ORGANOMETALLICS

Influence of the Formation of the Halogen Bond ArX---N on the Mechanism of Diketonate Ligated Copper-Catalyzed Amination of Aromatic Halides

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Supporting Information

ABSTRACT: The mechanism of cross-coupling reactions of aryl halides PhX (X = I, Br, Cl) with cyclohexylamine catalyzed by CuI associated with a diketonate ligand (ket = 2-acetyl-cyclohexanoate) has been investigated via DFT. Phenyl halides which can be involved in halogen-bond formation (X = I, Br)



with the anionic nitrogen of the intermediate $[(\text{ket})\text{Cu-NHCy}]^-$ can undergo intramolecular oxidative addition, which is in competition with the classical oxidative addition three-centered pathway, whereas those which cannot (X = Cl) undergo a classical oxidative addition, leading to the common complex (ket)Cu^{III}Ph(NHCy). The latter is involved in a faster reductive elimination, leading to PhNHCy. C₆F₅I, which involves the strongest C₆F₅I- -N halogen bond, generates the anion C₆F₅⁻ and consequently not the expected C–N cross-coupling product by substitution at the C–I bond, as evidenced experimentally.

INTRODUCTION

Copper complexes catalyze cross-coupling reactions of aryl halides with amines in the presence of a base and a ligand L (eq 1).¹

$$Ar - X + H_2 N - R \xrightarrow{Cu_{cat}} Ar - NHR$$
L, base
(1)

Reported mechanistic studies on dative N,N ligands have established that the active catalyst is a $(N,N)Cu^{I}-Nu$ species (Nu = amidate, imidate) that reacts with PhI in a mechanism which is still under debate, involving either an oxidative addition or an inner- or outer-sphere electron transfer.² Commercially available preligands such as 1,3-diketones were found to be highly efficient for C–N couplings from aryl iodide under mild conditions and more severe conditions with aryl bromides.³ A few fully theoretical papers dealing with 1,3-diketonate (ket) ligands recently appeared, proposing either an outer-sphere single electron transfer mechanism (SET)⁴ from an anionic [(ket)Cu^I–NHMe]⁻ complex toward PhI or an oxidative addition of a neutral (ket)-Cu^I(NH₂(CH₂)₃OH) complex to PhI via a prior PhI/amine exchange.⁵

In contrast, in a previous study involving $CyNH_2$ as primary amine,⁶ we demonstrated, by a combined theoretical and experimental approach, that the catalytically active species is the anionic [(ket)Cu^I-NHCy]⁻ (**A**), evidenced by cyclic voltammetry (CV) and ¹H NMR, in which the negative charge is mainly located on the nitrogen, as revealed by DFT calculations. Consequently, the preliminary interaction of this complex with PhI is a PhI---N interaction related to a halogen bond (Scheme 1, Figure 1).^{6,7} An intramolecular oxidative addition then took place affording an aryl-copper(III) intermediary Scheme 1. Mechanism of the Cu-Catalyzed Cross-Coupling Reaction between PhI and NH₂Cy in the Presence of Cs_2CO_3 as the Base in DMF (Entry 1 in Table 1)⁶



(C) which delivered the expected cross-coupling product after a reductive elimination which is faster than the oxidative addition (Scheme 1).⁶ The present work proposes a detailed analysis of the mechanism of the reaction involving the active anionic

Received: October 10, 2011 Published: February 1, 2012 complex [(ket)Cu–NHCy]⁻ (**A**) and aryl halides (ArX; X = I, Br, Cl, F). Namely, the role played by the halide X is studied in the context of possible formation of ArX---N halogen bonds. It is worthwhile to note that a SET between **A** and PhI was ruled out in our previous paper because of the difference between the reduction potential of PhI and the oxidation potential of complex **A** was too high ($\Delta E = \text{ca. 3 V}$).⁶ Since PhBr and PhCl are reduced at more negative potentials than is PhI, ΔE will be higher ($\Delta E = > 3$ V) and the SET even less favored.

