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Catalytic Asymmetric (4+3) Cyclizations of In Situ Generated *ortho*-Quinone Methides with 2-Indolylmethanols

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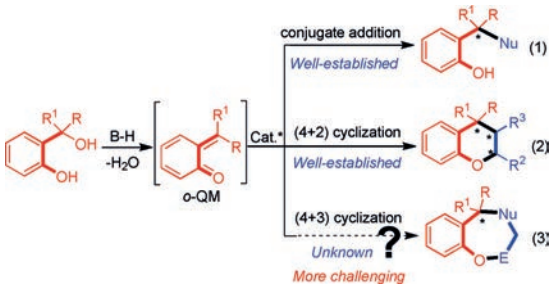
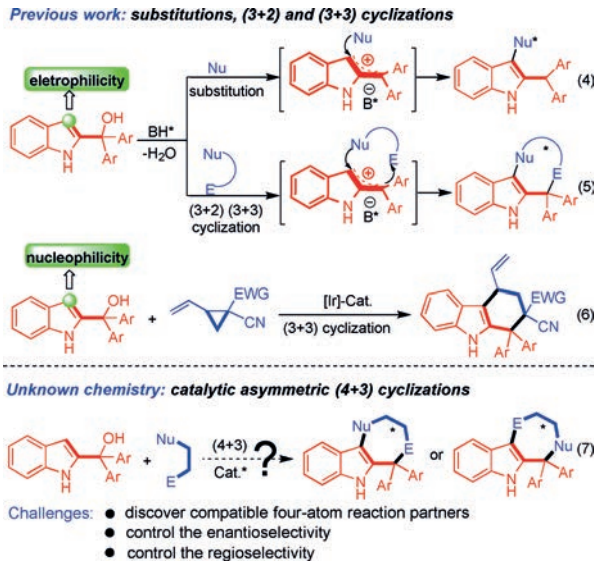
Abstract: *The first catalytic asymmetric (4+3) cyclization of in situ generated ortho-quinone methides with 2-indolylmethanols has been established, which constructed seven-membered heterocycles in high yields (up to 95%) and excellent enantioselectivity (up to 98%). This approach not only represents the first catalytic asymmetric (4+3) cyclization of o-hydroxybenzyl alcohols, but also enabled an unprecedented catalytic asymmetric (4+3) cyclization of 2-indolylmethanols. In addition, a scarcely reported catalytic asymmetric (4+3) cyclization of para-quinone methide derivatives was accomplished.*

Ortho-quinone methides (*o*-QMs) belong to a class of versatile building blocks, which have wide applications in catalytic asymmetric reactions for constructing chiral oxygen-containing frameworks.[1–3] Among them, *o*-hydroxybenzyl alcohols have recently been recognized as powerful precursors of *o*-QMs (Scheme 1), which can easily be transformed into *o*-QMs in the presence of a Brønsted acid (B-H).[4,5] Consequently, under the catalysis of chiral catalysts, a series of enantioselective conjugate additions[4] and (4+2) cyclizations[5] have been established [Scheme 1, Eq. (1),(2)]. However, in sharp contrast, catalytic asymmetric (4+3) cyclization of o-hydroxybenzyl alcohols remains unknown [Scheme 1, Eq. (3)]. More surprisingly, even racemic (4+3) cyclizations of *o*-hydroxybenzyl alcohols have scarcely been reported.[6] In fact, (4+3) cyclizations are much more challenging than (4+2) cyclizations owing to the unfavorable entropic factors and transannular interactions during the process of constructing seven-membered rings.[7,8] Therefore, it has become an urgent task to develop catalytic asymmetric (4+3) cyclizations of *o*-hydroxybenzyl alcohols. To fulfil this task, it is important to find a suitable three-atom reaction partner, which can react with *o*-hydroxybenzyl alcohols and be preferentially activated by chiral Brønsted acid to control the enantioselectivity.



Scheme 1. Catalytic asymmetric reactions involving *o*-hydroxybenzyl alcohols.

