

Synthesis and Asymmetric Resolution
of α -Azido-peroxides

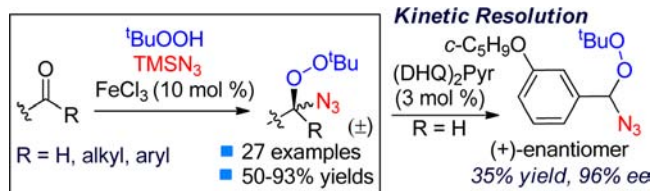
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ABSTRACT



An unprecedented synthesis of α -azido-peroxides has been developed using an FeCl_3 -catalyst starting from carbonyl, TMS-azide, and hydroperoxide. Further, a base promoted decomposition of synthesized secondary α -azido-peroxides to provide the corresponding *tert*-butyl esters has been disclosed. Finally, an asymmetric kinetic resolution of such α -azido-peroxides has also been developed to provide chiral α -azido-peroxides in excellent enantiopurity.

The design and synthesis of structurally distinct classes of organic peroxides have always been the center of attention because of their increasing importance in pharmaceutical, industrial, and laboratory syntheses.¹ For example, several synthetic peroxides have been successfully developed as active antimalarials inspired by the natural therapeutic drug candidate artemisinin.^{2–6} Many of them are

currently in phase III trials.⁷ In addition, such molecules display promising activity against tumor cells⁸ and viruses such as HIV⁹ and hepatitis B.¹⁰

An α -heteroatom-substituted peroxide pharmacophore is one of the salient structural features shared by most of these biologically active peroxides.¹¹ Unfortunately, relatively less attention has been paid to α -“N”-peroxy moieties, because of their limited availability and accessibility.^{11,12,14} Nevertheless, such moieties are present in active antimalarials,¹² including many natural products such as verruculogen^{13a} or dioxetanone^{13b} (Figure 1). Therefore, the expansion of the structural diversity of the

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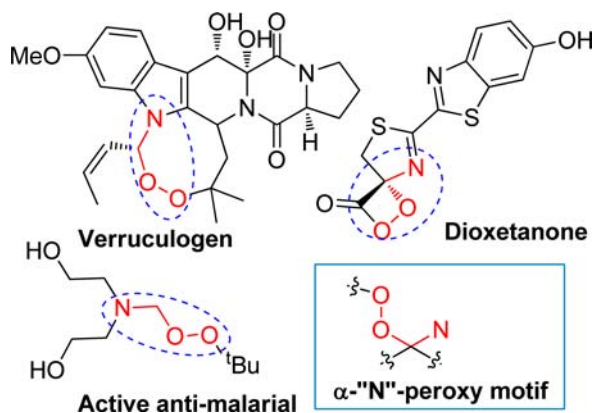


Figure 1. Natural products and biologically active molecules containing α -nitrogen substituted peroxides.

α -“N”-peroxy moiety might help to extend their plausible therapeutic utility.

The versatility of the azide functional group is manifested in key areas of chemistry (organic and bioorganic).¹⁶ One such application is their role as photoaffinity labeling reagents for biomolecules.¹⁷ It is also an essential “click” partner for the synthesis of a broad range of nitrogen containing heterocycles (for example tetrazoles and triazoles).¹⁸ Azides are useful precursors for the corresponding primary amines, nitrenes, and isocyanates.

Encouraged by the importance of peroxide and azide moieties, we became interested in synthesizing molecules containing both groups. We envisioned the synthesis of α -azido-peroxides, which was inspired by the above biological significance of α -heteroatom-substituted peroxide pharmacophore. Here, we have developed their one-pot, chemoselective synthetic protocol using a carbonyl substrate

Table 1. Catalyst Screening

entry	catalyst	TMS-N ₃ (equiv)	2a (%) ^a	2a:3 ^a
1	Sc(OTf) ₃	2.5	82	87:13
2	InCl ₃	2.5	72	84:16
3	AgOTf	2.5	89	87:13
4	AuCl ₃	2.5	74	83:17
5	Cu(ClO ₄) ₂ ·6H ₂ O	2.5	56	85:15
6	Bi(OTf) ₃	2.5	82	85:15
7	FeCl₃	2.5	100 (93)^b	96:4
8	Fe(acac) ₃	2.5	0	—
7	FeCl ₃	2.0	84	70:30
8	FeCl ₃	3	95	96:4

^aThe conversion and ratio were determined by ¹H NMR data of reaction mixture. ^bIn parentheses, isolated yield after 1 h reaction time.

