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The synthesis of cyclohexenone using L-proline immobilized on a silica gel catalyst by a continuous-flow approach†

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A facile and convenient method for the synthesis of cyclohexenone compounds was developed using an L-proline immobilized silica gel catalyst combined with a continuous-flow approach. Because of the mild reaction conditions, ease of catalyst recyclability, and product isolation, this reaction approach can potentially be used in a facile scale-up reaction or in industrial applications.

Cyclohexenone and cyclohexanone derivatives, as high-value molecules, serve as a common structural motif for many natural products and important intermediates of organic compounds such as dihydrojunenol, faurinone, β-cadinene and other natural products[1] because of their wide range of applications in pharmaceuticals, pesticides, photographic film materials, drugs and other important chemicals.[2] Traditionally, substituted cyclohexenones are prepared using the well-known Robinson annulation, which combines three reactions: Michael addition, intramolecular aldol reaction, and dehydration.[3] For example, Fuchs *et al.* introduced a multistep process starting with enantiopure epoxyvinyl sulfones for the preparation of chiral 4-alkylcycloalkenones and enantiopure 2,5-cyclohexadienone synthons.[4] Both Baran and Nicolaou's groups used Robinson annulations to produce dihydrojunenol and *ent*-7-epizingiberene, respectively.[5] Recently, Zhao *et al.*[6] and Lu *et al.*[7] separately used primary–secondary diamine and primary amino acid catalysts for the generation of α, β-unsaturated ketones with outstanding results.

L-Proline and its derivatives, as well-known asymmetric organocatalysts,[8] have found wide application in the catalysis of enantioselective aldol reactions[9] between aldehydes and acetone for C–C bond formation and Michael reactions under homogeneous conditions.[10] However, because of the inherent drawbacks of homogeneous catalysts (*e.g.*, short catalyst lifetime, large amount of organic solvent, and difficulties in catalyst separation and recovery), as well as practical difficulties,[11] heterogeneous catalysts based on L-proline immobilized on different solid supports (*e.g.*, organic polymers,[12] zeolites,[13] mesoporous silica[14] and iron oxide nanoparticles[15]) have been studied.

In addition, continuous-flow technologies have recently emerged as new strategies for the sustainable generation of fine chemicals and pharmaceuticals,[16] because of a number of advantages over traditional batch procedures such as a shorter reaction time, efficient mixing, and faster heat and mass transfer.[17] Although many research groups have used proline organocatalysts in continuous-flow approaches for aldol reactions,[18] a number of drawbacks still exist[19] such as (i) long processing times, (ii) difficulties in product separation, and (iii) low yields that restrict their applications.

Therefore, the development of a more sustainable and industrially reliable catalytic procedure for the aldol reaction is still of continuing interest and a significant challenge for synthetic chemists. Herein, we report a simple, green and efficient method for the aldol reaction by a continuous-flow approach in which L-proline was immobilized on silica gel to produce a heterogenous catalyst that triggered the aldol reaction in a silica-packed chromatographic column upon the flow of eluent. The described technique has many merits such as catalyst reclability, ease of product isolation, and mild reaction conditions.

Because of its thermal and kinetic stability as well as its chemical inertness, we chose silica as a solid support for proline immobilisation. The silica gel-supported proline catalyst was prepared by following the reaction conditions and procedures reported previously[20] and as illustrated in Scheme 1. These were divided into three steps. Firstly, silica gel powder was activated by sodium hydroxide to create hydroxyl groups on its surface, and it was reacted with aminopropyl triethoxysilane to afford

