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Accounts

Cinchona-based Sulfonamide Organocatalysts: Concept, Scope, and Practical Applications

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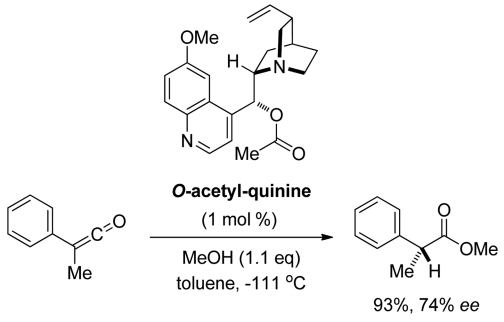
Cinchona-based bifunctional catalysts have been extensively employed in the field of organocatalysis due to the incorporation of both hydrogen-bonding acceptors (quinuclidine) and hydrogen-bonding donors (*e.g.*, alcohol, amide, (thio)urea and squaramide) in the molecule, which can simultaneously activate nucleophiles and electrophiles, respectively. Among them, cinchona-derived (thio)urea and squaramide catalysts have shown remarkable application potential by using their bifurcated hydrogen bonding donors in activating electrophilic carbonyls and imines. However, due to their bifunctional nature, they tend to aggregate *via* inter- and intramolecular acid-base interactions under certain conditions, which can lead to a decrease in the enantioselectivity of the reaction. To overcome this self-aggregation problem of bifunctional organocatalysts, we have successfully developed a series of sulfonamide-based organocatalysts, which do not aggregate under conventional reaction conditions. Herein, we summarize the recent applications of our cinchona-derived sulfonamide organocatalysts in highly enantioselective methanolytic desymmetrization and decarboxylative aldol reactions. Immobilization of sulfonamide-based catalysts onto solid supports allowed for unprecedented practical applications in the synthesis of valuable bioactive synthons with excellent enantioselectivities.

Key Words : Asymmetric catalysis, Cinchona-based sulfonamide, Textile organocatalysis, Desymmetrization, Aldol reaction

Introduction

Cinchona-based organocatalysts have revealed outstanding performances in a variety of asymmetric transformations, starting with the pioneering example of an asymmetric cyanohydrin synthesis by Bredig and Fiske in 1912.[1] A groundbreaking advance was reported by Pracejus in 1960 on the methanolysis of a ketene using 1 mol % of *O*-acetal quinine as a catalyst to afford an enantioenriched ester with good enantioselectivity (74% *ee*, Scheme 1).[2]

After a hiatus of several decades, organocatalysts re-emerged as surrogates for transition metal- and bio-catalysts.[3] Similar to the catalytically active center of enzymes, the presence of multiple functional groups in the organocatalyst's structure can effectively stabilize a reaction intermediate and/or transition state through hydrogen bonding, charge-charge, π-π and charge-π interactions.[4a] Cinchona alkaloid derivatives are one of the most attractive and practical organocatalysts due to their high accessibility and ease of modification.[4] The utilization of bifunctional cinchona derivatives has enabled a variety of asymmetric transformations, due to the incorporation of both hydrogen-bonding acceptors (quinuclidine) and hydrogen-bonding donors (*e.g.*, alcohol, amide, (thio)urea and squaramide) in the molecule, which can simultaneously



Scheme 1. Asymmetric methanolysis of a ketene.

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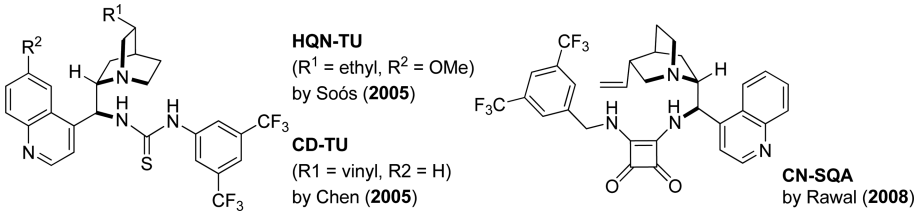


Figure 1. Representative structures of cinchona-based bifunctional catalysts.

activate both nucleophiles and electrophiles, respectively.[5] The representative privileged scaffolds for cinchona-based bifunctional catalysts are illustrated in Figure 1. In 2005, the Soós group[6] and the Chen group[7] independently introduced the 9-*epi*-amino cinchona-derived thiourea bifunctional organocatalyst. They applied the thiourea-based organocatalyst to the Michael addition of nitromethane and arylthiols to α,β-unsaturated carbonyl compounds with excellent enantioselectivity (up to 96% *ee*). Shortly thereafter, Rawal and coworkers developed a squaramide-based catalyst for the asymmetric Michael addition of 1,3-diketones to nitroolefins.[8] Since these pioneering developments, thiourea and squaramide catalysts have been employed in a wide variety of stereoselective reactions, as summarized in recent reviews and accounts.[5,9]

However, due to their bifunctional nature, bearing both acidic and basic moieties, these organocatalysts can autoassociate under concentrated reaction conditions or low temperatures.[10] Soós and coworkers reported a detailed NMR study, through NOE, confirming that thiourea-based catalysts are in equilibrium between the self-associated dimeric and monomeric forms in solution state (K (in D_8 toluene) = $[\mathbf{HQN\text{-}TU}_{dimer}]/[\mathbf{HQN\text{-}TU}_{monomer}]^2$ = 42011 mol/L at −65 °C[11a]), *via* hydrogen-bonding and T-type intermolecular π-π interactions (Figure 2(a)).[11] In addition, the X-ray crystal structure of squaramide-based catalyst **CN-SQA** shows that the catalyst exists as a hydrogen-bonded aggregate in the solid state (Figure 2(b)).[8] Due to their self-association phenomenon, in many catalytic reactions, the enantioselectivity of acid-base bifunctional organocatalysts such as **QN-TU** and **QN-SQA** usually significantly decreases with increasing concentration or decreasing temperature, indicating that self-association is a general problem affecting the efficiency of bifunctional acid-base catalysts.

