# A practical synthetic route to functionalized THBCs and oxygenated analogues *via* intramolecular Friedel–Crafts reactions†

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A practical catalytic approach to the synthesis of 4-substituted 1,2,3,4-tetrahydro-β-carbolines (THBCs, **1**) and 1,2,3,9-tetrahydropyrano[3,4-*b*]indoles (**2**) *via* $InBr_3$-catalyzed intramolecular Friedel–Crafts (F–C) cyclization is described. The use of cross-metathesis reaction represents a direct route to the cyclization precursors and the use of $InBr_3$ (5 mol%) allowed polycyclic indole compounds to be isolated in high yields under mild reaction conditions (rt, DCM, minutes). Finally, efforts toward the development of a stereocontrolled version of the present cyclization are presented, highlighting [salenAlCl] and bimetallic [$(salenAlCl)_2$–$InBr_3$] system as promising chiral Lewis acids (ee up to 60%).

The indole core is embedded in countless natural products showing potent agrochemical and pharmacological activities.[1] Among this plethora of compounds, polycyclic chiral and achiral systems are characterized by wide occurrence and primary roles in natural products, and continue to inspire synthetic chemists in developing practical, effective and environmentally benign protocols for their preparation.[2] In this regard, polyfunctionalized 1,2,3,4-tetrahydro-β-carbolines (THBCs, **1**),[3] 1,2,3,9-tetrahydropyrano-[3,4-*b*]indoles (**2**)[4] and more complex cyclic systems, embody L-tryptophan as well as tryptamine motifs, proven to possess a wide diversity of important medicinal activities such as anti-tumoral and[5] cardiovascular effects,[6] and as treatments for allergic rhinitis and asthma.[7] As a result, considerable efforts have been devoted toward the development of new, efficient intramolecular alkylations of indoles *via* activated as well as inactivated olefins.[8,9] The most famous synthetic approach for the construction of the **1**-type polycyclic systems is represented by the Pictet–Spengler (P–S) reaction (path a, Fig. 1).[10]

This biosynthetic protocol, initially documented as a valuable route to the synthesis of tetrahydroisoquinolines, was also successfully applied to THBCs by condensing various functionalized tryptamines and carbonylic compounds under acidic (Brønsted or Lewis) conditions. However, some intrinsic limitations of P–S procedures, namely the requirement of harsh conditions and a restricted applicability to the synthesis of biologically active 4-substituted-THBCs (in this case time-demanding protocols for the preparation of β-substituted tryptamine precursors are needed), call for the development of new and milder complementary protocols for the synthesis of polycyclic indole compounds. Synthetic alternatives to the P–S reaction have been recently proposed by us[11] and other groups,[12] (path b) involving a rational intramolecular alkylation of indoles at the C-3 position.

As a part of our research area addressed to the catalytic Friedel–Crafts-type (F–C)[13] functionalization of indoles,[14] we recently reported on the effectiveness of $InBr_3$ as a Lewis acid in promoting intramolecular F–C-type Michael conjugate addition of indole to enones.[15] Such a protocol allowed racemic 4-functionalized THBCs and oxygenated analogues **2** to be isolated in excellent yields under mild conditions (low catalyst loading, aqueous media).

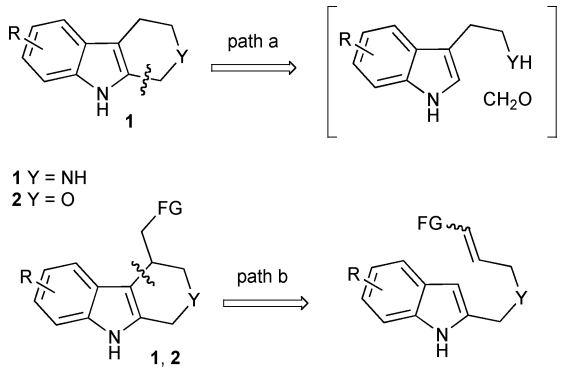


**Fig. 1** Comparison of the P–S approach (path a) and intramolecular F–C-type alkylation (path b) for the synthesis of polycyclic indole-containing compounds.

In the present contribution, we will document a full account of this investigation by updating and shortening the synthetic protocol for the polycyclic precursors **8**/**12**. Then, a stereocontrolled version of the present cyclization by using [salenAlCl] and unprecedented bimetallic [$(salenAlCl)_2$–$InBr_3$] will be presented.

## Results and discussion

### Multi-step synthesis optimization

**THBC precursors.** In order to develop a practical catalytic protocol for the construction of large libraries of polycyclic compounds, we firstly pointed our attention toward an optimal synthetic sequence for the corresponding precursors.

