Sequential Insertion of Alkynes, Alkenes, and CO into the Pd–C Bond of ortho-Palladated Primary Phenethylamines: from η^3-Allyl Complexes and Enlarged Palladacycles to Functionalized Arylalkylamines

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Cite This: Organometallics 2021, 40, 539–556

ABSTRACT: The eight-membered metallacycles arising from the insertion of 1 equiv of alkyne into the Pd–C bond of ortho-metalated homoveratrylamine and phentermine can further react with alkenes to give two different types of mononuclear complexes depending on the nature of the olefin. When terminal alkenes (styrene and ethyl acrylate) are used, a mixture of the anti/syn η^3-allyl Pd(II) complexes are isolated, which evolve slowly to the syn isomers by heating the mixtures appropriately. These η^3-allyl Pd(II) complexes do not react with CO or weak bases, but when they are treated with a strong base, such as KOtBu, they afford Pd(0) and the functionalized starting phenethylamines containing a 1,3-butadienyl substituent in an ortho position. When 2-norbornene was used instead of terminal alkenes, the strained olefin inserts into the alkenyl Pd(II) complex to afford a 10-membered norbornyl palladium(II) complex, in which the new C,N-chelate ligand is coordinated to the metal through an additional double bond, occupying three coordination positions. The reactivity of these norbornyl complexes depends on the substituents on the inserted alkenyl fragment, and thus they can further react with (1) KOtBu, to give Pd(0) and a tetrahydroisoquinoline nucleus containing a tricyclo[3.2.1]octyl ring, or (2) CO and TlOTf, to afford Pd(0) and amino acid derivatives or the corresponding lactones arising from an intramolecular Michael addition of the CO2H group to the α,β-unsaturated ester moiety. Crystal structures of every type of compound have been determined by X-ray diffraction studies.

INTRODUCTION

Palladium is one of the most versatile transition metals in organic synthesis, given its well-known ability to catalyze the formation of C–C and C–heteroatom bonds. Nevertheless, the extraordinarily high variability of applications of palladium relies just on a few elementary steps inherent to its reactivity, and among them, the migratory insertion reaction of an unsaturated ligand into a Pd–C bond stands out. Thus, a myriad of methods to functionalize alkenes, alkynes, or allenes through Pd catalysis have been reported so far.

Multicomponent reactions, where several reagents assemble sequentially giving rise to complex structures, are valuable protocols, since they represent an effective modular approach to green organic synthesis. Nevertheless, transition-metal-catalyzed processes involving the use of several unsaturated coupling partners in the reaction mixture are challenging fields due to the difficulty in controlling the order of reactivity: that is, the control of regioselectivity of the migratory insertion sequence for the different unsaturated reagents. Some successful examples of these types of reactions are the copolymerization of alkenes and CO (Scheme 1a) and the copolymerization of olefins with and without polar groups, among others. Moreover, impressive progress has been made on intramolecular cascade reactions where different unsaturated moieties are involved (Scheme 1b). In the latter case, however, the selectivity is usually determined by the structure of the substrate itself.

While catalytic conditions make difficult the aforementioned control of the selectivity, stoichiometric reactions can offer the advantage of stepwise insertion paths for the synthesis of valuable organic products. Our research group has previously reported the functionalization of primary phenethylamines through the isolation of...
ortho-palladated intermediates. These types of aryalkylamines constitute the core of many relevant biomolecules, such as neurotransmitters (i.e., dopamine), amino acids (i.e., phenylalanine), or marketed psychoactive drugs. The catalytic functionalization of these scaffolds has proven challenging, due to the strong coordination ability of the primary amine group to Pd(II). Hence, the study of the stoichiometric functionalization of primary phenethylamines can provide alternative routes to modify these interesting molecules. For instance, the sequential insertion of alkynes and CO or of alkynes, alkenes, and CO into the Pd–C bond of the ortho-metalated derivatives allowed us to synthesize medium-sized rings such as eight-membered benzazocinones (Scheme 2).

**RESULTS AND DISCUSSION**

**Insertion of Styrene or Ethyl Acrylate into the Pd–C Bond.** Synthesis and Structure of η³-Allyl Palladium(II) Complexes. The reaction of the previously described arylalkylamine a or b, arising from the monomointercalation of diphenylacetylene into the ortho-palladated homoveratrylamine and phentermine derivative A or B, with 2 equiv of CH₂=CHR (molar ratio Pd/alkene = 1/1; R = Ph (1), CO₂Et (2)) in CH₂Cl₂ at room temperature (16 h) gave a mixture of two complexes, which were identified as the anti and syn isomers of the η³-allyl Pd(II) complex 1 or 2 (Scheme 3).

We have previously reported the synthesis and isolation of stable eight-membered C₃N-pallacycles arising from the insertion of one molecule of alkyne into the Pd–C bond of ortho-palladated phentermine and homoveratrylamine (Chart 1). We present here the results of a study on the insertion of alkenes and alkenes/CO into these eight-membered alkenyl pallacycles. We have studied the new organometallic species generated upon each insertion, as well as the final functionalized organic products, formed through depalladation of the final organopalladacycle compounds. The overall processes generating the final organopalladacycle complexes involve the sequential insertion of (a) alkynes and alkenes or (b) alkynes, alkenes, and CO into the Pd–C bond of the ortho-metalated derivatives from the primary phenethylamines.

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**Chart 1. Previously Reported Eight-Membered Alkenyl Palladacycles Used as Starting Materials**

| Y   | X   | R   | R'  | anti/syn ratio |
|-----|-----|-----|-----|---------------|
| a   | Br  | OMe | Ph  | 2.5/1         |
| b   | Cl  | H   | Me  | 1.25/1        |
| c   | Cl  | H   | Me  | 2.75/1        |
| d   | Cl  | H   | CO₂Me | 1.25/1     |

The ratios correspond to the isolated solids and were estimated by the integrals of the CH allylic signals of both isomers in the ¹H NMR spectra of the mixtures.

After workup, a mixture of η³-allyl Pd(II) complexes anti-/syn-1a (2.5/1) or anti-/syn-2a (5/1) was isolated. Attempts to separate both isomers by fractional crystallization were unsuccessful. However, single crystals of anti-1a or anti-2a, suitable for X-ray diffraction studies, were obtained by slow diffusion of n-pentane into a solution of the mixture of anti-/syn-1a or anti-/syn-2a.
syn-1a or anti-/syn-2a in CH$_2$Cl$_2$. The ratio between isomers, for both 1a and 2a, practically did not change after 48 h in CDCl$_3$ solution at room temperature (by $^1$H NMR). However, the conversion to the $\textit{syn}$ isomers was complete after heating CDCl$_3$ solutions of the mixtures at 60 °C for 10 days ($\textit{syn}$-1a) or 48 h ($\textit{syn}$-2a; by $^1$H NMR; Figure 1 and Table 1).

Figure 1. $^1$H NMR spectra (4.6−5.0 ppm) of complex 2a (CDCl$_3$): (a) $\textit{anti}$-enriched mixture of complex 2a at room temperature (300 MHz) and (b) after heating at 60 °C for 8 h (400 MHz), (c) 24 h (300 MHz) and (d) 48 h (300 MHz).

Almost spectroscopically pure samples of $\textit{anti}$- and $\textit{syn}$-1b and $\textit{anti}$- and $\textit{syn}$-2b could be obtained by growing single crystals from the enriched mixtures.

