

Computational Insights into Nucleophilic Copper-Catalyzed Trifluoromethylation of Aryl Halides

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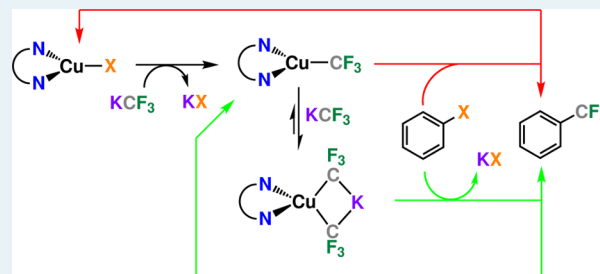
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Supporting Information

ABSTRACT: Nucleophilic copper-catalyzed trifluoromethylation of aryl halides is one of the most challenging reactions leading to fluorinated products. Although aryl iodides can be easily transformed, catalytic reactions with aryl bromides and chlorides are much more difficult; however, some stoichiometric reactions using these substrates have been published. In this report, the mechanism of the copper-catalyzed trifluoromethylation of aryl halides, based on the reaction developed by Amii et al. (*Chem. Commun.* **2009**, (14), 1909–1911), has been explored with DFT calculations. The computed catalytic cycles allow the interpretation of the experimental observations; electron-poor substrates produce faster reactions because their oxidative addition barrier, the rate-limiting step of the reaction, is lower. The proposed mechanism for the trifluoromethylation reaction also explains why the reactivity greatly decreases for aryl bromide and chloride substrates. The results obtained have been employed to propose alternative strategies and catalyst modifications that could improve the trifluoromethylation reaction studied. These modifications, which have been evaluated computationally, indicate that varying the nucleophilic trifluoromethylating agent has a significant impact on the reaction outcome that would allow the trifluoromethylation of the more challenging substrates. The slow addition of trifluoromethyltrimethylsilane (CF_3SiEt_3) into the reaction mixture also seems to be a good strategy to catalytically functionalize aryl iodides and even activated bromides and chlorides.

KEYWORDS: copper catalysis, nucleophilic trifluoromethylation, density functional theory, aryl halides, trifluoromethyltrimethylsilane, potassium (trifluoromethyl)trimethoxyborate, potassium trifluoroacetate



1. INTRODUCTION

One of the greatest challenges for pharmaceutical and agrochemical industries is the development of new fluorinated compounds as the presence of fluorine often improves the metabolic stability, bioavailability, and lipophilicity of organic moieties.¹ The trifluoromethyl group is probably one of the most relevant and appealing motifs in this area, and therefore, much effort has been devoted to building up new synthetic strategies to transfer the CF_3 group onto organic chemicals.² The traditional Swarts methodology,³ employed to transform an ArCCl_3 substrate into ArCCF_3 , requires harsh conditions and has a low substrate scope. Several new methods, based on the employment of different trifluoromethyl sources in metal-catalyzed (or mediated) reactions, have been developed recently. Electrophilic trifluoromethylating agents, for example the Umemoto⁴ or the Togni⁵ reagents, are generally used to promote the C–H functionalization of arenes.⁶ This same reaction can often be achieved with radical CF_3 sources such as potassium trifluoromethanesulfinate, CF_3I or NaSO_2CF_3 .⁷ Nevertheless, the best trifluoromethylating strategy seems to be the coupling of aryl halides with nucleophilic CF_3 reagents ($\text{K}[\text{CF}_3\text{B}(\text{OMe})_3]$, CF_3SiMe_3 , CF_3SiEt_3 , HCF_3 , trifluoroacetate salts, etc.) in copper- and palladium-catalyzed reactions.⁸ The copper-catalyzed trifluoromethylation of aryl iodides has been

successfully applied to obtain the corresponding fluorinated products even at low temperatures.^{2f,8e,g–k,9} In contrast, reactions employing aryl bromides and chlorides are much more challenging, and only some stoichiometric reactions have been reported.^{8j,9,10} More recently, these nucleophilic trifluoromethylating reagents have also been successfully employed in oxidative couplings with other nucleophilic substrates such as boronic acids and terminal alkynes.¹¹ The activity in this field has mainly focused on the development of new and improved synthetic platforms; in contrast, mechanistic trifluoromethylation studies are practically nonexistent and only some theoretical reports can be found in the literature, dealing with specific aspects of the reaction, for example, reductive elimination of $\text{Ar}-\text{CF}_3$ from Pd(IV) complexes,¹² as well as *cis* and *trans* influences in hypervalent iodine(III) trifluoromethylating agents.¹³ Computational trifluoromethylation studies, aiming to determine the operating mechanism, could lead to a better understanding and eventually to improved catalytic systems to carry out these reactions. In the literature, there is just one report dealing with a complete computational

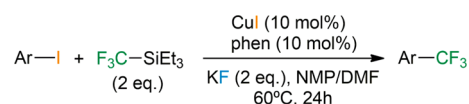
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trifluoromethylation study; in this previous study, the full catalytic cycle of the aerobic oxidative coupling of terminal alkynes with CF_3SiMe_3 has been explored using DFT.^{11h} In this work, a computational study for the copper-catalyzed trifluoromethylation of aryl halides is presented; we aim to provide a plausible mechanism able to explain the observed reactivity. For this purpose, the reaction reported by Amii et al.^{8e} (Scheme 1) has been employed as a case study. This

Scheme 1. Cu-Catalyzed Trifluoromethylation of Ar–I As Proposed by Amii et al.



reaction employed copper(I) iodide and the phenanthroline (phen) ligand to trifluoromethylate a range of aryl iodides with CF_3SiEt_3 and KF in a 1:1 mixture of NMP and DMF at 60 °C. Experimentally it was observed that the best yields are obtained for electron-poor aryl iodides (e.g., 90% for $p\text{-NO}_2\text{-C}_6\text{H}_4\text{I}$), whereas the more electron-rich substrates exhibited lower reactivities ($p\text{-Bu-C}_6\text{H}_4\text{I}$, 44%). In that report, experimental data for aryl bromides and chlorides obtained under the same reaction conditions were not available, possibly because they did not work, but it is expected that the mechanism for those substrates will remain the same regardless of the halide identity.