RESULTS AND DISCUSSION

Experimental Copper-Catalyzed Cross-Coupling Reactions. From an experimental point of view, aryl halides (ArX; X = I, Br, Cl, F) are known to show extremely different reactivity in Cu-catalyzed C–N couplings, from the absence of reaction observed in the case of aryl fluoride derivatives to good yields observed for aryl iodides.^{3,4} The cross-coupling reactions between ArI (Ar = Ph, *p*-F-C₆H₄–) and cyclohexylamine in the presence of Cs₂CO₃ and a catalytic amount of CuI associated to the diketone preligand ketH (2-acetylcyclohexanone) reported in our previous work⁶ have been extended to PhX (X = Br, Cl) (Table 1) and delivered the reactivity order PhI > PhBr \gg

Table 1. Amination of Aryl Halides^a

Conditions a, b X + H₂N 2 equiv Cs₂CO₃ ketH DMF, r.t. 1.9 mmol 1.5 eauiv a: Cul (5 % mol), ketH (20 % mol); b: no Cu, no ketH t (h) Product %ⁱ ()ⁱⁱ ArX 38 (56) 1 PhI a 22 Ph-NHCy 63 (35) 4-F-Ph-NHCy 2 4-F-C₆H₄-I 15 a 30 (60) 3 PhBr Ph-NHCy 22 а 3 (60) 4 PhCl 22 Ph-NHCy a 5 C₆F₅-I а 24 11 8 (77) 3 C_6F_5H 6 C₆F₅-I b 20 23 (75) 91(8) 7 C₆F₆ b 20 CyNH-C₆F₅

^{*a*}DMF 1 mL. Legend: (i) Product yield; (ii) Recovered ArX. Yields determined after workup by ¹H or ¹⁹F NMR of the crude mixture (see the Supporting Information).

PhCl (entries 1, 3, and 4). The latter has also been established with related ligands.^{2,3}

In addition, similar catalytic tests were conducted with C_6F_5I , expected to be more reactive than PhI due to the electronacceptor fluorines. Surprisingly, the desired cross-coupling product was never obtained by substitution at the C–I bond. Instead, slow and limited conversion of C_6F_5I led to three unexpected products (Table 1, entry 5): the amino product 1, formed by substitution of the fluorine in a position para to the iodine, the product 2, with similar substitution but with loss of the iodine atom, and pentafluorobenzene. This led us to conduct a reaction in the absence of CuI and ligand (entry 6, Table 1), which afforded product 1 as a result of a nucleophilic substitution at the fluorine in a position para to the iodide, in agreement with a classical S_NAr mechanism⁸ (independently tested in entry 7 on C_6F_6). Such reactions showed that, as expected, the C-I bond could not be activated in a classical S_NAr mechanism, in contrast to C-F bonds. However, in the presence of CuI and ligand, the formation of 2 and C₆F₅H, which both had lost their iodide atoms, suggested an activation of the C–I bond of C_6F_5I but without forming the desired C– N product at the C-I bond. Such results will be rationalized later on (vide infra).

Cross-Coupling Reactions via DFT Calculations. The key point allowing an explanation of the difference of reactivity might be that the oxidative addition appears to be promoted by the formation of a stable complex (type $B_{J_{\nu}}$ in Figure 1c)



Figure 1. (a) Schematic structure and labeling scheme of the anionic complex $[(\text{ket})\text{Cu-NHCy}]^-$ (A). (b) Computed electrostatic surface potential for A: the red color indicates negative charges. (c) Formation of complex B_I by halogen bonding.

exhibiting a sizable halogen bond between the halogen atom of ArX and the negative N of $[(\text{ket})\text{Cu}-\text{NHCy}]^-$ (complex A in Figure 1a,b), as reported by us for PhI (Figure 1c).⁶

Density functional theory (DFT) was applied to determine the structural and energetic features of the catalytic cycle involving PhI, PhBr, PhCl, and C_6F_5I . This method, in conjunction with hybrid exchange-correlation functionals, has become one of the major theoretical tools of quantum chemistry, notably thanks to its reliability, its low computational cost, and its range of applications. For these reasons, such an approach has been successfully applied to the study of a large number of catalytic reactions for more than a decade.⁹ More specifically, we made use of the

