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Highly Efficient and Practical Pyrrolidine–Camphor-Derived Organocatalysts for the Direct α-Amination of Aldehydes

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A series of pyrrolidine–camphor-derived organocatalysts (**1**–**4**) were designed and synthesised. These organocatalysts were used for direct α-amination of aldehydes with dialkyl azodicarboxylates to give the desired α-aminated products in high chemical yields (up to 92 %) and with high to excellent levels of stereoselectivity (up to >99 % *ee*). The reactions proceeded rapidly (within 5 min) with low catalyst loading (5 mol-%) at ambient temperature. Enantioselective aminations of asymmetric α,α-disubstituted aldehydes in the catalytic system were studied, with reasonable to high stereoselectivities (up to 75 % *ee*) being obtained. The utility of this methodology was demonstrated with the synthesis of derivatives of β-amino-γ-butyrolactone and a tetrasubstituted cyclohexane-derived amino alcohol with high stereoselectivities. Transition models were proposed for the asymmetric α-amination reactions; they involve hydrogen-bond interactions between the nucleophilic enamine formed in situ and the nitrogen source.

Introduction

The use of small organic molecules as catalysts in asymmetric synthesis has attracted much attention in recent years.[1] The first use of a metal-free, low-molecular-weight organic molecule in asymmetric synthesis was reported thirty years ago,[2] and L-proline was later rediscovered as an efficient enantioselective catalyst for intermolecular aldolisation.[3] The field of asymmetric organocatalysis has grown significantly since then. The increasing interest arises from a number of synthetic advantages of organocatalysts, because they are typically nontoxic, highly efficient, stable in air, compatible with aqueous reaction conditions and environmentally friendly.[4] More importantly, the development of new reaction modes becomes possible.[5] A variety of organocatalytic methods for enantioselective C–C and C–heteroatom bond formation have been developed: examples include aldol condensations, Michael and Mannich reactions, 1,3-dipolar cycloadditions, Diels–Alder reactions, α-functionalisation of aldehydes/ketones and hydride transfer.[6] The increasing demand for optically pure enantiomers in pharmaceuticals and in materials sciences has also promoted the development of organocatalytic processes.[7]

Among the many organocatalytic methods developed, electrophilic amination is an important chemical transformation. The use of α-amino acids and their derivatives as enzyme inhibitors, antibiotics and fundamental building blocks in the synthesis of natural products has led to the development of enantioselective carbon–nitrogen bond formation.[8] Several asymmetric variants for the α-amination of carbonyl compounds have been reported.[9] The metal-mediated enantioselective synthesis of α-hydrazino acids and α-amino acids has been demonstrated with 1,3-dicarbonyl compounds,[10] oxo esters[11] and metal enolates/silyl enols[12] as carbon nucleophiles.

The use of electrophilic reagents such as dialkyl azodicarboxylates (DAADs) makes this synthetic approach more attractive. The desired nitrogenous functionality is easily achievable through reductive cleavage of the N–N bond of the initial product. Remarkable advances in organocatalytic direct α-amination of aldehydes/ketones with DAADs have been made by List[13a] and Jørgensen[13b] (Scheme 1, below). L-Proline was used to catalyse α-amination of aldehydes with DAAD to install protected amino groups in high yields and with excellent enantioselectivities. The aminated products were further converted into oxazolidinones in a sequential processes. Various enantioselective α-amination of carbonyl compounds catalysed by different structural organocatalysts have also been documented.[14]

Although direct α-amination processes giving high chemical yields and high enantioselectivities have already been developed, several synthetic challenges, including substrate generality and catalyst practicality, still need to be addressed. Furthermore, the α-amination of unsymmetrical α,α-disubstituted aldehydes remains a challenging task. A class of novel pyrrolidine–camphor-derived organocatalysts were designed and synthesised recently in this laboratory.[15] Fortuitously, these organocatalysts have proven to be effective in catalysing Michael additions and α-amination of aldehydes: the desired α-aminated alcohols, for example, were obtained with high to excellent chemical yields and

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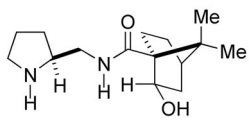
excellent enantioselectivities (up to >99% *ee*) in CH_2Cl_2 at 0 °C (with subsequent $NaBH_4$ reduction).[15a] Here we report a full account of our studies of α-amination of aldehydes with dialkyl azodicarboxylates as nitrogen sources catalysed by the pyrrolidine–camphor-derived organocatalysts **1**–**4** (Figure 1). Their synthetic utilities were demonstrated with the straightforward syntheses of derivatives of β-amino-γ-butyrolactone and a tetrasubstituted cyclohexane with high stereoselectivities.



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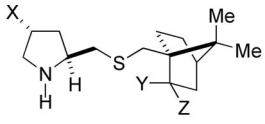
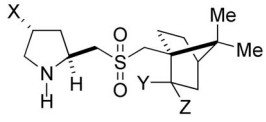
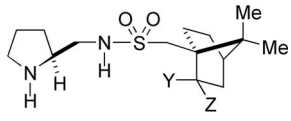


2a: X = H, Y,Z = O
2b: X = H, Y = H, Z = OH
2c: X = OH, Y,Z = O
2d: X = OH, Y = H, Z = OH
2e: X = OTBDPS, Y,Z = O
2f: X = OTBDPS, Y = H, Z = OH





3a: X = OTBDPS, Y,Z = O
3b: X = OTBDPS, Y = H, Z = OH

4a: Y,Z = O
4b: Y = H, Z = OH

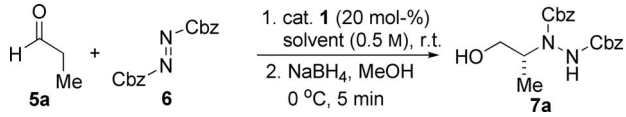
Figure 1. Structures of pyrrolidine–camphor derivatives.

