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Heterogeneous Chiral Copper Complexes of Amino Alcohol for Asymmetric Nitroaldol Reaction

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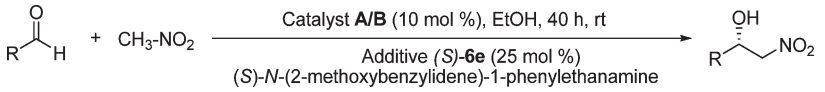

Chiral amino alcohols supported on mesoporous silicas were synthesized and evaluated as a new class of chiral ligands in copper-catalyzed nitroaldol reaction under heterogeneous and mild reaction conditions. The activity and enantioselectivity of the present catalytic system is immensely influenced by the presence of achiral and chiral bases as an additive. The heterogenized chiral copper(II) complex of amino alcohol was found to be an effective recyclable catalyst for the nitroaldol reaction of different aldehydes such as aromatic, aliphatic, alicyclic, and $\alpha-\beta$ unsaturated aldehydes to produce nitroaldol products with remarkably high enantioselectivity ($\geq$99%) and yields.

Introduction

Discovered in 1895, the Henry (nitroaldol) reaction is one of the well-established C−C bond forming processes in organic synthesis[1−3] to access valuable building blocks such as 1,2-amino alcohols and α-hydroxy carboxylic acids. However, the wide applicability of this transformation was hampered due to the nonavailability of suitable catalysts for imparting a definite stereochemistry to the newly generated stereogenic centers. Shibasaki reported the first asymmetric version of the nitroaldol reaction in 1992.[4] Since then various metal- and nonmetal-based catalysts[5] have been reported for the asymmetric nitroaldol reaction. Noticeably, chiral ligands such as BINOL,[4c−h,6] amino alcohol,[7] bis(oxazoline),[2b,c,8] bis(thiazoline),[9] bis(imidazoline),[10] sulfonyl diamine,[11] salen,[12]

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Schiff bases,[13a,14] thiols,[15] thiophene,[16] bipiperidine,[1a] aminopyridine,[17] oxabispidines,[18] with diverse metals, viz., Zn,[2d,19] Sm,[20] Cu,[1a,3b,17,21] Mg,[22a] Cr,[14a] La,[4a,d,21b] Li,[4c,e,6] Na,[4h] Ag,[13b] Pd,[4b] Zr,[4a] and Yb,[22b] have been used as catalyst for the Henry reaction. Among these, the Cu-catalyzed nitroaldol reaction performed at room temperature is intriguing due to its inexpensive and less toxic nature together with high catalytic activity under homogeneous reaction conditions.[1a,13,21] Further, due to mechanistic reasons both acidic and basic sites within a single catalytic system are preferred. For this reason a variety of bases, viz., potassium hydroxide,[23a,b] cetyltrimethyl ammonium hydroxide,[24a] sodium carbonate,[21b] triethyl amine,[21b] 2,6-lutidine,[11] pyridine,[11] and aromatic imines,[8b] have found application as additives to improve the efficiency of typically acidic metal complex based catalysts in nitroaldol reactions.

Heterogeneous asymmetric catalysis has attracted much attention due to its potential advantages, such as easy product separation, recycling of the expensive chiral catalysts, and the possibility of making a fix-bed reactor for conducting reactions on continuous mode.[25] Although fervent activity was seen in the asymmetric nitroaldol reaction under homogeneous condition, only a handful of recyclable homogeneous and heterogeneous catalysts have been reported.[2d,12d,16,22a,26a,26b] The synthesis of chiral metal complexes supported on various silicas for their use as asymmetric heterogeneous catalysts in various organic transformations including chiral lanthanum−lithium−binaphthol complex on silica for the nitroaldol reaction has been of continued interest to us.[6] Recently we have reported the synthesis of copper complexes of (*S*)-amino alcohol-supported silica as chiral stationary phase and chiral ligand exchange stationary phase for the chromatographic separation of racemic compounds.[27] Herein, we have investigated the application of these materials as recyclable heterogeneous catalysts for asymmetric nitroaldol reaction to afford chiral nitroalcohols in good to excellent yields and enantioselectivity. These materials, however, required a chiral imine as a promoter in order to show high catalytic performance.

