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Vinylidene *ortho*-Quinone Methides: Unique Chiral Reaction Intermediates in Catalytic Asymmetric Synthesis

Sachie Arae[a], Masaki Furusawa[b], Shota Beppu[b], Kazunobu Igawa[c], Katsuhiko Tomooka[c], and Ryo Irie*[a]

Abstract: Vinylidene *ortho*-quinone methides (**VQM**s) are one-carbon elongated homologues of *ortho*-quinone methides (**QM**s), well-known as useful reaction intermediates in organic transformations. These related quinone methides are quite distinct in terms of stereochemistry. Namely, **VQM**s are characterized by an exocyclic allenyl ketone unit merged with a dearomatized ring system and thus, can be rendered axially chiral by locating a substituent properly at the terminal methylene group of the allene moiety. It should be also noted that **VQM**s are tautomers of *ortho*-ethynylphenols and these isomeric species are correlated through a proton-shift (tautomerization). Focusing on these stereochemical and structural features, we have pursued the development of unprecedented asymmetric reactions involving enantioenriched **VQM** intermediates generated by chiral-base-catalyzed tautomerization of the ethynylphenol precursors. Indeed, commonly used chiral base catalysts such as cinchonine (**CN**) and cinchonidine (**CD**) have been successfully demonstrated to be effective to this end. In this account, we wish to briefly describe our recent studies on the asymmetric syntheses of optically active indeno[1,2-*c*]chromenes, benzofuro[3,2-*b*]indeno[1,2-*c*]chromenes, and benzo[*a*]carbazoles, based on the catalytic enantioselective generation of **VQM**s with **CN** or **CD** and the stereocontrolled intramolecular follow-up cyclization with tethered alkynes, benzofurans, and indoles, respectively.

Keywords: Asymmetric catalysis by chiral base · Cycloaddition · Dearomatization · Hydroarylation · Vinylidene *ortho*-quinone methide

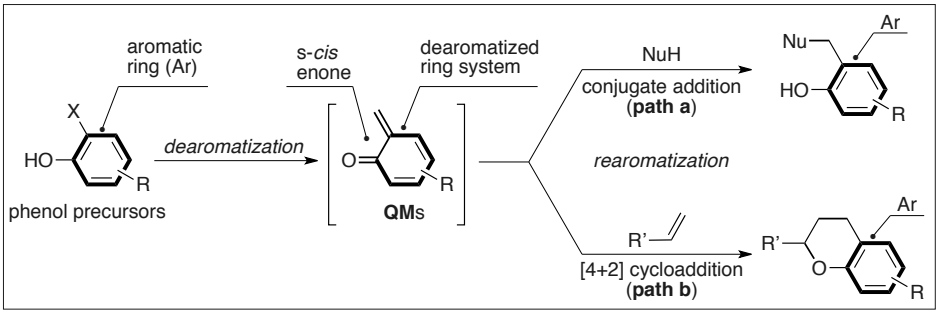
Ryo Irie was born in Fukuoka, Japan in 1967. He received his PhD in 1995 from Kyushu University, Japan, under the supervision of the late Professor Tsutomu Katsuki. He began his career as an assistant professor at Kyushu University in 1992 and was promoted to an associate professor there in 2003. During this time, he joined the lab of the late Professor Manfred Schlosser at Lausanne University in Switzerland as a postdoctoral researcher from 1996 to 1997. He achieved the rank of professor at Kumamoto University, Japan in 2007. His current research interests focus on the development of new catalytic enantioselective reactions for the asymmetric synthesis of chiral compounds with 'noncentral chirality'.

1. Introduction

ortho-Quinone methides (**QM**s) have long been known as versatile reaction intermediates and involved in many organic transformations, including those for chemical synthesis, biosynthesis, and chemical biology.[1] This is a result not only of the convenient generation of **QM**s through dearomatization of the corresponding phenol derivatives, but also their high reactivity (Scheme 1). Namely, **QM**s comprise a carbonyl and methylene group attached to a dearomatized ring system and accordingly serve as excellent Michael acceptors that readily undergo conjugate addition reactions with a variety of nucleophiles, owing to the driving force for rearomatization (**path a** in Scheme 1). Furthermore, the exocyclic enone substructure fixed to an s-*cis* conformation permits **QM**s to play the role of an electrophilic heterodiene in inverse-electron-demand [4+2] cycloadditions with electron-rich dienophiles, restoring the aromatic ring (**path b** in Scheme 1).

In contrast to the well-investigated **QM**s,[1] their one-carbon elongated homologues, vinylidene *ortho*-quinone methides (**VQM**s), have been far less studied (Scheme 2). **VQM**s are characterized by an exocyclic allenyl ketone unit and quite distinct from **QM**s in terms of stereochemistry. Unlike **QM**s, **VQM**s can be rendered

*Correspondence: Prof. R. Irie[a]
E-mail: irie@kumamoto-u.ac.jp
[a]Department of Chemistry
Faculty of Advanced Science and Technology
Kumamoto University
Kurokami 2-39-1, Chuo-ku, Kumamoto 860-8555, Japan
[b]Department of Chemistry
Graduate School of Science and Technology
Kumamoto University
Kurokami 2-39-1, Chuo-ku, Kumamoto 860-8555, Japan
[c]Institute for Materials Chemistry and Engineering,
Kyushu University,
6-1 Kasuga-koen, Kasuga, Fukuoka 816-8580, Japan



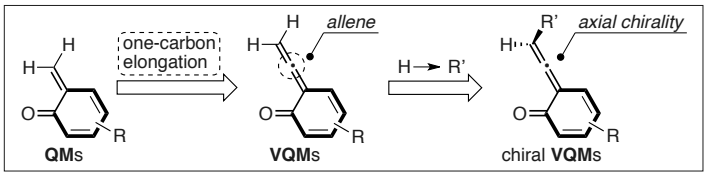
Scheme 1. *ortho*-Quinone methides (**QM**s): Outline of preparation and reactivity.

axially chiral by locating a substituent properly at the terminal methylene group of the allene moiety. Furthermore, **VQM**s are tautomers of *ortho*-ethynylphenols (Scheme 3). Focusing on these stereochemical and structural features, we envisioned the development of unprecedented asymmetric reactions involving enantioenriched **VQM** intermediates generated by enantioselective tautomerization of the ethynylphenol precursors with a chiral catalyst and the stereocontrolled follow-up reactions.

