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Organocatalytic Enantioselective Construction of Chiral Azepine Skeleton Bearing Multiple-Stereogenic Elements

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Abstract: Enantioselective construction of molecules bearing multiple stereogenic elements is increasingly related to the synthesis of enantiopure natural products, pharmaceuticals, and functional materials. However, atom-economical and enantioselective approaches to install multiple stereogenic elements in a small molecular template by limited chemical transformation remain challenging. We describe an organocatalytic enantioselective method for the preparation of polychiral molecules bearing four types of stereogenic elements in fused azepines via vinylidene *ortho*-quinone methide (**VQM**)-mediated intramolecular electrophilic aromatic substitution. This method was proved robust with a wide range of substrate scope (46-92% yield), with excellent diastereoselectivity (>20:1 dr) and enantioselectivity achieved (up to 97% ee). Optical properties and Ru^{3+}-induced fluorescence responses of these compounds suggest their potential applications in optoelectronic materials and heavy metal ion detection.

Introduction

The defined structure of chiral molecules bearing multiple stereogenic elements holds a special place in the development of bioactive compounds, advanced materials and asymmetric catalytic systems, whose absolute and relative configurations are both critically important for their inherent properties[1]. To date, a number of asymmetric catalytic strategies have been developed for the construction of multi-stereogenic chiral centers[2], and a few atroposelective protocols of multiaxis[3,4], multihelical[5] and multiplanar[6] systems have been recently explored (Figure 1a). However, to the best of our knowledge, catalytic enantioselective approaches installing more than three types of stereochemical elements into different sites of a substrate within a single step are intrinsically challenging and have not been reported[7]. Although such frameworks can be theoretically constructed through multiple synthetic steps, the construction process is time-consuming and normally involves the extensive assessment of reaction conditions. The direct, atom-economic and highly enantioselective transformations toward the construction of multiple stereogenic elements is arguably one of the least employed fields in asymmetric synthesis, probably due to the match/mismatch effects in formed additional stereogenic elements and the influences of the intrinsic selectivity of a chiral substrate on the facile formation of all possible stereoisomers (Figure 1b)[8].

Given the fact that current synthetic methods to afford chirality-enriched entities largely remain unfulfilling, we set out to explore this area by designing novel synthetic strategies. Theoretically, if one single cyclic skeleton can be compatible with more stereogenic elements, it may be used as the core template to overcome match/mismatch effects in the installation of multiple stereogenic elements. As a type of well-known and biologically interesting seven-membered heterocycle, heteropin[9] is considered as a hetero-analogue of cyclooctatetraene. When two aromatic moieties are fused to its core ring, it becomes a rigid molecule possessing a saddle-shaped structure and scarcely undergoing flipping[10]. As a result, the introduction of proper substituents into a fused heteropin scaffold can create unique saddle-shaped chiral molecules. To our surprise, only Shibata and co-workers reported two catalytic synthesis of chiral heteropin, in which multisubstituted sulfur-containing seven-membered ring (tribenzothiepins) was enantioselectively prepared through a transition-metal-catalyzed cycloaddition[11]. Recently, Scott J. Miller and co-workers reported an example of asymmetric catalytic construction of conformational chirality caused by the diaryl [*a*,*d*] cycloheptane ring system[12]. However, in general, achieving conformational chirality through asymmetric catalysis is still remain challenging. We speculated that the introduction of a nitrogen atom into the heteropin system to form azepine heterocycles might generate conformational behavior of the seven-membered ring and lead to stereogenic nitrogen center and C-N axial chirality. Moreover, with the proper aryl substitution attached to the azepine ring, an extra axial chiral biaryl chiral element can be installed as well, thus dramatically increasing the stereodiversity of target molecules.

Herein, we report a strategy based on organocatalytic annulation of **VQM** intermediates[13,14] to carbazole ring to form configurationally defined azepine heterocycles and realize the enantioselective construction of four types of fully controlled stereogenic elements in one single step (Figure 1c).

Results and Discussion

Reaction optimization. At the onset of our studies, we subjected1-(2-(9*H*-carbazol-9-yl)phenyl)ethynyl)naphthalen-2-ol (**1a**) to 10 mol% of various chiral bifunctional organocatalysts[15] under the standard conditions (0.05 M DCM, -60 °C and 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) as the brominating reagent) in the azepine cyclization reaction. Primarily, the survey

