# Activation of aromatic C-C bonds of 2,2'-bipyridine ligands

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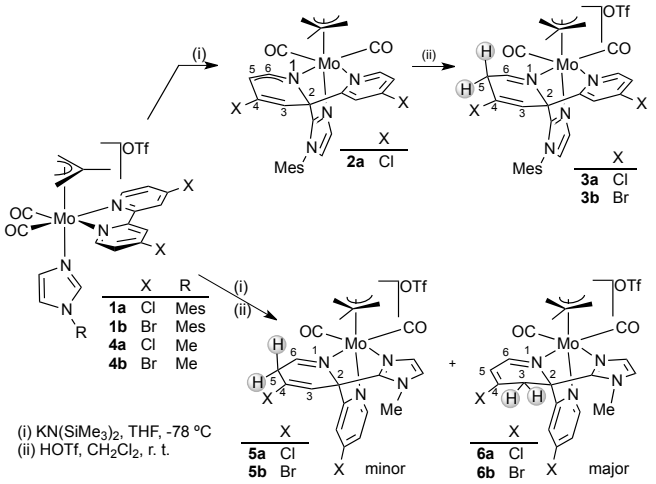
**Abstract:** 4,4'-disubstituted-2,2'-bipyridine ligands coordinated to Mo(II) and Re(I) cationic fragments become dearomatized by an intramolecular nucleophilic attack from a deprotonated N-alkylimidazole ligand in *cis* disposition. The subsequent protonation of these neutral complexes takes place on a pyridine carbon atom rather than at nitrogen, weakening an aromatic C-C bond and affording a dihydropyridyl moiety. Computational calculations allowed to rationalize the formation of the experimentally obtained products over other plausible alternatives.

Dearomatization of pyridines and other six-membered *N*-heterocycles is a challenging task that can provide a route to the synthesis of functionalized molecules present in many natural products and pharmaceuticals.[1] Whereas nucleophilic substitution of pyridine with retention of aromaticity is facile, especially if good leaving groups, such as halides, are present, synthesis of dihydropyridines by nucleophilic addition is complicated mainly because of their high tendency to regain aromaticity.[2] Organometallic reagents of the early transition and f-block metals typically metalate the *ortho* C-H bond of pyridine to afford $\eta^2$-(*C,N*)-pyridine complexes.[3] Related 2,2'-bipyridine (bipy) and 1,10-phenanthroline (phen) ligands have been widely employed in all areas of coordination chemistry;[4] however, prior to our work, dearomatization of transition metal-coordinated bipy and phen under mild conditions was unknown.[5] Dearomatization of bipy, phen and 2,2';6',2"-terpyridine (terpy) ligands coordinated to a magnesium center, via alkyl or hydride migration from the metal, has been recently reported.[6] This reactivity, by alkyl transfer, is reminiscent of that previously reported by Kiplinger *et al.* in the dearomatization of a terpy ligand coordinated to Lu(III).[7] As the outcome of some pyridine dearomatization reactions has been found to be dependent on the substitution pattern of the pyridines,[8] we have investigated the intramolecular nucleophilic attack to 4,4'-disubstituted bipy ligands[9] and the protonation of the resulting dearomatized products. The results include unprecedented protonations at some of the ring carbon atoms, with concomitant bond order reduction of one of the C-C bonds. These reactions, which have been demonstrated both in molybdenum and rhenium complexes, are the subject of this communication.

The addition of the equimolar amount of $KN(SiMe_3)_2$ to a solution of [Mo($\eta^3$-methallyl)(4,4'-$Cl_2$-bipy)$(CO)_2$(N-MesIm)]OTf (**1a**, $\eta^3$-methallyl= $\eta^3$-(2-methylallyl), 4,4'-$Cl_2$-bipy= 4,4'-dichloro-2,2'-bipyridine, N-MesIm= N-mesitylimidazole, mesityl= 2,4,6-trimethylphenyl) in THF at -78 °C led to the deprotonation of the central CH group of the imidazole, and to the C-C coupling product with the bipy ligand in *cis* disposition (Scheme 1).[10]

