Article

Palladium-Mediated Functionalization of Benzofuran and **Benzothiophene Cores**

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Supporting Information

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 from 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 anti-inflamatory, 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 functionalize the different positions within the heteroaromatic nuclei. As happens in many other aspects of chemistry, transitionmetal-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.²⁻⁶

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), amino acids (i.e., phenylalanine or tryptophan), or marketed psychoactive 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_rN_r , C_rS_r , $C_rS_$ (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 imine¹³ or a pyridine moiety,¹⁴ (2b) S,C,Npincer derivatives containing two five-membered rings,¹⁵ and (3b) C,N-five- or six-membered palladacycles metalated at the 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-benzo-

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furan and benzothiophene and (2) study the reaction of the new metallacycles with 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 ammoniums salts (triflate for the amine containing the benzofuran nucleus and chloride for the benzothiophene core) underwent C–H activation at the 2position 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 $[Pd{\kappa^2C,N-(C_8H_4O)-CH_2CH_2NH_2-3}(NCMe)_2]OTf$ (1a; Scheme 1), which

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



further reacted with NaCl to afford a yellow solid that precipitated from the reaction mixture. The IR and ¹H NMR spectra of this solid suggested the formulation $[Pd_2\{\kappa^2 C, N-(C_8H_4O)CH_2CH_2NH_2-3\}_2(\mu-Cl)_2]\cdot 2MeCN$ ($2a\cdot 2MeCN$), although other formulations cannot be ruled out. Complex 2a was obtained in analytically pure form by recrystallization of $2a\cdot 2MeCN$ from acetone. Complex $2a\cdot 2MeCN$ reacted with PPh₃ in a 1:2 molar ratio to give the mononuclear phosphino adduct $[PdCl\{\kappa^2 C, N-(C_8H_4O)CH_2CH_2NH_2-3\}(PPh_3)]$ (3a). For the synthesis of cationic derivatives, complex 1a was used as starting material. Thus, when 4-methyl-pyridine (4-pic) or ^tBuNC was added to a solution of 1a (molar ratio 2:1) in acetonitrile or CH_2Cl_2 , the complex $[Pd\{\kappa^2 C, N-(C_8H_4O)CH_2-CH_2NH_2-3\}(L)_2]OTf$ was isolated in moderate to good yield (L = 4-pic (4a; 62%), ^tBuNC (5a; 74%); Scheme 1).

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 $[Pd_2{\kappa^2C,N-(C_8H_4S)CH_2CH_2NH_2-3}_2(\mu-Cl)_2]$ ·2MeCN (**2b**·2MeCN; Scheme 2). Complex **2b**·

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



2MeCN reacted with neutral ligands (L) in a 1:2 molar ratio to give the mononuclear adducts $[PdCl{\kappa^2C,N-(C_8H_4S)CH_2-CH_2NH_2-3}(L)]$ (L = PPh₃, **3b**; 4-pic, **6b**; ^tBuNC, **7b**; XyNC, **8b**; Scheme 2).

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 belongs to an imine fragment.^{12,16}

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

The crystal structures of complexes $3a \cdot Et_2O$, 3b, 4a, $6b \cdot 1/$ $6CH_2Cl_2$, 7b, and $8b\cdot 1/4CH_2Cl_2\cdot 1/4Et_2O$ (Figures 1–6) have been determined by X-ray diffraction. The asymmetric unit of the crystal structures of complexes 6b·1/6CH₂Cl₂, 7b, and 8b· $1/4CH_2Cl_2 \cdot 1/4Et_2O$ 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 $3a \cdot Et_2O$, 7b, and $8b \cdot 1/4CH_2Cl_2$. $1/4Et_2O_1$, and slightly distorted for 3b, 4a, $6b\cdot 1/6CH_2Cl_2$). 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 $(4a, 6b \cdot 1/$ $6CH_2Cl_2$, 7b, and $8b\cdot 1/4CH_2Cl_2\cdot 1/4Et_2O$) or a twist-boat conformation ($3a \cdot Et_2O$, 3b). For complexes $3a \cdot Et_2O$, 3b, $6b \cdot$ $1/6CH_2Cl_2$, 7b, and $8b \cdot 1/4CH_2Cl_2 \cdot 1/4Et_2O$, 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 a *trans* position to the NH₂ 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.¹

The availability of the crystal structures of four complexes which only differed in the neutral ligand coordinated in the *trans* position with respect to the amino group allows us to



Figure 1. X-ray thermal ellipsoid plot of $3a \cdot Et_2O(50\% \text{ probability})$ 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).

compare the Pd–N bond lengths (Table 1), which increased along the sequence $6b \cdot 1/6CH_2Cl_2 < 7b \approx 8b \cdot 1/4CH_2Cl_2 \cdot 1/4Et_2O < 3b$ 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 75.5°) to avoid steric hindrance. Similarly, for complex 6b·1/6CH₂Cl₂, the aromatic ring of the 4-picoline is also rotated with respect to the coordination plane of the metal (angle of $59-90^{\circ}$, for the three independent molecules in the asymmetric unit). However, in complex 8b·1/4CH₂Cl₂, the xylyl ring of the isocyanide ligand is almost coplanar with the coordination plane of the metal (1° and 1.7° for both



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 $6b \cdot 1/6CH_2Cl_2$ (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.

molecules in the asymmetric unit). This feature allows the existence of intermolecular $\pi - \pi$ stacking interactions between the C₆H₄ and Xy rings. The geometrical parameters of the $\pi - \pi$ interactions 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



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**·1/4CH₂Cl₂·1/4Et₂O (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.

interesting are those transformations involving the direct functionalization of a C–H bond of the heteroaromatic core, 5,6,20 via the formation of an 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 arylcomplexes to afford organometallic iminoacyl,²¹ acyl-,²² and alkyl-derivatives²³ 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 synthesis of heteroarylalkyl amine derivatives containing the benzofuran and benzothiophene 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 on 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).

When XyNC was added to a suspension of **2b** in CH₂Cl₂ 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 ¹H NMR; Figure 7): the coordination complex **8b**, the iminoacyl complex **9b** (characterized by X-ray studies, see below), and [Pd₂Cl₂-(CNXy)₄] (which showed a very characteristic signal at δ 2.52 ppm). The latter compound was the only one isolated when additional XyNC (4 equiv) was added to the original yellow solution.^{27,29}

As we have stated in the previous section, complex 8b could be isolated in good yield by reacting the starting palladacycle 2. 2MeCN with 2 equiv of XyNC at 0 °C (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 1 equiv of XvNC (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 Et₂O into a solution of this mixture in CH₂Cl₂ led to the formation of two different types of crystals, which were manually separated: yellow needles, corresponding

Table 1. Selected Bond Lengths (Å) and	l Angles (deg) within the	e Coordination Sphere of	f Pd(II) for Complexe	es 3a•Et ₂ O, 3b,
6b·1/6CH ₂ Cl ₂ , 7b, and 8b·1/4CH ₂ Cl ₂ ·1	/4Et ₂ O			

		angles (deg)			
compound	Pd-N(1)	Pd-C(1)	Pd-L	Pd-Cl(1)	C(1)-Pd-N(1)
$3\mathbf{a} \cdot \mathbf{E} \mathbf{t}_2 \mathbf{O} \ (\mathbf{L} = \mathbf{P} 1)$	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)
$6b \cdot 1/6CH_2Cl_2 (L = N11)$	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)
$8b \cdot 1/4CH_2Cl_2 \cdot 1/4Et_2O$ (L = C12)	2.0609(16)	1.9900(17)	1.9439(18)	2.4073(5)	89.28(7)

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



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 NH₂ 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 8°), and rotated 54.7° and 62.3° 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 ¹H 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 ¹H and ¹³C{¹H} NMR spectra).

