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NHC-Catalyzed Reaction of Carboxylic Acids Using Allene Ketones as Substrates and Activating Reagents

Chengli Mou, Ya Lv, Jiamiao Jin, Huifang Chai, Tingting Li, Yonggui Robin Chi, and Zhichao Jin*

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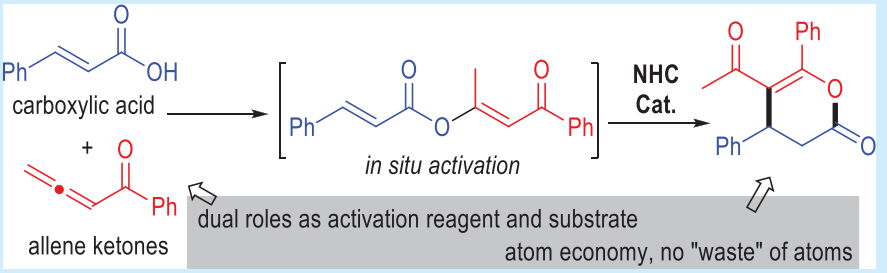

ABSTRACT: We present a new reaction between carboxylic acids and allene ketones mediated by *N*-heterocyclic carbene (NHC) catalysts, which exhibit, in principle, nearly perfect atom economy. In this new approach, allene ketones act as both an activating reagent and a reactant. All atoms in the substrates end up in the product without the need for coupling reagents. The present study aims to encourage further explorations of NHC catalytic reactions with alternative activation strategies and better atom economy.

Dihydropyranones are important structural motifs found in natural products, pharmaceutical compounds, and synthetic intermediates.[1] The dihydropyranone ring unit, particularly as a functional subunit of isocoumarins, has attracted significant attention because of its notable bioactivity, including antifungal, anti-inflammatory, and antimicrobial properties.[2] The dihydropyranone skeleton serves as a versatile building block for synthesizing biologically significant molecules, like nepetalactone,[3] neocucurbitacin D,[4] and (−)-7-deoxyloganin[5] (Figure 1a). Given the attractive biological activity and inherent structural importance, considerable efforts have been devoted to effectively access dihydropyranones. Notable examples include the Michael addition reaction catalyzed by isothiourea[6] or *N*-heterocyclic carbene (NHC)[7] catalysts, hetero-Diels−Alder reactions,[8] and a range of other versatile methods.[9] Further development of a mild and facile method for the synthesis of dihydropyranones starting from easily available materials remains highly desirable.

Carboxylic acid substrates are highly valuable in organic synthesis, medicinal chemistry, and biochemistry because of their widespread presence.[10] The diverse range of carboxylic acid substrates makes them integral to research and applications in organic chemistry by offering versatility and significance in various fields. However, catalytic activation of carboxylic acids often depends on additional activation reagents.[11] Existing methods often rely on additional reagents to overcome the inertness of the carboxylic acids. Reagents, such as PivCl, CDI, HATU, HOBt, DCC, and others, are commonly employed to activate carboxylic acids by forming highly reactive intermediates, facilitating further functionalization (Figure 1b). In 2009, Lupton and colleagues[12] demonstrated the use of NHC for the activation of enol-activated carboxylic acids in Michael addition reactions. In 2011, Smith et al.[6] developed an in situ activation method using PivCl to form mixed anhydrides, which enabled asymmetric Michael addition reactions catalyzed by isothioureas. In 2014, Scheidt and co-workers[13] reported that carboxylic acids could be transformed into NHC-bounded enolates via the in situ activation strategy in the presence of CDI. In addition, Ye and co-workers[14] demonstrated an elegant access to α,β-unsaturated acyl azlolium through mixed anhydride generated in situ from an α,β-unsaturated acid. In 2015,[15] we reported direct β-carbon activation of propionic acid by carbene organocatalysis. Moreover, Yao and colleagues[11b,16] used HATU to activate the carboxylic acid, thereby initiating a sequence of reactions catalyzed by NHC. Developing efficient carboxylic acid activation methods remains an active area of research in the field of organic synthesis.

