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COMMUNICATION

Insertion of benzyne into the Pd–C bond. Synthesis of unnatural amino acid derivatives by sequential insertion of benzyne and CO: 2,2'-functionalized biaryls containing alkylamino and carboxymethyl substituents. Isolation of stable carbopalladated-benzyne intermediates

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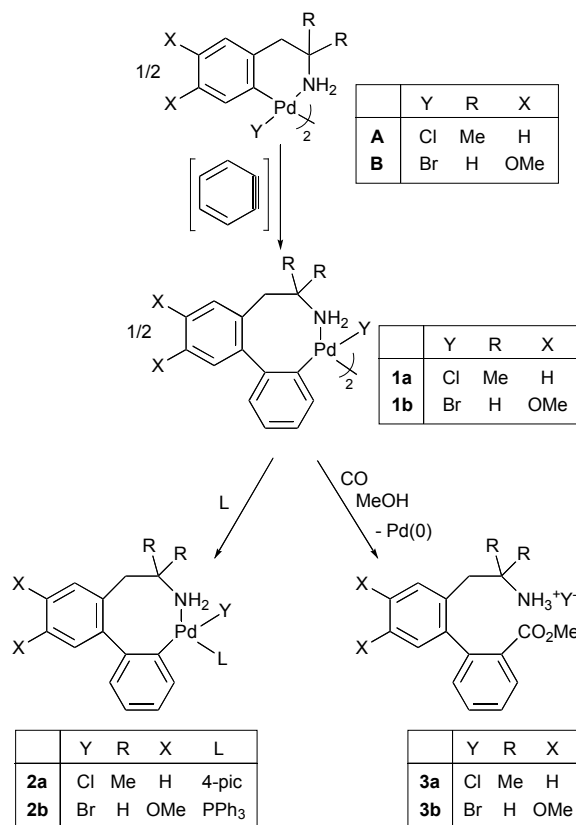
Reaction of ortho-palladated derivatives of phentermine and homoveratrylamine with benzyne allows the synthesis of enlarged eight-membered palladacycles resulting from the insertion of the aryne into the Pd–C bond, which subsequently react with CO, to render unnatural amino acid derivatives.

Carbometalation of benzyne is a key process in the transition metal catalyzed transformation of benzynes. One of the steps of the generally accepted mechanism for these type of reactions involves the insertion of the aryne into a M–C bond, to give a M–aryl organometallic intermediate, which further reacts to render the corresponding organic products.^{1,2} In order to prove this mechanism, several stoichiometric reactions between arynes and η^3 -allyl-,³ or aryl–Pd complexes^{2,4} have been tried. Unfortunately, only the organic compounds could be isolated. Similarly, stoichiometric reaction of benzyne and a C,C-nickelacyclopentene⁵ or a five-membered C,O-palladacycle⁶ afforded a dihydrophenanthrene or a dibenzopyranone.

Recently, we have described that the insertion of terminal alkenes into the Pd–C bond of metallacycles derived from primary phenethylamines leads to the synthesis of surprisingly stable eight-membered alkyl palladacycles, instead of the products resulting from a β -hydride elimination. We postulated that this occurred because of the existence of the strong Pd–NH₂ bond.⁷ This fact moved us to test the reactivity of these metallacycles towards benzyne, as the resulting eight-membered rings could also share this unprecedented stability.

Ortho-metalated complex [Pd(C,N-C₆H₄CH₂CMe₂NH₂-2)(μ -Cl)]₂ (**A**)⁸ or [Pd(C,N-C₆H₄CH₂CH₂CH₂NH₂-2-(OMe)₂-4,5)(μ -Br)]₂ (**B**)⁹ reacts with 2 equiv of benzyne, generated *in situ* from 2-(trimethylsilyl)phenyl triflate and CsF, in acetonitrile, at room temperature, to give the dimeric complex [Pd(C,N-C₆H₄{(C₆H₄CH₂CMe₂NH₂-2)-2'})(μ -Cl)]₂ (**1a**) (63%) or [Pd(C,N-C₆H₄{(C₆H₂CH₂CH₂NH₂-2-(OMe)₂-4,5)-2'})(μ -Br)]₂ (**1b**) (77%), which contains an eight-membered palladacycle arising from the insertion of one molecule of benzyne into the Pd–C bond (Scheme 1). These complexes are

the first isolated metallacycles obtained by direct carbopalladation of an aryne.



