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Nitrosoarene-Catalyzed HFIP-Assisted Transformation of Arylmethyl Halides to Aromatic Carbonyls under Aerobic Conditions

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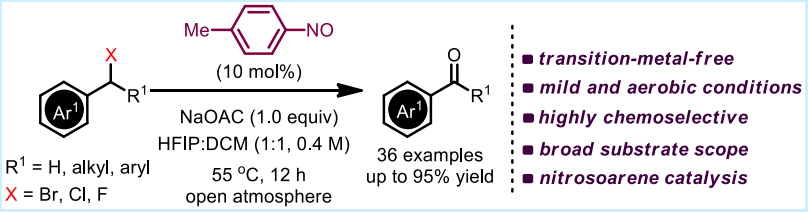

ABSTRACT: A rare metal-free nucleophilic nitrosoarene catalysis accompanied by highly hydrogen-bond-donor (HBD) solvent, 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), organocatalytically converts arylmethyl halides to aromatic carbonyls. This protocol offers an effective means to access a diverse array of aromatic carbonyls with good chemoselectivity under mild reaction conditions. The activation of arylmethyl halides by HFIP to generate stable carbocation and autoxidation of in situ generated hydroxylamine to nitrosoarene in the presence of atmospheric O_2 are the keys to success.

Aromatic aldehydes and ketones are vastly abundant, readily found in several natural products, and usually recognized for their pleasant fragrances. These organic compounds are very much cherished not only for their ubiquity in nature, but also as valuable building blocks and feedstock for organic synthesis.[1] The direct oxidation of oxygen-containing molecules can offer corresponding aldehydes or ketones using stoichiometric or catalytic processes.[2] In this context, previously, several transition-metal-based O_2-coupled oxidation routes have been documented.[3] The use of metal traces is necessary to carry out the redox process in order to inhibit the direct oxidation of organic molecules alone with molecular oxygen.[4] Simultaneously, to achieve two complementary methods, i.e., organocatalytic oxidation of desired molecule and reduction of molecular oxygen, enormous effort has been given from the scientific community.[5−7]

Apart from these direct oxidative techniques, another alternative method for synthesizing of aromatic carbonyls is from arylmethyl halides.[8] Along this line, in most of the cases, stoichiometric oxidants and transition-metal-based catalysts[9] have been used for this purpose. Several name reactions, for example, Hass−Bender oxidation,[10] Sommelet oxidation,[11] Kornblum oxidation,[12] Kröhnke reaction,[13] and Ganem oxidation[14] are well-known in the literature. These oxidation processes suffered from many drawbacks and challenges: (1) formation of unwanted byproducts, (2) harsh reaction conditions, and (3) functional group intolerance.[15] In pursuit of a suitable, alternative, and metal-free organocatalytic expedient decorum, transition-metal-free stoichiometric oxidative approaches have been reported right through.[16] Alongside, few environmentally benign organocatalytic methodologies for oxidative transformation of arylmethyl halides to carbonyl compounds have also been documented in the past few decades (Scheme 1a)[17−20] Recently, in 2018, Lambert and coworkers have come up with a newly modeled benzo[*c*]-cinnoline (BCC) catalyst for synthesizing aldehydes from alkyl halides (Scheme 1b).[21] This unique invention organocatalytically oxidizes primary alkyl halides involving nucleophilic attack, prototropic shift and hydrolysis as key steps.

