CHINESE JOURNAL OF CATALYSIS
Volume 28, Issue 8, August 2007
Online English edition of the Chinese language journal

Available online at www.sciencedirect.com
ScienceDirect

Cite this article as: Chin J Catal, 2007, 28(8): 673–675.

SHORT COMMUNICATION

Direct Asymmetric Aldol Reactions on Heterogeneous Bifunctional Catalyst

ZHONG Lin[1], XIAO Jianliang[1,2], LI Can[1,*]

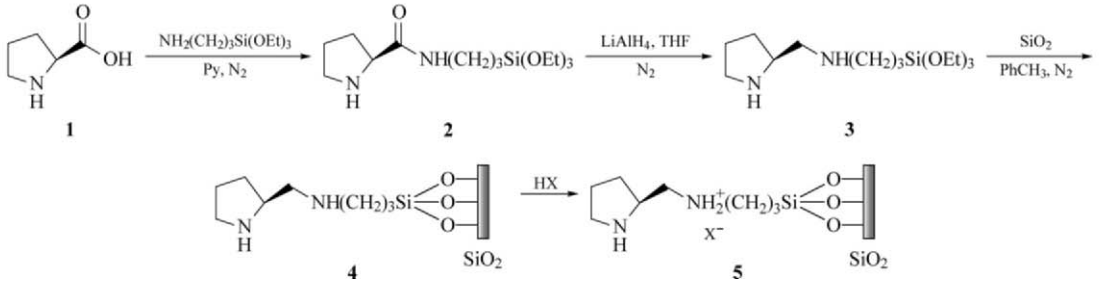
[1] State Key Laboratory of Catalysis, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, Liaoning, China
[2] Department of Chemistry, University of Liverpool, Liverpool L69 7ZD, UK

Abstract: A heterogeneous bifunctional catalyst was synthesized by incorporating chiral amine and acid groups into silica. This catalyst showed modest reactivity and enantioselectivity (up to 60% ee) for the direct asymmetric aldol reactions. It is suggested that the suitable incorporation between the amine and the acid groups in the bifunctional solid catalyst is crucial for the reactivity and the chiral induction of the reactions.

Key Words: asymmetric catalysis; aldol reaction; bifunctional catalyst; inorganic–organic material

The direct asymmetric aldol reaction is one of the most important C–C bond-forming reactions and has been widely used in constructing natural and nonnatural products [1]. A number of methods based on biological, organometallic, and organo-catalysis for this transformation have been reported [2]. Natural aldolases use combinations of acids and bases in their active sites to accomplish direct asymmetric aldol reactions [3]. Recently, an interesting report on bifunctional inorganic materials containing multiple catalytically active centers has highlighted the potential application of these materials to mimic aldolases [4], and some work relating to the concept for direct aldol reactions using the bifunctional catalyst with different active centers on solids has been carried out. However, the problem of developing a heterogeneous bifunctional catalyst for direct asymmetric aldol reactions still remains an open challenge [4,5]. Herein, we report bifunctional silica materials incorporated with the chiral amine and the acid groups for direct catalytic asymmetric aldol reactions, giving modest yields and enantioselectivities.

The preparation of silica-supported bifunctional materials involves the synthesis of the silica precursor **4**, which is then protonated with an acid (Scheme 1) [6]. Precursor **4** was characterized using infrared reflectance spectroscopy, ^{13}C cross-polarization and magic-angle spinning solid-state nuclear magnetic resonance (NMR) spectroscopy, and thermogravimetric and elemental analysis. Before grafting, the silica support (Qingdao Haiyang Chemicals Plant, China) showed a sharp peak at 3750 cm^{-1} [7], which is ascribed to the stretching frequency of free silanols. However, this IR peak disappears after grafting **3** on silica. The results indicate that the



Scheme 1 Synthesis of heterogeneous bifunctional catalyst **5**

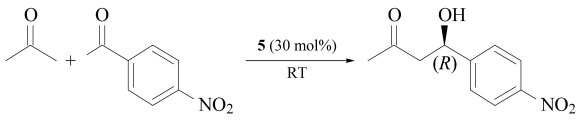
Received date: 2007-04-18.
*** Corresponding author.** Tel: +86-411-84379070; Fax: +86-411-84694447; E-mail: canli@dicp.ac.cn
Foundation item: Supported by the National Natural Science Foundation of China (20321303).

