Enantio- and Diastereoselective Synthesis of Chromeno[4,3-*b*]pyrrole Derivatives Bearing Tetrasubstituted Chirality Centers through Carbene Catalyzed Cascade Reactions

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Ⓢ Supporting Information

ABSTRACT: An NHC-catalyzed cascade cycloaddition reaction is developed for quick access to structurally sophisticated tetrahydrochromeno[4,3-*b*]pyrrole derivatives. A sterically congested tetrasubstituted chirality carbon center is formed during the cyclization process. All the α-, β-, and carbonyl carbons of the enal substrates are functionalized in chemo- and stereoselective fashion. The multicyclic chromeno[4,3-*b*]pyrrole products are generally afforded in good yields with excellent enantio- and diastereoselectivities. Heavily substituted pyrroline derivatives can be afforded from the chiral products through simple protocols.
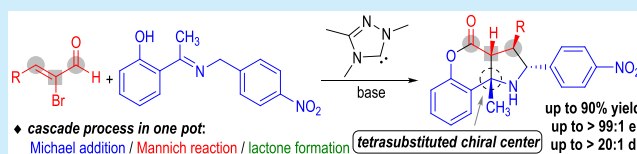
Tetrahydrochromeno[4,3-*b*] derivatives bearing multiple chirality centers are widely used in the development of human drugs with proven biological activities.[1] For example, the chiral molecule named MLS002174161 is a fully constrained rigid TRPV1 agonist and has potential applications in the treatment of localized chronic pain (Figure 1a).[1a] A variety of functional molecules containing tetrahydrochromeno[4,3-*b*]pyrrole cores possess partial agonist activities on TRPV1 and have been used in the mechanistic studies of analgesic agents (e.g., Figure 1a, **A**, **B**, and **C**).[1a] The HCl salt of azamedicarpin exhibits reliable inhibition activities against various microorganisms including bacteria and fungi.[1b] Therefore, the development of a facile and stereoselective method for the construction of tetrahydrochromeno[4,3-*b*]pyrrole frameworks is interesting.

N-Heterocyclic carbene (abbreviated as NHC or carbene) organocatalysis has experienced tremendous development in the past two decades.[2] A number of simple and readily available functional molecules can be activated by NHC catalysts to participate in various transformations in chemo- and stereoselective fashion.[3] α,β-Unsaturated acylazolium is one of the most important reactive intermediates generated from NHC catalysts and α,β-unsaturated carbonyl compounds.[4] The β-carbons of the α,β-unsaturated acylazolium intermediates are readily attacked by various nucleophiles through (hetero-) Michael addition reactions, with various cyclization products afforded in both enantioselective and nonasymmetric fashion.[5] Specifically, cascade cycloaddition reactions involving the functionalizations of all the α-, β-, and carbonyl carbons of the α,β-unsaturated acylazolium inter-

mediates have been disclosed in recent years (Figure 1b).[6] In 2013, Lupton and co-workers reported a facile synthesis of β-lactone derivatives through an NHC-catalyzed Ireland−Coates Claisen rearrangement, with all the α-, β-, and carbonyl carbon atoms of the α,β-unsaturated acylazolium intermediates functionalized in chemo- and diastereoselective fashion (Figure 1b, eq 1).[6a,e,h] Hui,[6b] Xu,[6i] Biju[6k] and co-workers reported a cascade cyclization process for the preparation of tricyclic δ-lactone molecules (Figure 1b, eq 2). Chiral pyrrolo[3,2-*c*]quinoline derivatives can be efficiently produced from rationally designed starting materials through a carbene-catalyzed Michael addition/Mannich reaction/lactam formation sequence (Figure 1b, eq 3).[6c,m] Similarly, cyclopenta[*c*]pyranone derivatives can be afforded in both chemo- and stereoselective fashion through various cascade addition reactions promoted by NHC organic catalysts (Figure 1b, eqs 4 and 5).[6f,g,j] In 2018, Biju and co-workers synthesized chiral pyrroloquinoline derivatives bearing up to four fused cyclic structures with good to excellent yields and enantioselectivities as single diastereomers (Figure 1b, eq 4).[6l] However, enantioselective synthesis of multicyclic molecules containing chromeno[4,3-*b*]pyrrole frameworks has not been reported.[7] It is also worth noting that the formation of a tetrasubstituted chirality center is challenging during the construction of the muticyclic fused structures.