		B _X			TS1			
	A	PhI	PhBr	C ₆ F ₅ I	PhI	PhBr	PhCl	C_6F_5I
Cu	0.51	0.55	0.53	0.57	0.79	0.79	0.66	0.77
Ν	-1.15	-1.09	-1.11	-1.05	-0.97	-0.96	-1.06	-0.91
O_1	-0.72	-0.77	-0.76	-0.77	-0.72	-0.72	-0.72	-0.72
O ₂	-0.74	-0.71	-0.71	-0.71	-0.70	-0.69	-0.70	-0.69
C_1		-0.28	-0.17	-0.40	-0.18	-0.14	-0.12	-0.37
		С		T82		D		
	Ph		C ₆ F ₅	Ph	C_6F_5		Ph	C ₆ F ₅
Cu	0.87		0.87	0.86	0.86		0.65	0.65
Ν	-0.77		-0.73	-0.76	-0.70	-	0.74	-0.73
O_1	-0.68		-0.65	-0.71	-0.70	-	0.77	-0.77
O ₂	-0.67		-0.63	-0.69	-0.68	-	0.73	-0.73
C_1	-0.15		-0.30	-0.11	-0.24		0.14	0.04

Table 2. Computed NPA Charges for the Different Complexes and TS Involved in the Cross-Coupling Reaction

hybrid exchange correlation functional PBE0,¹⁰ which has been proven to yield accurate and reliable thermochemistry data even in the case of reactions involving transition-metal ions.¹¹ This hybrid functional mixes 25% of Hartree-Fock exchange to the gradient corrected PBE exchange and correlation functional.¹² All calculations were carried out using Gaussian09.13 A 6-31+G(d) basis¹⁴ was used for all atoms (C, H, O, N, F, Cl, Br, and I) except for the metal (Cu), which was treated using a Stuttgart pseudopotential $(SDD)^{15}$ and associated basis set.¹⁶ This pseudopotential has been proven to slightly overestimate interaction energies, but general trends discussed here should be conserved. All structures corresponding to stationary points were obtained by fully optimizing in the absence of geometrical constraints, and they were characterized by subsequent frequency calculations as minima or first-order transition states (i.e., only one imaginary frequency). Solvent effects (here DMF) were included during both structural optimizations and frequency calculations using an implicit solvation model based on the polarizable continuum model (PCM) of Tomasi and co-workers¹⁷ as implemented in the Gaussian code.¹⁸ This method has been proven to provide an accurate description of bulk solvent effects on energy profiles, and it is actually one of the best compromises between efficiency and accuracy to simulate solvent in conjunction with a quantum chemical description of the reaction.¹⁹ Charge analysis was performed using the NBO²⁰ partition scheme. Reaction energies were corrected for basis set superposition error (BSSE) using the counterpoise method.^{21a} Selected reaction paths were followed by integrating the intrinsic reaction coordinate (IRC calculations).^{21b}

Activation Step. On the basis of our previous investigations by CV and ¹H NMR,⁶ it seems clear that, due to the presence of a basic medium, the active Cu^I complex is the anionic complex $[(\text{ket})\text{Cu}^I-\text{NHCy}]^-$ (A) generated by deprotonation by the base Cs_2CO_3 of the ligated NH₂Cy in (ket)Cu^I(NH₂Cy) (Scheme 1).²² It is difficult to investigate the equilibrium between the anionic complex A and its acidic form (ket)Cu^I(NH₂Cy) by DFT-type calculations because, under experimental conditions, the base Cs₂CO₃ is used in high concentration and it is present as a solid residue due to its rather low solubility. Thus, all the homogeneous equilibria in which this basis is involved are modified. In particular, it is likely that the deprotonation process occurs at the interface between the solid and the solution, making its modeling rather complex.²³ The structural and electronic features of the anionic complex **A**, in the absence of the substrate, were first analyzed (Table 2). As expected for a Cu(I) complex, the copper atom shows an inplane coordination of the three donor atoms (N, O₁, and O₂) of the ligands with a small deviation from perfect planarity $(d(OOCuN) = 13.6^\circ$; Table S1 in the Supporting Information). Of note, a bite angle of 83.8° was computed for the diketonate ligand. This bite angle is comparable to what was found in the case of the corresponding bidentate phenanthroline ligands (ca. 82° in Cu^I(dimethylphen)₂-type complexes).²⁴ Consequently, the copper atom is quite accessible to a substrate (e.g., ArX) so that an oxidative addition to the metal atom is fully compatible with its steric hindrance.

