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Synthesis of indanes *via* carbene-catalyzed single-electron-transfer processes and cascade reactions†

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A carbene-catalyzed cascade reaction is developed for the synthesis of multi-substituted indane derivatives. The reaction involves two sequential Michael-addition steps, of which the first step is enabled by an NHC-mediated radical process. This work demonstrates the synthetic potentials of NHC-mediated single-electron-transfer processes for efficient reactions and rapid synthesis.

Indane (benzocyclopentane) is a common scaffold widely found in natural products and commercially available pharmaceuticals. For example, indantadol (Fig. 1a), a mono-substituted amino indane, exhibits interesting bio-activities as an NMDA (*N*-methyl-D-aspartate) receptor antagonist and a MAO (monoamine oxidase) inhibitor. It is a potential drug candidate for neuropathic pain and chronic cough treatment.[1] Naturally occurring trisubstituted indane caraphenol B can be isolated from the dried roots of *caragana sinica*, a traditional Chinese medicine used for the treatment of hypertension and contusion (Fig. 1b).[2] In addition to medicinal applications, functional molecules bearing indane moieties have been used as organic catalysts[3] and ligands.[4] Reported methods for the synthesis of indane derivatives[5] include carbocyclization,[5a,b] ring contraction,[6] ring expansion[7] and synthetic derivatization of pre-existing indane rings.[8]

Our laboratory is interested in developing *N*-heterocyclic carbene (abbreviated as NHC or carbene) catalyzed activation and reaction modes for the rapid synthesis of functional molecules. In contrast to electron pair reactions, single-electron-transfer (SET) radical reactions mediated by NHC catalysts are much less developed. Studer first reported the NHC-catalyzed oxidation of aldehydes *via* an SET process with TEMPO as the oxidant.[9] We developed the reductive coupling of nitroalkenes *via* radical processes by using an NHC as the catalyst and an aldehyde as the reductant.[10] Rovis and our laboratories independently disclosed enal β-carbon reactions *via* NHC-mediated radical processes.[11] Radical reactions and evidence for the presence of radical intermediates in NHC-catalyzed reactions have also been reported by Redbein[12] and Ye.[13] We recently found that under the catalysis of NHC with an aldehyde as the reductant, radical intermediates could be generated from nitrobenzyl bromide for 1,2- and 1,4-addition reactions.[14] Building on our earlier

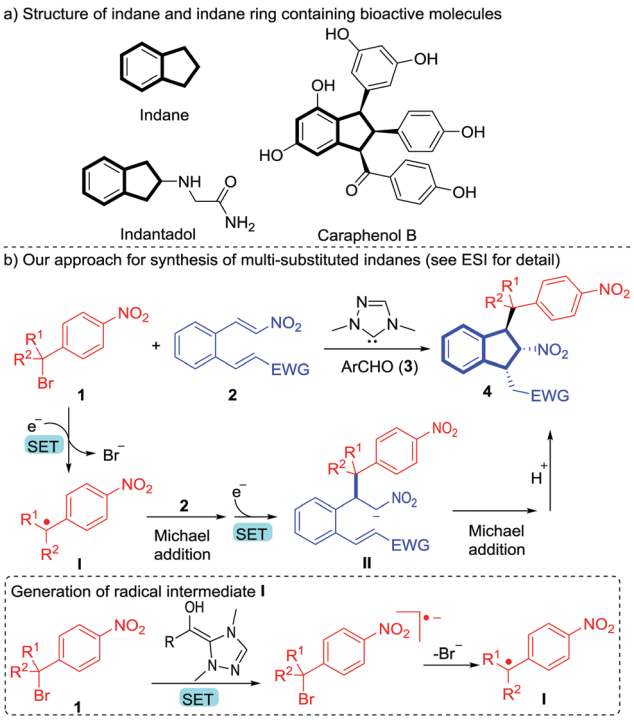

Fig. 1 Indane ring containing molecules and our synthetic approach to multi-substituted indane derivatives.

