

*Proximal* functionalization at the lower rim of calix[4]arenes is unprecedented in the literature. Several authors<sup>3,14-16</sup> have observed regioselective *distal* alkylation by using a variety of electrophiles, such as diazomethane, methyl tosylate, allyl bromide, benzyl bromide,  $\alpha$ -bromoacetates,  $\alpha$ -halo ketones, and chloroacetonitrile. Steric factors and stabilizing hydrogen bond effects of the de-

protonated monoalkylated species have been proposed to play an important role in determining the regioisomeric outcome.<sup>16</sup> In our case, the reversed regioselectivity may be ascribed to the tendency of the pyridine pendant group in the monoalkylated intermediate to establish favorable hydrogen bonding with the nearest hydroxy group, which results in a remarkable enhancement of its acidity and reactivity. The above effects are also believed to exert an important role in keeping and stabilizing calix[4]arenes 3-6 in the cone conformation.

The synthetic approach leading to *proximal* disubstituted calix[4]arenes in the cone conformation opens up new perspectives for the construction of calix[4]arenes with mixed ligating groups, for the synthesis of chiral trisubstituted calix[4]arenes, and for the selective *proximal* difunctionalization at the "upper rim".

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**Supplementary Material Available:** Experimental procedures and characterization data for 2a-c, 4, 5a, and 6a,b (4 pages). Ordering information is given on any current masthead page.

(13) 3b: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 250 MHz)  $\delta$  3.28 and 4.41 (AB q,  $J$  = 13.0 Hz, ArCH<sub>2</sub>Ar, 4 H), 3.37 and 4.36 (AB q,  $J$  = 13.7 Hz, ArCH<sub>2</sub>Ar, 2 H), 3.48 and 4.65 (AB q,  $J$  = 12.7 Hz, ArCH<sub>2</sub>Ar, 2 H), 4.88 and 5.34 (AB q,  $J$  = 13.0 Hz, OCH<sub>2</sub>Py, 4 H), 6.58 (t,  $J$  = 7.5 Hz, ArH, 2 H), 6.78 (t,  $J$  = 7.5 Hz, ArH, 2 H), 6.9-7.0 (m, ArH, 6 H), 7.05 (dd,  $J$  = 7.5, 1.6 Hz, ArH, 2 H), 7.14 (ddd,  $J$  = 7.3, 4.9, 1.1 Hz, 5-PyH, 2 H), 7.46 (ddd,  $J$  = 7.7, 7.3, 1.7 Hz, 4-PyH, 2 H), 7.56 (d,  $J$  = 7.8 Hz, 3-PyH, 2 H), 8.58 (d,  $J$  = 4.9 Hz, 6-PyH, 2 H), and 9.72 (b s, OH, 2 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 250 MHz)  $\delta$  30.92, 31.78, 31.90, 77.84, 120.00, 122.17, 122.80, 124.69, 128.18, 128.32, 128.66, 128.76, 128.87, 129.16, 134.46, 134.51, 136.95, 148.78, 151.47, 154.31, and 157.20.

(14) Ungaro, R.; Pochini, A.; Andreotti, G. D. *J. Incl. Phenom.* 1984, 2, 199.

(15) Collins, E. M.; McKervey, M. A.; Harris, S. J. *J. Chem. Soc., Perkin Trans. 1* 1989, 372.

(16) van Loon, J.-D.; Arduini, A.; Verboom, W.; Ungaro, R.; van Hummel, G. J.; Harkema, S.; Reinhoudt, D. N. *Tetrahedron Lett.* 1989, 30, 2681.

