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An Asymmetric Michael Addition of α,α-Disubstituted Aldehydes to Maleimides Leading to a One-Pot Enantioselective Synthesis of Lactones Catalyzed by Amino Acids

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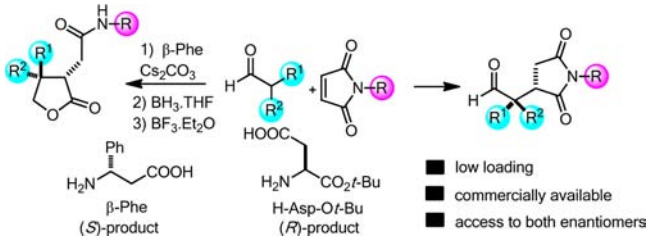
ABSTRACT



A cheap and fast construction of both enantiomers of substituted succinimides is reported. α- or β-amino acids, such as β-phenylalanine and α-*tert*-butyl aspartate, were found to be efficient organocatalysts for the reaction between α,α-disubstituted aldehydes and maleimides. Products containing contiguous quaternary-tertiary stereogenic centers are obtained in high to quantitative yields and excellent selectivities utilizing low catalyst loadings (0.5−3.5%). Finally, a one-pot efficient asymmetric synthesis of lactones is described.

The second decade of the 21st century has witnessed many milestones and breakthroughs in the field of asymmetric catalysis. In particular, the emerging field of Organocatalysis, which was ignored for many years, has undergone a rebirth,[1] often providing complex catalyst architectures that efficiently promote useful transformations.[2] An alternative approach taking advantage of the diversity of commercially available amino acids has been less thoroughly explored. Proline and its derivatives have long been utilized in this regard; more recently other amino acids and their derivatives have emerged as potential catalysts.[2c,3] Although most of these studies involve enamine intermediates,[2c] the nature and role of the side chain

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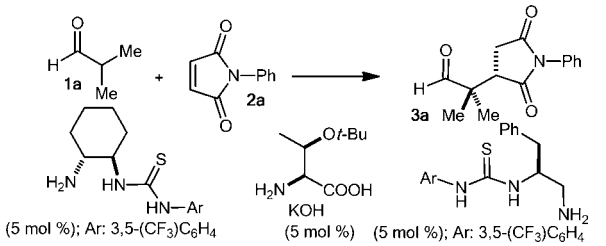
Scheme 1. Known Organocatalysts for the Michael Reaction between Isobutyraldehyde and Maleimide



of the amino acid seems to have been overlooked. Among Michael additions, the addition to maleimides represents an attractive transformation,[4] since substituted succinimides are valuable synthetic targets and precursors of biologically interesting substances.[5] The use of α-branched aldehydes as nucleophilic partners in the reaction with maleimides is scarcely documented,[6] a reaction that leads to the formation of quaternary centers.[7] As a model, the reaction between isobutyraldehyde (**1a**) and *N*-phenyl maleimide (**2a**) was chosen (Scheme 1). Cordova et al. demonstrated first the reaction between aldehydes and maleimides, but α-branched aldehydes led to low yields and enantioselectivities.[6a] Primary amine thioureas can catalyze this reaction (5−10 mol % catalyst loading).[6b−g] Finally, Nugent et al. utilized 5 mol % *tert*-butyl ether of threonine for the same transformation.[6h]

