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Oxidative Imidation of Benzylic and Cycloalkane C(sp^3)−H Bond Donors Using *N*-Aroyloxyquinuclidinium Salts and Nitriles under Photoredox Catalysis

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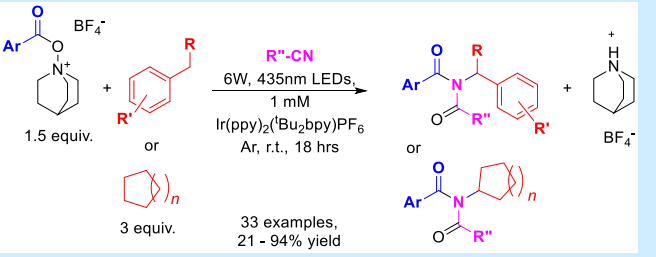
ABSTRACT: A series of *N*-aroyloxyquinuclidinium salts were prepared and used as reagents to perform efficient three-component Ritter−Mumm-type oxidative C−H imidation of donors of 1° and 2° benzylic C−H bonds used as limiting reagents with nitriles as a source of imide nitrogen under photocatalytic conditions; these reagents also exhibit somewhat lower reactivity toward cycloalkanes.



Carboxylic acid imides, in general,[1] and *N*-alkylimides, specifically,[2−10] constitute an important group of organic compounds occurring as natural products, used as bioactive substances,[1−7] specialty plastics,[1] and employed in organic synthesis.[8−10] In particular, *N*-benzyl-*N*-acylacetamides were used in the preparation of ketene aminal esters and a subsequent C−C cross-coupling of the latter,[8] whereas *N*-aroyl-*N*-alkyl-acetamides served as efficient donors of aroyl groups in Pd-catalyzed Suzuki−Miyaura C−C cross-coupling with arylboronic acids leading to diarylketones.[9] The traditional methods of preparation of *N*-alkylcarboximides are limited to acylation of amines or carboxamides,[10−14] and alkylation of metal carboximides.[15] The more attractive atom-economical methods employ oxidation of C−H bond donors, such as *N*-alkyl-*N*-benzylacetamides[16] and oxidative C−N coupling of carboxamides or carboximides with benzylic or alkanes C−H bond donors.[17−21] Examples of intermolecular reactions from the latter group include CuCl-catalyzed C(sp^3)−H imidation of toluene and cyclohexane with phthalimide[17,21] and succinimide[17] using ^{t}Bu$_2$O$_2$ as an oxidant (Scheme 1a) and I$_2$-promoted C−N coupling of carboxamides and methylarenes with ^{t}BuOOH as an oxidizing agent (Scheme 1b).[18] Interestingly, carboxylic acid amides fully outcompete carboximides in direct oxidative N−H alkylation with alkanes.[22] Some of the most versatile methods for the preparation of *N*-alkylimides[23] employing C−H functionalization are based on Ugi−Mumm-type multicomponent oxidative C−C coupling of C−H bond donors, isonitriles, and carboxylic acids.[24−27] An example of this chemistry is given in Scheme 1c where benzoyl peroxide serves as an oxidant and a source of carboxylate.[24] Considering preparation of *N*-alkylimides via C(sp^3)−H functionalization, only a limited number of examples of oxidative C−N coupling of alkanes have been reported,[17,21] and no methods for multicomponent oxidative C(sp^3)−H imidation have been developed.

