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Dehydroabietane-type bifunctional organocatalysts in asymmetric synthesis: recent progress

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Dehydroabietane-type bifunctional organocatalysts derived from rosane-type diterpenes of dehydroabietic acid (DHAA) and dehydroabietylamine (DA) have been utilized in a wide variety of highly enantioselective reactions. Since one well-documented review exclusively reported on the development of terpene-derived bifunctional thioureas in asymmetric organocatalysis in 2013, fragmentary progress on the dehydroabietane-type bifunctional thioureas and squaramides has been mentioned in other reviews. In this mini-review, we systematically analyze and reorganize the published literature on dehydroabietane-type bifunctional organocatalysts in the recent decade according to the type of catalysts. Our aim is for this review to provide helpful research information and serve as a foundation for further design and application of rosin-based organocatalysts.

1. Introduction

Rosin is an abundant, renewable and biodegradable natural resource.[1,2] Rosane-type diterpenes, especially abietic acid (AA), which is the primary component of rosin, along with dehydroabietic acid (DHAA, a well-defined dehydroabietane-type diterpene) and dehydroabietylamine (DA) (Fig. 1), have been extensively utilized as chiral building blocks for the synthesis of numerous natural and synthetic molecules with diverse chemical catalytic or biological activities that find wide applications in pharmaceuticals, medicine, asymmetric synthetic chemistry, and various other fields.[3–26] As depicted in Fig. 1, AA is a monocarboxylic acid diterpene possessing a unique chiral tricyclic rigid framework with two conjugated double bonds. It can be chemically converted into DHAA and others through disproportionation. After further modification of DHAA *via* various functional group transformations, several dehydroabietane-type derivatives such as commercial DA, nordehydroabietylamine,[10] and 7-amino dehydroabietate[11,12] can be fabricated.

Chiral thioureas and squaramides are representative organocatalysts in asymmetric synthesis that have been developed for enantioselective reactions.[11–34] Owing to their specific strong hydrogen-bonding capabilities combined with the notable features of the dehydroabietane scaffold, a series of effective bifunctional organocatalysts based on the dehydroabietane structure have been employed in various catalytic asymmetric reactions so far.[11–26]

The dehydroabietane-type bifunctional organocatalysts can be broadly classified into two categories according to their hydrogen-bonding donor structures: thioureas (**C1a–C8**, including immobilized thioureas) and squaramides (**C9–C11**) as illustrated in Fig. 2.

The literature has extensively investigated the significant achievements of dehydroabietane-type bifunctional thiourea and squaramide organocatalysts in various enantioselective

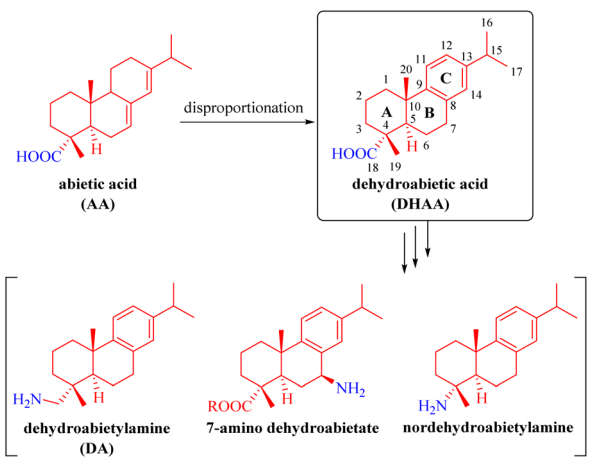

Fig. 1 Abietic and dehydroabietic acid derivatives.

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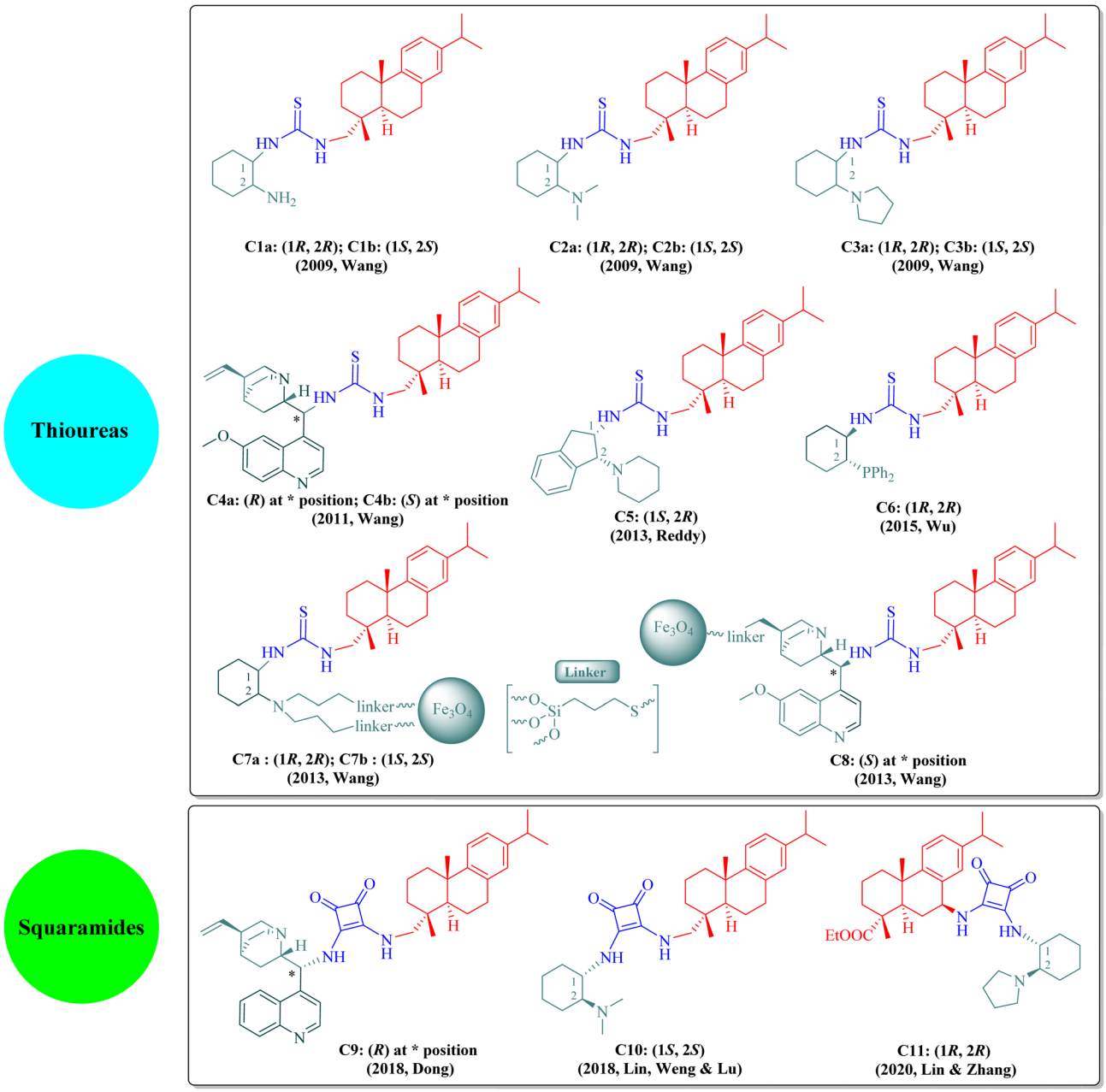


Fig. 2 Dehydroabietane-type bifunctional organocatalysts described in this review.

reactions. In 2013, Rivera and Paixão *et al.* published a well-documented review paper exclusively on the bulky and rigid chiral terpene-based bifunctional thiourea organocatalysts (2009–2012).[13] Since then, other review articles have sporadically introduced rosin-derived thiourea or squaramide organocatalysts from separate aspects such as asymmetric inverse-electron-demand Diels–Alder (IEDDA) reactions,[14] synthesis of spirooxindoles *via* organocascade strategies,[15] asymmetric cycloaddition reactions,[16] enantioselective syntheses of 3,4-dihydropyran derivatives,[17] supported hydrogen-bond organocatalysts,[18] novel catalysts for asymmetric Michael reactions,[19] sustainable organocatalysts from renewable resources,[20] 1,3-dipolar cycloadditions,[21] organocatalytic synthesis of aza-spirocyclic compounds,[22] asymmetric organocatalytic reactions for medicinal chemistry,[23] enantioselective inverse-electron-demand hetero-Diels–Alder (IEDHDA) reactions,[24] stereoselective synthesis and applications of spirocyclic oxindoles,[25] and catalytic stereoselective multicomponent reactions.[26] As shown in Fig. 2, these dehydroabietane-type organocatalysts generally contain two chiral moieties as the thiourea or squaramide substituents, namely, the dehydroabietane backbone and the other chiral skeleton such as *trans*-1,2-diaminocyclohexane, natural cinchona alkaloids, *cis*-1,2-diaminoindane, or *trans*-1-amino-2-diphenylphosphinocyclohexane, corporately

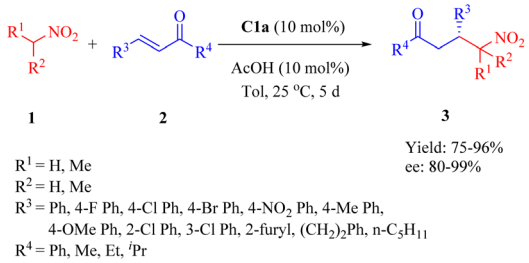
reinforcing high reactivity and stereoselectivity. Wang's group has made outstanding contributions to the development of rosin-derived bifunctional thiourea organocatalysts (**C1a–C4b** and **C7a–C8**) for highly enantioselective reactions. Additionally, other research groups have also focused on rosin-based bifunctional thiourea (**C5** and **C6**) and squaramide (**C9–C11**) organocatalysts employed in different asymmetric reactions. Nevertheless, to the best of our knowledge, all current dehydroabietane-type organocatalysts are derived from commercial DA, except the squaramide catalyst **C11** based on 7-amino dehydroabietate. Given our persistent interest in rosin-based organocatalysts and the advancements over the past decade, an updated review is imperative to facilitate the sustained utilization of natural rosin.

