



Equilibrium shift induced by chiral nanoparticle precipitation in rhodium-catalyzed disulfide exchange reaction



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ABSTRACT

Chiral silica (*P*)-nanoparticles grafted with (*P*)-helicene recognize the molecular structure of a chiral diol disulfide in the presence of monool disulfide and dibutyl disulfide. The (*P*)-nanoparticles selectively adsorb the diol disulfide, aggregate, and precipitate from solution. Under rhodium-catalyzed equilibrium among three disulfides, the diol disulfide is removed from solution by precipitation, which induces an equilibrium shift in the solution. By conducting the precipitation experiment twice, we obtained the diol disulfide in 37% yield from a statistical 1:2:1 equilibrium mixture of three disulfides. The method is applied to a racemic monool disulfide, and an optically active diol disulfide is obtained via kinetic resolution and equilibrium shift.

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1. Introduction

Catalysis is a phenomenon in which a chemical substance, a catalyst, changes a reaction course without affecting the relative thermodynamic stability of substrates and products.¹ When products are thermodynamically stable than substrate, a product can be obtained, in principle, in a high yield; when the relative stability is comparable between substrates and products or favors substrates, a product cannot be obtained in a high yield. Then, devices are needed to shift the equilibrium to products according to the principle of Le Chatelier.^{2,3} Reaction conditions are adjusted, or alternatively, one of the products is removed from the system. Because the reaction conditions available for a catalytic reaction are generally limited, particularly in solution, the removal method has a broader applicability.

Conventional methods of removing a product under equilibrium reaction employ the removal of inorganic byproducts such as water and metal salts from reaction mixture to the gas phase (reactive distillation),⁴ to the aqueous phase,⁵ or to the solid phase (precipitation).⁶ These methods, however, have a limitation of being highly dependent on the physical properties of the inorganic byproducts such as boiling point, vapor pressure, and solubility. It is not applicable to catalytic reactions forming only organic products, where the physical properties are relatively similar. A few

exceptions are reported for the equilibrium shift by the removal of an ester product in an acid/base-catalyzed transesterification reaction by membrane permeation.⁷ Polymer imprinting was examined in an enzyme-catalyzed amide formation reaction.⁸ These methods, however, suffer from low molecular recognition ability and a limited substrate scope. The development of a versatile method of recognizing a certain structure of an organic molecule in a catalytic equilibrium reaction in solution and of removing a product from the solution is desired. Note that such a method must be compatible with catalysis.

We have recently reported the use of chiral silica (*P*)-nanoparticles (*P*)-**1** loaded with (*P*)-1,12-dimethyl-8-methoxycarbonylbenzo[*c*]phenanthrene for the optical resolution of aromatic secondary alcohols.⁹ Up to 61% ee of (*S*)-isomer was obtained, which was induced by chiral recognition, adsorption, aggregation, and precipitation of the enantiomer by (*P*)-**1**. We also described that the double-helix structure of an ethynylhelicene oligomer was adsorbed and precipitated by (*P*)-**1** in the presence of a random-coil form,¹⁰ which shifted the equilibrium from a random-coil to a double-helix in solution. It has then become a subject of interest whether the nanoparticle method can be applied to the equilibrium shift of small organic molecules with molecular weights of several hundreds daltons under metal catalysis.

We have been developing metal-catalyzed transformations of organoheteroatom compounds,¹¹ which often provide equilibrium reactions. In the rhodium-catalyzed organic disulfide exchange reaction,¹² three disulfides, namely R¹SSR¹, R¹SSR², and R²SSR², are formed in a statistical 1:2:1 mixture under equilibrium. To obtain

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a single product in a higher yield, the equilibrium needs to be shifted. In this paper, we describe such reaction using the (*P*)-nanoparticles by the molecular recognition of R^1SSR^1 , adsorption, aggregation, and precipitation (Fig. 1). The reaction provides products in higher chemical yields than those determined by equilibrium. The equilibrium shift with concomitant kinetic resolution was also conducted in this study under disulfide exchange reaction catalyzed by an achiral rhodium catalyst.

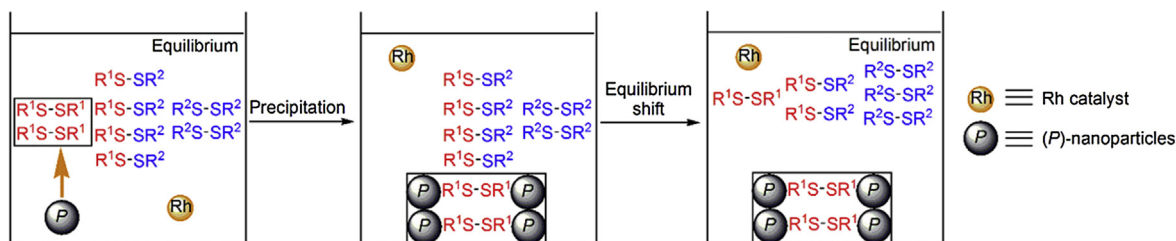


Fig. 1. Equilibrium shift in rhodium-catalyzed disulfide exchange reaction by removal of R^1SSR^1 .

