Synthesis and Evaluation of 5-Phenyl-1*H*-1,4-benzodiazepin-2(3*H*)-one-Based Palladium Complexes as Precatalysts in C−C Bond Forming Reactions

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The C−H activation of C-3-unsubstituted 1,4-benzodiazepin-2(3*H*)-ones (LH = **2a**−**c**) (**2a** = 1-methyl-5-phenyl-1*H*-1,4-benzodiazepin-2(3*H*)-one, **2b** = 1-benzyl-5-phenyl-1*H*-1,4-benzodiazepin-2(3*H*)-one, **2c** = benzyl-2-(2,3-dihydro-2-oxo-5-phenyl-1,4-benzodiazepin-1-yl)-acetate) with Na_2PdCl_4 afforded the insoluble palladacycles $[(L)PdCl]_2$ **3a**−**c**. Treatment of the latter with triphenylphosphine afforded the soluble monomeric triphenylphosphine analogues $[(L)Pd(PPh_3)Cl]$ **4a**−**c**. 1-Methyl-3-(2-(methylthio)ethyl)-5-phenyl-1*H*-1,4-benzodiazepin-2(3*H*)-one (LH = **2d**) reacted with Na_2PdCl_4 or with $PdCl_2(MeCN)_2$ to afford the monomeric *cis*-S−N-coordinated complex **5d** of the type $[(LH)PdCl_2]$. 3-((*tert*-Butylthio)-methyl)-1-methyl-5-phenyl-1*H*-1,4-benzodiazepin-2(3*H*)-one, **2e**, reacted with $Pd(OAc)_2$ in acetic acid and, following LiCl metathesis, yielded the monomeric *cis*-S−N-bound pincer palladacycle **6f**. X-ray structures of **5d** and **4a** have been determined. **3a** and **6f** were found to be effective precatalysts for Suzuki coupling reactions, and **3a**, **3c**, and **4a** were effective precatalysts in Heck couplings across a range of substrates.

Introduction

Palladacycles are a fascinating family of organometallic complexes with applications in many areas including total synthesis, materials science, and biological and supramolecular chemistry.[1] Moreover, they are often air stable, are readily synthesized, and possess a range of structures, ring sizes, types of metalated carbon (sp^2 aromatic or vinylic, sp^3), and different types of donor groups bound to palladium (P-, N-, S-, O-, Se-containing groups) (Figure 1). The stoichiometric applications of palladacycles in organic synthesis have been reviewed,[2] and an increasing number of attractive high turnover number (TON) catalytic applications are now known.[3,4]

The coordination chemistry of the pharmaceutically important 1,4-benzodiazepine skeleton has been studied in detail,[5] and it has been shown to act as a bidentate or monodentate ligand toward palladium. For example, the palladacycle **A** resulted from the C−H activation of the C(5) phenyl group in Valium using Na_2PdCl_4 as metallating agent, whereas the coordination complex **B** was synthesized using Prazepam as ligand and $PdCl_2(PhCN)_2$ as palladium source. Complex **A** was employed in a carbonylation reaction yielding the novel heterocycles **C** (Scheme 1).[5a,b]

We recently prepared a range of C-3-unsubstituted 1,4-benzodiazepine ligands as precursors to imine-bound palladacycles related to **A** employing similar C−H

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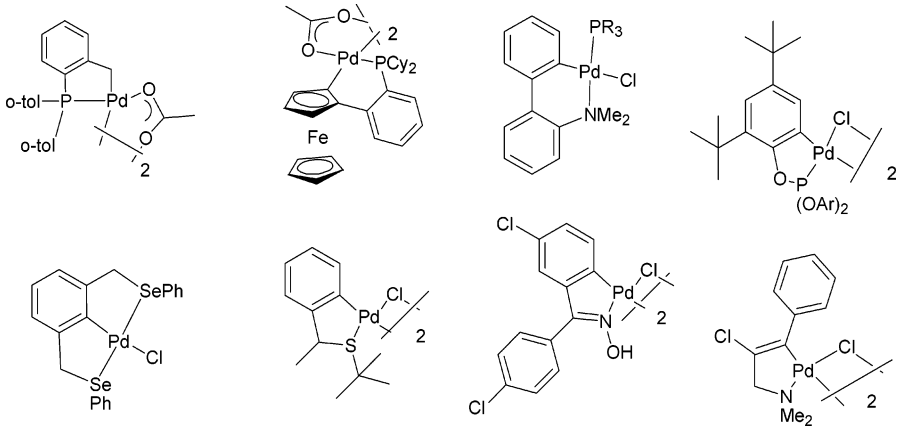
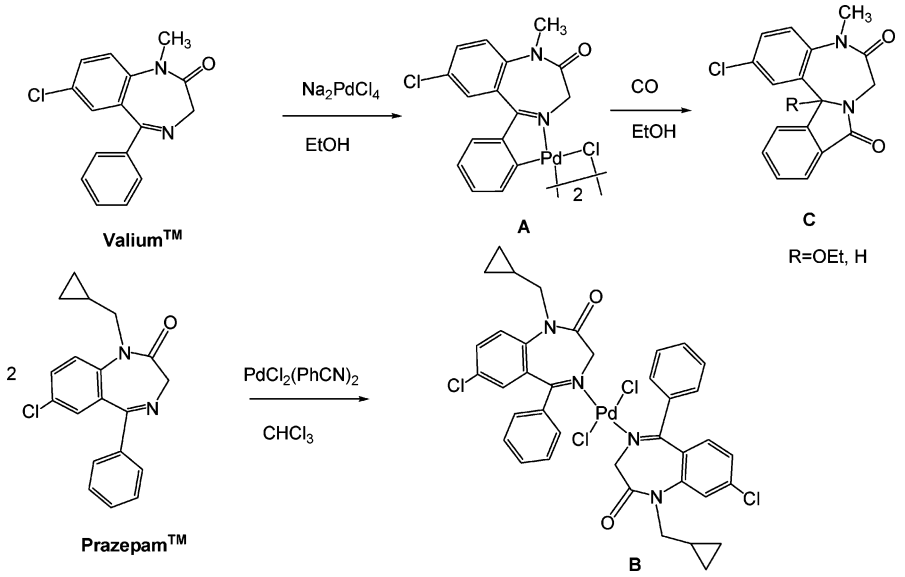


Figure 1. Examples of palladacycles employed in catalysis.

