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Introduction

The synthesis of pharmacologically important oxindoles *via* the asymmetric aldol reaction of isatin and the investigation of the organocatalytic activity of new alicyclic β -amino acid derivatives[†]

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This work involves the synthesis and subsequent development of a number of novel organocatalysts generated from β -amino acids bearing *diendo* and *diexo* norbornene skeletons to improve their catalytic characteristics. The aldol reaction between isatin and acetone selected as the model reaction, was used to test and study enantioselectivities. The potential impact on enantioselectivity control regarding enantiomeric excess (ee%) was probed by varying the reaction parameters, such as additive, solvent, catalyst loading, temperature and substrate range. The corresponding 3-hydroxy-3-alkyl-2-oxindole derivetives were produced by organocatalyst 7 with good enantioselectivity up to 57% ee in the presence of LiOH. Substrate screening was used to investigate a number of substituted isatins with excellent findings up to 99% ee. Another aspect of this effort involved employing high-speed ball mill apparatus to conduct a mechanochemical study to make this model reaction more environmentally benign and sustainable.

The synthesis of natural compounds poses a great challenge for synthetic organic chemists, and it is a subject that merits ongoing attention. Many different natural products have the oxindole core and these compounds also possess a great deal of scientific interest due to their extensive spectrum of biological activities, which raised the interest of chemists, pharmacists and biologists alike. For instance, arundaphine, convolutamydines, maremycins and CPC-1 possess biological properties, such as antioxidative, anti-HIV and neuroprotection activity.1-6 The study of pharmaceuticals incorporating the oxindole scaffold and the discovery of advantageous synthesis pathways will certainly be the focus of pharmaceutical research in the future. Due to the significance of a sustainable future in today's world, green chemistry is becoming desirable and more and more popular. Sustainable catalysis is the core of green chemistry. In comparison to metal and enzyme catalysis, organocatalysis has additional benefits, including chemical

efficiency, availability, low cost, durability and non-toxicity.^{7,8} There is still a need for innovative, efficient catalytic systems for the aldol reaction of isatin and ketones. Furthermore, it is crucial to have a better understanding of the aldol reaction in order to develop and use effective catalysts. The aldol reaction of isatin and ketones can be influenced by a number of different factors. The outcome of aldol reactions depends significantly on solvents used and the amount of solvents.^{2,9-13} When the amount of catalysts was increased, it was usual to witness abrupt drops in ee% followed by sudden increases. As Wang *et al.* reported in 2018, it is likely that this phenomenon is attributed to the retro-aldol reaction.¹⁴

Only a handful of research teams have studied organocatalysts in the aldol process with low catalyst loadings (0.5–1 mol%) reporting good¹⁵ or excellent results.¹⁶ These were superior to those obtained by employing 10 mol% of organocatalyst. When using substituted isatins in the aldol reaction between isatin and acetone in numerous studies typically better results were achieved in comparison to those found by the parent compound.^{9,10,17} Position and properties of the substituents of isatin have a significant impact on the yield and the enantioselectivity of the aldol reaction. Good results in ee from 77% up to 94% were obtained utilizing 4-chloroisatin, 4-bromoisatin, 4-methylisatin and 4,7-dichloroisatin as reagent.^{17,18} Good but slightly lower enantiomeric excesses were found when the same substituents were applied in C-5, C-6, or C-7 positions of isatin.^{17,18}

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Paper

Various other carbonyl compounds, for example, acetone, cyclohexanone and substituted cyclohexanone derivatives were also tested in the aldol reaction of isatin and ketones with fair to good results.¹⁹⁻²³

Over the past 20 years, there has been a strong incentive to develop effective organocatalysts to enhance the asymmetric aldol reaction of isatin and ketones, which is controlled by organocatalysts secondary amine such as proline derivatives.^{8,11,24-26} In 2016, Singh et al. discovered that proline (S)-N-((S)-1-phenylethyl)pyrrolidine-2-carboxamide derivative has stronger organocatalytic effects than simple (S)-proline.²⁷ In 2015, Chen et al. found that this model reaction was effectively catalysed by the Li⁺ salt of (S)-phenylalanine.¹⁰ However, only a small number of researchers have investigated the use of alicyclic amino acid derivatives as organocatalysts to synthesise the aforementioned oxindole derivatives.11 There are only a handful of cage-type amine organocatalysts with isoquinuclidine or 2-azanorbornane backbones described in the literature.²⁸ The majority of such catalysts are composed of the following components: a larger or more rigid backbone for steric influence, amino groups as enamine-forming sites around the side chains, and one or two sterically bulky phenyl groups on the side chain. In order to achieve good results in enantioselectivity, the presence of another asymmetric site may also be required.11,28

