Asymmetric Catalysis

Design of an Axially Chiral Amino Acid with a Binaphthyl Backbone as an Organocatalyst for a Direct Asymmetric Aldol Reaction**

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The direct catalytic asymmetric aldol reaction is one of the most fundamental transformations in organic synthesis, and several efficient asymmetric methodologies for this reaction using chiral metal catalysts[1] and organocatalysts[2–4] have recently been developed, of which catalysis by proline[2,3] and its derivatives[4] have been extensively explored. However, the reactivity and selectivity of some of these proline-catalyzed aldol reactions have serious limitations because of the difficulty in structurally modifying proline. Furthermore, a substoichiometric amount of proline is often necessary to achieve reasonable yields in the direct aldol reaction of aldehydes with acetone. Also, proline is known to react with electron-deficient aromatic aldehydes to form iminium salts, which undergo decarboxylation, even at room temperature.[5] Such degradation may induce the significant retardation of the proline-catalyzed aldol reactions. In this context, we were interested in designing an artificial amino acid catalyst **1** that would not undergo undesirable degradation through decar-

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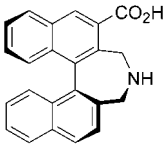
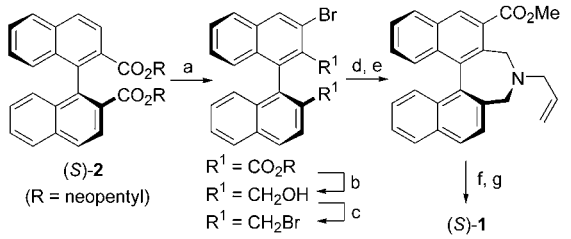


(*S*)-**1**

boxylation. Herein, we report a novel, robust amino acid catalyst **1** and its successful application to the direct asymmetric aldol reaction.

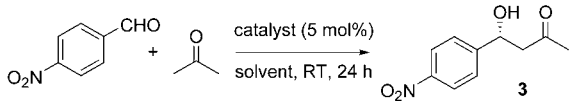
The requisite amino acid (*S*)-**1** was based on binaphthalene and prepared in a seven-step sequence from dineopentyl 1,1′-binaphthyl-2,2′-dicarboxylate ((*S*)-**2**; Scheme 1). The efficiency of this new catalyst was evaluated with the direct asymmetric aldol reaction: Reaction of 4-nitrobenzaldehyde with acetone was carried out in the



Scheme 1. Synthesis of (*S*)-**1**. Conditions: a) $Mg(TMP)_2$, THF; then Br_2; b) LAH, THF; c) BBr_3, CH_2Cl_2; d) allylamine, CH_3CN; e) 5 mol% $Pd(OAc)_2$, dppp, iPr_2NEt, CO, DMSO, MeOH; f) $Pd(OAc)_2$, PPh_3, *N*,*N*-dimethylbarbituric acid, CH_2Cl_2; g) 1 M NaOH, MeOH–THF. TMP = 2,2,6,6-tetramethylpiperidine, dppp = 1,3-bis(diphenylphosphino)propane.

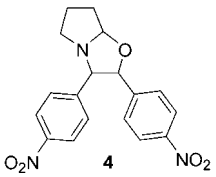
presence of 5 mol% of (*S*)-**1** at room temperature in dimethyl sulfoxide (DMSO) and the aldol adduct **3** was afforded in 70% yield and 93% *ee* (Table 1, entry 1). In contrast, the reaction with L-proline under the same reaction conditions

Table 1: Direct asymmetric aldol reaction of 4-nitrobenzaldehyde with acetone catalyzed by chiral amino acids.[a]



Entry	Catalyst	Solvent	Yield [%][b]	*ee* [%][c]
1	(*S*)-**1**	DMSO	70	93 (*R*)
2	L-proline	DMSO	18[d]	71 (*R*)
3	(*S*)-**1**	CH_3CN	32	95 (*R*)
4	(*S*)-**1**	NMP[e]	78	94 (*R*)
5	(*S*)-**1**	DMF	82	95 (*R*)

[a] The reaction was carried out at RT for 24 hours using 27 equivalents of acetone per equivalent of aldehyde in the presence of 5 mol% of catalyst. [b] Yield of product isolated by column chromatography. [c] The *ee* value of the product was determined by HPLC analysis using a chiral column (chiralpak AS-H, Daicel Chemical Industries). The absolute configuration was determined by comparison of the HPLC retention time of the product with reported data.[4e] [d] Bicyclic 1,3-oxazolidine **4** was isolated as a by-product in 48% yield (based on proline). [e] 1-Methyl-2-pyrrolidone.



