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Palladium-Mediated Functionalization of Benzofuran and Benzothiophene Cores

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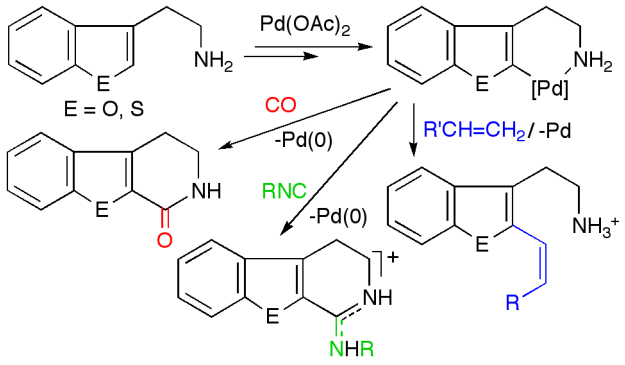


ABSTRACT

The palladation reactions of 2-heteroaromatic primary phenethylamines bearing a benzofuran and benzothiophene nuclei have been studied. We have assessed the reactivity of the corresponding dimeric six-membered palladacycles (arising from C–H metalation) toward neutral ligands and unsaturated species. The insertion reactions of isocyanides into the Pd–C bond of the aforementioned palladacycles allowed the isolation of the corresponding iminoacyl intermediates, which could later be decomposed to give the amidine derivatives containing these relevant heterocyclic cores. In contrast, the carbonylation and alkenylation reactions led to straightforward formation of lactams and alkenylated organic derivatives.

Interestingly, an unusual hydrogen-bond-promoted *E*-to-*Z* isomerization equilibrium of the resulting olefins was observed. Furthermore, we have studied the conditions to perform the alkenylation of the *N*-Boc derivatives of these substrates in a catalytic fashion. All the organometallic complexes (arising from the C–H activation of the heteroaromatic cores and insertion of isocyanides) and organic products (arising form the decomposition reactions) have been fully characterized, including the X-ray crystal structures of several organometallic and organic derivatives.

INTRODUCTION

Heteroaromatic compounds occupy a privileged position within the chemical sciences because of their numerous applications in functional materials and medicinal chemistry. More specifically, benzofuran and benzothiophene cores have attracted great attention due to their widespread presence in natural products, biologically active compounds and pharmaceuticals.[1] For instance, these nuclei are present in compounds that exhibit antiinflamatory, antimicrobial, antidepressant or anticancer activities to name a few. Some marketed drugs include raloxifene, zileuton, or amiodarone.

The importance of these heteroaromatic cores has prompted the development of synthetic methodologies to either construct these scaffolds from different precursors, or to functionalize the different positions within the heteroaromatic nuclei. As happens in many other aspects of chemistry, transition-metal-mediated or -catalyzed reactions constitute an extraordinarily useful tool to achieve a wide structural diversity in the substitution pattern of benzofuran and benzothiophene cores. Palladium has proven especially versatile to perform a broad range of cross coupling reactions involving these heteroaromatic scaffolds.[2,3,4-6]

We are particularly interested in the functionalization of arene/heteroarene nuclei bearing a tethered 2-aminoethyl moiety ($ArCH_2CH_2NH_2$),[7,8] since this type of structure is

present in many compounds with biological relevance, such as neurotransmitters (i.e., dopamine or triptamine), aminoacids (i.e., phenylalanine or tryptophan), or marketed psycoactive drugs (i.e., the phenethylamine scaffold family). For these reasons we set to study the functionalization of the benzofuran and benzothiophene cores bearing a 2-ethylamino substituent at the 3-position by means of a C–H palladation/functionalization sequence.

To our knowledge, very few palladacycles derived from the benzofuran or benzothiophene cores have been isolated, and they are mainly metalated at the 3-position of the heteroaromatic ring (see Chart 1 in the Experimental Section for the numbering scheme). These examples included: (1) For the benzofuran nucleus: (1a) *C,N*-,[9] *C,S*,-[10,11] or *C,Se*-five-membered palladacycles[10] metalated at C3 position; and (1b) *C,N*-six-membered palladacycles metalated at C3.[12] (2) For the benzothiophene nucleus: (2a) *C,N*-five-membered palladacycles metalated at C3, where the nitrogen atom belongs to an imine[13] or a pyridine moiety,[14] (2b) *S,C,N*-pincer derivatives containing two five-membered rings,[15] and (3b) *C,N*-five- or six-membered palladacycles metalated at C2 position, being the nitrogen part of an imine fragment.[12,16]

In this article we (1) describe the synthesis of unprecedented palladacycles containing 2-aminoethyl-benzofuran and benzothiophene and (2) study the reaction of the new metallacycles toward unsaturated molecules such as CO, isocyanides and alkenes. In all cases, decomposition of the organometallic intermediates arising from the insertion of the unsaturated species into the Pd–C bond afforded interesting organic derivatives. Finally, we reported also the catalytic alkenylation of the *N*-Boc protected starting amines.

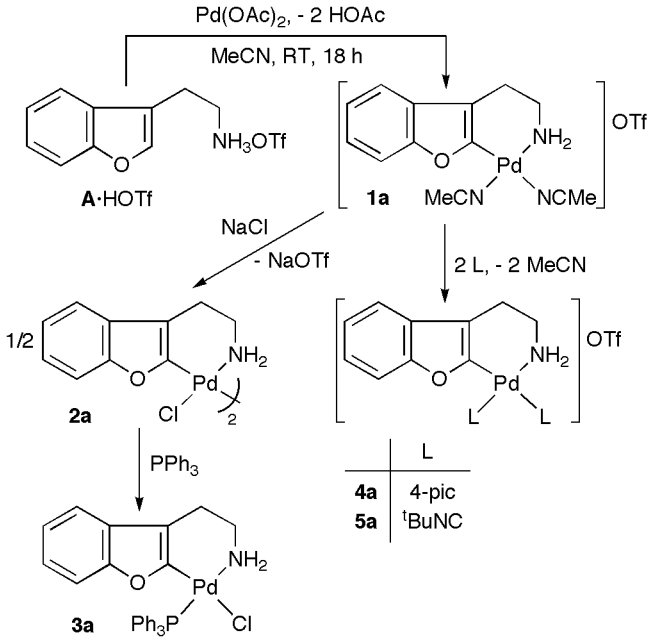
RESULTS AND DISCUSSION

Synthesis of the Cyclometalated Complexes Containing the Benzofuran and Benzothiophene Cores. The cyclopalladation of 2-(benzofuran-3-yl) and 2-(benzothiophene-

3-yl) ethanamines occurred under mild conditions, if the appropriate starting materials were selected. In both cases, the corresponding amoniums salts (triflate for the amine containing the benzofuran nucleus and chloride for the benzothiophene core) underwent C–H activation at 2-position of the heteroaromatic ring when treated with Pd(OAc) in acetonitrile, at room temperature.

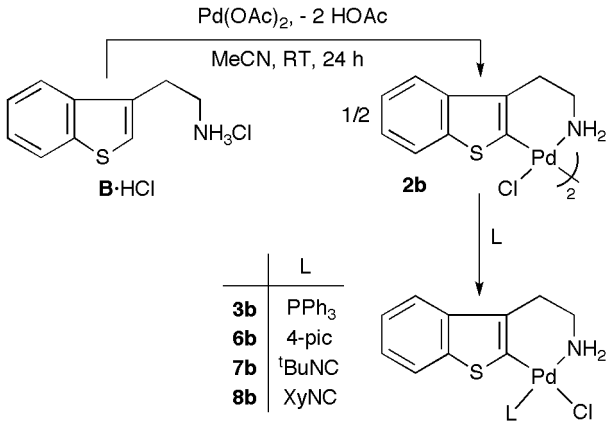
2-(Benzofuran-3-yl)ethanaminium triflate (**A**·HOTf) reacted with $Pd(OAc)_2$ in a 1:1 molar ratio to give HOAc and the cyclometalated solvento-complex [Pd{κ^2*C,N*-$(C_8H_4O)CH_2CH_2NH_2$-3}$(NCMe)_2$]OTf (**1a**; Scheme 1), which further reacted with NaCl to afford a yellow solid that precipitated from the reaction mixture. The IR and ^{1}H NMR spectra of this solid suggested the formulation [Pd_2{κ^2*C,N*-$(C_8H_4O)CH_2CH_2NH_2$-3}$_2$(μ-Cl)$_2$]·2MeCN (**2a**·2MeCN), although other formulations cannot be ruled out. Complex **2a** was obtained in analytically pure form by recrystallization of **2a**·2MeCN from acetone. Complex **2a**·2MeCN reacted with PPh_3 in a 1:2 molar ratio to give the mononuclear phosphino adduct [PdCl{κ^2*C,N*-$(C_8H_4O)CH_2CH_2NH_2$-3}(PPh_3)] (**3a**). For the synthesis of cationic derivatives, complex **1a** was used as starting material. Thus, when 4-methyl-pyridine (4-pic) or ^{t}BuNC was added to a solution of **1a** (molar ratio 2:1) in acetonitrile or CH_2Cl_2, the complex [Pd{κ^2*C,N*-$(C_8H_4O)CH_2CH_2NH_2$-3}$(L)_2$]OTf was isolated in moderate to good yield (L = 4-pic (**4a**; 62%), ^{t}BuNC (**5a**; 74%); Scheme 1).

Scheme 1. Synthesis of Cyclopalladated Derivatives of 2-(Benzofuran-3-yl)ethanamine



To prepare analogous complexes containing the benzothiophene ring, 2-(benzothiophene-3-yl)ethanaminium chloride (**B**·HCl) was reacted with $Pd(OAc)_2$ in a 1:1 molar ratio, in acetonitrile, at room temperature, to render HOAc and the cyclometalated complex $[Pd_2\{\kappa^2C,N\text{-}(C_8H_4S)CH_2CH_2NH_2\text{-}3\}_2(\mu\text{-}Cl)_2]\cdot 2MeCN$ (**2b**·2MeCN; Scheme 2). Complex **2b**·2MeCN reacted with neutral ligands (L) in a 1:2 molar ratio to give the mononuclear adducts $[PdCl\{\kappa^2C,N\text{-}(C_8H_4S)CH_2CH_2NH_2\text{-}3\}(L)]$ (L = PPh_3, **3b**; 4-pic, **6b**; ^{t}BuNC, **7b**; XyNC, **8b**; Scheme 2).

Scheme 2. Synthesis of Cyclopalladated Derivatives of 2-(Benzothiophene-3-yl)ethanamine



As mentioned in the Introduction, no palladacycles derived from a primary arylalkylamine containing either the benzofuran or the benzothiophene ring have been described previously. Moreover, there are only two precedents of similar *C*,*N*-palladacycles with the metal at the C3 position of the benzothiophene ring, and in both cases, the nitrogen atom belong to an imine fragment.[12,16]

Structure of the Cyclometalated Complexes Containing the Benzofuran and Benzothiophene Cores. The ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra of complexes **1a** and **2a,b** clearly showed that cyclometalation had taken place. Thus, the ^{1}H NMR signal corresponding to H2 of the starting material (**A·HOTf**: 7.88 (s); **B·HCl**: 7.59 (s) ppm) disappeared upon metalation.

Table 1. Selected Bond Lengths (Å) and Angles (deg) within the Coordination Sphere of Pd(II) for complexes **3a**·Et_2O, **3b**, **6b**·1/6CH_2Cl_2, **7b** and **8b·**1/4CH_2Cl_2·1/4Et_2O

Compound	Bond lengths (Å)				Angles (deg)
	Pd–N(1)	Pd–C(1)	Pd–L	Pd–Cl(1)	C(1)–Pd–N(1)
3a·Et_2O (L = P1)	2.1176(15)	1.9656(17)	2.2501(5)	2.3707(4)	88.99(7)
3b (L = P1)	2.0994(11)	1.9797(13)	2.2599(4)	2.3699(4)	88.35(5)
6b·1/6CH_2Cl_2 (L = N11)	2.041(4)	1.991(5)	2.051(4)	2.4314(13)	89.27(18)
7b (L = C11)	2.0659(19)	1.985(2)	1.943(2)	2.3984(5)	90.00(8)
8b·1/4CH_2Cl_2·1/4Et_2O (L = C12)	2.0609(16)	1.9900(17)	1.9439(18)	2.4073(5)	89.28(7)

The crystal structures of complexes **3a**·Et_2O, **3b**, **4a**, **6b**·1/6CH_2Cl_2, **7b** and **8b·**1/4CH_2Cl_2·1/4Et_2O (Figures 1–6) have been determined by X-ray diffraction. The asymmetric unit of the crystal structures of complexes **6b**·1/6CH_2Cl_2, **7b** and **8b·**1/4CH_2Cl_2·1/4Et_2O contain two (**8b**) or three independent molecules (**6b** and **7b**), along with some crystallization solvent. In all cases, the palladium center displayed a square-planar

geometry (almost perfect for **3a**·Et_2O, **7b** and **8b**·1/4CH_2Cl_2·1/4Et_2O, and slightly distorted for **3b**, **4a**, **6b**·1/6CH_2Cl_2). The metal is coordinated to the carbon (C1) and nitrogen (N1) atoms of the chelated arylalkylamino ligand, forming a six-membered metallacycle with an envelope (**4a**, **6b**·1/6CH_2Cl_2, **7b** and **8b**·1/4CH_2Cl_2·1/4Et_2O) or a twist-boat conformation (**3a**·Et_2O, **3b**). For complexes **3a**·Et_2O, **3b**, **6b**·1/6CH_2Cl_2, **7b** and **8b**·1/4CH_2Cl_2·1/4Et_2O the coordination sphere of the metal is completed with a chloro (Cl1) and the donor atom of a neutral ligand (P1, N11, C11A or C12A). In all cases, the monodentate ligands are placed in *trans* position to the NH_2 group, which is the expected geometry according to the transphobia scale for *C*-/*N*-donor, *C*-/*P*-donor and *C*-/*C*-donor pairs of ligands.[17]

The availability of the crystal structures of four complexes which only differed in the neutral ligand coordinated in *trans* position with respect to the amino group, allows us to compare the Pd–N bond lengths (Table 1), which increased along the sequence **6b**·1/6CH_2Cl_2 < **7b** ≈ **8b**·1/4CH_2Cl_2·1/4Et_2O < **3b** following the trend normally observed for the *trans* influence of these ligands: *N*-donor < *C*(sp)-donor < *P*-donor.[18]

In the cationic complex **4a**, the metal completes its coordination sphere with the nitrogen atoms (N11 and N22) of two picoline ligands. Both pyridine rings are almost perpendicular to the metal coordination plane (88.2 and 75.5º) to avoid steric hindrance. Similarly, for complex **6b**·1/6CH_2Cl_2 the aromatic ring of the 4-picoline is also rotated with respect to the coordination plane of the metal (angle of 59–90º, for the three independent molecules in the asymmetric unit). However, in complex **8b**·1/4CH_2Cl_2, the xylyl ring of the isocyanide ligand is almost co-planar with the coordination plane of the metal (1 and 1.7º for both molecules in the asymmetric unit). This feature allows the existence of intermolecular π–π stacking interactions between the C_6H_4 and Xy rings. The geometrical parameters of the π–π interactions are given in the Supporting Information.

