Catalysis Communications 11 (2010) 584–587

Contents lists available at ScienceDirect

Catalysis Communications

journal homepage: www.elsevier.com/locate/catcom

Cinchona-modified Ru catalysts for enantioselective heterogeneous hydrogenation of aromatic ketones

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ARTICLE INFO

Article history:
Received 13 September 2009
Received in revised form 25 November 2009
Accepted 16 December 2009
Available online 23 December 2009

Keywords:
Alkaloids
Asymmetric catalysis
Ruthenium
Ketones
Supported catalysts

ABSTRACT

In this communication, we describe the highly enantioselective heterogeneous hydrogenation of aromatic ketones catalyzed by Ph_3P stabilized Ru/γ-Al_2O_3, and modified by chiral diamines derived from cinchona alkaloids. A broad range of aromatic ketones over this catalyst can be hydrogenated to the corresponding alcohols with impressive enantioselectivity.

1. Introduction

"Green chemistry" favors the catalytic process induced by heterogeneous catalysts over homogeneous ones in view of their ease of handling, simple workup and regenerability [1–6]. However, up to now, there has been just very limited number of established enantioselective heterogeneous system compared with homogeneous ones mainly due to differences between homogeneous and heterogeneous catalysis. Chiral transition metal complexes, single-site catalysts with a defined shape and stereochemistry, induces, in general, higher enantioselectivity in asymmetric synthesis since they permit unidirectional introduction of the reacting species onto a prochiral substrate in the three-dimensional space to generate the asymmetric center. Conversely, heterogeneous catalysts are not as effective as chiral transition metal complexes due to their multisite active sites resulting from assorted crystal structures with different shapes and sizes, their steric restrictions, and also different form of coordination or adsorption of modifiers on complicated catalyst surface. Hence, creation of desired stereochemistry in heterogeneous catalysts to build high efficient chiral induction is a challenging problem [7]. We focus on the asymmetric hydrogenation of simple aromatic ketones, an important organic transformation, since the resulting chiral alcohols are versatile precursors to many natural products and drug molecules. These hydrogenation reactions are remarkably developed in homogeneous catalytic reactions reflected by the Nobel prize in 2001 awarded to Noyori et al. [8,9]. But when considering heterogeneous enantioselective hydrogenation of simple aromatic ketone and its derivatives, a few successful catalytic example was reported except our recent reports [10,11]. Such as, Zhao et al. [17] reported DPEN (1,2-diphenylethylene-diamine) and phosphine modified 5%Ru/γ-Al_2O_3 for the enantioselective hydrogenation of acetophenone with the best enantiometric excess of 60.5%. We previously reported DPEN modified 1%Ru/γ-Al_2O_3/2tpp (tpp = triphenylphosphine) for the asymmetric hydrogenation of aromatic ketones with the best enantioselectivity of 78% [11]. Very recently, we succeed in heterogeneous enantioselective hydrogenation of aromatic ketones employing cinchona- and phosphine-modified iridium as catalysts [10], with enantioselectivity up to 96%. As part of our ongoing research, we now introduce cinchona alkaloid derivatives, which were successfully applied in modifying heterogeneously enantioselective hydrogenation of α-functionalized ketones [12–14] and selected activated C=C bonds [15,16], as chiral modifiers in order to further optimize the stereochemistry of our catalyst system, and we herein report an impressive example in the asymmetric hydrogenation of simple aromatic ketone and its derivatives, with comparable ee's to that of the homogeneous system, catalyzed by Ph_3P stabilized Ru/γ-Al_2O_3 modified by chiral diamine derived from cinchona alkaloids.

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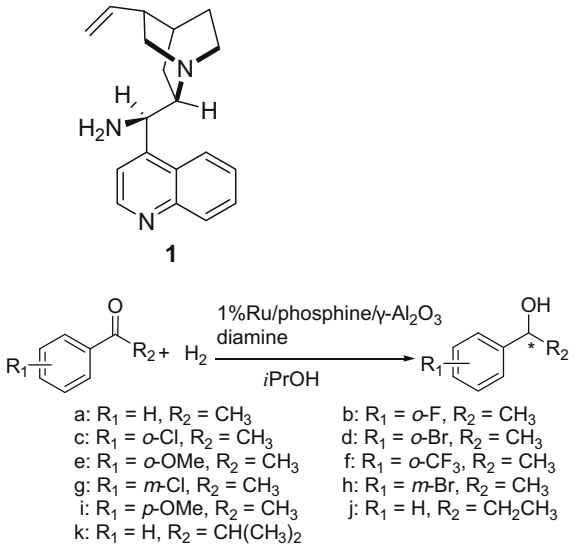
doi:10.1016/j.catcom.2009.12.024

