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Chiral Aryliodine-Mediated Enantioselective Organocatalytic Spirocyclization: Synthesis of Spirofurooxindoles via Cascade Oxidative C−O and C−C Bond Formation

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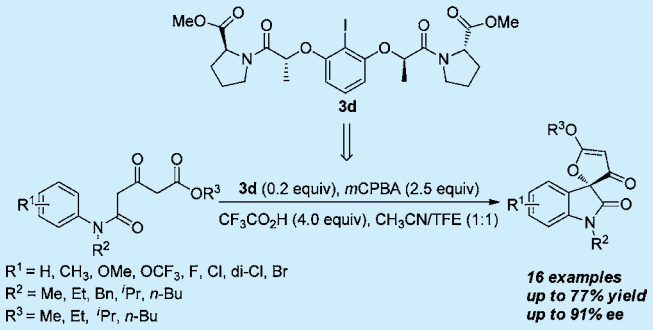
Supporting Information

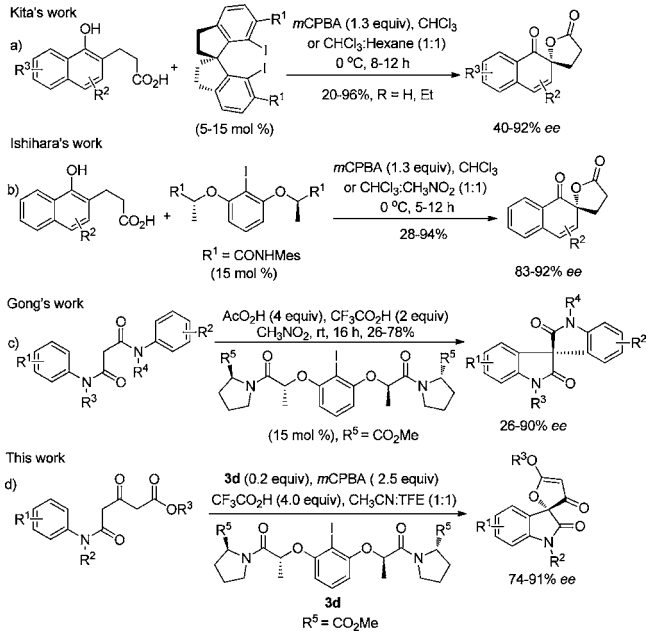
ABSTRACT: An enantioselective organocatalytic oxidative spirocyclization of alkyl 3-oxopentanedioate monoamide derivatives leading to the formation of diverse spirofurooxindoles with high enantioselectivity has been realized via chiral aryliodine-mediated cascade C−O and C−C bond formations. The reaction is postulated to proceed via oxidative C−O bond formation followed by oxidative C−C bond formation, with the latter being the enantioselectivity-determining step.



The spirofurooxindole framework is a common motif found in many bioactive natural products and pharmaceutical agents.[1] As both naturally occurring and pharmaceutically useful spirofurooxindoles bear a chiral quaternary center, the development of asymmetric syntheses for the assembly of this class of skeleton is highly desirable. Although existing asymmetric annulation methods can eventually afford spirofurooxindoles with high stereoselectivity,[2−5] most rely mainly on manipulation of oxindole derivatives, which are in turn prepared by multistep processes.[3,6] In this regard, the development of efficient protocols for the construction of such chiral skeletal structures is highly in demand.

Literature reports show that the applications of chiral hypervalent iodine reagents in enantioselective oxidation reactions with high stereoselectivities have received much attention in the past decade.[7] However, the utilization of catalytic organoiodine reagents in oxidative cross-coupling reactions using *m*CPBA or AcO_2H as the terminal oxidant has rarely been studied in organic synthesis.[8−11] Kita and coworkers[8] discovered that chiral iodoarenes with a rigid spirobiindane backbone could be used for enantioselective dearomatization of naphtholic substrates, giving optically active products with good to high enantioselectivity (Scheme 1a). In 2010, Ishihara reported the application of a conformationally flexible C_2-symmetric iodoarene catalyst to promote catalytic enantioselective spirocyclization of naphtholic substrates while affording optically active products with enantiomeric excess of up to 92%[9a] (Scheme 1b). Most recently, Gong and coworkers[10a] reported, based on our previous nonasymmetric reaction pattern,[12] an asymmetric oxidative intramolecular cross-coupling of C−H bonds using catalytic chiral iodine reagent in the presence of peracetic acid to give structurally diverse spirooxindoles in moderate yields with high levels of

