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Organocatalyzed Asymmetric Aldol Reaction of α-Keto Amides with A Tripeptide Catalyst

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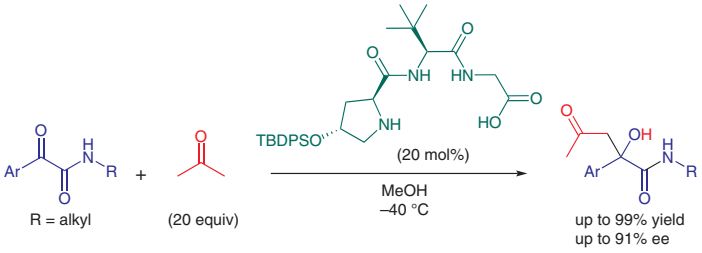

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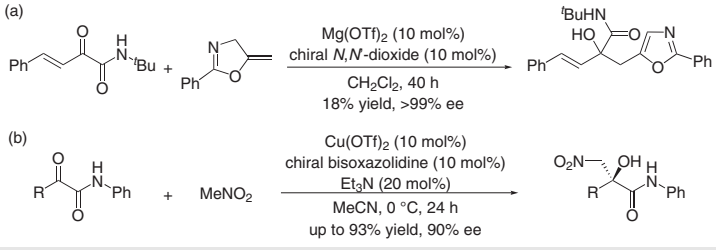
Abstract An organocatalyzed asymmetric aldol reaction of α-keto amides was developed. An N-terminal 4-*trans*-siloxyproline-based tripeptide with an L-*tert*-leucine unit adjacent to the 4-*trans*-siloxyproline residue was used to catalyze the reaction between various α-keto amides and acetone, to produce the corresponding aldol adducts with up to 99% yield and 91% ee.

Key words aldol reaction, asymmetric catalysis, peptide catalysis, organocatalysis, keto amides, hydroxy amides

Optically active acyclic α,α-disubstituted α-hydroxy amides are skeletons that frequently occur in natural products and biologically active compounds.[1] Therefore, new methods for the stereoselective preparation of these compounds are useful. Asymmetric nucleophilic addition to acyclic α-keto amides is a representative method for the synthesis of these compounds. Although the use of asymmetric nucleophilic additions to cyclic α-keto amides (e.g., isatins) to synthesize optically active 3,3-disubstituted 2-oxindoles is frequently reported,[2] reports on reactions involving acyclic α-keto amides are relatively scarce.[3–5] Also, most reports involve asymmetric polyfunctionalization and the nucleophilic addition of keto groups to yield endo- or exocyclic optically active amides.[3,4] To the best of our knowledge, there are only two reports of asymmetric and chemoselectively nucleophilic addition to the keto group of acyclic α-keto amides to synthesize acyclic α,α-disubstituted α-hydroxy amides.[5] In 2015, Feng and co-workers reported a magnesium-catalyzed asymmetric carbonyl–ene reaction of β,γ-unsaturated α-keto amides with 5-methyleneoxazoline [Scheme 1(a)].[5a] However, this reaction exhibits shortcomings in terms of its efficacy and substrate scope. In 2011, Xu and Wolf reported a copper-catalyzed asymmetric Henry reaction of various α-keto amides with nitromethane to prepare 2-substituted 2-hydroxy-3-nitropropanamides with high yields and enantioselectivities [Scheme 1(b)].[5b]

Although these two reported metal-catalyzed asymmetric reactions are excellent synthetic methods, no organocatalyzed asymmetric and chemoselective nucleophilic addition to the keto group of acyclic α-keto amides to construct acyclic α,α-disubstituted α-hydroxy amides has been reported. Furthermore, the asymmetric addition of simple ketones such as acetone, which have lower nucleophilicities than nitromethane (that is, the asymmetric aldol reaction of α-keto amides with simple ketones) is still difficult. Therefore, the organocatalyzed asymmetric aldol reac-



Scheme 1 Catalytic asymmetric reactions to synthesis acyclic α,α-disubstituted α-hydroxy amides: (a) Feng and co-workers, (b) Wolf and co-workers

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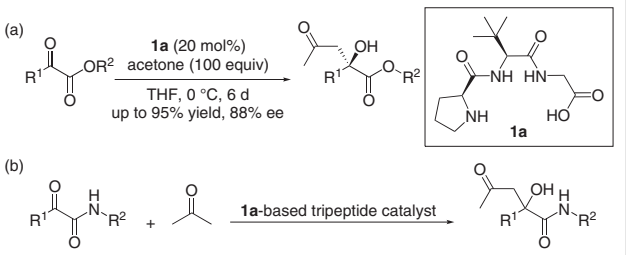
tion of α-keto amides with simple ketones as nucleophiles continues to be necessary and challenging.

