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Daniel Joven-Sancho, Noel Nebra. On the Existence and Relevance of Copper(III) Fluorides in Oxidative Trifluoromethylation. SYNLETT, 2024, 10.1055/a-2351-5090 . hal-04759058

HAL Id: hal-04759058

<https://hal.science/hal-04759058v1>

Submitted on 29 Oct 2024

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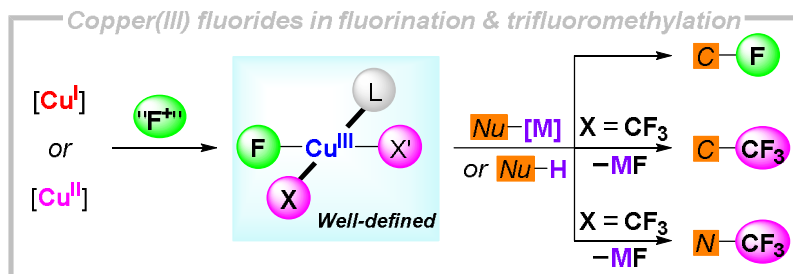
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On the Existence and Relevance of Copper(III) Fluorides in Oxidative Trifluoromethylation.

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Received:
Accepted:
Published online:
DOI:

Abstract Numerous reports invoke $\text{Cu}^{\text{III}}\text{-F}$ intermediates engaging in oxidative cross-couplings mediated by low/mid valent copper and formal sources of “ F^+ ” oxidants. These elusive and typically instable Cu^{III} fluorides have been rarely characterized or spectroscopically identified, making their existence and participation within catalytic cycles somehow questionable. We have authenticated a stable organocopper(III) fluoride that undergoes $\text{C}_{\text{sp}}\text{-CF}_3$ bond formation upon addition of silyl-capped alkynes following a $2e^- \text{Cu}^{\text{II}}/\text{Cu}^{\text{I}}$ redox shuttle. This finding strongly supports the intermediacy of Cu^{III} fluorides in C–C coupling. We review herein the *State of the Art* about well-defined Cu^{III} fluorides enabling cross-coupling reactions.

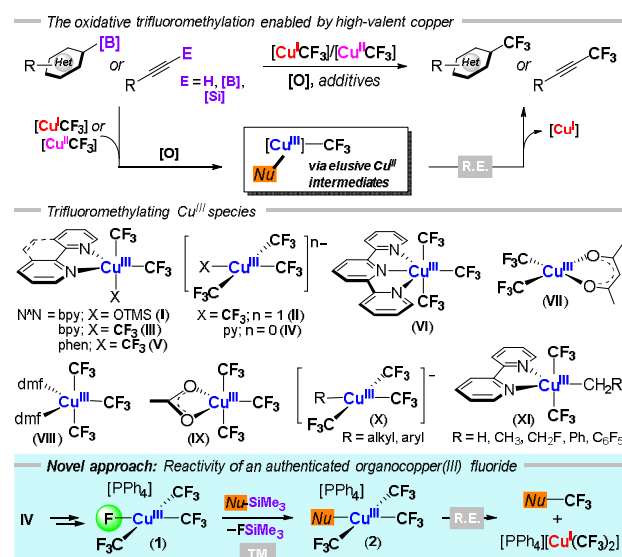
- 1 Introduction
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- 3 Design of an isolable –yet reactive– organocopper(III) fluoride
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Key words Trifluoromethylation, organocopper(III) compounds, Cu^{III} fluorides, oxidative cross-coupling, $2e^-$ redox shuttle.

1 Introduction

The oxidative trifluoromethylation¹ of nucleophiles rises up as an elegant tool for assembling high-value² trifluoromethylated alkynes³ or (hetero)aryls.⁴ These seminal works^{1,3–4} pointed to the transient life of trifluoromethylating Cu^{III} intermediates built from $\text{Cu}^{\text{I}}/\text{Cu}^{\text{II}}$ precursors and oxidants (air, O_2 , Ag salts; Scheme 1 top) –yet without any spectroscopic input. To this sense, the technically demanding detection of the assumed Cu^{III} effecting the C–C coupling rendered this mechanistic panorama uncertain. Some insight regarding the involvement of Cu^{III} in oxidative trifluoromethylation was brought by the NMR identification of $[\text{Cu}^{\text{III}}(\text{CF}_3)_2(\text{OTMS})(\text{bpy})]$ (**I**) (Scheme 1 middle) that arises from the aerobic oxidation of $[\text{Cu}^{\text{I}}(\text{CF}_3)(\text{bpy})]$ in presence of CF_3SiMe_3 .⁵ Interestingly, **I** reacts with phenylboronic acid and yields PhCF_3 within minutes.⁵ This encouraged Grushin’s team to efficiently synthesize Naumann’s Cu^{III} anion $[\text{Cu}^{\text{III}}(\text{CF}_3)_4]^-$ (**II**)^{6,7} by using

CuCl or “ligandless” CuCF_3 ,⁸ KF and CF_3SiMe_3 in air. Having **II** at hand, the trifluoromethylating competent $[\text{Cu}^{\text{III}}(\text{CF}_3)_3(\text{bpy})]$ (**III**)⁹ was achieved by reacting **II** vs. bpy in warm AcOH .⁷ After *ca.* 30 years of latency, these discoveries^{5,7} reignited $\text{Cu}^{\text{III}}\text{CF}_3$ chemistry, and related Cu^{III} compounds (**III–IX**) were lately synthesized.^{10,11} Noticeably, **III** and **IV** trifluoromethylated arylboron or alkylzinc reagents *via* intermediate formation of anions $[\text{Cu}^{\text{III}}(\text{CF}_3)_3(\text{R})]^-$ (**X**)¹² or the neutral $[\text{Cu}^{\text{III}}(\text{CF}_3)_2(\text{CH}_3)(\text{bpy})]$ (**XI**),¹³ while **VII–IX** (and **IV**) proved to be efficient radicalary trifluoromethylating agents of thiols, alkynes, or $\text{C}_{\text{aryl}}\text{-H}$ bonds.^{10b,11a}