In recent years, indolylmethanols have been identified as competent three-atom synthons in catalytic asymmetric reactions, especially under chiral B-H catalysis.[9–12] Notably, our group has discovered that the C3-position of 2-indolylmethanols can display electrophilicity in the presence of chiral B-H compounds (Scheme 2), thereby undergoing enantioselective substitutions [Scheme 2, Eq. (4)],[13] as well as (3+2) and (3+3) cyclizations [Scheme 2, Eq. (5)].[14] Interestingly, we have recently discovered that the C3-position of 2-indolylmethanols can also display nucleophilicity under iridium catalysis to accomplish a racemic (3+3) cyclization [Scheme 1, Eq. (6)].[15] Despite these rapid devel-



Scheme 2. Profile of 2-indolylmethanol-involved reactions and challenges in catalytic asymmetric (4+3) cyclizations of 2-indolylmethanols.

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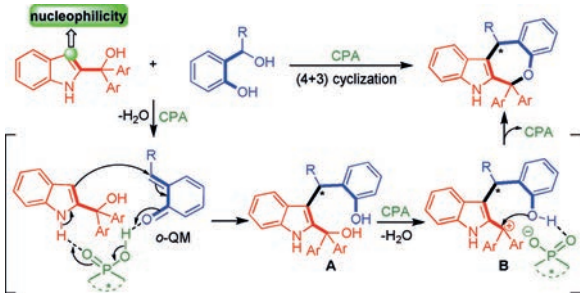
opments, catalytic asymmetric (4+3) cyclization of 2-indolylmethanols still remains unknown [Scheme 1, Eq. (7)]. This is because this transformation presents great challenges, including: 1) the discovery of compatible four-atom reaction partners to overcome unfavorable entropic factors and transannular interactions; 2) the selection of a suitable chiral catalyst to control the enantioselectivity; and 3) the finding of optimal reaction conditions to control the regioselectivity due to the multiple reactivity of the indole C3-position. Thus, it is also a formidable task to establish catalytic asymmetric (4+3) cyclizations of 2-indolylmethanols.

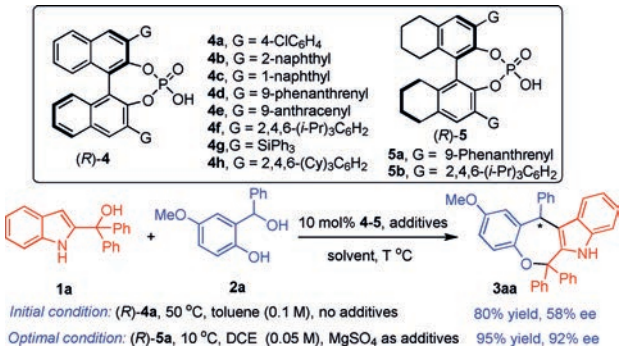
To accomplish these tasks, we considered whether 2-indolylmethanols could act as suitable three-atom reaction partners to perform catalytic asymmetric (4+3) cyclizations with *o*-hydroxybenzyl alcohols under the catalysis of chiral phosphoric acid (CPA).[16] Based on this consideration and our previous experience,[17] we designed a CPA-catalyzed asymmetric (4+3) cyclization of *o*-hydroxybenzyl alcohols with 2-indolylmethanols. As illustrated in Scheme 3, *o*-hydroxybenzyl alcohol could readily be transformed into *o*-QM in the presence of CPA. If the C3-position of 2-indolylmethanol could exhibit nucleophilicity, it would attack the *o*-QM to generate intermediate **A** with a chiral center. During this process, CPA would activate both 2-



Scheme 3. Design of the catalytic asymmetric (4+3) cyclization. This represents the first catalytic asymmetric (4 + 3) cyclization of 2-indolylmethanols and the first catalytic asymmetric (4 + 3) cyclization of o-hydroxybenzyl alcohols.

indolylmethanol and *o*-QM through hydrogen-bonding interactions to control the enantioselectivity. Subsequent dehydration of intermediate **A** would give carbocation intermediate **B**, which would further undergo an intramolecular nucleophilic addition to accomplish the (4+3) cyclization.