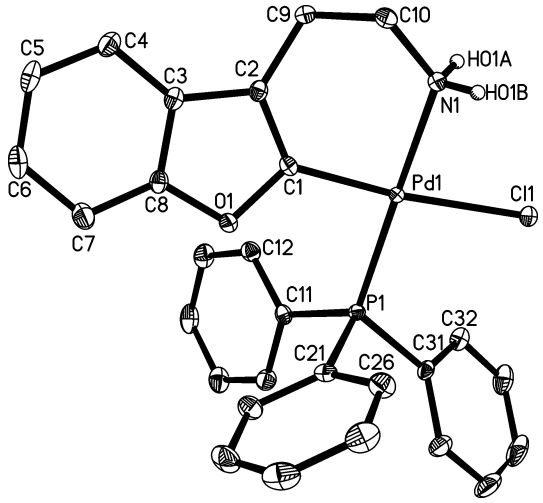


Figure 1. X-ray thermal ellipsoid plot of **3a**·Et_2O (50% probability) along with the labeling scheme. The solvent molecule and the hydrogen atoms bonded to carbon have been omitted for clarity. Selected bond lengths (Å) and angles (deg): Pd(1)–N(1) = 2.1176(15), Pd(1)–Cl(1) = 2.3707(4), Pd(1)–P(1) = 2.2501(5), Pd(1)–C(1) = 1.9656(17); N(1)–Pd(1)–Cl(1) = 84.55(4), Cl(1)–Pd(1)–P(1) = 95.609(17), P(1)–Pd(1)–C(1) = 90.76(5), C(1)–Pd(1)–N(1) = 88.99(7).

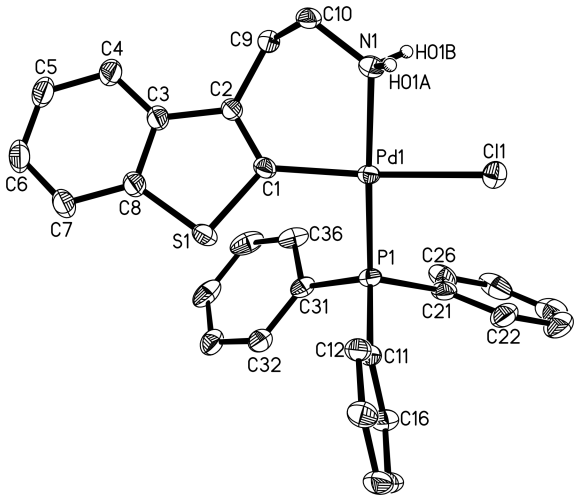


Figure 2. X-ray thermal ellipsoid plot of **3b** (50% probability) along with the labeling scheme. The hydrogen atoms bonded to carbon have been omitted for clarity. Selected bond lengths (Å) and angles (deg): Pd(1)–N(1) = 2.0994(11), Pd(1)–Cl(1) = 2.3699(4), Pd(1)–P(1) = 2.2599(4), Pd(1)–C(1) = 1.9797(13); N(1)–Pd(1)–Cl(1) = 86.66(3), Cl(1)–Pd(1)–P(1) = 92.029(15), P(1)–Pd(1)–C(1) = 93.37(4), C(1)–Pd(1)–N(1) = 88.35(5).

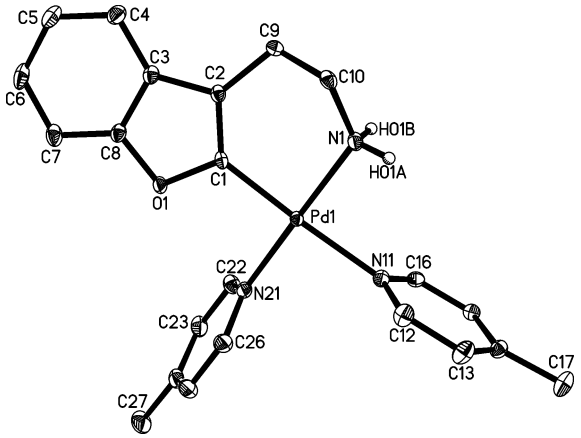


Figure 3. X-ray thermal ellipsoid plot of the cation of **4a** (50% probability) along with the labeling scheme. The hydrogen atoms bonded to carbon have been omitted for clarity. Selected bond lengths (Å) and angles (deg): Pd(1)–N(1) = 2.0565(13), Pd(1)–N(11) = 2.1305(13), Pd(1)–N(21) = 2.0359(13), Pd(1)–C(1) = 1.9619(15); N(1)–Pd(1)–N(11) = 88.14(5), N(11)–Pd(1)–N(21) = 91.10(5), N(21)–Pd(1)–C(1) = 91.76(6), C(1)–Pd(1)–N(1) = 89.01(6).

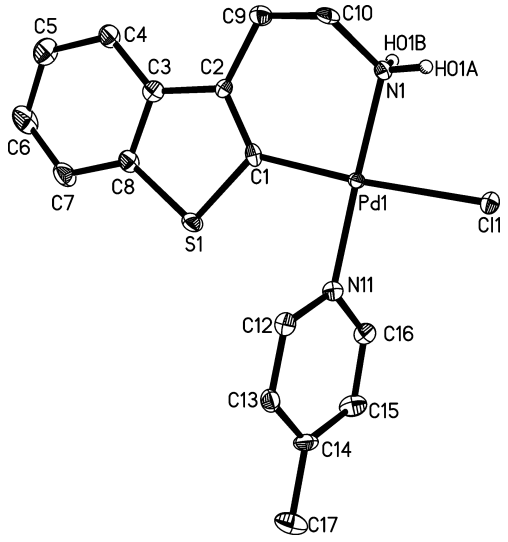


Figure 4. X-ray thermal ellipsoid plot of one (molecule 1) of the three independent molecules of the complex **6b**·1/6CH_2Cl_2 (50% probability) along with the labeling scheme. The crystallization solvent and the hydrogen atoms bonded to carbon have been omitted for clarity. Selected bond lengths (Å) and angles (deg): Pd(1)–N(1) = 2.041(4), Pd(1)–Cl(1) = 2.4314(13),

Pd(1)–N(11) = 2.051(4), Pd(1)–C(1) = 1.991(5); N(1)–Pd(1)–Cl(1) = 86.35(12), Cl(1)–Pd(1)–N(11) = 91.85(12), N(11)–Pd(1)–C(1) = 92.63(18), C(1)–Pd(1)–N(1) = 89.27(18). X-ray thermal elipsoid plots and selected bond lengths (Å) and angles (deg) for the other two independent molecules present in the asymmetric unit (molecules 2 and 3) are given in the Supporting Information.

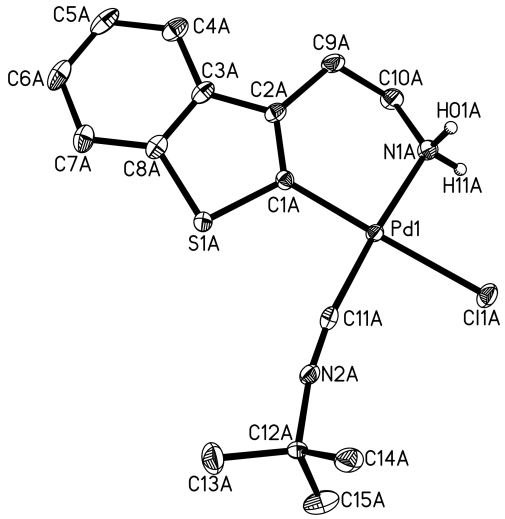


Figure 5. X-ray thermal ellipsoid plot of one (molecule 1) of the three independent molecules of the complex **7b** (50% probability) along with the labeling scheme. The hydrogen atoms bonded to carbon have been omitted for clarity. Selected bond lengths (Å) and angles (deg): Pd(1)–N(1A) = 2.0659(19), Pd(1)–Cl(1A) = 2.3984(5), Pd(1)–C(11A) = 1.943(2), Pd(1)–C(1A) = 1.985(2); N(1A)–Pd(1)–Cl(1A) = 88.21(5), Cl(1A)–Pd(1)–C(11A) = 87.78(6), C(11A)–Pd(1)–C(1A) = 94.01(9), C(1A)–Pd(1)–N(1A) = 90.00(8). X-ray thermal elipsoid plots and selected bond lengths (Å) and angles (deg) for the other two independent molecules present in the asymmetric unit (molecules 2 and 3) are given in the Supporting Information.

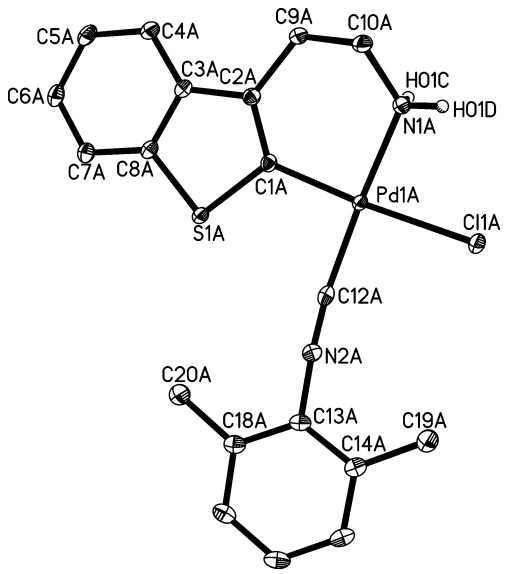


Figure 6. X-ray thermal ellipsoid plot of one (molecule A) of the two independent molecules of the complex **8b**·1/4CH_2Cl_2·1/4Et_2O (50% probability) along with the labeling scheme. The crystallization solvent and the hydrogen atoms bonded to carbon have been omitted for clarity. Selected bond lengths (Å) and angles (deg): Pd(1A)–N(1A) = 2.0609(16), Pd(1A)–Cl(1A) = 2.4073(5), Pd(1A)–C(12A) = 1.9439(18), Pd(1A)–C(1A) = 1.9900(17); N(1A)–Pd(1A)–Cl(1A) = 86.56(5), Cl(1A)–Pd(1A)–C(12A) = 90.51(5), C(12A)–Pd(1A)–C(1A) = 93.62(7), C(1A)–Pd(1A)–N(1A) = 89.28(7). X-ray thermal elipsoid plot and selected bond lengths (Å) and angles (deg) for the other independent molecule present in the asymmetric unit (molecule B) are given in the Supporting Information.

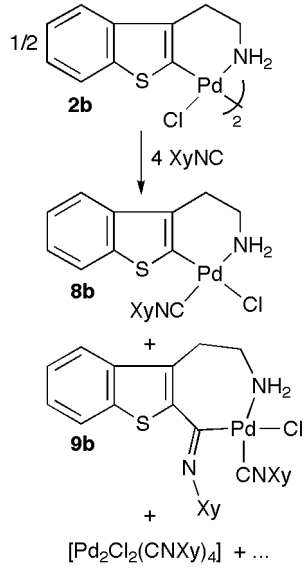
Stoichiometric Functionalization of 2-(Benzofuran-3-yl)- and 2-(Benzothiophene-3-yl)ethanamines. The pharmaceutical relevance of the benzofuran and benzothiophene cores has prompted the development of several methodologies for the functionalization of these moieties via transition metal mediated or catalyzed reactions.[19] Specially interesting are those transformations involving the direct functionalization of a C–H bond of the heteroaromatic core,[5,6,20] via the formation of a M–C bond that subsequently reacts with a coupling partner, for instance, an unsaturated molecule.

Unsaturated species, such as isocyanides, carbon monoxide and alkenes, readily insert into the Pd–C bond of aryl-complexes to afford organometallic iminoacyl,[21] acyl-,[22] and akyl-derivatives[23] or organic compounds upon further decomposition.[21,24] The accepted mechanism of these insertion reactions into the Pd–C bond involves (1) coordination of the unsaturated molecule to the metal center and (2) migratory insertion of the aryl group to the coordinated ligand.[25,26] These organometallic intermediates can be stable enough to be isolated or evolve through a reductive elimination process to afford the corresponding organic derivatives.[21,24]

We have previously applied this methodology (formation of a Pd–C bond, reaction with an unsaturated molecule, and decomposition of the formed organometallic compound) to the stoichiometric synthesis of amidines and amidinium salts, lactams and alkenylated compounds derived from primary benzyl and phenethylalkylamines.[23,27,28] Noteworthy, for these reactions, the catalytic cycle seems to fail, since ortho palladation of primary arylalkylamines does not occur (or is extremely slow) when an excess of the amine is present.[7] Due to their interesting properties, we sought to extend this methodology to the syntesis of heteroarylalkyl amine derivatives containing the benzofuran and benzothiophen nuclei.

Insertion Reactions of Isocyanides into the Pd–C Bond. The dimeric *C*,*N*-palladacycles reacted easily with RNC to afford mononuclear complexes with the isocyanide ligand coordinated in a *cis* position relative to the aryl group. Under adequate reaction conditions (depending of the electronic and steric properties of both the palladacycle and the isocyanide),[21,26] these compounds could evolve to the corresponding iminoacyl complexes, arising from the insertion of the isocyanide into the C–Pd bond. In order to get one of such complexes, we carried out the reaction of palladacycle **2b** with 4 equiv of XyNC (molar ratio Pd:RNC = 1:2; Scheme 3).

Scheme 3. Reaction of XyNC with the Palladacycle Derived from 2-(Benzothiophene-3-yl)ethanamine.



When XyNC was added to a suspension of **2b** in CH_2Cl_2 at room temperature, an orange solution was observed, which quickly changed its color to red, and then to yellow. From the last solution, a yellow solid (**X**) could be isolated, that proved to be a mixture of three products (by ^{1}H NMR; Figure 7): the coordination complex **8b**, the iminoacyl complex **9b** (characterized by X-ray studies, see below) and $[Pd_2Cl_2(CNXy)_4]$ (which showed a very characteristic signal at δ 2.52 ppm). The later compound was the only one isolated when four additional equiv of XyNC were added to the original yellow solution.[27,29]

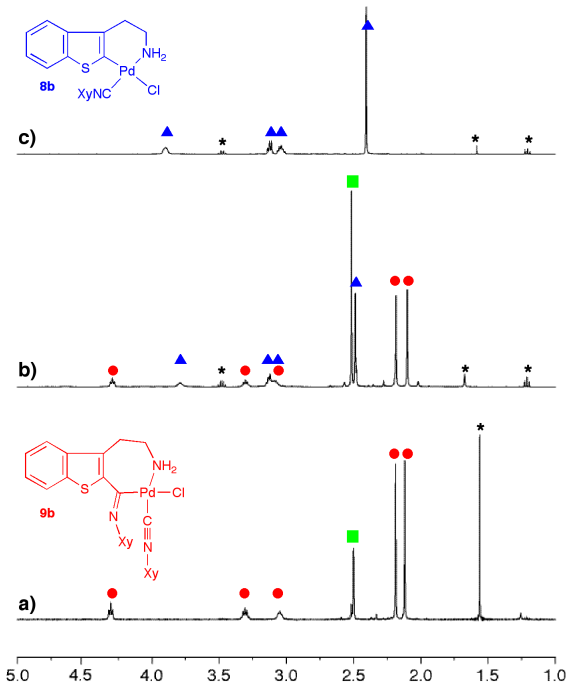
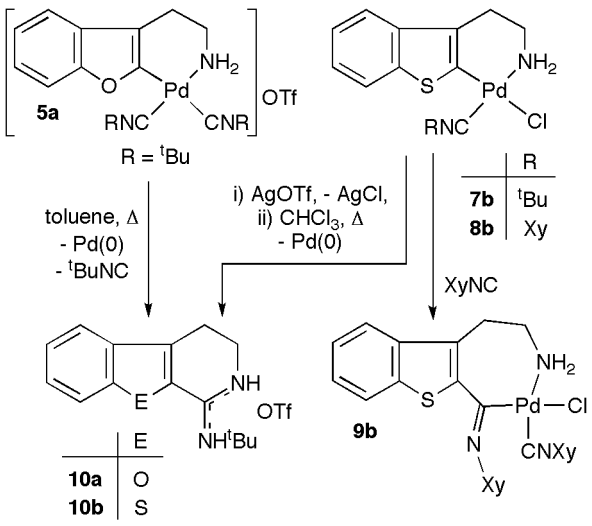


Figure 7. ^{1}H NMR spectra (1–5 ppm; $CDCl_3$) of: a) the iminoacyl complex **9b** (signals denoted by red circles); b) the yellow solid **X**, obtained by reaction of complex **2b** and 4 equiv of XyNC; and c) complex **8b** (signals denoted by blue triangles). The green square corresponds to the signal of $[Pd_2Cl_2(CNXy)_4]$, and the black asteriscks indicate the resonances corresponding to traces of solvents.