Consequently, although our previously reported syntheses of indolyl enones **5** proved to be general in scope (Scheme 1a), they showed some limitations in applicability. In particular, the subsequent double oxidative steps followed by the Wittig

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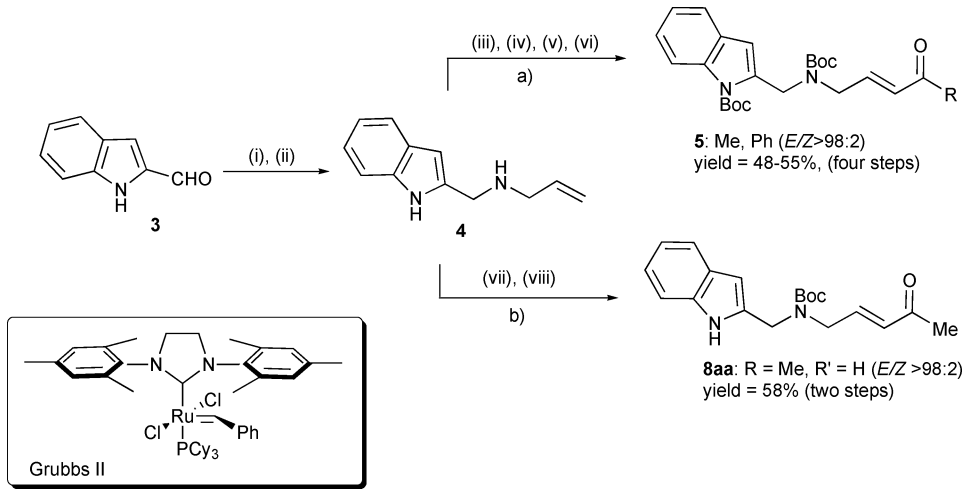



**Scheme 1** CM reaction as an alternative to the three-steps synthesis of THBC precursors. Reagents and conditions: (i) allyl amine, $MgSO_4$, DCM; (ii) $NaBH_4$, MeOH; (iii) $(Boc)_2O$ (3 eq.), TEA, DCM; (iv) $K_2Os_2O_2(OH)_4$, DABCO, $K_3Fe(CN)_6$, $K_2CO_3$; (v) $NaIO_4$, $SiO_2$, DCM; (vi) $RCOCH{=}PPh_3$, toluene; (vii) $(Boc)_2O$ (1.0 eq.), TEA, DCM; (viii) **7a**, Grubbs' II, DCM, 40 °C.

reaction (**4** → **5**) suffered from poor reproducibility, involving scarcely-stable indolyl aldehydes to be handled and requiring time-consuming purification procedures.

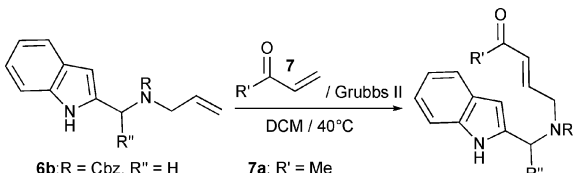
To overcome some of these obstacles and to speed up the entire process, we considered the olefin cross-metathesis (CM) reaction as a markedly shorter synthetic route.[16] In particular, CM between mono-protected indole **6**[17] and terminal α,β-unsaturated ketones would provide directly indolyl enones type **8**. In fact, despite the low tendency of α,β-unsaturated ketones to take part in metathesis coupling, the use of electron-deficient C=C double bonds in metallocarbene promoted cross-metathesis has been already fully documented.[18] Among all the catalysts tested, the use of a ruthenium–carbene complex, bearing the 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene ligand (Grubbs' II generation catalyst), yielded **8aa** in a stereochemically defined manner ($E : Z > 50 : 1$, 65% isolated yield), and without the need for protection of the NH group (Scheme 1b). Here, a range of polycyclic indole precursors **8** were synthesized with a definite *trans* double bond configuration, by varying both the protecting group on the amine nitrogen (R) and the substituent directly bound to the carbonyl moiety (R′).

From the data reported in Table 1, several conclusions can be drawn. Despite the highly coordinating character of **6**, they proved to be suitable partners for ruthenium based CM by furnishing **8** in moderate to good yields, and in the case of low conversions, discrete amounts of unreacted starting indolyl derivatives were recovered. Moreover, moderate yield was also obtained with phenylvinylketone (PVK) **7b**[19] (**8ab**, 38%, entry 6).

The substitution of the aminic nitrogen in the side chain by electron-withdrawing moieties was necessary in order to avoid poisoning of the ruthenium catalyst. For instance, when indole-containing tertiary allylic aminic groups in the side chain (**6e**) were employed, the desired **8ea** was obtained only in traces (entry 4). Here, even the employment of $Ti(OiPr)_4$ as an additive[20] did not lead to any appreciable improvement.

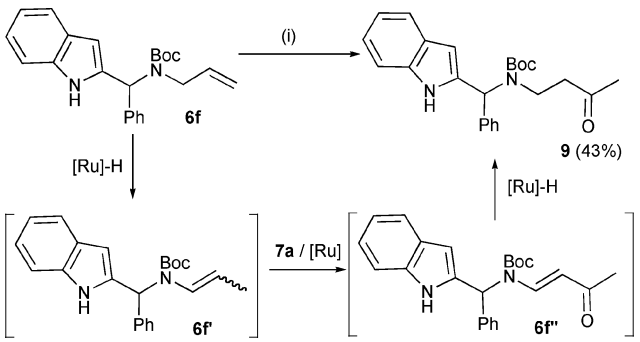
Interestingly, the presence of phenyl groups in proximity of the CM site (tethering chain, **6f**) was detrimental for the ruthenium mediated process. In this case in fact, the coupling mainly furnished the saturated indolyl ketone **9** (Scheme 2). The formation