Herein, we develop an NHC-catalyzed[17] reaction of carboxylic acids using allene ketones as substrates and activating reagents (Figure 1c). This approach eliminates the need for additional activation reagents and attains a 100% atom economy. The NHC-catalyzed Michael addition

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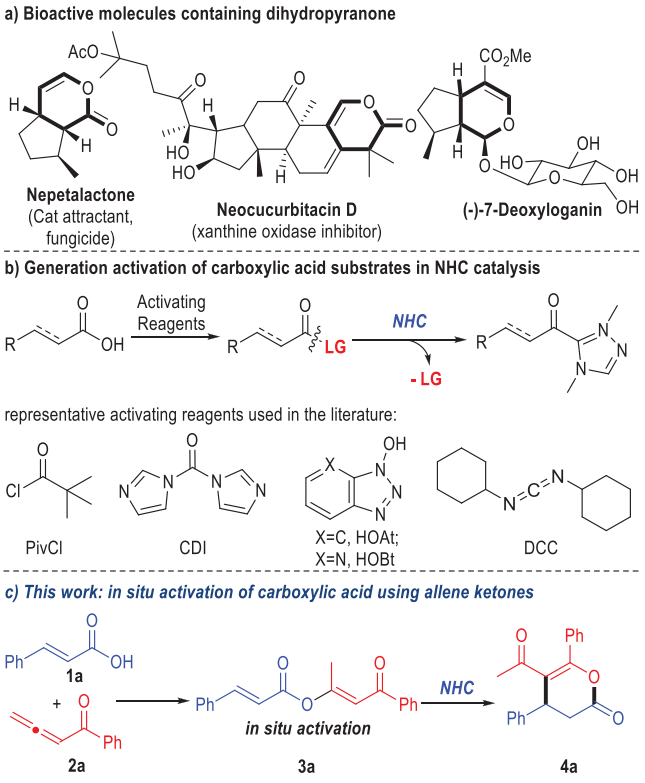


Figure 1. NHC catalytic reaction of carboxylic acids to prepare dihydropyranones.

reactions between α,β-unsaturated carboxylic acids and allene ketones, we have achieved the successful synthesis of diverse functional molecules featuring dihydropyranone frameworks, thereby attaining moderate to good yields.

Initially, α,β-unsaturated carboxylic acid **1a** and ketenone **2a** were selected for the condition optimization. Surprisingly, dihydropyranone product **4a** was successfully formed. We have extensively optimized the conditions, but the reaction yields and enantioselectivity remain low (see Scheme 1 and the Supporting Information). To make the reaction more efficient, we selected α-carbonyl vinyl ester **3a**, which is produced through the in situ reaction of carboxylic acid with allene ketones, as the model substrate for optimizing the reaction conditions in the Michael addition reaction (Table 1). First, various NHCs (**A**–**D**) were investigated using DBU as a base in THF (Table 1, entries 1–4). The expected substituted dihydropyranones **4a** were smoothly formed with yields of 28–39%. We also explored the morpholin-3-one-derived NHC **E**, but it did not enhance the yield of **4a**. The choice of base had a significant impact on the product yields. The utilization of organic bases or weak inorganic bases resulted in reduced product yields in the presence of NHC **A** (entries 6–9). However, the use of strong inorganic base Cs_2CO_3 led to further improvement in the product yield of **4a**. The reaction

Scheme 1. NHC-Catalyzed Reaction of Carboxylic Acid with Allene Ketone

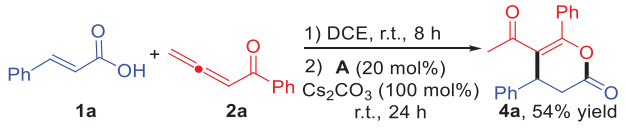
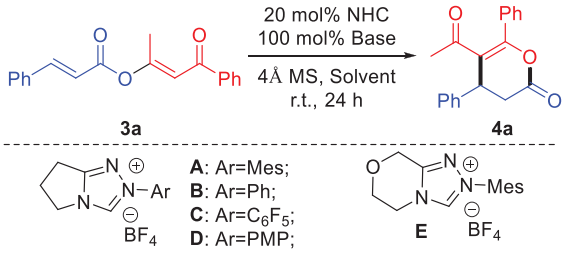


