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Synthesis of Heterocyclic Systems by Transition-Metal-Catalyzed Cyclization-Migration Reactions – A Diversity-Oriented Strategy for the Construction of Spirocyclic 3(2*H*)-Furanones and 3-Pyrrolones

Jörg T. Binder,[a] Benedikt Crone,[a] Stefan F. Kirsch,*[a] Clémence Liébert,[a] and Helge Menz[a]

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Two platinum(II)-catalyzed heterocyclization-migration reactions that provide five-membered heterocycle products are described. With 5 mol-% of $PtCl_2$ as a catalyst, 2-alkynyl-2-hydroxy carbonyl compounds **1** are converted into 3(2*H*)-furanones **2** at 80 °C in moderate to excellent yields under very mild reaction conditions. The reaction is proposed to proceed through an oxonium ion intermediate **B**, which triggers a stereospecific 1,2-shift analogous to an α-ketol rearrangement. When exploited in a different manner, the 2-alkynyl-2-hydroxy carbonyl compounds **1** afford 3-pyrrolones **3** in 33–81 % yield. For this purpose, the starting compounds **1** are treated with primary amines in the presence of 5 mol-% of $PtCl_2$ at 100 °C in a convenient one-pot process. These cyclization-migration reactions give novel access to 3(2*H*)-furanones and 3-pyrrolones in which the 2-position bears aryl or alkyl substituents. Synthetically challenging spirocyclic compounds can be prepared in this fashion by ring contraction. Studies that define the scope and limitations of the cyclization-migration synthesis of heterocyclic systems are also described.

Introduction

Cascade reactions that combine two distinct reactions into a single transformation are a powerful method for constructing architecturally complex molecules from relatively simple starting materials.[1,2] For some time, our group has been involved in the development of cascade reactions that are initiated by transition-metal-catalyzed π-activation for the synthesis of heterocyclic products.[3] Coupled with a diversity-oriented approach to heterocyclic compounds, these cascade reactions are particularly attractive because branching reaction pathways increase the structural diversity of products by altering the skeletal array.[4] This strategy is expected to rapidly evolve both molecular complexity and structural diversity, as a single compound is subjected to varying reaction conditions that enable tandem processes, leading to structurally distinct products. For example, one variant of this chemistry, the rearrangement-cyclization reaction, provides at least three structurally unique products (furans,[3c] pyrroles,[3b] and 2*H*-pyrans[3a]) from readily synthesized propargyl vinyl ethers. However, sequences involving rearrangement processes are relatively underdeveloped in the production of diversity.[5]

Nitrogen[6] and oxygen[7] heterocycles play important roles as structural elements of many naturally occurring and biologically active substances. Although a tremendous number of synthetic methods to approach heterocyclic compounds is known, the development of newer and more efficient protocols remains an area of ongoing interest in organic synthesis.[8,9] Only recently, has the transition-metal-catalyzed skeletal reorganization of unsaturated frameworks been appreciated to access heterocyclic compounds.[10] Owing to their exceptional ability to activate π-systems,[11] and especially alkynes,[12,13] toward intermolecular and intramolecular nucleophilic attack, strategies involving π-activation by soft noble-metal cations have become increasingly popular, mostly with Au^{I}, Au^{III}, Ag^{I}, and Pt^{II} compounds as transition-metal precatalysts.[14] While being operationally simple and convenient to perform (neither air nor humidity need to be excluded), such skeletal rearrangements provide an attractive and atom-economical route to functionalized heterocycles.[15]

Recently, Larock[16] and others[17] reported a transition-metal-catalyzed synthesis of substituted furans from 2-(1-alkynyl)-2-alken-1-ones, which produces highly substituted furans [Equation (1)].[18] This reaction is believed to proceed by the formation of an oxonium ion intermediate. As part of our program directed toward the development of a diversity-oriented use of tandem reactions for the synthesis of heterocyclic compounds,[19] we envisioned a general approach to the synthesis of 3(2*H*)-furanones **2** from 2-alkynyl-2-hydroxy carbonyl compounds **1**, which proceeds

[a] Department Chemie, Technische Universität München, Lichtenbergstr. 4, 85747 Garching, Germany
Fax: +49-89-2891-3315
E-mail: stefan.kirsch@ch.tum.de
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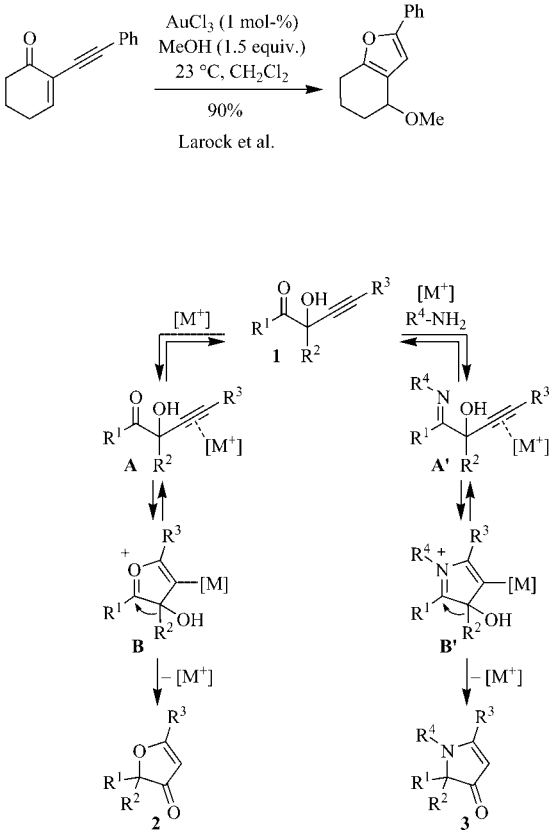
through the cationic cyclization sequence shown in Scheme 1. Coordination of the triple bond of propargylic alcohol **1** to a suitable transition-metal catalyst was expected to enhance the electrophilicity for an intramolecular nucleophilic attack. The intermediate oxonium ion **B** should then trigger an irreversible 1,2-shift analogous to a formal α-ketol rearrangement,[20] and subsequent protonation of the carbon–transition-metal bond should afford the 3(2*H*)-furanones **2** and regenerate the catalyst. To expand the diversity of structures available from propargylic alcohol **1**, we planned to utilize primary amines for an in situ condensation step, and the sequence concludes then with a 1,2-migration to the adjacent iminium ion to give 3-pyrrolones **3**. To the best of our knowledge, onium ion rearrangements have not been used to terminate cationic cyclizations, while the use of related pinacol rearrangements has been demonstrated to be a powerful strategy for designing cascade reactions by Overman[1a] and others.[21]



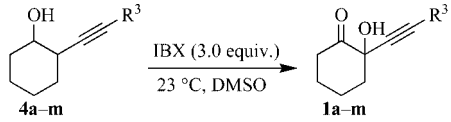
Scheme 1. Proposed pathway for the synthesis of 3(2*H*)-furanones and 3-pyrrolones.

We herein report a detailed study of transition-metal-catalyzed cyclization-migration reactions. As exemplified in Scheme 1, these unique reactions are particularly attractive, because a convenient one-pot process affords both 3(2*H*)-furanones **2** and 3-pyrrolones **3** from propargylic alcohols **1**.[22]

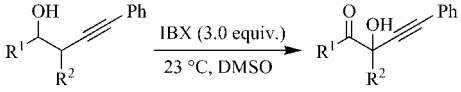
Results and Discussion

Preparation of Propargylic Alcohols

Numerous practical methods for the synthesis of 2-alkynyl-2-hydroxy carbonyl systems are now available. In general, these methods involve the addition of alkynes to 1,2-diketones to provide tertiary alkynyl alcohols.[9i,23] In the present study, we have developed a quite convenient synthesis for the required 2-alkynyl-2-hydroxy carbonyl compounds **1** from 2-alkynyl alcohol compounds **4** derived from simple oxiranes.[24] The key development in implementing this alternative sequence was our finding that *o*-iodoxybenzoic acid (IBX)[25] is an excellent reagent for the mild and regioselective α-hydroxylation of 2-alkynyl carbonyl compounds in DMSO at 23 °C without giving dehydrogenation products.[26–28] Both cyclic and acyclic propargylic alcohols **1a–o** are procurable on a large scale, although with variable (33–91%) yields, by the direct oxidation of 2-alkynyl alcohols **4** with 3.0 equiv. of IBX [Equations (2) and (3)].