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 adequate synthesis for 9b, we tried an alternative method to prepare this type of *N*-heterocycle derivative. When complex 7b, which contained coordinated ^tBuNC, an isocyanide less prone than XyNC to undergo polyinsertion reactions, was treated with



Figure 7. ¹H NMR spectra $(1-5 \text{ ppm}; \text{CDCl}_3)$ 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 $[\text{Pd}_2\text{Cl}_2(\text{CNXy})_4]$, and the black asterisks indicate the resonances corresponding to traces of solvents.

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 were 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 sixmembered 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 $(C(10)-N(1)-C(11), 121.8(3)^{\circ}; C(11)-N(2)-C(12),$ $128.9(3)^{\circ}$). In compound 10b, the cationic units were connected between them and to the triflate groups through hydrogen bonds, giving layers (see the Supporting Information).

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



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).

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 at 120 °C 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 CH₂Cl₂ at 65 °C, with CO in the presence of NEt₃, afforded Pd(0), HNEt₃Cl, and 3,4-dihydro[1]-benzothieno[2,3-c]pyridin-1(2H)-one (**11b**; Scheme 5) in moderate yields (54%). The NEt₃ 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 NEt₃ in CHCl₃ for ca. 18 h to afford 11a and metallic palladium (Scheme 5).



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).

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



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 ¹H NMR spectra of both lactams exhibited one signal between 6.40 and 6.72 ppm (δ : 6.72 (**11a**), 6.46 ppm (**11b**)), corresponding to the NH proton. In the ¹³C{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 POCl₃ (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.

Insertion of Methyl Acrylate into the Pd–C Bond. When complex 1a reacted with methyl acrylate (molar ratio 1:4) in CHCl₃, at 65 °C 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- 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



12a and *Z*-**12a** (final ratio *E*-**12a**:*Z*-**12a** ca. 1:3, after 18 h at 65 °C; Scheme 6 and Figure 10). The isolation of the *E* isomer, the kinetically favored product, could be attributed to its



Figure 10. ¹H 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/Et₂O (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 °C 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.

insolubility in the reaction media (CHCl₃), 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.

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



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 NH₃ group are depicted as dashed green lines.

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 NH₃ 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 CH₂N 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 NH₃ group in the former. Unfortunately, the NH₃ groups were not observed in the ¹H NMR after some time in acetone solution.

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

We tried an analogous alkenylation with the palladacycle containing the benzothiophene core. Thus, we carried out the reaction between complex $2b \cdot 2MeCN$ and AgOTf, and after removing the AgCl formed, we added methyl acrylate (molar ratio Pd:alkene 1:2) and heated the mixture in CHCl₃, at 65 °C for 48 h. In the reaction media, the alkenyl derivative *E*-12b (identified by ¹H 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 °C; Scheme 6). This process was slower for 12b than for 12a, likely due to the nature of the heteroatom in the ring.

Scheme 7. Proposed Mechanism for the Isomerization of 12a



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 include 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-NH₂ 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 nondirected Pdcatalyzed 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-aminoethyl-substituted benzofuran and benzothiophene cores, we converted the amines A and B into their corresponding N-Boc derivatives 13a and 13b (Boc = tertbutoxycarbonyl; Scheme 8).

We attempted the Pd-catalyzed C–H alkenylation of substrate 13a in a range of different conditions (see the SI). 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 °C in the presence of 2 equiv of Cu(OAc)₂ as the oxidant and 2 equiv of methyl acrylate (Scheme 9). Other combinations of solvents (MeCN, HOAc, 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 8. Synthesis of N-Boc Derivatives



Scheme 9. Optimized Conditions for the 2-Alkenylation of Substrates 13^a



^{*a*}For 13a, solvent = 1,2-dichloroethane, and for 13b, solvent = acetonitrile. The reported yields were determined 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 could 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 CDCl₃ on Bruker Avance 300 or 400 spectrometers at 298 K. Chemical shifts are referenced to internal TMS. Signals in the ¹H and ¹³C{¹H} 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 C₈H₄O and C₈H₄S, respectively. Inserted and coordinated XyNC are denoted by XyNCⁱ and XyNC^c, respectively. Melting points were determined on a Reichert apparatus and are uncorrected. Conductivities were measured with a Crison Micro CM2200 conductometer. Elemental analyses were carried out with a Carlo Erba 1106 microanalyzer. Infrared spectra were recorded in the range 4000-200 cm⁻¹ on a PerkinElmer 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 (C₈H₅O)CH₂CH₂NH₃OTf (A·HOTf). Trifluoromethanesulfonic acid (547 μ L, 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 °C and filtered. The solid was washed with Et₂O (2×5 mL) and air-dried to afford A·HOTf as a colorless solid. Yield: 1708 mg, 5.49 mmol, 88%. Anal. Calcd for C₁₁H₁₂F₃NO₄S (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 °C. $\Lambda_{\rm M}$ (Ω^{-1} cm² mol⁻¹): 114 (5.0 × 10⁻⁴ M in acetone). IR (cm⁻¹): ν (NH) 3202 br, vs ¹H NMR (300.1 MHz, DMSO- d_6): δ 2.94 (t, 2 H, CH₂Ar, ${}^{3}J_{HH}$ = 6.9 Hz), 3.13 (m, 2 H, CH₂N), 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, NH₃), 7.88 (s, 1 H, H2). ${}^{13}C{}^{1}H{}$ NMR (100.8 MHz, DMSO- d_6): δ 21.3 (s, CH₂Ar), 38.2 (s, CH₂N), 111.4 (s, CH4), 115.5 (s, C3), 119.6 (s, CH7), 120.6 (q, CF₃SO₃, ${}^{1}J_{CF} = 319.4 \text{ Hz}$, 122.6 (s, CH2), 124.5 (s, CH5), 127.3 (s, C3a), 143.0.3 (s, CH6), 154.8 (s, C7a).