Since $\textit{anti}$-1 and $\textit{anti}$-2 complexes practically did not isomerize to the $\textit{syn}$-1 and $\textit{syn}$-2 derivatives at room temperature (Table 1), both isomers should be formed during the reaction. We proposed that the formation of $\textit{anti}$/syn-1 or $\textit{anti}$/syn-2 could be envisioned by the mechanism depicted in Scheme 4. Insertion of one molecule of the alkene into the Pd−C bond of the starting palladacycle (a or b) would afford the 10-membered alkyl palladacycle I. For this intermediate,

Table 1. Isomerization Ratios for $\textit{anti}$/syn-1 and $\textit{anti}$/syn-2

| temperature | time (h) | 1a | 1b | 2a | 2b |
|-------------|---------|----|----|----|----|
| RT          | 0       | 2.5/1 | 2.5/1 | 5/1 | 12.5/1 |
|             | 12      | 2.5/1 | 4.2/1 |     | 12.5/1 |
|             | 16      |       | 12.5/1 |     |       |
|             | 24      | 2.5/1 | 4.2/1 | 3.3/1 | 12.5/1 |
|             | 48      | 2.5/1 | 2/1  |     |       |
| 60 °C       | 0       | 2.5/1 | 2.5/1 | 5/1 | 12.5/1 |
|             | 8       | 1.7/1 | 1/1  |     | 1/5   |
|             | 12      |       | 1/10 |     |       |
|             | 24      | 1.1/1 | 1/10 | 0/1 | 0/1   |
|             | 48      | 1/1.25 | 1/10 |     | 1/20  |
|             | 120     |       |     |     |       |
|             | 240     | 0/1   |     |     |       |

Enriched mixtures of both $\textit{anti}$ and $\textit{syn}$ isomers of 1b and 2b could be obtained due to the higher solubility of one of the two isomers in Et$_2$O. When a solution of the mixture $\textit{anti}$/syn-1b or $\textit{anti}$/syn-2b (1b, ratio 1.25/1, 0.161 mmol; 2b, ratio 1.25/1, 0.260 mmol) in CH$_2$Cl$_2$ (1b, 3 mL; 2b, 2 mL) was treated with Et$_2$O (15 mL), a mixture enriched in the $\textit{anti}$ (1b) or syn (2b) isomer precipitated (ratio $\textit{anti}$/syn: 1b, 3/1; 2b: 1/3). When the mother liquors were concentrated (1b: 3 mL; 2b: 5 mL) and treated with n-pentane (1b, 20 mL) or cooled to 0 °C in an ice bath (2b), a mixture enriched in the syn (1b) or $\textit{anti}$ (2b) isomer precipitated (ratio $\textit{anti}$/syn: 1b, 1/3; 2b: 3/1).

Scheme 4. Formation of $\textit{anti}$ and $\textit{syn}$ Isomers of $\eta^1$-Allyl Pd(II) Complexes

https://dx.doi.org/10.1021/acs.organomet.0c00787
Organometallics 2021, 40, 539−556
we propose that the R’ group is at the carbon atom bonded to Pd(II), because (1) this is the regiochemistry that explains the formation of the allyl moiety coordinated to Pd(II) in complexes 1a,b and 2a,b and (2) this is the most frequent regioisomer found in the insertion of electron-poor alkenes into the Pd–C bonds of neutral complexes. Intermediate I could undergo β-hydride elimination to give the cisoid-(diene)PdH species II. Syn addition of Pd–H to the alkene moiety with regioselectivity in contrast with its previous elimination results in the formation of the η²-allyl complex anti-1 or anti-2 (Scheme 4), which seems to be formed preferentially as the kinetic product. On the other hand, the transoid-(diene)PdH intermediate III could be generated from II upon decoordination and rotation of the tertiary olefin moiety, prior to the Pd–H addition step, hence giving rise to the formation of the syn isomer. The thermal isomerization of the complexes anti-1 and anti-2 to the syn isomers at 60 °C (Table 1) proceeded by the usual η²-η¹-η¹ rearrangement.

Complexes 1 and 2 were fully characterized by elemental analyses and NMR and IR spectroscopic techniques. The 1H NMR spectra of all the allyl complexes showed the diastereotopic nature of the hydrogen atoms of the NH2 and CH2 groups, as well as both of Me groups of the CMe2 moiety for 1b and 2b. The most characteristic signal was that corresponding to the methine group of the inserted fragment, which appeared as a doublet of doublets in the range 4.85–5.16 ppm for the anti isomers and 4.75–4.84 ppm for the syn isomers. The two coupling constants 3JHH (anti, 11.2 ≤ 3JHH ≤ 12.3 Hz, average value 11.7 Hz; syn, 9.6 ≤ 3JHH ≤ 11.0 Hz, average value 10.3 Hz; anti, 4.5 ≤ 3JHH ≤ 5.2 Hz, average value 4.7 Hz; syn, 3.7 ≤ 3JHH ≤ 4.2 Hz, average value 4.0 Hz) were slightly smaller for the syn isomers than for the anti isomers.

The crystal structures of the η²-allyl complexes anti-1a, anti-1b, syn-1b, anti-2a-CH2Cl2, anti-2b-CHCl3, and syn-2b were determined by X-ray diffraction (see the Supporting Information). The X-ray thermal ellipsoid plots of anti-1a and syn-2b are depicted in Figures 2 and 3, respectively. In both cases, the palladium atoms adopted a square-planar geometry (mean deviation from the plane Y–Pd(1)–X(1)–N(1) 0.0194 Å, where Y = centroid from C(7), C(8), and C(9) atoms). The halogeno ligand and the amino group of the metalated fragment were coordinated in cis positions. The other two coordination sites were occupied by the alkyl moiety, which was η²-bonded via C(7), C(8), and C(9), with C(7)–C(8)–C(9) angles of 119.4 and 122.5° for anti-1a and syn-2b, respectively.

Some catalytic transformations involving the sequential migratory insertion of alkynes and alkenes into a Pd–C3H,12,17,29 or a Pd–H15 bond have been reported in the literature. In these processes, substituted 1,3-butadienes are formed. The mechanism proposed for those catalytic transformations does not consider the formation of η²-allyl intermediates. In our case, however, the presence of a coordinating group, such as NH2, may favor the isomerization of the 1,3-butadiene to form a stabilized allyl Pd(II) complex. As far as we are aware, this is the first stoichiometric study where the sequential migratory insertion of an alkyl and an alkene has been studied.

Reactivity of the η²-Allyl Complexes. The nucleophilic attack to η²-allyl Pd(II) intermediates to give functionalized alkenes is a well-known strategy in organic synthesis. However, most of the times the key η²-allyl Pd(II) species are generated through the oxidative addition of allyl halides, pseudohalides or acetates to Pd(0). We wondered if the η²-allyl complexes 1 and 2 could undergo the attack of a suitable nucleophile to render an organic derivative. Hence, we performed a range of reactions with several nucleophiles, such as KCN, [Tl(acac)], p-toluidine, and the phosphorus ylide PhpCHCOMe. There was no reaction at room temperature with any of these nucleophiles. When the reaction mixture was heated in refluxing toluene, complicated mixtures were produced. The reaction of complex 1b and dimethyl malonate in the presence of Cs2CO3 (CHCl3, room temperature) afforded an anti/syn mixture of isomers of a new complex containing the η²-allyl moiety and a coordinated...
malonate, whose structures were not studied further. When a solution of this complex in CHCl₃ was heated at 60 °C, again a complicated mixture was obtained. In order to facilitate the nucleophilic attack, we performed the reaction of the η³-allyl complex 1b with p-toluidine in the presence of TIOTF, which would generate a cationic complex by replacing the Cl⁻ ligand by OTF⁻ in the coordination sphere of Pd(II). In this case, the stable cationic η³-allyl complex 3b was isolated, which contained a coordinated p-toluidine ligand (Scheme 5). This complex was stable in refluxing toluene and did not decompose to the expected organic product.

Scheme 5. Reactions of η³- Allyl Complex 1b with p-Toluidine

The ¹H NMR of complex 3b at room temperature showed some broad signals and seemed to correspond to a mixture of two isomers with a fluxional behavior (Figure 4). Perhaps the most significant resonances are those attributed to the Me groups: three sharp singlets at 1.45 (3 H), 1.42 (3 H), and 1.26 ppm (2.2 H) and two broad singlets at 2.28 (5.4 H) and 0.94 ppm (2.2 H). When the spectrum was measured at ~40 °C, the broad singlet below 1 ppm became sharper, and the signal at 2.28 ppm split into two new singlets with the relative intensities 3:2:2. According to these data, we assumed that both isomers, anti-/syn-3b, are formed in a 1.33/1 ratio, one of which presented a fluxional behavior in solution. The less stable isomer should be anti-3b due to steric hindrance of the toluidine ligand and the substituent on the terminal allylic carbon, and for it, it was reasonable to suppose that the neutral ligand could be coming in and out of the metal coordination sphere. The crystal structure of the η³-allyl complex syn-3b·CH₂Cl₂ was determined by X-ray diffraction (Figure 5), showing that

Figure 4. ¹H NMR spectra (0.6–3.0 ppm) of complex 3b (400 MHz) in CDCl₃ at 25 °C (bottom) and ~40 °C (top). The asterisk indicates the signal corresponding to H₂O. The blue and red circles correspond to the syn and anti isomers, respectively.