β-Amino amides with a cyclohexane skeleton were also studied in this model reaction. Under neat conditions, the best result was 37% ee (20 mol% catalyst loading without additives).¹¹ In the proposed reaction mechanism, the reaction of acetone with the NH₂ group of the catalyst generates an imine, which is in equilibrium with its enamine tautomer. Then the enamine orients isatin through π - π interactions between the phenyl ring of isatin and the enamine. Finally, the enamine motif performs nucleophilic attack on isatin and then hydrolysis regenerates the catalyst.¹¹ Regarding (*S*)-leucinol as organocatalyst in aldol reaction of isatin, a *syn*- and *anti*-enamine equilibration was proposed in the first steps of the catalytic cycle.²⁹

In recent years, there has been a surge in the utilisation of energy-efficient methods, including mechanochemical activation, ultrasonic irradiation and microwave heating. The use of high-speed ball milling (HSBM), a technique for advancing synthetically valuable processes without the need of solvents, increases gradually in organic synthesis.³⁰⁻³⁴ To estimate the energy transfer onto the material, a number of variables must be taken into account, including the rotation frequency of the mill, milling time, vessel radius, size, weight and number of balls, density, *etc.* In general, ball milling raises the interior temperature.³⁵⁻³⁷ Utilising HSBM to study the interaction between isatin and acetone has been rather uncommon up until now, although it has several benefits.^{34,38}

Due to these reasons, our aim was to synthesise novel *diendo* and *diexo* alicyclic amino acid derivatives with a norbornene skeleton. Furthermore, we also intended to investigate the catalytic activities of these compounds in the asymmetric aldol reaction between isatin (1a) and acetone (2) (Scheme 1). Additionally, we were interested in improving the catalytic efficacy of



Scheme 1 Aldol reaction between isatin (1a) and acetone (2).

model reaction and identifying environmentally more benign and sustainable approaches to synthesise molecules containing the oxindole moiety.

Results and discussion

According to the literature, 2-aminonorbornene ester enantiomer (–)-4 was prepared through diastereomer salt formation from racemic *diendo* 2-aminonorbornene ester (±)-4 utilising (+)-O,O'-dibenzoyltartaric acid (DBTA).³⁹ Following the hydrolysis of the free ester (–)-4, the resulting amino acid was then reacted with di-*tert*-butyl dicarbonate to produce the *diendo* norbornene *N*-Boc-protected amino acid (–)-5.⁴⁰ Urea (–)-6 was produced in a good yield when free ester (–)-4 and (S)-(–)- α methylbenzyl isocyanate were reacted in diethyl ether at ambient temperature. *N*-Boc-protected *diendo* norbornene amino acid (–)-5 was transformed into amide (–)-7 in tetrahydrofuran (THF) at room temperature, using (S)-(–)- α -methylbenzyl amine in the presence of N,N'-diisopropylcarbodiimide (DIC) and hydroxybenzotriazole (HOBt) (Scheme 2).

Racemic *diendo* 2-aminonorbornene ester (\pm)-4 was also resolved with (-)-DBTA and the resulting enantiomeric amino ester (+)-4 was converted with (*S*)-(-)- α -methylbenzyl isocyanate into urea derivative (-)-8.⁴¹

Enantiomeric *diendo* norbornene β -amino acid was obtained by hydrolysis of ester (+)-4 under microwave heating. Afterwards, *N*-Boc protection yielded (+)-5, which was subjected to acid–amine coupling reactions with various amines in the presence of DIC and HOBt. Using this process, the following catalyst materials were prepared: (–)-9 with the use of (*S*)-(–)-1-(2-naphthyl)ethylamine, (–)-10 applying (*S*)-(–)-1-(1-naphthyl)



Scheme 2 Reagents and conditions: (i) (1) (+)-DBTA, EtOH, 70 °C (2) NaOH, CHCl₃/H₂O; (ii) (1) MW, H₂O, 100 °C; (2) Boc₂O, dioxane/H₂O, r.t.; (iii) (S)-(-)- α -methylbenzyl isocyanate, Et₂O, r.t.; (iv) DIC, HOBt, (S)-(-)- α -methylbenzyl amine, THF, r.t., 24 h.



Scheme 3 Reagents and conditions: (i) (1) (–)-DBTA, EtOH, 70 °C, (2) NaOH, $CHCl_3/H_2O$; (ii) (S)-(–)- α -methylbenzyl isocyanate, Et₂O, r.t. (iii) (1) (–)-DBTA, EtOH, 70 °C; (2) NaOH, $CHCl_3/H_2O$, (3) MW, H₂O, 100 °C; 4. Boc₂O, dioxane/H₂O, r.t.; (iv) DIC, HOBt, corresponding amine, THF, r.t., 24 h. (v) HCl/EtOH, 100 °C, 1 h.

ethylamine, (+)-11, (+)-12 using (R)-(+)-1-(2-naphthyl)ethylamine, (+)-13, (+)-14 utilizing (R)-(+)-1-(1-naphthyl)ethylamine and (-)-15 using propargylamine (Scheme 3).

