Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron Letters 46 (2005) 2345–2349

Tetrahedron Letters

Chromium(III) catalyzed synthesis of allenes from propargyl derivatives via a carbometalation–elimination sequence

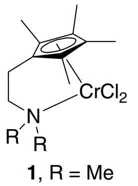
Gary A. Molander* and Erin M. Sommers

Roy and Diana Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, Philadelphia, PA 19104-6323, USA

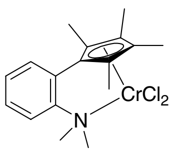
Received 13 October 2004; revised 26 January 2005; accepted 26 January 2005

Abstract—The *syn*-carbometalation/*syn*-elimination of propargyl substrates to form allenes has been achieved using cationic chromium(III) catalysts activated by alkylaluminums. The mechanism and scope of this transformation are presented.

During the past two decades, our laboratory has concentrated research efforts on adapting organometallic, specifically organolanthanide, complexes for small molecule synthesis. Despite the wide array of attractive transformations that have been achieved with organolanthanide catalysts,[1] several inherent limitations exist. The highly Lewis acidic organolanthanide complexes demand strict exclusion of moisture and oxygen and are intolerant of many functional groups, including terminal alkynes. In addition, the lanthanides catalyze intramolecular carbon–carbon bond-forming reactions but only following an initial hydrometalation step. This sequence forbids a single-step intermolecular carbometalation reaction. To expand our organometallic catalysis program and circumvent the obstacles of the lanthanide methods, we desired a new catalyst system that would display increased tolerance for functional groups using straightforward benchtop manipulations leading to a carbometalation rather than hydrometalation event. We envisioned known chromium olefin polymerization catalysts (**1**–**3**) as viable alternatives to the lanthanides and other group 4 carbometalation catalysts.[2,3] As later transition metals, chromium complexes were expected to be easier to synthesize and handle and more tolerant of a wider range of functionality than the lanthanides and group 4 metal systems. We began this program by exploring the utility of chromium(III) complexes in the carbometalation of alkynes.[†] Although we were able to effect the desired transformation (Eq. 1), organochromium complexes also proved to have low tolerance for functionality. In addition to this shortcoming, the chromium(III) complexes showed little regioselectivity with internal alkynes. However, we were able to synthesize several 1,1-disubstituted alkenes successfully in moderate yields using chromium(III) complexes. Despite their limitations, a curious result prompted us to explore the utility of these complexes for the synthesis of allenes. When propargyl alcohol derivatives were subjected to the reaction conditions, allenes were produced instead of the expected alkene products (Eq. 1). This transformation contrasts starkly to the carbometalation reaction reported by Negishi and co-workers with α-heterosubstituted substrates.[3b] Because allenes are present in many natural products and serve as useful synthons for synthetic transformations, the efficient synthesis of the allenyl functional group is an attractive pursuit.[4a,b] Many syntheses of allenes have been reported. However, the most widely used methods stem from organocuprate displacement of propargylic leaving groups.[4c] Therefore, we sought to explore the mechanism and scope of this unanticipated reaction. Herein we report the synthesis of stereodefined allenes through a *syn*-carbometalation/*syn*-elimination sequence.



1, R = Me
2, R = -(CH$_2$)$_4$-



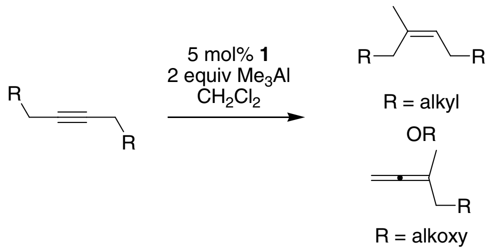
3

Keywords: Chromium(III) complexes; Allenes; Propargylic compounds.

* Corresponding author. Tel.: +1 215 573 8604; fax: +1 215 573 7165; e-mail: gmolandr@sas.upenn.edu

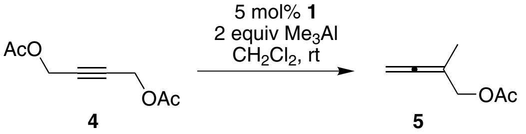
[†] See Supplementary material for summary.

