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β-Amino Acid Organocatalysts in the Asymmetric Michael Addition of Isobutyraldehyde to *N*-Substituted Maleimides

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Abstract: Asymmetric Michael additions of carbonyl compounds to *N*-substituted maleimides are among the most convenient reactions to prepare optically pure succinimide building blocks. Although a few β-amino acids were found to be highly efficient organocatalysts in the addition of α-branched aldehydes, the effect of their structure on the results of these reactions has not yet been investigated. In the present study, we disclose several unexpected and interesting structural effects of aliphatic and cycloaliphatic β-amino acids obtained in the enantioselective conjugate addition of isobutyraldehyde to *N*-benzylmaleimide. The dependence of the sense of the enantioselectivity on the bulkiness of the substituent on the β-carbon atom, the beneficial spatial arrangements of the functional groups in *cis* isomers with cyclohexane scaffold and the inversion of the enantioselectivity depending on the absence of a base additive observed with some *trans* isomers are unprecedented findings. The minor influence of the nitrogen substituent of the maleimide ring on both the reaction rate and the enantioselectivity was also evidenced using alicyclic β-amino acid prepared from an easily available terpene derivative.

Keywords: enantioselectivity; asymmetric organocatalysis; Michael addition; β-amino acid; maleimides; isobutyraldehyde

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1. Introduction

Asymmetric catalytic reactions are among convenient methods for preparing optically pure organic intermediates needed in the pharmaceutical and fine chemical industries [1–4]. Accordingly, the development of chiral catalysts is a main research area of the most recent half-century, leading to various favourable solutions applicable in numerous chemical transformations designed to create chiral centres in organic molecules [5–10]. At present, in addition to the widely applied enantioselective metal complexes, optically pure organic molecules are frequently employed as stereoselective catalysts [11–15]. These organocatalysts are competitive alternatives of the metal complexes, though their application is often associated with increased catalyst amounts and costs, difficulties in recovery and prolonged reaction times. Accordingly, searching for simple, highly active, stereoselective and less expensive chiral organocatalysts is still in the focus of the investigations.

Asymmetric organocatalytic conjugate additions are among the synthetically most useful reactions to create molecular complexity along with the generation of novel chiral centres in organic molecules [16–18]. The application of *N*-substituted maleimides as Michael acceptors affords chiral succinimides, which are valuable pharmaceutical intermediates [19–24]. Hence, several organocatalysts have been developed to promote the enantioselective addition of aldehydes, ketones, 1,3-dicarbonyl compounds and other nucleophiles to maleimides [25]. Among the most efficient catalysts, cinchona alkaloids [26–28], pyrrolidine derivatives [29,30], a variety of C_2-symmetric 1,2-diamine derivatives [31–46], oligopeptides [47,48] and primary amino acids have been utilised, the latter as salts formed

in situ or deposited on solid supports [49–56]. Primary amino acid derivatives afforded excellent enantioselectivities in the addition of α,α-disubstituted aldehydes to various *N*-substituted maleimides. The most efficient amino acids used as chiral sources in these asymmetric Michael additions are O-*tert*-butyl-L-threonine (O-^{t}Bu-L-Thr) and L-isoleucine (L-Ile) described by Nugent and co-workers [49,52], *S*-β-phenylalanine (β-Phe) and aspartic acid α-*tert*-butyl ester (H-Asp-O^{t}Bu) as well as several natural α-amino acids reported by Kokotos [50,51]. Substituted phenylglycines in combination with cinchona alkaloid derivatives were found to be efficient in the addition of aldehydes and ketones to maleimides by Zhao and co-workers [54]. Moreover, natural α-amino acids, such as L-phenylalanine (L-Phe), were intercalated into layered double hydroxides or adsorbed on inorganic oxides, leading to heterogeneous, recyclable chiral hybrid materials [55,56]. The structure of selected amino acids applied as catalysts is presented in Figure 1.

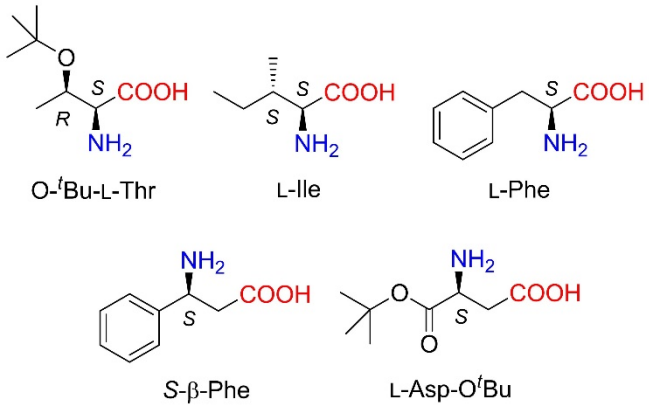
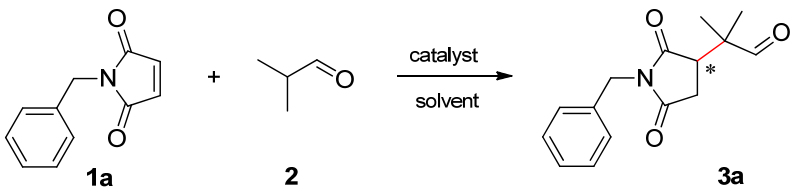


Figure 1. Amino acid organocatalysts found to be highly efficient in Michael additions of carbonyl compounds to *N*-substituted maleimides.

