

Chiral Nitroarenes as Enantioselective Single-Electron-Transfer Oxidants for Carbene-Catalyzed Radical Reactions

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Supporting Information Placeholder

ABSTRACT: A new class of chiral oxidants is developed. These readily accessible oxidants contain a nitro group for oxidation and a chiral sulfonamide moiety for stereo-selectivity control. The chiral information from the oxidants can effectively transfer to the substrates in carbene-catalyzed β -hydroxylation of enals via single-electron-transfer radical processes. We expect these oxidants to find unique applications in other asymmetric oxidations and oxygen-atom-transferring reactions.

Asymmetric oxidation can be realized via the use of chiral catalysts with achiral oxidants¹. Alternatively, the chiral induction can also be achieved by using chiral oxidants². The later approach may provide better solutions in certain cases, for example, when the chiral catalysts are less available or chiral inductions from catalysts are unsatisfactory. Several major classes of chiral oxidants have been proven to be powerful and efficient in asymmetric reactions, including chiral oxaziridines³, chiral hypervalent iodines⁴, chiral hydroperoxides⁵ and chiral dioxiranes⁶. In *N*-heterocyclic carbene (abbreviated as NHC or carbene) organic catalysis⁷, oxidation has become a key step in a large number of transformations. A main type of oxidant is quinone, first introduced by Studer⁸ (Figure 1b). Other oxidants include O₂⁹, activated MnO₂¹⁰, TEMPO¹¹, phenazine¹², riboflavin¹³, aromatic nitro and nitroso derivatives¹⁴. We have found nitroalkenes¹⁵ and polyhalides¹⁶ could behave as effective oxidants for the oxidation of aldehydes under NHC catalysis. Recently, Rovis^{17a} and our laboratory^{17b} independently reported the use of nitroarene molecules as oxidants for β -hydroxylation of enals via NHC-catalyzed radical reactions¹⁸. In all these oxidative reactions mediated by NHCs, the oxidants are achiral molecules. Here we report a new class of chiral oxidants containing a nitro group for oxidation and a chiral sulfonamide for stereo-selectivity control (Figure 1c). These oxidants are easily prepared in large quantities with diverse structures by coupling commercially available nitrobenzenesulfonyl chloride with chiral amines. With these chiral oxidants, highly enantioselective β -hydroxylation of enals are realized by using a simple achiral NHC as the catalyst (Figure 1d). Analysis on the fate of the oxidants and relative control experiments explained the main side reaction of the enals, providing

mechanistic insights to these radical reactions. Chiral oxidants that enable SET radical reactions with excellent chiral inductions are of limited studies. In addition to NHC catalysis, we expect this class of chiral oxidants to find unique applications in other asymmetric oxidative transformations.

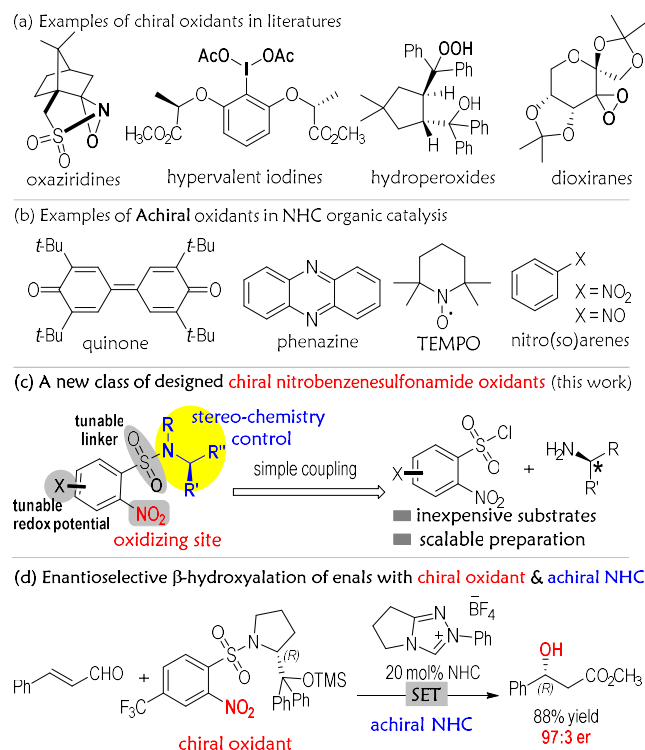
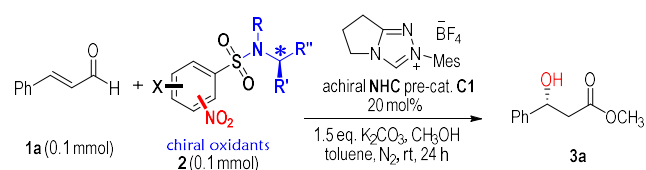


