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Catalytic enantioselective divergent reaction of thioimidates with naphthols: construction of *N,S*-acetal-containing tetrasubstituted carbon centers†

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Enantiopure *N,S*-acetals are distributed in numerous natural products and pharmaceuticals, exhibiting a broad spectrum of biological activities. Herein we open a new avenue for accessing *N,S*-acetal-containing tetrasubstituted carbon stereogenic centers through an enantioselective divergent reaction between cyclic α-carbonyl thioimidates and naphthols. Using 2-naphthols as nucleophilic partners, the reaction enabled the formation of structurally diverse furanonaphthobenzo[*b*]thiophene derivatives bearing two vicinal diheteroatom-containing tetrasubstituted carbon stereogenic centers with high optical purities through a domino aza-Friedel–Crafts/*O*-hemiacetalization of the exocyclic C=O bond. In contrast, the enantioselective addition of 1-naphthols/electron-rich phenols to cyclic α-carbonyl thioimidates led to the formation of *N,S*-acetal-containing tetrasubstituted carbon stereogenic centers in high yields and excellent enantioselectivities. DFT studies provide valuable insights into the reaction mechanism and the origin of enantioselectivity, as well as the reaction divergence observed with 2-naphthols and 1-naphthols, respectively. The results suggest that the C–C bond formation during the addition of naphthols to thioimidates is the enantioselectivity-determining step, while the rate-determining step is the C–H bond cleavage. Additionally, both kinetically and thermodynamically, the reaction with 2-naphthols favors the subsequent *O*-hemiacetalization to yield cyclization products, whereas the addition of 1-naphthols to thiomidates is thermodynamically driven for the synthesis of chiral *N,S*-acetals through the subsequent protonation process.

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Introduction

Sulfur-containing compounds play an important role in the field of medicinal chemistry and material disciplines.[1] In particular, optically active *N,S*-acetals have garnered considerable attention due to their presence in natural products and pharmaceuticals, exhibiting a wide range of biological activities.[2] As a result, significant efforts have been devoted to the catalytic enantioselective construction of chiral *N,S*-acetal structures (Scheme 1a),[3] including the enantioselective C–S bond formation through asymmetric α-sulfenylation of nitrogen-containing prochiral carbon centers (strategy 1),[4] asymmetric addition of thiols to imines (strategy 2),[5] and the enantioselective C–N bond formation *via* asymmetric α-amination of sulfur-containing prochiral carbon centers (strategy 3).[6] Although progress has been made, these methods are limited by the need for specific reagents, such as *N*-(sulfanyl)succinimides, thiols and azodicarboxylates, for the enantioselective formation of carbon–heteroatom bonds, thereby restricting the scope and applicability of these reactions. Along this line, we questioned whether the formation of enantiopure *N,S*-acetals could be achieved by the enantioselective C–C bond formation (strategy 4). If successful, this protocol would not only open a new avenue for accessing enantiopure *N,S*-acetals but also enrich the structural diversity of resulting products.

Thioimidates, featuring a thioether group attached to an imine (RS–CR=NR), are important building blocks in organic synthesis, particularly for the preparation of potentially useful

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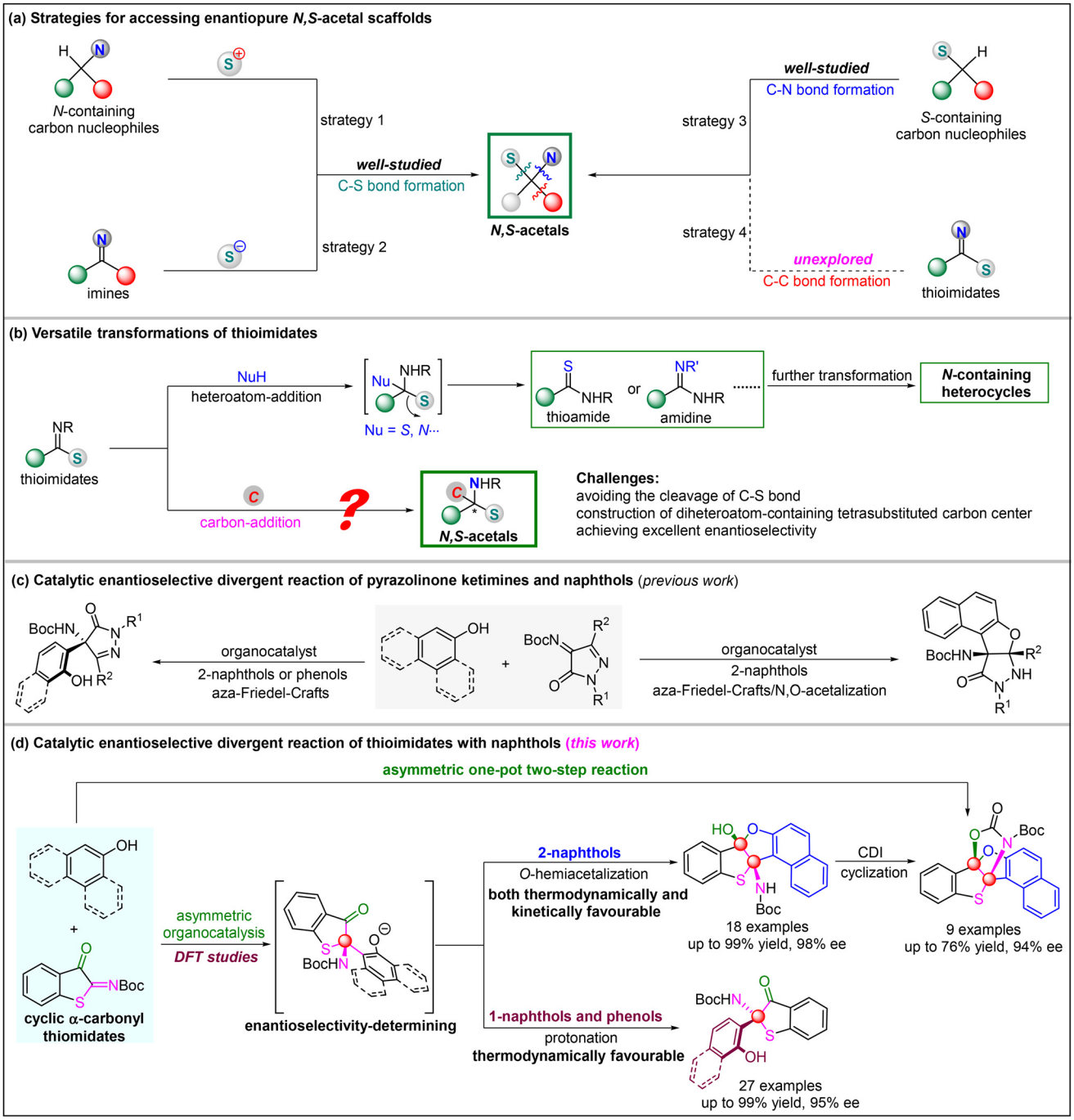