Rosin-derived bifunctional primary or tertiary amine thioureas have been identified as effective promoters for specific catalytic asymmetric reactions, including Michael addition reactions of β-nitroalkenes (**C1a**/**C1b**,[35] **C2a**/**C2b**,[36] and **C4a**[37]), Aldol reactions of α-isothiocyanato imides (**C3a**/**C3b**[38] and **C3b**[39]), Mannich reaction of α-isothiocyanato imides (**C4a**[40]), Michael/cyclization reactions involving α-isothiocyanato imides (**C3a**[41] and **C3b**[42]) and α,α-dicyanoolefins (**C4a**[43–45]), Friedel–Crafts alkylation (**C2b**/**C3a**[46]), and IEDDA reaction of cyclic keto/enolate salts (**C1b**[47]) (the optimal catalyst(s) denoted in parentheses for each reaction). This mini-review aims to provide a comprehensive overview of enantioselective reactions catalyzed by dehydroabietane-type bifunctional thioureas and squaramides (2013–2022), including certain reports not covered by the existing review[13] as supplementary content. We categorize and reorganize those reactions by different types of organocatalysts.

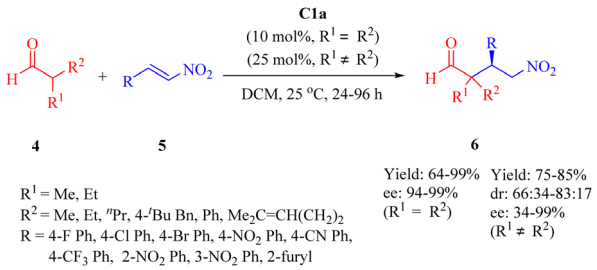
2. Dehydroabietane-type bifunctional thioureas

2.1. Asymmetric reactions catalyzed by dehydroabietane-type bifunctional thioureas with the *trans*-1,2-diaminocyclohexane scaffold

2.1.1. Asymmetric Michael addition reaction. In 2015, Wu *et al.* reported a highly enantioselective Michael addition of nitroalkanes **1** to α,β-unsaturated ketones **2** facilitated by primary amine thiourea **C1a** with acetic acid as additive, yielding γ-nitro ketones **3** with up to 99% ee (Scheme 1).[48] The diastereomer **C1b** exhibited relatively lower enantioselectivity compared to **C1a**, indicating that the DA moiety demonstrated better compatibility with the (1*R*,2*R*)-1,2-diaminocyclohexane scaffold. This observation contrasts with those reported by Wang in the Michael reaction involving methyl ketones and nitroolefins.[35] Additionally, the DA-derived thiourea containing a racemic 1,2-diaminocyclohexane backbone provided only a 4% ee value, which revealed that the DA moiety had negligible impact on stereocontrol. Notably, sterically hindered nitroalkanes such as nitrocyclopentane and 2-nitropropane did not affect the catalyst's efficiency and provided the corresponding adducts with excellent enantioselectivities.



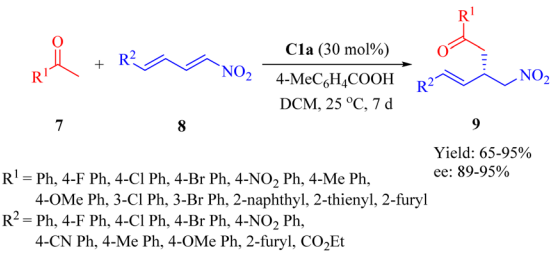
Scheme 1 Asymmetric Michael addition of nitroalkanes to α,β-unsaturated ketones.



Scheme 2 Asymmetric Michael addition of α,α-disubstituted aldehydes and β-nitroalkenes.

In 2016, Wu's group presented **C1a** for the asymmetric conjugate addition of α,α-disubstituted aldehydes **4** to β-nitroalkenes **5** to obtain γ-nitro aldehydes **6** (Scheme 2).[49] Except 2-phenylpropanal with relatively poor enantioselectivity (34% ee), various α,α-disubstituted aldehydes, including cyclohexanecarbaldehyde and 2-ethylbutanal with a large hindrance, exhibited excellent reactivity with a range of (hetero)aromtic nitroolefins, whereas aliphatic substituted nitroolefins were not tolerated under the optimal reaction conditions.

In 2017, Wu *et al.* demonstrated the use of **C1a** for the asymmetric Michael addition of (hetero)aromatic ketones **14** to α,β,γ,δ-unsaturated nitro compounds **15** in the presence of 4-methylbenzoic acid as additive to afford the products **16** with high enantioselectivities (Scheme 3).[50] The conjugate addition of aliphatic ketones such as acetone was more reactive than acetophenone even at lower catalyst loading (10 mol%), resulting in 85% yield and 87% ee (not shown in the scheme). Furthermore, this method enabled the total synthesis of (*R*)-3-



Scheme 3 Asymmetric Michael addition of (hetero)aromatic ketones to nitrodienes.

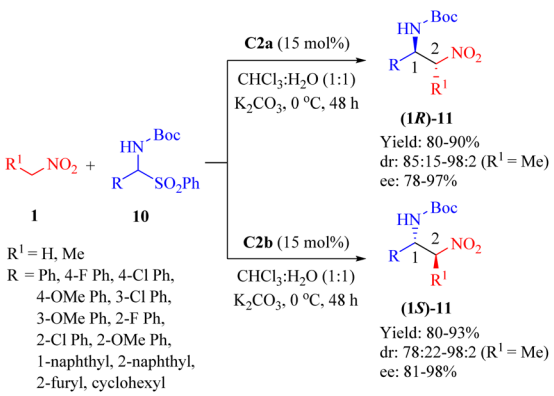
(aminomethyl)-5-phenylpentanoic acid, which was not achieved previously.

With respect to the investigated Michael reactions of nitroolefins by Wu's group, the diastereomer **C1b** efficiently promoted the enantioselective conjugation additions to furnish the corresponding products with opposite absolute configuration, showing that the DA moiety is compatible with both chiral 1,2-diaminocyclohexane with the configuration of (1*R*,2*R*) and (1*S*,2*S*). These observations were in agreement with Wang's previous report.[35] However, in these two reactions, it was found that the DA-derived primary amine thiourea containing a racemic 1,2-diaminocyclohexane skeleton led to the corresponding racemic Michael adducts but with retained yields. For comparison, the Michael reactions catalyzed by other thioureas without a rosin scaffold proceeded with excellent enantioselectivity, but the catalytic activities were lower than DA-derived thioureas. These results showed that the stereoselectivity mainly depended on the chiral *trans*-1,2-diaminocyclohexane scaffold, and that the chiral dehydroabietane structure did not affect the enantioselectivity but remarkable influence on the reactivity.

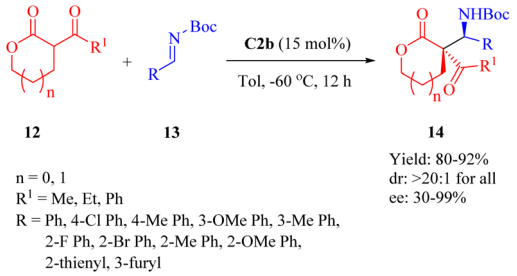
2.1.2. Asymmetric aza-Henry reaction. In 2009, Wang *et al.* employed the primary amine thioureas **C2a** and its diastereomer **C2b** for the first time to investigate the highly enantioselective aza-Henry reaction of nitroalkanes **1** and α-amidosulfones **10** (up to 98 : 2 *anti*/*syn*, and 98% ee) carried out in a doubly stereocontrolled manner (Scheme 4).[51] In this heterogeneous procedure, all reactions proceeded efficiently apart from cyclohexyl α-amido sulfone as substrate (R^1 = H, R = cyclohexyl).

