



HAL
open science

Trifluoromethoxylation of Arynes using 2,4-Dinitro-1-(trifluoromethoxybenzene) as Trifluoromethoxide Anion Source

Lilian Wisson, Gilles Hanquet, Fabien Toulgoat, Thierry Billard, Armen Panossian, Frédéric R. Leroux

► **To cite this version:**

Lilian Wisson, Gilles Hanquet, Fabien Toulgoat, Thierry Billard, Armen Panossian, et al.. Trifluoromethoxylation of Arynes using 2,4-Dinitro-1-(trifluoromethoxybenzene) as Trifluoromethoxide Anion Source. *European Journal of Organic Chemistry*, In press, 10.1002/ejoc.202400388 . hal-04591124

HAL Id: hal-04591124

<https://hal.science/hal-04591124>

Submitted on 28 May 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial - NoDerivatives 4.0 International License

Accepted Article

Title: Trifluoromethoxylation of Arynes using 2,4-Dinitro-1-(trifluoromethoxybenzene) as Trifluoromethoxide Anion Source

Authors: Lilian Wisson, Gilles Hanquet, Fabien Toulgoat, Thierry Billard, Armen Panossian, and Frederic R. Leroux

This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article.

To be cited as: *Eur. J. Org. Chem.* **2024**, e202400388

Link to VoR: <https://doi.org/10.1002/ejoc.202400388>

RESEARCH ARTICLE

Trifluoromethoxylation of Arynes using 2,4-Dinitro-1-(trifluoromethoxy)benzene as Trifluoromethoxide Anion Source

L. Wisson,^[a] G. Hanquet,^[a] F. Toulgoat,^{[b], [c]} T. Billard,^[c] A. Panossian,^{*[a]} and F. R. Leroux^{*[a]}

[a] L. Wisson, Dr. G. Hanquet, Dr. A. Panossian, Dr. F. R. Leroux
 Université de Strasbourg, Université de Haute-Alsace,
 CNRS, UMR 7042-LIMA, ECPM,
 67000 Strasbourg, France
 E-mail: frederic.leroux@unistra.fr, armen.panossian@unistra.fr

[b] Dr. F. Toulgoat
 CPE Lyon
 Campus LyonTech-La Doua, 43 Bd du 11 novembre 1918,
 69616 Villeurbanne, France

[c] Dr. F. Toulgoat, Dr. T. Billard
 Institute of Chemistry and Biochemistry (ICBMS-UMR CNRS5246)
 Univ Lyon, CNRS, Université Lyon1 43 Bd du 11 Novembre 1918,
 69622 Lyon, France

Supporting information for this article is given via a link at the end of the document.

Abstract: The trifluoromethoxy moiety, an emerging fluorinated group, shows interesting properties for pharmaceutical and agrochemical applications. However, only few methods have been reported for the direct introduction of this group on molecules with high efficiency, safety and low cost. Indeed, most of direct trifluoromethoxylation reagents are either expensive, hazardous or require preliminary synthesis before their use. Here we describe the use of 2,4-dinitro-1-(trifluoromethoxy)benzene (DNTFB) as an easy-to-handle, safe, commercially available and cheap source of trifluoromethoxide anion for the trifluoromethoxylation of arynes.

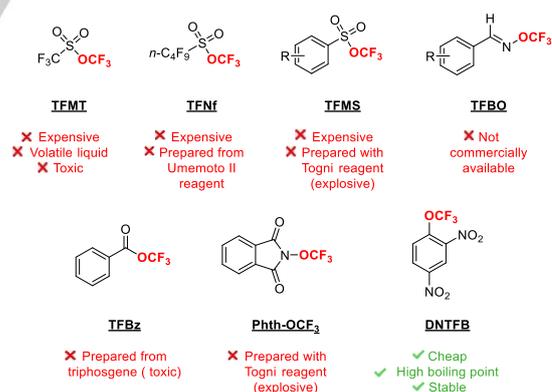
Introduction

Molecules bearing fluorinated groups represent a significant proportion of active compounds in pharmaceuticals and agrochemicals.^[1a-b] Among these fluorinated groups, the trifluoromethoxy unit (OCF₃) is modestly represented^[1] despite its interesting properties regarding electronegativity,^[2] hydrophobicity,^[3] electronic effects^[4] and conformation.^[5,6]

An explanation of the low number of CF₃O-containing pharmaceuticals and agrochemical ingredients is the few methods to access the trifluoromethyl ether motif, whether it is by dehalogenative or dechalcogenative fluorination, by radical or electrophilic *O*-trifluoromethylation or by direct introduction of the OCF₃ group.^[7] Concerning direct ways to construct CF₃O-carbon bonds, radical trifluoromethoxylation has been well studied on (hetero)aromatics and acetophenone derivatives.^[7a, 7d, 8] The direct introduction of the OCF₃ motif *via* the trifluoromethoxide anion (CF₃O⁻) has been the focus of research for the past decade.^[7a, 7e-g] Many sources of CF₃O⁻ have been developed and used on different substrates by nucleophilic substitution or metal-catalyzed reactions.^[9] However, these trifluoromethoxide anion sources suffer from various drawbacks (Figure 1a). Trifluoromethyl triflate (TFMT)^[9a,b], largely used to generate trifluoromethoxide salts,^[9a-b, 9d-f, 9i, 9o] is an expensive reagent but low boiling point liquid (bp 19 °C), which limits its applications. The Trifluoromethyl nonaflate (TFNf) was developed to overcome this

boiling point issue but it has to be prepared from the Umemoto II reagent.^[9n] Trifluoromethyl aryl sulfonates (TFMS)^[9g] have been developed as a substitute of the latter but they have to be prepared from explosive and expensive Togni's reagent.^[10] (*E*)-*O*-trifluoromethyl benzaldoximes (TFBO)^[9k] are safer to synthesize but they are not yet commercially available. Trifluoromethyl benzoate (TFBz), for its part, has to be prepared from triphosgene, a toxic solid.^[9h] Finally, even if *N*-trifluoromethylphthalimide (Phth-OCF₃)^[9p] is very easy to use, it has to be prepared from Togni's reagent like TFMS.