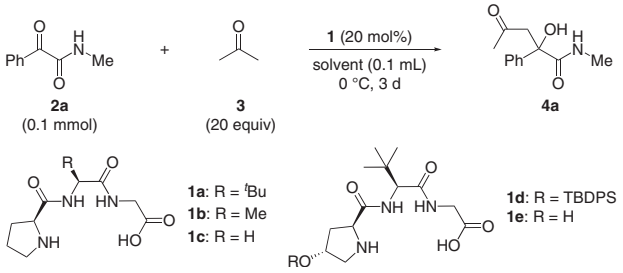
We recently reported a tripeptide-catalyzed asymmetric aldol reaction of activated ketones with acetone to produce optically active tertiary alcohols.[6] In particular, H-Pro-Tle-Gly-OH (**1a**) was an efficient catalyst for the reaction of α-keto esters, which exhibit an analogous acyclic 1,2-dicarbonyl structure to α-keto amides [Scheme 2(a)].[6c] During the course of our studies on the tripeptide-catalyzed asymmetric aldol reactions of activated ketones, we expanded the application of the tripeptide catalysts to the reaction of α-keto amides [Scheme 2(b)]. Here, we report an organocatalyzed asymmetric aldol reaction of α-keto amides with acetone in the presence of a tripeptide catalyst to synthesize acyclic α,α-disubstituted α-hydroxy amides.



Scheme 2 (a) Our previous work: tripeptide-catalyzed direct asymmetric aldol reaction of α-keto esters. (b) This work: organocatalytic asymmetric aldol reaction of α-keto amides with acetone in the presence of a tripeptide catalyst to synthesize acyclic α,α-disubstituted α-hydroxy amides.

At the outset, we investigated the reaction conditions for the asymmetric aldol reaction of *N*-methyl-2-oxo-2-phenylacetamide (**2a**) with acetone (**3**) catalyzed by tripeptide **1a** (Table 1, entries 1–11). The **1a**-catalyzed reaction in MeOH at 0 °C gave the corresponding α-hydroxy amide **4a** in quantitative yield and 65% ee (entry 1). When an aprotic solvent such as DMF, $CHCl_3$, THF, or toluene was used, the reaction rate and enantioselectivity declined compared with the reaction in MeOH (entries 2–5). In contrast, with H_2O as the reaction medium, although the enantioselectivity improved, the reaction rate decreased (entry 6). Furthermore, the reaction rates and enantioselectivities of the reaction in EtOH and *i*-PrOH were lower than those of the reaction in MeOH (entries 7 and 8). Additionally, the enantioselectivity was considerably improved when the reaction was conducted in MeOH at –40 °C compared with that in MeOH at 0 °C (entry 9). However, the reaction at –70 °C yielded only a small amount of **4a** (entry 10). The reaction hardly progressed in the presence of trifluoroacetic acid (entry 11). On the basis of these investigation (entries 1–11), we chose the reaction between **2a** and acetone (**3**; 20 equiv) in MeOH at –40 °C for five days as the best reaction conditions (entry 9).

Table 1 Optimization of the Reaction Conditions and Catalyst



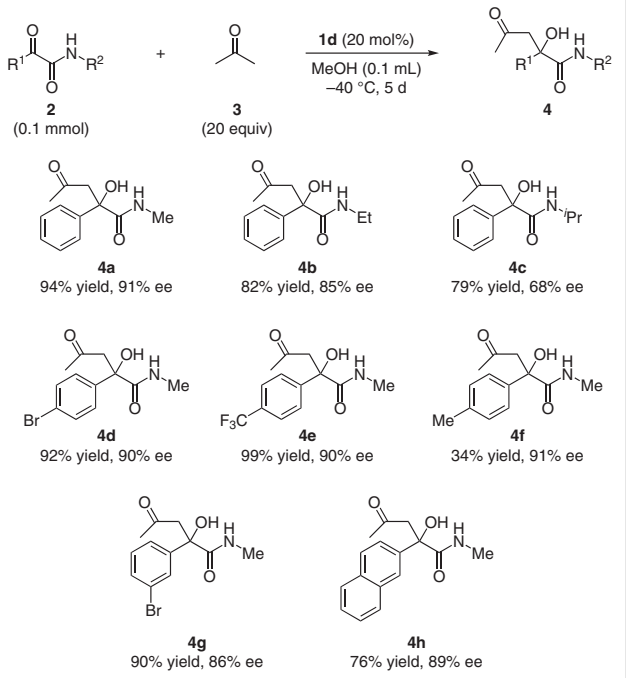
Entry	Catalyst	Solvent	Yield (%)[a]	ee[b] (%)
1	**1a**	MeOH	>99	65
2	**1a**	DMF	16	25
3	**1a**	$CHCl_3$	11	38
4	**1a**	THF	19	29
5	**1a**	toluene	–	–
6	**1a**	H_2O	46	78
7	**1a**	EtOH	70	43
8	**1a**	*i*-PrOH	54	32
9[c,d]	**1a**	MeOH	94	87
10[c,e]	**1a**	MeOH	6	89
11[c,d,f]	**1a**	MeOH	–	–
12[c,d]	**1b**	MeOH	10	78
13[c,d]	**1c**	MeOH	55	31
14[c,d]	**1d**	MeOH	94 (94)[g]	91
15[c,d]	**1e**	MeOH	6	78