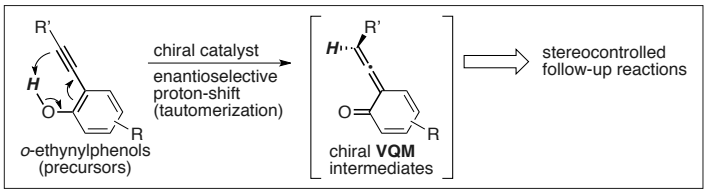
At the outset of the study, there were only a few reports on the manipulation of **VQM**s for non-asymmetric synthesis.[2] Youngs and co-workers first proposed the involvement of a **VQM** intermediate (**I**) in the tandem one-pot bicyclization of **A** and **B** to **C** (Scheme 4a):[2a] the primary product from the double Sonogashira coupling of **A** and **B** underwent a rapid proton-shift[3] to provide **VQM** (**I**) followed by intramolecular inverse-electron-demand [4+2] cycloaddition with the adjacent alkyne, leading to **C**. A photochemical method for generating **VQM**s was also disclosed by Freccero and co-workers.[2b] They induced an excited-state intramolecular proton-transfer (ESIPT) process in simple *ortho*-ethynylphenols by UV-irradiation to obtain the corresponding **VQM**s,[4] which were reactive to external nucleophiles. For example, **VQM** (**II**), converted from **D** by ESIPT, underwent intermolecular conjugate addition by $^{n}PrNH_2$ to primarily afford the enamine, which was finally transformed to imine **E** through tautomerization (Scheme 4b). On the other hand, a different approach based on a thermal acyl transfer to generating a **VQM** was reported by Vedejs and co-workers.[2c] They implied that the *O*-acetyl group in starting material **F** was transferred to the alkyne moiety at high temperature,[5] leading to the formation of **VQM** (**III**), which further underwent formal [4+1] cycloaddition to produce phospha-heterocycle **G** (Scheme 4c).

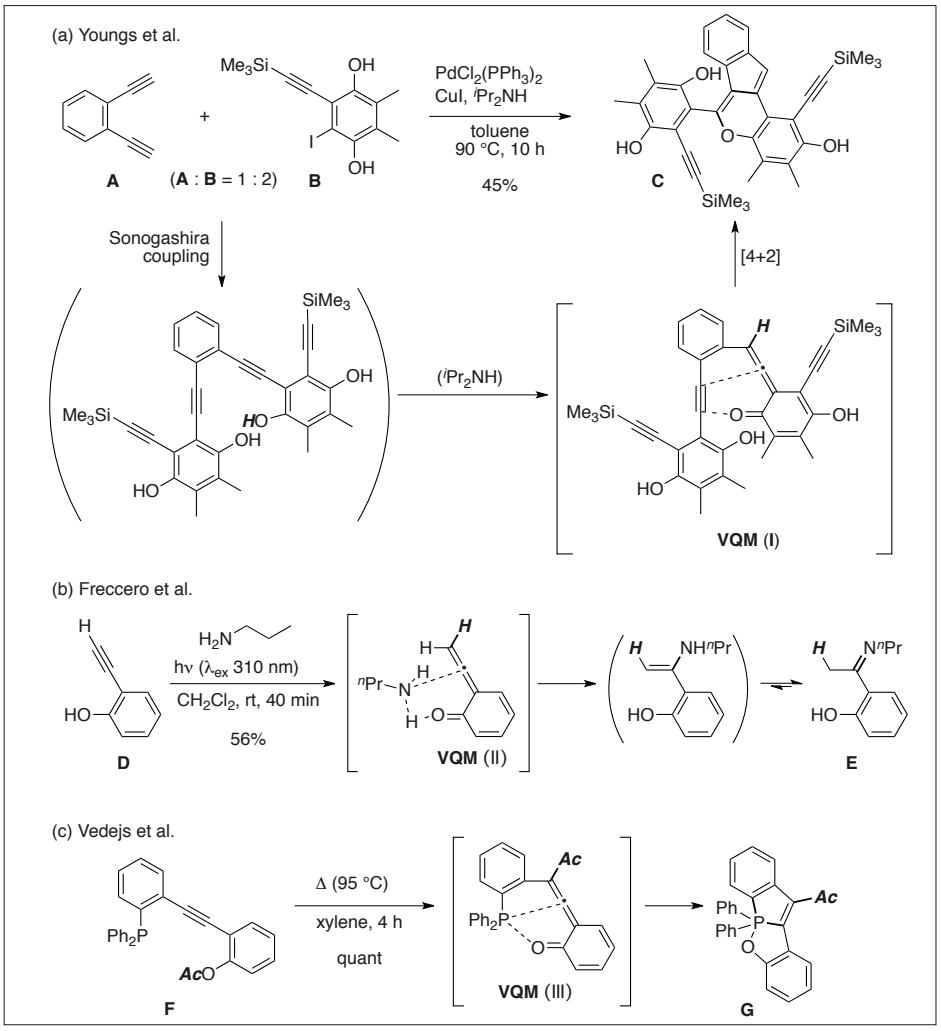
Among these precedented methods to generate **VQM**s,[6] the most interesting was in the proton-shift with a base catalyst that was implicated in Youngs' report.[2a] The potential base catalysis was more clearly shown in the course of our separate study on the Pd-catalyzed tandem cyclodehydrogenation[7] of *ortho*-phenylene-linked bis(naphthol) **H** to oxa-heterohelicene **I** (Scheme 5, **path a**). In this system, a side reaction to afford indeno[1,2-*c*]chromene **J**, which was reasonably ascribed to the simple base-catalyzed generation of a **VQM** intermediate **IV** from **H**, was also noted (Scheme 5, **path b**).[7b] This preliminary result encouraged us to launch the systematic research on the chiral-base-catalyzed enantioselective proton-shift of the ethynylnaphthol to manipulate the enantioen-

Scheme 2. Vinylidene *ortho*-quinone methides (**VQM**s): Structural motif and axial chirality.