**Table 1** Synthesis of indolyl enones **8** by cross-metathesis reaction[a]




| Entry | Indole | 7 | Product[b] | Yield (%)[c] |
|---|---|---|---|---|
| 1 | **6b** | **7a** | **8ba** | 34 (41) |
| 2 | **6c** | **7a** | **8ca** | 50 (10) |
| 3 | **6d** | **7a** | **8da** | 41 (20) |
| 4 | **6e** | **7a** | **8ea** | Traces |
| 5 | (±)-**6f** | **7a** | **8fa** | Traces (30)[d] |
| 6 | **6a** | **7b** | **8ab** | 38 (45) |

[a] All the reactions were carried out in degassed anhydrous $CH_2Cl_2$ (40 °C, 16 h) under a nitrogen atmosphere. [b] Isolated as the single *E* isomer (determined by $^1H$ NMR). [c] Isolated yields after flash chromatography. In brackets is the amount of starting material (**6**) recovered after purification. [d] See Scheme 2.




**Scheme 2** Reagents and conditions: (i) **7a**, Grubb's II, $CH_2Cl_2$, 40 °C.

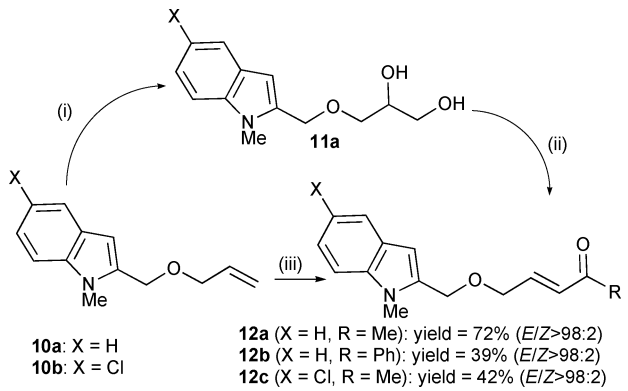
 

of the by-product calls for the presence in solution of ruthenium hydrido species responsible for the initial isomerization of (±)-**6f**, which could successively couple with MVK producing **6f**, finally reduced to **9**.[21]

To date, the influence of proximal aromatic rings on the reaction outcome is still unclear. However, we can speculate that this particular molecular framework might account for an accelerated decomposition in solution of the Grubbs' catalyst leading to [Ru]-H species or dinuclear ruthenium complexes.[22]

### Tetrahydropyranoindole precursors

The oxygenated THBC analogous 1,2,3,9-tetrahydropyrano-[3,4-*b*]indoles **2** have been categorized as belonging to potent analgesic families and some 1-acetic acid derivatives were successfully tested as anti-inflammatory agents as well. Despite the well recognized and diversified pharmacological activities, only very few routes to their synthesis have been reported to date.[4] Our previous study permitted the synthesis of *N*-methylated indolyl enone (**12a**) starting from the corresponding allyl ether **10a** in 29% overall yield. Also in this case, the improvement in terms of time and chemical yields guaranteed by the use of CM was evident. In particular, the optimal CM in comparison to the former pathway [(i), (ii), Scheme 3][15] furnished **12a**, **12b** and **12c** as the single *E* isomers in 72, 39 and 42% yield, respectively.

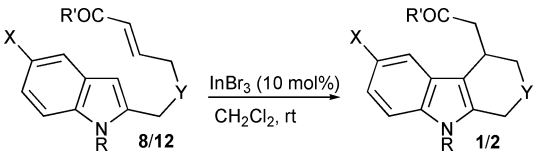



**Scheme 3** Reagents and conditions: (i) $K_2Os_2O_2(OH)_4$, DABCO, $K_3Fe(CN)_6$ (71%); (ii) $NaIO_4$, $SiO_2$, $MeCOCH{=}PPh_3$ (41%); (iii) $RCO\text{-}CH{=}CH_2$, Grubbs' II.

### $InBr_3$ catalyzed intramolecular F–C-type alkylation.

The importance of Friedel–Crafts cyclization is noteworthy, allowing the synthesis of prominent polyfunctionalized aromatic as well as heteroaromatic fused compounds to be performed in a straightforward manner. The initial procedure (stoichiometric amounts of Lewis acids as well as harsh reaction conditions) has been subsequently replaced by milder and more environmentally friendly catalytic approaches. In this context, innovative Lewis acids (LAs)[23] and transition-metal C–H activators[24] demonstrated their effectiveness for the intramolecular alkylation of several arenes by unfunctionalized as well as functionalized C=C double bonds, C≡C triple bonds and epoxides.[9] With particular regard to electron-rich aromatic systems, mild reaction conditions are essential in order to prevent side-reactions such as a drop in regiochemistry, poly-alkylations and competitive intermolecular processes. Additionally, the strength of the promoting agent is a crucial issue which must be carefully addressed.

