Letter

Hydroarylation of Alkenes Using Anilines in HFIP

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Hydroarylation of Alkenes Using Anilines in HFIP

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Supporting Information Placeholder

ABSTRACT: Providing new methods for the selective functionalization of small molecules is highly desirable, as installing molecular diversity in a desire position allows, for example, to modulate bioactive molecules. This work reports a method for the selective functionalization of anilines using HFIP as a solvent to promote an acid-catalyzed hydroarylation of olefins. Mechanistic experiments revealed that HFIP both protonates the alkene and selectively enables anilines towards the electrophilic aromatic substitution. This powerful strategy has been applied to the functionalization of the anti-inflammatory mefenamic acid with chemo- and regiocontrol.
KEYWORDS: Hydroarylation, aniline, alkene, HFIP, mefenamic acid.

Bioactive molecules containing the aniline motif in their chemical structure represent an important and heterogeneous toolbox to target a diverse array of medical issues. The aniline fragment is a ubiquitous structure in the core of important commercialized drugs, including anaesthetic, antidepressant, anticancer or anti-inflammatory medicines (Figure 1). Developing novel and selective methods for the functionalization of anilines is highly desirable and will provide a way to expand such a collection of active molecules.[1]

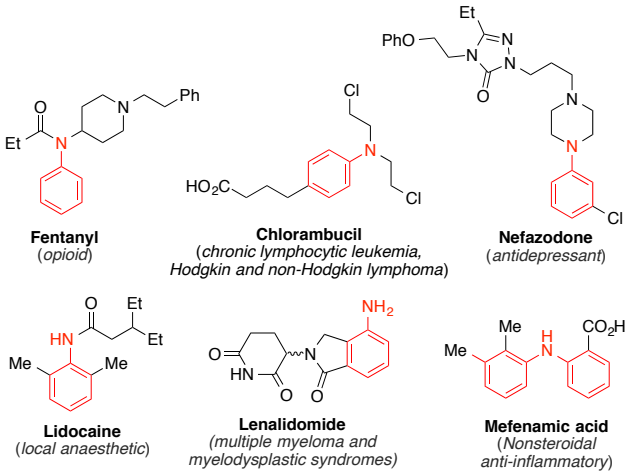


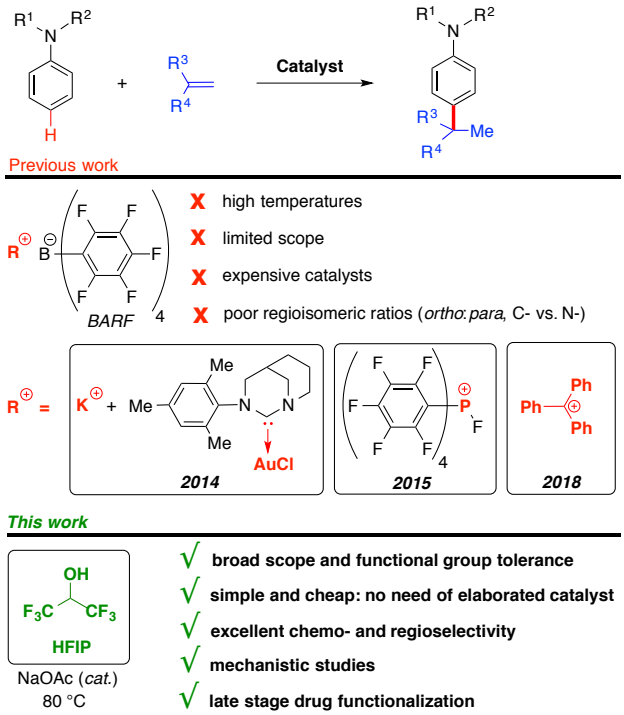
Figure 1. Bioactive molecules containing the aniline structure.

