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Synthesis of α-Peroxyesters via Organocatalyzed O−H Insertion of Hydroperoxides and Aryl Diazoesters

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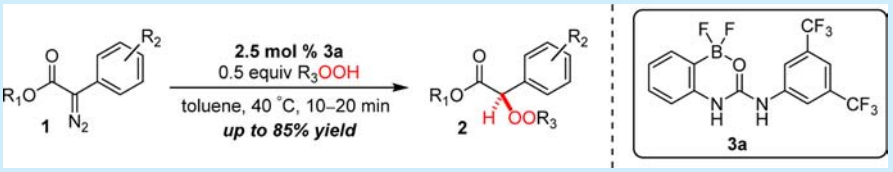
Supporting Information



ABSTRACT: The synthesis of α-aryl peroxyesters, an unprecedented class of organic peroxide, via hydrogen-bond donor catalyzed O−H insertions of hydroperoxides and α-aryl diazoesters is reported. The method is applicable to a diverse set of substrates and the corresponding α-peroxyesters are typically isolated in high yield. Both thermogravimetric analysis and reactions with traditional peroxide reducing agents demonstrate the stability of α-peroxyesters.

Peroxide-containing organic molecules are ubiquitous among a plethora of bioactive natural products[1] and other biologically relevant species (Figure 1).[2] Naturally occurring and synthetic peroxides are used as, or are being investigated for, treatments against several diseases such as malaria[3] and various cancers.[4] While several methods for the installation of the peroxide functional group do exist,[5] many of these methods are limited in substrate scope or reactivity pattern.[6] Given the potential of organic peroxides as bioactive compounds, new methods for their synthesis are necessary to exploit their prospective utility fully. One class of unexplored peroxides is α-aryl α-peroxyesters. While some examples of α-hydroperoxyamides have been reported as intermediates in, for example, the oxidation of chiral amide enolates with $^3O_2$, these compounds were reported to be unstable to chromatography and readily decomposed, thereby providing access to only the reduced (alcohol) product.[7] Still others have invoked peroxidic intermediates in radical oxidations of α-iodocarbonyls.[8] A substructure search[9] reveals few reports of compounds bearing a peroxide functional group at the α-position of an α-arylester, such as **2**.[10] This finding inspired us to pursue the synthesis of this class of peroxide.

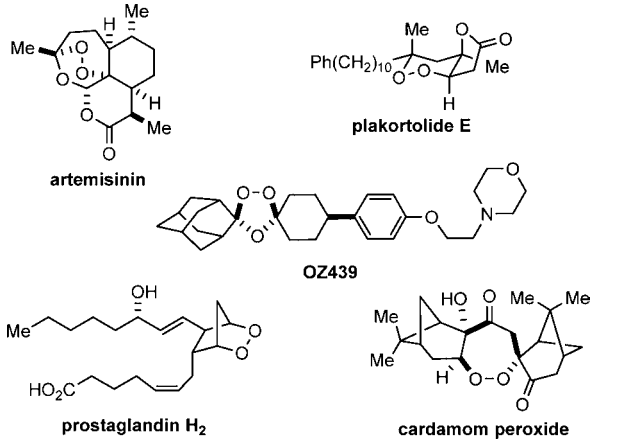


Figure 1. Biologically important peroxides.

Organocatalytic methods that offer analogous or orthogonal reactivity patterns to transition-metal-catalyzed processes are currently of great interest to the synthetic community. One important approach involves developing these processes via enhanced hydrogen-bond-donor (HBD) organocatalysis.[11] Recently, we have published the HBD-catalyzed S−H and O−H insertion of thiols and carboxylic acids with aryl diazoesters,[12] taking advantage of our enhanced HBD catalyst **3a**. As part of our ongoing investigation into organocatalytic reactions with diazo compounds, we questioned whether hydroperoxides could be competent insertion partners given their similar nucleophilicity and acidity to thiols. To our knowledge, with one exception,[13] hydroperoxides have not been shown to undergo either thermal or transition metal-catalyzed O−H insertions with diazo compounds. The latter is potentially precluded given the known reactivity of hydroperoxides with transition metals typically utilized (i.e., Cu(I), Cu(II), and Rh(II)) for X−H insertion reactions.[14] Herein, we report the HBD-catalyzed O−H insertion of hydroperoxides with aryl diazoesters.

