Palladium-Catalyzed β-C(sp^3)−H Nitrooxylation of Ketones and Amides Using Practical Oxidants

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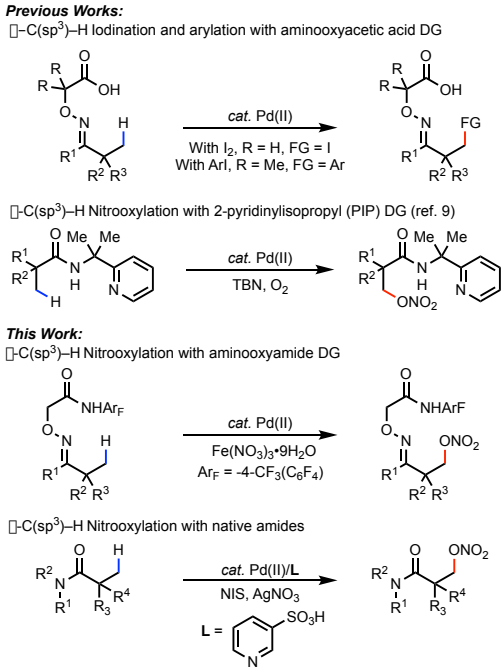
ABSTRACT: Herein we report a Pd(II)-catalyzed β-C(sp^3)−H nitrooxylation of ketones and native amides. The fine-tuned removable aminooxyamide auxiliary enabled β-C(sp^3)−H functionalization of various aliphatic ketones. Practical iron(III) nitrate nonahydrate was used as the nitrate source and a single-electron oxidant for Pd(II)/Pd(III)/Pd(IV) catalysis. For amide substrates, *N*-iodosuccinimide (NIS) was applied as a bystanding two-electron oxidant in combination with silver nitrate for β-C(sp^3)−H nitrooxylation. Palladacycle intermediates were isolated and characterized to elucidate the reaction mechanism for the C(sp^3)−H activation of ketones with the L, X-type imino-amide directing group.

Direct functionalization of unactivated C(sp^3)−H bonds has received broad attention as an attractive alternative to classical C−O bond forming reactions.[1] Compared to C(sp^3)−H functionalization methods for carboxylic acids and their derivatives, only a handful of reports exist for the C(sp^3)−H activation of ketones.[2,3] Recently, our group developed a versatile L, X-type bidentate directing group (DG) which enabled the β-C(sp^3)−H iodination and (hetero)arylation of ketones (Scheme 1).[3] However, catalytic methods that enable C−O bond formation in ketone substrates remain limited to oxidation reactions that use impractical reagents such as PhI(OAc)$_2$.[2a] Considering the ubiquity of carbonyl motifs in organic synthesis, it would be highly desirable to expand C(sp^3)−H oxidation protocols using more practical oxidants.

Among the many oxygen-containing functional groups, the applications of the nitrooxy group are unique and diverse. Organic nitrates can be found in various drugs such as nitric oxide (NO) donors,[4] used in high-performing energetic materials[5] and can be utilized as versatile handles to introduce other important functional groups in organic synthesis.[6] However, synthetic methods to access these useful compounds have remained underdeveloped.[7] Installations of the −ONO$_2$ functional group usually require pre-functionalized starting materials and harsh reagents, such as nitric acid.[6,7a] To address these shortcomings, various C−H functionalization protocols have been developed for the preparation of organic nitrate esters. Radical based HAT reactions are also used to achieve the nitrooxylation of benzylic or methylene C(sp^3)−H.[8] Recently, the Shi group reported the Pd(II)-catalyzed β-C(sp^3)−H nitrooxylation of aliphatic amides bearing the strongly coordinating bidentate 2-pyridinylisopropyl (PIP) directing group using tert-butyl nitrite (TBN).[9]

Scheme 1. Palladium Catalyzed β-C(sp^3)−H Functionalization of Ketones and Amides

