Carbenes

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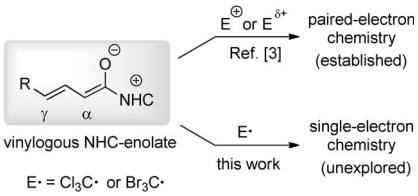
N-Heterocyclic Carbene Catalyzed γ-Dihalomethylenation of Enals by Single-Electron Transfer

*Wen Yang, Weimin Hu, Xiuqin Dong, Xin Li, and Jianwei Sun**

Abstract: *An N-heterocyclic carbene (NHC) catalyzed dihalomethylenation of enals is described. It is a rare example of merging NHC catalysis with single-electron chemistry, a challenging topic with limited previous success. The versatile carbon-centered trihalomethyl radicals have been demonstrated, for the first time, to be compatible with an NHC-bound intermediate, thus leading to efficient and regioselective intermolecular C–C bond formation. The mild process provides straightforward access to unsaturated δ,δ-dihalo esters.*

In the past decade, N-heterocyclic carbene (NHC) catalysis has received tremendous attention and has evolved as a versatile platform for the development of a broad range of new and selective processes.[1] The unique ability of NHCs to reverse the polarity of a number of functional groups, particularly aldehydes, has enabled direct and efficient bond formation with various electrophiles, a reaction which is otherwise less straightforward to achieve. However, despite the significant progress, efforts in this field have been largely confined to the study of a paired electron pathway between an NHC-bound nucleophile and either a positively or partially positively charged electrophile. In contrast, the development of NHC-catalyzed processes involving single-electron transfer (SET) is still in its infancy.[2]

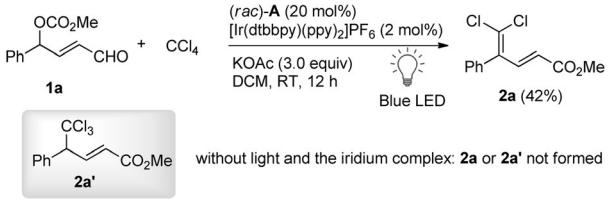
Since 2008, the pioneering studies by the groups of Studer, Rovis, and Chi have indicated that single-electron oxidation of nucleophilic NHC-bound intermediates is indeed feasible.[2] However, these studies primarily involved oxygen-centered radicals (from either TEMPO or a nitro compound) as the key external SET partner. Herein, we report a new example featuring the interplay between a vinylogous NHC-enolate and a carbon-centered radical, a trihalomethyl radical ($Cl_3C^{\bullet}$ or $Br_3C^{\bullet}$), thus leading to efficient γ-dihalomethylenation of enals by an intermolecular C–C bond formation. It is worth noting that although vinylogous NHC-enolates have been demonstrated to be highly useful in a diverse set of paired-electron processes, their reactivity toward radicals has remained unknown (Scheme 1).[3]



Scheme 1. Reactivity of vinylogous NHC-enolates.

Both dihalomethylene and trihalomethyl groups are not only important functional groups in organic synthesis, but also widely present in natural products and biologically important molecules.[4,5] Intrigued by the established generation and reactivity of trihalomethyl radicals,[6] we envisioned their possible merger with NHC catalysis.

We began our study with the enal **1a**, bearing a γ-leaving group, as the vinylogous NHC-enolate precursor (Scheme 2). CCl_4 was initially employed to generate the key trichloromethyl radical, a known process occuring under photoredox conditions.[7] Encouragingly, after considerable effort, we were pleased to observe successful C–C bond formation between $Cl_3C^{\bullet}$ and the enal. In the presence of a catalytic amount of the NHC precatalyst (*rac*)-**A**[8] and photoredox catalyst $[Ir(dtbbpy)(ppy)_2]PF_6$, combined with irradiation using a blue LED light, the γ-dichloromethylenation product **2a** was obtained with complete regioselectivity (γ versus α), albeit in moderate yield (42%).[9] It was believed that **2a** was presumably formed by elimination of HCl from the initial trichloromethylation product **2a′**, which could be observed during the progress of the reaction. It is important to note that the same process in the absence of the iridium catalyst and light did not give any desired product (**2a** or **2a′**). It is also worth mentioning that this process represents the first demonstration of NHC catalysis coupled with both radical chemistry and photoredox catalysis.[10]



Scheme 2. Preliminary results. DCM = dichloromethane, dtbbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine, ppy = 2-phenylpyridine.

