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Carbene-Catalyzed Reaction of Indolyl Methylenemalononitriles and Enals for Access to Complex Tetrahydrocarbazoles

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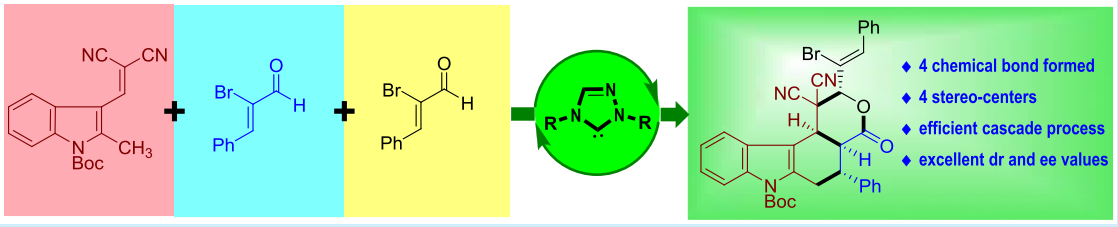

ABSTRACT: A carbene-catalyzed enantioselective cascade reaction of substituted methylenemalononitriles and α-bromoenals is disclosed. Key steps of this cascade process include a formal [4 + 2] cycloaddition, aldol reaction, and intramolecular lactonization. Our reaction offers streamlined and highly stereoselective access to complex tetrahydrocarbazole derivatives, with simultaneous formation of four chemical bonds and four chiral centers.

Chiral hydrocarbazoles are polycyclic indole architectures found in numerous natural products such as alkaloids that exhibit important bioactivities (Figure 1A).[1] For example, (+)-vincadifformine and its analogues display remarkable cytotoxicity in vitro against a total of 60 human tumor cell lines derived from nine cancer types.[2] (+)-Aristoteline has been used as anti-inflammation and pain-reducing drugs.[3] Uleine has been proven to be the major antimalarial indole alkaloid isolated from Aspidosperma parvifolium.[4] In recent years, enantioselective catalytic access to chiral hydrocarbazoles and their derivatives via transition-metal-free approaches have received considerable attention.[5] Most of the success in this regard relies on the use of chiral amine catalysts to activate one of the reaction partners via iminium[6] or enamine[7] catalytic pathways, as disclosed by the groups of MacMillan,[8] Melchiorre,[9] Chen,[10] Zanardi,[11] and others.[12] A potentially efficient approach to make this class of molecules is functionalization of indole derivatives.[13] In 2013, we reported that indole-3-carboxaldehydes could be activated via N-heterocyclic carbene (NHC) organic catalysis[14] to form *ortho*-quinodimethane intermediates for formal [4 + 2] reactions with reactive ketones[15] (Figure 1B). Based on studies from us and others, we postulate that reacting similar indole *ortho*-quinodimethane intermediates[16] with NHC-bound dienophiles[17] can effectively provide hydrocarbazoles bearing all-carbon rings fused with the indole skeleton (Figure 1C). Key steps in our approach (Figure 1C) include a formal [4 + 2] cycloaddition, aldol reaction, and intramolecular

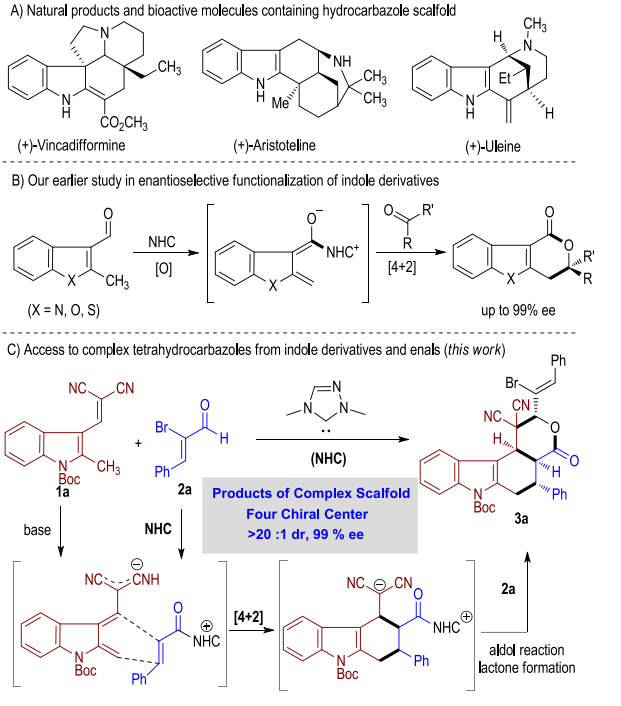

Figure 1. Rapid access to complex hydrocarbazole derivatives.

