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Review

Difunctionalization Processes Enabled by Hexafluoroisopropanol

Maciej Piejko, Joseph Moran,* and David Lebœuf*

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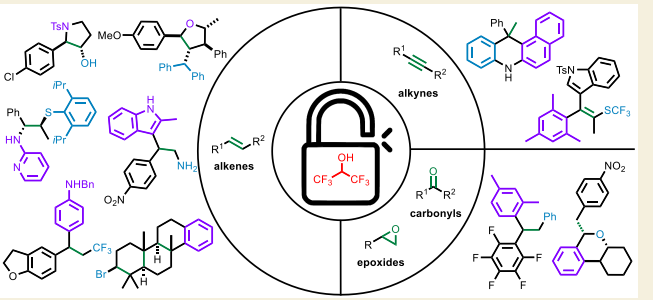
ABSTRACT: In the past 5 years, hexafluoroisopropanol (HFIP) has been used as a unique solvent or additive to enable challenging transformations through substrate activation and stabilization of reactive intermediates. In this Review, we aim at describing difunctionalization processes which were unlocked when HFIP was involved. Specifically, we focus on cyclizations and additions to alkenes, alkynes, epoxides, and carbonyls that introduce a wide range of functional groups of interest.



KEYWORDS: *HFIP, Difunctionalization, Cyclization, Carbocations, Alkenes, Alkynes, Epoxides, Carbonyls*

INTRODUCTION

Creating molecular complexity from feedstock or readily available precursors has been a long-standing endeavor for synthetic chemists. In this context, difunctionalization processes occurring in one-pot represent a straightforward way to achieve this task from alkene-, alkyne-, epoxide-, and carbonyl-containing substrates, among others. Over the past years, numerous approaches relying on transition metal catalysis, radical chemistry, photocatalysis and electrochemistry have thus been designed to provide densely functionalized products. All these methods are often powerful, elegant, and creative, but they may have constraints and limitations related to their utilization, including the use of expensive catalysts, harsh reaction conditions and complex set-ups. To find alternatives to these methods, new strategies have started to emerge in the literature, one of them having been the focus of our research group, namely the use of hexafluoroisopropanol (HFIP) as either a solvent or an additive.[1−7] Its use enables complex transformations in a regio- and diastereoselective fashion from commercially or readily available substrates under operationally simple and mild reaction conditions, while often exhibiting a large functional group tolerance. But why it is the case?

Hexafluoroisopropanol displays a set of unique properties which, altogether, are the reason for its ability to execute challenging reactions. Its wider utilization finds its origin in seminal studies by the group of Berkessel on the epoxidation of alkenes, which laid out a better understanding of its properties and its "positive" effect on reactivity.[8−10] They stressed that its H-bond donating ability could be increased through the formation of an H-bond network between molecules of HFIP, "boosting" the chemical reactivity. Moreover, the strong inductive effect associated with the presence of six fluorine atoms makes the hydroxyl proton more acidic (pK_a = 9.3) than its analogue isopropanol (pK_a = 17.1). As part of our research, we demonstrated that Lewis and Brønsted acid catalysts could template the H-bond network of HFIP, which can significantly lower the activation barriers for various transformations by augmenting the overall acidity of the promoter system.[11,12] At the same time its nucleophilicity remains low compared to other alcohols, which consequently decreases the probability of competition for reactions involving various electrophiles. Its Mayr solvent nucleophilicity parameter for a 99:1 HFIP/water mixture is among the lowest known to date (N_1 = −1.93).[13] Among other properties, HFIP possesses a relatively high dielectric constant (ε = 15.7), a high ionizing power (Y_{OTs} = 3.82) and is redox stable. But, in the end, what makes HFIP truly remarkable is the combination of all these properties that are not found with any other traditional organic solvent, currently allowing it to cover all the fields of modern homogeneous catalysis.[7] As a result, it is now routinely used for the design of new transformations, as recently illustrated by many groups. The aim of the present Review is to disclose recent emerging strategies relying on the use of HFIP to enable difunctionalization processes, focusing on transformations that do not involve any noble transition metal catalysts nor photocatalysts. For a detailed overview of the properties and applications of HFIP in synthesis, we refer the reader to a

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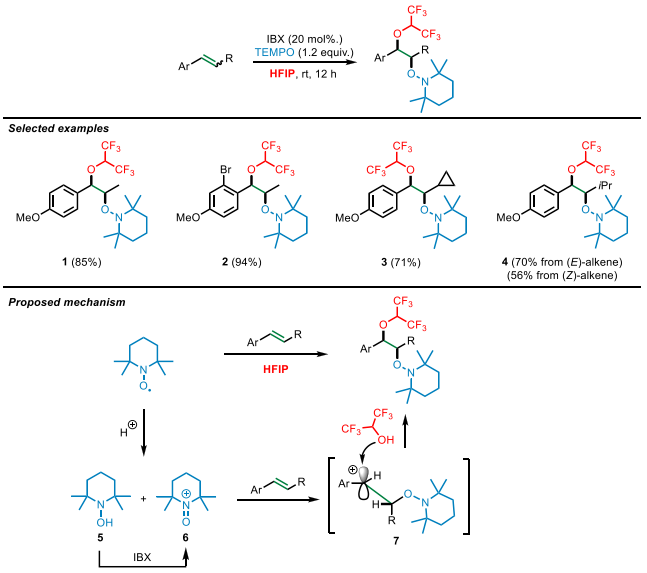
thorough review on the subject by the group of Aubé.[7] Here, we divided the Review into three parts based on the class of substrates: alkenes (i), alkynes (ii), epoxides and carbonyls (iii).

ALKENES

Among the first examples of utilization of HFIP in a metal-free difunctionalization of alkenes is the *syn*-dihydroxylation of electron-rich styrenes with a system featuring 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) and 2-iodobenzoic acid (IBX), which was reported by the group of Donohoe in 2016 (Scheme 1).[14] This method was inspired by their

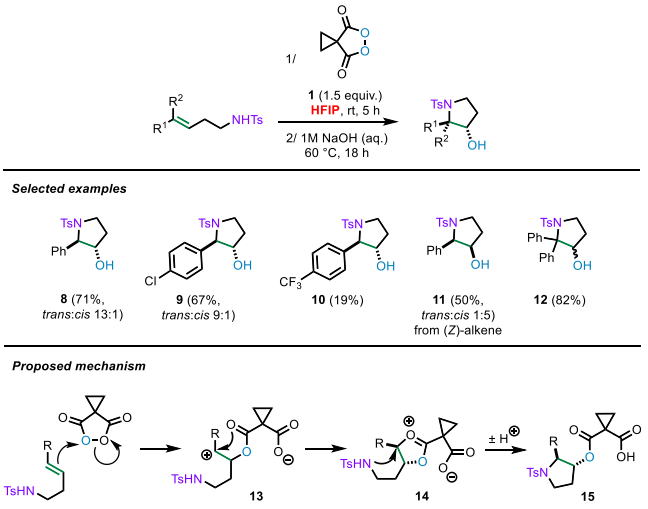
Scheme 1. *syn*-Dihydroxylation of Styrenes



previous study on the dimerization of styrenes, in which they observed the formation of a radical cation intermediate from the styrene in the presence of hypervalent iodine reagents in HFIP.[15] The idea here was to intercept this species by TEMPO followed by a nucleophilic addition of HFIP. The optimization study performed on *trans*-anethole revealed that using a catalytic amount of IBX in HFIP afforded product **1** in 85% yield with excellent diastereocontrol (>95:5). The reaction proved compatible with various electron-rich internal styrenes to provide the corresponding products in high yields. The proposed mechanism starts with the disproportionation of TEMPO in the acidic medium. The use of IBX enables the oxidation of hydroxylamine **5** into oxoammonium cation **6**, which improved the overall yield. This cation can then add to the styrene to form a benzylic cation intermediate. Finally, HFIP preferentially approaches the benzylic position antiperiplanar to the R group to avoid a steric clash, which explains the *syn* selectivity observed. The fact that both (*E*)- and (*Z*)-styrene led to the same *syn*-product (**4**) is consistent with the mechanistic proposal. The authors also hypothesize that the adjacent nitrogen atom might play a role in directing the addition of the nucleophile.

In 2018, the group of Tomkinson reported the oxyamination of *N*-tosyl-protected homoallylic amines in the presence of malonoyl peroxide (Scheme 2).[16] This group previously described the dioxygenation of alkenes in chlorinated solvents or perfluoro-*tert*-butanol;[17,18] however, in the case of oxyamination, the reaction only proceeded in HFIP, without

Scheme 2. Oxyamination of *N*-Tosyl-Protected Homoallylic Amines



requiring any catalyst. In addition, the nitrogen protecting group was critical for the success of the transformation as no reaction was observed, except for a tosyl protecting group. The high specificity observed with this protecting group suggests that its interaction with the solvent plays a crucial role in the reactivity profile, not to mention the possible activation of the peroxide by HFIP, even if these points were not addressed in this study. Various aromatic substituents at the terminal position of the olefin were tolerated, including electron-donating groups and moderate electron-withdrawing ones, to provide the corresponding pyrrolidines in yields ranging from 52 to 82%. On the other hand, the presence of a stronger electron-withdrawing group such as trifluoromethyl (**10**) led to a significant decrease in yield (19%). Here, using the (*E*)-alkene produced the resulting *trans* isomer **8** with a selectivity up to 13:1, whereas the (*Z*)-alkene provides the *cis* isomer **11** as a major compound. The proposed mechanism of this transformation starts with a nucleophilic addition of the alkene to the peroxide leading to cyclic dioxonium **14** after trapping of carbocation intermediate **13** by one of the carbonyls. A subsequent cyclization resulting from the addition of sulfonamide to the cyclic dioxonium leads to the formation of the pyrrolidine ring (**15**) in which the newly formed C−O and C−N bonds are in *trans* relationship.

In the same year, the group of Denmark reported an enantioselective Lewis base-catalyzed intermolecular sulfenocyclization of polyenes in HFIP (Scheme 3).[19] Their initial attempts to achieve cyclization of homogeranylarenes using established sulfenocyclization conditions were unsuccessful.[20−22] The transformation only proceeded with high efficiency by using HFIP as a solvent. The authors hypothesized, based on existing precedents,[23] that the effect of the solvent is due to solvophobic interactions which force the lipophilic polyene to minimize its surface area and, in doing so, facilitate access of the sulfur reactant to the reacting alkenyl functionality. Another feature of HFIP, which was already discussed in the context of other studies, is its assistance in generating catalytically active cationic species. Electron-rich and neutral homogeranylbenzenes cyclized in high yields however, electron-deficient substrates were not compatible with the reaction conditions and afforded complex mixtures. Importantly, all examples in the scope were synthesized with

