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Iron Catalysis

Synthesis of Unprotected β -Arylethylamines by Iron(II)-Catalyzed 1,2-Aminoarylation of Alkenes in Hexafluoroisopropanol

Valentyn Pozhydaiev, Marie Vayer, Claire Fave, Joseph Moran,* and David Lebœuf*

Abstract: β -Arylethylamines are prevalent structural motifs in molecules exhibiting biological activity. Here we report a sequential one-pot protocol for the 1,2-aminoarylation of alkenes with hydroxylammonium triflate salts and (hetero)arenes. Unlike existing methods, this reaction provides a direct entry to unprotected β -arylethylamines with remarkable functional group tolerance, allowing key drug-oriented functional groups to be installed in a two-step process. The use of hexafluoroisopropanol as a solvent in combination with an iron(II) catalyst proved essential to reaching high-value nitrogen-containing molecules.

Introduction

Aliphatic amines are at the core of fine chemical synthesis.^[1] They feature in more than 40 % of drug molecules but are also versatile precursors for constructing more complex bioactive molecules, natural products, and polymers (Scheme 1A).^[2] Consequently, accessing densely functionalized primary aliphatic amines, notably β -arylethylamines, represents an important challenge in synthetic chemistry.^[3] Since the functional groups embedded in those molecules significantly influence their biological properties, synthetic methods that can provide structurally complex aliphatic amines are fundamental to expand into biologically relevant chemical space. Currently, common methods to forge β -aryl aliphatic primary amines include 1,4-addition to

nitroalkenes,^[4] arylation of aziridines,^[5] and anti-Markovnikov hydroamination of alkenes.^[6] However, they often require engineered substrates, display limited functional group tolerance, or involve additional reduction or deprotection steps that further limit functional group compatibility.

Alkene difunctionalization^[7] is a straightforward way to assemble β -arylethylamines in a single step.^[8] In recent years, this challenge was taken up by several groups, notably Stephenson,^[9] Liu,^[10] and Engle^[11] (Scheme 1B).^[12,13] However, none of these strategies provide unprotected amines, and, in some cases, pre-activated (hetero)arenes or directing groups are required. Furthermore, they do not directly access several drug-relevant functional groups, including amides, sulfonamides, nitro groups, nitriles, phosphonates, and NH-indoles, among others. At least one of these functional groups are found in most pharmaceuticals since they provide key interactions between drugs and their biologic targets.^[14] Given these existing limitations, the arylation of alkenes to the corresponding unprotected β -arylethylamines remains an open challenge in synthesis.

Shu accessed β -phenylethylamines through the hydroamination of 1,1-disubstituted alkenes using ammonium carbonate as an aminating source (Scheme 1C).^[15] However, in this case, the aryl moiety must already be present in the alkene substrate. Furthermore, the alkene motif was unable to tolerate electron-withdrawing groups stronger than esters or a trifluoromethyl group and compatibility with *N*-heterocycles, notably with indole derivatives, was not explored. Alternatively, nitrogen-centered radicals are among the simplest ways to generate unprotected amines.^[16] Proven sources for the formation of those species are hydroxylamines,^[17] whose use has been exploited by the group of Morandi in iron(II)-catalyzed alkene aminochlorination, aminoazidation and aminohydroxylation (Scheme 1C).^[18] The use of (hetero)arene nucleophiles remains unexplored, which can be attributed to the fact that arenes are easily aminated under those reaction conditions, as illustrated by Morandi,^[19] Jiao,^[20] Ritter,^[21] Phipps,^[22] and others.^[17b]

