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Advanced Synthesis & Catalysis

Mechanochemical Transformation of CF_3 Group: Synthesis of Amides and Schiff Bases

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Abstract: We communicate two mild, solvent-free mechanochemical coupling transformations of CF_3 group with nitro compounds into amides or Schiff bases employing Ytterbia as a catalyst. This process proceeds via C–F bond activation, accompanied with utilisation of Si-based reductants/oxygen scavengers – reductants of the nitro group. The scope and limitations of the disclosed methodologies are thoroughly studied. To the best of our knowledge, this work is the first example of mechanical energy promoted transformation of the inert CF_3 group into other functionalities.

Keywords: Fluorine; Ytterbia; Mechanochemistry; C–F bond activation; Methodology

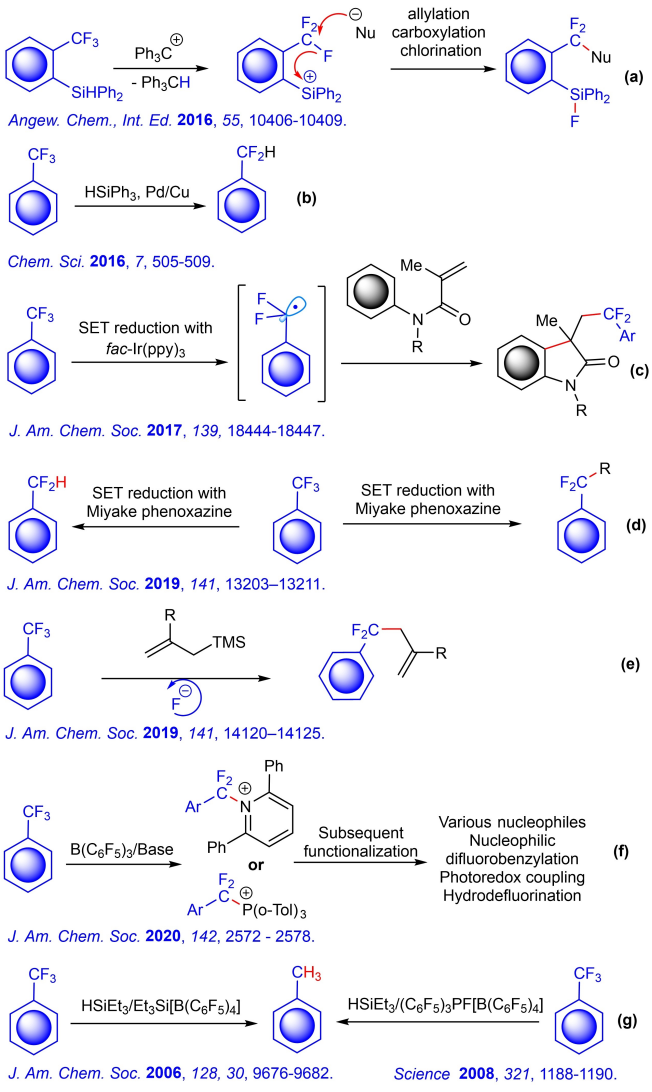
Introduction

The activation of highly stable bonds, in particular C(sp^3)–F bond,[1] still constitutes one of the challenges within the modern organic synthesis domain, which, to the best of our knowledge has never been addressed in the modern literature by employing mechanochemistry means. Of note, highly fluorinated scaffolds are omnipresent in complex organic molecules, organic materials, and pharmaceuticals due to their chemical, thermal and metabolic stability. Furthermore, fluorination is a desired structural feature that could modify chemical and physical properties, improve metabolism and sustainability of organic compounds upon exposure to external irradiation, thermal action and action of the cell media, both in vitro and in vivo.[2]

It is obvious, that a selective functionalisation of at least one fluorine atom of the polyfluoroalkyl group by substitution versus a new structural moiety would represent an interesting concept to verify the diversity of the polyfluoroalkyl-containing chemical space. The synthetic tactics that enable an effective introduction complex polyfluoroalkyl substituents has quite advanced nowadays.[2] In a view of this, the set of challenges are arising, namely the possibility to impose chemical transformations on the polyfluorinated moieties in order to achieve selective functionalisation of a particular C(sp^3)–F bond.[1] Synthetic chemistry community faces numerous challenges in this field which are related to the high stability and low reactivity of the polyfluorinated functional substituents and lack of

practical methodologies allowing the selective derivatisation.

Recent breakthroughs in the field made by Hosoya,[3] Lalic,[4a] König,[5] Jui,[6] Bandar,[7] Young,[8] Houk and Wang[9] as well as others[10,11] indicated that the CF_3 group, that previously considered to be chemically inert, can be swiftly transformed under relatively soft reaction conditions into several important functional groups (Scheme 1). Namely. Hosoya in 2016 succeeded to activate a single C–F bond in ortho-hydrosilyl-trifluoromethylarenes by using the trityl cation as a mean capable for the extraction of hydride ion from the silane moiety, therefor formed silicon-centred cation undergoes fluoride migration to deliver the difluoromethyl cation.[3] This specious is in turn being attacked by an appropriate external nucleophile giving rise to a corresponding derivatisation product.



Scheme 1. Reported mono-defluroantion/functionalization of CF_3 moiety.

As a quintessential, mono functionalisation of the CF_3 group by allylation, carboxylation, and chlorination were performed (Scheme 1a).[3] Lalic in his seminal work of 2016 focused on the selective reduction of the $ArCF_3$ to $ArCHF_2$, these studies revealed that the combination of palladium and copper catalysts enable mono-hydrodefluorination of various aromatic CF_3 substrates (Scheme 1b).[4a] Later, Stephan achieved mono-hydrodefluorination of $PhCF_3$, $PhCF_2H$ and Ph_2CFH by intra- and intermolecular silylium cation/phosphine Lewis pairs.[4a] In 2017, König developed a transformation of readily available $ArCF_3$ substrates into aryldifluoromethyl compounds by the selective mono defluorination employing Iridium visible-light catalysis merged with Lewis acid activation, followed by the subsequent radical induced cyclisation reaction of methacrylamides to form 1,3-dimethyl-2-oxoindolins (Scheme 1c).[5] Furthermore, Jui disclosed the visible-light-induced deflourination of trifluoromethyl arenes using as a photocatalyst the Miyake phenoxazine, that resulted in the development of methods for synthesis of $ArCF_2R$ and $ArCF_2H$ compounds starting directly from CF_3 precursors (Scheme 1d).[6] Next important milestone was established by Bandar, where the fluoride anion was used as a catalyst for C–F bond activation which presumably proceeded via a base-induced single electron transfer pathway, resulting in the coupling between trifluoromethylarenes and allylsilanes to reach the challenging allylated α,α-difluorobenzylic compounds was developed (Scheme 1e).[7] Very recently, Young introduced an original concept where the FLPs[12] were used for the activation of the C(sp^3)–F bond,[13] this transformation resulted in a single fluoride substitution and involves the formation of intermediary phosphonium or pyridinium salts (Scheme 1f).[8] Subsequently, the formed species were subjected to post-functionalisation reactions, among those are nucleophilic substitution, photoredox coupling and electrophilic transfer reactions. In the year 2021 Houk and Wang[9] succeeded in functionalisation of C(sp^3)–F bond on the instance of trifluoroacetamides and acetates utilising the spin-centre shifts concept. This unique process commenced with the activation of a carbonyl oxygen atom by a 4-dimethylaminopyridine-boryl radical, subsequently the spin-centre shift occurred which in turns triggered the C–F bond cleavage. Although theses protocols provide practical tools for CF_3 functionalisation, they suffer from several inherent drawbacks including high-cost catalysts and tedious to access reagents. Besides these pivotal works, which will definitely shape the future developments in this field, there are numerous other contributions that illustrated different aspects of selective and non-selective defluorination of CF_3 group.[10,11]

