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N-Heterocyclic Carbene-Catalyzed *β*-Indolylation of *α*-Bromoenals with Indoles

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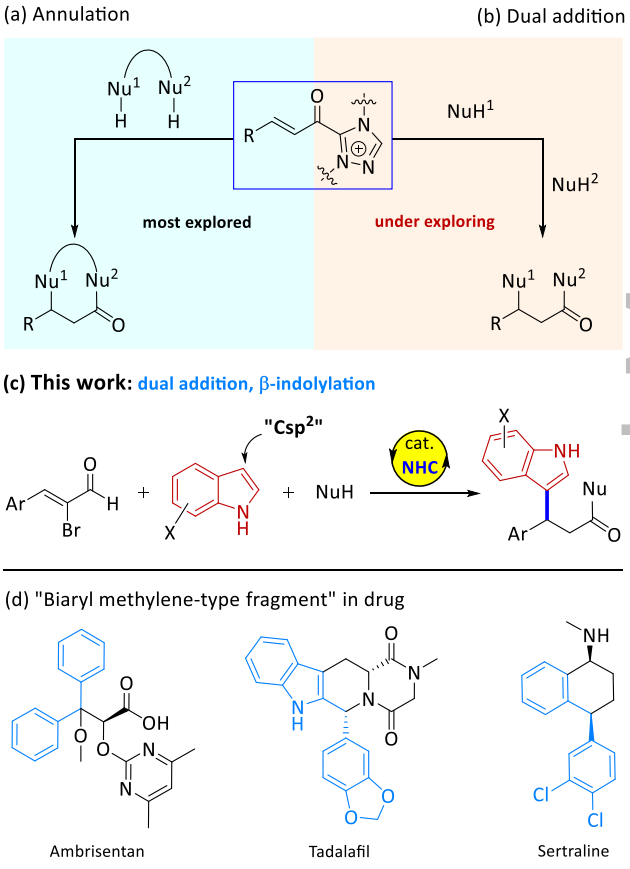
Abstract. An unprecedented example of NHC-catalyzed *β*-indolylation of *α*-bromoenals with indoles has been developed. This concise protocol features several advantages (mild reaction conditions, broad substrate scope) and constructs synthetically useful building blocks, namely *β*-biaryl methylene esters. Notably, the *β*-biaryl methylene-type fragment is widely found in natural products or pharmaceuticals.

Keywords: N-heterocyclic carbenes; *α*-bromoenals; *β*-indolylation; *β*-biaryl methylene-type esters; 1,4-addition

Over the past two decades, N-heterocyclic carbene (NHC) catalyzed organic reactions have been involved in numerous achievements in synthesis.[1] Generally, a given NHC catalyst can react with carbonyls to produce NHC-bound intermediates, e.g. Breslow intermediate,[2] enolate,[3] homoenolate,[4] etc. To our knowledge, the NHC-bound *α,β*-unsaturated acyl azoliums have been broadly applied in many organic transformations.[5] These successes may be due to the following factors. First, the readily available starting materials make it feasible to generate *α,β*-unsaturated acyl azoliums via an *in-situ* formation.[5a] Second, many successful examples suggest that the NHC-bound *α,β*-unsaturated acyl azoliums are highly active. According to known reports, the NHC-bound *α,β*-unsaturated acyl azoliums have been successfully explored in various annulation reactions (i.e. [3+2],[6] [3+3],[7] [3+4],[8] and others[9]). However, the 1,4-addition of *α,β*-unsaturated acyl azoliums so far has been rarely investigated (Scheme 1a vs Scheme 1b, annulation vs 1,4-addition). The biggest challenge may come from the competition of two nucleophiles (NuH^1 and NuH^2) with *α,β*-unsaturated acyl azoliums (Scheme 1b). It is no doubt that a vicious competition may result in some unwanted byproducts.

