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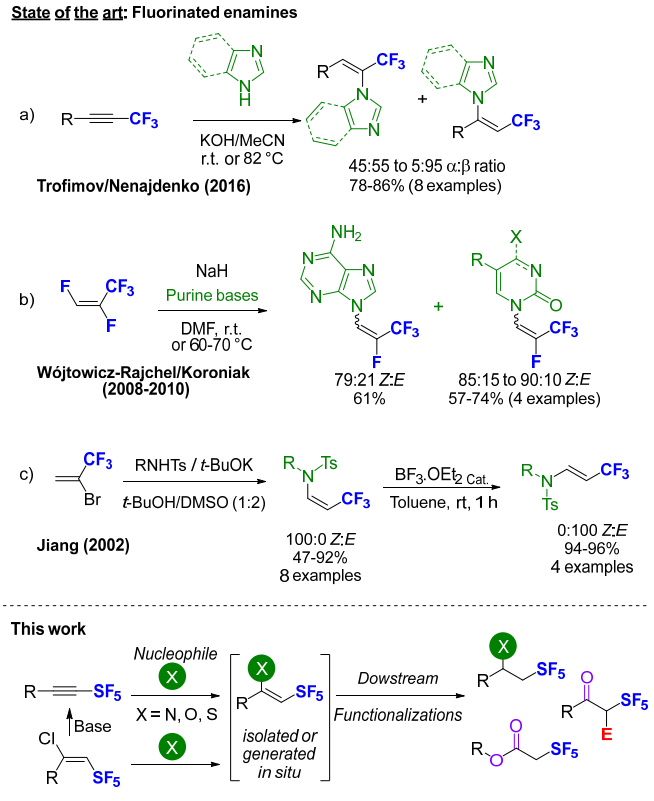
Abstract: Herein is described a fully regio- and stereoselective hydroelementation reaction of SF_5-alkynes with N, O and S-nucleophiles and further functionalization of the corresponding *Z*-(hetero)vinyl-SF_5 intermediates, a suitable platform to access α-SF_5 ketones and esters, β-SF_5 amines and alcohols under mild reaction conditions. Experimental and computational comparative studies between SF_5- and CF_3-alkynes have been performed to highlight and explain the difference of reactivity and selectivity observed between these two fluorinated motifs.

Introduction

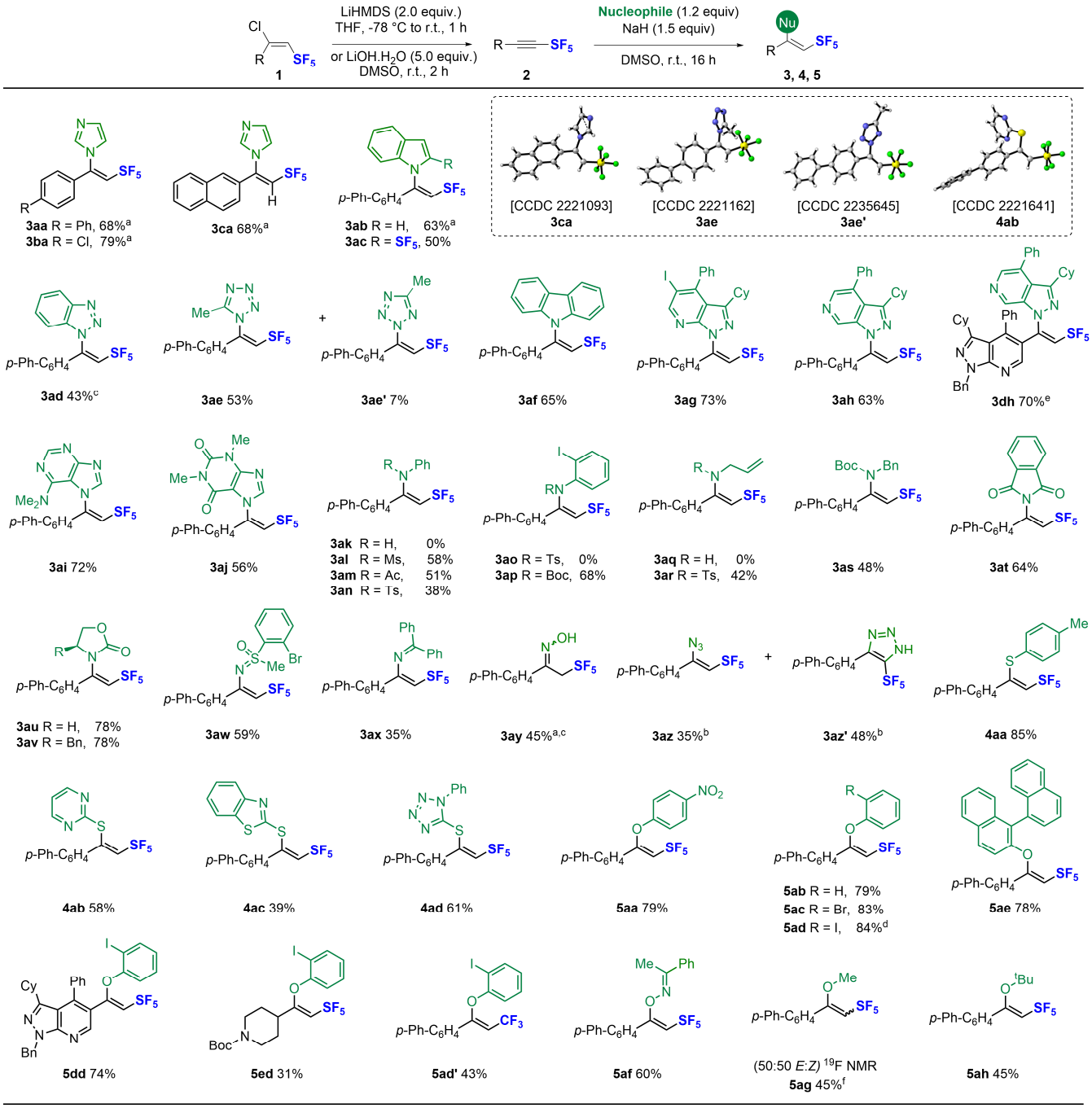
Enamine is a privileged functional group in organic chemistry and it has been worldwide spotlighted with the 2021 Nobel prize in Chemistry about organocatalysis.[1,2] Enamine chemistry has been widely used in organofluorine chemistry, especially for the stereoselective introduction of fluorine atoms and CF_3 group.[3] On the other hand, fluorinated enamines are also of great interest and can be readily prepared by fluoroalkylation,[4] fluorination of ynamides,[5] dehaloamination of haloalkenes,[6] Michael addition,[7] hydroamination of alkynes,[8] and other methods.[9] Nowadays, the pentafluorosulfanyl group (SF_5)[10] is growing in interest in many fields such as heterocyclic synthesis,[11] material science,[12] and medicinal chemistry,[13] and drug development are in progress.[14] However, synthetic routes to SF_5 compounds with structural diversity remain highly challenging and rely mainly on two general methods : the direct radical pentafluorosulfanylation of alkenes, alkynes, diazo ketones or [1.1.1]propelane,[15] or the oxidative fluorination of aromatic thiols, disulfide or derivatives.[16] SF_5-alkynes are readily accessible substrates which can be used in various transformations, such as cycloadditions, heterocyclic synthesis and hydrofunctionalization.[17] Great discoveries are also under investigation with the closely related R-SF_4-alkynes another class of promising SF_n subunits.[18] Surprisingly, the hydrofunctionalization of SF_5-alkynes has been poorly explored and is mainly limited to hydration and hydrofluorination.[19] Until recently, hydroamination of SF_5-alkynes was unknown,[20] but analogous reaction with CF_3-alkynes was studied by Trofimov and Nenajdenko (Scheme 1,a).[8] They observed that addition of imidazole derivatives on CF_3-alkynes was fully stereoselective, forming exclusively *Z*-isomers but the regioselectivity of the amination, in α- or β-position with respect to the CF_3, is highly dependent on the substitution of the aromatic ring of the CF_3-alkynes ranging from 45:55 to 5:95, but without a clear trend. Other syntheses of CF_3-enamines are known but rely mainly in addition/elimination strategies (Scheme 1,b-c).[6] Herein is reported a general procedure for the hydroamination of SF_5 alkynes **2** with a wide variety of nitrogen-nucleophiles, leading exclusively to a single β,*Z* regio- and stereoisomer, and this methodology can easily be extended to hydroetherification and hydrothioetherification reactions. Furthermore, it is demonstrated that these vinyl-SF_5 scaffolds are suitable platforms to access α-SF_5-ketones and esters, β-SF_5-amines and alcohols.