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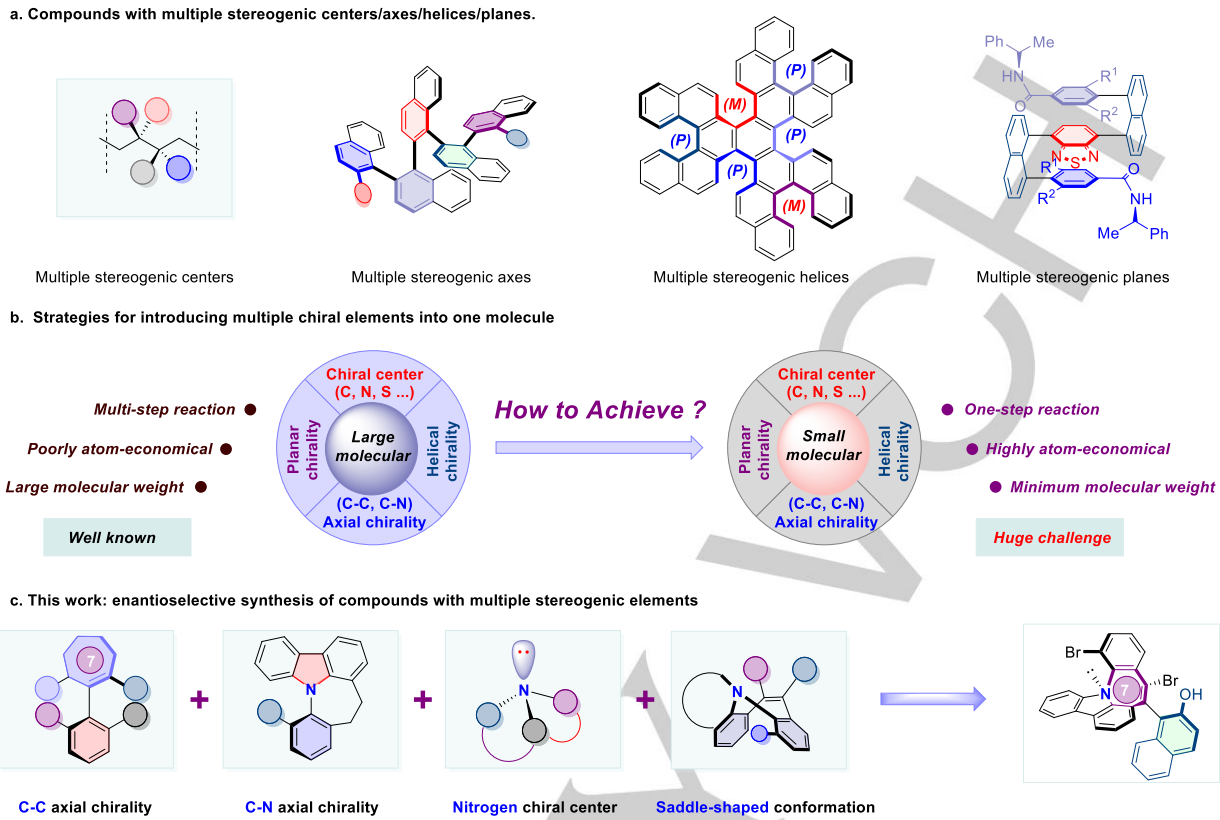

Figure 1. Multiple stereogenic chiral structures using azepine as the template. (a) Compounds with multiple stereogenic centers/ axes/ helices/ planes. (b) Strategies for introducing multiple chiral elements into one molecule. (c) This work: enantioselective synthesis of compounds with multiple stereogenic elements.

on cinchona alkaloid catalysts indicated significant impacts of the catalyst backbones on the outcome of the reaction. When catalyst **A**, **B**, **C**, **D** and **E** were used, the desired product **2a** was obtained in moderate yields, with poor to moderate enantioselectivities (Table 1, entries 1-5). To our delight, the reaction with catalyst **F** realized the enantiomeric excess up to 87% as well as moderate yield (entry 6). In further exploration, Takemoto's squaramide catalyst **G** only gave -62% ee and 69% yield and no product was detected in the reaction with dimeric cinchona alkaloid derivative $(DHQD)_2PHAL$ (entries 7, 8). In short, the catalyst investigation revealed that a crucial role of squaramide moiety in the transformation. It was ascribed to the low pKa values of the squaramide moiety and extended distances between the squaramide N−H bonds[16]. Solvent screening hinted that dichloromethane outperformed other counterparts, as no product was detected in most other solvents (acetone, ethyl acetate, tetrahydrofuran, N,N-dimethylformamide, diethyl ether and methanol) (entries 11-16). Although the reaction also took place in chloroform (45% yield) and toluene (78% yield), obvious enantioselectivity loss was noticed (entries 9, 10). Studies on the reaction temperature suggested low temperatures were vital to the product formation and high temperatures ruined the cyclization process (entries 17-19). The optimal outcome was realized at -78 °C (75% yield, 89% ee) and obvious decreases in both yield (57%) and ee (31%) were observed at 0 °C. When the reaction was performed at room temperature, only 35% conversion was achieved and the enantioselectivity dramatically declined (11% ee). The efficiencies of different brominating reagents such as N-bromosuccinimide (NBS), N-bromoacetamide (NBA) and N-bromophthalimide (NBP) were also examined (entries 20-22). NBS and NBP achieved elevated yields (80%) and NBS showed the better enantioselectivity than NBP (95% *versus* 89%). The better profile indicated that NBS was the optimal brominating reagent, so it was employed in the subsequent experiments. Finally, the increase in the concentration of reaction system led to a slightly decreased yield (78%), whereas the decreasing of reaction concentration (0.035 M and 0.025 M) led to the higher yields (82% and 85%, respectively) (entries 23-25). The concentration change of the reaction system within a certain range only made minor differences to the yields and almost showed no effect on the enantioselectivity. Finally, the reaction conditions of entry 25 were identified as the optimal one.

