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N-Heterocyclic Carbene-Catalyzed Radical Reactions for Highly Enantioselective β-Hydroxylation of Enals

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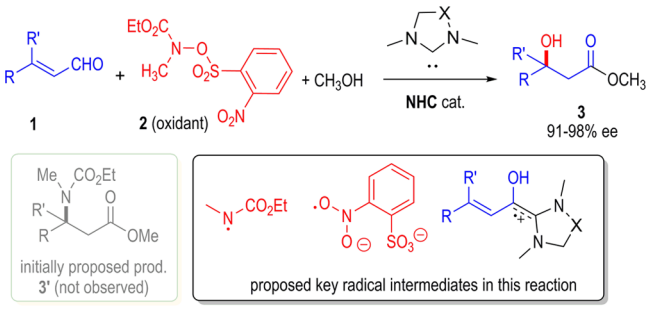
Supporting Information

ABSTRACT: An N-heterocyclic carbene-catalyzed β-hydroxylation of enals is developed. The reaction goes through a pathway involving multiple radical intermediates, as supported by experimental observations. This oxidative single-electron-transfer reaction allows for highly enantioselective access to β-hydroxyl esters that are widely found in natural products and bioactive molecules.

N-heterocyclic carbenes (NHCs) have been explored as organocatalysts to mediate a large range of reactions.[1] The majority of these reactions, however, involve electron-pair-transfer steps. On the other side, it has been envisioned that NHCs might be used to develop single-electron-transfer (SET) reactions.[2−4] The SET process[5] can provide valuable opportunities not readily available from electron pair chemistry for the activation of inert chemical bonds or direct assembling of functional molecules. Indeed, radical processes enabled by NHC catalyst in the living systems have been studied. For example, the thiamine pyrophosphate (TPP, precursor of a NHC) mediated oxidative decarboxylation of pyruvate to form acetyl-CoA and CO_2 is believed to proceed via SET/radical processes.[6] Despite of the significance and the in-principle feasibility, the development of NHC-mediated radical reactions in synthetic chemistry is still in its infancy. In 2008, Studer reported NHC-catalyzed oxidation of aldehydes using TEMPO.[2] The authors proposed that the reaction went through a radical cation formed via removal of one electron of the Breslow intermediate. Recently, we developed NHC-catalyzed reductive β,β-coupling reactions of nitroalkenes via SET processes.[4] The nitroalkene-derived radical anion was characterized using electron paramagnetic resonance (EPR) spectroscopy. Here we report carbene-catalyzed generation of unsaturated Breslow intermediate-derived radical cation for β-hydroxylation of enals (Scheme 1). The reaction affords β-hydroxyl esters, including those bearing quaternary β-carbon centers, in high enantioselectivities. Notably, β-hydroxyl (α-unsubstituted) esters and their derivatives are important building blocks and ubiquitous subunits present in biologically active compounds and natural products.[7,8] Our catalytic approach provides a concise and highly enantioselective access to this class of important compounds.

Scheme 1. NHC-Catalyzed β-Hydroxylation of Enals via Radical Intermediates



Our initial design was to achieve β-amination of enals (Scheme 1). We chose nitrobenzenesulfonic carbamate **2** (reductive peak potential measured as $E_p^{red} \sim -1.2$ V vs ferrocene/ferrocenium, see Supporting Information, SI), an N-centered radical precursor pioneered by MacMillan,[9] as an oxidant. Somewhat to our surprise, β-hydroxylation product (**3**) was obtained, and initially proposed amination product (**3′**) was not observed. It is important to note that near the completion of our study, Rovis et al. reported carbene-catalyzed β-hydroxylation of enals via SET processes using nitropyridine N-oxide as an oxidant.[3] In Rovis's reaction, a homoenolate radical cation intermediate was proposed; and the β-hydroxyl ester products were obtained in moderate yields and 63−92% ee. In our system, it appears a radical process involving both N- and O-centered radicals occurred. On the application side, our reaction affords products with excellent enantioselectivities (~95% ee for most products).

