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Highly Stereoselective Synthesis of Trisubstituted cis-[3]Cumulenols from Alkynylated Oxatitanacycles in the Presence of Lewis acids

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Summary: A highly efficient and stereoselective method for the synthesis of trisubstituted cis-[3]cumulenols via oxatitanacycles derived from titanium-mediated coupling of 1,3-butadiynes with aldehydes or ketones promoted by Lewis-acids is described.

[3]Cumulenes have attracted much attention in recent years since they have potential applications in antitumor drug design[1] and as advanced materials with unique electronic and photonic properties.[2] They are also versatile synthetic intermediates in organic synthesis,[3] for example, they can serve as useful building blocks for two-dimensional carbon networks such as radialenes.[3a,b] Although a number of methods are available for the construction of cumulenes,[1,4] surprisingly the stereoselective synthesis of cumulenes with reasonable generality is quite rare,[5,6] and these strategies have some limitations, more or less, such as restricted to specific substituted substrates or involved in multistage synthesis. During our continued interests in metallacycles,[7] we have shown that zirconium-mediated coupling of 1,3-butadiynes with aldehydes or ketones provides a convenient and stereoselective access to tetra-substituted *cis*-[3]cumulenols.[7g] However, the zirconocene method could only produce the fully substituted cumulenols. There has been no example for the stereoselective synthesis of trisubstituted [3]cumulenes, to the best of our knowledge. We now report here an effective Lewis-acids-promoted rearrangement of alkynylated oxatitanacycles. This method offers a new access to the stereoselective preparation of trisubstituted cumulene derivatives from easily accessible starting materials.

We have recently developed an convenient method for the selective titanation of 1,3-butadiynes using $Ti(O^iPr)_4/n$-BuLi reagent.[7c] The thus formed titanacyclopropenes undergo cross-coupling reactions with aldehydes to afford oxatitanacyclopentenes. Interestingly, upon treatment of these oxametallacycles with strong acid such as 3N HCl aqueous solution, a small amount of [3]cumulenols could be isolated as a byproduct.[7c] Inspired by these results, we further investigate such transformations in the presence of Lewis acids. We found out that treatment of the in situ generated oxatitanacyclopentene **3**[7c] with 1 equiv of $EtAlCl_2$[8] resulted in the formation of (*Z*)-2,5-bis(*tert*-butyl-dimethylsilyl)-1-phenylpenta-2,3,4-trien-1-ol **4a** in 84% yield as a single isomer (Z/E > 99:1 by ^{1}H NMR of the crude reaction mixture) as shown in Table 1, entry 1. $EtAlCl_2$ was found to be the most effective one for this reaction, while other Lewis acids, such as Cp_2TiCl_2 or $FeCl_3$ did not afford the desired products. Employing $BF_3\cdot Et_2O$ only led to a little formation of cumulenols. It should be noted that cumulenols in general have relatively low stability, therefore, an appropriate workup procedure is very important to the success in getting pure products. First, the reaction should be quenched

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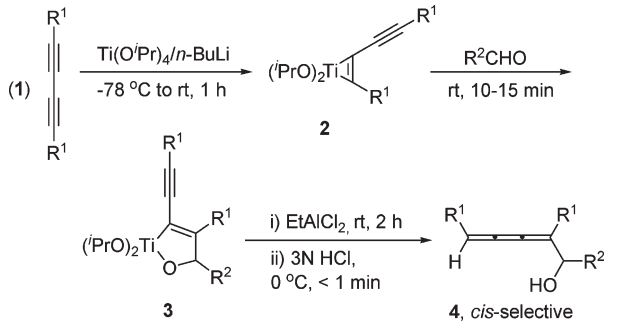
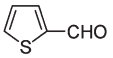
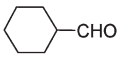
Table 1. $EtAlCl_2$-Mediated Formation of Tri-Substituted cis-[3]Cumulenols from Oxatitanacycles

