Photoinduced Nitroarenes as Versatile Anaerobic Oxidants for Accessing Carbonyl and Imine Derivatives

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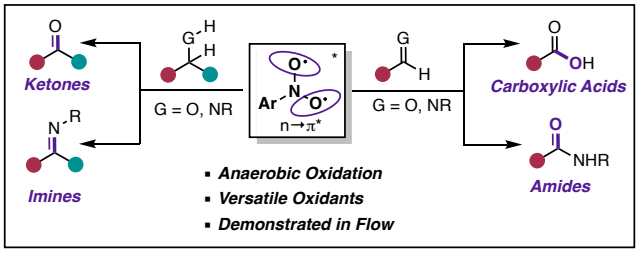
Supporting Information Placeholder

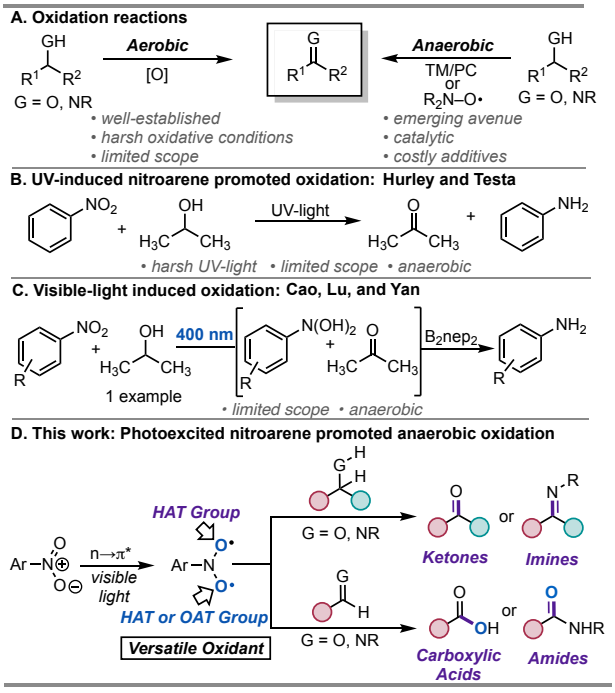


ABSTRACT: Herein, we report a protocol for the anaerobic oxidation of alcohols, amines, aldehydes, and imines promoted by photoexcited nitroarenes. Mechanistic studies support that photoexcited nitroarenes undergo double hydrogen atom transfer (HAT) steps with alcohols and amines to provide respective ketone and imine products. However, in the presence of aldehydes and imines, a successive HAT and oxygen atom transfer (OAT) event occurs to yield carboxylic acids and amides, respectively. This transformation is amenable to a continuous-flow photochemical setup, which led to significantly reduced reaction times.

Oxidations of C(sp^3)– and C(sp^2)–heteroatom systems are essential transformations in organic chemistry (Scheme 1).[1] The resulting products are important functionalities in pharmaceutically relevant compounds and can serve as versatile reaction intermediates in synthesis.[2] Classical oxidation methods such as Jones[3], Swern[4], and Baeyer-Villiger[5] are powerful, however, they are either conducted under harsh conditions or use super stoichiometric amounts of reagents. Furthermore, these reactions are often highly exothermic and can lead to undesired side products, like overoxidation, which limit substrate scope (Scheme 1A). Hypervalent iodine-based reagents like IBX[6] and DMP[7] offer milder reaction conditions but are limited in large-scale applications due to the issues of solubility, cost, and explosive nature. Recently, oxidative approaches employing nitroxyl radicals can be achieved catalytically under milder aerobic or anaerobic conditions.[8–10] The latter approach can lead to an expansion of substrate scope that complements classical oxidation strategies. However, the employment of *N*-hydroxyl based catalytic systems can suffer from the limitations of high catalyst loading, and poor functional group tolerance due to several factors such as overoxidation at benzylic sites, vicinal chelation, and preferential formation of transition-metal–phenolate species often leading to low yields of the products.[8] Hence, an anaerobic oxidation protocol that is economical, practical, and sustainable is highly warranted.