Scheme 1. Palladium-Containing 1,4-Benzodiazepine Complexes and a Carbonylation Reaction



activation reactions. Intrigued by the possibility of a tridentate binding mode to palladium, C-3-substituted 1,4-benzodiazepine ligands were synthesized by introducing a side chain containing a thioether group, derived from either cysteine or methionine. Herein we present results pertaining to the synthesis of 1,4-benzodiazepine-containing palladium complexes, their structural characterization in both solution and the solid state, and their application in catalysis.

Results and Discussion

1,4-Benzodiazepine Synthesis. The 1,4-benzodiazepines **1a**−**e** were made by a modification of the reported methods (EEDQ = 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline).[6] Alkyl substituents at the N-1 position were introduced by treatment with sodium hydride and reaction with the requisite alkyl halides, affording **2a**−**e**, which were characterized by ^{1}H, ^{13}C NMR and LCMS (Scheme 2).

Palladium Complexes. Treatment of **2a**−**c** with Na_2PdCl_4 in ethanol resulted in the formation of yellow or beige precipitates. Due to their low solubility, it was not possible to satisfactorily characterize these products by ^{1}H NMR spectroscopy. However, their treatment with triphenylphosphine afforded soluble products, whose spectral properties, particularly the shielded aromatic protons in their ^{1}H NMR spectra, characteristic of a metalated phenyl group *cis* to PPh_3, and a ^{31}P NMR singlet at ca. 41 ppm, were consistent with the monomeric structures **4a**−**c**.[7] By inference, the original precipitates were assigned the dimeric structures **3a**−**c**, which were, moreover, consistent with the combustion data obtained (Scheme 3).

The solid-state structure of the palladacycle **4a** was determined by an X-ray study of crystals obtained from a dichloromethane/hexane mixture. The palladacycle was found to have a distorted square planar configuration, probably as a result of steric encumbrance from the triphenylphosphine ligand, resulting in a C1−Pd−Cl1 bond angle of 171.84(7)° and a N1−Pd−P1 angle of 174.92(6)° (Table 1, Figure 2). Bond lengths in **4a** were found to be similar to those in related

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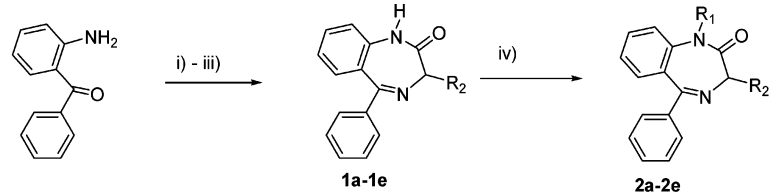
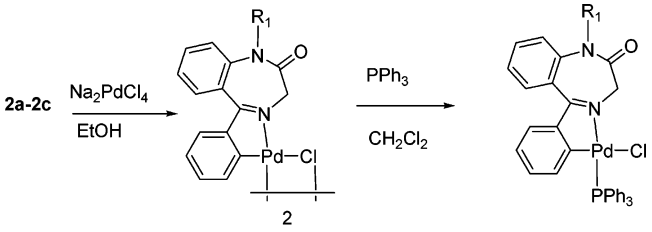
Scheme 2. 1,4-Benzodiazepine Synthesis



i) (FMOC)NHCH(R_2)CO_2H, EEDQ,THF, 16h.
ii) Et_2NH, MeCN, 2h.
iii) SiO_2 chromatography.
iv) NaH, R_1Br or R_1I

2a; R_1=CH_3, R_2=H
2b; R_1=Bn, R_2=H
2c; R_1=CH_2CO_2Bn, R_2=H
2d; R_1=CH_3, R_2=$(CH_2)_2SCH_3$
2e; R_1=CH_3, R_2=CH_2S*t*-Bu

Scheme 3. 1,4-Benzodiazepine Palladation



Scheme 4. Synthesis of the Coordination Complex 5d

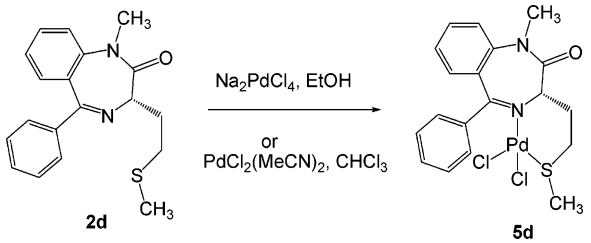


Table 1. Selected Bond Lengths (Å) and Angles (deg) for 4a

Bond Lengths			
Pd1–C1	2.015(2)	P1–C11	1.835(3)
Pd1–N1	2.0816(19)	N1–C7	1.297(3)
Pd1–P1	2.2653(6)	N1–C8	1.464(3)
Pd1–Cl1	2.3602(7)	N2–C9	1.362(3)
Bond Angles			
C1–Pd1–N1	80.20(9)	C11–P1–Pd1	111.12(8)
C1–Pd1–P1	94.81(7)	C2–C1–Pd1	130.57(19)
N1–Pd1–P1	174.92(6)	C7–N1–Pd1	115.76(16)
C1–Pd1–Cl1	171.84(7)	C8–N1–Pd1	124.92(16)
N1–Pd1–Cl1	92.86(6)	P1–Pd1–Cl1	92.19(3)
C31–P1–C21	100.53(12)	C6–C1–Pd1	112.72(17)
C31–P1–Pd1	113.02(8)	C21–P1–Pd1	118.48(9)

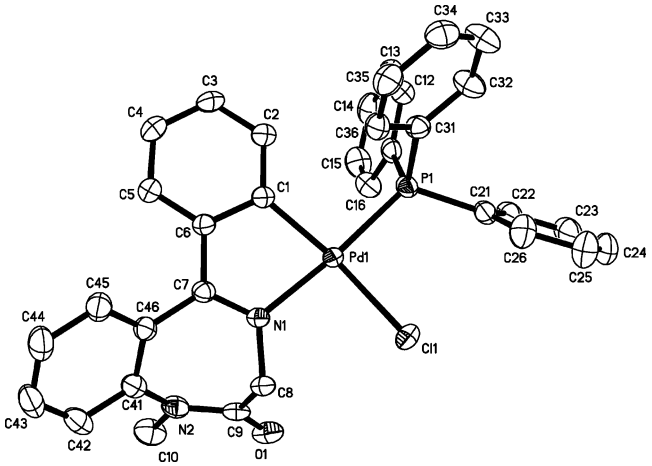


Figure 2. ORTEP diagram of **4a** (hydrogen atoms omitted for clarity).

palladacycles,[5b,9a] and the Pd–Cl bond length of 2.3602(7) Å reflects the high *trans* influence of the metalated carbon atom.

