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Titanium-Catalyzed Cascade Carboalumination of Dienes and Trienes

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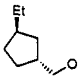
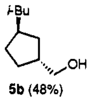
Herein reported is a novel inter–intra cascade carboalumination reaction of dienes and trienes with dialkylaluminum chlorides (R_2AlCl) in the presence of a catalytic amount ($\leq 2\%$) of a titanium alkoxide, *e.g.*, $Ti(OPr\text{-}i)_4$, which reveals some highly intriguing features. Most strikingly, in the absence of pre-existing chiral centers in the starting dienes, the formation of cyclopentane derivatives (**1**) is highly *trans*-selective with respect to the aluminomethyl and R groups, while that of cyclohexane derivatives (**2**) is highly *cis*-selective. The stereochemical results can be rationalized in terms of chair cyclohexane-like transition states **3** and **4** (Scheme 1).[1] Since the alumino group in the products can be readily replaced with a variety of groups includng H, D, halogens, *e.g.*, I and Br, and OH,[2] the reaction provides a novel and synthetically attractive route to stereodefined cyclopentane and cyclohexane derivatives. A Ti-catalyzed monocarboalumination of alkenes is known.[3] To our knowledge, however, no carbometalative cyclization using this reaction has been previously reported. Although some examples of stoichiometric cyclic carboalumination[4] and related reactions involving group 4 metals, *e.g.*, Ti,[5] are known, these reactions are not initiated by carbometalation but by hydrometalation or transmetalation. Consequently, the opportunity for introducing two new asymmetric carbon centers in the cyclization process is lacking. Moreover, the uncatalyzed version of cyclic carboalumination has been reported to be not readily applicable to the synthesis of six-membered rings.[4a] Yet another noteworthy recent advance in this area is the development of diene cyclization reactions catalyzed by lanthanides, *e.g.*, Y derivatives,[6] which is also initiated by hydrometalation.

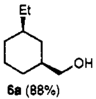
Typically, 1,6-heptadiene was treated with Et_2AlCl[7] (0.6 mol equiv, 20% excess) in hexanes in the presence of 2 mol % of $Ti(OPr\text{-}i)_4$ at 22 °C. After 24 h, oxygen was bubbled through for 2 h. The usual workup provided *cis*-(3-ethylcyclohexyl)methanol ($\geq 95\%$ *cis*) in 88% yield.[8] Under similar conditions, several other dienes, such as 1,5-hexadiene, diallyldimethylsilane, 2-methyl-1,5-hexadiene, and 4-methyl-1,6-heptadiene, have also been converted to five- and six-membered (3-alkylcycloalkyl-)methanols, *i.e.*, **5a**, **5b**, **6b**, **6c**, **7**, **10**, and **11a–c**. On the other hand, 1,4-pentadiene and 1,7-octadiene do not give the desired cyclization products in significant yields, the major monomeric products in these cases being uncyclized mono- and dialkylaluminated derivatives. Thus, the current scope of the reaction appears to be limited to five- and six-membered rings. Although we have not extensively investigated the effects of donor substituents, diallyl ether has failed to undergo the desired cyclization in a manner of 1,6-heptadiene or diallyldimethylsilane.



