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Pt-catalyzed cyclization/migration of propargylic alcohols for the synthesis of 3(2*H*)-furanones, pyrrolones, indolizines, and indolizinones

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Abstract

Several heterocycles such as furanones, pyrrolones, and indolizines, which are of pharmacological importance, are easily accessed via the Pt(II)-catalyzed heterocyclization/1,2-migration of propargylic ketols or hydroxy imine derivatives. This method sidesteps the challenges of traditional heteroaromatic oxygenation strategies such as regioselectivity and functional group tolerance in the syntheses of these heterocycles.
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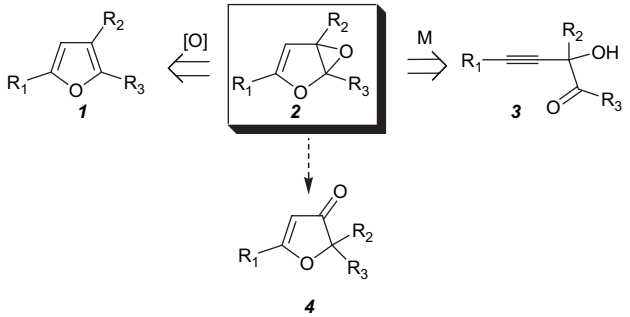
1. Introduction

The development of efficient and versatile strategies for the synthesis of heterocycles continues to be of significance in synthetic organic chemistry. The 3(2*H*)-furanones are a class of important heterocycles that are found in a variety of biologically active natural products such as the eremantholides[1] and jatrophone[2] as well as several medicinally active agents.[3] Various methods have been developed for the synthesis of these heterocycles, including the conversion of 3-alkoxy-furans to 2-alkoxy furanones[4] and the reaction of 3-silyloxyfurans with electrophiles[5] such as aldehydes. Most of the current approaches to furanones remain rather specialized or demand considerable investment in the preparation of the requisite precursor substrates.

For example, we have considered a route to 3(2*H*)-furanones via the oxygenation/rearrangement of furans (e.g., **1**, Scheme 1), which may proceed via the intermediacy of epoxide **2**. However, this approach possesses several distinct challenges such as (A) the difficulty of synthesis of the requisite furan (i.e., **1**), (B) the inherent instability of the furan and other functional groups (e.g., sulfides, aldehydes, etc.) to the oxygenation (epoxidation) conditions, and (C) the regioselectivity of the initial epoxidation.



Scheme 1. Proposed access to 3(2*H*)-furanones.

As a result of these challenges, we were encouraged to pursue alternate strategies that would provide ready access to **2** (or an equivalent) in one or two steps en route to an expedient synthesis of 3(2*H*)-furanones (i.e., **4**). In this article, we present our efforts that have led to the realization of 3(2*H*)-furanone compounds in short order.[6] An extension of this transformation to the expedient synthesis of other heterocycles such as pyrrolones, indolizines, and indolizidinones using nitrogen nucleophiles was subsequently developed and communicated by us.[7] A comprehensive account of these studies is presented herein.

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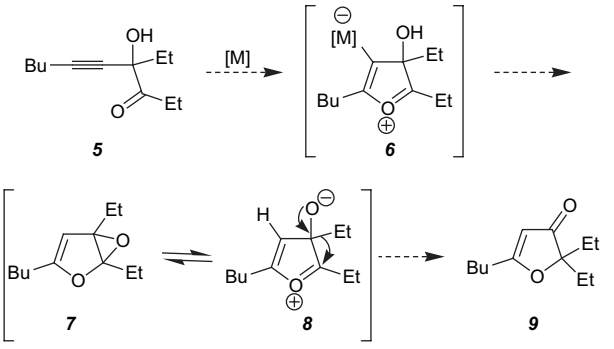
2. Results and discussion

