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Enantioselective Copper-Catalyzed Borylative Cyclization with Cyclic Imides

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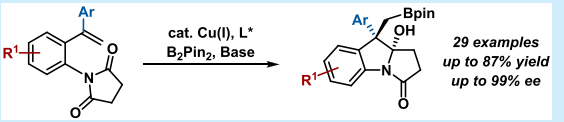
Supporting Information

ABSTRACT: An enantioselective borylative cyclization cascade utilizing cyclic imides has been developed. We employ a highly enantioselective borylcupration process that includes a 1,2-addition to a cyclic imide. The products contain a valuable hemiaminal and boronate handle for further elaborations within a congested framework. This work demonstrates the utility of cyclic imides as simple precursors to unlock access to sought-after polycyclic indolines. Futhermore, this report highlights the capability to harness reactive catalytic intermediates to exploit otherwise unreactive functional groups.

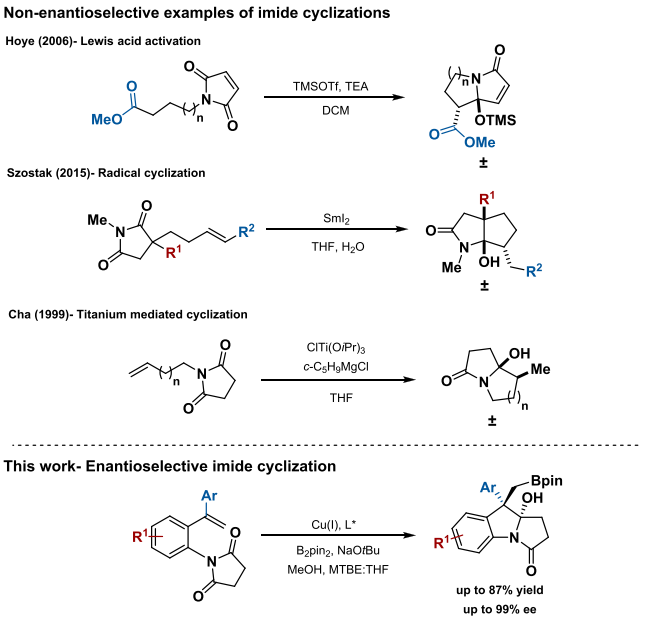


Cyclic imides have found limited use in asymmetric catalysis despite their potential to access valuable stereoenriched hemiaminals.[1] This is likely attributable to their relatively stable nature when compared to traditionally employed acyl groups such as ketones and aldeyhydes. Chiral hemiaminals and imides are ubiquitous in natural products and are often embedded in polycyclic systems.[2] As a result, hemiaminal-containing heterocycles have become key targets in organic synthesis. Although this framework appears readily accessible via cyclization from the corresponding imide, no enantioselective examples have been reported to date.[3] Several nonenantioselective cyclizations have been developed by Hoye,[4] Szostak,[5] Cha,[6] and others (Scheme 1);[7] however, these methods often employ stoichiometric Lewis or Brønsted acids, or radical initiators, thereby hindering asymmetric variants. To address this synthetic challenge, we envisioned harnessing a chiral benzylic copper intermediate to react with a tethered imide by employing an asymmetric borylcupration process.

The asymmetric addition of boron to olefins is an indispensable tool to readily introduce molecular complexity and flexibility. Copper catalysis has played a central role in fully realizing the potential of this concept, often via the 1,2-bisfunctionalization of alkenes.[8] Ito,[9] Hoveyda,[10] and Brown[11] have illustrated this approach by employing various π-systems and a plethora of external electrophiles. These methods initiate through an enantioselective borylcupration across a π-system, followed by electrophilic trapping of the organocopper intermediate. Carbonyl-based reagents, including acid halides,[12] esters,[13] ketones,[14] aldehydes,[15] and carbamoyl chlorides,[16] have been investigated as electrophiles; however, imides remain entirely unexplored.

We aimed to exploit the unrealized potential of cyclic imides as terminal electrophiles to access polycyclic indolines in a borylative cyclization.[17] This cascade reaction has been studied to assemble simple ring systems[18] and bicyclic carbocycles[19] while employing well-known electrophiles. The application of this strategy to access polycyclic heterocycles remains largely underexplored. Polycyclic indolines have been widely studied due to their prevalence in natural products and pharmaceutically relevant compounds.[20] These frameworks are often found in congested ring systems containing sensitive functionalities and contiguous stereocenters. Although numerous asymmetric strategies have been developed to assemble complex indolines,

Scheme 1. Cyclization Strategies Employing Cyclic Imides[a]



[a]Examples of imide cyclizations to access hemiaminals.