Scheme 1. State of the art and proposed strategy for the hydroelementation of SF_5-alkynes.

Results and Discussion

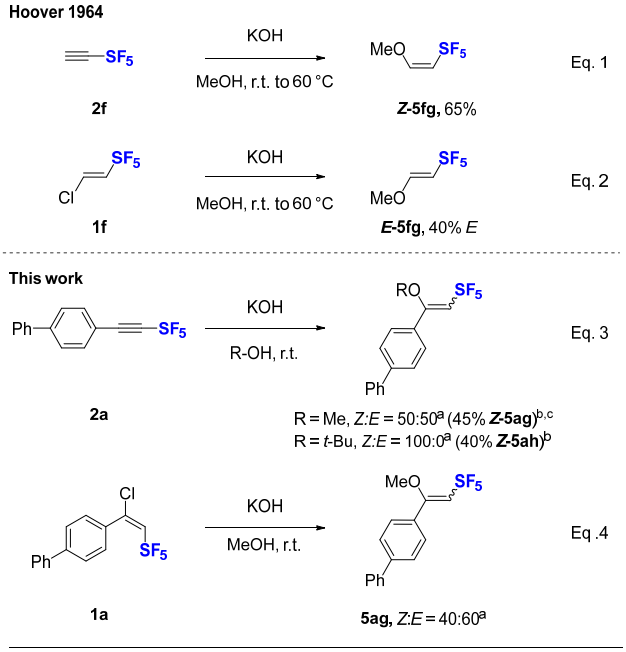
SF_5-alkynes were prepared from β,*E*-chloro-olefin **1** by dehydrochlorination under basic conditions.[15j, 21] We started the



Scheme 2. Scope and limitation for the N, O and S-nucleophilic addition. The reaction was performed from SF_5-alkyne **2** unless otherwise noted. [a] THF was used instead of DMSO with 2 equiv. of nucleophile without base, [b] Obtained from the reaction with NaN_3 as nucleophile, [c] KOH was used instead of NaH, [d] Same yield on 0.03, 0.3 and 0.6 mmol scale, [e] Reaction performed from the corresponding β,*E*-chloro-olefin **1**, [f] Only the *Z*-isomer was recovered after silica gel chromatography.

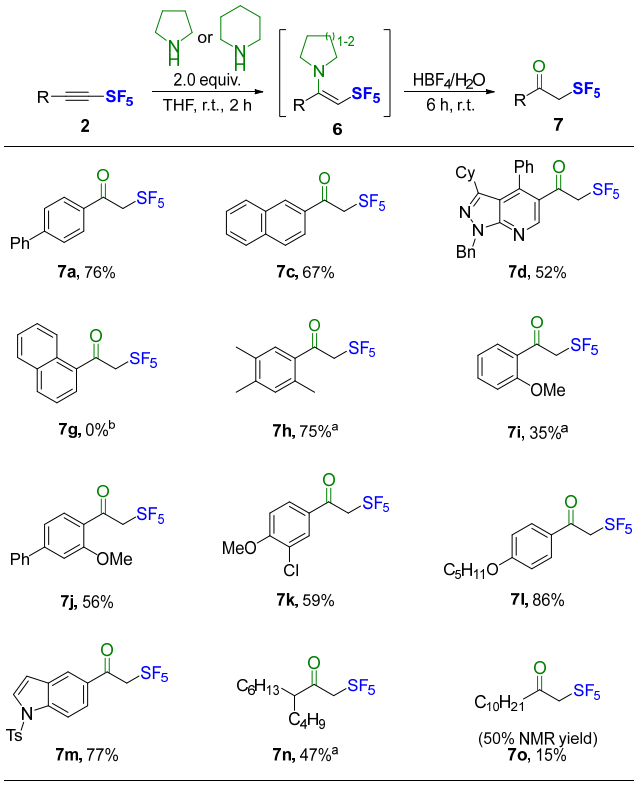
study by the reaction of biphenyl- 4-ethynyl pentafluorosulfane **2a** with 1.2 equiv. of imidazole at r.t. in THF that delivers the product **3aa** with a full conversion and 68% yield (Scheme 2). Compared to the analogous reaction with CF_3 alkynes,[8] we were delighted to note that an additional base was not required with SF_5-alkynes, and the reaction gave a single regio- and stereoisomer with introduction of the imidazole exclusively in β-position of the SF_5 with a *Z*-configuration, as confirmed by the X-ray diffraction of compound **3ca** (CCDC 2221093), **3ae** (CCDC 2221162), **3ae'** (CCDC 2235645) and **4ab** (CCDC 2221641).[22] Encouraged by this result we investigated the scope and the limitation of hydroamination of SF_5-alkynes by screening different amines and other N-containing nucleophiles. Unlike imidazole, we found that using a base achieved complete conversion in all cases. After a short optimization, we found that the combination of NaH in DMSO was compatible with a wide variety of nucleophiles, securing a good solubility of the system, a full conversion and still a perfect regio- and stereoselectivity. Several nitrogen-containing heteraromatic compounds can easily be introduced on SF_5-alkynes such as indole (**3ab**), benzotriazole (**3ad**), tetrazole (**3ae**), carbazole (**3af**), 6- or 7-aza-indazoles (**3ag-h**, **3dh**)[23] with yields ranging from 43 to 73%. In addition, the 2-SF_5-indole[21] is also a competent nucleophile in these conditions and provide compound **3ac** in 50% yield bearing two SF_5 motifs. Natural products such

as adenine and theophylline are well tolerated and underwent the reaction smoothly to give **3al** and **3aj** in good 72 and 56% yield, respectively. Secondary anilines protected with mesyl (**3al**), acetyl (**3am**), tosyl (**3an**) or even *tert*-butylcarbamate (**3ap**) are well tolerated with yields ranging from 38 to 68%. Aliphatic secondary amines such as N-Ts allyl amine (**3ar**) and N-Boc benzylamine (**3as**) can be introduced with a moderate 42 to 48% yield. Other N-nucleophiles such as phtalimide (**3at**), oxazolidinones (**3au-v**), sulfoximine (**3aw**) or even an imine (**3ax**) can be introduced easily in yields ranging from 35 to 78%. Interestingly, the addition of hydroxylamine in THF in the presence of KOH gave the oxime **3ay** with a decent yield of 45%. Furthermore, when NaN_3 was used as nucleophile in DMSO, it resulted in a mixture of the β,*Z*-N_3 addition product **3az** in 35% yield along with the corresponding cycloaddition triazole **3az'** in 48% yield. In this case, heating of the reaction at 60 °C and/or extended reaction time did not improve the **3az**:**3az'** ratio. Surprisingly, the use of CuI as additive suppressed the formation of **3az'** and **3az** was isolated in 60% yield as single SF_5-containing product. We then capitalized on this reaction and extended the scope of this transformation to sulfur- and oxygen-containing nucleophiles. Aromatic (**4aa**) and heteroaromatic thiols (**4ab-d**) were successfully introduced at the sulfur atom with yields ranging from 39 to 85%. Various phenols can also be introduced, with *p*-nitro (**5aa**), with *o*-halogens (**5ac-d**) or even with a bulky 1,1'-binapthyl structure (**5ae**). Noteworthy, substitution of the alkyne is also tolerated as in the case of heteroaromatic groups (**5dd**) or *N*-Boc piperidine (**5ed**) for instance. The reaction can be extended to a CF_3-alkyne, where 67% conversion was obtained with the formation of compound **5ad'** as single regio- and stereoisomer isolated in 43% yield. Interestingly, the introduction of oxygen nucleophile is not limited to phenols since an oxime (**5af**) can also be introduced in 60 % yield, and the addition of aliphatic alcohols such as MeOH (**5ag**) and *t*-BuOH (**5ah**) proceeds also well in these conditions. With MeOH, we observed for the first time a mixture of *E*:*Z* isomers (50:50) in NMR but the introduction of the MeOH only takes place in β-position of the SF_5, while only the β,*Z* isomer is observed with *t*-BuOH. In 1964, Hoover and co-workers described a similar nucleophilic addition of methanol in the presence of KOH as base towards SF_5-acetylene **2f** leading mainly to the *Z* isomer in 65% yield (Scheme 3, eq. 1). In contrast, nucleophilic addition of MeOH to the β,*E*-chloro-olefin **1f** provided mainly the *E* isomer in 40% yield suggesting mainly a substitution of the chlorine atom (Scheme 3, eq. 2).[24] As a comparison, we tested these conditions with the SF_5-alkyne **2a** and corresponding β,*E*-chloro-olefin **1a** (Scheme 3, eq. 3-4). Similar results were obtained in both cases with a *Z*:*E* mixture ranging from 50:50 to 40:60, which seems to indicate that a similar reaction pathway takes place by addition of methoxide onto SF_5-alkyne **2a** (as substrate or generated in-situ from **1a**). However, we noticed a clear difference of stability between the *Z*:*E* isomers **5ag**. Both *E*:*Z* isomers can easily be purified by silica gel column chromatography, however *Z* isomer is stable over time while degradation of the *E* isomer was observed in the NMR tube (See ESI for details, Figure S11). [25] During the investigation of the hydroamination of SF_5-alkynes, we found that some secondary amines such as pyrrolidine and piperidine were effectively transformed into corresponding enamines **6** as a single regio- and stereoisomer (Scheme 4), but they were somehow sensitive to purification and prone to partial hydrolysis over silica gel, delivering a mixture of SF_5-enamine **6** and SF_5-ketone **7**. For a long time, the α-SF_5-ketones were known in the literature but remained mostly anecdotal.[26] More recently, specific procedures for the synthesis of α-SF_5-ketones have been reported, such as gold catalyzed regioselective hydration of SF_5