a) Examples of nucleophilic trifluoromethoxylation reagents



b) DNTFB/DMAP system as a source of trifluoromethoxide anion

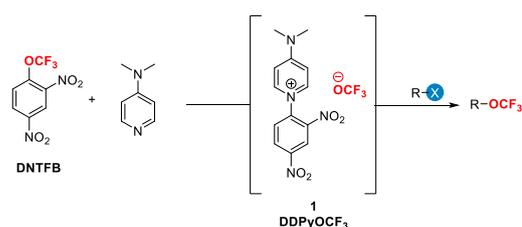


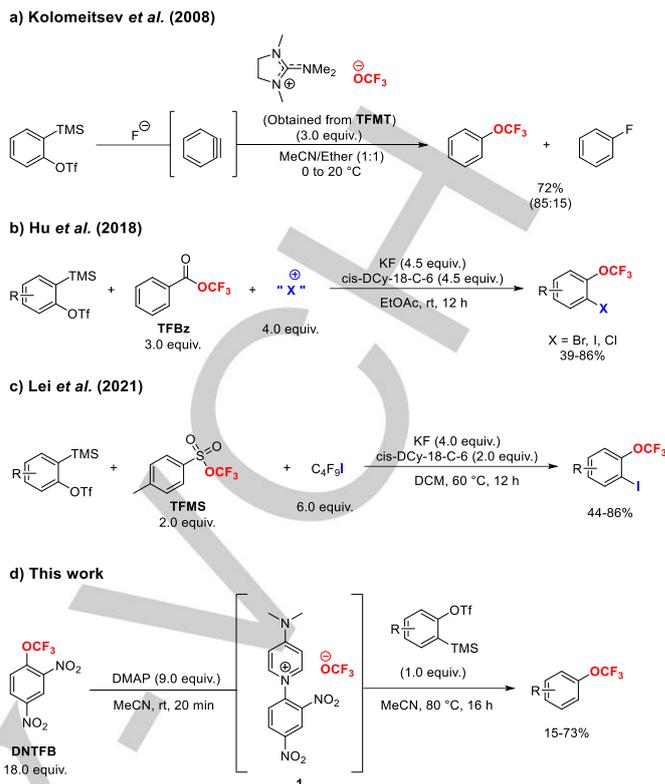
Figure 1. DNTFB as an attractive source of trifluoromethoxide anion

In 2010, some of us introduced 2,4-dinitro-1-(trifluoromethoxy)benzene (DNTFB) as a new trifluoromethoxide

RESEARCH ARTICLE

anion source.^[11] Indeed, the trifluoromethoxide anion can be obtained from this commercially available, cheap, easy-to-handle and stable reagent, in the presence of a fluoride salt. Recently and concomitantly, our groups^[12] and Sanford *et al.*^[13] improved the generation of the anion by using 4-dimethylaminopyridine (DMAP) in acetonitrile to form a stable pyridinium trifluoromethoxide solution (DDPyOCF₃, **1**) (Figure 1b). We already demonstrated that the DNTFB/DMAP system was able to trifluoromethoxylate aliphatic substrates via S_N reactions.^[12] In addition, it can also be used as difluorophosgene source to synthesize carbamoyl fluorides^[14] and acyl^[14, 15] fluorides with excellent yields.

In order to extend the scope of application of DDPyOCF₃ we were interested in the trifluoromethoxylation of *ortho*-arynes. *ortho*-Arynes^[16] are very reactive species which are formally presenting vicinal electrophilic and nucleophilic positions. The trifluoromethoxylation of arynes has been briefly reported by Kolomeitsev *et al.* in 2008 with TFMT as the trifluoromethoxide source and Kobayashi aryne precursors^[9a] as substrates (Scheme 1a). Few years later, Hu and co-workers^[9h] described an *ortho*-halogenotrifluoromethoxylation of arynes using TFBz with good to excellent yields (Scheme 1b). Finally, a similar work has been published by Lei *et al.*^[17] with TFMS as trifluoromethoxylation reagent with the same success (Scheme 1c). Despite the good results obtained by these groups, their methods suffer from the above-mentioned drawbacks concerning OCF₃ sources. Additionally, the trifluoromethoxylation of arynes often goes hand in hand with the introduction of a halogen in *ortho* position of the OCF₃ group. The prototrifluoromethoxylation of arynes was only described in two examples by Kolomeitsev.^[9a] We herein describe the complementary use of DNTFB as a cheap and easy-to-handle source of trifluoromethoxide anion for the trifluoromethoxylation of arynes generated from Kobayashi precursors (Scheme 1d).



Scheme 1. Aryne trifluoromethoxylation

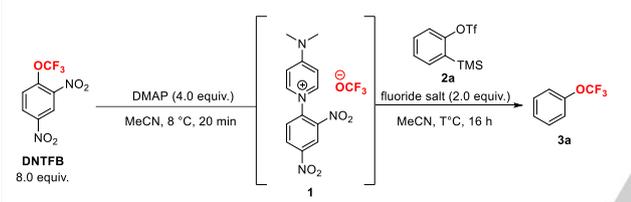
Results and Discussion

Inspired by the previous work on the trifluoromethoxylation of Kobayashi aryne precursors as mentioned above,^[9a, 9h, 17] we started to screen various fluoride sources in a two-tube set-up using benzyne precursor **2a** as a model substrate. This two-tube set-up was used to prevent as much as possible the activation of DNTFB by the fluorides used to trigger the generation of the aryne. In practice, a first sealed tube was used to preform the trifluoromethoxide salt **1** (DDPyOCF₃, Scheme 1d) and a second one contained the aryne precursor and a fluoride salt as its activator; the solution of **1** was then transferred from the first tube to the second. The first attempt, performed with cesium fluoride (CsF), only gave a medium conversion and a modest yield of trifluoromethoxybenzene **3a** (Table 1, entry 1). The use of KF led to a slightly better conversion but a lower yield (entry 2). These two fluoride salts are poorly soluble in acetonitrile (MeCN). Therefore, another fluoride salt, more soluble, was considered such as tetrabutylammonium difluorotriphenylsilicate (TBAT). In this case, moderate conversion was achieved but the yield increased to 27% (entry 3) compared to 16% and 11% obtained with inorganic fluoride salts. To improve the kinetics of the reaction, the temperature was increased from 25 °C to 40 °C and 60 °C (entries 4 and 5). To our delight, conversion raised up to 100% while a 30% yield was obtained. Variation of the temperature, the concentration and the molar ratio of the reactants did not show any improvement (for more details see the SI, Tables S1 to S6), and the yield of **3a** remained low to average, which was unsatisfying in view of the complete conversion of the aryne precursor. This could be explained, under the reaction conditions, by a too quick generation of benzyne with regard to the slow attack of the weak nucleophile that is F₃CO⁻, leading to

RESEARCH ARTICLE

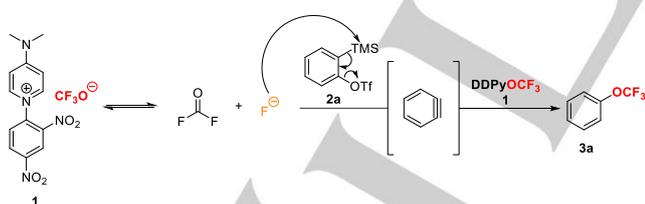
side-reactions of benzyne. This too fast release of benzyne would in turn be due to the combined action of the added fluoride source and of internal fluoride, released by the collapse of the trifluoromethoxide anion into fluorophosgene. Accordingly, we wondered whether we could turn this degradation of the trifluoromethoxide anion to our advantage and use DNTFB as the sole source of both trifluoromethoxide anion and fluoride (Scheme 2), slowing down the formation of the aryne and simplifying the system. A second advantage of this trick would be to no longer need a 2-tube setup. On the other hand, to balance the loss of trifluoromethoxide anion into the formation of fluoride and to maintain an excess of the weak nucleophile F_3CO^- , the amount of DNTFB and DMAP introduced in the reaction medium had to be increased to 18.0 and 9.0 equivalents respectively. To our satisfaction, the reaction carried out at 60 °C led to 89% conversion and a trifluoromethoxylation yield of 53% (Table 1, entry 6). Considering the better results obtained in the absence of any additional fluoride source, this strategy, taking place in only one tube, has therefore been more extensively investigated.