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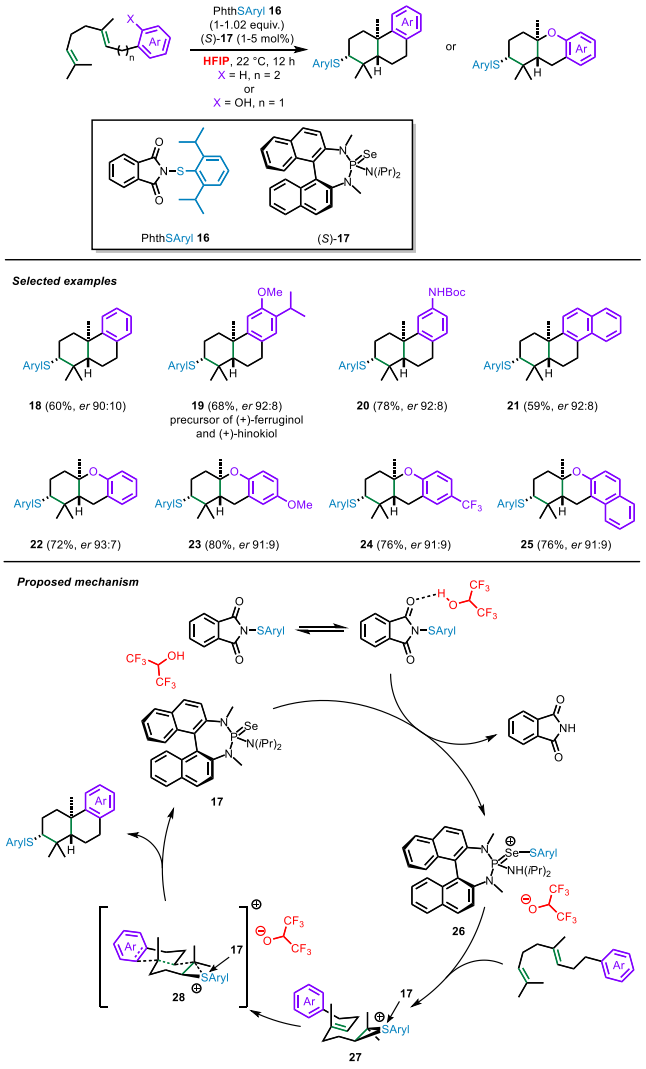
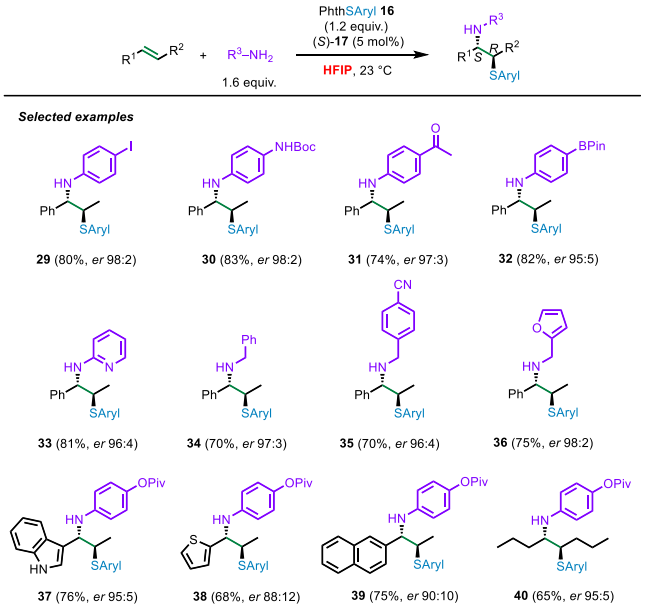
Scheme 3. Enantioselective Sulfenocyclization of Homogeranylarenes and *ortho*-Geranylphenols



high enantioselectivities (*er* ≥ 90:10) in the presence of chiral Lewis base (*S*)-**17**. In addition, to illustrate the synthetic utility of this transformation, this method was used to achieve the total synthesis of (+)-ferruginol and (+)-hinokiol from **19**. The cyclization was also applied to *ortho*-geranylphenols, which delivered the corresponding oxysulfenylated products in 67−80% yields with *er* ≥ 90:10. Here, the mechanism first involves the activation of sulfenylating agent **16** by HFIP, which then facilitates sulfur transfer to selenophosphoramide catalyst (*S*)-**17**. The next step is the transfer of the sulfenyl group to the alkene to form thiiranium ion **27**, which undergoes a stereospecific intramolecular nucleophilic capture (**28**) and a subsequent deprotonation to afford the product.

The previously described catalytic system for sulfenocyclization was also employed to perform intermolecular sulfenoamination of alkenes (Scheme 4).[24] The group of Denmark showed the broad utility of this method to achieve the enantioselective sulfenoamination of (*E*)-2-methylstyrene with a variety of aniline and benzyl amine nucleophiles. The key is that the amine must be nucleophilic enough to outcompete the solvent in intercepting the cationic intermediate. For instance, sulfonamides and amides were not suitable for this task. On the other hand, the reaction proved compatible with anilines and

Scheme 4. Enantioselective Sulfenoamination of Alkenes



benzylamines bearing electron-donating and -withdrawing groups as well as with 2-aminopyridine (**33**). The reaction was not limited to styrenes but could also be extended to vinyl heteroaromatics (**37** and **38**) and internal aliphatic alkenes (**40**). The products were obtained in high yields ranging from 61 to 87% with *er* up to 98:2. The mechanism proposed is identical to the one depicted above for the sulfenocyclization. Of note, the group of Denmark also described recently enantioselective inter- and intramolecular sulfenofunctionalization of unactivated cyclic and (*Z*)-alkenes.[25]

In the context of difunctionalizations of alkenes involving the use of electrophilic agents, the Donohoe group innovated with the use of alcohols as alkylating agents in stereoselective heterocyclizations.[26] The authors discovered that a simple titanium catalyst could generate carbocations from the respective allylic or benzylic alcohols, which would trigger the reaction with homoallylic alcohols to form densely functionalized tetrahydrofuran heterocycles and related compounds (Scheme 5). The process is a formal 5-endo-trig cyclization. The overall transformation proved to be highly diastereoselective as only the *trans* diastereoisomer was obtained in most cases. It is noteworthy that no other solvent than HFIP allowed this transformation to take place, which again showcases its unique properties. The reaction proceeded in overall high yields with respect to a variety of activated alcohols for which the electron-donating properties were associated with higher yields and lower reaction temperatures. Less activated allylic alcohols were also used but gave lower yields (**44**). The reaction was not limited to aliphatic alcohol nucleophiles but could also be extended to phenols (**47**) and carboxylic acids (**48**). Remarkably, by using enantiopure substrates as starting materials, the chiral information was completely transferred to the product (**49**).

The authors presented evidence for the existence of an allylic cationic intermediate, as a reaction initiated with two regioisomeric allylic alcohols yields the same product. This is in line with the fact that HFIP encourages the formation of carbocations due to its high ionizing power. NMR-based mechanistic studies revealed that the active catalytic species is formed upon replacing two isopropoxy ligands by two

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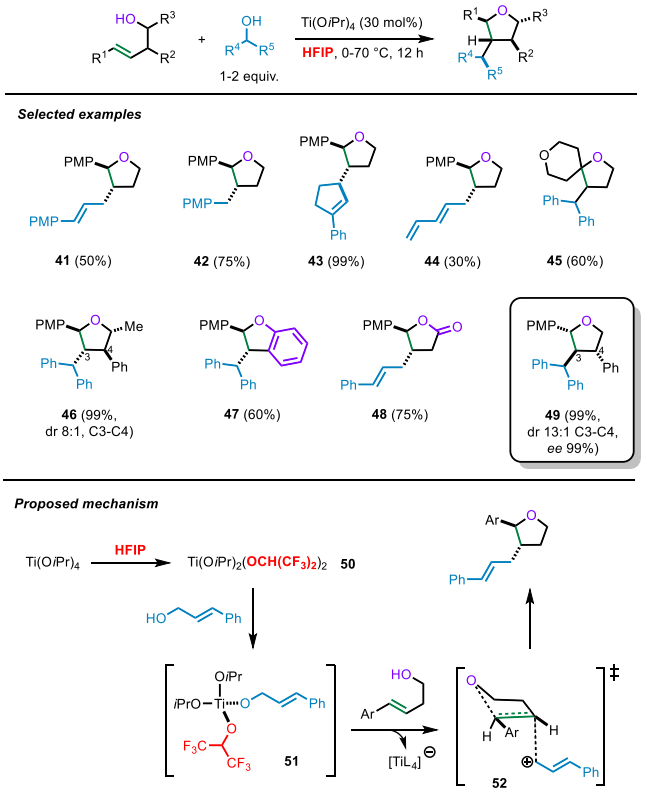
Scheme 5. Titanium(IV)-Catalyzed Preparation of Tetrahydrofurans and Related Compounds in HFIP[a]

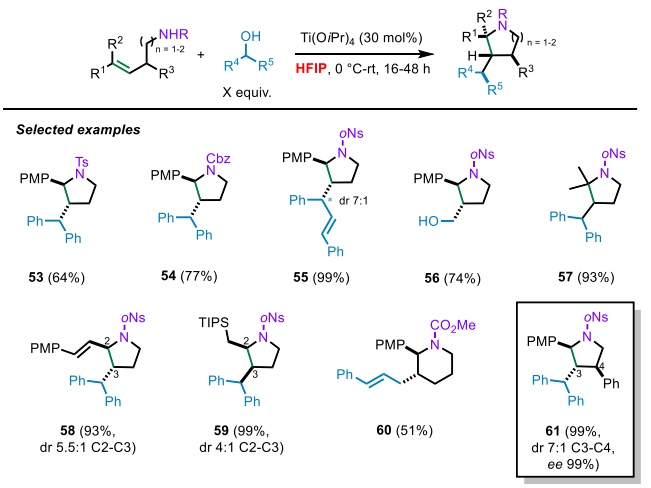


[a]PMP = *para*-methoxyphenyl.

hexafluoroisopropoxy moieties (**50**), which was then further involved in the reaction by substituting the newly introduced HFIP unit by the allylalkoxy group (**51**) before generating the reacting carbocation intermediate. From there, the cyclization with the homoallylic alcohol occurs via concerted *anti* addition across the double bond (**52**) to deliver the final product.

The same protocol was then applied to an analogous cyclization to form nitrogen heterocycles, notably pyrrolidines and piperidines (Scheme 6).[27] The reaction tolerates a variety

Scheme 6. Titanium(IV)-Catalyzed Synthesis of Pyrrolidines and Piperidines[a]

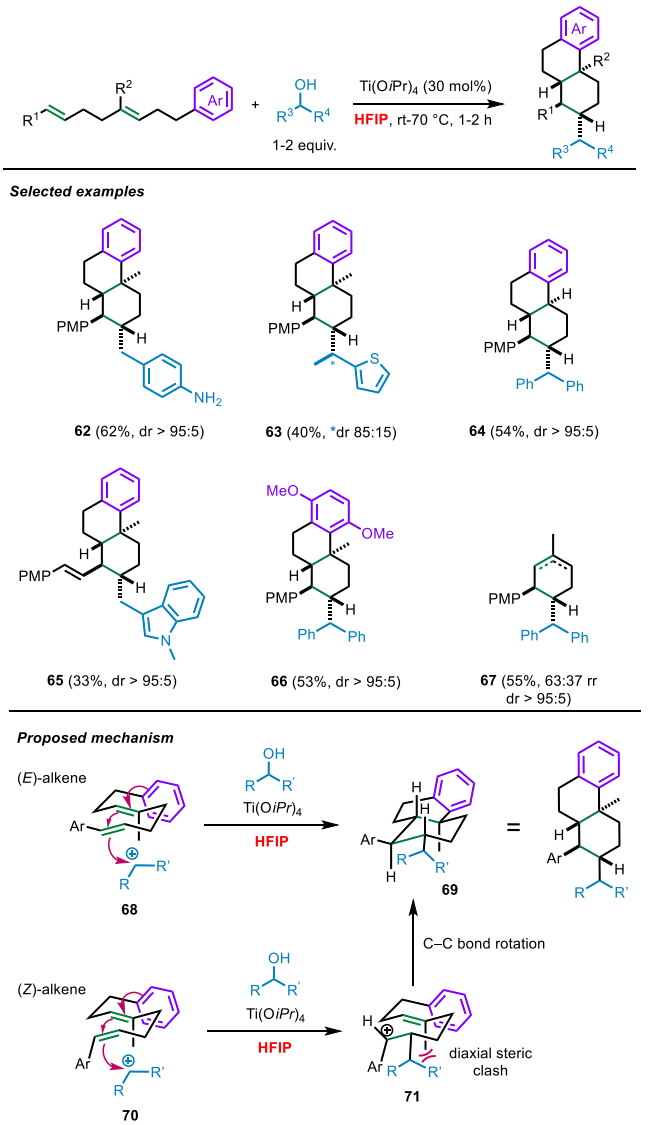


[a]PMP = *para*-methoxyphenyl.

of nitrogen functionalities such as sulfonamides and carbamates, but not alkylamines. Overall, the transformation displayed similar features as the ones regarding the synthesis of tetrahydrofurans, including the control of the diastereoselectivity and the transfer of chirality (**61**). Interestingly, in the presence of an allyl silane moiety, the selectivity is reversed in favor of the *cis* product (**59**), which might be explained by the fact that a *syn* addition minimizes the steric clash between functionalities.