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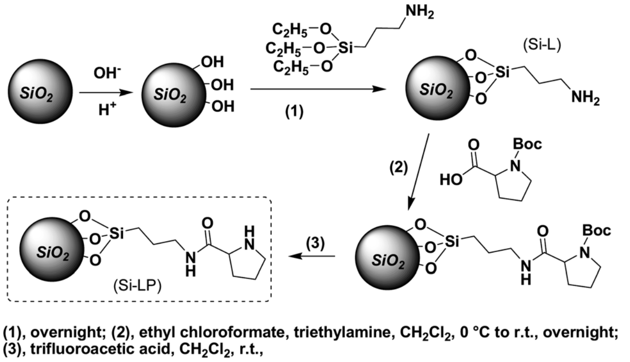
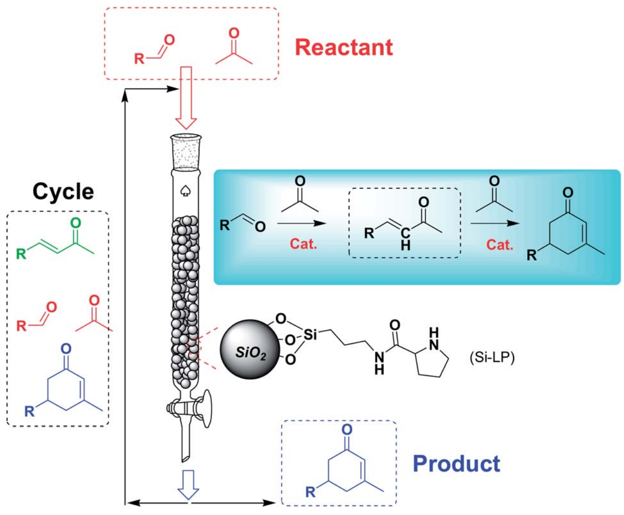
† Electronic supplementary information (ESI) available: Experimental procedures include a synthetic protocol for the construction of **Si-LP**, the synthesis of cyclohexenones from corresponding aldehydes. And also, the FTIR, TGA spectra of **Si-LP** and full spectroscopy data for all compounds. See DOI: 10.1039/c4ra01231c



Scheme 1 Illustration of proline functionalized silica gel.

silica gel (**Si-L**) with amino group modification on its surface. Upon activation by ethyl chloroformate, *N*-Boc-L-proline reacted with **Si-L** to form **Si-LP** (**Boc**). After removing the protecting groups from proline by trifluoroacetic acid (TFA) we obtained a silica gel-supported catalyst (**Si-LP**) as the final product. From the FTIR spectra of the **Si-LP** and the bare silica gel presented in Fig. S1,† we found that the two spectra had similar characteristics for most of the peaks except for three additional bands around 2832 cm^{-1}, 1640 cm^{-1} and 3200 cm^{-1} in the spectrum of **Si-LP**. These come from the stretching vibrations of the –CH$_2$–, –NHCO– and –NH-groups from proline, respectively, indicating the successful attachment of proline onto the surface of the silica gel.

The catalytic performance of **Si-LP** in the aldol reaction was evaluated in a model reaction between benzaldehyde and acetone, and this is shown in Scheme 2. First, the **Si-LP** powder (35 mL) was packed into an upright chromatographic column of 22 mm in diameter and 0.3 m in length. It was then rinsed with a sufficient amount of ethanol to remove the physically absorbed *N*-Boc-L-proline or L-proline on the surface of the silica gel. Then, an appropriate amount of benzaldehyde (102 μL, 1 mmol)



Scheme 2 Illustration of the aldol reaction triggered by **Si-LP** in a silica-packed chromatographic column.

Table 1 α, β-unsaturated cyclohexenones prepared from their corresponding aldehydes and acetone using the **Si-LP** catalyst[a]

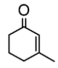
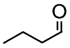
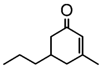
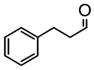
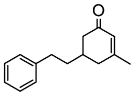
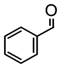
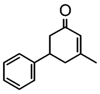
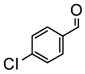
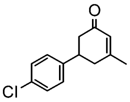
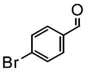
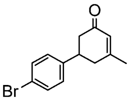
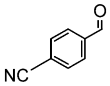
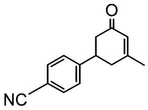
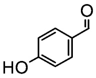
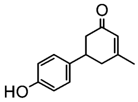
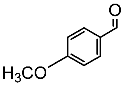
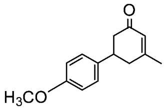
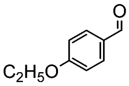
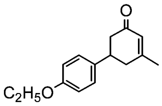
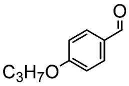
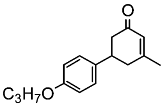
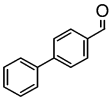
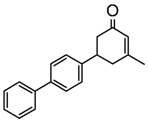
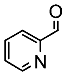
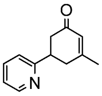
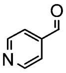
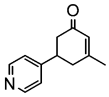
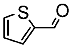
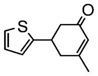
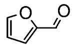
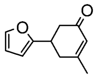
Entry	Aldehydes	Unsaturated cyclohexenones	Yield[b] (%)
1			55.7
2			50.5
3			79.3
4			82.1
5			88.9
6			>99
7			97.1
8			85.7
9			65.4
10			73.8
11			69.1
12			72.5
13			74.1
14			88.9
15			86.6

