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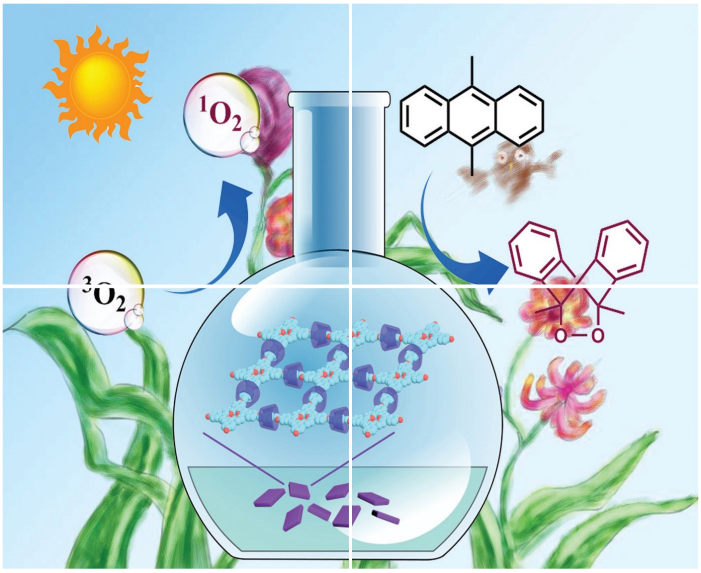

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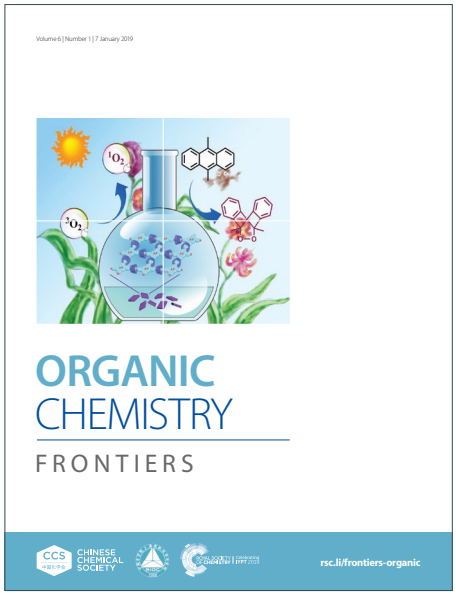

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ARTICLE

One-pot Dearomatizative *C*-Nucleophiles Telescoped Addition to Fluorinated 1,2,4-Oxadiazoles - Regioselective *N*-Functionalization

Davide Castiglione,[a] Sara Amata,[b] Federica Lauria,[a] Andrea Maranzana,[a] Salvatore Baldino,[a] Alexander Roller-Prado,[c] Laura Castoldi,[d*] Antonio Palumbo Piccionello,[b*] Vittorio Pace[e,f*] and Eisuke I. Comas Iwasita[a]

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The constitutive low aromaticity of easily accessible 5-trifluoromethyl-1,2,4-oxadiazoles is explored for the editing modification to the corresponding unprecedented *gem*-disubstituted 1,2,4-oxadiazolines. The operation consiting in the nucleophilic addition of diverse carbon-centered nucleophiles occurs with excellent regiocontrol (in almost all cases), thus furnishing selectively 2,5-dihydro or 4,5-dihydro isomers. The process - documenting also high chemocontrol – enables the further derivatization of the intermediate anion with externally added electrophilic platforms. Calculations supporting the experimental evidences, attribute a key role in controlling the regioselectivity to intrinsic steric factors of the nucleophiles thus, rationalizing the non optimal outcome observed in particular circumstances (*i.e.* with $LiCH_2Br$).

Introduction

Dihydro-1,2,4-oxadiazoles (*i.e.* 1,2,4-oxadiazolines) constitute an important class of *non*-aromatic five-membered heterocycles demonstrating significant adaptability in medicinal chemistry.[1] In particular, this motif is found in biologically active substances including anticancer,[2] anti-diabetic,[3] anti-Alzheimer,[4] kinase-inhibitors[5] and nicotinic receptor-antagonists.[6] In synthetic methodology, 1,2,4-oxadiazolines are suited for heterocyclic skeletal modifications conducting to imidazoles,[7] isoxazoles[8] and pyrrols.[9] Firstly introduced by Tiemann in 1889,[10] the cyclocondensative approach – between amidoximes and carbonyls - continues to represent the canonical logic for assembling dihydro-1,2,4-oxadiazoles (Scheme 1.1).[11] Though significant progresses have been documented, the relatively limited regiocontrol and the substrate specificity (*i.e.* lack of generality) continues to plague this conceptually straightforward technique.[12] Unfortunately, regioselective issues are pervasive and eclipse also the potential of generating the heterocycle through [3+2]- or [1,3]-cycloadditive strategies involving nitrile oxides and imines (Scheme 1.2a).[13] Although 4,5-dihydro-1,2,4-oxadiazole analogues are usually the predominant products, the switching to the combination of nitrones and nitriles could furnish 2,5-dihydro isomers in particular circumstances (Scheme 1.2b).[14] However, the development of methodologies conducting with high selectivity to the latter heterocyclic arrangement (*i.e.* 2,5-dihydro) are extremely rare and could pose significant limitations regarding practical aspects. Xuan and Xiao demonstrated the effectiveness of the visible-light-promoted [3+2]-cycloaddition of nitroso-arenes to 2*H*-azirines (Scheme 1.3a).[15] In this sense, the difficult access and manipulation of both precursors were successfully overcome in the elegant Li-Walsh's tactic relying on the transition-metal free SET-activation of less problematic (and common organic feedstocks) nitroarenes and imines (Scheme 1.3b).[13f,16] Accordingly, upon generating under basic conditions the 2-azaallyl anion, it supplies an electron to the nitro group, thus reducing it to the corresponding nitroso analogue. Concomitantly, this SET event produces the 2-azaallyl radical which by coupling with the nitroso species delivers 1,2,4-oxadiazolines.