More recently, the group of Donohoe described another highly stereoselective class of transformations driven by HFIP—polyene cyclization cascades—with primary and secondary allylic and benzylic alcohols (Scheme 7).[28] This

Scheme 7. Polyene Cyclization Driven by HFIP[a]



[a]PMP = *para*-methoxyphenyl.

way, even much more complex all-carbon scaffolds could be prepared in a single step under the above-mentioned conditions. The reaction worked effectively with a variety of electron-neutral and electron-rich arenes. Electron-deficient arenes gave lower yields and regioselectivities. In the absence of a terminal arene nucleophile, the reaction yielded cyclo-

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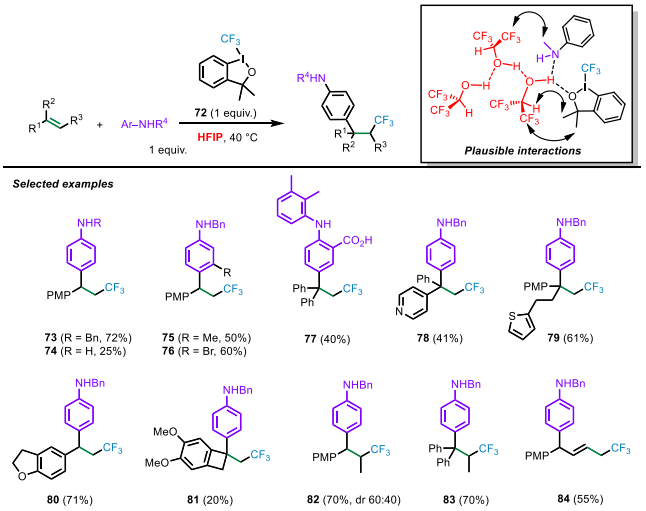
hexene products such as **67** with high diastereoselectivity. The proposed mechanism first involves the formation of the carbocation electrophile from secondary alcohols. The electrophile then undergoes addition to the nucleophile which is, at this stage, highly preorganized for an efficient cyclization (**68**). Both *E* and *Z* alkenes delivered the same product which led to the mechanistic hypothesis presented in Scheme 7. The reaction with a (*Z*)-alkene directly provides the preferred product, while the reaction with the (*E*)-alkene leads to the formation of the sterically congested carbocation **71**. A subsequent steric release arising from C−C bond rotation allows for the final ring-closure to **69**.

In 2023, electrophilic trifluoromethylative alkene difunctionalization reactions were disclosed by the group of Colomer. Following their previous work on the hydroarylation of styrenes,[29] they used anilines as nucleophilic partners (Scheme 8).[30] Interestingly, the use of anilines in difunctionalization

Scheme 8. Trifluoromethylarylation of Styrenes with Anilines in HFIP[a]

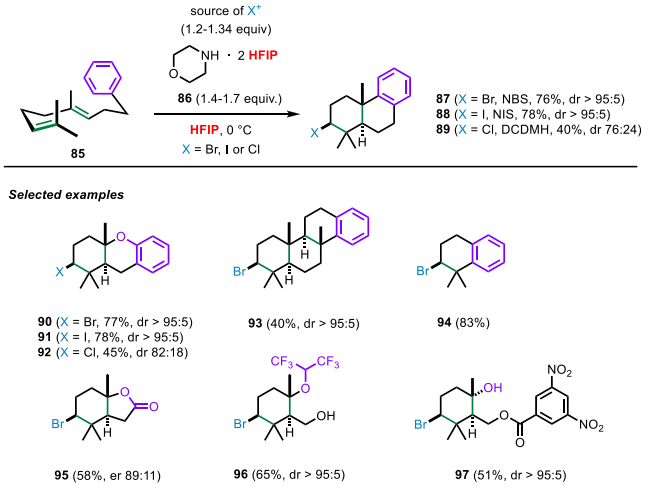


[a]PMP = *para*-methoxyphenyl.

processes remains scarce because of the traditional challenges associated with them, such as their unselective reactivity and tendency toward oxidation, which have limited their range of applications. Importantly, the method reported did not require any additive, transition metal, photocatalyst, or an excess of reagents. HFIP's unique properties, particularly its ability to establish a hydrogen bonding network with aniline and trifluoromethyl hypervalent iodine reagent, are instrumental in altering reactivity and achieving an exquisite selectivity. Various electron-donating and electron-withdrawing substituents on anilines were well-accommodated in reactions with electron-rich styrenes and 1,3-dienes. The only drawback is the decline in efficiency observed with primary anilines (**74**). Mechanistic experiments showed the preferential reaction occurring with anilines rather than a test competing nucleophile, anisole. A radical mechanism was excluded since, in the presence of TEMPO or BHT, no radical adducts were detected, which was further supported by radical clock experiments. By comparing the position of the peak corresponding to irreversible reduction in the cyclic voltammograms of the hypervalent iodine reagent in HFIP and acetonitrile (−1.75 and −0.58 V, respectively), the authors concluded that in HFIP, a more electrophilic species might be present. An extensive set of NMR experiments (DOSY, NOESY, and HOESY) revealed the formation of an extensive hydrogen bonded network that incorporates the aniline and allows the activation of the hypervalent iodine reagent to transfer the CF_3 group to the alkene. Importantly, additional kinetic studies showed that the *para*-C alkylation product and the hydroamination product are both initially formed during the reaction. However, the authors demonstrated that the latter undergoes a Hoffman-Martius rearrangement to generate the *para*-C alkylation compound, rendering it a parallel productive pathway.

Another example of efficient terpene cyclization, more specifically halocyclization, promoted by HFIP was reported by the group of Gulder (Scheme 9).[31] In the case of bromination,

Scheme 9. Halocyclization of Polyenes Promoted by HFIP



two common sources of electrophilic bromine were used: *N*-bromosuccinimide (NBS) and BDSB ($Et_2SBr{\cdot}SbCl_5Br$), which was described by the group of Snyder in 2009.[32] In case of iodination and chlorination, *N*-iodosuccinimide (NIS) and 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) were used, respectively. The optimization revealed that except HFIP, only one other solvent, nitromethane, in combination with BDSB enabled the reaction. The optimal conditions found in the study featured a Lewis-basic morpholine salt of HFIP (**86**), producing the halo-compounds in a few minutes. NMR experiments aiming at probing the mechanism of the reaction revealed that a discrete *N*-bromomorpholine intermediate complexed by HFIP was formed, which would be responsible for the halogen transfer to form a putative halirenium intermediate that could undergo further cyclization with arenes, phenols and carboxylic acids. The reaction does not occur when *O*-methyl HFIP is used, showcasing the importance of the H-bond network for this unique reactivity. Attempts to extend the applicability of the method to chlorocyclizations proved to be more challenging than with the analogous brominative or iodinative ring-closing reactions, as the corresponding products were obtained in moderate yields along with poorer diastereocontrol. The authors emphasized that the stereocontrol mostly depends on steric parameters, which was evidenced by varying the position of one or two nitro groups on an ester substituent. By employing 2-NO_2 or 4-NO_2 substituted benzoyl precursors, the dr dropped to 72:29 and 78:22, respectively, while 3-NO_2 and

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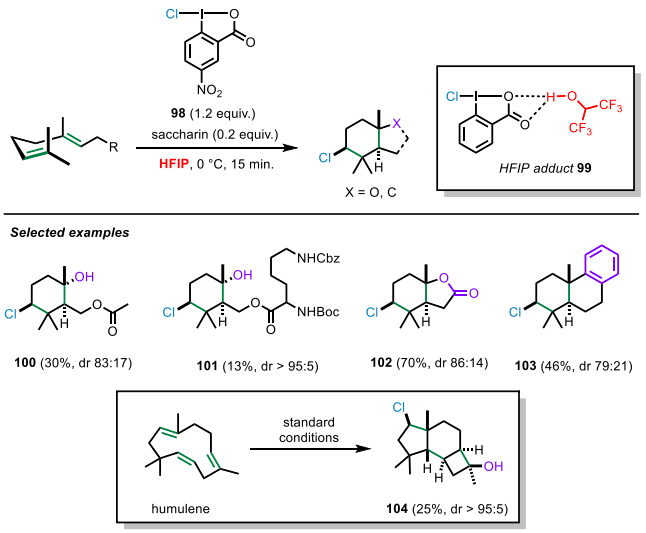
3,5-NO_2 derivatives gave the desired product in high diastereoselectivity (**97**, dr > 95:5). The method allowed access to various polycyclic structures such as lactones or steroid analogues as well as heteroatom-containing frameworks. When subjecting geraniol to the optimized conditions, the intermediate carbocation was trapped by the weakly nucleophilic HFIP molecule (**96**).

In a follow-up study, the same group adopted a different approach to achieve the direct chlorocyclization of polyenes (Scheme 10).[33] Besides HFIP, no other solvent or solvent

Scheme 10. Chlorocyclization of Polyenes in HFIP

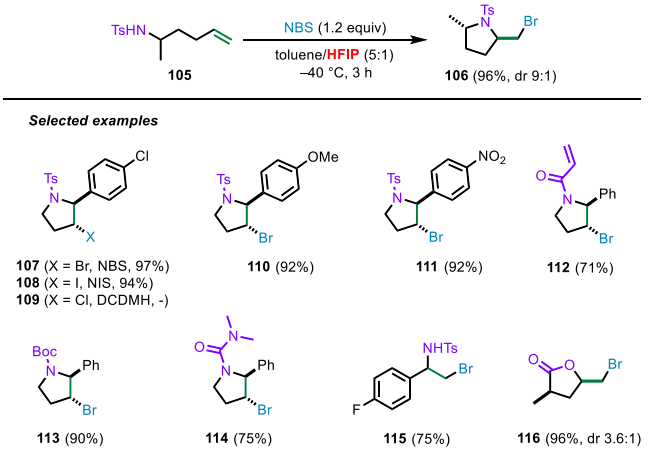


mixture was found to assist the reaction. The main challenge in the development of this transformation was the competing formation of an acyclic chlorine addition product. The authors showed that its formation could be reduced by using an electron-deficient hypervalent iodine serving as an electrophilic chlorinating agent. Previous studies by the group of Donohoe demonstrated how the reactivity of hypervalent iodine reagents could be enhanced in the presence of HFIP.[34] In the present example, the yields were further increased by employing saccharin as a Brønsted acid catalyst. The method tolerates several functional groups, including *N*-Boc or conjugated π-systems. The presence of a terminal aromatic moiety resulted in the formation of bi- or tricyclic products, due to intramolecular trapping by either O- or C-nucleophiles. More challenging transformations leading to complex terpene frameworks were also performed, demonstrating the utility of this method in the creation of molecular complexity. For instance, the transannular ring-closing of humulene gave 5-6-4 tricyclic skeleton **104** in 25% yield with an excellent diastereoselectivity (dr > 95:5).

Mechanistic studies suggest that the chlorinating agent is activated by forming an adduct with HFIP (**99**). Saccharin does not directly interact with the substrate or chlorinating agent, but rather plays a role in the further enhancement of the beneficial properties of H-bond network. Overall, the study suggests that the impact of HFIP comes from a positive synergistic effect of several factors, which enable the stabilization of cationic intermediates and promote specific conformations enabling stereoselective reaction outcomes.