**Scheme 1.** Reactivity of [Mo($\eta^3$-methallyl)(4,4'-$X_2$-bipy)$(CO)_2$(N-RIm)]OTf complexes.




The neutral complex **2a** was spectroscopically characterized in solution showing that the C-C coupling has taken place at the 2 (2') position of the bipy ligand,[11] and not at 6 (6´) as previously found for Re(I)(bipy)(imidazole) compounds.[12] This reaction reflects also the great influence of the chloro substituents at 4 and 4' positions of the bipy ligand, as it favors C-C coupling over formation of the imidazol-2-yl complex as found for the non-substituted bipy compounds [Mo($\eta^3$-methallyl)(bipy)$(CO)_2$(N-MesIm)]OTf.[13] It seems that the high electron withdrawing effect of the Cl substituents enhances the electrophilic character of the pyridyl rings making them the preferred site for the imidazole nucleophilic attack. The reaction of complex **2a** with HOTf in $CH_2Cl_2$ afforded immediately cationic species as evidenced by a large shift to higher wavenumbers of the $\nu_{CO}$ bands in the IR spectrum (from 1937, 1849 $cm^{-1}$ to 1954, 1869 $cm^{-1}$). The NMR data in $CD_2Cl_2$ solution clearly indicated that the protonation has occurred on a CH group of the dearomatized pyridyl affording a $CH_2$ moiety (Scheme 1). The $^1$H NMR spectrum of **3a** shows therefore an asymmetric dearomatized 4,4'-dichloro-2,2'-bipyridine, and a 2D $^1$H-$^1$H correlation spectroscopic (COSY) study clearly established that the two hydrogen multiplet at 3.55 ppm corresponds to the methylenic unit. Accordingly, a 2D HSQC

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showed that this signal corresponds to a peak at 35.8 ppm in the $^{13}C$ NMR spectrum, its $CH_2$ nature being confirmed by a DEPT-135 experiment. Figure 1a shows the solid-state structure of the cation of the analogous 4,4'-dibromobipy derivative, **3b**, determined by X-ray diffraction.[14]

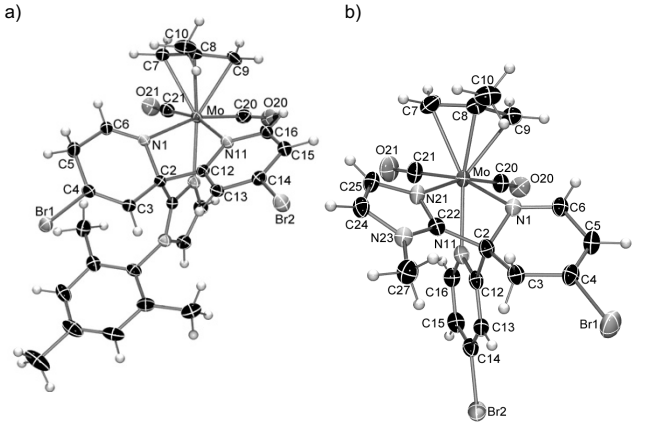



**Figure 1.** Molecular structures of the cations of **3b** (a) and **6b** (b), showing thermal ellipsoids at the 30% probability level.

The cationic complex consists of a *cis*-{Mo($\eta^3$-methallyl)$(CO)_2$} fragment bonded to a tridentante *N*-donor ligand that results from the C-C coupling between the N-MesIm central C atom and C2 of the bipy ligand. This is the first example of a bipy ligand dearomatized by nucleophilic attack to that position structurally determined.[15] Also worth of attention is the protonation at the C5-H group of the dearomatized ring rather than the amido nitrogen, affording as a result a dihydropyridyl group. Accordingly, C5-C6 and C4-C5 bond distances, of 1.516(6) Å and 1.491(6) Å, respectively, correspond to single bonds, and N1-C6 (1.308(6) Å) and C3-C4 (1.348(7) Å) bond distances are typical of double bonds. An example of a protonation of a pyridine carbon over nitrogen had been reported by Harman *et. al.*,[16] but in that case a 2,6-dimethoxypyridine ligand and a $\pi$-donor metal fragment were employed to favor a $\eta^2$-coordination to the metal.