(aldehyde and ketone), ^tBuOOH, and TMS-N₃ mediated by a simple iron(III) catalyst.

Moreover, we also have initiated the asymmetric kinetic decomposition of the synthesized α -azido-peroxides containing an α -hydrogen using a catalytic chiral base. This provided the highly enantioenriched α -azido-peroxides. Nevertheless, to date the asymmetric synthesis of peroxides is a challenging goal.^{14a,15} The only report for the synthesis of chiral α -“N”-peroxides has been by Antilla and co-workers.^{14a}

The initial screening of the catalyst started with various metal salts (10 mol %) such as InCl₃, AgOTf, Sc(OTf)₃, Bi(OTf)₃, FeCl₃, AuCl₃, and Cu(II) for the reaction of benzaldehyde (**1a**), TMS-N₃, and ^tBuOOH, which is summarized in Table 1. Although many of those catalysts worked smoothly, the chemoselectivity of α -azidoperoxide (**2a**) over 1,1-diperoxide (**3**) was found to be superior with FeCl₃ (entry 7). Also, the economical availability, non-toxicity, and mildness provided additional benefits.¹⁹

Next, the general applicability of this method was demonstrated by changing the aryl counterpart. Gratifyingly, aromatic aldehydes with a broad substitution pattern and of a different electronic nature were tolerated and provided the corresponding α -azido-peroxides (**2a–p**, Table 2) in good to excellent yields (entries 1 to 16). As expected, it was observed that the reactions with arenes, having strong electron-donating substituents (entries 6–12), resulted in compromised yields of the desired product. In general,

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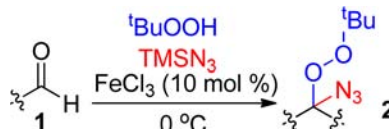
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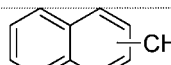
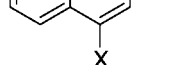
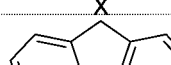
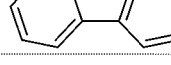
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Table 2. Synthesis of α -Azido-peroxides from Aldehydes^a


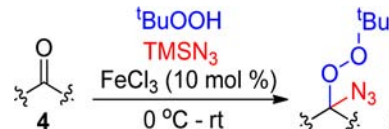
entry	aldehyde, 1	t/h	2 , [%] ^b
1	Ph (1a)	1	2a , 93/91 ^c
2	4-Me-C ₆ H ₄ CHO (1b)	1	2b , 87
3	4-Cl-C ₆ H ₄ CHO (1c)	1	2c , 89
4	2-F-C ₆ H ₄ CHO (1d)	0.5	2d , 55
5	3-F ₃ C-C ₆ H ₄ CHO (1e)	1.5 ^d	2e , 90
6	4-MeO-C ₆ H ₄ CHO (1f)	3	2f , 58
7	2-MeO-C ₆ H ₄ CHO (1g)	2	2g , 55
8	4-BnO-C ₆ H ₄ CHO (1h)	1	2h , 52
9	3-BnO-C ₆ H ₄ CHO (1i)	1.5 ^d	2i , 76
10	4- ^t Bu-2-MeO-C ₆ H ₄ CHO (1j)	2 ^d	2j , 62
11	2,4,6-tri-Me-C ₆ H ₂ CHO (1k)	1	2k , 52
12	3-Cyclopentyl-O-C ₆ H ₄ CHO (1l)	1.5	2l , 68
13	 X = H, α -CHO (1m)	1	2m , 88
14	 X = Me, α -CHO (1n)	1	2n , 50
15	 X = H, β -CHO (1o)	0.5	2o , 87
16	 β - (1p)	1	2p , 61
17	PhCH ₂ CHO (1q)	2	2q , 80
18	PhCH ₂ CH ₂ CHO (1r)	1	2r , 89
19	Me(CH ₂) ₅ CHO (1s)	1	2s , 85
20	ⁱ PrCH ₂ CHO (1t)	2	2t , 93
21	Cyclohexyl-CHO (1u)	2	2u , 84

