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Communication

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Enantioselective Construction of Vicinal Diaxial Styrenes and Multiaxis System via Organocatalysis

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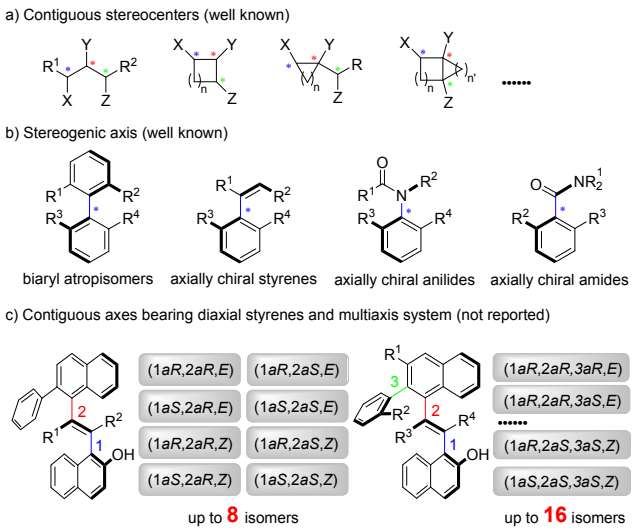
Supporting Information Placeholder

ABSTRACT: A highly diastereo- and enantioselective methodology for the asymmetric synthesis of vicinal diaxial styrenes and multiaxis system was achieved by organocatalysis. Various vicinal diaxial styrenes and multiaxis systems were obtained in excellent enantioselective manners. The mechanism studies revealed that a new tetra-substituted vinylidene *ortho*-quinone methide (**VQM**) intermediate was likely involved and accounted for the excellent enantioselectivity.

Compounds with contiguous elements of chirality,[1] which can offer a particularly broad range of topologies, are important scaffolds as various chiral ligands, catalysts and optical resolution agents. Accordingly, their syntheses have attracted wide attention from chemists and great progresses have been made in the construction of contiguous stereocenters (Scheme 1a). However, compared to various methods controlling contiguous stereocenters configuration,[2] current catalytic methods of the preparation of axially chiral scaffolds mostly focus on the single stereogenic axis (Scheme 1b).[3] Stereoselective methods of preparing the individual compound classes with two or more stereogenic axes are rarely reported.[4] Further, only few examples of asymmetrically generating different types of axial chirality in a single reaction step are available.[4d,4e,4g] The lack of a general and straightforward catalytic protocol to access compounds with multiple configurational axes has also hindered their preparation and applications in asymmetric synthetic chemistry. From the asymmetric catalytic chemistry point of view, the combination of different types of stereogenic axes (such as the combination of biaryl atropisomers and axially chiral styrenes) in a single molecule may provide geometrically chiral environments. Therefore, it is intriguing to explore a utilitarian strategy to realize this objective.

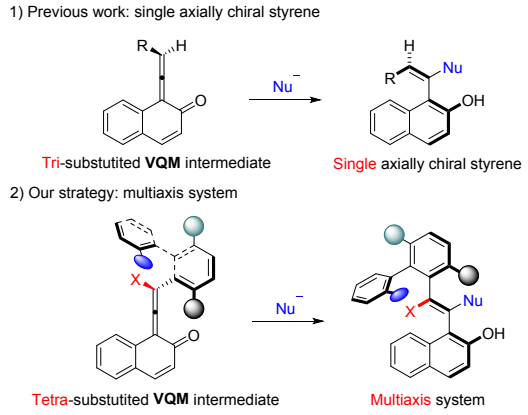
Recently, axially chiral styrenes as the new member of the axially chiral family has received extensive attention from synthetic chemists.[5] Consequently, a few examples of the enantioselective construction of axially chiral styrenes have been reported by the research groups of Baker,[5b] Miyano,[5c] Gu,[5d,5g] Smith,[5f] Tan[5e] and our group.[7f,7h] Despite these achievements, the preparation of contiguous axially chiral styrenes has not been realized to date, due to the following requirements: (1) the constructions of contiguous axially chiral styrenes rely on tetra-substituted olefin skeletons and the way to control the corresponding *E/Z* selectivity is the prerequisite; (2) the diastereo- and enantioselectivity should be controlled. Among these requirements, *E/Z* selectivity of tetra-substituted olefin is generally the critical issue, since their syntheses are of great challenges[6] due to the highly steric congestion of four substituents and the difficulties in controlling the stereochemistry. In addition, the generation of geometric isomers may also result in the failure of reaction design. All the mentioned difficulties probably caused the absence of successful reports.