Table 1. Survey of aryne trifluoromethoxylation with fluoride salts^[a]



Entry	Fluoride salt	Temperature (°C)	Conv. (2a, %) ^[b]	Yield (3a, %) ^[b]
1	CsF	25	58	16
2	KF	25	78	11
3	TBAT	25	57	27
4	TBAT	40	88	30
5	TBAT	60	100	30
6 ^[c]	-	60	89	53

[a] Conditions: DNTFB (4.0 mmol), DMAP (2.0 mmol), **2a** (0.5 mmol), fluoride salt (1.0 mmol), MeCN (5.0 mL), temperature, 16 h, MeOH (2.0 mmol) after 16 h. [b] Yields and conversions were determined by ¹⁹F NMR with α, α, α -trifluorotoluene (PhCF₃) as internal standard. [c] Modified conditions: DNTFB (9.0 mmol), DMAP (4.5 mmol), **1a** (0.5 mmol), MeCN (5.0 mL), 60 °C, 16 h, MeOH (2.0 mmol) after 16 h.

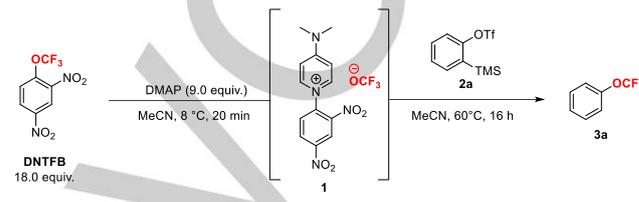


Scheme 2. Trifluoromethoxide anion degradation as a source of fluoride to activate the aryne precursor.

From this point on, we firstly decided to rise up the temperature of the reaction to 80 °C to increase the degradation rate of the trifluoromethoxide anion, which led to an improved trifluoromethoxylation yield of 64% (Table 2, entries 1–2). This degradation rate can also be modified by changing the ratio between DNTFB and DMAP.^[12] In fact, by decreasing this ratio from 2:1 (DNTFB:DMAP) to 1.5:1 at 60 °C (entry 3), the product **3a** was obtained with 57% yield and a total conversion. Other attempts to decrease the ratio and modify the temperature led to lower conversions and yields (entries 4 to 6). It has also been determined that the use of an ice bath to preform the F_3CO^- anion

is not necessary regarding the similar yield of 64% obtained with a preformation temperature of 35 °C (entries 7 vs 2). The preformation step can then be carried out at room temperature. However, the suppression of that step led to an important drop in the yield from 64% to 31% (entry 8). These last two results indicate that it is important to ensure that a high amount of trifluoromethoxide anion is present in solution when the aryne is formed, to quickly react with it. Moreover, the use of methanol (MeOH) as quenching agent at the end of the reaction was not mandatory either, regarding the similar yield of 62% obtained without quenching step (entry 9).

Table 2. Survey of aryne trifluoromethoxylation without fluoride salt^[a]



Entry	Deviation from standard conditions	Conv. (2a, %) ^[b]	Yield (3a, %) ^[b]
1	-	89	53
2	80 °C	100	64
3	13.5 equiv. of DNTFB	100	57
4	13.5 equiv. of DNTFB, 80 °C	97	58
5	9.9 equiv. of DNTFB	93	28
6	9.9 equiv. of DNTFB, 40 °C	100	46
7	Preformation of 1 at 35 °C, 80 °C	100	64
8	No preformation of 1 , 80 °C	100	31
9	No quench by MeOH, 80 °C	100	62

[a] Standard conditions: DNTFB (9.0 mmol), DMAP (4.5 mmol), **2a** (0.5 mmol), MeCN (5.0 mL), 60 °C, 16 h, followed by MeOH (2.0 mmol). [b] Yields and conversions were determined by ¹⁹F NMR with PhCF₃ as internal standard.

In order to determine if the reaction time can be lowered, an NMR survey was conducted to follow the consumption of aryne and DNTFB as well as the formation of trifluoromethoxybenzene **3a** over time (Figure 2). By analyzing the reaction every 45 minutes by quantitative ¹⁹F NMR analysis using α, α, α -trifluorotoluene as internal standard, we were able to follow the kinetics of the reaction. We noted that after only 20 minutes (Figure 2, top), which was the time of the first NMR analysis, almost 70% of the benzyne precursor **2a** had already reacted and around 35% of trifluoromethoxybenzene **3a** had been formed. The reaction thus starts very quickly. After about 2 hours, **2a** was totally consumed and after about 3 hours, the maximum yield of 47 % of **3a** was obtained. Regarding DNTFB (Figure 2, bottom, green curve), at the same time, a bit of the reactant was still present in the reaction medium, meaning that the F_3CO^- reservoir is not totally empty even if the trifluoromethoxylation reaction seems to be finished. Moreover, after about 4 hours, 5.49 mmol, (or 5.5 equiv.) of F_3CO^- were still present in solution, as shown by Figure 2, bottom, red curve. The same curve shows also that the trifluoromethoxide anion amount rapidly dropped after 290 minutes, which occurs concomitantly with the total consumption of DNFTB. In a precedent work,^[12a] we had shown that an excess of DNTFB was required to ensure the stability of the F_3CO^- salt. As soon as all the reservoir of DNTFB is emptied, the trifluoromethoxide anion cannot be regenerated by attack of endogenous fluoride onto DNTFB, and thus cannot be maintained at rather constant level. Since the aryne precursor in Figure 2 is fully consumed after 180

RESEARCH ARTICLE

min, the only fate of trifluoromethoxide is the equilibrium with COF_2 and F^- , the latter being itself able to activate DNTFB, releasing F_3CO^- which decomposes into COF_2 and F^- , and so on. The decomposition of DNTFB is thus auto-catalytic and can only be slowed down if the trifluoromethoxide is consumed by trapping with the aryne instead of releasing COF_2 and fluoride.