Several examples should be mentioned here that utilises silicon-containing reagents for the defluorina-

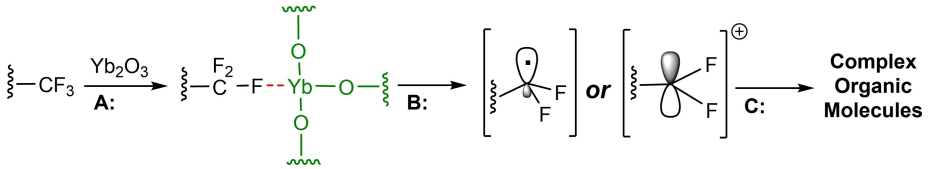
tion of CF_3 group.[11b–e] Ozerov reported room-temperature catalytic hydrodefluorination of Ar-CF_3 substrates utilising the Et_3SiH as the source of proton, which catalysed by $Et_3Si[B(C_6F_5)_4]$ and $HSiEt_3/(C_6F_5)_3PF[B(C_6F_5)_4]$ respectively (Scheme 1g).[11b,c] Authors hypothesized, that the initial step of the mechanism should consist in the abstraction of the fluoride by the Si-cationic species. 1,8-Naphthalenediyl core hydrogen-bridged disilyl cations developed by Müller were prone to cleave an aliphatic C–F bond resulting in the formation of the structure with the fluoride ion jammed between two silicon atoms – the so-called fluoronium species. As it was shown this transformation occurred via two electron-three-centre bond.[11d] Among those one has to admit that these strategies are possessing the high overall costs, involving expensive and hardly available reagents and catalysts, such as FLPs and Iridium-based photocatalysts, etc. Therefore, methodologies useful for the derivatisation of CF_3 group is of high need.

We embarked on the C(sp^3)–F bond activation chemistry having several notions: (1) To utilise the mechanic energy by using mechanochemistry tools for the transformation of CF_3 group by utilising the catalytic activation of the C(sp^3)–F bond with subsequent cleavage and functionalisation; (2) We aimed at developing synthetic means enabling deployment of the chemistry and exploration of the scope of elaborated synthetic protocols. We set the general synthetic scenario (Scheme 2) where we envisioned the activation of the C–F bond following the three reaction sequences: (A) Precoordination of an appropriate activator with good affinity to fluorine atom (we selected Yb_2O_3) of a CF_3 group, followed by the (B) Homolytic or heterolytic cleavage of the C–F bond. (C) The functionalisation of the formed carbon-centred radical or cationic species, that expected to lead to the formation of the altered complex organic molecules. Analysis of organometallic chemistry revealed numerous of metal complexes that possesses high affinity to C(sp^3)–F bonds and are capable to cleave it under particular reaction conditions.[14] Among those, trivalent lanthanides stand out by possessing a high affinity to fluorine and form strong bonds to fluorides, along with a capacity to cleave activated and nonactivated C–F bonds of organic compounds.[15] Of note, the Lewis acidity of lanthanides increases from left to right in the periodic table, whereby the oxophilicity decreases.[16] Therefore, following this pattern we understood that these features make ytterbium compounds[17] – optimal candidates for the development of the catalytic systems for activation of the aliphatic C–F bonds. We envisioned the use of Ytterbia (Yb_2O_3) as a possible agent for the polarisation of a C–F bond of the CF_3 group and hence make the CF_3 group susceptible to further synthetic derivatisation, in particular by coupling with external nucleophiles like amines. Very recently, Yoshida communicated a concept used for the diaryl ketones synthesis through C–F bound cleavage of trifluoromethyl group by utilising BBr_3 as Lewis acid, which consisted in acylation of electron-excessive aromatic compounds by benzotrifluorides.[18]

In view of the above, herein we are communicating two mechanochemistry-based mild strategies for straightforward transformation of diverse CF_3-contaning substrates into amides and Schiff bases by Yb_2O_3-promoted C–F bond activation by using silicon containing reagents such as elementary silicon and hexamethyldisilane respectively as reductants and electron donors. It appeared that the activation of CF_3 group can be achieved in the presence of excess of Yb_2O_3 under the solvent-free mechano-milling conditions at 30 Hz, followed by the subsequent coupling with appropriate amines or nitro compounds leveraging the corresponding amides or imines (Schemes 2 and 3).

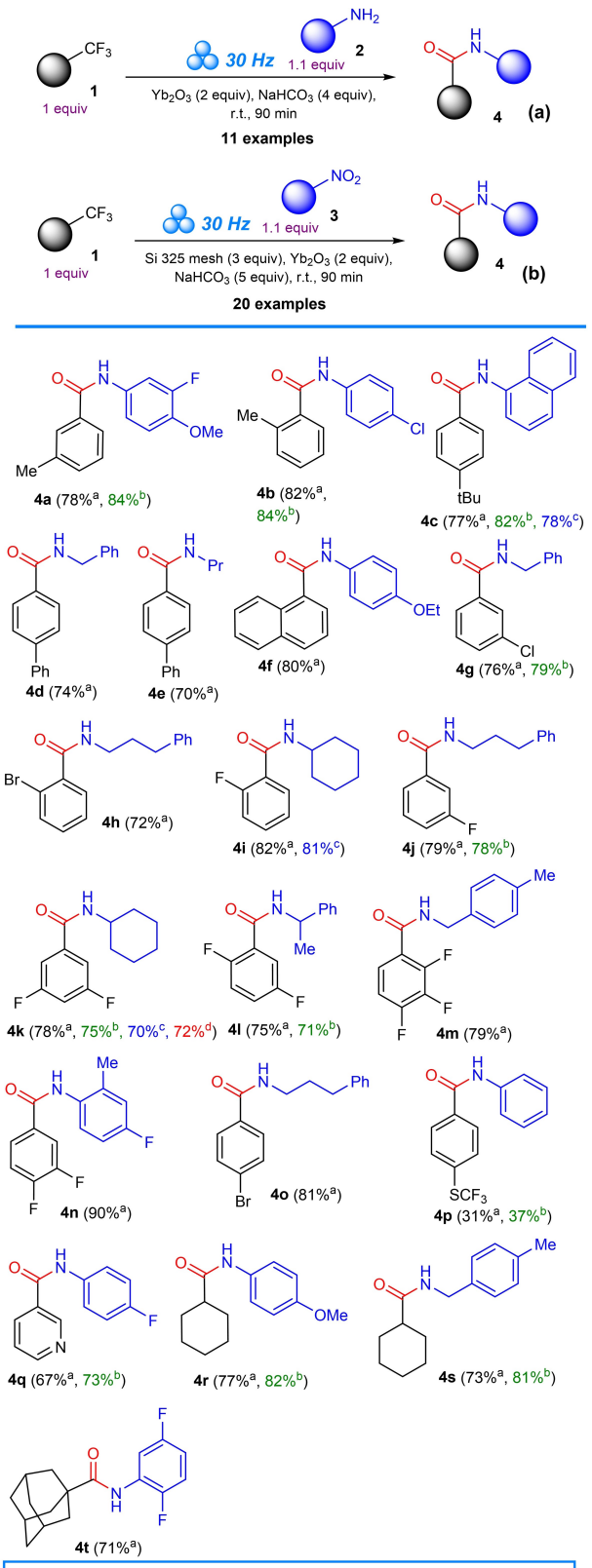
Results and Discussion

Our starting point was the identification of the appropriate reaction conditions for the synthetic scenario mentioned here (Tables S1–S3). Initially we started off by investigating the solvent-free mechano-milling conditions for the previously appointed synthetic scenario, given the example of the model reaction between the 1,3-difluoro-5-(trifluoromethyl) benzene and the cyclohexanamine utilizing Yb_2O_3 (Table S1). We expected that the transition-metals can facilitate the electron transfer, in particular from the



