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Can Simple Enones Be Useful Partners for the Catalytic Stereoselective Alkylation of Indoles?

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A new catalytic system for the first example of enantioselective Friedel−Crafts-type (FC) addition of indoles to simple enones is described. The use of an equimolar amount of chiral [Al(salen)Cl] and 2,6-lutidine (10 mol %) was found to be effective in promoting the conjugate addition of indoles to (*E*)-arylcrotyl ketones, furnishing the corresponding *β*-indolyl ketones in excellent yield and high enantioselectivity (ee up to 89%). The role of the base was investigated through spectroscopic as well as computational analyses, which suggested that in situ formation of a new chiral (base•[Al(salen)]) complex was operating under our reaction conditions. In particular, a stable cationic [Al(salen)] hexacoordinate trans complex with the additive base and the enone is suggested as being responsible for the stereocontrolled reaction. Finally, detailed monitoring of the reaction course was carried out showing that a conventional FC pathway induced by [Al(salen)Cl] acting as a Lewis acid is operating.

Introduction

The synthesis of indolyl-containing compounds[1] bearing a stereocenter adjacent to the heteoaromatic ring is of high chemical and biochemical importance. In fact, many pharmacologically and agrochemically active compounds are characterized by the presence of this framework in their molecular skeletons.[2] In this context, after the pioneering study of Kerr et al. on the use of $Yb(OTf)_3$ for the catalytic addition of indoles to electron-deficient carbon−carbon double bonds,[3] an ever-increasing number of mild, catalytic, and environmentally friendly FC alkylations of indoles via Michael-type addition have been described.[4] Homogeneous as well as heterogeneous catalysts showed their effectiveness in this protocol, and in some cases, both microwave irradiations and ultrasound activations were found to be beneficial by improving the chemical yields.[5] More recently, as a consequence of the astonishing growth of interest of both academic and industrial communities, the development of catalytic asymmetric FC strategies has been the subject of intensive studies in order to access enantiomerically enriched aromatic compounds bearing benzylic stereocenters.[6]

In particular, chiral Cu(I/II)-,[7] Sc(III)-,[8] and Pd(II)-based[9] Lewis acids proved to be highly effective promoters for stereoselective FC alkylations of indoles. In these cases, bidentate chelating carbonyls (*β*,*γ*-unsaturated α-ketoesters, arylidene malonates, α,*β*-unsaturated acyl phosphonates, α,*β*-unsaturated heteroaromatic thioesters) were required in order to achieve high levels of stereoinduction. On the other hand, the use of simple nonchelat-

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(1) (a) Sundberg, R. J. *Indoles*; Academic Press: San Diego, 1996. (b) Nicolaou, K. C.; Snyder, S. A. *Classic in Total Synthesis II*; Wiley-VCH: Weinheim, 2003.

(2) (a) Kozokowsi, A. P.; Greco, M. N. *J. Am. Chem. Soc.* **1980**, *102*, 1165. (b) Shinohara, T.; Suzuki, K. *Tetrahedron Lett.* **2002**, *43*, 6937.

(3) Harrington, P. E.; Kerr, M. A. *Synlett* **1996**, 1047.

(4) (a) Taylor, S. K.; May, S. A.; Stansby, E. S. *J. Org. Chem.* **1996**, *61*, 2075. (b) Manabe, K.; Aoyama, N.; Kobayashi, S. *Adv. Synth. Catal.* **2001**, *343*, 174. (c) Yadav, J. S.; Abraham, S.; Reddy, B. V. S.; Sabitha, G. *Synthesis* **2001**, 2165. (d) Yadav, J. S.; Subba Reddy, B. V.; Murthy, Ch. V. S. R.; Mahesh Kumar, G.; Madan, Ch. *Synthesis* **2001**, 783. (e) Reddy, R.; Jaquith, J. B.; Neelagiri, V. R.; Saleh-Hanna, S.; Durst, T. *Org. Lett.* **2002**, *4*, 695. (f) Nagumo, S.; Miyoshi, I.; Akita, H.; Kawahara, N. *Tetrahedron Lett.* **2002**, *43*, 2223. (g) Bandini, M.; Cozzi, P. G.; Giacomini, M.; Melchiorre, P.; Selva, S.; Umani-Ronchi, A. *J. Org. Chem.* **2002**, *67*, 3700. (h) Bandini, M.; Melchiorre, P.; Melloni, A.; Umani-Ronchi, A. *Synthesis* **2002**, 1110. (i) Bandini, M.; Fagioli, M.; Melloni, A.; Umani-Ronchi, A. *Synthesis* **2003**, 397. (j) Srivastava, N.; Banik, B. K. *J. Org. Chem.* **2003**, *68*, 2109. (k) Agnusdei, M.; Bandini, M.; Melloni, A.; Umani-Ronchi, A. *J. Org. Chem.* **2003**, *68*, 7126. (l) Ji, S.-J.; Wang, S.-Y. *Synlett* **2003**, 2074. (m) Ji, S.-H.; Zhou, M.-F.; Gu, D.-G.; Wang, S.-Y.; Loh, T.-P. *Synlett* **2003**, 2077. (n) Bartoli, G.; Bartolacci, M.; Bosco, M.; Foglia, G.; Giuliani, A.; Marcantoni, E.; Sambri, L.; Torregiani, E. *J. Org. Chem.* **2003**, *68*, 4594. (o) Ramesh, C.; Banerjee, J.; Pal, R.; Das, B. *Adv. Synth. Catal.* **2003**, *345*, 557. (p) Mujahid Alam, M.; Varala, R.; Adapa, S. R. *Tetrahedron Lett.* **2003**, *44*, 5115. (q) Vijender Reddy, A.; Ravinder, K.; Venkateshwar Goud, T.; Krishnaiah, P.; Raju, T. V.; Venkateswarlu, Y. *Tetrahedron Lett.* **2003**, *44*, 6257. (r) Yadav, J. Reddy, B. V. S.; Swamy, T. *Tetrahedron Lett.* **2003**, *44*, 9121. (s) Bandini, M.; Fagioli, M.; Umani-Ronchi, A. *Adv. Synth. Catal.* **2004**, *346*, 545.

