A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

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Accepted Article

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To be cited as: *Angew. Chem. Int. Ed.* **2023**, e202303388

Link to VoR: https://doi.org/10.1002/anie.202303388

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10.1002/anie.202303388

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Carbene-Catalyzed Intermolecular Dehydrogenative Coupling of Aldehydes with C(sp^3)-H Bonds

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Abstract: The development of catalyst-controlled methods for direct functionalization of two distinct C–H bonds represents an appealing approach for C–C formations in synthetic chemistry. Herein, we describe an organocatalytic approach for straightforward acylation of C(sp^3)–H bonds employing readily available aldehyde as “acyl source” involving dehydrogenative coupling of aldehydes with ether, amine, or benzylic C(sp^3)–H bonds. The developed method affords a broad range of ketones under mild conditions. Mechanistically, simple *ortho*-cyanoiodobenzene is essential in the oxidative radical N-heterocyclic carbene catalysis to give a ketyl radical and C(sp^3) radical through a rarely explored intermolecular hydrogen atom transfer pathway, rendering the acylative C–C formations in high efficiency under a metal- and light-free catalytic conditions. Moreover, the prepared products show promising anti-bacterial activities that shall encourage further investigations on novel agrochemical development.

The direct dehydrogenative coupling is an attractive strategy in forming new carbon-carbon bonds.[1] Pre-functionalization (such as halogenation) of substrates is not necessary, and both metal and organic catalysts can be used to mediate this class of transformations (Figure 1a).[1b,d-e] N-heterocyclic carbene (abbreviated as NHC) catalysis has shown diverse reaction modes in construction of carbon-carbon and carbon-heteroatom bonds via both electron-pair-transfer[2] and radical pathways[3]. In the past, focuses were mostly directed by utilizing NHC-bound intermediates to react with another reactive partners (such as sp^2-carbons of electron-deficient double bonds).[2] There are few studies looking into direct coupling of carbonyl compounds with typically non-reactive sp^3-carbon atoms via NHC catalysis.[4] A pre-functionalization of such otherwise inert C(sp^3)–H bonds (e.g., in the forms of redox-active esters or alkyl halides) are generally needed in coupling sp^3-carbon with NHC-bound radical intermediates, as disclosed by Scheidt,[5a-b] Ohmiya,[5c-e] Hong,[5f] and our laboratory[5g] (Figure 1b).[6] Recently, Li[7a] and Ohmiya[7b] showed that non-functionalized sp^3-carbon atom can couple with NHC-bound acyl radicals (Figure 1c).[7] In these otherwise elegant studies, the sp^3-carbon atom needs to be activated intramolecularly by a remotely