Substrate scope. Subsequently, the universality of the reaction was evaluated by exploring the substrate scope. As summarized in Scheme 1a, the methodology was proved quite robust with substrates bearing substituted 2-naphthols and achieved excellent enantioselectivities (92-97%) and moderate to good yields. With regard to the substituents on the 7-position of 2-naphthol (**2b**-**2d**), the reaction proceeded well with aryl-(Ph), electron-donating (OMe) or electron-withdrawing (Br) groups (yields > 89%) and no obvious electronic effect on electronic effect on stereoselectivity (ee > 94% and dr > 20:1) was found. An exception was detected that the linear 7-phenylethynyl modification decreased the yield (75%), yet it achieved excellent enantioselectivity (92%) (**2f**). As for 2-naphthols modified at its 6-

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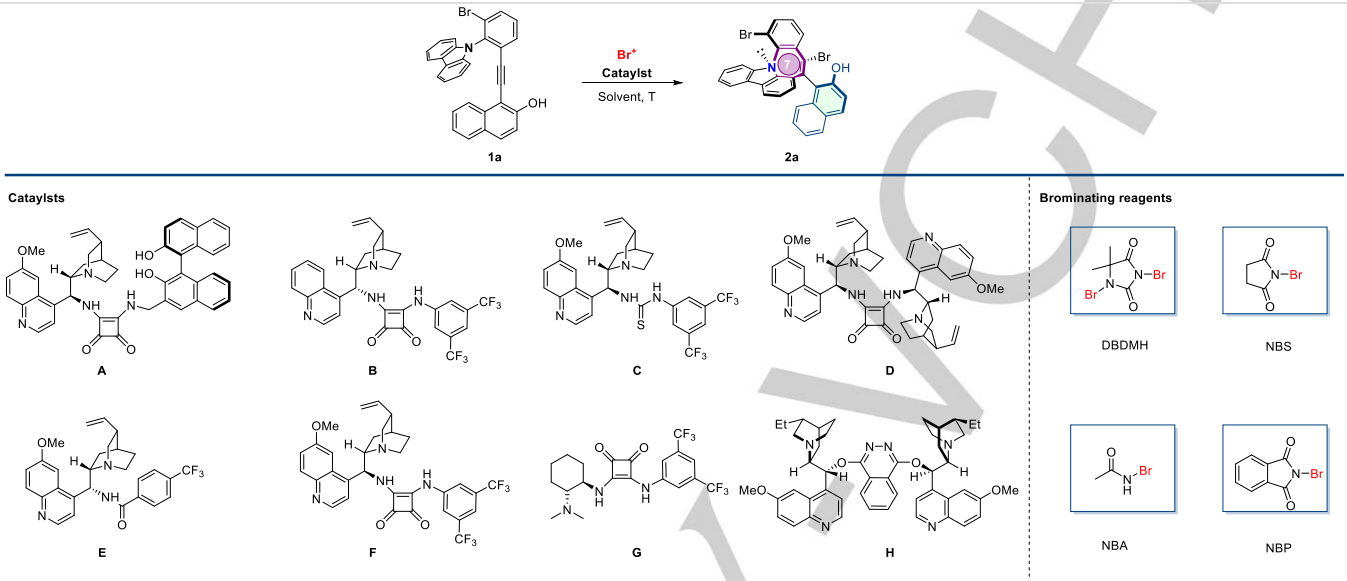
position, the electron-withdrawing (Br) group (**2e**) slightly raised the yield (89%), with excellent enantioselectivity (96%). Whereas the electron-donating (Et, *n*Pr, *i*Pr, and Cy) alkyls (**2g**-**2j**) led to moderate to good yields (54-83%), still all products were acquired with excellent enantioselectivities (93-97%). A bulky group (3-methoxybenzyl) at the 5-position of 2-naphthol (**2k)** was also found to be well tolerated as the enantioselectivity and the yield

Table 1. Optimization of the Reaction Conditions[a]



Entry	Catalyst	Solvent	T(°C)	Br⁺	Yield[b] (%)	dr[c]	ee[d] (%)
1	**A**	DCM	-60	DBDMH	79	>20:1	7
2	**B**	DCM	-60	DBDMH	66	>20:1	-62
3	**C**	DCM	-60	DBDMH	62	>20:1	0
4	**D**	DCM	-60	DBDMH	47	>20:1	-46
5	**E**	DCM	-60	DBDMH	58	>20:1	-40
6	**F**	DCM	-60	DBDMH	71	>20:1	87
7	**G**	DCM	-60	DBDMH	69	>20:1	-62
8	**H**	DCM	-60	DBDMH	ND	-	-
9	**F**	$CHCl_3$	-60	DBDMH	45	>20:1	49
10	**F**	Toluene	-60	DBDMH	78	>20:1	50
11	**F**	Acetone	-60	DBDMH	ND	-	-
12	**F**	EA	-60	DBDMH	ND	-	-
13	**F**	THF	-60	DBDMH	ND	-	-
14	**F**	DMF	-60	DBDMH	ND	-	-
15	**F**	Et_2O	-60	DBDMH	ND	-	-
16	**F**	CH_3OH	-60	DBDMH	ND	-	-
17	**F**	DCM	25	DBDMH	35	>20:1	11
18	**F**	DCM	0	DBDMH	57	>20:1	31
19	**F**	DCM	-78	DBDMH	75	>20:1	89
20	**F**	DCM	-78	NBS	80	>20:1	95
21	**F**	DCM	-78	NBA	45	>20:1	45
22	**F**	DCM	-78	NBP	80	>20:1	89
23[e]	**F**	DCM	-78	NBS	78	>20:1	96
24[f]	**F**	DCM	-78	NBS	82	>20:1	95
25[g]	**F**	DCM	-78	NBS	85	>20:1	95