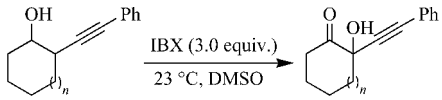


1a R^3 = Ph (80%) **1b** R^3 = 4-F-C_6H_4 (68%)
1c R^3 = 2-MeO-C_6H_4 (51%) **1d** R^3 = 4-*t*Bu-C_6H_4 (78%)
1e R^3 = 3-thienyl (70%) **1f** R^3 = *n*Pent (66%)
1g R^3 = CH_2(*c*-C_6H_{11}) (57%) **1h** R^3 = *c*-C_6H_{11} (47%)
1i R^3 = $(CH_2)_3$OTHP (74%) **1j** R^3 = CH_2OTHP (44%)
1k R^3 = 1-cyclohexenyl (33%) **1l** R^3 = 2-propenyl (45%)
1m R^3 = $SiMe_3$ (91%) (2)



4n **1n** $R^1 = R^2$ = Me (63%)
4o **1o** $R^1 = R^2$ = *n*Pr (77%) (3)

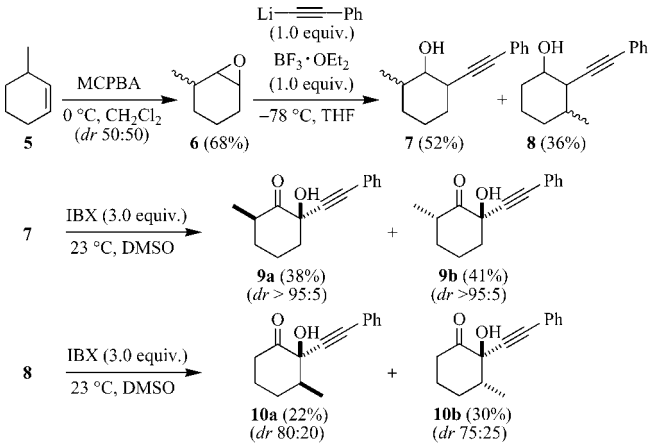
Whereas cyclopentanone **4p** was obtained in 55% yield, the IBX-mediated hydroxylation of the seven- and eight-membered ring systems gave the desired tertiary alcohols in poor yields accompanied by a significant amount of decomposition [Equation (4)].[29]



4p–r
1p *n* = 0 (55%)
1q *n* = 2 (3%)
1r *n* = 3 (26%) (4)

A representative series of 2-alkynyl-2-hydroxycyclohexanones bearing an additional methyl substituent was prepared from 3-methylcyclohexene (**5**) by the sequence illustrated in Scheme 2. Epoxidation of **5** provided epoxide **6** as a mixture of diastereomers (*dr* 50:50).[30] Alkynylation of

this inseparable mixture with lithium phenylacetylide[24] in the presence of $BF_3{\cdot}OEt_2$ at –78 °C in THF gave rise to the secondary alcohols **7** and **8**, which were separated by column chromatography. Both **7** and **8** were transformed in the presence of IBX in DMSO to the corresponding 2-alkynyl-2-hydroxycyclohexanones without showing diastereoselectivity; **9a** and **9b** were separated by column chromatography on silica gel (**9a**: *dr* > 95:5; **9b**: *dr* > 95:5); **10a** and **10b** were separated by semipreparative HPLC (**10a**: *dr* 80:20; **10b**: *dr* 75:25).[31] Stereochemical assignments for these compounds were made on the basis of NOESY experiments.



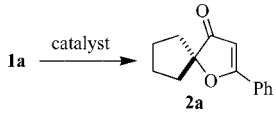
Scheme 2. Synthesis of **9a**, **9b**, **10a**, and **10b**.

Synthesis of 3(2*H*)-Furanones by a Transition-Metal-Catalyzed Heterocyclization/1,2-Migration Reaction

Substituted 3(2*H*)-furanones play an important role as structural elements of many natural products (e.g., eremantholide A,[32] jatrophone,[33] and geiparvarin[34]). Moreover, pharmaceutical activity, such as inhibitory activity on COX-2,[35] cytotoxic activity against tumor cells,[36] and inhibitory activity on MAO,[37] has been reported for several substances containing the 3(2*H*)-furanone moiety.[38] The construction of 3(2*H*)-furanones typically relies on classical condensation methods such as the acid-catalyzed cyclocondensation of substituted α′-hydroxy 1,3-diketones, whereas the bond formation between C5 and O1 is used in a cyclization step with the substitution pattern and the hydroxy group at C2 being installed at an earlier stage.[39,40] An alternative strategy involves unsaturated frameworks as starting materials for transition-metal-catalyzed 5-*endo* heterocyclizations.[41] A wide variety of other methods have been developed for the synthesis of these heterocycles, including the reaction of 3-silyloxyfurans with aldehydes,[42] transformation of 3-alkoxyfurans into 2-alkoxyfuranones,[43] intramolecular Wadsworth–Emmons condensation of γ-acyloxy-β-oxo phosphonates,[44] and cyclization of dianion equivalents with α-chloroacetic chlorides.[45] No attention has been paid to 2-alkynyl-2-hydroxy carbonyl compounds as possible 3(2*H*)-furanone precursors, although they are readily accessible and easily manipulated (as shown above). The utilization of 2-alkynyl-2-hydroxy carbonyl compounds for transition-metal-catalyzed cyclization-migration reactions should significantly expand the range of suitable starting materials for the synthesis of functionally substituted 3(2*H*)-furanones. Moreover, the projected synthetic route represents a significant departure from the conventional strategy for constructing 3(2*H*)-furanones, as the sequence affords the desired heterocycles through simultaneous C5–O1 bond formation and introduction of the substituents at C2.

Our preliminary studies have been carried out on the transition-metal-catalyzed conversion of alkynyl carbonyl compound **1a** into the spirocyclic 3(2*H*)-furanone **2a** (Table 1). These results were promising, as product formation was observed in the presence of gold(III), copper(I), silver(I), and platinum(II) salts. Among these salts, $AuCl_3$ is the most efficient catalyst based on reaction time and yield. For example, $AuCl_3$ (5 mol-%) provided the desired compound **2a** in CH_2Cl_2 at room temperature after 90 min in 83% yield (Table 1, Entry 1). Increasing the reaction temperature to 38 °C led to a slightly higher yield (95%). The use of cationic silver(I) and gold(I) complexes provided a low yield, mainly accompanied by a significant amount of decomposition (Table 1, Entries 2 and 3). $Pd(OAc)_2$, $(Ph_3P)AuCl$ and CuI are not efficient catalysts for this conversion. Alkynyl carbonyl compound **1a** was efficiently transformed into 3(2*H*)-furanone **2a** when heated in toluene at 80 °C in the presence of $PtCl_2$ (5 mol-%) (Table 1, Entry 7). However, $PtCl_2$-catalyzed isomerization was observed at an impractical rate at 23 °C in CH_2Cl_2, in part due to the poor solubility of $PtCl_2$ in CH_2Cl_2. In the absence of a transition-metal salt or in the presence of a catalytic amount of HBF_4, 3(2*H*)-furanone **2a** was not obtained at all.

Table 1. Transition metal-catalyzed conversion of **1a** into **2a**.



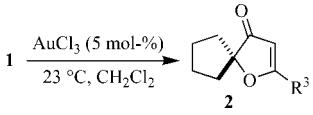
Entry	Catalyst	Time [min]	Yield[a] **2a** [%]	Yield[a,b] **1a** [%]
1[c]	$AuCl_3$	90	83	0
2[c]	$AgSbF_6$	90	50	12
3[c]	$(Ph_3P)AuBF_4$	90	0	10
4[c]	$(Ph_3P)AuCl$	90	0	96
5[d]	CuI	120	22	67
6[c]	$Pd(OAc)_2$	90	0	98
7[e]	$PtCl_2$	90	93	0
8[c]	$RuCl_3$	90	0	86
9[c]	HBF_4	90	0	23

[a] Isolated yield after column chromatography. [b] Recovered starting material **1a**. [c] Conditions: **1a** (0.03 M), 5 mol-% catalyst, 23 °C, CH_2Cl_2. [d] Conditions: **1a** (0.08 M), 10 mol-% catalyst, 80 °C, DMF. [e] Conditions: **1a** (0.03 M), 5 mol-% catalyst, 80 °C, toluene.

To probe the scope and limitations of the transition-metal-catalyzed cyclization-migration reactions, propargylic alcohols **1b**–**r** were allowed to react. As illustrated in

Table 2, the $AuCl_3$-catalyzed reaction is general for a range of substrates bearing different aryl substituents (R^3 = aryl) at the alkyne terminus. Unfortunately, substrates containing alkyl substituents (R^3 = alkyl) reacted considerably less cleanly than did their aryl analogues. Thus, treatment of propargylic alcohols **1h**, **1i**, and **1j** with $AuCl_3$ at 23 °C in CH_2Cl_2 afforded complex reaction mixtures, which contained only small amounts of the desired furanones. As an exception, substrate **1f** (R^3 = *n*Pent) reacted smoothly to give furanone **2f** in 66% yield (Table 2, Entry 5). Notably, solvent had a marked influence on catalytic efficiency. Reactions of 2-alkynyl-2-hydroxy carbonyl compound **1a** in the presence of 5 mol-% $AuCl_3$ at room temperature followed the order: CH_2Cl_2 (3 h, 93% yield) > C_6H_6 (3 h, 42% yield) > THF (3 h, 23% yield) ≈ CH_3CN (3 h, 20% yield). Varying the concentration of **1a** in CH_2Cl_2 revealed that the optimal concentration was 0.03 M. With substrate concentrations <0.01 M, the reaction was slowed markedly. On the other hand, increasing the concentration (>0.1 M) led to low yields due to concomitant decomposition of the starting material.

Table 2. $AuCl_3$-catalyzed conversion of **1** into **2**.[a]

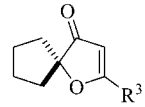
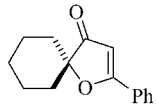
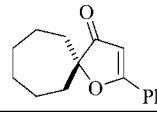


Entry	Substrate	R^3	Product	Yield[b] **2** [%]
1	**1b**	4-F-C_6H_4	**2b**	70 (4 h)
2	**1c**	2-MeO-C_6H_4	**2c**	81 (5 h)
3	**1d**	4-*t*Bu-C_6H_4	**2d**	75 (4 h)
4	**1e**	3-thienyl	**2e**	76 (5 h)
5	**1f**	*n*Pent	**2f**	66 (2 h)
6	**1h**	*c*-C_6H_{11}	**2h**	25 (7 h)
7	**1i**	$(CH_2)_3$OTHP	**2i**	11 (6 h)
8	**1j**	CH_2OTHP	**2j**	33 (18 h)

[a] Conditions: **1** (0.03 M), 5 mol-% $AuCl_3$, 23 °C, CH_2Cl_2. [b] Isolated yield after column chromatography.