Figure 5. Thermal ellipsoid plot (50% probability) of the cation of one (A) of the two independent molecules of the complex syn-3b·CH₂Cl₂ showing the labeling scheme. The solvent molecule and the hydrogen atoms bonded to carbon have been omitted for clarity. Selected bond lengths (Å) and angles (deg) are given for both independent molecules (A and A'). For A: Pd(1)−N(1) = 2.131(2), Pd(1)−N(2) = 2.161(2), Pd(1)−C(7)' = 2.100(2), Pd(1)−C(8)' = 2.138(2), Pd(1)−C(9) = 2.165(2), C(7)'−C(8)' = 1.454(3), C(8)−C(9) = 1.408(3); N(1)−Pd(1)−N(2) = 90.26(9), C(7)'−C(8)'−C(9) = 116.9(2), C(8)−C(9)−C(14) = 124.9(2). For A': Pd(1')−N(1') = 2.130(2), Pd(1')−N(2') = 2.163(2), Pd(1')−C(7') = 2.117(2), Pd(1')−C(8)' = 2.134(2), Pd(1')−C(9) = 2.165(2), C(7)'−C(8)' = 1.452(3), C(8)'−C(9) = 1.413(3); N(1')−Pd(1')−N(2') = 88.94(8), C(7)'−C(8)'−C(9) = 117.5(2), C(8)−C(9)−C(14) = 124.0(2).

The phenyl and benzy1 substituents at the meso and terminal carbon atoms of the allylic unit occupied mutually syn positions and indicating that this was, in fact, the most stable isomer. For this complex there were two independent molecules in the asymmetric unit (A and A'). For molecule A, the palladium atom exhibited a square-planar geometry (mean deviation from the plane: X = centroid from C(7), C(8), and C(9) atoms). Both amino groups were coordinated in the η⁶-moiety, which was η⁶-bonded via C(7), C(8), and C(9), formed a dihedral angle of 71.3° (metalated ring), 65.5° (phenyl ring at C7), 71.9° (phenyl ring at C8), 73.3° (phenyl ring at C14), and 92.4° (toluidine ring) with respect to the Pd coordination plane, to avoid steric hindrance. Hydrogen bond interactions were observed between the cationic palladium moiety and the OTF⁻ anion (see the Supporting Information).
Additionally, we studied the behavior of the anti/syn-1a,b complexes toward a strong base. The reaction of these complexes with KOtBu in toluene under a N2 atmosphere afforded Pd(0) and the functionalized phenethylamines containing a 1,3-butadienyl substituent in an ortho position (4a,b; Scheme 6). We did not observe intramolecular cyclization arising from the possible nucleophilic attack of the NH2 group to the η3-allyl moiety. The compound 4a was a colorless solid and was easily isolated, but 4b was obtained as a liquid. In order to get a more easily isolable derivative, triflic acid was added to a solution of compound 4b in diethyl ether (Scheme 6). The corresponding ammonium triflate 5b precipitated in the reaction mixture and was obtained as a white powder in moderate yield (50%).

Miura et al. described the intermolecular three-component coupling of aryl iodides, diarylacetylenes, and alkenes in the presence of palladium acetylacetonate and silver acetate as catalysts, to give the corresponding 1:1:1 and 1:2:1 coupling products (1,3-butadiene and 1,3,5-hexatriene derivatives, respectively). The mechanism proposed for these catalytic transformations followed the sequential steps analogous to those of the synthesis of compounds 4 reported here, (1) formation of an aryl Pd(II) complex (either by oxidative addition or C–H activation), (2) alkyne insertion into the Pd–C bond to form an alkenyl complex, (3) alkenyne insertion into the Pd–C bond to form an alkynyl intermediate, and (4) β-H elimination, assisted by a base, to afford the final diene. In our case, and due to the particular nature of the initial aryl group, we have been able to isolate all of the organometallic intermediates involved in the process.

The crystal structure of the ammonium triflate 5b·H2O was solved by X-ray diffraction studies (Figure 6) and showed a slightly distorted planar diene skeleton (mean deviation from the plane: C(7)−C(8)−C(9)−C(1)−C(14)−C(21)−C(31)−C(41) = 0.041 Å) with an E,E geometry. Within the butadiene fragment, the average C=C double-bond distance (C7−C8, C9−C14) was 1.35(2) Å, being slightly longer than that corresponding to the most substituted unsaturated unit, and the average single-bond value (C1−C7, C7−C8) was 1.48(2) Å. The aryl rings formed angles of 62.5, 20.8, 69.1, and 48.0° with respect to the diene plane, adopting a helical conformation and releasing steric hindrance.

We also attempted to insert a third unsaturated molecule into the Pd–C bonds of the η3-allyl complexes by bubbling CO through a solution of 1b in CH2Cl2 (room temperature, 4 h). Nevertheless, no reaction was observed, probably because these complexes were too stable. A similar reaction, with addition of TlOTf and use of THF as the solvent, led to a cationic complex with no CO inserted.

**Insertion of 2-Norbornene into the Pd–C Bond.**

**Synthesis and Structure of 10-Membered Norbornyl Palladium(II) Complexes.** In contrast to styrene or ethyl acrylate, when 1 equiv of 2-norbornene was added to a solution of the alkanyl complex b (arising from insertion of one molecule of diphenylacetylene into the Pd–C bond of palladacycle B; see Scheme 7 for its structural formula), no insertion reaction was observed, neither at room temperature nor on heating the mixture to 65 °C in CH2Cl2. We also attempted the insertion reactions using as starting materials the eight-membered palladacycles c and d, arising from the
insertion of methyl phenylpropiolate and 1-phenyl-1-propyne, respectively, into the Pd–C bond of complex B. When palladacycle d was used, the reaction at room temperature led to a new species that was tentatively assigned to the norbornene coordination monomer species 6d (Scheme 7), which could not be fully characterized, since it evolved easily to the starting dimeric complex d when we tried to crystallize it. Nevertheless, when these reaction mixtures (palladacycle c or d and 2-norbornene) were heated to 65 °C, we could successfully isolate the complexes 7c, d, where the insertion of the 2-norbornene moiety into the alkenyl Pd(II) complex had taken place (Scheme 7). These complexes have a monomeric nature, since the Pd center completes its coordination sphere with the intramolecular olefin moiety.

The crystal structures of complexes 7c·CHCl₃ and 7d·1/2CHCl₃ were solved by X-ray diffraction studies (see Figure 7 and the Supporting Information), and both showed similar features. For the complex 7c·CHCl₃, the atoms Cl(1), N(1), and C(1) together with the midpoint of the C(3)–C(4) double bond form a square plane around the palladium atom (mean deviation from the plane: Pd(1)–N(1) = 2.2185(19), Pd(1)–Cl(1) = 2.3589(5), Pd(1)–C(1) = 2.047(2), Pd(1)–C(3) = 2.159(2), Pd(1)–C(4) = 2.203(2), Pd(1)–X = 2.065, C(1)–C(2) = 1.553(3), C(2)–C(3) = 1.542(3), C(3)–C(4) = 1.403(3), C(4)–C(5) = 1.512(3); N(1)–Pd(1)–Cl(1) = 88.03(5), Cl(1)–Pd(1)–C(1) = 93.88(6), C(1)–Pd(1)–X = 76.7, X–Pd(1)–N(1) = 101.3, C(2)–C(3)–C(4) = 117.17(17), C(3)–C(4)–C(5) = 122.65(18). X represents the midpoint of the double bond C(3)–C(4).