(5) (a) Chakrabarty, M.; Basak, R.; Ghosh, N. *Tetrahedron Lett.* **2001**, *42*, 3913. (b) Chakrabarty, M.; Basak, R.; Ghosh, N.; Harigaya, Y. *Tetrahedron* **2004**, *60*, 1941.

(6) (a) Bolm, C.; Hildebrand, J. P.; Muniz, K.; Hermanns, N. *Angew Chem., Int. Ed.* **2001**, *40*, 3285. (b) Wang, Y.; Ding, K.; Dai, L. *Chemtracts: Org. Chem.* **2001**, *14*, 610. (c) Jørgensen, K. A. *Synthesis* **2003**, 1117. (d) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 550.

(7) (a) [Cu(II)/Box]: Zhuang, W.; Hansen, T.; Jørgensen, K. A. *Chem. Commun.* **2001**, 347. Zhuang, W.; Gathergood, N.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2001**, *66*, 1009. Jensen, K. B.; Thorhauge, J.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 160. Zhou, J.; Tang, Y. *J. Am. Chem. Soc.* **2002**, *124*, 9030. Zhou, J.; Tang, Y. *Chem. Commun.* **2004**, 432. (b) [Cu (I)/BINAP]: Johannsen, M. *Chem. Commun.* **1999**, 2233. Saaby, S.; Fang, X.; Gathergood, N.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 4114.

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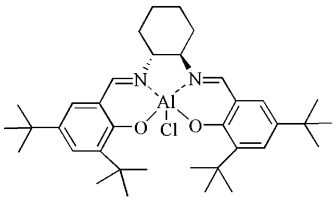


(*R,R*)-[Al(salen)Cl] **1a**

FIGURE 1. (*R,R*)-[Al(salen)Cl].

ing α,*β*-unsaturated ketones as electrophiles still represents a considerable synthetic challenge.[10] In fact, the steric similarity of the two carbonyl substituents renders the stereodifferentiation of the two enantiotopic faces of the unsaturated ketone a difficult task.

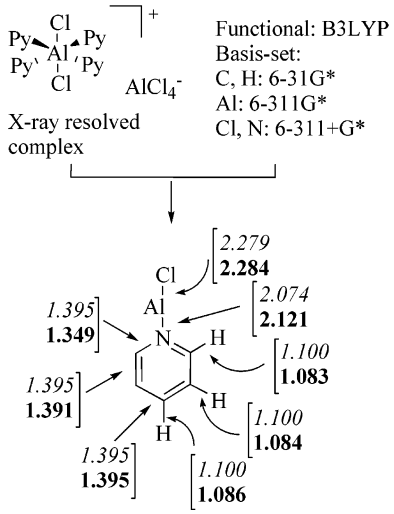
We recently reported on the effective enantioselective conjugate addition of indoles to (*E*)-arylcrotyl ketones in the presence of a chiral aluminum complex.[11] In particular, the combined use of [Al(salen)Cl] (**1a**, Figure 1)[12] and catalytic amounts of coordinating bases (10 mol %) were found to be beneficial to the stereochemical outcome of the reaction, leading the enantiomeric excess to be increased up to 89% when 2,6-lutidine was employed.

In this paper we report a full account of our investigation focusing on the generality of the procedure. To shed some light on the role of the additive on the stereoselection of the protocol, spectroscopic as well as theoretical investigations were performed. Both novel penta- and hexacoordinate complexes between [Al(salen)], the base, and a model α,*β*-unsaturated carbonyl have been fully optimized and characterized here, showing that an interaction between the coordinating base and the aluminum complex is involved. In particular, a stable cationic hexacoordinate chiral trans complex with the electrophile and the base is suggested to be responsible for the observed higher stereocontrol. Finally, both kinetic evidence and NLE (nonlinear effect) investigations call for a first-order dependence of the reaction rate on the [Al(salen)Cl] concentration, thereby ruling out a hypothetical pathway involving the simultaneous double interaction/activation of the Lewis acid with the electron-rich aromatic nucleophile and the carbonyl substrate.[13]

Computational Details

All calculations were carried out using the tools available in the Gaussian 98[14] package on an SGI Origin 3800 multi-processor system, using the DFT/B3LYP functional (i.e., Becke's three-parameter hybrid functional with the Lee−Yang−Parr correlation functional)[15] in combination with a mixed basis set: a split-valence type plus polarization for all C and H atoms (i.e., 6-31G*) and a triple-ζ valence type plus polarization for Al(III) (i.e., 6-311G*), including diffuse functions for N and O atoms (i.e., 6-311+G*). Indeed, since the N and O lone pairs strongly interact with Al(III), the use of diffuse functions is fundamental for a correct description of these interactions.[16] According to the literature, the functional and basis set used have been shown to yield reasonable energetic and structural results for metal-complexes of this kind, either in a penta- or hexacoordination status, including salen complexes with Al(III) and transition metals such as Mn(III) and Cu(II).[16−18] Anyway, to further validate the computational level employed, we calibrated DFT results on a known (i.e., X-ray resolved) structure: the cationic hexacoordinate complex $(AlPy_4Cl_2)^+$.[19] Remarkably, computational results agree very well with the experimental data (the error bar in bond distances being lower than 0.05 Å, Scheme 1) and

SCHEME 1. Calibration Analysis for the Functional and Basis Set Used: Comparison between Simulated and X-ray-Resolved Structures for the Cationic Complex $(AlPy_4Cl_2)^+$



(8) Evans, D. A.; Scheidt, K. A.; Fandrick, K. R.; Lam, H. W.; Wu, J. *J. Am. Chem. Soc.* **2003**, *125*, 10780.

(9) Bandini, M.; Melloni, A.; Tommasi, A.; Umani-Ronchi, A. *Helv. Chim. Acta* **2003**, *86*, 3753.

(10) Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172.

(11) Bandini, M.; Fagioli, M.; Melchiorre, P.; Melloni, A.; Umani-Ronchi, A. *Tetrahedron Lett.* **2003**, *44*, 5843.