In order to define possible sites for the interaction between aryl halides and complex A, both the electrostatic potential surface of A (Figure 1b) and the atomic charges computed using the NPA (Table 2) partition were analyzed. For the active complex A, analyses pointed out that the most electron-rich site was the nitrogen atom, whose NPA charge is computed to be -1.15e, while the copper atom displayed a net positive charge of (+0.51e) (Table 2). On the other hand, the halogen atom of the aromatic halides showed a more marked dependence of the halide atom. Indeed, while fluoride and chloride derivatives respectively showed a negative (-0.347e)and practically null (+0.006e) charge on the halide atom, both bromide and iodide derivatives showed a net positive charge on it, of +0.059e and +0.141e, respectively (Table 2). On the basis of this charge analysis, two different scenarios could be envisaged for the reaction of A with ArX to take place. Either complex A gave rise to a standard oxidative addition, via a three-center TS, or complex A could act as a nucleophile, activating the ArX via the formation of a halogen-amino bond, reminiscent of what occurs in metal-iodine exchange reactions.⁷ Clearly depending on the substrate ArX, one or the other reaction channel would be preferred. The possibility of the latter reaction path to take place might be related to the stability of the halogen-amido complex formed. The stabilization energy computed for the different adducts is reported in Table 3, together with the computed electron flux from complex A to ArX. This latter value was computed as the difference in total NPA charges between ArX in complex B_x and that of the free ArX, a negative value implying an electron flux from complex A to ArX (nucleophilic behavior).

First of all, one notes that, in the case of the fluoride and chloride compounds, no stable complex B_F or B_{CI} was found,

Table 3. Computed Stabilization Energies (in kcal mol⁻¹) Due to the Formation of Complex B_X and Computed Electron Flux^{*a*}

ArX	ΔE	flux (NBO)					
PhF							
PhCl							
PhBr	0.72	-0.06					
PhI	-4.92	-0.15					
C_6F_5I	-16.65	-0.28					
^{<i>a</i>} In e; see text for definition.							

the interaction between complex **A** and PhX (X = F, Cl) giving rise to an activated complex being fully repulsive. Thus, for these two systems only a classical oxidative addition mechanism had to be envisaged. On the other hand, the opposite behavior was found for PhI, for which the stable adduct **B**_I (-4.92 kcal mol⁻¹) was indeed computed. Less clear is the case of PhBr, for which the adduct **B**_{Br} formation was only very slightly endergonic (+0.72 kcal mol⁻¹), thus being fully possible under experimental conditions, although not as stabilizing as in the case of PhI. Introducing electron-withdrawing substituents (i.e., fluorine atoms) on the PhI ring, when considering the C₆F₅I molecule, further stabilized the formation of the adduct **B**'₁, since it magnified the electrophilic character of the iodine atom (computed NPA charge for the iodine atom in C₆F₅I: +0.22e versus +0.17e for PhI).

These theoretical outcomes suggested that PhI and PhBr could undergo an intramolecular oxidative addition preceded by the formation of a stable adduct of type B_X activating the Ar-X bond (X = I, Br). In contrast, a classical oxidative addition for PhCl would most probably—with more difficulty in comparison with the intramolecular case—take place due to the absence of C-Cl activation by the nucleophilic N atom of [(ket)Cu^I-NHCy]⁻.

Cross-Coupling Reaction As a Function of the Halide of ArX. As reported in our previous work, the interaction of complex A with PhI passed through the formation of a stable iodine—amino interaction, giving rise to a stable intermediate (B_I), as discussed in the previous section (Figure 1). This latter species easily evolved via a four-center TS (TS1; Figure 2a) to give the "distorted" square-planar Cu(III) complex C (Figure 2a), as in a classical oxidative addition.

In this context it is worth to note that at the TS state both the N–I and C–I distances are significantly elongated with respect to the stable adduct (B_I). From this TS, the stable complex C is formed by expulsion of the iodide ion. Once the Cu(III) intermediate C is formed, it rapidly evolves toward the product by reductive elimination, the second barrier (ca. 2 kcal mo Γ^1) being much smaller than the first one (Figure 2a). The rate-determining step is thus the formation of the first TS (**TS1**, four centers) and no accumulation of the Cu(III) intermediate (C) is thus expected, in agreement with our previous experimental study.⁶

This mechanism of the oxidative addition has then been compared to the more classical three-center oxidative addition when directly performed from **A**. The latter has been computed at the same level of theory (Figure 2b). By comparing the two reaction mechanisms, one notes that both pathways can be envisaged: the classical three-center path is slightly thermodynamically favored but begins with a strongly endothermic π complexation of the copper onto the C=C bond bearing the



