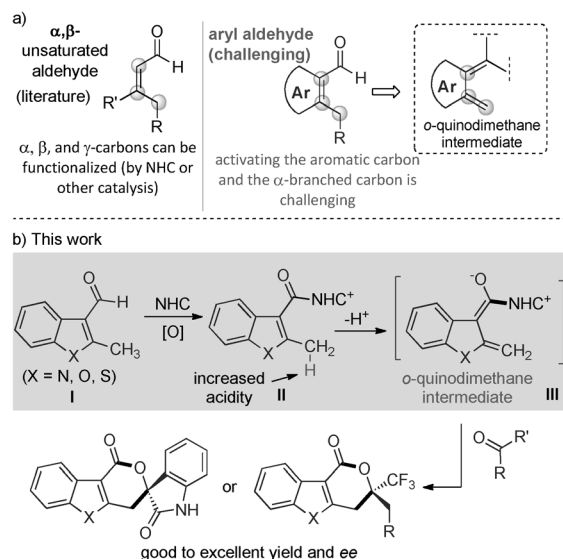


Functionalization of Benzylic C(sp³)–H Bonds of Heteroaryl Aldehydes through N-Heterocyclic Carbene Organocatalysis**

Xingkuan Chen, Song Yang, Bao-An Song,* and Yonggui Robin Chi*

Aromatic units are common scaffolds in bioactive molecules, natural products, and polymer materials. The catalytic functionalization of aromatic sp² carbon atoms and attached branched sp³ carbon atoms is therefore an important subject of research. Success in this area has mainly been achieved using functional-group-directed transition-metal-catalyzed C–H activation.^[1] With the pioneering work on trienamine organocatalysis^[2] by the groups of Jørgensen, Melchiorre, and Chen, the 2-methyl substituent of an α,β -unsaturated aldehyde (enal) with a 2-methylindole substituent in the β position could be activated.^[3] We were interested in using the addition of an N-heterocyclic carbene (NHC) organocatalyst^[4] to a carbonyl functional group as an initial step towards the development of new reactions. Aldehydes are the most extensively studied substrates in NHC catalysis.^[5] With saturated alkyl aldehydes or α,β -unsaturated aldehydes as the substrates, the NHC-catalyzed functionalization of α , β , and γ -carbon atoms has been achieved.^[6,7] However, when aryl aldehydes are used, only the carbonyl carbon could thus far be functionalized (through an acyl-anion intermediate or an NHC-bound ester intermediate). The catalytic activation of the aromatic carbon atoms and the branched carbon atoms of aryl aldehydes remains challenging (Scheme 1 a).

Although the long-term goal of this unusual activation of simple aryl aldehydes still remains elusive at this moment, herein we report our initial success with heteroaryl aldehydes that contain an indole, benzofuran, or benzothiophene moiety (Scheme 1 b). NHC-catalyzed oxidative activation of 2-meth-



Scheme 1. Catalytic activation and cyclization of 2-methyl indole aldehyde.

ylindole-3-carboxaldehyde (**I**) generates catalyst-bound heterocyclic *ortho*-quinodimethane (**III**) as a key intermediate.^[8] This intermediate then undergoes formal [4+2] cycloaddition with a trifluoromethyl ketone or an isatin to form a polycyclic lactone, which contains a quaternary or spirocyclic carbon center. Notably, compounds containing indole, trifluoromethyl, and/or isatin moieties, such as Efavirenz (anti-HIV),^[9] CJ-17493 (neurokinin 1 receptor antagonist)^[10] and NITD609 (anti-malarial)^[11] are used as pharmaceutical, agrochemical, or other bioactive agents.