2.1.3. Asymmetric Mannich reaction. Wang's previous report in 2011 demonstrated the quinine-derived thiourea **C4b** for the efficient asymmetric Mannich/cyclization reaction of α-isothiocyanato imides and *N*-Ts-aldimines.[40]

As early as 2010, Wang *et al.* revealed that **C2b** promoted the asymmetric Mannich reaction between lactones **12** and *N*-Boc-aldimines **13**, leading to the formation of the adducts **14** with excellent stereoselectivities (>20 : 1 dr for all, and up to 99% ee) containing two adjacent carbon centers, including a quaternary carbon atom (Scheme 5).[52] Although **C2a** provided high yield



Scheme 4 Asymmetric aza-Henry reaction of nitroalkanes and α-amidosulfones.



Scheme 5 Asymmetric Mannich reaction of lactones and *N*-Boc-aldimines.

and excellent diastereoselectivity, it showed an obvious decrease in enantioselectivity for the major diastereomer. **C3b** gave excellent diastereoselectivity, but relatively lower enantioselectivity. Regarding the substrates, both the size of lactone ring and substituents on aromatic imine had no impact on diastereoseletivity (>20 : 1 dr for all), but enantioselectivities clearly depended on the lactone ring size and R^1 substituent (91% ee for five cyclic lactone, $n = 0$, R^1 = Me; 57% ee for five cyclic lactone, $n = 0$, R^1 = Ph; 30% ee for six cyclic lactone, $n = 1$, R^1 = Ph). Overall, various (hetero)aromatic *N*-Boc-aldimines along with five cyclic lactone ($n = 0$, R^1 = Me) underwent this reaction to afford the corresponding products with high to excellent enantioselectivities (81–99% ee), although moderate enantioselectivity was observed when using *p*-chloro phenyl aldimines (75% ee).

The proposed mechanism involved the generation of ternary complex **A** through activation by rosin-derived tertiary amine thiourea catalyst simultaneously targeting both lactone ($n = 0$, R^1 = Me) and *N*-Boc-aldimines as illustrated in Fig. 3.

2.1.4. Asymmetric 1,3-dipolar cycloaddition reaction. In 2013, Wang *et al.* reported the first 1,3-dipolar cycloaddition reaction of homoserine lactone-derived cyclic imino esters **15** with methyleneindolinones **16** catalyzed by **C3a** to afford spiro [γ-butyrolactone-pyrrolidin-3,3′-oxindole] tricyclic skeletons **17** (Scheme 6).[53] as extensively described in several reviews.[15,16,21] Compared to the (1*S*,2*S*)-configuration of the diaminocyclohexane skeleton in the diastereomer **C3b**, the (1*R*,2*R*) configuration in **C3a** exhibited enhanced compatibility with the DA unit for this cycloaddition. In contrast, other DA-derived catalysts such as **C2b** and **C4b** displayed diminished levels of enantioselectivity.

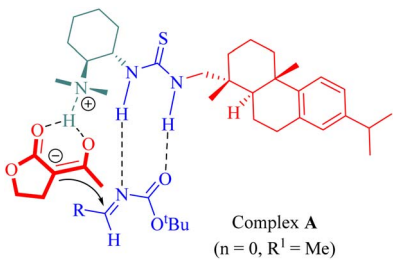


Fig. 3 Ternary complex A.

2.1.5. Asymmetric IEDDA and IEDHDA reaction. The catalytic asymmetric IEDDA[14] and IEDHDA[24] reactions have been explored using both metallic and organocatalytic methods to date, showcasing their immense potential. In 2003, Jøgensen pioneered the first organocatalytic asymmetric IEDHDA reaction employing enamine catalysis to elevate the energy of the $HOMO_{dienophile}$.[54] In 2012, Wang published an elegant asymmetric IEDHDA reaction facilitated by a single catalyst through a hydrogen-bonding dual activation strategy that simultaneously activates both the $HOMO_{dienophile}$ and the $LUMO_{diene}$.[47]

In 2012, Wang and colleagues reported another highly enantioselective IEDHDA reaction of 2-nitrocycloketones **18** and β,γ-unsaturated α-ketone esters **19** for the first time to synthesize functionalized dicyclic hemiketals **20** *via* a hydrogen-bonding dual $HOMO_{dienophile}$ and $LUMO_{diene}$-activation pathway (Scheme 7).[55] Evaluation of thiourea catalysts (**C1b**, **C2b**, **C3a**, **C3b** and **C4b**) revealed that **C3b** exhibited superior performance. Subsequently, different solvents were screened in combination with **C3b** to investigate their impact on the reaction outcome. Altering the solvent composition significantly influenced both yield and stereoselectivity, ultimately leading to the identification of a mixed solvent system with methyl *tert*-butyl ether (MTBE) and 1,2-dichloroethane (DCE) in a ratio of 1 : 1 as optimal.

The stereochemistry was elucidated by the proposed transition state as depicted in Fig. 4. The enones were activated by the thiourea moiety, while the chiral tertiary amine moiety influenced the enolization of 2-nitrocycloketone. The *endo*-selective reaction mode was achieved *via* the stereochemical control of 1,2-diaminocyclohexane and steric hindrance from the

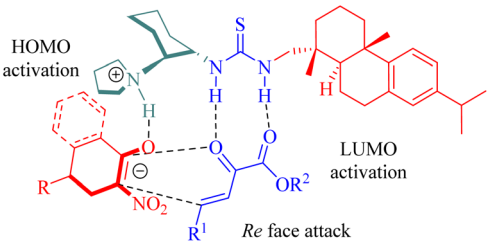
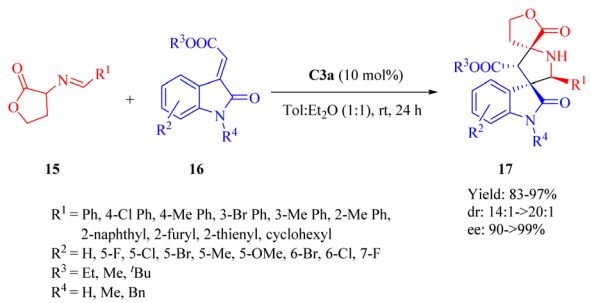


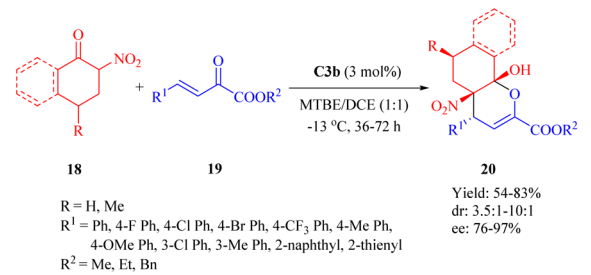
Fig. 4 A possible transition-state model.

dehydroabietane moiety of the thiourea. Activation of the enone occurred through attack from its *Re* face, whereas *exo*-selectivity was suppressed due to shielding effects on the *Si* face of the enol caused by the (1*S*,2*S*)-configuration of diaminocyclohexane and a bulky group.

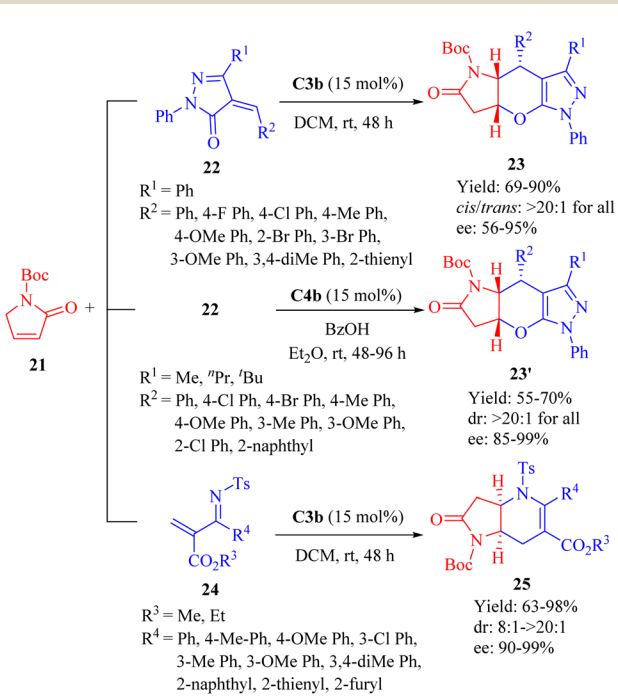
In 2013, Wang *et al.* disclosed the highly enantioselective IEDHDA [4 + 2] annulation involving α,β-unsaturated γ-butyrolactams **21** to efficiently assemble bridged tricyclic or bicyclic compounds in a single step through direct β,γ-selective activation (Scheme 8).[56] **C3b** effectively facilitated the reaction of **21** with unsaturated pyrazolones **22** (R^1 = Ph), affording β,γ-functionalized bridged tricyclic dihydropyranopyrrolidin-2-ones **23** with moderate to excellent enantioselectivities. In comparison to **21**, the α,β-unsaturated lactone exhibited negligible reactivity for this annulation (<5% yield). Furthermore, the cinchona thiourea **C4b** was also found suitable to this [4 + 2] annulation when the R^1 substituent varied. The reaction between **21** and **22** (R^1 = Me, ^{n}Pr or ^{t}Bu) outcome another set of β,γ-functionalized bridged tricyclic dihydropyranopyrrolidin-2-ones **23′** with good to excellent enantioselectivities. In addition, the catalytic system of **C3b**



Scheme 6 Asymmetric 1,3-dipolar cycloaddition reaction of homoserine lactone derived cyclic imino esters and methyleneindolinones.



