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Synthesis of Seven-Membered Ring Diazepin-2-ones via Palladium-Catalyzed Highly Regioselective Cyclization of 2-Vinylpyrrolidines with Aryl Isocyanates

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The first palladium-catalyzed ring-expansion reaction of 2-vinylpyrrolidines with aryl isocyanates to form seven-membered ring heterocycles is described. This regioselective reaction requires 5 mol % of $Pd_2(dba)_3 \cdot CHCl_3$ and 10 mol % of dppp at 40−60 °C in THF and results in the formation of 1,3-diazepin-2-ones in good isolated yields. When $Pd(OAc)_2$ and PPh_3 were utilized in the reaction, an intramolecular hydrogen migration occurs resulting in the formation of conjugated diene derivatives of urea.

New methods for the synthesis of seven-membered-ring compounds are attractive because of the potential biological activity[1,2] of some of these compounds. Such compounds are often difficult to prepare by conventional methods.[3] Despite the synthetic significance of seven-membered-ring heterocycles, only a few successful metal-catalyzed reactions are known for the preparation of these compounds.[4,5] Recently the use of three- or four-membered-ring heterocycles such as thiiranes,[6] aziridines,[7] oxiranes,[8] azetidines,[9] and oxetanes[10] in reaction with heterocumulenes to form five- or six-membered-ring heterocycles catalyzed by palladium complexes has attracted considerable attention. We previously reported

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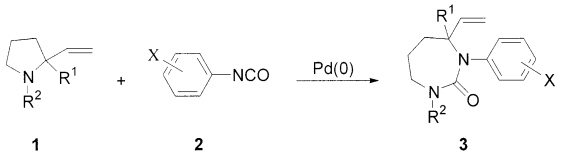
the use of isocyanates and carbodiimides as substrates for cycloaddition reactions with aziridines[7a] or azetidines[9c] catalyzed by palladium complexes, thus affording imidazolidinones or pyrimidinones, respectively. The products are obtained in good yields and in excellent regioselectivity. In contrast, however, there are no known methods for the effective reaction of five-membered-ring 2-vinylpyrrolidines[11] with heterocumulenes. Of course, pyrrolidines are not strained ring compounds in contrast to aziridines or azetidines, and thus the reaction may be sluggish, if it occurs at all. It was anticipated that should such a reaction take place, it could afford interesting seven-membered-ring heterocycles, and could lead to the development of new methodologies for other interesting carbon electrophiles.

Herein, we describe the first example of the highly regioselective palladium-catalyzed cyclization reaction of 2-vinylpyrrolidines with aryl isocyanates for the formation of 1,3-diazepin-2-one derivatives (eq 1). This new

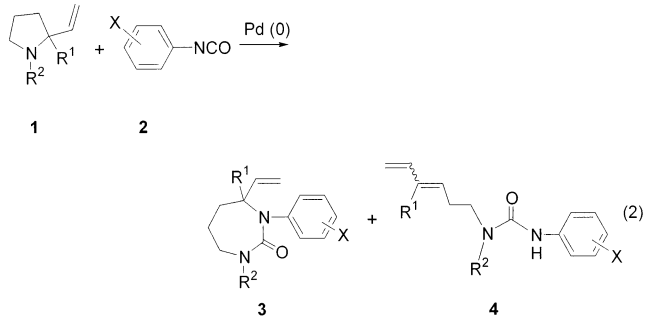


1 2 3 (1)

cyclization reaction provides a convenient method to synthesize 1,3-diazepin-2-one derivatives in one pot from easily available starting materials and significantly expands the scope of palladium-catalyzed cycloaddition reactions. In addition, the catalytic mechanism for the reaction catalyzed by $Pd(OAc)_2$ and PPh_3 is very interesting, and involves an unusual intramolecular hydrogen migration as well as an $\eta^3-\eta^1-\eta^3$ interconversion of a (π-allyl)palladium intermediate.

Results and Discussion

The reaction of *N*-butyl-2-vinylpyrrolidines **1a** or **1b** (1 mmol) with phenyl isocyanates **2a** (1 mmol) was first investigated by using reaction conditions similar to those described for the reaction of 2-vinylaziridines or azetidines with the heterocumulenes, i.e., 5 mol % of $Pd(OAc)_2$ and 20 mol % of PPh_3 in 3 mL of THF under argon atmosphere at room temperature for 24 h. However, **no** product was formed under these conditions, nor at higher catalyst loading (15 mol %). Complete conversion of **1a** (reaction was monitored by GC) resulted when **1a** was reacted with an excess of **2a** (1.5 equiv to **1a**) at ambient temperature and pressure in the presence of 10 mol % of $Pd(OAc)_2$ and 40 mol % of PPh_3 for 24 h. However, rather than the desired seven-membered-ring heterocycle **3a**, the product consisted of a mixture of trans and cis isomers of the conjugated diene derivative of urea **4a** in 82% yield (eq 2) (Table 1, entry 1). The isomers were inseparable by GC and TLC. Identifying features in the ^{1}H NMR spectrum include the olefin protons of the mixture of trans and cis isomers of conjugated dienes between 5 and 7 ppm, and the single proton peak of urea at 6.31 ppm, while the carbonyl carbon occurred at 154 ppm in the ^{13}C NMR. A strong absorption at 1650−1620



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cm^{-1}, typical of urea carbonyls, was present in the IR spectrum of **4a**. A similar result was also observed in the reaction of **1b** with **2a**, resulting in 50% conversion of **1b** and the formation of ring-opened product **4i** in 45% isolated yield (Table 1, entry 10). Use of a higher reaction temperature results in low yields of **4i**, possibly due to the reaction of phenyl isocyanate with itself in the presence of PPh_3. Increasing the catalyst loading still did not afford the desired product **3i**.

It is noteworthy that an electron-withdrawing or electron-donating substituent on aryl isocyanates significantly affects the nature of the formed product. When aryl isocyanates containing electron-withdrawing substituents on the aromatic ring (i.e. **2b**−**g**) were used for the reaction with **1a**, the reaction proceeded smoothly resulting in the formation of seven-membered-ring products **3** and ring-opened products **4** in good to excellent conversions and yields (70−100% conversion and 24−82% combined yield). The ratio of **3**/**4** is dependent on the amount of the catalyst used and the nature of the substrate. In most cases, the seven-membered-ring product **3** was obtained as a major component in the reaction of aryl isocyanates containing electron-withdrawing substituents. Increasing the amount of the catalyst can improve the yield of **3**, e.g. in the reaction of 2-vinylpyrrolidine **1a** with *p*-chlorophenyl isocyanate **2e**, use of 10 mol % of catalyst gave 22% of **3e** and 26% of **4e** (Table 1, entry 5). When the amount of catalyst was increased to 15 mol %, **3e** was obtained in 61% yield, and only a trace of **4e** was observed (Table 1, entry 6). Placing an electron-withdrawing substituent in the para position usually gave a mixture of **3** and **4** (Table 1, entries 2, 5, and 8), and the strength of the electron-withdrawing substituent on the aryl isocyanate did not significantly affect the amount of the dienes formed. For example, reaction of **1a** with *p*-bromophenyl isocyanate **2b** afforded **3b** and **4b** in 24% and 27% yield, respectively (Table 1, entry 2). Both **3g** and **4g** were also formed from the *p*-nitro reactant **2g** (Table 1, entry 8). However, an electron-withdrawing substituent in the ortho (Table 1, entries 3 and 7) or meta (Table 1, entry 4) position favored the formation of the cyclized product **3** in fine selectivity. When using *o*-chlorophenyl isocyanate **2c** and *m*-chlorophenyl isocyanate **2d** for the reaction, no ring-opened product **4c** and **4d** was observed and the desired product **3c** and **3d** was obtained in 60% and 36% yield, respectively (Table 1, entries 3 and 4). Reaction of **1a** and *o*-nitrophenyl isocyanate **2f** was fast and the substrate was nearly fully consumed in 24 h, while **3f** was obtained in 24% yield; on the other hand, one side product was obtained and isolated in ca. 20% yield. Unfortunately, attempts to identify this product failed (Table 1, entry

