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# Synthesis of 5-Azaspiro[2.4]heptan and Penta-Substituted Pyrrole Derivatives via Pd-Catalyzed Intramolecular Cyclization Reaction of Alkynyl Carboxamides

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# SYNTHESIS OF 5-AZASPIRO[2.4]HEPTAN AND PENTA-SUBSTITUTED PYRROLE DERIVATIVES VIA Pd-CATALYZED INTRAMOLECULAR CYCLIZATION REACTION OF ALKYNYL CARBOXAMIDES

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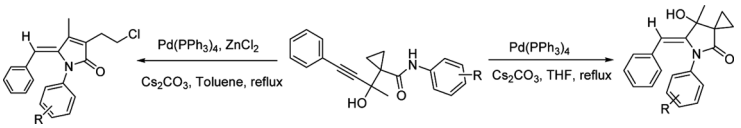
## GRAPHICAL ABSTRACT




**Abstract** *Penta-substituted pyrrole derivatives, including a three-membered ring (5-azaspiro[2.4]heptan), were readily prepared in moderate to excellent yields by the Pd-catalyzed intramolecular cyclization reaction of alkynyl carboxamide compounds. When an excess amount of $ZnCl_2$ acted as a Lewis acid and a source of halide, the one-pot bi-metallic system could afford more valuable penta-substituted chloroethyl pyrrole products under similar conditions. This indicates that the present method is a powerful tool for the preparation of a wide range of functionalized and polysubstituted pyrroles.*

**Keywords** Alkynyl carboxamide; 5-azaspiro[2.4]heptan; Pd-catalyzed; penta-substituted; pyrrole derivatives

## INTRODUCTION

Transition metal–catalyzed cyclization reactions represent an effective and straightforward methodology for the synthesis of cyclic and polycyclic structures, which have attracted much attention.[1] Among these methods, palladium catalysis has attracted great interest. During recent decades, palladium catalysts have emerged as extremely powerful tools for the construction of carbocyclic and heterocyclic

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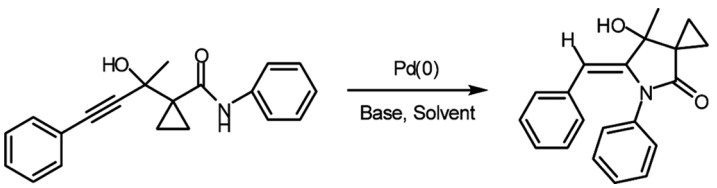
compounds.[2] Because the Pd-catalyzed procedure can tolerate many active groups, such as carbonyl and hydroxyl groups, and it can be employed in the synthesis of highly complex molecules.[3] Pd-catalyzed reactions have been expanded to generate pyridines,[4] oxazoles,[5] thiazoles,[5,6] thiophenes,[7] benzothiophenes,[8] pyrazines,[9] furans,[10] isoquinolines,[11] indoles,[12] and benzofurans[13] under various conditions.

Pyrroles and their derivatives occur in numerous pharmacologically active natural and synthetic products and display a variety of physiological activities.[14] Consequently, many methods for syntheses of diversely substituted pyrroles have been reported, and numerous references can be found.[15] Classic methods for synthesis of pyrrole derivatives have been developed (1) the Paal–Knorr reaction,[16] one of the most attractive methods in which 1,4-diketones and primary amines are converted to various pyrrole derivatives; (2) the Knorr reaction,[17] which assembles pyrroles by the reaction of α-aminoketones and β-ketoesters; (3) the Hantzsch reaction,[18] which is condensation of α-haloketones with 1,3-dicarbonyl compounds in the presence of ammonia; and (4) other methods[19] including conjugate addition reactions,[19h] transition metal–mediated reactions,[19i,j] reductive couplings,[19k] aza-Wittig reactions,[19l] and other multi–step operations.[19m,n] Although numerous strategies for synthesis of di-, tri-, and tetra-substituted pyrrole derivatives have been widely reported, access to penta-substituted pyrroles is somewhat limited.[20] It has been reported that penta-substituted pyrrole derivatives are potent hypocholesterolemic agents through the inhibition of HMG-CoA reductase, a key enzyme in the de novo synthesis of cholesterol.[21] On the other hand, 5-azaspiro[2,4]heptane substituents could enhance the activity of quinolone antibiotics, especially against both Gram-positive and Gram-negative bacteria.[22] The hydroxamate-spirocyclopropyl compounds are potent inhibitors of TNF-α convertase (TACE).[23] Therefore, the development of alternative strategies for synthesis of penta-substituted pyrrole and 5-azaspiro[2,4]heptane derivatives is of considerable importance.

Very recently, we reported synthesizing the polysubstituted 3-iodopyrans by electrophilic cyclization of alkynyl carboxamides with ICl, $I_2$, and N-iodosuccinimide (NIS).[24] In addition, we have also demonstrated that palladium-catalyzed reactions of propargylic compounds with soft nucleophiles can serve as a useful method for the construction of versatile carbon–carbon and carbon–heteroatom bonds such as furans,[25] indenes,[26] benz[*a*]anthracene,[27] and benzo[*b*]furan.[26c] In connection with our ongoing project on the Pd-catalyzed annulation reaction, we expected that alkynyl carboxamides would afford polysubstituted heterocyclic compounds via palladium catalysis (Scheme 1). Herein, we report our results on the cyclization reaction of these substrates to unusual penta-substituted pyrroles.




**Scheme 1.** Cyclization reaction of alkynyl carboxamides.

## RESULTS AND DISCUSSION

Based on the typical reaction condition explored in our earlier palladium-catalyzed synthesis of indenes,[26a] we started our investigation by using 0.3 equivalent of 1-(2-hydroxy-4-phenylbut-3-yn-2-yl)-*N*-phenylcyclopropanecarboxamide **1a**, 5mol% of $Pd(PPh_3)_4$, and 0.45 equivalent of $K_2CO_3$ in refluxing tetrahydrofuran (THF) under an argon atmosphere (Table 1, entry 1). Thin-layer chromatography (TLC) showed that the reaction was complete after 8 h under these conditions. The structure of the product was discerned by spectroscopic analysis and confirmed to be penta-substituted pyrrole derivative **2a**, rather than the pyran derivatives obtained by the previous electrophilic iodocyclization.[24] This prompted us to examine optimal conditions of the cyclization reaction of substrate **1a** to obtain more satisfactory results. The first investigation demonstrated that the base played an important role in this process. Although other common bases such as $Et_3N$, $Cs_2CO_3$, $Na_2CO_3$, and KO*t*-Bu were effective as well (entries 2–5), the weaker base NaOAc could not promote the hydroamination reaction (entry 6). The best result was obtained in the presence of $Cs_2CO_3$ (entry 2). Changing the solvent to toluene and $CH_3CN$ failed to improve the yield of the product **2a** (entries 7 and 8). Subsequently, different palladium species such as $Pd_2(dba)_3 \cdot CHCl_3$, $PdCl_2/PPh_3$, $Pd(OAc)_2/PPh_3$, and $Pd(PPh_3)_2Cl_2$ were also tested (entries 9–12). $Pd(PPh_3)_4$ proved to be the more efficient catalyst in this reaction. To exclude the possibility of base-mediated cyclization, the reaction was investigated in the absence of palladium catalyst. The reaction failed to proceed and nearly quantitative **1a** was recovered (entry 13), although Jacobi et al.[28] reported the *N*-benzyl acetylenic amides related the present substrates underwent cyclization to cyclic enamides using stoichiometric to excess amount of *n*-$Bu_4NF$ (TBAF). By way of comparison, for the present substrate, at best the