Table 1. Optimization of Reaction Conditions[a]



entry	NHC	base	solvent	yield (%)[b]
1	A	DBU	THF	39
2	B	DBU	THF	37
3	C	DBU	THF	28
4	D	DBU	THF	31
5	E	DBU	THF	29
6	A	NEt_3	THF	trace
7	A	DABCO	THF	18
8	A	Na_2CO_3	THF	15
9	A	K_2CO_3	THF	12
10	A	Cs_2CO_3	THF	45
11	A	Cs_2CO_3	EA	25
12	A	Cs_2CO_3	CH_3CN	16
13	A	Cs_2CO_3	PhCl	23
14	A	Cs_2CO_3	CH_2Cl_2	78
15	A	Cs_2CO_3	DCE	93 (88)[c]

[a]Unless otherwise specified, the reactions were carried out using **3a** (0.10 mmol), NHC (0.02 mmol), base (0.10 mmol), 4 Å MS (50 mg), and solvent (1.0 mL) at rt for 24 h. [b]Estimated via ^{1}H NMR analysis of crude reaction mixture with internal standard. [c]Isolated yield of **4a**.

was also solvent-sensitive (entries 11–15). When highly polar organic solvents other than THF were used, the yields of the target product **4a** decreased greatly (entries 11–13). Conversely, employing nonpolar organic solvents (entries 14 and 15) significantly increased the product yield. By using dichloroethane (DCE) as the solvent, compound **4a** could be isolated with a yield of 88%.

With the optimal reaction conditions in hand (Table 1, entry 15), we then examined the substrate scope of this NHC-catalyzed Michael addition reaction using substrates α-carbonyl vinyl ester **3** bearing different substitution patterns (Scheme 2). Both electron-donating and electron-withdrawing substituents could be installed on the benzene ring A to give various substituted dihydropyranones in good yields. Both bearing electron-donating and -withdrawing substituents on the *o*-position of the phenyl ring proceeded smoothly to give the desired cycloadducts in good to high yields under the optimized conditions (**4b**–**4e**). Ring A with *m*- and *p*-substituents on the phenyl ring also gave the corresponding cyclization products in moderate to good yields (**4f**–**4n**). Notably, when the phenyl ring was alkyl-substituted, the protocol could still work well (**4o**).

Furthermore, the scope of phenyl ring B with various substituents was then examined briefly. As can be seen, both electron-donating and -withdrawing substituents on the *o*-position of phenyl ring B proceeded smoothly to give the desired cycloadducts in high yields (**4p**–**4r**). The yield of all products was slightly reduced when the substituents were installed at the *m*-position (**4s**–**4v**). *p*-Substituents on the phenyl ring B with a strong electron-drawing group $-CF_3$

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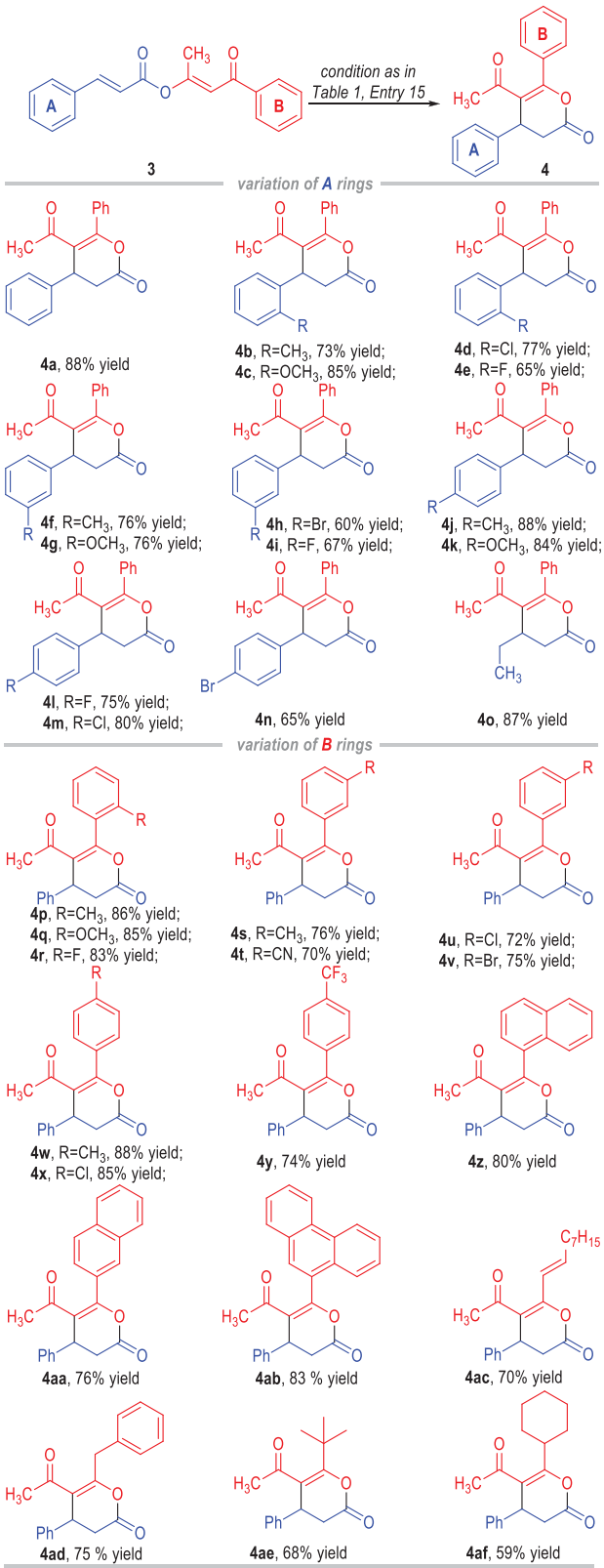
Scheme 2. Scope of the α-Carbonyl Vinyl Ester 3[a]



