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Visible-Light-Driven N-Heterocyclic Carbene-catalyzed γ - and ϵ -Alkylation with Alkyl Radicals

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Abstract: The merging of photoredox catalysis and N-heterocyclic carbene (NHC) catalysis for γ - and ε -alkylation of enals with alkyl radicals was developed. The alkylation reaction of γ -oxidized enals with alkyl halides worked well for the synthesis γ -multisubstituted- α , β -unsaturated esters, including those with challenging vicinal all-carbon quaternary centers. The synthesis of ε -multisubstituted- α , β - γ , δ -diunsaturated esters *via* unprecedented NHC-catalyzed ε -functionalization was also established.

Introduction

Over the past decades, N-heterocyclic carbenes (NHCs) have been demonstrated as powerful organocatalysts^[1] for the umpolung of aldehydes and enals via Breslow intermediate,^[2] homoenolate^[3] and dienolate^[4] to react with strong electrophiles with sp² carbon, such as active ketones and imines. However, NHC-catalyzed reaction with weak electrophiles with sp³ carbon, such as alkyl halides, for the construction of C(sp³)-C(sp³) is highly challenging. Recently, the NHC-catalyzed reaction through radical process showed great potential owing to its high activity (Scheme 1),^[5] including esterification of aldehydes via two consecutive single electron oxidation (reaction a),^[6] β hydroxylation of enals with oxygen radical (reaction b),^[7] the homo/cross-coupling of homoenolate and its radical (reaction c),^[8] and the cross coupling of homoenolate and enolate radicals (reaction d).^[9] Sun et al. reported an elegant NHC-catalyzed γ dihalomethylenation with trichloromethyl and tribromomethyl radicals (reaction e),^[10] and Nagao and Ohmiya et al. reported the decarboxylative alkylation of aldehydes via alkyl radicals (reaction f).^[11] These NHC-catalyzed reactions with specific oxygen or functionalized carbon-centered radicals promoted us to explore general NHC-catalyzed C(sp³)-C(sp³) bond formation with simple alkyl radicals.

The visible-light-driven photoredox catalysis is very useful to generate radical intermediates,^[12] and the cooperative photocatalysis provides unique approaches for various invaluable chemical transformations.^[13] For example, transition metal/photo-catalyzed $C(sp^2)$ - $C(sp^3)^{[14]}$ and $C(sp^3)$ - $C(sp^3)^{[15]}$ bonds formation were developed by MacMillan et al. The

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cooperative photoredox catalysis with amine catalysis,^[16] Brønsted acid catalysis^[17] are very successful. In 2012, Rovis et al. reported the first example of NHC/photo co-catalyzed umpolung addition of aldehydes to in situ generated iminium.^[18] In this paper, we report an NHC/photo co-catalyzed γ - and ε -alkylation of enals with simple alkyl radicals (Scheme 1, reaction g), which features readily available starting materials, good functional group compatibility and construction of vicinal all-carbon quaternary centers.



Scheme 1. NHC-catalyzed reactions with radicals. NHC = N-heterocyclic carbine, [O] = single electron oxidant, hv = visible light irradiation.

Results and Discussion

The NHC-catalyzed model reaction of γ -oxidized enal **1a** and iodoacetonitrile **2a** was investigated under visible light irradiation (Table 1). Although the reaction with thioazolium preNHC **5a** gave no desired product (entry 1), we are encouraged to find that the reaction with imidazolium preNHC **5b** afforded product **3a** in 12% yield with exclusive γ -regioselectivity (entry 2). It is interesting that *N*-phenyl triazolium preNHC **5c** and **5d** gave no

or only trace product (entries 3 &4), the *N*-mesityl preNHCs **5e**-**5g** showed promising yields (entries 5-7). These data implies that the benefit of bulky substituent of the catalyst. Thus, the sterically hindered tetracyclic preNHC **5h**^[19] was tested, which resulted in dramatically improvement of the yield (70%). Screening of the bases revealed that inorganic bases (K₂CO₃ and Cs₂CO₃) worked better than commonly used organic bases such as DBU, DIPEA and DABCO (entries 8-13), and the reaction in the presence of CsOAc afforded product **3a** in 86% isolated yield with exclusive γ -regioselectivity (entry 14).

Table 1: Optimization of the Reaction Conditions.^a



^aGeneral conditions: **1a** (0.5 mmol), **2a** (0.2 mmol), PC **4a** (2 mol%), preNHC **5** (20 mol%), base (2.0 equiv.), MeOH (40 μl), DCE (2 mL), 32W CFL, 24h, 25 ^oC under nitrogen protection. ^bIsolated yields.