Key results of condition optimization are briefed in Table 1. The search for suitable conditions indicated that nitrobenzenesulfonic carbamate **2** was an effective oxidant and K_2CO_3 was a suitable base for this β-hydroxylation reaction. When imidazolium NHC precursor **4a**[10] was used for the reaction carried out in THF with degassing, the β-hydroxyl ester product **3a** was obtained in encouraging 32% yield (entry 1). We next moved to triazolium NHCs and found that the use of amino indanol derived triazolium **4b**[11] as an NHC

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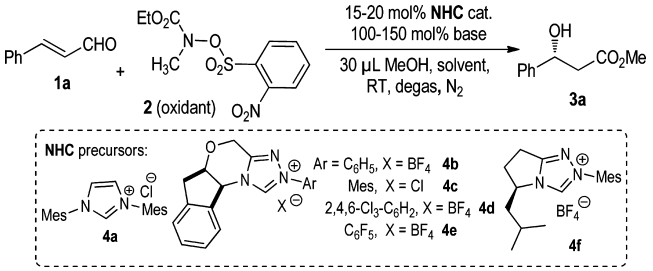
Table 1. Condition Optimization[a]



entry	condition	yield (%)[b]	ee (%)[c]
1	**4a**, K_2CO_3, THF	32	–
2	**4b**, K_2CO_3, THF	31	92
3	**4c**, K_2CO_3, THF	31	96
4	**4d**, K_2CO_3, THF	0	–
5	**4e**, K_2CO_3, THF	0	–
6	**4f**, K_2CO_3, THF	46	88
7	**4c**, K_2CO_3, toluene	61	96
8	**4c**, 150 mol % K_2CO_3, toluene	79	96
9[d]	**4c**, 150 mol % K_2CO_3, toluene	98 (95)	97
10[d,e]	**4c**, 150 mol % K_2CO_3, toluene	89 (87)	97

[a]Unless otherwise noted, reactions were carried out at RT using **1a** (0.1 mmol), **2** (0.05 mmol), catalyst (20 mol %), base (100 mol %), and 1.5 mL of solvent, MeOH was added via a needle 30 min after the reaction started. [b]Estimated via ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard; isolated yields are in parentheses. [c]Determined via HPLC analysis on a chiral stationary phase; the absolute configuration was determined by comparing the optical rotation of **3a** (and products in Table 2) with literature values (see SI). [d]The methanol was added at the same time as other substrates and reagents (see SI). [e]15 mol % catalyst was used.

precatalyst led to **3a** with 31% yield and excellent 92% ee (entry 2). A switch of the NHC catalyst to **4c**[12] with a bulkier N-mesityl substituent resulted in an improved ee (96%) with similar yield (entry 3). NHC precatalysts with electron-deficient N-aryl substituents (**4d**, **4e**)[13] led to no formation of **3a** (entries 4–5). This result is different from Rovis's study:[3] in his system triazolium-based NHCs with electron-deficient N-aryl substituents could mediate the reaction. The use of amino acid-derived NHC catalyst **4f**[14] afforded **3a** with an improved yield but unfortunately unsatisfactory ee (entry 6). We next chose NHC precatalyst **4c** for further optimization and found that toluene was a better solvent than THF (entry 7). We finally found that when methanol was added at the same time as other substrates/reagents with the use of 150 mol % base (relative to oxidant **2**), the product **3a** could be obtained in excellent yield and ee (entry 9). The use of 15 mol % NHC precatalyst could give satisfactory results as well (entry 10). Notably, 2 equiv of enal **1a** (relative to oxidant **2**) were used in this reaction. One equiv of the enal was exclusively oxidized to the corresponding α,β-unsaturated ester. Mechanistic origins for this observed result are illustrated in Scheme 2. As a technical note, it is essential to degas the reaction mixture and perform the reaction under N_2 protection. When the reaction was conducted under open air, the product (**3a**) was not detectable or observed in very low (<5%) yield.

