ChemPubSoc Europe

DOI: 10.1002/ejoc.201800092

EurJOC European Journal of Organic Chemistry

Full Paper

Photoactivatable Nitroxyl Donors

# Development of Photoactivatable Nitroxyl (HNO) Donors Incorporating the (3-Hydroxy-2-naphthalenyl)methyl Phototrigger

Yang Zhou,[a] Ruth B. Cink,[b] Zachary A. Fejedelem,[a] M. Cather Simpson,[c] Alexander J. Seed,[a] Paul Sampson,*[a] and Nicola E. Brasch*[b]

**Abstract:** A new family of photoactivatable HNO donors of general structure $RSO_2NHO$-PT [where PT represents the (3-hydroxy-2-naphthalenyl)methyl (3,2-HMN) phototrigger] has been developed, which rapidly releases HNO. Photogeneration of HNO was demonstrated using the vitamin $B_{12}$ derivative aquacobalamin as a trapping agent. The amount of sulfonate $RSO_2^-$ produced was essentially the same as the amount of HNO released upon photolysis, providing a convenient method to indirectly quantify HNO release. Two competing pathways were also observed; a pathway involving O–N bond cleavage leading to release of a sulfonamide, and a pathway resulting in release of the parent *N*hydroxysulfonamide $RSO_2NHOH$ (for HNO donors with Me- and Ph-containing leaving groups only). Up to approximately 70 % of the HNO-generating pathway was observed with the $CF_3$-containing leaving group, with HNO generation favored for small percentages of aqueous buffer in the acetonitrile/pH 7.00 phosphate buffer solvent mixture. Characterization of the photoproducts obtained from steady-state irradiation by NMR spectroscopy showed that the desired HNO-generating pathway was less favored for HNO donors with Me- and Ph-containing leaving groups compared to the $CF_3$-containing leaving group, suggesting that the excellent $CF_3$-containing leaving group promotes HNO generation.

## Introduction

The development of new nitroxyl (HNO) donors has received increasing attention due to their promise for the treatment of congestive heart failure,[1] a condition that adversely affects an estimated 5.7 million people in the United States.[2] The vasodilating properties of HNO donors have been demonstrated in both normal and failing hearts,[3] and result from the ability of HNO to improve $Ca^{2+}$ handling and enhance myofilament $Ca^{2+}$ sensitivity.[4] Recent studies with HNO donors in a pre-clinical model of heart failure demonstrated that HNO greatly improves cardiovascular performance of the failing heart by enhancing the contractility and relaxation of the heart.[5]

HNO is unstable in aqueous solution, due to rapid dimerization and further dehydration to yield nitrous oxide [equation (1)].[6] Therefore, HNO-containing molecules that decompose to release HNO, also known as HNO donors, are required to generate HNO in situ for chemical and biochemical studies of HNO reactivity. Various HNO donors have been reported,[7] including Angeli's salt (AS),[8] Piloty's acid (PA) and related derivatives,[9] other *N*-substituted hydroxylamines,[10] primary amine-based diazeniumdiolates,[11] acyloxy nitroso compounds,[12] precursors of acyl nitroso species,[13] and metal nitrosyls.[14] HNO donors are widely used in biochemical and biological studies of HNO reactivity,[7c] but their utility is limited for some applications, especially for use in kinetic and mechanistic studies. For example, a mixture of HNO and NO is obtained from the decomposition of some HNO donors at neutral pH.[11d,12d,13a,13e] In addition, highly alkaline (pH > 9) conditions are required for many donors to trigger HNO release.[9b,9e] Furthermore, HNO generation from current HNO donors is typically slow ($t_{1/2}$ ≈ min-to-h).[13h] Therefore, the development of HNO donors with fast HNO release profiles under neutral pH conditions remains an important challenge.

$$HNO + HNO \xrightarrow{k} [H_2N_2O_2] \longrightarrow N_2O + H_2O\ ;\ k \sim 8 \times 10^6\ M^{-1}\ s^{-1}\ (22\ ^oC) \quad (1)$$

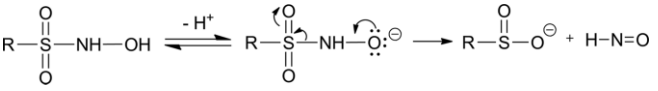
Photochemical approaches have been widely explored for the rapid in situ generation of molecules for chemical and biochemical studies.[15] However, only a limited number of photo-

[a] *Department of Chemistry and Biochemistry, Kent State University, Kent, OH 44242, USA*
*E-mail: psampson@kent.edu*
*www.kent.edu/sole/profile/paul-sampson*
[b] *School of Science, Auckland University of Technology*
*Private Bag 92006, Auckland 1142, New Zealand*
*E-mail: nbrasch@aut.ac.nz*
*www.brasch-group.com*
[c] *The Photon Factory, School of Chemical Sciences, The MacDiarmid Institute for Advanced Materials and Nanotechnology, The Dodd Walls Centre for Quantum and Photonic Technologies and Department of Physics, The University of Auckland*
*Private Bag 92019, Auckland, New Zealand*

*Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under https://doi.org/10.1002/ejoc.201800092.*

chemical approaches aimed at HNO generation have been reported. Doctorovich et al. employed a pH photoactuator to spatially and temporally increase the pH, resulting in HNO generation from decomposition of the 4-nitro derivative of Piloty's acid.[9c] This approach would presumably be applicable to other HNO donors that require alkaline solutions to decompose. Another approach is the use of photoactivatable HNO donors. Two classes of photoactive HNO donors have thus far been developed, which decompose via retrocycloaddition of a 1,2,4-oxadiazole-4-oxide[13c,13d,13f] or a photomediated retro-Diels–Alder reaction to generate acyl nitroso precursors of HNO.[13a,13d,13e] Acyl nitroso intermediates generated from laser flash photolysis of 1,2,4-oxadiazole-4-oxides were first reported to generate HNO in the presence of amine and thiolate nucleophiles by Toscano et al.[13c,13d] A series of related 1,2,4-oxadiazole-4-oxides were shown to slowly yield HNO upon exposure to sunlight.[13f] However, solutions of 1,2,4-oxadiazole-4-oxides are sensitive to ambient light,[16] and secondary photochemical reactions occur.[17] Ethyl nitrodiazoacetate and phenylcyanonitromethane nitronate have also been investigated as photoactive precursors of acyl nitroso species.[13d] Upon photolysis of phenylcyanonitromethane nitronate, a competing pathway involving a loss of nitrite ion also occurred. Hetero-Diels–Alder cycloadducts generate acyl nitroso intermediates upon photolysis, which subsequently hydrolyze to generate HNO ($t_{1/2}$ ≈ min).[13a,13e] A solvent-dependent mixture of HNO and NO was obtained, via photoinduced homolytic cleavage.[13d] HNO generation was also observed in the absence of light. As the authors point out, the proposed photochemical [4+2] cycloreversion is forbidden according to the Woodward–Hoffmann rules.[7d] Another retro Diels–Alder approach for HNO release has also been explored but the reaction instead was found to proceed via a thermal process.[13g] Hence, multiple issues compromise the use of photochemical cycloreversion as an on-demand approach for HNO generation.

Recently, we communicated the first example of a new class of photoactivatable HNO donors $RSO_2NHO$-PT (PT = phototrigger) incorporating the well-studied (3-hydroxy-2-naphthalenyl)methyl (3,2-HNM) phototrigger coupled to a trifluoromethanesulfonamidoxy moiety (R = $CF_3$).[18] Herein, full details of this investigation are provided alongside parallel studies with two other related sulfohydroxamate analogues (R = Me and Ph). The parent sulfohydroxamic acids ($RSO_2NHOH$), Piloty's acid (PA, R = Ph) and MSHA (R = Me), require deprotonation to give the conjugate base ($RSO_2NHO^-$) prior to HNO release, which occurs in basic solution [equation (2)].[9a,9b,9d,9e] The release of HNO from $RSO_2NHO^-$ is slow (for R = Me, $t_{1/2}$ = 488 min at pH 9.0 and 81 min at pH 12.0;[5b] for R = Ph, $t_{1/2}$ = 90 min at pH 9.0 and 29 min at pH 12.0[9b]).




(2)

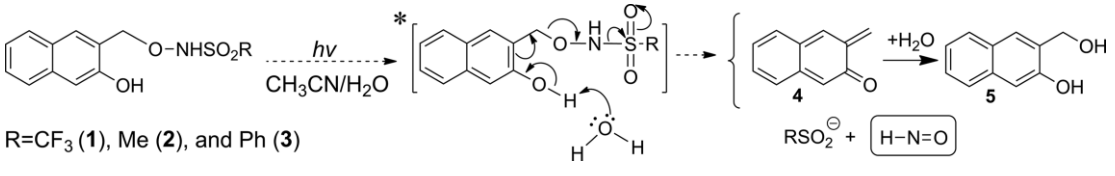
The photolabile 3,2-HNM protecting group was selected as the phototrigger due to its rapid photocleavage ($k_{release}$ ≈ $10^5$ $s^{-1}$) combined with good quantum and chemical yields.[19] By attaching Piloty's acid and its analogues to a light-sensitive 3,2-HNM phototrigger, we hypothesized that concerted elimination could lead directly to HNO release without the formation of an $RSO_2NHO^-$ intermediate (Scheme 1). Rapid hydration of the resulting *o*-naphthoquinone methide **4** would then afford the alcohol **5**. Since Piloty's acid ($PhSO_2NHOH$) and $MeSO_2NHOH$ are both well-established HNO donors, we targeted the corresponding HNM-based donors **2** (R = Me) and **3** (R = Ph) (Scheme 1). A further derivative **1** (R = $CF_3$) was also synthesized, to investigate the role of the $RSO_2^-$ moiety in facilitating HNO release. We hypothesized that incorporation of the better sulfinate leaving group in **1** may promote the desired elimination pathway. In this paper we present the synthesis of these HNO donors, and steady-state irradiation experiments to determine the products of photolysis and the amount of HNO released.