In this work, we present a synthetic protocol for a modular multicomponent Ritter−Mumm-type[28,29] oxidative imidation of donors of benzylic (**2**) and cycloalkane (**3**) C(sp^3)−H bonds using nitriles **4** as an imide nitrogen atom source and *N*-aroyloxyquinuclidinium tetrafluoroborates **1** as the third reaction component (Scheme 1d). The latter serve as oxidants and a source of one of the acyl fragments of the resulting *N*-benzyl imides **6** or their *N*-alkyl analogues **7**. The reaction works under blue LED light (435 nm) in the presence of a photoredox catalyst, such as [Ir(ppy)$_2$(^{t}Bu$_2$bpy)](PF$_6$), **5a**, and allows for a moderate- to high-yielding, up to 94%, preparation of **6** using alkylarenes **2** as *limiting reagents*, as well as a low-yielding, 22−26%, formation of **7** using 3 equiv of cycloalkanes **3**. Similar to oxidative benzylic C−H trifluoroacetoxylation employing *N*-trifluoroacetoxyquinuclidinium salts in DCM solutions,[30] the reaction in Scheme 1d may involve quinuclidine cation radicals, $\mathbf{Q}^{\bullet+}$, resulting from the one-electron reduction of **1**, along with corresponding carboxylate anions, with $\mathbf{Q}^{\bullet+}$ acting as a hydrogen atom abstractor with respect to C(sp^3)−H bond donors **2**−**3**. Overall in this work, we explore the synthetic applications of novel *N*-acyloxyquinuclidinium salts serving as stoichiometric reagents for C(sp^3)−H bond functionalization, thereby complementing studies by other groups employing $\mathbf{Q}^{\bullet+}$ as a catalyst in

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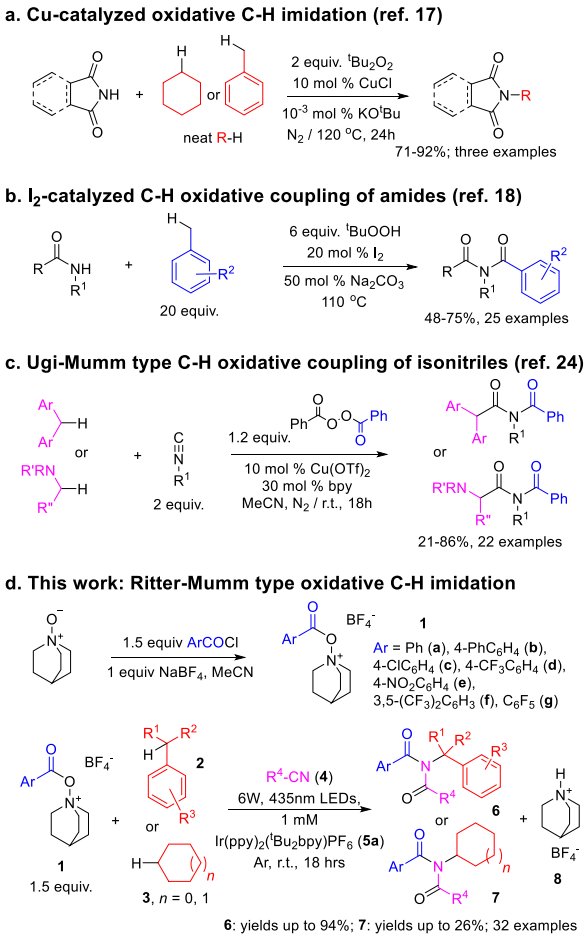
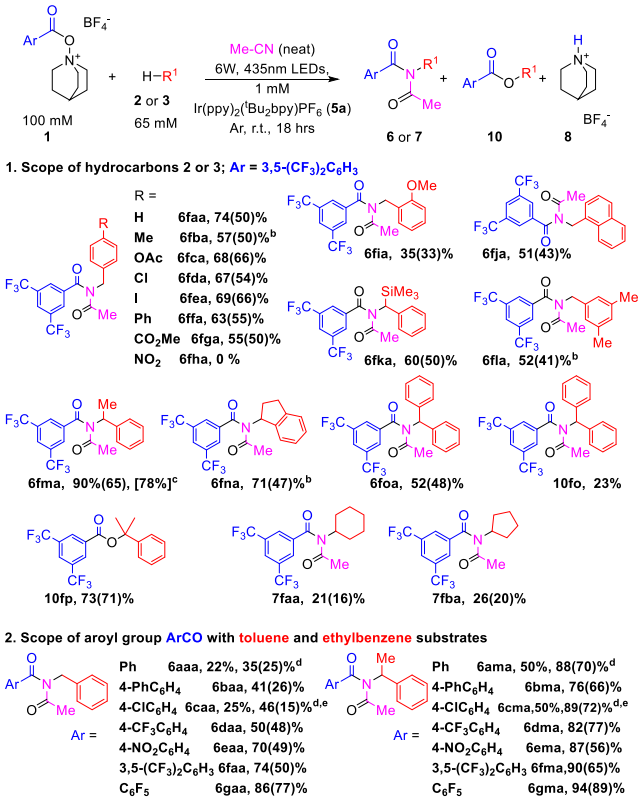
Scheme 1. Synthesis of *N*-Alkylimides via Oxidative Functionalization of C−H Bond Donors