**Table 1.** Optimization of the Pd-catalyzed intramolecular hydroamination procedure of alkynyl carboxamides **1a**[a]

| Entry | Catalysts | Base | Solvent | Yield (%)[b] |
|---|---|---|---|---|
| 1 | $Pd(PPh_3)_4$ | $K_2CO_3$ | THF | 53 |
| 2 | $Pd(PPh_3)_4$ | $Cs_2CO_3$ | THF | 71 |
| 3 | $Pd(PPh_3)_4$ | $Et_3N$ | THF | 62 |
| 4 | $Pd(PPh_3)_4$ | $Na_2CO_3$ | THF | 46 |
| 5 | $Pd(PPh_3)_4$ | KO*t*-Bu | THF | 61 |
| 6 | $Pd(PPh_3)_4$ | NaOAc | THF | No reaction |
| 7 | $Pd(PPh_3)_4$ | $Cs_2CO_3$ | Toluene | 36 |
| 8 | $Pd(PPh_3)_4$ | $Cs_2CO_3$ | $CH_3CN$ | 53 |
| 9 | $Pd_2(dba)_3 \cdot CHCl_3$ | $Cs_2CO_3$ | THF | 48 |
| 10 | $PdCl_2/PPh_3$ | $Cs_2CO_3$ | THF | 24 |
| 11 | $Pd(OAc)_2/PPh_3$ | $Cs_2CO_3$ | THF | 55 |
| 12 | $Pd(PPh_3)_2Cl_2$ | $Cs_2CO_3$ | THF | 60 |
| 13 | Free-catalyst | $Cs_2CO_3$ | THF | No reaction |
| 14 | *n*-$Bu_4NF$ | — | THF | <20[c] |

[a]Reactions were carried out on a 0.3 mmol scale in 3.0 mL of solvent under argon atmosphere with 1.0 equivalent of **1a**, 1.5 equivalents of base, and 0.05 equivalent of catalyst at reflux for 8 h.

[b]Isolated yields.

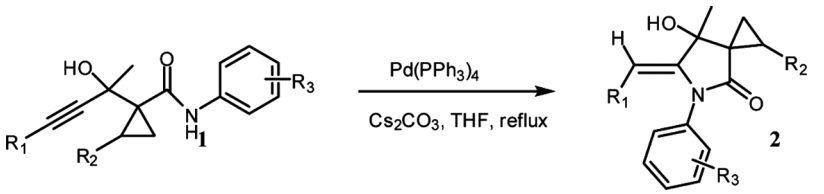
[c]1.0 eq TBAF was used.

reaction afforded only 20% of product **2a** after heating 24 h with 1.0 eq tetrabutylammonium fluoride (TBAF) (entry 14). Thus, we chose the following reaction conditions as optimum for all subsequent cyclization: 0.3 mmol of **1a**, 5 mol% $Pd(PPh_3)_4$, and 0.45 mmol $Cs_2CO_3$ in 3.0 mL THF were stirred at refluxing for 8 h.

With these evaluations in mind, we therefore proceeded to examine the scope of this procedure by studying other alkynyl carboxamides bearing different substituents on either the nitrogen atom or the carbon–carbon triple bond. The Pd-catalyzed hydroamination of both *N*-phenylcyclopropanecarboxamide **1a** and 2-methyl-*N*-phenylcyclopropanecarboxamide **1b** generated the corresponding polysubstituted 5-azaspiro[2.4]heptan-4-one in 71% and 68% yields, respectively, with only a trace amount of side products (Table 2, entries 1 and 2). It seems to indicate that the substituents in the α-position of carbonyl group have negligible effect on reactivity. Subsequently, the effect of substitution on the aniline ring has also been examined. In general, electron-donor substituents on the aniline ring played a positive role in the hydroamination process; when a methyl occurred on the aniline ring (in *ortho*-, *meta*-, or *para*-position), satisfactory results have been obtained (entries 3–5). Introduction of methoxy in *para*- and *ortho*-position gave different result: The former proceeded smoothly in good yield, and the latter gave only poor yield of desired product likely due to the steric hindrance of methoxy group in the *para*-position



**Table 2.** Pd-catalyzed cyclization of alkynyl carboxamides to 1,2,3,4,5-substituted pyrrole derivatives[a]




| Entry | $R_1$ | $R_2$ | $R_3$ | Product | Time (h) | Yield (%)[b] |
|---|---|---|---|---|---|---|
| 1 | Phenyl | H | H | **2a** | 8 | 71 |
| 2 | Phenyl | $CH_3$ | H | **2b** | 8 | 68 |
| 3 | Phenyl | H | 2-$CH_3$ | **2c** | 11 | 81 |
| 4 | Phenyl | H | 3-$CH_3$ | **2d** | 10 | 77 |
| 5 | Phenyl | H | 4-$CH_3$ | **2e** | 8 | 83 |
| 6 | Phenyl | H | 2-$OCH_3$ | **2f** | 20 | <5 |
| 7 | Phenyl | H | 4-$OCH_3$ | **2g** | 8 | 73 |
| 8 | Phenyl | H | 2-Cl | **2h** | 12 | 78 |
| 9 | Phenyl | H | 3-Cl | **2i** | 8 | 75 |
| 10 | Phenyl | H | 4-Cl | **2j** | 8 | 82 |
| 11 | Phenyl | H | 3-Br | **2k** | 9 | 78 |
| 12 | Phenyl | H | 4-Br | **2l** | 9 | 79 |
| 13 | *n*-Propyl | H | 4-Cl | **2m** | 20 | 49 |
| 14 | *n*-Pentyl | H | 4-Cl | **2n** | 20 | 53 |
| 15 | Phenyl | H | 2,4-Dimethyl | **2o** | 8 | 90 |

[a]Reactions were carried out on a 0.3 mmol scale in 3.0 mL of THF under argon with 1.0 equivalent of **1a**, 1.5 equivalents of $Cs_2CO_3$, and 0.05 equivalent of $Pd(PPh_3)_4$ at reflux for an appropriate time.
[b]Isolated yields.

(entries 6 and 7). In contrast, introducing electron-withdrawing groups on the aniline ring did not remarkably improve the reactivity of the present cyclization (entries 8–12). In general, substrates with Cl- substituents on the aniline ring were slightly less reactive than those bearing Br-substituents (to compare entries 9 and 11, 10 and 12). We next examined the effect of various substituents on the alkyne terminus. The results demonstrated that this cyclization was not limited to aryl substituted alkynes, and the reaction of alkyl substituted alkynes could also proceed smoothly (entries 13 and 14). However, the terminal alkyne in which the phenyl has been replaced by a hydrogen atom failed to give any recognizable products. Finally, we examined the possibility of introducing two substituents on the aniline ring under the same conditions. Penta-substituted pyrrole **2o** bearing two electron-donating methyl substituents on the aromatic ring was obtained in the best yield (entry 15).

All of the pyrrole derivatives were identified by spectroscopic methods. The stereochemistry of the products was further established by single-crystal x-ray analysis. Using this technique, the structure of product **2h** was unambiguously confirmed to be (Z)-6-benzylidene-5-(2-chlorophenyl)-7-hydroxy-7-methyl-5-azaspiro[2.4]heptan-4-one (Fig. 1). The atomic coordinates for **2h** have been deposited at the Cambridge Crystallographic Data Centre. CCDC-760179 contains the supplementary crystallographic data for this article. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Having developed a useful method for the synthesis of the penta-substituted pyrroles bearing an active three-membered ring, we next examined the transformations of the three-membered ring moiety because ring-opening products were considered more valuable molecules (Scheme 2). Accordingly, **2a** was treated with an excess amount of $ZnCl_2$ in refluxing THF to give the chloroethyl compound **3a** in

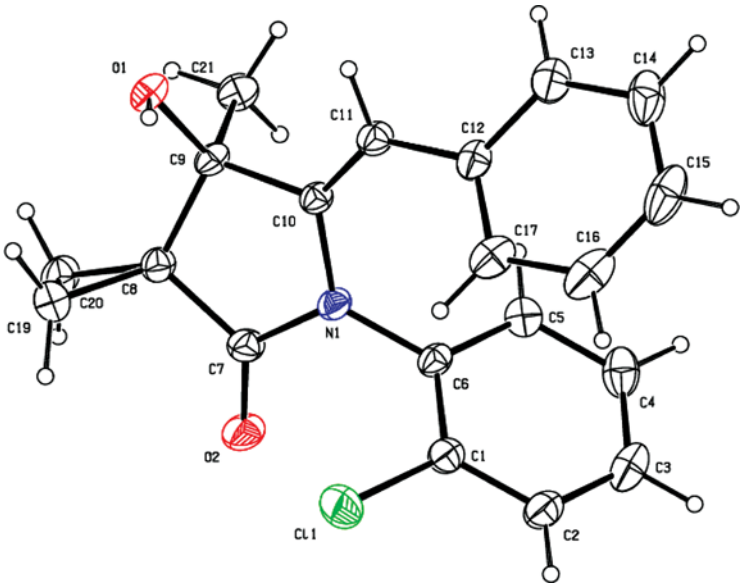
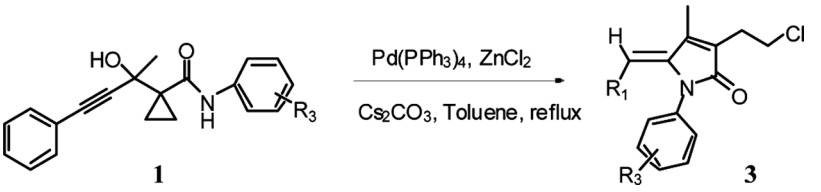