**Table 2** In(III)Br catalyzed intramolecular F–C[a]




| Entry | Starting | X/Y/R/R′ | Product | Yield (%)[b] |
|---|---|---|---|---|
| 1 | **8aa** | H/N-Boc/H/Me | **1aa** | —[c] |
| 2 | **8aa** | H/N-Boc/H/Me | **1aa** | 90 |
| 3 | **8ab** | H/N-Boc/H/Ph | **1ab** | 95 |
| 4 | **8ba** | H/N-Cbz/H/Me | **1ba** | 95 |
| 5 | **8ca** | $H/NCO_2Me/H/Me$ | **1ca** | 95 |
| 6 | **8da** | $H/NCOCF_3/H/Me$ | **1da** | 70 |
| 7 | **12a** | H/O/Me/Me | **2a** | 98 |
| 8 | **12b** | H/O/Me/Ph | **2b** | 91 |
| 9 | **12c** | Cl/O/Me/Me | **2c** | 98 |

[a] All the reactions were carried out in anhydrous $CH_2Cl_2$. [b] Isolated yields after flash chromatography. [c] In absence of $InBr_3$, reaction time 48 h.

In this context, we recently reported the use of $InBr_3$ (10 mol%) as a powerful activator for the intramolecular Michael-type addition of *N*,*N*′-diBoc-indolyl enones and *N*–Me–*O*-indole enones to give 4-substituted tetrahydro-β-carbolines **1** and 4-substituted tetrahydro-β-pyranoindoles **2**, respectively.[15] In this paper, we verified the generality in scope and applicability of the indium-catalyzed F–C protocol by extending the intramolecular alkylation also to *N*-(1)H indolyl derivatives **8**. As summarized in Table 2, $InBr_3$ proved tolerant for several protecting groups and substitution patterns in the cyclized products by furnishing excellent yields (70–98%) within a few minutes' reaction time. The effectiveness of In(III)Br as a F–C promoter was further stressed by running a model reaction in absence of catalyst. As a matter of fact, under these conditions the cyclization did not work to any extent, even after 48 h (entry 1).

### Stereoselective intramolecular F–C alkylation: towards the synthesis of enantiomerically enriched polycyclic indoles

Asymmetric intramolecular alkylations of aromatic systems are straightforward shortcuts to the synthesis of stereochemically defined polycyclic natural and unnatural compounds bearing benzylic stereocenters. Since the P–S pioneering paper,[25] the large volume of research efforts in this field led to the first example of stereoselective P–S reaction to be developed in the presence of chiral thioureas as catalysts.[26] Subsequently, List and co-workers described the use of functionalized chiral phosphoric acids as effective Brønsted acids for stereoselective P–S condensations.[27] In this context, a number of different catalytic and stereoselective alkylations of aromatics through intramolecular Michael-type reactions were reported.[28]

Again, a related stereoselective approach to the preparation of THBCs and THGCs (tetrahydro-γ-carbolines) in highly enantioselective manner was recently studied in our group through Pd-catalyzed intramolecular alkylation of indole allyl carbonates.[29]

On the other hand, asymmetric catalytic Friedel–Crafts-type reactions *via* conjugate addition of aromatic compounds to simple

α,β-unsaturated ketones still represent 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. In this context, we have reported on the effectiveness of [salenAlCl]–lutidine complexes in controlling the stereodiscriminating intermolecular Michael addition of indoles to both aryl enones and aryl nitroalkenes.[30]

Then, by choosing the *N*–Boc protected indolylmethyl enone **8aa** as the model substrate, a brief survey of commercially available, as well as *in situ*-formed, chiral aluminium-based LAs **13a**–**f** (20 mol%) were envisaged as catalysts and a collection of results is reported in Fig. 2.

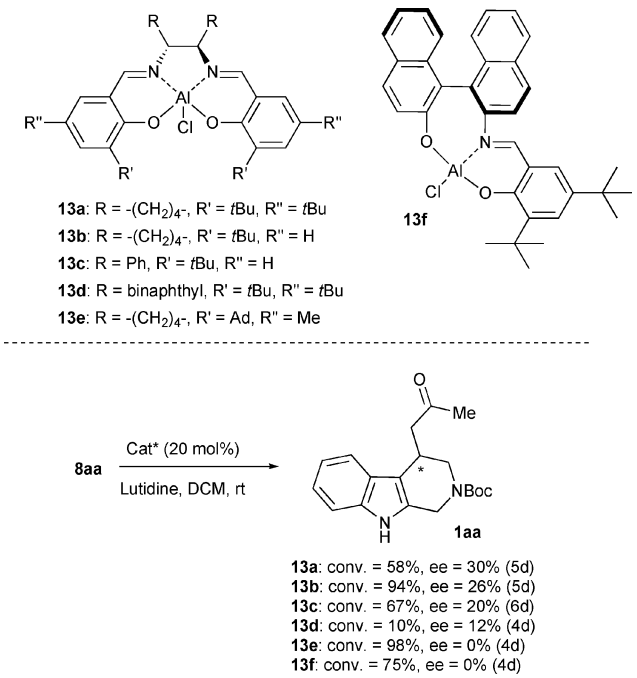
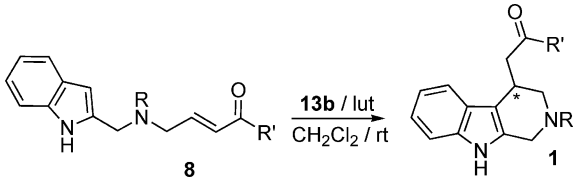



**Fig. 2** Survey of chiral aluminium LAs as catalysts for the stereoselective intramolecular F–C-type alkylations of **8aa**.

