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Palladium-Catalyzed C(sp^3)−H Nitrooxylation with *tert*-Butyl Nitrite and Molecular Oxygen

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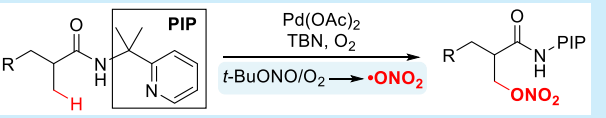
ABSTRACT: Herein, we report a Pd(II)-catalyzed nitrooxylation of unactivated methyl C(sp^3)−H bonds using commercial available and easily manageable *tert*-butyl nitrite as the precursor of ONO_2 radical under aerobic conditions. Environmentally benign molecular oxygen is used to initiate the generation of active radical reactant; it is also used as the terminal oxidant. A broad range of nitrooxylated aliphatic carboxamides were prepared in moderate to good yields under mild conditions.



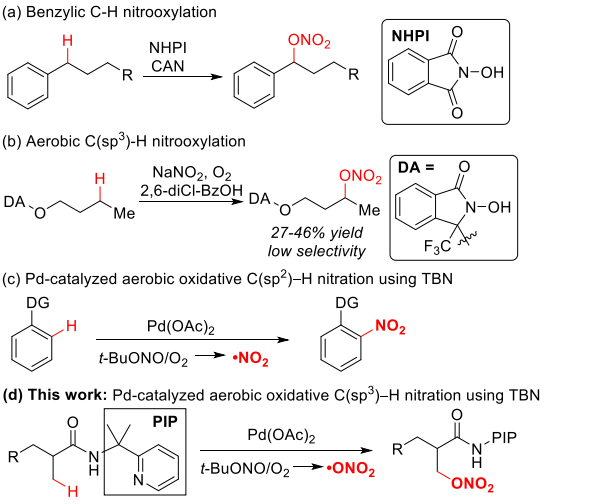
Organic nitrate esters are an important class of compounds, which are used for the treatment of vascular aliments and are widely present in pharmaceutical and bioactive compounds (Figure 1).[1] In addition, the nitrooxy

Figure 1. Commercial drugs containing nitrooxy group.

group can be transformed to C−N, C−O, and C−C functional groups.[2] Traditionally, esterification of alcohols with nitric acid was used to prepare organic nitrates.[3] However, this approach has several drawbacks, including hazardous reaction procedures, poor functional group tolerance, and harsh reaction conditions. Alternative strategies have been developed to access these compounds. In 2011, the Inoue group achieved the C−H nitrooxylation at benzylic positions by employing the *N*-hydroxyphthalimide (NHPI) catalyst and cerium(IV) ammonium nitrate (CAN) reagent (Scheme 1a).[4] In 2016, Kanai and co-workers reported an aerobic C(sp^3)−H nitrooxylation based on an *N*-hydroxyamide-derived directing activator (DA), albeit with low yields (27%−46%) and poor chemoselectivity with overoxidation (Scheme 1b).[5] Therefore, although these early efforts of radical involved C(sp^3)−H nitrooxylation strategies demonstrated the potential of direct transformation of C(sp^3)−H bonds into the nitrooxy group, the development of efficient methods for the C(sp^3)−H nitrooxylation under mild conditions using simple and readily available nitrooxylation reagents is still highly desirable.

In recent years, Pd-catalyzed C(sp^3)−H functionalization has become a powerful and versatile strategy to construct C−O and C−N bonds.[6] Among several catalytic cycles, those involving high-valent palladium, such as Pd(III) and Pd(IV), are major pathways that have been broadly employed,

Scheme 1. Development of C(sp^3)−H Nitrooxylation



generally using stoichiometric organic or inorganic oxidants, such as $PhI(OAc)_2$, $K_2S_2O_8$, BQ, and others.[6,7] However, the use of stoichiometric oxidants led to the generation of undesired byproducts, poor atom economy, and high cost. With respect to green chemistry, oxygen is regarded as a clean and inexpensive oxidant in organic synthesis.[8] Thus, the development of Pd-catalyzed C(sp^3)−H oxygenation using oxygen as the oxidant is highly demanding. Many elegant works have been reported on the use of oxygen as the sole oxidant; however, most of them were limited to the Pd^{II}/Pd^0