## Results and Discussion

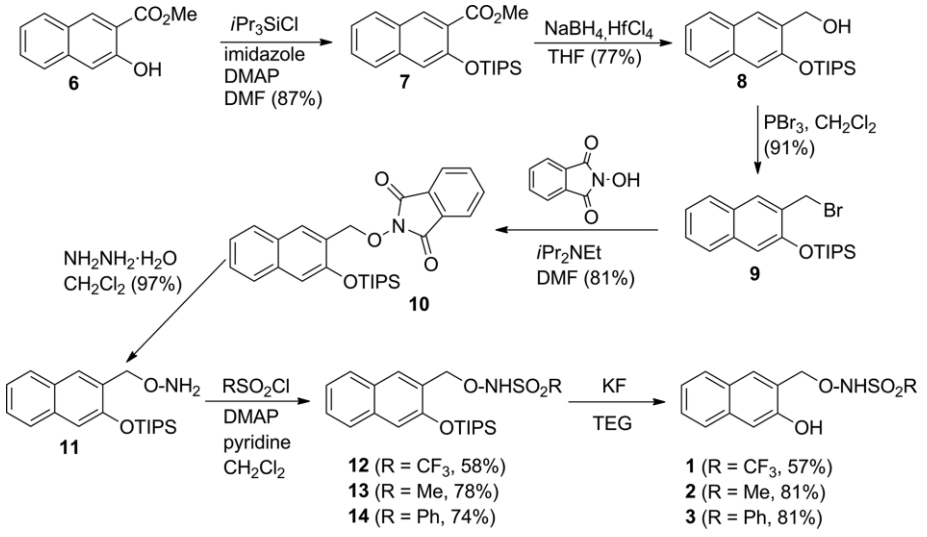
### Synthesis of HNO Donors 1–3

The synthesis of HNO donors **1**–**3** incorporating the 3,2-HNM phototrigger was achieved from commercially available methyl 3-hydroxy-2-naphthoate (**6**) via the route outlined in Scheme 2. The preliminary synthesis and photodecomposition of compound **1** have been reported in a recent communication.[18] Following triisopropylsilyl (TIPS) protection of naphthol **6**, the reduction of the resulting ester **7** was attempted. The reduction of **7** using $LiAlH_4$ proved to be a highly capricious reaction and, at best, only afforded alcohol **8** in low yields (ca. 20 %). A considerable amount of deprotected diol **5** was also recovered, consistent with cleavage of the silyl ether intermediate via intramolecular Al-Si hydride transfer from a hydridoaluminoxy intermediate with release of triisopropylsilane.[20]

Since the reactivity of a hydride reducing agent is influenced by the Lewis acidity of the counterion, $Hf(BH_4)_4$ was considered as an alternate reducing agent. Although very rarely used as a reducing agent in organic synthesis, the hard oxophilic character of hafnium renders this reagent an extremely effective and chemoselective reducing agent that may be used under mild conditions.[21] $Hf(BH_4)_4$ was prepared from the reaction of




Scheme 1. Proposed mechanism for release of HNO from HNO donors **1**–**3**.

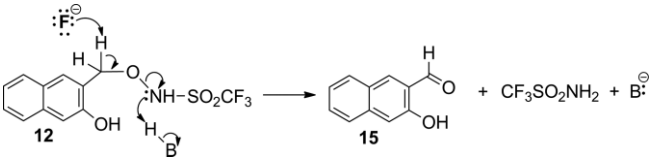



Scheme 2. Synthesis of HNM-based HNO donors **1**–**3**.

$NaBH_4$ and $HfCl_4$ in anhydrous THF. This reagent must be prepared under strictly anhydrous conditions due to the extremely hygroscopic nature of $HfCl_4$; failure to ensure anhydrous conditions resulted in a significant lowering of reaction yields. Under rigorously anhydrous conditions, the reduction of ester **7** to **8** using $Hf(BH_4)_4$ was achieved in 77 % yield and without any evidence of cleavage of the silyl ether.

Nucleophilic attack on $PBr_3$ by alcohol **8** gave **9**, and the hydroxylamine adduct **10** was subsequently generated in excellent yield using *N*-hydroxyphthalimide via an $S_N2$ reaction. The more common *tert*-butyldimethylsilyl (TBS) group was initially explored as the naphtholic *O*-protecting group. However, the TBS ether analogue of **9** was not sufficiently robust when exposed to the nucleophilic anion generated from *N*-hydroxyphthalimide in the presence of base catalysts including DBU,[22] $K_2CO_3$,[23] and NaOAc,[24] and instead resulted in formation of the desilylated derivative of **10**.[25]

Alkoxyamine **11** was obtained after treating **10** with hydrazine monohydrate. *N*-Sulfonylation of **11** using the appropriate sulfonyl chloride $RSO_2Cl$ (R = $CF_3$, Me or Ph) afforded the corresponding *O*-TIPS protected intermediates **12**–**14**, respectively.[26] TIPS deprotection using KF in tetraethylene glycol generated the three target products **1**–**3**.[27] Interestingly, the $^1H$ NMR and $^{19}F$ NMR spectra of the crude product **1** showed that cleavage of the N–O bond of **12** (ca. 5 %) also occurs, to give 3-hydroxy-2-naphthaldehyde (**15**) and trifluoromethanesulfonamide ($CF_3SO_2NH_2$). These byproducts are most likely generated by a fluoride-mediated elimination reaction, with abstraction of a benzylic proton by fluoride (Scheme 3) via a mechanism analogous to a reaction observed by Overman et al.[28] A similar elimination was not observed during removal of the TIPS group from compounds **13** and **14**, presumably due to the higher barrier for these elimination pathways when a less effective leaving group is present. Tetra-*n*-butylammonium fluoride (TBAF) was also used to remove the TIPS group, with the composition of the crude product mixture depending on the reaction time. Treating **12** with TBAF for approximately 1 h gave target **1** in 49 % yield, which was readily characterized based on diagnostic signals in the $^1H$ NMR and $^{19}F$ NMR spectra at $\delta$ 5.28 ($CH_2$) and –73.6 ppm, respectively. However, **12** was converted into another product at a shorter reaction time (ca. 10 min), with signals in the $^1H$ NMR and $^{19}F$ NMR spectra at $\delta$ 5.00 ($CH_2$) and –76.7 ppm, respectively.[29] The spectroscopic data indicated that TIPS deprotection was accompanied by N-O migration of the triflyl group to afford **16**, an isomer of target **1** (Figure 1). Interestingly, **16** can be converted into the target **1** simply by subjecting it to silica column chromatography using ethyl acetate as the eluant.




Scheme 3. Proposed mechanism for O–N bond cleavage of **12** by fluoride.

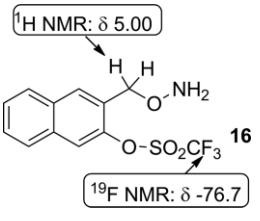


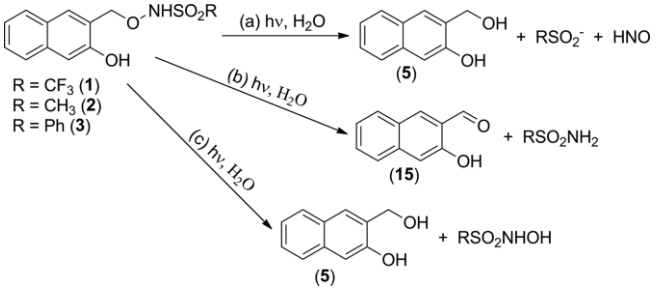

Figure 1. Isomer of target **1** obtained during the deprotection of **12** using TBAF with short reaction times.

## Characterization of the Photoproducts Obtained by Steady-State Irradiation of HNO Donors 1, 2, and 3

HNO donors **1**, **2**, and **3** were found to be stable in ambient room light [anaerobic phosphate buffer (pH 7.00, 5.0 mM) and

$CD_3CN$, 40:60 v/v, ≥ 1 d]. The compounds are stable in the presence of air for several months in the solid state. Upon photolysis, the 3,2-HNM phototrigger was expected to yield 3-hydroxy-2-naphthalenemethanol (diol, **5**) through hydration of the intermediate *o*-naphthoquinone methide (**4**), Scheme 1,[19] in addition to $RSO_2^-$ and HNO.

Steady-state irradiation experiments of **1**, **2**, and **3** were performed in a mixture of phosphate buffer (pH 7.00, 5.0 mM) and $CD_3CN$ (40:60, v/v) using a Rayonet photochemical reactor (RMR-600, 350 nm bulbs, 8 × 4 W bulbs) under strictly anaerobic conditions. The results for **1** have been reported in a recent communication, with $CF_3SO_2^-$ [Pathway (a), Scheme 4] and $CF_3SO_2NH_2$ [Pathway (b), Scheme 4] generated in a approximately 40:60 ratio (determined from $^{19}F$ NMR spectroscopic analysis).[18] The observed rate constant for the photodecomposition of **1** was determined by $^{19}F$ NMR spectroscopy from a plot of the peak area of the $CF_3$ group of **1** vs. time, giving $k_{obs}$ = 0.171 $min^{-1}$ ($t_{1/2}$ ca. 4.1 min; Figure 2).[18]




Scheme 4. The major decomposition pathways observed upon photolysis of HNO donors **1**–**3** [Note: Pathway (c) only occurs (in trace amounts) for **2** (R = $CH_3$) and **3** (R = Ph)].

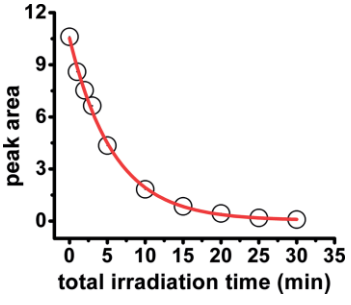



Figure 2. Best fit of the $^{19}F$ NMR peak area for the $CF_3$ moiety of HNO donor **1** (3.89 mM) in a mixture of phosphate buffer (5.0 mM, pH 7.00) and $CD_3CN$ (40:60, v/v) vs. time to a first-order rate equation, giving $k_{obs}$ = 0.171 ± 0.008 $min^{-1}$.

The products formed upon complete photodecomposition of **1** in a mixture of phosphate buffer (pH 7.0, 0.10 M) and $CD_3CN$ (40:60, v/v) were also characterized by $^1H$ NMR spectroscopy (Figure 3).[18] In addition to the expected diol **5**, aldehyde **15** was observed as a second major product [Pathway (b), Scheme 4].[18] Substantial secondary photodecomposition of **5** and **15** occurs, as observed by Popik and co-workers for **5** and related systems.[19b] Partial photolysis of **1** (60 % conversion) shows that the ratio of **5** to **15** (1:0.69) is the same (within experimental error) as the $CF_3SO_2^-/CF_3SO_2NH_2$ product ratio (1:0.74) as determined using $^{19}F$ NMR spectroscopy (Figure 3). Control experiments demonstrated that neither $CF_3SO_2^-$ nor $CF_3SO_2NH_2$ are photosensitive under the conditions of our experiments (data not shown).

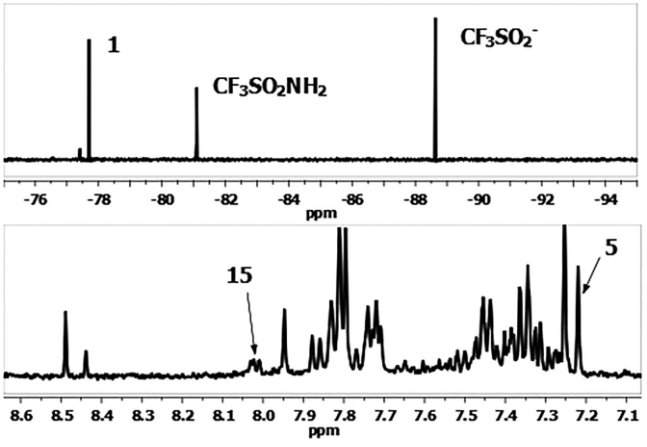



Figure 3. $^{19}F$ NMR (top) and $^1H$ NMR (bottom) spectra of the partial photolysis products of HNO donor **1** (1.00 mM, ca. 60 % conversion) in an anaerobic mixture of phosphate buffer (pH 7.0, 5.0 mM) and $CD_3CN$ (40:60, v/v). Peaks for **1** ($\delta$ –77.7 ppm), $CF_3SO_2NH_2$ ($\delta$ –81.1 ppm), and $CF_3SO_2^-$ ($\delta$ –88.7 ppm) are observed in the $^{19}F$ NMR spectrum. In the $^1H$ NMR spectrum, peaks for **1** [$\delta$ = 7.81 (d), 7.79 (s), 7.73 (d), 7.45 (t), 7.34 (t), 7.25 (s; used for integration)], **15** [$\delta$ = 8.43 (s), 8.02 (d; used for integration), 7.81 (d), 7.63 (t), 7.44 (t), 7.34 (s)] and **5** [$\delta$ = 7.82 (d), 7.81 (s), 7.71 (d), 7.42 (t), 7.34 (t), 7.22 (s; used for integration)] are observed. Unidentified peaks are observed at $\delta$ = 8.49, 7.95, 7.88, 7.86, 7.77, 7.52, 7.50, 7.31, 7.29 ppm, probably arising from photodecomposition of the primary photoproducts. The $^1H$ NMR spectrum is referenced to TSP in the same solvent mixture (external standard used) and the $^{19}F$ NMR spectrum is internally referenced to trifluorotoluene (–63.72 ppm).