## Dramatic Changes in Diastereoselectivity with the Quantity of Titanium Tetrachloride Used in Lewis Acid Mediated Reactions of Allylsilane with $\alpha$ -Amino Aldehydes<sup>1</sup>

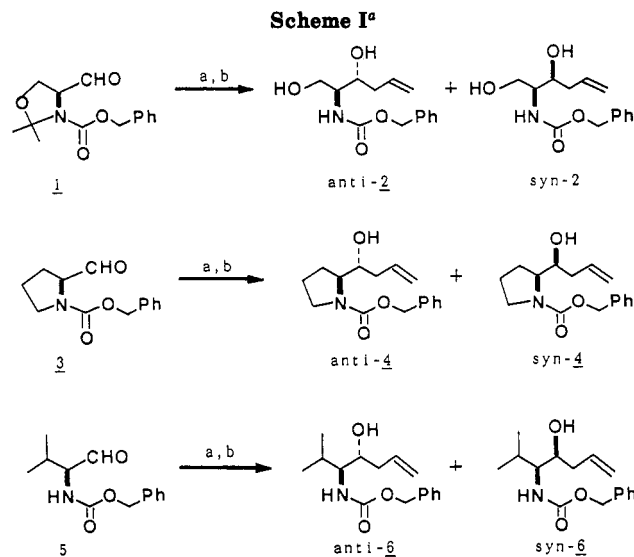
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**Summary:** Dramatic changes in diastereoselectivity, depending upon the quantity of titanium tetrachloride used in the Lewis acid mediated reactions of allylsilane with chiral  $\alpha$ -N-(carbobenzyloxy)amino aldehydes (1, 3, and 5), have been observed. These results are discussed, and the possibility that a 2:1 complex of aldehyde and TiCl<sub>4</sub> is being generated and its role are proposed.

**Sir:** Over the past 10 years, the Lewis acid mediated reactions of silyl nucleophiles with aldehydes and several other electrophiles have attracted the interest of synthetic organic chemists, especially from the standpoint of stereoselectivity.<sup>2</sup> While the development of this methodology has been impressive, a variety of reaction conditions have been adopted in order to make the reaction more selective. It has become customary for synthetic organic chemists to weigh a slightly excessive amount of TiCl<sub>4</sub> and transfer it into the reaction flask via a syringe in lab-scale (millimole) experiments, but the molar ratios of TiCl<sub>4</sub> to aldehyde are not necessarily accurate in this procedure. Furthermore, it has not been possible to determine the minimum quantity of TiCl<sub>4</sub> required in order



to provide satisfactory yields in the so-called stoichiometric TiCl<sub>4</sub>-mediated reactions of allylsilane with aldehyde.<sup>3</sup>

We disclose herein that the quantity of Lewis acid (TiCl<sub>4</sub>) added significantly affects the stereoselectivity in the Lewis acid mediated reactions<sup>4</sup> with three structurally

(3) Kiyooka, S.; Nakano, M., unpublished results. The TiCl<sub>4</sub>-mediated reaction of allylsilane with 2-phenylpropanal gave the product in ca. 80% yield by using 0.5 molar equiv of TiCl<sub>4</sub>, but the reaction with less than 0.4 molar equiv of TiCl<sub>4</sub> failed.

(1) Presented in part at the 58th Annual Meeting of the Chemical Society of Japan, Kyoto, April 1-4, 1989 (Abstracts of Papers, p 1624).

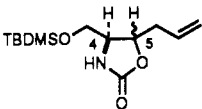
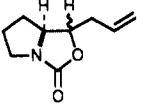
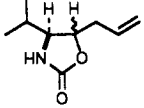
(2) Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* 1976, 1295. Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* 1982, 21, 555. Weidmann, B.; Seebach, D. *Ibid.* 1983, 22, 31. Reetz, M. T. *Ibid.* 1984, 23, 556. Heathcock, C. H.; Kiyooka, S.-I.; Blumenkopf, T. A. *J. Org. Chem.* 1984, 49, 4214. Heathcock, C. H.; Davidsen, S. K.; Hug, K. T.; Flippin, L. A. *Ibid.* 1986, 51, 3027. Keck, G. E.; Castellino, S.; Wiley, M. R. *Ibid.* 1986, 51, 5478. Reetz, M. T. *Organotitanium Reagents in Organic Synthesis*; Springer-Verlag: Berlin, 1986. Yamamoto, Y. *Acc. Chem. Res.* 1987, 20, 243. Reetz, M. T.; Jung A.; Bolm, C. *Tetrahedron* 1988, 44, 3889. Fujisawa, T.; Ukaji, Y. *Yuki Gosei Kagaku Kyokaiishi* 1989, 47, 186.