(12) Selected examples of [Al(salen)Cl]-catalyzed asymmetric organic transformations: (a) Myers, J. K.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 8959. (b) Evans, D. A.; Janey, J. M.; Magomedov, N.; Tedrow, J. S. *Angew. Chem., Int. Ed.* **2001**, *40*, 1884. (c) Jha, S. C.; Joshi, N. N. *Tetrahedron: Asymmetry* **2001**, *12*, 2463. (d) Sammins, G. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2003**, *125*, 4442. (e) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2003**, *125*, 11204. (f) Sammis, G. M.; Danjo, H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 9928. Chiral aluminum−Schiff base complexes have been fully characterized spectroscopically as well as crystallograpically: Atwood, D. A.; Harvey, M. J. *Chem. Rev.* **2001**, *101*, 37, and refs cited therein.

(13) Tarakeshwar, P.; Lee, J. Y.; Kim, K. S. *J. Phys. Chem. A* **1998**, *102*, 2253.

(14) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; 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.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.9; Gaussian, Inc.: Pittsburgh, PA, 1998.

(15) Becke, D. *J. Chem. Phys. A* **1993**, *98*, 5648.

(16) (a) Tunega, D.; Haberhauer, G.; Gerzabek, M.; Lischka, H. *J. Phys. Chem. A* **2000**, *104*, 6824. (b) Aquino, A. J. A.; Tunega, D.; Haberhauer, G.; Gerzabek, M.; Lischka, H. *Phys. Chem. Chem. Phys.* **2000**, *2*, 2845. (c) Aquino, A. J. A.; Tunega, D.; Haberhauer, G.; Gerzabek, M. H.; Lischka, H. *Phys. Chem. Chem. Phys.* **2001**, *3*, 1979.

(17) Cavallo, L.; Jacobsen, H. *Angew. Chem., Int. Ed.* **2000**, *39*, 589. (b) El-Bahraoui, J.; Wiest, O.; Feichtinger, D.; Plattner, D. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 2073. (c) Jacobsen, H.; Cavallo, L. *Chem.—Eur. J.* **2001**, *7*, 800.

(18) Thorhauge, J.; Roberson, M.; Hazell, R. G.; Jørgensen, K. A. *Chem.—Eur. J.* **2002**, *8*, 1888.

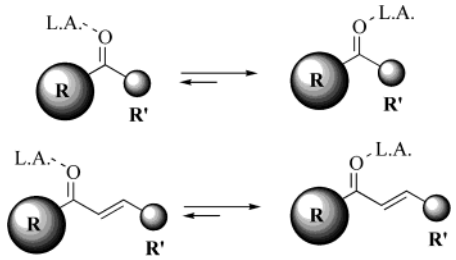
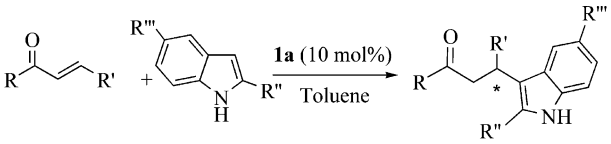


FIGURE 2. Pictorial representation of the dynamic coordination of chiral Lewis acids with carbonyls.

SCHEME 2. Enantioselectivity and Structure of the α,β-Unsaturated Ketone: A Narrow Dependence



2a: R=Me, R'=Ph **3a**: R"=Me, R'"=H
2b: R=Ph, R'=Ph **3b**: R"=H, R'"=OMe
2c: R=Ph, R'=Me **3c**: R"=H, R'"=H
2d: R=Me, R=Me

4aa: yield = 69%, ee = 11%
4ba: yield = 66%, ee = 32%
4ca: yield = 80%, ee = 55%
4da: yield = 61%, ee = 0%
4dc: yield = 43%, ee = 30%

with the X-ray crystallographic structures reported for similar [Al(salen)] complexes,[12b,20] thus proving the accuracy of these computations.

Both the two external salen *t*Bu-groups and the phenyl substituent of the ketone have been removed in the model system due to the computational cost. Finally, several conformers were optimized according to different orientations of the coordinating ligands (bases, carbonyls), but only the lowest energy minima have been shown here (a scan has been performed to unveil the stable conformations of the attacking base and enone).

Results and Discussion

In the field of our current studies focused on the development of new catalytic conjugate additions of indoles to enones,[4g−i,k,s] we recently described the stereoselective first version of this transformation as a means of [Al(salen)Cl] complex.[11] Stereoselective Lewis acid-catalyzed Michael additions to simple monodentate α,β-unsaturated carbonyl compounds are widely recognized to be challenging transformations, and a careful design of the structural characteristics of the electrophile must be done in order to guarantee high levels of stereoselection. Usually, suitable stereodiscrimination between the two enantiotopic faces of the ketone is obtained by adopting tailored structural motifs bearing markedly different sterically demanding substituents (R, R′) at the carbonyl moiety (Figure 2).

Taking these guidelines into account, our initial attempts toward the optimization of the reaction conditions were addressed into the comprehension/optimization of the above-mentioned sterical requirements. To this purpose, enones **2a**−**c**[21] were reacted at room temperature with 2-methylindole (**3a**) and **2d**[22] with indole **3c** in the presence of 10 mol % commercial [Al(salen)Cl] (**1a**) as the catalyst. The data collected in Scheme 2 clearly show that the highest chemical as well as optical yields were obtained with enone **2c** in which a sterically demanding aromatic group is bound to the carbonyl and a small aliphatic group (Me) is linked to the C−C double bond.

In this case, the desired β-indolyl ketone **4ca** was isolated in 80% yield and 55% enantiomeric excess. On the other hand, 4-phenyl-3-buten-2-one (**2a**), chalcone (**2b**), and 3-penten-2-one (**2d**) reacted with **3a** and **3c** (in the presence of [Al(salen)Cl], 10 mol %, toluene), giving rise to indolyl ketones **4** in moderate yields (43−69%) but with poor stereocontrol (up to 32%).

