

## Reexamination of CeCl<sub>3</sub> and InCl<sub>3</sub> as Activators in the Diastereoselective Mukaiyama Aldol Reaction in Aqueous Media

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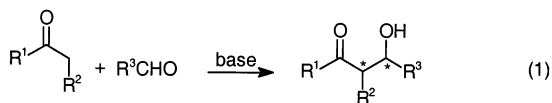
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**Abstract:** A search for suitable reaction conditions in Mukaiyama-type aldol condensations activated by CeCl<sub>3</sub> and InCl<sub>3</sub> revealed that the reaction proceeds best in *i*-PrOH/H<sub>2</sub>O (95:5). Contrary to literature precedent, no reaction was observed in pure water, and the encountered destruction of the starting silyl enol ether can be ascribed to initial hydrolysis of the Lewis acid. As anticipated from the dual parameter ( $pK_{\text{h}}$ , WERC value) characteristics of CeCl<sub>3</sub> and InCl<sub>3</sub>, the former proved more efficient as Lewis acid-promoter, in terms of reaction speed and yield. Nevertheless, InCl<sub>3</sub> was a superior catalyst during evaluation of the diastereoselectivity of the process. In this regard, determination of diastereoselectivity as a function of time showed that the InCl<sub>3</sub>-catalyzed reaction is irreversible, whereas the CeCl<sub>3</sub>-catalyzed reaction is a reversible process. In both cases, formation of the syn product is kinetically preferred, although  $\Delta\Delta G_{273\text{K}}^{\ddagger}(\text{InCl}_3) = 1.50$  kcal/mol versus  $\Delta\Delta G_{273\text{K}}^{\ddagger}(\text{CeCl}_3) = 0.38$  kcal/mol. Molecular modeling (semiempirical PM3, ab initio HF/3-21G\*, hybrid B3LYP/3-21G\*, and B3LYP/LANL2DZ) of the diastereoselective aldol reaction promoted by InCl<sub>3</sub> supports a “closed”, Zimmerman–Traxler transition state.

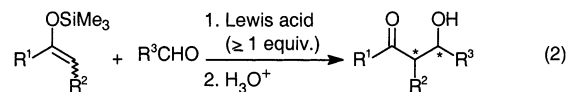
The aldol reaction is well-recognized as one of the most important carbon–carbon bond-forming reactions in organic synthesis. As can be appreciated in eq 1, two



stereogenic centers are generated in the aldol reaction and useful protocols must fulfill satisfactory levels of reaction yield, diastereoselectivity, and enantioselectivity.<sup>1</sup>

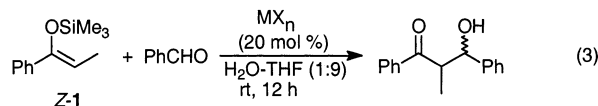
A most relevant variant of the classical aldol reaction (eq 1) was developed by Mukaiyama et al.,<sup>2</sup> who found that silyl enol ethers react with carbonyl compounds in the presence of Lewis acids to give aldol products in a highly chemoselective manner (eq 2). The other main

advantage in the Mukaiyama approach is the potential for catalytic, enantioselective reactions.<sup>3</sup>



A variety of Lewis acids have been used as catalysts in the Mukaiyama reaction (eq 2), including triarylcarenium ions,<sup>4a</sup> boron Lewis acids,<sup>4b</sup> tin Lewis acids,<sup>4c,d</sup> palladium Lewis acids,<sup>4e</sup> titanium Lewis acids,<sup>4f</sup> and copper Lewis acids.<sup>4g</sup> Most of these Lewis acids react rapidly with water and become deactivated in the process; thus, the reactions must be carried out under strict anhydrous conditions. Nevertheless, Kobayashi et al.<sup>5</sup> have recently shown that lanthanide triflates [Ln(OTf)<sub>3</sub>] can be used as efficient Lewis acids in aqueous media (typically, H<sub>2</sub>O–THF (1:4) or H<sub>2</sub>O–EtOH (1:9)), as their hydrolysis by water is generally slow. This development is quite remarkable because, in regard to the topic of interest in the present report, Mukaiyama-type aldol reactions can be carried out in aqueous media, avoiding the use of potentially toxic solvents and allowing the easy recovery of the active Lewis acid catalyst.