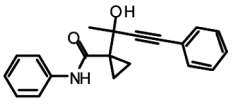
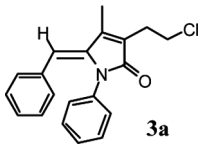
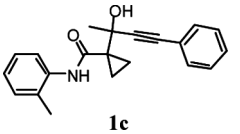
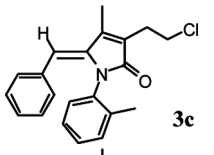
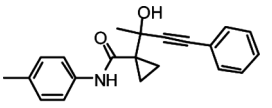
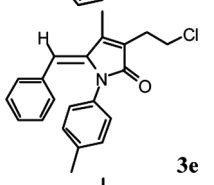
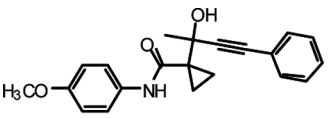
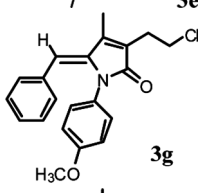
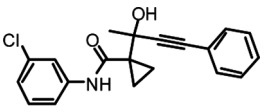
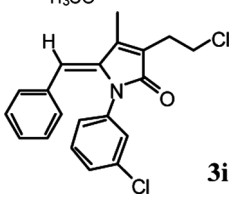

**Figure 1.** Structure of product **2h** by X-ray. (Figure is provided in color online.)

good yield. It was noteworthy that the zinc salts acted not only as Lewis acid but also as a source of halide in this transformation. Encouraged by this result, we attempted to carry out the one-pot transformation of **1a** to **3a** by using 0.3 equivalent of alkynyl carboxamides, 0.6 equiv. of $ZnCl_2$, 5 mol % of $Pd(PPh_3)_4$ and 0.45 equivalent of $Cs_2CO_3$ in refluxing toluene. As shown in Table 3, all tested *N*-phenylcyclopropane-carboxamides bearing both electron-withdrawing and electron-donor groups on the

**Table 3.** One-pot bimetallic-promoted cyclization of alkynyl carboxamides to polysubstituted chloroethyl pyrrole derivatives[a]




**1** **3**

| Entry | Adducts | Products | Time (h) | Yield (%)[b] |
|---|---|---|---|---|
| 1 |  **1a** |  **3a** | 12 | 66 |
| 2 |  **1c** |  **3c** | 16 | 75 |
| 3 |  **1e** |  **3e** | 12 | 77 |
| 4 |  **1g** |  **3g** | 12 | 62 |
| 5 |  **1i** |  **3i** | 19 | 66 |

[a]Reactions were carried out in 3.0 mL of refluxing toluene under argon with 0.3 equivalent of **1a**, 0.45 equivalent of $Cs_2CO_3$, 0.6 equivalent of $ZnCl_2$, and 5 mol% of $Pd(PPh_3)_4$ for an appropriate time.
[b]Isolated yields.

aniline ring afforded target chloroethylpyrroles in good overall yield (Table 3, entries 1–5). This study demonstrated that alkynyl carboxamides used in this reaction could be further employed for the synthesis of more advanced intermediates.

In summary, we have developed a new approach to the synthesis of 5-azaspiro [2.4]heptan and penta-substituted pyrrole derivatives by palladium-catalyzed cyclization of alkynyl carboxamides. A variety of N-phenylcyclopropane-carboxamides underwent this process to give the desired products in good to excellent yields. As the zinc salts acted as Lewis acids and a source of halides, the extended Pd-Zn bimetallic system afforded the penta-substituted chloroethylpyrroles and proved that the present method is a powerful tool for the preparation of a wide range of functionalized and polysubstituted pyrroles. Further extension of the substrate for synthesis of more valuable penta-substituted chloroethylpyrrole or bromoethylpyrrole derivatives are under way in our laboratory and will be reported in the near future.



## EXPERIMENTAL

Commercially available reagents and solvents were used without further purification. Alkynyl carboxamide compounds were prepared according to the literature procedures.[24] Melting points were determined with a microscopic apparatus and are uncorrected. Column chromatography was carried out on silica gel. $^{1}H$ NMR spectra were recorded with a 400-MHz spectrometer in $CDCl_3$ by using tetramethylsilane (TMS) as the internal standard. $^{13}C$ NMR spectra were recorded with a 100-MHz spectrometer in $CDCl_3$. Infrared (IR) spectra were recorded with a Fourier transform (FT)–IR spectrometer, and only the major peaks are reported. All new compounds were further characterized by elemental analysis.

### General Procedure for the Preparation of 5-Azaspiro[2.4]heptan-4-one 2

A mixture of alkynyl carboxamide **1** (0.30 mmol), $Cs_2CO_3$ (0.45 mmol), $Pd(PPh_3)_4$ (5 mol %), and THF (3.0 mL) was placed under an argon atmosphere in a 25-mL flask. The resulting mixture was then heated at 80 °C. When the reaction was considered complete as determined by TLC analysis, the reaction mixture was allowed to cool to room temperature, quenched with a saturated aqueous solution of ammonium chloride, and extracted with EtOAc. The combined organic extracts were washed with water and saturated brine. The organic layers were dried over $Na_2SO_4$ and filtered. Solvents were evaporated under reduced pressure. The residue was purified by chromatography on silica gel to afford the corresponding 5-azaspiro[2.4]heptan-4-one **2**.

### General Procedure for the Preparation of Penta-Substituted Chloroethylpyrrole Derivatives 3

$Cs_2CO_3$ (0.45 mmol), $Pd(PPh_3)_4$ (5 mol%), and $ZnCl_2$(0.6 mmol) were added to a solution of alkynyl carboxamide **1** (0.30 mmol) in toluene (3.0 mL). The resulting mixture was then heated under an argon atmosphere until reflux. When the reaction was considered complete, as determined by TLC analysis, the reaction mixture was

allowed to cool to room temperature, quenched with a saturated aqueous solution of ammonium chloride, and extracted with EtOAc. The combined organic extracts were washed with water and saturated brine. The organic layers were dried over $Na_2SO_4$ and filtered. Solvents were evaporated under reduced pressure. The residue was purified by chromatography on silica gel to afford the corresponding penta-substituted chloroethylpyrrole derivatives **3**.

**(Z)-6-Benzylidene-7-hydroxy-7-methyl-5-phenyl-5-azaspiro[2.4]heptan-4-one 2a.** Colorless solid; mp 115–116 °C. IR (KBr): 3414, 1713, 1661, 1496, 1387, 1341, 1174, 696 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta = 1.01$–$1.06$ (m, 1H), 1.14–1.20 (m, 1H), 1.22–1.27 (m, 1H), 1.35–1.40 (m, 1H), 1.49 (s, 3H), 2.41 (br s, 1H), 6.13 (s, 1H), 6.69–6.71 (t, $J = 1.6$ Hz, 2H), 6.83–6.88 (q, 3H), 6.95–7.01 (m, 5H) ppm.$^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta = 10.18$, 12.16, 26.31, 33.27, 73.60, 104.09, 125.26, 125.60, 126.20, 126.93, 127.95, 128.14, 134.16, 135.36, 146.35, 175.27 ppm. Anal. calcd. for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27, N, 4.59. Found: C, 78.34; H, 6.29; N, 4.54.