For the last couple of years, our laboratory has devoted attention toward exploring nitrosoarene reactivity. Recently, we displayed that aerobic O_2 (as a terminal oxidant) could oxidize in situ generated hydroxylamine derivatives to produce analogous nitrosoarene and engage it in a catalytic process as a redox catalyst.[22] This was our first thought process behind the documentation of exclusive and O_2-coupled metal-free organocatalytic oxidation approach. It is to be noted that a stoichiometric reaction involving an extension of Kröhnke oxidation of 2-hydroxy-4-nitrobenzylpyridinium bromide to produce 2-hydroxy-4-nitrobenzaldehyde was reported by Walker's group using stoichiometric *N*,*N*-dimethyl-*p*-nitrosoaniline as a crucial reactant.[23] To develop a catalytic process, we strategically hypothesized that the nucleophilic engagement of nitrosoarene **V** with benzyl halides **1** (via S_N1 or S_N2) might generate nitrosonium ion intermediate **VI** (Scheme 1c, this

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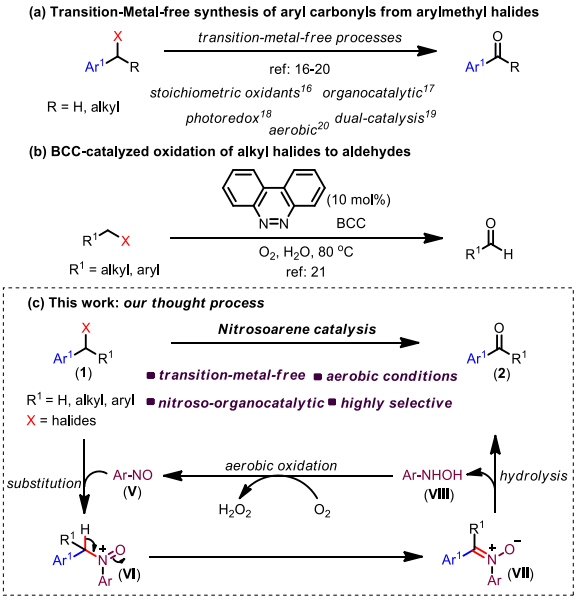
Scheme 1. (a) Transition-Metal-Free Oxidative Pathway of Synthesizing Aromatic Aldehydes and Ketones; (b) BCC-Catalyzed Oxidation Technique; (c) Proposed Work: Nitrosoarene Catalysis

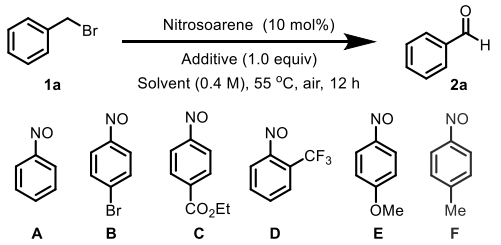


work, mechanistic hypothesis). Deprotonation can then furnish nitrone intermediate **VII**, which readily hydrolyzes to harness aromatic carbonyl and hydroxylamine derivative **VIII** (reduced form of **V**). In aerobic conditions, the autoxidation of hydroxylamine helps to close the catalytic cycle by regenerating nitrosoarene together with H_2O_2 as a sole byproduct. This will represent a transition-metal-free catalytic process for the synthesis of aromatic carbonyls. Herein, we have presented a nucleophilic nitrosoarene-catalyzed mild, efficient, and oxidative transformation technique to deliver ready feedstock aromatic carbonyls from corresponding arylmethyl halides under aerobic conditions (Scheme 1c, this work).

To pursue our thought process, the oxidative transformation of benzyl bromide (**1a**) was studied (Table 1; for full table see SI) in an open atmosphere at 55 °C (in a preheated oil bath) with nitrosobenzene (**A**, 10 mol %) as a catalyst in aprotic solvent DCM. A gradual change from aprotic to protic solvents, the yield of the desired product formation was increased significantly and a moderate yield was obtained in HFIP as a solvent (Table 1, entries 1−2). These significant changes in the yield indicated that nitrosobenzene is not nucleophilic enough to push the conversion in an S_N2 manner. Strong hydrogen-bond-donor (HBD) solvent HFIP[24] rather ionizes the C−X (X = halogen) bond and generates a reactive carbocation intermediate, which turned out to be a crucial and essential factor for the conversion.