Figure 2. Reaction paths computed for PhI: (a) intramolecular oxidative addition from complex B_I via halogen bond formation; (b) classical three-center oxidative addition from A.

iodine atom, whereas the four-center path takes place from a stabilized halogen-bonded precomplex (B_I) .^{25a}

In contrast to the evolution of TS1 (from \mathbf{B}_{L} Figure 2a), the transition state TS'1 (from $\mathbf{B}''_{\mathrm{L}}$ Figure 2b) evolved toward an intermediate complex \mathbf{F}_{L} in which the iodide is still coordinated to the copper(III) complex, which is thus anionic. After expulsion of the Γ anion, the Cu(III) complex (C) was formed exothermically (ca. 12 kcal mol⁻¹) (Figure 2b). This latter species rearranged through a reductive elimination to yield the stable product of the coupling reaction (D), as in Figure 2a.

As expected, if one substitutes the phenyl ring of PhI with electron-withdrawing groups (such as by five fluorine atoms), the stability of the halogen-bonded adduct \mathbf{B}'_{I} is enhanced (-4.92 kcal mol⁻¹ for PhI versus -16.65 kcal mol⁻¹ for C_6F_5I) (Figure 3). However, experimentally the cross-coupling did not work; no amination at the C–I bond was observed (entry 5, Table 1). To understand the origin of this apparent discrepancy between the computed and experimental data, the full reaction pathway for oxidative addition was studied in the case of C_6F_5I (Figure 3 and Table S2 (Supporting Information)).

Overall, the theoretical reactivities of PhI and C_6F_5I are very similar, and after the formation of the Cu(III) intermediate C and C', respectively, the energy barriers for the reductive elimination are comparable (2.21 kcal mol⁻¹ for PhI versus 4.33 kcal mol⁻¹ for C_6F_5I) (compare Figure 2a and 3). Nonetheless, one important difference can be noted: the formation of the very stable adduct **B**'₁ in the case of C_6F_5I involves a larger barrier



Figure 3. Reaction path computed for C_6F_5I based on an oxidative addition from complex B'_{1} .

 $(25.64 \text{ kcal mol}^{-1})$ for the oxidative addition leading to complex C'. As a consequence, the overall reaction rate and yield (dominated by this rate-determining step) is expected to decrease on going from PhI to C₆F₅I, as experimentally observed, since no C-N cross-coupling product was formed by substitution at the C–I bond of C_6F_5I (Table 1, entry 5). In other words, the adduct \mathbf{B}'_{I} formed with C_6F_5I seems to be too stable so that the reaction was blocked at the formation of B'_I. Nevertheless, one observes the formation of C₆F₅H and compound 2 (Table 1, entry 5). The C-I bond had been cleaved in both products without formation of the C-N coupling at the C-I bond, which rules out any oxidative addition. This suggests the formation of $C_6F_5^-$ with further protonation leading to C₆F₅H. The latter species will then undergo a S_NAr reaction with the amine in the presence of the base, ending with the formation of product 2. The formation of $C_6F_5^-$ is similar to what would happen in a classical halogen-metal exchange: for example, in the reaction ArI + BuLi \rightarrow ArLi + BuI.⁷ The evolution of B'_{I} according to this pathway was investigated by DFT calculations, which did reveal the formation of C_6F_5 together with the non-arylated Cu(III) complex E (Figure 4



Figure 4. Reaction path computed for $C_6F_{5}I$ involving the classical evolution of a strong halogen bond formation leading to halogenmetal exchange.

and Table S3 (Supporting Information)).²⁶ Such activation could not of course deliver the desired C–N cross-coupling product by substitution at the C–I bond of C_6F_5 –I, as experimentally observed (Table 1, entry 5).

From this study, one concludes that the N- - -I halogen bond formation in complex $B'_{1\nu}$ strongly exothermic in the case of

 C_6F_5I , favored the formation of the aryl anion and did not lead to a copper-catalyzed C–N cross-coupling reaction. The threecenter oxidative addition from **A** (Figure S1) appears quite unlikely, due to the high stability of the **B**'_I complex.