Scheme 3. Nucleophilic addition of alcoholates, MeOH *vs* *t*-BuOH. [a] *E*:*Z* ratio determined by ^{19}F and ^{1}H NMR, [b] Isolated yield into brackets, [c] Only the *Z* isomer was isolated after silica gel chromatography, while *E* isomer degraded overtime.

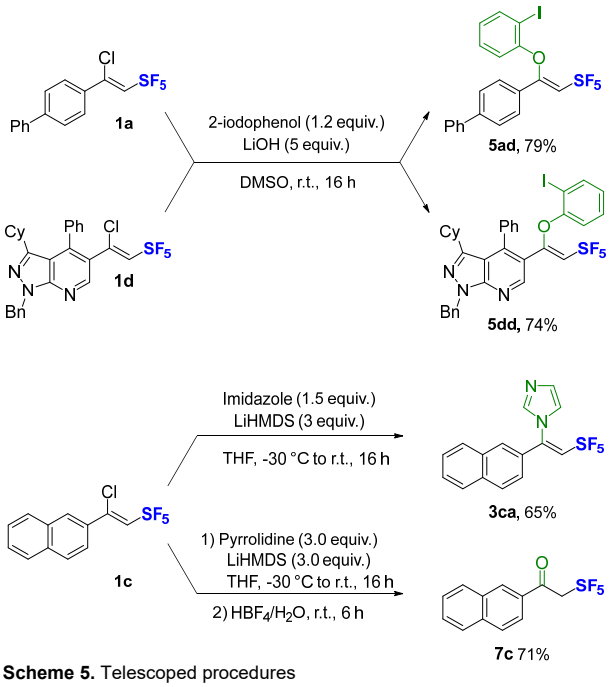
alkynes,[19b] direct pentafluorosulfanylation of α-diazo ketones,[15g] or ozonolysis of allylic SF_5 products.[27] The procedure described herein is a complementary approach and had the advantage of using mild reaction conditions and being a metal-free procedure. After some optimization, we found that pyrrolidine (2 equiv.) yielded enamine **6a^1** in 30 min at r.t. in THF, while the kinetic was slower with piperidine (2 equiv., r.t. 5h). Then, we found that acidic treatment either with diluted H_2SO_4 (10% in water) or HBF_4 (50% in water) were efficient conditions to fully hydrolyze the enamines **6a^1** and **6a^2** with good overall yields of 76% (**7a**) in both cases. In contrast, we observed that the hydrolysis was slower for **6a^1** (6 h) than for **6a^2** (30 min). For the scope of this transformation (Scheme 4), we used the pyrrolidine for 2h at r.t. and then HBF_4 50% in water for 6h at r.t. The reaction proceeded smoothly with aromatic, heteroaromatic and alkyl substituted alkynes in moderate to high yields. Surprisingly, substitution with a 2-naphtyl delivers the ketone **7b** in 67% yields while the 1-napthyl substitution (**2g**) stopped at the enamine form without full conversion. It rather looks like a special case because several examples of bulky ortho-substituted aryl ketones (**7d**, **7h-j**) were obtained in yields ranging from 35 to 75%. Nitrogen-heterocycles (**7d**, **7m**) are well tolerated and the reaction is also compatible with alkyl substrates although corresponding ketone **7n** and **7o** are quite volatile. Unlike the closely related RSF_4-alkyne derivatives,[18d] the hydrolysis of SF_5-alkynes directly with an acidic aqueous solution is unknown. Following recommendation from referee, we checked that hydrolysis of SF_5-alkynes **2a** was not possible using H_2SO_4 (10 mol%) or HBF_4 (50% in H_2O), thus showing the benefit to pass by the formation of enamine **6**.[25] In contrast, much more concentrated solution of H_2SO_4 proved to be effective to hydrolyze **2a** into **7a**, and after a short optimization we



Scheme 4. Scope and limitation for the formation of α-SF_5-ketones. [a] H_2SO_4 10% was used instead of HBF_4, [b] Enamine **6g** was partially obtained but not isolated.

found that using 80% aq. solution of H_2SO_4 in THF at r.t. give 94% of **7a** after 5 min, isolated in 68 % yield. Since SF_5-alkynes **2** are prepared from **1** by a base-mediated dehydrochlorination, we anticipated that the basic conditions we used for the hydroelementation would be suitable for both the dehydrochlorination step and the hydroelementation step, so we could perform this hydroelementation directly from **1** via a telescoped procedure (Scheme 5). So, we tested the hydroetherification from β,*E*-chloro-olefins **1a** and **1d** in the presence of LiOH, DMSO and 2-iodophenol as nucleophile and we obtained products **5ad** and **5dd** in 79 and 74% yield respectively over a two-step sequence. Similarly, hydroamination of **1c** with imidazole in the presence of LiHMDS delivered product **3ca** in 65% yield. We also confirmed it was possible to make the α-SF_5-ketone **7c** in 71% yield directly from **1c** by reaction with pyrrolidine in the presence of LiHMDS, followed by hydrolysis with aqueous HBF_4.

In the literature, the SF_5 group is often called "super CF_3" since many of its physicochemical properties are enhanced compared to CF_3.[10] However, the synthesis and reactivity of SF_5 compounds differ significantly from the CF_3 analogs. During the present study, we wondered why the hydroelementation of SF_5 alkynes was perfectly regio- and stereoselective, whereas the hydroamination of CF_3 alkynes in similar conditions yielded a mixture of regioisomers.[8] As comparison, Nenajdenko and coworkers described in 2016 the addition of imidazole and derivatives on CF_3-alkynes forming exclusively *Z*-stereoisomers but with α:β regioselectivity ranging from 45:55 to 5:95 without a clear trend about the influence of the alkyne substitution. Since our group also has a strong interest in the synthesis and reactivity of CF_3 alkynes,[28] we decided to reinvestigate this transformation experimentally on both CF_3- and SF_5-alkynes, using reactions conditions **X** (no base, THF, r.t., 2h) from the present report and conditions **Y** (20 mol% of KOH, MeCN, r.t., 24h) from Nenajdenko (See ESI, Figure S1).[8] We first observed that in conditions **X** or **Y**, the addition of imidazole on the SF_5-alkyne **2a** leads to a perfect β,*Z*-selectivity (**B1**). Surprisingly, with the analogous CF_3-alkyne **2a'** no reaction occurs in conditions **X**, even after 24h, but the reaction proceeds in conditions **Y** yielding a 25:75 **A1**:**B1** ratio in favor the β,*Z*-isomer (**B1**). Looking for a substrate giving a lower selectivity, we identified the CF_3-alkyne **2b'** which gave a 40:60 **A1**:**B1** ratio. [8]