Electrophilic aromatic substitution, and in particular Friedel-Crafts alkylation or acylation, is probably one of the most recurrent tools to derivatise aromatic compounds. While the traditional variants made use of acyl or alkyl halides as electrophilic partners,[2] an alternative strategy employs alkenes in combination with strong acids to generate an electrophilic species *in situ*.[3] However, the use of anilines in Friedel-Crafts reactions proved to be a challenging topic, as a results of: 1) low compatibility of the basic amino group and the commonly used Lewis acid catalysts, resulting in the deactivation of the latter, 2) poor chemo- and regioselectivity, compared to their methoxy counterparts, for example.[4] Pioneering work using gold catalysts in combination with weakly coordinating BARF salts [5] opened the door for anilines to be used in Lewis acid-catalyzed Friedel-Craft *para*-alkylation with alkenes as electrophilic component (Scheme 1, Previous work 2014).[6] Later on this idea has been exploited using aryl phosphonium (Scheme 1, Previous work 2015) [7] and triphenylcarbenium salts (Scheme 1, Previous work 2018) [8] as alternative strong Lewis acids. Despite of being great contributions, all without exception rely on the same expensive and elaborated catalysts using weakly coordinating BARF counteranion, with or without expensive transition metal catalysts.

Alternatively, Hexafluoroisopropanol (HFIP) has recently emerged as an important solvent with interesting properties that allows it to promote a unique reactivity. HFIP is a non-nucleophilic fluorinated alcohol with strong hydrogen-bond donor properties, establishing a hydrogen-bond network that is responsible of its exacerbated acidity. [9] In this context HFIP has been reported to activate carbonyl compounds,[10] epoxides,[11] alcohols,[12] halides,[13] phenols [14] and more recently alkynes [15] or alkenes,[16] however the latter are still underexplored.

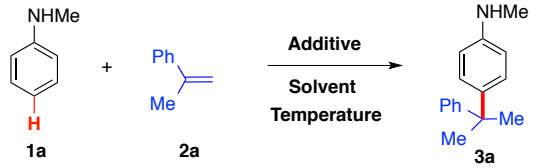
This work reports a new strategy for the selective functionalization of anilines with alkenes, using a very simple, cheap and atom-economic catalytic system, where HFIP plays the dual role of strong acid reacting with the olefin but also enhancing the reactivity of the aniline (Scheme 1, this work).

Scheme 1. Hydroarylation of alkenes using anilines



The study began using equimolecular amounts of aniline **1a** and alkene **2a** in HFIP at room temperature, with a 14% yield of the hydroarylation product **3a** (Table 1, entry 1). Increasing the temperature to 40 °C or 60 °C had little benefit, while using 80 °C doubled the yield up to 29% (Table 1, entries 2-4). Using excess of alkene (2.0 equivalents of **2a**) has a positive effect with a 41% yield (Table 1, entry 5). Finally, the use of additives (see supporting information for further details) revealed that substochiometric amount of sodium acetate has a notably effect in the outcome of the reaction with an 81% yield (Table 1, entry 6). The important effect of the solvent was demonstrated using other acidic solvents, such as trifluoroethanol, acetic acid or trifluoroacetic acid providing no satisfactory results in the hydroarylation reaction (Table 1, entries 7-9).

Table 1. Screening of conditions.



Entry	Additive	Solvent	Temperature	**3a** yield (%)[a]
1[b]	-	HFIP	25 °C	14
2[b]	-	HFIP	40 °C	19
3[b]	-	HFIP	60 °C	25
4[b]	-	HFIP	80 °C	29
5[c]	-	HFIP	80 °C	41
6[c]	**25 mol% NaOAc**	**HFIP**	**80 °C**	**81**
7[c]	25 mol% NaOAc	TFE	80 °C	0
8[c]	25 mol% NaOAc	AcOH	80 °C	traces
9[c]	25 mol% NaOAc	TFA	80 °C	0

