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Letter

Catalytic, Enantioselective C2-Functionalization of 3-Aminobenzofurans Using N-Heterocyclic Carbenes

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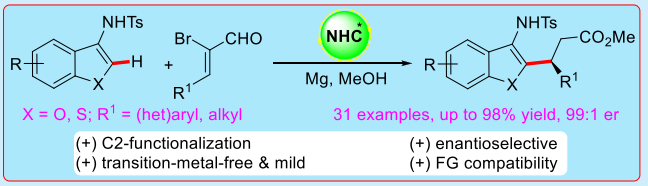
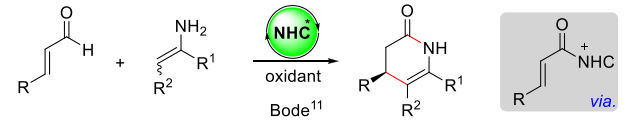
ABSTRACT: N-Heterocyclic carbene catalyzed enantioselective functionalization of 3-aminobenzofurans at the C2-position was realized using 2-bromoenals as the coupling partner. The reaction proceeds via generation of chiral α,β-unsaturated acylazoliums and follows an aza-Claisen rearrangement. The initially formed dihydropyridinone undergoes ring-opening catalyzed by Mg to afford the δ-amino acid derivatives. The reaction worked with 3-aminobenzothiophenes as well, and the C2-alkylated products were formed in moderate to high yields and selectivity.



Transition-metal-catalyzed chelation-assisted functionalization of the inert C−H bonds has emerged as a powerful and flexible synthetic strategy for the rapid access to complex molecules from simple starting materials.[1] A wide range of transition-metal catalysts were developed over the past years for the selective proximal and distal functionalization of C−H bonds.[2] With the proper choice of chiral ligands attached to the metal center, the corresponding enantioselective C−H bond functionalization reactions could be possible leading to enantiomerically pure products.[3] Intriguingly, the transition-metal-free, enantioselective functionalization of inert C−H bonds for the derivatization of arenes and heteroarenes has received only scant attention.[4] Herein, we report the N-heterocyclic carbene (NHC)-catalyzed enantioselective functionalization of 3-aminobenzofurans/benzothiophenes at the C2-position, where the reaction proceeds via the carbene-bound chiral α,β-unsaturated acylazolium intermediates.

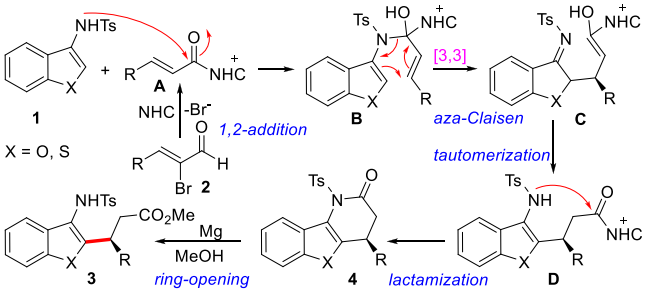
Catalysis using NHCs are widely utilized for the (un)-conventional access to various carbocycles, heterocycles and acyclic molecules and in many cases with remarkable enantioselectivity.[5] Among the various modes of carbene reactivity, the generation of α,β-unsaturated acylazoliums from various α,β-unsaturated aldehydes/acid derivatives is one of the important nonumpolung pathway.[6] The catalytically generated α,β-unsaturated acylazoliums are employed in the enantioselective synthesis of several heterocycles.[7,8] Nucleophiles could add to the α,β-unsaturated acylazoliums in a 1,4-pathway (proposed by Studer)[9] or in a 1,2-manner (suggested by Bode).[10] In 2011, Bode and co-workers demonstrated the NHC-catalyzed oxidative annulation of enals with vinylogous amides for the enantioselective synthesis of dihydropyridinones, and the reaction proceeds via the generation of α,β-unsaturated acylazolium intermediates (Scheme 1).[11,12] We envisioned that the hard nitrogen center of 3-aminobenzofurans **1** could add to the hard carbonyl center of α,β-unsaturated acylazolium intermediate **A** in a 1,2-pathway thus generating

Scheme 1. NHC-Catalyzed Reaction of Enals with Vinylogous Amides



the hemiaminal **B**, which is poised for an enantiodetermining aza-Claisen rearrangement to form **C** (Scheme 2).[13−15] Tautomerization of intermediate **C** could generate the NHC-azolium **D**, which undergoes lactamization to **4** followed by ring-opening to afford the C2-functionalized benzofuran **3**. Following this background, herein, we report a general, catalytic and enantioselective C2-functionalization of 3-amino-