[a] Reaction conditions: 1a (0.025 mmol, 1.0 equiv.), catalyst (0.0025 mmol, 10 mol%) in solvent (0.5 mL) at corresponding temperature for 30 min, then brominating reagents (0.025 mmol, 1.0 equiv.) at corresponding temperature for 2 h. [b] Isolated yield. [c] Only one dominant diastereomer formed. [d] Enantiomeric excess (ee) determined by HPLC. [e] Reaction in DCM (0.25 mL). [f] Reaction in DCM (0.75 mL). [g] Reaction in DCM (1.0 mL).

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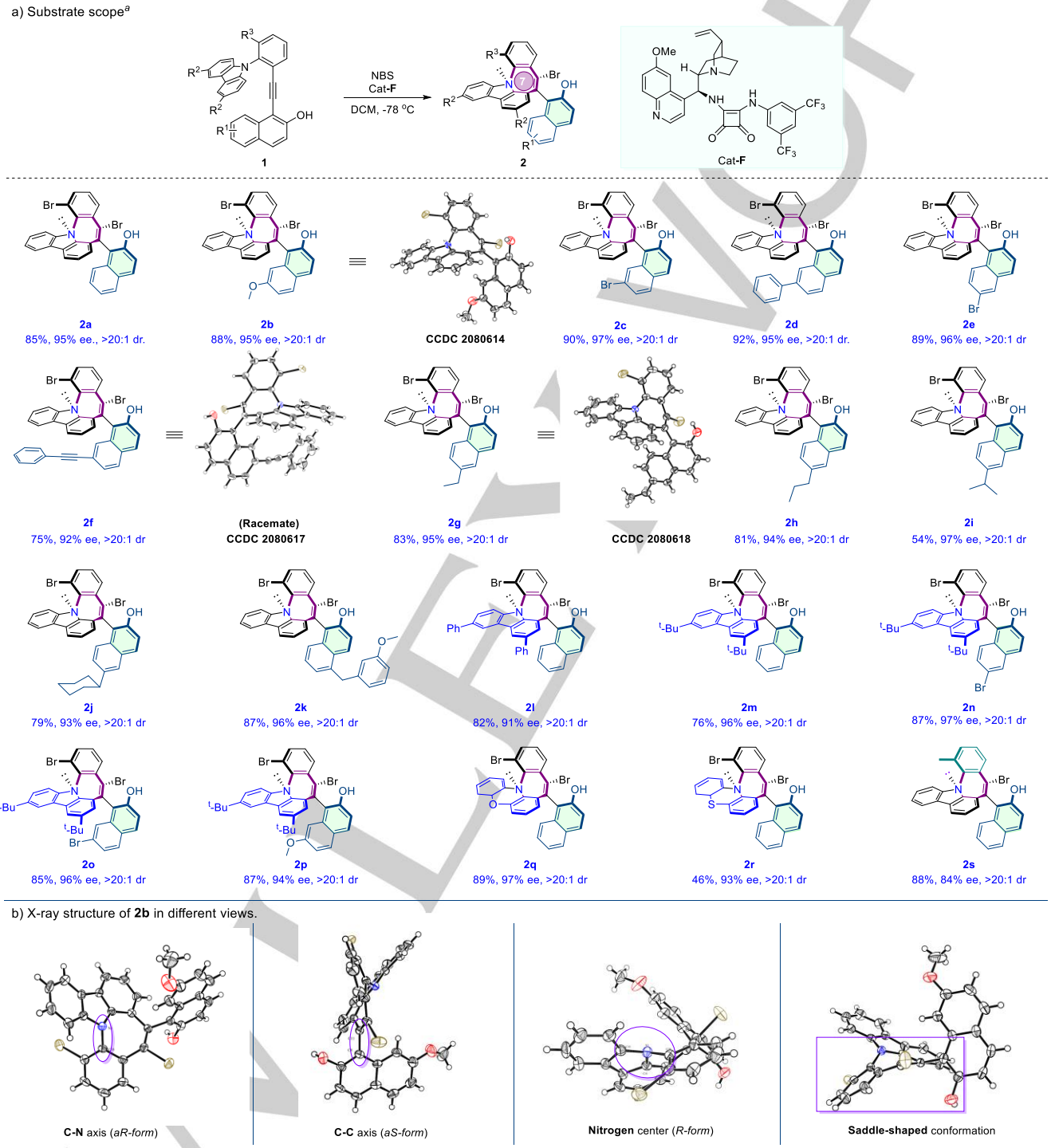
respectively reached 96% and 87%. Next, the scope of symmetric 3,6-disubstituted carbazoles was examined. Symmetric 3,6-disubstituted carbazoles bearing aryl-(Ph) and alkyl-(*t*-Bu) groups did not affect the cyclization reaction efficiency or stereoselectivity notably irrespective of substitutions (Br or OMe) on the 6- or 7-position of the 2-naphthols (**2l**-**2p**, 76-87% yields, 91-97% ee). In detail, 3,6-diphenyl carbazole product (**2l**) has a higher yield (82%) than that of 3,6-di-*tert*-butyl carbazole (**2m**, 76% yield). However, an electron-withdrawing (Br) group at the 6-position of the 2-naphthol (**2n**, 87% yield) compensated the conversion loss and a similar effect was also observed in the 7-substituted 2-naphthols (**2o** and **2p**, 85-87% yields) regardless of the electronic properties. This observation was also in accordance with non-substituted carbazole products (**2b**-**2e**). We further made more