Results and Discussion

The joining of a well-defined structural camphor scaffold to a pyrrolidine motif gave rise to a new family of bifunctional organocatalysts. The two natural scaffolds were linked through appropriate functionalities, such as amide (**1**), sulfide (**2a**–**f**), sulfone (**3a**–**b**) and sulfonamide (**4a**–**b**). The modular nature of the assembly allows for fine-tuning of the catalysis. Further functional-group modifications were possible at the C-4 position in the pyrrolidine moiety and at C-2 in the camphor system. In the former case a hydroxy group or its TBDPS derivative can be substituted, and in the latter either an oxo or an *exo*-hydroxy group can be incorporated. The synthesis is straightforward, from inexpensive commercially available starting materials, and each component can serve either as a nucleophilic or as an electrophilic partner in the preparation of these organocatalysts.[15a,15b]

For the direct α-amination reaction, propionaldehyde (**5a**) was chosen as a model substrate, and dibenzyl azodicarboxylate (**6**) was used as the nitrogenating agent in the presence of catalytic quantities of the organocatalyst **1**. We initially focused on the solvent effects in the direct α-amination reactions at ambient temperature. Treatment of **5a** with **6** in hexanes in the presence of **1** (20 mol-%) with subsequent $NaBH_4$ reduction gave the desired amino alcohol **7a** in 36% chemical yield and with a 53% *ee* (Table 1, Entry 1). Substantial improvements both in chemical yield (57%) and in enantioselectivity (85% *ee*) were obtained when the reaction was carried out in toluene (Table 1, Entry 2). The reactivities and enantioselectivities were only moderate in chlorinated solvents such as CH_2Cl_2 and $CHCl_3$ (Table 1, Entries 3 and 4). Low chemical yields (16%) and only moderate enantioselectivities (46% *ee*) were observed in THF over a period of 48 h (Table 1, Entry 5). Unsatisfactory results were obtained when the reaction was carried out with highly polar protic or aprotic solvents (Table 1, Entries 6–8). A poor chemical yield, but reasonable enantioselectivity, was obtained when H_2O was used as the reaction medium (Table 1, Entry 9). Although demonstrating only moderate stereoselectivity, the reaction proceeded with unusual speed, reaching completion within 1 min, when the reaction was carried out in brine or under solvent-free conditions (Table 1, Entries 10 and 11). The effects of acidic additives were subsequently evaluated. Although the reactivity was found to increase when the reaction was carried out in the presence of various Brønsted acids, the stereoselectivities were inferior to those observed in the case of toluene (Table 1, Entries 12–16).

Table 1. Solvent and additive effects of the direct α-amination of propionaldehyde (**5a**) with dibenzyl azodicarboxylate (**6**) at ambient temperature.[a,b]



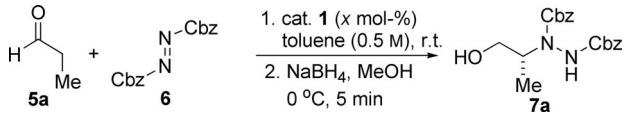
Entry	Solvent	Additive[c]	*t* [min]	Yield [%][d]	*ee* [%][e]
1	hexane		30	36	53
2	PhMe		30	57	85
3	CH_2Cl_2		30	34	70
4	$CHCl_3$		30	63	73
5	THF		48 h	16	46
6	DMSO		36 h	17	22
7	DMF		24 h	23	6
8	MeOH		6 h	18	16
9	H_2O		12 h	22	51
10	brine		1	44	60
11	neat		1	82	44
12	PhMe	AcOH	1	56	44
13	PhMe	TFA	5	62	54
14	PhMe	$PhCSO_3H$	5	51	77
15	PhMe	$PhCO_2H$	5	54	66
16	PhMe	DBSA	5	60	85

[a] Unless otherwise specified, all reactions were carried out with propionaldehyde (**5a**, 1.0 mmol), DBAD (**6**, 0.25 mmol) and **1** (20 mol-%). [b] Propionaldehyde was added to a reaction mixture of **6** and the organocatalyst **1**. [c] 20 mol-% of additive was used. [d] Isolated yield. [e] Determined by chiral HPLC analysis.

Studies of the active species that might be involved in asymmetric reactions catalysed by L-proline have been documented elsewhere.[16] The results might assist in the elucidation of a mechanistic explanation of the catalytic process. An interesting addition order/reactivity phenomenon was observed in our case. When propionaldehyde was added last to a reaction mixture of catalyst **1** and dibenzyl azodicarboxylate in toluene, the reaction went to completion in 30 min (Table 1, Entry 2). On the other hand, when dibenzyl azodicarboxylate was added last to a reaction mixture of catalyst **1** and the aldehyde in toluene, the

reaction rate increased remarkably and completion was reached in less than 1 min. The same level of stereoselectivity was retained (Table 2, Entry 1). The significant reactivity enhancement prompted us to fine-tune the catalysis conditions. This included a systematic study of the relative amounts of the catalyst **1** and the donor aldehyde, as well as of the reaction temperature. Poorer performance was generally observed when either 2.0 or 1.5 equiv. of propionaldehyde was treated with the dibenzyl azodicarboxylate and 20 mol-% of the catalyst **1** (Table 2, Entries 2 and 3). Lowering of the amount of the catalyst **1** to 5 mol-% restored both the reactivity and selectivity (Table 2, Entries 4 and 5), but the reactivity again dropped significantly when the amount of catalyst was reduced to only 1 mol-% (Table 2, Entry 6). The enantioselectivity was improved to 93% *ee* when the reaction was carried out at 0 °C, and this value rose to 97% *ee* at –20 °C (Table 2, Entries 7 and 8). At –40 °C the chemical yield increased to 92% with the level of enantioselectivity unchanged (Table 2, Entry 9). It is worth mentioning here that 4 equiv. of propionaldehyde and 5 mol-% of the organocatalyst **1** were used for this catalytic process at –40 °C.