Scheme 2. Envisioned C2-Functionalization of 3-Aminobenzofurans Using NHC Catalysis



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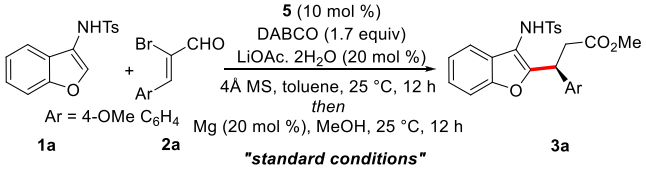
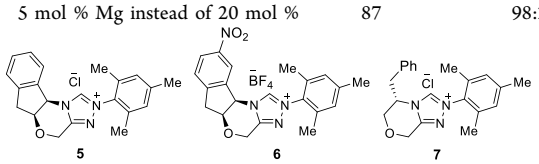
benzofurans and benzothiophenes, and the δ-amino acid derivatives are formed in good yield and selectivity.

The present studies were initiated by treating the *N*-tosyl 3-aminobenzofuran **1a** with 2-bromoenal **2a** in the presence of the carbene generated from the chiral triazolium salt **5**[16] using DABCO as the base and LiOAc·$2H_2O$ and 4 Å MS as additives followed by treatment with catalytic amount of Mg in methanol. Delightfully, under these conditions, the C2-alkylated benzofuran derivative **3a** was formed in 94% isolated yield and 98:2 enantiomeric ratio (Table 1, entry 1).[17] The

Table 1. Optimization of the Reaction Conditions[a]



entry	variation of the standard conditions	yield of **3a** (%)[b]	er of **3a** (%)[c]
1	*none*	*95 (94)*	*98:2*
2	**6** instead of **5**	88	95:5
3	**7** instead of **5**	84	93:7
4	without 4 Å MS and LiOAc.$2H_2O$	83	99:1
5	5 mol % of **5** instead of 10 mol %	81	98:2
6	1,4-dioxane instead of toluene	84	98:2
7	THF instead of toluene	85	98:2
8	CH_2Cl_2 instead of toluene	87	99:1
9	Cs_2CO_3 instead of DABCO	68	63:37
10	Et_3N instead of DABCO	70	62:38
11	DMAP instead of DABCO	71	97:3
12	DBU instead of DABCO	<5	nd
13	5 mol % Mg instead of 20 mol %	87	98:2

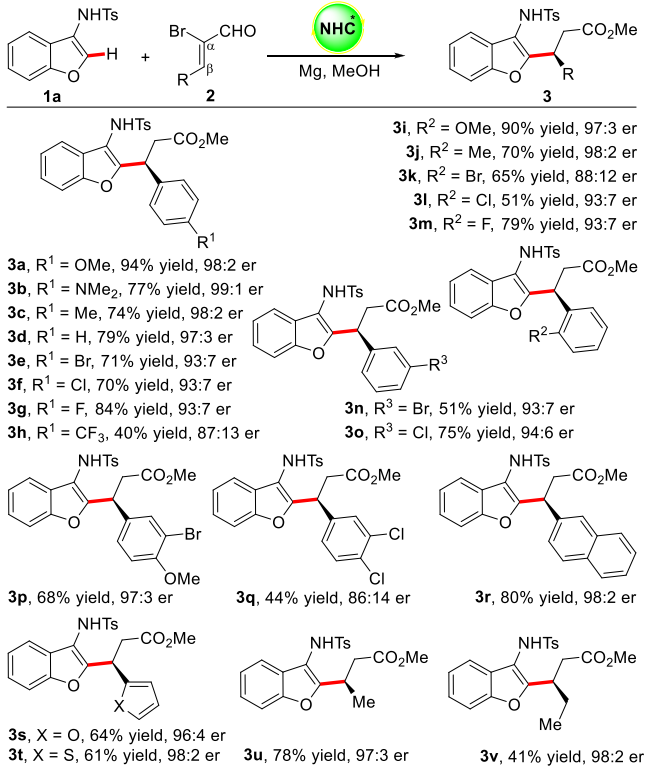


[a]Standard conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), **5** (10 mol %), toluene (1.0 mL), LiOAc·$2H_2O$ (20 mol %), 4 Å MS (25 mg), 25 °C, 12 h, followed by Mg (20 mol %) in methanol (2.0 mL) at 25 °C, 12 h. [b]The yields were determined by ^{1}H NMR analysis of crude reaction mixture using CH_2Br_2 as the internal standard. Isolated yield was provided in parentheses. [c]The er values were determined by HPLC analysis on a chiral stationary phase.