Figure 1: Designed chiral oxidants for asymmetric radical reactions

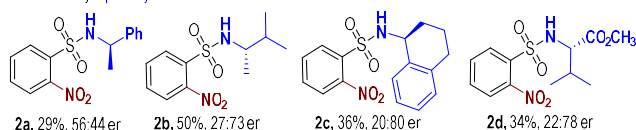
We first chose the β -hydroxylation of cinnamaldehyde (**1a**) under the catalysis of achiral triazolium NHC pre-catalyst **C1**^{19a} at

room temperature as a model reaction to search for suitable oxidants with good chiral inductions (Table 1). To our delights, nearly all nitrobenzenesulfonamides prepared from chiral amines provided product **3a** with obvious enantiomeric excess. Results from a selected set of chiral oxidants are presented in Table 1. We started with benzenesulfonamides with NO₂ as an *ortho*-substituent to study the effect of the chiral amine moieties of the oxidants. The use of oxidant bearing (*R*)-1-phenylethylamine (**2a**) gave the enal β -hydroxylation product **3a** with a low while encouraging er value (56:44 er). Replacing the phenyl unit of the amine in **2a** with an isopropyl substituent (oxidant **2b**) led to **3a** with significantly improved er (27:73 er). A limited survey indicated that further changing the steric bulkiness of primary amines could lead to better chiral inductions (e.g., oxidant **2c**). Simple amino acid-derived oxidants (e.g., **2d**) could also induce moderate to good enantioselectivities. Pyrrolidine-based chiral secondary amines (proline derivatives) as part of the oxidants were then examined (**2e-2h**). Oxidant bearing a diphenylprolinol trimethylsilyl ether unit (**2g**) stranded out from this screened and gave **3a** with 45% yield and 91:9 er. The relative

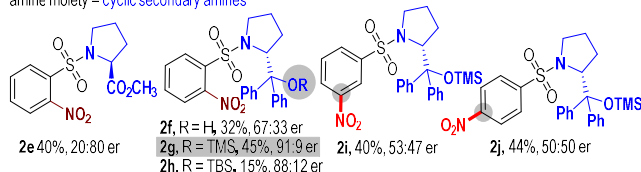
Table 1. Search for Chiral Oxidants^a



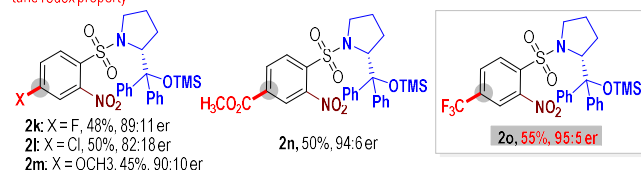
amine moiety = primary amines



amine moiety = cyclic secondary amines



tune redox property



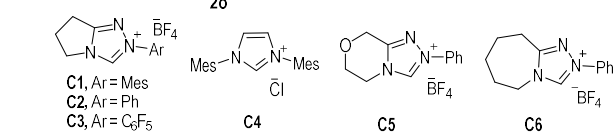
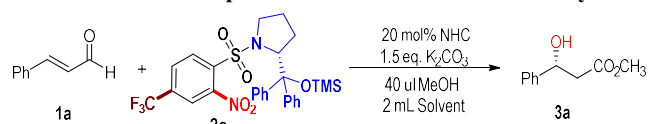
^aAll reactions were carried out in a glove box under N₂ (see SI). Reactions were carried out at room temperature using **1a** (0.1 mmol), **2** (0.1 mmol), **C1** (20 mol %), K₂CO₃ (150 mol %), 40 μ l MeOH and 2 mL of Toluene, for 24 hours. Yields were determined by ¹H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. Enantiomeric ratios were determined via HPLC analysis on a chiral stationary phase; the absolute configuration was determined by comparing the optical rotation of **3a** with literature values.

regio-position of NO₂ and the chiral sulfonamide moiety in the oxidants is critical for chiral induction. Placing NO₂ at the meta- or para-position led to nearly complete loss of reaction enantioselectivities (**2i** and **2j**). Last we introduced a third substituent to the benzene core of the oxidant to tune the redox property of the NO₂ and to modulate the steric effects for better yields and enantioselectivities (**2k-2o**). The installation of an electron-withdrawing CF₃

unit at the para-position (relative to the amide) of the benzene core led to **3a** with 55% yield and 95:5 er (oxidant **2o**).