**Table I. Diastereoselectivity as a Function of the Quantity of TiCl<sub>4</sub>**

entry	aldehyde	molar equiv of TiCl <sub>4</sub>	ratio <sup>a</sup> syn:anti	yield, <sup>b</sup> %
1	1	0.4	7:1	17 <sup>c</sup>
2	1	0.5	8:1	47
3	1	0.7	1:2	56
4	1	0.8	1:9	72
5	1	1.0	1:20	84
6	1	1.2	1:3	80
7	1	1.5	1:1	78
8	1	2.0	1:1	69
9	3	0.5	28:1	63
10	3	0.6	26:1	70
11	3	0.7	6.5:1	73
12	3	0.8	1:1	80
13	3	1.0	1:1	89
14	3	1.5	1:1	91
15	5	0.5	1:1	15 <sup>d</sup>
16	5	0.6	1.5:1	46
17	5	0.7	3:1	62
18	5	0.8	12:1	78
19	5	1.0	14:1	82
20	5	1.2	15:1	79
21	5	1.5	13:1	65

<sup>a</sup> Determined by <sup>13</sup>C NMR spectroscopy, with averages of at least three runs. <sup>b</sup> Isolated yield after chromatography. <sup>c</sup> This reduction in yield might arise from the stoichiometry of the reaction (ref 3). <sup>d</sup> In addition, an unknown ketonic compound was obtained in ca. 35% yield; the structural determination is underway.

**Table II. *J* Values between 4-H and 5-H in 4,5-Disubstituted Oxazolidin-2-ones**

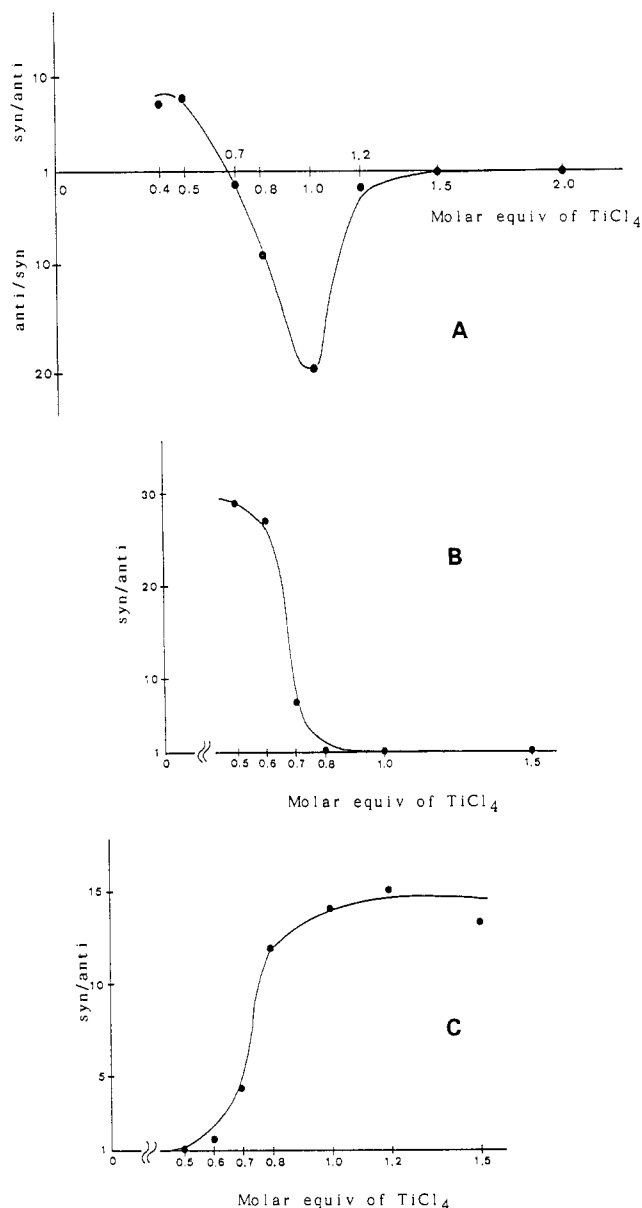
	cis	trans
	5.49	2.44
	7.25	3.96
	7.20	4.17

distinct aldehydes<sup>5</sup> derived from  $\alpha$ -amino acids. The results are briefly summarized in Table I; the syn/anti stereochemistry of products was assigned on the basis of that of the corresponding 4,5-disubstituted oxazolidin-2-ones, as shown in Table II.<sup>6</sup>