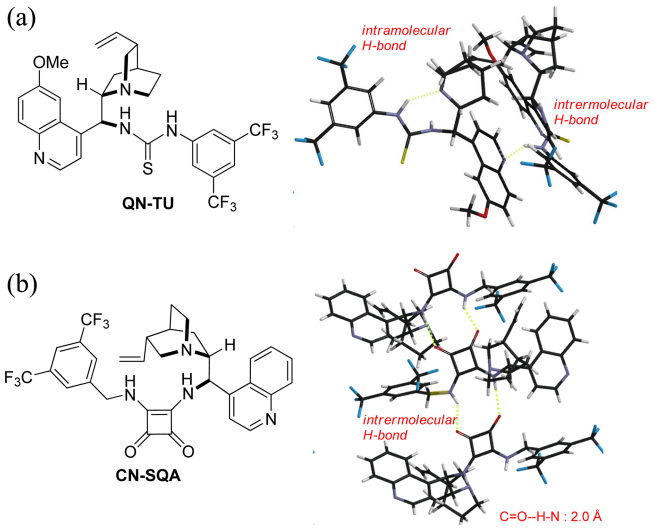


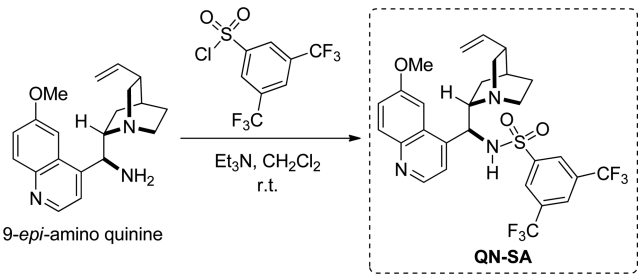
Figure 2. Self aggregation of bifunctional organocatalysts: (a) Dimeric structure of **QN-TU** in solution; (b) Crystal packing of **CN-SQA**.

To control the above-mentioned self-aggregation of bifunctional organocatalysts, our group designed and developed a new sulfonamide-derived bifunctional organocatalyst (Figure 3). Although a sulfonamide is intrinsically more acidic than a thiourea, this sulfonamide catalyst only possesses single hydrogen-bonding donor, making it less prone to dimerize. In addition, the tetrahedral sulfur atom offers higher flexibility than the sp^2 hybridized (thio)urea carbon atom,[12] increasing the π-π interaction between the quinoline ring and the aryl substituent of the sulfonamide. This π-π interaction might be particularly important in decreasing the intermolecular interactions of the catalyst, by positioning the catalytically active functional groups in high proximity.

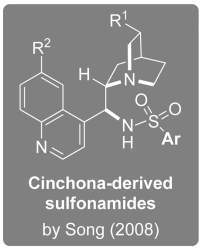
In this paper, we summarize recent applications of cinchona-based bifunctional sulfonamide catalysts, such as desymmetrization and decarboxylative aldol reactions. Additionally, a straightforward immobilization of sulfonamide catalysts onto solid supports, namely polystyrene and textile materials will be shown. Practical synthetic applications in the preparation of biologically active molecules will also be presented.

Results and Discussion

Alcoholytic Desymmetrization of Cyclic *meso*-Anhydrides. The catalytic alcoholytic desymmetrization reaction of cyclic *meso*-anhydrides is a powerful methodology to obtain enantioenriched hemiesters that possess two differentiated carbonyl moieties perfectly posed for further derivatizations.[13]



Scheme 2. Preparation of **QN-SA**.



QN-SA: R^1 = vinyl, R^2 = OMe, Ar= 3,5-$(CF_3)_2C_6H_3$
HQN-SA: R^1 = ethyl, R^2 = OMe, Ar= 3,5-$(CF_3)_2C_6H_3$
CD-SA: R^1 = vinyl, R^2 = H, Ar= 3,5-$(CF_3)_2C_6H_3$
HCD-SA: R^1 = ethyl, R^2 = H, Ar= 3,5-$(CF_3)_2C_6H_3$
QN-Ph-SA: R^1 = vinyl, R^2 = OMe, Ar= Ph
QN-TRIP-SA: R^1 = vinyl, R^2 = OMe, Ar= 2,4,6-$(i\text{-Pr})_3C_6H_2$
QN-TRIM-SA: R^1 = vinyl, R^2 = OMe, Ar= 2,4,6-$(CH_3)_3C_6H_2$
QN-1-Np-SA: R^1 = vinyl, R^2 = OMe, Ar= 1-Np
QN-2-Np-SA: R^1 = vinyl, R^2 = OMe, Ar= 2-Np
QN-*o*-Tolyl-SA: R^1 = vinyl, R^2 = OMe, Ar= *o*-tolyl
QN-*m*-Tolyl-SA: R^1 = vinyl, R^2 = OMe, Ar= *m*-tolyl
QN-*p*-Tolyl-SA: R^1 = vinyl, R^2 = OMe, Ar= *p*-tolyl
QN-*m*-Xylyl-SA: R^1 = vinyl, R^2 = OMe, Ar= *m*-xylyl
QN-Py-SA: R^1 = vinyl, R^2 = OMe, Ar= 1-pyrenyl
QN-Dn-SA: R^1 = vinyl, R^2 = OMe, Ar= dansyl

Figure 3. Structures of some cinchona-derived sulfonamides.

Due to the potential applicability of the methodology, various approaches have been developed by using enzymes, metal catalysts and organobase catalysts, including cinchona alkaloids and their derivatives. However, in the case of organocatalytic protocols, only a few reports were available with satisfactory enantioselectivity and/or reactivity by using monofunctional chiral base catalysts.[14]

In 2008, the Song[10] and Connon groups[15] independently reported a highly enantioselective example using thiourea-based **QN-TU** catalysts. It was assumed that the quinuclidine group of the catalyst could activate the nucleophile (alcohol or thiol), while the thiourea group could activate the electrophile (anhydride) by double hydrogen-bonding donors. In the presence of **QN-TU** (1–10 mol %), a range of substrates, including mono-, bi-, and tricyclic anhydrides, were smoothly converted to the corresponding hemiesters in excellent yields and *ee* values (up to 97% *ee*) under diluted reaction conditions. Interestingly, unusual enantioselectivity changes were observed in the **QN-TU** catalyzed desymmetrization reaction. Increasing the concentration (0.0625 M to 0.2 M) or decreasing the temperature (20 °C to −20 °C) resulted in lower enantioselectivity than diluted or high temperature reaction conditions (Figure 4).[10] Optimal enantioselectivity was obtained under highly diluted reaction conditions at room temperature ([**1**] = 0.00625 M: 96% *ee*, Figure 4(a)). As stated in the introduction, we assumed this could be due to the inevitable self-aggregation phenomenon caused by the acid-base bifunctional nature of the catalyst.

