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Jiewen Jiang,^{a,§} Jiajun Liu,^{a,§} Ling Yang,^a Ying Shao,^b Jiang Cheng,^b Xiaoguang Bao^{*,a} and Xiaobing Wan^{*,a}

Construct y-Peroxy

Cu-Based Carbene Involved in a Radical Process: A New Crossove

Through merging Cu-based carbene in a radical process, a novel crossover reaction has been successfully established, leading to the facile and efficient syntheses of various γ -peroxy esters compounds and 1,4-dicarbonyl compounds. Considering both Cu-based carbene complexes and radicals are extremely reactive, and therefore exist only in extraordinarily low concentrations, the high selectivity of this coupling reaction is unusual.

Reaction

Compounds

to

Transition-metal-based carbene complexes have proven in the past few decades to be highly efficient intermediates in various organic synthesis.¹ Among them, the copper carbene complexes,² which are mainly generated from copper-induced decomposition of diazo compounds, have been extensively employed in transformations such as X-H insertion,^{3a-c} cross-coupling,^{3d-f} cyclization and ylide reactions.^{3g-1, 4} Copper carbene complexes have also been found to play a key role in the cyclopropanation of styrenes with diazo compounds.⁴ In this transformation, the Cu(I) complexes are often proposed to be the catalytically active species (Scheme 1a).⁵

Despite the versatile reactivity of Cu-carbene complexes, little attention has been paid to their potential in crossover reactions with radicals.⁶ This is primarily due to the formidable chemoselectivity challenge posed by the fact that both Cu-based carbene complexes and radicals are extremely reactive, and therefore exist only in extraordinarily low concentrations. Recently, we developed a novel tandem reaction to construct various β -ester- γ -amino ketones involving the cross-coupling between Co-based carbene radical⁷ and α -aminoalkyl radicals.⁸ Herein, we envision an unprecedented crossover reaction between a Cu carbene generated *in situ* from copper complex and ethyl diazoacetate and the *t*-BuOO[•] radical to afford γ -peroxy esters (Scheme 1b). This would

xqbao@suda.edu.cn; wanxb@suda.edu.cn ^{b.}Jiangsu Key Laboratory of Advanced Catalytic Materials and

Technology, Changzhou University, Changzhou, 213164, China Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x undoubtedly broaden the utility of Cu carbene transfer reactions From a synthetic perspective, it also provides a simple method ... the concurrent installation of peroxy⁹ and ester functionalities, both of which are common structural motifs in a wide range of value organic molecules.

and

Scheme 1. Copper Carbene Complexes Involved Reaction.

Ester



The pilot reaction set-up comprised styrene (1a) and $\epsilon \sqrt{1}$ diazoacetate (2a) in the presence of Cu(acac)₂ (10 mol%), TBHP hydroperoxide, 2.9 and (tert-butvl equiv.) 1.4 diazabicyclo[2.2.2]octane (DABCO, 2.0 equiv.) in *i*PrOH. Stirring th mixture at 70 °C for 1 h afforded the desired product ethyl 4-(ter butylperoxy)-4-phenylbutanoate (3a) in 61% yield, which could t further improved to 76% if Cu(acac)₂ was replaced wit $Cu(NO_3)_2$ 3H₂O, while the side product ethyl 4-oxo-/ phenylbutanoate was isolated in the yield of 18% generated from the unavoidable Komblum-DeLaMare rearrangement (For mor details, see Table S1, Supporting Information). The reaction could be performed under atmospheric conditions, indicating its insusceptibility to both oxygen and moisture, and could be evily scaled up to 15 mmol with no significant loss in product formation efficiency (entry 10, Table S1).