In 2010, Bode et al. reported an elegant example of NHC-catalyzed Claisen rearrangement of kojic acids



Scheme 1. Strategies for NHC-catalyzed *β*-functionalization and representative biaryl methylene-based drugs.

with ynals, affording *β*-substituted esters in good to high yields.[10] Building upon mechanism, the *β*-substituted esters are truly generated from *β*-substituted *δ*-lactone intermediates with nucleophilic alcohols. In fact, this formal 1,4-addition reaction really belongs to a [3+3] annulation. Meanwhile, Bode and co-worker also reported a conjugated addition of 1-methylindole to *α,β*-unsaturated acyl

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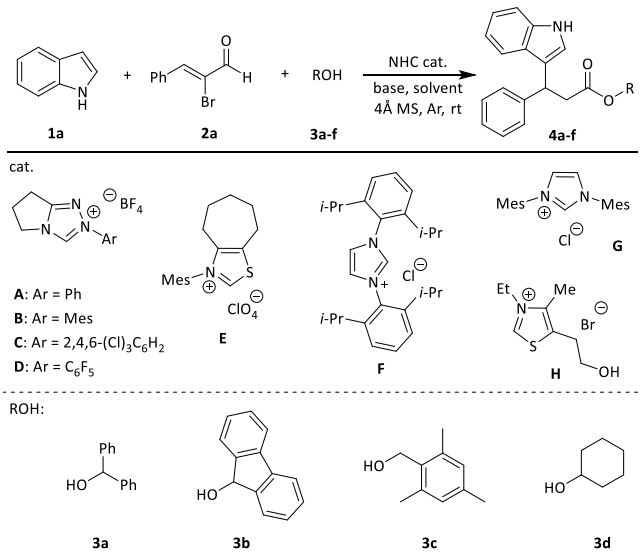
azolium. However, this process requires a stoichiometric amount of NHC and the conversion rate is low.[7f] Consequently, developing an efficient and catalytic 1,4-addition reaction of NHC-bound α,β-unsaturated acyl azoliums remains a huge challenge.

Herein, we report an unprecedented example of the NHC-catalyzed 1,4-addition of indoles to α-bromoenals that contains a formal formation of C_{sp2}—C_{sp3} (Scheme 1c, β-indolylation). Impressively, the biaryl methylene-type fragment is widely found in natural products and pharmaceuticals (Scheme 1d).[11]

Table 1. Optimization of the reaction conditions.[a]



entry	cat.	base	solvent	product	yield[b] (%)
1	none	K_2CO_3	DCM	**4a**	0
2	**A**	K_2CO_3	DCM	**4a**	< 5
3	**B**	K_2CO_3	DCM	**4a**	< 5
4	**C**	K_2CO_3	DCM	**4a**	15
5	**D**	K_2CO_3	DCM	**4a**	52
6	**E**	K_2CO_3	DCM	**4a**	< 5
7	**F**	K_2CO_3	DCM	**4a**	< 5
8	**G**	K_2CO_3	DCM	**4a**	8
9	**H**	K_2CO_3	DCM	**4a**	< 5
10	**D**	K_2CO_3	THF	**4a**	< 5
11	**D**	K_2CO_3	toluene	**4a**	45
12[c]	**D**	K_2CO_3	$CHCl_3$	**4a**	74
13	**D**	kO^{t}Bu	$CHCl_3$	**4a**	17
14	**D**	TEA	$CHCl_3$	**4a**	< 5
15	**D**	NaOAc	$CHCl_3$	**4a**	51
16	**D**	**LiOAc**	**$CHCl_3$**	**4a**	**91**
17	**D**	LiOAc	$CHCl_3$	**4b**[d]	83
18	**D**	LiOAc	$CHCl_3$	**4c**[e]	65
19	**D**	LiOAc	$CHCl_3$	**4d**[f]	86
20	**D**	LiOAc	$CHCl_3$	**4e**[g]	27
21	**D**	LiOAc	$CHCl_3$	**4f**[h]	43

