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Zirconocene-Initiated Intramolecular Hydride Transfer in *N*-Isoalkyl-Substituted Propargylamines

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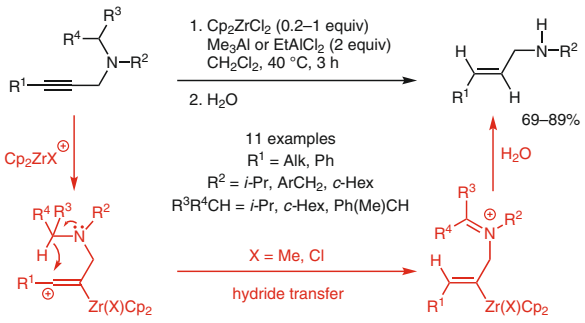

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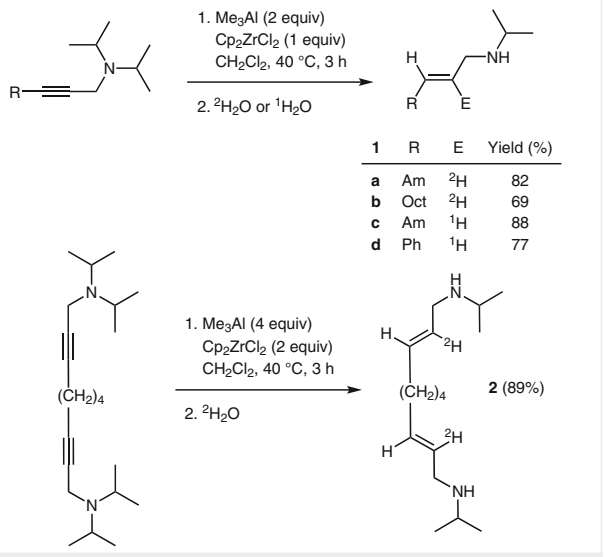
Abstract The unusual transformation of *N*-isoalkyl-substituted propargylamines into alkenylamines under the action of Cp_2ZrCl_2 and organoaluminum compounds (Me_3Al, $EtAlCl_2$) has been observed. The proposed mechanism, involving the *N*-isoalkyl-substituted propargylamine undergoing zirconocene-initiated intramolecular hydride transfer was supported by B3LYP/6-31G(d)/LanL2DZ calculations.

Key words alkenylamine, hydride transfer, negative hyperconjugation, propargylamine, zirconocene cation

Zirconium-catalyzed carbo-[1] and cycloalumination[2] of alkynes are among the preferred methods for the synthesis of trisubstituted alkenes. These methods are well suited for alkyl- and aryl-substituted alkynes and, therefore, they are widely used to synthesize natural products and their analogues.[3] However, the presence of a heterofunctional group in the alkyne substrate may promote side reactions. While studying Zr-catalyzed cycloalumination of acetylenic alcohols and substituted propargylamines, we ran across some limitations of the method as regards substituted propargyl alcohols, but the cycloalumination of alkyl-substituted propargylamines occurred regioselectively with high yield. All our subsequent attempts to perform the reaction of alk-2-ynyl-substituted *N*,*N*-dimethylamine and piperidine (*N*,*N*-dimethylhept-2-yn-1-amine, *N*,*N*-dimethylnon-2-yn-1-amine, 1-(non-2-yn-1-yl)piperidine) with Cp_2ZrCl_2-Me_3Al reagent were unsuccessful. This was surprising, because *N*,*N*-dimethylhept-2-yn-1-amine was only twofold less reactive towards cycloalumination than 5-decyne.[4] Despite the fact that methylalumination has been accomplished for heterosubstituted arylethynes containing O, S, and Cl[5] and even for propargyl alcohols,[6] by the beginning of our studies, there was a single example of methylalumination of substituted propargylamine (*N*-benzylpent-2-yn-1-amine); however, the yield of iodoalkene after iodinolysis was only 26%.[7] We were curious to find out why the substituted propargylamines we tested were inactive towards the Cp_2ZrCl_2-Me_3Al reagent. Then we turned to studies dealing with polymerization of nitrogen-containing monomers in the presence of titanium complexes,[8–10] according to which polymerization is possible only in the case where the nitrogen atom is shielded by bulky branched alkyl groups. Moreover, monomers containing a dimethyl- or diethylamino group almost completely deactivate the catalyst that is quite reasonable. It is known that Ti-catalyzed polymerization of olefins involves positively charged titanium complexes,[11] which can be easily bound to the substrate nitrogen atoms. The presence of bulky substituents at nitrogen prevents the complex formation and facilitates the reaction at the unsaturated bond. A similar situation may occur in the case of Zr-catalyzed methylalumination of substituted propargylamines. The mechanism of alkyne methylalumination under the action of Cp_2ZrCl_2 has been interpreted in different ways ranging from Zr-assisted direct methylalumination[12] to methylzirconation.[13] Possibly, the reaction of acetylenic compounds with Cp_2ZrCl_2-Me_3Al can proceed either as Al-assisted carbozirconation or as Zr-assisted carboalumination, depending on the unsaturated substrate.[14] In the general case, it can be stated that the reaction involves Al/Zr cationic species. We assumed that the presence of bulky substituents at the nitrogen atom in a substituted propargylamine molecule would be favorable for Zr-catalyzed methylalumination.

