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Construction of Quaternary Carbon Center via NHC Catalysis Initiated by an Intermolecular Heck-Type Alkyl Radical Addition

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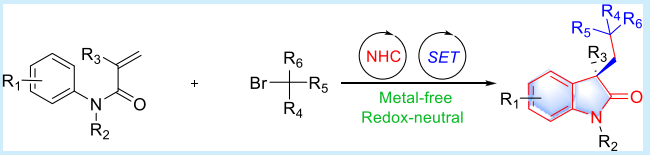
ABSTRACT: A quaternary carbon center containing an oxindole motif is constructed via NHC-catalyzed transition-metal and aldehyde-free intermolecular Heck-type alkyl radical addition initiated annulation. This redox-neutral protocol also features a simple procedure, broad substrate scope, good functional group tolerance and could be smoothly amplified to a gram scale. The mechanism study shows that the reaction possibly undergoes two folds of SET processes with an NHC radical cation intermediate involved.



Nitrogen-containing heterocycles with quaternary carbon centers are ubiquitous in nature. They are one of the most abundant and important classes of useful building blocks in organic synthesis.[1] In particular, 3,3′-disubstituted oxindole is an attractive structural motif found in numerous natural products and biologically active molecules as shown in Figure 1.[2]

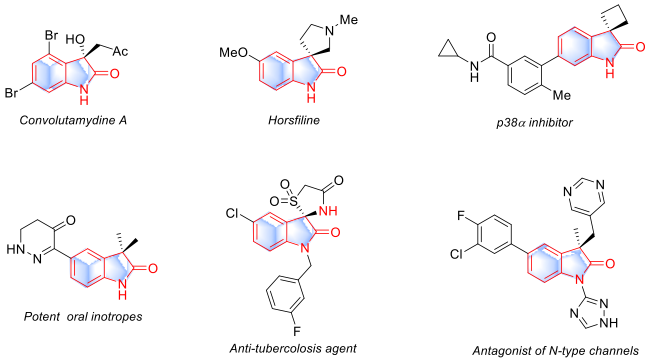


Figure 1. Selected drugs containing sulfone motifs.

Over the past few decades, the synthesis of oxindoles containing quaternary carbon atoms is still one of the central issues in organic synthesis because the reaction to construct quaternary carbon atoms usually suffers from the problem of steric hindrance.[3] Despite many efforts, current reported methods still do not allow the efficient synthesis of this type of functionalized quaternary carbon atoms. As a result, organic chemists continue to search for more straightforward and sustainable ways to prepare various oxindoles containing quaternary carbon centers with diversified functional groups. Among them, intermolecular radical addition to *N*-arylacylamides followed by tandem cyclization is one of the simplest and direct methods to construct such quaternary carbon centers.[4−6] To date, well-reported protocols are mainly based on transition-metal catalysis (Scheme 1, a).[4,6b] While transition-metal catalysts do provide remarkable efficiency for these transformations, they also suffer from high costs and toxicity, harsh reaction conditions, and poor selectivity. In this context, the demands for developing metal-free access to 3,3′-disubstituted oxindoles[5] have steadily increased since they meet the current fundamental research goals for sustainable, green, and clean organic synthesis.

Today, *N*-heterocyclic carbenes (NHCs) have wide applications involving in numerous important processes in organic synthesis,[7] coordination chemistry,[8] and materials science.[9] However, the chemistry of NHCs greatly depends on aldehydes or other substrates containing active carbonyl functional group (such as acyl fluoride or α,β-unsaturated ester).[7] For example, it is well-known that NHCs can either be directly used for umpolung of aldehyde functional groups or form the acyl azolium intermediates and work as electrophiles. Therefore, the exploration and development of new reactivity pathways which expand the range of suitable reaction partners beyond the traditional aldehydes is of great importance to this research field. In recent years, Ohmiya and others reported a series of novel NHC-catalyzed radical coupling reactions.[10] However, the scope of these transformations is still limited to aldehyde compounds. Recently, Severin et al. revealed that the NHC catalyst could undergo a SET process with oxidizing Lewis acids to afford NHC radical cation (Scheme 1, b).[11] Moreover, our group has just disclosed the first NHC-

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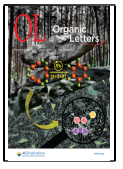