carbene generated from the triazolium salts **6** and **7** also showed good reactivity, but the yield and selectivity are less compared to the carbene generated from **5** (entries 2, 3). The additives are required for the excellent reactivity (entry 4), and lowering the loading of **5** to 5 mol % reduced the reactivity maintaining the high selectivity (entry 5). Toluene was found to be the optimal solvent for this transformation as the reactions performed in other solvents afforded **3a** in reduced yields (entries 6–8). The reactions performed in bases such as Cs_2CO_3, Et_3N, DMAP, and DBU returned inferior results, indicating that DABCO is the best base for this reaction (entries 9–12). Moreover, reducing the loading of Mg to 5 mol % reduced the yield of **3a** to 87% (entry 13).

Having the optimized conditions in hand, we then focused our attention on the substrate scope of the C2-functionalization reaction. Initially, the variation on 2-bromoenals was studied (Scheme 3). A series of 2-bromoenals bearing electron-

Scheme 3. Scope of 2-Bromoenals in the Reaction[a]



[a]General conditions: **1a** (0.25 mmol), **2** (0.375 mmol), **5** (10 mol %), DABCO (0.425 mmol), LiOAc·$2H_2O$ (20 mol %), 4 Å MS (50 mg), toluene (2.5 mL) 25 °C and 12 h followed by Mg (20 mol %) in MeOH (5.0 mL), 25 °C and 12 h. Yields of isolated products are given and the er value was determined by HPLC analysis on a chiral stationary phase.

releasing, -neutral, and -withdrawing groups at the 4-position of the β-aryl ring are well tolerated under the present conditions, and in all cases, the C2-alkylated product was formed in good yields and er values (**3a–3h**). However, with the $-CF_3$ group, the yield and selectivity were only moderate. Moreover, 2-bromoenals having substitution at the 2-position and 3-position as well disubstitution underwent smooth C2-functionalization, and the desired products are formed in moderate to good yield and high selectivity (**3i–3r**). In addition, substitution at the β-position of enal with heteroaryl moiety did not affect the outcome of the reaction and the corresponding furyl and thienyl products **3s** and **3t** were formed in good yield and selectivity. Furthermore, challenging aliphatic 2-bromoenals also worked under the optimized conditions leading to the desired C2-alkylated products in good yields (**3u**, **3v**).

Next, we evaluated the variation on 3-aminobenzofurans (Scheme 4). Benzofurans having Me, OMe, and halogen substitution at the 5-position are well tolerated under the present conditions to furnish the δ-amino acid derivatives in good yield and excellent er values (**3w–3aa**). Moreover, 6-fluoro-substituted substrate afforded the desired product **3ab** in 83% yield and 97:3 er. Interestingly, the present reaction is not limited to benzofurans, but instead 3-amino benzothiophenes also underwent smooth carbene-catalyzed reaction followed by ring-opening to deliver the C2-alkylated benzothiophenes in good yield and er values (**3ac–3ae**).[18] Disappointingly, the reactions performed using *N*-protected 3-

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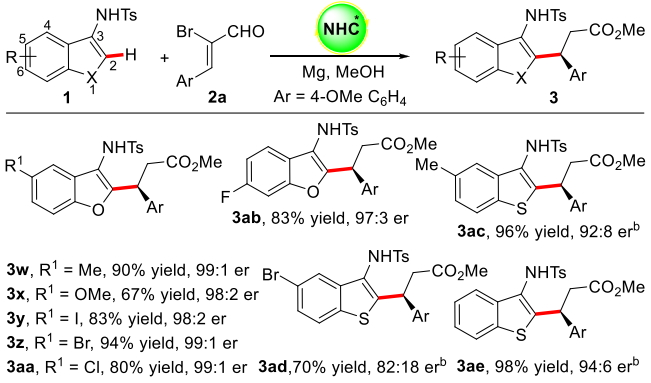
Scheme 4. Variation of 3-Amino Benzofurans[a]

