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Unexpected Titanium Shifts During Cyclopropanation of N,N-Dibenzylformamide with Ligand-Exchanged Titanium-Alkadiene Complexes¹

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Abstract: A number of readily available dienes and a triene were applied to exchange the alkene ligand on the in situ generated titanium-alkene complexes which react with N,N-dialkylcarboxamides to give N,N-dialkylcyclopropylamines. The ligand-exchanged intermediates were found to give the most highly substituted alkenylcyclopropylamines (abnormal products) in good yields (47–64%), rather than the least substituted alkenylcyclopropylamine (expected products). This has been attributed to an unforeseen and unprecedented titanium migration along the ligand. © 1998 Elsevier Science Ltd. All rights reserved.

Since the discovery by our group of the new titanium-mediated synthesis of N,N-dialkylcyclopropylamines 4 from N,N-dialkylcarboxamides 1 (Scheme 1),² which is an adaptation of the original Kulinkovich protocol for the conversion of esters to cyclopropanols,³ we have been further improving the methodology⁴ and exploring the scope and limitations as to extend the accessible substitution pattern of the cyclopropylamine ring system.

Sooner or later, we^{5,6} and others⁷ realized that the ligand exchange of alkenes 5 on the titanacyclopropane intermediate 6 to yield a differently substituted intermediate 2, which was also discovered by Kulinkovich et al.⁸ and utilized in the synthesis of highly functionalized cyclopropanols,^{8,9} could easily be adapted for the synthesis of cyclopropylamines with one, two, and three additional substituents on the cyclopropane ring from terminal^{5,6,7} and non-terminal alkenes.^{5,6} In this preliminary communication we would like to report on our novel observation that conjugated dienes and trienes are accepted by titanacyclopropane intermediates 6 as particularly good ligands, and the thus formed intermediates 2 generally reacted with dibenzylformamide to form cyclopropylamines with an unexpected substitution pattern.



Scheme 1

The reactions were carried out by generating the diisopropyloxytitanium intermediate from the respective diene and an alkenetitanium intermediate formed from methyltriisopropyloxytitanium and an alkylmagnesium halide in the presence of N,N-dialkylformamide. Cyclohexylmagnesium bromide was found to be superior to any other Grignard reagent previously advertised for this type of ligand-exchange-initiated transformation,^{7,9} and was simply added as the last reagent to a THF solution containing preformed

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MeTi(OiPr)₃, the diene and dibenzylformamide.¹⁰ Butadiene (9) was thus converted to 2-ethenyl-1-(N,N-dibenzylamino)cyclopropane (10) in 56% yield (Table 1, entry 1). Cyclopropylamine 10 had previously been obtained from but-3-en-1-ylmagnesium bromide in the presence of MeTi(OiPr)₃.⁴ Surprisingly, the reactions

Entry	Alkene Conditions Temp. [°C] Time		litions [] Time [h]	Product	Yield (%)	Diastereom. Ratio (<i>cis/trans</i>) ^a
1	9	_20 ^b	12	NBn ₂	56	1:2.7
2	11	0–5	15	Bn ₂ N 12	59	>98:2°
3		0–5	24	d		_
4	14	. 0–5	24	Bn ₂ N 15	64	1:5.3
5	16	0–5	18	Bn ₂ N 15	27	1:3
6		05	22	d		_
7		0–5	17	Bn ₂ N 19	51¢	>98:2°
8	20	0–5	26	NBn ₂	54	1:1.5:1.5

Table. 1. 2-Alkenyl-1-(*N*,*N*-dibenzylamino)cyclopropanes formed from *N*,*N*-dibenzylformamide and in situ generated titanium-diene complexes applying a ligand exchange approach.¹⁰

^a As by integration of the corresponding ¹H NMR signals. – ^b First example used to investigate whether dienes can participate as ligands in this process. – ^c The second diastereoisomer was not detected by ¹H NMR. – ^d No reaction observed. – ^e Commercially available myrcene after fractional distillation was only ~85–90% pure and therefore some minor products were observed resulting from the 10–15% polyene impurity in the starting material.

with substituted 1,3-dienes such as isoprene (11), 4-methyl-1,3-pentadiene (14) and myrcene (18) gave the alkenyldibenzylaminocyclopropanes 12, 15, and 19, respectively, derived from attack on the more highly substituted double bond of the conjugated diene unit rather than the expected products which would have been formed by attack on the least substituted double bond. As these expected products were not detected in any case,¹¹ and control experiments with 2,3-dimethylbutadiene (13) and 2,5-dimethyl-2,4-hexadiene (17) did not yield any cyclopropylamines, it must be concluded that only the alkenyldiisopropyloxytitanacyclopropane 22 is initially formed from a conjugated diene of type 11 by complexation at the least substituted double bond. It is conceivable that 22 then undergoes a titanium shift to the more highly substituted titanacyclopropane 24



Scheme 2

before it reacts with the carbonyl group in the formamide. This shift might occur via a 1-alkenyltitanacyclopropane 22 to 4-titanacyclopentene 23 rearrangement¹² – corresponding to an intramolecular carbotitanation of an alkene by an allyltitanium species – with subsequent ring contraction to give 24. Only if the latter were much more reactive than 22 this route would lead to the selective formation of the more highly substituted cyclopropylamine 30 via oxatitanacyclopentane 28. More likely, though, the formamide reacts with the kinetically favored, and also thermodynamically more stable 22 – as calculated at the B3LYP/6-311+G*//HF/3-21G level of theory – via a six-center transition structure^{12d} to yield the oxatitanacycloheptene 27 which can only cyclorevert to the observed more highly substituted cyclopropylamine 30. The sevenmembered ring intermediate 27 could also be formed by addition of formamide to 23 via a four-center transition structure¹³ or by ring enlargement of the vinyloxatitanacyclopentane 28.

