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Design of a Binaphthyl-Based Axially Chiral Amino Acid as an Organocatalyst for Direct Asymmetric Aldol Reactions

Taichi Kano, Osamu Tokuda, Jun Takai, and Keiji Maruoka*[a]

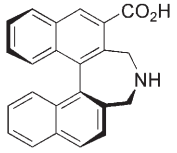
Abstract: A novel and robust binaphthyl-based amino acid was designed and successfully applied to the direct asymmetric aldol reaction. In some cases, this catalyst leads to higher yields and selectivities than the well-known proline catalyst. For instance, the direct asymmetric aldol reaction of acetone with 4-nitrobenzaldehyde in the presence of the binaphthyl-based amino acid catalyst proceeded smoothly to give the aldol adduct in 82% yield with 95% *ee*. This catalyst was also found to catalyze effectively the reactions of cyclic or unsymmetrical ketones to give the corresponding aldol adducts with excellent diastereo- and enantioselectivities.

Keywords: aldol reaction · amino acids · asymmetric catalysis · biaryl compounds · organocatalysis

Introduction

The direct catalytic asymmetric aldol reaction is one of the most useful carbon–carbon bond-forming reactions and provides optically enriched β-hydroxy carbonyl compounds. As the preparation of activated enolate-type species such as ketene silyl acetals is not necessary, the direct aldol reaction is considered to be environmentally benign and atom efficient. In recent years, there has been much effort toward the development of efficient asymmetric methodology with chiral metal catalysts, and several successful examples of such transformations have been reported.[1,2] More recently, with the increasing environmental consciousness, a wide variety of organocatalytic processes have been explored intensely[3] in which the direct asymmetric aldol reaction catalyzed by small chiral organic molecules such as proline has also been developed.[4]

Although the first example of such an organocatalytic direct asymmetric aldol reaction, which was the intramolecular cyclization catalyzed by proline, was reported in the early 1970s,[5] the proline-catalyzed intermolecular aldol reaction of ketones with aldehydes was realized by List, Lerner, and Barbas about 30 years later.[4a] Since these pioneering works, a number of proline derivatives have been designed, and their efficiency has been demonstrated in direct asymmetric aldol reactions.[6–8] Most of these catalysts have a highly nucleophilic pyrrolidine ring as a general key structure to allow high reactivity and selectivity. Indeed, 2-azetidinecarboxylic acid and pipecolic acid, which are proline analogues with a four- and a six-membered ring, respectively, were found to be much less effective catalysts for the direct asymmetric aldol reaction.[4d] Besides these observations, the design of structurally new proline catalysts has serious limitations owing to the difficulty in the modification of the pyrrolidine ring. Although significant progress has been made in organocatalytic direct asymmetric aldol reactions with the derivatization of carboxylic acid moiety of the parent proline, there is still a need for structurally and electronically novel catalysts to expand the scope of this methodology further. In this context, we were interested in the possibility of designing a certain artificial amino acid catalyst (*S*)-**1**, which has a rigid, chemically stable, and readily derivatizable binaphthyl backbone.[9] Herein we report the synthesis of the novel binaphthyl-based amino acid catalyst (*S*)-**1** and its successful application to the direct asymmetric aldol reaction.



(*S*)-**1**

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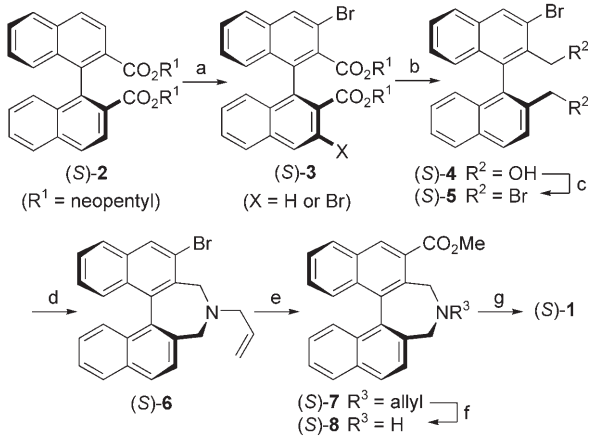
Results and Discussion

Preparation of Binaphthyl-Based Amino Acid (*S*)-1

The requisite binaphthyl-based amino acid (*S*)-**1** was prepared in a seven-step sequence from dineopentyl 1,1′-binaphthyl-2,2′-dicarboxylate ((*S*)-**2**) as shown in Scheme 1.



