

# Highly Regioselective Alkyne Cyclotrimerization Catalyzed by Titanium Complexes Supported by Proximally Bridged *p*-*tert*-Butylcalix[4]arene Ligands

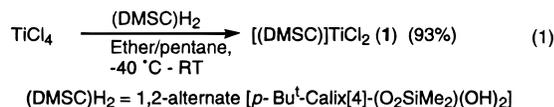
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Received March 8, 1999

Transition metal-catalyzed cycloaddition is involved in many of the most useful synthetic methods for assembling complex organic molecules.<sup>1</sup> Many transition metals catalyze the cyclotrimerization of alkynes to yield substituted benzenes.<sup>1,2</sup> However, the reaction rarely proceeds with high regioselectivity.<sup>1d</sup> Highly regiocontrolled synthesis of arenes is very attractive since arenes are important building blocks in organic synthesis. Our interest in the influence of ancillary ligands on organic transformations mediated by the group 4 metals led us to synthesize titanium complexes supported by a 1,2-alternate, dimethylsilyl-bridged *p*-*tert*-butylcalix[4]arene (DMSC) ligand. Whereas alkoxides have been effectively used as ancillary ligands in early transition metal organometallic chemistry,<sup>3</sup> the application of calixarenes as ancillary ligands in organotransition metal chemistry is relatively unexplored.<sup>4</sup> Herein, we describe highly regioselective, catalytic cyclotrimerization of terminal alkynes by DMSC-based titanium complexes.

The reaction of (DMSC)H<sub>2</sub><sup>5</sup> with TiCl<sub>4</sub> furnished [(DMSC)TiCl<sub>2</sub>] (**1**) in excellent yield, as an air- and moisture-sensitive orange solid<sup>6</sup> (eq 1). An X-ray crystallographic study of **1**



established that the calix[4]arene ligand exists in 1,2-alternate conformation and that a tetrahedral environment exists about the

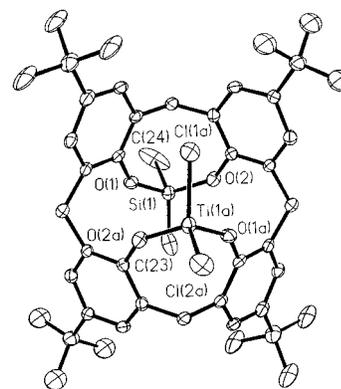


Figure 1. Molecular structure of **1**, showing the atom labeling scheme.

titanium center (Figure 1).<sup>7,8</sup> The calix[4]arene ligand clearly imposes different stereochemical environments at the two titanium-bound chlorides. That is, the steric environment around the endo chloride [Cl(1a), located inside the calix[4]arene cavity, above the centers of two aromatic rings] is more crowded than that around the exo chloride [Cl(2a)]. The solid-state structure of **1** is maintained in solution, as evidenced by the presence of two inequivalent SiMe<sub>2</sub> group methyls in both the <sup>1</sup>H and <sup>13</sup>C NMR spectra.<sup>6</sup> The endo Me is strongly shielded compared to the exo Me, most likely due to ring current effect.<sup>5,9</sup>

At 80 °C, in C<sub>6</sub>D<sub>6</sub>, and in the presence of excess sodium, **1** catalyzed the cyclotrimerization of terminal acetylenes (HC≡CR; R = Ph, *p*-C<sub>6</sub>H<sub>4</sub>Me, or SiMe<sub>3</sub>) to 1,2,4-trisubstituted benzenes with excellent regioselectivity (≥97%) and in excellent yield (Table 1, entries 1–3). <sup>1</sup>H and <sup>13</sup>C NMR and GC-MS analysis of the reaction mixtures showed that no acyclic oligomers were present. <sup>1</sup>H and <sup>13</sup>C NMR revealed induction periods of 20–40 min before any cyclotrimerization product could be detected. Presumably, the induction period is required to produce NaC≡CR (R = Ph, *p*-C<sub>6</sub>H<sub>4</sub>Me, or SiMe<sub>3</sub>) and to allow it to react with **1** to generate the corresponding bis(alkynyl)Ti(IV) species [(DMSC)Ti(C≡CR)<sub>2</sub>].<sup>10</sup> Reductive elimination<sup>11</sup> of RC≡C–C≡CR would give a putative Ti(II) intermediate which oxidatively couples two alkyne molecules to yield titanacyclopentadiene species (Scheme 1); metallacyclopentadiene intermediates have been implicated in alkyne cyclotrimerization reactions.<sup>2c,f,12–15</sup> The rate of formation of NaC≡CR evidently depends on the amount