Synthesis of (C₈H₅S)CH₂CH₂NH₃Cl (B·HCl). Under a nitrogen atmosphere, a Carius tube was charged with 3-cyanomethylbenzothiophene (2.5 g, 14.4 mmol), dry THF (15 mL), and BH₃. THF (20 mL of solution 1 M in TFH, 20 mmol), and the mixture was stirred at room temperature for 3.5 h. The reaction mixture was cooled to 0 $^{\circ}\text{C}$ 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 0.5 M) was added to the residue, and the mixture was heated at 100 °C for 1 h. The solvent was evaporated to ca. 20 mL, and the resulting suspension was washed with Et_2O (2 × 30 mL). The aqueous phase was basified with NaOH (solution 1 M) until pH = 12, and extracted with ethyl acetate $(2 \times 20 \text{ mL})$. 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 Et₂O/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 Et₂O/acetone (3×5) 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 C₁₀H₁₂ClNS (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 °C. IR (cm^{-1}) : $\nu(NH)$ 3340 br; $\delta(NH_2)$ 1603 m. ¹H NMR (300.1 MHz,

DMSO- d_6): δ 3.12 (br s, 2 H, CH₂N), 3.17–3.22 (m, 2 H, CH₂Ar), 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, NH₃). ¹³C{¹H} NMR (75.5 MHz, DMSO- d_6): δ 25.9 (s, CH₂Ar), 38.2 (s, CH₂N), 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{k²(C,N-(C₈H₄O)CH₂CH₂NH₂-3}(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 CH₃CN (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 Et₂O was added (25 mL). The suspension was filtered, and the solid was washed with Et_2O (2 × 5 mL) and air-dried to afford complex 1a as a yellow solid. Yield: 700 mg, 1.40 mmol, 87%. Anal. Calcd for C15H16F3N3O4SPd (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 °C. Λ_M $(\Omega^{-1} \text{ cm}^2 \text{ mol}^{-1})$: 113 (5.0 × 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-d₆): δ 2.37 (s, 6 H, MeCN), 2.67-2.69 (m, 2 H, CH₂N), 2.81 ("t", 2 H, CH₂Ar, ${}^{3}J_{HH} = 5.6$ Hz), 4.98 (br s, 2 H, NH₂), 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). ${}^{13}C{}^{1}H$ NMR (100.8 MHz, DMSO- d_6): δ 1.1 (s, Me), 23.1 (s, CH₂Ar), 40.9 (s, CH₂N), 110.0 (s, CH7), 115.4 (s, C3), 117.4 (s, CH4), 120.7 (q, CF_3SO_3 , ${}^1J_{CF} = 317.2 \text{ Hz}$), 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). ¹⁹F NMR (282.4 MHz): δ -78.02 (CF₃SO₃).

Synthesis of $[Pd_2(\mu-CI)_2{\kappa^2(C,N-(C_8H_4O)CH_2CH_2NH_2-3)_2]}$ 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 CH₃CN (50 mL). The resulting mixture was stirred at room temperature overnight and filtered over a plug of Celite. NaHCO₃ (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 $H_2O~(3\times 5~mL)$ and $Et_2O~(3\times 5~mL)$ 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 H₂O (3 mL) was added. The suspension was filtered and the solid was washed with H_2O (3 × 5 mL) and Et₂O (3 \times 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/CH2Cl2. Anal. Calcd for C₂₀H₂₀Cl₂N₂O₂Pd₂ (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 °C. IR (cm⁻¹): ν (NH) 3313 m, 3297 m, 3248 s, 3228 m; δ (NH₂) 1578 m. NMR data for 2a·2MeCN: ¹H NMR (300.1 MHz, DMSO- d_6): δ 2.06 (s, 3 H, MeCN), 2.63 (m, 2 H, CH₂N), 2.77 ("t", 2 H, CH₂Ar, ${}^{3}J_{HH}$ = 5.4 Hz), 4.88 (br s, 2 H, NH₂), 7.05–7.14 (m, 2 H, C₆H₄), 7.32–7.35 (m, 2 H, C₆H₄). ¹³C{¹H} NMR (75.5 MHz, DMSO- d_6): δ 1.1 (s, MeCN), 22.9 (s, CH₂Ar), 39.8 (s, CH₂N, partially obscured by the signal corresponding to the DMSO-d₆), 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 ${}^{13}C{}^{1}H{}$ signal corresponding to the CN group was not observed.

Synthesis of [Pd₂(μ -Cl)₂(κ ²(*C*,*N*-(C₈H₄S)CH₂CH₂NH₂-3}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 Et₂O (2 × 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 C₂₀H₂₀Cl₂N₂Pd₂S₂·2CH₃CN (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 °C. IR (cm⁻¹): ν (NH) 3207 s, 3133 s; ν (CN) 2318 m, 2290 w; δ (NH₂) 1595 m; ν (Pd–Cl) 318 m. ¹H NMR (300.1 MHz, DMSO-*d*₆): 2.06 (s, 3 H, MeCN), 2.65 (br s, 2 H, CH₂N), 2.91 ("t", 2 H, CH₂Ar, ³J_{HH} = 5.4 Hz), 4.60 (br s, 2 H, NH₂), 7.05 (b t, 1 H, H6, ${}^{3}J_{HH}$ = 7.2 Hz) 7.15 (b t, 1 H, H5, ${}^{3}J_{HH}$ = 7.2 Hz), 7.47 (br d, 1 H, H4, ${}^{3}J_{HH}$ = 7.8 Hz), 7.65 (br d, 1 H, H7, ${}^{3}J_{HH}$ = 7.8 Hz). ${}^{13}C{}^{1}H$ } NMR (75.5 MHz, DMSO- d_{6}): δ 1.1 (s, Me, MeCN), 28.4 (s, CH₂Ar), 41.1 (s, CH₂N), 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 $[Pd{\kappa^2(C,N-(C_8H_4O)CH_2CH_2NH_2-3}Cl(PPh_3)]\cdot Et_2O$ (3a·Et₂O). PPh₃ (115 mg, 0.438 mmol) was added to a suspension of 2a·2MeCN (150 mg, 0.218 mmol) in CH₂Cl₂ (10 mL), and the mixture was stirred for 15 min at room temperature. The solution was filtered through a plug of MgSO₄, solvent was removed from the filtrate to ca. 2 mL, and $Et_2O(20 \text{ mL})$ was added. The suspension was filtered, and the solid was washed with Et_2O (2 × 5 mL) and airdried to afford 3a·Et₂O as a pale yellow solid. Yield: 212 mg, 0.332 mmol, 76%. Anal. Calcd for C28H25ClNOPPd·C4H10O (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 °C (dec). IR (cm⁻¹): ν (NH) 3248 w, 3211 m, 3124 m. ¹H NMR (400.9 MHz): δ 1.25 (t, 6 H, MeCH₂O, ³J_{HH} = 7.2 Hz), 2.93 ("t", 2 H, CH₂Ar, ${}^{3}J_{HH}$ = 5.6 Hz), 3.06 (m, 2 H, CH₂N), 3.52 (q, 4 H, CH₂O, ${}^{3}J_{HH} = 7.2$ Hz), 3.53 (br s, 2 H, obscured by the signal of the CH₂O, NH₂), 6.55 (d, 1 H, H7, ${}^{3}J_{HH} = 8.0$ Hz), 6.88 (td, 1 H, H6, ${}^{3}J_{HH} = 7.6, {}^{4}J_{HH} = 1.2 \text{ Hz}), 7.04 \text{ (td, 1 H, H5, } {}^{3}J_{HH} = 7.4, {}^{4}J_{HH} = 0.8$ Hz), 7.27–7.35 (m, 7 H, H4 + *m*-H of PPh₃), 7.36–7.43 (m, 3 H, *p*-H, PPh₃), 7.66–7.75 (m, 6 H, *o*-H, PPh₃). ¹³C{¹H} NMR (100.8 MHz): δ 15.2 (s, MeCH₂O), 24.6 (s, CH₂Ar), 40.0 (s, CH₂N), 65.8 (s, CH₂O), 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, PPh₃, ${}^{3}J_{CP} = 11.0$ Hz), 128.7 (s, C3a), 130.2 (s, p-CH, PPh₃, ${}^{4}J_{CP} = 2.0$ Hz), 131.6 (d, *i*-C, PPh₃, ${}^{1}J_{CP}$ = 53.1 Hz), 134.5 (d, o-CH, PPh₃, ${}^{2}J_{PH}$ = 11.6 Hz), 156.4 (d, C7a, ${}^{4}J_{CP}$ = 3.5 Hz), 158.3 (d, C2, ${}^{3}J_{CP}$ = 5.3 Hz). ${}^{31}P{}^{1}H{}$ NMR (162.3 MHz): δ 38.9 (s, PPh₃). Single crystals suitable for an X-ray diffraction study were obtained by slow diffusion of Et₂O into a solution of 3a·Et₂O in CH₂Cl₂.