The screening revealed generally good conversions with moderate stereoselectivity. Among the catalysts tested, the Schiff–Al complex **13a** provided **1aa** with the highest enantiomeric excess (ee up to 30%). Due to the low reaction rate associated to these processes, the lowering of the reaction temperature was not accomplishable.

Along this line, the effect of concentration was also investigated. To this purpose, **8aa** was cyclized in the presence of **13b** (20 mol%) and lutidine (20 mol%) in a range of substrate concentrations (8–66 mM). Despite the known influence of concentration on intramolecular processes, in our cases the stereochemical outcome resulted only slightly affected ranging form 19% in 66 mM solution (98% HPLC conversion, 3d reaction time), to 27% in 8 mM reaction mixture (44% HPLC conversion, 14 d reaction time). Then, we chose complex **13b** as the model catalyst, and a range of variously-functionalized indolyl enones **8** were tested (Table 3). Entry 1 deals with the issue of substituent effects on the stereocontrol of the reaction. In particular, the presence of an aryl enone such as **8ab** does not significantly affect either yield or enantiomeric excess (98 and 27%, respectively). On the contrary, we observed an influence of the protecting group of the tethering

**Table 3** Stereoselective intramolecular F–C reactions catalyzed by **13b**–lutidene[a]




| Entry | Indole | Product | Yield (%)[b] | Ee (%)[c] |
|---|---|---|---|---|
| 1 | **8ab** | **1ab** | 98 | 27 |
| 2 | **8ba** | **1ba** | 69 | 11 |
| 3 | **8ca** | **1ca** | 98 | 11 |
| 4 | **8da** | **1da** | 47 | 0 |
| 5 | **8fa** | **1fa** | 95 | 29 |

[a] All the reactions were carried out in anhydrous $CH_2Cl_2$ (rt, 24 h, 20 mol% cat) under nitrogen atmosphere. [b] Isolated yields after flash chromatography. [c] Determined by HPLC with chiral column.

nitrogen on the F–C outcome. As a matter of fact, by substituting the Boc moiety with CBz, $CO_2Me$ and $COCF_3$ the chiral induction progressively dropped to a racemic product.

Interestingly, **13b**–lutidine (20 mol%) failed in promoting the intramolecular F–C alkylation of **12a**. This result underlines the importance of the *N*-(1) hydrogen during the whole catalytic cycle. After 5d stirring, we decided in any case to obtain the cyclized product and to this purpose we added $InBr_3$ (20 mol%) to the mixture already containing **13b** (20 mol%). Astonishingly, after 16 h stirring at rt, **2a** was obtained in 85% conversion and 50% ee! It was evident that catalysis under a heterobimetallic regime was operating.

In the last few years, catalyses under a cooperative regime have becoming an attractive alternative to conventional LAs, due to their superior selectivity and activity with respect to the individual components.[31] Although this approach has been extensively applied to stereocontrolled C–C bond forming reactions such as: nitro-aldol reactions, Michael reactions, hydrophosphonylations of aldehydes and imines, Diels–Alder reactions and epoxidations, to our knowledge heterobimetallic catalysts have never been employed in asymmetric F–C reactions.[32]

Then, **12a** was allowed to cyclize in the presence of a catalytic amount of **13a**–lutidine in combination with a series of LAs.

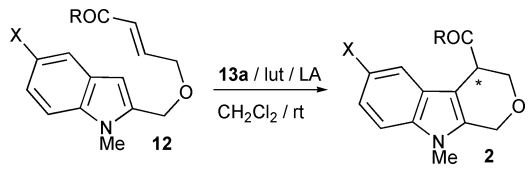
From the data reported in Table 4, $InBr_3$ proved to be the most effective LA partners of **13b** to control the stereochemistry of the reaction. In particular, while scandium and ytterbium triflates provided **2a** in high yields but in a racemic form, the enantiocontrol reached 54% ee (81% conversion) when $InBr_3$ was used in combination with commercially available [salenAlCl] **13a**.[33]

Such a level of stereoselectivity prompted us to investigate further the nature of the dual catalyst $\{[salenAlCl]_x$–$[InBr_3]_y\}$. Accordingly, intramolecular F–C alkylation of **12a** was carried out with chiral Al–In systems based on different initial **13a**–$InBr_3$ ratios (Table 4, entries 5–8).