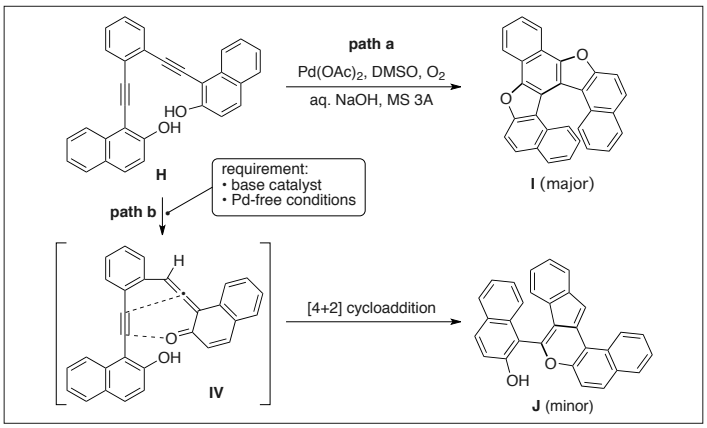


Scheme 3. Hypothetical profile of the enantioselective generation of chiral **VQM**s and their stereocontrolled follow-up reactions.





Scheme 4. Precedented reports on the synthetic potential of **VQM**s.



Scheme 5. Involvement of a **VQM** intermediate in the unexpected formation of **J** from **H**.

riched **VQM** intermediate thus generated for the following stereocontrolled intramolecular cyclizations. Indeed, commonly used chiral base catalysts such as cinchonine (**CN**) and cinchonidine (**CD**) have been demonstrated to be effective to this end.[8] In this account, we wish to briefly describe our recent studies on the asymmetric syntheses of optically active indeno[1,2-*c*]chromenes,[7c,9a] benzofuro[3,2-*b*]indeno[1,2-*c*]chromenes,[7c,9b] and benzo[*a*]carbazoles[9c] based on the catalytic enantioselective generation of **VQM**s with **CN** or **CD** and the stereocontrolled intramolecular follow-up cyclization with tethered alkynes, benzofurans, and indoles, respectively (Fig. 1).

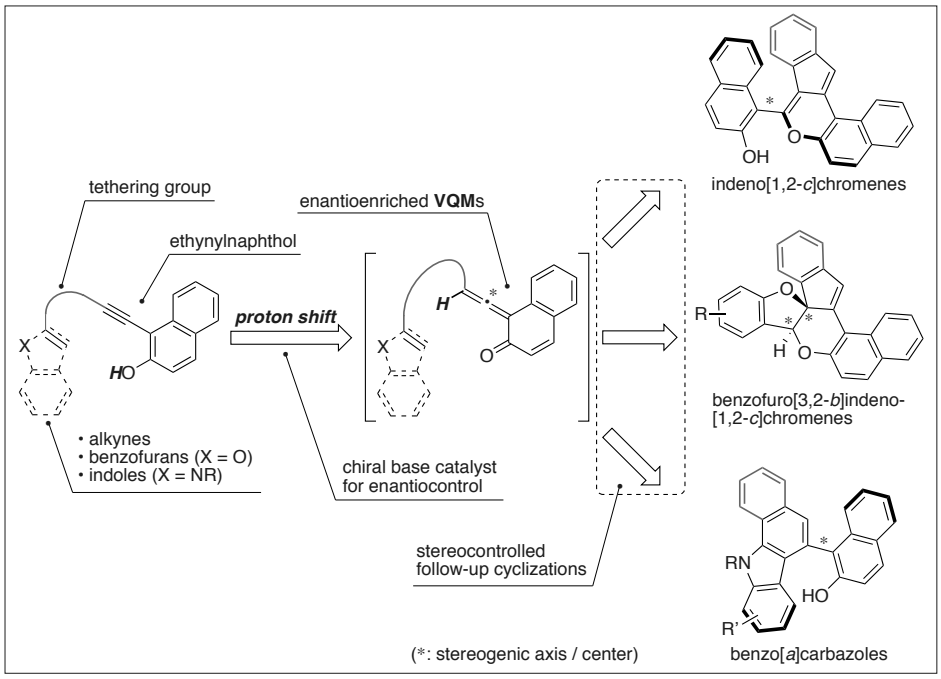


Fig. 1. Strategy for **VQM**-mediated catalytic asymmetric synthesis. Asterisks (*) indicate the stereogenic axis and centers.

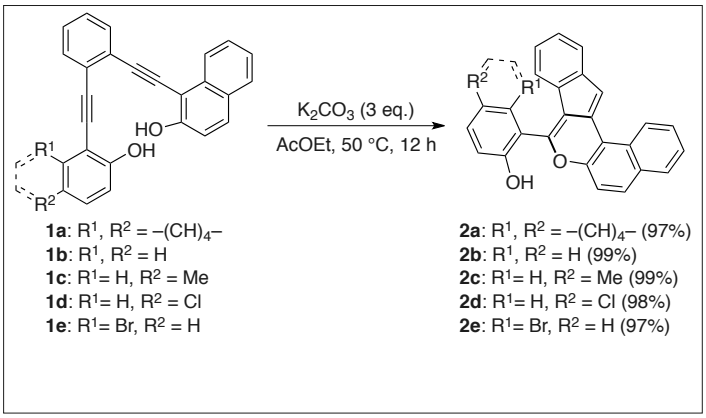
2. Asymmetric Synthesis of Indeno[1,2-*c*]chromenes with Axial Chirality[9a]

Following the unexpected results shown in Scheme 5, we examined various bases to effect the selective **VQM**-mediated cyclization. Consequently, the treatment of **1a** (≡ **H** in Scheme 5) with K_2CO_3 in AcOEt very effectively provided indeno[1,2-*c*]chromene **2a** (≡ **J** in Scheme 5) as the sole product in 97% yield (Scheme 6). Related unsymmetrical substrates **1b–e** bearing ethynylnaphthol and ethynylphenol units were also transformed into the corresponding products **2b–e**, respectively, all in excellent yields (97–99%).