Synthesis of $[Pd{\kappa^2(C,N-(C_8H_4S)CH_2CH_2NH_2-3}Cl(PPh_3)]\cdot Et_2O$ (3b). PPh₃ (100 mg, 0.38 mmol) was added to a suspension of 2b· 2MeCN (130 mg, 0.18 mmol) in CH₂Cl₂ (30 mL), and the resulting mixture was stirred for 30 min. The solution was filtered through a plug of MgSO₄, the filtrate was concentrated to ca. 3 mL, and npentane (30 mL) was added. The suspension was filtered, and the solid was washed with *n*-pentane $(2 \times 3 \text{ mL})$ and dried under vacuum to obtain complex 3b as a yellow solid. Yield: 136 mg, 0.23 mmol, 65%. Anal. Calcd for C₂₈H₂₅ClNPPdS (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 °C. IR (cm⁻¹): ν (NH) 3240 m, 3200 m, 3060 m. ¹H NMR (400.9 MHz): δ 2.75 (m, 2 H, CH₂N), 3.22 ("t", 2 H, CH₂Ar, ${}^{3}J_{HH}$ = 5.6 Hz), 3.48 (m, 2 H, NH₂), 7.00 (ddd, 1 H, H6, ${}^{3}J_{HH} = 8.0$, ${}^{3}J_{HH} = 7.2$, ${}^{4}J_{HH} = 1.2$ Hz), 7.19 (ddd, 1 H, H5, ${}^{3}J_{HH} = 8.0$, ${}^{3}J_{HH} = 7.2$, ${}^{4}J_{HH} = 7.2$, ${}^{4}J_{H}$ 1.2 Hz), 7.29-7.34 (m, 6 H, m-H, PPh₃), 7.37-7.40 (m, 3 H, p-H, PPh₃), 7.42 ("d", 1 H, H7, ${}^{3}J_{HH} = 8.0$ Hz), 7.55 ("d", 1 H, H4, ${}^{3}J_{HH} =$ 8.0 Hz), 7.61-7.65 (m, 6 H, o-H, PPh₃). ¹³C{¹H} NMR (75.5 MHz): δ 31.5 (s, CH₂Ar), 37.5 (d, CH₂N, ${}^{3}J_{\rm PC}$ = 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 , ${}^{3}J_{PC} = 11.0 \text{ Hz}$), 129.3 (s, C3), 130.6 (d, *p*-CH, PPh₃, ${}^{4}J_{PC} = 2.0$ Hz), 130.9 (d, *i*-C, PPh₃, ${}^{1}J_{PC}$ = 52.5 Hz), 134.8 (d, *o*-CH, PPh₃, ${}^{2}J_{PC}$ = 11.6 Hz), 138.3 (s, C2), 143.6 (s, C3a), 144.1 (d, C7a, ${}^{4}J_{PC}$ = 2.7 Hz). ³¹P{¹H} NMR (162.3 MHz): δ 34.6 (s, PPh₃). Single crystals suitable for an X-ray diffraction study were obtained by slow diffusion of *n*-pentane into a solution of **3b** in CHCl₃.