We performed an analogous experiment reversing the order of the addition of the unsaturated reagents. That is, we studied the reactivity of the previously reported norbornyl derivative e (arising from the insertion of 2-norbornene into the six-membered palladacycle B) toward alkynes (Scheme 8). A suspension of the norbornyl Pd(II) complex e in CHCl₃ was

Scheme 7. Sequential Insertion of Alkyne/2-Norbornene into the Pd–C Bond of Six-Membered Palladacycle B

Scheme 8. Sequential Insertion of Norbornene/Alkynes into the Pd–C Bond of Palladacycle B
heated to 65 °C in the presence of methyl phenylpropiolate. The complex 7d, which arose from a reverse insertion order of the reagent addition, was isolated in 20% yield from the reaction mixture. In this reaction, palladacycle b was also formed. The formation of 7d could be explained through the deinsertion of the 2-norbornene fragment in e to give the starting palladacycle B, which in turn would undergo the sequential insertion of the alkyne and 2-norbornene. The ability of this cyclic olefin to insert reversibly into Pd–aryl bonds is well-known. This behavior has promoted the use of norbornene as an essential ligand in the functionalization of haloarenes: for instance, in the versatile Catellani type reaction.\(^2\) We tried to apply this strategy to obtain the diphenylacetylene/2-norbornene insertion derivative. Nevertheless, the reaction of the norbornyl complex e with diphenylacetylene gave rise mainly to the stable eight-membered palladacycle \(\text{f} \), as noted above.

The synthesis of alkenyl palladacycles arising from the insertion of one molecule of alkyne into the Pd–C bond of a starting complex is not always a simple task, due to the possibility of di- and tri-insertion processes. This aspect is especially relevant when a very electrophilic alkyne, such as dimethyl acetylenedicarboxylate (DMAD), is used. We have previously tried to isolate the palladacycle f arising from monoinsertion of DMAD into the Pd–C bond of \(\text{B} \); nevertheless, mixtures of mono-, di-, and tri-inserted products were obtained (Scheme 9). We thought that performing the reaction of \(\text{B} \) and DMAD in the presence of 2-norbornene could drive the reaction to the formation of a sequential DMAD/norbornene insertion product, given the fact that norbornene seems to react readily with other monoinserted alkyne derivatives. Indeed, when a solution of the palladacycle \(\text{B} \) in CHCl\(_3\) was heated to 65 °C in the presence of 1 equiv of DMAD and 1 equiv of 2-norbornene, the alkyne/alkene sequential insertion product 7f was isolated in good yield (Scheme 9). The crystal structure of complex 7f was also solved by X-ray diffraction studies (see the Supporting Information) and showed features similar to those discussed for 7e-CHCl\(_3\).

Reactivity of the Norbornyl Complexes. We explored the reactivity of the complex 7f toward KOtBu in MeCN at 78 °C. From the reaction mixture, we could isolate the tetrahydroidoisoquinoline derivative 8f by treatment of the crude product with HOTf: that is, from the protonation of V (Scheme 10). A possible path to explain the formation of 8f would involve the intramolecular carbopalladation of the alkenyl moiety, giving rise to a cyclopropyl ring. The new organometallic intermediate IV would then undergo a C–N coupling process with reductive elimination of Pd(0). Several Pd-catalyzed procedures to promote the cyclopropanation of 2-norbornene have been reported in the literature.\(^3\) Some of these procedures rely on the migratory insertion of norbornene into a Pd alkynyl\(^1\) or Pd alkenyl\(^4\) complex, and some organometallic intermediates similar to complexes 7 have been proposed, where the alkenyl moiety is coordinated intramolecularly to Pd.

The crystal structure of 8f was solved by X-ray diffraction studies (Figure 8) and showed the isoquinoline nucleus derived from phentermine substituted at C1 with a methoxy carbonyl group and a tricyclo[3.2.1]octyl ring. It is worth noting that highly strained hydrocarbons such as this cyclopropane-containing norbornyl moiety have been tested as new highly energetic materials for liquid-fueled propulsion systems.\(^5\)

We studied whether a further insertion of an unsaturated molecule could be carried out in the complexes 7c,d,f, obtained after alkyne/norbornene insertion. Complex 7f did not react when it was stirred in CHCl\(_3\) in the presence of CO at room temperature for 5 h. When the reaction mixture was heated to 65 °C, a complicated mixture was formed. In order to facilitate the insertion of CO, we performed the reaction in the presence of TIOTf in acetone, hence generating a cationic Pd(II) intermediate in situ. In this case, the reaction afforded...
the lactone 9f and Pd(0) (Scheme 11). The formation of 9f could be explained as the result of the hydrolysis of the acyl Pd(II) intermediate generated upon CO insertion into the Pd−C bond present in 7f. Under those conditions, the carboxylic acid derivative underwent an intramolecular Michael addition of the CO2H group to the α,β-unsaturated ester moiety.

Scheme 11. Reactions of Complexes 7 with CO

When the cationic derivatives of complexes 7c,d (generated in situ) reacted with CO at room temperature, the amino acid derivatives 10c,d were obtained (Scheme 11). In the case of 10d, intramolecular cyclization to give 9d took place after heating at 65 °C in CHCl3 for 7 days. As expected, the derivative 10c was stable upon heating, since it was not activated for the Michael addition step, as occurred in the cases of the alkenyl complexes bearing a CO2Me substituent.

The crystal structure of 9f·Et2O has been solved by X-ray diffraction studies (Figure 9) and showed an ammonium salt derived from the starting phentermine containing a bicyclo[2.2.1]heptane lactone substituent. The hexahydro-4,7-methanoisobenzofuran-1(3H)-one core is a known compound that has attracted interest because of its potential use as a prostaglandin/thromboxane receptor antagonist. The most frequent routes for its synthesis involved (a) the cycloaddition reaction of furan-2(5H)-one and cyclopentadiene and (b) the oxidation of cis-2,3-bis(hydroxymethyl)bicyclo[2.2.1]-heptane, which could be performed in a stoichiometric way with standard organic oxidants or by catalysis, with the use of enzymes or transition metals.

The crystal structure of 10c has also been determined by X-ray diffraction studies (Figure 10), and it showed the ammonium salt derived from the sequential insertion of alkene/norbornene/CO into the initial phentermine palladacycle. Both substituents (the carboxylate and the alkenyl groups) at the norbornadienyl moiety were in an exo disposition.
Figure 10. Thermal ellipsoid plot (50% probability) of the cation of 10c·H2O along with the labeling scheme. The solvent molecule and the hydrogen atoms bonded to carbon have been omitted for clarity. Selected bond lengths (Å) and angles (deg): N(1)—C(8) = 1.518(2), C(3)—C(11) = 1.504(3), C(11)—C(14) = 1.342(3), C(14)—C(15) = 1.532(2), C(15)—C(16) = 1.582(2), C(16)—C(17) = 1.586(3), C(17)—O(1) = 1.218(2), C(17)—O(2) = 1.328(2), N(1)—C(8)–C(7) = 104.46(14), C(1)—(11)—C(14) = 121.73(17), C(11)—C(14)—C(15) = 121.56(17), C(14)—C(15)—C(16) = 118.26(15), C(15)—C(16)—C(17) = 116.58(15), C(16)—C(17)—O(1) = 126.22(17), C(16)—C(17)—O(2) = 111.65(16).

## CONCLUSION

In summary, the stoichiometric sequential insertion of alkynes and alkenes into the Pd–C bond of metalated phenethylamines has been studied. The result of these reactions depends on the nature of the olefin used. The insertion of styrene or ethyl acrylate into the eight-membered palladacycle arising from monoisertion of diphenylacetylene affords the η²-allyl species 1 or 2, via sequential β-H elimination/hydrapalladation steps. However, the insertion of 2-norbornene leads to norbornyl Pd(II) complexes with an alkenyl moiety intramolecularly coordinated to the metal center.

The treatment with a strong base of the organometallic complexes obtained upon the sequential insertion of alkyne/alkene (1, 2, and 7) also led to different results. While the η²-allyl complexes 1 and 2 afforded 1,3-butadienyl-substituted phenethylamines (4b and 5b), the norbornyl Pd derivative 7f gave a tetrahydrosoquinoline derivative upon cyclopropanation of the norbornene fragment and C–N coupling (8f).