This report is divided into two main sections; the first one describes the most likely mechanism for the copper-catalyzed trifluoromethylation of phenyl iodide. However, often more than one reaction pathway can be possible; in these cases the corresponding reaction steps have also been modeled to provide a complete description of the mechanism and to ensure the best pathway is selected. These computed alternative reaction mechanisms can be found in the [Supporting Information \(SI\)](#). Once the catalytic cycle for PhI is established, it will be applied to explore and explain the reactivity of other substrates (i.e., phenyl bromide, phenyl chloride, and *para*-substituted aryl iodides). The second section describes alternative proposals, based on the knowledge provided by the computed catalytic cycle, to improve the copper-catalyzed trifluoromethylation of aryl halides (e.g., effects of replacing trifluoromethylating agent and the ligand in the catalyst). An alternative synthetic strategy, aimed at better controlling the

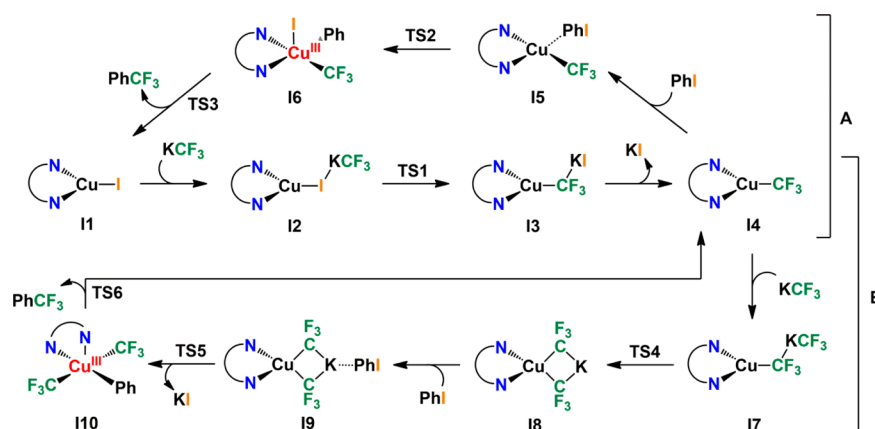
species formed during the reaction course, is also proposed and studied computationally.

2. COMPUTATIONAL DETAILS

All the structures have been optimized without restrictions using *N,N*-dimethylformamide as solvent with the dispersion-corrected B97D density functional,^{14,15} as implemented in the Gaussian09 package.¹⁶ The standard 6-31+G* basis set¹⁷ was used for all H, C, N, O, F, Si, Cl, and K atoms; the Stuttgart triple- ζ basis set (SDD),¹⁸ along with the associated ECP describing the core electrons, was employed for Cu, Br, and I. Additional reoptimization of the geometries, including frequencies, was employed to obtain improved solvated free energy values with larger basis sets. The aug-cc-pVTZ basis set including polarization and the associated electron core potential¹⁹ was employed for Cu, Br, and I, whereas all the other atoms were described with the 6-311+G** all-electron basis set.^{17b} In all cases, frequency calculations were carried out to confirm the nature of stationary points and transition states, allowing also the calculation of free energies at 25 °C for all the species involved in the catalytic cycles. All the free energy values reported in the text correspond to those obtained with the larger basis sets.

The (IEF-PCM) method,²⁰ including the radii and non-electrostatic terms for Truhlar and co-workers' SMD solvation model,²¹ was employed to compute the free energies of all the species in solvent. It has to be noted that the free energies computed for the more polar species, computed as neutral molecules, might be off by some kcal mol^{-1} , because the PCM method would not be able to fully account for their degree of dissociation in DMF. Experimentally, a 1:1 mixture of 1-methyl-2-pyrrolidone (NMP) and *N,N*-dimethylformamide (DMF) was employed as solvent, and in the calculations, only the latter was used because using a mixture of solvents in Gaussian09 is not allowed; nevertheless, the impact on the calculated free energies is expected to be small because both solvents are quite similar. Explicit solvation, adding DMF molecules to, for example, tricoordinated copper species, has also been taken into consideration. However, the inclusion of solvent molecules was found to have only a limited effect on the calculated free energies, often producing higher values, and was therefore discarded.

Scheme 2. Proposed Catalytic Cycles (Free Energies in kcal mol^{-1})



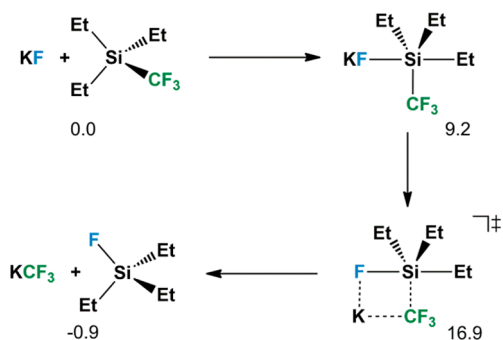
3. RESULTS AND DISCUSSION

3.1. Copper-Catalyzed Trifluoromethylation of Aryl Halides: Mechanistic Exploration. In this section, the reaction mechanism of Amii's trifluoromethylation of phenyl iodide is described. This mechanism will then be applied to different substrates to check its ability to describe the experimentally observed reactivity. The most likely catalytic cycles, closely related to each other, are shown in Scheme 2.

Two plausible catalytic cycles able to describe the trifluoromethylation reaction have been found, both leading to the formation of the desired product. The first one, shown in the upper part of Scheme 2 (pathway A), runs from **II** to **TS3**, whereas the second pathway is placed between **I4** and **TS6**, occupying the lower part of Scheme 2 (pathway B). The complex $[(\text{phen})\text{Cu}(\text{CF}_3)]$ (**I4**) constitutes the link between both pathways, and therefore, the catalytic cycle depends on the species trapped by **I4**, either PhI or KCF_3 , leading to the formation of **I5** (pathway A) and **I7** (pathway B), respectively. The detailed exploration of both mechanisms and their interplay is explained in the following paragraphs. Of course, other pathways could be possible; for example, KF could replace KCF_3 in the catalytic cycles producing different **I2** and **I7** species and thus generating fluorinated copper species which will deliver fluorobenzene as product. These alternative pathways have also been computed and proven to be uncompetitive with the ones shown in Scheme 2 (see [SI](#) for a complete description).