Synthesis of $[Pd{\kappa^2(C,N-(C_8H_4O)CH_2CH_2NH_2-3}(4-pic)_2]OTf$ (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 CH₃CN (50 mL). The resulting mixture was stirred at room temperature overnight. 4-Picoline (80 μ L, 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 Et₂O (25 mL) was added. The suspension was filtered, and the solid was washed with Et₂O (2 × 5 mL) and air-dried to afford 4a as a pale yellow solid. Yield: 150 mg, 0.25 mmol, 62%. Anal. Calcd for C₂₃H₂₄F₃N₃O₄SPd (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 °C (dec). $\begin{array}{l} \Lambda_{\rm M} \; (\Omega^{-1} \; {\rm cm}^2 \; {\rm mol}^{-1}): \; 120 \; (5.0 \times 10^{-4} \; {\rm M} \; {\rm in} \; {\rm acetone}). \; {\rm IR} \; ({\rm cm}^{-1}): \\ \nu({\rm NH}) \; 3291 \; {\rm m}, \; 3216 \; {\rm m}, \; 3146 \; {\rm s}; \; \nu({\rm C=\!\!N}) \; 1618 \; {\rm s}, \; 1595 \; {\rm s}. \; ^1{\rm H} \; {\rm NMR} \\ (400.9 \; {\rm MHz}, \; {\rm acetone-} d_6): \; \delta \; 2.40 \; ({\rm s}, \; 3 \; {\rm H}, \; {\rm Me}), \; 2.45 \; ({\rm s}, \; 3 \; {\rm H}, \; {\rm Me}), \\ 2.96-3.03 \; ({\rm m}, \; 4 \; {\rm H}, \; {\rm CH}_2{\rm N} + \; {\rm CH}_2{\rm Ar}), \; 4.63 \; ({\rm br} \; {\rm s}, \; 2 \; {\rm H}, \; {\rm NH}_2), \; 6.95- \\ 7.08 \; ({\rm m}, \; 3 \; {\rm H}, \; {\rm H5} + {\rm H6} + {\rm H7}), \; 7.34 \; ({\rm dd}, \; 1 \; {\rm H}, \; {\rm H}^3 \; J_{\rm HH} = 6.8 \; {\rm Hz}, \; ^3 J_{\rm HH} \\ = 0.8 \; {\rm Hz}), \; 7.43 \; ({\rm d}, \; 4 \; {\rm H}, \; m{\rm -H}, \; {\rm pic}, \; ^3 J_{\rm HH} = 6.0 \; {\rm Hz}), \; 8.70 \; ({\rm d}, \; 2 \; {\rm H}, \; {\rm o-H}, \\ {\rm pic}, \; ^3 J_{\rm HH} = 5.6 \; {\rm Hz}), \; 8.81 \; ({\rm d}, \; 2 \; {\rm H}, \; {\rm o-H}, \; {\rm pic}, \; ^3 J_{\rm HH} = 6.4 \; {\rm Hz}). \; ^{13}{\rm C}\{^1{\rm H}\} \\ {\rm NMR} \; (100.8 \; {\rm MHz}, \; {\rm acetone-} d_6): \; \delta \; 20.9 \; ({\rm s}, \; {\rm Me}, {\rm pic}), \; 21.0 \; ({\rm s}, \; {\rm Me}, {\rm pic}), \\ 24.2 \; ({\rm s}, \; {\rm CH}_2), \; 42.3 \; ({\rm s}, \; {\rm CH}_2), \; 110.4 \; ({\rm s}, \; {\rm CH5} \; {\rm or} \; {\rm CH7}), \; 115.2 \; ({\rm s}, \; {\rm C3} \; {\rm or} \; {\rm C3a}), \; 117.8 \; ({\rm s}, \; {\rm CH4}), \; 122.0 \; ({\rm s}, \; {\rm CH5} \; {\rm or} \; {\rm CH7}), \; 122.2 \; ({\rm s}, \; {\rm CH6}), \; 122.2 \; ({\rm q}, \; {\rm CF}_3{\rm SO}_3, \; ^1 J_{\rm CF} = \; 319.4 \; {\rm Hz}), \; 127.4 \; ({\rm s}, \; m{\rm -CH}, \; {\rm pic}), \; 127.6 \; ({\rm s}, \; m{\rm -CH}, \\ {\rm pic}), \; 129.9 \; ({\rm s}, \; {\rm C3} \; {\rm or} \; {\rm C3a}), \; 150.8 \; ({\rm s}, \; o{\rm -CH}, \; {\rm pic}), \; 152.5 \; ({\rm s}, \; {\rm C-Me}, \\ {\rm pic}), \; 152.9 \; ({\rm s}, \; o{\rm -CH}, \; {\rm pic}), \; 156.2 \; ({\rm S}, \; {\rm C2}), \; 157.9 \; ({\rm s}, \; {\rm C7a}). \end{array} \right$

Synthesis of $[Pd{\kappa^2(C,N-(C_8H_4O)CH_2CH_2NH_2-3}(CN^tBu)_2]OTf$ (5a). A solution of ^tBuNC (68 μ L, 0.60 mmol) in CH₂Cl₂ (15 mL) was added dropwise to a solution of 1a in CH₂Cl₂ (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 Et₂O (20 mL) was added. The suspension was filtered, and the solid was washed with Et₂O (2×5 mL) and air-dried to afford 5a as a light yellow solid. Yield: 129 mg, 0.22 mmol, 74%. Anal. Calcd for C₂₁H₂₉F₃N₃O₄SPd (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 °C (dec). $\Lambda_{\rm M} \ (\Omega^{-1} \ {\rm cm}^2 \ {\rm mol}^{-1})$: 128 (5.0 × 10⁻⁴ M in acetone). IR (cm⁻¹): ν (NH) 3235 s, 3152 m; ν (CN) 2243 s. ¹H NMR (400.9 MHz): δ 1.63 (s, 9 H, ^tBu), 1.70 (s, 9 H, ^tBu), 2.93 (t, 2 H, CH₂Ar, ³ $J_{HH} = 6.0$ Hz), 3.04-3.08 (m, 2 H, CH₂N), 4.22 (br s, 2 H, NH₂), 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). ¹³C{¹H} NMR (75.5 MHz): δ 23.7 (s, CH₂Ar), 29.8 (s, ^tBu), 29.9 (s, ^tBu), 40.6 (s, CH₂N), 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 ${}^{13}C{}^{1}H{}$ signal corresponding to the OTf group was not observed. ¹⁹F NMR (282.4 MHz): δ -77.9 (s, OTf).

Synthesis of $[Pd{\kappa^2(C,N-(C_8H_4S)CH_2CH_2NH_2-3}Cl(4-pic)]$ (6b). 4-Picoline (135 μ L, 1.39 mmol) was added to a suspension of 2. 2MeCN (500 mg, 0.70 mmol) in CH₂Cl₂ (40 mL), and the resulting mixture was stirred for 30 min. The solution was filtered through a plug of MgSO₄, the filtrate was concentrated to ca. 3 mL, and Et₂O (30 mL) was added. The suspension was filtered, and the solid was washed with Et₂O (2 \times 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 C₁₆H₁₇ClN₂PdS (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 °C. 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, ${}^{3}J_{HH}$ = 6.0 Hz), 7.19 (m, 1 H, H6), 7.30 (m, 1 H, H5), 7.52 (d, 1 H, H4, ${}^{3}J_{\rm HH} = 8.1$ Hz), 7.63 (d, 1 H, H7, ${}^{3}J_{\rm HH} = 7.8$ Hz), 8.24 ("d", 2 H, o-H, pic, ${}^{3}J_{HH} = 6.6 \text{ Hz}$). ${}^{13}C{}^{1}H}$ NMR (75.5 MHz): δ 21.0 (s, Me), 28.4 (s, CH₂Ar), 41.4 (s, CH₂N), 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 Et₂O into a solution of **6b** in CH₂Cl₂.

Synthesis of $[Pd{\kappa^2(C,N-(C_8H_4S)CH_2CH_2NH_2-3}Cl(CN^tBu)]$ (7b). A solution of 'BuNC (62.9 μ L, 0.56 mmol) in CH₂Cl₂ (15 mL) was added dropwise (ca. 15 min) to a suspension of 2.2MeCN (200 mg, 0.28 mmol) in CH₂Cl₂ (15 mL). The resulting yellow solution was stirred for 15 min and filtered through a plug of MgSO₄. The filtrate was concentrated, without heating, to ca. 1 mL, and Et₂O (20 mL) was added. A colorless solid appeared when the solvent from the mixture was evaporated to ca. 5 mL. Et₂O (15 mL) was added, and the resulting suspension was filtered, and the solid was washed with cold Et₂O $(2 \times 3 \text{ mL})$ 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 × 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 C₁₉H₁₉ClN₂PdS (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 °C. IR (cm⁻¹): ν (NH) 3250 s, 3202 m, 3130 m; ν (CN) 2213 vs ¹H NMR (300.1 MHz): δ 1.36 (s, 9 H, Me, ¹Bu), 2.98 (m, 2 H, CH₂N), 3.10 ("t", 2 H, CH₂Ar, ³J_{HH} = 5.1 Hz), 3.79 (br s, 2 H, NH₂), 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). ¹³C{¹H} NMR (75.5 MHz): δ 28.7 (s, CH₂Ar), 29.5 (s, Me, ¹Bu), 40.7 (s, CH₂N), 58.5 (s, CMe₃), 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 Et₂O.