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(4) See, for example: (a) Zanotti-Gerosa, A.; Solari, E.; Giannini, L.; Floriani, C.; Re, N.; Chiesi-Villa, A.; Rizzoli, C. *Inorg. Chim. Acta.* **1998**, *270*, 298. (b) Castellano, B.; Zanotti-Gerosa, A.; Solari, E.; Floriani, C. *Organometallics* **1996**, *15*, 4894. (c) Giannini, L.; Caselli, A.; Solari, E.; Floriani, C.; Chiesi-Villa, A.; Rizzoli, C.; Re, N.; Sgamellotti, A. *J. Am. Chem. Soc.* **1997**, *119*, 9709. (d) Olmstead, M. M.; Sigel, G.; Hope, H.; Xu, X.; Power, P. P. *J. Am. Chem. Soc.* **1985**, *107*, 8087.

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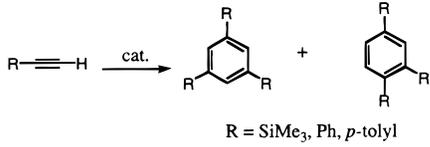
(6) Anal. Calcd for C<sub>46</sub>H<sub>58</sub>Cl<sub>2</sub>O<sub>4</sub>Si<sub>2</sub> (**1**): C, 67.23; H, 7.11; Cl, 8.63. Found: C, 67.39; H, 7.37; Cl, 8.73. <sup>1</sup>H NMR (C<sub>6</sub>D<sub>6</sub>) δ 7.17 (br, 4H, arom CH), 7.07 (d, *J* = 2 Hz, 2H, arom CH), 6.93 (d, 2H, arom CH), 4.50 (d, *J* = 14.3 Hz, 1H, calix-CH<sub>2</sub>), 4.46 (d, *J* = 14.3 Hz, 1H, calix-CH<sub>2</sub>), 3.89 (s, 4H, calix-CH<sub>2</sub>), 3.39 (d, *J* = 14.3 Hz, 1H, calix-CH<sub>2</sub>), 3.26 (d, *J* = 14.3 Hz, 1H, calix-CH<sub>2</sub>), 1.39 (s, 18H, *t*-Bu), 1.23 (s, 18H, *t*-Bu), 0.32 (s, 3H, exo-SiCH<sub>3</sub>), -1.46 (s, 3H, endo-SiCH<sub>3</sub>). Full characterization data are available as Supporting Information.

(7) Crystal data: space group, monoclinic C2/c; *Z* = 4, *a* = 20.750(1) Å, *b* = 17.0434(9) Å, *c* = 17.1877(9) Å, β = 124.79(1)°, *V* = 4991.9(4) Å<sup>3</sup>, *R*(*F* ≥ 4σ(*F*)) = 0.123, GOF = 1.19. Data for **1** were collected at 173 K on a Nonius Kappa CCD diffractometer. The calixarene moiety resides on an inversion center, although the moiety itself does not possess an inversion center. Thus, the structure was modeled with Si1 and Ti1 occupying the same position with 50% occupancies and equivalent thermal parameters. Two large peaks roughly 2.2 Å from Ti1 were labeled as Cl1 and Cl2 and given 50% occupancies, which subsequently led to the discovery of two smaller peaks roughly 1.8 Å from Si1, which were labeled C23 and C24, respectively. Full structural details are available as Supporting Information.

(8) Selected interatomic distances (Å): Ti1–Cl1 = 2.243(9), Ti1–Cl2 = 2.198(6), Ti1–O1 = 1.712(4), Ti1–O2 = 1.708(5). Selected bond angles (deg): Cl1–Ti1–Cl2 = 106.0(3), Cl1–Ti1–O1 = 110.4(3), Cl1–Ti1–O2 = 111.8(3), Cl2–Ti1–O1 = 110.7(2), Cl2–Ti1–O2 = 111.6(3), O1–Ti1–O2 = 106.4(2).

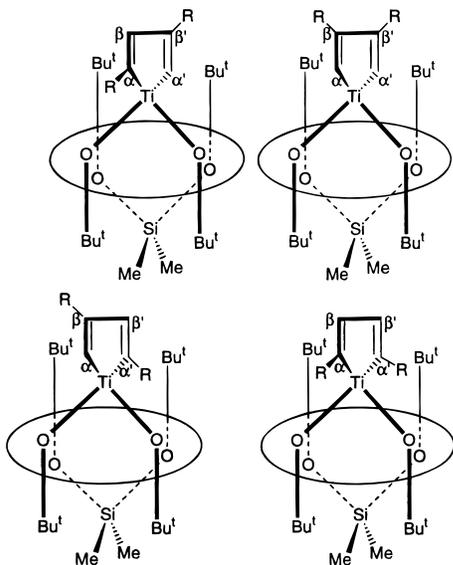
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(10) Under our reaction conditions, [(DMSC)TiCl<sub>2</sub>] (**1**) does not react with sodium metal even after 48 h.