Scheme 7 Asymmetric IEDDA reaction of 2-nitrocycloketones and β,γ-unsaturated α-ketone esters.



Scheme 8 Asymmetric IEDDA reaction of α,β-unsaturated γ-butyrolactams.

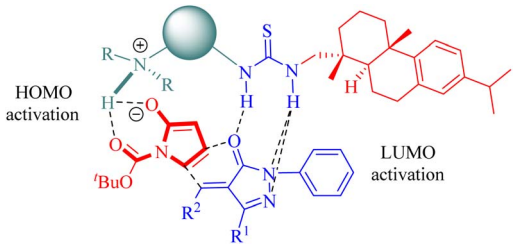
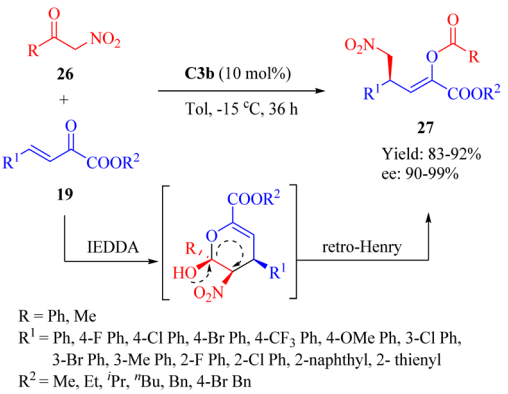


Fig. 5 A possible transition-state model of the β,γ-selective IEDDA reaction.

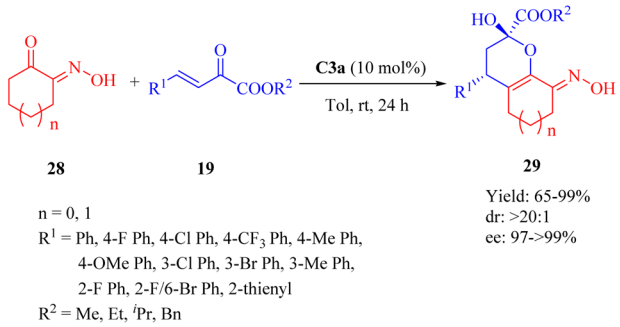
promoted the annulation of **21** with substituted *N*-tosyl-2-methylenebut-3-enoates **24** to furnish β,γ-functionalized bridged bicyclic dihydropyranopyrrolidin-2-ones **25** (Scheme 8).

Based on the experimental results, a plausible transition-state model was proposed to explain the stereochemistry of the β,γ-selective IEDDA reaction of α,β-unsaturated γ-butyrolactams (Fig. 5). The activation of both the β and γ positions in α,β-unsaturated γ-butyrolactams was achieved by simultaneous *in situ* formation of a 1,4-unsaturated enolate *via* the tertiary amine moiety of the catalyst, leading to an increase in HOMO energy, while the activation of the unsaturated pyrazolone occurred through weak hydrogen bonding with two thiourea hydrogen atoms resulting in a decrease in LUMO energy. This combination facilitated high *Re* face and *endo*-β,γ selectivity for obtaining the desired chiral product. These findings are consistent with the previous reports highlighting the primary stereochemical control exerted by the dehydroabietane moiety of the thiourea.[35,39–41,46,52]

In 2014, Zhang *et al.* reported the highly enantioselective Diels–Alder/inverse Henry reaction of α-nitroketones **26** and β,γ-unsaturated α-ketone esters **19** (Scheme 9).[57] **C2a–C3b** exhibited comparable yields, while **C3b** gave the best enantioselectivity. Conversely, **C4b** led to the least favorable result. The configuration of product **27** was determined by the chiral center in the diaminocyclohexane moiety, and both chiral moieties in **C3b** contributed to the observed enantioselectivities. A novel mechanism involving an unstable dihydropyran intermediate was proposed for this IEDDA and inverse Henry reaction.[17,20]



Scheme 9 Asymmetric IEDDA/Henry inverse reaction of α-nitroketones and β,γ-unsaturated α-ketone esters.



Scheme 10 Asymmetric Michael/cyclization of α-hydroxyimino cyclic ketones to β,γ-unsaturated α-keto esters.

2.1.6. Asymmetric Michael addition/cyclization reaction. In 2013, Wang *et al.* conducted the catalytic 1,5(6)-selective Michael/cyclization reaction of α-hydroxyimino cyclic ketones **28** with β,γ-unsaturated α-keto esters **19** in the presence of 10 mol% **C3a** to synthesize ring-fused dihydropynan compounds 29 with moderate to high yields and excellent diastereo- and enantioselectivities (>20 : 1 dr for all, and up to >99% ee) (Scheme 10).[58] **C3b** afforded the product with the opposite configuration in excellent diastereo- and enantioselectivity but lower yield. **C1a**, **C2a** and **C4a** exhibited excellent diastereoselectivity but lower yield and enantioselectivity. Remarkably, the electronic properties of substituents on β,γ-unsaturated α-ketone esters did not affect the diastereomeric ratio.

A plausible mechanism was proposed wherein tertiary amine activated α-hydroxyimino cyclic ketones while two hydrogen bonds from the chiral thiourea catalyst activated β,γ-unsaturated α-ketone esters, and subsequently, the nucleophilic attack occurred on the *Si* face of β,γ-unsaturated α-ketone ester(Fig. 6).

In 2013, Wang *et al.* discovered the enantioselective Michael-cyclization sequence of 3-isothiocyanato oxindoles **30** and unsaturated pyrazolones **22** utilizing **C3b** to construct the multicyclic spiro[oxindole/thiobutyrolactam/pyrazolone] core structures **31** with three consecutive stereocenters including two chiral spiro-quaternary carbon atoms (Scheme 11).[59] **C3a** produced the cycloadduct with the opposite configuration in excellent diastereoselectivity, but lower yield and enantioselectivity. **C4b** exhibited poor results in terms of yield, diastereo- and enantioselectivity. Remarkably, an unsaturated heteroaromatic pyrazolone (R^2 = 2-furyl) was effective for this reaction

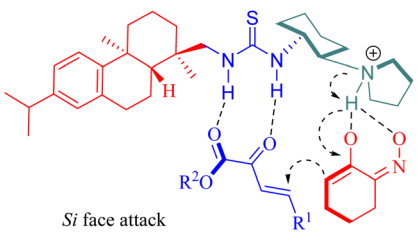
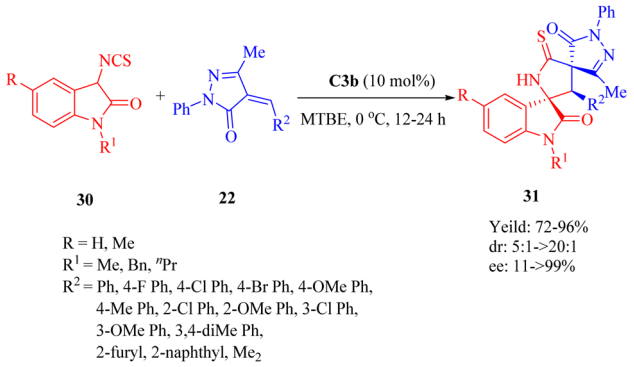


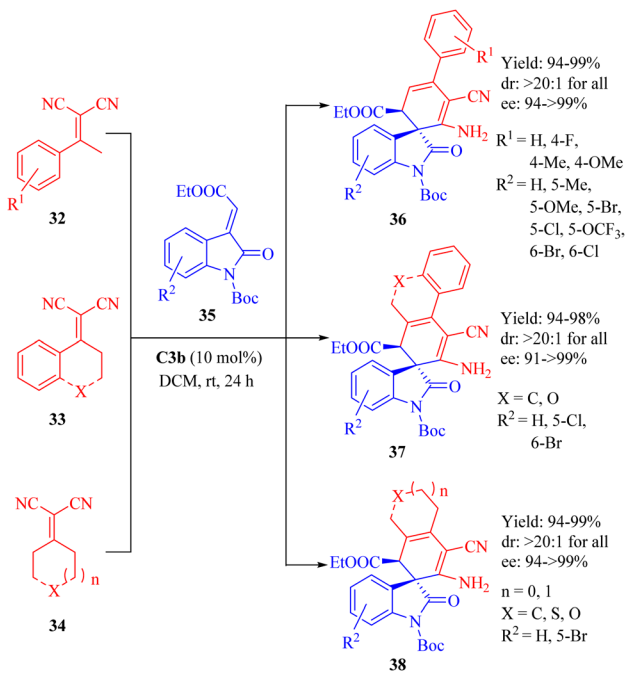
Fig. 6 A possible transition-state model of the asymmetric Michael/cyclization.



