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Indoline-3-Carboxylic Acid Derived Organocatalysts for the *anti*-Mannich Reaction

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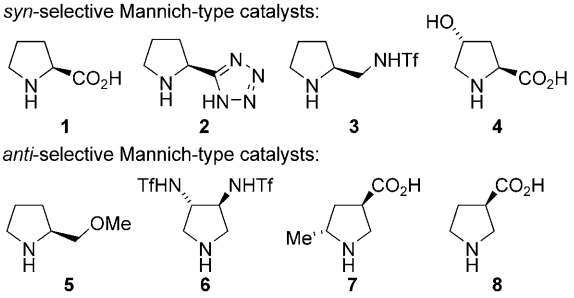
Abstract: Mannich type reactions of a preformed aldimine with various carbonyl compounds were investigated with a series of functionalised indoline derivatives as catalysts: indoline-3-carboxylic acid, the diphenylcarbinol analogue and O-protected silyl ether analogues. All compounds were readily prepared in enantiopure form by using an enzymatic kinetic resolution as a key step ($E \gg 100$). The alcohol and ether catalysts failed to induce complete chirality transfer but did afford the Mannich bases in good yields and high diastereomeric ratios, whereas the acid catalyst gave the products in a highly diastereo- and enantioselective manner. The absolute configuration of the products was determined by a *syn*–*anti* isomerisation protocol, initiated by the sterically demanding base 1,8-diazabicyclo[5.4.0]undec-7-ene.

Keywords: *Candida antarctica* lipase B (CAL-B) · diastereoselectivity · epimerization · kinetic resolution · organocatalysis

Introduction

In the past decade, asymmetric organocatalysis has emerged as a powerful tool for the synthesis of chiral building blocks.[1] Nowadays, it represents an attractive alternative to metal-based catalysts due to ease of handling, the availability of both catalyst enantiomers, price and miscellaneous environmental aspects (for example, toxicity). The most investigated and predominant catalyst in this area is the naturally occurring amino acid L-proline (**1**), which was found to be very effective in the intramolecular aldol reaction (Hajos–Parrish–Eder–Sauer–Wiechert reaction) in the early 1970s.[2] Despite its simplicity, the amino acid **1** has been used since then for a broad diversity of reactions, for example, inter- and intramolecular aldol, Mannich type and Michael reactions, aminations and cascade reactions, to furnish the products in good yield and often with good selectivity.[3a,b] Of course, **1** is not a "universal asymmetric catalyst" and also has its drawbacks. Beside the fact that most of the above named reactions need to be conducted in polar solvents (DMSO, DMF, alcohols), high catalyst loadings (up to 20 mol%) are often essential and are accompanied by long reaction times. Nevertheless, the concept of this reaction type has been assumed and a whole series of catalysts with various properties have been designed, most of them derivatives of **1** (Scheme 1).[3c–l] The subject of this publication is the Mannich reaction,[4] which generates β-amino carbonyl compounds or γ-carbonyl-α-amino acid derivatives through C–C bond formation. These structural motifs can be found in a broad range of pharmaceuticals and are common in natural products, justifying the importance of this reaction. Enantioselective approaches have not only been successfully investigated with metal species,[5] but also utilising organocatalysts.[6] Proline (**1**), for example, has been proven to be a



Scheme 1. Organocatalysts successfully employed in the Mannich type reaction.

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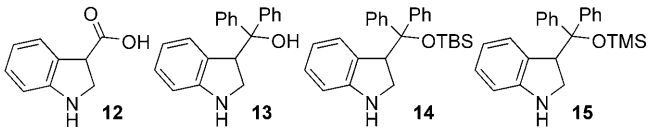
very efficient catalyst in the reaction with enolisable carbonyl compound donors. In all reported cases, the *syn* Mannich bases were obtained in high diastereomeric ratio (d.r.) and optical purity.[7] To overcome the lack of solubility, Ley and co-workers designed a tetrazole derivative **2** (Scheme 1), which was found to have a higher catalytic activity than **1** without loss of stereochemical control.[8] Other organocatalysts that have been successfully applied in the *syn*-selective Mannich type addition are sulfonamidomethyl-pyrrolidine[9] **3** (Tf = trifluoromethanesulfonyl) and 4-hydroxy-proline (**4**).[7e]

The first asymmetric *anti*-selective organocatalyst, (*S*)-methoxypyrrolidine (SMP, **5**),[10] was reported in 2002 by Barbas and Còrdova who described isolation of the products in high enantiomeric excess (*ee*) (up to 92%) and good yield (up to 78%). From thereon, considerable efforts have been devoted to find other catalysts that give the *anti* products in a highly diastereo- and enantioselective manner, but the reports are still limited.[11] Nevertheless, further improvements could be achieved by changing the substitution pattern in the pyrrolidine ring to produce highly *anti*-selective catalysts, such as the sulfonamide **6**,[12] 5-methyl-β-proline (**7**)[13] and β-proline (**8**)[14] (Scheme 1). Although **6** and **8** were very effective catalysts for the addition of preformed *N*-*p*-methoxyphenyl (PMP) protected α-imino ethylglyoxalate (**9**) to aldehydes and ketones, catalyst **7** was ineffective in the addition to ketones. The authors reasoned that the low reactivity originated from the slow formation of the enamine intermediate **10** due to the disfavoured interaction with the methyl group of the catalyst.[14a] The stereochemical outcome of the reaction (with aldehyde donors) catalysed by the β-proline catalysts **7** and **8** can be explained by a boat-like transition state, in which a reversal of facial selectivity is assumed (Scheme 2). In the case of catalyst **7**, the *cis* conformation of the enamine intermediate **10** ought to be favoured because of the sterically demanding methyl group at C-5; the enamine conformation **11** (s-*cis*/s-*trans*) of catalyst **8** should have similar free energies. Proton transfer from the acid onto the aldimine **9** suggests that only the *cis* conformer is properly positioned to allow C–C bond formation. As a result, nucleophilic attack from the *Si*-face of the enamine onto the *Si*-face of the aldimine **9** becomes possible to furnish the *anti* isomers.[14]

The seminal work of the groups of List[15a,b] and Seebach[15c,d] on proline catalysed reactions showed that there is an additional equilibrium between the enamine and the oxazolidine (derived from the addition of a carbonyl compound) but the exact mechanism of the β-proline catalysis remains unclear. Although some theoretical density functional theory (DFT) studies were performed, in relation to the position of the acidic function[16a] (α or β) and the stereoselectivity,[16b] an oxazolidinone intermediate cannot be ruled out.

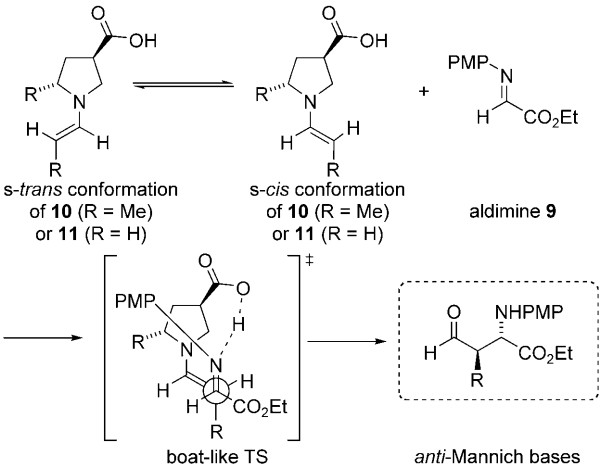
As a part of our ongoing project to apply biocatalysts in organic synthesis,[17] we report in detail our latest results on the chemoenzymatic synthesis of indoline-3-carboxylic acid (**12**) and derivatives **13**–**15** (TBS = *tert*-butyldimethylsilyl; TMS = trimethylsilyl) and their application as organocatalysts in the *anti* Mannich reaction.[18]



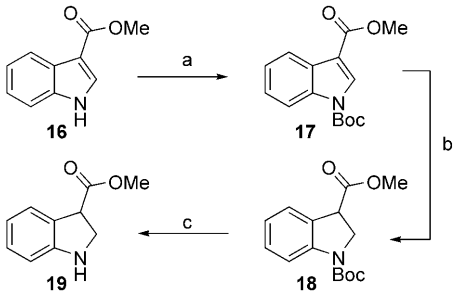
Results and Discussion

We started our synthesis (Scheme 3) from methyl indole-3-carboxylate (**16**), which was protected with Boc_2O (Boc = *tert*-butoxycarbonyl), under standard conditions, to furnish **17** in high yield (95%). Reduction of the double bond was achieved with Mg in MeOH[19] (**18**, 93% yield), followed by deprotection with trifluoroacetic acid (TFA) to give the racemic ester **19** in very good yield (97%).