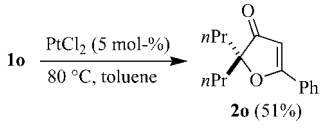
To further expand the scope of this method, we then examined the use of $PtCl_2$ to catalyze the formation of 3(2*H*)-furanones. Our expectation was that the platinum(II) salts may have an advantage over $AuCl_3$, offering greater substrate scope (e.g., R^3 = alkyl) while maintaining competitive yields for R^3 = aryl. Moreover, the use of non-hygroscopic $PtCl_2$ is more convenient due to the fact that, with $AuCl_3$, moisture should be excluded because of its strong hygroscopicity. As summarized in Table 3, a number of alkynes **1** were effectively converted into 3(2*H*)-furanones with particularly practical reaction conditions: 5 mol-% $PtCl_2$, 80 °C, and toluene (0.03 M). As with $AuCl_3$, the reaction tolerated substitution of the substrate with R^3 being both aromatic and heteroaromatic groups.[46] Gratifyingly, substrates containing alkyl, alkenyl, and silyl substituents at the alkyne terminus provided good yields of the desired products under the reaction conditions. In a similar fashion, substrates **1q** and **1r** were transformed into **2q** and **2r**, respectively (Table 3, Entries 13 and 14). Again in these cases, ring contraction was observed to give the corresponding six- and seven-membered ring systems. Substrate **1p** derived from cyclopentanone did not react in the presence of $PtCl_2$.

Table 3. $PtCl_2$-catalyzed conversion of **1** into **2**.[a]

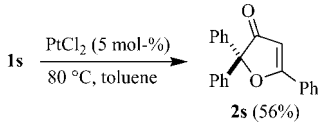
Entry	Substrate	Product	#	Yield[b] **2** [%]
1	**1b**	 R^3 = 4-F-C_6H_4	**2b**	90 (15 h)
2	**1c**	R^3 = 2-MeO-C_6H_4	**2c**	91 (18 h)
3	**1d**	R^3 = 4-*t*Bu-C_6H_4	**2d**	87 (18 h)
4	**1e**	R^3 = 3-thienyl	**2e**	65 (18 h)
5	**1f**	R^3 = *n*Pent	**2f**	65 (2 h)
6	**1g**	R^3 = CH_2(*c*-C_6H_{11})	**2g**	75 (12 h)
7	**1h**	R^3 = *c*-C_6H_{11}	**2h**	78 (3 h)
8	**1i**	R^3 = $(CH_2)_3$OTHP	**2i**	82 (4 h)
9	**1j**	R^3 = CH_2OTHP	**2j**	70 (6 h)
10	**1k**	R^3 = 1-cyclohexenyl	**2k**	68 (3 h)
11	**1l**	R^3 = 2-propenyl	**2l**	40[c] (10 h)
12	**1m**	R^3 = $SiMe_3$	**2m**	57 (19 h)
13	**1q**		**2q**	85[d] (4 h)
14	**1r**		**2r**	50 (24 h)

[a] Conditions: **1** (0.03 M), 5 mol-% $PtCl_2$, 80 °C, toluene. [b] Isolated yield after column chromatography. [c] Volatility of **2l** is likely responsible for the moderate yield. [d] Determined by ^{1}H NMR spectroscopy.

Whereas the present study focused mainly on the synthesis of spirocyclic 3(2*H*)-furanones, this new cyclization-migration reaction is also applicable to acyclic systems, although the yields were modest. For example, substrates **1o** (R^1 = R^2 = *n*Pr) and **1s** (R^1 = R^2 = Ph)[47] reacted by migration of alkyl and aryl groups [Equations (5) and (6)].



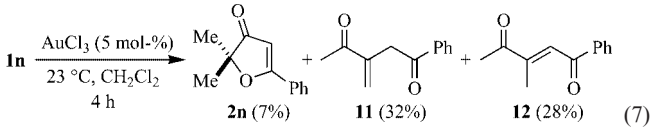
(5)



(6)

Unfortunately, substrates that contained a methyl group for R^2 provided poor yields of the desired products. The markedly reduced reactivity of these substrates is probably due to the decrease in the migratory aptitude for the methyl group, which facilitates competing reaction pathways such as the elimination of water. In the case of **1n**, the attempted formation of the naturally occurring compound bullatenone (**2n**)[48] gave (*E*)-endione **12** exclusively (79% yield) utilizing

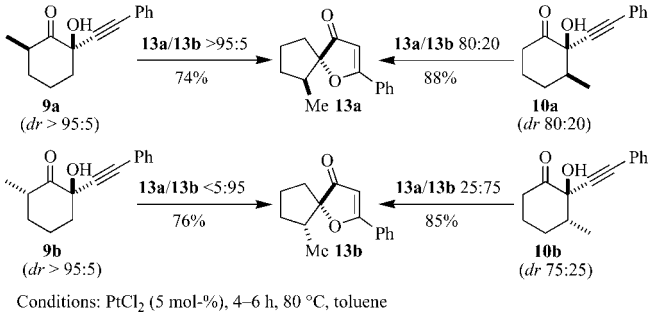
$PtCl_2$ (5 mol-%) in toluene at 80 °C for 12 h. The use of $AuCl_3$ at room temperature resulted primarily in the formation of the two enone products **11** (32% yield) and **12** (28% yield) after 4 h [Equation (7)].



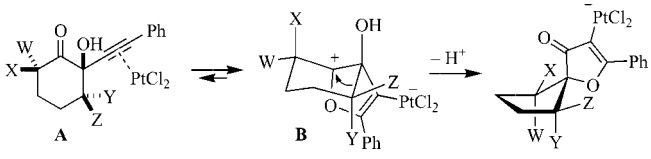
(7)

In both cases, the occurrence of **12** can be rationalized by a sequence consisting of elimination and subsequent triple-bond hydration. Although a Meyer–Schuster mechanism[49] cannot be ruled out for the direct formation of **12** from **1n**, the fact that enedione **12** can be prepared without concomitant formation of **11** with longer reaction times and higher temperatures is consistent with the generation of **12** by double-bond isomerization of **11**.

Of primary importance, the cyclization-migration sequence for the conversion of 2-alkynyl-2-hydroxy carbonyl compounds **1** to 3(2*H*)-furanones was found to proceed stereospecifically. As depicted in Scheme 3, the methyl-substituted compounds **9a** and **10a** led to 3(2*H*)-furanone **13a** exclusively, whereas **9b** and **10b** delivered **13b**.[50] The diastereomer observed in the 3(2*H*)-furanone synthesis reported here follows in each case from a rearrangement that is likely to proceed through the cyclic oxonium ion intermediate **B** (Scheme 4). The fact that both cyclohexanones **9a** and **10a** rearrange to give the same furanone product, as do **9b** and **10b**, is rationalized also by this model. Nevertheless, there exists no direct experimental proof for cationic intermediate **B**.

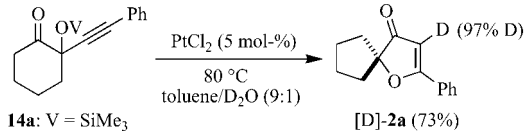


Scheme 3. Stereospecific course of the cyclization-migration reactions.



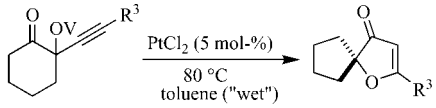
Scheme 4. Plausible mechanism (illustrated for the formation of **13a** and **13b** from **9a**: W = H, X = Me, Y = H, and Z = H; from **9b**: W = Me, X = H, Y = H, and Z = H; from **10a**: W = H, X = H, Y = H, and Z = Me; from **10b**: W = H, X = H, Y = Me, and Z = H).

We have also briefly examined the proposed proto-demetallation step to set free the platinum catalyst. When trimethylsilyl ether **14a** was subjected to the standard $PtCl_2$-catalyzed conditions with an excess of D_2O as an additive, deuterium incorporation into the 3(2*H*)-furanone at C-4 was observed [Equation (8)].



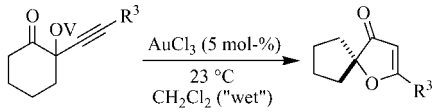
(8)

This result is consistent with the cyclization-migration mechanism as proposed in Schemes 1 and 4, in which the proto-demetallation at C4 is believed to be the final step in the domino process. In general, trialkylsilyl ethers **14** (V = $SiMe_3$) and **15** (V = $SiEt_3$) underwent $PtCl_2$-initiated ring-contracting cyclization to give the corresponding 3(2*H*)-furanones in good yields [Equation (9)].



(9)

These reactions were performed under otherwise identical conditions in undistilled toluene. Cleavage of the tetrahydropyranyl group of **14j** under the reaction conditions is likely responsible for the moderate yield in forming spirocycle **2j**. In the case of the catalyzed transformation **14a** → **2a**, tertiary alcohol **1a** was detected as an intermediate. Thus, we assume that the silyl ether is cleaved in the presence of $PtCl_2$ and "wet" toluene at 80 °C prior to the cyclization-migration process. The reactions of trimethylsilyl ethers **14** catalyzed by $AuCl_3$ in undistilled CH_2Cl_2 at room temperature were remarkably clean, taking place without the formation of significant amounts of byproducts [Equation (10)].



