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

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Supporting Information Placeholder

ABSTRACT: An *N*-heterocyclic carbene (NHC) catalyzed domino reaction triggered by $\alpha\delta$ -LUMO activation of $\alpha,\beta,\gamma,\delta$ -diunsaturated aldehyde has been developed for the formal [4+2] construction of multi-substituted arenes and 3-ylidenephthalide. These two products, formed in a highly chemo- and regio-selective 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 which allow for the development of highly selective and effective reactions.¹ To date, the carbonyl,² α ,³ β ,⁴ and γ -carbons⁵ 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 α,β -unsaturated ester⁶ or aldehyde⁷ under oxidative conditions affords an α,β -unsaturated azolium ester intermediate that can undergo formal 1,4-addition reactions. The three carbons (carbonyl, 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., $\alpha,\beta,\gamma,\delta$ -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 $\alpha,\beta,\gamma,\delta$ -diunsaturated aldehydes (Figure 1). The chemo-

selectivity issue between the β - and δ -carbons is addressed by introducing a substituent to block the reactivity of the β -carbon (Scheme 1)

Figure 1. NHC Catalyzed δ -Carbon Activation

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 multi-substituted benzene product **3**. When R is a reactive aryl ester unit (Scheme 1, path b), intramolecular transesterification forms 5-member 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 multi-substituted 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 multi-substituted arenes by using readily available substrates. The direct construction of benzene should find unique applications, for example, as recently demonstrated in Li's elegant synthesis¹¹ of natural products daphniphyllum, rubrifloridilactone and xiamycin via a 6π -electrocyclization/aromatization strategy.

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

TABLE 1. Condition Optimization^a

entry	NHC pre-catalyst (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%

^aReaction conditions: **1a** (0.1 mmol), **2a** (0.1 mmol) in the presence of NHC precatalyst (0.03 mmol), oxidant **5** (0.2 mmol) and Cs₂CO₃ (0.03 mmol) in THF at rt. ^b isolated yield. ^c with 10 mol% Cs₂CO₃.

The unsaturated aldehyde substrate (**1a**) was readily prepared in multi-gram scale via a 2-step well-developed protocol in over 80% overall yields¹²(see SI). As a technical note, it's 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 Studer¹³ 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 pre-catalysts **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 pre-catalyst **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 pre-catalyst **D**^{4a-b} (entry 5). At last we found that the use of 10 mol% of **D** and 10mol% of Cs₂CO₃ base was sufficient to promote the formation

of **3a** in 81% yield (entry 6). Although the combination of THF and Cs₂CO₃ was optimal, other common organic solvents (such as toluene, CH₂Cl₂, EtOAc, CH₃CN and DMF) and organic/inorganic bases (such as DBU, Et₃N, K₂CO₃, KO^tBu) 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).

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') of the ketone substrate could be replaced with other alkyl or aryl units (**3a1-b1**). When unsymmetrical diketones were used, the reaction was highly regio-selective 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.

CHART1. Substrate Scope^a

Variation of dienals (using **2a** as model substrate)

Variation of 1,3-dicarbonyl compounds (using **1a** as model substrate)

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

CHART2. Synthesis of 3-ylidenephthalide^a

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

Encouraged by the success of the [4+2] construction of multi-substituted 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 compounds.¹⁸ The synthesis of these molecules mainly relied on the formation of lactone ring via intramolecular cyclization of benzoic acid (bearing pre-installed 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 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 (R¹) of the ketone substrate could be replaced with other alkyl or aryl units (**4e-g**).

SCHEME2. Regio-selective reactions and access to both regio-isomers with unsymmetrical 1,3-diketone substrate

Mechanistically, the 3-ylidenephthalide product (**4**) was formed through an alternative pathway (Scheme 1; from **II'** to **4**): when an enal with R = CO₂Ar 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 regio-selectivities (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 regio-selectivity (e.g., in the formation of 3-ylidenephthalide) could also be applied to prepare the other regio-isomers of the multi-substituted arenes that were not directly accessible in the catalytic reaction. For example, opening of the lactone ring of **4f** afforded the other regio-isomer of **3g1** (**3h1**, Scheme 2).

