Journal Pre-proof

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PII: S1001-8417(24)00017-2
DOI: https://doi.org/10.1016/j.cclet.2024.109495
Reference: CCLET 109495

To appear in: *Chinese Chemical Letters*

Received date: 23 October 2023
Revised date: 22 December 2023
Accepted date: 2 January 2024

Please cite this article as: Kun Tang , Fen Su , Shijie Pan , Fengfei Lu , Zhongfu Luo , Fengrui Che , Xingxing Wu , Yonggui Robin Chi , Enones from aldehydes and alkenes by carbene-catalyzed dehydrogenative couplings, *Chinese Chemical Letters* (2024), doi: https://doi.org/10.1016/j.cclet.2024.109495

Chinese Chemical Letters
journal homepage: www.elsevier.com

Communication

Enones from aldehydes and alkenes by carbene-catalyzed dehydrogenative couplings

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Enones
Cross dehydrogenative coupling
N-Heterocyclic carbene
Aryl radical
Hydrogen atom transfer

ABSTRACT

Enones are widely explored in synthetic chemistry as fundamental building blocks for a wide range of reactions and exhibit intriguing biological activities that are pivotal for drug discovery. The development of synthetic strategies for highly efficient preparation of enones thereby receives intense attention, in particular through the transition metal-catalyzed coupling reactions. Here, we describe a carbene-catalyzed cross dehydrogenative coupling (CDC) reaction that enables effective assembly of simple aldehydes and alkenes to afford a diverse set of enone derivatives. Mechanistically, the *in situ* generated aryl radical is pivotal to "activate" the alkene by forming an allyl radical through intermolecular hydrogen atom transfer (HAT) pathway and thus forging the carbon-carbon bond formation with aldehyde as the acyl synthon. Notably, our method represents the first example on the enone synthesis through coupling of "non-functionalized" aldehydes and alkenes as coupling partners, and offers a distinct organocatalytic pathway to the transition metal-catalyzed coupling transformations.

Enones (or *α,β*-unsaturated ketones) represent a fundamental scaffold in organic synthesis for a broad spectrum of synthetic transformations, such as Michael additions, Diels-Alder reactions, epoxidations (Fig. 1A) [1-12]. Notably, the enone functionality is also ubiquitous in various natural products, pharmaceuticals and biologically active molecules [13-16]. A diverse set of strategies have been developed for the efficient synthesis of enones, such as aldol or Knoevenagel condensation, Wittig olefination, dehydrogenation of ketones [17-20]. Recently, cross-coupling reactions between vinyl and acyl moieties by means of transition metal catalysis has been intensively explored that offers an efficient approach for rapid assembly of *α,β*-unsaturated ketones. In this context, most of these transformations relied on the cross couplings of acyl electrophiles with vinyl metallic reagents as the partners that were enabled by palladium, copper or other metal catalysis (Fig. 1B, method a) [21-27]. Alternatively, direct coupling between vinyl triflate with acyl metallic reagent as nucleophile has been achieved, as reported by Lee and co-workers (Fig. 1B, method b) [28]. In addition, the enone synthesis via cross couplings could also be realized between two electrophiles. For instance, Shu group demonstrated an elegant enone synthesis from acyl fluorides and vinyl triflates by a reductive nickel catalysis (Fig. 1B, method c) [29]. Although the metal-catalyzed coupling reactions are highly effective and synthetically useful to provide a wide range of enone derivatives, the requirement of pre-installed C–(pseudo)halide or C–metal reagents has diminished its efficiency in atom and step economy. The strategy by cross dehydrogenative coupling (CDC) [30-36] of simple aldehydes and alkenes without additional prefunctionalization thereby represents as a highly appealing approach for enone synthesis, which to our knowledge, is not achieved yet (Fig. 1B, method d).