In a previous study of structurally related methyl-2,3-dihydro-1*H*-indencarboxylate, conditions for an enzymatic kinetic resolution were determined, established and optimised.[20] Therefore, we could adapt those findings and added the

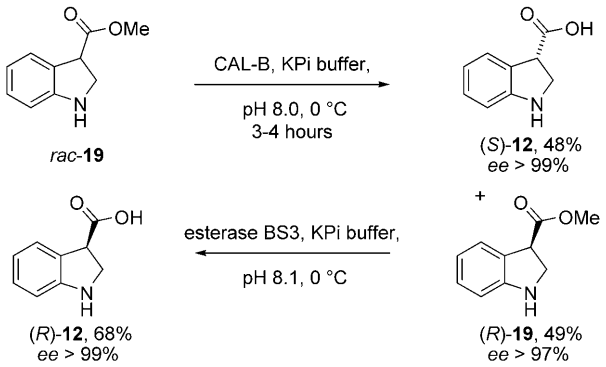


Scheme 2. Proposed transition state of β-proline catalysts **7** and **8** for the indirect *anti*-selective Mannich type addition onto the preformed aldimine **9**.[12,13]



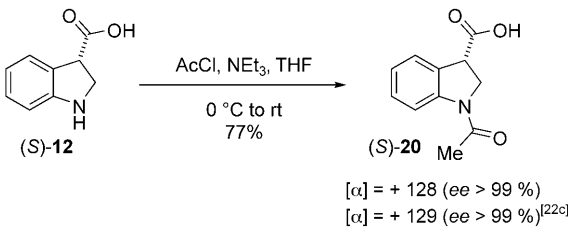
Scheme 3. Synthesis of *rac*-**19**. Reagents and conditions: a) NaH, Boc_2O, THF, 95%; b) Mg turnings, MeOH, 93%; c) TFA, CH_2Cl_2, 97%.

enzyme CAL-B (*Candida antarctica* lipase B) to a stirred solution of ester *rac*-**19** in a potassium phosphate buffer (pH 8.0; 100 mM). In contrast to our earlier results, we had to decrease the temperature of the reaction mixture to 0°C because although the product (*S*)-**12** was obtained in a respectable 95% *ee* at room temperature, this was too low for our purpose (full data not shown). At decreased temperatures (0°C), an ultimate enzymatic kinetic resolution was obtained at 50% conversion with an enantioselectivity $E \gg 100$ (Scheme 4). Both products were obtained in nearly optically pure form and in excellent yield [(*R*)-**19**: 49%, *ee* >97%; (*S*)-**12**: 48%, *ee* >99%]. Furthermore, 2.50 g of *rac*-**19** were completely resolved within 4 h by using only 200 mg of Novozyme435 (the immobilised form of *Candida antarctica* lipase B, Novo Nordisk, Denmark); the protein content in Novozyme435 was determined to be 2% w/w of the total mass.[21] A real catalytic ratio of 1:500 with respect to the enzyme/substrate net weight was used. This enzymatic kinetic resolution provides the first access to enantiopure (*S*)-**12** and derivatives, which are promising precursors for the ergoline framework, for example.[22a,b] The synthesis of acid (*R*)-**12** is also feasible. Whilst standard saponification leads to racemisation of the ester **19**, enzymatic hydrolysis of ester (*R*)-**19** with esterase BS3 (Codexis) furnishes the desired acid (*R*)-**12**.



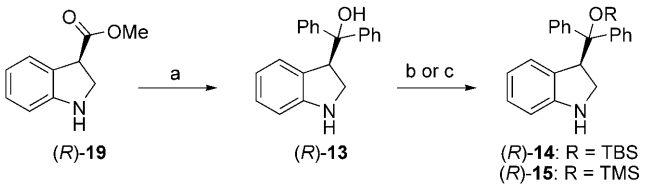
Scheme 4. Enzyme-mediated synthesis of (*R*)- and (*S*)-acid **12**.

The absolute configuration of the hydrolysed product (*S*)-**12** was determined by treating an analytical sample with acetyl chloride (Scheme 5) to give the known acetamide (*S*)-**20** in 77% yield, under unoptimised conditions.[22c]



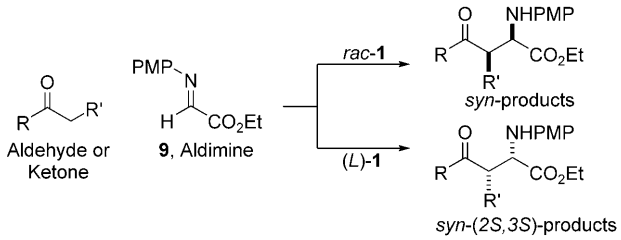
Scheme 5. Determination of the absolute configuration by means of chemical correlation.

To further investigate the use of indoline derivates as asymmetric organocatalysts, enantiopure ester (*R*)-**19** was subjected to a Grignard reaction to afford the diphenylcarbinol (*R*)-**13** in 51% yield (Scheme 6). α,α-Diaryl and silyl-protected-α,α-diaryl catalysts have been exploited in different reactions with remarkable success[23] therefore, the carbinol (*R*)-**13** was protected with a TBS or TMS group to afford the silyl ethers (*R*)-**14** and (*R*)-**15**, respectively.



Scheme 6. Synthesis of diphenylcarbinols **13**–**15**. Reagents and conditions: a) PhMgBr, Et_2O, 51%; b) TBSTf, 2,6-lutidine, CH_2Cl_2, 83%; c) TMSTf, 2,6-lutidine, CH_2Cl_2, 86%.

Determination of the absolute configuration: Prior to the investigation of the catalytic potential of compounds **12**–**15**, an analytical setup (HPLC) was needed for all transformations. Therefore, the *syn* products were synthesised according to literature procedures in racemic and enantiopure form (Scheme 7).[3c,7e]



Scheme 7. Synthesis of *syn* Mannich bases catalysed by **1**.

To determine the absolute configuration of the *anti* isomers we used a method recently disclosed by our group; a *syn–anti* epimerisation of aldehydes with 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) as base.[18] In contrast to previously described methods, which used imidazole as base for the epimerisation of various carbonyl compounds,[24] a significant enhancement on the reaction rate was obtained (20 min versus 17 h) by changing the base, without effect on the outcome of the reaction. Although there is a major difference in the carbonyl activity of aldehydes and ketones, our method ought to be transferable to ketones. As expected, the reaction times increased to 2.5 h for the ketones (note: imidazole promoted epimerisation of a 3-pentanone derived Mannich base took 7 days),[14a] HPLC (Figure 1) and ^1H NMR spectroscopic analysis revealed that no undesired side reaction occurred. Thus, when the product *syn*-**21** was epimerised at C-3 (**B**→**A**, Figure 1) all four possible iso-

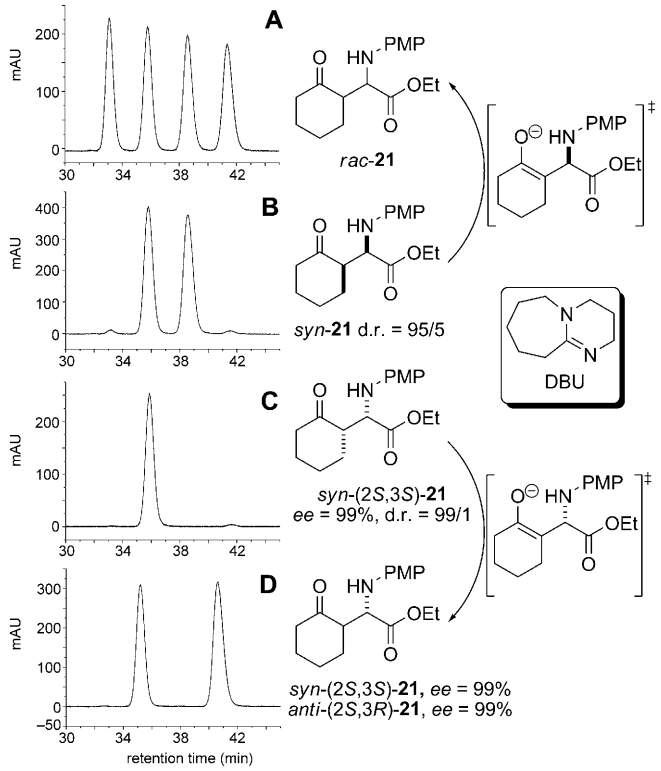


Figure 1. Representative procedure for the determination of the absolute configuration of the Mannich type reaction (controlled epimerisation of racemic *syn*-**21** and *syn*-(2*S*,3*S*)-**21**; DBU as base) and corresponding HPLC traces (column: Chiralpak IA (Daicel) [length: 25 cm, average internal diameter: 0.46 cm], flow rate: 0.5 mL min^{-1}, eluent: *n*-heptane/2-PrOH (92:8); R_t [(2*R*,3*S*)-**21**] = 33.1 min, R_t [(2*S*,3*S*)-**21**] = 35.8 min, R_t [(2*R*,3*R*)-**21**] = 38.6 min, R_t [(2*S*,3*R*)-**21**] = 41.4 min). **A**: racemic mixture of all diastereomers [*rac*-**21**] after epimerisation; **B**: *syn* diastereomers of compound **21** prepared with *rac*-**1**; **C**: enantiopure (2*S*,3*S*)-**21** prepared with (*S*)-**1**; **D**: ~1:1 mixture of epimers (2*S*,3*S*)-**21** and (2*S*,3*R*)-**21**, after epimerisation.

mers were formed in almost equal amounts. Likewise, the epimerisation of the enantiopure product (2*S*,3*S*)-**21** afforded the *anti* isomer (2*S*,3*R*)-**21** in an almost equal amount (**C**→**D**). This method was successfully applied for almost all of the aldehyde- and ketone-derived Mannich bases as part of our investigation (Table 1; not suitable for derivatives **27** and **28**).