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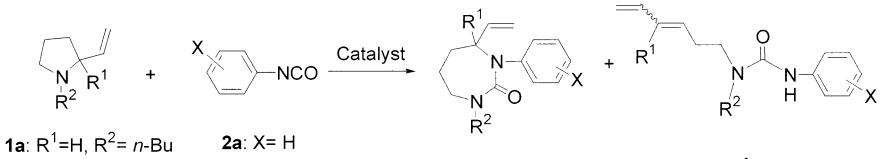
TABLE 1. Palladium-Catalyzed Cyclization Reactions of 2-Vinylpyrrolidines with Aryl Isocyanates



1a: R^1=H, R^2= *n*-Bu
1b: R^1=H, R^2= Cy
1c: R^1=Me, R^2= *n*-Bu

2a: X= H
2b: X= Br-*p*
2c: X= Cl-*o*
2d: X= Cl-*m*
2e: X= Cl-*p*
2f: X= NO_2-*o*
2g: X= NO_2-*p*
2h: X= MeO-*p*

entry	pyrrolidine **1**	ArNCO **2**	catalyst (mol %)[a]	*T* (°C)	reaction time (h)	conv (%)[c]	**3**, yield (%)[d]	**4**, yield (%)[d] (trans/cis)[e]	total yield (%) (**3** + **4**)
1	**1a**	**2a**	$Pd(OAc)_2$/PPh_3 (10/40)	rt	24	>98	**3a**, 0	**4a**, 82 (52/48)	82
2	**1a**	**2b**	$Pd(OAc)_2$/PPh_3 (10/40)	rt	48	90	**3b**, 24	**4b**, 27 (50/50)	51
3	**1a**	**2c**	$Pd(OAc)_2$/PPh_3 (10/40)	rt	36	75	**3c**, 60	**4c**, 0	60
4	**1a**	**2d**	$Pd(OAc)_2$/PPh_3 (10/40)	rt	48	45	**3d**, 36	**4d**, 0	36
5	**1a**	**2e**	$Pd(OAc)_2$/PPh_3 (10/40)	rt	36	73	**3e**, 22	**4e**, 26 (50/50)	48
6	**1a**	**2e**	$Pd(OAc)_2$/PPh_3 (15/60)	rt	24	78	**3e**, 61	**4e**, trace	61
7	**1a**	**2f**	$Pd(OAc)_2$/PPh_3 (10/40)	rt	24	>98	**3f**, 24	**4f**, 0	24
8	**1a**	**2g**	$Pd(OAc)_2$/PPh_3 (15/60)	rt	48	53	**3g**, 9	**4g**, 14 (58/42)	23
9	**1a**	**2h**	$Pd(OAc)_2$/PPh_3 (10/40)	rt	36	>98	**3h**, 0	**4h**, 65 (54/46)	65
10	**1b**	**2a**	$Pd(OAc)_2$/PPh_3 (15/60)	rt	48	50	**3i**, 0	**4i**, 45 (57/43)	45
11	**1b**	**2c**	$Pd(OAc)_2$/PPh_3 (15/60)	rt	72	60	**3k**, 28	**4k**, 0	28
12	**1b**	**2e**	$Pd(OAc)_2$/PPh_3 (15/60)	rt	48	62	**3l**, 15	**4l**, 36 (60/40)	51
13	**1b**	**2f**	$Pd(OAc)_2$/PPh_3 (15/60)	rt	48	41	**3m**, 16	**4m**, 0	16
14	**1c**	**2e**	$Pd(OAc)_2$/PPh_3 (15/60)	rt	72	58	**3o**, 0	**4o**, 30 (29/71)	30
15	**1b**	**2a**	$Pd_2(dba)_3$·$CHCl_3$ /dppp (5/10)	rt	48	<10	**3i**, trace	**4i**, 0	trace
16	**1b**	**2a**	$Pd_2(dba)_3$·$CHCl_3$ /dppp (5/10)[b]	60 (5 psi)	48	18	**3i**, 15	**4i**, 0	15

[a] $Pd(OAc)_2$ and PPh_3 (1:4 molar ratio) were premixed for 30 min in 3.0 mL of dry, degassed THF followed by addition of **1** and **2**. [b] $Pd_2(dba)_3$·$CHCl_3$ and dppp (1:2 molar ratio) were premixed for 30 min in 3.0 mL of dry, degassed THF followed by addition of **1** and **2**, under 5 psi and 60 °C in a glass autoclave. [c] The conversion was determined from GC by using biphenyl as an internal standard or was calculated based on the crude ^{1}H NMR of the mixture. [d] Isolated yield based on the amount of 2-vinylpyrrolidine **1** used. [e] Ratio determined by ^{1}H NMR.

7). Use of *p*-methoxyphenyl isocyanate as the reactant led to the ring-opened product **4h** in 100% conversion and 65% yield (Table 1, entry 9). These results may be understood based on the fact that an electron-withdrawing group on the aryl isocyanate, especially at the ortho or meta position, generally enhances the rate of the cyclization addition reaction and reduces the proportion of dienes formed. Aryl isocyanates with an electron-donating group, or without a substituent, only gave ring-opened products (Table 1, entries 1 and 9).

N-Cyclohexyl-2-vinylpyrrolidine **1b** exhibited less reactivity compared to **1a**, and this may be due to the steric effect of the cyclohexyl group. In the reaction of **1b** with aryl isocyanates, relatively low conversion was obtained (40−68% conversion), and the products were formed in 16−51% yield. Similar to **1a**, the choice of aryl isocyanate also has an effect on the resulting product. Reaction of **1b** with phenyl isocyanate **2a** only produces the ring-opened product **4i** (Table 1, entry 10). When *p*-chlorophenyl isocyanate **2e** was used, 15% and 36% **3l** and **4l** were obtained, respectively (Table 1, entry 12). Reaction of *o*-chlorophenyl isocyanate or *o*-nitrophenyl isocyanate with **1b** led to the exclusive formation of the cyclized products **3k** and **3m** in 28% and 16% yields, respectively (Table 1, entries 11 and 13). Analogous to the reaction of **1a** with **2f**, one unknown product was also isolated in the reaction of **1b** and **2f**. No cyclization occurred by introducing the methyl group in the 2-position of the pyrrolidine ring (**1c**). For example, in the reaction of **1c** with **2e** at ambient temperature and pressure, only **4o** was obtained with a slightly higher cis/trans ratio (71/29) than in the other cases (Table 1, entry14).