Table 2. Optimisation of the reaction conditions for the direct α-amination of propionaldehyde (**5a**) with dibenzyl azodicarboxylate (**6**) in toluene.[a,b]

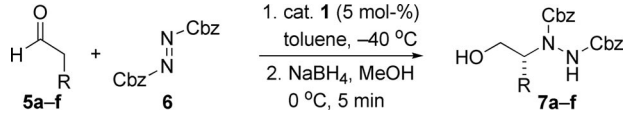


Entry	**1** [mol-%]	**5a** [equiv.]	*T* [°C]	*t* [min]	Yield [%][c]	*ee* [%][d]
1	20	4.0	r.t.	1	47	85
2	20	2.0	r.t.	5	49	27
3	20	1.5	r.t.	5	69	24
4	10	4.0	r.t.	2	67	79
5	5	4.0	r.t.	5	80	84
6	1	4.0	r.t.	36 h	71	87
7	5	4.0	0	25	84	93
8	5	4.0	–20	1 h	78	97
9	5	4.0	–40	2 h	92	97

[a] Unless otherwise specified, all reactions were carried out with propionaldehyde (**5a**, 1.0 mmol) and DBAD (**6**, 0.25 mmol). [b] DBAD (**6**) was added to a mixture of **5a** and **1** at the indicated temperature. [c] Isolated yield. [d] Determined by chiral HPLC analysis.

To assess the general utility of this asymmetric α-amination, we examined the reactions between a variety of alkyl-substituted aldehydes and dibenzyl azodicarboxylate (**6**) under the optimised reaction conditions (Table 3). All reactions were performed in toluene at –40 °C in the presence of **1** (5 mol-%), followed by reduction with $NaBH_4$ at 0 °C. The α-aminated products were generated in good to high chemical yields (55–92%) and with excellent enantioselectivities (95 to >99% *ee*, Table 3, Entries 1–6). These results compare favourably with the best results relating to organocatalysis reported in the literature. A gram-quantity reaction (1.0 g) was carried out with pentanaldehyde (**5d**) under the same conditions and give satisfactory results (67% chemical yield and 95% *ee*, Table 3, Entry 7).

Table 3. Direct α-amination of the aldehydes **5a**–**f** in the presence of the organocatalyst **1** under the optimised reaction conditions.[a]

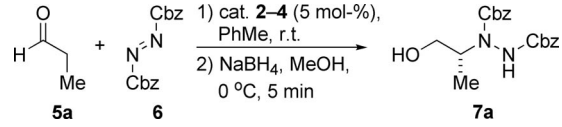


Entry	R^1	*t* [h]	Yield [%][b]	*ee* [%][c]
1	Me (**5a**)	2	92 (**7a**)	97
2	Et (**5b**)	2	70 (**7b**)	99
3	*i*Pr (**5c**)	2	64 (**7c**)	95
4	Pr (**5d**)	2	73 (**7d**)	99
5	Bu (**5e**)	2	77 (**7e**)	>99
6	Bn (**5f**)	1	55 (**7f**)	95
7[d]	Pr (**5d**)	2	67 (**7d**)	95

[a] Unless otherwise specified, all reactions were carried out with aldehydes **5a**–**f** (1.0 mmol) and DBAD (**6**, 0.25 mmol). In all cases DBAD (**6**) was added to a mixture of aldehyde and the catalyst. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] The reaction was scaled up and performed on **6** (1.0 g).

At this stage, excellent stereoselectivities had only been achieved when the reaction was performed at low temperature (–40 °C) for 2 h. The development of operationally simple processes is one of the central themes of organocatalysis, and the development of more convenient processes not requiring low-temperature conditions is important for ensuring a simple process. A screening of a series of pyrrolidine–camphor derivatives (**2**–**4**) at higher reaction temperatures was therefore carried out,[15a] and the results are presented in Table 4. For the catalysts screening, propionaldehyde (**5a**) was chosen as a test substrate with DBAD (**6**) in toluene at ambient temperature in the presence of the organocatalyst (5 mol-%). Treatment of propionaldehyde (**5a**) with DBAD (**6**) in the presence of the sulfide-linked catalyst **2a** in toluene, followed by $NaBH_4$ reduction, yielded **7a**. Interestingly, the aminated alcohol was obtained

Table 4. Enantioselective α-amination of **5a** with various organocatalysts (**2**–**4**) in toluene at ambient temperature.[a,b]

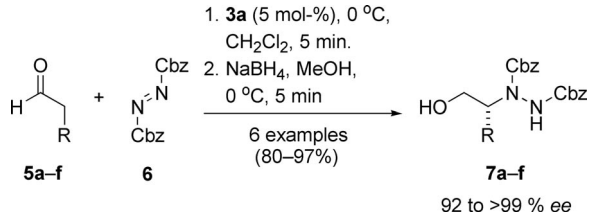


Entry	Catalyst	*t* [min]	Yield [%][c]	*ee* [%][d]
1	**2a**	5	96	–16
2	**2b**	5	88	2
3	**2c**	5	83	–52
4	**2d**	5	91	–39
5	**2e**	20	88	31
6	**2f**	5	68	74
7	**3a**	20	90	92
8	**3b**	30	92	90
9	**4a**	90	89	93
10	**4b**	30	78	94

[a] All reactions were carried out with propionaldehyde (**5a**) and DBAD (**6**) in toluene in the present of the organocatalyst (5 mol-%). [b] DBAD (**6**) was added to a mixture of **5a** and the catalyst at the ambient temperature. [c] Isolated yield. [d] Determined by chiral HPLC analysis.

with reversed stereoselectivity [(*S*) configuration] in excellent chemical yield (Table 4, Entry 1). The stereoselectivity was enhanced by the presence of a 4-hydroxy group in the pyrrolidine ring (Table 4, Entries 3 and 4). This indicated that the 4-hydroxy group plays a critical role in determining the stereoselectivity. On the other hand, the (*R*) isomer was obtained as the major product when the hydroxy group was protected as its TBDPS ether derivative (Table 4, Entries 5 and 6). Finally, when the reaction was catalysed by the sulfone-linked organocatalysts **3a** and **3b** the reaction proceeded smoothly at ambient temperature without significant deterioration of enantioselectivity (Table 4, Entries 7 and 8). Slight improvements in stereoselectivity and reduced reactivity were observed when the sulfonamide-linked catalysts **4a** and **4b** were used (Table 4, Entries 9 and 10).