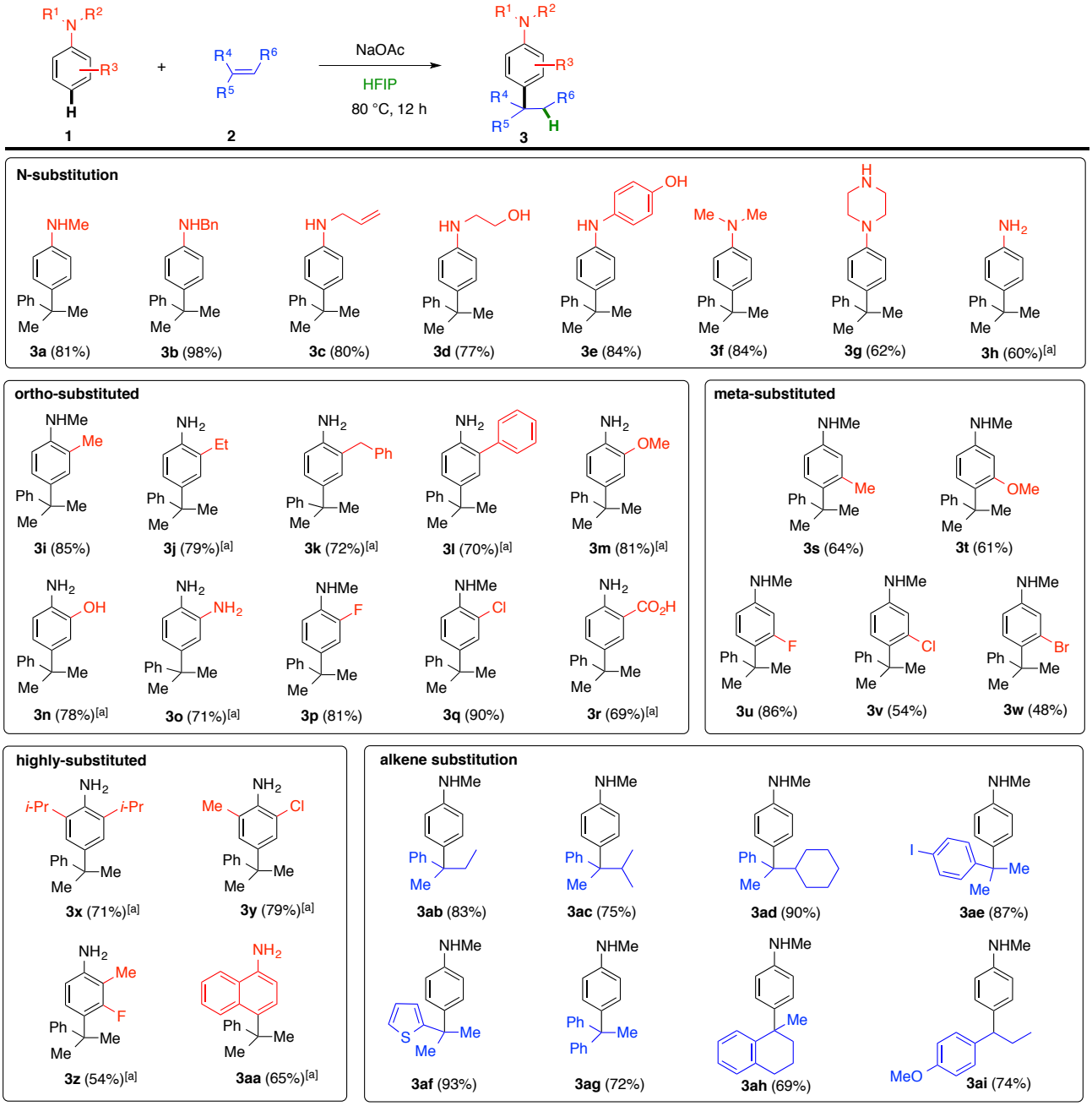
[a] NMR yield using 1,3,5-trimethoxybenzene as standard. [b] 1.0 equivalent of alkene **2a** was used. [c] 2.0 equivalent of alkene **2a** was used.

