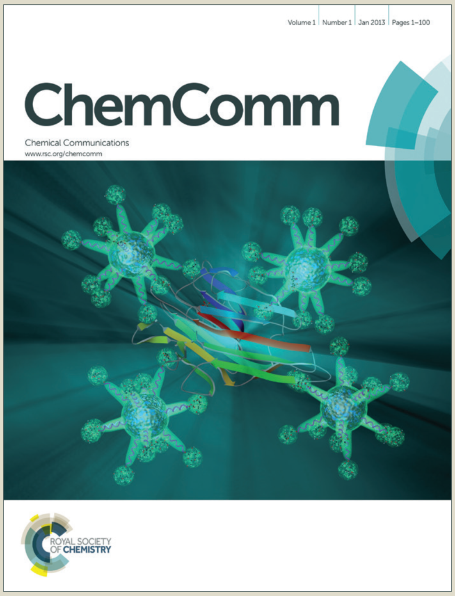
ChemComm

Accepted Manuscript



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

Chemical Communications

COMMUNICATION

Alternating Chiral Selectivity of Aldol Reactions under the Confined Space of Mesoporous Silica

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Chewei Yeh,[a] Yan-Ru Sun,[a] Shing-Jong Huang,[b] Yeun-Min Tsai [a]and Soofin Cheng[a]*

The chiral selectivities were altered and high diastereo- and enantio-selectivities of the products were obtained in water medium without adding acid co-catalysts when a primary-tertiary diamine catalyst was immobilized on mesoporous SBA-15 to form a recyclable catalyst for the direct asymmetric aldol reaction of cyclohexanone with *p*-nitrobenzaldehyde.

The aldol reaction provides an atom-economic route to synthesize β-hydroxy carbonyl compounds,[1] which have a broad range of applications in areas such as pharmaceuticals production,[2] along with the formation of new carbon-carbon bonds. *L*-proline was found by List and coworkers[3] in 2000 as an effective asymmetric catalyst in intermolecular aldol reactions. Since then much progress has been made in the development of organocatalysis for aldol reaction. [4]

Homogeneous aldol reactions often require tedious processes for product purification. Moreover, it is not economical that the elaborated chiral organocatalysts, which sometimes are prepared by long and troublesome processes, cannot be reused. Thus, catalysts of easy separation, recovery and recycling remain a scientific challenge of economic and environmental relevance.[5] A recent review summarized the results of about 360 catalysts studied from the beginning (2000) on asymmetric direct aldol reactions taking place in the presence of immobilized chiral organocatalysts.[6] The immobilization methods include covalent bonding, ligand grafting, microencapsulation, ion exchange, and electrostatic interactions. Various supports have been used, including organic polymers, such as polystyrene, poly(ethylene glycol), tentagel resin, chitosan, ionic liquids, etc. and inorganic solids, such as zirconium phosphonate, graphene oxide, clays, silica gel, and mesoporous silica. However, the most active catalysts are those already showed good performance under homogeneous conditions. The immobilized catalysts are usually emphasized on their regenerability and reusability. To the best of our knowledge, alternation of enantioselectivity of the products in aldol reaction through immobilization of a specific organic catalyst on solid supports has never been observed.

In 2007, Luo *et al.*[7] reported that chiral *trans-N,N*-dialkyl diaminocyclohexanes with the aid of strong acids such as trifluoromethanesulfonic acid and trifluoroacetic acid (TFA) in 1:1 molar ratio could nicely catalyze direct aldol reactions with high efficiency and chiral selectivity. The same group reported the first example of grafting a diamine chiral catalyst on magnetic nanoparticles and demonstrated high activity, stereoselectivity, and recyclability in direct aldol reactions.[8] However, the enantioselectivities were retained as those in homogeneous system. In the present study, a primary-tertiary diamine (*trans-N,N*-dialkylateddiaminocyclohexane, DDAC) catalyst was covalent bonded on mesoporous SBA-15 to form a recyclable catalyst. A remarkable alternation in chiral selectivities of the products in direct asymmetric aldol reaction of cyclohexanone with *p*-nitrobenzaldehyde was observed. Moreover, water can take the place of strong acid additives in the immobilized system to give high diastereo- and enantio-selectivities of the products.

