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# Chiral Aryliodine-Catalyzed Asymmetric Oxidative C−N Bond Formation via Desymmetrization Strategy

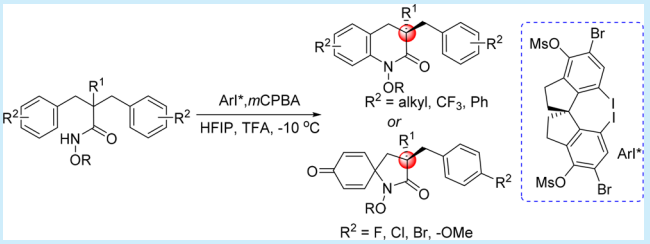
Qiang Ding,[†,‡] Huan He,[†,‡,§] and Qian Cai*[,†,‡]

[†]College of Pharmacy, Jinan University, No. 601 Huangpu Avenue West, Guangzhou 510632, China

[‡]Guangzhou City Key Laboratory of Precision Chemical Drug Development and [§]College of Chemical and Pharmaceutical Engineering, Hebei University of Science and Technology, Shijiazhuang 050018, China

Supporting Information

**ABSTRACT:** An asymmetric oxidative C−N bond-forming reaction is developed using a chiral diiodospirobiindane derivative as the catalyst and *m*CPBA as a terminal oxidant. The protocol is based on an asymmetric desymmetrization strategy and affords lactams or spirolactams according to the different substituents on the substrates. The products are obtained in good yields and moderate to high enantioselectivities.






Transition-metal-catalyzed coupling reactions of aryl halides or pseudohalides with nucleophiles, such as a Pd-catalyzed Buchwald−Hartwig reaction or copper-catalyzed Ullmann-type coupling reactions, have become the most important methods for the construction of aryl carbon−carbon and carbon−heteroatom bonds.[1] However, despite its enormous utility, the requirement of using prefunctionalized substrates such as aryl halides or aryl pseudohalides may cause synthetic inconvenience as it often takes multiple steps for prefunctionalization. Important alternatives to avoid the prefunctionalization of the aryl ring have been developed for the formation of aryl carbon−heteroatom bonds, such as transition-metal-catalyzed C−H activation/functionalization[2] and hypervalent iodine(III) reagent (or the hypervalent iodine(III) species generated in situ from ArI and oxidants) mediated oxidative coupling reactions.[3]

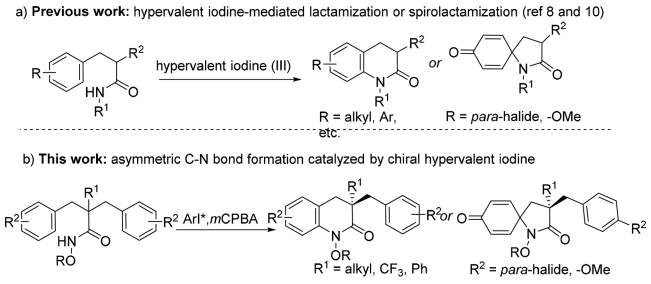
Hypervalent iodine(III)-promoted transformations have gained much attention from synthetic chemists due to its avoidance of transition metals, low toxicity, and mild reaction conditions.[4] The use of chiral hypervalent iodine(III) species in enantioselective transformations has also emerged in recent years, and many advances have been achieved,[5] such as asymmetric oxidation of sulfides to sulfoxides, dearomatization reactions, arylation reactions, α-functionalization of ketones, and functionalization of alkenes. However, chiral hypervalent iodine-promoted asymmetric reactions still remain one of the most challenging areas in asymmetric chemistry due to the limitation of reaction types, the poor availability of the chiral skeleton, and the unsatisfactory enantioselectivity in many reactions. Thus, it is highly desirable to develop chiral hypervalent iodine(III)-promoted novel asymmetric transformations.

We have developed a variety of transition-metal-catalyzed enantioselective aryl carbon−heteroatom coupling reactions[6] via the asymmetric desymmetrization strategy[7] for the formation of central chirality. The substrate scope has been constrained in some cases due to the limited availability of prefunctionalized aryl substrates. This prompted us to seek the possibility of using unprefunctionalized substrates, and our attention was turned to chiral hypervalent iodine mediated oxidative coupling reactions.