**(Z)-6-Benzylidene-7-hydroxy-1,7-dimethyl-5-phenyl-5-azaspiro[2.4]-heptan-4-one 2b.** Colorless solid; mp 135–136 °C. IR (KBr): 3421, 2929, 1710, 1661, 1387, 1336, 1180, 696 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta = 1.12$–$1.15$ (q, 1H), 1.39–1.40 (m, 4H) 1.48 (s, 3H), 1.51–1.56 (m, 1H), 2.08 (brs, 1H), 6.09 (s, 1H), 6.72–6.74 (m, 2H), 6.83–6.88 (m, 3H), 6.95–7.04 (m, 5H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta = 11.86$, 17.98, 20.47, 24.72, 36.68, 74.57, 103.91, 125.47, 125.64, 126.14, 126.96, 127.95, 128.21, 134.22, 135.57, 145.54, 174.36 ppm. Anal. calcd. for $C_{21}H_{21}NO_2$: C, 78.97; H, 6.63; N, 4.39. Found: C, 79.24; H, 6.67, N, 4.42.

**(Z)-6-Benzylidene-7-hydroxy-7-methyl-5-*o*-tolyl-5-azaspiro[2.4]heptan-4-one 2c.** Colorless solid; mp 99–100 °C. IR (KBr): 3398, 1707, 1642, 1405, 1184, 910, 730 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta = 1.05$–$1.10$ (m, 1H), 1.17–1.29 (m, 2H), 1.35–1.40 (m, 1H), 1.53 (s, 3H), 1.96 (s, 3H), 2.19 (brs, 1H), 6.11 (s, 1H), 6.64–6.66 (m, 2H), 6.77–6.86 (m 5H), 6.91–7.02 (m, 2H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta = 10.32$, 11.51, 17.77, 26.70, 32.69, 73.45, 103.58, 125.45, 125.95, 126.70, 127.07, 127.85, 128.16, 129.52, 130.48, 134.00, 134.77, 146.25, 175.15 ppm. Anal. calcd. for $C_{21}H_{21}NO_2$: C, 78.97; H, 6.63; N, 4.39. Found: C, 78.57; H, 6.60; N 4.35.

**(Z)-6-Benzylidene-7-hydroxy-7-methyl-5-*m*-tolyl-5-azaspiro[2.4]heptan-4-one 2d.** Colorless solid; mp 125–126 °C. IR (KBr): 3413, 2924, 1713, 1663, 1386, 1340, 1171, 733, 697 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta = 1.02$–$1.07$ (m, 1H), 1.15–1.20 (m, 1H), 1.23–1.28 (m, 1H), 1.36–1.41 (m, 1H), 1.51 (s, 3H), 2.04 (s, 3H), 2.21 (brs, 1H), 6.13 (s, 1H), 6.70–6.77 (m, 4H), 6.95 (m, 5H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta = 10.23$, 12.09, 20.87, 26.39, 33.26, 73.61, 103.94, 122.57, 125.61, 126.09, 126.82, 126.95, 127.81, 127.98, 134.39, 135.09, 137.82, 146.52, 175.17 ppm. Anal. calcd. for $C_{21}H_{21}NO_2$: C, 78.97; H, 6.63; N, 4.39. Found: C, 78.62; H, 6.56; N, 4.33.

**(Z)-6-Benzylidene-7-hydroxy-7-methyl-5-*p*-tolyl-5-azaspiro[2.4]heptan-4-one 2e.** Colorless solid; mp 105–106 °C. IR (KBr): 3395, 2925, 2252, 1709, 1392, 1157, 910, 734 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta = 1.00$–$1.16$ (m, 1H),

1.18–1.25 (m, 2H), 1.36–1.39 (m, 1H), 1.51 (s, 3H), 2.07 (brs, 1H), 2.16 (s, 3H), 6.12 (s, 1H), 6.65–6.74 (m, 2H), 6.81–6.89 (m, 7H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 10.16$, 12.08, 20.85, 26.38, 33.24, 73.69, 103.82, 125.15, 125.49, 126.89, 128.30, 128.55, 132.88, 134.24, 136.11, 146.66, 175.20 ppm. Anal. calcd. for $C_{21}H_{21}NO_2$: C, 78.97; H, 6.63; N, 4.39. Found: C, 78.43; H, 6.66; N, 4.35.

**(Z)-6-Benzylidene-7-hydroxy-5-(4-methoxyphenyl)-7-methyl-5-azaspir-o [2.4]heptan-4-one 2g.** Colorless solid; mp 113–114 °C. IR (KBr): 3406, 2929, 1710, 1661, 1512, 1341, 1249, 1178, 910, 830, 733 $cm^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 1.01$–1.07 (m, 1H), 1.14–1.19 (m, 1H), 1.22–1.27 (m, 1H), 1.34–1.40 (m, 1H), 1.49 (s, 3H), 2.49 (brs, 1H), 3.65 (s, 3H), 6.11 (s, 1H), 6.53 (d, $J = 9.2$ Hz, 2H), 6.69–6.71 (m, 2H), 6.87–6.90 (m, 5H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 10.24$, 12.04, 26.43, 33.09, 55.37, 73.51, 103.64, 113.29, 125.52, 126.55, 126.88, 128.29, 128.41, 134.19, 146.72, 157.76, 175.40 ppm. Anal. calcd. for $C_{21}H_{21}NO_3$: C, 75.20; H, 6.31; N, 4.18. Found: C, 74.88; H, 6.26; N, 4.16.

**(Z)-6-Benzylidene-5-(2-chlorophenyl)-7-hydroxy-7-methyl-5-azaspiro-[2.4] heptan-4-one 2h.** Colorless solid; mp 138–139 °C. IR (KBr): 3437, 2924, 2854, 1721, 1664, 1343, 1174, 764, 706 $cm^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 1.10$–1.14 (m, 1H), 1.19–1.32 (m, 2H), 1.39–1.43 (m, 1H), 1.57 (s, 3H), 2.25 (brs, 1H), 6.16 (s, 1H), 6.74–7.25 (m, 9H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 10.44$, 11.86, 26.46, 32.65, 73.54, 103.99, 125.62, 126.67, 126.82, 128.10, 128.81, 128.97, 129.75, 131.31, 133.23, 133.76, 145.50, 174.50 ppm. Anal. calcd. for $C_{20}H_{18}ClNO_2$: C, 70.69; H, 5.34; N, 4.12. Found: C, 70.93; H, 5.37; N, 4.13.

**(Z)-6-Benzylidene-5-(3-chlorophenyl)-7-hydroxy-7-methyl-5-azaspiro-[2.4] heptan-4-one 2i.** Colorless solid; mp 137–138 °C. IR (KBr): 3415, 1714, 1664, 1408, 1338, 1173, 911, 701 $cm^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 1.04$–1.11 (m, 1H), 1.18–1.31 (m, 2H), 1.36–1.43 (m, 1H), 1.50 (s, 3H), 2.21 (s, 1H), 6.19 (s, 1H), 6.71–6.74 (m, 2H), 6.84–6.98 (m, 7H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 10.51$, 12.28, 26.22, 33.35, 73.62, 104.61, 123.49, 125.65, 126.12, 126.26, 127.19, 128.01, 128.90, 133.72, 133.99, 136.31, 145.99, 175.07 ppm. Anal. calcd. for $C_{20}H_{18}ClNO_2$: C, 70.69; H, 5.34; N, 4.12. Found: C, 70.87; H, 5.33; N, 4.09.

**(Z)-6-Benzylidene-5-(4-chlorophenyl)-7-hydroxy-7-methyl-5-azaspiro-[2.4] heptan-4-one 2j.** Colorless solid; mp 121–122 °C. IR (KBr): 3413, 1714, 1663, 1493, 1387, 1339, 1173, 1091, 910, 733, 702 $cm^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 1.05$–1.10 (m, 1H), 1.17–1.22 (m, 1H), 1.25–1.30 (m, 1H), 1.37–1.42 (m, 1H), 1.50 (s, 3H), 2.21 (brs, 1H), 6.17 (s, 1H), 6.70–6.72 (d, $J = 7.2$ Hz, 2H), 6.89–6.99 (m, 7H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 10.47$, 12.22, 26.23, 33.32, 73.64, 104.38, 126.05, 126.47, 127.18, 128.05, 128.15, 128.28, 131.68, 133.95, 146.13, 175.15 ppm. Anal. calcd. for $C_{20}H_{18}ClNO_2$: C, 70.69; H, 5.34; N, 4.12. Found: C, 70.57; H, 5.39; N, 4.17.