The photodecomposition of HNO donor **2** (R = Me) was carried out under the same conditions [anaerobic mixture of phosphate buffer (pH 7.00, 5.0 mM) and $CD_3CN$ (40:60, v/v)]. Three methanesulfonyl-containing products were observed in the $^1H$ NMR spectra, with $MeSO_2^-$ [$\delta$ = 2.23, 9 %; Pathway (a), Scheme 4] $MeSO_2NH_2$ [$\delta$ = 3.08, 77 %; Pathway (b), Scheme 4] and $MeSO_2NHOH$ [$\delta$ = 3.05, 14 %; Pathway (c), Scheme 4] obtained after irradiating **2** for 40 min (Figure 4a). The observed first-order rate constant for the photodecomposition of **2** was 0.110 $min^{-1}$ ($t_{1/2}$ ca. 6.3 min; Figure 4b).

The photodecomposition of HNO donor **3** was also monitored by $^1H$ NMR spectroscopy (Figure 5a). $PhSO_2NH_2$, $PhSO_2^-$ and a trace amount of $PhSO_2NHOH$ were observed, with significant overlapping of peaks. The $PhSO_2NH_2/PhSO_2^-$ ratio was approximately 77:23 and, from the decrease in the peak area of the benzylic $CH_2$ group of **3**, an observed rate constant for photodecomposition, $k_{obs}$ = 0.096 $min^{-1}$, was obtained [$t_{1/2}$ ca. 7.2 min (Figure 5b)].

To demonstrate that HNO is indeed released from HNO donors **1**–**3**, the HNO donors were photolyzed in the presence of the HNO trap aquacobalamin [$H_2OCbl(III)^+$], which reacts stoichiometrically with HNO to form bright orange nitrosylcobalamin [$NO^-$-Cbl(III)].[18] Both $H_2OCbl(III)^+$ and $NO^-$-Cbl(III) were shown to be stable upon irradiation with light under the experimental conditions, and a control experiment showed that

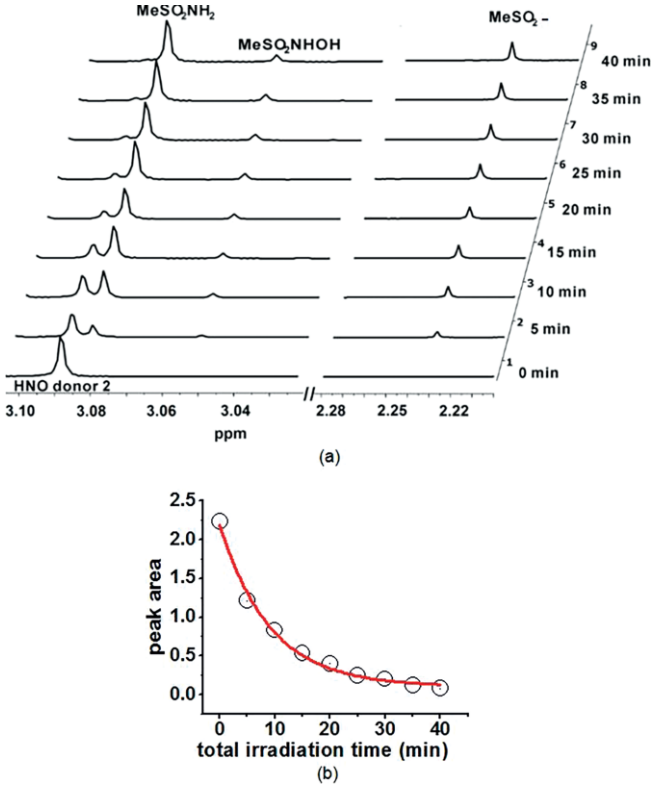



Figure 4. (a) $^1$H NMR spectra for the photodecomposition of HNO donor **2** (4.68 mM, 350 nm, 4 W) as a function of the total irradiation time in an anaerobic mixture of phosphate buffer (5.0 mM, pH 7.0) and $CD_3CN$ (40:60, v/v). (b) Best fit of the peak area for the $CH_3$ moiety of **2** vs. total irradiation time to a first-order rate equation, giving $k_{obs} = 0.110 \pm 0.008$ min$^{-1}$.

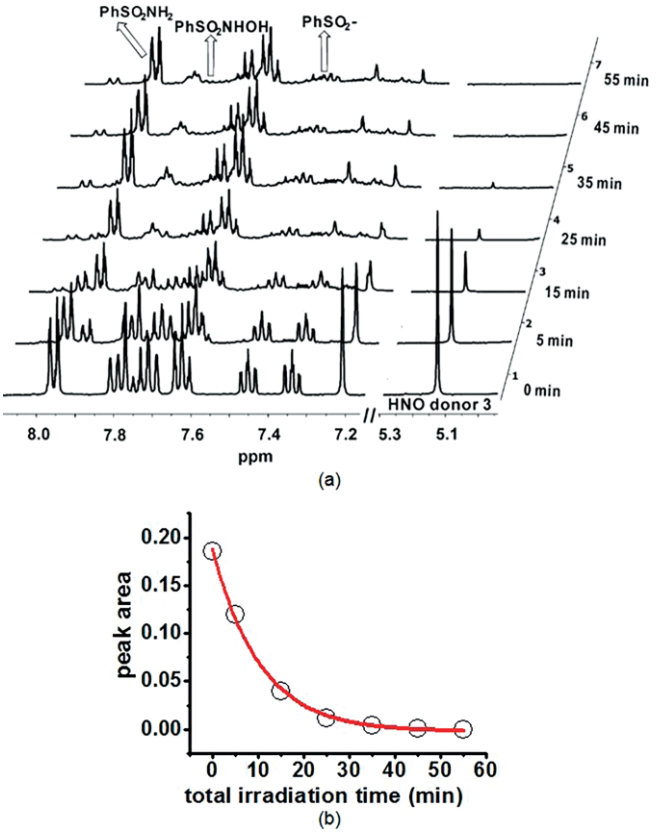



Figure 5. (a) $^1$H NMR spectra as a function of irradiation time for the photodecomposition of HNO donor **3** (3.08 mM, 350 nm, 8 × 4 W bulbs) in an anaerobic mixture of phosphate buffer (0.10 M, pH 7.0) and $CD_3CN$ (40:60, v/v). Peaks for $PhSO_2NH_2$ [$\delta$ = 7.93–7.89 ppm (2 H), 7.70–7.65 ppm (1 H), 7.63–7.59 ppm (2 H)], $PhSO_2^-$ [$\delta$ = 7.63–7.60 ppm (2 H), 7.52–7.43 ppm (3 H)] and a trace amount of $PhSO_2NHOH$ [$\delta$ = 7.94–7.91 ppm (2 H), 7.78–7.74 ppm (1 H), 7.67–7.63 ppm (2 H)] were observed, with significant overlapping of peaks. (b) Best fit of peak area vs. time for the benzylic proton peak of **3** to a first-order rate equation, giving $k_{obs} = 0.096 \pm 0.005$ min$^{-1}$.

there is no reaction between aquacobalamin and **1** in ambient room light.[18] Photolyzing HNO donor **1** in a solution of aquacobalamin resulted in UV/Vis spectral changes and isosbestic points characteristic of the conversion of $H_2OCbl(III)^+$ to $NO^-$-Cbl(III).[18] A similar experiment was carried out for HNO donor **2**. Figure 6 shows the UV/Vis spectral changes upon photolyzing a solution of **2** ($1.50 \times 10^{-4}$ M) in the presence of $H_2OCbl^+$ ($3.0 \times 10^{-5}$ M) using a Xe light source in a stopped-flow instrument. Excess **2** was used since, under these conditions, only approximately 20 % of the desired HNO-generating pathway occurs. Once again $H_2OCbl(III)^+$ is converted to $NO^-$-Cbl(III), with an isosbestic point observed at 491 nm, characteristic for the $H_2OCbl(III)^+/NO^-$-Cbl(III) conversion.[18] Formation of $NO^-$-Cbl(III) was also observed upon irradiating HNO donor **3** in the presence of aquacobalamin (Figure S1, Supporting Information). The observed rate constant for $NO^-$-Cbl(III) formation was also estimated from the data, and found to be similar for all HNO donors [$2.7 \times 10^{-3}$,[18] $1.1 \times 10^{-3}$ (inset to Figure 6) and $2.3 \times 10^{-3}$ s$^{-1}$ (inset to Figure S1, Supporting Information) for **1**, **2**, and **3**, respectively].

From Scheme 4, it can be seen that the percentage of sulfinate generated should be directly related to the percentage of HNO released from the HNO donor. To investigate whether HNO generation can be directly inferred from sulfinate formation, a solution of $H_2OCbl(III)^+$ (200.0 μM) and HNO donor **1** (200.0 μM) was partially photolyzed, to minimize secondary photochemistry of the initial photoproducts. Unreacted $H_2OCbl(III)^+$ was subsequently converted to $NO^-$-Cbl(III) by the addition of the established HNO donor Angeli's salt (2.5 mol equiv.) without further irradiation. Based on the UV/Vis spectral changes at

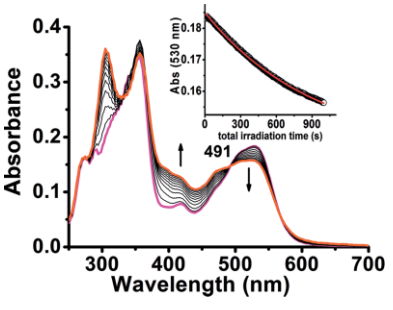



Figure 6. UV/Vis spectra for the reaction between $H_2OCbl(III)^+$ ($3.0 \times 10^{-5}$ M) and HNO donor **2** ($1.50 \times 10^{-4}$ M) using xenon light (150 W, monochromator slit width = 3.0 mm) in an anaerobic mixture of phosphate buffer (5.0 mm, pH 7.00) and $CH_3CN$ (40:60, v/v) at 25 °C. Inset: Fit of the absorbance data at 530 nm vs. time to a first-order rate equation, giving $k_{obs} = (1.1 \pm 0.1) \times 10^{-3}$ s$^{-1}$. Note: The stopped-flow instrument has a maximum data collection time of 1000 s.

530 nm (Figure 7), approximately 10 ± 2 % $NO^{-}$-Cbl(III) was generated, corresponding to the release of approximately 10 % HNO. The percentage of $CF_3SO_2^-$ formed was 16 ± 3 %, which is close to the percentage of $NO^{-}$-Cbl(III) formed within experimental error. Thus, the amount of sulfinate in the product solution is a useful indicator of the amount of HNO released upon photodecomposition of this family of HNO donors.