Herein, we report a chiral NHC-catalyzed cascade cycloaddition reaction for enantio- and diastereoselective synthesis

a) bioactive molecules containing chromeno[4,3-b]pyrrole cores

MLS002174161
(a rigid TRPV1 agonist)

A: R = 3-F
B: R = 5-F
C: R = 5-OCH₃
(potential TRPV₁ agonists)

azamedicarpin · HCl
(antimicrobial activities)

b) cascade reactions for 3-C functionalization of α,β-unsaturated acylaziliums:

c) *this work*: NHC-catalyzed cascade reaction for the synthesis of chromeno[4,3-b]pyrroles
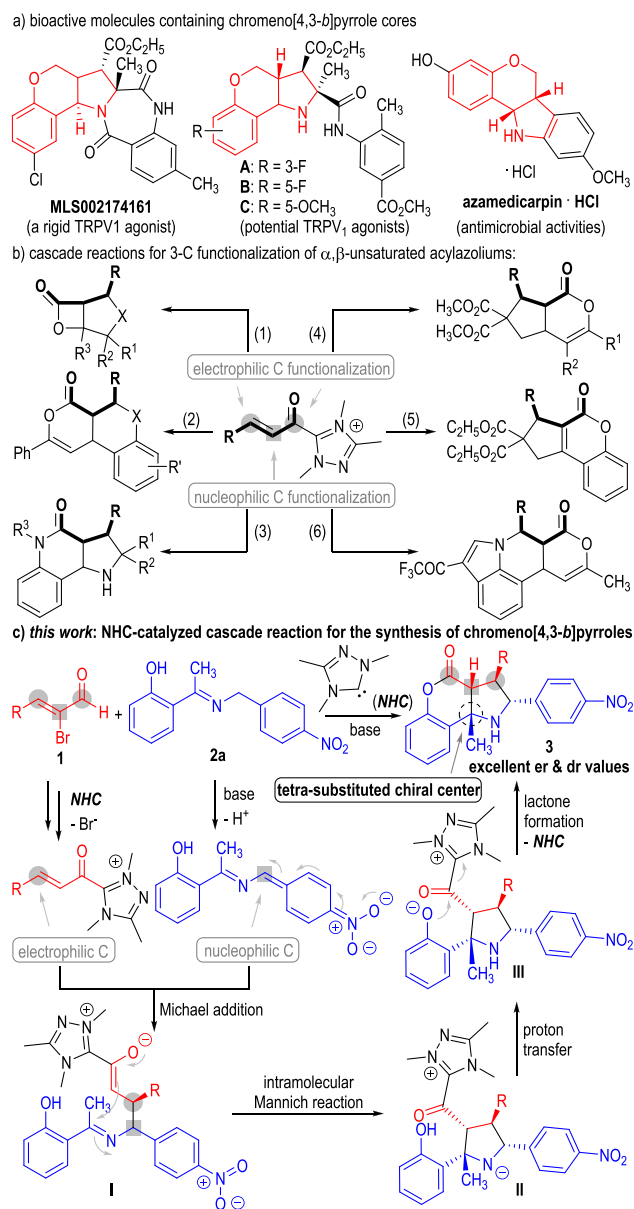
Figure 1. Bioactive chromeno[4,3-b]pyrrole derivatives and cascade reactions with NHC-bound acyl azolium intermediates.

of tetrahydrochromeno[4,3-b]pyrrole derivatives (Figure 1c). The benzylic carbon of the 4-nitrobenyl group in the rationally designed reaction substrate (2a) is activated as a nucleophilic carbon to react with the NHC-bound α,β-unsaturated acylazolium intermediates[8] through Michael addition and gives intermediate I. A sterically congested tetrasubstituted chirality carbon center is formed in excellent stereoselective fashion during the intramolecular Mannich reaction of the intermediate I and gives intermediate II bearing a chiral substituted pyrrolidine structure. After a proton transfer process, the final product 3 is readily formed through lactone formation from intermediate III, with the NHC catalyst released for additional catalytic cycles.