Resolution of racemic *diexo* aminonorbornene ester (±)-16 with (+)-*O*,*O*'-di-*p*-toluoyltartaric acid ((+)-DPTTA) in ethanol delivered enantiopure *diexo* aminonorbornene ester (+)-16. Free ester base (+)-16 was hydrolysed into the corresponding amino acid in a microwave reactor and then it was protected with Fmoc-OSu to produce *diexo N*-Fmoc-protected protected norbornene β-amino acid (+)-17.⁴² From enantiopure amino acid (+)-17, the following catalyst materials were prepared *via* acidamine coupling processes: (+)-18 using (*R*)-(+)-1-(2-naphthyl)ethylamine, (-)-19 utilizing (*S*)-(-)-1-phenylethylamine and (+)-20 using (*R*)-(+)-1-phenylethylamine (Scheme 4).

In the aldol reaction of isatin (1a) with acetone (2), a wide range of catalysts shown in Fig. 1 were investigated.



Scheme 4 Reagents and conditions: (i) (1) (+)-DPTTA, EtOH, 70 °C, (2) NaOH, CHCl₃/H₂O; (ii) (1) MW, H₂O, 100 °C; (2) Fmoc-OSu, acetone/ H₂O, NaHCO₃, r.t.; (iii) DIC, HOBt, chiral amine, THF, r.t., 24 h.

The ratio of catalysts to be evaluated in the aldol reaction of isatin (1a) and acetone (2) was often studied in the literature. At first, catalysts 7–21 were screened at a 20 mol% concentration at room temperature. In these reactions, a very small amount (1 mmol) of LiOH as co-catalyst was also used (Table 1).



Fig. 1 Structure of catalysts 6-21. Derivatives (-)-15 and (-)-21 were prepared according to literature procedure.^{10,40}

Table 1 Screening of organocatalysts 7-21 in the aldol reaction between isatin (1a) and acetone (2) in the presence of LiOH additive^a



Entry	Catalyst	Time (h)	Yield ^b	ee^{c} (%) (S) config.
1	(-)-6	2	95	15
2	(-)-7	0.5	94	43
3	(-)-8	5	90	5
4	(–)-9	4	89	Rac.
5	(–)-10	3	88	Rac.
6	(+)-11	2	90	48
7	(+)-12	2	92	51
8	(+)-13	3	90	7
9	(+)-14	2	96	49
10	(–)-15	1	94	3
11	(+)-18	3	89	23
12	(–)-19	2	80	3
13	(+)-20	3	85	23
14	(-)-21	6	96	53

^a Organocatalysts 6-21 (20 mol%), isatin (0.28 mmol), acetone (5 mL, 325 equiv.), LiOH (1 mmol) as additive, stirred at room temperature for specified time. ^b Isolated yield after purification by column chromatography. ^c The ee was determined by HPLC using Chiralpak IA column. ^d The absolute configuration was determined by comparison of the specific optical rotation with literature data.^{2,29,43,44}

Derivatives (-)-7, (-)-8, (+)-11, (+)-12 and (+)-14 gave quite good results presented in Table 1 (entries 2, 3, 6, 7 and 9). In all cases, high conversion values were observed shown already by TLC monitoring. A comparison of the results with respect to the enantiomeric excess of (+)-11 and (+)-13 showed that the use of β -amino acid derivative (+)-11, bearing the ((R)-1-(naphthalen-2yl)ethyl)carbamoyl substituted diendo norbornene scaffold as catalyst, gave a remarkably better result, than ((R)-1-(naphthalen-1-yl)ethyl)carbamoyl-substituted compound (+)-13 (Table 1 entry 6 and 8). One plausible explanation is that when the catalysts contain protecting groups, the transition state of the aldol reaction between isatin and acetone prefers the substituent (R)-(+)-1-(2-naphthyl)ethyl rather than the substituent of (*R*)-(+)-1-(1-naphthyl)ethyl. However, when the protective groups from (+)-11 and (+)-13 were removed, (+)-12 and (+)-14 produced HCl salts that performed better than their protected analogue counterparts (Table 1, entries 6 and 8 versus entries 7 and 9). When the Fmoc-protected *diexo* norbornene β -amino amides (+)-18 and (-)-19 were used instead of Boc-protected diendo norbornene β -amino amides (-)-7 and (+)-11, large drops were registered in enantiomeric excesses (in Table 1, compare entries 2 and 6 with entries 11 and 12). In the case of Fmoc as the protecting group, ee values in the aldol reaction between isatin and acetone dropped significantly. Supposedly, it is related to a structural reason, namely the significant steric demand of Fmoc in comparison to Boc. Obviously, this could affect the corresponding transition state.