As may be observed in Scheme 2, KCF_3 is the reagent responsible for taking the trifluoromethyl group into the catalytic cycle by transmetalation onto the copper(I) complexes **I1** and **I7**.²² KCF_3 is not initially added to the reaction, but it can be easily generated in solution from CF_3SiEt_3 and KF (Scheme 3).²³ In this process, KF coordinates to the silicon

Scheme 3. Generation of KCF_3 from CF_3SiEt_3 and KF (Free Energies in kcal mol^{-1})

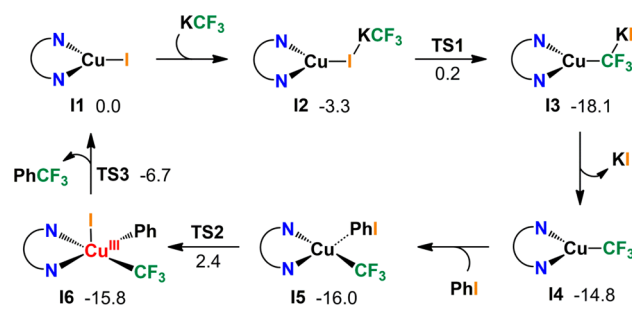


atom of CF_3SiEt_3 to form the corresponding hypervalent pentacoordinated species which lies $9.2 \text{ kcal mol}^{-1}$ above the separated reactants. The trifluoromethyl group is then transferred from the silicon to the potassium to deliver KCF_3 and FSiEt_3 ; the transition state mediating this transformation is $16.9 \text{ kcal mol}^{-1}$ higher than the starting materials and thus this process should be quite easy at 60°C . The reaction is, however, not very exergonic: the products are less than 1 kcal mol^{-1} lower in free energy than the reactants, indicating that an equilibrium should be established between them. A serious concern related to this mechanism is the stability of KCF_3 , because it has to remain present for long enough to react with the copper complexes. It has been proposed that this species

could easily undergo decomposition into potassium fluoride and the corresponding CF_2 carbene,²¹ but very recently, it has been stated that trifluoromethyl species (e.g., CF_3^-) could remain stable in solvent at low temperatures.²⁴ In this line, the calculations indicate that this decomposition is not as easy as expected, because it is endergonic by almost 9 kcal mol^{-1} . Hence, this process would not take place unless the newly formed CF_2 carbene is stabilized by another species present in the reaction mixture, which seems not to be the case.

A detailed description of pathway A, including the computed free energies for all the species, is shown in Scheme 4. The

Scheme 4. Detailed Description of Pathway A Including Relative Free Energies (in kcal mol^{-1})



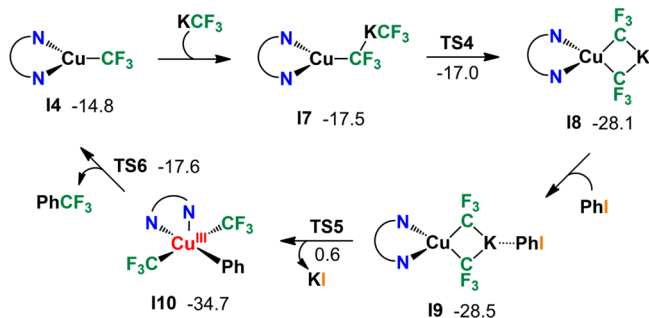
initial catalytic species of the reaction (**I1**) is formed by combination of CuI and the bidentate phenanthroline ligand. This complex reacts with KCF_3 to form **I2** where the potassium atom interacts with the iodide (K–I distance 3.63 \AA) while the CF_3 group lies quite far from the copper center (5.24 \AA). This process is slightly exergonic since **I2** is $3.3 \text{ kcal mol}^{-1}$ more stable than the separated reactants. The trifluoromethyl group is then transferred to the metal through the transmetalation transition state **TS1**, in this saddle point the Cu– CF_3 distance is substantially reduced to 3.03 \AA while the K–I distance remains practically the same (3.61 \AA). This process requires less than 4 kcal mol^{-1} and leads to the formation of **I3**, which lies at $-18.1 \text{ kcal mol}^{-1}$. In this complex the iodine atom has already been released from the metal and KI remains attached through an interaction between the potassium and the trifluoromethyl group; it was not possible to find the transition state for this process. All the optimizations trying to find an intermediate where the iodine was still on the copper atom ended up delivering **I3**, suggesting that the iodide release is barrierless.

The liberation of KI into the reaction mixture, with a free energy requirement of $3.3 \text{ kcal mol}^{-1}$, produces $[(\text{phen})\text{Cu}(\text{CF}_3)]$ (**I4**); this complex is key in the mechanism because its evolution determines the operating catalytic cycle. There are other alternative ways to reach **I4**, for example the iodide mediated direct trifluoromethyl transmetalation from CF_3SiEt_3 onto the metal species (see [SI](#)). However, those processes were found to have higher energy requirements and were consequently discarded. From **I4**, the reaction proceeds by the oxidative addition of phenyl iodide; before that, an adduct between the Cu– CF_3 complex and PhI is formed (**I5**), likely by the π -bonding of the phenyl ring of the substrate to the metal. In practice, PhI is found to lie quite far from the copper; in reality, dispersion forces, derived from the π -stacking between the aromatic rings of phenanthroline and PhI, seem to be the origin for the formation of **I5**. The free energy of this intermediate is, however, a bit lower (around 1 kcal mol^{-1})

than that for **I4**. After the formation of **I5**, the oxidative addition takes place. The concerted oxidative addition transition state (**TS2**) has been found to be 18.4 kcal mol⁻¹ higher than **I5**, indicating that this process should be quite fast under the reaction conditions. Other possible alternative pathways describing this step, namely, the σ -bond metathesis, the Single-Electron Transfer (SET), and Halogen Atom Transfer (HAT) pathways²⁵ have been analyzed, and found to have greater energy requirements than the oxidative addition (see **SI** for details). After the oxidative addition, the copper(III) complex **I6** is obtained. The geometry of this compound is a square pyramid, as should be expected for a five-coordinated d⁸ metal center, with the iodide occupying the axial position at a quite long distance (3.46 Å), whereas the phenyl and trifluoromethyl groups are situated *cis* to each other in the equatorial plane of the molecule. Other geometries, including those with one of the phenanthroline nitrogen donor atoms in the axial position and the corresponding *trans* isomers, were found to lie at higher energies. Not surprisingly, the reductive elimination of PhCF₃ from the copper(III) intermediate **I6** is very facile and requires only 9.1 kcal mol⁻¹. After the reductive elimination, the trifluoromethylated product is released, and the initial catalyst **II** is recovered.