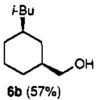
5a (72%)
$\geq 95\%$ *trans*



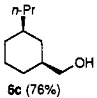
5b (48%)
$\geq 92\%$ *trans*



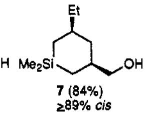
6a (88%)
$\geq 95\%$ *cis*



6b (57%)
$\geq 86\%$ *cis*

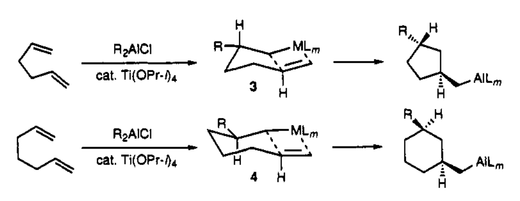


6c (76%)
$\geq 94\%$ *cis*

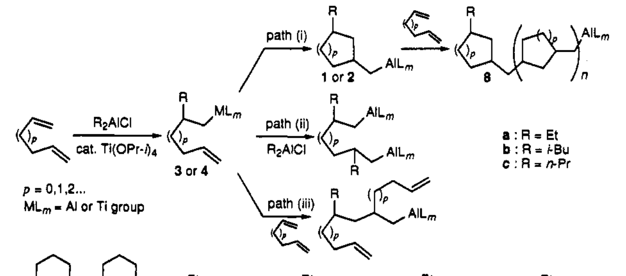


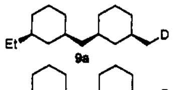
7 (84%)
$\geq 89\%$ *cis*

Scheme 1

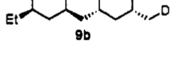


Scheme 2

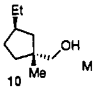




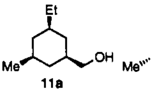
9a



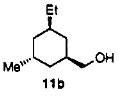
9b



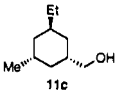
10



11a



11b



11c

Some other dialkylaluminum chlorides, such as $n\text{-}Pr_2AlCl$ and $i\text{-}Bu_2AlCl$ in addition to Et_2AlCl, also participate in this reaction. On the other hand, attempts to use trialkylalanes and alkylaluminum dichlorides, such as Et_3Al, $n\text{-}Pr_3Al$, $EtAlCl_2$, and $n\text{-}PrAlCl_2$, have been uniformly unsuccessful. With trialkylalanes, the starting dienes, *e.g.*, 1,6-heptadiene, remained essentially unchanged. The reaction of 1,6-heptadiene with Me_2AlCl led to the consumption of the diene without producing a significant amount (>5%) of the monomeric cyclization product. Although unidentified, the product appears to be polymeric. The mechanism of this reaction remains largely unclear. Nonetheless, the available data are consistent with one that involves inter- and intramolecular four-centered concerted carbometalation of alkenes similar to those suggested for related stoichiometric reactions.[5,6] The fact that the *n*-Pr group is incorporated as is rather than as *i*-Pr seems to rule out the involvement of metallacyclopentane intermediates.[9] In any of the reactions discussed herein, a putative initial intermediate **3** or **4** has at least three options, *i.e.*, paths (i)–(iii) in Scheme 2. Formation of the desired cyclization product **1** or **2** in high yield requires that the path (i) be substantially faster than the paths (ii) and (iii) as well as dimerization and polymerization via **1** or **2**. Evidently, this requirement can be met in cases where (a) the R group is Et and higher *n*-alkyl, *e.g.*, *n*-Pr, and (b) the desired ring sizes are five and six, *i.e.*, $p = 1$ and 2. In cases where $p = 0$ and 3, the path (i) must be slower

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(1) The C—M and C═C bonds in **4** may favor a gauche-like arrangement, and their coplanar relationship may involve some strain. This, however, should be compared with the other gauche-like arrangement, which must be relatively destabilized by the pseudoaxial terminal CH_2 group.

(2) (a) Mole, T.; Jeffrey, E. A. *Organoaluminum Compounds*; Elsevier: Amsterdam, 1972. (b) Zweifel, G.; Miller, J. A. *Org. React.* **1984**, *32*, 375.

(3) (a) Dzhemilev, U. M.; Ibragimov, A. G.; Vostrikova, O. S.; Tolstikov, G. A.; Zelenova, L. M. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1981**, 361. (b) Dzhemilev, U. M.; Ibragimov, A. G.; Vostrikova, O. S.; Tolstikov, G. A. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1985**, 207.

(4) (a) Hata, G.; Miyake, A. *J. Org. Chem.* **1963**, *28*, 3237. (b) Rienäcker, R.; Göthel, G. F. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 872. (c) Stefani, A. *Helv. Chim. Acta* **1974**, *57*, 1346. (d) Rienäcker, R.; Schwengers, D. *Liebigs Ann. Chem.* **1977**, 1633.