We found that *N*,*N*-diisopropyl-substituted propargylamines (*N*,*N*-diisopropyloct-2-yn-1-amine, *N*,*N*-diisopropylundec-2-yn-1-amine, and *N*,*N*-diisopropyl-3-phenylprop-2-yn-1-amine) proved to react with 2 equivalents of Me_3Al and 1 equivalent of Cp_2ZrCl_2 in dichloromethane at 40 °C to give after deuterolysis or hydrolysis *E*-alkenyl-

amines **1a–d** within 3 hours with high regio- and stereoselectivity and in high yield (77–88%, Scheme 1).[15] *N*,*N*,*N*,*N*-Tetraisopropyldeca-2,8-diyne-1,10-diamine containing two acetylenic bonds was easily converted, under the reaction conditions, into diamine **2** in 89% yield. The stereochemical configuration of the resulting allylamines was reliably established by single-crystal X-ray diffraction study of (*E*)-*N*-isopropyloct-1-en-1-aminium chloride and (*E*)-*N*-isopropyl-3-phenylprop-2-en-1-aminium chloride, obtained from the compounds **1c**,**d**, and by the NOESY spectra of the compounds **1c**,**d**, which showed coupling between the methylene group at nitrogen and the hydrogen atom at the double bond. The structure of obtained *E*-alkenylamines **1** and **2** did not correspond to the expected methylalumination products. First, the compounds **1** and **2** are formally the products of alkyne hydrometalation, which is unusual for Me_3Al. Second, one isopropyl group at the nitrogen atom is eliminated during the reaction.



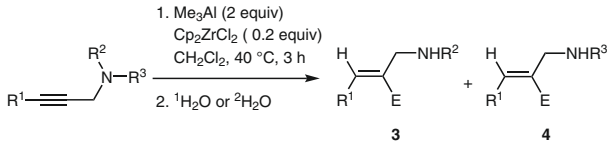
Scheme 1 The reaction of *N*,*N*-diisopropyl-substituted propargylamines with Cp_2ZrCl_2-Me_3Al reagent

We assumed that the deuterolysis product should have deuterium atoms attached to nitrogen. However, we did not detect a molecular ion corresponding to *N*-deuterium-substituted amine in the mass spectra of compounds **1a**,**b** and **3**. It is known that secondary amines often do not produce molecular ions because hydrogen at the nitrogen atom is readily eliminated. Also, the absence of deuterium at the nitrogen atom can be a consequence of column chromatography on silica gel used to isolate the products. The hydrogen atoms of functional groups such as CH_2OH, NH_2, NH, and COOH are well-known to easily exchange with deuterium (hence, deuterium atoms can be replaced by hydrogens) on any adsorbents.[16]

Further investigation of this reaction demonstrated that *N*,*N*-diisopropyl-substituted propargylamines are fully converted into *E*-alkenylamines **1** and **2** also under the action of 0.2 equivalents of Cp_2ZrCl_2 and 2 equivalents of Me_3Al, and also with $EtAlCl_2$ used instead of Me_3Al with catalytic or stoichiometric amounts of Cp_2ZrCl_2. However, the replacement of Cp_2ZrCl_2 by Cp_2TiCl_2 results in complete inhibition of the reaction. The reaction also does not occur if only Me_3Al or $EtAlCl_2$ is used without the zirconium salt.

