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Mechanistic Study of Indolizine Heterocycle Formation by Ruthenium(II)-Assisted Three-Component Cross-Coupling/Cyclization

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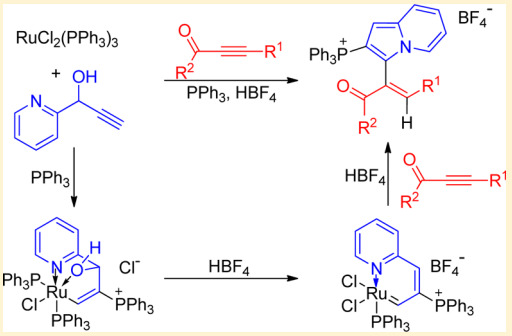
Supporting Information

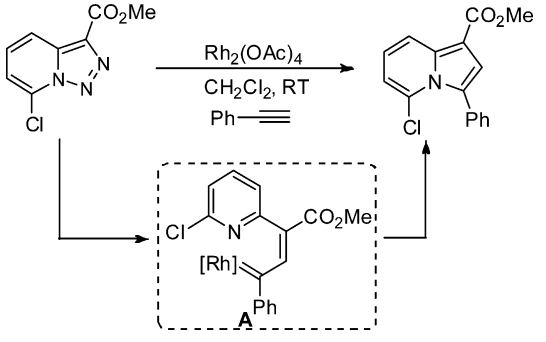
ABSTRACT: In the presence of the acid HBF_4, 3-alkenyl-2-phosphonium indolizines **3a–c** can be produced respectively by adding $PhC{\equiv}CCOCH_3$ (**2a**), $CH_3OCOC{\equiv}CCOOCH_3$ (**2b**), and $CH_3CH_2C{\equiv}CCOCH_3$ (**2c**) to a mixture of ruthenium complex $RuCl_2(PPh_3)_3$ and the propargyl alcohol (2-Py)CH(OH)C≡CH (**1**). We carefully investigated the mechanism of this reaction by means of structurally characterizing two key intermediates, ruthenium vinyl (**4**) and ruthenium carbene (**5**), and by deuterium-labeling experiments. A plausible mechanism is proposed, which involves addition of a proton to an alkyne carbon and the insertion of an alkyne into the Cα bond of an alkenylcarbene group, followed by an α-H elimination and reductive elimination.



INTRODUCTION

In recent years, the pharmacological potential of indolizines and related derivatives has become well recognized.[1] A number of biologically important natural products contain the indolizine framework.[2] As a result, a variety of methods for their synthesis have emerged.[1a,3] One of these strategies is the transition-metal-catalyzed cycloisomerization of easily available non-conjugated propargylpyridines or other organic molecules into indolizines.[4] Transition-metal-catalyzed cycloisomerizations typically proceed through metal–carbene intermediates.[5] For example, Gevorgyan and his co-workers reported the Rh-catalyzed transannulation of pyridotriazoles with alkynes to afford indolizines.[6] As shown in Scheme 1, the mechanism for the formation of indolizine was proposed, including one Rh-carbene intermediate, **A**.[6] To the best of our knowledge, this kind of metal-carbene intermediate has never been isolated.

Scheme 1. Proposed Rh-Carbene Intermediate in the Rh-Catalyzed Cycloisomerization



It is interesting that ruthenium-based catalysts are used extensively for promoting the synthesis of organic compounds; however, a ruthenium catalyst involved in the synthesis of indolizine is rare, and we are aware of just one example used in a catalyst screening.[6b] In the following we report a mechanistic study on the ruthenium-assisted formation of indolizines by a three-component cross-coupling/cyclization that, in the future, might assist in the development of ruthenium-catalyzed processes for the synthesis of the indolizine hetereocycle. The key feature of this mechanism proceeds through a thermally stable but reactive ruthenium carbene intermediate, which is similar to intermidiate **A** in Scheme 1.

RESULTS AND DISCUSSION

Efficient One-Pot Synthesis of 3-Alkenyl-2-phosphonium Indolizine Salts 3a–c. We found that $RuCl_2(PPh_3)_3$ can assist the synthesis of 3-alkenyl-substituted indolizines by coupling and cyclizing propargyl alcohols with alkynes. For example, in the presence of HBF_4, $RuCl_2(PPh_3)_3$ reacted with the easily accessible (2-Py)CH(OH)C≡CH (**1**) and commercially available alkyne $PhC{\equiv}CCOCH_3$ (**2a**), and the 3-alkenyl-2-phosphonium indolizines salt **3a** (R^1 = Ph, R^2 = CH_3) could be isolated, albeit in low yields of 10%, as shown in Scheme 2. The yield could be further improved to around 80% (NMR) if we first incubated $RuCl_2(PPh_3)_3$ together with **1**, PPh_3, and HBF_4 for 12 h before the addition of the alkyne **2a**. With different alkyne starting materials, two related indolizines, **3b** (R^1 = $COOCH_3$, R^2 = OCH_3) and **3c** (R^1 = CH_2CH_3, R^2 =