Scheme 1 (a) Strategies for accessing enantiopure *N,S*-acetal scaffolds. (b) Versatile transformations of thioimidates for well-studied heteroatom-addition and unexplored carbon-addition. (c) Catalytic enantioselective divergent reaction of pyrazolinone ketimines and naphthols. (d) Enantioselective divergent reaction of thioimidates with naphthols in this work.

thioamides, amidines, and peptide-bond isosteres.[7] Additionally, thioimidates could undergo cyclization to deliver value-added nitrogen-containing heterocyclic compounds, such as pyrrole, oxazole, and triazole rings.[8] In these reactions, the sulfur atom in the thioester moiety of thioimidates served as an excellent leaving group during nucleophilic attack by heteroatoms (*S*, *N*, *etc.*), facilitating the removal of sulfur and enabling further transformation (Scheme 1b). Leveraging the strong electrophilic nature of thioimidates, we hypothesized that the attack of a carbon nucleophile could lead to the formation of optically active *N,S*-acetals through enantioselective C–C bond formation. To our surprise, this area remains largely unexplored, likely due to the following potential challenges (Scheme 1b): (i) as mentioned above, the excellent leaving

ability of the thioester moiety makes it particularly difficult to prevent C–S bond cleavage;[9] (ii) the formation of diheteroatom-containing tetrasubstituted carbon stereogenic center poses a significant steric hindrance when a carbon nucleophile attacks thioimidates;[10] and (iii) the identification of a suitable catalytic system to achieve excellent enantioselectivity remains a critical issue.[11]

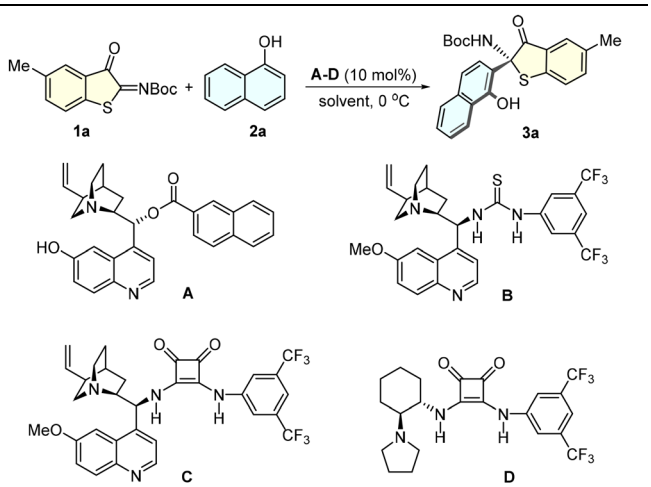
In 2015, Kostyuk and co-workers reported a ring-opening reaction of cyclic thioimidates with carbon nucleophiles, particularly with active methylene compounds.[12] It appears that the cyclic structure reduced the leaving ability of the thioester component, resulting in the formation of alkenyl sulfide compounds in good yields under harsh conditions. Inspired by this work, we first prepared a type of cyclic α-carbonyl thioimidates *via* the aza-Wittig reaction of benzo[*b*]thiophene-2,3-diones. We hypothesize that the cyclic structure in these compounds helps to prevent the cleavage of the C–S bond, allowing the formation of chiral *N*,*S*-acetals under a mild catalytic system. Additionally, further functionalization of the carbonyl group could facilitate the synthesis of more complex molecules.

Employing dual nucleophilic sites (*C*-nucleophilic site and *O*-nucleophilic site) of naphthols, Enders and Chauhan described a squaramide-catalyzed enantioselective divergent reaction between pyrazolinone ketoimines and naphthols for the preparation of chiral nitrogen-containing tetrasubstituted carbon stereogenic centers In 2017 (Scheme 1c).[13a] Our group reported an enantioselective [3 + 2] annulation of tryptanthrin-derived ketoimines and 2-naphthols to access indolo[2,1-*b*]quinazoline derivatives.[13b] As well as our ongoing interest in asymmetric synthesis of heteroatom-containing tetrasubstituted carbon stereogenic center,[14] we have recently opened a new avenue for accessing *N*,*S*-acetal-containing tetrasubstituted carbon stereogenic centers through an enantioselective divergent reaction between cyclic α-carbonyl thioimidates and naphthols/phenols (Scheme 1d). Notably, distinct reactivities were observed for 2-naphthols and 1-naphthols/phenols. Employing 2-naphthols as nucleophile partners, the reaction enabled the formation of structurally diverse furanonaphthobenzo[*b*]thiophene derivatives bearing two vicinal diheteroatom-containing tetrasubstituted carbon stereogenic centers with high optical purities through a domino aza-Friedel–Crafts/*O*-hemiacetalization of the exocyclic C=O bond. Moreover, using *N*,*N*-carbonyldiimidazole (CDI) as the cyclization reagent, enantiopure bridged-naphtho[2,1-*b*]furan derivatives were synthesized from cyclic α-carbonyl thioimidates and 2-naphthols *via* a one-pot two-step operation. In contrast, the reaction with 1-naphthols or electron-rich phenols allowed the formation of a wide range of *N*,*S*-acetal-containing tetrasubstituted carbon stereogenic centers in high yields and excellent enantioselectivities. DFT calculations were performed to gain valuable insights into the reaction mechanism and the origin of enantioselectivity, as well as the reaction divergence observed with 2-naphthols and 1-naphthols, respectively. The results suggest that the C–C bond formation during the addition of naphthols to thioimidates is the enantioselectivity-determining step, while the rate-determining step is the C–H bond cleavage. Additionally, both kinetically and thermodynamically, the reaction with 2-naphthols favors the subsequent *O*-hemiacetalization to yield cyclization products, whereas the addition with 1-naphthols is driven thermodynamically for the synthesis of enantiopure *N*,*S*-acetals through the subsequent protonation process. Herein, we present our findings on this subject with the hope of contributing to the advancement of this field.

