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PAPER

Enantioselective Friedel–Crafts alkylation of indole derivatives catalyzed by new $Yb(OTf)_3$-pyridylalkylamine complexes as chiral Lewis acids†

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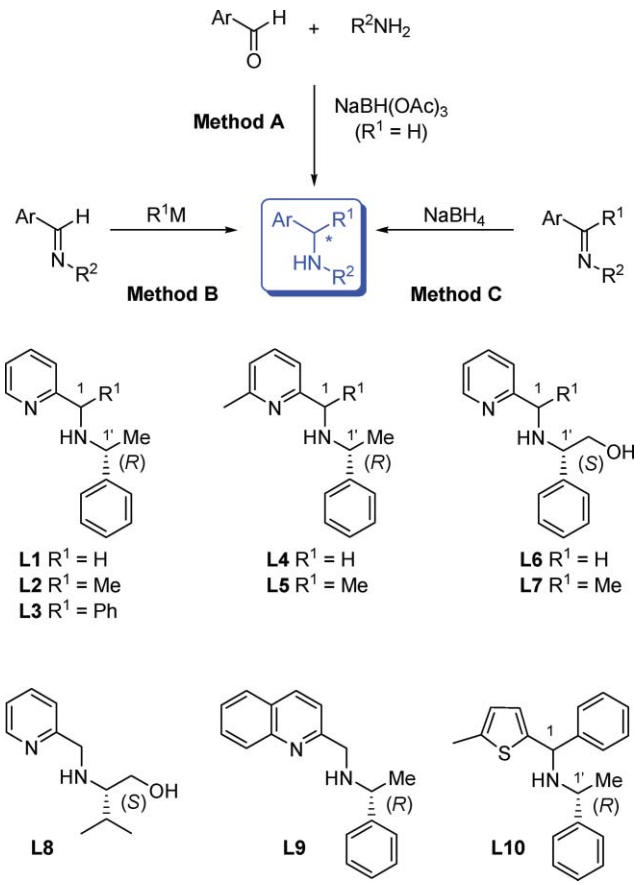
New $Yb(OTf)_3$-pyridylalkylamine complexes have been employed as chiral Lewis acids in the enantioselective Friedel–Crafts alkylation of indole derivatives with trifluoropyruvates. The influence of the substituents as well as the configuration of the ligands have been studied and allowed us to reach enantiomeric excesses up to 83%.

Introduction

The Friedel–Crafts (F–C) alkylation is one of the most important and powerful C–C bond-forming processes in organic chemistry. Over the past decade, the catalytic asymmetric version of this reaction has attracted the interest of the scientific community.[1] In this research field copper-based complexes have been extensively studied for the metal-catalyzed F–C alkylation of aromatics and heteroaromatics.[2] Despite the fact that lanthanides have proved to be good Lewis acids for catalyzing the F–C reaction,[3] the use of these rare earth metals as chiral Lewis acids in enantioselective F–C alkylation is scarcely reported and remains challenging.[4] Very recently, Feng and coworkers have developed the first example of metal controlled reversal of enantioselectivity in asymmetric F–C alkylation of indoles with β,γ-unsaturated-α-ketoesters using $AgAsF_6$ or $Sm(OTf)_3$-*N*,*N*′-dioxide complexes.[5] In this context, we report here new chiral ytterbium-based Lewis acids as catalysts for the asymmetric F–C alkylation of indole derivatives by trifluoropyruvates[6] with good yields and enantioselectivities using simple pyridylalkylamines as ligands.

Results and discussion

The targeted ligands were readily obtained from commercially available common reactants in one or two steps based on previous studies (Scheme 1). Ligands **L1**, **L4**, **L6**, **L8** and **L9** (R^1 = H) were prepared in one step by reductive amination of heteroaromatic aldehydes with enantiopure amines using sodium triacetoxyborohydride (Method A).[7] This process was very efficient as the desired products were isolated in quantitative yields. Ligands



Scheme 1 Synthesis of the pyridylalkylamine ligands

L2, **L5**, **L7** and **L10** were synthesized with moderate to good yields (49 to 72%) in two steps by condensation of aldehydes with enantiopure amines followed by the addition of organometallics to the neo-formed corresponding imines (Method B).[8] Finally **L3** was obtained in 90% yield over two steps including the formation of the corresponding ketimine and further reduction with sodium borohydride (Method C).[9] Thus these methodologies allowed

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us to prepare a variously substituted ligand family based on a pyridylalkylamine core.

Diastereomeric ligands **L2**, **L3**, **L5**, **L7** and **L10** were separated by column chromatography on silica gel. The absolute configuration of each diastereomer of **L2** was determined by comparison of their optical activity and NMR spectra with literature data.[8f,9,10] Configuration of the neo-formed tertiary carbon center in **L5**, was assigned according to **L2** analytical data. The (*1S*,*1′R*) absolute configuration of **L3** second eluted diastereomer was unambiguously established by X-ray diffraction analysis of the corresponding palladium(II) complex (Fig. 1).[11,12] Surprisingly, the established (*1S*,*1′R*) configuration is in disagreement with the one supposed in the literature.[13] In the case of **L7** and **L10**, the configurations of each diastereomer were not determined.

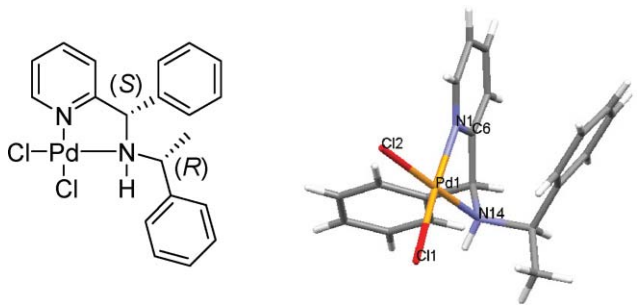


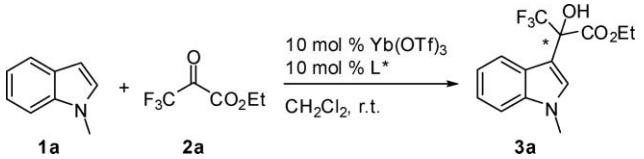
Fig. 1 X-ray crystal structure for (*1S*,*1′R*)-**L3** palladium dichloride complex.

We next screened the aforementioned panel of ligands in the Friedel–Crafts alkylation of *N*-methylindole **1a** to ethyl trifluoropyruvate **2a** catalyzed by $Yb(OTf)_3$-L* complexes. The catalytic species were prepared *in situ* by mixing $Yb(OTf)_3$ with the appropriate ligand in dichloromethane at room temperature. The pyruvate **2a** was then added followed by **1a** and the reaction mixture stirred overnight. The results are gathered in Table 1.

