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Continuous asymmetric Michael addition of ketones to β-nitroolefins over (1*R*,2*R*)-(+)-1,2-DPEN-modified sulfonic acid resin†

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A trifunctional catalyst was successfully prepared by bonding (1*R*,2*R*)-(+)-1,2-DPEN to sulfonic acid resin. The catalyst was characterized by elemental analysis, thermogravimetric (TG) analysis and infrared (IR) spectroscopy. The results indicated the coexistence of sulfonic, sulfonamido and primary amino groups on the surface of the resin. Based on the IR spectroscopy of the catalyst treated with a solution of acetone and β-nitrostyrene in toluene, the catalytic mechanisms were proposed. It was found that these three groups had a synergistic effect. Subsequently, the continuous Michael addition of acetone to β-nitrostyrene was achieved in a fixed-bed reactor over this catalyst and the reaction parameters were optimized. Under the optimized conditions moderate β-nitrostyrene conversion (65.5%) and excellent enantioselectivity (93.0%) were obtained. Finally, the generality of the catalyst was evaluated with the Michael addition of aldehydes or ketones to β-nitroolefins, and the catalyst exhibited moderate to excellent enantioselectivity (81.6% to 99.0% ee) except for the addition of isobutylaldehyde to β-nitrostyrene.

It is obvious that chiral compounds play crucial roles in biological processes. Asymmetric Michael addition of ketones (aldehydes) to nitroolefins is one of the most versatile methods for the construction of chiral compounds and thus attracts tremendous attention.[1] As early as 2001, List *et al.*[2] reported the enantioselective Michael addition of cyclohexanone to β-nitrostyrene catalyzed by L-proline. Since then, this reaction has always been taken as a model, and organocatalysts that are more efficient for this model keep emerging.[3] However, most of them presented poor catalytic performance for the Michael addition of acetone to nitrostyrene. Now, acetone is still a problematic substrate for the nitro-Michael addition.[4] In order to enhance the enantioselectivity and the yield, some studies have recently focused on the design of catalysts. Terakado *et al.*[5] employed (*S*)-homoproline hydrochloride as a catalyst for this Michael addition with less than 50% ee. Vijaikumar *et al.*[6] studied this asymmetric Michael addition in the presence of L-proline anchored on hydrotalcite clays with only 14% ee. Obviously, chiral proline derivatives displayed poor enantioselectivity for this reaction. Moreover, based on the chiral diamine skeletons, especially 1,2-diphenylethane-1,2-diamine[7] and cyclohexane-1,2-diamine,[8] thiophosphoramides,[9] sulfamides[10] and thioureas[11] were synthesized and evaluated for the asymmetric Michael addition of acetone to nitrostyrene. All of them exhibited satisfactory enantioselectivity, but separation from the reaction mixture and recycling are difficult. Portnoy *et al.*[12] immobilized the chiral diamine on dendronized Wang PS resin. Although sufficient yields and stereoselectivities were achieved, certain drawbacks still existed, such as complicated multi-step synthesis and requirement of acidic additives. Besides, the aforementioned operations were all carried out in flasks and the continuous asymmetric Michael additions were rarely touched.

In this paper, (1*R*,2*R*)-(+)-1,2-diphenylethylenediamine [(1*R*,2*R*)-(+)-1,2-DPEN] was selected and bonded to sulfonic acid resin by simple *N*-sulfonyl reaction (Fig. 1). Then, the continuous asymmetric Michael addition of acetone to β-nitrostyrene in a fixed-bed reactor was realized over the obtained (1*R*,2*R*)-(+)-1,2-DPEN-modified resin without any additives. The catalyst was characterized by elemental and TG analyses and IR spectroscopy to clarify the coexistence of sulfonic, sulfonamido and primary amino groups on the surface of the resin. Meanwhile, the catalyst was treated with a solution of acetone and β-nitrostyrene in toluene and then characterized by IR to investigate the catalytic mechanism. Finally, the reaction conditions were optimized and the

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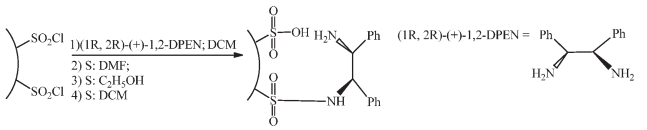


Fig. 1 The modification of sulfonic acid resin with (1*R*,2*R*)-(+)-1,2-DPEN.

generality of the catalyst was investigated under the optimized reaction conditions.