In 1966, Hurley and Testa studied the intermolecular oxidation of alcohol solvents in the presence of nitroarenes under harsh UV irradiation (Scheme 1B).[11] The authors uncovered that two sequential hydrogen atom transfer (HAT) events occur during the redox event with alcohol solvent. Very recently, the groups of Cao, Lu, and Yan redirected the aforementioned reactivity toward the visible light region for the photoreduction of nitroarenes with concomitant oxidation (Scheme 1C).[12,13] Though limited in scope, both approaches illustrate that photoinduced nitroarenes are capable of anaerobic alcohol oxidation.[14–16] Based on our previous

Scheme 1: Prior Methods and Hypothesized Work



work on hydrocarbon oxidation using nitroarene photochemistry,[17–19] we hypothesized the possibility of harnessing multiple HAT events with nitroarenes to promote the anaerobic oxidation of heteroatom systems under visible-light irradiation. Herein, we illustrate that the photoexcited state of the nitroarene can trigger a double HAT event with C(sp^3)–heteroatom systems to generate valuable ketone and imines, and a successive HAT and oxygen atom transfer (OAT) event at C(sp^2)–heteroatom systems to furnish synthetically useful carboxylic acids and amides.

Table 1: A) Scope of the Photoinduced Nitroarene Promoted Oxidation of Alcohols and Amines.[a] B) Scope of the Photoinduced Nitroarene Promoted Oxidation of Aldehydes and Imines.[a]