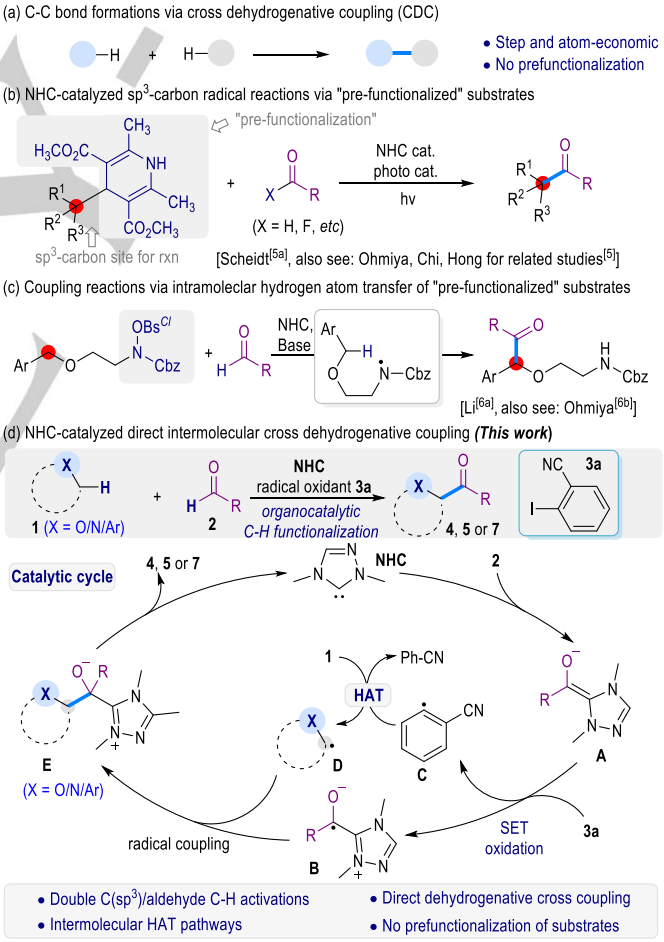

Figure 1. Radical NHC catalytic strategies for couplings with sp^3-carbons. Bs^{Cl} = 4-chlorobenzenesulfonyl; Cbz: carbobenzyloxy.

installed functional groups via a 1,5-hydrogen atom transfer process. Moreover, to the best of our knowledge, NHC-catalyzed direct intermolecular coupling of the aldehyde carbonyl C-H bond with a “non-functionalized” sp^3-carbon atom is not achieved yet.

10.1002/anie.202303388

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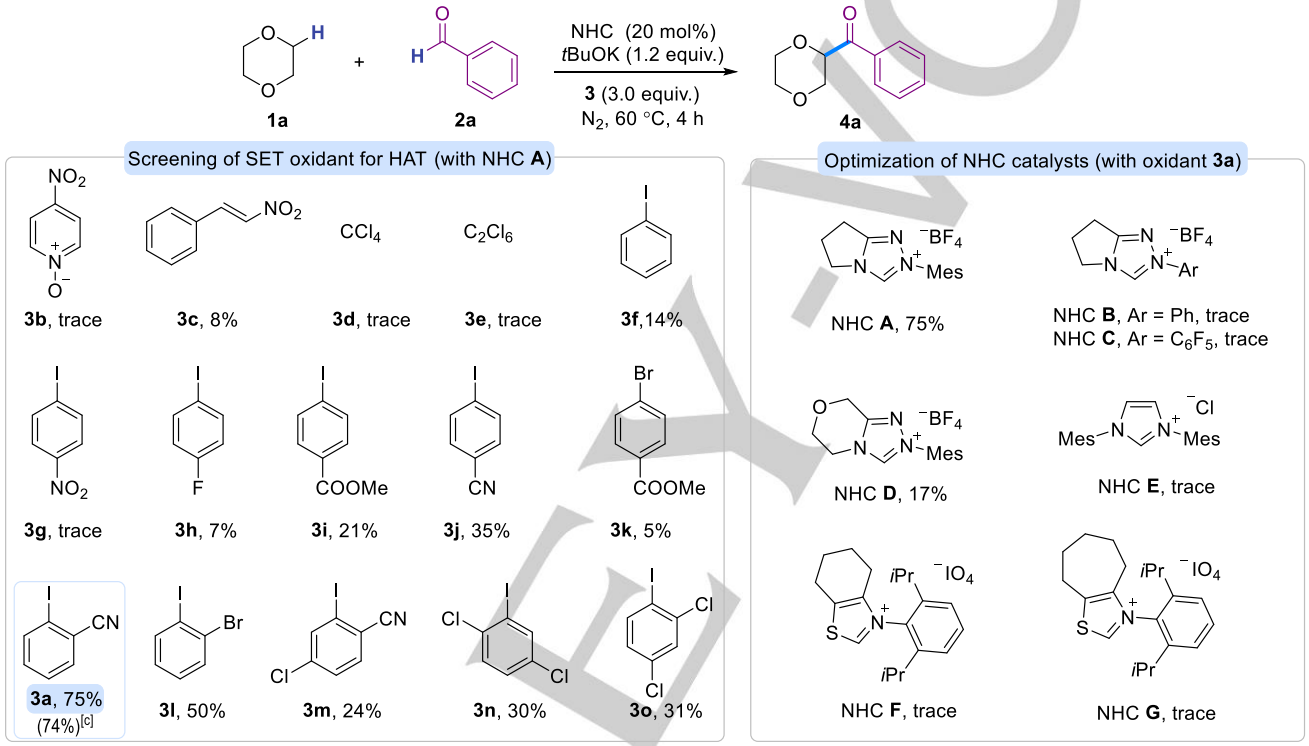
Built upon our interests in NHC-radical reactions, including our experience in exploring single-electron-transfer oxidants (such as halides) for NHC catalysis,[8][9] here we disclose the first straightforward intermolecular cross dehydrogenative coupling (CDC) reaction of aldehydes with C(sp^3)-H bonds under NHC radical catalysis (Figure 1d).[10] The key reaction step starts with single-electron-transfer oxidation of deprotonated Breslow immediate **A** by a halide (**3a**) to generate NHC-bound ketyl radical **B** and oxidant-derived aryl radical intermediate **C**. This aryl radical species (**C**) subsequently abstracts a hydrogen atom from a sp^3-carbon of the other substrate (**1**) via an intermolecular hydrogen atom transfer process to give radical intermediate **D**.[11] Reaction of intermediate **B** and **D** eventually leads to the direct coupling product with regeneration of the NHC catalyst. Multiple radical intermediates and several potential radical reactions are involved in a rather complicated solution, and we are very fortunate to obtain the cross coupling products in appreciable yields.[12] At present, our method shall allow for practical installation (and post-synthetic modification) of inexpensive common building blocks (such as dioxane and pyrrolidine) via acylation to various functional molecules. In the long round, our study may encourage further exploration of direct intermolecular radical coupling reactions of inert atoms.