Table 2 Screening of organocatalysts 6-15 in the aldol reaction between isatin and acetone without any additives^a



^a Reactions were carried out (20 mol% catalyst loading) with isatin derivatives (0.28 mmol) and acetone (5 mL, 325 equiv.). ^b Isolated yield after purification by column chromatography. c The ee was determined by HPLC using Chiralpak IA column. d The absolute configuration was determined by comparison of the specific optical rotation with literature data.2,29,43,4

91

3

48

8

(-)-15

When our catalysts were tested without LiOH as co-catalyst, only the hydrochloride salts (+)-12 (derived from (R)-(+)-1-(2naphthyl)ethylamine) and (+)-14 (derived from (R)-(+)-1-(1naphthyl)ethylamine) afforded good results (Table 2, entries 6 and 7). Furthermore, when only catalysts without LiOH were applied in the aldol reaction, treatment times had to be increased significantly.

Based on the results summarised in Tables 1 and 2, our best catalyst, compound (-)-7 was chosen for further tests. In the next steps the model reaction was optimised to increase the enantiomeric excess. Thus, the possible effects of additives, catalyst loading, solvent and temperature on the model reaction were studied.

First, various additives were examined in order to enhance the enantiomeric excess (ee%) (Table 3). We found that the LiOH originally applied is the best additive: in its presence, the reaction is both fast and moderately enantioselective (Table 3, entry 7). Other bases also accelerated the reaction, but failed to provide reasonable ee values (Table 3, entries 5 and 6). When LiOH was replaced with acids, the most commonly applied additives in this reaction according to the literature, the reaction became sluggish and barely enantioselective (Table 7, entries 1-3). Water as an additive failed as well (Table 7, entry 4). Therefore, we decided to use a very small amount of LiOH (1 mmol) together with our catalysts during further reactions.

Subsequently, by changing the catalyst loading from 5 mol% to 20 mol%, the impact of various catalyst loadings of (-)-7 was examined on the model reaction (Table 4). As shown in entry 1 of Table 4, the use of 5 mol% catalyst loading applied under the most environmentally benign condition, turned out to be the most enantioselective. Note, that in this case, a short treatment was satisfactory. When the catalyst loading was increased, a sharp reduction in ee values was observed followed by a rapid

 Table 3
 Screening of different additives using catalyst 7 in the aldol
 reaction between isatin (1a) and acetone (2).^a



Entry ^a	Additive	Time (h)	Yield ^b	ee^{c} (%) (S) config. ^d
1	TFA	12	75	15
2	HCOOH	12	70	13
3	Benzoic acid	12	80	Rac.
4	H_2O	12	84	3
5	NaOH	4	72	9
6	КОН	4	83	13
7	LiOH	0.5	94	43

^a Reactions were carried out with (-)-7 (20 mol%), isatin (0.28 mmol), acetone (5 mL, 325 equiv.) and additive (1 mmol) stirred at room temperature for specified time. ^b Isolated yield after purification by column chromatography. ^c The ee was determined by HPLC using Chiralpak IA column.^d The absolute configuration was determined by comparison of the specific optical rotation with literature data.^{2,29,43,4}

surge. Possible background processes, like the retro-aldol reaction, may explain this phenomenon.14

Then, the partially optimised model reaction (5 mol% (-)-7 catalyst, 1 mmol LiOH additive, room temperature) was performed in various bicomponent solvents (prepared by mixing 1-163 equivalents of acetone with a polar protic or a polar aprotic solvent) in order to study the possible solvent effects. In the case of ACN/acetone mixtures, the 1:1 mixture produced an almost racemic product, but decreasing the amount of acetone somewhat improved ee% (Table 5, entries 17-20). In all other cases, the 1:1 mixture provided the highest enantioselectivity, whereas decreasing the amount of acetone greatly decreased

Table 4 Screening of organocatalyst (-)-7 in varied loadings in the aldol reaction of isatin (1a) and acetone (2) in the presence of LiOH^a

	N N H 1a	O catalyst Me LiOF 2	: (−)- 7 I, rt (S	Ne HQ (S) N H S)-3a
Entry ^a	Catalyst mol%	Time (min)	Yield ^b	ee^{c} (%) (S) config. ^d
1	5	30	96	57
2	10	60	89	13
3	15	60	90	11
4	20	30	94	43

^a Organocatalyst (-)-7 in specified mol%, isatin (0.28 mmol) and acetone (5 mL, 325 equiv.) stirred at room temperature for specified times in the presence of LiOH (1 mmol). ^b Isolated yield after purification by column chromatography. ^c The ee was determined by HPLC using Chiralpak IA column. ^d The absolute configuration was determined by comparison of the specific optical rotation with literature data.2,29,43,44

Table 5 Screening of different solvents using catalyst (-)-7 in the aldol reaction between isatin (1a) and acetone (2).⁴