Very recently, from a systematic examination of the catalytic activity exhibited by group 1–15 metal chlorides, perchlorates, and triflates in the Mukaiyama aldol reaction of benzaldehyde with silyl enol ether **Z-1** in water–THF (1:9) (eq 3), Kobayashi concluded that the



catalytic activity of the metal cations depends on two parameters: (1) the hydrolysis constants,  $K_{\text{h}}$ , and (2) water exchange rate constants, WERC. In particular, highest catalytic activity was found in those metal cations with  $pK_{\text{h}}$  values in the range from about 4 to 10, and WERC values greater than  $3.2 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ .<sup>5d</sup>

As anticipated from the previous analysis, “borderline” indium(III) salts gave the aldol products in modest yields.<sup>5d</sup> Nevertheless, an influential review by Cintas<sup>6</sup> has elicited much interest in the utility of indium

(3) (a) Mukaiyama, T. *Aldrichim. Acta* **1996**, *29*, 59. (b) Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W. W.-L. *Chem. Rev.* **2002**, *102*, 2227. (c) Shibasaki, M.; Yoshikawa, N. *Chem. Rev.* **2002**, *102*, 2187.

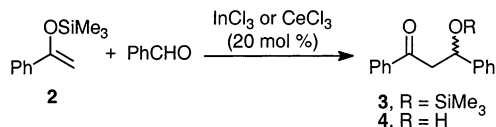
(4) (a) Denmark, S. E.; Chen, C.-T. *Tetrahedron Lett.* **1994**, *35*, 4327. (b) For two comprehensive reviews, see: Deloux, L.; Srebnik, M. *Chem. Rev.* **1993**, *93*, 763. Wallbaum, S.; Martens, J. *Tetrahedron: Asymmetry* **1992**, *3*, 1475. (c) Kobayashi, S.; Uchiro, H.; Shiina, I.; Mukaiyama, T. *Tetrahedron* **1993**, *49*, 1761. (d) Evans, D. A.; McMillan, D. W.; Campos, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 10859. (e) Sodeoka, M.; Ohrai, K.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 2648. (f) Carreira, E. M.; Singer, R. A.; Lee, W. *J. Am. Chem. Soc.* **1994**, *116*, 8837. (g) Evans, D. A.; Murry, J. A.; Kozlowski, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 5814.

(5) (a) Kobayashi, S. *Chem. Lett.* **1991**, 2087. (b) Kobayashi, S.; Hachiya, I. *J. Org. Chem.* **1994**, *59*, 3590. For Ln(OTf)<sub>3</sub>-catalyzed asymmetric aldol reactions in aqueous media, see: (c) Kobayashi, S.; Hamada, T.; Nagayama, S.; Manabe, K. *Org. Lett.* **2001**, *3*, 165. (d) Kobayashi, S.; Manabe, K. *Acc. Chem. Res.* **2002**, *35*, 209. (e) Manabe, K.; Kobayashi, S. *Chem. Eur. J.* **2000**, *6*, 4095.

(6) Cintas, P. *Synlett* **1995**, 1087.

(1) Some representative reviews: (a) Heathcock, C. H. *Aldrichim. Acta* **1990**, *23*, 99. (b) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1. (c) Paterson, I. *Org. React.* **1997**, *51*, 1. (d) Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095. (e) Denmark, S. E.; Stavenger, R. A. *Acc. Chem. Res.* **2000**, *33*, 432.

(2) (a) Mukaiyama, T.; Narasaka, K.; Banno, K. *Chem. Lett.* **1973**, 1012. (b) Mukaiyama, T. *Org. React.* **1982**, *28*, 203.

