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A novel simple bifunctional catalyst for the direct aldol reaction

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Abstract

Direct aldol reactions of aldehydes and ketones can proceed smoothly in the presence of a catalytic amount of naphthol/sodium naphtholate (5 mol%) to afford the corresponding products with yields up to 98%. Such a bifunctional catalyst is more moderate than strong acid or base employed in direct aldol reactions.

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The aldol reaction is one of key C–C bond forming reactions [1]. This reaction creates the β -hydroxy carbonyl compounds with great potential in organic synthesis [2]. Lots of emphasis recently has been given to nonmetallic small molecule catalysts as they are more efficient and friendly [3]. Barbas and List [4] have proved L-proline to be a powerful catalyst in the intramolecular direct aldol reaction and paved the way for the development of small organic molecules as catalysts. Since then, so many new organic catalysts containing both Lewis acid and Brønsted base sites in itself, called bifunctional catalysts, have been developed due to their higher selectivities as compared to acid or base alone [5]. This topic has been extensively reviewed by Shibasaki *et al.* [6]. We have found that the match of the acidity and basicity is very important to such reactions [7]. The discovery of a small single molecule used to catalyze aldol reaction is challenge [8]. In this letter, however, we will report the use of catalytic amount of the mixture of naphthol for acid sites and sodium naphtholate for basic sites as a novel simple and readily available bifunctional catalyst for the direct aldol reaction performed under moderate conditions.

1. Experimental

Typical experimental procedure: Ketone (5 mL) was added to a dried vial charged with aldehyde (1 mmol) and naphthol (0.05 mmol)/sodium naphtholate (0.05 mmol). The reaction was stirred at RT for the time in Table 5 followed by the extraction of the mixture with ethyl acetate. Organic layer was washed with brine and dried over anhydrous magnesium sulfate. After filtration and evaporation of the solvent, the residue was purified through column chromatography on silica gel to give the corresponding aldol products. The products from our direct aldol reactions have been confirmed by NMR

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Scheme 1. The catalysts evaluated in this study.

with Bruker-300 spectrometer. One representative spectroscopic data is present here: Entry 6: anti-diastereomer, ¹H NMR (CDCl₃, 300 MHz): δ 8.21–7.47 (m, 4H, Ar–H), 4.91–4.87 (m, 1H, OCH), 4.10 (s, 1H, OH), 2.63–2.54 (m, 1H, CH), 2.51–1.25 (m, 8H, CH₂). ¹³C NMR (CDCl₃, 300 MHz): δ 24.6, 27.6, 30.7, 42.6, 57.1, 73.9, 123.5, 127.8, 147.5, 148.3, 214.6.

2. Results and discussion

The reaction of acetone with *p*-nitrobenzaldehyde in excess of acetone (Scheme 1) was studied. When phenolates such as **1b**, **3b** and **4b** were used, the total yields of aldol products **III** and **IV** were between 66% and 94% as shown in Table 1. Surprisingly, only trace amount of aldol product (less than 1%) was observed for **2b**. Almost the same yields were obtained for **3b** and **4b**, but the reactivity of **4b** was higher than that of **3b** as shown the reduction of reaction time

	2								
Entry	Catalyst	Catalyst (eq)	Time (h)	III (%)	IV (%)	Total yield (%) ^b			
1	1b	0.3	12	49	17	66			
2	2b	0.3	12			Trace			
3	3b	0.3	12	93		93			
4	4b	0.3	4	91	3	94			
5	1a,1b	0.3	12	89	7	96			
6	2a,2b	0.3	12	3		3			
7	2a,1b	0.3	12	62	13	75			
8	2a,4b	0.3	12	47	10	57			
9	3a,3b	0.3	12	82	12	94			
10	4a,4b	0.3	2	94	2	96			
11	NaOH	0.3	12	25	33	58			

Table 1 The effect of catalysts on the direct aldol reactions^a.

^a The reactions were carried out at room temperature.