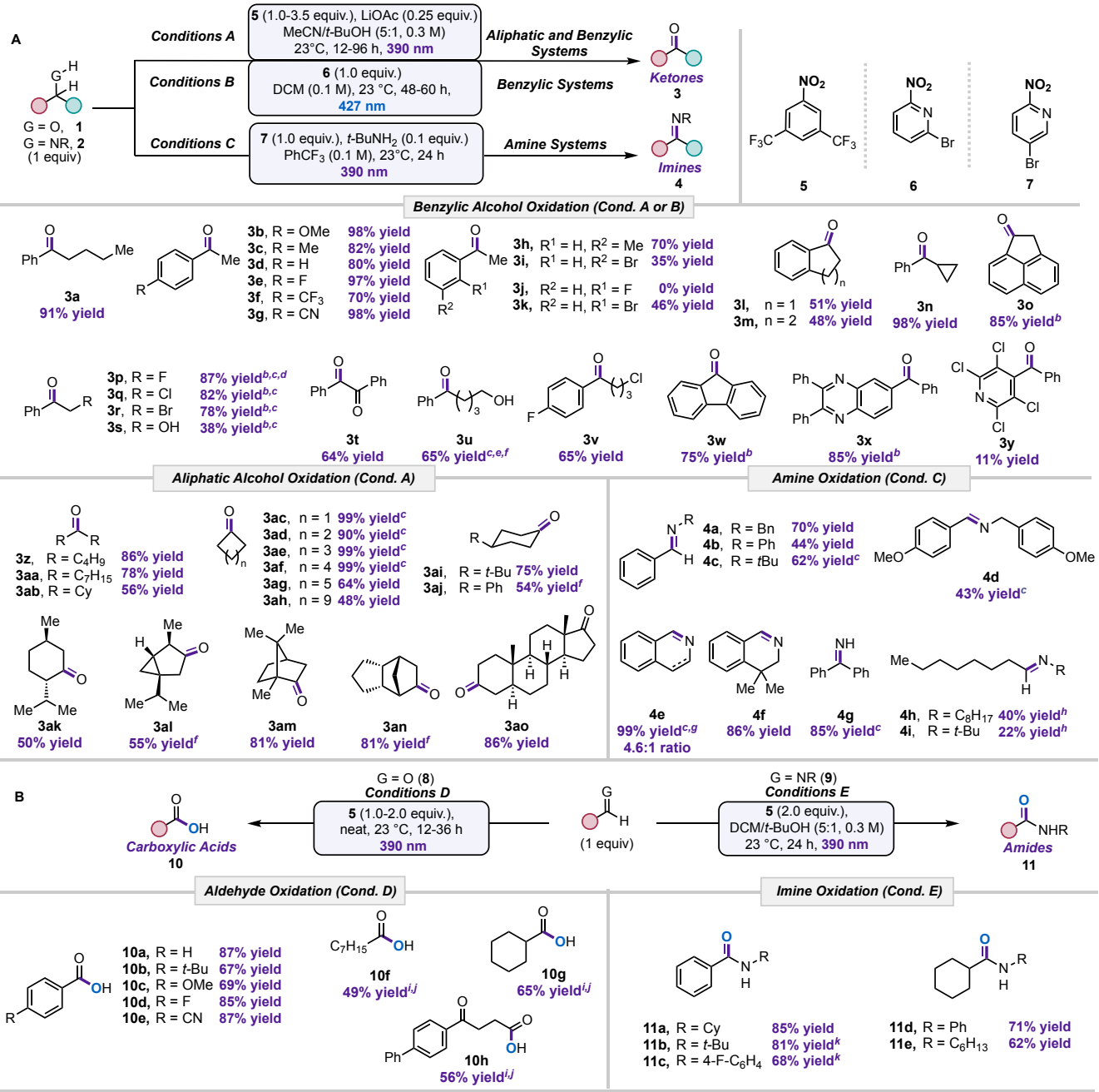


Table 1A-B. [a]Isolated yields. [b]Conditions B. [c]Denotes ^{1}H NMR yield using CH_2Br_2 as an external standard. [d]Under 390 nm. [e]In MeCN/H_2O (1:1, 0.3M). [f]No LiOAc. [g]0.5 M. [h]Denotes ^{1}H NMR yield using CH_2Cl_2 as an external standard. [i]MeCN (1 M), [j]H_2O (1.0 equiv.), [k]Neat.

We began our investigation by testing the conversion of 1-phenylpentan-1-ol **1a** to ketone **3a** under our previously reported conditions featuring 2-chloro-4-nitropyridine under 390 nm.[18] The oxidation was successful, resulting in 61% yield of **3a**. After an extensive optimization campaign (Table S1-4), the yield was increased to 91% with 3,5-bis(trifluoromethyl)nitrobenzene (**5**) under 390 nm irradiation at 0.1 mmol scale. After uncovering the optimized reaction conditions, the electronic effect of the oxidation reaction was investigated with 4-substituted-phenyl-1-ethanol derivatives (Table 1A, **1b-g**). It was found that transformation was not sensitive to the electronic patterns as substrates possessing both electron-rich and deficient groups resulted in good to excellent yields of the oxidation products **3b-g**. *Meta*- and *ortho*-substituted benzylic alcohols were also tested. **1h-i,k** gave **3h-i,k** in low to good yields, however, **1j** did not convert. Cyclic benzylic alcohol systems, such as indanol and tetrahydronaphthalenol, resulted in a moderate yield of the oxidation products **3l-m**. Acyclic α-substituted benzylic alcohols containing sensitive and important functional handles such as cyclopropyl **1n**, halogen **1p-r**, hydroxyl **1s**, and carbonyl groups **1t**, all resulted in corresponding oxidation products in good yields under conditions B (**3n-s**) and A (**3t**). Notably, benzylic alcohol

1u possessing a free aliphatic alcohol unit underwent site-selectivity oxidation at the benzylic position (**3u**). This selectivity preference is unlikely to occur under classical oxidation protocols.[8,20] Haloperidol (**3v**), a common antipsychotic, was synthesized from **1v** under this protocol in 61% yield.[21–23] Finally, diaryl substituted ketones of optoelectronic and medicinal relevance (**3w-x**), as well as halogenated heterocycle **3y** were afforded in low to good yields under the reaction conditions, highlighting the synthetic utility for late-stage oxidation.[24–27]