**Table 1.** Alkyne Cyclotrimerization at 80 °C


entry no.	alkyne	yield (%) <sup>d</sup>		isolated yield <sup>e</sup> (%)
		1,2,4-isomer	1,3,5-isomer	
1	trimethylsilylacetylene <sup>a</sup>	98	2	98
2	<i>p</i> -tolylacetylene <sup>a</sup>	97	3	
3	phenylacetylene <sup>a</sup>	>97	<3 <sup>f</sup>	95
4	trimethylsilylacetylene <sup>b</sup>	98	2	
5	trimethylsilylacetylene <sup>c</sup>	95	5	

<sup>a</sup> Catalyzed by [(DMSC)TiCl<sub>2</sub>] (**1**) activated with excess Na in toluene or C<sub>6</sub>D<sub>6</sub>. <sup>b</sup> Catalyzed by [(DMSC)TiCl<sub>2</sub>] (**1**) activated with NaC≡CSiMe<sub>3</sub> in toluene or C<sub>6</sub>D<sub>6</sub>. <sup>c</sup> Catalyzed by [(DMSC)Ti(C≡CSiMe<sub>3</sub>)<sub>2</sub>(THF)] (**2a**) in C<sub>6</sub>D<sub>6</sub>. <sup>d</sup> Ratios determined from GC-MS and <sup>1</sup>H NMR data. <sup>e</sup> Minor isomer not isolated. <sup>f</sup> The yield of 1,3,5-substituted isomer was estimated based on the result obtained for *p*-tolylacetylene. <sup>13</sup>C NMR data confirmed the major product as 1,2,4-substituted isomer and GC-MS showed only one peak. <sup>1</sup>H NMR data could not be used to characterize the 1,3,5-substituted isomer, presumably because of extensive peak overlap.

**Scheme 1**

of Na and alkyne in the reaction mixture as well as on the acidity of the alkyne. It is generally faster for phenylacetylene than for trimethylsilylacetylene. Consistent with this proposal, the use of preformed NaC≡CR shortens the induction period to <2 min, while the regioselectivity is maintained (Table 1, entry 4). Moreover, 1,4-bis(trimethylsilyl)butadiyne was detected by <sup>1</sup>H NMR and GC-MS.<sup>16</sup> The presence of an excess NaC≡CR or Na does not interfere with the cyclotrimerization process. Typically, 5 μmol

of [(DMSC)TiCl<sub>2</sub>] (**1**), 1000 μmol of alkyne, and 50 μmol of Na (or NaC≡CR) were used to effect the cyclotrimerization in 0.5 mL of C<sub>6</sub>D<sub>6</sub>. The reaction proceeded to 98% conversion after 5 h at 80 °C for trimethylsilylacetylene, and after 30 min for phenylacetylene and *p*-tolylacetylene (excluding the induction period).

We reasoned that DMSC-based bis(alkynyl)titanium(IV) derivatives would function as single-component alkyne cyclotrimerization catalysts under our reaction conditions and therefore investigated their synthesis. Reaction between Mg(C≡SiMe<sub>3</sub>)<sub>2</sub> and **1** gave brown-colored [(DMSC)Ti(C≡CSiMe<sub>3</sub>)<sub>2</sub>(THF)] (**2a**) in 94% yield; it was not possible to cleanly isolate a product in the absence of THF. **2a** is stable only as a THF adduct and must be stored as a solid at low temperature (-20 °C). Therefore, **2a** was characterized only in solution by <sup>1</sup>H NMR data.<sup>17</sup> It is not very stable in solution at 25 °C (*t*<sub>1/2</sub> ≈ 24 h).<sup>18</sup> **2a** reacts quantitatively with 4,4'-dimethyl-2,2'-dipyridyl (dmbpy) to give more stable [(DMSC)Ti(C≡CSiMe<sub>3</sub>)<sub>2</sub>(dmbpy)] (**2b**), which could be fully characterized.<sup>19</sup> As expected, **2a** catalyzed cyclotrimerization of trimethylsilylacetylene at 80 °C with excellent regioselectivity without need for activation with Na (Table 1, entry 5).<sup>20</sup> Although **2b** produces 1,4-bis(trimethylsilyl)butadiyne quantitatively, it does not catalyze alkyne cyclotrimerization under our conditions presumably, because the resulting Ti(II) species is stabilized by the strongly stabilizing 4,4'-dimethyl-2,2'-dipyridyl ligand.<sup>21</sup>

