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Synthesis and Evaluation of O^2-Derived Diazeniumdiolates Activatable via Bioorthogonal Chemistry Reactions in Living Cells

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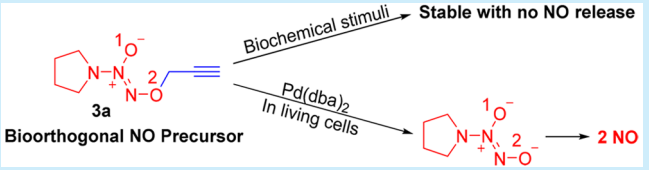
Supporting Information

ABSTRACT: A class of O^2-alkyl derived diazeniumdiolates **3a−f** and **4a−c** were designed and synthesized as new bioorthogonal NO precursors, which can be effectively uncaged in the presence of a palladium catalyst via bioorthogonal bond cleavage reactions to generate NO in living cancer cells, eliciting potent antiproliferative activity.



Over the past decade, bioorthogonal chemistry has become one main driving force in chemical biology, offering an unprecedented chance to dissect native biological processes via chemistry-enabled strategies.[1−3] From traditional "bond formation" reactions to "bond cleavage" reactions, bioorthogonal chemistry has been widely expanded to label, track, manipulate, or activate biomolecules of interest.[4] Recently, the bioorthogonal "bond cleavage" reactions have triggered great enthusiasm.[5] For example, photodeprotection of the *O*-nitrobenzyl (ONB) ether derivatives,[6] Cu(I) or palladium (Pd)-mediated depropargylation and deallylation reactions,[7,8] and tetrazine-triggered inverse electron-demand Diels−Alder (IEDDA) elimination reactions[9] were successfully employed to restore or activate proteins or prodrugs. Notably, the emerging Pd catalysts, which possess unique catalytic properties and good biocompatibility in living cells, could overcome the poor penetration capability of light[8] and cytotoxicity of the Cu(I) ions.[5,10] Among all reported palladium catalysts, Pd(0) catalysts show the best safety[11] and have been successfully used to activate bioorthogonal prodrugs **1a−c** (Figure 1A) of 5-fluoroacil,[12−14] vorinostat,[15] and gemcitabine,[16] respectively.

Nitric oxide (NO) is a widely distributed signaling messenger that mediates numerous physiological processes, including vasodilation, neurotransmission, and immune response.[17] Presently, NO is considered a potential cancer therapeutic agent, and several reviews have described the dichotomous role of NO in cancer biology.[18−21] Generally, an optimal concentration window of NO is preferable for cancer proliferation, while very low intracellular levels of NO induced by nitric oxide synthase (NOS) inhibition, or high levels of NO released by NO donors, could produce a cancer cell growth inhibitory effect.[22−24] Owing to its numerous biological functions and duality in cancer biology, the precise release of NO from the NO donors in location and dose-controlled manners is crucial for NO-based cancer therapy. Diazeniumdiolates (**2**), an important class of NO donor, can spontaneously liberate two molecules of NO under physiological conditions with a range of half-lives from a few seconds to several minutes.[25] Nevertheless, the O^2-derived diazeniumdiolates could generate stable precursors that can be enzymatically cleaved in cancer cells[26,27] to produce diazeniumdiolate anions and subsequently release NO in situ, exhibiting potent and selective antiproliferative activity. Some O^2-derived diazeniumdiolates, such as O^2-2,4-dinitrobenzene diazeniumdiolates[28] together with O^2-(6-oxocyclohex-1-en-1-yl)methyl diazeniumdiolates[29] and O^2-indolequinone diazeniumdiolate (INDQ/NO),[30] were reportedly activatable by glutathione S-transferase (GST)/GSH and NAD(P)H:quinone oxidoreduc-

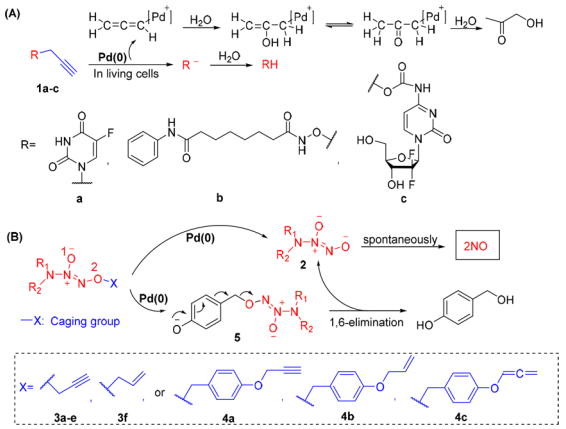


Figure 1. (A) Previous work: Bioorthogonal bond cleavage of *O*/*N*-propargyl prodrugs **1a−c** mediated by Pd(0) catalyst and the underlying mechanism. (B)This work: Rational for the design of new bioorthogonal O^2-derived diazeniumdiolates **3a−f** and **4a−c**.