Based on our long standing interest in *N*-heterocyclic carbene (NHC) organocatalysis [37-46,47-53], particularly our recent focus in radical NHC catalysis [54-56], we envisioned the preparation of enones *via* dehydrogenative cross coupling of aldehydes and alkenes. Herein, we disclosed a highly effective carbene catalytic system that allows for straightforward assembly of simple aldehydes and alkenes to afford various enones. Mechanistically, the aldehyde C-H activation to form the ketyl radical (**A**) was achieved by a single-electron oxidation of the deprotonated Breslow intermediate formed by aldehyde **1** and NHC catalyst. Simultaneously, H-abstraction of the C(sp^3)–H bonds by aryl radical intermediate **B** [57-58] in a fashion of intermolecular HAT pathway [59-65] enables an efficient activation of allylic C(sp^3)–H bonds through formation of species **C**. Cross coupling of ketyl radical **A** and carbon radical **C** would furnish the ketone products **4'**, followed by further migration of the double bond to afford the desired *α,β*-unsaturated ketone products **4** in high efficiency. Notably, our method represents the first example on the enone synthesis through CDC coupling of two

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"non-functionalized" aldehydes and alkenes as coupling partners, and offers a distinct organocatalytic pathway to the transition metal-catalyzed coupling transformations.

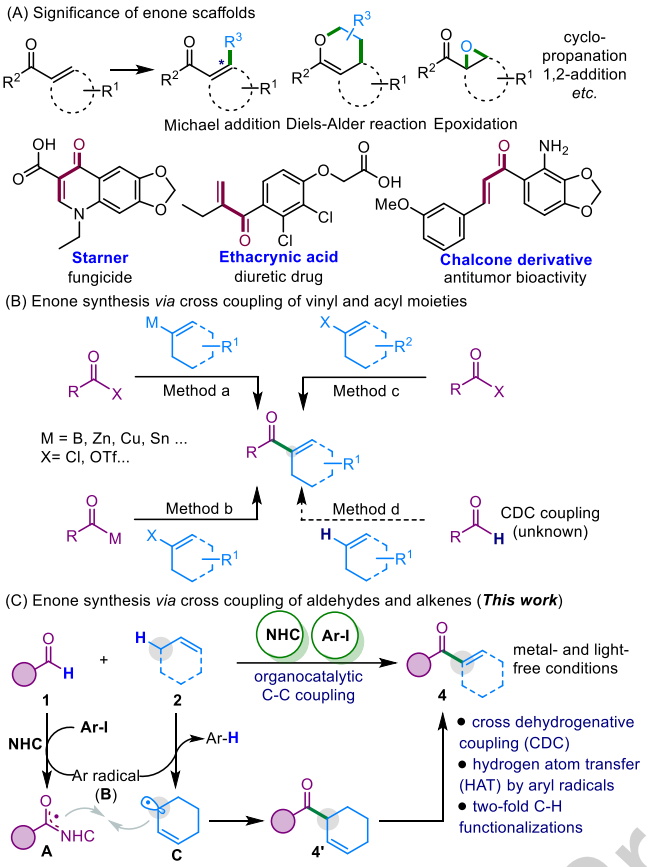
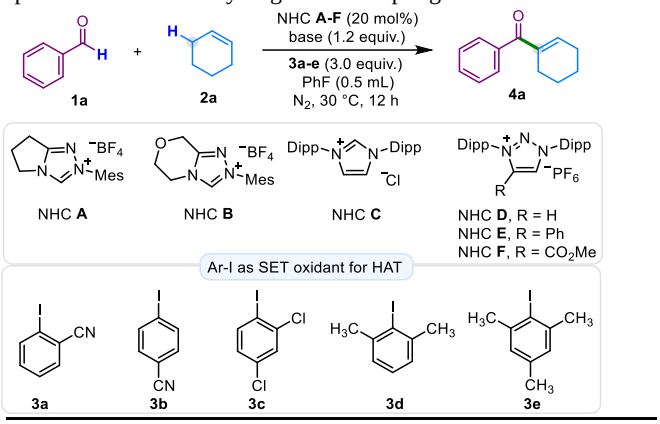


Fig. 1. Importance of enones and their synthesis *via* cross coupling of vinyl and acyl moieties.