A: Adsorption/Polarisation of C-F bond
B: Cleavage of the C-F bond
C: Follow-up functionalisation

Scheme 2. Synthetic scenario.



Scheme 3. Product scope of amides.

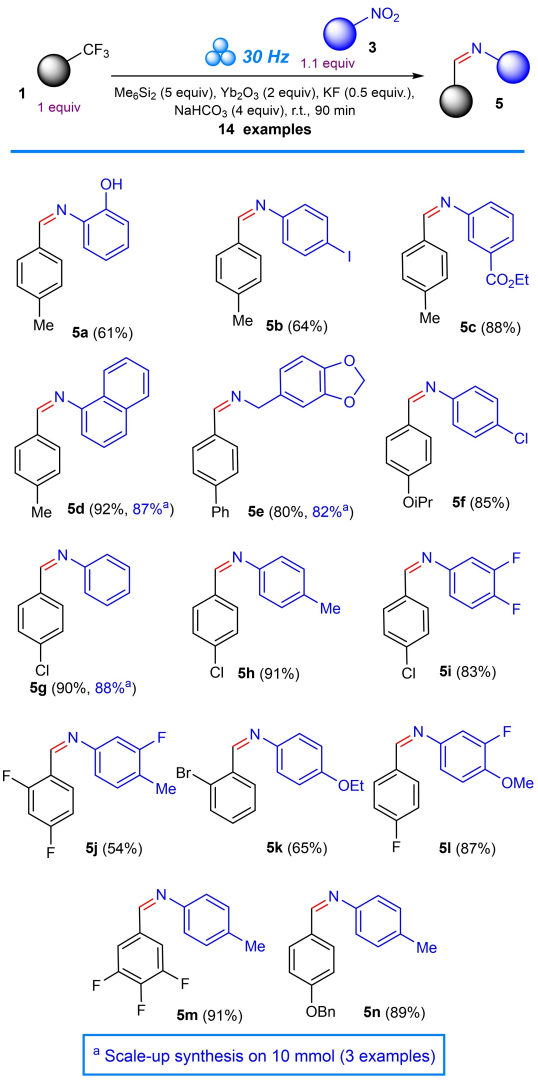
amine onto the CF_3 substrate. We tested several transition-metal catalysts, among those copper, iridium, rhodium, ruthenium, nickel and palladium containing ones. Unexpectedly, these metal complexes did not promote but hampered the reaction. Finally, the defluorination with subsequent formation of amide, as a result of the coupling with amine, proceeded smoothly by utilising the 1.1 equiv. of the corresponding amine, with Yb_2O_3 (2 equiv.) as an additive and $NaHCO_3$ (4 equiv.) as a base, by using molecular mill with the working frequency of 30 Hz, at room temperature. In general, the reaction in all cases reached its completion within 1.5 hours (90 minutes), enabling the preparation of the model compound **4k** in 75% yield (Table S1, Entry 12).

Thus, we succeeded in the synthesis of eleven amide compounds. Of note, most of the industrial amines are being prepared from the parental nitro compounds, majority of which are commercially available, low-priced compounds; thus further, we considered the utilisation of the nitro precursors instead of amines (Scheme 2b). Very recently, in 2017 and 2018 respectively, we reported the utilisation of hexamethyldisilane and silicon powder of 325 mesh in combination with an appropriate base and additives for the reductive transformation of a different range of organic compounds. Commencing this study, we took advantages of our previous developments[19] and made a step towards the application of this chemistry for the coupling of CF_3 group with amines and nitro compounds aiming the synthesis of amides and Schiff bases.

This notion indeed was successful and immediately resulted in the preparation of the first amide representative **4k** in 78% yield by addition of 3 equiv. of silicon powder of 325 mesh to the reaction cocktail. Further, we extended the scope of this protocol by twenty amide derivatives. In particular, we promoted those methods where amines and nitro compounds were utilised. Reflecting on the CF_3 components, both alkyl and aryl derivatives (including 3-pyridyl moiety) showcased good efficiency; numerous functional groups on the phenyl core, among those alkyls, phenyl, OAlk, as well as halogens including fluorine, were highly tolerable to this synthetic protocol. Of note, SCF_3 group on the nitro substrate stayed intact during the reaction, here however we observed substantial decrease of the yield (amide **4p**). The aromatic nitro substrates bearing CF_3, CF_2H, OCF_3 and OCF_2H substituents experienced a failure within both synthetic protocols. On the other hand, diverse alkyl and aryl nitro derivatives reacted swiftly under these reaction conditions.

Next, we focused on the elaboration of the synthesis of imines by the coupling reaction between the aliphatic and aromatic CF_3 substrates with amines and nitro compounds by utilising the hexamethyldisilane as

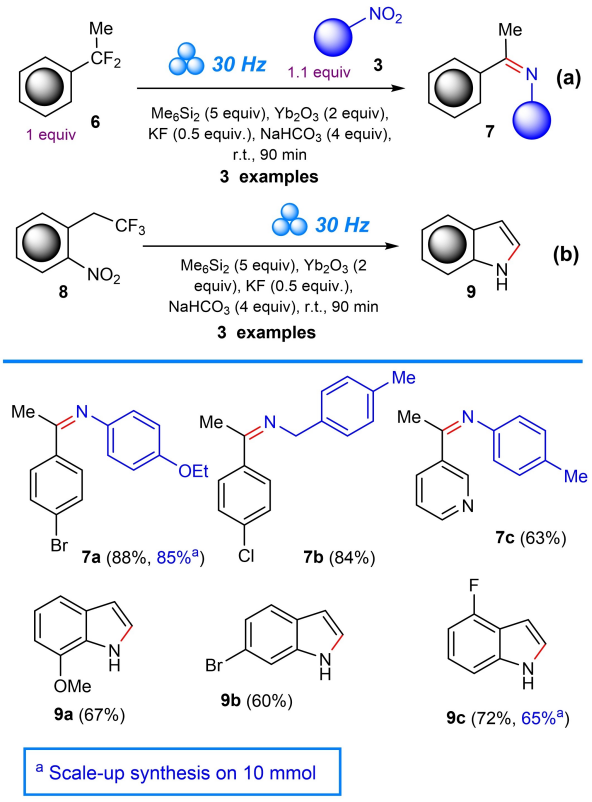
an oxygen scavenger under mechanochemical conditions (Scheme 4). It is noteworthy, that an optimised model rection between 1-chloro-4-(trifluoromethyl) benzene and 1-nitronbenzene delivered the corresponding imine **5g** in 90% yield by using hexamethyldisilane (5 equiv.), KF (0.5 equiv.), Yb_2O_3 (2 equiv.), $NaHCO_3$ (4 equiv.), using standard mechanochemical parameters (MM with the milling frequency of 30 Hz). The duration of the reaction never exceeded 1.5 hours at room temperature (Table S3). To our great delight the diverse set of nitro compounds was reactive within this synthetic protocol. This resulted in the library of fourteen imine derivatives which was successfully prepared. It is important to admit that the high efficiency of this synthetic methodology enabled the preparation of the final products. Both aliphatic and aromatic substrates were prone to react, making no difference in overall yields.