α-Bromocinnamaldehyde **1a** was chosen as the α,β-unsaturated acylazolium precursor[5c] to react with the multifunctional substrate **2a** under the catalysis of various NHC organic catalysts (Table 1). To our great delight, the target multicyclic product **3a** could be afforded in promising yield

Table 1. Condition Optimization[a]

| entry	NHC	base	solvent	yield (%)[b]	er[c]	dr[d]
1	A	Et₃N	THF	54	98:2	13:1
2	B	Et₃N	THF	22	89:11	12:1
3	C	Et₃N	THF	0		
4	D	Et₃N	THF	68	75:25	6:1
5	E	Et₃N	THF	46	83:17	8:1
6	A	DABCO	THF	78	96:4	14:1
7	A	K₂CO₃	THF	56	94:6	15:1
8	A	DBU	THF	<5		
9	A	Cs₂CO₃	THF	<5		
10	A	DABCO	EtOAc	84	97:3	10:1
11	A	DABCO	toluene	84	97:3	16:1
12	A	DABCO	CH₂Cl₂	84	98:2	4:1
13	A	DABCO	CH₃CN	<5		
14[e]	A	DABCO	mixture[f]	82	98:2	19:1

[a]General conditions (unless otherwise specified): **1a** (0.10 mmol), **2a** (0.15 mmol), NHC (0.02 mmol), base (0.10 mmol), 4 Å MS (150 mg), solvent (2.0 mL), 50 °C, 12 h. [b]Isolated yield of **3a**. [c]Er was determined via HPLC on chiral stationary phase. [d]Dr indicates the ratio of **3a:3a′** and was determined by ¹H NMR on the crude reaction mixture. [e]**1a** (0.10 mmol), **2a** (0.15 mmol), A (0.005 mmol), base (0.125 mmol), 4 Å MS (150 mg), solvent mixture (1.0 mL), 50 °C, 12 h. [f]Solvent mixture: EtOAc/toluene = 1/2.

with excellent enantio- and diastereoselecivities with the NHC **A**[9] used as the reaction catalyst (Table 1, entry 1). Aminoindanol derived NHC catalyst **B**[10] bearing an N-Ph group could only give the desired product **3a** in low yield, although with acceptable er and dr values (entry 2). Electron-deficient NHC catalysts were not effective for this transformation (e.g., entry 3). Electron-rich NHC catalysts derived from other chiral scaffolds could give the products (**3a**) in moderate yields and stereoselectivities (e.g., entries 4 and 5). The reactions went well with organic or inorganic bases with weak basicities, with the desired products (**3a**) afforded in moderate yields with good to excellent enantio- and diastereoselectivities (e.g, entries 6 and 7). Strong bases could not be used for this cascade cycloaddition reaction (e.g., entries 8 and 9). The product yields could be dramatically improved when switching THF to organic solvents with lower polarities, with retention of the reaction stereoselectivities (e.g., entries 10 to 12). Highly polar organic solvents were not suitable for this catalytic reaction (e.g., entry 13). Finally, our desired cyclopenta[c]pyranone product **3a** could be afforded in 82% yield with 98:2 er and 19:1 dr values with a reduced amount of NHC **A** (5 mol %) used as the reaction catalyst, DABCO as the base, and a mixture of EtOAc/toluene = 1/2 as the reaction solvent (entry 14).

The substrate scope of the α-bromo enals **1** was then examined to react with substrate **2a** under the optimized reaction conditions as stated in Table 1, entry 14. Both electron-withdrawing and -donating substituents could be