**(Z)-6-Benzylidene-5-(3-bromophenyl)-7-hydroxy-7-methyl-5-azaspiro-[2.4]heptan-4-one 2k.** Colorless solid; mp 135–136 °C. IR (KBr): 3415, 1713, 1664, 1384, 1338, 1176, 911, 734, 699 $cm^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 1.03$–1.09 (m, 1H), 1.15–1.21 (m, 1H), 1.24–1.29 (m, 1H), 1.35–1.40 (m, 1H), 1.48 (s, 3H), 2.40 (brs, 1H), 6.17 (s, 1H), 6.71–6.73 (m, 2H), 6.86–6.93 (m, 4H),

6.99 (d, $J = 7.6$ Hz, 1H), 7.00–7.09 (m, 2H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 10.54$, 12.24, 26.19, 33.29, 73.50, 104.60, 121.40, 123.98, 126.09, 127.16, 127.96, 128.48, 129.11, 129.12, 133.97, 136.37, 145.90, 175.13 ppm. Anal. calcd. for $C_{20}H_{18}BrNO_2$: C, 62.51; H, 4.72; N, 3.65. Found: C, 62.29; H, 4.62; N, 3.75.

**(Z)-6-Benzylidene-5-(4-bromophenyl)-7-hydroxy-7-methyl-5-azaspiro-[2.4]heptan-4-one 2l.** Colorless solid; mp 111–112 °C. IR (KBr): 3417, 1715, 1662, 1489, 1386, 1340, 1171, 910, 733, 701 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 1.04$–1.09 (m, 1H), 1.16–1.21 (m, 1H), 1.23–1.29 (m, 1H), 1.36–1.41 (m, 1H), 1.48 (s, 3H), 2.35 (brs, 1H), 6.16 (s, 1H), 6.69 (d, $J = 7.2$ Hz, 2H), 6.86–7.01 (m, 5H), 7.11 (d, $J = 8.4$ Hz, 2H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 10.47$, 12.23, 26.20, 33.30, 73.58, 104.42, 119.54, 126.02, 126.77, 127.17, 128.19, 130.98, 133.91, 134.41, 145.99, 175.12 ppm. Anal. calcd. for $C_{20}H_{18}BrNO_2$: C, 62.51; H, 4.72; N, 3.65. Found: C, 62.69; H, 4.70; N, 3.61.

**(Z)-6-Butylidene-5-(4-chlorophenyl)-7-hydroxy-7-methyl-5-azaspiro-[2.4] heptan-4-one 2m.** Colorless solid; mp 99–110 °C. IR (KBr): 3396, 2959, 2928, 1709, 1674, 1493, 1394, 1091, 911, 826, 734 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 0.70$–0.73 (t, $J = 7.2$ Hz, 3H), 0.86–0.88 (m, 1H), 1.00–1.02 (m, 1H), 1.11–1.32 (m, 9H), 1.99 (brs, 1H), 4.91 (t, $J = 7.2$ Hz, 1H), 7.21 (d, $J = 4.2$ Hz, 2H), 7.38 (d, $J = 4.2$ Hz, 2H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 10.56$, 11.46, 13.53, 22.76, 25.83, 28.25, 33.21, 73.21, 105.01, 127.82, 128.99, 132.77, 135.67, 145.37, 175.07 ppm. Anal. calcd. for $C_{17}H_{20}ClNO_2$: C, 66.77; H, 6.59; N, 4.58. Found: C, 66.50; H, 6.54; N, 4.55.

**(Z)-5-(4-Chlorophenyl)-6-hexylidene-7-hydroxy-7-methyl-5-azaspiro-[2.4] heptan-4-one 2n.** Colorless solid; mp 64–65 °C. IR (KBr): 3410, 3096, 2855, 1712, 1668, 982, 826 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 0.80$–0.83 (m, 3H), 0.97–1.45 (m, 15H), 2.02 (brs, 1H), 4.91 (t, $J = 7.2$ Hz, 1H), 7.21 (d, $J = 8.8$ Hz, 2H), 7.37 (d, $J = 8.8$ Hz, 2H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 10.55$, 11.44, 13.93, 20.19, 22.30, 26.28, 29.25, 31.23, 33.20, 73.19, 105.24, 127.79, 128.98, 132.76, 135.69, 145.18, 175.06 ppm. Anal. calcd. for $C_{19}H_{24}ClNO_2$: C, 68.35; H, 7.25; N, 4.20. Found: C, 68.07; H, 7.29; N, 4.19.

**(Z)-6-Benzylidene-5-(2,4-dimethylphenyl)-7-hydroxy-7-methyl-5-azaspiro[2.4]heptan-4-one 2o.** Colorless solid; mp 101–102 °C. IR (KBr): 3405, 3020, 2976, 1712, 1664, 1394, 1341, 1187, 911, 732, 701 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 0.99$–1.40 (m, 4H), 1.47 (s, 3H), 1.89 (s, 3H), 2.11 (s, 3H), 2.51 (brs, 1H), 6.05 (s, 1H), 6.61–6.65 (m, 2H), 6.78–6.87 (m, 6H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 10.16$, 11.45, 17.56, 20.72, 26.73, 32.56, 73.20, 103.36, 125.09, 126.49, 126.58, 126.77, 128.12, 130.91, 131.92, 133.81, 134.06, 137.48, 146.35, 175.01 ppm. Anal. calcd. for $C_{22}H_{23}NO_2$: C, 79.25; H, 6.95; N, 4.20. Found: C, 79.07; H, 6.91; N, 4.23.

**(Z)-5-Benzylidene-3-(2-chloroethyl)-4-methyl-1-phenyl-1*H*-pyrrol-2(5*H*) one 3a.** Yellowish oil. IR (KBr): 2923, 1699, 1497, 1391, 697 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 2.29$ (s, 3H), 2.92 (t, $J = 6.8$ Hz, 2H), 3.80 (t, $J = 6.8$ Hz, 2H), 6.42 (s, 1H), 6.50 (d, $J = 7.2$ Hz, 2H), 6.90 (t, $J = 7.6$ Hz, 3H), 6.95–7.05 (m, 5H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 10.63$, 27.74, 43.11, 111.44, 126.14, 126.69, 126.75, 126.92, 127.20, 128.05, 129.23, 133.55, 135.94, 138.82, 145.68,

170.92 ppm. Anal. calcd. for $C_{20}H_{18}ClNO$: C, 78.14; H, 5.60; N, 4.33. Found: C, 78.44; H, 5.66; N, 4.30.

**(Z)-5-Benzylidene-3-(2-chloroethyl)-4-methyl-1-*o*-tolyl-1*H*-pyrrol-2(5*H*)-one 3c.** Yellowish oil. IR (KBr): 2924, 1698, 1494, 1390, 1130, 756, 701 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta = 2.10$ (s, 3H), 2.27 (s, 3H), 2.92 (t, $J = 6.8$ Hz, 2H), 3.76–3.83 (m, 2H), 6.38 (s, 1H), 6.77 (d, $J = 7.6$ Hz, 2H), 6.81–6.96 (m, 7H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta = 10.60$, 18.09, 27.69, 43.10, 111.34, 125.89, 126.70, 126.99, 127.79, 128.39, 128.67, 129.84, 130.33, 133.19, 135.69, 135.92, 139.10, 145.15, 170.40 ppm. Anal. calcd. for $C_{21}H_{20}ClNO$: C, 74.66; H, 5.97; N, 4.15. Found: C, 74.24; H, 5.93; N, 4.20.