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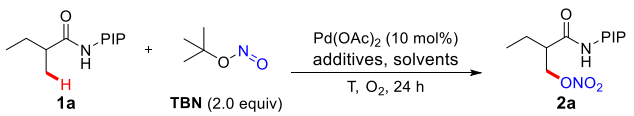
catalytic cycle pathway.[8,9] Recently, elegant works on Pd-catalyzed aerobic oxidative formation of C−O, C−N, and C−C bonds through reductive elimination from high-valent palladium species have been reported.[10] In 2015, the Jiao group reported the aerobic oxidation of Pd^{II} to Pd^{IV} using simple and commercially available *tert*-butyl nitrite (TBN) as the radical precursors to achieve the direct C(sp^2)−H nitration (Scheme 1c).[10g] Mechanistic studies revealed that TBN decomposed to the NO radical, which could be directly oxidized to the NO_2 radical by O_2. The in-situ-generated NO_2 radical enabled the facile C(sp^2)−H nitration.[10g] However, TBN has never been used as the source of the ONO_2 radical to enable the more challenging nitrooxylation reaction. Herein, we report that the readily available and easy-to-handle TBN could act as the precursor of ONO_2 radical to give the C(sp^3)−H nitrooxylation products.[11] Environmentally benign molecular oxygen is used as the terminal oxidant and reactant. Notably, this is the first example of using TBN as ONO_2 radical precursor in C−H activation reaction.

We performed our investigations using **1a** bearing a strong bidentate 2-pyridinylisopropyl (PIP) directing group[12,13] as the model substrate under O_2 atmosphere (Table 1). When the reaction was conducted in toluene at 100 °C, the desired product **2a** was obtained in 33% yield (Table 1, entry 1). A thorough screening of various solvents showed that toluene was the optimal solvent for this transformation (Table 1, entries 2−7). Notably, the yield could be significantly improved when using quaternary ammonium salts as additives (Table 1, entries 8 and 9). The use of 0.1 equiv of TBAOAc as an additive gave the desired product **2a** in 58% yield (Table 1, entry 9). The addition of TBAOAc might provide extra acetate to promote the acetate-mediated concerted metalation-deprotonation (CMD)-type C−H cleavage. Lowering the reaction temperature led to improved yield (Table 1, entries 9−11) and nitrooxylation product **2a** was obtained in 66% isolated yield when the reaction was conducted at 60 °C (Table 1, entry 11). As a control, no desired product was detected in the absence of Pd catalyst under standard conditions or higher temperature (Table 1, entries 12 and 13), suggesting that the Pd catalyst was crucial to the reaction.

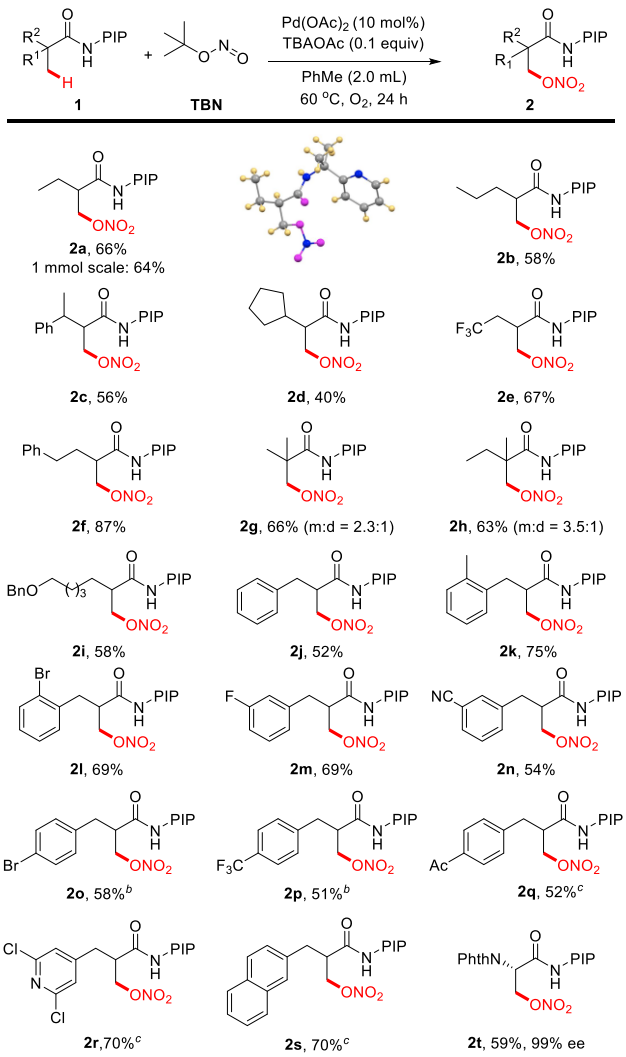
Table 1. Optimization of Reaction Conditions[a]