So, our assumption that the presence of bulky substituents at nitrogen prevents the complex formation and facilitates the reaction at the unsaturated bond was true. Therefore, the unreactivity of *N*-butyl-*N*-isopropyloct-2-yn-1-amine was not a surprise to us. Unfortunately, our attempts to extend the reaction to *N*,*N*-dibenzyl- and *N*,*N*-dicyclohexyl(1-alkynyl)amines were unsuccessful. These compounds were unreactive under the reaction conditions. This result was unexpected, because both benzyl and cyclohexyl groups are bulky substituents. Considering a special role of the *N*-isopropyl group, we prepared *N*-isopropylpropargylamines containing naphthalen-1-ylmethyl, 4-methoxybenzyl, and cyclohexyl substituents at the nitrogen atom. In the first two cases (Table 1, entries 1 and 2), the reaction with Me_3Al and Cp_2ZrCl_2 was accompanied by isopropyl group elimination and gave, after hydrolysis, *E*-alkenylamines **3a**,**b** in high yield (83–86%). In the case of propargylamines with *N*-cyclohexyl substituent (Table 1, entries 3–5), the yield of *E*-alkenylamines **3c–e** was lower, being only 48–58%, which was caused by the formation of cycloalkyl group elimination products **4c–e** in 11–18% yield, instead of the isopropyl elimination products. Note the high reactivity of *N*-isopropyl-*N*-(non-2-yn-1-yl)cyclohexanamine as compared with *N*-cyclohexyl-*N*-(non-2-yn-1-yl)-cyclohexanamine, which is unreactive under these conditions. In view of this fact we assumed that configuration of the substituent at the nitrogen atom or volatility of some derivative of the leaving group are the key factors determining the course of the reaction. However, *N*-(non-2-yn-1-yl)-*N*-(1-phenylethyl)cyclohexanamine we synthesized was selectively converted under the reaction conditions into (*E*)-*N*-(non-2-en-1-yl)cyclohexanamine **3d** in 85% yield (Table 1, entry 6). Thus, the 1-phenylethyl group is eliminated more readily than the isopropyl group; this discards the hypothesis about the necessary formation of a volatile compound.

Table 1 Cp_2ZrCl_2-Catalyzed Reaction of Substituted Propargylamines with Me_3Al



Entry	R^1	R^2	R^3	E	Yield of **3** (%)	Yield of **4** (%)
1	*n*-Hex	1-naphthylmethyl	*i*-Pr	^{1}H	**3a** 86	**4a** nd[a]
2	*n*-Am	4-methoxybenzyl	*i*-Pr	^{1}H	**3b** 83	**4b** nd
3	*n*-Am	*c*-Hex	*i*-Pr	^{1}H	**3c** 54	**4c** 15
4	*n*-Hex	*c*-Hex	*i*-Pr	^{1}H	**3d** 48	**4d** 18
5	*n*-Bu	*c*-Hex	*i*-Pr	^{2}H	**3e** 58	**4e** 11
6	*n*-Hex	*c*-Hex	1-phenyl-ethyl	^{1}H	**3d** 85	**4f** nd

[a] nd: not detected.

We were unable to find examples of similar transformations in the literature; therefore, we performed quantum chemical modeling for the *N*,*N*-diisopropylbut-2-yn-1-amine complex with the methylzirconocene cation $Cp_2Zr(+)Me$, which is formed in the reaction of Cp_2ZrCl_2 and Me_3Al. Since it has been assumed that bulky substituents prevent the interaction of cationic species with the nitrogen atom, we considered only those reactant configurations in which the zirconium atom interacts with the triple carbon–carbon bond. Using B3LYP/631G(d)/LanL2DZ calculations, several stationary points were located on the potential energy surface, corresponding to the complex in which the methylzirconocene cation is coordinated to a larger extent to the sp-hybridized carbon atom bearing the aminomethyl group. According to calculations, this coordination is favorable for pronounced polarization of the triple bond. In one conformation of the aminomethyl substituent, hydrogen attached to the tertiary carbon atom is proximate to the arising electrophilic site of the molecule. Notably, in this conformation, a pronounced HOMO electron density is concentrated on this hydrogen atom and the length of the CH bond is increased to 1.13 Å, compared to 1.09 Å for the length of the CH bond in adjacent isopropyl group. Obviously, this is a consequence of negative hyperconjugation of lone pair of nitrogen atom and antibonding orbitals σ^*_{CH} (Figure 1).