While the above preliminary results clearly corroborated the feasibility of the hypothesized radical process, unfortu-

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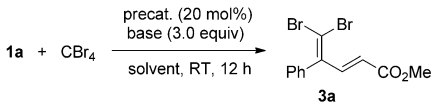
Table 1: Further evaluation with CBr_4.[a]



3a

Entry	Precat.	Base	Solvent	Yield [%][b]
1	**A**	KOAc	DCM	74
2	**B**	KOAc	DCM	17
3	**C**	KOAc	DCM	56
4	**D**	KOAc	DCM	< 5
5	**E**	KOAc	DCM	8
6	**F**	KOAc	DCM	13
7[c]	**A**	KOAc	DCM	82
8[c]	**A**	CsOAc	DCM	60
9[c]	**A**	DBU	DCM	16
10[c]	**A**	KOAc	toluene	51
11[c]	**A**	KOAc	CH_3CN	23
12[c]	**A**	KOAc	Et_2O	87

[a] Reaction scale: enal **1a** (0.05 mmol), CBr_4 (0.15 mmol), and solvent (0.5 mL). [b] Determined by ^1H NMR analysis of the crude reaction mixture with CH_2Br_2 as an internal standard. [c] Run with 4 Å molecular sieves (M.S.; 10 mg).

nately, further considerable efforts aimed at improving the efficiency proved fruitless. Thus, we next hypothesized that moving from CCl_4 to a more labile radical precursor, CBr_4, might be beneficial. In fact, with essentially the same set of reaction conditions, and even without the photoredox conditions, the reaction between **1a** and CBr_4 proceeded smoothly to form the corresponding product **3a** in 74% yield (Table 1, entry 1). The product structure was confirmed by X-ray crystallography. It is worth noting that the use of photoredox conditions in this case resulted in roughly the same yield. Different NHC precatalysts (**B–F**; Figure 1),

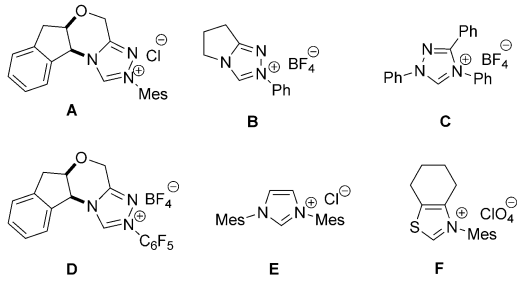
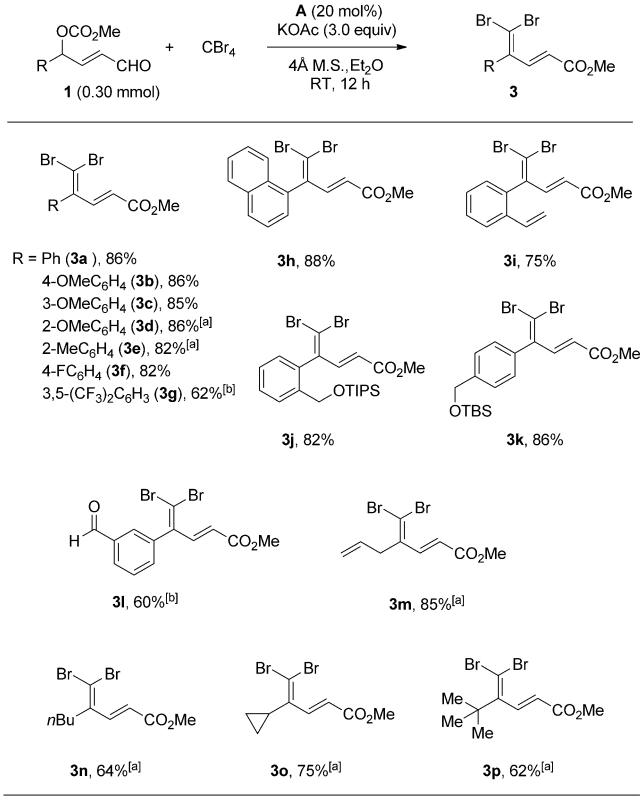


Figure 1. Structures of the precatalysts.

including other triazolium, diazolium, and thiazolium salts, resulted in lower yield (entries 2–6). Nevertheless, the reaction efficiency was improved when 4 Å molecular sieves were used as an additive (entry 7). Other bases, including CsOAc, Cs_2CO_3, K_3PO_4, DIPEA, and DBU, proved inferior. Further evaluation of other solvents identified Et_2O as the solvent of choice, thus providing the dibromomethylenation product **3a** in 87% yield.