Scheme 1. Synthesis of (*S*)-**1**. Conditions: a) $[Mg(tmp)_2]$, THF; Br_2; b) $LiAlH_4$, THF, 42% over two steps; c) BBr_3, CH_2Cl_2, 86%; d) allylamine, CH_3CN, 89%; e) $Pd(OAc)_2$ (5 mol%), dppp, iPr_2NEt, CO, DMSO, MeOH, 67% (+ 12% (*S*)-**6**); f) $Pd(OAc)_2$, PPh_3, *N*,*N*-dimethylbarbituric acid, CH_2Cl_2; g) NaOH (1 M), MeOH/THF, 90% over two steps. tmp = 2,2,6,6-tetramethylpiperidine, dppp = 1,3-bis(diphenylphosphino)propane, DMSO = dimethyl sulfoxide.

Bromination of the neopentyl ester (*S*)-**2** was achieved by *ortho* magnesiation with magnesium bis(2,2,6,6-tetramethylpiperamide) $[Mg(tmp)_2]$ and subsequent trapping with bromine.[10] Reduction of the resulting mixture of di- and monobrominated esters (*S*)-**3** with $LiAlH_4$ gave the corresponding diol (*S*)-**4** (42% yield over two steps) after chromatographic separation. Treatment of (*S*)-**4** with BBr_3 afforded tribromo compound (*S*)-**5** in 86% yield which was converted with allylamine into the cyclic amine (*S*)-**6** in 89% yield. Carboxylation of (*S*)-**6** with CO and $Pd(OAc)_2$ catalyst gave the methyl ester (*S*)-**7** in 67% yield with the recovery of 12% of (*S*)-**6**. Finally, $Pd(OAc)_2$-catalyzed deallylation of (*S*)-**7**, followed by hydrolysis of the resulting methyl ester (*S*)-**8** under basic conditions provided the binaphthyl-based amino acid (*S*)-**1** (90% yield over two steps), which was purified by using an ion-exchange resin.

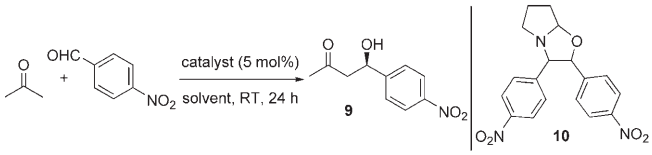
Abstract in Japanese:

剛直で安定なビナフチル骨格を有する新規アミノ酸触媒(*S*)-**1** を開発し、直截的不斉アルドール反応へと適用した。5 mol%の触媒(*S*)-**1** の存在下、アセトンと 4-ニトロベンズアルデヒドとの反応では、収率 82%、不斉収率 95%でアルドール付加体が得られており、既存のプロリン触媒と比較して、収率及びエナンチオ選択性の点でより高い触媒能を示した。また、本触媒は環状ケトンや非対称ケトンの反応においても、高ジアステレオ及びエナンチオ選択的にアルドール付加体を与えた。

Direct Asymmetric Aldol Reaction of Acetone and 4-Nitrobenzaldehyde with (*S*)-1

The efficiency of this new catalyst (*S*)-**1** was evaluated in a direct asymmetric aldol reaction. Thus, in the presence of binaphthyl-based amino acid (*S*)-**1** (5 mol%), the reaction of acetone with 4-nitrobenzaldehyde in DMSO at room temperature afforded the aldol adduct **9** in 70% yield with 93% *ee* (Table 1, entry 1). In contrast, the L-proline-cata-

Table 1. Direct asymmetric aldol reaction of acetone and 4-nitrobenzaldehyde with 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	78	94 (*R*)
5	(*S*)-**1**	DMF	82	95 (*R*)

[a] The reaction was carried out at room temperature for 24 h with 27 equivalents of acetone relative to 4-nitrobenzaldehyde in the presence of the catalyst (5 mol%). [b] Yield of product isolated by column chromatography. [c] The *ee* value of the product was determined by HPLC analysis with a chiral column (Chiralpak AS-H, Daicel Chemical Industries, Ltd.). The absolute configuration of **9** was determined by comparison of the HPLC retention time with the literature value.[6i] [d] Bicyclic 1,3-oxazolidine **10** was isolated in 48% yield (based on proline) as a by-product. NMP = 1-methyl-2-pyrrolidone; DMF = *N*,*N*-dimethylformamide.