The η³-allyl complexes 1 and 2 were unreactive toward CO insertion. In contrast, the norbornyl derivatives 7c,d,f afforded interesting amino acid or lactone derivatives upon CO insertion into the Pd–C bond and subsequent hydrolysis, under the appropriate conditions.

Overall, we have shown that the isolation of the organometallic intermediates obtained upon stepwise insertion of alkynes and alkenes into palladated phenethylamines allows the synthesis of functionalized primary phenethylamines. These stoichiometric routes avoid the problems associated with substrates that make difficult the development of catalytic processes (such as primary alkylamines) and allow the control of the regioselective insertion of the different unsaturated coupling partners.

## EXPERIMENTAL SECTION

**Caution! Special precautions should be taken in handling thallium(I) compounds, which are toxic.**

### General Procedures

Infrared spectra were recorded on a PerkinElmer 16F-PC-FT spectrometer. C, H, N, and S analyses were carried out with a LECO CHNS-932 microanalyzer. Conductance measurements and melting point determinations were carried out as described elsewhere. Unless stated otherwise, NMR spectra were recorded in CDCl₃ with Bruker Avance 300, 400, and 600 spectrometers. Chemical shifts are referenced to TMS (1H and 13C) signals. In the 1H and 13C NMR spectra of all compounds were assigned with the help of APT, HMQC, and HMQC experiments. High-resolution electrospray ionization mass spectra (ESI-MS) were recorded on an Agilent 6220 Accurate-Mass time-of-flight (TOF) LC/MS. Reactions were carried out at room temperature without special precautions against moisture unless specified otherwise. The groups C₆H₄ and C₆H₁₂ are denoted by Ar.

Free and inserted 2-norbornene are denoted by C₇H₁₀ (free), CH(νC₅H₈)CH (inserted), and nor (both, NMR signals).

Styrene, ethyl acrylate, 2-norbornene, dimethyl acetylenedicarboxylate (DMAD), methyl phenylpropiolate, p-toluidine (Tol), KOtBu, and HOTf (HO₃SCF₃) were used as received from commercial sources. The palladacycles [Pd(C₆H₄(CH₂CH₂NH₂)-2{(OMe)₂-4,5}(μ-Br)]₂ (A), [Pd(C₆H₄(CH₂CMe₂NH₂)-2{(OMe)₂-4,5}(μ-Br)]₂ (B), [Pd(C₆H₄(CH₂CH₂NH₂)-2{(OMe)₂-4,5}(μ-Br)]₂ (C), [Pd(C₆H₄(CH₂CMe₂NH₂)-2{(OMe)₂-4,5}(μ-Br)]₂ (D), and [Pd(C₆H₄(CH₂CH₂NH₂)-2{(OMe)₂-4,5}(μ-Br)]₂ (E) were prepared as previously reported. TlOTf was prepared by the reaction of Tl₂CO₃ and HO₃SCF₃ (1/2) in water and recrystallized from acetone/Et₂O. Chart 2 gives the numbering schemes for the new organometallic and organic derivatives.

**Synthesis of anti/syn-1a.** Styrene (23 μL, 0.202 mmol) was added to a solution of palladacycle a (110 mg, 0.100 mmol) in CH₂Cl₂ (10 mL), and the mixture was stirred for 20 h. The resulting...
mixture was filtered through a plug of Celite, the filtrate was concentrated to 1 mL, and EtO (15 mL) was added. The mixture was cooled to 0 °C, the resulting suspension was filtered, and the pale yellow solid was air-dried to give a mixture of anti-/syn-1a. Yield: 86 mg, 0.132 mmol, 66%. Mp: 145 °C. Anal. Calc. for C24H25BrN2O4Pd (648.9368): C, 59.32; H, 4.97; N, 2.16. Found: C, 59.32; H, 5.10; N, 2.19. IR (cm⁻¹): v(NH) 3319, m, 3258 w, 3206 m, 3135 w. The NMR spectra of this complex showed two sets of signals in approximately a 2.5/1 ratio (determined by ¹H integration), corresponding to the mixture anti-/syn-1a. Data for anti-1a (extracted from the mixture) are as follows.

¹H NMR (300.1 MHz): δ 1.36–1.70 (m, 1 H, NH), 1.88 (m, 1 H, CH₂Ar), 2.56 (br dd, 1 H, CH₂Ar, ²JHH = 15.3, ³JHH = 7.8 Hz), 2.76–2.85 (m, partially obscured by the resonance of MeO, 1 H, CH₂Ph), 2.86 (s, 3 H, MeO), 2.97–3.02 (br d, 1 H, CH₂N, ²JHH = 12.6 Hz), 3.22–3.35 (m, 2 H, 1 H of CH₂N + 1 H of NH), 2.38 (br dd, 1 H, CH₂N, ²JHH = 17.4, ³JHH = 7.5 Hz), 3.87 (1 H, MeO), 5.11 (dd, 1 H, CH₂N, ²JHH = 12.3, ³JHH = 4.5 Hz), 6.47 (1 H, s, H, H), 6.64 (1 s, H, H), 6.80–7.27 (m, 15 H, Ph). ¹³C{¹H} NMR (75.5 MHz): δ 35.2 (CH₂Ar), 39.1 (CH₂), 42.9 (CH₃), 54.7 (MeO), 55.9 (MeO), 85.0 (CH₃), 93.8 (C7), 111.9 (CH₆), 116.1 (CH₁), 123.6 (C8), 125.8 (CH₅), 126.8 (CH₆), 127.0 (CH₇), 127.3 (CH₈), 128.0 (CH₁₀), 128.4 (CH₁₈), 128.5 (CH₁₉), 128.6 (CH₁₆), 132.2 (C₁), 135.1 (i-C₈H₁₇), 140.4 (i-C₈H₁₇), 141.1 (i-C₈H₁₇), 143.6 (C₁₂), 146.4 (C₁₅), 148.3 (C₈).

anti/syn Isomerization of 1a. An NMR tube was charged with a 2.5:1 mixture of anti-/syn-1a (20 mg) and CDCl₃ (0.2 mL), and the solution was heated at 60 °C. The sample was checked by ¹H NMR periodically, until complete conversion. After 10 days at 60 °C, a spectroscopically pure sample of syn-1a was obtained. Data for syn-1a are as follows. ¹H NMR (400 MHz): δ 1.61–1.67 (m, 1 H, NH), 1.89 (br dd, 1 H, CH₂Ar, ²JHH = 15.3, ³JHH = 10.8 Hz), 2.47 (br dd, 1 H, CH₂N, ²JHH = 15.4, ³JHH = 8.0 Hz), 2.86–2.90 (m, 1 H, CH₂Ph), 3.23 (dd, partially obscured by the resonance of NH₃, 1 H, CH₂N, ²JHH = 12.0, ³JHH = 8.0 Hz), 3.02 (br d, 1 H, NH, ²JHH = 12.0 Hz), 3.42 (s, 3 H, MeO), 3.46 (br dd, 1 H, CH₂N, ²JHH = 14.2, ³JHH = 3.5 Hz), 3.87 (s, 3 H, MeO), 4.80 (dd, 1 H, CH₂, ²JHH = 11.0, ³JHH = 3.7 Hz), 6.39 (1 s, H, H), 6.60 (1 s, H, H), 6.19 (br d, 1 H, MeO), 7.04 (1 s, 3 H, Ph), 7.80 (1 s, 3 H, Ph), 7.85 (br d, 1 H, Ph, ²JHH = 6.0 Hz). ¹³C{¹H} NMR (75.5 MHz): δ 34.8 (CH₂Ar), 35.8 (CH₂Ph), 43.6 (CH₃N), 55.6 (MeO), 60.0 (MeO), 84.5 (CH), 90.8 (C₇), 110.0 (CH₆), 116.2 (CH₅), 124.0 (C₈), 126.0 (CH₆), 127.0 (CH₇), 127.3 (CH₈), 127.7 (CH₉), 128.4 (CH₁₈), 128.5 (CH₁₉), 129.0 (CH₂), 131.8 (C₁), 133.2 (i-C₈H₁₇), 133.7 (CH₇), 135.1 (i-C₈H₁₇), 140.5 (i-C₈H₁₇), 142.4 (C₂), 147.5 (C₁₅), 148.2 (C₈).