The optimal outcome in terms of chemical as well as optical yield was obtained by adopting a **13a**–In(III)$Br_3$ 2 : 1 ratio. In this case, **2a** was isolated in 80% yield and 60% enantiomeric excess (entry 7). On the contrary, when an Al–In 4 : 1 ratio was

**Table 4** Stereoselective intramolecular heterobimetallic F–C cyclization[a]




| Entry | **13a** (%) | LA (%) | **2** | Yield (%)[b] | Ee (%)[c] |
|---|---|---|---|---|---|
| 1 | 20 | — | — | —[d] | — |
| 2 | 10 | $Sc(OTf)_3$ (10) | **2a** | 93 | 7 |
| 3 | 10 | $Yb(OTf)_3$ (10) | **2a** | 95 | 7 |
| 4 | 10 | $In(OTf)_3$ (10) | **2a** | 82 | 43 |
| 5 | 10 | $InBr_3$ (10) | **2a** | 81 (70) | 54 |
| 6 | 20 | $InBr_3$ (10) | **2a** | 77 | 55 |
| 7 | 10 | $InBr_3$ (5)[e] | **2a** | 87 (80) | 60 |
| 8 | 10 | $InBr_3$ (2.5)[e,f] | **2a** | 93 | 2 |
| 9 | 10 | $InBr_3$ (2.5)[e] | **2a** | 63 | 25 |
| 10 | 10 | $InBr_3$ (5)[g] | **2a** | 70 | 5 |
| 11 | 10 | $InBr_3$ (5) | **2b** | 61 | 20 |
| 12 | 10 | $InBr_3$ (5)[e] | **2c** | 80 | 60 |

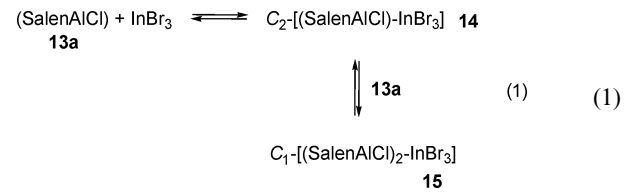
[a] All the reactions were carried out in anhydrous $CH_2Cl_2$ (rt) under nitrogen atmosphere; **13a** and lutidine were used in a 1 : 1 ratio. [b] HPLC conversion, isolated yields are in brackets. [c] Determined by HPLC with chiral column. [d] Reaction time 5 d. [e] A solution of $InBr_3$ in dry $Et_2O$ (0.30 M) was used. [f] TEA (10 mol%) was used as the base. [g] In absence of lutidine.

employed, **2a** was obtained in a 63% yield and 25% ee (entry 9). These results drove our attention towards the possibility to have different heterobimetallic species in solution with a rapid exchange equilibrium between them. In particular, the one constituted by two molecules of [salenAlCl] and one molecule of $InBr_3$ appeared to be the most effective during the stereodifferentiating step of the intramolecular process.

Also in the present bimetallic-catalyzed intramolecular alkylation, the use of a base in catalytic amount (lutidine) was necessary in order to achieve the highest ee (entry 7). As a matter of fact, when the model reaction was carried out in absence of base, the enantioselectivity dropped to 5% (entry 10). Again, aliphatic tertiary amines did not prove to be a suitable additive for the present intramolecular F–C. In fact, by replacing lutidine with TEA, **2a** was yielded in quantitative yield but in almost racemic form (ee = 2%, entry 8). This finding unambiguously proves the active role of the additive in the *in situ* catalyst formation between the aluminium and indium species.[34] The optimal conditions were finally also applied to **12b** and **12c** obtaining ee 20 and 60% in the cyclized products **2b**–**c**, respectively.

To gain some information on the nature of the $\{[salenAlCl]_x$–$[InBr_3]_y\}$ species in solution, a $^1H$ NMR analysis in $CD_2Cl_2$ with different **13a**–$InBr_3$ ratios was carried out (see the ESI). In particular, by adding 1 eq. of In(III)Br to a solution ($CD_2Cl_2$) of commercially available [salenAlCl], two new set of signals characteristic for unprecedented $C_2$-symmetry and $C_1$-symmetry $\{[salenAlCl]$–$InBr_3\}$ species were found. The new $C_2$-symmetry adduct appeared to be in a 75 : 25 ratio with the starting [salenAlCl] and the $C_1$-symmetrical species being the minor components of the mixture. On the basis of previously-reported evidence from salen–metal–LA adducts,[35] we tentatively assigned the new set of $C_2$-symmetry signals to the monomeric bimetallic $\{[salenAlCl]$–$InBr_3\}$ (**14**, eqn 1), in which the indium salt could coordinate the Al–Schiff base complex through the oxygen atoms of the salen counterpart.

Interestingly, when an excess of [salenAlCl] (Al–In 2 : 1) was added, an inversion of the population of the species in solution occurred, favouring the $C_1$-adduct (80 : 20 ratio). Analogously, the $C_1$-species can be attributed to a dimeric $\{[salenAlCl]_2\}$ complex tethered by one molecule of indium(III) salt (**15**).[36]




(1)

The aforementioned ratio between the two species can be further shifted toward the dimer **15** simply by adding an excess of **13a**. Here, the use of **13a**–$InBr_3$ in a 4 : 1 ratio gave rise to the exclusive formation of **15** with the concomitant presence of free [salenAlCl]. Such evidence concurred to rule out the formation of more complex multi-metallic aggregates, probably because of sterical reasons.

The role of the base was investigated spectroscopically as well. To this aim, $^1H$ NMR spectra of **13a**–In(III)Br–lutidine was recorded at rt for different Al–In ratios. Also in this case a mixture of species were present in equilibrium in solution showing similar pattern of NMR signals. However, because of the multitude of signals the spectra were difficult to rationalize.

