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Axially chiral styrene-based organocatalysts and their application in asymmetric cascade Michael/cyclization reaction†

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An axially chiral styrene-based organocatalyst, featuring a combination of axially chiral styrene-based structure and a pyrrole ring, has been designed and synthesized. This catalyst demonstrates remarkable capabilities in producing a wide range of densely substituted spirooxindoles that feature an alkyne-substituted quaternary stereogenic center. These spirooxindoles are generated through mild cascade Michael/cyclization reactions, resulting in high conversion rates and exceptional enantioselectivity. Our catalytic model, based on experiments, X-ray structure analysis and DFT calculations suggests that chiral matched π - π interactions and multiple H-bonds between the organocatalyst and substrates play significant roles in controlling the stereoselectivity of the reaction.

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Introduction

Catalytic asymmetric synthesis has emerged as a crucial strategy for obtaining enantiomerically pure compounds, and the key to achieving efficient asymmetric catalysis is the development of efficient chiral catalysts and ligands.¹ Axially chiral compounds, known for their intriguing atropisomerism, have played an important role in asymmetric synthesis. Binaphthyl and biphenyl axisymmetric skeletons have been extensively employed as catalysts and ligands in recent years, demonstrating decisive impact on asymmetric catalytic reactions.² Additionally, various axially chiral catalysts with distinct structures³ have also been reported successively with the development of more methodological studies.⁴ In contrast, the development of asymmetric axially chiral styrene-based catalysts has been delayed due to synthetic challenges. Meanwhile, significant progress has been made in catalytic asymmetric synthesis of axially chiral styrene-based structures,⁵ making it possible to apply this structure to catalysts and ligands.⁶ Promising results have been achieved using axially chiral styrene-based catalysts/ligands in asymmetric synthesis, as exemplified by the work of Bin Tan^{6a} and Bing-Feng Shi^{6b,d} in the synthesis of chiral phosphoric, phosphoramidite, and carboxylic acid derivatives and their application in several asymmetric transformations. Recently, Feng Shi group designed and synthesized a novel thiourea catalyst containing axially chiral