A conceptually distinct approach would rely on the regioselective editing of an easily accessible preformed heterocycle (Scheme 1.4). The grounding elements

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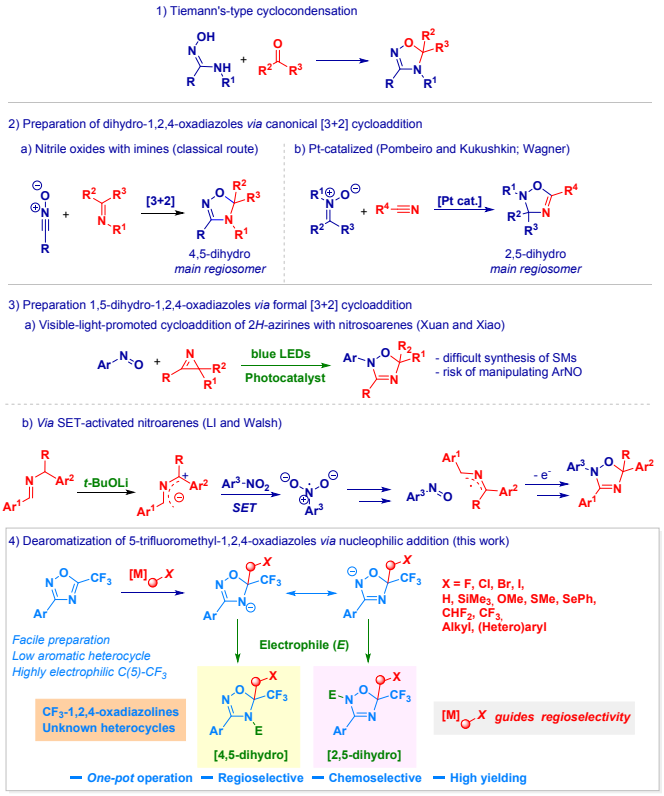
underpinning the reactivity of 1,2,4-oxadiazoles attribute to the C5 carbon a prominent electrophilic behaviour which would be implemented by the simultaneous installation of an adequate electron-withdrawing functionality. As documented recently in our group for imine surrogates,[17] the trifluoromethyl (CF_3) group is particularly suited for this purpose and – if successful - would gather the exploration of the unknown chemical space of trifluoromethyl-1,2,4-oxa*diazolines*. We would foresee unique properties for this new class of heterocycles as a consequence of the modulation imparted by the trifluoromethyl group in terms of physical-chemical parameters.[18] The following considerations are pertinent: a) the effectiveness of the tactic would depend on controlling the regiochemical outcome of the electrophilic trapping of the heterocyclic anion, potentially occurring at N2 and N4 positions; b) the intrinsic low aromaticity of the starting 1,2,4-oxadiazoles[11b,19] – index of aromaticity I_5 = 39[20] - would support the feasibility of the approach; c) the straightforward well-established preparative methods for these starting materials[21] would constitute a significant advantage compared to strategies paved on precursors of difficult access. Ideally, the regiocontrol should be predictable and tuned by the nature of the nucleophile used, as well as, ring opening/ring closing rearrangements (ANCORC type)[11b] should not come into play.



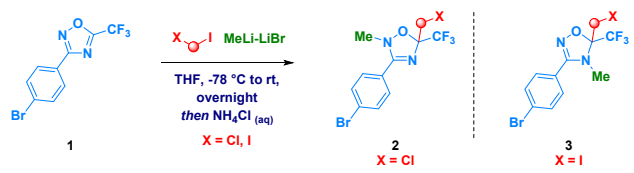
Scheme 1. General context of the presented work.

Herein, we describe the releasing of variously functionalized nucleophilic elements to the C5-carbon of 1,2,4-oxadiazoles, thus generating selectively one of the two possible 2,5-diydro or 4,5-dihydro regioisomers. Notably, the nucleophilic addition event conducts to a geminal disubstituted cluster, being the CF_3 a constitutive element, whereas the installed C1-synthon could vary depending on the operator's needings. Calculations support the experimental evidence of attributing to the attacking nucleophile a pivotal role in governing the regioselectivity of the process.