For all the tested ligands, the reaction proceeded with complete conversion of *N*-methylindole **1a** into the desired 3-substituted indole **3a** after 20 h. Enantiomeric excesses were measured by chiral HPLC on the purified indole derivative **3a** and the absolute configuration was determined by comparison with specific rotation values reported in the literature. The enantiomeric excesses varied to a great extent from 20% for the (*S*) enantiomer to 60% for the (*R*) one.

The influence of the presence and/or the nature of the R^1 substituent was studied. In the absence of a substituent (R^1 = H, entries 1, 6, 9, 11 and 12) only very low enantioselectivities could be obtained, regardless of the heterocyclic moiety. Slight increase of enantioselectivities (5 – 18%) were observed with **L2** and **L5** bearing a methyl substituent in the pseudo benzylic position (R^1 = Me, entries 2-3 and 7-8). Gratifyingly, moving from a methyl to a phenyl group (**L3**) provided the same level of enantioselectivity (20%) with the (*1R*,*1′R*) diastereomer and a good 60% ee with (*1S*,*1′R*)-**L3** (Table 1, entries 4-5). It is worth noting that the opposite senses of induction were observed for the (*1R*,*1′R*) and the (*1S*,*1′R*) diastereomers in the case of **L2** and **L3**, highlighting the crucial and beneficial role played by the stereo center bearing the R^1 substituent in the enantiodiscriminating step. Further screening involving the use of quinolyl- or thienyl-based ligands as well as tridendate ligands led to poor selectivities

Table 1 Screening of ligands in the Friedel–Crafts alkylation of *N*-methylindole **1a**[a]



Entry	L*	Yield (%)[b]	ee (%)[c]
1	**L1**	78	3 (*S*)
2	(*1R*,*1′R*)-**L2**	84	11 (*S*)
3	(*1S*,*1′R*)-**L2**	78	18 (*R*)
4	(*1R*,*1′R*)-**L3**	85	20 (*S*)
5	(*1S*,*1′R*)-**L3**	82	60 (*R*)
6	**L4**	80	1 (*S*)
7	(*1R*,*1′R*)-**L5**	78	3 (*S*)
8	(*1S*,*1′R*)-**L5**	86	5 (*R*)
9	**L6**	84	3 (*S*)
10	(*1′S*)-**L7**[d]	81	1 (*R*)
11	**L8**	74	6 (*R*)
12	**L9**	77	1 (*S*)
13	(*1′R*)-**L10**[d]	82	0

[a] Reactions were carried out with $Yb(OTf)_3$ (10 mol %), ligand (10 mol %), **1a** (0.25 mmol), and **2a** (0.275 mmol) in DCM (1.5 mL) at r.t. for 20 h. [b] Isolated yield (complete conversion was observed for each reaction). [c] Determined by chiral HPLC analysis (see ESI†). [d] Due to harsh purification, only one diastereomer tested.

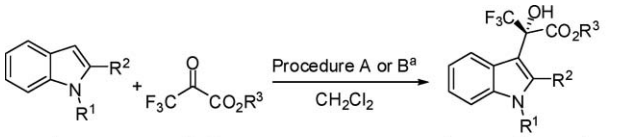
(Table 1, entries 9–13). $Sc(OTf)_3$ and $Sm(OTf)_3$ were tested as metal triflates with (*1S*,*1′R*)-**L3** but lower enantioselectivities were observed: respectively 50 and 30% at room temperature. A similar decrease in the enantioselectivities was observed in either toluene or acetonitrile.

Based on these results, **L3** in combination with $Yb(OTf)_3$ appeared as the best catalytic compromise in this reaction.

In order to increase the enantioselectivity we focused our attention on the reaction conditions using (*1R*,*1′S*)-**L3** as the ligand. In concordance with the aforementioned results, (*S*)-**3a** was obtained with 60% ee under the conditions described in Table 1 (Table 2, entry 1). We next examined the ligand/metal ratio (Table 2, entries 1–4). Interestingly, either 2 : 1 or 3 : 1 ratio provided **3a** with low selectivities in favour of the (*R*) isomer (entries 3-4). These results could be explained by the intervention of a high coordination number of Yb complex as catalytic species. In contrast, the use of a 0.5 : 1 ratio (entry 5) afforded (*S*)-**3a** with 56% ee, confirming a detrimental effect of an excess of ligand compared to metal. These results seemed to point an optimal 1 : 1 ligand/metal ratio. Thus, in order to rigorously control this ratio, we decided to prepare and isolate the $Yb(OTf)_3$-(*1R*,*1′S*)-**L3** complex on a larger scale.[14] The alkylation of 1-methylindole **1a** has been carried out using two procedures involving an *in situ* prepared complex (procedure A) and an isolated complex (procedure B). The latter is more reliable since slightly higher enantioselectivities were obtained proving a better control of the ligand/metal ratio.

The influence of the temperature was also examined (Table 2, entries 1, 6–12). At room temperature, the reaction between **1a** and **2a** in the presence of 10 mol % of $Yb(OTf)_3$-(*1R*,*1′S*)-**L3** complex gave **3a** with 61% ee. Lower temperatures were found beneficial to selectivity. Indeed, selectivities could be enhanced up to 82% ee at –20 °C (entry 10). It was also demonstrated

Table 2 Study of the reaction conditions of the Friedel–Crafts alkylation of indoles **1a–c**



1a-c **2a,b**

3a R^1 = Me, R^2 = H, R^3 = Et
3b R^1 = H, R^2 = H, R^3 = Et
3c R^1 = H, R^2 = Me, R^3 = Et
3d R^1 = Me, R^2 = H, R^3 = Me

Entry	(*1R,1′S*)-**L3** (mol %)	*T* (°C)	Time	Conv (%)[b]	Procedure	Product	ee (%)[c]
1	10	r.t.	20 h	100	A	**3a**	60 (*S*)
2	10	r.t.	20 h	100	B	**3a**	61 (*S*)
3	20	r.t.	20 h	100	A	**3a**	4 (*R*)
4	30	r.t.	20 h	100	A	**3a**	5 (*R*)
5	5	r.t.	20 h	100	A	**3a**	56 (*S*)
6	10	0	40 h	100	A	**3a**	65 (*S*)
7	10	0	40 h	100	B	**3a**	74 (*S*)
8	10	−10	48 h	100	A	**3a**	68 (*S*)
9	10	−20	72 h	100	A	**3a**	78 (*S*)
10	**10**	**−20**	**72 h**	**100**[d]	**B**	**3a**	**82 (*S*)**
11	10	−40	96 h	100	B	**3a**	83 (*S*)
12	10	−90	8 d	85	B	**3a**	76 (*S*)
13	10	r.t.	20 h	100	B	**3b**	56
14	**10**	**−20**	**72 h**	**100**	**B**	**3b**	**74**
15	10	r.t.	20 h	100	B	**3c**	45
16	**10**	**−20**	**72 h**	**100**	**B**	**3c**	**51**
17	10	r.t.	20 h	100	B	**3d**	54
18	**10**	**−20**	**72 h**	**100**	**B**	**3d**	**79**