The above reports indicate that, in addition to α-amino acids, β-amino acids may also afford excellent results in the asymmetric addition of aldehydes to maleimides. The application of β-amino acids as chiral organocatalysts in other stereoselective transformations has rarely been reported [57–59]. Because of the easy access to natural α-amino acids, the effect of their structure could be studied in detail. However, the influence of the substitution pattern of β-amino acids on their performance in asymmetric organocatalytic reactions is yet poorly explored. Accordingly, our aim in the present study is to investigate the effect of the structure of these compounds on the results obtained in the asymmetric organocatalytic Michael addition of an aldehyde to *N*-substituted maleimides.

2. Results

To evaluate the effect of the structure of β-amino acids, we selected the addition of isobutyraldehyde (**2**) to *N*-benzylmaleimide (**1a**) as a test reaction (see Scheme 1).



Scheme 1. Michael addition of isobutyraldehyde (**2**) to *N*-benzylmaleimide (**1a**).

A short screening of the influence of the reaction conditions was carried out using the easily available L-Asp-OEt (**4**) as the catalyst, derived from natural L-Asp. The results of these experiments are presented in Table 1. The examination of the effect of the basic additive in the ethyl acetate (EtOAc) solvent showed that the bases used in previous studies (Cs_2CO_3 and KOH [50,52]) afforded lower conversions and/or enantiomeric excesses (*ee*)

compared to LiOH, which offered full conversion and the highest *ee* (95%, entry 4). L-Asp, the parent natural amino acid, was inefficient in catalysing the reaction (in 6 h at 50 °C: conversion <1%) either using 1.5 or 3 eq of LiOH × H_2O (not included in Table 1). High conversion and *ee* values were obtained in other aprotic solvents as well (entries 5–8). However, EtOAc, a recommended organic solvent in the pharmaceutical industry [60], was found to be the most appropriate under these reaction conditions. Protic solvents provided decreased enantioselectivities (entries 9, 10). Accordingly, further reactions were carried out in EtOAc. Decreasing the amount of both the amino acid and the base led to a decrease in the conversion, without altering enantioselectivity (entries 11, 12). A shorter reaction time (6 h) did not afford a complete transformation of **1a,** provided the temperature was increased to 50 °C. This, however, resulted in a drop of the *ee* to 92% (entry 14). Increasing the amount of the solvent decreased the conversion without affecting the *ee* (entries 15 and 16 compared to entries 4 and 11, respectively). Furthermore, lowering the EtOAc amount slightly increased the conversion in parallel with a negligible decrease in the *ee* (94%, entry 17).

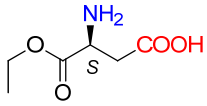
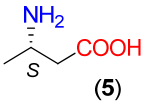
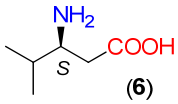
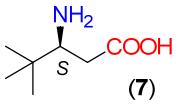
Table 1. Michael addition of **2** to **1a** catalysed by L-Asp-OEt (**4**): effect of reaction conditions [a].

Entry	Amount of 4 (mol%)	Additive [b]	Solvent; Amount (cm^3)	Time (h)	Conv (%) [c]	*ee* (%) [d]
1	10	–	EtOAc; 1	16	12	73
2	10	Cs_2CO_3	EtOAc; 1	16	85	73
3	10	KOH	EtOAc; 1	16	>99	87
4	10	LiOH × H_2O	EtOAc; 1	16	>99	95
5	10	LiOH × H_2O	CH_2Cl_2; 1	16	98	95
6	10	LiOH × H_2O	^{t}BuOMe; 1	16	>99	94
7	10	LiOH × H_2O	MeCN; 1	16	>99	93
8	10	LiOH × H_2O	$(Me)_2CO$; 1	16	95 (99 [e])	92
9	10	LiOH × H_2O	^{i}PrOH; 1	16	>99	78
10	10	LiOH × H_2O	MeOH; 1	16	52	50
11	5	LiOH × H_2O	EtOAc; 1	16	84	95
12	2.5	LiOH × H_2O	EtOAc; 1	16	50	95
13	10	LiOH × H_2O	EtOAc; 1	6	80	95
14 [f]	10	LiOH × H_2O	EtOAc; 1	6	98	92
15	10	LiOH × H_2O	EtOAc; 2	16	94	95
16	5	LiOH × H_2O	EtOAc; 2	16	55	95
17	5	LiOH × H_2O	EtOAc; 0.5	16	87	94

[a] Reaction conditions: 0.3 mmol **1a**, 1.2 mmol **2**, 24 °C. [b] 1.5 Equivalent additive relative to the amount of **4**. [c] Conversions determined by gas chromatography (GC-FID). [d] Enantiomeric excesses determined by GC-FID; the configuration of the excess enantiomer was *R*. [e] Chemoselectivity of **3a**, the adduct of acetone ≈1%. [f] Reaction at 50 °C.

On the basis of the above results, we carried out reactions with three commercially available optically pure aliphatic β-amino acids using ethyl acetate (EtOAc) solvent and LiOH × H_2O as base additive both at room temperature (rt, 24 °C) and 50 °C. Selected results are summarised in Table 2. Without the addition of LiOH × H_2O, all these amino acids provided low conversions. However, the bulkiness of the substituent on the β-carbon had a marked effect on both the conversion and *ee*, i.e., the conversions afforded by these catalysts decreased in the order **5** > **6** > **7**, whereas *ee* values increased in the same sequence (entries 4, 7, 11). Accordingly, the bulkiness of this substituent, in addition to hindering the reaction, also had a beneficial effect on the stereocontrol of the addition, affording 91% *ee* with catalyst **7** without the addition of a base additive (entry 11).

Table 2. Asymmetric Michael addition of **2** to **1a** catalysed by β-amino acids **4**–**7** [a].