Results and discussion

We began our study with the investigation of the reaction between cyclic α-carbonyl thioimidate **1a** and 1-naphthol **2a** in the presence of various bifunctional catalysts at 0 °C (Table 1). With the cinchona alkaloid-derived catalyst **A**, the reaction delivered the desired *N*,*S*-acetal **3a** in 76% yield but as a racemate (entry 1). The thiourea catalyst **B** produced **3a** in 89% yield and good enantioselectivity (entry 2). We were pleased to find that using the quinine-derived squaramide **C** as a catalyst

Table 1 Optimization of reaction conditions[a]



Entry	A–D	Solvent	Time (min)	Yield[b] (%)	ee[c] (%)
1	**A**	CH_2Cl_2	60	76	0
2	**B**	CH_2Cl_2	60	89	70
3	**C**	CH_2Cl_2	60	99	87
4	**D**	CH_2Cl_2	60	83	80
5	**C**	Toluene	30	87	84
6	**C**	THF	30	29	52
7	**C**	CH_3CN	30	50	35
8	**C**	$CHCl_3$	30	98	89
9	**C**	$ClCH_2CH_2Cl$	30	70	80
10[d]	**C**	$CHCl_3$	6	92	92
11[e]	**C**	$CHCl_3$	6	95	93
12[e,f]	**C**	$CHCl_3$	30	95	91

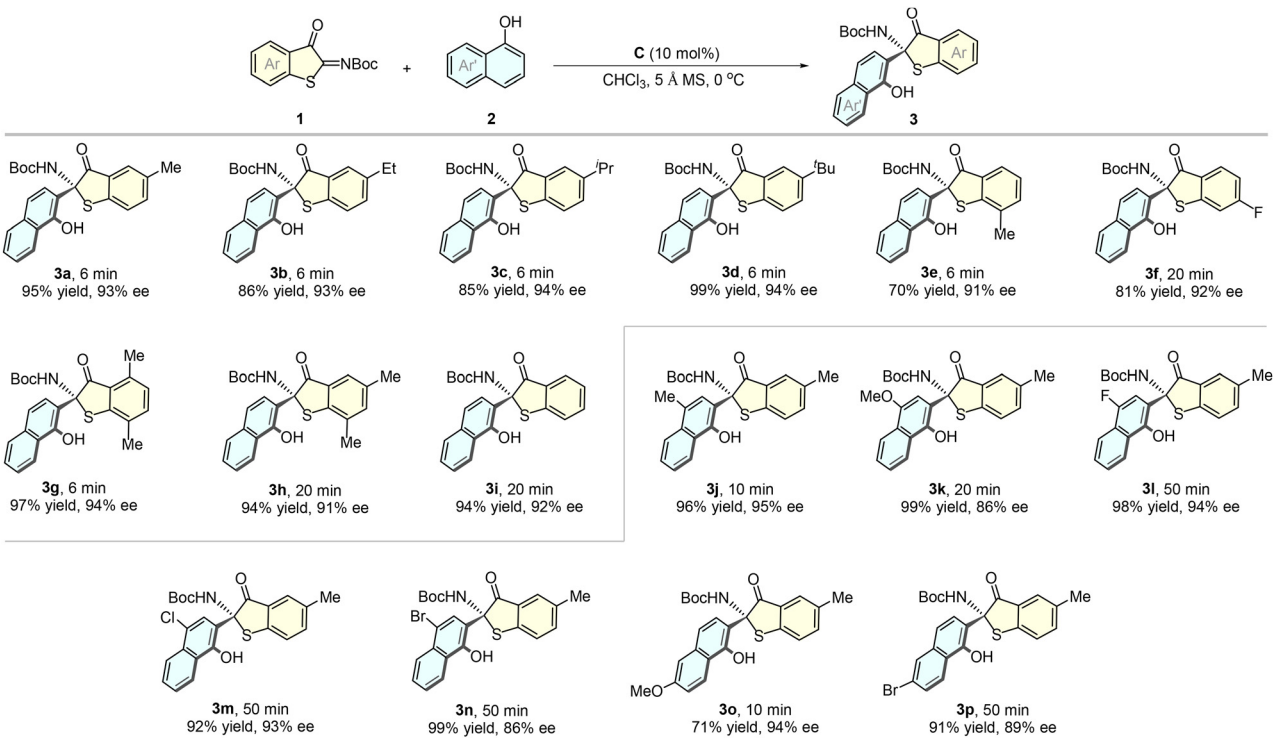
[a] Unless otherwise noted, the reaction was carried out with **1a** (0.15 mmol), **2a** (0.1 mmol), and 10 mol% catalyst in 1.0 mL of solvent at °C for the specified reaction time. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] 3 Å MS (50 mg) was added. [e] 5 Å MS (50 mg) was added. [f] 5 mol% catalyst **C** was used.

resulted in a quantitative yield of **3a** and 87% ee (entry 3). However, screening cyclohexanediamine-derived squaramide **D** led to a reduced ee value (entry 4). Further attempt was made to improve the enantioselectivity by exploring different solvents (entries 5–9). It was found that both the yield and enantioselectivity were significantly affected by different reaction media. Solvents such as THF and CH_3CN gave relatively lower yield and enantioselectivity (entries 6 and 7), while $CHCl_3$ proved to be optimal, affording **3a** in 98% yield and 89% ee (entry 8). Additionally, when 3 Å and 5 Å molecular sieve (MS) were used as additives, the reaction completed within 6 minutes, yielding **3a** in excellent yield with ee value increasing to 92% and 93%, respectively (entries 10 and 11). Reducing the load of catalyst **C** to 5 mol% resulted in a slight decrease in enantioselectivity (entry 12).