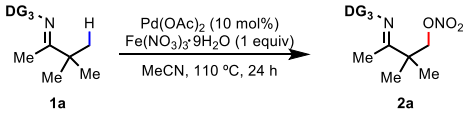


Herein, we report the Pd(II)-catalyzed β-C(sp^3)−H nitrooxylation of ketones with a bidentate aminooxyamide auxiliary using iron(III) nitrate nonahydrate as the nitrate source and sole oxidant.[10] Moreover, with the enhancing effect of a pyridine-3-sulfonic acid ligand, a broad range of neutral amides, including α-hydrogen-containing substrates and lactams, were successfully nitrooxylated without the installation of exogeneous directing groups. NIS was employed as the bystanding oxidant and silver nitrate as nitrate source.

We began our study with β-C(sp^3)−H nitrooxylation of pinacolone. Gratifyingly, the nitrooxylated product **2a** could be obtained in 20% yield using **DG$_1$** with TBN (See SI). The desired

product was observed in 23% yield when an electron-deficient amide (**DG$_3$**) was installed instead of the carboxylic acid (Table 1, entry 10).[11] After screening other nitrate sources (Table 1, entries 6–10), $Fe(NO_3)_3{\cdot}9H_2O$ was found to be the best reagent, providing the mono-selective nitrooxylation product in 81% isolated yield (Table 1, entry 1). Bidentate **DG$_1$** and **DG$_2$**, used for *β*-C(sp^3)–H iodination and (hetero)arylation respectively, did not afford any product with $Fe(NO_3)_3{\cdot}9H_2O$ as the nitrate source. Considering the previous success of using single electron-oxidants such as Ce(IV) and Fe(III) for the oxidation of Pd(II) to Pd(III) and subsequently Pd(IV) to promote reductive elimination,[12] $Fe(NO_3)_3{\cdot}9H_2O$ might function as one such oxidant in this reaction. Other amides **DG$_4$** and tridentate **DG$_5$** were also tried but provided products in lower yields than **DG$_3$** (Table 1, entries 2–5). Lowering or increasing the temperature from 110 °C resulted in lower yields (Table 1, entries 11–12).

Table 1. Evaluation of Conditions for the C(sp^3)–H Ni-trooxylation of Ketones[a,b]



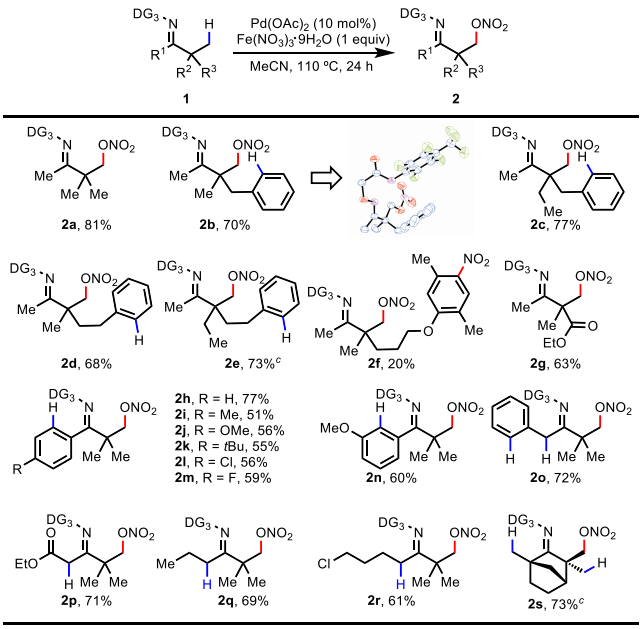
entry	deviation from conditions	Yield
1	None	81%
2	**DG$_1$** instead of **DG$_3$**	No Product
3	**DG$_2$** instead of **DG$_3$**	No Product
4	**DG$_4$** instead of **DG$_3$**	8%
5	**DG$_5$** instead of **DG$_3$**	25%
6	$Al(NO_3)_3{\cdot}9H_2O$ instead of $Fe(NO_3)_3{\cdot}9H_2O$	49%
7	$AgNO_2$ instead of $Fe(NO_3)_3{\cdot}9H_2O$	No Product
8	$AgNO_3$ instead of $Fe(NO_3)_3{\cdot}9H_2O$	No Product
9	$Cu(NO_3)_2{\cdot}3H_2O$ instead of $Fe(NO_3)_3{\cdot}9H_2O$	No Product
10	TBN instead of $Fe(NO_3)_3{\cdot}9H_2O$	23%
11	100 °C instead of 110 °C	45%
12	120 °C instead of 110 °C	41%