Scheme 5. Telescoped procedures

As expected, no reaction takes place in condition **X** with **2b'**, but only conditions **Y** are suitable to produce a 30:70 **A1**:**B1** ratio which is closely related to what they observed. With the analogous SF_5-alkyne **2b**, a perfect β,*Z* selectivity (**B1**) was observed in conditions **X**, while a 92:8 **B1**:**B2** mixture of stereoisomers was observed for the first time in conditions **Y**, and the structure was confirmed by NOE experiments.[25] However, we noticed that the β,*E*-isomer **B2** was poorly stable overtime. For instance, after keeping the mixture of isomers in an NMR tube under sunlight for a couple of days, **B1** remains intact whereas **B2** evolves to the corresponding ketone **7** and other by-products. In contrast with CF_3-alkynes, nucleophilic addition onto SF_5-alkynes always takes place at the β-position of the SF_5 motif, but how to explain this difference of regioselectivity? One could say that SF_5 (with an electronegativity of 3.65 vs 3.36 for CF_3) polarizes more the alkyne than CF_3 making the C≡C bond a better nucleophile acceptor. This is supported by the calculations of the NPA charges of the carbon atoms of the triple bond, C_α and C_β, for the fluorinated-alkynes **2a** and **2a'**. C_β bears a slightly positive charge (0.09 for **2a** and 0.07 for **2a'**) whereas for C_α it is negative (-0.30 for **2a** and -0.15 for **2a'**), leading to a more polarized bond in **2a** (Δq : 0.39 and 0.22 respectively, See ESI, table S3). On the other hand, the larger van der Waals volume of SF_5 (55.4 $Å^3$ vs

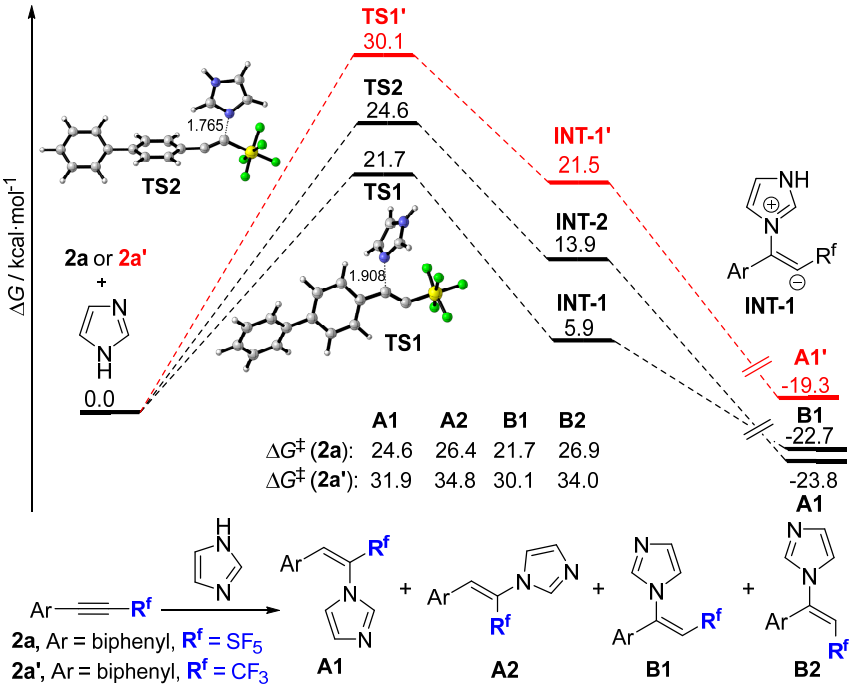


Figure 1. Energy profiles (ΔG in kcal/mol) computed at PCM(THF)-M06-2X/6-311+G**//M06-2X/def2-SVP level of theory for the hydroamination of SF_5/CF_3-alkynes (**2a**/**2a'**) with imidazole, affording **A1** (α, *Z*) and **B1** (β, *Z*) products. Activation barriers for the formation of all plausible hydroamination products (**A1**, **A2**, **B1** and **B2**) are also reported.

34.6 Å^3 for CF_3) closer to a *tert*-butyl group would argue more in favor of steric preferences. To elucidate the origin of the observed selectivity for SF_5-alkynes *i.e.* privileged nucleophilic attack on β-carbon, as well as the higher reactivity of SF_5-alkynes over CF_3-alkynes in conditions **X**, we computed the different energy profiles (PCM(THF)/M06-2X/6-311+G**//M06-2X/def2-SVP) for the hydroamination reaction over SF_5/CF_3-alkyne **2a**/**2a'** with imidazole in absence of base. The more relevant energy profiles associated to the formation of *Z*-isomers (**A1**, **B1**) are depicted in Figure 1 and the whole panorama (*Z*- and *E*-isomers) are reported in ESI, Figures S2-3). As displayed in Figure 1, the nucleophilic attack of the imidazole over the fluorinated-alkyne first forms a zwitterionic intermediate (**INT**), followed by a presumed fast and solvent-mediated proton transfer, leading to the final hydroamination product in a highly exothermic process (ΔG < -19 kcal/mol). This nucleophilic addition is the step governing the regioselectivity. In line with the experimentally observed regioselectivity, DFT calculations have shown that the attack at the β-carbon of SF_5-alkyne **2a** and leading to *Z*-isomer **B1** is kinetically favored over the attack at the α-carbon, affording *Z*-isomer **A1** ($\Delta G^{\ddagger}$= 21.7 *vs* 24.6 kcal/mol for **TS1** and **TS2**, respectively). Closer inspection of the optimized transition states suggests that **TS1** is an earlier TS than **TS2**, with a C···N distance of 1.908 Å and 1.765 Å, respectively. It is noteworthy that formation of *E*-isomers (**A2**, **B2**) are less kinetically favorable ($\Delta\Delta G^{\#}$ ~5 kcal/mol compared to **TS1**).

On the other hand, by comparing the processes involving **2a** and **2a'**, we found that the replacement of the SF_5 with CF_3 produces a considerable increase of the activation barrier of the nucleophilic attack at β-carbon ($\Delta G^{\ddagger}$= 21.7 *vs* 30.1 kcal/mol, respectively). This finding perfectly matches with the fact that the hydroamination reaction of SF_5-alkyne **2a** with imidazole occurs at r.t. but fails employing the analogous CF_3-alkyne **2a'**. As revealed by the C···N distance, the highest activation barrier for **TS1'** corresponds to a later TS with a C···N distance of 1.832 Å *vs* 1.908 Å, for respectively **TS1'** and **TS1**.

In order to further understand the origin of the β-selectivity observed for the SF_5-alkyne **2a**, we applied two powerful computational tools to quantitatively analyze the physical factors behind the reactivity trends, namely, the Activation Strain Model of reactivity (ASM) and the Energy Decomposition Analysis (EDA).[25] The Activation Strain Model (ASM) approach was used to assess the relative contributions of the strain (ΔE_{strain}) and interaction (ΔE_{int}) terms upon attack of imidazole at α-carbon and β-carbon of the alkyne. Figure 2 shows the corresponding activation strain diagrams along the entire reaction coordination ζ (selected as the C···N bond-forming distance) for the nucleophilic attack of imidazole on alkyne **2a** at β-carbon (dashed lines) and α-carbon (solid lines).

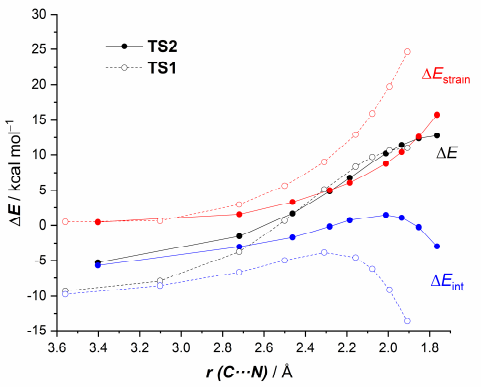


Figure 2. Activation strain diagrams computed along the IRC for the paths to **TS1** (attack at C_β, dashed lines) and **TS2** (attack at C_α, solid lines) of the hydroamination reaction of SF_5-alkyne **2a** with imidazole. Energy level: M06-2X/def2-SVP.