Scheme 1. Background and Project Synopsis



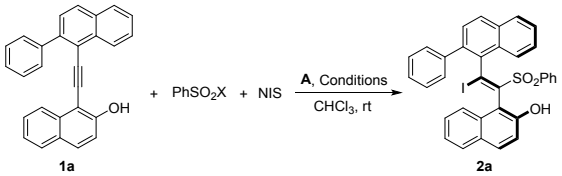
Vinylidene *ortho*-quinone methide (**VQM**)[7] contains multiple reactive sites and thus exhibits diverse and interesting reactivity for a wide variety of enantioselective transformations. Usually, the active **VQM** intermediate can be generated through a prototropic rearrangement (tautomerization) of 2-(phenylethynyl)phenol under basic conditions. So far, all the reports on **VQM** intermediate are focused on tri-substituted types. In view of these potential challenges, we aim to develop a new variant of **VQM** intermediate to solve these issues. Theoretically, a new type of tetra-substituted **VQM** species may be produced in the presence of a suitable electrophilic reagent during the process of prototropic rearrangement. Therefore, selecting the appropriate electrophilic reagent is the primary task of our project. Firstly, N-Iodosuccinimide (NIS),[8] which was widely used in organic

Scheme 2. Previous Work and Our Strategy



transformations, was selected as the potential electrophile. Combined with our findings on enantioselective addition of sulfone to in situ generated **VQM** intermediate,[7f] a reaction of $PhSO_2Na$, NIS and **1a** in the presence of catalyst **A**, L-proline and H_3BO_3 as additives was tested. As we envisaged, the desired product was successfully obtained while the yield and enantioselectivity were poor. Next, simplifying the reaction condition (condition B) did not improve the enantioselectivity and yield. Interestingly, the yield of the reaction was increased by replacing $PhSO_2Na$ with $PhSO_2H$, despite the enantioselectivity was still poor.

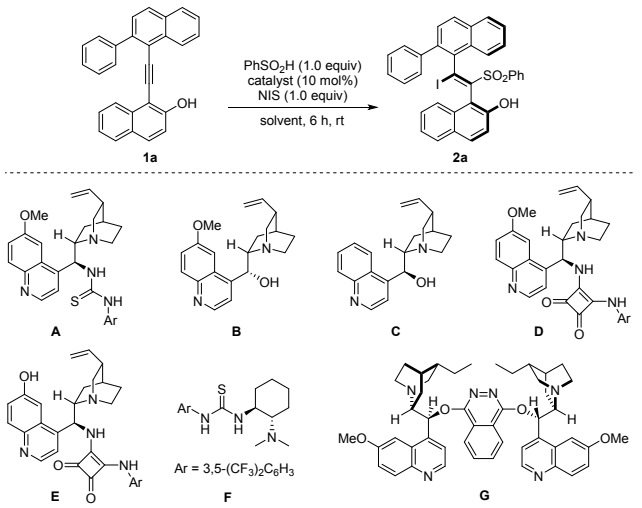
Scheme 3. Initial Attempt



The following survey was focused on identifying a suitable organocatalyst[9] for this asymmetric induction. The reaction with catalyst **A**, **B** and **C** gave poor enantioselectivities, albeit moderate yields of **2a** were obtained (Table 1, entries 1-3). The results obtained with catalysts **D** and **E** revealed that the quinine-derived squaramide catalysts realized the enantiomeric excess up to 92% and 94% as well as excellent yields (Table 1, entries 4, 5). Further investigation on Takemoto's thiourea catalyst **F** resulted in a significant decrease in atropselectivity (9% ee) and yield (Table 1, entry 6). Dimeric cinchona alkaloid derivative $(DHQD)_2PHAL$ almost did not work in this reaction. Catalysts screening results indicated that the squaramide species was crucial for this transformation. This is because of the low pKa value of the squaramide moiety and the extended distance between the squaramide N-H bonds. In addition, the distal N-aryl of the squaramide is also extended out compared to thioureas, which could also allow it to better control the stereo induction of the distal axis.[10] With the best catalyst in hand, the effect of the solvent on this reaction was also examined. A series of solvents were tested. DCM was found to be the best solvent since it ultimately delivered the product in excellent yield, diastereoselectivity, *E/Z* selectivity and enantioselectivity (93% yield, >20:1 dr, *E/Z* > 20, 95% ee).

