Asymmetric Catalysis

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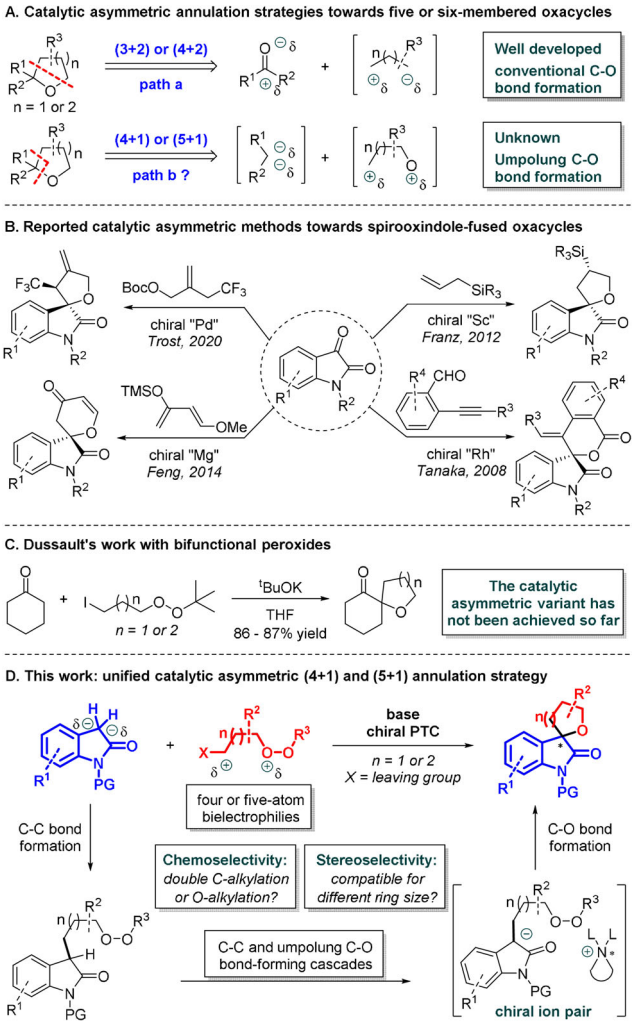
A Unified Catalytic Asymmetric (4 + 1) and (5 + 1) Annulation Strategy to Access Chiral Spirooxindole-Fused Oxacycles

Min Gao[+], Yanshu Luo[+], Qianlan Xu, Yukun Zhao, Xiangnan Gong, Yuanzhi Xia, and Lin Hu**

Abstract: *A unified catalytic asymmetric (N + 1) (N = 4, 5) annulation reaction of oxindoles with bifunctional peroxides has been achieved in the presence of a chiral phase-transfer catalyst (PTC). This general strategy utilizes peroxides as unique bielectrophilic four- or five-atom synthons to participate in the C–C and the subsequent umpolung C–O bond-forming reactions with one-carbon unit nucleophiles, thus providing a distinct method to access the valuable chiral spirooxindole-tetrahydrofurans and -tetrahydropyrans with good yields and high enantioselectivities under mild conditions. DFT calculations were performed to rationalize the origin of high enantioselectivity. The gram-scale syntheses and synthetic utility of the resultant products were also demonstrated.*

Introduction

Optically active five and six-membered oxygenated heterocycles are abundant in numerous biologically active natural products and drugs.[1,2] Catalytic asymmetric annulation reactions provide a powerful tool to access such scaffolds in a single step. In this context, Pd or Lewis acid-catalyzed (3 + 2) cycloadditions of carbonyl compounds with trimethylenemethanes and donor-acceptor cyclopropanes are leading strategies to access chiral tetrahydrofurans[3] (path a, Scheme 1 A). In addition, Lewis acid or Brønsted acid-catalyzed asymmetric (4 + 2) cycloadditions of carbonyl compounds with 1,3-dienes provide another powerful tool for the synthesis of chiral dihydropyrans with high enantioselectivity.[4] Despite these achievements, the complementary catalytic asymmetric (4 + 1) or (5 + 1) annulation reactions[5] featuring the direct coupling of one-carbon unit nucleophiles with appropriate bifunctional electrophiles via new bond disconnections, however, remain underdeveloped (path b, Scheme 1 A).



Scheme 1. Background and our synthetic strategy.