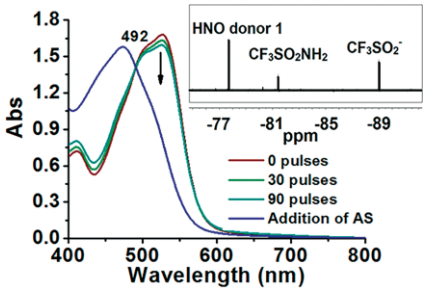



Figure 7. UV/Vis spectra for the partial photolysis of HNO donor **1** (200.0 μM) in the presence of the HNO trap $H_2OCbl(III)^+$ (200.0 μM) in aqueous phosphate buffer (pH 7.00, 5.0 mM) and $CD_3CN$ (40:60, v/v). Laser excitation at 266 nm, ca. 5 ns pulse width, ca. 60 mJ/pulse. Inset: $^{19}F$ NMR spectrum of the product mixture. The peak at $\delta$-77.70 ppm corresponds to **1**, –81.42 ppm to $CF_3SO_2NH_2$, and –89.00 ppm to $CF_3SO_2^-$. Approximately 28 % of **1** was photolyzed, generating 16 ± 3 % $CF_3SO_2^-$.

The amounts of $RSO_2$-containing products formed during photolysis of **1**–**3** are summarized in Table 1. In addition to the corresponding sulfinates and sulfonamides, $MeSO_2NHOH$ (14 %) and trace amounts of $PhSO_2NHOH$ (PA) were also observed in the product solutions derived from the photolysis of **2** and **3**, respectively [Pathway (c), Scheme 4]. In contrast, no traces of the corresponding $CF_3SO_2NHOH$ (or its conjugate base) were seen as intermediates during the photolysis of **1**. Control experiments showed that, while $MeSO_2NHOH$ and PA are stable in this solvent mixture, $CF_3SO_2NHOH$ deprotonates to give $CF_3SO_2NHO^-$, which then releases HNO and $CF_3SO_2^-$ upon decomposition ($t_{1/2}$ ca. 11.0 min).[18] Since $CF_3SO_2NHOH$ is photostable[18] and decomposes in this solvent mixture significantly more slowly than the observed rate of photodecomposition of **1** seen in the steady-state irradiation experiments ($t_{1/2}$ ca. 4.1 min), it is clear that any $CF_3SO_2NHO(H)$ generated as an intermediate would be observed in the $^{19}F$ NMR spectra during the photolysis of **1**. Given that it was not observed,[18] it is highly unlikely that a pathway involving $CF_3SO_2NHO(H)$ as an intermediate [Pathway (c), Scheme 4] is important for the photodecomposition of **1**. Notably, the presence of oxygen in aqueous MeCN solutions had no effect on the photoproduct ratios

Table 1. Summary of $RSO_2$-containing species generated from the photolysis of **1**–**3** in a mixture of phosphate buffer (pH 7.00, 0.10 M) and $CD_3CN$ (40:60, v/v).

| HNO Donor | $RSO_2^-$ [%] | $RSO_2NH_2$ [%] | $RSO_2NHOH$ [%] |
|---|---|---|---|
| **1** | 60 | 40 | 0 |
| **2** | 9 | 77 | 14 |
| **3** | 23 | 77 | –[a] |

[a] Small amounts were formed but were not precisely quantified due to the overlapping of $^1H$ NMR resonances of photolytic products.

from HNO donors **1**, **2**, and **3**, other than seeing partial oxidation of the $MeSO_2^-$ product to $MeSO_3^-$ (data not shown), suggesting that the pathways proceed through a singlet excited state(s).

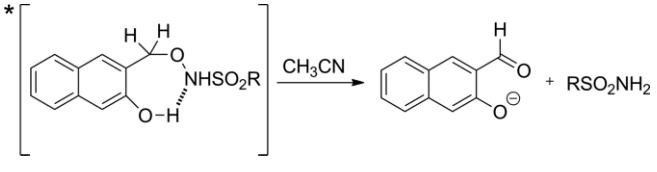
The leaving-group ability of sulfinates is correlated with the p$K_a$ values for the related conjugated acids [p$K_a$($MeSO_2H$) = 2.28,[30] p$K_a$($PhSO_2H$) = 2.7[31] and p$K_a$($CF_3SO_2H$) = –0.6[31]]. The amount of HNO generated (as measured by the sulfinate/sulfonamide ratio) during photolysis is approximately 1.5:1, 0.1:1, and 0.3:1 for the photolysis of **1** (R = $CF_3$), **2** (R = $CH_3$), and **3** (R = Ph), respectively. The superior leaving-group ability of $CF_3SO_2^-$ is therefore associated with increased HNO generation, although the relative amount of HNO released from photolysis of **2** and **3** does not closely correlate with the corresponding sulfinic acid p$K_a$ values, suggesting that other factors are also important. Interestingly, the leaving group had only a modest effect on the observed rate of photodecomposition of the HNO donor using a steady-state irradiation source ($t_{1/2}$ 0.17, 0.11, and 0.096 $min^{-1}$ for **1**, **2**, and **3**, respectively). We previously showed that the rate of photodecomposition is dependent on the intensity of the light source. Popik et al. have observed extremely rapid release of the ethoxy leaving group in a closely related 3,2-HNM-based system excited using a nanosecond laser pulse ($k_{release} \approx 10^5$ $s^{-1}$),[19b] suggesting that similar or faster release of the better leaving groups in our system might be expected under similar laser pulse conditions.

The effect of varying the ratio of acetonitrile to phosphate buffer (5.0 mM, pH 7.0) in the solvent mixture was investigated for **1** and **2**. For **1**, the photoproduct ratio was found to be highly solvent dependent, with approximately 70 % $CF_3SO_2^-$ generation in a mixture of phosphate buffer (pH 7.0, 0.10 M) and $CD_3CN$ (5:95, v/v), approximately. 60 % $CF_3SO_2^-$ in phosphate buffer:$CD_3CN$ (40:60 v/v), and only a trace amount of $CF_3SO_2^-$ (ca. 4 %) in $CD_3CN$ in the absence of aqueous buffer.[18] Increasing the volume percentage of water above 5 % resulted in a steady decrease in the amount of $CF_3SO_2^-$ (= HNO) generated, with approximately 30 % $CF_3SO_2^-$ generated in aqueous solution in the absence of $CD_3CN$.[18] Whereas photolysis of **2** in 40:60 (v/v) phosphate buffer (pH 7.0, 0.10 M)/$CD_3CN$ resulted in approximately 9 % $MeSO_2^-$, approximately 77 % $MeSO_2NH_2$, and approximately 14 % $MeSO_2NHOH$, irradiation of **2** in 95:5 (v/v) phosphate buffer (pH 7.0, 0.10 M)/$CD_3CN$ produced approximately 8 % $MeSO_2^-$, 58 % $MeSO_2NH_2$ and approximately 34 % $MeSO_2NHOH$, with the percentage of $MeSO_2NHOH$ doubling. As observed for HNO donor **1**, a near quantitative amount of the sulfonamide ($MeSO_2NH_2$, ca. 97 %) was formed upon photolysis of **2** in pure $CD_3CN$; trace amounts of additional photoproducts ($\delta$ = 3.02 and 3.48 ppm) were also seen that decomposed as photolysis proceeded. Formation of the aldehyde **15** was observed upon photolysis of **2** in anaerobic $CD_3CN$. The preceding results indicate that water is essential for Pathways (a) and (c), consistent with a mechanism involving excited-state proton transfer via water.[32] For both **1** and **2**, HNO generation is most favorable with small volume percentages of phosphate buffer in acetonitrile. That said, water plays an essential role in the photorelease of HNO from this family of HNO donors, regardless of leaving group.

To further probe the mechanisms of photodecomposition for **2**, steady-state photolysis of **2** was monitored by $^1$H NMR spectroscopy in anaerobic $CD_3CN$ and in an anaerobic mixture of deuterated phosphate buffer (0.10 M, pH 7.0) and $CH_3CN$ (5:95, v/v) (Figures S2 and S3 in the Supporting Information). The observed rate constant for photolysis was the same within experimental error in both solvent mixtures ($k_{obs}$ = 0.38 ± 0.07 and 0.43 ± 0.03 min$^{-1}$, respectively). In $CD_3CN$, only Pathway (b) is observed; however, in aqueous $CD_3CN$, Pathways (a), (b), and (c) (Scheme 4) are observed. Taken together with data showing that the percentages of the major photoproducts are unchanged within experimental error under aerobic conditions, these results are consistent with all pathways proceeding via the singlet excited state of the parent molecule, with intermolecular bonding between excited state species and solvent playing a key role in determining which photodecomposition mechanism(s) dominate.[33]

The desired HNO generation pathway (a) is expected to proceed via the facile water-assisted deprotonation of the naphtholic hydroxyl group of the excited state molecule (Scheme 1). The p$K_a$ of the hydroxyl group of 2-naphthol decreases from 9.30 in the ground state to approximately 2.6 (± 0.2) in the excited state.[19a] Thus, the singlet excited state of the naphtholic chromophore in our 3,2-HNM-based HNO donors will rapidly deprotonate, with water acting as the proton acceptor.[34] Subsequent elimination results in the formation of quinone methide **4**, which rapidly undergoes conjugate addition with water to give diol **5** (Scheme 1). To probe the importance of the parent (protonated) naphtholic hydroxyl group in the generation of HNO, the naphtholate conjugate base of **1** (1.00 mM) was irradiated in an anaerobic mixture of aqueous NaOH (0.10 M) and $CD_3CN$ (40:60 v/v). $CF_3SO_2NH_2$ (93 %) and $CF_3SO_2^-$ (7 %) were observed as products in this experiment (results not shown). Given that approximately 60 % $CF_3SO_2^-$ is observed when phosphate buffer (pH 7.0) is used as the aqueous component of the 40:60 v/v solvent mixture,[18] this is consistent with the protonated excited state parent molecule serving as a transient species in Pathway (a).

Oxygen–nitrogen bond cleavage also occurs upon photoexcitation of **1**–**3**, Scheme 4, Pathway (b), to give the corresponding sulfonamide $RSO_2NH_2$ and an aldehyde. Light-induced O–N bond homolysis has been reported by others for related systems.[35] O–N bond cleavage occurs for **1** regardless of whether aqueous phosphate buffer is present in the acetonitrile. Pathway (b), Scheme 4, could potentially occur via excited-state intramolecular proton transfer (ESIPT) from the naphtholic hydroxyl group to the nitrogen atom of the leaving group (Scheme 5). Subsequent or concerted deprotonation of the methylene carbon, presumably by a solvent molecule, would then produce the observed aldehyde photoproduct. Direct ESIPT from phenolic or naphtholic hydroxyl groups to nitrogen atoms was proposed for related systems in aprotic solvents.[36] However, given that Pathway (b) also occurs upon photoexcitation of the naphtholate conjugate base of **1**, another mechanism for Pathway (b) is likely at least under these conditions.




Scheme 5. A proposed pathway for excited-state intramolecular proton transfer to generate aldehyde **15** and the corresponding sulfonamide.

For R = Me and Ph, the parent sulfohydroxamic acid $RSO_2NHOH$ was also observed as a minor product. It is likely that water protonates the O atom of the leaving group in addition to removing a proton from the naphtholic hydroxyl group. Time resolved spectroscopy experiments combined with theoretical calculations are required to confirm or refute these mechanistic possibilities, although the former studies could be complex, given that multiple pathways occur simultaneously.

