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TITANIUM-CATALYZED CASCADE CARBOALUMINATION OF 2-ALKYL-SUBSTITUTED DIENES AND RELATED TRIENES

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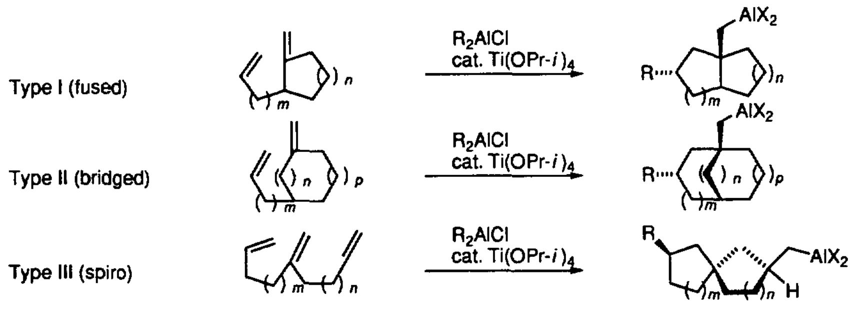
Abstract: The stereoselective "inter-intra" cascade carboalumination of dienes and trienes with Et_2AlCl and $Ti(OPr\text{-}i)_4$ provides a novel and stereoselective route to five- and six-membered rings including fused-, bridged-, and spiro-bicyclic structures with generation of quaternary carbon centers.

We have recently reported an "inter-intra" cascade carboalumination reaction[1,2] of 1,5- and 1,6-dienes and related trienes with dialkylaluminum halides, *e.g*, Et_2AlCl, catalyzed by $Ti(OPr\text{-}i)_4$. A related Zr-catalyzed reaction has also been subsequently reported.[3] In all but one case in the previous study,[1] monosubstituted alkene-containing dienes and trienes were used as the starting compounds. In a single, isolated case, however, a diene containing a 1,1-disubstituted alkene, *i.e.*, 2-methyl-1,5-hexadiene, was used, and the desired cyclization took place in high yield with facile generation of a quaternary carbon center with nearly complete control of the diastereochemistry of the two asymmetric carbon centers generated in the reaction.[1] The favorable results mentioned above prompted us to further explore the synthetic utility of the reaction of this category.

We now report our findings which may permit the following generalization. (1) The reaction appears to be reasonably general with respect to the formation of five- and six-membered rings. The formation of five-membered rings is highly stereoselective, but that of six-membered rings displays a lower level of selectivity. (2) The reaction can be exploited in the synthesis of fused bicycles (Type I), bridged bicycles (Type II), and spirobicycles (Type III) (Scheme 1). (3) A novel organoalane-assisted γ-hydroxylation of a *cis*-fused bicycloalkanemethanol with O_2 has been observed.

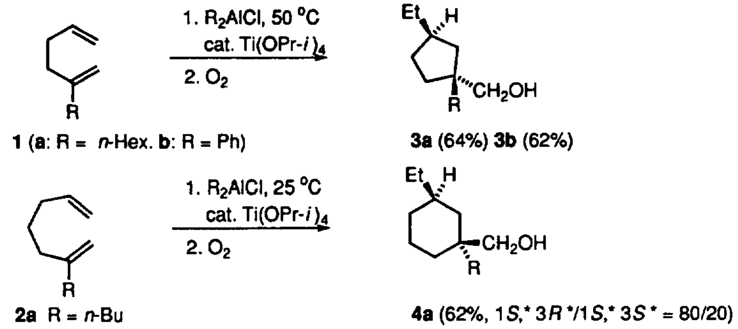
Scheme 1



R = Et. X = Et and/or Cl. *m, n, p* = 0, 1, 2....