**(Z)-5-Benzylidene-3-(2-chloroethyl)-4-methyl-1-*p*-tolyl-1*H*-pyrrol-2(5*H*)-one 3e.** Yellowish oil. IR (KBr): 1699, 1514, 1391, 1125, 813, 702 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta = 2.19$ (s, 3H), 2.27 (s, 3H), 2.91 (t, $J = 6.8$ Hz, 2H), 3.79 (t, $J = 6.8$ Hz, 2H), 6.39 (s, 1H), 6.84–6.90 (m, 6H), 6.93 (t, $J = 8.0$ Hz, 2H), 6.96–6.99 (m, 1H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta = 10.58$, 20.86, 27.72, 43.14, 111.28, 126.48, 126.73, 127.11, 128.64, 129.29, 133.33, 133.56, 135.95, 136.13, 138.95, 145.48, 170.96 ppm. Anal. calcd. for $C_{21}H_{20}ClNO$: C, 74.66; H, 5.97; N, 4.15. Found: C, 74.91; H, 6.02; N, 4.10.

**(Z)-5-Benzylidene-3-(2-chloroethyl)-1-(4-methoxyphenyl)-4-methyl-1*H*-pyrrol-2(5*H*)-one 3g.** Yellowish oil. IR (KBr): 1695, 1512, 1247 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta = 2.29$ (s, 3H), 2.93 (t, $J = 6.8$ Hz, 2H), 3.70 (s, 3H), 3.80 (t, $J = 6.8$ Hz, 2H), 6.41 (s, 1H), 6.58–6.60 (q, 2H), 6.87–6.90 (m, 3H), 6.92–7.03 (m, 4H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta = 10.57$, 27.74, 43.11, 55.44, 111.17, 113.50, 126.77, 126.83, 127.16, 127.87, 128.95, 129.28, 133.54, 139.13, 145.33, 157.89, 171.04 ppm. Anal. calcd. for $C_{21}H_{20}ClNO_2$: C, 71.28; H, 5.70; N, 3.96. Found: C, 71.04; H, 5.62; N, 3.97.

**(Z)-5-Benzylidene-3-(2-chloroethyl)-1-(3-chlorophenyl)-4-methyl-1*H*-pyrrol-2(5*H*)-one 3i.** Yellowish oil. IR (KBr): 1703, 1592, 1482, 1388, 1123, 782, 699 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta = 2.28$ (s, 3H), 2.91 (t, $J = 6.8$ Hz, 2H), 3.78 (t, $J = 6.8$ Hz, 2H), 6.46 (s, 1H), 6.87–7.02 (m, 9H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta = 10.63$, 27.64, 43.00, 111.81, 124.83, 126.16, 126.71, 126.98, 127.33, 127.39, 128.87, 129.02, 133.36, 133.60, 136.89, 138.48, 146.04, 170.65 ppm. Anal. calcd. for $C_{20}H_{17}Cl_2NO$: C, 67.05; H, 4.78; N, 3.91. Found: C, 67.28; H, 4.77; N, 3.95.



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## REFERENCES

1. (a) Diederich, F. In *Metal-Catalyzed Cross-Coupling Reactions*; P. J. Stang (Ed.); Wiley-VCH: Weinheim, 1998; (b) Tsuji, J. *Transition Metal Reagents and Catalysts: Innovation in Organic Synthesis*; Wiley: Chichester, 1995.

2. (a) Negishi, E. (Ed.). *Handbook of Organopalladium Chemistry for Organic Synthesis*; Wiley-Interscience: New York, 2002; (b) Tsuji, J. *Palladium Reagents and Catalysts: New Perspectives for the 21st Century*; Wiley: Chichester, 2004.
3. Madin, A.; O'Donnell, C. J.; Oh, T.; Old, D. W.; Overman, L. E.; Sharp, M. J. Total synthesis of (±)-gelsemine. *Angew. Chem. Int. Ed.* **1999**, *38*, 2934.
4. (a) Kadnikov, D. V.; Larock, R. C. Synthesis of coumarins via palladium-catalyzed carbonylative annulation of internal alkynes by *o*-iodophenols. *Org. Lett.* **2000**, *2*, 3643; (b) Lopez-Dober, M. P.; Castedo, L.; Granja, J. R. Synthesis of N-(3-arylpropyl)amino acid derivatives by Sonogashira types of reaction in aqueous media. *Org. Lett.* **2001**, *3*, 2823; (c) Novak, Z.; Szabo, A.; Rapasi, J.; Kotschy, A. Sonogashira coupling of aryl halides catalyzed by palladium on charcoal. *J. Org. Chem.* **2003**, *68*, 3327.
5. Dakin, L. A.; Langille, N. F.; Panek, J. S. Synthesis of the C1′–C11′ oxazole-containing side chain of leucascandrolide A: Application of a Sonogashira cross-coupling. *J. Org. Chem.* **2002**, *67*, 6812.
6. Branu, R. U.; Zeilter, K.; Muller, T. J. J. A novel one-pot pyrrole synthesis via a coupling–isomerization–Stetter–Paal–Knorr sequence. *Org. Lett.* **2001**, *3*, 3297.
7. Sarkar, A.; Okada, S.; Nakanishi, H.; Matsuda, H. A convenient synthesis of aromatic-ring-substituted diacetylenes. *Helv. Chim. Acta* **1999**, *82*, 138.
8. Yue, D.; Larock, R. C. Synthesis of 2,3-disubstituted benzo[*b*]thiophenes via palladium-catalyzed coupling and electrophilic cyclization of terminal acetylenes. *J. Org. Chem.* **2002**, *67*, 1905.
9. (a) Ohta, A.; Akita, Y.; Ohkuwa, T.; Chiba, M.; Fukunaga, R.; Miyafuji, A.; Nakata, T.; Tani, N.; Aoyagi, Y. Palladium-catalyze arylation of furan, thiophene, benzo[*b*]furan, and benzo[*b*]thiophene. *Heterocycles* **1990**, *31*, 1951; (b) Aoyagi, Y.; Inoue, A.; Koizumi, I.; Hashimoto, R.; Tokunaga, K.; Gohma, K.; Komatsu, J.; Sekine, K.; Miyafuji, A.; Kunoh, J.; Honma, R.; Akita, Y.; Ohta, A. Palladium-catalyzed cross-coupling reactions of chloropyrazines with aromatic heterocycles. *Heterocycles* **1992**, *33*, 257.
10. (a) Gelman, D.; Tsvelikhovsky, D.; Molander, G. A.; Blum, J. Palladium-catalyzed cross-alkynylation of aryl bromides by sodium tetraalkynylaluminates. *J. Org. Chem.* **2002**, *67*, 6287; (b) Ma, S.; Zhang, J. 2,3,4- or 2,3,5-Trisubstituted furans: Catalyst-controlled highly regioselective ring-opening cycloisomerization reaction of cyclopropenyl ketones. *J. Am. Chem. Soc.* **2003**, *125*, 12386; (c) Han, X.; Widenhoefer, R. A. Palladium-catalyzed oxidative alkoxylation of α-alkenyl β-diketones to form functionalized furans. *J. Org. Chem.* **2004**, *69*, 1738; (d) Ma, S.; Zhang, J. $Pd^0$-catalyzed cyclization reaction of aryl or alk-1-enyl halides with 1,2-dienyl ketones: A general and efficient synthesis of polysubstituted furans. *Chem. Commun.* **2000**, 117.
11. (a) Dai, G.; Larock, R. C. Synthesis of 3-substituted 4-aroylisoquinolines via Pd-catalyzed carbonylative cyclization of *o*-(1-alkynyl)benzaldimines. *Org. Lett.* **2002**, *4*, 193; (b) Dai, G.; Larock, R. C. Synthesis of 3-substituted 4-aroylisoquinolines via Pd-catalyzed carbonylative cyclization of 2-(1-alkynyl)benzaldimines. *J. Org. Chem.* **2002**, *67*, 7042.
12. (a) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Moro, L. Palladium-catalyzed cyclocarbonylation of *o*-ethynylphenols and vinyl triflates to form 3-alkylidene-2-coumaranones. *Eur. J. Org. Chem.* **1999**, 1137; (b) Cacchi, S.; Fabrizi, G.; Pace, P.; Marinelli, F. 6-Aryl-11*H*-indolo[3,2-*c*]quinolines through the palladium-catalyzed carbonylative cyclization of *o*-(*o*-aminophenyl)trifluoroacetanilide with aryl iodides. *Synlet.* **1999**, 620; (c) Arcadi, A.; Cacchi, S.; Carnicelli, V.; Marinelli, F. 2-Substituted-3-acylindoles through the palladium-catalysed carbonylative cyclization of 2-alkynyltrifluoroacetanilides with aryl halides and vinyl triflates. *Tetrahedron* **1994**, *50*, 437.
13. (a) Arcadi, A.; Cacchi, S.; Rosario, M. D.; Fabrizi, G.; Marinelli, F. Palladium-catalyzed reaction of *o*-ethynylphenols, *o*-((trimethylsilyl)ethynyl)phenyl acetates, and *o*-alkynylphenols with unsaturated triflates or halides: A route to 2-substituted-, 2,3-disubstituted-, and

2-substituted-3-acylbenzo[*b*]furans. *J. Org. Chem.* **1996**, *61*, 9280; (b) Hu, Y.; Zhang, Y.; Yang, Z.; Fathi, R. Palladium-catalyzed carbonylative annulation of *o*-alkynylphenols: Syntheses of 2-substituted-3-aroyl-benzo[*b*]furans. *J. Org. Chem.* **2002**, *67*, 2365.