Having defined the optimal reaction conditions, we next tested

Table 1. Optimization of the Reaction Conditions[a]

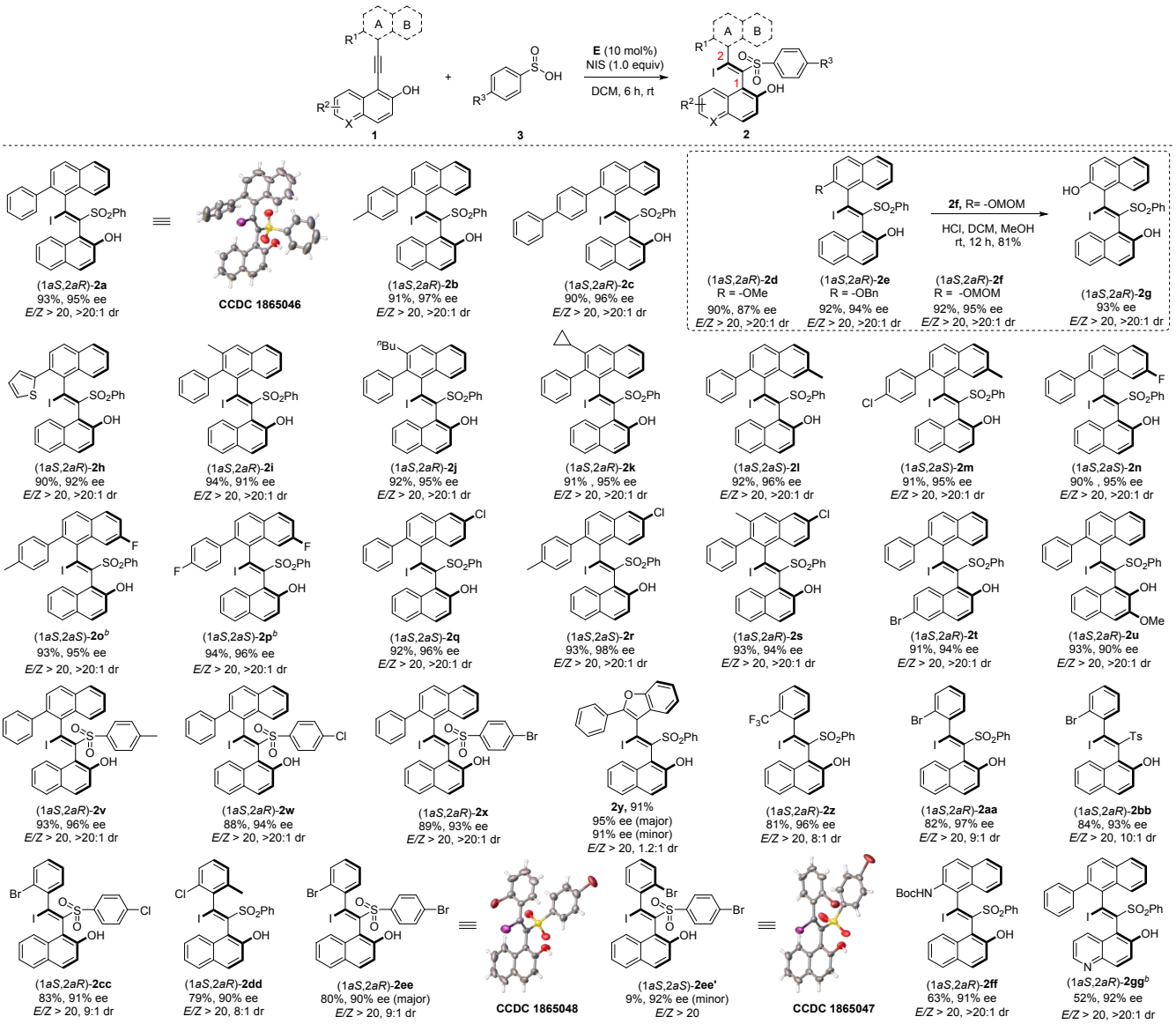


entry	catalyst	solvent	yield (%)[b]	ee (%)[c]	*E/Z*	dr
1	**A**	$CHCl_3$	55	11	>20	>20:1
2	**B**	$CHCl_3$	43	0	>20	>20:1
3	**C**	$CHCl_3$	53	1	>20	>20:1
4	**D**	$CHCl_3$	89	92	>20	>20:1
5	**E**	$CHCl_3$	92	94	>20	>20:1
6	**F**	$CHCl_3$	41	9	>20	>20:1
7	**G**	$CHCl_3$	37	3	>20	>20:1
8	**E**	DCM	93	95	>20	>20:1
9	**E**	toluene	69	5	>20	>20:1
10	**E**	1,4-dioxane	62	89	>20	>20:1
11	**E**	EA	55	55	>20	>20:1
12	**E**	Et_2O	78	8	>20	>20:1
13	**E**	DCE	80	30	>20	>20:1
14	**E**	CCl_4	61	2	>20	>20:1

[a]Conditions: **1a** (0.1 mmol), $PhSO_2H$ (0.1 mmol), catalyst (10 mol%) and NIS (0.1 mmol) in solvent (2.0 mL) at rt for 6 h. [b]Isolated yield. [c]Determined by HPLC analysis.

the scope of the atroposelective addition reaction. First, a panel of substituents on ortho position of naphthalene (R^1 groups) were tested (**1b-1f**). Phenyl groups with para methyl and phenyl substituents gave excellent enantioselectivities and yields (**2b**, **2c**). Next, we explored the substrate scope by examining various ether