(10)

Under these conditions, yields starting from trimethylsilyl ethers **14** are slightly superior to those realized with tertiary alcohols **1** in dry CH_2Cl_2. Notably, the reaction of aromatic substrates was as clean as the reaction of substrates **14f** and **14j** having alkyl substituents.

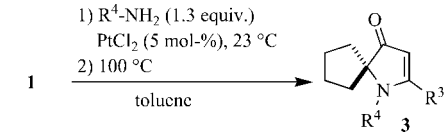
Synthesis of 3-Pyrrolones by a $PtCl_2$-Catalyzed Heterocyclization/1,2-Migration Reaction

To further broaden the diversity of structures available from 2-alkynyl-2-hydroxy carbonyl compounds, we then examined a conceptually novel approach to 3-pyrrolones. Our expectation was that, upon treatment with primary amines, the standard reaction conditions utilized for the synthesis of 3(2*H*)-furanones would deliver directly pyrrolone products. During the envisioned one-pot assembly, an additional amine condensation step was expected to occur before $PtCl_2$-catalyzed heterocyclization.[3b,51]

Despite the abundant literature available for both the significance and the preparation of 3(2*H*)-furanones, synthetic routes to their aza analogues, 3-pyrrolones, are rare. The vast majority of the previous routes to 3-pyrrolones have involved intramolecular condensation methods through bond formation between N1 and C5.[52] For example, this strategy has been effectively utilized to synthesize 3-pyrrolones as building blocks for the construction of non-peptide peptidomimetic scaffolds.[53] An alternative approach to the synthesis of substituted 3-pyrrolones is through Hg^{II}-mediated 5-*endo* cyclization of amino ynones.[54] Owing to their restricted availability, the pharmaceutical features of 3-pyrrolones lack detailed investigations. Therefore, we feel that a general strategy to access 3-pyrrolones starting from readily obtained 2-alkynyl-2-hydroxy carbonyl compounds may be useful.

To realize the single-step process, this new cyclization-migration sequence was initially examined with propargyl alcohol **1a** and aniline. As there was no precedent for the projected conversion, we set out to explore the feasibility of this transformation with the conditions previously employed for the synthesis of 3(2*H*)-furanones. Unfortunately, reaction of **1a** and aniline in the presence of catalytic amounts of $PtCl_2$ (5 mol-%) at 80 °C in toluene led to a complex reaction mixture, which only contained small amounts of the desired 3-pyrrolone **3aa**. Nevertheless, the product was characterized by diagnostic ^{13}C NMR signals at δ = 175.1 and 80.9 ppm. Further optimization revealed that a brief exposure of ketone **1a** and aniline to $PtCl_2$ (5 mol-%) in toluene at room temperature followed by reaction at 100 °C for 24 h furnished pyrrolone **3aa** in 75% yield. As summarized in Table 4, subjection of other 2-alkynyl-2-hydroxy carbonyl compounds **1** and amines (R^4-NH_2) to the general protocol [(1) substrate **1**, R^4-NH_2 (1.3 equiv.), $PtCl_2$ (5 mol-%), 23 °C, 30 min, toluene; (2) 100 °C, 24 h] afforded a number of related 3-pyrrolones **3**. Although product formation was observed in all cases, yields varied widely (33–81%). This reaction is not as general as the synthesis of 3(2*H*)-furanones discussed previously. For example, isobutylamine and **1a** provided 33% yield of the desired product, whereas isopropylamine was transformed in 81% yield to 3-pyrrolone **3ae**. Analysis of crude reaction mixtures by ^1H NMR spectroscopy indicated that the incomplete formation of the intermediate imine is most likely responsible for the low yields. Attempts to modify the condensation conditions to improve the yields of the one-pot sequence without isolation of the imine intermediates were unsuccessful.

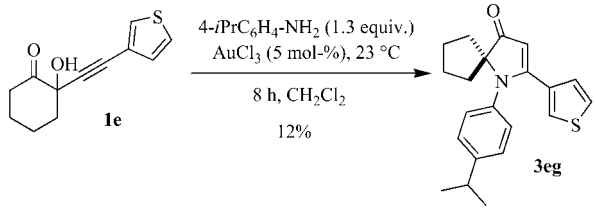
Table 4. $PtCl_2$-catalyzed conversion of **1** into **3**.[a]



Entry	Substrate	R^3	R^4	Product	Yield[b] **2** [%]
1	**1a**	Ph	Ph	**3aa**	75
2	**1a**	Ph	3-NO_2-C_6H_4	**3ab**	35
3	**1a**	Ph	CH_2Ph	**3ac**	37
4	**1a**	Ph	*i*Bu	**3ad**	33
5	**1a**	Ph	*i*Pr	**3ae**	81
6	**1d**	4-*t*Bu-C_6H_4	Ph	**3da**	52
7	**1e**	3-thienyl	3-Cl-C_6H_4	**3ef**	73
8	**1e**	3-thienyl	4-*i*Pr-C_6H_4	**3eg**	78
9	**1f**	*n*Pent	4-MeO-C_6H_4	**3fh**	73
10	**1j**	CH_2OTHP	Ph	**3ja**	44

[a] Conditions: **1** (0.03 M), R^3-NH_2 (1.3 equiv.), 5 mol-% $PtCl_2$, 100 °C, toluene. [b] Isolated yield after column chromatography.

In the presence of catalytic amounts of $AuCl_3$, the desired 3-pyrrolones were obtained in poor yields as exemplified for the one-pot synthesis of pyrrolone **3eg** [Equation (11)].



(11)

Conclusions

Two new variants of domino reactions initiated by transition-metal-catalyzed alkyne activation were described. In one, 2-alkynyl-2-hydroxy carbonyl compounds and 2-alkynyl-2-silyloxy carbonyl compounds are transformed into a variety of 3(2*H*)-furanones. This sequence is effectively catalyzed by $PtCl_2$ and $AuCl_3$. In the second more limited variant, identical starting compounds are utilized to give spirocyclic 3-pyrrolones in the presence of primary amines and catalytic amounts of $PtCl_2$. Both sequences are proposed to proceed through a heterocyclization followed by a 1,2-alkyl migration. The ability to transform simple 2-alkynyl-2-hydroxy carbonyl compounds into either 3(2*H*)-furanones or 3-pyrrolones illustrates the type of reaction pathways that are essential to rapidly evolve both diversity and complexity. From a synthetic point of view, the results described herein provide convenient access to two classes of heterocycles, which could find wide application in the design of pharmaceutically active compounds.

Experimental Section

General: All reactions involving water-sensitive chemicals were carried out in flame-dried glassware with magnetic stirring under Ar. Common solvents [pentane (P), ethyl acetate (EtOAc), tetrahydrofuran (THF), diethyl ether (Et_2O), and CH_2Cl_2] were distilled prior to use. All other reagents and solvents were used as received. ^1H NMR spectra were obtained with 500 MHz and 360 MHz FT-NMR spectrometers. ^{13}C NMR spectra were recorded at 90.6 MHz. Chemical shifts are reported in ppm relative to the solvent signal. Multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), m (multiplet), dd (doublet of doublets), and app (apparent). Flash chromatography was performed with E. Merck silica gel (43–60 μm). The eluent used is reported in parentheses. Thin-layer chromatography (TLC) was performed on precoated glass-backed plates (Merck Kieselgel 60 F_{254}), and components were visualized by observation under UV light or by treating the plates with $KMnO_4/H_2SO_4$ followed by heating.

Representative Procedure for the Alkynylation of Oxiranes.[24] Synthesis of *trans*-2-(2-Phenylethynyl)cyclohexanol (4a): A solution of *n*BuLi in hexanes (2.5 M, 4.8 mL, 12.1 mmol) was added dropwise at –78 °C to a solution of the phenylacetylene (1.21 mL, 11.0 mmol) in dry THF (40 mL). The resulting solution was stirred for 30 min at –78 °C, and then $BF_3{\cdot}Et_2O$ (1.39 mL, 11.0 mmol) was added, followed by a solution of cyclohexene oxide (1.08 g, 11.0 mmol) in THF (4 mL). The mixture was stirred at –78 °C for 4 h (until TLC analysis indicated complete consumption of the starting material). The reaction was quenched by the addition of saturated aqueous NH_4Cl (25 mL), and the layers were separated. The aqueous layer was extracted with diethyl ether (2 × 50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (10% EtOAc/P) to afford **4a** (1.61 g, 8.1 mmol, 81% yield). ^1H NMR (360 MHz, $CDCl_3$): δ = 1.24–1.34 (m, 3 H), 1.49 (dq, J = 12.7, 2.9 Hz, 1 H), 1.68–1.73 (m, 1 H), 1.77–1.81 (m, 1 H), 2.04–2.10 (m, 2 H), 2.34 (br. s, 1 H), 2.44 (ddd, J = 11.6, 9.3, 3.8 Hz, 1 H), 3.55 (dt, J = 9.7, 4.1 Hz, 1 H), 7.28–7.30 (m, 3 H), 7.40–7.43 (m, 2 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 24.4, 25.0, 31.2, 33.3, 39.8, 73.7, 82.9, 91.0, 123.5, 128.1, 128.4, 131.9 ppm. The NMR spectroscopic data are identical to those reported.[24]

