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Carboalumination of seven-membered-ring *trans*-alkenes

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Abstract

Seven-membered-ring *trans*-alkenes undergo rapid hydro- and carboalumination reactions in the absence of a catalyst with complete regio- and diastereoselectivity. Control experiments, including deuterium labeling, adding radical inhibitors, and using a radical clock, suggest that these reactions proceed by a concerted mechanism. The products of the reaction possess a new carbon–aluminum bond that can then undergo subsequent transformations, particularly oxidation, providing functionalized products as single stereoisomers.

Graphical Abstract

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Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, characterization, ^1H and ^{13}C NMR spectroscopic data, stereochemical proofs, and X-ray structures (PDF)

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Metal-catalyzed carboalumination reactions serve as powerful methods to construct carbon–carbon bonds with control of stereochemistry.¹ The ready availability of organoaluminum reagents and the versatility of subsequent transformations make these reactions useful in target-directed synthesis.² Among these methods, the enantioselective carboalumination of terminal alkenes in the presence of a chiral zirconium catalyst has proven to be synthetically attractive.³

The catalyst is required because the carbon–aluminum bond generally adds to an alkene only slowly at elevated temperatures in the absence of a catalyst.^{4–7} Nevertheless, some examples of the uncatalyzed hydroalumination of alkenes have been reported, although typically these reactions require elevated temperatures.^{8–9}

In this Letter, we demonstrate that carbon–aluminum and hydrogen–aluminum bonds can add across the carbon–carbon double bonds of highly strained alkenes rapidly at room temperature. These reactions, which proceed without a catalyst, occur with complete regiochemical and stereochemical control. The carbon–aluminum bond of the resulting adduct can be trapped with O₂ to form an alcohol stereoselectively.

The rapid, uncatalyzed hydroalumination and carboalumination reactions were discovered in the course of functionalizations of seven-membered ring *trans*-alkene **4a**, which was prepared from catalytically generated silylene intermediates, 1,3-pentadiene, and benzaldehyde (Scheme 1).¹⁰ The reaction (eq 1) with *i*-Bu₂AlH was expected to cleave the silicon–oxygen bond of the siloxane to provide the corresponding ring-opened hydrosilane.^{11–12} Instead, the carbon–carbon double bond reacted with *i*-Bu₂AlH within ten minutes to provide siloxane **5** in 66% yield after aqueous workup. Analysis of the reaction mixture by NMR spectroscopy prior to aqueous workup revealed the formation of a new product that disappeared upon addition of water. This reactive species, which could not be isolated, was tentatively assigned as the organoaluminum intermediate **5**. Upon protonation, this alane would provide the product of net addition of H₂ to the carbon–carbon double bond. The observation of a rapid hydroalumination of strained alkene **4a** contrasts with the fact that carbon–carbon bonds do not typically react with *i*-Bu₂AlH. An exception to that rule is the hydroalumination of the aromatic alkene indene, which occurs at elevated temperatures (80 °C) over several days.^{13–14}

Isolation of a minor compound from the reaction mixture indicated that another addition to the double bond had occurred. A small quantity of the siloxane **7l** was also isolated, which was formed as a single regio- and stereoisomer. This product could be formed by a similar reaction to the formation of **6** but, instead of the hydrogen–aluminum bond reacting, one of the isobutyl groups of *i*-Bu₂AlH was transferred.

A subsequent experiment verified that carbalumination reactions of these strained alkenes is rapid at room temperature. Addition of Me_3Al to seven-membered ring *trans*-alkene **4a** followed by addition of H_2O provided product **7a**, in which a methyl group had been transferred to the carbon–carbon double bond regioselectively and stereoselectively (eq 2). After extensive screening of temperature, additives, and other conditions, the reaction could be optimized to form the carbalumination product in 88% yield. This reaction also formed a small quantity of the siloxane **8**, in which a methyl group had been added to one end of the carbon–carbon double bond, and the hydrogen atom had been removed from the same atom. This product was formed in higher quantities as reaction times were increased before addition of water, which suggests that it is formed from the initial carbometallation product by a β -elimination pathway.¹⁵ No isomerization of the *trans*cycloalkene was observed, which contrasts with observations of the carbometallation of alkenes with Ph_3Al at elevated temperatures.⁴ Attempts to extend the carbometallation reaction to other organometallic reagents, such as MeLi , Et_2Zn , LiAlMe_4 , and LiCuMe_2 , were unsuccessful, emphasizing the importance of the Lewis acidic metal atom to facilitate the carbometallation.¹⁶

A deuterium-labeling experiment provided insight into the stereochemical course of the carbalumination reaction (eq 3). Addition of D_2O to the reaction mixture instead of H_2O formed the deuterated product d_1 -**7a** as a single stereoisomer. This observation supports the proposed formation of an alkylaluminum intermediate **5** that was suggested by in situ NMR spectroscopic studies. The deuterium atom was incorporated at only one carbon atom and in only one of the two diastereotopic positions of the methylene group. The stereochemistry of the deuteration indicates that the addition of the carbon–aluminum bond to the carbon–carbon double bond is a *syn* addition, considering that protonation of the resulting carbon–aluminum bond would occur with retention of configuration.¹³ Furthermore, unlike carbalumination of alkenes with Ph_3Al at elevated temperatures, isomerization at the sp^3 -hybridized carbon atom did not appear to occur.⁴