Results and discussion

As an effective catalyst for Michael addition of acetone to β-nitrostyrene, the amide group is required as a hydrogen bond donor apart from the primary amino group, ensuring the ability to form an enamine or imine.[11,13] In addition, acidic additives, such as hydrochloric acid,[5] sulfonic acid,[4b,14] carboxylic acid[4a,15]and even phenol,[9a] are necessary to accelerate the reaction.[9b,12a] In fact, the amide groups, the primary amino groups and the acidic additives played a synergistic effect on this asymmetric Michael addition. Therefore, in this paper, (1*R*,2*R*)-(+)-1,2-DPEN was selected and linked to sulfonic acid resin through a sulfamide bond. The formation of sulfamide bond favored the strengthening of the hydrogen bonding with β-nitrostyrene, and the sulfonic group derived from the hydrolysis of sulfonyl chloride served as acidic additive. The Michael addition of acetone to β-nitrostyrene was carried out over (1*R*,2*R*)-(+)-1,2-DPEN-modified sulfonic acid resin in a fixed-bed reactor with moderate conversion and excellent enantioselectivity. The satisfactory reactivity might be attributed to the synergistic effect of sulfonic, sulfonamido and primary amino groups on the surface of the resin. In order to confirm the coexistence of these three functional groups, the catalyst was characterized by elemental and TG analyses and IR spectroscopy.

The sulfur and nitrogen contents of (1*R*,2*R*)-(+)-1,2-DPEN-modified sulfonic acid resin were determined by elemental analysis. The results indicated that each gram of the catalyst contained 1.87 mmol of nitrogen and 1.99 mmol of sulfur. The sulfur content was lower than that of sulfonyl chloride resin (2.35 mmol g^{-1}), which was attributed to the introduction of (1*R*,2*R*)-(+)-1,2-DPEN. Meanwhile, 1.87 mmol g^{-1} of nitrogen content implied that about half of the sulfonyl chloride was consumed by (1*R*,2*R*)-(+)-1,2-DPEN to form sulfamide and the rest would be hydrolyzed into sulfonic acid in the catalyst post-processing. The TG and DTG profiles of the catalyst are shown in Fig. 2. The TG profile indicated that with the increase in temperature from 30 to 800 °C, there were two distinct weight losses in the ranges of 30–100 °C and 220–470 °C, corresponding to the desorption of absorbed water and the degradation of the catalyst, respectively. The DGT profile displayed three peaks in the range of 220–470 °C, which were possibly attributed to three stages of the catalyst degradation: the breakage of the sulfamide bond, desulfonation and the collapse of the resin skeleton. It was consistent with the results of the elemental analysis.

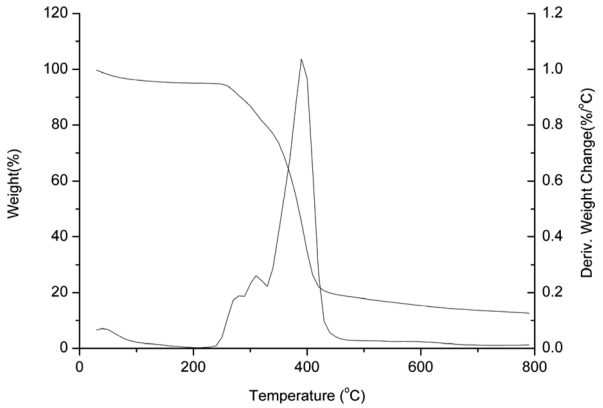


Fig. 2 TG and DTG profiles of (1*R*,2*R*)-(+)-1,2-DPEN-modified sulfonic acid resin.

The FTIR spectra of (1*R*,2*R*)-(+)-1,2-DPEN-modified sulfonic acid resin, (1*R*,2*R*)-(+)-1,2-DPEN and (1*R*,2*R*)-(+)1,2-DPEN-modified sulfonic acid resin treated with acetone and β-nitrostyrene are shown in Fig. 3a, b and c, respectively. As shown in Fig. 3, all of them displayed a peak at 3437 cm^{-1} belonging to the O–H stretching vibration of H_2O. In addition, the absorption peaks occurring at 1324 cm^{-1} and 1153 cm^{-1} (Fig. 3a) could be ascribed to the S=O asymmetric and symmetric stretching vibrations, respectively.[16] The peak around 1059 cm^{-1} corresponded to the N–SO_2 stretching vibration,[17] and another peak at 1537 cm^{-1} to the N–H bending vibration of sulfamide.[18] The presence of these four peaks confirmed that (1*R*,2*R*)-(+)-1,2-DPEN has been anchored on the surface of the resin by sulfamide bond. Meanwhile, the peak at 515 cm^{-1} was assigned to the absorption of the SO_3–H group[19] and the peak at 3367 cm^{-1} was the N–H stretching vibration of the amino group. Thus, a conclusion could be made that sulfonic, sulfonamido and primary amino groups coexisted on the surface of the resin.