## Conclusions

A novel family of photoactivatable HNO donors **1**, **2**, and **3** has been developed. Release of HNO was demonstrated for donors **1**, **2**, and **3** using the HNO trap aquacobalamin. The selectivity for release of HNO from the 3,2-HNM-photoprotecting group was shown to be strongly dependent on the leaving group, with the HNO donor containing the best leaving group (R = $CF_3$, **1**), generating the most HNO (ca. 70 % under the optimal solvent conditions). The solvent also plays a major role in determining the amount of HNO released, with maximum HNO release occurring with small volumes of buffer in the acetonitrile/aqueous buffer solvent mixtures. Ongoing studies are focused on improving the selectivity for the HNO generation pathway versus the other two competing pathways through the synthesis of analogues.

## Experimental Section

**General:** All reactions were carried out using anhydrous solvents under a nitrogen atmosphere. Unless otherwise noted, all commercial chemicals were used directly without further purification. Anhydrous pyridine, DMF, and DMSO were purchased and used directly. THF was freshly distilled from Na and benzophenone, and $CH_2Cl_2$ was freshly distilled from $CaH_2$. Column chromatography was performed on silica gel (60 Å, 40–63 μm) using ACS grade solvents [ethyl acetate, petroleum ether (boiling point range: 30–60 °C) and $CH_2Cl_2$] without further purification. All new synthetic compounds were fully characterized using $^1$H, $^{13}$C, and $^{19}$F NMR spectroscopy, and high-resolution mass spectrometry (HRMS) with a direct analysis in real time (DART) ion source. $^1$H, $^{13}$C, and $^{19}$F NMR spectra were recorded using a Bruker 400 MHz spectrometer with a 5 mm probe at 25 ± 1 °C. $^{19}$F NMR spectra were collected using a Bruker spectrometer (400 MHz) operating at 376 MHz with D1 = 5 s at 25 ± 1 °C. The $T_1$ values for $CF_3SO_2^-$ and $CF_3SO_3NH_2$ were subsequently determined to be 4.0 and 4.6 s, respectively. We expected that the relative amounts of $CF_3SO_2^-$ and $CF_3SO_2NH_2$ could be estimated from the peak areas even when a delay time of 5 s is used, given that their $T_1$ values are so similar. To confirm this assumption, the $^{19}$F NMR spectrum of a mixture of $CF_3SO_2^-$ and $CF_3SO_2NH_2$ was measured using D1 = 5 s and D1 = 20 s. The ratios of the peak areas for these spectra were the same within experimental error [(peak area $CF_3SO_2^-$):(peak area $CF_3SO_2NH_2$) = 1:1.2 and 1:1.3, re-

spectively]. All NMR spectroscopic data were processed using MestReC NMR software. Tetramethylsilane (TMS) was used as an internal reference in $^1H$ and $^{13}C$ NMR spectroscopy, and $CFCl_3$ was used as an internal reference in $^{19}F$ NMR spectroscopy. Melting points were measured using a Stuart capillary melting point apparatus or an Electrothermal melting point apparatus.

In spite of careful purification, some very small impurities remained in several early synthetic products as seen by additional signals in the upfield region of the $^1H$ NMR spectra, which appeared to be due to some inseparable impurities found in all batches of the commercial triisopropylsilyl chloride used. These small impurities were readily removed in subsequent steps.

Phosphate buffer solution (0.10 M and 5.0 mM, pH 7.00) was prepared using $KH_2PO_4$, and the pH of the buffer solution was adjusted using $H_3PO_4$ and/or NaOH. pH measurements were performed using an Orion Model 710A pH meter equipped with Mettler-Toledo Inlab 423 or 421 electrodes at room temperature. Phosphate buffer solution was degassed by bubbling with argon for ca. 24 h, and was stored under argon in an MBRAUN Labmaster 130 (1250/78) glovebox equipped with $O_2$ and $H_2O$ sensors.

Hydroxycobalamin hydrochloride (HOCbl•HCl, 98 %) was purchased from Fluka. Solid HOCbl•HCl was dissolved in phosphate buffer (0.100 M, pH 7.00) to obtain an $H_2OCbl(III)^+$ stock solution. The concentration of $H_2OCbl(III)^+$ was determined by converting $H_2OCbl(III)^+$ into dicyanocobalamin [$(CN)_2Cbl^-$] using KCN solution (0.10 M). The concentration of the final product $(CN)_2Cbl^-$ was determined using UV/Vis spectrometry ($\varepsilon_{367\ nm}$ = 30400 $M^{-1}$ $cm^{-1}$).[37]

All air-free UV/Vis spectrometric measurements were carried out using either a Cary 5000 or 100 spectrophotometer with a thermostatted (25.0 ± 0.1 °C) cell changer and WinUV Bio software (version 3.00). Schlenk cuvettes fitted with J-Young air-tight caps were used for all air-free UV/Vis spectrometric measurements. The UV data were analyzed using Microcal Origin version 8.0 software.

Air-tight J-Young NMR tubes (Wilmad, 535-JY-7) were used for all the $^1H/^{19}F$ NMR experiments conducted under anaerobic conditions. These NMR samples were freshly prepared using appropriate phosphate buffer and $CD_3CN$ mixtures inside a glovebox. Sodium 3-trimethylsilylpropanoate (TSP) was used as an internal standard for these $^1H$ NMR experiments unless otherwise noted, and trifluorotoluene (–63.72 ppm) in $CD_3CN$ prepared in a capillary tube was used as an external standard (inserted into the NMR tube) for $^{19}F$ NMR experiments.

### Synthesis of HNO Donors 1–3

**Methyl 3-(Triisopropylsilyloxy)-2-naphthoate (7):** To a stirred solution of **6** (4.00 g, 19.8 mmol), imidazole (2.01 g, 29.5 mmol) and DMAP (181.52 mg, 1.4858 mmol) in anhydrous DMF (20 mL) at room temperature was added triisopropylsilyl chloride (8.5 mL, *d* = 0.901 g/mL at 25 °C, 40 mmol) in one portion. The reaction mixture was stirred for 24 h at room temperature and was then quenched using saturated aqueous $NaHCO_3$ (200 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by gravity column chromatography (silica gel/1:9 ethyl acetate/petroleum ether) to give the title compound **7** as a pale yellow oil (6.17 g, 87 %). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 8.24 (s, 1 H), 7.78 (d, *J* = 8.0 Hz, 1 H), 7.64 (d, *J* = 8.0 Hz, 1 H), 7.44 (td, *J* = 7.6, 1.2 Hz, 1 H), 7.31 (td, *J* = 7.6, 1.2 Hz, 1 H), 7.19 (s, 1 H), 3.91 (s, 3 H), 1.38 (sept, *J* = 7.6 Hz, 3 H), 1.14 (d, *J* = 7.6 Hz, 18 H) ppm. $^{13}C$ NMR (101 MHz, $CDCl_3$): $\delta$ = 167.49, 151.80, 135.92, 132.40, 132.28, 128.57, 127.96, 127.85, 126.18, 124.30, 114.84, 52.02, 17.99, 13.08 ppm. HRMS: *m/z* (DART): calcd. for $MH^+$ 359.20370, found 359.20391.

**[3-(Triisopropylsilyloxy)naphthalen-2-yl]methanol (8):** A suspension was made by mixing $HfCl_4$ (1.5 g, 4.7 mmol) and $NaBH_4$ (0.40 g, 11 mmol) in anhydrous THF (10 mL) under argon at 3 °C using an ice/water bath. After stirring for 10 min, this mixture was warmed to room temperature and was stirred for an additional 2 h. Then, a solution of **7** (1.32 g, 3.68 mmol) in anhydrous THF (20 mL) was added to the suspension at room temperature. After stirring for 22 h at room temperature, the reaction mixture was quenched with chilled water (40 mL). The aqueous layer was extracted using ethyl acetate (3 × 15 mL) and the combined organic extracts were washed using saturated $NaHCO_3$ (40 mL) and brine (40 mL). The crude product was dried with $Na_2SO_4$ and the solvent was evaporated in vacuo, before being purified by column chromatography (silica gel/7:93 ethyl acetate/petroleum ether) to give the title compound **8** as a yellow-tinted oil (0.94 g, 77 %). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.77 (s, 1 H), 7.76 (d, *J* = 8.8 Hz, 1 H), 7.66 (d, *J* = 8.4 Hz, 1 H), 7.40 (td, *J* = 7.6, 1.2 Hz, 1 H), 7.33 (td, *J* = 7.6, 1.2 Hz, 1 H), 7.14 (s, 1 H), 4.86 (s, 2 H), 2.26 (s, 1 H), 1.42 (sept, *J* = 7.6 Hz, 3 H), 1.16 (d, *J* = 7.6 Hz, 18 H) ppm. $^{13}C$ NMR (101 MHz, $CDCl_3$): $\delta$ = 152.18, 133.99, 132.60, 128.95, 127.65, 127.30, 126.24, 126.05, 123.92, 112.74, 62.59, 18.09, 13.04 ppm. HRMS: *m/z* (DART): calcd. for $MH^+$ 331.20878, found 331.20859.

**[3-(Bromomethyl)naphthalen-2-yl]oxytriisopropylsilane (9):** To a stirred solution of compound **8** (2.23 g, 6.75 mmol) in anhydrous $CH_2Cl_2$ (20 mL) at 0 °C in an water/ice bath was added $PBr_3$ (0.962 mL, *d* = 2.88 g/mL at 20 °C, 10.2 mmol) in one portion. The reaction mixture was stirred at 0 °C for 30 min, and then was allowed to slowly warm to room temperature before being stirred for an additional 3.5 h. The reaction mixture was poured into saturated aq. $NaHCO_3$ (50 mL), extracted using $CH_2Cl_2$ (3 × 80 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The crude residue was purified by column chromatography (silica gel/3:97 $CH_2Cl_2$/petroleum ether) to give the title compound **9** as a white solid (2.41 g, 91 %). M.p. 77–79 °C. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.83 (s, 1 H), 7.73 (dd, *J* = 8.0, 0.4 Hz, 1 H), 7.64 (dd, *J* = 8.0, 0.4 Hz, 1 H), 7.40 (td, *J* = 7.2, 1.2 Hz, 1 H), 7.32 (td, *J* = 7.2, 1.2 Hz, 1 H), 7.13 (s, 1 H), 4.71 (s, 2 H), 1.45 (sept, *J* = 7.6 Hz, 3 H), 1.19 (d, *J* = 7.6 Hz, 18 H) ppm. $^{13}C$ NMR (101 MHz, $CDCl_3$): $\delta$ = 152.05, 134.78, 130.51, 129.66, 128.64, 127.66, 126.67, 126.23, 123.95, 112.89, 29.83, 18.17, 13.08 ppm. HRMS: *m/z* (DART): calcd. for $MH^+$ 393.12438, found 393.12416.

