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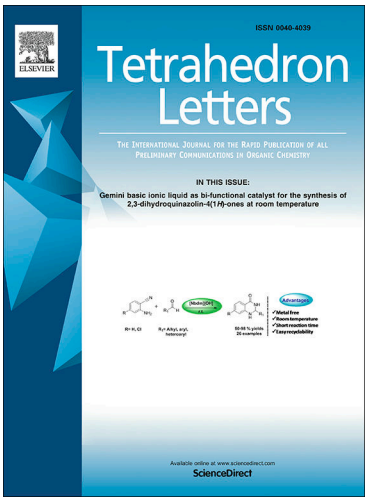

Highly stereoselective organocatalytic synthesis of pyrrolidinyl spirooxindoles containing halogenated contiguous quaternary carbon stereocenters

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Graphical Abstract

Highly stereoselective organocatalytic synthesis of pyrrolidinyl spirooxindoles containing halogenated contiguous quaternary carbon stereocenters

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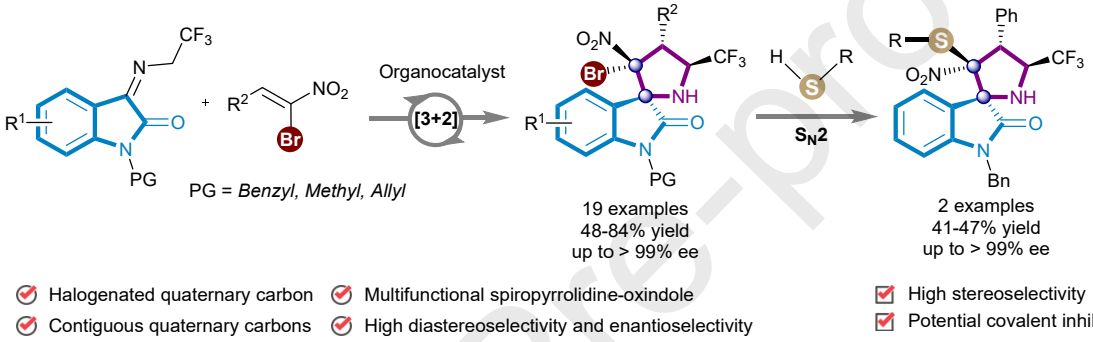

- Halogenated quaternary carbon
- Contiguous quaternary carbons
- Multifunctional spiropyrrolidine-oxindole
- High diastereoselectivity and enantioselectivity
- High stereoselectivity
- Potential covalent inhibitor

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Highly stereoselective organocatalytic synthesis of pyrrolidinyl spirooxindoles containing halogenated contiguous quaternary carbon stereocenters

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ABSTRACT

The highly stereoselective synthesis of pyrrolidine-fused spirooxindole derivatives bearing a carbon-halogen bond and contiguous quaternary carbon stereocenters was achieved *via* a [3+2] cycloaddition reaction. This method provided facile access to a collection of enantiomerically pure spiro[pyrrolidin-3,2'-oxindoles] containing halogenated contiguous quaternary carbon stereocenters in good to high yields (48-84%) and excellent stereoselectivity (up to >20:1 dr and >99% ee). The halogen-containing products can be stereoselectively transformed into sulfurated derivatives *via* nucleophilic substitution (S_N2) reactions, indicating that they may serve as candidates in the development of covalent inhibitors with potential biological activity.

Introduction

Quaternary carbon stereocenters (QCS), especially contiguous QCS (CQCS), are ubiquitous in natural products and pharmaceutical compounds (Fig. 1a).[1] Halogens are often found embedded in the tetrasubstituted stereocenters of compounds with high utility in organic synthesis and medicinal chemistry (Fig. 1b).[2] Chemists have largely focused on the synthesis of CQCS with all-carbon substituents and great efforts have been made in this field. However, the construction of halogenated CQCS has been less explored despite their unique versatility in enabling efficient transformations (Scheme 1a).[3] Existing routes to halogenated CQCS commonly rely on substitution or addition reactions to introduce halogen atoms (Scheme 1b, c).[3c,3d] However, a large amount of byproduct formation and tedious purification cannot be avoided through such methods. Therefore, developing atom- and step-economical approaches for the direct construction of halogenated CQCS under mild conditions would be highly desired. For example, stereoselective C–C bond formation *via* the addition of a bromo-substituted carbanion to a C=Y (Y=C, N, O) bond would serve as an idea pathway (Scheme 1d).[3e,3g,3n,3o] Steric congestion imposed by the vicinal quaternary stereocenters is the main challenge in this scenario.

