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A new coupling reaction of propargyl carbonates mediated by $Ti(OiPr)_2Cl_2/Mg$

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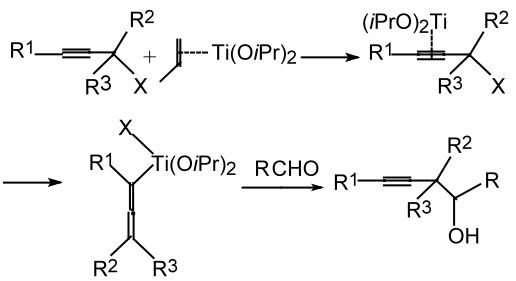
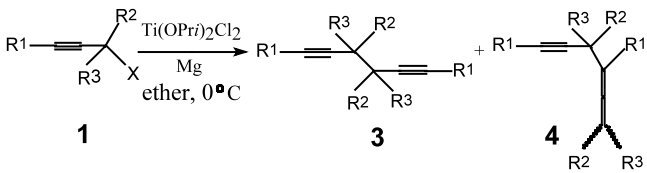
Abstract—A new homocoupling reaction of 1,1-disubstituted propargyl carbonates or 1-monosubstituted propargyl carbonates, mediated by $Ti(OiPr)_2Cl_2/Mg$ in ether at 0°C, was found to form symmetric 1,5-hexadiynes and 1-allenyl-5-ynes in moderate to high yields in various ratios.

Carbon–carbon bond forming reactions promoted by low-valent titanium are important methodologies used to construct complex molecular skeletons.[1] Pauson–Khand reactions[2] and McMurry reactions[3] have been extensively used in the syntheses of complex natural products. Recently F. Sato's group[4a] has developed a new method to prepare homopropargyl alcohols by the reaction of carbonyl compounds with the intermediate allenyltitanium formed from propargyl halides or carbonates and a low valent diisopropoxy(η^2-propene) titanium intermediate (Scheme 1).

Herein we would like to report an unexpected new coupling reaction of 1-substituted propargyl alcohol derivatives mediated by low-valent titanium to form 1,5-hexadiynes and 1-allenyl-5-ynes in moderate to high yield in various ratios. In reference to the recently reported titanium-mediated intramolecular cyclization of tethered propargyl alcohol derivatives[5] we found that when a 1,1-disubstituted propargyl carbonate **1a** (R^1 = Ph, R^2R^3 = -$(CH_2)_4$-) (Scheme 2) was treated with $Ti(OiPr)_2Cl_2/Mg$ in ethyl ether and then quenched with benzaldehyde, no homopropargyl alcohol was obtained as expected, but a new product was isolated instead.



Scheme 1.



	R^1	R^2	R3	X
a	Ph	-$(CH_2)_5$-		OAc
b	Ph	-$(CH_2)_5$-		OCO_2Et
c	Ph	CH_3	CH_3	OAc
d	Ph	CH_3	CH_3	OCO_2Et
e	nC_4H_9	CH_3	CH_3	OCO_2Et
f	nC_4H_9	Ph	H	OCO_2Et
g	Me_3Si	Ph	H	OCO_2Et
h	Ph	CH_3	H	OCO_2Et
i	Ph	nC_3H_7	H	OCO_2Et
j	Ph	Ph	H	OAc
k	Ph	Ph	H	OCO_2Et
l	H	Ph	H	OCO_2Et
m	H	4-FC_6H_4	H	OCO_2Et
n	H	4-$CH_3C_6H_4$	H	OCO_2Et
o	H	4-$O_2NC_6H_4$	H	OCO_2Et
p	CO_2Et	CH_3	CH_3	OCO_2Et
q	Ph	H	H	OCO_2Et

Scheme 2.

Keywords: C–C coupling; alkynes; diisopropoxytitanium dichloride; magnesium.