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Keiji Maruoka *was born in 1953 in Mie, Japan. He graduated from Kyoto Univ. (1976) and received his Ph.D. (1980) from the Univ. of Hawaii under the guidance of Prof. Hisashi Yamamoto. He then joined Nagoya Univ. and was eventually promoted to Associate Prof. (1990). He moved to Hokkaido Univ. as a full Prof. in 1995, and has now been a Prof. of chemistry at Kyoto Univ. since 2000. He has received many prizes and awards, and is a fellow of the Royal Society of Chemistry. His current research interests include bidentate Lewis acids in organic synthesis and practical asymmetric synthesis with designer chiral organocatalysts.*

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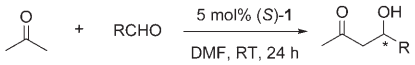
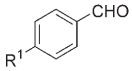
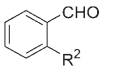
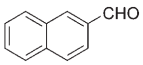
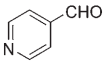
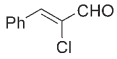
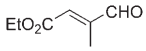
lyzed reaction under the same conditions gave the aldol product **9** in low yield with moderate enantioselectivity accompanied by 1,3-oxazolidine **10** (48% yield based on proline), which was derived from proline and 2 equivalents of 4-nitrobenzaldehyde (Table 1, entry 2). It should be noted that the formation of such a by-product was not observed in the case of binaphthyl-based amino acid (*S*)-**1** owing to its structural stability. We also examined the solvent effect in this direct asymmetric aldol reaction. Switching the solvent from DMSO to acetonitrile gave **9** in poor yield with slightly higher enantioselectivity (Table 1, entry 3). The use of amide solvents such as NMP and DMF was found to give the products in improved yields with high enantioselectivities (Table 1, entries 4 and 5).

Scope and Limitation

With the optimal reaction conditions in hand, the direct asymmetric aldol reaction of acetone with several other aromatic and olefinic aldehydes was executed (Table 2). Olefinic and heteroaromatic aldehydes as well as electron-deficient aromatic aldehydes were found to be suitable substrates (Table 2, entries 1–5 and 8–10). In general, the direct aldol reactions gave the corresponding aldol adducts in moderate to good yields. Furthermore, excellent levels of enantioselectivity (>95% *ee*) were observed in most cases. In contrast, the reaction with simple aromatic aldehydes such as benzaldehyde and β-naphthaldehyde gave the aldol adducts in low yields, albeit with excellent enantioselectivities (Table 2, entries 6 and 7).

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

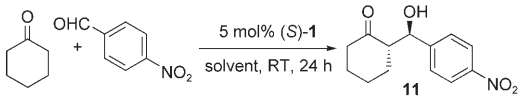


Entry	Aldehyde		Yield[b] [%]	*ee*[c] [%]
1		$R^1=NO_2$	82	95 (*R*)
2		$R^1=CN$	80	95 (*R*)
3		$R^1=Ac$	61	95
4		$R^2=Cl$	91	95 (*R*)
5		$R^2=OTf$	81	94
6		$R^2=H$	22	96 (*R*)
7[d]			35	96 (*R*)
8			76	95
9			73	90
10			81	96

[a] The reaction in DMF was carried out at room temperature for 24 h with 27 equivalents of acetone relative to the aldehyde in the presence of catalyst (*S*)-**1** (5 mol%). [b] Yield of product isolated by column chromatography. [c] The *ee* value of the product was determined by HPLC analysis with a chiral column (Chiralpak AS-H, AD-H or Chiralcel OD-H, Daicel Chemical Industries, Ltd.). The absolute configuration was determined by comparison of the HPLC retention time with literature data.[6i] [d] Excess acetone (108 equivalents) was used. Tf = trifluoromethanesulfonyl.

On the strength of these initial results, we next investigated the use of other ketones instead of acetone. Thus, cyclohexanone was treated with 4-nitrobenzaldehyde in the presence of (*S*)-**1** (5 mol%) in DMF at room temperature to give the aldol adduct **11** in 57% yield with excellent diastereoselectivity (*anti*/*syn* = 93:7) and good enantioselectivity (86% *ee* for the major *anti* isomer) (Table 3, entry 1). In the reaction of cyclohexanone, DMSO was found to serve as an effective solvent; indeed, both the yield and stereoselectivities were superior to those observed in DMF (Table 3, entry 2). Moreover, the use of higher catalyst loading (10 mol%) led to an improved yield and enantioselectivity (98% yield, *anti*/*syn* = 95:5, 98% *ee* for the major *anti* isomer) (Table 3, entry 3). This is in sharp contrast to the results obtained with proline catalyst (20 mol%) under the same conditions (65% yield, *anti*/*syn* = 63:37, 89% *ee* for the major *anti* isomer).[4d]