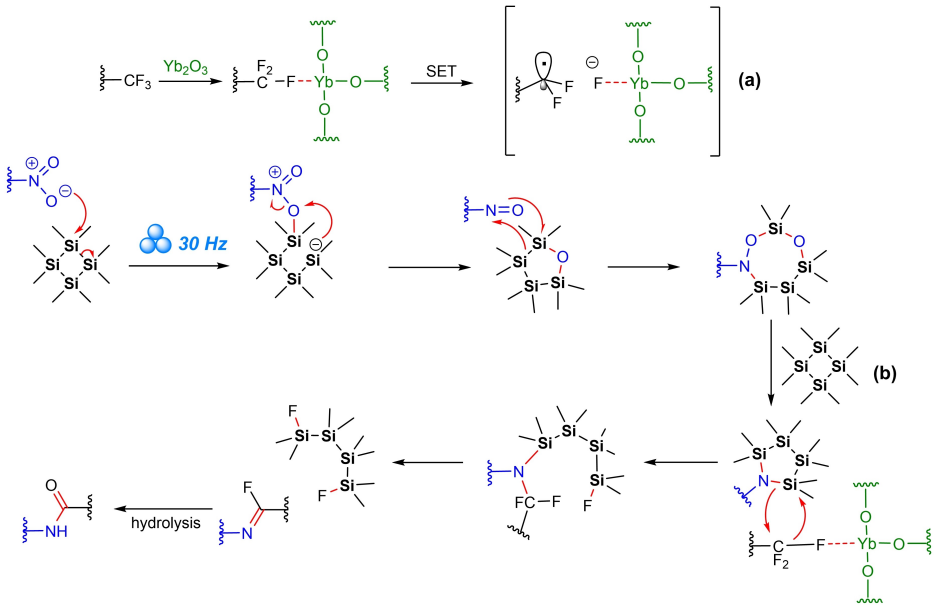
Scheme 4. Product scope of imines.

Difluoromethylene activation is also of interest and recently was reported by several research groups.[20] Furthermore, the methodology developed by us was also efficient in terms of the transformation of 1,1-difluoroethyl-benzenes **6** to corresponding N-substituted 1-arylethan-1-imines **7**, as well as for the assembly of NH-indoles **9** by intramolecular cyclisation of the 1-nitro-2-(2,2,2-trifluoroethyl)arenes **8** (Scheme 5). To further demonstrate the synthetic utility of these protocols the gram-scale reactions were performed by using 10 mmol, which successfully yielded the corresponding amides, imine and indoles with negligible discrepancy in yields (Schemes 3–5).

Next, we formulated the reaction mechanisms which due to their complexity are rather speculative. The reaction mechanism of the silicon-promoted amide synthesis starting from nitro compounds is depicted in the Scheme 6. As we hypothesised, the reaction sequence starts by the SET onto the polarized C–F bond (Scheme 6a), the formed intermediate we believe to enter the reaction, which is illustrated by the example of Si_4 unit and most probably commences with an attack of a lone electron pair of the oxygen of the nitro group onto the empty *d*-orbital of silicon; this leads to the cleavage of the Si–Si bond. The subsequent abstraction of the oxygen atom delivers the nitroso intermediate compound and leads correspond-



Scheme 5. Product scope of imines and indoles.



Scheme 6. Proposed mechanism of amide synthesis via silicon-initiated C–F activation.

ently to the insertion of this very oxygen between two silicon atoms (Scheme 6b). Of note, vide infra, in order to prove the existence of the nitroso intermediate, we reacted 1-nitrosonaphthalene with 1-(tert-butyl)-4-(trifluoromethyl)benzene under the standard reaction conditions which delivers the corresponding amide **4c** in 80% yield (Scheme 8a). As a next step, the intermediary nitroso compound undergoes the insertion into the oxatetrasilolane core to form the dioxazatetrasilepane scaffold, which finally, transforms into azatetrasilolidine scaffold. The latest intermediate in turn interacts with the preformed -CF_2-F/Yb_2O_3 species and through the C–F bond cleavage the corresponding imidoyl fluoride, that after hydrolysis transforms into the final amide. This step, we believe occurs via an electron transfer from Si^0 onto the CF_3 group. The used silicon ends up as SiO_2. Since the reaction does not take place in the absence of Yb_2O_3, we believe that this additive plays a pivotal role that can be described as the polarisation/activation of the C–F bond (Tables S1, S2).

In order to find support to the postulated mechanism we performed calculations of the reaction profile for amide synthesis through C–F bond activation, following the purpose to gain an idea about the associated kinetic barriers and thermodynamics of different steps involved. As it is depicted in the Figure 1, the reaction starts with complex formation between Si_4 unit and nitrobenzene held together through van der Waals interactions. This **vdW** complex is thermodynamically stable by 3.5 kcal mol^{-1} from the isolated reactants. Next, Si_4 unit abstracts oxygen of nitrobenzene to deliver nitrosobenzene and expands into oxatetrasilolane framework. A transition state for this reaction is located at the barrier of 34.5 kcal mol^{-1} from the van der Waals complex (**vdW1**). The oxygen atom interacts with two silicon atoms of Si_4 unit, although both interaction distances are different. The corresponding O–Si interaction distances are 1.97 and 2.73 Å, while in **vdW1** complex, interaction distances are 3.95 and 4.18 Å. The transition state is early in nature, as expected from Hammond postulate for highly exothermic reaction.[21] The abstraction of oxygen by Si_4 unit is thermodynamically a highly favourable reaction. The product of this step (**Int1**) is stable by 71.5 kcal mol^{-1} from the **vdW1** complex. The high thermodynamic stability of the product stems from two stable Si–O bonds. Before entering into the next step, the title intermediate (**Int1**) reorients itself to **Int2** which is well suited for cycloaddition of nitrosobenzene with the oxatetrasilolane unit. This reorientation is thermodynamically favourable by 5.6 kcal mol^{-1}. In **Int1**, the N–O motif of nitroso group interacts with oxygen of cycloxotetrasilane unit, whereas in **Int2**, the N–O motif interacts with Si–Si fragment of this very unit. The cycloaddition step of nitrosobenzene has kinetic demand of 34.5 kcal mol^{-1}. In the transition state (**TS_2**), the N=O group makes a four membered cyclic structure with two silicon atoms, the oxatetrasilolane core. The N–Si and O–Si bond distances are 2.32 and 2.02 Å, respectively. The cycloaddition type reaction is thermodynamically a highly favourable process ($E_R = -61.3$ kcal mol^{-1}). The seven membered dioxazatetrasilepane structure (**Int3**) reorients itself into another structure (**Int4**) before undergoing elimination of nitrene. The nitrene produced here can insert itself into another Si_4 unit. The activation barrier for nitrene elimination from **Int4** is