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After full characterization by IR, MS, ^{1}H, ^{13}C NMR and EA and X-ray crystallographic analysis (Fig. 1),[6] this proved to be the homocoupling product **3a**. That means benzaldehyde does not take part in the reaction. A series of propargyl esters as substrates have been tested for this new intermolecular homocoupling reaction. The results are shown in Table 1.

The results in Table 1 using a variety of propargyl esters as substrates show that: (a) 1,1-disubstituted propargyl esters produce the homocoupled compounds smoothly with high yields (entries 1–5); (b) the reactions with 1-mono-aryl propargyl carbonates also result in homocoupled products in good yields (entries 6, 7, 11) but the coupling reactions of acetates (entry 10) or 1-monoalkyl propargyl carbonates (entries 8 and 9) usually proceed slowly with moderate yields and a considerable amount of recovered starting materials. There was always a certain amount of 1-allenyl-5-alkyne in the product of the coupling reactions. The coupling reaction of 1-aryl propargyl carbonates containing no substituent on the terminal triple bond gave moderate yields (entries 12–14) with concomitant formation of 1-allenyl-5-alkyne, but alkynes containing a Me_3Si group on the terminal triple bond carbon gave much better results (entry 7). For most 1-monosubstituted propargyl carbonates a mixture of meso and dl isomers in various ratios were obtained. The ratio can be roughly estimated based on their ^{1}H NMR (for compounds **3g**, **3h**, **3j**, **3l**, **3m**, **3n, 3o**) or ^{13}C NMR (for compound **3f**), but we have not determined which is the meso or dl isomer except for **3j**;[7] (c) ethyl 3-ethoxycarbonyl-1,1-dimethylpropargyl carbonate **1p** was transformed to the β-elimination product without any coupling product being isolated (entry 16); (d) the coupling reaction of the 3-phenylpropargyl carbonate, in which there is no 1-substituent, did not occur at all (entry 17). In that case most starting material was recovered even though the reaction period was extended to 24 h. When a more active propargyl mesylate was used, only propargyl chloride was isolated.

Table 1. Homocoupling of propargyl esters mediated by $Ti(OiPr)_2Cl_2/Mg$[a]

Entry	Propargyl ester	Products	Yield (%)[b]	Ratio[c] (**3**/**4**)
1	**1a**	**3a**	89[d,l]	
2	**1b**	**3b**	94[l]	
3	**1c**	**3c**	76	
4	**1d**	**3d**	81	
5	**1e**	**3e, 4e**	70	52:48
6	**1f**	**3f, 4f**	82	54:46
7	**1g**	**3g, 4g**	89[d]	87:1
8	**1h**	**3h**	45[e]	
9	**1i**	**3i, 4i**	42[f]	70:30
10	**1j**	**3j, 4j**	53[g]	71:29[k]
11	**1k**	**3k, 4k**	83	81:19[k]
12	**1l**	**3l, 4l**	48	50:50
13	**1m**	**3m, 4m**	46.6	52:48
14	**1n**	**3n, 4n**	49	55:45
15	**1o**	**3o**	55[h]	
16	**1p**		43[i]	
17	**1q**		Little[j]	

[a] Reaction conditions: propargyl ester:$Ti(OiPr)_2Cl_2$:Mg = 1:1.2:2 (mmol); 0°C for 1 h; then room temperature for 3–4 h.
[b] Isolated yield after purification on silica gel column chromatography (petroleum ether).
[c] The ratio was determined by the isolated yields of **3** and **4** after purification on column chromatography.
[d] Homocoupling product crystal was obtained by recrystalization in CH_3CN and used for X-ray structure analysis.
[e] 30% starting material was recovered.
[f] 28% starting material was recovered.
[g] 29% starting material was recovered.
[h] Reaction for 24 h at room temperature and 38% starting material was recovered.
[i] Only 1,1-dimethyl-3-ethoxycarbonylallene was isolated and 45% starting material was recovered.
[j] Reaction for 24 h at room temperature and most starting material did not change.
[k] The ratio was estimated by the ^{1}H NMR of the product mixture, since the relevant 1-allenyl-5-alkyne was unstable and difficult to be separated in pure form.
[l] It contains one sixth 1-(1′-cyclopentenyl)-2-phenylethyne.

