The reagent Et_2AlX/CH_2N_2 in cyclopropanation of sterically hindered olefins, as well as oxygen- and nitrogen-containing unsaturated compounds

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A transition-metal-free method of cyclopropanation of sterically hindered olefins, substituted allylic alcohols, allylamines, and vinyl silyl ethers was developed using diazomethane in the presence of organic aluminum halides.

Key words: organoaluminum compounds, diazomethane, aluminum carbenoids, cyclopropanation.

Reactions of metal carbenoids with olefinic compounds is one of the most well-known and widely used approaches for the design of cyclopropane systems.[1] The most commonly used are zinc carbenoids, which are the basis of such well-known cyclopropanation reagents as the Simmons—Smith, Furukawa, Wittig, Shi, and Charette reagents.[2] Recently, we have demonstrated the high efficiency of aluminum carbenoids in cyclopropanation of sterically hindered[3,4] and nitrogen-containing olefins[5,6] as compared to the reagents based on CH_2N_2 and zinc carbenoids traditionally used for cyclopropanation. This feature determines the prospects of using aluminum carbenoids for the synthesis of cyclopropane and polycyclopropane compounds. However, the relatively high price of CH_2I_2 used in the generation of aluminum carbenoid using trialkylalanes significantly limits the practical importance of the developed methods for preparation of poorly available cyclopropane compounds. In addition, it is known that aluminum carbenoids can also be prepared by the reaction of organic aluminum halides with a diazomethane solution. From the practical point of view, the "diazomethane" method is more preferable. However, depending on the method for generating aluminum carbenoids, the composition of the reaction mixture and the reactivity of aluminum carbenoids can significantly differ. While the reactivity of aluminum carbenoid obtained from diiodomethane was studied using a wide range of unsaturated substrates, very little is known of such studies of an organoaluminum reagent based on diazomethane. We can mention only the innovative work of Hoberg[7] on cyclopropanation of 1-pentene and our work on cyclopropanation of fulvenes,[8,9] in which poorly available polycyclopropane compounds were synthesized in high yields and selectivity using the reagent Et_2AlX/CH_2N_2. In this regard, we hoped that the diazomethane method for generating aluminum carbenoid could prove to be a practically useful approach to the synthesis of cyclopropane compounds from sterically hindered olefins, as well as oxygen- and nitrogen-containing unsaturated compounds, the interest in which has recently grown significantly due to the high synthetic potential of donor-acceptor cyclopropanes.[10,11]

Initially, we investigated the cyclopropanation reaction of sterically hindered olefins:[12] 2-cyclopropylideneadamantane, 2-cyclobutylideneadamantane, bicyclobutylidene, and 2,2′-bi(adamantanylidene). It was found that the reaction of 2-cyclopropylideneadamantane with 5 equiv. of CH_2N_2 (solution in CH_2Cl_2) and 5 equiv. of Et_2AlCl for 5 h at room temperature proceeds with complete conversion of the starting olefin, but unselectively gives a difficult-to-separate mixture of products. When Et_2AlCl was replaced with Et_2AlI, which was generated by the reaction of equimolar amounts of Et_3Al and I_2 in CH_2Cl_2, 2-cyclopropylideneadamantane was selectively converted to the cyclopropanation product **1a** in 87% yield without the formation of rearrangement by-products (Scheme 1, Table 1).

Cyclopropanation of 2-cyclobutylideneadamantane, bicyclobutylidene, and 2,2′-bi(adamantanylidene) in the presence of Et_2AlI also proceeds selectively.

Thus, the reactivity of aluminum carbenoids with respect to sterically hindered olefins depends little on the method of their generation. However, the high Lewis acidity of diethylaluminium chloride does not allow its use for cyclopropanation of readily rearrangeable polycyclic compounds; in this case it is advisable to use diethylaluminum iodide, which has a lower Lewis acidity.

Aluminum carbenoids generated from CH_2I_2 and trialkylalanes have proven themselves in the synthesis of cyclopropyl alcohols and amines from allylic alcohols, vinyl silyl ethers, allylamines, and enamines. A remarkable feature of these processes is that the reaction with nitrogen-containing unsaturated compounds is not accompanied