Our design plan was to identify an amino acid based catalyst that is commercially available and could afford better catalytic activities primarily allowing for a decreased catalyst loading. Often, both enantiomers of a chiral compound are required in the pharmaceutical industry or organic synthesis.[8] Unfortunately, the efficient preparation of both enantiomers is usually a daunting task, and to untangle this problem, diastereoselective catalytic motifs are employed.[6g,9] Although the simplest solution would be the use of the other enantiomer of the catalyst, this is either not readily available or fairly expensive. Thus, although (*R*)-amino acids are commercially available, since they are expensive relative to (*S*)-amino acids, our design uses (*S*)-amino acid derivatives to gain access in both series of enantiomers as highlighted in Figure 1. Building on Nugent's contribution[6h] and our own experience,[10] the primary amine of an α-amino acid activates the aldehyde via enamine formation. A synclinical addition to the electrophile for the C−C forming reaction occurs, which is directed by metal complexation leading to one enantiomer of the product (Figure 1, intermediate **I**). Herein, the approach of the electrophile is controlled by the electrostatic interactions with the catalyst, while the amino acid side chain can contribute in the enantioselectivity by blocking the front face. Utilizing an (*S*)-α-amino acid with its carboxylic group blocked by a bulky *tert*-butyl ester and by having a free carboxylic group in the amino acid side chain (e.g., α-*tert*-butyl aspartate, α-*tert*-butyl glutamate), the facial control of the reaction can be switched by adopting intermediate **II** (Figure 1). The nucleophile activation occurs in a similar manner; however, the electrophile is guided from the front face, instead of the back face, through a similar complexation with the free carboxylic group of the side chain. Finally, *β*-amino acids, such as *β*-phenylalanine,[11,12] are expected to behave similarly to

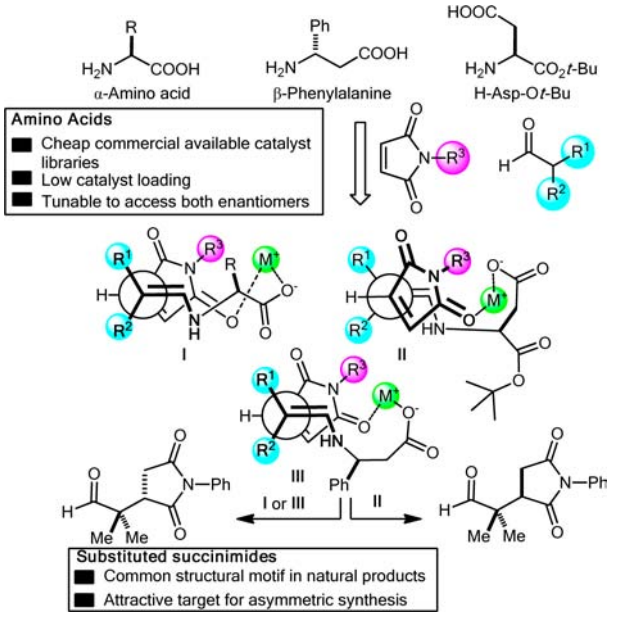


Figure 1. Proposed activation and reaction intermediates.

α-amino acids through the slightly varied intermediate **III** (Figure 1). To test our hypothesis, a variety of amino acids and their derivatives were tested.[11] After catalyst optimization, *tert*-Leu, Phe, *β*-Phe, and Trp were identified as the best catalysts (see Supporting Information (SI)). However,

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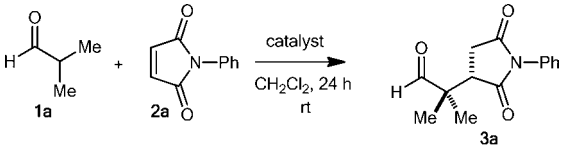
(11) For a detailed report on catalyst screening, optimization conditions, and the choice of *β*-phenylalanine and α-*tert*-butyl aspartate as the optimum catalysts, see SI.

(12) For *β*-amino acids as catalysts for Mannich reactions, see: Dziedzic, P.; Cordova, A. *Tetrahedron: Asymmetry* **2007**, *18*, 1033.

Table 1. Various Amino Acids As Catalysts in the Michael Addition of Isobutyraldehyde to *N*-Phenyl Maleimide



