COMMUNICATION

ChemComm
www.rsc.org/chemcomm

Sonochemical asymmetric hydrogenation of isophorone on proline modified Pd/Al_2O_3 catalysts

Shilpa C. Mhadgut, Imre Bucsi, Marianna Török and Béla Török*

Department of Chemistry, Michigan Technological University, 1400 Townsend Drive, Houghton, MI 49931, USA. E-mail: btorok@mtu.edu

Received (in Corvallis, OR, USA) 24th November 2003, Accepted 26th February 2004
First published as an Advance Article on the web 19th March 2004

The sonochemical asymmetric hydrogenation of isophorone (3,3,5-trimethyl-2-cyclohexenone) by proline-modified Pd/Al_2O_3 catalysts is described; presonication of a commercial Pd/Al_2O_3-proline catalytic system resulted in highly enhanced enantioselectivities (up to 85% ee).

As one of the most versatile methods in asymmetric synthesis, enantioselective hydrogenations pioneered by Knowles, Noyori, and Kagan have attracted great attention.[1] Heterogeneous catalytic hydrogenation processes modified by inexpensive, readily available natural products are, however, novel alternatives for homogeneous methods.[2] The recyclable, stable solid catalysts could replace sensitive, toxic metal complexes.[3] The vigorous expansion in the field of heterogeneous chiral hydrogenations has been summarized in several reviews.[4,5] Especially, asymmetric hydrogenation of α-ketoesters on cinchona-modified platinum catalysts has received significant attention.[5] A number of successful examples when enantiomeric excesses (ee) exceed 95% have been published recently.[6] Similar high ee values were reported in the hydrogenation of β-ketoesters on tartrate-modified Raney-Ni catalyst.[7]

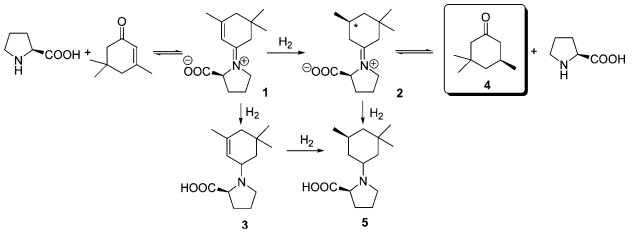
In contrast, highly selective heterogeneous processes are still under development for enantioselective hydrogenation of C=C double bonds. Chiral hydrogenation of methoxypyrone on cinchona-modified Pd/TiO_2 gave very high enantioselectivity (up to 94% ee) at small scales (1 mg), but selectivity was lost at higher substrate/catalyst ratios.[8] Other remarkable examples include the hydrogenation of 2-methyl-2-pentenoic acid (66% ee)[9] and α-phenylcinnamic acid (72% ee).[10] Besides cinchona alkaloids, (*S*)-proline was also used as chiral modifier for C=C double bond hydrogenation of isophorone.[11] The system was extensively studied and the highest ee obtained was 56%.[12] A recent review by Studer *et al*. gives complete coverage on heterogeneous catalytic asymmetric hydrogenations.[13]

After the first application of ultrasound in catalysis[14] it has been extended to asymmetric hydrogenations as reviewed.[15] A detailed study concerning the effect of ultrasonic variables on asymmetric hydrogenations was published recently.[16] As the growing number of recent papers indicates, the application of ultrasounds in heterogeneous catalysis is expanding rapidly.[17]

Continuing our efforts on heterogeneous asymmetric catalysis, here we report the highly improved asymmetric hydrogenation of isophorone over proline modified Pd/Al_2O_3 catalysts.† The great advantage of ultrasonic pretreatment will be shown and an interpretation for this effect will be proposed.