TABLE 1. Screening of Solvents for the Enantioselective Addition of 3a to 2c Catalyzed by [Al(Salen)Cl][a]

entry[a]	solvent	yield of **4ca** (%)[b]	ee of **4ca** (%)[c]
1	toluene	80	55
2	Et_2O	67	31
3	THF	20	5
4	CH_3CN	60	12
5	*n*-Hex/toluene (85:15)	95	22
6	CH_2Cl_2	95	31
7	toluene	88	31[d]

[a] All reactions were carried out at room temperature under a nitrogen atmosphere, employing 10 mol % [Al(salen)Cl] for a reaction time of 24 h. [b] Chemical yields are given on the isolated product after chromatographic purification. [c] Enantiomeric excesses were determined by HPLC analysis with chiral column (Chiralcel OD). [d] Reagent-grade toluene was utilized as the solvent.

A subsequent screening of solvents led us to establish toluene as the solvent of choice. As a matter of fact, when more polar media, namely, Et_2O, THF, and CH_3CN, were examined, **4ca** was isolated in lower enantioselectivity (Table 1, entries 2−4). Moreover, the decreased stereoinduction recorded with reagent-grade toluene (ee, 31%, entry 7) indicates that anhydrous conditions are necessary in order to achieve high enantiocontrols.

Our efforts to optimize the reaction conditions were also addressed to explore the effectiveness of other chiral Al-Schiff base complexes **1b**−**e** in promoting the addition of **3a** to **2c** (Figure 3). However, the commercially available [Al(salen)Cl] complex furnished the highest enantioselectivity.

For instance, while the di-*tert*-butyl-salen aluminum complex **1b** provided **4ca** in 90% and 39% ee, both Al-Schiff base complexes characterized by different chiral backbones (**1c**, **1e**) and a chiral ligand bearing sterically demanding adamantyl substituents (**1d**) promoted the reaction to some extent with no enantiocontrol.

In keeping with our mechanistic hypothesis in which the incoming indole reacts with the Lewis acid-activated/coordinated enone to give the aluminum enolate **5** as an intermediate,[23] we considered plausible the presence in

(19) Pullmann, P.; Hensen, K.; Bats, J. W. *Z. Naturforsch. B* **1982**, *37*, 1312.

(20) (a) Duxbury, J. P.; Warne, J. N. D.; Mushtaq, R.; Ward, C.; Thornton-Pett, M.; Jiang, M.; Greatrex, R.; Kee, T. P. *Organometallics* **2000**, *19*, 4445. (b) Atwood, D. A.; Jegier, J. A.; Rutherford, D. *Inorg. Chem.* **1996**, *35*, 63.

(21) Ketone **2c** was synthesized following the known procedure: Brown, C. D.; Chong, J. M.; Shen, L. *Tetrahedron* **1999**, *55*, 14233.

(22) Arisawa, M.; Torisawa, Y.; Kawahara, M.; Yamanaka, M.; Nishida, A.; Nakagawa, M. *J. Org. Chem.* **1997**, *62*, 4327.

(23) For examples of enolates of Al−porphyrin and Al−Schiff base complexes, see: (a) Kuroki, M.; Watanabe, T.; Aida, T.; Inoue, S. *J. Am. Chem. Soc.* **1991**, *113*, 5903. (b) Cameron, P. A.; Gibson, V. C.; Irvine, D. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 2141.

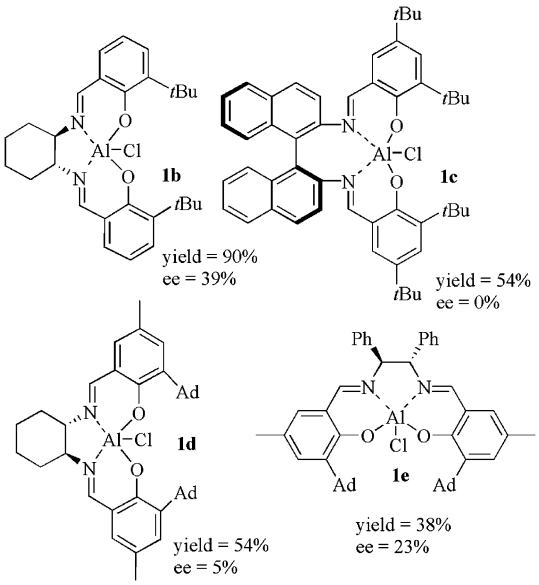
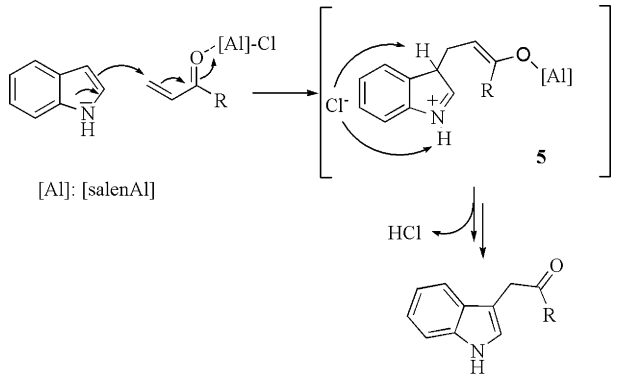


FIGURE 3. Screening of Al−Schiff base complexes in the FC alkylation of **3a**.

SCHEME 3. Hypothesis of Michael-Type Mechanism for the [Al(salen)Cl]-Catalyzed 1,4-Addition



solution of non-negligible amounts of hydrochloric acid that could promote the reaction through a nonstereoselective pathway (Scheme 3).

In light of these considerations, the effect of some base scavengers on the chemical and optical outcome of the 1,4-addition of **3a** to **2c** was taken into account. The results obtained, employing 10 mol % **1a** as the catalyst, are summarized in Table 2.