In order to explore the mechanism we carried out the following experiments. (1) The coupling reactions of compounds **1a** and **1k** proceeded smoothly with comparable yield using 0.5:1 (mole ratio) of $Ti(OiPr)_2Cl_2$: substrate **1a** (or **1k**) instead of a 1:1 ratio. That means only one mole of $Ti(OiPr)_2Cl_2$ is needed for the coupling of two moles of propargyl carbonate. (2) A cross coupling reaction of 1,1-dimethyl-3-phenylpropargyl carbonate **1d**: 3-phenylpropargyl carbonate **1q**: $Ti(OiPr)_2Cl_2$ (1:1:1 molar ratio) was carried out but no cross coupling product was detected except the homocoupling product of **3d**. This excludes a mechanism whereby a monoallenyltitanium intermediate, which could be produced in our system,[8] attacks the electrophilic C1 of a second **1d** molecule to form the homocoupling products since the primary 3-phenylpropargyl carbonate **1q** should be more active to S_N2 attack than the tertiary 1,1-dimethyl-3-phenylpropargyl carbonate **1d**. (3) We have carried out an experiment to verify the role of Mg as follows: $Ti(OiPr)_2Cl_2$ was treated first with Mg powder in dry ether under N_2 at 0°C, and then the supernatant solution was transferred under N_2 to a propargyl carbonate solution **1d** in ether without Mg present at 0°C, but only a small amount of coupling product was isolated. When the supernatant solution was transferred to a propargyl carbonate **1d** solution in ether with Mg present in the same manner, the homocoupling product **3d** was formed in normal yield. This means that the monoallenyltitanium intermediates **2** do not couple each other, but they couple with each other in the presence of Mg.

A radical coupling reaction mechanism is tentatively suggested as shown in Scheme 3, based on the fact that the more substituents at C1 the propargyl carbonates possess, the higher the yield of the coupling product. The oxidative insertion of low-valent $Ti(OiPr)_2$, formed from $Ti(OiPr)_2Cl_2$ and Mg in ether at 0°C, to the triple bond of the propargyl carbonate produces an allenyltitanium intermediate. A propargyl radical could then be formed on the Mg surface through a SET process and two propargyl radicals couple with each other to form the homocoupling product. In a radical detection test