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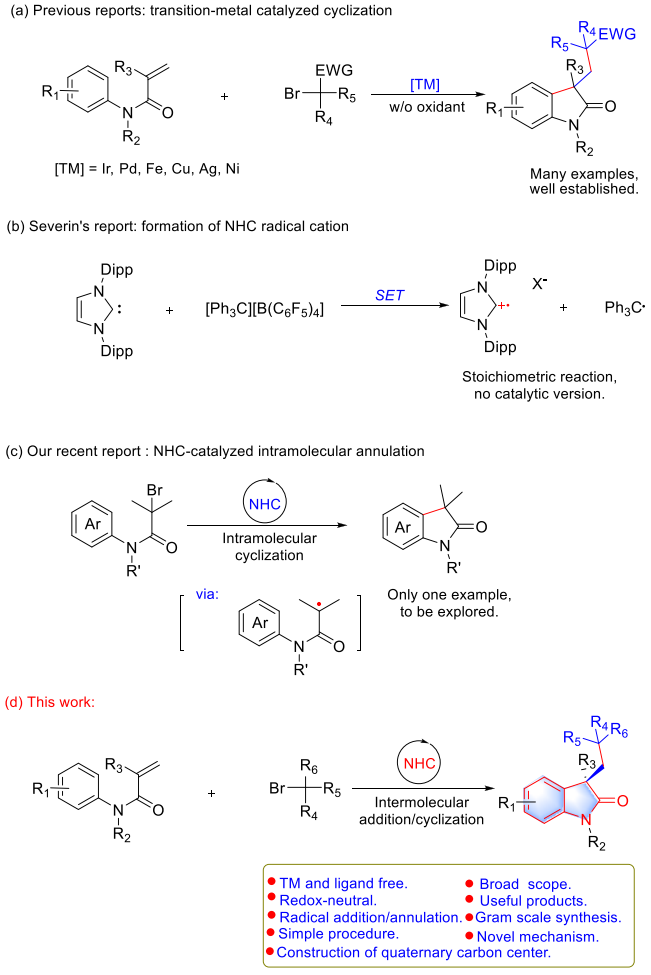
Scheme 1. Synthesis of Oxindoles with Quaternary Carbon Centers

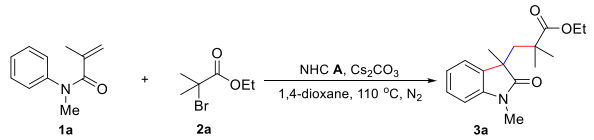


catalyzed aldehydes and active carbonyl group free intramolecular radical cyclization reaction, thus broadening the scope of NHC catalysis (Scheme 1, c).[5d] *Herein, we report an example of NHC-catalyzed intermolecular Heck-type alkyl radical addition initiated intramolecular annulation reaction leading to the rapid and efficient construction of quaternary carbon center at the 3-position of oxindoles.*

Initial condition optimization was performed with *N*-phenyl acylamide **1a** and α-bromo ester **2a** in the presence of NHC catalyst **A** and Cs_2CO_3 in MeCN under argon (Table 1). Gratifyingly, the cyclization product **3a** was obtained in 67% yield (entry 1). This yield can be further improved to 86% when tends to 1,4-dioxane (entry 5). Other solvents, such as toluene, DMSO, and *n*-Bu_2O, all dramatically decreased the yields (entries 2−4). Among the organic and inorganic bases screened, Cs_2CO_3 is the best one (entries 5−10). The structure of the NHC catalysts also plays an important role in this reaction, as was illustrated in entries 5, 11−13 (for more details, see the Supporting Information). The reactions were totally shut down in the absence of NHC catalyst or base (entries 14 and 15). Finally, the best reaction conditions were defined as **1a** (1.0 equiv), **2a** (1.5 equiv), NHC **A** (20 mol %), and Cs_2CO_3 (2.0 equiv) in 1,4-dioxane at 110 °C.

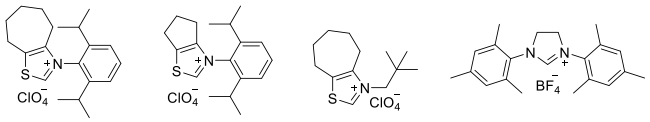
The scopes and limitations of this intermolecular radical addition initiated oxindole synthesis were carefully examined, and the results are summarized in Table 2. Generally, this