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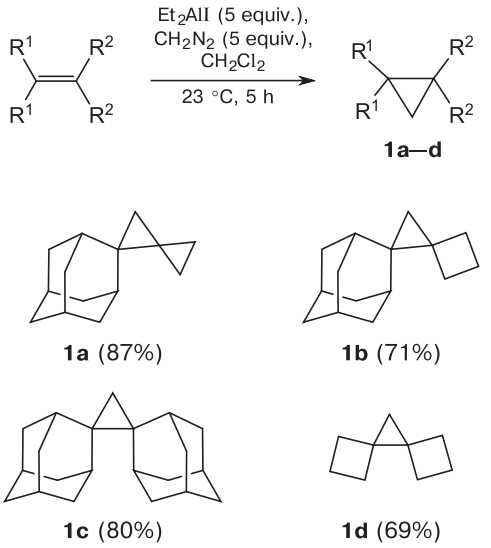
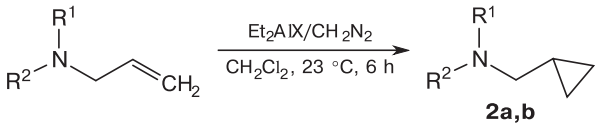
Scheme 1



by side *N*-alkylation. The latter reaction is a serious problem in the preparation of cyclopropylamines using the Simmons—Smith reagent. In this regard, cyclopropanation with aluminum carbenoids generated from diiodomethane and trialkylalanes is a good alternative to the Kulinkovich—de Meijere reaction. However, the high acidity of aluminum halides can be a serious problem in the diazomethane method for generating aluminum carbenoids. Vinyl silyl ethers and enamines are unstable in the presence of strong Lewis acids, while allylamines can form with them poorly reactive adducts.

Continuing the study of the reactivity of aluminum carbenoids generated using CH_2N_2, we tried to develop a method for cyclopropanation of allylamines with a reagent based on diazomethane and diethylaluminium chloride. Unfortunately, high yields of cyclopropylamines were achieved only with a large excess of CH_2N_2 and Et_2AlCl, when a solution of CH_2N_2 was added in portions over 6 h (Scheme 2), or with a large excess of CH_2N_2 and Me_2AlI, which is very different from the positive results we obtained earlier[4] when the reagent based on CH_2I_2 was used. The reason for this may be a higher concentration of aluminum halides in solution in the case of the reaction with diazomethane, which leads to the binding of a significant amount of allylamine to a less reactive complex. In the case of CH_2I_2, aluminum halide is formed after the cyclopropanation step and can be bound by the resulting cyclopropylamine. Thus, when comparing the diiodomethane and diazomethane methods for the generation of aluminum carbenoids in the reaction with allylamines, the former should be preferred.

Scheme 2



2: $R^1 = R^2 = Et$ (**a**), $R^1 + R^2 = (CH_2)_5$ (**b**)

The high Lewis acidity of Et_2AlCl favors the decomposition of vinyl silyl ethers under the reaction conditions, and their cyclopropanation with diazomethane satisfactorily proceeds only when 3 mol. equiv. of Et_2AlI is used (Scheme 3). The yields of cyclopropyl alcohols **3a—c** and **4** were from 63 to 83%. Cyclopropanation of (*E*)-oct-2-en-1-ol and geraniol proceeded in good yield when 5 mol. equiv. of Et_2AlI and CH_2N_2 were used, giving compound **5** and a mixture of diastereomers **6** and **6′** in a ratio of ~1 : 1.

In conclusion, the high Lewis acidity of aluminum chloride poses a serious problem in the cyclopropanation of substituted oxygen- and nitrogen-containing unsaturated compounds with the Et_2AlCl/CH_2N_2 reagent system. Replacing Et_2AlCl with Et_2AlI solves this problem, however, the necessity to use a large excess of the iodide somewhat eliminates the advantages of the diazomethane method for the generation of aluminum carbenoids.