The enantioenriched spirooxindoles bearing five- or six-membered oxacycle moieties are privileged scaffolds that have been extensively investigated in the medicinal programs for new drug development.[6] Many catalytic asymmetric (3 + 2) cyclization reactions have been reported for the preparation of chiral γ-butyrolactone-based spirooxindoles in the presence of N-heterocyclic carbene or other organocatalysts.[7] Surprisingly, few precedents are available for the catalytic asymmetric synthesis of chiral tetrahydrofuran- or

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pyran-based spirocyclic systems (Scheme 1B). Recently, Trost and Franz reported the Pd- and Lewis acid-catalyzed asymmetric (3+2) cycloadditions of isatin with trifluoromethylallyl carbonate and allyl silane to access spirooxindole-fused tetrahydrofurans with high enantioselectivities.[8] Tanaka and Feng described the Rh- and Lewis acid-catalyzed asymmetric (4+2) cycloadditions of isatin with 2-alkynylbenzaldehydes and Danishefsky diene for the construction of chiral spirocyclic pyranones.[9] However, all these reactions required the use of specific 1,3- or 1,4-dipole equivalents as substrates, thus rendering them only suitable for the preparation of individual five- or six-membered oxacycle products. Herein, we report a unified catalytic asymmetric (*N*+1) (*N*= 4, 5) annulation strategy for the general synthesis of chiral spirooxindole-fused tetrahydrofurans and tetrahydropyrans by employing simple oxindoles as one-carbon nucleophiles and bifunctional peroxides as unique four- or five-atom bielectrophiles under mild phase-transfer catalytic conditions.

Unlike previous cyclization methods, the critical ring-closing C–O bond in this protocol was constructed via a umpolung approach.

Electrophilic reactivity of dialkyl peroxides towards strong carbon nucleophiles such as organolithium and Grignard reagents for the synthesis of ethers was well known,[10] but exploiting such umpolung C–O bond-forming strategy for the construction of oxygen heterocycles has only received less attention.[11,12] Dussault and co-workers first reported two examples of cyclization reactions of *tert*-butyl 3-iodopropyl and *tert*-butyl 3-iodobutyl peroxides with cyclohexanone under the stronger KO^{t}Bu basic conditions[11a] (Scheme 1C). Recently, our group also developed the general (4+1) and (5+1) annulation reactions of β-keto esters and other active methylene compounds with a wide range of bifunctional peroxides bearing allylic halide appendages for the synthesis of 2,2-disubstituted tetrahydrofurans and dihydropyrans in the presence of KOH or Cs_2CO_3 base.[12] However, application of such bielectrophilic peroxides to the asymmetric catalytic annulation process has not been realized so far.

The mild basic conditions of our protocol prompted us to assemble the chiral spirooxindoles by selecting oxindoles as one-carbon nucleophiles[13] via asymmetric phase-transfer catalysis.[14] We envisioned that an intermolecular C–C bond formation, followed by a critical stereoselective intramolecular C–O bond formation from the chiral ion pair intermediate, would generate the chiral spirocyclic oxacycles in a single step (Scheme 1D). Moreover, by devising the linkage of peroxides as four- or five-atom components, this tandem process could be facilely developed into the synthesis of chiral spirooxindole-fused tetrahydrofurans and tetrahydropyrans in a unified fashion. Although such design seems straightforward, several challenges are associated with this catalytic asymmetric process. First, the competitive double intermolecular *C*-alkylation or the *O*-alkylation pathways, which could terminate the tandem process, are the primary concerns. Second, whether high enantioselectivity could be consistently obtained for the formation of oxacycles with different ring size is quite uncertain. Third, dialkyl peroxides possessing a sterically more hindered and electronically less polarized O–O bond[15] are less reactive substrates. Actually, compared to the well-documented catalytic asymmetric α-hydroxylation and α-benzoyloxylation of reactive alkyl hydroperoxides[16,17] and benzoyl peroxides,[18] the similar catalytic asymmetric α-alkoxylation of dialkyl peroxides has not been reported yet.

