Synthesis of Tetrahydrothiazin-2-imines by the Regiospecific Palladium(II)-Catalyzed Cycloaddition of Azetidines and Isothiocyanates. Isolation of Bis(azetidine)palladium Dichloride, a Key Catalytic Intermediate

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Azetidines react regiospecifically with isothiocyanates in the presence of bis(benzonitrile)palladium dichloride to form tetrahydro-1,3-thiazin-2-imines in 82–98% yields. A dichloro bis(azetidine)-palladium(II) complex, obtained from $(PhCN)_2PdCl_2$ and an azetidine, was found to be catalytically active for the cycloaddition reaction of azetidines with isothiocyanates.

Introduction

A great deal of attention has recently been paid to cycloaddition reactions of three-membered ring heterocycles with heterocumulenes owing to their applications in the synthesis of five-membered ring heterocycles.[1–15] Comparatively few publications have appeared on cycloaddition reactions of four-membered ring heterocycles with heterocumulenes, and most have utilized oxetanes as reactants.[16–18]

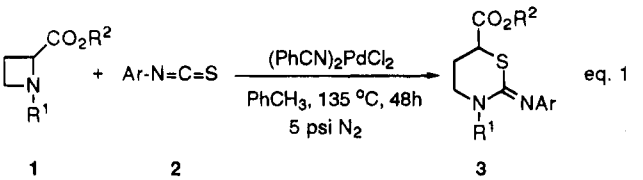
The concept of transition metal-catalyzed cycloaddition reactions of four-membered ring azetidines with heterocumulenes is an attractive one since azetidines can be easily synthesized by a variety of methods,[19] and an appreciable number of six-membered ring heterocycles are of considerable interest.[20] We recently reported the first transition metal-catalyzed cycloaddition of azetidines with carbodiimides, which gave tetrahydropyrimidin-2-imines in high yields.[21]

In continuation of our study on the palladium-catalyzed cycloaddition reaction of azetidines with heterocumulenes, we now describe the bis(benzonitrile)palladium dichloride-catalyzed cycloaddition reaction of azetidines with isothiocyanates which proceeds in a completely regioselective manner affording tetrahydro-1,3-thiazin-2-imines in excellent yields. In addition, a catalytically active intermediate, dichlorobis(azetidine)-palladium(II) complex, was isolated and characterized by analytical and spectral methods.

Results and Discussion

Taking into account the results for the regiospecific cycloaddition reactions of 1,2-disubstituted aziridines and aryl isothiocyanates which gave thiazolidinimines in high yields,[21b] we initiated a study of cycloaddition reactions involving 1,2-disubstituted azetidines as substrates. If aziridines and azetidines behave similarly, one could anticipate the formation of 1,3-thiazine derivatives.

When 1-*tert*-butyl-2-carbomethoxyazetidine (**1**, R^1 = $C(CH_3)_3$, R^2 = CH_3) was reacted with an equimolar amount of *p*-chlorophenyl isothiocyanate **2** (Ar = *p*-ClC_6H_4) in toluene at 135 °C, using bis(benzonitrile)palladium dichloride (10 mol %) as the catalyst, the tetrahydro-1,3-thiazin-2-imine **3** (Ar = *p*-ClC_6H_4, R^1 = $C(CH_3)_3$, R^2 = CH_3) was formed in 90% yield (eq 1). The cycloaddition



of the aryl isothiocyanate to the azetidine (**1**, R^1 = $C(CH_3)_3$, R^2 = CH_3) occurs exclusively into the nitrogen–carbon bond of **1** bearing an alkoxycarbonyl substituent at position 2. The reaction proceeds for aryl isothiocyanates having chloro or nitro substituents and a variety of azetidine-2-carboxylates (see Table 1). However, 1-*tert*-butyl-2-methylazetidine did not react with aryl isothiocyanates under similar reaction conditions, presumably because an electron-withdrawing group was required at the 2-position to polarize the N–C bond.

