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Formation of Spirocyclic Compounds from Heck Cyclizations Invoking Cyclic Enamides

Gedu Satyanarayana and Martin E. Maier*

Institut für Organische Chemie, Universität Tübingen, Auf der Morgenstelle 18, 72076 Tübingen, Germany

martin.e.maier@uni-tuebingen.de

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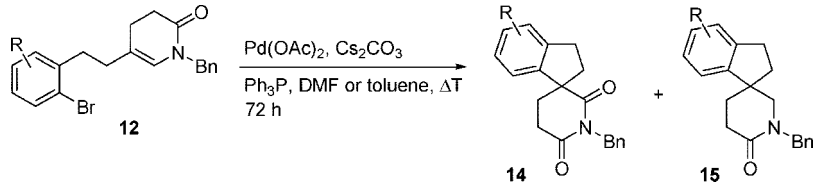

The palladium-mediated transformation of 3,4-dihydro-2(1*H*)-pyridinones **12** featuring a (2-bromophenyl)ethyl substituent in the 5-position produces spirocyclic products, imides **14** and amides **15**. The formation of these products can be explained by insertion of the enamide double bond into the initial aryl−Pd bond followed by oxidation or reduction of the organopalladium intermediate. Alternatively, formation of these spiro compounds might proceed via acyliminium ion intermediates.

Introduction

A typical feature of the Heck reaction is the transformation of an organopalladium species into another one by insertion of an alkyne or alkene into the initial Pd−C bond.[1] In the case of an alkene, the insertion is followed by elimination of PdHX, provided that a β-hydrogen is available for *syn*-elimination. For example, Heck reactions on cyclohexene or other cyclic alkenes with aryl halides lead to 3-arylcyclohexenes (cyclohex-2-en-1-ylbenzenes) or other double-bond isomers.[2] If a β-hydride elimination is not possible other intramolecular reactions can occur. A famous example is the Catellani process[3,4] where the insertion product from norbornene undergoes an intramolecular C−H insertion leading to a palladacycle that can be used for further transformations. Furthermore, substrates for intramolecular Heck reactions have been constructed, that contain 1,1-disubstituted alkenes, forcing the initial organopalladium species to enter into useful domino reactions.[5–8]

Commonly, normal alkenes or electron-poor alkenes are used in the Heck reaction.[1] However, even electron-rich alkenes such as enol ethers and enamides have been employed as well. In general, enamides undergo Heck coupling with the carbon next to the nitrogen atom.[9] The transformation of the aryl iodide **1** containing an enamide appendage illustrates an intramolecular example that follows this rule (Figure 1).[10,11] Via intermediate ***A*** the spiro compound **2** was formed. The thallium salt additive prevented migration of the double bond. An unusual case is the cyclization of enamide **3**.[12] The alkene insertion should lead

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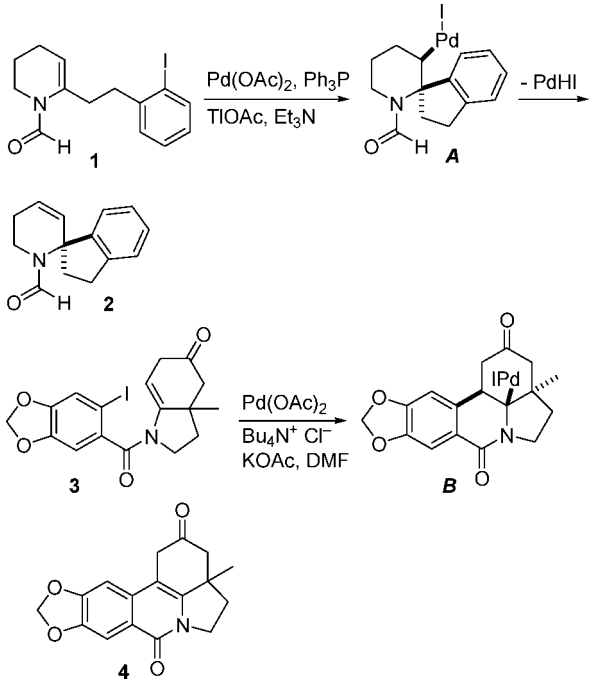

FIGURE 1. Examples of intramolecular Heck reactions onto cyclic enamides.