Scheme 4. Insertion of RNC into the Pd–C bond of Cyclopalladated Derivatives of 2-(Benzofuran-3-yl) and 2-(Benzothiophene-3-yl)ethanamines.



As we have stated in the previous section, complex **8b** could be isolated in good yield by reacting the starting palladacycle **2**·2MeCN with two equiv of XyNC at 0 ºC (Scheme 1; 74%). At higher temperatures, a variable amount of di-inserted complex **9b** was always obtained. The easy insertion of the isocyanide into the Pd–C bond of **8b** resembles the behavior of the reported palladacycle derived from benzyl methyl sulfide,[30] which underwent rapid isocyanide insertion at room temperature. However, all of our attempts to isolate pure complex **9b** were fruitless. Thus, the reaction of complex **8b** with one equiv of XyNC (under different experimental conditions; Scheme 4) always afforded a mixture of complexes **8b**, **9b** and $[Pd_2Cl_2(CNXy)_4]$ (4:2:1, after 48 h at room temperature). Slow diffusion of Et_2O into a solution of this mixture in CH_2Cl_2 led to the formation of two different types of crystals, which were manually separated: yellow needles, corresponding to complex **8b**, and a few orange blocks, corresponding to the iminoacyl complex **9b**, whose crystal structure was determined by X-ray diffraction studies (Figure 8). The seven-membered metallacycle adopted a twist-boat conformation. The palladium center was coordinated to Cl (Cl1), the NH_2 group (N1), the terminal carbon atom of the isocyanide ligand (C12), and the carbon atom of the inserted isocyanide (C11), in a slightly-distorted square-planar geometry (mean deviation from the coordination plane of Pd(II), 0.043 Å). Both Xy rings are almost parallel (angle between planes of 8º), and rotated 54.7 and 62.3º with respect to the Pd(II) coordination plane, avoiding steric hindrance. Similar features are observed in related iminoacyl derivatives.[28] The discrete molecules of complex **9b** are associated through N–H···Cl hydrogen bonds giving dimers (details, including symmetry operations are given in the Supporting Information).

The ^{1}H NMR of the collected orange blocks, which happened not to be completely separable, corresponded to a mixture of complex **9b** and $[Pd_2Cl_2(CNXy)_4]$. In complex **9b**,

steric hindrance prevents rotation around the Xy–N bond of the inserted isocyanide, and the two Me groups become unequivalent, as well as the meta protons and the meta and ortho carbon atoms of the xylyl ring (as observed in its ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra).

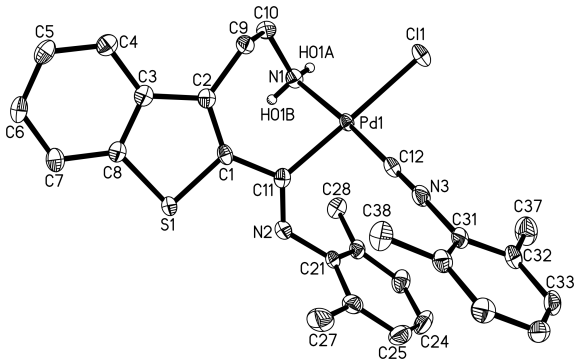


Figure 8. X-ray thermal ellipsoid plot of **9b** (50% probability) along with the labeling scheme. The hydrogen atoms bonded to carbon have been omitted for clarity. Selected bond lengths (Å) and angles (deg): Pd(1)–Cl(1) = 2.4026(8), Pd(1)–N(1) = 2.106(2), Pd(1)–C(11) = 2.002(3), Pd(1)–C(12) = 1.929(3), C(11)–N(2) = 1.273(4), C(12)–N(3) = 1.154(4); Cl(1)–Pd(1)–N(1) = 90.02(7), N(1)–Pd(1)–C(11) = 86.37(10), C(11)–Pd(1)–C(12) = 89.28(11), C(12)–Pd(1)–Cl(1) = 94.47(8), C(1)–C(11)–N(2) = 116.3(2), C(11)–N(2)–C(21) = 124.3(2), Pd(1)–C(11)–N(2) = 126.8(2), Pd(1)–C(12)–N(3) = 179.7(3), C(12)–N(3)–C(31) = 171.7(3).

Our original goal was to employ the iminoacyl complex **9b** to obtain the corresponding amidinium salt, *via* thermal depalladation. However, as we could not develop an adequated synthesis for **9b**, we tried an alternative method to prepare this type of *N*-heterocycle derivative. When complex **7b,** which contained coordinated ^{t}BuNC, an isocyanide less prone than XyNC to undergo polyinsertion reactions, was treated with AgOTf (OTf = O_3SCF_3) and heated in toluene, the amidinium salt **10b** was obtained (50% yield; Scheme 4), along with metallic palladium. The NMR spectra of compound **10b** was in agreement with the proposed structure. Additionally, the crystal structure of **10b** was determined by X-ray diffraction studies (Figure 9). It corresponded to the *Z* isomer, reflecting the thermodynamic

stability of this geometry. The six-membered aza-ring adopted a twisted boat conformation, and the atoms C(10), N(1), C(11), N(2), and C(12) were almost coplanar (mean deviation from the plane 0.021 Å). Delocalization of electron density between the atoms N(1), C(11) and N(2) was confirmed by the similar N(1)–C(11) and N(2)–C(11) bond distances (1.324(4) and 1.323(4) Å, respectively) and the angles around both nitrogen atoms (C(10)-N(1)-C(11), 121.8(3); C(11)–N(2)–C(12), 128.9(3) deg). In compound **10b**, the cationic units were connected between them and to the triflate groups through hydrogen bonds giving layers (see the Supporting Information).

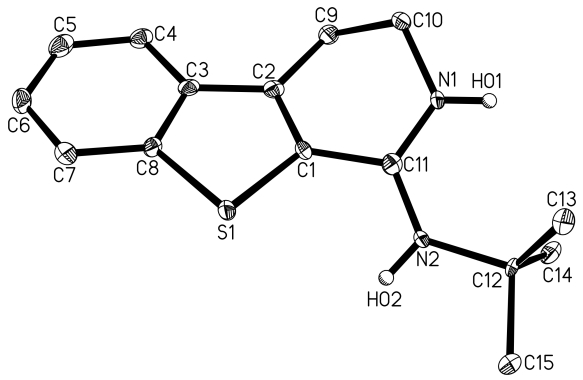


Figure 9. X-ray thermal ellipsoid plot of the cation of compound **10b** (50% probability) along with the labeling scheme. The hydrogen atoms bonded to carbon have been omitted for clarity. Selected bond lengths (Å) and angles (deg): N2–C12 = 1.500(4), N2–C11 = 1.315(2), N1–C11 = 1.323(4), N1–C10 = 1.475(4), C1–C11 = 1.460(4); C11–N2–C12 = 128.9(3), C11–N1–C10 = 121.8(3), N1–C11–N2 = 124.6(3), N1–C11–C1 = 115.4(3), N2–C11–C1 = 120.0(3).

To prepare the *N*-heterocycles derived from the benzofuran ring, the cationic complex **5a** was a more effective starting material. Complex **5a**, heated in toluene al 120 ºC for ca. 18 h, evolved to the amidinium salt **10a** and metallic palladium (Scheme 4).

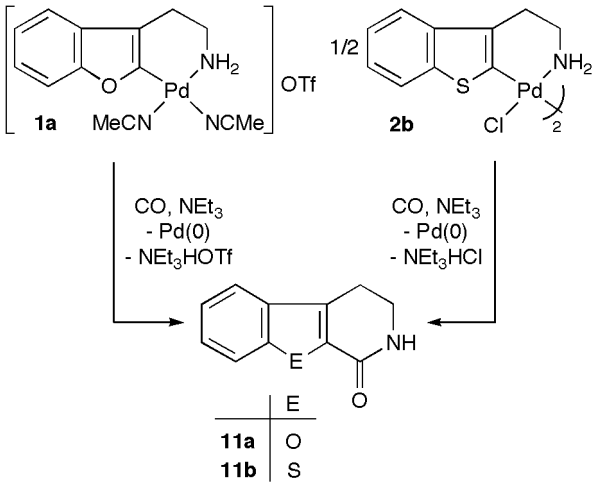
Insertion of Carbon Monoxide into the Pd–C Bond. The reaction of **2b**, in CH_2Cl_2 at 65 ºC, with CO in the presence of NEt_3, afforded Pd(0), $HNEt_3Cl$ and 3,4-dihydro[1]benzothieno[2,3-*c*]pyridin-1(2*H*)-one (**11b**; Scheme 5) in moderate yields (54%). The NEt_3 played a double role in the reaction: it coordinated to Pd(II), improving the solubility of the starting material, and reacted with the HCl formed during the coupling process.

To prepare the lactam derived from the benzofuran ring, the cationic complex **1a** was used as starting material. The solvento-complex **1a** reacted with CO and NEt_3 in $CHCl_3$ for ca. 18 h to afford **11a** and metallic palladium (Scheme 5).

The compounds **11a** and **11b** were characterized by IR and NMR spectroscopy and high-resolution mass spectrometry (HR-ESIMS). The NMR data supported the structures of these compounds, depicted in Scheme 5. The ^{1}H NMR spectra of both lactams exhibited one signal between 6.40 and 7.20 ppm (δ: 7.20 (**11a**), 6.46 ppm (**11b**)), corresponding to the NH proton. In the $^{13}C\{^1H\}$ NMR spectra, the CO group appeared between 161 and 164 ppm (δ: 161.2 (**11a**), 163.9 ppm (**11b**)). In addition, the IR spectra of both compounds showed bands in the region of 1652−1685 cm^{-1}, attributed to ν(C=O).

Chapman et al. reported the synthesis of lactam **11b** in 1970 through cyclization of *N*-ethoxycarbonyl-*2*-(3-benzo[*b*]thienyl)ethanamine with P_2O_5 and $POCl_3$ (Bischler-Napieralski reaction), although no NMR data were provided.[31] Curiously, in spite of its structural interest, no other synthesis has been published since then. To our knowledge, no synthesis of compound **11a** has been reported.

Scheme 5. Insertion of CO into the Pd–C bond of Cyclopalladated Derivatives of 2-(Benzofuran-3-yl) and 2-(Benzothiophene-3-yl)ethanamines.



Insertion of Methyl Acrylate into the Pd–C Bond. When complex **1a** reacted with methyl acrylate (molar ratio 1:4) in $CHCl_3$, at 65 ºC for 18 h, decomposition to metallic palladium took place and the alkenyl derivative *E*-**12a** was isolated in moderate yield (56%; Scheme 6). In acetone solution, *E*-**12a** underwent an isomerization process to render a mixture of *E*-**12a** and *Z*-**12a** (final ratio *E*-**12a**:*Z*-**12a** ca. 1:3, after 18 h at 65 ºC; Scheme 6 and Figure 10). The isolation of the *E* isomer, the kinetically favored product, could be attributed to its insolubility in the reaction media ($CHCl_3$), as isomerization took place in solution (acetone) at room temperature. Both isomers were distinguished by a NOESY experiment carried out on the mixture *E/Z*-**12a**, which showed a correlation between the hydrogen atoms of the double bond for the *Z*-isomer (Scheme 6). No correlation was observed for the *E* isomer.

Scheme 6. Insertion of Methyl Acrylate into the Pd–C Bond of the Palladacycles Derived from 2-(Benzofuran-3-yl) and 2-(Benzothiophene-3-yl)ethanamines.

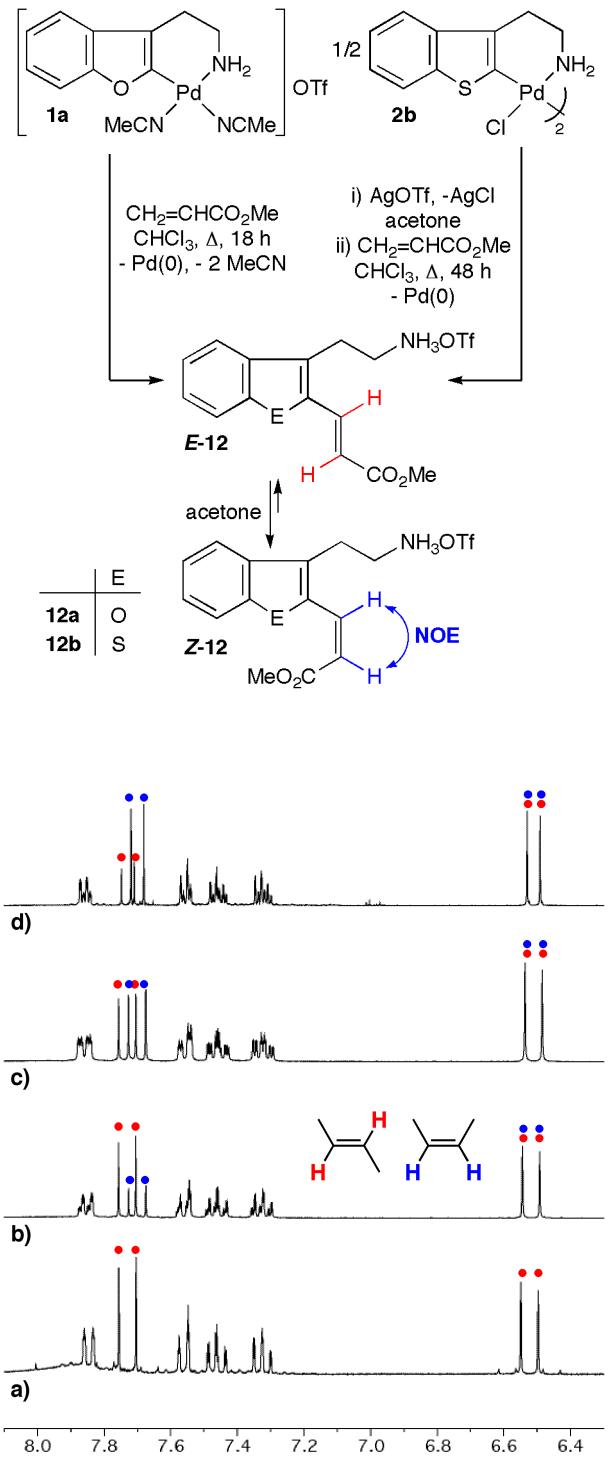
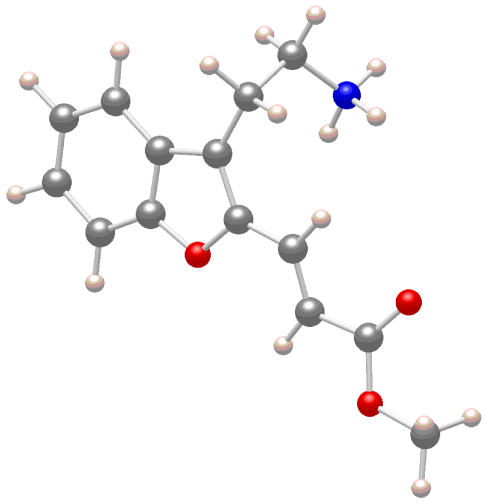


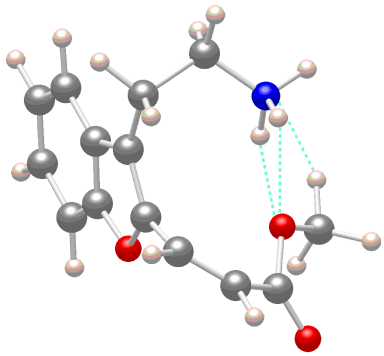
Figure 10. ^{1}H NMR spectra (6.3–8.1 ppm; acetone-d_6) of complex **12a**: a) the crude of the reaction (only *E* isomer); b) recrystallized product from acetone/Et_2O (2:1 mixture of *E*/Z isomers); c) after ca. 4 h at room temperature dissolved in acetone-d_6 (1:1 mixture of *E*/Z isomers); d) after 18 h at 65 ºC dissolved in acetone-d_6 (1:3 mixture of *E*/Z isomers). The red and blue circles correspond to the alkenylic protons of the *E* and *Z* isomers, respectively.