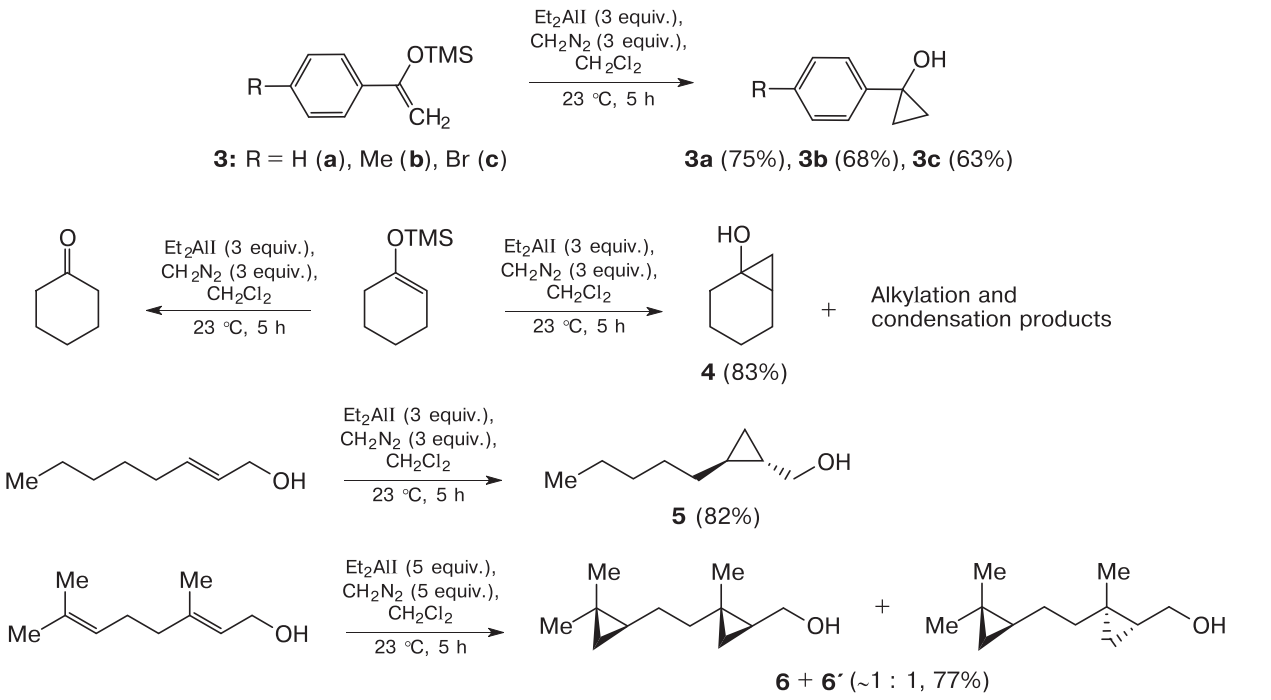
Table. 1. Cyclopropanation of allylamines with the reagent Et_2AlX/CH_2N_2 (see Scheme 2)

Entry	Allylamine		R_2AlX	CH_2N_2 (equiv.)	R_2AlX (equiv.)	Product	Yield of **2** (%)
	R^1	R^2					
1	Et	Et	Et_2AlCl	5	5	**2a**	55
2	Et	Et	Me_2AlI	20	7	**2a**	88
3	Et	Et	Et_2AlI	20	5	**2a**	40*
4	Et	Et	Et_2AlCl	20	7	**2a**	83**
5	Et	Et	Et_2AlCl	20	2	**2a**	25
6	Et	Et	Bu^i_2AlI	20	7	**2a**	40
7	$(CH_2)_5$		Et_2AlI	10	3	**2b**	39

* Extra 2 equiv. of I_2 were added.

** The solution of CH_2N_2 was added in portions over 6 h.

Scheme 3



Experimental

The following commercially available organoaluminum compounds were used in the work: 97% Me_3Al from Aldrich, 98% Et_3Al, 97% $Bu^i{}_3Al$, 88% Et_2AlCl (Redkinsky Pilot Plant, Inc.). Argon of pure grade (USSR State Standard Specifications 10157-73) was used as an inert atmosphere. The starting compounds: alkylidenecyclopropanes and alkylidenecyclobutanes,[13] biadamantanylidene,[14] and vinyl silyl ethers[15] were synthesized using known procedures. 2-Alkenylamines were prepared by the reaction of 2-alkenyl bromides with secondary amines. The reaction products were analyzed by gas-liquid chromatography on Carlo Erba (a 25 m×0.2 mm Hewlett Packard Ultra-1 glass capillary column, flame-ionization detector, operating temperature 50—170 °C, carrier gas helium), Chrom-5 and Tsvet-102 chromatographs (flame-ionization detector, 1-, 2-, and 3-m columns 3 mm in diameter; stationary phase silicone SE-30 (5%) on Chromaton N-AW-HMDC (0.125—0.160 mm), carrier gas helium (50 mL min^{-1}), column temperature 50—220 °C). Mass spectra were recorded on a Finnigan 4021 instrument with an ionizing electron energy of 70 eV and an ionization chamber temperature of 200 °C. ^1H and ^{13}C NMR spectra were recorded on Bruker Avance 400 (100.62 MHz for ^{13}C and 400.13 MHz for ^1H) and Bruker Avance 500 spectrometers (125.78 MHz for ^{13}C and 500.17 MHz for ^1H), using Me_4Si and $CDCl_3$ (δ_C 77.36) as internal standards for ^1H and ^{13}C NMR spectra, respectively. Chemical shifts are given in the δ scale. Elemental composition of compounds was determined using a CARLO ERBA-1106 instrument. Thin layer chromatography was performed on Silufol UV-254 plates.