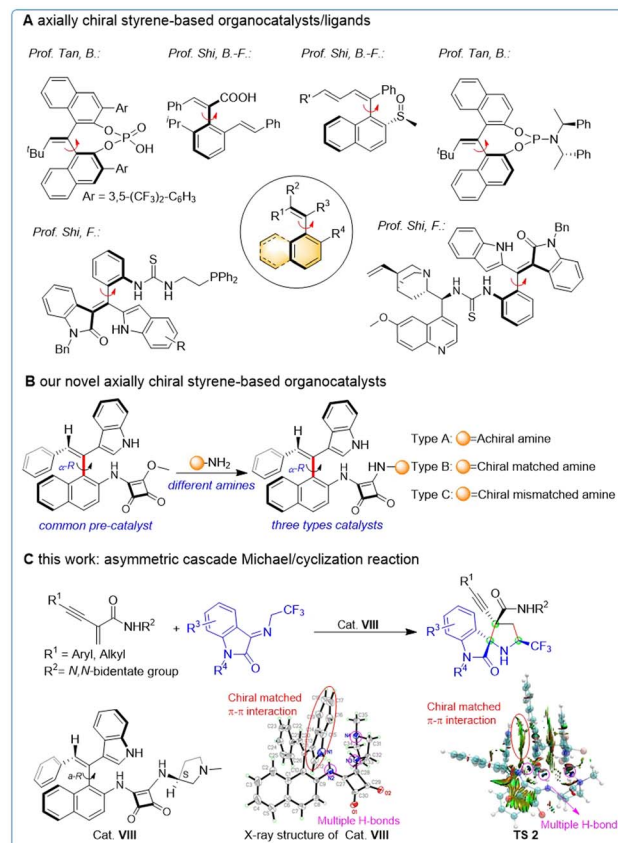
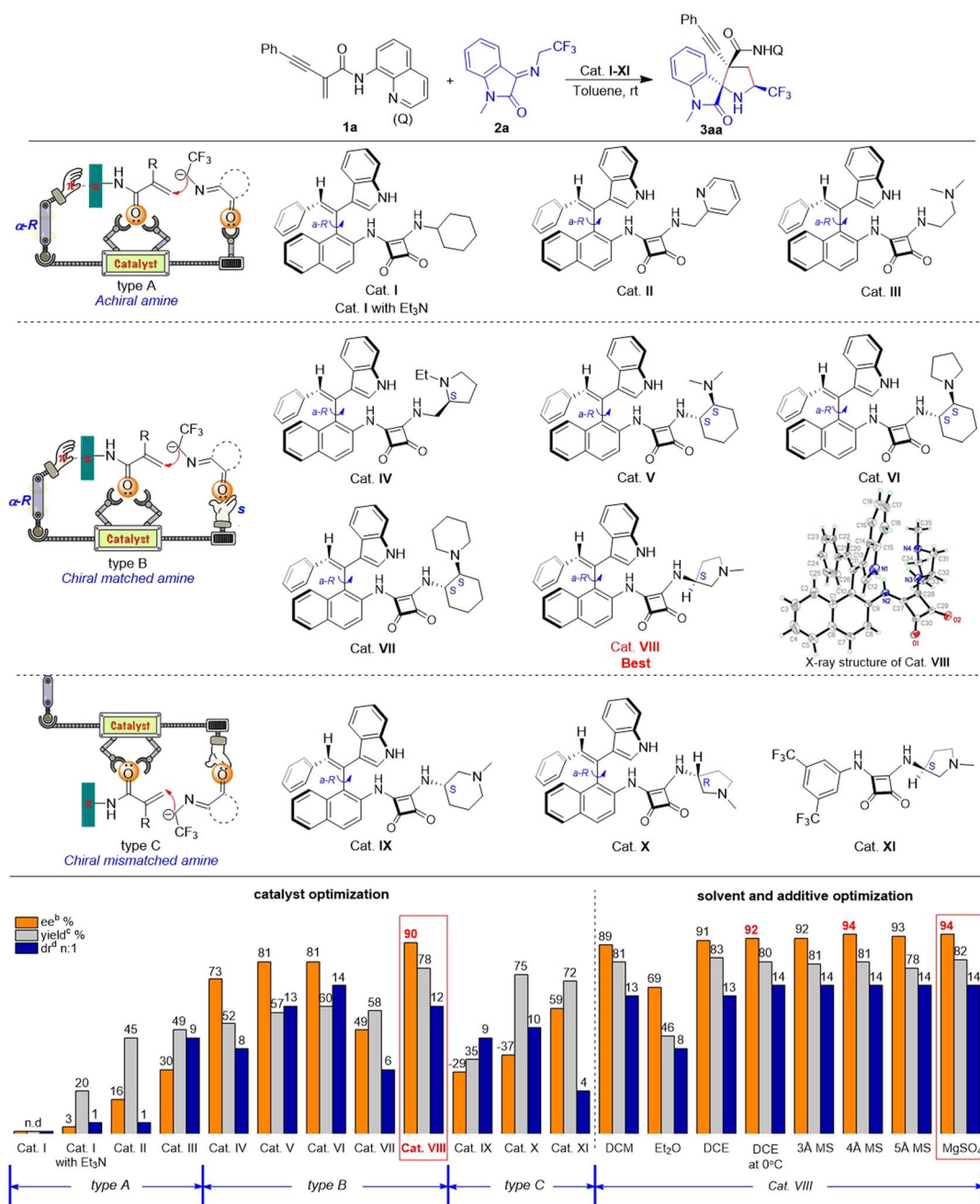


Fig. 1 The developed axially chiral styrene-based organocatalysts/ligands and our work.

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Table 1 Optimization of organocatalyst^a

^a Reaction conditions: 1a (0.1 mmol), 2a (0.15 mmol) and organocatalyst (10 mol%) in Toluene (1.0 mL) stirred at the indicated temperature for 24 h. ^b The ee value was determined by HPLC analysis. ^c Isolated yield. ^d The dr value was determined by ¹H NMR analysis.

