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β-*tert*-Butyl aspartate as an organocatalyst for the asymmetric α-amination of α,α-disubstituted aldehydes

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ABSTRACT

The enantioselective α-amination reaction of α,α-disubstituted aldehydes can lead to a variety of enantioenriched amino aldehydes, amino alcohols, and amino acids. After screening a variety of amino acids and their derivatives, we identified a cheap, simple, commercially available aspartic acid derivative that can catalyze efficiently the reaction between α,α-disubstituted aldehydes and dialkyl azodicarboxylates. The reaction proceeds smoothly leading to the corresponding α-aminated adducts in moderate to quantitative yields and moderate to high enantioselectivities (up to 96% ee). Finally, the conversion of these adducts to α,α-disubstituted quaternary amino acids is also described.

1. Introduction

Stereoselective transformations for the creation of functionalized optically active molecules with structural diversity were always the ultimate target for organic chemists. Since the appearance of Organocatalysis,[1,2] a plethora of simple to complex molecular architectures that have been employed in numerous organic transformations providing elegant solutions to long-standing problems and affording novel reactions. Optically active nitrogen-containing molecules are versatile and important building blocks in organic synthesis. Especially α-amino acids and their derivatives are key intermediates for the construction of important biological and pharmaceutical units. A variety of methods for their construction have been developed, among them the α-amination of carbonyl compounds has received a lot of attention.[3] Shortly after the simultaneous report on the α-amination of aldehydes by Jorgensen and co-workers and List,[4] Brase, and co-workers reported the α-amination of α,α-disubstituted aldehydes.[5a] However, 50 mol % proline had to be employed to provide moderate to high yield and enantioselectivities of up to 86% ee. Later on, the same group reported a full account of their work, as well as how the use of microwave irradiation can reduce the reaction time from a few days to just hours.[5b–c] A route to transform these organocatalyzed products to α,α-disubstituted amino acids was also reported.[5b] Non-proteogenic α-amino acids, especially α,α-disubstituted amino acids that are known to be sterically constrained, are bound to play key roles in improving the conformational properties and activity of peptides. Herein, we report the use of simple α-amino acid derivatives, such as β-*tert*-butyl aspartate, which were found to be excellent in promoting the same transformation leading to products in high yields and enantioselectivities.

2. Results and discussion

After the initial report from Brase,[5a] Barbas, and co-workers utilized proline tetrazole as the catalyst for the α-amination of 3-(4-bromophenyl)-2-methylpropanal (95% yield, 80% ee) to provide a route to a product of pharmaceutical importance.[6] In 2011, three publications from different groups reported the use of primary amine catalysts that efficiently catalyzed the reaction between α,α-disubstituted aldehydes and azodicarboxylates (Fig. 1).[7–9] Xu, Wang, and co-workers utilized non-natural amino acid hydrochloride **1** as the catalyst for the reaction between aryl, alkyl aldehydes, and diethyl or di-isopropyl azodicarboxylate.[7] Utilizing 20 mol % catalyst, the reaction proceeded smoothly affording the products in moderate to excellent yields and enantioselectivities. However, in order to provide a direct route to α,α-disubstituted amino acids, di-*tert*-butyl azodicarboxylate has to be employed, since it is easier to cleave the N–N bond. Unfortunately, catalyst **1** provided high enantioselectivity but low yield (33%).[7] Lu and co-workers reported that a combination of 9-amino(9-deoxy)*epi*-quinine with (−)-camphorsulfonic acid could catalyze efficiently

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the reaction between aryl, alkyl aldehydes, and di-*tert*-butyl azodicarboxylate leading to excellent yields and selectivities utilizing 10 mol % catalyst loading.[8] They have also demonstrated that in principle lower amount of the catalytic pair **2** can catalyze the reaction in prolonged reaction time (0.5 mol %, 36 h).[8] The similar catalytic motif **3** was employed by Greck and co-workers at 5 mol % leading to slightly inferior results.[9]

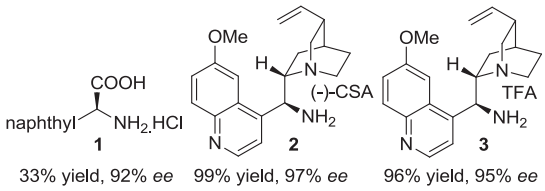
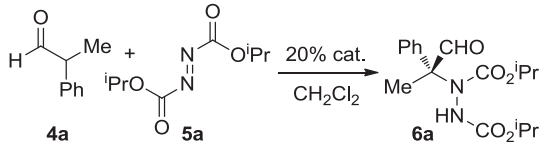


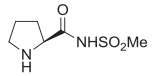
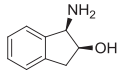
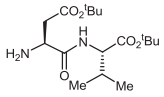
Fig. 1. Primary amine organocatalysts employed in the reaction between α,α-disubstituted aldehydes and di-*tert*-butyl azocarboxylate.