Treatment of the sulfur-containing 1,4-benzodiazepine **2d** with Na_2PdCl_4, according to the same conditions used to obtain **3a**–**c**, afforded a precipitate, which was sufficiently soluble for ^{1}H NMR characterization. In the product, S–Pd coordination was evidenced by a significant ^{1}H NMR downfield shift of the SMe signal (δ = 2.76 ppm) compared with the free ligand (δ = 2.06 ppm).[8] An identical product was obtained after treatment of **2d** with $PdCl_2(MeCN)_2$, suggesting the chelated-monomeric structure **5d**, which was unequivocally determined by a single-crystal X-ray structure measurement (Scheme 4, Figure 3).

Crystals of **5d** were grown from a chloroform/hexane mixture and were found to be racemic and to contain a molecule of chloroform in the asymmetric unit. The unit cell contains eight molecules of $CHCl_3$. There is no Pd–C bond, and the metal is part of a six-membered boat-shaped ring with a *cis*-S,N arrangement (Figure 3 and Table 2). The Pd–Cl bond lengths of around 2.33 Å are as expected. In the absence of a bulky phosphine ligand, the anticipated square planar arrangement is less distorted than in **4a**, with bond angles including N1–Pd–S1 of 90.95(9)° and S1–Pd–Cl2 of 176.33(4)°.

In an attempt to form a palladacycle analogue by C–H activation chemistry, **2d** was reacted with $Pd(OAc)_2$ in acetic acid followed by LiCl metathesis. However, ^{1}H NMR analysis of the crude reaction mixture revealed the presence of more than one species in solution. Hence, we concentrated our efforts on the corresponding reaction of the cysteine-derived 1,4-benzodiazepine **2e**. Reaction of the latter with $Pd(OAc)_2$ afforded the acetate analogue **6e**, evidenced by the presence of only eight aromatic protons, a singlet for a single acetate group, and a downfield shift of 0.3 ppm

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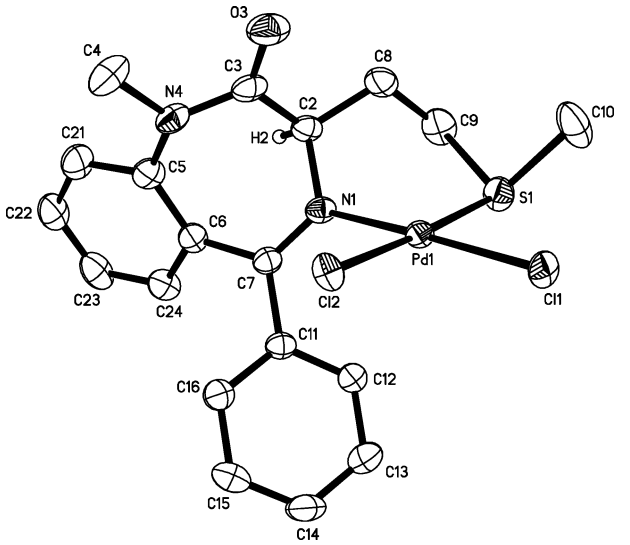
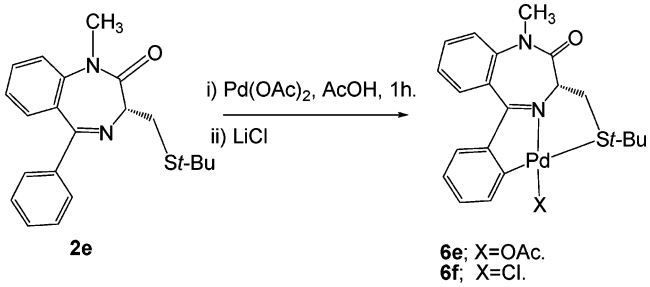


Figure 3. ORTEP diagram of **5d** (hydrogen atoms, with the exception of (H2), omitted for clarity).

Table 2. Selected Bond Lengths (Å) and Angles (deg) for 5d

	Bond Lengths		
Pd1−N1	2.055(3)	Pd1−S1	2.2858(10)
Pd1−Cl1	2.3301(9)	Pd1−Cl2	2.3445(8)
S1−C9	1.815(4)	S1−C10	1.820(5)
N1−C7	1.297(5)	N1−C2	1.489(5)
	Bond Angles		
N1−Pd1−S1	90.95(9)	C9−S1−C10	99.0(2)
N1−Pd1−Cl1	177.77(9)	C9−S1−Pd1	103.73(15)
S1−Pd1−Cl1	88.48(4)	C10−S1−Pd1	106.24(18)
N1−Pd1−Cl2	89.24(9)	C7−N1−C2	116.7(3)
S1−Pd1−Cl2	176.33(4)	C7−N1−Pd1	123.7(2)
Cl1−Pd1−Cl2	91.47(3)	C2−N1−Pd1	119.1(2)

Scheme 5. Synthesis of the Palladacycles 6e and 6f



of the S*t*-Bu group compared with **2e**, attributed to an S−Pd bond, in its ^{1}H NMR spectrum.[8] The chloro analogue **6f** was formed by a metathesis reaction with excess LiCl in acetone.

Carbon−Carbon Bond Forming Reactions Mediated by 3−6. Palladacycles are well-established precatalysts in Suzuki and Heck reactions, acting, after activation, as a source of catalytically active Pd(0).[1,3] As a preliminary assessment of the use of palladacycles **3**, **4**, and **6** in C−C bond forming reactions, we found that the reaction of **3a** with excess 3-tolylboronic acid afforded the ortho-arylated benzodiazepine **7a** as the main product (Scheme 6).[9]

This result suggested that **3a** could act as a source of Pd(0), and accordingly, it was found to be an effective precatalyst (0.5 mol % Pd) for the Suzuki coupling of phenylboronic acid with the electron-rich (poor coupling partner) 4-bromoanisole, affording 4-methoxybiphenyl in 90% yield (100% consumption of 4-bromoanisole, entry 1, Table 3). Building on the promising activity of **3a** we tested other derivatives for catalytic activity in the same reaction, which is often used as a benchmark for catalytic performance.[1] Palladacycle **6f** had a catalytic performance similar to **3a** (87% yield of 4-methoxybiphenyl, entry 7), and the coordination complex **5d** had good activity (81% yield of 4-methoxybiphenyl, entry 5). The latter result is not surprising, as the related Pd(II) coordination complexes $PdCl_2(SEt_2)_2$[10a] and $Pd(OAc)_2$[10a−c] as well as other complexes,[3f] including $[Pd(NCOC_2H_4CO)(PPh_3)_2Br]$,[10d] are also effective precatalysts for this type of transformation.