Table 1 (*Contd.*)

Entry	Aldehydes	Unsaturated cyclohexenones	Yield^b (%)
16			76.6

^{a} All the reactions were carried out at room temperature and under atmospheric pressure. ^{b} GC yield.

and acetone (100 mL, 1362 mmol) was charged and eluted with dehydrated ethanol (250 mL) at room temperature and at atmospheric pressure at a flow rate of around 0.1 mL min^{-1}. The reaction solution relied on gravity downflow. The collected solution was recharged into the chromatography column and this procedure was repeated 10 times. The resultant product mixture was subjected to GC, GC-MS and NMR analysis. The chemical structure of the product was verified by NMR spectroscopy (Fig. S3†) and the yield was about 82.1%, as determined by GC measurement (Table 1, entry 4). In the above reaction process we observed that the α, β-unsaturated ketones were generated as intermediates (Scheme 2), which further reacted with acetone to afford the final α, β-unsaturated cyclohexenones *via* Michael addition and Robinson cyclization.

Under the conditions used for the formation of α, β-unsaturated cyclohexenone from benzaldehyde and acetone, we further examined the catalytic ability of **Si-LP** using other aldehyde substrates that contain aromatic, aliphatic or heterocyclic subgroups (Table 1). As shown in Table 1, almost all the aldehyde substrates were quantitatively converted to their corresponding cyclohexenone products (Table 1, entries 2–16). For example, aromatic aldehydes such as *p*-bromobenzaldehyde and *p*-cyanobenzaldehyde (Table 1, entries 6 and 7) gave the highest yields of around 99 and 97.1%, respectively (Table 1, entries 4 and 5). Other *para*-substituted substrates as well as benzaldehyde that contain methoxy, ethoxy, propoxy, phenyl, hydroxy or chloro groups exhibited a relatively high conversion with acceptable yields (Table 1 entries 8–12 and 5). The yields for heterocyclic aldehydes (Table 1, entries 13–16) were still attractive at 74.1% to 88.9%. In the control, when the synthesis was performed as a batch reaction, under the same conditions, the yield was obviously lower than that from the continuous-flow approach (Table S1†).

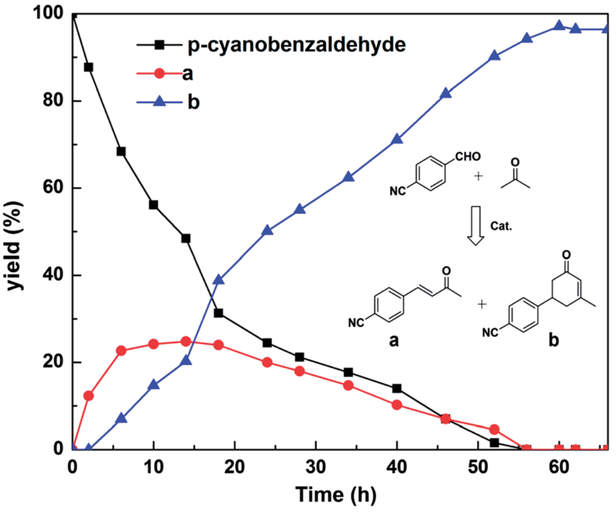


Fig. 1 Time–conversion plots for the generation of α, β-unsaturated cyclohexenones from *p*-cyanobenzaldehyde and acetone with **Si-LP** as the catalyst.

Electron-withdrawing effects have a great impact on these reactions. The substrates containing chloro, bromo or cyano groups enhanced the electron-withdrawing effects of the benzene rings, which resulted in a higher yield (Table 1, entries 5–7) compared with substrates containing methoxy, ethoxy or propoxy groups (Table 1, entries 9–11). Additionally, substrates containing obvious electron-donating groups such as formaldehyde, butyraldehyde, *p*-biphenylaldehyde and *p*-hydroxybenzaldehyde gave yields of 50.5, 55.7, 72.5 and 85.7% (Table 1, entries 1, 2, 8 and 12), respectively.

To obtain more information about the mechanism of this catalytic process, GC measurements were carried out to study the model reaction between *p*-cyanobenzaldehyde and acetone with **Si-LP** as the catalyst over time. The kinetic curve of the transformation from *p*-cyanobenzaldehyde to cyclohexenone is shown in Fig. 1. During the reaction, the concentration of a appeared to increase over the first 18 h and then decreased upon its conversion to the cyclohexenone compound b. The reaction is complete in 60 h. α, β-unsaturated ketone a was observed to be an intermediate in the reaction between the aldehyde and acetone, and it can further react with acetone to afford cyclohexenone b *via* Michael addition and Robinson cyclization.