(4) (a) Dependence of diastereoselectivity of Lewis acid catalyzed Diels-Alder reaction (TiCl<sub>4</sub>): Poll, T.; Sobczak, A.; Hartmann, H.; Helmchen, G. *Tetrahedron Lett.* 1985, 26, 3095. (b) Intramolecular allylation (SnCl<sub>4</sub>): Denmark, S. E.; Henke, B. R.; Weber, E. *J. Am. Chem. Soc.* 1987, 109, 2512.

(5) The Cbz group was used instead of the Boc group because of its stability toward acidic conditions. *N*-Cbz-L-serinal acetonide 1: [ $\alpha$ ]<sub>D</sub><sup>17</sup> -69° (c = 1.00, CHCl<sub>3</sub>), was prepared by DIBAL reduction (-78 °C) of the acetonide obtained from *N*-Cbz-L-serine methyl ester; the optical purity was not determined. The aldehydes of 3 and 5 were obtained in a similar procedure: *N*-Cbz-prolinal, [ $\alpha$ ]<sub>D</sub><sup>21</sup> -70° (c = 1.08, CHCl<sub>3</sub>); *N*-Cbz-valinal, [ $\alpha$ ]<sub>D</sub><sup>22</sup> +63° (c = 1.09, CH<sub>2</sub>Cl<sub>2</sub>).

(6) A mixture of *syn*-2 and *anti*-2 could not be separated by chromatography, but protection of their primary hydroxy groups with TBDMSO permitted separation of the isomers; mixtures of *syn*-4/*anti*-4 and *syn*-5/*anti*-5 were separable. These isomers were converted to the corresponding 4,5-disubstituted oxazolidin-2-ones under the usual basic conditions. The coupling constants between 4-H and 5-H of the derivatives are known to be cis > trans: Fujikawa, S.; Inui, T.; Shiba, T. *Bull. Chem. Soc. Jpn.* 1973, 43, 3308. Garigipati, R. S.; Freyer, A. J.; Whittle, R. R.; Weireb, S. M. *J. Am. Chem. Soc.* 1984, 106, 7861. Kano, S.; Yokomatsu, T.; Iwasawa, H.; Shibuya, S. *Tetrahedron Lett.* 1987, 28, 6331; *Chem. Lett.* 1987, 1531.



**Figure 1.** Observed diastereoselectivity as a function of the quantity of titanium tetrachloride used in the reactions of *N*-Cbz-serinal acetonide 1 (A), *N*-Cbz-serinal 3 (B), and *N*-Cbz-valinal 5 (C) with allylsilane.

A high anti stereoselectivity (20:1) was observed in the reaction of allylsilane with *N*-Cbz-L-serinal acetonide 1.<sup>7,8</sup> The magnitude of this selectivity, however, was not always constant. Thus, a detailed study of the reaction conditions was undertaken which led to two improvements. First, in order to measure conveniently and accurately the required quantity of TiCl<sub>4</sub>, a 1 M TiCl<sub>4</sub> solution in dichloromethane was prepared; an aliquot from the solution was then transferred via syringe into the reaction flask. Second, to the precooled TiCl<sub>4</sub> solution (-78 °C) was added a solution of the aldehyde in CH<sub>2</sub>Cl<sub>2</sub> slowly over the course of 30 min; the resulting solution was then stirred for more than 1 h

(7) Syn selectivity on *N*-Boc-serinal acetonide. ZnCl<sub>2</sub>: Garner, P. *Tetrahedron Lett.* 1984, 25, 5855. Al reagent: Newman, H. *Ibid.* 1971, 4571. Mg-CuI reagent: Herold, P. *Helv. Chim. Acta* 1988, 71, 354.