installed on the *o*-position of the *β*-phenyl group of the enal **1a**, with the corresponding products afforded in good yields with excellent er values as single diastereomers (**3b** to **3e**; Scheme 1). Substituents were also well tolerated on the *m*-position of
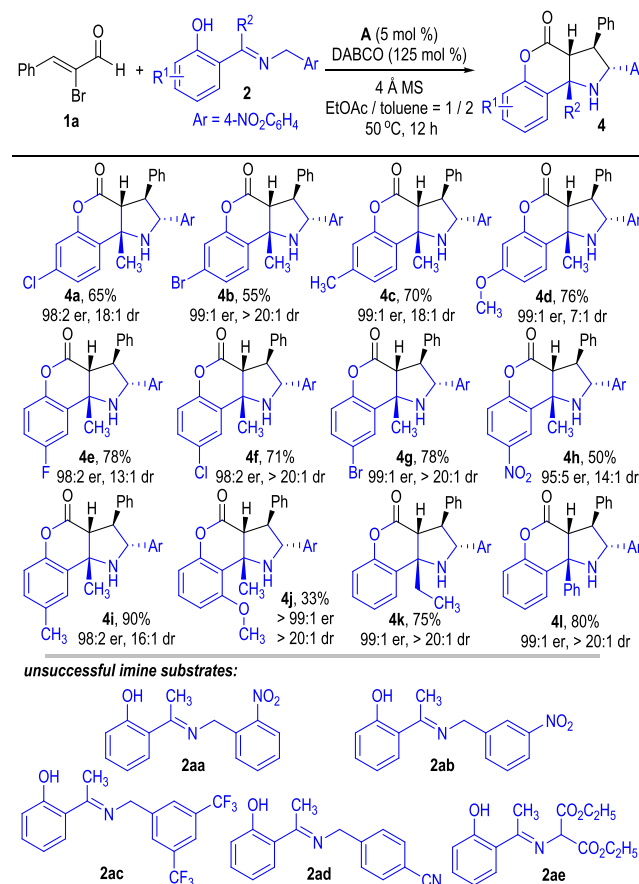
Scheme 1. Scope of α-Bromo Enals 1[a]
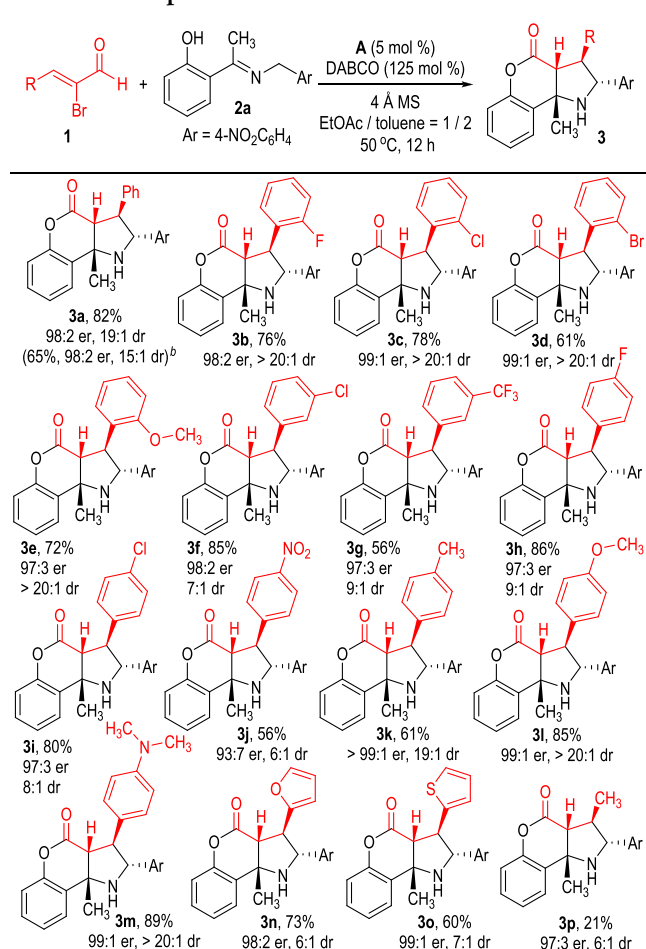
[a]Reaction conditions as stated in Table 1, entry 14. Yields are isolated yields after purification via SiO$_2$ column chromatography. Er values were determined via HPLC on chiral stationary phase. Dr values were determined by ^{1}H NMR on the crude reaction mixture. [b]The reaction was carried out at 5 mmol scale based on **1a**.

the *β*-phenyl group, although the dr values of the products were slightly decreased (**3f** and **3g**). Electron-withdrawing substituents on the *p*-position of the phenyl rings gave the cyclopenta[*c*]pyranone products in moderate to good yields with excellent er and moderate dr values (**3h** to **3j**), while electron-donating groups on these positions could give the optically pure products in good yields as single diastereomers (**3k** to **3m**). The *β*-phenyl group on the enal **3a** could be switched to various heteroaromatic groups with retention of the product optical purities, although the reaction yields and diastereoselectivities were slighly decreased (**3n** and **3o**). Gratifyingly, an aliphatic enal substrate could also be used in this NHC-catalyzed cascade cycloaddition process and give the tricyclic product **3p** with excellent er and good dr values, although the yield was poor under the current reaction conditions.