Compared to the base-free protocol (entry 1, Table 2), the use of 10 mol % base generally reduced the rate of the process but increased the enantioselectivity on the desired *β*-indolyl ketone **4ca**. Among all the additives screened, 2,6-lutidine (lut) was the base of choice, affording **4ca** in 65% yield and 79% ee (entry 5, Table 2). Interestingly, lowering the loading of catalyst to 5 mol % did not significantly affect either the chemical or optical outcomes of the Michael addition, but longer reaction times (72 h) were needed in order to reach comparable conversion (entry 7). In contrast, the highly sterically hindered 2,6-di-*tert*-butylpyridine (entry 8) and the heterofunctionalized 2-cyano-pyridine (entry 9) led to a surprising decrease in stereoselectivity. Such unexpected results and the remarkable correlation between

TABLE 2. Screening of Bases as Possible Additives for the [Al(Salen)Cl]-Catalyzed Conjugate Addition of Indole 3a to 2c

entry[a]	base (%)	yield of **4ca** (%)[b]	ee of **4ca** (%)[c]
1	none	80	55 (*R*)[d]
2	aniline (10)	70	71 (*R*)
3	pyridine (10)	54	76 (*R*)
4	Et_3N (10)	65	77 (*R*)
5	2,6-lut (10)	65	79 (*R*)
6	2,6-lut (10)	87[e]	77 (*R*)
7	2,6-lut (5)	67[f]	77 (*R*)
8	2,6-di*t*Bu-py (10)	59	29 (*R*)
9	2-CN pyridine (10)	87	25 (*R*)
10	Et_3N (100)	18	66 (*R*)
11	2,6-lut (50)	25	86 (*R*)

[a] All reactions were carried out in anhydrous toluene at room temperature for a reaction time of 48 h unless otherwise specified. [b] Isolated yield after flash chromatography. [c] Determined by chiral HPLC analysis with Chiralcel OD column. [d] Reaction time = 24 h. [e] Reaction was carried out using an excess of **2c** (1.5 equiv) with respect to **3a** (1 equiv). [f] Performed with 5 mol % [Al(salen)Cl] as the catalyst. Reaction time = 72 h.

the coordinating ability of the additive and the observed stereoselectivity prompted us to examine a plausible coordinating action of the base on the aluminum catalyst.[24] As a partial support of the latter hypothesis, we observed that the chiral Lewis acid−Brønsted base ratio significantly affects the outcome of the reaction. In fact, using an excess of base with respect to the organometallic catalyst (TEA 100%, lut 50%, entries 10−11) dramatically affected the turnover of the catalytic cycle (coordination poisoning of the catalyst), but high ees were still observed (66−86%).

The optimization of the reaction conditions was then followed by the study of the scope and generality of the protocol. To this aim, we investigated the reaction of a series of acyclic enones with **1a**/lut (10 mol %) in toluene at room temperature.[25]

The synthesis of the α,*β*-unsaturated aryl ketones was readily accomplished following known procedures. In particular, while enones **2e**−**j** were obtained by classic Friedel−Crafts acylation of the corresponding substituted aromatic compounds (Scheme 4a),[26a] ketones bearing strong electron-withdrawing substituents (**2l**−**m**) and ortho-substituted aryl groups (**2k**) were synthesized in three steps starting from the corresponding arylaldehyde in moderate overall yields (13−25%) under nonoptimized conditions (Scheme 4b).[26b]

Then, data collected in Table 3 show that α,*β*-unsaturated substrates bearing electron-withdrawing substituents on the aromatic ring (**2h**−**j**, **2l**, and **2m**) generally allowed the indolyl derivatives to be isolated in excellent chemical yields (90−98%) and good enantioselectivity.

In particular, pentafluoro derivative **2m** smoothly reacted with **3a**, providing **4ma** in 90% yield and 88% enantiomeric excess (entry 9, Table 3). Ketones **2e** and **2f** bearing electron-rich aromatic rings bound to the

(24) (a) Miller, J. A.; Jin, W.; Nguyen, S. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 2953. (b) Cozzi, P. G.; Dolci, L. S.; Garelli, A.; Montalti, M.; Prodi, L.; Zaccheroni, N. *New J. Chem.* **2003**, *27*, 692.

(25) Use of cyclic enones such as 2-cyclopenten-1-one and 2-cyclohexen-1-one furnished the desired indolyl derivatives only in traces.

(26) (a) Oare, D. A.; Henderson, M. A.; Sanner, M. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 132. (b) Toy, P. H.; Dhanabalasingam, B.; Newcomb, M.; Hanna, I. H.; Hollenberg, P. F. *J. Org. Chem.* **1997**, *62*, 9114.

SCHEME 4. Synthesis of α,β-Unsaturated Aryl Ketones

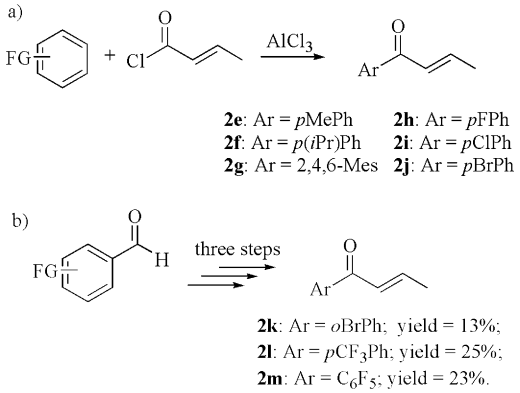


TABLE 3. Stereoselective Addition of 3a to (*E*)-Enones Catalyzed by [Al(Salen)Cl]/Lut Complex

entry[a]	enone	product	yield (%)[b]	ee (%)[c]
1	**2e**	**4ea**	80	73 (*R*)
2	**2f**	**4fa**	58	49 (*R*)
3	**2g**	**4ga**	nr[d]	
4	**2h**	**4ha**	96	78 (*R*)
5	**2i**	**4ia**	98	80 (*R*)
6	**2j**	**4ja**	92	78 (*R*)
7	**2k**	**4ka**	27	32 (*R*)
8	**2l**	**4la**	95	77 (*R*)
9	**2m**	**4ma**	90	88 (*R*)

[a] All reactions were carried out at room temperature, employing 10 mol % [Al(salen)Cl] and 10 mol % lutidine for a reaction time of 48 h. [b] Chemical yields are given for the isolated product after chromatographic purification. [c] Enantiomeric excesses were determined by HPLC analysis with chiral column (Chiralcel OD). Absolute configuration of adducts **4** was assigned as *R* by analogy (elution times of the HPLC analysis and optical rotation) to **2ca**. [d] No reaction.

carbonyl moiety showed lower reactivity under the present reaction conditions, affording **4ea** and **4fa** in 73 and 49% enantiomeric excess, respectively. On the other hand, bulky mesitylcrotyl ketone **2g** and *o*Br-phenyl derivative **2k** were not found to be suitable substrates for the alkylation of 2-methylindole probably due to the obstructed coordination of the carbonyl with the chiral aluminum catalyst (entries 3, 7).