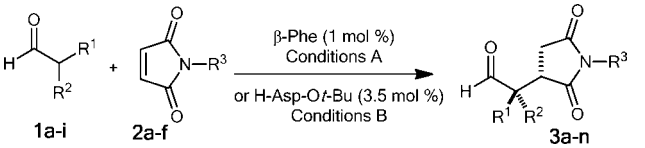
entry	catalyst (x mol %)	yield (%)[a]	ee (%)[b]
1	*tert*-Leu, KOH (2)	55	99
2	*tert*-Leu (5)[c]	-	-
3	Phe, KOH (2)	100	>99
4	β-Phe, KOH (2)	100	>99
5	β-Phe, KOH (1)	71[d]	99
6	β-Phe, KOH (0.5)	99[e]	98
7	**β-Phe, Cs_2CO_3 (1)**	**100 (96)**	**>99**
8	β-Phe, Cs_2CO_3 (0.5)	63	98
9	H-Asp-O*t*-Bu, KOH (5)	100	-84
10[f]	**H-Asp-O*t*-Bu, KOH (3.5)**	**99 (87)**	**-92**
11[f]	H-Asp- O*t*-Bu, KOH (10)	100	-96

[a] NMR yield; isolated yield in parentheses. [b] The ee was determined by chiral HPLC. [c] No KOH was added. [d] Reaction time: 48 h, 98% yield. [e] Reaction time: 72 h. [f] Ratio of aldehyde/maleimide 5:1.

with a 2 mol % catalyst loading, only Phe and *β*-Phe afforded a quantitative conversion to the product (entries 1, 3, 4, Table 1). In the absence of KOH, no reaction occurred (entry 2, Table 1). A further decrease in the catalyst loading could be achieved; however, for quantitative conversion to the product, the additive had to be changed (entries 5−7, Table 1). Thus, the desired product could be isolated in 96% yield and >99% *ee*. Decreasing the catalyst loading led to lower conversions that required prolonged reaction times to get to completion (entry 8, Table 1). Finally, after experimentation,[11] α-*tert*-butyl aspartate was identified as the optimum catalyst to lead to the other enantiomer (entries 9−11, Table 1).

Then, the substrate scope was evaluated (Table 2). *N*-Substituted maleimides were well tolerated (entries 1−12, Table 2). Both electron-donating and -withdrawing substituted aromatics on the maleimide are well tolerated (entries 3−6, Table 2). In the change to alkyl-substituted maleimides, benzyl maleimide was observed to perform similarly to aryl maleimides, while, for *N*-aliphatic maleimides, only for the preparation of the opposite enantiomer, a higher catalyst loading was required for high yields (entries 7−12, Table 2). A variety of aldehydes were also utilized successfully (entries 13−28, Table 2). For symmetrical α,α-disusbstituted aldehydes, high yields and selectivities were observed although a longer reaction time was required (entries 13−18, Table 2). Cyclic carboxyaldehydes performed equally well (entries 13−16, Table 2). When cyclopropyl carboxyaldehyde was used, only starting material was recovered. When the steric bulkiness of the substituents of the aldehyde was increased from methyl to ethyl, the reaction became more difficult and a higher catalyst loading was required (entries 17−18,

Table 2. Substrate Scope of the Michael Addition



	R^1, R^2, R^3	conditions[a]	yield (%)[b]	dr[c]	ee[d]
1	Me, Me, Ph (**3a**)	A	96	-	>99 (*S*)
2		B	87	-	92 (*R*)
3	Me, Me, 4-BrPh (**3b**)	A	92	-	98 (*S*)
4		B	85	-	92 (*R*)
5[e]	Me, Me, 4-NO_2Ph (**3c**)	A	100	-	98 (*S*)
6		B	74	-	86 (*R*)
7	Me, Me, Bn (**3d**)	A	91	-	99 (*S*)
8[f]		B	80	-	94 (*R*)
9	Me, Me, Me (**3e**)	A	86	-	>99 (*S*)
10[g]		B	77	-	94 (*R*)
11[f,g]	Me, Me, *c*-hexyl (**3f**)	A	100	-	94 (*S*)
12[h,i]		B	73	-	82 (*R*)
13[e,f]	-$(CH_2)_5$-, Ph (**3g**)	A	100	-	99 (*S*)
14[f]		B	79	-	92 (*R*)
15[f]	-$(CH_2)_4$-, Ph (**3h**)	A	100	-	>99 (*S*)
16[f,g]		B	100	-	90 (*R*)
17[f,g]	Et, Et, Ph (**3i**)	A	98	-	98 (*S*)
18[i,j]		B	73	-	89 (*R*)
19[g]	Me, Ph, Ph (**3j**)	A	89	90:10	94(94)
20[j]		B	81	89:11	72(10)
21[e,f]	Me, *n*-Pr, Ph (**3k**)	A	85	77:23	98(99)
22[g,i]		B	98	63:37	23(31)
23[f,g]	Me,$(CH_2)_2$C= C(Me)$_2$ Ph(**3l**)	A	98	78:22	>99(99)
24[f,g]		B	84	75:25	>99(99)
25[f]	H, *n*-Pentyl, Ph (**3m**)	A	92	56:44	>99(99)
26[f,j]		B	57	50:50	93(90)
27[f,j]	H, Me, Ph (**3n**)	A	76	54:46	99(99)
28[h,i]		B	54	52:48	86(88)