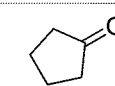
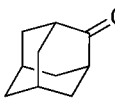
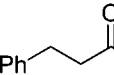
^a Reaction conditions: aldehyde (1.0 mmol), TMS-N₃ (2.5 mmol), ^tBuOOH (1.0 mmol), FeCl₃ (0.1 mmol, 10 mol %) in dry CH₂Cl₂.
^b Isolated yield. ^c Performed in 20 mmol scale (see Supporting Information). ^d The reaction was carried out at -15 °C.

such electron-rich aromatic peroxides are quite sensitive because of the competing Baeyer–Villiger rearrangement. Eventually, we extended the current methodology toward various aliphatic aldehydes. And encouragingly, such substrates provided the corresponding azido-peroxides (**2q–u**, Table 2) in excellent yields (80 to 90%) (entries 17–21).

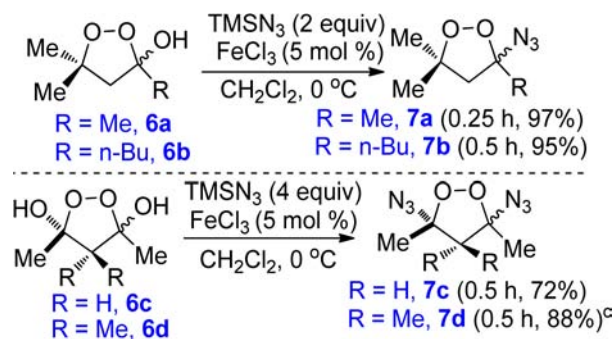
Next, we were prompted to explore the chemical reactivity of ketones. Various cyclic ketones (**4a–e**, Table 3) were examined under standard conditions. Significantly, the corresponding α -azido-peroxides (**5a–e**) were obtained in high to excellent yields (entries 1–5). Even, the acyclic ketone (**4f**) provided the corresponding desired product (**5f**) (entry 6).

Further, structurally challenging endoperoxy-acetals (**6a–b**) were also treated with TMS-N₃ under FeCl₃-catalyzed reaction conditions (Scheme 1). An excellent chemoselective formation of the desired endoperoxy-azides

Table 3. Synthesis of α -Azido-peroxides from Ketones^a


entry	ketone, 4	t/h	5 , [%], ^b (<i>dr</i>) ^c
1	X = H (4a)	0.3	5a , 90
2	X = Ph (4b)	0.25	5b , 85 (1:1)
3	X = ^t Bu (4c)	0.5	5c , 84 (1:1.6)
4	 (4d)	0.25	5d , 60
5	 (4e)	12	5e , 77
6	 (4f)	6	5f , 51

^a Reaction conditions: ketone **4** (1.0 mmol), TMS-N₃ (2.5 mmol), ^tBuOOH (1.0 mmol), FeCl₃ (0.1 mmol, 10 mol %) in dry CH₂Cl₂ for 30 min at 0 °C then at rt above given time. ^b Isolated yield. ^c Diastereomeric ratio (*dr*) based on ¹H NMR of reaction mixture.

Scheme 1. Synthesis of α -Azido-endoperoxides^{a,b}

^a Reaction conditions: **6** (1.0 mmol), TMS-N₃ (2.0 mmol for monoacetal and 4.0 mmol for diacetal), FeCl₃ (0.05 mmol, 5 mol %) in CH₂Cl₂. ^b Isolated yield. ^c The reaction was carried out at rt.

(**7a–b**) were observed. Moreover, endoperoxy-1,3-diacetals (**6c–d**) were also tested and provided the corresponding 1,3-diazo endoperoxides (**7c–d**).

Differential scanning calorimetry/thermal gravimetric analysis (DSC/TGA) were demonstrated for selected compounds. The synthesized azido-peroxides (**2p** and **5b**) undergo exothermic decomposition, but only upon heating to above 155 and 140 °C, respectively.²⁰

Control experiments were performed to understand the probable mechanism of the current process (Scheme 2). This clearly indicates that the reaction proceeds through

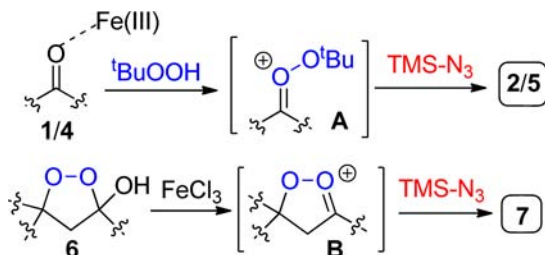
(20) For spectra, see the Supporting Information.