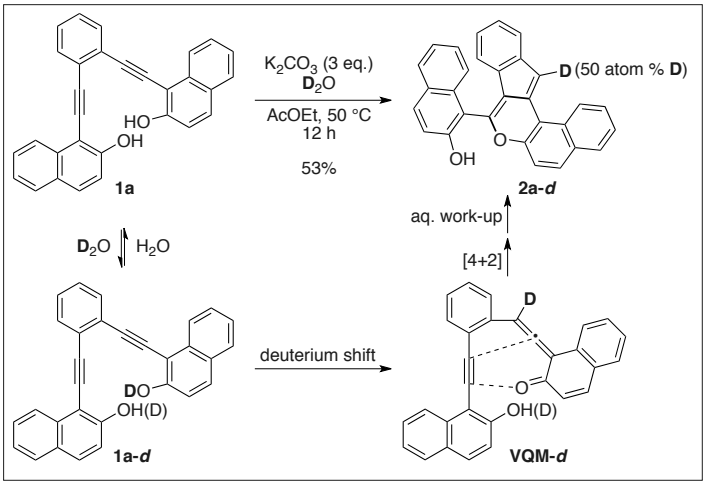
The involvement of a **VQM** intermediate in the cyclization of **1a** to **2a** was supported by a deuterium-labeling experiment. When the reaction was carried out in the presence of D_2O, the deuterated product, **2a-*d*** with 50 atom % **D**, was obtained (Scheme 7). This can be ascribed to the preformation of the *O*-deuterated **1a-*d*** upon H–D exchange of **1a**, followed by the deuterium shift to generate the *C*-deuterated **VQM-*d***, which would undergo intramolecular [4+2] cycloaddition with the tethered alkyne to provide **2a-*d***.

We further attempted to render the reaction catalytic and identified Et_3N to be an effective catalyst: treatment of **1a** with 10 mol % of Et_3N in $CHCl_3$ at room temperature for 24 h provided **2a** in 96% (Scheme 8). It should be also noted that **2a** is axially chiral and stereochemically stable enough not to suffer from racemization at room temperature. Thus, we surveyed various chiral amines for the catalytic asymmetric cyclization of **1a** and found that the common cinchona alkaloids, including cinchonine (**CN**), cinchonidine (**CD**), quinidine (**QD**), and quinine (**QN**), displayed moderate levels of enantioselectivity (Scheme 8). For example, **CN** was used as the chiral base catalyst (10 mol %) to obtain (–)-**2a** in 60% ee and 90% yield.[10] This should indicate that **CN** converts **1a** to an enantioenriched VQM followed by the stereocontrolled cyclization, leading to the formation of **2a** with the axial chirality defined by that of the **VQM**. Notably, the *O*-acetyl derivative of **CN** (**CN-OAc**) showed much lower catalytic activity and enantioselectivity (40% yield, 32% ee), implying that besides the tertiary amino group, the secondary hydroxy group of **CN** may play a pivotal role in the enantioselective **VQM**-generating step.[7c]

Scheme 6. Base-promoted cyclization of **1** to **2**.



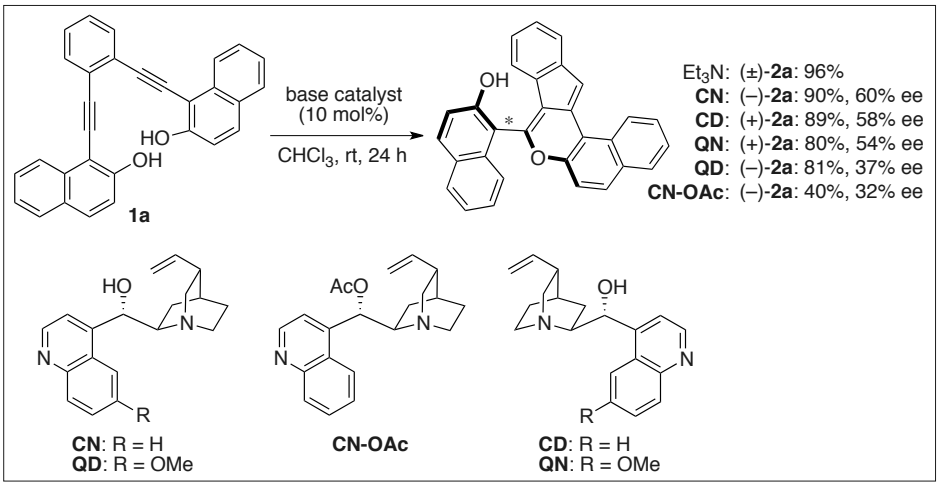
Scheme 7. Deuterium-labeling experiment to provide an insight into the reaction mechanism.



3. Asymmetric Synthesis of Benzofuro[3,2-*b*]indeno[1,2-*c*] chromenes[9b]

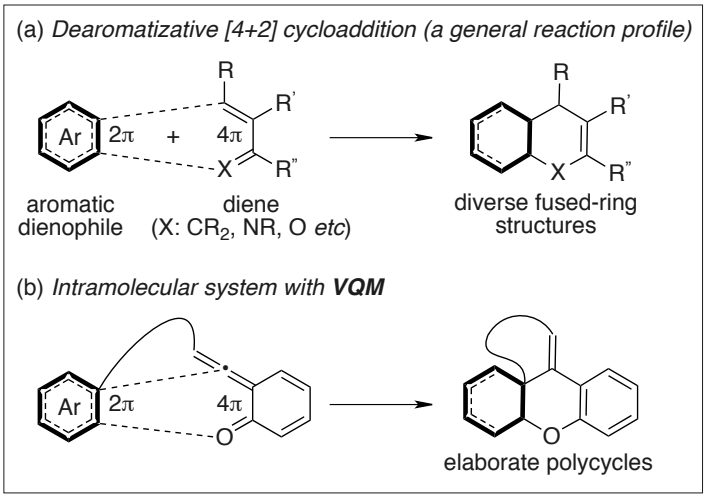
Catalytic enantioselective dearomatizative [4+2] cycloaddition is synthetically highly attractive as a route to the construction of diverse, chiral cyclic structures with a fused six-membered ring, increasing molecular complexity.[11] We are particularly interested in variations of aromatic double bonds (2π synthons) and dienes (4π synthons), which have been less explored and remain formidable challenges (Scheme 9a).