A variety of substituted styrenes were then tested under the optimal reaction conditions identified above. As shown in Scheme 2, the electronic properties of the functional groups on the phenyl rir 1 in most cases did not produce a significant impact on the reaction efficiency. For example, ether, ester, sulfonate and halogens we e all shown to be well tolerated. The noteworthy exception was

^a Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry, Chemical Engineering and Materials Science, Soochow University, Suzhou 215123, P. R. China.Fax: (+86) 512-65880334; Tell: (+86) 512-65880334; E-mail:

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nitrile, whose strong electron-withdrawing ability might have facilitated the subsequent DABCO-promoted Kornblum-DeLaMare rearrangement¹⁰ of the desired peroxy product into a y-ketoester, resulting in the lower yield of 3f. Ortho-substitution of styrenes did not negatively affect the formation of product 3n. Unfortunately, aliphatic alkene was not suitable reaction partner for this transformation and no desired product 3o was detected in the reaction mixture.

Scheme 2. Scope of Olefins^a



1 (0.5 mmol), 2a (1.0 mmol), Cu(NO3)2 3H2O (0.05 mmol), TBHP (1.45 mmol), DABCO (1.0 mmol) in 3.0 mL i-PrOH was stirred at 70 °C for 1 h.

Several diazo compounds were also chosen to expand the applicability of the strategy as shown in Scheme 3. Isopropyl 2diazoacetate, allyl 2-diazoacetate and dimethyl 2-diazomalonate could all furnish the corresponding products with moderate yields.

Scheme 3. Scope of Diazo Compounds^a 10 mol% Cu(NO3)2.3H2O 2.0 equiv. DABC 2.9 equiv. TBHP 3.0 mL *i*-PrOH air, 70 °C, 1 h CO₂Me 4d, yield: 59% 4c, yield: 46%

^a1a (0.5 mmol), 2 (1.0 mmol), Cu(NO₃)₂·3H₂O (0.05 mmol), TBHP (1.45 mmol), DABCO (1.0 mmol) in 3.0 mL i-PrOH was stirred at 70 °C for 1 h.

To probe whether the peroxyester products resulted from the cyclopropanation of styrene, ethyl 2-phenylcyclopropane-1carboxylate (5) was used as a model substrate. However, the predicted 3a was not detected (Scheme 4), suggesting that the involvement of a cyclopropane intermediate was unlikely. On the other hand, the addition of TEMPO (2,2,6,6-tetramethyl-1piperidinyloxy) to the reaction depicted in Table S1 was observed to suppress the product 3a formation and lead to the identification of three radical adducts 6a-8a (Scheme 5), which consequently impluse the role of 6b-8b as the key mechanistic Phtermediates Chatter transformation.

Scheme 4. Investigation on Reaction Mechanism.



Scheme 5. Trapping of Radical Intermediates by TEMPO.



Since the existence of a redox cycle between the Cu(II) and C species in the presence of TBHP,^{4e} computational studies wer carried out to address the question: which Cu species is more read to activate 2a to afford a Cu-carbene complex, Cu(I) or Cu(II)? The energy profile for the Cu(I) species, CuNO₃-DABCO, promote ' activation of 2a to afford a Cu-carbene intermediate was shown in Figure 1. The predicted energy barrier for breaking the C-N bond 2ato release a dinitrogen is only 6.0 kcal/mol relative to the separated $2a + CuNO_3$ -DABCO. After the leaving of a dinitrogen, the Cu-carbene intermediate (INT2) is formed, which is exothermic by 21.1 kcal/molrelative to 2a + CuNO3-DABCO. For the Cu(II) spece Cu(NO₃)₂-DABCO, catalyzed activation of 2ato form a Cu-carbene intermediate, however, a much higher energy barrier (26.5 kcal/mol) obtained. Moreover, the resulted intermediate was thermodynamically unstable (see SI, Figure S1). Thus, one can conclude that the activation of 2a is readily promoted by Cu(1), instead of Cu(II) species.



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Figure 1. Energy profile for the activation of 2a by Cu(I) species to form a Cu-carbene intermediate. H atoms on DABCO are omitted for clarity. Bond lengths are shown in Å.