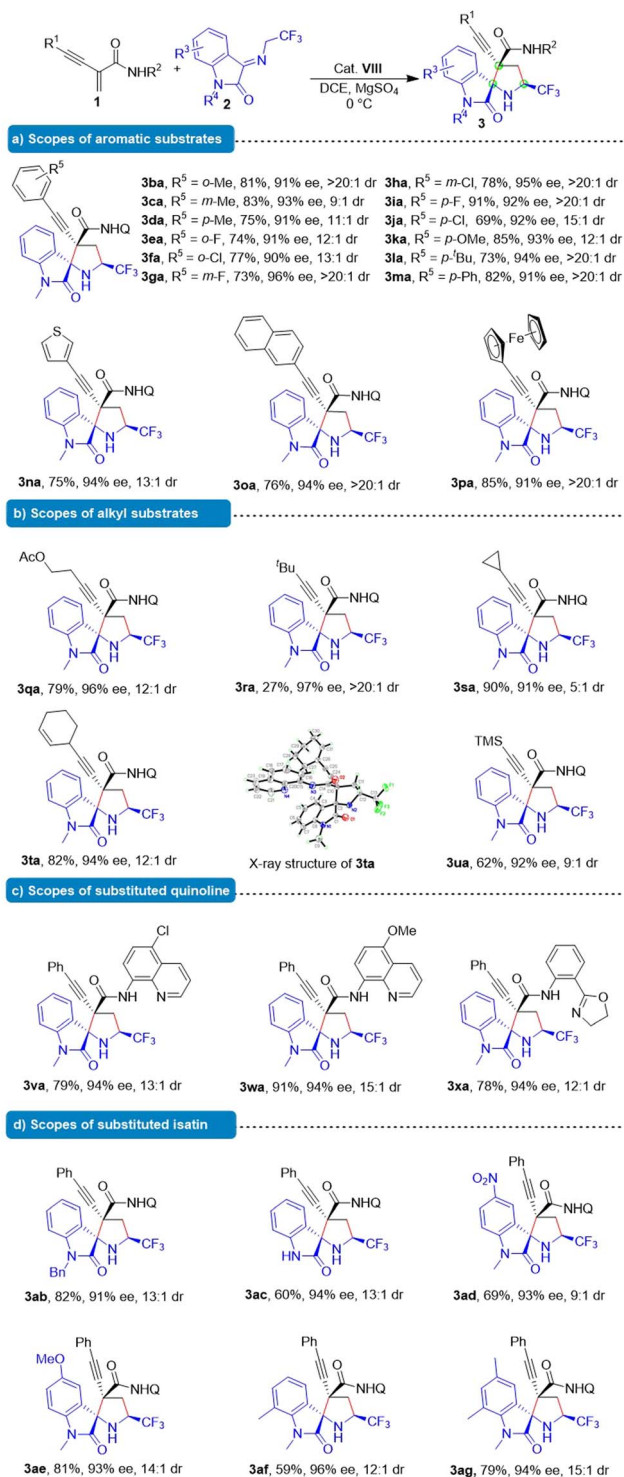
styrene, which was validated by calculation^{6c,e} (Fig. 1A). These highly innovative studies have significantly broadened the scope of applications for axially chiral styrene and have inspired the development of novel axially chiral catalysts and ligands (Table 1).

Based on our interest in synthesizing axially chirality,^{5b,7} as well as our experiences in constructing nitrogen-containing compounds,⁸ we designed and synthesized a series of axially chiral styrene-based organocatalysts with exocyclic double

bonds. These catalysts were categorized into racemic amines, chiral matched amines, and chiral mismatched amines based on their different active groups (Fig. 1B).

Furthermore, spiro[pyrrolidin-3,2-oxindoles] have been recognized as a crucial moiety in numerous natural products and clinical candidates.⁹ Here, we report the synthesis of a variety of spirooxindoles through asymmetric cascade Michael/cyclization reactions¹⁰ of enynamides^{8b} and ketimines



Table 2 Substrate scopes^a

^a Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), MgSO₄ (60 mg) and cat. **VIII** (10 mol%) in DCE (2.0 mL) stirred at 0 °C for 24 h.

utilizing our axially chiral styrene-based organocatalysts. The X-ray structure analysis and DFT calculation of cat. **VIII** demonstrated its ability to promote stereoselective control of the

reaction through π - π interactions and multiple H-bonds (Fig. 1C).