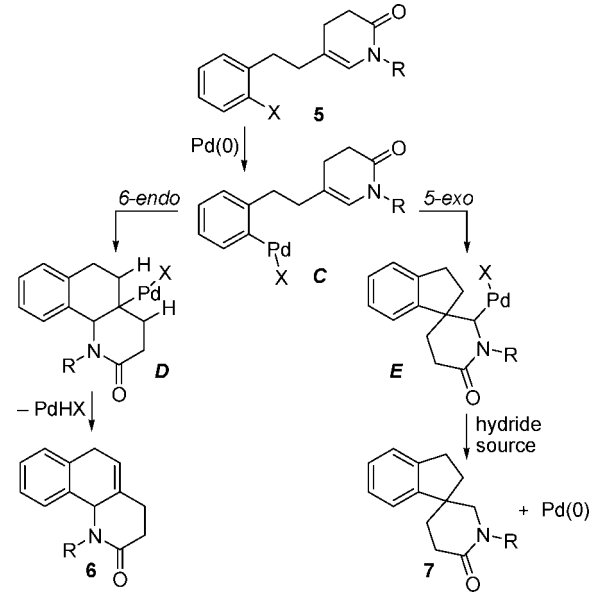

FIGURE 2. Possible products in the intramolecular Heck reaction of aryl halides connected to a cyclic enamide via a C-2 tether; X = halide, R = alkyl, aryl.

to intermediate ***B***, which has no *syn* β-hydrogen next to the Pd−I substituent. Double bond formation to pentacycle **4** can only be explained by epimerization of the Pd-bearing center, possibly through the corresponding iminium ion.

As a result of our interest in the synthesis of nitrogen-containing scaffolds,[13,14] we planned to investigate the palladium-catalyzed transformation of aryl halides of type **5**, containing a cyclic enamide connected via a two carbon tether (Figure 2). The aryl-palladium intermediate ***C*** might attack the enamide double bond either in a 5-*exo*- or a 6-*endo*-mode. The 6-*endo*-pathway would lead to intermediate ***D*** with hydrogen atoms available for subsequent β-hydride elimination. This way the annulated ring system **6** or a double bond isomer thereof might be formed. The spiro mode seems more likely in terms of stereoelectronic considerations.[15,1] However, this pathway would generate intermediate ***E*** without a C−H vicinal to the C−PdX bond. Regeneration of the Pd(0) should be possible in the presence of a hydride source, which would correspond to a well-known reductive Heck cyclization.[16–18] This should result in spiro amides like **7**. While less common then annulated systems, spirocyclic ring systems can be found in a variety of natural and unnatural products.[19,20]

Results and Discussion

The corresponding substrates of type **5** were easily prepared from bromoiodobenzenes[21–24] **8a**−**f**. A Jeffery−Heck coupling[25] of these aryl iodides with 3-butenol led to the corresponding 4-(2-bromo)phenyl-butanals **9a**−**f** in reasonable yields ranging from 65% to 85% (Scheme 1, Table 1). Subsequent enamine formation using pyrrolidine in the presence of K_2CO_3 followed by Michael addition to ethyl acrylate furnished the formyl esters **11a**−**f**.[26] Cyclization to the enamides **12a**−**f** was accomplished by heating the formyl esters with benzylamine in the presence of acetic acid.

Using one of the enamides, 1-benzyl-5-[2-(2-bromo-5-methoxyphenyl)ethyl]-3,4-dihydropyridin-2(1*H*)-one (**12d**), its pal-

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SCHEME 1. Synthesis of Cyclic Enamides 12a−f via Heck Coupling, Michael Addition of Enamines 10a−f to Ethyl Acrylate, and Cyclization of 4-Formyl Esters 11a−f with Benzylamine

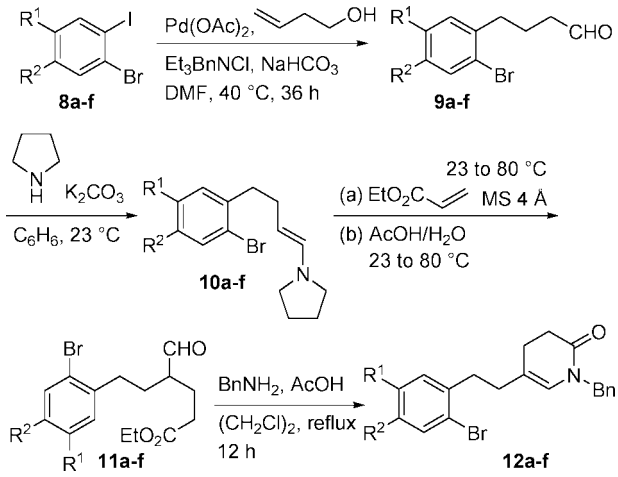
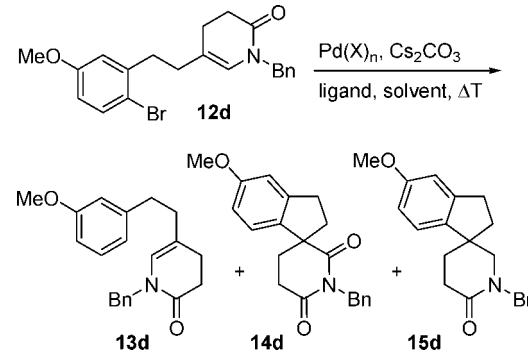