In summary, we successfully developed an efficient, environmentally friendly method for the generation of cyclohexenone using a L-proline immobilized silica gel catalyst by a continuous-flow approach. Because of the many advantages exhibited by our system such as catalyst recyclability, ease of product isolation and mild reaction conditions, this system may be a useful guideline for the design of more efficient methods of cyclohexenone production with industrial application possibilities. Further investigations into the L-proline immobilized silica gel catalyst for wider applications are ongoing in our laboratory.

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Notes and references

1 (*a*) J. Becker and K. Bergander, *Angew. Chem., Int. Ed.*, 2008, **47**, 1654–1657; (*b*) T. Findley, D. Sucunza, L. Miller, D. Davies and D. Procter, *Chem. –Eur. J.*, 2008, **14**, 6862–6865.
2 (*a*) S. Senguttuvan and S. Nagarajan, *J. Heterocycl. Chem.*, 2009, **46**, 1346–1348; (*b*) B. D. Chong and Y. I. Ji, *J. Org.*

Chem., 1997, **62**, 9323–9325; (*c*) D. B. Ramachary and K. Ramakumar, *J. Org. Chem.*, 2007, **72**, 1458–1463.

3 (*a*) N. Itagaki and M. Kimura, *Org. Lett.*, 2005, **7**, 4185–4188; (*b*) G. Stork and A. Brizzolara, *J. Am. Chem. Soc.*, 1963, **85**, 207–222; (*c*) V. H. Rawal and S. A. Kozmin, *J. Am. Chem. Soc.*, 1999, **121**, 9562–9573; (*d*) L. A. Paquette, R. Guevel, S. Sakamoto and I.-H. Kim, *J. Org. Chem.*, 2003, **68**, 6069–6107; (*e*) Y. Inokoishi, N. Sasakura, K. Nakano, Y. Ichikawa and H. Kotsuki, *Org. Lett.*, 2010, **12**, 1616–1619; (*f*) Y. K. Liu, C. Ma, K. Jiang, T. Y. Liu and Y. C. Chen, *Org. Lett.*, 2009, **11**, 2848–2851; (*g*) L. Chen, S. Luo, J. Li, X. Li and J. P. Cheng, *Org. Biomol. Chem.*, 2010, **8**, 2627–2632; (*h*) Y. Hayashi, M. Toyoshima, H. Gotoh and H. Ishikawa, *Org. Lett.*, 2008, **11**, 45–48; (*i*) H. Yang and R. G. Carter, *Org. Lett.*, 2010, **12**, 3108–3111; (*j*) M. D. Pierce, R. C. Johnston, S. Mahapatra, H. Yang, R. G. Carter and P. H. Y. Cheong, *J. Am. Chem. Soc.*, 2012, **134**, 13624–13631; (*k*) T. I. Houjeiry, S. L. Poe and D. T. McQuade, *Org. Lett.*, 2012, **14**, 4394–4397.

4 J. Evarts, E. Torres and P. L. Fuchs, *J. Am. Chem. Soc.*, 2002, **124**, 11093–11101.

5 (*a*) K. Chen and P. S. Baran, *Nature*, 2009, **459**, 824–828; (*b*) K. C. Nicolaou and D. Sarlah, *Angew. Chem., Int. Ed.*, 2007, **119**, 4792–4795.

6 H. F. Cui, Y. Q. Yang, Z. Chai, P. Li, C. W. Zheng, S. Z. Zhu and G. Zhao, *J. Org. Chem.*, 2009, **75**, 117–122.

7 (*a*) L. W. Xu, J. Luo and Y. Lu, *Chem. Commun.*, 2009, **14**, 1807–1821; (*b*) L. W. Xu and Y. Lu, *Org. Biomol. Chem.*, 2008, **6**, 2047–2053.

8 *Handbook of asymmetric heterogeneous catalysis*, ed. K. Ding and Y. Uozumi, Wiley-VCH, Germany, 2008.

9 (*a*) X. Liu, R. S. Ding, L. He, Y. M. Liu, Y. Cao, H. Y. He and K. N. Fan, *ChemSusChem*, 2013, **6**, 604–608; (*b*) J. Seayad, P. K. Patra, Y. Zhang and J. Y. Ying, *Org. Lett.*, 2008, **10**, 953–956.