Experimentally, we started with the reaction between an aryl aldehyde (**1a** or **1b**) and trifluoroacetophenone (**2a**) to form the proposed lactone product **3a** (Table 1). Triazolium salt **A** was employed as the NHC precatalyst, and quinone **4** (developed by Studer et al. as an oxidant for NHC catalysis)^[12d] was chosen as the oxidant, to transform the acyl anion intermediate into an NHC-bound ester-equivalent, acyl azolium ion **II**. Similar oxidation methods for forming acyl azolium ions from aldehydes have been studied by several groups, and by our laboratory.^[12] With simple 2-methylbenzaldehyde (**1a**) as the substrate, the desired lactone product was not observed under various conditions. Instead, 2-methylbenzaldehyde was partially oxidized to the corresponding carboxylic acid. Indole moieties, however, exhibit unique reactivity when compared to phenyl groups; thus we moved to examine 2-methylindole-3-carboxaldehyde (**1b**) as a model substrate, and succeeded in isolating **3b** in 67% yield

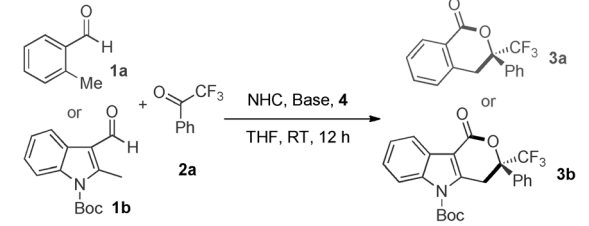
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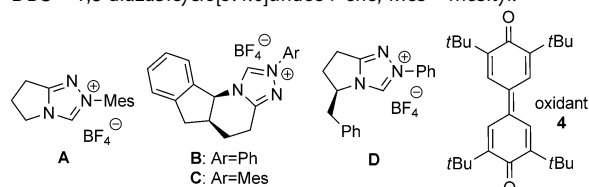
Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/ange.201305861>.

Table 1: Optimization of the reaction conditions for the reaction of **1** with **2a**.^[a]



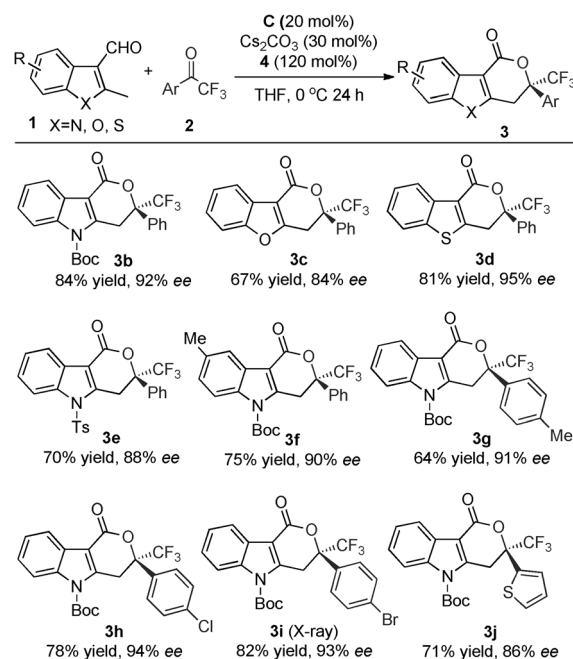
Entry	Aldehyde	Cat.	Base (mol %)	Yield [%] ^[b]	ee [%] ^[c]
1	1a	A	Cs ₂ CO ₃ (50)	0	—
2	1b	A	Cs ₂ CO ₃ (50)	67	—
3	1b	B	Cs ₂ CO ₃ (50)	72	79
4	1b	C	Cs ₂ CO ₃ (50)	78	88
5	1b	D	Cs ₂ CO ₃ (50)	89	37
6	1b	C	K ₂ CO ₃ (50)	55	40
7	1b	C	Na ₂ CO ₃ (50)	trace	—
8	1b	C	DBU (50)	trace	—
9	1b	C	Cs ₂ CO ₃ (30)	75	89
10 ^[d]	1b	C	Cs ₂ CO ₃ (30)	70	91
11 ^[d,e]	1b	C	Cs ₂ CO ₃ (30)	84	91

[a] Standard conditions (unless otherwise specified): **1** (0.1 mmol), **2a** (0.1 mmol), **4** (100 mol %), NHC (20 mol %), base (50 mol %), THF (1 mL), RT, 12 h. [b] Yields of isolated products (**3b**) after purification by column chromatography. [c] Determined by HPLC analysis on a chiral stationary phase. [d] 0 °C, 24 h. [e] **1b** (1.2 equiv), **4** (1.2 equiv). DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, Mes = mesityl.