[a] Procedure A: $Yb(OTf)_3$ (10 mol %), (*1R,1′S*)-**L3** (x mol %), **1a** (0.25 mmol), and **2a** (0.275 mmol) in DCM (1.5 mL). Procedure B: $Yb(OTf)_3$-(*1R,1′S*)-**L3** (10 mol %), **1a–c** (0.25 mmol), and **2a**,**b** (0.275 mmol) in DCM (1.5 mL). [b] Determined by ^1H NMR of the crude mixture. [c] Determined by chiral HPLC analysis (see ESI†). [d] The product was isolated in 88% yield.

that temperatures below −20 °C, only affected the reaction times and no further improvement of the enantiomeric excesses were observed (entries 11-12).

With these conditions in hand we screened different substrates in this reaction. The F–C alkylation of indole **1b** with ethyl trifluoropyruvate provided **3b** with 56% ee at room temperature and 74% ee at −20 °C (Table 2, entries 13-14),[15] whereas lower selectivities (45% and 51% at respectively room temperature and −20 °C) were observed with 2-methylindole **1c** (entries 15-16). The alkylation of *N*-methylindole **1a** with methyl trifluoropyruvate **2b** instead of ethyl trifluoropyruvate did not affect the enantioselectivities (entries 17-18) and **3d** was obtained with a 79% ee at −20 °C. Finally *N*,*N*-dimethylaniline and *N*,*N*-dimethyl-*m*-anisidine were also tested. In both case a full conversion was observed after 48 h at room temperature confirming the activity of the catalyst. However racemic mixtures were obtained.

Conclusions

In summary, we have developed a new $Yb(OTf)_3$-pyridylalkyamine catalytic system for the asymmetric F–C alkylation of indole derivatives with trifluoropyruvates. Screening various structural parameters has led us to identify a ligand with suitable substitution and configuration for this reaction. Under optimized conditions, the desired indole derivatives **3a–d** were obtained in 51 to 82% ee using $Yb(OTf)_3$-(*1R,1′S*)-**L3** complex. It should be highlighted that both diastereomers of **L3** provided the product with the opposite configuration showing the importance of the stereo center bearing the R^1 substituent on the enantioselectivity. Further experiments are in progress to improve the selectivity by making structural modifications of the pyridylalkylamine backbone and to study the scope of this reaction.

Experimental

General methods

All non-aqueous reactions were carried out under an atmosphere of argon in flame- or oven-dried glassware with magnetic stirring. All reagents and solvents obtained from commercial sources were used without further purification unless otherwise noted. CH_2Cl_2 was distilled over CaH_2 before use. THF and Et_2O were distilled over sodium metal. Thin layer chromatography (TLC) was performed on silica gel 60 F_{254} and the plates were visualized with UV light (254 nm) or a potassium permanganate solution (1 g with 2 g of K_2CO_3 in 200 mL of water). The crude products were purified by preparative thin layer chromatography on silica gel 60 PF_{254} or by column chromatography using silica gel Merck 60. Known compound structures were assigned by comparison with the literature spectroscopic data. ^1H and ^{13}C NMR spectra were recorded on a Brücker AM 360, AM 300, DPX 200 and DPX 250 spectrometers; Chemical shifts for ^1H and ^{13}C were referenced internally according to the residual solvent resonances and reported in ppm relative to $CDCl_3$ (7.26 ppm for ^1H and 77.0 ppm for ^{13}C). All coupling constants (*J* values) are given in hertz (Hz). Data appear in the following order: chemical shift in

ppm, multiplicity (s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet), coupling constant J, number of protons, and assignment.

General procedure for the synthesis of L1, L4, L6, L8 and L9

To a stirred solution of aldehyde (1 eq) and chiral amine (1 eq) in 1,2-dichloroethane (10 mL for 2.5 mmol of aldehyde) was added sodium triacetoxyborohydride (1.5 eq). The mixture was stirred at rt under argon atmosphere for 16 h and the reaction was quenched by adding saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum to yield the crude product.

(*R*)-1-Phenyl-*N*-((pyridin-2-yl)methyl)ethylamine (L1)[9]. The reaction was performed on 500 mg (4.67 mmol) of pyridine-2-carboxaldehyde, 566 mg (4.67 mmol) of (*R*)-1-phenylethylamine and 1.48 g (7.00 mmol) of sodium triacetoxyborohydride. The crude product was purified by flash chromatography on silica gel, using ethyl acetate/petroleum ether (6/4) as eluent, to afford **L1** as an orange oil (91%, 899 mg). $[\alpha]_D^{20}$ +38.9 (*c* 1.01, $CHCl_3$); Lit.[9] $[\alpha]_D^{20}$ −46.9 (*c* 13.1, acetone) for the (*S*) isomer. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.60 (d, J = 3.8 Hz, 1H, Ar), 7.65 (t, J = 7.0 Hz, 1H, Ar), 7.15–7.45 (m, 7H, Ar), 3.88 (q, J = 6.6 Hz, 1H, CH–N), 3.80 (s, 2H, CH_2–N), 1.99 (brs, 1H, NH), 1.46 (d, J = 6.6 Hz, 3H, Me). ^{13}C NMR ($CDCl_3$, 90 MHz) δ 160.0 (C_{quat}, Ar), 149.4 (Ar), 145.5 (C_{quat}, Ar), 136.4 (Ar), 128.6 (2C, Ar), 127.0 (Ar), 126.9 (2C, Ar), 122.5 (Ar), 121.9 (Ar), 58.1 (CH–N), 53.2 (CH_2–N), 24.5 (Me).