Spectra a, b and c were recorded in a 300 Mz spectrometer, while spectrum d was recorded in a 400 Mz spectrometer

For disubstituted alkenes, generally *E* isomers are more stable than *Z* isomers,[32] and are also the standard outcome products of the Heck-coupling reactions.[33] Thus, this isomerization seemed surprising. We developed optimized 3D molecular structures for the cations of *E*- and *Z*-**12a** with the software Spartan 14 (Figure 11), and the model predicted the *E* isomer to be ca. 29.6 kJ mol^{-1} more stable than the *Z* form. However, the proximity of the OMe substituent on the alkenyl moiety to the NH_3 group in *Z*-**12a** could lead to the formation of hydrogen bonds, which would stabilize this configuration. Noteworthy, the ^1H NMR spectra of both isomers in acetone-d_6 were quite similar, although the CH_2N group in *Z*-**12a** appeared at higher frequencies than the one of *E*-**12a** (*Z*-**12a**: 4.24 ppm; *E*-**12a**: δ 3.59–3.69 ppm), which supported the existence of hydrogen bond involving the adjacent NH_3 group in the former. Unfortunately, the NH_3 groups were not observed in the ^1H NMR after some time in acetone solution.



cation of *E*-**12a**

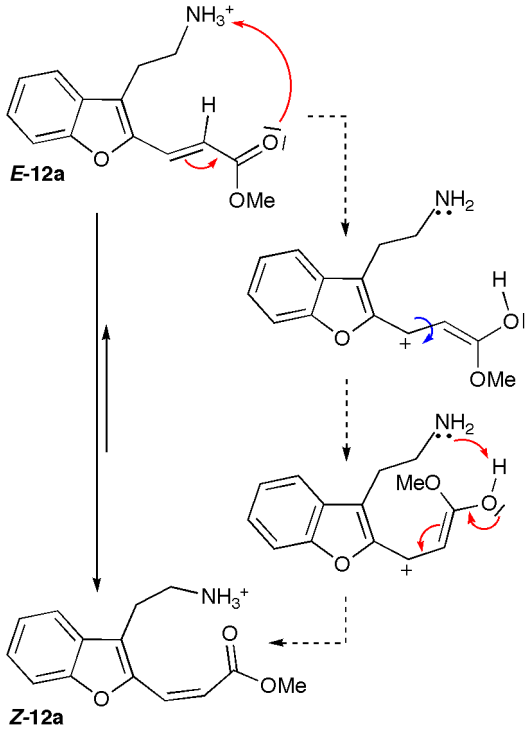


cation of *Z*-**12a**

Figure 11. Optimized 3D molecular models obtained with the software Spartan 14 for the cation of: a) *E*- and b) *Z*-**12a**. In *Z*-**12a**, the possible hydrogen bonds involving the NH_3 group are depicted as dash green lines.

A logical reaction pathway for the isomerization (Scheme 7) would involve: (1) proton transfer from the ammonium group to the carbonyl moiety, rendering a carbocation that could be stabilized by the benzofuranyl group; (2) rotation of the σ C–C bond and (3) regeneration of the ammonium group and restoration of the double C=C bond with *Z* configuration. We have described a similar *E* to *Z* isomerization process promoted by intramolecular hydrogen bond interactions.[34]

Scheme 7. Proposed Mechanism for the Isomerization of **12a**

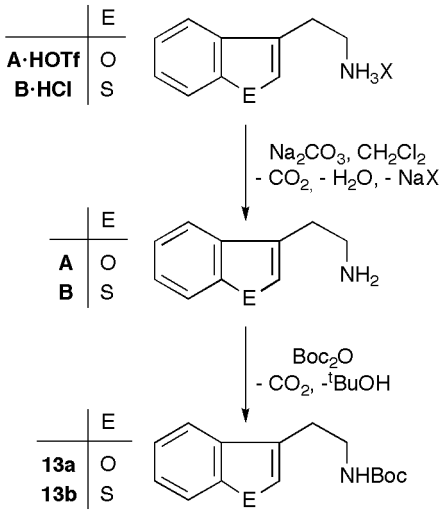


We tried an analogous alkenylation with the palladacycle containing the benzothiophene core. Thus, we carried out the reaction between complex **2b**·2MeCN and AgOTf and, after removing the AgCl formed, we added methyl acrylate (molar ratio

Pd:alkene 1:2) and heated the mixture in $CHCl_3$, at 65 ºC for 48 h. In the reaction media, the alkenyl derivative *E*-**12b** (identified by ^{1}H NMR in acetone-d_6) precipitated along with metallic palladium. Similarly to what happened to *E*-**12a**, in acetone solution *E*-**12b** isomerizated to render a mixture of *E*-**12b** and *Z*-**12b** (final ratio *E*-**12b**:*Z*-**12b** ca. 1:1.3, after 24 h at 65 ºC; Scheme 6). This process was slower for **12b** than for **12a**, likely due to the nature of the heteroatom in the ring.

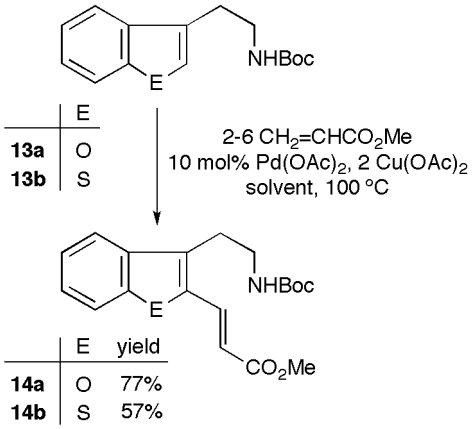
Catalytic Alkenylation of *N*-Substituted Derivatives of 2-(Benzofuran-3-yl)- and 2-(Benzothiophene-3-yl)ethanamine. The Pd-catalyzed arylation and alkynylation at the C2 position of benzofuran and benzothiophene nuclei assisted by suitable directing groups (such as carboxylic acids or thioamides at the 3-position of the heteroarene) have been reported.[4,5,35] Nevertheless, there are no precedents for related directed alkenylation. Furthermore, none of the published studies includes substrates containing a tethered directing amino group at the 3-position of the heterocycle. Notwithstanding, the strong coordination ability of primary amines to Pd hampers the development of catalytic methodologies of substrates containing alkyl-NH_2 moieties as directing groups.[7] Only some specific aryl substrates bearing bulky alkyl groups on the primary amine have been successfully functionalized under Pd-catalysis.[36] On the other hand, the non-directed Pd-catalyzed alkenylation at the C2 position of benzothiophene and benzofuran rings via oxidative coupling with olefins has indeed been reported to occur in a range of different conditions.[3,6] In order to attempt the catalytic alkenylation of the 3-ethylamine-substituted benzofuran and benzothiophene cores, we converted the amines **A** and **B** into their corresponding *N*-Boc derivatives **13a** and **13b** (Boc = *tert*-butoxycarbonyl; Scheme 8).

Scheme 8. Synthesis of *N*-Boc Derivatives



We attempted the Pd-catalyzed C–H alkenylation of substrate **13a** in a range of different conditions (see the S.I. file). A 77% yield of the alkenylated product **14a** was obtained when the reaction was carried out using a 10 mol% of $Pd(OAc)_2$ in 1,2-dichloroethane at 100 ºC in the presence of two equivalents of $Cu(OAc)_2$ as the oxidant and two equivalents of methyl acrylate (Scheme 9). Other combinations of solvents (MeCN, AcOH or toluene) and oxidants (AgOAc or 1,4-benzoquinone) afforded lower yields of the desired compound **14a**. The catalytic alkenylation of substrate **13b** worked better using acetonitrile as solvent instead of 1,2-dichloroethane. The yields of these catalytic transformations are comparable to those reported for the undirected alkenylation of benzofuran and benzothiophene cores.[3,6]

Scheme 9. Optimized conditions for the 2-alkenylation of substrates **13**. For **13a**, solvent = 1,2-dichloroethane, and for **13b**, solvent = acetonitrile. The reported yields were determiend by ^{1}H NMR, using an internal standard.



CONCLUSION

In conclusion, we have investigated the functionalization of benzothiophene and benzofuran cores bearing a tethered aminoethyl moiety, through the palladation of the C–H bond at the C2 position of the ring. The palladation reactions, assisted by the coordination of the pending primary amine moiety, take place under mild conditions if the appropriate ammonium salts were used as starting materials. The insertion reactions of isocyanides and carbon monoxide into the Pd–C bond of the six-membered palladacycles led, upon decomposition of the organometallic intermediates formed, to cyclic amidines and lactams. Under the right conditions, the iminoacyl intermediates arising from the reactions with isocyanides can be isolated. The alkenylation of the starting substrates was studied stoichiometrically, and later carried out catalytically for the *N*-Boc protected amines. Interestingly, the isolated *E*-alkenylated products arising from the Heck-type coupling reactions on the cyclopalladated primary amines evolved to the *Z* isomers in acetone solution.

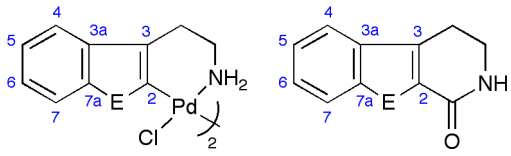
EXPERIMENTAL SECTION

General Considerations, Materials and Instrumentation. Unless otherwise noted, all preparations were carried out at room temperature under atmospheric conditions. Synthesis grade solvents were obtained from commercial sources. All other reagents were obtained from commercial sources and used as received.

Unless otherwise stated, NMR spectra were recorded in $CDCl_3$ on Bruker Avance 300 or 400 spectrometers at 298 K. Chemical shifts are referenced to internal TMS. Signals in the ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra of all complexes were assigned with the help of APT, HMQC and HMBC techniques. The groups 2-(benzofuran-3-yl)ethanamine and 2-(benzo[*b*]thiophen-3-yl)ethanamine are denoted by Ar or by C_8H_4O and C_8H_4S, respectively. Inserted and coordinated XyNC are denoted by $XyNC^{i}$ and $XyNC^{c}$, respectively. Melting points were determined on a Reichert apparatus and are uncorrected. Conductivities were measured with a Crison Micro CM2200 conductimeter. Elemental analyses were carried out with a Carlo Erba 1106 microanalyzer. Infrared spectra were recorded in the range 4000–200 cm^{-1} on a Perkin-Elmer Spectrum 100 spectrophotometer, using Nujol mulls between polyethylene sheets. High resolution ESI mass spectra were recorded on an Agilent 6220 Accurate-Mass TOF LC/MS.

Chart 1 gives the numbering schemes for the new palladacycles and the organic derivatives.

Chart 1. Numbering Schemes for the New Palladium(II) Complexes and the Organic Derivatives[a]



[a] For the convenience of the reader, the notation of the free ligands is maintained in the cyclopalladated complexes.

Synthesis of $(C_8H_5O)CH_2CH_2NH_3OTf$ (A·HOTf). Trifluoromethanesulfonic acid (547 µL, 6.20 mmol) was added dropwise to a cold solution of 2-(benzofuran-3-yl)ethanamine (1000 mg, 6.20 mmol) in ether (20 mL) in an ice bath. The suspension was stirred for 10 min at 0 ºC and filtered. The solid was washed with Et_2O (2 x 5 mL) and air-

dried to afford **A**·HOTf as a colorless solid. Yield: 1708 mg, 5.49 mmol, 88%. Anal. Calcd for $C_{11}H_{12}F_3NO_4S$ (311.277 g/mol): C, 42.44; H, 3.89; N, 4.50; S, 10.30. Found: C, 42.55; H, 3.98; N, 4.38; S, 10.32. Mp: 165 ºC. Λ_M (Ω^{-1} cm^2 mol^{-1}): 114 (5.0 x 10^{-4} M in acetone). IR (cm^{-1}): ν(NH) 3202 br, vs. ^{1}H NMR (300.1 MHz, DMSO-d_6): δ 2.94 (t, 2 H, CH_2Ar, $^3J_{HH}$ = 6.9 Hz), 3.13 (m, 2 H, CH_2N), 7.31 (m, 2 H, H6 + H5), 7.56–7.59 (m, 1 H, H4), 7.66–7.69 (m, 1 H, H7), 7.76 (br s, 3 H, NH_3), 7.88 (s, 1 H, H2). ^{13}C{^{1}H} NMR (100.8 MHz, DMSO-d_6): δ 21.3 (s, CH_2Ar), 38.2 (s, CH_2N), 111.4 (s, CH4), 115.5 (s, C3), 119.6 (s, CH7), 120.6 (q, CF_3SO_3, $^1J_{CF}$ = 319.4 Hz), 122.6 (s, CH2), 124.5 (s, CH5), 127.3 (s, C3a), 143.0.3 (s, CH6), 154.8 (s, C7a).

Synthesis of $(C_8H_5S)CH_2CH_2NH_3Cl$ (B·HCl). Under nitrogen atmosphere, a Carius tube was charged with 3-cyanomethylbenzothiophene (2.5 g, 14.4 mmol), dry THF (15 mL) and BH_3·THF (20 mL of solution 1M in TFH, 20 mmol), and the mixture was stirred at room temperature for 3.5 h. The reaction mixture was cooled to 0 ºC in an ice bath, and methanol was added dropwise until bubbling stopped (ca. 20 mL). The solvent was removed, aqueous HCl (40 mL of solution 0.5M) was added to the residue, and the mixture was heated at 100 ºC for 1 h. The solvent was evaporated to ca. 20 mL, and the resulting suspension was washed with Et_2O (2 x 30 mL). The aqueous phase was basified with NaOH (solution 1M) until pH = 12, and extracted with ethyl acetate (2 x 20 mL). The organic layers were combined, the solvent was removed, and concentrated HCl was added (5 mL). The water was removed, a 4:1 mixture of Et_2O/acetone (30 mL) was added to the residue and the suspension was vigorously stirred. The suspension was filtered, and the solid was washed with a 4:1 mixture of Et_2O/acetone (3 x 5 mL) and vacuum-dried to give **B·HCl** as a colorless solid, which was stored protected from moisture. Yield: 1.82 g, 8.52 mmol, 59%. Anal. Calcd for $C_{10}H_{12}ClNS$ (213.73 g/mol): C, 56.20; H, 5.66; N, 6.55; S, 15.00. Found: C, 56.30; H, 5.74; N, 6.44; S, 14.97. Mp: 204 ºC. IR (cm^{-1}): ν(NH) 3340 br; δ(NH_2) 1603 m. ^{1}H NMR (300.1 MHz,

DMSO-d_6): δ 3.12 (br s, 2 H, CH_2N), 3.17–3.22 (m, 2 H, CH_2Ar), 7.40 (m, 2 H, H5 + H6), 7.59 (s, 1 H, H2), 7.90 (m, 1 H, H4), 7.98 (m, 1 H, H7), 8.35 (br s, 3 H, NH_3). $^{13}C\{^1H\}$ NMR (75.5 MHz, DMSO-d_6): δ 25.9 (s, CH_2Ar), 38.2 (s, CH_2N), 121.6 (s, CH4) 123.0 (s, CH7), 123.9 (s, CH2), 124.2 (s, CH5), 124.5 (s, CH6), 131.7 (s, C3), 138.3 (s, C3a) 139.7 (s, C7a).