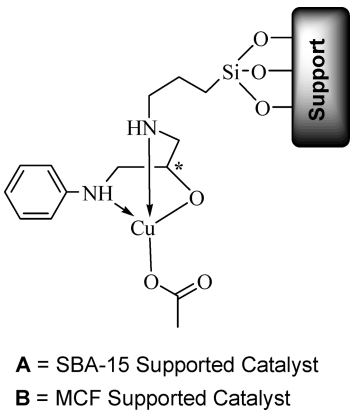

FIGURE 1. Schematic presentation of chiral copper complex supported on silica.

Results and Discussion

Siliceous hexagonal SBA-15 and mesostructured cellular foams (MCF) have substantially large pores (7−35 nm), which make them potential materials as catalyst support. Chiral complex supported on SBA-15, henceforth designated as catalyst **A** was synthesized and characterized by various physicochemical and spectral studies according to our previous report.[27] To see the effect of pore size on the catalytic performance of the copper complex we have also prepared MCF (a bigger pore size silica) supported catalyst **B**.[28] Both the supported complexes (**A** and **B**; Figure 1) were used as catalysts in nitroaldol reaction of various aldehydes at room temperature.

To start with, we have carried out the nitroaldol reaction of benzaldehyde with nitromethane as model substrates in the presence of catalyst **A** and **B** in ethanol at rt. Both of catalysts **A** and **B** provided the nitroaldol product in ∼90% yield with ee values of 75% and 80%, respectively (Table 1, entries 1 and 2). Both SBA-15 and MCF have similar BET surface area but ultralarge pore size and a hydrothermally robust framework of MCF might have contributed toward better enantioselectivity of nitroaldol products. Next, we evaluated the role of various organic bases **4**−**6a**−**e** as additives with complex **A** as a representative heterogeneous

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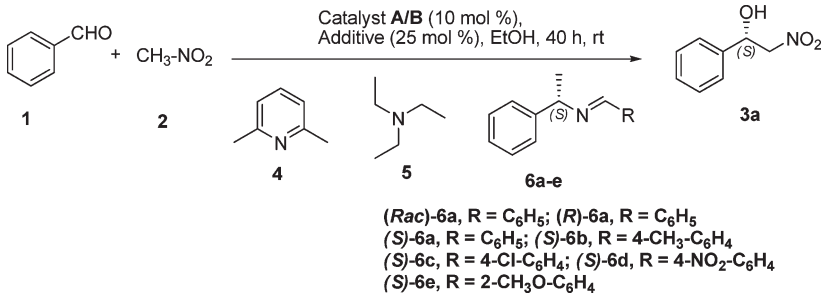
(28) See the Supporting Information for details.

TABLE 1. Screening of Catalyst and Additives for Asymmetric Nitroaldol Reaction[a]



entry	materials[b]	yield[c] (%)	ee[d] (%)
1	catalyst **A**	90	75
2	catalyst **B**	91	80
3	catalyst **A** + 2,6-lutidine (**4**)	30	
4	catalyst **A** + triethyl amine (**5**)	90	19 (*S*)
5	catalyst **A** + (*rac*)-**6a**	86	66 (*S*)
6	catalyst **A** + (*R*)-**6a**	85	52 (*R*)
7	catalyst **A** + (*S*)-**6a**	85	72 (*S*)
8	catalyst **A** + (*S*)-**6b**	96	75 (*S*)
9	catalyst **A** + (*S*)-**6c**	95	77 (*S*)
10	catalyst **A** + (*S*)-**6d**	92	74 (*S*)
11	catalyst **A** + (*S*)-**6e**	97	97 (*S*)
12	catalyst A + (*S*)-**6e**[e]	96	95 (*S*)
13	catalyst **A** + (*S*)-**6e**[f]	40	96 (*S*)
14	catalyst **A** + (*S*)-**6e**[g]	16	92 (*S*)
15	SBA-15		
16	MCF		
17	SBA-15 + (*S*)-**6e**		