(Table 1, entry 2). Chiral NHC catalysts were then studied (for a selection, see entries 3–5), and aminoindanol-derived catalyst **C** was found to afford **3b** in 78 % yield and with an encouraging 88 % ee, when Cs₂CO₃ was used as the base (entry 4). Further optimization showed that the use of K₂CO₃ as the base led to significant drops in both reaction yield and ee (entry 6). Na₂CO₃ and the organic base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were completely ineffective (entries 7–8). Finally, with Cs₂CO₃ as the base and using a slight excess (1.2 equiv) of **1b** at 0 °C, the lactone product was obtained in an acceptable 84 % yield and 91 % ee (Table 1, entry 11).

With acceptable reaction conditions in hand, we evaluated the scope of the reaction (Scheme 2). Remarkably, the nitrogen atom in the indole aldehyde **1b** could be replaced with oxygen or sulfur atoms. For example, 2-methylbenzofuran carboxaldehyde reacted well, to give product **3c** in 67 % yield and 84 % ee. Similarly, the use of 2-methylbenzothio-phenone aldehyde effectively led to **3d** in 81 % yield and 95 % ee. The *tert*-butoxycarbonyl (Boc) protecting group of **1b** could be replaced with a tosyl (Ts) unit (**3e**). Various trifluoromethyl ketones with (hetero)aryl substituents were suitable substrates (**3f–j**).^[13] However, the desired products could not be obtained when the 2-methyl substituent on the

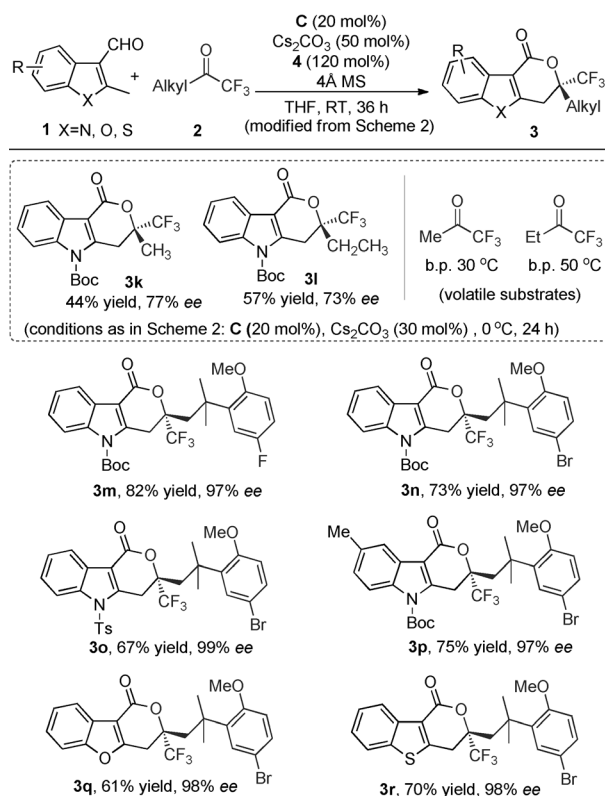


Scheme 2. Examples of aldehydes and trifluoromethyl aryl ketones used. Unless otherwise noted, all reactions were conducted in THF (1.0 mL), using **1** (0.12 mmol) and **2** (0.1 mmol). Yields of isolated products are given. Enantiomeric excess values were determined by HPLC analysis on a chiral stationary phase.

indole moiety was replaced by benzylic or –CH₂CO₂Et groups.

We next studied aliphatic trifluoromethyl ketones (Scheme 3). This effort was motivated in part by the fact that many anti-inflammatory drugs and bioactive compounds (such as Efavirenz, ZK-216348,^[14] and Mapracorat^[15]) are synthesized from aliphatic trifluoromethyl ketones. When methyl or ethyl trifluoromethyl ketones were employed under the same conditions used in Scheme 2 (Cs₂CO₃ (30 mol %), 0 °C, 24 h), the corresponding products (**3k** and **3l**) could be isolated in moderate yields and 73–77 % ee. The relatively low yields were mainly due to the low boiling points and the volatile nature of the ketones. When the same conditions (Cs₂CO₃ (30 mol %), 0 °C, no molecular sieves; Scheme 2) were applied to trifluoromethyl ketones with longer alkyl substituents (**3m** and **3n**; Scheme 3), only traces of the desired products could be obtained. Further optimization showed that the use of Cs₂CO₃ (50 mol %) in the presence of 4 Å molecular sieves (4 Å MS) at room temperature effectively led to the desired products with good to excellent yields. In all cases, the lactone products were obtained in 97–99 % ee (**3m–r**). Notably, aryl aldehydes containing benzofuran and thiophene moieties were suitable substrates as well (**3q** and **3r**).