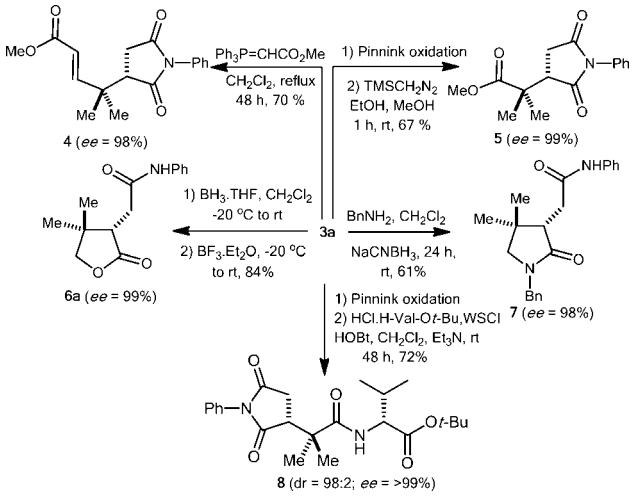
[a] **Conditions A**: *β*-Phe (1 mol %), Cs_2CO_3 (1 mol %), maleimide (0.40 mmol), CH_2Cl_2 (1 mL), aldehyde (0.44 mmol), 24 h, rt. **Conditions B**: H-Asp-O*t*-Bu (3.5 mol %), KOH (3.5 mol %), maleimide (0.40 mmol), CH_2Cl_2 (1 mL), aldehyde (2.00 mmol), 24 h, rt. [b] Isolated yield. [c] The dr was determined by ^{1}H NMR. [d] The ee was determined by chiral HPLC; ee of the minor diastereomer in parentheses. [e] 2 mol % catalyst. [f] Reaction time: 48 h. [g] 5 mol % catalyst. [h] 20 mol % catalyst. [i] Reaction time: 72 h. [j] 10 mol % catalyst.

Table 2). Next, a variety of nonsymmetrical aldehydes were utilized, since in this manner the formation of two contiguous (quaternary-tertiary) stereogenic centers will be possible (entries 19−24, Table 2). In all cases, higher catalyst loadings were required to achieve acceptable yields and selectivities. In the case of aryl, alkyl substituted aldehydes, a 9:1 dr was observed; unfortunately, the aspartate catalyst provided a decreased *ee* (72% *ee*) (entries 19−20, Table 2). To explore the limits of this protocol, propyl-methyl aldehyde was utilized (entries 21−22, Table 2). *β*-Phe afforded the product in high yield, with a 3:1 dr and excellent *ee*; unfortunately the aspartate led to low selectivities. The results improved slightly when a small and a larger aliphatic substituent were employed

