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# Gas-phase studies of copper(I)-mediated CO<sub>2</sub> extrusion followed by insertion of the heterocumulenes CS<sub>2</sub> or phenylisocyanate.

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**Abstract:**

The gas-phase extrusion-insertion reactions of the copper complex  $[(\text{Bphen})\text{Cu}^{\text{I}}(\text{O}_2\text{CC}_6\text{H}_5)]^{2-}$  (Bphen = bathophenanthroline), generated via electrospray ionization, was studied in a linear ion trap mass spectrometer with the combination of collision-induced dissociation (CID) and ion-molecule reaction (IMR) events. Multistage mass spectrometry ( $\text{MS}^n$ ) experiments and density functional theory (DFT) demonstrated that extrusion of carbon dioxide from  $[(\text{Bphen})\text{Cu}(\text{O}_2\text{CC}_6\text{H}_5)]^{2-}$  (CID) gives the organometallic intermediate  $[(\text{Bphen})\text{Cu}(\text{C}_6\text{H}_5)]^{2-}$ , which subsequently reacts with carbon disulfide (IMR) via insertion to yield  $[(\text{Bphen})\text{Cu}(\text{SC}(\text{S})\text{C}_6\text{H}_5)]^{2-}$ . The fragmentation of the product ion resulted in the formation of  $[\text{Bphen}]^{2-}$ ,  $[(\text{Bphen})\text{Cu}]^-$  and  $\text{C}_6\text{H}_5\text{CS}_2^-$  under CID conditions. The formation of the latter two charge separation products thus provides evidence of C-C bond formation in the IMR step. Although analogous studies with isocyanate, which is isoelectronic with  $\text{CS}_2$ , showed a poor reactivity in the gas phase, the mechanistic understanding obtained from these model studies encourages future development of a solution phase protocol for the synthesis of amides from carboxylic acids and isocyanates mediated by copper(I) complexes.

**Introduction**

The past two decades have witnessed a renaissance in the exploration of new catalytic transformations of carboxylic acids.<sup>1</sup> The motivations for these contemporary studies include: (i) carboxylic acids exhibit huge structural variety (R can be alkyl, alkenyl, alkynyl, aryl, heteroaryl, etc); (ii) many are manufactured as bulk commodity chemicals; (iii) when not commercially available they can often be readily made using well-established procedures (e.g. oxidation of primary alcohols or alkylarenes); (iv) they usually exhibit high stability and thus are easy to store and handle; and (v) catalytic transformations of carboxylic acids have great potential to become eco-friendly “green organic chemistry” alternatives to existing processes that proceed via transmetalation reactions<sup>2</sup> involving stoichiometric amounts of organometallic reagents.<sup>3</sup> Of the various metal catalyzed reactions that have been recently explored, those that exploit carbon dioxide extrusion to produce reactive organometallics from carboxylic feedstocks present exciting opportunities for development of decarboxylative bond transformations involving C-X (X = H, C, S etc) bond forming reactions.<sup>1</sup>

During studies on the gas-phase decarboxylation of metal carboxylates and the subsequent reactions of the resultant organometallic ions,<sup>4</sup> it occurred to us that the isoelectronic analogy between CO<sub>2</sub> and heterocumulenes<sup>5</sup> opens the door to developing a new class of reactions for organic synthesis that we have termed ExIn (Extrusion-Insertion).<sup>6</sup> In our first study of ExIn reactions, we examined the transformation of a copper(I) coordinated acetate anion into a dithioacetate anion after decarboxylation.<sup>5</sup> The formation of CH<sub>3</sub>CS<sub>2</sub><sup>-</sup> in both the ion-molecule reaction (IMR) of [CH<sub>3</sub>Cu<sup>I</sup>CH<sub>3</sub>]<sup>-</sup> with CS<sub>2</sub> (eq. 1) and via collision induced dissociation (CID) of the adduct (eq. 2) provided evidence that C-C bond formation had occurred.