Entry ^a	Solvent	Acetone equiv.	Time (h)	Yield ^b	ee^{c} (%) (S) config. ^d
1	MeOH	163	12	56	39
2	MeOH	65	12	50	7
3	MeOH	6.5	12	67	1
4	MeOH	1	12	48	7
5	EtOH	163	12	73	28
6	EtOH	65	12	75	25
7	EtOH	6.5	12	50	1
8	EtOH	1	12	69	3
9	$2M2B^{e}$	163	12	60	7
10	$2M2B^{e}$	65	12	70	7
11	$2M2B^{e}$	6.5	12	55	1
12	$2M2B^{e}$	1	12	46	1
13	THF	163	12	78	15
14	THF	65	12	81	1
15	THF	6.5	12	86	5
16	THF	1	12	74	1
17	ACN	163	12	83	3
18	ACN	65	12	86	1
19	ACN	6.5	12	80	9
20	ACN	1	12	89	11

^a Reactions were carried out with (-)-7 (5 mol%), isatin (0.28 mmol), acetone (amount given in the table) and solvent (overall volume: 5 mL), in the presence of LiOH (1 mmol), stirred at room temperature for the specified time. ^b Isolated yield after purification by column chromatography. ^c The ee was determined by HPLC using Chiralpak IA column. ^d The absolute configuration was determined by comparison of the specific optical rotation with literature data.^{2,29,43,44} e 2-Methyl-2-butanol.

ee% (Table 5, entries 1-16). This was especially true for acetone/ 2-methyl-2-butanol (2M2B) and acetone/THF mixtures, whereas the presence of MeOH and EtOH was better tolerated. However, because all the above mixtures provided inferior yield and ee% compared to pure acetone (Table 4, entry 1), acetone was utilised as a solvent in further studies.

Finally, the effect of temperature was investigated ranging from -20 °C to 75 °C, under the already optimised conditions (Table 6). As shown, both too high and too low temperatures gave unsatisfactory results (Table 6, entries 1, 2, 4 and 5). On the other hand, when the reaction was carried out at room temperature, it worked really effectively (Table 6, entry 3). Notably, performing reactions at room temperature is quite convenient from a practical viewpoint.

We were interested in exploring the issue of substrates after adjusting the reaction conditions; therefore, various substituted isatin derivatives were examined in model reactions. The purpose of the study was to determine the effect of substitution of the aromatic ring on isatin. Hence, 5-iodoisatin (1b), 7chloroisatin (1c), 5-fluoroisatin (1d), 5-nitroisatin (1e), 5-methylisatin (1f), 4,7-dichloroisatin (1g) and 5-bromoisatin (1h) were 1

4

5

 75^b

Table 6 Screening of the effect of the temperature on the aldol reaction^a between isatin and acetone



^a Isatin (0.28 mmol), organocatalyst (–)-7 (5 mol%) and LiOH (1 mmol) were dissolved in acetone (5 mL, 325 equiv.) and stirred at the specified temperature for the specified time. ^b Microwave reactor: 50 °C, 75 °C. ^c Isolated yield after purification by column chromatography. ^d The ee was determined by HPLC using Chiralpak IA column. e The absolute configuration was determined by comparison of the specific optical rotation with literature data.^{2,29,43,4}

0.5

87

Rac

examined. As described in Table 7, catalysts (-)-7 (entries 2, 6, 10, 13, 16, 19 and 22), (-)-8 (entries 3, 7, 11, 14, 17, 20 and 23), (+)-14 (entries 4 and 8) and (-)-21 (entries 1, 5, 9, 12, 15, 18, 21 and 24) were studied under the optimised reaction conditions (acetone as solvent, 5-20 mol% catalyst, room temperature, LiOH additive (1 mmol) in the cases of catalysts (-)-7 and (-)-8, no additives in the cases of catalysts (+)-14 and (-)-21).

First, results with our norbornene catalyst derivatives are discussed. Aldol reaction of 5-iodoisatin (1b) and acetone yielded moderate to good (27-45%) ees (Table 7, entries 2-4). When 7-chloroisatin (1c) and acetone were applied as substrates, catalyst (-)-7 gave the (S) product with 81% enantiomeric excess (Table 7, entry 6). Then we studied catalyst (-)-8 (ref. 41) with 7chloroisatin and the enantiomeric excess reached an excellent value of 93% of the (S) product (Table 7, entry 7). Experiments with 5-fluoroisatin (1d), 5-nitroisatin (1e) and 5-methylisatin (1f) gave moderate results regarding ee% (Table 7, entries 10-11, 13–14 and 16–17). In contrast, 4,7-dichloroisatin (1g)provided the (S) product with excellent enantiomeric excesses of 99% and 83% (Table 7, entries 19 and 20). Testing 5-

Table 7 Substrate scope with various isatin derivatives using organocatalysts (-)-7, (-)-8, (+)-14 and (-)-21 in the aldol reaction^a with acetone, starting from commercially available isatins 1a-h