With those optimal conditions in hand, the scope of the reaction was then evaluated. With respect to the aniline component, substitution on the nitrogen is well tolerated. Among the model substrate with a methyl substituent (Figure 2, **3a**), other aliphatic mono-substituted examples include benzylic, allylic or derivatives containing extra functional groups (Figure 2, **3b**, **3c** and **3d**). Aromatic substitution is also viable, exclusively reacting via the aromatic ring with the unsubstituted *para* position (Figure 2, **3e**). Disubstituted anilines perform well in the reaction and both acyclic and heterocyclic piperazine derivative afforded the expected products (Figure 2, **3f** and **3g**). Finally, the challenging free aniline can be selectively alkylated, increasing the loading of NaOAc, to achieve a respectable 60% isolated yield (Figure 2, **3h**).

The aromatic ring of the aniline can be extensively modified and both *ortho* and *meta* positions have been interrogated. Concerning the *ortho* position methyl, ethyl or benzyl substituents are competent substrates (Figure 2, **3i**, **3j** and **3k**), while aromatic substitution affords a beautiful biphenyl derivate (Figure 2, **3l**). Electron donating heteroatoms can be easily incorporated, for example, both methoxy and hydroxy groups give the expected product in excellent yields and exquisite *para* regiocontrol (Figure 2, **3m** and **3n**). Another interesting example of an electron-rich hetero-substitution is the product of reacting *ortho*-phenylenediamine where the monoalkylation is achieved in high yields (Figure 2, **3o**). Electron-withdrawing substituents, such as halides performed extremely well, and both fluorine and chlorine derivatives are formed in high yields (Figure 2, **3p** and **3q**). Unfortunately, aldehyde and ester derivatives do not react (probably because HFIP interacts with the carbonyl moieties and deactivate the aromatic ring). However, a carboxylic acid is well tolerated and the product of reacting anthranilic acid is isolated in a respectable 69% (Figure 2, **3r**). The *meta* position of the aromatic ring was investigated in a similar manner and some representative examples illustrate the versatile scope. Both aliphatic and electron rich heteroatoms can be accommodated, albeit in slightly diminished yield (Figure 2, **3s** and **3t**). Electron deficient halides provide from excellent to good yields starting from fluoro and moving to chloro or bromo substitution (Figure 2, **3u**, **3v** and **3w**). In view of these results, where fluoro-containing example behaves extremely well and the productivity of methyl derivative is compromised, it is sensible to state that the limitation in the *meta* position might well be related to steric factors rather than electronics. Not only does monosubstitution works, but substrates bearing several substituents in

different combinations complete the scope. Substituting both *ortho* positions either with aliphatic substituents (Figure 2, **3x**) or with an aliphatic and a halide (Figure 2, **3y**) gives very good results. Simultaneous *ortho* and *meta* substitution is well tolerated, even in the bicyclic 1-aminonaphthalene (Figure 2, **3z** and **3aa**).

Finally, the alkene component was studied modifying the model 1,1-disubstituted alkene, α-methylstyrene. Both lineal, branched and cyclic aliphatic substitution is well tolerated with excellent results (Figure 2, **3ab**, **3ac** and **3ad**). The aromatic ring tolerates functional groups that can be used as a handle for further diversification, for example an iodide in cross-coupling reactions (Figure 2, **3ae**). Aromatic heterocycles can be accommodated and thiophene derivative is isolated in 93% yield (Figure 2, **3af**). Two aromatic rings can be incorporated and interesting triarylmethane can be easily accessed (Figure 2, **3ag**). Cyclic alkenes are viable substrates and tetrahydronaphthyl derivative gives the expected product (Figure 2, **3ah**). Lastly, *trans*-anethole, a 1,2-disubstituted alkene, can engage in the reaction, thus expanding the substrate scope with an example that does not contain an all-carbon quaternary centre (Figure 2, **3ai**). While *para*-methoxystyrene also works, styrene gives traces of the product and other aliphatic alkenes, including 1-hexene, 3-hexene, 1-methylcyclohexene, 1-methylcyclopentene or an internal cyclobutene, did not provide the desired product, recovering the alkene starting material.