Next, unactivated aliphatic alcohols were studied. It was found that the employment of nitroarene **5** under 390 nm and the use of LiOAc as an additive to shorten the reaction time were optimal for the oxidation of unactivated alcohols (Table S5).[28] Secondary acyclic alcohols containing linear hydrocarbon chains yielded the oxidation products with good efficiency under the reaction conditions (**3z**, **3aa**). However, sterically encumbered dicyclohexylmethanol **1ab** resulted in a moderate yield of **3ab**. Cyclic alcohols featuring small to large ring sizes gave good to excellent yields under the reaction conditions (**3ac-3ag**); however, a decreased yield of 51% for **3ah** was observed due to overoxidation of secondary C(sp^3)–H sites. Next, 4-substituted cyclohexanol substrates were exposed to the reaction conditions, resulting in fair to moderate yields of the desired ketone products **3ai-3aj**. Fortunately, competitive C–H hydroxylation of the tertiary sites was not observed.[18] The oxidation of naturally occurring terpenes **1ak-1an** and steroid **1ao** were tested to gauge the applicability of our protocol for late-stage oxidation of medicinally relevant compounds. The oxidation of L-(-)-menthol and thujone precursor proceeded moderately well **3ak-3al**, while the oxidation of borneol was highly efficient under the reaction conditions **3am**. Corodane (**3an**) was obtained in 81% yield via the oxidation of **1an** under our conditions. Lastly, the reaction of *trans*-androsterone **1ao** generated **3ao** in 86% yield.

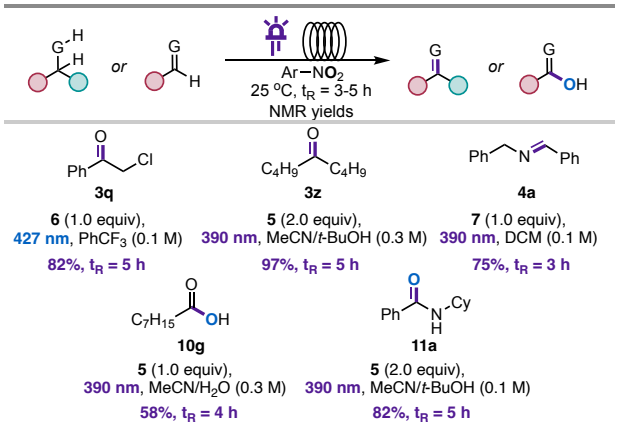
With the success of oxidizing alcohols, we investigated if amines (**2**)[29–31] could be oxidized in the presence of photoexcited nitroarenes (Table 1A, **2**→**4**). Exposure of conditions A and B to dibenzyl amine **2a** resulted in a low yield of the desired oxidation product **4a**. Further optimization revealed the use of nitroarene **7** in $PhCF_3$ as solvent under 390 nm irradiation led to increased overall reaction efficiency (Conditions C, Table S6-7). Other benzylic amines, **2b-c** were tested, giving the corresponding imines **4b-c** in good yields. Electron-rich amine **2d** was tolerated under the reaction conditions but **4d** was prone to hydrolysis. Cyclic amines **2e** and **2f** gave the corresponding imine in good yields (**4e-f**). Amine **2e** led to the dihydroisoquinoline **4e** and overoxidized aromatic isoquinoline (**4e'**) in a 4.6:1 ratio with a 99% total NMR yield. Free amine **2g** gave the corresponding imine **4g** in 85% yield. Aliphatic amines reacted quickly and generated the desired oxidation product, **4h-i** in low yield with concomitant overoxidation to the amide (*vide infra*).

Next, we questioned if the reactivity of this photoexcited nitroarene-promoted oxidation could be recapitulated with C(sp^2)–heteroatom systems, such as aldehydes[32,33] (**8**) and imines[34,35] (**9**) (Table 1B). It was discovered that the employment of nitroarene **5** under 390 nm irradiation promoted the oxidation of aldehydes to acids (**8**→**10**, Conditions D, Table S8-9). Oxidation of benzaldehyde **8a** resulted in 87% yield of benzoic acid **10a** under the optimized conditions. Varying the electronic pattern of aromatic aldehydes did not affect the reaction yields, as electron-donating and withdrawing substituted aromatic aldehydes generated the corresponding carboxylic acids products in high yield **10b-d**. Next, aliphatic aldehydes were tested. Oxidation of octanal **8f** and cyclohexanecarboxaldehyde **8g** afforded the corresponding products **10f** and **10g** in 49% and 65% yield, respectively. To illustrate the synthetic utility of the transformation, the synthesis of therapeutic Fenbufen[36–38] (**10h**) was achieved in 87% yield via oxidation of **8h**.