The yielded Cu-carbene intermediate (INT2) may undergo hydrogen abstraction reaction to afford an organocopper intermediate. To determine the most energetically favourable mechanistic pathway, three potential donor bonds, including the O-H of *i*-PrOH, that of TBHP, and the secondary C-H of *i*-PrOH, were subjected to computational studies. The results suggested that abstracting the secondary hydrogen of *i*-PrOH (Figure S2) enjoyed a much lower energy barrier (only 6 kcal/mol) than cleaving the O-H bond of *i*-PrOH or TBHP (Figure S3 and S4). The calculation was consistent with the experimental finding that 3-pentanol, which also contained a secondary hydrogen, could be used as a substitute solvent (Scheme 6a), while the tertiary t-BuOH could not (Scheme 6b). As further evidence, conducting the coupling reaction in perdeuterated *i*-PrOH furnished α -deuterated **3a** (Scheme 6c); however, the use of TBHP-d1 and undeuterated i-PrOH mainly led to the formation of undeuterated 3a (Scheme 6d).



One may envision that the afforded Cu-carbene intermediate might undergo cyclopropanation in the presence of styrene.⁴ Computational studies on the cyclopropanation reaction (Figure S5) indicate that the energy barrier (7.4 kcal/mol) is 1.4 kcal/mol higher than the most favourable H-abstraction from *i*-PrOH. Thus, the intermediate INT7 is more feasible to be formed from the Cucarbene intermediate via H-abstraction reaction.

In the presence of ^tBuOOH, INT7 might beoxidized to INT15 via an oxidative addition (OA) step (Figure S6). Subsequently, INT15 could undergo the homolytic cleavage of the Cu-C bond to generate On the other hand, INT7 might participate in an intermolecular organocuprationreaction¹¹ with styrene to generate INT19 (Figure S7). Computational studies suggested that the formation of INT19 has a higher free-energy

barrier than the OA of ^tBuOOH onto INT7, and hence to form Subsequently, the yielded 6b would add to the styre here double bloose to afford the benzylic radical **7b** (Figure S8). Eventually, the targe product 3a could be furnished via the radical cross-couplingo 7 and ^tBuOO• generated in situ from a catalytic redox cycle of Cu(... and TBHP.¹²







 a 1 (0.5 mmol), 2a (1.0 mmol), Cu(acac)₂ (0.05 mmol), TBHP (1.45 mmol), DABC \cdot (1.5 mmol) in 3.0 mL i-PrOH was stirred at 70 °C for 1 h.

1,4-Dicarbonyl compounds are important building blocks for the synthesis of heterocyclic compounds.¹³ We recently demonstrated that the tert-butyl peroxy group could be readily converted to carbonyl via Komblum-DeLaMare rearrangement.8, 14 Combined with the Cu-catalyzed coupling of styrene, TBHP and e nyl diazoacetate we developed herein, this will allow facile preparatic of 1,4-dicarbonyl compounds. We theorized that the two reaction could be performed in one pot by allowing DABCO used in th radical coupling step to also serve as the base for the subsequer rearrangement. To test this idea, the coupling reaction wa prolonged and the target product ethyl 4-oxo-4-phenylbutanoat. 9a was isolated in 53% yield. It was then discovered that the yie' could be further increased to 72% by using $Cu(acac)_2$ as the cata

radical 6b (INT16) and	a Cu(II)	species.
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(For more details, see Table S2, Supporting Information). The synthetic application of this tandem reaction system could be extended to a variety of 1,4-dicarbonyl compounds as shown in Scheme 8.

In summary, we have developed an unprecedented crossover reaction that combined Cu carbene and radical intermediates in a single catalytic cycle, allowing simple and efficient synthesis of various γ -peroxy ester derivatives and 1,4-dicarbonyl compounds. The result represents a significant technological advancement in the fields of both copper carbene and radical chemistry. Further investigations that aim to expand the repertoire of crossover reactions between these two fields are currently underway in our laboratory.

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⁹These authors contribute equally.

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