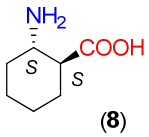
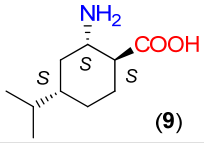
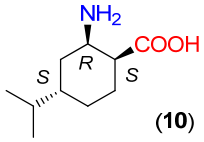
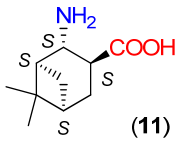
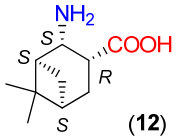
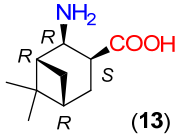
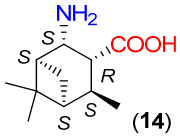
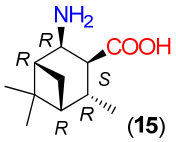
Entry	Catalyst	$LiOH \times H_2O$ Amount (eq) [b]	Temp. (°C)	Time (h)	Conv (Yield) (%) [c]	*ee* (%) (*config.*) [d]
1	 L-Asp-OEt (**4**)	–	24	16	12 (nd)	73 (*R*)
2		1.5	24	16	>99 (91)	95 (*R*)
3		1.5	50	6	98 (90)	92 (*R*)
4	 (**5**)	–	24	16	47 (nd)	24 (*S*)
5		1.5	24	16	97 (88)	81 (*S*)
6		1.5	50	6	88 (80)	78 (*S*)
7	 (**6**)	–	24	16	35 (nd)	84 (*R*)
8		1.5	24	16	91 (81)	94 (*R*)
9		1.5	24	24	>99 (92)	94 (*R*)
10		1.5	50	6	74 (nd)	94 (*R*)
11	 (**7**)	–	24	16	18 (nd)	91 (*S*)
12		1.5	24	16	32 (nd)	94 (*S*)
13 [e]		1.5	24	48	>99 (93)	95 (*S*)
14		1.5	50	24	81 (70)	94 (*S*)

[a] Reaction conditions: 0.03 mmol (10 mol%) catalyst, 0.3 mmol **1a**, 1.2 mmol **2**, 1 cm^3 EtOAc. [b] Compared to the amount of β-amino acid. [c] Conversions by GC-FID; in parenthesis, the yields of the product purified by flash chromatography; nd: not determined. [d] Enantiomeric excess and the configuration of the excess enantiomer by GC-FID. [e] Reaction using 0.06 mmol (20 mol%) catalyst.

The structure of the amino acids had a similar effect on the conversion when they were transformed in situ to their lithium salts by the addition of 1.5 equivalent (eq, compared to the amount of the β-amino acid) $LiOH \times H_2O$. Under these conditions, the reactions were faster. As a result, close to complete transformations could be reached with **6** and **7**, having ^{i}Pr and ^{t}Bu groups in the β position. Note, however, that these catalysts needed longer reactions (entries 9, 13) and an increased amount of catalyst **7** (entry 13). The presence of the base increased the enantioselectivities as well, thus high *ee* values (94–95%) were obtained with **6** or **7**. High conversions were reached in less time by increasing the reaction temperature to 50 °C without a significant decrease in the *ee* values (entries 10, 14). It is interesting that the configuration of the excess enantiomer afforded by **7** (*i.e.*, *S*) was opposite to that obtained using **4** or **6**. Compound **5** also provided an excess of the *S* enantiomer; however, the chiral centre in this compound had the opposite stereoarrangement compared to the other amino acids. Thus, the bulkiness of the substituent of the β-carbon atom influenced both the magnitude and the sense of stereodifferentiation.

The above-detected effects of the β-amino acid structure motivated us to examine compounds with more rigid backbone, such as cycloaliphatic derivatives. The results obtained using β-amino acids having cyclohexane structural motifs in the molecule are presented in Table 3. Initially, we tested the commercially available optically pure (1*S*,2*S*)-2-aminocyclohexane-1-carboxylic acid (**8**). Our results show a peculiar behaviour (entries 1–5). Although in the absence of $LiOH \times H_2O$, **8** afforded the same conversion as **5**, possibly due to the lack of branching next to the C2 atom, the *ee* value was higher and of the opposite sense compared to that provided by **5** (entry 1). The sense of the enantioselectivity can be considered inverted as compared to **6** as well, as the opposite arrangement of the NH_2 group in **6** and **8** should provide opposite enantiomers in excess. Still, both compounds provided the *R* product as the major enantiomer. Both the observed value and the sense of the enantioselectivity may be either due to the rigidity of the ring or to the additional C1 (α-C) chiral centre of the molecule compared to the aliphatic α-unsubstituted **5** or **6**. The moderate conversion reached with **8** in the absence of the base could be increased by decreasing the amount of solvent (0.5 cm^3) or increasing the temperature (50 °C) and extending the reactions to 24 h (entries 2, 3). Meanwhile, the *ee* values remained close to the one determined previously (*R* enantiomer in excess).

Table 3. Asymmetric Michael addition of **2** to **1a** catalysed by β-amino acids **8**–**15** having a cyclohexane backbone [a].

