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Catalytic enantioselective conjugate addition of indoles to simple α,β-unsaturated ketones

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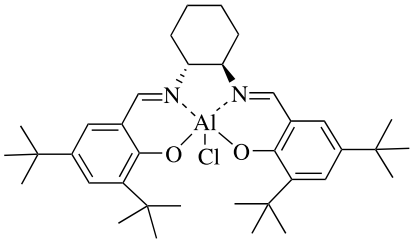
Abstract—Chiral [Al(salen)Cl] complex (10 mol%) in the presence of 2,6-lutidine (10 mol%) was found to be effective in catalysing the enantioselective Friedel–Crafts-type conjugate addition of indoles (**3**) to (*E*)-arylcrotyl ketones (**2**), furnishing the corresponding β-indolyl ketones in excellent yield and high enantioselectivity (ee up to 89%).

The catalytic asymmetric alkylation of aromatic and heteroaromatic compounds is a valuable method for the synthesis of highly functionalised enantiomerically enriched molecules. Since the pioneering study published by Casnati and Casiraghi on the enantioselective *ortho*-hydroxy alkylation of phenol with aldehydes,[1] many efforts have been devoted to the exploitation of new catalytic stereocontrolled Friedel–Crafts procedures.[2] Of particular relevance are the asymmetric 1,2-additions and 1,4-additions of electron-rich aromatic compounds to carbonyls mediated by chiral Lewis acids (by homogeneous[3] as well as heterogeneous catalysis[4]) and by optically active organic catalysts.[5]

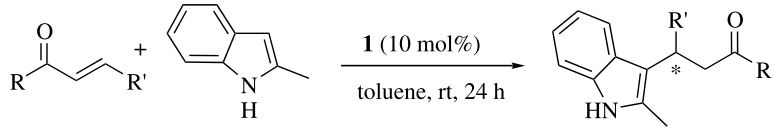


(*R,R*)-[Al(salen)Cl] **1**

Figure 1.

Despite numerous and significant advances in this field, the asymmetric catalytic Friedel–Crafts-type conjugate addition of aromatic compounds to simple α,β-unsaturated ketones still represents a considerable synthetic challenge. In fact, the steric similarity of the two carbonyl substituents renders the stereodifferentiation of the two faces of the unsaturated ketones a difficult task. As a continuation of our previous study on the $InBr_3$ catalysed addition of indoles to enones,[6] we now describe the first stereoselective version of this process employing the commercially available chiral (*R,R*)-[Al(salen)Cl] complex (Fig. 1, **1**) as the catalyst.[7]

Our initial attempts were carried out using (*E*)-enones **2a–c** and 2-methylindole (**3a**) in the presence of 10 mol% of **1** in toluene at room temperature. The data



2a: R=Me, R'=Ph
2b: R=Ph, R'=Ph
2c: R=Ph, R'=Me

3a

4aa: y = 69%, *ee* = 11%
4ba: y = 66%, *ee* = 32%
4ca: y = 80%, *ee* = 55%

Scheme 1. Asymmetric conjugate addition reaction catalysed by [Al(salen)Cl] (**1**).

Keywords: aluminium; asymmetric catalysis; indole; ketones; Michael reaction.
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Table 1. Screening of amines as possible additives for the [Al(salen)Cl] catalysed conjugate addition of indole **3a** (1.5 equiv.) to **2c** (1 equiv.)[a]

Entry	Additive (%)	*t* (h)	**4ca** (%)[b]	Ee (%)[c]
1	None	24	80	55 (*R*)
2	Aniline (10)	48	70	71 (*R*)
3	Pyridine (10)	48	54	76 (*R*)
4	Et_3N (10)	48	65	77 (*R*)
5	2,6-Lutidine (10)	48	65	79 (*R*)
6	2,6-di*t*Bu-pyridine (10)	48	59	29 (*R*)