Entry ^a	Catalyst	R^1	R^2	Product	Time (h)	Yield ^b	ee^{c} (%) (S) config. ^d
1	(-)-21	Н	Н	3a	48	92	53
2	(_)-7	51	Н	3b	72	67	27
3	(-)-8	51	Н	3b	72	82	35
4	(+)-14	51	Н	3b	50	84	45
5	(-)-21	51	Н	3b	48	78	65
6	(_)-7	Н	Cl	3c	72	75	81
7	(-)-8	Н	Cl	3c	72	90	93
8	(+)-14	Н	Cl	3c	70	93	39
9	(–)-21	Н	Cl	3c	48	81	98
10	(-)-7	5F	Н	3 d	72	63	30
11	(-)-8	5F	Н	3 d	72	67	47
12	(-)-21	5F	Н	3 d	72	72	37
13	(_)-7	$5NO_2$	Н	3e	72	76	45
14	(-)-8	$5NO_2$	Н	3e	72	80	9
15	(-)-21	$5NO_2$	Н	3e	72	73	41
16	(-)-7	5Me	Н	3f	72	74	5
17	(-)-8	5Me	Н	3f	72	69	15
18	(-)-21	5Me	Н	3f	72	65	39
19	(-)-7	4Cl	Cl	3g	72	70	99
20	(-)-8	4Cl	Cl	3g	72	77	83
21	(-)-21	4Cl	Cl	3g	72	82	97
22	(-)-7	5Br	Н	3h	72	64	79
23	(-)-8	5Br	Н	3h	72	68	75
24	(-)-21	5Br	Н	3h	72	70	49

^a The isatin derivative (0.28 mmol) and the catalyst system [5 mol% (-)-7 and 1 mmol LiOH; 5 mol% (-)-8 and 1 mmol LiOH; 20 mol% (+)-14; or 20 mol% (-)-21] were dissolved in acetone (5 mL, 325 equiv.), and stirred at room temperature for the specified time. ^b Isolated yield after purification by column chromatography. ^c The ee was determined by HPLC using Chiralpak IA column. ^d The absolute configuration was determined by comparison of the specific optical rotation with literature data.^{10,18,43,45},

bromoisatin (**1h**) gave good results (Table 7, entries 22–23), especially with catalyst (–)-7 (Table 7, entry 22, 79% enantiomeric excess). In general, organocatalysts have been found to give better results in ee% values with chlorinated and brominated isatins compared to isatin itself. Guo *et al.* made similar observations when a chiral diamine catalyst was investigated in the asymmetric cross aldol reaction of isatin and acetone.¹⁷

Different substituted isatins were also screened with acetone and catalyst (–)-21 (Table 7, entries 1, 5, 9, 12, 15, 18, 21 and 24).¹⁰ Note that this catalyst was already known in the literature, but it was not examined with these substituted isatin derivatives. In each case, in particular, when 7-chloroisatin (**1c**) and 4,7-dichloroisatin (**1g**) were used, very good enantiomeric excesses were observed (Table 7, entries 9 and 21, 98% and 97% ees). These results are in agreement with the behaviour of our catalysts (–)-7 and (–)-8 derived from β -amino acids as well as the experiences of Guo *et al.* To sum up, moderately electronwithdrawing chlorine or bromine substituents at the C-4, C-5 and/or C-7 positions of the isatin ring are beneficial to the enantiomeric excess in the case of a wide variety of catalysts.¹⁷

One of our goals was to study the model reaction using cyclohexanone as well. However, these reactions could not be



Fig. 2 Structure of catalysts 22–25.

successfully monitored because, in our measurement setup, the *syn* and *anti* isomers and enantiomers of the products could not be separated on the chiral IA column.

The norbornene skeleton is a rigid and sterically bulky structure, which has a significant impact on the outcome of reactions.

In order to demonstrate the necessity of norbornene skeleton of our organocatalysts, its potential impacts were investigated. Therefore, a few β -amino acid derivatives containing other skeletons [(+)-22, (+)-23, (+)-24 and (+)-25] were synthesised (Fig. 2). These compounds have the same chiral side chain moieties, which were effective with our best catalysts. In the model reaction, they all gave racemic aldol products. On the basis of these results, we propose that the norbornene skeleton has a significant effect on the organocatalytic activity.

In order to interpret our results correctly, it is important to notice that our catalysts, based on their functional groups, can be divided into three distinct groups.

The first group, β -carbamido esters, has only two representatives [(–)-6 and (–)-8]. In both cases, the presence of LiOH greatly accelerated reactions and somewhat increased enantioselectivity, but with isatin, ee of the product never increased above 15% (see Table 1, entries 1 and 3 and Table 2, entries 1 and 3). Therefore, detailed discussion of these catalysts is omitted.

The second group, β -amino amide hydrochloride salts, has 2 representatives – (+)-**12** and (+)-**14**. Their enantioselectivity is moderate to good (49–57%) and it is only weakly affected by the presence or absence of LiOH (see Table 1, entries 7 and 9 and Table 2, entries 6 and 7). Interestingly, the side chain chiral



Scheme 5 Mechanism of asymmetric cross aldol reaction with β -amino amide hydrochloride salt catalyst (+)-12.