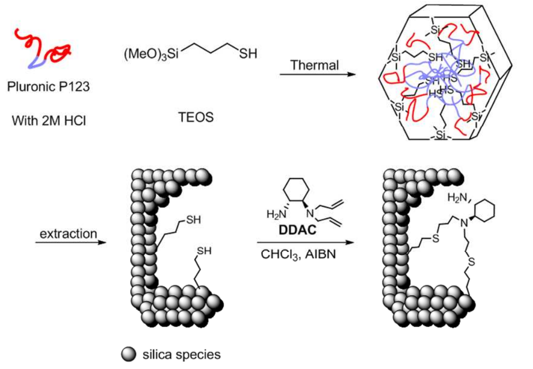
The chiral diaminocyclohexane catalyst (*trans-N,N*-diallyl diaminocyclohexane, abbreviated DDAC) was anchored on the thiol-functionalized mesoporous SBA-15 (SH-SBA-15) through AIBN-mediated thiol-ene reaction (Scheme 1).[9] The resultant material is termed DDAC-SH-SBA-15. SH-SBA-15 was synthesized by one-pot co-condensation of tetraethyl orthosilicate (TEOS) and 3-mercaptopropyltrimethoxysilane (MPTMS) in 2 M HCl containing Pluronic P123 as the pore-directing agent, following the procedures reported in Reference 10 to achieve homogeneous distribution of the catalytic sites.[10] The reactant molar compositions were 0.017 P123: 1 TEOS: 0.1 MPTMS: 7.9 HCl: 220 H_2O.

The XRD patterns of SH-SBA-15 displayed three well-resolved peaks in the region of 2θ = 0.9-1.8° indexed to the (100), (110), and (200) diffraction planes of the 2D hexagonal *p*6*mm* mesostructure (Figure S1, ESI). Slight shifts toward higher angles and decreases in intensity were observed after the chiral amine was anchored onto the SH-SBA-15 support. The SEM and TEM images of SH-SBA-15 and DDAC-SH-SBA-15 showed no changes in rod-shaped morphology and the retaining of cylindrical mesoporous channels of the 2D-hexagonal structures. N_2 adsorption-desorption isotherms of both SH-SBA-15 and DDAC-SH-SBA-15 samples show type IV isotherms and H1 hysteresis loops (Figure S2, ESI), characteristics of the large tubular pores of SBA-15 materials. The steep capillary

---

[a] *Department of Chemistry, National Taiwan University*
No. 1, Roosevelt Rd. Sec. 4, Taipei 10617, Taiwan.
Fax: (+886)-2-33668671, Email: chem1031@ntu.edu.tw.
[b] *Instrumentation Center, National Taiwan University, No. 1, Roosevelt Rd. Sec. 4, Taipei 10617, Taiwan..*

† Electronic Supplementary Information (ESI) available: experimental details, characterization, and additional catalytic results are available. See DOI: 10.1039/x0xx00000x



Scheme 1 The preparation route of *trans-N,N*-dialkylateddiaminocyclohexanes functionalized mesoporous silica.

condensations at P/P_0 around 0.40-0.70 indicate a uniform pore size distribution. The pore diameters, estimated by BJH method on the adsorption branches of the isotherms, decrease from 4.9 nm for SH-SBA-15 to 4.1 nm for DDAC-SH-SBA-15 (Table S1, ESI). Moreover, the BET surface area and pore volume were remarkably decreased from 615 to 265 m^2/g and 0.59 to 0.29 cm^3/g, respectively. These results suggest that DDAC was successfully immobilized on SBA-15. The elemental analysis showed that the N loading on DDAC-SH-SBA-15 was about 1.08 mmol/g and S loading of 1.17 mmol/g. The N/S atomic ratio of around 1 indicates that the divinyl-substituted chiral DDAC is probably attached to SH-SBA-15 through a di-substitution reaction.

The thermogravimetric (TG) analyses have been carried out to compare the thermal stabilities of the SH-SBA-15 materials before and after anchoring of DDAC. The TG profiles show that the total weight losses of SH-SBA-15 and DDAC-SH-SBA-15 are 11.8 and 30.1 wt%, respectively (Figure S3, ESI). SH-SBA-15 has only a one-step weight loss appeared at 250-420 ^oC, due to the decomposition of thiol group, while DDAC-SH-SBA-15 has another weight loss at higher temperatures of 520-700 ^oC. Moreover, the weight loss in the lower temperature region is also increased after DDAC is anchored. These additional weight losses are all attributed to the decomposition of the DDAC moiety.