Our investigations began with the reaction of aryl-diazoester **1a** and *tert*-butyl hydroperoxide (TBHP) in the presence of 10 mol % of catalyst **3a** (Table 1). We initially screened several common solvents and found toluene to be the optimal solvent, providing 33% of the desired product at a concentration of 0.5

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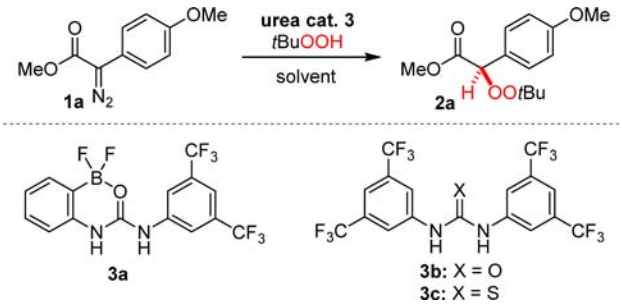
Table 1. Optimization of O−H Insertion Reaction



entry[a]	3 (mol %)[b]	solvent	temp (°C)	TBHP (equiv)	time	yield[c] (%)	
1	**3a** (10)	Et_2O	rt	1.3	4 h	20	solvent
2	**3a** (10)	MTBE	rt	1.3	5 h	21	
3	**3a** (10)	DCE	rt	1.3	10 min	17	
4	**3a** (10)	MeCN	rt	1.3	24 h	nd	
5	**3a** (10)	toluene	rt	1.3	20 min	33	
6	**3a** (5)	toluene	rt	1.3	20 min	35	catalyst loading
7	**3a** (2.5)	toluene	rt	1.3	30 min	50	
8	**3a** (0)	toluene	rt	1.3	24 h	trace	
9	**3a** (2.5)	toluene	rt	0.5	3 h	80	TBHP equiv/temp
10	**3a** (2.5)	toluene	40	0.5	10 min	83	
11	**3a** (0)	toluene	40	0.5	24 h	12	
12	**3b** (2.5)	toluene	40	0.5	24 h	trace	catalyst structure
13	**3c** (2.5)	toluene	40	0.5	6 h	76	

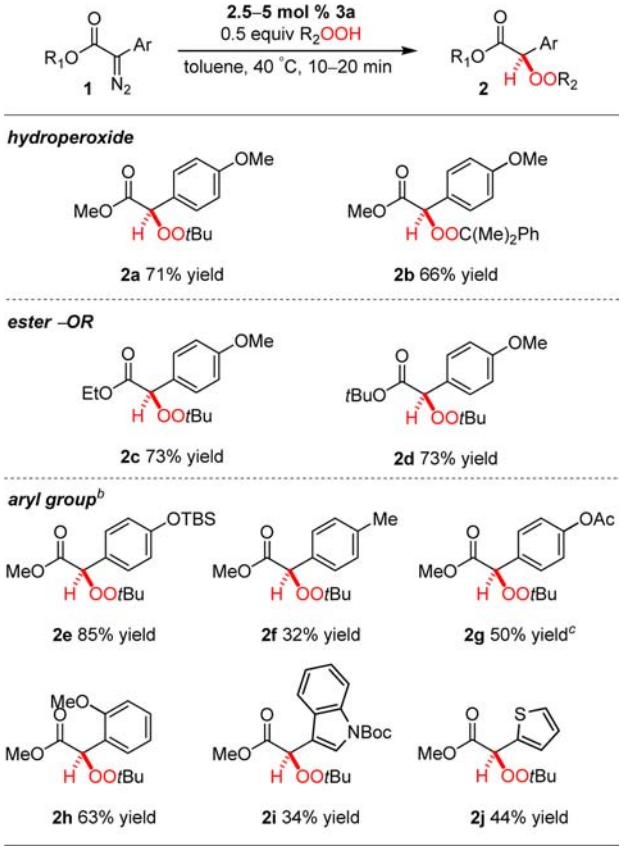
[a]Reactions performed with 0.1 mmol of **1a**. [b]Catalyst loading relative to **1a**. [c]Yields determined by ^{1}H NMR analysis and based upon limiting reagent.

M at 23 °C. Reducing the catalyst loading to 5 and 2.5 mol % provided 35% and 50% of the desired product, respectively, albeit with a concurrent increase in reaction time. A key discovery was the requirement for excess diazo compound in the reaction to obtain optimal yields of product. When 0.5 equiv of TBHP was used, an increase in yield from 50% to 80% was observed (entry 9).[15] At this point, we found that increasing the temperature to 40 °C provided the same yield but with much shorter reaction times (10 min vs 3 h, entry 10). Under our optimized conditions, no product formation was detected when catalyst was omitted from the reaction;[16] after 24 h, only 12% of product could be observed (entry 11). Other urea catalysts (**3b** and **3c**) provided lower yields with longer reaction times, or failed to react (entries 12 and 13).

