Solvent- and Catalyst-Free Direct Aldol Reactions†

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Aldol reaction between simple benzaldehydes and ketones successfully happened in solvent- and catalyst-free condition. The desired products were obtained in moderate yield at suitable temperature. Heat was assumed as the driving force for the reaction. This approach has obvious advantages to fully meet the requirement of the principles of green chemistry.

Keywords aldol reaction, aldehyde, ketone, green chemistry, solvent- and catalyst-free

Introduction

The formation of C—C bonds has been the main topic since the synthetic methods were employed to prepare natural products and pharmaceutical substances in organic chemistry.[1] The aldol reaction first discovered by Wurtz has been confirmed one of the most important reactions to create carbon-carbon bond.[2,3] Application of aldol reaction to synthesize polyoxygenated architectures from two carbonyl compounds has been extensively successful in pharmaceutical target production and material industry.[3] Compared with the reactions using enol or enolate derivatives as the substrate, the direct aldol reaction is more convenient and atom economic.[4] However, it still presents challenges. Most of the direct aldol reactions suffered from laborious stoichiometric processes.[1] In order to avoid these processes without changing the levels of the selectivity, catalytic methods were fully developed.[5] Catalysts such as enzymes, catalytic antibodies, small organic molecules and their derivatives have been widely used to perform the direct aldol reaction in recent years.[3] For example, bifunctional transition metal complexes have been well established to catalyze the direct aldol reaction of aldehydes with ketones, which can be compared mechanistically to the type II aldolases.[6] Proline-catalyzed intramolecular direct aldol reaction first discovered by Hajos and Eder in 1971 and then developed by List, Barbas and other chemists have taken great advantage of the enamine mechanism to obtain the desired products, which were analogous to the type I aldolases.[7,8] Even so, the excessive use of the reactants, the long reaction times and the high catalyst loading are also employed to complete the reaction.[9] This might be a serious drawback for the general application of the reaction.

Consideration of the principles of green chemistry, running reactions successfully in an environment friendly and atom economic way has become more and more important for modern organic synthesis.[10-12] In our previous work, we found that water was a suitable medium for the direct asymmetric aldol reaction of various cyclic ketones with aryl aldehydes catalyzed by a primary-tertiary diamine-Brösted acid.[13a] No organic solvents were needed for either the reaction or the extraction. These advantages are clear from the perspective of green chemistry. Aldol reactions conducted in solvent- or catalyst-free conditions are drawing more attentions because of their highly obvious advantages from the perspective of green chemistry.[11,12] Yuan recently reported an efficient catalyst-free aldol condensation of ketones with isatins in the presence of molecular sieves 4 Å using DMF as the solvent.[14] Numerous desired products were obtained in good to excellent yields. This green approach has the advantages such as catalyst free and mild reaction condition. However, the highly reactive β-carbonyl group existing in isatin derivatives seems very necessary to ensure the reaction highly efficient.

To the best of our knowledge, there are not any works about the aldol reaction of simple ketones with aldehydes under solvent- and catalyst-free condition. Although little attentions have been made on this issue by chemists, it is really very important in view of green chemical process. So it is very significant to explore the

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aldol reaction without the presence of other species. Herein, we report our results.

Experimental

Unless otherwise stated, ^{1}H NMR spectra were recorded on Bruker NMR spectrometers in CD_3COCD_3 at 300 MHz. All chemical shifts were reported relative to TMS as external standards. Benzaldehyde derivatives (**1a**—**1i**) were purified by column chromatography on silica gel before use. Benzaldehyde derivatives (**1j**, **1k**) and ketones (**2a**—**2g**) were purified by distillation before use.

Synthesis

Typical procedure for the aldol reaction of benzaldehyde derivatives (1a—1k) and ketones (2a—2g) in solvent- and catalyst-free condition In a 2 mL sealed tube, **1** (1 equiv.) and **2** (2 equiv.) were added under nitrogen atmosphere. The reaction mixture was then stirred at 100 ℃ for 40 h. After being cooled to room temperature, the crude products were purified by silica gel chromatography using ethyl acetate/petroleum ether (1∶4 to 1∶2, *V*∶*V*) as eluent to give the corresponding products **3**.[13]

2-(Hydroxy-(4-nitrophenyl)methyl)cyclohexanone (3a-*syn*)[13] Light yellow solid. ^{1}H NMR (CD_3COCD_3, 300 MHz) δ: 8.20 (d, J=8.8 Hz, 2H), 7.66 (d, J=8.8 Hz, 2H), 5.44 (t, J=3.8 Hz, 1H, C**H**OH), 4.35 (d, J=4.1 Hz, 1H, OH), 2.82—2.77 (m, 1H), 2.46—2.27 (m, 2H), 2.02—1.92 (m, 1H), 1.86—1.83 (m, 1H), 1.79—1.70 (m, 2H),1.67—1.56 (m, 2H).