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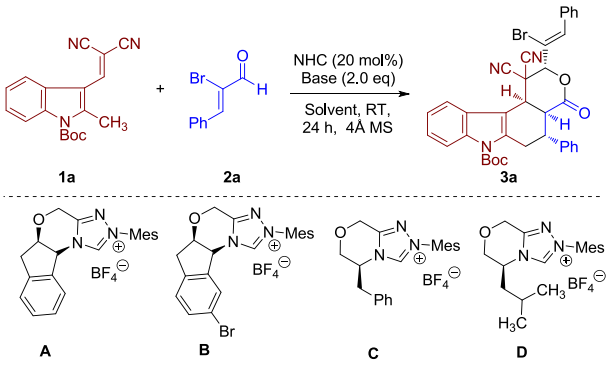
lactonization (see Supporting Information for a complete pathway). The catalytic reaction efficiently builds two new rings and four chiral centers. The reaction products contain multiple functional groups and can be readily transformed to diverse hydrocarbazole derivatives. Our catalytic strategy can be extended from indole-based substrates to other allylidene malononitriles, providing quick access to multicyclic hydropyranone products.

We started by using methylenemalononitrile **1a** and α-bromoenal **2a** as model substrates to search for suitable conditions (Table 1). NHC **A** gave the desired tetrahydrocarbazole product **3a** in a promising yield and excellent ee (entry 1). Other NHC catalysts bearing different *N*-substitutnets could also provide the target products with excellent ee values, albeit with lower yields (entries 2−4). By increasing the amount of Et_3N to 3.0 equiv, the product could be obtained in a moderate yield (54% yield, entry 5). Then the amount of **2a** was examined (entries 6−8). To our delight, the yield of **3a** could be improved to 73% with 3 equiv of **2a** used (entry 6). A further increase of the amount of **2a** led to a slight drop of the reaction yield (entries 7−8). Strong organic or inorganic bases (e.g., entries 9, 10) could not be used for this reaction. A variety of organic solvents could be used in this reaction, and the product could be obtained in excellent enantioselectivities but in lower yields (e.g., entries 11−14). Finally, we established the optimal reaction conditions for this reaction: using NHC **A** as catalyst, **2a** (3.0 equiv), Et_3N (3.0 equiv) as the base, and THF as the solvent. In this case, the desired product was obtained in a good yield with excellent enantioselectivity. As a technical note, the desired product **3a** we obtained in these cases are single diastereomers (dr >20:1).

With acceptable conditions in hand (Table 1, entry 6), we first examined various substituted methylenemalononitriles **1** for this transformation (Scheme 1). Different substituents on the indole core of **1** were well tolerated. Substitution at the 5- or 6-positions with electron-withdrawing or electron-donating groups gave the products **3b** to **3g** with moderate to good yields and excellent enantioselectivities. The *N*-Boc group of **1a** could be switched to an *N*-Ts group, with the desired product **3h** afforded in a moderate yield and excellent optical purity. Electron-donating *N*-substituents were not effective for this transformation. Benzofuranmalononitrile could also work in this cascade cycloaddition reaction, with the corresponding product **3i** afforded in a moderate yield with excellent enantioselectivity. We have also examined the benzothiophene-derived malononitrile substrate, but the reaction yield was very low. Replacement of the dicyano unit on the substrate **1a** with a cyanoester unit also led to no product formation.