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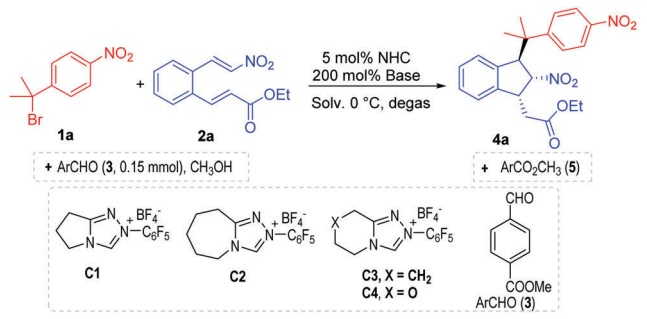
studies,[14b] here we report an efficient cascade reaction for the synthesis of multi-substituted indanes *via* an NHC-catalyzed radical process as a key step (Fig. 1b). In this process, the NHC catalyst reacts with an aldehyde to form the Breslow intermediate as a formal reductant that subsequently converts nitrobenzyl bromide (**1**) to a radical intermediate **I**. This radical intermediate eventually undergoes a formal Michael addition to the nitroalkene branch of substrate **2** to form intermediate **II**. The resulting nucleophilic α-carbon of the nitroalkene (**II**) is then trapped by the other electron-deficient alkene branch to eventually form the indane product (**4**) (see the ESI† for details). The indane adducts are obtained with multiple substituents. The indane products from our catalytic reactions can be readily transformed into heterocyclic molecules with three fused rings.

We used α,α-dimethyl 4-nitrobenzyl bromide **1a** and modified nitroalkene **2a** as model substrates to optimize the reaction conditions. Key results are summarized in Table 1. Fortunately, when we carried out the reaction using methyl 4-formylbenzoate **3** as a reductant, 5 mol% pyrrolidone-derived NHC **C1**[15] as the catalyst, and 2 equivalents of DIEA as the base at 0 °C, the desired cascade product **4a** was obtained in 86% yield (entry 1), along with excellent diastereoselectivity (only one diastereomer was obtained). Based on our previous work that only electron-deficient NHC-catalysts were efficient for the generation of radical intermediate **I**, other N-C_6F_5 substituted NHC precursors **C2–C4** were screened. However, no better results were obtained (entries 2–4). The inorganic base K_2CO_3 and stronger organic base DBU also provided the desired product in moderated yields (entries 5–6). Using toluene as the solvent along with 10 equivalents of CH_3OH as an additive afforded the product **4a** in 75% yield (entry 7). When the reaction was performed in the absence of the NHC precursor, no product was observed (entry 8).

Table 1 Reaction optimization[a]



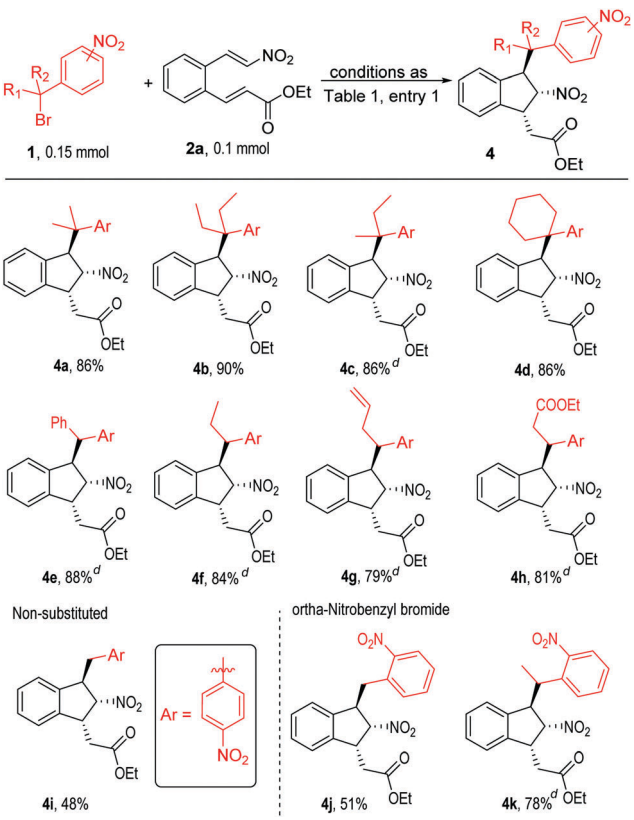
Entry	NHC	Base	Solvent	Yield (%)[a]
1	**C1**	DIEA	CH_3OH	88 (86)[b]
2	**C2**	DIEA	CH_3OH	31
3	**C3**	DIEA	CH_3OH	42
4	**C4**	DIEA	CH_3OH	59
5	**C1**	K_2CO_3	CH_3OH	53
6	**C1**	DBU	CH_3OH	46
7[c]	**C1**	DIEA	Toluene	75
8	w/o NHC	DIEA	CH_3OH	No reaction