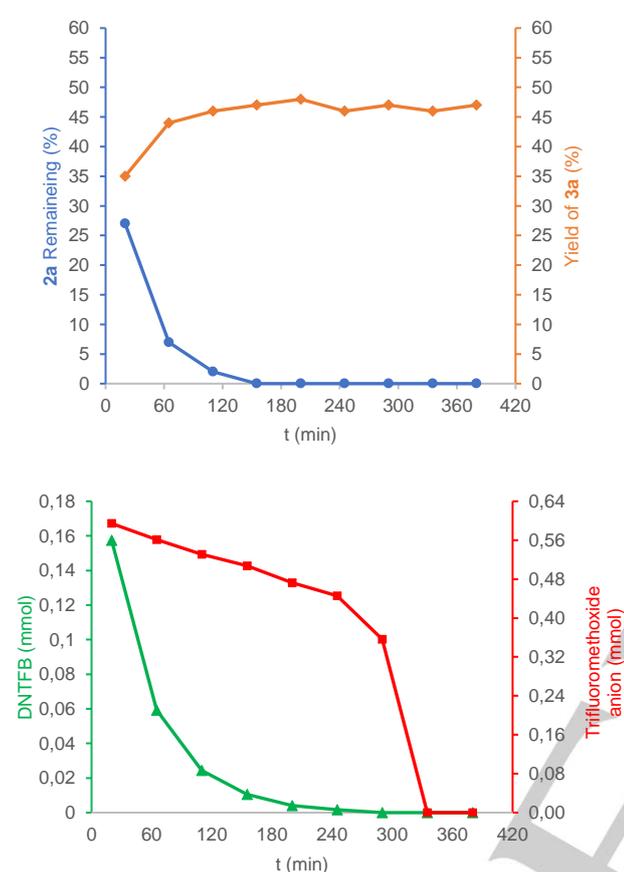


Figure 2. ^{19}F NMR monitoring of the consumption of aryne precursor **2a** (top, ● blue curve), **3a** formation (top, ◆ orange curve), DNTFB consumption (bottom, ▲ green curve) and trifluoromethoxide anion consumption (bottom, ■ red curve). Reaction conditions: **2a** (0.08 mmol, 1.0 equiv.), DMAP (0.72 mmol, 9.0 equiv.), DNTFB (1.47 mmol, 18.4 equiv.), CD_3CN (800 μL), 75 °C. ^{19}F NMR with PhCF_3 as internal standard.

With all this information in hand, we tried to reduce the reaction time. Under batch conditions, the yield was slightly decreased to 58% with a conversion of 96% after 3 hours (Table 3, entries 1–2). In line with the NMR study summarized in Figure 2, after 6 hours (entry 3), results obtained were the same than after 16 hours (entry 1). However, the use of 3-(trimethylsilyl)naphthalen-2-yl trifluoromethanesulfonate **2b** instead of **2a** led to lower efficiency than expected with a yield of 44% of 2-(trifluoromethoxy)naphthalene **3b** after 6 hours versus 52% after 16 hours (entries 4 and 5). The 16 hours reaction time was thus maintained for the rest of the study. Pursuing the optimization of the procedure, we also considered to add the aryne precursor in two portions to check whether the aryne was diverted from its course to other reaction pathways before the addition of CF_3O^- . Thus, the first half of precursor **2a** was added at the beginning of the reaction and the second half after 3 hours (entry 6). At the end of the 16 h reaction time, the yield was finally lower than under

standard conditions (entry 1) with only 57% of **3a** observed by NMR analysis.

Table 3. Application of the NMR survey results to batch conditions^[a]

Entry	Deviation from standard conditions	Conv. (2a , %) ^[b]	Yield (3a , %) ^[b]
1	-	100	64
2	3 h instead of 16 h	96	58
3	6 h instead of 16 h	100	64
4	2b instead of 2a	100	52 (3b)
5 ^[d]	2b instead of 2a	100	44 (3b)
6 ^[c] , [d]	Addition of 2a in two portions	97	57

[a] Standard conditions: DNTFB (9.0 mmol), DMAP (4.5 mmol), **2a** (0.5 mmol), MeCN (5.0 mL), 80 °C, 16 h, MeOH (2.0 mmol) after 16 h. [b] Yields and conversions were determined by ^{19}F NMR with PhCF_3 as internal standard. [c] 0.5 equiv. of **2a** at the beginning of the reaction and additional 0.5 equiv. added after 3 h. [d] 6 h instead of 16 h.

We also tried to perform the difunctionalization of arynes by halogenating the position adjacent to the trifluoromethoxy group, using electrophilic bromine sources in the same way Hu *et al* reported (Scheme 1).^[9h] We firstly used 1,2-dibromo-1,1,2,2-tetrafluoroethane (Table 4, entry 1) as electrophile, leading to the obtention of 22% of the protonated product **3b** and only 3% of the desired 2-bromo-3-(trifluoromethoxy)naphthalene **3b'**.

Table 4. *ortho*-Bromotrifluoromethoxylation of **2b**^[a]

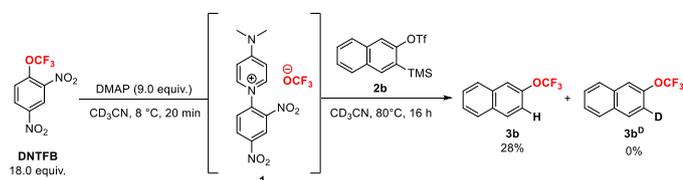
Entry	"Br ⁺ " source	Yield (3b , %) ^[b]	Yield (3b' , %) ^[b]
1	$\text{BrCF}_2\text{CF}_2\text{Br}$	22	3
2	$n\text{-C}_6\text{F}_{13}\text{Br}$	47	6
3	$\text{C}_6\text{F}_5\text{Br}$	39	4

[a] Standard conditions: DNTFB (9.0 mmol), DMAP (4.5 mmol), **2b** (0.5 mmol), "Br⁺" source (2.0 mmol), MeCN (5.0 mL), 80 °C, 16 h. [b] Yields and conversions were determined by ^{19}F NMR with PhCF_3 as internal standard.

The use of 1-bromoperfluorohexane (entry 2) and 1-bromoperfluorobenzene (entry 3) also gave **3b** as the major product and only low yields of 6% and 4% respectively for **3b'**. Hence, protonation was privileged over bromination. We thus investigated the origin of the proton preventing the *ortho* functionalization. The first hypothetical source of protons was acetonitrile. Indeed, it has already been reported that phenyl anions generated from addition of a nucleophile on arynes can abstract a proton from acetonitrile.^[18] To check this assumption, we used CD_3CN as solvent for the trifluoromethoxylation of 3-

RESEARCH ARTICLE

(trimethylsilyl)naphthalen-2-yl trifluoromethanesulfonate **2b** (Scheme 3). Under these conditions, only the protonated 2-(trifluoromethoxy)naphthalene **3b** was isolated with a yield of 28 % and no deuterated 2-(trifluoromethoxy)naphthalene-3-d **3b^D** was observed neither by NMR or GCMS analyses. Regarding this result, it seems that the proton is not provided by acetonitrile.



Scheme 3. Trifluoromethoxylation of **2b** in deuterated acetonitrile (isolated yields are given).