SCHEME3. Synthetic applicability.

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-dione²¹ **6**, phthalazine²² **7**, isochromanone²³ **8**, and isocoumarin²⁴ **9** via straightforward processes, as shown in Scheme 3.

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 multi-substituted 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 regio-selective 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.

ASSOCIATED CONTENT

Supporting Information

Experimental details and NMR Spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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REFERENCES

- (1) For selected reviews since 2010, see: (a) Moore, J. L.; Rovis, T. *Top. Curr. Chem.* **2010**, *291*, 77. (b) Nair, V.; Menon, R. S.; Biju, A. T.; Sinu, C. R.; Paul, R. R.; Jose, A.; Sreekumar, V. *Chem. Soc. Rev.* **2011**, *40*, 5336. (c) Izquierdo, J.; Hutson, G. E.; Cohen, D. T.; Scheidt, K. A. *Angew. Chem. Int. Ed.* **2012**, *51*, 11686. (d) Ryan, S. J.; Candish, L.; Lupton, D. W. *Chem. Soc. Rev.* **2013**, *42*, 4906. (e) Mahatthananchai, J.; Bode, J. W. *Acc. Chem. Res.* **2014**, *47*, 696. (f) Chauhan, P.; Enders, D. *Angew. Chem. Int. Ed.* **2014**, *53*, 1485. (g) Hopkinson, M. N.; Richter, C.; Schedler, M.; Glorius, F. *Nature* **2014**, *510*, 485.
- (2) For selected reviews of carbonyl carbon activation via NHC catalysis, see: (a) Alaniz, J. R.; de; Rovis, T. *Synlett* **2009**, 1189. (b) Bugaut, X.; Glorius, F. *Chem. Soc. Rev.* **2012**, *41*, 3511.
- (3) For selected examples of α -carbon activation via NHC catalysis, see: (a) He, M.; Struble, J. R.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 8418. (b) Zhang, Y. R.; He, L.; Wu, X.; Shao, P. L.; Ye, S. *Org. Lett.* **2008**, *10*, 277. (c) Zhao, X.; Ruhl, K. E.; Rovis, T. *Angew. Chem., Int. Ed.* **2012**, *51*, 12330. (d) Hao, L.; Du, Y.; Lv, H.; Chen, X.; Jiang, H.; Shao, Y.; Chi, Y. R. *Org. Lett.* **2012**, *14*, 2154. (e) Lee, A.; Younai, A.; Price, C. K.; Izquierdo, J.; Mishra, R. K.; Scheidt, K. A. *J. Am. Chem. Soc.* **2014**, *136*, 10589.
- (4) For selected examples of β -carbon activation via NHC catalysis, see: (a) Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 14370. (b) Burstein, C.; Glorius, F.; *Angew. Chem. Int. Ed.* **2004**, *43*, 6205. (c) Nair, V.; Vellalath, S.; Poonoth, M.; Suresh, E. *J. Am. Chem. Soc.* **2006**, *128*, 8736. (d) Jang, K. P.; Hutson, G. E.; Johnston, R. C.; McCusker, E. O.; Cheong, P. H.-Y.; Scheidt, K. A. *J. Am. Chem. Soc.* **2014**, *136*, 76. (e) Fu, Z.; Xu, J.; Zhu, T.; Leong, W. W. Y.; Chi, Y. R. *Nat. Chem.* **2013**, *5*, 835. (f) Li, J.-L.; Sahoo, B.; Daniliuc, C.-G.; Glorius, F. *Angew. Chem. Int. Ed.* **2014**, *53*, 10515. (g) White, N. A.; Rovis, T. *J. Am. Chem. Soc.* **2014**, *136*, 14674. (h) Zhang, Y.; Du, Y.; Huang, Z.; Xu, J.; Wu, X.; Wang, Y.; Wang, M.; Yang, S.; Webster, R. D.; Chi, Y. R. *J. Am. Chem. Soc.* **2015**, *137*, 2416.