Synthesis of $[Pd{\kappa^2(C,N-(C_8H_4S)CH_2CH_2NH_2-3}Cl(CNXy)]$ (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 CH₂Cl₂ (10 mL) at -15 °C. The resulting solution was stirred for 3 min at -15 °C and filtered through a plug of MgSO₄. The filtrate was concentrated under vacuum, without heating, to ca. 1 mL, and Et₂O (20 mL) was added. The resulting suspension was filtered, and the solid was washed with Et_2O (2 × 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 Et₂O (2×3 mL) and airdried to give a second crop of complex 8b as a colorless solid (22 mg). Yield: 227 mg, 0.51 mmol, 76%. Anal. Calcd for C₁₉H₁₉ClN₂PdS (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 °C. IR (cm⁻¹): ν(NH) 3272 m, 3203 m, 3132 m; ν (CN) 2192 s. ¹H NMR (400.9 MHz): δ 2.41 (s, 6 H, Me, Xy), 3.04 (m, 2 H, CH₂N), 3.13 ("t", 2 H, CH₂Ar, ${}^{3}J_{HH}$ = 4.8 Hz), 3.90 (br s, 2 H, NH₂), 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, ${}^{3}J_{HH} = 8.0$ Hz), 7.45 ("d", 1 H, H4, ${}^{3}J_{HH} = 8.0$ Hz), 7.62 ("d", 1 H, H7, ${}^{3}J_{HH}$ = 7.4 Hz). ¹³C{¹H} NMR (100.8 MHz): δ 19.0 (s, Me, Xy), 28.7 (s, CH₂Ar), 40.7 (s, CH₂N), 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/ 4CH2Cl2·1/4Et2O suitable for an X-ray diffraction study were obtained by slow diffusion of Et₂O into a solution of 8b in CH₂Cl₂.

Synthesis of [Pd{k²(C,N-(C(=NXy)C₈H₄S)CH₂CH₂NH₂-3}Cl-(CNXy)] (9b). A solution of XyNC (42 mg, 0.32 mmol) in CH₂Cl₂ (5 mL) was added dropwise (ca. 8 min) to a solution of complex 8b (150 mg, 0.33 mmol) in CH₂Cl₂ (10 mL) at 0 °C. The mixture was stirred at 0 °C for 1.5 h. Several changes in its color were observed until eventually it turned yellow. An aliquot (ca. 1 mL) was extracted from the reaction, the solvent was removed, and the residue was dissolved in CDCl₃. The ¹H 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 ¹H NMR analysis of a new aliquot 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 Et₂O (20 mL) was added. The resulting suspension was filtered, and the solid was washed with Et₂O (2×5 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 $(Et_2O/CH_2Cl_2 \text{ ratio} =$ 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 ¹³C{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, Xyⁱ), 3.05 (m, 2 H, NH₂), 3.30 (m, 2 H, CH₂N), 4.31 ("t", 2 H, CH₂Ar, ${}^{3}J_{HH} = 5.6$ Hz), 6.77–6.85 (m, 1 H, pH, Xyⁱ), 6.62 ("d", 2 H, *m*-H, Xyⁱ, ${}^{3}J_{HH} = 6.4$ Hz), 7.02 ("d", 2 H, *m*-H, Xy^c, ${}^{3}J_{HH} = 7.6$ 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). ${}^{13}C{}^{1}H{}$ NMR (100.8 MHz): δ 18.6 (s, Me, Xy^c), 19.4 (s, Me, Xyⁱ), 30.4 (s, CH₂Ar), 41.7 (s, CH₂N), 121.9 (s, CH4), 122.6 (s, CH7), 123.5 (s, *p*-CH, Xyⁱ), 124.2 (s, CH5), 126.4 (s, CH6), 127.0 (s, *C*–Me, Xyⁱ), 127.7 (s, *m*-CH, Xy^c), 127.8 (s, *m*-CH, Xyⁱ), 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, Xyⁱ), 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 Et₂O into a solution of C in CH₂Cl₂.

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 °C 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 C₁₅H₁₉N₂O [(M – OTf)⁺] 243.1492, found 243.1488. IR (cm⁻¹): ν (NH) 3270 m br. ¹H NMR (400.9 MHz): 1.54 (s, 9 H, ¹Bu), 3.03 (t, 2 H, CH₂Ar, ³J_{HH} = 7.6 Hz), 3.93 (t, 2 H, CH₂N, 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). ¹³C{¹H} NMR (100.8 MHz): δ 18.9 (s, CH₂Ar), 27.9 (s, Me, ¹Bu), 41.0 (s, CH₂N), 112.5 (s, CH7), 121.6 (q, CF₃SO₃, 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(2H)-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 CHCl₃ (30 mL). The mixture was protected from light and stirred for 24 h. The suspension was filtered through a plug of MgSO₄, 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 MgSO₄, the filtrate was concentrated to ca. 1 mL, and Et₂O (15 mL) was added. The solvent was completely removed, and Et₂O (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 offwhite solid (46 mg). Pure complex 10b was obtained by preparative TLC, in silica gel with a fluorescent indicator. The solid was dissolved in acetone (2 mL), and a 9:1 mixture of CH₂Cl₂/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 CH₂Cl₂/ 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 °C. 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. ¹H NMR (300.1 MHz): δ 1.65 (s, 9 H, Me, ^tBu), 3.35 (t, 2 H, CH₂N, ${}^{3}J_{HH}$ = 7.2 Hz), 4.03 (br t, 2 H, CH₂Ar, ${}^{3}J_{HH}$ = 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). ¹³C{¹H} NMR (75.5 MHz): δ 22.7 (s, CH₂Ar), 28.4 (s, Me, ^tBu), 41.5 (s, CH₂N), 55.8 (s, CMe₃), 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 ${}^{13}C{}^{1}H$ 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 CHCl₃.