**TABLE 1. Solvent Effect on the Mukaiyama-Type Aldol Condensation**

entry	Lewis acid (20 mol %)	solvent(s)	temp (°C)	time (h)	yield of <b>3</b>	yield of <b>4</b>
1	InCl <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub>	0	24	14	
2	InCl <sub>3</sub>	toluene	0	24	17	
3	InCl <sub>3</sub>	CH <sub>3</sub> CN	0	24	39	9
4	InCl <sub>3</sub>	H <sub>2</sub> O	25	24		
5	InCl <sub>3</sub>	H <sub>2</sub> O/EtOH (1:9)	25	18		43
6	InCl <sub>3</sub>	H <sub>2</sub> O/ <i>i</i> -PrOH (1:19)	25	18		55
7	CeCl <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub>	0	24	28	
8	CeCl <sub>3</sub>	toluene	0	24	35	
9	CeCl <sub>3</sub>	CH <sub>3</sub> CN	0	24	45	16
10	CeCl <sub>3</sub>	H <sub>2</sub> O	25	24		traces
11	CeCl <sub>3</sub>	H <sub>2</sub> O/EtOH (1:9)	25	12		67
12	CeCl <sub>3</sub>	H <sub>2</sub> O/ <i>i</i> -PrOH (1:19)	25	12		90

reagents in synthesis. Furthermore, Loh and co-workers<sup>7</sup> reported in 1996 that InCl<sub>3</sub> was an efficient catalyst in aldol reactions of silyl enol ethers with aldehydes *in pure water*. This report was subsequently questioned by Kobayashi et al.,<sup>8</sup> who repeated the experiments and found that hydrolysis of the Mukaiyama silyl enol ethers is faster than the desired condensation, unless the Lewis acid (InCl<sub>3</sub>) is used neat or in micellar systems.

With this background, we would like to communicate our own results in the area, in particular the evaluation of InCl<sub>3</sub> ( $pK_{\text{a}} = 4.0$ ; WERC value =  $4.0 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$ ) and CeCl<sub>3</sub> ( $pK_{\text{a}} = 8.3$ ; WERC value =  $2.17 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$ ) as Lewis acid catalysts in Mukaiyama-type aldol reactions.

## Results and Discussion

**Solvent Effect.** First of all, a search was undertaken for the best reaction conditions (solvent, temperature, reaction time) in the aldol condensation of trimethylsilyl enol ether **2**<sup>9</sup> with benzaldehyde, in the presence of 0.2 equiv of the Lewis acid activator (Table 1).

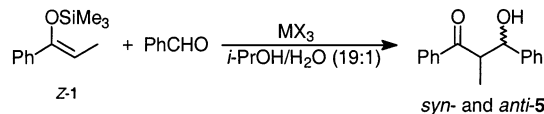
Salient observations are the following: (1) No aldol reaction takes place in pure water (entries 4 and 10 in Table 1), presumably as a consequence of partial hydrolysis of the Lewis acid, which induces destruction of the silyl enol ether. This result is contrary to Loh's reports,<sup>7</sup> but in line with Kobayashi's analysis.<sup>8</sup> (2) Poor to moderate yields of the silylated aldol product **3** were found in aprotic solvents CH<sub>2</sub>Cl<sub>2</sub>, toluene, or CH<sub>3</sub>CN. Essentially quantitative desilylation of **3** to give **4** was achieved with tetrabutylammonium fluoride.<sup>10</sup> (3) The best yields of the desired aldol product **4** were obtained

(7) (a) Loh, T.-P.; Pei, J.; Cao, G.-Q. *Chem. Commun.* **1996**, 1819. (b) Loh, T.-P.; Chua, G.-L.; Vittal, J. J.; Wong, M.-W. *Chem. Commun.* **1998**, 861.

(8) Kobayashi, S.; Busujima, T.; Nagayama, S. *Tetrahedron Lett.* **1998**, 39, 1579.

(9) Prepared according to literature procedures: (a) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, 34, 2324. (b) Matano, Y.; Azuma, N.; Suzuki, H. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1739.

(10) Cf.: (a) Greene, T. W. *Protective Groups in Organic Synthesis*; Wiley: New York, 1981; pp 39–43. (b) Kocienski, P. *J. Protecting Groups*; Thieme: Stuttgart, Germany, 1994.