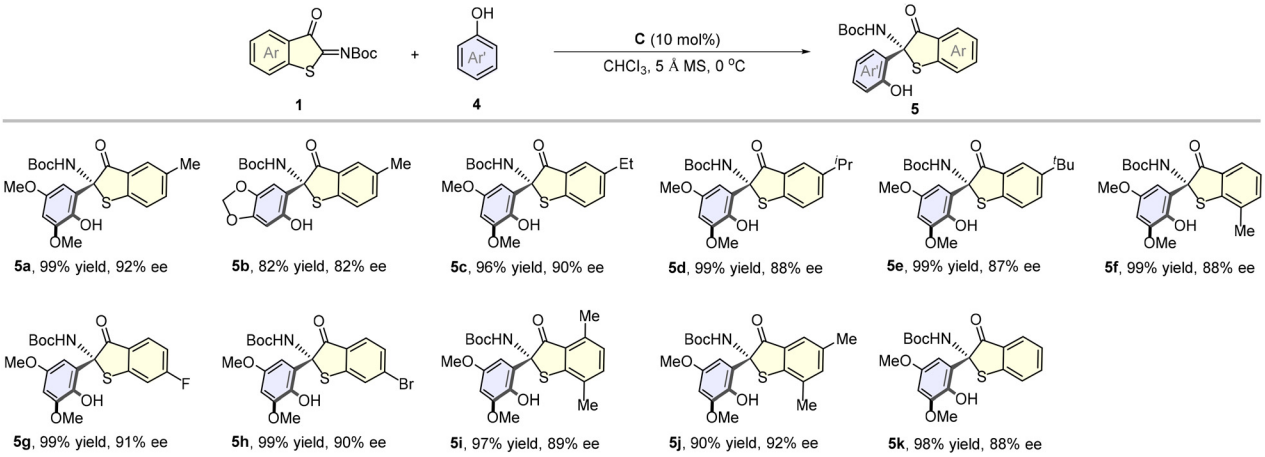
With the optimized conditions established, the substrate scope was then investigated (Scheme 2). Cyclic α-carbonyl thioimidates **1** with various electron-donating substituents at the C5-position, such as methyl, ethyl, isopropyl and *tert*-butyl, reacted smoothly to give the corresponding products **3a–d** in excellent results, indicating that the size of the functional groups had almost no influence on the reactivity and enantioselectivity. Furthermore, cyclic thioimidates substituted with 7-methyl and 6-fluoro were also tolerated, delivering products **3e** and **3f** in good yields with 91% and 92% ee, respectively. Disubstituted cyclic thioimidates were also amenable to the developed protocol, furnishing high yields and ee values for products **3g** and **3h**. Additionally, the electroneutral substrate could afford product **3i** in 97% yield and 92% ee. On the other hand, regardless of the electron-donating or electron-withdrawing substituents at the C4-position of 1-naphthols, their reactions with **1a** presented very high reactivity and the corresponding adducts **3j–n** could be obtained in excellent yields and up to 95% ee. Moreover, the introduction of different substituents at the C6-position of 1-naphthols was also endured, as exemplified by the formation of products **3o** and **3p** with 94% and 89% ee, respectively.

To our delight, the developed protocol was also feasible to the enantioselective addition of electron-rich phenols to cyclic α-carbonyl thioimidates. As demonstrated in Scheme 3, under optimized reaction conditions, 3,4-dimethoxyphenol **4a** and sesamol **4b** enabled the formation of the corresponding adducts **5a** and **5b** in good yields and enantioselectivities. Cyclic thioimidates with either electron-donating or electron-withdrawing substituent on the aryl ring could reacted smoothly with **4a** to generate the corresponding products **5c–h** in excellent yields and high ee values. Additionally, dimethyl-substituted substrates were also tolerated under the reaction conditions, affording products **5i** and **5j** in 97% yield with 89% ee and 99% yield with 90% ee, respectively. Furthermore, the cyclic thioimidate without substituents on the aryl ring also successfully produced the expected product **5k** with satisfactory results.

Encouraged by the above success, we sought to extend the methodology to the enantioselective addition of 2-naphthols to cyclic α-carbonyl thioimidates for further conforming the

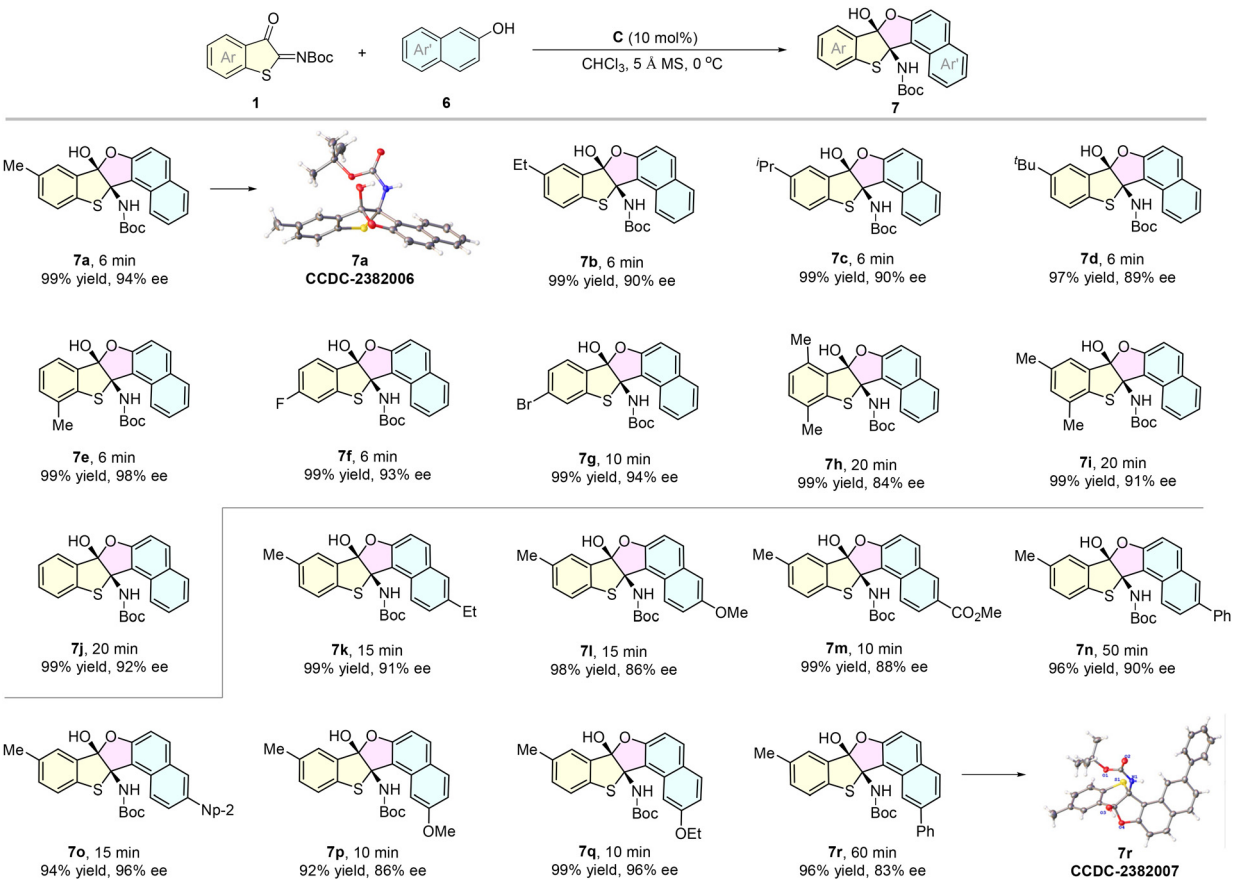


Scheme 2 Substrate scope of cyclic α-carbonyl thioimidates and 1-naphthols. Reaction conditions: **1** (0.15 mmol), **2** (0.1 mmol), 5 Å MS (50 mg) and 10 mol% **C** in 1.0 mL of $CHCl_3$ at °C for the specified reaction time.