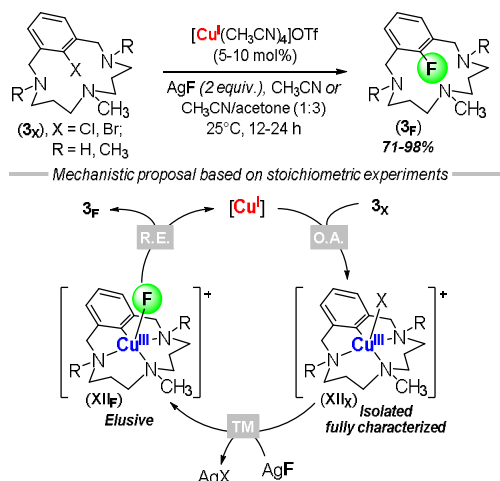
Scheme 1. State of art and concept disclosed herein. Schematic representation of the oxidative trifluoromethylation of (hetero)aryls or alkynes enabled by high-valent copper (top). Selected trifluoromethylating $\text{Cu}^{\text{III}}\text{CF}_3$ platforms **I–XI** prepared through Cu^{I} -to- Cu^{III} oxidation triggered by air, O_2 , AgF or aryl-radical-enabled oxidative addition of alkyl iodides (middle).^{5–7,10–13} Entry to the $\text{Cu}^{\text{III}}\text{-F}$ **1** and its application in trifluoromethylation *via* transmetalation reaction with silyl-capped alkynes and related compounds (bottom).

Given the synthetic utility of alkynes, a singular case example of oxidative trifluoromethylation is represented by their selective

trifluoromethylation at terminal position. Strikingly, despite the relevance and often invoked participation of Cu^{III} acetylides in catalysis,¹⁴ their isolation and characterization is commonly out of reach. Accordingly, attesting the plausible intermediacy of $(\text{RC}\equiv\text{C})\text{-Cu}^{\text{III}}\text{-CF}_3$ fragments in alkyne trifluoromethylation constitutes an undeniable challenge in Cu^{III} chemistry. Meanwhile, recent work by Zhang^{10b} and Beier^{11a} using **IV**, **VI** or **VII** seems to indicate the involvement of $\cdot\text{CF}_3$ radicals with no need for $\text{RC}\equiv\text{C}\text{-Cu}^{\text{III}}$ bond creation. Against this intricate backdrop, we wanted to kill two birds with the same stone. We hypothesized that a stable organocopper(III) fluoride (**1**) may undergo transmetalation with silyl-capped alkynes and related compounds, leading to the Cu^{III} anions of type **2** (including Cu^{III} acetylides), and we thus envisioned the preparation and authentication of **1** seeking to establish the viability of $\text{Cu}^{\text{I}}/\text{Cu}^{\text{III}}$ redox cycles in the oxidative trifluoromethylation of alkynes.¹⁵

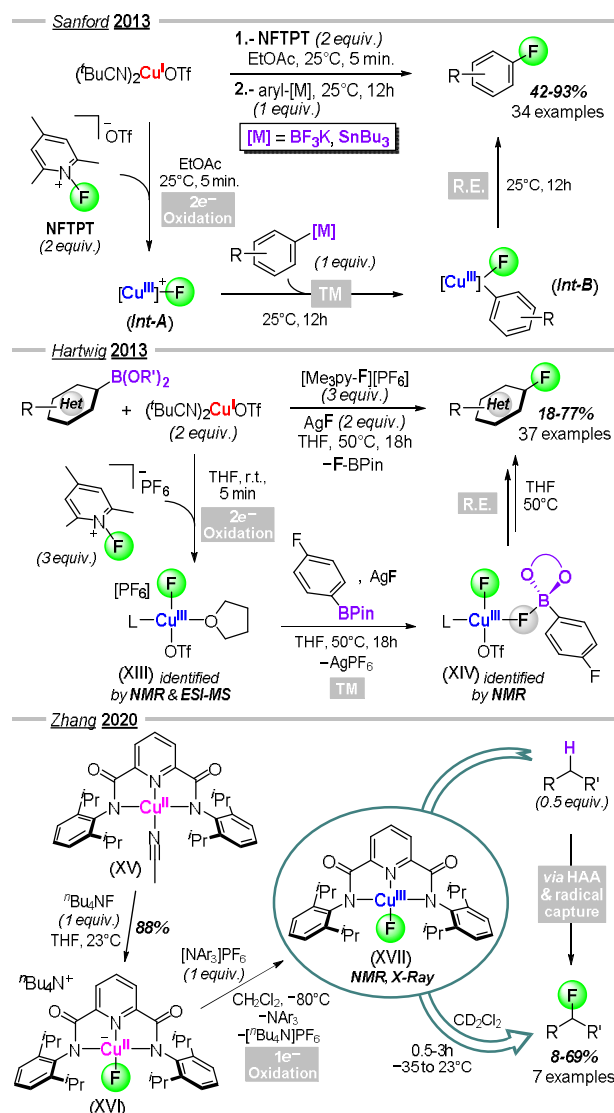
2 Brief history of coupling competent Cu^{III} fluorides

Copper catalysis has been extensively used in cross-coupling reactions as a greener and cost-effective alternative to palladium. This is the case of the venerable Ullmann–Goldberg reaction that was discovered back in 1901 and allows the functionalization of aryl halides using nucleophiles.¹⁶ Mechanistically, despite the scarcity of well-defined organocopper(III) species,¹⁷ $\text{Cu}^{\text{I}}/\text{Cu}^{\text{III}}$ redox cycles are often invoked by mimicking Pd chemistry. It took ca. 110 years to unveil this $2e^-$ redox scenario, when Stahl and Ribas¹⁸ brilliantly demonstrated the operability of a $\text{Cu}^{\text{I}}/\text{Cu}^{\text{III}}$ redox pair in C–heteroatom bond formation through the isolation and reactivity examination of a family of aryl- Cu^{III} intermediates **XII_X** that were conveniently stabilized by the rigid coordination of an aryl-triazamacrocyclic ligand. Interestingly, this strategy was extended to aromatic fluorination, and the corresponding aryl-X macrocyclic ligands **3_X** ($X = \text{Cl}, \text{Br}, \text{I}; R = \text{H}, \text{CH}_3$) furnished the fluorinated derivatives **3_F** via transient formation of the aryl- Cu^{III} species **XII_X** and **XII_F** (see Scheme 2 below).^{19,20} Although the authors failed to detect the fluoro- Cu^{III} **XII_F**, its formation by halide exchange of **XII_X** and AgF seems to be feasible, thus triggering the reductive elimination (R.E.) of the aryl-F coupled product **3_F** and the Cu^{I} -catalyst, which re-oxidizes into the resting state Cu^{III} species **XII_X** in presence of **3_X**. This was additionally supported by XANES/EXAFS analysis that pointed to an easy building of aryl- $\text{Cu}^{\text{III}}\text{-X}$ fragments upon the coordination of *N*-donor directing groups.²¹