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centre also has low impact on their enantioselectivity. Reactions utilizing these catalysts are greatly accelerated by LiOH. We propose that these catalysts follow a mechanism that is very similar to that described by Gavendova et al.11 First, condensation of acetone with the free amine form of the catalyst yields an imine. Then, LiOH deprotonates this imine to form a rather nucleophilic aza-enolate. Reprotonation of this aza-enolate produces a nucleophilic enamine. The side chain aryl group of these active species interacts with isatin via π - π stacking, orienting isatin in such a way that Re-face attack of the azaenolate or enamine is preferred over Si-face attack (Scheme 5). This mechanism explains that enantioselectivity is an inherent property of the catalyst (Li⁺ is not involved in orientation of the reactants). It also accounts for the effect of LiOH on the rate of the reaction. First, OH⁻ accelerates tautomerisation of imines to enamines. Second, the aza-enolate intermediates of this basepromoted tautomerisation are more nucleophilic and more reactive than enamines. Finally, LiOH deprotonates the hydrochloride derivative of the catalyst, transforming it into the catalytically active free amine form.

The third group, *N*-Boc-protected β -amino amides, was the focus of our investigation. As a consequence, this group has the highest number of representatives (9 compounds). In this group, the effect of LiOH was investigated only in the case of four-membered derivatives.

It was found that LiOH accelerates aldol reactions catalysed by (-)-7, (-)-9, (+)-11 and (-)-15, and it also significantly increases enantioselectivity of catalysts (-)-7 and (+)-11 (compare Table 1, entries 2, 4, 6 and 10 with Table 2, entries 2, 4, 5 and 8). In the case of catalyst (-)-7, other bases were investigated as well, but they mostly increased reaction rates (see Table 3, entries 4–7).

Because nucleophilicity of the Boc-protected nitrogen is greatly reduced, enamine formation between *N*-Boc-protected β amino amide catalysts and acetone is unlikely. We propose that these catalysts utilise a different mechanism. First, the reaction of LiOH with acetone generates a lithium enolate, which exists as a close ion pair in the reaction media of moderate polarity. It is known that Li⁺ has much stronger coordinative ability than other alkali metal ions (because the small size of Li⁺ results in high surface charge density), and Li⁺ preferentially interacts with hard Lewis bases (*e.g.* oxygen-donor ligands). Consequently, the Li⁺ counterion of the enolate can interact with the hard carbonyl oxygen donor atoms of the catalyst, too. Moreover, the catalyst also interacts with isatin *via* π - π stacking. As a result of these interactions, the enolate and isatin are oriented in such a way that the *Re*-face attack is favoured (Scheme 6).



Scheme 6 The key step of the mechanism of asymmetric cross aldol reaction with catalyst (–)-7.

This mechanism is in accordance with our observations. In the absence of OH⁻, the nucleophile would be the enol form of acetone, which is less reactive than the enolate of acetone. Therefore, OH⁻ is responsible for accelerating the reaction. Note that any base with sufficient solubility can perform this role (see Table 3, entries 4–7). In contrast, enantioselectivity requires specifically Li⁺, because its unique coordinative ability is necessary for orientation of the enolate.

As part of our work, mechanochemical investigations were undertaken to make the model reaction more sustainable and environmentally benign. We studied the model reaction under HSBM conditions, testing catalyst loading, milling frequency and reaction time. All high-speed ball milling measurements were initially performed using a Retsch 400 Mixer Mill equipped with a 10 mL agate jar and 5 mm agate balls. In order to prevent temperature rise of the mill, we applied pauses during the milling process. However, when using higher frequencies, this approach turned out to be futile. Neither catalyst loading higher than 5 mol% nor using too low and too high frequencies yielded successful results. At too low frequency, the reaction time was very long. In contrast, when using a too high frequency, the product was racemic. The most effective milling frequencies, which produced satisfactory results, were found to be 15 and 20 Hz (Table 8). It may be surmised that increasing the milling frequency causes an increase of the temperature, which is known to decrease enantioselectivity in solution-phase experiments (see Table 6, entries 3-5).