TABLE 1. Yields for Transformations Leading to Piperidinones 12a−f

R^1	R^2	coupling step (%)	Michael addition (%)	cyclization to enamide (%)
H	H	**9a** (85)	**11a** (74)	**12a** (85)
H	Me	**9b** (72)	**11b** (71)	**12b** (82)
H	CO_2Me	**9c** (65)	**11c** (67)	**12c** (69)
OMe	H	**9d** (71)	**11d** (72)	**12d** (84)
OMe	OMe	**9e** (76)	**11e** (74)	**12e** (75)
H	OMe	**9f** (71)	**11f** (72)	**12f** (80)

ladium-catalyzed transformation was studied under various conditions (Table 2). With regard to the palladium source, base, and solvent, classical conditions [$Pd(OAc)_2$, PPh_3, Cs_2CO_3, DMF, 120 °C, 72 h] were employed. Since we expected the 5-*exo* cyclization mode to be preferred as mentioned above,[1,15] we ran the reaction in the presence of a hydride source (triethylsilane and sodium formate, entries 1 and 2) in order to release Pd(0) from the putative intermediate ***E*** (Figure 2). While these reactions did indeed produce the spiro amide **15d**, its yield was low or moderate in the case of sodium formate (37%). The major product turned out to be the debrominated enamide **13d**. Then we wanted to see which products were formed without an external hydride source (entries 3−8). Analysis of the reaction mixture by LC−MS indicated three products, one of them being the debrominated compound **13d**. The other two turned out to be the spiro compounds **14d** and **15d**. Running the reaction at lower temperature (100 °C, entry 4) increased the yield for spiro amide **15d**. It seems that higher temperatures favors the oxidation product, imide **14d**. The reaction worked equally well in toluene as solvent, giving a combined yield of 61% for the two spiro compounds (entry 5). We also examined other palladium catalysts in place of $Pd(OAc)_2$. Since these catalysts already contain at least two phosphine ligands, no additional Ph_3P was added (entries 6−8). Experiments 6 and 7, which were run in DMF at 120 °C, showed $Pd(PPh_3)_2Cl_2$ to be better than $Pd(PPh_3)_4$, since the latter gave more (35%) of the debrominated product **13d**. In toluene as solvent and $Pd(PPh_3)_4$ as catalyst (entry 8), the formation of the debrominated product **13d** (7%) could be essentially suppressed in favor of the imide **14d** (45%). Considering the total yield of the two spiro compounds toluene is the ideal solvent, giving a combined yield of 75%.

TABLE 2. Reaction of Piperidinone 12d with a Palladium Catalyst, Base, and Ph_3P under Different Conditions[a]



entry	catalyst	ligand	solvent	temp (°C)	**13d** (%)	**14d** (%)	**15d** (%)
1[b]	$Pd(OAc)_2$	PPh_3	DMF	120	46	trace	18
2[c]	$Pd(OAc)_2$	PPh_3	DMF	120	40	trace	37
3	$Pd(OAc)_2$	PPh_3	DMF	120	10	21	33
4	$Pd(OAc)_2$	PPh_3	DMF	100	11	9	44
5	$Pd(OAc)_2$	PPh_3	toluene	120	15	24	37
6	$Pd(PPh_3)_2Cl_2$		DMF	120	19	24	37
7	$Pd(PPh_3)_4$		DMF	120	35	18	32
8	$Pd(PPh_3)_4$		toluene	120	7	45	30

[a] Typical conditions: $Pd(OAc)_2$ (0.1 equiv), PPh_3 (0.2 equiv), Cs_2CO_3 (4 equiv), aryl bromide **12d** (0.16−0.2 M), 72 h. [b] In the presence of Et_3SiH (1.5 equiv). [c] In the presence of HCO_2Na (1.5 equiv).