**TABLE 2. Diastereoselectivity of Aldol Reactions Promoted by CeCl<sub>3</sub> and InCl<sub>3</sub>**

entry	MCl <sub>3</sub> (mol %)	temp (°C)	time (h)	yield (%)	dr (syn:anti)
1	InCl <sub>3</sub> (100)	0	6	63	96:4
2	InCl <sub>3</sub> (20)	0	24	65	92:8
3	InCl <sub>3</sub> (20)	25	24	71	92:8
4	CeCl <sub>3</sub> (100)	0	3	91	41:59
5	CeCl <sub>3</sub> (20)	0	18	85	44:56
6	CeCl <sub>3</sub> (20)	25	24	88	48:52

in a water–2-propanol (1:19) solvent mixture (entries 6 and 12 in Table 1). As anticipated from  $pK_{\text{a}}$ /WERC value dual parameter considerations,<sup>5d</sup> CeCl<sub>3</sub> proved more efficient than InCl<sub>3</sub> as a Lewis acid activator (compare entries 5 and 11, as well as entries 6 and 12 in Table 1). (See, however, next section.)

**Lewis Acid Effect on Diastereoselectivity.** Once we had established suitable reaction conditions for the Mukaiyama-type aldol condensation promoted by CeCl<sub>3</sub> and InCl<sub>3</sub> [*i*-PrOH–H<sub>2</sub>O (19:1), rt, 12 and 18 h, respectively], we proceeded to evaluate the diastereoselectivity of the process. To this end, the trimethylsilyl ether derived from propiophenone, **Z-1**,<sup>9</sup> was reacted with benzaldehyde, with the results collected in Table 2. Diastereomeric ratios were determined by measurement of signal ratios in <sup>1</sup>H and <sup>13</sup>C NMR spectra. The assignment of the relative configuration of products *syn-5* and *anti-5* was done by analysis of vicinal coupling constants, as described by Denmark et al.<sup>11</sup>

Inspection of Table 2 confirms that CeCl<sub>3</sub> is a more efficient Lewis acid activator than InCl<sub>3</sub>. Indeed, yields with CeCl<sub>3</sub> fall in the 85–91% range (entries 4–6), whereas moderate yields are seen with InCl<sub>3</sub>, 63–71% (entries 1–3). Nevertheless, much better diastereoselectivities were achieved with InCl<sub>3</sub>: dr = 92–96:8–4. By comparison, diastereomeric ratios with CeCl<sub>3</sub> are a disappointing 41–48:59–42.

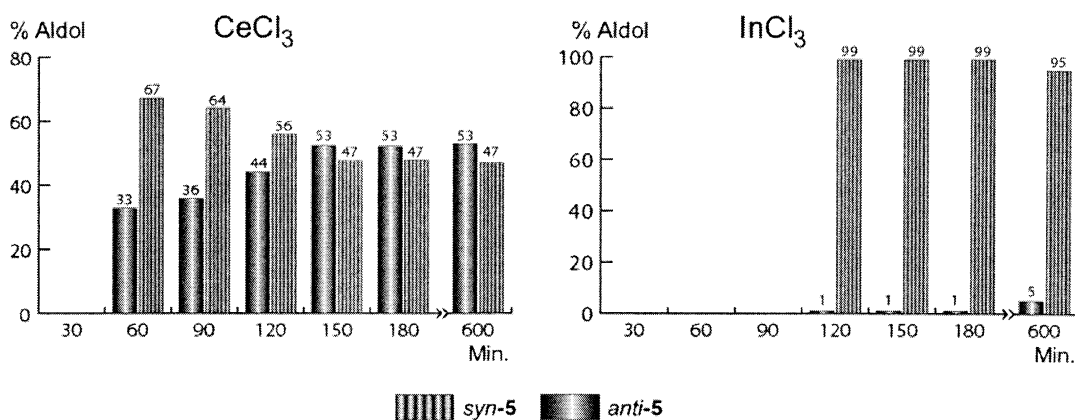
Interestingly, determination of the diastereomeric product ratio with time indicates that such ratio remains constant in the case of the InCl<sub>3</sub>-promoted reaction (i.e., the reaction is kinetically controlled, with great predominance of the *syn* product), whereas the CeCl<sub>3</sub>-activated reaction initially affords a *syn*:*anti* ratio equal to 67:33 that then gradually changes until an equilibrium *syn*:*anti* ratio of 47:53 dr is attained (Figure 1).

The epimerization process *syn-5* ⇌ *anti-5* observed with CeCl<sub>3</sub> could in principle be ascribed to a retro-Aldol reaction; however, a control experiment in which *syn-5* was treated with CeCl<sub>3</sub> in the presence of *p*-nitrobenzaldehyde afforded varying amounts of *anti-5*, but no appreciable formation of aldol product **6** (Scheme 1).