We also screened the possible effect of the number of milling balls. The results demonstrated that in the case of urea

 Table 8
 Screening of the effect of the milling frequency on the aldol reaction^a in HSBM condition between isatin and acetone



Entry	Catalyst	Frequency (Hz)	Time (min)	Yield ^b	$ee\%^{c}(S)$ config. ^d
1	(-)-8	15	30	50	N.D.
2	(-)-8	15	60	56	31
3	(-)-8	15	120	48	33
4	(-)-8	20	30	61	19
5	(-)-8	20	60	59	35
6	(-)-8	20	120	43	21
7	(-)-21	15	30	67	57
8	(-)-21	15	60	65	39
9	(-)-21	15	120	61	23
10	(-)-21	20	30	70	47
11	(-)-21	20	60	69	37
12	(-)-21	20	120	61	31
	. ,				

^{*a*} A mixture of isatin (0.28 mmol), LiOH (1 mmol), organocatalyst (5 mol%) and acetone (30 μ L, 1.95 equiv.) was milled with 3 balls at the specified frequency for the specified time. ^{*b*} Isolated yield after purification by column chromatography. ^{*c*} The ee was determined by HPLC using Chiralpak IA column. ^{*d*} The absolute configuration was determined by comparison of the specific optical rotation with literature data.^{2,43-45}

Table 9 Screening of the effect of the number of milling balls at already optimised frequency and catalyst loading on the aldol reaction in HSBM condition between isatin and acetone^{α}



Entry	Catalyst	Frequency (Hz)	Number of milling balls	Yield ^b	$ee\%^{c}(S)$ config. ^d
1	(-)-8	20	3	68	35
2	(-)-8	20	4	70	96
3	(-)-8	20	5	61	5
4	(–)-21	15	3	69	57
5	(-)-21	15	4	73	45
6	(-)-21	15	5	64	33

 a A mixture of isatin (0.28 mmol), LiOH (1 mmol), organocatalyst (5 mol%) and acetone (30 μ L, 1.95 equiv.) was milled with the specified number of balls for the already optimised time. In the case of catalyst (–)-8, milling time was 60 min, while regarding catalyst (–)-21 the milling time was 30 min. b Isolated yield after purification by column chromatography. c The ee was determined by HPLC using Chiralpak IA column. d The absolute configuration was determined by comparison of the specific optical rotation with literature data.^{2,43-45}

derivative (–)-8, applying 4 balls gave the best results (Table 9, entries 1–3), while in the case of catalyst (–)-21, increasing the number of balls to 4 or 5 provided inferior results in ee% (Table 9, entries 4–6).

Conclusions

In conclusion, organocatalysts **6–25** were synthesised, characterised and tested in the aldol reaction between isatin and acetone as a model reaction. The application of these organocatalysts significantly shortened the reaction time. By employing alicyclic amino acid derivatives as organocatalysts, it was successfully established that a norbornene skeleton, a substituted aromatic chiral amine and an amino group attached to the norbornene backbone are required to provide good control of enantioselectivity. It was observed that reactions took place more rapidly when LiOH was present. In the cases of a few catalysts, the presence of LiOH was also beneficial to enantioselectivity.

Our best working organocatalyst (–)-7 was used to optimise the model reaction. LiOH proved to be the most efficient additive. 5 mol% catalyst loading provided better results than higher catalyst loadings. Possible solvent effects were studied by performing the reaction in acetone/cosolvent mixtures. Numerous polar cosolvents were used, and the acetone/ cosolvent ratio was varied within a wide range. With our catalyst (–)-7, pure acetone as solvent provided the best results. Room temperature, the most environmentally benign condition, proved to be the best choice concerning the use of our catalyst. In the end, under the fully optimised conditions (5 mol% catalyst loading, 3.57 equiv. LiOH additive, acetone as both the solvent and the substrate, room temperature), the aldol adduct formed in 96% yield and 57% ee (S) in a mere 30 minutes.

We suggest that β -amino amide catalysts, which have a free primary amino group, promote the investigated cross aldol

reaction *via* enamine catalysis. In these cases, the main role of LiOH is to accelerate the reaction. In contrast, *N*-protected β -amino amides follow a different mechanism, which involves coordination of both the catalyst and the enolate of acetone to the same Li⁺ ion. In these cases, LiOH has a double role: it accelerates the reaction and provides enantioselectivity.

Substituent effects were studied by transforming various substituted isatins. When 7-chloroisatin were used as substrate, catalyst (–)-7 gave the (*S*) product with high ee (81%). With urea derivative (–)-8 in the case of 7-chloroisatin, enantioselectivity reached an outstanding value of 93% providing the (*S*) product. Reaction of 4,7-dichloroisatin in the presence of catalysts (–)-7 and (–)-8 provided the (*S*) product in excellent ees (99% and 83%, respectively). The analogous reaction of 5-bromoisatin in the presence of catalysts (–)-7 and (–)-8 provided the (*S*) product in good ees (79% and 75%, respectively). When there is an electron-withdrawing group in the C-4, C-5 or C-7 position, organocatalysts, in general, provided better ee values. Oxindole derivatives **3a-h** were isolated and characterized.

HSBM was employed to perform the model reaction in a more environmentally and ecologically benign way. Most importantly, solvent usage was greatly decreased. We thoroughly examined the effects of catalyst loading, milling frequency and reaction time. The transformation of isatin in the presence of catalyst (–)-8 was improved in HSBM conditions up to an ee of 96%. Catalyst (–)-21 also showed superior performance under HSBM conditions.

Conflicts of interest

There are no conflicts to declare.

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