silanol groups are condensated with triethoxysilane groups of the amine, resulting in the formation of **4**. In addition, the appearance of the bending C–H vibration at 2927 cm^{-1} further confirms that the (*S*)-*N*-(pyrrolidin-2-ylmethyl)-propan-1-amine group has been successfully grafted on the surface of silica. The ^{13}C NMR spectrum exhibits a chemical shift at 9.8 characteristic of the carbon that is attached to the silicon atom [8]. The chemical shift of the carbons of the alkyl carbon and the cyclic *C*H is observed in the region of 16–24, whereas the carbons of NH*C*H_2 exhibit chemical shifts in the range of 50–65 [9]. The results showed that the organic functional groups are intact after grafting. The loading of the functional group for the precursor is found to be about 0.45 mmol/g of dry SiO_2, as determined using thermogravimetric analysis and elemental analysis.

The heterogeneous bifunctional catalysts were then tested for the aldol reaction of acetone with *p*-nitrobenzaldehyde (Table 1). Catalyst precursor **4** gives the aldol product **8** with 58% yield and 16% ee after 24 h (entry 1). However, to our delight, when a bifunctional catalyst formed upon the addition of 30% equivalents AcOH (pK_a = 4.76) is used, both the reactivity and the enantioselectivity of the reaction are increased to 75% and 36%, respectively (entry 2). Further increase in the acidity of the additive using CF_3COOH (pK_a = 0.23) in the reaction furnishes **8** with a significantly decreased yield and a slightly increased enantioselectivity (entry 3). However, the addition of a very strong organic acid, such as TsOH (pK_a = – 6.50), gives rise to product **8** with only 27% yield and 30% ee (entry 4).

Other organic acids whose pK_a varies in the range of 1.23–4.20 are also screened for the reaction with the bibifunctional catalyst system. It is found that the reactivity and the enantioselectivity of the reaction with these organic acids are not as good as that with AcOH (Table 1, entries 2 and 5–7). The results strongly indicate that the suitable acid functionality is crucial for the reactivity and the chiral selectivity in the reaction [10,11]. Interestingly, the catalyst functionalized with L-tartaric acid shows the same enantioselectivity as that functionalized with racemic tartaric acid, and the chiral acid exhibits somewhat a lower enantioselectivity than that with AcOH. The results demonstrate that the chiral group of an acid has no beneficial effect on the asymmetric induction in the reaction (entries 8–10) [11], suggesting that these groups are not involved in the transition state that determines the stereochemistry. In addition, the addition of Lewis acids gives the product with lower yield and enantioselectivity as compared with the addition of AcOH (entries 11 and 12).

Table 1 Direct asymmetric aldol reaction of acetone with *p*-nitrobenzaldehyde catalyzed by heterogeneous bifunctional catalyst **5**



6 **7** **8**

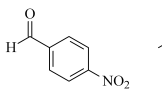
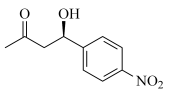
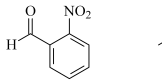
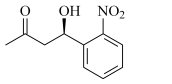
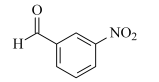
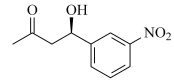
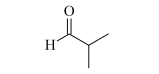
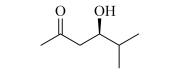
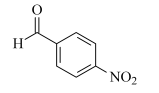
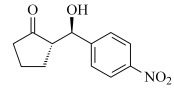
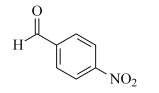
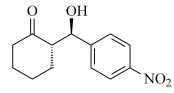
Entry	Acid (30 mol%)	pK_a	*t*/h	*Y* [a]/%	ee [b] (%)
1	no acid		24	58	16
2	AcOH	4.76	24	75	36
3	CF_3COOH	0.23	40	37	40
4	TsOH	– 6.50	40	27	30
5	PhCOOH	4.20	24	61	28
6	HCOOH	3.45	24	71	27
7	oxalic acid	1.23, 4.19	24	65	34
8	L-tartaric acid	2.99, 4.40	24	69	33
9	DL-tartaric acid	2.99, 4.40	24	68	33
10	(*R*)-BINOL		24	40	17
11	$Zn(OAc)_2$		24	43	18
12	$Cu(OTf)_2$		24	25	11

The aldol reactions were performed with 0.25 mmol *p*-nitrobenzaldehyde, 30 mol% catalyst, and 1 ml acetone at room temperature for 24–40 h unless stated otherwise.