A different explanation for the enhanced reactivity of the bimetallic complex could also arise from a study conducted by Atwood and co-workers on heterobimetallic [salenAl]–Ga complexes. In this case, the achiral salts did not act as distinct LAs, but the gallium(III) halide concurred in the formation of unexpected solvent-free pentacoordinated cationic aluminium complexes.[37] However, this working hypothesis was ruled out by synthesizing a cationic salen–Al complex through chloride extraction by $AgSbF_6$ in $CH_2Cl_2$, and by testing it in the model cyclization. Under these conditions, **2a** was obtained only in traces (reaction time 72 h) in a markedly lower enantiomeric excess (ee = 7%).

## Conclusions

In this study we have presented a new synthetic strategy for the formation of polycyclic indolyl-containing compounds by updating and optimizing our previously reported protocol. In particular, the introduction of the CM reaction for stereocontrolled C=C bond formation shortened the synthetic sequence for the desired indolyl enones. Then, the development of a stereoselective version of the present cyclization with chiral Lewis acid was discussed. The use of chiral Al-based LAs furnished the targeted THBCs in good yield and moderate enantioselectivity. Interestingly, cyclizations of *O*-tethered enones **12** were performed in the presence of a new chiral (Al–In) system, affording the corresponding tetrahydropyranyl derivative **2** of ee up to 60%. Spectroscopic investigations on the nature of this catalytic system revealed the presence in solution of several heterometallic species in equilibrium being the bimetallic $\{[salenAlCl]_2$–$InBr_3\}$ probably involved in the enantiodiscriminating step of the cyclization.