This astonishing finding with HFIP is corroborated with the literatures reported earlier.[25] We screened several other nitrosoarene as catalysts (entry 3), among them 1-methyl-4-nitrosobenzene (**F**) proved to be the best catalyst with 52% yield of benzaldehyde in HFIP (entry 4). Very pleasingly, with the implementation of the cosolvent (entries 5−8) explicitly when DCM was mixed with HFIP (1:1), the desired oxidative product **2a** was isolated in 58% yield (entry 8). Use of H_2O as an additive did not give satisfactory conversion of **2a** (entry 9). The introduction of base as an additive in the reaction medium guided us to achieve an adequate yield of **2a** (entries 10−12).

Table 1. Optimization Study and Reaction Set-up[a]



entry	catalyst	solvent	additive	yield (%)[b]
1	A	DCM, MeOH, IPA, TFE	–	<10−15
2	A	HFIP	–	42
3	B, C, D, E	HFIP	–	40−45
4[c]	F	HFIP	–	52
5	F	HFIP:IPA (4:1)	–	45
6	F	HFIP:MeCN (4:1)	–	48
7	F	HFIP:DCM (4:1)	–	50
8[c]	F	HFIP:DCM (1:1)	–	58
9[c,d]	F	HFIP:DCM (1:1)	H_2O	45
10[c]	F	HFIP:DCM (1:1)	Et_3N	69
11[c]	F	HFIP:DCM (1:1)	DIPEA	<15
12[c,e]	F	HFIP:DCM (1:1)	NaOAc	72
13	F	DCM	NaOAc	<5
14[f]	F	HFIP:DCM (1:1)	NaOAc	25
15	F	HFIP:DCM (1:1)	NaOAc	NR

[a]Reaction conditions: **1a** (1.0 equiv, 0.2 mmol), nitrosoarene (10 mol %, 0.02 mmol), base (1.0 equiv, 0.2 mmol), solvent (undistilled, 0.4 M), 55 °C, air, 12 h. [b]Yields were determined using 1,3,5-trimethoxybenzene as an internal ^1H NMR standard. [c]Isolated yield. [d]25% of $PhCH_2OH$ was isolated along with **2a**. [e]1.0 mmol scale reaction provided 64% (68 mg) isolated yield of **2a**. [f]Reaction conducted at room temperature. NR = No Reaction.

NaOAc as a base gave the best result by furnishing **2a** in 72% isolated yield (entry 12). However, without HFIP as a solvent, in the presence of NaOAc, only a trace amount of **2a** was formed (entry 13). A reduced yield (25%) of product **2a** was found at room temperature reaction conditions (entry 14). The reaction was completely shut down in the absence of catalyst **F** (entry 15).

During exploration of substrate scope, starting from simple benzyl bromide to electron-rich arylmethyl halides such as Me, ^{t}Bu, SMe, OBn, OMe groups as substituents on the aromatic ring, irrespective of their position, produced respective aldehydes **2a−i** in good to excellent yields (62−95%). Mesityl benzyl bromide also responded to the reaction purveying **2j** in 70% yield. Benzyl chloride and 1-(chloromethyl)-4-isopropylbenzene also produced benzaldehydes **2a′** and **2e′**, respectively, albeit in moderate to good yield (53% and 75% respectively). Benzyl bromides bearing halogen atom (Cl, Br, and F) at different positions of the aromatic ring (*ortho*, *meta*, and *para*) reacted smoothly to furnish the resultant substituted aryl aldehydes **2k−p** in good yields (57−64%). Fluoride as leaving group also provided corresponding aromatic aldehydes **2l′** and **2m′** in moderate yields. This methodology was also effectively applied over electron-poor arylmethyl bromides to convert them into aldehydes **2q,r** in low to moderate yields. The oxidation was also efficiently worked with polycyclic arylmethyl bromides and **2s,t** were isolated in good yields. The present reaction etiquette can also be applied to allylic bromide derivative to obtain cinnamaldehyde **2u** in 50% yield. Unfortunately, aliphatic and heterocyclic methyl halides did