Application: With a reliable analytical setup and the pure compounds **12**–**15** in hand, we initially started to investigate the catalytic efficacy of diphenylcarbinol **13**. The reactions were carried out with 15 mol% **13** at room temperature in toluene (Table 2). In all cases, the reactions were highly diastereoselective, which demonstrated the importance of the β-functionality for *anti* stereocontrol. Moreover, excellent yields of all products **22**–**28** were obtained (up to 95%) in a short period of time. For instance, with propanal as the donor, the Mannich product (±)-*anti*-**27** could be obtained in only 10 min and with a remarkable yield and selectivity (93%, d.r. > 99:1; Table 2, entry 6).

Table 1. Summary of the retention times of Mannich products **21**–**26**, based on the controlled epimerisation with DBU as base.

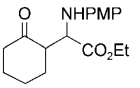
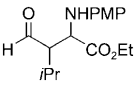
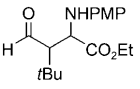
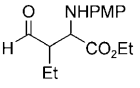
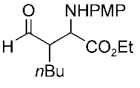
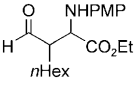
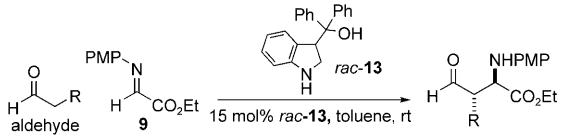
Compound	Retention times [min]	HPLC conditions
	(2*R*,2*S*)-**21** = 33.1 (2*S*,3*S*)-**21** = 35.8 (2*R*,3*R*)-**21** = 38.6 (2*S*,3*R*)-**21** = 41.4	column: Chiralpak IA (Daicel) flow rate: 0.5 mL min^{-1} solv.: *n*-heptane/2-PrOH (92/8) detection: λ = 220 nm
	(2*R*,3*R*)-**22** = 13.1 (2*S*,3*R*)-**22** = 16.1 (2*S*,3*S*)-**22** = 17.6 (2*R*,3*S*)-**22** = 20.8	column: Chiralpak IC (Daicel) flow rate: 1.5 mL min^{-1} solv.: *n*-hexane/2-PrOH (96/4) detection: λ = 240 nm
	(2*R*,3*R*)-**23** = 17.0 (2*S*,3*R*)-**23** = 21.4 (2*S*,3*S*)-**23** = 27.7 (2*R*,3*S*)-**23** = 30.8	column: Chiralpak IC (Daicel) flow rate: 1.5 mL min^{-1} solv.: *n*-hexane/2-PrOH (98/2) detection: λ = 250 nm
	(2*R*,3*R*)-**24** = 28.4 (2*S*,3*R*)-**24** = 30.5 (2*S*,3*S*)-**24** = 37.4 (2*R*,3*S*)-**24** = 39.3	column: Chiralpak IC (Daicel) flow rate: 1.5 mL min^{-1} solv.: *n*-hexane/2-PrOH (98/2) detection: λ = 254 nm
	(2*R*,3*R*)-**25** = 13.9 (2*S*,3*R*)-**25** = 15.7 (2*S*,3*S*)-**25** = 17.4 (2*R*,3*S*)-**25** = 21.2	column: Chiralpak IC (Daicel) flow rate: 1.5 mL min^{-1} solv.: *n*-hexane/2-PrOH (96/4) detection: λ = 240 nm
	(2*R*,3*R*)-**26** = 13.5 (2*S*,3*R*)-**26** = 14.5 (2*S*,3*S*)-**26** = 16.6 (2*R*,3*S*)-**26** = 19.8	column: Chiralpak IC (Daicel) flow rate: 1.5 mL min^{-1} solv.: *n*-hexane/2-PrOH (96/4) detection: λ = 240 nm

Table 2. Indirect *anti*-selective Mannich reaction with diphenylcarbinol *rac*-**13** as catalyst.



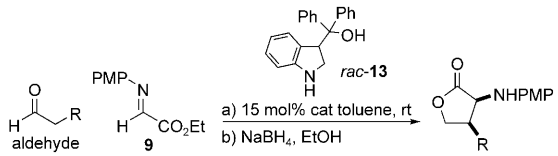
Entry	R	Product	Time	d.r. [*anti*/*syn*]	Yield [%]
1[a]	*i*Pr	(±)-*anti*-**22**	1 h	> 98:2	79
2[a]	*t*Bu	(±)-*anti*-**23**	12 h	> 96:4	74
3[b]	Et	(±)-*anti*-**24**	0.5 h	> 98:2	78
4[b]	*n*Bu	(±)-*anti*-**25**	0.5 h	> 99:1	95
5[a]	*n*-Hex	(±)-*anti*-**26**	3 h	> 97:3	90
6[a]	Me	(±)-*anti*-**27**	10 min	> 99:1	93
7[b]	Ph	(±)-*anti*-**28**	1 h	> 98:2	–

[a] RCHO (5 equiv). [b] RCHO (2 equiv).

Even very bulky substrates, such as isovaleraldehyde (Table 2, entry 1) or 3,3-dimethylbutanal (Table 2, entry 2), gave the respective products (±)-*anti*-**22** and (±)-*anti*-**23** in high yield and diastereoselectivity, though the reaction times were elongated. The best results were obtained by using *n*-butanal as a donor (Table 2, entry 4). The product (±)-*anti*-**25** could be isolated in 95% yield with a d.r. > 99:1 within 0.5 h. Thus, diphenylcarbinol *rac*-**13** provides a superior access to the *anti* isomers. During the construction of the an-

alytical setup for compounds **21**–**28**, we had to face two major problems. Whilst compound **27** was readily isolated by filter flash chromatography (the d.r. could be determined by ^{1}H NMR analysis of the crude product), the product decomposes under standard HPLC conditions. In contrast, compound **28** was not even stable under chilled chromatographic conditions (the instability of the *syn* product was observed previously by Janey and co-workers[25] in their synthesis of the enzyme inhibitor DPP-IV). Thus, no determination of the *ee* was possible at this stage. To overcome this problem, both products were reduced with $NaBH_4$ to the corresponding primary alcohols, which underwent lactonisation during the workup procedure. Based on the method previously described by Ley et al.,[8] a modified procedure was developed for both compounds with diphenylcarbinol *rac*-**13** as a catalyst (Table 3). To shorten the purification steps, the reduction was performed immediately after the consumption of aldimine **9**, without isolation of the crude product.

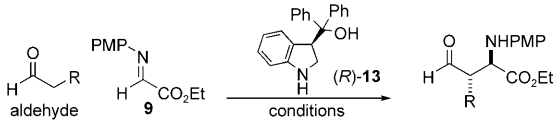
Table 3. Highly selective one-pot two-step synthesis of functionalised amino lactones.



Entry	R	Product	Time	d.r. [*anti*/*syn*]	Yield [%]
1	Me	(±)-*syn*-**29**	70 min	>99:1	79
2	Ph	(±)-*syn*-**30**	2 h	95:5	57

As can be seen from Table 3, this technique worked well and afforded *syn* lactones **29** and **30** without notable loss of diastereoselectivity. Moreover, the improved reaction sequence provides rapid access to highly functionalised *syn*-1-amino-2-alkyl- and *syn*-1-amino-2-aryl-γ-lactones in good yield (up to 79% over two steps). Enantiopure diphenylcarbinol (*R*)-**13** was next investigated under the same conditions (room temperature, toluene). Whilst the yields and diastereoselectivities were reproducible in all cases, the enantioinduction was poor at room temperature (data not shown). Another series of experiments were performed at decreased temperatures (Table 4) with unsatisfactory results; various concentrations, catalyst loadings and temperatures were investigated with only moderate success. Notably, the yields (up to 91%) and diastereoselectivity (d.r. up to >99:1) were very high, but the *ee* did not exceed ~30% (Table 4, entries 1, 2 and 5).

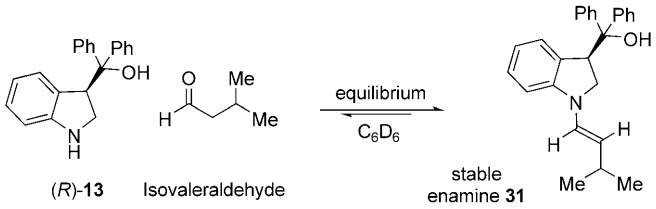
Table 4. Application of catalyst (*R*)-**13** in the *anti*-selective Mannich type reaction.



Entry	Cat. loading [mol%]	R	Product	*T* [°C]	Time [days]	*ee* [%] [*anti*]	d.r. [*anti*/*syn*]	Yield [%]
1[a]	20	*i*Pr	(2*S*,3*R*)-**22**	−20	3	27	>98:2	91
2[a]	20	*i*Pr	(2*S*,3*R*)-**22**	−45	8	32	>99:1	73
3[a]	20	*n*Bu	(2*S*,3*R*)-**25**	−45	5	26	>99:1	83
4[b]	15	*n*Bu	(2*S*,3*R*)-**25**	−20	0.5	8	94:6	81
5[b]	15	*n*Bu	(2*S*,3*R*)-**25**	−40	2.5	34	>98:2	86

[a] Toluene (5 mL per mmol **9**). [b] Toluene (1 mL per mmol **9**).