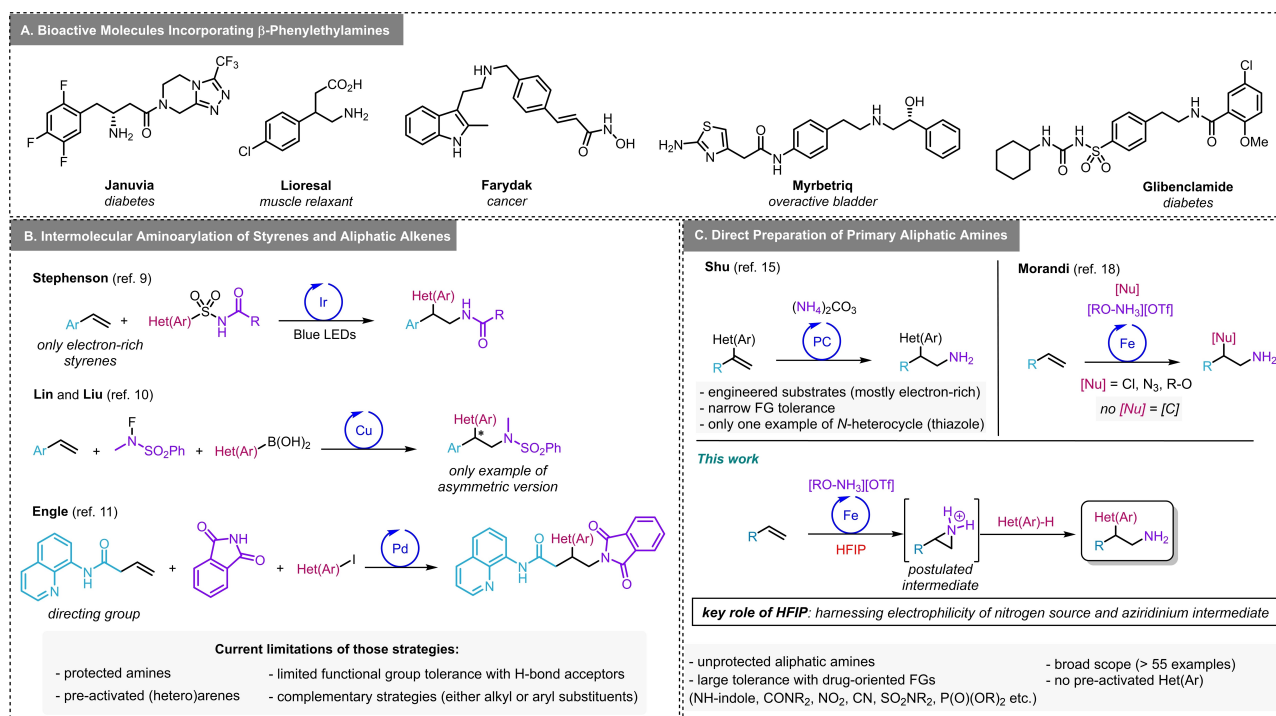
We envisaged a one-pot/two-step aminoarylation process featuring the amination of the alkene with hydroxylamines followed by the addition of a (hetero)arene nucleophile to trigger the ring-opening of a postulated aziridinium intermediate. The reaction would take place at the most substituted position of the aziridinium in analogy with our recent work on the arylation of phenoniums.^[23,24] We speculated that the use of hexafluoroisopropanol (HFIP) would allow us to overcome the problem of compatibility

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Scheme 1. Importance of β -phenylethylamines and strategies to access them. FG = functional group.

between (hetero)arenes and hydroxylamine radical chemistry and to widen the scope of compatible functional groups.^[25] Based on our previous studies on the reactivity of deactivated styrenes and epoxides,^[23,26] we suspected that HFIP could simultaneously stabilize radical and cationic intermediates while enhancing the electrophilicity of the key amine-centered radical and aziridinium components, allowing highly deactivated substrates to be used in the reaction.

Here, we disclose that HFIP enables 1,2-arylamination of alkenes to directly access unprotected β -arylethylamines under conditions compatible with a broad range of functional groups. The user-friendly reaction offers a valuable alternative to well-established strategies for the aminoarylation of alkenes.

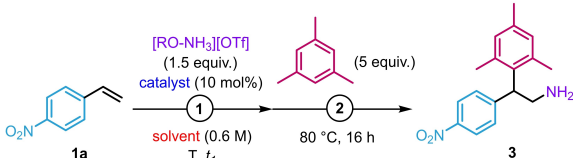
Results and Discussion

Optimization Studies

We began our optimization studies with 4-nitrostyrene **1a** as a model substrate and [MsO-NH₃][OTf] as an aminating agent (1.5 equiv), using FeSO₄·7H₂O as a catalyst (10 mol %) in HFIP (0.6 M) (Table 1).^[21] Initially, the first step was carried out at 60 °C for 6 h, before adding mesitylene as an arene nucleophile (5 equiv). After 16 h at 80 °C, the target product **3** was isolated in 48 % yield (entry 1). Of note, no amination of the nitrobenzene ring was observed under those reaction conditions. Decreasing the temperature to 60 °C for the second step resulted in a significant drop in yield (16 %) (entry 2). We then tested a series of common hydroxylammonium salts but none of