Scheme 2. Reaction Scope in Hydrocarbon R^1−H and Aroyl Group ArCO and Product Yields[a]



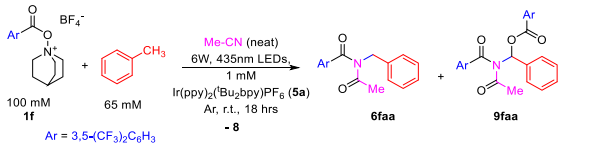
[a]Formation of **10** (>5%) was only observed for diphenylmethane and isopropylbenzene; NMR and isolated yields (in parentheses) are reported. [b]The reaction was performed using 500 mM substrate. [c]The reaction was performed on a 1.00 mmol scale; isolated yield. [d]$Ir(ppy)_3$ (1.0 mM) was used. [e]Oxidant was used at 50 mM, and the substrate at 32.5 mM for solubility reasons.

electrochemical[31] and photoredox C−H bond functionalization.[32−34]

We started our work with the preparation of a readily accessible[35] *N*-benzoyloxyquinuclidinium tetrafluoroborate (**1a**) (Scheme 1d). Excitingly, in the presence of 1.5 mol % of catalyst **5a**, we were able to engage **1a** (1.5 equiv) in C−H functionalization of toluene used as a limiting reactant with MeCN solvent as the third reaction component to produce the imide **6aaa** in 22% yield (Scheme 2.2). The more electron-poor analogues **1d−1g** performed better than **1a** in the imidation reaction; therefore, *N*-(3,5-bis(trifluoromethyl)-benzoyloxy)quinuclidinium tetrafluoroborate **1f**, which is easy to track by NMR spectroscopy, was used for reaction optimization (Table 1).

With toluene as a substrate, 1.5 equiv of **1f**, and 1.5 mol % of **5a**, the derived *N*-benzylimide **6faa** was produced in 74% NMR yield after 18 h of reaction. A potential byproduct, benzyl 3,5-bis(trifluoromethyl)benzoate ester, was not detected, but a product of overoxidation of **6faa**, the aminal derivative **9faa**, formed in 1:8.0 molar ratio to **6faa** (entry 1). A slightly higher 2:1 **1f**/ toluene ratio did not noticeably affect the reaction outcome (entry 2). In turn, when a 3-fold excess of toluene was employed, the formation of **9faa** was completely suppressed, but the yield of **6faa** dropped to 63% (entry 3). The use of 1.5 mol % of $Ir(ppy)_3$, **5b**, which is a less oxidizing photocatalyst,[36] instead of **5a**, led to an even lower yield of **6faa** of 44% (entry 4). Similarly, the less reducing photoredox

Table 1. Optimization of the Reaction Conditions



entry	deviation from the conditions above	yield[a] of **6faa**, %	**6faa**/**9faa**
1	none	74%	8.0:1
2	50 mM toluene	76%	7.6:1
3	300 mM toluene	63%	1:0[b]
4	1 mM $Ir(ppy)_3$ (**5b**)	44%	1:0[b]
5	1 mM $Ru(bpy)_3(PF_6)_2$ (**5c**)	33%	1:0[b]
6	0.5 equiv of $Zn(OTf)_2$	69%	23:1
7	no light or no catalyst	0%	n/a

[a]NMR yields were calculated by using 1,4-dioxane as an internal standard. [b]Compound **9faa** was not detected.

catalyst, $Ru(bpy)_3(PF_6)_2$, **5c**,[36] was also less effective with a 33% yield of **6faa** (entry 5). Remarkably, when 0.5 equiv of $Zn(OTf)_2$ was used as a Lewis acid additive, the **6faa**/**9faa** molar ratio increased to 23:1, but the yield of the target compound **6faa** dropped to 69% (entry 6). A series of control experiments showed that no reaction occurred after 18 h when either photocatalyst **5** or the LED's light was absent (entry 7).