Solid state ^{13}C CP-MAS NMR spectra of the SH-SBA-15 and DDAC-SBA-15 samples are shown in Figure 1. The ^{13}C CP-MAS NMR spectrum reveals three intense peaks at 11, 19, and 25 ppm, corresponding to the C atoms on the O_3Si-CH_2-CH_2-CH_2-SH or O_3Si-CH_2-CH_2-CH_2-S-CH_2- tethers displayed in sequence from left to right.

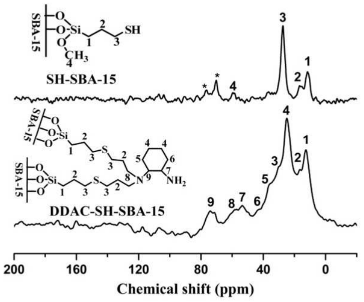
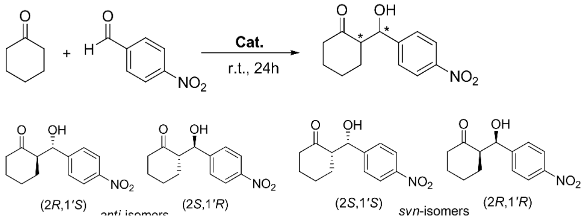


Figure 1 Solid-state ^{13}C CP-MAS NMR spectra of SH-SBA-15 and DDAC-SH-SBA-15. DDAC-SH-SBA-15.

The disappearances of allyl carbons at 120 and 135 ppm and C atoms on cyclohexane at 40-80 ppm are also evident. These results demonstrate again that DDAC derivatives are successfully anchored onto SH-SBA-15 through thiol-ene addition reaction.

To set a reference, DDAC was used as a homogeneous catalyst for the cross-aldol condensation between *p*-nitrobenzaldhyde (NBA) and cyclohexanone (CH) (1NBA: 10CH: 0.1DDAC equiv ratio) under ambient temperature. Four products of two *anti*-isomers and two *syn*-isomers were obtained, as shown in Scheme 2. The catalytic results are summarised as Entries 1’ and 2’ in Table 1. In consistence with the literature reports, the *anti*/*syn* ratio of the 2-(Hydroxy(4-nitrophenyl)methyl) cyclohexan-1-one products is 76/24 obtained with trifluoroacetic acid (TFA) as the additive (entry 1’). The role of the acidic additive was suggested to be related to its possible function in facilitating the enamine catalytic cycle.[11] When a weak acid such as terephthalic acid (*p*TPA) was added, the conversion



Scheme 2 Direct aldol reaction between *p*-nitrobenzaldhyde and cyclohexanone and the four isomer products.

Table 1 Direct aldol reactions over DDAC and that immobilized on SBA-15

Entry	Additive	Conv. [a] [%]	*Anti* : *syn*[b]	Selectivity [%][c] (2*R*,1’*S*)	(2*S*,1’*R*)	(2*S*,1’*S*)	(2*R*,1’*R*)
1’[d]	TFA	95	76 : 24	74.9(97)	1.1	22.0(83)	2.0
2’[d]	*p*TPA	43	42 : 58	39.9(90)	2.1	50.6(75)	7.4
3	—	41	56 : 44	54.0(93)	2.0	31.2(42)	12.8
4	TFA	76	27 : 73	23.6(75)	3.4	35.4	37.6(3)
5	$(CF_2COOH)_2$	79	24 : 76	17.0(42)	7.0	37.2	38.8(2)
6	CH_3COOH	61	60 : 40	57.6{92}	2.4	24.4(22)	15.6
7	*p*TPA	63	76 : 24	73.7(94)	2.3	7.6	16.4(37)
8	H_2O	70	85 : 15	81.6(92)	3.4	2.9	12.1(61)
9[e]	H_2O	trace	—	—	—	—	—

The reactions were carried out with cyclohexanone (0.2 mL, 2 mmol), aldehyde (0.20 mmol, 1 equiv), the catalyst DDAC and additive (0.02 mmol, 0.1 equiv) without solvent at RT for 24 h. [a] Conversion of *p*-nitrobenzaldhyde determined by HPLC analysis with external standard. [b] Determined by ^1H NMR. [c] The products’ configurations determined by chiral-phase HPLC analysis and comparing with reported data; values in parenthesis are e.e. selectivities. [d] Homogeneous system. [e] Me_3Si-DDAC-SH-SBA-15 catalyst.