Later, the approach used by the group of Gulder was extended by our group to the haloamidation and halolactonization of alkenes to access pyrrolidine, piperidine and lactone scaffolds (Scheme 11).[35] In this case, while using HFIP as a

Scheme 11. Haloamidation and Halolactonization of Alkenes Promoted by HFIP



solvent proved particularly effective, only moderate diastereocontrol was observed. Further investigation showed that using toluene or DCM as a solvent with HFIP as an additive is optimal, providing high yields and excellent control of the diastereoselectivity. The reaction was carried out using diversely *N*-protected aminoalkenes or with unsaturated carboxylic acids. The method was applicable to a wide range of electron-rich and electron-deficient alkenes. Various nitrogen functionalities were tolerated such as sulfonamides, amides, carbamates and even ureas, which was a previous limitation for such a process. *N*-bromosuccinimide and *N*-iodosuccinimide were used as sources of electrophilic halides. In turn, chlorination remained a limitation under the optimized reaction conditions, reminiscent of the issues encountered in the previous studies by the group of Gulder.

Next, DFT calculations were performed on model substrate **105** to gain insights into the mechanism (Scheme 12). After considering various scenarios involving possible neutral, ionic, and radical pathways, the initial conclusion was that the first step would involve the formation of a commonly invoked bromonium intermediate, which could easily undergo cyclization upon attack of the nitrogen atom with bromonium ring opening. The energy bias of 2.1 kcal/mol between the two diastereoisomers was consistent with experimental results. The main problem encountered in the computational study was that no pathway was found to be plausible due to high energies of the intermediates. However, another plausible pathway inspired by the work of Borhan[36] was studied in which the nitrogen atom donates electron density to the alkene while concurrently the alkene interacts with the bromine atom. By exploring this pathway, a transition state corresponding to a concerted C–N and C–Br bond formation was located. Interestingly, by adding a varying number of HFIP molecules, the barrier was modified with an optimal value obtained for 3 solvent molecules (14.2 kcal/mol). This further illustrates and reinforces the argument that in the case of complex solvation systems such as HFIP, in which the solvent directly participates in the transformation, implicit solvation models are not always sufficient.

In a variant of olefin halofunctionalization, the group of Gilmour recently illustrated the utility of HFIP as an additive

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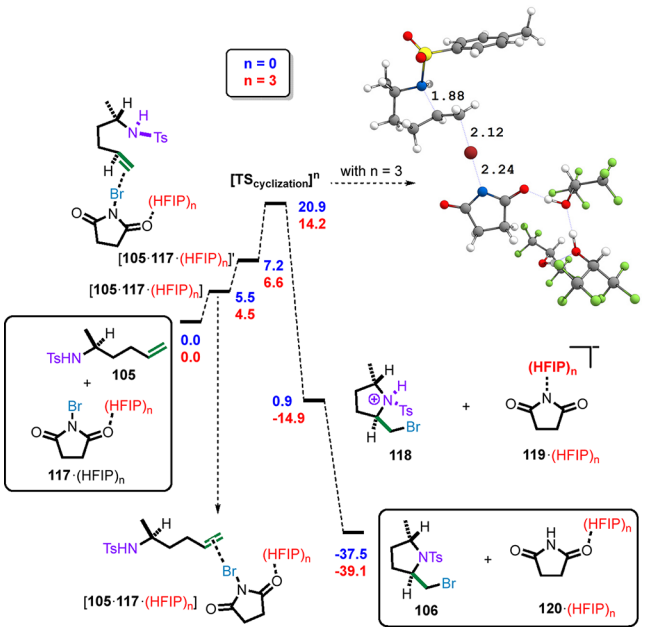
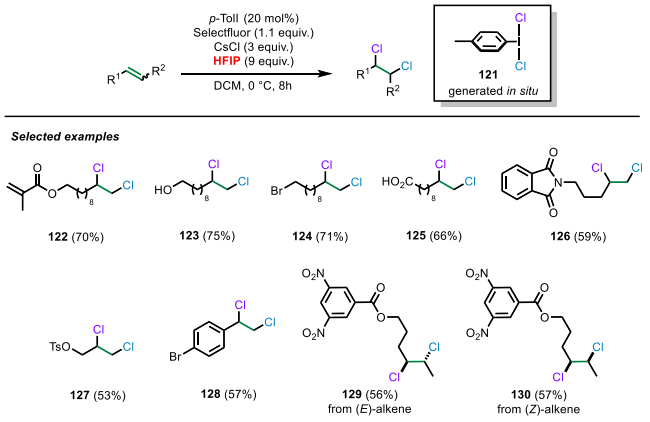
Scheme 12. Computed Mechanism for the Haloamidation of *N*-Tosylaminoalkene 105 Assisted by HFIP



to enable vicinal dichlorination of unactivated alkenes (Scheme 13).[37] The transformation relied on the use of chlorine donor

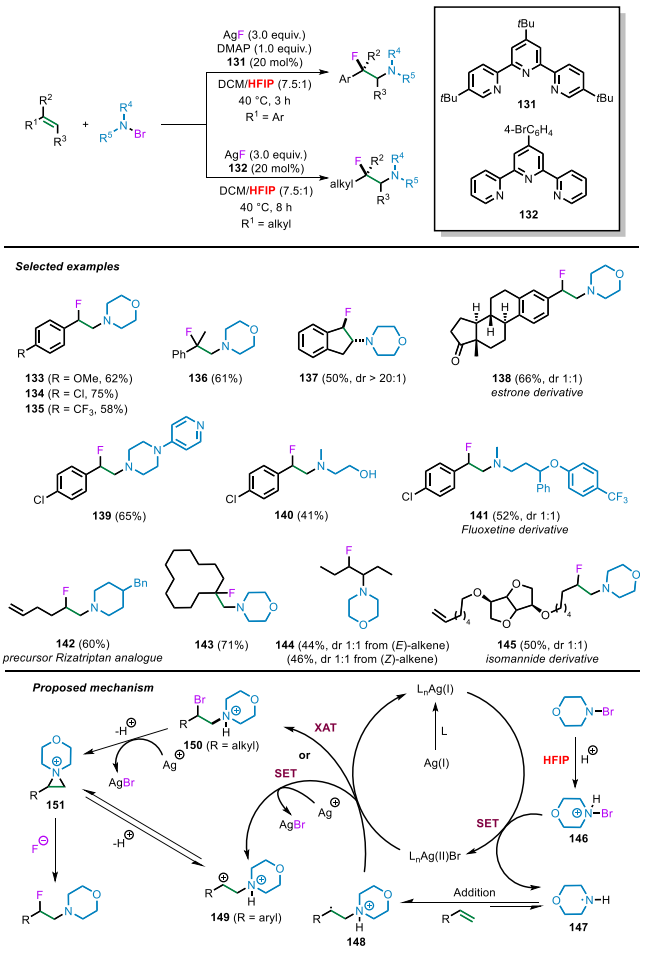
Scheme 13. Vicinal Dichlorination of Alkenes Using HFIP as an Additive



para-TolICl$_2$ **121** generated *in situ* from *para*-iodotoluene, Selectfluor, and cesium chloride. It is important to stress that, in the absence of HFIP, no product was detected. The reagent engages in a I(I)/I(III) catalytic cycle and enables the formation of vicinal dichlorides in a stereospecific fashion with a good functional group tolerance. The reaction was compatible with both terminal and internal aliphatic alkenes as well as styrenes (**128**) to afford the vicinal dichlorides in yields ranging from 45 to 77%. (*E*)-Alkenes yielded *anti*-configured products (**129**), while (*Z*)-alkenes yielded *syn*-configured ones (**130**). Control experiments using methylated HFIP as well as isopropanol showed that HFIP is essential to the proper functioning of the reaction. This is likely due to the hydrogen-bond network reinforced by its acidic properties that allows the activation of the active species, without which the transformation was not effective and only trace amounts of products were obtained.

Recently, Fu and co-workers disclosed an intermolecular three-component aminofluorination of alkenes using HFIP as a cosolvent, in which halides are the nucleophilic partners (Scheme 14).[38] The method is based on generating nitrogen-

Scheme 14. Aminofluorination of Alkenes Using HFIP as a Cosolvent



centered radicals from electron-rich *N*-bromodialkylamines in an umpolung reaction, silver fluoride (AgF) acting as both nucleophilic fluorinating agent and reductant. The authors assumed that the role of HFIP was to be an efficient proton donor to obtain protonated amines, while maintaining the nucleophilicity of the fluoride anion. The use of a tridentate ligand was also required to facilitate the single electron transfer (SET) step in the radical formation between AgF and *N*-bromodialkylamine. In the absence of ligand, the reaction proceeded with lower efficiency. Attempts at an asymmetric version did not result in any enantiomeric excess. Following in-depth optimization studies, the authors displayed a remarkable scope regarding this transformation. The reaction proved compatible with styrenes, both terminal and internal, incorporating electron-donating and -withdrawing substituents, producing a large range of aminofluorinated derivatives in high yields. The reaction demonstrated a good functional group compatibility, including ester, halide, azide, and free hydroxyl groups, among others. Additionally, cyclic and acyclic *N*-bromodialkylamines, including those derived from drug molecules such as fluoxetine (**141**), participated in the reaction to yield the target products. The study also extended to

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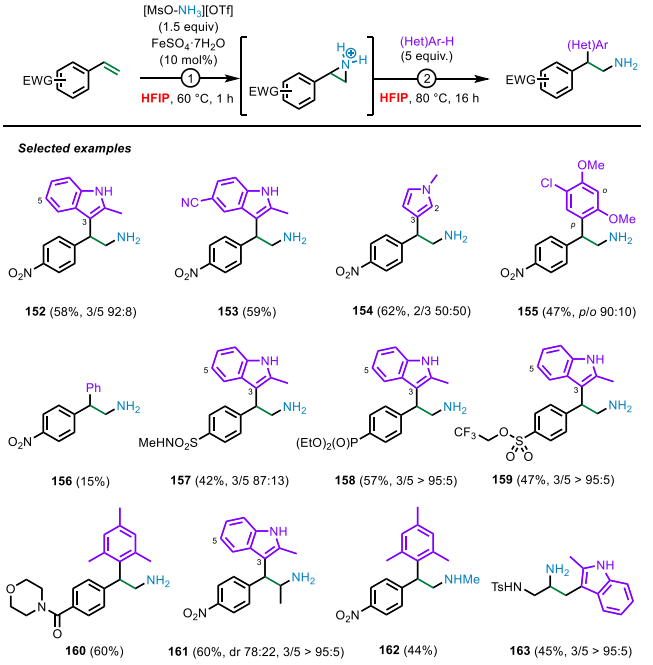
terminal and internal aliphatic alkenes, for which both HFIP and a tridentate ligand were found to be essential for the aminofluorination. Various functional groups and diverse alkene scaffolds were tolerated, showcasing the versatility of the reaction. The methodology was further applied to late stage aminofluorination of alkenyl derivatives of pharmaceuticals and natural products such as estrone (**138**), ibuprofen, or isomannide (**145**). The method was also applied for the synthesis of valuable β-fluoroamine-containing rizatriptan analogue (**142**).