We then examined the scope of various substituted α-bromoenals **2** (Scheme 2). Electron-withdrawing and -donating groups were well tolerated on the benzene rings of the substrate **2**, with all the desired multicyclic tetrahydrocarbazoles **3** afforded in good yields and excellent ee values as single

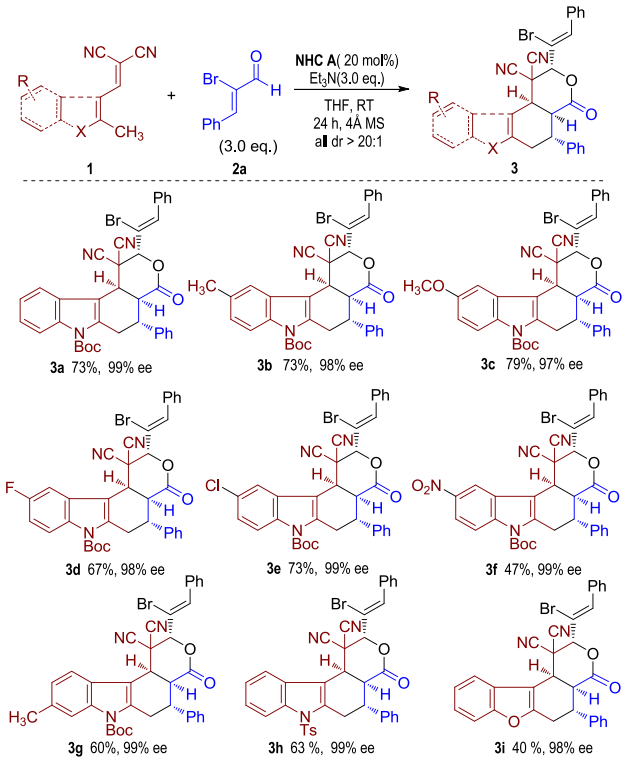
Table 1. Optimization of Reaction Conditions[a]



entry	NHC	base	solvent	yield (%)[b]	ee[c]
1	**A**	Et_3N	THF	30	99
2	**B**	Et_3N	THF	22	99
3	**C**	Et_3N	THF	21	99
4	**D**	Et_3N	THF	21	99
5[d]	**A**	Et_3N	THF	54	99
6[e]	**A**	Et_3N	THF	73	99
7[f]	**A**	Et_3N	THF	70	99
8[g]	**A**	Et_3N	THF	69	99
9[e]	**A**	DBU	THF	–	–
10[e]	**A**	Cs_2CO_3	THF	–	–
11[e]	**A**	Et_3N	DCM	45	99
12[e]	**A**	Et_3N	DCE	45	99
13[e]	**A**	Et_3N	$PhCH_3$	44	99
14[e]	**A**	Et_3N	1,4-dioxane	33	99

[a]General conditions (unless otherwise specified): **1a** (0.05 mmol), **2a** (0.10 mmol), base (0.10 mmol), NHC (0.01 mmol), 4 A MS (50 mg), THF (1.0 mL), rt, 24 h. Dr values for all the products (>20:1) were determined by crude ^{1}H NMR. [b]Isolated yield of **3a**. [c]Ee was determined via HPLC on chiral stationary phase. [d]**1a** (0.05 mmol), **2a** (0.10 mmol), base (0.15 mmol). [e]**1a** (0.05 mmol), **2a** (0.15 mmol), base (0.15 mmol). [f]**2a** (0.2 mmol), base (0.15 mmol) were used. [g]**2a** (0.25 mmol), base (0.15 mmol) was used.

Scheme 1. Scope of Methylenemalononitriles 1[a]



[a]Reaction conditions as stated in Table 1, entry 6. Yields are isolated yields after purification via SiO_2 column chromatography. Dr values for all the products (>20:1) were determined by crude ^{1}H NMR. Ee values were determined via HPLC on chiral stationary phase.