Slight further improvements were achieved when the reaction was performed in CH_2Cl_2 at 0 °C. Various aldehydes (**5a**–**f**) were used to demonstrate the utility of this convenient catalytic process in the presence of the catalyst **3a** in CH_2Cl_2. The corresponding amino alcohols **7a**–**f** were obtained in high chemical yields (80–90%) and with excellent stereoselectivities (92–>99% *ee*) under the optimised reaction conditions (Scheme 1).[15a]

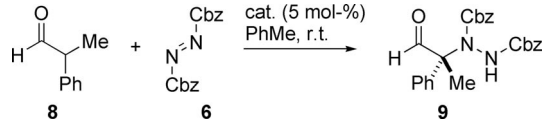


Scheme 1. Direct α-amination of various aldehydes (**5a**–**f**) with DBAD (**6**) in the presence of the organocatalyst **3a**.

Encouraged by the above results, we next explored the amination of unsymmetrical α,α-disubstituted aldehydes. The synthesis of α,α-disubstituted amino acids is an interesting topic due to their biological importance. Numerous research groups have reported on the enantioselective amination of α,α-disubstituted aldehydes with DAADs.[14c,14g,14h,14m,14n] The aminated products were obtained with moderate to good chemical yields and stereoselectivities. These reaction conditions suffered from several disadvantages such as the requirements for high catalyst loadings (up to 50 mol-%), thermal or microwave reaction conditions and prolonged reaction times (3–9 d);[14m,14n] so the development of appropriate organocatalytic systems for the amination of α,α-disubstituted aldehydes remains desirable.

Initially, 2-phenylpropanal (**8**) was used as the nucleophilic donor to react with DBAD (**6**) in the presence of the catalyst **1** (5 mol-%). As expected, the reactivity was significantly decreased, and moderate chemical yield and enantioselectivity were obtained (Table 5, Entry 1). In searching for better reaction conditions, we screened the available pyrrolidine–camphor derivatives (**2a**–**f**, **3a**–**b** and **4a**–**b**) in this process. With the sulfide-derived organocatalysts **2a**–**c** the aminated product **9** was obtained in moderate to good yields but with poor selectivity (Table 5, Entries 2–4). The enantioselectivity was improved (40% *ee*) when **2d** was employed as the catalyst (Table 5, Entry 5). The TBDPS ether derivative **2f** failed to improve the enantioselectivity but decreased the chemical yield (Table 5, Entry 7). Both the chemical yield and the enantioselectivity were unsatisfactory when **3a** and **3b** were used (Table 5, Entries 8–9). The best enantioselectivity was achieved when the sulfonamide-derived organocatalyst **4a** was used (Table 5, Entries 10–11).

Table 5. Direct α-amination of 2-phenylpropanal (**8**) with DBAD (**6**) catalysed by the pyrrolidine–camphor-derived organocatalysts **1**–**4**.[a]



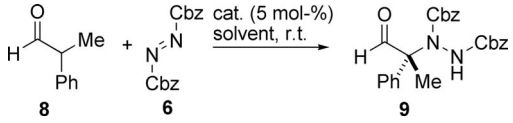
Entry	Cat.	*t* [d]	Yield [%][b]	*ee* [%][c]
1	**1**	1	53	42
2[d]	**2a**	7	32	racemic
3	**2b**	7	93	9
4[d]	**2c**	7	32	–2
5	**2d**	4	61	40
6	**2e**	–	–	–
7[d]	**2f**	7	19	45
8[d]	**3a**	7	26	15
9[d]	**3b**	7	42	20
10	**4a**	1	45	67
11	**4b**	4	50	50

[a] Unless otherwise specified, all reactions were carried out with the aldehyde **8** (1.0 mmol) and DBAD (**6**, 0.25 mmol). [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Starting material was recovered.

Solvent effects for catalysts **4a** and **4b** were next studied, and the results are listed in Table 6. In general, the solvent did not have a great effect in this catalytic process, with the α-aminated product **9** being obtained in moderate yields and with moderate to good enantioselectivities. When the reaction was carried out in nonpolar solvents such as toluene and CH_2Cl_2 with **4a**, the product was obtained with a moderate enantioselectivity (Table 6, Entries 1 and 2). In polar solvents such as THF, MeOH, MeCN, brine and water, however, both the yields and the enantioselectivities of the aminated product were decreased to some extent (Table 6, Entries 3–7). On the other hand, CH_2Cl_2 was found to be the best solvent for the reaction when **4b** was used as the catalyst, giving the highest enantioselectivity for **9** (75% *ee*) with a moderate yield (Table 6, Entry 9). Use of **4b** in all other solvents produced **9** with moderate yields and selectivities (Table 6, Entries 8 and 10–14).

An unexpected oxadiazine-derived product – benzyl 2-(benzyloxy)-5-ethyl-5,6-dihydro-6-hydroxy-5-methyl-1,3,4-oxadiazine-4-carboxylate (**11**) – was isolated in 47% yield when 2-methylbutanal (**10**) was treated with dibenzyl azodicarboxylate under the same reaction conditions (Scheme 2). This cyclic acetal product might originate from further cyclisation of the desired α-amination product.