The effect of the temperature on the efficiency of **1a**/lut to catalyze this stereoselective FC-type protocol was further examined. To this purpose, more reactive α,β-unsaturated ketones were reacted with **3a** at different temperatures, and the results obtained are reported in Table 4 (entries 1−4).

In all cases, the enones **2** underwent the FC process in good yield and moderate to good enantioselectivity. For instance, ketone **2i** smoothly reacted with **3a** at −20 °C, furnishing the corresponding 1,4-adduct **4ia** in 89% ee and 68% yield after 96 h (entry 3). Analogous results were obtained with **2c**, **2h**, and **2j** at temperatures ranging from −15 to 0 °C. The capacity of complex **1a**/lut to effectively promote the conjugate addition of various indoles to aryl enones was further evaluated by reacting 5-methoxyindole **3b** and indole **3c** at room temperature with carbonyls **2c**, **2j**, and **2m** (entries 5−7, Table 4). In these cases, the desired 1,4-adducts were isolated in satisfactory yields and slightly lower enantiomeric excess (64%); however, by using 20 mol % catalyst in the reaction between **2m** and **3c**, the indolyl derivative **4mc** was isolated in 67% yield and 80% ee (entry 8).

TABLE 4. Stereoselective Addition of Indoles to (*E*)-Enones Catalyzed by [Al(Salen)Cl]/Lut Complex[a]

entry	*T* (°C)	enone	indole	product	yield (%)[b]	ee (%)[c]
1	10	**2c**	**3a**	**4ca**	48	84 (*R*)
2	0	**2h**	**3a**	**4ha**	25	82 (*R*)
3	−20	**2i**	**3a**	**4ia**	68	89 (*R*)[d]
4	−15	**2j**	**3a**	**4ja**	78	84 (*R*)
5	rt	**2c**	**3b**	**4cb**	35	64
6	rt	**2c**	**3c**	**4cc**	41	64
7	rt	**2j**	**3b**	**4jb**	72	64
8	rt	**2m**	**3c**	**4mc**	67	80[e] (*R*)

[a] All reactions were carried out employing 10 mol % [Al(salen)-Cl] and 10 mol % lutidine for a reaction time of 48 h unless otherwise specified. [b] Chemical yields are given for the isolated product after chromatographic purification. [c] Enantiomeric excesses were determined by HPLC analysis with chiral column (Chiralcel OD). [d] Reaction time = 96 h. [e] Reaction was carried out by using 20 mol % catalyst.

Mechanistic Considerations. In an effort to ascertain the precise role of the basic additive in the reaction course, ^{1}H NMR spectra of an equimolar solution of **1a** and base (i.e., Et_3N, lut) were collected. Such an analysis confirmed that a rapid and quantitative complexation occurred when the additive and the aluminum complex were dissolved in CD_2Cl_2 at room temperature. In particular, the signals of the free Al-Schiff base complex disappeared to give new sets of signals representative for the formation of a new Al-base species. For the case of Et_3N, a comparison of some diagnostic signals of **1a** (Figure 4a) and **1a**·Et_3N (in brackets, Figure 4b) is as follows: δ 8.34[7.80] (CH=N), 7.58[7.41] (Ar), 7.18[7.03] (Ar).

To validate this hypothesis, we recorded the ^{1}H NMR spectra in the presence of sterically demanding and noncoordinating 2,6-di*t*Bu-py, and in this case, no significant base−aluminum interaction was observed. On the other hand, the spectra recorded when lutidine was added to a solution of **1a** in CD_2Cl_2 appeared to be fluxional and more difficult to interpret, indicating that some complex equilibria are taking place in solution.

Then, further insight into the postulated mechanism and into the key structures involved in the reactive process was obtained by carrying out accurate, unconstrained optimizations at a fully correlated level (DFT) on a realistic model for the [Al(salen)]-catalyst/coordinating-additive/substrate-enone system. The optimized lowest energy minima likely involved in the key steps of the present asymmetric catalysis are shown in Figure 5 (the higher energy conformers are not shown here).

Interestingly, while the model carbonyl substrate (3-methyl-acrolein) and additive-base model used (trimethylamine, TMA) generate stable cationic pentacoordinate [Al(salen)] complexes **6a**,**b**, the corresponding neutral (i.e., chloride-bound) hexacoordinate systems are unstable, in agreement with the relative ease of displacing chloride groups, as observed in similar [Al(salen)] complexes.[12b,20] On the other hand, when a coordinating base (TMA) is used together with the enone, a very stable cationic hexacoordinate complex **6c** can be formed (where the enone and the base are both bound to Al according to a trans arrangement). This system could be considered the hypothetical starting point for the reaction with

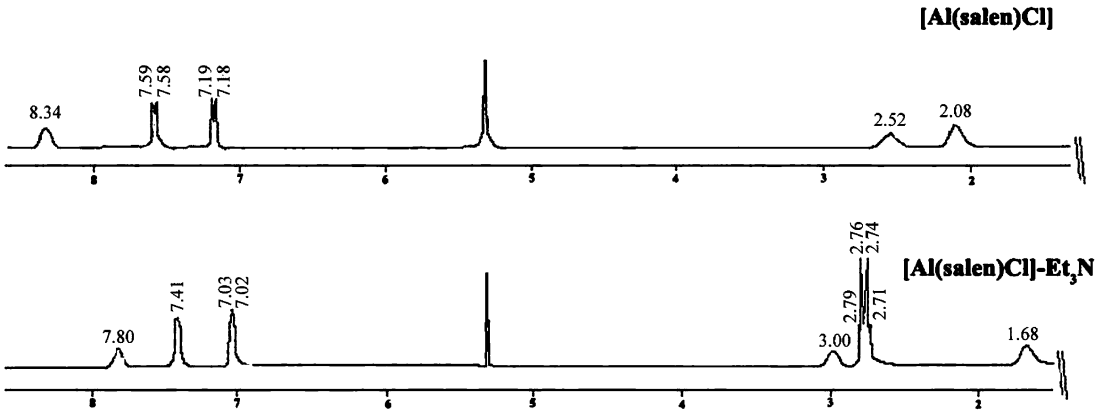


FIGURE 4. (a) ^{1}H NMR spectra of commercial [Al(salen)Cl] (CD_2Cl_2, rt). (b) ^{1}H NMR spectra recorded after the addition of TEA (1:1 ratio) (CD_2Cl_2, rt).