[a]Reaction conditions: benzaldehyde (0.4 m.mol) with nitromethane (5.5 m.mol) in 1 mL of absolute ethanol for 40 h at rt. [b]Different mesoporous materials, catalyst **A**/**B** and additive (**4**,**5**,**6a**−**e**) were used. [c]Isolated yield after column chromatography. [d]Determined by HPLC with chiralcel OD column 85:15, *n*-hexane:2-propanol, flow 0.8 mL/min. [e]Benzaldehyde (0.4 mmol) with nitromethane (4.0 mmol) keeping other reaction parameters constant. [f]Benzaldehyde (0.4 mmol) and nitromethane (2.0 mmol). [g]Benzaldehyde (0.4 mmol) and nitromethane (0.8 mmol) keeping other reaction parameters constant.

catalyst for the nitroaldol of benzaldehyde and nitromethane. 2,6-Lutidine **4** as an additive negatively impacted the catalytic reaction while with triethylamine **5** as an additive the reaction mostly took the racemic pathway (entries 3 and 4). The use of an imine derived racemic methylbenzyl amine and benzaldehyde as an additive imparted very good conversion (86%) and good ee (66%) (entry 5), but when the *R*-form of the imine was used as an additive, though the conversion remained the same (85%), there was a marked drop in ee (52%) of the product (entry 6). Significantly, the use of the (*S*)-form of imine improved the ee (72%) of the product greatly (entry 7). These observations led us to conclude that imines are a good class of additive for this system and its chirality works in tandem with the chirality of the core catalyst (Cu-complex of the (*S*)-amino alcohol). In all probability the imine coordinates with the Cu to form a mixed ligand complex whose activity and enantioselctivity is better than those of original catalyst. Since (*S*)-imine worked better with the (*S*)-form of the catalyst, next we studied the effect of substituents on imines keeping its chirality as *S*. Both electron-withdrawing as well as electron-donating substituents on the imine improved the catalytic performance of the catalyst for the enantioselective nitroaldol reaction of benzaldehyde with nitromethane (entries 8−10). However, excellent isolated yield (>97%) with highest enantioselectivity (ee, 97%) of nitroaldol product was obtained when (*S*)-*N*-(2-methoxybenzylidene)-1-phenylethanamine **6e** was used as an additive (entry 11). Such behavior of chiral additives was previously observed by us in the asymmetric epoxide ring-opening reaction.[29] The equivalent ratio of substrate to nitromethane was also varied. On reducing the substrate to nitromethane 1:10 there was no significant change in yield and ee of the product in 40 h (entry 12); however, a further reduction in the quantity of nitromethane drastically reduced the yield of the product with some loss in ee (entries 13 and 14). It is noteworthy that the supports (SBA-15, entry 15 and MCF, entry 16) and combination of support and additive (entry 17) failed to catalyze the nitroaldol reaction under our reaction conditions. These experiments clearly show that the supports and additives alone or in combination do not impart any catalytic activity and all the catalytic activity (entries 1−11) is due to the copper complex anchored on silica.

Solvents had a considerable effect on the asymmetric nitroaldol of benzaldehyde (Table 2). All the solvents, viz., toluene, tetrahydrofuran (THF), diethyl ether (DEE), dichloromethane (DCM) (entries 1−4), and ethanol, explored in the present study to carry out the nitroaldol reaction were able to catalyze the reaction well, but it was ethanol that imparted the highst chiral induction (entry 5). We also carried out this reaction in the absence of a solvent; however, there was no product formation even after 40 h (entry 6). In view of the above, our subsequent nitroaldol reactions were conducted in ethanol as reaction medium.

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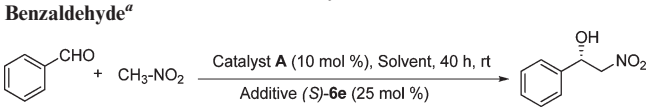
TABLE 2. Effect of Solvent on Asymmetric Nitroaldol Reaction of Benzaldehyde[a]