We then chose oxidant **2o** for further reaction optimizations to identify suitable achiral NHC catalysts and conditions (Table 2). Using toluene as solvent, K₂CO₃ as base, we examined achiral NHC pre-catalysts **C1-C6** for reactions at room temperature. *N*-phenyl substituted achiral triazolium NHC pre-catalyst **C2**^{19b} is more efficient than *N*-mesyl substituted catalyst **C1** and *N*-C₆F₅ substituted catalyst **C3**^{19c}. With **C2** as catalyst, **3a** was formed in 63% yield and 94:6 er (entry 3). Imidazolium salt **C4** could also promote this oxidation reaction, albeit with a slightly lower yield and er (entry 4). A few other *N*-Ph substituted achiral triazolium NHC pre-catalysts (e.g., **C5** and **C6**) were also examined, but did not give better results than **C2** (entries 5 and 6). We then chose **C2** as the NHC pre-catalyst to study the effects of solvents (entries 8-10) and found that Et₂O performed better than toluene, leading to **3a** with an improved 70% yield and similar er (entry 10). Decreasing the reaction temperature from rt to -10 °C led to a small increase on er value (entry 11). We finally found that changing the loading of **1a** and **2o** from 1:1 (molar ratio) to 1.5:1 could lead to **3a** in 88% isolated yield and 97:3 er at -10 °C (entry 12).

Table 2. Condition Optimization on Achiral NHC Catalysts^a

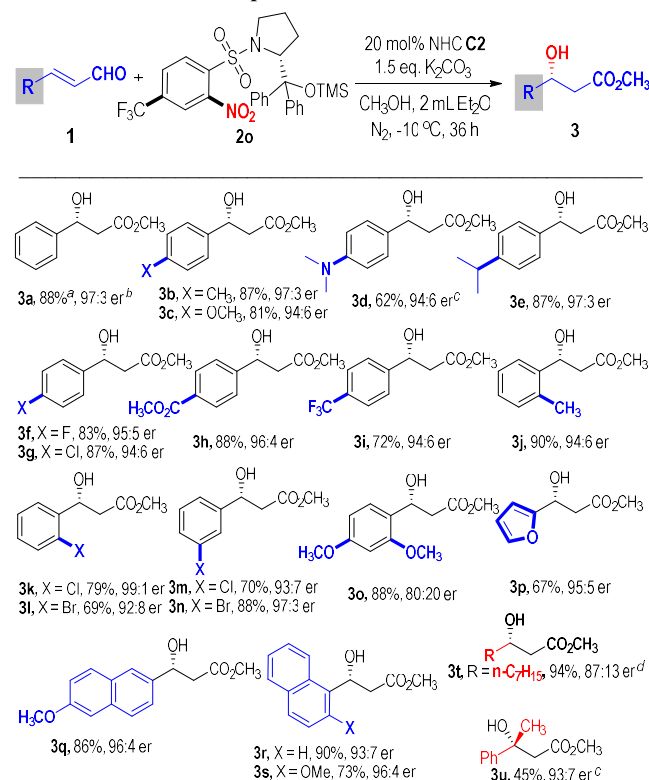


entry	NHC	solvent	yield (%) ^b	er ^c
1	--	Toluene	n.r.	--
2	C1	Toluene	55	95:5
3	C2	Toluene	63	94:6
4	C3	Toluene	30	92:8
5	C4	Toluene	48	81:19
6	C5	Toluene	60	94:6
7	C6	Toluene	43	81:19
8	C2	CH ₂ Cl ₂	38	69:31
9	C2	THF	52	90:10
10	C2	Et ₂ O	70	95:5
11 ^d	C2	Et ₂ O	67	97:3
12 ^e	C2	Et ₂ O	91 (88)	97:3
13 ^f	C2	Et ₂ O	77	96:4

^aAll reactions were carried out in a glove box under N₂ (see SI). Reactions were carried out at room temperature using **1a** (0.1 mmol), **2o** (0.1 mmol), NHC (20 mol %), K₂CO₃ (150 mol %), 40 μ l MeOH and 2 mL of solvent, for 24 hours. ^bEstimated via ¹H NMR analysis of crude reaction mixture with 1,3,5-trimethoxybenzene as an internal standard. Isolated yield in parentheses based on **2o**. ^cEnantiomeric ratio determined via HPLC analysis on a chiral stationary phase. ^dAt -10 °C for 36 hrs. ^e0.15 mmol **1a** was used, at -10 °C for 36 hrs. **2 mmol 1a & 2o** was used, gram-scale reaction. Isolated yield.

With an optimized condition in hand (Table 1, entry 12), we next examined the generality of this oxidative process for the β -hydroxylation of different enals (Table 3). Placing substituents with different stereo electronic properties to para-carbon of the β -phenyl enals was well tolerated, leading to the corresponding hydroxylation products with good yields and around 95:5 er values (**3a-3i**). Substituents at ortho- (**3j-3l**) or meta-position (**3m, 3n**) of the enal β -phenyl units led to slight increases on enantioselectivities. Furan and naphthalene substituted enals reacted effectively as well to give the corresponding β -hydroxylation products with excellent yields and er values (**3p-3s**). Enals with β -alkyl substituents reacted nicely as well to give products **3t** with excellent yields and 87:13 er. An enal with two substituents at the β -carbon was also tolerated, giving desired product in moderate yield and 92:8 er (**3u**).