Encouraged by these results, in subsequent studies we showed that gas-phase (Scheme 1A) and solution-phase (Scheme 1B) mechanistic work on 1,10-phenanthroline (phen) ligated palladium complexes can guide the development of one-pot synthetic methods for the palladium mediated ExIn synthesis of amides, thioamides and amidines (Scheme 1C).<sup>6</sup> Given that related phen ligated copper complexes have a long history in decarboxylation reactions<sup>7</sup> and are still being used to develop new decarboxylative coupling reactions,<sup>8</sup> here we examine the decarboxylation of a suitable model system and the subsequent reactions of the resultant organometallic species with heterocumulenes.

### Scheme 1 Here

Unlike Cu(I) organometallic binuclear complexes [(L)Cu<sub>2</sub>(O<sub>2</sub>CAr)]<sup>+</sup> (L = neutral ligand) for which reactivity can be readily studied by MS,<sup>9</sup> 1,10-phenanthroline complexes [(phen)Cu<sup>I</sup>(O<sub>2</sub>CR)] complexes have no net charge and so cannot be directly detected by MS. Our recent strategy<sup>10</sup> to overcome this issue has employed 4,7-diphenyl-1,10-phenanthroline-disulfonic acid disodium salt as a fixed charge phen ligand (Bphen), since it allows ready formation of the copper carboxylate complexes via electrospray ionization (ESI) and the sulfonate sites are well away from the {Cu} reactive site and should thus not significantly perturb reactivity.<sup>11</sup> Here we study the gas-phase decarboxylation of [(Bphen)Cu<sup>I</sup>(O<sub>2</sub>CR)]<sup>2-</sup>

and the gas-phase ion-molecule reactions of the organometallic ion  $[(\text{Bphen})\text{Cu}^{\text{I}}(\text{R})]^{2-}$  with the heterocumulenes  $\text{CS}_2$  and  $\text{PhNCO}$  (Scheme 2).

### Scheme 2 Here

## Experimental

### Reagents

Methanol, copper(I)acetate, Bathophenanthroline disulfonic acid, benzoic acid, carbon disulfide, and phenyl isocyanate were obtained from Aldrich and used without further purification.

### Sample preparation

The gas-phase collision-induced dissociation (CID) of  $[(\text{Bphen})\text{Cu}^{\text{I}}(\text{O}_2\text{CAr})]^{2-}$  to form  $[(\text{Bphen})\text{Cu}^{\text{I}}(\text{Ar})]^{2-}$  and subsequent ion-molecule reaction studies were conducted in a similar manner to those reported for the reactivity studies of  $[(\text{phen})\text{Pd}(\text{CH}_3)]^+$ .<sup>12</sup> For example, 10  $\mu\text{L}$  of methanolic solutions of copper salt (5 mM), benzoic acid (10 mM) and ligand (10 mM) were mixed and then diluted to a final concentration of 0.05 mM in Cu. The solution was transferred via syringe pump operating at 10  $\mu\text{L min}^{-1}$  to the electrospray ionization source of a Thermo Finnigan LTQ ESI mass spectrometer previously modified to allow the introduction of neutral reagents into the ion trap.<sup>13</sup> Data was collected with three micro-scans and between 20-100 duplicate spectra.

### Mass Spectrometry Source Condition

Typical electrospray source conditions were:

**Collision Induced Dissociation (CID):** Sheath Gas = 10 arbitrary units, Auxiliary Gas = 5 arbitrary units, Sweep Gas = 0 arbitrary units, Spray Voltage = 4 kV, Capillary Temp. = 250 °C, Capillary Voltage = 2 V, Tube Lens Voltage = 75 V. The precursor ion was mass selected with a window of 1  $m/z$  and collision induced dissociation was carried out using the helium bath gas by activating the ion with an activation time of 30 ms. A normalized collision energy (NCE) was chosen to deplete the precursor ion to 10%.

**Ion Molecule Reaction (IMR):** Sheath Gas = 10 arbitrary units, Auxiliary Gas = 5 arbitrary units, Sweep Gas = 0 arbitrary units, Spray Voltage = 4 kV, Capillary Temp. = 250 °C, Capillary Voltage = 2 V, Tube Lens Voltage = 75 V.

