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## Calix[n]arene/Ti(IV) complexes as active catalysts in aldol reaction of Chan's diene

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Abstract—The aldol condensation of Chan's diene with benzaldehyde is catalyzed by only 8% mol of the calix[n]arene/Ti(O-i-Pr)\_4 complexes. Studies have revealed that the size of calixarene molecule and the number of hydroxyl groups affected the efficiency of the reaction. The reaction conditions (solvent and temperature) have been examined. © 2003 Elsevier Ltd. All rights reserved.

The aldol condensation of Chan's diene 1,<sup>1</sup> the dianion equivalent of methyl acetoacetate, has emerged as a powerful preparative reaction because it allows the formation of a polyfunctional C-5 fragment 3 usable in the total synthesis of complex molecules<sup>2-5</sup> (Scheme 1).

It is reported that 1 reacts with stoichiometric or catalytic amount of Lewis acids<sup>6</sup> to give the adduct 3 in good yield. Excellent progress in the development of enantioselective reaction variants has been made. The most notable achievements concern the addition of Chan's diene to aldehydes through catalysis by chiral Lewis acids.<sup>7,8</sup> We have recently described a highly enantioselective aldol reaction of 1 promoted by catalytic amounts (2–8% mol) of chiral (R)- or (S)-BINOL/ Ti(IV) complexes.<sup>9,10</sup>

In the course of our investigation devoted to efficient approaches to compounds of type 3, we have investigated the possibility to use calix[n] arene-based Ti(IV) complexes in the catalytic aldol reaction of Chan's diene.

The ready availability of calixarenes,<sup>11</sup> in conjunction to the fine control of their molecular dimensions (by changing the value of n), and to the easy introduction

of various functional groups, make them very attractive ligands for incorporating transition-metals ions.

Metallo-calixarene complexes have been reported by several authors, including Atwood,<sup>12</sup> Pedersen,<sup>13</sup> and Harrowfield.<sup>14</sup> Recently, Floriani<sup>15</sup> has reported the synthesis of calix[4]arene/Ti(IV) complexes having very satisfactory catalytic properties in the epoxidation of allylic alcohols.16

More recently, Miyano et al.<sup>17</sup> have reported that a dinuclear titanium(IV) complex of *p-tert*-butylthiacalix[4]arene showed high catalytic activity in the Mukaiyama aldol reaction of aldehydes with sylyl enol ethers, while Casolari et al.<sup>18</sup> described a very high activation of the zirconium-BINOL catalyst by *p-tert*-



## Scheme 1.

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butylcalix[4]arene in the enantioselective allylation of aldehydes.

Herein, we report the first and efficient synthesis of aldol **3a** using catalytic amount (8% mol) of calix[n]arene/Ti(IV) complexes (Scheme 2).

We examined the aldol reaction between the silyloxy diene 1 and benzaldehyde 2a, as a representative aldehyde, (Scheme 2) in the presence of a calix[*n*]arene/Ti(IV) complex formed in situ by treating the appropriate calixarene (Fig. 1) with Ti(O-*i*-Pr)<sub>4</sub>. The reaction was conducted under the conditions [molecular sieves (m.s.), THF,  $-78^{\circ}$ C (2h), rt (16 h)] recently reported for a Ti(IV)/BINOL catalytic system.<sup>10</sup> The silylated aldol produced was directly deprotected using Carreira's procedure<sup>19</sup> to give aldol **3a**.

The experimental results are summarized in Table 1. Interestingly, a high catalytic activity (77% yield) was observed using *p-tert*-butylcalix[4]arene (6)<sup>20</sup> as ligand (entry 1). This activity was even higher (96% yield) using the larger homologue *p-tert*-butylcalix[6]arene (7)<sup>21</sup> (entry 2), but decreased when the macrocycle size was increased to the octameric *p-tert*-butylcalix[8]arene (8)<sup>22</sup> (entry 3). It is worthy to note that in all these instances the catalytic activity of calixarene/Ti(IV) complexes was clearly superior to that of Ti(O-*i*-Pr)<sub>4</sub>, which yielded only 4% of aldol adduct (entry 4). These data indicate that the complexes act as Lewis acid, enhancing the reactivity of the aldehyde toward the Chan's diene.

In order to gain further insight into the calixarene structural features necessary to give an appreciable catalytic activity, we extended the above conditions to other variously substituted calixarenes. In particular, *tert*-butyl depleted calix[4]arene  $6a^{23}$  led to a significant enhancement of activity (95% yield, entry 5) with respect to the parent butylated counterpart (77%, entry 1). Probably this improvement could be ascribed to an increased solubility of calixarene ligand observed under the experimental conditions.

Table 1. Aldol reaction of 2a with 1 to produce 3a via Scheme 2 [conditions: molecular sieves (m.s.), THF,  $-78^{\circ}$ C (2 h)+rt (16 h)]

Entry	Calix[n]arene	Yield% <sup>a</sup>
1	6	77
2	7	96
3	8	56
4	Ti(O- <i>i</i> -Pr) <sub>4</sub>	4
5	6a	95
5	6b	10
7	6c	17
3	6d	_
)	6e	69
10	8a	44
1	8b	58 <sup>b</sup>

<sup>a</sup> Yields were obtained by <sup>1</sup>H NMR analysis.