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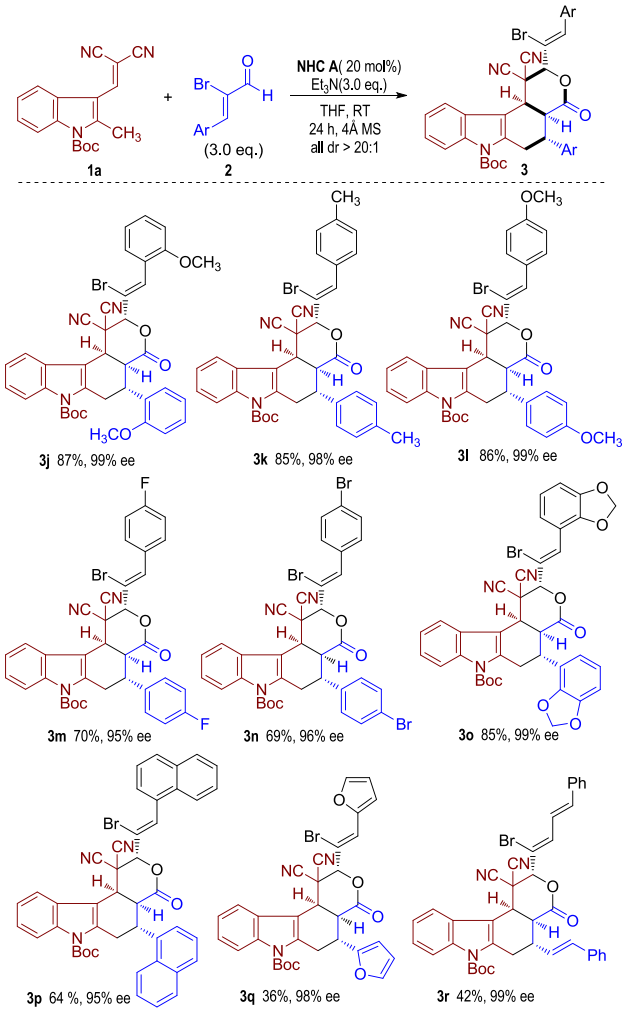
Scheme 2. Scope of α-Bromoenals 2[a]



[a]Reaction conditions as stated in Table 1, entry 6. Yields are isolated yields after purification via SiO_2 column chromatography. Dr values for all the products (>20:1) were determined by crude ^1H NMR. Ee values were determined via HPLC on chiral stationary phase.

diastereomers (**3j** to **3o**). In addition, the β-phenyl group of the α-bromoenal **2a** could be replaced with a 1-naphthyl group, with the corresponding product **3p** afforded in a moderate yield and excellent enantioselectivity. Moreover, the β-phenyl group of the α-bromoenal **2a** could also be switched to a furanyl group or even an alkenyl group, although the optically pure products **3q** and **3r** could only be afforded in low yields under the current catalytic conditions.

To our delight, cinnamaldehyde could also be used instead of the α-bromoenals **2** as the reaction substrates in this transformation, although the enantiomerically pure product **3s** could only be afforded in 33% yield (Figure 2a). The application of other electrophiles such as imines or electron-deficient ketones in this cascade cyclization process remained unsuccessful (Figure 2b).

The versatility of the cascade reaction could be further demonstrated by using allylidene malononitriles **4** instead of **1** as the reaction substrates (Scheme 3). 1-Tetralone-derived allylidene malononitriles worked well under the current reaction conditions and gave the desired products **5a** and **5b** in good yields with excellent enantioselectivities. However, 1-

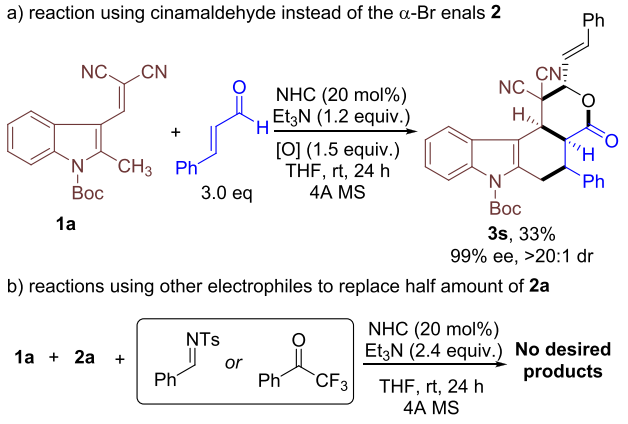
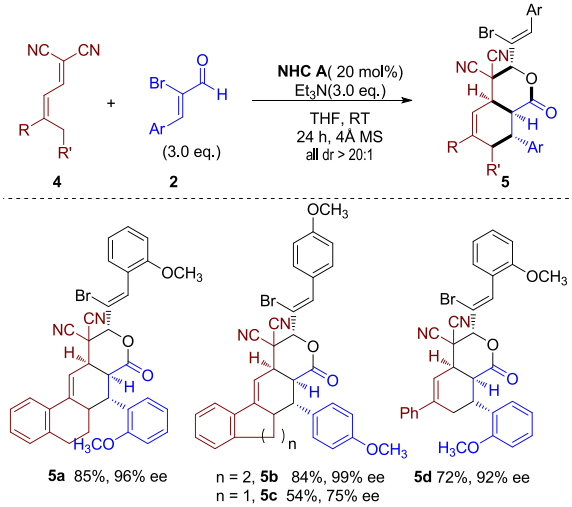


Figure 2. Examination of various electrophiles.