^b Isolated yield.

Table 2			
The influence	of time	on the	reactions ^a .

Entry	4a,4b (eq)	Time (h)	III (%)	IV (%)	V (%)	Total yield (%) ^b
1	0.3	1	88	2		90
2	0.3	2	94	2		96
3	0.3	4	94	3	1	98
4	0.3	8	92	3	4	99
5	0.3	12	90	5	4	99

^a The reactions were carried out at room temperature.

^b Isolated yield.

Table 3			
The influence of catalyst	amount on	the	reactions ^a .

Entry	Catalyst	Catalyst (eq)	Time (h)	III (%)	IV (%)	Total yield (%) ^b
1	4a,4b	0.3	2	94	2	96
2	4a,4b	0.2	2	94	3	97
3	4a,4b	0.1	2	93	4	97
4	4a,4b	0.05	2	90	6	96
5 ^c	4a,4b	0.05	2	78	16	94
6	4a,4b	0.025	2	86	7	93
7	4a,4b	0.01	2	65	18	83

^a The reactions were carried out at room temperature.

^b Isolated yield.

^c The reaction was carried out at 0 °C.

Table 4

The influence of catalysts components on the reactions^a.

Entry	Catalyst (eq)		Time (h)	III (%)	IV (%)	Total yield (%) ^b	
	4a	4b					
1	0.025	0.075	2	90	1	91	
2	0.05	0.05	2	90	6	96	
3	0.075	0.025	2	85	13	98	

^a The reactions were carried out at room temperature.

^b Isolated yield.

from 12 h to 4 h. With the addition of 0.3 equivalents phenol **1a–4a** as co-catalysts, the reactivity was enhanced (Table 1, entries 5, 7, and 10). The use of the mixture of naphthol and sodium naphtholate brought the yield up to 96% in 2 h with the distinct chemoselective (Table 1, entry 10). Such results are very impressive as compared to sodium hydroxide alone (Table 1, entry 11).

The best solvent for this direct aldol reaction was acetone among those investigated solvents such as acetone, DMF, THF, MeOH, EtOH, $C_6H_5CH_3$, and CH_2Cl_2 . The influence of reaction time, temperature, quantity and ratio of catalyst components on the reaction was investigated (Tables 2–4). The satisfied yield of the desired product **III** could be achieved within 2 h (Table 2, entries 1 and 2). With an increase in reaction time, the aldol product **III** was translated into product **IV** slowly and **IV** (Table 2, entries 3–5). The chemoselectivity of the reaction decreased with a decrease in temperature (Table 3, entries 4 and 5). The catalyst loading can be reduced to 0.05 equiv. without compromising the yield (Table 3, entry 4) and the best ratio for catalyst components was 1:1 (Table 4, entry 2).

Currently, we assume this reaction occurs through a bifunctional conjugated acid–base mechanism as shown in Scheme 2. With this type of bifunctional acid–base catalyst, compounds without modification are able to undergo the reaction with much higher yields than those obtained on strong acid or base as catalysts. The reason for this might be due to the synergic function from the conjugated acid–base or the existences of more equilibriums as compare to acid or base alone as a catalyst. We further evaluated the reactivity of different substrates under the optimal conditions (Table 5). The aldol reaction of aromatic aldehydes with ketones proceeded very well with reasonable yields (76–98%, Table 5). Interestingly, few dialdol products were observed.



Scheme 2. Proposed mechanism of this aldol reaction.