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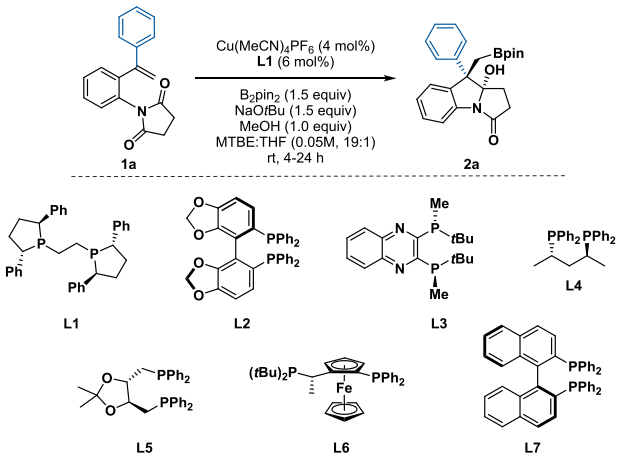
access to densely functionalized scaffolds remains a challenge.[21]

We initiated our work by screening conditions based on our previous report and found optimal conditions utilizing (*S,S*)-Ph-BPE as a chiral ligand.[16] The product was obtained in 80% yield as a single diastereomer in 97% ee. Other chiral ligands demonstrated significantly lower enantioselectivities (Table 1, entries 2−7). A solvent mixture of MTBE/THF (19:1) was employed; while MTBE was an effective solvent for high enantioselectivity, THF was required to improve the solubility of the substrate. Other ethereal solvents such as THF or dioxane delivered poorer results (Table 1, entries 8−9). It was found that one equivalent of methanol provided the best results, as bulkier alcohols showed lower enantioselectivities (Table 1, entries 10−12). Throughout the optimization, product **2a** was only obtained as a single diastereomer.

Table 1. Optimization of Reaction Conditions

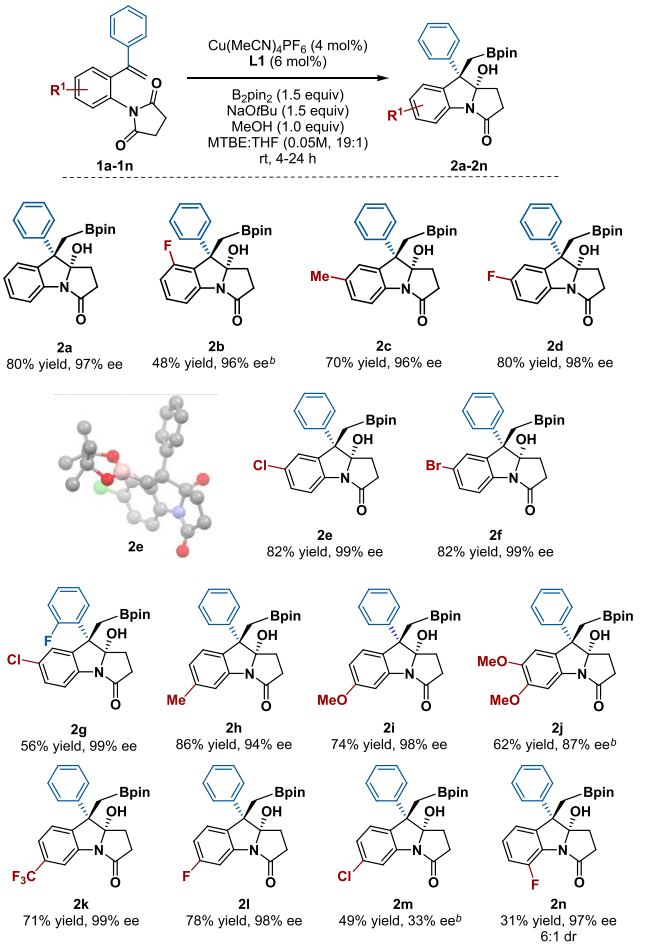


entry	variation of standard condition	conversion [%]	yield [%][a]	ee[b]
1	none	full	>83 (80)	97
2	**L2** instead of **L1**	full	81	−19
3	**L3** instead of **L1**	full	84	68
4	**L4** instead of **L1**	full	74	−53
5	**L5** instead of **L1**	full	81	45
6	**L6** instead of **L1**	74	20	−17
7	**L7** instead of **L1**	77	53	9
8	THF instead of MTBE/THF	full	39	89
9	dioxane instead of MTBE/THF	full	63	81
10	2 equiv of MeOH instead of 1 equiv	76	67	95
11	*i*PrOH instead of MeOH	full	72	95
12	*tert*-amyl alcohol instead of MeOH	full	79	95

[a]NMR yield determined by using 1,3,5-trimethoxybenzene as standard; isolated yield in parentheses. [b]Determined by chiral HPLC using OD-H column eluting with 25% IPA in hexanes.