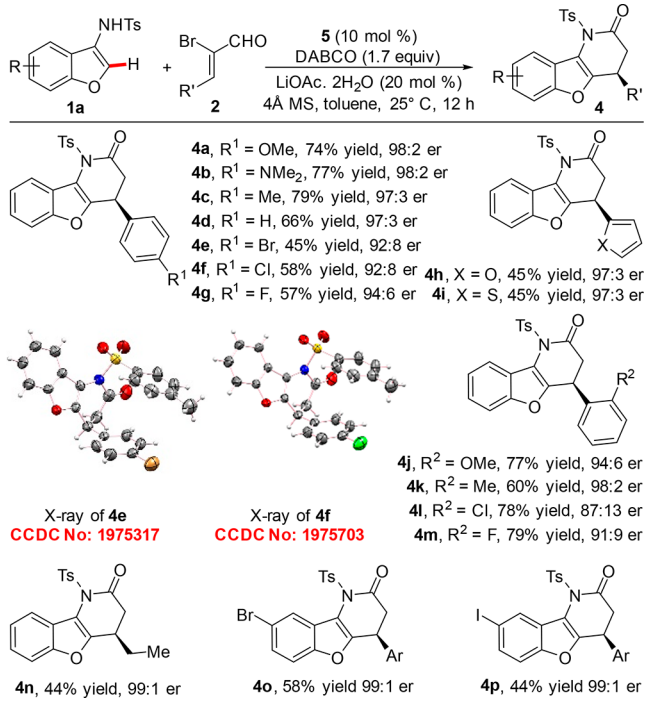


[a]General conditions: **1** (0.25 mmol), **2a** (0.375 mmol), **5** (10 mol %), DABCO (0.425 mmol), LiOAc·2H_2O (20 mol %), 4 Å MS (50 mg), toluene (2.5 mL) 25 °C and 12 h followed by Mg (20 mol %) in MeOH (5.0 mL), 25 °C and 12 h. [b]1.0 equiv of Mg was used and the reaction mixture stirred for 36 h.

aminoindoles did not afford the desired C2-alkylated products under the optimized reaction conditions.

Interestingly, when the NHC-catalyzed reaction was performed without the treatment of Mg, the intermediate dihydropyridinone derivative was indeed isolable. Thus, the treatment of **1a** with **2a** in the presence of NHC generated from **5** afforded the tricyclic dihydropyridinone **4a** in 74% yield and 98:2 er (Scheme 5). The dihydropyridinone formation was taking place with a series of electronically different 2-bromoenals. Substitution was well tolerated at the 4-position and 2-position of the β-aryl ring (**4b**−**4g** and **4j**−**4m**).

Scheme 5. Enantioselective Synthesis of Dihydropyridinones[a]

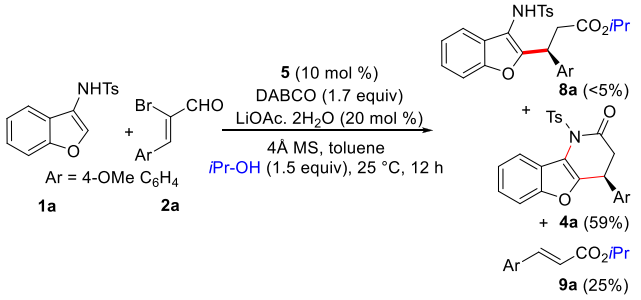


[a]General conditions: **1** (0.25 mmol), **2** (0.375 mmol), **5** (10 mol %), DABCO (0.425 mmol), LiOAc·2H_2O (20 mol %), 4 Å MS (50 mg), toluene (2.5 mL), 25 °C and 12 h.

Moreover, β-heteroaryl as well as β-alkyl-substituted 2-bromoenals also furnished the target benzofuran-fused dihydropyridinone in moderate to good yields and er values (**4h**, **4i**, and **4n**). In the case of the 4-Br (**4e**) and 4-Cl derivatives (**4f**), the structure and the absolute stereochemistry of the chiral center was confirmed using single-crystal X-ray analysis. The structure and stereochemistry of the δ-amino acid derivatives **3** were concluded in analogy with **4e** and **4f**. Finally, the 5-bromo- and 5-iodo-substituted benzofuran substrates also worked fine to afford the tricyclic products in moderate to good yields and high selectivity (**4o**, **4p**).