Substituents were also well tolerated on the phenyl rings of the phenol moieties of the multifunctional substrates **2**

(Scheme 2). For instance, substituents could be installed on the 5- and 4-position of the phenol moieties regardless of their

Scheme 2. Scope of Substrates 2[a]

[a]Reaction conditions as stated in Table 1, entry 14. Yields are isolated yields after purification via SiO$_2$ column chromatography. Er values were determined via HPLC on chiral stationary phase. Dr values were determined by ^{1}H NMR on the crude reaction mixture.

electronic properties, with the corresponding products afforded in moderate to excellent yields with excellent enantio- and diastereoselectivities (**4a** to **4i**). Substitution on the 3-position of the phenol ring led to a decrease in the product yield, although the stereoselectivities of the reaction remained excellent (**4j**). It is worth noting that the methyl group on the imine moiety of **2a** could be replaced with an ethyl group or even an aromatic phenyl group, with the corresponding target products afforded in good yields with excellent enantioselectivities as single diastereomers (**4k** and **4l**). The 4-nitrobenzyl group on the imine substrate **2** is crucial to this cascade cycloaddition reaction. Replacing the 4-nitrophenyl group with other electron-withdrawing groups resulted in no formation of the desired products (Scheme 2, **2aa** to **2ae**). This might be due to either the decreased acidities of the benzyl C(sp^3)−H bonds (e.g., **2ab**, **2ac**, **2ad**, **2ae**) or the increased steric hindrance of the nucleophilic carbon centers (e.g., **2aa**, **2ae**).[11]

As a technical note, this catalytic reaction could also be carried out at gram scales without erosion on the enantioselectivity, although the product yield and diastereoselectivity were slighly decreased (e.g., Scheme 1, **3a**).

The lactone ring of the chiral chromeno[4,3-*b*]pyrrole product **3a** afforded from our methodology could be broken through a trans-esterification process and gave the heavily substituted pyrroline **5** in moderate yield with retention of the excellent optical purity and diastereomeric ratio (Figure 2).
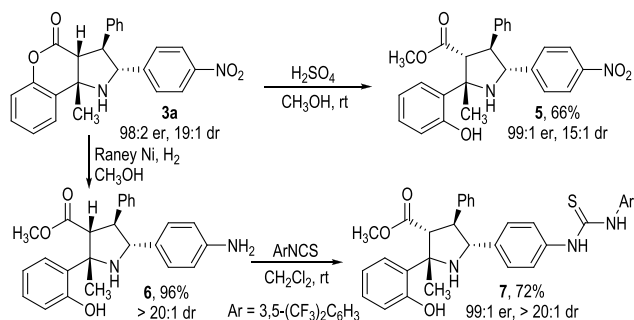

Figure 2. Synthetic transformations of chiral product **3a**.

Chiral pyrroline derivatives have been widely used as efficient organic catalysts in asymmetric secondary amine-catalyzed reactions.[12] The nitro group of **3a** could be effectively reduced by Raney Ni under a H_2 atmosphere in almost quantitative yield without erosion of the product stereoselectivities (**6**). Chiral primary amine **6** could be transformed to thiourea **7** in good yield with retention of the optical purity as a single diastereomer. Both chiral primary amines and thioureas are preliminary functional groups in asymmetric synthesis.[13]

In summary, we have developed an NHC-catalyzed cascade cycloaddition reaction for facile synthesis of optically pure tetrahydrochromeno[4,3-*b*]pyrrole derivatives. The multicyclic products have been afforded in generally good yields with excellent enantio- and diastereoselectivities. A sterically congested tetrasubstituted chirality carbon center was formed during the cascade cyclization process. All the α-, β-, and carbonyl carbons of the enal substrates were functionalized in chemo- and stereoselective fashion. The chiral tetrahydro-chromeno[4,3-*b*]pyrrole products afforded from our methodology could be transformed to heavily substituted pyrroline derivatives with excellent optical purities. All of the chiral products afforded from our protocols contain free secondary amino groups and have potential applications in asymmetric organic synthesis.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.org/doi/10.1021/acs.orglett.9b04371.

Experimental procedures and spectral data for all new compounds (PDF)

Accession Codes

CCDC 1960143 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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