[a]Reaction conditions: **1a** (0.6 mmol), **2a** (0.4 mmol), NHC cat. (10 mol %), base (0.6 mmol), **3a** (0.44 mmol), DCM (2.0 mL), 4Å MS (50 mg), Ar, room temperature, 48 h. [b] Isolated yield after flash column chromatography. [c]24 h. [d]**3b** (0.44 mmol) was used. [e] **3c** (0.44 mmol) was used. [f] **3d** (0.44 mmol) was used. [g] methanol (**3e**) (0.44 mmol) was used. [h] ethanol (**3f**) (0.44 mmol) was used.

We commenced our study by examining the model reaction of indole **1a** with α-bromoenal **2a** in the presence of alcohol **3a**. As shown in Table 1, no reaction was observed without catalyst, indicating that promoter is essential for effective β-indolylation (entry 1). A later screening demonstrated that catalyst **D** has a superior catalytic activity than others (Table 1, entries 2-9). Apparently, solvents and bases exhibited a significant effect on reaction performance (Table 1, entries 10-16). Eventually, the optimal condition was identified to be a combination of 10 mol % of cat. **D**, LiOAc (1.5 equiv.), $CHCl_3$ (2.0 mL), 4Å MS (50 mg), **3a** (0.44 mmol), and room temperature (Table 1, entry 16). This reaction can not only be used to synthesize benzhydryl esters, but also to construct a diverse set of alkyl esters. When, for example, 9-fluorenol (**3b**), mesitylmethanol (**3c**) or cyclohexanol (**3d**) was used, the β-indolyl alkyl esters were achieved regularly (Table 1, entries 17-19). When methanol or ethanol was used as an esterification reagent, the chemical yield was low, which may be due to an unexpected competitive reaction that eventually leads to an early termination of the reaction (Table 1, entries 20-21).

Having the optimal conditions in hands, we sought to explore the scope of α-bromoenals. As shown in Scheme 2, a number of α-bromoenals with multiple substituents (e.g. methyl, methoxy, fluoro, bromo) performed well in this transformation, giving thei corresponding products in high to excellent yields (**4a–j**). When the naphthalene or heterocyclic ring replaced phenyl ring in α-bromoenals, their corresponding products were obtained in high yields (**4k–p**). In addition, β-alkyl α-bromoenals also led to their corresponding products in excellent yields (**4q–t**).

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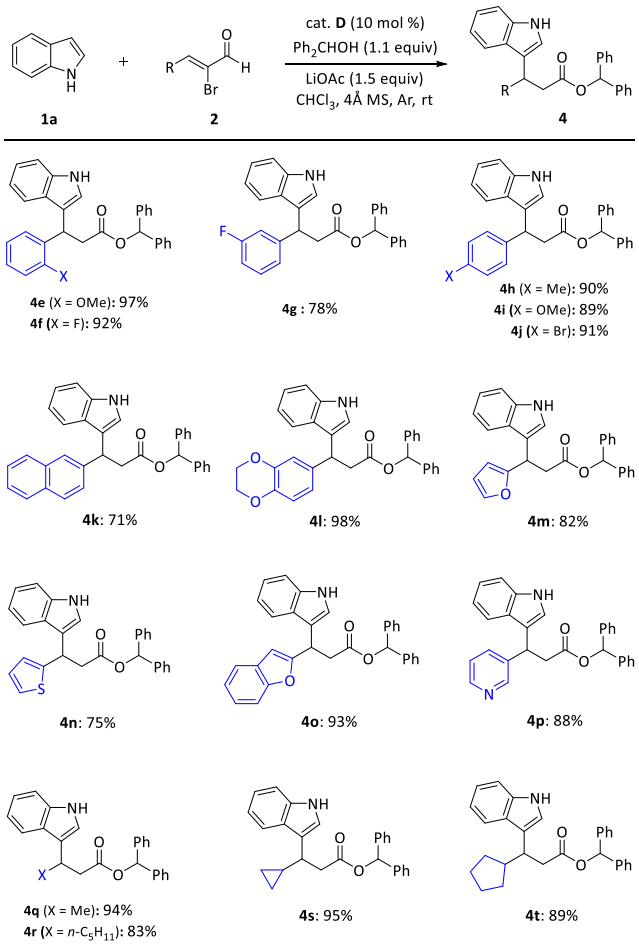
Scheme 2. Scope of α-bromoenals.[a]