To further demonstrate the utility of the oxidative catalytic generation of heterocyclic *ortho*-quinodimethane intermediates from indole aldehydes, we next evaluated isatins as reactive ketone electrophiles (Scheme 4). It has been shown that compounds containing isatin or isatin-derived units exhibit interesting biological properties, such as anticonvulsant, antimicrobial, antitumor, antiviral, anti-HIV,



Scheme 3. Examples of alkyl trifluoromethyl ketones used. Unless otherwise noted, all reactions were conducted in THF (1.0 mL), using **1** (0.12 mmol) and **2** (0.1 mmol). Yields of isolated products are given. Enantiomeric excesses were determined by HPLC analysis on a chiral stationary phase.

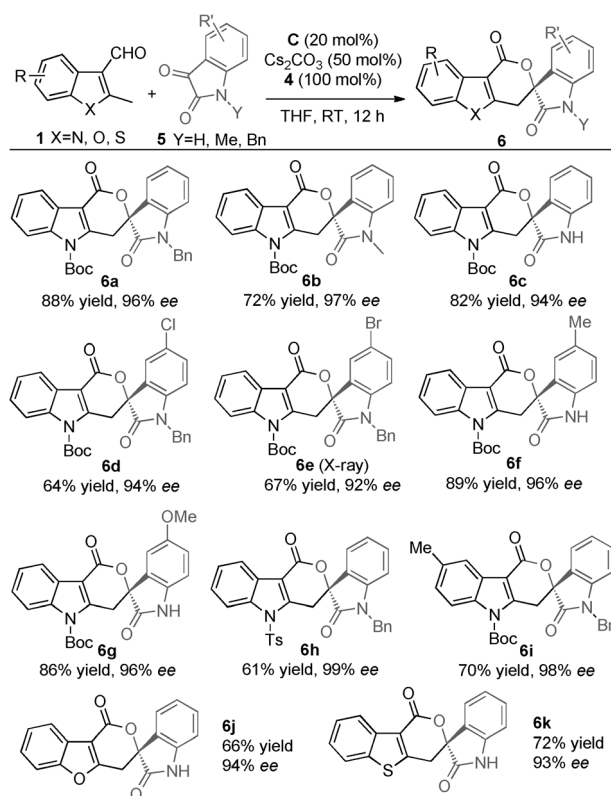
and antitubercular activities.^[16] A slight modification of the conditions used for trifluoromethyl ketones led to an efficient method for the conversion of isatins (Scheme 4). The spirocyclic lactone products (**6a–k**) were obtained in good to excellent yields and over 90% *ee*. Similarly, aldehydes containing benzofuran and benzothiophene moieties were suitable substrates as well (**6j** and **6k**).

In summary, we have developed an NHC-catalyzed activation of the sp³ carbon atom of α -branched indole 3-carboxaldehydes to produce *ortho*-quinodimethane intermediates, which further undergo a highly enantioselective formal [4+2] cycloaddition with trifluoromethyl ketones and isatins to give multicyclic and spirocyclic lactones, respectively; α -branched benzofuran and benzothiophene aldehydes are also suitable substrates for this reaction. Further studies to develop an effective method for the activation of challenging 2-methylbenzaldehyde and other branched all-carbon (non-heteroaromatic) aryl aldehydes are currently underway in our laboratory.

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Scheme 4. Isatins as ketone electrophiles. All reactions were conducted in THF (1.0 mL), using **1** (0.1 mmol) and **5** (0.1 mmol). Yields of isolated products, after purification by column chromatography, are given. Enantiomeric excess values were determined by HPLC analysis on a chiral stationary phase. Bn = Benzyl.

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