Scheme 2. Ullmann-type fluorination of aryl halides **3_X** involving Cu^{III} -key intermediates of type **XII** demonstrated by Ribas.¹⁹

Another masterpiece, this time regarding oxidative fluorination, was reported shortly after by Ye and Sanford.²² Akin to high-valent silver,^{23,24} the fluorination of an array of aryl-stannanes and aryl-trifluoroborates was achieved presumably from the Cu^{III} fluorides **Int-A** and **Int-B** built *in situ* from $(t\text{BuCN})_2\text{Cu}^{\text{I}}\text{OTf}$ and *N*-fluoro-2,4,6-trimethylpyridinium triflate (**NFTPT**; Scheme 3 top). Other variants saw light using different organometallic partners and/or oxidants,²⁵ yet commonly pointing to the participation of Cu^{III} fluorides of type **Int-B** with no spectroscopic clue. The existence²⁶ of the assumed Cu^{III} fluorides effecting the C–F coupling was first noticed by Hartwig and co-workers,²⁷ who managed to detect the $\text{Cu}^{\text{III}}\text{-F}$ and $\text{F-Cu}^{\text{III}}\text{-F}$ species **XIII** and **XIV** by using ESI-MS spectrometry and/or NMR spectroscopy (Scheme 3 middle). Indeed, the cocktail composed of $(t\text{BuCN})_2\text{Cu}^{\text{I}}\text{OTf}$, an arylboronic ester, AgF and $[\text{Me}_3\text{py-F}][\text{PF}_6]$ yields the corresponding fluoroarene in up to 77% yield. Interestingly, the forging of an elusive aryl- $\text{Cu}^{\text{III}}\text{-F}$ complex from **XIV** occurs through a rate-limiting boron-to- Cu^{III} aryl-group transfer, which most likely infers an easy aryl-F bond creation from Cu^{III} .



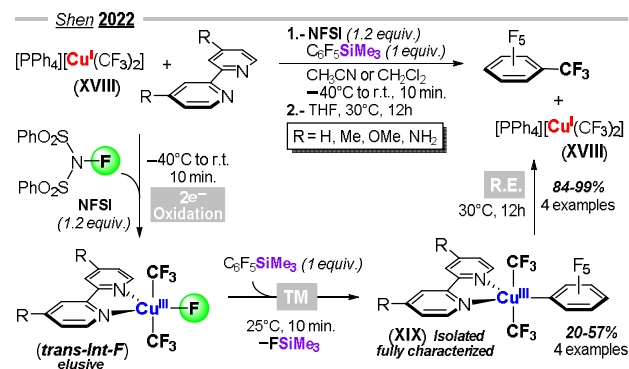
Scheme 3. Oxidative fluorination enabled by a $\text{Cu}^{\text{III}}\text{-F}$. Sanford's fluorination of arylboron derivatives and aryl-stannanes (top),²¹ NMR identification of the fluorinating competent $\text{Cu}^{\text{III}}\text{-F}$ species **XIII**–**XIV** (Hartwig, middle),²⁷ and first crystallographically authenticated $\text{Cu}^{\text{III}}\text{-F}$ **XVII** with utility in alkyl-H fluorination (Zhang, bottom).^{28a} L = 2,4,6-collidine (Me₃py).

Crystallographic authentication of a molecular Cu^{III} fluoride was lacking until 2020 when Zhang's group^{28a} reported the synthesis and characterization of **XVII** being stabilized by a dianionic triazadentate ligand (Scheme 3 bottom). Profound mechanistic investigation convincingly proved that **XVII** enables C–H bond fluorination of alkanes *via* H-atom abstraction (HAA) followed by an \cdot alkyl radical capture. Soon after, the same group developed an electrocatalytic variant for C–H bond fluorination of alkanes using **XVII**, the only well-defined Cu^{III} fluoride being catalytically competent in fluorination.

Taken together, it seems clear that Cu^{III} fluorides might be formed by adding "F⁺" oxidants,^{24–27} or alternatively, a fluoride source and an oxidant,^{28a,29} to low-valent copper. Similarly, the capacity of aryl-Cu^{III}-F fragments to undergo 2e⁻ R.E. processes and forge C–F bonds seems to be feasible.²⁷ Conversely, the role of Cu^{III} fluorides in reminiscent C–C³⁰ and C–heteroatom³¹ (mainly C–N)^{31a–e} bond formations remains ambiguous, despite the ubiquitous presence of "formally" Cu^{III} fluorides in mechanistic depictions dealing with the hydrocarbon functionalization of *N*-fluorinated amines [Hofmann–Löffler–Freitag (HLF) reaction].³² An insightful contribution by Muñiz and coworkers³³ reported the building of both pyrrolidine (**5**) or piperidine (**6**) scaffolds from the *N*-fluorosulfamides of type **4** using only 1 mol% of [(ⁱPr₂Tp)Cu^I(NCCH₃)] (Scheme 4 left). DFT investigations pointed to the oxidation of the Cu^I catalyst by **4** leading to a Cu^{II}-F *Int-C'* bearing a ligand-centered radical that is lower in energy (by *ca.* 10 kcal/mol) than its closed shell Cu^{III}-F, *Int-C*. According to calculations, *Int-C'* evolves *via* 1,5-HAT to form an analogous Cu^{II}-F *Int-D'* displaying a carbon-centered radical (rate-determining step), which later releases the coupled product **5/6** bringing back the Cu^I catalyst. Nevertheless, definitive consensus regarding the true nature of the *in situ* formed high-valent copper fluoride is yet to come, and different pathways depicting a Cu^{III}-F resembling *Int-C* have been proposed by others.^{30a,31b–d} Indeed, variations of this protocol³⁴ using arylboronic derivatives as coupling partners were independently discovered by Zhu^{34a} and Nagib^{34b} affording the C–C coupled products **7** (Scheme 4 right). By contrast, despite the similarity between both approaches, Zhu^{34a} and Nagib^{34b} suggested the transient formation of the Cu^{III} fluorides of type *Int-E* that effect the C–C bond formation under mild conditions.

