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N-Heterocyclic Carbene-Catalyzed δ-Carbon LUMO Activation of Unsaturated Aldehydes

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Supporting Information

ABSTRACT: An N-heterocyclic carbene (NHC) catalyzed domino reaction triggered by a δ-LUMO activation of α,β−γ,δ-diunsaturated enal has been developed for the formal [4 + 2] construction of multisubstituted arenes and 3-ylidenephthalide. These two products, formed in a highly chemo- and regioselective manner, were obtained via different catalytic pathways due to a simple change of the substrate. The activation of the remote δ-carbon of unsaturated aldehydes expands the synthetic potentials of NHC organocatalysis.

N-Heterocyclic carbene (NHC) organocatalysts enable unique reaction modes that allow for the development of highly selective and effective reactions.[1] To date, the carbonyl[2] and α-,[3] β-,[4] and γ-carbons[5] of (unsaturated) aldehydes and esters have been successfully activated by NHC catalysts for a diverse set of reactions (Figure 1). For example, addition of NHC catalyst to

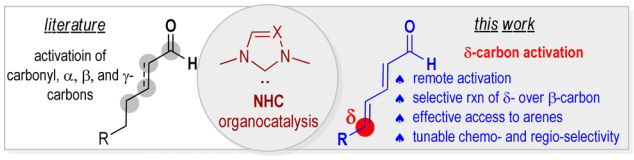

Figure 1. NHC catalyzed δ-carbon activation.

α,β-unsaturated ester[6] or aldehyde[7] under oxidative conditions affords an α,β-unsaturated azolium ester intermediate that can undergo formal 1,4-addition reactions. The three carbons (carbonyl and α- and β-carbons) of the α,β-unsaturated aldehydes/esters can participate in the formation of new molecules. In principle, the synthetic potential of NHC-catalyzed reactions of aldehydes can be significantly expanded by introducing additional conjugated C═C bonds to the aldehydes. However, in enals conjugated with an additional C═C bond (e.g., α,β−γ,δ-diunsaturated aldehydes), the activation of the δ-carbon to participate in new bond formation is challenging and remains undeveloped under NHC catalysis.[8] Typically, the β-carbon (or carbonyl carbon) is more reactive, and the δ-carbon remains untouched in NHC-catalyzed reactions, as reported by Glorius,[4f] Ma,[7d] and in our previous work.[6c] In addition, when nucleophiles such as enols and enamides were used to react with unsaturated azolium ester intermediates, 1,2-addition of the enol (oxygen) or enamide (nitrogen) to the azolium ester carbonyl carbon could occur. This 1,2-addition followed by [3,3]-rearrangement, as proposed by Bode,[7b,c] would favor reaction on the β-carbon.

Here we report the first NHC-catalyzed activation of the δ-carbon of α,β−γ,δ-diunsaturated aldehydes (Figure 1). The chemoselectivity issue between the β- and δ-carbons is addressed by introducing a substituent to block the reactivity of the β-carbon (Scheme 1)

A postulated reaction pathway is illustrated in Scheme 1. Key catalytic steps include oxidative[7a] conversion of unsaturated aldehyde to unsaturated acyl azolium intermediate **I**; 1,6-addition of 1,3-diketone substrate **2** (through its enol isomer) to **I**, followed by aldol reaction and intramolecular β-lactone formation leading to bicyclic adduct **IV**, with the regeneration of NHC catalyst. Decarboxylation followed by spontaneous oxidative aromatization finally affords the multisubstituted benzene product **3**. When R is a reactive aryl ester unit (Scheme 1, path b), intramolecular transesterification forms a 5-membered lactone (**II**′ to **VI**). Isomerization (**VI** to **VII**)[9] followed by aldol reaction then produces **VIII**, which undergoes further transformations to eventually form the 3-ylidenephthalide product **4** via a process similar to the conversion of **III** to **3**. Notably, the synthesis of multisubstituted arenes typically starts with a pre-existing benzene unit, and the introduction of substituents requires long steps with rather tedious functional group manipulations. We previously reported an NHC-catalyzed formal [3 + 3] reaction for the synthesis of substituted benzenes.[5d,10] Our present reaction, built upon a newly developed δ-carbon activation and formal [4 + 2] reaction, provides a highly effective and scalable approach in constructing the benzene unit and preparing multisubstituted arenes by using readily available substrates. The direct construction of benzene should find unique applications, for example, as recently demonstrated in Li's elegant synthesis[11] of natural products daphniphyllum, rubriflordilactone, and xiamycin via a 6π-electrocyclization/aromatization strategy.