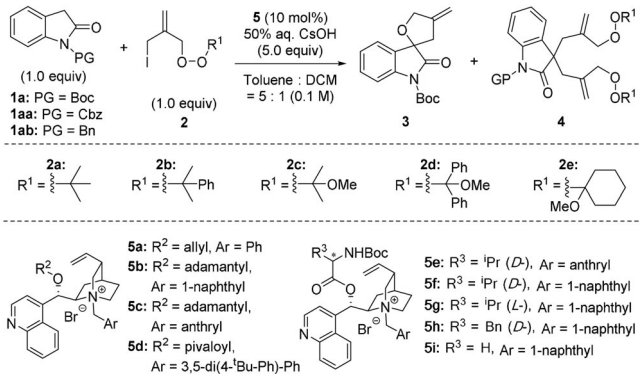
Results and Discussion

Bearing these issues in mind, we commenced our investigation by exploring the reaction of *N*-Boc-oxindole **1a** (Boc: *tert*-butoxycarbonyl) with peroxide **2a**[19] in the presence of cinchona alkaloid-derived phase-transfer catalysts **5** and CsOH base. Indeed, we noticed that the double *C*-alkylation was the severe side reaction that needed to be addressed first, as treatment of **1a** with *tert*-butyl peroxide **2a** at −20 °C always produced compound **4** as the major product with commonly used catalysts **5a–c** (**3:4** = 1:2, Table 1, entries 1–3). Notably, catalyst **5d** bearing a very bulky triphenyl moiety could improve the ratio of the desired product **3**; however, the enantioselectivity was found to be very poor (Table 1, entry 4). In spite of these difficulties, catalyst **5c** still generated the product **3** with 50% *ee*. This promising result encouraged us to further investigate the influence of varying the structure of peroxides on the reaction. We speculated that peroxides possessing enhanced O–O bond reactivity may facilitate the critical ring-closing C–O bond formation, thus in turn improving the chemoselectivity of the reaction. In fact, the structure of the peroxides had a significant impact on the reaction. Peroxide **2b** bearing a cumenyl group dramatically improved the chemoselectivity to 5:1 (Table 1, entry 5). More impressively, peroxides **2c–e** bearing ketal moieties completely suppressed the side product **4**. Peroxide **2e** even afforded the product **3** in 80% *ee* and 75% yield by using **5c** as a catalyst at −40 °C (**3:4** > 20:1, Table 1, entries 6–9).

To further improve the enantioselectivity of the reaction, we screened many other phase-transfer catalysts. We found that incorporation of an amino acid subunit into the catalyst significantly affected the outcomes of stereoselectivity (Table 1, entries 10–14). For example, catalyst **5f** and **5g** bearing *N*-Boc-*D*- and *L*-valine moieties afforded **3** in 86% and 57% *ee*, respectively, while catalyst **5i** bearing less hindered glycine structure only produced **3** in 30% *ee*.

At this stage, other reaction parameters were then evaluated. Using toluene or dichloromethane (DCM) as solvent drastically decreased the *ee* of **3** (Table 1, entries 15–16). Lowering the temperature to −60 °C led to freezing of the 50% aqueous solution of CsOH, thus product **3** was obtained in lower *ee* and yield. Instead, 80% aqueous solution of CsOH performed well at such cryogenic temperature and improved the *ee* of **3** to 90%, albeit with a prolonged reaction time to reach the full conversion (Table 1, entries 17–19). Mechanistically, one molar of methoxide should be released from the peroxy cyclohexyl ketal after the C–O bond-forming step. This in situ generated base should in turn deprotonate the oxindole substrate for further annulation reaction; however, the reaction conversion turned out to be low when reducing the CsOH to 1.0 equivalent, and **3a** was obtained in 35%

Table 1: Optimization of the reaction conditions.



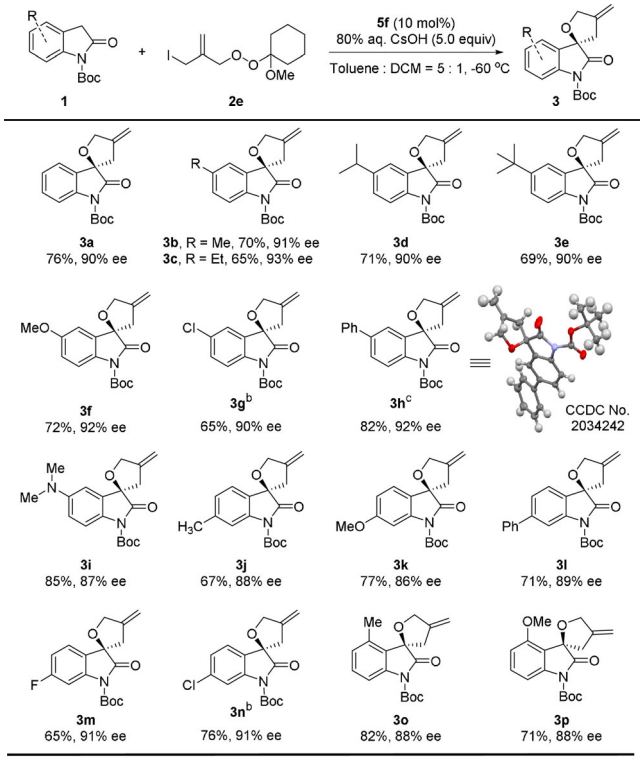
entry	substrates		catalyst	*T* [°C]	time [h]	**3**:**4**[a]	yield of **3** [%][b]	*ee* of **3** [%][c]
			Initial screening of catalysts					
1	**1a**	**2a**	**5a**	−20	8	1:2	30	24
2	**1a**	**2a**	**5b**	−20	10	1:2	25	34
3	**1a**	**2a**	**5c**	−20	12	1:2	31	50
4	**1a**	**2a**	**5d**	−20	8	2:1	43	8
			Impact of peroxide structures on the reaction					
5	**1a**	**2b**	**5c**	−20	4	5:1	45	63
6	**1a**	**2c**	**5c**	−20	4	>20:1	61	66
7	**1a**	**2d**	**5c**	−20	4	>20:1	63	68
8	**1a**	**2e**	**5c**	−20	4	>20:1	78	74
9	**1a**	**2e**	**5c**	−40	8	>20:1	75	80
			Further screening of catalysts					
10	**1a**	**2e**	**5e**	−40	8	>20:1	71	81
11	**1a**	**2e**	**5f**	−40	8	>20:1	70	86
12	**1a**	**2e**	**5g**	−40	8	>20:1	73	57
13	**1a**	**2e**	**5h**	−40	8	>20:1	42	64
14	**1a**	**2e**	**5i**	−40	12	>20:1	33	30
			Optimization of other reaction parameters					
15	**1a**	**2e**	**5f**	−40	8	>20:1	48	64[d]
16	**1a**	**2e**	**5f**	−40	7	>20:1	45	19[e]
17	**1a**	**2e**	**5f**	−60	10	>20:1	50	75
18	**1a**	**2e**	**5f**	−60	4	>20:1	53	76[f]
19	**1a**	**2e**	**5f**	−60	16	>20:1	64	90[g]
20	**1a**	**2e**	**5f**	−60	36	>20:1	35	90[g,h]
21	**1aa**	**2e**	**5f**	−60	15	>20:1	23	42[g]
22	**1ab**	**2e**	**5f**	−60	36	/	/	/[i]
23	**1a**	**2e**	**5f**	−60	16	>20:1	76	90[g,j]