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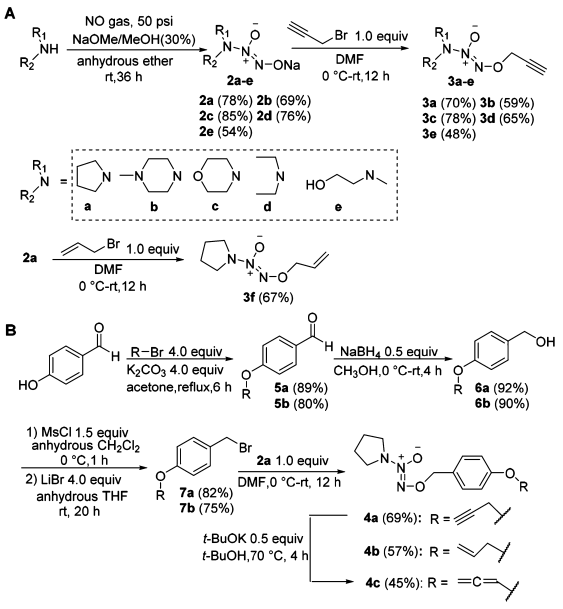
tase (DT-diaphorase), respectively, which are overexpressed in cancer cells. However, current enzymatically triggered O^2-derived diazeniumdiolates mentioned above could inevitably produce off-target effects because those enzymes are overexpressed rather than exclusively expressed in cancer cells.[31,32] Inspired by the bioorthogonal chemistry-based prodrug strategy, especially the Pd(0)-mediated depropargylation and deallylation reactions, we hypothesized that the modification of O^2-site in diazeniumdiolates with propargyl or allyl moieties, which may be exclusively cleaved in the presence of Pd(0) catalysts via bioorthogonal bond cleavage reactions, could produce a new class of bioorthogonal NO precursors that may have potential high specificity relative to the existing enzymatically triggered NO precursors. To test this hypothesis, we designed and synthesized three new types of O^2-derived diazeniumdiolates: O^2-propargyl diazeniumdiolates **3a**−**e**, O^2-allyl diazeniumdiolates **3f**, and O^2-(4-alkyloxybenzyl) diazeniumdiolates **4a**−**c** (Figure 1B). It was proposed that **3a**−**f** can be cleaved from the O^2-propargyl or O^2-allyl groups in the presence of Pd(0) catalysts to produce diazeniumdiolate anion **2** and spontaneously release NO, while **4a**−**c** can be cleaved from the *O*-propargyl, *O*-allyl, or *O*-1,2-allenyl groups[33] by Pd(0) catalysts to generate O^2-(4-hydroxylbenzyl) diazeniumdiolate intermediates **5**, which then generate diazeniumdiolate anion **2** via a well-known self-immolative 1,6-elimination reaction[34] to spontaneously liberate NO under physiological conditions. We further investigated their antiproliferative activity against different cancer cells, the stability in PBS or plasma, and the capability to release NO in the presence or absence of a Pd(0) catalyst in living cells.

The synthetic route of the target compounds **3a**−**f** and **4a**−**c** is depicted in Scheme 1. The reactions of NO gas (50 psi) with the