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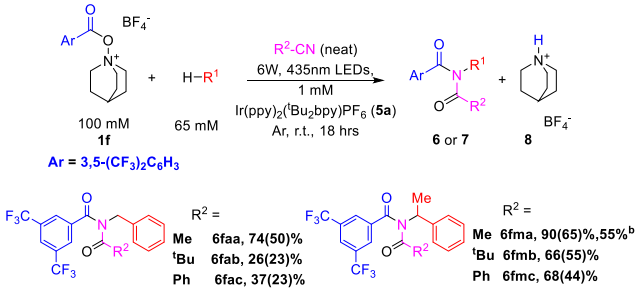
Using the optimized reaction conditions (Table 1), we proceeded to the evaluation of the reaction scope in C−H bond donors, the aroyl group donors **1** (Scheme 2), and nitriles **4** (Scheme 3). All reaction products in Schemes 2 and 3 were isolated as pure compounds and characterized by ^{1}H, ^{13}C, and ^{19}F (when appropriate) NMR spectroscopy and high-resolution ESI-MS(+).

Scheme 3. Reaction Scope in Nitrile with 1f and Toluene or Ethylbenzene as Other Reaction Components[a]



[a]NMR and isolated yields (in parentheses) are reported. [b]A 39:1 (v/v) DCM/MeCN mixture was used.

A series of *para*-R-substituted toluene derivatives with R ranging from electron-donating methyl to electron-accepting methoxycarbonyl reacted with **1f** and MeCN to produce the derived *N*-benzylimides **6faa**−**6fga** in 55−69% NMR yields. The most electron-deficient 4-nitrotoluene was unreactive. 1-Methylnaphthaline, benzyltrimethylsilane, and mesitylene afforded the derived *N*-benzylimides **6fja**, **6fka**, and **6fka**, respectively, in good 51−60% yields, whereas the reaction of *o*-methoxytoluene was less efficient with 35% yield of **6fia**. To avoid the formation of polyfunctionalized products of *p*-xylene, mesitylene, and indane, which have several reaction sites, a 5:1 substrate/**1f** ratio was used, which resulted in the formation of imides **6fba**, **6fla**, and **6fna** in 52−71% yields. Besides indane, other donors of 2° benzylic C−H bonds, ethylbenzene and diphenylmethane, afforded the derived imides **6fma** and **6foa** in good to excellent 52−90% yields. Notably, among all these substrates, the formation of benzylic ester byproducts **10** was only detectable (>5% by NMR) for diphenylmethane where the benzhydryl ester **10fo** formed in 23% NMR yield.

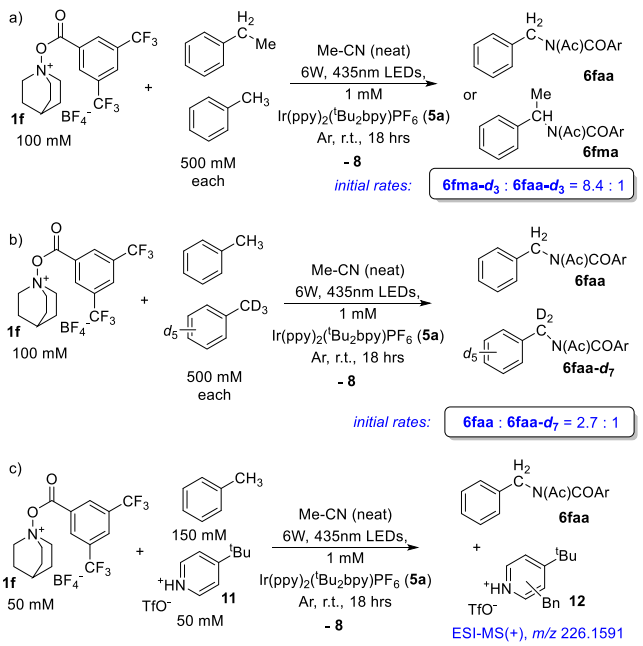
The imidation of ethylbenzene was also carried out on a 1.00 mmol scale and resulted in a 78% isolated yield of **6fma**. Notably, in contrast to the 1° and 2° C−H bond donors above, a 3° C−H bond donor, isopropylbenzene, gave mostly the derived ester **10fp** (73% yield). Finally, methylheteroarenes 2-methylfuran, 2-methylthiophene, and 4-methylpyridine did not afford the corresponding imides.[36] In turn, cyclohexane and cyclopentane used in a 3:1 ratio to **1f** produced the expected *N*-alkylimides **7faa** and **7fba**, in 21% and 26% yield, respectively.