Results and Discussion

3-(4-bromophenyl)-5-(trifluoromethyl)-1,2,4-oxadiazole (**1**) was selected as the model substrate for the addition of $LiCH_2Cl$ generated *in situ* from chloroiodomethane and MeLi-LiBr (Table 1).[22] By running the reaction at -78 °C in THF for 1 h, the generation of 5-chloromethyl-2-methyl-2,5-dihydro-1,2,4-oxadiazole derivative **2** was observed as the major product (49% yield, entry 1), being its structure unambiguously confirmed by X-ray analysis (see Scheme 2). Presumably, the anionic intermediate generated after the carbenoid attack, is sufficiently reactive to trap - at low temperature - the electrophilic MeI formed during the carbenoid generation event (ICH_2Cl + MeLi-LiBr → $LiCH_2Cl$ + MeI) *via* Li-I exchange.[23] The effectiveness of the *N*-methylation was implemented by prolonging the reaction time and allowing the mixture to slowly reach rt (entries 2- 3). The progressive increasing of the nucleophile loading was critical to secure the maximization of the yield up to 86% (entries 4-5). The positive effect of employing a supra-stoichiometric amount of carbenoid is related to its intrinsic tendency to undergo degradative Kirmse's α-elimination processes.[24] As a matter of fact – *coeteris paribus* – reactions run in less coordinative solvents (2-MeTHF, CPME and TBME) resulted dramatically unproductive, as a consequence of the facilitated decomposition of the carbenoid. The augmenting the nucleophile to 2.2 equiv promoted the reaction and, **2** was isolated in 78% yield (entry 4); however, to maximise the efficiency, it was essential to use 2.8 equiv, which allowed the isolation of **2** in excellent 86% yield. By running the reaction in more sustainable - but less coordinating - solvents (known to promote Kirmse's α-elimination process), such as diethyl ether, 2-methyltetrahydrofuran (2-MeTHF),[25] cyclopentyl methyl ether (CPME)[26] or *tert*-butyl methyl ether (TBME)[27] only traces of the product were observed (entries 6-9). Finally, a brief screening on the use of carbenoids of a different nature was carried out. The reaction with the less nucleophilic magnesium carbenoid $ClMgCH_2Cl$[28] did not generate isolable products, regardless the adoption of Barbier and *non*-Barbier conditions (entries 10 and 11). Conversely, when **1** was reacted with $LiCH_2I$[17a] - generated from CH_2I_2 and MeLi-LiBr – the regioisomer 4-methyl-4,5-dihydro-1,2,4-oxadiazole derivative **3** was surprisingly isolated in 88% yield, as the unique reaction product (entry 12). It should be emphasized that – to the best of our knowledge – C1-halocarbenoids have not been previously employed in nucleophilic additions to heterocycles.[22b]

Table 1. Reaction optimization.