The authors performed a series of experiments to gain insights into the intricate reaction mechanism. An electrophilic addition was identified as the product-determining step. The addition of radical scavengers (TEMPO and BHT) completely shut down the reaction, resulting in the isolation of a radical adduct. A radical clock experiment confirmed the involvement of an alkylaminyl radical intermediate in the reaction. The electronic effects of substituents on the reaction rate of styrene derivatives were further explored to obtain Hammett parameters. The results suggest that a positive charge is generated at the benzylic position. The monitoring of the aminofluorination of cyclohexene revealed the disappearance of *N*-bromomorpholine within 1 h, and an aziridinium ion intermediate was detected by ESI-MS. This intermediate could also be prepared *in situ* from a β-bromoamine and AgF, showing a similar reaction profile to that of cyclohexene over an 8-h period. Cyclic voltammetry experiments were conducted to understand the unique role of the silver salt and ligand in the reaction. The obtained results showed the feasibility of a single electron transfer (SET) process between AgF and *N*-bromomorpholine in the presence of HFIP. The addition of ligand **131** significantly decreased the oxidation potential, indicating an easiest SET process with *N*-bromomorpholine and emphasizing the crucial role of the ligand in enhancing the efficiency of the aminofluorination reaction (75% with **131** versus 12% without **131**). Based on all these experiments, the following mechanism was proposed: Following the complexation of silver with the tridentate ligand and the protonation of *N*-bromomorpholine by HFIP, a SET process between the resulting aminium **146** and Ag(I) complex occurs to generate a Ag(II)Br complex and protonated alkylaminyl radical **147**. Addition of alkene to **147** produces carbon radical **148**, which can then undergo either oxidation to form dication **149** via SET or halogen atom transfer (XAT) to generate β-bromoamine **150**. Intermediate **149** can also attain an equilibrium with aziridinium **151** thanks to a stabilization by the adjacent nitrogen atom. Nucleophilic ring-opening of aziridinium **151** by fluoride would result in the formation of the aminofluorinated product. While a radical chain reaction pathway involving XAT cannot be ruled out, it is unlikely for unactivated alkenes due to the slow oxidation of aliphatic carbon radicals.

Difunctionalization of alkenes assisted by HFIP can also introduce primary aliphatic amines, as exemplified by our recent report on the synthesis of unprotected β-(hetero)-arylethylamines by iron(II)-catalyzed 1,2-aminoarylation of alkenes.[39] Directly inspired by previous studies of the Morandi group,[40−42] we developed a simple and direct one-pot transformation that yielded the corresponding unprotected amines in moderate to high yields (Scheme 15) using hydroxylammonium salts as a formal free amine source. In the presence of an iron(II) catalyst, those salts can generate a nitrogen-centered radical that reacts with an alkene to form an

Scheme 15. Iron(II)-Catalyzed 1,2-Aminoarylation of Highly Electronically Deactivated Styrenes in HFIP



aziridinium intermediate.[43] Following a ring-opening arylation, unprotected β-(hetero)arylethylamines that are common motifs in bioactive molecules were formed. Here, we assumed that HFIP increased the electrophilicity of the key nitrogen-centered radical as well as the electrophilicity of the aziridinium intermediate so that even highly deactivated substrates could be used. Conventional organic solvents did not afford any target product. Additional experiments revealed that by lowering the reaction temperature to 40 °C and in the absence of any nucleophile, the azidirine could be isolated in 36% yield, thus supporting a mechanism proceeding via an aziridinium intermediate. The reaction scope showed that a wide variety of electron-rich (hetero)arenes could be employed. Weak arene nucleophiles such as benzene could also be used, albeit in a lower yield. Remarkably, a broad range of electron-withdrawing groups were tolerated, including sulfonamide, phosphonate, sulfonyl ester and amide, leading to compounds possessing drug-relevant functional groups. Allylic alkenes were also successfully described; however, the regioselectivity was reversed due to a swapped order of electrophilicity at the azidirine carbon atoms. Secondary amines were also shown to be compatible with this method. Very recently, Chu and Ellman reported a related metal-free aminoarylation to produce unprotected amines, also in HFIP.[44] They reported a wide scope, most notably including disubstituted aliphatic alkenes as substrates, and indoles as nucleophiles. This type of strategy was also employed by Berhal and Prestat in oxyamination of terminal alkenes.[45]

ALKYNES

Difunctionalization processes promoted by HFIP were not limited to alkenes but could also be carried out with alkynes. For instance, following our previous work on the *ortho*-C alkylation of anilines with alkenes,[46] we sought to apply this strategy to aryl alkynes to yield the corresponding 9,10-dihydroacridines from diarylamines (Scheme 16),[47] whose access usually requires lengthy syntheses. The idea was to use

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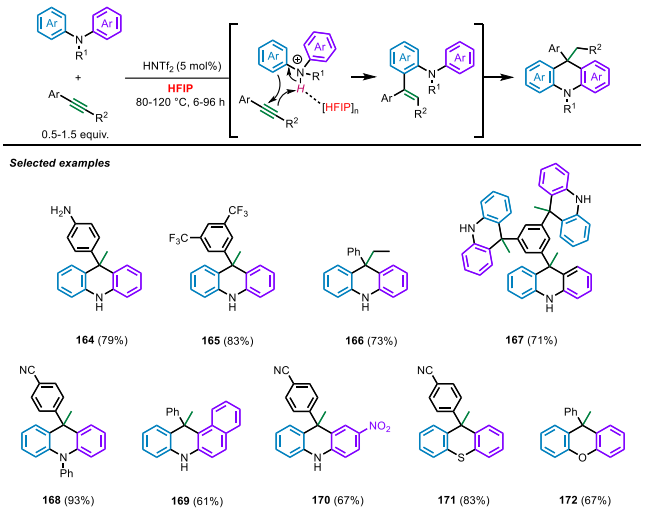
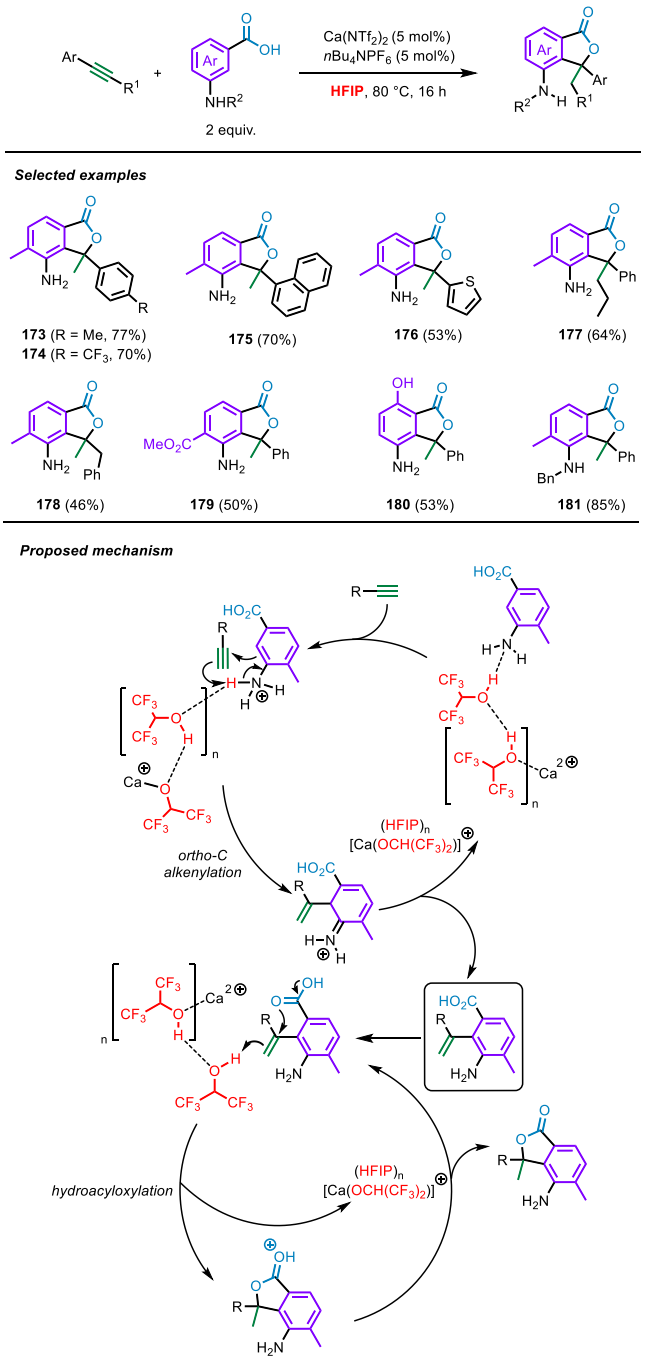
Scheme 16. Synthesis of 9,10-Dihydroacridines via an *ortho*-C Alkenylation/Hydroarylation Sequence between Anilines and Aryl Alkynes in HFIP



Scheme 17. Synthesis of Phthalides through an *ortho*-C Alkenylation/Hydroacyloxylation Sequence between 3-Aminobenzoic Acids and Aryl Alkynes in HFIP



the H-bond network of HFIP to harness the electrophilicity of the anilinium intermediate to favor the *ortho*-C alkenylation process. Then, a subsequent intramolecular hydroarylation would deliver the target product. Our investigations revealed that HFIP is crucial for the reaction to take place, as again no other solvent allowed the transformation. The scope of the method exhibited a broad variety of terminal and internal aryl alkynes incorporating electron-donating and -withdrawing groups. On the other hand, no reaction was observed with aliphatic alkynes. The scope of arylamines similarly revealed wide applicability with the possibility of installing unsymmetrical diarylamines (**170**). The reaction was also extended to triarylamines (**168**) and naphthyl-containing substrates (**169**). Another important feature of this approach is the possibility to use diphenyl sulfide or ether to deliver the corresponding thioxanthene (**171**) and xanthene (**172**), respectively. Interestingly, in collaboration with the group of Dell'Amico, we demonstrated the utility of compound **169** as a powerful photocatalyst for defunctionalization and polymerization.[48]

Taking the same approach, the group of Wang designed a new strategy to obtain phthalide 3-aminobenzoic acids in a regioselective fashion (Scheme 17).[49] Not surprisingly, using HFIP as a solvent was indispensable and a Lewis acidic calcium catalyst proved optimal for this reaction. This approach combined the *ortho*-C alkenylation of anilines with an hydroacyloxylation of alkenes previously reported by our group.[50] In addition to favoring the *ortho*-C alkenylation, HFIP likely prevents any trapping of the catalyst by the carboxylic acid functionality thanks to its strong H-bond donating ability. The scope of aryl alkynes showed that the method is generally applicable to a large variety of neutral and moderately deactivated systems. The main limitations of this method is that aliphatic alkynes such as 1-hexyne, sterically hindered 1,2-diaryl alkynes and more basic *N*,*N*-dialkylanilines did not react under the optimized conditions. The study of the 3-aminobenzoic acid pattern indicated that the presence of electron-withdrawing or -donating groups on the aryl ring did not influence the reactivity. Mechanistic experiments showed that the first step of the reaction is the *ortho*-C alkenylation, forming a vinylbenzoic acid (intermediate isolated by conducting the reaction at room temperature instead of 80 °C), which then undergoes an intramolecular hydroacyloxylation to provide the final phthalide.