### Molecular modelling

Gaussian 09<sup>14</sup> was used to fully optimise all structures at the M06<sup>15</sup> level of density functional theory (DFT). The Stuttgart Dresden (SDD) basis set and effective core potential were used for the copper atom.<sup>16</sup> The 6-31G(d) basis set was used for other atoms.<sup>17</sup> This basis set combination will be referred to as BS1. Frequency calculations were carried out at the same level of theory as those for the structural optimisation. Transition structures were located using the Berny algorithm. Intrinsic reaction coordinate (IRC) calculations were used to confirm the connectivity between transition structures and minima.<sup>18</sup>

To further refine the energies obtained from the M06/BS1 calculations, we carried out single-point energy calculations for the structures with a larger basis set (BS2) at the M06 level of theory. BS2 utilizes def2-TZVP for all atoms.<sup>19</sup> To estimate the corresponding enthalpy,  $\Delta H$ , and Gibbs energies,  $\Delta G$ , the corrections were calculated at the M06/BS1 levels and finally added to the corresponding single-point energies.

To examine potential isomers of the  $[(\text{Bphen})\text{Cu}^{\text{I}}(\text{O}_2\text{CC}_6\text{H}_5)]^{2-}$  complex, DFT optimisations were also carried out using the M06/6-31G(d)SDD and M06/6-31+G(d)SDD levels of theory in both the condensed phase and the gas phase. The formed were carried out in methanol using CPCM approach.<sup>20</sup>

In the DFT calculated energy surfaces we report both  $\Delta H$  and  $\Delta G$  at 298 K. Under the low energy CID conditions used, the ions undergo multiple collisions with the helium bath gas resulting in slow “heating” until fragmentation occurs.<sup>21</sup> While the effective temperature is unknown, the  $\Delta G$  value provides an estimate that accounts for entropic effects. Under the low-pressure IMR conditions used, only the total energy of the separated reactants is available to fuel reactivity and so  $\Delta H$  provides a measure of whether a reaction is possible or not,<sup>22</sup> while comparing  $\Delta G$  between two related reactions will provide a guide to their relative reactivities.

### Results and discussion

**Formation of  $[(\text{Bphen})\text{Cu}^{\text{I}}(\text{O}_2\text{CC}_6\text{H}_5)]^{2-}$  and DFT calculations on the binding mode of  $\text{Cu}^{\text{I}}(\text{O}_2\text{CC}_6\text{H}_5)$  to  $[\text{Bphen}]^{2-}$**

In this work, 4,7-diphenyl-1,10-phenanthroline-disulfonic acid disodium salt (Bphen), copper acetate and benzoic acid are dissolved in methanol and then injected into the mass spectrometer under ESI to generate a dianion complex,  $[(\text{Bphen})\text{Cu}^{\text{I}}(\text{O}_2\text{CC}_6\text{H}_5)]^{2-}$ , **1**. Since the ligand  $[\text{Bphen}]^{2-}$  possesses two potential binding sites for copper acetate, we next turned to DFT calculations to calculate the relative stabilities in both methanol and the gas phase of the two isomers where the Cu binds to the: (i) two nitrogens of the phen, isomer **1a**; (ii) the sulfonate group, isomer **1b**. Table 1 shows that the complex binding through the nitrogen is strongly favored in methanol. While there are no crystal structures of copper complexes of Bphen, this is consistent with: (i) the specific development of Bphen as a ligand to bind metal cations at the phen site in protic solvents;<sup>23</sup> (ii) studies showing that the binding constant for metal cation on phen are almost identical to those of Bphen;<sup>24</sup> (iii) crystal structures of related sulfonate ligands where copper binds to nitrogen donors rather than the sulfonate group.<sup>25</sup>

### Table 1 Here

In the gas phase with the 6-31G(d) basis set, even though the binding preference is reversed, the difference in the Gibbs free energies between the two binding modes only minimally favors oxygen binding by 1.4 kcal/mol. When the 6-31+G(d) basis set is used isomer **1a** is favored in the gas-phase. Given that the  $[(\text{Bphen})\text{Cu}^{\text{I}}(\text{O}_2\text{CC}_6\text{H}_5)]^{2-}$  complex is formed in solution it is highly likely that isomer **1a** is formed in our experiments and all subsequent DFT calculations focussed on this isomer.