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With the optimized conditions in hand, the scope of the reaction was investigated (Table 2). It was found that γ -aryl enals bearing electron-withdrawing and electron-donating groups were all tolerated and gave the desired γ -alkylation products **3b-3I** in good yields with exclusive γ -regioselectivity. The ortho-substituted (2-Me, 2-vinyl), ortho, meta-disubstituted (2,4-dimethyl) or ortho, meta, para-trisubstituted (2,4,6-trimethyl) aryl groups showed no significant negative effect on the reaction (3i-3I). The reaction of the enals with γ -2-naphthyl gave the corresponding product (3m) in 85% yield. Then the compatibility of functional groups was then explored. It was found that silvl ether (3n), primary alcohol (3o), alkenes (3h, 3j, 3p) and even alkyne (3q) were all well tolerated to afford the desired products in moderate to excellent yields. It is noteworthy that the reaction of enals with additional C-C double or triple bond, which is effective radical acceptor, occurred exclusively at the γ-position of enal rather than the additional unsaturated C-C bonds. Besides the primary cyanomethyl radical, secondary and tertiary cvanoalkyl radicals (3r-3t) were also successfully applied for the reaction, giving the desired γ -cyanoalkylation products in high yields. Alkyl enals with various substituents (isopropyl, cyclohexyl, allyl etc.) at the γ position were also tested to give the products **3u-3z** in good yields. Additionally, the alkoxylcarbonylmethyl and tertiary cyanoalkyl radicals (3y-3z) went smoothly, giving the desired products in moderate yields.

The construction of all-carbon quaternary center (ACQC) is very challenging in organic synthesis.^[20] Although some successful strategies for the construction of ACQCs have been developed over the past decades, new methods with good scope and functional group tolerance are still highly desired.^[16b] Gratifyingly, y-dialkylated enals were all tolerated for the reaction, giving the corresponding products (3aa-3ad) bearing ACQC in good yields. The reaction with various alkyl radical precursors (primary and secondary cyanoalkyl, ester-alkyl, benzyl radicals) afforded the target compounds (3ae-3ak) bearing ACQC in moderate to good yields. The catalytic construction of molecules with vicinal ACQCs is extremely challenging in organic synthesis. We were happy to find that the photo/NHC co-catalyzed cross coupling of γ -dialkylenals and tertiary radical precursors alkyl electrophiles worked well for the construction of vicinal ACQCs (Table. 3). The reaction of γ -dialkyl enals (methyl, *n*-butyl, and allyl) with tertiary cyanoalkyl radicals (methyl, cyclohexyl, and cyclopentyl) gave the products (3al-3ap) in good yields. Various other types of tertiary alkyl radicals derived from benzyl, esters, and malonates worked for the reaction to give the desired products (3aq-3as) in moderate to good yields. Interestingly, aalkylmalonate radicals (methyl, benzyl, allyl) gave the cross coupling products (3as-3az) in good to excellent yields. The multifunctionalized compound 3ay, bearing a vicinal diallyl ACQC affords many possible transformations for the access of complex molecules in organic synthesis.

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Table 2: Reaction scope^a



^aAll reactions were performed on a 0.3 mmol scale. For each compound the isolated yield is given in percent. * **2a** (X = I) was used, ** **2b** (X = Br) was used; ⁱdiastereomeric ratio (dr) were determined by ¹H NMR spectroscopy of raw product. EWG = electron-withdrawing group; DCE = 1, 2-dichloroethane; CFL = compact fluorescent light.

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Table 3: Construction of vicinal all-carbon quaternary centers^a



^a All reactions were performed on a 0.3 mmol scale. * 2a (X = I) was used, ** 2b (X = Br) was used

Table 4: NHC-catalyzed ε-functionalization^a



^aAll reactions were performed on a 0.3 mmol scale. * 2a (X = I) was used, ** 2b (X = Br) was used.