Aryl-substituted amides have been reported to undergo intramolecular lactamization[8,9] or spirolactamization[10] in the presence of hypervalent iodine species. We envisioned that an asymmetric oxidative C−N bond-forming reaction may be achieved through a catalytic desymmetrization process by chiral hypervalent iodine(III) generated in situ from chiral ArI and *m*CPBA (Scheme 1). Herein, we would like to disclose the details of this research.

Our research was initiated with the asymmetric desymmetrization of 2-benzyl-*N*-isopropoxy-2-methyl-3-phenyl propanamide (**1a**) as a model case. The reaction was first explored in different solvents under the catalysis of 10 mol % of diiodospirobiindane (C1) with *m*CPBA as a terminal oxidant.

**Scheme 1. Lactamization or Spirolactamization via Asymmetric Oxidative C−N Bond Formation**

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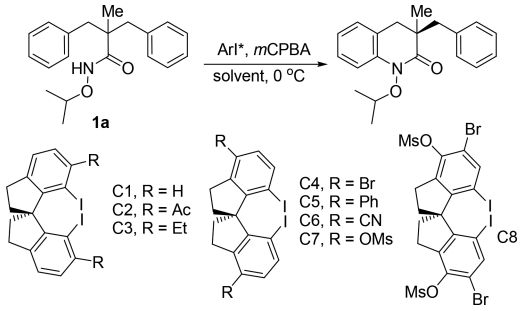
It was found that HFIP is the best solvent, which afforded the coupling product **2a** in 60% yield and 28% ee at room temperature (Table 1, entries 1−5). It has been reported by

**Table 1. Screening Reaction Conditions for Cyclization**[a]



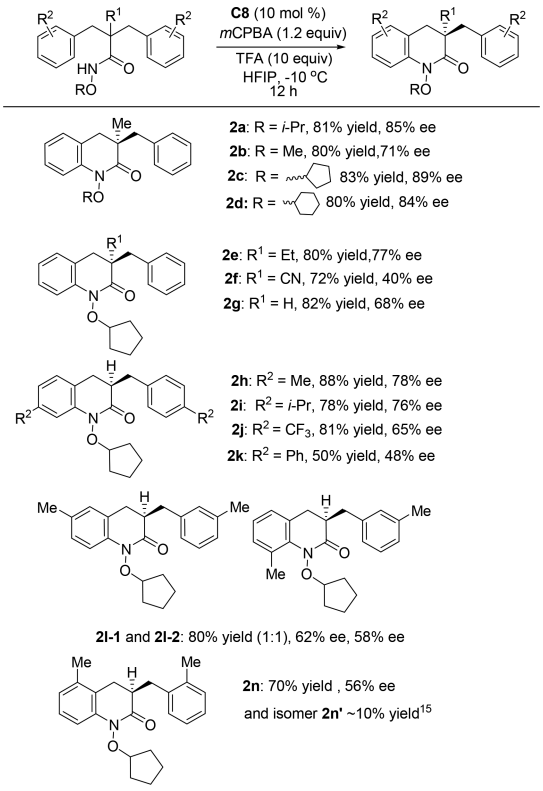

| entry | ArI | solvent | additive | yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|---|
| 1 | C1 | HFIP | | 60 | 28 |
| 2 | C1 | *i*-PrOH | | 50 | 0 |
| 3 | C1 | MeCN | | 62 | <10 |
| 4 | C1 | DCM | | 55 | <5 |
| 5 | C1 | toluene | | 60 | <10 |
| 6 | C1 | HFIP | TFA (1.5 equiv) | 68 | 46 |
| 7 | C1 | HFIP | TFA (5.0 equiv) | 70 | 50 |
| 8 | C1 | HFIP | TFA (10.0 equiv) | 72 | 51 |
| 9 | C1 | TFA | | 87 | 44 |
| 10 | C2 | HFIP | TFA (10.0 equiv) | 67 | 40 |
| 11 | C3 | HFIP | TFA (10.0 equiv) | 65 | 30 |
| 12 | C4 | HFIP | TFA (10.0 equiv) | 70 | 61 |
| 13 | C5 | HFIP | TFA (10.0 equiv) | 80 | 60 |
| 14 | C6 | HFIP | TFA (10.0 equiv) | 78 | 54 |
| 15 | C7 | HFIP | TFA (10.0 equiv) | 79 | 60 |
| 16 | C8 | HFIP | TFA (10.0 equiv) | 84 | 69 |
| **17**[d] | **C8** | **HFIP** | **TFA (10.0 equiv)** | **81** | **85** |

[a]Reagents and conditions: **1a** (0.1 mmol), ArI* (0.01 mmol), *m*CPBA (0.12 mmol), HFIP (0.5 mL), rt, 4 h. [b]Isolated yield. [c]Enantiomeric ratio was determined through HPLC. [d]−10 °C.