The behavior of N-methylimidazole (N-MeIm) complexes [Mo($\eta^3$-methallyl)(4,4'-$X_2$-bipy)$(CO)_2$(N-MeIm)]OTf (X= Cl, **4a**; Br, **4b**) towards $KN(SiMe_3)_2$ and HOTf at -78 °C was found to be analogous to that described above for compounds **1a**,**b**, affording the C5-H protonated complexes (**5a**,**b**), which were fully characterized (the solid state structure of the cation of the dibromobipy, **5b**, is shown in Figure S1).[10] In contrast, when the protonation reaction was carried out at room temperature two isomers were obtained (Scheme 1). The minor products were, for both the Cl- and Br-substituted bipy complexes, the C5-H protonated species (**5a,b**), and the spectroscopic data in solution of the major products (**6a**,**b**) showed very similar features to those of **5a,b** indicating closely related structures. However, in **6a**,**b** the protonation has occurred at C3-H group of the dearomatized pyridyl group. These results indicate that **5a**,**b** are the kinetically preferred isomers, whereas under thermodynamic control mixtures of **5a**,**b** and **6a**,**b** are obtained. Figure 1b shows the molecular structure of the cation of **6b** confirming the C-C coupling of the central C atom of the N-MeIm and C2 of the bipy ligand, with the concomitant dearomatization of the pyridyl group involved. The protonation site is, indeed, the C3-H group as evidenced by the C2-C3 and C3-C4 bond distances, of 1.516(6) Å and 1.491(6) Å, respectively, clearly indicative of single C-C bonds. The different geometry found for N-MesIm and N-MeIm final products can be attributed to the larger steric hindrance of the mesityl substituent, which in a geometry like that of **5a**,**b** could clash with the methyl group of the methallyl ligand. In solution some molybdenum allyl dicarbonyl complexes are sterochemically non-rigid, reflecting the small difference in stability between the different geometries. Therefore, the fact that a particular geometry is found in the solid state could be due to packing factors.[17]

DFT calculations[18] on Mo(II) compounds showed that the Br substituents at 4 and 4' positions of the bipy ligand make the coupling of the imidazole central C atom and the C2 of the bipy the preferred pathway of evolution of the deprotonated species (route A2 in Figure 2). For the N-MeIm complex this route is 4.8 kcal·mol$^{-1}$ more favorable than route A1 (which would afford the bipy C6 coupling products $\mathbf{P_{A1}}$, as found for {Re$(CO)_3$} complexes),[12] and 3.0 kcal·mol$^{-1}$ lower in Gibbs energy than route B (leading to imidazol-2-yl products $\mathbf{P_B}$, found for analogous non-substituted bipy derivatives),[12] as it is shown in Figure 2. Similar results are obtained for the N-MesIm complex.[10]

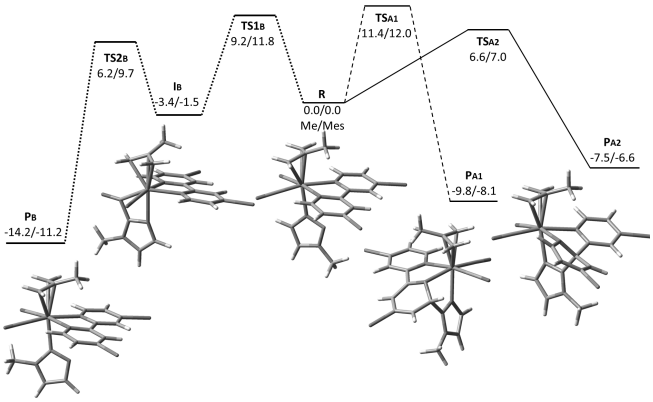
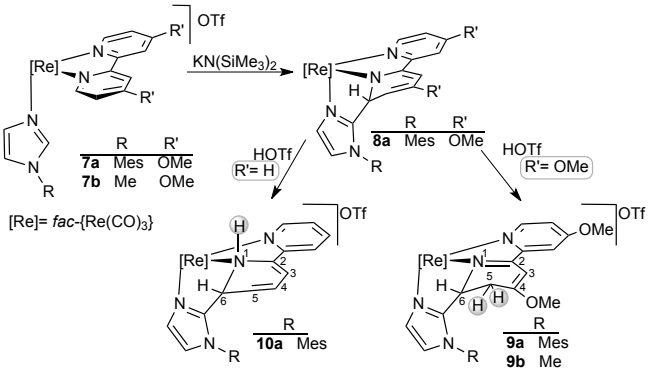



**Figure 2.** Gibbs energy profile in THF solution (kcal·mol$^{-1}$) of the mechanisms for the deprotonation of complexes **4b** and **1b**.