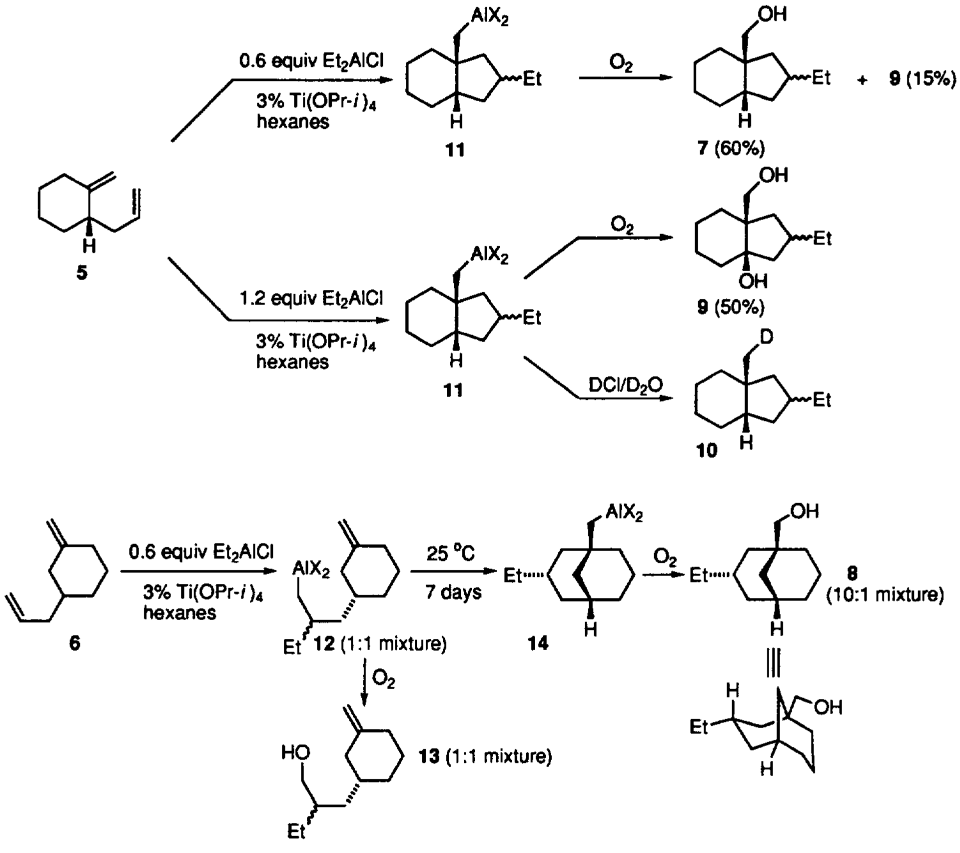
To probe the scope of the "inter-intra" cascade carboalumination of dienes represented by **1** and **2** with R_2AlCl and $Ti(OPr\text{-}i)_4$, **1a**, **1b**, and **2a** were prepared[4] and treated with 0.6 molar equiv of Et_2AlCl and 3 mol % of $Ti(OPr\text{-}i)_4$ in hexanes under argon at either 25 or 50 °C. As indicated by the results summarized in Scheme 2, all three dienes underwent the desired "inter-intra" cascade carboalumination to give, after oxidation with O_2, cyclopentanemethanols **3a** and **3b** and a cyclohexanemethanol **4a** in reasonable yields. Furthermore, the diastereoselectivity for the formation of the cyclopentane derivatives **3a** and **3b** was ≥98% based on ^1H and ^{13}C NMR spectroscopy as in the previously reported case.[1] The assigned diastereochemistry was supported by NOE measurements. However, the formation of **4a** was only 80% diastereoselective, the major isomer being *1S,*3R** based on NMR spectroscopic analysis. More disappointing was the reaction of 1,5-nonadiene (an *E* and *Z* mixture) which gave a complex mixture without a significant amount of the desired cyclization product under comparable conditions. Thus, while 1,1-disubstituted alkenes may cleanly undergo the Ti-catalyzed carboalumination, 1,2-disubstituted alkenes may not.

