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Highly regioselective [2+2+2] cycloaddition of terminal alkynes catalyzed by titanium complexes of *p-tert*-butylthiacalix[4]arene

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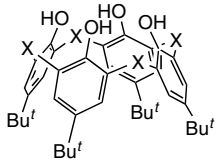
Abstract—Mono- and dinuclear titanium complexes of *p-tert*-butylthiacalix[4]arene were applied as a catalyst for [2+2+2] cycloaddition of terminal alkynes. They showed high catalytic activity and regioselectivity toward 1,3,5-trisubstituted benzenes over 1,2,4-trisubstituted isomers. The regioselectivity was rationalized in terms of the steric effect of the thiacalixarene skeleton and the coordination of the bridging sulfur atom to the titanium center.

Soon after the discovery of a practical synthesis of *p-tert*-butylthiacalix[4]arene (**1**), in which the four methylene bridges of conventional *p-tert*-butylcalix[4]arene (**2**) are replaced by epithio linkages, many researchers have embarked on the study of this new host compound. With the progress of research, it has become clear that the thiacalixarene and its derivatives are not a simple substitute for the conventional calixarenes but that they should be recognized as quite unique host molecules of vast possibilities to be developed.[1] One of the most noteworthy features of thiacalixarenes is their coordination ability toward metal ions without the need to modify the upper and/or lower rim, as is the case for the conventional calixarenes. This is attributed to the coordination of the sulfur to a metal center in cooperation with the phenoxy oxygens, as revealed by solvent extraction studies and X-ray crystallographic analyses.[2] Furthermore, thiacalixarenes can form not only mono- but also polynuclear metal complexes by virtue of the heterogeneous coordination sites.[3] Therefore, our attention has been focused on designing polynuclear metal complexes of the thiacalixarenes, which may be useful for metal catalysts. As the first successful example of our efforts in this line, we have recently reported that *syn*-(**3**) and *anti*-dinuclear titanium(IV) complexes (**4**) can be readily prepared by simply mixing thiacalixarene **1** with $TiCl_4$ in dichloromethane and *syn*-complex **4** showed high catalytic activity in the Mukaiyama-aldol reaction, indicating the double-activation ability of complex **4** as a bidentate Lewis acid toward aldehydes.[4]



1: X = S
2: X = CH_2

On the other hand, highly regiocontrolled cyclotrimerization of alkynes is an attractive method for the preparation of multi-substituted benzenes.[5,6] Recently, Ladipo and co-workers reported that the titanium complex of a methylene-bridged calix[4]arene (**5**) catalyzed the cyclotrimerization of terminal alkynes to give 1,2,4-trisubstituted benzenes selectively.[7] Herein, we report that titanium complexes of thiacalix[4]arenes show the opposite regioselectivity, giving 1,3,5-trisubstituted benzenes in good to excellent yield.

Keywords: Calixarene; Titanium complex; Alkyne cyclotrimerization.
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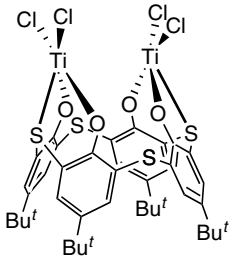

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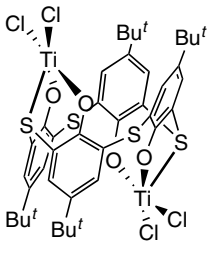