[a] Determined by ^{1}H NMR. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Toluene as solvent (low solubility for **5f**). [e] DCM as solvent. [f] Solid CsOH. [g] 80% aq. CsOH. [h] 1.0 equiv of 80% aq. CsOH. [i] <10 conversion. [j] 1.2 equiv of **2**.

yield and 90% *ee* (Table 1, entry 20). Next, oxindole substrates bearing other types of protecting groups such as benzyloxycarbony (Cbz) and benzyl (Bn) groups were examined (Table 1, entries 21–22). A severe hydrolysis side reaction of Cbz-protected substrate **1aa** was observed under the basic conditions, thus leading to much lower yield and *ee* of **3**, while the Bn-protected substrate **1ab** was found to be less reactive and almost no reaction happened at −60°C. Upon further optimization (see the Supporting Information for details), we finally identified the optimal conditions by conducting the reaction of Boc-protected oxindole **1a** and peroxide **2e** (1.2 equiv) at −60°C by using 10 mol% of **5f** as catalyst and 5.0 equiv of CsOH (80% aq.) as base in 5:1 Toluene/DCM co-solvent systems (Table 1, entry 23).

With the optimal conditions in hand, we first probed the scope of oxindoles for the catalytic asymmetric (4+1) annulation reactions. As shown in Table 2, a wide range of

Table 2: Substrate scope for (4 + 1) annulation reactions.[a]

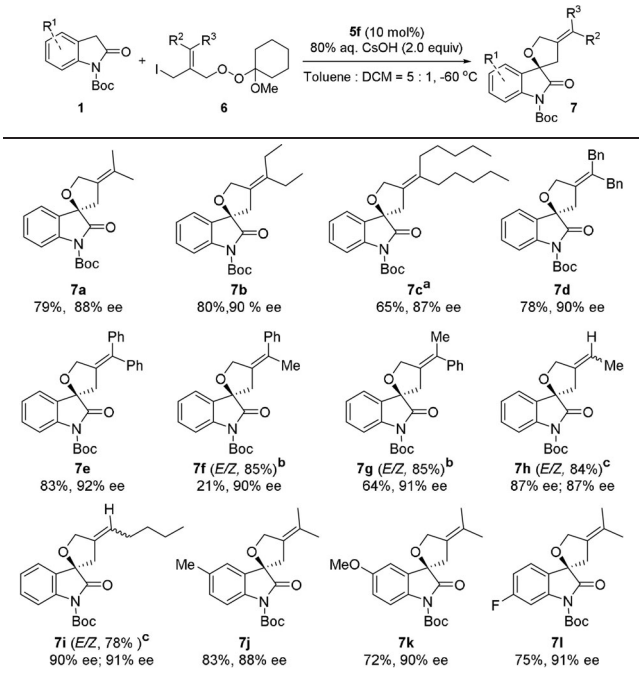


[a] Reaction conditions: **1** (0.2 mmol), **2e** (0.24 mmol), catalyst **5f** (10 mol%), and 80% aq. CsOH (1.0 mmol) in 2.0 mL solvent. [b] 0.05 M reaction solution. [c] The absolute configuration was determined to be *R*; see the Supporting Information for details.

N-Boc-oxindoles performed well in this reaction (65–85% yield, 86–93% *ee*). 5-Substituted substrates bearing either electron-donating or electron-withdrawing groups on the phenyl ring uneventfully afforded the products with more than 90% *ee* (Table 2, **3a**–**h**). Notably, substrate **1i** bearing a strongly electron-donating *N*,*N*-dimethylamino group, which appears to be sensitive to the peroxide reagent, was still compatible with current conditions and provided the product **3i** in 85% yield and 87% *ee*. Moreover, substrates bearing different 4-, and 6-substitutents on the phenyl ring had slightly influence on the reaction, also consistently affording the spirocyclic tetrahydrofuran products with good yields and high enantioselectivities (Table 2, **3j**–**p**).