(5) (a) Clawson, L.; Soto, J.; Buchwald, S. L.; Steigerwald, M. L.; Grubbs, R. H. *J. Am. Chem. Soc.* **1985**, *107*, 3377. (b) Young, J. R.; Stille, J. R. *Organometallics* **1990**, *9*, 3022. (c) Rigollier, P.; Young, J. R.; Fowley, L. A.; Stille, J. R. *J. Am. Chem. Soc.* **1990**, *112*, 9441. (d) Young, J. R.; Stille, J. R. *J. Am. Chem. Soc.* **1992**, *114*, 4936.

(6) See, for example: Molander, G. A.; Hoberg, J. O. *J. Am. Chem. Soc.* **1992**, *114*, 3123 and pertinent papers cited therein.

(7) Dialkylaluminum chlorides used herein are either commercially available or prepared from trialkylalanes and $AlCl_3$.

(8) All new isolated cyclization products were characterized and identified by spectroscopic analyses, including high-resolution mass spectroscopy.

(9) (a) Swanson, D. R.; Rousset, C. J.; Negishi, E.; Takahashi, T.; Seki, T.; Saburi, M.; Uchida, Y. *J. Org. Chem.* **1989**, *54*, 3521. (b) Takahashi, T.; Seki, T.; Nitto, Y.; Saburi, M.; Rousset, C. J.; Negishi, E. *J. Am. Chem. Soc.* **1991**, *113*, 6266 (c) Negishi, E.; Takahashi, T. *Acc. Chem. Res.* **1994**, *27*, 124.

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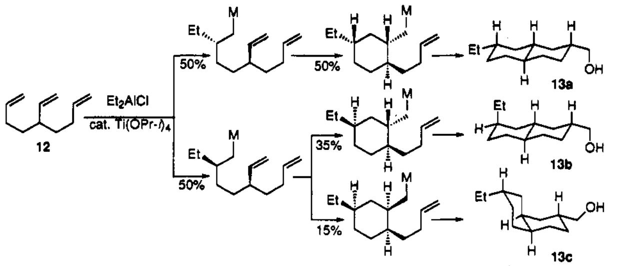
than others. The Ti-catalyzed reaction of 1,5-hexadiene and 1,6-heptadiene with i-Bu_2AlCl at 60 °C provided the desired products **1b** and **2b**, which were converted via oxidation to **5b**[10] (48% yield) and **6b** (57% yield). The lower yields of these products relative to those derived from Et_2AlCl and n-Pr_2AlCl must be attributable to the fact that i-Bu_2AlCl contains β-branched isoalkyl groups similar to those in **1** and **2**. It is therefore likely that **1b** and **2b** compete for dienes with i-Bu_2AlCl, leading to oligomers and polymers represented by **8**. These oligomers and polymers can also be obtained through the use of an excess of the starting diene. Thus, for example, the Ti-catalyzed reaction of 1,6-heptadiene with Et_2AlCl in a 4:1 molar ratio at 60 °C for 12 h produced, after deuterolysis with D_2O, a nearly 1:1 mixture of **9a** and **9b** in 53% GLC yield (≥95% D incorporation). A very similar product mixture was also obtained by treating preformed **2b** with 1,6-heptadiene (diene/Al = 4) at 60 °C for 12 h. These results indicate that, while diastereoselection within a ring can be nearly perfect, there is virtually no intermolecular diastereoselection. The formation of higher oligomers,[11] such as 4- to 8-mers of 1,6-heptadiene, was also observed by plasma desorption mass spectroscopy in cases where the diene/Al ratio was 8.