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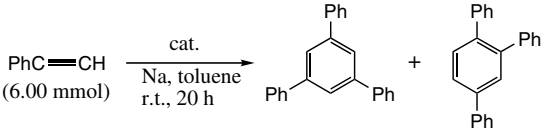
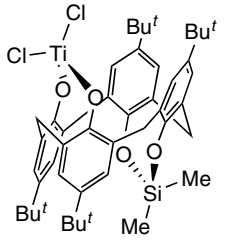
The cyclotrimerization of ethynylbenzene was carried out in toluene at room temperature with 0.25 mol % catalyst loading (15.0 μmol) in the presence of finely cut sodium metal (0.2 mmol) to activate the catalyst.[8] *syn*-Dinuclear titanium complex **3** gave a mixture of 1,3,5- and 1,2,4-triphenylbenzene in the ratio of 77:23 in good yield (65%) (Table 1, entry 1). Both the regioselectivity and the product yield were significantly improved by changing the catalyst from *syn*-complex **3** to *anti*-complex **4** (entry 2). It has been reported that titanium complex **5**, bearing a calix[4]arene ligand of 1,2-alternate conformation, catalyzed the cyclotrimerization of ethynylbenzene to give the 1,3,5- and 1,2,4-regioisomers in the ratio of 1:99.[7] Therefore, it is interesting to note that complexes **4** and **5**, both having a calixarene skeleton of the same conformation, showed opposite regioselectivities to each other. In order to gain insight into the origin of the regioselectivity, performance of bisphenol-type ligands **6**–**9** was examined. The titanium complex was generated in situ by the treatment of $TiCl_4$ with a ligand in toluene for 30 min before the addition of ethynylbenzene and sodium metal (entries 3–8). The complex of *O*,*O*′-disiloxane-1,3-diyl-bridged thiacalixarene **6**[9] showed high 1,3,5-selectivity (entry 3), which was comparable to that achieved with *anti*-complex **4**. On the other hand, its methylene-bridged analog **7**[9] showed high 1,2,4-selectivity (entries 4 and 5), although the reaction was sluggish and required higher temperature to be completed. These observations indicate that the bridging sulfur atoms strongly affect the regioselectivity, as well as the catalytic activity. However, it should be noted that both the sulfur-bridged bisphenol **8** and its methylene-bridged analog **9** showed similar 1,2,4-selectivity to that obtained with $TiCl_4$ (entries 6–9). Therefore, it may be concluded that the steric environment imposed by the thiacalixarene skeleton is also important for the 1,3,5-selectivity.

Table 1. Cyclotrimerization of ethynylbenzene catalyzed by titanium complexes



Entry	Cat. (μmol)	Yield (%)[a]	1,3,5-isomer: 1,2,4-isomer[b]
1	**3** (15.0)	65	77:23
2	**4** (15.0)	95	85:15
3	**6** (100)–$TiCl_4$ (90.0)	93	83:17
4	**7** (100)–$TiCl_4$ (90.0)	12	6:94
5[c]	**7** (100)–$TiCl_4$ (90.0)	94	1:99
6	**8** (100)–$TiCl_4$ (90.0)	95	32:68
7	**9** (100)–$TiCl_4$ (90.0)	85	33:67
8[c]	**9** (100)–$TiCl_4$ (90.0)	94	35:65
9	$TiCl_4$ (90.0)	<44	37:63

[a] Isolated yield.
[b] Determined by ^1H NMR analysis.
[c] The reaction was carried out at 80 °C for 1 h.



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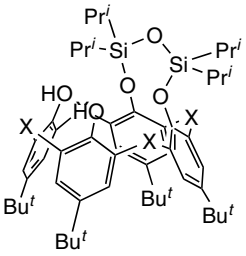
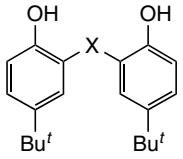


6: X = S
7: X = CH_2

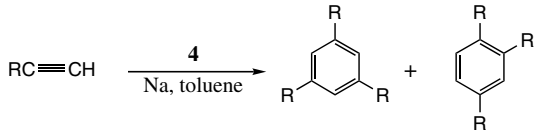


8: X = S
9: X = CH_2

The cyclotrimerization of other terminal alkynes was examined by using *anti*-complex **4** as a catalyst (Table 2). Reaction of 4-ethynyltoluene proceeded smoothly to give the 1,3,5-trisubstituted benzene in excellent yield with high regioselectivity (entry 1). On the other hand, 1-ethynyl-4-(trifluoromethyl)benzene, as well as aliphatic alkynes, did not give the desired compounds even at elevated temperature (entries 2–5). We reasoned that a titanacyclopentadiene intermediate[10] (vide infra) (Fig. 1) would not be formed from dichloride **4** with these alkynes and therefore tried pretreating the dichloride with sodium phenylacetylide before addition of the alkynes (entries 6–12).[11] By using this method, 1-ethynyl-4-(trifluoromethyl)benzene gave the trisubstituted benzenes with almost complete 1,3,5-selectively, though in poor yield (entry 6). Elongation of the reaction time did not improve the product yield, leaving a large portion of the substrate intact, which may be attributed to the deactivation of the catalyst during the course of the reaction. On the other hand, aliphatic alkynes gave the corresponding 1,3,5-trisubstituted benzenes in good yield with varying regioselectivity (entries 7–9). The reaction of ethynyltrimethylsilane was sluggish even at 50 °C to give the 1,3,5-trisubstituted benzene in poor yield, while more bulky 3,3-dimethyl-1-butyne did not give the desired compounds under the conditions (entries 10 and 11).