Finally, the oxidation of imines to amides was examined (**9**→**11**). Under conditions E (Table S10), *N*-cyclohexyl-1-phenylmethanimine (**9a**) to afford *N*-cyclohexylbenzamide (**10a**) in 85% yield. Benzyl imines such as *N*-alkyl (**9b**) and aryl imine (**9c**) generated the expected amide products (**11b-c**) in good yield. Aliphatic imines containing *N*-phenyl and -hexyl substituents were subjected to the reaction conditions and resulted in 71% and 62% yield of amides **11d** and **11e**, respectively.

While the reported approach provides a complementary method to existing oxidations, the extended reaction times provide an opportunity for improvement. We postulated that reduced reaction times could be achieved under photochemical, continuous-flow conditions (Scheme 2).[39] A flow reactor consisting of a syringe pump to control residence time (t_R) and a coil of fluorinated ethylene propylene (FEP) Teflon tubing irradiated by two LED lamps (General procedure F, see SI) was used to test the oxidation of one representative molecule from each substrate class assessed in batch. Markedly, it was found that the oxidation of benzylic alcohol **1q** to **3q** was achieved in 5 h under continuous-flow compared to 60 h in batch with the same reaction efficiency. Next, aliphatic alcohol **1z** was efficiently oxidized to **3z** in higher reaction yields (97%) in 5 h through continuous-flow vs lower reaction yield (86%) in 96 h via batch. Amine **2a** was also amenable to flow conditions delivering **4a** in 3 h compared to the 48 h required for batch oxidation. Both aldehyde (**8g**) and imine (**9a**) substrates could be oxidized to their respective carboxylic acid **10g** and amide **11a** in under 5 h with similar reaction yields compared to batch set-up (Scheme 2). Overall, we found that reaction conditions in batch did not require re-optimization to be implemented in flow, and the vastly shorter reaction times led to 4 to 25-fold productivity improvements in mmol/h of the desired products.

Scheme 2: Continuous-Flow Photochemical Oxidations

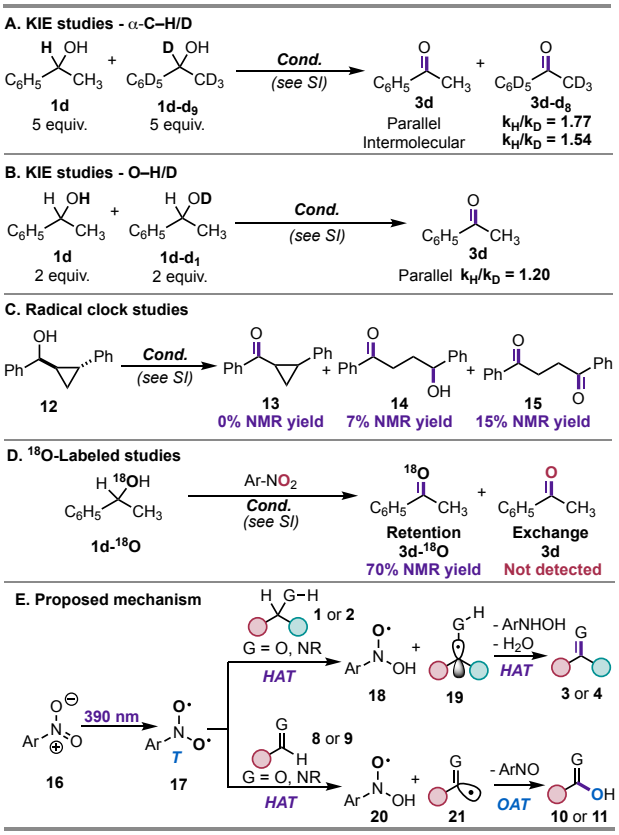


After establishing the scope and synthetic utility of the transformation, the mechanism was interrogated for the oxidation