One can conclude that $Pd(OAc)_2$ and PPh_3 can be employed as effective catalysts for the reaction of 2-vinylpyrrolidines **1** and aryl isocyanates **2** at ambient temperature and pressure, but the catalyst system is not suitable for all the isocyanates to form the desired cyclization products. Ultimately, we found that $Pd_2(dba)_3$·$CHCl_3$ and dppp is the preferred catalyst system for this reaction, and in some cases, the dpppentane can also give good results (Table 2, entries 4 and 5). Performing the reaction at ambient temperature and pressure by using $Pd_2(dba)_3$·$CHCl_3$ and dppp only affords trace amounts of the cyclized product. However, at elevated temperature (40−60 °C) and pressure (5 psi), the cyclized product **3** is formed selectively (**4** is not observed) in reactions using **1a** and **1b** with **2** (Table 2). For example, reaction of **1b** with **2a** gave traces of **3i** after 2 days at ambient temperature and pressure (Table 1, entry 15). However, **3i** can be obtained in 15% yield with 18% conversion of **1b** at 60 °C under 5 psi (Table 1, entry 16).

Identifying features in the ^{1}H/^{13}C NMR spectra characteristic of the 1,3-diazepin-2-ones **3** were the vinyl protons between 5 and 6 ppm, the C4 hydrogen at 4.3−4.4 ppm, and the carbonyl carbon at 160 ppm. An intense absorption band at ∼1650 cm^{-1}, typical of urea carbonyls, was present in the IR spectra of **3**. In all the reactions

investigated, isocyanates with an electron-withdrawing group on the phenyl ring afford good to excellent conversion. 2-Vinylpyrrolidines **1** with different substituents exhibited different reactivity toward aryl isocyanates **2**. Usually higher conversions were obtained in the reaction of **1a** with isocyanates containing electron-withdrawing substituents on the aromatic ring (**2b**−**g**). The reactions can be carried out in a shorter time, and in some cases at a relative low temperature. For example, in the reaction of **1a** with **2b** and **2g**, **3b** and **3g** were obtained in 60% and 70% isolated yields, respectively, after reaction for 12 h at 40 °C (Table 2, entries 2 and 7). Reactions of **2c** and **2e** with **1a** afford 93% and 97% conversions, and **3c** and **3e** were isolated in 80% and 82% yields, respectively (Table 2, entries 3 and 5). Use of **1a** in reaction with phenyl isocyanate **2a** produced **3a** in good yield, but in only moderate conversion (Table 2, entry 1). Reaction of **1a** with *p*-methoxyphenyl isocyanate **2h** resulted in a lower conversion and yield (Table 2, entry 8).

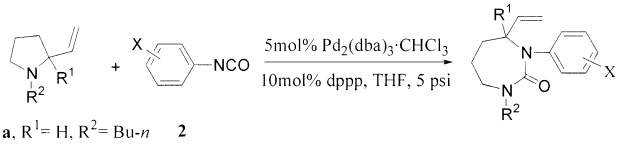
When *N*-cyclohexyl-2-vinylpyrrolidine **1b** was used as the substrate, a little longer reaction time was needed because of the lower reactivity of **1b**, and the products were obtained in moderate to good yield. Reaction of **1b** with phenyl isocyanate **2a** was slow, with only 18% conversion in 2 days, affording the product **3i** in 15% yield (Table 2, entry 9). When **1b** was reacted with aryl isocyanates containing an electron-withdrawing group (**2b**, **2c**, **2e**, and **2f**), the products were obtained in 32−48% yield (Table 2, entries 10−13). Reaction of *p*-nitrophenyl isocyanate **2g** with **1b** occurred efficiently to give **3n** in 59% yield (Table 2, entry 14). In both the reactions of **1a** and **1b** with *o*-nitrophenyl isocyanate **2f**, although good conversions were achieved, the desired products were isolated in lower yield due to the formation of unknown side products. Attempts to prepare **3p** by the reaction of **1c** with **2g** failed even at higher catalyst loading, with the ring-opened product **4p** obtained in 60% yield (Table 2, entry 15). Similar results were observed in the reactions of **1c** with other aryl isocyanates, and may be due to the steric effect of the methyl group at the 2-position of the pyrrolidine.

A possible mechanism for the palladium-catalyzed cycloaddition reaction is outlined in Scheme 1. Initial alkene coordination with a palladium(0) complex leads to the formation of a η^3-intermediate **5**. The nucleophilic nitrogen of the resulting intermediate should react readily with the electrophilic aryl isocyanate carbon atom giving rise to intermediate **6**. Cyclization of the latter (path A) would afford the desired seven-membered-ring product **3**, and regenerate the original palladium(0) complex. Alternatively, hydrogen migration of **6** (path B) affords the uncyclized product **4**, and releases the original palladium(0) catalyst.[12] Path B is operative with PPh_3 as the added ligand, as the lower basicity renders the (π-allyl)palladium intermediate less reactive toward electrophilic ring closing. In addition, we used the bidentate phosphine ligands dppf and BINAP, which have similar basicity to Ph_3P, in the reaction of **1a** and *p*-chlorophenyl isocyanate **2e**. Use of 10 mol % of $Pd(OAc)_2$ and 20 mol % of dppf gave **3e** and **4e** with a 60/40 ratio in 69% isolated yield and 81% conversion. When 30 mol % of racemic BINAP and 15 mol % of $Pd(OAc)_2$ were used as the catalyst system, there was only 13% conversion and in 9% total yield of **3e** and **4e** in a 38/62 ratio. The more basic bidentate phosphine ligand dpppentane gave the cyclized product **3e** in high selectivity (85/15 ratio of **3e**/**4e**), and in good yield. No products were observed with use of trialkylphosphines such as tri-*n*-butylphosphine and tricyclohexylphosphine as ligands.