Pathway B is followed whenever **I4** reacts with a second KCF₃ unit, instead of PhI, to deliver intermediate **I7** (Scheme 5). The relative free energies for this pathway are computed

Scheme 5. Detailed Description of Pathway B Including Relative Free Energies (in kcal mol⁻¹)



from the starting materials in order to keep them at the same level as the ones obtained for pathway A. **I7** is 2.7 kcal mol⁻¹ more stable than the preceding reaction intermediate, indicating that **I4** can effectively trap a second KCF₃ molecule. The transmetalation of the trifluoromethyl group to the copper is quite straightforward, because the transition state (**TS4**) mediating the transformation of **I7** into **I8** lies just 0.5 kcal mol⁻¹ higher in energy than the former. In addition, **I8** is the most stable intermediate so far (-28.1 kcal mol⁻¹), indicating that this stage should be strongly favored. In this complex, the potassium cation remains quite close to both trifluoromethyl groups compensating the charge of the [(phen)Cu(CF₃)₂]⁻ unit and actively collaborating in trapping the phenyl iodide substrate (**I9**), which allows the reaction to proceed.

In **I9**, the potassium cation establishes a π -bonding interaction with the phenyl ring of the substrate, with K-C_{ph} distances around 3.23 Å. This new intermediate seems to be thermodynamically favored because it lies slightly lower than the previous intermediate and at -28.5 kcal mol⁻¹ below the starting materials. The next stage is the oxidative addition of PhI (**TS5**); because the coordination sphere of copper is quite

crowded, the C_{ph}-I bond cleavage is promoted by the halide coordination to the potassium atom. The Cu-C_{ph} distance (2.26 Å) is quite similar to the one found in the oxidative addition transition state of pathway A (**TS2**, 2.24 Å), whereas the Cu-I distance is much longer (3.62 vs 2.87 Å), indicating that the halide is not migrating onto the metal but onto the potassium: the K-I distance (3.57 Å) is a bit longer than the one found in free KI (3.47 Å) (Figure 1). A strong molecular

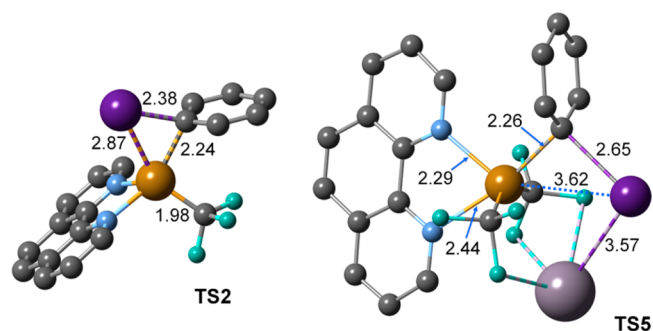


Figure 1. Structures of **TS2** and **TS5** (distances in Å, H atoms omitted for clarity).

reorganization is needed to bring the phenyl ring close to the copper, and therefore, the energetic requirement for this transition state is very high (+29.1 kcal mol⁻¹).

After the oxidative addition, the newly formed KI leaves the coordination sphere, and the corresponding square pyramidal copper(III) complex **I10** is obtained, with one of the nitrogen atoms of the phenanthroline occupying the axial position at a long distance (2.31 Å). In this intermediate, the phenyl ring lies between the two trifluoromethyl groups; other isomers of this complex were also computed (e.g., with the phenyl ring between one trifluoromethyl and the phenanthroline ligand or with a CF₃ or the phenyl in the axial position), but none of them was found to be lower in free energy. The transition states leading to these alternative structures could not be located. It has to be noted that **I10** constitutes the lowest free energy intermediate along all the reaction pathways explored (-34.7 kcal mol⁻¹). The Ph-CF₃ reductive elimination from **I10** is higher than the one found in pathway A, but it remains at a reasonable level (+17.1 kcal mol⁻¹) and should be quite easy to overcome at 60 °C. After the reductive elimination, PhCF₃ is released, taking the catalytic cycle back to the starting species of pathway B (**I4**).

The computed overall Gibbs free energy of both catalytic cycles is -56.9 kcal mol⁻¹, indicating that the whole process is thermodynamically favored. The calculated free energies of the species in the catalytic cycle allow the calculation of the apparent activation energies for the studied pathways, which is directly related to the turnover frequency. This can be easily done by means of the energetic span model developed by Kozuch and Shaik.²⁶ This methodology states that the activation barrier corresponds to the energy difference between the highest and the lowest species when the latter appears first in the catalytic cycle, as in this case for both pathways. Thus, the activation barrier for pathway A has a value of 20.5 kcal mol⁻¹ (computed as the free energy difference between **I3** and **TS2**); in the case of pathway B, the reaction barrier rises to 29.1 kcal mol⁻¹, corresponding to the oxidative addition stage (from **I9** to **TS5**). These results seem to indicate that pathway A should be preferred, but in fact, a more detailed analysis

concludes that pathway B is the operating mechanism. First, both pathways share one structure (**I4**), and the evolution of this species, that is, the substrate trapped (PhI or KCF₃), determines which pathway will be followed. In the reaction mixture, there is 1 equivalent of PhI and 2 equivalents of KCF₃, which is easily formed from CF₃SiEt₃ and KF. In consequence, the probability of **I4** meeting the latter is doubled. In addition, catching a KCF₃ to form **I7** is thermodynamically favored over trapping a phenyl iodide (**I5**) by more than 1 kcal mol⁻¹. Second, all the intermediates and transition states in pathway B are lower in free energy than those in pathway A (except for **I3**), which means that the species in Pathway B are expected to form preferentially in the reaction course, that is, **I9** becomes the resting state of the reaction. Third, the computed barriers for both catalytic cycles are quite different: 20.5 and 29.1 kcal mol⁻¹ for pathways A and B, respectively. A low barrier, such as the one corresponding to pathway A, is expected to produce a very fast reaction that should be completed in a few seconds at 60 °C; however, as observed in the experiments, this is not the case. All this evidence indicates that pathway B is the preferred one; nevertheless, pathway A cannot be completely ruled out and could operate in parallel although with lower productivity.