DG$_1$= **DG$_2$**= **DG$_3$**= **DG$_4$**= **DG$_5$**=

[a]Conditions: Substrate (0.05 mmol, 1.0 equiv), $Pd(OAc)_2$ (10 mol %), nitrate source (1 equiv), MeCN (2 mL), 110 ºC, under air, 24 h. [b]Isolated yields.

With the optimal conditions established, we set out to explore the scope of ketones (Table 2). We began exploring the scope using various methyl ketones (**2a**–**g**). Alkyl substituted ketones were *β*-nitrooxylated in good-to-excellent yields (**2q**, **2s**). Notably, C(sp^3)–H bonds were selectively functionalized, even in the presence of potentially reactive C(sp^2)–H bonds in aromatic systems nearby the directing group (**2b**–**e**). The structure of **2b** was confirmed by X-ray crystallography. A ketone derived from gemfibrozil was nitrooxylated at the *β*-methyl group and also nitrated on the aromatic ring (**2f**). Presumably, the aromatic nitration side reaction led to the low yield of **2f**. A variety of *meta*- and *para*- substituted aromatic rings in acetophenone-derived substrates remained intact under the nitrooxylation conditions (**2h**–**n**). Remarkably, no *α*-nitrooxylation was observed in the presence of acidic *α*-hydrogens and only *β*-C(sp^3)–H nitrooxylation products were obtained (**2o**–**p**), demonstrating the effectiveness of the bidentate directing

Table 2. Substrate Scope for C(sp^3)–H Nitrooxylation of Ketones[a,b,c]



[a]Conditions: Substrate (0.05 mmol, 1.0 equiv), $Pd(OAc)_2$ (10 mol %), $Fe(NO_3)_3{\cdot}9H_2O$ (1 equiv), MeCN (2 mL), 110 ºC, under air, 24 h. [b]Isolated yields. [c]$Al(NO_3)_3{\cdot}9H_2O$ instead of $Fe(NO_3)_3{\cdot}9H_2O$.

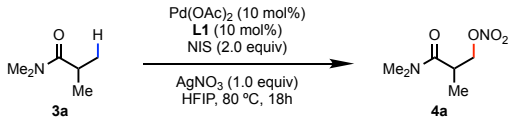
group. To our satisfaction, a variety of functional groups, including ester (**2g**, **2p**), methoxy (**2j**, **2n**), chloro (**2l**, **2r**) and fluoro (**2m**) substituents, were tolerated under the reaction conditions. The bicyclic natural product fenchone was nitrooxylated with good monoselectivity, despite the presence of three *α*-methyl groups (**2s**). Ketone derivatives with an α-tertiary carbon were unreactive under these conditions, indicating the importance of the Thorpe-Ingold effect for reactivity.

Amides are common functional groups among both drugs and natural products. Correspondingly, in recent years great attention has been directed towards the C(sp^3)–H activation of amides. However, the scope for the majority of these reactions was limited to amides bearing bespoke directing motifs, such as perfluorinated amides or bidentate directing groups.[1g,13] Recently, our group reported the C(sp^3)–H activation of native amides directed by the oxygen of carbonyls. The key to the success of this strategy was the use of a pyridine-3-sulfonic acid ligand, which enhances reactivity by stabilizing the substrate-bound Pd species.[14] Despite these advances, C(sp^3)–H functionalizations of native amides are limited to C–C bond formations, including arylation, olefination and [3+2] reactions.[14,15] Inspired by our findings on C(sp^3)–H nitrooxylation of ketone substrates, we decided to explore the scope of this transformation with amide substrates using a pyridine-3-sulfonic acid ligand.