As illustrated in Scheme 1, it was envisaged that intermediates such as **2** could be readily accessed from propargylic alcohols (e.g., **3**) via a carbophilic Lewis acid-mediated cyclization followed by proton transfer. The viability of this transformation is supported by several related literature reports using Ag(I) by Marshall,[8] and Au(III) by Liu,[9] Larock,[10] and Hashmi[11] among others. In turn, rearrangement of **2** could yield 3(2*H*)-furanone **4**. Investigations of this transformation began with alkynyl ketone **5** (Scheme 2), which was available in one-step from 3,4-hexanedione using the method of Chisholm.[12] Our past success using $PtCl_2$ as a carbophilic Lewis acid to mediate transformations involving alkynes[13] made it a starting point of our investigations.

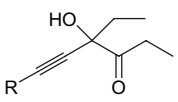
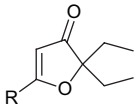
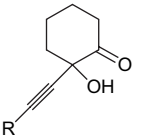
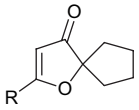
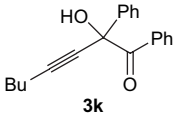
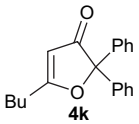
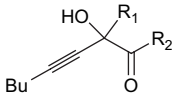
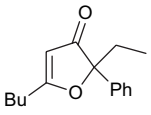


Scheme 2. A proposed mechanism for the synthesis of 3(2*H*)-furanones.

Although various Lewis acids (e.g., $InCl_3$, $BF_3{\cdot}OEt_2$) and Brønsted acids such as HCl were also investigated for the conversion of **5** to 3(2*H*)-furanone **9**, in the end, $PtCl_2$ proved to be the ideal catalyst. This was due in part to the operational simplicity of using the air- and moisture-tolerant Pt(II) salts, as well as the consistency in yield and amenability to scale up when this catalyst was used. The reaction can be run at low catalyst loadings (2 mol % $PtCl_2$), although a longer period of time is required for the reaction to reach completion. However, the use of a 2 mol % $PtCl_2$ loading under an atmosphere of CO, following the precedent of Fürstner,[14] leads to comparable reaction rates as to when a 10 mol % loading is used. Furthermore, the reaction gave comparable yields in the presence of 1 equiv of H_2O.

As illustrated in Table 1, the reaction is general for a range of substrates. Significant variability can be achieved at the alkyne terminus as alkyl (**3a** and **3b**) and aryl substituents (**3c–f**) are well tolerated (entry 1). In addition, the formation of spiro-furanone products appears to be general if cyclic substrates are employed (**3g–j**, entry 2). The migrating group is not restricted to alkyl fragments as phenyl groups migrate just as readily (entry 3). Furthermore, a high level of versatility may be achieved in the furanone product by beginning with an appropriately functionalized propargylic alcohol (**3l** and **3m**, entry 4). Importantly, sensitive functional groups such as sulfides, which will not survive the oxidative transformation of furans to 3(2*H*)-furanones (i.e., **1**→**3**, Scheme 1), remain intact under the $PtCl_2$-catalyzed conditions (see **3j**, entry 2).

Table 1
$PtCl_2$-catalyzed formation of furanone products[a]

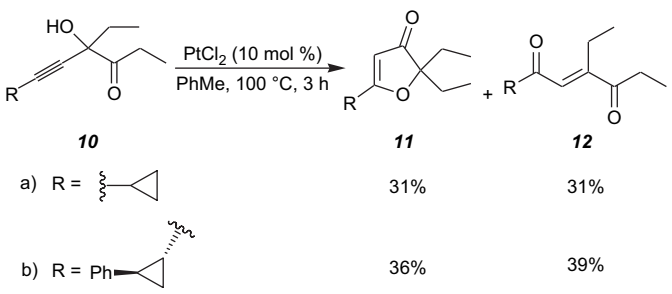
Entry	Substrate	Product	Yield (%)
1			
	3a (R=*n*-Bu)	**4a** (R=*n*-Bu)	65
	3b (R=*i*-Pr)	**4b** (R=*i*-Pr)	48
	3c (R=2-furyl)	**4c** (R=2-furyl)	38
	3d (R=Ph)	**4d** (R=Ph)	56
	3e (R=*p*-MeOPh)	**4e** (R=*p*-MeOPh)	65
	3f (R=*p*-NO_2Ph)	**4f** (R=*p*-NO_2Ph)	48
2			
	3g (R=*n*-Bu)	**4g** (R=*n*-Bu)	76
	3h (R=Ph)	**4h** (R=Ph)	66
	3i R = 	**4i** R = 	89
	3j (R=*p*-MeSPh)	**4j** (R=*p*-MeSPh)	76
3			77
	3k	**4k**	
4[b]			60
	3l (R_1, R_2=Et, Ph)	**4l**	
	3m (R_1, R_2=Ph, Et)		