2. Results and discussion

Phosphine stabilized 1%Ru/γ-Al_2O_3 catalysts were prepared according to our previously reported method [11]. This catalyst system was well elucidated to be a heterogeneous catalysis by conventional filtering test [17,18], etc. in our previous report [11]. The solution and catalyst were separated at the end of the hydrogenation or at low conversion (15%), by high speed centrifugation under argon atmosphere. It was found that the reacted solution had no catalytic activity after some fresh substrate was introduced in it. However, the catalyst obviously maintained the hydrogenation activity and enantioselectivity. After the first hydrogenation of acetophenone, the filtrate was determined by ICP-AES, only 0.03% Ru and 0.36% PPh_3 were leached to the organic solvent. The molar ratio of PPh_3/Ru leached into solution is large (12:1), which might poisoned metal Ru leached into the solution according to literature [10,28] and experiment phenomena (Fig. 2 in Supplementary material). Furthermore, the content of Cl in 1%Ru/γ-Al_2O_3/2tpp was measured by X-ray photoelectron spectroscopy (XPS) [19], and no Cl was detected. The catalysts are remarkably stable in the solid state and can be stored open to air.

IR is effective for the investigation of the mutual ligand–metal–support interactions of solid catalysts [10,29]. Information on the interaction between the metal and the phosphine was confirmed by FTIR methods in which the red shift of the P-C_6H_5 deformation around 1434 cm^{-1} in 1%Ru/γ-Al_2O_3/2tpp is an indication of the coordination of PPh_3 to the metal. Interaction between the cinchona alkaloid and the metal was also confirmed by FTIR analysis in which the blue shift of the N–H deformation around 3366 cm^{-1} in 1%Ru/γ-Al_2O_3/2tpp/diamine **1** is an indication of the coordination of the amine with the metal. It is worth noting that similar phenomena were observed in our previous report [10].

Asymmetric hydrogenation of aromatic ketones was performed in a 20 ml stainless autoclave with a magnetic stirrer bar, by using PPh_3 stabilized 1%Ru/γ-Al_2O_3 as a catalyst, in the presence of chiral diamine **1** (9-amino(9-deoxy)epicinchonine) (Scheme 1) derived from natural cinchona alkaloid as chiral modifier. Up to 99% conversion and 83% ee were obtained for the asymmetric hydrogenation of acetophenone. However, the hydrogenation of acetophenone catalyzed by 1%Ru/γ-Al_2O_3 just showed a conversion of as low as 4% and an ee of 10% in the presence of chiral diamine **1**. Classically modified 1%Ru/γ-Al_2O_3 catalyst with tpp and chiral modifier **1** obtained 39% conversion and 68% ee (40 °C, 40 h). These indicate that phosphine not only stabilized the metal particles in the preparation of catalyst but also served to additionally modify the supported metal with diamine in the asymmetric hydrogenation. Because of the famous Ru/phosphine/diamine catalyst in homogeneous catalysis [8,9], the homogeneous $RuCl_2[P(C_6H_5)_3]_3$/diamine **1** catalyst was also investigated according to the literature [9] for the hydrogenation of acetophenone but poor result was given (50% ee). Mercury-poisoning experiment [20–23], which can selectively poison metal nanoparticles, by forming an amalgam with mercury, is now used to clarify whether Noyori-type Ru(II) catalyst confined in the porous γ-Al_2O_3 solids or ligands modified Ru(0) catalyst plays the catalytic role in our system. In such an experiment for our system, the conversion in the presence of modifier **1** was 24% after the initial 60 min; mercury was then added under argon atmosphere and the reaction was completely terminated as evidenced by no change in the conversion (24.5%) after an additional reaction time of 2 h (Fig. 3 in Supplementary material). So, the possibility of Noyori-type Ru(II) catalyst confined in the porous γ-Al_2O_3 solids is denied. Since the properties of the stabilizers greatly influence the particle size and dispersion of the reduced metal in the catalyst, phosphines, such as tris(4-methoxyphenyl)phosphine (motpp), tris(4-trifluoromethylphenyl)phosphine (tftpp), tris(sodium-m-sulfonatophenyl) phosphine (tppts), 1,2-bis(diphenylphosphinomethyl)benzene (bdpx), 2,2′-bis(diphenylphosphinomethyl)-1,1′-biphenyl (bisbi), were tested (Table 2 in Supplementary material), however, none of them were better than the simple PPh_3. Furthermore, the influence of molar ratio of PPh_3 to Ru on the catalytic performance was investigated. When the initial molar ratio of PPh_3 to Ru is 2:1 in the preparation of catalysts, the highest activity and enantioselectivity was obtained. Increasing or decreasing the ratio of PPh_3 to Ru was unfavorable to both the activity and the enantioselectivity (Fig. 2 in Supplementary material). Since the choice of solvent has a great impact on the enantioselectivity of the hydrogenation, different solvents were tested (Table 1 in Supplementary material). *i*PrOH is the best choice for a solvent. The reaction in methanol or ethanol is much slower, while H_2O, THF and toluene are not usable. Similar to some previous work [11,17], the results during solvent choice indicated that solvent polarity obviously influence hydrogenation activity and enantioselectivity. In the absence of H_2, no conversion was observed with or without modifier. So, the absence of transfer hydrogenation was confirmed according to literature [9]. Ligand acceleration, which is commonly perceived in heterogeneous catalytic systems [10,11,24], is also observed in this system. Cinchona modifiers not only render the catalyst enantioselective but strongly accelerate the hydrogenation. However, if in the absence of modifier **1**, the conversion of acetophenone hydrogenation was only 4% and the racemic product was obtained (Fig. 1 in Supplementary material). The addition of both modifier **1** and KOH greatly enhanced the activity (Table 1, entry 1). Similar to some recent reports [17,25], a high modifier concentration is needed in the simple aromatic ketone asymmetric hydrogenation. By using 1 mol% (compared to supported metal Ru) of chiral diamine **1**, the enantioselectivity was maintained during the asymmetric hydrogenation at a prolonged time (40 °C, 40 h, 100% conversion and 72% ee). Similar to homogeneous [8,9] and some heterogeneous [11,17] reactions, a base is necessary to accelerate the reaction. The addition of different bases, such as *t*BuOK (17% conversion and 80% ee), LiOH (2% conversion and 40% ee), NaOH (96% conversion and 78% ee), KOH (99% conversion and 83% ee), can enhance both the activity and the enantioselectivity more or less. For the alkali metal hydroxides both activity and enantioselectivity decrease in the order of $K^+ > Na^+ > Li^+$. However, if there is no base in the reaction solution, the conversion was only 2% with 32% ee. The results during base choice indicated that the positive effect