In 2021, building on previous reports,[51−53] the group of Lautens designed an elegant metal-free alkyne chloroacylation to prepare methylene oxindoles from alkyne-tethered carbamoyl chlorides (Scheme 18).[54] During their initial investigations, they demonstrated that the cycloisomerization of an aromatic carbamoyl chloride bearing an *ortho*-alkyne moiety could be achieved in fluorinated alcohol solvents such as TFE and HFIP, the latter providing higher yields, to afford the corresponding methylene oxindole. In further optimization, they found that HFIP had only to be used as an additive with

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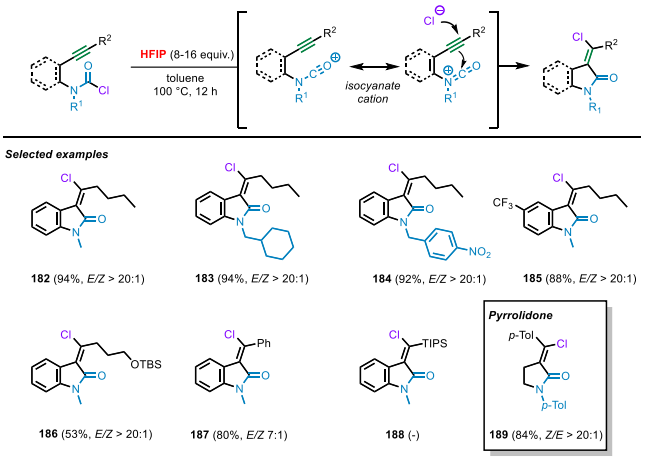
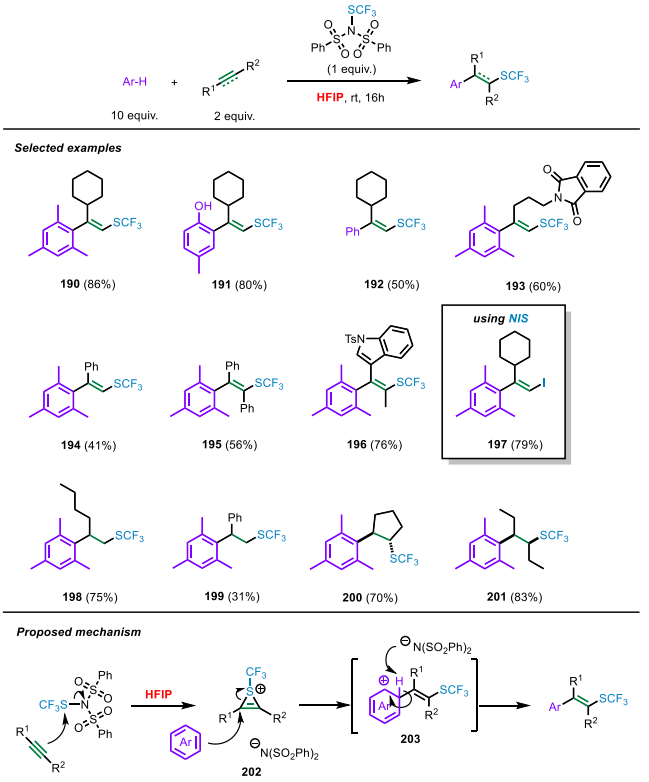
Scheme 18. HFIP-Assisted Chloroacylation of Alkynes to Access Methylene Oxindoles



toluene as a main solvent. Using these optimized conditions, the target products were obtained in high yields (up to 96%) along with an excellent *E*/*Z* selectivity (>20:1). Interestingly, this unprecedented *E*-selectivity notably complements previous Pd^{II}-catalyzed alkyne chloroacylation methods.[51−53] Various aromatic and aliphatic N-substituents were tolerated regardless of their electronic and steric properties. Besides, the approach was also applied to the synthesis of pyrrolidones (**189**). One of the main drawbacks of this method is, however, the use of substrates possessing acid-sensitive moieties such as OTBS or OBoc, which led to either lower yields or decomposition. Deactivating the alkyne moiety with a silyl group also shut down the reactivity (**188**). Additionally, the reaction did not proceed when a bromo substituent is present at the *ortho* position of the carbamoyl group since it most likely impacts its conformation relative to the plane of the ring. Computational and experimental investigations point toward a pathway proceeding via an isocyanate cationic intermediate, which then cyclized upon chloride addition to the alkyne. Of note, this activation of the carbamoyl chloride is reminiscent of the work of the group of Aubé on Friedel−Crafts arylation of acyl chlorides in HFIP.[55]

Recently, the group of Ellman described a three-component Friedel−Crafts reaction in HFIP without the assistance of a Lewis or Brønsted acid, which unlocked the synthesis of alkyl and alkenyl trifluoromethyl sulfides (Scheme 19).[56] It should be noted that prior methods to achieve such transformations had to be performed under cobalt or photoredox catalysis.[57,58] The reaction optimization revealed that $(PhSO_2)_2NSCF_3$ is the most efficient electrophilic source of SCF_3 and that HFIP is the only solvent providing high efficacy, even though it was not rationalized. Other fluorinated alcohols such as TFE or perfluoro-*tert*-butanol also allowed this reaction to take place, albeit in significantly lower yields. Exploring the scope of alkenyl trifluoromethyl sulfides, the authors emphasized that typical arenes used in Friedel−Crafts arylation were compatible with the method using either terminal or internal alkynes. However, their electronic properties proved crucial for the overall efficiency of the reaction since weak arene nucleophiles such as bromobenzene did not react under the optimized conditions, whereas electron-rich 1,3,5-trimethoxybenzene underwent electrophilic aromatic substitution with the trifluoromethylthiolating reagent. The reaction mechanism is thought to proceed via the formation of a thiiranium

Scheme 19. Friedel−Crafts Trifluoromethylthiolation of Alkynes and Alkenes Promoted by HFIP



intermediate followed by a ring-opening arylation (**202**). Mechanistic experiments revealed that the alkyne must react faster with $(PhSO_2)_2NSCF_3$ than the arene to avoid the unproductive S_EAr pathway. This, in turn, explains why electron-rich arenes are not compatible with this method. The transformation was then extended to the synthesis of alkyl trifluoromethyl sulfides from a variety of internal and terminal alkenes or alkenyl iodides using NIS as an electrophilic source (**197**).

EPOXIDES AND CARBONYLS

The difunctionalization of epoxides is much less common than that of alkenes and alkynes. Yet, epoxides constitute fundamental building blocks in organic synthesis. In this context, our idea was that, following intermolecular opening of the epoxide by a nucleophilic arene, the newly installed arene unit could allow intramolecular displacement of the resulting alcohol to generate an intermediate phenonium ion.[59] From there, an intermolecular nucleophilic addition by a second arene partner would provide direct access to the polyarylethanes. Here, we hypothesized that the acidity of the acid catalyst/HFIP system would enable the activation of the alcohol without requiring any preactivation. After the completion of the first step, we found that simply increasing the temperature was sufficient to trigger the second arylation, affording the corresponding diarylation product (Scheme 20). While the first step could be conducted in various solvents, the second step only worked in HFIP. Various electron-rich nucleophilic arenes containing alkyl, methoxy, halide, and hydroxy substituents were examined in reaction with styrene oxides and aliphatic oxiranes, affording the diarylated products in 40−92% yields. Remarkably, two different arenes were installed in this diarylation reaction sequentially by playing on

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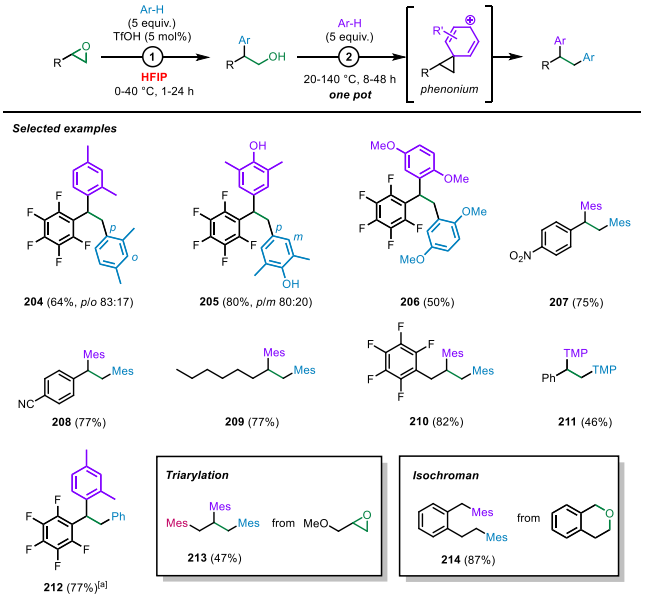
Scheme 20. One-Pot Dehydrodiarylation of Epoxides in HFIP[a]

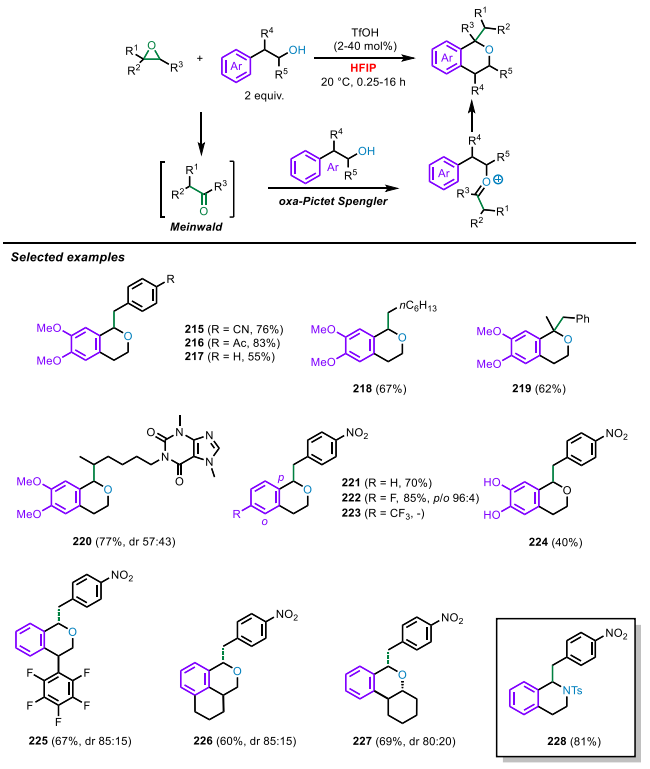


[a]92:8 ratio of regioisomers. Mes = 1,3,5-trimethylbenzene. TMP = 1,3,5-trimethoxyphenyl.

their nucleophilicity. For example, by using benzene as the first nucleophile followed by *meta*-xylene as a second arene, 1,1,2-triarylethane **212** was obtained with three different arene units in moderate to high yields. Finally, it was also possible to carry out triarylation of glycidol ethers (**213**) and diarylation of isochromans (**214**) following the same approach. The mechanism proposed was supported by experiments with enantiopure oxiranes and DFT calculations, which indicate that for aromatic substrates the barrier for phenonium formation is significantly lower in HFIP than in other solvents.

In another study on epoxide reduction with triethylsilane in HFIP, we discovered that the reaction initially went through a Meinwald rearrangement to give the corresponding aldehyde, which is subsequently reduced.[60] This observation inspired us to use epoxides as surrogates of reactive aldehydes that are not always bench-stable and often more expensive than the parent epoxides. This practical transformation allowed us to develop a new strategy to access densely functionalized isochromans from 2-arylethanols via an oxa-Pictet–Spengler reaction (Scheme 21), displaying a wide scope in contrast to existing methods.[61] Regarding this reaction, the use of virtually any other solvent, including TFE, only led to a direct ring-opening of the epoxide by the nucleophile. The study of the epoxide scope showed that even highly electronically deactivated systems incorporating cyano, nitro, amide, ester, or ketone groups were well-tolerated to afford products in high yields. The alcohol scope revealed that both electron-rich as well as moderately electron-deficient substrates could be used as nucleophiles. In turn, the presence of stronger electron-withdrawing groups such as CF_3 prevented the oxa-Pictet–Spengler reaction. Gratifyingly, polysubstituted 2-arylethanols also worked smoothly to provide complex scaffolds in one-pot (**225**–**227**). Importantly, using N-protected amines instead of alcohols led to the corresponding tetrahydroisoquinolines (**228**). The main limitation here is that free amines cannot be used, which is probably due to catalyst quenching. Using this

Scheme 21. Synthesis of Isochromans and Tetrahydroisoquinolines via a Sequential Meinwald Rearrangement/oxa-Pictet–Spengler Reaction



newly developed protocol allowed access to various drug-like molecules such as **220**.

