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Trimerization of enones under air enabled by NHC/NaOtBu *via* a SET radical pathway†

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An unusual trimerization of enone *via* a formal [2 + 2 + 2] process is disclosed. The reaction is initiated by a radical process enabled by NaOtBu and N-heterocyclic carbene (NHC). Molecular oxygen (air) is involved in key steps of the radical intermediate formation and carbon–carbon bond cleavage in this trimerization reaction to form highly substituted cyclohexane derivatives. In previous studies, alkali metal *tert*-butoxides such as NaOtBu were mainly employed to generate radical intermediates from aryl halides. Here we provide a new avenue in using NaOtBu and combined NHC/NaOtBu to generate radical intermediates from enones for further reactions.

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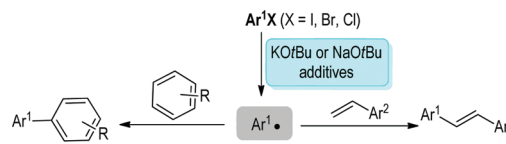
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Introduction

Alkali metal *tert*-butoxides such as NaOtBu or KOtBu have been proved to be good electron donors as pioneered by Stowell in 1981.¹ In recent years, NaOtBu or KOtBu has been utilized to generate aryl radicals from aryl halides for coupling reactions with arenes or styrene, as investigated by Shi,² Shirakawa/Hayashi,³ Lei,⁴ Studer⁵ and others (Fig. 1a).⁶ In these reactions, typically bidentate nitrogen-containing compounds (such as phenanthroline and DMEDA) were used as ligands or additives to enable the single-electron-transfer (SET) processes. In all these reports, aryl radical is suggested as the key intermediate. The generation of aryl radical from aryl halide and addition of the aryl radical to arene or olefin are generally accepted as the key steps.

Here we report a new process mediated by NaOtBu and N-heterocyclic carbene (NHC) for radical reactions of enones that affords unusual trimerization products (Fig. 1b). NHC and NaOtBu were used to enable a SET process that initiates a radical reaction of enone (**1a**) under air to eventually give intermediate **A**. Reaction of radical intermediate **A** with one molecule of enone forms intermediate **B** that undergoes further reactions with another molecule of enone **1a**, leading to tri-

(a) KOtBu/NaOtBu-mediated cross-coupling reactions between aryl halides and arenes/styrenes



(b) *This Work:* NHC/NaOtBu-Enabled Unusual [2+2+2] Trimerization of Enones *via* Radical Pathway

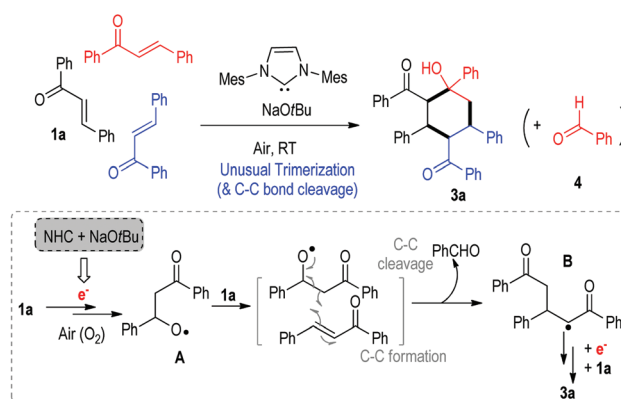


Fig. 1 KOtBu/NaOtBu-mediated SET reactions: (a) Reported cross-coupling reactions between aryl halides and arenes or styrenes. (b) Our NHC/NaOtBu-triggered formal [2 + 2 + 2] radical cycloaddition of enones.