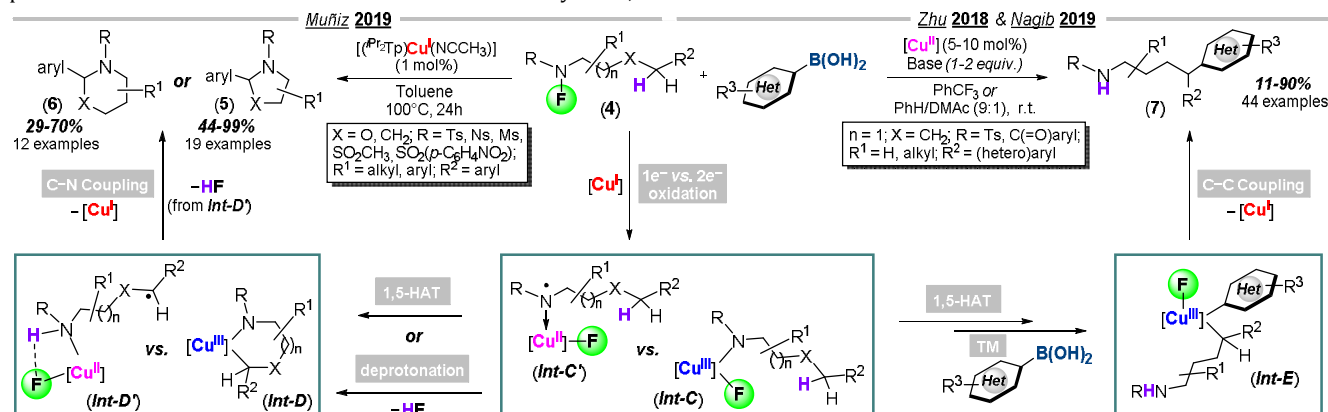
A closely related work disclosing the isolation and reactivity examination of [Cu^{III}(CF₃)₂(C₆F₅)(N[^]N)] (**XIX**), an elusive pentacoordinated intermediate in arene trifluoromethylation,

has been recently reported by Shen and co-workers.³⁵ To this end, the authors reacted the Cu^I homoleptic anion [Cu^I(CF₃)₂]⁻ (**XVIII**) with a family of *p*-functionalized bpy ligands, *N*-fluorobenzenesulfonimide (**NFSI**) and C₆F₅SiMe₃ to achieve the corresponding aryl-Cu^{III} compounds of type **XIX**, that were isolated in moderate yields (20–57%; Scheme 5). The formation of **XIX** from **XVIII** and **NFSI** presumes the transient building of an elusive Cu^{III}-F of type *Int-F*, displaying either *trans*- or *cis*-disposition of the two CF₃ ligands (by analogy to **XIX** and **XI**, only the *trans-Int-F* is depicted in Scheme 5). Once characterized, the instability and propensity of the aryl-Cu^{III} species **XIX** to undergo aryl–CF₃ bond forming reaction was confirmed upon mild heat (30°C) overnight that smoothly produced C₆F₅CF₃ in excellent yields (84–99%). Profound mechanistic investigations (kinetic analyses; stoichiometric experiments using the radical trap scavengers TEMPO, BHT or 1,4-dinitrobenzene; DFT analysis) indicate that the aryl–CF₃ coupling event from **XIX** occurs exclusively through a synchronous Cu^{III}–aryl and Cu^{III}–CF₃ bond breaking / aryl–CF₃ bond forming process.



Scheme 5. 2e⁻ oxidation of [Cu^I(CF₃)₂]⁻ (**XVIII**) into [Cu^{III}(CF₃)₂(C₆F₅)(N[^]N)] (**XIX**) using **NFSI** as an oxidant in presence of bpy-functionalized ligands and C₆F₅TMS reported by Shen.³⁵

As this section intends to reflect, the controversy on the nature of the "formally" Cu^{III} fluorides enabling C–N and C–C couplings represents an intriguing debate in contemporary Cu chemistry. It was then our goal to design an easy-to-handle Cu^{III}-F allowing to probe these singular reactivity patterns. In hopes of establishing whether or not a well-defined Cu^{III}-F may be engaged in C–C or C–heteroatom couplings, we logically questioned ourselves how to enhance the stability of an organocopper(III) fluoride (see section below).

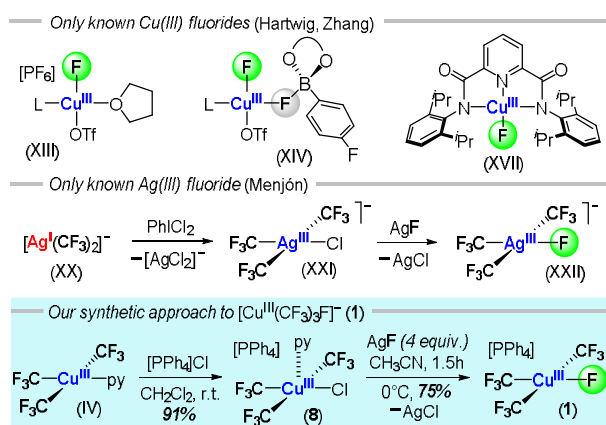


Scheme 4. Cyclizing C–N couplings of *N*-fluorosulfamides **4** leading to pyrrolidine (**5**) or piperidine (**6**) scaffolds (Muñiz,³³ left), and divergent reactivity leading to C–C bond formation upon addition of arylboronic acids (Zhu^{34a} & Nagib,^{34b} right).

3 Design of an isolable –yet reactive– organocopper(III) fluoride

As abovementioned, it was our purpose to synthesize a Cu^{III}-F compound that serves as a motif to develop a number of organic transformations, but being stable enough to be handled as a solid, which makes it a more practical and useful reagent. Given the ability of the CF₃ group to stabilize high oxidation states, such as +III in copper, it was hypothesized that this perfluoroalkyl ligand would be an ideal candidate to enhance chances of isolating an easy-to-handle organocopper(III) fluoride. Not in vain both authors has proven expertise in MCF₃ chemistry. On one hand, Dr. Nebra got in touch with Cu^{III}CF₃ chemistry during his postdoctoral stint in Grushin's laboratory, and published two seminal works on: *i*) the synthesis of [Cu^{III}(CF₃)₄]⁻ (**II**) and the efficient trifluoromethylating agent [Cu^{III}(CF₃)₃(bpy)] (**III**);⁷ and *ii*) the identification of [Cu^{III}(CF₃)₂(OTMS)(bpy)] (**I**)⁵ as a key intermediate of the Chan-Evans-Lam-like trifluoromethylation of arylboronic acids. It's worth mentioning that his experience in MCF₃ realm is also radiated to distinct late TMs.³⁶ On other hand, Dr. Joven-Sancho carried out Ph.D studies in Menjón's group working on the synthesis of Pd^{III} and Ag^{III} compounds stabilized by CF₃ ligands.³⁷ Of special relevance to this highlight is the synthesis of the first organosilver(III) fluoride, [PPh₄][Ag^{III}(CF₃)₃F] (**XXII**; Scheme 6 middle),³⁸ that allows the trifluoromethylation of thiols successfully and represents a rare example of a well-defined Ag^{III} compound being active in cross-coupling. The synthesis of **XXII** from [Ag^{III}(CF₃)₃Cl]⁻ (**XXI**) using AgF as a fluoride source, together with the analogous preparation of the related Au^{III}-F anion [Au^{III}(CF₃)₃F]⁻ from [Au^{III}(CF₃)₃Cl]⁻,³⁹ inspired us to tackle the difficult challenge of preparing and isolating the first organocopper(III) fluoride, [Cu^{III}(CF₃)₃F]⁻ (**1**), in (almost) gram scale and high yield.⁴⁰