The scope of this reaction is quite general (Table 2). We first evaluated β-(hetero)aryl enals and found that placing various substituents on the aryls have little effect on the reaction outcomes (**3a–g**). Essentially all products (**3a–j**) were obtained with excellent yields and ee. Enals with a β-alkyl substituent reacted exceptionally well too, providing products **3k–o** with 81–99% yields and 96–97% ee. Enals with two substituents at the β-carbon were also excellent substrates, leading to products (**3p–v**) bearing β-quaternary carbon centers with moderate yields and excellent enantioselectivities. Notably, among these β-hydroxyl esters, **3e** is a natural product named pisoninol I that exhibits antitubercular activity;[7] and **3o** was found to be a potent membrane-perturbing agent on human erythrocytes.[8]

The proposed reaction pathway is illustrated in Scheme 2. The Breslow intermediate **A** formed between NHC catalyst and enal **1a** undergoes an oxidative SET process with oxidant **2** to generate three intermediates: N-centered radical **B1**,[9] nitroaryl molecule **B2** (reductive peak potential measured as $E_p^{red} \sim -1.8$ V vs ferrocene/ferrocenium, see SI), and Breslow intermediate-derived radical cation **B3**. The radical cation **B3** undergoes a deprotonation to form a neutral radical intermediate **B3′** that goes through a subsequent oxidation by nitroaryl compound **B2** to provide a nitro radical anion **C** and an α,β-unsaturated azolium ester intermediate **F**. The resulting