**2-[(3-Triisopropylsilyloxynaphthalen-2-yl)methoxy]isoindoline-1,3-dione (10):** The procedure used followed a method reported by Zlotorzynska and Sammis.[22] To a stirred solution of *N*-hydroxyphthalimide (613.67 mg, 3.7618 mmol) and *N*-ethyldiisopropylamine (0.65 mL, *d* = 0.742 g/mL at 25 °C, 3.7 mmol) in anhydrous DMF (25 mL) was added all at once a solution of compound **9** (1.35 g, 3.43 mmol) in anhydrous DMF (5 mL) at room temperature. The reaction mixture was stirred and heated at 70 °C for 7 h. The cooled reaction mixture was partitioned between ethyl acetate (50 mL) and water (200 mL), and the aqueous layer was extracted with ethyl acetate (3 × 80 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The crude residue was purified by column chromatography (silica gel/15:85 ethyl acetate/petroleum ether) to yield the title compound **10** as a white solid (1.33 g, 81 %). M.p. 93–96 °C. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 8.01 (s, 1 H), 7.79 (m, 2 H), 7.76 (d, *J* = 8.0 Hz, 1 H), 7.71 (m, 2 H), 7.64 (d, *J* = 8.4 Hz, 1 H), 7.41 (td, *J* = 8.4, 1.2 Hz, 1 H), 7.30 (td, *J* = 8.4, 1.2 Hz, 1 H), 7.15 (s, 1 H), 5.45 (s, 2 H), 1.43 (sept, *J* = 7.6 Hz, 3 H), 1.15 (d, *J* = 7.6 Hz, 18 H) ppm. $^{13}C$ NMR (101 MHz, $CDCl_3$): $\delta$ = 163.51,

152.39, 134.86, 134.29, 130.97, 129.05, 128.57, 127.97, 126.62, 126.26, 123.79, 123.44, 112.73, 75.16, 18.10, 13.08 ppm. (Note: One aromatic $^{13}C$ NMR signal was obscured due to accidental signal equivalence). HRMS: *m/z* (DART): calcd. for $MH^+$ 476.22516, found 476.22527.

***O*-{[3-(Triisopropylsilyloxy)naphthalen-2-yl]methyl}-hydroxylamine (11):** To a stirred solution of compound **10** (1.33 g, 2.80 mmol) in anhydrous $CH_2Cl_2$ (10 mL) at 0 °C in a water/ice bath was added hydrazine monohydrate (0.274 mL, *d* = 1.032 g/mL at 25 °C, 5.65 mmol) in one portion. The reaction mixture was slowly warmed to room temperature and was stirred for an additional 4 h. After the white suspension was filtered off, the filtrate was washed with water (100 mL) and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 80 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to yield the title compound **11** as a colorless oil (0.94 g, 97 %). The target product was used directly without any further purification. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.81 (s, 1 H), 7.77 (d, *J* = 8.0 Hz, 1 H), 7.65 (d, *J* = 8.0 Hz, 1 H), 7.40 (td, *J* = 8.4, 1.2 Hz, 1 H), 7.32 (td, *J* = 8.4, 1.2 Hz, 1 H), 7.13 (s, 1 H), 4.93 (s, 2 H), 1.42 (sept, *J* = 7.6 Hz, 3 H), 1.16 (d, *J* = 7.6 Hz, 18 H), (Note: The $NH_2$ signal was obscured due to rapid proton exchange.) ppm. $^{13}C$ NMR (101 MHz, $CDCl_3$): $\delta$ = 152.41, 134.23, 129.26, 128.72, 127.67, 126.19, 126.08, 123.71, 112.87, 109.98, 74.02, 18.11, 13.05 ppm. HRMS: *m/z* (DART): calcd. for $MH^+$ 346.21968, found 346.21971.

**1,1,1-Trifluoro-*N*-{[3-(triisopropylsilyloxy)naphthalen-2-yl]-methoxy}methanesulfonamide (12):** (The procedure used followed a method reported by Gajewiak and Prestwich.[26]) To a stirred solution of compound **11** (0.94 g, 2.7 mmol), DMAP (331.26 mg, 2.7115 mmol) and anhydrous pyridine (0.218 mL, *d* = 0.978 g/mL at 25 °C, 2.70 mmol) in anhydrous $CH_2Cl_2$ (20 mL) at –15 °C was added dropwise a solution of trifluoromethanesulfonyl chloride (0.376 mL, *d* = 1.583 g/mL at 25 °C, 3.53 mmol) in anhydrous $CH_2Cl_2$ (5 mL). The reaction mixture was slowly warmed to 10 °C over 30 min and was stirred for another 2 h. The reaction mixture was washed with saturated aq. $CuSO_4$ (100 mL), and the aqueous layer extracted with $CH_2Cl_2$ (3 × 80 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The crude residue was purified by column chromatography (silica gel/50:50 $CH_2Cl_2$/petroleum ether) to yield the title product **12** as a highly viscous colorless oil (0.75 g, 58 %). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.82 (s, 1 H), 7.78 (d, *J* = 8.0 Hz, 1 H), 7.66 (d, *J* = 8.0 Hz, 1 H), 7.54 (s, 1 H), 7.43 (td, *J* = 7.2, 1.2 Hz, 1 H), 7.35 (td, *J* = 7.2, 1.2 Hz, 1 H), 7.16 (s, 1 H), 5.24 (s, 2 H), 1.41 (sept, *J* = 7.6 Hz, 3 H), 1.15 (d, *J* = 7.2 Hz, 18 H) ppm. $^{13}C$ NMR (101 MHz, $CDCl_3$): $\delta$ = 152.49, 135.02, 131.56, 128.43, 127.89, 126.96, 126.29, 125.79, 124.14, 119.38 (q, *J* = 326 Hz), 113.09, 76.53, 18.03, 13.01 ppm. $^{19}F$ NMR (376 MHz, $CDCl_3$): $\delta$ = –73.44 ppm. HRMS: *m/z* (DART): calcd. for $MH^+$ 478.16897, found 478.16900.

**1,1,1-Trifluoro-*N*-[(3-hydroxynaphthalen-2-yl)methoxy]methanesulfonamide (1):** (The procedure used followed a method reported by Song et al.[27a]) A KF stock solution (0.15 M) was prepared by dissolving spray-dried potassium fluoride (73.29 mg, 1.261 mmol) in anhydrous tetraethylene glycol (8.42 mL) under sonication. To a stirred solution of compound **12** (119.56 mg, 0.25033 mmol) in anhydrous $CH_2Cl_2$ (0.5 mL) at room temperature was added the KF stock solution (0.15 M, 5 mL, 0.8 mmol) in one portion. The reaction mixture was stirred at room temperature for 2 h before being partitioned between water (300 mL) and ethyl acetate (80 mL). The aqueous layer was extracted with ethyl acetate (3 × 80 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The crude residue was purified by column chromatography (silica gel/30:70 ethyl acetate/petroleum ether) to obtain the title compound **1** as a pale yellow solid (46.23 mg, 57 %). M.p. 103–107 °C. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.79 (s, 1 H), 7.79 (d, *J* = 8.4 Hz, 1 H), 7.69 (d, *J* = 8.4 Hz, 1 H), 7.47 (td, *J* = 7.6, 1.2 Hz, 1 H), 7.36 (td, *J* = 7.6, 1.2 Hz, 1 H), 7.21 (s, 1 H), 5.28 (s, 2 H), (Note: The NH and OH signals were obscured due to rapid proton exchange.) ppm. $^{13}C$ NMR (101 MHz, $CDCl_3$): $\delta$ = 152.28, 135.29, 132.12, 128.56, 128.02, 127.45, 126.15, 124.27, 121.85, 119.34 (q, *J* = 326 Hz), 110.83, 77.26 ppm. $^{19}F$ NMR (376 MHz, $CDCl_3$): $\delta$ = –73.50 ppm. HRMS: *m/z* (DART): calcd. for $MH^+$322.03554, found 322.03549.

***N*-{[3-(Triisopropylsilyloxy)naphthalen-2-yl]methoxy}methanesulfonamide (13):** (The procedure used followed a method reported by Gajewiak and Prestwich.[26]) To a stirred mixture of **11** (362.11 mg, 1.0479 mmol), DMAP (128.20 mg, 1.0494 mmol) and anhydrous pyridine (0.084 mL, *d* = 0.978 g/mL at 25 °C, 1.04 mmol) in anhydrous $CH_2Cl_2$ (20 mL) at - 20 °C was added dropwise a solution of methanesulfonyl chloride (0.106 mL, *d* = 1.48 g/mL at 25 °C, 1.37 mmol) in anhydrous $CH_2Cl_2$ (4 mL). The reaction mixture was slowly warmed to 10 °C over 30 min and was stirred for another 2 h. The reaction mixture was quenched using saturated aq. $CuSO_4$ (100 mL), and the aqueous layer was extracted using $CH_2Cl_2$ (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The crude residue was purified by column chromatography (silica gel/10:90 ethyl acetate/petroleum ether), to give the title compound **13** as a colorless oil (346.55 mg, 78 %). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.85 (s, 1 H), 7.78 (d, *J* = 8.4 Hz, 1 H), 7.66 (d, *J* = 8.4 Hz, 1 H), 7.43 (td, *J* = 8.8, 1.2 Hz, 1 H), 7.34 (td, *J* = 8.8, 1.2 Hz, 1 H), 7.15 (s, 1 H), 6.80 (s, 1 H), 5.24 (s, 2 H), 3.05 (s, 3 H), 1.41 (sept, *J* = 7.6 Hz, 3 H), 1.15 (d, *J* = 7.6 Hz, 18 H) ppm. $^{13}C$ NMR (101 MHz, $CDCl_3$): $\delta$ = 152.52, 134.81, 131.23, 128.52, 127.84, 126.92, 126.70, 126.25, 124.00, 113.02, 75.42, 36.98, 18.09, 13.03 ppm. HRMS: *m/z* (DART): calcd. for $M^+$ 424.19723, found 424.19725.

***N*-[(3-Hydroxynaphthalen-2-yl)methoxy]methanesulfonamide (2):** (The procedure used followed a method reported by Song et al.[27a]) To a stirred solution of compound **13** (187.43 mg, 0.44243 mmol) in anhydrous $CH_2Cl_2$ (0.5 mL) at room temperature was added KF dissolved in tetraethylene glycol (5.80 mL, 0.15 M, 0.87 mmol) in one portion. After stirring for 30 min at room temperature, the reaction mixture was poured into water (400 mL) and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The crude residue was purified by column chromatography (silica gel/30:70 ethyl acetate/petroleum ether) to give the title compound **2** as a white solid (96.31 mg, 81 %). M.p. 157–159 °C. $^1H$ NMR (400 MHz, [$D_6$]DMSO): $\delta$ = 10.05 (s, 1 H), 10.02 (s, 1 H), 7.81 (s, 1 H), 7.80 (d, *J* = 8.0 Hz, 1 H), 7.68 (d, *J* = 8.0 Hz, 1 H), 7.40 (td, *J* = 7.6, 1.2 Hz, 1 H), 7.28 (td, *J* = 7.6, 1.2 Hz, 1 H), 7.17 (s, 1 H), 5.04 (s, 2 H), 3.04 (s, 3 H) ppm. $^{13}C$ NMR (101 MHz, [$D_6$]DMSO): $\delta$ = 153.61, 134.22, 129.37, 127.55, 127.26, 126.21, 125.52, 125.15, 122.81, 108.48, 73.50, 36.38 ppm. HRMS: *m/z* (DART): calcd. for $MH^+$ 268.06381, found 268.06376.