Preliminary evidence of self-aggregation of thiourea-based catalyst was obtained by performing ^{1}H-NMR analysis of **QN-TU** at different concentrations and temperatures.[10] At −78 °C, one of the N-H protons of the thiourea group was split in the downfield region, indicating the formation of two different species.[10] This conclusion was also supported by extensive NMR studies performed by the Soós group.[11a] Moreover, in order to determine self-aggregation and intermolecular interactions of catalyst **QN-TU**, we conducted a Diffusion Ordered Spectroscopy (DOSY) analysis.[16] The diffusion coefficients (D [10^{-10} m^2s^{-1}]) of **QN-TU** and **QN-SQA** catalysts were measured. When the concentration was increased, a lower diffusion constant was observed for both catalysts (in the case of **QN-TU**, from 5.86×10^{-10} m^2s^{-1} (1 mM) to 3.97×10^{-10} m^2s^{-1} (200 mM) in CH_2Cl_2). This result

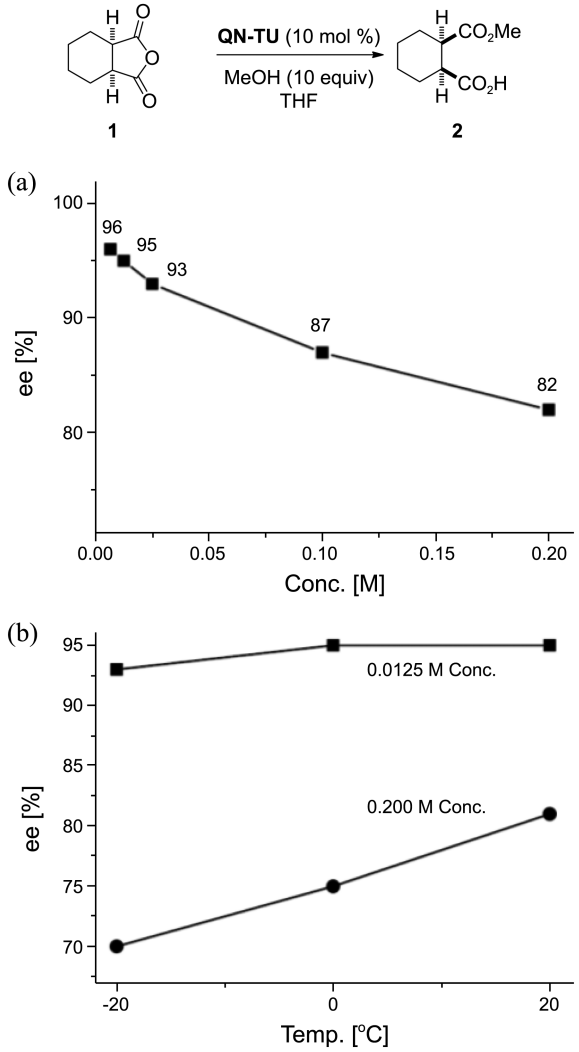


Figure 4. Effect of (a) concentration and (b) temperature on the enantioselectivity in the methanolysis of **1** catalyzed by **QN-TU**.[15]

confirmed strong intermolecular interactions of the thiourea-based catalysts in non-polar reaction solvents, leading to the formation of higher molecular weight species.[17] We concluded that due to the self-aggregation phenomenon, the enantioselectivity of bifunctional organocatalysts such as **QN-TU** and **QN-SQA** is sensitive to reaction conditions such as concentration and temperature. Thus, we decided to provide a self-aggregation-free bifunctional organocatalyst to satisfy the criteria of catalytic activity and enantioselectivity in a wide range of reaction conditions.

Catalyst **QN-SA** was synthesized simply by treating the corresponding free amine with arylsulfonyl chloride in the presence of the base (Scheme 2). A series of new cinchona sulfonamide derived organocatalysts could thus be prepared without any difficulty (Figure 3). To test the catalytic activity of this new class of bifunctional catalysts, we conducted the desymmetrization reaction of *meso*-anhydride **1** using **QN-SA**. As presented in Figure 5, the self-aggregation phenomenon seems to be absent when the reaction is performed in the presence of catalyst **QN-SA**. Constant

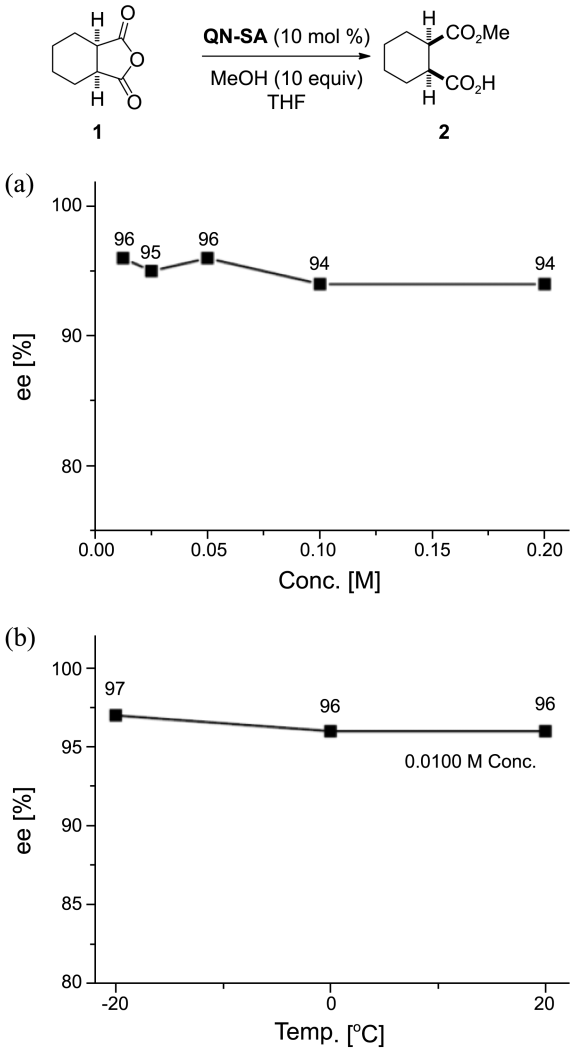
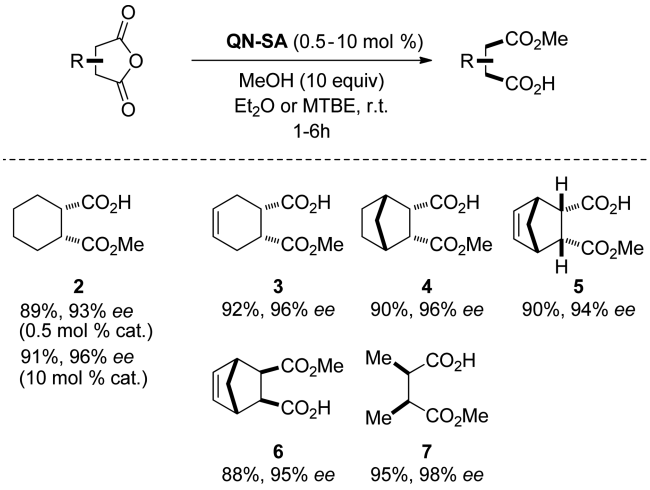


Figure 5. Effect of (a) concentration and (b) temperature on the enantioselectivity in the methanolysis of **1** catalyzed by **QN-SA**.

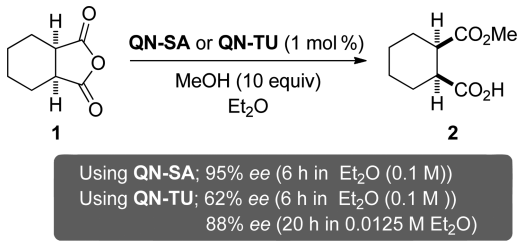
enantioselectivities were observed regardless of the reaction temperature and concentration, confirming our hypothesis.