It was observed that products of structural type **4** were formed as a mixture of trans and cis stereoisomers. This lack of stereospecificity can be explained by the facile conversion between intermediates **6a** and **6b** via a well-established $\eta^3-\eta^1-\eta^3$ mechanism (Scheme 2).[13]

In summary, the catalyst system comprising 5 mol % of $Pd_2(dba)_3{\cdot}CHCl_3$ and 10 mol % of dppp is effective for the synthesis of 1,3-diazepin-2-one derivatives, by ring-opening and cyclization of 2-vinylpyrrolidines with aryl isocyanates, usually affording products in reasonable yields. Use of $Pd(OAc)_2$ and PPh_3 gave both the seven-

TABLE 2. Cyclization Reactions of 2-Vinylpyrrolidines with Aryl Isocyanates Catalyzed by 5 mol % of $Pd_2(dba)_3{\cdot}CHCl_3$ and 10 mol % of Dppp in THF[a]



1a, R^1= H, R^2= Bu-*n* **2**
1b, R^1= H, R^2= Cy
1c, R^1= Me, R^2= Bu-*n*

3

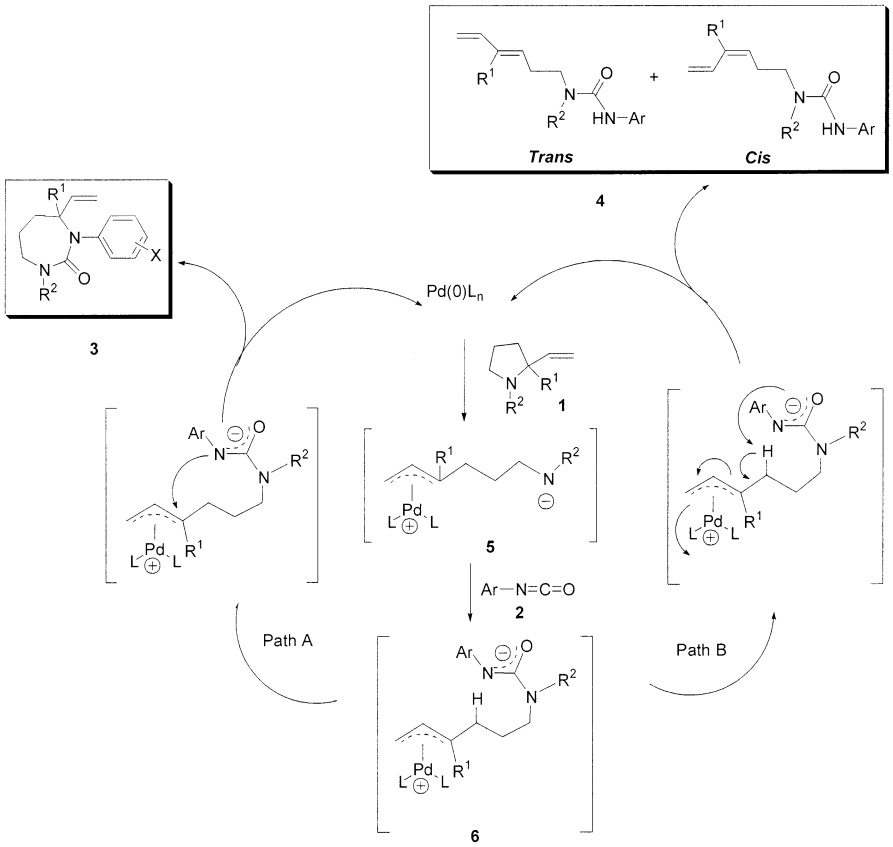
entry	1	aryl isocyanate **2**	temp (°C)	time (h)	conv (%)[b]	**3**, yield (%)[c]
1	**1a**	**2a** (X = H)	60	12	70	**3a**, 62
2	**1a**	**2b** (X = Br-*p*)	40	12	>98	**3b**, 60
3	**1a**	**2c** (X = Cl-*o*)	60	48	93	**3c**, 80
4	**1a**	**2d** (X = Cl-*m*)	50	36	63	**3d**, 50[d]
5	**1a**	**2e** (X = Cl-*p*)	40	18	97	**3e**, 82[d]
6	**1a**	**2f** (X = NO_2-*o*)	40	12	81	**3f**, 37
7	**1a**	**2g** (X = NO_2-*p*)	40	<12	>98	**3g**, 70
8	**1a**	**2h** (X = MeO-*p*)	60	48	24	**3h**, 11
9	**1b**	**2a** (X = H)	60	48	18	**3i**, 15
10	**1b**	**2b** (X = Br-*p*)	60	36	72	**3j**, 32
11	**1b**	**2c** (X = Cl-*o*)	60	48	67	**3k**, 42
12	**1b**	**2e** (X = Cl-*p*)	60	48	62	**3l**, 48
13	**1b**	**2f** (X = NO_2-*o*)	60	24	75	**3m**, 35
14	**1b**	**2g** (X = NO_2-*p*)	60	<12	90	**3n**, 59
15	**1c**	**2g** (X = Cl-*o*)	60	24	82	**3p**, 0 [e]

[a] $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mol %) and dppp (10 mol %) were premixed for 30 min in 3.0 mL of dry, degassed THF followed by addition of **1** and **2**. [b] The conversion was determined from GC by using biphenyl as an internal standard, or was calculated based on the crude ^1H NMR of the mixture. [c] Isolated yield based on the amount of 2-vinylpyrrolidine **1** used. [d] Using dpppentane as ligand. [e] $Pd_2(dba)_3{\cdot}CHCl_3$ (7.5 mol %) and dppp (15 mol %) were used and ring-opened product **4p** was obtained in 60% yield.

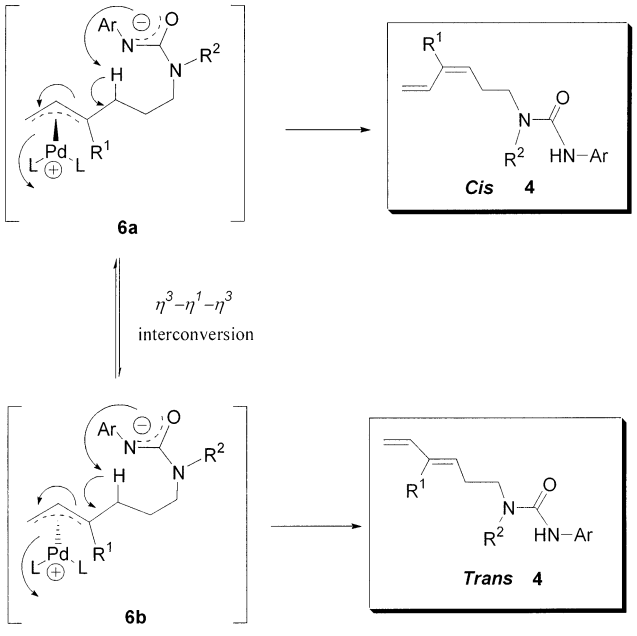
(12) One reviewer suggested that the mechanism in the reaction to form the diene derivatives may involve β-hydride elimination from an η^1-palladium species. This is a possible pathway that we cannot exclude.

(13) (a) Godleski, S. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon Press: Oxford, UK, 1991; Vol. 4, Chapter 3.3, pp 585−662. (b) Trost, B. M.; Hung, M.-H. *J. Am. Chem. Soc.* **1984**, *106*, 6837. (c) Trost, B. M.; Bunt, R. C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 99. (d) Dawson, G. J.; Williams, J. M. J.; Coote, S. J. *Tetrahedron Lett.* **1995**, *36*, 461. (e) Auburn, P. R.; Mackenzie, P. B.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2033. (f) Trost, B. M.; Krische, M. J.; Radinov, R.; Zanoni, G. *J. Am. Chem. Soc.* **1996**, *118*, 6297. (g) Trost, B. M.; Murphy, D. J. *Organometallics* **1985**, *4*, 1143.