Scheme 3. Reaction of Allylidene Malononitriles with α-Bromoenals[a]



[a]Reaction conditions as stated in Table 1, entry 6. Yields are isolated yields after purification via SiO_2 column chromatography. Dr values for all the products (>20:1) were determined by crude ^1H NMR. Ee values were determined via HPLC on chiral stationary phase.

indanone-derived allylidene malononitrile only gave the desired product **5c** in 54% yield with 75% ee at this moment. β-Methylcinnamaldehyde-derived allylidene malononitrile could also be used in this transformation, with the desired product **5d** afforded in a good yield and excellent enantioselectivity.

The chiral tetrahydrocarbazoles products can be used in various transformations (Scheme 4). The Boc group in **3a** could be removed by acid and gave **6** in a good yield. **3a** could be efficiently oxidized to carbazole derivative **7** with retention of the optical purity. Furthermore, the C═C bond of **3a** could be hydrogenated and debrominated to give **8** in a good yield. Chiral alkynes **9** and **10** could be efficiently afforded from **3a** through the Sonogashira coupling process without obvious erosion of the optical purities. The C−O bond of the lactone motif could be broken under mild basic conditions and give the heavily substituted product **11** and **12** in good yields and stereoselectivities. The malononitrile moiety of **3a** could be smoothly converted to a carboxylate group, with compound **13** afforded in a good yield.

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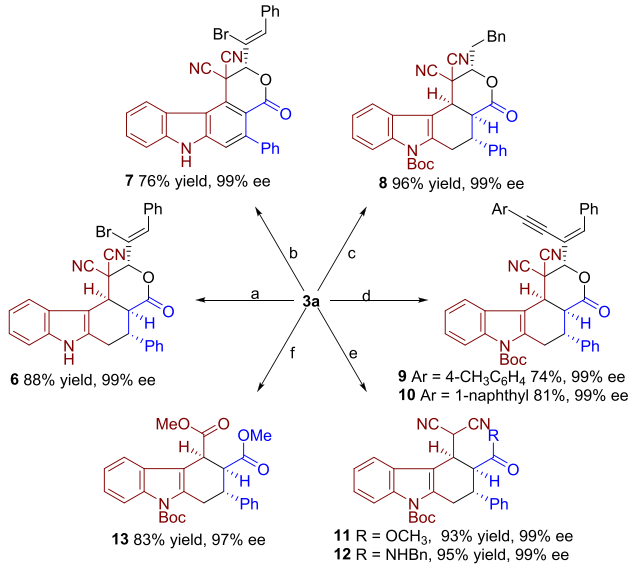
Scheme 4. Synthetic Transformations of Chiral Products 3a



[a]DCM/TFA (v = 1:1), 40 °C, 2 h. [b]DDQ, PhCl, reflux, 12 h. [c]Pt/C, H_2, EtOH/THF (v = 1:1), rt, 5 h. [d]CuI, $PdCl_2(PPh_3)_2$, Et_3N, THF, rt, 24 h. [e]For **11**: K_2CO_3, MeOH, rt, 0.5 h; for **12**: $BnNH_2$, THF, rt, 48 h. [f]*m*CBPA, K_2CO_3, MeOH, 0 °C, 0.5 h.

In summary, we have developed a new NHC-catalyzed cascade reaction for efficient synthesis of tetrahydrocarbazole derivatives. The optically pure products bear multiple cycles with four chiral centers. The afforded products could be used in various transformations and gave a variety of chiral functional molecules in good yields.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00418.

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

Accession Codes

CCDC 1921695 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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Author Contributions

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Notes

The authors declare no competing financial interest.

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