Consequently, a wide range of *meso*-anhydrides could be converted to their corresponding hemiesters in excellent yields and *ee*s using the newly developed catalyst **QN-SA** under mild reaction conditions (**2-7**, up to 95% yield and 98% *ee*, Scheme 3). Moreover, the catalyst loading could be lowered to 0.5 mol% while maintaining very good levels of enantioselectivity (**2** of Scheme 3, 93% *ee*). To the best of our knowledge, this level of enantioselectivity for the desymmetrization of *meso*-anhydrides, with less than 1 mol % of catalyst loading, is unprecedented.

To highlight the advantage of self-aggregation-free catalyst **QN-SA** over thiourea-based catalyst **QN-TU**, we conducted a comparative experiment summarized in Scheme 4. Under the same reaction conditions (0.5 mmol of **1**, 5.0 mmol of MeOH, 5 mL Et_2O and 1 mol % of catalyst), **QN-SA** showed excellent enantioselectivity (95% *ee*), whereas **QN-TU** was only moderately enantioselective (62% *ee*). The stereoselectivity of **QN-TU** can only be increased to



Scheme 3. Enantioselective methanolytic desymmetrization of *meso*-succinic anhydrides.

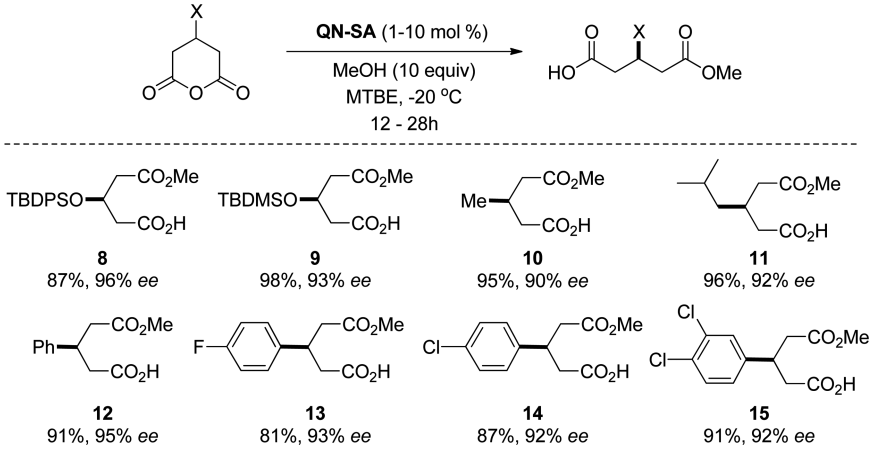


Scheme 4. Methanolytic desymmetrization of **1** with catalysts **QN-SA** and **QN-TU**.

88% *ee* under highly diluted conditions ([**1**] = 0.0125 M), albeit at the lower reaction rate.

Having obtained a highly active catalyst **QN-SA** for the desymmetrization of *meso*-succinic anhydrides, we then focused on a more challenging substrate class, 3-substituted *meso*-glutaric anhydrides, which are important building blocks for the synthesis of a variety of biologically interesting pharmaceutical compounds. For example, 3-alkyl/aryl-glutaric acid monoesters (**10-15**) are used as key intermediates for the synthesis of γ-aminobutyric acid (GABA) analogues (*e.g.*, baclofen·HCl and pregabalin),[17] selective serotonin receptor antagonists (*e.g.*, paroxetin·HCl),[18] and potent P2X7 receptor antagonists.[19] Silyl-protected 3-hydroxyglutaric hemiesters **8** and **9** can also be used as chiral synthons[20] in the preparation of HMG-CoA reductase inhibitors called statins that have inhibitory activity that suppresses the biosynthesis of cholesterol. Although a great deal of focus has been placed on the catalytic stereoselective transformation of *meso*-glutaric anhydrides to enantiomerically enriched hemiesters, the results were unsatisfactory in terms of enantioselectivity and production costs. In addition, the substrate scope of the reaction was narrow and a very long reaction time was required.[13a]

Hence, we decided to evaluate the performance of catalyst **QN-SA** in the desymmetrization of *meso*-glutaric anhydride derivatives. A variety of 3-substituted *meso*-glutaric anhydrides could be smoothly converted to the corresponding 1,5-di-



Scheme 5. Enantioselective methanolytic desymmetrization of *meso*-glutaric anhydrides.

carbonyl compounds in excellent yields and enantioselectivities (**8-15**, up to 96% *ee*, Scheme 5).[21]

Figure 6 shows a performance comparison of newly developed catalyst **QN-SA** and bifunctional catalysts, **QN-TU** and **QN-SQA**, in the desymmetrization of *meso*-glutaric anhydride **16** at a range of temperatures between –20 and 20 °C. Consistent with our expectations, the selectivity of catalyst **QN-SA** remained constant upon variation of the reaction conditions. In the case of catalysts **QN-TU** and **QN-SQA**, the enantioselectivity of the product decreases significantly towards lower temperatures (from 89% to 80% *ee* for catalyst **QN-TU**, and 85% to 80% *ee* for catalyst **QN-SQA**). This might indicate that self-aggregation takes place in these cases, yet is negligible for **QN-SA** under the reaction conditions.

Further evidence for the self-aggregation-free nature of the catalyst **QN-SA** can be obtained from analysis of its single crystal structure. As shown in Figure 7(b), it shows no

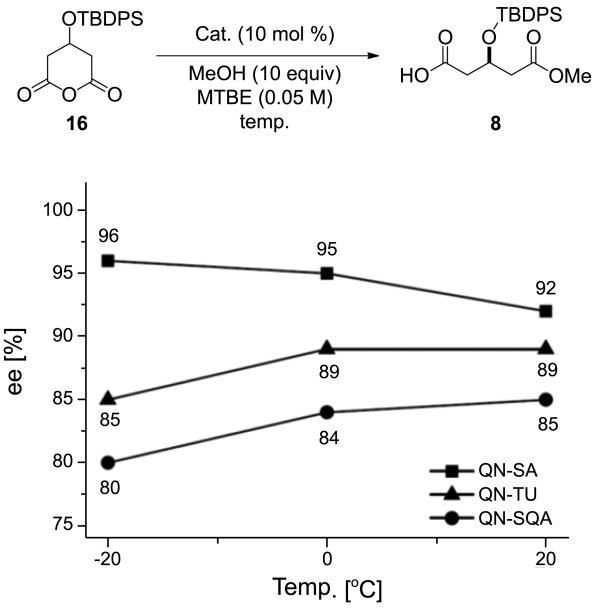


Figure 6. Effect of the reaction temperature on the enantioselectivity in the methanolytic desymmetrization of **16**.

significant intermolecular hydrogen-bonding or π-π interactions. The three-dimensional crystal structure (Figure 7(a)) indeed shows that the key functional groups (quinuclidine and N-H) are positioned in close proximity due to the π-π alignment of the aryl group of sulfonamide and the quinoline ring, while efficiently exposing the catalytically active center.