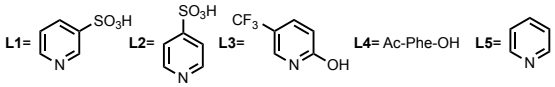
However, the best conditions for the nitrooxylation of ketones did not afford any desired product when *N*,*N*-dimethylisobutyramide (**3a**) was applied, even with the pyridine-3-sulfonic acid ligand (**L1**). We hypothesized that the addition of a

stronger bystanding oxidant,[16] which would enable facile access to high-valent Pd(IV) species, could accelerate the desired C–O bond forming reductive elimination step to give the nitrooxylation product. Gratifyingly, we could observe **4a** with 10% yield when *N*-iodosuccinimide (NIS) was added to the system as an external oxidant and hexafluoroisopropanol (HFIP) was used as the solvent (Table 3, entry 3). After screening other nitrate sources, silver nitrate was found to be the best nitrate source, providing the mono-selective nitrooxylation product in 96% ^{1}H NMR yield (Table 3, entry 1). When **L1** was removed from the system, the yield dropped significantly to 27% (Table 3, entry 8). 4-Pyridinesulfonic acid (**L2**) also exhibited a ligand effect, but delivered the product in lower yield than **L1** (entry 9). Other types of ligands such as 2-pyridone ligand (**L3**), mono-*N*-protected amino acid (**L4**) and pyridine (**L5**) were also tested and showed similar yields to conditions using no ligand (Table 3, entries 10–12).

Table 3. Evaluation of Conditions for C(sp^3)–H Nitrooxylation of Native Amides[a,b]



entry	deviation from conditions	Yield
1	None	96%
2	$Fe(NO_3)_3$•$9H_2O$ instead of $AgNO_3$, no NIS	No Product
3	$Fe(NO_3)_3$•$9H_2O$ instead of $AgNO_3$	10%
4	$(NH_4)_2Ce(NO_3)_6$ instead of $AgNO_3$	23%
5	$NaNO_3$ instead of $AgNO_3$	29%
6	$Ce(NO_3)_3$•$6H_2O$ instead of $AgNO_3$	No Product
7	TBN instead of $AgNO_3$	No Product
8	No **L**	27%
9	**L2** instead of **L1**	66%
10	**L3** instead of **L1**	25%
11	**L4** instead of **L1**	24%
12	**L5** instead of **L1**	24%

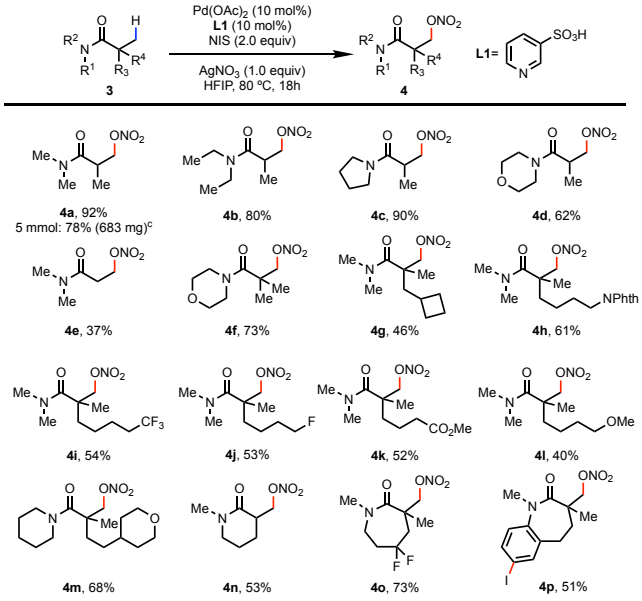


[a]Conditions: Substrate **3a** (0.10 mmol, 1.0 equiv), $Pd(OAc)_2$ (10 mol %), nitrate reagent (1.0 equiv), NIS (2.0 equiv), HFIP (1 mL), 80 °C, under air, 18 h. [b]The yields were determined by ^{1}H NMR analysis of the crude product using dibromomethane (CH_2Br_2) as the internal standard.