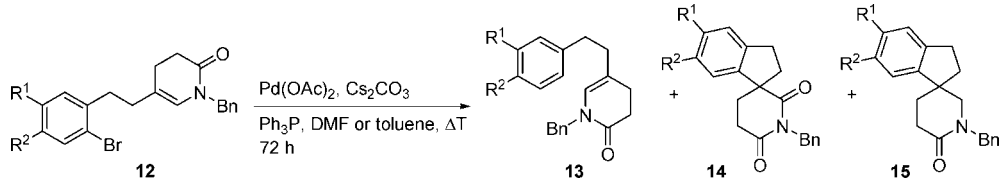
The ^{13}C NMR DEPT spectrum of imide **14d** shows the expected five methylene groups. The quaternary spiro center resonates at $\delta = 54.2$ ppm. The imide carbonyl functions appear at $\delta = 172.2$ and 175.8 ppm, respectively. In the spiro amide **15d** the quaternary spiro center is shifted to higher field, resonating at $\delta = 45.8$ ppm. As compared to **14d** the diastereotopic protons of the NCH_2Ph group of amide **15d** show a classical AB-system in the ^1H NMR spectrum with two doublets ($\delta = 4.77$ and 4.29 ppm) separated by 0.48 ppm. Similar patterns and features are seen in the NMR spectra of the other examples (vide infra). An additional AB-system appears due to the presence of the methylene group at C2′ ($\delta = 3.13$ and 2.96 ppm).

In a similar manner, the other enamides **12a−f** (except for **d**) were transformed to the spiro compounds **14a−f** and **15a−f**, respectively. In these cases the conditions from entry 4 ($Pd(OAc)_2$, PPh_3, DMF, 120 °C, 72 h) and entry 8 ($Pd(PPh_3)_4$, toluene, 120 °C, 72 h) were used. With the latter conditions we wanted to see whether the preferential formation of the spiro imides in toluene would be observed with the other substrates as well. These results are summarized in Table 3.

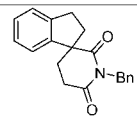
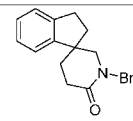
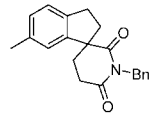
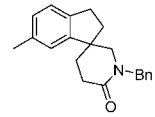
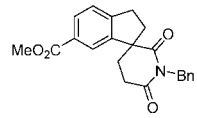
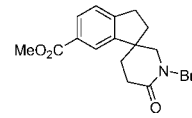
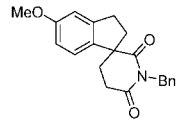
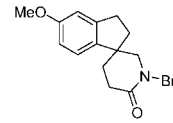
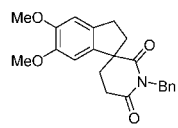
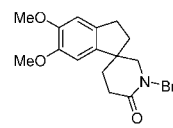
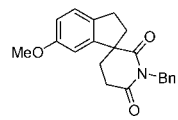
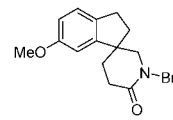
The formation of these spiro derivatives can be explained by a Heck cyclization (Scheme 2). Thus, it seemed that the initial arylpalladium species ***F*** inserts the enamide double bond generating an intermediate of type ***G***. This intermediate might be converted to either the imide **14** or the amide **15**. Alternatively, the iminium ion ***H*** might be a possible intermediate en route to **14** and **15**. In this case, instead of a β-hydride elimination, the palladium might be expelled by formation of the iminium ion ***H***. The imide **14** is then formed by oxidation of the iminium ion ***H***. The amide **15** would be the result of a reduction of the iminium ion ***H***.

Although in general terms the mechanism in Scheme 2 seems plausible, the source of the oxygen that leads to the imides **14** and the source of the hydride required for reduction of the

TABLE 3. Palladium-Catalyzed Transformation of 5-(2-Bromophenyl)ethyl-Substituted 3,4-Dihydro-2(1*H*)-pyridinones 12a−f [a]



12 **13** **14** **15**

entry	substrate	**13a-f** [%][b]	**13a-f** [%][c]	**14a-f**	**14a-f** [%][b]	**14a-f** [%][c]	**15a-f**	**15a-f** [%][b]	**15a-f** [%][c]
1	**12a**	13	8		19	45		38	28
2	**12b**	10	7		17	46		38	32
3	**12c**	15	10		11	41		24	25
4	**12d**	11	7		9	45		44	30
5	**12e**	8	12		16	40		45	20
6	**12f**	18	10		16	43		41	27

[a] Reaction conditions: $Pd(OAc)_2$ (0.1 equiv), PPh_3 (0.2 equiv), Cs_2CO_3 (4 equiv), DMF (0.18−0.2 M), 120 °C, 72 h or $Pd(PPh_3)_4$ (0.1 equiv), Cs_2CO_3 (4 equiv), toluene (0.18−0.2 M), 120 °C, 72 h. [b] Yield in DMF as solvent. [c] Yield in toluene as solvent.