### Formation of $[(\text{Bphen})\text{Cu}^{\text{I}}(\text{C}_6\text{H}_5)]^{2-}$

The dianion complex,  $[(\text{Bphen})\text{Cu}^{\text{I}}(\text{O}_2\text{CC}_6\text{H}_5)]^{2-}$ , **1** readily undergoes decarboxylation to form  $[(\text{Bphen})\text{Cu}^{\text{I}}(\text{C}_6\text{H}_5)]^{2-}$ , **3**, under collision-induced dissociation (CID) (Figure 1a, eq. 3). Besides the major decarboxylation pathway, two other minor pathways involving loss of  $[\text{Bphen}]^{2-}$  ( $m/z$  245, eq. 4) and loss of  $\text{C}_6\text{H}_5\text{CO}_2^-$  ( $m/z$  121, eq. 5) were detected.



## Figure 1 Here

The DFT calculated potential energy diagram for the three competing fragmentation pathways are shown in Figure 2. Decarboxylation exhibits the lowest energy barrier compared with the other two fragmentation channels.  $[(\text{Bphen})\text{Cu}^{\text{I}}(\text{O}_2\text{CC}_6\text{H}_5)]^{2-}$ , **1a**, exhibits a slightly different mechanism to the decarboxylation of  $[(\text{phen})\text{Pd}(\text{O}_2\text{CC}_6\text{H}_5)]^+$  reported previously, where the two oxygens of the carboxylate group coordinate with palladium showing similar Pd-O bond distances and where two transition states were required for decarboxylation – the first involving formation of a reactive conformation of the carboxylate group, the second involving a four-centred transition states for extrusion of  $\text{CO}_2$ .<sup>6(a)</sup> In contrast, in **1a**, only one oxygen of the carboxylate group is directly coordinated to the copper centre, in a conformation directly related to the decarboxylation four-centered transition state, **TS1a-2**. The initial product complex  $[(\text{Bphen})\text{Cu}^{\text{I}}(\text{C}_6\text{H}_5)(\text{O}_2\text{C})]^{2-}$ , **2**, from which facile loss of  $\text{CO}_2$  occurs, leads to the phenyl copper complex,  $[(\text{Bphen})\text{Cu}^{\text{I}}(\text{C}_6\text{H}_5)]^{2-}$ , **3**, which exhibits a 3-coordinate T-shaped structure. A similar mechanism was reported by Lin's group in 2011, for DFT calculations on decarboxylation of benzoic acids by neutral Cu-phen complexes.<sup>22</sup>

## Figure 2 Here

**Ion-molecule reaction of  $[(\text{Bphen})\text{Cu}^{\text{I}}(\text{C}_6\text{H}_5)]^{2-}$  with  $\text{CS}_2$  and  $\text{PhNCO}$** 

Since aryl copper compounds are known to react with heterocumulenes,<sup>23</sup> we next examined the bimolecular ion-molecule reactions of the mass-selected organometallic ion  $[(\text{Bphen})\text{Cu}^{\text{I}}(\text{C}_6\text{H}_5)]^{2-}$ , **3**, with carbon disulfide (eq. 6) in a  $\text{MS}^3$  experiment.  $[(\text{Bphen})\text{Cu}^{\text{I}}(\text{C}_6\text{H}_5)]^{2-}$  reacts extremely slowly with  $\text{CS}_2$  (at less than 0.04% of the collision rate) to give a minor signal of an adduct, which might correspond to the insertion product  $[(\text{Bphen})\text{Cu}^{\text{I}}(\text{S}_2\text{CC}_6\text{H}_5)]^{2-}$ , **5**.  $[(\text{Bphen})\text{Cu}^{\text{I}}(\text{C}_6\text{H}_5)]^{2-}$  was found to be unreactive with phenyl isocyanate under the experimental conditions used, with no adduct (eq. 7) being formed.