The reaction was also carried out over shorter reaction times (2 h), and complex **6f** was the most effective precatalyst, with a high yield of 4-methoxybiphenyl (92%) observed (entry 8). Attempts to use lower catalyst loadings of **3a** and **6f**, over 27 h, led to moderate TONs, 1620 with **3a** (entry 4) and 1440 with **6f** (entry 9), which are far inferior to many of the known palladacycle systems.[1,3]

3a (0.5 mol % Pd) was tested in Suzuki coupling reactions of aryl chlorides with phenylboronic acid under the same conditions. Using the deactivated substrate, 4-chloroanisole, only a 4% yield of 4-methoxybiphenyl was obtained, and with a more activated halide, 4-chloroacetophenone, a modest conversion (56%) and yield (34%) of 4-phenylacetophenone were observed. Changing the base (K_2CO_3, K_3PO_4, n-Bu_4NBr) and/or solvent (DMA, DMF, *o*-xylene) did not improve the coupling of $PhB(OH)_2$ with 4-chloroacetophenone. The use of a phosphine as a co-ligand in palladacycle-mediated coupling reactions has been described.[4c,11] Hence, when we combined PCy_3 with **3a** (0.5 mol % Pd) for the coupling of $PhB(OH)_2$ with 4-chloroacetophenone, quantitative consumption of 4-chloroacetophenone was observed and an 81% isolated yield of 4-phenylacetophenone was found. Under identical conditions, with the deactivated substrate, 4-chloroanisole, a 41% conversion of the starting chloride was observed, along with a 38% yield of 4-methoxybiphenyl (Scheme 7).

In line with our earlier studies, we have also probed the catalytic activity of some of the above complexes in the Heck reaction of various aryl halides and alkenes.[12] The soluble and well-defined monomeric complex **4a** was selected and compared with the dimeric, less soluble, phosphine-free precursors **3a** and **3c**.

As an initial point of comparison, the three selected palladacycles were tested as precatalysts for the coupling of olefins with the, less-reactive, electron-rich aryl halides and in particular aryl bromides. As can be seen from Table 4, good activity was observed, and as expected, aryl iodides were more reactive than their bromo congeners.[4a,12] For example, a 97% yield of (*E*)-butyl 3-*p*-tolylacrylate was observed with 4-iodotoluene

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Scheme 6. Ortho-Functionalization of 3a

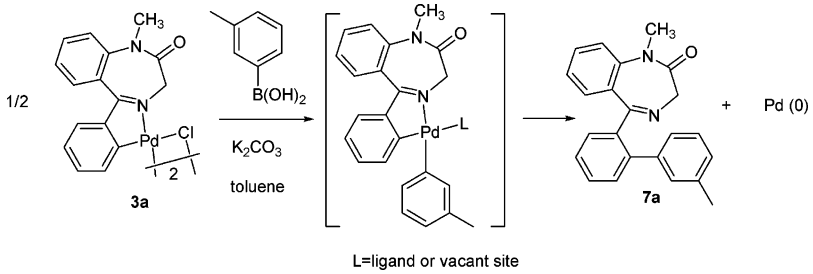
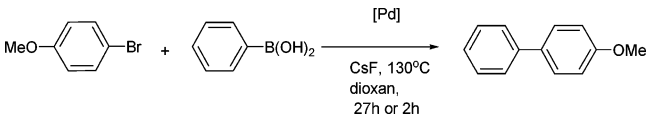


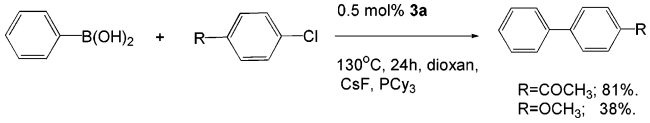
Table 3. Suzuki Coupling of 4-Bromoanisole and $PhB(OH)_2$ with Palladacycles 3a and 6f or Complex 5d



entry	**3** (mol % [Pd])	yield[a] (conversion)[b]	reaction time (h)
1	**3a** (0.5)	90 (100)	27
2	**3a** (0.5)	71 (94)	2
3	**3a** (0.2)	86 (100)	27
4	**3a** (0.05)	81 (100)	27
5	**5d** (0.5)	81 (100)	27
6	**5d** (0.5)	59 (74)	2
7	**6f** (0.5)	87 (98)	27
8	**6f** (0.5)	92 (100)	2
9	**6f** (0.05)	72 (92)	27
10	**6f** (0.005)	15 (43)	27

[a] GC yield of 4-methoxybiphenyl (using undecane as an internal standard). [b] GC conversion of 4-bromoanisole (using undecane as an internal standard).

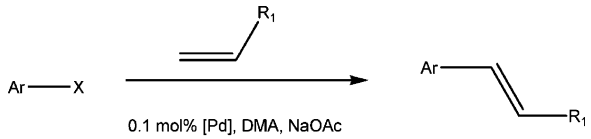
Scheme 7. Suzuki Coupling of 4-Chloroarenes with $PhB(OH)_2$ Catalyzed by 3a



as substrate, using **3a** as precatalyst (entry 1, Table 4), whereas with its bromo analogue a lower yield of product (74%) was observed (entry 4). A similar trend was observed when employing **3c** as precatalyst, where a 91% yield of coupled product was observed using 4-iodotoluene as aryl halide (entry 2) versus a 57% yield with 4-bromotoluene (entry 5). The palladacycles **3c** and **4a** gave lower yields of coupling product than **3a**; for example, the yield of (*E*)-butyl 3-*p*-tolylacrylate was 91% (**3c**, entry 2) and 90% (**4a**, entry 3) compared with 97% (**3a**, entry 1), and this trend was repeated for the formation of (*E*)-butyl cinnamate from bromobenzene (compare entries 6−8). Gratifyingly, (*E*)-stilbene analogues were formed in good yields from the coupling of styrene with aryl bromides mediated by **3a** (entries 10 and 11).