Table 3. Direct asymmetric aldol reaction of cyclohexanone and 4-nitrobenzaldehyde with (*S*)-**1**.[a]



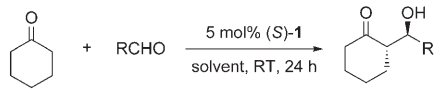
Entry	Solvent	Yield[b] [%] (*anti*/*syn*)[c]	*ee*[d] [%] (*anti*)	*ee*[d] [%] (*syn*)
1	DMF	57 (93:7)	86 (2*S*,1′*R*)	37
2	DMSO	94 (96:4)	94 (2*S*,1′*R*)	7
3[e]	DMSO	98 (95:5)	98 (2*S*,1′*R*)	5

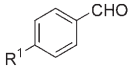
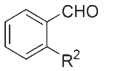
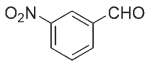
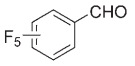
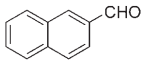
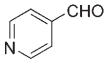
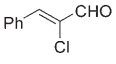
[a] The reaction was carried out at room temperature for 24 h with 10 equivalents of cyclohexanone relative to 4-nitrobenzaldehyde in the presence of (*S*)-**1** (5 mol%). [b] Yield of product isolated by column chromatography. [c] The diastereomeric ratio was determined by ^{1}H NMR spectroscopy. [d] The *ee* value of the product was determined by HPLC analysis with a chiral column (Chiralpak AD, Daicel Chemical Industries, Ltd.). The absolute configuration of the major *anti* isomer was determined by comparison of the HPLC retention time with literature data.[6j] [e] (*S*)-**1**: 10 mol%.

Table 4 shows the results of the direct asymmetric aldol reaction of cyclohexanone with various aldehydes under conditions similar to those outlined above. In the case of electron-deficient aromatic aldehydes and an olefinic aldehyde, the reactions proceeded smoothly to give the corresponding aldol adducts in good to excellent yields (Table 4, entries 2–11, 13, and 14), whereas benzaldehyde or β-naphthaldehyde led to products in moderate yields (Table 4, entries 1 and 12). Notably, all the aldehydes employed in this study underwent the direct aldol reaction with high levels of diastereoselectivity (*anti*/*syn* > 88:12) and excellent enantioselectivity (>95% *ee*).

Selected results of the direct asymmetric aldol reaction of other cyclic ketones with 4-nitrobenzaldehyde are summarized in Table 5. When the six-membered cyclic ketones tetrahydrothiopyran-4-one and tetrahydropyran-4-one were employed instead of cyclohexanone, satisfactory yields and

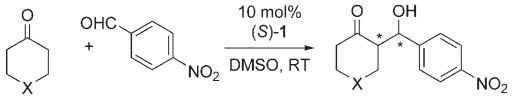
Table 4. Direct asymmetric aldol reaction of cyclohexanone and various aldehydes with (*S*)-**1**.[a]



Entry	Aldehyde		Yield[b] [%] (*anti*/*syn*)[c]	*ee*[d] [%] (*anti*)	*ee*[d] [%] (*syn*)
1[e]		R^1=H	38 (91:9)	98	16
2		R^1=NO_2	98 (95:5)	98	5
3		R^1=CN	95 (89:11)	97	37
4		R^1=CF_3	98 (95:5)	99	2
5		R^1=OTf	89 (94:6)	98	18
6		R^1=Ac	90 (93:7)	98	16
7		R^2=NO_2	94 (>95:5)	99	83
8		R^2=F	99 (>95:5)	99	–
9		R^2=OTf	97 (>95:5)	99	23
10			98 (95:5)	96	5
11			95 (>95:5)	95	18
12			47 (88:12)	97	37
13			93 (>95:5)	97	12
14			87 (95:5)	97	30

[a] The reaction was carried out at room temperature for 24–48 h with 10 equivalents of cyclohexanone relative to the aldehyde in the presence of (*S*)-**1** (10 mol%) in DMSO. [b] Yield of product isolated by column chromatography. [c] The diastereomeric ratio was determined by ^{1}H NMR spectroscopy. [d] The *ee* value of the product was determined by HPLC analysis with a chiral column (Chiralpak AD, AD-H, AS-H or Chiralcel OD-H, Daicel Chemical Industries, Ltd.). [e] The reaction was performed for 126 h.