Synthesis of 2a. Method a. Styrene (52 mL, 0.453 mmol) was added to a solution of palladacycle b (200 mg, 0.213 mmol) in CHCl₃ (10 mL). The solution was stirred for 12 h, the solvent was concentrated to ca. 5 mL, EtO (5 mL) was added, and the resulting suspension was filtered through a plug of Celite. The filtrate was concentrated to ca. 1 mL, and n-pentane (20 mL) was added. The suspension was filtered, and the pale yellow solid was washed with n-pentane (2 x 5 mL) and air-dried to give a mixture of anti-/syn-2a (ratio ca. 1/5 by ¹H NMR). Yield: 201 mg, 0.312 mmol, 85%. Mp: 169 °C. Anal. Calc. for C₃₂H₂₆BrN₂O₂Pd (684.9011): C, 54.01; H, 0.03; N, 2.15. Found: C, 54.25; H, 0.09, N, 2.19. IR (cm⁻¹): ν(NH) 3293 w, 3214 br; ν(CO) 1727 s, 1711 s. Data for anti-2a are as follows. ¹H NMR (400 MHz): δ 1.19 (1 H, Me), 1.35 (1 H, Me), 7.29 (1 H, CH₂Ar, ²JHH = 10.8, ³JHH = 4.8 Hz). 1H NMR (500 MHz): δ 1.15, 1.30 (each 1 H, Me), 5.10 (dd, 1 H, CH₂Ar, ²JHH = 10.8, ³JHH = 4.8 Hz). 13C{¹H} NMR (125 MHz): δ 141.1 (Me₃C₅H), 131.5 (CH₂Ar), 94.3 (CH₂CO₂Et), 42.9 (CH₃N), 56.0 (MeO), 60.8 (CH₂O), 79.1 (CH), 93.8 (C₇), 112.5 (CH₆), 116.4 (CH₅), 123.9 (C₈), 126.8 (CH₇), 127.2 (CH₈), 127.9 (CH₉), 128.0 (CH₁₀), 131.4 (CH₂), 133.5 (br s, CH₂), 134.9 (i-C₈H₁₇), 135.1 (CH₃), 138.4 (C₂), 139.7 (i-C₈H₁₇), 140.0 (C₁₅), 142.2 (i-C₈H₁₇).

anti/syn Isomerization of 2a. An NMR tube was charged with a 5/1 mixture of anti-/syn-2a (20 mg) and CDCl₃ (0.6 mL), and the solution was heated at 60 °C. The sample was checked by ¹H NMR periodically, until complete conversion. After 48 h at 60 °C, a
spectroscopically pure sample of syn-2a was obtained. Data for syn-2a are as follows. 1H NMR (300.1 MHz): δ 1.10 (t, 3 H, MeH, JHH = 7.2 Hz), 1.67 (br d, 1 H, NH, JHH = 10.8 Hz), 1.88 (dd, 1 H, CH, JHH = 15.6, JHH = 10.8 Hz), 2.49 (dd, 1 H, CHAr, JHH = 15.3, JHH = 6.6 Hz), 2.80 (dd, 1 H, CH₂CO₂Et, JHH = 18.0, JHH = 10.2 Hz), 2.90 (m, partially obscured by the resonance of CH₂CO₂Et, 0.262 mmol), 0.262 mmol). In a Carius tube, KOtBu (190 mg, 1.55 mmol) was added to the mixture and stirred for 2 h. The solvent was removed, and CH₂Cl₂ (15 mL) was added. The suspension was filtered through a plug of Celite, p-toluidine (17 mg, 0.155 mmol) was added to the filtrate, and the mixture was stirred for another 30 min. The solvent was concentrated to ca. 1 mL and subjected to 5% Na₂CO₃ solution, until no change was observed. After 48 days at 60 °C, a 1/2 anti-syn-2b mixture was obtained.

Synthesis of anti-syn-2b. anti-syn-2b (60 mg, 0.0667 mmol) was added to a solution of complex 1b (90 mg, 0.157 mmol) in acetone (10 mL), and the resulting mixture was stirred for 2 h. The solvent was removed, and CH₂Cl₂ (15 mL) was added. The suspension was filtered through a plug of Celite, p-toluidine (17 mg, 0.155 mmol) was added to the filtrate, and the mixture was stirred for another 30 min. The solvent was concentrated to ca. 1 mL and n-pentane was added. The suspension was filtered, and the pale yellow solid was washed with cold n-pentane (2 × 5 mL) and air-dried to afford an anti-syn-3b mixture of ratio ca. 1/3 by 1H NMR). Yield: 60.0 mg, 0.0766 mmol, 48%. Mp: 120 °C. δ (C₅H₅NO, Pd) (793.237): C, 60.38; H, 5.17; N, 3.30; S, 4.04. IR (cm⁻¹): ν(NH) 3295 w, 3251 m, 3159 w. Data for anti-3b (minor isomer, extracted from the mixture) are as follows. 1H NMR (400.9 MHz, 20 °C): δ 1.45 (s, 3 H, Me, CMe₂), 1.48 (s, 3 H, Me, CMe₂), 1.70 (br d, 1 H, CH₂, JHH = 10.8 Hz), 2.06 (d, 1 H, CH₂, JHH = 15.2 Hz), 2.20–2.29 (m, 1 H, CH₂, overlapped with one H of CH₃ of the major isomer), 2.29 (s, 3 H, Me, Tol), 2.44–2.55 (m, 1 H, CH₂, overlapped with one H of CH₃ of the major isomer), 2.73 (dd, 1 H, CH, JHH = 14.8, JHH = 9.2 Hz), 4.13 (br d, 1 H, NH, JHH = 11.2 Hz), 4.74 (dd, 1 H, CH, JHH = 8.8, JHH = 6.0 Hz), 5.33 (br d, 1 H, NH, JHH = 11.2 Hz), 5.54 (br d, 1 H, NH, JHH = 10.4 Hz), 6.32–7.55 (m, 23 H, Ph + Ar, overlapped with the aromatic protons of the major isomer). Data for syn-3b (major isomer, extracted from the mixture) are as follows. 1H NMR (400.9 MHz, 20 °C): δ 1.45 (s, 3 H, Me, CMe₂), 1.48 (s, 3 H, Me, CMe₂), 1.70 (br d, 1 H, CH₂, JHH = 10.8 Hz), 2.06 (d, 1 H, CH₂, JHH = 15.2 Hz), 2.20–2.29 (m, 1 H, CH₂, overlapped with one H of CH₃ of the major isomer), 2.29 (s, 3 H, Me, Tol), 2.44–2.55 (m, 1 H, CH₂, overlapped with one H of CH₃ of the major isomer), 2.73 (dd, 1 H, CH, JHH = 14.8, JHH = 9.2 Hz), 4.13 (br d, 1 H, NH, JHH = 11.2 Hz), 4.74 (dd, 1 H, CH, JHH = 8.8, JHH = 6.0 Hz), 5.33 (br d, 1 H, NH, JHH = 11.2 Hz), 5.54 (br d, 1 H, NH, JHH = 10.4 Hz), 6.32–7.55 (m, 23 H, Ph + Ar, overlapped with the aromatic protons of the minor isomer). Data for both isomers are as follows. 1H NMR (100.8 MHz, 20 °C): δ 2.07 (Me, Tol, major), 2.08 (Me, Tol, minor), 25.9 (Me, CMe₂, major), 27.4 (Me, CMe₂, major), 33.8 (CH₂, minor), 34.8 (Me, CMe₂, minor), 34.8 (Me, CMe₂, minor), 41.4 (CH₂, major), 46.5 (CH₃, minor), 47.2 (CH₃, major), 52.6 (CMe₂, major), 53.0 (CMe₂, minor), 84.6 (CH₂, minor), 86.6 (CH₂, major), 87.1 (C, minor), 93.7 (CH, major), 188.8 (CH, major), 119.8 (CH, minor), 119.9 (q, CF₃, JCF₃ = 318.8 Hz, 124.1 (C, major), 126.3 (CH), 126.4 (CH), 126.5 (CH), 126.7 (C, major), 127.1 (CH), 127.2 (CH), 127.3 (CH), 127.4 (CH), 127.6 (CH), 127.7 (CH), 127.8 (CH), 127.9 (CH), 128.0 (CH), 128.1 (CH), 128.1 (CH), 128.4 (CH), 128.6 (CH), 128.7 (CH), 129.0 (CH), 129.7 (CH), 129.8 (CH), 130.0 (CH), 131.5 (CH), 131.9 (CH), 132.7 (CH), 133.1 (C, major), 133.6 (C, minor), 134.1 (C, minor), 134.9 (CH), 135.7 (C, major), 137.7 (C, major), 138.2 (C, minor), 138.5 (CH, minor), 138.8 (C, major), 139.0 (C, major), 139.4 (C, minor), 139.6 (C, major), 139.7 (C, major), 139.9 (C, major), 140.8 (C, major), 141.2 (C, major).
in dry toluene (10 mL), under a nitrogen atmosphere. The mixture was heated at 100 °C for 12 h. Decomposition to metallic palladium was observed. The solvent was removed, and CH2Cl2 (20 mL) was added to the residue. The resulting suspension was filtered through a plug of Celite, the filtrate was concentrated to ca. 1 mL, and air-dried to give a yellow solid. The resulting suspension was added to a solution of palladium chloride (250 mg, 0.308 mmol) in CH2Cl2 (10 mL), under a nitrogen atmosphere. The mixture was heated at 65 °C for 12 h. The resulting suspension was filtered through a plug of Celite, the yellow solid was removed from the filtrate, and Et2O (20 mL) was added. The resulting suspension was filtered, and the solid was washed with Et2O (2 x 5 mL) and air-dried to give complex \( \text{C}_8\text{H}_8\text{N}_2\) as a yellow solid. Yield: 258 mg, 0.416 mmol, 67%. Ms: 182 °C dec. Anal. Calc. for \( \text{C}_8\text{H}_8\text{N}_2\): C, 80.46; H, 5.82; N, 13.72. Found: C, 80.34; H, 5.71; N, 13.81.