On the other hand, the spiropyrrolidine-oxindole motif represents an attractive synthetic target because it widely exists

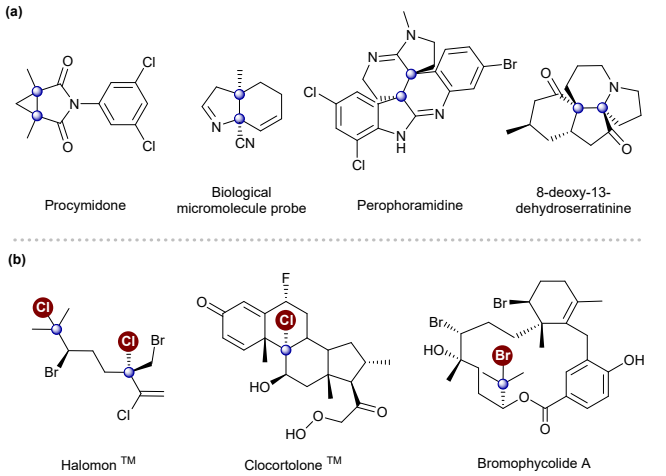
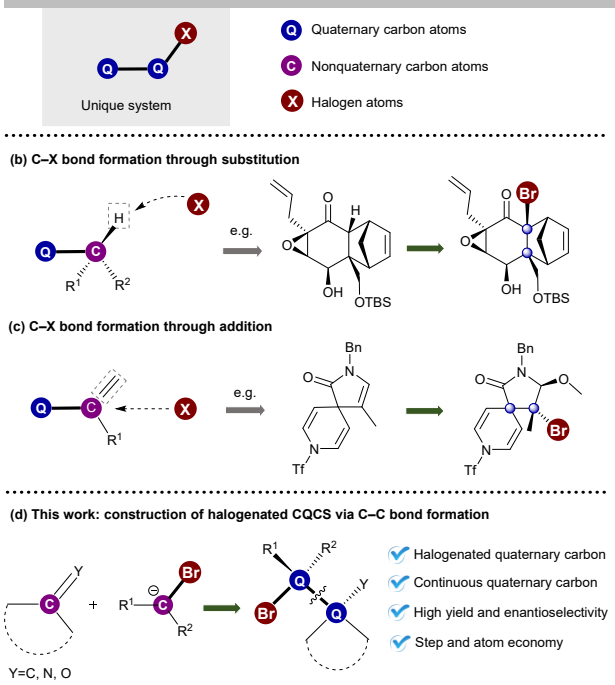


Figure 1. (a) Bioactive compounds containing CQCS. (b) Medicinal compounds with halogenated QCS.

in many natural products and has been reported to possess various types of bioactivity.[4] In 2013, Xu and co-workers reported that isatin derived ketimines can serve as efficient azomethine ylide precursors to construct chiral spiropyrrolidine-oxindoles *via* [3+2] cycloaddition.[5] In 2015, Wang and co-workers developed the *N*-(2,2,2-trifluoroethyl) isatin ketimines, which could be used in the rapid assembly of CF_3-containing