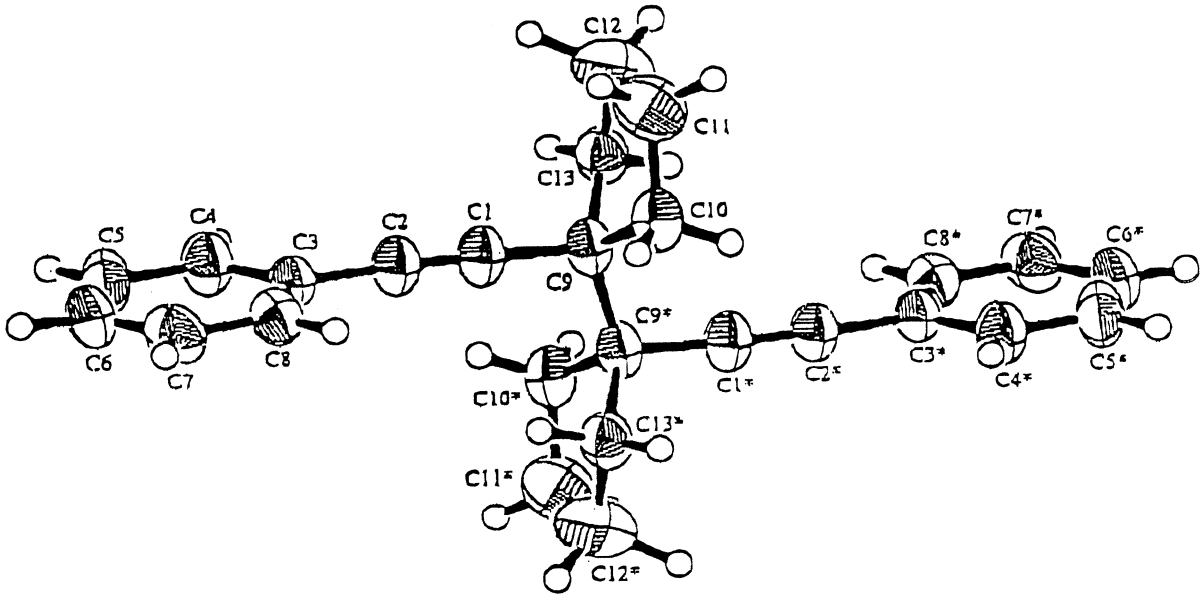
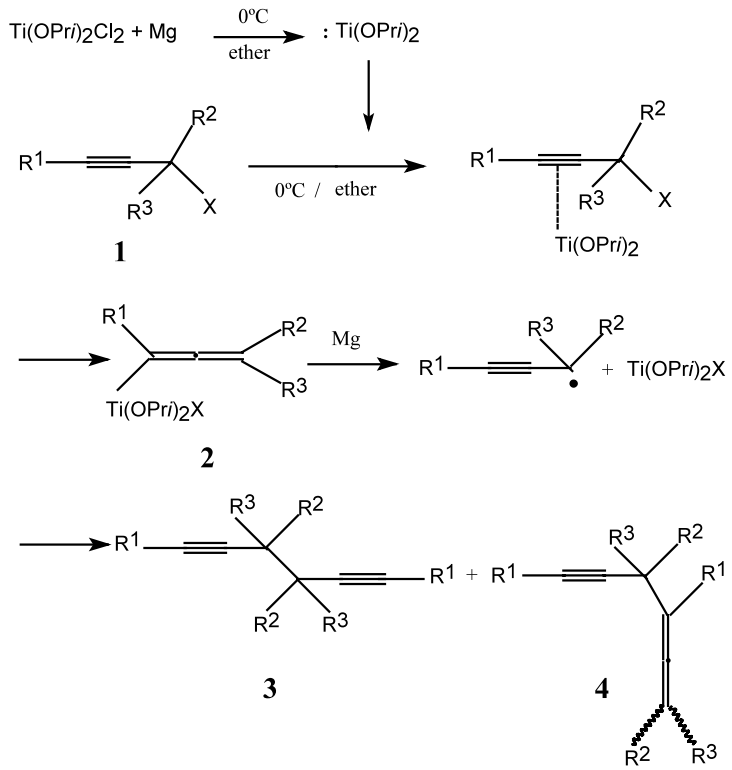


Figure 1.



Scheme 3.

using **1a** as substrate and 2-nitroso-2-methyl-propane as scavenger no ESR signal could be detected. Therefore, the radical mechanism needs further proof, although it looks reasonable. It is interesting that the best solvent for this homocoupling reaction is ethyl ether, while the reactions carried out in THF or benzene resulted in product mixtures from deoxygenated reduction.[9]

In conclusion, we have developed a new intermolecular carbon–carbon bond forming coupling reaction, which can be used for the syntheses of symmetric 3,3,4,4-tetra-substituted 1,5-hexadiynes, with vicinal quaternary carbons, and 3,4-di-substituted 1,5-hexadiynes, in good to high yields. These kinds of 1,5-hexadiynes with high hindrance are not easy to be synthesized by known methodology.[10]

Typical experimental procedure: To activated Mg powder (48 mg, 2 mmol) in ethyl ether (10 ml) was added 0.8 M $Ti(O\textit{i}Pr)_2Cl_2$ in benzene (1.5 ml, 1.2 mmol) at 0°C and the mixture was stirred for 1 h at 0°C. Ethyl 1,1-dimethyl-3-phenylpropargyl carbonate **1c** (228 mg, 1 mmol) was added dropwise and reacted for 1 h at 0°C and for 3–4 h at room temperature. After workup with