them improved the yield of the reaction (entries 3–6). Either the amination did not occur in the first step (entries 3–5) or the amination of the nitrobenzene also took place as a side reaction (entry 6). By closely monitoring the first step, its reaction time could be reduced to 1 h, providing the aminoarylation product **3** in a slightly better yield (51 %) (entry 7). Regarding the optimization, the screening of a series of Fe^{II} salts revealed that FeSO₄·7H₂O and Fe(OTf)₂ are equally effective (entries 8–12). We opted for the former in our studies as it is cheap and air-insensitive. As anticipated, the reaction did not afford product **3** in conventional organic solvents (entries 13–17), highlighting the critical role of HFIP in the transformation. Other parameters such as the concentration, the temperature in the first step, and the number of equivalents of [MsO-NH₃][OTf] were evaluated but they did not improve the reactivity, leading to either degradation or side reactions (entries 18–21).^[27] The applicability of this protocol was demonstrated at a larger scale (5.46 mmol), which allowed the preparation of aminoarylated compound **3** in 54 % yield (2.95 mmol, 840 mg) (entry 7).

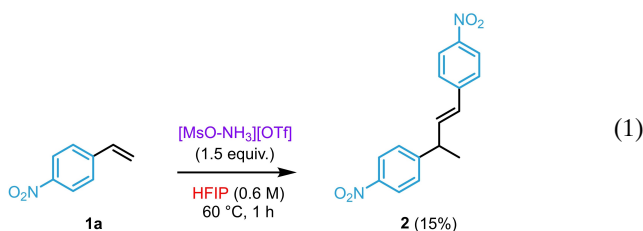
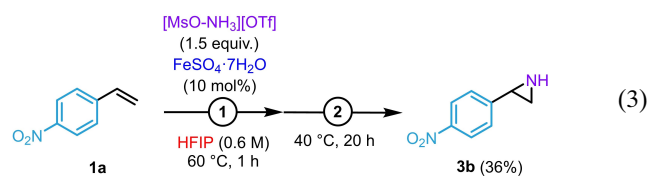
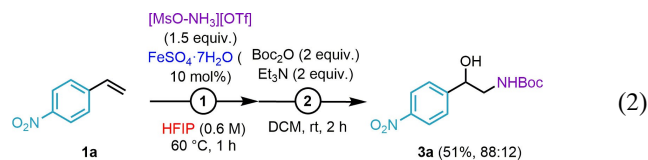
From there, we tried to determine where the loss in yield occurred and to identify what side products and intermediates were generated. After the first step, a mixture of several products was obtained. However, conducting this step in the absence of iron(II) catalyst allowed us to monitor the reaction by ¹H NMR and to observe the formation of the dimer of 4-nitrostyrene (**2**), which likely undergoes subsequent reactions in the presence of iron. This compound was isolated in 15 % yield [Eq. (1)], accounting for 30 % of starting material. The formation of this product from a highly deactivated styrene might be explained by the acidic

Table 1: Optimization of the reaction conditions for the formation of aminoarylation compound **3**.^[a]