In the copper case, it was reasoned that the previously reported [Cu^{III}(CF₃)₃(py)] (**IV**) may be a suitable entry point to **1**, as it's easily available^{10b,11b} in large amounts, and avoids the tricky oxidation and handling of unstable Cu^ICF₃ precursors. The choice of pyridine (py) as an ancillary ligand to stabilize the T-shaped Cu^{III}(CF₃)₃ fragment isn't casual: it first avoids unnecessary waste of costly bidentate ligands; and secondly, its monodentate nature favors an easy replacement by X-type ligands,⁴¹ *i.e.* halides.



Scheme 6. Known Cu^{III} fluorides (top),^{27,28} the guiding synthesis of the related Ag^{III} anion [Ag^{III}(CF₃)₃F]⁻ (**XXII**) (middle),³⁹ and the synthetic route to its homologous Cu^{III} fluoride, [Cu^{III}(CF₃)₃F]⁻ (**1**).⁴⁰

Accordingly, we simply performed the addition of PPh₄Cl (0.95 equiv.) to a CH₂Cl₂ solution of **IV** instantaneously forming [PPh₄][Cu^{III}(CF₃)₃(py)Cl] (**8**). Surprisingly, in contrast to its Ag^{III}

analog **XXI**, careful characterization of **8** by NMR spectroscopy, profound crystallographic studies pointing to its high fluxionality (inverse Berry pseudorotation), and EA, unveiled the retention of the py ligand forming a pentacoordinated Cu^{III} center that nicely illustrates the higher electrophilicity of Cu^{III} vs. Ag^{III}. Based on Menjón's work,^{38,39} but not only,⁴² one of the best ways to obtain a given M–F resides on the halide exchange using AgF driven by the lower solubility of AgX salts with heavier halides. Indeed, **1** was successfully prepared from the Cu^{III}-Cl **8** by halide substitution using AgF in gentle excess at 0°C. After removal of the AgX salts by filtration on celite, the Cu^{III}-F complex [PPh₄][Cu^{III}(CF₃)₃F] (**1**) was isolated in satisfying yield (75%) and nearly gram scale,⁴³ being fully characterized by multinuclear NMR, Sc-XRD (Figure 2B) and EA. Interestingly, close inspection of the XRD-determined structure of **1** indicates: *i*) a shortened Cu^{III}–C2 bond length (1.915(2) Å) owing to the weaker *trans*-influence of the fluoride vs. the chloride or py ligands (Cu^{III}–C2 bond lengths of 1.932(6) and 1.959(3) Å in **8**, respectively), while keeping the average Cu^{III}–C bond distance (1.964 Å) of the two mutually *trans*-CF₃ ligands unaltered; and *ii*) an elongation of its Cu^{III}–F bond distance by *ca.* 0.037 or 0.062 Å compared to **XVII**^{28a} or the inorganic binary salt Cs[Cu^{III}F₄],²⁶ resp. This foretells a high reactivity of the Cu^{III}–F bond, in line with previous reports about unstable Cu^{III} fluorides.^{27,28} On other side, **1** displays the larger M–F bond stretching frequency within the series of homologous [M^{III}(CF₃)₃F]⁻ anions: M = Cu (572 cm⁻¹), Ag (492 cm⁻¹)³⁸ & Au (511 cm⁻¹).³⁹ This trend highlights a certain stability of **1** additionally supported by its compatibility with regular glassware and remarkable stability in solid state (note that, in sharp contrast, the Ag^{III}-F **XXII** must be prepared and stored in quartz and Teflon, resp.). Although **1** can be stored in the glovebox at –40 °C for weeks without any sign of decomposition, its behavior in solution suggests a nice balance between stability –given its high oxidation state– and reactivity, that we seek to exploit in C–CF₃ coupling (see below).

4 Alkyne trifluoromethylation: scope and mechanism

The abovementioned evidences of a highly reactive, yet stable, Cu^{III}–F bond in **1** prompted us to essay its reactivity towards terminal alkynes. Heating equimolecular mixtures of phenyl acetylene and **1** results in the formation of the corresponding trifluoromethylated alkyne **10a** in modest yields, although accompanied by notable amounts of dead-end [Cu^{III}(CF₃)₄]⁻ (**II**). This initial attempt encouraged us to find optimal conditions limiting the formation of **II** and maximizing the alkynyl–CF₃ production. To this sense, the use of silyl-capped alkynes (**9a-u**) brings along two major advantages: *i*) it avoids the formation of HF by forming TMSF instead; and *ii*) the forging of the strong Si–F bond drives the challenging Si-to-Cu^{III} alkynyl-group transfer. After much trials, we were delighted to find that the model substrate, trimethylsilylphenylacetylene (**9a**), does react with **1** under mild conditions (heat up to 45°C for 60 min. either in CH₂Cl₂ or THF) and leads to PhC≡C–CF₃ (**10a**) in quantitative yield. To test the robustness of this procedure, the reactivity of **1** towards an array of alkynylsilanes **9a-u** was explored under optimal conditions (Figure 1). Phenyl ring substitution doesn't seem to affect the trifluoromethylation process, with exception of the biphenyl derivative **9k** and those bearing carbonyls (**9ij**), that gave rise to the corresponding coupled products in only 51–76% yield. Of note, the alkynes **9o-r** decorated with the 3-furyl, 3-

thiofuryl or pyridyl skeletons, and the alkylic ones (**9_{s-u}**), were trifluoromethylated in excellent yields (81–98%), but selective isomerization to the allene **10_t** was observed in the benzylic case. Nearly quantitative transformations (>88%) were observed either with electron-donating groups (R = OMe, NH₂, alkyl) or electron-poor arenes (R = halogens, CF₃, CN), and the broad tolerance to functional groups offers remarkable possibilities in late stage trifluoromethylation. Interestingly, the Cu^{III} nature in **1** avoids/minimizes unwanted side-reactivity patterns such as aryl–X bond breaking in **10_c** and **10_d**, or the Glaser-type homocoupling, that are typically found in Cu^I enabled protocols. To further illustrate the applicability of **1**, two preparative experiments were carried out to isolate (and characterize) the trifluoromethylated alkynes **10_c** and **10_d** in good yields (85% and 73%, respectively).