SCHEME 1



SCHEME 2



membered product and an interesting ring-opened conjugated diene derivative of urea. The latter may initiate the development of new methodologies for other interesting carbon electrophiles. This methodology expands the scope of palladium-catalyzed cycloaddition reactions and opens new doors for the catalytic formation of seven-membered-ring heterocycles.

Experimental Section

All reactions and manipulations of chemicals were carried out using standard Schlenk techniques under an atmosphere of argon. 2-Vinylpyrrolidines were prepared according to the literature.[11] THF was dried over Na/benzophenone and distilled prior to use. All NMR spectra were recorded with $CDCl_3$ as the solvent with reference to residual $CHCl_3$ (^{1}H at 7.24 ppm and ^{13}C at 77.0 ppm). Infrared spectra were recorded on a Fourier transform spectrometer and are reported in wavenumbers (cm^{-1}).

General Procedure for the Palladium-Catalyzed Cycloaddition Reaction of 2-Vinylpyrrolidines (1a, 1b, and 1c) with Aryl Isocyanates 2. $Pd(OAc)_2$ (3.77 mg, 0.017 mmol, 10 mol % to **1**) or $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mol %) was weighed into a Schlenk tube under a stream of argon, 3 mL of dry THF was added, and the solution was degassed. Triphenylphosphine (17.57 mg, 0.067 mmol, 40 mol % to **1**) or dppp (10 mol %) was added, followed by 0.17 mmol of **1a**, **1b**, or **1c** and then phenyl isocyanate (30 mg, 0.25 mmol). The progress of the reaction was monitored by GC and the crude product was purified by silica chromatography with pentane/ether 2:1 as eluant to afford **4** and then the 1,3-diazepin-2-ones **3**. Further purification was effected using preparative TLC.

1-Butyl-3-phenyl-4-vinyl-1,3-diazepin-2-one (3a) (X = H, R^1 = H, R^2 = Bu-*n*): 62% yield; colorless oil; IR (neat) ν 3059, 2955, 2928, 2870, 1655, 1597, 1545, 1498, 1468, 1420, 1309, 1259 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, 3H, J = 7.3 Hz), 1.23−1.38 (m, 2H), 1.50−1.61 (m, 2H), 1.62−1.75 (m, 2H), 1.93−2.00 (m, 2H), 3.16−3.34 (m, 1H), 3.36−3.44 (m, 3H), 4.44 (br, 1H), 5.15 (d, 1H, J = 10.5 Hz), 5.23 (d, 1H, J = 17.3 Hz), 5.85−5.96 (m, 1H), 7.06−7.14 (m, 3H), 7.24−7.29 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.9, 146.1, 137.8, 128.7, 125.4, 124.7, 116.4, 61.7, 49.6, 48.5, 31.3, 30.4, 22.3, 20.3, 13.9; MS (*m*/*e*) 272 (M^+); EIHRMS calcd for $C_{17}H_{24}N_2O$ 272.18885, found 272.18917.

1-Butyl-3-(*p*-bromophenyl)-4-vinyl-1,3-diazepin-2-

one (3b) (X = Br-*p*, R¹ = H, R² = Bu-*n*): 60% yield; light yellow oil; IR (neat) ν 3080, 2956, 2930, 2867, 1651, 1489, 1468, 1420, 1250 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (t, 3H, J = 7.3 Hz), 1.32−1.34 (m, 2H), 1.51−1.62 (m, 2H), 1.69−1.76 (m, 2H), 1.91−2.00 (m, 2H), 3.18−3.24 (m, 1H), 3.32−3.41 (m, 3H), 4.44 (br, 1H), 5.15 (d, 1H, J = 10.6 Hz), 5.20 (d, 1H, J = 17.3 Hz), 5.82−5.89 (m, 1H), 6.99 (d, 2H, J = 8.9 Hz), 7.36 (d, 2H, J = 8.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.3, 145.1, 137.5, 131.7, 126.8, 117.5, 116.7, 61.5, 49.6, 48.3, 31.2, 30.4, 22.2, 20.3, 13.8; MS (*m*/*e*) 350 (M^+), 352 (M^+ + 2); EIHRMS calcd for $C_{17}H_{23}N_2OBr$ 350.09938, found 350.10185.

1-Butyl-3-(*o*-chlorophenyl)-4-vinyl-1,3-diazepin-2-one (3c) (X = Cl-*o*, R¹ = H, R² = Bu-*n*): 80% yield; colorless oil; IR (neat) ν 3067, 2956, 2862, 1655, 1469, 1422, 1245 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, 3H, J = 7.3 Hz), 1.27−1.34 (m, 2H), 1.55−1.57 (m, 2H), 1.70−1.74 (m, 2H), 1.94−1.96 (m, 1H), 2.02−2.12 (m, 1H), 3.23−3.26 (m, 1H), 3.30−3.32 (m, 1H), 3.47 (br, 2H), 4.36 (br, 1H), 5.12 (d, 1H, J = 10.5 Hz), 5.20 (d, 1H, J = 17.4 Hz), 5.89−5.99 (m, 1H), 7.08−7.10 (m, 1H), 7.21−7.23 (m, 1H), 7.32−7.36 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.6, 143.7, 137.7, 132.3, 129.8, 127.8, 127.4, 126.6, 116.5, 62.9, 49.7, 48.2, 31.5, 30.3, 22.1, 20.2, 13.9; MS (*m*/*e*) 306 (M^+), 308 (M^+ + 2); EIHRMS calcd for $C_{17}H_{23}N_2OCl$ 306.14988, found 306.14703.

1-Butyl-3-(*m*-chlorophenyl)-4-vinyl-1,3-diazepin-2-one (3d) (X = Cl-*m*, R¹ = H, R² = Bu-*n*): 50% yield; colorless oil; IR (neat) ν 3077, 2957, 2865, 1651, 1594, 1468, 1418, 1248 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, 3H, J = 7.3 Hz), 1.21−1.41 (m, 2H), 1.48−1.62 (m, 2H), 1.67−1.76 (m, 2H), 1.88−1.98 (m, 2H), 3.17−3.26 (m, 1H), 3.31−3.44 (m, 3H), 4.38 (m, 1H), 5.17 (d, 1H, J = 10.6 Hz), 5.22 (d, 1H, J = 17.4 Hz), 5.81−5.92 (m, 1H), 6.98−7.05 (m, 2H), 7.10−7.20 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.5, 147.5, 137.7, 134.5, 129.9, 125.1, 124.6, 123.3, 117.2, 61.5, 49.9, 48.5, 31.4, 30.7, 22.4, 20.6, 14.3; MS (*m*/*e*) 306 (M^+), 308 (M^+ + 2); EIHRMS calcd for $C_{17}H_{23}N_2OCl$ 306.14988, found 306.15224.