As observed in Figure 2, the ΔE_{strain} term, which quantifies the required energy to distort the reactants, is considerably smaller for the nucleophilic attack at the α-carbon compared to the same attack at the β-carbon (at a quasi-similar C···N distance of about 1.9 Å, close to **TS1**, ΔE_{strain} : 10.4 for C_α and 24.6 kcal/mol for C_β, see Table S1). Consequently, this term is not at all responsible for the β-selectivity. In sharp contrast, the interaction term (ΔE_{int}) between the reactants is much more stabilizing for the process involving the β-carbon along the whole reaction coordinate, meaning that ΔE_{int} term is solely responsible for the experimentally observed β-selectivity. With the help of the EDA method (M06-2X/TZ2P//M06-2X/def2-SVP), we further analyzed the ΔE_{int} term by decomposing it into three different chemically meaningful terms: (i) the Pauli repulsion term, ΔE_{pauli}, that quantifies destabilizing interactions between occupied orbitals and is a measure for any steric repulsion, (ii) the ΔV_{elstat} term corresponding to the quasi-classical electrostatic interaction between the reactants and (iii) the ΔE_{orb} accounting for the stabilizing orbital interactions between occupied orbital of one reactant with unoccupied orbital of the other reactant. Although we computed the EDA terms along the whole reaction coordinate (see ESI, figure S5), for a direct comparison between the attack at β- or α-carbon, we analyzed the EDA terms at a consistent similar distance C···N distance of ~1.9 Å, close to **TS1**. At this point, $\Delta\Delta E_{orb}$ and $\Delta\Delta V_{elstat}$ terms are relatively small ($\Delta\Delta E_{orb}$ = 3.7 and $\Delta\Delta V_{elstat}$ = 2.7 kcal/mol, in favor of C_β). The largest difference between the two attacks finds its origin in the destabilizing Pauli repulsion term ($\Delta\Delta E_{Pauli}$ = 8.5 kcal, see ESI Table S2), which is much larger for C_α attack. This result suggests that the origin of the β-selectivity observed for **2a** is mainly due to a larger steric repulsion upon attack at C_α, thus preventing the formation of hydroaminated α-isomer.

To understand the higher reactivity of the SF_5-alkyne **2a** compared to the CF_3-alkyne **2a'**, we applied again the ASM/EDA methodology for the privileged nucleophilic attack at β-carbon. We found that the ΔE_{strain} term for the process involving **2a** and the process involving **2a'** are nearly identical along the reaction coordinate (Figure 3). However, the ΔE_{int} term is more stabilizing for the nucleophilic addition of imidazole on SF_5-alkyne than CF_3-alkyne. According to EDA analysis, at a similar distance close to **TS1** (C···N ~ 1.91 Å), the largest difference between the attacks on **2a** and **2a'** is found in the orbital term (ΔE_{orb}), which is more stabilizing for **2a** [$\Delta\Delta E_{Pauli}$: 3.2, $\Delta\Delta V_{elstat}$= -2.3 and $\Delta\Delta E_{orb}$= -5.8 kcal/mol, see ESI table S4 and Figure S7]. The Natural Orbital for Chemical Valence (NOCV) extension of the EDA method shows that the main orbital interaction ΔE_{orb1} comes from the charge flow of the density from the nitrogen lone pair of imidazole to the empty $\pi^*_{C\equiv C}$ orbital of alkyne (See Figure 4). The highest orbital stabilization for **2a** (ΔE_{orb1} : - 47.5 kcal/mol *vs* -42.7 kcal/mol in **2a'**) can be correlated to a more accessible LUMO ($\pi^*_{C\equiv C}/\pi^*_{CC}{}^{aryl}$ (alkyne)) in SF_5-alkyne compared to CF_3-alkyne (-1.2 eV in **2a** *vs* -1.0 eV in **2a'**, see Figure S10).

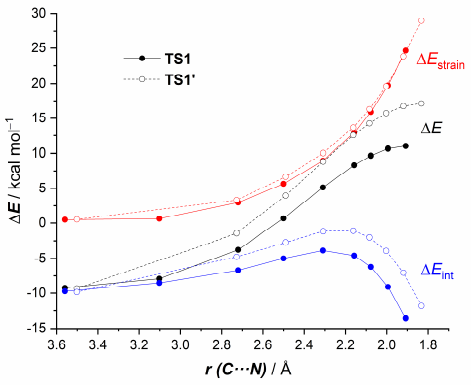


Figure 3. Activation strain diagrams computed along the IRC for the privileged path through **TS1** (attack at C_β for **2a**, dashed lines) and **TS1'** (attack at C_β for **2a'**, solid lines) of the hydroamination reaction of the fluorinated alkynes with imidazole. Energy level: M06-2X/def2-SVP.

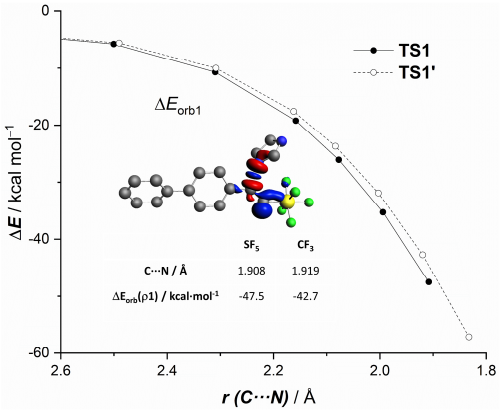
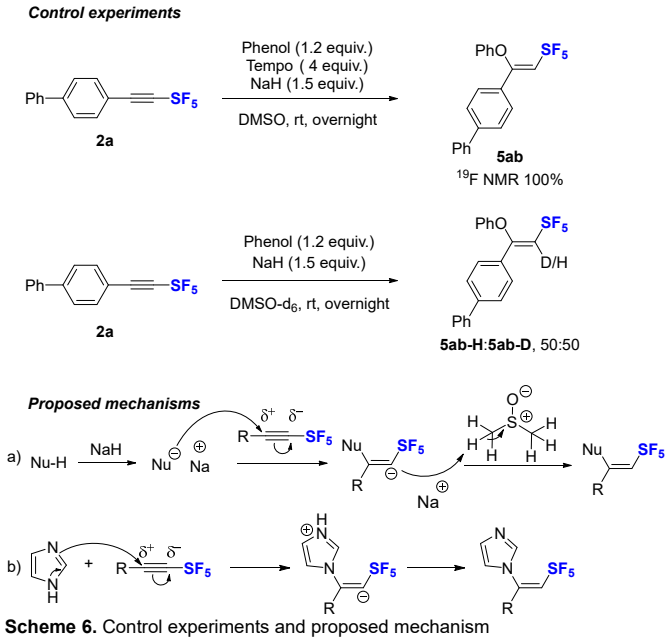