Results and discussion

Screening of the reaction conditions

We initiated our investigation by employing enynamide **1a** and ketimine **2a** as substrates, using squaramide catalyst **I** in toluene. Cat. **I** lacking an active group was found to be ineffective in catalyzing the reaction, hence we attempted to introduce triethylamine for catalysis. The intermolecular synergistic catalysis of cat. **I** and triethylamine exhibited superior results as compared to pure triethylamine catalysis, and the target product was obtained with a yield of 20%. The introduction of intramolecular basic groups such as pyridine (cat. **II**) and alkylamine (cat. **III**) in the catalyst promoted the reaction yield (45–49% yield). However, enantioselectivity control of these catalysts was inadequate (16–30% ee), and achieving chiral control of the reaction *via* a single axial chirality proved to be challenging. On the basis of these phenomena, we considered replacing the reactive site with an *S*-configuration chiral amine to create an enantiomeric match with the αR -configuration axially chiral styrene, thereby synergistically catalyzing the reaction. To our delight, catalysts **IV–VIII**, designed based on this approach, exhibited moderate to good capacity in controlling reactivity (52–78% yield) and stereoselectivity (>6 : 1 dr, 49–90% ee). The spatial structure of the optimal catalyst **VIII** was confirmed by X-ray crystallography. We speculate that the near-planar conformation of the enynamides may interact with the axially chiral portion of the catalyst structure, potentially enhancing the enantioselectivity of the reaction. The axially chirality of the styrene formed a suitable catalyst pocket with squaramide and pyrrole rings, and we hypothesized that the catalyst could promote chiral control of the reaction *via* chiral matched π - π interaction and multiple H-bonds. To validate our conjecture, we synthesized enantiomerically mismatched catalysts **IX–XI**. Cat. **IX–X** with mismatched chiral amines were unable to control the enantioselectivity (–29% to –37% ee) of the reaction, while cat. **XI** with mismatched π - π interaction exhibited poor stereoselectivity in terms of enantio- and diastereoselectivities (59% ee, 4 : 1 dr). Moreover, in this reaction, the catalytic performance of our novel organocatalyst was significantly superior to that of conventional commercially available catalysts (see ESI, Table S1[†]). Then, in the presence of the optimal catalyst **VIII**, the reaction conditions were further evaluated for solvents, temperature, and additives, revealing that the optimal reaction conditions were as follows: **1a** (0.2 mmol), **2a** (0.3 mmol), MgSO₄ (60 mg), and 10 mol% cat. **VIII** in DCE (2.0 mL) at 0 °C for 24 h (see ESI, Table S2[†]).

Substrate scopes

After determining the optimal reaction conditions, we investigated the scope of application of the Michael/cyclization reaction. First, we expanded the scope of functionalized benzene rings in order to examine the generality of this asymmetric formal cascade Michael/cyclization reaction. As shown in



Table 2, a wide range of enynamide **1** were utilized as competent substrates in the reaction with ketimine **2a**. Methyl substitution at various positions on the benzene ring led to high yields (75–83%), ees (91–93%) and >9 : 1 dr (**3ba–3da**). Different substituents on the aromatic ring such as halogen (**3ea–3ja**), methoxy (**3ka**), *tert*-butyl (**3la**) and phenyl (**3ma**) were tolerated and no obvious electronic effect of the substituent was observed. Additionally, the reaction could be successfully extended to 3-thiophen-3-yl, naphthyl, and ferrocene delivering the desired products in 75–85% yield, 91–94% ees and >11 : 1 dr (**3na–3pa**).

Encouraged by these results, this methodology was applied to alkyl-substituted starting materials. Fortunately, these substrates (**3qa–3ta**) afforded the desired products with excellent stereoselectivity (91–97% ee, >5 : 1 dr), except for the *tert*-butyl substrate which displayed lower reactivity (27% yield). Notably, the silyl substituent in the chiral **3ua** product allowed for a wide range of further transformations, leading to the construction of a synthetically useful skeleton in 62% yield, 92% ee and 9 : 1 dr, which could be readily converted into a terminal alkyne. In addition, other enynamides containing intramolecular hydrogen bonds could also efficiently participated in the reaction (**3va–3xa**). We also examined the influence of substituents on ketimine **2** on the reaction. Methyl-(**3aa**) and benzyl-protected (**3ab**) ketimines as well as unprotected ketimine (**3ac**) at the 1-position were also good 1,3-dipoles, resulting in good to high yields and excellent enantioselectivities and diastereoselectivities. Substituents with either electron-withdrawing or electron-donating groups residing at varying positions on the isatin ring were well tolerated (**3ad–3ag**), affording the desired products with high enantioselectivities (93–96% ee).