Table 3. Substrates Scope of Enals^a



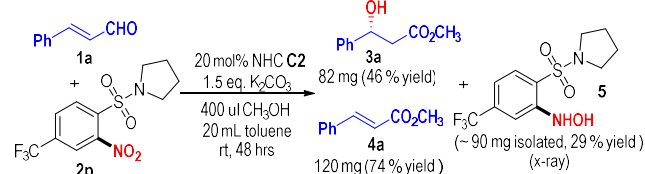
^aIsolated yield based on **2o**. ^bEnantiomeric ratio determined via HPLC analysis on a chiral stationary phase. ^c0.15 mmol **1** was used, at room temperature for 36 hrs. ^dDetermined via HPLC analysis on chiral stationary phase after derivatization (see SI).

We next performed several experiments to understand the fate of the oxidants by using a simplified achiral oxidant **2p** as a model (Scheme 1). In addition to the desired enal β -hydroxylation product **3a** (obtained in 82 mg, 46 % isolated yield based on **2p**), two major side products were isolated with structures confirmed (Scheme 1a). One side product was α,β -unsaturated ester **4a** derived from enal **1a**. This ester was isolated in about 120 mg (74 % yield relative to oxidant **2p**). Another major by-product was a hydroxyl amine (**5**) that was obtained in about 90 mg (29 % yield relative to **2p**) with structure confirmed by single crystal X-ray analysis. This observation, together with previous studies from Rovis and our own laboratory¹⁷, suggests a reaction pathway proposed in Scheme 2b. Under

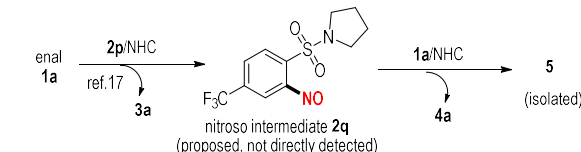
the catalysis of NHC, SET oxidation¹⁸ of enal by oxidant **2p** generate product **3a**. During this step, the nitroarene oxidant was reduced to a nitroso intermediate (**2q**)¹⁷. The nitroso intermediate (**2q**) then behaved as an oxidant^{17a} to convert enal **1a** to the corresponding α,β -unsaturated ester (**4a**) with the formation of hydroxylamine **5**. To support the postulated pathway (oxidation of **1a** to **4a** by **2q**), we synthesized the nitroso compound **2q** and subjected it to the reaction of enal under NHC catalysis (Scheme 3c). Our experiments showed that with nitroso **2q** as the oxidant, enal **1a** was converted to the unsaturated ester with 71% yield. The β -hydroxylation product (**3a**) was not observed. Our experimental observation is different from Rovis's earlier proposal (See article's SI)^{17a}, in which they proposed that nitroso compound could oxidize enal to the β -hydroxylation product. In our redox process, nitroso **2q** was converted to hydroxyl amine **5** and multiple unidentified complexes. These unidentified complexes likely initiate from reactions involving hydroxyl amine **5** and the nitroso compound **2q**²⁰. As a technical note, similar reactions using chiral oxidant such as **2o** gave complicated mixtures that were challenging to analyze in part due to the instability of the TMS ether in the oxidant.

Scheme 1. Experiments for understanding reaction pathways

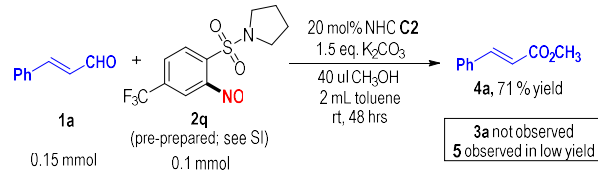
(a) Distribution of desired product (**3a**) and main side products (**4a** and **5**)



(b) Proposed key pathway for the formation of **5** from reduction of oxidant **2p**



(c) Experimental verification for the oxidation of **1a** to **4a** by nitroso compound **2q**



In summary, we have developed a new class of nitroarenes-based chiral oxidants for achiral NHC-catalyzed enantioselective transferring of oxygen atoms to enals via SET radical processes. These oxidants can be readily prepared with diverse structures in large quantities by coupling commercially available and inexpensive nitrobenzenesulfonyl chloride and chiral amines. Further exploration in using these new chiral oxidants for other asymmetric oxidation reactions beyond NHC catalysis is in progress in our laboratory. We are also developing effective methods for regenerating the oxidants in situ (by terminal oxidants such as oxygen) and thus the oxidants can be used in catalytic amounts.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for all new compounds. 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 interests.

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