Scheme 11 Asymmetric Michael/cyclization of 3-isothiocyanato oxindoles to unsaturated pyrazolones.

with >20 : 1 dr and 96% ee. However, poor enantioselectivity (11% ee) was observed for an unsaturated pyrazolone with dimethyl groups ($R^2 = Me_2$), in spite of good yield and excellent diastereoselectivity. Encouragingly, there was no obvious impact on both reactivity and enantioselectivity when a relatively large-scale reaction was conducted even under only 0.2 mol% ligand loading.

In 2013, Wang *et al.* reported the **C3b**-catalyzed asymmetric vinylogous Michael addition/cyclization cascade reaction between ketone-derived electron-deficient α,α-dicyanoalkenes **32–34** and 3-alkylideneoxindoles **35** (Scheme 12).[60] This resulted in the formation of spirooxindole derivatives **36–38** with one all-carbon spiro-quaternary carbon atom in excellent stereoselectivities (up to >20 : 1 dr and 99% ee). In this cyclization, the diastereomer **C3a** provided the product with the opposite



Scheme 12 Asymmetric Michael/cyclization of α,α-dicyanoalkenes to 3-alkylideneoxindoles.

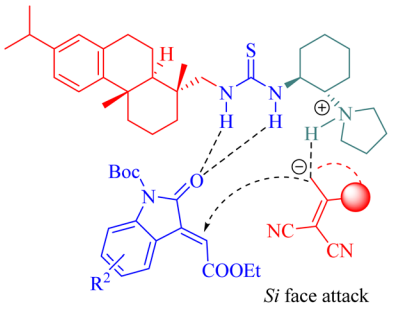


Fig. 7 A possible transition-state model of the asymmetric Michael/cyclization.

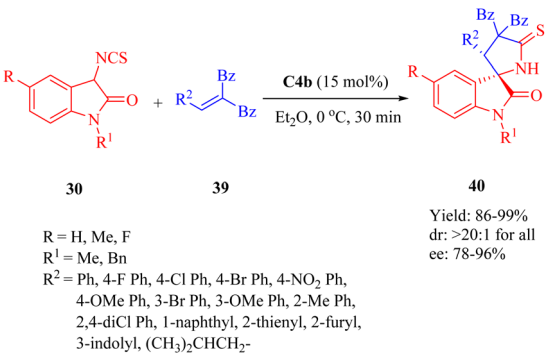
configuration in excellent diastereoselectivity but lower enantioselectivity.

Substrates were activated by tertiary amine thioureas as described in Fig. 7, and the generated vinylogous carbanion subsequently attacked from the *Si* face of activated 3-alkylideneoxindoles to form the corresponding intermediate leading to the final products through a cyclization-tautomerization sequence.

2.2. Asymmetric reactions catalyzed by dehydroabietane-type bifunctional thioureas with the cinchona alkaloid scaffold

The dehydroabietane-type cinchona thiourea **C4a** was found to be suitable for the asymmetric Mannich/cyclization reaction,[40] while its diastereomer **C4b** was employed in the enantioselective Diels–Alder [4 + 2] annulation (see Section 2.1.5).

In 2013, Wang *et al.* presented **C4b** for the first highly efficient asymmetric Michael addition/cyclization of compound **30** toward electron-deficient olefins **39**, leading to the diverse functionalized 3,2′-pyrrolidinyl spirooxindoles **40** with a chiral spiro-quaternary carbon center (Scheme 13).[61] This method demonstrated practicality for both aromatic- and aliphatic-substituted alkenes (up to 99% yield, >20 : 1 dr and 96% ee). Electron-withdrawing and electron-donating groups at different positions on the aromatic ring (R^2) of olefins were well-tolerated. Moreover, reactions with the substrates possessing heteroaromatic rings and a larger hindrance 1-naphthyl worked



Scheme 13 Asymmetric Michael/cyclization of 3-isothiocyanato oxindoles to electron-deficient olefins.

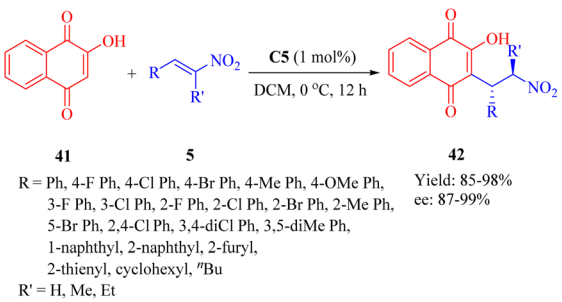
well, except the substrate containing a 2-furyl group which gave only a moderate enantioselectivity (78% ee).

2.3. Asymmetric reactions catalyzed by dehydroabietane-type bifunctional thioureas with the *cis*-1,2-diaminoindane scaffold

In 2013, Reddy *et al.* developed a series of bifunctional rosin- and sugar-indane tertiary amine thiourea catalysts as well as indane-based squaramides, inspired by the success of natural rosin- and sugar-derived thiourea organocatalysts.[62] Initially, the asymmetric Michael addition of 2-hydroxy-1,4-naphthoquinone **41** to β-nitroalkenes **5** was conducted using indane-based tertiary amine thioureas or squaramides. Remarkably, the DA-indane thiourea **C5** exhibited high efficiency in this conjugate addition even at low catalyst loading (1 mol%), resulting in excellent enantioselectivities (up to 99% ee, R = ^{n}Bu, and R′ = H) (Scheme 14). Furthermore, this same catalyst demonstrated positive effects on the reactions between compound **41** and α-branched β-nitrostyrenes (R = Ph, and R′ = Me, Et), leading to admirable diastereoselectivities (only one single diastereomer detected for each) and remarkable enantioselectivities (95% and 98% ee values, respectively).

A possible transition state model was proposed in Fig. 8. **C5** activated the nitroalkenes through doubly hydrogen bonding with its thiourea groups while simultaneously activating substrate **41** *via* its indane tertiary amine moiety. The nucleophile attacked from the *Si* face of the activated nitroalkene.

Moreover, the conjugate additions of 1,3-dicarbonyl compounds to β-nitroolefins **5** were also investigated (Scheme 15). Indeed, the utilization of catalyst **C5** enhanced the



Scheme 14 Asymmetric Michael addition of 2-hydroxy-1,4-naphthoquinone to β-nitroalkenes.

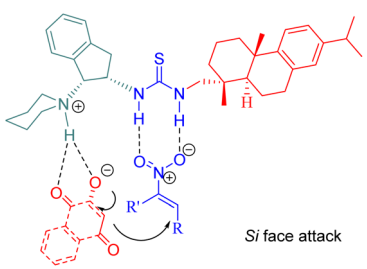
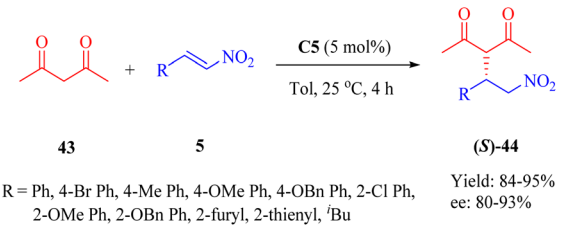
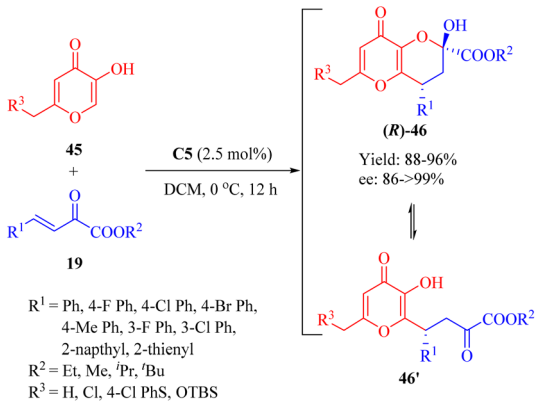


Fig. 8 A possible transition-state model of the asymmetric Michael reaction.



Scheme 15 Asymmetric Michael addition of 1,3-dicarbonyl compounds to β-nitroalkenes.



Scheme 16 Asymmetric Michael/hemiketalization of kojic acid derivatives to β,γ-unsaturated α-ketone esters.