[a]Reaction conditions as stated in Table 1, entry 15. Yields are isolated yields.

resulting in a slight reduction in yield (**4y**). Moreover, the aromatic fused rings instead of phenyl rings, like 1-naphthalene and 2-naphthalene, also worked well in this NHC-catalyzed Michael addition reaction (**4z**–**4ab**). The corresponding products could be given in good yield when replacing phenyl ring B with the alkenyl group (**4ac**). The aromatic phenyl ring B in the substrate could also be switched into an aliphatic benzyl group and *t*-butyl group without much erosion on the reaction yields (**4ad**, **4ae**). However, when the cyclohexyl group was substituted for phenyl ring B, the yield of the target product (**4af**) could only be achieved at a moderate level.

The NHC-catalyzed Michael addition reaction of α-carbonyl vinyl ester **3a** can be carried out at a 1.0 mmol scale without much erosion on the product yield (Figure 2a). We have also

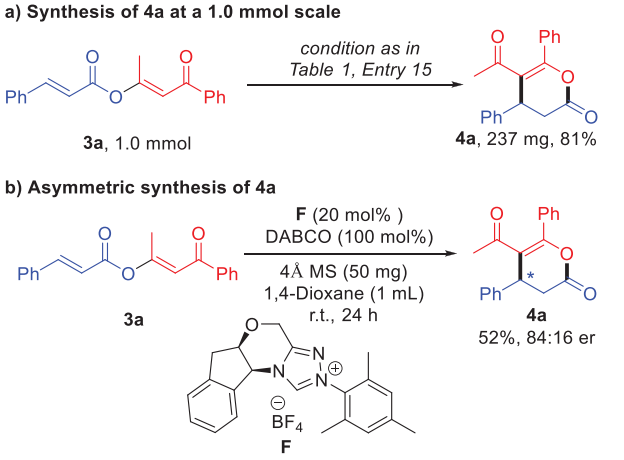


Figure 2. Synthesis of **4a** at a 1.0 mmol scale and asymmetric synthesis of **4a**.

explored the enantioselective reaction using various chiral NHC catalysts (Supporting Information, Table 4). The dihydropyranone **4a** could be obtained in 52% yield with an 84:16 er value by using NHC-**F** and DABCO in 1,4-dioxane (Figure 2b).

In summary, we have developed an NHC-catalyzed Micheal addition reaction for quick and efficient synthesis of dihydropyranone molecules. Substituents with various electronic and steric effects are well tolerated, with the target products afforded in good to excellent yields. It is noteworthy to mention that in situ activation of α,β-unsaturated carboxylic acid can be effectively accomplished using allene ketone. Additionally, the allene ketone serves a dual role as both an activating reagent and a substrate, which greatly enhances the atom economy in the reaction.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its online Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c03623.