Catalyst Immobilization on Solid Support. In spite of their eco-friendly and low toxicity characteristics, organocatalysts display relatively low turnover numbers compared to transition metal catalysts. Another disadvantage which hampers the widespread use of organocatalysts is the fact

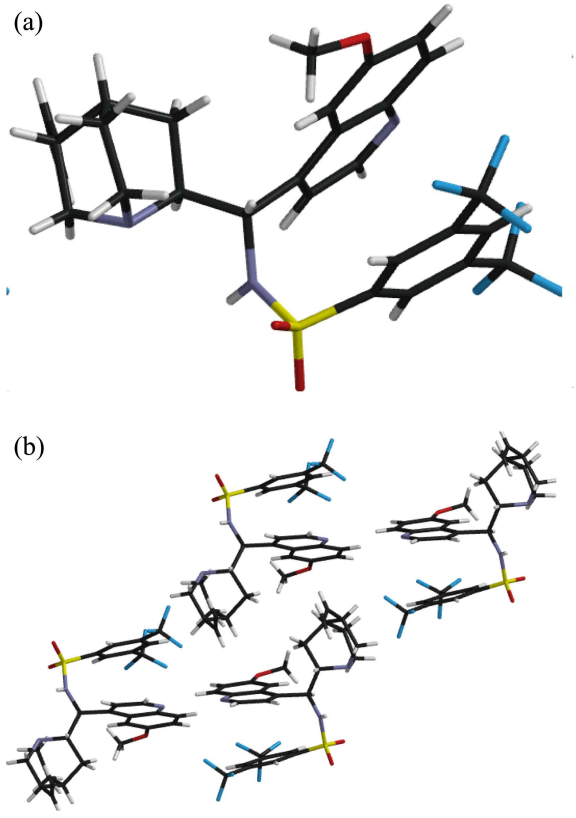
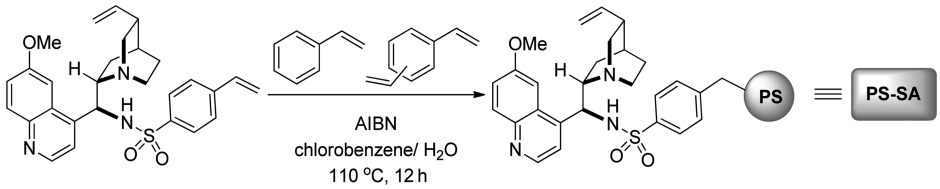


Figure 7. (a) X-ray crystal structure of **QN-SA**; (b) Schematic drawing of the crystal packing of **QN-SA**.

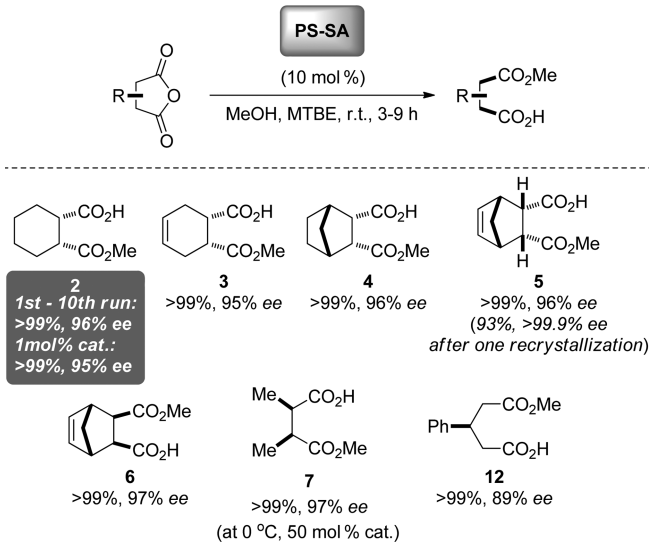


Scheme 6. Preparation of polystyrene-supported organocatalyst **PS-SA**.

that their synthesis often requires several synthetic steps. Particularly in industrial applications, where the catalyst is considered a contaminant (even in significantly low loading), a facile recovery of the organocatalysts from the reaction mixture is vital. To increase the efficiency of organocatalysis and circumvent the aforementioned drawbacks, the development of recoverable catalytic systems is highly valuable. In this context, we developed a recyclable polystyrene-supported sulfonamide-based catalyst **PS-SA** (Scheme 6).[22]

Gratifyingly, heterogeneous polymer catalyst **PS-SA** provided excellent catalytic activity and enantioselectivity (up to 97% *ee*) for the desymmetrization of several *meso*-anhydrides (Scheme 7). Moreover, a very low catalyst loading (1 mol %) was sufficient to complete the desymmetrization of cyclic anhydride **2** (> 99%, 95% *ee*) within a few hours. Additionally, the robustness of **PS-SA** provided long-term stability under heterogeneous reaction conditions, allowing the catalyst to be recycled while maintaining the same levels of enantioselectivity (> 10 cycles). The purification process was conducted by simple filtration of the mixture, affording the recovered solid catalyst and the pure product after evaporation of the solvent. The recovered catalyst could be further used to explore the substrate scope represented in Scheme 7. The corresponding hemiesters from mono-, di-, and tricyclic anhydrides could thus be obtained in high yields and excellent enantioselectivities (> 99% yield, up to 97% *ee*).

Recently, an unprecedented heterogeneous textile-supported organocatalytic system has been reported.[23] Our group, in collaboration with the List and Opwis groups, reported that our sulfonamide catalyst **QN-SA** can be readily immobilized onto textile materials with irradiation of UV light. It should be pointed out that this immobilization can proceed without

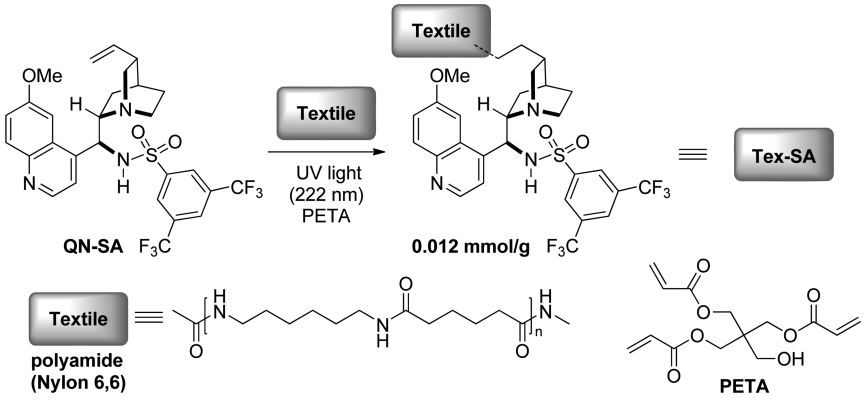


Scheme 7. Enantioselective methanolytic desymmetrization of *meso*-cyclic anhydrides.

any modification of the catalyst. Preliminary results seem to indicate that the C3 position of **QN-SA** can be directly immobilized onto the surface of the textile material, providing **Tex-SA** (Scheme 8).