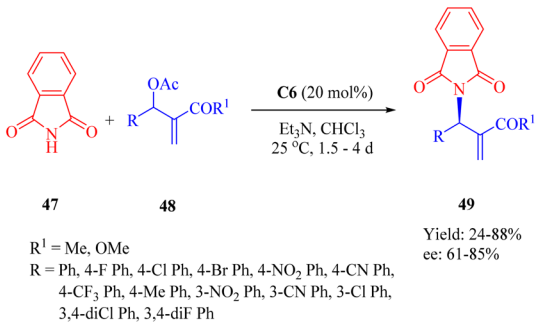
reaction of 2,4-pentanedione **43** and compound **5** with high reactivities and enantioselectivities (up to 95% yield and 93% ee), albeit with a higher catalyst loading. In addition, efficient Michael reaction of other 1,3-dicarbonyl compounds such as malonate esters with β-nitrostyrene was observed under similar reaction conditions, however, the enantioselectivity did not exceed 93% ee (not shown in the scheme).

Subsequently in 2014, Reddy and coworkers discovered the enantioselective Michael/hemiketalization reaction (a type of cascade reaction) of various derivatives **45** from kojic acid (R^3 = OH, a fungal metabolite with diverse biological activities) and β,γ-unsaturated α-ketone esters **19** promoted by the tertiary amine thiourea **C5** with a catalyst loading of 2.5 mol% (Scheme 16).[63] This reaction efficiently constructed chiral tetrahydro pyrano[3,2-*b*]pyran scaffolds **46** with high enantioselectivities (up to 99% ee). A rapid equilibrium was observed between the cyclic hemiketal **46** and the Michael-type adduct **46′**, similarly to the equilibriums previously studied.[64]

2.4. Asymmetric reactions catalyzed by dehydroabietane-type bifunctional thioureas with the *trans*-1-amino-2-diphenylphosphinocyclohexane scaffold

In 2015, Wu and Sha *et al.* investigated the allylic amination reaction of phthalimide **47** and Morita–Baylis–Hillman (MBH) acetates **48** using the thiourea **C6** (Scheme 17).[65]

In the catalytic process, nucleophilic addition of the phosphine **C6** to MBH acetates occurred, followed by the acetoxy group departure to form a cationic (*E*)-enone intermediate. This



Scheme 17 Asymmetric allylic amination of phthalimide and Morita–Baylis–Hillman acetates.

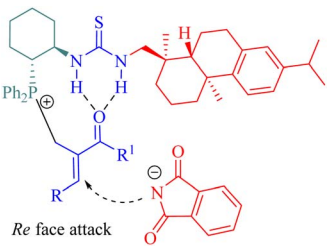


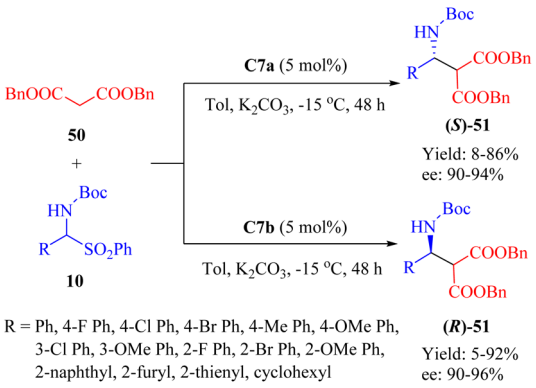
Fig. 9 A possible transition-state model of the asymmetric MBH reaction.

intermediate was activated through the hydrogen-bonding interaction. A nucleophile generated from deprotonated phthalimide by triethylamine attacked the *Re* face of cationic enone to produce chiral amines **49** (Fig. 9). Catalyst screening revealed that the dehydroabietane part matched well with the (1*R*,2*R*)-cyclohexyl backbone to reach a high level of enantioselectivity.

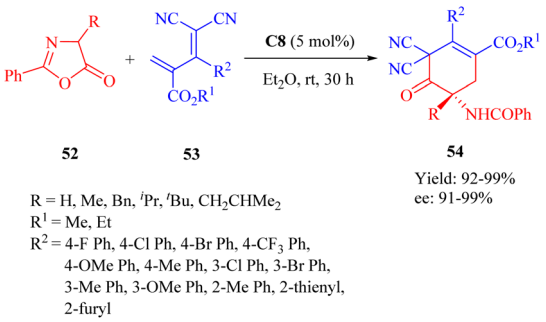
3. Immobilized dehydroabietane-type bifunctional thioureas

The immobilization of hydrogen-bond organocatalysts offers heterogeneous systems that provide various advantages for a sustainable approach in green chemistry, including chemical stability, facile work-up, and/or potential reusability. Several kinds of supports have been employed while preserving the benefits of the homogeneous catalysts.[19] Among these support material, magnetic nanoparticles (MNPs) are considered ideal due to their special magnetic behavior, high specific surface area, chemical durability, and low toxicity.[66] Therefore, MNPs hold great promise as versatile catalyst supports for catalytic synthetic transformations under environmentally friendly reaction conditions.

In 2013, Wang *et al.* developed a new class of MNPs-supported tertiary amine thioureas, namely **C7a** and its diastereomer **C7b**, to facilitate the asymmetric Mannich reaction between dibenzyl malonate **50** and α-amidosulfones **10** (Scheme 18).[67] Under identical conditions, these immobilized thioureas exhibited higher catalytic activities compared to the



Scheme 18 Asymmetric heterogeneous Mannich reaction of dibenzyl malonate and α-amidosulfones.



Scheme 19 Asymmetric heterogeneous IEDDA reaction of azlactones and multisubstituted dicyano-2-methylenebut-3-enoates.

free thioureas **C2a** and **C2b**, whose ligand loading must be 15 mol% for achieving high yield and enantioselectivity. With the exception of an aliphatic substrate (yielding only 5% and 8%, R = cyclohexyl, ee not determined), a range of aromatic amido sulfones with various substituents successfully underwent the reaction. Notably, these two catalysts were reproducible up to 15 times with a minimal impact on enantioselectivity.

In the same year, Wang *et al.* developed the MNPs-supported cinchona thiourea **C8** for the highly enantioselective heterogeneous IEDDA reaction of azlactones **44** with multisubstituted dicyano-2-methylenebut-3-enoates **45** through a double $HOMO_{dienophiles}$ and $LUMO_{dienes}$ activation manner (Scheme 19).[68] Additionally, the immobilized catalyst exhibited excellent stability and recyclability over 10 cycles without any noticeable loss of activity.

4. Dehydroabietane-type bifunctional squaramides

Over and above thioureas, squaramides have emerged as highly efficient hydrogen-bonding donors. Drawing inspiration from the extensive utilization of squaramide organocatalysts in asymmetric transformations,[12,14,15,17–21] several research groups have endeavored to develop novel dehydroabietane-type bifunctional squaramides, although successful examples remain limited.

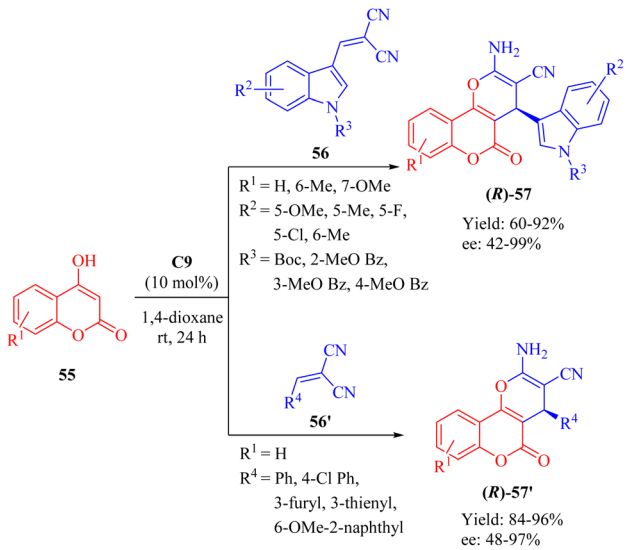
4.1. Asymmetric reactions catalyzed by dehydroabietane-type bifunctional squaramides with the cinchona alkaloid scaffold

In 2018, Dong *et al.* developed a DA-cinchonine-derived squaramide **C9** for the asymmetric domino reaction of 4-hydroxy-2H-chromen-2-ones **55** and substituted methylene malononitriles **56**/**56′** (Scheme 20).[69] This methodology successfully afforded a range of optically active pyrano[3,2-*c*]chromene derivatives **57**/**57′** with moderate to excellent enantioselectivities. The resulting cyclic products were evaluated for their inhibitory activities against acetylcholinesterase (AChE) *in vitro*. Quite notably, it was observed that the (*S*)-configured product exhibited higher bioactivity than the (*R*)-configured counterpart, except for the significantly potent product **57′** containing 6-OMe-2-naphthyl group where both enantiomers displayed similar activities.