[a] Reaction conditions: substrate (0.1 M of substrate), 5 mol % $PtCl_2$ in PhMe at 100 °C for 8 h.

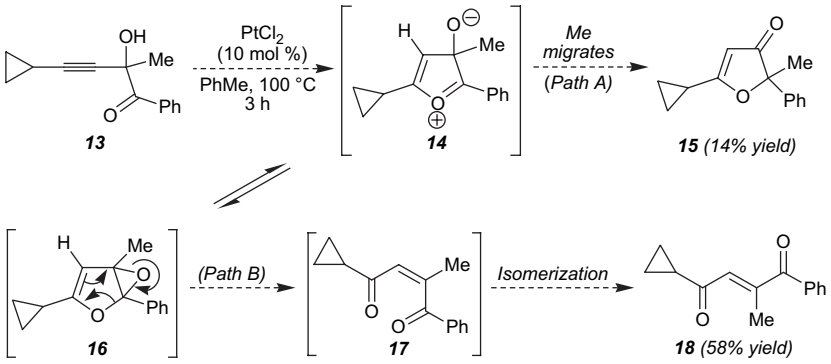
[b] An inseparable 1:2 mixture (as determined by ^{1}H NMR) of propargylic alcohols **3l** and **3m** was used for the formation of **4l**.

In a subset of the transformations of propargylic alcohols (see **10a** and **10b**, Scheme 3) studied to date, significant amounts of enedione products (**12a** and **12b**) were obtained in addition to the desired 3(2*H*)-furanone products.[15] This appears to correlate with an increase in the rate of other competing fragmentation processes relative to the migratory aptitude of the alkyl substituent alpha to the tertiary alcohol (e.g., the ethyl group, see **10**).

Insight into the mechanism for the formation of the enedione products was gained upon reaction of **13** (Scheme 4).



Scheme 3. Divergent reactivity in the $PtCl_2$-catalyzed transformation.



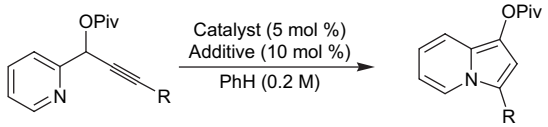
Scheme 4. A possible rationale for the formation of enediones.

Consistent with our initial proposal, whereas 3(2*H*)-furanone products such as **15** (14% yield) may arise via a concerted migration[16] involving the Me substituent (see **14**, Path A), competing epoxidation by collapse of the zwitterionic intermediate **14** may lead to epoxydihydrofuran **16**. In turn, **16** may be converted to the observed enedione products via epoxide opening and ring fragmentation (path B).[17,18] The major *E*-alkene diastereomer observed for the enedione product (**18**, 58% yield)[19] presumably arises via Pt(II)-catalyzed or thermal isomerization of **17** following ring opening under the reaction conditions.[20]