(*R*)-1-Phenyl-*N*-((6-methylpyridin-2-yl)methyl)ethylamine (L4). The reaction was performed on 300 mg (2.48 mmol) of 6-methylpyridine-2-carboxaldehyde, 300 mg (2.48 mmol) of (*R*)-1-phenylethylamine and 787 mg (3.72 mmol) of sodium triacetoxyborohydride. The product was obtained without further purification as an orange oil (100%, 562 mg). $[\alpha]_D^{20}$ +32.7 (*c* 1.00, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.50 (t, J = 7.5 Hz, 1H, Ar), 7.22–7.40 (m, 5H, Ar), 7.00 (d, J = 7.5 Hz, 2H, Ar), 3.84 (q, J = 6.6 Hz, 1H, CH–N), 3.72 (s, 2H, CH_2–N), 2.54 (s, 3H, Me of Py), 2.24 (brs, 1H, NH), 1.42 (d, J = 6.6 Hz, 3H, Me). ^{13}C NMR ($CDCl_3$, 90 MHz) δ 159.1 (C_{quat}, Ar), 157.9 (C_{quat}, Ar), 145.6 (C_{quat}, Ar), 136.5 (Ar), 128.4 (2C, Ar), 126.9 (Ar), 126.8 (2C, Ar), 121.3 (Ar), 119.2 (Ar), 58.1 (CH–N), 53.2 (CH_2–N), 24.5 (Me), 24.4 (Me). HRMS (ESI) Calcd for $C_{15}H_{19}N_2$ (MH^+): 227.1548; found: 227.1541.

(*S*)-2-((Pyridin-2-yl)methylamino)-2-phenylethanol (L6)[16]. The reaction was performed on 250 mg (2.33 mmol) of pyridine-2-carboxaldehyde, 320 mg (2.33 mmol) of (*S*)-(+)-2-phenylglycinol and 742 mg (3.50 mmol) of sodium triacetoxyborohydride. The crude product was purified by flash chromatography on silica gel, using dichloromethane/methanol/ammonia (32% in water) (100/3/2) as eluent, to afford **L6** as an orange oil (83%, 442 mg). $[\alpha]_D^{20}$ +72.4 (*c* 1.02, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.56 (d, J = 4.9 Hz, 1H, Ar), 7.63 (dt, J = 7.6, J = 1.8 Hz, 1H, Ar), 7.13–7.41 (m, 7H, Ar), 3.60–3.96 (m, 5H, CH–N, CH_2–N, CH_2–O). ^{13}C NMR ($CDCl_3$, 90 MHz) δ 159.8 (C_{quat}, Ar), 149.3 (Ar), 140.8 (C_{quat}, Ar), 136.7 (Ar), 128.8 (2C, Ar), 127.7 (Ar), 127.6 (2C, Ar), 122.6 (Ar), 122.2 (Ar), 67.2 (CH_2–O), 64.7 (CH–N), 52.7 (CH_2–N).

(*S*)-2-((Pyridin-2-yl)methylamino)-3-methylbutan-1-ol (L8)[17]. The reaction was performed on 300 mg (2.80 mmol) of pyridine-2-carboxaldehyde, 289 mg (2.80 mmol) of (*S*)-(+)-valinol and 890 mg (4.20 mmol) of sodium triacetoxyborohydride. The crude product was purified by flash chromatography on silica gel, using dichloromethane/methanol/ammonia (32% in water) (100/3/2) as eluent, to afford **L8** as an orange oil (80%, 435 mg). $[\alpha]_D^{20}$ +29.5 (*c* 1.02, $CHCl_3$); Lit.[16] $[\alpha]_D^{20}$ +28.2 (*c* 1.00, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.55 (d, J = 4.8 Hz, 1H, Ar), 7.65 (dt, J = 7.6, J = 1.8 Hz, 1H, Ar), 7.14–7.30 (m, 2H, Ar), 4.03 and 3.93 (AB system, J_{AB} = 14.8 Hz, 2H, CH_2–N), 3.67 and 3.44 (ABX system, J_{AX} = 3.9, J_{BX} = 7.2, J_{AB} = 10.9 Hz, 2H, CH_2–O), 2.43–2.53 (m, 1H, CH–N), 1.84 (m, J = 6.8 Hz, 1H, CH of *i*-Pr), 0.99 (d, J = 6.8 Hz, 3H, Me), 0.93 (d, J = 6.8 Hz, 3H, Me). ^{13}C NMR ($CDCl_3$, 90 MHz) δ 160.4 (C_{quat}, Ar), 149.3 (Ar), 136.8 (Ar), 122.5 (Ar), 122.2 (Ar), 65.0 (CH–N), 61.6 (CH_2–O), 52.7 (CH_2–N), 29.8 (CH of *i*-Pr), 19.7 (Me of *i*-Pr), 19.0 (Me of *i*-Pr).

(*R*)-1-Phenyl-*N*-((quinolin-2-yl)methyl)ethylamine (L9). The reaction was performed on 200 mg (1.27 mmol) of quinoline-2-carboxaldehyde, 154 mg (1.27 mmol) of (*R*)-1-phenylethylamine and 405 mg (1.91 mmol) of sodium triacetoxyborohydride. The crude product was purified by flash chromatography on silica gel, using ethyl acetate/petroleum ether/ammonia (32% in water) (20/80/1) as eluent, to afford **L9** as an orange oil (86%, 287 mg). $[\alpha]_D^{20}$ +29.1 (*c* 1.05, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.13 (d, J = 8.2 Hz, 1H, Ar), 8.03 (d, J = 8.5 Hz, 1H, Ar), 7.76 (d, J = 8.1 Hz, 1H, Ar), 7.69 (ddd, J = 8.4, J = 7.0, J = 1.3 Hz, 1H, Ar), 7.53–7.24 (m, 7H, Ar), 3.99 (s, 2H, CH_2–N), 3.94 (q, J = 6.7 Hz, 1H, CH–N), 1.50 (d, J = 6.8 Hz, 3H, Me). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.3 (C_{quat}, Ar), 147.8 (C_{quat}, Ar), 145.5 (C_{quat}, Ar), 136.3 (Ar), 129.4 (Ar), 129.0 (Ar), 128.6 (2C, Ar), 127.6 (Ar), 127.3 (C_{quat}, Ar), 127.0 (Ar), 126.9 (2C, Ar), 126.0 (Ar), 120.7 (Ar), 58.3 (CH–N), 53.7 (CH_2–N), 24.6 (Me). HRMS (ESI) Calcd for $C_{18}H_{19}N_2$ (MH^+): 263.1548; found: 263.1539.

***N*-[(1-(Pyridin-2-yl)ethyl)]-*N*-[(1′*R*)-1′-phenylethyl]amine (L2)[8f,10].** A solution of pyridine-2-carboxaldehyde (500 mg, 4.67 mmol) and (*R*)-1-phenylethylamine (622 mg, 5.13 mmol) in dry THF (20 mL) was stirred at rt over anhydrous $MgSO_4$ for 24 h. The reaction mixture was filtered through a pad of celite, washed with DCM and the solvents were removed under vacuum to yield the corresponding imine (100%, 997 mg).