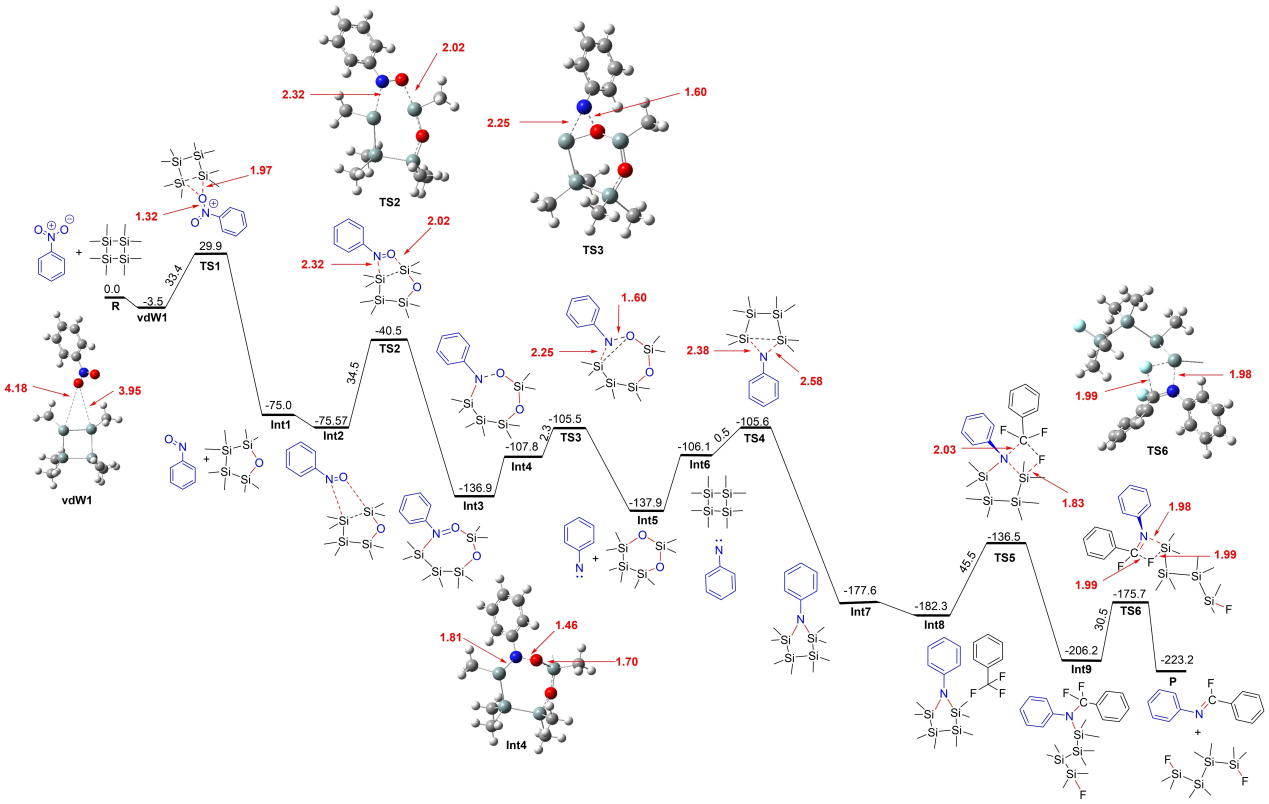
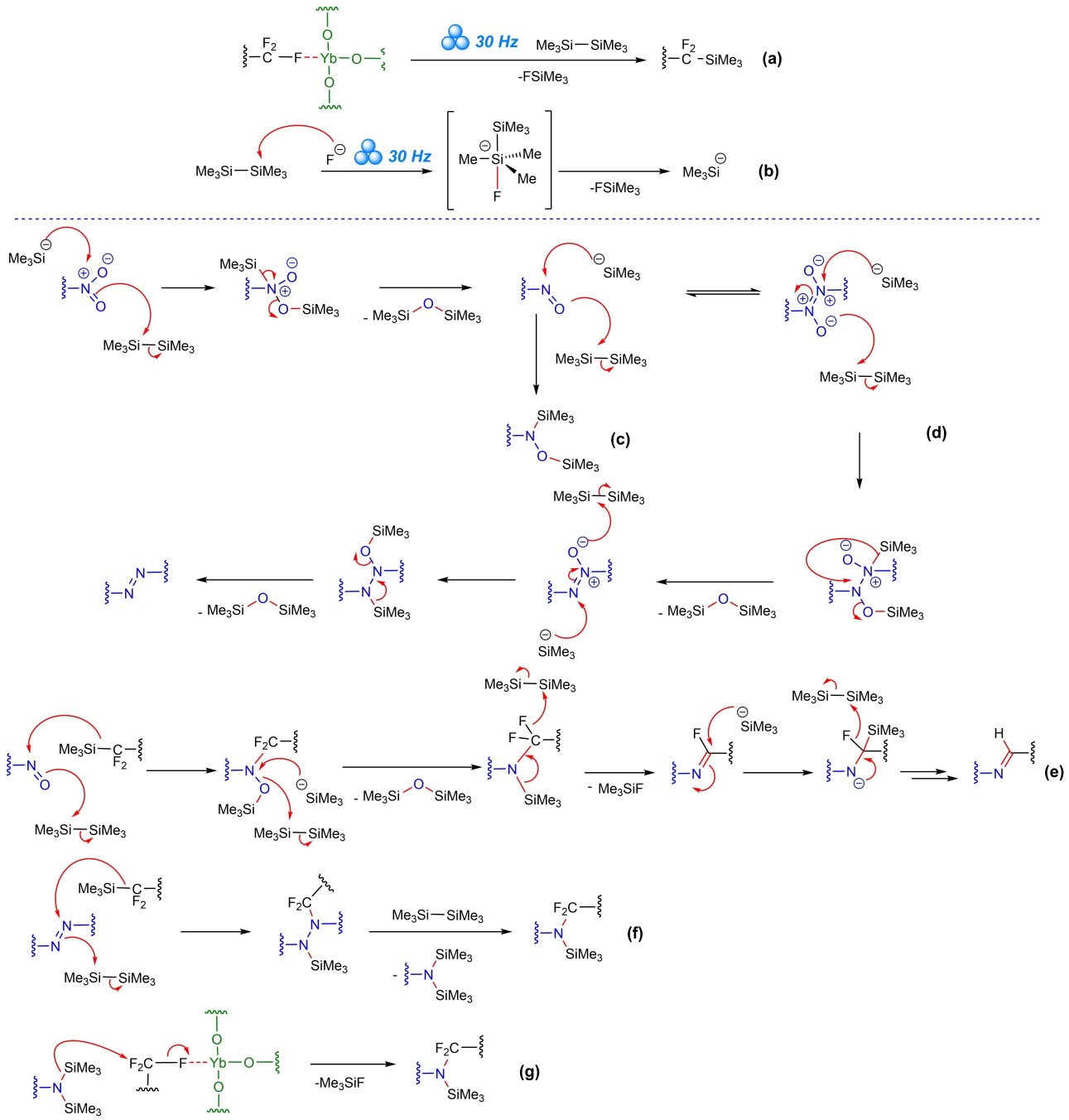