The proposed catalytic cycles also allow the rationalization of the stoichiometric trifluoromethylation reaction employing [(phen)Cu(CF₃)₂] (**I4**) as starting material, as often found in the literature.^{8j,9,10} Under those conditions, the mechanism would start with **I4** and then follow pathway A because there is no other trifluoromethyl source that could lead to pathway B, finishing with [(phen)Cu] (**I1**) and PhCF₃. The associated reaction barrier, corresponding to the oxidative addition process, would then be much lower (just 18.4 kcal mol⁻¹) than the ones computed for the catalytic cycles. These results indicate that stoichiometric reactions should be much faster than their catalytic analogues, in clear agreement with what is observed experimentally.

The proposed mechanism has been applied to a range of different substrates, including other phenyl halides and substituted phenyl iodides in order to check its performance when compared to the experimental results found in the literature. Experimentally, it has been observed that similar reactions with aryl bromides are quite slow and only (super)stoichiometric metal amounts give satisfactory yields.^{8j,9,10} The activation of aryl chlorides seems to be much more difficult, and only a small subset of electron-poor substrates have been reported in the literature to produce the trifluoromethylated products.⁹ The proposed catalytic cycles have been recomputed for PhBr and PhCl, and in these cases, the initial catalyst **I1** has been replaced by the corresponding [(phen)CuX] (X = Br, Cl) species to account for the appropriate catalytic system. The associated free energy of all the steps, along with those for PhI, can be found in Table 1.

As may be observed, the catalytic activation barriers in pathway B for phenyl iodide, bromide, and chloride are 29.1, 33.2, and 35.8 kcal mol⁻¹, respectively. These results clearly agree with the experimental observations: aryl bromides and chlorides can only be trifluoromethylated with stoichiometric copper–CF₃ amounts because under those conditions the activation barrier remains well below 30 kcal mol⁻¹ (23.2 and 26.2 kcal mol⁻¹ for PhBr and PhCl, respectively).

Results are also good when comparing the behavior of different aryl iodides. Experimentally it was observed that electron-poor phenyl iodides reacted faster than the electron-rich ones—that is, the yields for *p*-NO₂-C₆H₄I and *p*-Bu-

Table 1. Computed Free Energies (in kcal mol⁻¹) for the Catalytic Cycles of Different Aryl Halides

pathway	step/substrate	PhI	PhBr	PhCl
A	I1	0.0	0.0	0.0
	I2	-3.3	-2.7	-1.7
	TS1	0.2	0.7	-0.6
	I3	-18.1	-20.2	-18.0
	I4	-14.8	-15.4	-15.0
	I5	-16.0	-13.3	-13.8
	TS2	2.4	7.8	11.2
	I6	-15.8	-4.4	-5.5
	TS3	-6.7	3.5	1.9
	catalytic barrier	20.5	28.0	29.2
	stoichiometric barrier	18.4	23.2	26.2
	B	I7	-17.5	-18.1
TS4		-17.0	-17.7	-17.2
I8		-28.1	-28.7	-28.3
I9		-28.5	-28.4	-28.8
TS5		0.6	4.5	7.0
I10		-34.7	-29.8	-32.1
TS6		-17.6	-12.7	-15.0
catalytic barrier		29.1	33.2	35.8

C₆H₄I, under the same reaction conditions, are 90 and 44%, respectively.^{8e} The free energy profiles for these substrates have also been computed (Table 2). Once again, pathway B

Table 2. Computed Free Energies (in kcal mol⁻¹) for the Catalytic Cycles of Substituted Aryl Iodides

pathway	step/substrate	PhI	<i>p</i> -NO ₂ -C ₆ H ₄ I	<i>p</i> -Bu-C ₆ H ₄ I
A	I1	0.0	0.0	0.0
	I2	-3.3	-3.3	-3.3
	TS1	0.2	0.2	0.2
	I3	-18.1	-18.1	-18.1
	I4	-14.8	-14.8	-14.8
	I5	-16.0	-14.9	-15.7
	TS2	2.4	-0.2	2.6
	I6	-15.8	-14.3	-15.2
	TS3	-6.7	-5.2	-6.9
	catalytic barrier	20.5	17.9	20.7
	stoichiometric barrier	18.4	14.7	18.3
	B	I7	-17.5	-17.5
TS4		-17.0	-17.0	-17.0
I8		-28.1	-28.1	-28.1
I9		-28.5	-26.1	-30.4
TS5		0.6	-3.2	-0.2
I10		-34.7	-36.5	-34.6
TS6		-17.6	-17.9	-17.2
catalytic barrier		29.1	24.9	30.2

constitutes the preferred operating mechanism and therefore the highest reaction step is the oxidative addition (**TS5**); the difference between the *p*-NO₂ and *p*-Bu substituted substrates is significant, and the barrier found for the former is almost 5 kcal mol⁻¹ lower, confirming that electron-poor phenyl iodides produce faster reactions. The rest of the reaction stages remain practically the same. For instance, the barrier for reductive elimination, which should also be affected by the substitution, does not change substantially: 17.1, 18.6, and 17.4 kcal mol⁻¹ for PhI, *p*-NO₂-C₆H₄I, and *p*-Bu-C₆H₄I, respectively. Extrapolating this trend to aryl bromides and chlorides also explains

the observed reactivity for these more challenging substrates; experimentally, only the electron-poor substrates can be successfully activated in stoichiometric reactions.