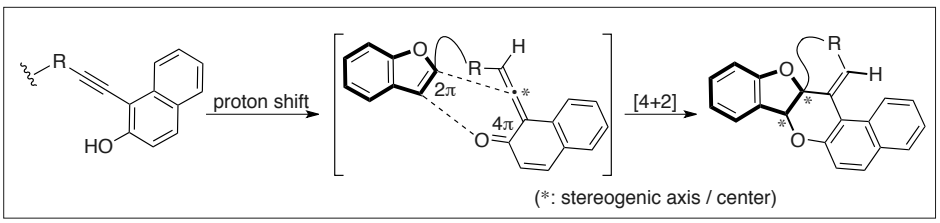
Dearomatization is usually an energetically disfavored process, and the dienes should be reactive enough to compensate for this drawback. **QM** is one of such dienes, and benefits reactions with electron-rich arenes due to its electrophilic nature.[1] Thus, it was conceived that tethering a **VQM** to a nucleophilic aryl group would allow the stereocontrolled intramolecular inverse-electron-demand [4+2] cycloaddition to assemble elaborate chiral polycyclic structures otherwise difficult to access (Scheme 9b).[12] On the basis of this working hypothesis, linked ethynylnaphthol-benzofuran systems were designed for the chiral-base-catalyzed generation of **VQM**s and the follow-up dearomatizative cycloadditions to provide enantioenriched densely-fused oxa-polyheterocyclic compounds with consecutive quaternary and tertiary asymmetric carbon atoms (Scheme 10).[13]



Scheme 8. Catalytic asymmetric cyclization of **1a** to **2a** with common cinchona alkaloids, including cinchonine (**CN**), cinchonidine (**CD**), quinine (**QN**), quinidine (**QD**), and *O*-acetyl cinchonine (**CN-OAc**), as chiral bases.

Scheme 9. Dearomatizative [4+2] cycloaddition to manipulate aromatic double bonds as dienophiles (2π synthons) with dienes (4π synthons).





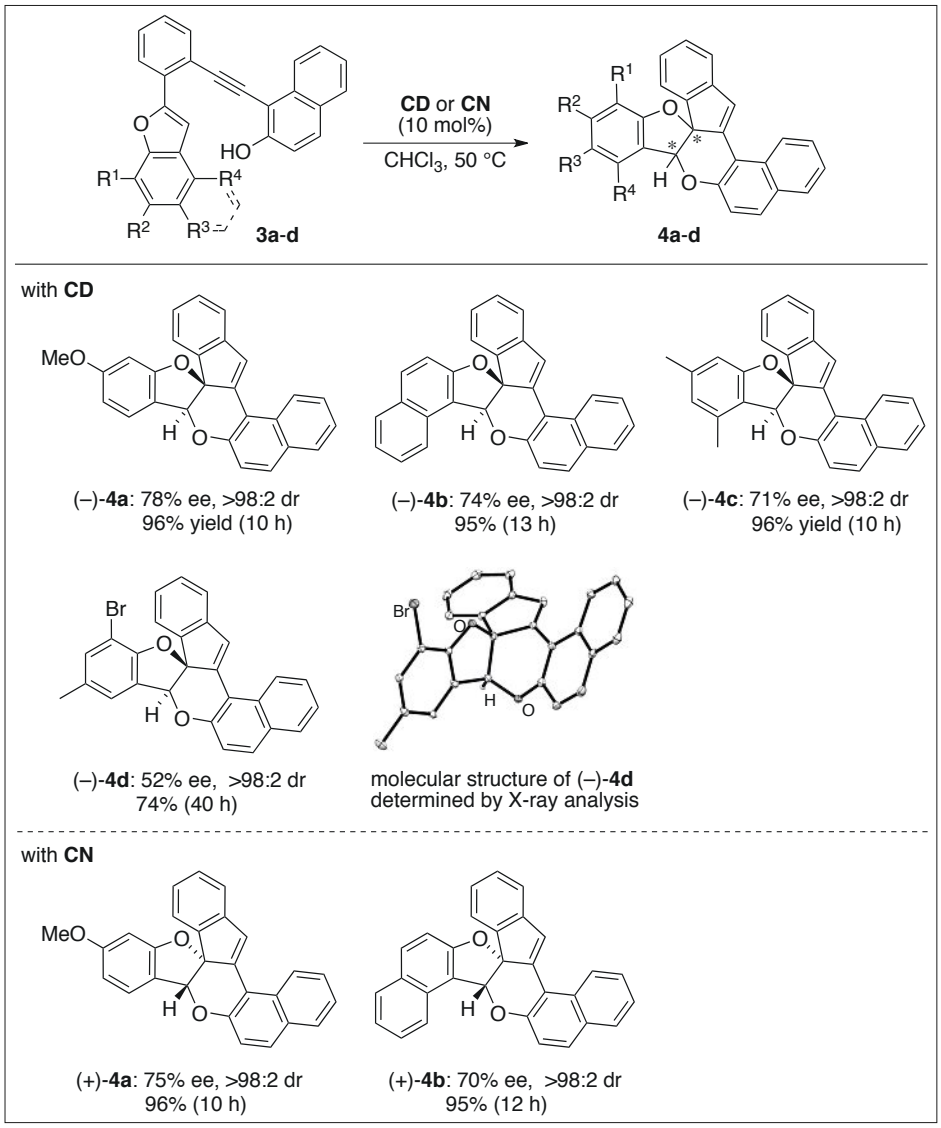
Scheme 10. **VQM**-mediated intramolecular dearomatizative [4+2] cycloaddition of benzofurans.

Indeed, we treated *ortho*-phenylene-linked ethynylnaphthol-benzofurans **3a**, **3b**, **3c**, and **3d** with **CD** (10 mol %) in $CHCl_3$ at 50 °C and obtained the enantioenriched benzofuro[3,2-*b*]indeno[1,2-*c*] chromene derivatives,[14] (–)-**4a** (78% ee), (–)-**4b** (74% ee), (–)-**4c** (71% ee), and (–)-**4d** (52% ee), respectively, as single diastereomers in good to high yields (Scheme 11).[15] The absolute configuration of (–)-**4d** was unambiguously determined to be (*S*,*S*) by X-ray crystallography and the same stereochemical assignment has been tentatively applied to the other levorotatory products. Furthermore, **CN** also served as an effective catalyst, converting **3a** and **3b** to the opposite enantiomers, (+)-**4a** (75% ee) and (+)-**4b** (70% ee), respectively.

