Highly enantioselective direct aldol reaction catalyzed by cinchona derived primary amines†

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Highly enantioselective aldol reactions of aldehydes with cyclic ketones catalyzed by a primary amine derived from cinchonine are reported. Aromatic aldehydes reacted with various cyclic ketones cleanly to afford the *anti*-aldol adducts in up to 99% yield, with good diastereoselectivities (up to 9 : 1) and excellent enantioselectivities (up to 99% ee).

Since the pioneering work of List *et al.*[1] with enantioselective aldol reactions in the presence of proline as catalyst, organocatalysts have demonstrated their significant importance in asymmetric C–C or heteroatom–C bond formation. In both types of transformations, the amino acid proline has been widely employed as a versatile organocatalyst.[2] Despite the high efficiency shown in a series of reactions, proline suffers from serious problems such as poor solubility in organic solvents, a tendency to react with electron-deficient aromatic aldehydes to form iminium salts that decarboxylate even at room temperature,[3] and difficulties in modulating its reactivity through structure modification. To solve these problems, Maruoka and coworkers reported a novel organocatalyst derived from optically pure binaphthol.[4] Another alternative was the transformation of proline to its prolinamide derivatives.[5] Recently, Chen's group developed a simple primary–tertiary diamine-Brønsted acid catalyst that has been successfully applied in direct aldol reactions.[6] The catalytic system is highly efficient for both linear and cyclic aliphatic ketones.

Cinchona derivatives have been versatile catalysts in many organic transformations due to their excellent performance. Cinchona derived amines such as **1** and **2** can also be readily prepared from a known protocol.[7] These amines have been employed as efficient organocatalysts in enantioselective Michael reactions in high yields and enantioselectivities *via* enamine or iminium intermediates. For example, Chen developed a highly efficient enantioselective Michael addition of α,α-dicyanoalkene[8] as well as 1,3-dicarbonyl compounds[9] to α,β-unsaturated ketones using cinchonine derived amines as the organocatalyst. Connon and McCooey developed a highly enantioselective addition of aldehydes and ketones to nitroolefins catalyzed by readily accessible alkaloid derivatives.[10] Very recently, Melchiorre *et al.* reported an organocatalytic asymmetric Friedel–Crafts alkylation of indoles with α,β-unsaturated ketones by the successful application of an iminium ion activation strategy toward enones using the salt formed with this amine and *N*-protected phenyl glycine.[11] The asymmetric aldol reaction presents the most versatile protocols for the preparation of optically enriched β-hydroxyl ketones. To our knowledge, although Barbas *et al.* firstly employed the amine in the direct aldol reaction,[12] there is no report of asymmetric aldol reactions catalyzed by cinchonine derived amines. To probe the potential application of cinchona derived amines in direct aldol reactions, we initiated an enantioselective aldol reaction between aldehydes and cyclic ketones. Herein, we disclose our preliminary results toward this work.

We were pleased to find that 9-amino-9-deoxy-epi-cinchonine **1** (Fig. 1, 10 mol%) exhibited high catalytic activity for the asymmetric aldol reaction of 4-nitrobenzaldehyde with cyclohexanone at room temperature. The corresponding adduct was cleanly isolated in 74% yield with a promising 87% ee after 39 h and the *anti*-isomer was favorably formed with 1.6 : 1 dr (entry 1, Table 1). The enantioselectivity increased to 95% ee when the reaction was conducted in the presence of TFA (10 mol%), and **1** (10 mol%) with dr 6.9 : 1 (entry 2, Table 1). The employment of triflic acid (10 mol%) further enhanced the enantioselectivity and reactivity. The amount of triflic acid used considerably affected the reactivity of the catalyst. Fifteen mol% of acid in combination with 10 mol% of catalyst was suitable for the reaction in terms of enantioselectivity, diastereoselectivity and reactivity (99% ee, 9 h, entry 5, Table 1). To our surprise, the reaction was very slow when 20 mol% of triflic acid was used (15 h, 77% yield, entry 6). Although 9-amino-9-deoxy-epi-cinchonidine (**2**) gave 94% of ee, the adduct with the opposite configuration was obtained (entry 8).

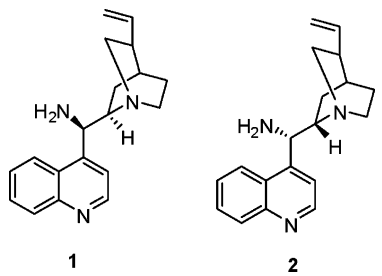

Fig. 1 Structure of amines derived from cinchona.