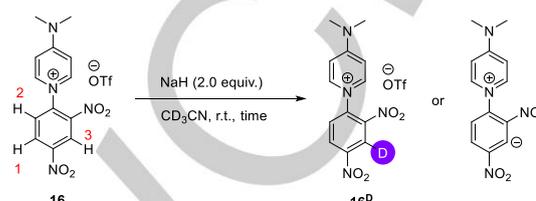
The second hypothesis was water traces in commercial anhydrous acetonitrile. In order to eliminate this possibility, acetonitrile with different levels of dryness was used. Employing standard reaction grade MeCN (Table 5, entry 2) led to an expected decline of yield, going down to 54%. However, the use of MeCN dried over phosphorus pentoxide (P_2O_5) then calcium hydride (CaH_2) (Table 5, entry 3) did not really show differences in yield compared to the reference experiment using commercial anhydrous acetonitrile (Table 5, entry 1). Residual water traces in the solvent are thus unlikely to serve as proton source. Third, we questioned the presence of water traces in reagents. DMAP was recrystallized and dried before use and substrate **2a** was employed as received from the supplier, as it did not contain any water traces by NMR analysis. We thus focused our attention on DNTFB as it was the reagent present in the largest amount and was also used as received from the supplier. However, when DNTFB had been dried over a weekend over CaH_2 , the reaction afforded a yield of 61%, i.e. similar to the one obtained with non-dried DNTFB (Table 5, entry 4 vs entry 1).

Table 5. Survey on the origin of the proton <i>ortho</i> to OCF_3 . ^[a]			
Entry	Deviation from standard conditions	Conv. (2a , %) ^[b]	Yield (3a , %) ^[b]
1	-	100	64
2	Reaction grade MeCN (from Fisher Scientific)	100	54
3	MeCN freshly distilled on P_2O_5 and CaH_2	100	60
4 ^[c] , ^[d]	DNTFB dried over CaH_2	100	61

[a] Standard conditions: DNTFB (9.0 mmol), DMAP (4.5 mmol), **2a** (0.5 mmol), MeCN (5.0 mL), 80 °C, 16 h, followed by MeOH (2.0 mmol). [b] Yields and conversions were determined by ^{19}F NMR with $PhCF_3$ as internal standard. [c] DNTFB dried over CaH_2 for 72 h and introduced through a syringe filter (0.2 μm , PTFE). [d] No quench with MeOH.

The protonation of the intermediate generated from nucleophilic attack of trifluoromethoxide onto the aryne is thus not due to trace water in either acetonitrile or the reagents. The last hypothesis was the abstraction of a proton from the *N*-arylpyridinium cation $DDPy^+$ and more especially of the proton located between the two nitro groups, which we presumed to be the most acidic. To validate this assumption, we prepared its triflate salt **16** ($DDPyOTf$), hence comprising the same $DDPy^+$ cation as in **1**,

and we made it react with NaH in deuterated acetonitrile in order to observe the corresponding deuterated compound (**16^D**) or the related carbanion (Scheme 4). By following the integration of proton signals over time we were able to observe a decrease in the relative intensity corresponding to proton H3 compared to the ones of H1 and H2. Indeed, after 4 h of reaction, the signal of H3 only integrated for 0.18 against 1.0 for H1 and 1.05 for H2 (Table 6, entry 3).

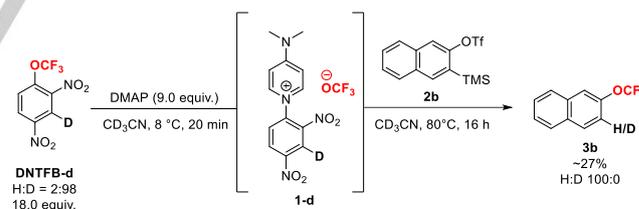


Scheme 4. Deprotonation and deuteration of pyridinium triflate salt **16** by NaH.

Table 6. NMR study of the deprotonation of **16** over time by NaH.

Entry	Reaction time (h)	H1 NMR integration	H2 NMR integration	H3 NMR integration
1	0.5	1.00	1.02	0.78
2	2	1.00	1.05	0.41
3	4	1.00	1.05	0.18

It is therefore not unreasonable to think that the $DDPy^+$ cation is the proton source in our system, preventing the *ortho*-functionalization that should be concomitant to trifluoromethoxylation. To confirm this assumption, we used deuterated DNTFB in a trifluoromethoxylation of naphthalene derivative **2b** expecting a deuteration of the final compound. Unfortunately, this experiment did not show any deuteration of trifluoromethoxynaphthalene **3b** (Scheme 5) indicating that the $DDPy^+$ cation might not be the only proton source in our system.

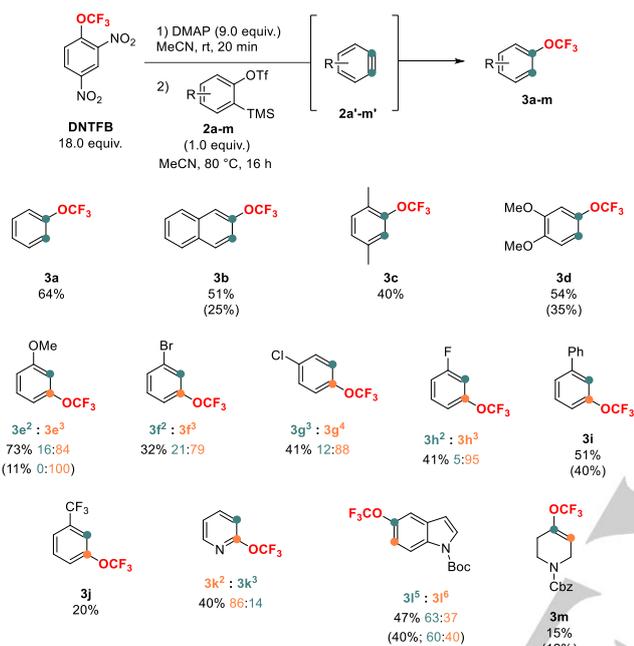


Scheme 5. Deuteration of **3b** using deuterated DNTFB.

With the optimized conditions in hand, involving 18 equivalents of DNTFB and 9 equivalents of DMAP at 80 °C for 16 h, we then started to study the scope of the reaction (Scheme 6). The trifluoromethoxylation of the naphthalene derivative gave the desired product with a slightly lower ^{19}F NMR yield of 51% for **3b** with regard to **3a**, and 25% after isolation due to its volatility. With an aryne hindered by methyl groups, namely 2,3-didehydro-1,4-dimethylbenzene, the yield decreased to 40% (**3c**). Using aromatic cycles substituted by methoxy groups, yields were medium to good. Indeed, 54% of **3d** and 73% of global NMR yield of **3e²** and **3e³** were obtained. Moreover, the regioselectivity obtained was good (84:16) in favor of *meta*-substituted **3e³**. Purification afforded only the major regioisomer with 11% yield. The trifluoromethoxylation of halogenated arynes gave modest yields due to the deactivation of the aromatic ring. Brominated products **3f²** and **3f³** were obtained with a global yield of 32% and

RESEARCH ARTICLE

with a corresponding 21:79 *ortho/meta* ratio, whereas chlorinated products **3g³** and **3g⁴** and fluorinated products **3h²** and **3h³** both gave 41 % of global yields with good to excellent regioselectivity—respective ratios of 88:12 and 95:5—in favor of **3g⁴** (*para*-substituted) and **3h³** (*meta*-substituted). The same observation can be made concerning the phenylated and trifluoromethylated substrates **2i** and **2j** that gave, after treatment with the DNTFB/DMAP system, an isolated yield of 40% for 3-(trifluoromethoxy)-1,1'-biphenyl **3i** and an NMR yield of 20 % for 3-(trifluoromethoxy)benzotrifluoride **3j** as solely observed regioisomers.