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merization product **3a**. Notably, adducts such as **3a** could only be prepared from acetophenone and benzaldehyde under harsh conditions in previous reports.^{7,8} In our process (from **A** to **B**), one carbon–carbon bond is cleaved with the release of an aldehyde side product (**4**) that was experimentally verified. In our present study, N-heterocyclic carbenes (NHCs) were

used in combination with NaOtBu to promote the generation of radical intermediates from enones for further reactions. NHCs as organic catalysts were traditionally used in electron-pair reactions.⁹ In recent years, NHC-mediated reactions *via* SET radical processes emerged as a new type of reaction mode for unconventional transformations.¹⁰ Studer reported NHC-catalyzed oxidation of aldehydes using TEMPO as an oxidant *via* a radical pathway.¹¹ Our group reported reductive β,β -coupling of nitroalkenes and reductive coupling of nitrobenzyl bromides with activated ketones/imines *via* a NHC-mediated SET process.^{12,13} Rovis and our laboratories independently reported β -hydroxylation of enals *via* NHC-catalyzed SET processes.^{14,15} Recently, studies from Rehbein suggested that NHC-mediated benzoin reactions likely go through a radical pathway.¹⁶

Results and discussion

We started by using chalcone (**1a**) as a model substrate (Table 1). When **1a** was mixed with 150 mol% NaOtBu in Et₂O for 48 hours, the unconventional trimerization product **3a** was obtained in 25% yield (entry 1). The structure and relative configuration of **3a** was confirmed *via* X-ray analysis. We then moved to search for ligands that can improve the reaction. We tested 1,10-phenanthroline previously used in the coupling reactions of aryl halides and arenes,^{2a,3a} and found the yield of **3a** was improved to 59% (see ESI†). At the same time, we found that the addition of 20 mol% imidazolium-based NHC could significantly improve the yield of **3a** (80% yield, entry 2). The use of triazolium-based NHCs led to lower yields of **3a**

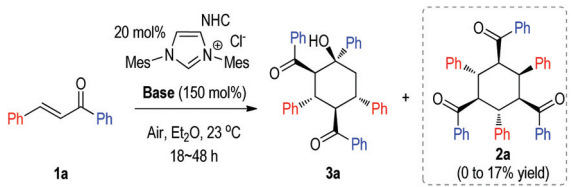
(see ESI†). The choice of bases was important for this reaction: KOtBu was much less effective than NaOtBu (entry 3); and other typical bases such as NaOH, K₂CO₃ and Et₃N were ineffective (entries 4–7). Reducing the NHC catalyst loading from 20 mol% to 10 mol% led to a slight drop in reaction yield (from 80% to 60% yields, entries 2 and 8). The reaction did not proceed without the presence of base (entry 9). When the loading of base (NaOtBu) was reduced to 20 mol% (to generate free carbene from the imidazolium salt), no formation of **3a** was observed (entry 10). This result (entry 10) suggested that free NHC alone could not mediate this reaction. Replacing Et₂O with other organic solvents (such as toluene and CH₃CN) led to **3a** with moderate to good yields (entries 11–13, and ESI†). As a technical note, “side product” **2a** was observed in trace to around 17% yield under our conditions, that might be formed *via* further reactions of radical anion generated by one electron reduction of chalcone **1a** by NHC/NaOtBu with another two molecules of **1a** to give a new trimerized radical anion, which undergoes 6-*exo*-trig radical cyclization and sequential one electron oxidation to afford **2a** (for detailed proposed mechanism for **2a**, see ESI†). To the best of our knowledge, the observation of **2a** was mentioned in only one report under electrochemical conditions during Fournier’s study on the effect of counter ions for the electroreduction of chalcone.¹⁷

With an acceptable condition in hand, we evaluated the scope of enones (Table 2) by first varying the aryl substituent next to the carbonyl group. Placing different substituents on this phenyl ring (**3b–d**) or replacing the phenyl unit with a naphthyl group (**3e**) were all well tolerated. We then studied the effects of substituents on the β -phenyl group of enone and found that the reactions went smoothly to give corresponding products in moderate to good yields (**3f–k**). Enones with β -naphthyl or heteroaryl units reacted effectively as well (**3l, 3m**). Replacing both phenyl units of **1a** with other aryl substituents were well tolerated (**3n–r**).