(8) Anti selectivity on *N*-Boc-serinal acetonide. (a) Lithium reagents: Garner, P.; Park, J. M.; Malecki, E. *J. Org. Chem.* 1988, 53, 4395. Herold, P. *Helv. Chim. Acta* 1988, 71, 354. Nimkar, S.; Menaldino, D.; Merrill, A. H.; Liotta, D. *Tetrahedron Lett.* 1988, 29, 3037. (b) Si-F<sup>-</sup> reagent: Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A. *Tetrahedron* 1987, 43, 3533.

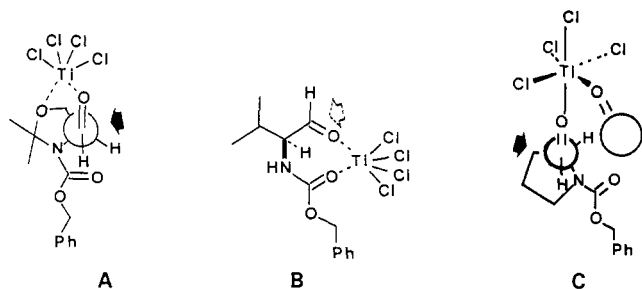


Figure 2.

in order to allow time for the coordinative interactions between the aldehyde and  $\text{TiCl}_4$  to be completely established at this low temperature. After adding allylsilane over the course of 30 min and stirring for 20 min, the reaction was then quenched with water.<sup>9</sup>

From the above experiments, it was shown that the quantity of  $\text{TiCl}_4$  added is clearly an important factor in controlling the reaction course. The reaction selectivity versus the quantity of  $\text{TiCl}_4$  added produced a unique curve, as shown in Figure 1A. Undoubtedly, maximum anti selectivity was observed with values near 1.0 equiv. of  $\text{TiCl}_4$ , but the range of effective concentrations of  $\text{TiCl}_4$  over which the anti isomer dominated was very limited. The anti selectivity decreased as the quantity of  $\text{TiCl}_4$  was decreased from 1.0 molar equiv, and the syn isomer was, surprisingly, ultimately favored over the anti by a ratio of 8:1 with 0.5 equiv of  $\text{TiCl}_4$ . On the other hand, the anti selectivity rapidly decreased as the quantity of  $\text{TiCl}_4$  was increased over 1.0 equiv.

We interpret this trend in terms of two differently derived species (aldehyde- $\text{TiCl}_4$ , 1:1 and 2:1 complexes), which could proceed to the respective transition states. The existence of substrate-Lewis acid 2:1 complexes has been previously reported<sup>10</sup> in solid and/or solution states. Thus, the selectivity found with 0.5 equiv of  $\text{TiCl}_4$  could be described as arising from reaction via the 2:1 complex. On the other hand, the anti selectivity observed with 1.0 equiv is consistent with  $\beta$ -chelation, a characteristic of aldehydes with  $\beta$ -alkoxy groups; in such cases,  $\beta$ -chelation

is more effective than  $\alpha$ -chelation (Figure 2A). The disturbance of  $\beta$ -chelation, with excess  $\text{TiCl}_4$  over 1.0 equiv, resulted in lower anti selectivity.

In the case of *N*-Cbz-prolinal **3**, it is extremely interesting to note that high syn selectivity<sup>11</sup> (28:1) was obtained in the reaction with 0.5 equiv of  $\text{TiCl}_4$ , but not with 1.0 equiv, as shown in Figure 1B. This selectivity apparently arises from a transition state via the aldehyde- $\text{TiCl}_4$  2:1 complex and is consistent with the result with serinal **1**. The complete lack of selectivity with 1.0 equiv is undoubtedly attributable to the difficulty in achieving  $\alpha$ -chelation, which must intervene between the aldehyde carbonyl and *N*-Cbz groups.