We next investigated the effect of solvent on the reaction, with screening results summarized in Table 2. All the solvents tested gave almost the same enantioselectivities. Good yields were obtained in THF, toluene, and water with different reaction times of 4 to 23 h and dr ranging from 4.8–9.8 : 1. The reaction was apparently retarded by DMSO and DMF with yields of only ~70% after a long reaction time (44–45 h). Water had a significant impact on reaction speed, but a deleterious effect on diastereoselectivity. From these results, solvent had little effect

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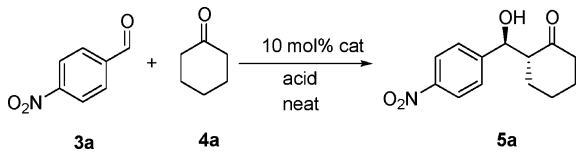
Table 1 Reactions between 4-nitrobenzaldehyde and cyclohexanone

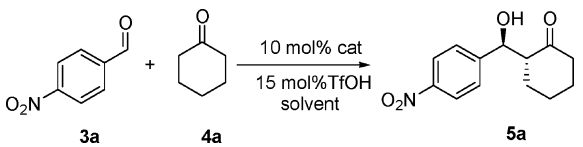


3a 4a 5a

Entry	Acid (%)	Yield (%)	ee (%)	dr
1[a]	—	74	87	1.6 : 1
2	TFA (10)	55	95	6.9 : 1
3	TfOH (5)	99	98	6.3 : 1
4	TfOH (10)	97	98	9.4 : 1
5	TfOH (15)	99	99	9.2 : 1
6	TfOH (20)	77	98	8.9 : 1
7[b]	TfOH (7.5)	81	98	7.8 : 1
8[c]	TfOH (15)	76	−94	9.9 : 1

[a] Unless otherwise stated, the reaction was carried out with 0.25 mmol of 4-nitrobenzaldehyde and 0.5 mL (4.8 mmol) of cyclohexanone, the enantioselectivity was measured using chiral AD-H, dr was measured according to ^{1}H NMR of crude product. [b] In the presence of 5 mol% of catalyst **1**. [c] Catalyst **2** used instead.

Table 2 Effect of solvent on the reaction



3a 4a 5a

Entry	Solvent	Time/h	Yield (%)[a]	ee (%)[b]	dr[c]
1	Neat	9	99	99	9.2 : 1
2[d]	THF	17	98	99	9.8 : 1
3[d]	DMSO	45	77	97	3.5 : 1
4[d]	DMF	44	74	97	5.0 : 1
5[d]	Toluene	23	94	98	8.6 : 1
6[d]	H_2O	4	97	97	4.8 : 1
7[d]	$CHCl_3$	22	84	98	7.0 : 1
8[d]	EtOH	20	79	98	6.6 : 1
9[d]	CH_2Cl_2	12	82	98	7.5 : 1
10[d]	Et_2O	19	98	98	8.1 : 1
11[e]	DMF-H_2O	24	94	97	4.1 : 1
12[f]	Neat	38	90	98	5.0 : 1
13[g]	Neat	96	11	91	2.4 : 1
14[h]	Neat	23	81	98	7.8 : 1

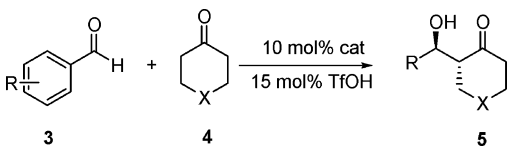
[a] Isolated yield. [b] Determined by chiral AD-H. [c] Determined by ^{1}H NMR. [d] The reaction was carried out with 0.25 mmol of aldehyde, 0.5 mL of cyclohexanone and 1 mL of solvent. [e] Volume ratio 1 : 1. [f] The reaction was carried out at 0 °C. [g] The reaction carried out at −16 °C. [h] 5 mol% of catalyst **1** was used.

on enantioselectivity but greatly affected the reaction time and dr. Neat cyclohexanone was suitable as both reactant as well as solvent in terms of enantioselectivity and catalyst reactivity.

Although the enantioselectivities were excellent in all cases, the diastereomeric ratio was only about 90 : 10. To further improve the diastereoselectivity, we investigated the effect of temperature on the reaction. To our disappointment, the reaction proceeded very slowly under low temperature with decreased diastereoselectivity. For example, the reaction carried out at −16 °C for 96 h afforded only 11% yield (91% ee, 2.4 : 1 dr, entry 13). At higher temperature, the ee dropped significantly (40 °C, 92% ee, 2.0 : 1 dr *vs.* 60 °C, 86% ee, 1.7 : 1 dr. See ESI†) It is noteworthy that only 5 mol% of amine **1** can catalyze the reaction affording the product in 81% yield and 98% ee, although the reaction was not as fast (entry 13). Thus, 10 mol% of catalyst in combination with 15 mol% triflic acid, cyclohexanone as solvent, and room temperature were chosen for the optimal conditions.