An NBO analysis of the non-hydrogen atoms of the bipy ligand reveals that the most favorable site for a nucleophilic attack of the central imidazole C atom is C2 as it displays the highest positive NBO charge,[19] leading to the lowest kinetic barrier, which is the determinant factor in the formation of the observed products. All attempts to locate a transition state for the protonation of the neutral intermediates with HOTf failed, so the discussion of the formation of the products is based on their relative energies. In agreement with the experimental results, the species protonated at C3 and C5 are more stable than those protonated at N1 (*e. g.* for the N-MesIm derivative 6.6 and 8.6 kcal·mol$^{-1}$ respectively more stable), although N1 presents the largest negative NBO charge (see Tables S2 and S3). The formation of only the isomer protonated at C5 for the N-MesIm complex can be attributed to steric effects.

The addition of $KN(SiMe_3)_2$ to previously cooled (-78 ˚C) THF solutions of $[Re(CO)_3(4,4'\text{-}(OMe)_2\text{-bipy})(N\text{-}R'Im)]OTf$ (R'= Mes, **7a**; Me **7b**) afforded the corresponding neutral species, too unstable for isolation. The mesityl derivative (**8a**) could be characterized by means of $^1H$ NMR, showing the pattern of a dearomatized bipy complex,[12] but remarkably the signal of the C5-H group was very upfield shifted, at 3.46 ppm. Electrophilic interception of these neutral species was achieved by addition of the equimolar amount, in each case, of HOTf to afford stable cationic compounds **9a** and **9b** respectively (see Scheme 2), which were spectroscopically characterized in solution, and in the case of **9a** in the solid-state by X-ray diffraction (Figure 3).




**Scheme 2.** Reactivity of $[Re(CO)_3(4,4'\text{-}R'_2\text{-bipy})(N\text{-}RIm)]OTf$ (R= Me, Mes; R'= H, OMe) complexes.

The spectroscopic data of the new complexes **9a,b** supported the novel structure shown in Figure 3, and are in agreement with the formation of C-C coupled products between the imidazole central C atom and C6 of the bipy ligands. The pyridyl group involved in this nucleophilic attack became dearomatized and protonated at the C5-H group, probably as a consequence of the strong electron-releasing effect of the methoxy groups (the analogous reaction of the non-substituted diimine complexes $[Re(CO)_3(N\text{-}N)(N\text{-}MesIm)]OTf$ (N-N= bipy; phen) complexes afforded the nitrogen-protonated derivatives as shown in Scheme 2).[20] The employment of the 4,4'-dimethoxy-2,2'-bipy does not change the reactivity pattern previously found for the deprotonation of the analogous [Re(CO)3(bipy)(N-Rim)]OTf compounds leading to dearomatized products by attack to the C6 position of the bipy ligand.[12] However, the presence of the OMe substituents directs the protonation step towards the C5-H group rather than towards the dearomatized pyridine nitrogen atom.

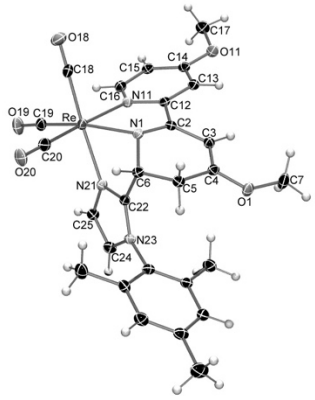



**Figure 3.** Molecular structure of the cation of **9a**, showing thermal ellipsoids at the 30% probability level.

The mechanism for the C-C coupling reaction is assumed to be similar to that found for the non-substituted $\{(bipy)Re(CO)_3\}$ complexes.[13] In the DFT computations no TS was found either for the protonation of the rhenium neutral complexes. In the case of the non substituted bipy, the computations reveal that the N1, C3, and C5 protonation sites of the attacked pyridine ring render products with similar stability. In contrast, when OMe substituents are present at the 4 and 4' positions the protonation at C5 becomes 11.9/9.8 and 12.3/10.3 kcal/mol more favorable than those at C3 or N1 atoms for N-MesIm/N-MeIm complexes, respectively (see Tables S5 and S6). On the basis of these data, we believe that the small energy difference in the stability of the protonated complexes in the parent bipy complexes determines the protonation at the N1 atom due to its greater negative NBO charge and the better accessibility of its electron lone pair (see Table S7). However, the presence of methoxy susbtituents stabilizes the C5 protonated species, and the relative stability of the products seems to predominate over the electronegative character of the atoms of the attacked pyridine ring.