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## References

1 R. T. Brown, in *Indoles, Part 4*, ed. J. E. Saxton, Wiley-VCH, New York, 1983; R. J. Sundberg, *Indoles*, Academic Press, San Diego, 1996.
2 For some representative syntheses of natural indole occurring products see: K. C. Nicolau, S. A. Snider, in *Classic in Total Synthesis II*, Wiley-VCH, Weinheim, 2003.
3 N. Khorana, C. Smith, K. Herrick-Davis, A. Purohit, M. Teitler, B. Grella, M. Dukat and R. A. Glennon, *J. Med. Chem.*, 2003, **46**, 3930–3937.
4 L. G. Humber, *Med. Res. Rev.*, 1987, **7**, 1; D. Mobilio, L. G. Humber, A. H. Katz, C. A. Demerson, P. Hughes, R. Brigance, K. Conway, U. Shah, G. Williams, F. Labbadia, B. De Lange, A. Asselin, J. Schmid, J. Newburger, N. P. Jensen, B. M. Weichman, T. Chau, G. Neuman, D. D. Wood, D. Van Engel and N. Taylor, *J. Med. Chem.*, 1988, **31**, 2211–2217.
5 S. K. Rabindran, H. He, M. Singh, E. Collins, K. I. Annable and L. M. Greeberger, *Cancer Res.*, 1998, **58**, 5850.
6 C. S. Stinson, *Chem. Eng. News*, 2001, **79**, 79–97.
7 T. Ulven and E. Kostenis, *J. Med. Chem.*, 2005, **48**, 898–900.
8 C. Nevado and A. M. Echavarren, *SYNLETT*, 2005, 167–182.
9 M. Bandini, E. Emer, S. Tommasi and A. Umani-Ronchi, *Eur. J. Org. Chem.*, DOI: 10.1002/ejoc.200500995.
10 E. D. Cox and J. M. Cook, *Chem. Rev.*, 1995, **95**, 1797–1842.
11 M. Bandini, A. Melloni and A. Umani-Ronchi, *Org. Lett.*, 2004, **6**, 3199–3202.
12 For recent synthesis of tetrahydrocarbazoles *via* intramolecular alkylation of indoles with unactivated olefins see: C. Liu, X. Han, X. Wang and R. A. Widenhoefer, *J. Am. Chem. Soc.*, 2004, **126**, 3700–3701; C. Liu and A. Widenhoefer, *J. Am. Chem. Soc.*, 2004, **126**, 10250–10251.
13 G. A. Olah, *Friedel–Crafts Chemistry*, ed. G. A. Olah, Wiley, New York, 1973; R. M. Roberts and A. A. Khalaf, *Friedel–Crafts Chemistry: A Century of Discovery*, Marcel Dekker, New York, 1984.
14 For a review see: M. Bandini, A. Melloni, S. Tommasi and A. Umani-Ronchi, *SYNLETT*, 2005, 1199–1222.
15 M. Agnusdei, M. Bandini, A. Melloni and A. Umani-Ronchi, *J. Org. Chem.*, 2003, **68**, 7126–7129.
16 For a recent review on the use of olefin cross-metathesis reaction for the synthesis of natural compounds see: S. J. Connon and S. Blechert, *Angew. Chem., Int. Ed.*, 2003, **42**, 1900–1921; K. C. Nicolaou, P. G. Bulger and D. Sarlah, *Angew. Chem., Int. Ed.*, 2005, **44**, 4490–4527.
17 The importance in using *N*–H free indoles **6** instead of *N*–Boc derivatives **4** lies in the higher nucleophilic character of the mono-protected indole core in the final catalytic intramolecular cyclization.
18 A. K. Chatterjee, J. P. Morgan, M. Scholl and R. H. Grubbs, *J. Am. Chem. Soc.*, 2000, **122**, 3783–3784; J. Louie, C. W. Bielawski and R. H. Grubbs, *J. Am. Chem. Soc.*, 2001, **123**, 11312–11313; T.-L. Choi, A. K. Chatterjee and R. H. Grubbs, *Angew. Chem., Int. Ed.*, 2001, **40**, 1277–1279.
19 S. Harada, N. Kumagai, T. Kinoshita, S. Matsunaga and M. Shibasaki, *J. Am. Chem. Soc.*, 2003, **125**, 2582–2590.
20 Q. Yang, W.-J. Xiao and Z. Yu, *Org. Lett.*, 2005, **7**, 871–874.
21 B. Alcaide, P. Almendros and J. M. Alonso, *Chem.–Eur. J.*, 2003, **9**, 5793–5799.
22 S. H. Hong, M. W. Day and R. H. Grubbs, *J. Am. Chem. Soc.*, 2004, **126**, 7414–7415.
23 H. Inoue, N. Chatani and S. Murai, *J. Org. Chem.*, 2002, **67**, 1414–1417, and references therein.
24 For some representative examples: E. J. Hennessy and S. L. Buchwald, *J. Am. Chem. Soc.*, 2003, **125**, 12084–12085; Z. Shi and C. He, *J. Am. Chem. Soc.*, 2004, **126**, 5964–5965; H. Yamabe, A. Mizuno, H. Kusama and N. Iwasawa, *J. Am. Chem. Soc.*, 2005, **127**, 3248–2349.
25 A. Pictet and T. Spengler, *Ber. Dtsch. Chem. Ges.*, 1911, **44**, 2030–2036.
26 M. S. Taylor and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2004, **126**, 10558–10559.
27 J. Seayad, A. Seayad and B. List, *J. Am. Chem. Soc.*, 2006, **128**, 1086–1087.
28 For some representative examples: H. L. van Lingen, W. Zhuang, T. Hansen, F. P. J. T. Rutjes and K. A. Jørgensen, *Org. Biomol. Chem.*, 2003, **1**, 1953–1958; M. G. Banwell, D. A. S. Beck and J. A. Smith, *Org. Biomol. Chem.*, 2004, **2**, 157–159.
29 M. Bandini, A. Melloni, F. Piccinelli, R. Sinisi, S. Tommasi and A. Umani-Ronchi, *J. Am. Chem. Soc.*, 2006, **128**, 1424–1425.
30 M. Bandini, M. Fagioli, P. Melchiorre, A. Melloni and A. Umani-Ronchi, *Tetrahedron Lett.*, 2003, **44**, 5843–5846; M. Bandini, M. Fagioli, M. Garavelli, A. Melloni, V. Trigari and A. Umani-Ronchi, *J. Org. Chem.*, 2004, **69**, 7511–7518; M. Bandini, M. Rovinetti, S. Tommasi and A. Umani-Ronchi, *Chirality*, 2005, **17**, 522–529.
31 For a comprehensive review see: M. Shibasaki and N. Yoshikawa, *Chem. Rev.*, 2002, **102**, 2187–2210; G. M. Sammis, H. Danjo and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2004, **126**, 9928–9929; Y. N. Belokon, M. North, V. I. Maleev, N. V. Voskoboev, M. A. Moskalenko, A. S. Peregudov, A. V. Dmitriev, N. S. Ikonnikov and H. B. Kagan, *Angew. Chem., Int. Ed.*, 2004, **43**, 4085–4089.
32 Ir(III)/Sn(IV) heterobimetallic catalyst was recently applied to not stereoselective Friedel–Crafts alkylations of aromatics with *p*-activated alcohols: J. Choudhury, S. Podder and S. Roy, *J. Am. Chem. Soc.*, 2005, **127**, 6162–6163.
33 In this process, no significant differences in terms of stereo-outcome were observed by means of **13a** or **13b** as chiral sources.
34 J. A. Miller, W. Jin and S. T. Nguyen, *Angew. Chem., Int. Ed.*, 2002, **41**, 2953–2956; J. A. Miller, B. A. Gross, M. A. Zhuravel, W. Jin and S. T. Nguyen, *Angew. Chem., Int. Ed.*, 2005, **44**, 3885–3889.
35 H. Aoi, M. Ishimori and T. Tsuruta, *Bull. Chem. Soc. Jpn.*, 1975, **48**, 1360; C.-K. Shin, S.-J. Kim and G.-J. Kim, *Tetrahedron Lett.*, 2004, **45**, 7429–7433; S. S. Thakur, W. Li, S.-J. Kim and G.-J. Kim, *Tetrahedron Lett.*, 2005, **46**, 2263–2266, and references therein.
36 Nonlinearity of the present F–C reaction is consistent with the hypothesis that at least two units of [salenAlCl] are directly involved in the stereodifferentiating step of the cyclization.
37 M.-A. Muñoz-Hernández, B. Sannigrahi and D. A. Atwood, *J. Am. Chem. Soc.*, 1999, **121**, 6747–6748.

 