2-(Hydroxy-(4-nitrophenyl)methyl)cyclohexanone (3a-*anti*)[13] Light yellow solid. ^{1}H NMR (CD_3COCD_3, 300 MHz) δ: 8.21 (d, J=8.8 Hz, 2H), 7.67 (d, J=8.8 Hz, 2H), 5.11 (dd, J=7.4, 3.9 Hz, 1H, C**H**OH), 4.54 (d, J=3.9 Hz, 1H, OH), 2.83—2.76 (m, 1H), 2.49—2.31 (m, 2H), 2.03—1.95 (m, 1H), 1.85—1.74 (m, 1H), 1.72—1.55 (m, 3H), 1.39—1.29 (m, 1H).

2-(Hydroxy-(2-nitrophenyl)methyl)cyclohexanone (3b-*syn*)[13] Light yellow solid. ^{1}H NMR (CD_3COCD_3, 300 MHz) δ: 7.96 (d, J=8.1 Hz, 1H), 7.89 (d, J=7.9 Hz, 1H), 7.73 (t, J=7.5 Hz, 1H), 7.51 (t, J=8.5 Hz, 1H), 5.91 (t, J=3.8 Hz, 1H, C**H**OH), 4.42 (d, J=4.6 Hz, 1H, OH), 2.79—2.72 (m, 1H), 2.45—2.27 (m, 2H), 1.88—1.74 (m, 4H), 1.65—1.59 (m, 2H).

2-(Hydroxy-(2-nitrophenyl)methyl)cyclohexanone (3b-*anti*)[13] Light yellow solid. ^{1}H NMR (CD_3COCD_3, 300 MHz) δ: 7.82 (d, J=7.9 Hz, 1H), 7.79 (d, J=7.4 Hz, 1H), 7.71 (t, J=7.5 Hz, 1H), 7.53 (t, J=8.2 Hz, 1H), 5.44 (dd, J=7.9, 4.5 Hz, 1H, C**H**OH), 4.55 (d, J=4.4 Hz, 1H, OH), 2.93—2.85 (m, 1H), 2.51—2.31 (m, 2H), 1.82—1.44 (m, 6H).

2-(Hydroxyl-(3-nitrophenyl)methyl)cyclohexanone (3c-*syn*)[13] Light yellow solid. ^{1}H NMR (CD_3COCD_3, 300 MHz) δ: 8.28 (s, 1H), 8.11 (d, J=7.9 Hz, 1H), 7.82 (d, J=7.7 Hz, 1H), 7.62 (t, J=8.0 Hz, 1H), 5.44 (t, J=3.8 Hz, 1H, C**H**OH), 4.39 (d, J=4.1 Hz, 1H, OH), 2.86—2.80 (m, 1H), 2.47—2.27 (m, 2H), 2.04—1.99 (m, 1H), 1.86—1.76 (m, 3H), 1.69—1.59 (m, 2H).

2-(Hydroxyl-(3-nitrophenyl)methyl)cyclohexanone (3c-*anti*)[13] Light yellow solid. ^{1}H NMR (CD_3COCD_3, 300 MHz) δ: 8.28 (s, 1H), 8.14 (d, J=8.2 Hz, 1H), 7.83 (d, J=7.9 Hz, 1H), 7.63 (t, J=7.9 Hz, 1H), 5.12 (dd, J=7.3, 4.1 Hz, 1H, C**H**OH), 4.55 (d, J=3.8 Hz, 1H, OH), 2.87—2.79 (m, 1H), 2.50—2.31 (m, 2H), 2.03—1.97 (m, 1H), 1.84—1.77 (m, 1H), 1.73—1.58 (m, 3H), 1.41—1.29 (m, 1H).

4-(Hydroxy-(2-oxocyclohexyl)methyl)benzonitrile (3d-*syn*)[13] Light yellow solid. ^{1}H NMR (CD_3COCD_3, 300 MHz) δ: 7.72 (d, J=8.5 Hz, 2H), 7.59 (d, J=8.2 Hz, 2H), 5.39 (t, J=3.8 Hz, 1H, C**H**OH), 4.25 (d, J=4.1 Hz, 1H, OH), 2.79—2.73 (m, 1H), 2.46—2.27 (m, 2H), 2.03—1.98 (m, 1H), 1.86—1.80 (m, 1H), 1.77—1.71 (m, 2H), 1.67—1.57 (m, 2H).