The alkyne cyclotrimerization with titanium complex **5** is believed to involve a titanacyclopentadiene intermediate, which undergoes a Diels–Alder-type reaction with an alkyne molecule to give a 7-titana-2,5-norbornadiene

Table 2. Cyclotrimerization of alkynes catalyzed by complex **4**



Entry	Alkyne	Temp. (°C)	Time (h)	Yield (%)[a]	1,3,5-isomer:1,2,4-isomer[b]
1	4-$MeC_6H_4C{\equiv}CH$	23	3.5	95	95:5
2	4-$CF_3C_6H_4C{\equiv}CH$	23	15	0	—
3	4-$CF_3C_6H_4C{\equiv}CH$	80	15	0	—
4	$BuC{\equiv}CH$	23	15	0	—
5	$BuC{\equiv}CH$	80	15	0	—
6[c]	4-$CF_3C_6H_4C{\equiv}CH$	23	3.5	30	~100:0
7[c]	$PrC{\equiv}CH$	23	15	73	75:25
8[c]	$BuC{\equiv}CH$	23	15	73	78:22
9[c]	$OctC{\equiv}CH$	23	15	71	95:5
10[c]	$Me_3SiC{\equiv}CH$	50	15	14	100:0
11[c]	$Bu^tC{\equiv}CH$	50	15	0	—
12[c]	$PhC{\equiv}CMe$	23	20	0	—

[a] Isolated yield.
[b] Determined by ^1H NMR analysis.
[c] Sodium phenylacetylide was added.

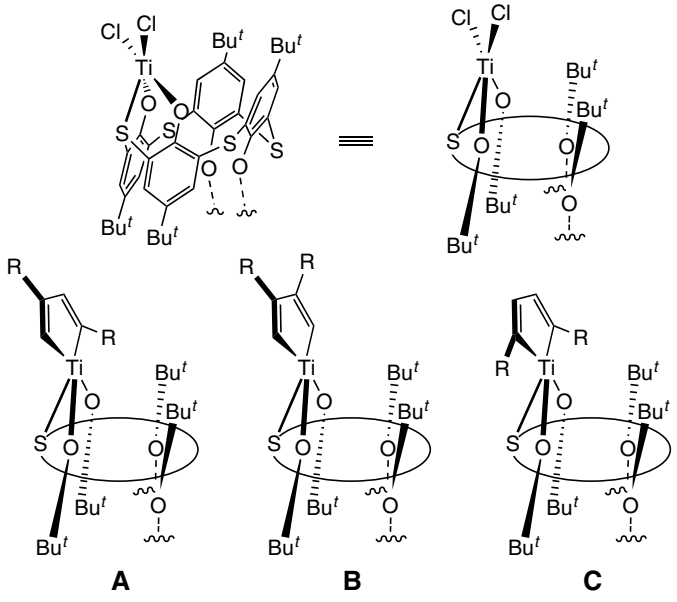
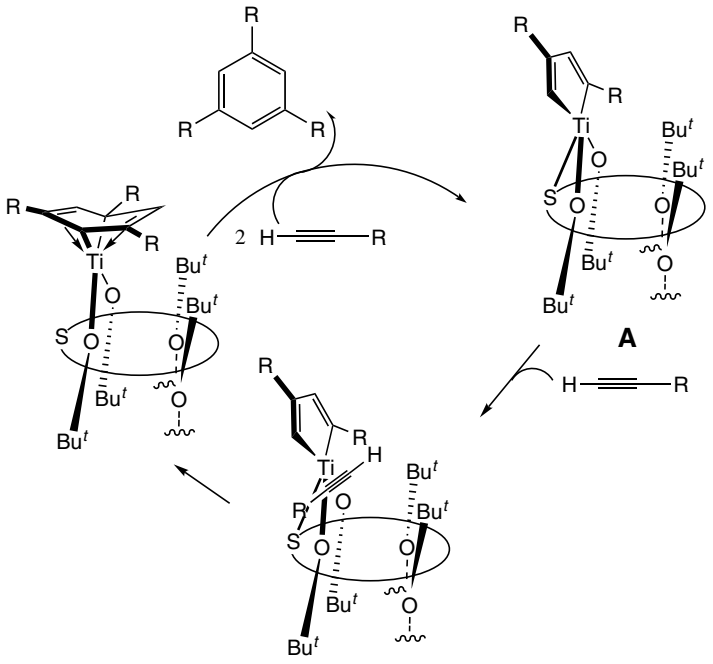


