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Highly Efficient Organocatalyzed Direct Asymmetric Aldol Reactions of Hydroxyacetone and Aldehydes

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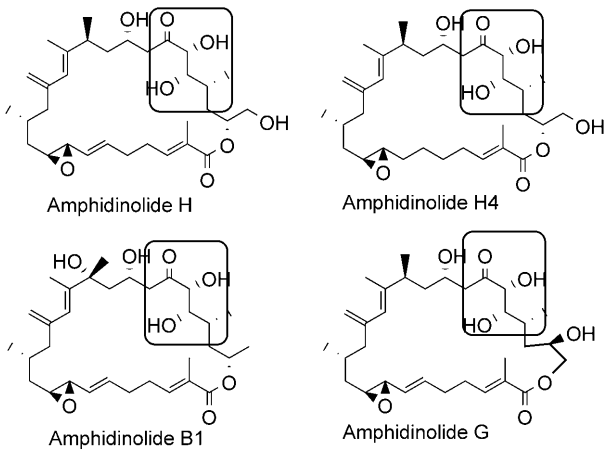
Abstract: Novel organocatalysts derived from L-threonine and L-leucine have been synthesized for catalyzing direct aldol reactions of hydroxycetone and unactivated aliphatic aldehydes with as low as 2 mol% loading of the catalyst, good to excellent yields and excellent enantioselectivities have been achieved for aliphatic aldehydes, whereas aromatic aldehydes yield only moderate enantioselectivities.

Keywords: aldehydes; aldol reaction; 1,2-diols; hydroxyacetone; organic catalysis

The α,β-dihydroxy ketone moiety is the core structure unit in a number of natural macrolide amphidinolides (Scheme 1).[1] Many of these compounds have shown strong cytotoxicity in anti-cancer studies.[1b,c] Their biological activities make them extremely attractive targets for synthetic organic chemists.[2] As for the construction of the key α,β-dihydroxy ketone moiety, several approaches have been reported.[2] Typically two strategies are used to control the stereochemistry: one uses chiral auxiliary,[2a–e] and the other one uses the Sharpless AD process.[2g–i] Nonetheless, both methods require several additional steps to transform the initial amide or ester groups into the desired ketone functional group *via* the corresponding Weinreb amide.



Scheme 1. The α,β-dihydroxy ketone unit in amphidinolides.

As part of our efforts in the total synthesis of amphidinolides H, G and B,[2h,i] we envisioned that a direct aldol reaction of hydroxyacetone with the corresponding aldehydes should produce the C_3 unit with the simultaneous control of the two hydroxy-substituted stereogenic centers. Since the pioneering work of List[3] and Barbas,[4] organocatalysts have been widely utilized in the direct aldol reactions between ketones and aldehydes, and notable advances have been achieved over the last a few years in this field.[5]

The use of hydroxyacetone as a donor in the direct aldol reaction was firstly introduced by List and coworkers.[3b] This reaction provided a product with a valuable 1,2-diol moiety. Since then extensive efforts have been made to improve the stereocontrol in this reaction with either hydroxyacetone or protected hydroxyacetone as the substrates.[6] So far high levels of enantioselectivity have been achieved with both the *syn* and the *anti* products by utilizing chiral catalysts derived from primary and secondary amines.

However, the aldol acceptors of these reactions are usually limited to aromatic aldehydes and α-hydroxy or α-amino aliphatic aldehydes. While it has been reported that branched aliphatic aldehydes are also effective aldol acceptors in some cases,[3,4] linear aliphatic aldehydes are bad substrates in terms of yield and stereoselectivities.[6] Furthermore, the catalyst loading in these reactions typically ranges from 15 to

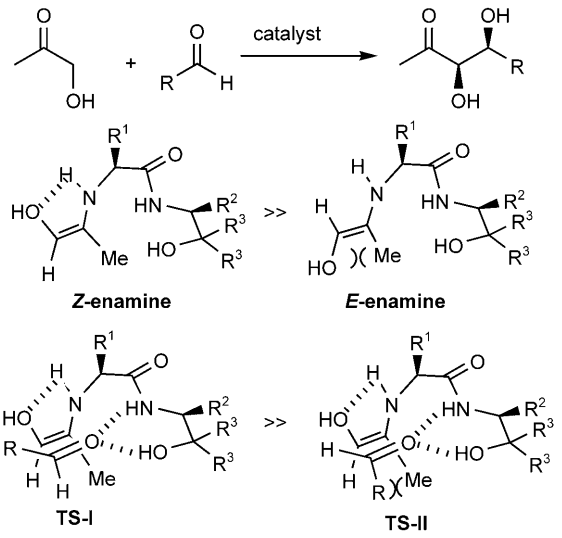
30 mol%. Such a high catalyst loading will cause cost concerns if the reaction is to be applied in a large-scale synthesis. Herein we would like to report our preliminary results on using organocatalysts prepared from primary amino acids and an aminol derived from tryptophan.[7] As shown by our results, these new catalysts are able to address both of the aforementioned issues.