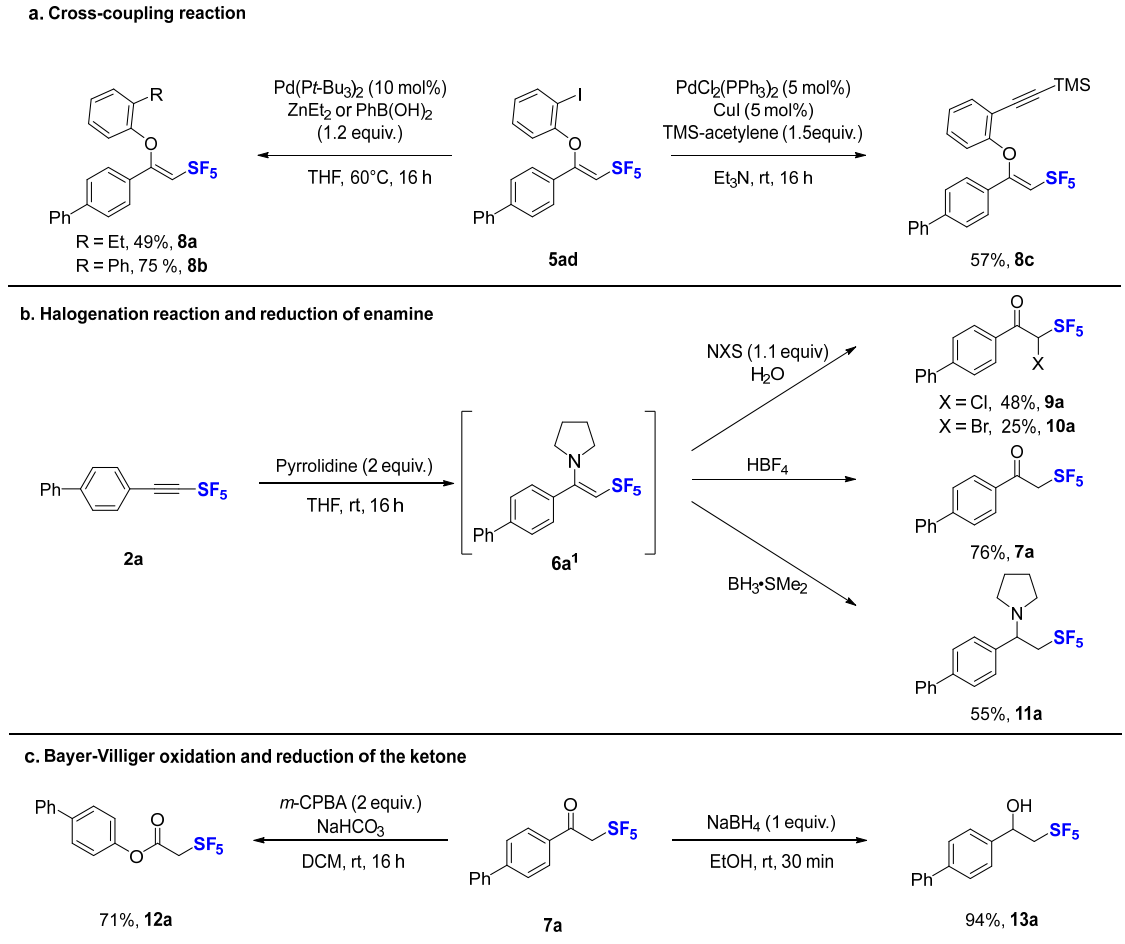
Figure 4. Plot of the evolution of the orbital interaction energy contribution ($\Delta E_{orb,1}$ in kcal/mol) of the main pairwise orbital interaction between the fluorinated-alkynes and imidazole all along the process for the attack at C_β.**TS1** is in solid line and **TS1'** in dashed line. Plot of the contours of deformation density contribution ($\Delta\rho_{orb,1}$) of the main pairwise orbital interaction and associated orbital interaction energy contribution (ΔE_{orb1} in kcal/mol).

In order to generalize our study, we computed the activation barriers for the attack at the α/β-carbons of SF_5-alkyne **2a** and affording *Z*-isomers **A1/B1**, for two other nucleophiles experimentally reported in Scheme 4 and involving similar experimental conditions (without base) *i.e.* pyrrolidine and piperidine. DFT calculations (see ESI for details, Table S6) indicate the attack at C_β is still kinetically favored, in line with the experimental results. The activation barriers for the nucleophilic attack at β-carbon were computed lower in energy than for imidazole, at $\Delta G^{\ddagger}$= 15.5 and 15.2 kcal/mol, respectively for pyrrolidine and piperidine, suggesting more reactive nucleophiles. In addition, a lower energy difference between the two transition states associated with the attacks in α and β was found for pyrrolidine and piperidine ($\Delta\Delta G^{\#}$: -1.5 and -1.0 kcal/mol, respectively) compared to imidazole ($\Delta\Delta G^{\#}$: -2.9 kcal/mol) but did not impact the selectivity. As these DFT studies fully support the experimental selectivities, we then embarked in control experiments to gain further insights into the mechanism (Scheme 6).[8,29]

The reaction proceeds smoothly in the presence of 4 equiv. of TEMPO and gave the desired product **5ab** without inhibition of the reaction. When DMSO-d_6 was used as solvent a mixture of deuterated and not deuterated product was obtained in a 50:50 ratio, showing the crucial role of the solvent in this reaction acting as a H/D-donor. Moreover, the incorporation of deuterium took place only on the olefin in α-position of the SF_5.[25]



Scheme 6. Control experiments and proposed mechanism



Scheme 7. Downstream functionalizations

A higher proportion of **5ab-D** was expected, but the 50:50 H:D ratio could be explained by first the reaction of NaH with DMSO-d_6 which then deprotonate the phenol to form at least 1.2 equiv. of DMSO-d_5 in a huge excess of DMSO-d_6 then a strong kinetic isotope effect is observed in favor of the reprotonation rather than deuteration. These two observations are in good agreement with an ionic rather than a radical pathway which allow us to propose the following mechanisms: a) After deprotonation of the nucleophile with base, a nucleophilic attack of the anion on the SF_5-alkyne take place at the most electron deficient β-position of

the SF_5-alkyne to form an alkenyl anion intermediate, which is subsequently protonated with the solvent, or b) for reaction proceeding without base like for imidazole for instance, the most nucleophilic nitrogen attacks the most electron deficient β-position of the SF_5-alkyne to form a zwitterionic intermediate which delivers the product after prototropy.

Finally, we studied some downstream functionalizations. Palladium-catalyzed Negishi cross-coupling with diethylzinc delivered **8a** in 49% yield. Suzuki-Miyaura cross-coupling with phenyl boronic acid (**8b**) and Sonogashira cross-coupling with TMS-acetylene (**8c**) were also performed in 75 and 57% yields, respectively (Scheme 7,a). Intermediate enamine **6a**[1] can react with an electrophilic halogen source such as NCS or NBS to form α-chloro or α-bromo α-SF_5-ketones (**9a**, **10a**) in presence of water to quench the intermediate iminium (Scheme 7,b). Enamine **6a**[1] can also be reduced with $BH_3.SMe_2$ to form the corresponding amine **11a** in decent 55% yield. Finally, reduction of the α-SF_5-ketone **7a** was performed in high yield (94% **13a**) using sodium borohydride in ethanol. Moreover, we succeeded to perform a Baeyer–Villiger oxidation on the ketone **7a** leading to the corresponding ester **12a** in 71% yield (Scheme 7,c).

Conclusion

In summary, we have developed an efficient and general hydroelementation reaction on SF_5-alkynes. The reaction tolerates a wide range of N-, O-, and S-nucleophiles and gives the corresponding adducts in good yields and in all the cases as a single regio- and stereoisomer. A complementary synthesis of α-SF_5-ketones was performed under mild condition and without any use of metals. Moreover, it was shown that these transformations can also be performed directly from the corresponding β,*E*-chloro-olefins which shorten the synthesis by one step. A selection of downstream functionalizations was demonstrated, including C-C cross coupling, halogenation, reduction and Baeyer–Villiger oxidation. DFT calculations were also performed to better understand the impact on reactivity of the SF_5 compared to the CF_3 group, which nuance the comparison of SF_5 as a super CF_3, but seems to indicate that they have very distinct properties and reactivities. DFT calculations combined with ASM/EDA analyses were performed to have better insight on the β-selectivity for SF_5-alkyne and the impact of the fluorinated group (SF_5 *vs* CF_3) for the hydroamination reaction with imidazole. The origin of the β-selectivity for the SF_5-alkyne is related to a lower steric repulsion (ΔE_{Pauli}) upon attack at C_β. Compared to CF_3-alkyne, the C_β-nucleophilic attack of imidazole on SF_5-alkyne occurs in the absence of base thanks to better orbital interaction between the nitrogen lone pair of imidazole and the empty $\pi^*_{C\equiv C}$ (alkyne), which is more accessible in energy than in CF_3-alkyne.

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Keywords: pentafluorosulfanyl • enamine • hydroelementation • regioselective • stereoselective

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[1] https://www.nobelprize.org/prizes/chemistry/2021/summary/

[2] For reviews about enamine, see: a) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471-5569; b) D. Enders, C. Grondal, M. R. M. Hüttl, *Angew. Chem. Int. Ed.* **2007**, *46*, 1570-1581.