[a] Yield (based on **2a**) was estimated *via* ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [b] Isolated yield in parentheses. [c] 10 equivalents of CH_3OH was used.

With the optimized reaction conditions in hand (Table 1, entry 1), we then investigated the generality of this cascade reaction. Initially, the scope of nitrobenzyl bromides was evaluated using modified nitroalkene **2a** as the model substrate. α,α-Disubstituted nitrobenzyl bromides used as substrates proceeded excellently in this cascade reaction. The desired products were isolated in 86–90% yields (**4a–4d**). Nitrobenzyl bromides bearing one substituent at the α-position also worked well under our standard conditions, yielding the desired products in 79–88% (**4e–4h**). Readily convertible functional groups on **1**, such as allyl and ester units, were also tolerated in this reaction (**4g** and **4h**). α-Non-substituted nitrobenzyl bromide was also suitable for this reaction, providing the corresponding indane derivative **4i** in 48% yield. Switching the nitro group to the *ortho*-position could also lead to the desired products without any loss of the reaction yields (**4j** and **4k**). The low yields of non-substituted nitrobenzyl bromides compared to those of α-substituted nitrobenzyl bromides were likely due to the lower stability of the corresponding nitrobenzyl radical intermediates (Table 2).[16]

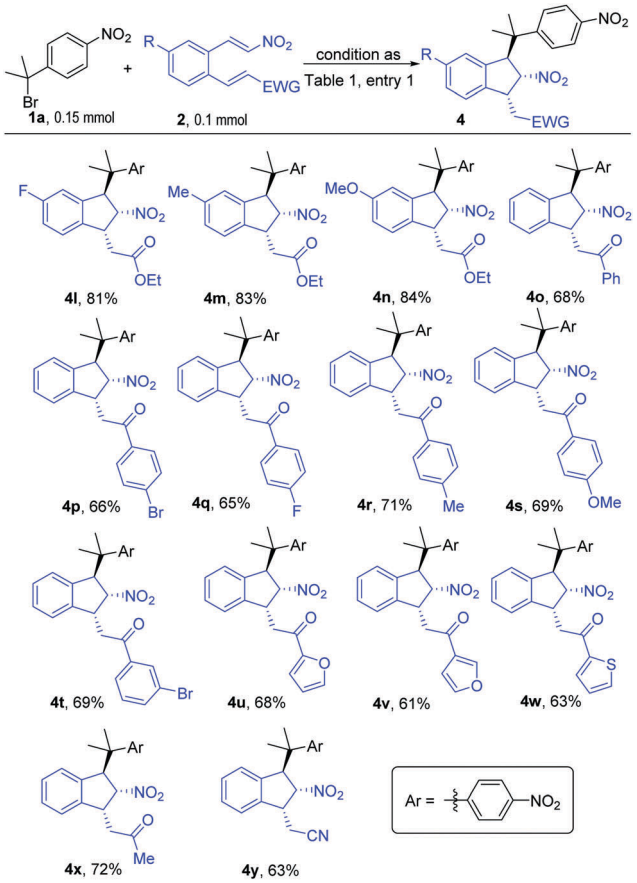
Then we turn our attention to study the generality of modified nitroalkenes. When placing an α,β-unsaturated ester as a Michael acceptor unit to nitroalkene, different substituents on the phenyl ring were well tolerated, providing the desired products