In order to understand this catalytic reaction, the catalyst was immersed into a solution of acetone (1.33 mol L^{-1}) and β-nitrostyrene (0.133 mol L^{-1}) in 20 mL of toluene for 48 h at

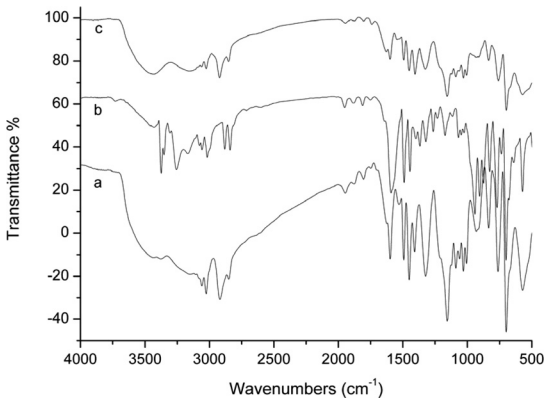


Fig. 3 The infrared spectra of (1*R*,2*R*)-(+)-1,2-DPEN-modified sulfonic acid resin (a), (1*R*,2*R*)-(+)-1,2-DPEN (b), and (1*R*,2*R*)-(+)-1,2-DPEN-modified sulfonic acid resin treated with acetone and β-nitrostyrene (c).

ambient temperature and then characterized by FT-IR. The results are shown in Fig. 3c. Obviously, the peak of the N–H stretching vibration of the amino group disappeared and this might be attributed to the formation of imine or enamine intermediate with acetone. Moreover, the N–H bending vibration of sulfamide has an upshift of 5 cm^{-1} for the hydrogen bond between sulfamide and β-nitrostyrene.

On the basis of the IR analysis, combined with the results reported by Lin *et al.*[10] and Lital *et al.*,[12a] the catalytic mechanism was proposed as shown in Fig. 4. (1*R*,2*R*)-(+)-1,2-DPEN-modified sulfonic acid resin behaved as a trifunctional catalyst. First, acetone was activated *via* protonation or the hydrogen bonding interaction with the sulfonic acid group. The nucleophilic addition and the following dehydration yielded imine intermediate **1**.[10,12a] In addition, the hydrogen bonding between the sulfonamido group and the nitro group enhances the electrophilicity of β-nitrostyrene and the enantioselectivity. Subsequently, the imine intermediate **1** was balanced with the enamine intermediate, which attacked the activated β-nitrostyrene to form the highly enantioselective imine intermediate **2**. It was easily transformed into the Michael adduct by nucleophilic addition of H_2O and the subsequent deamination with the aid of sulfonic acid. It was obvious that the sulfonic group favored the activation of acetone and the release of the Michael adduct. Importantly, sulfonic, sulfonamido and primary amino groups played a synergistic role on the formation of the target compound. In order to further confirm the catalytic mechanism and improve the reaction, the effects of temperature, acetone/β-nitrostyrene molar ratio and solvents on the Michael addition of acetone to β-nitrostyrene were investigated.

Initially, the influence of temperature on the asymmetric Michael addition of acetone to β-nitrostyrene was investigated and the results are shown in Table 1. It was found that with the increase in temperature from 25 to 45 °C, the conversion of β-nitrostyrene increased from 65.5% to 78.3%, whereas the enantioselectivity of the Michael adduct decreased from 93.0% to 74.9%. There is no doubt

Table 1 The influence of temperature on the addition of acetone to β-nitrostyrene[a]

Temperature/°C	Conversion[c]/%	ee[b,c]/%
25	65.5	93.0
35	77.6	75.7
45	78.3	74.9

[a] Reaction conditions: solution of 1.33 mmol of acetone and 0.133 mmol of β-nitrostyrene in 20 mL of toluene; charging rate: 0.6 mL h^{-1}. [b] The results were determined by HPLC using an AS column. [c] The conversion was obtained by HPLC using an AS column and each data point is a median of three consecutive and similar analytical results.

that the elevated temperature favored Michael addition of acetone to β-nitrostyrene. However, as the temperature increased, the proportion of protonated acetone that directly attacked β-nitrostyrene to generate the raceme was enhanced (Fig. 5), which may be the main reason for the decrease in the enantioselectivity.