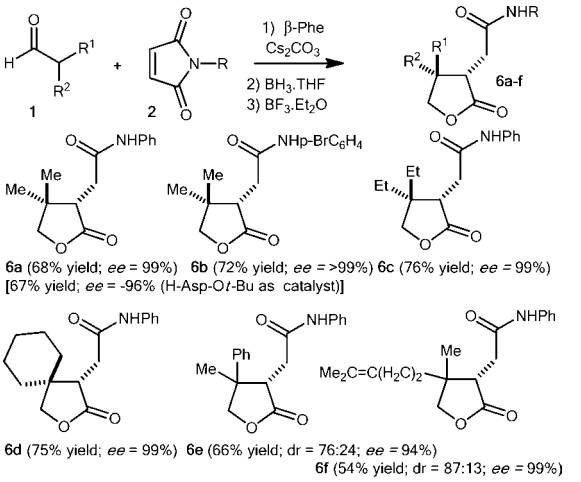
on the aldehyde (entries 23–24, Table 2). Although the yield and the dr remained at similar levels, the *ee* was profoundly improved. In the case of model **I** of Figure 1, it seems that when a bulky aryl moiety is utilized, it is placed in the position of R^2, while the smaller methyl group prefers to occupy the position of R^1, leading to high selectivities. When moieties of similar bulkiness, such as methyl and *n*-propyl, are utilized, both can be placed in both positions. This distribution in both positions lead to low levels of selectivities. However, when one of the groups utilized is bulkier than the other, the adoption of the R^1/R^2 positions in the model resembles more the aryl/alkyl case leading back to higher selectivities. Finally, linear aldehydes, heptanal and propanal, were utilized (entries 25–28, Table 2). In both cases, a 1:1 dr was observed; however, the *ee*'s remained excellent. In order to prove the validity of our initial design plan, NMR, IR, and MS experiments were performed, which support the formation of an enamine intermediate and the formation of the product having the catalyst on (for details, see SI).

A variety of transformations can be performed to result in various products. A Wittig reaction led to **4**, while oxidation followed by esterification gave **5** (Scheme 2). Reduction utilizing $NaBH_4$ led to lactone **6a** in high yield via the alcohol. Unfortunately, racemization occurred under the basic reaction conditions leading to products of low enantiopurity (20% *ee*). To bypass this problem, an alternative route was established. The initial reduction can be performed using borane, and the addition of $BF_3 \cdot Et_2O$ in the reaction mixture afforded the lactone in 84% yield and 99% *ee*. Reductive amination afforded lactame **7**, while oxidation followed by coupling with a valine derivative gave rise to peptidomimetic **8** (Scheme 2). Since the reduction of the aldehyde led to a lactone, a one-pot protocol to the asymmetric synthesis of lactones could be provided (Scheme 3). While basic conditions led to erosion of the *ee* and stronger reducing agents led to an overoxidized mixture of products, a slow reduction to the alcohol with

Scheme 2. Transformations of the Michael Addition Product **3a**



Scheme 3. Asymmetric One-Pot Synthesis of Lactones



$BH_3 \cdot THF$ at −20 °C, followed by the addition of $BF_3 \cdot Et_2O$, resulted in a smooth transformation. Substituted maleimides can be employed without loss of *ee*, while other substituted aldehydes can be employed leading to a variety of products (**6a**–**f**), such as spirolactone **6d** in high *ee*'s (Scheme 3). Aldehydes with different substituents can be employed leading to lactones **6e,f** bearing quaternary centers. However, in these cases slightly lower yields and selectivities were obtained. In addition, the model reaction was performed at a larger scale (17 mmol), leading to similar results.

In conclusion, we have demonstrated that a variety of amino acids can be employed as catalysts for the reaction of α,α-disubstituted aldehydes with maleimides with a low catalyst loading. *β*-Phe can be used at a catalyst loading as low as 0.5 mol % to promote the reaction in high to excellent yields and selectivities. Furthermore, α-*tert*-butyl aspartate can be used to provide the opposite enantiomer, although a slightly higher catalyst loading was required (3.5 mol %). A number of easy transformations were then undertaken to highlight the utility of the product. Reduction of the product led to lactone formation, and thus, an efficient one-pot protocol was developed leading to a number of lactones in high yields and selectivities. Other studies to highlight the use of amino acids and their derivatives as chiral promoters in organic transformations are underway in our laboratories.

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Supporting Information Available. Experimental procedures, catalyst and conditions optimization including NMR and HPLC data, as well as mechanistic investigations. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.