Scheme 3 Substrate scope of cyclic α-carbonyl thioimidates with electron-rich phenols. Reaction conditions: **1** (0.15 mmol), **4** (0.1 mmol), 5 Å MS (50 mg) and 10 mol% **C** in 1.0 mL of $CHCl_3$ at °C for 20 min.

practicability. It was remarkable to observe that 2-naphthols **6** reacted smoothly with cyclic α-carbonyl thioimidates **1**, undergoing an elegant aza-Friedel–Crafts/*O*-hemiacetalization to give the furanonaphthobenzo[*b*]thiophene derivatives **7** in excellent yields and enantioselectivities under the same catalyst system. With these promising results, we explored the substrate scope of this transformation (Scheme 4). The reaction proved to be unbiased towards various substituted cyclic α-carbonyl thioimidates with either electron-donating, electron-withdrawing or neutral groups, regardless of the positions of the aryl ring,



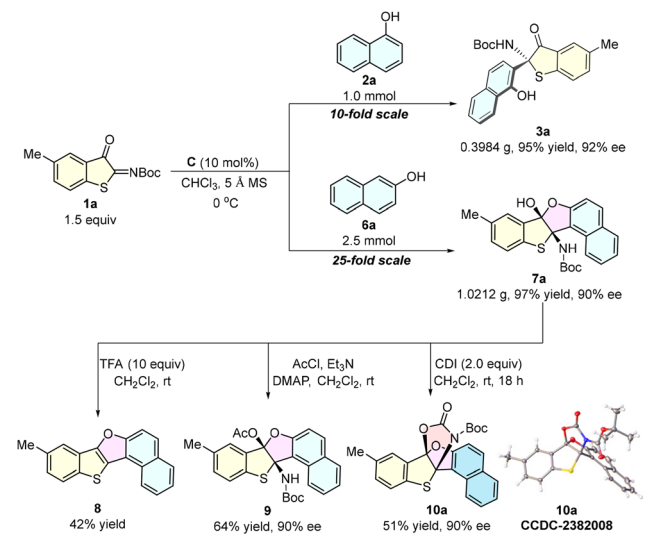
Scheme 4 Substrate scope of cyclic α-carbonyl thioimidates and 2-naphthols. Reaction conditions: **1** (0.15 mmol), **6** (0.1 mmol), 5 Å MS (50 mg) and 10 mol% **C** in 1.0 mL of $CHCl_3$ at °C for the specified reaction time.

enabling the formation of desired products **7a–j** in up to quantitative yield and 98% ee. Next, the influence of substituents in 2-naphthols was studied. Assorted 2-naphthols substituted with an electron-donating or electron-withdrawing group at the C6-position yielded the respective products **7k–m** in satisfactory outcomes. When 6-phenyl and 6-naphthyl substituted 2-naphthols were employed as nucleophiles, products **7n** and **7o** were obtained in high yields with 90% and 96% ee, respectively. Moreover, 2-naphthols bearing different groups at the C7-position also afforded the expected products **7p–r** in high yields and stereoselectivities (up to 99% yield and 96% ee). The structure and relative configuration of products **7a** and **7r** were unambiguously determined by X-ray crystallographic study of single crystal,[15] and the absolute configuration of **3a** and **7a** was assigned by comparison of the electronic chiral circular dichroism (ECD) spectrum with the theoretically calculated results.[16]

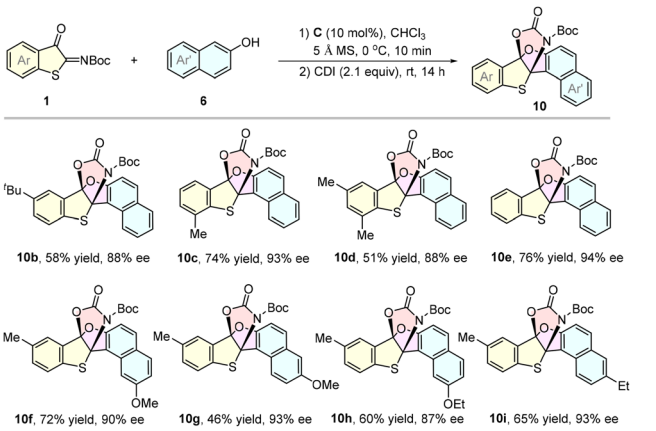
To demonstrate the synthetic efficiency and utility of this enantioselective divergent reaction of cyclic α-carbonyl thioimidates with naphthols, the preparative scale reaction was carried out. As shown in Scheme 5, the 10-fold scale reaction of cyclic thioimidate **1a** and 1-naphthol **2a** proceeded effectively to provide product **3a** in 95% yield with almost constant enantioselectivity. When the reaction of **1a** and 2-naphthol **6a** was carried out on a gram scale, the product **7a** was obtained in excellent yield and 90% ee within 15 min. Next, we conducted downstream transformations to showcase the synthetic value (Scheme 5). The treatment of **7a** with trifluoroacetic acid in CH_2Cl_2 resulted in the rearomatization product **8** in 42% yield *via* elimination process. The esterification product **9** was obtained by reacting **7a** with acetylchloride, resulting in 64% yield without any loss of the enantioselectivity. Ultimately, the reaction of **7a** with CDI gave the bridged-naphtho[2,1-*b*]furan **10a** in moderate yield with 90% ee. The structure and configuration of product **10a** was unambiguously determined to be (7a*R*,12a*S*) by single crystal X-ray crystallography.[15]

Encouraged by the successful formation of compound **10a** with novel bridged structure, we aimed to prepare bridged-naphtho[2,1-*b*]furan derivatives from cyclic α-carbonyl thioimidates and 2-naphthols as starting materials, with CDI as the cyclization reagent in a one-pot two-step process. As shown in Scheme 6, various cyclic α-carbonyl thioimidates bearing either an electron-donating or electron-neutral substituent on the aromatic ring could react smoothly with 2-naphthol **6a**, yielding the corresponding bridged-naphtho[2,1-*b*]furan derivatives **10b–e** in good outcomes (up to 76% yield and 94% ee). Moreover, 2-nathphols with a substituent at the C6- or C7-position of the naphthyl ring were successfully employed, delivering the desired products **10f–i** in moderate yields and high enantioselectivities.