entry	additive	solvent	temperature, t (°C)	yield[b] (%)
1	–	toluene	100	38
2	–	MeCN	100	trace
3	–	dioxane	100	15
4	–	DCE	100	20
5	–	THF	100	trace
6	–	*t*-BuOH	100	trace
7	–	PhCl	100	22
8	TBAI	toluene	100	54[c]
9	TBAOAc	toluene	100	58
10	TBAOAc	toluene	80	70
11	**TBAOAc**	**toluene**	**60**	**70 (66)**[c]
12[d]	TBAOAc	toluene	60	0
13[d]	TBAOAc	toluene	100	0

[a]Reaction conditions: **1a** (0.2 mmol), TBN (2.0 euqiv), $Pd(OAc)_2$ (10 mol %), additive (0.1 equiv) in 2 mL solvent at temperature t (°C) under O_2 for 24 h. [b]^{1}H NMR yield using CH_2Br_2 as internal standard. [c]Isolated yield. [d]No $Pd(OAc)_2$.

Scheme 2. Scope of Aliphatic Carboxamides[a]



[a]Reaction conditions: **1** (0.2 mmol), TBN (2.0 equiv), $Pd(OAc)_2$ (10 mol %), TBAOAc (0.1 equiv) in toluene (2.0 mL) under O_2 at 60 °C for 24 h. [b]At 45 °C. [c]At 80 °C. The ellipsoids drawn at 30% probability level.

With the optimized reaction conditions in hand, the efficiency and practicality of the strategy was further proved by the compatibility with a range of aliphatic carboxamides (Scheme 2). Aliphatic carboxamides bearing α-tertiary carbons with different alkyl chains were compatible, giving the desired products in moderate to good yields (40%−87% yield, **2a**−**2f**). Carboxamide **1e** with trifluoromethyl group at the β-position was also tolerated well and gave the product **2e** in 67% yield. Notably, aliphatic carboxamides with more sterically hindered α-quaternary carbons were still compatible to this reaction protocol and gave the nitrooxylation products in good yields, albeit with a mixture of mononitrooxylation (m) and dinitrooxylation (d) (**2g**, 66%, m:d = 2.3:1; **2h**, 63%, m:d = 3.5:1). Carboxamide **1i** bearing a benzyl ether also reacted smoothly, giving **2i** in 58% yield. A broad range of electron-donating and electron-withdrawing substituents on the