Catalyst **Tex-SA** showed a very similar level of enantioselectivity to the unsupported catalyst **QN-SA**, even if a slightly longer reaction time was required. Remarkably, the immobilized textile catalyst was extremely robust and, for more than 250 cycles, the recovered catalyst showed no significant erosion of catalytic activity and enantioselectivity (Figure 8).

A series of *meso*-anhydrides was successfully converted to the corresponding hemiesters in excellent yields and selec-



Scheme 8. Reaction conditions for the photochemical immobilization of sulfonamide catalyst.

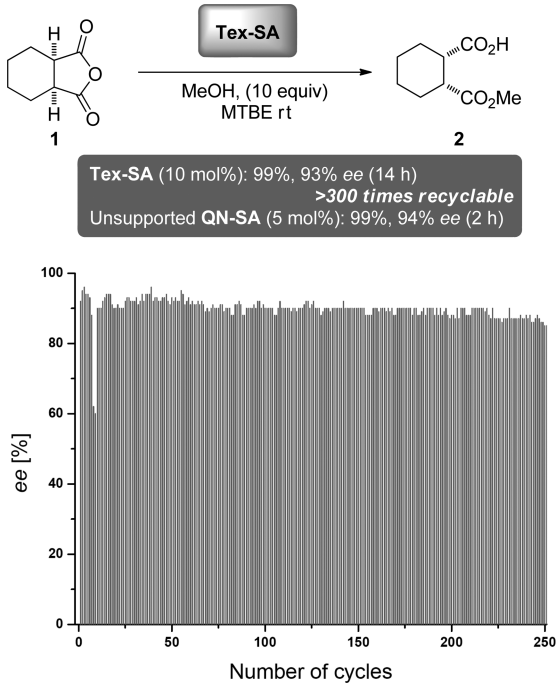
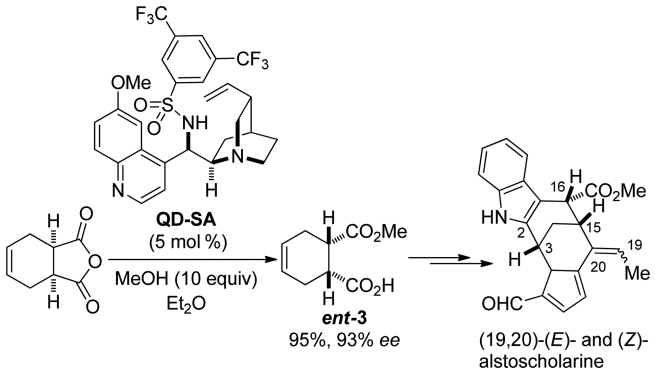


Figure 8. Performance of the textile-supported sulfonamide catalyst **Tex-SA**.

tivities with immobilized catalyst **Tex-SA** (Scheme 9). In particular, TBDPS-protected 1,5-dicarbonyl compound **8**, a useful synthon for the synthesis of various statin derivatives, was successfully obtained in gram scale when employed in a continuous flow reaction system (10 cycles, > 99% yield, 94% *ee*, Scheme 9).

Synthetic Applications for the Synthesis of Bioactive Compounds. Zhu and coworkers applied our sulfonamide-based catalyst **QD-SA** to the desymmetrization of a *meso*-anhydride in the protecting group-free total synthesis of natural products, (*E*)- and (*Z*)-alstoscholarine.[24] They successfully obtained enantioenriched hemiester ***ent*-3** (93% *ee*), employed as a key intermediate in the synthesis of both (*E*)- and (*Z*)-products (Scheme 10).

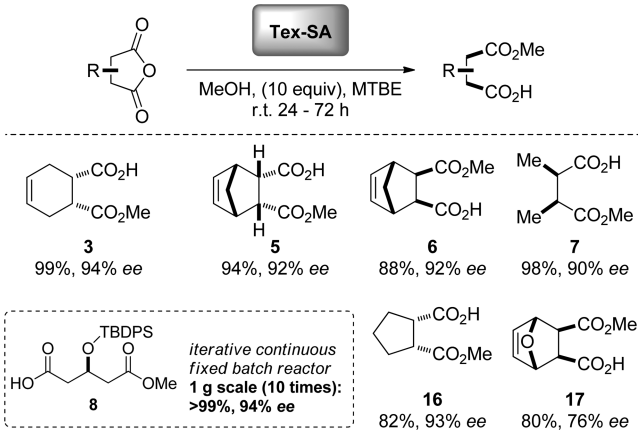


Scheme 10. Total synthesis of (*E*)- and (*Z*)-Alstoscholarine.

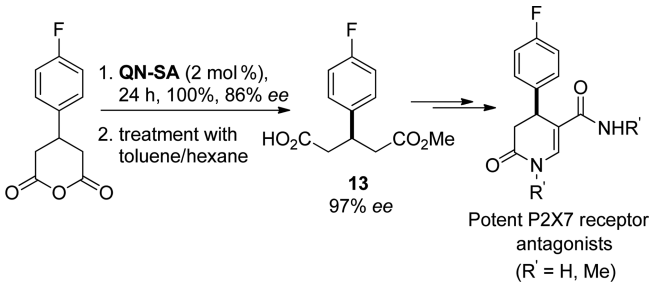
In 2010, the Roche company also applied our desymmetrization protocol in the industrial scale synthesis of new drug candidates.[19b] The company reported the preparation of hemiester **13** with 97% *ee* in multi-ten kilogram scale, as an intermediate in the synthesis of potent P2X7 receptor antagonists (Scheme 11).

We have also shown an application of the desymmetrization of *meso*-anhydrides using catalyst **QN-SA** toward the synthesis of blockbuster drug (*S*)-pregabalin, an anticonvulsant drug used for the treatment of neuropathic pain. The intermediate hemiester **18** was obtained as a benzylester in excellent yield and enantioselectivity (93% yield, 98% *ee*, Scheme 12). This eventually led to the exploitation of a short and practical route for the total synthesis of (*S*)-pregabalin.[21]

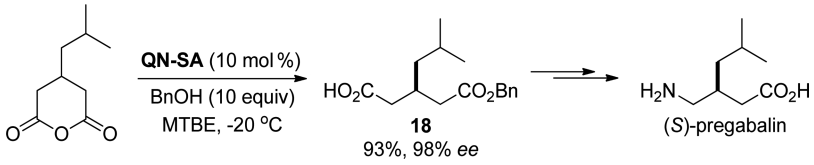
Biomimetic Decarboxylative Aldol Reaction. It is well known that nature utilizes malonic acid half thioesters



Scheme 9. Enantioselective methanolytic desymmetrization of *meso*-cyclic anhydrides.



