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Direct Asymmetric *syn*-Aldol Reactions of Linear Aliphatic Ketones with Primary Amino Acid-Derived Diamines

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Abstract: We have designed a novel class of chiral diamine organocatalysts based on natural primary amino acids that efficiently catalyze *syn*-selective aldol reactions of challenging linear ketones, such as 2-butanone, and aromatic aldehydes. In the presence of trifluoroacetic acid (TFA) as Brønsted acid and 2,4-dinitrophenol (DNP) as co-catalyst, *syn*-aldol products have been obtained with excellent enantioselectivities of up to > 99% *ee*.

Keywords: aldol reaction; aliphatic ketones; chiral diamines; *syn*-diastereoselectivity; primary amino acids

In the past decade intensive research has focused on the design of various chiral pyrrolidine derivatives for asymmetric enamine-catalyzed reactions.[1] Within this 'aminocatalytic gold rush', an overwhelming number of novel, highly efficient organocatalysts appeared in the literature and at present, asymmetric aminocatalysis is widely regarded as a well-established and powerful synthetic tool for the enantioselective functionalization of carbonyl compounds.[2] However, in spite of the tremendous success of secondary amines as enamine-based catalysts, primary amino acids have only rarely been considered for this kind of catalysis. In 2004/2005 the first reports on primary amines as enamine-based catalysts appeared in the literature.[3,4] Simple acyclic amino acids and peptides, as well as thiourea-primary amines have been successfully applied in asymmetric aldol reactions, Mannich reactions and/or Michael additions. These initial investigations demonstrate that enamine intermediates derived from primary amines can be generated effectively. Moreover, primary amine catalysts show advantages in asymmetric catalysis since the presence of a hydrogen on the nitrogen can play a role in both promoting the formation of an active intermediate and controlling the stereoselectivity.[4b,c] As a consequence of these findings, primary amines have been further established during the past few years as valuable enamine catalysts, complementing the traditional secondary amino catalysis.[4,5] Although important progress has been accomplished recently, the development of primary amine catalysts is still far behind in comparison with secondary amine catalysis. Hence, it is of great interest to further explore the potential of primary

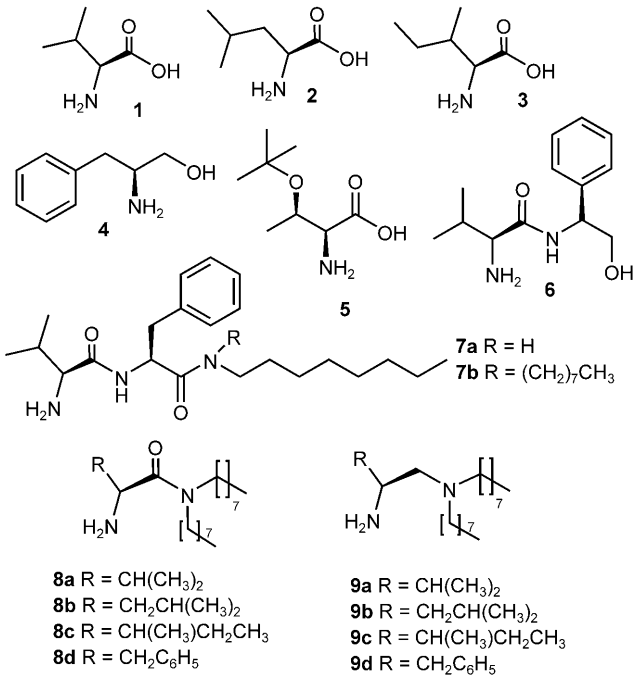


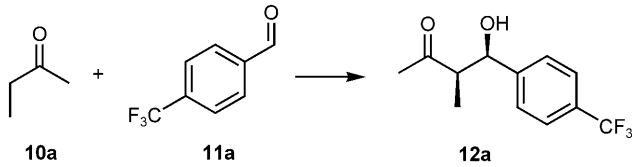
Figure 1. Overview of catalysts screened in the model reaction.

amines as organocatalysts in order to extend the utility of enamine-based catalysis.