4-(Hydroxy-(2-oxocyclohexyl)methyl)benzonitrile (3d-*anti*)[13] Light yellow solid. ^{1}H NMR (CD_3COCD_3, 300 MHz) δ: 7.74 (d, J=8.2 Hz, 2H), 7.60 (d, J=8.5 Hz, 2H), 5.04 (dd, J=7.3, 4.1 Hz, 1H, C**H**OH), 4.45 (d, J=3.8 Hz, 1H, OH), 2.80—2.72 (m, 1H), 2.49—2.33 (m, 2H), 2.01—1.96 (m, 1H), 1.81—1.60 (m, 4H), 1.39—1.29 (m, 1H).

2-(Hydroxy-(4-(trifluoromethyl)phenyl)methyl)-cyclohexanone (3e-*syn*)[13] Light yellow solid. ^{1}H NMR (CD_3COCD_3, 300 MHz) δ: 7.65 (d, J=8.4 Hz, 2H), 7.59 (d, J=8.4 Hz, 2H), 5.40 (t, J=3.7 Hz, 1H, C**H**OH), 4.19 (d, J=4.1 Hz, 1H, OH), 2.80—2.73 (m, 1H), 2.46—2.27 (m, 2H), 2.03—2.00 (m, 1H), 1.86—1.56 (m, 5H); ^{19}F NMR (CD_3COCD_3, 282 MHz) δ: −63.18 (s, 3F).

2-(Hydroxy-(4-(trifluoromethyl)phenyl)methyl)-cyclohexanone (3e-*anti*)[13] Light yellow solid. ^{1}H NMR (CD_3COCD_3, 300 MHz) δ: 7.68 (d, J=8.1 Hz, 2H), 7.61 (d, J=8.1 Hz, 2H), 5.03 (dd, J=7.9, 3.8 Hz, 1H, C**H**OH), 4.41 (d, J=3.8 Hz, 1H, OH), 2.80—2.72 (m, 1H), 2.45—2.32 (m, 2H), 2.01—1.97 (m, 1H), 1.81—1.60 (m, 4H), 1.39—1.29 (m, 1H); ^{19}F NMR (CD_3COCD_3, 282 MHz) δ: −63.27 (s, 3F).

2-((4-Bromophenyl)(hydroxy)methyl)cyclohexanone (3f-*syn*)[13] Light yellow solid. ^{1}H NMR (CD_3COCD_3, 300 MHz) δ: 7.48 (d, J=8.5 Hz, 2H), 7.32 (d, J=8.4 Hz, 2H), 5.27 (t, J=3.8 Hz, 1H, C**H**OH), 4.05 (d, J=4.0 Hz, 1H, OH), 2.73—2.66 (m, 1H), 2.44—2.27 (m, 2H), 2.01—1.96 (m, 1H), 1.85—1.59 (m, 5H).

2-((4-Bromophenyl)(hydroxy)methyl)cyclohexanone (3f-*anti*)[13] Light yellow solid. ^{1}H NMR (CD_3COCD_3, 300 MHz) δ: 7.50 (d, J=8.4 Hz, 2H), 7.33 (d, J=8.5 Hz, 2H), 4.91 (dd, J=7.9, 3.6 Hz, 1H, C**H**OH), 4.29 (d, J=3.6 Hz, 1H, OH), 2.73—2.64 (m, 1H), 2.48—2.32 (m, 2H), 2.01—1.95 (m, 1H), 1.82—1.75 (m, 1H), 1.72—1.58 (m, 3H), 1.36—1.22 (m, 1H).

2-((4-Chlorophenyl)(hydroxy)methyl)cyclohexanone (3g-*syn*)[13] Light yellow solid. ^{1}H NMR (CD_3COCD_3, 300 MHz) δ: 7.38 (d, J=8.7 Hz, 2H), 7.33 (d, J=8.7 Hz, 2H), 5.29 (t, J=3.7 Hz, 1H, C**H**OH),

4.08 (d, J=4.1 Hz, 1H, OH), 2.73—2.66 (m, 1H), 2.44—2.25 (m, 2H), 2.02—1.96 (m, 1H), 1.86—1.55 (m, 5H).

2-((4-Chlorophenyl)(hydroxy)methyl)cyclohexanone (3g-*anti*)[13] Light yellow solid. ^{1}H NMR (CD_3COCD_3, 300 MHz) δ: 7.39 (d, J=8.4 Hz, 2H), 7.35 (d, J=8.4 Hz, 2H), 4.92 (dd, J=8.2, 3.5 Hz, 1H, C**H**OH), 4.31 (d, J=3.5 Hz, 1H, OH), 2.73—2.64 (m, 1H), 2.48—2.32 (m, 2H), 2.02—1.95 (m, 1H), 1.81—1.56 (m, 4H), 1.35—1.23(m, 1H).