Electron-poor (activated) aryl bromides readily coupled with *n*-butylacrylate in the presence of **3a**, **3c**, or **4a** (Table 5). The palladacycle **3c** afforded better yields for the coupling of *n*-butylacrylate with 4-acetobromobenzene (89%, entry 2) and 4-cyanobromobenzene (82%, entry 5) than **3a** (71%, entry 1, 70%, entry 4, respectively). With the palladacycle **4a**, for the coupling of *n*-butylacrylate with 4-acetobromobenzene, a 64% yield was observed (entry 3), whereas with 4-cyanobromobenzene, a 90% yield was observed (entry 6). In the case of

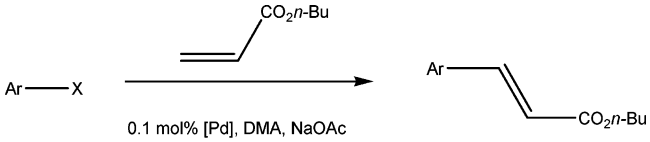
Table 4. Heck Coupling Reactions of Electron-Rich Aryl Halides and Olefins



entry[a]	[Pd]	ArX	R_1	yield (%)[b]	conversion[c] (%)
1	**3a**	4-MeC_6H_4I	CO_2n-Bu	97 (84%)[d]	98
2	**3c**	4-MeC_6H_4I	CO_2n-Bu	91	91
3	**4a**	4-MeC_6H_4I	CO_2n-Bu	90	95
4	**3a**	4-MeC_6H_4Br	CO_2n-Bu	74	75
5	**3c**	4-MeC_6H_4Br	CO_2n-Bu	57	63
6	**3a**	C_6H_4Br	CO_2n-Bu	96	96
7	**3c**	C_6H_4Br	CO_2n-Bu	95	95
8	**4a**	C_6H_4Br	CO_2n-Bu	78	78
9	**3a**	4-$MeOC_6H_4Br$	CO_2n-Bu	70	88
10	**3a**	4-MeC_6H_4Br	Ph	86	89
11	**3a**	C_6H_5Br	Ph	85	91

[a] Reaction conditions: 0.1 mol % [Pd], DMA (5 mL), NaOAc (1.4 mmol), alkene (1.2 mmol), ArX (1 mmol), and *n*-Bu_4NBr (0.2 mmol), 120 °C, 24 h (time after which the reaction was analyzed). [b] GC yield in (*E*)-butyl 3-arylacrylate or (*E*)-stilbenes (using undecane as an internal standard). [c] GC conversion. [d] Isolated yield.

Table 5. Heck Coupling Reactions of Electron-Poor Aryl Halides with *n*-Butyl Acrylate



entry[a]	[Pd]	ArX	yield (%)[b]	conversion (%)[c]
1	**3a**	4-$MeCOC_6H_4Br$	71	91
2	**3c**	4-$MeCOC_6H_4Br$	89 (89%)[d]	91
3	**4a**	4-$MeCOC_6H_4Br$	64	90
4	**3a**	4-CNC_6H_4Br	70	85
5	**3c**	4-CNC_6H_4Br	82	90
6	**4a**	4-CNC_6H_4Br	90	90
7	**3a**	4-$NO_2C_6H_4Br$	96	99
8	**3c**	4-$NO_2C_6H_4Br$	83	86
9	**4a**	4-$NO_2C_6H_4Br$	70	91
10	**3a**	4-$CF_3C_6H_4Br$	98	98
11	**3c**	4-$CF_3C_6H_4Br$	94	98
12	**4a**	4-$CF_3C_6H_4Br$	69	90
13	**3a**	4-$MeCOC_6H_4Cl$	31	45
14[e]	**3a**	4-$MeCOC_6H_4Cl$	8	12

[a] Reaction conditions: 0.1 mol % [Pd], DMA (5 mL), NaOAc (1.4 mmol), alkene (1.2 mmol), ArX (1 mmol), and *n*-Bu_4NBr (0.2 mmol), 120 °C, 24 h (time after which the reaction was analyzed). [b] GC yield in (*E*)-butyl 3-arylacrylate or (*E*)-stilbenes (using undecane as an internal standard). [c] GC conversion. [d] Isolated yield. [e] At 150 °C.

4-nitrobromobenzene, yields of coupling product with *n*-butylacrylate were higher with **3a** (96%, entry 7) than with **3c** (83%, entry 8) or **4a** (70%, entry 9). A similar

trend was observed for the coupling of *n*-butylacrylate with 4-trifluoromethylbromobenzene (98%, **3a**; 94%, **3b**; 69%, **4a**, respectively, entries 10−12). As with the Suzuki coupling reactions (Table 3), activated chlorides were poor coupling partners and yields were worse at elevated temperatures (entries 13 and 14, Table 5). In a few cases isolated yields were obtained and were in agreement with those determined by GC (entry 1, Table 4, and entry 2, Table 5).

Conclusion

We have demonstrated that the 1,4-benzodiazepine system is a modular and versatile ligand for the preparation of palladium complexes. Air-stable palladacycles **3a**−**c** and the "SCN pincer"[13] palladacycle **6f** were prepared by C−H activation reactions, and the reaction of **3a**−**c** with PPh_3 led to the monomeric **4a**−**c**. The novel monomeric coordination complex **5d** was formed from the reaction of **2d** with Na_2PdCl_4 or $PdCl_2(MeCN)_2$.[14] Complexes **3a** and **6f** displayed moderate activity in Suzuki coupling reactions, whereas **3a**, **3c**, and **4a** had moderate activity in Heck couplings, which may be due to poor catalyst longevity.[3b] Future studies will be aimed at preparing 1,4-benzodiazepine-containing complexes to address this issue.

Experimental Section

General Procedures. All procedures were carried out in air using commercial high-grade solvents (Fluka & Aldrich Sureseal). Palladium salts were purchased from Aldrich and used without further purification. Amino acids and coupling agents were purchased from Novabiochem. ^{1}H, ^{13}C{^{1}H}, and ^{31}P{^{1}H} NMR spectra were recorded on a Bruker AC 300 spectrometer at 300, 75, and 120 MHz, respectively. Mass spectra were carried out on a Waters ZQ spectrometer. Optical activity measurements were recorded with a sodium lamp at 589 nM at 20 °C on an Optical Activity A10 polarimeter. Elemental analyses were carried out by the Cambridge University Microanalysis Service. Flash chromatography was carried out on silica gel (Merck silica 60 (0.040−0.064 mm grade)). Catalytic test reactions were performed as described previously.[12,15]

Synthesis. 5-Phenyl-1*H*-1,4-benzodiazepin-2(3*H*)-one, 1a. 2-Aminobenzophenone (1.18 g, 6.00 mmol), EEDQ (1.48 g, 6.00 mmol), and FMOC-Gly-OH (1.78 g, 6.00 mmol) were combined in anhydrous THF (25 mL) and left to stir at room temperature overnight. After dilution with ethyl acetate (40 mL) and successive washings with potassium hydrogen sulfate solution (10%, 20 mL), saturated sodium hydrogen carbonate (20 mL), and brine, the organic layer was dried ($MgSO_4$), filtered, and concentrated. The crude product was treated with a 20% solution of diethylamine in acetonitrile (30 mL) at room temperature for 2 h. After evaporation of the volatiles followed by flash chromatography (70:30 ethyl acetate/hexane) an oil was obtained (0.99 g, 70%). ^{1}H NMR ($CDCl_3$): δ 8.65 (1H, s), 7.56−7.35 (7H, m), 7.19 (2H, m), 4.34 (2H, s). ^{13}C NMR ($CDCl_3$): δ 172.9, 171.6, 139.9, 139.3, 132.1, 131.7, 130.7, 130.1, 128.5, 127.6, 123.6, 121.7, 57.1. ($C_{15}H_{12}N_2O$); *m/z* 237 (MH+, 100%). Alternatively, the method of Stafford *et al.* was used.[6a]