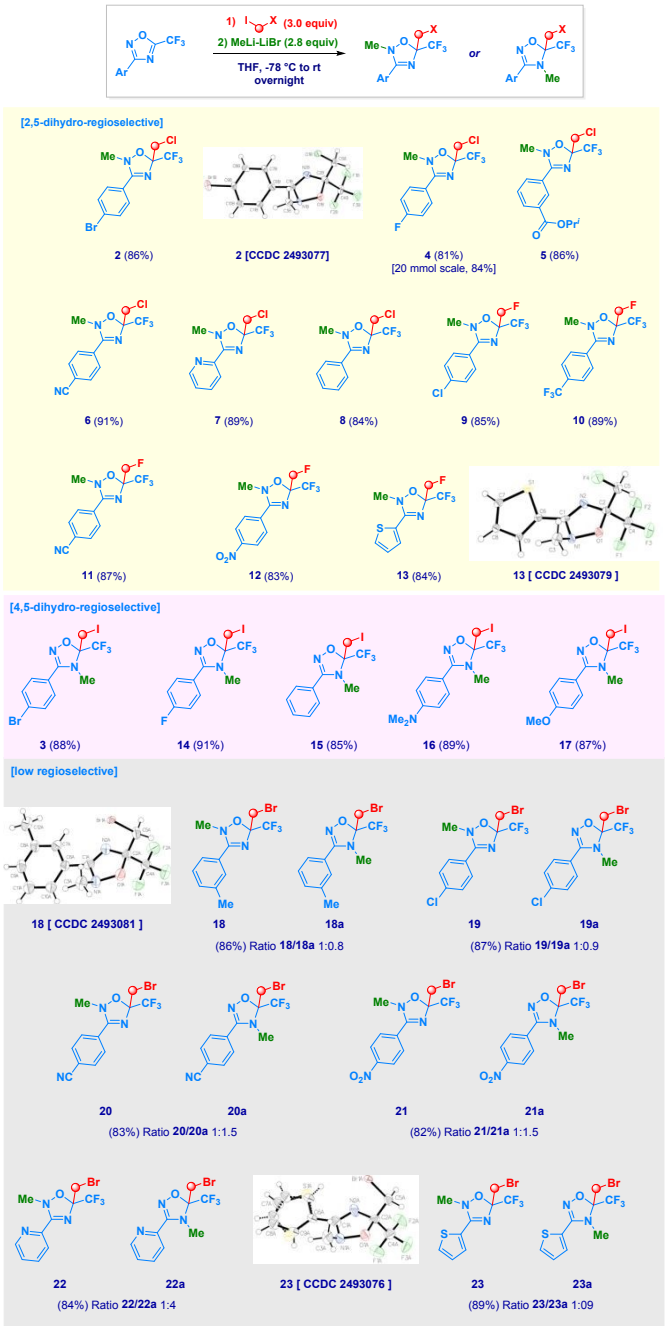


Entry	Homologating agent (equiv)	Solvent	Yield of **2** (%)[a]	Yield of **3** (%)[a]
1[b]	$LiCH_2Cl$ (1.6)	THF	49	-
2[c]	$LiCH_2Cl$ (1.6)	THF	63	-
3	$LiCH_2Cl$ (1.6)	THF	71	-
4	$LiCH_2Cl$ (2.2)	THF	78	-
5	$LiCH_2Cl$ (2.8)	THF	86	-
6	$LiCH_2Cl$ (2.8)	Et_2O	37	-
7	$LiCH_2Cl$ (2.8)	2-MeTHF	traces	-
8	$LiCH_2Cl$ (2.8)	CPME	traces	-
9	$LiCH_2Cl$ (2.8)	TBME	traces	-
10[d]	$ClMgCH_2Cl$ (2.8)	THF	-	-
11[e]	$ClMgCH_2Cl$ (2.8)	THF	-	-
12	$LiCH_2I$ (2.8)	THF	-	88

Unless otherwise stated, reactions were run from -78 °C to rt, overnight. [a] Isolated yields. [b] Reaction time 1 h, temperature -78 °C. [c] Reaction time 5 h. [d] Reaction run starting from ICH_2Cl and *i*-PrMgCl-LiCl under Barbier condition. [e] Reaction run starting from ICH_2Cl and *i*-PrMgCl-LiCl under *non*-Barbier conditions.

With the optimal conditions in hand, we next explored the scope of the reaction with the primary goal of confirming the halocarbenoid-imparted regioselectivity. Indeed, the addition of both $LiCH_2Cl$ and $LiCH_2F$[29] provided 5-halomethyl-2-methyl-2,5-dihydro-oxadiazoles (**2**, **4**-**13**) in yields up to 91% with almost complete regiocontrol, also in case of scaling up to 20 mmol (**4**). Whereas nucleophilic additions of $LiCH_2I$ were terminated with the selective methylation at N4, thus yielding 5-iodomethyl-4-methyl-4,5-dihydro derivatives (**3**, **14**-**17**) as the exclusive reaction products. The installation of the bromomethyl-chain released from $LiCH_2Br$[30] was particularly intriguing since mixtures of the two possible regioisomers (**18**/**18a**-**23**/**23a**) corresponding to N2 and N4 methylation were obtained in relative ratios ranging from 1:0.8 to 1:4, as deducted by integrated structural analysis (^{1}H-, ^{13}C-NMR and X-rays) on selected compounds (**2**, **13**, **18**, **23** and **24**). *Vide infra* for a plausible rationalization of this unexpected halocarbenoid-imparted regioselectivity. The protocol was, however, highly flexible for introducing carbenoids into variously functionalized 1,2,4-oxadiazoles. Thus, the presence of halogens (**2**, **3**, **9**, **10**, **19**/**19a**) did not interfere with the transformation, despite the well-known possibility of undergoing collateral halogen-metal exchange. This is particularly relevant for sp^2-hybridized carbons featuring chlorine (**9**, **19**/**19a**) and (**2**-**3**) bromine atoms.[31] Electrophilic functional groups [*e.g.* ester (**5**) and nitrile (**6**, **11**, **20**)] potentially sensitive to organolithiums were perfectly tolerated thus, conferring also an excellent chemocontrol. Moreover, the basicity of MeLi and lithium carbenoids did not affect aromatic heterocycles susceptible of lithiation [pyridine[32] (**7**, **22**/**22a**)] and thiophene[33] (**13**, **23**-**23a**)].

The halomethylation of oxadiazoles featuring the often problematic (with RLi reagents) nitro group[34] could be successfully accomplished (**12** and **21**/**21a**) in high chemical yield. The presence of electron-releasing functionalities on the phenyl ring at C3 was not detrimental, as indicated in the cases of a tertiary amine (**16**) and an ethereal functionality (**17**). Though the electrophilicity of 1,2,4-oxadiazoles could sensitively be affected, the overall result is negligible, being their reactivity comparable to systems in which more inert substituents were present [*e.g.* Me (**18**/**18a**)].