The details of the alkyne cyclotrimerization mechanism are currently under investigation. Titanacyclopentadiene intermediates are probably involved in the reaction, in line with mechanisms proposed for related compounds.<sup>2e-h</sup> Four different intermediate disubstituted titanacyclopentadiene species are possible, each possessing different steric properties (Scheme 1). We are particularly interested in determining the influence of the stereochemical environment imposed at titanium by the 1,2-alternate, DMSC ligand on formation of titanacyclopentadiene complexes and their subsequent reactions with a third equivalent of alkyne to regioselectively produce arenes.

In summary, new catalysts for highly regioselective alkyne cyclotrimerization were developed from titanium compounds supported by 1,2-alternate, dimethylsilyl-bridged *p*-*tert*-butylcalix[4]arene. Further reactivity studies of these and related complexes are underway in our laboratory with emphasis on determining the scope of alkyne cyclotrimerizations and elucidating the reaction mechanism.

**Acknowledgment.** Thanks are expressed to the Kentucky National Science Foundation EPSCoR Program (Grant number EPS-9452895) for support of this work and to the Chemistry Department of the University of Kentucky for the award of fellowships to O.V.O. The authors also thank Professor Jack Selegue for helpful discussions.

**Supporting Information Available:** Preparation and chemical characterization data for **1**, **2a** and **2b**, experimental details for the cyclotrimerization reactions, a summary of crystallographic parameters, atomic coordinates and equivalent isotropic displacement parameters, bond lengths and angles, anisotropic displacement parameters, and hydrogen coordinates and isotropic displacement parameters for **1** (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>. JA990740B

(11) For examples of carbon-carbon bond formation between alkynyl groups in C<sub>2</sub>H<sub>3</sub>M(C≡CR)<sub>2</sub> (M = Ti, Zr, or V; R = H or Ph) to give dimetallic M<sub>2</sub> species with bridging diacetylide ligands, see: (a) Pulst, S.; Arndt, P.; Heller, B.; Baumann, W.; Kempe, R.; Rosenthal, U. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1112. (b) Pellny, P.-M.; Peulecke, N.; Burkalov, V. V.; Tillack, A.; Baumann, W.; Spannenberg, A.; Kempe, R.; Rosenthal, U. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2615. (c) Stucky, G. D.; Sekutowski, D. G. *J. Am. Chem. Soc.* **1976**, *98*, 1376.

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(16) Identified by GC-MS and comparison of <sup>1</sup>H NMR data with that of an authentic sample.

(17) (**2a**): <sup>1</sup>H NMR (C<sub>6</sub>D<sub>6</sub>) δ 7.13–7.20 (m, 6H, arom CH), 7.03 (d, 2H, arom CH), 5.49 (d, *J* = 14 Hz, 1H, calix-CH<sub>2</sub>), 4.39 (d, *J* = 14 Hz, 1H, calix-CH<sub>2</sub>), 4.30 (d, *J* = 16 Hz, 2H, calix-CH<sub>2</sub>), 4.0–4.1 (br, 4H, THF), 3.91 (d, *J* = 16 Hz, 2H, calix-CH<sub>2</sub>), 3.49 (br d, *J* = 14 Hz, 2H, calix-CH<sub>2</sub>), 1.55 (br, 4H, THF), 1.43 (s, 18H, *t*-Bu), 1.25 (s, 18H, *t*-Bu), 0.10 (s, 18H, SiMe<sub>3</sub>), 0.04 (s, 3H, exo-SiMe), -1.48 (s, 3H, endo-SiMe). In addition, protonolysis of **2a** with MeOH produced trimethylsilylacetylene in near-quantitative yield.

(18) Decomposition of **2a** yields a complex mixture of products. Nonetheless, 1,4-bis(trimethylsilyl)butadiyne could be readily identified.

(19) Anal. Calcd for C<sub>68</sub>H<sub>88</sub>N<sub>2</sub>O<sub>4</sub>Si<sub>2</sub>Ti (**2b**): C, 72.30; H, 7.85; N, 2.48. Found: C, 72.04; H, 8.21; N, 2.42. Full characterization data are available as Supporting Information.

(20) The slight decrease in regioselectivity is due presumably to a change in the stereochemical environment about titanium (from tetrahedral geometry) as a result of the coordination of a THF molecule.

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