Based on our hypothesis, we initiated our study on the dehydrogenative coupling reaction with benzaldehyde (**1a**) and cyclohexene (**2a**) as the model substrates (Table 1). Classical triazolium NHC catalysts **A**-**B** were first chose by employment of *ortho*-cyanoiodobenzene (**3a**) as the single-electron oxidant to test our synthetic strategy. Gratifyingly, both reactions afforded the desired coupling product **4a**, albeit in relatively poor yield (entries 1 and 2). While imidazoline NHC **C** failed to give the product, NHC **D**-**F** featuring a mesoionic scaffold [66-70] furnished the desired product **4a** in a significantly improved yield, probably owing to the strong reduction potential of the deprotonated Breslow Intermediates (BIs) derived from mesoionic carbene (MIC) (entries 4-6). Considering the pivotal role of the oxidant **3** in the radical generations, we then turned our effort to examine the effect of various aromatic iodides to achieve a more efficient catalytic system for the coupling reaction (entries 7-10). We were pleased to find that the use of a sterically hindered iodide **3e** was superior to provide the coupling product **4a** in 71% yield (entry 10), which probably suppressed the undesired reaction pathway triggered by the aryl radicals. Other bases, like Na*t*BuO and Cs_2CO_3 (entries 11 and 12, see Table S2 in Supporting information for details), were also investigated, which could not give better results. Notably, the big difference between reactions with *t*BuOK and *t*BuONa might be owing to the poor solubility of NaO*t*Bu in the reaction medium (PhF), which would decrease its basicity to form the key deprotonated Breslow intermediate.

Table 1

Optimization of the dehydrogenative coupling reaction.[a]



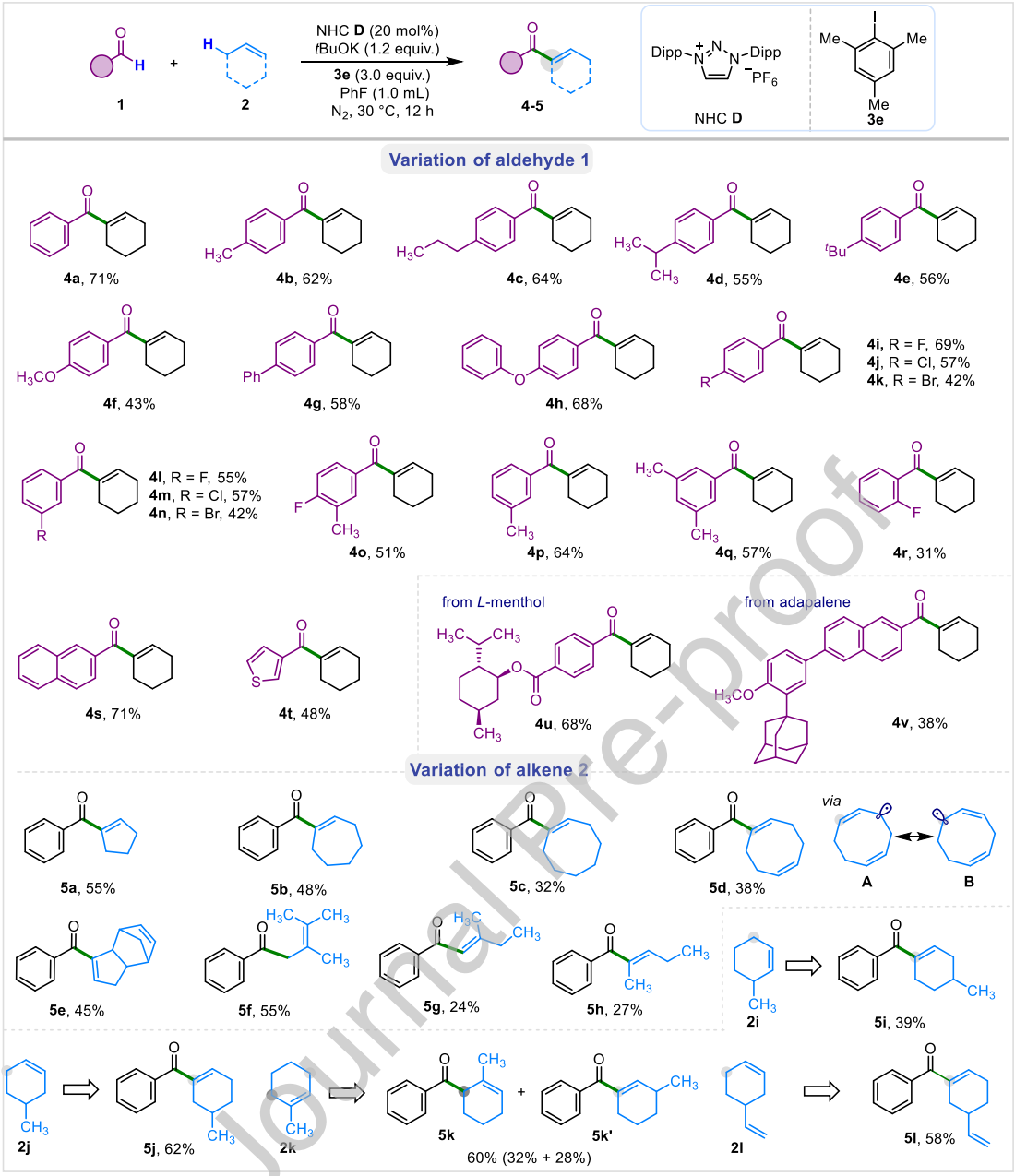
Entry	NHC	Ar-I (**3**)	Base	Yield (%)[b]
1	**A**	**3a**	*t*BuOK	9
2	**B**	**3a**	*t*BuOK	<5
3	**C**	**3a**	*t*BuOK	-
4	**D**	**3a**	*t*BuOK	50
5	**E**	**3a**	*t*BuOK	35
6	**F**	**3a**	*t*BuOK	43
7	**D**	**3b**	*t*BuOK	47
8	**D**	**3c**	*t*BuOK	41
9	**D**	**3d**	*t*BuOK	63
10	**D**	**3e**	*t*BuOK	71 (71)
11	**D**	**3e**	*t*BuONa	-
12	**D**	**3e**	Cs_2CO_3	20