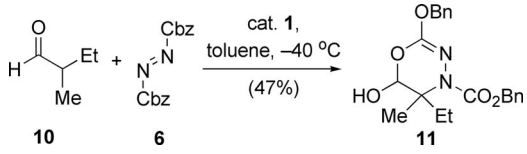
Table 6. Solvent effects on the direct α-amination of 2-phenylpropanal (**8**) with DBAD (**6**).[a]



8 **6** **9**

Entry	Cat.	Solvent	*t* [d]	Yield [%][b]	*ee* [%][c]
1	**4a**	PhMe	1	45	67
2	**4a**	CH_2Cl_2	7	32	67
3	**4a**	THF	3	24	63
4	**4a**	MeOH	2	32	60
5	**4a**	MeCN	7	39	51
6	**4a**	brine	3	17	54
7	**4a**	H_2O	2	20	50
8	**4b**	PhMe	4	50	50
9	**4b**	CH_2Cl_2	7	46	75
10	**4b**	THF	3	33	63
11	**4b**	MeOH	3	48	48
12	**4b**	MeCN	7	45	55
13	**4b**	brine	3	49	63
14	**4b**	H_2O	2	46	60

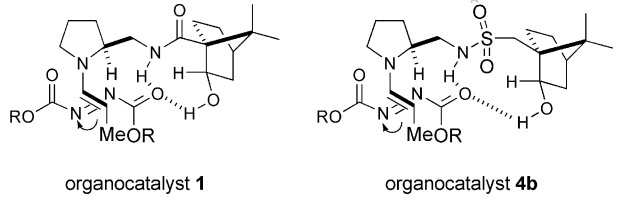
[a] Unless otherwise specified, all reactions were carried out with the aldehyde **8** (1.0 mmol) and DBAD (**6**, 0.25 mmol). [b] Isolated yield. [c] Determined by chiral HPLC analysis.



10 **6** **11**

Scheme 2. Reaction between 2-methylbutanal (**10**) and DBAD catalysed by **3**.

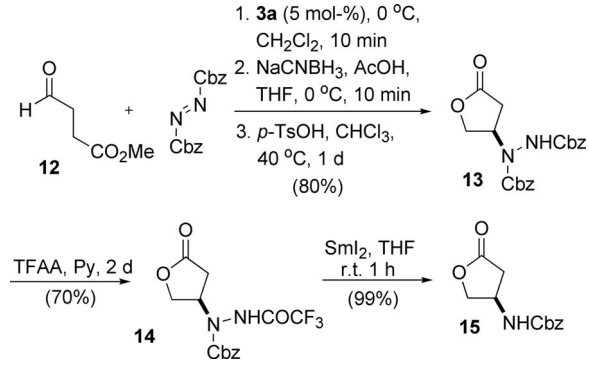
It is interesting to note that the newly generated absolute configuration of the product is organocatalyst-dependent. The pyrrolidine–camphor derivatives bearing a *trans*-4-hydroxy group in the pyrrolidine ring (**2c**–**d**) gave the (*S*) enantiomer as the major product (Table 4, Entries 3 and 4). On the other hand, the corresponding protected TBDPS ether derivatives (**2e**–**f** and **3a**–**b**) afforded the (*R*) enantiomers as the major products (Table 4, Entries 5–8). Plausible transition-state models to explain the high stereoselectivities of the α-aminated adducts obtained in the catalytic system were proposed (Figure 2).[13a,13b] The organocatalyst should react with the aldehyde to form a nucleophilic enamine. For the amide- and sulfonamide-linked organocataysts (**1** and **4**), the reactive nitrogen reagent should be brought close to the bottom face with the assistance of hydrogen-bond interactions. In the cases of **2c** and **2d**, on the other hand, the activation should occur from the same side as the 4-hydroxy group in the pyrrolidine moiety to organise the transition state. These steps should be followed by a *re*-facial attack of the enamine onto the DBAD in the cases of the organocatalysts **1** and **4**, whereas the addition should occur from the *si* face of the nucleophiles derived from **2c** and **2d**.



organocatalyst **1** organocatalyst **4b**

Figure 2. Plausible transition models for the α-amination catalysed by **1** and **4b**.

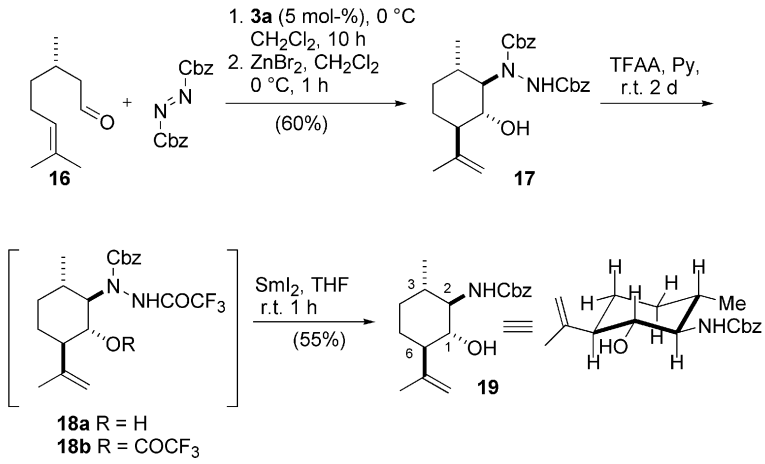
Aminobutyrolactones are potent positive allosteric modulators/stimulators of the $GABA_A$ receptors and serve as important intermediates in natural products synthesis.[17] Enantioselective syntheses of β-aminobutyrolactones starting from L- or D-aspartic acid have been documented. We envisioned that β-amino-γ-butyrolactones should be readily available by α-amination of the starting methyl 4-oxobutanoate (**12**, Scheme 3). To test this hypothesis, compound **12** was subjected to the α-amination conditions, and **3a** (5 mol-%) was used as the organocatalyst. This was followed by $NaCNBH_3$ reduction of the aldehyde and subsequent acid-catalysed lactonisation to afford the corresponding butyrolactone **13** in high chemical yield (80%) and with high enantioselectivity (88% *ee*; HPLC analysis). The reductive cleavage reaction was problematic at the beginning. Many attempts failed to remove the NHCbz group. After extensive studies, optimized reaction conditions were finally developed. A Cbz group in the γ-lactone **13** was cleaved and the trifluoroacetyl derivative **14** was obtained after trifluoroacetic anhydride (TFAA) treatment for 2 d. This was subsequently reduced with SmI_2 in THF to give the β-amino-γ-butyrolactone derivative **15** in high overall chemical yield (70%).[14g,14h] The chemical structure of **15** was fully characterised by IR, ^1H and ^{13}C NMR spectroscopy and HRMS analyses. The absolute stereochemistry of the newly generated stereogenic centre was assigned as (*R*) by comparison of the optical rotation with the literature value {$[\alpha]_D^{30}$ = +47.3 (*c* = 0.40, $CHCl_3$)} {literature value for the (*S*) enantiomer: $[\alpha]_D^{20}$ = –54.9 (*c* = 2.27, $CHCl_3$)}.[17a]



12 **13** **14** **15**

Scheme 3. Synthesis of the β-amino-γ-butyrolactone derivative **15**.