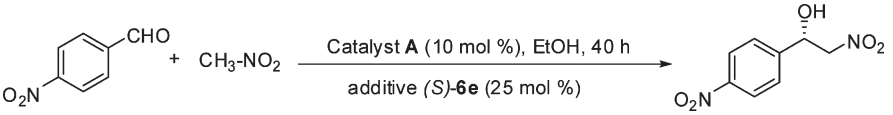
entry	solvent	yield[b] (%)	ee[c] (%)
1	toluene	98	19
2	tetrahydrofuran (THF)	92	28
3	diethyl ether (DEE)	95	10
4	dichloromethane (DCM)	93	22
5	ethanol	97	97
6	sovent free condtion		

[a]The reaction was carried out by using benzaldehyde (0.4 mmol), nitromethane (5.5 mmol), catalyst **A** (10 mol %), and additive (*S*)-**6e** (25 mol %) in 1 mL of solvent for 40 h. [b]Isolated yield by column chromatography. [c]Determined by HPLC with chiralcel OD column, 85:15, *n*-hexane:2-propanol, flow 0.8 mL/min.

Conventionally, on reducing the reaction temperature an increase in ee of the product is observed; however, when we conducted the nitroaldol reaction of 4-nitrobenzaldehyde as model substrate at −10 and 0 °C there was a marked decrease in the yield (26% and 40%) and ee (38% and 18%) of the product (Table 3; entries 1 and 2). Expectedly, on increasing the reaction temperature from rt to 40 °C there was a drop in the ee (42%) (entry 4).

Having optimized the reaction condition next we evaluated the present nitroaldol protocol for various aldehydes having aromatic, aliphatic, α,β-unsaturated, and alicyclic substituents and the results are summerized in Table 4. All the aldehydes used in the present study have undergone nitroaldol reaction to give the corresponding nitroaldol product in good to excellent isolated yields (61−97%) with low, moderate, or excellent enantioselectivity (ee, 5−99%) depending upon the substrate. Benzaldehyde and most of the

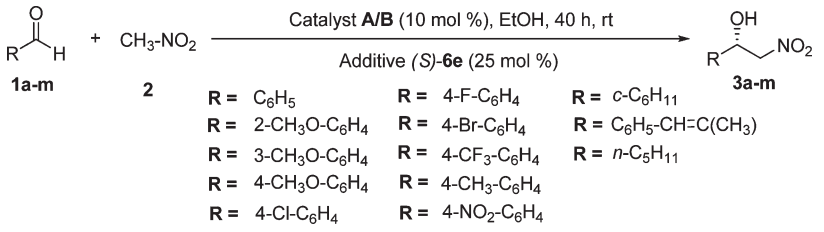
TABLE 3. Optimization of Reaction Temperature of Asymmetric Nitroaldol Reaction[a]



entry	temp (°C)	yield[b] (%)	ee[c] (%)
1	−10	26	38
2	0	40	18
3	rt (28)	62	64
4	40	64	42

[a]The reaction was carried out by using 4-nitrobenzaldehyde (0.4 mmol), nitromethane (5.5 mmol), catalyst **A** (10 mol %), and additive (*S*)-**6e** (25 mol %) in 1 mL of absolute ethanol for 40 h. [b]Isolated yield by column chromatography. [c]Determined by HPLC with chiralcel OD column, 85:15, *n*-hexane:2-propanol, flow 0.8 mL/min.

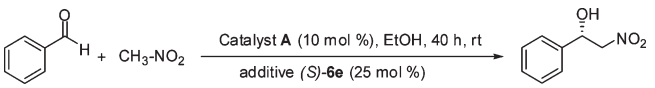
TABLE 4. Asymmetric Nitroaldol Reaction of Aldehydes and Nitromethane Catalyzed by Catalyst A[a]/B[b] with Chiral Imine as Additive



entry	R	product (**3**)	yield[e] (%)	ee[f] (%)
1 (2)	C_6H_5	**3a**	97 (94)	97 (96) (*S*)
3	2-CH_3O-C_6H_4	**3b**	70	69 (*S*)
4	3-CH_3O-C_6H_4	**3c**	92	94 (*S*)
5 (6)	4-CH_3O-C_6H_4	**3d**	85 (83)	95 (89) (*S*)
7 (8)	4-Cl-C_6H_4	**3e**	72 (78)	76 (80)(*S*)
9	4-F-C_6H_4	**3f**	68	30 (*S*)
10	4-Br-C_6H_4	**3g**	73	99 (*S*)
11 (12)	4-F_3C-C_6H_4	**3h**	72 (75)	98 (78) (*S*)
13 (14)	4-CH_3-C_6H_4	**3i**	85 (86)	5 (9) (*S*)
15	4-NO_2-C_6H_4	**3j**	62	64 (*S*)
16	*c*-C_6H_{11}[c]	**3k**	93	89 (*S*)
17	C_6H_5-CH=C(CH_3)	**3l**	76	98 (*R*)
18	*n*-C_5H_{11}[d]	**3m**	61	92 (*R*)