Table 2 Examples of nitrobenzyl bromides[a,b,c]



[a] Reaction conditions as in Table 1, entry 1. [b] Yield of isolated product. [c] Unless otherwise mentioned, only one isomer was obtained. [d] For **4c**, **4e–4h**, and **4k**, d.r. between 1.1 : 1 and 1.5 : 1, determined *via* ^{1}H NMR.

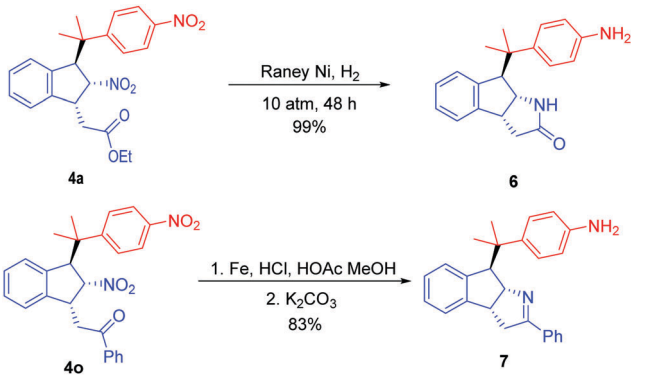
Table 3 Examples of modified nitroalkenes[a,b]



[a] Reaction conditions as in Table 1, entry 1. [b] Yield of isolated product.

in high yields (**4l–4n**). Nitroalkene bearing an α,β-unsaturated ketone as a Michael acceptor unit worked smoothly as well, albeit with moderate yield (**4o**). The structure of **4o** was confirmed *via* X-ray crystallographic analysis[17] (see ESI†). The installation of electron-withdrawing (**4p–q**) or electron-donating (**4r** and **4s**) substituents at the *para*-position of the phenyl ring of the Michael acceptor unit were all tolerated, with the annulation products obtained in 66–71% yields (**4p–4s**). A functional group substituted on the *meta*-position of the Michael acceptor unit also suitable for the reaction (**4t**). The aryl ring of the Michael acceptor unit could be changed to heteroaryl rings without any loss of the reaction yields (**4u–4w**). The aryl ring of the Michael acceptor unit could be replaced with an alkyl group, giving the desired product in 72% yield (**4x**). Finally, we found that α,β-unsaturated nitrile could also serve as a suitable Michael acceptor unit in this reaction and the product (**4y**) was provided in 63% yield (Table 3).

The cascade annulation products obtained in our catalytic reactions can readily undergo further transformations. For example, **4a** could be reduced *via* hydrogenation with RANEY® nickel to the corresponding amine, which was followed by intramolecular transesterification to form a tricyclic amide **6** in quantitative yield.[18] The product **4o** could be transformed into a fused ring product **7** in 83% yield *via* a reductive amination and subsequent annulation process (Scheme 1).



Scheme 1 Synthetic transformations of product **4a** and **4o**.

In summary, we have developed an NHC catalyzed cascade annulation reaction for the synthesis of indane derivatives. The reaction is initiated *via* an NHC-mediated SET process that converts nitro-benzyl bromide to a benzylic radical intermediate as a key step. The multi-substituted indane products were obtained as a single diastereomer with good yields. The straightforward transformation of the catalytic reaction products can lead to heterocyclic molecules with three fused rings. This study highlights the potentials of developing radical reactions enabled by carbene catalysts under mild conditions for the rapid synthesis of functional molecules.

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Conflicts of interest

There are no conflicts to declare.

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