On the basis of this design, we tried the reaction of 2-indolylmethanol **1a** with *o*-hydroxybenzyl alcohol **2a** in the presence of CPA **4a** (Scheme 4). Gratifyingly, the designed (4+3) cyclization indeed occurred to give seven-membered product **3aa** in a high yield of 80% and a moderate enantioselectivity of 58% *ee*. To improve the enantioselectivity, we performed condition optimization by screening CPAs **4**–**5**, additives, solvent, reaction temperature, and concentration (see the Supporting Information). Finally, using CPA **5a** as the catalyst and magnesium sulfate as additives, the (4+3) cyclization in dichloroethane (DCE) afforded product **3aa** in the highest yield of 95% and the best



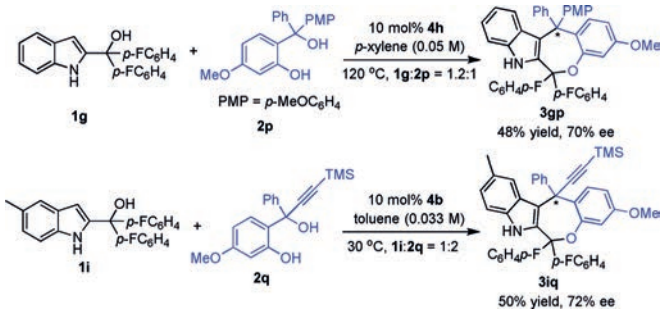
Scheme 4. Catalysts and model reaction employed for condition optimization.

enantioselectivity of 92% *ee*. It is worth noting that there was only a regioisomer (**3aa**) was observed.

After establishing the optimal reaction conditions, we examined the generality of the catalytic asymmetric (4+3) cyclization. As shown in Table 1, this reaction could be applicable to a wide range of 2-indolylmethanols **1** (entries 1–8) and *o*-hydroxybenzyl alcohols **2** (entries 9–22) bearing different substituents, generating products **3** with regiospecificity in high yields and excellent enantioselectivity. It is worth noting that 2-indolylmethanol **1h** bearing two alkyl groups (*i*-Pr) could serve as a suitable substrate to give product **3ha** in an acceptable yield and good enantioselectivity (entry 8). Notably, apart from aromatic groups (entries 13–20), aliphatic groups such as methyl and *iso*-propyl groups could successfully serve as suitable R^3 groups for substrates **2**, which participated in the (4+3) cyclization in good yields and high enantioselectivity (entries 21–22).

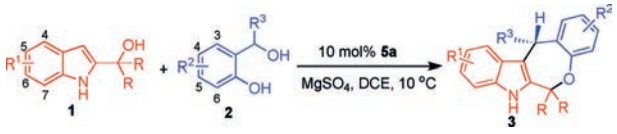
Moreover, disubstituted *o*-hydroxybenzyl alcohols **2p**–**2q** could participate in the catalytic asymmetric (4+3) cyclizations to give products **3gp** and **3iq**, which bear an all-carbon quaternary stereogenic center in moderate yields and considerable enantioselectivities (Scheme 5)

To expand the applicability of the reaction, we investigated whether *ortho*-hydroxyphenyl-substituted *para*-quinone methides (*p*-QMs) **6** could be utilized as four-atom reaction partners to perform (4+3) cyclizations with 2-indolylmethanols **1**. Although this class of *p*-QM derivatives (**6**) has been engaged in a series of catalytic asymmetric (4+2) and (4+1) cyclizations,[19] catalytic asymmetric (4+3) cyclizations of such reactants have rarely been reported.[20] It was calculated that *p*-QM derivatives **6** could be transformed into



Scheme 5. Using disubstituted *o*-hydroxybenzyl alcohols as substrates.

Table 1: Generality of the (4+3) cyclization between substrates **1** and **2**.[a]