Table 2 clearly indicated that with the increase in acetone/β-nitrostyrene molar ratio from 10 : 1 to 25 : 1, the conversion of β-nitrostyrene essentially remained unchanged due to the supersaturation of active sites of the catalyst. Meanwhile, the enantioselectivity dramatically decreased from 93.0% to 76.5%. It was not hard to understand that the excess acetone would lead to the increase in the mixed solvent polarity. It possibly weakened the hydrogen bonding between β-nitrostyrene and the amino group of sulfamide, resulting in the decreased enantioselectivity of the Michael adduct. Therefore, the effects of solvent polarity on the catalytic activity and enantioselectivity were subsequently investigated.

Table 3 revealed that solvents presented a significant effect on the conversion of β-nitrostyrene and the enantioselectivity of the adduct. Polar solvents such as methanol, acetone, acetonitrile and tetrahydrofuran resulted in moderate to good β-nitrostyrene conversion (55.1–99.6%) and poor enantioselectivity (38.7–58.4%). By contrast, nonpolar or weak polar solvents such as toluene, dichloromethane, chloroform and tetrachloromethane gave poor to moderate β-nitrostyrene conversion (31.6–65.5%) and better enantioselectivity (82.4–93.0%). Obviously, toluene was the most suitable solvent for the Michael addition of acetone to β-nitrostyrene with respect to the β-nitrostyrene conversion and the enantioselectivity of the Michael adduct. As mentioned above, the hydrogen bonding with β-nitrostyrene was also crucial to improve the enantioselectivity. However, polar solvents always weakened or retarded the formation of hydrogen bonds between β-nitrostyrene and the amino group

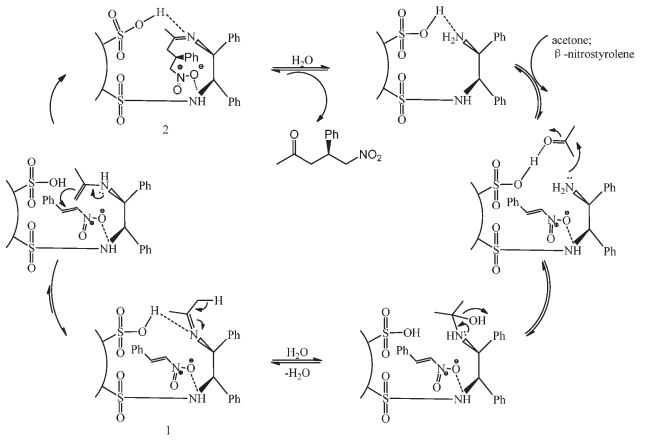


Fig. 4 The mechanism of the Michael addition of acetone to β-nitrostyrene over (1*R*,2*R*)-(+)-1,2-DPEN-modified sulfonic acid resin.

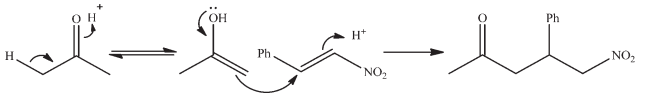


Fig. 5 The Michael addition of acetone to β-nitrostyrene catalyzed by sulfonic acid.

Table 2 The influence of molar ratio on the addition of acetone to β-nitrostyrene[a]

Molar ratio[b]	Conversion[d]/%	ee[c,d]/%
10 : 1	65.5	93.0
15 : 1	65.0	84.2
20 : 1	65.3	82.8
25 : 1	65.6	76.5

[a] Reaction conditions: solution of 0.133 mmol of β-nitrostyrene in 20 mL of toluene; charging rate: 0.6 mL h^{-1}; temperature: 25 °C. [b] The molar ratio of acetone and β-nitrostyrene. [c] The results were determined by HPLC using an AS column. [d] The conversion was obtained by HPLC using an AS column and each data point is a median of three consecutive and similar analytical results.

Table 3 The influence of solvents on the addition of acetone to β-nitrostyrene[a]

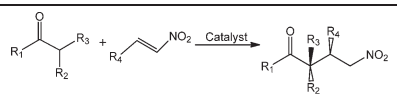
Solvents	Conversion[c]/%	ee[b,c]/%
Toluene	65.5	93.0
DCM	44.4	88.3
$CHCl_3$	34.1	82.4
CCl_4	31.6	91.8
THF	96.5	38.7
CH_3CN	55.1	57.2
Acetone	88.7	49.5
CH_3OH	99.6	58.4

[a] Reaction conditions: solution of 1.33 mmol of acetone and 0.133 mmol of β-nitrostyrene in 20 mL of toluene; charging rate: 0.6 mL h^{-1}; temperature: 25 °C. [b] The results were determined by HPLC using an AS column. [c] The conversion was obtained by HPLC using an AS column and each data point is a median of three consecutive and similar analytical results.

of sulfamide; thus, the enantioselectivity decreased. Besides, the ionization of sulfonic acid was also promoted by polar solvents. β-Nitrostyrene was activated by protonation and then reacted with the enamine intermediate to yield raceme. That may be another reason for the decrease in the enantioselectivity. Above all, the sulfonic, the primary amino and the sulfonamido groups exhibited important impacts on both the conversion of β-nitrostyrene and the enantioselectivity of the Michael adduct.