Scheme 1 Synthesis of benzyne inserted derivatives

Complex **1a** or **1b** reacts with 2 equiv of γ -picoline (pic) or PPh₃ to give [Pd(C,N-C₆H₄{(C₆H₄CH₂CMe₂NH₂-2)-2'})Cl(pic)] (**2a**; 95%) or [Pd(C,N-C₆H₄{(C₆H₂CH₂CH₂NH₂-2-(OMe)₂-4,5)-2'})Br(PPh₃)] (**2b**, 70%; Scheme 1), respectively, the crystal structures of which have been solved by X-ray diffraction studies (Figures 1 and 2). In both structures, the metal forms part of an eight-membered ring that adopts a boat conformation. The molecules of both

complexes are associated through hydrogen bonds, forming dimers (**2a**: classical hydrogen bond interactions N–H···Cl; **2b** non classical hydrogen interaction between an aromatic proton and the oxygen atoms of both OMe groups of an adjacent molecule[†]).

Complex **1a** or **1b** in MeOH inserts CO to give metallic palladium and a rare 2,2'-functionalized biaryl containing an alkylamino and a carboxymethyl substituents, [2'-MeO₂CC₆H₄C₆H₄CH₂CMe₂NH₃-2]Cl (**3a**; 61%) or [2'-MeO₂CC₆H₄C₆H₄CH₂CH₂CH₂NH₃-2-(OMe)₂-4,5]Cl (**3b**; 73%). Compounds **3a** and **3b** are the methyl ester derivatives of unnatural N⁷-amino acids. The synthesis of the amine with R = X = H has been reported and used to prepare the corresponding 5,6,7,8-tetrahydrodibenz[c,e]azocine,¹⁰ a derivative of which, apogalanthamine, is known for its anti-Alzheimer activity.¹¹

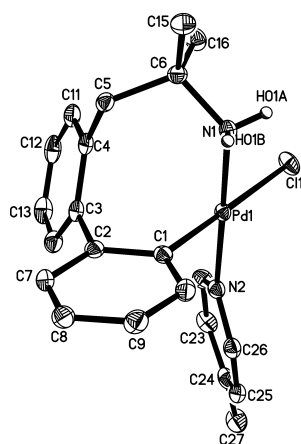


Fig. 1 Ellipsoid representation of **2a** (50% probability)

Complexes **1** and **2** are actual models for the carbopalladated benzynes proposed as intermediates in the transition-metal-catalyzed reactions involving arynes. To our knowledge, the only precedent of the isolation of such type of intermediate is that reported of a Ni–alkynyl addition to benzyne.¹² Nevertheless, the complex was obtained in poor yield (24%) and only characterized by IR spectroscopy and elemental analysis. The products of the insertion of benzyne into the C–Si bond of silylynamines,¹³ silacyclopropanes¹⁴ and silacyclopropenes¹⁵ have also been isolated, although, again, in poor yields (17–37%). A different type of reaction, involving benzyne and η^2 -benzyne–M(0) complexes (M = Ni, Pd, Pt)¹⁶ that gives 2,2'-biaryl complexes, has been reported.¹⁷ As in the case of the insertion of terminal alkenes into the Pd–C bond of the related metallacycles, the isolation of complexes **1** and **2** can be attributed to the strong Pd–NH₂ bond.

In summary, we report the synthesis of 2,2'-functionalized biaryls through the sequential insertion of benzyne and CO into the Pd–C bond of ortho-palladated primary phenethylamines. The eight-membered carbopalladated-benzyne intermediates, arising from the insertion of benzyne into the Pd–C bond, have been isolated and characterized, as well as two mononuclear derivatives, the crystal structures of which have been determined by X-ray diffraction. The isolation of these model complexes may constitute the key to

fully understand the proposed mechanisms for metal-catalyzed cyclotrimerization of arynes or the two- and three-component couplings involving arynes. Further studies to expand the scope of these reactions are currently in progress.

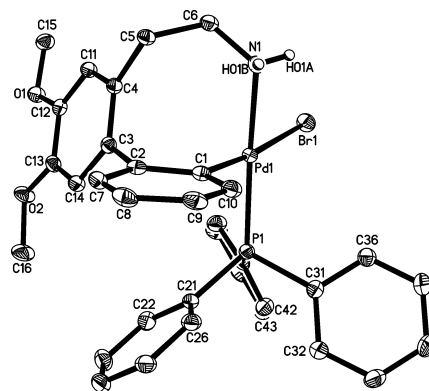


Fig. 2 Ellipsoid representation of **2b** (50% probability)

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Notes and references

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[†] Electronic Supplementary Information (ESI) available: Experimental details, spectroscopic data, and table listing the crystal data, CIF files of **2a** and **2b**·CH₂Cl₂. CCDC 874140–874141. See DOI: 10.1039/b000000x/

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