Scheme 11. Industrial scale synthesis of potent P2X7 receptor antagonists.



Scheme 12. Preparation of (*S*)-Pregabalin.

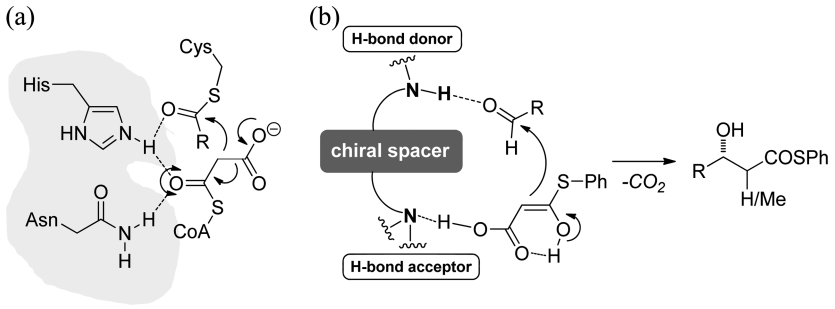
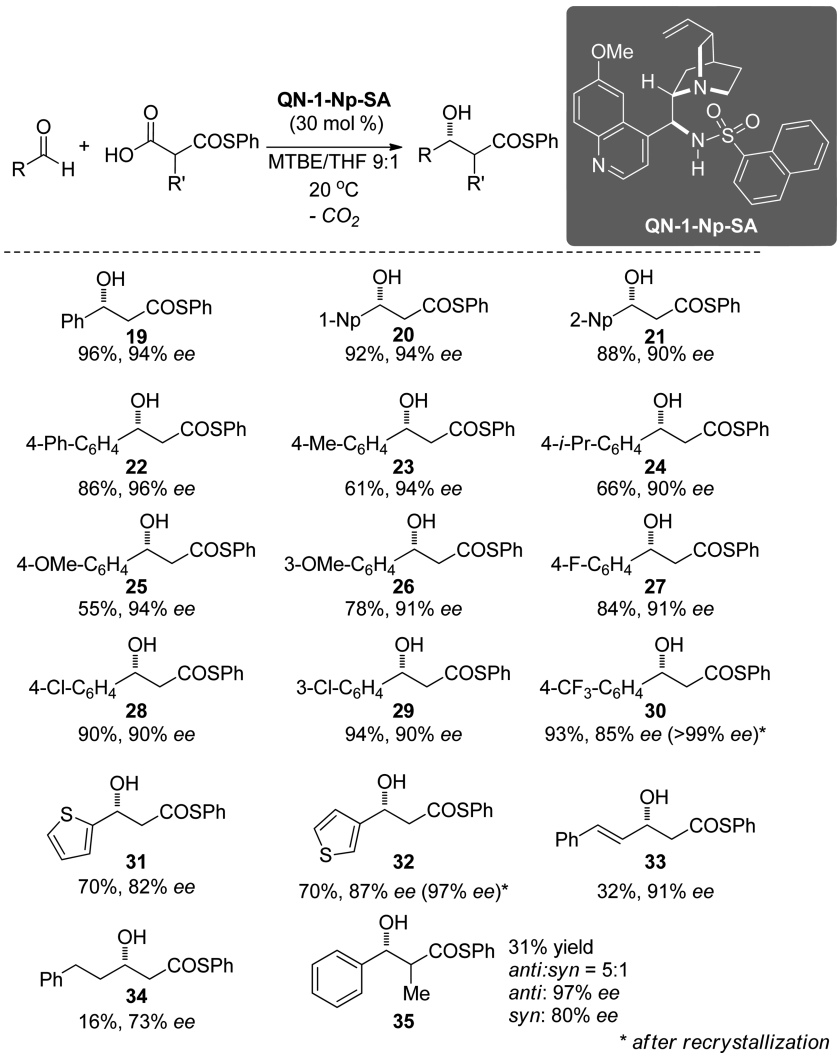


Figure 9. (a) Reaction mechanism of the polyketide synthase. (b) Plausible working hypothesis for the organocatalytic aldol reaction of MAHT with a chiral bifunctional catalyst.

(MAHTs) as enolate precursors in the synthesis of polyketides and fatty acids (Figure 9(a)).[25] Inspired by nature's process, Shair and coworkers reported a pioneering work on the asymmetric additions of MAHTs to aldehydes catalyzed by a Cu(II)/bis-oxazoline complex.[26] Since then, MAHTs have been employed in organocatalytic Michael additions, Mannich reactions, and aldol reactions.[27] However, organocatalytic aldol reactions of MAHTs to non-activated aldehydes have remained challenging.

Recognizing the similarities between the bifunctional mode of activation of sulfonamide-based catalysts and the mode of action of a polyketide synthase, we presumed that a biomimetic decarboxylative aldol reaction of MAHTs could be catalyzed by these organocatalysts (Figure 9(b)). As mentioned previously, the hydrogen-bonding ability of a sulfonamide can be easily tuned by changing the aryl substituent. After screening different aryl groups, we found that the optimal catalyst was **QN-1-Np-SA**, incorporating a



Scheme 13. Organocatalytic enantioselective decarboxylative aldol reaction of MAHTs to aldehydes.

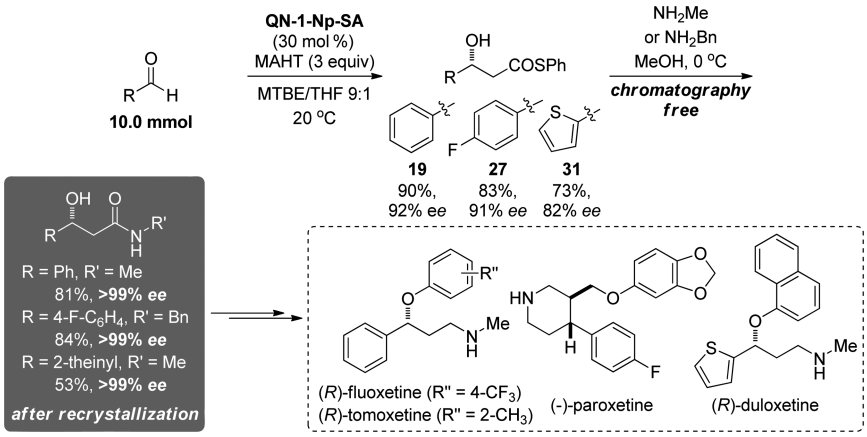
1-naphthyl moiety. With **QN-1-Np-SA**, we found that a wide range of aromatic and hetero-aromatic aldehydes could be successfully converted to the corresponding chiral β-hydroxy thioesters (**19-35**) in good yields and excellent enantioselectivities (Scheme 13).[28]

To demonstrate the synthetic utility of this decarboxylative aldol reaction of MAHTs, we conducted the multi-gram scale syntheses of key intermediates **19**, **27**, and **31** for the synthesis of some antidepressant drugs such as (*R*)-Fluoxetine, (*R*)-Tomoxetine, (−)-Paroxetine, and (*R*)-Duloxetine. In all cases, catalyst **QN-1-Np-SA** led to high yield and enantioselectivity (Scheme 14).