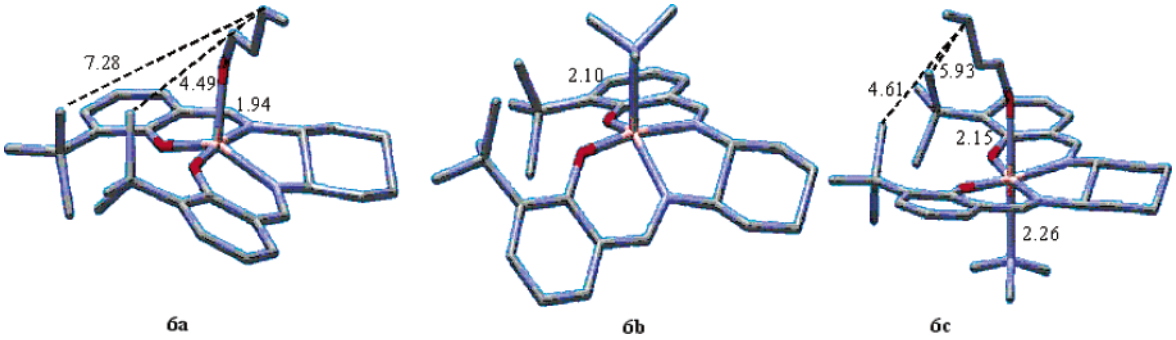


FIGURE 5. Structure of the calculated cationic pentacoordinate (**6a** and **6b**) and hexacoordinate (**6c**) [Al(salen)] complexes with the enone alone (**6a**), the coordinating base alone (**6b**), and the enone plus the bases (TMA: **6c**). Hydrogen atoms have been removed for clarity. The dissociated chloride counteranion is not illustrated here. Distances and angles are in Å and degrees, respectively.

indole. Remarkably, a significant thermodynamic driving force exists for nonsterically congested (i.e., coordinating) bases, which pushes the [Al(salen)]-catalyst/coordinating-base/substrate-enone system toward the cationic trans hexacoordinate complex. Indeed, this is the lowest energy minimum optimized so far, the relative energies for the three optimized structures **6c**, **6a**, **6b** being 0.0, 7.8, and 12.0 kcal/mol, respectively. On the contrary, with a sterically congested base (i.e., noncoordinating, such as 2,6-di*t*Bu-py), no stable hexacoordinate complexes are formed in solution (consistent with ^{1}H NMR spectra, no stable hexacoordinate complexes could be located using 2,6-di*t*Bu-py). Moreover, by means of lutidine as a coordinating base (which is sterically more congested than Me_3N, although not as much as 2,6-di*t*Bu-py), a significantly longer Al−N bond is computed, revealing a slightly bound complex and a possible equilibrium between bound and unbound forms, in agreement with the recorded ^{1}H NMR spectra (fluxional set of signals were recorded at room temperature in CD_2Cl_2).

As previously described for Mn−salen complexes,[17] and also in the case of Al-Schiff systems, the presence of an axial ligand profoundly affects the overall conformation of the salen ligand. In fact, while the minimized structures of the pentacoordinate Al-complexes (**6a**,**b**) showed the typical steplike conformation, the simultaneous presence of a carbonyl compound as well as a base trans-coordinated to the aluminum center (cationic hexacoordinate species) evidenced a cup-shaped conformation (**6c**). Although the mechanism for the reaction is not unveiled here, these results still agree with the available observations (i.e., NMR analysis and base-coordinating-activity/enantioselectivity correlation). In particular, the overall conformation change of the hexacoordinate catalytic species led the α,*β*-unsaturated compound to closer vicinity at the *t*Bu-groups, favoring better stereodiscrimination during the indole attack at the less shielded enantiotopic face of the activated electrophile.

In the FC reactions, the role of Lewis acids is generally limited to the formation of highly reactive electrophiles that subsequently react with the aromatic compound. However, recent experimental[27] as well as theoretical[13] studies proved that the Lewis acid can play an additional role in the reaction course by interacting also with the aromatic compound, significantly increasing its nucleophilicity. In this context, of particular relevance is the colorimetric observation reported by Ottoni and coworkers in the Lewis acid ($AlCl_3$, $TiCl_4$, $SnCl_4$)-mediated FC acylation of indoles. In this case, the formation of a highly reactive indolyl-metal species was supposed to be the real nuclophile of the FC process. To shed some light on the operative role of [Al(salen)Cl] (**1a**) in the catalytic cycle of the present FC-type alkylation of indoles, we carried out a kinetic study investigating the dependence of the reaction rate on the concentration of **1a**. The initial

(27) Ottoni, O.; Neder, A. de V. F.; Dias, A. K. B.; Cruz, R. P. A.; Aquino, L. B. *Org. Lett.* **2001**, *3*, 1005.