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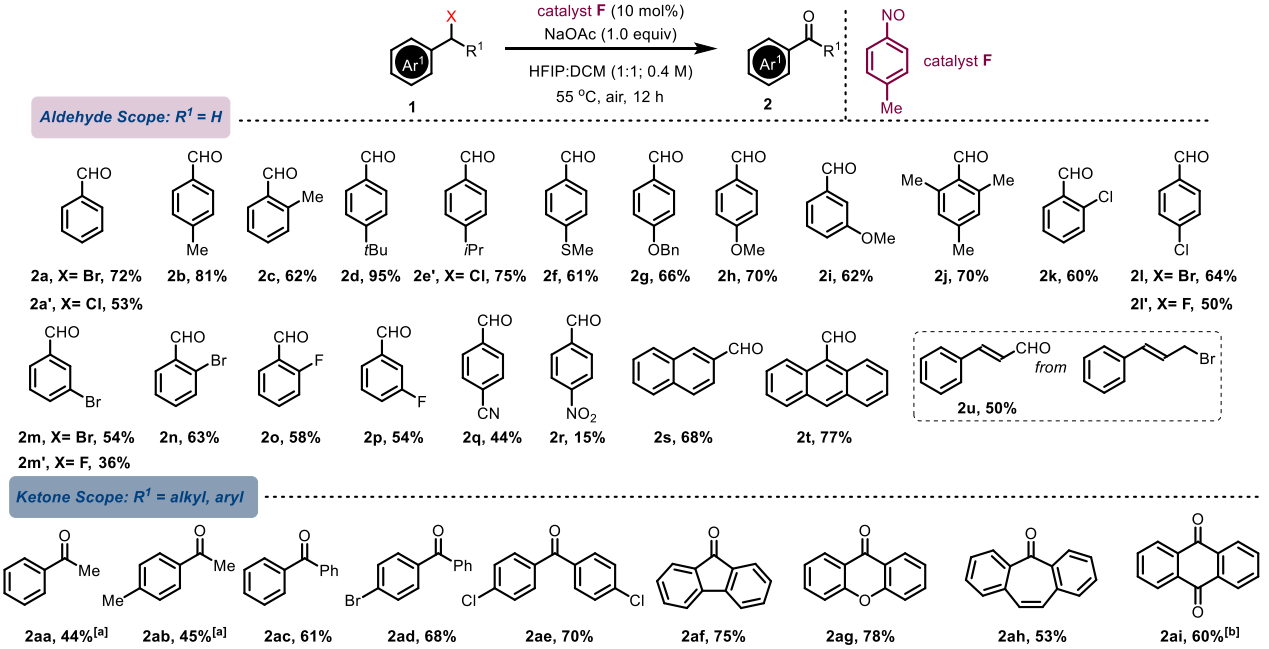
Scheme 2. Substrate Scope[c]



[a]Volatile compounds. [b]15 mol % of catalyst **F**. [c]Reaction conditions: **1** (1.0 equiv, 0.2 mmol), **F** (10 mol %, 0.02 mmol), NaOAc (1.0 equiv, 0.2 mmol), HFIP/DCM (1:1) (0.5 mL), 55 °C, air, 12 h. Yields mentioned are isolated yields.

not respond to our optimized reaction conditions (for details, see SI).

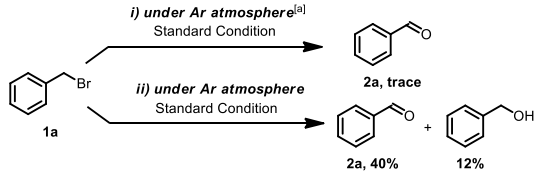
After compelling exploration of primary arylmethyl bromides, we set our goal for synthesizing aromatic ketones from secondary arylmethyl bromides ($R^1 \neq H$). In this regard, acetophenone **2aa** and 4-methylacetophenone **2ab** were afforded in moderate yields. When R^1 = aryl group, the conversion went very smoothly to equip several substituted benzophenone derivatives **2ac**–**ae** in satisfactory outcome (61–70%). Delightfully, some important classes of aromatic ketones such as 9-fluorenone **2af**, xanthone **2ag**, 5-dibenzosuberenone **2ah**, and anthraquinone **2ai** (with 15 mol % of catalyst **F**) were synthesized in good yield (53–75%) applying this current methodology (Scheme 2).