Next, we examined the applicability of our methodology by varying the substitution on the aryl backbone (Scheme 2). Product **2b** was obtained in lower yield likely due to the increased steric bulk around the olefin; however, high enantioselectivity was maintained. A methyl group (**2c**) and various halogens (**2d**, **2e**, **2f**) were all tolerated with good yields and excellent enantioselectivities when situated *meta* relative to the alkene. The absolute stereochemistry was determined for **2e** by single crystal X-ray diffraction (CCDC 1944263), and all products are assigned their stereochemistry by analogy. A substrate bearing a chloride as well as an *ortho*-fluoride on the pendant ring (**2g**) showed no decrease in ee; however, it was obtained in only moderate yield. While electron-rich substituents (**2h**, **2i**) were tolerated in good yields and enantioselectivities, product **2j**, containing the dimethoxy substituents, was obtained in lower yield and enantioselectivity after 24 h. Electron-poor substituents such as trifluoromethyl (**2k**) and fluoride (**2l**) yielded products in excellent enantioselectivities. Consistent with our previous report,[16] product **2m** containing a *para*-chloride was obtained with very poor enantioselectivity. The analogous bromide substrate yielded only trace product (see Supporting Information (SI) for details). A fluoride substituent positioned *ortho* to the succinimide furnished product **2n** in high ee; however, poor yield and a lower dr were observed.

Scheme 2. Reaction Scope with Varied Aryl Backbone



[a]Reaction scope with varied aryl backbone (0.2 mmol scale) for 4 h unless otherwise indicated. All reported yields are after isolation; all observed in >20:1 dr unless otherwise indicated; ee determined by chiral HPLC. [b]Run for 24 h.

Following this study, we surveyed substitution patterns on the pendant aromatic ring (Scheme 3). We observed that methoxy and ethyl substituents (**4a** and **4b**) were tolerated with excellent enantioselectivities at the *meta* position. However, when examining electron-poor substituents (**4c** and **4e**), we observed lower enantioselectivities. Interestingly, introducing a chloride in the backbone (**4d**) led to an increase in enantioselectivity to 98% ee. Other *meta* substituents

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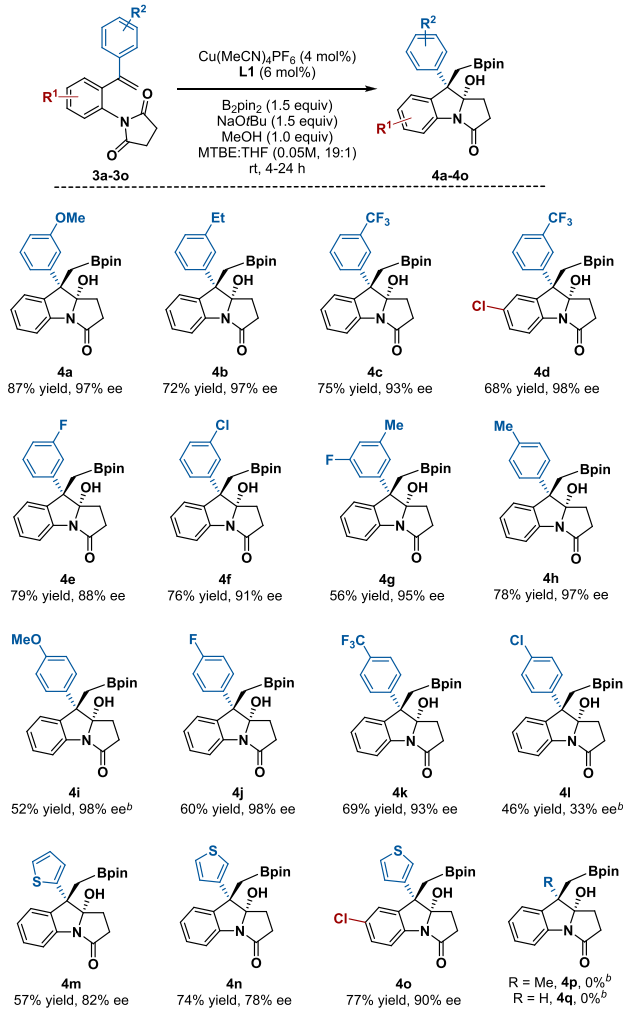
Scheme 3. Reaction Scope with Varied Alkenyl Substituents[a]