[a] Determined by ^{1}H NMR analysis with 1,1,2,2-tetrachloroethane as internal standard.
[b] Determined by HPLC analysis.
[c] For 5 days.
[d] At –40 °C.
[e] At –70 °C.
[f] In the presence of trifluoroacetic acid (20 mol%).
[g] Isolated yield after silica gel column chromatography.

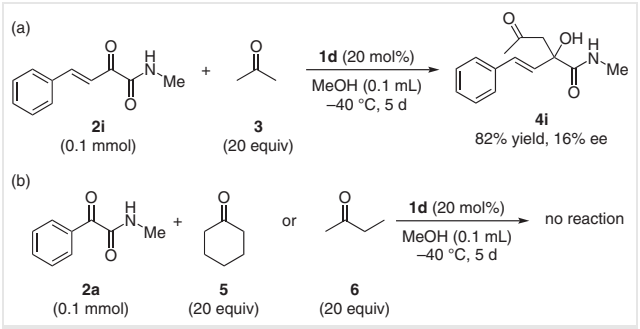
Next, we investigated the efficacy of catalysts for the reaction between **2a** and acetone (**3**) under the optimized reaction conditions (Table 1, 12–15). Catalysts **1b** and **1c**, in which the *tert*-butyl group of **1a** was replaced by a Me group and a H atom, respectively, were used as catalysts, revealing the effect of the *tert*-butyl group of **1a** in the **1a**-catalyzed reaction (entries 12 and 13). **1b**- and **1c**-catalyzed reactions produced **4a** with lower yields and enantioselectivities than did the **1a**-catalyzed reaction. These results indicate that the *tert*-butyl group of **1a** plays an important role in the reaction rate and enantioselectivity. Furthermore, the reaction catalyzed by the 4-*trans*-siloxyproline-based catalyst **1d** progressed with a similar reaction rate and a higher enantioselectivity compared with the **1a**-catalyzed reaction (entry 14). However, the rate and enantioselectivity of reaction with the 4-*trans*-hydroxyproline-based catalyst **1e** were considerably lower (entry 15). Therefore,

4-*trans*-siloxyproline-based tripeptide **1d** was found to be the best catalyst for this reaction, and the **1d**-catalyzed reaction under the optimized reaction conditions afforded **4a** with a 94% yield and a 91% ee (entry 14).

The substrate scope of this reaction under the optimized reaction conditions was then studied (Scheme 3). α-Keto amides **2a–c** with various alkyl groups on the secondary amide nitrogen were subjected to the reaction. The *N*-methyl amide **2a** reacted with acetone (**3**) to give the corresponding α-hydroxy amide **4a** with high chemical yield and high enantioselectivity. The reactions of the *N*-ethyl amide **2b** and of the *N*-isopropyl amide **2c** similarly gave products **4b** and **4c**, respectively, in good chemical yields and high enantioselectivities. Further, α-keto amides with sterically more compact alkyl groups on the secondary amide group provided the corresponding α-hydroxy amides **4a–c** with higher chemical yields and enantioselectivities. *N*,*N*-Dimethyl-2-oxo-2-phenylacetamide did not react with acetone (**3**). The effects of the addition of electron-withdrawing and -donating groups at the 4-position of the phenyl group in **2a** were then investigated. The reaction of **2d** with a bromo group as a weakly electron-withdrawing group produced **4d** with a high chemical yield and enantioselectivity. Similarly, amide **2e**, which contained a trifluoromethyl group instead of the bromo group in **2d**, reacted smoothly and stereoselectively with **3**. The reaction of **2f** with an electron-donating methyl group afforded **4f** with a high enantioselectivity and medium chemical yield. Furthermore, the aldol reaction of **2g**, which had a bromo group at the 3-position of the phenyl group, afforded **4g**. The reaction of *N*-methyl-2-(2-naphthyl)-2-oxoacetamide (**2h**) was highly stereoselective, producing **4h**. Thus, the **1d**-catalyzed reactions of various α-keto amides **2a–h** afforded the corresponding α-hydroxy amides **4a–h** with high enantioselectivities.