[a] The reactions were performed with **1a** (0.05 mmol, 1.0 equiv.), **2a** (1 mmol, 20.0 equiv.), NHC (20 mol%), **3a-e** (0.15 mmol, 3.0 equiv.), and base (0.06 mmol, 1.2 equiv.) under N_2 atmosphere at 30 °C for 12 h.

[b] Yields of **4a** were determined *via* ^{1}H NMR analysis with 1,3,5-trimethoxybenzene as an internal standard; Isolated yield in the parenthesis; Mes = 2,4,6-trimethylphenyl, Dipp = 2,6-diisopropylpheny.

With the optimal reaction conditions established (Table 1, entry 10), we set out to verify the generality of the NHC-catalyzed direct dehydrogenative coupling reaction for enone synthesis (Scheme 1). Aldehyde substrates **1b**-**1h** possessing various units on at the *para* position of the phenyl ring, such as Me, *n*-Pr, *i*-Pr, *t*-Bu, as well electron rich OMe, Ph, OPh, were initially explored, leading to corresponding enone products **4b**-**4h** in 43%-68% yields. Notably, halogen atoms (F, Cl and Br) were also compatible to deliver the products **4i**-**4k** in 42%-69% yields, offering transferable handles for further synthetic transformations. Various substitution patterns on the aldehyde phenyl group were also investigated. For instance, F, Cl, Br, Me groups at the *meta* or *ortho* positions of aldehyde **1** afforded the corresponding enone products **4o**-**4r** in 31%-64% yields. Moreover, the phenyl ring could also be replaced with 2-naphthalenyl (**4s**) and heterocyclic thienyl group (**4t**). Aldehydes incorporated with important moieties, such as (L)-menthol and adapalene, proceeded smoothly under the catalytic conditions to

afford the enone products **4u** and **4v** in 68% and 38% yield, respectively, that significantly expands the synthetic utility of the developed method.