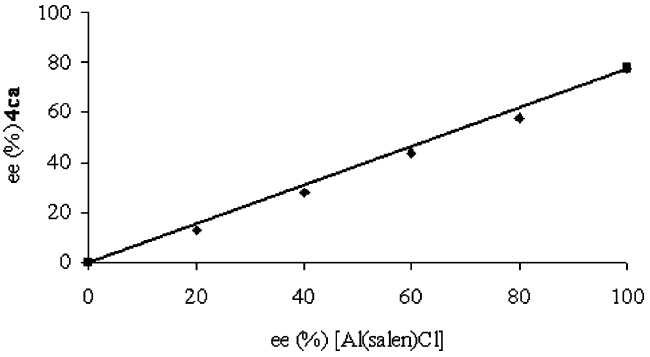


FIGURE 6. NLE curve of the [Al(salen)Cl] catalyzed Michael addition of indoles to arylenones.

reaction rates of the addition of 2-methylindole to the model ketone **3c**, calculated at different concentrations $[C]_0$ of [Al(salen)Cl] complex, were measured following each run from 8% completion to 18−25% conversion, and all the conjugate additions were monitored up to at least 75% conversion. From the trends of the curves recorded at different catalyst concentrations (7.5−22.5 mM, see Supporting Information), it appears that the rate of FC reaction was strongly affected by the total [Al(salen)Cl] concentration. The reaction order with respect to the catalyst was obtained by plotting log[rate] versus $\log[C]_0$.

The first-order dependence of the reaction rate on the concentration of **1a** clearly suggested that, in the rate-determining step of the catalytic cycle (nucleophilic addition of the indole to the β-position of the enone), a single molecule of [Al(salen)Cl] complex is involved, acting as the activator of the carbonyl substrate. This finding ruled out the possible double role played by the catalyst, that could operate as a concomitant electrophilic/nucleophilic activator. More evidence on the real role of the aluminum catalyst in the reaction course came from studies concerning the NLE of the enantioselective conjugate addition of **3a** with **2c** in the presence of **1a**-lut (10 mol %) as the catalyst system.[28] In fact, the dependence of the enantiomeric excess (ee) of the product (**4ca**) on the optical purity of the catalyst (**1a**) was examined and reported in Figure 6.

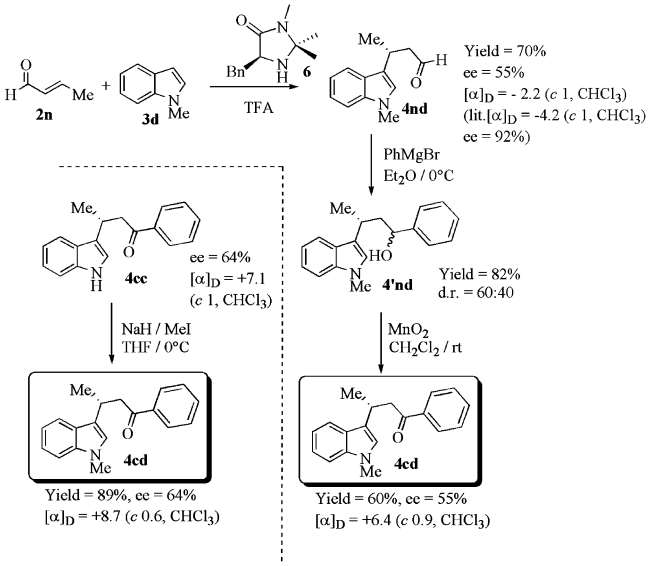
The absence of NLE in our process allows us to speculate that a single molecule of catalyst is involved in the stereochemistry-determining step of the reaction pathway, supporting the single activation effect previously proposed.

Finally, the stability of the active catalytic species during the entire reaction course of the stereoselective addition of **3a** to **2c** was confirmed by monitoring the enantiomeric excess of periodic aliquots of the reaction mixture by HPLC analysis with chiral OD column. In fact, the level of stereoinduction was found to be nearly constant at about 76−79% (see Supporting Information).

Absolute Configuration Assignment. In efforts to establish the absolute configuration of the 1,4-adducts **4**, we undertook a chemical correlation between the 1-phenyl-3-(*1H*-indol-3-yl)-butane-1-one **4 cc**[3] (ee = 64%, $[\alpha]_D = +7.4$, *c* 1 $CHCl_3$, Table 4, entry 6) and the known (*R*)-3-(*N*-methyl-indol-3-yl)-butyraldehyde (**4nd**).

(28) Girard, C.; Kagan, H. B. *Angew. Chem., Int. Ed.* **1998**, *37*, 2922.

SCHEME 5. Absolute Configuration Assignment for 4cc



To this purpose, by the asymmetric organo-catalyzed FC alkylation reaction of indoles described by MacMillan and co-workers,[10] we first synthesized the (*R*)-β-indolyl aldehyde **4nd** in 70% yield and 55% enantiomeric excess by reacting *N*-Me-indole (**3d**) with (*E*)-crotonaldehyde **2n** in the presence of imidazolidinone **6** and TFA (20 mol %, Scheme 5).

Then, **4nd** was easily converted into the corresponding indolyl alcohol (**4nd**, yield 82%) as a diasteoisomeric mixture (60:40) by reaction with PhMgBr in Et_2O at 0 °C. Finally, the unresolved diastereomeric mixture was converted to (*R*)-**4cd** by oxidation with MnO_2, in CH_2Cl_2 (yield 60%, ee 55%). Comparison of both the optical rotation value and chiral HPLC retention times with **4cd** (obtained by *N*H-methylation of **4cc**) proved *R* to be the absolute configuration of the 1,4-adduct **4cc**. The absolute configuration of the indolyl ketones **4** was assigned by analogy.

Conclusion

In summary, we have developed a novel, effective catalytic Friedel−Crafts-type alkylation of indoles through 1,4-addition to aryl ketones in the presence of [Al(salen)-Cl] (10 mol %). The optical outcome of the process can be significantly increased by adding a catalytic amount of coordinating base. Theoretical as well as spectroscopic evidence suggests that an interaction between the additive and the aluminum center is involved, leading to new highly stereoselective chiral catalysts. Particular attention has been devoted to the generality of the process that guarantees the synthesis of a range of β-indolyl ketones in excellent yields and good enantiomeric excesses. Computational evidence allows formulation of a mechanistic hypothesis that is in agreement with the experimental observations and NMR data. In particular, a stable cationic hexacoordinate complex, formed by [Al(salen)] with the substrate and the additive base (in a trans configuration), has been computed and suggested as being responsible for the enhanced enantioselectivity.

Studies concerning the effectiveness of this [Al]·base system in new Lewis acid-catalyzed transformations are currently under way.

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Supporting Information Available: Experimental procedures and analytical and spectral characterization data for all the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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