To a stirred solution of the crude imine (500 mg, 2.38 mmol) in dry THF (18 mL) at 0 °C was added dropwise methylmagnesium bromide (1.67 mL, 5.00 mmol, 3M solution in diethyl ether). The mixture was stirred at 50 °C for 20 h and the reaction was quenched by adding water. The aqueous layer was extracted with Et_2O and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel, using petroleum ether/ethyl acetate/ammonia (32% in water) (90/10/1) as eluent, to afford the two desired diastereoisomers (52%, 281 mg). The first eluted diastereoisomer (1*R*,1′*R*)-**L2** was isolated as an orange oil (122 mg). $[\alpha]_D^{20}$ +171.1 (*c* 0.56, $CHCl_3$); Lit.[8f] $[\alpha]_D^{20}$ −170.0 (*c* 1, $CHCl_3$) for (1*S*,1′*S*)-**L2**. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.61 (d, J = 3.8 Hz, 1H, Ar), 7.61 (dt, J = 7.6, J = 1.8 Hz, 1H, Ar), 7.05–7.35 (m, 7H, Ar), 3.60 (q, J = 6.7 Hz, 1H, CH–N), 3.45 (q, J = 6.6 Hz, 1H, CH–N), 2.04 (brs, 1H, NH), 1.31 (d, J = 6.7 Hz, 3H, Me), 1.28 (d, J = 6.6 Hz, 3H, Me). ^{13}C NMR ($CDCl_3$, 90 MHz)

δ 165.1 (C_{quat}, Ar), 149.8 (Ar), 145.9 (C_{quat}, Ar), 136.4 (Ar), 128.6 (2C, Ar), 127.0 (3C, Ar), 122.1 (Ar), 121.9 (Ar), 56.5 (CH–N), 55.9 (CH–N), 25.3 (Me), 23.6 (Me). The second diastereoisomer (1*S*,1′*R*)-**L2** was isolated as a dark orange oil (159 mg). $[\alpha]_D^{20}$ –8.1 (*c* 0.98, $CHCl_3$); Lit.[8f] $[\alpha]_D^{20}$ +8.2 (*c* 1.1, $CHCl_3$) for (1*R*,1′*S*)-**L2**.^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.54 (d, *J* = 3.8 Hz, 1H, Ar), 7.59 (dt, *J* = 7.6, *J* = 1.8 Hz, 1H, Ar), 7.05–7.35 (m, 7H, Ar), 3.87 (q, *J* = 6.6 Hz, 1H, CH–N), 3.81 (q, *J* = 6.6 Hz, 1H, CH–N), 1.97 (brs, 1H, NH), 1.39 (d, *J* = 6.6 Hz, 6H, Me).^{13}C NMR ($CDCl_3$, 90 MHz) δ 164.8 (C_{quat}, Ar), 149.4 (Ar), 145.9 (C_{quat}, Ar), 136.5 (Ar), 128.5 (2C, Ar), 126.9 (Ar), 126.9 (2C, Ar), 121.9 (Ar), 121.4 (Ar), 56.4 (CH–N), 55.4 (CH–N), 23.8 (Me), 22.2 (Me).

***N*-[(1-(6-Methylpyridin-2-yl)ethyl)]-*N*-[(1′*R*)-1′-phenylethyl]-amine (L5).** A solution of 6-methylpyridine-2-carboxaldehyde (600 mg, 4.95 mmol) and (*R*)-1-phenylethylamine (660 mg, 5.45 mmol) in dry THF (25 mL) was stirred at rt over anhydrous $MgSO_4$ for 24 h. The reaction mixture was filtered through a pad of celite, washed with DCM and the solvents were removed under vacuum to yield the corresponding imine (100%, 1.142 g).

To a stirred solution of the crude imine (400 mg, 1.78 mmol) in dry THF (14 mL) at 0 °C was added dropwise methylmagnesium bromide (1.25 mL, 3.74 mmol, 3M solution in diethyl ether). The mixture was stirred at 50 °C for 20 h and the reaction was quenched by adding water. The aqueous layer was extracted with Et_2O and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel, using petroleum ether/ethyl acetate/ammonia (32% in water) (95/5/1) as eluent, to afford the two desired diastereoisomers (49%, 209 mg). The first eluted diastereoisomer (1*R*,1′*R*)-**L5** was partially separated and isolated as a light yellow solid (50 mg). $[\alpha]_D^{20}$ +174.3 (*c* 0.38, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.49 (t, *J* = 7.6 Hz, 1H, Ar), 7.20–7.37 (m, 5H, Ar), 7.00 (d, *J* = 7.6 Hz, 1H, Ar), 6.91 (d, *J* = 7.6 Hz, 1H, Ar), 3.58 (q, *J* = 6.7 Hz, 1H, CH–N), 3.48 (q, *J* = 6.7 Hz, 1H, CH–N), 2.56 (s, 3H, Me of Py), 1.99 (brs, 1H, NH), 1.28 (d, *J* = 6.7 Hz, 6H, Me). ^{13}C NMR ($CDCl_3$, 60 MHz) δ 163.9 (C_{quat}, Ar), 158.2 (C_{quat}, Ar), 145.6 (C_{quat}, Ar), 136.4 (Ar), 128.4 (2C, Ar), 126.9 (Ar), 126.9 (2C, Ar), 121.3 (Ar), 118.6 (Ar), 56.4 (CH–N), 55.8 (CH–N), 25.1 (Me), 24.7 (Me), 23.6 (Me). HRMS (ESI) Calcd for $C_{18}H_{21}N_2$ (MH^+): 241.1705; found: 241.1693. The second diastereoisomer (1*S*,1′*R*)-**L5** was partially separated and isolated as a light yellow oil (130 mg). $[\alpha]_D^{20}$ –4.9 (*c* 0.96, $CHCl_3$).^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.47 (t, *J* = 7.6 Hz, 1H, Ar), 7.20–7.32 (m, 5H, Ar), 7.00 (d, *J* = 7.3 Hz, 1H, Ar), 6.97 (d, *J* = 7.4 Hz, 1H, Ar), 3.84 (q, *J* = 6.6 Hz, 1H, CH–N), 3.79 (q, *J* = 6.6 Hz, 1H, CH–N), 2.53 (s, 3H, Me of Py), 2.31 (brs, 1H, NH), 1.39 (d, *J* = 6.6 Hz, 3H, Me), 1.36 (d, *J* = 6.6 Hz, 3H, Me). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.0 (C_{quat}, Ar), 158.2 (C_{quat}, Ar), 145.9 (C_{quat}, Ar), 136.4 (Ar), 128.4 (2C, Ar), 126.9 (Ar), 126.8 (2C, Ar), 121.3 (Ar), 118.6 (Ar), 56.4 (CH–N), 55.7 (CH–N), 25.1 (Me), 24.7 (Me), 23.6 (Me). HRMS (ESI) Calcd for $C_{18}H_{21}N_2$ (MH^+): 241.1705; found: 241.1698.