With the best conditions in hand, we next explored the scope of amide substrates (Table 4). A series of butyric acid-derived amides were functionalized in good yields with excellent mono-selectivity (**4a**–**4d**). Scaling up to 5 mmol reaction of **3a** afforded 78% isolated yield (683 mg of **4a**) demonstrating the potential scalability of amide nitrooxylation. A propionamide substrate delivered the nitrooxylated product in moderate yield (**4e**). The low yield of this substrate is probably due to the diminished Thorpe-Ingold effect. An α-quaternary substrate derived from pivalic acid provided the product in 73% yield (**4f**). An amide bearing a cyclobutane ring afforded the desired product in moderate yield (**4g**). Substrates bearing a protected amine as well as trifluoromethyl, fluorine, ester and ether functional groups were all tolerated (**4h**–**4m**). Interestingly, a 6-membered lactam substrate bearing an α-hydrogen was also compatible with this reaction (**4n**), showing the generality of the amide-directed nitrooxylation. Functionalized 7-membered lactams were also compatible substrates for the nitrooxylation reaction as well (**4o**–**4p**). For the benzofused lactam, C(sp^2)–H iodination also took place on the *para*-position of the nitrogen (**4p**). It is noteworthy that the nitrooxylation reactions were highly mono-selective.

We were pleased to observe the formation of palladacycle intermediates **5** and **5a** by treating **1a** with 1.2 equiv of $Pd(OAc)_2$ in MeCN at 60 °C.[3a] Complex **5** was isolated in 88% yield by trapping with triphenylphosphine (PPh_3) and complex **5a** in 81% yield by trapping with pyridine (Scheme 2a). The structure of **5** was confirmed by X-ray crystallography. These intermediates provide direct evidence for the L, X-coordination mode of the imino-amide group, confirming its role as the directing moiety for C–H activation. Complexes **5** and **5a** were then tested catalytically or stoichiometrically for C–H nitrooxylation. **1a** could be *β*-nitrooxylated in 44% yield using 10 mol% **5** as the catalyst under the standard conditions (Scheme 2b). Reaction of **5** with 1.0 equiv of $Fe(NO_3)_3$·$9H_2O$ in MeCN at 70 °C yielded

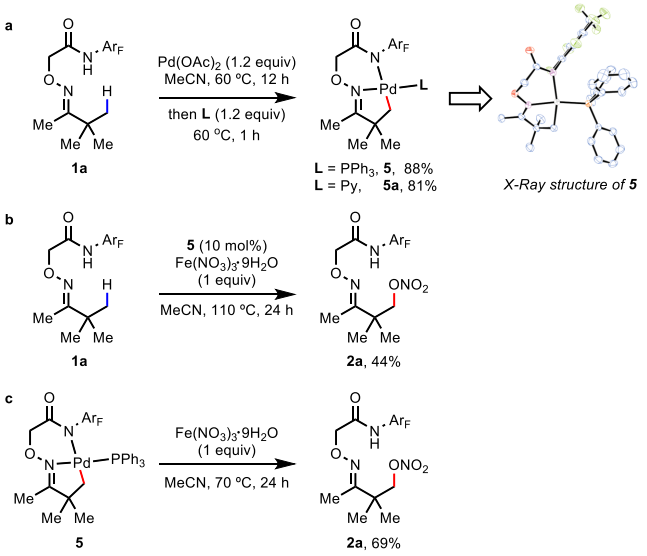
Table 4. Substrate Scope for C(sp^3)–H Nitrooxylation of Amides[a,b,c]



[a]Conditions: Substrate (0.10 mmol, 1.0 equiv), $Pd(OAc)_2$ (10 mol%), **L1** (10 mol %), NIS (2.0 equiv), $AgNO_3$ (1.0 equiv), HFIP (1 mL), 80 °C under air, 18 h. [b]Isolated yields. [c]5 mmol scale, 40 h.