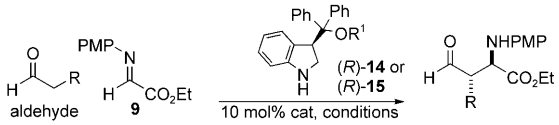
The promising results concerning the yield and diastereoselectivity (Tables 2–4) prompted an NMR study to determine which step was responsible for the low enantioinduction reported in Table 4. Therefore, catalyst (*R*)-**13** was allowed to react with isovaleraldehyde at room temperature in C_6D_6 and the reaction was monitored over 24 h. A stable enamine intermediate **31** was found (Scheme 8, see Experimental Section for full characterisation) but no unexpected side reaction (for example, aldol reaction of the donor aldehyde) or decomposition was detected.



Scheme 8. ^{1}H NMR experiment to determine if the aldehyde is responsible for the decomposition of catalyst **13** during the reaction.

Additional experiments performed revealed that the diphenylcarbinol catalyst **13** decomposes during the reaction. For this reason, silyl-protected catalysts **14** and **15** were investigated (Table 5). Both **14** and **15** were proven to be

Table 5. Application of silyl-protected carbinols (*R*)-**14** and (*R*)-**15** in the *anti*-selective Mannich reaction.



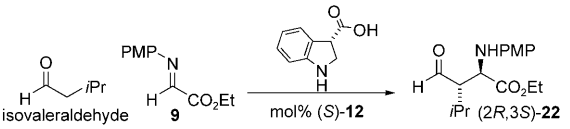
Entry	R^1	R	Product	*T* [°C]	Time [h]	*ee* [%] [*anti*]	d.r. [*anti*/*syn*]	Yield [%]
1[a]	TBS	*i*Pr	(2*S*,3*R*)-**22**	RT	30	*rac*	97:3	35
2[b]	TBS	*n*Bu	(2*S*,3*R*)-**25**	RT	12	2	71:29	19
3[a]	TBS	*n*Bu	(2*S*,3*R*)-**25**	RT	30	30	79:21	27
4[b]	TBS	*n*Bu	(2*S*,3*R*)-**25**	−10	48	32	86:14	40
5[a]	TMS	*i*Pr	(2*S*,3*R*)-**22**	RT	48	12	89:11	33
6[b]	TMS	*n*Bu	(2*S*,3*R*)-**25**	0	72	27	96:4	35

[a] Toluene (5 mL per mmol **9**). [b] Toluene (1 mL per mmol **9**).

stable during the reaction and purification process but the product yields, d.r. and *ee* were only moderate. The low yields are caused by double Mannich condensation,[26] whereas the low d.r. and *ee* may arise from the sterically demanding silyl protecting groups. Moreover, antagonistic effects were also observed. Highly concentrated reactions mixtures afforded the product **25** after a short period of time (12 h, Table 5, entry 2), however, the side products prevailed and the d.r. and *ee* were poor again. A slight improvement was observed at higher dilution (*ee* = 30%, d.r. [*anti*/*syn*] = 79:21, Table 5, entry 3). Interestingly, the activation barrier for both product-forming steps was very low with catalyst **15**. Upon performing the reaction at temperatures beneath −10 °C almost no conversion could be detected after two days, whilst at temperatures above −10 °C full conversion of the aldimine **9** was observed. Thus, decreasing the temperature to further optimise the reaction was not feasible because of this barrier.

Nevertheless, encouraged by these results we investigated the aromatic amino acid (*S*)-**12**. Isovaleraldehyde was added to preformed aldimine **9** under various conditions to afford adduct (2*R*,3*S*)-**22**. A solvent screen with 10 mol% catalyst loading gave disappointing results. Although high *anti* selectivity was obtained in all solvents explored (Table 6, entries 1–7), low yields and almost no enantioinduction were observed (Table 6, entries 1–6). During these attempts, we found that the low yield results from the formation of several side reactions, for example, double Mannich condensation, decomposition of the aldimine **9** and transimination. Clearly, the temperature had to be decreased to avoid side reactions, as described earlier by other groups.[7f,12b] With toluene as the best solvent with respect to the *ee* (68%) and d.r. (96:4) (Table 6, entry 7), further optimisation studies were performed by lowering the temperature from −20 to −40 °C (Table 6, entry 7 versus 8). As expected, the stereochemical outcome significantly depends on the temperature applied; the decrease in temperature was accompanied by a consistent improvement of diastereo- and enantioselectivity. In the best case (−45 °C, 15 mol% catalyst loading) a d.r. of 98:2 with an *ee* of 90% was obtained (Table 6, entry 10).

Table 6. Solvent effects in the indirect Mannich type reaction catalysed by (*S*)-**12**.

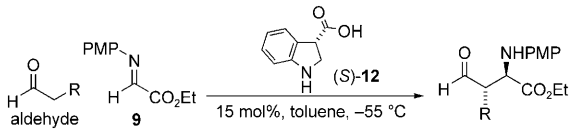


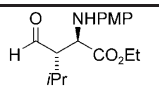
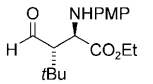
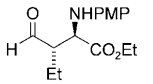
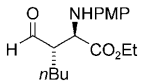
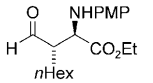
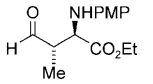
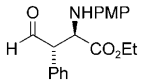
Entry	Solvent	Time	Cat. loading [mol%]	*T* [°C]	*ee* [%] [*anti*]	d.r. [*anti*/*syn*]	Yield [%]
1	DMSO	15 h	10	RT	14	88:12	24
2	DMF	18 h	10	RT	11	83:17	35
3	CH_2Cl_2	20 h	10	RT	25	87:13	17
4	THF	30 h	10	RT	22	79:21	22
5	MeCN	1 days	10	+4	23	92:8	32
6	2-PrOH	2 days	10	−20	7	70:30	23
7	toluene	21 h	5	−20	68	96:4	26
8	toluene	3 days	10	−40	72	98:2	53
9	toluene[a]	5 days	10	−40	*rac*	88:12	21
10	toluene	2.5 days	15	−45	90	98:2	34

[a] 1 mol% Trifluoroacetic acid.

Further experiments were performed to increase the reaction rate by the addition of TFA (trifluoroacetic acid) but, beside the fact that only racemic products were obtained (Table 6, entry 9), the reaction time was considerably prolonged. A further decrease in temperature to −55 °C gave a gratifying result; the product (2*R*,3*S*)-**22** was formed in 55% yield with a respectable 98:2 diastereoselectivity and *ee* > 98% (Table 7, entry 1). Moreover, we were surprised that even at those low temperatures and inert conditions, double Mannich condensation and transimination could not be fully suppressed. As a compromise, we decided to investigate the scope of the catalyst (*S*)-**12** without further decreasing the temperature, sustaining acceptable reaction conditions. Various branched (Table 7, entries 1 and 2), linear (Table 7, entries 3–6) and aromatic (Table 7, entry 7) aldehydes were subjected to the established conditions. We were pleased to find that most of the reactions performed gave almost exclusively one single diastereomer (d.r. > 97:3) in nearly perfect enantioselectivity (*ee* up to > 98%). Notably, even with 3,3-dimethylbutanal, which does not react in the presence of

Table 7. Application of amino acid (*S*)-**12** in the *anti* Mannich type reaction.



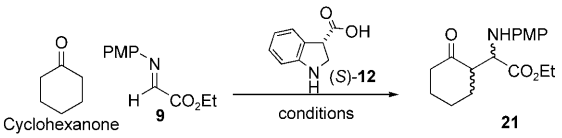
Entry	Product	Time [days]	*ee* [%] [*anti*]	d.r. [*anti*/*syn*]	Yield [%]
1		5	> 98	98/2	55
2		10	> 98	98/2	70
3		5	> 97	98/2	73
4		5	> 97	98/2	78
5		5	> 97	97/3	49
6		5	n. d.	98/2	< 15[a]
7		2	> 94	98/2	47[a]

[a] Over two steps after reduction to the primary alcohol with $NaBH_4$.

proline (**1**) as catalyst,[7e] the Mannich adduct (2*R*,3*S*)-**23** could be isolated in good yield (70%) and respectable d.r. (>98:2) and *ee* (>98%) (Table 7, entry 2). Interestingly, when phenylacetaldehyde was used as the donor, the reaction time was only two days, despite the low temperature of −55°C. Furthermore, only a slight decrease in *ee* was observed after the reduction with $NaBH_4$. Thus, the product (2*R*,3*S*)-**28** was obtained in 47% yield and good stereoselectivity (Table 7, entry 7). When propanal was used as the donor almost no product could be obtained (Table 7, entry 6). GC-MS analysis revealed that mostly the aldol product of the donor aldehyde was formed. Various addition methods of the aldehyde were investigated (dropwise; one portion), but only <15% of the product could be isolated in the best case.

We were also interested if catalyst (*S*)-**12** allowed the construction of Mannich bases when using ketones as donors. Cyclohexanone was arbitrarily chosen and was reacted with aldimine **9** in different solvents. In analogy to the aldehydes, no enantio- and almost no diastereoselectivity was observed at room temperature (Table 8). The best results concerning the solvent (MeCN and toluene) were further examined. The temperature was decreased as was previously described for the aldehydes (Table 6). The yields were moderate to good in most of the reactions performed (up to 69%, Table 8, entry 1) over a short period of time; at room temperature all reactions were complete in <24 h, with exception of that conducted in DMSO (Table 8, entry 6). Interestingly, a change of stereoselectivity compared with the aldehydes was observed. Whilst all the aldehydes gave almost exclusively the *anti* isomers, cyclohexanone afforded the *syn* adduct (d.r.=72:28 in the best case, Table 8, entry 7). We reason that this might be caused by the steric interaction with the aromatic ring. Nevertheless, a decrease of temperature to −20°C (MeCN as solvent) improved the enantioselectivity to 73% for the *anti* isomer (Table 8, entry 3) but the major product was still the *syn* base. Thus, catalyst (*S*)-**12** is not suitable for the *anti*-selective Mannich type addition of ketones to the preformed aldimine **9**.