0040-4039/$ - see front matter
doi:10.1016/j.tetlet.2005.01.143



(1)

At the outset of our studies, 1,4-bisacetoxy-2-butyne, **4**, was subjected to 5 mol% of catalyst and 2 equiv of Me_3Al to yield 1-acetoxy-2-methyl-2,3-butadiene in 73% yield (Eq. 2).[5] Allene product formation transpires via substitution of an acetoxy leaving group. This substitution could occur via several mechanistic pathways: a *syn*-carbometalation/*syn*-elimination, a *syn*-carbometalation/*anti*-elimination, an *anti* or *syn* S_N2' reaction, or a non-stereospecific S_N1 reaction. We ventured to explore the details of this transformation with the reaction shown in Table 1.



(2)

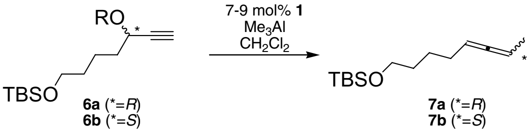
When the acetate derivative **6a** (entry 1) was subjected to 5 mol% of **1** and 1.5 equiv of Me_3Al, a chiral non-racemic allene **7a** was formed in 17% ee based on chiral GC analysis. To delineate the absolute stereochemistry of the allene, we compared the chromium catalyzed reaction with an organocuprate reaction. We subjected the enantiomeric acetate **6b** to organocuprate reaction conditions known to afford 36% of a mixture of *anti* S_N2' product (57% ee) and the reduced allene. The allene isolated from this reaction was identical to that formed in the chromium catalyzed reaction of **6a**.[6] These results indicate that the reaction catalyzed by chromium likely undergoes *syn*-carbometalation/*syn*-elimination or a *syn* S_N2' reaction. While a *syn* S_N2' mechanism cannot be eliminated based on our results, our previous carbometalation of alkynes suggests a carbometalation occurs followed by a *syn* elimination. Only one other example of a *syn*-addition/*syn*-elimination sequence has been reported in the organocuprate literature.[7]

An enantiomeric excess of 17% is not synthetically useful. Therefore, we screened leaving groups that maintained the stereochemical integrity in the formed allene. Table 1 highlights the results of this study. A general trend emerges from the results; the poorer the leaving group, the better the retention of stereochemical integrity from substrate to product. For example, one of the poorest leaving groups studied, *tert*-butyldimethylsilanoxy (entry 7), provides the highest optical yields. The optical yield is also susceptible to changes in the equivalents of Me_3Al used. The highest optical yields were obtained when only 1 equiv of Me_3Al was used. The excess of Me_3Al may act as a Lewis acid, promoting ionization of the leaving group in an S_N1-type reaction. Additionally, the temperature of the reaction affects the outcome. Each leaving group showed poorer optical yields when the temperature was raised beyond ambient temperature. Even the *tert*-butyldimethylsilanoxy group suffered from a dramatic loss of ee when the temperature was raised to 55 °C.

Before proposing a mechanism, one other aspect bears discussion. Surprisingly, the regiochemistry of organometallic insertion on the alkyne is opposite to that observed during our studies of the carbometalation of non-directing, internal, unsymmetrical alkynes.[†] In the present transformation, the chromium with its bulky substituents are placed at the more sterically congested terminus of the alkyne. This observed phenomenon suggests that the alkoxy substituent coordinates to the chromium, directing it to the proximal carbon of the alkyne.

To rationalize the observed results, we propose the mechanism shown (Fig. 1). Activation of **1** to give complex **A** is a well-documented and accepted first step in the olefin polymerization literature.[8] Complex **A**, pos-

Table 1. Leaving group studies



Entry	*R*, configuration	Catalyst loading (mol%)	Me_3Al (equiv)	Time	Temperature (°C)	Optical yield[a] (% ee)
1	Ac, *R*	7	1.0	5.5 h	0 to rt	19 (17)
2	Bn, *R*	8	1.5	19 h	rt	56 (50)
3	Bn, *R*	8	1.7	2.5 h	55	36 (32)
4	CO_2Me, *S*	10	1.8	30 min	rt	0
5	CO_2NHPh, *S*	10	1.8	30 min	rt	85 (73)
6	CO_2NH*t*-Bu, *S*	10	2.0	9 h	rt	n/a[b]
7	TBS, *R*	7	1.0	24 h	rt	96 (85)
8	TBS, *R*	9	1.5	6.5 h	55	67 (60)

[a] Optical yield = (ee product/ee substrate) × 100.