The unsaturated aldehyde substrate (**1a**) was readily prepared in multigram scale via a 2-step well-developed protocol in over

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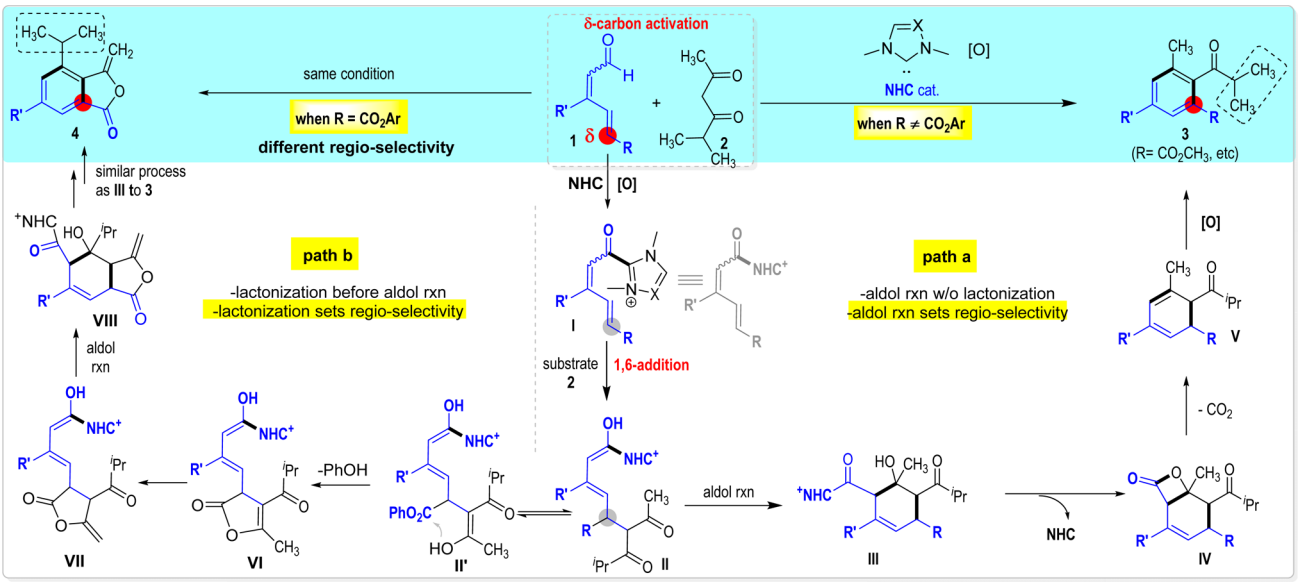
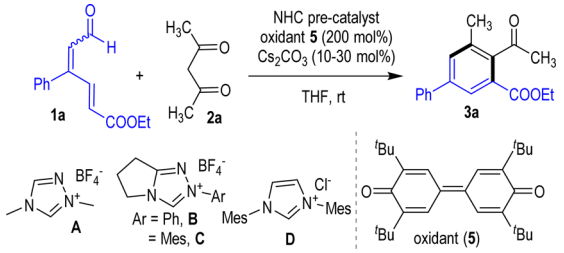
Scheme 1. δ-Activation and Selective Reactions: Proposed Pathway



80% overall yields[12] (see SI). As a technical note, it is not necessary to separate the *E*/*Z* isomers of **1a**, as both isomers participate in our catalytic reactions to give the same product with essentially the same yields. With aldehyde **1a** and 1,3-diketone **2a** as the model substrates and quinone **5** pioneered by Studer[13] as an oxidant, we first found that in the absence of NHC catalyst, the proposed product **3a** was not formed (Table 1, entry 1). Use of triazolium NHC precatalysts **A**[13] and **B**[14] led to trace amounts of **3a** (entries 2−3). We then found that by replacing the *N*-phenyl group of precatalyst **B** with an *N*-mesityl substituent (catalyst **C**),[15] **3a** could be formed in 52% yield (entry 4). The reaction could be further improved by using imidazolium NHC precatalyst **D**[4a,b] (entry 5). At last we found that the use of 10 mol % of **D** and 10 mol % of Cs_2CO_3 base was sufficient to promote the formation of **3a** in 81% yield (entry 6). Although the combination of THF and Cs_2CO_3 was optimal, other common organic solvents (such as toluene, CH_2Cl_2, EtOAc, CH_3CN, and DMF) and organic/inorganic bases (such as DBU, Et_3N, K_2CO_3, and KO^{t}Bu) could also be used (see Supporting Information, SI). It is also worth noting that in all cases, no formal 1,4-addition (reaction of the unsaturated aldehyde β-carbon) byproducts were observed. The main side reaction was oxidation of the aldehyde to carboxylic acid followed by an intramolecular Michael reaction forming a lactone byproduct in trace amounts (see SI).[16] Decreased amount of oxidant led to lower conversion of **1a** (see SI), and intermediate **V** was not observed, suggesting that the oxidative aromatization (**V** to **3**, Scheme 1) was a facile step that was likely faster than oxidation of the Breslow intermediate converting aldehyde to acyl azolium (**1** to **I**, Scheme 1).