decreased and the *anti*/*syn* ratio of the product was inversed (entry 2'). Moreover, the reaction became very sluggish, affording only trace products if no acids were added. Similar result was observed when water was added as the additive. That indicates that water is too weak as an acid to assist the direct aldol reaction. The transition-state model of the protonated catalytic center was proposed by Luo *et al.*,[7] showing that *E*-isomer of the enamine and steric hindrance between the cyclohexene and benzene rings were the main factors for formation of *anti*-isomer with (2*R*,1'*S*) enantioselectivity in this reaction (Scheme S1).

When immobilized DDAC-SH-SBA-15 was used as the catalyst (10 mol%), the aldol reaction is markedly accelerated even without any additive (entry 3), in contrast to the trace conversion over pristine organocatalyst. With TFA as the additive, the reaction rate is increased but is slightly slower than that of the pristine organocatalyst (entry 4). However, it is surprising to find that the *anti*/*syn* ratio of the products is reversed from 76/24 obtained in homogeneous system to 27/73 after the chiral diamines DDAC were immobilized on SBA-15. Products of similar reversed *anti*/*syn* ratio are observed with 2,2,3,3-tetrafluoro succinic acid as the additive (entry 5). Nevertheless, the enantioselectivities of syn-isomers are rather low with these strong acid additives.

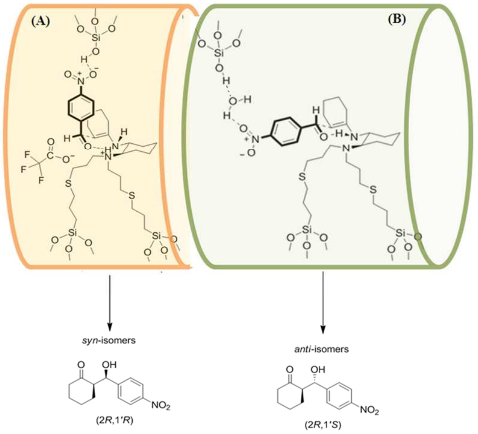
If weak acid additives were introduced, the diastereoselectivities over DDAC-SH-SBA-15 were found to be also reversed from that observed in homogeneous system (entries 6-7). Moreover, (2*R*,1'*S)* isomer is the main product, similar to that observed in the homogeneous system with strong acid additives. To our delight, an extremely high *anti*/*syn* ratio of 85/15 and (2*R*,1'*S*) enantioselectivity of 92% were obtained when water was used as the additive (entry 8). This finding is unique since water is not an effective additive in the homogeneous system.

Changes in stereoselectivity with supported catalysts were previously reported in enantioselective reactions promoted by immobilized metallic complexes.[12] A complete reversion in anti/syn ratio and an increase in the enantioselectivity of the major product were described in the Mukaiyama-aldol reaction of 1-phenyl-1-trimethylsilyloxyethene with α-ketoesters catalyzed by clay supported bis(oxazoline)–copper complexes. It is attributed to a change in the symmetry of the complex when it is placed in the vicinity of the clay surface. That reason however is not applicable to our case with the organic catalyst.

The opposite catalytic performance and different product selectivities observed on SBA-15 immobilized catalyst is obviously attributed to the confined space in the mesoporous silica. With strong acid additives, the gegen ion may adhere to protonated catalytic center in the confined space (Scheme 3A). It repels the aldehyde substrate from approaching the catalytic center and the unfavorable *syn* isomers are formed as the main products. The low enantioselectivities of *syn* products confirm this proposal. More interestingly, high enantioselectivities of *anti*-aldol (2*R*,1'*S)* product were obtained when less acidic additives or even water were added (Table 1, entries 6-8). These results were totally contrary to that observed under homogeneous condition.