1-Methyl-5-phenyl-1*H*-1,4-benzodiazepin-2(3*H*)-one, 2a.[6b] The product from the previous step (0.50 g, 2.12 mmol) was stirred with sodium hydride (60% suspension in paraffin oil, 0.12 g, 3.00 mmol) in DMF (10 mL) for 0.5 h under Ar. Thereafter, iodomethane (264 μL, 4.24 mmol) was added and the reaction was monitored by TLC until complete. After dilution with ethyl acetate (30 mL), the organic layer was washed with brine (2 × 30 mL) and water (20 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The product was obtained as a solid after column chromatography (7:3 ethyl acetate/pentane) (0.47 g, 48%). ^{1}H NMR ($CDCl_3$): δ 7.63−7.16 (9H, m), 4.83 (1H, d), 3.81 (1H, d), 3.41 (3H, s). ^{13}C NMR ($CDCl_3$): δ 170.8, 170.5, 144.5, 139.2, 131.7, 130.9, 130.7, 129.9, 128.6, 124.1, 121.4, 57.4, 35.2 ($C_{16}H_{14}N_2O$); *m/z* 251 (MH+, 100%).

1-Benzyl-5-phenyl-1*H*-1,4-benzodiazepin-2(3*H*)-one, 2b. This was made on a 0.5 mmol scale (0.163 g, 55%) according to the method used for the synthesis of **2a** except that benzyl bromide was used instead of methyl iodide. ^{1}H NMR ($CDCl_3$): δ 7.47−7.06 (14H, m), 5.63 (1H, d, J(HH) = 15.3 Hz), 4.89 (1H, d, J(HH) = 10.2 Hz), 4.79 (1H, d, J(HH) =15.3 Hz), 3.90 (1H, d, J(HH) = 10.2 Hz). ^{13}C NMR ($CDCl_3$): δ 171.0, 169.8, 142.6, 139.2, 137.2, 131.6, 130.9, 130.7, 130.6, 129.9, 129.0, 128.5, 127.8, 127.6, 124.8, 122.7, 57.4, 50.0 ($C_{22}H_{18}N_2O$); *m/z* 327 (MH+, 100%).

Benzyl 2-(2,3-dihydro-2-oxo-5-phenyl-1,4-benzodiazepin-1-yl)acetate, 2c. This was made on a 1.9 mmol scale (0.364 g, 50%) according to the method used for the synthesis of **2a** except that benzyl bromoacetate was used instead of methyl iodide. ^{1}H NMR ($CDCl_3$): δ 7.61−7.20 (14H, m), 5.28 (2H, s), 4.85 (1H, d), 4.69 (1H, d), 4.53 (1H, d), 3.88 (1H, d). ^{13}C NMR ($CDCl_3$): δ 171.0, 170.0, 169.2, 143.1, 135.6, 132.0, 131.0, 130.8, 130.0, 129.7, 128.9, 128.8, 128.6, 124.9, 121.5, 67.6, 56.8, 49.9 ($C_{24}H_{20}N_2O_3$); *m/z* 385 (MH+, 20%).

3-(*S*)-(2-(Methylthio)ethyl)-5-phenyl-1*H*-1,4-benzodiazepin-2(3*H*)-one, 1d. 1d was made on a 6 mmol scale according to the method used for **1a** (0.99 g, 54%) except that (*L*)-FMOC-Met-OH was used instead of FMOC-Gly-OH. ^{1}H NMR ($CDCl_3$): δ 8.05 (1H, s), 7.53 (3H, m), 7.42 (4H, m), 7.15 (2H, m), 3.81 (1H, dd, J(HH) = 5.4 Hz), 2.84 (1H, m), 2.53 (2H, m), 2.13 (3H, s).

3-(*S*)-1-Methyl-3-(2-(methylthio)ethyl)-5-phenyl-1*H*-1,4-benzodiazepin-2(3*H*)-one, 2d. 1d was treated with sodium hydride followed by iodomethane, on a 0.62 mmol scale, as for the synthesis of **2b**. The product was obtained as an oil (0.17 g, 85%) after flash chromatography (3:1 dichloromethane/ethyl acetate): α_D^{293} (+93.8°, CH_2Cl_2, *c* 1). ^{1}H NMR ($CDCl_3$): δ 7.61−7.29 (8H, m), 7.17 (1H, m), 3.76 (1H, m), 3.40 (3H, s), 2.76−2.43 (4H, m), 2.06 (3H, s). ^{13}C NMR ($CDCl_3$): δ 169.5, 167.6, 142.6, 137.7, 130.4, 129.3, 129.2, 128.6, 128.1, 127.2, 122.8, 120.2, 60.8, 34.1, 30.1, 29.7, 14.5 ($C_{19}H_{20}N_2OS$); *m/z* 325 (MH+, 100%).

3-(*S*)-(*tert*-Butylthio)methyl)-5-phenyl-1*H*-1,4-benzodiazepin-2(3*H*)-one, 1e. 1e was made on a 5.4 mmol scale according to the method used for **1a** (1.0 g, 60%) except that (*L*)-FMOC-Cys(*t*-Bu)-OH was used instead of FMOC-Gly-OH. ^{1}H NMR ($CDCl_3$): δ 10.36 (1H, s), 7.53−7.00 (9H, m), 3.72 (1H, t, J(HH) = 6.6 Hz), 3.43 (2H, m), 1.34 (9H, s).

3-(*S*)-(*tert*-Butylthio)methyl)-1-methyl-5-phenyl-1*H*-1,4-benzodiazepin-2(3*H*)-one, 2e. 2e was made from **1e** on a 2.96 mmol scale according to the method used for **2a** (0.40 g, 40%): α_D^{293} (+93.0°, CH_2Cl_2, *c* 1). ^{1}H NMR ($CDCl_3$): δ 7.53−7.02 (9H, m), 3.61 (1H, t, J(HH) = 5.1 Hz), 3.33 (2H, m), 3.29 (3H, s), 1.23 (9H, s). ^{13}C NMR ($CDCl_3$): δ 170.3, 168.8, 144.0, 139.0, 131.8, 130.7, 130.1, 129.5, 128.6, 124.2, 121.7, 64.8, 42.7, 35.5, 31.4 ($C_{21}H_{24}N_2OS$); *m/z* 353 (MH+, 25%).