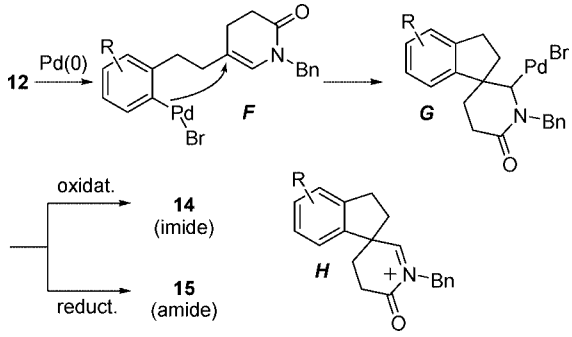
iminium ion to the amides **15** are not yet clear. An initial hypothesis was that the hydride comes from the DMF solvent. This was tested with DMF-D_7 on enamide **12a** (Scheme 3.) However, according to LC−MS and the ^1H and ^{13}C NMR spectra, the spiro compound **15a** did not show any incorporation of a deuterium. The only conclusion that can be drawn from this result is that the hydride most likely comes from the phosphine ligand. Furthermore, precursors of the imide **14a** might provide a hydride equivalent. This hydride transfer might be mediated by Pd as is the case in the formation of aldehydes **9** (Scheme 1).[27] In fact, a recent paper also describes some examples for a reductive Heck cyclization without an added hydride source.[8f]

Using enamide **12b**, further studies were conducted in order to delineate the effects of the palladium source and the base or additive (Table 4.) Entry 1 was run in the presence of sodium formate and $Pd(PPh_3)_2Cl_2$ demonstrating that the prefential formation of the debrominated byproduct **13b** and spiro amide **15b** is independent of the palladium source. Entries 2 and 3 show that for the reaction in toluene the catalyst $Pd(PPh_3)_4$ gives a higher overall yield (78%) for the two spiro compounds **14b** and **15b**. Changing the base from Cs_2CO_3 to Hünig's base (entry 4) shut down the reaction completely. From this experiment we conclude that Cs_2CO_3 serves not only as base but possibly also as an oxygen soure, explaining the formation of the imides **14**.

In summary, we could demonstrate the facile synthesis of spiro compounds **14** and **15** from easily accessible cyclic enamides **12**. These enamides carry a (2-bromophenyl)ethyl substituent in the 5-position that makes it possible to trigger a palladium-mediated reaction cascade resulting in spiro-imides **14** and amides **15**. The starting materials, the cyclic enamides **12**, are easily available from bromoiodobenzenes **8** via a Heck coupling with butenol with concomitant internal reduction of the double bond (redox reaction) leading to 4-aryl-butanals **9**. After conversion of the aldehydes **9** to the corresponding enamines **10**, a Michael reaction with ethyl acrylate gave rise to the formyl esters **11**. These could be cyclized with benzyl amine in the presence of acetic acid to the enamides **12**.

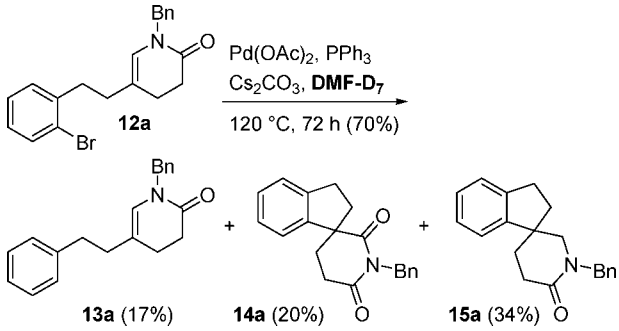
(27) For an example, where iridium functions as a hydride shuttle, see: Yamaguchi, R.; Kawagoe, S.; Asai, C.; Fujita, K.-i. *Org. Lett.* **2008**, *10*, 181–184, and references therein.

SCHEME 2. Proposed Mechanism Explaining Formation of 14 and 15[a]



[a] For simplicity phosphine ligands are omitted.