[b] The carbamate was removed under the reaction conditions.

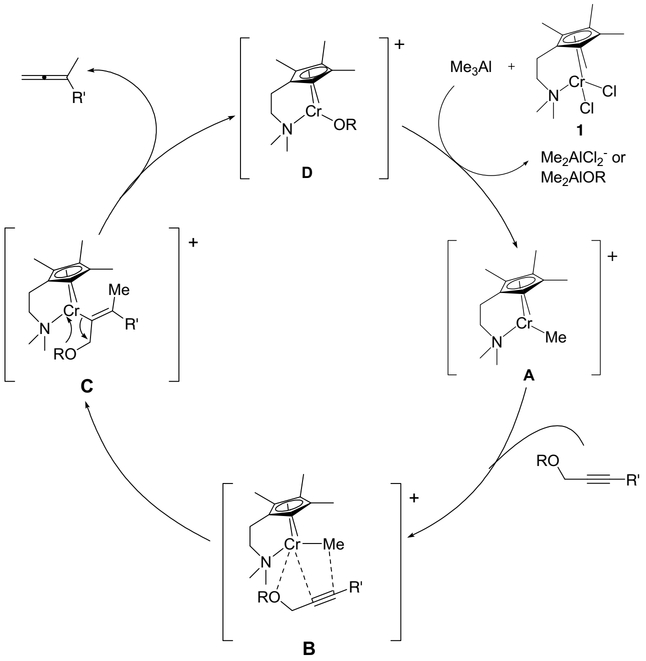
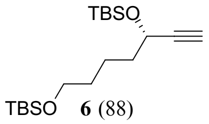
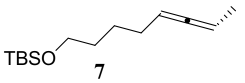
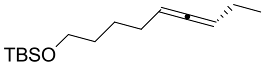
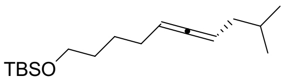
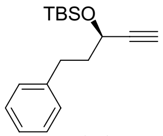
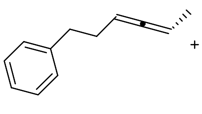
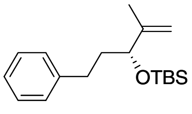
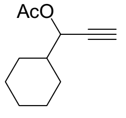
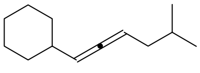


Figure 1. Proposed catalytic cycle.

sessing an open coordination site, is poised to coordinate an alkyne to give complex **B**. The alkyne then undergoes a carbometalation reaction through a *syn*-addition to give intermediate **C**. At this point, when no α-oxygenated substituent is present, the alkenylchromium species is transmetalated to aluminum yielding an alkenylaluminum intermediate, regenerating the active species. However, when an α-oxygenated substituent is present, a *syn* β-elimination occurs to release the allene product and generate a chromium alkoxide intermediate (**D**). This intermediate can be transformed to the active species (**A**) in a manner analogous to that of the initial precatalyst **1**.