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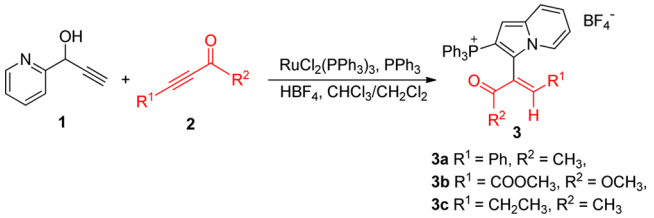
Scheme 2. Synthesis of Indolizine-2-phosphonium Salts 3a–c



CH_3), could be also synthesized in the same fashion. A crystal structure of **3a** is shown in Figure 1 and confirms the formation of indolizine **3a**, whereas the indolizines **3b** and **3c** were identified by NMR and HRMS.

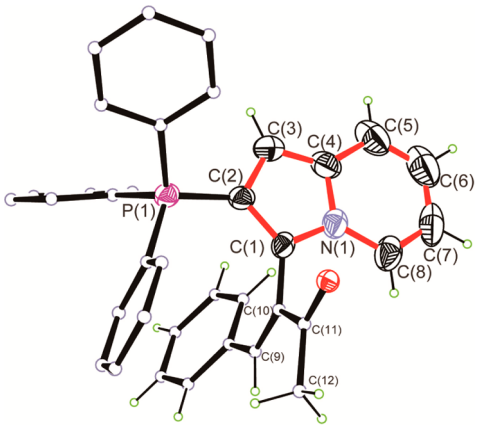
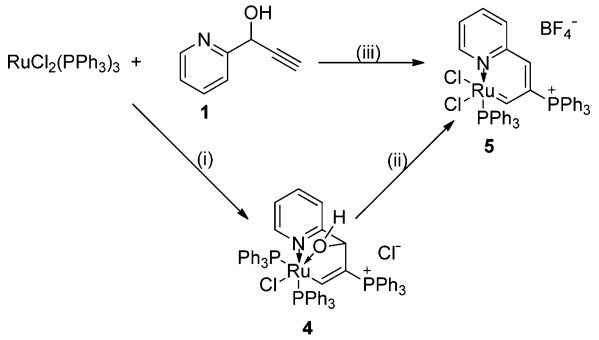


Figure 1. X-ray molecular structure for the cation of complex **3a** drawn with 50% probability. The hydrogen atoms in PPh_3 moieties are omitted for clarity. Selected bond lengths [Å] and angles [deg]: N(1)–C(1) 1.368(6), C(1)–C(2) 1.391(6), C(2)–C(3) 1.411(6), C(3)–C(4) 1.365(7), C(4)–C(5) 1.431(7), C(5)–C(6) 1.330(8), C(6)–C(7) 1.428(8), C(7)–C(8) 1.348(8), C(8)–N(1) 1.388(6), C(1)–C(10) 1.490(6), C(10)–C(9) 1.317(7), C(2)–P(1) 1.772(5); N(1)–C(1)–C(2) 105.8(4), C(1)–C(2)–C(3) 108.8(4), C(2)–C(3)–C(4) 107.9(4), C(3)–C(4)–N(1) 106.7(4), C(4)–N(1)–C(1) 110.8(4).

Identification of the Intermediate [Ru(CHC(PPh$_3$)C(OH)(2-Py))Cl(PPh$_3$)$_2$]Cl (4). In order to elucidate this $RuCl_2(PPh_3)_3$-assisted transformation, we attempted to isolate potential intermediates by reacting $RuCl_2(PPh_3)_3$ with **1** in CH_2Cl_2 for 7 h and obtained a yellow precipitate, which we referred to as complex **4** (Scheme 3).

X-ray crystallographic analysis of complex **4** revealed a ruthenium vinyl structure (Figure 2). The coordination geometry around the ruthenium atom can be rationalized as a distorted octahedron with one phosphorus atom of PPh_3 ligands and the nitrogen atom of the pyridine occupying trans positions (P(1)–Ru(1)–N(1) = 166.94(11)°), while one chloride atom and another PPh_3 ligand are cis to each other (Cl(3)–Ru(1)–P(2) = 82.26(10)°). The Ru(1)–C(1) bond length is 1.986(4) Å, and distance of C(1)=C(2) bonds in the metallacycle of **4** is 1.354(6) Å. These bond distances are similar to those of reported ruthenium vinyl complexes (1.984 and 1.346 Å).[7] The NMR spectra of **4** also exhibited the characteristic chemical shifts of a Ru-vinyl complex: a low-field resonance at 11.3 ppm in the ^{1}H NMR corresponds to a proton atom bound to ruthenium (Ru*CH*) due to the effect of the