Scheme 3 Substrate scope. Isolated yields are reported; the ee was determined by HPLC analysis.



Scheme 4 Failed reactions: (a) the reaction of β,γ-unsaturated α-keto amides **2i** and **3**; (b) the reactions of **2a** with cyclohexanone (**5**) or butan-2-one (**6**)

Next, the reaction between the β,γ-unsaturated α-keto amide **2i** and acetone (**3**) was examined [Scheme 4(a)]. Although this reaction progressed smoothly, the enantioselectivity of this reaction was lower than that of the reaction of **2a**. We believe that the reason for the lower enantioselectivity of the former reaction compared with the latter is related to the difference in the steric environment of the styryl group in **2i** and the phenyl group in **2a**. Next, cyclohexanone (**5**) and butan-2-one (**6**) were used as nucleophiles [Scheme 4(b)]; however, these reactions did not afford corresponding aldol adducts, probably, because of the bulkiness of **5** and **6**.

The catalytic cycle of this reaction was assumed to be similar to that of the proline-catalyzed asymmetric aldol reaction (Figure 1).[7] Therefore, acetone (**3**) is activated by enamine formation through reaction with the amino group of **1d**. The C–C bond is then formed by nucleophilic addition of the enamine to **2**, generating the iminium–aldol intermediate. Finally, the aldol adduct is formed by hydrolysis of the

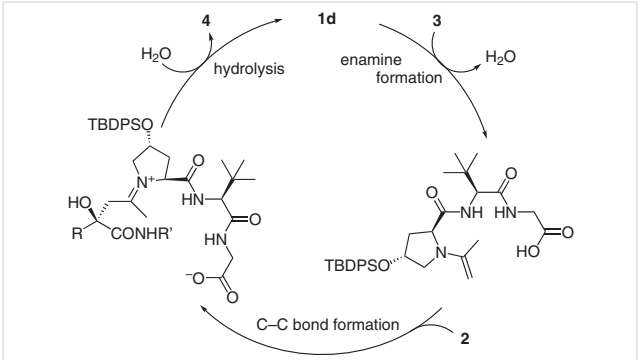


Figure 1 A plausible catalytic cycle

iminium cation. In this reaction, the absolute configuration of the aldol adduct **4** is determined at the C–C bond-formation step.

In conclusion, we have developed an organocatalyzed asymmetric aldol reaction of α-keto amides with acetone in the presence of a tripeptide catalyst. The desired α,α-disubstituted α-hydroxy amides were obtained in up to 99% yield and 91% ee. Further studies pertaining to the expansion of the substrate scope, the determination of the absolute configuration of the aldol adduct, and the investigation of the origin of enantioselectivity are currently underway in our group.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-1380-6436.

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(8) **Aldol Products 4a–h; General Procedure**

A mixture of **1d** (20 μmol, 10.7 mg), MeOH (0.1 mL), and acetone (**3**; 2 mmol, 0.15 mL) was stirred at –40 °C for 10 min. The appropriate α-keto amide **2** (0.1 mmol) was added, and the mixture was stirred at –40 °C for 5 d then concentrated under reduced pressure. The aldol product was purified by column chromatography (silica gel, hexane–EtOAc). The enantiomeric excess of the aldol adduct was determined by chiral HPLC.

2-Hydroxy-*N*-methyl-4-oxo-2-phenylpentanamide (4a)

White solid, 20.8 mg (94%, 91% ee); mp 71–73 °C; $[\alpha]_D^{23}$ +169.4 (*c* = 0.13, $CHCl_3$). HPLC [Daicel CHIRALPAK AD-H, hexane–*i*-PrOH (90:10), 1.0 mL/min, 254 nm, 35 °C]: t_R (minor) = 10.9 min; t_R (major) = 12.3 min. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.59–7.57 (m, 2 H), 7.37–7.32 (m, 2 H), 7.28 (tt, *J* = 7.3, 1.5 Hz, 1 H), 6.78 (br s, 1 H), 5.34 (s, 1 H), 3.67 (d, *J* = 17.6 Hz, 1 H), 2.79 (d, *J* = 17.6 Hz, 1 H), 2.76 (d, *J* = 5.0 Hz, 3 H), 2.24 (s, 3 H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 212.2, 174.1, 141.3, 128.4, 127.8, 124.4, 78.2, 50.8, 31.3, 26.1. HRMS (EI): *m/z* [M$^+$] calcd for $C_{12}H_{15}NO_3$: 221.1052; found: 221.1029.