10 (*a*) K. Sakthivel and W. Notz, *J. Am. Chem. Soc.*, 2001, **123**, 5260–5267; (*b*) X. Wu and C. He, *Chem. Commun.*, 2011, **47**, 8415–8417; (*c*) N. Zotova and A. Franzke, *J. Am. Chem. Soc.*, 2007, **129**, 15100–15101; (*d*) M. Gruttadauria and S. Riela, *Tetrahedron Lett.*, 2004, **45**, 6113–6116; (*e*) B. List and L. Hoang, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 5839–5842; (*f*) A. G. Doyle and E. N. Jacobsen, *Chem. Rev.*, 2007, **107**, 5713–5743.

11 (*a*) A. Martínez-Castañeda and H. Rodríguez-Solla, *J. Org. Chem.*, 2012, **77**, 10375–10381; (*b*) M. Gruttadauria and F. Giacalone, *Chem. Soc. Rev.*, 2008, **37**, 1666–1688; (*c*) R. Mestres, *Green Chem.*, 2004, **6**, 583–603; (*d*) G. J. Kelly and F. King, *Green Chem.*, 2002, **4**, 392–399.

12 (*a*) K. Akagawa and S. Sakamoto, *Tetrahedron Lett.*, 2005, **46**, 8185–8187; (*b*) J. Kofoed and J. Nielsen, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 2445–2447; (*c*) D. Font and S. Sayalero, *Org. Lett.*, 2008, **10**, 337–340.

13 (*a*) *Microreactors in Organic Chemistry and Catalysis*, ed. T. Wirth, Wiley-VCH, Singapore, 2013; (*b*) F. Calderón and R. Fernández, *Adv. Synth. Catal.*, 2005, **347**, 1395–1403.

14 (*a*) E. A. Prasetyanto and S. C. Lee, *Chem. Commun.*, 2008, **17**, 1995–1997; (*b*) C. Aprile and F. Giacalone, *Green Chem.*, 2007, **9**, 1328–1334.

15 S. Luo and X. Zheng, *Chem. Commun.*, 2008, **44**, 5719–5721.

16 (*a*) S. B. Ötvös, Ph.D. Dissertation, University of Szeged Institute of Pharmaceutical Chemistry, Szeged, 2013; (*b*) J. Wegner and S. Ceylan, *Chem. Commun.*, 2011, **47**, 4583–4592; (*c*) F. Lévesque and P. H. Seeberger, *Org. Lett.*, 2011, **13**, 5008–5011; (*d*) D. B. Ushakov, K. Gilmore, D. Kopetzki, D. T. McQuade and P. H. Seeberger, *Angew. Chem., Int. Ed.*, 2014, **53**, 557–561.

17 (*a*) J. G. Stevens and R. A. Bourne, *Green Chem.*, 2009, **11**, 409–416; (*b*) J. Wegner and S. Ceylan, *Adv. Synth. Catal.*, 2012, **354**, 17–57; (*c*) F. E. Valera and M. Quaranta, *Angew. Chem., Int. Ed.*, 2010, **49**, 2478–2485; (*d*) S. Martín, R. Porcar, E. Peris, M. I. Burguete, E. García-Verdugo and S. V. Luis, *Green Chem.*, 2014, **16**, 1639–1647.

18 (*a*) A. Massi and A. Cavazzini, *Tetrahedron Lett.*, 2011, **52**, 619–622; (*b*) O. Bortolini and A. Cavazzini, *Chem. –Eur. J.*, 2013, **19**, 7802–7808; (*c*) Y. Arakawa and M. Wiesner, *Adv. Synth. Catal.*, 2011, **353**, 1201–1206.

19 (*a*) E. Alza and S. A. Sayalero, *Chem. –Eur. J.*, 2009, **15**, 10167–10172; (*b*) N. Nikbin and P. Watts, *Org. Process Res. Dev.*, 2004, **8**, 942–944; (*c*) N. T. Phan and D. H. Brown, *Green Chem.*, 2004, **6**, 526–532.

20 (*a*) A. Zamboulis and N. J. Rahier, *Tetrahedron: Asymmetry*, 2009, **20**, 2880–2885; (*b*) B. Karimi and A. Biglari, *Angew. Chem., Int. Ed.*, 2007, **46**, 7210–7213; (*c*) E. G. Doyagüez and F. Calderón, *J. Org. Chem.*, 2007, **72**, 9353–9356; (*d*) D. Dhar and I. Beadham, *Proc. – Indian Acad. Sci., Chem. Sci.*, 2003, **115**, 365–372.