With optimized conditions in hand, we set out to explore the scope of the newly discovered reaction. Peroxide **2a** was formed in 71% isolated yield under the standard conditions. In addition to TBHP, cumene hydroperoxide efficiently undergoes the insertion reaction (**2b**). Changing the OR linkage of the ester had little effect; ethyl or *tert*-butyl esters were both well tolerated (**2c** and **2d**). However, the optimized conditions provided lower yields than desired for aryl-diazoesters bearing a less activating (i.e., electron donating, vide infra) group at the 4-position of the aryl ring, and increasing the catalyst loading to 5 mol % was required. For example, 4-OAc- and 4-Me-substituted aryl diazoesters afforded moderate yields of the desired product (**2f** and **2g**). Substitution at the 2-position of the aryl side chain was tolerated well (**2h**). Other aryl side chains such as *N*-Boc-protected indole (**2i**) and 2-thiophene (**2j**) also underwent the O−H insertion reaction. Highly deactivated substrates (e.g., Ar = 4-$CF_3C_6H_4$) failed to provide the desired product even at elevated temperatures and with prolonged reaction times.

To alleviate concerns surrounding the potential instability of the products, the stability of this new class of peroxide was

Scheme 1. Substrate Scope of O−H Insertions[a]



[a]Isolated yields based upon hydroperoxide. [b]Five mol % **3a**. [c]Determined by ^{1}H NMR analysis.

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investigated using thermogravimetric analysis (TGA) as well as by interrogation with a variety of chemical agents known to destroy dialkyl peroxides. TGA revealed that peroxide **2a** undergoes slow decomposition at temperatures between approximately 90−160 °C (Figure 2).[17] Reaction of **2a** with

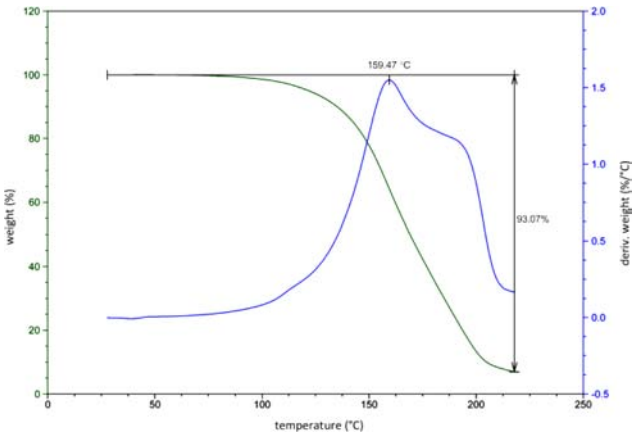
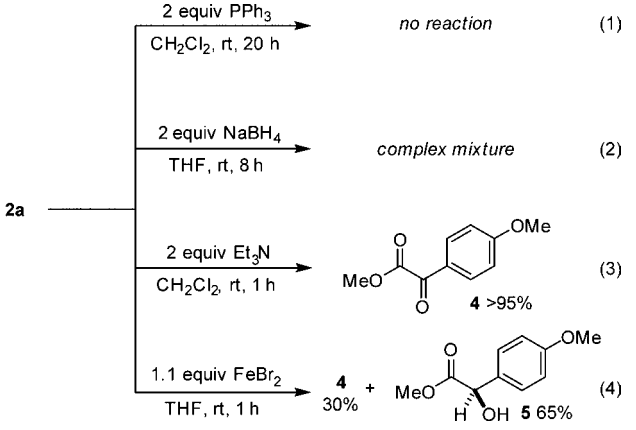


Figure 2. TGA analysis of peroxide **2a**.

various reducing agents also reveals the stability of the peroxides.[18] PPh_3 failed to reduce the peroxide bond at rt, while heating for 20 h at 60 °C in THF converted 50% of the starting material to α-ketoester **4**; reaction with $NaBH_4$ gave rise to a complex mixture of products, requiring 8 h to consume the starting material (Scheme 2, eqs 1 and 2). Reaction with Et_3N cleanly afforded **4** in quantitative yield whereas O−O scission with Fe(II) provided a mixture of **4** and alcohol **5** (Scheme 2, eqs 3 and 4).[19]