(*S*)-2-(1-(Pyridin-2-yl)ethylamino)-2-phenylethanol (L7). A solution of pyridine-2-carboxaldehyde (213 mg, 2.00 mmol) and (*S*)-(+)-2-phenylglycinol (300 mg, 2.2 mmol) in dry THF (25 mL) was stirred at rt over anhydrous $MgSO_4$ for 24 h. The reaction mixture was filtered through a pad of celite, washed with DCM and the solvents were removed under vacuum to yield the corresponding imine (100%, 451 mg).

To a stirred solution of the crude imine (451 mg, 2.00 mmol) in dry THF (15 mL) at 0 °C was added dropwise methylmagnesium bromide (2.07 mL, 6.20 mmol, 3M solution in diethyl ether). The mixture was stirred at 50 °C for 20 h and the reaction was quenched by adding water. The aqueous layer was extracted with Et_2O and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel, using dichloromethane/methanol/ammonia (32% in water) (100/2/2) as eluent, to afford the two desired diastereoisomers (72%, 326 mg). The first eluted diastereoisomer (1′*S*)-**L7** was partially separated and isolated as an orange oil (96 mg). $[\alpha]_D^{20}$ +5.9 (*c* 1.02, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.49 (d, *J* = 4.2 Hz, 1H, Ar), 7.56 (dt, *J* = 7.7, *J* = 1.8 Hz, 1H, Ar), 7.05–7.32 (m, 7H, Ar), 3.83–3.94 (m, 2H, CH–N), 3.75 and 3.58 (ABX system, J_{AX} = 4.0, J_{BX} = 7.9, J_{AB} = 10.7 Hz, 2H, CH_2–O), 2.74 (brs, 2H, NH and OH), 1.42 (d, *J* = 6.6 Hz, 3H, Me). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.9 (C_{quat}, Ar), 149.0 (Ar), 140.9 (C_{quat}, Ar), 136.5 (Ar), 128.5 (2C, Ar), 127.4 (Ar), 127.3 (2C, Ar), 121.9 (Ar), 121.3 (Ar), 66.3 (CH_2–O), 62.0 (CH–N), 56.1 (CH–N), 21.7 (Me). HRMS (ESI) Calcd for $C_{15}H_{19}N_2O$ (MH^+): 243.1497; found: 243.11492. The second diastereoisomer was not isolated pure and the ^{1}H NMR chemical shifts were deduced from spectra of the diastereoisomeric mixture. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.58 (d, *J* = 5.6 Hz, 1H, Ar), 7.64 (dt, *J* = 7.6, *J* = 1.8 Hz, 1H, Ar), 7.05–7.40 (m, 7H, Ar), 3.59–3.96 (m, 4H, 2 CH–N and CH_2–O), 1.35 (d, *J* = 6.7 Hz, 3H, Me).

***N*-[(5-Methylthiophen-2-yl)(phenyl)methyl]-*N*-[(1′*R*)-1′-phenylethyl]amine (L10).** A solution of 5-methylthiophen-2-carboxaldehyde (500 mg, 3.96 mmol) and (*R*)-1-phenylethylamine (528 mg, 4.36 mmol) in dry THF (20 mL) was stirred at rt over anhydrous $MgSO_4$ for 24 h. The reaction mixture was filtered over a pad of celite, washed with DCM and the solvents were removed under vacuum to yield the corresponding imine (81%, 732 mg).

To a stirred solution of the crude imine (350 mg, 1.53 mmol) in dry Et_2O (20 mL) at 0 °C was added dropwise phenyllithium (1.78 mL, 3.20 mmol, 1.8 M solution in dibutyl ether). The mixture was stirred at rt for 18 h and the reaction was quenched by adding water. The aqueous layer was extracted with Et_2O and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel, using petroleum ether/diethyl ether (98/2) as eluent, to afford the two desired diastereoisomers (53%, 249 mg). The first eluted diastereoisomer (*1′R*)-**L10** was partially separated and isolated as a colourless oil (46 mg). $[\alpha]_D^{20}$ +42.5 (*c* 0.16, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.23–7.42 (m, 10H, Ar), 6.48–6.51 (m, 1H, Ar), 6.38–6.42 (m, 1H, Ar), 4.69 (s, 1H, CH–N), 3.64 (q, *J* = 6.6 Hz, 1H, CH–N), 2.41 (s, 3H, Me), 1.80 (brs, 1H, NH), 1.33 (d, *J* = 6.6 Hz, 3H, Me). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 147.2 (C_{quat}, Ar), 145.2 (C_{quat}, Ar), 143.1 (C_{quat}, Ar), 138.9 (C_{quat}, Ar), 128.5 (4C, Ar), 127.6 (2C, Ar), 127.4 (Ar), 127.0 (Ar), 126.8 (2C, Ar), 124.4 (Ar), 124.0 (Ar), 59.9 (CH–N), 54.9 (CH–N), 24.7 (Me), 15.3 (Me). HRMS (ESI) Calcd for $C_{20}H_{21}NNaS$ ($M+Na^+$): 330.1292; found: 330.1298. The second diastereoisomer was not isolated pure and the ^{1}H NMR chemical shifts were deduced from the spectra of the diastereoisomeric mixture. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.20–7.45 (m, 10H, Ar),

6.55–6.63 (m, 2H, Ar), 4.81 (s, 1H, CH–N), 3.85 (q, J = 6.7 Hz, 1H, CH–N), 2.46 (s, 3H, Me), 1.70 (brs, 1H, NH), 1.38 (d, J = 6.7 Hz, 3H, Me).