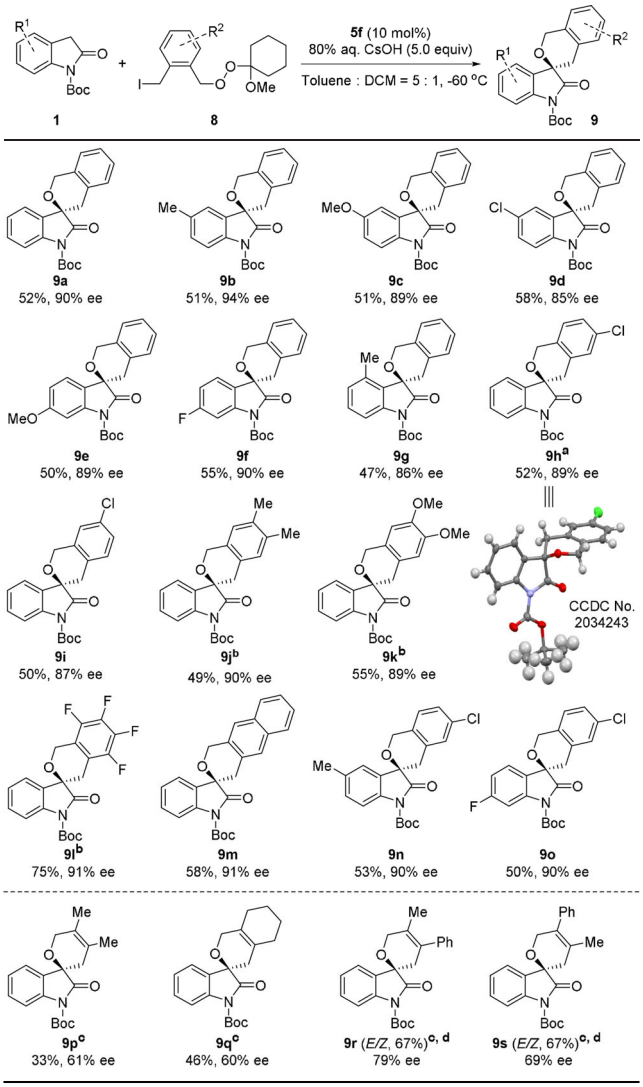
Next, we found the catalytic asymmetric (4+1) annulations could also be applied to the substituted allyl peroxides **6** (Table 3). Under the identical conditions, a range of optically active spirocyclic tetrahydrofurans including the challenging tetrasubstituted olefin-containing products, which were difficult to access from the existing methods, could be directly prepared with high enantioselectivities. Peroxide substrates bearing dialkyl and diaryl groups on the terminal olefinic

Table 3: Substrate scope for peroxides.



[a] 0.05 M reaction solution. [b] 1:3 *E*/*Z* mixture of peroxides was used. [c] 1:1 *E*/*Z* mixture of peroxides was used.

Table 4: Substrate scope for (5 + 1) annulation reactions.



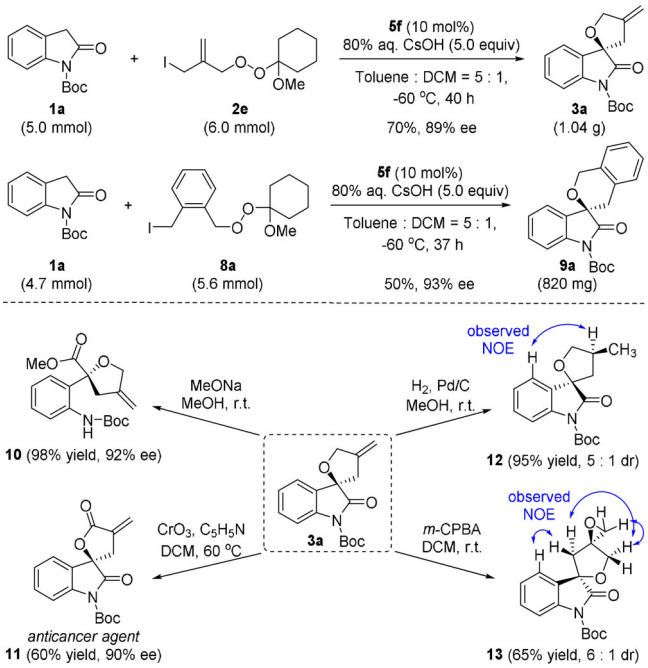
[a] The absolute configuration was determined to be *R*; see the Supporting Information for details. [b] 2.0 equivalents of 80% aq. CsOH were used. [c] 4-bromo-but-2-enyl peroxide was used. [d] 1:3 *E*/*Z* mixture of peroxides was used.