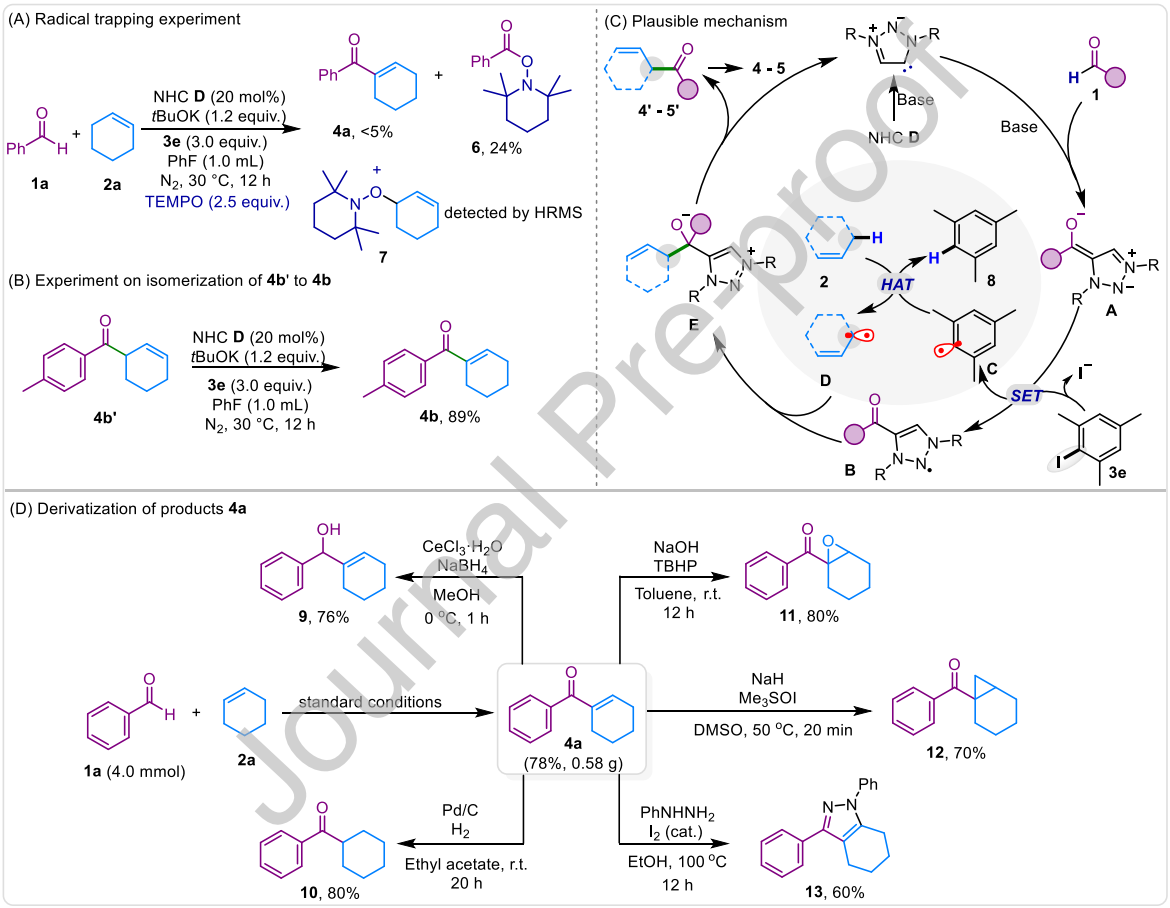


Scheme 1. Substrate scope for the coupling reactions. The reactions were performed with **1** (0.10 mmol, 1.0 equiv.), **2** (2.0 mmol, 20.0 equiv.), NHC **D** (20 mol%), **3e** (0.3 mmol, 3.0 equiv.), and *t*BuOK (0.12 mmol, 1.2 equiv.) under N_2 atmosphere at 30 ºC for 12 h; Isolated yield; Dipp = 2,6-diisopropylphenyl.

We next turned to explore the scope with respect to various olefins (Scheme 1). Cyclic alkenes with five- to eight-membered rings proceeded smoothly to afford the coupling products **5a-5d** with modest yields (32%-55%). Notably, the reaction with cyclooctadiene involved an isomerization of allyl radical **A** to **B**, which couples with aldehyde **1a** to give the product **5d** after migration of the double bond to the conjugate position. The flavor molecule, dicyclopentadiene underwent smoothly in the catalytic reaction to afford the corresponding product **5e** in 45% yield. Acyclic alkenes were also feasible for the desired dehydrogenative coupling reactions. In these cases, the *tetra*-methylethylene afforded the coupling product **5f** in 55% yield, while migration of the double bond to conjugate position of the carbonyl group was not observed, probably owing to substantial stability of the fully substituted double bond. Reaction with 2-methylbut-2-ene (**2g**) and 2-pentene (**2h**) under the optimal condition furnished the enone product **5g-5h** in a relatively dropped 24% and 27% yield, respectively. We further employed an array of substituted cyclohexene (**2i-2k**) in this dehydrogenative coupling reaction, affording the products **5i-5k** in 39%-62% yields. Intriguingly, the reactions showed distinct site selectivities depending on the different substitution patterns on the cyclohexene scaffold with a preference of site selectivity at the less hindered positions. We have never observed any corresponding coupling products at the tertiary sites, presumably owing to the notable steric hinderance between the tertiary C-H bonds and the mesityl radical species that