Representative Procedure for the IBX-Mediated α-Hydroxylation.[26] Synthesis of 2-Hydroxy-2-(2-phenylethynyl)cyclohexanone (1a): IBX (0.42 mmol, 118 mg) was added to a solution of alcohol **4a** (84 mg, 0.42 mmol) in DMSO (0.9 mL), and the reaction vial was sealed, protected from light, and the mixture was stirred at room temperature. After 4 h, additional IBX (0.84 mmol, 235 mg) was added. The reaction mixture was then stirred at room temperature for 11 h (until TLC analysis indicated complete consumption of starting material), diluted with CH_2Cl_2 (10 mL), and stirring was continued for 30 min to precipitate the insoluble byproduct, which was removed by filtration. The precipitate was washed with CH_2Cl_2 (2 × 5 mL), and the combined filtrates were subsequently treated with saturated aqueous $NaHCO_3$ (20 mL). The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic phases were washed with water (30 mL) and brine (30 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (10% EtOAc/P) to afford **1a** as a pale yellow oil (72 mg, 0.34 mmol, 80% yield): R_f = 0.39 (20% EtOAc/P). ^1H NMR (500 MHz, $CDCl_3$): δ = 1.69 (dt, J = 13.6, 3.9 Hz, 1 H), 1.76 (dt, J = 3.5, 13.1 Hz, 1 H), 1.91–1.93 (m, 1 H), 2.12 (tt, J = 13.6, 3.6 Hz, 1 H), 2.11–2.20 (m, 1 H), 2.57–2.61 (m, 2 H), 3.04 (dt, J = 6.2, 13.7 Hz, 1 H), 4.32 (s, 1 H), 7.33–7.38 (m, 3 H), 7.46 (dd, J = 7.3, 1.4 Hz, 2 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 22.9, 27.7, 37.3, 42.5, 74.1, 87.5, 87.8, 122.0, 128.3, 128.8, 131.8, 207.5 ppm. LRMS (EI): m/z (%) = 214 (80) $[M]^+$, 185 (62), 157 (58), 129 (100). HRMS: calcd. for $C_{14}H_{14}O_2$ 214.0994, found 214.0993.

Synthesis of 2-Alkynyl-2-hydroxy Carbonyl Compounds 9 and 10: According to the preparation of **4a**, a solution of 2-methyl-7-oxabicyclo[4.1.0]heptane (**6**,[30] 850 mg, 7.59 mmol) in THF (32 mL) was treated with (2-phenylethynyl)lithium [from *n*BuLi (8.36 mmol) and phenylacetylene (0.83 mL, 7.59 mmol)] and $BF_3{\cdot}Et_2O$ (0.95 mL, 7.59 mmol) at –78 °C for 3 h. The regioisomers **7** and **8** were separated by flash chromatography (10% EtOAc/P), and the less polar fraction provided **7** (844 mg, 3.95 mmol, 52% yield) as a colorless oil, which was a mixture of diastereomers. The more polar fraction provided **8** (584 mg, 2.73 mmol, 36% yield) as a yellow oil, which was a mixture of diastereomers. According to the preparation of **1a**, a solution of **7** (211 mg, 0.99 mmol) in DMSO (2 mL) was oxidized with IBX (840 mg, 3 mmol) at room temperature for 16 h. Purification by flash chromatography (5% EtOAc/P) provided **9a** (86 mg, 0.38 mmol, 38% yield) and **9b** (92 mg, 0.41 mmol, 41% yield), which were >95% pure by ^1H NMR analysis. According to the preparation of **1a**, a solution of **8** (262 mg, 1.22 mmol) in DMSO (2.5 mL) was oxidized with IBX (1.04 g, 3.70 mmol) at room temperature for 24 h. **10a** and **10b** were separated by semipreparative HPLC [YMC ODS-A, 250 mm × 20 mm, 50:50 H_2O/CH_3CN, 15 mL/min, 254 nm; **10a**, t_R = 21.1 min; **10b**, t_R = 22.7 min]. **10a** was obtained as a colorless oil (61 mg, 0.27 mmol, 22% yield), which was contaminated to the extent of 20% with **10b**. **10b** was obtained as a colorless oil (83 mg, 0.37 mmol, 30%), which was contaminated to the extent of 25% with **10a**. **9a:** ^1H NMR (360 MHz, $CDCl_3$): δ = 1.14 (d, J = 6.6 Hz, 3 H), 1.54–1.69 (m, 2 H), 1.74–1.87 (m, 1 H), 2.11–2.19 (m, 2 H), 2.52–2.60 (m, 1 H), 3.14–3.24 (m, 1 H), 4.38 (s, 1 H), 7.30–7.34 (m, 3 H), 7.42–7.47 (m, 2 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 14.5, 22.5, 36.9, 41.1, 43.3, 74.4, 87.3, 88.4, 122.2, 128.5, 128.9, 131.9, 209.6 ppm. HRMS: calcd. for $C_{15}H_{16}O_2$ 228.1150, found 228.1150. **9b:** ^1H NMR (500 MHz, $CDCl_3$): δ = 1.39 (d, J = 7.4 Hz, 3 H), 1.73–1.76 (m, 1 H), 1.83–1.98 (m, 3 H), 2.05–2.10 (m, 1 H), 2.37–2.40 (m, 1 H), 2.94–2.99 (m, 1 H), 3.94 (s, 1 H), 7.28–7.32 (m, 3 H), 7.38–7.44 (m, 2 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 18.6, 19.3, 34.1, 41.7, 43.0, 76.1, 87.6, 88.8, 122.6, 128.9, 129.4, 132.1, 210.1 ppm. HRMS: calcd. for $C_{15}H_{16}O_2$ 228.1150, found 228.1142. **10a:** ^1H NMR (500 MHz, $CDCl_3$): δ = 0.91 (d, J = 7.2 Hz, 3 H), 1.82–1.99 (m, 3 H), 2.44–2.56 (m, 2 H), 2.71–2.76 (m, 1 H), 3.00–3.08 (m, 1 H), 4.18 (s, 1 H), 7.30–7.34 (m, 3 H), 7.44–7.46 (m, 2 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 12.3, 22.2, 29.1, 37.1, 44.0, 76.6, 86.9, 89.0, 122.2, 128.4, 128.9, 131.9, 208.3 ppm. HRMS: calcd. for $C_{15}H_{16}O_2$ 228.1150, found 228.1139. **10b:** ^1H NMR (250 MHz, $CDCl_3$): δ = 1.28 (d, J = 6.0 Hz, 3 H), 1.63–2.10 (m, 5 H), 2.48–2.56 (m, 1 H), 2.97–3.07 (m, 1 H), 4.30 (s, 1 H), 7.31–7.34 (m, 3 H), 7.44–7.47 (m, 2 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 16.0, 26.2, 31.0, 36.8, 46.9, 78.2, 85.7, 88.5, 122.2, 128.5, 128.9, 131.9, 207.8 ppm. LRMS (EI): m/z (%) = 228 (82) $[M]^+$, 199 (69), 157 (50), 129 (100). HRMS: calcd. for $C_{15}H_{16}O_2$ 228.1150, found 228.1148.

Representative Procedure for 3(2*H*)-Furanone Formation Catalyzed by $AuCl_3$ (Method A). 2-Phenyl-1-oxaspiro[4.4]non-2-en-4-one (2a): A solution of $AuCl_3$ (5 mol-%, 7.0 mg) in MeCN (0.5 mL) was added to a solution of **1a** (100 mg, 0.46 mmol) in CH_2Cl_2 (16 mL), and the reaction vial was sealed. The resulting solution was stirred at room temperature for 90 min (until TLC analysis indicated complete consumption of the starting material). The solvent was re-

moved under reduced pressure. Purification of the residue by flash chromatography on silica gel (P/EtOAc, 85:15) gave furanone **2a** as a colorless solid (82 mg, 0.38 mmol, 83% yield); R_f = 0.42 (P/EtOAc, 80:20). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.95–2.10 (m, 8 H), 6.01 (s, 1 H) 7.50 (tt, J = 7.0, 1.5 Hz, 2 H), 7.57 (tt, J = 7.0, 1.5 Hz, 1 H), 7.84 (dt, J = 7.0, 1.5 Hz, 2 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 25.7 (t), 37.2 (t), 98.9 (s), 99.9 (d), 127.1 (d), 128.8 (d), 129.4 (s), 132.5 (d), 183.7 (s), 206.1 (s) ppm. LRMS (EI): *m*/*z* (%) = 214 (42) $[M]^+$, 173 (90), 102 (100), 77 (12). HRMS: calcd. for $C_{14}H_{14}O_2$ 214.0994, found 214.0991.

Representative Procedure for 3(2*H*)-Furanone Formation Catalyzed by $PtCl_2$ (Method B). 2-Phenyl-1-oxaspiro[4.4]non-2-en-4-one (2a): $PtCl_2$ (5 mol-%, 6.3 mg) was added to a solution of **1a** (100 mg, 0.46 mmol) in toluene (16 mL), and the reaction vial was sealed. The resulting pale yellow solution was stirred at 80 °C for 90 min (until TLC analysis indicated complete conversion). The mixture was concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (P/EtOAc, 85:15) gave furanone **2a** as a colorless solid (93 mg, 0.43 mmol, 93% yield).