All tetrahydro-1,3-thiazin-2-imines **3** are new compounds. The structure of the products **3** was determined

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Table 1. Reaction of Azetidines with Isothiocyanates Catalyzed by $(PhCN)_2PdCl_2$[a]

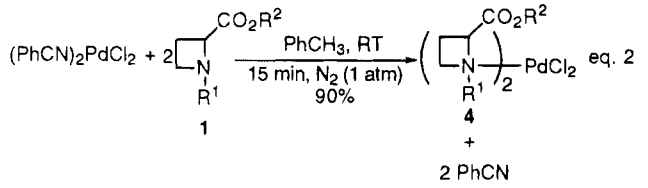
2, Ar =	1		yield of 3[b] (%)
	R^1	R^2	
Ph	$C(CH_3)_3$	$C_6H_5CH_2$	82
p-ClC_6H_4	$C(CH_3)_3$	CH_3	90
p-ClC_6H_4	$C(CH_3)_3$	$C_6H_5CH_2$	93
p-$NO_2C_6H_4$	$C(CH_3)_3$	$C_6H_5CH_2$	98
p-$NO_2C_6H_4$	C_6H_{11}	CH_3	85
p-$NO_2C_6H_4$	$C(CH_3)_3$	CH_3	92
p-$NO_2C_6H_4$	1-adamantyl	CH_3	89

[a] Reaction conditions: azetidine (1.0 mmol), isothiocyanate (1.0 mmol), $(PhCN)_2PdCl_2$ (0.1 mmol), $PhCH_3$ (2.0 mL), 135 °C, 48 h, 5 psi N_2. [b] Isolated yield of pure materials.

by spectroscopic data, i.e., IR, ^1H NMR, ^{13}C NMR, MS, and elemental analysis (see Experimental Section). The imine and carbonyl stretching absorption bands of **3** are observed in the IR spectrum at 1602–1612 cm^{-1} and 1732–1739 cm^{-1}, respectively.[22] The resonance signals for the imine and carbonyl carbon appeared at δ 153.92–157.26 and δ 171.60–172.26 ppm, respectively, in the ^{13}C NMR spectra, and molecular ion peaks were found in the mass spectra of **3**.[23]

While the reaction of azetidines with isothiocyanates was in progress, the palladium(II) catalyst was added to the reaction mixture at room temperature. In all cases, the addition of bis(benzonitrile)palladium dichloride caused the precipitation of solid material which dissolved upon heating the mixture to the reaction temperature. It was assumed that the solid product which forms at room temperature may play an important role in the cycloaddition reaction.

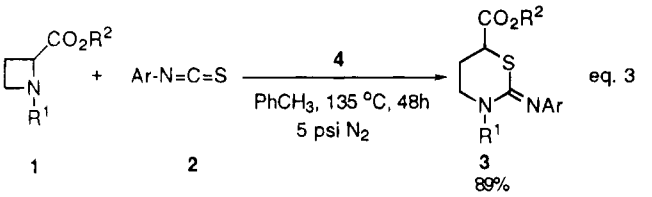
When a catalytic amount (10 mol %) of $(PhCN)_2PdCl_2$ was added to an equimolar mixture of an azetidine (**1**, $R^1 = C(CH_3)_3$, $R^2 = CH_3$) and an aryl isothiocyanate at room temperature, a dark-brown powder was isolated in almost quantitative yield (based on palladium). Complex **4** was then readily synthesized in high yield by the stoichiometric reaction of the azetidine (**1**, $R^1 = C(CH_3)_3$, $R^2 = CH_3$) with $(PhCN)_2PdCl_2$ in toluene at room temperature (eq 2). The complex was identified as dichloro-



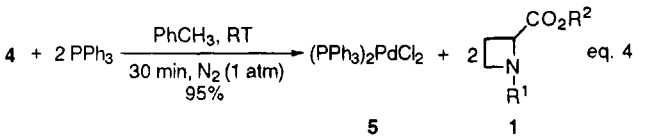
($R^1 = C(CH_3)_3$, $R^2 = CH_3$)

bis(1-*tert*-butyl-2-carbomethoxyazetidine)palladium(II), on the basis of elemental analysis, IR, and FAB-MS.[24,25] A carbonyl stertching band occurred in the infrared spectrum at 1752 cm^{-1} with Pd–Cl absorptions at 352 and 342 cm^{-1}. The FAB mass spectrum showed a cluster of isotopic peaks of the protonated complex **4** at m/e 517–527 in accord with calculated relative abundances.

Compound **4** is air stable and insoluble in common organic solvents. It does dissolve in both DMF and DMSO, but unfortunately these solvents also cause the decomposition of **4**. Consequently, we were unable to record an NMR spectrum. It is conceivable that this complex is the key catalytic species for the cycloaddition reaction. Indeed, reaction of 1-*tert*-butyl-2-carbomethoxyazetidine (**1**, $R^1 = C(CH_3)_3$, $R^2 = CH_3$) with *p*-chlorophenyl isothiocyanate (**2**, Ar = *p*-ClC_6H_4), effected under the usual conditions but in the presence of 10 mol % of **4** instead of $(PhCN)_2PdCl_2$, afforded the same cycloaddition product, tetrahydro-1,3-thiazin-2-imine (**3**, $R^1 = C(CH_3)_3$, $R^2 = CH_3$, Ar = *p*-ClC_6H_4), in 89% yield [90% using $(PhCN)_2PdCl_2$] (eq 3).