The involvement of a **VQM** intermediate was supported by DFT calculations on the reaction pathway from simple substrate **3e** with a basic benzofuran ring to **4e** (Fig. 2). Furthermore, the follow-up intramolecular [4+2] cycloaddition was calculated to proceed through a concerted but asynchronous transition state, in which C(2) (benzofuran)–C_{sp} (**VQM**) bond formation precedes C(3)–O bond formation (C(2)–C_{sp} 1.97 Å vs. C(3)–O 2.72 Å). On the basis of the experimental and theoretical outcomes (Scheme 10 and Fig. 2), a chirality-relay mechanism for the stereochemical course of the enantioselective cyclization from **3** to **4** is postulated (Scheme 12): (i) the enantioselective proton-shift of **3** to generate the enantioenriched **VQM** intermediate with an a_1S configuration at the allene moiety by using **CD** and with an a_1R configuration by using **CN**, respectively; (ii) the axial chirality of a_1 defines that of a_2 at the benzofuran moiety to set up the (a_1S,a_2S)- or (a_1R,a_2R)-**VQM**, which leads to the proper transition state for the [4+2] cycloaddition (see Fig. 2); and (iii) the **VQM** adds across the furan C(2)–C(3) double bond in a stereospecific *syn* fashion to determine the absolute configurations at the two consecutive asymmetric carbon atoms of the final product, producing (*S*,*S*)-**5** from (a_1S,a_2S)-**VQM** and (*R*,*R*)-**5** from (a_1R,a_2R)-**VQM**.

4. Asymmetric Synthesis of Axially Chiral Benzo[*a*]carbazoles[9c]

It should be noted that although the treatment of **3** with a base catalyst mostly produces **4**, it occasionally yields minor byproduct **5** through C(3)–C_{sp} (**VQM**) bond formation (Scheme 13, X = O).[9b] This alternative reaction is formally the electrophilic aromatic substitution of the benzofuran. Despite its limited availability, **5** was fascinating due to its unique



Scheme 11. Catalytic asymmetric dearomatizative [4+2] cycloaddition of **3** to **4** catalyzed by **CD** or **CN**.

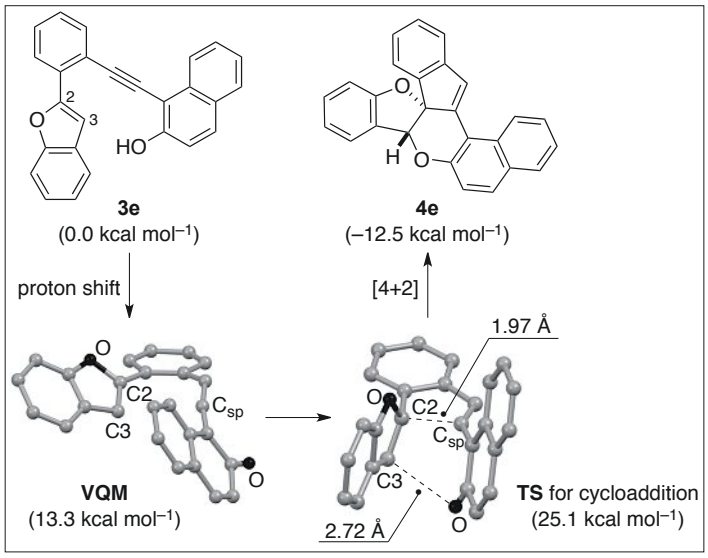


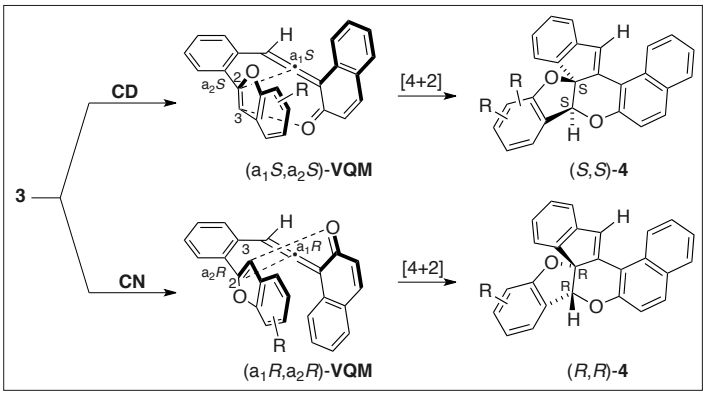
Fig. 2. Energy diagram for the reaction of **3e** to **4e**.

stereochemical feature, axial chirality. Thus, we addressed the development of a new **VQM** system to permit the catalytic asymmetric synthesis of axially chiral compounds related to **5**. Benzofuran generally reacts with an electrophile at the C(2) position rather than the C(3) position, as described above,[16] which explains why **VQM**s derived from **3** basically prefer the formation of **4** over **5**. In contrast, the isoelectronic 1*H*-indole is in general more reactive at the C(3) position.[15] 1*H*-Indole is also distinct from benzofuran in that it displays lower reactivity in dearomatization reactions, owing to its larger aromatic stabilization energy.[17] We accordingly conceived that a chiral **VQM** intermediate from **6**, the indole counterpart of **3**, should result in electrophilic aromatic substitution at the C(3) position, that is, hydroarylation of alkynes with indoles, to afford the axially chiral benzo[*a*]carbazoles **7** (Scheme 13, X = NR).[18–21]

