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Direct asymmetric aldol reaction of hydroxyacetone promoted by chiral tertiary amines

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ABSTRACT

The tertiary amine-catalyzed direct asymmetric aldol reaction of hydroxyacetone with a variety of aromatic aldehydes is developed. Using 5–10 mol % of quinidine as catalyst, the direct aldol condensation products were obtained in reasonable yields and with asymmetric induction (up to 47% ee). The present approach is extended to asymmetric organocatalytic strategies for the preparation of 1,2-diols.

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Since the first reports of the proline-catalyzed direct asymmetric aldol reaction,[1] numerous organocatalysts have been designed which improved the catalyst reactivity, the enantioselectivity, and substrate scope.[2] Despite these important advances, some limitations still exist. The organocatalytic direct aldol reaction which generates polyoxygenated compounds from hydroxyacetone has been the subject of increasing research and is still regarded as an interesting synthetic challenge.

Hydroxyacetone and dihydroxyacetone-based aldol reactions are of considerable importance because they provide expedient access to both natural carbohydrates and unnatural polyhydroxylated molecules of significance in medicine.[3] For a long time, the direct catalytic asymmetric aldol reaction of α-hydroxylated ketones with aldehydes had only been achieved with protein-catalysts such as aldolases and catalytic antibodies.[4] Since 2000, several reports have addressed the aldol addition using both organometallic and proline catalysis.[5] Of the diastereo- and enantioselective direct aldol reactions, *anti*-selective variants have been available using proline.[5c] Recently, a number of *syn*-selective direct asymmetric aldol additions catalyzed by secondary[6] and primary[7] amines have been reported, but which are limited to protected hydroxy- and dihydroxyacetones.

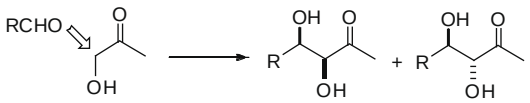
The development of stereoselective organocatalysts for direct aldol reactions with unprotected hydroxyketones[8] still remains an important goal because of enantio- and chemoselectivity issues.[9]

Although chiral primary and secondary amines have been explored in asymmetric organocatalysis, tertiary amines are mostly overlooked for the direct asymmetric aldol reaction. This is certainly because of mechanistic considerations where iminium ions[10] or enamines[11] are likely to be active intermediates in the catalytic cycle. Only primary or secondary amines can act as efficient promoters for such processes. In general, the direct asymmetric tertiary amine-catalyzed intermolecular aldol addition of aldehydes to ketones is unknown.[12] In this Letter, we report the effectiveness of a tertiary amine-based organocatalyst for the asymmetric aldol reaction of unprotected hydroxyacetone with aldehydes (Scheme 1).

The direct aldol reaction of hydroxyacetone with benzaldehyde was selected as a model for catalyst screening and evaluation. A series of chiral tertiary amine catalysts (Scheme 2) were tested in the reaction and the results are listed in Table 1. Aldol adduct **7** was produced by all the tertiary amines tested when solvent-free conditions were employed (Table 1, entries 1–3).

The reaction of the aldehydes was observed only at the hydroxylated carbon atom, leaving the methyl ketone untouched. Moreover, diol **7** was isolated with good degrees of *syn*-selectivity. Disappointingly, the ee was only 14%, when 5 mol % of quinidine was used as the catalyst. The solvent had a strong effect; after DCM addition, the ee increased to 28% (entry 4). Further dilution with the same solvent saw a drop in conversion and consequently in yield, but an increase in ee to 47% (entry 5). Higher catalyst loading resulted in a significant increase in yield albeit with a loss in ee (entries 6 and 9). The reaction was very slow at 0 °C (14% yield after 20 h, entry 10). The use of other solvents as well as various additives was not advantageous. Thus, the conditions of entry 6 were adopted for further reactions as a compromise between yield and ee.

From the tertiary amines tested, quinine and quinidine showed the best catalytic activity leading to opposite enantiomers of aldol **7**.



Scheme 1. Direct asymmetric aldol reaction of hydroxyacetone.