Scheme 3. Trapping of Intermediates 4 and 5



(i) CH_2Cl_2, PPh_3, RT, 7 h, 75%
(ii) $CHCl_3$,NH_4Cl, HBF_4, RT, 6 h, 90%
(iii) $CHCl_3$, HBF_4, RT, 12 h, 80% (NMR)

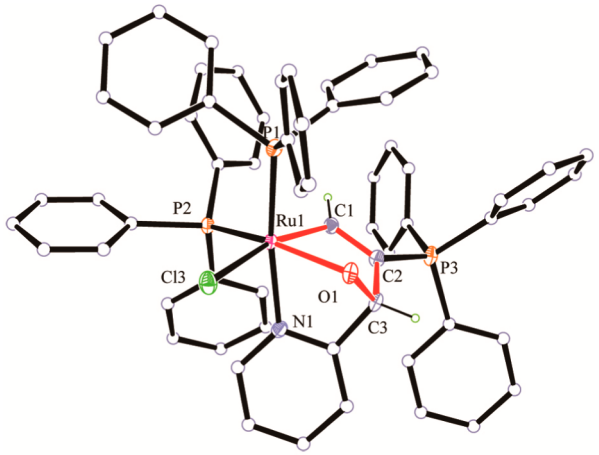


Figure 2. X-ray molecular structure for the cation of complex **4** drawn with 50% probability. The hydrogen atoms in PPh_3 moieties are omitted for clarity. Selected bond lengths [Å] and angles [deg]: Ru(1)–C(1) 1.986(4), C(1)–C(2) 1.354(6), C(2)–C(3) 1.533(6), C(3)–O(1) 1.462(5), O(1)–Ru(1) 2.227(3), Ru(1)–P(2) 2.2780(13), Ru(1)–C1(3) 2.5145(12), Ru(1)–P(1) 2.3291(13), Ru(1)–N(1) 2.120(4); Ru(1)–C(1)–C(2) 114.5(4), C(1)–C(2)–C(3) 113.9(4), C(2)–C(3)–O(1) 106.5(4), C(3)–O(1)–Ru(1) 97.9(2), O(1)–Ru(1)–C(1) 77.77(16).

metal atom and phosphonium group on C2. This value is in the range of our reported Os-vinyl compound (Os*CH* is 12.2 ppm).[8] In its ^{13}C NMR, typical downfield signal at 241.6 ppm could be assigned to a carbon atom that is directly bound to the metal (Ru*CH*). The doublet signal at 105.8 ppm was assigned to *CP*Ph$_3$ due to the phosphorus-containing ligand. The ^{31}P NMR spectrum of **4** consists of a singlet and two doublets: 7.9 ppm corresponds to *CP*Ph$_3$; the doublets at 41.0 and 61.1 ppm correspond to two PPh_3 groups that are coordinated to ruthenium. The 26.7 Hz coupling constant between the two PPh_3 groups suggested that they are coordinated cis to each other.

Identification of the Intermediate [RuCHC(PPh$_3$)CH(2-Py)Cl$_2$PPh$_3$]BF$_4$ (5). Treatment of ruthenium vinyl **4** with HBF_4 afforded the Ru-carbene **5** by protonation of the hydroxyl group followed by dehydration. Ru-carbene **5** could be directly produced also by treatment of $RuCl_2(PPh_3)_3$, **1**, and HBF_4 all together in chloroform. The solid-state structure of **5** was established by X-ray diffraction. As shown in Figure 3, the geometry of the ruthenium center can be viewed as a square-

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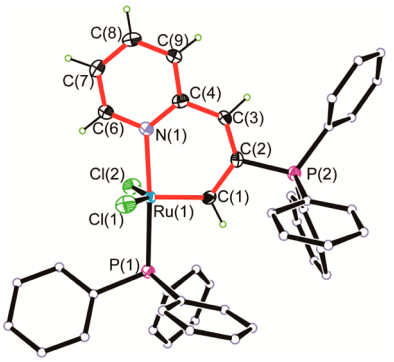


Figure 3. Molecular structure for the cation of **5** (ellipsoids at the 50% probability level). Counteranion and hydrogen atoms in PPh_3 are omitted for clarity. Selected bond lengths [Å] and angles [deg]: Ru(1)−C(1) 1.834(3), C(1)−C(2) 1.458(4), C(2)−C(3) 1.336(5), C(3)−C(4) 1.449(5), N(1)−C(4) 1.360(4), Ru(1)−N(1) 2.117(3). N(1)−Ru(1)−C(1) 92.62(12), Ru(1)−C(1)−C(2) 125.8(2), C(1)−C(2)−C(3) 127.5(3), C(2)−C(3)−C(4) 127.6(3), C(3)−C(4)−N(1) 119.5(3), C(4)−N(1)−Ru(1) 126.9(2), Cl(1)−Ru(1)−Cl(2) 148.08(3), Cl(1)−Ru(1)−C(1) 107.96(10), Cl(2)−Ru(1)−C(1) 103.81(10).