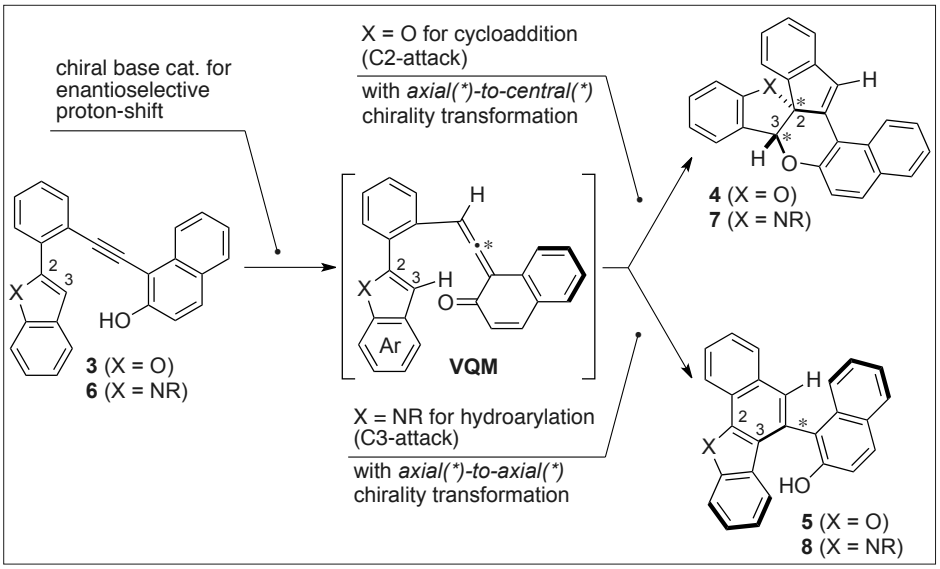
The working hypothesis on the regioselectivity was proven by using an achiral base. The treatment of benzofuran **3a** with 10 mol % of NEt_3 afforded **4a** in 68% yield along with **5a** in 23% yield (Scheme 14, X = O). In sharp contrast, the reaction of 1*H*-indole **6a** (X = NH) under similar conditions produced **8a** in 93% yield without any trace of **7a** (Scheme 14, X = NH). It is also remarkable that **8a** is stereochemically stable enough for optical resolution by chiral HPLC at room temperature. Its energy barrier to racemization was determined to be 38.8 kcal/mol by kinetic analysis.

Next the enantioselective transformation of **6a** by using **CD** as a chiral base catalyst in CH_2Cl_2 was attempted (Table 1). Disappointingly, (–)-**8a** was obtained with low enantioselectivity (20% ee), although the reaction proceeded under very mild conditions in high yield (95%) (entry 1). In contrast, it was found that enantioselectivity was dramatically enhanced for *N*-methyl indole **6b**, which gave (–)-**8b** in 95% ee and 93% yield (entry 2). The high enantioselectivity and chemical yield (94% ee, 97%) were also attained with only 1 mol % of catalyst, despite requiring a longer reaction time (entry 3). Furthermore, a gram-scale synthesis of (–)-**8b** was successfully demonstrated without decay of the enantioselectivity and chemical yield (entry 4). **CN** was also an effective catalyst, converting **6b** to enantiomeric product (+)-**8b** in 90% ee and 94% yield (entry 5). The treatment of related indoles **6c**–**g** having different *N*-substituents with **CD** also produced the highly enantioenriched products **8c**–**g**, respectively (90–95% ee, 94–97% yields, entries 6–10). In addition, *N*-methyl derivatives **6h**–**k** with various substituents on the indole ring underwent hydroarylation to provide **8h**–**k** in very high enantioselectivities (94–96% ee) and chemical yields (95–96%) (entries 11–14).

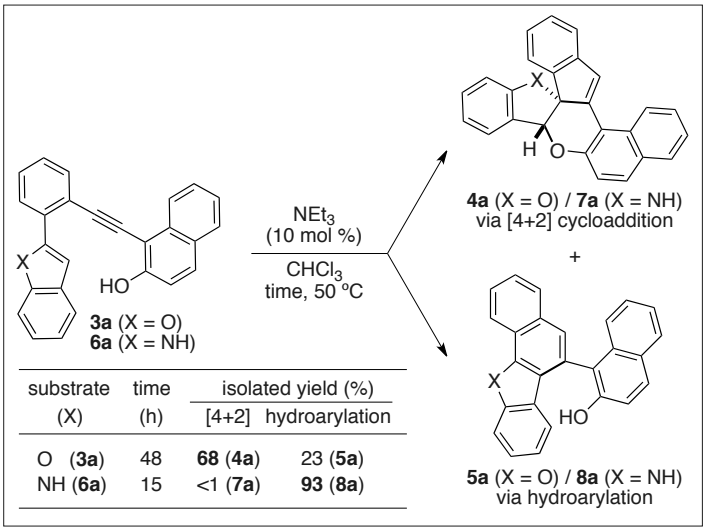
On the other hand, whereas **6l** (R^2, R^4 = Me) was converted to highly enantioenriched **8l** (82% yield, 96% ee), significant formation of by-product **7l** (14% yield, 64% ee) was also observed (entry 15, Fig. 3). Similarly, **6m** (R^2 = OMe) furnished a mixture of **8m** (48 yield, 96% ee) and **7m**



Scheme 12. Plausible stereochemical courses of the asymmetric cycloaddition of **3** to **4**.



Scheme 13. Contrasting cyclization pathways of benzofurans **3** (cycloaddition) and indoles **6** (hydroarylation).



substrate (X)	time (h)	isolated yield (%) [4+2]	isolated yield (%) hydroarylation
O (**3a**)	48	**68** (**4a**)	23 (**5a**)
NH (**6a**)	15	<1 (**7a**)	**93** (**8a**)

Scheme 14. NEt_3-catalyzed hydroarylation of benzofuran **3a** and indole **6a**.

(41% yield, 23% ee, entry 16). These results are ascribed to the electron-donating effects of the R^2 and R^4 substituents, which increase the nucleophilicity of the C(2) carbon atom of the indole ring, thereby prompting the dearomatizative cycloaddition pathway to furnish **7**.

The absolute configurations of (–)-**8b**, (+)-**8e**, and (–)-**8h** were all determined to be S_a by X-ray crystallographic analysis, regardless of their signs of specific rotation. This indicates that, as is the case for the furan system **3**, **CD** and **CN** convert the indole system **6** to the enantioenriched **VQM** intermediate with an absolute configuration of S_a and R_a, respectively (Scheme 15). The follow-up intramolecular electrophilic aromatic substitution, including the two steps of the C–C bond-forming addition reaction and the proton migration, should proceed in a stereospecific fashion to produce enantioenriched **8**, the axial chirality of which is defined by that of the **VQM**.