2-((2,4-Dichlorophenyl)(hydroxy)methyl)cyclohexanone (3h-*syn*)[13] Light yellow solid. ^{1}H NMR (CD_3COCD_3, 300 MHz) δ: 7.62 (d, J=8.5 Hz, 1H), 7.43 (d, J=1.9 Hz, 1H), 7.39 (dd, J=8.3, 2.0 Hz, 1H), 5.67 (t, J=3.1 Hz, 1H, C**H**OH), 4.32 (d, J=4.3 Hz, 1H, OH), 2.72—2.66 (m, 1H), 2.48—2.30 (m, 2H), 1.87—1.75 (m, 2H), 1.77—1.58 (m, 4H).

2-((2,4-Dichlorophenyl)(hydroxy)methyl)cyclohexanone (3h-*anti*)[13] Light yellow solid. ^{1}H NMR (CD_3COCD_3, 300 MHz) δ: 7.62 (d, J=8.3 Hz, 1H), 7.45—7.39 (m, 2H), 5.34 (dd, J=8.5, 4.1 Hz, 1H, C**H**OH), 4.45 (d, J=4.0 Hz, 1H, OH), 2.79—2.72 (m, 1H), 2.50—2.34 (m, 2H), 1.83—1.48 (m, 6H).

2-(3-Biphenyl-(hydroxy)methyl)cyclohexanone (3i-*syn*)[13] Light yellow solid. ^{1}H NMR (CD_3COCD_3, 300 MHz) δ: 7.66—7.64 (m, 3H), 7.53—7.32 (m, 6H), 5.39 (t, J=3.7 Hz, 1H, C**H**OH), 4.03 (d, J=4.1 Hz, 1H, OH), 2.81—2.75 (m, 1H), 2.46—2.28 (m, 2H), 2.03—1.99 (m, 1H), 1.86—1.56 (m, 5H).

2-(3-Biphenyl-(hydroxy)methyl)cyclohexanone (3i-*anti*)[13] Light yellow solid. ^{1}H NMR (CD_3COCD_3, 300 MHz) δ: 7.67—7.65 (m, 3H), 7.56 (d, J=7.6 Hz, 1H), 7.49—7.33 (m, 5H), 4.98 (dd, J=8.2, 3.5 Hz, 1H, C**H**OH), 4.29 (d, J=3.5 Hz, 1H, OH), 2.81—2.73 (m, 1H), 2.45—2.36 (m, 2H), 1.99—1.96 (m, 1H), 1.83—1.60 (m, 4H), 1.42—1.29 (m, 1H).

2-(Hydroxy(phenyl)methyl)cyclohexanone (3j-*syn*)[13] Light yellow solid. ^{1}H NMR (CD_3COCD_3, 300 MHz) δ: 7.37—7.27 (m, 4H), 7.20 (t, J=7.1 Hz, 1H), 5.31 (t, J=3.6 Hz, 1H, C**H**OH), 3.92 (d, J=3.8 Hz, 1H, OH), 2.72—2.65 (m, 1H), 2.45—2.26 (m, 2H), 2.02—1.97 (m, 1H), 1.86—1.73 (m, 3H), 1.68—1.54 (m, 2H).

2-(Hydroxy(phenyl)methyl)cyclohexanone (3j-*anti*)[13] Light yellow solid. ^{1}H NMR (CD_3COCD_3, 300 MHz) δ: 7.37—7.23 (m, 5H), 4.88 (dd, J=8.2, 3.4 Hz, 1H, C**H**OH), 4.20 (d, J=3.4 Hz, 1H, OH), 2.72—2.63 (m, 1H), 2.48—2.38 (m, 2H), 2.01—1.96 (m, 1H), 1.80—1.52 (m, 4H), 1.36—1.20 (m, 1H).

2-(Hydroxy(*p*-tolyl)methyl)cyclohexanone (3k-*syn*)[13] Light yellow solid. ^{1}H NMR (CD_3COCD_3, 300 MHz) δ: 7.23 (d, J=7.9 Hz, 2H), 7.11 (d, J=7.9 Hz, 2H), 5.25 (t, J=3.5 Hz, 1H, C**H**OH), 3.85 (d, J=3.9 Hz, 1H, OH), 2.69—2.62 (m, 1H), 2.41—2.31 (m, 2H), 2.29 (s, 3H), 1.99—1.98 (m, 1H), 1.85—1.55 (m, 5H).