To achieve the *anti*-aldol product, some forces should be present to keep the aldehyde and cyclohexene in *E*-geometry under the catalytic transition-state. One of the possible forces is the hydrogen-bonding between the nitro-group at the *para*-position of the benzaldehyde and surface silanol group, as shown in Scheme 3B. This kind of interaction is probably more drastic if the less acidic additive or water is present. In addition, water may also contribute the cage effect and trap the reactants and the organic moieties around catalytic centers. These two roles of water probably account for the high *anti*/*syn* ratio of 85/15 and enantioselectivity of 92% obtained when water was used as additive (Table 1, entry 8). The importance of the nitro-group on *p*-nitrobenzaldehyde in hydrogen-bonding was examined by using benzaldehyde to take the place of *p*-nitrobenzaldehyde as the reactant, and it was found that both the aldehyde conversion and enantioselectivity decreased markedly (Table S2, ESI).

In order to provide evidence of the roles of the silanol groups, DDAC-SH-SBA-15 was refluxed in a toluene solution containing trimethylsilyl chloride for 24 h to convert the surface silanol to trimethylsilyl ether. The catalytic performance of resultant Me_3Si-DDAC-SH-SBA-15 in the aldol reaction of CH and NBA is poor and only trace amount of aldehyde conversion is obtained (Table 1, entry 9). This result confirms the importance of the hydrogen-bonding provided by the silanol groups on the silica wall in the catalytic reaction.



Scheme 3 Proposed transition states for *syn*- and *anti*-aldoladducts in the confined space of DDAC-SH-SBA-15.

The recyclability of the catalyst was examined by separating the spent catalysts from the liquid products by simple filtration, and the recovered catalyst was used in the next run. Entries 1-3 in Table S3 (ESI) show the results under the same reaction condition as that of Entry 8, Table 1 but using 0.2 mL water as the solvent without acid additive. The recycled catalyst shows only slight decrease in conversions, diastereoselectivities and enantioselectivities. Another series of experiments were carried out to see if the changes in stereoselectivity over the supported DDAC catalyst was permanent. The same sample of solid catalyst using water additive was recovered by filtration, washing with acetylacetone and methanol, and used with TFA additive for second run, and finally recovered and reused again with water. The results were shown in Entries 2-4 in Table S2 (ESI). The recyclability of the catalyst and the dependence of anti/syn ratios and enantioselectivities on the additives were clearly demonstrated.

In conclusion, SBA-15 immobilized primary-tertiary diamine catalyst developed in this work demonstrated unprecedented alternation of the diastereoselectivity of the products in asymmetric direct aldol reactions, attributing to the confined space of mesopores and the interaction of the surface silanol groups with the intermediate species in the transition state. High *anti*-diastereoselectivities of the products were obtained when water was added in direct aldol reaction of cyclohexanone with *p*-nitrobenzaldehyde, providing a green route for organic synthesis.

This work was financially supported by the Ministry of Science and Technology, Taiwan. Acknowledgements are extended to C.-W. Lu and C.-Y. Lin of Instrumentation Center, College of Science, NTU for elemental analyses and EM experiments.

References

1. B.M. Trost and C.S. Brindle, *Chem. Soc. Rev*. 2010, ***39*,** 1600.
2. A. Kleemann, J, Engels, B. Kutscher and D. Reichert, *Pharmaceutical Substances: Syntheses, Patents, Applications;* Thieme: Stuttgart, 2011.
3. B. List, R. A. Lerner and C.F. Barbas III, *J. Am. Chem. Soc.* 2000, **122**, 2395.
4. M.M. Heravi and S. Asadi, *Tetrahedron Asymm*., 2012, **23**, 1431.
5. M. Gruttadauria, F. Giacalone, and R. Noto, *Chem. Soc. Rev*. 2008, **37**, 1666.
6. M. Bartók, *Catal. Rev. Sci. Eng.,* 2015, **57**, 192–255.
7. S. Luo, H. Xu, J. Li, L. Zhang and J.-P. Cheng, *J. Am. Chem. Soc.* 2007, **129**, 3074.
8. S. Luo, X. Zheng and J.-P. Cheng, *Chem. Commun.*, 2008, 5719.
9. P. Yu, J. He, C. Guo, *Chem. Commun.* 2008, 2355.
10. D. Margolese, J.A. Melero, S.C. Christiansen, B.F. Chmelka and G.D. Stucky, *Chem. Mater.* 2000, **12**, 2448.
11. A.B. Northrup and D.W.C. MacMillan, *J. Am. Chem. Soc.* 2002, **124**, 6798.
12. M.J. Fabra, J.M. Fraile, C.I. Herrerías, F.J. Lahoz, J.A. Mayoral and I. Pérez, *Chem. Commun*. 2008, 5402