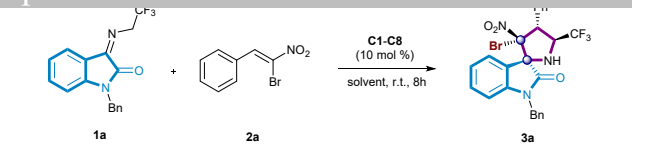


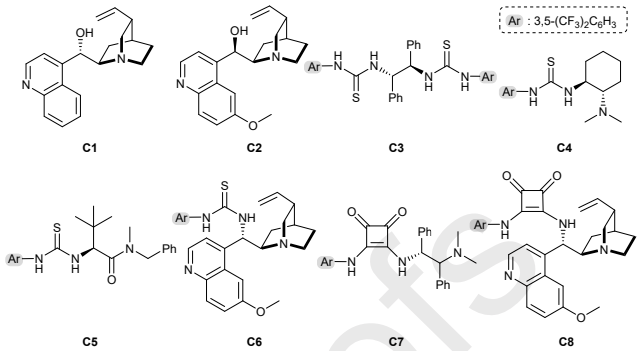
Scheme 1. Strategies for the construction of halogenated CQCS.

spiro-[pyrrolidine-oxindole] derivatives.[6] Given the recent achievements in the asymmetric synthesis of spiropyrrolidine-oxindoles,[7] it would be interesting to incorporate chiral halogenated CQCS and CF_3 groups into a pyrrolidine-fused spirooxindole skeleton. Based on our continuing interest in the construction of drug-like frameworks,[8] herein we described the direct synthesis of spiro[pyrrolidin-3,2'-oxindoles] containing halogenated CQCS and CF_3 units. (*Z*)-α-Bromonitroalkenes were selected as the C2-synthons because they are highly reactive and versatile in organic synthesis and easily accessible.[9] In the asymmetric [3+2] cycloadditions of isatin-derived ketimines with α-bromonitroalkenes, four contiguous chiral stereocenters, including two CQCS (one halogenated CQCS), could be built directly through a C–C bond formation pathway.

Results and Discussion

We initiated our study by investigating the [3+2] cycloaddition reaction of isatin-derived ketimine **1a** and (*Z*)-α-bromonitroalkene **2a**. As summarized in Table 1, spiro[pyrrolidin-3,2'-oxindole] **3a** containing halogenated CQCS and CF_3 units was obtained with good diastereoselectivity at room temperature when Cinchona alkaloids (**C1** or **C2**) were used as the catalyst. However, only low reaction yield and poor enantioselectivity could be obtained (Entry 1 and 2). The chiral bis(thiourea) catalyst **C3** provided an unsatisfactory result (Entry 3). Both yield and enantioselectivity were improved by employing bifunctional tertiary amine-thiourea catalysts (Entries 4-6, **C4**-**C6**). To achieve better conversion and stereocontrol, the tertiary amine-squaramide catalyst **C7** was tested in the reaction, providing **3a** in 73% yield with >20:1 dr, and 87% ee (Entry 7). Moreover, the cinchonidine-derived squaramide catalyst **C8** further improved the yield and enantioselectivity (Entry 8). Product **3a** could be obtained under complete stereocontrol (84% yield, >20:1 dr, and >99% ee). Then different solvents were evaluated (Entries 9-13) where CH_2Cl_2 proved to be the optimal choice. The high enantioselectivity was maintained when the catalyst loading was reduced to 5 mol% (Entry 14). The practicality of this method was demonstrated by a scale-up





Entry	Catalyst	Solvent	Yield **3a** [%][b]	dr[c]	ee [%][d]
1	**C1**	CH_2Cl_2	34	11:1	43
2	**C2**	CH_2Cl_2	39	11:1	-21
3	**C3**	CH_2Cl_2	43	11:1	33
4	**C4**	CH_2Cl_2	59	17:1	75
5	**C5**	CH_2Cl_2	59	17:1	60
6	**C6**	CH_2Cl_2	66	18:1	53
7	**C7**	CH_2Cl_2	73	>20:1	87
8	**C8**	CH_2Cl_2	84	>20:1	>99
9	**C8**	MeOH	23	12:1	40
10	**C8**	Toluene	48	13:1	51
11	**C8**	THF	67	17:1	79
12	**C8**	MeCN	68	>20:1	85
13	**C8**	$C_2H_4Cl_2$	79	>20:1	92
14[e]	**C8**	CH_2Cl_2	71	>20:1	>99
15[f]	**C8**	CH_2Cl_2	70	>20:1	>99