Entry	Catalyst	$LiOH \times H_2O$ Amount (eq) [b]	Temp. (°C)	Time (h)	Conv (Yield) (%) [c]	*ee* (%) (*config.*) [d]
1 [e]	 (**8**)	–	24	16	47 (nd)	52 (*R*)
2		–	24	24	76 (66)	51 (*R*)
3 [e]		–	50	24	84 (75)	49 (*R*)
4 [e]		1.5	24	16	>99 (92)	82 (*S*)
5 [e]		1.5	50	6	99 (90)	82 (*S*)
6	 (**9**)	–	24	24	63 (nd)	37 (*S*)
7		2.2	24	24	95 (87)	65 (*S*)
8		2.2	50 [e]	6	77 (66)	61 (*S*)
9	 (**10**)	–	24	24	52 (nd)	60 (*R*)
10		2.2	24	24	>99 (91)	93 (*R*)
11		2.2	50	24	>99 (92)	94 (*R*)
12	 (**11**)	–	24	44	56 (nd)	64 (*R*)
13		–	24	96	91 (80)	62 (*R*)
14		–	50	24	83 (75)	61 (*R*)
15		2.2	24	72	88 (79)	14 (*S*)
16		2.2	50	24	77 (65)	10 (*S*)
17	 (**12**)	–	24	44	10 (nd)	36 (*S*)
18		2.2	24	24	72 (63)	87 (*S*)
19		2.2	24	44	>99 (90)	88 (*S*)
20	 (**13**)	–	50	24	37 (nd)	40 (*R*)
21		2.2	24	24	68 (60)	95 (*R*)
22		2.2	50	24	88 (77)	92 (*R*)
23	 (**14**)	–	24	24	29 (nd)	11 (*S*)
24		2.2	24	24	95 (86)	92 (*S*)
25	 (**15**)	–	24	24	14 (nd)	14 (*R*)
26		2.2	24	24	96 (88)	94 (*R*)

[a] Reaction conditions: 0.03 mmol (10 mol%) catalyst **8** or **9**–**15** hydrochlorides, 0.3 mmol **1a**, 1.2 mmol **2**, 0.5 cm^3 EtOAc. [b] Compared to the amount of β-amino acid (hydrochloride). [c] Conversions by GC-FID; in parenthesis, the yields of the product purified by flash chromatography; nd: not determined. [d] Enantiomeric excess and the configuration of the excess enantiomer by GC-FID. [e] Reaction in 1 cm^3 EtOAc.

By the addition of $LiOH \times H_2O$, in addition to a substantial increase in the rate shown by the close to full conversions reached at both temperatures, *ee* values increased. Furthermore, the opposite product enantiomers (*S*) were formed in excess compared to reactions without the additive (entries 4, 5). Previously, in Michael additions of **2** to maleimides, a solvent-dependent switch of the enantioselectivity direction was reported with certain cyclohexane-1,2-diamine derivatives [41,61]. A turn in the sense of enantioselection was also observed when L-Asp-O^{t}Bu was replaced with *S*-β-Phe, which differs in the substituent on the β-carbon (COO^{t}Bu vs. phenyl, see Figure 1) [50]. However, to the best of our knowledge, the change in the excess enantiomer configuration by the addition of a base

has not yet been reported in reactions of aldehydes and maleimides. We note that, in the presence of LiOH × H_2O, both catalysts, i.e., **5** and **8**, provided the same *S* enantiomer in excess (*ee* 81–82%). Thus, the unusual enantiodiscrimination occurs with **8** without being transformed into its Li salt.

Due to the above observations, we set out to study the effect of the structure of other β-amino acids with cyclohexane backbone. Although a relatively good *ee* value was obtained with the use of the Li salt of **8** (82%), it did not reach those afforded by the more β-hindered compounds **6** and **7**. Thus, we focused on 2-aminocyclohexane-1-carboxylic acids bearing additional substituents on the ring to increase the enantioselectivity. The preparation of substituted cycloaliphatic β-amino acid series has been reported using monoterpenes as chiral, easily available natural starting materials [62–65]. Thus, stereoisomers of 2-amino-4(*S*)-isopropylcyclohexane-1-carboxylic acid (**9**, **10**) were obtained from *S*-perillaldehyde [65], whereas bicyclic stereoisomers could be prepared from apopinenes (**11**–**13**) [63,64] and *cis*-δ-pinenes (**14**, **15**) [62]. These compounds were stored and used as hydrochloride salts. Consequently, larger amounts of the base were needed for their in situ transformation to lithium carboxylates. Based on the results obtained in reactions catalysed by **8**, the solvent amount was decreased to 0.5 cm^3. Selected results achieved with these β-amino acids are also presented in Table 3.

The compound having the COOH and the NH_2 groups in *trans* arrangement (**9**) afforded low enantioselectivity, which increased in the presence of the base to moderate values (entries 6–8). Although the configurations of the C1 and C2 chiral centres in **8** and **9** were the same, the inversion observed with **8** was not detected when **9** was applied. Thus, without the addition of LiOH × H_2O, the *S* enantiomer formed in excess. The stereoisomer with the *cis* arrangement of the functional groups (**10**) afforded a high conversion and *ee* when LiOH × H_2O was added to the reaction slurry (entries 10, 11). The *R* product enantiomer was formed in excess with this compound. Accordingly, the configuration of the C2 atom determined the sense of the enantioselectivity, whereas that of the C1 did not influence the *ee* direction. Since **8** and **9** provided significantly lower *ee* values than **10**, the good performance obtained with the latter compound may be attributed to the close spatial arrangement of the *cis* functional groups.

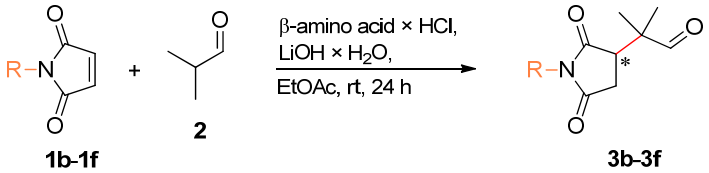
To further test the effect of the substitution pattern of the cycloaliphatic β-amino acids, next we used bicyclic derivatives **11**–**15** (see Table 3). Compound **11** having *trans* orientation of the NH_2 and COOH groups showed a similar inversion of the sense of the enantioselectivity in the absence of LiOH × H_2O, as observed with **8** (entries 12–16).