Bifunctional prolinamide catalysts were firstly reported by List and co-workers.[8a] With continuous contributions from Gong's and other groups,[6h,p,8] These catalysts have proved to be highly effective in promoting aldol reactions and Mannich reactions.

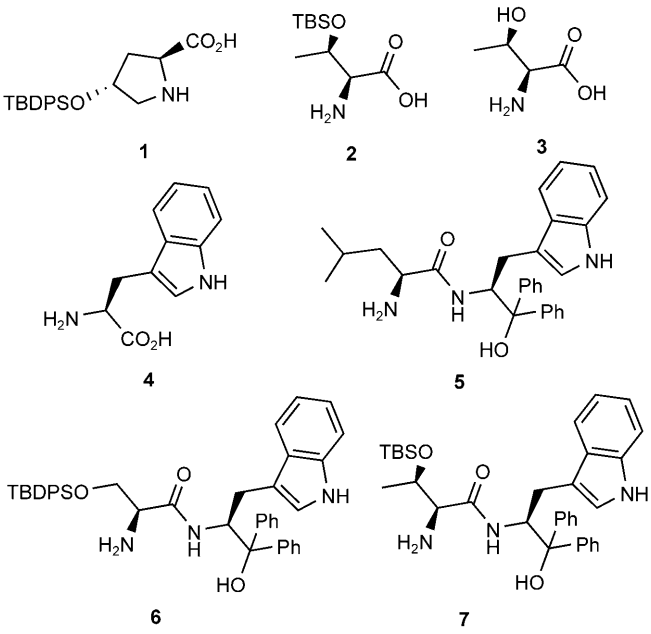
As for the hydroxyacetone substrate, it is well accepted that the formation of a *Z*-enamine with a stabilizing hydrogen bond predominates.[6n,8f] As shown in the favored transition state **TS-I** of the catalysis (Scheme 2), the lack of steric repulsion between the OH and Me groups in the *Z*-enamine may also help to favor this intermediate.[8h] According to Gong's hypothesis, the two hydrogen bonds formed between the aldehyde and the amide and hydroxy moieties of the catalyst activate the substrate and control its approach.[8] Thus, the favored transition state **TS-I** leads to the formation of the *syn* aldol product with high level of stereocontrols (both *de* and *ee*).

With isobutyraldehyde and hydroxyacetone as the model substrates, we screened several bifunctional amide catalysts (**5**–**7**) synthesized in this lab (Figure 1) for the direct aldol reactions. For comparison purposes, four readily available amino acids (**1**–**4**) with similar structural features were also studied. The screening results are collected in Table 1.

The reactions were initially carried out using xylene as the solvent.[9] As shown in Table 1, simple amino acids (such as L-threonine **3**, L-tryptophan **4**) and



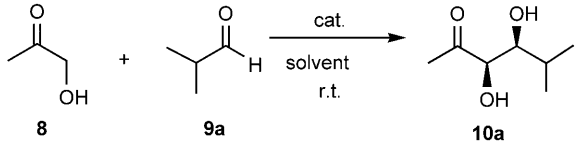
Scheme 2. Plausible transition states in the bifunctional amide-catalyzed aldol reaction of hydroxyacetone.



TBS = *tert*-butyldimethylsilyl, TBDPS = *tert*-butyldiphenylsilyl

Figure 1. Catalysts screened in the direct aldol reactions.

Table 1. Results of catalyst screening.[a]



Entry	Cat. (mol%)	Solvent	Time [h]	Yield[b] [%]	*syn*/*anti*[c]	*ee*[d] [%]
1	**1** (15)	xylene	48	–[e]	–	–
2	**2** (15)	xylene	48	–	–	–
3	**3** (20)	xylene	48	–	–	–
4	**4** (20)	xylene	48	<10	–	–
5	**5** (8)	xylene	24	91	>20:1	95
6	**6** (8)	xylene	24	91	>20:1	96
7	**7** (8)	xylene	24	93	>20:1	98
8	**7** (2)	xylene	80	95	>20:1	98
9[f]	**7** (0.4)	xylene	48	47	>20:1	95
10	**7** (8)	THF	24	93	>20:1	97
11	**7** (8)	DCM	24	93	>20:1	97
12	**7** (8)	Toluene	24	95	>20:1	97

[a] All the reactions were performed with **8** (3 mmol, 3 equiv.) and **9a** (1 mmol) in 1 mL solvent at room temperature. For details see Supporting Information.
[b] Isolated yield.
[c] Determined by ^{1}H NMR.
[d] The *ee* of the major isomer, determined by chiral HPLC.
[e] Almost no formation of the product.
[f] The reaction was conducted at 60 °C.

their siloxyl derivatives (such as **1** and **2**) are not suitable organocatalysts for this reaction (Table 1, entries 1–4) due to their poor catalytic activities. In

striking contrast, when 8 mol% of the bifunctional amide catalysts **5**–**7** were employed, high levels of diastereoselectivity (>20:1) and *ee* values (95–98%) as well as excellent yield (>91%) may be obtained for the desired aldol product (entries 5–7). Among these three bifunctional amide catalysts employed, catalyst **7** derived from L-threonine provides the best results in terms of yield and enantioselectivity (entry 7).