Scheme 1. Modifier used and the general reaction.

Table 1
Enantioselective hydrogenation of aromatic ketones catalyzed by 1%Ru/phosphine/γ-Al_2O_3/diamine system.[a].

Entry	Substrate	Yield (%)	ee [%]	Config[b]
1	a	99	83	*S*
2[c]	a	>99	81	*S*
3	b	98	88	*S*
4	c	>99	91	*S*
5	d	>99	92	*S*
6	e	>99	98	*S*
7	f	>99	81	*S*
8	g	99	70	*S*
9	h	>99	66	*S*
10	i	97	86	*S*
11	j	99	78	*S*
12	k	50	15	*R*

[a] Reaction was carried out at 40 °C using diamine **1** as chiral modifier. Substrate: in a 2 ml *i*PrOH solution at [0.43 M], P_{H_2}: 6.0 MPa. Substrate/Ru/diamine = 500:1:2. [KOH] = 0.18 mol L^{-1}. Reaction time: 5 h. Products were analyzed by a GC instrument with an FID detector and β-DEX™ 120 capillary column.
[b] Determined by sign of rotation.
[c] The terminal double bond of modifier **1** was hydrogenated, reaction time: 3 h.

of the bases routed in both the strength of the base and the properties of its cation. These results suggest that a proper stabilizers, molar ratio of P/Ru, solvent and the combination of chiral diamine and KOH are helpful for the formation of the active catalytic species with chiral induction.

From established heterogeneous systems, it is easy to find that a small change in the structure of modifiers lead to interesting influence on the activity, the enantioselectivity, and the configuration of the product, providing useful information for understanding the reaction mechanism [26]. In our system, when the double bond in modifier **1** was hydrogenated, the reaction rate was enhanced for the hydrogenation of acetophenone, but the enantioselectivity was slightly decreased (Table 1, entry 1, 2). This result is an indication that double bond in the modifier **1** is helpful in creating a favorable steric environment for enantioselectivity. Furthermore, reaction rate acceleration was observed from the kinetic data of ligand **1** (Fig. 3 in Supplementary material). NMR indicated that terminal double bond in the modifier **1** has been hydrogenated after catalytic hydrogenation. When 9-amino(9-deoxy)epicinchonidine was used as a modifier, acetophenone was completely hydrogenated to corresponding alcohol product in the opposite configuration, however, the enantiometric excess is just 45%. Further employing 9-amino(9-deoxy)epiquinine as a modifier in the hydrogenation of acetophenone, the reaction progressed slowly with a low enantioselectivity (40 °C, 5 h, 30% conversion and 13% ee) in *R* configuration. This indicates the high specific correlation between the catalyst and substrate. Other modifiers, such as cinchonine, cinchonidine and quinine were tested, and the amine group in the 9-position of the modifier is essential (Table 3 in Supplementary material).