The optimized protocol was then expanded to a wide variety of aldehydes and cyclic ketones (Table 3‡). The results of these trials indicated that the reaction is dramatically dependent on the electronic effect of the substituent. For example, 4-, 3-, 2-nitrobenzaldehyde and 4-trifluoro-methylbenzaldehyde underwent aldol reaction smoothly with cyclohexanone in good to excellent yields (74–99%) and excellent enantioselectivities (97–99% ee, entries 1, 5, 6 and 9, Table 3). Unsubstituted aromatic aldehydes were less reactive, because benzaldehyde, furyl-aldehyde, and 1-naphthylaldehyde afforded only low to moderate yields, but very good enantioselectivities (entries 11–13). The substrates with electron donating groups at the aromatic ring were not suitable for the reaction. For example, 4-methoxy-benzaldehyde reacted with cyclohexanone for 48 h yielding the corresponding product in only 19% yield and 89% ee (entry 15, Table 3). Cyclopentanone was also employed in the aldol reaction which showed less desired enantioselectivity compared to cyclohexanone in our catalytic system. 4- and 2-nitrobenzaldehyde afforded the corresponding product in 86% and 84% ee respectively (entries 2 and 7). In almost all cases, the diastereoselectivity is not high, with the structures of both aldehydes and ketones having significant impact on the dr value. The highest diastereomeric ratio was observed when 4-nitrobenzaldehyde and cyclohexanone were combined (entry 1, Table 3). We also tested the catalytic system in the aldol

Table 3 Enantioselective direct aldol reaction of aldehydes and cyclic ketones



3 4 5

Entry	R	X	Yield (%)	ee (%) *anti–syn*	dr
1	4-$NO_2C_6H_4$	CH_2	99	99 : 65	9.2 : 1
2	4-$NO_2C_6H_4$	—[a]	70	86 : 67	5.0 : 1
3	4-$NO_2C_6H_4$	O[c]	92	91 : 78	5.4 : 1
4	4-$NO_2C_6H_4$	S[b]	38	94 : 57	3.0 : 1
5	3-$NO_2C_6H_4$	CH_2	74	97 : 25	3.2 : 1
6	2-$NO_2C_6H_4$	CH_2	98	97 : n.d.	7.5 : 1
7	2-$NO_2C_6H_4$	—[a]	99	84 : 63	2.4 : 1
8	2-$NO_2C_6H_4$	O[c]	44	87 : 71	3.2 : 1
9	4-$CF_3C_6H_4$	CH_2	99	98 : 58	2.3 : 1
10	4-FC_6H_4	CH_2	58	94 : 29	1.7 : 1
11	C_6H_5	CH_2	31	86 : 54	1.0 : 1
12	Fural	CH_2	39	63 : 94	1 : 2.5
13	1-Naphthyl	CH_2	55	93 : 16	4.9 : 1
14	4-Cl	CH_2	70	91 : 16	4.1 : 1
15	4-$CH_3OC_6H_4$	CH_2	19	89 : 14	3.7 : 1
16[d]	4-NO_2		25	56	—

[a] Cyclopentanone used. [b] 2 Equivalents of ketone used. [c] 5 Equivalents of ketone used. [d] Neat acetone used instead of cyclic ketone in the presence of 10 mol% of catalyst and 15 mol% of triflic acid.

reaction with acetone, but unfortunately, a 25% yield and 56% ee were obtained when neat acetone was applied under the optimal conditions.

In conclusion, an enantioselective direct aldol reaction of cyclic ketones with different aromatic aldehydes catalyzed by cinchona derived amines has been reported with high yields, good diastereoselectivity, and up to 99% ee. The aromatic aldehydes with electron withdrawing groups are suitable substrates for this reaction. This provides a practical and convenient method for the synthesis of optically enriched hydroxyl ketones.

Acknowledgements

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Notes and references

‡ General procedure for the aldol reaction: to a mixture of catalyst **1** (0.025 mmol) and TfOH (0.0375 mmol) was added cyclohexanone (1 mL), cyclopentanone (1 mL), tetrahydro-4*H*-puran-4-one (1.25 mmol) or tetrahydrothiopuran-4-one (0.50 mmol). The reaction mixture was stirred for 5 min in a closed system and then aldehyde (0.25 mmol) was added. The reaction mixture was stirred for 9–166 h (monitored by TLC). The reaction was quenched with saturated ammonium chloride solution (10 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organic layer was dried (Na_2SO_4 and concentrated *in vacuo*). The crude product was purified by flash column chromatography to give pure aldol adduct. Diastereoselectivity was determined by ^{1}H NMR analysis of the crude aldol product.

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