Besides, there was growing attention for the application of primary amine-based catalysts in direct asymmetric aldol reactions, in particular because they exhibit *syn*-diastereoselectivity. Recently, the research groups of Cheng, Barbas, Lu and Gong have independently reported successful applications of primary amines based on different chiral structural scaffolds as highly enantioselective *syn*-aldol catalysts.[6] Subsequently, stimulated by this pioneering work, those and other groups designed similar catalysts for *syn*-aldol reactions with comparable results.[7] Some theoretical studies on the origins of the observed *syn*-selectivity for selected catalyst–ketone combinations have been published as well.[8] Nevertheless, in general, these primary amines have proved to be effective *syn*-aldol catalysts only for a limited group of ketone donors, this is mainly for cyclic ketones and protected or unprotected (di)hydroxyacetones. Direct asymmetric *syn*-aldol reactions with linear aliphatic ketones have been less investigated. Only Cheng and co-workers have reported a highly selective primary amine catalyst for *syn*-aldol reactions with a broad range of ketones.[5i,6a–c,7a] For methyl alkyl ketones, such as 2-butanone, good results with high enantioselectivities for *syn*-aldol products are quite rare to date. Hence, despite some remarkable advances, the design of simple and efficient organocatalysts that enable *syn*-aldol reactions with high enantioselectivity remains an important challenge.

In this paper, we present a novel class of chiral diamine catalysts based on L-(iso)leucine, L-valine and L-phenylalanine for highly enantioselective *syn*-aldol reactions of linear aliphatic ketones. Inspired by the previous reports on *syn*-selective aldol reactions, we prepared a series of different types of primary amino acid derivatives, as illustrated in Figure 1 (**6–9**). Considering the target substrate group as mentioned above, we selected the aldol reaction of 2-butanone and 4-(trifluoromethyl)benzaldehyde as a model reaction to evaluate the synthesized organocatalysts. Together with some commercially available primary amino acids and their derivatives (Figure 1, **1–5**), cata-

Table 1. Results of catalyst screening.[a]



10a **11a** **12a**

Entry	Catalyst	Yield[b] [%]	rr[b] *b/l*	*dr*[b] *syn/anti*	*ee*[c] [%]
1	**1**	<5	n.d.[d]	n.d.	n.d.
2	**2**	<1	n.d.	n.d.	n.d.
3	**3**	30	15/1	3/2	74
4	**4**	10	2/1	5/2	41
5	**5**	74	3/1	2/1	74
6	**6**	65	3/2	4/1	28
7	**7a**[e]	29	6/1	3/2	18
8	**7b**	28	7/2	5/2	40
9	**8a**	<10	n.d.	n.d.	n.d.
10	**8b**	10	11/1	1/1	38
11	**8c**/TFA	<5	n.d.	n.d.	n.d.
12	**8d**	<1	n.d.	n.d.	n.d.
13	**9a/TFA**	**71**	**5/2**	**5/2**	**96**
14	**9b/TFA**	**39**	**7/1**	**7/2**	**94**
15	**9c/TFA**	**59**	**7/1**	**3/1**	**97**
16	**9d/TFA**	**82**	**8/1**	**3/1**	**96**

[a] All reactions were performed under neat conditions in **10a** (2 mL) with **11a** (0.25 mmol) and 20 mol% catalyst at room temperature and analyzed after 20 h, unless indicated otherwise.
[b] Determined with GC and verified with ^{1}H NMR (rr = regioisomer ratio, *b/l* = ratio of branched and linear products).
[c] The *ee* of the major *syn*-isomer, determined by chiral GC.
[d] Not determined.
[e] After 68 h of reaction.