- (5) For selected examples of γ -carbon activation via NHC catalysis, see: (a) Mo, J.; Chen, X.; Chi, Y. R. *J. Am. Chem. Soc.* **2012**, *134*, 8810–8813. (b) Chen, X.; Yang, S.; Song, B.-A.; Chi, Y. R. *Angew. Chem. Int. Ed.* **2013**, *52*, 11134–11137. (c) Wang, M.; Huang, Z.; Xu, J.; Chi, Y. R. *J. Am. Chem. Soc.* **2014**, *136*, 1214. (d) Zhu, T.; Zheng, P.; Mou, C.; Yang, S.; Song, B.-A.; Chi, Y. R. *Nat. Commun.* **2014**, *5*, 5027. (e) Liu, R.; Yu, C.; Xiao, Z.; Li, T.; Wang, X.; Xie, Y.; Yao, C. *Org. Biomol. Chem.* **2014**, *12*, 1547.
- (6) (a) Candish, L.; Lupton, D. W. *Chem. Sci.* **2012**, *3*, 380. (b) Candish, L.; Levens, A.; Lupton, D. W. *J. Am. Chem. Soc.* **2014**, *136*, 14397. (c) Cheng, J.; Huang, Z.; Chi, Y. R. *Angew. Chem. Int. Ed.* **2013**, *52*, 8592.
- (7) For selected examples, see: (a) Sarkar, S. D.; Studer, A. *Angew. Chem. Int. Ed.* **2010**, *49*, 9226. (b) Kaeobamrung, J.; Mahatthananchai, J.; Zheng, P.; Bode, J. W. *J. Am. Chem. Soc.* **2010**, *132*, 8810. (c) Mahatthananchai, J.; Kaeobamrung, J.; Bode, J. W. *ACS Catal.* **2012**, *2*, 494. (d) Wang, G.; Chen, X.; Miao, G.; Yao, W.; Ma, C. J. *Org. Chem.* **2013**, *78*, 6223. (e) Mo, J.; Shen, L.; Chi, Y. R. *Angew. Chem. Int. Ed.* **2013**, *52*, 8588. (f) Yang, Y.-J.; Zhang, H.-R.; Zhu, S.-Y.; Zhu, P.; Hui, X.-P. *Org. Lett.* **2014**, *16*, 5048. (g) Bera, S.; Samanta, R. C.; Daniliuc, C. G.; Studer, A. *Angew. Chem. Int. Ed.* **2014**, *53*, 9622.
- (8) For selected examples of organocatalytic δ -carbon activation, see: (a) Bernardi, L.; López-Cantarero, J.; Niess, B.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 5772. (b) Murphy, J. J.; Quintard, A.; McArdle, P.; Alexakis, A.; Stephens, J. C. *Angew. Chem. Int. Ed.* **2011**, *50*, 5095. (c) Uraguchi, D.; Yoshioka, K.; Ueki, Y.; Ooi, T. *J. Am. Chem. Soc.* **2012**, *134*, 19370. (d) Tian, X.; Liu, Y.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2012**, *51*, 6439. (e) Dell'Amico, L.; Albrecht, L.; Naicker, T.; Poulsen, P. H.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2013**, *135*, 8063. (f) Silvi, M.; Chat-terjee, I.; Liu, Y.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2013**, *52*, 10780.
- (9) Rajendra, G.; Miller, M. J. *J. Org. Chem.* **1987**, *52*, 4471.
- (10) For a recent example of NHC catalyzed synthesis of functionalized benzaldehydes, see: Candish, L.; Levens, A.; Lupton, D. W. *Chem. Sci.* **2015**, *6*, 2366.