***N*-[(Pyridin-2-yl)(phenyl)methyl)]-*N*-[(1′*R*)-1′-phenylethyl]-amine (L3)[13].** A solution of 2-benzoylpyridine (2.00 g, 10.92 mmol), (*R*)-1-phenylethylamine (1.45 g, 12.01 mmol) and 4-methylbenzenesulfonic acid (207 mg, 1.09 mmol) in toluene (50 mL) was refluxed for 40 h using a Dean–Stark apparatus. After cooling, the solvent was removed and the residue was dried under vacuum. The crude imine was dissolved in MeOH (60 mL) and sodium borohydride (413 mg, 10.92 mmol) was added portionwise at 0 °C. The mixture was stirred overnight at rt and the reaction was quenched by adding saturated aqueous NH_4Cl. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with a saturated aqueous NaCl solution, dried over $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel, using petroleum ether/ethyl acetate (from 95/5 to 90/10) as eluent, to afford the two desired diastereoisomers (91%, 2.86 g). The first eluted diastereoisomer (1*R*,1′*R*)-**L3** was partially separated and isolated as a light yellow oil (432 mg). $[\alpha]_D^{20}$ +11.4 (*c* 1.00, $CHCl_3$); Lit.[13] $[\alpha]_D^{20}$ +11.5 (*c* 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.60 (d, J = 4.9 Hz, 1H, Ar), 7.63 (dt, J = 7.6, J = 1.8 Hz, 1H, Ar), 7.10–7.35 (m, 12H, Ar), 4.78 (s, 1H, CH–N), 3.65 (q, J = 6.6 Hz, 1H, CH–N), 2.63 (brs, 1H, NH), 1.38 (d, J = 6.6 Hz, 3H, Me). ^{13}C NMR ($CDCl_3$, 90 MHz) δ 162.8 (C_{quat}, Ar), 149.7 (Ar), 145.7 (C_{quat}, Ar), 143.4 (C_{quat}, Ar), 136.5 (Ar), 128.6 (2C, Ar), 128.6 (2C, Ar), 127.7 (2C, Ar), 127.2 (Ar), 127.1 (Ar), 127.0 (2C, Ar), 122.8 (Ar), 122.1 (Ar), 65.3 (CH–N), 55.9 (CH–N), 24.5 (Me). The second diastereoisomer (1*S*,1′*R*)-**L3** was partially separated and isolated as a light yellow oil (554 mg). $[\alpha]_D^{20}$ +103.4 (*c* 1.00, $CHCl_3$); Lit.[13] $[\alpha]_D^{20}$ +101.2 (*c* 1.23, $CHCl_3$).^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.56 (d, J = 4.9 Hz, 1H, Ar), 7.50 (dt, J = 7.6, J = 1.8 Hz, 1H, Ar), 7.20–7.35 (m, 10H, Ar), 7.05–7.12 (m, 2H, Ar), 4.71 (s, 1H, CH–N), 3.66 (q, J = 6.7 Hz, 1H, CH–N), 2.63 (brs, 1H, NH), 1.41 (d, J = 6.6 Hz, 3H, Me). ^{13}C NMR ($CDCl_3$, 90 MHz) δ 162.4 (C_{quat}, Ar), 149.6 (Ar), 146.0 (C_{quat}, Ar), 143.2 (C_{quat}, Ar), 137.0 (Ar), 130.0 (2C, Ar), 129.2 (2C, Ar), 129.1 (2C, Ar), 128.6 (Ar), 127.8 (Ar), 127.4 (2C, Ar), 122.7 (Ar), 122.3 (Ar), 65.4 (CH–N), 55.4 (CH–N), 25.2 (Me).

This reaction was also performed with the (*S*)-1-phenylethylamine to give (1*S*,1′*S*)-**L3** and (1*R*,1′*S*)-**L3** with similar results.

Preparation of the $PdCl_2$-(1*S*,1′*R*)-L3 complex. To a stirred solution of (1*S*,1′*R*)-**L3** (50 mg, 0.17 mmol) in MeOH (4 mL) was added Na_2PdCl_4 (51 mg, 0.17 mmol). The mixture was stirred at rt for 16 h, then the solvent was removed by evaporation under vacuum. The residue was then filtered through a pad of silica gel [firstly eluted with ethyl acetate/petroleum ether (4/6) to remove traces of **L3** and then eluted with ethyl acetate] to afford the corresponding palladium complex as a yellow solid (96%, 76 mg). ^{1}H NMR ([d_6]DMSO, 300 MHz) δ 8.43 (d, J = 6.0 Hz, 1H, Ar), 8.09 (d, J = 7.2 Hz, 2H, Ar), 7.95 (d, J = 8.1 Hz, 2H, Ar), 7.72 (dt, J = 7.7, J = 1.3 Hz, 1H, Ar), 7.40–7.55 (m, 3H, Ar), 7.05–7.25 (m, 5H, Ar), 6.54 (s, 1H, NH), 5.45 (s, 1H, CH–N), 4.04–4.15 (m, 1H, CH–N), 1.74 (d, J = 6.7 Hz, 3H, Me). ^{13}C NMR ([d_6]DMSO, 75 MHz) δ 165.7 (C_{quat}, Ar), 148.3 (Ar), 139.8 (Ar), 138.4 (C_{quat}, Ar), 137.8 (C_{quat}, Ar), 129.6 (2C, Ar), 129.0 (Ar), 128.9 (2C, Ar), 128.5 (2C, Ar), 128.3 (Ar), 127.9 (2C, Ar), 123.4 (Ar), 122.7 (Ar), 73.5 (CH–N), 64.7 (CH–N), 21.4 (Me). HRMS (ESI-, MeOH) Calcd for $C_{20}H_{19}N_2{}^{35}Cl_2{}^{104}Pd$ (M–H): 460.9966; found: 460.9968.

Synthesis of ethyl 3,3,3-trifluoro-2-hydroxy-2-(1-methyl-1*H*-indol-3-yl)propanoate 3a[6d,6e] using procedure A. In a flame dried schlenk tube, $Yb(OTf)_3$ (15.5 mg, 0.025 mmol) and (1*R*,1′*S*)-**L3** (7.2 mg, 0.025 mmol) were dissolved in freshly distilled CH_2Cl_2 (0.5 mL) under argon atmosphere. The mixture was stirred 2 h at rt and a solution of ethyl trifluoropyruvate (46.8 mg, 0.275 mmol) in freshly distilled CH_2Cl_2 (0.5 mL) was added. The reaction mixture was stirred for another 1.5 h at rt and the schlenk tube was placed at –20 °C. A solution of *N*-methylindole (32.8 mg, 0.25 mmol) in freshly distilled CH_2Cl_2 (0.5 mL) was added and the mixture was stirred at –20 °C. After completion of the reaction (72 h at –20 °C, monitored by TLC), water was added and the aqueous layer was extracted several times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by preparative TLC, using pentane/diethyl ether (7/3) as eluent, to afford **3a** as a white solid (82%, 62 mg) with 78% ee determined by HPLC analysis [CHIRALPAK IA column 250 × 4.6 (L × I.D.) 5 μm, hexane/2-propanol (v/v: 9/1) at 0.5 mL min^{-1}, 254 nm, 20 °C]: 18.64 min (*S*), 21.72 min (*R*). ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.94 (d, J = 7.9 Hz, 1H, Ar), 7.16–7.36 (m, 4H, Ar), 4.30–4.56 (m, 3H, OH and CH_2), 3.76 (s, 3H, N–Me), 1.37 (t, J = 7.2 Hz, 3H, Me of CO_2Et).

Preparation of the $Yb(OTf)_3$-(1*R*,1′*S*)-L3 complex. In a flame dried schlenk tube, $Yb(OTf)_3$ (322.6 mg, 0.520 mmol) and (1*R*,1′*S*)-**L3** (150 mg, 0.520 mmol) were dissolved in freshly distilled CH_2Cl_2 (30 mL) under argon atmosphere. The mixture was stirred 18 h at rt and the solvent was evaporated under vacuum to give a white powder (472 mg). The complex was stored and weighed under argon in a glove box.