Synthesis of [Pd{κ^2(*C*,*N*-(C_8H_4O)$CH_2CH_2NH_2$-3}$(NCMe)_2$]OTf (1a). A solution of **A·HOTf** (500 mg, 1.61 mmol) in CH_3CN (15 mL) was added to a solution of $Pd(OAc)_2$ (360 mg, 1.61 mmol) in CH_3CN (10 mL), and the resulting mixture was stirred at room temperature overnight. The mixture was filtered through a plug of Celite, the filtrate was concentrated to ca. 1 mL without heating, and Et_2O was added (25 mL). The suspension was filtered, and the solid was washed with Et_2O (2 x 5 mL) and air-dried to afford complex **1a** as a yellow solid. Yield: 700 mg, 1.40 mmol, 87%. Anal. Calcd for $C_{15}H_{16}F_3N_3O_4SPd$ (497.79 g/mol): C, 36.19; H, 3.24; N, 8.44; S, 6.44. Found: C, 36.41; H, 3.15; N, 8.35; S, 6.45. Mp: 108 ºC. Λ_M (Ω^{-1} cm^2 mol^{-1}): 113 (5.0 x 10^{-4} M in acetone). IR (cm^{-1}): ν(NH) 3270 s, 3233 s, 3156 s; ν(CN) 2337 m, 2320 m, 2309 m, 2292 m. ^1H NMR (400.9 MHz, DMSO-d_6): δ 2.37 (s, 6 H, MeCN), 2.67–2.69 (m, 2 H, CH_2N), 2.81 ("t", 2 H, CH_2Ar, $^3J_{HH}$ = 5.6 Hz), 4.98 (br s, 2 H, NH_2), 7.10–7.13 (m, 2 H, H5 + H6), 7.39–7.41 (m, 1 H, H4), 7.44–7.46 (m, 1 H, H7). $^{13}C\{^1H\}$ NMR (100.8 MHz, DMSO-d_6): δ 1.1 (s, Me), 23.1 (s, CH_2Ar), 40.9 (s, CH_2N), 110.0 (s, CH7), 115.4 (s, C3), 117.4 (s, CH4), 120.7 (q, CF_3SO_3, $^1J_{CF}$ = 317.2 Hz), 121.8 (s, CH6 or CH5), 122.2 (s, CH6 or CH5), 128.1 (s, C3a), 149.0 (br s, C2), 156.3 (s, C7a). ^{19}F NMR (282.4 MHz): δ –78.02 (CF_3SO_3).

Synthesis of [Pd_2(μ-Cl)$_2${κ^2(*C*,*N*-(C_8H_4O)$CH_2CH_2NH_2$-3}$_2$]·2MeCN (2a·2MeCN). The ammonium triflate **A·HOTf** (500 mg, 1.606 mmol) was added to a suspension of $Pd(OAc)_2$ (366 mg, 1.630 mmol) in CH_3CN (50 mL). The resulting mixture was stirred at room temperature overnight and filtered over a plug of Celite. $NaHCO_3$ (1 g, 11.90 mmol)

was added to the filtrate, the resulting suspension was stirred for 1 h, and then filtered over a plug of Celite. NaCl (1 g, 17.11 mmol) was added to the filtrate, and the suspension was stirred for 1 h. The solvent was removed from the mixture to ca. 10 mL, and the suspension was filtered. The solid was washed with H_2O (3 x 5 mL) and Et_2O (3 x 5 mL) and air-dried to give a first crop of complex **2a**·2MeCN as a pale yellow solid (140 mg). The filtrate was concentrated to ca. 5 mL and H_2O (3 mL) was added. The suspension was filtered and the solid was washed with H_2O (3 x 5 mL) and Et_2O (3 x 5 mL) and air-dried to give a second crop of complex **2a**·2MeCN as a pale yellow solid (280 mg). Yield: 420 mg, 0.61 mmol, 76%. An analytically pure sample of complex **2a** was obtained by recrystallization from acetone/CH_2Cl_2. Anal. Calcd for $C_{20}H_{20}Cl_2N_2O_2Pd_2$ (604.098 g/mol): C, 39.76; H, 3.34; N, 4.64. Found: C, 39.86; H, 3.23; N, 4.59. Dec pt: 180 ºC. IR (cm^{-1}): ν(NH) 3313 m, 3297 m, 3248 s, 3228 m; δ(NH_2) 1578 m. NMR data for **2a**·2MeCN: ^{1}H NMR (300.1 MHz, DMSO-d_6): δ 2.06 (s, 3 H, MeCN), 2.63 (m, 2 H, CH_2N), 2.77 ("t", 2 H, CH_2Ar, $^3J_{HH}$ = 5.4 Hz), 4.88 (br s, 2 H, NH_2), 7.05–7.14 (m, 2 H, C_6H_4), 7.32–7.35 (m, 2 H, C_6H_4). $^{13}C\{^1H\}$ NMR (75.5 MHz, DMSO-d_6): δ 1.1 (s, *Me*CN), 22.9 (s, CH_2Ar), 39.8 (s, CH_2N, partially obscured by the signal corresponding to the DMSO-d_6), 109.9 (s, CH), 113.6 (s, C3), 117.2 (s, CH), 121.4 (s, CH), 121.7 (s, CH), 128.6 (s, C3a), 156.2 (s, C7a), 157.1 (s, C2). The $^{13}C\{^1H\}$ signal corresponding to the CN group was not observed.

Synthesis of [$Pd_2(\mu$-Cl)$_2\{\kappa^2$(*C*,*N*-(C_8H_4S)$CH_2CH_2NH_2$-3}$_2$]·2MeCN (2b·2MeCN). The ammonium salt **B·HCl** (525 mg, 2.34 mmol) was added to a suspension of $Pd(OAc)_2$ (500 mg, 2.34 mmol) in acetonitrile (50 mL), and the mixture was stirred for 24 h. A yellow precipitate was slowly formed. The suspension was filtered, and the solid was washed with Et_2O (2 x 3 mL) and dried under vacuum to afford the complex **2b**·2MeCN as a yellow solid. Yield: 689 mg, 0.96 mmol, 82%. Anal. Calcd for $C_{20}H_{20}Cl_2N_2Pd_2S_2$·$2CH_3CN$ (718.334 g/mol): C, 40.13; H, 3.65; N, 7.80; S, 8.93. Found: C, 40.02; H, 3.62; N, 7.72; S, 9.05. Mp:

210 ºC. IR (cm^{-1}): ν(NH) 3207 s, 3133 s; ν(CN) 2318 m, 2290 w; δ(NH_2) 1595 m; ν(Pd–Cl) 318 m. ^{1}H NMR (300.1 MHz, DMSO-d_6): 2.06 (s, 3 H, MeCN), 2.65 (br s, 2 H, CH_2N), 2.91 ("t", 2 H, CH_2Ar, $^3J_{HH}$ = 5.4 Hz), 4.60 (br s, 2 H, NH_2), 7.05 (b t, 1 H, H6, $^3J_{HH}$ = 7.2 Hz) 7.15 (b t, 1 H, H5, $^3J_{HH}$ = 7.2 Hz), 7.47 (br d, 1 H, H4, $^3J_{HH}$ = 7.8 Hz), 7.65 (br d, 1 H, H7, $^3J_{HH}$ = 7.8 Hz). ^{13}C{^{1}H} NMR (75.5 MHz, DMSO-d_6): δ 1.1 (s, Me, MeCN), 28.4 (s, CH_2Ar), 41.1 (s, CH_2N), 119.0 (s, CH4), 120.7 (s, CH7), 121.1 (s, CH6), 122.2 (s, CH5), 126.6 (s, C3), 132.5 (C2), 138.7 (s, C3a), 143.2 (s, C7a).

Synthesis of [Pd{κ^2(*C*,*N*-(C_8H_4O)$CH_2CH_2NH_2$-3}Cl(PPh_3)]·Et_2O (3a·Et_2O). PPh_3 (115 mg, 0.438 mmol) was added to a suspension of **2a**·2MeCN (150 mg, 0.218 mmol) in CH_2Cl_2 (10 mL), and the mixture was stirred for 15 min at room temperature. The solution was filtered through a plug of $MgSO_4$, solvent was removed from the filtrate to ca. 2 mL, and Et_2O (20 mL) was added. The suspension was filtered, and the solid was washed with Et_2O (2 x 5 mL) and air-dried to afford **3a**·Et_2O as a pale yellow solid. Yield: 212 mg, 0.332 mmol, 76%. Anal. Calcd for $C_{28}H_{25}ClNOPPd·C_4H_{10}O$ (638.464 g/mol): C, 60.20; H, 5.53; N, 2.19. Found: C, 60.14; H, 5.52; N, 2.04. Mp: 208 ºC (dec). IR (cm^{-1}): ν(NH) 3248 w, 3211 m, 3124 m. ^{1}H NMR (400.9 MHz): δ 1.25 (t, 6 H, *Me*CH_2O, $^3J_{HH}$ = 7.2 Hz), 2.93 ("t", 2 H, CH_2Ar, $^3J_{HH}$ = 5.6 Hz), 3.06 (m, 2 H, CH_2N), 3.52 (q, 4 H, CH_2O, $^3J_{HH}$ = 7.2 Hz), 3.53 (br s, 2 H, obscured by the signal of the CH_2O, NH_2), 6.55 (d, 1 H, H7, $^3J_{HH}$ = 8.0 Hz), 6.88 (td, 1 H, H6, $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.2 Hz), 7.04 (td, 1 H, H5, $^3J_{HH}$ = 7.4, $^4J_{HH}$ = 0.8 Hz), 7.27–7.35 (m, 7 H, H4 + *m*-H of PPh_3), 7.36–7.43 (m, 3 H, *p*-H, PPh_3), 7.66–7.75 (m, 6 H, *o*-H, PPh_3). ^{13}C{^{1}H} NMR (100.8 MHz): δ 15.2 (s, *Me*CH_2O), 24.6 (s, CH_2Ar), 40.0 (s, CH_2N), 65.8 (s, CH_2O), 109.5 (s, CH7), 114.7 (s, C3), 116.5 (s, CH4), 121.0 (s, CH5), 121.2 (s, CH6), 127.8 (d, *m*-CH, PPh_3, $^3J_{CP}$ = 11.0 Hz), 128.7 (s, C3a), 130.2 (s, *p*-CH, PPh_3, $^4J_{CP}$ = 2.0 Hz), 131.6 (d, *i*-C, PPh_3, $^1J_{CP}$ = 53.1 Hz), 134.5 (d, *o*-CH, PPh_3, $^2J_{PH}$ = 11.6 Hz), 156.4 (d, C7a, $^4J_{CP}$ = 3.5 Hz), 158.3 (d, C2, $^3J_{CP}$ = 5.3 Hz). ^{31}P{^{1}H} NMR (162.3 MHz): δ 38.9 (s, PPh_3). Single crystals

suitable for an X-ray diffraction study were obtained by slow diffusion of Et_2O into a solution of of **3a**·Et_2O in CH_2Cl_2.

Synthesis of [Pd{κ^2(*C,N*-(C_8H_4S)$CH_2CH_2NH_2$-3}Cl(PPh_3)]·Et_2O (3b). PPh_3 (100 mg, 0.38 mmol) was added to a suspension of **2b**·2MeCN (130 mg, 0.18 mmol) in CH_2Cl_2 (30 mL), and the resulting mixture was stirred for 30 min. The solution was was filtered through a plug of $MgSO_4$, the filtrate was concentrated to ca. 3 mL, and *n*-pentane (30 mL) was added. The suspension was filtered, and the solid was washed with *n*-pentane (2 x 3 mL) and dried under vacuum to obtain complex **3b** as a yellow solid. Yield: 136 mg, 0.23 mmol, 65%. Anal. Calcd for $C_{28}H_{25}ClNPPdS$ (580.406 g/mol): C, 57.94; H, 4.34; N, 2.41; S, 5.52. Found: C, 57.88; H, 4.45; N, 2.47; S, 5.56. Mp: 164 ºC. IR (cm^{-1}): ν(NH) 3240 m, 3200 m, 3060 m. ^{1}H NMR (400.9 MHz): δ 2.75 (m, 2 H, CH_2N), 3.22 ("t", 2 H, CH_2Ar, $^3J_{HH}$ = 5.6 Hz), 3.48 (m, 2 H, NH_2), 7.00 (ddd, 1 H, H6, $^3J_{HH}$ = 8.0, $^3J_{HH}$ = 7.2, $^4J_{HH}$ = 1.2 Hz), 7.19 (ddd, 1 H, H5, $^3J_{HH}$ = 8.0, $^3J_{HH}$ = 7.2, $^4J_{HH}$ = 1.2 Hz), 7.29–7.34 (m, 6 H, *m*-H, PPh_3), 7.37–7.40 (m, 3 H, *p*-H, PPh_3), 7.42 ("d", 1 H, H7, $^3J_{HH}$ = 8.0 Hz), 7.55 ("d", 1 H, H4, $^3J_{HH}$ = 8.0 Hz), 7.61–7.65 (m, 6 H, *o*-H, PPh_3). $^{13}C\{^1H\}$ NMR (75.5 MHz): δ 31.5 (s, CH_2Ar), 37.5 (d, CH_2N, $^3J_{PC}$ = 6.3 Hz), 119.1 (s, CH4), 121.1 (s, CH6), 121.4 (s, CH7), 122.7 (s, CH5), 128.1 (d, *m*-CH, PPh_3, $^3J_{PC}$ = 11.0 Hz), 129.3 (s, C3), 130.6 (d, *p*-CH, PPh_3, $^4J_{PC}$ = 2.0 Hz), 130.9 (d, *i*-C, PPh_3, $^1J_{PC}$ = 52.5 Hz), 134.8 (d, *o*-CH, PPh_3, $^2J_{PC}$ = 11.6 Hz), 138.3 (s, C2), 143.6 (s, C3a), 144.1 (d, C7a, $^4J_{PC}$ = 2.7 Hz). $^{31}P\{^1H\}$ NMR (162.3 MHz): δ 34.6 (s, PPh_3). Single crystals suitable for an X-ray diffraction study were obtained by slow diffusion of *n*-pentane into a solution of **3b** in $CHCl_3$.

Synthesis of [Pd{κ^2(*C,N*-(C_8H_4O)$CH_2CH_2NH_2$-3}(4-pic)$_2$]OTf (4a). The ammonium triflate **A·HOTf** (125 mg, 0.40 mmol) was added to a solution of $Pd(OAc)_2$ (90 mg, 0.40 mmol) in CH_3CN (50 mL). The resulting mixture was stirred at room temperature overnight. 4-Picoline (80 μL, 0.80 mmol) was added and the solution was stirred at room

temperature for 2 h. The suspension was filtered through a plug of Celite, the filtrate was concentrated to ca. 1 mL, and Et_2O (25 mL) was added. The suspension was filtered, and the solid was washed with Et_2O (2 x 5 mL) and air-dried to afford **4a** as a pale yellow solid. Yield: 150 mg, 0.25 mmol, 62%. Anal. Calcd for $C_{23}H_{24}F_3N_3O_4SPd$ (601.05 g/mol): C, 45.89; H, 4.02; N, 6.98; S, 5.33. Found: C, 45.87; H, 4.10; N, 6.88; S, 5.35. Mp: 180 ºC (dec). Λ_M (Ω^{-1} cm^2 mol^{-1}): 120 (5.0 x 10^{-4} M in acetone). IR (cm^{-1}): ν(NH) 3291 m, 3216 m, 3146 s; ν(C=N) 1618 s, 1595 s. ^{1}H NMR (400.9 MHz, acetone-d_6): δ 2.40 (s, 3 H, Me), 2.45 (s, 3 H, Me), 2.96–3.03 (m, 4 H, CH_2N + CH_2Ar), 4.63 (br s, 2 H, NH_2), 6.95–7.08 (m, 3 H, H5 + H6 + H7), 7.34 (dd, 1 H, H4, $^3J_{HH}$ = 6.8 Hz, $^3J_{HH}$ = 0.8 Hz), 7.43 (d, 4 H, *m*-H, pic, $^3J_{HH}$ = 6.0 Hz), 8.70 (d, 2 H, *o*-H, pic, $^3J_{HH}$ = 5.6 Hz), 8.81 (d, 2 H, *o*-H, pic, $^3J_{HH}$ = 6.4 Hz). ^{13}C{^{1}H} NMR (100.8 MHz, acetone-d_6): δ 20.9 (s, Me, pic), 21.0 (s, Me, pic), 24.2 (s, CH_2), 42.3 (s, CH_2), 110.4 (s, CH5 or CH7), 115.2 (s, C3 or C3a), 117.8 (s, CH4), 122.0 (s, CH5 or CH7), 122.2 (s, CH6), 122.2 (q, CF_3SO_3, $^1J_{CF}$ = 319.4 Hz), 127.4 (s, *m*-CH, pic), 127.6 (s, *m*-CH, pic), 129.9 (s, C3 or C3a), 150.8 (s, *o*-CH, pic), 152.5 (s, *C*–Me, pic), 152.9 (s, *o*-CH, pic), 156.2 (S, C2), 157.9 (s, C7a).