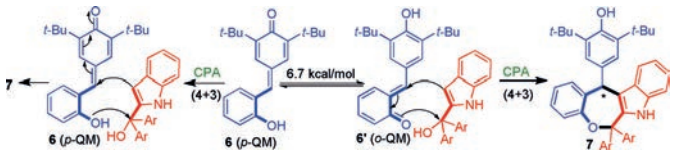
Entry	R^1/R (**1**)	R^2/R^3 (**2**)	**3**	Yield [%][b]	*ee* [%][c]
1	H/Ph (**1a**)	4-MeO/Ph (**2a**)	**3aa**	95	92
2	4-Me/Ph (**1b**)	4-MeO/Ph (**2a**)	**3ba**	42	90
3	5-Me/Ph (**1c**)	4-MeO/Ph (**2a**)	**3ca**	95	90
4	5-MeO/Ph (**1d**)	4-MeO/Ph (**2a**)	**3da**	95	92
5	5-F/Ph (**1e**)	4-MeO/Ph (**2a**)	**3ea**	95	92
6	5-Br/Ph (**1f**)	4-MeO/Ph (**2a**)	**3fa**	80	96
7	H/*p*-FC_6H_4 (**1g**)	4-MeO/Ph (**2a**)	**3ga**	95	98
8[d]	H/*i*-Pr (**1h**)	4-MeO/Ph (**2a**)	**3ha**	42	90
9	H/Ph (**1a**)	4-F/Ph (**2b**)	**3ab**	80	90
10	H/Ph (**1a**)	5-F/Ph (**2c**)	**3ac**	92	84
11	H/Ph (**1a**)	6-Me/Ph (**2d**)	**3ad**	86	84
12	H/Ph (**1a**)	H/Ph (**2e**)	**3ae**	95	90
13	H/Ph (**1a**)	H/*m*-$MeOC_6H_4$ (**2f**)	**3af**	95	90
14	H/Ph (**1a**)	H/*m*-FC_6H_4 (**2g**)	**3ag**	67	90
15	H/Ph (**1a**)	H/*m*-ClC_6H_4 (**2h**)	**3ah**	90	90
16	H/Ph (**1a**)	H/*p*-MeC_6H_4 (**2i**)	**3ai**	95	90
17	H/Ph (**1a**)	H/*p*-ClC_6H_4 (**2j**)	**3aj**	95	90
18[e]	H/Ph (**1a**)	4-MeO/*p*-$MeOC_6H_4$ (**2k**)	**3ak**	82	92
19	H/Ph (**1a**)	4-MeO/*p*-FC_6H_4 (**2l**)	**3al**	95	92
20[e]	H/Ph (**1a**)	4-MeO/*o*-MeC_6H_4 (**2m**)	**3am**	95	84
21	H/Ph (**1a**)	4-MeO/Me (**2n**)	**3an**	72	96
22	H/Ph (**1a**)	H/*i*-Pr (**2o**)	**3ao**	64	86

[a] Unless indicated otherwise, the reaction was carried out in 0.1 mmol scale in DCE (2 mL) with $MgSO_4$ (100 mg) for 20 h, and the molar ratio of **1**/**2** was 1.2:1. The absolute configuration of **3aa** was determined to be *S* by single-crystal X-ray analysis.[18] [b] Yield of isolated product. [c] The enantiomeric excess (*ee*) was determined by HPLC. [d] Performed at 40 °C in toluene (4 mL) without $MgSO_4$, and the molar ratio of **1h**/**2a** was 1:1.2. [e] Using toluene (4 mL) as solvent.

o-QMs **6′** due to the small isomerization energy.[19d] It is thus reasonable that substrates **6** can serve as precursors of *o*-QMs to carry out an enantioselective (4+3) cyclization with 2-indolylmethanols **1** under the catalysis of CPA (Scheme 6).

Based on this design, we tried the reaction of 2-indolylmethanol **1a** with *p*-QM derivative **6a** under the promotion of CPA **4a** (Scheme 7). As expected, the desired (4+3) cyclization product **7aa** was generated with regiospecificity and in high yield, albeit in an almost racemic form. The subsequent elaboration of reaction conditions (see the Supporting Information) ultimately led to excellent enantioselectivity of 92 % *ee* with a high yield of 95 %.

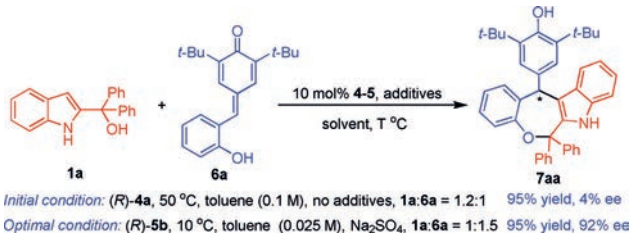
Under the optimal reaction conditions, the applicability of the cyclization between substrates **1** and **6** was investigated (Table 2). The reaction demonstrated a wide scope in terms of substrates **1** and **6**, delivering products **7** with regiospecificity



Scheme 6. Design of (4+3) cyclization using substrates **6** as *o*-QM precursors.

in good yields (55–95 %) and high enantioselectivity (80–98 %).