Table 1. Optimization of the dehydrogenative coupling reaction.[a][b]



[a] The reactions were performed with **2a** (0.05 mmol), **1a** (1.0 mL), NHC (20 mol%), **3** (0.15 mmol), and *t*BuOK (0.06 mmol, 1.2 equiv.) under N_2 atmosphere at 60 ºC for 4 h; [b] Isolated yield of **4a** based on aldehyde **2a**; [c] Reaction performed in the dark.

We commenced our study by investigating the dehydrogenative coupling between 1,4-dioxane (**1a**) and benzaldehyde (**2a**) in the presence of carbene pre-catalyst NHC **A** to search for suitable conditions (Table 1). Various oxidants featuring the capacity of single-electron oxidations of Breslow intermediates in previous studies,[7,8][10a] such as nitro compounds **3b**-**c** and halides **3d**-**f** were carefully screened (Table 1, **3b**-**f**). Gratifyingly, aryl iodide **3f** was relatively effective to give the desired product **4a** in 14% yield, demonstrating the feasibility of our CDC reaction involving diradical formations through intermolecular hydrogen atom transfer (HAT) strategy. We next tested a diverse set of aryl halides (**3g**-**o**) and found that **3a** shows to be superior, furnishing the product **4a** in 75% yield. Furthermore, several typical NHCs **B**-**G** were examined by using aryl iodide **3a** as the oxidant. We found the mesityl substituent on triazolium core was essential (NHC **A**) whereas Ph and C_6F_5 substituted NHC **B**-**C** gave a trace amount of product **4a**. Other NHC catalysts, eg. **D** and **E**, as well as the thiazolium catalyst **F** and **G** failed to afford satisfactory results. Furthermore, the transformation did not lead to significant improvement on the reaction yield by evaluating the effects of other bases and reaction temperatures (Supporting Information, Table S1-2). It's worth noting that control experiments by performing the reaction in the dark gave rise to the desired product in a similar high yield of 74%, revealing that the light irradiation is not necessary for the developed dehydrogenative cross coupling reaction.

With the optimal conditions established by using oxidant **3a** and NHC **A**, we set out to identify the generality of the NHC-catalyzed ether C(sp^3)–H acylation under light- and metal-free conditions[12] (Table 2). Initially, we investigated the scope with respect to aldehyde **2** (Table 2, **4a**-**m**). The catalytic conditions tolerated a diverse set of groups and substitution patterns on the aromatic moieties of **2**. For instance, Me, Et, and *i*Pr units at the *para* or *meta* positions of the phenyl group of aldehydes gave the corresponding acylation products **4b**-**4e** in 44-77% yields. Notably, aldehydes possessing electron-withdrawing fluoro-, chloro- or bromo-groups delivered the corresponding products **4f**-**j** in