The copper-catalyzed trifluoromethylation of aryl iodides reported by Amii et al. is only functional for iodo-substituted substrates. The formation of the stable ditrifluoromethylated copper species, easily obtained by transmetalation from KCF_3 onto the catalyst, substantially raises the reaction barrier, making it inaccessible for the more energetically demanding aryl bromides and chlorides. Nevertheless, the computed free energy profiles show that limiting the formation of these ditrifluoromethylated copper species could provide much lower barriers for all the aryl halides studied. The barriers obtained in pathway A (Table 1), either catalytic or stoichiometric, indicate that aryl bromides and chlorides would be able to engage in catalytic trifluoromethylation processes. The immediate solution that comes to mind is exerting a more strict control on the amount of free KCF_3 in solution; this could be easily done by slowly adding CF_3SiEt_3 and KF over time. In fact, this procedure has been successfully applied in other copper-catalyzed and -mediated trifluoromethylation reactions.^{11a,b,27}

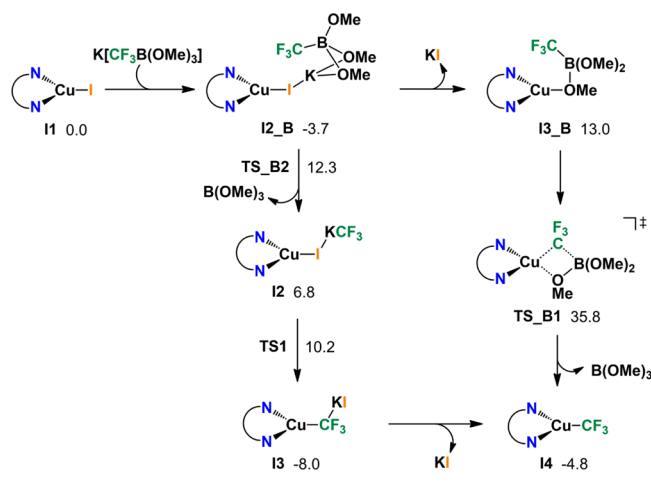
Another option could be replacing CF_3SiEt_3 by other nucleophilic trifluoromethyl source that does not easily release KCF_3 in solution thereby ensuring that just one CF_3 group is placed on the metal during the reaction; for example, potassium (trifluoromethyl)trialkoxoborates ($\text{K}[(\text{CF}_3)\text{B}(\text{OR})_3]$, $\text{R} = \text{Me}, \text{Bn}$) or trifluoroacetate salts could be suitable candidates to assume this role. Using a totally different approach, the catalytic system could be designed to produce lower oxidative addition barriers because the substrate activation is, in all cases, the rate-limiting step of the trifluoromethylation process. For this purpose, other ligands, more electron-rich than phenanthroline, would be the ideal candidates (e.g., polydentate N-ligands and mono- or bidentate P-ligands (phosphines or phosphites)). It is known, however, that copper(I) tends to form more robust catalysts with nitrogen-donor ligands and those should be the focus for new developments. Some of these new proposals to improve the copper-catalyzed trifluoromethylation of aryl halides have been computationally explored.

3.2. Modified Copper-Catalyzed Trifluoromethylation of Aryl Halides. As mentioned above, two possible modifications of the catalytic system reported by Amii et al. have been considered. The first one consists of replacing the nucleophilic trifluoromethylating agent mixture ($\text{CF}_3\text{SiEt}_3/\text{KF}$) by another one that fulfils certain critical aspects. First, the new source has to be stable in the reaction media; that is, KCF_3 should not be released easily into the reaction mixture, and second, the trifluoromethylating reagent has to be able to transfer just one CF_3^- group onto the copper catalyst, possibly by transmetalation. Among all the existing nucleophilic CF_3 sources, two suitable candidates for computational exploration are potassium (trifluoromethyl)trimethoxyborate $\text{K}[(\text{CF}_3)\text{B}(\text{OMe})_3]$ and potassium trifluoroacetate CF_3COOK . The direct KCF_3 release in DMF from $\text{K}[(\text{CF}_3)\text{B}(\text{OMe})_3]$ and CF_3COOK , with the concomitant formation of $\text{B}(\text{OMe})_3$ and CO_2 , requires 13.2 and 9.2 kcal mol^{-1} , respectively, indicating this process is unlikely to happen.

$\text{K}[(\text{CF}_3)\text{B}(\text{OMe})_3]$ has been successfully employed in a catalytic trifluoromethylation reaction^{8h} very similar to the one studied in this report, demonstrating that both electron-rich and -poor substrates could be functionalized with good yields at 60 °C. Two possible pathways have been computed to generate **I4** from the starting copper species **I1** and $\text{K}[(\text{CF}_3)\text{B}(\text{OMe})_3]$,

Scheme 6. Initially, **I1** reacts with the borate to form complex **I2_B**, which is lower in free energy by more than 3 kcal mol^{-1} .

Scheme 6. Formation of **I4 Using $\text{K}[(\text{CF}_3)\text{B}(\text{OMe})_3]$ as Trifluoromethyl Source (Free Energies in kcal mol^{-1})**



Then two competing pathways are possible; the first one, corresponding to the classical iodide/borate replacement, would lead to **I3_B**, and after the transmetalation step (**TS_B1**), **I4** would be obtained. Although the free energy change indicates this pathway should be spontaneous, the massive transmetalation barrier (+39.5 kcal mol^{-1} , computed from **I2_B**) seems to prevent the reaction to evolve through this sequence.