Control experiments provided additional insight into the reaction mechanism. A radical mechanism is unlikely considering that addition of a radical scavenger, (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO), had no effect on the carbalumination reaction (eq 4). The importance of ring strain was demonstrated by experiments using alkene **5**, the *cis*

isomer of alkene **4a**: alkene **9** did not react with trimethylaluminum, even after seven days (eq 5). Sufficient strain was needed, as norbornene **10** did not undergo carboalumination at room temperature (eq 6). Carboalumination of alkene **9** and norbornene **10** did not occur with added AgOCOCF_3 , which suggests that the presence of silver salts, which could have remained from the synthesis of the alkene **4a**, were not sufficient to cause a reaction.

Taken together, these results provide experimental evidence to support the idea that carboalumination of alkenes is a concerted reaction that proceeds through a four-membered ring transition state (Figure 1).^{5,17–18} This mechanism is consistent with other addition reactions involving Group 13 species.¹⁹ The regioselectivity likely results because, in this transition state, partial positive charge would develop on the carbon atom β to the silicon atom, which should lend stability by hyperconjugation.²⁰

The carboalumination reaction is general for a number of seven-membered ring *trans*-alkenes (Table 1). The reaction tolerated substrates possessing electron-rich and electron-poor aromatic rings. Heterocyclic aromatic groups, such as furan and thiophene groups, were not affected. The reaction was not sensitive to steric effects, as demonstrated by the formation of product **7h** and **7j**. Carboalumination occurred only at a strained double bond in a substrate with two double bonds, leading to product **7j**. This observation confirms that the reaction is strain-promoted. Additionally, other trialkylaluminum reagents, such as triethylaluminum and triisobutylaluminum, both produced the expected products **7k** and **7l**, respectively. In the case of triisobutylaluminum, small quantities of the hydroalumination product were also observed. In all cases, addition of the carbon–aluminum bond to the carbon–carbon double bond was completely stereo- and regioselective.

The carbon–aluminum bond formed in the carboalumination reaction can also be oxidized to form a carbon–oxygen bond with control of stereochemistry. Addition of Me₃Al to *trans*alkene **4a** followed by exposure to O₂ resulted in the formation of alcohol **12a** as a single stereoisomer, whose structure was established by X-ray diffraction studies (Table 2). The stereoselective oxidation of alanes was general for a range of substrates. In two cases (**12f** and **12i**), some of the product formed by protonation of the carbon–aluminum bond was observed as a side-product. Other commercially available trialkylaluminum reagents (**12k** and **12l**) were also compatible with the carboalumination/oxidation sequence.

The formation of oxidation products **12j** and *epi*-**12j** provides additional information about the mechanisms of the oxidation and carboalumination reactions. The formation of these products is consistent with the generation of a radical upon treatment of the alkylaluminum intermediate with O₂^{21–22} followed by a 5-hexenyl radical cyclization and trapping of the resulting radical with O₂.²³ The presence of TEMPO during the oxidation of the organoaluminum intermediates prohibited the reaction, providing evidence that this reaction involves radical intermediates. Although the oxidation of the carbon–aluminum bond shown in Table 2 proceeded via radical intermediates, it nevertheless occurred with retention of configuration. It is possible that the radical intermediate either reacted with O₂ more rapidly than it could undergo stereochemical inversion,^{24–25} which is consistent with the fact that the reactions of radicals with O₂ occur at rates that approach the diffusion limit.²⁶ The fact that no cyclized product was observed during the carboalumination reaction and protonation of the resulting alane leading to siloxane **7j** (Table 1) provides evidence that neither of these reactions involved radical intermediates.

Efforts to transform the carbon–aluminum bond into other functional groups were unsuccessful. No reaction was observed when the alane intermediates were treated with electron-deficient alkenes and epoxides.^{27–28} Halogenation formed a complex mixture from which the alkyl halide could not be isolated.²⁹ Subjecting the presumed intermediate to a number of cross-coupling conditions yielded only the products of protonation (i.e., **7a**).³⁰

In conclusion, carboalumination of highly strained alkenes occurs with trialkylaluminum reagents at room temperature. The reaction occurs with complete stereoselectivity and regioselectivity to provide alanes that can be oxidized stereoselectively. Mechanistic studies provide evidence that the carboalumination reaction proceeds through a concerted mechanism, but the subsequent oxidation reaction involves radical intermediates.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Possible Transition State

Scheme 1. Synthesis of seven-membered-ring *trans*-alkenes

Table 1.Substrate Scope of Carboalumination^a

^aYields based on *trans*-alkene.

^bIsolated yield after two steps from diene.

^cYield of product of net hydrogenation, resulting from hydroalumination, based on *trans*-alkene.

Table 2.

Substrate Scope of Oxidation^a

^aYields based on *trans*-alkene.

^bIsolated yield after two steps from diene.

^cYield of product **7** resulting from protonation of the carbon–aluminum bond, based on *trans*-alkene.