Figure 1. Energy profile diagram for the formation of amide from nitrobenzene on silica. All energies are in kcal mol^{-1} from isolated reactants at 0 kcal mol^{-1} reference. The barriers were calculated for 298 K. All bond lengths are in Angstroms (Å).

quite low (2.3 kcal mol^{-1}) with the transition state is quite early in nature. The N–Si and N–O bond distances in **TS$_3$** are 2.25 and 1.60 Å, respectively. The product of this step (**Int5**) is about 30.1 kcal mol^{-1} more stable than the reactants (**Int4**). The nitrene insertion in Si_4 unit is again a process with very little kinetic demand (only 0.5 kcal mol^{-1}). The distances of N–Si bond in **TS$_4$** are 2.38 and 2.58 Å, respectively. It is noteworthy that the mechanistic pathway explored here is continuously downhill where each step is producing much energy. Heterolytic cleavage of C–F bond of the model trifluorobenzene on Si_4 unit is achieved via a four-membered transition state which is located at a barrier of 45.5 kcal mol^{-1} from **Int8**. The N–C and Si–F bond distances are 2.03 and 1.83 Å, respectively. The reaction is driven mainly through the stable Si–F bond which has much shorter bond length (in **TS$_5$**) than N–C bond length. The products are stable by 23.9 kcal mol^{-1} than the reactant for this step (**Int8**). In the last step of this mechanism, linear N-silane moiety in **Int9** abstracts a fluorine atom from the adjacent carbon atom to deliver fluoroimine species which in turn can be hydrolysed to produce the final amide under the reaction conditions. The energy of activation and energy of reaction for this step are 30.5 and +12 kcal mol^{-1}, respectively. The last step is the only one which is endothermic in nature. The kinetic and thermodynamic analysis of the steps shown clearly illustrate that the mechanism is a viable one because all barriers are accessible under the reaction conditions.

The mechanism of the imine synthesis through the C–F bond activation is illustrated in the Scheme 7. This mechanism has visible similarities with the one of nitroarenes reduction by hexamethyldisilane recently proposed by us.[19] It is obvious that the titled transformation is rather a complex process and encompasses several sub-reactions. The first step, most probably, would be the Ytterbia-promoted mechanochemical transformation of the corresponding CF_3 substrate to the (difluoromethyl)trimethylsilane derivative (Scheme 7a) and the reaction of the hexamethyldisilane with fluoride anion to deliver the trimethylsilane anion, which most probably acts as an electron donor (Scheme 7b). It is obvious that this transfer occurs by the coordination of the fluoride onto the Me_3Si group via the formation of the corresponding intermediate with penta-coordinated silicon atom (Scheme 7b).[22]

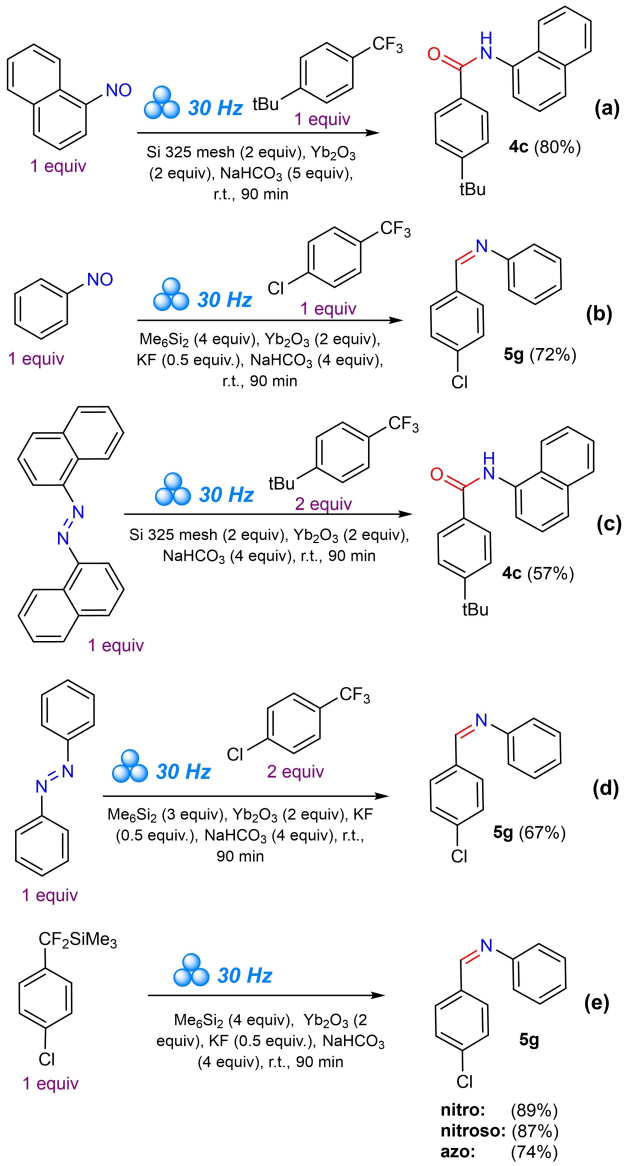
Simultaneously, as it is depicted in the Schemes 7c and d the nitro counterpart is being reduced step-wise by hexamethyldisilane. This path encompasses eight main steps and involves formation of three key intermediates – nitroso compound, azo compound and



Scheme 7. Mechanism of imine synthesis via C–F activation using hexamethyldisilane.

N-(trimethylsilyl)silanamine; where in turn each would react further with the CF_3 substrate delivering the final imine product (Schemes 7e–g). The presence of KF is indispensable, its absence visibly reduces the reaction rate of the reactions and the overall yields.

To probe the suggested reaction mechanisms for our synthetic protocols, several reactions involving the expected intermediates were performed (Scheme 8). First, we focused on reacting nitroso compounds under the optimised reaction conditions (Schemes 8a, b). Namely, 1-nitrosonaphthalene and nitrosobenzene successfully was coupled with 1-(tert-butyl)-4-(trifluoromethyl)benzene and 1-chloro-4-(trifluoromethyl)benzene, resulting in the isolation of corresponding amide **4c** and imine **5g**. In turn, the same result was obtained by reacting 1,2-di-(naphthalen-1-yl)diazene and azobenzene with 1-(tert-butyl)-4-(trifluoromethyl)benzene and 1-chloro-4-(trifluoromethyl)benzene (Schemes 8c, d). Unusual from the synthetic point of view is the silylation-



Scheme 8. Control experiments to probe reaction mechanism.

defluorination reaction that ends in the formation of (difluoromethyl)trimethylsilane, which we postulated as the first intermediate within the presented mechanism (Scheme 7a). The reaction of ((4-chlorophenyl) difluoromethyl)trimethylsilane with nitrobenzene, nitrosobenzene and azobenzene under the standard reaction condition resulted in the formation of the expected imine **5g** in 89%, 87%, 74% yields respectively (Scheme 8e).