Entry	Catalyst	[RO-NH ₃][OTf]	Solvent	T	t ₁	Yield ^[b] [%]
1	FeSO ₄ ·7H ₂ O	[MsO-NH ₃][OTf]	HFIP	60	6	48
2 ^[c]	FeSO ₄ ·7H ₂ O	[MsO-NH ₃][OTf]	HFIP	60	6	16
3	FeSO ₄ ·7H ₂ O	[PivO-NH ₃][OTf]	HFIP	60	6	–
4	FeSO ₄ ·7H ₂ O	[PNBO-NH ₃][OTf]	HFIP	60	6	–
5	FeSO ₄ ·7H ₂ O	[TsO-NH ₃][OTf]	HFIP	60	6	–
6	FeSO ₄ ·7H ₂ O	[NsO-NH ₃][OTf]	HFIP	60	6	27
7	FeSO₄·7H₂O	[MsO-NH₃][OTf]	HFIP	60	1	51 (54)^[d]
8	Fe(OTf) ₂	[MsO-NH ₃][OTf]	HFIP	60	1	52 ^[e]
9	Fe(OAc) ₂	[MsO-NH ₃][OTf]	HFIP	60	1	45 ^[e]
10	Fe(acac) ₂	[MsO-NH ₃][OTf]	HFIP	60	1	31 ^[e]
11	FeCl ₂	[MsO-NH ₃][OTf]	HFIP	60	1	44 ^[e]
12	FePc	[MsO-NH ₃][OTf]	HFIP	60	1	–
13	FeSO ₄ ·7H ₂ O	[MsO-NH ₃][OTf]	Toluene	60	1	–
14	FeSO ₄ ·7H ₂ O	[MsO-NH ₃][OTf]	MeNO ₂	60	1	–
15	FeSO ₄ ·7H ₂ O	[MsO-NH ₃][OTf]	1,2-DCE	60	1	–
16	FeSO ₄ ·7H ₂ O	[MsO-NH ₃][OTf]	<i>i</i> PrOH	60	1	–
17	FeSO ₄ ·7H ₂ O	[MsO-NH ₃][OTf]	TFE	60	1	25 ^[e]
18 ^[f]	FeSO ₄ ·7H ₂ O	[MsO-NH ₃][OTf]	HFIP	60	1	40
19	FeSO ₄ ·7H ₂ O	[MsO-NH ₃][OTf]	HFIP	40	1	–
20	FeSO ₄ ·7H ₂ O	[MsO-NH ₃][OTf]	HFIP	80	1	–
21 ^[g]	FeSO ₄ ·7H ₂ O	[MsO-NH ₃][OTf]	HFIP	60	1	13

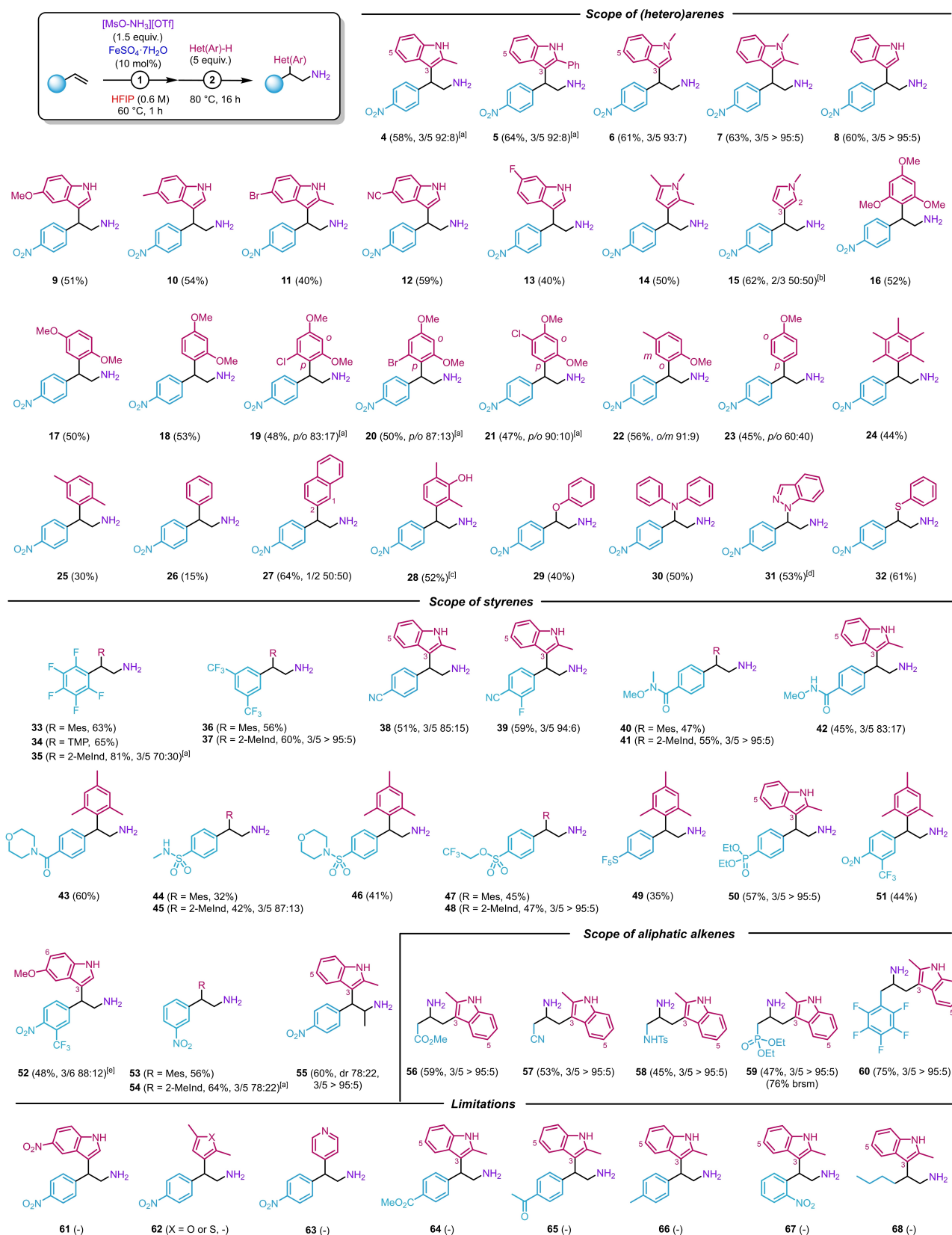
[a] Standard reaction conditions: (1) **1a** (0.3 mmol), [RO-NH₃][OTf] (1.5 equiv.) and catalyst (10 mol%) in solvent (0.6 M), 60 °C, 1 h (in a sealed tube) then (2) mesitylene (5 equiv.), 80 °C, 16 h. [b] Isolated yield. [c] Second step at 60 °C. [d] 5.46 mmol scale. [e] NMR yield using triethylsilane as an external standard. [f] 0.2 M. [g] [MsO-NH₃][OTf] (2.5 equiv.). PNB = *para*-nitrobenzoyl. Pc = phthalocyanine.