carbon were well tolerated and generally afforded the products with more than 90% *ee* (Table 3, **7a–g**). In the cases of **6f–h**, a pair of *E*/*Z* peroxides, which were prepared from the corresponding 1,4-diol precursors as mixtures, could be directly used for the reaction. The geometry of the double bond had no noticeable impact on the stereoselectivity of the reaction (Table 3, **7f–i**). It should be noted that products **7f** and **7g** could be separated as pure forms by simple chromatography after the reaction. Meanwhile, oxindoles with substituents at different positions (e.g., 5-Me, 5-MeO, 6-F) were also compatible for the reaction, which furnished the corresponding products with good yields and high enantioselectivities (Table 3, **7j–l**).

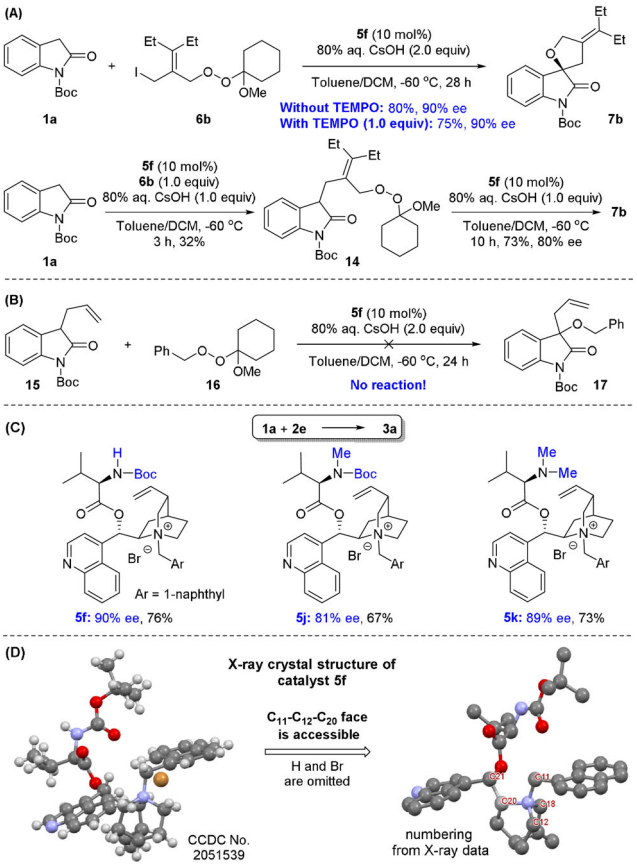
Encouraged by the generality of the reaction, we decided to expand the above protocol to the (5 + 1) annulation process. Accordingly, we reinvestigated the catalytic asymmetric reactions by searching suitable five-atom bielectrophilic peroxide partners. After extensive experiments, we found that peroxides **8** bearing benzylic functionality could cyclize with **1** under the established conditions of the (4 + 1) process (Table 4). More importantly, a range of oxindole and peroxide substrates, regardless of the positions and electronic properties of substituents on each phenyl ring, were well tolerated for this new (5 + 1) process and successfully afforded the structurally diverse spirooxindole-tetrahydropyrans **9a–o** with high enantioselectivities (Table 4, 85–94% *ee*). For example, the interesting tetrafluorophenyl product **9l** as well as the hybrid products **9n**,**o** could be efficiently generated over 90% *ee* (Table 4, **9l–o**). Meanwhile, other alkyl substituted bifunctional peroxides were also tested for current (5 + 1) annulations. We found that 4-bromo-but-2-enyl peroxides provided better results than the corresponding iodides. However, the spirooxindole products **9p–s** were generated in moderate enantioselectivities (Table 4, 60–79% *ee*). It had to be mentioned that considerable amounts of double *C*-alkylation side products were still inevitably formed in these (5 + 1) reactions, thus giving relatively lower yields of the desired products compared to the (4 + 1) ones.

To explore the practicality of the newly developed reaction, scalable (4 + 1) and (5 + 1) annulations of peroxides **2e** and **8a** were examined under the standard conditions. As shown in Scheme 2, both processes still performed well at around 5 mmol scale, affording products **3a** and **9a** without noticeable drop of the yields. Interestingly, the enantioselectivity of (5 + 1) process was even improved at large scale.

Owing to the synthetic versatility of the olefin and carbonyl functionalities, chiral spirocyclic oxacycles prepared



Scheme 2. Scale-up synthesis and derivatization.