Barton[11] that hypervalent iodine could be activated by acid additives, and the effect of acid promoters has also been investigated in other asymmetric transformations.[12] Thus, we investigated the effect of acid promoters in our reactions. It revealed the enantioselectivity could be improved to about 50% ee by adding 5 or 10 equiv of TFA (Table 1, entries 6−8).[13] Further additions of TFA led to a slight reduction of enantioselectivity, and 44% ee was obtained with TFA as the solvent (Table 1, entry 9). Further modifications on the catalyst were then conducted. The introduction of substituents on the *ortho*-position of iodides seemed detrimental to the enantioselectivity, as observed in the case of C2 and C3[14] (Table 1, entries 10 and 11). However, better enantioselectivities were observed when suitable substituted groups were installed on the *para*-positions of the two iodine atoms (Table 1, entries 12−15). Finally, chiral catalyst C8 was found to afford the desired product with 84% yield and 69% ee at room temperature (Table 1, entry 16). Similar yield and better enantioselectivity (81% yield and 85% ee) were obtained by reducing the reaction temperature to −10 °C (Table 1, entry 17).

With the optimized conditions in hand, we then explored the substrate scope, and the results are shown in Scheme 2. The effect of different alkoxy substituents on the nitrogen of

**Scheme 2. Asymmetric Oxidative Lactamization**




amide was first examined. It revealed that substrate **1c**, with a cyclopentyloxy substituent, delivered the corresponding product **2c** with an enantioselectivity better than that of **2a**. Then we explored different substituents, such as −Et, −CN, and hydrogen on the prochiral carbon center. The corresponding lactam products **2e−g** were obtained in good yields and moderate enantioselectivity. The substrates with different substituents, such as Me-, *i*-Pr-, Ph-, or $CF_3$- on the *para*-positions of the aryl rings and a hydrogen atom at the prochiral carbon center (**1h−k**), were then explored and also afforded the desired coupling products with high yields and moderate enantioselectivity (**2h−k**). For substrate **1l** with methyl groups on the *meta*-positions of two aryl rings, two regioisomers **2l-1** and **2l-2** were formed in a 1:1 ratio and were found with 62 and 58% ee, respectively. However, for substrate **1n** with *o*-methyl groups on the two aryl rings, one rearrangement product was also isolated in addition to the normal coupling product **2n**.[15] Finally, the absolute configurations of products **2a** and **2g** were assigned as *R* by reducing these compounds to their corresponding tetrahydroquinolines and comparing them with our previously reported literature data.[16]

It was reported by Kikugawa[8f,g] and Kita[10] that 3-arylpropanamides with halide or −OR groups on the *para*-positions of aryl rings will undergo oxidative spirocyclization to afford interesting dearomatizing[17−19] N-fused spirolactam products. Such patterns were also observed in desymmetrization reactions. As shown in Scheme 3, the reaction of **3a** afforded spirolactam **4a** in high yield and good enantioselectivity. Similar results were obtained in the cases of **3b−d** with F, Br, and −OMe on the aryl rings. Corresponding products **4b−d** were delivered in high yields and low to moderate enantioselectivity. Similarly, substrates **3e−f**, with variant substituents (H or Et) on the prochiral carbon, have