The azetidine ligands in complex **4** were easily replaced by triphenylphosphine giving rise to the known bis(triphenylphosphine)palladium dichloride and a free azetidine ligand (eq 4). These results explain why $(PPh_3)_2PdCl_2$ is inactive for cycloaddition as well as why the reaction is inhibited by triphenylphosphine.[15,21] It should be also noted that the failure to perform the cycloaddition in DMF and DMSO can probably be explained by the instability of **4** in these solvents.



($R^1 = C(CH_3)_3$, $R^2 = CH_3$)

On the basis of the results obtained from the study of the catalytically active intermediate **4**, a pathway can be proposed for the palladium-catalyzed cycloaddition reaction (Scheme 1). Reaction of $(PhCN)_2PdCl_2$ with 2 molar equiv of the azetidine affords the palladium–azetidine N-donor ligand complex **4**. Reaction of the latter with the aryl isothiocyanate can form **6**, in which there is π-complexation of one of the double bonds of aryl isothiocyanate to palladium.[26] Subsequent cycloaddition of the azetidine to the uncomplexed double bond of the aryl isothiocyanate ligand, possibly *via* a four-membered transition state **7**, may afford **8**.[21] Reaction of **8** with additional azetidine would give the corresponding tetrahydro-1,3-thiazin-2-imines **3** and regenerate **4**.

In conclusion, the reaction of substituted azetidines with aryl isothiocyanates is smoothly catalyzed by bis(benzonitrile)palladium dichloride affording the corresponding cycloaddition products in excellent yields. It has been shown that this regiospecific reaction occurs *via* a bis(azetidine)palladium(II) dichloride intermediate.

Experimental Section

General Methods. A Fisher-Johns apparatus was used for melting point determinations. The following spectrometers were used to obtain spectral data: Bomem MB 100-C15 (FT-IR); Bruker AMX 500, Varian XL-300, and Gemini 200 (NMR);

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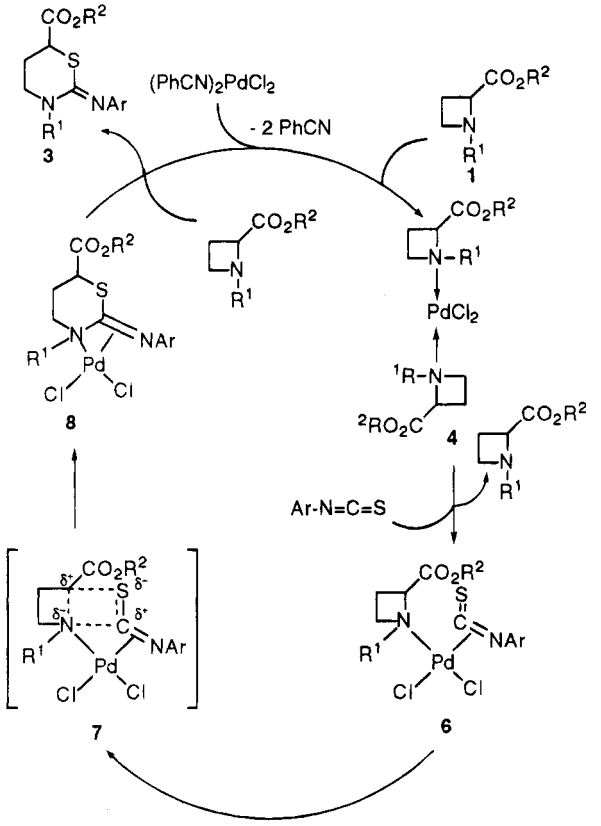
Scheme 1



VG 7070 E (MS). The azetidines,[27-29] isothiocyanates, and palladium catalysts[30] were either purchased or prepared according to literature procedures. The organic solvents were dried and distilled prior to use. Elemental analyses were carried out by MHW Laboratories, Phoenix, AZ. All reactions were conducted under a dry nitrogen atmosphere.