Scheme 1. Substrate scope. [a] Reaction conditions: 1 (0.2 mmol, 1.0 equiv.), catalyst-F (0.02 mmol, 10 mol%) in DCM (8.0 mL) at -78 °C for 30 min, then NBS (0.2 mmol, 1.0 equiv.) at -78 °C for 2 h.

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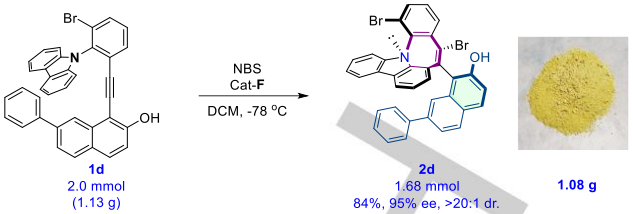
variations at the carbazole ring of the substrates. The replacement of the carbazole with a phenoxazine ring (**2q**) retained excellent enantioselectivity (97% ee) and led to a higher yield (89%). Furthermore, the replacement of the carbazole with a phenothiazine group was found to be also employable for the reaction and gave **2r** with excellent enantioselectivity in moderate yield. Finally, when the bromine atom on the benzene ring is replaced by a methyl group, the ee value of the target product **2s** decreases slightly (84% ee), although a good reaction yield was obtained. In summary, this part of the investigation suggested a broad substrate spectrum of the given methodology.

In addition, the absolute configurations of **2b** and **2g** were detected to be ($aR_{C\text{-}N\ axis}$, $aS_{C\text{-}C\ axis}$, R_N) by single-crystal X-ray crystallographic analysis and others were assigned to analogue. As expected, the seven-membered azepine ring had a saddle-shaped conformation. The nitrogen atom and the axial chiral biaryl (*aS*-form) across from it are situated above the plane, whereas the bromine substituted benzene ring and the phenyl part of carbazole was below the plane. It was also ascertained that the absolute configuration of the nitrogen atom was in its R_N-form, whereas the chiral C-N axis was in its *aR*-form. In this way, four types of stereogenic elements were stereoselectively constructed in this molecule (Scheme 1b).

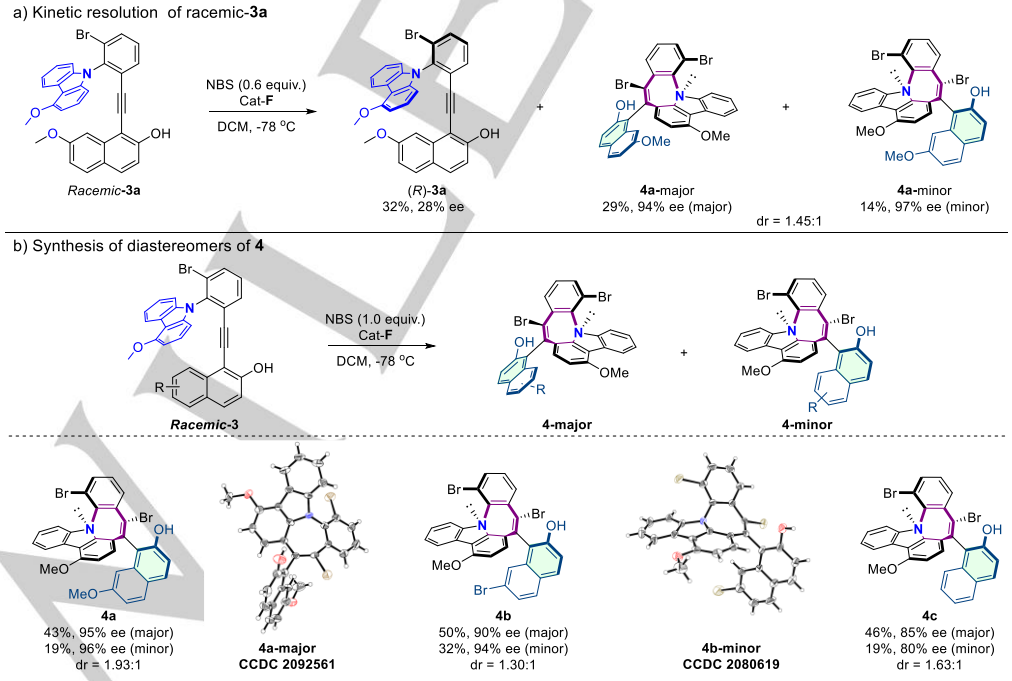
To demonstrate the synthetic practicability of this catalytic asymmetric transformation, the reaction was scaled up to 2.0 mmol and the desired product **2d** was obtained in 84% yield with 95% ee and >20:1 dr (Scheme 2). The encouraging results imply that the catalytic asymmetric reactions have the potential for a large-scale production.