With our current oxidation decorum in hand, we were keen to apply the methodology to synthesize drug molecules in a transition-metal-free pathway. A pharmaceutical drug used for breast cancer treatment, DMU-212 (**5**),[26] was synthesized via Wittig reaction with aldehyde **4** in excellent yield (see SI, section 8 for details). Prior to this conversion, one of the key starting materials 3,4,5-trimethoxybenzaldehyde **4** was synthesized from analogous benzyl bromide **3** using our standard reaction condition with 63% yield.

To extend this current methodology's applicability, we performed chemoselective reactions taking advantage of the higher reactivity of benzylic bromides (see SI, section 8 for details). Marginally higher loading of catalyst (15 mol %) selectively oxidized benzylic bromide to aromatic carbonyl compounds leaving other aliphatic C-halogen bonds intact. For example, substrates **6** and **8** were chemoselectively converted to their carbonyl counterparts **7** and **9**, respectively with moderate yield.[27]

To have a clear picture of the mechanistic pathway, we executed some control experiments (Scheme 3). At first, the role of aerobic O_2 was investigated by setting up the standard reaction with **1a** at inert atmosphere (in Glove-Box, O_2 and

Scheme 3. Control Experiments[b]



[a]Freshly distilled solvents were used in glovebox. [b]Reaction conditions: **1** (1.0 equiv, 0.2 mmol), **F** (10 mol %, 0.02 mmol), NaOAc (1.0 equiv, 0.2 mmol), HFIP/DCM (1:1) (0.5 mL), 55 °C, 12 h. Yields mentioned are isolated yields.

H_2O level >5 ppm) using dry and freshly distilled solvent. After the dedicated time, trace amount (<5%) of product **2a** was isolated (Scheme 3, part i), verifying that O_2 has an unprecedented impact in this transformation. The trace amount of yield also indicates the importance of water for the hydrolysis of nitrone intermediate **VII**.[28] As proposed, terminal oxidation of arylhydroxylamine to nitrosoarene can be achieved by molecular oxygen to yield H_2O_2 as byproduct, closing the nitroso-organocatalytic cycle.[29a] Beside this, the terminal oxidation of arylhydroxylamine to nitrosoarene can also be accomplished using H_2O_2.[29b] The role of H_2O_2 in this terminal oxidation step was further proved when the optimized reaction was conducted under inert atmosphere (without O_2) with 1 equiv of H_2O_2 (35 wt % of H_2O solution), producing **2a** and benzyl alcohol (formed due to the presence of water in H_2O_2, 35 wt % of H_2O solution) in 40% and 12% isolated yield, respectively (Scheme 3, part ii). This result indicates that H_2O_2 is indeed a feasible oxidant for the reoxidation of arylhydroxylamine to nitrosoarene.

On the basis of the control experiments and literature evidence,[21,22,25] a plausible O_2-coupled nitroso-organocatalyzed reaction mechanism is proposed in Scheme 4. It is evident that the use of HFIP, one of the most potent HBD