General Procedure for the Palladium-Catalyzed Cycloaddition Reaction of Azetidines and Isothiocyanates. A mixture of azetidine (1.0 mmol), isothiocyanate (1.0 mmol), and bis(benzonitrile)palladium dichloride (0.038 g, 0.10 mmol) in toluene (2.0 mL) was heated with stirring in a glass autoclave for 48 h, at 135 °C (oil bath temperature) under a slight pressure of nitrogen (5 psi). After being cooled to room temperature, the autoclave was opened and the red-brown homogeneous solution was filtered through Celite. The filtrate was concentrated by rotary evaporation, and the crude product was purified by silica gel thin-layer chromatography using 1:1 chloroform/toluene as the developer. Melting points, IR, NMR, MS, and analytical data for **3** are as follows:

3-*tert*-Butyl-6-carbobenzoxy-*N*-phenyl-3,4,5,6-tetrahydro-1,3-thiazin-2-imine (**3**, $R^1 = C(CH_3)_3$, $R^2 = CH_2C_6H_5$, Ar = Ph): 82% yield; oil; IR ($CHCl_3$) ν (C=N) 1612, (C=O) 1732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.58 (s, 9H, $C(CH_3)_3$), 2.23 (m, 1H, CH_2 ring), 2.50 (m, 1H, CH_2 ring), 3.41 (m, 1H, CH_2N), 3.55 (m, 1H, CH_2N), 3.88 (dd, 1H, $CHCO_2$, J = 5.4 and 8.2 Hz), 5.23 (dd, 2H, $CH_2C_6H_5$, J = 12.3 and 14.1 Hz), 7.23-7.43 (m, 10H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 29.04 (CH_3), 29.81 (CH_2), 42.98 (CH_2N), 44.04 ($CHCO_2$), 59.11 ($C(CH_3)_3$), 68.15 ($CH_2C_6H_5$), 122.50, 123.25, 129.06, 129.15, 129.35, 129.50 (CH-aromatic), 136.12, 150.26 (quaternary aromatic carbons), 153.92 (C=N), 171.95 (C=O); MS (m/e) 382 $[M]^+$. Anal. Calcd for $C_{22}H_{26}N_2O_2S$: C, 69.08; H, 6.85; N, 7.32. Found: C, 69.25; H, 6.42; N, 7.32.

3-*tert*-Butyl-6-carbomethoxy-*N*-(*p*-chlorophenyl)-3,4,5,6-tetrahydro-1,3-thiazin-2-imine (**3**, $R^1 = C(CH_3)_3$, $R^2 = CH_3$, Ar = p-ClC_6H_4): 90% yield; oil; IR ($CHCl_3$) ν (C=N) 1606, (C=O) 1736 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (s, 9H, $C(CH_3)_3$), 2.30 (m, 2H, CH_2 ring), 3.41 (m, 2H, CH_2N), 3.69 (s, 3H, CH_3), 3.81 (dd, 1H, $CHCO_2$, J = 6.1 and 8.1 Hz), 6.70-7.20 (m, 4H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 28.91 (CH_3), 29.87 (CH_2), 42.92 (CH_2N), 43.98 ($CHCO_2$), 53.39 (CH_3), 59.27 ($C(CH_3)_3$), 123.69, 129.38 (CH-aromatic), 128.17, 148.69 (quaternary aromatic carbons), 154.24 (C=N), 172.26 (C=O); MS (m/e) 340 $[M]^+$, 342 $[M + 2]^+$. Anal. Calcd for $C_{16}H_{21}ClN_2O_2S$: C, 56.38, H, 6.21; N, 8.22. Found: C, 56.81; H, 6.18; N, 8.32.

3-*tert*-Butyl-6-carbobenzoxy-*N*-(*p*-chlorophenyl)-3,4,5,6-tetrahydro-1,3-thiazin-2-imine (**3**, $R^1 = C(CH_3)_3$, $R^2 = CH_2C_6H_5$, Ar = p-ClC_6H_4): 93% yield; oil; IR ($CHCl_3$) ν (C=N) 1606, (C=O) 1733 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.46 (s, 9H, $C(CH_3)_3$), 2.22 (m, 1H, CH_2), 2.43 (m, 1H, CH_2), 3.42 (m, 2H, CH_2N), 3.84 (dd, 1H, $CHCO_2$, J = 5.4 and 8.4 Hz), 5.15 (dd, 2H, $CH_2C_6H_5$, J = 12.2 and 15.0 Hz),6.66-7.36 (m, 9H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 28.92 (CH_3), 29.72 (CH_2), 42.95 (CH_2N), 43.99 ($CHCO_2$), 59.23 ($C(CH_3)_3$), 68.19 ($CH_2C_6H_5$), 123.74, 129.13, 129.18, 129.28, 129.37 (CH-aromatic), 128.14, 135.87, 148.70 (quaternary aromatic carbons), 154.24 (C=N), 171.77 (C=O); MS (m/e) 416 $[M]^+$, 418 $[M + 2]^+$. Anal. Calcd for $C_{22}H_{25}ClN_2O_2S$: C, 63.37; H, 6.04; N, 6.72. Found: C, 63.50; H, 5.98; N, 6.80.