2-(Hydroxy(*p*-tolyl)methyl)cyclohexanone (3k-*anti*)[13] Light yellow solid. ^{1}H NMR (CD_3COCD_3, 300 MHz) δ: 7.23 (d, J=8.1 Hz, 2H), 7.13 (d, J=7.9 Hz, 2H), 4.83 (dd, J=8.3, 3.3 Hz, 1H, C**H**OH), 4.13 (d, J=3.2 Hz, 1H, OH), 2.69—2.60 (m, 1H), 2.41—2.37 (m, 2H), 2.30 (s, 3H), 2.01—1.96 (m, 1H), 1.80—1.53 (m, 4H), 1.34—1.22 (m, 1H).

2-(Hydroxy(4-nitrophenyl)methyl)cyclopentanone (3l-*syn* and 3l-*anti*)[13] Light yellow solid. ^{1}H NMR (CD_3COCD_3, 300 MHz) δ: 8.23—8.19 (m, 2H), 7.71—7.62 (m, 2H), 5.37 (t, J=3.6 Hz, 1H, C**H**OH) (*syn*), 5.12 (dd, J=6.3, 2.9 Hz, 1H, C**H**OH) (*anti*), 4.93 (d, J=2.8 Hz, 1H, OH) (*anti*), 4.78 (d, J=4.5 Hz, 1H, OH) (*syn*), 2.67—1.66 (m, 7H).

3-Hydroxy-3-(4-nitrophenyl)-1-phenylpropan-1-one (3m)[13] Light yellow solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.22 (d, J=8.7 Hz, 2H), 7.99—7.88 (m, 2H), 7.67—7.55 (m, 3H), 7.48 (t, J=7.6 Hz, 2H), 5.51—5.39 (m, 1H, C**H**OH), 3.88 (d, J=2.7 Hz, 1H, OH), 3.47—3.25 (m, 2H).

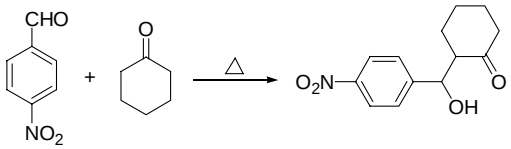
3-(4-Nitrobenzylidene)pentane-2,4-dione (3n)[13] Light yellow solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.25 (d, J=8.7 Hz, 2H), 7.56 (d, J=8.6 Hz, 2H), 7.49 (s, 1H), 2.46 (s, 3H), 2.29 (s, 3H).

1-Hydroxy-2-methyl-1-(4-nitrophenyl)pentan-3-one (3o)[13] Light yellow solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.26—8.17 (m, 2H), 7.55—7.40 (m, 2H), 5.24 (brs, 1H, C**H**OH) (*syn*), 4.92—4.84 (m, 1H, C**H**OH) (*anti*), 3.59—3.49 (m, 1H, OH) (*syn*), 3.32—3.23 (m, 1H, OH) (*anti*), 2.98—2.77 (m, 1H), 2.69—2.29 (m, 2H), 1.30—0.97 (m, 6H).

Results and discussion

To begin with, the reaction between 4-nitrobenzaldehyde and cyclohexanone was investigated under solvent-free condition without catalyst. As shown in Table 1, the reaction temperature has great influence on the reaction. For example, treatment of 4-nitrobenzaldehyde (**1a**) with cyclohexanone (**2a**) at room temperature gave no desired product **3a** (Entry 1). Increasing the reaction temperature caused the aldol condensation to occur. Generally, higher temperature corresponded to higher yield of **3a** (Entries 2—5). Changing the reaction temperature from 100 to 120 ℃, however, the yield of **3a** was slightly decreased (Entry 6). This might be due to the dehydration of **3a** at this temperature and the elimination happened accordingly. The molar ratio of the reactant has little influence on the reaction. Increasing the amount of **2a** from 2 to 5 equivalents almost made no difference to the yield of **3a** (Entry 5 and 7). In addition, the aldol reaction was slightly influenced by the presence of oxygen. Running the reaction under nitrogen atmosphere, **3a** was obtained in lower yield (Entry 8). Oxygen existing in the reaction system might oxidate **1a** to 4-nitrobenzoic acid, which could catalyze the aldol condensation. The reaction time also significantly influenced the reaction. Shortening the reaction time from 30 to 10 h decreased the yield of **3a** gently (Entries 8—10). At last, 79 % of **3a** was obtained at 100 ℃ for 40 h under solvent- and catalyst-free condition (Entry 11).