To gain insight into the mode of addition of 3-amino-benzofuran **1a** to the catalytically generated α,β-unsaturated acylazoliums **A**, a reaction of **1a** with **2a** under the present conditions in the presence of *i*Pr-OH was conducted. Interestingly, the C2-alkylated product **8a** possibly derived from the 1,4-addition from the C2-position of **1a** to **A** was not observed, and the desired dihydropyridinone **4a** was isolated in 59% yield along with the cinnamyl ester **9a** in 25% yield (Scheme 6). The absence of the formation of 1,4-addition

Scheme 6. Study toward the Mechanism of the Reaction



product **8a** and the formation of **4a** is likely an evidence for the initial 1,2-addition operating in the present case. Control experiments indicated that **4a** cannot be converted into **8a** in the presence of *i*Pr-OH with or without Mg. Notably, related 1,4-addition product in the reaction of dimethyl malonate to **A** was demonstrated by Studer and co-workers.[9a] Moreover, intermolecular competition experiments carried out between **1a** and methyl (*Z*)-3-aminobut-2-enoate indicated that **1a** reacts ∼65 times faster than the acyclic vinylogous amide, which likely sheds light on the high nucleophilicity of **1a**.[17]

A proposed mechanism of the reaction is presented in Scheme 7. The nucleophilic attack of the NHC generated from **5** to the 2-bromoenal **2** followed by the proton transfer generates the Breslow intermediate **I**,[19] which is converted into the key α,β-unsaturated acylazolium **II** via bromide elimination.[6] The 1,2-addition of **1** to intermediate **II** generates the hemiaminal **III**, which undergoes an aza-Claisen rearrangement to form **IV**.[10a−c,11] The intermediate **IV** could undergo a tautomerization to generate the NHC-azolium **V**, which undergoes a facile lactamization to form the dihydropyridinone **4**, which is subsequently ring-opened to afford the C2-functionalized benzofuran **3**. Notably, related ring-opening of dihydropyridinones using Mg was reported by Ye and co-workers.[10e]

The δ-amino acid derivative synthesized using the present method can be easily *N*-arylated under transition-metal-free conditions using arynes as the aryl source.[20] Thus, treatment of **3a** with benzyne generated from the triflate **10a** using KF (in the presence of 18-crown-6 as additive) afforded the *N*-

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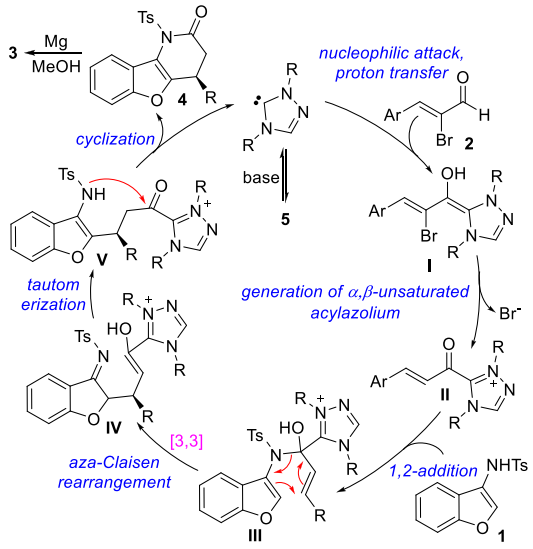
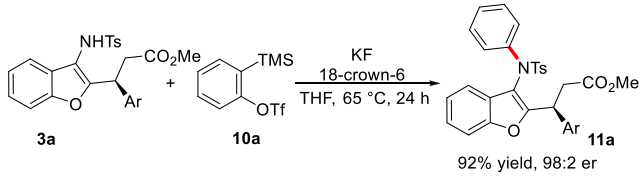
Scheme 7. Tentative Mechanism of the Reaction



arylated product **11a** in 92% yield, preserving the enantiopurity (Scheme 8).

Scheme 8. *N*-Arylation Using Arynes as Aryl Source



In conclusion, we have demonstrated the enantioselective, mild, and transition-metal-free method for the functionalization of 3-aminobenzofurans at the C2-position.[21] The reaction of 3-aminobenzofurans with 2-bromoenals afforded the *δ*-amino acid derivatives in moderate to good yields and high enantioselectivity. The initially formed chiral *α,β*-unsaturated acylazoliums underwent a 1,2-addition and an aza-Claisen rearrangement to form the dihydropyridinone intermediate, which was subsequently ring-opened by using Mg to afford the C2-alkylated product. Further studies on related NHC-catalyzed reactions are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications Web site. The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01112.

Details on experimental procedure, characterization data, and HPLC data of all *δ*-amino acid derivatives and dihydropyridinones (PDF)

Accession Codes

CCDC 1975317 and 1975703 contain 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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(21) Performing the present C2-functionalization reaction on a 1.0 mmol scale afforded **3a** in 80% yield and 98:2 er, demonstrating that the method is scalable and practical.

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