3-*tert*-Butyl-6-carbobenzoxy-*N*-(*p*-nitrophenyl)-3,4,5,6-tetrahydro-1,3-thiazin-2-imine (**3**, $R^1 = C(CH_3)_3$, $R^2 = CH_2C_6H_5$, Ar = p-$NO_2C_6H_4$): 98% yield; oil; IR ($CHCl_3$) ν (C=N) 1606 cm^{-1}, ν (C=O) 1733 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (s, 9H, $C(CH_3)_3$), 2.23 (m, 1H, CH_2), 2.42 (m, 1H, CH_2), 3.37 (m, 1H, CH_2N), 3.55 (m, 1H, CH_2N), 3.87 (dd, 1H, $CHCO_2$, J = 5.2 and 8.8 Hz), 5.15 (dd, 2H, $CH_2C_6H_5$, J = 12.1 and 16.9 Hz), 6.74-8.05 (m, 9H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 28.95 (CH_3), 29.67 (CH_2), 43.36 (CH_2N), 43.93 ($CHCO_2$), 59.93 ($C(CH_3)_3$), 68.30 ($CH_2C_6H_5$), 122.72, 125.52, 129.21, 129.32 (CH-aromatic), 135.78, 142.98, 154.33 (quaternary aromatic carbons), 156.48 (C=N), 171.60 (C=O); MS (m/e) 427 $[M]^+$. Anal. Calcd for $C_{22}H_{25}N_3O_4S$: C, 61.81; H, 5.89; N, 9.83. Found: C, 62.00; H, 5.74; N, 9.91.

3-Cyclohexyl-6-carbomethoxy-*N*-(*p*-nitrophenyl)-3,4,5,6-tetrahydro-1,3-thiazin-2-imine (**3**, $R^1 = C_6H_{11}$, $R^2 = CH_3$, Ar = p-$NO_2C_6H_4$): 85% yield; oil; IR ($CHCl_3$) ν (C=N) 1602, (C=O) 1739 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95-1.91 (m, 10H, CH_2 of cyclohexyl), 2.26 (m, 2H, CH_2 ring), 3.35 (m, 2H, CH_2N), 3.68 (s, 3H, CH_3), 3.91 (t, 1H, $CHCO_2$, J = 7.1 Hz), 4.56 (m, 1H, CHN), 6.83-8.09 (m, 4H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 26.19, 26.32, 28.30 (CH_2 of cyclohexyl), 30.38 (CH_2 ring), 40.65 (CH_2N), 43.34 (CHN), 53.51 (CH_3), 56.76 ($CHCO_2$), 123.54, 125.41 (CH-aromatic), 143.04, 150.83 (quateranry aromatic carbons), 157.26 (C=N), 171.63 (C=O); MS (m/e) 377 $[M]^+$. Anal. Calcd for $C_{11}H_{23}N_3O_4S$: C, 57.28; H, 6.14; N, 11.13. Found: C, 57.63; H, 5.79; N, 11.16.

3-*tert*-Butyl-6-carbomethoxy-*N*-(*p*-nitrophenyl)-3,4,5,6-tetrahydro-1,3-thiazin-2-imine (**3**, $R^1 = C(CH_3)_3$, $R^2 = CH_3$, Ar = p-$NO_2C_6H_4$): 92% yield; oil; IR ($CHCl_3$) ν (C=N) 1610, (C=O) 1738 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.42 (s, 9H, $C(CH_3)_3$), 2.27 (m, 2H, CH_2 ring), 3.48 (m, 2H, CH_2N), 3.72 (s, 3H, CH_3), 3.82 (dd, 1H, $CHCO_2$, J = 5.7 and 8.5 Hz), 6.79-8.07 (m, 4H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 28.92 (CH_3), 29.75 (CH_2), 43.31 (CH_2N), 43.90 ($CHCO_2$), 53.45 (CH_3), 59.95 ($C(CH_3)_3$), 122.66, 125.50 (CH-aromatic), 142.94, 154.16 (quaternary aromatic carbons), 156.54 (C=N), 172.08 (C=O); MS (m/e) 351 $[M]^+$. Anal. Calcd for $C_{16}H_{21}N_3O_4S$: C, 54.69; H, 6.02; N, 11.96. Found: C, 54.55; H, 6.10; N, 11.84.