Having explored the scope of C−H bond donors, we next probed the reactivity of other *N*-acyloxyquinuclidinium salts **1** using toluene and ethylbenzene as representative 1° and 2° benzylic C−H bond donors (Scheme 2, bottom). The reaction of *N*-benzoyloxy derivative **1a** with toluene and MeCN to give the corresponding imide **6aaa** was more efficient in the presence of a more reducing[36] catalyst **5b** (35% yield of **6aaa** with **5b** vs 22% with **5a**). Similarly, **1c**, toluene, and MeCN produced imide **6caa** in a better 46% yield in the presence of **5b** compared with 25% yield in the presence of **5a**. Other oxidants, including **1b** and more electron-poor **1d**, **1e**, and **1g**, all reacted with toluene under the optimized reaction conditions (Table 1) to afford the derived imides in increasing yields of 41%, 50%, 70%, and 86%, respectively. The reactions involving ethylbenzene instead of toluene were more efficient under otherwise identical conditions, with the yields of the derived imides ranging from 76% to 94%. Notably, an attempted reaction of *N*-acetyloxyquinuclidinium tetrafluoroborate **1h** with *p*-xylene failed to produce any imide.[36]

To find out how the nature of nitrile **4** affects the imidation reaction, two more nitriles were tested and employed as solvents: pivalonitrile **4b** and benzonitrile **4c**. In these experiments, we used **1f** as the oxidant and toluene and ethylbenzene as C−H bond donors (Scheme 3). The more sterically encumbered and less polar pivalonitrile produced the derived imides in lower yields than MeCN for both hydrocarbons; the difference was more significant for toluene with 26% yield of pivalonitrile-derived **6fab** versus 74% for acetonitrile-derived **6faa** and less so for ethylbenzene with 66% yield of pivalonitrile-derived **6fmb** versus 90% of acetonitrile-derived **6fma**. Benzonitrile performed slightly better than pivalonitrile with 37% yield of toluene derivative **6fac** and 68% yield of ethylbenzene-derived **6fmc**. Interestingly, when MeCN solvent was replaced with a 39:1 DCM/MeCN mixture in the reaction of **1f** and ethylbenzene, the target imide **6fma** was produced in a respectable 55% yield in spite of a much lower 7.4:1 molar ratio of MeCN/hydrocarbon.[36]

To characterize the substrate selectivity of **1f** with respect to 2° (ethylbenzene) and 1° (toluene) benzylic C−H bonds in MeCN-d_3 solutions, we measured the initial rates of formation of the corresponding imides **6fma**-d_3 and **6faa**-d_3 under pseudo-first-order reaction conditions. Using competition experiments, ethylbenzene was found to be 8.4 ± 0.4 times more reactive than toluene (Scheme 4a). The deuterium kinetic isotope effect was estimated similarly by employing 1:1 mixtures of toluene and toluene-d_8 with the resulting k_H/k_D = 2.7 ± 0.1 (Scheme 4b). These observations are consistent with the reaction mechanism involving a product-determining