Subsequent to the studies on the formation of 3(2*H*)-furanones, we have discovered that these novel transformations of tertiary propargylic alcohols are not restricted to cyclizations involving oxygen nucleophiles (i.e., carbonyl groups), as nitrogen nucleophiles readily participate to provide important azaheterocycles. For example, indolizines (e.g., **21**, Scheme 5) and related derivatives, which have significant pharmacological potential,[21] may be realized if one begins with the pyridinyl propargylic alcohol **19**. Because of the importance of indolizines from a pharmacological standpoint, a variety of methods for their syntheses have emerged.[22] On the basis of our precedent for the formation of furanones, which was achieved prior to the initiation of our work with nitrogen nucleophiles, we reasoned that substrates such as **19** (Scheme 5), which possess a pyridine fragment, could participate in metal-catalyzed cycloisomerizations to access a range of nitrogen-containing heterocycles (e.g., indolizines related to **21**).

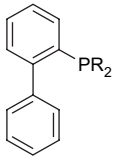
Optimization of the general transformation **19**→**21** was conducted with propargylic ester **22a** (Table 2) prepared from pyridine-2-carboxaldehyde by the addition of ethynyl Grignard reagent and subsequent acylation.[23] Initially, we found that both $PtCl_4$ (entry 1) and $PtCl_2$ (entry 2) at 5 mol % loading effected the transformation of **22a** (0.20 M in PhH, 70 °C) to the desired C-1 substituted indolizine **23a**

Table 2
Cycloisomerization of terminal alkyne propargylic ester substrates



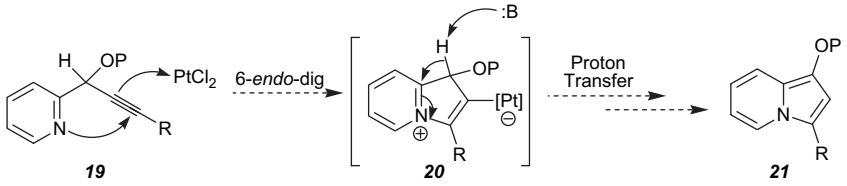
22a (R = H)
22b (R = Bu)

23a (R = H)
23b (R = Bu)

Entry	Substrate	Catalyst	Additive	Temp (°C)	Time (h)	Yield of **23** (%)
1	**22a**	$PtCl_4$	—	70	18	34
2	**22a**	$PtCl_2$	—	70	20	31
3	**22a**	$PtCl_2$	 R= *t*-Bu (***24***)	70	20	43
4	***22a***	***$PtCl_2$***	R= Cy (***25***)	***70***	***8***	***79***
5	**22b**	$PtCl_2$	—	70	10	81
6	***22b***	***$PtCl_2$***	***24***	***70***	***3***	***95***
7	**22b**	$PtCl_2$	***25***	70	9	95
8	**22b**	$PtCl_2$	—	40	36	No reaction
9	**22b**	$PtCl_2$	***24***	40	12	95
10	**22b**	$PtCl_2$	***25***	40	36	33
11	***22b***	***$InCl_3$***	—	***40***	***4***	***85***

under similar conditions.[24] Because $PtCl_2$ is less sensitive to moisture as compared to $PtCl_4$, we continued our studies with this salt, which greatly simplified the experimental setup.

Further optimization revealed that the introduction of bulky, electron-rich phosphine ligands such as 2-(di-*tert*-butylphosphino)biphenyl[25] (**24**, entry 3) or 2-(di-cyclohexylphosphino)biphenyl (**25**, entry 4) led to a pronounced increase in the yield of the indolizine product **23a**, with **25** proving to



Scheme 5. Proposed hetero-cycloisomerization.

be the best additive of those surveyed (79% yield). Phosphine ligands have been shown to facilitate Pt(II)-catalyzed reactions involving nitrogen nucleophiles in studies by Widenhoefer on the hydroamination of olefins.[26] In these studies, Widenhoefer reported that a 1:1 ratio of Pt(II) salt to exogenous phosphine (Pt/PR_3) was critical to success.[27] We reasoned that the use of bulky phosphines would favor the formation of a 1:1 Pt/PR_3 complex. It should be noted that in our studies, these ligands were consistently superior to PPh_3 for the formation of indolizines from the corresponding propargylic alcohols.