With the optimized reaction conditions, we explored the scope of the dibromomethylenation process. As shown in Scheme 3, a range of enals bearing different aryl and alkyl

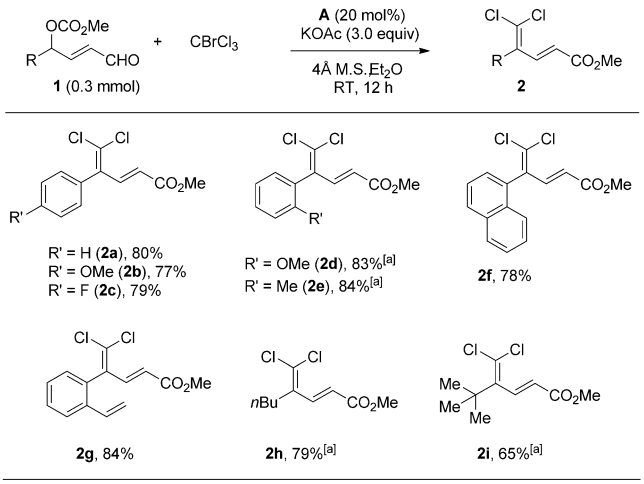


Scheme 3. Scope of the γ-dibromomethylenation. Yield of isolated product provided. [a] Before work-up, the reaction was treated with NaOMe (0.30 mmol) in Et_2O and stirred for 30 min. [b] Run for 24 h. TBS = *tert*-butyldimethylsilyl, TIPS = triisopropylsilyl.

substituents at the γ position all smoothly participated in the efficient intermolecular C–C bond-formation process. The corresponding dibromomethylenation products were all formed with excellent regio- and stereoselectivity. The mild reaction conditions can tolerate a diverse set of functional groups, such as ethers, olefins, silyl-protected alcohols, and even aldehydes. The reaction exhibited reasonable reactivity, even with steric hindrance in close proximity to the reaction center (**3p**). Notably, the incorporation of a cyclopropyl group at the γ position did not result in ring-opening of this three-membered ring (**3o**), particularly considering the involvement of a possible radical center in the adjacent position.

With the success of dibromomethylenation using CBr_4, we were further encouraged to revisit the dichloromethylenation. We envisioned that the use of CCl_3Br might lead to much more facile formation of the $Cl_3C^{\cdot}$ radical (versus the use of CCl_4). Indeed, to our delight, under identical reaction conditions, the reaction of **1a** with CCl_3Br proceeded smoothly to afford the desired dichloro product **2a** in 80% yield (Scheme 4). Further study of the reaction indicated that this dichloromethylenation process exhibits an equally broad substrate scope.

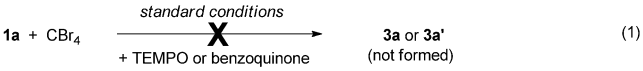
A possible mechanism is depicted in Scheme 5. The catalytic cycle begins with the addition of the NHC to the enal substrate **1**. The resulting Breslow intermediate **I** undergoes elimination and deprotonation to form the key intermediate vinylogous enolate **II**. The carbonate leaving group expelled

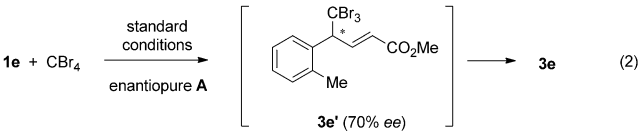


Scheme 4. Scope of the γ-dichloromethylenation. Yield of the isolated product provided. [a] Before work-up, the reaction was treated with NaOMe (0.30 mmol) in Et_2O and stirred for 30 min.

from this step collapses to CO_2 and methanol, which is a nucleophile that will be important to turn over the catalytic cycle in a later stage. Next, **II** may react by two possible pathways. In path a, it undergoes single-electron oxidation by CBr_4 to form the radical cation **III** with concomitant formation of $Br_3C^{\bullet}$. Subsequent radical–radical recombination gives the activated acyl species **IV**. Finally, acyl substitution by methanol regenerates the NHC catalyst and delivers the γ-tribromomethylated intermediate, which leads to the observed product **3** by HBr elimination. Alternatively, as shown in path b, **II** could form a C–C bond with the electrophilic radical $Br_3C^{\bullet}$ to generate the radical zwitterion **V**, which then undergoes SET oxidation by CBr_4 to generate the same intermediate **IV**. The SET product $Br_3C^{\bullet}$ can be utilized for the next catalytic cycle.[11] Currently, we cannot rule out either pathway. However, the tolerance of the cyclopropyl group at the γ-position (**3o**) may be more consistent with path b, in which the radical clock cannot function (in contrast to **III** in path a).