Table 5	
Direct aldol reactions of aldehydes with ketones catalyzed by naphthol (4a)/sodium naphtholate (4b) ^a	

Entry	I	П	Time (h)	III (%)	IV (%)	Total yield (%) ^b
1	Acetone	4-Nitrobenzaldehyde	2	90	6	96
2	Acetone	2-Nitrobenzaldehyde	2	87	10	97
3	Acetone	3-Nitrobenzaldehyde	2	91		91
4	Acetone	Benzaldehyde	2	76		76
5	Acetone	2,4-Dichlorobenzaldehyde	2	93		93
6	Cyclohexanone	4-Nitrobenzaldehyde	1.5	98°		98
7	2-Butanone	4-Nitrobenzaldehyde	1.5	34/59 ^d		93
8	Acetophenone	4-Nitrobenzaldehyde	1	90		90
9	Acetophenone	3-Nitrobenzaldehyde	1	92		92
10	Acetophenone	2-Nitrobenzaldehyde	1	92		92

^a The reactions were carried out at room temperature with 0.05eq catalysts.

^b Isolated yield.

^c Yield represents the combined yield of diastereomers, and the anti:syn = 1:1.

^d Methylene/methyl. Reaction at the methyl, and the anti:syn = 48:52.

3. Conclusions

In summary, the combination of naphthol/sodium naphtholate as a simple and readily available bifunctional catalyst has been developed to facilitate the direct aldol reaction. Through this catalyst, the direct aldol reaction can be performed at room temperature with yield up to 98% and trace level of side products. In addition, no prior modification of the carbonyl substrates such as deprotonation or silylation is required.

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References

- [1] (a) B.M. Trost, L. Fleming, C.H. Heathcock, Comprehensive Organic Synthesis, vol. 2, Pergamon, Oxford, 1991;
 - (b) P.I. Dalko, L. Moisan, Angew. Chem. Int. Ed. 43 (2004) 5138, Angew. Chem. Int. Ed. 40 (2001) 3726;
 - (c) N. Mase, F. Tanaka, C.F. Barbas, III Org. Lett. 5 (2003) 4369;
 - (d) Y. Hayashi, Angew. Chem. Int. Ed. 45 (2006) 5527;
 - (e) D.W.C. Macmillan, A.B. Northrup, J. Am. Chem. Soc. 124 (2002) 6798.
- [2] (a) T. Mukaiyama, Tetrahedron 55 (1999) 8609;
 (b) K.C. Nicolaou, D. Vourloumis, N. Winssinger, Angew. Chem. Int. Ed. 39 (2000) 44;
 (c) A.B. Northrup, D.W.C. MacMillan, Angew. Chem. Int. Ed. 43 (2004) 2152.
- [3] (a) H. Gröger, J. Wilken, Angew. Chem. Int. Ed. 40 (2001) 529;
 - (b) B. List, Synlett (2001) 1675;
 - (c) B. Alcaide, P. Almendros, Eur. J. Org. Chem. (2002) 1595;
 - (d) B. Alcaide, P. Almendros, Angew. Chem. Int. Ed. 42 (2003) 858.
- [4] (a) B. List, R.A. Lerner, C.F. Barbas, J. Am. Chem. Soc. 122 (2000) 2395;
 - (b) W. Notz, B. List, J. Am. Chem. Soc. 122 (2000) 7386;
 - (c) K. Sakthivel, W. Notz, T. Bui, et al. J. Am. Chem. Soc. 123 (2001) 5260;
 - (d) B. List, P. Pojarliev, C. Castello, Org. Lett. 3 (2001) 573;
 - (e) N. Mase, C.F. Barbas, J. Am. Chem. Soc. 128 (2006) 734.
- [5] (a) S. Kanwar, S. Trehan, Tetrahedron Lett. 46 (2005) 1329;
- (b) K. Oisaki, D.B. Zhao, et al. Tetrahedron Lett. 46 (2005) 4325.
- [6] (a) E.M. Vogl, H. Gröger, M. Shibasaki, Angew. Chem. 111 (1999) 1672;
 (b) E.M. Vogl, H. Gröger, M. Shibasaki, Angew. Chem. Int. Ed. 38 (1999) 1570.
- [7] A. Berkessel, H. Gröger, Asymmetric Organocatalysis, Wiley-VCH, Weinheim, 2005.
- [8] M.J. Climent, A. Corma, V. Fornés, et al. Adv. Synth. Catal. 344 (2002) 1090.