[a] Unless noted otherwise, reactions were performed with **1a** (0.10 mmol), **2a** (0.15 mmol), catalyst (10 mol%) in solvent (2 mL) at room temperature. [b] Isolated yield of pure diastereomer **3a**. [c] Determined by ^{1}HNMR spectroscopy. [d] Determined by HPLC on a Chiralpak AD-H column (20% 2-propanol/n-hexane, 1 mL/min), UV 254 nm. [e] Catalyst (5 mol%) was used. [f] The reaction was scaled up to 1.0 mmol.

experiment, which afforded **3a** in 70% yield with >99% ee, suggesting that this procedure is quite reliable (Entry 15).

Using the optimized catalyst and reaction conditions, various isatin-derived ketimines **1** and (*Z*)-α-bromonitroalkenes **2** were evaluated for conversion to the enantioenriched spiro[pyrrolidin-3,2'-oxindoles] **3** containing halogenated CQCS and CF_3 units (Table 2). Using **2a** as the nitroalkene partner, ketimine substrates bearing chloro-, bromo- and alkyl groups on the oxindoles gave products **3c**-**3g** in 70%-80% yield and excellent stereoselectivity (up to >20:1 dr and >99% ee). 5-Fluoro-isatin-derived ketimine **1b** afforded **3b** in modest yield with complete stereocontrol. Subsequently, various α-bromonitroalkenes were examined in the reaction. Substrates **2** with electron-donating or -withdrawing substituents (F, Cl, Br, Me, and MeO) at different positions of the phenyl ring were well tolerated. The corresponding products **3h**-**3p** were obtained in 62%-82% yield with high diastereoselectivity and excellent enantioselectivity (95%->99% ee). In order to further probe the steric influence of the R^2 group on the reaction we tested sterically bulky naphthalene substituted α-bromonitroalkene **2q**. A slightly

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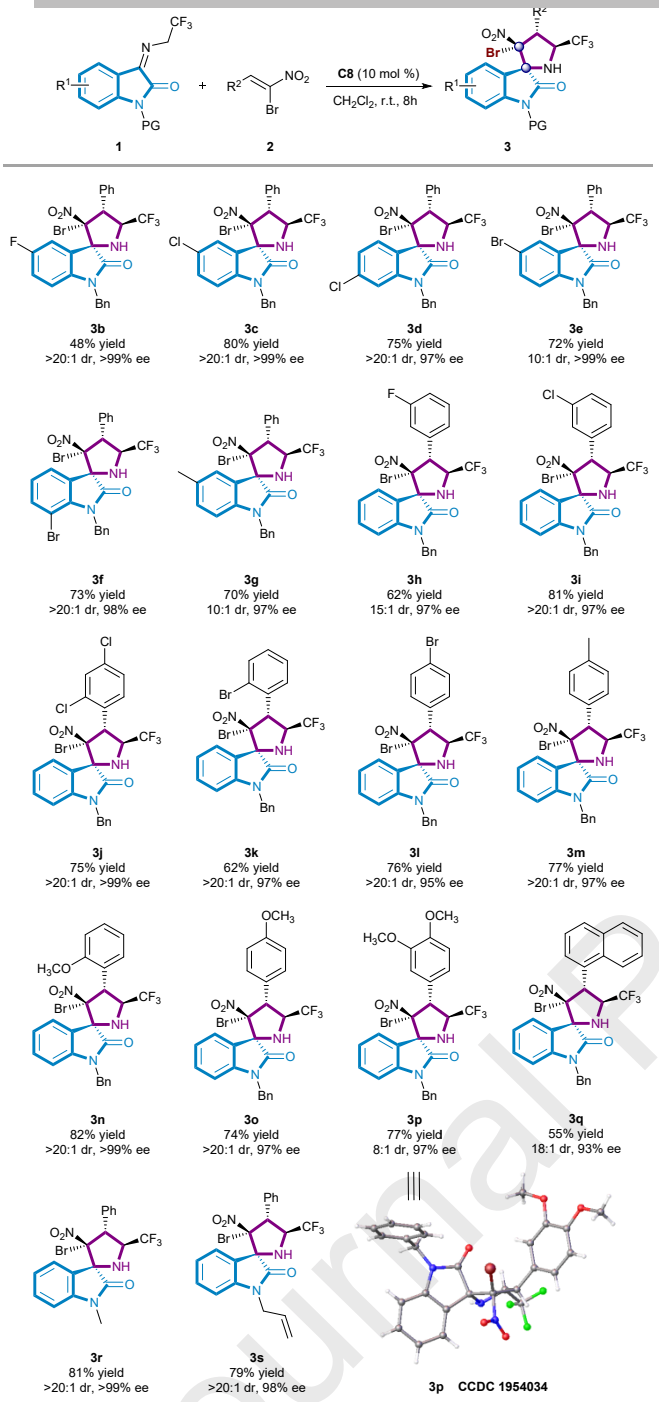
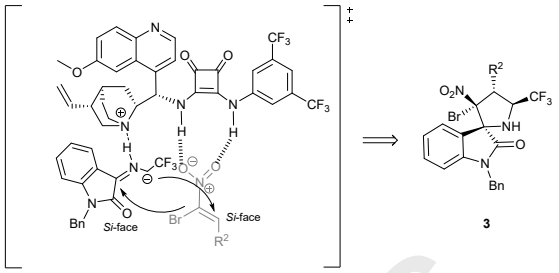