[a] Isolated yield after separation by silica gel.

[b] Determined by a high-performance liquid chromatograph (Chiralpak AD-H).

Table 2 Direct asymmetric aldol reactions of aldehydes with ketones catalyzed by heterogeneous bifunctional catalyst **5**

Aldehyde	Ketone	Product	*t*/h	*Y*/%	ee (%)
			24	75	36
			40	78	31
			40	65	33
			46	67	60
			26	87[a]	20[c]
			40	72[b]	26[d]

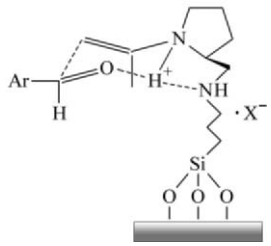
Reaction time: 24–46 h.

[a] Isolated yield of the mixture of *anti/syn* product, with *anti/syn* molar ratio = 55/45.

[b] Isolated yield of the mixture of *anti/syn* product, with *anti/syn* molar ratio = 50/50.

[c] ee(*syn*) = 60%.

[d] ee(*syn*) = 31%.



Scheme 2 Plausible transition state of a model reaction mediated by the bifunctional catalyst

The solid catalyst, bifunctionalized with the amine and AcOH, was also examined with different aldehydes and ketones (Table 2). The catalysts exhibit modest reactivity and enantioselectivity for the acyclic and the cyclic ketones; however, low or no diastereoselectivity is observed for the cyclic ketones. In the case of substituted benzaldehyde as the ketone acceptor, *p*-nitrobenzaldehyde affords the aldol product with the highest yield and enantioselectivity. It is worth noting that isobutylaldehyde can give the product with 67% yield and 60% ee.

To highlight the possible catalytic model of the bifunctional catalyst for the direct asymmetric aldol reactions, a plausible transition state of the reaction of acetone with *p*-nitrobenzaldehyde is suggested in Scheme 2. In the reaction, the amino group of pyrrolidine is responsible for the enamine formation with acetone, and through hydrogen bonding, the carbonyl group of the aldehyde is activated by the other protonated amine group. The *Re* face of the activated aldehyde is attacked by the enamine, resulting in a six-membered chair-like transition structure. The reactivity and the chiral induction of the aldol reaction are critically influenced by the cooperative effect between the amine and the acid groups in the catalysts.

In summary, a heterogeneous catalyst bifunctionalized with the chiral amine and the acid groups has been developed for the direct asymmetric aldol reactions with modest yield and enantioselectivity. The synergistic effect between the amine and the acid groups is crucial for the reactivity and the enantioselectivity in the reactions. Although there is a room for improvement in both the yield and the stereoselectivity, our findings may provide a general approach to prepare inorganic–organic catalysts with bifunctional or multiple type of active centers for chiral synthesis.

Acknowledgement

The authors thank Dr. YANG Hengquan for his help with IR spectroscopy measurements.

References

[1] Carreira E M. In: Jacobsen E N, Pfaltz A, Yamamoto H eds. Comprehensive Asymmetric Catalysis, Vol Ⅲ. Heidelberg: Springer-Verlag Press, 1999. 997

[2] Palomo C, Oiarbide M, Garcia J M. *Chem Soc Rev*, 2004, **33**(2): 65

[3] List B. In: Mahrwald R ed. Modern Aldol Reactions, Vol I. Weinheim: Wiley-VCH, 2004. 161

[4] Zeidan R K, Hwang S-J, Davis M E. *Angew Chem Int End*, 2006, **45**(38): 6332

[5] Bass J D, Solovyov A, Pascall A J, Katz A. *J Am Chem Soc*, 2006, **128**(11): 3737

[6] Foucault A, Caude M, Oliveros L. *J Chromatogr*, 1979, **185**(1): 345

[7] Wang H, Liu X J, Xia H A, Liu P, Gao J B, Ying P L, Xiao J L, Li C. *Tetrahedron*, 2006, **62**(5): 1025

[8] Dufaud V, Davis M E. *J Am Chem Soc*, 2003, **125**(31): 9403

[9] Jiang D M, Yang Q H, Wang H, Zhu G R, Yang J, Li C. *J Catal*, 2006, **239**(1): 65

[10] Guillena G, del Carmen Hita M, Najera C. *Tetrahedron*, 2006, **17**(10): 1493

[11] Gryko D, Zimnicka M, Lipinski R. *J Org Chem*, 2007, **72**(3): 964