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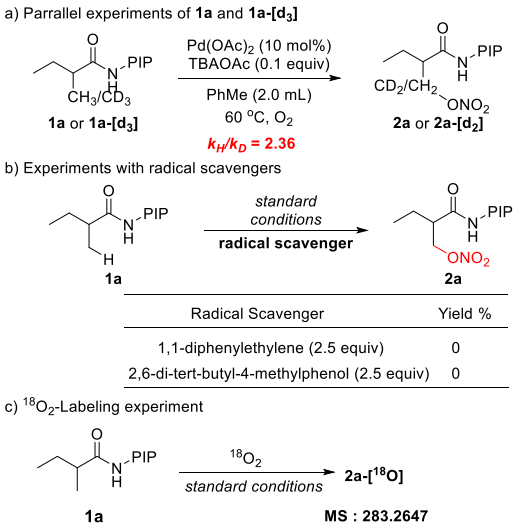
aromatic ring were tolerated well (51%−75% yield, **2j**−**2q**). In addition, carboxamides bearing a pyridyl group and an electron-rich naphthyl group also reacted well, giving the corresponding products **2r** (70%) and **2s** (70%) when the reaction temperature was increased to 80 °C. Note that the *N*-phthaloyl protected alanine **1t** was also compatible with the reaction, affording the corresponding product **2t** in 59% yield without any racemization (99% ee). The structure of the nitrooxylation product **2a** was determined by X-ray crystallographic analysis.

To gain more insight into the mechanism, a range of experiments were conducted. The kinetic isotope effect (KIE) experiments were conducted and a KIE value of k_H/k_D = 2.36 was obtained (Scheme 3a), indicating that the C−H cleavage

Scheme 3. Mechanistic Studies

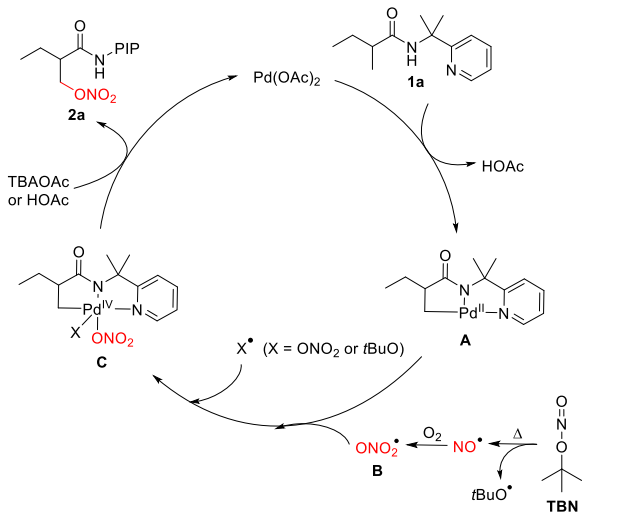


step is likely the rate-determining step of the reaction pathway. The addition of 1,1-diphenylethylene or 2,6-di-*tert*-butyl-4-methylphenol as a radical quencher inhibited the reaction completely (Scheme 3b), indicating that a radical process might be involved. We then performed the reaction under the $^{18}O_2$ atmosphere; the mass of the product **2a**-[^{18}**O**] shows that ^{18}O was incorporated into the product (Scheme 3c; see Section 2.3 in the Supporting Information for details).

Based on the above studies and previous reports,[10g,11] a plausible mechanism for the Pd(II)-catalyzed aerobic oxidation of unactived C(sp^3)−H bonds is presented (Scheme 4). Coordination of **1a** with palladium acetate is followed by a rate-determining C−H activation step to form palladacycle **A**. Meanwhile, TBN could decompose to generate the NO radical, which could be oxidized to ONO_2 radical **B** by O_2.[10g,11] Oxidation of palladacycle **A** with ONO_2 radical **B** gives high-valent Pd(IV) complex **C**. The C−O bond formation through reductive elimination then affords the corresponding desired nitrooxylation product **2a**, along with the regeneration of $Pd(OAc)_2$ by ligand exchange.

In summary, we have developed a Pd(II)-catalyzed nitrooxylation of unactivated C(sp^3)−H bonds using commercial available *tert*-butyl nitrite (TBN) as ONO_2 radical precursor for the first time. Oxygen is employed as oxygen source to initiate the generation of active radical reactants and as the terminal oxidant. The nitrooxylation reaction may proceed

Scheme 4. Proposed Mechanism



through a Pd-mediated radical pathway involving a $Pd^{II/IV}$ catalytic cycle.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03794.

Experimental details and spectral data for all new compounds (PDF)

Accession Codes

CCDC 2021467 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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