Noteworthy, when we run the reduction of nitro compounds under our standard reaction conditions, we encountered the situation when the silicon powder of 325 mesh was prone to reduce swiftly the nitro substrates leveraging the corresponding amines in 72–94% yields (Scheme 9a). The hexamethyldisilane-based protocol also delivered the amines however in relatively low yields (41–55%); of note this reaction needed protracted exposition (160 minutes) to mechano-milling conditions (Scheme 9b). These results are in a good agreement with our recent works[19] published in 2018 and 2017 respectively, where we observed similar behavior of nitro and nitroso compounds under the hydrolytic condition. The formation of possible products like nitroso and azo compounds etc. was not observed. In contrary, when we set 1-nitrosonaphthalene and 1,2-di(naphthalen-1-yl)diazene respectively under investigation within the reaction conditions of both protocols, we detected formation of the corresponding amines (Schemes 9c–f). Admittedly, the reductions by silicon powder of 325 mesh proceeds smoothly and was accomplished withing 60 minutes and the final amine was isolated in 90% and 93% yield. The efficiency of hexamethyldisilane as a reducing agent is inferior, since the reactions to its completion took 150 minutes and the amine was produced in 55% and 50% yield.

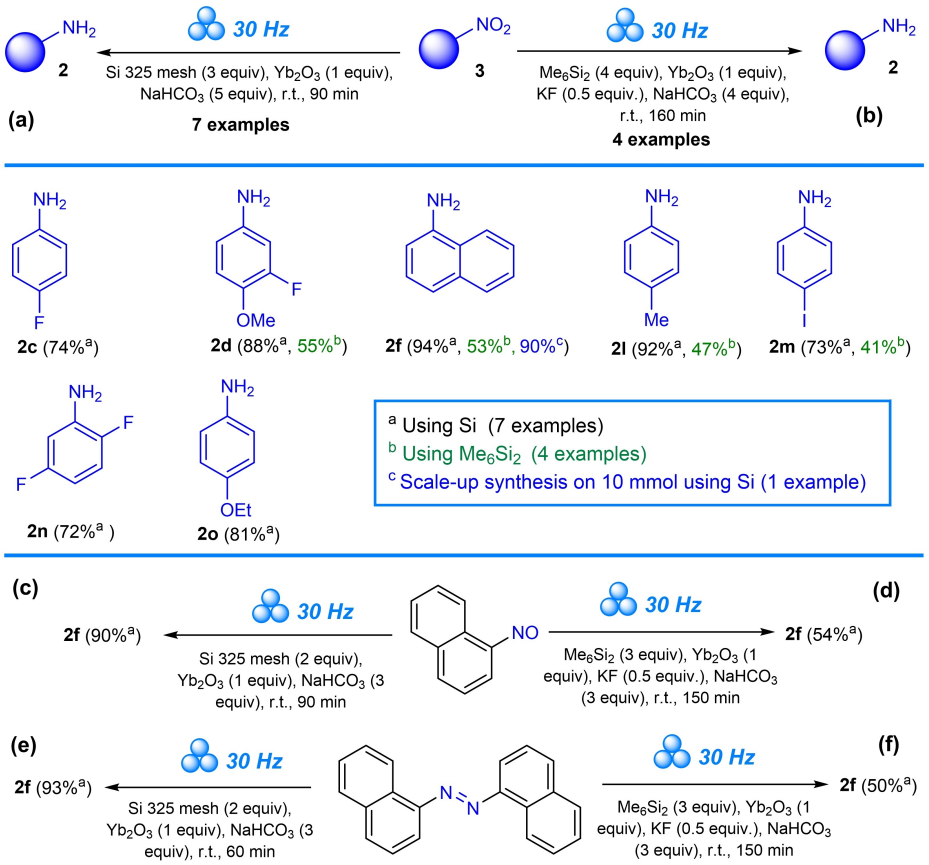
These observations gave some additional insights into the reaction mechanism of the both C–F activation synthetic protocols. Namely. (1) The synthesis of the amides can follow two different pathways, by reaction starting from amines and by the one from nitro compounds. (2) These two pathways may also occur simultaneously. (3) Regarding the imine formation, the nitro compounds can be reduced to amines by hexamethyldisilane with low rate, and the amines does not enter this protocol; thus, the imine formation reaction follows only one pathway starting from the nitro compounds.

Conclusion

In conclusion, we should note that within this study we succeeded in laying the foundation of mechanochemistry-based methods - the activation of the three C–F bonds of CF_3 group by using Yt_2O_3 under the mild, solvent-free mechano-milling conditions. This methodology resulted in the development tactics towards amides and Schiff bases. The scope and limitation of the methods presented here were studied in details. The further efforts of our laboratory will be directed onto the utilisation of this concept for the preparation of other classes of organic compounds, in particular we believe that this tactic will be applicable towards the synthesis of phosphazo compounds, λ^4-sulfanimines, λ^6-sulfanone, phosphor and sulphur ylides, as well as for the formation of C–C single, double and triple bonds, etc.

Experimental Section

General: Commercially available starting materials, reagents, catalysts, anhydrous and degassed solvents were used without further purification. Flash column chromatography was per-



Scheme 9. Product scope of amines.

formed with Merck Silica gel 60 (230–400 mesh). The solvents for column chromatography were distilled before the use. Thin layer chromatography was carried out by using Merck TLC Silica gel 60 F_{254} and visualised by short-wavelength ultraviolet light or by treatment with potassium permanganate ($KMnO_4$) stain. ^1H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker 250, 400 and 500 MHz at 20 °C. All ^1H NMR spectra are reported in parts per million (ppm) downfield of TMS and were measured relative to the signals for $CHCl_3$ (7.26 ppm) and DMSO (2.50 ppm). All $^{13}C\{^1H\}$ NMR spectra were reported in ppm relative to residual $CHCl_3$ (77.00 ppm) or DMSO (39.70 ppm) and were obtained with ^1H decoupling. Coupling constants, *J*, are reported in Hertz (Hz). Gas chromatographic analyses was performed on Gas Chromatograph Mass Spectrometer GCMS-QP2010 Ultra instrument. Mechanochemical synthesis was performed by using the Retsch MM400 mill and using the standard kit. Liquid chemicals were dosed through gas tight micro syringes. Isolation of obtained compounds was achieved by column chromatography on Silica gel. Non-commercially available CF_3,[23] CF_2,[24] and NO_2[25] substrates were prepared according to the known literature. All commercially available compounds were purchased from appropriate vendors.

Computational methodology: Gaussian 09 package is used for simulations of the mechanistic part of the current study. Geometry optimisation of ground state and transition is carried out at B3LYP/6-31g(d,p) level of theory.[26] B3LYP functional is cost effective and not only for mechanistic studies, but also for the geometry optimisation of natural and synthetic compounds including polymers.[27] True minima are confirmed through absence of imaginary frequency whereas transition states are confirmed through one imaginary frequency in normal mode analysis. Moreover, eigen vector of the imaginary frequency are analysed to confirm that these correspond to motion along reaction coordinates.[28] All energy values reported in this study are electronic energies at 0 K.

General procedure for the synthesis of amines 2 by the reduction of NO_2 substrates 3 using elemental Si: In air, to 5 mL grinding vessel (made of stainless) equipped with three balls (made of stainless, diameter: 5 mm) was placed consequently Si 325 mesh (99 mg, 3.0 mmol, 3 equiv.), Yb_2O_3 (394 mg, 1.0 mmol, 1 equiv.), $NaHCO_3$ (420 mg, 5 mmol, 5 equiv.); then the appropriate NO_2 substrate (1.0 mmol, 1.0 equiv.) was added and the reaction vessel was properly capped. Finally, the reaction vessel was installed on the mill and subjected to milling at 30 Hz for 90 minutes. After completion of the reaction, the content of the vessel was generously treated with distilled water and dichloromethane, filtrated and the organic layer was separated. The water layer was extracted two times with dichloromethane and the combined organic layer was washed consequently with brine and distilled water. Finally, the dichloromethane solution was properly dried and concentrated in vacuum. The resulted crude

was directly subjected to gradient flash chromatography on silica gel to isolate the desired amine derivative.