Table 8. Solvent screen of the reaction of (*S*)-**12** with cyclohexanone.



Entry	Solvent	Conditions	Time	*ee* [%] [*syn*]	*ee* [%] [*anti*]	d.r. [*syn*/*anti*]	Yield [%]
1[a]	2-PrOH	10 mol%, RT	3 h	10	21	53:47	69
2[a]	toluene	10 mol%, RT	6 h	4	6	64:36	67
3[b]	toluene	15 mol%, −20°C	7 days	32	73	59:41	60
4[a]	MeCN	10 mol%, RT	2 days	60	62	65:35	65
5[b]	MeCN	20 mol%, −20°C	6 days	42	33	58:42	50
6[a]	DMSO	10 mol%, RT	31 h	11	7	53:47	53
7[a]	dioxane	10 mol%, RT	23 h	16	10	72:28	47
8[a]	2-Me-THF	10 mol%, RT	20 h	19	25	60:40	39

[a] Solvent (5 mL per mmol **9**). [b] Solvent (1 mL per mmol **9**).

Conclusion

A short and efficient reaction sequence was established for the synthesis of enantiopure indoline-3-carboxylic acid ((*S*)-**12**) that used an enzymatic kinetic resolution as the key step ($E \gg 100$).[27,28] The remaining ester, (*R*)-**19**, was subjected to a Grignard reaction to afford a series of novel diphenylcarbinols (*R*)-**13**–(*R*)-**15** which were investigated in the *anti* Mannich type reaction. Whilst acid (*S*)-**12** afforded the products in a highly diastereo- and enantioselective manner (d.r. up to >98:2; *ee* up to >98%) under the optimised conditions, the carbinol (*R*)-**13** failed in the enantioinduction due to decomposition. Even though, the *anti* Mannich bases were obtained with amino alcohol (*R*)-**13** in excellent yield (up to 95%) and remarkable diastereoselectivity (d.r. >99:1), the *ee* did not exceed ~30%. Furthermore, an improved procedure for the determination of the absolute configuration by controlled *syn–anti* isomerisation was established for various aldehydes and ketones, by using DBU as base.

Experimental Section

All starting materials were obtained from commercial suppliers and used as received, unless stated otherwise. The reactions were carried out with standard Schlenk techniques under Ar or N_2 atmosphere in oven-dried (120°C) glassware. Solvents were dried and purified by conventional methods or by a solvent purification system (MBraun) prior to use. Preparative chromatographic separations were performed by column chromatography on Merck silica gel 60 (0.063–0.200 μm). Solvents for flash chromatography (petroleum ether/ethyl acetate) were distilled before use. Petroleum ether refers to a fraction with a boiling point between 40–60°C. TLC was carried out with pre-coated plastic plates (Polygram SIL G/UV, Macherey–Nagel) with detection by UV (254 nm) and/or by staining with cerium molybdenum solution [phosphomolybdic acid (25 g), $Ce(SO_4)_2 \cdot H_2O$ (10 g), concd sulfuric acid (60 mL), H_2O (940 mL)]. Optical rotation was measured at 20°C on a Perkin–Elmer Polarimeter 241 MC against the sodium D-line. ^1H and ^{13}C NMR spectra were recorded at 20°C on a Bruker Avance DRX 600 spectrometer; chemical shifts are given in ppm relative to Me_4Si (^1H: Me_4Si=0 ppm) or relative to the resonance of the solvent (^{13}C: $CDCl_3$=77.0 ppm, MeOD=50.4 ppm).

See the Supporting Information for full details and all spectroscopic data.

1-*tert*-Butyl-3-methyl-1*H*-indole-3-carboxylate (17): According to the literature procedure,[29] **16** (1.87 g, 10.7 mmol) was dissolved in THF (50 mL) and cooled to 0°C, before NaH (333 mg, 13.9 mmol) was added. After effervescence had ceased, Boc_2O (3.03 g, 13.9 mmol) was added in one portion, under vigorous stirring, whereupon a precipitate was formed. The mixture was allowed to warm to room temperature and stirred overnight, then was extracted with CH_2Cl_2 (4×20 mL) against saturated NH_4Cl solution (100 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by filter flash chromatography (petroleum ether/ethyl acetate 95:5) and **17** was obtained in 95% yield (2.81 g,

10.21 mmol) as a colourless powder. Spectroscopic data are full in agreement with those reported in literature.[29] M.p. 127.0 °C (125–127 °C)[29]; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.69 (s, 9H, C(Me)$_3$), 3.94 (s, 3H, OMe), 7.33–7.39 (m, 2H, arom.-H), 8.16 (m, 1H, arom.-H), 8.17 (br s, 1H, arom.-H), 8.27 ppm (s, 1H, 2-H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 28.1 (C(*Me*)$_3$), 51.5 (COO*Me*), 85.1 (*C*(Me)$_3$), 112.2 (C-3), 115.2, 121.7, 124.0, 125.1 (arom.-CH), 127.5 (C-2), 132.0 (arom.-C$_{ipso}$), 135.6 (arom.-C$_{ipso}$), 149.0 (N*C*O), 164.7 ppm (*C*OOMe); IR (attenuated total reflectance (ATR) film): $\tilde{\nu}$ = 3170, 2977, 2948, 1811, 1743 (NC=O), 1707 (C=O), 1557, 1451, 1367, 1244, 2241, 739 cm^{-1}; GC-MS (EI, 70 eV): *m*/*z* (%): 175 (39) [$C_{10}H_8NO_2^+$], 144 (100) [$C_9H_6NO^+$], 116 (20) [$C_8H_6N^+$]; elemental analysis calcd (%) for $C_{15}H_{17}NO_4$ (275.30): C 65.44, H 6.22, N 5.09; found: C 65.30, H 6.19, N 4.92.

1-*tert*-Butyl-3-methyl-1*H*-indoline-3-carboxylate (18): Mg turnings (1.39 g, 57.1 mmol) were added in one portion to a stirred solution of **17** (3.14 g, 11.41 mmol) in MeOH (350 mL) and CH_2Cl_2 (100 mL) and gas evolution was observed within 15 min (if necessary, the temperature of the exothermic reaction was controlled with a water/ice bath). After all the Mg had reacted (~2–3 h) and the starting material had completely been converted (TLC control), the mixture was poured onto aqueous saturated NH_4Cl solution (500 mL) and was acidified to pH 4.0 with aqueous 2N HCl solution, whereupon the formed precipitate dissolved. The aqueous layer was extracted with CH_2Cl_2 (4×25 mL) and EtOAc (1×50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Subsequent filter flash chromatography (petroleum ether/ethyl acetate 95:5) afforded **18** as colourless oil in 93% yield (2.95 g, 10.6 mmol). Spectroscopic data are full in agreement with those reported in literature.[29] ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.57 (s, 9H, C(Me)$_3$), 3.78 (s, 3H, OMe), 4.10 (br s, 1H, 2-H$_a$), 4.21 (dd, *J* = 5.9 Hz, *J* = 6.5 Hz, 1H, 3-H), 4.39 (br s, 1H, 2-H$_b$), 6.96 (dt, *J* = 1.1, 7.5 Hz, 1H, arom.-H), 7.23 (t, *J* = 7.7 Hz, 1H, arom.-H), 7.35 (d, *J* = 7.6 Hz, 1H, arom.-H), 7.88 ppm (br s, 1H, arom.-H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 28.5 (C(*Me*)$_3$), 49.8 (C-2), 52.6 (COO*Me*), 81.0 (*C*(Me)$_3$), 115.0, 122.3, 125.1 (arom.-CH), 129.0 (arom.-C$_{ipso}$), 142.7 (arom.-C$_{ipso}$), 152.1 (N*C*O), 171.9 ppm (COO*Me*); IR (ATR film): $\tilde{\nu}$ = 2977, 1739 (NC=O), 1698 (C=O), 1485, 1390, 1166, 1131, 1014 cm^{-1}; GC-MS (EI, 70 eV): *m*/*z* (%): 176 (25) [$C_{10}H_{10}NO_2^+$], 118 (100) [$C_8H_8N^+$]; elemental analysis calcd (%) for $C_{15}H_{19}NO_4$ (277.32): C 64.97, H 6.91, N 5.05; found: C 64.75, H 7.04, N 4.76.