Scheme 2. Scope of the method with different $LiCH_2X$ reagents.

Experimental evidence of the hypothesized mechanism was ascertained by generating d_3-labeled methyl iodide during the

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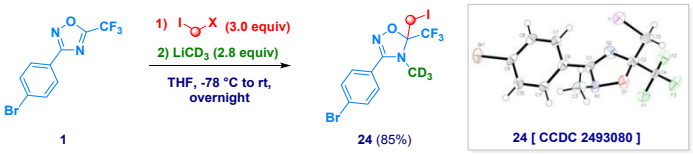
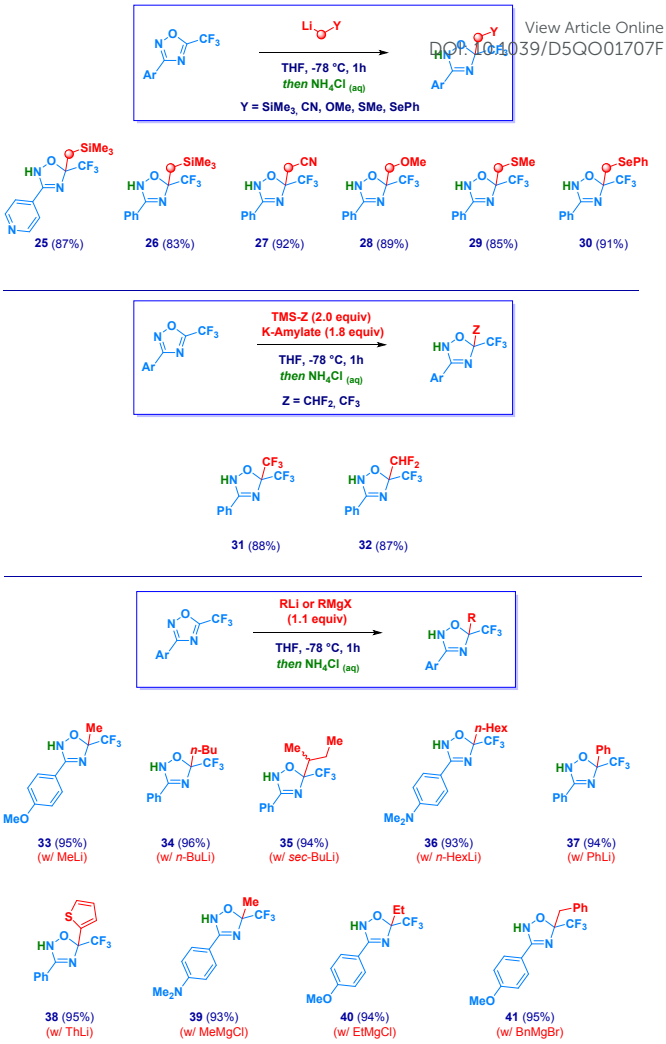
carbenoid formation event starting from CH_2I_2 and CD_3Li.[23,35] While the iodomethyl- fragment was introduced in the standard CH_2I form, the methyl group attacked by the heteroaromatic anion was deuterated (CD_3), thus confirming both the origin of the electrophilic moiety and the site of functionalization (N4, **24** - scheme 3).



Scheme 3. Carbenoid generation with MeLi-d_3 for validating the mechanistic hypothesis.

With the aim of expanding the dearomatizative concept to different α-substituted methyl-type carbanions, we were delighted in validating the protocol with $LiCH_2SiMe_3$ (**25**-**26**), $LiCH_2CN$[36] (**27**), $LiCH_2OMe$[37] (**28**), $LiCH_2SMe$[38] (**29**), $LiCH_2SePh$,[39] (**30**). As a consequence of the generation of these nucleophiles through distinct tactics rather than I/Li exchange (which forms electrophilic MeI), the acidic quenching provides *N-H* dihydro-1,2,4-oxadiazoles (Scheme 4).

Furthermore, the *gem*-functionalization could be effectively accomplished with poly-fluorinated C1-units. Therefore, upon the Lewis base mediated activation of $TMSCF_3$ (Ruppert-Prakash reagent)[40] and $TMSCHF_2$,[41] *gem*-bis(trifluoromethyl) **31** and *gem*-difluoromethyl-trifluoromethyl **32** derivatives were prepared in high yield. Collectively, the protocol constitutes a versatile tool *en route* to rare systems presenting at the same carbon atom two distinct fluorinated chains. Finally, the addition of *non*-functionalized organolithiums[42] and organomagnesiums[42b] enabled the preparation of 5-alkyl and 5-aryl 2,5-dihydro-1,2,4-oxadiazoles (**33**-**41**). These results highlight the generality of the methodology which allows the productive use not only of linear alkyl elements but, also more sterically hindered ones as the *sec*-butyl fragment (**35**) or less nucleophilic (hetero)aromatic rings (**36** and **37**).