Table 1 Optimization of the reaction conditions in the absence of solvent and catalyst



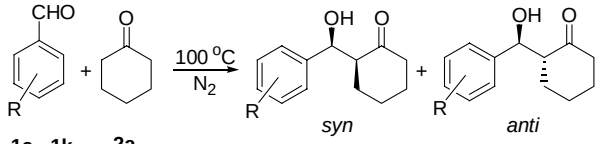
1a **2a** **3a**

Entry	**1a**∶**2a**[a]	*T*/℃	Time/h	Yield[b](**3a**)/%
1	5∶1	25	30	0
2	5∶1	40	30	6
3	5∶1	60	30	13
4	5∶1	80	30	32
5	5∶1	100	30	67
6	5∶1	120	30	63
7	2∶1	100	30	66
8[c]	2∶1	100	30	53
9[c]	2∶1	100	20	43
10[c]	2∶**1**	100	10	16
11[c]	2∶1	100	40	79

[a] The molar ratio. [b] Isolated yield. [c] Conducted under nitrogen atmosphere.

With the optimized reaction condition at hand, we firstly explored the scope of the reaction by using various benzaldehyde derivatives **1a**—**1k** and cyclohexanone **2a** as the substrates. As shown in Table 2, these aldol reactions were all proceeded without solvent and catalyst to give the desired products. The type of the substituents located on benzene ring has great influence on the reaction. For example, benzaldehydes bearing electron-withdrawing groups at *para*-position (**1a**, **1d** and **1e**) favored the aldol condensation (Entry 1, Entry 4 and Entry 5), while those with electron-donating groups at *para*-position (**1i**, **1j** and **1k**) frustrated the reaction (Entry 9—11). The position of the substituents on the benzene ring also influenced the reaction. Changing the nitro group from *para*- to *orth*-position resulted in lower yield of **3b** (Entries 1—2). In addition, only 35% of **3c** was found when nitro group was attached to the *meso*-position on benzene (Entry 3). This indicated that electron-withdrawing groups at *para*-position on benzene ring activated the carbonyl group, while those located at *meso*-position deactivated the aldehyde. This phenomenon could be explained by the conjugated effect and inductive effect known before. In the case of aldehyde **1f** and **1g**, only moderated yields were obtained (Entries 6—7). It seemed that the electron-withdrawing ability of halogen was not strong enough to activate the aldehyde. Introducing another chlorine atom on the *orth*-position of benzene, however, the reaction was greatly improved, giving **3h** in 69% yield (Entry 8). The type of the substituents on the benzene ring showed some effects on the diasteroselectivity of the reaction. The molar ratio of the *anti* and *syn* adducts was changed from 0.25∶1 to 0.98∶1 depending on the character and location of the substituents (Entries 1—11). Compared with those aldol reactions using catalysts, the diasteroselectivity was very poor. But the diasteroselectivities were all thermodynamically controlled.

Table 2 Direct aldol reactions under solvent- and catalyst-free conditions



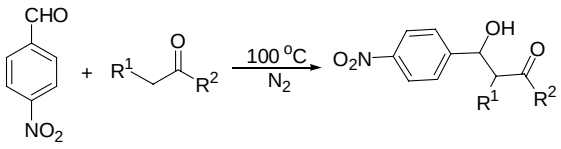
1a–**1k** **2a** **3a**–**3k**

Entry	R	Time/h	*T*/℃	Yield[a]/%	*anti*/*syn*[b]
1	4-NO_2 (**1a**)	40	100	79 (**3a**)	0.72∶1
2	2-NO_2 (**1b**)	40	100	61 (**3b**)	0.72∶1
3	3-NO_2 (**1c**)	40	100	35 (**3c**)	0.73∶1
4	4-CN (**1d**)	40	100	77 (**3d**)	0.45∶1
5	4-CF_3 (**1e**)	40	100	58 (**3e**)	0.93∶1
6	4-Br (**1f**)	40	100	33 (**3f**)	0.59∶1
7	4-Cl (**1g**)	40	100	30 (**3g**)	0.98∶1
8	2,4-Cl (**1h**)	40	100	69 (**3h**)	0.78∶1
9	3-Ph (**1i**)	40	100	36 (**3i**)	0.79∶1
10	H (**1j**)	40	100	35 (**3j**)	0.82∶1
11	4-CH_3 (**1k**)	40	100	44 (**3k**)	0.25∶1

[a] Isolated yield. [b] Determined by ^{1}H NMR spectra.

Encouraged by the results above, we extended the reaction to other ketones. As shown in Table 3, cyclo-

Table 3 Direct aldol reactions under solvent- and catalyst-free conditions



1a **2b**–**2g** **3l**–**3o**

Entry	R^1	R^2	Time/h	*T*/℃	Yield[a]/%
1	$(CH_2)_3$ (**2b**)	$(CH_2)_4$ (**2b**)	40	100	76 (**3l**, *anti*∶*syn*=0.43∶1)
2	H (**2c**)	Ph (**2c**)	40	100	15 (**3m**)
3	CH_3CO (**2d**)	CH_3 (**2d**)	40	100	78 (**3n**)
4	H (**2e**)	CH_3 (**2e**)	40	100	trace
5	CH_3 (**2f**)	CH_3CH_2 (**2f**)	40	100	22 (**3o**, *anti*∶*syn*=0.73∶1)

[a] Isolated yield.