Scheme 6 Trifluoromethoxylation of arynes with the DNTFB/DMAP system. Yields and ratios determined by ¹⁹F NMR with PhCF₃ as internal standard (isolated yields in parentheses).

The DNTFB/DMAP system was also applied to the trifluoromethoxylation of heteroaromatic substrates. 2,3-Pyridine precursor **2k** led to 2- and 3-(trifluoromethoxy)pyridines **3k²** and **3k³** with a global yield of 40% and a good ratio of 86:14 in favor of **3k²**.^[19] Moderate yields were also obtained starting from indolyne precursor **2l**, which furnished **3l⁵⁻⁶** with a lower regioselective ratio of 63:37 in favor of *N*-Boc-protected 5-(trifluoromethoxy)indole **3l⁵** before purification and 60:40 after column chromatography. In all other cases, good regioselectivities were observed. Finally, the trifluoromethoxylation conditions applied to the 3-piperidine precursor **2m** gave a low isolated yield of 12% of **3m** as a single regioisomer. In terms of regioselectivity preferences, the results obtained for **3e-f,h,j-m** are in accordance with calculations reported by Santelli *et al.*,^[20] Garg, Houk *et al.*,^[21] and Iwata, Shindo *et al.*^[22] regarding the distortion angle of the active triple bond. Indeed, according to the distortion theory, the addition of a nucleophile onto an aryne is favored on the carbon showing the largest bond angle (See SI for details). Concerning the indolyne generated from precursor **2l**, only a small difference between angles on each extremity of the triple bond has been calculated,^[20b] consistently with the observed poor regioselectivity. On the other hand, for product **3g³⁻⁴**, the calculated distortion between the angles of the triple bond of the aryne intermediate was low. However, the regioselectivity observed was predominant

in favor of **3g⁴**. Finally, for product **3i**, the calculated structure of the corresponding aryne intermediate shows no sensible distortion of the triple bond (see SI for details) and the full regioselectivity in favor of the 1,3-disubstituted product should rather be ascribed to steric hindrance exerted by the phenyl group.

Conclusion

In this report, we have disclosed the use of the DNTFB/DMAP system to activate Kobayashi aryne precursors and trifluoromethoxylate the resulting arynes in modest to good yields and good regioselectivities in most cases. The trifluoromethoxide anion acted as both the nucleophile and the source of fluoride upon collapse of F₃CO⁻. Although the amount of DNTFB used was significant, the low cost of this stable and easy-to-use trifluoromethoxide anion source allows the synthesis of trifluoromethoxylated compounds at reasonable costs. Interestingly, electrophilic halogen-bearing reagents proved ineffective to concomitantly introduce a halogen atom in *ortho* position of the trifluoromethoxy group, due to the rapid protonation of the aryl carbanion intermediate. After discarding usual proton sources, we considered the *N*-arylpiperidinium cation DDPy⁺, a specific attribute of the DNTFB/DMAP system, but experiments could not reveal its role as protonating agent. All in all, this method is therefore complementary to other work in the literature on *ortho*-halogenotrifluoromethoxylations of arynes.

Experimental Section

Typical procedure for the trifluoromethoxylation reaction

In a 10 mL screw-cap sealed tube under argon, DNTFB (1.40 mL, 9.00 mmol, 18.0 equiv.) was added to a solution of DMAP (550 mg, 4.50 mmol, 9.0 equiv.) in anhydrous acetonitrile (4 mL). The tube was closed and the resulting solution was stirred for 20 min at room temperature. Then, the aryne precursor (0.50 mmol, 1.0 equiv.) in solution in anhydrous acetonitrile (1 mL) was added in the tube and the latter was tightly closed. The reaction mixture was stirred for 16 h at 80 °C. The tube was then allowed to cool down to room temperature and an aliquot was taken for yield and conversion determination by quantitative ¹⁹F NMR analysis (using α,α,α -trifluorotoluene as internal standard). The reaction medium was transferred to a separatory funnel and distilled water (10 mL) was added. After shaking and separation, the aqueous layer was extracted with pentane (3 x 10 mL). The combined organic layers were washed with brine (3 x 10 mL), dried over MgSO₄ and concentrated under vacuum. The product was purified by flash column chromatography using the appropriate solvent system.

Acknowledgements

We gratefully acknowledge the French Agence Nationale de la Recherche (ANR) (grant number ANR-20-CE07-0004-02, AP-PET-I), the CNRS, the Université de Strasbourg, the Université Lyon 1, CPE-Lyon and the French Fluorine Network (GIS-Fluor) for support. Finally, the authors also thank Dr. Emeric Wasielewski (NMR platform) and Matthieu Chessé (analytical

RESEARCH ARTICLE

facilities) of the LIMA (UMR7042 CNRS-Unistra-UHA), as well as the analytical facilities of the Fédération de Chimie "LeBel" (FR2010) of the Université de Strasbourg, who contributed, by their valuable technical and scientific support, to the achievement of this research project.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: 2,4-Dinitro-1-(trifluoromethoxy)benzene • Trifluoromethoxylation • Aryne • Trifluoromethoxide anion • Fluorine