To gain further insight into the reaction mechanism and the origin of enantioselectivity, density functional theory (DFT) calculations were performed. Based on the two distinct activation mechanisms proposed by Takemoto and Pápai *et al.*,[17] we explored four possible activation pathways between the catalyst **C** and the substrate 1-naphthol (**2a**). As shown in Fig. 1, the direct addition of 1-naphthol **2a** to catalyst **C** initially forms a stable binary complex (**IM1a**), which is 3.2 kcal mol^{-1} more stable than the initial reactants. The subsequent addition of **1j** to **IM1a** leads to four different pathways (denoted as path a, path b, path c, and path d) based on the direction of the attack. Among these pathways, path a (black line) and path b (blue line) result in the *S*-configuration intermediates **IM3a** and **IM3b**, respectively, while path c (red line) and path d (purple line) yield the *R*-configuration complexes **IM3c** and **IM3d**, respectively. It should be noted that the formation of the complexes **IM2a–2d** is slightly thermodynamically unstable in terms of Gibbs free energy due to the



Scheme 5 Scale-up synthesis and downstream transformations.



Scheme 6 The reaction of cyclic α-carbonyl thioimidates and 2-naphthols for the synthesis of bridged-naphtho[2,1-*b*]furans with one-pot two-step operation. Reaction conditions: **1** (0.15 mmol), **6** (0.1 mmol), 5 Å MS (50 mg) and 10 mol% **C** in 1.0 mL of $CHCl_3$ at °C for 10 min, then CDI (2.1 equiv.) was added for additional 14 h at room temperature.

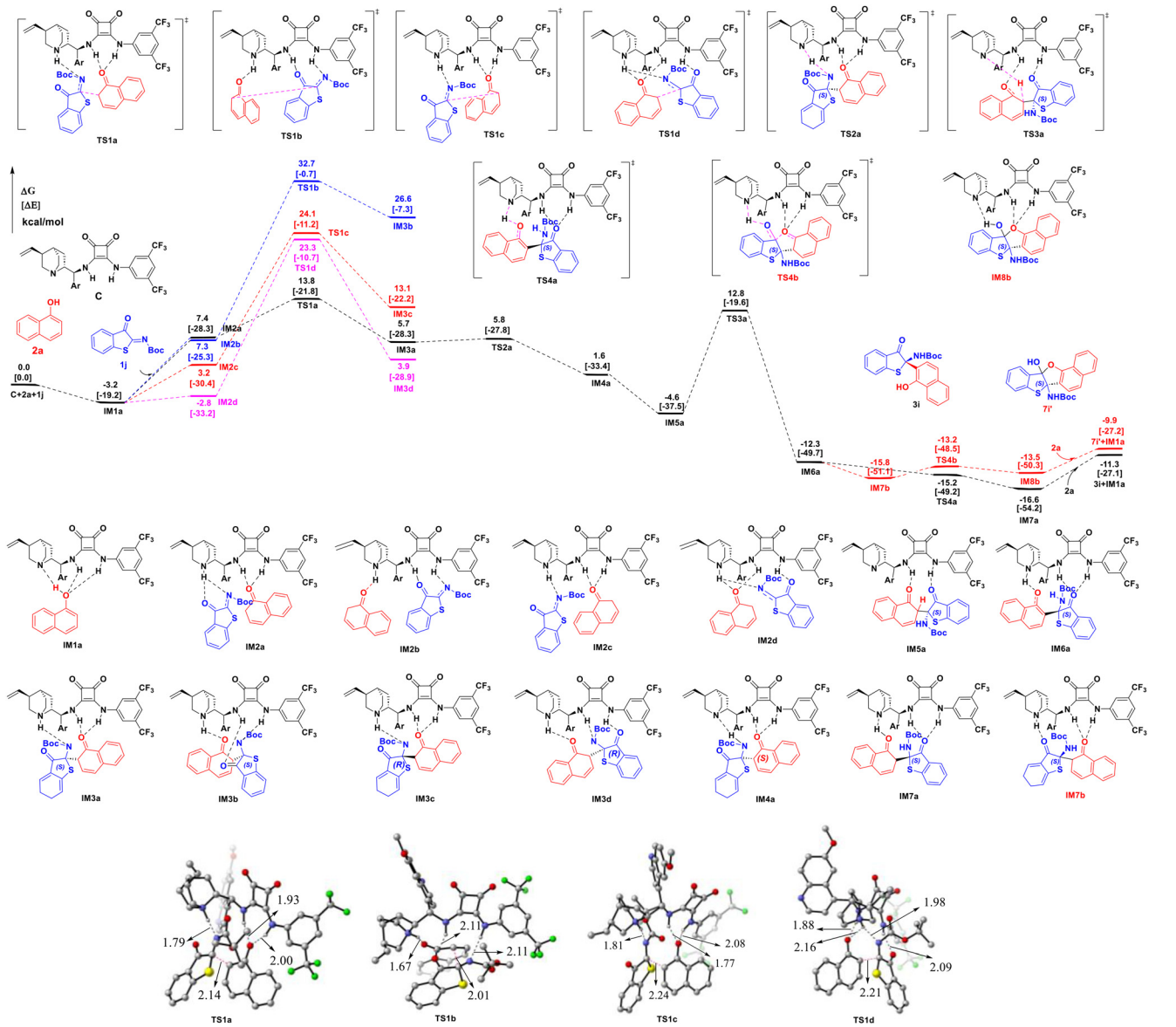


Fig. 1 Calculated energy profiles with four activation pathways for **2a** and **1j** mediated by catalyst **C** at the M06-2X/6-311++G(2d,p)/SMD(chloroform)//M06-2X/6-31G(d,p)/SMD(chloroform) level of theory. Key interatomic distances were given in Å. Non-interacting hydrogen atoms had been omitted for clarity (color code, C: grey, O: red, H: white, N: blue, F: green, S: yellow).