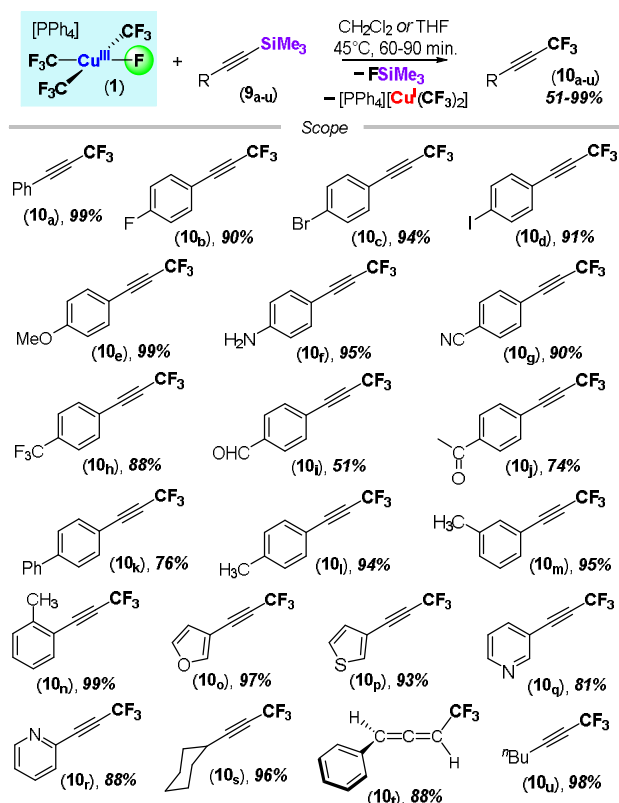


Figure 1. Trifluoromethylation of silyl-capped alkynes **9_{a-u}** enabled by the Cu^{III}-F compound **1** (Contreras-García & Nebra).⁴⁰

Once established the scope of the transformation using **1** as a trifluoromethylating agent, our attention turned back to the operating mechanism enabling the double C–Si bond breaking / alkynyl–CF₃ bond forming sequence. Accordingly, **1** was reacted overnight with an excess of trimethylsilylphenylacetylene (**9_a**) at low temperature (–40°C) forming selectively the desired Cu^{III} acetylide [PPh₄][Cu^{III}(CF₃)₃(C≡CPh)] (**2_{C≡CPh}**), which was isolated in good yield and characterized by NMR and Sc-XRD (see Figure 2C). As one might expect, the average Cu^{III}–C bond length of the mutually *trans*-CF₃ groups (1.9565 Å) in **2_{C≡CPh}** remains unaffected; conversely, its Cu^{III}–C2 bond distance (1.945(2) Å) becomes elongated upon alkylation, corroborating the weaker *trans*-influence of the fluoride vs. an acetylide ligand. Of note, the existence of Cu^{III} acetylides has been proposed in Cu catalysis without spectroscopic evidence, and the isolation and authentication of **2_{C≡CPh}** partially validates previous claims invoking Cu^{III} acetylides as pivotal intermediates in coupling

reactions enabled by copper.¹⁴ To further confirm their plausible participation in C–C coupling, the thermal decomposition of **2_{C≡CPh}** was monitored by ¹⁹F NMR evidencing the concomitant formation of the coupled product **10_a** and the reduced Cu^I homoleptic anion, [Cu^I(CF₃)₂][–] (**XVIII**) (Figure 2A). This study points to a concerted 2e[–] Cu^{III}/Cu^I reduction of **2_{C≡CPh}** upon mild heat (45°C) releasing **10_a** in nearly quantitative yield (94%). Remarkably, the addition of radical trap agents (*i.e.* diphenylacetylene or PBN) has no impact on the efficiency of the alkyne trifluoromethylation affording **10_a** in almost identical yield (93% and 91%, respectively). The irrelevant difference in yield (<10%) for the formation of **10_a** from **1** and **9_a**, or from **2_{C≡CPh}** (either in presence or absence of additives), falls within the margin of NMR error and definitively argues in favour of the intermediacy of **2_{C≡CPh}** in the C_{sp}–CF₃ bond creation. In addition, the most plausible mechanisms involving **2_{C≡CPh}** as an intermediate in the C_{sp}–CF₃ coupling were mapped using DFT calculations (M06-L functional, Def2TZVP basis set, PCM approximation to simulate a CH₂Cl₂ solution). These theoretical investigations indicate that, under our optimal conditions, the formation of the alkynyl–CF₃ bond most likely proceeds through a concerted pathway (*i.e.* Si-to-Cu^{III} alkynyl-group transfer to build **2** followed by R.E. step) rather than radicalary mechanisms, as suggested by others.^{10b,11a}