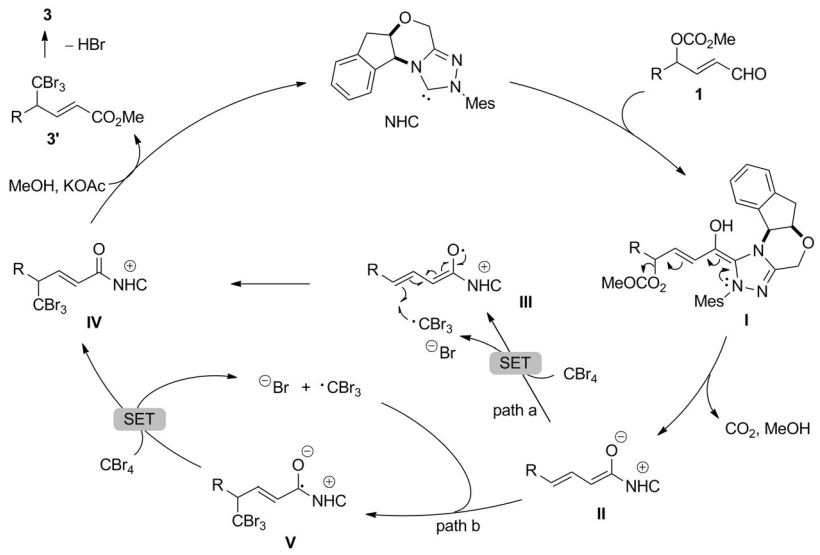
To gain more insight into the reaction mechanism, we carried out some control experiments. First of all, in the presence of a radical scavenger, such as either TEMPO (2,2,6,6-tetramethylpiperidine N-oxyl radical) or benzoquinone, formation of **3a** (or the precursor **3a′**) was not observed from the standard reaction of **1a** with CBr_4 [Eq. (1)], and is consistent with the proposed SET mechanism. Furthermore, with the enantiopure precatalyst **A**, we were able to isolate and characterize the enantioenriched γ-tribromomethylation intermediate **3e′** [70% *ee*, Eq. (2)].[12] The preliminary data suggested that further realization of an asymmetric version of this protocol is highly promising. Its conversion into the final product **3e** was also confirmed.





The dibromomethylenated products can be converted into other useful molecules (Scheme 6). For example, the dibromo unit can undergo a Suzuki cross-coupling reaction to form the dienoate **4** with a tetrasubstituted olefin unit. The saturated ester **5** and diene **6** can also be efficiently synthesized after simple transformations. Furthermore, after ester reduction and protection, the dibromomethylene unit in **3a** can be converted into an alkyne moiety (**7**) by rearrangement.

In summary, we have developed an efficient NHC-catalyzed dihalomethylenation process. It is a new and rare example of merging NHC catalysis with single-electron chemistry, an emerging and important, but challenging topic which has thus far lacked general exploration. In our study, the versatile carbon-centered trihalomethyl radicals have been demonstrated for the first time to be compatible with an NHC-bound intermediate (i.e., vinylogous enolate), thereby leading to efficient and regioselective intermolecular C–C bond formation. The mild process with broad substrate scope and excellent functional-group compatibility provides straightforward access to unsaturated δ,δ-dihalo esters.



Scheme 5. Proposed mechanism.

Acknowledgments

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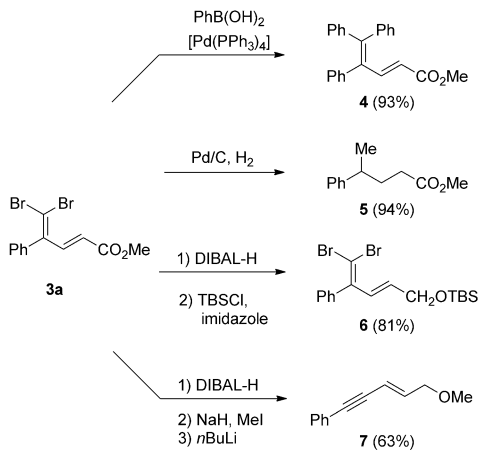

Scheme 6. Product transformations.

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Keywords: carbenes · halogens · olefination · organocatalysis · radicals

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[12] a) Since the elimination of **3e′** to **3e** is facile, **3e′** was only isolated in 19% yield, but the combined yield of **3e′**and **3e** is 79%. b) In the Supporting Information, we also included more preliminary results, including a case with the all-substituted γ-position and some examples with other SET partners.

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