## Figure 3 Here

The DFT calculated potential energy diagram for the insertion reaction between  $[(\text{Bphen})\text{Cu}^{\text{I}}(\text{C}_6\text{H}_5)]^{2-}$ , **3**, and  $\text{CS}_2$  is shown in Figure 3(a). The key transition state to form the dithiocarboxylate copper complex, **5**, is **TS4-5**, and has an enthalpic barrier of 0.7 kcal/mol. The product contains a  $\kappa_2$ -coordinated dithiobenzoate, which is consistent with the binding mode determined via X-ray crystallography on monomeric phosphine complexes  $[(\text{Ph}_3\text{P})_2\text{Cu}^{\text{I}}(\text{S}_2\text{CR})]$ .<sup>23,24</sup> The DFT calculated potential energy diagram for the insertion reaction between  $[(\text{Bphen})\text{Cu}^{\text{I}}(\text{C}_6\text{H}_5)]^{2-}$ , **3**, and phenyl isocyanate, shown in Figure 3(b), highlights that insertion can proceed via two transition states which differ in the coordination mode of the isocyanate. The one in which the O atom coordinates with the Cu centre, **TS4b-5bO**, is lower in energy than the one in which the N atom coordinates with the Cu centre, **TS4b-5bN**. Nonetheless, **TS4b-5bO**, has a higher barrier than **TS4-5** for the insertion of  $\text{CS}_2$ , consistent with the experimentally relative reactivities, where a very slow rate of reaction observed for  $\text{CS}_2$  and PhNCO is unreactive.

In our previous work on the insertion of phenyl isocyanate into the Pd-C bond of the cationic complex  $[(\text{phen})\text{Pd}(\text{Ph})]^+$  (Scheme 1A), we found that the transition state associated with N-coordination of PhNCO (related to **TS4b-5bN** in Fig. 3b) shows a much lower energy barrier than the one with O-coordinated complex (related to **TS4b-5bO**).<sup>6(c)</sup> This is consistent with known differences in the chemistry of copper and platinum.<sup>25</sup>

#### CID of $[(\text{Bphen})\text{Cu}^{\text{I}}(\text{S}_2\text{CC}_6\text{H}_5)]^{2-}$

To gain further evidence for the formation of a dithiocarboxylate copper complex,  $[(\text{Bphen})\text{Cu}^{\text{I}}(\text{S}_2\text{CC}_6\text{H}_5)]^{2-}$  was mass-selected in a  $\text{MS}^4$  experiment and subjected to CID. (Figure 1c). The major fragmentation channel is the formation of free ligand  $[\text{Bphen}]^{2-}$  ( $m/z$  245) via loss of  $\text{C}_6\text{H}_5\text{CS}_2\text{Cu}^{\text{I}}$  (eq. 8), which contrasts with the case of the coordinated benzoate, where the related loss of  $\text{C}_6\text{H}_5\text{CO}_2\text{Cu}^{\text{I}}$  is only a minor channel (Figure 1a, eq. 4). Another two minor channels observed were related to deinsertion of carbon disulfide to form  $[(\text{Bphen})\text{Cu}^{\text{I}}(\text{C}_6\text{H}_5)]^{2-}$  (eq. 9) and formation of dithiocarboxylate anion,  $\text{C}_6\text{H}_5\text{CS}_2^-$ , ( $m/z$  153) together with the ligated copper anion (eq. 10). The minor ion at  $m/z$  213 is likely due to secondary fragmentation of the free ligand  $[\text{Bphen}]^{2-}$  ( $m/z$  245) via loss of  $\text{SO}_2$  (eq. 11).