Scheme 1. Synthetic Route of Compounds 3a−f and 4a−c



different secondary amines in the presence of NaOMe in ether offered diazeniumdiolates sodium salts **2a**−**e**, which were subsequently treated with propargyl bromide to produce the target compounds **3a**−**e**. Similarly, pyrrolidinyl diazeniumdiolate **2a** was treated with allyl bromide to give **3f**. Starting from 4-hydroxy benzaldehyde, the condensation of the hydroxyl group with propargyl bromide or allyl bromide gave 4-propargyloxy benzaldehyde **5a** and 4-allyloxy benzaldehyde **5b**, respectively. The subsequent reduction of **5a**−**b** offered alcohols **6a**−**b**, which were brominated to furnish benzyl bromides **7a**−**b**. Condensation of **7a**−**b** with **2a** resulted in O^2-(4-propargyloxybenzyl) diazeniumdiolate **4a** and O^2-(4-allyloxybenzyl) diazeniumdiolate **4b**, respectively. Interestingly, the reaction of **4a** with *t*-BuOK in *t*-BuOH[33] successfully furnished *O*-1,2-allenyl analogue **4c**, while a similar effort on **3a** did not produce O^2-1,2-allenyl pyrrolidinyl diazeniumdiolate.

We first investigated the antiproliferative activity of target compounds **3a**−**e** against human colon carcinoma HCT116 cells, human ovarian OVCAR5 cells, human leukemia HL-60 cells, and human lung cancer A549 cells in the presence or absence of a Pd(0) catalyst. It was reported that $Pd(dba)_2$, an air-stable Pd(0) catalyst,[35−37] exhibited better safety relative to other Pd(0) catalysts.[10] In our experiment, the treatment of HCT116, A549, HL-60, and OVCAR5 cells with $Pd(dba)_2$ (10 μM) for 72 h did not affect cell viability (>90%) (Figure S1), suggesting good biocompatibility to cancer cells. Furthermore, it has been reported that the 3 h incubation of A549 cells with $Pd(dba)_2$ is sufficient for intracellular uptake of the catalyst to trigger depropargylation or deallylation reactions in living cells.[8] In these regards, the four cancer cells were pretreated without or with $Pd(dba)_2$ (1 μM) for 3 h, rinsed, and then resuspended with **3a**−**e** (1 μM) for an additional 48 h, and cell survival was determined by MTT assay. As shown in Figure 2, without the pretreatment of

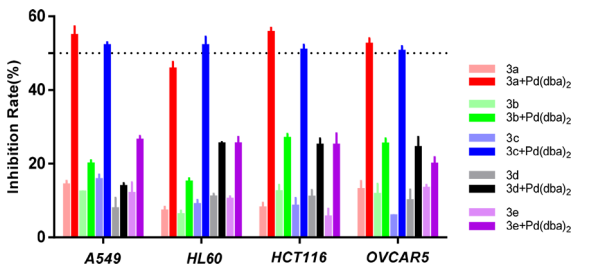


Figure 2. Antiproliferative activity of **3a**−**e** against four cancer cells without or with the pretreatment of $Pd(dba)_2$. A549, HL-60, HCT116, and OVCAR5 cells were incubated without or with the pretreatment of $Pd(dba)_2$ (1 μM) for 3 h, followed by being rinsed and resuspended with **3a**−**e** (1 μM) for 48 h, and cell proliferation was assessed by the MTT assay. Error bars represent ±SD from three independent experiments.

$Pd(dba)_2$, all test compounds (1 μM) exhibited weak antiproliferative activity (inhibitory rates ranging from 5.5% to 15.7%) against four cancer cells. In sharp contrast, with the pretreatment of $Pd(dba)_2$ (1 μM) for 3 h, all test compounds, especially **3a** and **3c**, exhibited significantly enhanced antiproliferative activity (inhibitory rates ranging from 45.7% to 55.6%), suggesting that $Pd(dba)_2$ could trigger bioorthogonal cleavage of an O^2-propargyl bond to liberate diazeniumdioalte anion **2**, which released NO spontaneously in situ, generating a cancer cell growth inhibitory effect.

Next, we selected **3a** and HCT116 cells to study the effect of different concentration ratios of $Pd(dba)_2$/**3a** on cell growth inhibitory activity. HCT116 cells were pretreated with different concentrations of $Pd(dba)_2$ (0.25, 0.5, and 1 μM) for 3 h, followed by being rinsed and resuspended with **3a** (1 μM) for another 48 h. As shown in Figure S2A, with the pretreatment of an equivalent concentration of $Pd(dba)_2$ (1 μM), **3a** (1 μM) exhibited the most potent cell growth inhibitory activity against HCT116 cells. Additionally, the impact of incubation time on the antiproliferative activity was investigated. HCT116 cells were pretreated with $Pd(dba)_2$ (1 μM) for 3 h, followed by being