substituents (R^1 groups) at naphthalene (ring A). All the substrates (**1d-1f**) were converted into the desired products with similar efficiencies and selectivities. Under acidic conditions, deprotection of **2f** afforded (1*aS*,2*aR*)-Bi-2-Naphthol (**2g**) which could be used as new naphthalenediol skeleton in the design of catalysts. Heterocyclic substituent at the naphthalene (ring A) was well tolerated to our reaction system and thiophene substituent successfully led to the desired product **2h** with excellent stereoselectivity and yield. Furthermore, substrates with the alkyl substituents on ring A of naphthalene were found to be employable for the reaction and gave axially chiral adducts **2i-2k** with excellent enantioselectivities (91-95% ee). Next, a series of substituents at different positions of naphthalene (ring B) were tested and tolerated in this reaction, thus allowing the preparation

Table 2. Substrate Scope[a]



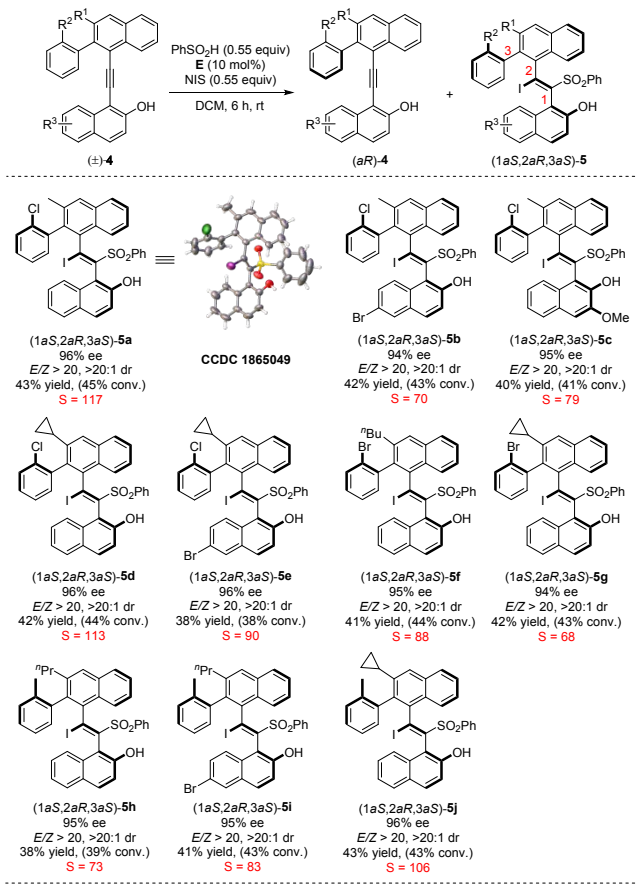
[a]Conditions: **1** (0.1 mmol), **3** (0.1 mmol), **E** (10 mol%) and NIS (0.1 mmol) in DCM (2.0 mL) at rt. [b]Due to poor solubility of the substrate in DCM, 4.0 mL DCM was used.