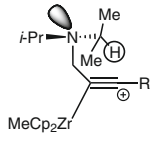
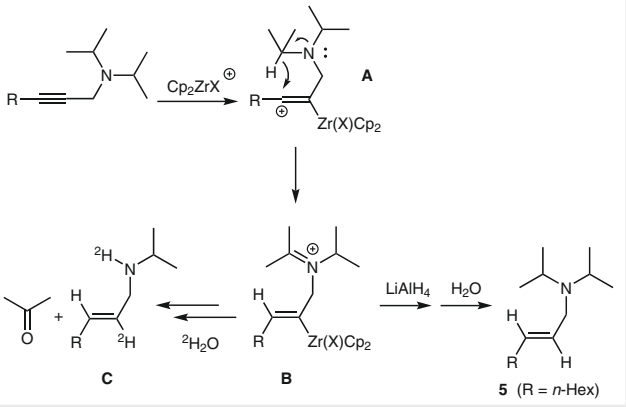


Figure 1 Hypothesized negative hyperconjugation in the complexes of *N*,*N*-diisopropyl-substituted propargylamines

Using B3LYP/6-31G(d)/LanL2DZ calculations, the transition state was located, corresponding to the hydrogen transfer from the tertiary carbon atom of the isopropyl group to the electrophilic sp-hybridized carbon atom. The activation barrier of the process is only 4.7 kcal/mol and the change of free energy of the reaction is –15.9 kcal/mol. As result the rearrangement of intermediate **A** (Scheme 2) gives iminium salt **B**. Deuterolysis of the latter affords *E*-alkenylamine **C**. It is known that the α-hydrogen atom in tertiary amines is prone to hydride abstraction.[17] However the carbon–carbon double bond to be reduced usually needs to be strongly activated by adjacent electron-withdrawing substituents such as CF_3, CN, COOR, NO_2.[18] The evidence in favor of this mechanism is the finding that the addition of sixfold excess of $LiAlH_4$ to the reaction mixture led to the formation of (*E*)-*N*,*N*-diisopropylnon-2-en-1-amine (**5**) in good yield (80%) when R = *n*-Hex (Scheme 2).



Scheme 2 Plausible mechanism of the conversion of substituted propargylamines into *E*-alkenylamines under the action of cationic zirconocene complexes

The reaction of *N*,*N*-diisopropyloct-2-yn-1-amine with 2 equivalents of Me_3Al and 1 equivalent of Cp_2ZrCl_2 at 40 °C does not proceed in hexane. There are two possible explanations for this result: (a) nonpolar solvent does not contribute to the stabilization of the intermediate **A**; (b) cationic zirconocene complexes in nonpolar solvent are electrophilic enough to be easily bound to the substrate nitrogen atoms.

So, as regards the nature of the cationic species, we are inclined to the opinion that they are either $Cp_2Zr(+)Me$ or $Cp_2Zr(+)Cl$, depending on the organoaluminum compound used (Me_3Al or $EtAlCl_2$). This conclusion is supported by the fact that the reactions do not proceed in the presence of Cp_2TiCl_2, which is similar to Cp_2ZrCl_2 in many aspects. That is, the nature of the metal has a crucial role for the reaction, which implies direct involvement of the metal ion in the reaction site.