Further applications. We then explored the possible application scope of the reaction system. The replacement of symmetric 3,6-disubstituted carbazoles with 4-substituted



Scheme 2. Gram-scale synthesis.

carbazole endowed it with a C-N chiral axis and led to racemic substrates **3a**-**3c**. When the reaction proceeded with 0.6 equiv. NBS, kinetic resolution (KR) of racemic-**3a** could also be achieved to afford the unreacted (*R*)-**3a** and cyclization products **4a** with a diastereoselectivity ratio of 1.45:1 (Scheme 3a.). Interestingly, when the amount of NBS was increased to 1.0 equiv., all the raw materials can be consumed, a pair of diastereomers of **4a** can be easily obtained with excellent enantioselectivities (95% and 96% ee, respectively). This finding suggested a practical strategy for accessing enantio-pure chemicals with the mentioned C-N chiral axis. Moreover, an electron-withdrawing (Br) group on the 7-position of the 2-naphthol raised the yields of both isomers (major and minor product of **4b**, 50% and 32% yields) with excellent enantioselectivities (90% and 94%). In contrast, when there is no substituent at the 7-position of 2-naphthol, the stereoselectivity of the two isomers of **4c** is slightly reduced (85% and 80%, respectively), indicating an important role of substituent at the 7-position in this process. In order to figure out which stereogenic element has an inverted configuration during this transformation, we determined the absolute configurations of **4a**-major and **4b**-minor by X-ray crystallographic analysis[19]. As show in Scheme



Scheme 3. Catalytic kinetic resolution of racemic-**3a** and synthesis of diastereomers of **4**. Reaction conditions: **3** (0.2 mmol, 1.0 equiv.), catalyst-**F** (0.02 mmol, 10 mol%) in DCM (8.0 mL) at -78 °C for 30 min, then NBS (0.6 equiv. or 1.0 equiv.) at -78 °C for 2 h.

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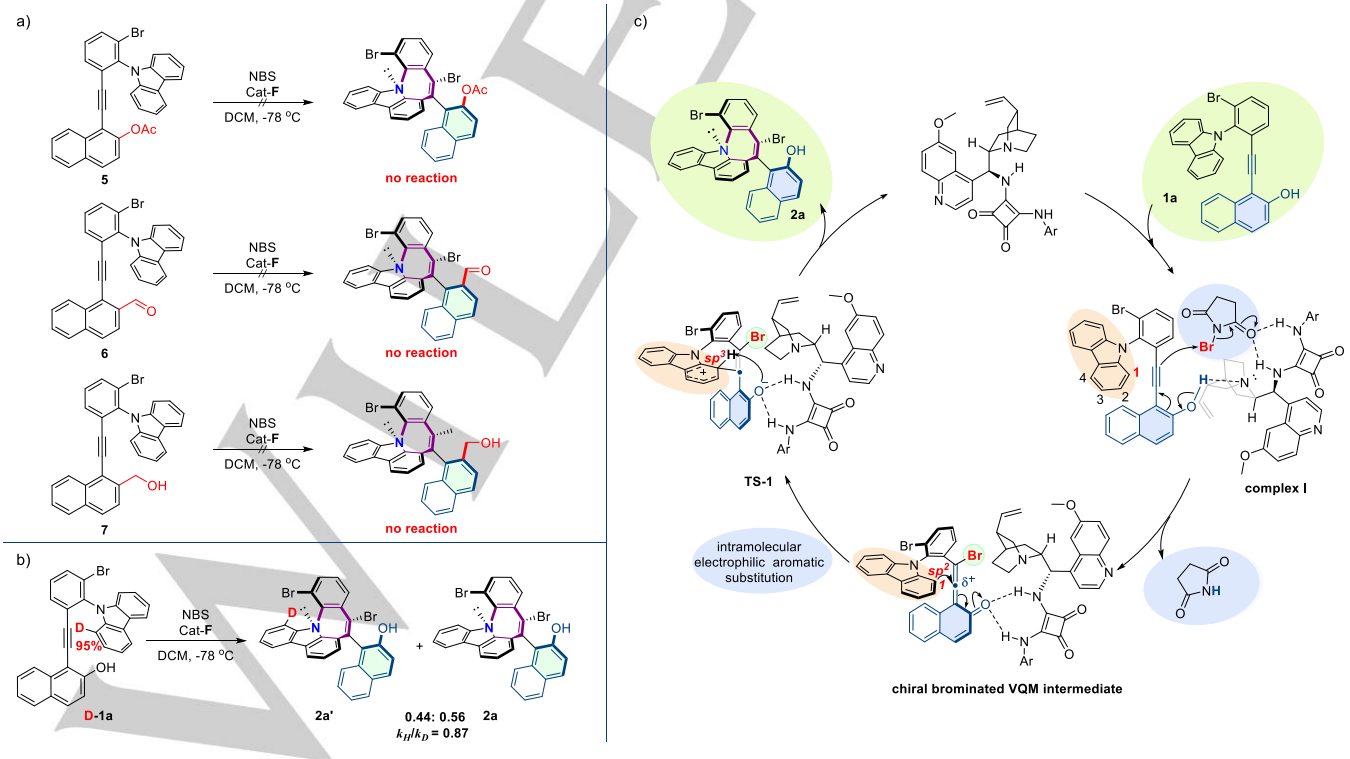
3b, the absolute configuration of the C-N axis and N atom of **4a**-major ($aS_{C\text{-}N\ axis}$, S_N-form) was opposite with **4b**-minor ($aR_{C\text{-}N\ axis}$, R_N-form). Meanwhile, the saddle-shaped conformation of the seven-membered ring has reversed, resulting in the nitrogen atom and the axial chiral biaryl across from it turned below the plane, whereas the bromine substituted benzene ring and the phenyl part of carbazole were above the plane. Nevertheless, the configuration of the C-C axis remained the same (*aS*-form), and this led to the formation of diastereomers of product **4**.