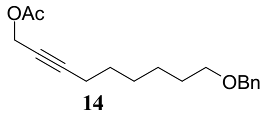
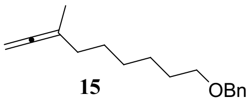
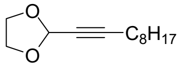
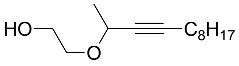
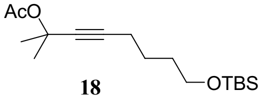
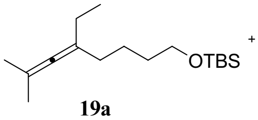
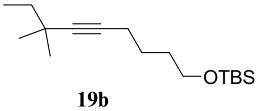
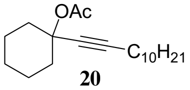
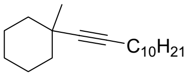
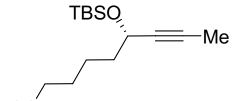
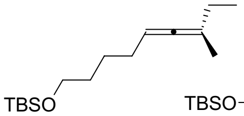
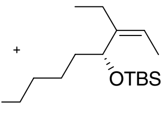
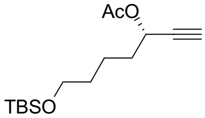
After determining the optimal leaving group, the catalyst loading was optimized and the scope of the reaction was explored. It should be noted that the reaction does not proceed when the chromium(III) catalyst is absent from the reaction mixture. Table 2 lists the results of expanding this method to other substrates (entries 4–10) and organometallic nucleophiles (entries 1–3, 11). Different trialkylaluminum species, such as Et_3Al and i-Bu_3Al, were able to effect the transformation in high optical yield by transferring an ethyl and *iso*-butyl group, respectively. To widen the utility of the transformation, Et_2Zn was substituted for an alkylaluminum species. The reactivity of Et_2Zn was significantly attenuated compared to the alkylaluminums. For example, good leaving groups, such as acetate and methyl carbonate, were necessary to achieve good yields of the allene product. In contrast to Me_3Al, Et_2Zn reacted with the TBS derivative in less than 10% yield (based on GC) to yield a 1:2 mixture of allene and the regioisomeric carbometalated alkene. In addition, the benzyloxy

Table 2. Chromium catalyzed synthesis of allenes

Entry	Substrate (% ee)	Product	R–M[a]	% Yield (% ee)
1	 **6** (88)	 **7**	Me_3Al	83 (86)[b]
2	**6** (90)	 **8**	Et_3Al	82 (85)
3	**6** (90)	 **9**	i-Bu_3Al	79 (82)
4	 **10** (84)	 **11a** +  **11b**	Me_3Al	**11a** = 20 (81) **11b** = 4
5	 **12**	 **13**	i-Bu_3Al	n/a[c]

(*continued on next page*)

Table 2 (*continued*)

Entry	Substrate (% ee)	Product	R–M[a]	% Yield (% ee)
6	 **14**	 **15**	Me_3Al	54
7	 **16**	 **17**	Me_3Al	71
8	 **18**	 **19a** +  **19b**	Et_3Al	**19a** = 19 **19b** = —[d]
9	 **20**	 **21**	Me_3Al	80
10	 **22** (90)	 **23a** +  **23b**	Et_3Al	**23a** = 50[e] **23b** = <1
11	 **24** (90)	**8**	Et_2Zn	59 (14)

[a] Reagents and conditions: 7–10 mol% **1**, 1.0–2.0 equiv Me_3Al, CH_2Cl_2, rt.

[b] The alkene produced by the regioisomeric carbometalation was observed by GC/MS and crude NMR (<5%) but never isolated.

[c] Isolated in toluene due to the volatility of the product.

[d] Compound **19b** is contaminated by an unidentifiable side product.

[e] Compound **23a** could not be resolved by chiral GC.

derivative gave one turnover of the alkene product (by GC). The diminished ee of the acetate derivative, regardless of the nucleophiles, indicates that the reaction proceeds through a non-stereospecific ionization/substitution pathway when the leaving group is readily ionized. However, the regiospecificity of the Et_2Zn reactions is puzzling, and the actual mechanism is likely more complicated than we propose; perhaps a bimetallic species defines the active catalyst.

Similar to our original studies, little functionality can be present in the substrate.[†] For example, a simple phenyl ring (entry 4) initiates side reactions that lower the isolated yield significantly. Entry 6 highlights an example of the formation of a terminal allene. Because the product allene is achiral, using the less atom economical *tert*-butyldimethylsilanoxy leaving group is unnecessary. Entries 8 and 9 illustrate how the steric environment also affects the outcome of the reaction. The bulky cyclohexyl group hinders allene formation, and only the Reetz product is observed.[9] In contrast, the dimethyl analogue (entry 8) gives the allene as the minor product. Finally, we attempted to access a chiral non-racemic 1,1,3-trisubstituted allene (entry 10). In addition to a modest yield of the allene product, we isolated <1% of the regioisomeric carbometalation product.