Synthetic application

To showcase the synthetic utility of this protocol, gram-scale reaction and derivatization reactions were briefly implemented (Fig. 2A). Substrate **1a** (2 mmol) underwent the formal cascade Michael/cyclization reaction with **2a** (3 mmol) at standard conditions, affording **3aa** (886 mg) in 82% yield without erosion of optical purity. The estradiol derivative **1y** was well tolerated and gave 3,2'-pyrrolidinyl spirooxindole **3ya** in 76% yield with excellent stereochemical integrity and high diastereoselectivity (19 : 1 dr). These results indicated the utility of the reaction for late-stage modification of macromolecules. For spiro[pyrrolidin-3,2-oxindoles] **3aa**, the quinoline moiety could be removed by treatment with 2-iodoxybenzoic acid (IBX), affording primary amide **4aa**.¹¹ Moreover, further treatment of **4aa** with LiAlH₄ at 0 °C in THF provided lactam **5aa** containing a polyheterocyclic scaffold in 41% yield without compromising ee (Fig. 2C). The present protocol enables convenient access to various synthetically challenging stereochemically defined nitrogenous heterocycles bearing an alkyne-substituted quaternary carbon centre as important chiral building blocks in organic synthesis.

Proposed mechanistic DFT calculations

In order to reveal the key role of the catalyst in the enantioselectivity control of the cascade Michael/cyclization reaction, we

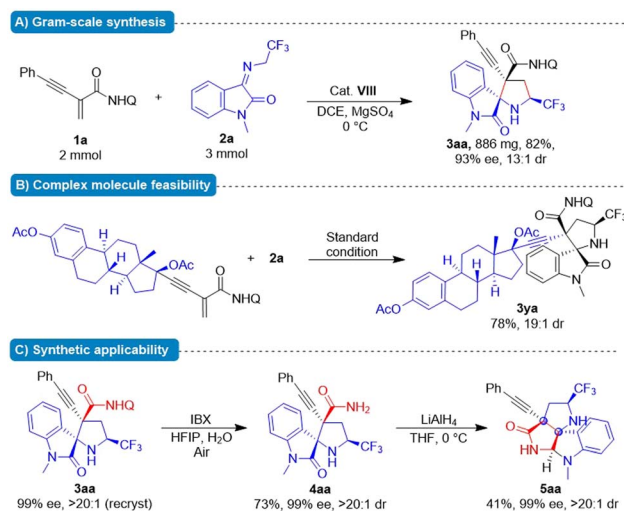


Fig. 2 Studies on gram-scale reaction, applicability of complex molecules and further synthesis application.

performed density functional theory (DFT) calculations at the M06-2X/6-311++G(d,p) (solvent = DCE, SMD)//M06-2X/6-31G(d,p) (vacuum) level to investigate the reaction pathway¹² (see ESI, Fig. S4†). The computational analysis demonstrated that catalyst **VIII** efficiently activated both enynamide **1a** and ketimine **2a** by means of chiral matched π - π interactions and multiple H-bonds, leading to the formation of **Int D**. Subsequently, carbon nucleophile attacks the double bond, initiating asymmetric Michael addition and generating **Int E**, which possesses a newly formed chiral center. This is followed by intramolecular asymmetric Mannich reaction, resulting in the formation of **Int F**. Finally, the desired chiral spiro product **3aa** is produced as it dissociates, effectively regenerating the catalyst (Fig. 3).

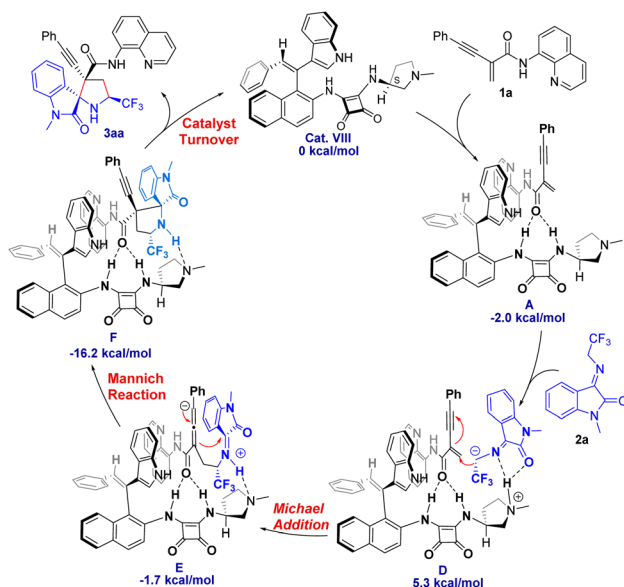


Fig. 3 Proposed catalytic cycle.