Synthesis of [Pd{κ^2(*C,N*-(C_8H_4O)$CH_2CH_2NH_2$-3}($CN^tBu)_2$]OTf (5a). A solution of ^{t}BuNC (68 μL, 0.60 mmol) in CH_2Cl_2 (15 mL) was added dropwise to a solution of **1a** in CH_2Cl_2 (10 mL), and the mixture was stirred at room temperature for 2 h. The suspension was filtered through a plug of Celite, the filtrate was concentrated to ca. 2 mL, and Et_2O (20 mL) was added. The suspension was filtered, and the solid was washed with Et_2O (2 x 5 mL) and air-dried to afford **5a** as a light yellow solid. Yield: 129 mg, 0.22 mmol, 74%. Anal. Calcd for $C_{21}H_{29}F_3N_3O_4SPd$ (581.08 g/mol): C, 43.34; H, 4.85; N, 7.22; S, 5.51. Found: C, 43.20; H, 4.90; N, 7.17; S, 5.64. Mp: 135 ºC (dec). Λ_M (Ω^{-1} cm^2 mol^{-1}): 128 (5.0 x 10^{-4} M in acetone). IR (cm^{-1}): ν(NH) 3235 s, 3152 m; ν(CN) 2243 s. ^{1}H NMR (400.9 MHz): δ 1.63 (s, 9 H, ^{t}Bu), 1.70 (s, 9 H, ^{t}Bu), 2.93 (t, 2 H, CH_2Ar, $^3J_{HH}$ = 6.0 Hz), 3.04–3.08 (m, 2 H, CH_2N), 4.22 (br s,

2 H, NH_2), 7.15–7.17 (m, 2 H, H6 + H7), 7.27–7.29 (m, 1 H, H5), 7.38–7.40 (m, 1 H, H4). $^{13}C\{^1H\}$ NMR (75.5 MHz): δ 23.7 (s, CH_2Ar), 29.8 (s, ^tBu), 29.9 (s, ^tBu), 40.6 (s, CH_2N), 109.8 (s, CH5), 116.1 (s, C3), 117.9 (s, CH4), 121.7 (s, CH7), 122.8 (s, CH6), 127.8 (s, C3a), 157.4 (s, C7a), 160.9 (s, C2). The $^{13}C\{^1H\}$ signal corresponding to the OTf group was not observed. ^{19}F NMR (282.4 MHz): δ –77.9 (s, TfO).

Synthesis of [Pd{κ^2(*C,N*-(C_8H_4S)$CH_2CH_2NH_2$-3}Cl(4-pic)] (6b). 4-Picoline (135 μL, 1.39 mmol) was added to a suspension of **2**·2MeCN (500 mg, 0.70 mmol) in CH_2Cl_2 (40 mL) and the resulting mixture was stirred for 30 min. The solution was filtered through a plug of $MgSO_4$, the filtrate was concentrated to ca. 3 mL, and Et_2O (30 mL) was added. The suspension was filtered, and the solid was washed with Et_2O (2 x 3 mL) and dried under vacuum to give complex **6b** as a pale yellow solid. Yield: 423 mg, 1.03 mmol, 72%. Anal. Calcd for $C_{16}H_{17}ClN_2PdS$ (411.244 g/mol): C, 46.73; H, 4.17; N, 6.81; S, 7.80. Found: C, 46.43; H, 4.19; N, 6.56; S, 7.68. Dec pt: 218 ºC. IR (cm^{-1}): ν(NH) 3252 m, 3191 m, 3123 m; ν(C=N) 1616 m. ^1H NMR (300.1 MHz): δ 2.17 (s, 3 H, Me), 3.03–3.11 (m, 4 H, CH_2N + CH_2Ar), 4.19 (br s, 2 H, NH_2), 6.37 (d, 2 H, *m*-H, pic, $^3J_{HH}$ = 6.0 Hz), 7.19 (m, 1 H, H6), 7.30 (m, 1 H, H5), 7.52 (d, 1 H, H4, $^3J_{HH}$ = 8.1 Hz), 7.63 (d, 1 H, H7, $^3J_{HH}$ = 7.8 Hz), 8.24 (“d”, 2 H, *o*-H, pic, $^3J_{HH}$ = 6.6 Hz). $^{13}C\{^1H\}$ NMR (75.5 MHz): δ 21.0 (s, Me), 28.4 (s, CH_2Ar), 41.4 (s, CH_2N), 119.5 (s, CH4), 121.4 (s, CH7), 122.1 (s, CH6), 123.2 (s, CH5), 125.6 (s, *m*-CH, pic), 128.6 (s, C3), 134.3 (s, C2), 139.6 (s, C3a), 142.1 (s, C7a), 150.0 (s, *p*-C, pic), 152.7 (s, *o*-CH, pic). Single crystals suitable for an X-ray diffraction study were obtained by slow diffusion of Et_2O into a solution of **6b** in CH_2Cl_2.

Synthesis of [Pd{κ^2(*C,N*-(C_8H_4S)$CH_2CH_2NH_2$-3}Cl(CN^tBu)] (7b). A solution of ^tBuNC (62.9 μL, 0.56 mmol) in CH_2Cl_2 (15 mL) was added dropwise (ca. 15 min) to a suspension of **2**·2MeCN (200 mg, 0.28 mmol) in CH_2Cl_2 (15 mL). The resulting yellow

solution was stirred for 15 min and filtered through a plug of $MgSO_4$. The filtrate was concentrated, without heating, to ca. 1 mL, and Et_2O (20 mL) was added. A colorless solid appeared when the solvent from the mixture was evaporated to ca. 5 mL. Et_2O (15 mL) was added, and the resulting suspension was filtered, and the solid was washed with cold Et_2O (2 x 3 mL) and air-dried, to give a first crop of complex **7b** as a colorless solid (133 mg). The filtrate was concentrated to ca. 5 mL, the resulting suspension was filtered, and the solid was washed with cold Et_2O (2 x 3 mL) and air-dried to give a second crop of complex **7b** as a colorless solid (52 mg). Yield: 185 mg, 0.46 mmol, 83%. Anal. Calcd for $C_{19}H_{19}ClN_2PdS$ (401.248 g/mol): C, 44.90; H, 4.77; N, 6.98; S, 7.99. Found: C, 44.88; H, 4.74; N, 6.79; S, 7.86. Mp: 120 ºC. IR (cm^{-1}): ν(NH) 3250 s, 3202 m, 3130 m; ν(CN) 2213 vs. ^{1}H NMR (300.1 MHz): δ 1.36 (s, 9 H, Me, ^{t}Bu), 2.98 (m, 2 H, CH_2N), 3.10 ("t", 2 H, CH_2Ar, $^3J_{HH}$ = 5.1 Hz), 3.79 (br s, 2 H, NH_2), 7.19 (m, 1 H, H6), 7.27 (m, 1 H, H5), 7.58 (d, 1 H, H4, $^3J_{HH}$ = 7.8 Hz) , 7.75 (d, 1 H, H7, $^3J_{HH}$ = 7.8 Hz). $^{13}C\{^1H\}$ NMR (75.5 MHz): δ 28.7 (s, CH_2Ar), 29.5 (s, Me, ^{t}Bu), 40.7 (s, CH_2N), 58.5 (s, *C*Me_3), 119.7 (s, CH4), 121.1 (s, CH7), 122.2 (s, CH6), 123.1 (s, CH5), 127.5 (s, C3), 132.7 (s, C2), 138.7 (s, C3a), 143.3 (s, C7a). The signal corresponding to the CN group of the coordinated isocyanide was not observed. Single crystals suitable for an X-ray diffraction study were obtained by slow diffusion of *n*-pentane into a solution of **7b** in Et_2O.

Synthesis of [Pd{κ^2(*C*,*N*-(C_8H_4S)$CH_2CH_2NH_2$-3}Cl(CNXy)] (8b). A solution of XyNC (86 mg, 0.66 mmol) in CH_2Cl_2 (10 mL) was added dropwise (ca. 7 min) to a suspension of **2**·2MeCN (240 mg, 0.33 mmol) in CH_2Cl_2 (10 mL) at –15 ºC. The resulting solution was stirred for 3 min at –15 ºC and filtered through a plug of $MgSO_4$. The filtrate was concentrated under vacuum, without heating, to ca. 1 mL, and Et_2O (20 mL) was added. The resulting suspension was filtered, and the solid was washed with Et_2O (2 x 3 mL) and air-dried to give a first crop of complex **8b** as a colorless solid (205 mg). The filtrate was

concentrated to ca. 5 mL, the resulting suspension was filtered, and the solid was washed with cold Et_2O (2 x 3 mL) and air-dried to give a second crop of complex **8b** as a colorless solid (22 mg). Yield: 227 mg, 0.51 mmol, 76%. Anal. Calcd for $C_{19}H_{19}ClN_2PdS$ (449.292 g/mol): C, 50.79; H, 4.26; N, 6.23; S, 7.14. Found: C, 50.84; H, 4.26; N, 6.12; S, 7.15. Mp: 193 ºC. IR (cm^{-1}): ν(NH) 3272 m, 3203 m, 3132 m; ν(CN) 2192 s. ^{1}H NMR (400.9 MHz): δ 2.41 (s, 6 H, Me, Xy), 3.04 (m, 2 H, CH_2N), 3.13 ("t", 2 H, CH_2Ar, $^3J_{HH}$ = 4.8 Hz), 3.90 (br s, 2 H, NH_2), 7.00 (d, 2 H, *m*-H, Xy, $^3J_{HH}$ = 7.6 Hz), 7.07 (m, 1 H, H6), 7.15 (m, 1 H, H5), 7.16 (t, 1 H, *p*-H, Xy, $^3J_{HH}$ = 8.0 Hz), 7.45 ("d", 1 H, H4, $^3J_{HH}$ = 8.0 Hz), 7.62 ("d", 1 H, H7, $^3J_{HH}$ = 7.4 Hz). $^{13}C\{^1H\}$ NMR (100.8 MHz): δ 19.0 (s, Me, Xy), 28.7 (s, CH_2Ar), 40.7 (s, CH_2N), 119.4 (s, CH4), 121.0 (s, CH7), 122.3 (s, CH6), 123.2 (s, CH5), 125.8 (br s, *i*-C, Xy), 127.4 (s, C3), 127.9 (s, *m*-CH, Xy), 129.7 (s, *p*-CH, Xy), 132.8 (s, C2), 136.3 (s, *C*–Me, Xy), 138.3 (s, C3a), 140.1 (s, CN), 143.4 (s, C7a). Single crystals of **8b**·1/4CH_2Cl_2·1/4Et_2O suitable for an X-ray diffraction study were obtained by slow diffusion of Et_2O into a solution of **8b** in CH_2Cl_2.

Synthesis of [Pd{κ^2(*C*,*N*-(C(=NXy)C_8H_4S)$CH_2CH_2NH_2$-3}Cl(CNXy)] (9b). A solution of XyNC (42 mg, 0.32 mmol) in CH_2Cl_2 (5 mL) was added dropwise (ca. 8 min) to a solution of complex **8b** (150 mg, 0.33 mmol) in CH_2Cl_2 (10 mL) at 0 ºC. The mixture was stirred at 0º C for 1.5 h. Several changes in its colour were observed until eventually it turned yellow. An aliquote (ca. 1 mL) was extracted from the reaction, the solvent was removed, and the residue was dissolved in $CDCl_3$. The ^{1}H NMR spectrum of this solid proved it to be a mixture of **8b** (the starting material) and **9b** (4:1 ratio). The reaction mixture was stirred at room temperature for 20 h. The ^{1}H NMR analysis of a new aliquote showed a similar mixture to the previous one (ratio **8b**/**9b** = 2:1). After 24 h more, this ratio did not change. The solution was concentrated to ca. 2 mL, and Et_2O (20 mL) was added. The resulting suspension was filtered, and the solid was washed with Et_2O (2 x 5 mL) and air-dried to give a yellow solid **C** (121 mg). The ^{1}H NMR of this solid proved it to be a mixture ca. 4:2:1 of

complexes **8b**, **9b** and $[Pd_2Cl_2(NCXy)_4]$. This yellow solid **C** was dissolved in CH_2Cl_2 (6 mL), the solution was distributed in three test tubes, and Et_2O was slowly added to them (Et_2O/CH_2Cl_2 ratio = 4:1). After 48 h, the formation of two types of crystals was observed: pale yellow needles and yellow-orange blocks. Both types of crystals were manually separated with the help of a glass capillary. The yellow needles corresponded to complex **8b** previously characterized. The yellow-orange blocks corresponded to complex **9b**, whose crystalline structure could be determined by X-ray diffraction studies. Enough orange crystals were collected to register their ^1H and $^{13}C\{^1H\}$ NMR spectra. Apart from complex **8b**, the sample also contained small amounts of $[PdCl_2(CNXy)_4]$. The NMR data of complex **9b** were extracted from the mixture. ^1H NMR (400.9 MHz): δ 2.12 (s, 6 H, Me, Xy^c), 2.19 (s, 6 H, Me, Xy^i), 3.05 (m, 2 H, NH_2), 3.30 (m, 2 H, CH_2N), 4.31 (“t”, 2 H, CH_2Ar, $^3J_{HH}$ = 5.6 Hz), 6.77–6.85 (m, 1 H, *p*-H, Xy^i), 6.62 ("d", 2 H, *m*-H, Xy^i, $^3J_{HH}$ = 6.4 Hz), 7.02 ("d", 2 H, *m*-H, Xy^c, $^3J_{HH}$ = 7.6 Hz), 7.13–7.20 (m, 1 H, *p*-H, Xy^c), 7.38–7.45 (m, 2 H, H5 + H6), 7.82–7.87 (m, 2 H, H4 + H7). $^{13}C\{^1H\}$ NMR (100.8 MHz): δ 18.6 (s, Me, Xy^c), 19.4 (s, Me, Xy^i), 30.4 (s, CH_2Ar), 41.7 (s, CH_2N), 121.9 (s, CH4), 122.6 (s, CH7), 123.5 (s, *p*-CH, Xy^i), 124.2 (s, CH5), 126.4 (s, CH6), 127.0 (s, *C*–Me, Xy^i), 127.7 (s, *m*-CH, Xy^c), 127.8 (s, *m*-CH, Xy^i), 129.5 (s, *p*-CH, Xy^c), 133.2 (s, C3), 135.3 (s, *C*–Me, Xy^c), 139.6 (s, C3a), 141.3 (s, C7a), 141.8 (s, C2), 151.8 (s, *i*-C, Xy^i), 167.0 (s, C=N). The signals corresponding to the CN group and the *i*-C of the coordinated isocyanide were not observed. Single crystals of **9b** suitable for an X-ray diffraction study were obtained by slow diffusion of Et_2O into a solution of **C** in CH_2Cl_2.