Palladacycles [(L)PdCl]$_2$ 3a−c. Typically the ligand **2a**−**c** was stirred with 0.9 equiv of Na_2PdCl_4 in EtOH (20 mL)

(13) (a) Holton, R. A.; Nelson, R. V. *J. Organomet. Chem.* **1980**, *201*, C35. (b) Ebeling, G.; Meneghetti, M. R.; Rominger, F.; Dupont, J. *Organometallics* **2002**, *21*, 3221. (c) Dangel, B. D.; Godula, K.; Youn, S. W.; Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2002**, *124*, 11856.

(14) For the formation of coordination complexes rather than palladacycles when employing Na_2PdCl_4 as metallating agent, see (a) Dunina, V. V.; Gorunova, O.; Kuz'mina, L. G.; Livantsov, M. V.; Grishin, Y. K. *Tetrahedron: Asymmetry* **1999**, *10*, 3951. (b) Zhao, Y.; Helliwell, M.; Joule, J. A. *Arkivoc* **2000**, *1*, 360.

(15) (a) Rosa, G. R.; Ebeling, G.; Dupont, J.; Monteiro, A. L. *Synthesis* **2003**, *18*, 2894. (b) Zim, D.; Gruber, A. S.; Ebeling, G.; Dupont, J.; Monteiro, A. L. *Org. Lett.* **2000**, *2*, 2881.

Table 6. Crystal Data and Structure Refinement for 4a

empirical formula	$C_{34}H_{28}ClN_2OPPd$	
fw	653.40	
cryst syst	tetragonal	
space group	$P4_2/n$	
Z	8	
unit cell dimens	$a = 25.6119(4)$ Å	$\alpha = 90°$
	$b = 25.6119(4)$ Å	$\beta = 90°$
	$c = 9.6401(2)$ Å	$\gamma = 90°$
volume	6323.61(19) Å^3	
density (calcd)	1.37 g/cm^3	
absorp coeff	0.75 mm^{-1}	
max. and min. transmn	0.93 and 0.77	
cryst shape	polyhedron	
cryst size	0.36 × 0.10 × 0.10 mm^3	
cryst color	yellow	
θ range for data collection	1.1 to 27.5°	
index ranges	$-33 \le h \le 33$,	
	$-33 \le k \le 32$,	
	$-12 \le l \le 12$	
no. of reflns collected	64 421	
no. of indep reflns	7274 (R(int) = 0.0437)	
no. of obsd reflns	5776 ($I > 2\sigma(I)$)	
no. of data/restraints/params	7274/0/362	
goodness-of-fit on F^2	1.11	
final R indices ($I > 2\sigma(I)$)	R1 = 0.030, wR2 = 0.081	
largest diff peak and hole	0.79 and −0.56 e Å^{-3}	

Table 7. Crystal Data and Structure Refinement for 5d

empirical formula	$C_{19}H_{20}Cl_2N_2OPdS\cdot CHCl_3$	
fw	621.10	
cryst syst	orthorhombic	
space group	*Pbca*	
Z	8	
unit cell dimens	$a = 12.4292(2)$ Å	$\alpha = 90°$
	$b = 15.3175(3)$ Å	$\beta = 90°$
	$c = 25.2577(5)$ Å	$\gamma = 90°$
volume	4808.67(15) Å^3	
density (calcd)	1.72 g/cm^3	
absorp coeff	1.43 mm^{-1}	
max. and min. transmn	0.92 and 0.61	
cryst shape	polyhedron	
cryst size	0.38 × 0.37 × 0.06 mm^3	
cryst color	orange	
θ range for data collection	2.3 to 27.5°	
index ranges	$-16 \le h \le 16$,	
	$-19 \le k \le 19$,	
	$-32 \le l \le 32$	
no. of reflns collected	47 344	
no. of indep reflns	5500 (R(int) = 0.0332)	
no. of obsd reflns	4619 ($I > 2\sigma(I)$)	
no. of data/restraints/ params	5500/0/277	
goodness-of-fit on F^2	1.04	
final R indices ($I > 2\sigma(I)$)	R1 = 0.040, wR2 = 0.114	
largest diff peak and hole	1.90 and −1.08 e Å^{-3}	

for 48 h at room temperature. The precipitate was isolated by filtration, washed with further EtOH and then chloroform (10 mL each), and dried in vacuo. The complexes **3a**−**c** were obtained in 70% yield and were too insoluble for NMR determinations.

3a: Anal. Calcd for $(C_{16}H_{13}ClN_2OPd)_2\cdot CHCl_3$: C, 43.96; H, 3.02; N, 6.21. Found: C, 44.16; H, 3.12; N, 6.26. **3b**: Anal. Calcd for $(C_{22}H_{17}ClN_2OPd)_2\cdot 0.5CHCl_3$: C, 51.28; H, 3.30; N, 5.30. Found: C, 51.21; H, 3.30; N, 5.30. **3c**: Anal. Calcd for $(C_{24}H_{19}ClN_2O_3Pd)_2$: C, 54.88; H, 3.65; N, 5.35. Found: C, 54.30; H, 3.61; N, 5.28 (too insoluble for purification).

Reaction of 3a−c with Triphenylphosphine. Equimolar quantities of PPh_3 and **3** were stirred in dichloromethane (10 mL) overnight. After filtration through Celite, the filtrate was concentrated in vacuo and hexane added to afford a precipitate. The latter was collected by filtration and dried in vacuo.

4a: ^{1}H NMR ($CDCl_3$): δ 7.72−7.27 (19H, m), 7.09 (1H, m), 6.85 (1H, m), 6.58 (2H, m), 6.12 (1H, d, J(HH) = 12.3 Hz), 3.75 (1H, d, J(HH) = 12.3 Hz), 3.41 (3H, s). ^{31}P ($CDCl_3$): δ 41 (s).

4b: ^{1}H NMR ($CDCl_3$): δ 7.83−7.40 (19H, m), 7.07 (5H, m), 6.92 (2H, m), 6.56 (2H, m), 6.18 (1H, dd, J(HH) = 15.3 Hz, J(HH) = 3 Hz), 5.38 (1H, d, J(HH) = 12.0 Hz), 4.95 (1H, d, J(HH) = 15.3 Hz), 3.90 (1H, dd). ^{31}P ($CDCl_3$): δ 41 (s).