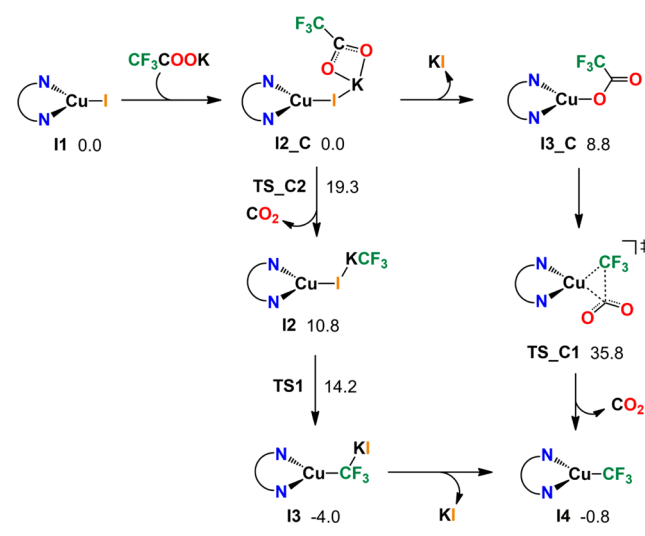
The alternative computed pathway implies the formation of KCF_3 from the coordinated $\text{K}[(\text{CF}_3)\text{B}(\text{OMe})_3]$ in **I2_B**. The transition state governing this process (**TS_B2**), is just 16.0 kcal mol^{-1} higher than the previous species, indicating this pathway should be much easily accessible than the classical one. After the formation of KCF_3 and the release of $\text{B}(\text{OMe})_3$, **I2** is obtained. It has to be noted that this complex lies 10.5 kcal mol^{-1} higher in free energy than **I2_B** (and 6.8 kcal mol^{-1} above the starting materials) and as a consequence, its formation would be limited. Nevertheless, whenever **I2** is formed, it is likely to evolve by cleaving the $\text{K}-\text{CF}_3$ bond onto the copper atom because the height of **TS1** is lower than that of **TS_B2**. Thus, once **I2** is obtained, the reaction follows exactly the same pathways as described above, with pathways A and B competing to deliver the trifluoromethylated product. Table 3 shows the free energy values computed for both catalytic cycles when $\text{K}[(\text{CF}_3)\text{B}(\text{OMe})_3]$ is employed. In this case, getting to pathway B is much more difficult than above because **I5** is more than 8 kcal mol^{-1} lower in free energy than **I7**, and thus, it is expected that the only operative mechanism is the one described by pathway A. The catalytic reaction barrier is 20.5 kcal mol^{-1} for PhI , corresponding to the energy difference between **I3** and **TS2**. Using this trifluoromethylating system, it should be possible to carry out the reaction with electron-rich aryl iodides; for example, the barrier for $p\text{-Bu-C}_6\text{H}_4\text{I}$ is just 20.7 kcal mol^{-1} , corresponding to the one computed for this substrate in pathway A. Moreover, the barriers for phenyl bromide and chloride are significantly reduced from 33.2 and 35.8 kcal mol^{-1} to 28.0 and 29.2 kcal mol^{-1} , respectively, indicating that the trifluoromethylation of these substrates should be possible.

Table 3. Computed Free Energies (in kcal mol⁻¹) for the Catalytic Trifluoromethylation of Phenyl Iodide with K[(CF₃)B(OMe)₃] and CF₃COOK

pathway	step/CF ₃ agent	K[(CF ₃)B(OMe) ₃]	CF ₃ COOK
A	I1	0.0	0.0
	I2_B/I2_C	-3.7	0.0
	TS_B2/TS_C2	12.3	19.3
	I2	6.8	10.8
	TS1	10.2	14.2
	I3	-8.0	-4.0
	I4	-4.8	-0.8
	I5	-5.9	-1.9
	TS2	12.5	16.5
	I6	-5.7	-1.7
	TS3	3.3	7.3
B	catalytic barrier	20.5	20.5
	I7	2.6	10.5
	TS4	3.1	11.0
	I8	-8.0	-0.1
	I9	-8.3	-0.4
	TSS	20.8	28.7
	I10	-14.6	-6.6
	TS6	2.5	10.5
	catalytic barrier	29.1	29.1

An alternative nucleophilic CF₃ source studied is potassium trifluoroacetate (CF₃COOK); this species has not been used in catalytic trifluoromethylation reactions but in copper-mediated [LCu(OCOCF₃)] (L= carbene ligand) trifluoromethylation decarboxylative processes.^{8g} A very similar reaction mechanism to the one computed for K[(CF₃)B(OMe)₃] has been found when using CF₃COOK (Scheme 7 and Table 3). Again the

Scheme 7. Formation of I4 Using CF₃COOK as Trifluoromethyl Source (Free Energies in kcal mol⁻¹)



classical transmetalation pathway consisting of iodide replacement by trifluoroacetate and cleavage of the C–CF₃ bond on the copper center seems impossible. The reaction between potassium acetate and I1 to form I2_C is found to be thermoneutral, but the evolution to I3_C and the transmetalation transition state (TS_C1) are very endergonic (+8.8 and +35.8 kcal mol⁻¹, respectively), preventing the reaction to occur this way. In fact, when [LCu(OCOCF₃)] was employed

in decarboxylative trifluoromethylation reactions, high temperatures (170–180 °C) were required to furnish the corresponding products,^{8g} in agreement with the high computed barrier. In order to reach TS_C1, a significant reorganization of the molecular fragments is required; the copper–oxygen bond in I3_C is cleaved and the carboxylic carbon atom gets much closer to the copper atom to form CO₂. The strength of the breaking C–C bond is probably responsible for the large amount of energy required to transfer the CF₃ group from trifluoroacetate to the metal. In contrast, generating KCF₃ from the coordinated potassium trifluoroacetate is much easier, and a relatively low barrier of 19.3 kcal mol⁻¹ has been found to mediate this stage (TS_C2). After that, I2 is obtained (although higher in energy than in the previously computed mechanism and thus with a more limited extent), and the reaction follows then the catalytic pathway A because in this case pathway B is even more disfavored than when employing K[(CF₃)B(OMe)₃]. Interestingly, the computed results indicate that the catalytic version should be much faster than the stoichiometric reaction employing the preformed [LCu(OCOCF₃)] species because the reaction barriers for both are 20.5 and 27.0 kcal mol⁻¹, respectively.