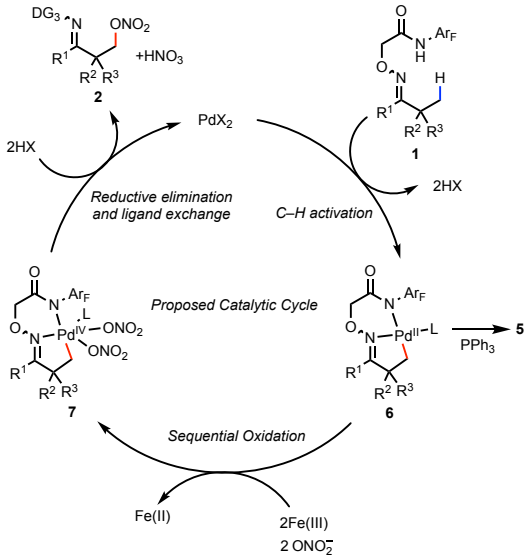
2a in 69% yield (Scheme 2c). Complex **5a** was nitrooxylated in similar yield under the same conditions (See SI). These results serve as direct evidence that the C–H activation occurs through a five-membered palladacycle intermediate followed by oxidation with iron(III) nitrate and reductive elimination to give the nitrooxylation product.[10,17] Facile removal of the auxiliary was achieved by treating the nitrooxylation product **2j** with 4 M HCl in 1,4-dioxane and water at 80 °C, providing *β*-nitrooxylated free ketone **2j'** in 60% yield.[18] Moreover, nitrate esters could serve as precursors to the corresponding alkyl alcohols (See SI).

Scheme 2. Synthesis and Characterization of the Palladacycles



Based on our observations of isolated intermediates and literature reports,[9,19] we propose the putative Pd(II)/Pd(III)/Pd(IV) catalytic cycle for the ketone nitrooxylation reaction (Scheme 3). Substrate coordination followed by C–H cleavage by an acetate anion results in the bicyclic palladacycle intermediate **6**. Considering Fe(III)'s ability to serve as a single electron oxidant,[12] it is likely that the intermediate **6** is oxidized to form a Pd(III) species, and oxidized again to afford Pd(IV) species **7**. The high-valent Pd(IV) intermediate **7** then undergoes reductive elimination to form a C–O bond and release the product. Ligand exchange regenerates the $Pd(OAc)_2$ and produce HNO_3. The Fe(II) can be oxidized into Fe(III) by HNO_3 generated during the course of the reaction.[19b]

Scheme 3. Proposed Catalytic Cycle



In summary, Pd(II)-catalyzed *β*-C(sp^3)–H nitrooxylation reactions of various ketones using a simple directing group and native amide substrates are reported. Fine tuning of the bidentate directing group structure proved crucial for high reactivity in ketone substrates. Iron(III) nitrate nonahydrate acted as the oxidant and nitrate source for the C(sp^3)–H nitrooxylation of ketone substrates. The *β*-C(sp^3)–H nitrooxylation of neutral amides was enabled by applying NIS as a bystanding oxidant and silver nitrate as the nitrate source. In this case, the pyridine 3-sulfonic acid ligand was found to be optimal in achieving excellent reactivity. The characterization of the palladacycle intermediates provides evidence for the L, X-type coordination mode of the aminooxyamide auxiliary in ketone substrates. A tentative Pd(II)/Pd(III)/Pd(IV) catalytic cycle for ketone substrates is proposed.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge at http://pubs.acs.org.

Additional screening tables, detailed experimental procedures, compound characterization data for all new compounds, and data for computations (PDF)

Accession Codes

CCDC 2076322 (Compound **2b**) and CCDC 2076323 (Compound **5**) contain 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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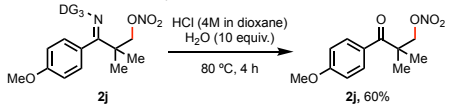

2j **2j**, 60%

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