It was also gratifying to find that reducing the catalyst loading to 2 mol% leads to no loss of stereoselectivity. It just takes a longer time for the reaction to complete at this loading (entry 8).

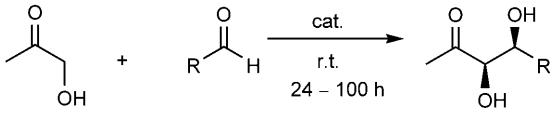
Further reduction in the catalyst loading (to 0.4 mol%) and elevated reaction temperature (60 °C) lead to the aldol adduct with only slightly inferior enantioselectivity. Nevertheless, the yield of product decreased significantly (entry 9). To the best of our knowledge, this is the first example where a relatively low catalyst loading (2 mol%) has been achieved in the organocatalyzed direct aldol reaction of simple aliphatic aldehydes.[10] Such catalytic efficiency is comparable to that of the metal-catalyzed aldol reactions.[11] Other solvents, such as THF, DCM and toluene, are also good solvents for this reaction, as no loss of diastereoselectivity and enantioselectivity was observed with these solvents (entries 10–12).

The scope of this novel aldol reaction was then investigated, and the results are summarized in Table 2. Several aliphatic aldehydes were tested as the acceptors. As shown in Table 2, excellent enantioselectivities were achieved (93–98% *ee*) in all cases (entries 1–8). Surprisingly enough, for some of the substrates, reactions with low loadings of the catalyst produce higher chemical yield and diastereoselectivity as compared with those with high loadings (entry 2 *vs.* 1, 4 *vs.* 3). The reason for this abnormal behavior is still not clear. It should be noted that the current method provides a highly efficient way for the preparation of the *syn* dihydroxy ketones. For example, the previous synthesis of *syn*-**10b** by the Sharpless AD reaction requires 1 mol% $K_2OsO_2(OH)_4$ and 5 mol% $(DHQD)_2PHAL$ to secure a high conversion.[12]

Recently Gong's and Barbas' groups reported that bifunctional amide catalysts successfully promote the aldol reaction between aromatic aldehydes and hydroxyacetone or dihydroxyacetone.[8] To further understand the scope and limitations of our catalysts, some aromatic aldehydes were also studied as the aldol acceptors (Table 3). It is interesting to find that *o*-substituted aldehydes are better substrates than their *p*-substituted counterparts in terms of reactivity and stereoselectivity (entry 4 *vs.* 3 and 6 *vs.* 5). Furthermore, *p*-nitrobenzaldehyde, which has been widely used as a model substrate in the direct adol chemistry due to its reactivity, is not as reactive as *o*-choro- and *o*-bromobenzaldehydes (entries 2, 4 and 6).

In order to show the synthetic potential of the developed method, aldehyde **13** was prepared and used as an acceptor in the aldol reaction with hydroxyacetone, with **7** as the catalyst (Figure 2). The reaction

Table 2. Reaction of **8** with aliphatic aldehydes **9**.[a]

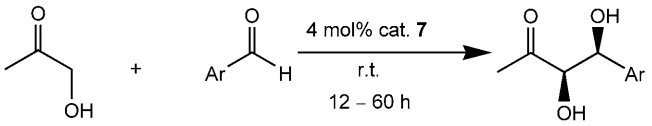


8 **9** **10**

Entry	Cat. (mol%)	R	Yield[b] [%]	*syn/anti*[c]	*ee*[d] [%]
1	**7** (8)	*n*-Pr (**9b**)	50	15:1	97
2	**7** (2)	*n*-Pr (**9b**)	92	>15:1	98
3	**7** (8)	*n*-Bu (**9c**)	88	8:1	93
4	**7** (2)	*n*-Bu (**9c**)	93	15:1	97
5	**5** (8)	*n*-pentyl (**9d**)	76	10:1	97
6	**7** (8)	*n*-pentyl (**9d**)	83	10:1	97
7	**7** (2)	*n*-pentyl (**9d**)	87	>10:1	97
8	**7** (2)	*i*-Bu (**9e**)	98	>30:1	96

[a] All the reactions were performed with **8** (3 mmol, 3 equiv.) and **9** (1 mmol) in 1 mL xylene at room temperature for 24–100 h. For details, see Supporting Information.
[b] Yield of the isolated product after column chromatography.
[c] Determined by ^{1}H NMR analysis of the crude product.
[d] The *ee* value of the major isomer as determined by chiral HPLC analysis.