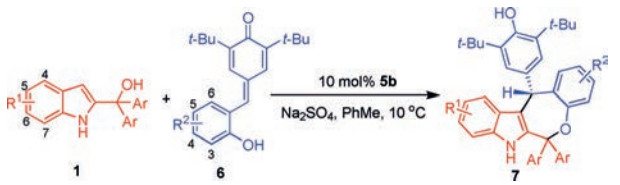
To gain some insight into the reaction mechanism, we performed some control experiments (Scheme 8). First, to investigate the role of N-H group in 2-indolylmethanols, we employed *N*-methyl-protected 2-indolylmethanol **1r** as a substrate in the reactions with *o*-QM precursors **2a** and **6a**, respectively. In the first case, no reaction occurred [Scheme 8, Eq. (8)]. In the second case, although the (4+3) cyclization occurred, product **7ra** was generated in an extremely low yield of 20 % with a moderate enantioselectivity of 64 % *ee* [Scheme 8, Eq. (9)]. These results indicated that the N-H group of 2-indolylmethanols played an important role in controlling the reactivity and the enantioselectivity via forming a hydrogen bond with CPA. Then, to study the possible reaction pathway, we monitored the reaction of **1a** with **6a** under the standard conditions [Scheme 8, Eq. (10)]. It was found that a small amount of product **7aa** was generated within one hour (25 % yield, 95 % *ee*). At the same time, a substantial amount of compound **8** was yielded (47 % yield, 78 % *ee*). We conceived that compound **8** might be an intermediate product toward the formation of final product **7aa** via dehydration. To test this hypothesis, compound **8** with 78 % *ee* was subjected to the standard reaction conditions for 20 h [Scheme 8, Eq. (11)]. As expected, most of compound **8** was transformed into final product **7aa** with a small amount of recovered **8**, which demonstrated that compound **8** was indeed an intermediate of the (4+3) cyclization.



Scheme 7. Model reaction employed for condition elaboration.

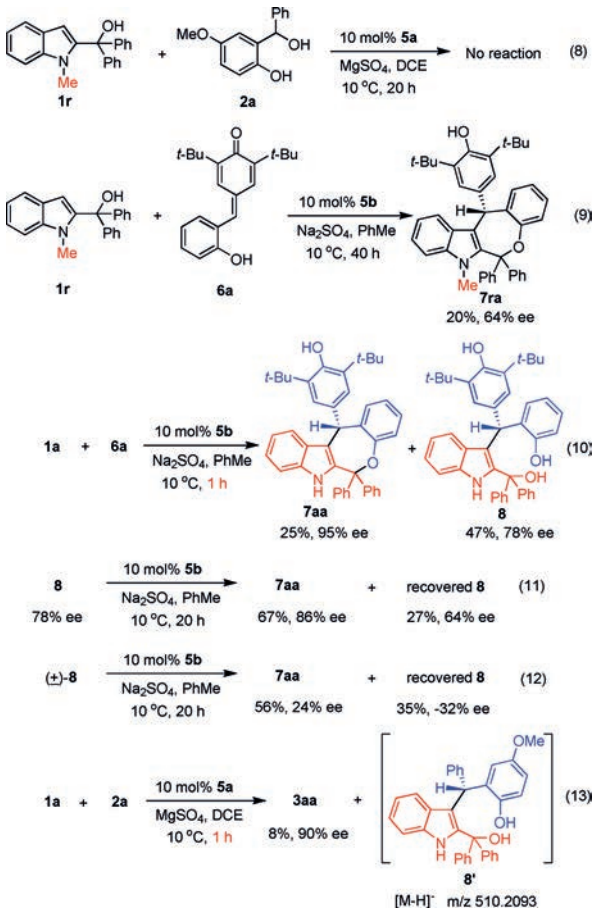
Very interestingly, in this transformation, the enantioselectivity of **7aa** was increased to 86 % *ee*, while that of recovered **8** was decreased to 64 % *ee*, which implies that there might be a kinetic resolution during this process. To confirm this assumption, racemic **8** was subjected to the standard conditions for 20 h [Scheme 8, Eq. (12)], which afforded product **7aa** in 56 % yield with 24 % *ee*. More importantly, *ent*-**8** was recovered in 35 % yield with 32 % *ee*, thus verifying that there was a moderate degree of kinetic resolution of **8** during the step of intramolecular cyclization. Notably, intermediate **8** was generated in a good enantioselectivity of 78 % *ee* via the first step of nucleophilic addition of 2-indolylmethanol **1a** to *o*-QM precursor **6a**; while in the second step, **7aa** was obtained with a low enantioselectivity of 24 % *ee* starting from