[a]Reaction conditions: aldehydes (0.4 mmol), nitromethane (5.5 mmol), catalyst **A**/**B** (10 mol %) and additive (*S*)-**6e** (25 mol %) in 1 mL of absolute ethanol for 40 h. [b]Values in parentheses are for catalyst **B**. [c]Cyclohexyl group. [d]linear pentyl group. [e]Yield of the corresponding isolated products **3** based on compounds **1**. [f]Determined by HPLC with chiral OD, OD-H, and AD columns; the absolute configuration of the products was assigned by comparison with the literature value.[21]

TABLE 5. Recycling Study of Enantioselective Nitroaldol Reaction with Catalyst A[a]



entry	catalytic run	yield[b] (%)	ee[c] (%)
1	1	97	97
2	2	97	97
3	3	96	97
4	4	95	96

[a]The reaction was carried out by using benzaldehyde (0.4 mmol), nitromethane (5.5 mmol), catalyst (10 mol %) **A**, and additive (*S*)-**6e** (25 mol %) in 1 mL of absolute ethanol for 40 h. [b]Isolated yield by column chromatography. [c]Determined by HPLC with chiralcel OD column, 85:15, *n*-hexane:2-propanol, flow 0.8 mL/min.

substitued benzaldehydes gave the corresponding nitroalcohols in very good to excellent ee (64−99%) except for 4-fluoro benzaldehyde (ee, 30%) and 4-methyl benzaldehyde (ee, 5%). Among the 2-, 3-, and 4-methoxy-substituted benzaldehydes, the ee values for 3- and 4-methoxy benzaldehyde were at par (∼95%, entries 4 and 5) but it was less for 2-methoxy benzaldehyde (ee 69%, entry 3). Alicyclic aldehyde, viz., cyclohexanal, was also smoothly converted to nitroaldols in excellent yield (93%) with high ee (89%, entry 16). The present protocol was also extended to α-methyl-*trans*-cinnamaldehyde, which gave the respective nitroalcohol in 76% isolated yield and excellent ee (98%), but in this perticular case we got the *R* enantiomer in excess (entry 17). Inversion of chirality was also observed in the nitroaldol product (yield 61%, ee 92%) obtained with linear aliphatic aldehyde (1-hexanal) as a substrate (entry 18). As of now, the cause of this inversion is unknown.

To study the confinement effect of the catalyst on catalytic activity and enantioselectivity, we have synthesized the MCF supported copper complex of chiral amino alcohol (designated as catalyst **B**) and used it as catalyst under the optimized reaction conditions of catalyst **A** and a few representative data are shown in parentheses in Table 4. We expected that due to large pores in MCF silica there will be over all an increase in the product yield and enantioselectivity; however, the data (Table 4, entries 2, 6, 8, 12, and 14) showed no such advantage. Ironically, there was no clear trend obtained in terms of increase or decrease in product yield and ee values.

An attempt was made to recycle catalyst **A** in the nitroaldol reaction of benzaldehyde under the optimized reaction condition. After the first catalytic run, the product was isolated by filteration and the solid mass was Soxhlet-extracted with toluene. The recovered solid was then dried in a vacuum desiccator overnight and used directly as catalyst in the next catalytic run. However, each cycle required addition of a fresh amount of chiral imine ((*S*)-**6e**; 25 mol %) to achieve the performance of fresh catalyst. The chiral imine was recovered quantitatively while isolating the product from the filtrate by column chromatography. Four catalytic runs were successfully carried out with the same catalyst with no observable loss in its performance (Table 5, entries 1−4).