Initially, the reaction between aldehyde **4a** and di-isopropyl azocarboxylate **5a** was evaluated (Table 1). A number of secondary and primary amines were tested for their efficiency in this transformation. Proline was rather a poor catalyst for this reaction since prolonged reaction time was required and the enantioselectivity of the reaction was mediocre (entry 1, Table 1), in accordance with literature.[7] Proline sulfonamides are known to perform in some reactions better that proline itself,[10] but, in this reaction provided inferior results (entry 2, Table 1). In the case of α,α-disubstituted carbonyl compounds, primary aminocatalysts can more easily form the required enamine intermediate. Thus, based on our previous knowledge on organocatalysis,[11] a number of primary aminocatalysts were tested. Although amino alcohols and glucosamine led to inferior results (entries 3 and 4, Table 1), amino acids and their derivatives proved in some cases quite efficient catalysts (entries 5–14, Table 1). Histidine, aspartic acid, and asparagine led only to traces, but phenylalanine and β-phenylalanine provided **6a** in quantitative yields and slightly inferior enantioselectivity than proline in shorter reaction time (entries 5–9, Table 1). Although aspartic acid did not catalyze the reaction, β-alkyl aspartates proved to be far more efficient than proline (entries 10–12, Table 1). β-*tert*-Butyl aspartate provided **6a** in quantitative yield, with high enantioselectivity in 24 h (entry 11, Table 1). α-*tert*-Butyl aspartate led to high enantioselectivity but poor yield (entry 12, Table 1), while di-*tert*-butyl aspartate provides the opposite enantiomer of the product, although in low yield and enantioselectivity after prolonged reaction time (entry 13, Table 1). Dipeptide H-Asp(O^{t}Bu)-Val-O^{t}Bu proved to be equally efficient with β-*tert*-butyl aspartate, but prolonged reaction time was required (entry 14, Table 1).

Once the optimum catalyst was found, the reaction conditions were scrutinized in order to obtain optimum results (Table 2). Initially, a number of different solvents were evaluated (entries 1–9, Table 2). Although a number of solvents provided the product in quantitative yield, THF proved to give the higher enantioselectivity (entry 9, Table 2). It is known that in some organocatalyzed processes, acid additives have positive impact on the outcome of the reaction.[12] Thus, the addition of a number of acid additives and

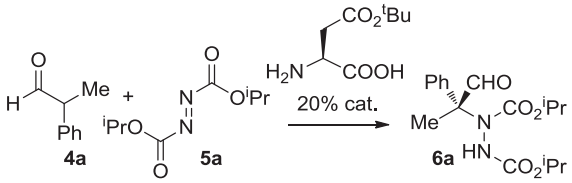
Table 1
Reaction between aldehyde **4a** and di-isopropyl azocarboxylate **5a** utilizing a variety of organocatalysts[a]



Entry	Catalyst	Reaction time (h)	Yield (%)[b]	ee (%)[c]
1	Proline	96	71	66
2		120	21	n.d.
3		72	30	51
4	Glucosamine. HCl	120	—	—
5	L-Histidine	120	Traces	n.d.
6	L-Phenylalanine	24	100	66
7	L-β-Phenylalanine	24	92	61
8	L-Aspartic acid	120	Traces	n.d.
9	L-Asparigine	120	Traces	n.d.
10	L-Asp(OBn)–OH	72	84	78
11	L-Asp(O^{t}Bu)–OH	24	100	84
12	L-Asp-O^{t}Bu	24	26	90
13	L-Asp(O^{t}Bu)–O^{t}Bu	120	50	−51
14		48	100	82

[a] Reaction Conditions: catalyst 20 mol %, CH_2Cl_2 (1.0 mL), aldehyde **4a** (0.40 mmol) and **5a** (0.20 mmol).
[b] Yield determined by ^{1}H NMR of the crude reaction mixture.
[c] The enantiomeric excess (ee) was determined by chiral HPLC. n.d.: not determined.

Table 2
Reaction between aldehyde **4a** and di-isopropyl azocarboxylate **5a** utilizing β-*tert*-butyl aspartate as the catalyst[a]



Entry	Reaction conditions	Reaction time (h)	Yield (%)[b]	ee (%)[c]
1	CH_2Cl_2	24	100	84
2	$CHCl_3$	24	100	82
3	1,2-DCE	24	100	80
4	Toluene	120	71	60
5	Benzene	120	65	59
6	Dioxane	24	100	73
7	H_2O	48	100	0
8	Et_2O	48	67	75
9	THF	24	100	90
10	THF, AcOH	24	72	88
11	THF, 4-NBA	24	77	85
12	THF, 4-NBA, H_2O	24	89	83
13[d]	THF	24	100	85
14[e]	THF	24	100	91
15[f]	THF	24	72	90
16[e,g]	THF	24	100[h]	93
17[e,i]	THF	24	100	91

[a] Reaction conditions: β-*tert*-butyl aspartate 20 mol %, solvent (1.0 mL), aldehyde **4a** (0.40 mmol), and **5a** (0.20 mmol).
[b] Yield determined by ^{1}H NMR of the crude reaction mixture.
[c] The ee was determined by chiral HPLC.
[d] 10 mol % of catalyst was used.
[e] The reaction was performed at 0 °C.
[f] The reaction was performed at −20 °C.
[g] Aldehyde:azocarboxylate 1.5:1.
[h] 93% isolated yield.
[i] Aldehyde:azocarboxylate 1.2:1. 1,2-DCE:1,2-dichloroethane, 4-NBA: 4-nitrobenzoic acid.