- (11) (a) Lu, Z.; Li, Y.; Deng, J.; Li, A. *Nat. Chem.* **2013**, *5*, 679. (b) Li, J.; Yang, P.; Yao, M.; Deng, J.; Li, A. *J. Am. Chem. Soc.* **2014**, *136*, 16477. (c) Meng, Z.; Yu, H.; Li, L.; Tao, W.; Chen, H.; Wan, M.; Yang, P.; Edmonds, D. J.; Zhong, J.; Li, A. *Nat. Commun.* **2015**, *6*, 6096.
- (12) (a) Yasmin, N.; Ray, J. K. *Synlett*, **2010**, 6, 924. (b) Singha, R.; Dhara, S.; Ray, J. K. *Tetrahedron Lett.* **2013**, *54*, 4841.
- (13) Sarkar, S. D.; Grimme, S.; Studer, A. *J. Am. Chem. Soc.* **2010**, *132*, 1190. Also see references 7a.
- (14) Reynolds, N. T.; de Alaniz, J. R.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 9518.
- (15) Bode, J. W.; Sohn, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 13798.
- (16) For similar reactions, see: (a) Park, J. H.; Bhilare, S. V.; Youn, S. W. *Org. Lett.* **2011**, *13*, 2228. (b) Youn, S. W.; Song, H. S.; Park, J. H. *Org. Lett.* **2014**, *16*, 1028. (c) Young, S. W.; Song, H. S.; Park, J. H. *Org. Biomol. Chem.* **2014**, *12*, 2388.
- (17) similar products have already been efficiently obtained using [3+3] construction in our previous study, as shown in references 5d, so we only provide some representative examples here.
- (18) (a) Rukachaisirikul, V.; Rodglin, A.; Sukpondma, Y.; Phongpaichit, S.; Buatong, J.; Sakayaroj, J. *J. Nat. Prod.* **2012**, *75*, 853. (b) Ortar, G.; Moriello, A. S.; Morera, E.; Nalli, M.; Marzo, V. D.; Petrocellis, L. D. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 5614. (c) Rambabu, D.; Kumar, G. P.; Kumar, B. D.; Kapavarapu, R.; Rao, M. V. B.; Pal, M. *Tetrahedron Lett.* **2013**, *54*, 2989.
- (19) (a) Kumar, M. R.; Irudayanathan, F. M.; Moon, J. H.; Lee, S. *Adv. Synth. Catal.* **2013**, *355*, 3221. (b) Nebra, N.; Monot, J.; Shaw, R.; Martin-Vaca, B.; Bourissou, D. *ACS Catal.* **2013**, *3*, 2930.
- (20) (a) Danoun, G.; Mamone, P.; Gooßen, L. J. *Chem. Eur. J.* **2013**, *19*, 17287. (b) He, X.; Xue, F.; *Tetrahedron Lett.* **2014**, *55*, 1956.
- (21) Buckle, D. R.; Morgan, N. J.; Ross, J. W.; Smith, H.; Spicer, B. A. *J. Med. Chem.* **1973**, *16*, 1334.
- (22) (a) Wang, L.-X.; Zhou, X.-B.; Xiao, M.-L.; Jiang, N.; Liu, F.; Zhou, W.-X.; Wang, X.-K.; Zheng, Z.-B.; Li, S. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 3739. (b) Ibrahim, H. S.; Eldehna, W. M.; Abdel-Aziz, H. A.; Elaasser, M. M.; Abdel-Aziz, M. M. *Eur. J. Med. Chem.* **2014**, *85*, 480.
- (23) Abdoulaye, D.; Martin, K.; Moussa, C.; Léopold, K.; Odile, N. G.; Jean-Pierre, A.; Adama, S. *Res. J. Chem. Sci.* **2011**, *1*, 88.
- (24) (a) Kimura, M.; Waki, I.; Kokubo, M. *Japan. J. Pharmacol.* **1978**, *28*, 693. (b) Beaument, K.; Clough, J. M. *Tetrahedron Lett.* **1984**, *25*, 3025.