Another application regarding the use of carbonyls was a cooperative Friedel–Crafts alkylation of electron-deficient arenes to afford bisarylated compounds by the group of Hazra (Scheme 22).[62,63] Through an initial examination of Friedel–Crafts reactions with aromatic aldehydes, the authors noticed that classical conditions could not be used. However, by relying on HFIP as a cosolvent in combination with *para*-toluenesulfonic acid as a catalyst, they were able to obtain the target diarylated products. Control experiments in the absence of either the acid or HFIP highlighted how they were crucial for the reaction. The substrate scope spanned electronically neutral as well as deactivated and strongly deactivated arenes as nucleophiles, producing the bisarylated compounds in good overall yields. This method was then successfully applied to more challenging substrates incorporating electron-deficient arenes, basic heteroatoms, and dialdehydes. Finally, its utility was exemplified in the synthesis of natural products and bioactive molecules as well as in late-stage functionalization. The reaction mechanism was also studied by means of DFT computations. The first important feature is that the coordination of HFIP molecules to the acid greatly increases its acidity (a decrease of 2.8 units of pK_a). The computed mechanism starts with the formation of hydrogen bonds between the aldehyde oxygen atom and the proton of the acid (**238**). In the next step, the arene adds to the carbonyl via a hydrogen bonded cyclic intermediate in which the hydrogen of the nucleophilic arene interacts with the oxygen atom of the acid (**239**). In this first concerted addition, the benzyl alcohol intermediate is formed (**240**). In a subsequent step, a similar nucleophilic addition occurs with a second molecule of arene,

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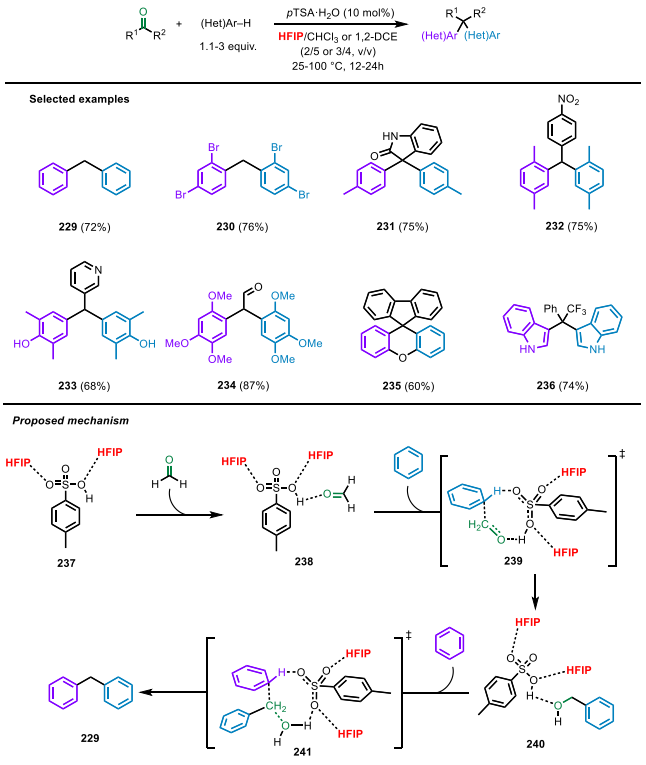
Scheme 22. Cooperative Friedel-Crafts Arylation of Carbonyls through Brønsted Acid Activation by HFIP



which proceeds through a similar transition state (**241**) to finally generate the bisarylated product **229**.

CONCLUSION

To conclude, we presented an overview of the recent examples of difunctionalization enabled by HFIP. We focused on the reactions of alkenes, alkynes, epoxides, and carbonyls as electrophiles. Some studies highlighted in this Review open new possibilities to access compounds of interest otherwise accessible only by methods using transition metal catalysis and/or harsh conditions while others expand the scope of well-known and widely used transformations to challenging substrates. The understanding of mechanisms of the reactions presented here is however still insufficient, and future mechanistic studies as well as state-of-the-art computational methods should improve the knowledge of how HFIP affects the properties of substrates as well as how it participates in various reactions.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article.

AUTHOR INFORMATION

Corresponding Authors

Joseph Moran − *Institut de Science et d'Ingénierie Supramoléculaires (ISIS), CNRS UMR 7006, Université de Strasbourg, 67000 Strasbourg, France; Department of Chemistry and Biomolecular Sciences, University of Ottawa, Ottawa, Ontario K1N 6N5, Canada; Institut Universitaire de France (IUF), 75005 Paris, France;* orcid.org/0000-0002-7851-6133; Email: moran@unistra.fr

David Lebœuf − *Institut de Science et d'Ingénierie Supramoléculaires (ISIS), CNRS UMR 7006, Université de Strasbourg, 67000 Strasbourg, France;* orcid.org/0000-0001-5720-7609; Email: dleboeuf@unistra.fr

Author

Maciej Piejko − *Institut de Science et d'Ingénierie Supramoléculaires (ISIS), CNRS UMR 7006, Université de Strasbourg, 67000 Strasbourg, France;* orcid.org/0000-0002-2742-5688

Complete contact information is available at: https://pubs.acs.org/10.1021/acsorginorgau.3c00067

Author Contributions

CRediT: **Maciej Piejko** investigation, writing-original draft; **Joseph Moran** funding acquisition, supervision, writing-review & editing; **David Leboeuf** conceptualization, supervision, writing-review & editing.

Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Colomer, I.; Chamberlain, A. E. R.; Haughey, M. B.; Donohoe, T. J. Hexafluoroisopropanol as a Highly Versatile Solvent. *Nat. Rev. Chem.* **2017**, *1*, No. 0088.

(2) Sinha, S. K.; Bhattacharya, T.; Maiti, D. Role of Hexafluoroisopropanol in C−H Activation. *React. Chem. Eng.* **2019**, *4*, 244−253.

(3) An, X.-D.; Xiao, J. Fluorinated Alcohols: Magic Reaction Medium and Promoters for Organic Synthesis. *Chem. Rec.* **2020**, *20*, 142−161.

(4) Yu, C.; Sanjosé-Orduna, J.; Patureau, F.; Pérez-Temprano, M. Emerging Unconventional Organic Solvents for C−H Bond and Related Functionalization Reactions. *Chem. Soc. Rev.* **2020**, *49*, 1643−1652.

(5) Pozhydaiev, V.; Power, M.; Gandon, V.; Moran, J.; Lebœuf, D. Exploiting Hexafluoroisopropanol (HFIP) in Lewis and Brønsted Acid-Catalyzed Reactions. *Chem. Commun.* **2020**, *56*, 11548−11564.

(6) Bhattacharya, T.; Ghosh, A.; Maiti, D. Hexafluoroisopropanol: The Magical Solvent for Pd-Catalyzed C−H Activation. *Chem. Sci.* **2021**, *12*, 3857−3870.

(7) Motiwala, H. F.; Armaly, A. M.; Cacioppo, J. G.; Coombs, T. C.; Koehn, K. R. K.; Norwood, V. M., IV; Aubé, J. HFIP in Organic Synthesis. *Chem. Rev.* **2022**, *122*, 12544−12747.

(8) Berkessel, A.; Adrio, J. A. Kinetic Studies of Olefin Epoxidation with Hydrogen Peroxide in 1,1,1,3,3,3-Hexafluoro-2-propanol Reveal a Crucial Catalytic Role for Solvent Clusters. *Adv. Synth. Catal.* **2004**, *346*, 275−280.

(9) Berkessel, A.; Adrio, J. A.; Hüttenhain, D.; Neudörfl, J. M. Unveiling the "Booster Effect" of Fluorinated Alcohol Solvents: Aggregation-Induced Conformational Changes and Cooperatively Enhanced H-Bonding. *J. Am. Chem. Soc.* **2006**, *128*, 8421−8426.

(10) Berkessel, A.; Adrio, J. A. Dramatic Acceleration of Olefin Epoxidation in Fluorinated Alcohols: Activation of Hydrogen Peroxide by Multiple H-Bond Networks. *J. Am. Chem. Soc.* **2006**, *128*, 13412−13420.