**Synthesis of \( \text{C}_8\text{H}_8\text{N}_2\).** In a Carius tube, KO'Bu (250 mg, 2.04 mmol) was added to a solution of \( \text{C}_8\text{H}_8\text{N}_2\) (120 mg, 0.209 mmol) in dry toluene (10 mL), under a nitrogen atmosphere. The mixture was heated at 100 °C for 12 h. Decomposition to metallic palladium was observed. The solvent was removed, and EtO (20 mL) was added to the residue. The suspension was filtered through a plug of Celite, and the solvent was removed from the filtrate to give crude 4b as an oily residue, which was characterized by HR-NMR. Data for 4b are as follows: \( \text{H} \) NMR (400 MHz): \( \delta \) 0.99 (br s, 2 H, NH), 1.04 (s, 3 H, Me, CM3e), 1.09 (s, 3 H, Me, CM3e), 2.34, 2.54 (AB system, 2 H, CH2Ar, \( \frac{J_{HH}}{2} = 13.6 \) Hz, 6.20 (d, 1 H, CH =, \( \frac{J_{HH}}{2} = 15.6 \) Hz, 6.81–6.85 (m, 2 H, 6.96–7.00 (m, 3 H, 7.03 (d, 1 H, CH=, \( \frac{J_{HH}}{2} = 16.0 \) Hz), 7.10–7.47 (m, 14 H). Crude 4b was dissolved in CH2Cl2 (5 mL), HOTH (0.05 mL, 0.565 mmol) was added, and the resulting solution was stirred for 30 min. The solvent was concentrated to ca. 1 mL, EtO (20 mL) was added, and the mixture was cooled to 0 °C. The resulting suspension was filtered, and the solid was washed with EtO (2 x 5 mL) and air-dried to give the salt \( \text{C}_8\text{H}_8\text{N}_2\) as a colorless solid. Yield: 63 mg, 0.105 mmol, 50%. Mp: 131 °C. \text{NMR} (\( \frac{1}{2} \text{CHCl}_3 \)): 30.52 (M + CF\text{SO}_3\text{H}), 30.52 (M + CF\text{SO}_3\text{H}), 30.52 (M + CF\text{SO}_3\text{H}). IR (cm\(^{-1}\)) e (NH) 3313 w, 3250 w.1H NMR (300.1 MHz): \( \delta \) 0.82 (br d, 1 H, NH2, \( \frac{J_{HH}}{2} = 9.6 \) Hz), 0.95 (br d, 1 H, CH, nor, \( \frac{J_{HH}}{2} = 10.2 \) Hz), 1.07 (br d, 1 H, CH, nor, \( \frac{J_{HH}}{2} = 7.5 \) Hz), 1.12 (s, 3 H, Me, CM3e), 1.20–1.27 (m, 2 H, CH2, nor), 1.37–1.50 (m, 2 H, CH2, nor), 1.64 (s, 3 H, Me, CM3e), 2.05 (br d, 1 H, CH, nor, \( \frac{J_{HH}}{2} = 9.9 \) Hz), 2.14 (br s, 1 H, CH, nor), 2.20 (br d, 1 H, CH, nor, \( \frac{J_{HH}}{2} = 9.6 \) Hz), 2.35 (s, 3 H, Me=C=), 2.57 (d, 1 H, CH2Ar, \( \frac{J_{HH}}{2} = 12.9 \) Hz), 3.09 (br s, 1 H, CH, nor), 3.65 (d, 1 H, H5, \( \frac{J_{HH}}{2} = 7.8 \) Hz), 3.96 (d, 1 H, CH, nor, \( \frac{J_{HH}}{2} = 12.9 \) Hz), 6.67 (d, 1 H, H6, \( \frac{J_{HH}}{2} = 7.8 \) Hz), 6.76 (m, 1 H, H5), 7.01 (m, 2 H, H4 + H3), 7.18–7.25 (m, partially obscured by the resonance of CHCl3), 3.74 (br d, 2 H, o-H, \( \frac{J_{HH}}{2} = 7.8 \) Hz). \text{C} NMR (75.5 MHz): \( \delta \) 21.5 (CH3), 27.9 (Me=C=), 28.5 (CH2, nor), 28.9 (CH2, nor), 30.7 (Me, CM3e), 30.9 (Me, CM3e), 37.3 (CH2, nor), 40.1 (CH3, nor), 41.1 (CH3, nor), 48.1 (C8, nor), 68.7 (CH3), 77.8 (C7), 107.7 (C7), 126.3 (CH5), 126.7 (CH4), 126.8 (p-CH3), 131.0 (br s, CH6 or o-CH of Ph), 131.1 (CH6 or o-CH of Ph), 132.7 (C8), 135.2 (C7), 138.6 (i-C or Ph), 142.6 (C7). The \text{C} resonance corresponding to o-CH of Ph was overlapped with the signal of CH6 or o-CH.
Sustainability of 8f. In a Carius tube, KO\textsubscript{Bu} (50 mg, 0.445 mmol) was added to a solution of complex 7f (120 mg, 0.228 mmol) in dry CH\textsubscript{2}Cl\textsubscript{2} under an N\textsubscript{2} atmosphere (10 mL), and the mixture was heated at 78 °C for 3 days. Deposition of metallic palladium was observed. The solvent was removed, n-pentane (20 mL) was added, and the mixture was filtered through a plug of Celite. The solvent was removed from the filtrate, the residue was dissolved in Et\textsubscript{2}O (10 mL), and HOTF (0.01 mL, 0.113 mmol) was added. The resulting suspension was filtered, and the solid was washed with Et\textsubscript{2}O (2 × 2 mL) and air-dried to give compound 8f as a colorless solid. Yield: 143 mg, 0.263 mmol, 94%. Mp: 178 °C. Analytical data for 8f: exact mass calculated for C\textsubscript{25}H\textsubscript{32}F\textsubscript{3}NO\textsubscript{9}S (579.592): C, 51.80; H, 5.56; N, 2.41; S, 5.53. Found: C, 51.80; H, 5.47; N, 2.42; S, 5.51.