1-Butyl-3-(*p*-chlorophenyl)-4-vinyl-1,3-diazepin-2-one (3e) (X = Cl-*p*, R¹ = H, R² = Bu-*n*): 82% yield; colorless oil; IR (neat) ν 3071, 2957, 2929, 2858, 1650, 1492, 1468, 1258 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (t, 3H, J = 7.3 Hz), 1.29−1.35 (m, 2H), 1.51−1.61 (m, 2H), 1.70−1.75 (m, 2H), 1.90−1.98 (m, 2H), 3.18−3.24 (m, 1H), 3.31−3.41 (m, 3H), 4.33−4.36 (m, 1H), 5.15 (d, 1H, J = 10.6 Hz), 5.19 (d, 1H, J = 17.3 Hz), 5.82−5.89 (m, 1H), 7.6 (d, 2H, J = 8.9 Hz), 7.21 (d, 2H, J = 8.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.4, 144.6, 137.4, 129.8, 128.7, 126.6, 116.7, 61.7, 49.6, 48.3, 31.2, 30.4, 22.2, 20.3, 13.9; MS (*m*/*e*) 306 (M^+), 308 (M^+ + 2); EIHRMS calcd for $C_{17}H_{23}N_2OCl$ 306.14988, found 306.15133.

1-Butyl-3-(*o*-nitrophenyl)-4-vinyl-1,3-diazepin-2-one (3f) (X = NO_2-*o*, R¹ = H, R² = Bu-*n*): 37% yield; light yellow oil; IR (neat) ν 3077, 2957, 2930, 2870, 1651, 1469, 1423, 1243 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.90 (t, 3H, J = 7.1 Hz), 1.21−1.40 (m, 2H), 1.48−1.60 (m, 2H), 1.63−1.77 (m, 2H), 1.90−2.15 (m, 2H), 3.26 (q, 2H, J = 6.9 Hz), 3.40−3.44 (m, 2H), 4.37−4.44 (m, 1H), 5.12−5.14 (m, 1H), 5.21 (d, 1H, J = 10.2 Hz), 5.87−6.04 (m, 1H), 7.21−7.29 (m, 1H), 7.39−7.56 (m, 2H), 7.83 (dd, 1H, J = 8.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 160.4, 140.2, 137.2, 135.9, 133.3, 128.2, 125.8, 124.8, 117.2, 63.0, 49.8, 47.9, 31.6, 30.1, 21.8, 20.2, 13.8; MS (*m*/*e*) 317 (M^+); EIHRMS calcd for $C_{17}H_{23}N_3O_3$ 317.17393, found 317.17293.

1-Butyl-3-(*p*-nitrophenyl)-4-vinyl-1, 3-diazepin-2-one (3g) (X = NO_2-*p*, R¹ = H, R² = Bu-*n*): 70% yield; light yellow oil; IR (neat) ν 3085, 2957, 2932, 2871, 1674, 1596, 1503, 1469, 1418, 1336, 1316, 1303, 1112 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, 3H, J = 7.3 Hz), 1.33−1.40 (m, 2H), 1.58−1.73 (m, 2H), 1.81−1.89 (m, 2H), 1.92−2.04 (m, 2H), 3.27−3.45 (m, 4H), 4.37−4.42 (m, 1H), 5.21 (d, 1H, J = 10.5 Hz), 5.29 (d, 1H, J = 17.3 Hz), 5.77−5.87 (m, 1H), 6.98 (d, 2H, J = 9.3 Hz), 8.09 (d, 2H, J = 9.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 150.2, 141.0, 136.2, 124.9, 118.0, 117.3, 58.2, 48.6, 46.5, 30.3, 29.3, 21.8, 20.2, 13.8; MS (*m*/*e*) 317 (M^+); EIHRMS calcd for $C_{17}H_{23}N_3O_3$ 317.17393, found 317.17458.

1-Butyl-3-(*p*-methoxyphenyl)-4-vinyl-1,3-diazepin-2-one (3h) (X = MeO-*p*, R¹ = H, R² = Bu-*n*): 11% yield; colorless oil; IR (neat) ν 3077, 2954, 2931, 2805, 1644, 1511, 1468, 1422, 1242 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, 3H, J = 7.3 Hz), 1.19−1.34 (m, 2H), 1.49−1.63 (m, 2H), 1.70−1.77 (m, 2H), 1.87−2.01 (m, 2H), 3.15−3.24 (m, 1H), 3.28−3.47 (m, 3H), 3.75 (s, 3H), 4.28−4.33 (m, 1H), 5.11 (d, 1H, J = 10.5 Hz), 5.17 (d, 1H, J = 17.3 Hz), 5.84−5.95 (m, 1H), 6.81 (d, 2H, J = 8.9 Hz), 7.08 (d, 2H, J = 8.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.2, 157.2, 139.2, 137.9, 128.0, 116.3, 114.0, 63.1, 55.4, 49.7, 48.6, 31.4, 30.4, 22.4, 20.3, 13.9; MS (*m*/*e*) 302 (M^+), 303 (M^+ + 1); EIHRMS calcd for $C_{18}H_{26}N_2O_2$ 302.19942, found 302.19822.

1-Cyclohexyl-3-phenyl-4-vinyl-1,3-diazepin-2-one (3i) (X = H, R¹ = H, R² = Cy): 15% yield; colorless oil; IR (neat) ν 3064, 2928, 2854, 1644, 1597, 1468, 1416, 1248 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04−1.41 (m, 4H), 1.56−1.94 (m, 10H), 3.17−3.26 (m, 1H), 3.36−3.44 (m, 1H), 3.93−4.01 (br, 1H), 4.40−4.41 (m, 1H), 5.13 (d, 1H, J = 10.5 Hz), 5.21 (d, 1H, J = 17.3 Hz), 5.86−5.92 (m, 1H), 7.04−7.13 (m, 3H), 7.23−7.28 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.1, 146.5, 138.2, 129.1, 125.4, 124.7, 116.7, 62.1, 56.1, 43.1, 31.3, 30.8, 26.3, 26.1, 23.6; MS (*m*/*e*) 298 (M^+); EIHRMS calcd for $C_{19}H_{26}N_2O$ 298.20450,found 298.20643.

1-Cyclohexyl-3-(*p*-bromophenyl)-4-vinyl-1,3-diazepin-2-one (3j) (X = Br-*p*, R¹ = H, R² = Cy): 32% yield; colorless oil; IR (neat) ν 3077, 2928, 2854, 1647, 1489, 1416, 1248 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08−1.37 (m, 4H), 1.64−1.97 (m, 10H), 3.18−3.25 (m, 1H), 3.35−3.41 (m, 1H), 3.97 (br, 1H), 4.32−4.35 (m, 1H), 5.14 (d, 1H, J = 10.5 Hz), 5.19 (d, 1H, J = 18.9 Hz), 5.81−5.90 (m, 1H), 6.98 (d, 2H, J = 8.7 Hz), 7.35 (d, 2H, J = 8.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.5, 145.4, 137.8, 132.0, 126.8, 117.5, 117.0, 61.8, 56.1, 42.8, 31.2, 30.8, 26.2, 26.0, 23.5; MS (*m*/*e*) 376 (M^+), 378 (M^+ + 2); EIHRMS calcd for $C_{19}H_{25}N_2OBr$ 376.11503, found 376.11303.