Representative Procedure for 3(2*H*)-Furanone Formation Catalyzed by $AuCl_3$ with "wet" CH_2Cl_2 and Trimethylsilyl Ethers 14 (Method C). 2-Phenyl-1-oxaspiro[4.4]non-2-en-4-one (2a): A solution of $AuCl_3$ (5 mol-%, 13.0 mg) in MeCN (0.5 mL) was added to a solution of trimethylsilyl ether **14a** (150 mg, 0.52 mmol) in undistilled CH_2Cl_2 (30 mL), and the flask was protected from light. The resulting solution was stirred in an open flask at room temperature for 120 min. The solvent was removed under reduced pressure. Purification of the residue by flash chromatography on silica gel (P/EtOAc, 85:15) gave furanone **2a** as a colorless solid (103 mg, 0.48 mmol, 93% yield).

2-(4-Fluorophenyl)-1-oxaspiro[4.4]non-2-en-4-one (2b): Method A: 70% yield, Method B: 90% yield. ^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.86–2.02 (m, 6 H), 2.05–2.16 (m, 2 H), 5.95 (s, 1 H), 7.16 (t, J = 8.5 Hz, 2 H), 7.76–7.87 (m, 2 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 25.8, 37.3, 99.2, 99.8, 116.2 (d, J = 22 Hz), 125.8 (d, J = 22 Hz), 129.5 (d, J = 9 Hz), 165.4 (d, J = 255 Hz), 182.6, 205.9 ppm. LRMS (EI): *m*/*z* (%) = 232 (48) $[M]^+$, 191 (100), 120 (95). HRMS: calcd. for $C_{14}H_{13}FO_2$ 232.0900, found 232.0898.

2-(2-Methoxyphenyl)-1-oxaspiro[4.4]non-2-en-4-one (2c): Method A: 81% yield, Method B: 91% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.86–2.11 (m, 8 H), 3.93 (s, 3 H), 6.35 (s, 1 H), 6.97–7.09 (m, 2 H), 7.45–7.55 (m, 1 H), 7.92 (dd, J = 7.8 Hz, J = 1.7 Hz, 1 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 25.9, 37.3, 55.7, 96.4, 105.1, 111.5, 118.3, 120.7, 128.4, 133.8, 159.3, 179.8, 207.8 ppm. LRMS (EI): *m*/*z* (%) = 244 (40) $[M]^+$, 203 (100), 132 (59). HRMS: calcd. for $C_{15}H_{16}O_3$ 244.1099, found 244.1101.

2-(4-*tert*-Butylphenyl)-1-oxaspiro[4.4]non-2-en-4-one (2d): Method A: 75% yield, Method B: 87% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.33 (s, 9 H), 1.92–2.09 (m, 8 H), 5.96 (s, 1 H), 7.61 (dd, J = 6.4 Hz, J = 8.6 Hz, 4 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 25.8, 31.2, 35.2, 37.3, 98.9, 99.4, 125.9, 126.6, 127.1, 156.5, 183.9, 206.1 ppm. LRMS (EI): *m*/*z* (%) = 270.1 (28) $[M]^+$, 229.1 (100), 143.2 (35). HRMS: calcd. for $C_{18}H_{22}O_2$ 270.1620, found 270.1618.

2-(Thiophen-3-yl)-1-oxaspiro[4.4]non-2-en-4-one (2e): Method A: 76% yield, Method B: 65% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.86–2.09 (m, 8 H), 5.81 (s, 1 H), 7.37–7.44 (m, 2 H), 7.96 (dd, J = 2.5 Hz, J = 1.7 Hz, 1 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 25.8, 37.3, 98.8, 99.8, 126.2, 127.2, 128.6, 132.1, 179.1, 206.0 ppm. LRMS (EI): *m*/*z* (%) = 220 (55) $[M]^+$, 179 (99), 108 (100). HRMS: calcd. for $C_{12}H_{12}O_2S$ 220.0558, found 220.0560.

2-Pentyl-1-oxaspiro[4.4]non-2-en-4-one (2f): Method A: 66% yield, Method B: 65% yield, Method C: 76% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.90 (t, J = 6.8 Hz, 3 H), 1.28–1.41 (m, 4 H), 1.57–1.70 (m, 2 H), 1.76–2.03 (m, 8 H), 2.46 (t, J = 7.6 Hz, 2 H), 5.39 (s, 1 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 14.0, 22.4, 25.7, 25.9, 31.0, 31.4, 37.0, 98.6, 102.4, 192.5, 206.8 ppm. LRMS (EI): *m*/*z* (%) = 208 (19) $[M]^+$, 167 (100), 124 (9), 96 (15). HRMS: calcd. for $C_{13}H_{20}O_2$ 208.1463, found 208.1465.

2-(Cyclohexylmethyl)-1-oxaspiro[4.4]non-2-en-4-one (2g): Method B: 75% yield. ^{1}H NMR (360 MHz, $CDCl_3$): δ = 0.95–1.05 (m, 2 H), 1.07–1.34 (m, 3 H), 1.67–2.04 (m, 14 H), 2.37 (d, J = 6.8 Hz, 2 H), 5.39 (s, 1 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 25.8, 26.2, 26.3, 33.2, 36.1, 37.1, 38.8, 98.6, 103.4, 191.3, 206.7 ppm. LRMS (EI): *m*/*z* (%) = 234 (17) $[M]^+$, 193 (100), 179 (9), 124 (14). HRMS: calcd. for $C_{15}H_{22}O_2$ 234.1620, found 234.1620.

2-Cyclohexyl-1-oxaspiro[4.4]non-2-en-4-one (2h): Method A: 25% yield, Method B: 78% yield. ^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.18–1.46 (m, 2 H), 1.67–2.07 (m, 14 H), 2.35–2.47 (m, 1 H), 5.36 (s, 1 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 25.7, 25.8, 25.9, 30.0, 37.1, 39.8, 98.2, 100.6, 196.0, 206.9 ppm. LRMS (EI): *m*/*z* (%) = 220 (15) $[M]^+$, 179 (100). HRMS: calcd. for $C_{14}H_{20}O_2$ 220.1463, found 220.1466.

2-[3-(Tetrahydropyran-2-yloxy)propyl]-1-oxaspiro[4.4]non-2-en-4-one (2i): Method A: 11% yield, Method B: 82% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.51–1.59 (m, 4 H), 1.64–1.71 (m, 1 H), 1.74–2.01 (m, 11 H), 2.59 (t, J = 7.6 Hz, 2 H), 3.38–3.54 (m, 2 H), 3.75–3.88 (m, 2 H), 4.57 (t, J = 3.4 Hz, 1 H), 5.42 (s, 1 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 19.9, 25.7, 25.9, 26.6, 28.2, 31.0, 37.2, 62.7, 66.5, 98.9, 99.3, 102.8, 192.0, 206.9 ppm. LRMS (EI): *m*/*z* (%) = 280 (1) $[M]^+$, 152 (90), 137 (38), 85 (100). HRMS: calcd. for $C_{16}H_{24}O_4$ 280.1675, found 280.1676.

2-[3-(Tetrahydropyran-2-yloxy)methyl]-1-oxaspiro[4.4]non-2-en-4-one (2j): Method A: 33% yield, Method B: 70% yield, Method C: 82% yield. ^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.57–1.76 (m, 4 H), 1.77–1.93 (m, 8 H), 1.94–2.08 (m, 2 H), 3.51–3.59 (m, 1 H), 3.80–3.89 (m, 1 H), 4.32 (d, J = 16.1 Hz, 1 H), 4.50 (d, J = 16.1 Hz, 1 H), 4.72 (t, J = 3.2 Hz, 1 H), 5.65 (s, 1 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 19.0, 25.4, 25.7, 30.3, 37.1, 62.2, 63.3, 98.6, 99.2, 102.5, 188.4, 206.1 ppm. LRMS (EI): *m*/*z* (%) = 252 (2) $[M]^+$, 211 (23), 152 (78), 85 (100). HRMS: calcd. for $C_{14}H_{20}O_4$ 252.1362, found 252.1352.

2-(Cyclohex-1-enyl)-1-oxaspiro[4.4]non-2-en-4-one (2k): Method B: 68% yield. ^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.62–1.69 (m, 2 H), 1.70–1.78 (m, 2 H), 1.80–1.93 (m, 6 H), 1.95–2.05 (m, 2 H), 2.21–2.30 (m, 4 H), 5.49 (s, 1 H), 6.82–6.83 (m, 1 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 21.7, 22.1, 24.7, 25.8, 26.0, 37.2, 98.0, 99.3, 128.5, 135.6, 184.3, 206.6 ppm. LRMS (EI): *m*/*z* (%) = 218 (33) $[M]^+$, 177 (100), 106 (38), 91 (23). HRMS: calcd. for $C_{14}H_{18}O_2$ 218.1307, found 218.1306.

2-(Prop-2-enyl)-1-oxaspiro[4.4]non-2-en-4-one (2l): Method B: 40% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.80–1.98 (m, 8 H), 2.00 (s, 3 H), 5.40 (s, 1 H), 5.58 (s, 1 H), 5.93 (s, 1 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 19.0, 25.8, 37.2, 98.6, 101.5, 121.3, 134.0, 183.8, 207.0 ppm. LRMS (EI): *m*/*z* (%) = 178 (50) $[M]^+$, 137 (100), 66 (90). HRMS: calcd. for $C_{11}H_{14}O_2$ 178.0994, found 178.0993.

2-(Trimethylsilanyl)-1-oxaspiro[4.4]non-2-en-4-one (2m): Method B: 57% yield. ^{1}H NMR (360 MHz, $CDCl_3$): δ = 0.26 (s, 9 H), 1.72–1.80 (m, 2 H), 1.83–2.00 (m, 6 H), 5.76 (s, 1 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = –2.8, 26.1, 37.7, 97.2, 114.2, 201.1, 209.0 ppm. LRMS (EI): *m*/*z* (%) = 210 (25) $[M]^+$, 169 (100), 98 (23), 83 (34), 73 (42). HRMS: calcd. for $C_{11}H_{18}O_2Si$ 210.1076, found 210.1074.