Some representative examples are listed in Table 1 for the asymmetric hydrogenation of aromatic ketones catalyzed by Ph_3P stabilized Ru/γ-Al_2O_3 modified by diamine **1**. The extent of the enantioselectivity appears to be delicately influenced by the structure of the diamine auxiliary as well as the substituent in the substrate. Ortho-substituent of acetophenone is favorable to improve the enantioselective of the hydrogenation, electron-donating group in the ortho-position of aromatic ring is remarkably helpful, and the highest enantiomatic excess was obtained in the hydrogenation of 2′-methoxyacetophenone (Table 1, entry 6). The enantiometric excess gradually decreases with the increase of the electron-drawing effect in the ortho-position (Table 1, entry 3–7). This is an indication that electronic effect in the ortho-position influences the enantioselectivity during the hydrogenation. It was found that when the substituent is in the meta- or para- position (Table 1, entry 8–10), the degree of enantioselection was sharply decreased in comparison to ortho-substituted counterparts. The enantioselectivity also noticeably decreased by increasing the bulkiness of the alkyl group from methyl to primary alkyls (Table 1, entry 1, 11). When the alkyl is isopropyl, the opposite enantiomer is formed with lower reactivity (Table 1, entry 12). The switch in chirality provides valuable hints to the nature of modifier-substrate-metal surface [1–6], mainly in the size of the alkyl group in the substrate. Conclusions can be made that different activities and enantioselectivities are traced to the electronic and steric effects of the substrates.

3. Conclusion

In conclusion, PPh_3 stabilized supported ruthenium catalyst, when modified by chiral diamine derived from cinchona alkaloids, exhibits high activity and impressive enantioselectivity for the hydrogenation of simple aromatic ketones, especially ortho-substituted aromatic ketones. The work reported herein succeed in the creation of modified heterogeneous catalysts for highly enantioselective heterogeneous hydrogenation of simple aromatic ketones. Additional works are ongoing.

4. Experimental section

Aromatic ketones were purchased from Aldrich. $RuCl_3{\cdot}3H_2O$ (Institute of Kunming Noble Metals, China) were used as received without further purification. Triphenylphosphine (PPh_3) and other reagents were of analytical grade. Purities of H_2 and N_2 were 99.99% and 99.9%. The surface area of γ-Al_2O_3 was 154 $m^2\ g^{-1}$. tppts [tris(sodium-m-sulfonatophenyl) phosphine], motpp [tris(4-methoxyphenyl)phosphine], tftpp [tris(4-trifluoromethylphenyl)phosphine], bdpx [1,2-bis(diphenylphosphinomethyl)benzene] and bisbi [2,2′-bis(diphenylphosphinomethyl)-1,1′-biphenyl] were synthesized according to known methods in our laboratory [11]. Phosphine stabilized 1%Ru/γ-Al_2O_3 catalysts were prepared according to our previously reported method [11] (1%Ru/γ-Al_2O_3/2tpp, S_{BET} = 135 $m^2\ g^{-1}$. The reduction of the S_{BET} indicates the attachment of the Ru-tpp to γ-Al_2O_3 surface). Cinchona alkaloid derivatives were synthesized according to literature [27].

The hydrogenation was performed in a 20 ml stainless autoclave with a magnetic stirrer bar. The desired amounts of catalyst (20 mg), diamine, base, solvent and substrate were added into the autoclave and then the autoclave was sealed and purged with pure hydrogen several times. After the reactants were heated to the desired temperature, the reaction timing began. The products were analyzed by a GC instrument with an FID detector and β-DEX120 capillary column. With the exception of aromatic alcohol, no other products were detected (GC–MS and NMR). The conversion and ee for each reaction were determined three times from three separate runs with an uncertainty of less than 0.5%.

Acknowledgements

This work was financially supported by the National Natural Science Foundation of China (No. 20272037) and the Doctor's Foundation of Education Ministry of China (No. 20030610022).

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.catcom.2009.12.024.

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