Scheme 1. Catalytic Asymmetric Intramolecular C−C and C−O Oxidative Cross-Coupling Reactions



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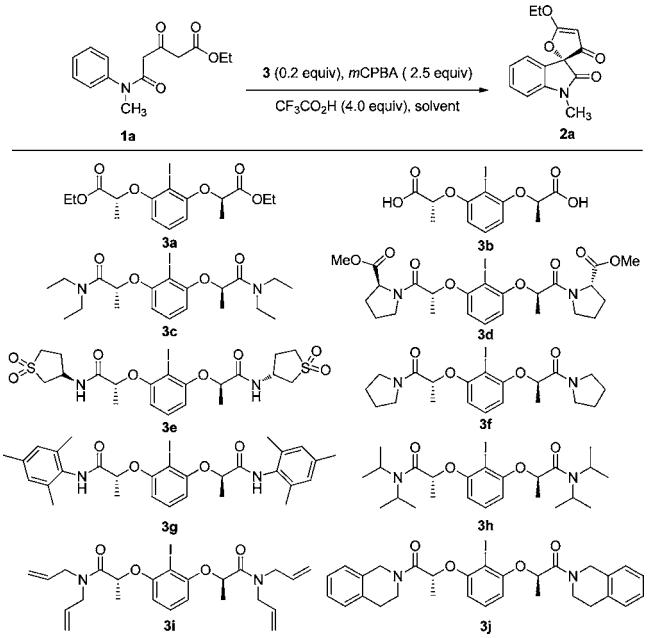
enantioselectivity (Scheme 1c). In all of these works, the assembly of oxygen- or nitrogen-containing spirocyclic compounds was accomplished via oxidative functionalization of phenolic or malonic derivatives. Extending the asymmetric synthetic approach to tricarbonyl compounds, we herein report a novel preparation of a series of optically active spirofurooxindoles via cascade C−O/C−C cross-coupling reactions catalyzed by a flexible[9a,c] C_2-symmetric chiral iodoarene with *m*CPBA as the terminal oxidant (Scheme 1d).

At the outset of the study, we envisaged that the reaction of ethyl 5-(methyl(phenyl)amino)-3,5-dioxopentanoate (**1a**) with hypervalent iodine reagents might undergo some oxidative coupling reaction to give the oxindole product through oxidative C−C bond formation with subsequent 3-hydroxylation.[12] The readily prepared **1a** was selected as a model substrate to probe the feasibility of the possible transformation. To our delight, treatment of **1a** with 2.2 equiv of phenyliodine bis(trifluoroacetate) (PIFA) in 2,2,2-trifluoroethanol (TFE) resulted in the formation of the unexpected but interesting spirofurooxindole **2a** (the structure of which was unambiguously confirmed through X-ray crystallographic analysis) in 85% yield, albeit as an optically inactive racemic mixture (see the Supporting Information). The initial investigation of the enantioselectivity was carried out using a 20 mol % loading of the chiral organoiodine **3a** along with 2.5 equiv of *m*CPBA in TFE at room temperature. The transformation indeed took place, and the desired product **2a** was obtained in moderate yield but with poor enantioselectivity (Table 1, entry 1). Replacing ester **3a** with the acid version, **3b**, resulted in a much improved *ee* value (44%) (Table 1, entry 2). Inspired by Gong's work,[10a] we also prepared and investigated catalysts **3c** and **3d**. Surprisingly, amide catalysts **3c** and **3d** were found to significantly improve the *ee* to 80% and 83%, respectively (Table 1, entries 3 and 4). Further attempts to improve the reaction outcome by switching to other catalysts such as chiral aryl iodides **3e**−**j** proved to be unfruitful (Table 1, entries 5−10). Notably, solvent screening studies showed that CH_3CN further promoted the enantioselectivity to 88% *ee* but unfortunately lowered the yield (Table 1, entry 12). In an attempt to improve the yield, we applied a mixed solvent of CH_3CN and TFE with various volumetric ratios (Table 1, entries 13−15), and the best result was obtained using a 1:1 volumetric ratio (Table 1, entry 14). Finally, application of reduced dosages of TFA and catalyst **3d** resulted in much decreased yields and unimproved *ee* values (Table 1, entries 16−18).