The reaction efficiency was substantially different when internal alkyne substrates (e.g., **22b**) were used (entries 5–11). Similarly in these cases, bulky phosphine additives led to higher yields of the indolizine products (i.e., **23b**, entries 6 and 7) as compared to the cases when phosphines were not added (entry 5) or when triphenylphosphine was used as the additive (not shown). For example at 40 °C, there was no reaction with $PtCl_2$ alone as catalyst (entry 8) whereas with **24** and **25** as additives (entries 9 and 10, respectively), product formation was observed, with **24** proving to be superior. Indium trichloride also catalyzes the indolizine-forming reaction (entry 11) but the scope was limited to internal alkyne substrates. We believe that the lack of success of $InCl_3$ in catalyzing the cycloisomerization of terminal alkyne substrates may be the result of the competing formation of indium acetylides under the reaction conditions, consistent with the observations of Shibasaki.[28]

As shown in Figure 1, a range of indolizines are obtained utilizing either Pt(II) (5 mol % of $PtCl_2$, 10 mol % of 2-(di-*tert*-butylphosphino)biphenyl (**24**), 0.2 M in PhH, 70 °C) or In(III) (5 mol % of $InCl_3$, 0.2 M in PhH, 70 °C). The pivalate protective group was found to give the highest yields (see **26**–**29**) compared to other acyl protecting groups (e.g., acetate and benzoate) for a range of alkyl-, cycloalkyl-, aryl-, and alkenyl-substituted indolizines. Silyl protective groups (e.g, TBS) may also be employed, but the products are generally isolated in lower yield (57% yield of **30**).[29] This is likely due to the relative instability of the corresponding silylated indolizines toward purification.

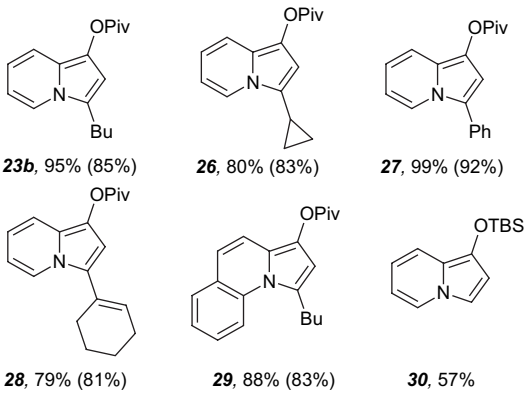
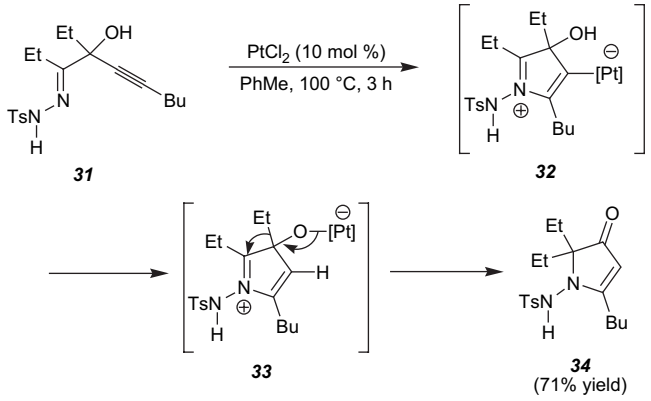


Figure 1. Pt(II)- and In(III)-catalyzed cycloisomerizations. Yields are indicated for reactions using $PtCl_2$ and $InCl_3$ (in parentheses). For a full description of reaction details, including the identity of propargylic ester substrates, see Supplementary data.

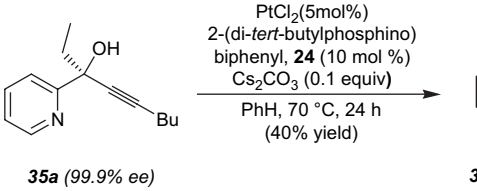
By direct analogy to our observations involving the furanone-forming reactions, we hypothesized that tertiary propargylic alcohol substrates such as **31** (Scheme 6) could provide a platform for heterocyclizations that involve a 1,2-shift.[30]



Scheme 6. Tandem cyclization/1,2-migration of **31**.