Synthesis of 4-Dihydro[1]benzofuran[2,3-c]pyridin-1(2H)one (11a). NEt₃ (5 mL, 35.87 mmol) was added to a solution of 1a (150 mg, 0.3 mmol) in $CHCl_3$ (5 mL) under a 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 °C. IR (cm⁻¹): ν (CO) 1685 s. ESI-HRMS calcd for C₁₁H₁₀NO₂, 188.0706 [(M + H)⁺]; found, 188.0712. ¹H NMR (400.9 MHz): δ 3.04 (t, 2 H, CH₂Ar, ³J_{HH} = 7.2 Hz), 3.75 (td, 2 H, CH₂N, 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). ¹³C{¹H} NMR (75.5 MHz): δ 20.5 (s, CH₂Ar), 41.2 (s, CH₂N), 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(2H)-one (11b). NEt₃ (146 μ L, 1.05 mmmol) was added to a suspension of 2b·2MeCN (188 mg, 0.26 mmol) in CHCl₃ (15 mL), in a Carius tube. A CO atmosphere (1.2 atm) was established, and the mixture was stirred for 48 h at 65 °C. 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 NHEt₃Cl. The filtrate was again filtered through a plug of MgSO₄, the filtrate was concentrated to ca. 1 mL, and Et₂O (15 mL) was added. The resulting suspension was filtered, and the colorless solid was air-dried and identified as NHEt₃Cl (60 mg) by ¹H NMR. The filtrate was concentrated to ca. 1 mL, and npentane (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 °C. IR (cm⁻¹): ν (NH) 3211 br m; ν (CO) 1651 s. ESI-HRMS: calculated exact mass for C₁₁H₁₀NOS, 204.0483 [(M + 1)⁺]; found, 204.0481. ¹H NMR (400.9 MHz): δ 3.09 ("t", 2 H, CN₂Ar, ${}^{3}J_{HH} = 7.2$ Hz), 3.75 (td, 2 H, CH₂N, ${}^{3}J_{HH} = 7.2$, ${}^{3}J_{HH} = 2.4$ 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). ${}^{13}C{}^{1}H$ NMR (75.5 MHz): δ 22.9 (s, CH₂Ar), 41.2 (s, CH₂N), 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 μ L, 1.20 mmol) was added to a solution of 1a (150 mg, 0.30 mmol) in CHCl₃ (3 mL), and the mixture was stirred at 65 °C overnight. The resulting suspension was filtered to give crude E-12a (by ¹H NMR) as a gray 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 Et₂O was added (15 mL). The solvent was partially removed to ca. 10 mL, and Et₂O (10 mL) was added. The suspension was filtered, and the solid was washed with Et₂O (2 × 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 °C. $\Lambda_{\rm M}$ (Ω^{-1} cm² mol⁻¹): 108 (5.0 × 10⁻⁴ M in acetone). IR (cm⁻¹): ν (NH) 3162 br m; ν (CO) 1705 s. ESI-HRMS calcd for C₁₄H₁₆NO₃, 246.1130 [(M - OTf)⁺]; found, 246.1129. ¹H NMR (300.1 MHz, acetone- d_6): <u>E isomer</u>: δ 3.48–3.52 (m, 2 H, CH₂Ar), 3.59–3.69 (br m, 2 H, CH₂N), 3.77 (s, 3 H, Me), 6.52 (d, 1 H, =CH, ${}^{3}J_{HH} = 15.6$ Hz), 7.33 (ddd, 1 H, H5, ${}^{3}J_{HH} = 8.4$, ${}^{3}J_{HH} = 7.6$, ${}^{4}J_{HH} = 1.2$ Hz), 7.46 (td, 1 H, H6, ${}^{3}J_{HH} = 7.4$, ${}^{4}J_{HH} = 1.2$ Hz), 7.56 (dt, 1 H, H7, ${}^{3}J_{HH} = 7.2$, ${}^{4}J_{\rm HH}$ = 1.2 Hz), 7.71 (d, 1 H, =CH, ${}^{3}J_{\rm HH}$ = 15.3 Hz), 7.85 (ddd, 1 H, H4, ${}^{3}J_{HH} = 8.4$, ${}^{4}J_{HH} = 1.5$, ${}^{4}J_{HH} = 0.9$ Hz), 7.90 (br s, 3 H, NH₃). <u>Z</u> isomer (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, CH₂N, ${}^{3}J_{HH} = 7.2$ Hz), 6.52 (d, 1 H, =CH, ${}^{3}J_{HH}$ = 15.6 Hz, overlapped with the corresponding signal of the *E* isomer), 7.33 (ddd, 1 H, H5, ${}^{3}J_{HH} = 8.4$, ${}^{3}J_{HH} = 7.6, {}^{4}J_{HH} = 1.2 \text{ Hz}), 7.47 \text{ (td, 1 H, H6, } {}^{3}J_{HH} = 7.4, {}^{4}J_{HH} = 1.2 \text{ Hz})$

Hz), 7.57 (dt, 1 H, H7, ${}^{3}J_{HH} = 7.2$, ${}^{4}J_{HH} = 1.2$ Hz), 7.70 (d, 1 H, = CH, ${}^{3}J_{HH} = 15.3$ Hz), 7.86 (ddd, 1 H, H4, ${}^{3}J_{HH} = 8.4$, ${}^{4}J_{HH} = 1.5$, ${}^{4}J_{HH} = 0.9$ Hz), 7.90 (br s, 3 H, NH₃, overlapped with the corresponding signal of the *E* isomer). ${}^{13}C{}^{1}H{}$ NMR (75.5 MHz, acetone-*d*₆): <u>*E*</u> isomer (minor isomer, extracted from the 1:3 equilibrium mixture of *E*/*Z* isomers): δ 22.2 (s, CH₂Ar), 40.9 (s, CH₂N), 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 (major isomer, extracted from the 1:3 equilibrium mixture of *E*/*Z* isomers): δ 22.4 (s, CH₂Ar), 48.2 (s, CH₂N), 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).</u>

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 MgSO₄, the solvent was removed from the filtrate, and CHCl₃ (40 mL) was added. The suspension was transferred to a Carius tube, methyl acrylate (75 μ L, 0.832 mmol) was added, and the mixture was stirred for 48 h at 65 °C. 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 MgSO₄. The filtrate was concentrated to ca. 1 mL, and Et₂O (20 mL) was added. The suspension was filtered, and the solid was washed with CH_2Cl_2 (3 × 5 mL) and Et_2O (3 × 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 °C. IR (cm⁻¹): ν (NH) 3162 m; ν (CO) 1711 s; ν (C=C) 1617 m. ESI-HRMS: exact calculated mass for C14H16NO2S, 262.0896 $[(M + 1)^+]$; found, 262.0895. ¹H NMR (300.1 MHz, acetone-d₆): <u>E</u> isomer: δ 3.52–3.60 (br m, 2 H, CH₂N), 3.63–3.71 (m, 2 H, CH_2Ar), 3.77 (s, 3 H, Me), 6.33 (d, 1 H, =CH, ${}^{3}J_{HH}$ = 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, ${}^{3}J_{HH}$ = 15.3 Hz). The signal corresponding to the NH3 group was obscured by resonances of the aromatic protons. Z isomer (extracted from the 1:1.3 equilibrium mixture of E/Z isomers): δ 3.63–3.69 (m, 2 H, CH₂Ar, 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, CH₂N, ${}^{3}J_{HH} = 7.8$ Hz), 6.33 (d, 1 H, =CH, ${}^{3}J_{HH} = 15.6$ 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. ¹³C{¹H} NMR (75.5 MHz, acetone- d_6): <u>*E* isomer</u>: δ 24.1, 24.2 (s, CH₂Ar), 48.2, 40.3 (s, CH₂N), 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 ¹H 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 (Boc₂O; 154 mg, 0.70 mmol) was added, and the mixture was stirred for 12 h at room temperature. CH_2Cl_2 (30 mL) and distilled water (30 mL) were added, and the organic phase was collected and dried over MgSO₄. The suspension was filtered, and 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. ¹H NMR (400.9 MHz): δ 1.43 (s, 9 H, ¹Bu), 2.88 (t, 2 H, CH₂Ar, ³J_{HH} = 6.8 Hz), 3.45 (m, 2 H, CH₂N), 4.65 (s, 1 H, NH), 7.22 (td, 1 H, HS or H6, ³J_{HH} = 7.6, ³J_{HH} = 1.2 Hz), 7.29 (td, 1 H, HS or H6, ³J_{HH} = 1.6 Hz,), 7.45 (s, 1 H, H2), 7.47 (br s, 1 H, H4), 7.56 (br d, 1 H, H7, ³J_{HH} = 7.6 Hz). ¹³C{¹H} NMR (100.8 MHz): δ 24.3 (s, CH₂Ar), 28.4 (s, Me, ¹Bu), 39.9 (s, CH₂N), 79.3 (s, CMe₃), 111.5 (s, CH4), 117.3 (s, C3), 119.5 (s, CH7), 122.4 (s, C7a), 155.8 (s, CO).