Control experiments and preliminary mechanistic studies. To shed light on the mechanism of this cyclization reaction with the formation of multistereogenic elements, some control experiments were carried out. When the naphthyl hydroxyl was protected by acetyl group or replaced with a formaldehyde or methanol group to block the formation of **VQM** intermediate, the reaction did not take place and only the starting material was recovered from the reaction system (Scheme 4a). Hence, the **VQM** system might be involved in this highly stereo-controlled transformation. In addition, the kinetic isotope effect (KIE) was measured based on parallel reactions of **D-1a** and **1a** to give **2a'** and **2a** (Scheme 4b). As shown in Scheme 4b, 1-deuterated carbazole was converted into a mixture of deuterated product **2a'** and non-deuterated product **2a**. As a result, a k_H/k_D value of 0.87 was obtained, indicating that the C−H bond cleavage might not be the rate-determining step of this transformation. We speculate that the reaction involves an *inverse* secondary isotope effect (KIE<1)[17]. In this case, there will be a process in which the aromatic ring forms a carbocation transition state. In the process of forming a transition state, the substituted C-H bond may be hybridized from near sp^2 to near sp^3, and this process might be the rate-determining step[18]. On the basis of both previous studies and our observations, we speculated that two stereospecific steps should be involved in this process: the C−C bond-forming addition reaction and the proton migration to produce enantioenriched azepine ring with the stereo control of four types of stereogenic elements. In detail, a plausible reaction mechanism was proposed based on the reaction of **1a** with NBS in the presence of catalyst **F** (Scheme 4c). First, complex **I** was generated through the coordination of NBS and catalyst **F** with **1a** and then chiral brominated **VQM** intermediate was enantioselectively formed via proton shift. In this case, the C1 position on the carbazole aromatic ring is sp^2 hybridized. Next, the sp^3 hybridized carbocation transition state **TS-1** was generated by the intramolecular electrophilic aromatic substitution at the C1 position of the carbazole moiety. In addition, a complementary naphthyl-azepine biaryl was formed to construct the second stereogenic axis.

Photophysical properties investigations. We further investigated the photophysical properties of several selected compounds. The UV/Vis absorption spectra of the tested compounds in DCM are presented in Figure 2a. Although these compounds had different absorption curves, their maximum absorption peaks were observed at similar wavelengths (229-239 nm). The emission spectra (Figure 2b) and the CIE diagram (Figure 2c) of the tested compounds exhibited similar fluorescence patterns under the irradiation of UV light (543-584 nm). Among all the chemicals, **2l** had the longest wavelength of emission band, whereas non-substituted **2a** had the shortest wavelength of emission band, indicating a causal role of the 3,6-diphenyl substitution on carbazole in the red-shift (ca. 40 nm).



Scheme 4. Control experiments and preliminary mechanistic studies. (a) Control experiments. (b) Isotopic labeling experiment. (c) Plausible catalytic cycle.