Table 1. Conditions Optimization[a]



entry	solvent	catalyst	base	yield[b] (%)
1	MeCN	NHC **A**	Cs_2CO_3	67
2	toluene	NHC **A**	Cs_2CO_3	15
3	DMSO	NHC **A**	Cs_2CO_3	14
4	*n*-Bu_2O	NHC **A**	Cs_2CO_3	43
5	1, 4-dioxane	NHC **A**	Cs_2CO_3	86
6	1, 4-dioxane	NHC **A**	DBU	9
7	1, 4-dioxane	NHC **A**	Et_3N	34
8	1, 4-dioxane	NHC **A**	NaOAc	16
9	1, 4-dioxane	NHC **A**	$NaHCO_3$	45
10	1, 4-dioxane	NHC **A**	*t*-BuOK	38
11	1, 4-dioxane	NHC **B**	Cs_2CO_3	56
12	1, 4-dioxane	NHC **C**	Cs_2CO_3	<5
13	1, 4-dioxane	NHC **D**	Cs_2CO_3	<5
14	1, 4-dioxane		Cs_2CO_3	ND
15	1, 4-dioxane	NHC **A**		ND

[a]Reaction on a 0.25 mmol scale, using **1a** (1.0 quiv.), **2a** (1.5 equiv), NHC (20 mol %), base (2.0 equiv), solvent (0.25 mL), 110 °C, under N_2, 24 h. [b]NMR yield. ND = not detected. For structures of NHC catalysts **A**−**D**, see:



reaction had a good functional group tolerance and an acceptable substrate scope. Various acrylamides **1a**−**h** with a broad substitution pattern and different electronic natures at the *ortho*-, *meta*-, and *para*-positions on the phenyl ring can be well applied, thus smoothly affording the related oxindole products (**3a**−**h**) in middle to good yields. It was worth noting that substrates containing fluorine atoms (**1f**, **1g**), which widely distribute in many drugs,[12] were also nicely compatible with this radical process. Substrates with different *N*-protecting substituents, such as methyl, ethyl, benzyl, phenyl, and *p*-methylphenyl groups, all could be efficiently converted into the desired products (**3a**, **3i**−**m**) in acceptable yields. Next, different radical precursors were tested. Among them, α-bromo esters **1n**−**p**, α-bromo keto **1q**, α-bromo nitriles **1r**−**s**, and even CX_4 (X = Cl, Br) **1t**−**u** all work well to generate the oxindoles with related quaternary carbon centers (**3n**−**u**). In particular, more sterically hindered substrate **1v** also afforded related cyclization product **3v**, thus further extending the scope of this conversion. Currently, other halogen compounds, such as benzyl bromide, allyl bromide, and 2-bromopentane all failed to give the desired products. Chiral NHCs were also tested; however, no ee values were detected (for details, see the Supporting Information).

Next, we investigated the regioselectivity of the cyclization process of this transformation. Asymmetric disubstituted *N*-arylacylamide **1w** with different aromatic rings can smoothly undergo this reaction and only gave the pyridinyl moiety cyclization product **3w** (Scheme 2, a), thus indicating the excellent selectivity of the alkyl radical addition/annulation process toward the heterocycle. However, the reaction of *N*-