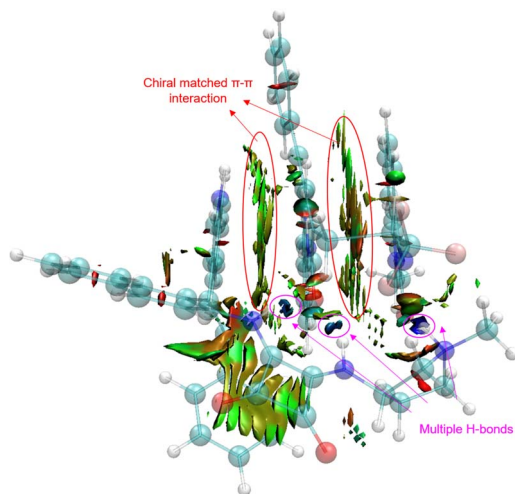


Fig. 4 Visualization of noncovalent interactions in TS2.

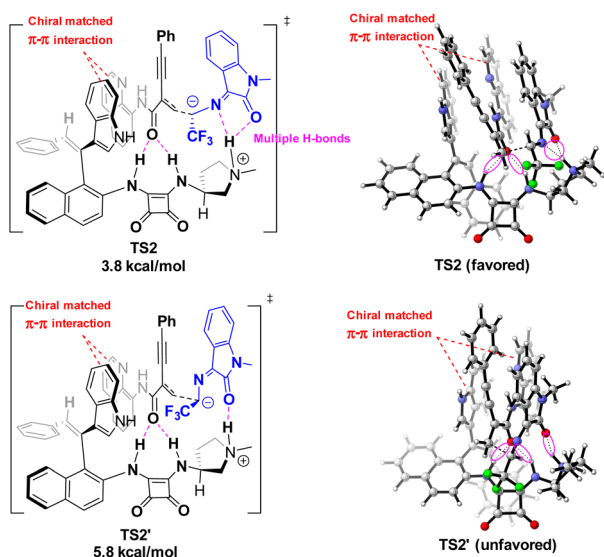


Fig. 5 The structures of key nucleophilic attack transition states TS-2 at M06-2X/6-311++G(d,p) (solvent = DCE, SMD)//M06-2X/6-31G(d,p) (vacuum) level.

To visualize the interaction between catalyst and substrates, we performed NCI analysis on noncovalent key interactions in TS2. As shown in Fig. 4, the substrate **1a**, which is nearly planar,^{8b} formed a more apparent chiral matched π - π interaction by being parallel and in close proximity to the axially chiral indole (Fig. 4). On the other hand, multiple N-H bonds in pyrrole and squaramide form multiple hydrogen bonds with the intermediate. These weak interactions fix the intermediate in the catalyst pocket and synergistically control the stereoselectivity of the reaction. Interestingly, similar catalytic phenomena had also occurred in the synthesis of nonbiaryl naphthalene-1,2-diamine reported previously by our group.^{7a}

The asymmetric addition of carbon anion to double bonds was a key step to control the enantioselectivity of the reaction. The conformations of the key transition states TS2 optimized by

DFT along different attack directions were shown in Fig. 5. Compared to TS2', TS2 has a lower relative Gibbs free energy barrier ($\Delta\Delta G = 2.0 \text{ kcal mol}^{-1}$) due to the dual H-bond interaction between isatin and pyrrole.

Conclusions

In summary, we have successfully developed a novel axially chiral styrene-based squaramide organocatalyst that combines axial chirality and a pyrrole structure to effectively control the stereoselectivity of the reaction. More importantly, based on experimental results and X-ray structural analysis, we established a catalytic model through DFT calculations, revealing that the catalytic pocket effectively regulates stereoselectivity *via* chiral matched π - π interactions and multiple H-bonds. In addition, we have achieved the synthesis of a diverse range of densely substituted spirooxindole compounds featuring alkynyl substituent quaternary stereogenic centers, with impressive outcomes such as high yields (up to 85%), excellent enantioselectivity (up to 96% ee), and high diastereomeric ratios (>20 : 1 dr). These findings contribute to a more comprehensive understanding of the catalyst and facilitate the design and development of axially styrene-based chiral catalysts and ligands in the future.

Data availability

All detailed procedures, characterization data, and spectra are available in the ESI.†

Author contributions

Y. Hao performed the experiments and analyzed the data. Z.-H. Li perform the theoretical calculations. Y. Hao, Z.-G. Ma, R.-X. Liu, R.-T. Ge, Q.-Z. Li, T.-M. Ding and Shu-Yu Zhang supervised the research and co-wrote the manuscript. S.-Y. Zhang conceived the project.

Conflicts of interest

The authors declare no competing financial interests.

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