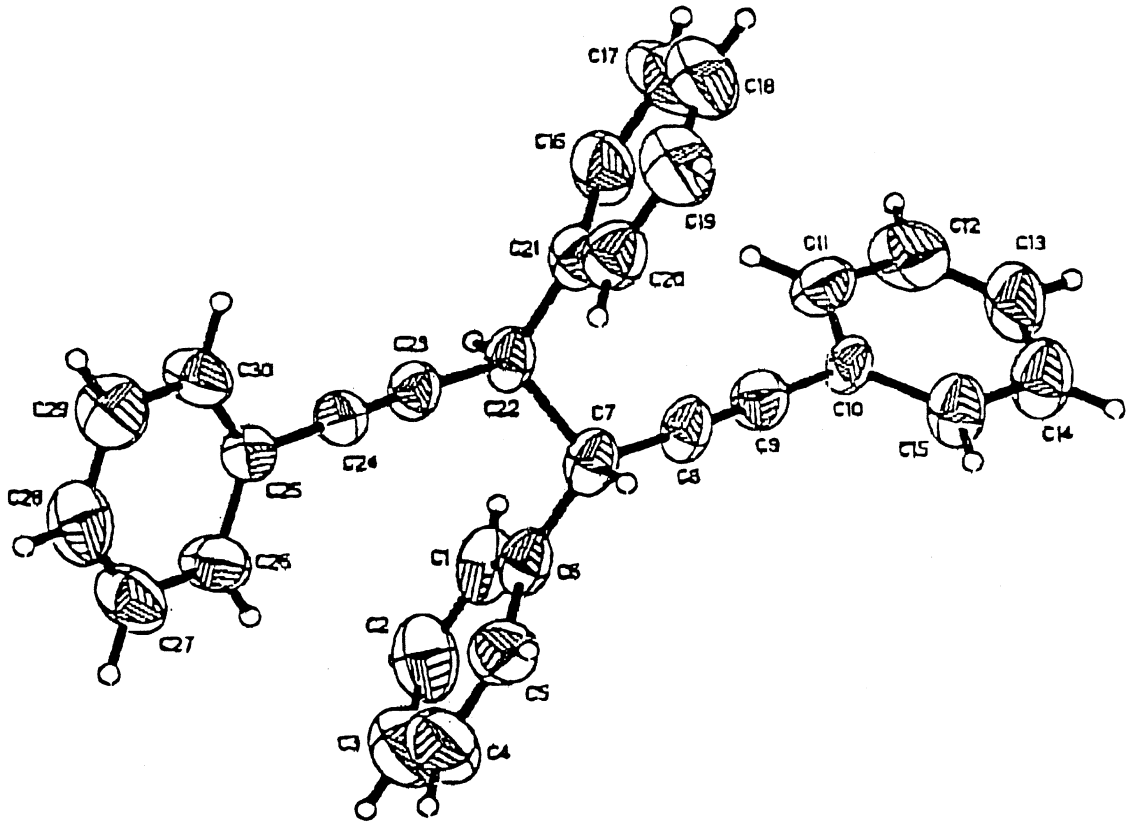


Figure 2.

2N HCl the separated aqueous layer was extracted with diethyl ether and the combined ether layer washed with brine and dried over Na_2SO_4. Column chromatography on silica gel (petroleum ether) gave 1,6-diphenyl-3,3,4,4-tetramethyl-1,5-diyne **3c** (115 mg, 81% yield) as white solid,[10] mp 99.5°C (recrystalized from acetonitrile); IR (KBr): $v=3030$ (phenyl C-H), 2235 (C≡C), 1598, 1491 (phenyl nucleus) cm^{-1}; ^1H NMR (300 Hz, $CDCl_3$, 25°C, TMS): $\delta=7.43$–7.25 (m, 10H; $2\times C_6H_5$), 1.45 (12H, s; $4\times CH_3$); ^{13}C NMR (300 MHz, $CDCl_3$, 25°C): $\delta=131.6$, 128.2, 127.6, 124.1, 95.4, 82.1, 39.1, 26.0; MS (70 eV): m/z (%): 286 (M^+) (16), 271 (20), 243 (8), 143 (100), 128 (20), 91 (5), 77 (3), 65 (1), 51 (2), 41 (2). EA: calcd. for $C_{22}H_{22}$: C, 92.31; H, 7.69. Found: C, 91.97; H, 7.80.