Scheme 3. Mechanistic investigations.

from current method are valuable building blocks for further transformations. As shown in Scheme 2, compound **3a** was readily converted into chiral 2,2-disubstituted tetrahydrofuran **10** in 98% yield and 92% *ee* by a single step of hydrolysis in methanol. Similarly, treatment of **3a** with CrO_3 in DCM readily furnished the γ-lactone **11** in 60% yield and 90% *ee*. This spirooxindole-γ-butyrolactone compound has been used as a potent anticancer agent.[6b] Meanwhile, the double bond in the above products provides an additional handle for structural variations. For example, compound **3a** could be stereoselectively hydrogenated or oxidized by *meta*-chloroperbenzoic acid (*m*-CPBA) to give compound **12** and the rigid bis-spirocyclic epoxide **13** in 5:1 and 6:1 dr, respectively. The relative configurations of these compounds were unambiguously confirmed by the nuclear Overhauser effect (NOE) analysis (see the Supporting Information for details).

Finally, to gain insights about this annulation process, we conducted the following control experiments (Scheme 3A). We found that adding 1.0 equivalent of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) as radical scavenger to the reaction mixture of **1a** and **6b** did not affect the yield and *ee* of product **7b** markedly under the standard conditions. Meanwhile, we could detect and isolate the *C*-alkylation intermediate **14** at the early stage of the reaction. After resubmitting this intermediate to the standard conditions, the final product **7b** was obtained in 73% yield and 81% *ee*. These data indicated that the current catalytic annulations probably proceeded via a C–C → C–O bond-forming sequence, wherein both bonds were more likely formed via a nucleophilic substitution mechanism instead of a radical pathway.

As shown in Table 1, incorporation of a *D*-*N*-Boc-valine subunit into the catalyst **5f** significantly improved the enantioselectivity of the reaction. To elucidate if a hydrogen-bonding between the N-H moiety and the substrate played an important role in this enhancement, we prepared the catalyst **5j** by replacing the Boc-N-H moiety in **5f** with Boc-N-Me structure. Under the same conditions as **5f**, this catalyst promoted the reaction of **1a** and **2e** in 80% *ee* (Scheme 3C). We also synthesized the catalyst **5k** bearing two identical methyl groups on the nitrogen atom. Interestingly, this new catalyst performed as equally well as the optimal catalyst **5f** (**3a**: 89% *ee* vs. 90% *ee*). These data implied that the hydrogen-bonding might not involve in the stereodetermining transition state. More importantly, we obtained the X-ray crystal structure of catalyst **5f**, in which the N-H moiety is far away from the open face of the cinchonium salt wherein the reaction is most likely to happen. On the basis of these results, we justified that an additional hydrogen-bond interaction between the catalyst and substrate could be reasonably ruled out.

The crystal structure of **5f** also provides insightful information to rationalize the plausible transition state of **5f**-catalyzed annulation reactions. For chiral quaternary ammonium salts catalyzed asymmetric phase-transfer reactions, the catalytic efficiency essentially hinges on how the three of the catalyst's tetrahedral faces surrounding the cationic nitrogen center could be effectively blocked and while one face is adequately left open for the substrate docking.[20] As exhibited in Scheme 3D, three tetrahedral faces in cinchonium salt **5f**, namely C_{12}-C_{18}-C_{20}, C_{11}-C_{12}-C_{18},

and C_{11}-C_{18}-C_{20}, are sufficiently shielded by the quinuclidine backbone, the naphthalene ring, and the quinoline/ isopropyl/ vinyl components, respectively. Only the C_{11}-C_{12}-C_{20} face is accessible for the enolate of *C*-alkylation intermediate to approach. The remarkable features of this open face include a nearly co-planar quinoline and naphthalene rings with respect to the C_{11}-C_{21} axis and a rigid quinuclidine backbone beneath the aryl plane. The isopropyl and *N*-Boc segments of *D*-valine subunit reside at the rear of the quinoline and naphthalene rings, respectively. This spacial arrangement provides a well-defined pocket to execute the chiral recognition of the approaching enolate. Moreover, detailed two-dimensional NMR experiments revealed that catalyst **5 f** adopted the similar conformation in solution (see the Supporting Information for details).

To better understand the origin of high enantioselectivity of the **5 f**-catalyzed annulation reactions, density functional theory (DFT) calculations were conducted to analyze the C–O bond-forming transition states leading to compound **7 a**.[21] As shown in Figure 1, the transition state **TS-S** that derives from the *si* face attack of the oxindolyl enolate by peroxide would give an (*S*)-configurated product **7 a**. The **TS-R** that is from the *re* face attack would yield an (*R*)-enantiomer. It was found that the **TS-S** (13.7 kcal mol^{-1}) was energetically disfavored due to the steric repulsion between the substrate's bulky cyclohexyl ketal moiety and the catalyst's quinoline ring, while the **TS-R** (11.5 kcal mol^{-1}) was more favorable by placing the bulky peroxy ketal group and various olefinic substituents at the open naphthalene side. The calculated energy difference between the two transition states was 2.2 kcal mol^{-1}, which was in line with the experimental observations of **5 f**-catalyzed reactions that generated the products with *R* absolute configuration and high enantioselectivity.