In summary, it seems that both potassium (trifluoromethyl)-trimethoxyborate K[(CF₃)B(OMe)₃] and potassium trifluoroacetate CF₃COOK would furnish good catalytic systems for the trifluoromethylation of aryl iodides. They could possibly also be used in trifluoromethylations of electron-rich aryl iodides and even for the more activated versions of aryl bromides and chlorides.

The second strategy to improve these trifluoromethylation reactions consists of the modification of the catalytic system. As mentioned above, replacing the phenanthroline ligand by another that produces a lower oxidative addition barrier could be beneficial since this is, in all the cases studied, the rate-limiting step of the reaction. It is known that, in general, strongly electron-donating ligands tend to provide lower oxidative addition barriers. There is a plethora of possible electron-rich ligands that could be employed for this purpose—for example, mono- and polydentate amines, phosphines or phosphites. However, it has been stated that harder ligands make more stable catalysts with copper, and thus, only N-donor ligands will be studied. With all this information in hand, a bidentate N-donor ligand: *N,N,N',N'*-tetramethylethylenediamine (TMEDA) has been selected to test the ligand influence in the trifluoromethylation reaction of aryl halides. Thus, the proposed catalytic cycle described above (Scheme 2) has been recomputed using [(TMEDA)CuX] as catalyst for the three possible PhX substrates (X = I, Br, Cl) with the trifluoromethylating mixture CF₃SiEt₃/KF. Intermediate I7 and the transition states TS1 and TS4 have not been recalculated, but given the similarity between the ligands and the complexes obtained, they should not be expected to have a major impact on the reaction profile. The corresponding computed free energies can be found in Table 4. As before, the catalytic reaction follows pathway B, as long as the amount of CF₃SiEt₃/KF added to the reaction mixture is not controlled, because the ditrifluoromethylated copper species are much more stable than those present in pathway A. The purely oxidative addition step barriers, calculated as the energy difference between I9 and TSS (25.2, 30.2, and 30.6 kcal mol⁻¹ for PhI, PhBr, and PhCl, respectively) are, in all cases, lower than those computed with the original [(phen)CuX] systems: 29.1, 33.2, and 35.8 kcal mol⁻¹. Although these results

Table 4. Computed Free Energies (in kcal mol⁻¹) for the Catalytic Cycles of Different Aryl Halides Using [(TMEDA)CuX] as Catalyst

pathway	step/substrate	PhI	PhBr	PhCl
A	I1	0.0	0.0	0.0
	I2	1.1	-1.3	-0.8
	I3	-17.9	-19.4	-18.8
	I4	-15.3	-16.2	-16.3
	I5	-10.5	-9.6	-10.2
	TS2	2.3	7.5	10.6
	I6	-18.1	-6.7	-8.0
	TS3	-8.1	3.7	2.5
	catalytic barrier	20.2	26.9	29.4
	stoichiometric barrier	17.6	23.7	26.9
B	I8	-27.5	-28.5	-28.6
	I9	-22.3	-21.7	-20.8
	TS5	2.9	8.5	9.8
	I10	-22.4	-17.8	-20.6
	TS6	-13.1	-8.5	-11.4
	catalytic barrier	30.4	37.0	38.4

are encouraging, the reaction barriers have to be computed from the lowest energy point of the reaction, that is, complex I8; therefore, the activation free energies are worse than those obtained with Amii's catalytic system: 30.4, 37.0, and 38.4 kcal mol⁻¹, for phenyl iodide, bromide, and chloride, respectively. Thus, the ligand replacement studied does not seem to produce a better catalyst, although, as expected, the oxidative addition barriers are considerably lower. This should not be completely unexpected; usually reaction design and modification faces this kind of situation where one variation is beneficial for a certain reaction step but detrimental for another one, making the whole reaction optimization an unsolvable problem.

4. CONCLUSIONS

The mechanism for the copper-catalyzed nucleophilic trifluoromethylation of aryl halides, based on the first reaction of this kind reported by Amii et al., has been explored with DFT calculations. The formation of KCF₃, easily obtained from the initial CF₃SiEt₃ and KF, is responsible for a significant increase in the reaction barrier due to the formation of ditrifluoromethylated copper species such as K[(phen)Cu(CF₃)₂]. The reaction barriers computed for phenyl iodide, bromide, and chloride clearly agree with the experimental observations that only the former can be employed successfully in catalytic reactions using this system. However, the calculations also indicate that activated aryl bromides and chlorides could be employed in stoichiometric reactions. In the case of substituted aryl halides, the reaction is faster for electron-poor substrates, as observed experimentally, because the oxidative addition barrier, which is the highest energy transition state along the reaction pathway, is significantly lower.

Two different alternative proposals, based on the computational results obtained with Amii's catalytic system, have been tested with a view to suggesting improvements to this nucleophilic trifluoromethylation reaction. The first one consists of the employment of other, more controllable, nucleophilic CF₃ sources which could help to prevent the formation of K[(phen)Cu(CF₃)₂]. Replacing the original CF₃SiEt₃/KF source by potassium (trifluoromethyl)-trimethoxyborate and potassium trifluoroacetate seems to be beneficial. The second proposal is aimed at lowering the

oxidative addition barrier which is, in all cases, the highest energy point in the reaction profile. Replacing the phenanthroline ligand of the catalyst by the more electron-donating TMEDA should, in principle, provide a better catalytic system. In fact, the pure oxidative addition barrier is lowered significantly when the latter is employed but the energy difference to the resting state of the reaction becomes higher and thus no improvement should be expected.

Finally, the best option for improving Amii's trifluoromethylation reaction seems to be controlling the amount of KCF₃ released into the reaction mixture to avoid the formation of K[(phen)Cu(CF₃)₂]. This could be easily done by adding the trifluoromethylating agent slowly during the reaction course. By doing this, it should be possible to carry out the catalytic trifluoromethylation of aryl iodides and activated bromides and chlorides, with similar outcomes to those found in stoichiometric reactions.

■ ASSOCIATED CONTENT

Supporting Information

The following file is available free of charge on the ACS Publications website at DOI: 10.1021/cs500872m.

Includes all computed free energies and optimized structures, along with alternative reaction pathways (PDF).

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Notes

The authors declare no competing financial interest.

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