Table 5. Direct asymmetric aldol reaction of cyclic ketones and 4-nitrobenzaldehyde with (*S*)-**1**.[a]



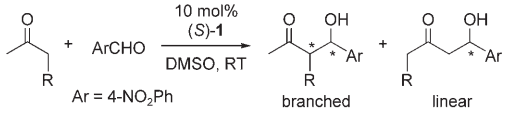
Entry	Ketone		Yield[b] [%] (*anti*/*syn*)[c]	*ee*[d] [%] (*anti*)	*ee*[d] [%] (*syn*)
1		X=CH_2	98 (95:5)	98 (2*S*, 1′*R*)	5
2		X=S	80 (89:11)	99 (3*S*, 1′*R*)	–
3		X=O	92 (96:4)	98	45
4			30 (50:50)	75	55

[a] The reaction was carried out at room temperature for 24–48 h with 5–10 equivalents of ketone relative to 4-nitrobenzaldehyde in the presence of 10 mol% of (*S*)-**1** in DMSO. [b] Yield of product isolated by column chromatography. [c] The diastereomeric ratio was determined by ^{1}H NMR spectroscopy. [d] The *ee* value of the product was determined by HPLC analysis with a chiral column (Chiralpak AD, AD-H, or AS-H, Daicel Chemical Industries, Ltd.). The absolute configuration was determined by comparison of the HPLC retention time or the sign of the optical rotation with literature data.[6j,11]

stereoselectivities were attained (Table 5, entries 2 and 3). Notably, desulfurization of the aldol adduct derived from tetrahydrothiopyran-4-one was reported to give products equivalent to those that would be obtained from 3-pentanone.[11] In contrast to six-membered cyclic ketones, the use of cyclopentanone gave a disappointing result in terms of both *anti*/*syn* ratio and their enantioselectivity (Table 5, entry 4).

Finally, we investigated the use of a series of acyclic unsymmetrical ketones in the direct asymmetric aldol reaction catalyzed by binaphthyl-based amino acid (*S*)-**1** (Table 6).

Table 6. Direct asymmetric aldol reaction of unsymmetrical ketones and 4-nitrobenzaldehyde with (*S*)-**1**.[a]



Entry	R	Yield[b] [%] (branched[c]/linear)	*ee* [%] (branched)[d,e]	*ee* [%] (linear)[e]
1	Me	72 (2.6:1)	99	91
2	Pr	57 (1:1.6)	99	87
3	Bn	50 (1:2.0)	99	99
4	*i*Pr	26 (linear only)	–	89

[a] The reaction was carried out at room temperature for 48–120 h with 7–11 equivalents of ketone relative to 4-nitrobenzaldehyde in the presence of (*S*)-**1** (10 mol%) in DMSO. [b] Yield of product isolated by column chromatography. [c] All diastereomeric ratios of branched products were determined to be >94:6 (*anti*/*syn*) by ^{1}H NMR spectroscopy. [d] The *ee* value is that of the major *anti* isomer. [e] The *ee* value of the product was determined by HPLC analysis with a chiral column (Chiralpak AS-H, AD-H, or Chiralcel OD-H, Daicel Chemical Industries, Ltd.).

The reaction of 2-butanone with 4-nitrobenzaldehyde afforded the *anti* aldol adduct with a branched carbon chain as a major regioisomer and diastereomer, with virtually complete enantioselectivity (Table 6, entry 1). Interestingly, the use of proline as catalyst for this reaction exclusively gave the aldol adduct with a linear carbon chain.[4d] As the alkyl group R of the unsymmetrical ketones became larger, the linear aldol adduct became more dominant (Table 6, entries 2 and 3); thus the reaction of 4-methylpentan-2-one gave the linear adduct as the only product (Table 6, entry 4).

Reaction Mechanism

To understand the reactivity difference between proline and binaphthyl-based amino acid (*S*)-**1**, a kinetic study with acetone and 4-nitrobenzaldehyde as substrates was carried out (Figure 1). When 5 mol% of (*S*)-**1** was used as catalyst, the yield of the aldol product **9** gradually increased with longer reaction time. In contrast, the reaction with proline catalyst proceeded more rapidly than that with (*S*)-**1** for the first 30 min and then stopped at low conversion, accompanied by the formation of a substantial amount of 1,3-oxazolidine **10** as by-product. These observations can be explained by the consumption of proline under the reaction conditions. As shown in Scheme 2, proline is known to decompose by de-