Synthesis of *N*-(3,4-Dihydrobenzofuran[2,3-*c*]pyridin-1(2*H*)-ylidene)butan-1-aminium Triflate (10a). A solution of **5a** (90 mg, 0.15 mmol) in toluene was stirred at 120 ºC overnight in a Carius tube. The suspension was filtered through a plug of Celite, the solvent was removed from the filtrate, and the residue was dried under vacuum to give the

compound **10a** as a yellow oil. Yield: 18 mg, 0.04 mmol, 29%. ESI-HRMS: calcd for $C_{15}H_{19}N_2O$ [$(M–OTf)^+$] 243.1492, found 243.1488. IR (cm^{-1}): ν(NH) 3270 m br. ^{1}H NMR (400.9 MHz): 1.54 (s, 9 H, ^{t}Bu), 3.03 (t, 2 H, CH_2Ar, $^3J_{HH}$ = 7.6 Hz), 3.93 (t, 2 H, CH_2N, $^3J_{HH}$ = 8.0 Hz), 7.07 (br s, 1 H, NH), 7.32 (br t, 1 H, H5, $^3J_{HH}$ = 8.4 Hz), 7.47 (ddd, 1 H, H6, $^3J_{HH}$ = 8.0, $^3J_{HH}$ = 7.2, $^4J_{HH}$ = 1.2 Hz), 7.57–7.59 (m, 2 H, H4 + H7), 8.42 (br s, 1 H, NH). ^{13}C{^{1}H} NMR (100.8 MHz): δ 18.9 (s, CH_2Ar), 27.9 (s, Me, ^{t}Bu), 41.0 (s, CH_2N), 112.5 (s, CH7), 121.6 (q, CF_3SO_3, $^1J_{CF}$ = 319.0 Hz), 121.3 (s, CH4), 124.8 (s, CH5), 127.8 (s, C3), 129.3 (s, CH6), 137.8 (s, C2), 148.9 (s, C3a), 156.2 (s, C7a).

Synthesis of *N*-(3,4-Dihydrobenzothiophen[2,3-*c*]pyridin-1(2*H*)-ylidene)butan-1-aminium Triflate (10b). AgOTf (58 mg, 0.22 mmol) was added to a solution of complex **7b** (90 mg, 0.22 mmol) in $CHCl_3$ (30 mL). The mixture was protected from light and stirred for 24 h. The suspension was filtered through a plug of $MgSO_4$, and the yellow filtrate was refluxed for 72 h. Decomposition to metallic palladium was observed. The solvent was eliminated from the mixture, and acetone (20 mL) was added to the residue. The suspension was filtered to remove the metallic palladium. The solution was filtered again through a plug of $MgSO_4$, the filtrate was concentrated to ca. 1 mL, and Et_2O (15 mL) was added. The solvent was completely removed, and Et_2O (15 mL) was added to the residue. The mixture was stirred for 24 h, the suspension was filtered, and the solid was air-dried to give crude compound **10b** as an off-white solid (46 mg). Pure complex **10b** was obtained by preparative TLC, in silica gel with fluorescent indicator. The solid was dissolved in acetone (2 mL) and a 9:1 mixture of CH_2Cl_2/MeOH was used as eluent. The second least retained fraction was collected. The product was extracted from the silica gel using a 8:1 mixture of CH_2Cl_2/MeOH. The solvent was removed, acetone (15 mL) was added to the residue, the resulting suspension was filtered, and the solvent was removed from the filtrate to afford pure compound **10b** as a colorless solid. Yield (crude **10b**): 46 mg, 0.11 mmol, 50%. Mp: 160 ºC.

IR (cm^{-1}): ν(NH) 3256 s; ν(C=N) 1627 s, 1574 s. ESI-HRMS: calculated exact mass for $C_{15}H_{19}N_2S$, 259.1269 [$(M–CF_3SO_3)^+$]; found, 259.1268. ^{1}H NMR (300.1 MHz): δ 1.65 (s, 9 H, Me, ^{t}Bu), 3.35 (t, 2 H, CH_2N, $^3J_{HH}$ = 7.2 Hz), 4.03 (br t, 2 H, CH_2Ar, $^3J_{HH}$ = 7.2 Hz), 7.61 (m, 2 H, H7 + H6), 8.05 (m, 1 H, H4), 8.10 (m, 1 H, H5), 8.10 (br s, 1 H, NH, overlapped with H5), 8.70 (br s, 1 H, NH). $^{13}C\{^1H\}$ NMR (75.5 MHz): δ 22.7 (s, CH_2Ar), 28.4 (s, Me, ^{t}Bu), 41.5 (s, CH_2N), 55.8 (s, CMe_3), 124.0 (s, CH5), 124.3 (s, CH4), 126.6 (s, CH7), 129.8 (s, CH6), 137.5 (s, C3a), 142.4 (s, C7a), 145.1 (s, C3), 154.7 (s, C2). The $^{13}C\{^1H\}$ resonances corresponding to the C=N and the triflate groups were not observed. Single crystals suitable for an X-ray diffraction study were obtained by slow evaporation of a solution of **10b** in $CHCl_3$.

Synthesis of 4-Dihydro[1]benzofuran[2,3-*c*]pyridin-1(2*H*)-one (11a). NEt_3 (5 mL, 35.87 mmol) was added to a solution of **1a** (150 mg, 0.3 mmol) in $CHCl_3$ (5 mL) under CO atmosphere (1.5 atm), and the mixture was stirred at room temperature overnight. The resulting suspension was filtered through a plug of Celite, and the solvent was removed from the filtrate. The residue was purified by flash chromatography using a 3:97 mixture of *n*-hexane/ethyl acetate as eluent. The solvent was removed, and the residue was vacuum-dried to afford pure lactam **11a** as a colorless solid. Yield: 15 mg, 0.08 mmol, 27%. Mp: 146 ºC. IR (cm^{-1}): ν(CO) 1685 s. ESI-HRMS calcd for $C_{11}H_{10}NO_2$, 188.0706 [$(M+H)^+$]; found, 188.0712. ^{1}H NMR (400.9 MHz): δ 3.04 (t, 2 H, CH_2Ar, $^3J_{HH}$ = 7.2 Hz), 3.75 (td, 2 H, CH_2N, $^3J_{HH}$ = 7.2, $^4J_{HH}$ = 2.8 Hz), 6.72 (br s, 1 H, NH), 7.30–7.34 (m, 1 H, H5), 7.42–7.46 (m, 1 H, H6), 7.58–7.60 (m, 2 H, H7 + H4). $^{13}C\{^1H\}$ NMR (75.5 MHz): δ 20.5 (s, CH_2Ar), 41.2 (s, CH_2N), 112.6 (s, CH7), 120.9 (s, CH4), 123.5 (s, CH5), 125.1 (s, C3), 125.8 (s, C3a), 127.4 (s, CH6), 143.6 (s, C2), 155.7 (s, C7a), 161.2 (s, CO).

Synthesis of 3,4-Dihydro[1]benzothieno[2,3-*c*]pyridin-1(2*H*)-one (11b). NEt_3 (146 μL, 1.05 mmmol) was added to a suspension of **2b**·2MeCN (188 mg, 0.26 mmol) in $CHCl_3$ (15 mL), in a Carius tube. A CO atmosphere (1.2 atm) was established, and the mixture was stirred for 48 h at 65 ºC. Decomposition to metallic palladium was observed. The solvent was eliminated from the mixture, and acetone (20 mL) was added to the residue. The suspension was filtered to collect a black solid (98 mg) which was a mixture of metallic palladium and $NHEt_3Cl$. The filtrate was again filtered through a plug of $MgSO_4$, the filtrate was concentrated to ca. 1 mL, and Et_2O (15 mL) was added. The resulting suspension was filtered, and the colorless solid was air-dried and identify as $NHEt_3Cl$ (60 mg) by ^1H NMR. The filtrate was concentrated to ca. 1 mL, and *n*-pentane (15 mL) was added. A sticky solid was formed. The solvent was removed, and the residue was vacuum-dried to afford crude lactam **11b** as a cream-colored solid (58 mg). Crude **11b** was purified by flash chromatography using a 15:85 mixture of *n*-hexane/ethyl acetate as eluent. The solvent was removed, and the residue was vacuum-dried to afford pure lactam **11b** as a colorless solid. Yield (crude **11b**): 58 mg, 0.29 mmol, 54%. Yield (pure **11b**): 25 mg, 0.13 mmol, 23%. Mp: 150 ºC. IR (cm^{-1}): ν(NH) 3211 br m; ν(CO) 1651 s. ESI-HRMS: calculated exact mass for $C_{11}H_{10}NOS$, 204.0483 [$(M+1)^+$]; found, 204.0481. ^1H NMR (400.9 MHz): δ 3.09 ("t", 2 H, CN_2Ar, $^3J_{HH}$ = 7.2 Hz), 3.75 (td, 2 H, CH_2N, $^3J_{HH}$ = 7.2, $^3J_{HH}$ = 2.4 Hz), 6.46 (br s, 1 H, NH), 7.42–7.49 (m, 2 H, H5 + H6), 7.74–7.76 (m, 1 H, H4), 7.89–7.92 (m, 1 H, H7). $^{13}C\{^1H\}$ NMR (75.5 MHz): δ 22.9 (s, CH_2Ar), 41.2 (s, CH_2N), 122.9 (s, CH4), 123.4 (s, CH7), 124.7 (s, CH5), 126.9 (s, CH6), 131.0 (s, C2), 137.5 (s, C3a), 140.0 (s, C3), 141.9 (s, C7a), 163.9 (s, CO).

Synthesis of 2-(2-(3-Methoxy-3-oxoprop-1-enyl)benzo[*b*]furan-3-yl)ethanaminium Triflate (12a). Methyl acrylate (108 μL, 1.20 mmol) was added to a solution of **1a** (150 mg, 0.30 mmol) in $CHCl_3$ (3 mL), and the mixture was stirred at 65 ºC overnight. The resulting suspension was filtered to give crude *E*-**12a** (by ^1H NMR) as a grey

solid (80 mg). Crude *E*-**12a** was dissolved in acetone, and the mixture was filtered through a plug of Celite. The filtrate was concentrated to ca. 0.5 mL, and Et_2O was added (15 mL). The solvent was partially removed to ca. 10 mL, and Et_2O (10 mL) was added. The suspension was filtered, and the solid was washed with Et_2O (2 x 3 mL) and air-dried to give a 2:1 mixture of *E*/*Z*-**12a** as a colorless solid. Yield (*E*/*Z*-**12a**): 33 mg, 0.083 mmol, 28%. Mp: 204 ºC. Λ_M (Ω^{-1} cm^2 mol^{-1}): 108 (5.0 x 10^{-4} M in acetone). IR (cm^{-1}): ν(NH) 3162 br m; ν(CO) 1705 s. ESI-HRMS calcd for $C_{14}H_{16}NO_3$, 246.1130 [(M–OTf)$^+$]; found, 246.1129. ^{1}H NMR (300.1 MHz, acetone-d_6): <u>*E*-isomer</u>: δ 3.48–3.52 (m, 2 H, CH_2Ar), 3.59–3.69 (br m, 2 H, CH_2N), 3.77 (s, 3 H, Me), 6.52 (d, 1 H, =CH, $^3J_{HH}$ = 15.6 Hz), 7.33 (ddd, 1 H, H5, $^3J_{HH}$ = 8.4, $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.2 Hz), 7.46 (td, 1 H, H6, $^3J_{HH}$ = 7.4, $^4J_{HH}$ = 1.2 Hz), 7.56 (dt, 1 H, H7, $^3J_{HH}$ = 7.2, $^4J_{HH}$ = 1.2 Hz), 7.71 (d, 1 H, =CH, $^3J_{HH}$ = 15.3 Hz), 7.85 (ddd, 1 H, H4, $^3J_{HH}$ = 8.4, $^4J_{HH}$ = 1.5, $^4J_{HH}$ = 0.9 Hz), 7.90 (br s, 3 H, NH_3). <u>*Z*-isomer</u> (extracted from the 1:3 equilibrium mixture of *E*/*Z* isomers): δ 3.48–3.56 (m, 2 H, CH_2Ar, overlapped with the corresponding signal of the *E*-isomer), 3.77 (s, 3 H, Me, overlapped with the corresponding signal of the *E*-isomer), 4.24 (t, 2 H, CH_2N, $^3J_{HH}$ = 7.2 Hz), 6.52 (d, 1 H, =CH, $^3J_{HH}$ = 15.6 Hz, overlapped with the corresponding signal of the *E*-isomer), 7.33 (ddd, 1 H, H5, $^3J_{HH}$ = 8.4, $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.2 Hz), 7.47 (td, 1 H, H6, $^3J_{HH}$ = 7.4, $^4J_{HH}$ = 1.2 Hz), 7.57 (dt, 1 H, H7, $^3J_{HH}$ = 7.2, $^4J_{HH}$ = 1.2 Hz), 7.70 (d, 1 H, =CH, $^3J_{HH}$ = 15.3 Hz), 7.86 (ddd, 1 H, H4, $^3J_{HH}$ = 8.4, $^4J_{HH}$ = 1.5, $^4J_{HH}$ = 0.9 Hz), 7.90 (br s, 3 H, NH_3, overlapped with the corresponding signal of the *E*-isomer). ^{13}C{^{1}H} NMR (75.5 MHz, acetone-d_6): <u>*E*-isomer</u> (minor isomer, extracted from the 1:3 equilibrium mixture of *E*/*Z* isomers): δ 22.2 (s, CH_2Ar), 40.9 (s, CH_2N), 52.0 (s, Me), 112.1 (s, CH7), 119.1 (s, =CH), 120.6 (s, C3), 121.5 (s, CH4), 124.3 (s, CH5), 128.1 (s, CH6), 129.5 (s, =CH), 150.1 (s, C2), 155.7 (s, C7a), 167.1 (s, CO). The ^{13}C{^{1}H} resonance corresponding to C3a was not observed or overlapped with the corresponding signal of the *Z* isomer. <u>*Z*-isomer</u> (major isomer, extracted from the 1:3 equilibrium mixture of *E*/*Z* isomers):

δ 22.4 (s, CH_2Ar), 48.2 (s, CH_2N), 52.0 (s, Me), 112.2 (s, CH7), 119.2 (s, =CH), 120.6 (s, C3), 121.4 (s, CH4), 124.4 (s, CH5), 128.2 (s, CH6), 129.2 (s, C3a), 129.4 (s, =CH), 150.1 (s, C2), 155.6 (s, C7a), 167.1 (s, CO).