3-(1-Adamantyl)-6-carbomethoxy-*N*-(*p*-nitrophenyl)-3,4,5,6-tetrahydro-1,3-thiazin-2-imine (**3**, R^1 = 1-adamantyl, $R^2 = CH_3$, Ar = p-$NO_2C_6H_4$): 89% yield; mp 126-127 °C; IR ($CHCl_3$) ν (C=N) 1608, (C=O) 1737 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.52-2.20 (m, 15H, 1-adamantyl), 2.25 (m, 2H, CH_2 ring), 3.35 (m, 1H, CH_2N), 3.55 (m, 1H, CH_2N), 3.65 (s, 3H, CH_3), 3.81 (m, 1H, $CHCO_2$), 6.80-8.05 (m, 4H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 30.07, 30.68, 36.87 (CH, CH_2-adamantyl), 40.67 (CH_2 ring), 42.03 (CH_2N), 44.03 ($CHCO_2$), 53.44 (CH_3), 61.38 (C-adamantyl), 122.69, 125.49 (CH-aromatic), 142.81,

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154.16 (quaternary aromatic carbons), 156.47 (C=N), 172.24 (C=O); MS (*m/e*) 429 $[M]^+$. Anal. Calcd for $C_{22}H_{27}N_3O_4S$: C, 61.52; H, 6.34; N, 9.78. Found: C, 61.81; H, 6.32; N, 9.62.

Synthesis of Dichlorobis(1-*tert*-butyl-2-carbomethoxyazetidine)palladium(II). To a solution of 1.5 g (3.9 mmol) of bis(benzonitrile)palladium dichloride in 20 mL of toluene (N_2 atmosphere) was added drop-by-drop a solution of 1.3 g (7.8 mmol) of 1-*tert*-butyl-2-carbomethoxyazetidine in 5 mL of toluene. The reaction mixture was then stirred at ambient temperature for 15 min. The product, a dark-brown precipitate, was removed by filtration and washed with petroleum ether. The yield was 90% (1.8 g): IR (KBr pellet) ν (PdCl) 342, 352, and ν (C=O) 1752 cm^{-1}; FAB-MS (*m/e*) 517–527 $[MH]^+$. Anal. Calcd for $C_{18}H_{34}Cl_2N_2O_4Pd$: C, 41.59; H, 6.59; N, 5.39. Found: C, 41.38; H, 6.43; N, 5.35.

Procedure for the Dichlorobis(1-*tert*-butyl-2-carbomethoxyazetidine)palladium(II)-Catalyzed Cycloaddition Reaction of 1-*tert*-Butyl-2-carbomethoxyazetidine and *p*-Chlorophenyl Isothiocyanate. A mixture of azetidine (1.0 mmol), isothiocyanate (1.0 mmol), and bis(1-*tert*-butyl-2-carbomethoxyazetidine)palladium dichloride (0.052 g, 0.10 mmol) in toluene (2.0 mL) was heated with stirring in a glass autoclave for 48 h at 135 °C (oil bath temperature) under a slight pressure of nitrogen (5 psi). The workup procedure was the same as that described for the $(PhCN)_2PdCl_2$-catalyzed cycloaddition reaction of azetidines and isothiocyanates. The isolated yield of **3** was 0.30 g: 89% yield.

Reaction of Dichlorobis(1-*tert*-butyl-2-carbomethoxyazetidine)palladium(II) with Triphenylphosphine. To a solution of 1.05 g (4.0 mmol) of triphenylphosphine in 10 mL of toluene (N_2 atmosphere) was slowly added of 1.04 g (2.0 mmol) of bis(1-*tert*-butyl-2-carbomethoxyazetidine)palladium dichloride. The reaction mixture was then stirred at ambient temperature for 30 min. The product, bis(triphenylphosphine)-palladium dichloride (yellow precipitate), was removed by filtration and washed with petroleum ether. The yield was 95% (1.3 g): The complex was found to be identical (^{31}P NMR ($CDCl_3$) δ 23.3 (s)) to that for an authentic sample.

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Supplementary Material Available: ^1H NMR and ^{13}C NMR specrta for compounds **3** (14 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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