Experimental procedures and spectral data for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Zhichao Jin − *National Key Laboratory of Green Pesticide, Key Laboratory of Green Pesticide and Agricultural*

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Bioengineering, Ministry of Education, Guizhou University, Guiyang 550025, China; orcid.org/0000-0003-3003-6437; Email: zcjin@gzu.edu.cn

Authors

Chengli Mou − *School of Pharmacy, Guizhou University of Traditional Chinese Medicine, Guiyang 550025, China*

Ya Lv − *National Key Laboratory of Green Pesticide, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Guizhou University, Guiyang 550025, China*

Jiamiao Jin − *National Key Laboratory of Green Pesticide, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Guizhou University, Guiyang 550025, China*

Huifang Chai − *School of Pharmacy, Guizhou University of Traditional Chinese Medicine, Guiyang 550025, China*

Tingting Li − *National Key Laboratory of Green Pesticide, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Guizhou University, Guiyang 550025, China;* orcid.org/0000-0003-2657-4646

Yonggui Robin Chi − *National Key Laboratory of Green Pesticide, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Guizhou University, Guiyang 550025, China; School of Chemistry, Chemical Engineering, and Biotechnology, Nanyang Technological University, Singapore 637371, Singapore;* orcid.org/0000-0003-0573-257X

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.3c03623

Author Contributions

C.M. contributed to designs and most of the experiments. Z.J. conceptualized and directed the project and drafted the manuscript with assistance from all coauthors. All authors contributed to part of the experiments and/or discussions.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Liblikas, I.; Santangelo, E. M.; Sandell, J.; Baeckstrom, P.; Svensson, M.; Jacobsson, U.; Unelius, C. R. Simplified Isolation Procedure and Interconversion of the Diastereomers of Nepetalactone and Nepetalactol. *J. Nat. Prod.* **2005**, *68*, 886−890. (b) Yang, J.; Wearing, X. Z.; Le Quesne, P. W.; Deschamps, J. R.; Cook, J. M. Enantiospecific Synthesis of (+)-alstonisine via a Stereospecific Osmylation Process. *J. Nat. Prod.* **2008**, *71*, 1431−1440. (c) Cui, C. M.; Li, X. M.; Meng, L.; Li, C. S.; Huang, C. G.; Wang, B. G. 7-Norergosterolide, a Pentalactone-containing Norsteroid and Related Steroids from the Marine-derived Endophytic Aspergillus Ochraceus EN-31. *J. Nat. Prod.* **2010**, *73*, 1780−1784. (d) Dagenais, R.; Lussier, T.; Legault, C. Y. Iodine(III)-Mediated Contraction of 3,4-Dihydropyranones: Access to Polysubstituted γ-Butyrolactones. *Org. Lett.* **2019**, *21*, 5290−5294. (e) Lussier, T.; Legault, C. Y. Iodine(III)-Mediated Enantioselective Oxidative Contraction of Dihydropyranones. *Org. Lett.* **2023**, *25*, 2825−2829.

(2) (a) Payne, S. L.; Rodriguez-Aristegui, S.; Bardos, J.; Cano, C.; Golding, B. T.; Hardcastle, I. R.; Peacock, M.; Parveen, N.; Griffin, R. J. Mapping the ATP-Binding Domain of DNA-Dependent Protein Kinase (DNA-PK) with Coumarin- and Isocoumarin-Derived Inhibitors. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3649−3653. (b) Zheng, W.; Ji, Y. B.; Li, W. L.; Dong, J.; Chen, N.; Yu, X. F.; Wu, J.; Zhao, D.; Xiang, Z. A Pair of New Isocoumarin Epimers from Soil Fungus Hypoxylon sp. *J. Asian Nat. Prod. Res.* **2017**, *19*, 993−999.

(3) Sengupta, S. K.; Hutchenson, K. W.; Hallahan, D. L.; Gonzalez, Y. I.; Manzer, L. E.; Jackson, S. C.; Scialdone, M. A.; Kou, B. Hydrogenation of Naturally-Derived Nepetalactone as a Topical Insect Repellent. *ACS Sustain. Chem. Eng.* **2018**, *6*, 9628−9639.

(4) Jiang, H. Z.; Hu, S.; Tan, R. X.; Tan, R.; Jiao, R. H. Neocucurbitacin D, a Novel Lactone-type Norcucurbitacin as Xanthine Oxidase Inhibitor from Herpetospermum Pedunculosum. *Nat. Prod. Res.* **2020**, *34*, 1728−1734.