Table 2. Effect of additives and optimization of reaction conditions.[a]

Entry	Additive	Yield[b] [%]	rr[b] *b/l*	*dr*[b] *syn/anti*	*ee*[c] [%]
1	TFA	34	7/1	4/1	96
2	TfOH[d]	28	n.d.[e]	1/1	7
3	HCOOH[d]	<10	n.d.	n.d.	n.d.
4	CCl_3COOH	no reaction			
5	mNO_2bzac	<10	n.d.	n.d.	n.d.
6	$H_3PW_{12}O_{40}$[f]	15	13/1	3/2	52
7	p-TSA	23	5/2	5/2	96
8	DNP	24	4/1	4/1	94
9	TFA/PhCOOH	42	9/1	7/2	96
10	TFA/AcOH	44	11/1	7/2	95
11	TFA/mNO_2bzac	31	10/1	4/1	96
12	**TFA/DNP**	**49**	**9/1**	**4/1**	**95**
13	**TFA/DNP**[g]	**58**	**9/1**	**4/1**	**97**
14	**TFA/DNP**[f,g]	**92**	**9/1**	**4/1**	**97**

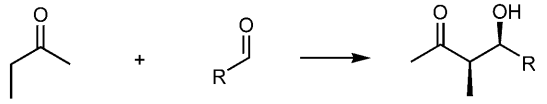
[a] All reactions were performed under neat conditions in **10a** (2 mL) with **11a** (0.25 mmol), 15 mol% of catalyst **9b** and 15 mol% additive at room temperature, and analyzed after 20 h, unless indicated otherwise.
[b] Determined with chiral GC and verified with ^{1}H NMR (rr = regioisomer ratio, *b/l* = ratio of branched and linear products).
[c] The *ee* of the major *syn*-isomer, determined by chiral GC.
[d] 20 mol% of catalyst.
[e] Not determined.
[f] After 68 h of reaction.
[g] Reaction in 0.5 mL of 2-butanone.

lysts **6–9** were tested in the model reaction under neat conditions and ambient temperature. The screening results are summarized in Table 1.

From the examined amino acids and their derivatives, L-isoleucine and the *t*-BuO-L-threonine give the best results (Table 1, entries 3 and 5). Amide catalysts **6** and **7a**, **b** derived from the L-Val-L-Phe dipeptide, show rather moderate activity and poor enantioselectivity for the *syn*-product (entries 6–8). Furthermore, the catalytic performance of amides **8a–d** in the model reaction is inferior to all previously tested amines (entries 9–12). To our delight, primary-tertiary diamine catalysts **9a–d** display good diastereoselectivities and very high enantioselectivities of up to 97% *ee* for the *syn*-product in the presence of TFA as Brønsted acid (entries 13–16). Very recently, Li et al. reported the design of a primary-tertiary diamine derived from L-phenylalanine.[9] Despite excellent enantioselectivities in the aldol reaction of hydroxyacetone, poor results were obtained with 2-butanone as the ketone donor under neat conditions (36% *ee* for the *syn*-isomer). Hence, to the best of our knowledge, these are the highest *ee* values achieved for the *syn*-selective aldol reaction of 2-butanone and an aromatic aldehyde catalyzed by a primary amino acid-derived organocatalyst.

Encouraged by these results, we chose catalyst **9b** for further optimization. The model reaction was carried out in aqueous and non-aqueous solvents with different polarities (Supporting Information, Table S1). The catalytic performance of diamines **9a–d** in the model reaction was found to be highly solvent-dependent. In general, neither polar nor apolar organic solvents improve the efficiency of **9b** in the model reaction. The use of water as a solvent or co-solvent increases the activity of **9b** compared to the reaction in purely organic solvents, with only a marginal decline in *ee* with respect to the solvent-free reaction (Supporting Information, Table S1, entries 3–7 and 10). For catalyst **9d**, a similar trend is observed (Supporting Information, Table S1, entries 14–16). Nevertheless, optimal activity and selectivity were obtained under neat conditions. From Table 2, it becomes clear that the choice of the acidic additive also has an important influence on the activity and selectivity of catalyst **9b**. Interestingly, in spite of successful applications with previously reported primary-tertiary diamines, TfOH almost completely suppresses the model reaction catalyzed by **9b** (Table 2, entry 2). In the optimized reactions with acetone and 2-pentanone catalyzed by **9d** (*vide infra*, Table 4, entries 9 and 13), replacing TFA by TfOH could not improve the overall performance of catalyst **9d**. Considering these observations, it is important to notice that, in absence of a diamine catalyst, the aldol reactions of 2-butanone, acetone and 2-pentanone are catalyzed by TfOH