Figure 1. Schematic representation of possible regioisomers of the titanacyclopentadiene intermediate.

complex.[7b] Reductive elimination of the 1,4-cyclohexadiene-3,6-diyl ligand gives the cyclotrimerization product. The stereochemical course of the reaction in this study can be rationalized by the preferential formation of a thermodynamically stable titanacyclopentadiene and the sterically favored approach of the third alkyne molecule to the intermediate: Figure 1 shows possible regioisomers of the titanacyclopentadiene **A**–**C**, having different steric environments from each other. It seems that both complexes **B** and **C** are less stable than complex **A** because of the steric repulsion between the two substituents on the 1,3-butadiene-1,4-diyl ligand (**B**) and that between each of the substituents and the calixarene ligand (**C**), respectively. Therefore, the thermodynamically most stable complex **A** will selectively form and mediate the reaction. This may be supported by the fact that 1,3,5-trisubstituted benzenes are major products, because complexes **B** and **C** should exclusively afford 1,2,4-trisubstituted benzenes, regardless of the manner in which the complexes react with the alkyne molecule. The titanacyclopentadiene ring in complex **A** is oriented toward the calixarene ring, owing to the coordination of a bridging sulfur atom to the titanium center, and forms a cavity passing through the calixarene ring in cooperation with the two benzene rings of the thiacalixarene moiety. The third alkyne molecule will approach the metalacycle from the same side to the cavity in such ways that the alkynyl group is almost parallel to the calixarene ring and that the substituent resides apart from the 1-substituent on the 1,3-butadiene-1,4-diyl ligand to avoid steric repulsion (Scheme 1). The resulting 1,3,5-trisubstituted 7-titana-2,5-norbornadiene complex should



Scheme 1.

selectively afford the 1,3,5-trisubstituted benzene. On the other hand, the titanacyclopentadiene intermediate generated from complex **5** reportedly has a tetrahedral titanium center, to which a 1,3-disubstituted 1,3-butadiene-1,4-diyl ligand is coordinated, directing the 1-substituent outside the calixarene ring to avoid steric repulsion.[7] The third alkyne molecule approaches the metalacycle with the substituent pointing outside the calixarene ring to give a 1,2,4-trisubstituted 7-titana-2,5-norbornadiene complex, which explains the 1,2,4-selectivity. Therefore, it may be concluded that the coordination of the sulfur atom strongly affects the steric environment around the titanium center in the titanacyclopentadiene intermediate, leading to the observed high 1,3,5-selectivity.

In conclusion, we have shown here that the titanium complexes of *p-tert*-butylthiacalix[4]arene can be used as an efficient catalyst for the cyclotrimerization of terminal alkynes to afford 1,3,5-trisubstituted benzenes regioselectively. One of the most important factors to determine the regioselectivity was assumed to be the coordination of the bridging sulfur to the titanium center.

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8. Typical procedure for the cyclotrimerization of alkynes (Table 1, entry 2): To a suspension of *anti*-complex **4** (14.3 mg, 15.0 μmol) in toluene (4.0 ml) were added finely cut sodium (5.0 mg, 0.2 mmol) and ethynylbenzene (613 mg, 6.00 mmol) and the mixture was stirred at room temperature for 20 h. The mixture was quenched by successive addition of methanol (2.0 ml) and 2 M HCl

(2.0 ml) and extracted with chloroform. The extract was dried over $MgSO_4$ and evaporated to leave a residue, which was chromatographed on silica gel with hexane to give a mixture of 1,2,4- and 1,3,5-triphenylbenzene (582 mg, 95%). The ratio of the 1,2,4- and 1,3,5-isomers was determined to be 15:85 by ^1H NMR analysis ($CDCl_3$, 500 MHz).

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11. Typical procedure for the cyclotrimerization of alkynes by using a catalyst pretreated with sodium phenylacetylide (Table 2, entry 7): sodium phenylacetylide was prepared by treatment of ethynylbenzene (61.3 mg, 0.60 mmol) with a large excess of finely cut sodium (100 mg, 4.35 mmol) in toluene (4.0 ml) for 1 h. To the mixture was added *anti*-complex **4** (47.7 mg, 50.0 μmol) and the resulting mixture was stirred for 2 h before addition of 1-pentyne (2.72 g, 40.0 mmol). After stirring for 15 h, the mixture was worked up and purified as before to give a mixture of 1,2,4- and 1,3,5-tripropylbenzene (1.99 g, 73%) in the ratio of 25:75.