To gain insights into reaction pathway, we performed several control experiments (Table 3). When 1.0 equivalent of TEMPO was added to the reaction mixture under the standard condition, the yield of **3a** dropped from 80% to 16% (entry 1). The formation of **3a** was completely suppressed when 3.0 equivalents of TEMPO was added (entry 2). These experiments with TEMPO suggest that our reaction likely go through SET radical pathways. Air is necessary as no reaction occurred when the reaction was performed under N₂ (entry 3), supporting the involvement of O₂ in our reaction.

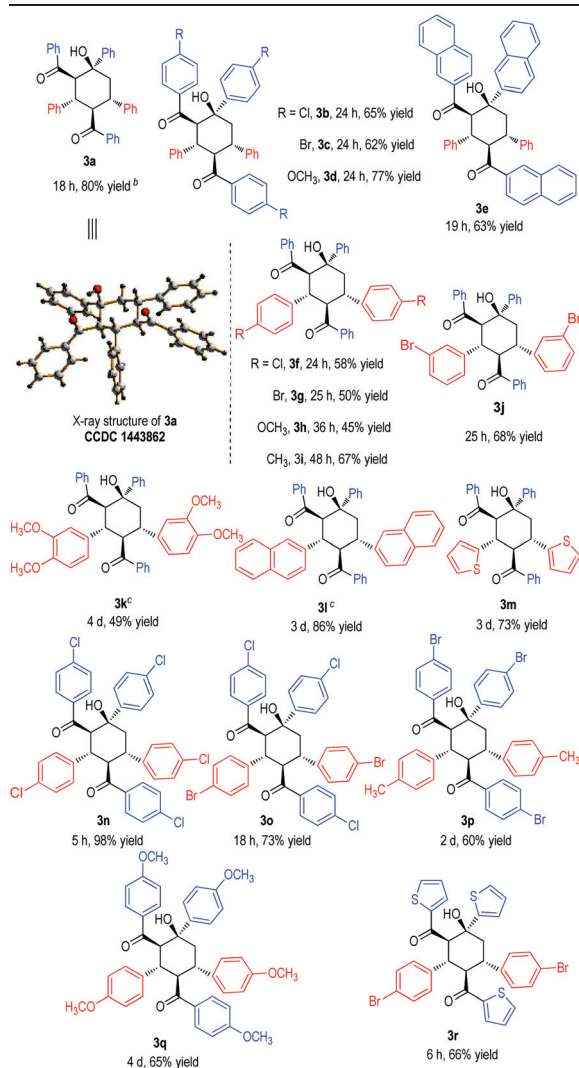
Interestingly, when the reaction was carried out under pure oxygen (O₂ balloon) (entry 4), no formation of **3a** was observed. This can be ascribed to the high concentration of oxygen, as the reduction potential of **1a** (–1.85 V *vs.* Fc/Fc⁺ (Fc = ferrocene)) was found to be smaller than the that of O₂ by approximately 500 mV (reduction potential of O₂ is –1.25 V *vs.* Fc/Fc⁺).¹⁸ When the reaction was carried out under air, the concentration of **1a** was much greater than dissolved molecular oxygen and **1a** was able to be reduced by one electron from NHC–NaOtBu. When the reaction was conducted under

Table 1 Condition optimization^a



Entry	Condition	Yield ^b of 3a (%)
1	NaOtBu, w/o NHC, 48 h	25
2	NaOtBu, 20 mol% NHC, 18 h	80
3	KOtBu, 20 mol% NHC, 48 h	30
4	Mg(OtBu) ₂ , 20 mol% NHC, 48 h	0
5	NaOH, or K ₂ CO ₃ , 20 mol% NHC, 48 h	0
6	NaOMe, or KOMe, 20 mol% NHC, 48 h	0
7	DBU, or Et ₃ N, 20 mol% NHC, 48 h	0
8	As entry 2, 10 mol% NHC, 48 h	60
9	As entry 2, w/o base, 48 h	0
10	As entry 2, with 20 mol% NaOtBu, 48 h	0
11	As entry 2, solvent = toluene, 36 h	65
12	As entry 2, solvent = CH ₃ CN, 24 h	71
13	As entry 2, solvent = THF, 24 h	55

^a Unless otherwise noted, the reaction was carried out in a 4 mL vial with 0.1 mmol chalcone **1a**, 20 mol% NHC and 150 mol% base in 1.5 mL solvent under air at room temperature. ^b Isolated yield.