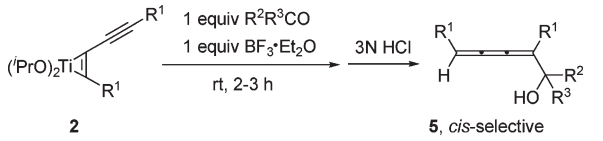


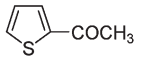
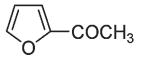
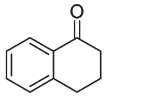
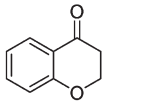
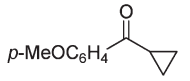
Entry	Butadiyne	Aldehyde	Product	Yield(%)[a]
1	TBS—≡—≡—TBS **1a**	PhCHO	**4a**	84
2	**1a**	*p*-ClC$_6$H$_4$CHO	**4b**	76
3	**1a**	*p*-MeC$_6$H$_4$CHO	**4c**	80
4	**1a**	*p*-MeOC$_6$H$_4$CHO	**4d**	90
5	**1a**	3,4,5-triMeOC$_6$H$_2$CHO	**4e**	86
6	**1a**		**4f**	83
7	**1a**		**4g**	64[b]
8	**1a**	^{i}PrCHO	**4h**	66
9	TMS—≡—≡—TMS **1b**	PhCHO	**4i**	53
10	Bu—≡—≡—Bu **1c**	PhCHO	-	[c]
11	Ph(CH$_2$)$_2$—≡—≡—(CH$_2$)$_2$Ph **1d**	PhCHO	-	[c]
12	Ph—≡—≡—Ph **1e**	PhCHO	-	[c]

[a] Isolated yields. [b] Containing small amount of byproduct. [c] No formation of cumulenols.

at 0 °C for a short time (< 1 min), then after extraction and washing with base, a small amount of Et_3N was added to the extract during drying and evaporation to avoid decomposition. It was also recommended to carry out evaporation at the temperature less than 30 °C and store the products at low temperature under argon atmosphere. Under these conditions, the desired **4a**−**4i** could be obtained in 53−90% yields with high purity.[9] In all cases, only *cis*-cumulenols were obtained, indicating that a high degree of stereoselectivity was achieved in this reaction.[10] As shown in Table 1, a wide variety of aldehydes could be used in this reaction. The aryl aldehydes bearing electron-donating or -withdrawing substituents were all compatible with this reaction (entries 2−5). A thienyl group could also be incorporated into the final product, leading to **4f** in 83% yield (entry 6). Aliphatic aldehydes resulted in a satisfactory yields of **4g**,**4h** (64−66%, entries 7−8). A TMS-substituted butadiyne usually gave lower yield of cumulenol than TBS-substituted ones due to the lower yield of the corresponding titanacyclopropene **2b** (entry 9). However, alkyl- or aryl- substituted butadiynes failed to generate the cumulenols (entries 10−12). The structure of cis-cumulenols has been confirmed by X-ray crystallographic analysis of **4e**.[11] It was also found that a cis-trans isomerization of cumulenols occurred by adding a trace amount of iodine to the isolated sample of cis-cumulenols.[5e] For example, using this method, a 0.7:1 (*Z*/*E*) mixtures of **4a** and its isomer were formed within 20 min at room temperature, and *trans*-**4a** could be easily separated by column chromatography.[12]

Table 2. $BF_3 \cdot Et_2O$-Mediated Formation of Tri-Substituted cis-[3]Cumulenols by the Reaction with Ketones



Entry	Butadiyne	Ketone	Product	Yield(%)[a]
1	TBS—≡—≡—TBS **1a**	PhCOCH$_3$	**5a**	59
2	**1a**	*p*-FC$_6$H$_4$COCH$_3$	**5b**	54
3	**1a**	*p*-MeOC$_6$H$_4$COCH$_3$	**5c**	50
4	**1a**	PhCOPh	**5d**	71
5	**1a**		**5e**	60
6	**1a**		**5f**	48
7	**1a**		**5g**	46
8	**1a**		**5h**	53
9	**1a**		**5i**	77[b]
10	Ph—≡—≡—Ph **1e**	PhCOCH$_3$	**5j**	26

[a] Isolated yields. [b] The reaction was carried out by first reaction with ketone for 2.5 h followed by addition of $EtAlCl_2$ and stirred for 2 h.

Next, we proceeded to investigate the reactions with ketones. In fact, only a slight reaction occurred for the coupling reactions of titanacyclopropenes **2** with ketones such as acetophenone in the absence of Lewis acid, however, the reaction was dramatically accelerated by the addition of 1 equiv of $BF_3 \cdot Et_2O$, and the *cis*-[3]cumulenol **5a** with a tertiary alcohol structure was obtained in 59% yield (Table 2, entry 1). In this case, the use of $EtAlCl_2$ did not lead to good results, and most of the titanacyclopropene remained. Results given in Table 2 indicated that the reaction applied to a broad range of ketones, especially, a bulky substrate such

(9) In all cases, oxatitanacycle **3** could be formed within 10−15 min as indicated by TLC monitoring of the hydrolysis product. We found that prolonging the reaction time in this step to 6 h followed by addition of $EtAlCl_2$ resulted in no formation of cumulenols.

(10) The *Z*/*E* ratio is > 99:1 as indicated by crude ^{1}H NMR in most cases.