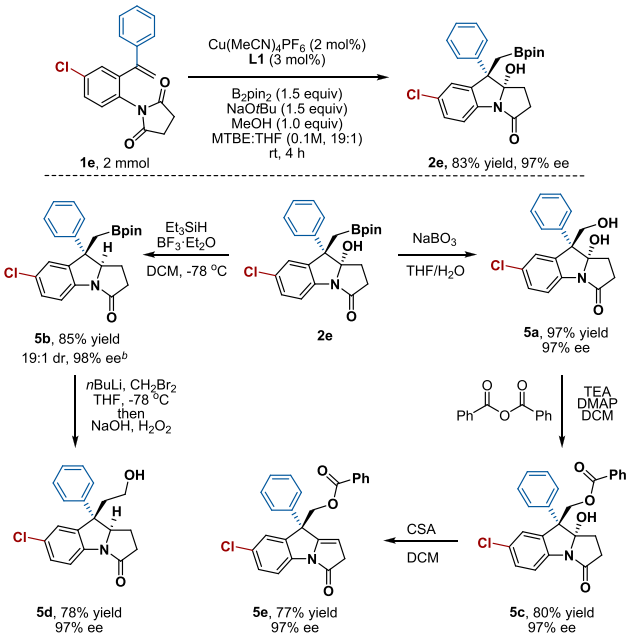


[a]Reaction scope with varied alkenyl substituents (0.2 mmol scale) for 4 h unless otherwise indicated. All reported yields are after isolation; all observed in >20:1 dr unless otherwise indicated; ee determined by chiral HPLC. [b]Run for 24 h.

including chloride (**4f**) and a disubstituted aryl ring (**4g**) were tolerated in moderate yields and good enantioselectivities. Product **4h** containing a *para*-methyl substituent was obtained in 78% yield and 97% ee. In the case of a methoxy substituent (**4i**), we observed a slower reaction that required 24 h; however, the product was obtained in excellent enantioselectivity. Electron-withdrawing substituents at the *para* position (**4j** and **4k**) gave excellent ee but led to a slight decrease in yield. Analogous to **2m**, product **4l** was obtained in lower yield and enantioselectivity. When aromatic rings were replaced with 2-thienyl (**4m**) or 3-thienyl (**4n**) groups, the products were obtained in lower enantioselectivities (82% and 78% ee respectively). However, introduction of a chloride to the aryl backbone (**4o**) restored enantioselectivity to 90% ee. Unfortunately, products bearing a methyl (**4p**) or no substituent (**4q**) could not be obtained (see SI for details). The analogous six-membered ring product could be obtained in poor yields and stereoselectivity (see SI for details).

To demonstrate the scalability of this process we performed the reaction using 2 mmol of **1e** while reducing the catalyst and ligand loadings (Scheme 4). Product **2e** was obtained in

Scheme 4. Scale-up and Derivatizations[a]



[a]Large scale reaction using 2 mmol of substrate (above). Derivatizations of product (below). All reported yields are after isolation; dr determined by ^{1}H NMR analysis of crude; ee determined by chiral HPLC. [b]Batch of **2e** used was 98% ee.

83% yield and 97% ee which was in good agreement with the small-scale result. Next, we aimed to showcase the versatility of the carbon−boron bond. We began with oxidation using sodium perborate and obtained alcohol **5a**, in 97% yield. The resulting primary alcohol could be selectively acylated in 80% yield (**5c**). Treatment of **5c** with CSA furnished enamine **5e** in 77% yield. Alternatively, the hemiaminal could be reduced with triethylsilane in the presence of a Lewis acid to provide **5b**, in 85% yield in 19:1 dr. We also successfully performed Matteson homologation followed by oxidation to obtain product **5d** in 78% yield, with minimal loss in enantiomeric purity.

In summary, we have developed an enantioselective copper-catalyzed borylation/1,2-imide addition cascade reaction to assemble boron-containing indolines. Our reaction exploits tethered imides as electrophiles to generate highly congested molecular frameworks. The process was found to be highly diastereo- and enantioselective and tolerated a variety of aryl substituents. The highly functionalized indoline products served as valuable platforms to access a diverse library of new indolines. This work demonstrates the utility of copper catalysis to assemble complex boron-containing heterocycles and establishes a new method to access biologically relevant indolines.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03144.

Experimental procedures, characterization data, ^{1}H/^{13}C NMR spectra, X-ray structures of **2e**, and HPLC spectra for new compounds (PDF)

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Accession Codes

CCDC 1944263 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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