Under the optimized conditions, a series of substrates were prepared to investigate the scope and generality of this newly established method. To our delight, substrates bearing alkyl R^2 groups of various sizes, including ethyl (**1b**), isopropyl (**1c**), *n*-butyl (**1d**), and benzyl (**1e**), were all converted to the desired products with excellent *ee* values in fairly good yields (Scheme 2, **2b**−**e**). Notably, nearly enantiomerically pure products **2b** and **2d** (≥98% *ee*) were obtained after a single recrystallization. The absolute configuration of **2** was determined to be *R* from X-ray crystallographic analysis of **2b** (Figure 1). Substituent-effect results also showed that both electron-donating and electron-withdrawing R^1 groups were well-tolerated (Scheme 2, **2f**−**k**). While the electronic nature of the substituent did not seem to exert any negative effect on the *ee* value, a consistent correlation with the yield was observed: electron-withdrawing halogen R^1 groups slightly improved the yield (Scheme 2, **2i**−**k**) while electron-donating groups (−Me, −OMe, and −OCF_3) slightly reduced the yield (Scheme 2, **2f**−**h**). Also, substrate **1l** with chloro substituents at the 3- and 4-positions of the *N*-aryl moiety was converted to the two expected regioisomeric products **2l** and **2l′** in an overall yield of 58% with high *ee* values (Scheme 2). Disappointingly, a steric effect was observed in the reaction of *ortho*-substituted substrate **1m**, which delivered the anticipated product in a much lower yield with slightly decreased enantioselectivity (Scheme 2, **2m**). Moreover, subsequent investigations revealed that modifications of the R^3 group in the ester subunit also led to *ee* values similar to that for **1a**, albeit in slightly reduced yields (Scheme 2, **2n**−**p**).

Table 1. Optimization of the Reaction Conditions[a]



entry	3	solvent	yield (%)[b]	*ee* (%)[c]
1	**3a**	TFE	67	4
2	**3b**	TFE	69	44
3	**3c**	TFE	53	80
4	**3d**	TFE	70	83
5	**3e**	TFE	53	63
6	**3f**	TFE	45	67
7	**3g**	TFE	28	33
8	**3h**	TFE	53	71
9	**3i**	TFE	45	70
10	**3j**	TFE	62	65
11	**3d**	CH_3NO_2	41	82
12	**3d**	CH_3CN	47	88
13	**3d**	TFE/CH_3CN (1/2 v/v)	54	86
14	**3d**	**TFE/CH_3CN (1/1 v/v)**	**63**	**87**
15	**3d**	TFE/CH_3CN (2/1 v/v)	65	82
16[d]	**3d**	TFE/CH_3CN (1/1 v/v)	54	85
17[e]	**3d**	TFE/CH_3CN (1/1 v/v)	39	86
18[f]	**3d**	TFE/CH_3CN (1/1 v/v)	53	86

[a]Unless otherwise stated, the reaction of **1a** (0.2 mmol) was carried out at rt for 8 h in solvent (4.0 mL) in the presence of chiral catalyst **3** (20 mol %), *m*CPBA (2.5 equiv), and CF_3CO_2H (4.0 equiv). [b]Isolated yield. [c]The *ee* percentage values were determined by chiral HPLC analysis. [d]CF_3CO_2H (2.0 equiv). [e]Catalyst **3d** (10 mol %). [f]Catalyst **3d** (15 mol %).