reaction conditions that favor its initial protonation prior to its dimerization.^[25b] In parallel, the aminated product obtained at the first step was protected with a Boc group to facilitate its characterization, delivering the corresponding aminoalcohol **3a** along with its regioisomer in 51 % yield (ratio 88:12) [Eq. (2)]. This result is in line with the yield obtained for the product **3**, demonstrating that the first step is the bottleneck of the reaction. Regarding the mechanism, decreasing the temperature to 40 °C in the absence of a nucleophile allowed us to isolate aziridine **3b** in 36 % yield [Eq. (3)], supporting the formation of an aziridinium intermediate in the reaction.



Reaction Scope

With the optimized conditions in hand (Table 1, entry 7), we explored the scope of the reaction, initially evaluating the reactivity of various electron-rich (hetero)arenes with 4-nitrostyrene **1a** (Scheme 2). Substrate **1a** underwent the reaction sequence smoothly with a diverse set of indoles to provide the corresponding products **4–13** in yields ranging from 40 to 64%.^[28] Here, two products—separable by flash column chromatography—were obtained in the case of 2-methylindole (**4**), resulting from the nucleophilic addition at



Scheme 2. Scope of 1,2-aminoarylation of alkenes. [a] Regioisomers were separated by flash column chromatography. [b] Second step at 40 °C. [c] O-alkylation product obtained in 20% yield. [d] Product of addition at the terminal position observed (around 10% yield). [e] Product unstable and thus protected by a Boc group for characterization. Mes = 1,3,5-trimethylphenyl. TMP = 1,3,5-trimethoxyphenyl. 2-MeInd = 2-methylindole. brsm = based on recovered starting material.