Scheme 4. Generality of the method with different (functionalized) carbon-nucleophiles.

Newly synthesized dihydro-1,2,4-oxadiazoles could be surmised to further derivatization (Scheme 5). For example, the lithiation of compound **15** followed by the addition of TMSOTf, gave compound **42** thus, showing the reactivity of the C(sp^3)-I bond previously introduced (path *a*). Also, the N-H functionality could be subjected to amidation to gather the *N*-acyl derivative **43** (*path b*). The mechanistic study – conferring a key role to the genesis of carbenoid – suggests that forming it without releasing an electrophilic exchange collateral product (*e.g.* MeI), could offer the opportunity to engage an externally added functionalizing element. PhLi proved to be an excellent alternative to MeLi-LiBr for generating $LiCH_2Cl$ and PhI so obtained did not interfere with the electrophilic quenching, as initially endorsed with the simple acidic quenching (**44**-**45**, NH_4Cl aq.). More interestingly, this was the case also with externally added reactive carbon electrophiles [benzyl bromide (**46**), allyl bromide (**47**) and methyl iodide (**48**-**49**, *path c*). In agreement with the results shown above, the *N*-alkylation of these anionic intermediates generated by the installation of *non*-bulky fragments (*e.g.* -CH_2Cl and Me-) occurs with full regioselectivity at the position 2, as again confirmed by the X-ray analysis of compound **46**.

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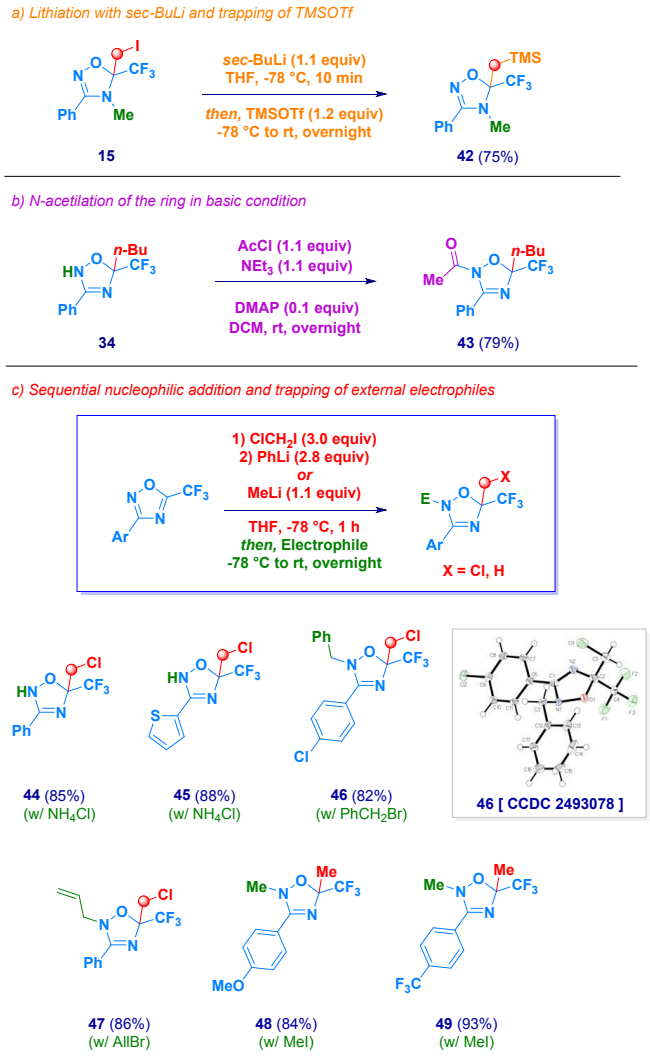
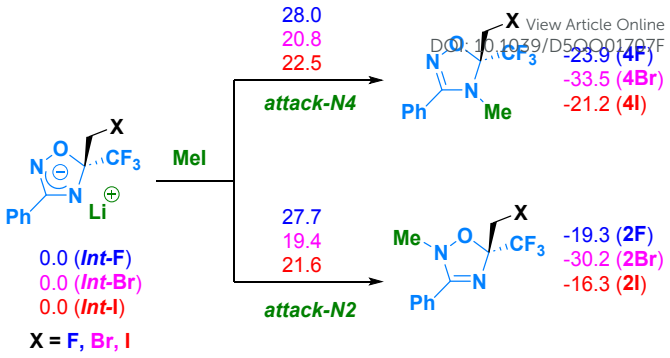


Scheme 5. Synthetic manipulation of dihydro-1,2,4-oxadiazoles and sequential nucleophile addition/trapping with external electrophiles.