(5) (a) Candish, L.; Lupton, D. W. The Total Synthesis of (−)-7-Deoxyloganin via N-Heterocyclic Carbene Catalyzed Rearrangement of α,β-Unsaturated Enol Esters. *Org. Lett.* **2010**, *12*, 4836−4839. (b) Candish, L.; Lupton, D. W. Concise Formal Synthesis of (−)-7-Deoxyloganin via N-Heterocyclic Carbene Catalysed Rearrangement of α,β-Unsaturated Enol Esters. *Org. Biomol. Chem.* **2011**, *9*, 8182−8189.

(6) Belmessieri, D.; Morrill, L. C.; Simal, C.; Slawin, A. M.; Smith, A. D. Organocatalytic Functionalization of Carboxylic Acids: Isothiourea-Catalyzed Asymmetric Intra- and Intermolecular Michael Addition-Lactonizations. *J. Am. Chem. Soc.* **2011**, *133*, 2714−2720.

(7) (a) Rong, Z. Q.; Jia, M. Q.; You, S. L. Enantioselective N-Heterocyclic Carbene-Catalyzed Michael Addition to α,β-Unsaturated Aldehydes by Redox Oxidation. *Org. Lett.* **2011**, *13*, 4080−4083. (b) Mahatthananchai, J.; Kaeobamrung, J.; Bode, J. W. Chiral N-Heterocyclic Carbene Catalyzed Annulations of Enals and Ynals with Stable Enols: A Highly Enantioselective Coates-Claisen Rearrangement. *ACS Catal.* **2012**, *2*, 494−503. (c) Yetra, S. R.; Kaicharla, T.; Kunte, S. S.; Gonnade, R. G.; Biju, A. T. Asymmetric N-Heterocyclic Carbene (NHC)-Catalyzed Annulation of Modified Enals with Enolizable Aldehydes. *Org. Lett.* **2013**, *15*, 5202−5205. (d) Wu, X.; Zhang, Y.; Wang, Y.; Ke, J.; Jeret, M.; Reddi, R. N.; Yang, S.; Song, B. A.; Chi, Y. R. Polyhalides as Efficient and Mild Oxidants for Oxidative Carbene Organocatalysis by Radical Processes. *Angew. Chem., Int. Ed.* **2017**, *56*, 2942−2946. (e) Cao, J.; Gillard, R.; Jahanbakhsh, A.; Breugst, M.; Lupton, D. W. Enantioselective N-Heterocyclic Carbene Catalysis via Acyl Azolium without Exogenous Oxidants. *ACS Catal.* **2020**, *10*, 11791−11796.

(8) Arumugam, S.; Popik, V. V. Light-Induced Hetero-Diels-Alder Cycloaddition: a Facile and Selective Photoclick Reaction. *J. Am. Chem. Soc.* **2011**, *133*, 5573−5579.

(9) (a) Evans, D. A.; Thomson, R. J.; Franco, F. Ni(II) Tol-BINAP-Catalyzed Enantioselective Michael Reactions of β-Ketoesters and Unsaturated N-Acylthiazolidinethiones. *J. Am. Chem. Soc.* **2005**, *127*, 10816−10817. (b) Itoh, K.; Hasegawa, M.; Tanaka, J.; Kanemasa, S. Enantioselective Enol Lactone Synthesis under Double Catalytic

Conditions. *Org. Lett.* **2005**, *7*, 979−981. (c) Chen, J.-Q.; Chen, Q.; Chen, B.; Wu, J. Visible-Light-Induced Alkoxycarbonylation/Cyclization of 1,7-Enynes: Synthesis of Dihydropyranones Containing all-Carbon Quaternary Centers. *Org. Chem. Front.* **2023**, *10*, 2018−2023.