Table 3. Reaction of **10a** with different aromatic aldehydes under optimized conditions.[a]

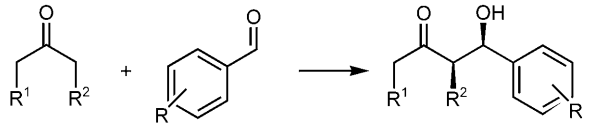


10a **11a – e** **12a – e**

Entry	R	Cat.	Yield[b] [%]	rr[b] *b/l*	*dr*[b] *syn/anti*	*ee*[c] [%]
1	4-$CF_3C_6H_4$	**9a**	94	4/1	3/1	96
2		**9b**	92	9/1	4/1	97
3		**9c**	97	9/1	3/1	97
4[d]		**9d**	92	11/1	4/1	98
5	4-$NO_2C_6H_4$	**9b**	99	13/1	4/1	94
6		**9c**	97	10/1	3/1	96
7	2-$NO_2C_6H_4$	**9b**	98	6/1	7/2	96
8		**9c**	99	4/1	3/1	98
9	2-ClC_6H_4	**9b**	90	>20/1	6/1	96
10		**9c**	**98**	**>20/1**	**8/1**	**>99**
11	1-Napth	**9b**	39	7/1	7/2	86
12		**9c**	36	9/1	3/1	87
13[e]		**9c**	18	9/1	5/2	91

[a] All reactions were performed under neat conditions with **10a** (0.5 mL) and aldehyde (0.25 mmol) in the presence of 15 mol% **9**/TFA/DNP at room temperature and analyzed after 68 h, unless indicated otherwise.
[b] Determined with GC or HPLC and verified with ^{1}H NMR (rr = regioisomer ratio, *b/l* = ratio of branched and linear products).
[c] The *ee* of the major *syn*-isomer, determined by chiral GC or HPLC.
[d] After 20 h of reaction.
[e] Reaction without DNP.

Table 4. Reaction of different ketones and aromatic aldehydes under optimized conditions.[a]



10a – f 11a – c,f,g 12a – 17

Entry	Cat.	R^1, R^2, R	Yield[b] [%]	Dr[b] *syn/anti*	*ee*[c] [%]
1	**9b**	H, Me, 4-CF_3	**92**	**4/1**	**97**
2	**9a**	Me, Me, 4-CF_3	50	**8/1**	**98**
3	**9b**		29	**7/1**	> **99**
4	**9c**		**93**	**5/1**	**96**
5	**9d**		69	**6/1**	**99**
6	**9a**	H, H, 4-CF_3	92	-	64
7	**9b**		95	-	62
8	**9c**		97	-	77
9	**9d**		**93**	-	**83**
10	**9a**	H, Et, 4-CF_3[d]	60	5/2	45
11	**9b**		31	5/2	52
12	**9c**		87	2/1	50
13	**9d**		93	2/1	42
14	**9c**	H, OH, 2-NO_2	**98**	**23/1**	**97**
15	**9d**		**99**	**25/1**	**98**
16	**9b**	H, OH, 4-NO_2	**93**	**11/1**	**90**
17[e]	**9b**		98	5/1	86
18	**9b**	H, OH, 4-CF_3	99	9/2	84
19[f]	**9c**		> **99**	**5/1**	**91**
20	**9c**	H, OH, 4-Cl	96	9/2	89
21[f]	**9c**		87	9/2	88
22[g]	**9b**	-$(CH_2)_3$-, 4-Br	92	1/7	60[h]
23	**9c**		93	1/2	70
24[f]	**9c**		96	1/2	68