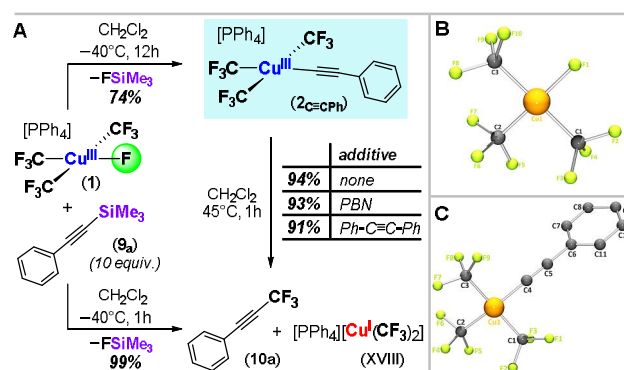


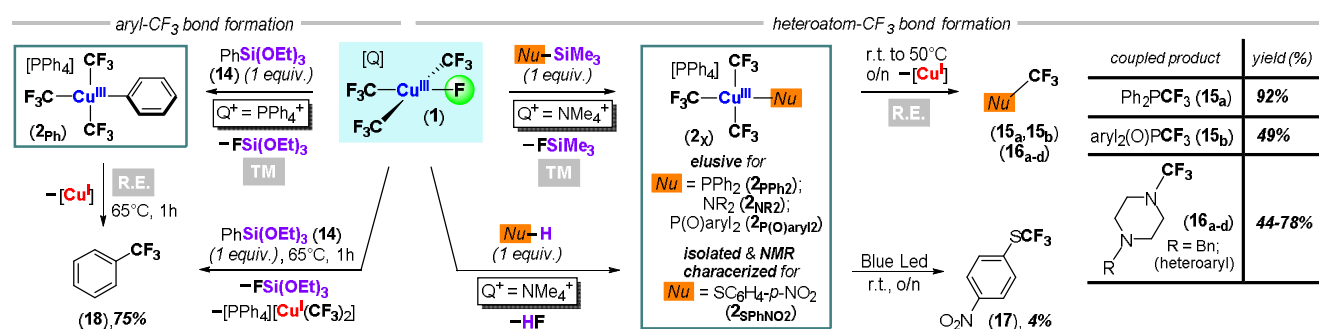
Figure 2. Synthesis of the Cu^{III} acetylide **2_{C≡CPh}** and stoichiometric experiments supporting a Cu^{III}/Cu^I redox scenario in the C_{sp}–CF₃ bond forging event (A) (Contreras-García & Nebra).⁴⁰ Depiction of the XRD-determined structures of **1** (B) and **2_{C≡CPh}** (C) with ellipsoid drawing at 50% probability. Hydrogen atoms and the PPh₄⁺ cation are omitted for clarity reasons.

5 Extension to aryl–CF₃ and C–heteroatom couplings

Right after our publication⁴⁰ on the isolation and the reactivity studies of [PPh₄][Cu^{III}(CF₃)₃F] (**1**), Shen and co-workers reported a novel synthesis of [Cu^{III}(CF₃)₃F][–] (**1**) but being stabilized by distinct cations (NMe₄⁺ or NBu₄⁺) upon addition of ammonium fluorides to the py-Cu^{III} precursor **IV**.⁴⁴ Having **1** at hand, the authors expanded the reactivity of **1** towards protic substrates (acetic acid, thiols, phosphines) and a large variety of silanes (Me₃SiX) besides alkynes (Scheme 7 right), yet displaying similar outcome. Reacting **1** with the P–H bonds of Ph₂PH (**11_a**) and (aryl)₂P(O)H [aryl = bis(3,5-dimethylphenyl); **11_b**] at room temperature leads to the coupled products Ph₂PCF₃ (**15_a**) and (aryl)₂P(O)CF₃ (**15_b**) in 92% and 49% yield, respectively. By the same token, **1** does react with TMS-protected secondary amines **12_{a-d}** forging the corresponding C–N bond under mild heat (50°C), although only in moderate to good yields (44–78%; Scheme 7 right). For the two latter C–heteroatom bond forming reactions enabled by **1**, the authors failed to detect any Cu^{III}

intermediate, but succeeded to isolate the thiolate-Cu^{III} complex [NMe₄][Cu^{III}(CF₃)₃SPh^{NO2}] (Ph^{NO2} = *p*-nitrophenyl; **2**_{SPhNO2}), which decomposed upon blue light irradiation leading to [Cu^{III}(CF₃)₄]⁻ (**II**) and CF₃SPh^{NO2} in poor yield (4%). It's worth to mention that similar trifluoromethylthioethers (RSCF₃) have been synthesized by Menjón³⁸ when mixing the homologous [PPh₄][Ag^{III}(CF₃)₃F] (**XXII**) and thiols upon mild heat (40°C). Although unreported, our group has observed aryl-CF₃ bond formation by reacting **1** with arylsilanes under non-optimized conditions.⁴⁵ Nonetheless, heated to 65°C, a 1:1 mixture of **1** and PhSi(OEt)₃ (**14**) yields benzotrifluoride (**18**; 75%) in only 1 hour. These observations, by analogy to the reactivity of **1** vs. silyl-capped alkynes (see Section 4 above), seem to indicate the existence and key player role of [Cu^{III}(CF₃)₃(X)]⁻ platforms **2_x** (X = PR₂, NR₂, SPh^{NO2}, Ph) in the oxidative trifluoromethylation of nucleophiles, independently of the nature of the nucleophilic heteroatom or the carbon hybridation (sp², sp). Despite the lack of mechanistic studies, these transformations—at least in some instances—may operate via 2e⁻ Cu^{III}/Cu^I redox shuttles in similar fashion to the one evidenced for the trifluoromethylation of alkynes (Figure 2).

In the same work,⁴⁴ the Shen's group has synthesized a number of Cu^{III} complexes having general formula [Q][Cu^{III}(CF₃)₃(X)] (**2_x**; X = C₆F₅, CN, N₃, Cl, OO^tBu, NCS, OAc; Q = NMe₄⁺ or NBu₄⁺) through the transmetallation reaction between **1** and XSiMe₃. The resulting compounds of type **2_x** were used as a model platform to evaluate and establish a *trans*-influence scale of X-type ligands, as similarly done in related Ag^{III} and Au^{III} systems.⁴⁶ In these cases, their enhanced stability compared to those bearing phosphines (**2**_{PR2}) or amines (**2**_{NR2}) allows their isolation, but disables the X-CF₃ bond formation. Nevertheless, given their scarcity and important contribution to C-C and C-heteroatom bond forming reactions, the isolation of novel organocopper(III) species is of utmost relevance. To this sense, we strongly believe that the authentication of the organocopper(III) fluoride, [Cu^{III}(CF₃)₃F]⁻ (**1**), along with its proven versatility in C-C and C-heteroatom bond formations, will open new avenues in Cu^{III} chemistry and further applications exploiting the reactive behavior of **1** and analogous Cu^{III} halides are to come in the next years.