inevitable overestimation of entropic contributions. However, they become thermodynamically more stable in terms of electronic energies, implying that the formation of these complexes is feasible. In the located intermediate **IM2a** of path a, the two NH groups of the squaramide activated the O of **2a**, as indicated by the NH···O distances of 1.76 and 1.74 Å (Fig. S3†), respectively. Meanwhile, the O and N of **1j** coordinated to the protonated tertiary amine group of the quinuclidine, with the key distances of N–H···O at 2.06 Å and N–H···N at 2.24 Å, respectively, also playing an important role in stabilizing the **IM2a** complex. After overcoming a small barrier of 6.4 kcal mol^{-1} *via* the transition state **TS1a** (*i.e.*, **IM1a** → **TS1a**), the new C–C bond formation between **1j** and **2a** occurs, generating the thermodynamically more stable *S*-configuration intermediate **IM3a**. The key bond distance for the C–C bond formation (*i.e.*, 2.14 Å, Fig. 1) in the optimized **TS1a**, along with the correct vibration mode of the only imaginary frequency, confirm the correct transition state. Note that the favourable N–H···N (*i.e.*, 1.79 Å) and N–H···O (*i.e.*, 1.93 and 2.00 Å) interactions, also play significant roles in stabilizing the transition state **TS1a**. The C–C bond formation barrier, measured from the lower intermediate **IM1a**, is predicted to be 17.0 kcal mol^{-1}, which is still experimentally feasible under mild conditions. In path b, **IM2b** is initially generated as the NH groups of squaramide simultaneously activate **1j** (*i.e.*, N–H···O: 2.30 Å, N–H···N: 2.30 Å, see Fig. S3†), while the ammonium of NH function of the quinuclidine activates **2a** (1.88 Å, see Fig. S3†). Although **IM2b** is comparable to **IM2a** in terms of energetics, the

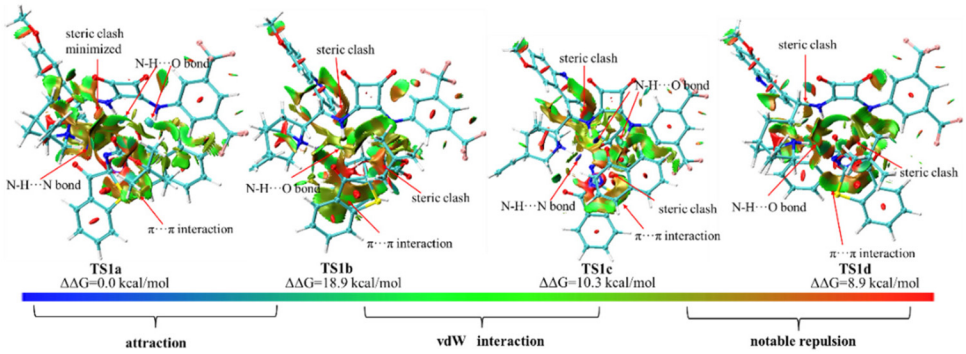


Fig. 2 Noncovalent interaction analysis of the transition state **TS1a**–**TS1d**.

subsequent C–C bond formation step becomes kinetically unfavourable due to the higher barrier *via* transition state **TS1b**, which is 18.9 kcal mol^{-1} higher in free energy than **TS-1a**. In path c and path d, although the intermediates **IM2c** and **IM2d** are more stable than **IM2a**, the higher free energy barriers for the subsequent C–C bond formation step (27.3 and 26.5 kcal mol^{-1}, respectively), measured from the more stable **IM1a**. As comparisons in Fig. 1, the barriers for the key C–C bond formation step follow the sequence: **TS1a** (17.0 kcal mol^{-1}, path a) < **TS1d** (26.5 kcal mol^{-1}, path d) < **TS1c** (27.3 kcal mol^{-1}, path c) < **TS1b** (35.9 kcal mol^{-1}, path b). Therefore, path a is the kinetically most favourable reaction pathway. Subsequent to the formation of **IM3a**, the thermodynamically more stable intermediate **IM4a** can be easily generated by crossing a very low barrier of 0.1 kcal mol^{-1} (*i.e.*, **IM3a** → **TS2a**), implying that the proton transfer step can occur facilely.

Next, intermediate **IM4a** undergoes an easy isomerization process, leading to the more stable **IM5a**. After crossing a