The formation of the same cyclopropylamine 15 from 2-methyl-1,3-pentadiene (16) as from 4-methyl-1,3-pentadiene (14) most probably arises by initial isomerization of 16 to 14 under the conditions employed. The fact that the conjugated 6-methyl-1,3,5-heptatriene (20) yields only the 2,3-dialkenylcyclopropylamine 21 arising from attack at the central double bond in 20 may be taken to indicate that the reacting species is actually the less substituted titanacyclopropane of type 22 or a titanacyclopentene of type 23 rather than the most highly substituted titanacyclopropane of type 24.

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- Representative experimental procedure for compound 12 and spectroscopic data for 12, 15, 19: 10. Methylmagnesium chloride (1.79 mL, 3 M solution in THF) was added dropwise to a solution of titanium tetraisopropoxide (1.43 mL, 4.88 mmol) in anhydrous THF (15 mL) over a period of 5-10 min at 0-5 °C under an argon atmosphere. After stirring for a further 5 min a solution (6 mL) of dibenzylformamide (1.0 g, 4.44 mmol) in anhydrous THF was added in one portion followed by addition of isoprene (0.488 mL, 4.88 mmol). Cyclohexylmagnesium bromide (2.69 mL, 2.0 M solution in ether) was then added dropwise over 45-50 min. The reaction mixture was allowed to warm to room temperature over 15 h before quenching with water (2.5 mL) (extremely exothermic). When the resulting precipitate had become colorless (ca. 15 min) it was removed by filtration, washed with ether (20 mL), and the combined filtrates were concentrated. The residue was subjected to radial chromatography (t-butyl methyl ether / n-hexane, 2:98, 10:90 gradient) on silica gel affording 0.73 g (59%) of compound 12 as a colorless oil. (Found: C, 86.37; H, 8.18%; requires C₂₀H₂₃N, C, 86.59; H, 8.36%). δ_H 0.51, t, J 4.8, 1 H; 0.81, dd, J 4.8, 7.4, 1 H; 1.24, s, 3 H; 1.90, dd, J 4.8, 7.4, 1 H; 3.63, AB, J 13.6, 4 H; 4.87, s, 1 H; 4.92, d, J 10.4, 1 H; 5.45, dd, J 10.4, 17.3, 1 H; 7.25–7.38, m, 10 H; δ_C 15.19; 21.50; 26.00; 49.94; 57.79; 109.69; 126.80; 127.99; 129.48; 138.25; 145.56. 15: (Found: C, 86.78; H, 8.49%; requires $C_{21}H_{25}N$, C, 86.55; H, 8.65%). (Major) δ_H 0.99, s, 3 H; 1.09, s, 3 H; 1.14, dd, J 4.0, 9.3, 1 H; 1.70, d, J 4.0, 1 H; 3.60, s, 4 H; 4.90, m, 1 H; 4.95, s, 1 H; 5.49, m, 1 H; 7.22–7.41, m, 10 H; δ_{C} 20.74; 20.97; 26.52; 35.88; 55.97; 57.86; 114.12; 126.80; 127.98; 129.52; 137.46; 138.33; (minor) δ_H 1.07, s, 6 H; 1.39, dd, J 7.3, 10.0, 1 H; 1.85, d, J 7.3, 1 H; 3.60, AB, J 13.9, 4 H; 5.02, dd, J 2.2, 10.3, 1 H; 5.15, dd, J 2.2, 17.2, 1 H; 5.91, dt, J 10.3, 17.2, 1 H; 7.22–7.41, m, 10 H; δ_{C} 15.14; 24.33; 26.99; 33.47; 52.09; 56.26; 114.69; 126.82; 128.00; 129.64; 135.77; 137.68. 19: (Found: C, 87.20; H, 9.18%; requires $C_{25}H_{31}N$, C, 86.90; H, 9.04%). δ_{H} 0.49, t, J 5.0, 1 H; 0.91, bt, J 5.0, 1 H; 1.62, s, 3 H; 1.73, s, 3 H; 1.81, dd, J 5.0, 7.2, 1 H; 1.85–2.05, m, 2 H; 2.05–2.29, m, 2 H; 3.62, AB, J 13.8, 4 H; 4.84, dd, J 1.3, 17.3, 1 H; 4.91, dd, J 1.3, 10.6, 1 H; 5.17, m, 1 H; 5.65, dd, J 10.6, 17.3, 1 H; 7.25–7.35, m, 10 H; $\delta_{\rm C}$ 17.68; 19.24; 25.72; 26.67; 29.80; 30.75; 50.94; 57.58; 110.75; 124.95; 126.80; 127.98; 129.49; 131.11; 138.18; 143.50.
- 11. Actually, when homoprenylmagnesium bromide in the presence of $Ti(OiPr)_4$ was treated with ethyl acetate, both isomeric cyclopropanols, the less and the more highly substituted, were isolated in comparable yields, albeit in only 2.4 and 3.6%.⁶
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