of alcohols to ketones (Scheme 3). Based on the mechanistic studies from our lab,[17–19] and others,[40,41] we proposed that the oxidation reaction is initiated by hydrogen atom transfer (HAT) of the α-C(sp^3)–H bond with the photoexcited state of the nitroarene. To verify this, kinetic isotope effect (KIE) studies of **1d**/**1d-d$_9$** were conducted (Scheme 3A). KIE values of 1.77 and 1.54 were obtained for parallel and intermolecular studies, respectively. Next, a parallel study of the second HAT step was investigated with **1d**/**1d-d$_1$** and resulted in a secondary KIE of 1.2 (Scheme 3B). These studies suggest that the first HAT participates in the rate-limiting step of the transformation.[9] To support the radical nature of the transformation, radical clock **12** was subjected to the reaction conditions (Scheme 3C).[42] Although low conversion of 23% was observed, the oxidation product with the cyclopropane moiety preserved was not observed **13**. Only the ring opening over-oxidation products **14** and **15** were detected. The presence of **14** indicates that radical recombination of the formed alkyl radical and the formed *N*-hydroxy-*N*-phenylhydroxylamine radical via oxygen atom transfer (OAT) from the nitroarene could be possible in the oxidation reaction.[11] To distinguish if a recombination event is operative, ^{18}O-labeled substrate **1d-^{18}O** was tested (Scheme 3D). Upon exposure to the reaction conditions, the ^{18}O-incorporated retention product **3d-^{18}O** was obtained with no scrambling product detected. Hence, supporting that the oxidation of C(sp^3)–heteroatom systems do not occur through radical recombination but rather a double HAT event.

Based on the above studies the following mechanism is proposed for the oxidation of C(sp^3)–heteroatom systems (Scheme 3E). Visible light irradiation of the nitroarene **16** results in triplet diradical intermediate[17,43] **17** that engages in HAT of α-C(sp^3)–H bond of **1** or **2** to generate alkyl radical **19** and *N*-hydroxy-*N*-phenylhydroxylamine radical **18**. Subsequent HAT of the aforementioned intermediates results in the desired oxidation products **3** or **4** and *N*-phenylhydroxylamine byproduct (see SI). For oxidation of C(sp^2)–heteroatom systems, we propose that HAT of **8** or **9** yields acyl radical **21** and *N*-hydroxy-*N*-phenylhydroxylamine radical **20**. Radical recombination of the latter intermediates generates the OAT products **10** or **11** and condensation byproducts stemming from the nitrosoarene.[18] An alternative mechanism proposed by Hurley and Testa involves a secondary oxidation step via photoinduced homolysis of the *N*-hydroxy-*N*-phenylhydroxylamine byproduct and subsequent HAT of the formed N- and O-centered radicals with the C(sp^3)–H heteroatom systems cannot be ruled out at this stage.[12,44]

Scheme 3: Mechanistic Studies and Proposed Mechanism



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In conclusion, we have illustrated that nitroarenes are potent photooxidants capable of oxidizing C(sp^3)– and C(sp^2)–heteroatom systems to generate synthetically useful ketones, imines, carboxylic acids, and amides with good reaction efficiency. The synthetic utility of the transformation is highlighted by its amenability to continuous-flow photochemical setup. Mechanistic studies support that photoexcited nitroarene promoted oxidation of C(sp^3)–heteroatom systems occur via double HAT, while C(sp^2)–heteroatom systems proceed via successive HAT and OAT events. Due to the anaerobic nature of the transformation and the practicality of using nitroarenes oxidants, this protocol provides a sustainable alternative complementary to established oxidation methods.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS publications website. Experimental details, optimization studies, characterization data, and NMR spectra (PDF).

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The manuscript was written through the contributions of all authors. All authors have given approval for the final version of the manuscript. Ms. Sharon Lim is acknowledged for her assistance in the optimization studies during the early stages of the project.

Notes

Any additional relevant notes should be placed here.

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