Considering jointly the experimental data and the theoretical computations, the results obtained can be rationalized. Thus, for the Mo(II) species the high electron withdrawing effect of the bromide (or chloride) substituents makes the resonant forms **A** and **B** (Chart 1) stronger contributors (in this order) compared to the more conventional form with the lone pair on the amido-like nitrogen (**C** in Chart1). In good agreement, C3 and C5 display high electron density charges (-0.35 e and -0.47 e, respectively for the N-MesIm complex)[19] making them preferred protonation sites. Furthermore, a topological analysis of the electron density of the dearomatized bipy ligand at the neutral species confirms the presence of double bonds for the N1-C6 and C3-C4 interactions (electron density values about 0.3300 $eÅ^{-3}$, see Table S4), while the remaining distances within the attacked pyridyl ring correspond to single bonds (*i. e.* **A** in Chart 1). Experimental NMR data of **2a** clearly agree with the proposed zwitterionic nature.[11]

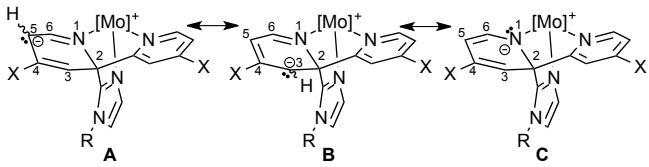



**Chart 1.** Resonant forms of the dearomatized bipy ligand.

For Re(I) compounds the main resonant form is of **C** type (N1 displays virtually tetrahedral geometry, in contrast with the planar at nitrogen geometry of the Mo complexes). However, the strongly donor OMe groups enhance the electron density charge at C5 (evidenced by the signal of the C5-H remarkably upfield shifted in the $^{1}$H NMR spectrum, as mentioned above) which becomes protonated in the reaction with HOTf.

In summary, the nature of the substituents at 4 and 4' positions of the bipy ligand is responsible for the unprecedented reaction patterns found in the dearomatization of bipyridine ligands coordinated to Mo(II) and Re(I) organometallic fragments. The deprotonation/protonation sequence studied herein transforms a pyridyl into a dihydropyridyl group, weakening aromatic C-C bonds (that are single bonds in the products) instead of the usually more reactive C-N bond. This process could provide an entry to aromatic C-C bond cleavage. Further study of the effect of different substituents at 4 and 4' positions of the bipy ligand onto the reactivity of both molybdenum and rhenium complexes is ongoing in our laboratory.

## Acknowledgements

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**Keywords:** pyridine activation • C-C coupling • DFT calculations • molybdenum • rhenium

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[10] See Supporting Information for further experimental details.

[11] In the $^{1}$H NMR spectrum of **2a** in solution the signals corresponding to C3-H and C5-H are remarkably upfield shifted, at 4.24 and 4.15 ppm, respectively. Accordingly, in the $^{13}$C NMR the signals at 87.6 and 95.5 ppm correspond to C5 and C3 atoms, respectively. See Supporting Information for full characterization details.

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[14] CCDC 1484487, 1484488, 1484489, 1050352 and 1484490 (**3b**, **5b**, **6b**, **9a** and **10a**, respectively) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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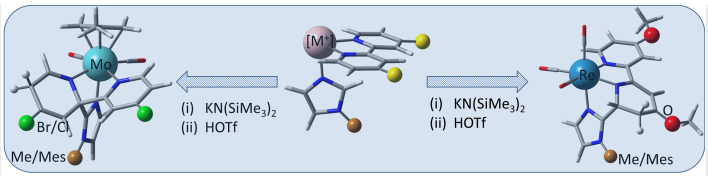
[18] Computations were performed at the PCM(UFF)-B3LYP/6-31+G(d) (LANL2DZ + *f* for Mo and Re) level of theory. All the Gibbs energy values cited in the text include the dispersion energy correction (see Supporting Information for more details).

[19] The values of the NBO analysis are reported in Table S2 in the Supporting Information.

[20] The X-ray structure of the bipy complex, **10a**, is given in the Supporting Information (Figure S2), along with spectroscopic data for both bipy and phenanthroline complexes.

**Entry for the Table of Contents**

## COMMUNICATION




Dearomatized pyridyl moieties (resulting from an intramolecular nucleophilic attack) prefer to react (with HOTf) through an aromatic C-C bond rather than through the already activated C-N bond. As a consequence, a pyridyl ring of a 2,2'-bipyridine ligand (one of the most widely used ligands, considered remarkably inert) is transformed into a dihydropyridyl group with the result of a weakening of an aromatic C-C bond.

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***Page No. – Page No.***

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