NHC-catalyzed remote functionalization of carbonyl compounds is a challenge.^[21] Our group reported the first example of NHC-catalyzed γ functionalization of acyl chloride $^{\rm [4a]}$ in 2011. Chi et al. reported the pioneering NHC-catalyzed $\gamma^{\rm [4c]}$ and $\delta^{\mbox{\tiny [22]}}\mbox{-functionalization of enals or dienals. To the best of our$ knowledge, there is no example for NHC-catalyzed ε -functionalization.^[23] To address this problem, we designed a series of peroxidized enals bearing vinyl or 1-propenyl substituents at the γ position which may deliver ϵ functionalization products via trienolate intermediate (Table 4). We were happy to find that the reaction of enal 6a bearing vinyl substituent at the γ position with iodoacetonitrile under our optimized condition gave the desired product 7a in 56% yield with the exclusive ϵ -selectivity. Different alkyl radical precursors (primary, secondary and tertiary alkyl radicals) were all tolerated, giving the corresponding products (7b-7f) in good to excellent yields. Enal 6b bearing 1-propenyl substituents were also investigated to give the corresponding products (7g-7j) in moderate to good yields.



Scheme 2. Primitive results of enantioselective reaction

Promising enantioselectivities are observed when chiral NHC precursor **5i** was used as the catalyst for synthesis of chiral **3a*** and **3az*** with vicinal ACQCs (Scheme 2).



The resulting product with multifunctional groups present opportunities for many further chemical transformations. For example, the hydrogenation of compound **3b** under Pd/C followed by selective reduction of cyano group by NiCl₂/NaBH₄ and lactamization gave 7-membered lactam **8** in 67% overall yield (Scheme 3a). Compound **3ay** bearing vicinal diallyl ACQCs was subjected to ring-closed metathesis using Grubb's II catalyst to give the corresponding multisubstituted cyclohexene **9** in 87% yield (Scheme 3b).

Several control experiments were carried out to clarify the reaction mechanism (Scheme 4). The reaction in the absence of light, photocatalyst, or NHC gave no or only trace desired product (Scheme 4a). The reaction was totally inhibited when the radical scavenger of 2,2,6,6-tetramethylpiperidine *N*-oxyl radical (TEMPO) was added, while the radical coupling adduct between cyanomethyl radical and TEMPO was detected by high resolution mass spectrum (HR-MS) (Scheme 4b). The reaction of enal **1ba** and **1bb**, bearing a cyclopropyl group at the γ position, with iodoacetonitrile gave the desired products **3ba** and **3bb** in 82% and 86% yield respectively without the formation of ring-opening product **3ba'** and **3bb'**, which suggests the non-involvement of the γ -radical generated from enals (Scheme 4c).

(a) Control experiments



(b) Trap of the radical from iodoacetonitrile



(c) Investigation on the possilbe involvement of the radical from enal by radical clock



The plausible mechanism is depicted in Figure 1. The alkyl radical I is generated from alkyl halide via photocatalysis, which reacts with the dienolate intermediate^[4b] II, generated from γ -oxidized enals via NHC catalysis, to give homoenolate radical III. The following single-electron transfer (SET) oxidation of homoenolate radical III by the radical cation IV of photocatalyst affords α , β -unsaturated acyl azolium intermediate V and finishes the photocatalytic cycle. The acyl azolium intermediate V is trapped by methanol as the nucleophile to give the final product γ -alkylated- α , β -unsaturated esters 3 and regenerates the NHC catalyst.

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Figure 1. Proposed mechanism.

Conclusion

The γ - and ϵ -alkylation of enals with simple alkyl radicals via the merging of photoredox and NHC catalysis was developed. The reaction features operational simplicity, exclusive γ or ϵ -regioselectivity, well tolerance of functional groups and efficient construction of challenging vicinal all carbon quaternary centers. The combination of alkyl radical via photocatalysis and dienolate/trienolate intermediates via NHC catalysis is the key step for the reaction.

Experimental Section

General procedure: To a 5 mL screw-cap vial equipped with a magnetic stir bar was charged with Ru(bpy)₃(PF₆)₂ **4a** (5.2 mg, 2.0 mol%), preNHC **5h** (25 mg, 20 mol%), CsOAc (115 mg, 0.6 mmol), enal **2** or **6** (0.75 mmol), alkyl electrophile (0.3 mmol), MeOH (60 µl, 1.5 mmol) and DCE (3.0 mL). The tube was evacuated and backfilled with N₂ for three times. The mixture was then irradiated by 32 W CFL at room temperature until the full consumption of the enal, normally 24 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel to furnish the product **3** or **7**.

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S. Ye conceived and directed the project. L. Dai designed and performed most of experiments. Z.-H, Xia, Y.-Y. Gao., Z.-H. Gao performed the experiments. All the authors analyzed the data. L. Dai, Z.-H. Gao and S. Ye wrote the manuscript.

Keywords: photocatalysis • N-heterocyclic carbene • cooperative catalysis • remote alkylation • quaternary carbon

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