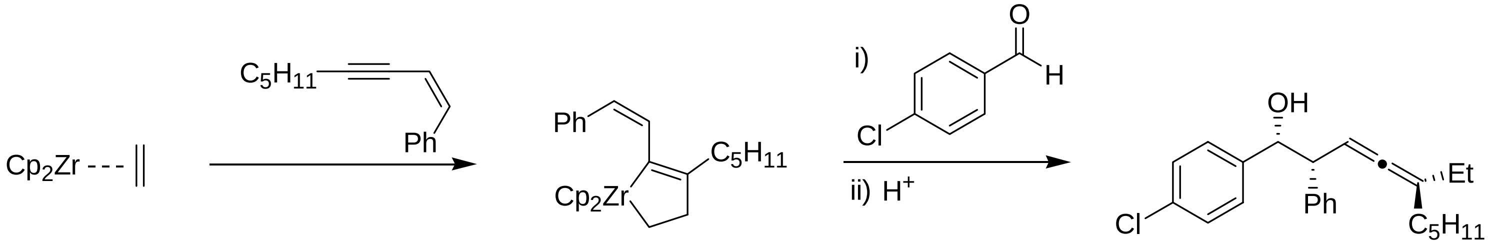
(*x-ray*)

- no obvious trend in aldehyde reactivity

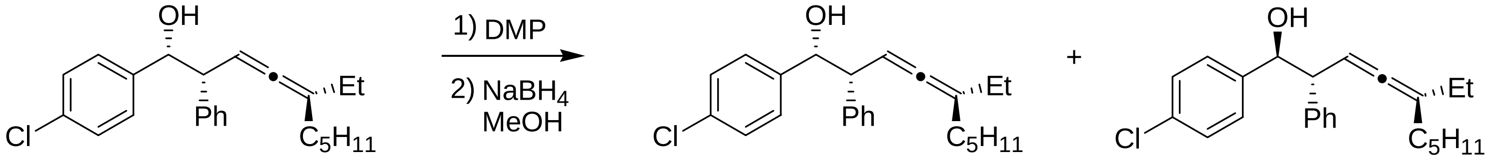
Reaction Scope and Limitations



54%



53%
(dr 5.5 : 1, separable)
(*x-ray* of major diast.)

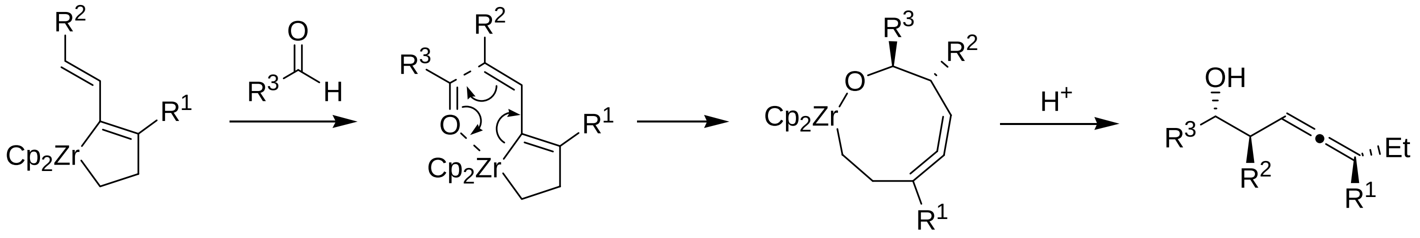


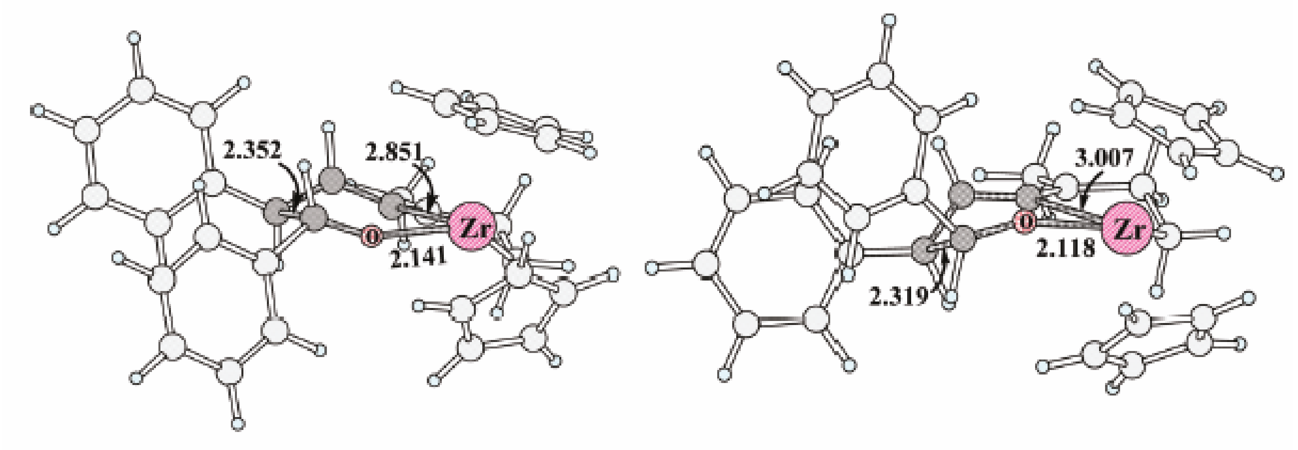
75%
(1*R*, 2*R*, *R*$_a$)

17%
(1*S*, 2*R*, *R*$_a$)

Ketones were not successful under the reaction conditions

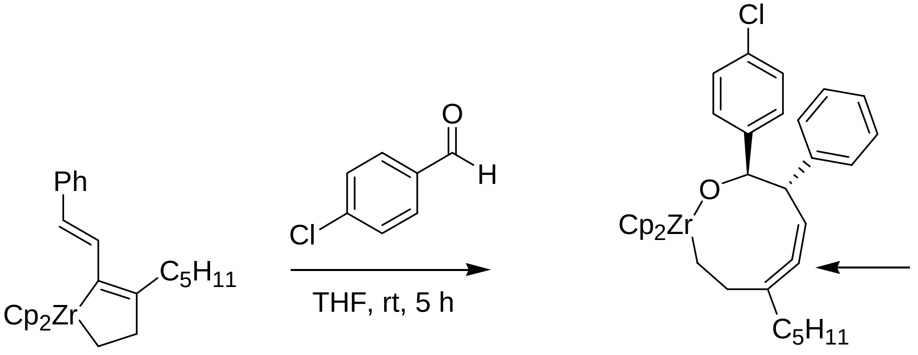
Proposed Mechanism





Ts-(1R*, 2S*, R*a) 0.0

Ts-(1S*, 2S*, R*a) 2.1



THF, rt, 5 h

204.2 ppm (^{13}C NMR)

77%
(^{1}H NMR Yield,
CH_2Br_2 internal std.)

Summary

- Mild Zr-mediated stereoselective synthesis of allenes containing multiple stereocenters
- Highly chemoselective
- Broad scope with respect to aldehyde; Ketones were unsuccessful
- Sterically encumbered enynes were successfully utilized
- Appears to be currently limited to ethyl substituent