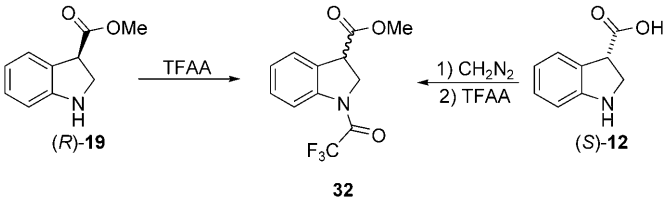
Methyl indoline 3-carboxylate (*rac*-19): Trifluoroacetic acid (9.2 mL, 119.3 mmol) was added to a stirred solution of *rac*-**18** (2.20 g, 7.95 mmol) in dry CH_2Cl_2 (40 mL), under vigorous stirring at room temperature. The reaction was stirred until no starting material could be detected by TLC (1 h) and was then neutralised by the addition of small portions of aqueous saturated $NaHCO_3$ solution at 0 °C. The mixture was extracted with CH_2Cl_2 (4×10 mL) and the combined organic layers were dried over $MgSO_4$. After filtration and concentration under reduced pressure, the residue was purified by filter flash chromatography (petroleum ether/ethyl acetate 80:20) to give *rac*-**19** in 97% yield (1.36 g, 7.67 mmol) as yellow–brownish oil. Spectroscopic data are full in agreement with those reported in literature.[29] ^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.75 (dd, *J* = 9.6, 9.6 Hz, 1H, 2-H$_a$), 3.77 (s, 3H, COOMe), 3.94 (dd, *J* = 9.6, 7.5 Hz, 1H, 2-H$_b$), 4.20 (dd, *J* = 9.6, 7.5 Hz, 1H, 3-H), 6.67 (d, *J* = 7.8 Hz, 1H, arom.-H), 6.75 (dt, *J* = 1.0, 7.5 Hz, 1H, arom.-H), 7.09 (m, 1H, arom.-H), 7.30 ppm (ddt, *J* = 0.6, 1.2, 7.5 Hz, 1H, arom.-H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 47.2 (C-3), 49.3 (C-2), 52.3 (COO*Me*), 110.1, 119.0, 125.2 (arom.-CH), 126.0 (arom.-C$_{ipso}$), 128.8 (arom.-CH), 151.1 (arom.-C$_{ipso}$), 172.7 ppm (CO); IR (ATR film): $\tilde{\nu}$ = 3376 (NH), 2951, 2881, 1727 (C=O), 1604, 1488, 1464, 1434, 1316, 1251, 1196, 1170, 1019, 745 cm^{-1}; GC-MS (EI, 70 eV): *m*/*z* (%): 177 (28) [M^+], 118 (100) [$C_8H_8N^+$].

Enzymatic kinetic resolution of ester *rac*-19: In a typical run, (2.50 g, 14.11 mmol) of *rac*-**19** was emulsified in potassium phosphate buffer (150 mL, 100 mM, pH 8.0), under vigorous stirring at 0 °C. The enzyme (200 mg, Novozyme435) was added and the pH was maintained at pH > 8.0 during the reaction by addition of aqueous 1N NaOH solution. After the consumption of 95% of the theoretical amount, the enzyme was filtered off and the aqueous phase was extracted with CH_2Cl_2 (5×20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Subsequent filter flash chromatography (petroleum ether/ethyl acetate 80:20) afforded the ester (*R*)-**19** in 49% yield (1.24 g, 7.00 mmol) as a yellow–brownish oil. Spectroscopic data are as reported for the racemate (see above). $[\alpha]_D^{20} = -85.5$ (*c* = 0.81, $CHCl_3$, *ee* > 97%).

The remaining aqueous phase was concentrated under reduced pressure at 30 °C on a rotary evaporator (elevated temperatures may lead to racemisation). The residue was purified by filter flash chromatography (ethyl acetate/methanol 90:10) to give acid (*S*)-**12** in 48% yield (1.11 g, 6.80 mmol) as a colourless powder that turned brownish upon drying. Obtained data are full in agreement with those reported in literature.[29] $[\alpha]_D^{20} = +111.1$ (*c* = 1.06, MeOH, *ee* > 99%); m.p. 177–178 °C (180–181 °C);[22c,28] ^{1}H NMR (600 MHz, MeOD): δ = 3.54 (dd, *J* = 9.6, 9.6 Hz, 1H, 2-H$_a$), 3.69 (dd, *J* = 9.6, 7.8 Hz, 1H, 2-H$_b$), 4.04 (dd, *J* = 9.6, 7.8 Hz, 1H, 3-H), 6.59 (d, *J* = 7.8 Hz, 2H, arom.-H), 6.62 (dt, *J* = 1.0, 7.5 Hz, 1H, arom.-H), 6.94 (m, 1H, arom.-H), 7.18 ppm (ddt, *J* = 0.6, 1.2, 7.5 Hz, 1H, arom.-H); ^{13}C NMR (151 MHz, MeOD): δ = 49.0 (C-3), 50.2 (C-2), 111.9, 120.6, 126.0 (arom.-CH), 128.8 (arom.-C$_{ipso}$), 129.5 (arom.-CH), 152.5 (arom.-C$_{ipso}$), 176.0 ppm (COOH); IR (ATR film): $\tilde{\nu}$ = 3334 (NH), 2936, 2501, 1713 (C=O), 1463, 1376, 1241, 1200, 759 cm^{-1}; GC-MS (EI, 70 eV): *m*/*z* (%) = 163 (18) [M^+], 117 (100) [$C_8H_7N^+$]; elemental analysis calcd (%) for $C_9H_9NO_2$ (163.17): C 66.25, H 5.56, N 8.58; found: C 65.88, H 5.64, N 8.22.

Enzymatic hydrolysis of ester (*R*)-19: A crude-cell-extract solution of esterase BS3 (*Bacillus subitilis* esterase 3, Codexis, 268 U/mL, stabilised in glycerine, 400 μL) was added to a stirred solution of ester (*R*)-**19** (250 mg, 1.41 mmol, *ee* > 97%) in potassium phosphate buffer (25 mL, 100 mM, pH 8.1) at 0 °C. The reaction was monitored with a pH electrode and was kept at pH 8.1 by the addition of small portions of aqueous 1N NaOH solution. After consumption of the theoretical amount of base, the solution was concentrated under reduced pressure at 30 °C on a rotary evaporator. Subsequent filter flash chromatography on silica (ethyl acetate/MeOH 90:10) afforded acid (*R*)-**12** in 68% yield (155 mg, 0.95 mmol) as a colourless powder, which turned brownish upon concentration. Spectroscopic data are identical to those reported for the enantiomer (see above). $[\alpha]_D^{20} = -106.3$ (*c* = 0.6, MeOH, *ee* > 97%).

Determination of the *ee* of acid (*S*)-12 and ester (*R*)-19: The *ee* was determined by chiral HPLC analysis (column: Chiralpak OD-H (4.6×250 mm), solvent: *n*-hexane/2-PrOH = 99.8:0.2, flow = 0.75 mL min^{-1}, retention time (R_t) [(3*S*)-**32**] = 32.85 min, R_t [(3*R*)-**32**] = 40.32 min) minutes after derivatisation to methyl 1-(2,2,2-trifluoroacetyl)indoline-3-carboxylate (**32**) (Scheme 9).



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Scheme 9. Derivatisation of acid (*S*)-**12** and ester (*R*)-**19**.

*Derivatisation of ester (*R*)-**19***: An analytical sample of (*R*)-**19** (2 μL) was treated with trifluoroacetic acid anhydride (10 μL) in an Eppendorf vial and stirred vigorously at 30 °C on an Eppendorf Thermomix apparatus for 10 min. Aqueous saturated $NaHCO_3$ solution (500 μL) and *n*-heptane (300 μL) were added. After effervescence had ceased and the layers had separated, an aliquot of the organic layer (150 μL) was withdrawn and analysed by chiral HPLC, as described above.

*Derivatisation of acid (*S*)-**12***: An analytical sample of (*S*)-**12** (1 mg) was treated with a solution of diazomethane in Et_2O (1 mL, 0.45 M). After effervescence ceased, the solvent was removed on an Eppendorf Thermomix apparatus (30 °C) and the residue was treated with trifluoroacetic acid anhydride, as described above. M.p. 74.0 °C; ^{1}H NMR (600 MHz,

$CDCl_3$): $\delta = 3.80$ (s, 3H, COOMe), 4.35 (dd, $J = 4.8$, 9.7 Hz, 1H, 2-H_a), 4.39 (dd, $J = 10.5$, 9.7 Hz, 1H, 2-H_b), 4.75 (dd, $J = 4.8$, 10.6 Hz, 1H, 3-H), 7.20 (dt, $J = 1.0$, 7.6 Hz, 1H, arom.-H), 7.35 (m, 1H, arom.-H), 7.49 (d, $J = 7.7$ Hz, 1H, arom.-H), 8.22 ppm (d, $J = 8.1$ Hz, 1H, arom.-H); ^{13}C NMR (151 MHz, $CDCl_3$): $\delta = 45.9$ (C-2), 50.0 (C-3), 53.2 (COO*Me*), 118.4 (NCO*C*F_3), 125.5, 126.3, 128.7 (arom.-CH), 129.7 (arom.-C_{ipso}), 141.6 (N*C*OCF$_3$), 171.0 ppm (*C*O_2Me); ^{19}F NMR (565 MHz, $CDCl_3$): $\delta =$ 72.6 ppm (s, 3F, CF_3); IR (ATR film): $\tilde{\nu} = 3071$, 2970, 2942, 1734 (C=O), 1689 (C=O), 1485, 1440, 1253, 1190, 1136, 1082, 760 cm^{-1}; GC-MS (EI, 70 eV): *m*/*z* (%): 273 (42) [M^+], 214 (100) [$M^+ - CO_2Me$], 117 (42) [$C_8H_7N^+$]; elemental analysis calcd (%) for $C_{12}H_{10}F_3NO_3$ (273.21): C 52.75, H 3.69, N 5.13; found: C 52.50, H 4.00, N 4.85.