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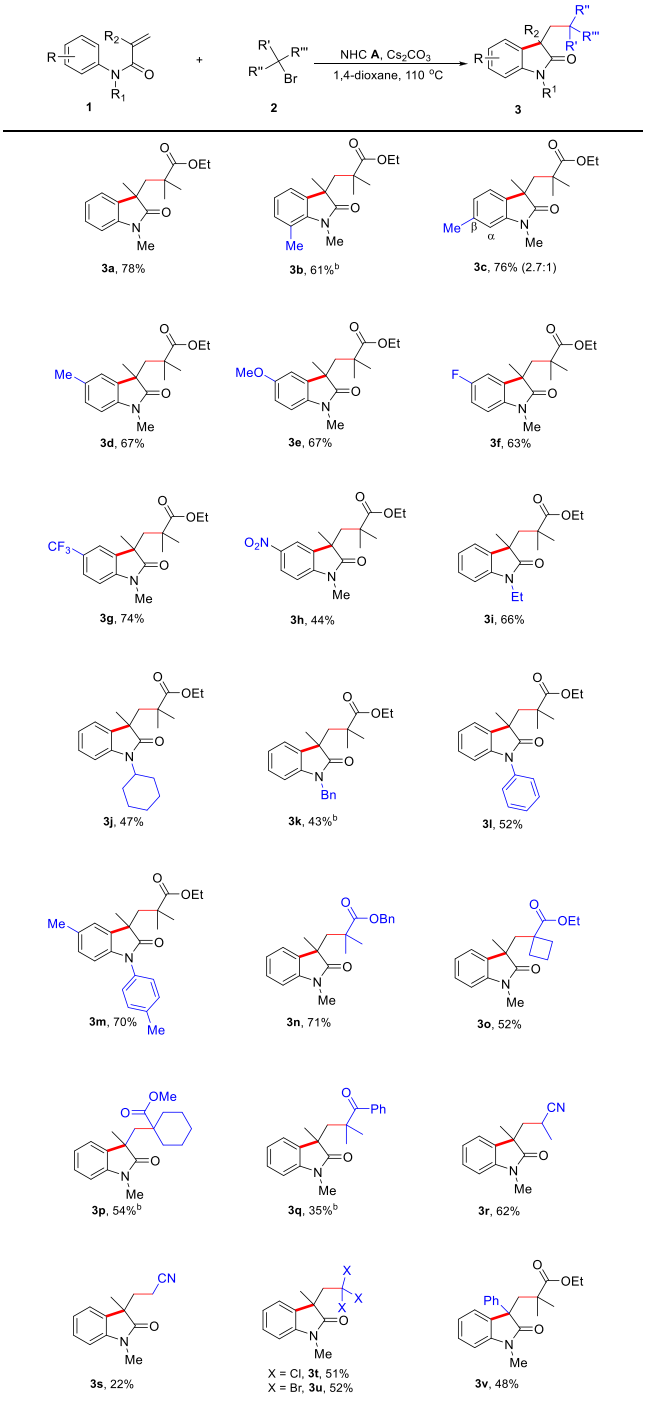
Table 2. Substrate Scope[a]



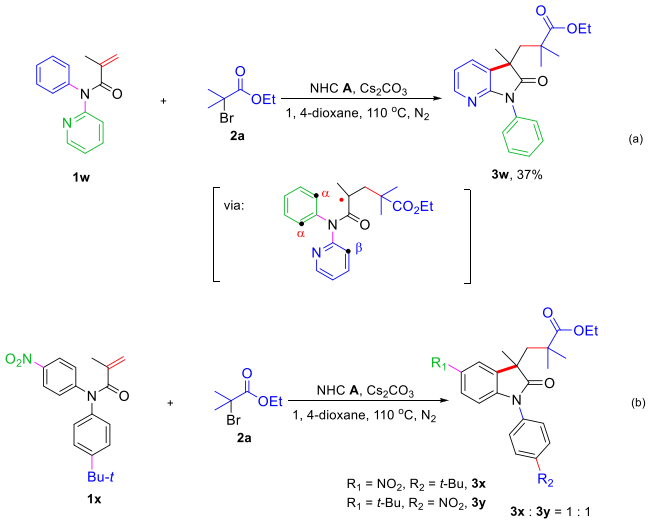
[a]Isolated yield. [b]Reaction at 130 °C using NHC **A** (40% mol), **2** (3.0 equiv), and Cs_2CO_3 (3.0 equiv).

aryl acrylamide **1x** with a different electronic nature at the *para*-position on the phenyl ring mainly afforded a related mixture of the cyclization products **3x**–**3y** (Scheme 2, b).

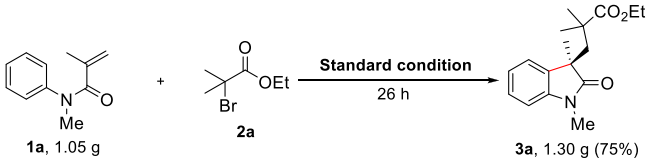
In addition, the reaction can be effectively scaled up to 1 g with similar synthetic efficiency (Scheme 3), which further exhibited the practical application of this NHC-catalyzed transformation.

This method allowed quick access to a series of free hydroxyl molecules containing indoline motifs (Scheme 4). For example, the both carbonyl functional groups of the ester

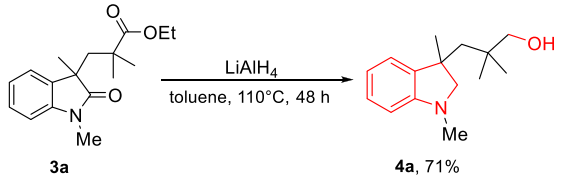
Scheme 2. Selectivity of the Cyclization Process



Scheme 3. Gram-Scale Synthesis



Scheme 4. Reduction of the Product



and amide in **3a** can be efficiently reduced to *N*-methyl indoline **4a** with a free hydroxyl in good yield upon treatment with $LiAlH_4$ in toluene,[4d] which provides the possibility for further structure modification.