Citronellal (**16**, Scheme 4) is an important synthon in various natural products and pheromone syntheses.[18] The 1,4-conjugate addition of citronellal to methyl vinyl ketone in the presence of an amine base is known from previous



Scheme 4. α-Amination of (*S*)-citronellal (**16**) with DBAD and subsequent cyclisation reaction.

studies.[19] An enantioselective 1,4-conjugate addition of citronellal to vinyl sulfone was recently reported by Alexakis and co-workers,[19d] and the use of citronellal as a donor partner with *trans*-β-nitrostyrene catalysed by the pyrrolidine–camphor-derived organocatalysts was reported earlier.[20] A tetrasubstituted cyclohexane derivative was obtained in good overall chemical yield and with excellent diastereoselectivity. To demonstrate the utility of the developed methodology further, the α-amination of citronellal with DBAD catalysed by **3a** (5 mol-%) was carried out. After extensive modification of the conditions, to our satisfaction, a one-pot cyclisation reaction was achieved. The reaction was performed with (*S*)-citronellal (**16**) and DBAD in the presence of the organocatalyst **3a** (5 mol-%) in CH_2Cl_2 at 0 °C. The ene-type cyclisation of the aminated product was followed by $ZnBr_2$ treatment to afford the cyclic compound **17** with a 60% chemical yield. After a similar reductive cleavage process (TFAA, pyridine; SmI_2, THF), the tetrasubstituted cyclohexane **19** was obtained in a 55% chemical yield.

The structure of **19** was initially elucidated by IR, ^1H and ^{13}C NMR spectroscopy and HRMS analyses. A single-crystal X-ray diffraction of the product **19** failed, and the absolute stereochemistry determination was carried out by 2-D NMR spectroscopic techniques. Careful analyses of the ^1H, ^1H COSY and NOESY spectra allowed the assignment of the characteristic protons. The signals of the four methine protons show them to reside in the axial positions in the cyclohexane ring. The chemical shifts can be assigned as δ = 3.28 (1-H_a), 3.20 (2-H_a), 1.41 (3-H_a), 2.12 (6-H_a) ppm. The characteristic axial–axial proton coupling constants (J = 13.0 and 13.0 Hz) of 1-H_a with 2-H_a and 6-H_a indicated the chair conformation of **19**. The absolute stereochemistry of product **19** was determined to be (1*R*,2*R*,3*R*,6*S*).

Conclusions

An efficient and practical method for the organocatalytic α-amination of various aldehydes with DBAD has been presented. The operationally simple reaction proceeded rapidly with low catalyst loadings (5 mol-%), and the α-aminated products were generally obtained in high chemical yields and with high to excellent levels of stereoselectivity. Various pyrrolidine–camphor-derived organocatalysts (**1**–**4**) are easily accessible from the inexpensive starting materials L-proline and camphorsulfonic acid. The pyrrolidine–camphor derivatives **4a** and **4b** were found to be efficient for the α-amination of α,α-disubstituted aldehydes to the nitrogen resource. The synthetic utility was demonstrated by the preparation of β-amino-γ-butyrolactone and tetrasubstituted cyclohexyl amino alcohol derivatives in good overall chemical yields and with high stereoselectivities.

Experimental Section

Synthesis of the α,α-Disubstituted α-Aminated Product 9: Dibenzyl azodicarboxylate (**6**; 0.159 mg, 0.5 mmol) was added at ambient temperature to a stirred solution of the organocatalyst (0.025 mmol) and 2-phenylpropionaldehyde (**8**; 0.27 mL, 2.0 mmol) in the indicated solvent (1.0 mL). The reaction mixture was stirred for the time needed. After azodicarboxylate had been consumed, as indicated by TLC analysis, the reaction mixture was directly purified by flash column chromatography on silica gel with ethyl acetate/hexanes (1:8 to 1:6) to afford the pure α-aminated aldehyde **9** as a colourless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.61–1.98 (m, 3 H), 5.31 (m, 4 H), 6.80 (s, 1 H), 6.90–7.71 (m, 15 H), 9.66 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.50, 67.96, 68.80, 73.34, 126.83, 127.66, 127.81, 128.11, 128.27, 128.38, 128.49, 128.53, 129.00, 135.03, 135.27, 136.49, 155.92, 156.14, 192.63 ppm. IR (CH_2Cl_2, KBr): $\tilde{\nu}$ = 3280, 2955, 1740, 1715, 1257, 1219 cm^{-1}. HRMS (ESI): calcd. for $C_{25}H_{24}N_2O_5$ 455.1577; found 455.1586. HPLC (Daicel Chiralpak AS-H column; hexanes/*i*PrOH, 88:12; flow rate 1.2 mL min^{-1}; λ = 220 nm): $t_r(R)$ = 38.24 min; $t_r(S)$ = 53.39 min.