4c: ^{1}H NMR ($CDCl_3$): δ 7.83−7.32 (24H, m), 7.07 (1H, m), 6.85 (1H, m), 6.58 (2H, m), 6.18 (1H, dd, J(HH) = 12.3 Hz), 5.17 (2H, dd, J(HH) = 12.3 Hz), 4.73 (1H, d, J(HH) = 15.3 Hz), 4.42 (1H, d, J(HH) = 15.3 Hz), 3.86 (1H, d, J(HH) = 12.3 Hz). ^{31}P ($CDCl_3$): δ 41 (s).

Coordination Complex [(LH)PdCl$_2$] 5d. This complex was made (0.080 g, 32%) by the method employed for **3**, using ligand **2d** (0.17 g, 0.53 mmol) and Na_2PdCl_4 (0.147 g, 0.5 mmol): α_D^{293} (+52.0°, CH_2Cl_2, c 1). Anal. Calcd for $C_{19}H_{20}Cl_2N_2OPdS.CHCl_3$: C, 38.67; H, 3.41; N, 4.51. Found: C, 38.97; H, 3.60; N, 4.54. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.65 (5H, m), 7.45 (1H, d, J(HH) = 8.4 Hz), 7.19 (3H, m), 3.97 (1H, m), 3.54 (1H, m), 3.49 (3H, s), 2.76−2.39 (5H, m), 2.61 (1H, m).

Palladacycle 6e. 2e (0.12 g, 0.34 mmol) and palladium acetate (0.070 g, 0.31 mmol) were stirred in acetic acid at 90 °C for 1 h. After cooling, the reaction mixture was filtered over Celite, then concentrated in vacuo. The resulting oil was washed with hexane and dried in vacuo. **6e** was obtained as a beige solid after crystallization from dichloromethane/hexane (0.15 g, 94%). ^{1}H NMR ($CDCl_3$): δ 7.69 (2H, m), 7.38 (2H, m), 7.17 (2H, m), 6.99 (2H, m), 4.27 (1H, d, J(HH) = 6.6 Hz), 3.38 (4H, m), 3.00 (1H, m), 2.05 (3H, brs), 1.51 (9H, s). Anal. Calcd for $C_{23}H_{26}N_2O_3PdS$: C, 53.44; H, 5.07; N, 5.42. Found: C, 53.04; H, 5.06; N, 5.23.

Palladacycle 6f. 6e (0.15 g, 0.29 mmol) was stirred with LiCl (0.085 g, 2.00 mmol) in acetone for 30 min. After evaporation of the volatiles, the resulting solid was extracted with dichloromethane (3 × 20 mL) and filtered over Celite. The filter cake was washed with acetone (30 mL), and the combined filtrates were concentrated in vacuo to one-tenth their volume. A beige solid was obtained by the addition of hexane, collected by filtration, and dried in vacuo (0.144 g, 94%): α_D^{293} (+488.2°, CH_2Cl_2, c 0.5). Anal. Calcd for $C_{21}H_{23}ClN_2OPdS\cdot 0.5$acetone: C, 51.73; H, 5.02; N, 5.36. Found: C, 51.61; H, 4.74; N, 5.63. ^{1}H NMR ($CDCl_3$): δ 7.99 (1H, d, J(HH) = 7.8 Hz), 7.73 (2H, m), 7.40 (2H, m), 7.23 (1H, t, J(HH) = 8.0 Hz), 7.05 (1H, m), 6.99 (1H, m), 4.39 (1H, d, J(HH) = 6.3 Hz), 3.44 (1H, m), 3.43 (3H, s), 3.02 (1H, dd, J(HH) = 6.3 Hz, J(HH) = 5.1 Hz), 1.62 (9H, s). ^{13}C NMR ($CDCl_3$): δ 179.7, 168.6, 160.5, 143.0, 135.5, 133.4, 132.5, 130.6, 130.2, 125.8, 125.7, 124.9, 122.9, 64.0, 49.8, 36.1, 33.2, 30.2. ^{13}C DEPT 135 NMR ($CDCl_3$): δ 135.5, 133.4, 132.5, 130.6, 130.2, 125.8, 124.9, 122.9, 64.0, 36.1, 30.2 (all CH), 33.2 (CH_2).

1-Methyl-5-(2-(3-tolyl)phenyl)-1*H*-1,4-benzodiazepin-2(3*H*)-one, 7a. A toluene (15 mL) mixture of **3a** (0.10 g, 0.25 mmol), 3-tolylboronic acid (0.17 g, 1.25 mmol), and potassium carbonate (0.25 g, 1.81 mmol) was stirred under Ar at 110 °C for 18 h. After cooling, the resulting black mixture was filtered over Celite and the fitrate was concentrated in vacuo. The residue was taken up in ethyl acetate (10 mL), washed with brine, and dried ($MgSO_4$). Filtration and evaporation of the solvent gave the crude product, which after flash chromatography (5:1 hexane/dichloromethane to 3:1 dichloromethane/ethyl acetate) afforded an oil of limited purity (0.028 g, purity ca. 80% by ^{1}H NMR). ^{1}H NMR ($CDCl_3$): δ 7.49 (1H, m), 7.46 (2H, m), 7.23 (2H, m), 6.90 (5H, m), 6.70 (2H, m), 4.80 (1H, d, J(HH) = 8.4 Hz), 3.68 (1H, d, J(HH) = 10.2 Hz), 3.10 (3H, s), 2.17 (3H, s) ($C_{23}H_{20}N_2O$); m/z 341 (MH+, 100%).

X-ray Structure Determination. Data were collected on a Bruker Smart CCD diffractometer at 200 K. Mo Kα radiation was used, and the intensities were corrected for Lorentz and polarization effects. An empirical absorption correction was applied using SADABS[16] based on the Laue symmetry of the

reciprocal space. Relevant crystal and data collection parameters are given in Tables 6 and 7. The structures were solved by direct methods and refined against F^2 with a full matrix least-squares algorithm by using the SHELXTL software package.[16] Unless otherwise noted, hydrogen atoms were considered at calculated positions and refined using appropriate riding models. CCDC 281941 (**5d**) and 281942 (**4a**) contain the supplementary crystallographic data for the structures. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

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Supporting Information Available: Tables of full crystal data, atomic coordinates, calculated hydrogen coordinates, anisotropic thermal parameters, and a complete list of bond lengths and angles are available free of charge via the Internet at http:/pubs.acs.org.

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