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Table 1. IC_{50} Values (μM) of Compounds 3a and 3c against HCT116, A549, and CCD-841CoN Cells in the Presence or Absence of $Pd(dba)_2$[a]

	3a	3a + Pd	FI[b]	3c	3c + Pd	FI[b]
HCT116	27.2 ± 3.8	1.4 ± 0.1	19	32.6 ± 2.5	1.3 ± 0.1	25
A549	33.9 ± 4.6	1.5 ± 0.1	23	25.0 ± 3.9	1.5 ± 0.1	17
CCD-841CoN	68.1 ± 4.4	–	–	86.7 ± 5.1	–	–

[a]Cells were incubated without or with different concentrations of $Pd(dba)_2$ for 3 h, rinsed, and then resuspended with equivalent concentrations of test compounds for 72 h. Cell viability was assessed by the MTT assay, and IC_{50} values were calculated accordingly. Data were expressed as the mean ± SD of each group of cells from three individual experiments. [b]FI (fold increase) is defined as IC_{50} (compd alone)/IC_{50} (compd plus $Pd(dba)_2$).

rinsed and resuspended with **3a** (1 μM) for 24, 48, and 72 h, respectively. It was found that the 72 h incubation group exhibited an improved inhibition rate relative to the 24 and 48 h groups (Figure S2B). These data indicated that an equivalent concentration of catalyst to test compound and a 72 h reaction time could be optimal for a bioorthogonal reaction between **3a** and $Pd(dba)_2$ in HCT116 cells.

Accordingly, we determined the IC_{50} values of **3a** and **3c** without or with the pretreatment of $Pd(dba)_2$ against HCT-116 and A549 cells by using the optimized conditions, including an equivalent concentration of $Pd(dba)_2$ and a 72 h incubation time. As summarized in Table 1, **3a** and **3c** exhibited weak antiproliferative activity against HCT116 and A549 cells (IC_{50}'s ranging from 25.0 to 33.9 μM), which may be due to the potential thiol−yne click reactions in living cells.[38,39] In contrast, with the pretreatment of $Pd(dba)_2$, **3a** and **3c** elicited much improved antiproliferative activity against the cells (IC_{50}'s ranging from 1.3 to 1.5 μM) with fold increase (FI) values ranging from 17 to 25. Additionally, the cell growth inhibitory effects of **3a** and **3c** on human normal colonic epithelial CCD 841 CoN cells in the absence of $Pd(dba)_2$ were examined, and the IC_{50} values were 68.1 and 86.7 μM, respectively. These results demonstrated that **3a** and **3c** exhibited much lower antiproliferative activity to normal cells than cancer cells in the absence of the $Pd(dba)_2$ catalyst, whereas they produced potent antiproliferative activity against cancer cells with the pretreatment of $Pd(dba)_2$. Meanwhile, in the LDH assay (Table S1), **3a** exhibited similar IC_{50} values to those in MTT assay against HCT116 cells in the presence or absence of $Pd(dba)_2$. Next, the antiproliferative activity of two fragments of **3a** after $Pd(dba)_2$ mediated biorthogonal reaction, i.e., diazeniumdiolate **2a** and hydroxyacetone, was examined by MTT assay with JS-K as a positive control (Table S2). Expectedly, JS-K (IC_{50} 1.2 μM) displayed potent antiproliferative activity, whereas hydroxyacetone (IC_{50} 259.9 μM) showed weak activity. Interestingly, both **2a** (IC_{50} 155.0 μM) and **2a** plus hydroxyacetone (IC_{50} 120.1 μM) exhibited weak activity. One plausible reason is that the poor cell membrane penetrability and short half-life of **2a** in cell culture medium resulted in fast NO release in the medium rather than the cells.[40] On the basis of the former results, IC_{50} values of the analogue compounds **3f** and **4a−c** against HCT116 cells were further examined by MTT assay (Table S3). Expectedly, all the test compounds elicited more significant antiproliferative activity in the presence of $Pd(dba)_2$ (IC_{50}'s ranging from 1.5 to 7.0 μM) than in the absence of $Pd(dba)_2$ (26.9−32.7 μM). Notably, the reaction of $Pd(dba)_2$ with the propargyl moiety could form an [allenyl-Pd(II)] complex (Figure 1A), which is a good electrophile and may react with some biomolecules. Accordingly, we studied the cell growth inhibitory effect of (4-(prop-2-yn-1-yloxy)phenyl)methanol (**6a**) which has a propargyl group without NO production. It was found that **6a** showed a weak inhibitory rate (7.29% at 1 μM for 72 h), and the pretreatment of $Pd(dba)_2$ did not enhance the inhibitory rate of **6a** (Figure S3), suggesting that the [allenyl-Pd(II)] complex may have little influence on biological activity.