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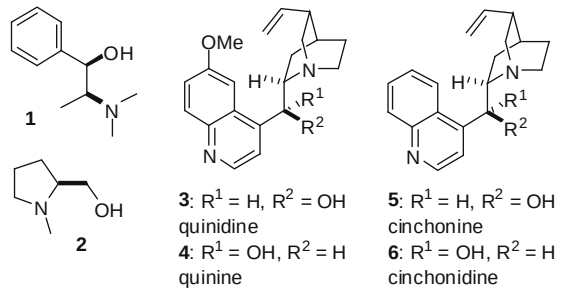
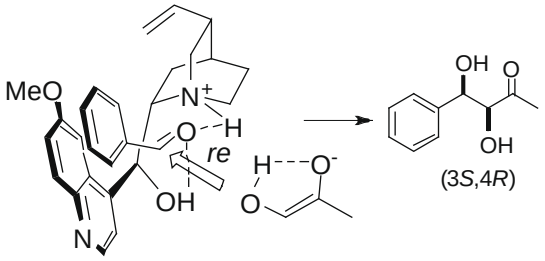


Scheme 2. Tertiary amine organocatalysts examined in this study.



Scheme 3. Proposed structure of the substrate-quinidine complex.

We speculate that the deprotonation of hydroxyacetone is induced by the nitrogen atom of the catalyst, and the resulting *Z*-enolate might be stabilized through hydrogen bonding. The aldehyde is also activated by the catalyst. The carbonyl group is coordinated by the hydrogen-bonding network through the protonated nitrogen atom. The hydroxy group can fix efficiently this structure via additional hydrogen bonding. Thus quinidine activates both the ketone donor via deprotonation and the aldehyde through efficient formation of the hydrogen bonds. The *si* face of the coordinated aldehyde carbonyl is shielded by the catalyst, allowing nucleophilic attack of hydroxyacetone predominantly from the *re* face.

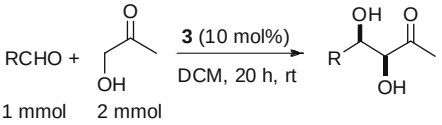
The stereochemistry of the resulting aldol depends on the configuration of the alkaloid hydroxy group. The use of quinidine led to formation of the aldol **7** with the favored (3*S*,4*R*) configuration. By employing suitable pseudoenantiomeric quinine as the catalyst, the aldol product with (3*R*,4*S*) configuration was formed predominantly (Scheme 3).

Formation of hydrogen bonds in the active site is crucial for activation of the substrate and for the observed levels of asymmetric induction. This mechanism is supported by the observation of the inactivity of the catalyst when the hydroxy group is protected (**4**, R^2 = OAc or OTBS). Commercial $(DHQD)_2PHAL$ was also uncreative in this study.

The optimized protocol was then expanded to a wide variety of aldehydes. The results indicated that the reaction is highly dependent on the electronic nature of the aldehyde. Activated chloro- and nitro-substituted aldehydes underwent the aldol reaction smoothly with hydroxyacetone in good to excellent yields (Table 2). Unsubstituted benzaldehyde was less reactive and afforded only moderate yields (Table 1). Unsaturated cinnamaldehyde and an aliphatic substrate were less reactive but more selective substrates (Table 2, 44% and 40% ee, respectively, entries 5 and 6).

In summary, we have developed an organocatalytic asymmetric direct aldol-type reaction of hydroxyacetone promoted by quinidine alkaloids. To the best of our knowledge, this is the first example of an asymmetric aldol reaction of hydroxyacetone with an achiral aldehyde promoted by tertiary amine.[14] Although the stereoselectivity remains to be improved further, the presented

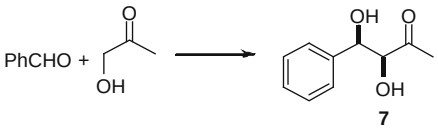
Table 2
Direct asymmetric aldol reaction of hydroxyacetone with various aldehydes catalyzed by quinidine



Entry	Aldehyde (R)	Yield[a] (%)	Ratio *syn*/*anti*	ee *syn*%
1	2-Cl–C_6H_4–	96	50/50	23
2	2-NO_2–C_6H_4–	61	68/32	25
3	4-Cl–C_6H_4–	51	72/28	32 (3*S*,4*R*)[b]
4	4-NO_2–C_6H_4–	62	77/23	34
5	C_6H_4–CH=CH–	22	78/22	44
6	C_6H_4–CH_2–CH_2–	11	90/10	40

[a] Isolated yield.
[b] Determined by HPLC according to literature data, see Ref. 7a.