Scheme 2



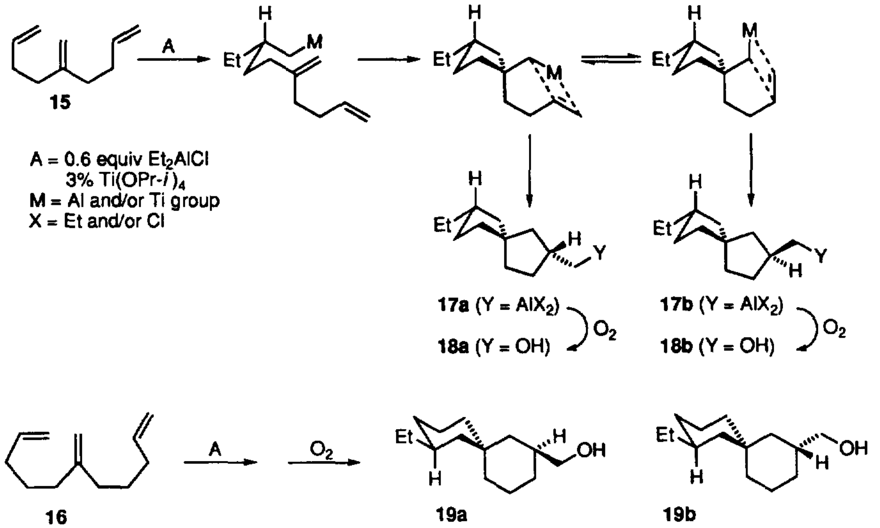
The reactions of 2-allyl-1-methylenecyclohexane[5] (**5**) and 3-allyl-1-methylenecyclohexane[5] (**6**) under the standard carboalumination conditions, *i.e.*, Et_2AlCl (0.6 equiv) and 3 mol% $Ti(OPr\text{-}i)_4$ in hexanes under argon, provided a couple of prototypical examples of conversion of monocyclic dienes into fused and bridged bicyclic compounds **7** and **8**, respectively, in moderate yields (Scheme 3). As suspected, **7** was an essentially 1:1 diastereomeric mixture, but both of the isomers were essentially 100% *cis*-fused. Thus, the initial intermolecular ethylmetalation step is hardly influenced by the preexisting asymmetric carbon center. However, the subsequent cyclization step must be strongly influenced by the same asymmetric carbon center in producing the observed *cis*-fused bicyclic compound but not by the second asymmetric carbon center generated in the ethylmetalation step. The results suggest that, in order to prepare diasteromerically and/or enantiomerically pure products by this method, an enantioselective intermolecular alkylalumination of monosubstituted alkenes such as that reported recently by us[6] which should additionally provide a matched combination with the preexisting chiral center would be required.[7] Interestingly, the formation of **7** was accompanied by a 15% yield of a diol **9**. Since a 20% excess of Et_2AlCl is used in the standard conditions, its participation in the oxidation step was suspected. Indeed, when 1.2 molar equiv (2.4 fold excess) of Et_2AlCl was used, **9** obtained in 50% yield was the only detectable monomeric cyclization product. Since deuterolysis of the carboalumination product gave only a monodeuterated derivative **10**, the carboalumination product may be represented by **11**, which must then be converted to **9** during the oxidation step. To further probe this matter, the monool **7** was successively treated with 5 equiv of Et_2AlCl and O_2. This reaction indeed gave **9** in 43% yield, the balance of the starting alcohol remaining unreacted. On the other hand, the presence or absence of $Ti(OPr\text{-}i)_4$ did not significantly affect the course of oxidation. Since no such dihydroxylation was observed in the formation of **8** even in the presence of an excess of Et_2AlCl, it is likely that a coplanar arrangement of C—Al and γ C—H bonds is required for the anomalous dihydroxylation reaction. The reaction of **6** also revealed some unexpected features. Unlike all the other cases herein reported, this reaction produced the intermolecular ethylalumination product **12** as an essentially 1:1 diastereomeric mixture. After oxidation, **13** was obtained as a 1:1 diastereomeric mixture. Upon standing at 25 °C for 7 days, however, **12** was slowly converted to a mixture of organoalanes, presumably **14**, which gave, upon oxidation, a 55% yield of **8** as an isomeric mixture. Contrary to our expectation, the major isomer of **8** accounting for albout 90% of the isolated product was the *endo*-ethyl isomer. The stereochemical assignment was based on detailed analysis of ^{13}C NMR spectra in the light of extensive data for similar bicyclic derivatives compiled in the literature.[8] It is not clear at this time what factor is responsible for the observed enrichment of one diastereomer, although kinetic resolution appears to be likely.