[3] For selective reviews about stereoselective fluorination reactions, see: a) V. Bizet, T. Besset, J.-A. Ma, D. Cahard, *Curr. Top. Med. Chem.* **2014**, *14*, 901-940; b) V. Bizet, D. Cahard, in *"Stereoselective Synthesis of Drugs and Natural Products"* (Chapter 44), Ed. Wiley-Blackwell. 2013, ISBN: 978-1-1180-3217-6, pp. 1347-1376; c) G. Valero, X. Companyó, R. Rios, *Chem. Eur. J.* **2011**, *17*, 2018-2037; d) J.-A. Ma, D. Cahard, *Chem. Rev.* **2008**, *108*, PR1-PR43.

[4] a) K. Zhao, J.-Y. Guo, T. Guan, Y.-X. Wang, J.-Y. Tao, Y. Zhang, Q.-H. Zhang, K. Ni, T.-P. Loh, *Org. Chem. Front.* **2021**, *8*, 4086-4094; b) T.-H. Zhu, Z.-Y. Zhang, J.-Y. Tao, K. Zhao, T.-P. Loh, *Org. Lett.* **2019**, *21*, 6155-6159; c) R. Rey-Rodriguez, P. Retailleau, P. Bonnet, I. Gillaizeau, *Chem. Eur. J.* **2015**, *21*, 3572-3575; d) C. Feng, T.-P. Loh, *Chem. Sci.* **2012**, *3*, 3458-3462.

[5] a) B. Métayer, A. Angeli, A. Mingot, K. Jouvin, G. Evano, C. T. Supuran, S. Thibaudeau, *J. Enzyme Inhib. Med. Chem.* **2018**, *33*, 804-808; b) Y. Xi, G. Zhu, L. Tang, S. Ma, D. Zhang, R. Zhang, G. He, H. Zhu, *Org. Biomol. Chem.* **2017**, *15*, 7218-7226; c) B. Métayer, G. Compain, K. Jouvin, A. Martin-Mingot, C. Bachmann, J. Marrot, G. Evano, S. Thibaudeau, *J. Org. Chem.* **2015**, *80*, 3397-3410; d) G. Compain, K. Jouvin, A. Martin-Mingot, G. Evano, J. Marrot, S. Thibaudeau, *Chem. Commun.* **2012**, *48*, 5196-5198.

[6] a) V. M. Muzalevskiy, Z. A. Sizova, V. V. Panyushkin, V. A. Chertkov, V. N. Khrustalev, V. G. Nenajdenko, *J. Org. Chem.* **2021**, *86*, 2385-2405; b) V. M. Muzalevskiy, Z. A. Sizova, V. T. Abaev, V. G. Nenajdenko, *Org. Biomol. Chem.* **2021**, *19*, 4303-4319; c) H. Wójtowicz-Rajchel, M. Pasikowska, A. Olejniczak, A. Katrusiak, H. Koroniak, *New J. Chem.* **2010**, *34*, 894-902; d) H. Wójtowicz-Rajchel, H. Koroniak, A. Katrusiak, *Eur. J. Org. Chem.* **2008**, 368-376; e) B. Jiang, F. Zhang, W. Xiong, *Tetrahedron* **2002**, *58*, 265-270.

[7] a) J. Wu, H. Zhang, X. Ding, X. Tan, H. C. Shen, J. Chen, L. Song, W. Cao, *Tetrahedron* **2020**, *76*, 131518; b) B. J. Murray, T. G. F. Marsh, D. S. Yufit, M. A. Fox, A. Harsanyi, L. T. Boulton, G. Sandford, *Eur. J. Org. Chem.* **2020**, 6236-6244; c) J. Wu, H. Zhang, X. Ding, X. Tan, H. C. Shen, J. Chen, W. He, H. Deng, L. Song, W. Cao, *J. Fluorine Chem.* **2019**, *220*, 54-60.

[8] B. A. Trofimov, L. V. Andriyankova, L. P. Nikitina, K. V. Belyaeva, A. G. Mal'kina, A. V. Afonin, I. A. Ushakov, V. B. Kobychev, V. M. Muzalevskiy, V. G. Nenajdenko, *J. Fluorine Chem.* **2016**, *188*, 157-163.

[9] a) H. Zeng, Y. Cai, H. Jiang, C. Zhu, *Org. Lett.* **2021**, *23*, 66-70; b) C. Liu, E. Shi, F. Xu, Q. Luo, H. Wang, J. Chen, X. Wan, *Chem. Commun.* **2015**, *51*, 1214-1217; c) K. Isa, M. Minakawa, M. Kawatsura, *Chem. Commun.* **2015**, *51*, 6761-6764.

[10] For general reviews about SF_5, see: a) R. Kordnezhadian, B.-Y. Li, A. Zogu, J. Demaerel, W. M. De Borggraeve, E. Ismalaj, *Chem. Eur. J.* **2022**, *28*, e202201491; b) M. Magre, S. Ni, J. Cornella, *Angew. Chem. Int. Ed.* **2022**, *61*, e202200904; c) G. Haufe, *Tetrahedron* **2022**, *109*, 132656; d) D. Rombach, H.-A. Wagenknecht, *Synthesis* **2022**, *54*, 4883-4894; e) Y. Kraemer, E. N. Bergman, A. Togni, C. R. Pitts, *Angew. Chem. Int. Ed.* **2022**, *61*, e202205088; f) D. J. Burton, Y. Wang, V. Bizet, D. Cahard, in *Encyclopedia of Reagents for Organic Synthesis*, **2020**, DOI: 10.1002/047084289X.rn00413.pub2; g) Ponomarenko, G.-V. Röschenthaler, in *Frontiers of Organofluorine Chemistry*, **2019**, pp. 251-279; h) P. R. Savoie, J. T. Welch, *Chem. Rev.* **2015**, *115*, 1130-1190; i)

N. v. H. Cortney, R. S. Paul, T. W. John, *Curr. Org. Chem.* **2015**, *19*, 1592-1618.

[11] a) M. Sani, M. Zanda, *Synthesis* **2022**, *54*, 4184-4209; b) P. Beier *In Emerging Fluorinated Motifs: Synthesis, Properties and Applications*; Cahard, D., Ma, J.-A., Eds.: Wiley-VCH: Weinheim, Germany, **2020**; *Vol 2*, pp 551−570; c) B. Cui, N. Shibata *Phosphorus, Sulfur Silicon Relat. Elem.* **2019**, *194*, 658−663; d) P. Das, E. Tokunaga, N. Shibata *Tetrahedron Lett.* **2017**, *58*, 4803−4815; e) O. S. Kanishchev, W. R. Dolbier, *In Advances in Heterocyclic Chemistry*, Scriven, E. F. V., Ramsden, C. A., Eds.; Academic Press, **2016**; Vol. *120*, pp 1− 42.

[12] J. M. W. Chan *J. Mater. Chem. C* **2019**, *7*, 12822−12834.

[13] a) M. Inoue, Y. Sumii, N. Shibata, *ACS Omega* **2020**, *5*, 10633-10640; b) L. Xing, T. Honda, L. Fitz, I. Ojima, in *Fluorine in Life Sciences: Pharmaceuticals, Medicinal Diagnostics, and Agrochemicals* (Eds.: G. Haufe, F. R. Leroux), Academic Press, **2019**, pp. 181-211; c) M. F. Sowaileh, R. A. Hazlitt, D. A. Colby *ChemMedChem* **2017**, *12*, 1481−1490;

[14] a) R. Gujjar, F. El Mazouni, K. L. White, J. White, S. Creason, D. M. Shackleford, X. Deng, W. N. Charman, I. Bathurst, J. Burrows, D. M. Floyd, D. Matthews, F. S. Buckner, S. A. Charman, M. A. Phillips, P. K. Rathod *J. Med. Chem.* **2011**, *54*, 3935−3949; b) J. T. Welch, D. S. Lim *Bioorg. Med. Chem.* **2007**, *15*, 6659−6666; c) D. S. Lim, J. S. Choi, C. S. Pak, J. T. Welch *J. Pestic. Sci.* **2007**, *32*, 255−259.