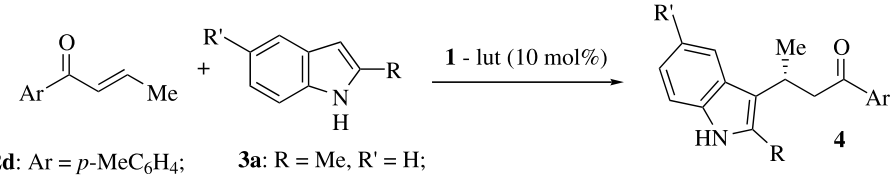
[a] All the reactions were carried out in anhydrous toluene at room temperature.
[b] Isolated yield after flash chromatography.
[c] Determined by chiral HPLC analysis with Chiralcel OD column.

reported in Scheme 1 show that the highest enantioselectivity was achieved when an aromatic group in the ketone's skeleton is bound to the carbonyl moiety, and a small aliphatic group R′ is linked to the C–C double bond (**2c**).[8] In the latter case, the β-indolyl ketone was isolated in 80% yield and 55% ee.

A considerable increase of stereoselectivity of the process was achieved by using aluminium-coordinating amines in catalytic amount.[9] In Table 1, we summarise the chemical and optical outcomes of the 1-4 addition of **3a** to **2c** employing 10 mol% of **1** in the presence of a range of amines. The use of 10 mol%[10] of additive generally reduced the rate of the process. However, the stereoselection significantly increased up to 79% ee when 2,6-dimethylpyridine (2,6-lutidine, lut) was utilised (yield 65%, entry 5).[11] On the contrary, by adding the sterically congested 2,6-di*t*butylpyridine (2,6-di*t*Bu-py) a significant drop in stereoinduction was observed (ee = 29% entry 6, Table 1).

The key role of the amines could be rationalised by assuming their coordination on the aluminium centre of **1** leading to a new catalytic species [Al(salen)Cl]/amine. In this context, ^1H NMR studies of equimolar solutions of [Al(salen)Cl] and amine (i.e. Et_3N or lut, dry CD_2Cl_2, rt) confirmed a quantitative complexation between additive and aluminium complex **1**,[12] while analogous experiments carried out in the presence of 2,6-di*t*Bu-py did not show any significant base–aluminium interaction.

Table 2. Stereoselective addition of indoles to (*E*)-enones catalysed by [Al(salen)Cl]/lut complex[a]



2d: Ar = *p*-MeC_6H_4;
2e: Ar = *p*-*i*PrC_6H_4;
2f: Ar = *p*-FC_6H_4;
2g: Ar = *p*-ClC_6H_4;
2h: Ar = *p*-BrC_6H_4;
2i: Ar = C_6F_5;
2j: Ar = *p*-$CF_3C_6H_4$

3a: R = Me, R' = H;
3b: R = R' = H;
3c: R = H, R' = OMe;

Entry	Enone	Indole	Product	Yield (%)[b]	Ee (%)[c]
1	**2c**	**3a**	**4ca**	48[d]	84 (*R*)
2	**2c**	**3b**	**4cb**	35	64 (*R*)
3	**2c**	**3c**	**4cc**	41	65 (*R*)
4	**2d**	**3a**	**4da**	80	73 (*R*)
5	**2e**	**3a**	**4ea**	58	49 (*R*)
6	**2f**	**3a**	**4fa**	96	78 (*R*)
7	**2g**	**3a**	**4ga**	98	80 (*R*)
8	**2g**	**3a**	**4ga**	68[e]	89 (*R*)
9	**2h**	**3a**	**4ha**	92	78 (*R*)
10	**2h**	**3a**	**4ha**	78[f]	86 (*R*)
11	**2i**	**3a**	**4ia**	90	88 (*R*)
12	**2i**	**3b**	**4ib**	67	80 (*R*)[g]
13	**2j**	**3a**	**4ja**	95	77 (*R*)

[a] All the reactions were carried out in anhydrous toluene at room temperature for 48 h unless otherwise specified.
[b] Isolated yield after flash chromatography.
[c] Determined by chiral HPLC analysis with Chiralcel OD column. The absolute configuration was assigned *R* by assuming, for all the indoles tested, the same spatial stereodifferentiation induced by (*R*,*R*)-**1** (Fig. 3).
[d] The reaction was carried out at 0°C (72 h reaction time).
[e] The reaction was carried out at −15°C (96 h reaction time).
[f] The reaction was carried out at −20°C (72 h reaction time).
[g] The reaction was carried out in the presence of 20 mol% of catalytic system.