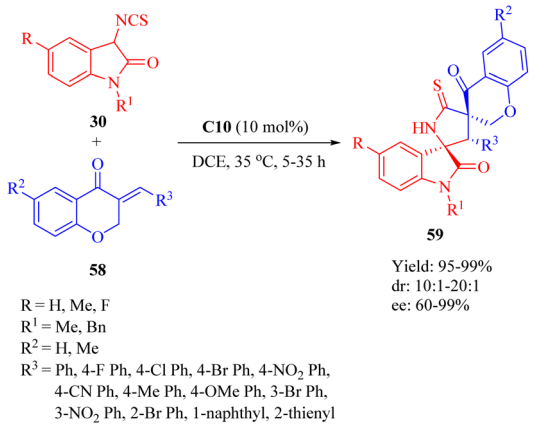
4.2. Asymmetric reactions catalyzed by dehydroabietane-type bifunctional squaramides with the *trans*-1,2-diaminocyclohaxane scaffold

In 2018, our group developed a DA-derived tertiary amine squaramide **C10** for the asymmetric Michael/cyclization cascade reaction of 3-isothiocyanato oxindoles **30** with (*E*)-3-arylidenechroman-4-ones **58** to successfully construct a series of spirocyclic compounds **59** with three continuous stereocenters, including two spiro-quaternary carbon centers, in high yields and stereoselectivities (Scheme 21).[11] The gram-scale preparation of this reaction did not compromise its stereoinduction and reactivity. Moreover, through substitution and oxidation reactions, these spirocyclic compounds would be transformed into other chiral spirocyclic skeletons with considerable yield and stereoselectivities.

In addition, to rationalize the stereochemical outcome of this cycloaddition, a catalytic transition state model was proposed as shown in Fig. 10.



Scheme 20 Asymmetric domino reaction of 4-hydroxy-2*H*-chromen-2-ones and methylene malononitriles.



Scheme 21 Asymmetric Michael/cyclization of 3-isothiocyanato oxindoles to (*E*)-3-arylidenechroman-4-ones.

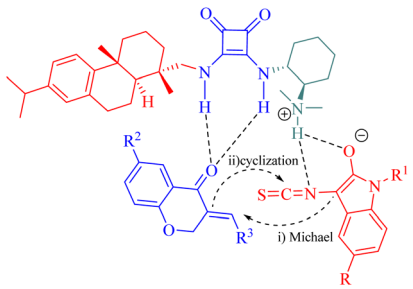
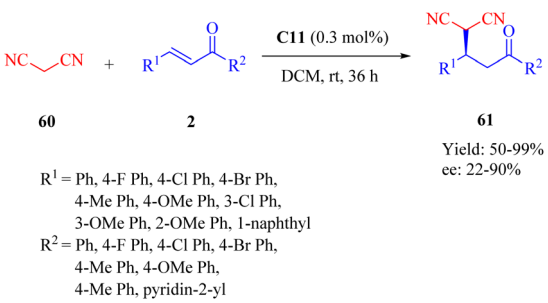


Fig. 10 A possible transition-state model.

The novel dehydroabietane-type tertiary amine squaramide **C11** was designed and synthesized by our group in 2020 and successfully applied for the asymmetric Michael reaction of malononitrile **60** to α,β-unsaturated ketones **2**, leading to chiral γ-cyano carbonyl compounds **61** under significantly low catalyst loading (0.3 mol%) (Scheme 22).[12]

In the transition state formation, both malononitrile and α,β-unsaturated ketones interacted *via* hydrogen bonding with the squaramide moiety and the tertiary amine moiety of **C11**, respectively. Subsequent nucleophilic attack of malononitrile on the *Si* face of activated α,β-unsaturated ketones offered the (*R*)-configured products (Fig. 11).



Scheme 22 Asymmetric Michael addition of malononitrile to α,β-unsaturated ketones.

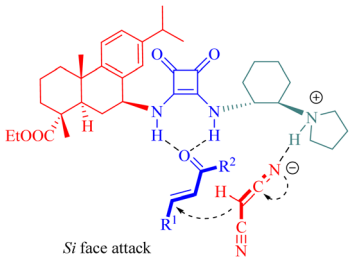


Fig. 11 Proposed model of nucleophilic attack.

5. Conclusions

Rosin-based bifunctional organocatalysts, particularly, dehydroabietane-type bifunctional thioureas and squaramides, have demonstrated remarkable efficacy in facilitating extensive enantioselective reactions over the past decade, as summarized in this concise review. Despite their significant contributions to this captivating research field of asymmetric organocatalysis, there remain several topics worthy of discussion concerning the development of rosin-based organocatalysts. Firstly, in those successful asymmetric reactions, bifunctional thiourea and squaramide organocatalysts generally feature the dehydroabietane backbone together with a secondary chiral scaffold such as *trans*-1,2-diaminocyclohexane, cinchona alkaloids, *cis*-1,2-diaminoindane, and 1-amino-2-diphenylphosphinecyclohexane. This combination of two chiral moieties appears an additive effect. Therefore, it is anticipated that the second chiral scaffold can be diversified by incorporating various chiral amino acids or alternative chiral skeletons. Secondly, most dehydroabietane-type organocatalysts have undergone structural modifications at the C-4 position on the A ring of the DHAA skeleton, except one example for B-ring modification at the C-7 position.[12] In particular, derivatization of the amino moiety at the C-18 position has been performed, resulting in the activation site appears distant from the steric atmosphere of rosin. Consequently, the stereoselectivity and absolute configuration of the products primarily rely on the secondary chiral unit, such as the chiral *trans*-1,2-diaminocyclohexane scaffold. It is worth noting that while the chiral dehydroabietane structure does not significantly impact enantioselectivity, it exerts a remarkable influence on reactivity. However, no catalyst resulting from simultaneous modifications on both A and B rings has been reported yet. To fully exploit and elucidate the potential of the chiral tricyclic rigid skeleton found in dehydroabietane-type diterpenes, a rational design approach for novel organocatalysts by modifying both A and B rings to achieve desired catalytic activities represents an intriguing avenue for future research. These insights are expected to significantly contribute to the further refinement and practical implementation of rosin-based organocatalysts.

Author contributions

Conceptualization, Z.-W. Zhang, Y.-Q. Deng and N. Lin; funding acquisition, Z.-W. Zhang, Y.-Q. Deng and N. Lin; writing—original draft preparation, S.-W. Liu, H.-P. Huang, Y.-H. Xie and R.-C. Huang; writing—review and editing, Z.-W. Zhang, Y.-Q. Deng and N. Lin.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

1 A. J. D. Silvestre and A. Gandini, *Monomers, Polymers and Composites from Renewable Resources*, M. N. Belgacem and A. Gandini, Elsevier, Amsterdam, The Netherlands, 2008, ch. 4, pp. 67–88.
2 B. K. Yadav, B. Gidwani and A. Vyas, *J. Bioact. Compat. Polym.*, 2016, **31**, 111–126.
3 C. Faustino, Í. Neto, P. Fonte and A. Macedo, *Curr. Pharm. Design*, 2018, **24**, 4362–4375.
4 J. Wiemann, A. Al-Harrasi and R. Csuk, *Anti-Cancer Agents Med. Chem.*, 2020, **20**, 1756–1767.
5 S. Kugler, P. Ossowicz, K. Malarczyk-Matusiak and E. Wierzbicka, *Molecules*, 2019, **24**, 1651.
6 F. Steppeler, D. Iwan, E. Wojaczyńska and J. Wojaczyński, *Molecules*, 2020, **25**, 401.
7 R. J. Rafferty, R. W. Hicklin, K. A. Maloof and P. J. Hergenrother, *Angew. Chem., Int. Ed.*, 2014, **53**, 220–224.
8 R. Tapia, H. Bouanou, E. Alvarez, R. Alvarez-Manzaneda, R. Chahboun and E. Alvarez-Manzaneda, *J. Org. Chem.*, 2014, **79**, 4405–4413.
9 S. Bhowmick, S. S. Kunte and K. C. Bhowmick, *Tetrahedron: Asymmetry*, 2014, **25**, 1292–1297.
10 W.-G. Huang, H.-S. Wang, G.-B. Huang, Y.-M. Wu and Y.-M. Pan, *Eur. J. Org Chem.*, 2012, **2012**, 5839–5843.
11 N. Lin, X.-W. Long, Q. Chen, W.-R. Zhu, B.-C. Wang, K.-B. Chen, C.-W. Jiang, J. Weng and G. Lu, *Tetrahedron*, 2018, **74**, 3734–3741.
12 N. Lin, Q.-X. Wei, L.-H. Jiang, Y.-Q. Deng, Z.-W. Zhang and Q. Chen, *Catalysts*, 2020, **10**, 14.