The above observation, together with literature precedent,<sup>12</sup> leads to the conclusion that CeCl<sub>3</sub> most likely promotes the epimerization *syn-5* ⇌ *anti-5* via keto-

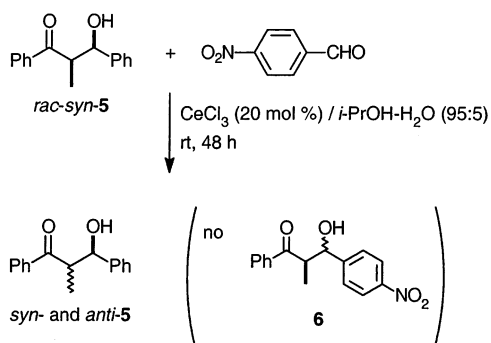
(11) Denmark, S. E.; Wang, K.-T.; Stavenger, R. A. *J. Am. Chem. Soc.* **1997**, 119, 2333 and Supporting Information for this paper.

(12) See, for example: Ward, D. E.; Sales, M.; Sasmal, P. K. *Org. Lett.* **2001**, 3, 3671.

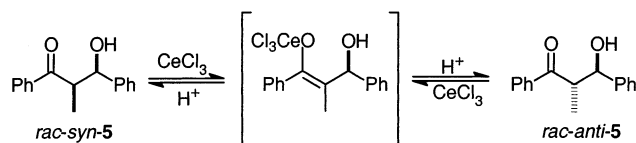


**FIGURE 1.** Diastereomeric (*syn-5/anti-5*) product ratios as a function of time. The reactions were carried out at 0 °C, with 20 mol % of Lewis acid catalyst.

### SCHEME 1



### SCHEME 2



enolization (Scheme 2). Epimerization via ketoenolization is presumably favored by the greater Lewis acidity of Ce(III), with respect to In(III).<sup>13</sup>

Table 3 collects diastereoselectivity data obtained with additional aldehydes, both aliphatic (acetaldehyde, isobutyraldehyde, and pivalaldehyde) and aromatic (*p*-anisaldehyde, *p*-nitrobenzaldehyde, and *p*-chlorobenzaldehyde). It is appreciated that similar observations were recorded: faster but less stereoselective aldol addition in the presence of CeCl<sub>3</sub>, and slower and highly diastereoselective addition with InCl<sub>3</sub> as Lewis acid catalyst.

**Molecular Modeling of the Lewis Acid-Activated Complexes.** From the kinetic studies discussed above (cf. Figure 1 and text), it is apparent that the difference in activation energies for the aldol reactions catalyzed by InCl<sub>3</sub> and CeCl<sub>3</sub> is substantial. Indeed, with InCl<sub>3</sub> as Lewis acid, silyl enol ether *Z-1* reacts with benzaldehyde under kinetic control to give a ca. 94:6 ratio of the *syn* and *anti* aldol products; this suggests a  $\Delta\Delta G_{273K}^\ddagger = 1.50$  kcal/mol, favoring formation of *syn-5*. By contrast, the *syn:anti* ratio of diastereomeric products **5** at short

**TABLE 3.** Diastereoselectivity of Aldol Reactions with Both Aliphatic and Aromatic Aldehydes, Promoted by CeCl<sub>3</sub> and InCl<sub>3</sub>