C2 and C5. The reaction was tolerant to the presence of both electron-donating and -withdrawing groups at C5 (**9–12**) with no impact on the yield. The compound **12** obtained from the reaction between **1a** and 5-cyanoindole is an illustrative example of how our methodology enables the rapid synthesis of densely functionalized scaffolds, as four different nitrogen functionalities (nitro, cyano, NH-indole and primary NH₂) were all installed in one-pot. The reaction could be applied to pyrrole derivatives to afford compounds **14** and **15** in 50 and 62 % yield, respectively. Moreover, the reaction sequence is not limited to heteroarenes but could also be extended to electron-rich arenes, notably to methoxy-substituted arenes. In most cases, the products were obtained in good yields (**16–23**, 45–56 %) and excellent regioselectivity (up to 90:10), except for anisole (**23**). Additional halide groups could be introduced together with methoxy groups without compromising the reactivity (**19–21**). The steric hindrance displayed by pentamethylbenzene did not hamper the reactivity, as the corresponding product **24** was obtained in 44 % yield. While less electron-rich arenes such as *p*-xylene (**25**) or even benzene (**26**) could also be used in the transformation, we observed a decrease in yield (30 and 15 %, respectively). As anticipated, naphthalene reacted unselectively to generate a 1:1 mixture of two regioisomers, albeit in high yield (**27**, 64 %). In the case of phenol, only the *O*-alkylation occurred to form **29** in 40 % yield. The same applied to diphenylamine (**30**, 50 %). Increasing the steric hindrance around the OH functionality can reverse this trend, predominantly delivering 52 % of *C*-alkylation vs. 20 % *O*-alkylation in the case of 2,6-dimethylphenol (**28**). Indazole provided product **31** in 58 % yield. It is noteworthy that thioanisole underwent demethylation under our reaction conditions to afford the product of aminosulfidation **32** (61 %).

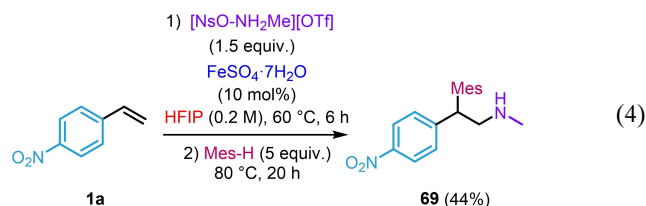
Mesitylene and 2-methylindole were then chosen as nucleophiles to examine the scope of this transformation with styrenes, focusing on substrates bearing functional groups that could be relevant to the synthesis of bioactive compounds. Remarkably, our protocol proved compatible with a broad range of deactivated styrenes, affording the corresponding products **33–55** in yields ranging from 35 to 81 %. Gratifyingly, the products formed incorporate a broad range of functional groups of biological relevance that were hitherto never described, including nitro, cyano, amide, sulfonamide, sulfonate ester, pentafluorosulfanyl, phosphonate, and morpholine groups. Compounds such as **52**, arising from the reaction between 4-nitro-3-trifluoromethylstyrene and 5-methoxyindole, can bear up to five different functional groups often found in marketed pharmaceuticals. Furthermore, non-terminal styrene underwent the reaction smoothly, producing compound **55** as a mixture of diastereoisomers in 60 % yield.

Importantly, the transformation is not restricted to styrene derivatives, as allyl substrates that are stable under highly acidic conditions readily react with 2-methylindole to yield aminoarylation compounds **56–60** in 45–75 %. However, we noticed an inversion of regioselectivity as the reaction produced branched aliphatic amines. It might be explained by the presence of electron-withdrawing groups

that reduce the electrophilicity of the internal position of the aziridinium intermediate, favoring the nucleophilic addition at the terminal position. The reaction is notably tolerant to ester, cyano, sulfonamide, phosphonate and pentafluorophenyl groups.

Regarding the limitations of this transformation, 5-nitroindole did not yield the target product **61**, reacting with itself following an oligomerization process.^[29] The reaction is also not compatible with furan and thiophene derivatives, which decomposed under the reaction conditions. In the case of pyridine (**63**), no reaction was observed, likely due to the trapping of the active species by pyridine. Additionally, styrenes containing an ester (**64**), a ketone (**65**), or, more generally, electron-rich olefins (**66**) did not provide the target products, as they rapidly oligomerized under our standard conditions in the first step. The same applied to 1-hexene (**68**). We also noticed that the presence of a nitro group at the *ortho* position was incompatible with the reaction (**57**), for reasons unclear.