Although use of (*S*)-proline as a modifier in enantioselective hydrogenations[11,12,18] was established long ago, recent publications on application of proline and similar systems in asymmetric catalysis[19] renewed the interest in this "old-new" chiral modifier. As a test reaction, the hydrogenation of isophorone was selected. The mechanism proposed earlier involves formation and hydrogenation of intermediate **1** to dihydroisophorone (**4**).[12] As a result of a possible side reaction, **5** can also form in the system. Other chiral auxiliaries resulted in no ee increase.[18] Pd/C catalysts showed the best performance.[11]

Although, we did not have access to those catalysts,[12] our experience with commercial Pd/C catalysts was not favourable. Among the catalysts tested Pd/Al_2O_3 gave the best ee values. The chemoselectivity (ratio of **4** and **5**) was also found to be favourable.



Since our reaction conditions do not involve high temperature reaction of proline and isophorone, formation of **5** can be highly suppressed (less than 5%). As a result, a 5% Pd/Al_2O_3 (Engelhard, code 40692) reference catalyst was selected for further studies. Testing proline derivatives (*e.g.* isomeric hydroxy-prolines, prolinols, or proline esters) and related structures (*e.g.* MacMillan's catalyst or nicotine) as modifiers we found that, in agreement with the literature,[11] the best modifier is proline. Both proline enantiomers gave ee values up to 35% ee. The proline derivatives resulted in decreased ee values, and other modifiers gave poor enantioselectivities. It is worth noting, that the recently developed MacMillan catalyst,[19] that induces excellent ee in homogeneous reactions, completely failed in the hydrogenations. It is most likely due to the weak adsorption capability of the MacMillan catalyst. According to the above data further studies were carried out using (*S*)-proline as modifier.

The application of ultrasonic irradiation is usually beneficial in catalytic hydrogenations.[16] It was found that the major effect is enhanced adsorption of the chiral modifier as sonication removes surface impurities. Accordingly, we studied the effect of ultrasonics on the present system. The effect of different presonication methods on the catalyst under standard conditions are summarized in Table 1.

The data clearly show that presonication results in enantioselectivity improvement only when both catalyst and modifier are present in the solvent. "Modifier-free" presonication and presence of substrate during pretreatment decreased enantioselectivity.

Similar to our previous experience the ee values passed through a maximum as a function of sonication time. It was found that 20 min presonication resulted in the highest optical yields. Based on the above experiments we concluded that for our model system, the optimum occurs when the catalyst/modifier system is sonicated in the solvent for 20 min. Further investigations will be carried out using these conditions.

As the effect of hydrogen is crucial in hydrogenation systems, we studied the effect of hydrogen pressure on the reaction. The ee *vs*. hydrogen pressure functions with and without presonication are illustrated on Fig. 1.

Table 1 Effect of presonication method on the hydrogenation of isophorone at RT and 10 bar hydrogen pressure (standard system (see Notes), 20 min presonication) ((*S*) product formed in excess)

Components in the pretreated system	Presonication	ee (%)
Catalyst + Solvent + Modifier	No	34
Catalyst + Solvent	Yes	18
Catalyst + Solvent + Modifier	Yes	52
Catalyst + Solvent + Modifier + Reactant	Yes	22

DOI: 10.1039/b315244h

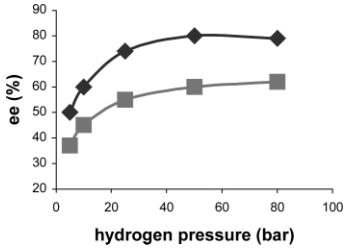


Fig. 1 Effect of hydrogen pressure on enantiomeric excess in the hydrogenation of isophorone on (*S*)-proline modified Pd/Al_2O_3 catalyst (■ no sonication, ◆ 20 min presonication, standard system.

As the results show, presonication increased optical yields throughout the hydrogen pressure range. The best ee value obtained with presonication exceeds 80% ee. As we are able to achieve a steady ee value above 40 bar hydrogen pressure 50 bar pressure was selected for further investigations.

The effect of catalyst/substrate ratio on selectivity is also an important parameter. We studied the effect of different substrate amounts on enantioselectivity. Fig. 2 illustrates the ee *vs.* isophorone amount obtained with and without ultrasonic irradiation. We observed maximum ee in both cases corresponding to a 1 : 2 isophorone–proline ratio. Using optimized conditions we were able to obtain an unprecedented high enantiomeric excess (85% ee for (*S*) product) in the present reaction.