<sup>b</sup> Toluene was used as solvent.



Scheme 2.







The number of OH groups also plays a major role with respect to catalytic activity. In fact, tripropoxy-p-tertbutylcalix[4]arene **6b**,<sup>24</sup> blocked in the cone conformation and possessing only a single free phenolic OH, showed only a modest activity (10%, entry 6). Only a slight improvement (17 and 12%, entries 7 and 8) was observed with two distally- or proximally-positioned OH groups, respectively, by using 1,3-dimethoxy-*p*-tert-butylcalix[4]arene  $6c^{25}$  or 1,2-dimethoxy-*p*-tert-butylcalix[4]arene  $6d^{26}$  However, a significant burst in activity was observed with monomethoxy-p-tert-butylcalix[4]arene 6e,<sup>27</sup> containing three contiguous OH groups, which showed an activity (69%, entry 9) approaching that of the parent unsubstituted calix[4]arene 6 (77%, entry 1). These results suggest that three contiguous phenolic OH groups, very likely, are a minimal requirement in order to strongly tricoordinate Ti(IV) cation. This conclusion seems to be confirmed by the finding that calix[8]arenes 8a<sup>28</sup> and 8b,<sup>29</sup> distallybridged with tetramethylene and crown-3 moieties, respectively, showed a catalytic activity (44 and 58%, respectively, entries 10 and 11) similar to that of the parent calix[8]arene 8 (56%, entry 3), probably only limited by solubility factor. In the attempt to improve the results, we also investigated the influence of reaction conditions (Table 2). By using the conditions recently reported for Ti(IV)/BINOL,<sup>10</sup> the aldol adduct was obtained in 77% yield using 8% mol of the p-tertbutylcalix[4]arene/Ti(IV) complex (entry 1). Since calix[4]arene 6 has a low solubility in THF, we used toluene as reaction medium, but the aldol adduct was obtained only in 36% yield (entry 2).

The temperature strongly influences the outcome of aldol reaction. In fact, when the reaction was analyzed after the 2 h stirring period at  $-78^{\circ}$ C, no **3a** could be detected (entry 3). Instead, omission of the low-temperature step and carrying out the reaction for 16 h at room temperature (entry 4) led to a good yield (65%).

The 2 h step at  $-78^{\circ}$ C followed by a 30 min period at room temperature (entry 5) led to a very similar yield (63%). These results clearly shown that the reaction should be performed for 2 h at  $-78^{\circ}$ C and 16 h at room temperature (our protocol for the same reaction catalyzed by BINOL/Ti(IV) complex).

It is probable that 2 h at  $-78^{\circ}$ C are necessary to generate more efficient catalytic species and that the aldol reaction continues at room temperature.

Table 2. Aldol reaction of 2a with 1 to produce 3a catalyzed by Ti(IV)/*p*-*tert*-butylcalix[4]arene (6) in the presence of molecular sieves

Entry	Solvent	Temperature/time	Yield (%) <sup>a</sup>
1	THF	-78°C (2 h)+rt (16 h)	77
2	Toluene	-78°C (2 h)+rt (16 h)	36
3	THF	-78°C (2 h)	_
4	THF	rt (16 h)	65
5	THF	-78°C (2 h)+rt (0.5 h)	63

<sup>a</sup> Yields were obtained by <sup>1</sup>H NMR analysis.

In conclusion, the collected data show that the calixarene/Ti(IV) complexes can be used as efficient catalyst in aldol reaction of Chan's diene. In addition the procedure is simple and no particular drying is required for calixarene ligands. Future work in our laboratory will be addressed to extend this procedure to different aldehydes and to examine asymmetric or dissymmetric calix[n]arenes in order to produce chiral aldol adducts.

A typical experimental procedure is described for the aldol reaction of 1 with benzaldehyde using the *p*-tertbutylcalix[4]arene/Ti(IV) complex. A mixture of Ti(O-i- $Pr_{4}$  (0.08 mmol), *p-tert*-butylcalix[4]arene 6 (0.08 mmol), and molecular sieves (340 mg) in THF (5 mL) was stirred at rt for 1 h. The mixture was cooled to -78°C and then benzaldehyde (1 mmol) was added dropwise. After 30 min, silyloxydiene 1 (2 mmol) was added in a similar way. The resulting solution was stirred under an N<sub>2</sub> atmosphere at -78°C for 2 h. After warming at rt the mixture was stirred overnight (16 h). The mixture was cooled to -78°C and TFA (0.4 mL) was added. Then the solution was warmed to rt and stirred for 1 h after which desilylation was complete. The reaction mixture was diluted with ether and a saturated aqueous solution of NaHCO<sub>3</sub> (2 mL) was added dropwise. The mixture was stirred until the evolution of gas ceased (30 min), then the organic layer was separated, washed with brine, dried over MgSO<sub>4</sub>, and concentrated in vacuo to afford a yellow oil containing **3a** with traces of reagents.

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