Notably, the present catalytic asymmetric hydroarylation can be performed under previously unknown transition-metal-free conditions.[19] Since benzo[*a*]carbazole is a conspicuous π-conjugated framework that exhibits remarkable physical characteristics,[22] this study provides a platform for the development of organic molecules with chiroptical properties, and suggests a significant impact in the field of materials science.[23]

5. Conclusion

This report introduces a unique method for catalytic asymmetric synthesis based on the enantioselective generation of axially chiral **VQM** intermediates and the stereocontrolled follow-up cyclization.[7c,9] Although **VQM**s had not been employed for asymmetric catalysis at the outset of our study,[2] they are currently being applied in various asymmetric transformations, including intramolecular [4+2] cycloadditions.[9a–c,10,15] alkyne hydroarylations,[9d] and intermolecular Michael additions,[24] which will rapidly expand their synthetic utility. Further investigations are in progress in our laboratory to discover new **VQM**-mediated asymmetric transformations, clarify their reaction mechanisms, and develop their applications for the synthesis of useful chiral functional materials.

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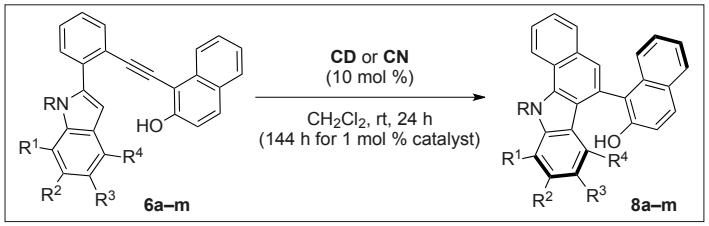
[4] **VQM**s are only detectable by laser flash photolysis in dry organic solvents.

[5] The acyl-transfer may be promoted by the internal phosphine and proceed through an acyl phosphonium intermediate as suggested by the authors.

Table 1. Enantioselective hydroarylation of indoles **6** with **CD** or **CN** as a chiral base catalyst[a]



Entry	Substrate	Catalyst	R_N	R^1	R^2	R^3	R^4	Product	Yield [%]	Ee [%]
1	**6a**	**CD**	H	H	H	H	H	(–)-**8a**	97	20
2	**6b**	**CD**	Me	H	H	H	H	(S_a)-(–)-**8b**	93	95
3[b]	**6b**	**CD**	Me	H	H	H	H	(S_a)-(–)-**8b**	97	94
4[c]	**6b**	**CD**	Me	H	H	H	H	(S_a)-(–)-**8b**	92	95
5	**6b**	**CD**	Me	H	H	H	H	(R_a)-(+)-**8b**	94	90
6	**6c**	**CD**	Et	H	H	H	H	(–)-**8c**	97	94
7	**6d**	**CD**	MOM	H	H	H	H	(+)-**8d**	95	95
8	**6e**	**CD**	Bn	H	H	H	H	(S_a)-(+)-**8e**	97	90
9	**6f**	**CD**	PMB	H	H	H	H	(+)-**8f**	94	91
10	**6g**	**CD**	Ph	H	H	H	H	(+)-**8g**	95	91
11	**6h**	**CD**	Me	Cl	H	Cl	H	(S_a)-(–)-**8h**	96	94
12	**6i**	**CD**	Me	H	H	Me	H	(–)-**8i**	95	96
13	**6j**	**CD**	Me	Me	H	H	H	(+)-**8j**	96	95
14	**6k**	**CD**	Me	Me	H	Me	H	(+)-**8k**	96	96
15[d]	**6l**	**CD**	Me	H	Me	H	Me	(+)-**8l**	82	96
16[d]	**6m**	**CD**	Me	H	OMe	H	H	(+)-**8m**	48	96

[a]Reactions were carried out with **6** (0.1 mmol) and catalyst (10 mol %) unless otherwise mentioned. [b]Reaction was carried out with **CD** (1 mol%). [c]Reaction was carried out with **6b** (1.10 g, 3 mmol). [d]A significant amount of by-product from the intramolecular dearomatizative [4+2] cycloaddition was also obtained.

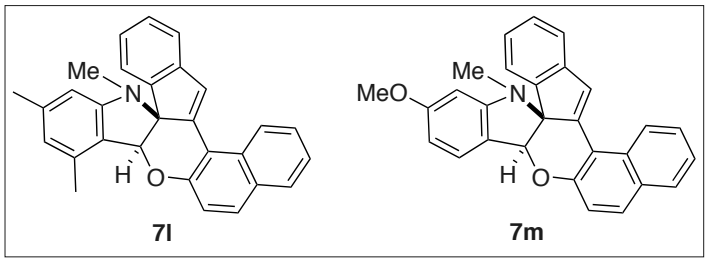
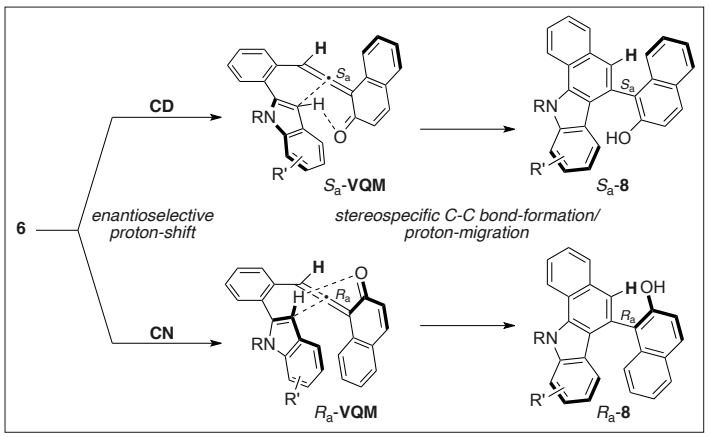


Fig. 3. Structures of **7l** and **7m**.



Scheme 15. Plausible stereochemical courses of the asymmetric hydroarylation of **6** to **8**.

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