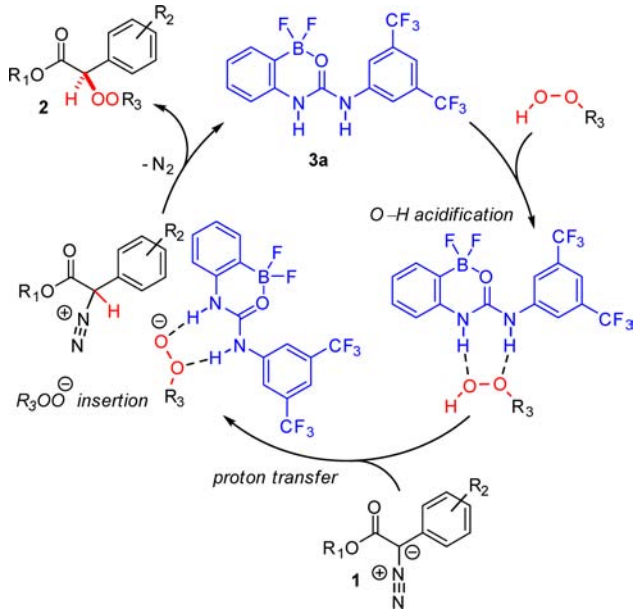
Scheme 2. Reduction of the O−O Bond



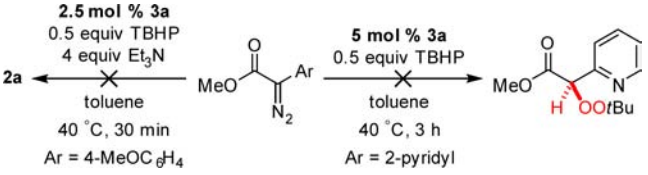
Drawing upon observations from related work,[12] a possible catalytic cycle is shown in Scheme 3. Initial complexation and acidification of the hydroperoxide with **3a** is followed by deprotonation of the hydroperoxide by aryl diazoester **1**. Insertion of the peroxy anion via either an S_N1- or S_N2-like attack affords the product and N_2 gas while releasing the catalyst. Interestingly, recent computational work has shown a remarkable increase in acidity of X−H protons upon interaction with hydrogen-bond-donor organocatalysts.[20]

In support of the above mechanism, an aryl diazoester bearing a basic side chain (2-pyridyl) was subjected to the reaction conditions (Scheme 4). No product was formed, and

Scheme 3. Possible Catalytic Cycle for O−H Insertion



Scheme 4. Reaction of 2-Pyridyl Diazoester



quantitative recovery of the starting material was observed by ^1H NMR spectroscopic analysis. Furthermore, a second experiment found that **2a** was not observed when Et_3N was added to the standard conditions. No product was formed, and the starting material was recovered quantitatively. These findings are in alignment with the proposed deprotonation of the acidified hydroperoxide by the aryl diazoester. They are also consistent with the observation that less electron rich (i.e., less basic) aryl diazoesters are outperformed by their more electron rich counterparts in terms of overall yield of the desired product.

To conclude, a new class of peroxide has been synthesized via a novel organocatalytic O−H insertion of hydroperoxides with aryl diazoesters.[21] The products are stable under typical storage and handling conditions and pave the way for continued exploration of other natural and synthetic frameworks and their bioactivity analysis.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectra, and characterization 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 interest.

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(15) All catalyst loadings are relative to the starting diazo compound. Yields are determined based upon the limiting reagent.
(16) NMR analysis of the unpurified reaction mixture indicated quantitative recovery of starting material.
(17) For representative examples of TGA analysis of organic peroxides, see: (a) Krabbe, S. W.; Do, D. T.; Johnson, J. S. *Org. Lett.* **2012**, *14*, 5932−5935. (b) Kyassa, S.−K.; Puffer, B. W.; Dussault, P. H. *J. Org. Chem.* **2013**, *78*, 3452−3456.
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(21) ***Safety note***: While no problems were encountered surrounding the stability of the peroxides or diazo compounds throughout the course of this work, as always, proper attention must be paid to the potential for rapid, exothermic decompositions of organic peroxides or diazo compounds. For references pertaining to safe handling of peroxides, see: (a) Medard, L. A. *Accidental Explosions: Types of Explosive Substances*; Ellis Horwood Limited: Chichester, 1989; Vol. *2*;. (b) Zabicky, J. In *The Chemistry of the Peroxide Group*; Rappoport, Z., Ed.; John Wiley & Sons: Chichester, 2006; Vol. 2, Part 2, pp 597−773. (c) Patnaik, P. A. *Comprehensive Guide to the Hazardous Properties of Chemical Substances*, 3rd ed.; John Wiley & Sons: Hoboken, NJ, 2007.