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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 catalysts³ and ligands.⁴ Reported methods for the synthesis of indane derivatives⁵ include carbocyclization,^{5a,b} ring contraction,⁶ ring expansion⁷ 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

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

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 Redbein¹² 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

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† Electronic supplementary information (ESI) available: Experimental procedures, mechanistic details, spectroscopic data and copies of ¹H and ¹³C NMR spectra. CCDC 1560178. For ESI and crystallographic data in CIF or other electronic format see

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 C1¹⁵ 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-C₆F₅ substituted NHC precursors C2–C4 were screened. However, no better results were obtained (entries 2–4). The inorganic base K₂CO₃ 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 CH₃OH 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 ₃ OH	88 (86) ^b
2	C2	DIEA	CH ₃ OH	31
3	C3	DIEA	CH ₃ OH	42
4	C4	DIEA	CH ₃ OH	59
5	C1	K ₂ CO ₃	CH ₃ OH	53
6	C1	DBU	CH ₃ OH	46
7 ^c	C1	DIEA	Toluene	75
8	w/o NHC	DIEA	CH ₃ OH	No reaction

^a Yield (based on 2a) was estimated *via* ¹H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. ^b Isolated yield in parentheses. ^c 10 equivalents of CH₃OH 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* ¹H 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 analysis¹⁷ (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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