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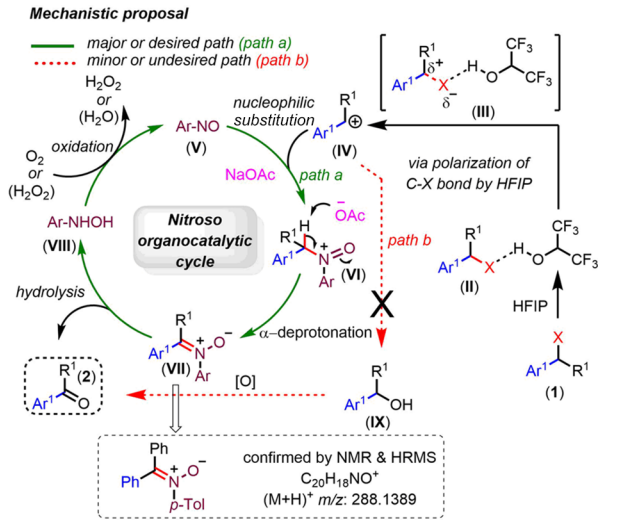
Scheme 4. Proposed Mechanistic Pathway



solvents (α = 1.96),[25b] has an imperative role in our reaction. According to our proposed pathway, strong hydrogen bonding interaction between benzyl halide **1** and HFIP initiates the process by forming complex **II**. This complex is then transformed into carbocationic intermediate **IV** via the polarization of C-halogen bond (intermediate **III**) along with hydrogen bonded halide species. The nucleophilic trapping of **IV** with nitrosoarene **V** prompts the formation of nitrosonium ion intermediate **VI**, which undergoes α-deprotonation to yield nitrone intermediate **VII** (detected by NMR and HRMS; for details see SI). The active nitrone intermediate **VII** is prone to hydrolysis to give the desired aromatic carbonyl compound along with hydroxylamine derivative **VIII**. Finally, the oxidation of hydroxylamine (either by O_2 or H_2O_2)[29] regenerates nitrosoarene catalyst by closing the catalytic cycle (path a). Alternatively, the carbocationic intermediate **IV** can be trapped by H_2O to generate benzyl alcohol **IX** as an intermediate which would have been further oxidized (either under aerobic conditions or in the presence of nitrosoarene) to provide the desired carbonyl compound. The control experiment with benzyl alcohol **IX** indicates that **IX** cannot be an intermediate (see SI, section 9a).

The proposal of arylhydroxylamine as an intermediate in our suggested catalytic cycle was verified by running the reaction with catalytic amount of 4-methylphenylhydroxylamine (see SI, section 9b for details). Slight changes in the solvent concentration (1.6 M, rest remained same, 0.8 mmol reaction scale) gratifyingly provided the desired product **2a** in 56% yield using 10 mol % of 4-methylphenylhydroxylamine as a catalyst. This experiment strongly supports the mechanism proposed by us.

In conclusion, we have developed a novel and rare O_2-coupled transition-metal-free nitrosoarene-catalyzed method under mild conditions. In this report, nitrosoarene has been portrayed as an efficient organocatalyst to carry out oxidation of arylmethyl halides to aromatic aldehydes and ketones. Using the ability of nitrosoarene to undergo nucleophilic attack to the engendered carbocation from arylmethyl halides assisted by HFIP and hydrolysis of nitrone intermediate, a mechanistically sound unique oxidative catalytic cycle has been outlined. The autoxidation of hydroxylamine to nitrosoarene under aerobic conditions has exquisitely enabled the controlled oxidation protocol.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02272.

Experimental procedures, mechanistic evidence, and spectral data for the newly synthesized products (PDF)

FAIR data, including the primary NMR FID files, for compounds **2a**–**2ai**, **4**, **5**, **7**, **9**, and **VII** (ZIP)

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Notes

The authors declare no competing financial interest.

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(27) In case of substrate **6**, the yield might be low due to the presence of an electronegative nonbenzylic Br atom beside benzylic one. Nevertheless, we can still recover the starting materials in both the cases.
(28) A stoichiometric reaction (with 1 equiv of F) using undistilled and degassed solvent (also deoxygenated using three cycles of freeze−pump−thaw) under argon atmosphere delivered the desired product with 62% isolated yield, signifying the importance of the hydrolysis of nitrone intermediate for the catalyst turnover.
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