General procedure for the alkylation of indoles 1a–c using procedure B. In a flame dried schlenk tube, $Yb(OTf)_3$-(1*R*,1′*S*)-**L3** complex (22.7 mg, 0.025 mmol) and ethyl or methyl trifluoropyruvate **2a**,**b** (0.275 mmol) were dissolved in freshly distilled CH_2Cl_2 (1 mL) under argon atmosphere. The mixture was stirred 2 h at rt and the schlenk tube was placed at –20 °C. A solution of indole **1a–c** (0.25 mmol) in freshly distilled CH_2Cl_2 (0.5 mL) was added and the mixture was stirred at –20 °C. After completion of the reaction (72 h at –20 °C, monitored by TLC), water was added and the aqueous layer was extracted several times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum to yield the crude product.

Ethyl 3,3,3-trifluoro-2-hydroxy-2-(1-methyl-1*H*-indol-3-yl)-propanoate 3a[6d,6e]. The reaction was performed according to procedure B with 46.8 mg (0.275 mmol) of ethyl trifluoropyruvate and 32.8 mg (0.25 mmol) of *N*-methylindole. The crude product was purified by preparative TLC, using pentane/diethyl ether (7/3) as eluent, to afford **3a** as a white solid (82%, 62 mg) with 82% ee determined by HPLC analysis [CHIRALPAK IA column 250 × 4.6 (L × I.D.) 5 μm, hexane/2-propanol (v/v: 9/1) at 0.5 mL min^{-1}, 254 nm, 20 °C]: 18.78 min (*S*), 21.83 min (*R*). $[\alpha]_D^{20}$ +22.0 (*c* 0.5, $CHCl_3$); Lit.[6d] $[\alpha]_D^{20}$ +21.3 (*c* 2.19, $CHCl_3$) for (*S*)-**3a** for 89% ee. The analyses are identical as previously.

Ethyl 3,3,3-trifluoro-2-hydroxy-2-(1*H*-indol-3-yl)propanoate 3b[6c–6e]. The reaction was performed according to procedure

B with 46.8 mg (0.275 mmol) of ethyl trifluoropyruvate and 29.3 mg (0.25 mmol) of indole. The crude product was purified by preparative TLC, using pentane/diethyl ether (7/3) as eluent, to afford **3b** as a colorless oil (78%, 56 mg) with 74% ee determined by HPLC analysis [CHIRALPAK IA column 250 × 4.6 (L × I.D.) 5 μm, hexane/2-propanol (v/v: 85/15) at 0.7 mL min^{-1}, 254 nm, 20 °C]: 13.05 min (major), 15.85 min (minor). $[\alpha]_D^{20}$ +11.6 (*c* 0.54, $CHCl_3$); Lit.[6d] $[\alpha]_D^{20}$ +12.3 (*c* 1.91, $CHCl_3$) for **3b** for 83% ee. ^1H NMR ($CDCl_3$, 250 MHz) δ 8.24 (brs, 1H, NH), 7.94 (d, J = 7.5 Hz, 1H, Ar), 7.55–7.12 (m, 4H, Ar), 4.58 (s, 1H, OH), 4.45 (dq, J = 10.7, 7.1 Hz, 2H, CH_2), 4.41 (dq, J = 10.7, 7.1 Hz, 2H, CH_2), 1.36 (t, J = 7.1 Hz, 3H, Me of CO_2Et).

Ethyl 3,3,3-trifluoro-2-hydroxy-2-(2-methyl-1*H*-indol-3-yl)-propanoate 3c. The reaction was performed according to procedure B with 46.8 mg (0.275 mmol) of ethyl trifluoropyruvate and 32.8 mg (0.25 mmol) of 2-methylindole. The crude product was purified by preparative TLC, using pentane/diethyl ether (7/3) as eluent, to afford **3a** as a colorless oil (76%, 58 mg) with 51% ee determined by HPLC analysis [CHIRALPAK IA column 250 × 4.6 (L × I.D.) 5 μm, hexane/2-propanol (v/v: 85/15) at 0.7 mL min^{-1}, 254 nm, 20 °C]: 11.92 min (minor), 14.55 min (major). $[\alpha]_D^{20}$ −3.7 (*c* 0.44, $CHCl_3$). ^1H NMR ($CDCl_3$, 250 MHz) δ 8.04 (brs, 1H, NH), 7.85 (d, J = 7.7 Hz, 1H, Ar), 7.38–7.04 (m, 3H, Ar), 4.62–4.23 (m, 2H, CH_2), 4.06 (s, 1H, OH), 2.53 (s, 3H, Me), 1.38 (t, J = 7.2 Hz, 3H, Me of CO_2Et). ^{13}C NMR ($CDCl_3$, 63 MHz) δ 169.4 (CO), 135.3 (Ar), 134.6 (Ar), 126.8 (Ar), 123.9 (q, J = 283.2 Hz, CF_3), 121.6 (CH, Ar), 120.5 (CH, Ar), 120.2 (CH, Ar), 110.4 (CH, Ar), 103.9 (Ar), 77.5 (q, J = 31.1 Hz, C–OH), 63.6 (CH_2), 14.1 (Me), 13.9 (Me of CO_2Et). HRMS (ESI+) Calcd for $C_{14}H_{14}F_3NNaO_3$ (M+Na): 324.0818; found: 324.0810.

Methyl 3,3,3-trifluoro-2-hydroxy-2-(1-methyl-1*H*-indol-3-yl)-propanoate 3d[6c]. The reaction was performed according to procedure B with 42.9 mg (0.275 mmol) of methyl trifluoropyruvate and 32.8 mg (0.25 mmol) of *N*-methylindole. The crude product was purified by preparative TLC, using pentane/diethyl ether (7/3) as eluent, to afford **3d** as a white solid (81%, 58 mg) with 79% ee determined by HPLC analysis [CHIRALPAK IA column 250 × 4.6 (L × I.D.) 5 μm, hexane/2-propanol (v/v: 85/15) at 0.7 mL min^{-1}, 254 nm, 20 °C]: 10.98 min (major), 12.08 min (minor). $[\alpha]_D^{20}$ +24.1 (*c* 0.5, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.87 (d, J = 8.1 Hz, 1H, Ar), 7.41–7.24 (m, 3H, Ar), 7.19 (ddd, J = 8.1, 6.8, 1.4 Hz, 1H, Ar), 4.35 (s, 1H, OH), 3.97 (s, 3H, Me), 3.82 (s, 3H, N–Me).

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Notes and references

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