hindered the HAT process to form the tertiary carbon radical. For instance, the 3-methyl cyclohexene (**2i**) gave the product **5i** with C-C bond formation at the *para*-position of the methyl group, while 4-methyl substituted substrate **2j** delivered the coupling product **5j** at 6-position of the cycloalkene **2j**. Additionally, an inseparable mixture of **5k** (without migration of double bond) and **5k'** was obtained when 1-methylcyclohexene (**2k**) was employed, resulted from allyl radical generation at 3 or 6 positions of **2k**. Butadiene dimer **2l** was also suitable to give rise to the enone product **5l** in 58% yield.

A TEMPO-trapping experiment was carried out to shed insights on the plausible reaction mechanism. Three equivalents of TEMPO were added to the catalytic conditions as illustrated in Scheme 2A. The desired dehydrogenative coupling reaction was significantly suppressed with product **4a** afforded in less than 5% yield. Radical trapping adducts with aldehyde (**6**), and cyclohexene (**7**) were successfully detected that supports the proposed radical pathway. In addition, a migration of double bond from the allylic ketone **4b'** was observed by subjection of **4b'** under the catalytic conditions for 12 h, leading to the desired enone product **4b** in 89% yield (Scheme 2B). Built upon these experiments and the substrate scope with substituted cyclohexenes, as well as our and others' previous reports [55,57,58,66], a plausible mechanism for the carbene-catalyzed enone synthesis was proposed in Scheme 2C. Firstly, deprotonated Breslow intermediate **A** underwent a single-electron oxidation by aromatic iodide **3e**, which led to carbene-bound radical **B** and aryl radical **C**. Subsequently, hydrogen atom transfer (HAT) between species **C** and alkene **2** facilely occurred, giving rise to arene **8** and allyl radical **D**. Further radical-radical coupling with the persistent catalyst-bound radical species **B** would eventually afford the desired enone products **4**-**5** after migration of the double bond in ketone **4'**-**5'** and elaborated the NHC catalyst for the next catalytic cycle.



Scheme 2. Preliminary insights on the mechanism and synthetic transformations of the obtained product.

The catalytically generated enone products **4** can readily undergo further transformations as demonstrated in Scheme 2D. Reduction of the carbonyl moiety of **4a** under $CeCl_3/NaBH_4$ afforded an allyl alcohol **9** with 76% yield. The double bond of the enone could also be selectively reduced to give ketone **10** in 80% yield. Treatment with TBHP/NaOH readily furnished the epoxide **11**. Moreover, cyclopropanation could be prepared upon subjection with Me_3SOI/NaH to give **12** with a good yield. Reaction of the enone **4a** with phenylhydrazine produced a heterocyclic compound **13** containing a pyrazole unit.

Fascinated by the diverse biological activities of the *α,β*-unsaturated ketone scaffold [71], we performed preliminary studies of the antimicrobial activities with the prepared enone derivatives to develop potent antibacterial agrochemicals for crop protection (Table 2). Intriguingly, most products exhibited significant inhibitory activity against *Xanthomonas oryzae* pv. *oryzae* (*Xoo*), a pathogen that could lead to bacterial leaf blight (BLB) disease posing threat on rice plant [72]. Notably, **4j** with a *para*-chloro group displayed a promising inhibition rate of 84.76% against *Xoo* at a concentration of 100 μg/mL, which was superior than the positive control with commercial bactericides,

thiodiazole-copper (**TC**) and bismerthiazol (**BT**). Meanwhile, the obtained enone products also showed notable efficiencies on the inhibition of *Xanthomonas axonopodis.* pv. *citri* (*Xac*), a bacterial that would cause lesion on the surface of the plant, leading to plant necrosis [73]. In this context, compound **4i** exhibited a good inhibitory activity of 69.02%, which is comparable to the inhibitory efficacy of **BT** (67.83%) and better than that of **TC** (49.77%). These findings expand the potential of our products as novel lead structures to search for potent antibacterial agents.