In a preliminary study, upon treatment of hydrazone **31** with $PtCl_2$ (10 mol %) for 3 h at 100 °C, pyrrolone **34** was formed in 71% yield. This transformation likely proceeds via zwitterion **32** and platina-alkoxide **33**, in an analogous fashion to the furanones.[31]

Despite our initial success in transforming **31** to pyrrolone **34**, the reaction conditions were ineffective at low catalyst loadings especially for substrates containing a pyridine fragment. Following a comprehensive study of various additives, solvents, and temperatures, optimized conditions (5 mol % $PtCl_2$, 10 mol % 2-(di-*tert*-butylphosphino)biphenyl, 0.1 equiv Cs_2CO_3, 100 °C), which were readily applicable to several tertiary propargylic alcohol substrates (**35a**–**e**, Table 3) were identified. This provided the corresponding indolizinones (**36a**–**e**) in modest to good yields. The addition of substoichiometric quantities of a base (Cs_2CO_3), which may facilitate proton transfer events prior to the 1,2-migration event, was found to be critical.[32] To probe the nature of the 1,2-migrations, enantioenriched **35a** (99.9% ee, Eq. 1) was subjected to the optimized reaction conditions and provided **36a** in 97% ee, which corroborated a highly stereoselective 1,2-migration.[33–35]

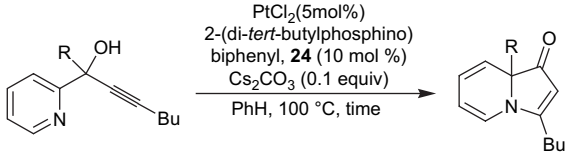


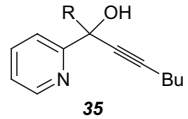
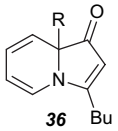
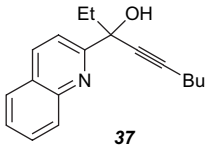
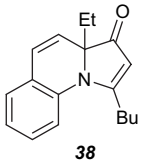
35a *(99.9% ee)* **36a** *(97% ee)* (1)

3. Conclusion

In conclusion, we report an expedient synthesis of 3(2*H*)-furanones from propargylic alcohols that may be accessed in one step from 1,2-diketones using an efficient Rh(I)-catalyzed alkyne addition developed in the laboratories of Chisholm. The reaction tolerates sensitive functional groups such as nitro groups and sulfides, which may be unstable or easily oxidized

Table 3
Pt-catalyzed formation of indolizinones



Entry	Substrate	Time (h)	Product	Yield (%)
1	 **35**		 **36**	
	(**a**) R=Et	48		66
	(**b**) R=Me	168		40
	(**c**) R=3,5-bis(MeO)Ph	120		66
	(**d**) R=Ph	48		70[a]
	(**e**) R=*c*-C_3H_5	144		44
2	 **37**	48	 **38**	36

[a] Cs_2CO_3 was not used as an additive.

(sulfides) under traditional protocols for the formation of these heterocycles from the oxygenation of furans or other related heteroaromatic compounds. The overall transformation is not restricted to the synthesis of 3(2*H*)-furanones as indolizines and indolizinones may also be formed using substrates bearing a nitrogen nucleophile. While $PtCl_2$ alone, as well as in the presence of phosphine additives, has been found to be generally effective, $InCl_3$ has also proven to be a highly competent catalyst for a subset of these transformations involving internal alkyne substrates. The work reported herein presents an observed significant effect of bulky electron-rich phosphines on the hetero-cycloisomerization transformations involving Pt(II) catalysis, which we anticipate will find wide applicability in other cycloisomerization reactions. This work has also described the competing formation of enedione byproducts in the Pt-catalyzed cycloisomerization of keto propargyl alcohols, and a tentative mechanism for the formation of these compounds is proposed. Further studies to probe the mechanisms of these transformations, broaden the scope to include other examples of chirality transfer, and identify conditions to shorten the reaction times are underway. Additionally, applications of these heterocycles in natural product synthesis are currently under investigation and will be reported in due course.