A theoretical study was carried out to examine the three primary dissociation pathways of  $[(\text{Bphen})\text{Cu}^{\text{I}}(\text{S}_2\text{CC}_6\text{H}_5)]^{2-}$ . The major channel of  $\text{Bphen}^{2-}$  loss presents the lowest free energy barrier (8.9 kcal/mol), compared with the other two pathways (Figure 3(a)). It is interesting to compare the gas-phase fragmentation chemistry of  $[(\text{Bphen})\text{Cu}^{\text{I}}(\text{X}_2\text{CC}_6\text{H}_5)]^{2-}$  ( $\text{X} = \text{O}$  or  $\text{S}$ ). Both experiment and theory highlight that the copper carboxylate complex prefers to undergo decarboxylation (eq. 3) while copper dithiocarboxylate complex prefers to undergo loss of ligand (eq. 8). This is likely to be due a number of factors including model heterolytic bond dissociation energy of gas-phase  $\text{CuL}_2^+$  complexes, which are known to higher for sulfur ligands relative to their oxygen counterparts than  $\text{O-Cu}$ .<sup>26</sup>

## Conclusion

Here the ExIn reactions of a ligated copper carboxylate complex with heterocumulene species have been explored under multistage mass spectrometric conditions. A bathophenanthroline ligated arylcopper complex, formed via decarboxylation, presented limited reactivity with carbon disulfide and poor reactivity with phenyl isocyanate. Gratifyingly, the same insertion reaction of  $\text{CS}_2$  into the  $\text{Cu-C}$  bond observed in solution for the neutral complex  $[(\text{phen})\text{Cu}^{\text{I}}(\text{C}_6\text{H}_5)]^{27}$  also occurs in the gas phase for the related fixed charge complex,  $[(\text{Bphen})\text{Cu}^{\text{I}}(\text{C}_6\text{H}_5)]^{2-}$ . The differences in the fragmentation chemistry of  $[(\text{Bphen})\text{Cu}^{\text{I}}(\text{X}_2\text{CC}_6\text{H}_5)]^{2-}$  ( $\text{X} = \text{O}$  and  $\text{S}$ ) are rationalised by differenced in the  $\text{Cu-X}$  bond strengths. Computational mechanistic studies are consistent with the experimental results, encouraging future studies with the aim of developing synthetic protocols for the synthesis of amides in the solution phase in which expensive palladium catalysts are replaced by non-toxic first row transition metal catalysts.

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### Scheme Captions:

**Scheme 1:** Example of a mechanism-based approach guiding the development of new methods in organic synthesis: gas-phase (A) and solution-phase NMR studies (B), and one-pot synthesis of thioamides, amidines and amides from carboxylic acids (C).