1-Cyclohexyl-3-(*o*-chlorophenyl)-4-vinyl-1,3-diazepin-2-one (3k) (X = Cl-*o*, R¹ = H, R² = Cy): 42% yield; white solid; mp 120−121 °C; IR (neat) ν 3078, 2926, 2853, 1650, 1468, 1446, 1421, 1270 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99−1.37 (m, 4H), 1.58−2.15 (m, 10H), 3.33−3.38 (m, 1H), 3.40−3.47 (m, 1H), 3.95−3.99 (m, 1H), 4.37−4.38 (m, 1H), 5.11 (d, 1H, J = 10.5 Hz), 5.19 (d, 1H, J = 17.2 Hz), 5.90−5.99 (m, 1H), 7.05−7.10 (m, 1H), 7.19−7.24 (m, 1H), 7.33 (d, 2H, J = 8.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.6, 143.7, 137.7, 132.2, 129.8, 127.6, 127.4, 126.5, 116.5, 62.7, 55.7, 42.5, 30.7, 30.4, 25.8, 25.7, 22.9; MS (*m*/*e*) 332 (M^+); EIHRMS calcd for $C_{19}H_{25}N_2OCl$ 332.16553, found 332.16418.

1-Cyclohexyl-3-(*p*-chlorophenyl)-4-vinyl-1,3-diazepin-2-one (3l) (X = Cl-*p*, R¹ = H, R² = Cy): 48% yield; colorless oil; IR (neat) ν 3077, 2929, 2854, 1646, 1492, 1461, 1418, 1248 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.03−1.10 (m, 1H), 1.30−1.38 (m, 3H), 1.57−1.67 (m, 4H), 1.74−1.82 (m, 4H), 1.88−1.93 (m, 1H), 1.96−2.03 (m, 1H), 3.18−3.24 (m, 1H), 3.36−3.42 (m, 1H), 3.95−3.99 (m, 1H), 4.31−4.33 (m, 1H), 5.13 (d, 1H, J = 10.5 Hz), 5.18 (d, 1H, J = 17.3 Hz), 5.84−5.91 (m, 1H), 7.04 (d, 2H, J = 8.8 Hz), 7.21 (d, 2H, J = 8.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.7, 145.0, 137.9, 129.9, 129.0, 126.6, 116.9, 62.1, 56.1, 42.9, 31.2, 30.8, 26.2, 26.0, 23.4; MS (*m*/*e*) 332 (M^+), 334 (M^+ + 2); EIHRMS calcd for $C_{19}H_{25}N_2OCl$ 332.16553, found 332.16382.

1-Cyclohexyl-3-(*o*-nitrophenyl)-4-vinyl-1,3-diazepin-2-one (3m) (X = NO_2-*o*, R¹ = H, R² = Cy): 35% yield; light yellow oil; IR (neat) ν 3080, 2930, 2855, 1645, 1524, 1420, 1349, 1245 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03−1.40 (m, 5H), 1.58−1.77 (m, 8H), 2.07−2.18 (m, 1H), 3.26−3.34 (m, 1H), 3.41−3.49 (m, 1H), 3.90−3.96 (m, 1H), 4.41−4.43 (m, 1H), 5.13 (d, 1H, J = 5.3 Hz), 5.18 (d, 1H, J = 12.1 Hz), 5.91−5.99 (m, 1H), 7.23 (t, 1H, J = 7.7 Hz), 7.41 (d, 1H, J = 8.0 Hz), 7.51 (t, 1H, J = 7.7 Hz), 7.83 (d, 1H, J = 8.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.9, 147.0, 140.4, 137.6, 133.5, 128.3, 125.9, 125.1,

117.5, 63.1, 56.4, 42.6, 31.6, 30.9, 30.7, 26.1, 23.1; MS (*m*/*e*) 343 (M^+); EIHRMS calcd for $C_{19}H_{25}N_3O_3$ 343.18958, found 343.1905.

1-Cyclohexyl-3-(*p*-nitrophenyl)-4-vinyl-1,3-diazepin-2-one (3n) (X = NO_2-*p*, R^1 = H, R^2 = Cy): 59% yield; light yellow oil; IR (neat) ν 3077, 2930, 2855, 1667, 1595, 1503, 1415, 1317, 1303, 1111 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.08−1.40 (m, 5H), 1.65−1.88 (m, 8H), 1.98−2.06 (m, 1H), 3.29−3.34 (m, 2H), 4.19−4.29 (br, 1H), 4.33−4.36 (br, 1H), 5.20 (dd, 1H, J = 10.5 Hz), 5.32 (dd, 1H, J = 17.3 Hz), 5.78−5.89 (m, 1H), 6.93 (d, 2H, J = 9.3 Hz), 8.08 (d, 2H, J = 9.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.7, 150.2, 140.6, 136.3, 125.0, 117.6, 117.1, 58.2, 55.2, 41.0, 30.8, 29.1, 25.6, 25.4, 23.4; MS (*m*/*e*) 343 (M^+); EIHRMS calcd for $C_{19}H_{25}N_3O_3$ 343.18958, found 343.1863.

4a (X = H, R^1 = H, R^2 = Bu-*n*): 82% yield; colorless oil; IR (neat) ν 3332, 3040, 2958, 2872, 1644, 1596, 1537, 1531, 1500, 1488, 1445, 1402, 1372, 1311, 1241 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.94 (t, 3H, J = 7.1 Hz), 1.26−1.41 (m, 2H), 1.52−1.67 (m, 2H), 2.34−2.56 (m, 2H), 3.23−3.40 (m, 4H), 5.04−5.28 (m, 2H), 5.41−5.54 (m, 0.48H, cis), 5.62−5.77 (m, 0.52H, trans), 6.06−6.39 (m, 1.52H), 6.31 (s, 1H, NH), 6.54−6.72 (m, 0.48H, cis), 6.95−7.00 (m, 1H), 7.21−7.41 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 154.8, 139.1, 136.6, 133.5, 131.7, 130.8, 128.8, 128.2, 122.8, 119.7, 118.4, 116.3, 47.7, 31.8, 30.7, 27.0, 20.2, 13.9; MS (*m*/*e*) 270 (M^+ − 2), 270 (M^+); EIHRMS calcd for $C_{17}H_{24}N_2O$ 272.18885, found 272.18708.