It follows from Table 1 that the capability of elimination decreases in the following series of *N*-substituents: *N*-1-phenylethyl > *N*-isopropyl > *N*-*c*-Hex. According to Scheme

2, the ease of hydrogen transfer from the tertiary carbon atom should be determined by (a) stability of the iminium salt thus formed; (b) lower steric hindrance in the transition state leading to intermediate **B**. According to B3LYP/6-31G(d,p) calculations, the relative free energy of the formation of the iminium salt from amine increases in the series of amines: *N*,*N*-dimethyl-1-phenylethan-1-amine (–3.91 kcal/mol) < *N*,*N*-dimethylcyclohexanamine (–1.85 kcal/mol) < *N*,*N*-dimethylpropan-2-amine (0 kcal/mol). The higher capability of the isopropyl group for hydrogen atom transfer compared with the cyclohexyl group can be due to steric factors. A more intricate issue is the lack of reactivity of *N*-cyclohexyl-*N*-(non-2-yn-1-yl)cyclohexanamine under the reaction conditions as compared with the reactive *N*-isopropyl-*N*-(non-2-yn-1-yl)cyclohexanamine. According B3LYP/6-31G(d)/LanL2DZ calculations, the activation barrier of the hydride transfer step in the case of *N*-cyclohexyl-*N*-(non-2-yn-1-yl)cyclohexanamine is 5.8 kcal/mol. This represents a slight difference from the value calculated for the diisopropyl derivative (4.7 kcal/mol), but it may be somewhat underestimated because insufficient account was taken of the steric interactions of the two bulk cyclohexyl groups.

In summary, the unusual transformation of *N*-isoalkyl-substituted propargylamines into alkenylamines under the action of $Cp_2ZrCl_2$and organoaluminum compounds (Me_3Al, $EtAlCl_2$) was first observed. According to proposed plausible mechanism of the conversion, *N*-isoalkyl-substituted propargylamines undergo zirconocene-initiated intramolecular hydride transfer that was confirmed by B3LYP/6-31G(d)/LanL2DZ calculations. Obviously, one of the most important factors of the transformation is the presence of negative hyperconjugation of lone pair of nitrogen atom and antibonding orbitals σ^*_{CH} located at the isoalkyl group.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1609336.

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(15) **(*E*)-2-*d*-*N*-Isopropyloct-2-en-1-amine (1a)**To a 25 mL, argon-swept flask, equipped with a magnetic stirrer and rubber septum, was added Cp_2ZrCl_2 (585 mg, 2 mmol) suspended in CH_2Cl_2 (5 mL) and Me_3Al (0.38 mL, 4 mmol; caution: organoaluminums are pyrophoric and can ignite on contact with air, water or any oxidizer!) at room temperature. To the solution was added *N*,*N*-diisopropyloct-2-yn-1-amine (418 mg, 2 mmol) at room temperature and stirred for 3 h at 40 °C. Then, the reaction mixture was diluted with with hexane (5 mL), and D_2O (3 mL) was added dropwise while cooling the reactor flask in an ice bath. The precipitate was filtered on a filter paper. The aqueous layer was extracted with diethyl ether (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous $CaCl_2$. Evaporation of solvent and purification of the residue by column chromatography (hexane/ethyl acetate, 5:1) gave a colourless oil; yield 279 mg (82%); R_f = 0.8 (hexane/ethyl acetate, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.85 (t, *J* = 6.9 Hz, 3 H, C(11)H_3), 1.02 (d, *J* = 6.3 Hz, 6 H, C(5,6)H_3), 1.17–1.30 (m, 4 H, C(9,10)H_2), 1.30–1.37 (m, 2 H, C(8)H_2), 1.98 (q, *J* = 7.1 Hz, 2 H, C(7)H_2), 2.74–2.83 (m, 1 H, C(4)H_1), 3.14 (s, 2 H, C(1)H_2), 5.45–5.60 (m, 1 H, C(3)H_1). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.97 (C(11)), 22.47 and 31.35 (C(9) and C(10)), 22.88 (2 C, C(5,6)), 28.93 (C(8)), 32.25 (C(7)), 47.99 (C(4)), 49.30 (C(1)), 128.08 (t, $^1J_{CD}$ =18.5 Hz, C(2)), 132.34 (C(3)). MS (EI): *m*/*z* (%) = 170 (4) [M]$^+$, 155 (22), 141 (<1), 127 (2), 111 (8), 99 (12), 82 (7), 69 (31), 44 (100), 41 (21). Anal. Calcd (%) for $C_{11}H_{22}DN$: C, 77.57; N, 8.22. Found: C, 77.7; N, 8.3.
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