As far as PhBr is concerned, the formation of the adduct B_{Br} was barrierless and slightly thermodynamically unfavorable (+0.72 kcal mol⁻¹) (Figure 5). The overall reaction followed a



Figure 5. Reaction path computed for PhBr.

pathway identical with what was observed for PhI, with reaction barriers associated with the formation of both **TS1** and **TS2** very close to the values computed for PhI (24 and 2 kcal mol⁻¹ for PhBr with respect to 22 and 2 kcal mol⁻¹ for PhI in Figure 2a). Due to the similar activation barriers computed for the three-center and four-center pathways (22.5 kcal mol⁻¹ vs 23.69 kcal mol⁻¹; Figure S2 (Supporting Information) and Figure 5, respectively) both channels must be envisaged.^{25b}

In the case of PhCl, a complex of type \mathbf{B}_{Cl} was not formed (no halogen bond formation). A standard intermolecular oxidative addition mechanism was thus computed, as depicted in Figure 6. After a π complexation of the copper center onto



Figure 6. Reaction path computed for PhCl.

the C==C bond bearing the Cl atom (thermodynamically unfavored by 14.81 kcal mol⁻¹) a three-center (Ph–Cu–Cl) transition state (TS'1, Figure 6) was computed, which is 26 kcal mol⁻¹ higher in energy with respect to the reactants. This transition state provided the intermediate anionic complex F_{Cl} in which the halogen is directly coordinated to the copper(III) complex. After

expulsion of the C Γ anion, the Cu(III) complex **C** was formed exothermically (ca. 9 kcal mol⁻¹). This latter species could easily rearrange through a reductive elimination to yield the stable product of the coupling reaction **D**, as also established in the case of PhI and PhBr (common intermediate complex **C**).

The formation of C is highly exothermic, -16 kcal mol⁻¹ for PhI compared to -9 kcal mol⁻¹ for PhCl, but the overall reaction barrier computed for PhI is smaller (22.9 kcal mol⁻¹ via complex **B**_I (Figure 2a), 16.7 kcal mol⁻¹ from complex **A** (Figure 2b)) than for PhCl (26.04 kcal mol⁻¹, Figure 6). The larger activation energy of the oxidative addition step computed for PhCl explains the experimentally observed lower reactivity of PhCl (Table 1, entry 4).

Finally, it should be mentioned that no stable adduct nor reasonably low in energy TS for oxidative addition was found for PhF. This finding is in agreement with the results in entries 5-7 in Table 1, which showed that the arylated amine 1 formed in the presence of copper by substitution of one F in C_6F_5I (entry 5) was in fact not catalyzed by copper but was formed via a S_NAr reaction, in agreement with the experiments performed in the absence of copper (entries 6 and 7). In other words, free copper S_NAr reactions on ArF are faster than copper-catalyzed cross-coupling at a Ar_{F5} –I bond.

CONCLUSIONS

We have reported herein the results of experimental and theoretical studies of diketonate-ligated Cu(I)-catalyzed C-N crosscoupling between aryl halides and cyclohexylamine, leading to C-N bond formation. It is established that a halogen-bonded complex B_X (X = I, Br) is formed by complexation of the halogen atom of PhI and PhBr to the nucleophilic nitrogen of $[(\text{ket})\text{Cu}(\text{NHCy})]^-$ (A). These complexes **B**_X can undergo an intramolecular oxidative addition (four-center pathway), which is computed to be in competition with the classical three-center oxidative addition pathway, slightly thermodynamically favored for PhI but with a similar energy barrier for PhBr. Both pathways ultimately lead to the same (ket)Cu(Ph)(NHCy) copper-(III) complex, which undergoes a faster reductive elimination, leading to PhNHCy. In contrast, in the case of PhCl only the classical oxidative addition takes place, due to the lack of halogen bond formation. The DFT calculations reflect the observed overall reactivity of aryl halides in the investigated C-N crosscouplings (ArI > ArBr \gg ArCl).

The lack of reactivity in C–N coupling at the C–I bond of electron-deficient aryl iodides such as C_6F_5I has been explained. Due to a very strong halogen bond in complex B'_I , this intermediate complex does not undergo intramolecular oxidative addition as B_I does but instead evolves via the classical formation of the anion $C_6F_5^-$ and after protonation to S_NAr -type products by substitution at a C–F bond. No C–N product by substitution at the C–I bond of C_6F_5I could thus be formed.