Caution! All the operations with diazomethane must be carried out in a fume hood behind a safety screen. The use of thick rubber gloves and goggles is a must. Contact of diazomethane solutions with ground-glass joints, scratched and chipped glassware must be avoided. The glass reactor must be sealed with rubber septa; the edges of all glass tubes must be thoroughly melted. A Teflon-coated magnetic rod must be used for stirring. Exposure of diazomethane solutions to direct sunlight or a strong artificial light source can cause an explosion.

Preparation of a solution of diazomethane in dichloromethane. Diazomethane was obtained according to a modified procedure described in the work.[16] A 45—50% aqueous KOH (100 mL) and CH_2Cl_2 (25 mL) were placed into a ground joint-free conical flask equipped with a Teflon-coated magnetic rod and a thermometer with cooling to −5 °C and purging of argon at a rate of 80 mL min^{-1}. *N*-Methyl-*N*-nitrosourea (2.5 g) was added in small portions with continuous stirring maintaining the temperature under 0 °C. The solution was stirred at −5 °C for 2 h. Then, the upper aqueous layer was decanted, the organic layer was dried over granular KOH in the refrigerator. The concentration of diazomethane in the solution was determined by reverse titration with benzoic acid using a 0.1 *M* solution of KOH. The yield of CH_2N_2 was 45—50%.

Synthesis of polycyclic compounds by the reaction of the reagent Et_2AlI/CH_2N_2 with sterically hindered olefins (general procedure). The reactor was a 50-mL single-neck round-bottom glass flask without ground joints. Iodine (1.27 g, 5 mmol) was placed in the reactor equipped with a Teflon-coated magnetic rod, immersed into an ice-water bath, and mounted on a magnetic stirrer. The flask was sealed with a rubber septum (14/23 joints), which was pierced with two needles for argon inlet/outlet through silicone hoses. A bubbler filled with silicone oil was connected to the end of the outlet hose. The flask was purged with dry argon. Then CH_2Cl_2 (10 mL) and Et_3Al (0.75 mL, 5 mmol) were sequentially syringed through the septum and

the mixture was stirred for 15 min at 0 °C. Next, an olefin (1 mmol) was syringed, followed by the addition of a 0.4 *M* solution of diazomethane in CH_2Cl_2 (12.5 mL, 5 mmol of CH_2N_2) in from four to five portions over 2 min at 0 °C, periodically opening the reactor under an enhanced flow of argon. The temperature was raised to ambient (23 °C) and the mixture was stirred for another 6 h, followed by the work-up with 15% aqueous HCl (10 mL). The aqueous layer was extracted with diethyl ether (3×5 mL), the extract was combined with the organic layer, dried over anhydrous $CaCl_2$, and concentrated *in vacuo*. Individual compounds were isolated by column chromatography (compounds **1a—c**) or by distillation under reduced pressure (compound **1d**).

Dispiro[cyclopropane-1,1′-cyclopropane-2′,2″-adamantane] (1a). The yield was 87%. R_f 0.71 (ethyl acetate—hexane, 1 : 20). ^1H and ^{13}C NMR spectra are identical to those described in the work.[3]

Dispiro[cyclobutane-1,1′-cyclopropane-2′,2″-adamantane] (1b). The yield was 71%. R_f 0.65 (ethyl acetate—hexane, 1 : 20). ^1H and ^{13}C NMR spectra are identical to those described in the work.[3]

Dispiro[adamantane-2,1′-cyclopropane-2′,2″-adamantane] (1c). The yield was 80%. R_f 0.43 (ethyl acetate—hexane, 1 : 20). M.p. 124—126 °C. ^1H and ^{13}C NMR spectra are identical to those described in the work.[4]

Dispiro[3.0.3^5.1^4]nonane (1d). The yield was 69%. B.p. 75—78 °C (20 Torr). ^1H and ^{13}C NMR spectra are identical to those described in the work.[3]