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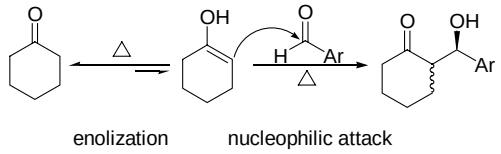
pentanone reacted well with **1a**, giving **3l** in 76% yield with a diastereoselectivity of 0.43∶1 (Entry 1). Employing acyclic ketones **2c**, **2e** and **2f** as the aldol donors, however, the desired products were obtained in very low yield (Entries 2, 4 and 5). When *β*-diketone **2d** was used, the corresponding aldol product **3n** was obtained in 78% yield (Entry 3). **2a**, **2b** and **2d** have been known to be susceptible to enolization by heat. This suggested that ketones which could be easily enolated favored the solvent- and catalyst-free aldol reaction.

Based on the results above, we proposed that heat was the driving force for the reaction. Ketones were firstly converted to enols by heat (Scheme 1). Subsequently nucleophilic attack on aldehydes resulted in the formation of the aldol adducts.

Scheme 1



Conclusions

In conclusion, aldol reaction between benzaldehyde derivatives and ketones could successfully happen under solvent- and catalyst-free condition. The desired products were favorably obtained at suitable temperature. This approach has obvious advantages, which fully met the requirements of the principles of green chemistry.

References

1 Trost, B. M.; Brindle, C. S. *Chem. Soc. Rev.* **2010**, *39*, 1600.

2 Wurtz, A. *Bull. Soc. Chim. Fr.* **1872**, *17*, 436.

3 Mahrwald, R. *Modern Aldol Reactions*, Wiley-VCH, Berlin, **2004**.

4 Chen, X.-H.; Yu, J.; Gong, L.-Z. *Chem. Commun.* **2010**, *46*, 6437.

5 Trost, B. M. *Science* **1991**, *254*, 1471.

6 (a) Yamada, Y. M. A.; Yoshikawa, N.; Sasai, H.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1997**, *36*, 1871.
(b) Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 4168.
(c) Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003.
(d) Trost, B. M.; Ito, H.; Siloff, E. R. *J. Am. Chem. Soc.* **2001**, *123*, 3367.
(e) Evans, D. A.; Downey, C. W.; Hubbs, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 8706.
(f) Machajewski, T. D.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352.

7 (a) Hajos, Z. G.; Parrish, D. R. *DE 2102623*, **1971** [*Chem. Abstr.* **1972**, *76*, 59072].
(b) Eder, U.; Sauer, G. R.; Wiechert, R. *DE 2014757*, **1971** [*Chem. Abstr.* **1972**, *76*, 14180].
(c) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615.
(d) Eder, U.; Sauer, R.; Wiechert, R. *Angew. Chem., Int. Ed.* **1971**, *10*, 496.

8 (a) Pidathala, C.; Hoang, L.; Vignola, N.; List, B. *Angew. Chem., Int. Ed.* **2003**, *42*, 2785.
(b) Chandler, C. L.; List, B. *J. Am. Chem. Soc.* **2008**, *130*, 6737.
(c) List, B.; Lerner, R. A.; Barbas, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395.
(d) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F. *J. Am. Chem. Soc.* **2001**, *123*, 5260.
(e) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386.
(f) Wu, Q.; Liu, B.-K.; Lin, X.-F. *Curr. Org. Chem.* **2010**, *14*, 1966.

9 Banon-Caballero, A.; Guillena, G.; Najera, C. *Green Chem.* **2010**, *12*, 1599.

10 (a) Anastas, P. T.; Kirchhoff, M. M. *Acc. Chem. Res.* **2002**, *35*, 686.
(b) Anastas, P. T.; Warner, J. C. *Green Chemistry, Theory and Practice*, Oxford University Press, Oxford, **1998**.
(c) Noyori, R. *Chem. Commun.* **2005**, 1807.
(d) Metzger, J. O. *Angew. Chem., Int. Ed.* **1998**, *37*, 2975.
(e) Tanaka, K. *Solvent-free Organic Synthesis*, Wiley-VCH, Weinheim, **2003**.
(f) Kaupp, G. *Top. Curr. Chem.* **2005**, 95.