Table 2: Applicability of the (4+3) cyclization between substrates **1** and **6**.[a]

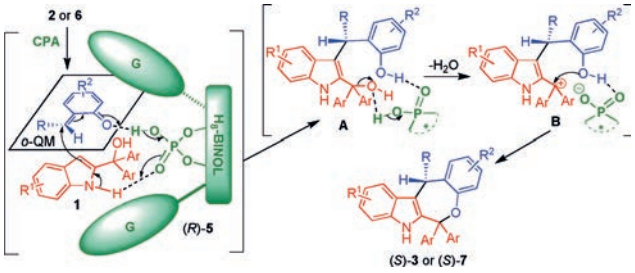


entry	R^1/Ar (**1**)	R^2 (**6**)	**7**	yield [%][b]	*ee* [%][c]
1	H/Ph (**1a**)	H (**6a**)	**7aa**	95	92
2	5-MeO/Ph (**1d**)	4-OMe (**6b**)	**7db**	82	92
3	5-F/Ph (**1e**)	H (**6a**)	**7ea**	92	94
4	5-Cl/Ph (**1j**)	H (**6a**)	**7ja**	87	96
5	5-Br/Ph (**1f**)	H (**6a**)	**7fa**	85	94
6	6-Cl/Ph (**1k**)	H (**6a**)	**7ka**	73	92
7	7-Br/Ph (**1l**)	H (**6a**)	**7la**	55	96
8	H/*p*-FC_6H_4 (**1g**)	H (**6a**)	**7ga**	95	90
9	H/*p*-ClC_6H_4 (**1m**)	H (**6a**)	**7ma**	76	96
10	H/*p*-MeC_6H_4 (**1n**)	H (**6a**)	**7na**	95	80
11[d]	H/*m*-FC_6H_4 (**1o**)	H (**6a**)	**7oa**	85	96
12	H/*m*-ClC_6H_4 (**1p**)	H (**6a**)	**7pa**	60	94
13	H/*m*-$MeOC_6H_4$ (**1q**)	H (**6a**)	**7qa**	90	98
14	H/Ph (**1a**)	4-MeO (**6b**)	**7ab**	86	96
15	H/Ph (**1a**)	5-Me (**6c**)	**7ac**	94	90
16	H/Ph (**1a**)	5-F (**6d**)	**7ad**	95	90

[a] Unless indicated otherwise, the reaction was carried out in 0.1 mmol scale in toluene (4 mL) with Na_2SO_4 (100 mg) for 40 h, and the molar ratio of **1**/**6** was 1:1.5. The absolute configuration of **7fa** was determined to be *S* by single-crystal X-ray analysis.[18] [b] Yield of isolated product. [c] The enantiomeric excess (*ee*) was determined by HPLC. [d] The volume of toluene was 1 mL.



Scheme 8. Control experiments to investigate the reaction mechanism.



Scheme 9. Suggested reaction pathway.

racemic **8**. These outcomes imply that the enantioselectivity of formation of the final product **7aa** is mainly controlled in the first step, and the moderate kinetic resolution of intermediate **8** during the second step further increases the enantioselectivity. So, CPA plays a crucial role in controlling the enantioselectivity during both steps. Moreover, in the reaction of **1a** with **2a**, we detected the signal of intermediate **8′** by HR-MS after stirring the reaction mixture for one hour [Scheme 8, Eq. (13)], which indicates that the two (4+3) cyclizations have similar mechanisms.