entry	aldehyde	MX <sub>3</sub>	temp (°C)	time (h)	product	yield (%)	dr (syn:anti)
1	benzaldehyde	CeCl <sub>3</sub>	25	18	<i>rac-5</i>	85	44:56
2	<i>p</i> -nitrobenzaldehyde	CeCl <sub>3</sub>	25	12	<i>rac-6</i>	78	39:61
3	<i>p</i> -anisaldehyde	CeCl <sub>3</sub>	25	18	<i>rac-7</i>	73	34:66
4	<i>p</i> -chlorobenzaldehyde	CeCl <sub>3</sub>	25	15	<i>rac-8</i>	66	40:60
5	acetaldehyde	CeCl <sub>3</sub>	0	12	<i>rac-9</i>	83	45:55
6	isobutyraldehyde	CeCl <sub>3</sub>	0	18	<i>rac-10</i>	47	36:64
7	pivalaldehyde	CeCl <sub>3</sub>	0	18	<i>rac-11</i>	39	44:56
8	benzaldehyde	InCl <sub>3</sub>	25	24	<i>rac-5</i>	71	92:8
9	<i>p</i> -nitrobenzaldehyde	InCl <sub>3</sub>	25	18	<i>rac-6</i>	60	68:32
10	<i>p</i> -anisaldehyde	InCl <sub>3</sub>	25	24	<i>rac-7</i>	61	95:5
11	<i>p</i> -chlorobenzaldehyde	InCl <sub>3</sub>	25	18	<i>rac-8</i>	51	90:10
12	acetaldehyde	InCl <sub>3</sub>	0	18	<i>rac-9</i>	63	96:4
13	isobutyraldehyde	InCl <sub>3</sub>	0	18	<i>rac-10</i>	42	95:5
14	pivalaldehyde	InCl <sub>3</sub>	0	18	<i>rac-11</i>	31	98:2

reaction times is 67:33, which indicates a smaller  $\Delta\Delta G_{273K}^\ddagger = 0.38$  kcal/mol. Again, the activation energy is lower for the transition state leading to *syn-5*.

In his recent review, Mahrwald<sup>14</sup> concluded that the described stereochemical outcome of the Mukaiyama reaction cannot be explained by classical “closed” transition state models (Zimmermann–Traxler models); instead, “open” transition state models offer best agreement with the experimental data. To gain some mechanistic insight into the indium chloride catalyzed Mukaiyama reaction of interest,<sup>14</sup> we performed semiempirical (PM3),<sup>15</sup> ab initio (HF/3-21G\*),<sup>16</sup> and hybrid (B3LYP/3-21G\* and B3LYP/LANL2DZ)<sup>16</sup> theoretical calculations on the six “open” Lewis acid-activated arrangements that can in principle afford the *anti* and *syn* products **5** (Scheme 3).

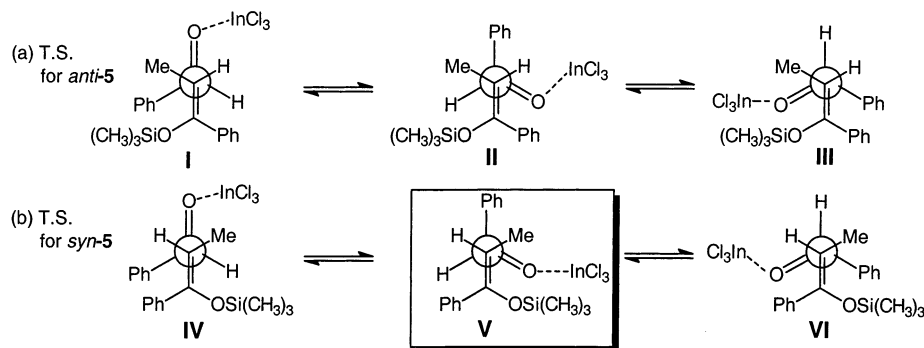
Table 4 collects the calculated energies for optimized geometries of the “open” transition states leading to *anti* (**I–III**) and *syn* (**IV–VI**) aldol products in the reaction

(14) For meaningful computational comparison of diastereomeric transition states, it is recommended that relative energies differ by at least 0.5 kcal/mol: Juaristi, E. *Introduction to Stereochemistry and Conformational Analysis*; Wiley: New York, 1991; p 170.

(15) PC Spartan-Pro, version 1.0; Wavefunction, Inc.: Irvine, CA, 1999.

(13) Cf.: Fukuzumi, S.; Ohkubo, K. *Chem. Eur. J.* **2000**, *6*, 4532.