11 For some selected examples of solvent-free reactions, see: (a) Berkessel, A.; Roland, K.; Neudorfl, J. M. *Org. Lett.* **2006**, *8*, 4195.
(b) Rodriguez, B.; Rantanen, T.; Bolm, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 6924.
(c) Carlone, A.; Marigo, M.; North, C.; Landa, A.; Jorgensen, K. A. *Chem. Commun.* **2006**, 4928.
(d) Hayashi, Y.; Aratake, S.; Itoh, T.; Okano, T.; Sumiya, T.; Shoji, M. *Chem. Commun.* **2007**, 957.
(e) Rodriguez, B.; Bruckmann, A.; Bolm, C. *Chem.-Eur. J.* **2007**, *13*, 4710.
(f) Rantanen, T.; Schiffers, I.; Bolm, C. *Org. Process Res. Dev.* **2007**, *11*, 592.
(g) Li, P.; Wang, L.; Wang, M.; Zhang, Y. *Eur. J. Org. Chem.* **2008**, 1157.
(h) Hayashi, Y.; Urushima, T.; Aratake, S.; Okano, T.; Obi, K. *Org. Lett.* **2008**, *10*, 21.
(i) Almasi, D.; Alonso, D. A.; Najera, C. *Adv. Synth. Catal.* **2008**, *350*, 2467.
(j) Almasi, D.; Alonso, D. A.; Balaguer, A.-N.; Najera, C. *Adv. Synth. Catal.* **2009**, *351*, 1123.
(k) Zeng, X.; Zhong, G. *Synthesis* **2009**, 1545.
(l) Worch, C.; Bolm, C. *Synlett* **2009**, 2425.
(m) Martins, M. A. P.; Frizzo, C. P.; Moreira, D. N.; Buriol, L.; Machado, P. *Chem. Rev.* **2009**, *109*, 4140.
(n) Pravst, I.; Zupan, M.; Stavber, S. *Curr. Org. Chem.* **2009**, *13*, 47.
(o) Walsh, P. J.; Li, H.; de Parrodi, C. A. *Chem. Rev.* **2007**, *107*, 2503.

12 For some examples about catalyst-free reactions, see: (a) Watahiki, T.; Matsuzaki, M.; Oriyama, T. *Green Chem.* **2003**, *5*, 82.
(b) Watahiki, T.; Ohba, S.; Oriyama, T. *Org. Lett.* **2003**, *5*, 2679.

(c) Iwanami, K.; Hinakubo, Y.; Oriyama, T. *Tetrahedron Lett*. **2005**, *46*, 5881.
(d) Iwanami, K.; Oriyama, T. *Synlett* **2006**, 112.
(e) Khatik, G. L.; Kumar, R.; Chakraborti, A. K. *Org*. *Lett*. **2006**, *8*, 2433.
(f) Zhang, M.; Jiang, H. F.; Liu, H. L.; Zhu, Q. H. *Org*. *Lett*. **2007**, *9*, 4111.
(g) Wang, G.-W.; Gao, J. *Org*. *Lett*. **2009**, *11*, 2385.
(h) Alagiri, K.; Prabhu, K. R. *Chem*. *Eur*. *J*. **2011**, *17*, 6922.
(i) Chunavala, K. C.; Joshi, G.; Suresh, E.; Adimurthy, S. *Synthesis* **2011**, 635.
(j) Xin, Y.; Zhao, J.-W.; Gu, J.-W.; Zhu, S.-Z. *J*. *Fluorine Chem*. **2011**, *132*, 402.
(k) Nagarapu, L.; Mallepalli, R.; Yeramanchi, L.; Bantu, R. *Tetrahedron Lett*. **2011**, *52*, 3401.
(l) Nadimpally, K. C.; Thalluri, K.; Palakurthy, N. B.; Saha, A.; Mandal, B. *Tetrahedron Lett*. **2011**, *52*, 2579.
13 (a) Lin, J.-H.; Zhang, C.-P.; Xiao, J.-C. *Green Chem*. **2009**, *11*, 1750.
(b) Wang, G.-W.; Zhang, Z.; Dong, Y.-W. *Org*. *Process Res*. *Dev*. **2004**, *8*, 18.
(c) Zhu, M.-K.; Xu, X.-Y.; Gong, L.-Z. *Adv*. *Synth*. *Catal*. **2008**, *350*, 1390.
(d) Wu, Y.; Zhang, Y.; Yu, M.; Zhao, G.; Wang, S. *Org*. *Lett*. **2006**, *8*, 4417.
(e) Mase, N.; Nakai, Y.; Ohara, N.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas III, C. F. *J*. *Am*. *Chem*. *Soc*. **2006**, *128*, 734.
14 Chen, W.-B.; Liao, Y.-H.; Du, X.-L.; Zhang, X.-M.; Yuan, W.-C. *Green Chem*. **2009**, *11*, 1465.

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