(10) For reviews, see: (a) Goossen, L. J.; Rodriguez, N.; Goossen, K. Carboxylic Acids as Substrates in Homogeneous Catalysis. *Angew. Chem., Int. Ed.* **2008**, *47*, 3100−3120. (b) Varenikov, A.; Shapiro, E.; Gandelman, M. Decarboxylative Halogenation of Organic Compounds. *Chem. Rev.* **2021**, *121*, 412−484. (c) Kang, G.; Strassfeld, D. A.; Sheng, T.; Chen, C. Y.; Yu, J. Q. Transannular C-H Functionalization of Cycloalkane Carboxylic Acids. *Nature* **2023**, *618*, 519−525. For examples, see: (d) Zuo, Z.; Ahneman, D. T.; Chu, L.; Terrett, J. A.; Doyle, A. G.; MacMillan, D. W. Merging Photoredox with Nickel Catalysis: Coupling of α-Carboxyl sp^3-Carbons with Aryl Halides. *Science* **2014**, *345*, 437−440. (e) Liu, Y.; Chen, Q.; Mou, C.; Pan, L.; Duan, X.; Chen, X.; Chen, H.; Zhao, Y.; Lu, Y.; Jin, Z.; Chi, Y. R. Catalytic Asymmetric Acetalization of Carboxylic Acids for Access to Chiral Phthalidyl Ester Prodrugs. *Nat. Commun.* **2019**, *10*, 1675. (f) Ren, S. C.; Yang, X.; Mondal, B.; Mou, C.; Tian, W.; Jin, Z.; Chi, Y. R. Carbene and Photocatalyst-Catalyzed Decarboxylative Radical Coupling of Carboxylic Acids and Acyl Imidazoles to Form Ketones. *Nat. Commun.* **2022**, *13*, 2846.

(11) (a) Que, Y.; Lu, Y.; Wang, W.; Wang, Y.; Wang, H.; Yu, C.; Li, T.; Wang, X. S.; Shen, S.; Yao, C. An Enantioselective Assembly of Dihydropyranones through an NHC/LiCl-Mediated in Situ Activation of α,β-Unsaturated Carboxylic Acids. *Chem.—Asian J.* **2016**, *11*, 678−681. (b) Wang, Y.; Pan, J.; Dong, J.; Yu, C.; Li, T.; Wang, X. S.; Shen, S.; Yao, C. N-Heterocyclic Carbene-Catalyzed [4 + 2] Cyclization of Saturated Carboxylic Acid with o-Quinone Methides through in Situ Activation: Enantioselective Synthesis of Dihydrocoumarins. *J. Org. Chem.* **2017**, *82*, 1790−1795. (c) Zhang, W.; Xu, J.; Cao, J.; Fang, C.; Zhu, J.; Lu, T.; Du, D. N-Heterocyclic Carbene-Mediated Formal [3 + 3] Annulation of Isatin-Derived α,β-Unsaturated Acids: Access to Functionalized 3,4′-Spirooxindole δ-Lactones. *Tetrahedron* **2017**, *73*, 3249−3254. (d) Huy, P. H.; Mbouhom, C. Formamide Catalyzed Activation of Carboxylic Acids-Versatile and Cost-Efficient Amidation and Esterification. *Chem. Sci.* **2019**, *10*, 7399−7406. (e) Deng, X.; Guo, J.; Zhang, X.; Wang, X.; Su, W. Activation of Aryl Carboxylic Acids by Diboron Reagents towards Nickel-Catalyzed Direct Decarbonylative Borylation. *Angew. Chem., Int. Ed.* **2021**, *60*, 24510−24518.

(12) Ryan, S. J.; Candish, L.; Lupton, D. W. N-Heterocyclic Carbene-Catalyzed Generation of α,β-Unsaturated Acyl Imidazoliums: Synthesis of Dihydropyranones by Their Reaction with Enolates. *J. Am. Chem. Soc.* **2009**, *131*, 14176−14177.

(13) Lee, A.; Younai, A.; Price, C. K.; Izquierdo, J.; Mishra, R. K.; Scheidt, K. A. Enantioselective Annulations for Dihydroquinolones by in Situ Generation of Azolium Enolates. *J. Am. Chem. Soc.* **2014**, *136*, 10589−10592.

(14) Chen, X. Y.; Gao, Z. H.; Song, C. Y.; Zhang, C. L.; Wang, Z. X.; Ye, S. N-Heterocyclic Carbene Catalyzed Cyclocondensation of α, β-Unsaturated Carboxylic Acids: Enantioselective Synthesis of Pyrrolidinone and Dihydropyridinone Derivatives. *Angew. Chem., Int. Ed.* **2014**, *53*, 11611−11615.