SCHEME 3. Spiro Cyclization of Enamide 12a in the Presence of DMF-D_7

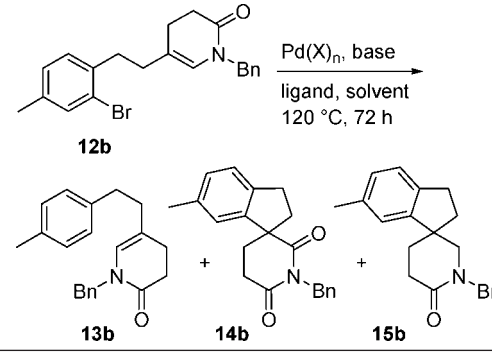


Formation of the spiro compounds **14** and **15** can be explained by insertion of the enamide double bond into the aryl−Pd bond. Oxidation of the alkene insertion product on the one hand and reduction on the other hand leads to the imides **14** and the amides **15**, respectively. Alternatively, the resulting intermediate might expel Pd(0) and HBr generating an iminium ion. Preliminary studies show that the hydride required for the reduction of the putative iminium ion or palladium intermediate is not coming from the solvent. The fact that carbonate as a base is essential points to the fact that the oxygen atom in the imides might originate from the carbonate. Although we could show the preparative value of the transformation, further studies are required in order to clarify the exact mechanism. These transformations are unprecedented and further illustrate the power of transition metal catalyzed transformations.

Experimental Section

Ethyl 6-(2-Bromophenyl)-4-formylhexanoate (11a). To a magnetically stirred solution of the aldehyde[28] **9a** (3.0 g, 13.2 mmol) in C_6H_6 (12 mL) was added anhydrous K_2CO_3 (5.47 g, 39.6 mmol) followed by pyrrolidine (2.2 mL, 26.4 mmol). The reaction mixture was stirred for 6 h at room temperature. Then the mixture was treated with saturated aqueous $NaHCO_3$ solution, extracted with diethyl ether (3 × 30 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo to provide the crude enamine **10a**. To the crude enamine in CH_3CN (12 mL) at 5 °C was added molecular sieves (4 Å, 2 g) followed by ethyl acrylate (2.3 mL, 21.1 mmol). The resultant mixture was stirred for 2 h at room temperature and then refluxed for 2 h. After cooling of the mixture to room temperature, AcOH (3.4 mL) in H_2O (13 mL) was added followed by refluxing of the mixture for 2 h. After cooling to ambient temperature, the mixture was treated with 3 N HCl, and extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were washed with saturated NaCl solution, dried (Na_2SO_4), and filtered. Concentration of the filtrate and purification of the crude product by flash chromatography (ethyl acetate/hexane, 1:8) furnished the aldehyde ester **11a** (3.2 g, 74% for two steps) as colorless oil. $R_f = 0.4$ (ethyl acetate/hexane, 3:97 to 1:8); ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 9.65 (1 H, s, CH═O), 7.51 (1 H, d, $J = 8.1$ Hz, 3′-H), 7.28−7.15 (2 H, m, Ar−H), 7.06 (1 H, ddd, $J = 9.2$, 8.1, 2.3 Hz, Ar−H), 4.12 (2 H, q, $J = 7.1$ Hz, OCH_2CH_3), 2.86−2.64 (2 H, m, 6-H), 2.50−2.20 (3 H, m), 2.10−1.88 (2 H, m, 2-H), 1.92−1.64 (2 H, m, 3-H), 1.24 (3 H, t, $J = 7.1$ Hz, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ [ppm] 203.8 (CH═O), 172.9 (OC═O), 140.5 (C-1′), 132.9 (C-3′), 130.4 (CH), 128.0 (CH), 127.6 (CH), 124.2 (C-2′), 60.5 (OCH_2CH_3), 50.6 (C-4), 33.5 (C-6), 31.5 (C-2), 28.8 (C-5), 23.5 (C-3), 14.2 (OCH_2CH_3).

TABLE 4. Spiro Cyclization of Enamide 12b in the Presence of Various Additives



entry	catalyst	base	additive	solvent	13b (%)	14b (%)	15b (%)
1	$Pd(PPh_3)_2Cl_2$	Cs_2CO_3	HCO_2Na	DMF	45	trace	40
2	$Pd(PPh_3)_2Cl_2$	Cs_2CO_3		toluene	trace	32	28
3	$Pd(PPh_3)_4$	Cs_2CO_3		toluene	7	46	32
4	$Pd(PPh_3)_4$	$(i\text{Pr})_2\text{NEt}$		toluene			