14. (a) Yates, F. S. In *Comprehensive Heterocyclic Chemistry*; A. J. Boulton, A. McKillop (Eds.); Pergamon: Oxford, 1984; (b) Bean, G. P. In *Pyrroles, Part 1*; R. A. Jones (Ed.); John Wiley and Sons: New York, 1990; vol. 48, pp. 105–294; (c) Jones, R. A. In *Pyrroles: Part 2*; E. C. Taylor, A. Weissberger (Eds.); John Wiley and Sons: New York, 1992; vol. 2, p. 511; (d) Jones, R. A.; Bean, G. P. The chemistry of pyrroles. In *Organic Chemistry*; A. T. Blomquist, H. S. Wassermann (Eds.); Academic: London, 1977; vol. 34.
15. (a) Lainton, J. A. H.; Hoffman, J. W.; Martin, B. R.; Compton, D. R. 1-Alkyl-3-(1-naphthoyl)pyrroles: A new class of cannabinoid. *Tetrahedron Lett.* **1995**, *36*, 1401; (b) De Leon, C. Y.; Ganem, B. A new approach to porphobilinogen and its analogs. *Tetrahedron* **1997**, *53*, 7731; (c) Hayakawa, Y.; Kawasaki, K.; Seto, H. 1. Structure of a new antibiotic, roseophilin. *Tetrahedron Lett.* **1992**, *33*, 2701; (d) Yoshida, W. Y.; Lee, K. K.; Carroll, A. R.; Scheuner, P. A complex pyrrolo-oxazinone and its iodo derivative isolated from a tunicate. *Helv. Chim. Acta* **1992**, *75*, 1721; (e) Lehuedu, J.; Fauconneau, B.; Barrier, L.; Ourakow, M.; Piriou, A.; Vierfond, J. M. Synthesis and antioxidant activity of new tetraarylpyrroles. *Eur. J. Med. Chem.* **1999**, *34*, 991; (f) Dong, Y.; Naranjan, N.; Ablaza, S. L.; Yu, S. X.; Bolvig, S.; Forsyth, D. A.; Le Quesne, P. W. Quararibea metabolites: Total synthesis and conformational studies of (±)-funebrine and (±)-funebral. *J. Org. Chem.* **1999**, *64*, 2657; (g) Arrowsmith, J.; Jennings, S. A.; Clark, A. S.; Stevens, M. F. G. Antitumor imidazotetrazines: Conjugation of the antitumor agents mitozolomide and temozolomide to peptides and lexitropsins bearing DNA major and minor groove-binding structural motifs. *J. Med. Chem.* **2002**, *45*, 5458; (h) Robertson, J.; Hatley, R. J. D.; Watkin, D. J. Preparation of the tricyclic ketopyrrole core of roseophilin by radical macrocyclisation and Paal–Knorr condensation. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3389.
16. (a) Banik, B. K.; Samajdar, S.; Banik, I. Simple synthesis of substituted pyrroles. *J. Org. Chem.* **2004**, *69*, 213; (b) Balme, G. Pyrrole syntheses by multicomponent coupling reactions. *Angew. Chem., Int. Ed.* **2004**, *43*, 6238; (c) Bharadwaj, A. R.; Scheidt, K. A. Catalytic multicomponent synthesis of highly substituted pyrroles utilizing a one-pot Sila-Stetter/Paal–Knorr strategy. *Org. Lett.* **2004**, *6*, 2465; (d) Ballini, R.; Barboni, L.; Bosica, G.; Petrini, M. 2,5-Dialkylfurans and nitroalkanes as source of 2,3,5-trialkylpyrroles. *Synlett.* **2000**, 391; (e) Minetto, G.; Raveglia, L. F.; Sega, A.; Taddei, M. Microwave-assisted Paal-Knorr reaction: Three-step regiocontrolled synthesis of polysubstituted furans, pyrroles, and thiophenes. *Eur. J. Org. Chem.* **2005**, 5277.
17. (a) Kleinspehn, G. G. A novel route to certain 2-pyrrolecarboxylic esters and nitriles. *J. Am. Chem. Soc.* **1955**, *77*, 1546; (b) Fabiano, E.; Golding, B. T. On the mechanism of pyrrole formation in the Knorr pyrrole synthesis and by porphobilinogen synthase. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3371; (c) Alberola, A.; Ortega, A. G.; Sadaba, M. L.; Sanudo, C. Versatility of Weinreb amides in the Knorr pyrrole synthesis. *Tetrahedron* **1999**, *55*, 6555. (e) Braun, R. U.; Zeitler, K.; Mueller, T. J. J. A novel one-pot pyrrole synthesis via a coupling–isomerization–Stetter–Paal–Knorr sequence. *Org. Lett.* **2001**, *3*, 3297.
18. (a) Katritzky, A. R.; Ostercamp, D. L.; Yousaf, T. I. The mechanisms of heterocyclic ring closures. *Tetrahedron* **1987**, *43*, 5171; (b) Trautwein, A. W.; Süßmuth, R. D.; Jung, G. Hantzsch pyrrole synthesis on solid support. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2381.
19. (a) South, M. S.; Jakuboski, T. L.; Westmeyer, M. D.; Dukesherer, D. R. Novel cyclization reactions of dichloroazodienes. *Tetrahedron Lett.* **1996**, *37*, 1351; (b) Padwa, A.; Deen, D. C.; Hertzog, D. C.; Wadler, W. R.; Zhi, L. Novel cyclization reactions of dichloroazodienes. *Tetrahedron* **1992**, *48*, 7565; (c) Danks, T. N.; Velo-Rego, D. Reaction of a chromium carbene complex with 1-azadienes and the synthesis of trisubstituted

pyrroles. *Tetrahedron Lett.* **1994**, *35*, 9443; (d) Furstner, A.; Bogdanovic, B. New developments in the chemistry of low-valent titanium. *Angew. Chem., Int. Ed.* **1996**, *35*, 2442; (e) Gilchrist, T. L. Synthesis of aromatic heterocycles. *J. Chem. Soc., Perkin Trans. 1* **1998**, 615; (f) Gabriele, B.; Salerno, G.; Fazio, A. General and regioselective synthesis of substituted pyrroles by metal-catalyzed or spontaneous cycloisomerization of (Z)-(2-en-4-ynyl)amines. *J. Org. Chem.* **2003**, *68*, 7853; (g) Bashiardes, G.; Safir, I.; Barbot, F.; Laduranty, J. A new method for the synthesis of plurisubstituted pyrroles. *Tetrahedron Lett.* **2003**, *44*, 8417; (h) Dieter, R. K.; Yu, H. A facile synthesis of polysubstituted pyrroles. *Org. Lett.* **2000**, *2*, 2283; (i) Iwasawa, N.; Maeyama, K.; Saitou, M. Reactions of propargyl metallic species generated by the addition of alkynyllithiums to Fischer-type carbene complexes. *J. Am. Chem. Soc.* **1997**, *119*, 1486; (j) Yang, Q.; Alper, H.; Xiao, W.-J. Efficient method for the synthesis of chiral pyrrolidine derivatives via ring-closing enyne metathesis reaction. *Org. Lett.* **2007**, *9*, 769; (k) Furstner, A.; Weintritt, H.; Hupperts, A. A new, titanium-mediated approach to pyrroles: First synthesis of lukianol A and lamellarin O dimethyl ether. *J. Org. Chem.* **1995**, *60*, 6637; (l) Katritzky, A.; Jiang, J.; Steel, P. J. 1-Aza-1,3-bis(triphenylphosphoranylidene)propane: A novel $CHCH_2N$ synthon. *J. Org. Chem.* **1994**, *59*, 4551; (m) Arcadi, A.; Rossi, E. Synthesis of functionalised furans and pyrroles through annulation reactions of 4-pentynones. *Tetrahedron* **1998**, *54*, 15253; (n) Periasamy, M.; Srinivas, G.; Bharati, P. Conversion of aryl methyl ketimines to 2,5-diarylpyrroles using $TiCl_4/Et_3N$. *J. Org. Chem.* **1999**, *64*, 4204.