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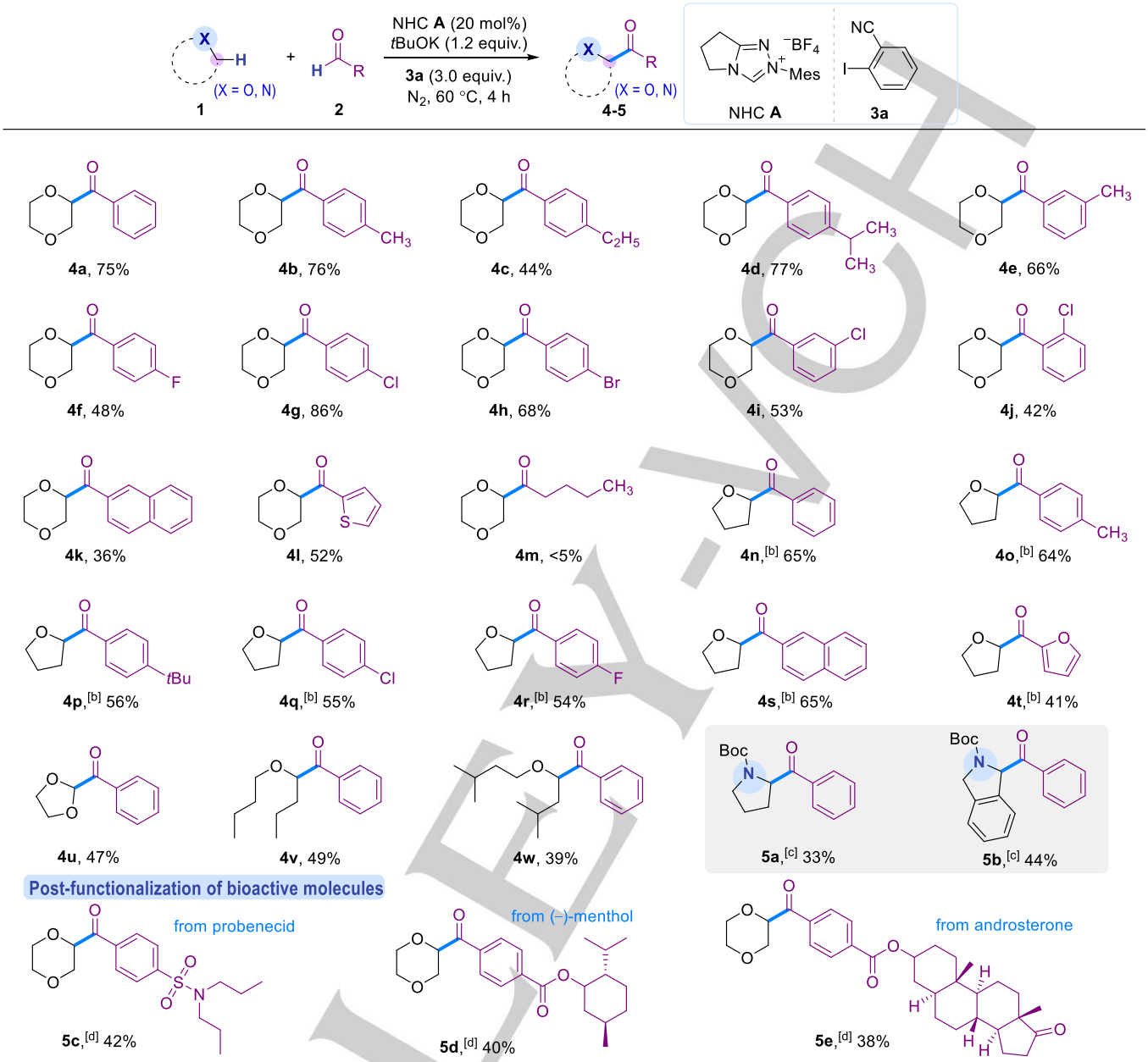
Table 2. Substrate scope of the dehydrogenative coupling of aldehydes with C(sp^3)–H bonds.[a]



[a] The reactions were conducted with **2** (0.1 mmol, 1.0 equiv.), NHC **A** (20 mol%), **3a** (0.3 mmol), *t*BuOK (0.12 mmol, 1.2 equiv.) in **1** (2.0 mL) under N_2 atmosphere at 60 °C for 4 h; Isolated yields; [b] Reactions performed at 50 °C for 4 h; [c] Reactions were performed with **2a** (0.1 mmol, 1.0 equiv.), *N*-heterocycle **1** (25.0 equiv. for **5a**; 5.0 equiv. for **5b**), NHC **A** (20 mol%), **3a** (0.3 mmol), *t*BuOK (0.12 mmol) in CH_3CN (2.0 mL) under N_2 atmosphere at 90 °C for 12 h; [d] Reactions for 12 h. Boc = *t*-butyloxycarbonyl.