- [1] a) M. Inoue, Y. Sumii, N. Shibata, *ACS Omega* **2020**, *5*, 10633–10640; b) Y. Ogawa, E. Tokunaga, O. Kobayashi, K. Hirai, N. Shibata, *iScience* **2020**, *23*, 101467; c) J. Liu, W. Lin, A. E. Sorochinsky, G. Butler, A. Landa, J. Han, V. A. Soloshonok, *J. Fluorine Chem.* **2022**, *257–258*, 109978.
- [2] J. E. Huheey, *J. Phys. Chem.* **1965**, *69*, 3284–3291.
- [3] C. Hansch, A. Leo, S. H. Unger, K. H. Kim, D. Nikaitani, E. J. Lien, *J. Med. Chem.* **1973**, *16*, 1207–1216.
- [4] a) R. W. Taft, E. Price, I. R. Fox, I. C. Lewis, K. K. Andersen, G. T. Davis, *J. Am. Chem. Soc.* **1963**, *85*, 709–724; b) R. W. Taft, E. Price, I. R. Fox, I. C. Lewis, K. K. Andersen, G. T. Davis, *J. Am. Chem. Soc.* **1963**, *85*, 3146–3156.
- [5] L. Kang, S. E. Novick, Q. Gou, L. Spada, M. Vallejo-López, W. Caminati, *J. Mol. Spectrosc.* **2014**, *297*, 32–34.
- [6] I. F. Shishkov, L. V. Khristenko, L. V. Vilkov, H. Oberhammer, *J. Phys. Chem. A* **2004**, *108*, 4966–4970.
- [7] a) A. Tlili, F. Toulgoat, T. Billard, *Angew. Chem. Int. Ed.* **2016**, *55*, 11726–11735; b) T. Besset, P. Jubault, X. Pannecoucke, T. Poisson, *Org. Chem. Front.* **2016**, *3*, 1004–1010; c) K. N. Lee, J. W. Lee, M.-Y. Ngai, *Tetrahedron*, **2018**, *74*, 7127–7135; d) J. W. Lee, K. N. Lee, M.-Y. Ngai, *Angew. Chem. Int. Ed.* **2019**, *58*, 11171–11181; e) Y. Cao, R. Ahmadi, M. R. P. Heravi, A. Issakhov, A. G. Ebadi, E. Vessally, *RSC Adv.* **2021**, *11*, 39593–39606; f) Q. Wang, X. Zhang, A. E. Sorochinsky, G. Butler, J. Han, V. A. Soloshonok, *Symmetry* **2021**, *13*, 2380; g) S. Barata-Vallejo, S. M. Bonesi, A. Postigo, *Chem. Eur. J.* **2022**, *28*, e202201776.
- [8] a) H. Di Loreto, J. Czarnowski, *J. Fluorine Chem.* **1995**, *74*, 199–201; b) W. J. Peláez, G. A. Argüello, *Tetrahedron Lett.* **2010**, *51*, 5242–5245; c) F. Venturini, W. Navarrini, A. Famulari, M. Sansotera, P. Dardani, V. Tortelli, *J. Fluorine Chem.* **2012**, *140*, 43–48; d) W. Zheng, J. W. Lee, C. A. Morales - Rivera, P. Liu, M. Ngai, *Angew. Chem. Int. Ed.* **2018**, *57*, 13795–13799; e) W. Zheng, C. A. Morales - Rivera, J. W. Lee, P. Liu, M. Ngai, *Angew. Chem. Int. Ed.* **2018**, *57*, 9645–9649; f) B. J. Jelier, P. F. Tripet, E. Pietrasiak, I. Franzoni, G. Jeschke, A. Togni, *Angew. Chem. Int. Ed.* **2018**, *57*, 13784–13789; g) J. W. Lee, S. Lim, D. N. Maienshein, P. Liu, M. Ngai, *Angew. Chem. Int. Ed.* **2020**, *59*, 21475–21480; h) T. Duhail, T. Bortolato, J. Mateos, E. Anselmi, B. Jelier, A. Togni, E. Magnier, G. Dagousset, L. Dell'Amico, *Org. Lett.* **2021**, *23*, 7088–7093.
- [9] a) A. A. Kolomeitsev, M. Vorobyev, H. Gilland, *Tetrahedron Lett.* **2008**, *49*, 449–454; b) O. Marrec, T. Billard, J.-P. Vors, S. Pazenok, B. R. Langlois, *J. Fluorine Chem.* **2010**, *131*, 200–207; c) C. Huang, T. Liang, S. Harada, E. Lee, T. Ritter, *J. Am. Chem. Soc.* **2011**, *133*, 13308–13310; d) J. Barbion, S. Pazenok, J.-P. Vors, B. R. Langlois, T. Billard, *Org. Process Res. Dev.* **2014**, *18*, 1037–1040; e) G.-F. Zha, J.-B. Han, X.-Q. Hu, H.-L. Qin, W.-Y. Fang, C.-P. Zhang, *Chem. Commun.* **2016**, *52*, 7458–7461; f) G. Yin, X. Mu, G. Liu, *Acc. Chem. Res.* **2016**, *49*, 2413–2423; g) S. Guo, F. Cong, R. Guo, L. Wang, P. Tang, *Nat. Chem.* **2017**, *9*, 546–551; h) M. Zhou, C. Ni, Y. Zeng, J. Hu, *J. Am. Chem. Soc.* **2018**, *140*, 6801–6805; i) Y.-M. Yang, J.-F. Yao, W. Yan, Z. Luo, Z.-Y. Tang, *Org. Lett.* **2019**, *21*, 8003–8007; j) J. Newton, B. J. Jelier, M. Meanwell, R. E. Martin, R. Britton, C. M. Friesen, *Org. Lett.* **2020**, *22*, 1785–1790; k) Y. Li, Y. Yang, J. Xin, P. Tang, *Nat Commun* **2020**, *11*, 755; l) A. Turksoy, T. Scattolin, S. Bouayad-Gervais, F. Schoenebeck, *Chem. Eur. J.* **2020**, *26*, 2183–2186; m) X. Jiang, P. Tang, *Chin. J. Chem.* **2021**, *39*, 255–264; n) Z. Lu, T. Kumon, G. B. Hammond, T. Umemoto, *Angew. Chem. Int. Ed.* **2021**, *133*, 16307–16313; o) J. Saiter, T. Guérin, M. Donnard, A. Panossian, G. Hanquet, F. R. Leroux, *Eur. J. Org. Chem.* **2021**, *2021*, 3139–3147; p) W.-J. Yuan, C.-L. Tong, X.-H. Xu, F.-L. Qing, *J. Org. Chem.* **2023**, *88*, 4434–4441; o) D. Chen, Y. Luo, L. Lu, Q. Shen, *Organometallics* **2024**, ASAP DOI 10.1021/acs.organomet.4c00073.
- [10] N. Fiederling, J. Haller, H. Schramm, *Org. Process Res. Dev.* **2013**, *17*, 318–319.
- [11] O. Marrec, T. Billard, J.-P. Vors, S. Pazenok, B. R. Langlois, *Adv. Synth. Catal.* **2010**, *352*, 2831–2837.
- [12] a) C. Bonnefoy, E. Chefdeville, A. Panossian, G. Hanquet, F. R. Leroux, F. Toulgoat, T. Billard, *Chem. Eur. J.* **2021**, *27*, 15986–15991; b) C. Bonnefoy, A. Panossian, G. Hanquet, F. R. Leroux, F. Toulgoat, T. Billard, *Chem. Eur. J.* **2023**, *29*, e202301513
- [13] G. Duran-Camacho, D. M. Ferguson, J. W. Kampf, D. C. Bland, M. S. Sanford, *Org. Lett.* **2021**, *23*, 5138–5142.
- [14] C. Bonnefoy, E. Chefdeville, C. Tourvieille, A. Panossian, G. Hanquet, F. Leroux, F. Toulgoat, T. Billard, *Chem. Eur. J.* **2022**, e2022015.
- [15] a) T. Billard, in 26th Winter Fluorine Conference, American Chemical Society, **2023**, p. WFC2023; b) A. V. R. D. Lisboa, G. Duran-Camacho, A. K. Ehrlicher, M. R. Lasky, M. S. Sanford, *Org. Lett.* **2023**, *25*, 9025–9029; c) C. Bonnefoy, A. Gallego, C. Delobel, B. Raynal, M. Decourt, E. Chefdeville, G. Hanquet, A. Panossian, F. R. Leroux, F. Toulgoat, T. Billard, *Eur. J. Org. Chem.* **2024**, e202400142.
- [16] For selected reviews, see: a) H. Pellissier, M. Santelli, *Tetrahedron*, **2003**, *59*, 701–730; b) R. Sanz, *Org. Prep. Proced. Int.* **2008**, *40*, 215–291; c) P. M. Tadross, B. M. Stoltz, *Chem. Rev.* **2012**, *112*, 3550–3577; d) J. Shi, L. Li, Y. Li, *Chem. Rev.* **2021**, *121*, 3892–4044.
- [17] M. Lei, H. Miao, X. Wang, W. Zhang, C. Zhu, X. Lu, J. Shen, Y. Qin, H. Zhang, S. Sha, Y. Zhu, *Tetrahedron Lett.* **2019**, *60*, 1389–1392.
- [18] For selected examples, see: a) M. Jeganmohan, C.-H. Cheng, *Chem. Commun.* **2006**, 2454; b) S.-E. Sun, D. M. Chenoweth, *Org. Lett.* **2016**, *18*, 4080–4083; c) L. Zhang, X. Li, Y. Sun, W. Zhao, F. Luo, X. Huang, L. Lin, Y. Yang, B. Peng, *Org. Biomol. Chem.* **2017**, *15*, 7181–7189; d) K. Neog, D. Dutta, B. Das, P. Gogoi, *Org. Biomol. Chem.* **2019**, *17*, 6450–6460.
- [19] Yields were determined based on an analogy with 2-chloro-6-(trichloromethoxy)pyridine and 2-chloro-5-(trichloromethoxy)pyridine from B. Manteau, P. Genix, L. Brelot, J.-P. Vors, S. Pazenok, F. Giornal, C. Leuenberger, F. R. Leroux, *Eur. J. Org. Chem.* **2010**, *2010*, 6043–6066.
- [20] P. Maurin, M. Ibrahim-Ouali, J.-L. Parrain, M. Santelli, *J. Mol. Struct. THEOCHEM.* **2003**, *637*, 91–100.
- [21] a) G.-Y. J. Im, S. M. Bronner, A. E. Goetz, R. S. Paton, P. H.-Y. Cheong, K. N. Houk, N. K. Garg, *J. Am. Chem. Soc.* **2010**, *132*, 17933–17944; b) A. E. Goetz, S. M. Bronner, J. D. Cisneros, J. M. Melamed, R. S. Paton, K. N. Houk, N. K. Garg, *Angew. Chem. Int. Ed.* **2012**, *51*, 2758–2762; c) J. M. Medina, J. L. Mackey, N. K. Garg, K. N. Houk, *J. Am. Chem. Soc.* **2014**, *136*, 15798–15805; d) T. C. McMahon, J. M. Medina, Y.-F. Yang, B. J. Simmons, K. N. Houk, N. K. Garg, *J. Am. Chem. Soc.* **2015**, *137*, 4082–4085.
- [22] T. Iwata, M. Hyodo, T. Fujiwara, R. Kawano, L. Kuhn, I. V. Alabugin, M. Shindo, *Synthesis* **2022**, *54*, 4971–4978.