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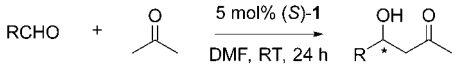
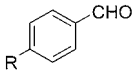
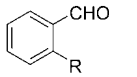
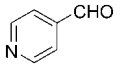
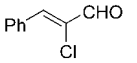
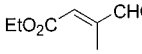
gave **3** in low yield with moderate enantioselectivity, together with 1,3-oxazolidine **4** (48% yield based on proline) derived from proline and two equivalents of 4-nitrobenzaldehyde (entry 2). It should be noted that the formation of such a by-product was not observed with **1** because of its structural stability. We also examined the solvent effect in this reaction: Changing the solvent from DMSO to acetonitrile gave **3** in low yield with slightly higher enantioselectivity (entry 3), whereas the use of amide solvents, such as *N*-methylpyrrolidone (NMP) and *N*,*N*-dimethylformamide (DMF), gave improved yields with high enantioselectivities (entries 4 and 5).

After establishing the optimal reaction conditions, the direct asymmetric aldol reaction of other electron-deficient aldehydes with acetone was carried out (Table 2). Olefinic,

Table 2: Direct asymmetric aldol reaction of aldehydes with acetone catalyzed by (*S*)-**1**.[a]



Entry	Aldehyde	R	Yield [%][b]	*ee* [%][c]
1		NO_2	82	95 (*R*)[d]
2		CN	80	95 (*R*)[d]
3		Ac	61	95
4		Cl	91	95 (*R*)[d]
5		OTf	81	94
6		NA	76	95
7		NA	73	90
8		NA	81	96

[a] The reaction in DMF was carried out at RT for 24 hours using 27 equivalents of acetone per equivalent of aldehyde in the presence of 5 mol% of catalyst (*S*)-**1**. [b] Yield of product isolated by column chromatography. [c] The *ee* value of the product was determined by HPLC analysis using a chiral column (chiralpak AS-H, AD-H, or OD-H, Daicel Chemical Industries). [d] The absolute configurations were determined by comparison of the HPLC retention times of the product with reported data.[4e] OTf = triflate.

heteroaromatic, and aromatic aldehydes were found to be suitable substrates, with the direct aldol reactions generally giving the corresponding aldol adducts in moderate to good yields. Furthermore, excellent enantioselectivities were observed in most cases (> 95% *ee*).

The spatial distance between the amino and carboxyl groups for (*S*)-**1** was determined by MM2 calculations using CS Chem3D, and was shown to be longer than that for L-proline (Figure 1).

In summary, we have shown that the binaphthyl-based amino acid **1** is an efficient catalyst for direct asymmetric aldol reactions of aldehydes with acetone. Most successful organic catalysts for various asymmetric reactions are derived from chiral natural products, such as amino acids and

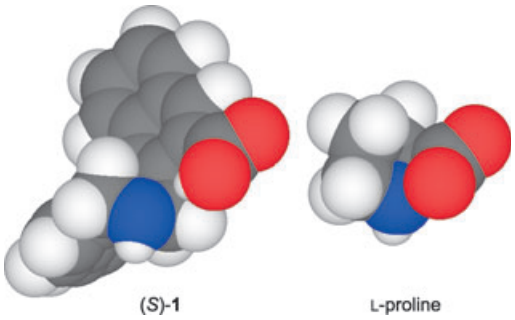


Figure 1. Space-filling models of (*S*)-**1** and L-proline by MM2 calculations.

cinchona alkaloids, and therefore there are certain limitations on possible structural modifications, especially in the design of more efficient catalysts. In this regard, the preparation and use of **1** opens up the possibility of developing structurally and electronically novel catalysts that have high reactivities and selectivities in asymmetric catalysis. Further investigations concerning the effectiveness of **1** and related catalysts for other asymmetric reactions are currently underway.

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