Table 1. Condition Optimization[a]



entry	NHC precatalyst (mol %)	yield[b] (%)
1	no NHC	0
2	**A** (30)	trace
3	**B** (30)	trace
4	**C** (30)	52%
5	**D** (30)	82%
6[c]	**D** (10)	81%

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.1 mmol) in the presence of NHC precatalyst (0.03 mmol), oxidant **5** (0.2 mmol), and Cs_2CO_3 (0.03 mmol) in THF at rt. [b]Isolated yield. [c]With 10 mol % Cs_2CO_3.

With acceptable conditions in hand, the scope of the reaction was evaluated (Chart 1). 1,3-Diketone **2a** was selected as a model substrate to study the generality of the enal substrates. The R substituent at the δ-carbon of the aldehydes could be various alkyl alcohol ester units (**3a**−**d**), various aryl substituents with different electronic properties (**3e**−**i**),[17] or a CN group (**3j**). The substituent at the aldehyde β-carbon (R′) could be different (hetero)aryl units with various substituents or various substitution patterns (**3k**−**t**). Placing a *tert*-butyl substituent on the aldehyde β-carbon was also tolerated (**3u**−**v**). Replacing the β-phenyl unit of **1a** with a proton, Cl, or Br led to no formation of the benzene products: in these cases, the β-carbon formal 1,4-addition adducts (6-membered lactones) were obtained.[7d] Putting a methyl unit on the enal β-carbon led to complicated mixtures, with only trace amounts of the desired benzene product formed. The scope of the 1,3-dicarbonyl substrates was also examined by using **1a** as a model aldehyde. β-Ketoesters with various ester groups (**3w**−**y**) worked well. The methyl unit (R^1) of the ketone substrate could be replaced with other alkyl or aryl units (**3a1**−**b1**). When unsymmetric diketones were used, the reaction was highly regioselective and only one isomer was obtained (products **3d1**−**f1**). The sterically less bulky ketone moiety preferentially participated in the aldol reaction step (**II** to **III**, Scheme 1) of the catalytic reaction.

Encouraged by the success of the [4 + 2] construction of multisubstituted benzenes, we next moved on to other arenes. 3-Ylidenephthalides became one class of our target molecules because these moieties are widely present in many bioactive

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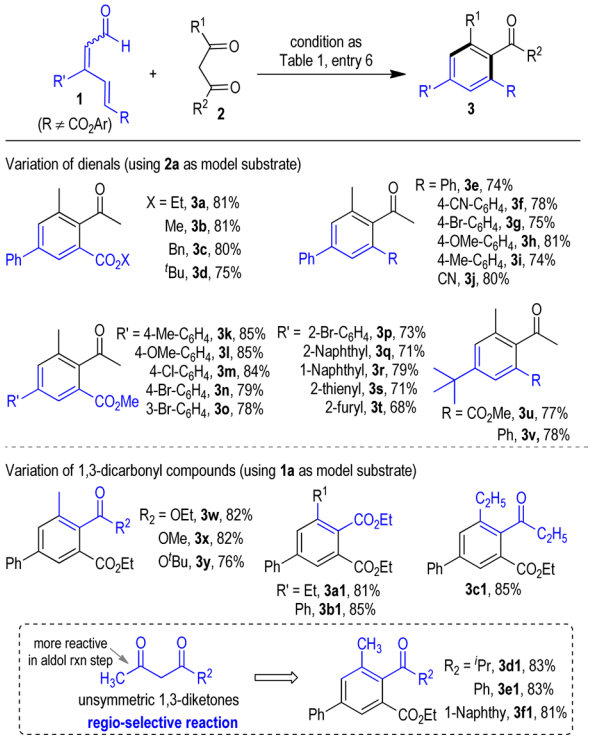
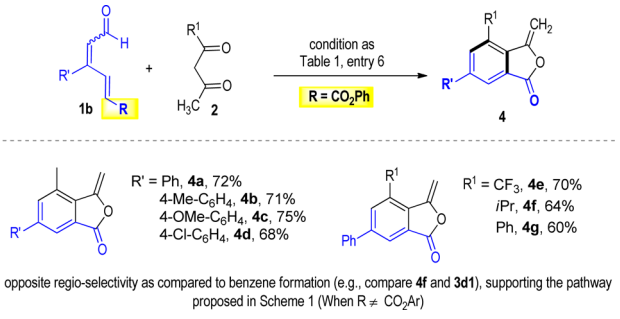
Chart 1. Substrate Scope[a]