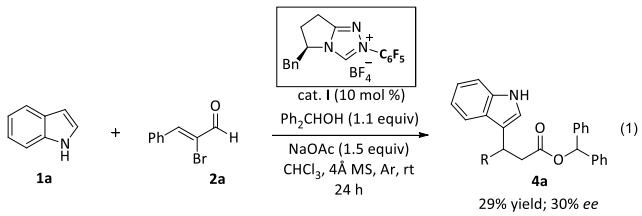


[a] Reaction conditions: **1a** (0.6 mmol), **2** (0.4 mmol), cat. **D** (10 mol %), LiOAc (0.6 mmol), **3a** (0.44 mmol), $CHCl_3$ (2 mL), 4Å MS (50 mg), Ar, room temperature, 48 h.

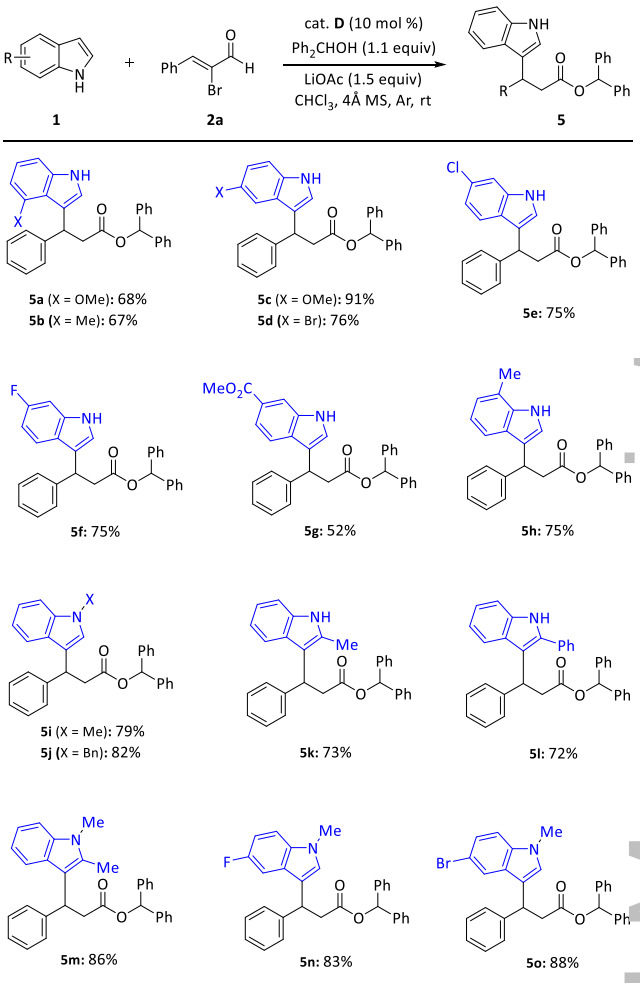
The generality of indoles **2** was further investigated (Scheme 3). When indole substrates bear electron-donating or electron-withdrawing groups at C2 or C4-C7 position, good to high yields were achieved regularly (**5a–l**, 52–91%). Pleasingly, N-substituted indoles also provided their corresponding products in high yields (Scheme 3, **5m–o**). Apart from indoles, we also tried some other nucleophiles, such as pyrrole, benzofuran, and benzothiophene, but the results showed that the reaction either did not occur or led to undesired products.