In conclusion, we have successfully synthesized allenes from propargylic *tert*-butyldimethylsilyl ethers in modest yields and high optical purity. The reaction appears to proceed through a *syn*-carbometalation/*syn*-elimination sequence. Because allenes represent a useful class of compounds both as natural products and synthons for further transformations, efforts from our laboratory continue to focus on the use of transition metal catalysis to synthesize chiral, non-racemic allenes with broad substrate scope.

Acknowledgements

We are grateful for financial support from NIGMS (GM 48580) and the Merck Research Laboratories. In addition, E.S. is funded by a Department of Education GAANN Fellowship.

Supplementary data

Full experimental details are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.01.143.

References and notes

1. (a) Molander, G. A.; Romero, J. A. C. *Chem. Rev.* **2002**, *102*, 2161–2185; (b) Molander, G. A. *Chemtracts* **1998**, *11*, 237–263; (c) Molander, G. A.; Dowdy, E. D. Lanthanide- and Group 3 metallocene catalysis in small molecule synthesis. In *Topics in Organometallic Chemistry*; Kobayashi, S., Ed.; Springer: Berlin, 1999; pp 119–154, 2(Lanthanides).
2. (a) Döhring, A.; Göhre, J.; Jolly, R. W.; Kryger, B.; Rust, J.; Verhovnik, G. P. J. *Organometallics* **2000**, *19*, 388–402; (b) Enders, M.; Fernández, P.; Kaschke, M.; Kohl, G.; Ludwig, G.; Pritzkow, H.; Rudolph, R. *J. Organomet. Chem.* **2002**, *641*, 81–89.
3. (a) Van Horn, D. E.; Negishi, E. *J. Am. Chem. Soc.* **1978**, *100*, 2252–2254; (b) Rand, C. L.; Van Horn, D. E.; Moore, M. W.; Negishi, E. *J. Org. Chem.* **1981**, *46*, 4093–4096; (c) Negishi, E.; Van Horn, D. E.; Yoshida, T.; Rand, C. L. *Organometallics* **1983**, *2*, 563–565; (d) Negishi, E. *Acc. Chem. Res.* **1987**, *20*, 65–72; (e) Negishi, E.; Kondakov, D. Y.; Van Horn, D. E. *Organometallics* **1997**, *16*, 951–957; (f) Negishi, E.; Huo, S. *Pure Appl. Chem.* **2002**, *74*, 151–157; (g) Negishi, E.; Van Horn, D. E.; Yoshida, T. *J. Am. Chem. Soc.* **1985**, *107*, 6639–6647; (h) Marek, I.; Chinkov, N.; Banon-Tenne, D. Carbometallation reactions. In *Metal-Catalyzed Cross-Coupling Reactions*; De Meijere, Armin, Diederich, Francois, Eds., 2nd ed.; Wiley-VCH: Weinheim, 2004.
4. (a) Schuster, H. F.; Coppola, G. M. *Allenes in Organic Synthesis*; Wiley: New York, 1984, and references therein; (b) Hoffman-Röder, A.; Krause, N. *Angew. Chem., Int. Ed.* **2004**, *43*, 1196–1216; (c) Rona, R.; Crabbé, P. *J. Am. Chem. Soc.* **1968**, *90*, 4733–4734.
5. No allene product was observed in the absence of chromium. Only starting material and 1-acetoxy-2-butyn-4-ol were recovered.
6. Rona, R.; Crabbé, P. *J. Am. Chem. Soc.* **1969**, *91*, 3289–3293.
7. (a) Alexakis, A.; Mangeney, P.; Normant, J. F. *Tetrahedron Lett.* **1985**, *26*, 4197–4200; (b) Marek, I.; Mangeney, P.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1986**, *27*, 5499–5502; (c) Alexakis, A.; Marek, I.; Mangeney, P.; Normant, J. F. *J. Am. Chem. Soc.* **1990**, *112*, 8042–8047.
8. (a) Theopold, K. H. *Chemtech* **1997**, 26–32, and references therein; (b) Theopold, K. H. *Eur. J. Inorg. Chem.* **1998**, 15–24, and references therein.
9. (a) Miller, D. B. *J. Org. Chem.* **1966**, *31*, 908–912; (b) Reetz, M. T.; Wenderoth, B.; Peter, R.; Steinbach, R.; Westermann, J. *J. Chem. Soc., Chem. Commun.* **1980**, 1202–1204.