Table 2 Substrate scope^a

^a Unless otherwise noted, the reactions were conducted in 8 mL vials with 0.2 mmol enones, 20 mol% NHC and 150 mol% of NaOtBu in 3 mL diethyl ether. The reaction mixture was stirred at room temperature (23 °C) under air till the enones were fully converted as monitored by TLC. ^b Isolated yield. ^c 0.2 mL THF was added to increase the solubility.

Table 3 Control experiments to elucidate reaction mechanism

Entry	Condition	Yield of 3a (%)
1	Under air, 1.0 equiv. TEMPO	16
2	Under air, 3.0 equiv. TEMPO	0
3	Degassed, under N ₂ atmosphere	0
4	Degassed then connected to O ₂ balloon	0 (3 runs)

pure oxygen, the dissolved oxygen content would be higher (and be reduced), suppressing the reaction of **1a**.

We also conducted electron paramagnetic resonance (EPR) spectroscopic analysis of the reaction mixture of **1a** in diethyl ether containing 20 mol% of NHC and 1.5 equivalents of NaOtBu. An exchange broadened and persistent radical signal was obtained at room temperature with a *g*-value of 2.0050 (Fig. 2), albeit with a low resolution. The EPR spectrum suggests the presence of a radical anion. To further understand the radical intermediate, we conducted cyclic voltammetry studies. Cyclic voltammetry experiments performed on **1a** showed that **1a** could be reduced at approximately −1.85 V vs. ferrocene 0/+ (Fig. 3). However, the chemical irreversible nature of the voltammetric reduction process indicated that the radical anion form of **1a** (intermediate **I** in Scheme 1) could not be the long-lived radical that was detected *via* the EPR experiments (Fig. 2), as the CV experiments indicate that it is relatively short-lived (lifetime $\ll$ 1 s). Therefore, the radical anion detected by EPR in Fig. 2 might be intermediate **II** (Scheme 1), although unambiguous assessment is not feasible at this point.

Based on these mechanistic studies above and results from LC-MS studies (see ESI[†]), a postulated reaction pathway is illustrated in Scheme 1. The reaction begins with a NHC-assisted release of an electron of NaOtBu^{3,6c} to initiate the

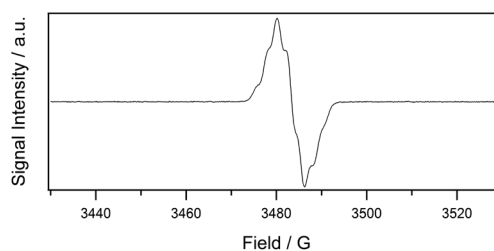


Fig. 2 Continuous wave X-band room-temperature EPR spectrum of the reaction mixture of 20 mol% NHC, 1.5 equiv. of NaOtBu and chalcone **1a** in diethyl ether. The modulation amplitude = 0.2 G and sweep time = 30 s.