Table 3. Reaction of **8** with aromatic aldehydes **11**.[a]



8 **11** **12**

Entry	Ar	Solvent	Time [h]	Yield[b] [%]	*syn/anti*[c]	*ee*[d] [%]
1	4-$NO_2C_6H_4$	Toluene	36	91	4:1	80
2	4-$NO_2C_6H_4$	Xylene	50	68	5:1	82
3	4-ClC_6H_4	Xylene	50	86	4:1	76
4	2-ClC_6H_4	Xylene	12	99	9:1	83
5	4-BrC_6H_4	Xylene	60	68	3:1	76
6	2-BrC_6H_4	Xylene	12	94	5:1	79

[a] All the reactions were performed with **8** (3 mmol, 3 equiv.) and **11** (1 mmol) in 1 mL xylene at room temperature for 12–60 h. For details, see Supporting Information.
[b] Yield of the isolated product after column chromatography.
[c] Determined by ^{1}H NMR analysis of the crude product.
[d] The *ee* value of the major isomer as determined by chiral HPLC analysis.

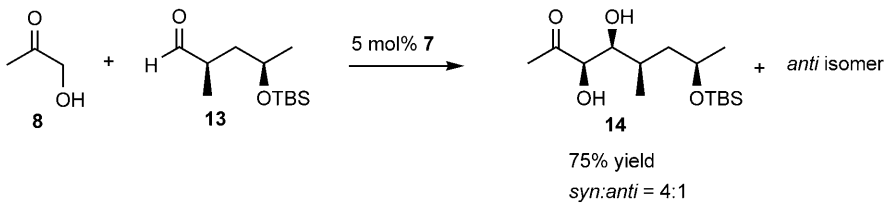


Figure 2. Aldol reaction of aldehyde **13** and hydoryxacetone.

was carried out with 5 mol% **7** as the catalyst under the standard reaction conditions with a reaction time of 18 h. The desired product **14** was obtained in 75% yield.[13] The absolute stereochemistry of **14** was determined by comparison with the *syn*-isomer obtained from Sharpless asymmetric dihydroxylation using AD-mix-α.[2e,12] Compound **14** is a key building block of amphidinolide B1. These results demonstrate that our methodology is very useful in the synthesis of building blocks of natural products.

In summary, we have developed novel L-threonine- and L-leucine-derived organocatalysts for the direct aldol reactions of hydroxyacetone and unactivated aliphatic aldehydes. Excellent yields, diastereoselectivities, and enantioselectivities have been achieved with as low as 2 mol% of these catalysts. These catalysts prove to be highly specific for aliphatic aldehydes, while for aromatic aldehydes only moderate enantioselectivities can be obtained. The method developed herein is of high synthetic potential. The application of this method in the synthesis of amphidinolide is currently underway in our laboratory and will be reported in due course.

Experimental Section

Representative Procedure

To a mixture of catalyst **7** (11 mg, 0.02 mmol) and hydroxyacetone **8** (210 μL, 3 mmol) in xylene (1 mL) was added aldehyde **9a** (90 uL, 1 mmol). The mixture was stirred at room temperature for 24–100 h under an inert atmosphere of argon. The reaction mixture was purified directly by column chromatography (ethyl acetate:hexane = 1:6 to 1:4) to afford the aldol product **10a** as a colorless oil; yield: 95%; *syn*:*anti* > 20:1; the *ee* of *syn* isomer was 98% [by chiral HPLC analysis using a chiralcel AS-H column, $\lambda = 275$ nm, *i*-PrOH:hexane = 10:90, 1 mL min^{-1}, $t_R = 10.17$ min (minor), $t_R = 12.8$ min (major)]. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta =$ 4.70–4.26 (d, $J = 3$ Hz, 1H), 3.71–3.74 (d, $J = 3$ Hz, 1H), 3.50–3.55 (t, $J = 9.9$ Hz, 1H), 2.27 (s, 3H), 1.80–2.00 (m, 2H), 1.03–1.10 (d, $J = 6$ Hz, 3H), 0.98–1.03 (d, $J = 6$ Hz, 3H); $[\alpha]_D^{25}$: −82.0 (*c* 0.98, $CHCl_3$).

Supporting information

Experimental details and characterization data of the new compounds are available as Supporting Information.

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[9] Using xylene as solvent was of benefit in previously reported results, see ref.[8f]

[10] Typically 15–30 mol% catalyst loading was required, see ref.[8]

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[13] *ent*-**7** was also tested as catalyst, the yield was 79%. But the isolation of the *syn* isomer from other isomers by column chromatography was not successful.