2. Result and discussion

3-Aminopropylated silica nanoparticles of 70 nm average diameter were grafted with (*P*)-1,12-dimethyl-8-methoxycarbonylbenzo[*c*]phenanthrene-5-carboxylate, and the resulting nanoparticles (*P*)-1 were used in this study. To know the molecular recognition ability of (*P*)-1, a precipitation experiment was conducted. (*P*)-1 in chlorobenzene was sonicated and mixed with (*R*)-2-hydroxy-2-phenylethyl butyl disulfide (*R*)-2 in the same solvent. The suspension was allowed to settle at 25 °C. The top of the suspension cleared after 25 h, and the precipitation was completed after 29 h, which is noted as [25 h/29 h] in this work. In the absence of (*R*)-2, (*P*)-1 started to precipitate only after 48 h and completed after 52 h, [48 h/52 h]. To determine the effect of the molecular structure on the precipitation, the same experiments were conducted using symmetric disulfides, bis{(*R*)-2-hydroxy-2-phenylethyl} disulfide (*R,R*)-3 and dibutyl disulfide **4**, where precipitation occurred by [20 h/24 h] and [52 h/59 h], respectively. (*P*)-1 was found to recognize and precipitate (*R,R*)-3 over (*R*)-2 and **4** (Fig. 2). When the enantiomeric (*S,S*)-3 and (*S*)-2 were treated, precipitation occurred by [33 h/36 h] and [36 h/40 h], respectively. Chiral recognition in the precipitation of disulfides by (*P*)-1 favored the (*R*)-isomers.

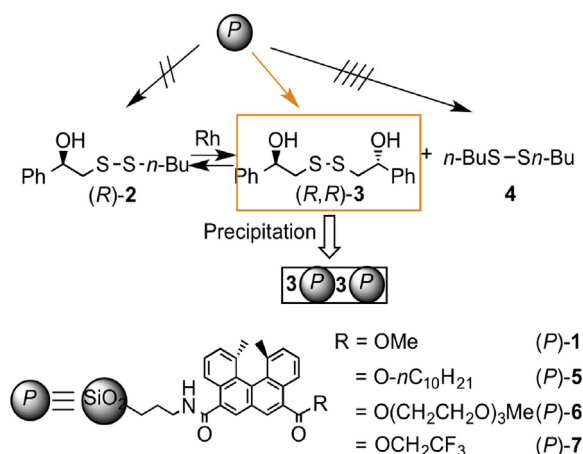


Fig. 2. Molecular recognition and equilibrium shift in rhodium-catalyzed disulfide exchange reaction.

The equilibrium state of the disulfides in chlorobenzene was determined as a statistical mixture of (*R*)-2:(*R,R*)-3:**4**=1:2:1 by independent forward and backward reaction experiments, from which an equilibrium constant $K=[(R,R)\text{-3}][\text{4}]/[(R)\text{-2}]^2=0.25$ was obtained (Scheme S4).

On the basis of the above results, the rhodium-catalyzed equilibrium reaction among (*R*)-2, (*R,R*)-3, and **4** was examined, where (*R,R*)-3 was removed by taking advantage of its higher affinity to

(*P*)-1 (Fig. 2). A mixture of (*R*)-2 (0.25 mmol) in chlorobenzene was treated with RhH(PPh₃)₄ (20 mol %), trifluoromethanesulfonic acid (40 mol %), and (*p*-tolyl)₃P (80 mol %) at room temperature for 24 h. Then, (*P*)-1 (13 mg, containing 2.0 μmol of helicene) in chlorobenzene was sonicated for 3 min and added to the solution. The mixture was allowed to settle for another 24 h, and precipitates were separated from the supernatant by centrifugation. The supernatant contained (*R,R*)-3 (6%), (*R*)-2 (30%), and **4** (33%) (Table 1, entry 1), which are under equilibrium as determined by the calculated $K=0.22$. The precipitates were suspended in chloroform and sonicated to liberate (*R,R*)-3 (27%) and (*R*)-2 (3%), where **4** was not detected. The yield of (*R,R*)-3 increased from 25% under equilibrium to 33% against the maximum yield of 50%; the 27% yield of (*R,R*)-3 was obtained in the precipitate and 6% remained in the supernatant. The selectivity of precipitation for (*R,R*)-3 and (*R*)-2 turned out to be 9:1. The results revealed substantial molecular recognition for disulfides by (*P*)-1 and the selective removal of (*R,R*)-3 from solution. Note that rhodium-catalysis was not affected by (*P*)-1.

Equilibrium can still be shifted by repeating the precipitation experiment on the supernatant. The disulfides formed in the supernatant were treated with (*P*)-1 in chlorobenzene for 24 h. Then, from the precipitate, (*R,R*)-3 (8%) and (*R*)-2 (2%) were obtained, and (*R*)-2 (17%), (*R,R*)-3 (2%), and **4** (39%) remained in the supernatant. Thus, from an equilibrium mixture containing (*R,R*)-3 at 25%, the (*R,R*)-3 was separated in 35% (27+8%) yield by precipitating twice with 2% remaining in solution, and (*R,R*)-3 in a total yield of 37% was obtained. In principle, repeating the procedures can shift the equilibrium to the theoretical 50% yield of (*R,R*)-3.

The scale of the once-precipitation reaction could be slightly increased for (*R*)-2 (0.4 mmol) and (*P*)-1 (21 mg, containing 3.2 μmol of helicene) to confirm the stoichiometry of the heterogeneous reaction, where (*R,R*)-3 was obtained in the precipitates in 26% (0.10 mmol) isolated yield and 8% (0.032 mmol) in the supernatant. Note that the amount of silica nanoparticles (*P*)-1 used here is comparable to that of substrates, which contrasts to silica gel chromatography that uses a large excess of silica gel relative to the amount of substrates. It is also notable that (*P*)-1 with 3.2 μmol of helicene removed 100 μmol of (*R,R*)-3 from solution. This is an advantage of this method, although the mechanism is not clear at present.

Solvent effect was examined in 1,2-dichlorobenzene, 1,3-bis(trifluoromethyl)benzene, bromobenzene, and toluene, where

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