Scheme 2. Proposed Reaction Pathway

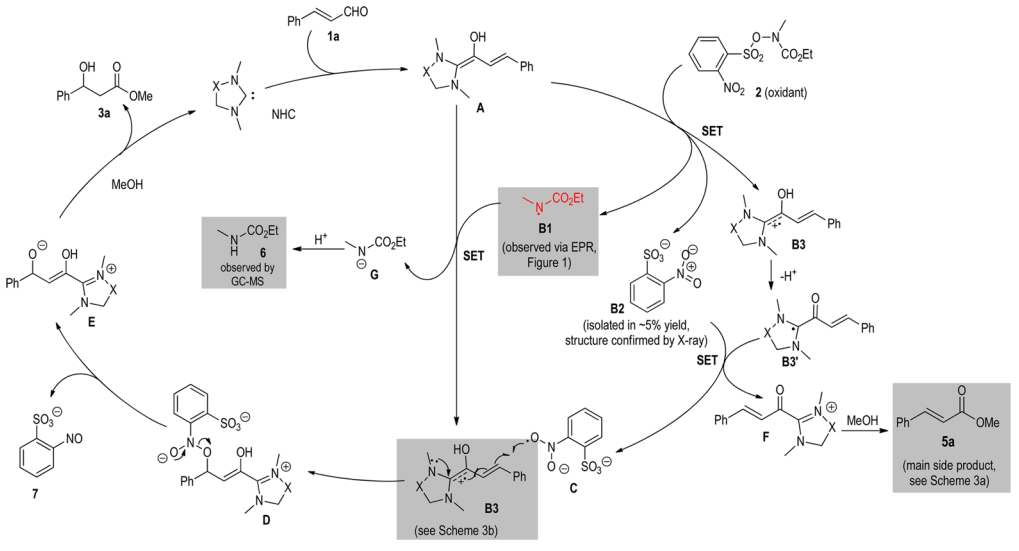


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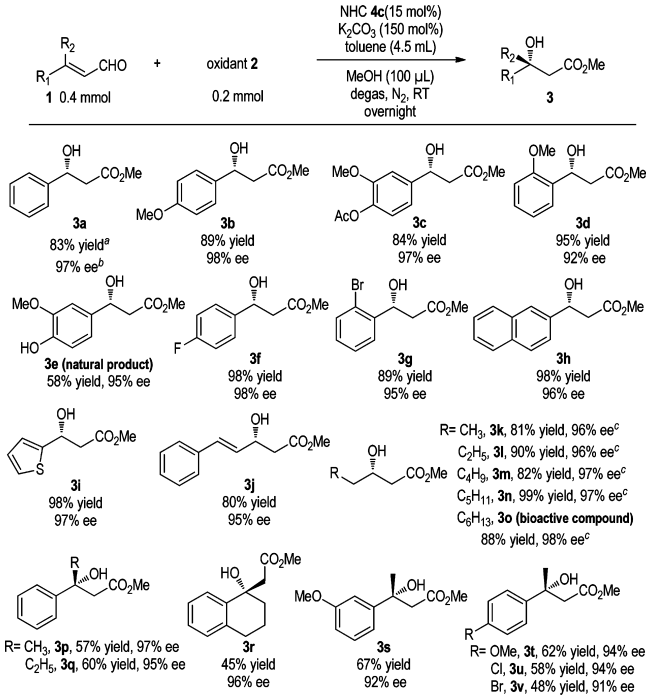
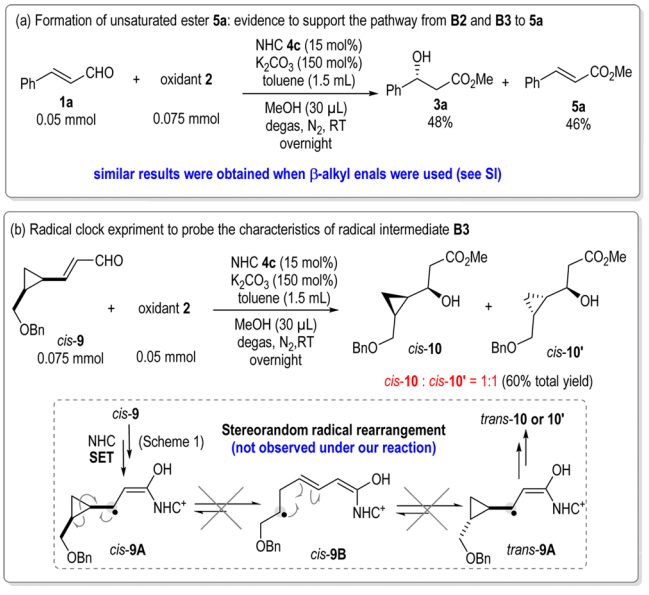
Table 2. Substrates Scope



[a]Isolated yields. [b]Determined via HPLC analysis on a chiral stationary phase. [c]Determined via HPLC analysis on a chiral stationary phase after derivatization (see SI).

intermediate **F** is trapped by CH_3OH to yield ester **5a** as a side product (see Scheme 3a) with the regeneration of NHC catalyst. In the productive pathway leading to β-hydroxylation of enal, the N-centered radical **B1** undergoes a SET process to abstract one electron from another equivalent of Breslow intermediate **A** to form anther Breslow intermediate-derived radical cation **B3** and a carbamate anion **G**. The carbamate anion intermediate **G** is then protonated to generate carbamate **6** (confirmed by GC-MS). We propose a pathway similar to that of Rovis[3] for the conversion of radical intermediates **B3** and **C** to yield the final product **3a**. Specifically, a reaction between two radical intermediates **B3** and **C** affords adduct **D** with the creation of a new C−O bond on the formal enal β-carbon. Subsequent N−O bond cleavage of **D** gives a nitroso compound **7**[3] and intermediate **E**. A reaction of intermediate **E** with CH_3OH (proton transfers followed by ester formation) yields desired product **3a** with the regeneration of the NHC catalyst.

Scheme 3. Experiments to Probe Reaction Mechanism



The mechanistic pathway proposed above is supported by several experimental studies. The existence of the N-centered radical **B1** was first supported by the observation of carbomate **6** (GC-MS). Much clearer evidence came from EPR spin trapping experiments using DMPO.[15] The EPR spectrum of the DMPO trapped radical is shown in Figure 1a. A simulated spectrum could be matched to the experimental data by assuming that the major hyperfine coupling occurred to two nonequivalent nitrogen atoms and one hydrogen atom (Figure 1b).