of structurally diverse, enantioenriched axially chiral adducts **2l**-**2r** (95-98% ee). Among the tested substrates, the substituents on both of R^1 and naphthalene ring were well tolerated. The introduction of three substituents on naphthalene also worked well to give high enantioselectivity (**2s**, 94% ee). To further investigate the scope of our reaction, substituents such as bromine and methoxy were introduced to the naphthol ring (R^2 substituents). Gratifyingly, the products **2t** and **2u** were formed with excellent enantioselectivities and high yields. To expand the utility of this synthetic method, different substituted $PhSO_2H$ compounds were also examined. Not only methyl substituent but also para chloride and bromide were employable for the reaction and gave axially chiral products with excellent enantioselectivities and high yields. When naphthalene was replaced by benzofuran, the reaction still proceeded smoothly to give desired axially chiral adduct, albeit the diastereoselectivity of the product decreased. Finally, replacing naphthalene ring with a series of ortho substituted phenyl groups gave the enantioenriched adducts **2z**-**2ee** in slightly lower yields and satisfying diastereoselectivities with excellent enantioselectivities. Substrates with nitrogen atom at different positions were also investigated. Although those substrates gave moderate yields, the ee values remained at an excellent level (**2ff**, **2gg**). The absolute configuration of **2a** was determined to be (1*aS*,2*aR*) by single crystal X-ray crystallographic analysis, others were assigned by analogue.

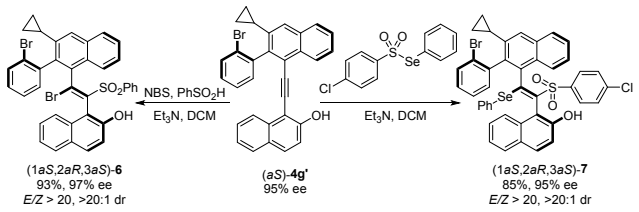
Motivated by the obtained results, we further expanded this methodology to the preparation of adducts with three elements of axial chirality. We regarded the compounds containing vicinal diaxial styrenes and a biaryl axis as our target molecule. First, a rotating hindered biaryl axis was constructed by introducing two sterically hindered substituents (R^1 and R^2 groups) on the basis of **1a** skeleton. With this strategy, we envisaged a kinetic resolution process, in which one of the enantiomers of the racemic (±)-**4** was

Table 3. Substrate Scope and Transformations

a) Substrate Scope[a]



b) Synthetic Transformations

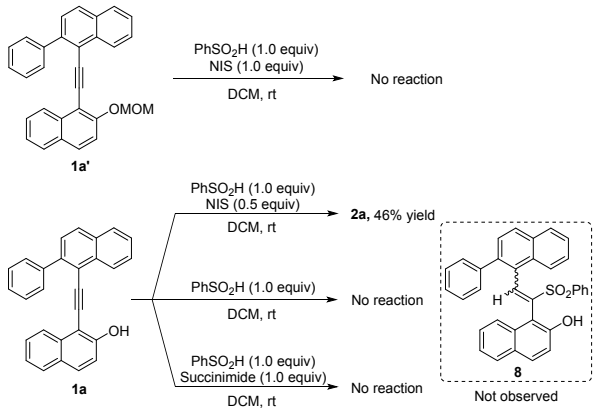


[a]Conditions: (±)-**4** (0.1 mmol), $PhSO_2H$ (0.55 mmol), **E** (10 mol%) and NIS (0.55 mmol) in DCM (2.0 mL) at rt for 6 h. All the reported S values were the average of 3 times of repetition.

converted into tetra-substituted **5** with three stereogenic axes and the unreacted chiral **4** remained. Under the optimal reaction conditions, the substrates investigation showed that this transformation tolerated a broad variety of substrates. The substituents on R^1, R^2 and R^3 groups with different electronic properties were well tolerated and afforded the desired products with excellent enantioselectivities (94%-96% ee). The absolute configuration of the multiaxial chiral **5a** was unambiguously determined to be (1*aS*,2*aR*,3*aS*) by single crystal X-ray crystallographic analysis. Although the enantioselectivities of unreacted **4** were not high (60%-78%) (see Supporting Information for details), an excellent enantioselectivity could be obtained after recrystallization. Next, various transformations of **4** were performed. When **4g'** reacted with NBS and $PhSO_2H$ in the presence of triethylamine, the corresponding multiaxial chiral **6** was obtained in high yield with excellent diastereo- and enantioselectivity. The same level result was obtained when **4g'** reacted with Se-phenyl 4-chlorobenzenesulfonoselenoate.