In view of the sharply contrasting stereoselectivity profiles shown above, we sought rigorous stereochemical assignments of a few representative products. The *cis* configuration of **6** and **7** was indicated by a distinct ^1H NMR signal (ddd) at δ 0.4–0.6 ppm for H-2 that is *cis* to the two adjacent substituents. This appears to be a generally reliable indicator. To further support the above assignment, however, an authentic 3:1 mixture of the *trans* and *cis* isomers of **6a** was prepared from cyclohexenone via (a) conjugate addition of EtMgCl catalyzed by CuCN,[12] (b) Wittig methylenation, and (c) hydroboration (BH_3·THF) and oxidation with NaOH and 30% H_2O_2. Comparison of the ^1H and ^{13}C NMR spectra of the two isomers permitted their unambiguous stereochemical assignments.[13] Similarly, a roughly 1:1 mixture of the *cis* and *trans* isomers of **5a** was prepared from cyclopentenone via conjugate addition of BEt_3[14] followed by Wittig methylenation and hydroboration–oxidation. A detailed analysis of ^1H and ^{13}C NMR spectra of the 1:1 stereoisomeric mixture vis-à-vis those of the sample derived from 1,5-hexadiene clearly established that **5a** obtained from 1,5-hexadiene was ~95% *trans*.[15] Somewhat unexpected but poteníally useful is that 2-methyl-1,5-hexadiene reacted regio- and stereoselectively with the representative reagent combination, *i.e.*, Et_2AlCl (0.6 mol equiv) and 2 mol % of $Ti(OPr$-$i)_4$, to give, after oxidation, a 79% yield of **10** as a ≥98% isomerically pure species which displayed stereochemically informative NOE signals. In contrast with the very favorable effects of a substituent on a double bond, the effects of the pre-existing sp^3-hybridized stereogenic centers displayed mixed but readily interpretable stereoselectivity features. Thus, for example, the reaction of 4-methyl-1,6-heptadiene[16] with the standard reagent combination gave, after oxidation, a 2:1:1 mixture of **11a–11c** in 77% combined yield. The results are consistent with (a) nonstereoselective initial ethylmetalation to give a 1:1 diastereomeric mixture, (b) highly stereoselective cyclization of one diastereomer to give **11a**, which can have three equatorial substituents, and (c) nonstereoselective cyclization of the other diastereomer to give a 1:1 mixture of **11b** and **11c**, each of which can have two equatorial substituents.

Scheme 3



Finally, the feasibility of achieving an inter–intra–intra cascade carbometalation with **12**[17] was explored. Its reaction with the standard reagent combination was slow but complete in 72 h at 22 °C to give, after oxidation, a 50:35:15 mixture of **13a–13c** in 83% combined yield. The results can be accommodated by a similar explanation as presented above and illustrated in Scheme 3. The results and interpretation presented above provide a rational foundation on which to pursue further stereochemical control of this promising cyclization reaction.

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Supplementary Material Available: Text describing experimental procedure (3 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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[10] Although i-Bu_2AlCl can act as a hydroaluminating agent, the extent of hydroalumination–cyclic carboalumination is <2%, as judged by the ^{13}C and ^1H NMR spectra of the crude product mixtures.

[11] For Zr-catalyzed polymerization of dienes, see: (a) Resconi, L.; Waymouth, R. M. *J. Am. Chem. Soc.* **1990**, *112*, 4953. (b) Coates, G. W.; Waymouth, R. M. *J. Am. Chem. Soc.* **1991**, *113*, 6270. (c) Kesti, M. R.; Waymouth, R. M. *J. Am. Chem. Soc.* **1992**, *114*, 3565. (d) Kesti, M. R.; Coates, G. W.; Waymouth, R. M. *J. Am. Chem. Soc.* **1992**, *114*, 9679.

[12] House, H. O.; Fisher, W. F., Jr. *J. Org. Chem.* **1969**, *34*, 3615.

[13] Whitesell, J. K. *Stereochemical Analysis of Alicyclic Compounds by C-13 NMR Spectroscopy*; Chapman and Hall: New York, 1987.

[14] Brown, H. C.; Kabalka, G. W. *J. Am. Chem. Soc.* **1970**, *92*, 714.

[15] Specifically, the HETCOR spectrum of the 1:1 mixture of the *cis* and *trans* isomers of **5a** clearly indicates that the two H atoms on C-2 of the *cis* isomers appear at δ 0.67 (m) and 1.88 (m) ppm, and those of the *trans* isomer are much closer together at δ 1.25 (m) and 1.45 (m) ppm.

[16] Frangin, Y.; Gaudemar, M. *Bull. Soc. Chim. Fr.* **1976**, 1173.

[17] 5-Ethenyl-1,8-nonadiene was prepared from 5-iodo-1,8-nonadiene and vinyl cuprate according to: Lipshutz, B. H.; Wilhelm, R. S., Floyd, D. M. *J. Am. Chem. Soc.* **1981**, *103*, 7672.