Synthesis of the 1,3,4-Oxadiazine Acetal 11: Dibenzyl azodicarboxylate (**6**; 0.159 mg, 0.5 mmol) was added at ambient temperature to a stirred solution of the organocatalyst **1** (6.7 mg, 0.025 mmol) and 2-methylbutyraldehyde (**10**; 0.22 mL, 2.0 mmol) in toluene (1.0 mL). The reaction mixture was stirred for 4 d. The reaction mixture was directly purified by flash column chromatography on silica gel with ethyl acetate/hexanes (1:8 to 1:4) to give the cyclic

acetal **11** as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (m, 3 H), 1.16 (m, 3 H), 1.31–1.89 (m, 2 H), 3.5 (s, 1 H), 5.15 (s, 2 H), 5.22 (s, 2 H), 6.98 (s, 1 H), 7.33–7.31 (br., 10 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.42, 16.65, 26.85, 29.65, 40.76, 67.99, 69.11, 128.02, 128.33, 128.50, 128.52, 128.59, 134.72, 135.36, 152.97, 155.42 ppm. IR (CH_2Cl_2, KBr): $\tilde{\nu}$ = 3299, 2967, 2930, 1747, 1725, 1232 cm^{-1}. LRMS (EI): calcd. for $C_{21}H_{24}N_2O_5$ 384.1685; found 384.1688.

Synthesis of the β-Amino-γ-butyrolactone Derivative 15

Compound 13: A stirred solution of the organocatalyst **3a** (42 mg, 0.075 mmol) and methyl 4-oxobutanoate (**12**; 0.32 mL, 3.0 mmol) in CH_2Cl_2 (5.0 mL) was cooled to 0 °C, and dibenzyl azodicarboxylate (**6**; 0.5 g, 1.5 mmol) was added at the same temperature. The reaction mixture was stirred at 0 °C for 10 min, and THF (5.0 mL) was added. $NaBH_3CN$ (0.14 g, 2.25 mmol) was added portionwise to the resulting mixture, followed by the addition of AcOH (5 drops) over 10 min. The mixture was quenched with satd. aqueous NH_4Cl and extracted with CH_2Cl_2 (2 × 30 mL). The combined organic phases were separated, dried with $MgSO_4$, filtered and concentrated. The residue was redissolved in $CHCl_3$ (5.0 mL), and *p*TsOH·H_2O (86 mg, 0.45 mmol) was added. The mixture was stirred at 40 °C for 24 h, quenched with H_2O (20 mL) and neutralised with $NaHCO_3$ (1.0 M). The resulting mixture was extracted with CH_2Cl_2 (3 × 30 mL), and the layers were separated. The combined organic phases were washed with brine, dried with $MgSO_4$, filtered and concentrated. A mixture of hexanes/CH_2Cl_2 (3:2, 30 mL) was added to the resulting cloudy oil, and centrifugation was carried out. The organic solvents were decanted, and the β-amino-γ-butyrolactone derivative **13** was collected (0.46 g, 80%) as a white powder. M.p. 143.1–144.2 °C. ^{1}H NMR (400 MHz, [D_6]-DMSO): δ = 2.47 (m, 1 H), 2.91 (m, 2 H), 3.97–4.56 (m, 2 H), 4.92–5.31 (m, 5 H), 7.33 (br., 10 H), 9.19–9.90 (m, 1 H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 31.55, 54.00, 66.52, 67.31, 71.26, 127.40, 127.49, 127.6, 127.98, 128.02, 128.39, 135.97, 136.11, 154.62, 156.87, 175.53 ppm. IR (CH_2Cl_2, KBr): $\tilde{\nu}$ = 3261.99, 1768, 1746, 1683, 1515, 1235 cm^{-1}. HRMS (ESI): calcd. for $C_{20}H_{20}N_2O_6Na$ [M + Na^+] 407.1219; found 407.1222. HPLC (Daicel Chiralpak OD-H column, 88% *ee*; hexanes/*i*PrOH, 85:15; flow rate 1.2 mL min^{-1}; λ = 220 nm): t_r(*R*) = 39.34 min; t_r(*S*) = 55.59 min.

Compound 14: A solution of the β-amino-γ-butyrolactone derivative **13** (0.2 g, 0.52 mmol) in pyridine (2.0 mL) was brought to 50 °C for 12 h. The mixture was cooled to ambient temperature, and trifluoroacetic anhydride (0.44 mL, 2.08 mmol) was added dropwise. The mixture was stirred at ambient temperature for 48 h and then diluted with CH_2Cl_2. The solution was extracted with aqueous HCl (1.0 N) and with CH_2Cl_2 (3 × 50 mL). The combined organic phases were washed with brine, dried with $MgSO_4$, filtered, concentrated and purified by flash column chromatography (silica gel; hexanes/ethyl acetate, 1:4 to 1:2) to afford **14** (0.125 g, 70%) as a light yellow oil. $[a]_D^{30}$ = –21.7 (*c* = 3.08, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.68 (dd, *J* = 18.5, 3.6 Hz, 1 H), 2.76 (dd, *J* = 18.5, 8.3 Hz, 1 H), 4.38 (d, *J* = 5.12 Hz, 2 H), 5.03 (m, 1 H), 5.16 (s, 2 H), 7.25–7.41 (m, 5 H), 9.86 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.05, 55.28, 69.02, 71.74, 115.3 (q, 1 C), 127.89, 128.06, 128.55, 134.68, 135.01, 153.79,176.04 ppm. HRMS (ESI): calcd. for $C_{14}H_{13}F_3N_2O_5Na$ 369.0674 $[M]^+$; found 369.0670.

(*R*)-3-[(Benzyloxycarbonyl)amino]-γ-butyrolactone (15): Nitrogen was bubbled through a solution of compound **14** (87 mg, 0.25 mmol) in THF (3 mL) for 5 min. A solution of SmI_2 (10 mL, 0.1 M solution in THF) was added dropwise under N_2, and the solution was stirred at ambient temperature for 1 h. A second portion of SmI_2 (10 mL) was added dropwise until the blue colour remained for more than 5 min. The solvent was removed in vacuo. The residue was dissolved in aqueous $Na_2S_2O_3$ and extracted with CH_2Cl_2 (2 × 30 mL). The combined organic phases were washed with brine, dried with $MgSO_4$, filtered, concentrated and purified by flash column chromatography (silica gel; hexanes/ethyl acetate, 1:3 to 1:2) to afford (*R*)-**15** (62 mg, 99%) as the major product. $[a]_D^{30}$ = +47.3 (*c* = 0.40, $CHCl_3$).[17a] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.46 (dd, *J* = 17.3 and 2.7 Hz, 1 H), 2.81 (dd, *J* = 17.3, 7.5 Hz, 1 H), 4.21 (d, *J* = 7.5 Hz, 1 H), 4.46 (m, 2 H), 5.10 (s, 2 H), 5.42 (s, 1 H), 7.28–7.40 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.62, 47.90, 67.05, 73.52, 128.09, 128.28, 128.51, 135.86, 155.74, 175.35 ppm. IR (CH_2Cl_2, KBr): $\tilde{\nu}$ = 3314, 2913, 1774, 1699, 1537, 1263 cm^{-1}. HRMS (EI): calcd. for $C_{12}H_{13}NO_4$ $[M]^+$ 235.0845; found 235.0839.