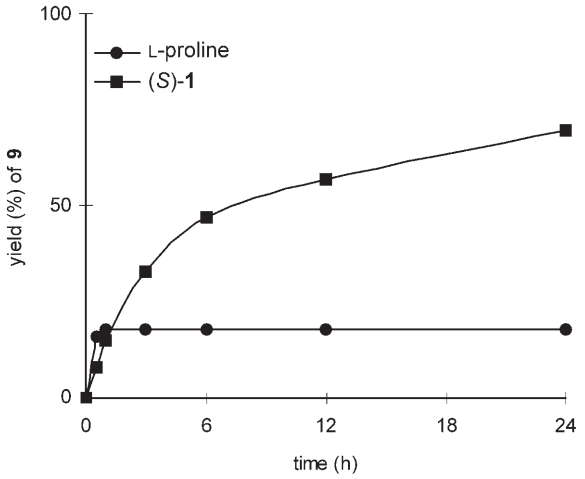
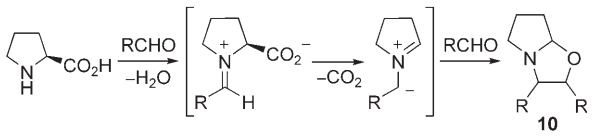


Figure 1. Direct aldol reaction of acetone with 4-nitrobenzaldehyde using proline or (*S*)-**1** as catalyst. Conditions: 4-nitrobenzaldehyde, catalyst (5 mol%), and acetone (27 equiv) in DMSO (0.125 M) at room temperature.



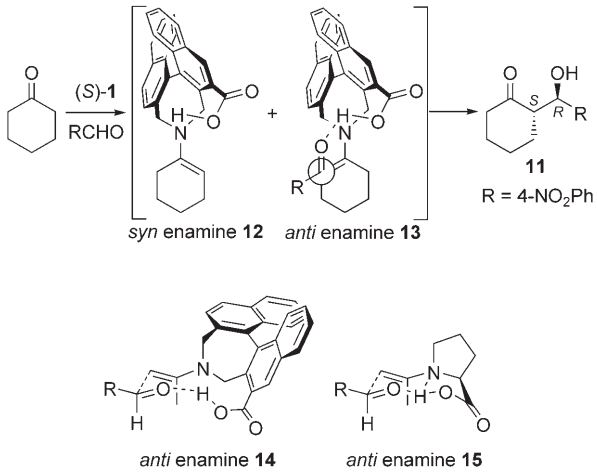
Scheme 2. Formation of 1,3-oxazolidine **10** as a by-product.

carboxylation of an iminium salt, which is formed in the presence of an electron-deficient aldehyde, followed by cycloaddition of the resulting azomethine ylide with another equivalent of aldehyde to give the corresponding 1,3-oxazolidine **10** (Table 1, entry 2).[12] On the other hand, binaphthyl-based amino acid (*S*)-**1** is chemically stable, and consequently, the reaction promoted by (*S*)-**1** leads to a better yield despite the slower reaction rate owing to the low nucleophilicity of the benzylic amine moiety in (*S*)-**1** (Table 1, entry 1).

The absolute stereochemistry of the *anti* aldol adduct **11**, which was obtained as a major isomer in the reaction of cyclohexanone with 4-nitrobenzaldehyde catalyzed by (*S*)-**1**, was determined to be (2*S*,1′*R*) by chiral HPLC analysis and comparison with the literature data[6j] (Table 4, entry 2; Scheme 3). On the basis of the observed stereochemistry, a plausible transition state is proposed in which the *Re* face of an aldehyde approaches the *Re* face of the *anti* enamine **13**. Hence, the reaction of an aldehyde with acetone in the presence of (*S*)-**1** presumably proceeds by way of *anti* enamine structure **14**, similar to the *anti* enamine **15** transition state in the proline-catalyzed reaction.[4a,o]

Conclusions

We have designed and synthesized a novel and robust binaphthyl-based axially chiral amino acid, which was utilized as a catalyst in the direct asymmetric aldol reaction of ketones with aldehydes. Several reactions with this amino acid catalyst are more efficient than the proline-catalyzed reactions in terms of yield and enantioselectivity and hence represent a rare example of the highly enantioselective direct aldol reaction with a non-proline-derived artificial organocatalyst. Thus, our axially chiral amino acid offers the possibility of a new catalyst design for the various asymmetric reactions catalyzed by proline and its derivatives.



Scheme 3. Proposed transition state models for the aldol reaction catalyzed by (*S*)-**1**.

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