In contrast, the reaction of acyclic *N*-Cbz-valinal **5** using 1.0 equiv of  $\text{TiCl}_4$  resulted in high syn selectivity, which tends to substantiate the validity of an ordinary  $\alpha$ -chelation mechanism, via a 1:1 complex, as shown in Figure 2B. The  $\alpha$ -chelation in such an acyclic system is stable enough to withstand the presence of excess  $\text{TiCl}_4$ , as shown in Figure 1C. From this point of view, the absence of  $\alpha$ -chelation in serinal and prolinal systems may be traceable to a common structure which contains the  $\alpha$ -cyclic moiety. A similar syn selectivity, in a 5:1 ratio, was observed in the case of *N*-Cbz-phenylalaninal, as expected.

The diastereofacial selectivity is obviously achieved via conformations demanding entirely different steric factors, in the case where  $\alpha$ -chelation is hindered by the inherent structural characteristics of the aldehydes (**1** and **3**) in the Lewis acid mediated reactions. We accordingly invoke the role of an aldehyde- $\text{TiCl}_4$  2:1 complex, in order to explain the high syn stereoselectivity unexpectedly observed at 0.5 molar equiv of  $\text{TiCl}_4$ . It could be envisioned that the diastereoface may be *amphiphilically*<sup>12</sup> distinguished by the second aldehyde coordinated to the  $\text{TiCl}_4$ , as shown in Figure 2C. Further studies on diastereoselectivity as it pertains to the quantity of Lewis acid used, on representative acyclic aldehydes, are in progress and will be reported in due course.

**Acknowledgment.** This research was supported by a Grant-in-Aid (No. 1540430) from the Ministry of Education, Science, and Culture of Japan.

(9) After acidic workup, the crude allylated materials consisted of deprotected product and five- and six-membered acetonides; treatment with 10%  $\text{HCl}$ -THF gave a mixture of *syn*-**2** and *anti*-**2**.

(10)  $\text{TiCl}_4$ - $2\text{CH}_3\text{CO}_2\text{C}_2\text{H}_5$  complex: Kletenik, Y. B.; Osipov, O. A. *Zh. Obshch. Khim.* 1961, 31, 710.  $\text{SnCl}_4$  and aldehyde 1:2 complex: Keck, G. E.; Castellino, S. *Tetrahedron Lett.* 1987, 28, 281. Denmark, S. E.; Wilson, T.; Willson, T. M. *J. Am. Chem. Soc.* 1988, 110, 984.  $\text{SnCl}_4$  and methacrylonitrile cis 1:2 complex: Hirai, H.; Ikegami, T.; Makishima, S. *J. Polym. Sci., A-1* 1969, 7, 2059.

(11) This product may be useful as a convenient chiral synthetic building block for alkaloids: Hanson, G. J.; Baran, J. S.; Lindberg, T. *Tetrahedron Lett.* 1986, 27, 3577.

(12) Amphiphilic effect: The second coordinated aldehyde in the 2:1 complex may fulfill the role of a bulky aluminum reagent such as "MAD" to achieve the moderate anti-Cram selectivity: Maruoka, K.; Itoh, T.; Sukurai, M.; Nonoshita, K.; Yamamoto, H. *J. Am. Chem. Soc.* 1988, 110, 3588. LePage, T. J.; Wiberg, K. B. *Ibid.* 1988, 110, 6642.

## Construction of Fused-Ring Skeletons Based on Photochemical Rearrangements of Bicyclo[3.2.1]oct-6-en-2-ones and Application to a Total Synthesis of ( $\pm$ )- $\Delta^9(12)$ -Capnellene

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**Summary:** A method for preparation of bicyclo[3.3.0]oct-7-en-2-ones has been developed on the basis of the photochemical [1,3]-acyl migration of 8,8-disubstituted bicyclo[3.2.1]oct-6-en-2-ones and applied to a total syn-

thesis of ( $\pm$ )- $\Delta^9(12)$ -capnellene, a linear triquinane.

**Sir:** Photochemical behavior of  $\beta,\gamma$ -unsaturated ketones has been investigated extensively.<sup>1</sup> From a synthetic point