5-Phenyl-2,2-dipropylfuran-3-one (2o): Method B: 51% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.87 (t, J = 7.3 Hz, 6 H), 1.28–1.41 (m, 4 H), 1.82 (dd, J = 9.0 Hz, J = 7.6 Hz, 4 H), 6.00 (s, 1 H), 7.45–7.59 (m, 3 H), 7.84 (dd, J = 8.1 Hz, J = 1.4 Hz, 2 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 14.3, 16.3, 38.7, 94.6, 101.4, 127.3, 129.0, 129.2, 132.7, 184.8, 206.9 ppm. LRMS (EI): m/z (%) = 244 (2) $[M]^+$, 202 (100), 173 (82), 102 (64). HRMS: calcd. for $C_{16}H_{20}O_2$ 244.1463, found 244.1462.

2-Phenyl-1-oxaspiro[4.5]dec-2-en-4-one (2q): Method B: 85% yield. ^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.67–1.86 (m, 10 H), 5.98 (s, 1 H), 7.46–7.58 (m, 3 H), 7.84–7.88 (m, 2 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 22.1, 24.7, 32.1, 90.9, 99.4, 127.3, 129.0, 129.6, 132.6, 183.6, 207.0 ppm. LRMS (EI): m/z (%) = 228 (39) $[M]^+$, 173 (100), 102 (71). HRMS: calcd. for $C_{15}H_{16}O_2$ 228.1150, found 228.1151.

2-Phenyl-1-oxaspiro[4.6]undec-2-en-4-one (2r): Method B: 50% yield. ^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.68–2.00 (m, 12 H), 5.91 (s, 1 H), 7.45–7.57 (m, 3 H), 7.81–7.86 (m, 2 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 22.8, 29.3, 35.6, 93.7, 98.7, 127.2, 128.9, 129.6, 132.6, 183.4, 208.2 ppm. LRMS (EI): m/z (%) = 242 (49) $[M]^+$, 173 (100), 102 (71). HRMS: calcd. for $C_{16}H_{18}O_2$ 242.1307, found 242.1306.

2,2,5-Triphenylfuran-3-one (2s): Method B: 56% yield. ^{1}H NMR (360 MHz, $CDCl_3$): δ = 6.12 (s, 1 H), 7.31–7.40 (m, 6 H), 7.51–7.60 (m, 7 H), 7.98 (d, J = 7.0 Hz, 2 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 93.1, 99.9, 126.8, 127.4, 128.6, 128.6, 128.9, 129.1, 133.1, 138.5, 184.3, 202.2 ppm. LRMS (EI): m/z (%) = 312 (65) $[M]^+$, 165 (64), 105 (100), 77 (29). HRMS: calcd. for $C_{22}H_{16}O_2$ 312.1150, found 312.1148.

Attempted Synthesis of Bullatenone (2n): According to Method A, a solution of 3-hydroxy-3-methyl-5-phenylpent-4-yn-2-one (**1n**, 100 mg, 0.53 mmol) in CH_2Cl_2 (17 mL) was treated with $AuCl_3$ (5 mol-%, 7.2 mg) at 23 °C for 4 h. Purification of the crude product by repeated flash chromatography on silica gel (P/EtOAc, 80:20) provided bullatenone (**2n**), 3-methylene-1-phenylpentane-1,4-dione (**11**), and (*E*)-3-methyl-1-phenylpent-2-ene-1,4-dione (**12**). **Bullatenone (2n):**[48] 7% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.49 (s, 6 H), 5.96 (s, 1 H), 7.43–7.55 (m, 3 H), 7.80–7.84 (m, 2 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ =23.1, 88.8, 98.4, 127.1, 128.8, 129.0, 132.6, 183.5, 207.1 ppm. **3-Methylene-1-phenylpentane-1,4-dione (11):** 32% yield. ^{1}H NMR (360 MHz, $CDCl_3$): δ = 2.42 (s, 3 H), 3.96 (s, 3 H), 5.94 (s, 1 H), 6.24 (s, 1 H), 7.46 (t, J = 7.9 Hz, 2 H), 7.56 (t, J = 7.3 Hz, 1 H), 7.97 (d, J = 7.8 Hz, 2 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ =25.7 (CH_3), 41.1 (CH_2), 128.5 (CH_2), 128.7 (CH), 129.0 (CH), 133.6 (CH), 137.0 (C), 143.8 (C), 197.5 (C), 199.1 (C) ppm. **(*E*)-3-Methyl-1-phenylpent-2-ene-1,4-dione (12):** 28% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.09 (s, 3 H), 2.48 (s, 3 H), 7.44 (s, 1 H), 7.48–7.62 (m, 3 H), 7.93–7.56 (m, 2 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 14.3 (CH_2), 26.6 (CH_2), 129.0 (CH), 129.3 (CH), 131.9 (CH), 134.1 (CH), 137.7 (C), 147.4 (C), 193.5 (C), 200.3 (C) ppm. HRMS: calcd. for $C_{12}H_{12}O_2$ 188.0837, found 188.0839. The double-bond geometry was determined by NOESY experiments.

Synthesis of 6-Methyl-2-phenyl-1-oxaspiro[4.4]non-2-en-4-one (13): According to Method B, a solution of **9a** (dr > 95:5, 60 mg, 0.26 mmol) in toluene (9 mL) was treated with $PtCl_2$ (5 mol-%, 3.8 mg) at 80 °C for 4 h. ^{1}H NMR analysis of the crude reaction mixture indicated a **13a/13b** ratio of >95:5. Purification of the crude product by flash chromatography on silica gel (P/EtOAc, 85:15) provided **13a** in 74% yield (44 mg, 0.19 mmol). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.00 (d, J = 7.11 Hz, 3 H), 1.61–1.75 (m, 1 H), 1.85–2.24 (m, 5 H), 2.37–2.52 (m, 1 H), 5.93 (s, 1 H), 7.44–7.58 (m, 3 H), 7.82 (td, J = 7.1 Hz, J = 1.5 Hz, 2 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 14.6, 23.2, 33.7, 35.8, 44.3, 99.8, 100.7, 127.4, 129.2, 129.6, 132.7, 184.4, 206.4 ppm. LRMS (EI): m/z (%) = 228 (18) $[M]^+$, 187 (44), 173 (60), 102 (100). HRMS: calcd. for $C_{15}H_{16}O_2$ 228.1150, found 228.1153. According to Method B, a solution of **10a** (*dr* 80:20, 54 mg, 0.24 mmol) in toluene (8 mL) was treated with $PtCl_2$ (5 mol-%, 3.2 mg) at 80 °C for 5 h. ^{1}H NMR analysis of the crude reaction mixture indicated a **13a/13b** ratio of 80:20. Purification of the crude product by flash chromatography on silica gel (P/EtOAc, 85:15) provided **13a** in 88% yield (48 mg, 0.21 mmol). According to Method B, a solution of **9b** (dr > 95:5, 89 mg, 0.39 mmol) in toluene (13 mL) was treated with $PtCl_2$ (5 mol-%, 5.0 mg) at 80 °C for 4 h. ^{1}H NMR analysis of the crude reaction mixture indicated a **13b/13a** ratio of >95:5. Purification of the crude product by flash chromatography on silica gel (P/EtOAc, 85:15) provided **13b** in 76% yield (68 mg, 0.30 mmol). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 0.87 (d, J = 6.8 Hz, 3 H), 1.60–1.71 (m, 1 H), 1.80–2.09 (m, 4 H), 2.17–2.26 (m, 1 H), 2.29–2.40 (m, 1 H), 6.04 (s, 1 H), 7.46–7.57 (m, 3 H), 7.83 (dt, J = 1.6, 7.0 Hz, 2 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 11.9, 23.2, 33.6, 36.5, 4.7, 100.5, 101.3, 127.2, 129.0, 129.3, 132.6, 184.3, 205.8 ppm. LRMS (EI): m/z (%) = 228 (20) $[M]^+$, 187 (38), 173 (65), 102 (100). HRMS: calcd. for $C_{15}H_{16}O_2$ 228.1150, found 228.1144. According to Method B, a solution of **10b** (*dr* 75:25, 41 mg, 0.18 mmol) in toluene (6 mL) was treated with $PtCl_2$ (5 mol-%, 2.4 mg) at 80 °C for 6 h. ^{1}H NMR analysis of the crude reaction mixture indicated a **13b/13a** ratio of 75:25. Purification of the crude product by flash chromatography on silica gel (P/EtOAc, 85:15) provided **13b** in 85% yield (35 mg, 0.15 mmol).