Scheme 2. Control Experiments^{a,b}

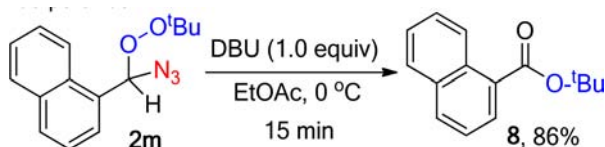


^a Reaction conditions: **2a** or **3** (0.5 mmol), FeCl_3 (10 mol %) in CH_2Cl_2 . ^b Isolated yield after column chromatography.

Scheme 3. Proposed Mechanism



Scheme 4. Base Promoted Decomposition of Secondary α -Azido-peroxide



the formation of a *peroxy-carbenium ion intermediate* (**A** or **B**), followed by nucleophilic addition of the azide (Scheme 3).

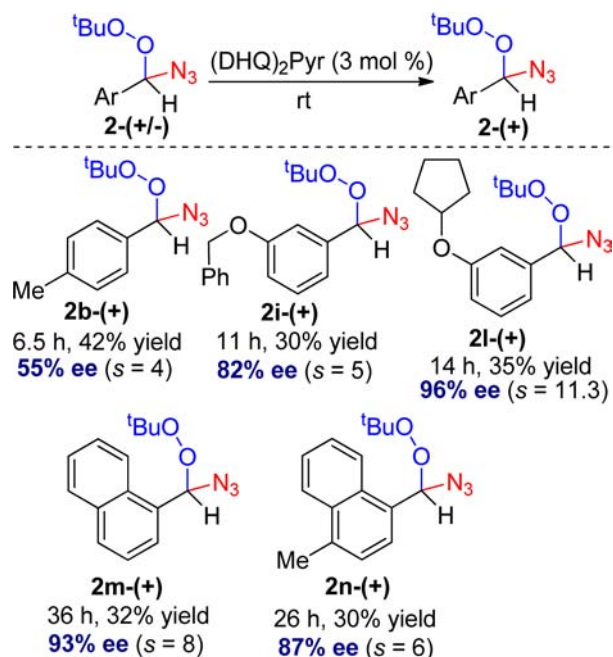
To explore the synthetic utility and reactivity pattern of such synthesized molecules, we treated these secondary α -azido-peroxides (**2m**) with DBU as the base, as inspired by the Kornblum–DeLaMare rearrangement²¹ (Scheme 4). However, we observed an unusual “*tert*- BuO^- ” transfer to provide the corresponding *tert*-butyl esters **8** in good yields. It is noteworthy to mention that methods for the synthesis of such tertiary esters are very limited.²²

Encouraged by this result, we turned our attention for the development of the corresponding asymmetric variants. Various secondary α -azido-peroxides (**2b**, **2i**, **2l**, **2m**, and **2n**) underwent a facile enantioselective asymmetric decomposition in the presence of 3 mol % of $(\text{DHQ})_2\text{Pyr}$, thus giving access to the corresponding chiral α -azido-peroxides

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Scheme 5. Chiral Base Catalyzed Kinetic Resolution: Synthesis of Chiral α -Azido-peroxides^{a–d}



^a Reaction conditions: **2** (0.35 mmol), $(\text{DHQ})_2\text{Pyr}$ (3.0 mol %), 0.0105 mmol) in EtOAc . ^b Isolated yield after column chromatography.

^c Enantiomeric excess (% ee) values were determined by chiral HPLC analysis. ^d The selectivity factor (s) was calculated from the determined yield and ee (see Supporting Information).

[**2b**(+), **2i**(+), **2l**(+), **2m**(+), and **2n**(+), respectively] with good to excellent enantiopurities (from 55% to 96% ee) (Scheme 5).

In conclusion, a simple chemoselective methodology for the synthesis of α -azido-peroxides, a new class of organic peroxides, has been developed *via* a one-pot, three-component reaction of carbonyl, peroxide, and TMS-N_3 using an iron(III) catalyst. Further, asymmetric kinetic resolution of the synthesized secondary α -azido-peroxides provided a single enantiomer with high enantiopurity. Further studies on the application of such a class of compounds and an understanding of the detailed reaction mechanism for such base promoted decomposition are under active consideration in our group.

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Supporting Information Available. Experimental procedures, characterization data, and copies of spectra for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.