1-Acetyl-2,3-dihydroindoline-3-carboxylate [(*S*)-20]: NEt_3 (127 μL, 919 μmol) was added to a stirred solution of (*S*)-**12** (50.0 mg, 306 μmol) in dry CH_2Cl_2 (5 mL) at 0 °C. After 5 min, AcCl (24.1 μL, 321 μmol) was added dropwise. The mixture was allowed to reach room temperature and stirred overnight. The solvent was removed with a rotary evaporator and the residue was purified by filter flash chromatography (petroleum ether/ethyl acetate/acetic acid 50:49:1) to afford the acetylated amino acid (*S*)-**20** as a colourless powder in 77% yield (48 mg, 234 μmol). Obtained data are full in agreement with those reported in the literature.[21c] $[\alpha]_D^{20} = +127.8$ ($c = 0.18$, MeOH, *ee* >99%); $[\alpha]_D^{20} = +129.1$ ($c = 1.0$, MeOH, *ee* >99%);[21c] ^{1}H NMR (600 MHz, [D_6]DMSO): $\delta = 2.20$ (s, 3H, COMe), 4.26 (dd, $J = 14.1$, 7.2 Hz, 1H, 2-H_a), 4.31 (dd, $J = 7.2$, 8.8 Hz, 1H, 3-H), 4.33 (dd, $J = 14.1$, 8.8 Hz, 1H, 2-H_b), 7.04 (dt, $J = 1.0$, 7.5 Hz, 1H, arom.-H), 7.23 (dt, $J = 1.0$, 7.5 Hz, 1H, arom.-H), 7.40 (d, $J = 7.5$ Hz, 1H, arom.-H), 8.07 ppm (d, $J = 7.9$ Hz, 1H, arom.-H); ^{13}C NMR (151 MHz, [D_6]DMSO): $\delta = 24.0$ (CO*C*H_3), 39.7 (C-3), 50.6 (C-2), 115.9, 123.2, 125.0, 128.3 (arom.-CH), 129.3, 142.5 (arom.-C_{ipso}), 168.4 (*C*OMe), 172.6 ppm (*C*OOH); IR (ATR film): $\tilde{\nu} = 2985$, 1732 (C=O), 1668 (C=O), 1482, 1400, 746 cm^{-1}; GC-MS (EI, 70 eV): *m*/*z* (%): 160 (8) [$M^+ - CO_2$], 118 (100) [$C_8H_8N^+$]; MS (ESI, positive ion): *m*/*z* (%): 206 (100) [M^+].

Indolin-3-yldiphenylmethanol (*rac*-13): The ester **19** (929 mg, 5.21 mmol) was dissolved in dry Et_2O (200 mL) at room temperature, before PhMgBr (9.3 mL. 2.8 M in Et_2O) was added dropwise. The reaction was allowed to stir overnight and PhMgBr (1 equiv) was added (TLC control). The reaction mixture was poured onto aqueous saturated NH_4Cl solution (100 mL) and washed with brine (2×20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. Subsequent flash chromatography (petroleum ether/ethyl acetate 90:10) afforded *rac*-**13** in 51% yield (793 mg, 2.63 mmol) as a brownish powder. M.p. 136–138 °C; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 3.51$ (dd, $J = 6.9$, 9.6 Hz, 1H, 2-H_a), 3.56 (dd, $J = 9.4$ Hz, 1H, 2-H_b), 4.70 (dd, $J = 6.9$, 9.2 Hz, 1H, 3-H), 6.14 (d, $J = 7.6$ Hz, 1H, arom.-H), 6.45 (dt, $J = 1.1$, 7.5 Hz, 1H, arom.-H), 6.63 (d, $J = 7.8$ Hz, 1H, arom.-H), 7.02 (tq, $J = 0.6$, 8.0 Hz, 1H, arom.-H), 7.19 (m, 1H, arom.-H), 7.24 (m, 1H, arom.-H), 7.29–7.35 (m, 4H, arom.-H), 7.56–7.60 ppm (m, 1H, arom.-H); ^{13}C NMR (151 MHz, $CDCl_3$): $\delta = 49.8$ (C-2), 50.8 (C-3), 79.8 ((Ph)$_2$*C*-OH), 109.9, 118.4, 125.6, 126.0 (arom.-CH), 126.4 (arom.-C_{ipso}), 126.6, 126.9, 128.3, 128.6 (arom.-CH), 146.1 (arom.-C_{ipso}), 146.4 (arom.-C_{ipso}), 153.3 ppm (arom.-C_{ipso}); IR (ATR film): $\tilde{\nu} = 3326$ (NH), 3200 (OH), 1600, 1488, 1447, 1247, 1165, 741, 701 cm^{-1}; GC-MS (EI, 70 eV): *m*/*z* (%): 301 (1) [M^+], 118 (100) [$C_8H_8N^+$], 77 (88) [$C_6H_5^+$]; elemental analysis calcd (%) for $C_{21}H_{19}NO$ (301.38): C 83.69, H 6.35, N 4.65; found: C 82.48, H 6.36, N 4.48.

(*R*)-Indolin-3-yldiphenylmethanol [(*R*)-13]: The pure enantiomer was prepared according to the procedure reported for the racemate above. $[\alpha]_D^{20} = -93.4$ ($c = 0.53$, $CHCl_3$, *ee* >97%). *Determination of* ee *by HPLC*: column: Chiralpak IC (4.6×250 mm), solvent: *n*-hexane/2-PrOH = 80:20, flow = 1.0 mL min^{-1}, R_t [(3*R*)-**13**] = 7.0 min, R_t [(3*S*)-**13**]) = 8.44 min.

3-[(*tert*-Butyldimethylsilyloxy)diphenylmethyl]indoline [(*R*)-14]: 2,6-Lutidine (400 mg, 3.73 mmol) and TBSOTf (987 mg, 3.73 mmol) were sequentially added to a stirred solution of alcohol **13** (450 mg, 1.49 mmol) in dry CH_2Cl_2 (5 mL), dropwise at 0 °C. The reaction was allowed to reach room temperature and stirred overnight, then quenched with half-saturated aqueous NH_4Cl solution (10 mL). The mixture was further diluted with EtOAc (50 mL) and washed with brine (2×50 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. Subsequent filter flash chromatography with a chilled column (petroleum ether/ethyl acetate/triethylamine 95:4:1) afforded the protected alcohol (*R*)-**14** in 83% yield (513 mg, 1.23 mmol) as a colourless foam. $[\alpha]_D^{20} = -89.4$ ($c = 1.28$, $CHCl_3$, *ee* >97%); m.p. 92–96 °C; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 0.19$ (s, 3H, SiMe), 0.20 (s, 3H, SiMe), 0.91 (s, 9H, C(Me)$_3$), 2.26 (s, 1H, NH), 3.59 (dd, $J = 6.0$, 10.5 Hz, 1H, 2-H_a), 3.68 (dd, $J = 10.3$, 10.4 Hz, 1H, 2-H_b), 4.63 (dd, $J = 6.0$, 10.2 Hz, 1H, 3-H), 6.10 (d, $J = 7.5$ Hz, 1H, arom.-H), 6.31 (td, $J = 1.0$, 7.4 Hz, 1H, arom.-H), 6.61 (d, $J = 8.0$ Hz, 1H, arom.-H), 6.95 (m, 1H, arom.-H), 7.17–7.24 (m, 2H, arom.-H), 7.23–7.34 (m, 4H, arom.-H), 7.52–7.62 ppm (m, 4H, arom.-H); ^{13}C NMR (151 MHz, $CDCl_3$): $\delta = -4.44$ (Si-CH_3), −4.38 (Si-CH_3), 21.0 (*C*(CH$_3$)$_3$), 27.0 (C(*C*H$_3$)$_3$), 50.6 (C-3), 53.5 (C-2), 80.4 (C-O), 110.5, 116.5, 126.0, 126.27, 126.30, 126.8, 127.0 (arom.-CH), 128.0 (arom.-C_{ipso}), 128.4, 128.7 (arom.-CH), 146.1, 146.7, 155.0 ppm (arom.-C_{ipso}); IR (ATR film): $\tilde{\nu} = 3550$ (NH), 3061, 2927, 1597, 1480, 1249, 953, 743, 701 cm^{-1}; MS (ESI, 70 eV): *m*/*z* (%): 416 (100) [M+H$^+$], 118 (17) [$C_8H_8N^+$]; elemental analysis calcd (%) for $C_{27}H_{33}NOSi$ (415.64): C 78.02, H 8.00, N 3.37; found: C 78.00, H 7.94, N 3.20.

Determination of the ee by HPLC: Column: Chiralpak IA (4.6×250 mm), solvent: *n*-heptane/2-PrOH = 98:2, flow = 0.5 mL min^{-1}, detection $\lambda =$ 250 nm, R_t [(3*S*)-**14**] = 10.89 min, R_t [(3*R*)-**14**] = 14.85 min.