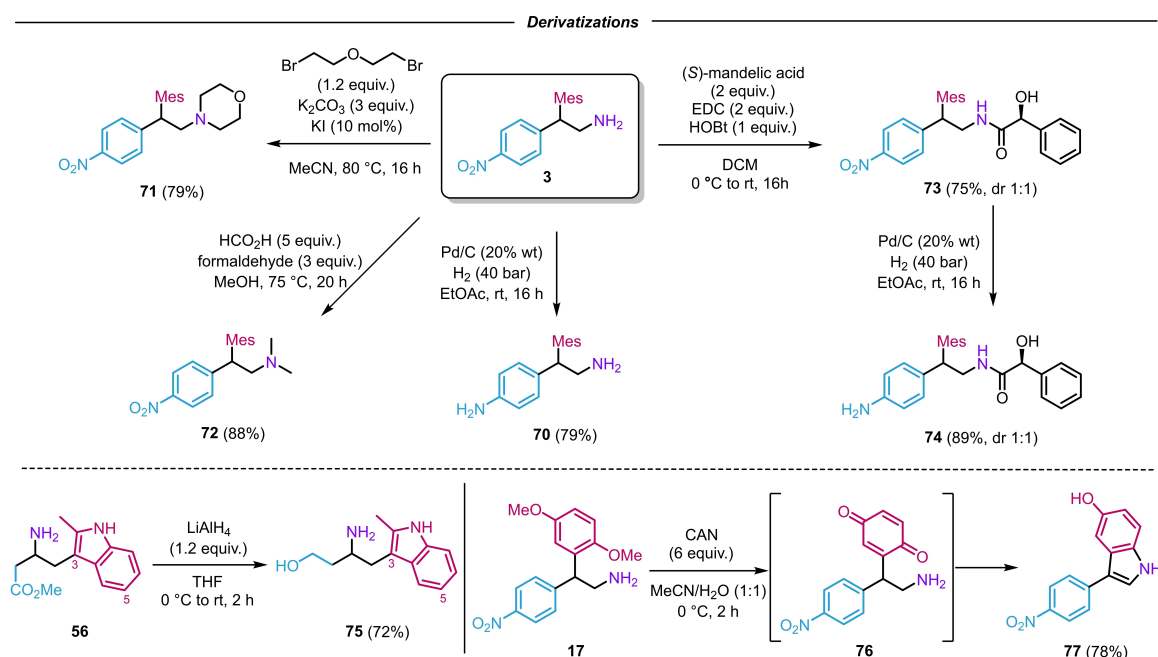
It is important to point out that the reaction sequence is not limited to the preparation of primary amines but can also be employed to introduce secondary amines by using tailored hydroxylammonium salts. For instance, [NsO–NH₂Me][OTf]^[19b] delivered aminoarylation product **69** with a secondary aliphatic amine (44 % yield) [Eq. (4)].



The synthetic utility of this transformation was also highlighted by a series of derivatizations to obtain compounds bearing pharmaceutically relevant moieties (Scheme 3). For instance, the nitro group of **3** was readily reduced with H₂ on Pd/C to furnish the corresponding aniline **70** in 79 % yield. It also reacted with 2-bromoethyl ether to install a morpholine unit (**71**, 79 %).^[30] Eschweiler–Clarke methylation afforded *N,N*-dimethylamine **72** in 88 % yield. The amide coupling with (*S*)-mandelic acid, and the subsequent reduction of the nitro group furnished compound **74**, which can be used to synthesize analogs of Myrbetriq. In turn, ester **56** was also reduced to give the aminoalcohol **75** in 72 % yield. Interestingly, the aminoarylation of product **17** incorporating a 1,4-dimethoxybenzene group led to indole **77** in the presence of cerium ammonium nitrate (CAN) (78 %), which resulted from the in situ cyclization of quinone intermediate **76**.

Conclusion

In summary, we have reported a practical method for the 1,2-aminoarylation of alkenes, allowing a direct access to unprotected β -arylamines. This simple yet far from trivial sequential one-pot protocol relies on the combination of a cheap iron catalyst with HFIP. This reaction is operationally



Scheme 3. Applications of 1,2-aminoarylation of alkenes. Mes = 1,3,5-trimethylphenyl. EDC = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide. HOBT = 1-hydroxybenzotriazole. CAN = cerium ammonium nitrate.

simple, scalable and exhibits broad functional group tolerance, notably with respect to drug-oriented functional groups. In addition, the compounds obtained can be rapidly functionalized to generate more complex molecules. Finally, this study represents yet another example of how HFIP can facilitate desirable reactivity when classical solvents fail.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

Keywords: Aliphatic Amine · Alkene · Aminoarylation · Hexafluoroisopropanol · Iron

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