[a]Reaction conditions as in Table 1, entry 6. Yields are isolated yields.

compounds.[18] The synthesis of these molecules mainly relied on the formation of lactone ring via intramolecular cyclization of benzoic acid (bearing preinstalled functional groups) with alkyne,[19] ketone,[20] or by CO insertion.[18b] To the best of our knowledge, the synthesis of 3-ylidenephthalide through the construction of a new benzene core is unprecedented. Here we found that by using enal **1b** bearing a phenol ester unit as the substrate (e.g., Chart 2), the catalytic reaction under otherwise

Chart 2. Synthesis of 3-Ylidenephthalide[a]

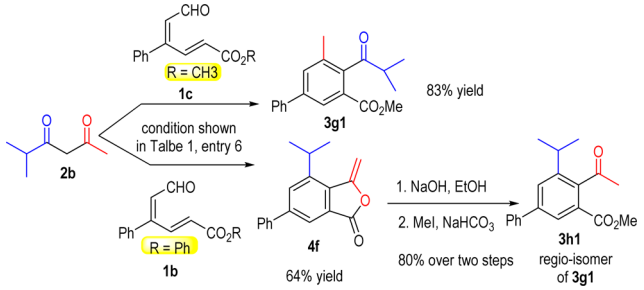


[a]Reaction conditions as in Table 1, entry 6. Yields are isolated yields.

identical conditions afforded the 3-ylidenephthalide product **4**. Similar with the substrate scope in benzene formation, the substituent at the aldehyde β-carbon (R′) could be aryl units with different electronic properties (**4a**−**d**), and the methyl unit (R^1) of the ketone substrate could be replaced with other alkyl or aryl units (**4e**−**g**).

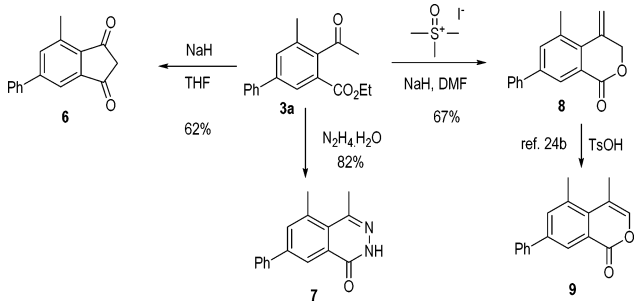
Mechanistically, the 3-ylidenephthalide product (**4**) was formed through an alternative pathway (Scheme 1; from **II**′ to **4**): when an enal with R = CO_2Ar was used, the 5-membered ring lactone moiety was formed (**II**′ to **VI**) before the aldol reaction (**VI** to **VII** to **VIII**) occurred. This mechanistic proposal was supported by the observed regioselectivities (e.g., comparing **4f** with **3d1**). Specifically, in the formation of **4f**, the aldol reaction occurred on the more sterically bulky ketone moiety, while in the formation of benzene product **3d1**, the aldol reaction took place on the less bulky ketone moiety. Such regioselectivity (e.g., in the formation of 3-ylidenephthalide) could also be applied to prepare the other regioisomers of the multisubstituted arenes that were not directly accessible in the catalytic reaction. For example, opening of the lactone ring of **4f** afforded the other regioisomer of **3g1** (**3h1**, Scheme 2).

Scheme 2. Regioselective Reactions and Access to Both Regioisomers with Unsymmetrical 1,3-Diketone Substrate



Lastly, we showed that the substituted benzene adduct **3a** could be readily transferred to other functional molecules. The multisubstituted benzene adduct **3a** could be transformed to indane-1,3-dione[21] **6**, phthalazine[22] **7**, isochromanone[23] **8**, and isocoumarin[24] **9** via straightforward processes, as shown in Scheme 3.

Scheme 3. Synthetic Applicability



In summary, we have developed an NHC organocatalytic strategy for the δ-LUMO activation of enals. Our method employs readily available starting materials and provides rapid access to multisubstituted arenes via a [4 + 2] process to construct a benzene framework. A simple change of the substrate leads to alternative catalytic pathways that allow for different products to be obtained in a highly regioselective manner. Our activation of the remote δ-carbon of unsaturated aldehydes expands the synthetic potentials of NHC organocatalysis. It is expected that previously unattainable reactions involving the δ-carbon and likely multiple carbons of unsaturated aldehydes will become feasible with our approach.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental details and NMR spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b02219.

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Notes

The authors declare no competing financial interest.

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