The gram scale synthesis was performed on 10 mmol of the starting nitro substrate in a 25 mL grinding vessel by using three 10 mm balls.

General procedure for the synthesis of amines 2 by reducing NO_2 substrates 3 using Me_6Si_2: In air, to 5 mL grinding vessel (made of stainless) equipped with three balls (made of stainless, diameter: 5 mm) was placed consequently Me_6Si_2 (584 mg, 4.0 mmol, 4 equiv.), Yb_2O_3 (394 mg, 1.0 mmol, 1.0 equiv.), KF (29 mg, 0.5 mmol, 0.5 equiv.), $NaHCO_3$ (336 mg, 4 mmol, 4 equiv.); then the appropriate NO_2 substrate (1.0 mmol, 1.0 equiv.) was added and the reaction vessel was properly capped. Finally, the reaction vessel was installed on the mill and subjected to milling at 30 Hz for 160 minutes. After completion of the reaction, the content of the vessel was generously treated with distilled water and dichloromethane, filtrated and the organic layer was separated. The water layer was extracted twice with dichloromethane and the combined organic layer was washed consequently with brine and distilled water. Finally, the dichloromethane solution was properly dried and concentrated in vacuum. The resulted crude was directly subjected to gradient flash chromatography on silica gel to isolate the desired amine derivative.

General procedure for the synthesis of amides 4 by the reaction of CF_3 substrates 1 with amines 2: In air, to 5 mL grinding vessel (made of stainless) equipped with three balls (made of stainless, diameter: 5 mm) was placed consequently an appropriate CF_3 substrate (1.0 mmol, 1.0 equiv.), Yb_2O_3 (788 mg, 2.0 mmol, 2.0 equiv.), $NaHCO_3$ (336 mg, 4 mmol, 4 equiv.); then the appropriate amine (1.1 mmol, 1.1 equiv.) was added and the reaction vessel was properly capped. Finally, the reaction vessel was installed on the mill and subjected to milling at 30 Hz for 90 minutes. After completion of the reaction, the content of the vessel was generously treated with distilled water, filtrated and finally properly dried in vacuum. The resulted crude was directly subjected to gradient flash chromatography on silica gel to isolate the desired amide derivative.

The gram scale synthesis was performed on 10 mmol of the starting amine in a 25 mL grinding vessel by using three 10 mm balls.

General procedure for the synthesis of amides 4 by the reaction of CF_3 substrates 1 with NO_2 substrates 3: In air, to 5 mL grinding vessel (made of stainless) equipped with three balls (made of stainless, diameter: 5 mm) was placed consequently an appropriate CF_3 substrate (1.0 mmol, 1.0 equiv.), Si 325 mesh (99 mg, 3.0 mmol, 3 equiv.), Yb_2O_3 (788 mg, 2.0 mmol, 2.0 equiv.), $NaHCO_3$ (420 mg, 5 mmol, 5 equiv.); then the appropriate NO_2 substrate (1.1 mmol, 1.1 equiv.) was added and the reaction vessel was properly capped. Finally, the reaction vessel was installed on the mill and subjected to milling at 30 Hz for 90 minutes. After completion of the reaction, the content of the vessel was generously treated with distilled water, filtrated and finally properly dried in vacuum. The resulted crude was directly subjected to gradient flash chromatography on silica gel to isolate the desired amide derivative.

The gram scale synthesis was performed on 10 mmol of the starting amine in a 25 mL grinding vessel by using three 10 mm balls.

General procedure for the synthesis of imines 5 by the reaction of CF_3 substrates 1 with NO_2 substrates 3: In air, to 5 mL grinding vessel (made of stainless) equipped with three balls (made of stainless, diameter: 5 mm) was placed consequently an appropriate CF_3 substrate (1.0 mmol, 1.0 equiv.), Me_6Si_2 (731 mg, 5.0 mmol, 5 equiv.), Yb_2O_3 (788 mg, 2.0 mmol, 2.0 equiv.), KF (29 mg, 0.5 mmol, 0.5 equiv.), $NaHCO_3$ (336 mg, 4 mmol, 4 equiv.); then the appropriate NO_2 substrate (1.1 mmol, 1.1 equiv.) was added and the reaction vessel was properly capped. Finally, the reaction vessel was installed on the mill and subjected to milling at 30 Hz for 90 minutes. After completion of the reaction, the content of the vessel was generously treated with distilled water, filtrated and finally properly dried in vacuum. The resulted crude was directly subjected to gradient flash chromatography on silica gel to isolate the desired amide derivative.

The gram scale synthesis was performed on 10 mmol of the starting amine in a 25 mL grinding vessel by using three 10 mm balls.

General procedure for the synthesis of imines 7 by the reaction of CF_2 substrates 6 with NO_2 substrates 3: In air, to 5 mL grinding vessel (made of stainless) equipped with three balls (made of stainless, diameter: 5 mm) was placed consequently an appropriate CF_3 substrate (1.0 mmol, 1.0 equiv.), Me_6Si_2 (731 mg, 5.0 mmol, 5 equiv.), Yb_2O_3 (788 mg, 2.0 mmol, 2.0 equiv.), KF (29 mg, 0.5 mmol, 0.5 equiv.), $NaHCO_3$ (252 mg, 3 mmol, 3 equiv.); then the appropriate NO_2 substrate (1.1 mmol, 1.1 equiv.) was added and the reaction vessel was properly capped. Finally, the reaction vessel was installed on the mill and subjected to milling at 30 Hz for 90 minutes. After completion of the reaction, the content of the vessel was generously treated with distilled water, filtrated and finally properly dried in vacuum. The resulted crude was directly subjected to gradient flash chromatography on silica gel to isolate the desired amide derivative.

The gram scale synthesis was performed on 10 mmol of the starting amine in 25 mL grinding vessel by using three 10 mm balls.

General procedure for the synthesis of indoles 9 by the cyclisation reaction of compounds 8: In air, to 5 mL grinding vessel (made of stainless) equipped with three balls (made of stainless, diameter: 5 mm) was placed consequently an appropriate compound **8** (1.0 mmol, 1.0 equiv.), Me_6Si_2 (731 mg, 5.0 mmol, 5 equiv.), Yb_2O_3 (788 mg, 2.0 mmol, 2.0 equiv.), KF (29 mg, 0.5 mmol, 0.5 equiv.), $NaHCO_3$ (336 mg, 4 mmol, 4 equiv.); then the reaction vessel was properly capped. Finally, the reaction vessel was installed on the mill and subjected to milling at 30 Hz for 90 minutes. After completing the reaction, the content of the vessel was generously treated with distilled water, filtrated and finally properly dried in vacuum. The resulted crude was directly subjected to gradient flash chromatography on silica gel to isolate the desired amide derivative.

The gram scale synthesis was performed on 10 mmol of the starting amine in a 25 mL grinding vessel by using three 10 mm balls.

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