Conclusion

In conclusion, we have successfully used chiral copper complex supported on SBA-15 and MCF silicas (**A** and **B**) in the asymmetric nitroaldol reaction in the presence of chiral imine as an additive. These supported catalysts showed remarkable catalytic activity and enantioselectivity over a range of substrate, viz., aromatic, alicyclic, α,β-unsaturated, and aliphatic aldehydes, to give the respective products in high isolated yield and excellent enantioselectivity at mild reaction condition (10 mol % catalyst loading, room temperature) with the added advantage of catalyst recycling. To the best of our knowledge, the chiral imine (**6e**) as additive was used for the first time in combination with chiral copper complexes supported on SBA-15 and MCF silicas as most efficient recyclable catalysts for the asymmetric nitroaldol reaction of aldehydes with nitromethane.

Experimental Section

Synthesis of Silica-Supported Copper Complexes of (*S*)-Amino Alcohol. Silica immobilized chiral copper complex and their precursors were synthesized as per our previously reported paper.[27]

General Procedure for the Preparation of Chiral Imine. To a stirred solution of aldehyde (8 mmol) in absolute ethanol (10 mL), racemic (*R*)/(*S*)-(−)-α-methyl benzylamine (1.27 mL, 10 mmol) was added at 0 °C. The reaction mixture was then refluxed (78−80 °C) for 12 h.[28] The completion of the reaction was monitored on silica gel TLC plate. The solvent was removed from the reaction mixture and the crude imine was purified by silica gel column chromatography, using *n*-hexane/ethyl acetate (EtOAc) (90:10) as mobile phase. Chiral purity of the imine was checked through HPLC using a Chiralcel OD column, *n*-hexane/2-propanol 85:15, 0.8 mL min^{-1}.

Typical Procedure of Asymmetric Nitroaldol Reaction. Asymmetric nitroaldol reactions were carried out in magnetically stirred screw cap vials under dry and inert conditions. Silica supported chiral copper(II) complex (108 mg, 0.04 mmol) was added to absolute ethanol (1 mL) at rt. The reaction mass was stirred after addition of a chiral imine as an additive (0.1 m.mol) and then aldehyde (0.4 m.mol) and nitromethane (0.3 mL, 5.5 m. mol) were added to the resulting light green suspension and stirring was continued for 40 h at rt. The completion of the reaction was monitored by TLC. The mixture was filtered and the residue was washed with dry ethanol. The solvent was removed from combined filtrate and washings and the residue was purified by column chromatography by using *n*-hexane/EtOAc (90:10). Enantiomeric excess was determined by HPLC analysis using chiral column OD, OD-H, and AD.

Spectral Data of (*S*)-1-(4-Bromophenyl)-2-nitroethanol 3g. Compound **3g** was synthesized by using a typical procedure and purified by column chromatography (95:5, *n*-hexane:EtOAc) to give dark yellow oil (73% yield). FT-IR 3399, 2976, 2926, 2016, 1748, 1588, 1490, 1445, 1369, 1261, 1168, 1046, 880, 824, 729, 605 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 3.39 (s, 1H), 4.40−4.62 (m 1H), 5.37−5.43 (dd, J = 3.6, 8.8 Hz, 2H), 7.25−7.28 (d, J = 8.2 Hz, 2H), 7.50−7.54 (d, J = 8.2 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) 51.3, 52.4, 125.5, 128.2, 128.5, 137.6. Anal. Calcd for $C_8H_8NO_3Br$: C, 39.05; H, 3.28; N, 5.69. Found: C, 38.79; H, 3.25; N, 5.70. HPLC analysis: Chiralcel OD (85:15, *n*-hexane:2-propanol, flow 0.8 mL/min), major enantiomer t_r = 19.1 min, minor enantiomer t_r = 22.2 min. $[\alpha]^{27}_D$ +27.5 (*c* 0.8, CH_2Cl_2). TOF−MS (ESI+): found $C_8H_8NO_3Br$ m/z 246 (M^+).

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Supporting Information Available: General synthesis and experimental procedures, all required characterization data, and copies of ^1H, ^{13}C NMR spectra and HPLC chromatograms for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.