(11) See Supporting Information.

(12) Several trans-[3]cumulenols have been prepared by this method; see Supporting Information.

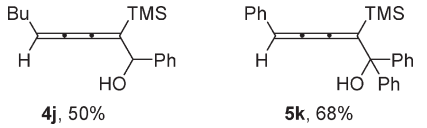
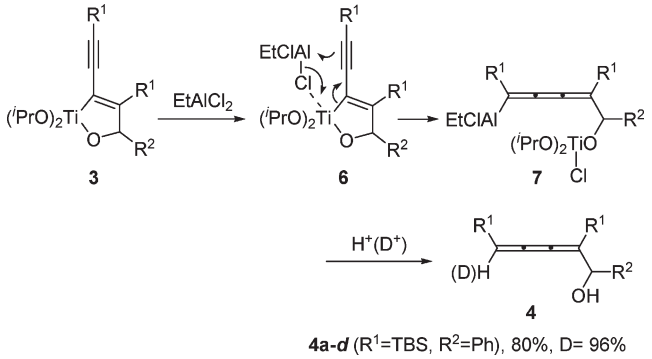


Figure 1

Scheme 1



4a-*d* (R^1=TBS, R^2=Ph), 80%, D= 96%

as benzophenone worked well to provide **5d** in 71% yield (entry 4). Interestingly, it was also found that a cyclopropyl ketone such as cyclopropyl(4-methoxyphenyl)methanone could react directly with titanacyclopropene without the use of any Lewis acids to produce a mixture of enynol and cumulenol after hydrolysis. For achieving cumulene formation in this case, the reaction was best performed by first reacting with ketone to form oxatitanacyclopentene followed by addition of $EtAlCl_2$ (entry 9). Again the substituent on butadiynes plays an important role for the reaction, bisphenyl-substituted butadiyne only afforded a low yield of cumulenol **5j** (entry 10). The structure of cumulene **5d** has been verified by X-ray crystallography.[11]

When unsymmetrical substituted butadiynes were employed, regioselective coupling and rearrangement reactions have been observed. For example, cumulenol **4j** or **5k** was obtained as a sole product in 50 and 68% yields, respectively, by the reaction with alkyl-, silyl- or phenyl-, silyl-substituted butadiyne (Figure 1).

A possible mechanism accounted for the $EtAlCl_2$ promoted transformation to cumulenols is given in Scheme 1. The crucial step is the transmetalation of alkynyl titanium **3** with $EtAlCl_2$,[13] which proceeds, presumably via an cyclic S_E2' process to produce the dimetalated derivative **7**, hydrolysis of **7** afforded cumulenol **4**. Moreover, in a deuteration experiment with benzaldehyde and **1a**, the deuterated compound **4a**-*d* was obtained in 80% yield with high deuterium incorporation (D = 96%). The stereoselectivity might be induced by coordination of the chlorine in $EtAlCl_2$ to the titanium center, which resulted in a cis addition of Al to the alkyne moiety via a cyclic transition state. For $BF_3 \cdot Et_2O$ mediated reaction, $BF_3 \cdot Et_2O$ may play a dual role for both of the activation of ketone toward nucleophilic attack and promote a propargylic/cumulenic-metal rearrangement,[14] however, the detailed process is still not clear yet.

In summary, we have developed an efficient and convenient method for the stereoselective synthesis of trisubstituted cis-[3]cumulenols from titanacycles mediated by Lewis-acids, which are not easily accessible by other methods. These cumulene derivatives are attractive substrates for further synthetic manipulations.

Experimental Section

A Typical Procedure for the $EtAlCl_2$-Mediated Formation of Trisubstituted cis-[3]Cumulenols from Oxatitanacycles. To a stirred solution of 1,4-bis(*tert*-butyldimethylsilyl)buta-1,3-diyne **1a** (0.5 mmol, 139 mg) and $Ti(O^iPr)_4$ (0.625 mmol, 0.19 mL) in THF (5 mL) was added *n*-BuLi (1.25 mmol, 0.78 mL, 1.6 M solution in hexane) dropwise at −78 °C under argon. The solution was warmed up to room temperature and stirred at the same temperature for 1 h. Benzaldehyde (0.5 mmol, 51 μL) was added and stirred for 10−15 min. Then $EtAlCl_2$ (0.56 mL, 0.9 M in hexane) was added to the mixture. After stirring for 2 h at room temperature, the reaction mixture was quenched at 0 °C with 3 N HCl for a short time (< 1 min) and extracted with EtOAc. The combined organic extracts were washed with saturated $NaHCO_3$ solution and brine, a small amount of Et_3N was added to avoid decomposition, and then dried over $MgSO_4$. The solvent was evaporated in vacuo in the temperature less than 30 °C, and the residue was purified by flash chromatography on silica gel to afford (*Z*)-[3]cumulenol **4a** in 84% yield. It was also recommended to store the products under argon atmosphere at low temperature.