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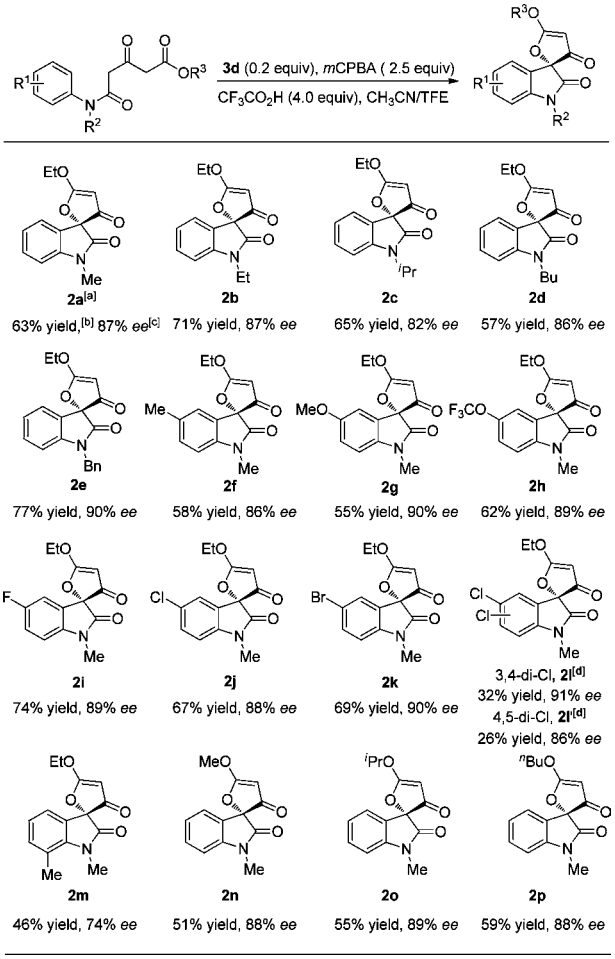
Scheme 2. Substituent-Effect Studies of the Spirocyclization Reaction[a]



[a]Unless otherwise stated, the reaction of **1a** (0.2 mmol) was carried out at rt for 8 h in solvent (4.0 mL) in the presence of the chiral catalyst **3d** (20 mol %), *m*CPBA (2.5 equiv), and CF_3CO_2H (4.0 equiv). [b]Isolated yields are shown. [c]The *ee* values were determined by chiral HPLC analysis. [d]The two products could be separated by chiral HPLC, and the **2l**:**2l′** ratio was 1.2:1.

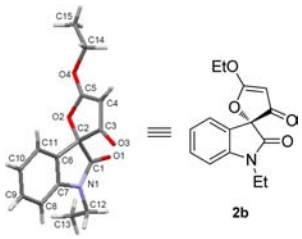
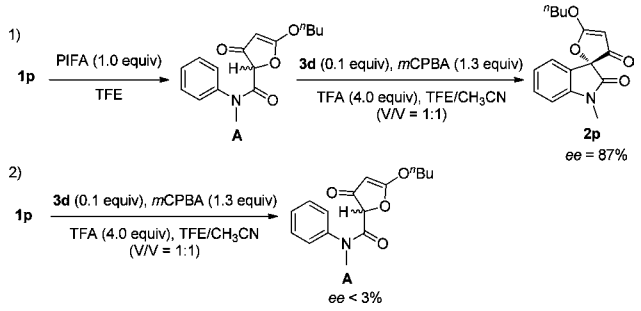


Figure 1. X-ray structure of (*R*)-**2b**.