4b (X = Br-*p*, R^1 = H, R^2 = Bu-*n*): 27% yield; light yellow oil; IR (neat) ν 3320, 3109, 3082, 2957, 2930, 2871, 1643, 1588, 1525, 1489, 1413, 1385, 1306, 1287, 1240 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.94 (t, 3H, J = 7.3 Hz), 1.33−1.41 (m, 2H), 1.53−1.63 (m, 2H), 2.38 (q, 1H, J = 7.2 Hz), 2.49 (q, 1H, J = 7.3 Hz), 3.26 (t, 2H, J = 7.6 Hz), 3.35 (t, 2H, J = 7.2 Hz), 5.01−5.27 (m, 2H), 5.47 (q, 0.5H, cis, J = 8.6 Hz), 5.64−5.74 (m, 0.5H, trans), 6.08−6.35 (m, 1.5H), 6.29 (s, 1H, NH), 6.55−6.68 (m, 0.5H, cis), 7.24 (d, 2H, J = 8.9 Hz), 7.35 (d, 2H, J = 8.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.0, 138.7, 137.0, 134.0, 132.2, 132.1, 131.9, 131.1, 128.5, 121.6, 119.0, 116.9, 115.6, 48.1, 48.0, 47.9, 32.2, 31.1, 27.4, 20.6, 14.3; MS (*m*/*e*) 350(M^+), 352 (M^+ + 2); EIHRMS calcd for $C_{17}H_{23}N_2OBr$ 350.09938, found 350.09946.

4h (X = MeO-*p*, R^1 = H, R^2 = Bu-*n*): 65% yield; colorless oil; IR (neat) ν 3333, 3044, 2957, 2932, 2872, 2835, 1650, 1634, 1608, 1513, 1463, 1420, 1373, 1297, 1244, 1179 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, 3H, J = 7.3 Hz), 1.30−1.40 (m, 2H), 1.50−1.61 (m, 2H), 2.34−2.41 (m, 1H), 2.45−2.53 (m, 1H), 3.25 (t, 2H, J = 7.6 Hz), 3.32−3.36 (m, 2H), 3.75 (s, 3H), 5.10−5.25 (m, 2H), 5.46 (q, 0.46H, cis, J = 8.8 Hz), 5.64−5.74 (m, 0.54H, trans), 6.10−6.35 (m, 1.54H), 6.21 (s, 1H, NH), 6.56−6.77 (m, 0.46H, cis), 6.81 (d, 2H, J = 8.9 Hz), 7.23 (d, 2H, J = 8.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.0, 155.7, 137.1, 133.8, 132.5, 132.0, 131.4, 128.7, 123.4, 122.5, 118.7, 116.6, 114.4, 55.9, 48.2, 48.0, 32.3, 31.2, 30.0, 27.5, 20.6, 14.3; MS (*m*/*e*) 302 (M^+); EIHRMS calcd for $C_{17}H_{24}N_2O$ 302.1994, found 302.1986.

4i (X = H, R^1 = H, R^2 = Cy): 45% yield; colorless solid; IR (neat) ν 3322, 3075, 2929, 2855, 1634, 1595, 1530, 1500 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.07−1.51 (m, 5H), 1.62−1.83 (m, 5H), 2.34−2.55 (m, 2H), 3.20−3.44 (m, 2H), 3.94−3.97 (br, 1H), 5.03−5.30 (m, 2H), 5.42−5.55 (m, 0.43H, cis), 5.64−5.79 (m, 0.57H, trans), 6.08−6.40 (m, 1.57H), 6.36 (s, 1H, NH), 6.59−6.73 (m, 0.43H, cis), 6.98−7.02 (m, 1H), 7.20−7.37 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 155.0, 139.2, 136.5, 133.5, 131.7, 131.4, 130.7, 128.8, 128.0, 122.7, 119.7, 118.8, 116.7, 55.3, 42.8, 42.7, 33.9, 31.4, 29.2, 25.9, 25.5; MS (*m*/*e*) 298 (M^+); EIHRMS calcd for $C_{17}H_{24}N_2O$ 298.20452, found 298.20391.

4l (X = Cl-*p*, R^1 = H, R^2 = Cy): 36% yield; colorless oil; IR (neat) ν 3322, 3113, 3044, 2930, 2855, 1634, 1592, 1525, 1493, 1450, 1308, 1238 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.07−1.48 (m, 5H), 1.60−1.88 (m, 5H), 2.35−2.42 (m, 1H), 2.45−2.58 (m, 1H), 3.21−3.28 (m, 2H), 3.88−3.93 (m, 1H), 5.04−5.29 (m, 2H), 5.43−5.52 (m, 0.4H, cis), 5.66−5.75 (m, 0.6H, trans), 6.10−6.38 (m, 1.6H), 6.36 (s, 1H, NH), 6.55−6.68 (m, 0.4H, cis), 7.01−7.29 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.2, 138.3, 136.8, 134.0, 132.2, 131.8, 131.1, 129.1, 128.3, 128.0, 121.3, 119.3, 117.2, 55.8, 43.2, 43.1, 34.3, 31.8, 29.5, 26.3, 25.8; MS (*m*/*e*) 332 (M^+), 334 (M^+ + 2); EIHRMS calcd for $C_{19}H_{25}N_2OCl$ 332.1655, found 332.1666.

4o (X = Cl-*p*, R^1 = Me, R^2 = Bu-*n*): 30% yield; light yellow oil; IR (neat) ν 3332, 3117, 3057, 2959, 2930, 2872, 1650, 1634, 1593, 1530, 1455, 1493, 1416, 1378, 1307, 1091 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.94 (t, 3H, J = 7.3 Hz), 1.28−1.40 (m, 2H), 1.53−1.61 (m, 2H), 1.78 (s, 0.71H, trans), 1.82 (s, 2.29H, cis), 2.23 (m, 0.71H, trans), 2.47 (m, 1.29H, cis), 3.23−3.36 (m, 4H), 4.98−5.28 (m, 2H), 5.41 (t, 0.71H, cis, J = 7.8 Hz), 5.51 (t, 0.29H, trans, J = 7.8 Hz), 6.23−6.43 (m, 0.29 H), 6.29 (s, 1H, NH), 6.69−6.79 (m, 0.71 H, cis), 7.18−7.33 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.7, 140.8, 138.4, 137.8, 136.8, 135.2, 132.9, 129.0, 128.3, 127.6, 126.4, 120.8, 116.4, 115.0, 113.8, 112.1, 47.8, 47.6, 47.5, 30.7, 28.4, 27.5, 26.6, 26.4, 20.2, 19.9, 13.8, 11.8; MS (*m*/*e*) 320 (M^+); EIHRMS calcd for $C_{18}H_{25}N_2OCl$ 320.16553, found 320.16301.

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Supporting Information Available: ^1H and ^{13}C NMR spectra of compounds **3a**−**n**, **4a**,**b**, **4h**,**i**, **4l**, and **4o**; ^1H COSY spectra of compounds **3c**,**d**, **3g**, and **3l**,**m**; ^1H−^{13}C HMQC spectra of compounds **3b**−**e, 3g,** and **3l**−**n**. This material is available free of charge via the Internet at http://pubs.acs.org.

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