Comparing the performances reached with the three compounds having *S*-C1 and *S*-C2 configurations (**8**, **9** and **11**), one can see that the enantioselectivity direction in the absence of base varies. Thus, under these conditions, the effect of the configurations of these centres may be overwritten by other geometrical characteristics of the molecule. The in situ formation of the lithium salt of **11** by the addition of LiOH × H_2O resulted in a product mixture in which the *S* adduct was in slight excess. Accordingly, using the lithium salts, the configuration of the centre bearing the amino group (C2) determines the sense of enantioselectivity, as mentioned before. Compounds **12** and **13** with the functional groups in *cis* arrangements offered low conversion and *ee* values in the absence of base (entries 17, 20) and both values increased significantly by the addition of LiOH × H_2O (entries 18, 19 and 21, 22). These two enantiomeric amino acids provided the opposite Michael adduct enantiomers in excess, in accordance with the configuration of the C2 chiral centre. The other β-amino acid enantiomeric pair (**14** and **15**) having both *cis* NH_2 and COOH groups also allowed the formation of the opposite product enantiomers in excess, affording high conversion and *ee* values, when they were transformed to lithium salts. Interestingly, these derivatives, although bearing an additional methyl group near the carboxylate moiety, provided better conversions in one-day reactions than **13**, which has a similar structure, but lacks the methyl group bonded to C6.

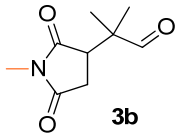
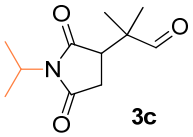
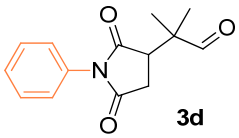
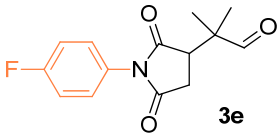
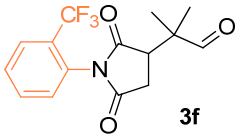
Finally, we examined the effect of the nitrogen substituent of maleimide on the results obtained with β-amino acids **15** and **14**, which provided high conversion and *ee* values

at rt in 24 h in the addition of **2** to **1a** (Table 3, entries 24, 26). The results found with other maleimide derivatives (**1b–1f**) are presented in Table 4. A decrease in the size of the substituent, i.e., a change to methyl group (**1b**), afforded enantioselectivities similar to those obtained with the *N*-benzyl derivative **1a**, however with slightly decreased conversions (entries 1, 2). An increased conversion was obtained with the α-branched isopropyl derivative (**1c**). Moreover, in reactions of *N*-phenyl or its ring-substituted derivatives (**1d–1f**), complete transformations and similar *ee* values were attained, even when the CF_3 substituent was in the *ortho* position. This functional group may have a hindering effect, as observed previously with L-Phe catalyst adsorbed on an inorganic oxide surface [56].

Table 4. Asymmetric Michael addition of **2** to *N*-substituted maleimides catalysed by β-amino acids **15** [a] or **14** [b].



1b-1f **3b-3f**

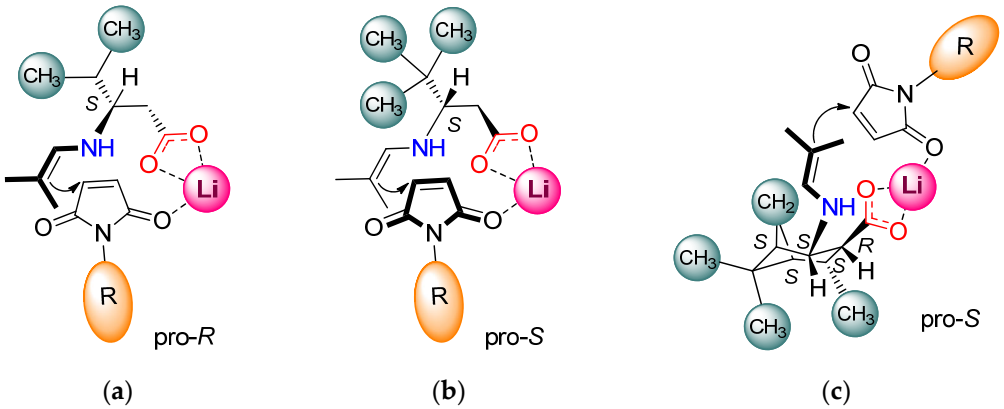
Entry	Product	Conv (Yield) (%) [c]	*ee* (%) (*config.*) [d]
1	 **3b**	92 (85)	95 (*R*)
2 [b]		93 (85)	92 (*S*)
3	 **3c**	97 (90)	96 (*R*)
4	 **3d**	>99 (93)	96 (*R*)
5 [b]		>99 (92)	95 (*S*)
6	 **3e**	99 (92)	93 (*R*)
7	 **3f**	99 (93)	95 (*R*)

[a] Reaction conditions: 0.03 mmol (10 mol%) catalyst **15** × HCl, 2.2 eq LiOH × H_2O (compared to **15** × HCl), 0.3 mmol **1b–1f**, 1.2 mmol **2**, 0.5 cm^3 EtOAc, rt, 24 h. [b] Reaction using 0.03 mmol (10 mol%) **14** × HCl catalyst. [c] Conversions by GC-FID; the yields of the isolated products in parenthesis. [d] Enantiomeric excess and the configuration of the excess enantiomer by GC-FID.