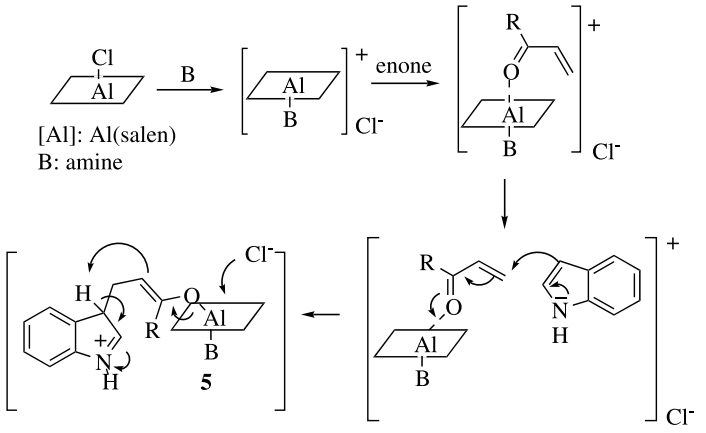


Figure 2. Mechanism hypothesis for the [Al(salen)Cl]/amine catalysed 1,4-addition.

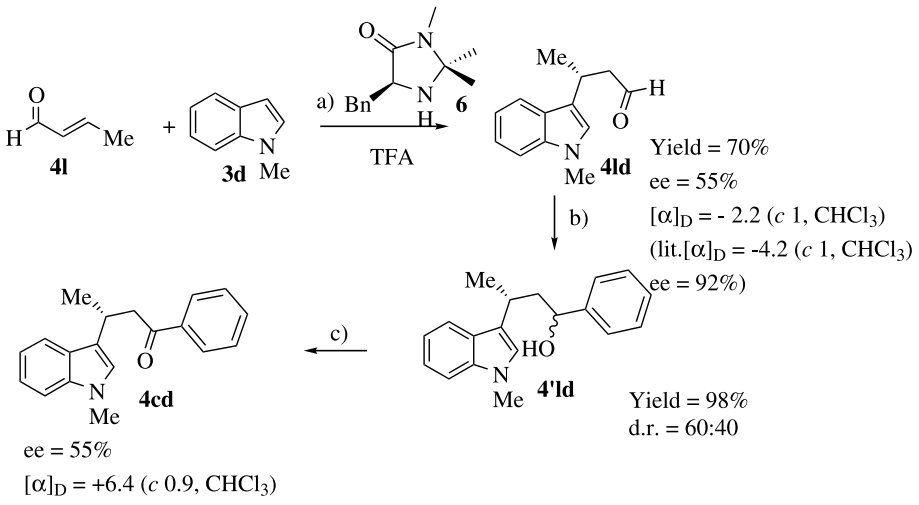


Figure 3. (a) **5**/TFA (20 mol%), H_2O/*i*PrOH, −30°C. (b) PhMgBr/Et_2O/0°C. (c) MnO_2/CH_2Cl_2/rt.

To prove the generality of the method, a range of (*E*)-arylcrotyl ketones (**2d–j**, 1 equiv.) was synthesised[13] and reacted with indoles **3a–c** (1.5 equiv.) in the presence of 10 mol% of the complex **1**/lut prepared in situ (Table 2). The protocol furnished excellent chemical yields and high ee's with α,β-unsaturated ketones bearing electron poor aromatic rings (**2f–j**). In these cases, in fact, the enantioselectivity was good-ranging from 77 to 89%.