The structure of **4h** was confirmed by X-ray single crystal analysis and other products were assigned by analogy.[12]

At the same time, we also attempted the asymmetric β-indolylation of α-bromoenals with indoles. Unfortunately, the best result so far is 29% yield and 30% *ee* (Equation 1, chiral cat. **I**) (For details, see Supporting Information).



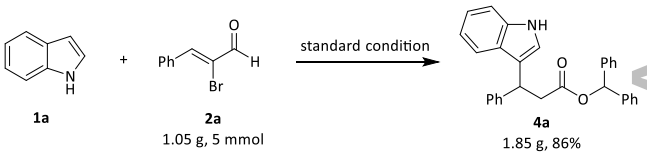
Scheme 3. Scope of indole.[a]



[a] Reaction conditions: **1** (0.6 mmol), **2a** (0.4 mmol), cat. **D** (10 mol %), LiOAc (0.6 mmol), **3a** (0.44 mmol), $CHCl_3$ (2.0 mL), 4Å MS (50 mg), Ar, room temperature, 48 h.

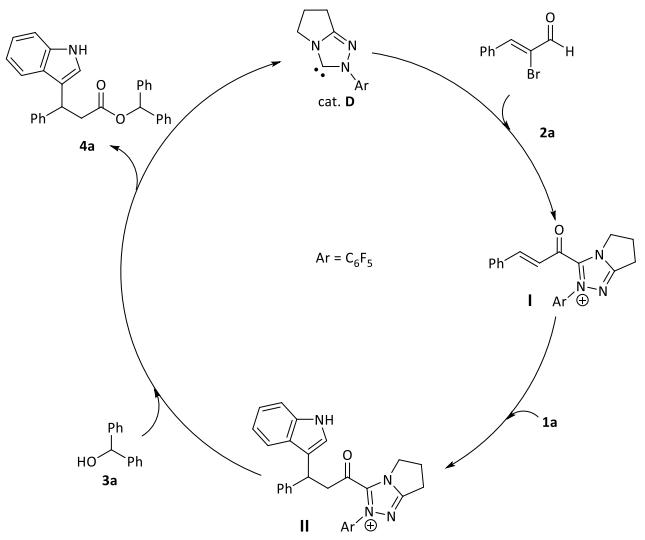
A gram-scale synthesis was carried out. No significant loss of yield was observed, implying that the catalytic β-indolylation of α-bromoenals with indoles can be scaled up (Scheme 4, 1.85 g, 86%).

Scheme 4. Gram-scale synthesis.



A postulated mechanism is illustrated in Scheme 5.[13] The addition of NHC pre-catalyst **D** to α-bromoenal **2a** generates an NHC-bound α,β-unsaturated acyl azolium intermediate **I**.[5a] Then acyl azolium **I** reacts with **1a** to deliever intermediate **II**. Finally, nucleophilic addition of **3a** to **II** furnishes **4a** and releases the NHC catalyst for next catalytic cycle.

Scheme 5. Postulated mechanism.



In summary, an unprecedented NHC-catalyzed β-indolylation of α-bromoenals with indoles has been described. A number of biaryl methylene fragment-based products was generated by using simple and readily available starting materials. Good to high yields and broad scope are generally observed. Further investigations on asymmetric version are currently underway in our laboratory.

Experimental Section

A mixture of **1** (0.4 mmol), **2** (0.6 mmol), **3** (0.44 mmol), NHC cat. (0.04 mmol), LiOAc (0.6 mmol), and 4Å MS (50 mg) in anhydrous $CHCl_3$ (2.0 mL) was stirred at room temperature for 48 h. After completion, solvent was removed under reduced pressure and purified by column chromatography to give the product as white solid or colorless oil.

Acknowledgements

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[12] CCDC-1911939 (**4h**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[13] To further understand the mechanism, two control experiments were conducted in order to exclude other potential reaction pathways. Please see the details in Supporting Information.

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UPDATE

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