General conditions: 0.2 mmol of aniline **1**, 0.4 mmol of alkene **2** and 0.05 mmol of NaOAc in 1.0 mL of HFIP. [a] 1.0 equivalent of NaOAc was used.

Figure 2. Scope of the hydroarylation of alkenes using anilines in HFIP.

It is important to emphasize that in all cases an exquisite C- (vs. N-) and *para* (vs. *ortho*) regiocontrol was observed, a challenging limitation commonly stated in the literature.[17]

With the aim of fully understanding the role of HFIP mechanistic experiments were designed to shed light into this effective transformation. Using deuterated HFIP-OD, the model aniline **1a** and terminal alkene **2a**, full incorporation of deuterium on the olefinic carbon confirms the protonation of the alkene by the solvent HFIP. Moreover, the *ortho* positions of the aniline suffer a high degree of deuterium exchange (Figure 3a, **3a-D$_3$**) and treating aniline **1a** with NaOAc in HFIP-OD (with no added alkene) ratifies this H-D exchange in both *ortho* and *para* positions (see supporting information). Reacting anilines **1a** or **1x** with 1,2-disubstituted alkene **2i** results in the same deuterium labelling pattern (full D-incorporation in the olefin carbon and high D-exchange in the *ortho* positions) and high *anti*/*syn* diastereoselection (Figure 3a, **3ai-D$_3$** and **3an-D**).[18] A striking behaviour observed during the scope evaluation is the total *para* selectivity in favour of the amino vs. the methoxy group (Figure 2, **3m** and **3t**). In a competition experiment using equimolecular amounts of aniline **1a** and the exceptionally good Friedel-Crafts substrate trimethoxybenzene **4**,[19] the hydroarylation product **3a** is exclusively formed (Figure 3b), reinforcing the selective activation of anilines using NaOAc/HFIP.