42-86% yields, displaying a transferable handle for further elaboration. In the cases of chloro-tethered benzaldehydes (**4g** and **4i-j**), the *para*-substituted substrate gave the product **4g** in an excellent yield, whereas analogues with *meta*- or *ortho*-chloro substitution led to the corresponding product **4i** or **4j** in a modest yield (53% and 42% respectively). Moreover, naphthyl aldehyde as well as heteroaromatic aldehyde containing thienyl group could readily proceed under the optimal conditions to furnish the coupling products **4k** and **4l**. Unfortunately, this protocol was not compatible for aliphatic aldehyde that led to formation of desired coupling product **4m** in <5% yield.

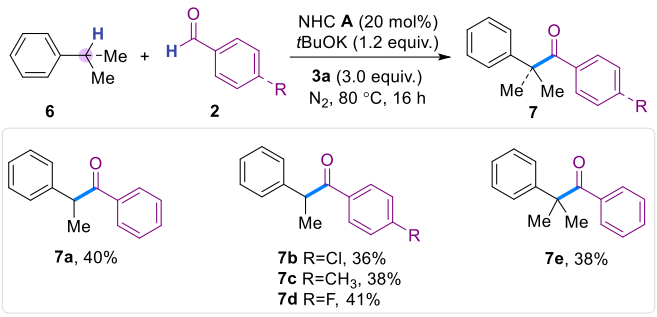
We next turned to examine the scope with respect to various cyclic or acyclic ethers (Table 2, **4n-w**). THF was applicable in the acylating coupling reactions with an array of aromatic aldehydes, resulting in products **4n-t** in good yields (41-65%). Reaction with 1,3-dioxolane delivered the product **4u** in 47% yield that features a transferable acetal functionalization group. Acyclic ether could also engage in the coupling reaction with benzaldehyde under identical reaction conditions, leading to corresponding ketones **4v-w** in moderate yields. Furthermore, typical *N*-heterocycles, such as *N*-Boc-pyrrolidine and isoindoline were also compatible to undergo through the proposed CDC reaction pathway to furnish corresponding C(sp^3)–H acylation products **5a** and **5b**. As a technical note, CH_3CN as the solvent and an elevated temperature (90 °C) were optimized in these coupling reactions. Intriguingly, aldehydes derived from biologically active molecules were also feasible to give rise to **5c**, **5d** and **5e** in modest yields

10.1002/anie.202303388

that significantly expands the scope and synthetic utility of this intermolecular dehydrogenative coupling methodology.

Notably, the developed dehydrogenative coupling reaction is not limited to ethers and amines. Aromatics featuring a benzylic C(sp^3)–H could also be activated through intermolecular HAT to generate benzylic radicals and thus allowing for rapid coupling with aldehyde **2** (Table 3). The corresponding products **7a-e** were readily afforded by increasing the temperature slightly to 80 °C. Noteworthy is that our NHC catalytic method features a distinct HAT pathway comparing to Studer's elegant benzylic acylations via dual NHC and photoredox catalysis.[4b]

Table 3. Dehydrogenative acylation of benzylic C(sp^3)–H bonds.[a][b]



[a] The reactions were performed with **2** (0.1 mmol, 1.0 equiv.), **6** (2.0 mL), NHC **A** (20 mol%), **3a** (0.3 mmol), *t*BuOK (0.12 mmol, 1.2 equiv.) and under N_2 atmosphere at 80 °C for 16 h; [b] Isolated yields of **7** based on aldehyde **2**.