Next, the decomposition rates and NO release kinetics of **3a−f**, **4a−c** in the presence of an equivalent concentration of $Pd(dba)_2$ in PBS (pH = 7.4) were examined by HPLC and Griess assays,[41] respectively (Figure S4). Compound **3a** was quickly degraded (about 49.9% remained at 0.5 h, and 20.6% remained at 24 h) with a large amount of NO generation (up to 58.0% of theoretical maximum yield at 24 h) (Figure S4A). Importantly, **3a** exhibited excellent stability in PBS (pH = 7.4) and bovine plasma even after incubation for 24 h (Figure S5). Furthermore, the NO release behaviors of **3a−f** and **4a−c** in HCT116 cells without or with the pretreatment of $Pd(dba)_2$ were investigated by using a well-known NO sensitive fluorophore probe, 4-amino-5-(methylamino)-2′,7′-difluorofluorescein diacetate (DAF-FM DA).[42] All the compounds alone generated very low fluorescence in HCT116 cells as in the case of the blank control. In contrast, with the pretreatment of an equivalent concentration of $Pd(dba)_2$, they generated significant fluorescence in HCT116 cells. Interestingly, the amounts of NO release in cells from the compounds were correlated with their IC_{50}'s (Figure 3A and Figure S6A). For example, **3a** with an IC_{50} of 1.4 μM exhibited a relative mean fluorescence intensity (MFI) of 9.70, whereas **4a** with an IC_{50} of 7.0 μM exhibited a relative MIF of 4.26. Moreover, **3a** generated significant fluorescence in a dose-dependent manner in HCT116 cells (Figure 3B and Figure S6B), suggesting $Pd(dba)_2$ could effectively induce bioorthogonal cleavage of **3a** and produce a diazeniumdiolate anion, which released NO spontaneously in living cells.

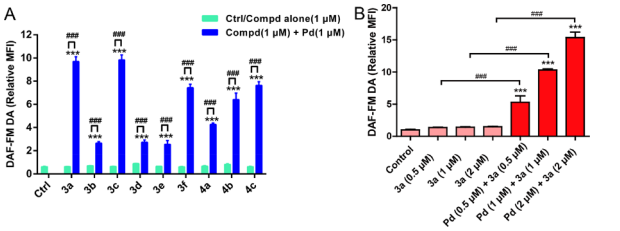

Figure 3. NO release behavior of **3a−f**, **4a−c** (A) and **3a** (B) in HCT116 cells. HCT116 cells were treated without or with $Pd(dba)_2$ at the indicated concentrations for 3 h, followed by the equivalent concentrations of test compound for 8 h, and then stained with DAF-FM DA and analyzed by fluorescence-activated cell sorting (FACS). Data are presented as means ± SD (n = 3). ***P < 0.001 vs control group, $^{###}P$ < 0.001.

Herein, we report, for the first time, a new class of O^2-alkyl derived diazeniumdiolates **3a−f** and **4a−c**, which can be uncaged by a biocompatible Pd(0) catalyst ($Pd(dba)_2$) via bioorthogonal bond cleavage reactions to liberate NO in living cells. O^2-Propargyl pyrrolidinyl diazeniumdiolate **3a** is metabolically

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stable in plasma and can be effectively activated by $Pd(dba)_2$ to generate NO, exhibiting potent antiproliferative activity against cancer cells. Compared to previously reported O^2-derived diazeniumdiolates, which could be activated by hydrolytic enzymes[28−30,43] or other biochemical stimuli,[44] this class of bioorthogonal NO precursors may exhibit high specificity to the introduced Pd(0) catalyst rather than pathological microenvironments in cancer cells. Notably, the Pd-labile NO precursors would serve to expand the therapeutic potential of NO-based anticancer agents and the scope of biorthogonal chemistry utility in the near future.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00423.

Experimental procedures and compound characterization for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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