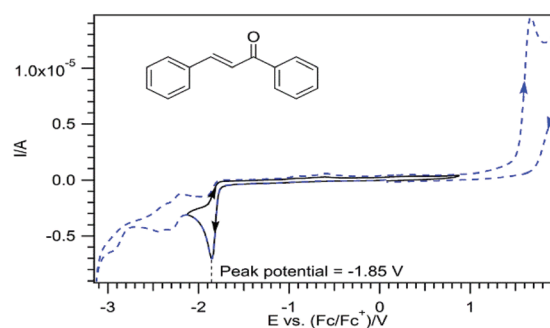
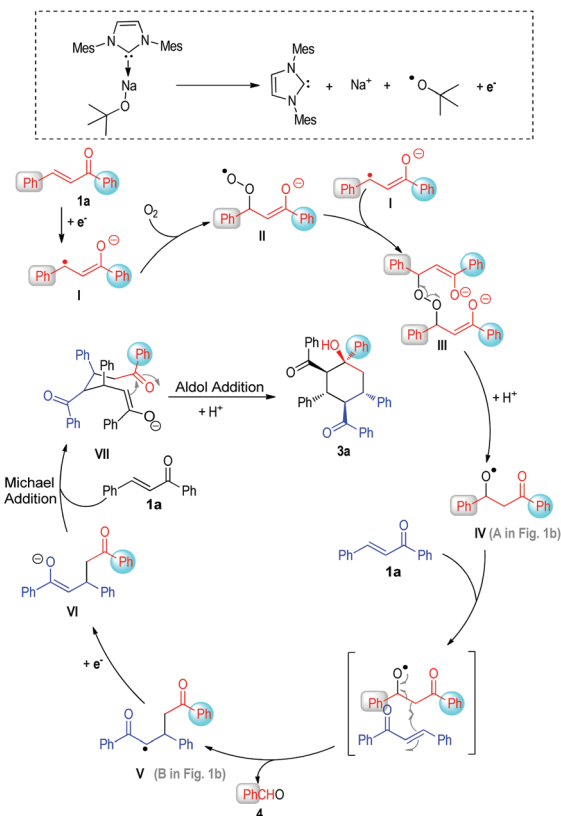


Fig. 3 Cyclic voltammograms of 5 mM of the analyte recorded at a 1 mm diameter planar circular glassy carbon electrode in acetonitrile containing 0.2 M *n*-Bu₄NPF₆ as the supporting electrolyte, at a scan rate of 0.1 mV s^{−1} and at 22 ± 2 °C.



Scheme 1 Proposed reaction pathway.

formation of enone-derived radical anion intermediate **I**.^{5b,19} This process also gives an alkoxy radical^{6c} that collapses via known decomposition pathways.²⁰ Reaction of **I** with molecular oxygen forms intermediate **II**.^{21,22} A combination of two radical intermediates **I** and **II** affords **III** that undergoes a subsequent homolytic breaking of the O–O bond to form **IV**. Reaction of **IV** with one more molecule of **1a** via a currently undetermined mechanism generates intermediate **V**.²³ This process is associated with a C–C bond cleavage that leads to an aldehyde adduct (PhCHO).^{22,24} Intermediate **V** undergoes a SET process followed by a cascade reaction (involving Michael addition and Aldol addition) to eventually provide the multi-substituted cyclohexane product **3a**.

Conclusions

In summary, we have developed a NHC/NaOtBu-mediated radical reaction of enones. The reaction proceeds through NHC/NaOtBu-enabled SET to form enone-derived radical anion intermediate that then reacts with molecular oxygen to afford peroxide radical. Subsequent reactions of peroxide radical via the formation of multiple chemical bonds and the cleavage of one C–C bond eventually form multisubstituted cyclohexanes as the enone unusual trimerization products. NaOtBu and similar bases were previously used to generate reactive radical intermediates from aryl halides. Our study

provides a new avenue in using NaOtBu and combined NHC/NaOtBu to generate radical intermediates from enones. Further mechanistic studies and design of NHC/alkali metal *tert*-butoxides for new reaction modes are in progress.

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- 22 X. Jia, Y. Zhu, Y. Yuan, X. Zhang, S. Lu, L. Zhang and L. Luo, *ACS Catal.*, 2016, **6**, 6033.
- 23 One reviewer commented that intermediate **IV** may undergo HAT process to give β -hydroxyketone, which then goes through retro-aldol reaction and Michael reaction to give intermediate **VI**. Here, we should state that: (1) it's hard for intermediate **IV** to occur HAT process under our reaction conditions, because there is no good hydrogen atom source in the reaction system; (2) the β -hydroxyketone derived from intermediate **IV** is quite stable, if it really exists, we could have observed (by GC-MS, LC-MS or other method); (3) it's very hard for such β -hydroxyketone to occur retro-aldol reaction on the basis of literature study, particularly under our reaction conditions.
- 24 We could observe the formation of side product aldehyde **4** in our reaction by GC-MS. The aldehyde was finally isolated in its reduced form as benzylic alcohol at the end of the reaction. Unfortunately, the mechanism for the transformation of aldehyde to corresponding benzylic alcohol is currently unclear.