20. (a) Dhawan, R.; Arndtsen, B. A. Palladium-catalyzed multicomponent coupling of alkynes, imines, and acid chlorides: A direct and modular approach to pyrrole synthesis. *J. Am. Chem. Soc.* **2004**, *126*, 468; (b) Wang, Y. L.; Zhu, S. Z. Convenient synthesis of polyfunctionalized β-fluoropyrroles from rhodium(II)-catalyzed intramolecular N−H insertion reactions. *Org. Lett.* **2003**, *5*, 745; (c) Binder, J. T.; Kirsch, S. F. Synthesis of highly substituted pyrroles via a multimetal-catalyzed rearrangement−condensation−cyclization domino approach. *Org. Lett.* **2003**, *8*, 2151; (d) Magnus, N. A.; Staszak, M. A.; Udodong, U. E.; Wepsiec, J. P. Synthesis of 4-cyano pyrroles via mild Knorr reactions with β-ketonitriles. *Org. Process Res. Dev.* **2006**, *10*, 899; (e) Alizadeh, A.; Babaki, M.; Zohreh, N. Solvent-free synthesis of penta-substituted pyrroles: One-pot reaction of amine, alkyl acetoacetate, and fumaryl chloride. *Tetrahedron* **2009**, *65*, 1704.
21. (a) Procopiou, P. A.; Draper, C. D.; Hutson, J. L.; Inglis, G. G.; Ross, B. C.; Watson, N. S. Inhibitors of cholesterol biosynthesis, 2: 3,5-Dihydroxy-7-(*N*-pyrrolyl)-6-heptenoates, a novel series of HMG-CoA reductase inhibitors. *J. Med. Chem.* **1993**, *36*, 3658; (b) Roth, B. D.; Blankley, C. J.; Chucholowski, A. W.; Ferguson, E.; Hoefle, M. L.; Ortwine, D. F.; Newton, R. S.; Sekerke, C. S.; Sliskovic, D. R.; Stratton, C. D.; Wilson, M. W. Inhibitors of cholesterol biosynthesis, 3: Tetrahydro-4-hydroxy-6-[2-(1H-pyrrol-1-yl)ethyl]-2H-pyran 2-one inhibitors of HMG-CoA reductase, 2: Effects of introducing substituents at positions three and four of the pyrrole nucleus. *J. Med. Chem.* **1991**, *34*, 357; (c) Jendralla, H.; Baader, E.; Bartmann, W.; Beck, G.; Bergmann, A.; Granzer, E.; von Kerekjarto, B.; Kesseler, K.; Krause, R.; Schubert, W.; Wess, G. Synthesis and biological activity of new HMG-CoA reductase inhibitors, 2: Derivatives of 7-(1H-pyrrol-3-yl)-substituted-3,5-dihydroxyhept-6(E)-enoic(-heptanoic) acids. *J. Med. Chem.* **1990**, *33*, 61; (d) Roth, B. D.; Ortwine, D. F.; Hoefle, M. L.; Stratton, C. D.; Sliskovic, D. R.; Wilson, M. W.; Newton, R. S. Inhibitors of cholesterol biosynthesis, 1: *trans*-6-(2-Pyrrol-1-ylethyl)-4-hydroxypyran-2-ones, a novel series of HMG-CoA reductase inhibitors, 1: Effects of structural modifications at the 2- and 5-positions of the pyrrole nucleus. *J. Med. Chem.* **1990**, *33*, 21.
22. (a) Yoshida, T.; Yamamoto, Y.; Orita, H.; Kakiuchi, M.; Kato, H. Structures and total synthesis of two novel bis(bibenzyls), paleatins A and B, from the liverwort *Marchantia paleacea* var. Diptera. *Chem. Pharm. Bull.* **1996**, *44*, 1376; (b) Kim, S.-Y.; Park, H. B.;

Cho, J.-H.; Yoo, K. H.; Oh, C.-H. Synthesis and antibacterial activities of novel oxazolidinones having spiro[2,4]heptane moieties. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2558.
23. Guo, Z.; Orth, P.; Wong, S.-C.; Lavey, B. J.; Shih, N.-Y.; Niu, X.; Lundell, D. J.; Madison, V.; Kozlowski, J. A. Discovery of novel spirocyclopropyl hydroxamate and carboxylate compounds as TACE inhibitors. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 54.
24. Xie, Y.-X.; Yan, Z.-Y.; Wang, D.-Z.; Wu, L.-Y.; Qian, B.; Liu, X.-Y.; Liang, Y.-M. Synthesis of polysubstituted 3-iodopyrans by electrophilic cyclization. *Eur. J. Org. Chem.* **2009**, 2283.
25. Duan, X.-H.; Liu, X.-Y.; Guo, L.-N.; Liao, M.-C.; Liu, W.-M.; Liang, Y.-M. Palladium-catalyzed one-pot synthesis of highly substituted furans by a three-component annulation reaction. *J. Org. Chem.* **2005**, *70*, 6980.
26. (a) Guo, L.-N.; Duan, X.-H.; Liu, X.-Y.; Liang, Y.-M. Palladium-catalyzed carboannulation of propargylic carbonates and nucleophiles to 2-substituted indenes. *J. Org. Chem.* **2007**, *72*, 1538; (b) Guo, L.-N.; Duan, X.-H.; Bi, H.-P.; Liu, X.-Y.; Liang, Y.-M. Synthesis of indenes via palladium-catalyzed carboannulation of diethyl 2-(2-(1-alkynyl)phenyl) malonate and organic halides. *J. Org. Chem.* **2006**, *71*, 3325; (c) Bi, H.-P.; Guo, L.-N.; Gou, F.-R.; Duan, X.-H.; Liu, X.-Y.; Liang, Y.-M. Highly regio- and stereoselective synthesis of indene and benzo[*b*]furan derivatives via a Pd-catalyzed carboannulation of propargyl carbonates with nucleophiles. *J. Org. Chem.* **2008**, *73*, 4713; (d) Duan, X.-H.; Guo, L.-N.; Bi, H.-P.; Liu, X.-Y.; Liang, Y.-M. Synthesis of 2-substitued 3-aroylindenes via palladium-catalyzed carbonylative cyclization of diethyl 2-(2-(1-alkynyl)phenyl)malonates with aryl halides. *Org. Lett.* **2006**, *8*, 5777; (e) Bi, H.-P.; Guo, L.-N.; Duan, X.-H.; Gou, F.-R.; Huang, S.-H.; Liu, X.-Y.; Liang, Y.-M. Highly regio- and stereoselective synthesis of indene derivatives via electrophilic cyclization. *Org. Lett.* **2006**, *9*, 397.
27. Ren, Z.-H.; Guan, Z.-H.; Liang, Y.-M. Highly regioselective synthesis of benz[*a*]anthracene derivatives via a Pd-catalyzed tandem C-H activation/biscyclization reaction. *J. Org. Chem.* **2009**, *74*, 3145.
28. Jacobi, P. A.; Brielmann, H. C.; Hauck, S. I. Toward the synthesis of biologically important chlorins, isobacteriochlorins, and corrins: Cyclic enamides from acetylenic amides. *J. Org. Chem.* **1996**, *61*, 5013.