Scheme 1. Radical trapping experiment

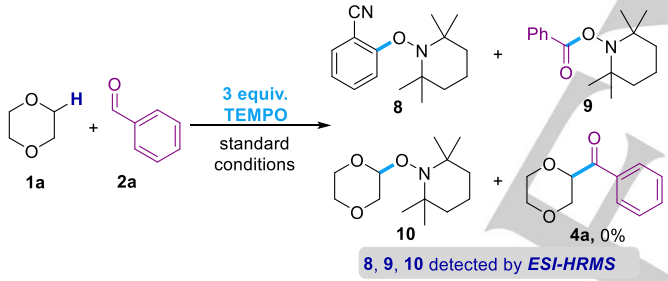


Table 4. In vitro antibacterial activity of the target compounds against *Xoo*.[a]

Compounds	*Xoo* inhibition rate [%] (100 μg/mL)
4h	54.69 ± 5.75
4n	68.96 ± 0.21
4o	61.82 ± 1.94
4r	53.91 ± 3.89
5b	69.43 ± 5.89
BT[b]	80.99 ± 0.40

[a] All data were average data of three replicates; [b] Commercial bactericide, used as the positive control. BT = Bismerthiazol. *Xoo* = *Xanthomonas oryzae* pv. Oryzae.

To shed insights on the possible reaction pathway, a TEMPO-trapping experiment was performed by addition of three equivalents TEMPO to the optimal conditions as illustrated in Scheme 1. TEMPO adducts of the aryl radical **C** (**8**), benzaldehyde (**9**), and dioxane (**10**) were all detected by ESI-HRMS, strongly supporting our proposed HAT reaction process (Figure 1 and Supporting Information). Notably, the corresponding ketone product **4a** was not detected which was inhibited by the free TEMPO radical.

By consideration of the intriguing biological activity of dioxane and other heterocyclic motifs,[13a] we also examined the anti-bacterial activities of the rapidly assembled ketone products for novel agrochemical development in crop protection (Table 4). Several products obtained from our reactions exhibit significant inhibitive activities against *Xanthomonas oryzae* pv. Oryzae (abbreviated as *Xoo*), which could cause bacterial leaf blight on rice and seriously affect the global rice agriculture.[13b] These results demonstrate the promising potential of our method in rapid derivation of structural diversity to search for high effective agrochemical candidates.

In summary, we have disclosed an organocatalytic approach for straightforward acylation of C(sp^3)–H bonds with readily available aldehydes as "acyl source" by means of radical NHC organocatalysis. A wide array of cyclic and acyclic ethers, amines, as well as benzylic carbons are readily functionalized by radical formations through intermolecular hydrogen atom transfer (HAT). The *ortho*-cyanoiodobenzene is pivotal to giving the key NHC-bound ketyl radical and carbon free radical from HAT with C(sp^3)–H bonds, providing a diverse set of ketone products through radical-radical couplings in high efficiency under light- and metal-free conditions. Furthermore, the prepared products show significant anti-bacterial activities that shall encourage further investigations on novel agrochemical development. We anticipate that the NHC-catalyzed cross dehydrogenative couplings through HAT processes will allow broad-ranging implementations in C–C bond-forming transformations from widespread C-H bonds and open new avenues for the rapid assembly of functional molecular systems.

Acknowledgements

We acknowledge funding supports from the National Natural Science Foundation of China (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.

Keywords: N-Heterocyclic carbene • Radical NHC catalysis • Cross dehydrogenative coupling (CDC) • Hydrogen atom transfer • Organocatalytic C-H functionalization

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10.1002/anie.202303388

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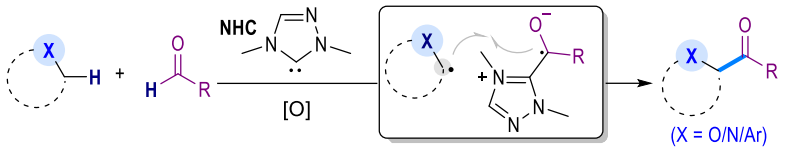

organocatalytic dehydrogenative coupling, C-H functionalization, radical pathways

An NHC-catalyzed intermolecular dehydrogenative coupling of aldehyde with ether, amine or benzylic C(sp^3)–H bonds is disclosed via metal- and light-free radical pathways.