Scheme 4. Mechanistic Tests



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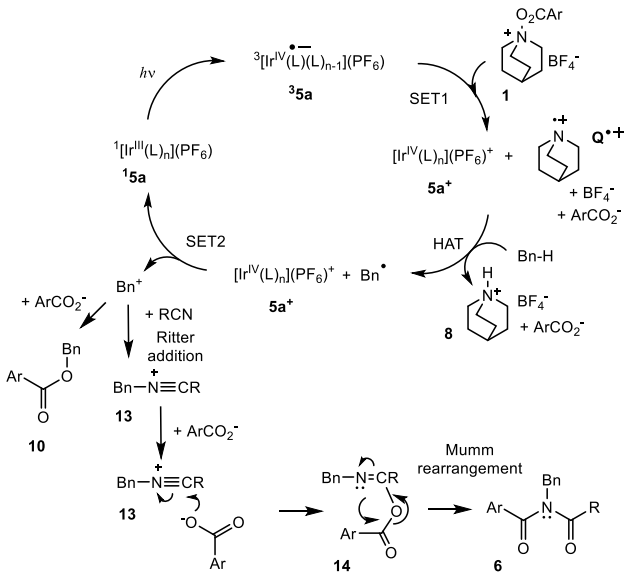
hydrogen atom transfer from a hydrocarbon benzylic C−H bond to $Q^{\bullet+}$, similar to the oxidative benzylic C−H trifluoroacetoxylation using *N*-trifluoroacetoxyquinuclidinium salts.[30] Benzylic radicals resulting from a hydrogen atom transfer (HAT) reaction with toluene were trapped using 4-*tert*-butylpyridinium triflate **11** in a form of a product **12** of Minisci-type oxidative coupling[37] that was detected using ESI-MS(+) technique (Scheme 4c). Altogether, on the basis of our observations, we propose a mechanism of the imidation reaction shown in Scheme 5 with toluene as a representative substrate.

Scheme 5. Proposed Mechanism for Oxidative Imidation of C(sp^3)−H Bond Donors Using *N*-Aroyloxyquinuclidinium Salts and Nitriles under Photoredox Catalysis with 5a



An electron-transfer (step SET1) from a photocatalyst-excited state ^{3}**5a** to *N*-aroyloxyquinuclidinium salt **1** produces a quinuclidine cation radical $Q^{\bullet+}$, along with an oxidized form of the photocatalyst, **5a**$^+$, and an arenecarboxylate $ArCO_2^-$.[38] Subsequent hydrogen atom transfer (step HAT)[38] from Bn-H to $Q^{\bullet+}$ leads to a benzylic radical $Bn^\bullet$, which is oxidized by **5a**$^+$ to form a carbocation Bn$^+$ (step SET2).[39] A Ritter addition of the latter to a nitrile RCN produces nitrilium cation **13**. This step may be endergonic for more stabilized and/or bulky carbocations, such as benzhydryl and cumyl. In such a case, quenching of Bn$^+$ with arenecarboxylate $ArCO_2^-$ becomes more competitive and leads to the formation of the corresponding carboxylates **10**. A higher reactivity of cycloalkane-derived radicals and/or carbocations may lead to their engagement in some fast side reactions, thereby resulting in lower yields of the derived *N*-alkylcarboximides **7**. Next, nitrilium cation **13** can be quenched with $ArCO_2^-$ to form an iminoanhydride **14** that undergoes a Mumm rearrangement[40] to *N*-alkylcarboximide **6**. Finally, *N*-benzylimides **6** (Scheme 5), which have benzylic C−H bonds, can undergo another C−H functionalization via α-nitrogen-stabilized carbocations that, similar to benzhydryl and cumyl cations, form esters **9**.

In summary, in this work we introduce a series of novel *N*-aroyloxyquinuclidinium salts that serve as efficient reagents in multicomponent Ritter−Mumm-type oxidative C−H imidation of 1° and 2° benzylic C−H bond donors with carbonitriles as a source of the imide nitrogen atom; these reagents exhibit somewhat lower reactivity toward cycloalkanes.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c01966.

Description of all experimental procedures, DFT calculations and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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