An extra merit of catalyst **5 f** is noteworthy to mention. There could be a favorable entropic effect, which was endowed by the structurally well-defined chiral pocket of the catalyst **5 f**, to facilitate the formation of the C–O bond by reducing the motion of the structured enolate when lining up with the antibonding σ* orbital of the O–O bond.[20b] For comparison, an intermolecular α-alkoxylation reaction of 3-allyl oxindole **15** and dialkyl peroxide **16** was conducted under the similar catalytic conditions, but no reaction occurred at all (Scheme 3 B). This result again proved that catalytic asymmetric α-alkoxylation of dialkyl peroxides is rather different from the well-established α-hydroxylation and α-benzoyloxylation reactions of reactive hydroperoxides and peresters.

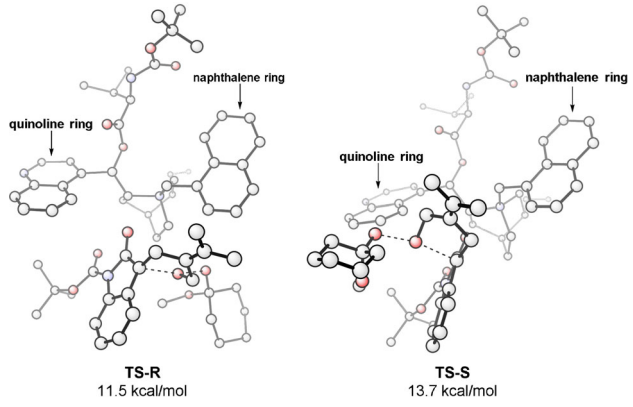


Figure 1. DFT calculated geometries and relative free energies of the C–O bond-forming transition states (for clarity, hydrogen atoms are omitted).[21].

Conclusion

In summary, we have developed a unified phase-transfer-catalyzed asymmetric ($N+1$) ($N=4$, 5) annulation reaction of oxindoles with various peroxide bielectrophiles, giving rise to a wide range of chiral spirooxindole-tetrahydrofurans and -tetrahydropyrans with good yields and high enantioselectivities. This general ($N+1$) annulation strategy utilized 2-iodomethylallyl and 2-iodomethylbenzyl peroxides as unique four- and five-atom umpoled synthons to construct the critical ring-closing C–O bond via an electrophilic alkoxylation approach, thus providing a simple and distinct method for the synthesis of chiral five- and six-membered oxacycles under mild conditions. A plausible transition state model was proposed to rationalize the origin of high enantioselectivity of the reaction based on the DFT calculations. Meanwhile, the gram-scale synthesis and the flexible transformations of the resultant spirooxindole-oxacycle products into other biologically important chiral scaffolds such as highly functionalized tetrahydrofurans and γ-butyrolactones in one step were also demonstrated.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: annulation reaction · organocatalysis · oxygen heterocycles · peroxides · umpolung reaction

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[19] According to our synthetic practice in the lab, peroxides **2**, **6**, and **8** used in current work could be prepared and purified ranging from hundreds of milligrams to grams scale by regular experimental operations, such as extraction, concentration, and silica gel chromatography (see the Supporting Information for details). Additionally, most of these peroxides could be stored at −20 °C fridge for weeks without noticeable decomposition, but they slowly turned to complex black mixtures when placing at room temperature probably duo to the sensitivity of iodide functionality to light. Although we did not encounter any laboratory incidents in carrying out the synthesis and relating reactions of these compounds during the course of this project, organic peroxides are potentially explosive! We recommend that all the reactions should be cautiously conducted in fume hood with a safety shield. For a comprehensive discussion of the hazards and safe handling of peroxides, see: D. E. Clark, *Chem. Health Saf.* **2001**, *8*, 12 – 22.

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[22] Deposition numbers 2034242 (for **3h**), 2034243 (for **9h**), and 2051539 (for **5f**) 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.

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Research Articles

Asymmetric Catalysis

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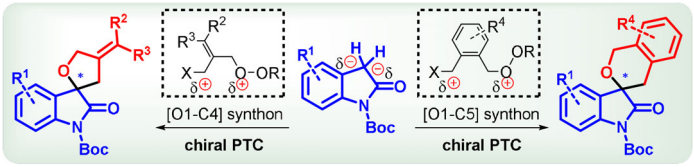
A Unified Catalytic Asymmetric (4 + 1) and (5 + 1) Annulation Strategy to Access Chiral Spirooxindole-Fused Oxacycles



Peroxides, which function as umpoled bielectrophilic synthons, enable the unified catalytic asymmetric (4 + 1) and (5 + 1) annulation reactions in the presence of a phase-transfer catalyst (PTC). This new strategy provides an unconventional protocol to access the biologically important chiral spirooxindole-tetrahydrofurans and -tetrahydropyrans in good yields and high enantioselectivities (up to 94 % *ee*).