Synthesis of functionally substituted cyclopropanes by the reaction of the reagent Et_2AlCl/CH_2N_2 with substituted nitrogen-containing unsaturated compounds (general procedure). A Teflon-coated magnetic rod was placed in a 50-mL reactor immersed into an ice-water bath and mounted on a magnetic stirrer, the reactor was sealed with a rubber septum and purged with dry argon. Then CH_2Cl_2 (5 mL), Et_2AlCl (0.5 mL, 3.5 mmol), and allylamine (0.5 mmol) were sequentially syringed through the septum at 0 °C. A 0.4 *M* solution of diazomethane in CH_2Cl_2 (25 mL, 10 mmol of CH_2N_2) was added in six portions over 6 h at room temperature (23 °C), periodically opening the reactor under an enhanced flow of argon. Then a 3 *M* solution of EtMgBr in diethyl ether (10 mL) was added to the reaction mixture cooled to 0 °C (ice-water bath) (the organomagnesium compound is necessary to remove the by-produced iodoethane from the reaction mixture, which, when the reaction mixture is concentrated, can react with the amine, giving quaternary salt), stirred for 1 h, hydrolyzed with 25% aqueous NaOH (5 mL), and filtered through a paper filter. The aqueous layer was extracted with diethyl ether, the extract was combined with the organic layer, dried over anhydrous $CaCl_2$, and concentrated *in vacuo*. Individual compounds **2a**,**b** were isolated by distillation under reduced pressure.

***N*-(Cyclopropylmethyl)-*N*-ethylethaneamine (2a).** The yield was 83%. B.p. 136—140 °C. ^1H and ^{13}C NMR spectra are identical to those described in the work.[6]

1-(Cyclopropylmethyl)pyperidine (2b). The yield was 72%. B.p. 71—75 °C (10 Torr). ^1H and ^{13}C NMR spectra are identical to those described in the work.[6]

Synthesis of functionally substituted cyclopropanes by the reaction of the reagent Et_2AlCl/CH_2N_2 with substituted oxygen-containing unsaturated compounds (general procedure). Iodine (0.76 g, 3 mmol) (or 1.27 g (5 mmol) of iodine for the reaction with geraniol) was placed in a reactor equipped with a magnetic Teflon-coated rod, immersed into an ice-water bath, and mounted on a magnetic stirrer. The flask was sealed with a rubber septum and purged with dry argon. Then CH_2Cl_2 (10 mL) and Et_3Al (0.45 mL, 3 mmol) (or 0.75 mL (5 mmol) of Et_3Al for the reaction with geraniol) were sequentially syringed through the septum and the mixture was stirred for 15 min at 0 °C. Next, substituted allylic alcohol (1 mmol) was syringed, followed by the addition of a 0.4 *M* solution of diazomethane in CH_2Cl_2 (7.5 mL (3 mmol) of CH_2N_2 or 12.5 mL (5 mmol) of CH_2N_2 for the reaction with geraniol) in from four to five portions over 2 min at 0 °C, opening the reactor periodically with an enhanced argon flow. The temperature was raised to ambient (23 °C), the mixture was stirred for 6 h and worked-up with 15% aqueous HCl (10 mL). The aqueous layer was extracted with diethyl ether (3×5 mL), the extract was combined with the organic layer, dried over anhydrous $CaCl_2$, and concentrated *in vacuo*. Individual compounds (compounds **3—5**) and a mixture of diastereomers (compounds **6** and **6′**) were isolated by column chromatography.

1-Phenylcyclopropan-1-ol (3a). The yield was 75%. R_f 0.39 (ethyl acetate—hexane, 1 : 10). ^1H and ^{13}C NMR spectra are identical to those described in the work.[5]

1-(*p*-Tolyl)cyclopropan-1-ol (3b). The yield was 68%. R_f 0.54 (ethyl acetate—hexane, 1 : 10). ^1H and ^{13}C NMR spectra are identical to those described in the work.[5]

1-(4-Bromophenyl)cyclopropan-1-ol (3c). The yield was 63%. R_f 0.47 (ethyl acetate—hexane, 1 : 10). ^1H and ^{13}C NMR spectra are identical to those described in the works.[5,17]

Bicyclo[4.1.0]heptan-1-ol (4). The yield was 83%. R_f 0.68 (ethyl acetate—hexane, 1 : 10). ^1H and ^{13}C NMR spectra are identical to those described in the work.[18]

(1*RS*,2*RS*)-(2-Pentylcyclopropyl)methanol (5). The yield was 82%. R_f 0.58 (ethyl acetate—hexane, 1 : 5). ^1H and ^{13}C NMR spectra of compound **5** are identical to those described in the work.[19]

{(1*RS*,2*RS*)-2-[2-((*RS*)-2,2-Dimethylcyclopropyl)ethyl]-2-methylcyclopropyl}methanol (6) and {(1*RS*,2*RS*)-2-[2-((*SR*)-2,2-dimethylcyclopropyl)ethyl]-2-methylcyclopropyl}methanol (6′). The yield was 77%. R_f 0.68 (ethyl acetate—hexane, 1 : 5). ^1H and ^{13}C NMR spectra of compounds **6** and **6′** are identical to those described in the work.[20]

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