Based on the control experiments and the absolute configurations of products,[18] we suggested a possible reaction pathway to explain the chemistry and stereochemistry of the reaction (Scheme 9). In the presence of CPA **5**, substrates **2** or **6** easily were transformed into *o*-QM. Then, 2-indolylmethanols **1** and *o*-QM were simultaneously activated by (*R*)-**5** via the formation of hydrogen bonds, which facilitated an enantioselective addition to give intermediate **A**. The subsequent dehydration of **A** gave rise to carbocation intermediate **B**, which underwent an intramolecular cyclization under the promotion of CPA anion via hydrogen-bonding and ion-pairing interactions to afford final products **3** or **7** with observed *S* configurations. To better understand the reaction mechanism of the (4+3) cyclization, we performed density functional theory (DFT) calculations on the reaction pathway, which are in accordance with our suggested reaction pathway and have rationalized the formation of intermediates **A** and **B**. In addition, the DFT calculations supported the kinetic resolution of compound **8** to form the final product and explained why (*S*)-**7aa** was preferentially generated during the process of kinetic resolution (see the Supporting Information).

Moreover, we performed several 1 mmol scale reactions with decreased catalyst loading to demonstrate the utility of the reaction. The large-scale reactions successfully afforded products in maintained high yields and excellent enantioselectivity (see the Supporting Information).

To demonstrate the usefulness of this (4+3) cyclization method, we performed some post-functionalizations of compounds **3** and **7**, such as methylation, allylation, Suzuki coupling, and demethylation, which smoothly afforded products **9**–**13** in good yields and with maintained high enantio-

selectivity (see the Supporting Information). In addition, to investigate the usefulness of the synthesized products, some selected compounds **3** and **7** were subjected to the test of in vitro cytotoxicity to breast cancer cell line MCF-7, which found that all the tested compounds exhibited moderate to strong cytotoxicity toward MCF-7 cell lines (see the Supporting Information). The catalytic asymmetric (4+3) cyclizations can thus provide useful methods for synthesizing enantioenriched compounds **3** and **7** with structural diversity, which will be helpful for discovering drug candidate compounds.

In summary, we have established catalytic asymmetric (4+3) cyclizations of in situ generated *ortho*-quinone methides with 2-indolylmethanols, which were used to construct seven-membered oxygen-containing frameworks in high yields and excellent enantioselectivity. This approach not only represents the first catalytic asymmetric (4+3) cyclization of 2-indolylmethanols, but also enabled the first catalytic asymmetric (4+3) cyclization of *o*-hydroxybenzyl alcohols. In addition, we accomplished the first Brønsted acid catalyzed asymmetric (4+3) cyclization of *para*-quinone methide derivatives. These reactions will not only greatly contribute to the chemistry of *ortho*-quinone methides and indolylmethanols, but also serve as powerful methods for the construction of enantioenriched seven-membered heterocycles.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: (4+3) cyclization · asymmetric catalysis · enantioselectivity · organocatalysis · *ortho*-quinone methide

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Communications

Organocatalysis

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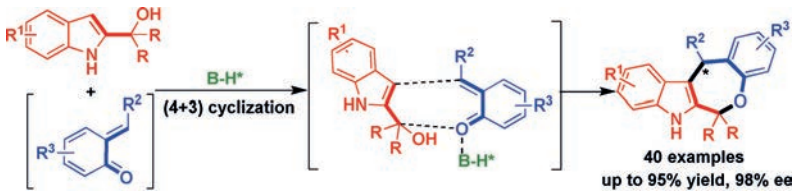
Catalytic Asymmetric (4+3) Cyclizations of In Situ Generated *ortho*-Quinone Methides with 2-Indolylmethanols



The first catalytic asymmetric (4+3) cyclization of in situ generated *ortho*-quinone methides with 2-indolylmethanols was developed, and was used to construct seven-membered heterocycles in high yields and excellent enantioselectivity. This approach represents the first catalytic asymmetric (4+3) cyclization of *o*-hydroxybenzyl alcohols, and also enabled the unprecedented catalytic asymmetric (4+3) cyclization of 2-indolylmethanols.