13 S. Narayanaperumal, D. G. Rivera, R. C. Silva and M. W. Paixão, *ChemCatChem*, 2013, **5**, 2756–2773.
14 X. Jiang and R. Wang, *Chem. Rev.*, 2013, **113**, 5515–5546.
15 D. Cheng, Y. Ishihara, B. Tan and C. F. Barbas, *ACS Catal.*, 2014, **4**, 743–762.
16 F. E. Held and S. B. Tsogoeva, *Catal. Sci.*, 2016, **6**, 645–667.
17 G. Desimoni, G. Faita and P. Quadrelli, *Chem. Rev.*, 2018, **118**, 2080–2248.
18 A. Franconetti and G. de Gonzalo, *ChemCatChem*, 2018, **10**, 5554–5572.
19 S. Kamal, A. F. Zahoor, S. Ahmad, R. Akhtar, I. Khaliq, W. Qurban and A. Mehreen, *Curr. Org. Chem.*, 2020, **24**, 1397–1458.
20 S. Meninno, *ChemSusChem*, 2020, **13**, 439–468.
21 G. Molteni and A. Silvani, *Eur. J. Org Chem.*, 2021, **2021**, 1653–1675.
22 A. Laviós, A. Sanz-Marco, C. Vila, G. Blay and J. R. Pedro, *Eur. J. Org Chem.*, 2021, **2021**, 2268–2284.
23 B. Han, X.-H. He, Y.-Q. Liu, G. He, C. Peng and J.-L. Li, *Chem. Soc. Rev.*, 2021, **50**, 1522–1586.
24 V. Laina-Martín, J. A. Fernández-Salas and J. Alemán, *Chem.–Eur. J.*, 2021, **27**, 12509–12520.
25 A. J. Boddy and J. A. Bull, *Org. Chem. Front.*, 2021, **8**, 1026–1084.
26 D. M. Patel, P. J. Patel and H. M. Patel, *Eur. J. Org Chem.*, 2022, **2022**, e202201119.
27 N. Melnyk, I. Iribarren, E. Mates-Torres and C. Trujillo, *Chem.–Eur. J.*, 2022, **28**, e202201570.
28 P. Chauhan, S. Mahajan, U. Kaya, D. Hack and D. Enders, *Adv. Synth. Catal.*, 2015, **357**, 253–281.
29 X. Han, H.-B. Zhou and C. Dong, *Chem. Rec.*, 2016, **16**, 897–906.
30 B. L. Zhao, J. H. Li and D. M. Du, *Chem. Rec.*, 2017, **17**, 994–1018.
31 Y. Lin and D. Du, *Chinese J. Org. Chem.*, 2020, **40**, 3214–3236.
32 D. Krištofíková, V. Modrocká, M. Mečiarová and R. Šebesta, *ChemSusChem*, 2020, **13**, 2828–2858.
33 A. Biswas, A. Ghosh, R. Shankhdhar and I. Chatterjee, *Asian J. Org. Chem.*, 2021, **10**, 1345–1376.
34 S. Vera, A. García-Urricelqui, A. Mielgo and M. Oiarbide, *Eur. J. Org Chem.*, 2023, **26**, e202201254.
35 X. Jiang, Y. Zhang, A. S. C. Chan and R. Wang, *Org. Lett.*, 2009, **11**, 153–156.
36 X. Jiang, Y. Zhang, X. Liu, G. Zhang, L. Lai, L. Wu, J. Zhang and R. Wang, *J. Org. Chem.*, 2009, **74**, 5562–5567.
37 X. Liu, H. Song, Q. Chen, W. Li, W. Yin, M. Kai and R. Wang, *Eur. J. Org Chem.*, 2012, **2012**, 6647–6655.
38 X. Jiang, G. Zhang, D. Fu, Y. Cao, F. Shen and R. Wang, *Org. Lett.*, 2010, **12**, 1544–1547.
39 X. Jiang, Y. Cao, Y. Wang, L. Liu, F. Shen and R. Wang, *J. Am. Chem. Soc.*, 2010, **132**, 15328–15333.
40 X. Jiang, Y. Wang, G. Zhang, D. Fu, F. Zhang, M. Kai and R. Wang, *Adv. Synth. Catal.*, 2011, **353**, 1787–1796.
41 Y. Cao, X. Jiang, L. Liu, F. Shen, F. Zhang and R. Wang, *Angew. Chem.*, 2011, **123**, 9290–9293; *Angew. Chem., Int. Ed.*, 2011, **50**, 9124–9127.
42 L. Liu, Y. Zhong, P. Zhang, X. Jiang and R. Wang, *J. Org. Chem.*, 2012, **77**, 10228–10234.
43 G. Zhang, Y. Zhang, X. Jiang, W. Yan and R. Wang, *Org. Lett.*, 2011, **13**, 3806–3809.
44 X. Jiang, Y. Sun, J. Yao, Y. Cao, M. Kai, N. He, X. Zhang, Y. Wang and R. Wang, *Adv. Synth. Catal.*, 2012, **354**, 917–925.
45 G. Zhang, Y. Zhang, J. Yan, R. Chen, S. Wang, Y. Ma and R. Wang, *J. Org. Chem.*, 2012, **77**, 878–888.
46 X. Jiang, L. Wu, Y. Xing, L. Wang, S. Wang, Z. Chen and R. Wang, *Chem. Commun.*, 2012, **48**, 446–448.
47 X. Jiang, X. Shi, S. Wang, T. Sun, Y. Cao and R. Wang, *Angew. Chem.*, 2012, **124**, 2126–2129; *Angew. Chem., Int. Ed.*, 2012, **51**, 2084–2087.
48 X.-Y. Wu, F. Sha, X.-T. Guo and J. Shen, *Synthesis*, 2015, **47**, 2063–2072.
49 X.-T. Guo, F. Sha and X.-Y. Wu, *Res. Chem. Intermed.*, 2016, **42**, 6373–6380.
50 X.-Y. Wu, X.-T. Guo and F. Sha, *Synthesis*, 2017, **49**, 647–656.
51 X. Jiang, Y. Zhang, L. Wu, G. Zhang, X. Liu, H. Zhang, D. Fu and R. Wang, *Adv. Synth. Catal.*, 2009, **351**, 2096–2100.
52 X. Jiang, D. Fu, G. Zhang, Y. Cao, L. Liu, J. Song and R. Wang, *Chem. Commun.*, 2010, **46**, 4294–4296.
53 L. Wang, X.-M. Shi, W.-P. Dong, L.-P. Zhu and R. Wang, *Chem. Commun.*, 2013, **49**, 3458–3460.
54 K. Juhl and K. A. Jørgensen, *Angew. Chem.*, 2003, **115**, 1536–1539; *Angew.Chem. Int. Ed.*, 2003, **42**, 1498–1501.
55 X. Jiang, L. Wang, M. Kai, L. Zhu, X. Yao and R. Wang, *Chem.–Eur. J.*, 2012, **18**, 11465–11473.
56 X. Jiang, L. Liu, P. Zhang, Y. Zhong and R. Wang, *Angew. Chem.*, 2013, **125**, 11539–11543; *Angew. Chem., Int. Ed.*, 2013, **52**, 11329–11333.
57 H.-R. Zhang, J.-J. Xue, R. Chen, Y. Tang and Y. Li, *Chin. Chem. Lett.*, 2014, **25**, 710–714.
58 L. Liu, D. Zhang, P. Zhang, X. Jiang and R. Wang, *Org. Biomol. Chem.*, 2013, **11**, 5222–5225.
59 Q. Chen, J. Liang, S. Wang, D. Wang and R. Wang, *Chem. Commun.*, 2013, **49**, 1657–1659.
60 X.-M. Shi, W.-P. Dong, L.-P. Zhu, X.-X. Jiang and R. Wang, *Adv. Synth. Catal.*, 2013, **355**, 3119–3123.
61 Y.-M. Cao, F.-F. Shen, F.-T. Zhang and R. Wang, *Chem.–Eur. J.*, 2013, **19**, 1184–1188.
62 B. V. S. Reddy, M. Swain, S. M. Reddy and J. S. Yadav, *RSC Adv.*, 2013, **3**, 8756–8765.
63 B. V. S. Reddy, M. Swain, S. M. Reddy, J. S. Yadav and B. Sridhar, *RSC Adv.*, 2014, **4**, 42299–42307.
64 S.-L. Zhao, C.-W. Zheng, H.-F. Wang and G. Zhao, *Adv. Synth. Catal.*, 2009, **351**, 2811–2816.
65 X. Zhao, T. Kang, J. Shen, F. Sha and X. Wu, *Chin. J. Chem.*, 2015, **33**, 1333–1337.
66 Z. Zeng, Y. Chen, X. Zhu and L. Yu, *Chin. Chem. Lett.*, 2022, **34**, 107728.
67 H. Zhu, X. Jiang, X. Li, C. Hou, Y. Jiang, K. Hou, R. Wang and Y. Li, *ChemCatChem*, 2013, **5**, 2187–2190.
68 X. Jiang, H. Zhu, X. Shi, Y. Zhong, Y. Li and R. Wang, *Adv. Synth. Catal.*, 2013, **355**, 308–314.
69 J. Zheng, M. He, B. Xie, L. Yang, Z. Hu, H.-B. Zhou and C. Dong, *Org. Biomol. Chem.*, 2018, **16**, 472–479.