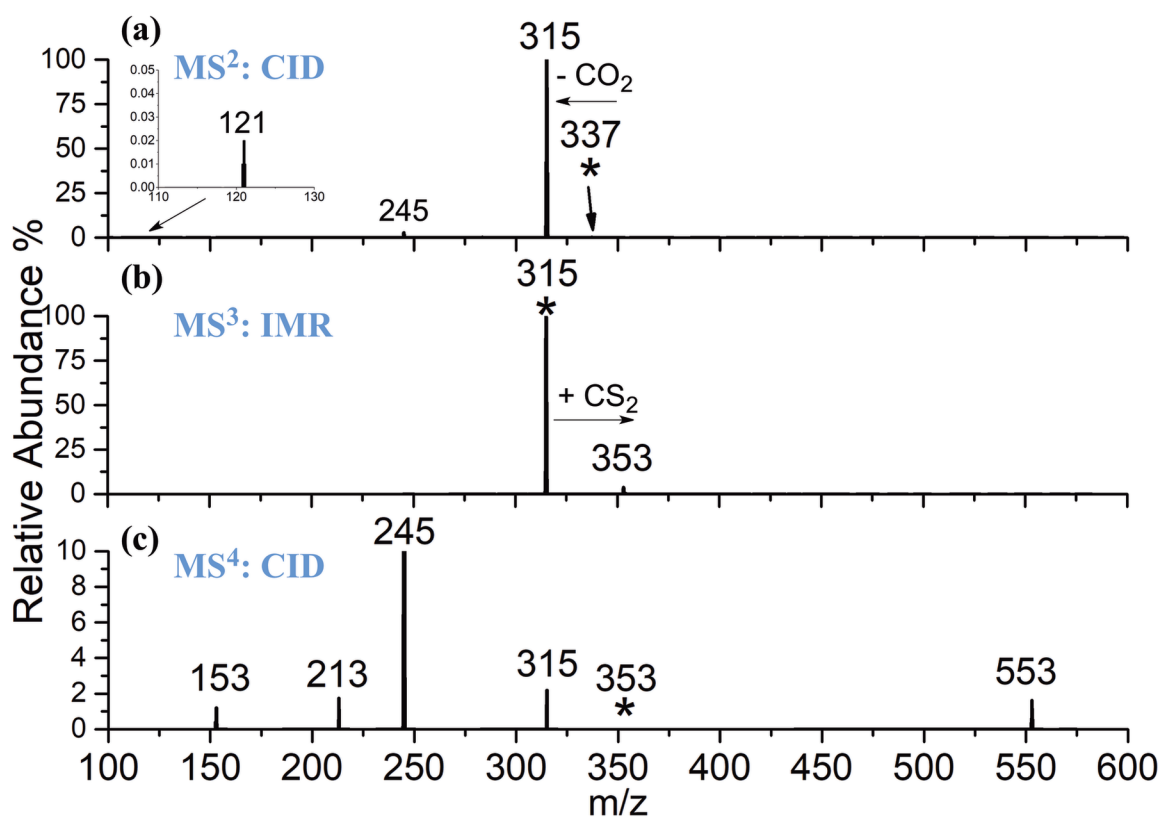
**Scheme 2.** Gas-phase collision-induced dissociation of fixed charge ligated copper benzoate,  $[(\text{Bphen})\text{Cu}^1(\text{O}_2\text{CC}_6\text{H}_5)]^{2-}$  for the synthesis of  $[(\text{Bphen})\text{Cu}^1(\text{O}_2\text{CC}_6\text{H}_5)]^{2-}$ , and the subsequent ion-molecule reaction with carbon disulfide and phenylisocyanate, followed by CID of the inserted product,  $[(\text{Bphen})\text{Cu}^1(\text{X}(\text{Y})\text{CC}_6\text{H}_5)]^{2-}$ .

**Figure Captions:**

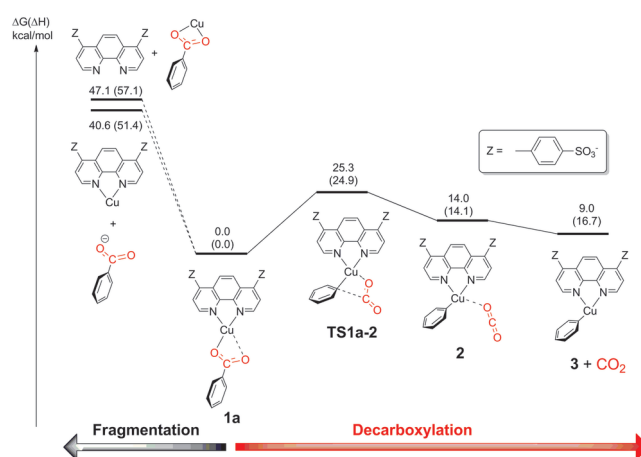
**Figure 4.** LTQ MS<sup>n</sup> spectra of unimolecular and bimolecular reactions associated with key steps of the ExIn reaction: (a) MS<sup>2</sup> experiment involving extrusion of CO<sub>2</sub> from [(Bphen)Cu<sup>I</sup>(O<sub>2</sub>CC<sub>6</sub>H<sub>5</sub>)]<sup>2-</sup> (*m/z* 337) under CID at a normalized collision energy of 20 (arbitrary unit) (eq. 3). The inset shows an expansion so that the minor benzoate product ion (eq. 5) can be observed; (b) MS<sup>3</sup> experiment involving an ion-molecule reaction between the organometallic ion [(Bphen)Cu<sup>I</sup>(C<sub>6</sub>H<sub>5</sub>)]<sup>2-</sup> (*m/z* 315) and carbon disulfide (reaction time: 3000 ms) (eq. 6); (c) MS<sup>4</sup> experiment involving CID on selected IMR product (*m/z* 353) at a normalized collision energy of 20 (eqs. 8-10). The concentration of CS<sub>2</sub> in ion-molecule reaction is  $1.1 \times 10^{10}$  molecule cm<sup>-3</sup>. The mass-selected ions are denoted by asterisks.