(15) Jin, Z.; Jiang, K.; Fu, Z.; Torres, J.; Zheng, P.; Yang, S.; Song, B. A.; Chi, Y. R. Nucleophilic β-Carbon Activation of Propionic Acid as a 3-Carbon Synthon by Carbene Organocatalysis. *Chem.—Eur. J.* **2015**, *21*, 9360−9363.

(16) Que, Y.; Xie, Y.; Li, T.; Yu, C.; Tu, S.; Yao, C. An N-Heterocyclic Carbene-Catalyzed Oxidative γ-Aminoalkylation of Saturated Carboxylic Acids through in Situ Activation Strategy: Access to delta-Lactam. *Org. Lett.* **2015**, *17*, 6234−6237.

(17) For reviews on NHC catalysis, see: (a) Enders, D.; Niemeier, O.; Henseler, A. Organocatalysis by N-Heterocyclic Carbenes. *Chem. Rev.* **2007**, *107*, 5606−5655. (b) Bugaut, X.; Glorius, F. Organocatalytic umpolung: N-Heterocyclic Carbenes and Beyond. *Chem. Soc. Rev.* **2012**, *41*, 3511−3522. (c) Grossmann, A.; Enders, D. N-Heterocyclic Carbene Catalyzed Domino Reactions. *Angew. Chem., Int. Ed.* **2012**, *51*, 314−325. (d) Ryan, S. J.; Candish, L.; Lupton, D. W. Acyl Anion Free N-Heterocyclic Carbene Organocatalysis. *Chem. Soc. Rev.* **2013**, *42*, 4906−4917. (e) Hopkinson, M. N.; Richter, C.; Schedler, M.; Glorius, F. An Overview of N-Heterocyclic Carbenes. *Nature* **2014**, *510*, 485−496. (f) Mahatthananchai, J.; Bode, J. W. On the Mechanism of N-Heterocyclic Carbene-Catalyzed Reactions involving Acyl Zzoliums. *Acc. Chem. Res.* **2014**, *47*, 696−707. (g) Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A.; Rovis, T. Organocatalytic Reactions Enabled by N-Heterocyclic Carbenes. *Chem. Rev.* **2015**, *115*, 9307−9387. (h) Menon, R. S.; Biju, A. T.; Nair, V. Recent Advances in Employing Homoenolates Generated by N-Heterocyclic Carbene (NHC) Catalysis in Carbon-Carbon Bond-Forming Reactions. *Chem. Soc. Rev.* **2015**, *44*, 5040−5052. (i) Murauski, K. J. R.; Jaworski, A. A.; Scheidt, K. A. A Continuing Challenge: N-Heterocyclic Carbene-Catalyzed Syntheses of γ-Butyrolactones. *Chem. Soc. Rev.* **2018**, *47*, 1773−1782. (j) Chen, X.; Wang, H.; Jin, Z.; Chi, Y. R. N-Heterocyclic Carbene Organocatalysis: Activation Modes and Typical Reactive Intermediates. *Chin. J. Chem. .* **2020**, *38*, 1167−1202. (k) Li, T.; Jin, Z.; Chi, Y. R. N-Heterocyclic Carbene-Catalyzed Arene Formation Reactions. *Sci. China Chem.* **2022**, *65*, 210−223. (l) Song, R.; Xie, Y.; Jin, Z.; Chi, Y. R. Carbene-Catalyzed Asymmetric Construction of Atropisomers. *Angew. Chem., Int. Ed.* **2021**, *60*, 26026−26037. (m) Lv, J.; Xu, J.; Pan, X.; Jin, Z.; Chi, Y. R. Carbene-Catalyzed Activation of Cyclopropylcarbaldehydes for Mannich Reaction and δ-lactam Formation: Remote Enantioselecitvity Control and Dynamic Kinetic Asymmetric Transformation. *Sci. China Chem.* **2021**, *64*, 985−990. (n) Nie, G.; Huang, X.; Wang, Z.; Pan, D.; Zhang, J.; Chi, Y. R. Umpolung of Donor−Acceptor Cyclopropanes via N-Heterocyclic Carbene Organic Catalysis. *Org. Chem. Front.* **2021**, *8*, 5105−5111. (o) Yang, X.; Wang, H.; Jin, Z.; Chi, Y. R. Development of Green and Low-Cost Chiral Oxidants for Asymmetric Catalytic Hydroxylation of Enals. *Green Synth. Catal.* **2021**, *2*, 295−298.

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