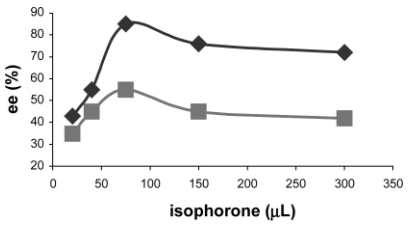


Fig. 2 Effect of reactant amount on enantiomeric excess in the hydrogenation of isophorone on (*S*)-proline modified Pd/Al_2O_3 catalyst (■ no sonication, ◆ 20 min presonication, standard system, 50 bar).

As ultrasounds initiate important changes on the catalyst[16] we studied the catalysts by high-resolution electron microscopy. It was observed that presonication decreased the mean metal particle size from 4.1 nm to 3.2 nm (after 10 min), 1.8 nm (after 20 min), 1.4 nm (after min), respectively. The particle size decrease was not dependent on the use of proline. According to Table 1, modifier-free sonication decreased ee values. As a result we propose that the surface cleaning effect of ultrasounds enhanced both adsorption of the modifier and the modifier induced surface restructuring of the metal.[21] The joint effect of the two phenomena resulted in more effective enantiodifferentiation. We also suggest that the key factor (or the first step in the mechanism) in achieving high ees in this system is adsorption of proline on the catalyst surface. Without strong modifier adsorption high enantioselectivity cannot be achieved in these cases.

In conclusion, our method successfully enhanced the enantiodifferentiation (up to 85% ee) in the hydrogenation of isophorone by proline-modified Pd/Al_2O_3 catalyst. Most importantly, our results clearly indicated that enhanced modifier adsorption is a crucial factor in this process. Based on these findings design of new catalysts capable of strong adsorption of proline may open up new effective heterogeneous catalytic processes for C=C double bond hydrogenation of α,β-unsaturated carbonyl compounds.

Financial support provided by the Michigan Space Grant Consortium, ACS Petroleum Research Fund and Michigan Technological University is highly appreciated. Authors thank Prof. D. K. Bates for valuable discussion.

Notes and references

† All chemicals used were of analytical grade and purchased form Aldrich and Acros. The catalyst used was 5% Pd/Al_2O_3 (Engelhard, code 40692).

General procedure for hydrogenation of isophorone. Presonication of catalyst-modifier systems and hydrogenation reactions were carried out at 25 °C as described earlier.[20] The standard system included 50 mg of 5% Pd/Al_2O_3, 1.0 mmol of (*S*)-proline, 5 ml of MeOH, and 1.0 mmol substrate. Alterations will be noted separately. The absolute configuration of the major product was determined by comparison with a known sample. Product identification was monitored by GC-MS (Shimadzu QP 5050 System), while the enantiomeric excesses (ee % = $|[R] - [S]| \times 100/([R] + [S])$) were determined at close to 100% conversion (> 98%) by gas chromatography (HP 5890 GC-FID, 30 m long Betadex (Supelco) capillary column).

Transmission electron microscopy (TEM). Measurements were performed with a JEOL 4000FX HREM as described earlier.[20]