Supporting informations

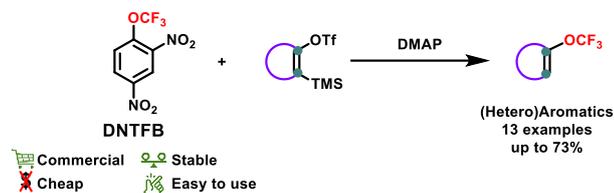
- [23] A. F. Burchat, J. M. Chong, N. Nielsen, *J. Organomet. Chem.* **1997**, *542*, 281–283.
- [24] D. Peña, A. Cobas, D. Pérez, E. Guitián, *Synthesis* **2002**, *10*, 1454–1458.
- [25] B. S. Shaibu, R. K. Kawade, R.-S. Liu, *Org. Biomol. Chem.* **2012**, *10*, 6834–6839.
- [26] M. Damrath, L. D. Caspers, D. Duvinage, B. J. Nachtsheim, *Org. Lett.* **2022**, *24*, 2562–2566.

RESEARCH ARTICLE

- [27] X. Li, Y. Sun, X. Huang, L. Zhang, L. Kong, B. Peng, *Org. Lett.* **2017**, *19*, 838–841.
- [28] J. Shi, L. Li, C. Shan, J. Wang, Z. Chen, R. Gu, J. He, M. Tan, Y. Lan, Y. Li, *J. Am. Chem. Soc.* **2021**, *143*, 2178–2184.
- [29] A. F. C. Rossini, A. C. A. Muraca, G. A. Casagrande, C. Raminelli, *J. Org. Chem.* **2015**, *80*, 10033–10040.
- [30] B. Michel, M. F. Greaney, *Org. Lett.* **2014**, *16*, 2684–2687.
- [31] M. Dai, Z. Wang, S. J. Danishefsky, *Tetrahedron Lett.* **2008**, *49*, 6613–6616.
- [32] H. Kaneko, T. Ikawa, Y. Yamamoto, S. Arulmozhiraja, H. Tokiwa, S. Akai, *Synlett* **2018**, *29*, 943–948.
- [32] B. V. Moreira, A. C. A. Muraca, C. Raminelli, *Synthesis* **2017**, *49*, 1093–1102.
- [33] S. Yoshida, K. Shimomori, T. Nonaka, T. Hosoya, *Chem. Lett.* **2015**, DOI 10.1246/cl.150535.
- [34] M. A. Walters, J. J. Shay, *Synth. Commun.* **1997**, *27*, 3573–3579.
- [35] D. L. Comins, S. P. Joseph, R. R. Goehring, *J. Am. Chem. Soc.* **1994**, *116*, 4719–4728.
- [36] C. Chatalova-Sazepin, M. Binayeva, M. Epifanov, W. Zhang, P. Foth, C. Amador, M. Jagdeo, B. R. Boswell, G. M. Sammis, *Org. Lett.* **2016**, *18*, 4570–4573.
- [37] S. Krishanmoorthy, S. D. Schnell, H. Dang, F. Fu, G. K. S. Prakash, *J. Fluor. Chem.* **2017**, *203*, 130–135.
- [38] A. V. Nyuchev, T. Wan, B. Cendón, C. Sambiagio, J. J. C. Struijs, M. Ho, M. Gulías, Y. Wang, T. Noël, *Beilstein J. Org. Chem.* **2020**, *16*, 1305–1312.
- [39] A. Gevorgyan, K. H. Hopmann, A. Bayer, *Green Chem.* **2021**, *23*, 7219–7227.
- [40] A. E. Goetz, N. K. Garg, *J. Org. Chem.* **2014**, *79*, 846–851.
- [41] T. T. Nguyen, *R. Soc. Open Sci.* **2021**, *8*, 210954.

RESEARCH ARTICLE

Entry for the Table of Contents



The trifluoromethoxylation of arynes has been little reported in the literature mainly due to the limited number of stable trifluoromethoxide anion sources existing. We describe herein the trifluoromethoxylation of arynes using 2,4-dinitro-1-(trifluoromethoxy)benzene (DNTFB) as a cheap and easy-to-use source of F_3CO^- . The released trifluoromethoxide anion was used as both a source of fluoride to generate the aryne and a nucleophile for the trifluoromethoxylation reaction.