[15] Selected examples: a) Y. Kraemer, C. Ghiazza, A. N. Ragan, S. Ni, S. Lutz, J. C. Fettinger, N. Nöthling, R. Goddard, J. Cornella, C. R. Pitts *Angew. Chem. Int. Ed.* **2022**, *61*, e202211892; b) A. Taponard, T. Jarrosson, L. Khrouz, M. Médebielle, J. Broggi, A. Tlili, *Angew. Chem. Int. Ed.* **2022**, *61*, e202204623; c) J.-Y. Shou, F.-L. Qing, *Angew. Chem. Int. Ed.* **2022**, *61*, e202208860; d) J.-Y. Shou, X.-H. Xu, F.-L. Qing, *J. Fluorine Chem.* **2022**, *261-262*, 110018; e) D. Rombach, B. Birenheide, H.-A. Wagenknecht, *Chem. Eur. J.* **2021**, *27*, 8088-8093; f) A. Gilbert, M. Birepinte, J.-F. Paquin, *J. Fluorine Chem.* **2021**, 109734; g) J. Y. Shou, X. H. Xu, F. L. Qing, *Angew. Chem., Int. Ed*. **2021**, 60, 15271−15275; h) A. Gilbert, P. Langowski, M. Delgado, L. Chabaud, M. Pucheault, J.-F. Paquin, *Beilstein J. Org. Chem.* **2020**, *16*, 3069-3077; i) A. Gilbert, J.-F. Paquin, *J. Fluorine Chem.* **2019**, *221*, 70-74; j) S. Aït-Mohand, W. R. Dolbier, *Org. Lett.* **2002**, *4*, 3013-3015.

[16] a) K. Tanagawa, Z. Zhao, N. Saito, N. Shibata, *Bull. Chem. Soc. Jpn* **2021**, *94*, 1682-1684; b) C. R. Pitts, D. Bornemann, P. Liebing, N. Santschi, A. Togni, *Angew. Chem. Int. Ed.* **2019**, *58*, 1950-1954; c) J. Ajenjo, B. Klepetářová, M. Greenhall, D. Bím, M. Culka, L. Rulíšek, P. Beier, *Chem. Eur. J.* **2019**, *25*, 11375-11382; d) P. Das, E. Tokunaga, N. Shibata, *Tetrahedron Lett.* **2017**, *58*, 4803-4815; e) B. Cui, M. Kosobokov, K. Matsuzaki, E. Tokunaga, N. Shibata, *Chem. Commun.* **2017**, *53*, 5997-6000; f) B. Cui, S. Jia, E. Tokunaga, N. Saito, N. Shibata, *Chem. Commun.* **2017**, *53*, 12738-12741; g) M. Kosobokov, B. Cui, A. Balia, K. Matsuzaki, E. Tokunaga, N. Saito, N. Shibata, *Angew. Chem. Int. Ed.* **2016**, *55*, 10781-10785; h) K. Lummer, M. V. Ponomarenko, G.-V. Röschenthaler, M. Bremer, P. Beier, *J. Fluorine Chem.* **2014**, *157*, 79-83.

[17] L. Popek, T. M. Nguyen, N. Blanchard, D. Cahard, V. Bizet, *Tetrahedron* **2022**, *117-118*, 132814.

[18] a) P. Das, K. Niina, T. Hiromura, E. Tokunaga, N. Saito, N. Shibata *Chem. Sci.* **2018**, *9*, 4931-4936; b) K. Maruno, K. Hada, Y. Sumii, O. Nagata, N. Shibata *Org. Lett.* **2022**, *24*, 3755-3759; c) K. Maruno, K. Niina, O. Nagata, N. Shibata Org. Lett. **2022**, *24*, 1722-1726; d) K. Iwaki, K. Tanagawa, S. Mori, K. Maruno, Y. Sumii, O. Nagata, N. Shibata *Org. Lett*. **2022**, *24*, 3347−3352; e) K. Iwaki, K. Maruno, O. Nagata, N. Shibata *J. Org. Chem.* **2022**, *87*, 6302-6311.

[19] a) R. Gauthier, M. Mamone, J.-F. Paquin, *Org. Lett.* **2019**, *21*, 9024-9027; b) M. Cloutier, M. Roudias, J.-F. Paquin, *Org. Lett.* **2019**, *21*, 3866-3870.

[20] During the writing of this article, two preprints about the same topic appeared in ChemRxiv: a) J. O. Wenzel, F. Jester, D. Rombach, *ChemRxiv* **2022**, DOI 10.26434/chemrxiv-2022-brg1w; b) H. Kucher, J. O. Wenzel, D. Rombach, *ChemRxiv* **2022**, DOI 10.26434/chemrxiv-2022-01jhn. This content is a preprint and has not been peer-reviewed.

[21] V. Debrauwer, I. Leito, M. Lõkov, S. Tshepelevitsh, M. Parmentier, N. Blanchard, V. Bizet, *ACS Org. Inorg. Au* **2021**, *1*, 43-50.

[22] X-ray diffraction presented using CYLview20; Legault, C. Y., Université de Sherbrooke, **2020** (http://www.cylview.org)

[23] N. Brach, V. Le Fouler, V. Bizet, M. Lanz, F. Gallou, C. Bailly, P Hoehn, M. Parmentier, N. Blanchard. *Org. Process Res. Dev*. **2020**, *24*, 776-786.

[24] F. W. Hoover, D. D. Coffman, *J. Org. Chem.* **1964**, *29*, 3567-3570.

[27] See supporting information for more experimental and computational details.

[26] a) G. Kleemann, K. Seppelt, *Chem. Ber.* **1979**, *112*, 1140-1146; b) T. Henkel, T. Krügerke, K. Seppelt, *Angew. Chem.* **1990**, *102*, 1171-1172; c) W. R. Dolbier, S. AitMohand,T. D. Schertz, T. A. Sergeeva, J. A. Cradlebaugh, A. Mitani, G. L. Gard, R. W. Winter, J. S. Thrasher, *J. Fluorine Chem.* **2006**, *127*, 1302-1310; d) J. Welch, S. Ngo, D. Lim, WO 2009026191A1, **2009**.

[27] F.-F. Feng, J.-A. Ma, D. Cahard, *J. Org. Chem.* **2021**, 86, 13808–13816.

[28] a) C. Tresse, C. Guissart, S. Schweizer, Y. Bouhoute, A.-C. Chany, M.-L. Goddard, N. Blanchard, G. Evano *Adv. Synth. Catal.* **2014**, *356*, 2051-2060; b) N. Blanchard, S. Schweizer, C. Tresse, P. Bisseret, J. Lalevée, G. Evano *Org. Lett.* **2015**, *17*, 1794-1797; c) C. Tresse, S. Schweizer, P. Bisseret, J. Lalevée, G. Evano, N. Blanchard *Synthesis* **2016**, *48*, 3317-3330; d) C. Guissart, A. Dolbois, C. Tresse, S. Saint-Auret, G. Evano, N. Blanchard *Synlett* **2016**, *27*, 2575-2580.

[29] a) Z. Bo, Z. Ji-Jun, H. Sheng, T. Dong-Huai, L. Jiang-Wei, Z. Wei, L. Jian. *Tetrahedron Lett.* **2020**, 61, 151693; b) M. Patel, R. K. Saunthwal, A. K. Verma. *Acc. Chem. Res*. **2017**, 50, 240–254.

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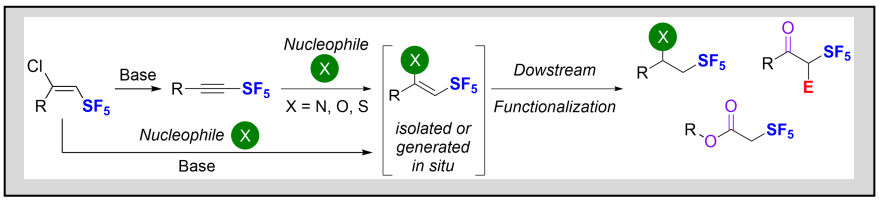

Herein, fully regio- and stereoselective hydroamination, hydroetherification and hydrothioetherification reactions of SF_5-alkynes and further functionalizations of the corresponding *Z*-(hetero)vinyl-SF_5 intermediates towards α-SF_5-ketones, α-SF_5-ester and β-SF_5-amine are described. Experimental and computational comparative studies with CF_3-alkynes are also discussed.

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