Synthesis of 9f. TIOTf (84 mg, 0.237 mmol) was added to a solution of complex 7f (125 mg, 0.237 mmol) in acetone (15 mL), and the mixture was stirred at room temperature for 12 h under an CO\textsubscript{2} atmosphere, using a toy balloon. Decomposition to metallic palladium was observed. The suspension was filtered through a plug of Celite, the filtrate was concentrated to ca. 1 mL, and Et\textsubscript{2}O (20 mL) was added. The suspension was filtered, and the solid was washed with Et\textsubscript{2}O (2 × 5 mL) and air-dried to give complex 9f as a yellow bright solid. Yield: 247 mg, 0.469 mmol, 75%. Method B. In a Carius tube, a solution of dimethyl acetylenedicarboxylate (65 µL, 0.529 mmol) and 2-norborene (50 mg, 0.531 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (5 mL) was added to a solution of palladacycle B (150 mg, 0.312 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (15 mL), and the mixture was heated at 65 °C for 8 h. The resulting solution was filtered through a plug of Celite, the filtrate was concentrated to ca. 2 mL, and Et\textsubscript{2}O (20 mL) was added. The suspension was filtered, and the solid was washed with Et\textsubscript{2}O (2 × 5 mL) and air-dried to give complex 9f as a yellow bright solid. Yield: 90 mg, 0.171 mmol, 33%. Method C. In a Carius tube, KO\textsubscript{Bu} (50 mg, 0.445 mmol) was added to a solution of complex 7f (120 mg, 0.228 mmol) in dry CH\textsubscript{2}Cl\textsubscript{2} under an N\textsubscript{2} atmosphere (10 mL), and the mixture was heated at 78 °C for 3 days. Decomposition to metallic palladium was observed. The solvent was removed, n-pentane (20 mL) was added, and the mixture was filtered through a plug of Celite. The solvent was removed from the filtrate, the residue was dissolved in Et\textsubscript{2}O (10 mL), and HOTF (0.01 mL, 0.113 mmol) was added. The resulting suspension was filtered, and the solid was washed with Et\textsubscript{2}O (2 × 2 mL) and air-dried to give compound 9f as a colorless solid. Yield: 143 mg, 0.263 mmol, 94%. Mp: 178 °C. Analytical data for 9f: exact mass calculated for C\textsubscript{25}H\textsubscript{32}F\textsubscript{3}NO\textsubscript{9}S (579.592): C, 51.80; H, 5.56; N, 2.41; S, 5.53. Found: C, 51.80; H, 5.47; N, 2.42; S, 5.51.

Synthesis of 9g. In a Carius tube, KO\textsubscript{Bu} (50 mg, 0.445 mmol) was added to a solution of complex 7f (120 mg, 0.228 mmol) in dry CH\textsubscript{2}Cl\textsubscript{2} under an N\textsubscript{2} atmosphere (10 mL), and the mixture was heated at 78 °C for 3 days. Decomposition to metallic palladium was observed. The solvent was removed, n-pentane (20 mL) was added, and the mixture was filtered through a plug of Celite. The solvent was removed from the filtrate, the residue was dissolved in Et\textsubscript{2}O (10 mL), and HOTF (0.01 mL, 0.113 mmol) was added. The resulting suspension was filtered, and the solid was washed with Et\textsubscript{2}O (2 × 2 mL) and air-dried to give compound 9g as a colorless solid. Yield: 143 mg, 0.263 mmol, 94%. Mp: 178 °C. Analytical data for 9g: exact mass calculated for C\textsubscript{25}H\textsubscript{32}F\textsubscript{3}NO\textsubscript{9}S (579.592): C, 51.80; H, 5.56; N, 2.41; S, 5.53. Found: C, 51.80; H, 5.47; N, 2.42; S, 5.51.
with n-pentane (2 × 5 mL) and air-dried to give the compound 10c as a colorless solid. Yield: 84 mg, 0.152 mmol, 94%. Mp: 160 °C. C_{12}H_{28}N_{2}O_4 (571.5 mol^-1 cm^-3): 117.1 (c = 5.00 × 10^-4 M). Compound 10c was hygroscopic, and no satisfactory elemental analysis could be obtained. ESI-HRMS (m/z): exact mass calc for C_{28}H_{34}NO_{4} 484.25090 [M - CF_{3}SO_{3}] +: found, 484.2509. IR (cm^-1): ν(NH) 3486 br; ν(CO) 1715 vs, 1626 s. H NMR (500 MHz, 1 CH_{3}OD, 5.12 ppm): 5.12 (d, 1 H, CH, nor, 3 J_{HH} = 3.6 Hz), 3.73 (s, 3 H, MeO), 3.43 (d, 1 H, CH2Ar, 2 J_{HH} = 10.0 Hz), 6.46 (br s, 1 H, CH, nor). 13C{1H} NMR (125 MHz): δ 22.9 (Me_{2}C), 58.2 (CH_{7}), 89.7 (C_{8}), 127.1 (CH_{5}), 127.6 (C_{6}).

Synthesis of 10d and 9d. In a Carius tube, TIOTF (50 mg, 0.141 mmol) was added to a solution of complex 7d·1/2CHCl_{3} (75 mg, 0.124 mmol) in acetonitrile (15 mL), and the mixture was stirred for 2 h. CHCl_{3} was bubbled through the suspension for 2 min, and the mixture was filtered through 1 atm. The tube was sealed, and the mixture was stirred at room temperature for 15 h. Dehydration of the organic suspension was achieved by two filtration through a plug of Celite, the solvent was removed from the filtrate, and EtO (20 mL) was added. The resulting suspension was filtered through a plug of Celite, and the filtrate was concentrated to ca. 1 mL, and n-pentane (20 mL) was added. The resulting suspension was filtered, and the solid was washed with n-pentane (2 × 5 mL) and air-dried to give the compound 10d as a colorless solid. Yield: 60 mg 0.100 mmol, 81%. Mp: 122 °C. C_{36}H_{52}N_{4}O_{4} (854.8 mol^-1 cm^-3); 78.3 (c = 7.4 × 10^-4 M). Compound 10d was hygroscopic, and no satisfactory elemental analysis could be obtained. ESI-HRMS (m/z): exact mass calc for C_{36}H_{52}N_{4}O_{4} 848.42820 [(M - CF_{3}SO_{3})^+] +; found, 848.4284. IR (cm^-1): ν(NH) 3486 br; ν(CO) 1715 vs, 1626 s. H NMR (500 MHz, 1 CH_{3}OD, 5.12 ppm): 5.12 (d, 1 H, CH, nor, 3 J_{HH} = 3.4 Hz), 3.73 (s, 3 H, MeO), 3.43 (d, 1 H, CH2Ar, 2 J_{HH} = 10.0 Hz), 6.46 (br s, 1 H, CH, nor). 13C{1H} NMR (125 MHz): δ 22.9 (Me_{2}C), 58.2 (CH_{7}), 89.7 (C_{8}), 127.1 (CH_{5}), 127.6 (C_{6}).
Relevant crystallographic data, details of the refinements, and details (including symmetry operators) of hydrogen bonds for the compounds anti-1a, anti-1b, syn-1b, anti-2a-CH2Cl2, syn-2a, anti-2b-CHCl3, syn-2b, syn-3b-CH2Cl2, 6b-H2O, 7c-CHCl3, 7d-1/2CHCl3, 7f, 8f, 9d, 9f-Et2O, and 10c-H2O are given in the Supporting Information.

### ASSOCIATED CONTENT

#### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.organomet.0c00787.

For anti-1a, anti-1b, syn-1b, anti-2a-CH2Cl2, syn-2a, anti-2b-CHCl3, syn-2b, syn-3b-CH2Cl2, 6b-H2O, 7c-CHCl3, 7d-1/2CHCl3, 7f, 8f, 9d, 9f-Et2O, and 10c-H2O, relevant crystallographic data, details of the refinements, details of hydrogen bonds (including symmetry operators), and NMR spectra (PDF)

### Accession Codes

CCDC 2047166–2047181 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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#### Notes

The authors declare no competing financial interest.

### ACKNOWLEDGMENTS

We thank the Ministerio de Ciencia, Innovación y Universidades (Spain), FEDER (Project PGC2018-100719-B-I00), and Fundación Séneca (19890/GERM/15) for financial support.

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