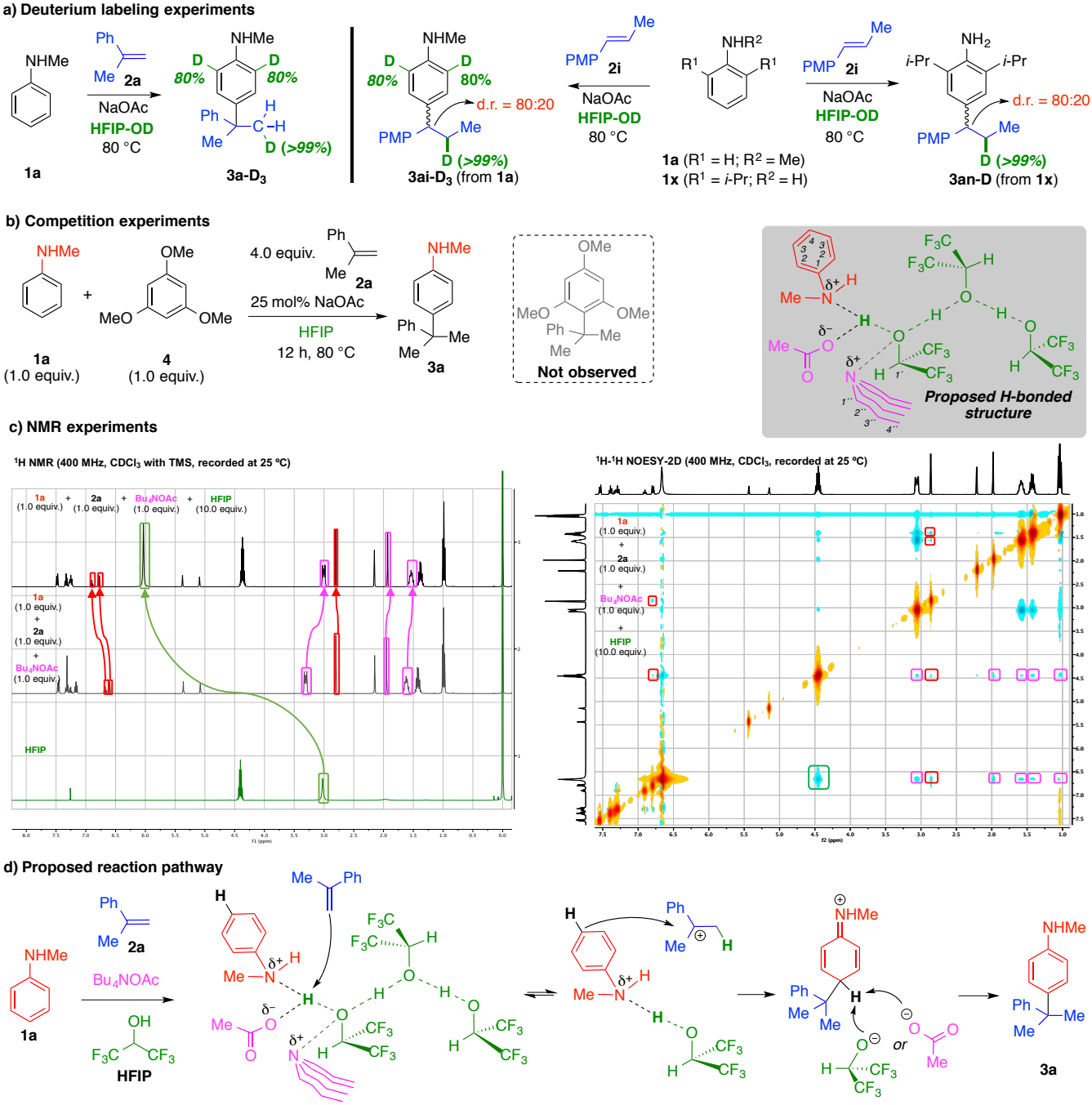


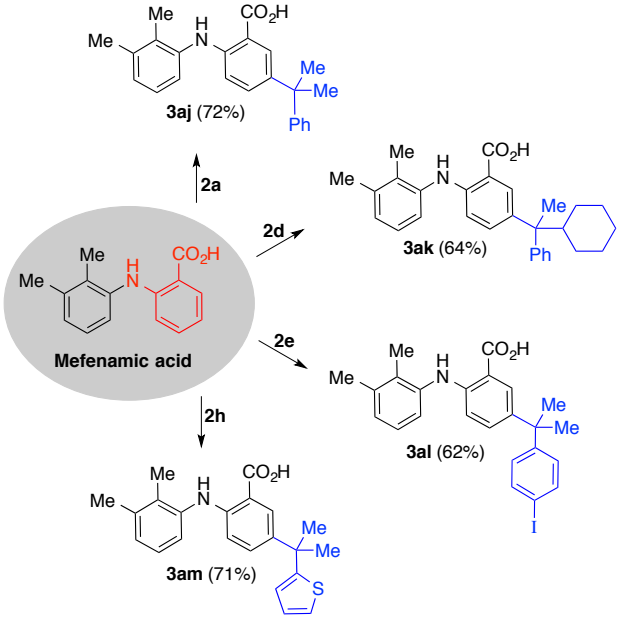
Figure 3. Mechanistic experiments.

In order to elucidate the potential interactions between the base (NaOAc), the aniline and HFIP, a set of NMR experiments were designed, with $CDCl_3$ as the supporting solvent for its neutral behavior with respect to any interactions between species, TMS was added as a reference and Bu_4NOAc (that also catalyzes the reaction, see supporting information, additive screening) was used instead of NaOAc for its better solubility in $CDCl_3$. First the ^{1}H-NMR of individual species (HFIP, **1a**, **2a** and Bu_4NOAc) and binary mixtures of HFIP and every single species (**1a**, **2a** and Bu_4NOAc) were recorded (see supporting information). This was followed by the ^{1}H-NMR of all species mixed together (**1a**, **2a** and Bu_4NOAc) with and without HFIP (Figure 3c, left) where an upfield shift of the acetate (Figure 3c left, pink) and a downfield shift of the aniline (Figure 3c left, red) and HFIP (Figure 3c left, green) signals is clearly observed. Finally, both 1D-nOe (see supporting information) and 2D-NOESY (Figure 3c right) experiments revealed a strong spatial connection between both the CH and OH of HFIP with the aniline and the acetate signals (Figure 3c right, red and pink boxes respectively and see supporting information for further details). Taken together these results support the hydrogen-bonding between the exceptionally acidic OH of the HFIP network [20] and both the aniline and the acetate.[21]