3-[Diphenyl(trimethylsilyloxy]methylindoline [(*R*)-15]: 2,6-Lutidine (89 mg, 830 μmol) and TMSOTf (150 mg, 664 μmol) were added dropwise sequentially to a stirred solution of alcohol (*R*)-**13** (100 mg, 332 μmol) in dry CH_2Cl_2 (5 mL) at 0 °C. The reaction was allowed to reach room temperature and stirred overnight, then quenched with half-saturated aqueous NH_4Cl solution (10 mL). The mixture was further diluted with EtOAc (50 mL) und washed with brine (2×50 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. Subsequent filter flash chromatography with a chilled column (petroleum ether/triethylamine 98:2) afforded the protected alcohol (*R*)-**15** in 86% yield (107 mg, 286 μmol) as a brownish oil. $[\alpha]_D^{20} = -37.3$ ($c = 0.7$, $CHCl_3$, *ee* >97%); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = -0.15$ (s, 9H, $SiMe_3$), 3.40 (s, 1H, NH), 3.57 (dd, $J = 5.7$, 10.2 Hz, 1H, 2-H_a), 3.62 (dd, $J = 9.7$, 10.1 Hz, 1H, 2-H_b), 4.61 (dd, $J = 5.7$, 9.6 Hz, 1H, 3-H), 6.37 (dd, $J = 1.0$, 8.2 Hz, 1H, arom.-H), 6.54 (dt, $J = 1.0$, 7.5 Hz, 1H, arom.-H), 6.92 (m, 2H, arom.-H), 7.24 (m, 8H, arom.-H), 7.36 ppm (m, 2H, arom.-H); ^{13}C NMR (151 MHz, $CDCl_3$): $\delta = 2.1$ (Si(*C*H$_3$)$_3$), 49.2 (C-2), 51.9 (C-3), 84.0 (*C*O), 110.2, 118.2, 126.9, 127.2, 127.4, 127.5, 127.6, 128.1, 128.8, 128.9, 129.0 (arom.-CH), 144.0, 144.8, 153.5 ppm (arom.-C_{ipso}); IR (ATR film): $\tilde{\nu} = 3389$ (NH), 2953, 1607, 1249, 1066, 835, 700 cm^{-1}; GC-MS (EI, 70 eV): *m*/*z* (%): 373 (1) [M^+], 255 (100) [$C_{16}H_{19}OSi^+$], 118 (27) [$C_8H_8N^+$].

Determination of ee by HPLC: Column: Chiralpak IA (4.6×250 mm), solvent: *n*-heptane/2-PrOH = 96:4, flow = 0.5 mL min^{-1}, detection $\lambda =$ 250 nm, R_t [(3*S*)-**15**] = 11.1 min, R_t [(3*R*)-**15**] = 19.1 min.

General procedure for the addition of aldehydes to *N*-(*p*-methoxybenzyl)-α-imino ethyl glyoxalate (9) catalysed by (*S*)-12: Compound (*S*)-**12** was added in one portion to a stirred solution of aldimine **9** (207 mg, 1.0 mmol) in dry toluene (5 mL). The mixture was stirred for 10 min, cooled to −55 °C and treated with aldehyde (5 equiv). The reaction mixture was stirred as indicated in Table 6 and was then purified by chilled filter flash chromatography with varying mixtures of petroleum ether and ethyl acetate.

General procedure for the addition of aldehydes to *N*-(*p*-methoxybenzyl)-α-imino ethyl glyoxalate (9) catalysed by (*R*)-13 or *rac*-13: Compound (*R*)-**13** or *rac*-**13** (45 mg, 0.15 mmol) was added in one portion to a stirred solution of aldimine **9** (207 mg, 1.0 mmol) in dry toluene (5 mL). The mixture was stirred for 5 min and then treated with aldehyde (2 equiv). The mixture was stirred as indicated in Table 1 and was then subjected to chilled filter flash chromatography (no extraction necessary) with varying mixtures of petroleum ether and ethyl acetate to afford the corresponding *anti* Mannich base.

Controlled epimerisation of the Mannich bases for the determination of the absolute configuration: DBU (2 μL) was added to a stirred solution of the Mannich base (1.0 mg) in dry CH_2Cl_2 (1.0 mL). The mixture was vigorously stirred at room temperature. After 15 min (in the case of aldehydes) or 30 min (in the case of ketones), an aliquot (50 μL) was with-

drawn. The aliquot was extracted from saturated aqueous NH_4Cl solution (500 μL) with *n*-heptane (500 μL). An aliquot of the organic layer (200 μL) was taken and analysed by chiral HPLC, as described above.

(±)-*syn*-3-(4-Methoxyphenylamino)-4-methyldihydrofuran-2-one: Compound *rac*-**13** (45 mg, 0.15 mmol) and aldehyde (1.5 equiv) were added to a stirred solution of aldimine **9** (207 mg, 1.00 mmol) in toluene (5 mL). After full conversion had been detected (as judged by TLC, Table 3), the reaction mixture was cooled to 0 °C, diluted with EtOH (5 mL) and treated with $NaBH_4$ (378 mg, 10.0 mmol). The reaction was stirred at this temperature for 1 h and then poured onto saturated aqueous NH_4Cl solution (100 mL). EtOAc (50 mL) was added and the organic phase was washed with saturated aqueous NH_4Cl (2×25 mL) and brine (1×50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Subsequent filter flash chromatography (chilled column, petroleum ether/ethyl acetate 85:15) afforded the product in 79% yield (175 mg, 0.79 mmol) as an orange oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.0 (d, J = 7.2 Hz, 3H, Me), 3.0 (dddq, J = 5.0, 7.2, 7.2, 9.2 Hz, 1H, 4-H), 3.76 (s, 3H, OMe), 4.05 (br s, 1H, NH), 4.12 (dd, J = 3.0, 7.1 Hz, 1H, 3-H), 4.14 (dd, J = 9.2, 9.2 Hz, 1H, 5-H_a), 4.45 (dd, J = 5.0, 9.2 Hz, 1H, 5-H_b), 6.62 (d, J = 8.9 Hz, 2H, arom.-H), 6.81 ppm (d, J = 8.9 Hz, 2H, arom.-H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 12.6 (Me at C-4), 35.2 (C-4), 55.8 (OMe at C-4′), 57.6 (C-3), 72.2 (C-5), 114.2, 115.0 (arom.-CH), 140.7, 152.9 ppm (arom.-C_{ipso}), 176.1 (C-2); IR (ATR film): $\tilde{\nu}$ = 3378 (NH), 2968, 1769 (C=O), 1512, 1239, 1164, 820 cm^{-1}; GC-MS (EI, 70 eV): *m*/*z* (%): 221 (100) [M^+], 134 (54) [$C_8H_8NO^+$].

*Determination of ee of the (S)-**12** catalysed reaction by HPLC*: Column: Chiralpak IC (4.6×250 mm), solvent: *n*-hexane/2-PrOH = 80:20, flow = 1.3 mL min^{-1}, detection λ = 254 nm, R_t [(3*R*,4*S*)-**29**] = 21.20 min, R_t [(3*S*,4*R*)-**29**] = 36.40 min.

(±)-*syn*-3-(4-Methoxyphenylamino)-4-phenyldihydrofuran-2(3*H*)-one: Compound *rac*-**13** (45 mg, 0.15 mmol) and aldehyde (1.5 equiv) were added to a stirred solution of aldimine **9** (207 mg, 1.00 mmol) in toluene (5 mL). After full conversion had been detected (as judged by TLC, Table 2), the reaction mixture was cooled to 0 °C, diluted with EtOH (5 mL) and treated with $NaBH_4$ (378 mg, 10.0 mmol). The reaction was stirred at this temperature for 1 h and then poured onto of a saturated aqueous NH_4Cl solution (100 mL). EtOAc (50 mL) was added and the organic phase washed with saturated aqueous NH_4Cl (2×25 mL) and brine (50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Subsequent filter flash chromatography (chilled column, petroleum ether/ethyl acetate 80:20) afforded the product in 60% yield (169 mg, 0. 60 mmol) as an orange powder. M.p. 127–130 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.53 (br d, J = 6.7 Hz, 1H, NH), 3.75 (s, 3H, OMe), 4.53 (ddd, J = 0.9, 5.2, 8.0 Hz, 1H, 4-H), 4.52 (dd, J = 6.7, 7.8 Hz, 1H, 3-H), 4.70 (dd, J = 0.9, 9.8 Hz, 1H, 5-H_a), 4.74 (dd, J = 5.4, 9.8 Hz, 1H, 5-H_b), 6.54 (d, J = 9.0 Hz, 2H, arom.-H), 6.77 (d, J = 9.0 Hz, 2H, arom.-H), 7.07 (m, 2H, arom.-H), 7.28 ppm (m, 3H, arom.-H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 45.6 (C-4), 55.9 (OMe at C-4′), 58.4 (C-3), 71.3 (C-5), 127.9, 128.1, 129.2, (arom.-CH), 136.4, 140.3, 153.1 (arom.-C_{ipso}), 175.7 ppm (C-2); IR (ATR film): $\tilde{\nu}$ = 3345 (NH), 1759 (C=O), 1409, 1133, 810 cm^{-1}; GC-MS (EI, 70 eV): *m*/*z* (%): 283 (55) [M^+], 134 (100) [$C_8H_8NO^+$]; determination of *ee* of the (*S*)-**12** catalysed reaction by HPLC: column: Chiralpak IC (4.6×250 mm), solvent: *n*-hexane/2-PrOH = 80:20, flow = 1.3 mL min^{-1}, detection λ = 254 nm, R_t [(3*R*,4*S*)-**30**] = 22.66 min, R_t [(3*S*,4*R*)-**30**] = 48.55 min.

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