1 G. Consiglio, in *Encyclopedia of Catalysis*, ed. I. T. Horváth, Wiley, New York, 2003, **vol. 1**, p. 407.
2 M. Bartók and Á. Molnár, Heterogeneous Catalytic Hydrogenation, in *Chemistry of Functional Groups*, Suppl. A3. ed. S Patai, Wiley, Chichester, 1997, ch. 16, p. 843; G. V. Smith and F. Notheisz, *Heterogeneous Catalysis in Organic Chemistry*, Academic Press, San Diego, 1999.
3 D. E. de Vos, I. F. J. Vankelecom and P. A. Jacobs, eds., *Chiral Catalyst Immobilization and Recycling*, Wiley-VCH, Weinheim, 2000.
4 A. Baiker and H.-U. Blaser, *Handbook of Heterogeneous Catalysis*, G. Ertl, H. Knözinger and J. Weitkamp, eds., Wiley-VCH, Weinheim, 1997, **vol. 5**, p. 2422.
5 H.-U. Blaser, H.-P. Jalett, M. Müller and M. Studer, *Catal. Today*, 1997, **37**, 441; A. Baiker, *J. Mol Catal. A*, 2000, **163**, 205.
6 B. Török, K. Felföldi, K. Balázsik and M. Bartók, *Chem. Commun.*, 1999, 1725; M. Studer, S. Bukhardt and H.-U. Blaser, *Chem. Commun.*, 1999, 1727; C. Leblond, J. Wang, J. Liu, T. Andrews and Y. Sun, *J. Am. Chem. Soc.*, 1999, **121**, 4920; K. Balázsik, K. Szöri, K. Felföldi, B. Török and M. Bartók, *Chem. Commun.*, 2000, 555; M. Studer, S. Burkhardt, A. F. Indolese and H. U. Blaser, *Chem. Commun*, 2000, 1327; M. von Arx, T. Mallat and A. Baiker, *Angew. Chem., Int. Ed.*, 2001, **40**, 2302; M. Sutyinszki, K. Szöri, K. Felföldi and M. Bartók, *Catal. Commun.*, 2002, **3**, 125.
7 T. Sugimura, T. Osawa, S. Nakagawa, T. Harada and A. Tai, *Stud. Surf. Sci. Catal.*, 1996, **101**, 231.
8 W. R. Huck, T. Mallat and A. Baiker, *Catal. Lett.*, 2002, **80**, 87.
9 K. Borszeky, T. Mallat and A. Baiker, *Tetrahedron: Asymm.*, 1997, **8**, 3745; I. Kun, B. Török, K. Felföldi and M. Bartók, *Appl. Catal. A: Gen.*, 2000, **203**, 71.
10 Y. Nitta and K. Kobiro, *Chem. Lett*, 1996, 897.
11 A. Tungler, *React. Kinet. Catal. Lett.*, 2001, **74**, 271.
12 A. Tungler, T. Máthé, J. Petró and T. Tarnai, *J. Mol. Catal.*, 1991, **61**, 259.
13 M. Studer, H.-U. Blaser and C. Exner, *Adv. Synth. Catal.*, 2003, **345**, 45.
14 J. W. Chen, J. A. Chang and G. V. Smith, *Chem. Eng. Symp. Ser.*, 1971, 67.
15 K. S. Suslick, *Handbook of Heterogeneous Catalysis*, G. Ertl, H. Knözinger and J. Weitkamp, eds., Wiley-VCH, Weinheim, 1997, **vol. 3**, p. 1350; B. Török, K. Balázsik, K. Felföldi and M. Bartók, *Ultrasonics Sonochem.*, 2001, **8**, 191.
16 B. Török, K. Balázsik, M. Török, K. Felföldi and M. Bartók, *Catal. Lett.*, 2002, **81**, 55.
17 J. P. Mikkola, T. Salmi, R. Sjoholm, P. Maki-Arvela and H. Vainio, *Stud. Surf. Sci. Catal.*, 2000, **130C**, 2027; J. J. Lee, H. Kim and S. H. Moon, *Appl. Catal. B: Environ.*, 2003, **41**, 171.
18 É. Sipos, A. Tungler and I. Bitter, *J. Mol. Catal. A*, 2003, **198**, 167.
19 N. A. Paras and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2001, **123**, 4370; B. List, *Tetrahedron*, 2002, **58**, 5573.
20 B. Török, K. Felföldi, G. Szakonyi, K. Balázsik and M. Bartók, *Catal. Lett.*, 1998, **52**, 81.
21 R. Hess, F. Krumeich, T. Mallat and A. Baiker, *Catal. Lett.*, 2004, **92**, 141.