The selectivity of the process was rationalized with a DFT study (See ESI for more details). Comprehensive evaluations were conducted to identify the optimal strategy for an accurate description of the reacting system. This included a conformational search (using the CREST program)[43] to determine the most stable starting molecule, prediction of the most nucleophilic sites, and evaluation of the effect of solvation to quantify the steric effects (using Multiwfn software).[44] Figures have been obtained by the program Molden.[45]



Scheme 6. Reaction mechanisms for compounds with different halogen atoms (X=F, Br, or I). Fluorine in blue, bromine in pink, and iodine in red. Free energies in kcal mol^{-1} at 195 K, calculated using CCSD(T)/def2-TZVP//M06-2X/def2-TZVP in PCM (THF).

Calculations using the PCM model (Scheme 6), indicate that anions generated from 1,2,4-oxadiazole – presenting respectively fluoride or iodine (***Int*-F** and ***Int*-I**), react with MeI (formed as a collateral product during the carbenoid preparation) according to S_N2-type mechanism. Because the nucleophilicity is exhibited by both N2 and N4, regioisomers **4F** and **2F** (with fluorine) and **4I** and **2I** (with iodine) could be obtained upon the reaction with MeI (Figure 1). Experimentally, only compounds **2F** and **4I** were generated. Whereas, in the presence of bromine, both **2Br** and **4Br** were observed. However, in the case of fluorine the transition state (**TS *Int*-F - 2F**) leading to the experimental product **2F**, did not differ significantly from **TS *Int*-I - 4I** from which **4I** is obtained. Regarding the reaction energies, the experimental product (**2F**) was 4.6 kcal mol^{-1} higher than that of **4F**, respectively -19.3 kcal mol^{-1} and -23.9 kcal mol^{-1}. With iodine, the transition state leading to the experimentally observed product (**TS *Int*-I - 2I**) is 0.9 kcal mol^{-1} higher than **TS *Int*-I - 4I**, despite the reaction energy of **4I** (the experimental product), being more stable than **2I**, -21.2 kcal mol^{-1} and -16.3 kcal mol^{-1}, respectively. In the case of bromine, the transition states leading to the two different products differ by 1.4 kcal mol^{-1} (**TS *Int*-Br - 4Br** and **TS *Int*-Br - 2Br**): with such an energy difference, only **2Br** should be observed.

PCM simulation of the solvent could not explain the observed product distribution in the case of bromine. However, when three molecules of THF were explicitly included in the calculations, the energy difference between the two barriers decreased to 0.8 kcal mol^{-1} which is qualitatively in (better) agreement with the experimental findings (Scheme 7).

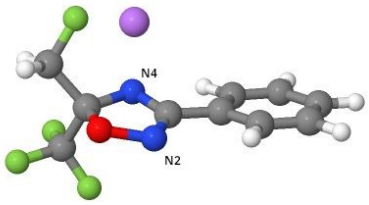


Figure 1. ***Int*-F** molecule, in which the nitrogen atom near the oxygen in the oxadiazole ring is referred to as N2, as described in this section, whereas the nitrogen at position 4 coordinated with the Li atom (pink) is referred to as N4.

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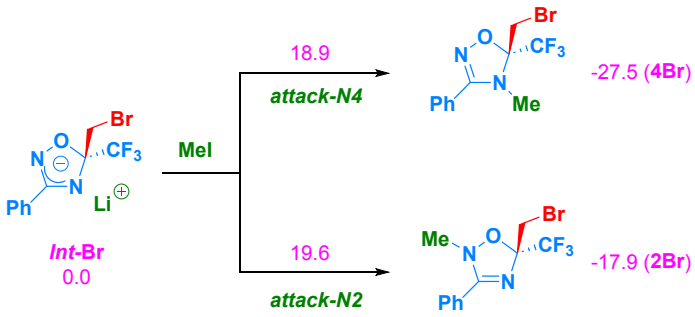

Scheme 7. The reaction mechanisms for the compound with bromine and the three explicit solvent molecules (not shown for clarity; see Figure S13 in ESI). Free energy in kcal mol^{-1} at 195 K, calculated using CCSD(T)/def2-TZVP//M06-2X/def2-TZVP in PCM(THF).

To explain the regioselectivity, an electronic effect was ruled out because the nucleophilicity of the two nitrogen atoms was unchanged regardless of the orientation of the halogen atom in the molecule and the two different lithium coordination sites; as also indicated in Table 2, the nitrogen in the 2-position consistently exhibited higher nucleophilicity, irrespective of the lithium position.

Table 2. Condensed nucleophilicity indices, N_{Nu}^{A}, for nitrogen at the 2 and 4-position. Expressed as *e*eV*, where *e* is the elementary charge. The figure on the right shows the ***Int***-F molecule, in which the nitrogen atom near the oxygen in the isoxazole ring is referred to as N2, while the nitrogen at position 4 is referred to as N4. Only the most stable structures were considered. For more details, see ESI.

Compound	N2	N4
F	0.62602	0.51844
I	0.6361	0.53307
Br	0.57182	0.49387

The most stable conformation for each compound (with Li bound to N2 or N4; Figures 2 and 3) containing fluorine and iodine was considered. The geometries were optimized, and the energies were decomposed into three terms according to the EDA-SBL approach (Table 2).