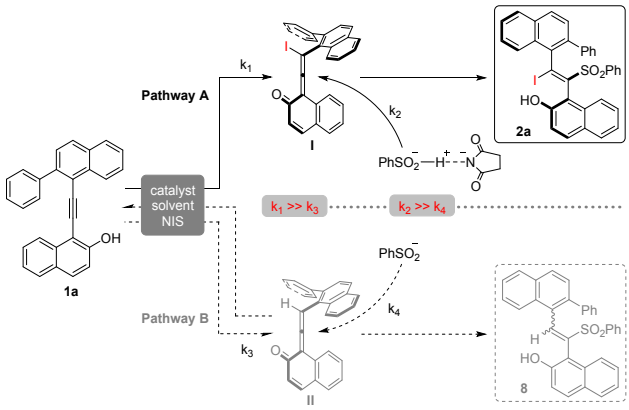
To gain insight into the reaction mechanism, a series of control experiments were performed. For example, the reaction did not lead to any axially chiral styrenes when **1a'**, in which the hydroxyl was protected thus not capable of generating the **VQM** intermediate, was used as substrate. This result excluded the possibility of direct activation of alkynes by NIS and proved that **VQM** intermediate participated in the reaction. When the reaction was performed with 0.5 equiv of NIS, the conversion of substrate **1a** remained at 46%. However, compound **8**, which was believed to be generated through tri-substituted **VQM** intermediate, was not obtained. Additionally, in the absence of NIS, the reaction did not occur, indicating that NIS was essential for both generating the active tetra-substituted **VQM** intermediate and activating $PhSO_2H$. Finally, replacing NIS by succinimide did not provide any product. All the above experimental results implied that the active tetra-substituted **VQM** intermediate was involved in our reaction.

Scheme 4. Preliminary Mechanistic Studies



Based on the experimental results, a plausible reaction pathway is outlined in Scheme 5. Catalyst **E** quickly reacts with **1a** and generates tetra-substituted **VQM** intermediate **I** in the presence of NIS. Meanwhile, the released succinimide anion captures a proton from $PhSO_2H$ thus giving the corresponding $PhSO_2H$ anion with nucleophilic property. Finally, a nucleophilic addition of the activated sulfinate anion to the highly active tetra-substituted **VQM** intermediate **I** occurs thus furnishing the product **2a**. Another reaction pathway involving a tri-substituted **VQM** intermediate **II** is suppressed maybe due to the competitive reactions in the process of generating tri-substituted **VQM** intermediate **II** and tetra-substituted **VQM** intermediate **I**.

Scheme 5. Proposed Reaction Pathway



In conclusion, we have developed a diastereo- and enantioselective catalytic method which afforded highly poly chiral axial motifs. The reactions proceeded smoothly under mild reaction conditions and showed broad substrate scope affording the desired products containing two to three stereogenic axes in good yields with excellent diastereo- and enantioselectivities. The control experiments performed showed that the generation of tetra-substituted **VQM** intermediate was the key to the excellent enantioselectivity. The obtained unique topology may contribute to the development of new chiral catalysts or ligands. Moreover, the investigation of the fluorescent properties of these scaffolds is ongoing in our laboratory.

ASSOCIATED CONTENT

Supporting Information

Experimental procedure and characterization data for all the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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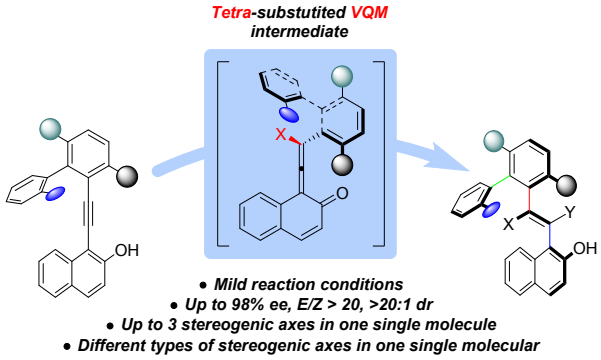
Tetra-substutited VQM
intermediate
OH
X
O
X
Y
OH
• Mild reaction conditions
• Up to 98% ee, E/Z > 20, >20:1 dr
• Up to 3 stereogenic axes in one single molecule
• Different types of stereogenic axes in one single molecular