A series of experiments were carried out in order to shed light on the reaction mechanism. When the reaction mixtures were exposed to various radical scavengers, such as TEMPO and O_2, substantially diminished yields were obtained, thus indicating the possible involvement of radical intermediates (Scheme 5). Moreover, the observation of BHT-adduct **4b** further confirmed the generation of related radical intermediate, which is possibly produced under the action of NHC catalyst, and thus initiated the reaction by adding onto the double bond followed by subsequent annulation reactions (for more details, see the Supporting Information).

Based on the above experiments and reported literatures,[5d,11,13,14] we proposed a mechanism for this transformation (Scheme 6). Initially, sterically hindered NHC could serve as a single-electron reductant and donate one electron to α-bromo ester **2a**, as proven by Severin et al.[11] and our recent work,[5d] giving rise to the formation of persistent NHC radical cation **B** and related α-carbon radical **A**, which can be trapped by external addition of BHT. Downstream carbon radical **A** added onto the C=C double bond would generate radical **C**, which then quickly underwent another intramolecular radical addition to form intermediate **D**. Next, a base-promoted

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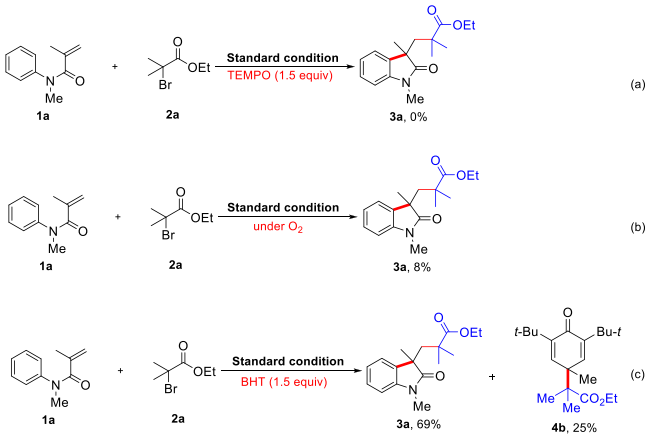
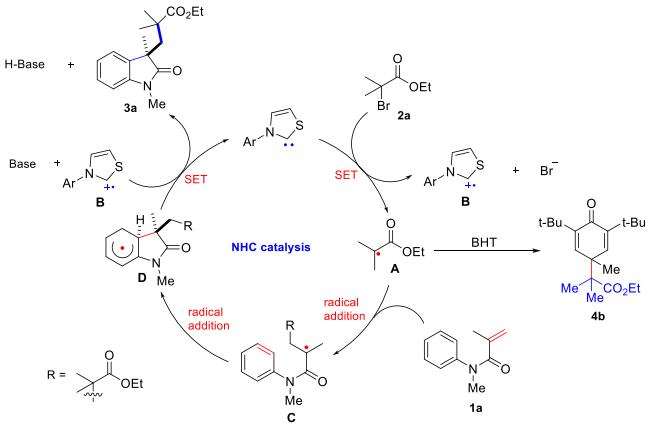
Scheme 5. Radical-Capture Experiments



Scheme 6. Proposed Mechanism



homolytic aromatic substitution (HAS) reaction[13,14] occurred smoothly accompanied by the second SET process and followed by deprotonation of **D**. Finally, the oxindole products with quaternary carbon centers were efficiently accessed and the catalytic cycle was successfully fulfilled.

In summary, we have reported a novel, green, and sustainable NHC-catalyzed transition-metal and active carbonyl functional group free method for the efficient construction of various oxindoles with quaternary carbon centers. This reaction is proposed to undergo NHC radical cation intermediate. The NHC catalyst in this transformation possibly has two aspects functions: first, it works as a single-electron reductant to donate one single electron to α-bromo esters (or other radical precursors) to form related α-carbon radicals for this conversion; second, it also works as a catalyst in this reaction. Excellent regioselectivity was achieved when employing asymmetrically heterocyclic substituted *N*-arylacrylamide, which found immediate synthetic applications. Further exploration of the synthetic utilities of this NHC-catalyzed radical chemistry and insights into more details of the mechanism are currently in progress in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01400.

General experimental procedures, characterization data, and copies of ^{1}H, ^{19}F and ^{13}C NMR spectra for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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