The asymmetric Michael addition of aldehydes or ketones to nitroolefins over (1*R*,2*R*)-(+)-1,2-DPEN-modified sulfonic acid resin in a fixed-bed reactor was investigated. As shown in Table 4, the Michael addition of acetone to nitroolefins gave the desired adducts with excellent enantioselectivity (>90%) and moderate to high nitroolefin conversion (47.1% to 95.7%). The conversion of 4′-methoxy-β-nitrostyrene (47.1%) was lower compared with that of other nitroolefins due to the effect of the electron-donating group. Furthermore, the Michael addition of aldehydes or ketones to β-nitrostyrene was performed. Excellent β-nitrostyrene conversion and Michael adduct enantioselectivity were observed when cyclohexanone or *n*-butanal was employed. By contrast, the Michael addition of cyclopentanone and

Table 4 Asymmetric Michael addition of aldehydes or ketones to nitroolefins[a]



R_1, R_2, R_3	R_4	Conversion[c]/%	ee[b,c]/%	dr[d] (*syn*/*anti*)
CH_3–, H–, H–	Ph–	65.5	93.0	—
CH_3–, H–, H–	4-Cl–Ph–	95.7	92.8	—
CH_3–, H–, H–	2-Cl–Ph–	90.9	96.7	—
CH_3–, H–, H–	4-MeO–Ph–	47.1	94.9	—
–$(CH_2)_4$–	Ph–	95.5	94.5	93 : 7
–$(CH_2)_3$–	Ph–	29.7	85.2	98 : 2[e]
Et–, Me–, H–	Ph–	16.3	81.6	>99 : 1
H–, Et–,H–	Ph–	98.7	>99.0%	>99 : 1
H–, Me–,Me–	Ph–	Trace	—	—

[a] Reaction conditions: solution of 1.33 mmol of ketones and 0.133 mmol of nitroolefins in 20 mL of toluene; charging rate: 0.6 mL h^{-1}; temperature: 25 °C. [b] The results were determined by HPLC using an AS column. [c] The conversion was obtained by HPLC using an AS column and each data point is a median of three consecutive and similar analytical results. [d] The dr value was determined by HPLC apart from the adduct of cyclopentanone. [e] The dr value was determined by ^{1}H NMR of the crude product.

3-pentanone exhibited lower β-nitrostyrene conversion and enantioselectivity. In addition, only traces of the Michael adducts of isobutylaldehyde were detected. The poor reactivity and enantioselectivity were mainly attributed to the steric hindrance which restricted the formation of the imine intermediate.

Conclusion

A trifunctional catalyst was successfully prepared by simple *N*-sulfonylation of (1*R*,2*R*)-(+)-(1,2)-DPEN with sulfonyl chloride resin. The catalyst was characterized by elemental and TG analyses and IR spectroscopy. The results indicated the coexistence of sulfonic, sulfonamido and primary amino groups on the surface of the resin. Furthermore, the catalyst was treated with the solution of acetone and β-nitrostyrene in toluene and then characterized by IR spectroscopy. Based on the IR analysis, the catalytic mechanism was proposed. It was found that sulfonic, sulfonamido and primary amino groups possibly had a synergistic effect on the conversions of β-nitrostyrene and the enantioselectivities of the Michael adduct. The catalyst was employed for the continuous Michael addition of acetone to β-nitrostyrene in a fixed-bed reactor and the reaction parameters were optimized. Under the optimized conditions moderate β-nitrostyrene conversion (65.5%) and excellent enantioselectivity (93.0%) were obtained. Finally, the generality of the catalyst was investigated with the Michael addition of aldehydes or ketones to nitroolefins. The catalyst exhibited moderate to excellent enantioselectivity (81.6% to 99.0% ee) except for the Michael addition of isobutylaldehyde to β-nitrostyrene. The reason might be attributed to the steric hindrance which restricted the formation of the imine intermediate.

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