Table 1
Direct asymmetric aldol reaction of hydroxyacetone with benzaldehyde catalyzed by tertiary amines



Entry	Calalyst	Conditions	Yield[a] (%)	Ratio *syn*:*anti*	ee *syn*[b] (%)
1	**1** (5 mol %)	PhCHO (1 mmol), hydroxyacetone (2 mmol), neat, rt, 20 h	75	69/31	12 (3*R*,4*S*)
2	**2** (5 mol %)	PhCHO (1 mmol), hydroxyacetone (2 mmol), neat, rt, 20 h	92	73/27	Racemic
3	**3** (5 mol %)	PhCHO (1 mmol), hydroxyacetone (2 mmol), neat, rt, 20 h	65	72/28	14 (3*S*,4*R*)
4	**3** (5 mol %)	PhCHO (1 mmol), hydroxyacetone (2 mmol), CH_2Cl_2 (0.3 mL), rt, 20 h	36	76/24	28 (3*S*,4*R*)
5	**3** (5 mol %)	PhCHO (1 mmol), hydroxyacetone (2 mmol), CH_2Cl_2 (1 mL), rt, 20 h	12	74/26	47 (3*S*,4*R*)
6	***3** (10 mol %)*	*PhCHO (1 mmol), hydroxyacetone (2 mmol), CH_2Cl_2 (1 mL), rt, 20 h*	*46*[13]	*79/21*	*36 (3S,4R)*
7	**4** (10 mol%)	PhCHO (1 mmol), hydroxyacetone (2 mmol), CH_2Cl_2 (1 mL), rt, 20 h	28	76/24	37 (3*R*,4*S*)
8	**3** (10 mol %)	PhCHO (1 mmol), hydroxyacetone (2 mmol), CH_2Cl_2 (1 mL), rt, 48 h	54	77/23	26 (3*S*,4*R*)
9	**3** (20 mol %)	PhCHO (1 mmol), hydroxyacetone (2 mmol), CH_2Cl_2 (1 mL), rt, 20 h	52	75/25	25 (3*S*,4*R*)
10	**3** (10 mol %)	PhCHO (1 mmol), hydroxyacetone (2 mmol), CH_2Cl_2 (1 mL), 0 °C, 20 h	14	82/18	42 (3*S*,4*R*)
11	**5** (10 mol %)	PhCHO (1 mmol), hydroxyacetone (2 mmol), CH_2Cl_2 (1 mL), rt, 20 h	19	75/25	31 (3*S*,4*R*)
12	**6** (10 mol %)	PhCHO (1 mmol), hydroxyacetone (2 mmol), CH_2Cl_2 (1 mL), rt, 20 h	35	76/24	31 (3*R*,4*S*)
13	**3** (10 mol %)	PhCHO (2 mmol), hydroxyacetone (1 mmol), CH_2Cl_2 (1 mL), rt, 20 h	17	80/20	37 (3*S*,4*R*)
14	**4** (10 mol %)	PhCHO (1 mmol), hydroxyacetone (2 mmol), DME (1 mL), rt, 20 h	10	77/23	42 (3*R*,4*S*)

[a] Isolated yield.
[b] Determined by HPLC according to literature data, see Ref. 7a.

work provides a useful concept for the design of novel chiral organocatalysts.

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13. *Catalytic asymmetric aldol reaction of hydroxyacetone with benzaldehyde*: To a solution of DCM (1 mL) and quinidine (32.4 mg, 0.1 mmol), benzaldehyde (102 μL, 1.0 mmol) was added followed by hydroxyacetone (137 μL, 2.0 mmol) and the resulting mixture was stirred at room temperature for 20 h. The reaction mixture was than diluted with ethyl acetate and washed twice with water and brine. The organic layer was dried with anhydrous Na_2SO_4 and evaporated. The pure aldol product (*syn*/*anti* mixture) was obtained by flash chromatography on a silica gel column (hexanes/ethyl acetate, 3:2) in 46% yield as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.36 (m, 5H, Ph), 4.95 (dd, 1H, J = 3.0, 6,0 Hz, H-3), 4.41 (m, 0.2H, H-4, *anti*); 4.31 (dd, 0.8H, J = 3.4, 4.8 Hz, H-4, *syn*), 3.77 (d, 1H, J = 5.2 Hz, OH), 3.33 (d, 0.2H, J = 3.8 Hz, OH), 3.17 (d, 0.8H, J = 6.8 Hz, OH), 2.18 (s, 2.4H, H-1, *syn*), 1.91 (s, 0.6H, H-1, *anti*); ^{13}C NMR (50 MHz, $CDCl_3$): δ 26.3 (*syn*), 27.6 (*anti*), 74.0 (*syn*), 74.9 (*anti*), 80.6 (*syn*), 81.0 (*anti*), 126.1, 126.2, 128.2, 138.8, 128.6, 207.7; HPLC: Chiralpak AD-H, hexane/*i*-PrOH (9:1), flow rate = 1 mL/min (λ = 220 nm) *syn*: t_1 = 13.8 (major), t_2 = 18.9, *anti*: t = 12.6 (unseparated enantiomers).
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