In the product with iodine, the conformation with Li bound to N2 (Figure 2a) is the most stable, and the energy decomposition analysis (EDA-SBL) suggested that iodine's larger steric bulk influences its conformation and leads to different products under identical conditions. As shown in Table S9 (ESI), when iodine was replaced with fluorine (**I → F**, Figure 2b) - and keeping the same conformation - the steric energy was 9.3 kcal mol^{-1}. In contrast, when fluorine was replaced with iodine (**F → I**) (Figure 3), the steric energy increased significantly to 19.4 kcal mol^{-1}.

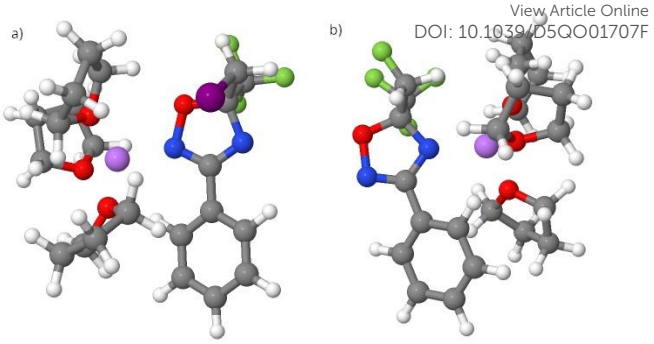

Figure 2. The figure shows, on the left (a), the ***Int*-I** compound, while (b) ***Int*-F** in which the fluorine atom has been replaced with iodine (F → I). (b) is 0.4 kcal mol^{-1} less stable than (a)

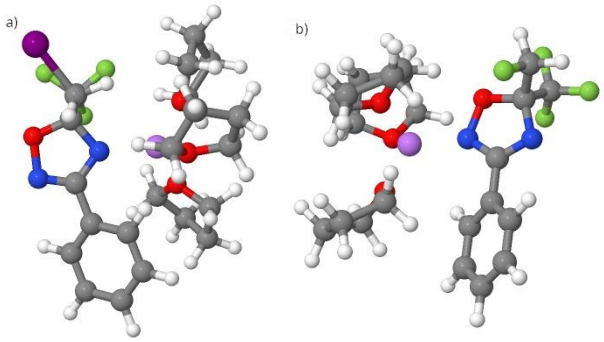

Figure 3. The figure shows, on the left (a), the structure of ***Int*-F** compound, while in (b) it is indicated the structure of ***Int*-I** in which the iodine atom has been replaced with fluorine (I → F). (b) is 4.7 kcal mol^{-1} less stable than (a).

This scenario suggested a significant steric bulk in the second case, which could explain why iodine adopts a specific conformation, leading to different products under the same conditions. The atomic radius of bromine is intermediate between those of F and I, and the steric effect is no longer dominant to the stability of the two intermediates; therefore, both products are observed.

Conclusions

In summary, we introduced a novel synthetic approach for the preparation of dihydro-1,2,4-oxadiazoles through the direct addition of carbon-nucleophiles to 5-trifluoromethyl-1,2,4-oxadiazoles. The dearomatization process occurs *via* the regioselective nucleophilic attack at C5 and – in the case of halogenated C1-species (*i.e.* carbenoids) - the nature of the competent halogen is the key factor imparting regioselectivity to the process. Thus, in case of using chloromethyl- and fluoromethyl- lithiums, only 2,5-dihydro- isomers were generated; whereas, by switching to iodomethyl-lithium 4,5-dihydro-isomers were obtained. The nucleophilicity of the anionic intermediate enables the further functionalization of the ring with externally added electrophilic partners. The portfolio of carbon nucleophiles amenable for the transformation is wide, as documented with diverse (α-

substituted) carbanions and fragments released upon the proper genesis of *ate* complexes (*e.g.* activated $TMSCHF_2$ and $TMSCF_3$) The transformation takes place under full chemocontrol and maintains the chemical integrity of sensible functionalities (halogen, nitrile, ester, pyridine, thiophene). The unambiguous assignment of regioisomers was deducted by the X-ray analysis, the use of deuterium-labelled reagents, whereas DFT calculations supported the experimental observations.

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Conflicts of Interest

The authors declare no competing interests.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.
The data supporting this article have been included as part of the electronic supplementary information (ESI).
CCDC 2493077 (compound **2**), CCDC 2493079 (compound **13**), CCDC 2493081 (compound **18**), CCDC 2493076 (compound **23**), CCDC 2493080 (compound **24**) and CCDC 2493078 (compound **46**) are available at https://www.ccdc.cam.ac.uk/.

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Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

The data supporting this article have been included as part of the electronic supplementary information (ESI). CCDC 2493077 (compound **2**), CCDC 2493079 (compound **13**), CCDC 2493081 (compound **18**), CCDC 2493076 (compound **23**), CCDC 2493080 (compound **24**) and CCDC 2493078 (compound **46**) are available at https://www.ccdc.cam.ac.uk/.