Although the mechanistic details of the present reaction are still under investigation, a working model involving a crucial stereocontrolled formation of an intermediate octahedral Schiff base–aluminium enolate **5** can be supposed (Fig. 2).[14]

The absolute configuration of the adduct **4cb** [ee = 64%, $[\alpha]_D = +7.4$ (*c* 1 $CHCl_3$), Table 2, entry 2] was assigned *R* by comparison of both optical rotation value and chiral HPLC retention times of the compound **4cd** (obtained by *N*H-methylation of **4cb**) with the same adduct synthesised in three steps starting from the enantioselective organocatalytic FC alkylation of **3d** with (*E*)-crotonaldehyde **4l** using the MacMillan's imidazolidinone **6** (Fig. 3).[15] The (*R*)-indolyl aldehyde **4ld** (ee = 55%) was then reacted with PhMgBr in Et_2O at 0°C to obtain **4′ld** in 98% yield and 60:40 diastereoisomeric ratio. Finally, the desired ketone (*R*)-**4cd** was easily synthesised by oxidation of **4′ld** with MnO_2 [ee = 55%, $[\alpha]_D = +6.4$ (*c* = 0.9 $CHCl_3$)].

In summary, this study demonstrates the effectiveness of chiral [Al(salen)Cl]/amine complexes as catalysts for the enantioselective Friedel–Crafts-type conjugate addition of indoles to (*E*)-arylcrotyl ketones. This simple process provides easy access to a large library of highly functionalised β-indolyl ketones possessing a stereocentre in the β-position in excellent yields and high enantiomeric excesses. Studies addressed towards the comprehension of the reaction mechanism are currently under investigation.

Typical experimental procedure: [Al(salen)Cl] (18 mg, 0.03 mmol) and 2,6-lutidine (3.5 μL, 0.03 mmol) were added to anhydrous toluene (1 mL) and the mixture was stirred for about 5 min at room temperature, then **2g** (54 mg, 0.3 mmol) was added to the solution followed by **3a** (59 mg, 0.45 mmol). During the reaction

the colour of the solution turned red–orange. After 48 h stirring, the reaction was quenched with a saturated solution of $NaHCO_3$ (5 mL), the two layers were separated and the aqueous phase was extracted with Et_2O (3×5 mL). Finally, the collected organic phases were dried over Na_2SO_4 and concentrated under reduced pressure to give a pale orange oil, which was then purified by flash chromatography (silica gel, cyclohexane/Et_2O 85/15, R_f=0.3). The (*R*)-**4ga** was isolated as a pale yellow viscous oil (92 mg, 98% yield) in 80% ee. Chiral analysis was carried out by HPLC (Chiralcel OD *i*PrOH/hexane (20:80), flow rate 0.7 mL min^{-1}, 225 nm; t_r-(*S*)=11.44 min, t_r-(*R*)=15.11 min); $[\alpha]_D=-54$ (*c* 0.98 in $CHCl_3$). Analytical data for **4ga**: IR (Nujol) ν=3398, 3055, 2963, 1695, 1587, 1456, 1091 cm^{-1}; MS (70 eV): *m*/*z* (%): 311 (20) [M^+], 281 (18), 253 (10), 207 (82), 191 (15), 158 (100), 139 (22), 130 (18), 111 (12), 75 (9); ^{1}H NMR (200 MHz, $CDCl_3$, 25°C, TMS): δ=8.4 (br, 1H), 7.77–7.81 (m, 2H), 7.65–7.69 (m, 1H), 7.23–7.36 (m, 4H), 7.06–7.14 (m, 2H), 3.73 (q, *J*=7.0 Hz, 1H), 3.43–3.55 (m, 1H), 3.30 (dd, *J*=7.0 Hz, *J*=16.2 Hz, 1H), 2.38 (s, 3H), 1.50 (d, *J*=7.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C, TMS): δ=198.86, 160.19, 139.10, 135.47, 130.36, 129.37, 128.63, 120.63, 118.91, 118.87, 115.10, 110.53, 45.50, 27.43, 21.02, 11.88.

Acknowledgements

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11. It is also notable that by using an excess of enone **2c** (1.5 equiv.) with respect to the indole **3a** (1 equiv.), **4ca** was obtained with a comparable enantiomeric excess (77%) but with a significantly higher yield (87%).
12. Comparison of diagnostic ^{1}H NMR signals of commercial **1** and **1**·Et_3N in brackets (CD_2Cl_2, rt, 300 MHz): 8.34[7.80] (2H, CH=N), 7.58[7.41] (2H, Ar), 7.18[7.03] (2H, Ar).
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