Scheme 7. Ph-CF₃ and heteroatom-CF₃ (C-N, C-P, C-S) couplings enabled by **1** upon addition of silanes [PhSi(OEt)₃ (**14**), R₂NSiMe₃ (**12**_{a-d})] or protic substrates [Ph₂PH (**11**_a), aryl₂(O)PH (**11**_b), *p*-nitrothiophenol (**13**)] discovered by our group (left)⁴⁵ and the Shen's group (right).⁴⁴

5 Summary and outlook

Copper salts are useful reagents in cross-coupling reactions of tremendous repercussions in organic synthesis. By contrast, the mechanisms associated to these transformations remain uncertain quite frequently. For instance, within the context of oxidative trifluoromethylations mediated by copper, Cu^I/Cu^{III} redox cycles are often invoked without spectroscopic evidence. A classic case example of oxidative trifluoromethylations is exemplified by the selective trifluoromethylation of alkynes at terminal position, a singular transformation for which several reports suggest the intermediacy of RC≡C-Cu^{III}-CF₃ compounds.¹⁴ Conversely, most recent studies dealing with alkyne trifluoromethylation using Cu^{III}CF₃ species pointed to pathways involving •CF₃ radical release from high-valent copper,^{10b,11a} evidencing the current dispute on the role and existence of Cu^{III} acetylides in synthesis and catalysis. On the other hand, solid proofs for the existence and involvement of Cu^{III}-F species in C-F bond forging reactions has been provided by the groups of Hartwig²⁷ and Zhang,^{29a} either through Cu^I-to-Cu^{III} or Cu^{II}-to-Cu^{III} oxidation by using "F⁺" oxidants (*i.e.* [Me₃py-F][PF₆]) or a fluoride source and an oxidant (*i.e.* [N(aryl)₃][PF₆]), respectively. In our humble opinion, the lack of an isolable and easy-to-handle Cu^{III} fluoride inhibited the translation of this chemistry to C-C and C-heteroatom bond forming reactions, in spite of the numerous reports claiming the participation of "formally" Cu^{III} fluorides in oxidative C-C³⁵ and C-N³³ couplings using "F⁺" oxidants^{22,25,27} or *N*-fluorosulfamide derivatives.³⁰⁻³⁴

This suspense regarding the impact of Cu^{III}-F species in cross-couplings other than C-F bond creation prompted us and the Shen's team to investigate the synthesis and reactivity of an hypothetical Cu^{III}-F anion, [Cu^{III}(CF₃)₃F]⁻ (**1**), that may be conveniently stabilized by the CF₃ ligands. This reasoning proved right and **1** was efficiently prepared and authenticated from the py-Cu^{III} precursor **IV** upon addition of PPh₄Cl and subsequent halide exchange using AgF, or alternatively, by adding NR₄F (R = Me, ⁿBu) to **IV**. Compound **1** displays a remarkable stability being stored in a glove-box as a solid for weeks. This might be attributed to the existence of Inverted Ligand Field (ILF)⁴⁷ in **1**, a molecular orbital arrangement having the frontier molecular orbitals mainly contributed by the ligands, which has recently been studied in related group 11 metallic complexes bearing perfluorinated ligands.⁴⁸ The diverging behaviour of compounds showing ILF vs. those displaying classical ligand field arrangements represents a rising research field with multiple implications in catalysis, theory and spectroscopy.⁴⁹

The independent reactivity investigations by Shen and us have demonstrated the suitability of [Cu^{III}(CF₃)₃F]⁻ (**1**) to build an array of unprecedented [Cu^{III}(CF₃)₃(X)]⁻ complexes **2_x** (with X = C≡CR, SR, Ph, NR₂, PR₂) by simply adding readily available silanes or acidic substrates under mildness. Some of these complexes **2_x** underwent X-CF₃ bond formation upon mild heat, as clearly exemplified by the smooth but high yielding trifluoromethylation of alkyne-silanes **9_{a-u}** enabled by **1** after heating (45°C) for 1-1.5 h. A thorough mechanistic study for the trifluoromethylation of

the model alkyne **9a** combining stoichiometric experiments and DFT calculations unveiled a pathway going through an initial building of the Cu^{III} acetylide **2c_{C≡CH}**, followed by a concerted 2e⁻ R.E. step that releases the coupled product, PhC≡CCF₃ (**10a**), and [Cu^I(CF₃)₂]⁻ (**XVIII**). The extraordinary balance between stability and reactivity shown by [Cu^{III}(CF₃)₃F]⁻ (**1**) places it as an ideal organocopper(III) synthon, and brings new vistas in Cu^{III} chemistry such as the screening of its reactivity against boranes and related organometallics, or the study of its utility in HAA processes.

Funding Information

Financial support from the CNRS, the Université Paul Sabatier, and the Agence Nationale de la Recherche (ANR-JCJC-20-CE07-0023; acronym Ni4Rf) is gratefully acknowledged. D.J-S thanks the ANR for postdoctoral funding.

Acknowledgment

We are thankful to Dr. N. Mézailles for continuous support.

Conflict of Interest



The authors declare no conflict of interest.

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Biosketches

	<p>Daniel Joven-Sancho, born in Morés (Spain), studied Chemistry and the Master in Molecular Chemistry and Homogeneous Catalysis in the University of Zaragoza. He accomplished his doctoral studies in the same University under the supervision of Dr. M. Baya and Dr. B. Menjón dealing with trifluoromethyl derivatives of Ag^{III}. In June 2022 he moved to Toulouse (France) for a 1 year postdoctoral stay with Dr. N. Nebra mainly focused on the development of high oxidation organometallic compounds and their application in the trifluoromethylation of organic molecules. Since the fall of 2023, he is part of Prof. L. Greb's group (Heidelberg University), investigating the synthesis and applications of heavy main group compounds with unusual geometries. Dr. Joven-Sancho has published 12 articles (h index = 7) and several presentations in International Congresses. He was awarded as the Best Young Speaker in the 19th European Symposium on Fluorine Chemistry (Warsaw, 2019).</p>
	<p>Noel Nebra was born and raised in Pravia (Asturias). He completed his PhD on Ru catalysis in 2009 at the University of Oviedo mentored by Profs. J. Gimeno and V. Cadierno, and he then carried out two consecutive postdoctoral stints with Drs. D. Bourissou (LHFA, Toulouse) and V. Grushin (ICIQ, Tarragona) dealing with ligand design, the handling of highly reactive species and fluorinated organometallics. Since 2014, Dr. Nebra holds a CNRS position at LHFA (Toulouse) and investigates unusual organometallics (Ni^{IV}, Ag^{III} & Cu^{III}) with application in trifluoromethylation. Up to now, Dr. Nebra has published 43 articles (h index = 25), 3 book chapters, and he has been selected as the recipient of the "2020 ICT Award" and the "2021 GEQO-RSEQ Award" to Young Researchers.</p>