(11) Vuković, V. D.; Richmond, E.; Wolf, E.; Moran, J. Catalytic Friedel−Crafts Reactions of Highly Electronically Deactivated Benzylic Alcohols. *Angew. Chem., Int. Ed.* **2017**, *56*, 3085−3089.
(12) Qi, C.; Gandon, V.; Lebœuf, D. Calcium(II)-Catalyzed Intermolecular Hydroarylation of Deactivated Styrenes in Hexafluoroisopropanol. *Angew. Chem., Int. Ed.* **2018**, *57*, 14245−14249.
(13) Ammer, J.; Mayr, H. Solvent Nucleophilicities of Hexafluoroisopropanol/Water Mixtures. *J. Phys. Org. Chem.* **2013**, *26*, 59−63.
(14) Colomer, I.; Barcelos, R. C.; Christensen, K. E.; Donohoe, T. J. Orthogonally Protected 1,2-Diols from Electron-Rich Alkenes Using Metal-Free Olefin syn-Dihydroxylation. *Org. Lett.* **2016**, *18*, 5880−5883.
(15) Colomer, I.; Barcelos, R. C.; Donohoe, T. J. Catalytic Hypervalent Iodine Promoters Lead to Styrene Dimerization and the Formation of Tri- and Tetrasubstituted Cyclobutanes. *Angew. Chem., Int. Ed.* **2016**, *55*, 4748−4752.
(16) Alamillo-Ferrer, C.; Curle, J. M.; Davidson, S. C.; Lucas, S. C. C.; Atkinson, S. J.; Campbell, M.; Kennedy, A. R.; Tomkinson, N. C. O. Alkene Oxyamination Using Malonoyl Peroxides: Preparation of Pyrrolidines and Isoxazolidines. *J. Org. Chem.* **2018**, *83*, 6728−6740.
(17) Griffith, J. C.; Jones, K. M.; Picon, S.; Rawling, M. J.; Kariuki, B. M.; Campbell, M.; Tomkinson, N. C. O. Alkene Syn Dihydroxylation with Malonoyl Peroxides. *J. Am. Chem. Soc.* **2010**, *132*, 14409−14411.
(18) Picon, S.; Rawling, M.; Campbell, M.; Tomkinson, N. C. O. Alkene Dihydroxylation with Malonoyl Peroxides: Catalysis Using Fluorinated Alcohols. *Org. Lett.* **2012**, *14*, 6250−6253.
(19) Tao, Z.; Robb, K. A.; Zhao, K.; Denmark, S. E. Enantioselective, Lewis Base-Catalyzed Sulfenocyclization of Polyenes. *J. Am. Chem. Soc.* **2018**, *140*, 3569−3573.
(20) Edstrom, E. D.; Livinghouse, T. Formation of Episulfonium Ions from Alkenes. Application to the Synthesis of Higher Order Carbocycles via Episulfonium Ion Initiated Polyene Cyclizations. *J. Org. Chem.* **1987**, *52*, 949−951.
(21) Moore, J. T.; Soldi, C.; Fettinger, J. C.; Shaw, J. T. Catalytic Alkene Cyclization Reactions for the Stereoselective Synthesis of Complex "Terpenoid-like" Heterocycles. *Chem. Sci.* **2013**, *4*, 292−296.
(22) Schevenels, F. T.; Shen, M.; Snyder, S. A. Alkyldisulfanium Salts: Isolable, Electrophilic Sulfur Reagents Competent for Polyene Cyclizations. *Org. Lett.* **2017**, *19*, 2−5.
(23) *Foldamers: Structure, Properties, and Applications*; Hecht, S., Huc, I., Eds.; Wiley-VCH: Weinheim, 2007.
(24) Roth, A.; Denmark, S. E. Enantioselective, Lewis Base-Catalyzed, Intermolecular Sulfenoamination of Alkenes. *J. Am. Chem. Soc.* **2019**, *141*, 13767−13771.
(25) Matviitsuk, A.; Panger, J. L.; Denmark, S. E. Enantioselective Inter- and Intramolecular Sulfenofunctionalization of Unactivated Cyclic and (*Z*)-Alkenes. *ACS Catal.* **2022**, *12*, 7377−7385.
(26) Zhu, Y.; Colomer, I.; Thompson, A. L.; Donohoe, T. J. HFIP Solvent Enables Alcohols to Act as Alkylating Agents in Stereoselective Heterocyclization. *J. Am. Chem. Soc.* **2019**, *141*, 6489−6493.
(27) Cox, L.; Zhu, Y.; Smith, P. J.; Christensen, K. E.; Sidera Portela, M.; Donohoe, T. J. Alcohols as Alkylating Agents in the Cation-Induced Formation of Nitrogen Heterocycles. *Angew. Chem., Int. Ed.* **2022**, *61*, No. e202206800.
(28) Aynetdinova, D.; Jacques, R.; Christensen, K. E.; Donohoe, T. J. Alcohols as Efficient Intermolecular Initiators for a Highly Stereoselective Polyene Cyclisation Cascade. *Chem.—Eur. J.* **2023**, *29*, No. e202203732.
(29) Colomer, I. Hydroarylation of Alkenes Using Anilines in Hexafluoroisopropanol. *ACS Catal.* **2020**, *10*, 6023−6029.
(30) Corral Suarez, C.; Colomer, I. Trifluoromethylarylation of Alkenes Using Anilines. *Chem. Sci.* **2023**, *14*, 12083−12090.
(31) Arnold, A. M.; Pöthig, A.; Drees, M.; Gulder, T. NXS, Morpholine, and HFIP: The Ideal Combination for Biomimetic Haliranium-Induced Polyene Cyclizations. *J. Am. Chem. Soc.* **2018**, *140*, 4344−4353.
(32) Snyder, S. A.; Treitler, D. S. $Et_2SBr{\cdot}SbCl_5Br$: An Effective Reagent for Direct Bromonium-Induced Polyene Cyclizations. *Angew. Chem., Int. Ed.* **2009**, *48*, 7899−7903.
(33) Binder, J.; Biswas, A.; Gulder, T. Biomimetic Chlorine-Induced Polyene Cyclizations Harnessing Hypervalent Chloroiodane−HFIP Assemblies. *Chem. Sci.* **2023**, *14*, 3907−3912.
(34) Colomer, I.; Batchelor-McAuley, C.; Odell, B.; Donohoe, T. J.; Compton, R. G. Hydrogen Bonding to Hexafluoroisopropanol Controls the Oxidative Strength of Hypervalent Iodine Reagents. *J. Am. Chem. Soc.* **2016**, *138*, 8855−8861.
(35) Qi, C.; Force, G.; Gandon, V.; Lebœuf, D. Hexafluoroisopropanol-Promoted Haloamidation and Halolactonization of Unactivated Alkenes. *Angew. Chem., Int. Ed.* **2021**, *60*, 946−953.
(36) Ashtekar, K. D.; Vetticatt, M.; Yousefi, R.; Jackson, J. E.; Borhan, B. Nucleophile-Assisted Alkene Activation: Olefins Alone Are Often Incompetent. *J. Am. Chem. Soc.* **2016**, *138*, 8114−8119.
(37) Sarie, J. C.; Neufeld, J.; Daniliuc, C. G.; Gilmour, R. Catalytic *Vicinal* Dichlorination of Unactivated Alkenes. *ACS Catal.* **2019**, *9*, 7232−7237.
(38) Li, Y.; Bao, J.; Zhang, Y.; Peng, X.; Yu, W.; Wang, T.; Yang, D.; Liu, Q.; Zhang, Q.; Fu, J. Three-Component Aminofluorination of Alkenes with Electronically Rich Amino Sources. *Chem.* **2022**, *8*, 1147−1163.
(39) Pozhydaiev, V.; Vayer, M.; Fave, C.; Moran, J.; Lebœuf, D. Synthesis of Unprotected *β*-Arylethylamines by Iron(II)-Catalyzed 1,2-Aminoarylation of Alkenes in Hexafluoroisopropanol. *Angew. Chem., Int. Ed.* **2023**, *62*, No. e202215257.
(40) Legnani, L.; Morandi, B. Direct Catalytic Synthesis of Unprotected 2-Amino-1-Phenylethanols from Alkenes by Using Iron(II) Phtalocyanine. *Angew. Chem., Int. Ed.* **2016**, *55*, 2248−2251.
(41) Legnani, L.; Prina-Cerai, G.; Delcaillau, T.; Willems, S.; Morandi, B. Efficient Access to Unprotected Primary Amines by Iron-Catalyzed Aminochlorination of Alkenes. *Science* **2018**, *362*, 434−439.
(42) Chatterjee, S.; Harden, I.; Bistoni, G.; Castillo, R. G.; Chabbra, S.; van Gastel, M.; Schnegg, A.; Bill, E.; Birrell, J. A.; Morandi, B.; Neese, F.; DeBeer, S. A Combined Spectroscopic and Computational Study on the Mechanism of Iron-Catalyzed Aminofunctionalization of Olefins Using Hydroxylamine Derived N-O Reagent as the 'Amino' Source and 'Oxidant'. *J. Am. Chem. Soc.* **2022**, *144*, 2637−2656.
(43) Gasser, V. C. M.; Makai, S.; Morandi, B. The Advent of Electrophilic Hydroxylamine-Derived Reagents for the Direct Preparation of Unprotected Amines. *Chem. Commun.* **2022**, *58*, 9991−10003.
(44) Chu, D.; Ellman, J. A. Stereospecific Synthesis of Unprotected, *α,β*-Disubstituted Tryptamines and Phenethylamines from 1,2-Disubstituted Alkenes via a One-Pot Reaction Sequence. *Org. Lett.* **2023**, *25*, 3654−3658.
(45) Kirby, G.; Prestat, G.; Berhal, F. Iron-Catalyzed Intermolecular Oxyamination of Terminal Alkenes Promoted by HFIP Using Hydroxylamine Derivatives. *J. Org. Chem.* **2023**, *88*, 4720−4729.
(46) Wang, S.; Force, G.; Guillot, R.; Carpentier, J.-F.; Sarazin, Y.; Bour, C.; Gandon, V.; Lebœuf, D. Lewis Acid/Hexafluoroisopropanol: A Promoter System for Selective *ortho*-C-Alkylation of Anilines with Deactivated Styrene Derivatives and Unactivated Alkenes. *ACS Catal.* **2020**, *10*, 10794−10802.
(47) Wang, S.; Force, G.; Carpentier, J.-F.; Sarazin, Y.; Bour, C.; Gandon, V.; Lebœuf, D. Modular Synthesis of 9,10-Dihydroacridines through an *Ortho*-C Alkenylation/Hydroarylation Sequence between Anilines and Aryl Alkynes in Hexafluoroisopropanol. *Org. Lett.* **2021**, *23*, 2565−2570.
(48) Bortolato, T.; Simionato, G.; Vayer, M.; Rosso, C.; Paolini, L.; Benetti, E. M.; Sartorel, A.; Lebœuf, D.; Dell'Amico, L. The Rational Design of Reducing Organophotoredox Catalysts Unlocks Proton-Coupled Electron-Transfer and Atom Transfer Radical Polymerization Mechanisms. *J. Am. Chem. Soc.* **2023**, *145*, 1835−1846.
(49) Liu, Q.; Zhou, Z.; Kuang, M.; Gao, H.; Yi, W.; Wang, S. Direct Assembly of Phthalides via Calcium(II)-Catalyzed Cascade *Ortho*-C-Alkenylation/Hydroacyloxylation of 3-Aminobenzoic Acids with Alkynes in Hexafluoroisopropanol. *Org. Lett.* **2022**, *24*, 1575−1580.

https://doi.org/10.1021/acsorginorgau.3c00067
ACS Org. Inorg. Au 2024, 4, 287−300

(50) Qi, C.; Yang, S.; Gandon, V.; Lebœuf, D. Calcium(II)- and Triflimide-Catalyzed Intramolecular Hydroacyloxylation of Unactivated Alkenes in Hexafluoroisopropanol. *Org. Lett.* **2019**, *21*, 7405−7409.
(51) Le, C. M.; Hou, X.; Sperger, T.; Schoenebeck, F.; Lautens, M. An Exclusively *Trans* -Selective Chlorocarbamoylation of Alkynes Enabled by a Palladium/Phosphaadamantane Catalyst. *Angew. Chem., Int. Ed.* **2015**, *54*, 15897−15900.
(52) Le, C. M.; Sperger, T.; Fu, R.; Hou, X.; Lim, Y. H.; Schoenebeck, F.; Lautens, M. Stereoselective Synthesis of Methylene Oxindoles via Palladium(II)-Catalyzed Intramolecular Cross-Coupling of Carbamoyl Chlorides. *J. Am. Chem. Soc.* **2016**, *138*, 14441−14448.
(53) Sperger, T.; Le, C. M.; Lautens, M.; Schoenebeck, F. Mechanistic Insights on the Pd-Catalyzed Addition of C−X Bonds across Alkynes − a Combined Experimental and Computational Study. *Chem. Sci.* **2017**, *8*, 2914−2922.
(54) Rodríguez, J. F.; Zhang, A.; Bajohr, J.; Whyte, A.; Mirabi, B.; Lautens, M. Cycloisomerization of Carbamoyl Chlorides in Hexafluoroisopropanol: Stereoselective Synthesis of Chlorinated Methylene Oxindoles and Quinolinones. *Angew. Chem., Int. Ed.* **2021**, *60*, 18478−18483.
(55) Vekariya, R. H.; Aubé, J. Hexafluoro-2-propanol-Promoted Intermolecular Friedel-Crafts Acylation Reaction. *Org. Lett.* **2016**, *18*, 3534−3537.
(56) Chu, D.; Ellman, J. A. Three-Component Friedel−Crafts Transformations: Synthesis of Alkyl and Alkenyl Trifluoromethyl Sulfides and Alkenyl Iodides. *Org. Lett.* **2022**, *24*, 2921−2925.
(57) Boerth, J. A.; Ellman, J. A. A Convergent Synthesis of Functionalized Alkenyl Halides through Cobalt(III)-Catalyzed Three-Component C−H Bond Addition. *Angew. Chem., Int. Ed.* **2017**, *56*, 9976−9980.
(58) Dagousset, G.; Simon, C.; Anselmi, E.; Tuccio, B.; Billard, T.; Magnier, E. Generation of the SCF_3 Radical by Photoredox Catalysis: Intra- and Intermolecular Carbotrifluoromethylthiolation of Alkenes. *Chem.—Eur. J.* **2017**, *23*, 4282−4286.
(59) Zhang, S.; Vayer, M.; Noël, F.; Vuković, V. D.; Golushko, A.; Rezajooei, N.; Rowley, C. N.; Lebœuf, D.; Moran, J. Unlocking the Friedel-Crafts Arylation of Primary Aliphatic Alcohols and Epoxides Driven by Hexafluoroisopropanol. *Chem.* **2021**, *7*, 3425−3441.
(60) Vayer, M.; Zhang, S.; Moran, J.; Lebœuf, D. Rapid and Mild Metal-Free Reduction of Epoxides to Primary Alcohols Mediated by HFIP. *ACS Catal.* **2022**, *12*, 3309−3316.
(61) Muller, C.; Horký, F.; Vayer, M.; Golushko, A.; Lebœuf, D.; Moran, J. Synthesis of Functionalised Isochromans: Epoxides as Aldehyde Surrogates in Hexafluoroisopropanol. *Chem. Sci.* **2023**, *14*, 2983−2989.
(62) Singh, S.; Mondal, S.; Tiwari, V.; Karmakar, T.; Hazra, C. K. Cooperative Friedel−Crafts Alkylation of Electron-Deficient Arenes via Catalyst Activation with Hexafluoroisopropanol. *Chem.—Eur. J.* **2023**, *29*, No. e202300180.
(63) Singh, S.; Mondal, S.; Vodnala, N.; Hazra, C. K. Hydrogen Bonding Network-Enabled Brønsted Acid-Catalyzed Friedel−Crafts Reactions: A Green Approach to Access Unsymmetrical Diaryl- and Triarylmethanes. *Green Chem.* **2023**, *25*, 1014−1022.

https://doi.org/10.1021/acsorginorgau.3c00067
ACS Org. Inorg. Au 2024, 4, 287−300