[a] All reactions were performed under neat conditions with ketone (0.5 mL) and aldehyde (0.25 mmol) in the presence of 15 mol% **9**/TFA/DNP at room temperature and analyzed after 68 h, unless indicated otherwise.
[b] Determined with GC or HPLC and verified with ^{1}H NMR.
[c] The *ee* of the major *syn*-isomer, determined by chiral GC or HPLC.
[d] Regioisomer ratio (rr) for **9a**, **9b**, **9c** and **9d**: *b/l* (branched/linear) = 1/1, 1/1, 2/1, 2/1 respectively.
[e] NMP:hexane 1:1 (200 μL) was used as the solvent.
[f] Reaction without DNP.
[g] 0.5 mmol cyclohexanone and water (0.5 mL) as the solvent.
[h] The *ee* of the major *anti*-isomer, determined by chiral HPLC.

through general acid catalysis (Supporting Information, Table S2, entries 2, 6 and 10), yielding the aldol product as a racemic mixture. With TFA under neat conditions, no reaction occurs without a catalyst, suggesting that a weaker Brønsted acid is required for efficient catalysis with diamines **9a–d**. Very recently, 2,4-dinitrophenol (DNP) has been employed as a co-catalyst to improve the activity and enantioselectivity of inefficient primary amine-based organocatalysts in asymmetric aldol reactions.[10] Here, the addition of DNP significantly improved the activity of the **9b**/TFA catalytic system in the model reaction (Table 2, entry 12).

Next, the application of the **9**/TFA/DNP catalytic system in the aldol reaction of 2-butanone was further examined. Therefore, different aromatic aldehydes were tested as aldol acceptors under optimized conditions. As shown in Table 3, excellent yields and enantioselectivities of up to >99% *ee*, and good diastereoselectivities are achieved (entries 1–10), except for the reaction with 1-naphthylaldehyde, the catalytic performance of **9b** and **9c** is rather moderate (entries 11–13).

In order to further explore the scope and limitations of this novel catalytic system, diamines **9a–d** were applied in the aldol reaction of various ketones and aromatic aldehydes under optimized conditions (Table 4). From all ketones, the symmetrical 3-pentanone displays the highest stereoselectivity with an enantiomeric excess of up to >99% for the *syn*-prod-

uct (entries 2–5). Furthermore, good stereoselectivity and good to excellent enantioselectivities (98% *ee*, entry 15) are achieved with hydroxyacetone as the ketone donor (entries 14–21). With acetone, despite good activity, the enantioselectivity of **9a–d** is rather moderate (entries 6–9) and with 2-pentanone the selectivity for the branched product is limited (entries 10–13), as also was observed for the cyclohexanediamine catalyst by Cheng and co-workers.[6a] In accordance with previous reports on primary amine-based aldol catalysts, **9b** and **9c** exhibit *anti*-selectivity for aldol reactions of cyclic ketone donors (entries 22–24).

In summary, we have designed simple chiral diamine organocatalysts based on natural primary amino acids with hydrophobic side chains that efficiently catalyze *syn*-aldol reactions of challenging linear aliphatic ketones, such as 2-butanone, and unprotected hydroxyacetone. Excellent yields and enantioselectivities of up to >99%, and good diastereoselectivities were obtained in the presence of TFA as Brønsted acid and DNP as co-catalyst. This work illustrates the synthetic utility of primary amino acid-based structures for the development of effective organocatalysts that promote direct *syn*-selective aldol reactions.

Experimental Section

Representative Procedure for the Aldol Reaction

Organocatalyst **9b**·TFA (15 mol%) and co-catalyst DNP (15 mol%) were mixed together with the ketone (0.5 mL) at room temperature, followed by the addition of the aldehyde (0.25 mmol). The reaction mixture was stirred for a given time and extracted with ethyl acetate and water. The organic phase was analyzed with NMR and chiral GC to calculate yields and regio- and diastereomeric ratios. The enantiomeric excess (*ee*) was determined with chiral GC or chiral HPLC.

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