4. Experimental section

4.1. Materials and methods

All air or moisture sensitive reactions were conducted in flame-dried glassware under an atmosphere of nitrogen using dry, deoxygenated solvents. Toluene and benzene were distilled over calcium hydride. Platinum catalysts and phosphine ligands were purchased from Strem or Johnson Matthey. All other reagents were purchased from Aldrich, Acros, or Lancaster and used without further purification. Reaction temperatures were controlled by an IKAmag® or OptiChem® temperature modulator. Thin layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV and anisaldehyde stain. Fisher silica gel 240–400 mesh (particle size 0.032–0.063) was used for flash chromatography. Pt-catalyzed reactions were performed in Schlenk flasks unless otherwise noted. ^1H and ^{13}C NMR spectra were recorded on a Bruker AV-500 (at 500 MHz and 125 MHz, respectively), Bruker DRX-500 (at 500 MHz and 125 MHz, respectively) or on a Bruker AVB-400 (at 400 MHz and 100 MHz, respectively) in chloroform-*d* or benzene-d_6 at 23 °C, unless otherwise stated. Chemical shifts were referenced to the residual solvent peak, which was set at δ=7.26 for ^1H NMR and δ=77.0 for ^{13}C NMR, for $CDCl_3$; and δ=7.15 for ^1H NMR and δ=128.6 for ^{13}C NMR, for C_6D_6. Data for ^1H NMR are reported as follows: chemical shifts (δ ppm); multiplicity, (s=singlet, d=doublet, t=triplet, q=quartet, dd=doublet of doublet, dt=doublet of triplet, dq=doublet of quartet, qd=quartet of doublet, m=multiplet, br=broad resonance), coupling constants (Hz), and integration in parentheses. Data for ^{13}C NMR are reported in terms of chemical shift. IR spectra were recorded on a Nicolet MAGNA-IR 850 spectrometer and are reported in frequency of absorption (cm^{-1}). Low and high resolution mass spectral data were obtained from the University of California, Berkeley Mass Spectral Facility, on a VG 70-Se Micromass spectrometer for FAB, and a VG Prospec Micromass spectrometer for EI. Enantiomeric excess was determined by HPLC using a Shimatzu 10A VP series chiral HPLC. Optical rotation data was obtained using a Perkin–Elmer 241 Polarimeter with a 589 nm sodium lamp.

4.2. Representative procedure for the formation of furanones

4.2.1. 5-Butyl-2,2-diethylfuran-3(2H)-one (*4a*)

A 20 mL Schlenk tube equipped with a stir bar was charged with platinum(II) chloride (5 mg, 0.02 mmol, 0.1 equiv). To the tube was added a solution of **3a** (39 mg, 0.2 mmol) in toluene (2.0 mL). The Schlenk tube was sealed, and the reaction mixture was heated to 100 °C for 3 h, then cooled to 23 °C. Silica gel (250 mg) was added to the reaction mixture and the solvent was removed by rotary evaporation. The adsorbed product was purified by flash chromatography (20 mL silica gel, 8:1 hexanes/ethyl acetate), to yield 25 mg (65%) of a light yellow oil. ^1H NMR ($CDCl_3$, 500 MHz) δ 5.40 (s, 1H), 2.50 (t, *J*=7.0 Hz, 2H), 1.75 (qd, *J*=7.3, 1.2 Hz, 4H), 1.65 (dt, *J*=15.3, 7.6 Hz, 2H), 1.41 (sext., *J*=7.4 Hz, 2H), 0.94 (t, *J*=7.4 Hz, 3H), 0.78 (t, *J*=7.4 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 207.1, 193.5, 104.1, 94.4, 30.5, 28.8, 28.4, 22.3, 13.7, 7.2; IR (film) ν_{max} 2970, 2937, 1702, 1596, 1460 cm^{-1}; HRMS (EI^+) calcd for $[C_{12}H_{20}O_2]^+$: *m/z* 196.1463, found 196.1469.