3. Discussion

In the present study, exploring the effect of the structure of chiral β-amino acids applied as catalysts in the asymmetric addition of isobutyraldehyde to *N*-benzylmaleimide, several remarkable results were observed. For interpreting these observations, we recall that the conjugate additions of aldehydes and ketones to maleimides catalysed by primary amine–hydrogen-bond donor groups containing bifunctional organocatalysts occur through the formation of an enamine intermediate [25,31,32,34,39–43,45]. The maleimide is activated by hydrogen bonding, whereas the stereochemical outcome of the reaction is determined by the preferential direction of the approach of the enamine found in the proximity of

the chiral centre to the activated electrophile. In reactions catalysed by salts of primary amino acids, the maleimide interacts via electrostatic forces or by hydrogen bonding with other additives (sulfamides, thioureas, surface Brønsted or Lewis acidic sites) [49,50,54–56]. During catalysis by β-amino acid salts, similar transition states are likely to operate, as envisaged by Kokotos [50]. The opposite sense of enantioselectivities obtained using **6** compared to **7** may be due to the significant steric hindrance of the *tert*-butyl group, which may have a strong shielding effect. The bulkiness of this group may change the orientation of the carboxylate anion compared to the smaller substituents (^{i}Pr), as illustrated in Figure 2a,b, leading to a lower reaction rate and inversion of the enantioselectivity.



(**a**) (**b**) (**c**)

Figure 2. Proposed transition states formed in the asymmetric addition of **2** to *N*-substituted maleimides catalysed by β-amino acids in the presence of LiOH × H_2O: (**a**) **6**; (**b**) **7**; (**c**) **14**.

β-Amino acids with cyclohexane framework with the COOH and NH_2 groups in the 1,2-positions following their in situ transformation to lithium salts showed that the configuration of the excess enantiomer is determined by the chirality of C2 (*i.e.*, β-carbon), both when the functional groups are in *trans* or *cis* arrangement. However, the *ee* values were low to moderate with the *trans* derivatives (up to 82% with **8**), with a strongly detrimental effect of additional substituents on the ring (compare **8**, **9**, **11**). In contrast, the *cis* stereoisomers (**10**, **12**, **13**, **14**, **15**) provided high *ee* values (88–95%). Moreover, a comparison of the performances of the identically substituted stereoisomers (**9** vs. **10**; **11** vs. **12** or **13**) showed that the *cis* isomers also afford better reaction rates.

A plausible reason of this behaviour is the closer spatial arrangement of the *cis* functional groups compared to that of the *trans*, leading to a more directed and efficient interaction of the enamine and the activated electrophile. Additional substituents on the cyclohexane scaffold had a limited influence on the stereoselectivity, having a more significant effect on the rate, probably affecting the formation of the enamine intermediates. Thus, the bicyclic structure of **13** or **12**, presumably due to branching on C3 (next to the amine group), allowed slower reactions compared to the 4-^{i}Pr-substituted **10**, similar to the effect of γ-branching in **6**. However, the *trans*-methyl group substitution on C6 (next to the carboxylate group, **14** and **15**) increased the rate compared to **12** or **13**, attributable to the beneficial steric constraints of the opposite side of the molecule compared to the position of the functional groups (Figure 2c), thus contributing to the favourable positioning of the activated electrophile. The nitrogen substituent of maleimide also had a small steric effect on the rate of the additions, as indicated by comparing the reactions of maleimides substituted with Me, Bn, ^{i}Pr, 2-CF_3-Ph, 4-F-Ph and Ph groups, which provided increasing conversions in this order.

Finally, an interesting inversion of the sense of enantioselectivity was noted with two *trans*-cyclohexane-2-amino-1-carboxylic acids in the absence of the base additive. This change in the configuration of the excess enantiomer may be caused by the stronger attachment of the electrophile to the catalysts. This, in combination with the less efficient arrangement of the functional groups (*trans*), leads to the preferential attack at the opposite enantioface of the electrophile compared to that interacting with the lithium cation. It must

be noted that this effect is strongly affected by the substitution pattern of the cyclohexane ring, as the unsubstituted **8** and the heavily substituted **11** offered inversions, in contrast to the C4-substituted **9** derivative.

4. Materials and Methods

The optically pure β-amino acids were either commercial products used as received (**4**–**8**) or prepared in previous studies (**9**–**15**) and stored and used as hydrochlorides [60–63]. Isobutyraldehyde (**2**) and *N*-substituted maleimides **1a**, **1b** and **1d** were purchased from commercial sources (Sigma-Aldrich, St. Louis, MO, USA). Maleimides **1c**, **1e** and **1f** were prepared during our previous study [56]. Solvents of analytical grade and high-purity additives were commercial products and used as received (Merck KGaA, Darmstadt, Germany).

Products formed in catalytic reactions were analysed by gas chromatography using Agilent Techn. 6890 N GC-5973 MSD (GC-MSD, Agilent Co., Santa Clara, CA, USA) equipped with a 30 m long DB-1MS UI (J&W, Agilent) capillary column for mass spectrometric identification of the compounds and Agilent 7890A GC-FID (GC-FID, Agilent Co., Santa Clara, CA, USA) equipped with chiral capillary columns (Cyclosil-B, 30 m × 0.25 mm, J&W, Agilent or Hydrodex g-TBDAc, 25 m × 0.25 mm, Macherey-Nagel) for quantitative analysis. The adducts were purified by flash chromatography using silica gel 60, 40–63 µm. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker DRX-500 spectrometer (Bruker Corp., Millerica, MA, USA) at 500 (^{1}H) and 125 (^{13}C) MHz in $CDCl_3$ solvent.