Table 2
In vitro antibacterial activity of the target compounds against *Xoo* and *Xac*[a]

Compd	*Xoo* inhibition rate [%] (100 μg/mL)	Compd	*Xac* inhibition rate [%] (100 μg/mL)
4d	50.66 ± 4.47	**4e**	56.11 ± 1.86
4i	65.25 ± 5.91	**4i**	69.02 ± 4.06
4j	84.76 ± 0.48	**4j**	55.77 ± 1.42
4k	75.01 ± 5.13	**4k**	65.32 ± 3.41
4l	63.42 ± 3.11	**4l**	63.21 ± 2.36
4o	56.35 ± 2.21	**4m**	67.30 ± 2.65
4p	73.54 ± 1.49	**4o**	64.02 ± 3.21
4q	57.13 ± 3.23	**4p**	53.61 ± 7.74
BT[b]	43.23 ± 6.31	**BT**[b]	67.83 ± 1.21
TC[b]	63.45 ± 2.38	**TC**[b]	49.77 ± 1.18

[a] All data were average data of three replicates.
[b] Commercial bactericide, used as the positive control. BT = Bismerthiazol. TC = Thiodiazole-copper.

In summary, we have developed an organocatalytic approach for straightforward coupling of the aldehyde and alkenes. A wide array of enone derivatives were obtained in high efficiency through the carbene-catalyzed cross dehydrogenative couplings involving a key hydrogen atom transfer (HAT) process by the in situ generated aryl radical intermediate. Notably, our method constitutes as the first example for the direct coupling of simple aldehyde and alkene without prefunctionalization for rapid assembly of enone scaffolds, that offers an alternative approach to the transition metal catalyzed coupling reactions. Ongoing studies in our laboratory include development of the carbene-catalyzed dehydrogenative coupling approach for broad implementation in C-C bond-forming coupling reactions and further explorations with the obtained enone products for potent antibacterial agents.

Acknowledgments

We acknowledge funding supports from the National Natural Science Foundation of China (Nos. 21732002, 22061007, 22071036, and 22207022); Frontiers Science Center for Asymmetric Synthesis and Medicinal Molecules, National Natural Science Fund for Excellent Young Scientists Fund Program (Overseas), the starting grant of Guizhou University [(2022)47)], Department of Education, Guizhou Province [Qianjiaohe KY number (2020)004]; The 10 Talent Plan (Shicengci) of Guizhou Province ([2016] 5649); Science and Technology Department of Guizhou Province [Qiankehe-jichu-ZK[2022]zhongdian024], ([2018]2802, [2019]1020), QKHJC-ZK[2022]-455; Department of Education of Guizhou Province (QJJ(2022)205); Program of Introducing Talents of Discipline to Universities of China (111 Program, D20023) at Guizhou University; Singapore National Research Foundation under its NRF Investigatorship (NRF-NRFI2016-06) and Competitive Research Program (NRF-CRP22-2019-0002); Ministry of Education, Singapore, under its MOE AcRF Tier 1 Award (RG7/20, RG70/21), MOE AcRF Tier 2 (MOE2019-T2-2-117), and MOE AcRF Tier 3 Award (MOE2018-T3-1-003); a Chair Professorship Grant, and Nanyang Technological University.

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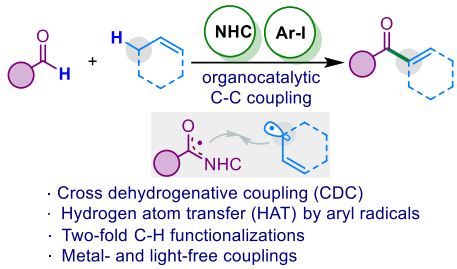
Graphical Abstract



A carbene-catalyzed cross dehydrogenative coupling (CDC) reaction that enables effective assembly of simple aldehydes and alkenes to afford a diverse set of enone derivatives is disclosed. Mechanistically, the in situ generated aryl radical is pivotal to "activate" the alkene by forming an allyl radical through intermolecular hydrogen atom transfer (HAT) pathway, thus forging the direct carbon-carbon bond formation with aldehyde and offering a distinct organocatalytic pathway to the transition metal-catalyzed coupling transformations.