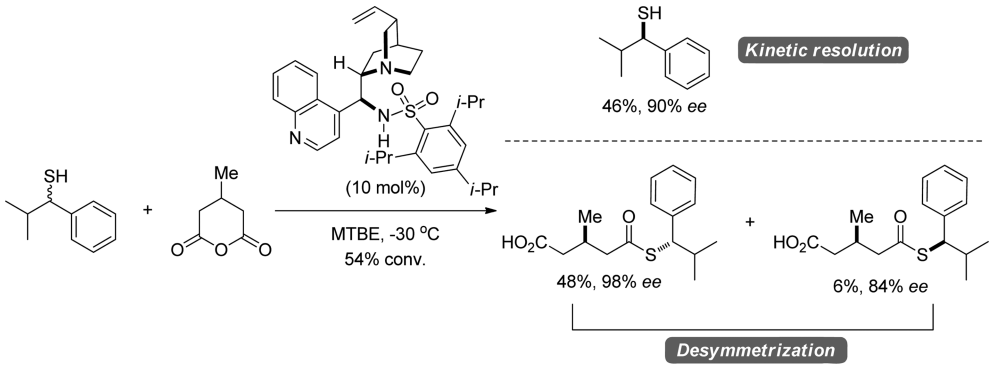
Miscellaneous Reactions. Recently, Connon and coworkers developed a one-pot catalytic desymmetrization/kinetic resolution method using a sulfonamide-based catalyst. In this reaction, a *meso*-anhydride is desymmetrized with a racemic secondary thiol as nucleophile, which led to the simultaneous resolution of less reactive thiol enantiomer. The authors showed that the less reactive (*R*)-enantiomer also reacted to some extent to give the minor diastereomer (Scheme 15).[29]

In 2008, Lu and coworkers reported the deracemization of α-substituted β-ketoesters through a stereoselective Michael addition to nitroolefins, catalyzed by a quinidine-derived sulfonamide (Scheme 16).[30]

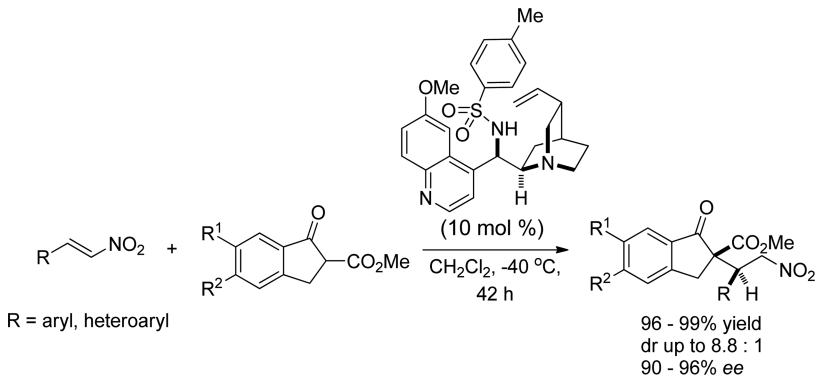
Shibata and coworkers reported an organocatalytic en-



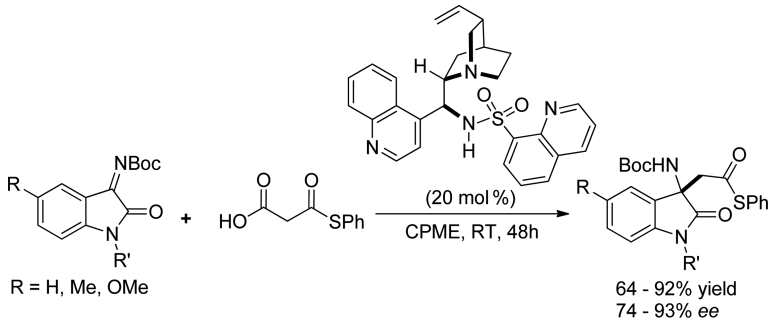
Scheme 14. Practical application of aldol products to valuable drug precursors.



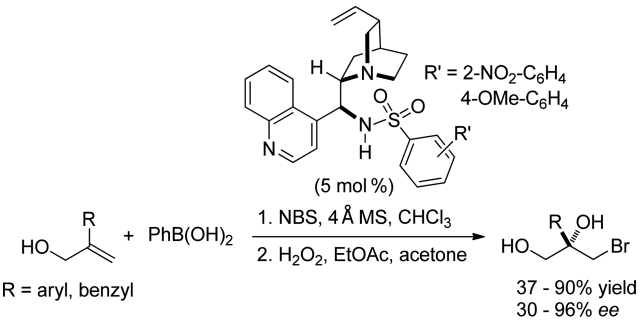
Scheme 15



Scheme 16



Scheme 17



Scheme 18

antioselective decarboxylative addition of malonic acid half thioesters to the ketimines derived from isatins using a cinchonine-derived sulfonamide catalyst (Scheme 17).[31]

Recently, Ma group reported an asymmetric bromohydroxylation of 2-aryl-2-propen-1-ols using a quinine-derived sulfonamide catalyst (Scheme 18).[32]

Conclusion

In this paper, we have attempted to summarize recent development in the field of bifunctional cinchona-derived sulfonamide organocatalysis. The self-aggregation phenomenon, a problem generally associated with bifunctional catalysts, has been effectively suppressed by the introduction of a new sulfonamide catalytic site in a cinchona-based catalyst structure. The dual activation mechanism of this new catalyst motif renders it particularly powerful for the desymmetrization of *meso*-anhydrides. The robustness of the catalyst's skeleton enabled immobilization on solid supports, such as polystyrene polymers and nylon textile materials. The obtained heterogeneous catalysts showed high catalytic activity and excellent enantioselectivity, along with outstanding recyclability. The desymmetrization methodology could be applied in the synthesis of potent drug candidates, natural products, and blockbuster pharmaceuticals. Finally, the latest developments of bio-inspired organocatalytic decarboxylative aldol reactions of MAHTs with aldehydes together with various other applications of sulfonamide cinchona-based catalysts, showed the generality of these new bifunctional catalysts in asymmetric organocatalysis.

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