Asymmetric Michael additions were carried out in 4 cm^3 closed glass vials using magnetic agitation (800 rpm). In a typical run, 0.03 mmol β-amino acid was suspended by stirring in the solvent (EtOAc) followed by the addition of LiOH × H_2O. After 10 min stirring, 0.3 mmol *N*-substituted maleimide was added. Reactions were started by the addition of 1.2 mmol isobutyraldehyde. Reactions at 50 °C were carried out by immersing the vials in a preheated oil bath. After the desired reaction time, the mixture was diluted to 3 cm^3 with EtOAc, the catalyst was extracted into 1 cm^3 saturated NH_4Cl(aq) solution, the aqueous phase was washed twice with 1 cm^3 of EtOAc, and the unified organic phases were dried over $MgSO_4$ and analysed by gas chromatography using *n*-decane as internal standard. The conversion and the enantiomeric excess (*ee*) values were calculated using the results of the GC-FID analysis as shown previously [56]. The absolute configuration of the excess enantiomer was assigned based on our previous report [56]. The raw product was obtained by evaporating the solvent and the unreacted aldehyde and purified further by flash chromatography using hexane (mixture of isomers)/EtOAc or hexane (mixture of isomers)/^{t}BuOMe and characterised as given below and in our recent report. Chromatograms and spectra of the products were in agreement with the published data [56].

*(R)-2-(1-Benzyl-2,5-Dioxopyrrolidin-3-yl)-2-Methylpropanal (**3a**).* Table 2, entry 2, eluted with hexane (mixture of isomers)/EtOAc 4/1, white solid, 71.8 mg (yield 91%), enantiomeric ratio 97.5(*R*)/2.5(*S*); GC-MSD *m*/*z*(rel int) = *259*(M^+, 1), *231*(100), *216*(48), *189*(13), *138*(30), *106*(21), *91*(80), *83*(16), *69*(30), *55*(8), *41*(13); GC-FID, Cyclosil-B column, retention times (min) = 55.6 (**1a**), 174.3 (*R*-**3a**), 179.6 (*S*-**3a**). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 1.16 (s, 6H), 2.45 (dd, *J* = 5.4, 18.3 Hz, 1H), 2.81 (dd, *J* = 9.4, 18.3 Hz, 1H), 3.03 (dd, *J* = 5.4, 9.4 Hz, 1H), 4.65 (q, *J* = 14.1 Hz, 2H), 7.24-7.33 (m, 3H), 7.36 (d, *J* = 6.9 Hz, 2H), 9.49 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) = 19.1, 19.9, 31.4, 42.4, 44.9, 48.0, 127.9, 128.6, 128.7, 135.6, 175.3, 177.4, 202.6.

*(R)-2-Methyl-2-(1-Methyl-2,5-Dioxopyrrolidin-3-yl)Propanal (**3b**).* Table 4, entry 1, eluted with hexane (mixture of isomers)/EtOAc 5/1, pale yellow oil, 46.7 mg (yield 85%), enantiomeric ratio 97.5(*R*)/2.5(*S*); GC-MSD *m*/*z*(rel int) = *183*(M^+, 2), *155*(41), *140*(66), *113*(61), *83*(30), *69*(100), *55*(13), *41*(33); GC-FID, Hydrodex g-TBDAc column, retention times (min) = 12.9 (**1b**), 92.1 (*R*-**3b**), 92.9 (*S*-**3b**). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 1.17 (d, *J* = 5.2 Hz, 6H), 2.42 (dd, *J* = 5.4, 18.3 Hz, 1H), 2.78 (dd, *J* = 9.3, 18.3 Hz, 1H), 2.94 (s, 3H), 3.01 (dd, *J* = 5.4, 9.3 Hz, 1H), 9.47 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) = 19.2, 20.0, 24.8, 31.4, 45.0, 47.9, 175.8, 177.8, 202.7.

*(R)-2-(1-Isopropyl-2,5-Dioxopyrrolidin-3-yl)-2-Methylpropanal (**3c**).* Table 4, entry 3, eluted with hexane (mixture of isomers)/^{t}BuOMe 2/1, transparent oil, 57.0 mg (yield 90%), enantiomeric ratio 98(*R*)/2(*S*); GC-MSD *m*/*z*(rel int) = *211*(M^+, 4), *183*(39), *168*(41), *141*(57), *126*(53), *99*(23), *83*(23), *69*(100), *55*(16), *41*(31); GC-FID, Cyclosil-B column, retention times (min) = 17.0 (**1c**), 105.2 (*R*-**3c**), 107.8 (*S*-**3c**). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 1.18 (d, *J* = 2.1 Hz, 6H), 1.37 (d, *J* = 6.95 Hz, 6H), 2.38 (dd, *J* = 5.3, 18.2 Hz, 1H), 2.74 (dd, *J* = 9.5, 18.2 Hz, 1H), 2.96 (dd, *J* = 5.3, 9.5 Hz, 1H), 4.37 (h, *J* = 6.95 Hz, 1H), 9.52 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) = 18.8, 19.1, 19.1, 20.0, 31.3, 43.9, 44.7, 48.0, 175.6, 177.7, 202.7.