**Figure 5.** DFT calculated energy surface for decarboxylation of [(Bphen)Cu<sup>I</sup>(O<sub>2</sub>CC<sub>6</sub>H<sub>5</sub>)]<sup>2-</sup>, **1a**, (eq. 3) together with the energetics associated with losses of copper benzoate (eq. 4) and benzoate (eq. 5). The relative Gibbs energies and enthalpies (in parentheses) are given in kcal/mol and were calculated at the M06/BS2//M06/BS1 level of theory.

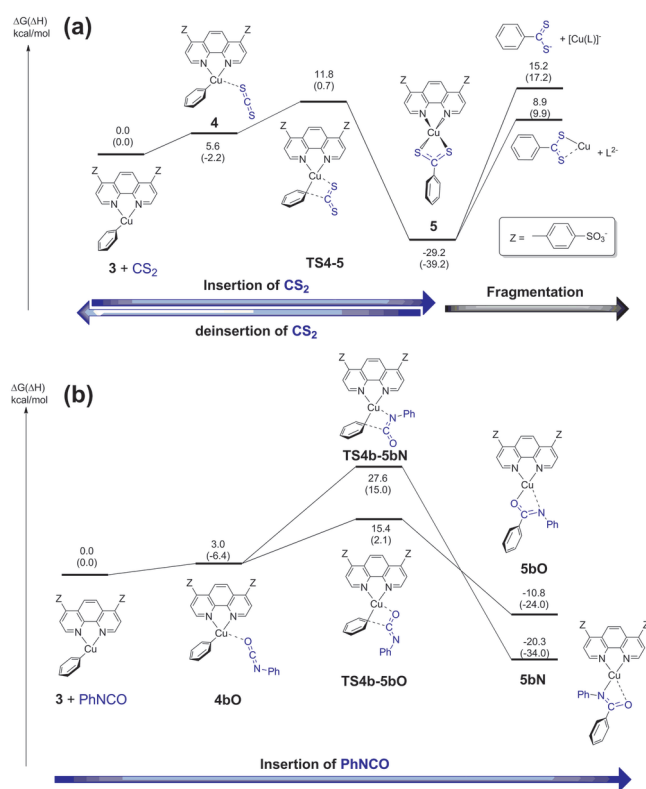
**Figure 6.** DFT calculated energy surface for ion-molecule reaction of [(Bphen)Cu<sup>I</sup>(C<sub>6</sub>H<sub>5</sub>)]<sup>2-</sup>, **3** with: (a) CS<sub>2</sub> (eq. 6); (b) phenyl isocyanate. The energetics associated with the CID fragmentation reactions (eqs. 8-10) of the insertion product, **5** are also shown in (a). The relative Gibbs and enthalpy energies (in parentheses) are given in kcal/mol and were calculated at the M06/BS2//M06/BS1 level of theory.



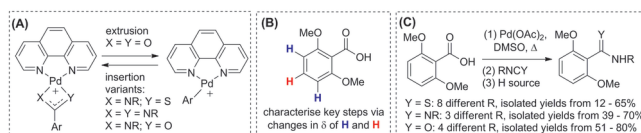
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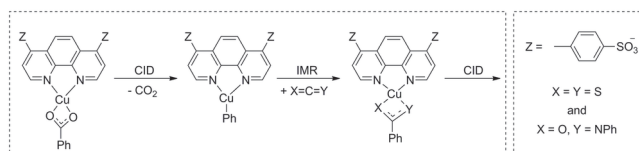
JMS\_4579\_Figure 2.tif



JMS\_4579\_Figure 3.tif



JMS\_4579\_Scheme 1.tif



JMS\_4579\_Scheme 2.tif