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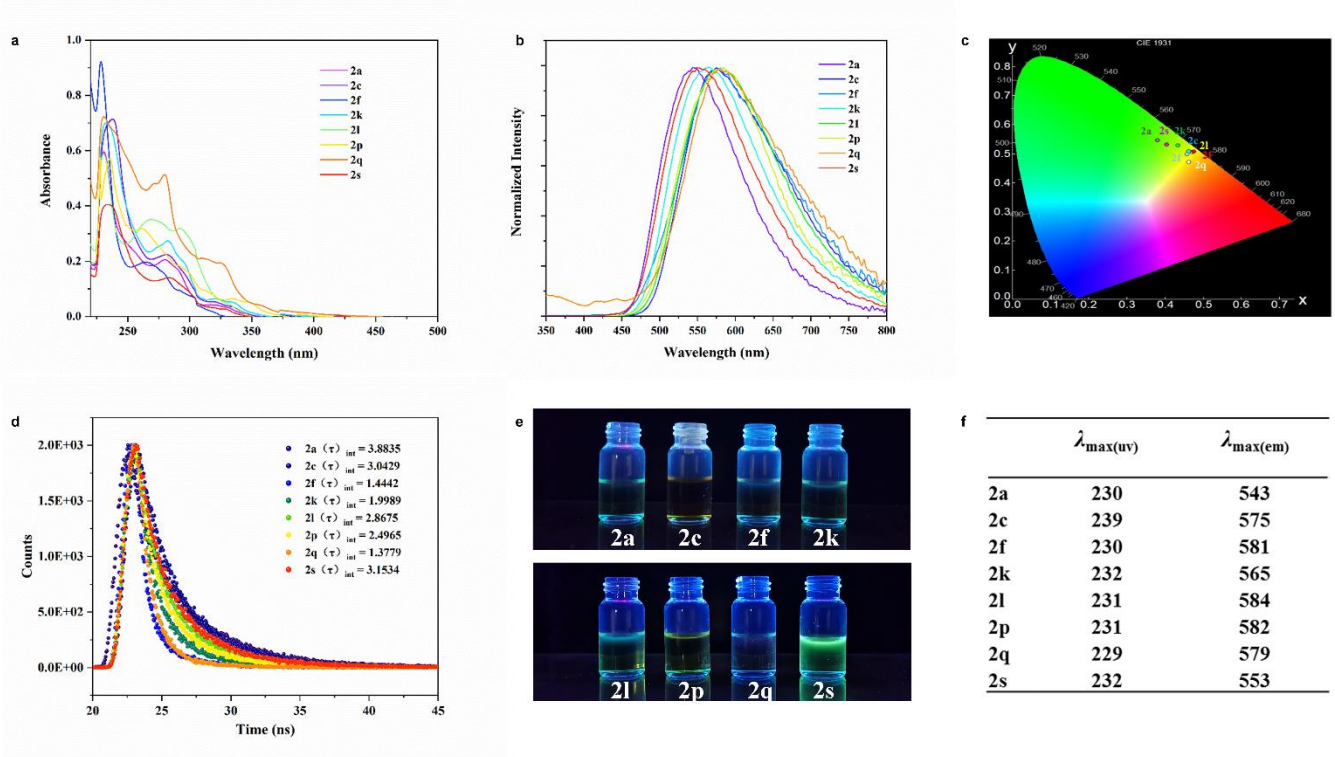

f

	$\lambda_{max(uv)}$	$\lambda_{max(em)}$
2a	230	543
2c	239	575
2f	230	581
2k	232	565
2l	231	584
2p	231	582
2q	229	579
2s	232	553

Figure 2. Photophysical properties of several selected compounds. (a) UV/Vis absorption spectra. (b) Fluorescence spectra. (c) Fluorescence lifetime decay curves. (d) CIE diagram. (e) Photos under irradiation of UV (λ = 365 nm) light. (f) Longest wavelengths of UV/Vis absorption (2×10^{-5} M in DCM) and emission (excitation wavelength: 300 nm, solid powder).

The fluorescent emission half-life (τ) time of all compounds showed sharp distinctions. **2a** had the longest half-life time, 3.88 ns, which was almost 3-folds of that of **2q**, 1.38 ns (Figure 2d). Hence, substitutions on the scaffold reduced the fluorescent lifetime and caused red-shift. In addition, the replacement of carbazole with phenoxazine led to major variations in optical properties. We also explored the potential of **2b** as fluorescence sensors for the purpose of detecting transition metal ions. Compared with some cations, such as Na^+, K^+, Mg^{2+}, Bi^{3+}, Ce^{3+}, In^{3+} and Zr^{4+}, Ru^{3+} exhibited the most significant effect upon the fluorescence property of **2b**. The outcome indicated that **2b** could be used as a selective Ru^{3+} detection fluorescence sensor (see Supporting Information).

Conclusion

In conclusion, we developed a perfectly atom-economic and highly enantioselective organocatalytic process for the construction of chiral molecules bearing four distinct stereogenic elements. Our reaction was enabled via intramolecular electrophilic aromatic substitution of carbazole moiety with in situ generated chiral **VQM** intermediate in the presence of confined chiral hydrogen bonding bifunctional catalysts so as to provide access to the valuable enantiopure azepine ring system. With this methodology, four types of stereogenic elements including chiral nitrogen center, C-N axial chirality, C-C axial chirality and conformational behavior of the seven-membered ring were stereoselectively constructed. Further utility of this process was illustrated by catalytic resolution of non-symmetrical substrates to access more complicated molecules. In addition, optical properties of certain compounds were investigated, including UV absorption, fluorescence irradiation and emission and they showed potential application prospects in chiral organic optoelectronic materials. Further study on the fluorescence response behaviors induced by heavy metal ions suggested the potential application of these compounds in Ru^{3+} detection.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: asymmetric catalysis • multiple stereogenic elements • seven-membered ring • azepine • organocatalytic

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[19] Deposition Numbers 2080614 (for **2b**), 2080617 (for **2f**), 2080618 (for **2g**), 2092561 (for **4a**-major) and 2080619 (for **4b**-minor) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/ structures.

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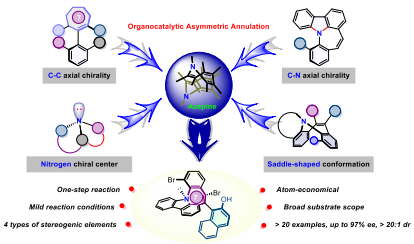

An organocatalytic enantioselective method for the preparation of polychiral molecules via vinylidene *ortho*-quinone methide (**VQM**)-mediated intramolecular electrophilic aromatic substitution was developed. With this methodology, four types of stereogenic elements including chiral nitrogen center, C-N axial chirality, C-C axial chirality and conformational behavior of the seven-membered ring were stereoselectively constructed.