1-Benzyl-5-[2-(2-bromophenyl)ethyl]-3,4-dihydropyridin-2(1*H*)-one (12a). To a magnetically stirred solution of the formyl ester **11a** (1.8 g, 5.5 mmol) in CH_2ClCH_2Cl (10 mL) at room temperature were added sequentially benzyl amine (1.2 mL, 11 mmol) and AcOH (0.3 mL, 5.5 mmol) followed by refluxing of the mixture for 12 h. After cooling, the reaction mixture was treated with aqueous $NaHCO_3$ solution and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and filtered. Concentration of the filtrate followed by flash chromatography (ethyl acetate/hexane, 1:9 to 1:2) furnished the cyclic enamide **12a** (1.7 g, 85%) as brown viscous oil. $R_f =$ 0.45 (ethyl acetate/hexane, 1:2); IR (neat) ν_{max}/cm^{-1} 3062, 3030, 2925, 2838, 1667, 1496, 1439, 1408, 1212, 1026, 957, 751, 703; ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 7.55 (1 H, dd, $J = 7.9$, 1.0 Hz, 3′-H), 7.40−7.28 (3 H, m, Ar−H), 7.28−7.18 (3 H, m, Ar−H), 7.16 (1 H, dd, $J = 7.4$, 1.8 Hz, 6′-H), 7.08 (1 H, ddd, $J = 9.2$, 7.9, 1.8 Hz, 4′-H), 5.79 (1 H, s, 6-H), 4.66 (2 H, s, NCH_2Ph), 2.84 (2 H, CH_2Ar) and 2.62 (2 H, CH_2C-5) [2 t, $J = 7.9$ Hz], 2.36 (2 H, 4-H) and 2.34 (2 H, 3-H) [2 t, $J = 8.1$ Hz]; ^{13}C NMR (100 MHz, $CDCl_3$) δ [ppm] 168.8 (NC═O), 140.5 (C-1′), 137.2 (C), 132.8 (C-3′), 130.3 (CH), 128.5 (2 C, CH), 127.7 (CH), 127.4 (3 C, CH), 127.3 (CH), 124.7 (C-6), 124.2 (C-2′), 118.8 (C-5), 48.8 (NCH_2Ph), 34.7 (CH_2Ar), 34.0 (CH_2C-5), 31.2 (C-3), 24.2 (C-4); HRMS (ESI) calcd for $C_{20}H_{21}BrNO$ $[M + H]^+$ 370.0801, found 370.0801.

Palladium-Catalyzed Spiro Cyclization of 5-(2-Bromophenyl)-ethyl-Substituted Enamide 12a. To a solution of the bromoenamide **12a** (188 mg, 0.51 mmol) in anhydrous DMF (3 mL), in an oven-dried Schlenk tube fitted with a rubber septum, were added Ph_3P

(28) (a) Kuwabe, S.-i.; Torraca, K. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 12202–12206. (b) Qadir, M.; Priestley, R. E.; Rising, T. W. D. F.; Gelbrich, T.; Coles, S. J.; Hursthouse, M. B.; Sheldrake, P. W.; Whittall, N.; Hii, K. K. *Tetrahedron Lett.* **2003**, *44*, 3675–3678.

(26.6 mg, 20 mol%), Cs_2CO_3 (662 mg, 2 mmol), and $Pd(OAc)_2$ (11.4 mg, 10 mol%) at room temperature under nitrogen atmosphere. The magnetically stirred reaction mixture was heated in an oil bath at 120 °C for 3 days. The mixture was cooled to room temperature and washed with aqueous 3N HCl solution. After separation of the layers, the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with saturated NaCl solution, dried (Na_2SO_4), and filtered. Evaporation of the filtrate and purification of the crude material by flash chromatography (ethyl acetate/hexane, 1:9 to 1:4) furnished as first fraction the imide **14a** (30 mg, 19%) as brown viscous oil. Further elution of the column using ethyl acetate/hexane (1:4 to 1:3) gave the debromoenamide **13a** (20 mg, 13%) as brown viscous oil. Continuation of the elution with ethyl acetate/hexane (1:3 to 3:2) provided the amide **15a** (56 mg, 38%) as brown viscous oil.