## SCHEME 3



**TABLE 4. Calculated Relative Energies for "Open"  $\text{InCl}_3$ -Promoted Transition States Leading to *anti*-5 (I–III) and *syn*-5 (IV–VI) (See Scheme 3)**

	$E_{rel}$ (kcal/mol)			
	PM3	HF/3-21G*	B3LYP/3-21G*	B3LYP/LANL2DZ
<b>I</b>	6.313	4.597	6.115	14.940
<b>II</b>	4.103	2.822	5.082	6.835
<b>III</b>	8.804	7.701	12.599	9.324
<b>IV</b>	7.759	7.177	11.290	12.405
<b>V</b>	<b>0.000</b>	<b>0.000</b>	<b>0.000</b>	<b>0.000</b>
<b>VI</b>	3.055	10.253	5.178	11.008
<b>VII</b>	<b>0.000</b>	<b>0.000</b>	<b>0.000</b>	<b>0.000</b>
<b>VIII</b>	5.539	5.669	6.909	4.889

of silyl enol ether *Z*-1 with benzaldehyde, and activated by  $\text{InCl}_3$ .<sup>17</sup> All methods predict that transition state **V** is lowest in energy, affording aldol product *syn*-5, as experimentally observed.

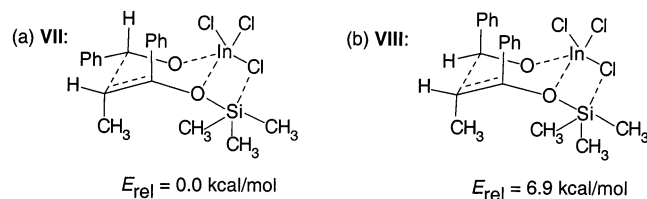
Interestingly, geometry reoptimization of **V** at the B3LYP/3-21G\* level of theory afforded "closed" transition state **VII** (Scheme 4a). By comparison, optimization of the corresponding Zimmerman–Traxler transition state leading from **III** to *anti*-5 (**VIII** in Scheme 4b) is estimated to be 6.9 kcal/mol higher in energy. Therefore, at the levels of theory explored in this work, we conclude that *syn* isomers are generated via a chelated (closed) model in the  $\text{InCl}_3$ -activated reactions. By contrast, open transition structure **II** is calculated to be the most favorable structure leading to the *anti* isomer, but this TS is estimated to be significantly higher in energy.

(16) *Gaussian 98*, Revision A.7; Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A.; Stratmann, R. E., Jr.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Pettersson, G. A.; Ayala, P. Y.; Cui, Q.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Lui, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, D. J.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian, Inc.*: Pittsburgh, PA, 1998.

(17) Nuclei beyond the third row such as Ce(III) require an approximate treatment, via effective core potentials which include some relativistic effects. Although the LANL2DZ is the best known basis set for this purpose, so far we have been unable to manage cerium at this level of theory.

(18) Curran, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 5826.

## SCHEME 4



**Conclusions.** (1) Evaluation of both aprotic ( $\text{CH}_2\text{Cl}_2$ , toluene,  $\text{CH}_3\text{CN}$ ) and aqueous media as solvents for Mukaiyama-type aldol condensations promoted by  $\text{CeCl}_3$  and  $\text{InCl}_3$  showed *i*-PrOH/ $\text{H}_2\text{O}$  (95:5) to give the highest yields.

(2) As anticipated by Kobayashi's dual parameter generalization,  $\text{CeCl}_3$  proved to be a superior Lewis acid activator than  $\text{InCl}_3$  in terms of reaction speed and chemical yield. Nevertheless,  $\text{InCl}_3$  should be the catalyst of choice since high diastereoselectivity is then achieved.

(3) Kinetic studies revealed that the  $\text{InCl}_3$ -catalyzed aldol reaction is irreversible, whereas the  $\text{CeCl}_3$ -catalyzed process is reversible. In both cases, kinetic control favors formation of the *syn*-5 diastereomeric product, although the difference in activation energy is much larger with  $\text{InCl}_3$ .

(4) Molecular modeling at various levels of theory supports a "closed" transition state in the highly diastereoselective aldol condensation of *Z*-1 with PhCHO, when promoted by  $\text{InCl}_3$ .

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**Supporting Information Available:** General experimental information, general procedures for Mukaiyama aldol reactions catalyzed with  $\text{CeCl}_3$  and  $\text{InCl}_3$ , general procedure for desilylation of aldol products, physical and spectroscopic data for *Z*-1, **2**, **3**, **4**, *syn*-5, *anti*-5, and **6–11**, and computational results (Cartesian coordinates for intermediates **I–VIII**). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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