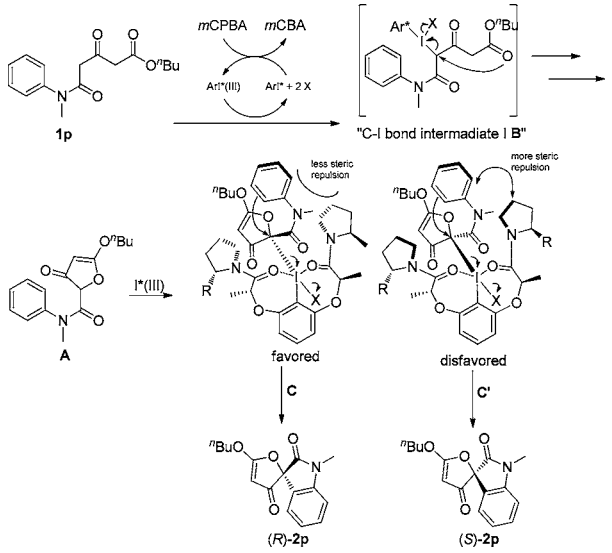
Control experiments were carried out, and the results are depicted in Scheme 3. First, when 1.0 equiv of PIFA was used as the sole oxidant, substrate **1p** was converted into the racemic intermediate **A**, which was transformed into the optically active product **2p** with an equal 87% *ee* under the optimized organocatalytic conditions (Scheme 3, eq 1). Furthermore, substrate **1p** was converted into the racemic intermediate **A** under the same optimized conditions (Scheme 3, eq 2). These results indicate that enantioselection occurred during the late-stage C−C bond formation step.

Scheme 3. Control Experiments for Mechanistic Studies



A plausible mechanism has been proposed and is described in Scheme 4. First, substrate **1p** reacts with the iodine(III)

Scheme 4. Plausible Mechanistic Pathway for the Formation of 2p



reagent, generated in situ from reaction of the chiral iodobenzene and *m*CPBA, to give a C−I(Ph) bond intermediate **B**.[9a,d,13,14] It is worthy of note that in Gong's work,[10a] it was the *O*-enolate (O−I−Ar*) intermediate that was generated, possibly on the basis of the mechanism we proposed.[12] On the basis of the computational results reported by Sunoj,[13] we now tentatively propose that it is the *C*-enolate (C−I−Ar*) intermediate **B** that is formed from the reaction of substrate **1p** and the hypervalent iodine species. This intermediate proceeds to form intermediate **A** through intramolecular C−O bond formation. Further oxidation of intermediate **A** as a result of the formation of another C−I bond affords the chiral intermediates **C** and **C′**, which further leads to the formation of the optically active product **2p** through an intramolecular C−C bond formation/C−I bond cleavage process.[10a] The chiral intermediates **C** and **C′** are thought to have intramolecular n−σ^* interactions between the electron-deficient iodine(III) center and the carbonyl groups.[9a,d] In a comparison of the two configurations of the chiral intermediate, the aniline moiety in **C** is facing away from the bulky substituent, making the *Si* face of the 2-furanone moiety open to nucleophilic attack by the benzene ring, while in contrast, the *Re* face of the 2-furanone moiety in **C′** is more shielded by the bulky cyclic amide, thus making the

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spirocyclization process more difficult to occur. As a result, product (*R*)-**2p** is formed in a more favored way.

In summary, we have disclosed an unprecedented cascade cross-coupling reaction involving the sequential formation of a C−O bond and a C−C bond catalyzed by a flexible chiral iodoarene of C_2-symmetry and resulting in the asymmetric synthesis of the biologically important spirofurooxindole skeleton.[15] This protocol provides a convenient pathway to access optically active spirofurooxindoles with excellent enantioselectivity. Further investigation of the applications of this methodology is in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02816.

Experimental procedures and compound characterization data (PDF)
Crystallographic data for **2a** (CIF)
Crystallographic data for (*R*)-**2b** (CIF)

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Notes

The authors declare no competing financial interest.

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(15) We also replaced the aniline moiety with a phenol and examined the spirolactonization of the analogous ester substrate. Unfortunately, no desired spirolactone product was obtained under our present conditions (see the Supporting Information for details).

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