4.3. Representative procedure for the formation of indolizines

4.3.1. 3-Butylindolizin-1-yl pivalate (**23b**)

Platinum(II) chloride (5 mg, 18 μmol) and 2-(di-*tert*-butylphosphino)biphenyl (11 mg, 36 μmol) were added to a solution of pivalate **22b** (100 mg, 0.36 mmol) in benzene (2 mL) in a 1-dram vial. The vial was sealed and heated at 70 °C for 3 h. The mixture was then filtered, concentrated by rotary evaporation, and purified by flash chromatography (4:1 hexanes/EtOAc) to yield 95 mg (95%) of **23b** as a yellow oil. ^{1}H NMR (500 MHz, C_6D_6) δ 7.30 (d, J=9.01 Hz, 1H), 7.04 (d, J=7.10 Hz, 1H), 6.76 (s, 1H), 6.32 (dd, J=8.99, 6.42 Hz, 1H), 6.06 (t, J=6.76 Hz, 1H), 2.26 (t, J=7.65 Hz, 2H), 1.40–1.32 (m, 2H), 1.27 (s, 9H), 1.18–1.10 (m, 2H), 0.74 (t, J=7.34 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 175.7, 127.1, 121.3, 120.9, 120.7, 116.1, 114.0, 109.6, 105.0, 38.9, 29.0, 27.0, 25.2, 22.4, 13.6; IR (film) ν_{max} 2958, 2931, 2871, 1749, 1278, 1120, 728 cm^{-1}; HRMS (EI) calcd for $[C_{17}H_{23}NO_2]^+$: m/z 273.1729, found 273.1732.

4.4. Representative procedure for the formation of indolizinones

4.4.1. (±)-3-Butyl-8a-ethylindolizin-1(8aH)-one (**36a**)

Platinum(II) chloride (3 mg, 12 μmol), 2-(di-*tert*-butylphosphino)biphenyl (7 mg, 23 μmol), and cesium carbonate (7 mg, 23 μmol) were added to a solution of (±)-**35a** (50 mg, 0.23 mmol) in benzene (1 mL) and the solution was heated at 100 °C in a sealed vial with stirring. Once the reaction was judged complete by TLC (48 h) the mixture was concentrated by rotary evaporation and the residue purified by flash chromatography (4:1 hexanes/EtOAc) to yield 33 mg (0.15 mmol, 66%) of **36a** as a yellow oil. ^{1}H NMR (500 MHz, C_6D_6) δ 5.95 (d, J=9.28 Hz, 1H), 5.84 (d, J=7.07 Hz, 1H), 5.61 (dd, J=9.26, 5.37 Hz, 1H), 4.99 (t, J=6.21 Hz, 1H), 4.82 (s, 1H), 1.92–1.82 (m, 1H), 1.80–1.64 (m, 3H), 1.16–1.04 (m, 2H), 1.03–0.93 (m, 2H), 0.80 (t, J=7.41 Hz, 3H), 0.65 (t, J=7.29 Hz, 2H); ^{13}C NMR (125 MHz, C_6D_6) δ 201.0, 175.0, 123.7, 122.2, 121.8, 108.1, 98.3, 70.3, 31.4, 28.4, 26.2, 22.1, 13.3, 6.5; IR (film) ν_{max} 2960, 2932, 2873, 1675, 1534, 1433, 725, 689 cm^{-1}; HRMS (EI) calcd for $[C_{14}H_{19}NO]^+$: m/z 217.1467, found 217.1467.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.02.103.

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