*(R)-2-(1-Phenyl-2,5-Dioxopyrrolidin-3-yl)-2-Methylpropanal (**3d**).* Table 4, entry 4, eluted with hexane (mixture of isomers)/EtOAc 10/1, white solid, 68.4 mg (yield 93%), enantiomeric ratio 99(*R*)/1(*S*); GC-MSD *m*/*z*(rel int) = *245*(M^+, 1), *217*(75), *202* (100), *175*(13), *147*(18), *119*(18), *93*(40), *83*(52), *69*(33), *55*(12), *41*(23); GC-FID, Cyclosil-B column, retention times (min) = 54.0 (**1d**), 198.5 (*R*-**3d**), 200.5 (*S*-**3d**). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 1.30 (d, *J* = 16.0 Hz, 6H), 2.62 (dd, *J* = 5.5, 18.3 Hz, 1H), 2.97 (dd, *J* = 9.6, 18.3 Hz, 1H), 3.15 (dd, *J* = 5.5, 9.6 Hz, 1H), 7.27 (d, *J* = 7.4 Hz, 2H), 7.39 (tr, *J* = 7.4 Hz, 1H), 7.47 (tr, *J* = 7.4 Hz, 2H), 9.52 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) = 19.6, 20.2, 31.8, 45.0, 48.5, 126.5, 128.7, 129.1, 131.8, 174.7, 176.8, 202.7.

*(R)-2-(4-Fluorophenyl-2,5-Dioxopyrrolidin-3-yl)-2-Methylpropanal (**3e**).* Table 4, entry 6, eluted with hexane (mixture of isomers)/^{t}BuOMe 1/1.5, off-white solid, 72.7 mg (yield 92%), enantiomeric ratio 98(*R*)/2(*S*); GC-MSD *m*/*z*(rel int) = *263*(M^+, 3), *235*(65), *220* (100), *193*(14), *165*(23), *137*(18), *111*(33), *83*(60), *69*(29), *55*(11), *41*(17); GC-FID, Cyclosil-B column, retention times (min) = 55.0 (**1e**), 194.0 (*R*-**3e**), 196.5 (*S*-**3e**). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 1.32 (d, *J* = 33.0 Hz, 6H),), 2.62 (dd, *J* = 5.6, 18.3 Hz, 1H), 2.97 (dd, *J* = 9.6, 18.3 Hz, 1H), 3.11 (dd, *J* = 5.6, 9.6 Hz, 1H), 7.15 (tr, *J* = 8.4 Hz, 2H), 7.27 (dd, *J* = 4.9, 8.4 Hz, 2H), 9.50 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) = 19.9, 20.4, 31.9, 44.9, 48.6, 116.1, 116.3, 127.7, 128.3, 128.4, 161.3, 163.3, 174.6, 176.8, 202.7.

*(R)-2-((2-Trifluoromethyl)phenyl)-2,5-Dioxopyrrolidin-3-yl)-2-Methylpropanal (**3f**).* Table 4, entry 7, eluted with hexane (mixture of isomers)/EtOAc 4/1, off-white solid, 87.4 mg (yield 93%), enantiomeric ratio 97.5(*R*)/2.5(*S*); GC-MSD *m*/*z*(rel int) = *313*(M^+, 1), *285*(84), *270*(28), *250*(100), *222*(29), *168*(21), *83*(97), *69*(98), *55*(21), *41*(37); GC-FID, Cyclosil-B column, retention times (min) = 39.0 (**1f**), 104.5 (*R*-**3f**), 106.0 (*S*-**3f**). ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm) = 1.22-1.34 (m, *J* = 56.8, 64.1 Hz 6H), 2.60-2.73 (m, *J* = 6.7, 18.3, 5.1, 18.0 Hz, 1H), 3.01 (m, *J* = 9.8, 18.0 Hz, 1H), 3.07-3.42 (m, 1H), 7.17-7.36 (m, *J* = 7.8 Hz, 1H), 7.58 (m, 1H), 7.68 (dd, *J* = 7.5, 14.8 Hz, 1H), 7.79 (tr, *J* = 7.0 Hz, 1H), 9.44-9.60 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) = 18.9, 19.4, 20.5, 20.8, 29.7, 31.7, 32.5, 45.2, 45.9, 127.4, 127.5, 127.6, 130.0, 130.1, 130.8, 133.3, 174.3, 176.1, 176.7, 202.7.

5. Conclusions

We carried out a study exploring the effect of the structure of the β-amino acid organocatalyst used in the asymmetric Michael addition of isobutyraldehyde to *N*-substituted maleimides. The rate of the addition of the aldehyde to *N*-benzylmaleimide decreases, whereas the enantiomeric excess increases, as the bulkiness of the substituent on the β-carbon increases. Moreover, large groups, such as *tert*-butyl, in this position may cause an inversion of the sense of enantioselectivity. The results, obtained with various substituted 2-aminocyclohexane-1-carboxylic acids prepared from commercially available natural terpenes and transformed in situ into lithium salts, indicate that the configuration at the β-carbon atom determines the sense of the enantioselectivity. However, the *cis* spatial arrangement of the functional groups is necessary for obtaining high rates and enantiomeric excesses. Other substituents on the cyclohexane scaffold influenced the rate of the addition and had a small effect on the *ee* values as well. In contrast, depending on substituents on the ring, the *trans* isomers provided the opposite enantiomers in excess in the absence of the base additive compared to that obtained with the lithium salts. The most efficient cyclic β-amino acids were also used in addition of isobutyraldehyde to several maleimides,

revealing a minor effect of the nitrogen substituent of the maleimide on the rate. Based on the experimental results, we proposed possible transition state structures, which explain the yet undisclosed inversions of the enantioselectivity either caused by bulky substituents or triggered by the lack of the base additive.

Author Contributions: Conceptualisation, G.S. and Z.S.; methodology, V.K.; validation, V.K. and G.S.; formal analysis, V.K. and G.S.; investigation, V.K.; resources, G.S. and Z.S.; data curation, V.K. and G.S.; writing—original draft preparation, G.S.; writing—review and editing, V.K., Z.S. and G.S.; visualisation, V.K. and G.S.; supervision, G.S.; project administration, G.S. and Z.S.; funding acquisition, V.K., G.S. and Z.S. All authors have read and agreed to the published version of the manuscript.

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