[a] Reactions were performed with **1a** (0.10 mmol), **2a** (0.15 mmol), **C8** (10 mol%) in CH_2Cl_2 (2 mL) at room temperature. [b] Yield of products isolated as diatereomeric mixtures. The dr value was determined by ^{1}HNMR analysis of the crude reaction mixture. The ee value was determined by chiral HPLC analysis of the major diastereoisomer.

decreased yield was observed, while the stereoselectivity was not affected (**3q**).

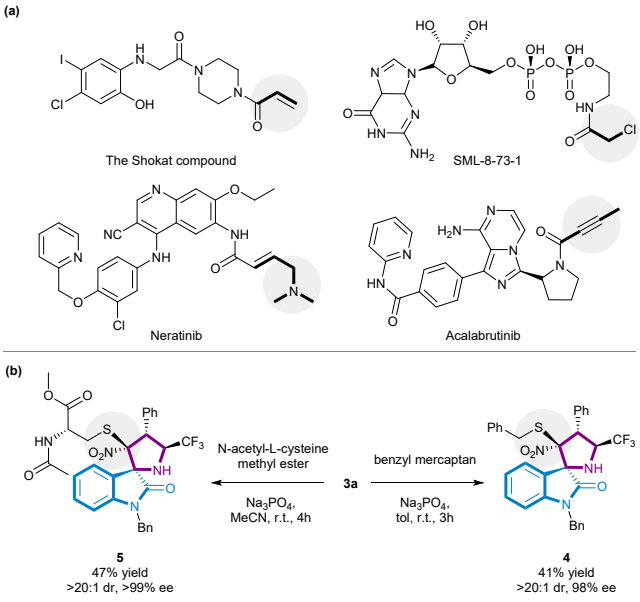
Different *N*-protecting groups on isatin-derived ketimine **1**, such as the methyl and allyl group, were also compatible (**3r** and **3s**). The absolute configuration of product **3p** was assigned unambiguously *via* single-crystal X-ray analysis, and a plausible transition state model is proposed to explicate the observed stereochemical preference. As shown in Scheme 2, cinchonidine-derived squaramide catalyst **C8** promotes the [3+2] cycloaddition reaction in a dual activation model. *N*-(2,2,2-Trifluoroethyl) isatin ketimines are activated by deprotonation by the tertiary reacting carbon anion. Concurrently, the H-bonding activation of (*Z*)-α-bromonitroalkene by the squaramide moiety of catalyst **C8** facilitates nucleophilic attack from the *Si*-face by the carbon anion. Subsequently, the newly formed α-carbon anion attacks



Scheme 2. Proposed transition state for the [3+2] cycloaddition reaction.

the *Si*-face of the isatin ketimines, thus leading to the formation of spiro[pyrrolidin-3,2'-oxindoles] bearing four contiguous chiral stereocenters including two CQCS (one halogenated CQCS).