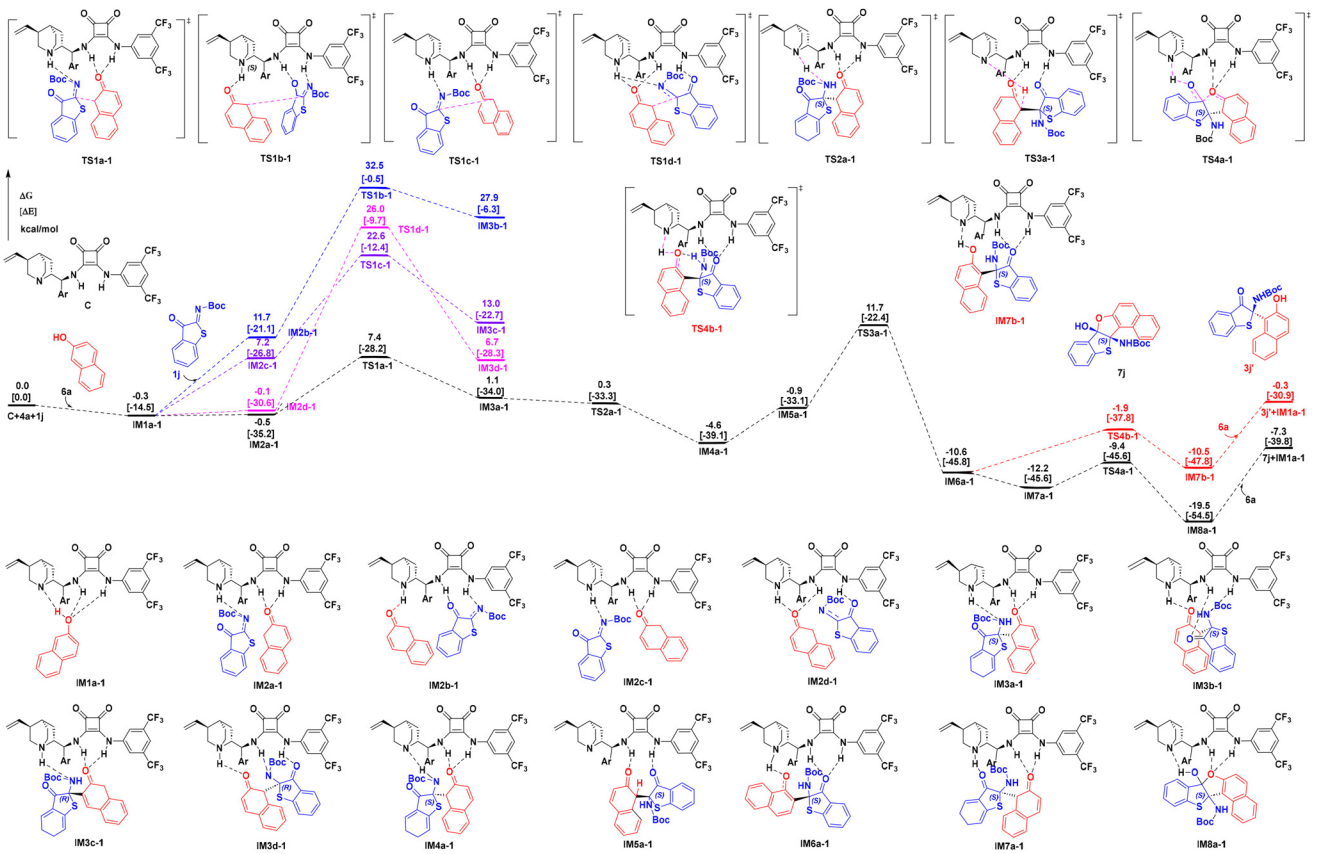


Fig. 3 Calculated energy profiles with four activation pathways for **6a** and **1j** mediated by catalyst **C** at the M06-2X/6-311++G(2d,p)/SMD(chloroform)//M06-2X/6-31G(d,p)/SMD(chloroform) level of theory. Key interatomic distances were given in Å. Non-interacting hydrogen atoms had been omitted for clarity.

barrier of 17.4 kcal mol^{-1} (*i.e.*, **IM5a** → **TS3a**), the H atom migrates from the **2a** to the N atom in the quinuclidine, generating the thermodynamically more stable intermediate **IM6a**. Subsequently, **IM6a** goes through a barrierless hydrogen transfer (from N of the quinuclidine to O of **2a**) *via* the transition state **TS4a**, yielding the thermodynamically more stable intermediate **IM7a**. With another equivalent of reactant **2a**, the final *S*-configuration product **3i** will be released, regenerating the active species **IM1a** for the next catalytic cycle.

We also explored the reaction course for the formation of cyclization product **7i′**. However, it is both kinetically and thermodynamically (*i.e.*, **IM7b** → **TS4b** → **7i′**) less favourable than that of product **3i** (*i.e.*, **IM6a** → **TS4a** → **3i**), which is good agreement with the experimental observations. Based on the discussions above, the C–C bond formation (17.0 kcal mol^{-1}, **IM1a** → **TS1a**) is the enantioselectivity-determining step (EDS), while the C–H bond cleavage (17.4 kcal mol^{-1}, **IM5a** → **TS3a**) should be the rate-determining step (RDS) in the entire catalytic cycle. The overall reaction is exergonic by 11.3 kcal mol^{-1}, providing the thermodynamic driving force for the reaction to proceed.

To gain insight into the large free energy barrier differences for **TS1a**, **TS1b**, **TS1c** and **TS1d**, we conducted a noncovalent interaction (NCI) analysis. As depicted in Fig. 2, the dark blue surfaces between the squaramide and the substrates in **TS1a** indicate strong attractive interactions, characterized by the stronger N–H···O and N–H···N interactions. Moreover, in **TS1a**, the larger green areas between **1j** and **2a** contribute to stronger π···π interactions. The favourable noncovalent interactions were similar in **TS1b**, **TS1c** and **TS1d**, but significant steric hindrance effects between the quinoline and the squaramide groups of the catalyst were observed, which should be the origin of the higher barriers for the transition states of **TS1b–TS1d**.

The detailed geometric and energetic results for 2-naphthol **6a** and cyclic α-carbonyl thioimidates **1j** are also recovered (Fig. 3). Similar to 1-naphthol **2a**, the formation of the *S*-configuration intermediate was kinetically and thermodynamically favourable, and the enantioselectivity- and rate-determining step for the 2-naphthol was predicted to be the C–C bond formation (7.7 kcal mol^{-1}, **IM1a-1** → **TS1a-1**) and C–H bond cleavage (16.3 kcal mol^{-1}, **IM4a-1** → **TS3a-1**) step, respectively. Nonetheless, the formation of the final product **7j** (*i.e.*, **IM7a-1** → **TS4a-1** → **7j**) is both kinetically and thermodynamically favourable than that of product **3j′** (*i.e.*, **IM6a-1** → **TS4b-1** → **3j′**), which agrees very well with the experimental observations. Additionally, noncovalent interaction (NCI) analysis for **TS1a-1–TS1d-1** was also conducted, indicating the higher barriers for the transition states of **TS1b-1–TS1d-1** are due to the significant steric hindrance effects (see Fig. S4†).

Conclusions

In summary, we have successfully opened a new avenue for the preparation of *N*,*S*-acetal-containing tetrasubstituted carbon stereogenic centers through an enantioselective divergent reaction between cyclic α-carbonyl thioimidates and naphthols. When 2-naphthols were used as nucleophilic partners, the reaction enabled the formation of structurally diverse furano-naphthobenzo[*b*]thiophene derivatives bearing two vicinal diheteroatom-containing tetrasubstituted carbon centers, achieving high optical purities (up to 98% ee) through a domino aza-Friedel–Crafts/*O*-hemiacetalization of the exocyclic C═O bond. Moreover, enantioenriched bridged-naphtho[2,1-*b*]furan derivatives could be efficiently prepared from cyclic α-carbonyl thioimidates and 2-naphthols as starting materials, with CDI as the cyclization reagent in a one-pot two-step operation. In contrast, the use of 1-naphthols or electron-rich phenols as nucleophiles led to the formation of enantioenriched *N*,*S*-acetal-containing tetrasubstituted carbon stereogenic centers with excellent yields and enantioselectivities (up to 99% yield and 94% ee). The synthetic utility of the methodology was showcased by scale-up experiments and versatile transformations of the product. DFT calculations provide valuable insights into the reaction mechanism and the origin of enantioselectivity, as well as the reaction divergence observed with 2-naphthols and 1-naphthols, respectively. The findings indicate that the C–C bond formation during the addition of naphthols to cyclic thioimidates is the enantioselectivity-determining step, while the rate-determining step is the C–H bond cleavage. Additionally, both kinetically and thermodynamically, the reaction with 2-naphthols favors the subsequent *O*-hemiacetalization to form the corresponding cyclization products, whereas the addition of 1-naphthols to thioimidates is thermodynamically driven for the synthesis of *N*,*S*-acetals through the subsequent protonation process.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

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