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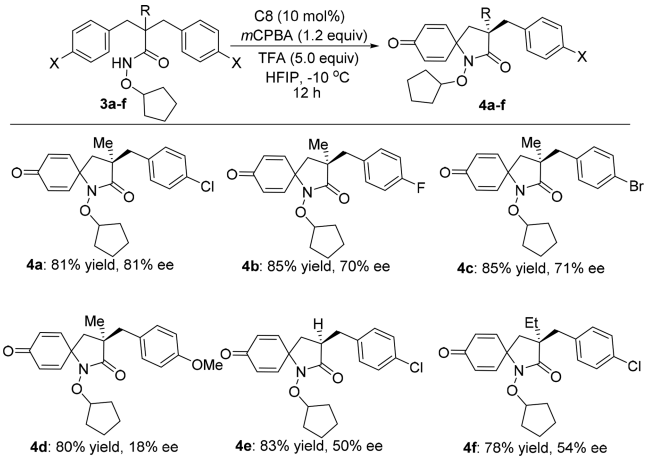
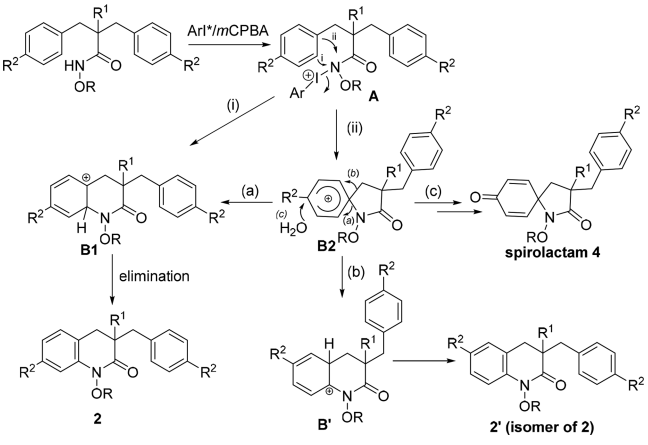
**Scheme 3. Asymmetric Oxidative Spirolactamization**




also been explored and furnished the corresponding spirolactam products **4e–f** in high yields and moderate enantioselectivities.

Although hypervalent iodine(III)-promoted reactions have been studied for a long time, the mechanism is far from being fully understood. Based on the literature reports,[4,8−10] the C−N bond-forming mechanism may be through the reactions of key intermediate nitrenium ion **A**, which was formed by reacting the amide substrates with a hypervalent iodine(III) species (Scheme 4). Intramolecular attack of nitrenium ion by

**Scheme 4. Proposed Mechanism**




the aryl ring may lead to the formation of two intermediates, **B1** or **B2**. Intermediate **B1** could furnish lactams via simple elimination. Intermediate **B2** may undergo different pathways to form variant products, which are governed by the nature of the substrates and showed great uncertainty in our observations. For the reactions of **3a–f**, the attack of spiro intermediate **B2** by water or solvent led to the formation of spirolactam **4a–f**, as proposed by Kikugawa[8f,g] and Kita.[10b] However, intermediate **B2** may also undergo N-migration (path a) or C-migration (path b) to form intermediate **B1** or **B′**, respectively, which may further be transformed into **2** or **2′** via elimination. As observed in our experiments, substrates **1e–l**, bearing different substituents on the aryl rings but with a hydrogen atom at the prochiral center, afforded lactams **2e–l**, and no isomers of **2′** were isolated. However, in the reaction of **1n**, a small amount of byproduct **2n′** was isolated, and the structure was confirmed to be the C-migration product.[15] Thus, we cannot exclude the C-migration mechanism to form **B′** and lead to the formation of **2′** in other cases. A similar rearrangement mechanism was also reported in recent literature.[20] Our observations further confirmed the possibility of such a rearrangement and showed the mechanistic complications in hypervalent iodine(III)-promoted reactions.

In summary, we have developed a chiral aryliodine-catalyzed oxidative C−N bond-forming reaction. Intramolecular desymmetrization reactions transformed amide into lactams or spirolactams in moderate to good enantioselectivities. Although the mechanisms for reaction selectivity and enantiocontrol are unclear, some interesting results have been observed, which may provide important hints in further development of hypervalent iodine-promoted asymmetric reactions.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01849.

Full experimental and characterization data, including $^{1}H$ and $^{13}C$ NMR for all the new compounds, chiral HPLC spectra for the products (PDF)

## ■ AUTHOR INFORMATION

### Corresponding Author

*E-mail: caiqian@jnu.edu.cn.

### ORCID

Qian Cai: 0000-0002-5700-3275

### Notes

The authors declare no competing financial interest.

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