Therefore, the formation of stabilizing halogen-bonded complexes between $[(ket)Cu(NHCy)]^-$ and aryl halides can lead to a four-center oxidative addition pathway which is in competition with the classical three-center path. Nevertheless, a strong halogen-bonding complexation can disable both oxidative addition pathways and lead to a reduction process of the aryl halide.

ASSOCIATED CONTENT

S Supporting Information

Text, figures, and tables giving experimental details, computed structural parameters of the different species involved in the

catalytic cycles, reaction paths computed for C_6F_5I and PhBr following the classical oxidative addition path, and computed imaginary frequencies associated with all TS. This material is available free of charge via the Internet at http://pubs.acs.org.

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REFERENCES

 (1) For reviews, see: (a) Cristau, H.-J.; Cellier, P. P.; Spindler, J.-F.; Taillefer, M. Eur. J. Org. Chem. 2004, 695–709. (b) Beletskaya, I. P.; Cheprakov, A. V. Coord. Chem. Rev. 2004, 248, 2337–2364. (c) Evano, G.; Blanchard, N.; Toumi, T. Chem. Rev. 2008, 108, 3054–3131.
 (d) Monnier, F.; Taillefer, M. Angew. Chem., Int. Ed. 2009, 48, 6954– 6971. (e) Sperotto, E.; van Klink, G. P. M; van Koten, G.; de Vries, J. G. Dalton Trans. 2010, 39, 10338–10351.

(2) (a) Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. J. Am. Chem. Soc. 2005, 127, 4120–4121. (b) Tye, Z.; Weng, J. W.; Johns, A. M.; Incarvito, A. C. D.; Hartwig, J. F. J. Am. Chem. Soc. 2008, 130, 9971–9983. (c) Srieter, E. R.; Bhayana, B.; Buchwald, S. L. J. Am. Chem. Soc. 2009, 131, 78–88. (d) Zhang, S. L.; Liu, L.; Fu, Y.; Guo, Q.-X. Organometallics 2007, 26, 4546–4554.

(3) (a) Shafir, A.; Buchwald, S. L. J. Am. Chem. Soc. 2006, 128, 8742– 8743. (b) Shafir, A.; Lichtor, P. A.; Buchwald, S. L. J. Am. Chem. Soc. 2007, 129, 3490–3491. (c) Altman, R. A.; Koval, E. D.; Buchwald, S. L. J. Org. Chem. 2007, 72, 6190–6199. (d) Altman, R. A.; Hyde, A. M.; Huang, X.; Buchwald, S. L. J. Am. Chem. Soc. 2008, 130, 9613– 9620. (e) Monnier, F.; Taillefer, M. Angew. Chem., Int. Ed. 2008, 47, 3096–3099. (f) Xia, N.; Taillefer, M. Angew. Chem., Int. Ed. 2009, 48, 337–339. (g) Larsson, P.-F.; Correa, A.; Carril, M.; Norrby, P.-O.; Bolm, C. Angew. Chem., Int. Ed. 2009, 48, 5691–5693.

(4) Jones, G. O.; Liu, P.; Houk, K. N.; Buchwald, S. T. J. Am. Chem. Soc. 2010, 132, 6205–6213.

(5) Yu, H.; Jiang, Y.; Fu, Y.; Liu, L. J. Am. Chem. Soc. 2010, 132, 18078-18091.

(6) Franc, G.; Cacciuttolo, Q.; Lefèvre, G.; Adamo, C.; Ciofini, I.; Jutand, A. *ChemCatChem* **2011**, *3*, 305–309.

(7) For halogen bonds involving aryl iodides see: (a) Reich, H. J.; Green, P.; Phillips, N. H. J. Am. Chem. Soc. 1989, 111, 3444–3445.
(b) Reich, H. J.; Whipple, W. L. Can. J. Chem. 2005, 83, 1577–1587.
(c) Metrangolo, P.; Neukirch, H.; Pilati, T.; Resnati, G. Acc. Chem. Res. 2005, 38, 386–395.

(8) Battioni, P.; Brigaud, O.; Desvaux, H.; Mansuy, D.; Traylor, T. G. *Tetrahedron Lett.* **1991**, *32*, 2893.