***N*-{[3-(Triisopropylsilyloxy)naphthalen-2-yl]methoxy}benzenesulfonamide (14):** (The procedure used followed a method reported by Gajewiak and Prestwich.[26]) To a stirred mixture of **11** (335.20 mg, 0.97005 mmol), DMAP (118.66 mg, 0.97127 mmol) and anhydrous pyridine (0.078 mL, *d* = 0.978 g/mL at 25 °C, 0.96 mmol) in anhydrous $CH_2Cl_2$ (20 mL) at - 20 °C was added dropwise a solution of benzenesulfonyl chloride (0.161 mL, *d* = 1.384 g/mL at 25 °C, 1.26 mmol) in anhydrous $CH_2Cl_2$ (4 mL) at –20 °C. The reaction mixture was slowly warmed to room temperature over 30 min and was stirred for another 2 h. The reaction mixture was quenched using saturated aq. $CuSO_4$ (200 mL), and the aqueous layer was

extracted using $CH_2Cl_2$ (3 × 50 mL). The combined organic extracts were dried with $MgSO_4$ and the solvent was removed in vacuo. The crude residue was purified by column chromatography (silica gel/10:90 ethyl acetate/petroleum ether) to yield the title compound **14** as a colorless oil (346.55 mg, 74 %). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.95 (m, 2 H), 7.77 (s, 1 H), 7.75 (d, $J$ = 8.0 Hz, 1 H), 7.63 (m, 2 H), 7.52 (m, 2 H), 7.41 (td, $J$ = 7.6, 1.2 Hz, 1 H), 7.33 (td, $J$ = 7.6, 1.2 Hz, 1 H), 7.10 (s, 1 H), 6.86 (s, 1 H), 5.21 (s, 2 H), 1.33 (sept, $J$ = 7.6 Hz, 3 H) 1.08 (d, $J$ = 7.6 Hz, 18 H) ppm. $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta$ = 152.40, 136.81, 134.64, 133.69, 130.51, 128.99, 128.55, 127.80, 127.31, 126.54, 126.23, 123.91, 112.94, 75.23, 18.03, 12.95. (Note: One aromatic $^{13}$C NMR signal was obscured due to accidental signal equvalence.) ppm. HRMS: $m/z$ (DART): calcd. for $MH^+$ 486.21288, found 486.21296.

***N*-[(3-Hydroxynaphthalen-2-yl)methoxy]benzenesulfonamide (3):** (The procedure used followed a method reported by Song et al.[27a]) To a stirred solution of compound **14** (716.52 mg, 1.4752 mmol) in anhydrous $CH_2Cl_2$ (1.0 mL) at room temperature was added KF dissolved in tetraethylene glycol (19.8 mL, 0.15 M, 3.0 mmol) in one portion. After stirring for 30 min at room temperature, the reaction mixture was poured into water (400 mL) and the aqueous layer was extracted with ethyl acetate (3 × 80 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The crude residue was purified by column chromatography (silica gel/30:70 ethyl acetate-petroleum ether) to give the title compound **3** as a white solid (394.82 mg, 81 %). M.p. 172–175 °C. $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta$ = 10.50 (s, 1 H), 10.00 (s, 1 H), 7.90 (m, 2 H), 7.70 (d, $J$ = 8.0 Hz, 1 H), 7.74 (s, 1 H), 7.72 (m, 1 H), 7.64 (m, 3 H), 7.38 (td, $J$ = 8.0, 1.2 Hz, 1 H), 7.27 (td, $J$ = 8.0, 1.2 Hz, 1 H), 7.14 (s, 1 H), 5.05 (s, 2 H) ppm. $^{13}$C NMR (101 MHz, [D$_6$]DMSO): $\delta$ = 153.60, 137.20, 134.21, 133.35, 129.57, 128.92, 127.92, 127.48, 127.18, 126.18, 125.45, 124.96, 122.76, 108.45, 73.55. (Note: Two aromatic $^{13}$C NMR resonances were obscured due to accidental signal equvalence.) ppm. HRMS: $m/z$ (DART): calcd. for $MH^+$ 330.07946, found 330.07941.

### Photolysis of HNO Donor 2 and 3 in the Presence of $H_2OCbl(III)^+$ Using a Stopped-flow Instrument

The photodecomposition of HNO donor **2** in the presence of $H_2OCbl(III)^+$ was carried out under strictly anaerobic conditions using an Applied Photophysics SX20 stopped-flow instrument equipped with a photodiode array detector, using Pro-Data SX (version 2.1.4) and Pro-Data Viewer (version 4.1.10) software. To create strictly anaerobic conditions, the system was pre-treated with anaerobic aqueous sodium dithionite to remove any traces of oxygen and then thoroughly flushed with anaerobic water. The system was continuously purged with nitrogen gas during the data collection process. The anaerobic reactant solutions were prepared in a glovebox. Hamilton gas-tight syringes were used to introduce the reaction solutions into the reservoir syringes of the stopped-flow instrument. Both $H_2OCbl(III)^+$ and nitrosylcobalamin [$NO^-$-Cbl(III)] are stable under irradiation using a xenon lamp (150 W) with a monochromator slit width of 3.0 mm. The photodecomposition of HNO donor **2** or **3** ($1.50 \times 10^{-4}$ M) was also carried out under the xenon lamp of the stopped flow instrument (150 W, monochromator slit width = 3.0 mm) in the presence of $H_2OCbl(III)^+$ ($3.0 \times 10^{-5}$ M) in an anaerobic mixture of phosphate buffer (pH 7.00, 5.0 mM) and $CH_3CN$ (40:60, v/v) at 25 °C.

### Determination of the Amount of HNO Released from HNO Donor 1 Using the HNO Trap $H_2OCbl(III)^+$

All samples were prepared under strictly anaerobic conditions inside a glovebox. A stock solution of $H_2OCbl(III)^+$ was prepared by dissolving HOCbl·HCl in aqueous phosphate buffer (pH 7.00, 5.0 mM) and $CD_3CN$ (40:60, v/v) and the solution was left to equilibrate for 24 h. An HNO donor **1** stock solution in $CD_3CN$ was also prepared. A solution of $H_2OCbl(III)^+$ (200.0 μM) and HNO donor **1** (200.0 μM) in a mixture of phosphate buffer (pH 7.00, 5.0 mM) and $CD_3CN$ (4.0 mL, 40:60, v/v) was prepared in a cuvette fitted with a J-Young air tight cap inside a glovebox. The sample was irradiated using a Q-smart 450 pulsed Nd:YAG laser fitted with 2$^{nd}$ and 4$^{th}$ harmonic generators (1 Hz, ca. 5 ns pulse width, ca. 60 mJ/pulse) for three sets of 10 pulses and six sets of 10 pulses with mixing between the sets of pulses. UV/Vis spectra and $^{19}$F NMR spectra were periodically recorded at 25 °C.

## Acknowledgments

The authors acknowledge the U.S. National Science Foundation (CHE-1306644 and CHE-1545770), and AUT for funding support. We are also grateful to Dr. Mahinda Gangoda for assistance with NMR spectroscopy and Dr. Jacob Shelley for assistance with HRMS experiments.

**Keywords:** Arenes · Sulfonamides · Bioinorganic chemistry · Photolysis · Photochemistry

[1] G. Hasenfuss, J. R. Teerlink, *Eur. Heart J.* **2011**, *32*, 1838–1845.
[2] D. Mozaffarian, E. J. Benjamin, A. S. Go, D. K. Arnett, M. J. Blaha, M. Cushman, S. R. Das, S. de Ferranti, J. P. Despres, H. J. Fullerton, V. J. Howard, M. D. Huffman, C. R. Isasi, M. C. Jimenez, S. E. Judd, B. M. Kissela, J. H. Lichtman, L. D. Lisabeth, S. M. Liu, R. H. Mackey, D. J. Magid, D. K. McGuire, E. R. Mohler, C. S. Moy, P. Muntner, M. E. Mussolino, K. Nasir, R. W. Neumar, G. Nichol, L. Palaniappan, D. K. Pandey, M. J. Reeves, C. J. Rodriguez, W. Rosamond, P. D. Sorlie, J. Stein, A. Towfighi, T. N. Turan, S. S. Virani, D. Woo, R. W. Yeh, M. B. Turner, C. Amer Heart Assoc Stat, S. Stroke Stat, *Circulation* **2016**, *133*, E38–E360.
[3] a) K. M. Miranda, N. Paolocci, T. Katori, D. D. Thomas, E. Ford, M. D. Bartberger, M. G. Espey, D. A. Kass, M. Feelisch, J. M. Fukuto, D. A. Wink, *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 9196–9201; b) N. Paolocci, T. Katori, H. C. Champion, M. E. St. John, K. M. Miranda, J. M. Fukuto, D. A. Wink, D. A. Kass, *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 5537–5542.
[4] a) M. Eberhardt, M. Dux, B. Namer, J. Miljkovic, N. Cordasic, C. Will, T. I. Kichko, J. de la Roche, M. Fischer, S. A. Suárez, D. Bikiel, K. Dorsch, A. Leffler, A. Babes, A. Lampert, J. K. Lennerz, J. Jacobi, M. A. Marti, F. Doctorovich, E. D. Högestätt, P. M. Zygmunt, I. Ivanovic-Burmazovic, K. Messlinger, P. Reeh, M. R. Filipovic, *Nat. Commun.* **2014**, *5*, Article number: 4381; b) W. D. Gao, C. I. Murray, Y. Tian, X. Zhong, J. F. DuMond, X. Shen, B. A. Stanley, D. B. Foster, D. A. Wink, S. B. King, J. E. Van Eyk, N. Paolocci, *Circ. Res.* **2012**, *111*, 1002–1011; c) C. G. Tocchetti, W. Wang, J. P. Froehlich, S. Huke, M. A. Aon, G. M. Wilson, G. Di Benedetto, B. O'Rourke, W. D. Gao, D. A. Wink, J. P. Toscano, M. Zaccolo, D. M. Bers, H. H. Valdivia, H. Cheng, D. A. Kass, N. Paolocci, *Circ. Res.* **2007**, *100*, 96–104; d) Q.-C. Yong, L.-F. Hu, S. Wang, D. Huang, J.-S. Bian, *Cardiovasc. Res.* **2010**, *88*, 482–491.
[5] a) A. Arcaro, G. Lembo, C. G. Tocchetti, *Current Heart Failure Reports* **2014**, *11*, 227–235; b) B. K. Kemp-Harper, J. D. Horowitz, R. H. Ritchie, *Drugs* **2016**, *76*, 1337–1348; c) H. N. Sabbah, C. G. Tocchetti, M. Wang, S. Daya, R. C. Gupta, R. S. Tunin, R. Mazhari, E. Takimoto, N. Paolocci, D. Cowart, W. S. Colucci, D. A. Kass, *Circ. Heart Fail.* **2013**, *6*, 1250–1258.
[6] V. Shafirovich, S. V. Lymar, *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 7340–7345.
[7] a) J. F. DuMond, S. B. King, *Antioxid. Redox Signaling* **2011**, *14*, 1637–1648; b) Z. R. Miao, S. B. King, *Nitric Oxide* **2016**, *57*, 1–14; c) K. M. Miranda, H. T. Nagasawa, J. P. Toscano, *Curr. Top. Med. Chem.* **2005**, *5*, 649–664; d) H. Nakagawa, *J. Inorg. Biochem.* **2013**, *118*, 187–190.
[8] A. Angeli, *Gazz. Chim. Ital.* **1896**, *26*, 17–25.
[9] a) K. Aizawa, H. Nakagawa, K. Matsuo, K. Kawai, N. Ieda, T. Suzuki, N. Miyata, *Bioorg. Med. Chem. Lett.* **2013**, *23*, 2340–2343; b) F. T. Bonner, Y. H. Ko, *Inorg. Chem.* **1992**, *31*, 2514–2519; c) G. Carrone, J. Pellegrino, F. Doctorovich, *Chem. Commun.* **2017**, *53*, 5314–5317; d) O. Piloty, *Ber.*

*Dtsch. Chem. Ges.* **1896**, *29*, 1559–1567; e) K. Sirsalmath, S. A. Suárez, D. E. Bikiel, F. Doctorovich, *J. Inorg. Biochem.* **2013**, *118*, 134–139.