Acknowledgements

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6. Crystallographic data (excluding structure factors) for the structures of compounds **3a** and **3j** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 148682 and 148681, respectively. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambride CB21EZ, UK (fax: (+) 1223–336-033; e-mail: deposit@ccdc.cam.ac.uk).

7. Representative products are **3j**: **1,3,4,6-Tetraphenyl-1,5-hexadiyne**
   Mp 163.4±0.5°C (recrystallized in acetonitrile). IR (KBr): $\nu = 3028$ (phenyl C-H), 2200 (C≡C), 1598, 1489 (phenyl nucleus) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 25°C): $\delta =$ 7.30–7.20 (m, 20H; 4×C_6H_5), 4.21 (s, 2H; 2×CH); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): $\delta = 138.73$, 131.62, 128.93, 128.21, 128.08, 127.98, 127.37, 123.53, 89.45, 85.40, 46.53; MS (70 eV): m/z: 338 (M^+, 3), 295 (3), 270 (3), 219 (4), 169 (48), 168 (93), 167 (100), 165 (49), 153 (46), 152 (47), 129 (43), 115 (21), 97 (23), 71 (44), 57 (55), 43 (28). EA: calcd for $C_{30}H_{22}$: C, 94.24; H, 5.76; found: C, 93.95; H, 5.33.
   Before recrystalisation from acetonitrile the ^1H NMR spectrum of compound **3j** showed that it is a mixture consisting of *syn* (δ 4.23) and *anti* isomers (δ 4.21) in a 1:1 ratio. Since the crystal structure of recrystallized **3j** has been shown to be a meso isomer, the ^1H NMR spectrum of which shows a singlet peak at δ 4.21, by X-ray-crystallographic analysis (Fig. 2)[6] we attribute the peak δ 4.23 to the *anti* isomer. We attribute the peak at lower field to the *anti* isomer and that at higher field to the *syn* isomer.
   Compound 4e: 7, 7-dimethyl-8-(2′-methyl-1′-propenyli-denyl)-5-dodecyne
   Colorless oil. IR (neat): $\nu = 2961$, 2933 (C-H), 2238 (C≡C), 1960 (C=C=C), 1460, 1376, 1364 ($C(CH_3)_2$) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 25°C): $\delta = 2.15$ (t, ^3J (H, H) = 6.7 Hz, 2H; CH_2), 2.05 (t, ^3J (H, H) = 7.1 Hz, 2H; CH_2), 1.65 (d, ^6J (H, H) = 4.1 Hz, 6H; 2×CH_3), 1.30–1.44 (m, 8H; 4×CH_2), 1.25 (d, ^5J (H, H) = 3.6 Hz, 6H; 2×CH_3), 0.90 (t, ^3J (H, H) = 7.0 Hz, 6H; 2×CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): $\delta = 197.13$, 109.32, 98.24, 87.07, 79.97, 34.49, 31.38, 30.67, 29.95, 28.54, 22.58, 21.98, 20.87, 18.57, 14.25, 13.73; MS (70 eV): m/z: 246 (M^+, 3), 231 (8), 203 (13), 189 (88), 161 (12), 147 (25), 133 (28), 119 (24), 91 (19), 81 (100), 67 (30), 55 (23), 41 (40); HRMS m/z: calcd for $C_{18}H_{30}$: 246.23475; found: 246.23253.
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9. In all coupling reactions a certain amount of the reduction product mixture stemmed from deoxygenated reduction, β-elimination and/or further rearrangement of the triple bond to an allene, which was difficult to separate.
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