The overall reaction pathway would be in agreement with an electrophilic aromatic substitution mechanism (Figure 3d).[22] While the alkene is protonated by HFIP, producing a stabilized carbocationic intermediate, the amino group of the aniline becomes "protected" via H-bonding to HFIP. Therefore the aniline reacts selectively with the electrophilic species via the aromatic ring (C- vs. N-), generating a Wheland-type intermediate, what is thought to be the rate determining step.[22f] Proton abstraction to rearomatize the aniline is achieved either by the conjugated base of the proton source, or by the added base (acetate) in a more productive manner, affording the observed product.

To illustrate the application of this method in the selective functionalization of bioactive molecules the anti-inflammatory mefenamic acid, also evaluated against Alzheimer's disease with promising results, was used as a target.[23] Efforts to build a library of derivatives from mefenamic acid have previously used either the alkylation or acylation of the amino group and the amidation of the carboxylic acid as diversity points. This simple strategy has produced analogues of the parent compound where the bioactivity was compromised, meaning that both the amino and the carboxylic acid are essential to preserve the active function.[24] Selective modification of the aromatic rings introducing molecular diversity would open the door for a new family of derivatives. Mefenamic acid is a particularly challenging example that exceeds the scope presented above, where the amine shares two distinct aromatic groups, each one bearing different substituents, both of them potentially reactive towards the hydroarylation process described. Thus a chemoselective process is also required. Slightly modifying the general conditions, lowering the temperature to 60 °C to prevent decarboxylation observed at 80 °C,[25] results in a remarkably highly selective and productive functionalization of mefenamic acid. Four different alkenes from the scope above were used to illustrate the viability of the process, introducing the model dimethylbenzyl structure (Scheme 2, **3aj**) but also diverse chemical motifs, such as a cyclohexyl (Scheme 2, **3ak**), an aryl iodide, that could potentially be further functionalized (Scheme 2, **3al**) or the heteroaromatic thiophene (Scheme 2, **3am**).

Scheme 2. Mefenamic acid selective derivatization.



General conditions: 0.2 mmol of **mefenamic acid**, 0.4 mmol of alkene **2** and 0.05 mmol of NaOAc in 1.0 mL of HFIP, 12 h, 60 °C.

In summary a new protocol for the hydroarylation of alkenes using anilines has been developed, that entails the use of HFIP as a unique solvent to promote the reaction. Mechanistic experiments revealed that the acidic nature of HFIP both serves to protonate the alkene and to promote the selective reaction of the aniline via hydrogen bonding. The application of this new method has been found in the selective functionalization of the anti-inflammatory drug mefenamic acid.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and characterization data of all new compounds, including NMR spectra (PDF)

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Notes

The author declares no competing financial interests.

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6834. For a recent example where the *ortho* regioselectivity is observed using alkynes see ref. 15.

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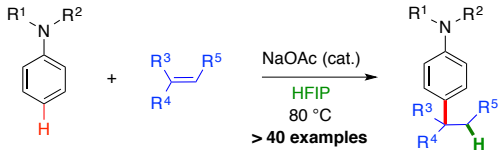
A new method for the selective functionalization of anilines with olefins using HFIP as a unique solvent to promote the reaction has been developed. This new protocol involves cheap, mild and atom-economic conditions, where HFIP plays a double role as strong acid protonating the alkene and activating the aniline towards the hydroarylation. This powerful method has been applied in the selective derivatization of the anti-inflammatory mefenamic acid.



√ **broad scope and functional group tolerance**

√ **simple and cheap: no need of elaborated catalyst**

√ **excellent chemo- and regioselectivity**

√ **mechanistic studies**

√ **drug functionalization**