[10] a) D. A. Guthrie, N. Y. Kim, M. A. Siegler, C. D. Moore, J. P. Toscano, *J. Am. Chem. Soc.* **2012**, *134*, 1962–1965; b) D. A. Guthrie, A. Ho, C. G. Takahashi, A. Collins, M. Morris, J. P. Toscano, *J. Org. Chem.* **2015**, *80*, 1338–1348; c) D. A. Guthrie, S. Nourian, C. G. Takahashi, J. P. Toscano, *J. Org. Chem.* **2015**, *80*, 1349–1356.

[11] a) D. Andrei, D. J. Salmon, S. Donzelli, A. Wahab, J. R. Klose, M. L. Citro, J. E. Saavedra, D. A. Wink, K. M. Miranda, L. K. Keefer, *J. Am. Chem. Soc.* **2010**, *132*, 16526–16532; b) G. Bharadwaj, P. G. Z. Benini, D. Basudhar, C. N. Ramos-Colon, G. M. Johnson, M. M. Larriva, L. K. Keefer, D. Andrei, K. M. Miranda, *Nitric Oxide* **2014**, *42*, 70–78; c) Z. Huang, J. Kaur, A. Bhardwaj, N. Alsaleh, J. A. Reisz, J. F. DuMond, S. B. King, J. M. Seubert, Y. Zhang, E. E. Knaus, *J. Med. Chem.* **2012**, *55*, 10262–10271; d) D. J. Salmon, C. L. Torres de Holding, L. Thomas, K. V. Peterson, G. P. Goodman, J. E. Saavedra, A. Srinivasan, K. M. Davies, L. K. Keefer, K. M. Miranda, *Inorg. Chem.* **2011**, *50*, 3262–3270.

[12] a) J. F. DuMond, M. W. Wright, S. B. King, *J. Inorg. Biochem.* **2013**, *118*, 140–147; b) S. Mitroka, M. E. Shoman, J. F. DuMond, L. Bellavia, O. M. Aly, M. Abdel-Aziz, D. B. Kim-Shapiro, S. B. King, *J. Med. Chem.* **2013**, *56*, 6583–6592; c) H. A. H. Mohamed, M. Abdel-Aziz, G. E. A. A. Abuo-Rahma, S. B. King, *Bioorg. Med. Chem.* **2015**, *23*, 6069–6077; d) X. Sha, T. S. Isbell, R. P. Patel, C. S. Day, S. B. King, *J. Am. Chem. Soc.* **2006**, *128*, 9687–9692.

[13] a) Y. Adachi, H. Nakagawa, K. Matsuo, T. Suzuki, N. Miyata, *Chem. Commun.* **2008**, 5149–5151; b) R. N. Atkinson, B. M. Storey, S. B. King, *Tetrahedron Lett.* **1996**, *37*, 9287–9290; c) A. D. Cohen, B.-B. Zeng, S. B. King, J. P. Toscano, *J. Am. Chem. Soc.* **2003**, *125*, 1444–1445; d) A. S. Evans, A. D. Cohen, Z. A. Gurard-Levin, N. Kebede, T. C. Celius, A. P. Miceli, J. P. Toscano, *Can. J. Chem.* **2011**, *89*, 130–138; e) K. Matsuo, H. Nakagawa, Y. Adachi, E. Kameda, H. Tsumoto, T. Suzuki, N. Miyata, *Chem. Commun.* **2010**, *46*, 3788–3790; f) M. G. Memeo, D. Dondi, B. Mannucci, F. Corana, P. Quadrelli, *Tetrahedron* **2013**, *69*, 7387–7394; g) K. P. Schultz, D. W. Spivey, E. K. Loya, J. E. Kellon, L. M. Taylor, M. R. McConville, *Tetrahedron Lett.* **2016**, *57*, 1296–1299; h) A. D. Sutton, M. Williamson, H. Weismiller, J. P. Toscano, *Org. Lett.* **2012**, *14*, 472–475; i) B.-B. Zeng, J. Huang, M. W. Wright, S. B. King, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5565–5568.

[14] a) M. A. Rhine, A. V. Rodrigues, R. J. B. Urbauer, J. L. Urbauer, T. L. Stemmler, T. C. Harrop, *J. Am. Chem. Soc.* **2014**, *136*, 12560–12563; b) C. H. Switzer, T. W. Miller, P. J. Farmer, J. M. Fukuto, *J. Inorg. Biochem.* **2013**, *118*, 128–133; c) Y.-T. Tseng, C.-H. Chen, J.-Y. Lin, B.-H. Li, Y.-H. Lu, C.-H. Lin, H.-T. Chen, T.-C. Weng, D. Sokaras, H.-Y. Chen, Y.-L. Soo, T.-T. Lu, *Chem. Eur. J.* **2015**, *21*, 17570–17573.

[15] a) P. Klán, T. Šolomek, C. G. Bochet, A. Blanc, R. Givens, M. Rubina, V. Popik, A. Kostikov, J. Wirz, *Chem. Rev.* **2013**, *113*, 119–191; b) A. E. Pierri, D. A. Muizzi, A. D. Ostrowski, P. C. Ford, in *Luminescent and photoactive transition metal complexes as biomolecular probes and cellular reagents, Vol. 165* (Ed. K. K. W. Lo), Springer-Verlag Berlin, Berlin, **2015**, pp. 1–45; c) F. I. Rosell, A. G. Mauk, *Coord. Chem. Rev.* **2011**, *255*, 737–756.

[16] a) F. De Sarlo, A. Guarna, *J. Chem. Soc., Perkin Trans. 1* **1976**, 1825–1827; b) P. Quadrelli, P. Caramella, *Curr. Org. Chem.* **2007**, *11*, 959–986.

[17] P. Quadrelli, M. Mella, P. Caramella, *Tetrahedron Lett.* **1999**, *40*, 797–800.

[18] Y. Zhou, R. B. Cink, R. S. Dassanayake, A. J. Seed, N. E. Brasch, P. Sampson, *Angew. Chem. Int. Ed.* **2016**, *55*, 13229–13232; *Angew. Chem.* **2016**, *128*, 13423–13426.

[19] a) L. G. Arnaut, S. J. Formosinho, *J. Photochem. Photobiol. A* **1993**, *75*, 1–20; b) A. Kulikov, S. Arumugam, V. V. Popik, *J. Org. Chem.* **2008**, *73*, 7611–7615.

[20] a) R. Bloch, L. Gilbert, C. Girard, *Tetrahedron Lett.* **1988**, *29*, 1021–1024; b) E. F. J. de Vries, J. Brussee, A. van der Gen, *J. Org. Chem.* **1994**, *59*, 7133–7137; c) P. Saravanan, S. Gupta, A. DattaGupta, S. Gupta, V. K. Singh, *Synth. Commun.* **1997**, *27*, 2695–2699.

[21] a) H. Ishitani, H. Suzuki, Y. Saito, Y. Yamashita, S. Kobayashi, *Eur. J. Org. Chem.* **2015**, 5485–5499; b) J. Zhang, X. Gao, C. Zhang, J. Ma, D. Zhao, *Synth. Commun.* **2009**, *39*, 1640–1654.

[22] M. Zlotorzynska, G. M. Sammis, *Org. Lett.* **2011**, *13*, 6264–6267.

[23] J. Shen, R. Woodward, J. P. Kedenburg, X. Liu, M. Chen, L. Fang, D. Sun, P. G. Wang, *J. Med. Chem.* **2008**, *51*, 7417–7427.

[24] D. P. Sebesta, S. S. O'Rourke, R. L. Martinez, W. A. Pieken, D. P. C. McGee, *Tetrahedron* **1996**, *52*, 14385–14402.

[25] P. M. Wood, L. W. L. Woo, J.-R. Labrosse, M. P. Thomas, M. F. Mahon, S. K. Chander, A. Purohit, M. J. Reed, B. V. L. Potter, *ChemMedChem* **2010**, *5*, 1577–1593.

[26] J. Gajewiak, G. D. Prestwich, *Tetrahedron Lett.* **2006**, *47*, 7607–7609.

[27] a) J. W. Lee, H. Yan, H. B. Jang, H. K. Kim, S.-W. Park, S. Lee, D. Y. Chi, C. E. Song, *Angew. Chem. Int. Ed.* **2009**, *48*, 7683–7686; *Angew. Chem.* **2009**, *121*, 7819–7822; b) H. Yan, J.-S. Oh, C. E. Song, *Org. Biomol. Chem.* **2011**, *9*, 8119–8121.

[28] S. M. Canham, D. J. France, L. E. Overman, *J. Org. Chem.* **2013**, *78*, 9–34.

[29] Z. Huang, Z. Liu, J. Zhou, *J. Am. Chem. Soc.* **2011**, *133*, 15882–15885.

[30] F. Wudl, D. A. Lightner, D. J. Cram, *J. Am. Chem. Soc.* **1967**, *89*, 4099–4101.

[31] S. Braverman, T. Pechenick, Y. Zafrani, *ARKIVOC* **2004**, *part ii*, 51–63.

[32] L. Stryer, *J. Am. Chem. Soc.* **1966**, *88*, 5708–5712.

[33] N. Agmon, *J. Phys. Chem. A* **2005**, *109*, 13–35.

[34] a) L. M. Tolbert, L. C. Harvey, R. C. Lum, *J. Phys. Chem.* **1993**, *97*, 13335–13340; b) L. M. Tolbert, K. M. Solntsev, *Acc. Chem. Res.* **2002**, *35*, 19–27.

[35] W. R. Grither, J. Korang, J. P. Sauer, M. P. Sherman, P. L. Vanegas, M. Zhang, R. D. McCulla, *J. Photochem. Photobiol. A* **2012**, *227*, 1–10.

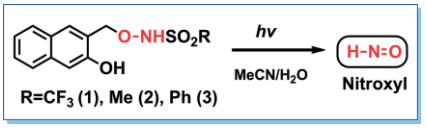
[36] a) T. Elsaesser, W. Kaiser, *Chem. Phys. Lett.* **1986**, *128*, 231–237; b) O. F. Mohammed, S. Luber, V. S. Batista, E. T. J. Nibbering, *J. Phys. Chem. A* **2011**, *115*, 7550–7558.

[37] H. A. Barker, R. D. Smyth, H. Weissbach, J. I. Toohey, J. N. Ladd, B. E. Volcani, *J. Biol. Chem.* **1960**, *235*, 480–488.

Received: January 18, 2018

**Photoactivatable Nitroxyl Donors**






A new family of photoactivatable HNO donors (**1**–**3**) has been developed that incorporate the (3-hydroxy-2-naphthalenyl)methyl (3,2-HNM) phototrigger. The desired HNO-generating pathway is favored only with the excellent $SO_2CF_3$ leaving group (**1**).

**DOI: 10.1002/ejoc.201800092**