(*Z*)-2,5-Bis-(*tert*-butyl-dimethylsilyl)-1-phenyl-penta-2,3,4-trien-1-ol (4a). Purification of the crude product by flash chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 30:1) afforded the title compound as a yellow oil in 84% yield. ^{1}H NMR (C_6D_6, Me_4Si, 300 MHz): δ 0.06 (s, 3H), 0.18−0.20 (m, 9H), 0.97 (s, 18H), 2.86 (bs, 1H), 5.47 (s, 1H), 6.15 (d, J = 0.6 Hz, 1H), 7.09−7.19 (m, 3H), 7.42 (d, J = 7.5 Hz, 2H). ^{13}C NMR (C_6D_6, Me_4Si, 75 MHz): δ −5.30, −5.28, −4.75, −4.72, 17.52, 18.56, 26.54, 27.07, 77.61, 114.49, 127.77, 127.78, 128.49, 136.97, 143.46, 174.40, 183.56. IR (neat) 3458, 2954, 2929, 2885, 2858, 1734, 1691, 1471, 1254, 838, 778, 699 cm^{-1}. HRMS (EI) for $C_{23}H_{38}OSi_2$ $[M]^+$: calcd, 386.2461; found, 386.2473.

A Typical Procedure for the $BF_3 \cdot Et_2O$-Mediated Formation of Trisubstituted cis-[3]Cumulenols by the Reaction with Ketones. To a stirred solution of 1,4-bis(tert-butyldimethylsilyl)buta-1,3-diyne **1a** (0.5 mmol, 139 mg) and $Ti(O^iPr)_4$ (0.625 mmol, 0.19 mL) in THF (5 mL) was added *n*-BuLi (1.25 mmol, 0.78 mL, 1.6 M solution in hexane) dropwise at −78 °C under argon. The solution was warmed up to room temperature and stirred at the same temperature for 1 h. $PhCOCH_3$ (0.5 mmol, 59 μL) and $BF_3 \cdot Et_2O$ (0.5 mmol, 64 μL) were added and stirred for 2−3 h. Then, the reaction mixture was quenched with 3 N HCl for a short time (< 1 min) and extracted with EtOAc. The combined organic extracts were washed with saturated $NaHCO_3$ solution and brine, a small amount of Et_3N was added to avoid decomposition, and then dried over $MgSO_4$. The solvent was evaporated in vacuo in the temperature less than 30 °C and the residue was purified by flash chromatography on silica gel to afforded the (*Z*)-[3]cumulenol **5a** in 59% yield. It was also recommended to store the products under argon atmosphere at low temperature.

(*Z*)-3,6-Bis-(*tert*-butyl-dimethylsilyl)-2-phenyl-hexa-3,4,5-trien-2-ol (5a). Purification of the crude product by flash chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 80:1) afforded the title compound as a yellow oil in 59% yield. ^{1}H NMR (C_6D_6, Me_4Si, 300 MHz): δ 0.10 (s, 3H), 0.20 (s, 3H), 0.21 (s, 3H), 0.23 (s, 3H), 0.97 (s, 9H), 1.05 (s, 9H), 1.67 (s, 3H), 6.24 (s, 1H), 7.04−7.18 (m, 3H), 7.57−7.59 (m, 2H). ^{13}C NMR (C_6D_6, Me_4Si, 75 MHz): δ −5.21, −5.14, −3.74, −2.98, 17.47, 18.69, 26.54, 27.72, 33.02, 79.53, 113.48, 125.63, 126.90, 128.26, 141.14, 147.69, 175.28, 183.81. IR (neat) 3507, 2954, 2929, 2884,

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(14) For $BF_3 \cdot Et_2O$ induced 1,3-isomerization of α-(alkoxy)allyl stannanes, see: Marshall, J. A.; Welmaker, G. S.; Gung, B. W. *J. Am. Chem. Soc.* **1991**, *113*, 647.

2857, 1683, 1577, 1471, 1252, 837, 824, 810, 779 cm^{-1}. HRMS (EI) for $C_{24}H_{40}OSi_2$ $[M]^+$: calcd, 400.2618; found, 400.2611.

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Supporting Information Available: Experimental details, NMR spectra of all new products, and CIF files giving crystallographic data of compounds **4e** and **5d**. This material is available free of charge via the Internet at http://pubs.acs.org.