(9) van Santen, R. A., Sautet, P., Eds. Front Matter in *Computational Methods in Catalysis and Materials Science: An Introduction for Scientists and Engineers*; Wiley-VCH: Weinheim, Germany, 2009.

(10) Adamo, C.; Barone, V. J. Chem. Phys. 1999, 110, 6158-6170.

(11) Coquet, R.; Tada, M.; Iwasawa, Y. Phys. Chem. Chem. Phys. 2007, 9, 6040–6046.

(12) Perdew, J. P.; Burke, K.; Ernzerhof, M. Phys. Rev. Lett. 1996, 77, 3865-3868.

(13) Frisch, M. J.; et al. *Gaussian 09, revision A.02*; Gaussian, Inc., Wallingford, CT, 2009.

(14) (a) Krishnan, R.; Binkley, J. S.; Seeger, R.; Pople, J. A. J. Chem. Phys. **1980**, 72, 650–654. (b) Clark, T.; Chandrasekhar, J.; Spitznagel, G. W.; Schleyer, P. v. R. J. Comput. Chem. **1983**, 4, 294–301.

(15) Szentpaly, L. v.; Fuentealba, P.; Preuss, H.; Stoll, H. Chem. Phys. Lett. 1982, 93, 555.

(16) Kuchle, W.; Dolg, M.; Stoll, H.; Preuss, H. J. Chem. Phys. 1994, 100, 7535.

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(17) Miertus, S.; Scrocco, E.; Tomasi, J. Chem. Phys. 1981, 55, 117–129.

(18) Scalmani, G.; Frisch, M. J.; Mennucci, B.; Tomasi, J.; Cammi, R.; Barone, V. J. Chem. Phys. **2006**, *124*, 094107.

(19) Mennicci, B.; Cammi, R. Continuum Solvation Models in Chemical Physics: From Theory to Applications; Wiley: Chichester, U.K., 2007.

(20) Foster, J. P.; Weinhold, F. J. Am. Chem. Soc. 1980, 102, 7211-7218.

(21) (a) Boys, S. F.; Bernardi, F. Mol. Phys. 1970, 19, 553.
(b) Hratchian, H. P.; Schlegel, H. B. J. Chem. Phys. 2004, 120, 9918-24.

(22) For deprotonation of ligated amine, see: (a) Louie, J.; Hartwig, J. F. Angew. Chem., Int. Ed. **1996**, 35, 2359–2361. (b) Barder, T. E.; Buchwald, S. T. J. Am. Chem. Soc. **2007**, 129, 12003–12010. (c) Franc, G.; Jutand, A. Dalton Trans. **2010**, 39, 7873–7875.

(23) For related problems in Pd-catalyzed reactions see: Meyers, C.; Maes, B. U. W.; Loones, K. T. J.; Bal, G.; Lemière, G. L. F.; Dommisse, R. A. J. Org. Chem. **2004**, *69*, 6010–6017.

(24) Lavie-Cambot, A.; Cantunel, M.; Leydet, Y.; Jonusauskas, G.; Bassani, D. M.; McClenaghan, N. D. *Coord. Chem. Rev.* **2008**, *252*, 2572–2584.

(25) (a) The existence of a possible direct equilibrium between the halogen-bonded complexes B_I and $B_I''_I$ was also investigated. No transition state was found. Indeed, in complex B_{ν} the geometric constraint is high between both reactants and the angle $\theta(\rm NIC)$ is close to 180° (Table S1, Supporting Information). The rotation of the phenyl iodide from B_I to its position in complex $B_I''_I$ cannot take place, due to the repulsion of the lone pairs of the nitrogen atom and those of the iodide atom. As soon as the NIC angle was set inferior to 150° , the separated PhI and [(ket)Cu-NHCy]⁻ were formed. Consequently, there is no crossing between the two depicted mechanisms for the oxidative addition. (b) Similar computations^{25a} for $B_{\rm Br}$ and $B''_{\rm Br}$ revealed that there is no crossing between the two mechanisms also in this case.

(26) The Cu(I) has been oxidized to Cu(III), similar to what happens in a classical halogen-metal exchange ArI + BuLi \rightarrow ArLi + BuL, in which the anionic Bu in BuLi has been oxidized to form BuI while ArI has been reduced to Ar⁻ in ArLi, except that in the present case the halogen bond was not a C- - I bond but a N- - I bond.