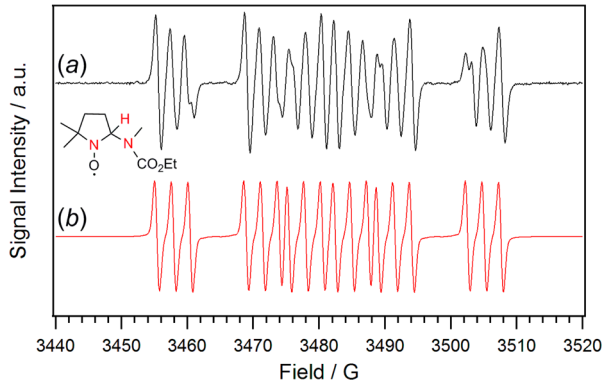


Figure 1. (Black line) EPR spectra of the radical derived from trapping B1 with DMPO at 22(±2) °C in toluene according to the reaction in Scheme 2. (Red line) Simulated EPR spectrum based on hyperfine coupling constants of 1N = 13.55 G, 1N = 2.53 G, 1H = 20.10 G, and with a line width of 0.75 G.

The generation of intermediate **B2** was confirmed experimentally. This anion **B2** was obtained in its potassium salt form with around 5% yield, and its structure was confirmed via X-ray diffraction (see SI).

In our catalytic reaction, the α,β-unsaturated ester **5a** (Scheme 2) was obtained as the major side product with yield similar to the desired β-hydroxylation product **3a**. Among the 2 equiv of enal substrate used, 1 equiv is converted to unsaturated ester **5**, as illustrated in Scheme 2. This pathway is also supported by results from our initial condition optimizations when excess amount of oxidant was used (Scheme 3a). The use of excess oxidant did not improve the yield of **3a**. For example, when enal **1a** (0.05 mmol) was exposed to 1.5 equiv of oxidant **2** (0.075 mmol), 48% yield (relative to **1a**) of β-hydroxyl ester and 46% yield of α,β-unsaturated ester were isolated (Scheme 3a). Results similar to those using β-aryl enal **3a** were obtained when β-alkyl enals (e.g., **3n**, **3o**) were used (see SI). The results support that our system is different from that of Rovis.[3] Under our condition, half of the enal is converted to α,β-unsaturated ester, as proposed in our mechanism. Thus, for preparation applications (Table 2), enals and the oxidant were used in 2:1 molar ratio to ensure effective use of the oxidant.

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The structural characteristics of α,β-unsaturated Breslow intermediate-derived radical cation **B3** (Scheme 2) were studied by "radical clock" experiments (Scheme 3b). When the *cis*-cyclopropyl-substituted enal **9** was used in our reaction system, the relative configurations of the cyclopropyl in the final ester products (*cis*-**10** and *cis*-**10′**) were retained (Scheme 3b). This observation suggested that prior to the desired C−O bond formation (from **B3** and **C** to **D**, Scheme 2) of the enal β-carbon, a β-carbon-centered radical is unlikely dominated. Because a β-carbon-centered radical (e.g, *cis*-**9A**, Scheme 3b) will likely lead to stereorandom radical rearrangement that results in isomerization of the *cis*-cyclopropyl unit to the *trans*-isomer. Such a rearrangement was not observed under our reaction condition. These results suggested that the radical spin is more likely delocalized between the enal formal carbonyl carbon and the triazolium NHC unit, supporting the structure of intermediate **B3** as proposed in Scheme 2. Related radical cation intermediate derived from aldehyde under NHC catalysis using TEMPO as an oxidant was proposed by Studer et al. in their aldehyde oxidation reactions.[2]

The oxygen ends up in the β-hydroxylation product **3a** likely come from the NO_2 unit of oxidant **2** (Scheme 2, reaction between **B3** and **C** to form the C−O bond on the enal β-carbon). When a similar oxidant with the "NO_2" group removed is used, no β-hydroxylation product **3a** is formed (see SI).

In summary, we have developed a NHC-catalyzed oxidative SET of enals that introduces a hydroxyl group to the β-carbon of enals. Mechanistic studies suggested that a radical pathway was operating with the generation of multiple radical intermediates. The catalytic reaction allows for highly enantioselective entry into β-hydroxyl esters with important utilities. We expect this study to encourage more adventures into NHC-catalyzed SET reactions, a challenging arena that will likely bring surprises and fruitful returns. Further studies on the multiple possible radical intermediates present in the present work for novel reaction development are in progress.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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