Synthesis of tert-Butyl 2-(Benzo[b]thiophen-3-yl)ethylcarbamate (13b). Na₂CO₃ (496 mg, 4.68 mmol) was added to a suspension of $\mathbf{B}\cdot\mathbf{HCl}$ (500 mg, 2.34 mmol) in CH_2Cl_2 (50 mL). The suspension was stirred for 2.5 h at room temperature, and di-tertbutyl dicarbonate (Boc₂O; 562 mg, 2.57 mmol) was added. After 24 h, the mixture was washed with distilled water $(3 \times 50 \text{ mL})$. The organic phase was dried over MgSO4, 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, npentane (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 °C. 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. ¹H NMR (400.9 MHz): δ 1.44 (s, 9 H, Me, ^tBu), 3.05 ("t", 2 H, CH₂Ar, ${}^{3}J_{HH}$ = 6.8 Hz), 3.49 (m, 2 H, CH₂N), 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, ${}^{3}J_{HH}$ = 8.0 Hz), 7.86 (m, 1 H, H7). ${}^{13}C{}^{1}H$ NMR (100.8 MHz): δ 28.4 (s, Me, ^tBu), 29.1 (s, CH₂Ar), 40.1 (s, CH₂N), 79.3 (s, CMe₃), 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 μ L, 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. CH₂Cl₂ (25 mL) was added to the resulting suspension, and the mixture was washed with aq. NH₃ (10%; 2×20 mL). The organic layer was collected, dried over a plug of MgSO₄, and filtered. The solvent was removed from the filtrate to afford crude 14a. Crude 14a was dissolved in CH2Cl2 (2 mL) and purified by preparative TLC in silica gel with a 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 ¹H NMR). IR (cm⁻¹): $\nu(\text{NH})$ 3372 br w; $\nu(\text{CO})$ 1714 s, 1635 m. ESI-HRMS calcd for $C_{19}H_{23}NNaO_5$, 368.1468 [(M + Na)⁺]; found, 368.1472. ¹H NMR (300.1 MHz): δ 1.43 (s, 9 H, ^tBu), 3.02 (t, 2 H, CH₂N, ³J_{HH} = 6.6 Hz), 3.39-3.44 (m, 2 H, CH₂Ar), 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, ${}^{3}J_{HH}$ = 15.6 Hz). ${}^{13}C{}^{1}H$ NMR (75.5 MHz): δ 24.5 (s, CH₂Ar), 28.3 (s, ^tBu), 40.5 (s, CH₂N), 51.7 (s, Me), 79.4 (s, CMe₃), 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 μ L, 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 °C for 48 h. Solvent was removed to ca. 1 mL, and CH₂Cl₂ (25 mL) was added to the resulting suspension. The mixture was washed with aq. NH₃ (10%; 2 × 30 mL). The organic layer was collected, dried over a plug of MgSO₄, and filtered. The solvent was removed from the filtrate to afford crude **14b** as a yellow oil. Crude **14b** was dissolved in CH₂Cl₂ (2 mL) and purified by column cromatography using aluminum oxide and eluting with a 4:1 mixture of petroleum ether/ethyl acetate. Yield: 57% (by ¹H NMR). Isolated yield: 36 mg, 0.10 mmol, 40%. ESI-HRMS calcd for C₁₉H₂₃NNaO₄S, 384.1245 [(M + Na)⁺]; found, 384.1239. ¹H NMR (300.1 MHz): δ 1.43 (s, 3H, 'Bu), 3.20 (t, 2 H, CH₂Ar, ³*J*_{HH} = 6.0 Hz), 3.35–3.42 (m, 2 H, CH₂N), 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). ¹³C{¹H} NMR (75.5 MHz): δ 27.4 (s, CH₂Ar), 28.3 (s, 'Bu), 40.9 (s, CH₂N), 51.8 (s, Me), 79.4 (s, CMe₃), 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 for compounds 3a·Et₂O, 3b, 4a, 6b·1/6CH₂Cl₂, 7b, 8b·1/4CH₂Cl₂·1/4Et₂O, 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 D8 QUEST diffractometer. Data were recorded at 100(2) K, using graphite-monochromated Mo-Ka radiation ($\lambda = 0.71073$ Å), and ω - and ϕ -scan mode. Multiscan absorption corrections were applied for all complexes. Structure Solution and Refinements. Crystal structures were solved by a dual method, and all non-hydrogen atoms were refined anisotropically on F^2 using the program SHELXL-2014/7 (3a·Et₂O, 3b, 4a, 6b·1/ $6CH_2Cl_2$, 7b, 9b, and 10b)³⁷ or SHELXL-2016/6 (8b·1/4CH₂Cl₂·1/ 4Et₂O)³⁸ Hydrogen atoms were refined as follows: Compounds 3a· Et₂O, **6b**·1/6CH₂Cl₂, **7b**, **9b**, and **10b**: NH₂, free with SADI; methyl, rigid group; all others, riding. Complex 3b: NH2, free with DFIX; all others, riding. Complex 4a: NH₂, free; methyls, rigid group; all others, riding. Complex 8b·1/4CH2Cl2·1/4Et2O: NH2, 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 $\mbox{\AA}^3$ 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·1/6CH₂Cl₂: An ill-defined region of residual electron density over an inversion center was interpreted as half a molecule of dichloromethane, disordered over two positions, with a ca. 37:13 occupancy distribution. For 8b·1/4CH₂Cl₂·1/4Et₂O: A poorly resolved region of residual electron density was interpreted as the superposition of half a molecule of dichloromethane and half a molecule of Et₂O. The carbon and the oxygen atoms of the Et₂O were refined as isotropic.

ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organo-met.8b00682.

¹H and ¹³C{¹H}-APT NMR spectra of compounds 10– 14, crystallographic data for compounds 3a·Et₂O, 3b, 4a, 6b·1/6CH₂Cl₂, 7b, 8b·1/4CH₂Cl₂·1/4E_{t2}O, 9b, and 10b, and details of hydrogen bonds (including symmetry operators) (PDF)

Accession Codes

CCDC 1866905, 1866907, and 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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