Covalent inhibition is a rapidly growing discipline within drug discovery.[10] With regard to the development of covalent inhibitors, the main covalent warheads used to target cysteine have been reported (Scheme 3a).[11] Considering the unique structure of bromide **3**, we explored the transformations using them as alkylating reagents. When **3a** was treated with nucleophiles containing mercapto groups, such as benzyl mercaptan or *N*-protected cysteine methyl ester, high enantiomerically pure spiro[pyrrolidin-3,2'-oxindoles] **4** and **5** with sulfurated CQCS were formed (Scheme 3b). The reversed configuration of the previous carbon-bromine quaternary centers indicated that the reactions proceeded through a S_N2 process. The covalent binding of the products to cysteine enables us to use these halogenated scaffolds to develop potential covalent inhibitors with biological activity.



Scheme 3. (a) Selection of covalent warheads that have been used to target cysteine. (b) S_N2 reaction of **3a** with benzyl mercaptan and *N*-protected cysteine methyl ester.

Conclusion

In summary, we have developed a highly stereoselective [3+2] cycloaddition reaction of isatin-derived ketimines and (*Z*)-α-bromonitroalkenes using a cinchona alkaloid-derived tertiary amine-squaramide catalyst under mild conditions. This reaction highlights the efficient construction of multifunctional

and CF_3 units, each of which are highly important structural motifs in medicinal chemistry research. The halogen-containing products can be stereoselectively transformed into sulfurated derivatives by nucleophilic substitution (S_N2) reactions, indicating that they may serve as interesting compounds in the exploitation of covalent inhibitors with potential biological activity. Further studies on the bioactivity of the resulting compounds are underway in our laboratories.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Graphical Abstract

Highly stereoselective organocatalytic synthesis of pyrrolidinyl spirooxindoles containing halogenated contiguous quaternary carbon stereocenters

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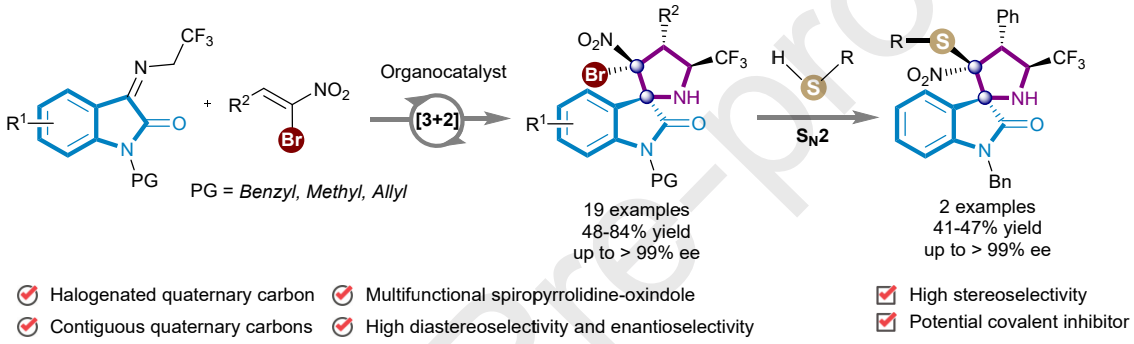

12.

Highlights

1. Access to halogenated contiguous quaternary carbon stereocenters (CQCS).

2. Halogenated CQCS and CF_3 group were introduced into spiro[pyrrolidin-3,2'-oxindoles].

3. High stereoselectivity and high efficiency.

4. The transformation of the products discloses potential use as covalent inhibitors.

13.