Scheme 3



We have also explored the feasibility of achieving spirobicyclization of trienes (Type III process in Scheme 1). To this end, **15**[4] and **16**[4] were prepared and subjected to the standard carboalumination conditions. As expected, the reaction of **15** gave an essentially 1:1 mixture of **17** which, on oxidation with O_2, gave a 1:1 mixture of **18** in 49% yield. The reaction of **16** was less clean, but the two major isomeric products **19a** and **19b** were obtained in 55% combined yield in a roughly 1:1 ratio (Scheme 4). The results may be readily explained as follows. The first cyclization step is diastereo-controlled as discussed previously[1] and earlier in this paper. In the second cyclization step, however, the potentially stereo-differentiating chiral center is the Et-bearing asymmetric carbon atom, and this evidently has little or no influence on the second cyclization process, leading to an essentially 1:1 epimeric mixture with respect to the hydroxymethyl-bearing carbon center (Scheme 4). The results indicate that it should, in principle, be feasible to fully control the stereochemistry at all three asymmetric carbon centers, if a highly enantioselective carbometalation reaction of monosubstituted alkenes such as that reported recently by us[6] could undergo a similar bicyclization reaction. Attempts are being made to further develop stereo-controlled cyclic carboalumination catalyzed by Ti and Zr complexes.

Scheme 4



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2. For a Ti-catalyzed monocarboalumination of mono-enes, see (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.
3. Shaughnessy, K. H.; Waymouth, R. M. *J. Am. Chem.* **1995**, *117*, 5873.
4. 1,5-Hexadiene derivatives **1a**, **1b**, and **15** were prepared via carbocupration of the corresponding alkynes with $H_2C{=}CH(CH_2)_2Cu{\cdot}MgBr_2$, while 1,6-heptadienes **2a** and **16** were prepared similarly using $H_2C{=}CH(CH_2)_3Cu{\cdot}MgBr_2$ (Normant, J. F.; Alexakis, A. *Synthesis* **1981**, 841).
5. 2- and 3-Allylmethylenecyclohexanes were prepared by the Wittig methylenation of 2-allylcyclohexanone (Howard, W. L.; Lorette, N. B. *Org. Synth. Coll. Vol. 5*, **1973**, 25) and 3-allylcyclohexanone (Hosomi, A.; Sakurai, H. *J. Am. Chem. Soc.* **1977**, *99*, 1673).
6. (a) Kondakov, D. Y.; Negishi, E. *J. Am. Chem. Soc.* **1995**, *117*, 10771. (b) Kondakov, D. Y.; Negishi, E. *J. Am. Chem. Soc.* **1996**, *118*, 1577.
7. Our attempts to achieve enantioselective carboalumination of monosubstituted alkenes catalyzed by chiral Ti complexes have thus far been unsuccessful. Application of the Zr-catalyzed enantioselective carboalumination[6] to these cases is currently under investigation.
8. Assignment of the endo orientation of the 3-Et group is primarily based on comparison of the observed ^{13}C NMR chemical shift of C-7 (16.9 ppm) in **8** with those of the corresponding carbon atoms in *endo*- and exo-3-methylbicyclo[3.3.1]nonanes (16.0 and 24.9 ppm, respectively) reported in the literature (Whitesell, J. K. *Stereochemical Analysis of Alicyclic Compounds by C-13 NMR Spectroscopy*; Chapman and Hall: New York, 1987).

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