Synthesis of (*E*)-2-(2-(3-Methoxy-3-oxoprop-1-enyl)benzo[*b*]thiophen-3-yl)ethanaminium Triflate (12b). AgOTf (107 mg, 0.42 mmol) was added to a suspension of **2b**·2MeCN (150 mg, 0.21 mmol) in acetone (20 mL). The mixture was protected from light and stirred for 24 h. The suspension was filtered through a plug of $MgSO_4$, the solvent was removed from the filtrate, and $CHCl_3$ (40 mL) was added. The suspension was transferred to a Carius tube, methyl acrylate (75 μL, 0.832 mmol) was added, and the mixture was stirred for 48 h at 65 ºC. Decomposition to metallic palladium was observed. The solvent was removed, and acetone (20 mL) was added. The suspension was filtered to collect a black solid. The filtrate was filtered again through a plug of $MgSO_4$. The filtrate was concentrated to ca. 1 mL, and Et_2O (20 mL) was added. The suspension was filtered, and the solid was washed with CH_2Cl_2 (3 x 5 mL) and Et_2O (3 x 5 mL) and air-dried to afford crude compound *E*-**12b** (by ^1H NMR) as a brown solid (100 mg). Yield (crude **12b**): 100 mg, 0.24 mmol, 58%. Mp: 210 ºC. IR (cm^{-1}): ν(NH) 3162 m; ν(CO) 1711 s; ν(C=C) 1617 m. ESI-HRMS: exact calculated mass for $C_{14}H_{16}NO_2S$, 262.0896 [$(M+1)^+$]; found, 262.0895. ^1H NMR (300.1 MHz, acetone-d_6): <u>*E*-isomer</u>: δ 3.52–3.60 (br m, 2 H, CH_2N), 3.63–3.71 (m, 2 H, CH_2Ar), 3.77 (s, 3 H, Me), 6.33 (d, 1 H, =CH, $^3J_{HH}$ = 15.6 Hz), 7.43–7.51 (m, 2 H, H5 + H6), 7.92–7.96 (m, 1 H, H7), 8.04–8.08 (m, 1 H, H4), 8.06 (d, 1 H, =CH, $^3J_{HH}$ = 15.3 Hz). The signal corresponding to the NH_3 group was obscured by resonances of the aromatic protons. <u>*Z*-isomer</u> (extracted from the 1:1.3 equilibrium mixture of *E*/*Z* isomers): δ 3.63–3.69 (m, 2 H, CH_2Ar, overlapped with the corresponding signal of the *E*-isomer), 3.77 (s, 3 H, Me, overlapped with the corresponding signal of the *E*-isomer), 4.16 (t, 2 H, CH_2N, $^3J_{HH}$ = 7.8 Hz), 6.33 (d, 1 H, =CH, $^3J_{HH}$ = 15.6 Hz), 7.43–7.52 (m, 2 H, H5 + H6, overlapped with the corresponding signals of the *E*-

isomer), 7.92–7.96 (m, 1 H, H7, overlapped with the corresponding signal of the *E*-isomer), 8.02 (d, 1 H, =CH, $^{3}J_{HH}$ = 15.6 Hz), 8.04–8.08 (m, 1 H, H4, overlapped with the corresponding signal of the *E*-isomer). The signal corresponding to the NH_3 group was obscured by resonances of the aromatic protons. $^{13}C\{^{1}H\}$ NMR (75.5 MHz, acetone-d_6): <u>*E*-isomer</u>: δ 24.1, 24.2 (s, CH_2Ar), 48.2, 40.3 (s, CH_2N), 51.1 (s, Me), 119.7 (s, =CH), 122.6 (s, CH4 or CH7), 122.8 (s, CH4 or CH7), 125.1 (s, CH5 or CH6), 127.0 (s, CH5 or CH6), 134.6 (s, =CH), 134.8 (s, C3 or C3a), 135.9 (s, C2), 139.1 (s, C7a), 139.5 (s, C3 or C3a), 166.0 (s, CO). The signal corresponding to the methylene carbons of isomer *E*-**12b** appeared split, probably because the presence in solution of an equilibrium (for instance, deprotonation of the aminium group) or two different species generated by hydrogen bonding in solution. This splitting is not due to the *E*/*Z* isomerization, as checked by the ^{1}H NMR of the sample, which correspondes to the pure *E*-isomer.

Synthesis of *tert*-Butyl 2-(Benzo[*b*]furan-3-yl)ethylcarbamate (13a). Na_2CO_3 (205 mg, 1.93 mmol) was added to a solution of **A·HOTf** (200 mg, 0.64 mmol) in CH_2Cl_2 (10 mL), and the mixture was stirred at room temperature for 1 h. Di-*tert*-butyl dicarbonate (Boc_2O; 154 mg, 0.70 mmol) was added, and the mixture was stirred for 12 hours at room temperature. CH_2Cl_2 (30 mL) and distilled water (30 mL) were added, and the organic phase was collected and dried over $MgSO_4$. The suspension was filtered, ad the solvent was completely removed from the filtrate to give **13a** as a dense yellow oil. Yield: 157 mg, 0.60 mmol, 94%. Anal. Calcd for $C_{15}H_{19}NO_3$ (261.136 g/mol): C, 68.94; H, 7.33; N, 5.36. Found: C, 68.85; H, 7.34; N, 5.22. IR (cm^{-1}): ν(NH) 3430 vs, 3357 vs; ν(CO) 1698 s. ^{1}H NMR (400.9 MHz): δ 1.43 (s, 9 H, ^{t}Bu), 2.88 (t, 2 H, CH_2Ar, $^{3}J_{HH}$ = 6.8 Hz), 3.45 (m, 2 H, CH_2N), 4.65 (s, 1 H, NH), 7.22 (td, 1 H, H5 or H6, $^{3}J_{HH}$ = 7.6, $^{3}J_{HH}$ = 1.2 Hz), 7.29 (td, 1 H, H5 or H6, $^{3}J_{HH}$ = 7.6, $^{3}J_{HH}$ = 1.6 Hz,), 7.45 (s, 1 H, H2), 7.47 (br s, 1 H, H4), 7.56 (br d, 1 H, H7, $^{3}J_{HH}$ = 7.6 Hz). $^{13}C\{^{1}H\}$ NMR (100.8 MHz): δ 24.3 (s, CH_2Ar), 28.4 (s, Me, ^{t}Bu), 39.9 (s,

CH_2N), 79.3 (s, *C*Me_3), 111.5 (s, CH4), 117.3 (s, C3), 119.5 (s, CH7), 122.4 (s, CH5), 124.3 (s, CH6), 127.9 (s, C3a), 141.8 (s, CH2), 155.4 (s, C7a), 155.8 (s, CO).

Synthesis of *tert*-Butyl 2-(Benzo[*b*]thiophen-3-yl)ethylcarbamate (13b). Na_2CO_3 (496 mg, 4.68 mmol) was added to a suspension of **B·HCl** (500 mg, 2.34 mmol) in CH_2Cl_2 (50 mL). The suspension was stirred for 2.5 h at room temperature, and di-*tert*-butyl dicarbonate (Boc_2O; 562 mg, 2.57 mmol) was added. After 24 h, the mixture was washed with distilled water (3 x 50 mL). The organic phase was dried over $MgSO_4$, the suspension was filtered, the solvent was removed from the filtrate, and *n*-pentane (20 mL) was added to the colorless residue. The solvent was again removed, *n*-pentane (20 mL) was added, and the suspension was vigorously stirred. The suspension was filtered, and the solid was air-dried to give pure compound **13b** as a colorless solid. Yield: 558 mg, 2.01 mmol, 86%. Mp: 59 ºC. IR (cm^{-1}): ν(NH) 3364 s; ν(CO) 1694 s. ESI-HRMS: exact calculated mass for $C_{15}H_{19}NNaO_2S$, 300.1034 [$(M+Na)^+$]; found, 300.1026. ^{1}H NMR (400.9 MHz): δ 1.44 (s, 9 H, Me, ^{t}Bu), 3.05 ("t", 2 H, CH_2Ar, $^3J_{HH}$ = 6.8 Hz), 3.49 (m, 2 H, CH_2N), 4.63 (br s, 1 H, NH), 7.16 (s, 1 H, H2), 7.37 (m, 2 H, H5 + H6), 7.77 (br d, 1 H, H4, $^3J_{HH}$ = 8.0 Hz), 7.86 (m, 1 H, H7). $^{13}C\{^1H\}$ NMR (100.8 MHz): δ 28.4 (s, Me, ^{t}Bu), 29.1 (s, CH_2Ar), 40.1 (s, CH_2N), 79.3 (s, *C*Me_3), 121.6 (s, CH4), 122.4 (s, CH2), 122.9 (s, CH7), 124.0 (s, CH5), 124.3 (s, CH6), 133.5 (s, C3), 138.8 (s, 3a), 140.5 (s, C7a), 155.8 (s, CO).

Synthesis of (*E*)-Methyl 3-(3-(2-(*tert*-Butoxycarbonyl)ethyl)benzo[*b*]furan-2-yl)acrylate (14a). In a Carius tube, $Pd(OAc)_2$ (10 mg, 0.043 mmol), $Cu(OAc)_2$ (78 mg, 0.43 mmol) and methyl acrylate (77.2 μL, 0.86 mmol) were added to a solution of **13a** (112 mg, 0.43 mmmol) in 1,2-dichloroethane (3 mL), and the mixture was refluxed for 16 h. CH_2Cl_2 (25 mL) was added to the resulting suspension, and the mixture was washed with aq. NH_3 (10%; 2 x 20 mL). The organic layer was collected, dried over a plug of $MgSO_4$, and filtered.

The solvent was removed from the filtrate to afford crude **14a**. Crude **14a** was dissolved in CH_2Cl_2 (2 mL) and purified by preparative TLC in silica gel with fluorescent indicator, eluting with a 7:1 mixture of petroleum ether/ethyl acetate. The most retained fraction was collected, and the product was extracted from the silica gel using ethyl acetate (50 mL). The solvent was removed to give compound **14a** as a yellow oil. Yield: 77% (by ^{1}H NMR). IR (cm^{-1}): ν(NH) 3372 br w; ν(CO) 1714 s, 1635 m. ESI-HRMS calcd for $C_{19}H_{23}NNaO_5$, 368.1468 [$(M+Na)^+$]; found, 368.1472. ^{1}H NMR (300.1 MHz): δ 1.43 (s, 9 H, ^{t}Bu), 3.02 (t, 2 H, CH_2N, $^3J_{HH}$ = 6.6 Hz), 3.39–3.44 (m, 2 H, CH_2Ar), 3.81 (s, 3 H, Me), 4.64 (br s, 1 H, NH), 6.57 (d, 1 H, =CH, $^3J_{HH}$ = 15.6 Hz), 7.22–7.28 (m, 1 H, H5), 7.34–7.40 (m, 1 H, H6), 7.44–7.48 (m, 1 H, H7), 7.56–7.62 (br s, 1 H, H4), 7.59 (d, 1 H, =CH, $^3J_{HH}$ = 15.6 Hz). ^{13}C{^{1}H} NMR (75.5 MHz): δ 24.5 (s, CH_2Ar), 28.3 (s, ^{t}Bu), 40.5 (s, CH_2N), 51.7 (s, Me), 79.4 (s, *C*Me_3), 111.4 (s, CH7), 117.8 (s, =CH), 120.3 (s, CH4), 121.9 (s, C3), 123.1 (s, CH5), 126.8 (s, CH6), 128.9 (s, =CH), 128.9 (s, C3a), 149.0 (s, C2), 154.9 (s, C7a), 155.7 (s, C-Boc), 167.2 (s, CO).

Synthesis of (*E*)-Methyl 3-(3-(2-(*tert*-Butoxycarbonyl)ethyl)benzo[*b*]thiophen-2-yl)acrylate (14b). In a Carius tube, $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), $Cu(OAc)_2$ (45 mg, 0.25 mmol) and methyl acrylate (135 μL, 1.50 mmol) were added to a solution of **13b** (70 mg, 0.25 mmol) in acetonitrile (3 mL), and the mixture was heated 110 ºC for 48 h. Solvent was removed to ca. 1 mL and CH_2Cl_2 (25 mL) was added to the resulting suspension. The mixture was washed with aq. NH_3 (10%; 2 x 30 mL). The organic layer was collected, dried over a plug of $MgSO_4$, and filtered. The solvent was removed from the filtrate to afford crude **14b** as a yellow oil. Crude **14b** was dissolved in CH_2Cl_2 (2 mL) and purified by column cromatography using aluminium oxide and eluting with a 4:1 mixture of petroleum ether/ethyl acetate. Yield: 57% (by ^{1}H NMR). Isolated yield: 36 mg, 0.10 mmol, 40%. ESI-HRMS calcd for $C_{19}H_{23}NNaO_4S$, 384.1245 [$(M+Na)^+$]; found, 384.1239. ^{1}H NMR (300.1

MHz): δ 1.43 (s, 3H, ^{t}Bu), 3.20 (t, 2 H, CH_2Ar, $^{3}J_{HH}$ = 6.0 Hz), 3.35–3.42 (m, 2 H, CH_2N), 3.81 (s, 3 H, Me), 4.64 (br s, 1 H, NH), 6.32 (d, 1 H, =CH, $^{3}J_{HH}$ = 15.3 Hz), 7.37–7.40 (m, 2 H, H4 + H5), 7.76–7.80 (m, 2 H, H6 + H7), 7.56–7.62, 7.98 (d, 1 H, =CH, $^{3}J_{HH}$ = 15.6 Hz). $^{13}C\{^{1}H\}$ NMR (75.5 MHz): δ 27.4 (s, CH_2Ar), 28.3 (s, ^{t}Bu), 40.9 (s, CH_2N), 51.8 (s, Me), 79.4 (s, *C*Me_3), 119.0 (s, =CH), 122.5 (s, CH6 or CH7), 122.9 (s, CH6 or CH7), 124.8 (s, CH4 or CH5), 126.6 (s, CH4 or CH5), 135.1 (s, C2), 135.3 (s, =CH), 137.6 (s, C3), 139.3 (s, C7a), 139.9 (s, C3a), 155.8 (C-Boc), 167.0 (s, CO).

Single Crystal X-ray Structure Determinations. Relevant crystallographic data, details of the refinements, and details (including symmetry operators) of hydrogen bonds, and CIF files for compounds **3a**·Et_2O, **3b**, **4a**, **6b**·1/6CH_2Cl_2, **7b**, **8b**·1/4CH_2Cl_2·1/4Et_2O, **9b** and **10b** are given in the Supporting Information. *Data Collection*. Crystals suitable for X-ray diffraction were mounted in inert oil on a glass fiber and transferred to a Bruker diffractometer. Data were recorded at 100(2) K, using graphite-monochromated Mo-Ka radiation (λ = 0.71073 Å), and ω- and ϕ-scan mode. Multiscan absorption corrections were applied for all complexes. *Structure Solution and Refinements*. Crystal Structures were solved by dual method and all non hydrogen atoms refined anisotropically on F^2 using the program SHELXL-2014/7 (**3a**·Et_2O, **3b**, **4a**, **6b**·1/6CH_2Cl_2, **7b**, **9b** and **10b**)[37] or SHELXL-2016/6 (**8b**·1/4CH_2Cl_2·1/4Et_2O)[38] Hydrogen atoms were refined as follows: Compounds **3a**·Et_2O, **6b**·1/6CH_2Cl_2, **7b**, **9b**, and **10b**: NH_2, free with SADI; methyl, rigid group; all others, riding. Complex **3b**: NH_2, free with DFIX; all others, riding. Complex **4a**: NH_2, free; methyls, rigid group; all others, riding. Complex **8b**·1/4CH_2Cl_2·1/4Et_2O: NH_2, free with DFIX; ordered methyl, rigid group; all others, riding. *Special features*: For **3b**: A region of residual electron density could not be interpreted in terms of realistic solvent molecules, even allowing for possible disorder. For this reason the program SQUEEZE, which is part of the PLATON system,[39] was employed to remove mathematically the effects of the solvent. Standard

deviations of refined parameters should be interpreted with caution. The void volume per cell was 594 $Å^3$ with a void electron count per cell of 146. This additional solvent was not taken into account when calculating derived parameters such as the formula weight, because the nature of the solvent was uncertain. For **6b**·1/6CH_2Cl_2: An ill-defined region of residual electron density over an inversion centre was interpreted as half a molecule of dichloromethane, disordered over two positions, with a ca. 37:13 occupancy distribution. For **8b**·1/4CH_2Cl_2·1/4Et_2O: An poorly-resolved region of residual electron density was interpreted as the superposition of half a molecule of dichloromethane and half a molecule of Et_2O. The carbon and the oxygen atoms of the Et_2O were refined as isotropic.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: xxxxx.

^1H and $^{13}C\{^1H\}$-APT NMR spectra of compounds **10–14**, crystallographic data for compounds **3a**·Et_2O, **3b**, **4a**, **6b**·1/6CH_2Cl_2, **7b**, **8b**·1/4CH_2Cl_2·1/4$E_{t2}O$, **9b** and **10b**, and details of hydrogen bonds (including symmetry operators) (PDF)

Accession Codes

CCDC 1866905, 1866907, 1866924–1866929 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.

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