Representative Procedure for 3-Pyrrolone Formation Catalyzed by $PtCl_2$ (Method D). 1,2-Diphenyl-1-azaspiro[4.4]non-2-en-4-one (3aa): $PtCl_2$ (5 mol-%, 3.2 mg) was added to a solution of **1a** (50 mg, 0.23 mmol) and aniline (27.8 mg, 0.30 mmol) in toluene (8 mL), and the reaction vial was sealed, protected from light, and stirred at room temperature for 30 min. The reaction mixture was then heated to 100 °C and stirred at 100 °C for 24 h. The mixture was concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (P/EtOAc, 70:30) gave 3-pyrrolone **3aa** as a colorless solid (49.9 mg, 0.17 mmol, 75% yield). R_f = 0.65 (P/EtOAc, 70:30). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.50–1.61 (m, 2 H), 1.81–1.92 (m, 2 H), 2.00–2.23 (m, 4 H), 5.57 (s, 1 H), 7.03–7.07 (m, 2 H), 7.24–7.33 (m, 3 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 26.5, 36.5, 80.9, 101.0, 127.2, 128.4, 128.9, 129.2, 129.3, 130.3, 131.7, 140.3, 175.1, 205.8 ppm. LRMS (EI): m/z (%) = 289 (30) $[M]^+$, 248 (100), 130 (29), 77 (21). HRMS: calcd. for $C_{20}H_{19}NO$ 289.1467, found 289.1466.

1-(3-Nitrophenyl)-2-phenyl-1-azaspiro[4.4]non-2-en-4-one (3ab): Method D: 35% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.53–1.59 (m, 2 H), 1.86–2.03 (m, 4 H), 2.11–2.23 (m, 2 H), 5.64 (s, 1 H), 7.22–7.40 (m, 7 H), 7.89–7.91 (m, 1 H), 8.02–8.06 (m, 1 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 26.5, 36.6, 80.9, 103.3, 121.6, 123.1, 128.7, 128.9, 130.0, 130.9, 130.9, 134.7, 142.0, 148.6, 174.6, 205.5 ppm. LRMS (EI): /z (%) = 334 (25) $[M]^+$, 293 (100), 175 (22), 84 (72). HRMS: calcd. for $C_{20}H_{18}N_2O_3$ 334.1317, found 334.1317.

1-Benzyl-2-phenyl-1-azaspiro[4.4]non-2-en-4-one (3ac): Method D: 37% yield. ^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.59–1.68 (m, 2 H), 1.83–1.92 (m, 4 H), 2.04–2.09 (m, 2 H), 4.62 (s, 2 H), 5.23 (s, 1 H), 7.13–7.17 (m, 2 H), 7.20–7.28 (m, 3 H), 7.32–7.41 (m, 5 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 26.4, 35.8, 47.3, 79.1, 98.7, 126.5, 127.5, 127.7, 128.7, 128.8, 130.3, 131.8, 138.7, 176.8, 205.1 ppm. LRMS (EI): m/z (%) = 303 (39) $[M]^+$, 262 (34), 212 (100), 91 (45). HRMS: calcd. for $C_{21}H_{21}NO$ 303.1623, found 303.1624.

1-Isobutyl-2-phenyl-1-azaspiro[4.4]non-2-en-4-one (3ad): Method D: 33% yield. ^{1}H NMR (360 MHz, $CDCl_3$): δ = 0.73 (d, J = 6.6 Hz, 6 H), 1.58–1.70 (m, 1 H), 1.78–1.86 (m, 2 H), 1.88–1.95 (m, 2 H), 1.97–2.13 (m, 4 H), 3.15 (d, J = 8.0 Hz, 2 H), 5.06 (s, 1 H), 7.34–7.37 (m, 2 H), 7.43–7.45 (m, 3 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 20.3, 26.7, 28.0, 35.5, 51.3, 78.9, 98.4, 127.6, 128.7, 129.9, 132.8, 176.5, 205.1 ppm. LRMS (EI): *m*/*z* (%) = 269 (25) $[M]^+$, 226 (100). HRMS: calcd. for $C_{18}H_{23}NO$ 269.1780, found 269.17780.

1-Isopropyl-2-phenyl-1-azaspiro[4.4]non-2-en-4-one (3ae): Method D: 81% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.13 (d, J = 7.0 Hz, 6 H), 1.81–2.11 (m, 8 H), 3.66–3.77(m, 1 H), 4.94 (s, 1 H), 7.33–7.45 (m, 5 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 24.2, 26.8, 35.2, 48.1, 79.5, 99.4, 128.0, 128.2, 129.5, 134.0, 176.5, 204.7 ppm. LRMS (EI): *m*/*z* (%) = 255 (60) $[M]^+$, 212 (100), 110 (33), 67 (34). HRMS: calcd. for $C_{17}H_{21}NO$ 255.1623, found 255.1623.

2-(4-*tert*-Butylphenyl)-1-phenyl-1-azaspiro[4.4]non-2-en-4-one (3da): Method D: 52% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.25 (s, 9 H), 1.45–1.51 (m, 2 H), 1.79–1.86 (m, 2 H), 2.00–2.13 (m, 4 H), 5.52 (s, 1 H), 7.01–7.05 (m, 2 H), 7.22–7.29 (m, 7 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 26.5, 31.2, 34.9, 36.5, 81.0, 100.6, 125.4, 127.2, 128.6, 128.7, 129.2, 129.3, 140.5, 153.9, 175.0, 205.7 ppm. LRMS (EI): *m*/*z* (%) = 345 (5) $[M]^+$, 304 (18), 145 (21), 121 (100). HRMS: calcd. for $C_{24}H_{27}NO$ 345.2093, found 345.2095.

1-(3-Chlorophenyl)-2-(thiophen-3-yl)-1-azaspiro[4.4]non-2-en-4-one (3ef): Method D: 73% yield. ^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.40–1.45 (m, 2 H), 1.74–1.92 (m, 4 H), 2.01–2.09 (m, 2 H), 5.50 (s, 1 H), 6.84 (dd, J = 1.8, 4.5 Hz, 1 H), 6.90 (td, J = 1.6, 7.5 Hz, 1 H), 7.06 (t, J = 1.9 Hz, 1 H), 7.13–7.17 (m, 2 H), 7.19–7.24 (m, 2 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 26.4, 36.4, 80.7, 100.2, 126.3, 127.6, 127.7, 128.0, 128.8, 129.4, 130.3, 132.1, 135.0, 141.7, 168.4, 205.2 ppm. LRMS (EI): *m*/*z* (%) = 329 (32) $[M]^+$, 290 (37), 288 (100), 164 (24). HRMS: calcd. for $C_{18}H_{16}ClNO$ 329.0641, found 329.0581.

1-(4-Isopropylphenyl)-2-(thiophen-3-yl)-1-azaspiro[4.4]non-2-en-4-one (3eg): Method D: 78% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.25 (d, J = 6.9 Hz, 3 H), 1.40–1.33 (m, 2 H), 1.77–1.83 (m, 2 H), 1.94–2.17 (m, 4 H), 2.86–2.98 (m, 1 H), 5.52 (s, 1 H), 6.91 (dd, J = 1.4, 5.0 Hz, 1 H), 7.00–7.04 (m, 2 H), 7.11–7.20 (m, 4 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 24.0, 26.3, 33.8, 36.3, 80.7, 98.6, 125.7, 127.4, 128.0, 128.7, 129.5, 132.4, 137.6, 148.9, 168.5, 205.3 ppm. LRMS (EI): *m*/*z* (%) = 337 (30) $[M]^+$, 296 (100), 186 (18). HRMS: calcd. for $C_{21}H_{23}NOS$ 337.1500, found 337.1507.

1-(4-Methoxyphenyl)-2-pentyl-1-azaspiro[4.4]non-2-en-4-one (3fh): Method D: 73% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.82 (t, J = 6.5 Hz, 6 H), 1.18–1.33 (m, 6 H), 1.43–1.55 (m, 2 H), 1.71–1.92 (m, 4 H), 1.98–2.06 (m, 4 H), 2.14 (t, J = 7.7 Hz, 2 H), 3.84 (s, 3 H), 5.11 (s, 1 H), 6.90–6.94 (m, 2 H), 7.05–7.08 (m, 2 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.0, 22.4, 26.0, 26.9, 29.1, 31.5, 35.9, 55.6, 79.9, 96.1, 114.7, 130.6, 131.3, 159.5, 179.0, 204.7 ppm. LRMS (EI): *m*/*z* (%) = 313 (34) $[M]^+$, 272 (100), 257 (29), 229 (22). HRMS: calcd. for $C_{20}H_{27}NO_2$ 313.2042, found 313.2039.

1-Phenyl-2-[(tetrahydropyran-2-yloxy)methyl]-1-azaspiro[4.4]non-2-en-4-one (3ja): Method D: 44% yield. ^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.28–1.33 (m, 2 H), 1.45–1.68 (m, 4 H), 1.76 (br. s, 4 H), 1.88–1.96 (m, 2 H), 2.03–2.07 (m, 2 H), 3.42–3.48 (m, 1 H), 3.62–3.67 (m, 1 H), 4.02 (d, J = 15.2 Hz, 1 H), 4.31 (d, J = 15.2 Hz, 1 H), 4.55 (t, J = 3.1 Hz, 1 H), 5.40 (s, 1 H), 7.17–7.19 (m, 2 H), 7.39–7.44 (m, 3 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 18.7, 25.4, 26.0, 30.2, 35.9, 61.8, 62.5, 80.4, 96.8, 98.3, 128.8, 129.7, 129.8, 137.9, 174.8, 205.1 ppm. LRMS (EI): *m*/*z* (%) = 327 (18) $[M]^+$, 242 (54), 227 (58), 198 (100). HRMS: calcd. for $C_{20}H_{25}NO_3$ 327.1834, found 327.1832.

Supporting Information (see also the footnote on the first page of this article): ^{1}H NMR spectra of **2a**–**s**, **13a**–**b**, and **13aa**–**13ja**, and copies of ^{13}C NMR spectra of **2a**–**s**, **13a**–**b**, and **3aa**–**3ja**.

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