Synthesis of the Tetrasubstituted Cyclohexyl Amino Alcohol 19

Compound 17: A stirred solution of the organocatalyst **3a** (83 mg, 0.15 mmol) and (*S*)-citronellal (**16**; 1.08 mL, 6.0 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 °C, and dibenzyl azodicarboxylate (**6**; 1.0 g, 3.0 mmol) was added at the same temperature. The reaction mixture was stirred at 0 °C for 10 h, which was followed by the addition of $ZnBr_2$ (0.88 g, 3.9 mmol) at 0 °C for 1 h. The reaction mixture was quenched with brine (5.0 mL) and extracted with CH_2Cl_2 (2 × 20 mL). The layers were separated, and the combined organic phases were washed with brine, dried with $MgSO_4$, filtered and concentrated. The product was purified by flash column chromatography (silica gel; hexanes/ethyl acetate, 1:8 to 1:4) to afford **17** (0.81 g, 60%) as a white solid. M.p. 156.3–157.2 °C. $[a]_D^{24}$ = –24.3 (*c* = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.65–0.93 (m, 3 H), 1.07–1.40 (m, 2 H), 1.44–1.67 (m, 2 H), 1.67–1.87 (m, 4 H), 2.09–2.36 (m, 1 H), 3.23–3.96 (m, 2 H), 4.36–4.71 (m, 1 H), 4.82 (s, 2 H), 5.04–5.42 (m, 4 H), 6.36–6.64 (m, 1 H), 7.17–7.48 (m, 10 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.21, 19.15, 19.55, 29.72, 32.86, 50.64, 68.09, 68.35, 69.70, 69.97, 111.21, 127.76, 128.06, 128.16, 128.34, 128.39, 128.51, 135.15, 135.76, 146.76, 157.40, 158.40 ppm. IR (CH_2Cl_2, KBr): $\tilde{\nu}$ = 3469, 3269, 2923, 1724, 1266, 886 cm^{-1}. HRMS (EI): calcd. for $C_{26}H_{32}N_2O_5$ 452.2311; found 452.2305.

Compound 19: A solution of the aminated compound **17** (0.1 g, 0.22 mmol) in pyridine (1.5 mL) was brought to 50 °C for 12 h. The reaction mixture was allowed to cool to ambient temperature, and trifluoroacetic anhydride (0.13 mL, 0.88 mmol) was added dropwise. The mixture was stirred for 48 h. The solution was diluted with CH_2Cl_2 (30 mL) and quenched with aqueous HCl (5.0 mL, 1.0 N). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic phases were washed with brine, dried with $MgSO_4$, filtered and concentrated. The product was purified through silica gel (hexanes/ethyl acetate, 1:4) to afford the cyclohexanol **18a** and its trifluoroacetyl derivative **18b** as a brown oil. The residue was dissolved in THF (3.0 mL), and nitrogen was bubbled through the solution for 5 min. A solution of SmI_2 (9.0 mL, 0.1 M solution in THF) was added dropwise under N_2. The solution was stirred for 1 h, which was followed by the dropwise addition of a second portion of SmI_2 (9.0 mL of 0.1 M solution in THF) until the blue colour remained for more than 5 min. The mixture was concentrated in vacuo, and aqueous $Na_2S_2O_3$ (1.0 M) was added to the residue. The solution was extracted with CH_2Cl_2 (2 × 20 mL), and the layers were separated. The combined organic phases were washed with brine, dried with $MgSO_4$, filtered, concentrated and purified by flash column chromatography (silica gel; hexanes/ethyl acetate, 1:8 to 1:4) to afford the product **19** (66 mg, 55%) as a white solid. M.p. 128.0–

129.9 °C. $[\alpha]_D^{30}$ = –8.1 (*c* = 0.40, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.99 (d, *J* = 6.1 Hz, 3 H), 1.18 (dd, *J* = 13.0, 13.0 Hz, 1 H), 1.36 (d, *J* = 13.0 Hz, 1 H), 1.41 (m, 1 H), 1.64 (d, *J* = 13.0 Hz, 1 H), 1.72 (s, 3 H), 1.77 (d, *J* = 13.0 Hz, 1 H), 2.12 (dd, *J* = 13.0, 10.0 Hz, 1 H), 2.31 (s, 1 H), 3.20 (m, 1 H), 3.28 (dd, *J* = 13.0, 13.0 Hz, 1 H), 4.62 (s, 1 H), 4.85 (s, 1 H), 4.88 (s, 1 H), 5.12 (s, 2 H), 7.28–7.39 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.57, 19.11, 29.15, 33.23, 36.87, 52.87, 62.30, 66.77, 74.57, 112.63, 127.97, 128.42 (2 C), 136.51, 146.01, 157.34 ppm. IR (CH_2Cl_2, KBr): $\tilde{\nu}$ = 3417, 3255, 2930, 1679, 1565, 887 cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{25}NO_3Na$ $[M]^+$ 326.1732; found 326.1724.

Supporting Information (see footnote on the first page of this article): ^1H, ^{13}C, 2D NMR spectral data of new compounds and HPLC chromatograms of the aminated products.

Acknowledgments

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