1-Benzyl-5-(2-phenylethyl)-3,4-dihydropyridin-2(1*H*)-one (13a). R_f = 0.65 (ethyl acetate/hexane, 4:1); IR (neat) ν_{max}/cm^{-1} 3032, 2924, 2852, 1667, 1495, 1454, 1409, 1211, 1029, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 7.50−7.10 (10 H, m, Ar−H), 5.79 (1 H, s, 6-H), 4.68 (2 H, s, NCH_2Ph), 2.75 (2 H, CH_2Ar) and 2.62 (2 H, CH_2C-5) [2 t, J = 7.9 Hz], 2.37 (2 H, 4-H) and 2.35 (2 H, 3-H) [2 t, J = 8.4 Hz]; ^{13}C NMR (100 MHz, $CDCl_3$) δ [ppm] 168.8 (NC═O), 141.3 (C-1), 137.3 (C), 128.6 (2 C, CH), 128.3 (4 C, CH), 127.5 (2 C, CH), 127.3 (CH), 126.0 (CH), 124.6 (C-6), 119.2 (C-5), 48.8 (NCH_2Ph), 35.6 (CH_2Ar), 34.2 (CH_2C-5), 31.2 (C-3), 24.3 (C-4); HRMS (ESI) calcd for $C_{20}H_{22}NO$ $[M + H]^+$ 292.1696, found 292.1697.

1′-Benzyl-2,3-dihydro-2′*H*,6′*H*-spiro[indene-1,3′-piperidine]-2′,6′-dione (14a). R_f = 0.8 (ethyl acetate/hexane, 4:1); IR (neat) ν_{max}/cm^{-1} 3064, 3032, 2925, 2852, 1722, 1674, 1604, 1496, 1477, 1455, 1428, 1376, 1356, 1164, 1079, 1030, 1012, 764, 739, 701; ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 7.41 (2 H, d, J = 7.6 Hz, 7-H), 7.36−7.22 (5 H, m, Ar−H), 7.17 (1 H, t, J = 7.6 Hz, 6-H), 6.98 (1 H, d, J = 7.6 Hz, 4-H), 5.08 (1 H, d) and 5.03 (1 H, d) [J = 13.7 Hz, NCH_2Ph], 3.20−2.95 (2 H, m, 3-H), 2.95−2.65 (3 H, m), 2.22 (1 H, ddd, J = 14.0, 8.4, 5.6 Hz, 5′-H), 2.12 (1 H, ddd, J = 12.7, 7.6, 5.09 Hz, 4′-H), 2.02 (1 H, ddd, J = 13.5, 7.1, 5.6 Hz, 5′-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ [ppm] 175.5 (C-2′), 172.1 (C-6′), 144.2 (C-7a), 143.8 (C-3a), 137.4 (C), 128.9 (2 C, CH), 128.4 (2 C, CH), 128.2 (CH), 127.4 (CH), 126.7 (CH), 125.2 (CH), 123.2 (CH), 55.0 (C-(1,3′)), 43.3 (NCH_2Ph), 36.4 (C-3), 30.2 (C-2), 30.1 (C-5′), 28.7 (C-4′); HRMS (ESI) calcd for $C_{20}H_{20}NO_2$ $[M + H]^+$ 306.1489, found 306.1487.

1′-Benzyl-2,3-dihydro-6′*H*-spiro[indene-1,3′-piperidin]-6′-one (15a). R_f = 0.4 (ethyl acetate/hexane, 4:1); IR (neat) ν_{max}/cm^{-1} 3064, 3029, 2926, 2852, 1643, 1604, 1488, 1454, 1417, 1358, 1248, 761, 735, 702; ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 7.40−6.90 (9 H, m, Ar−H), 4.77 (1 H, d) and 4.28 (1 H, d) [J = 14.5 Hz, NCH_2Ph], 3.16 (1 H, d, J = 12.5 Hz) and 2.97 (1 H, dd, J = 12.5, 2.0 Hz) [2′-H], 2.79 (1 H, ddd, J = 16.3, 8.7, 4.8 Hz), 2.74−2.45 (3 H, m), 2.14 (1 H, ddd, J = 13.2, 9.7, 7.4 Hz), 1.94 (1 H, ddd, J = 12.7, 8.1, 4.6 Hz), 1.89−1.75 (1 H, m), 1.76−1.65 (1 H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ [ppm] 169.4 (NC═O), 146.7 (C-7a), 143.4 (C-3a), 136.9 (C), 128.5 (2 C, CH), 128.4 (2 C, CH), 127.5 (CH), 127.4 (CH), 126.5 (CH), 124.8 (CH), 122.6 (CH), 55.9 (C-2′), 50.2 (NCH_2Ph), 46.5 (C-(1,3′)), 35.0 (C-3), 31.7 (C-5′), 29.6 (C-2′), 29.5 (C-2); HRMS (ESI) calcd for $C_{20}H_{22}NO$ $[M + H]^+$ 292.1696, found 292.1696.

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Supporting Information Available: Experimental procedures and characterization for all new compounds reported and copies of NMR spectra for important intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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