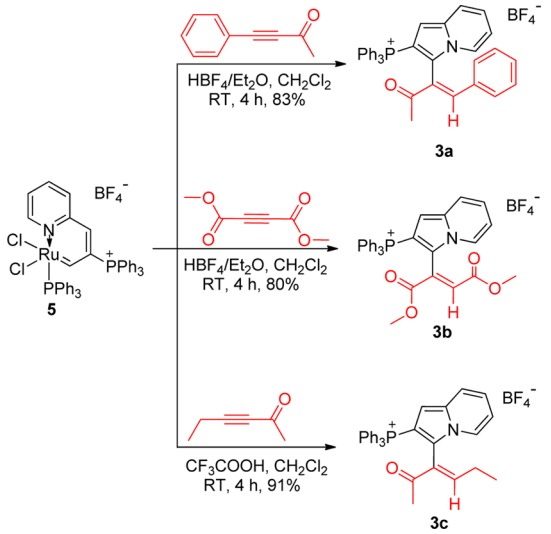
based pyramid as Grubbs' first-generation catalyst,[9] in which the five coordination sites are occupied by C(1), N(1), two chloride atoms, and one phosphorus atom of the phosphine ligand. Complex **5** contains an essentially planar six-membered ring, as reflected by the deviation of rms = 0.009 Å from the plane of the best fit of the Ru(1), C(1), C(2), C(3), C(4), and N(1) chain. The value through the C(4), N(1), C(6), C(7), C(8), and C(9) chain (pyridine plane) is 0.0366 Å. The dihedral angle between the plane through C(1), C(2), C(3), C(4), and C(5) and the pyridine plane is 1.9°, which proves that the two cycles are nearly planar. As expected, there is a clear alternation of the bond lengths around the six-membered ring of Ru(1)/C(1)/C(2)/C(3)/C(4)/N(1). The Ru(1)═C(1) bond length (1.834(3) Å) is similar to that in Ru═$CHPhCl_2(PCy_3)_2$ (1.838(3) Å).[10] The bond lengths of C(1)−C(2) and C(2)−C(3) are 1.458(4) and 1.336(5) Å, consistent with the value of C−C single bonds and C═C double bonds, respectively. All these parameters strongly support a 1,3-butadiene moiety in complex **5**.

The solid-state structure of **5** is fully supported by NMR spectroscopy. In the ^1H NMR spectrum, the α-H proton signal is found at 17.1 (dd, apprant t, J(PH) = 12.5 Hz) ppm. Similar proton patterns have been observed for the analogous vinylcarbene complexes $Cl_2(PPh_3)_2Ru(═CH−CH═CPh_2)$[9] and ruthenabenzenes $[Ru(CHC(PPh_3)CHC(PPh_3)CH)Cl_2(PPh_3)_2]Cl$.[11] In its ^{31}P NMR spectrum, two singlets at 40.3 and 22.0 ppm correspond to $RuPPh_3$ and $CPPh_3$, respectively. In the ^{13}C NMR spectrum, the metal-bound carbon atom α-C shows typical downfield signals at 258.3 ppm, which is in the same range as those found for a variety of known ruthenium carbene complexes,[12] and the β-C connected to PPh_3 displays a signal at 116.3 (J(PC) = 87.4 Hz) ppm.

Formation of 3-Alkenyl-2-phosphonium Indolizine Salt 3 from Ru-Carbene 5. Ru-carbene **5** turns out to be very active toward alkynes such as PhC≡CCOCH$_3$ (**2a**), CH$_3$OCOC≡CCOOCH$_3$ (**2b**), and CH$_3$CH$_2$C≡CCOCH$_3$ (**2c**). Under acid conditions (HBF_4 or CF_3COOH), addition of **2a**, **2b**, and **2c** to a CH_2Cl_2 solution of complex **5** at room temperature leads to 3-alkenyl-2-phosphonium indolizine salts **3a**, **3b**, and **3c** quantitatively. These results suggest that the Ru-carbene is the key intermediate for the formation of indolizine.

Ru-carbenes have been proposed as key intermediates and efficient catalysts in many reactions, and many scientists therefore have been trying to isolate related Ru-carbenes.[7] However, the isolation of carbenes from reaction systems is extremely difficult because metal carbenes are often highly reactive and sensitive to air. To the best of our knowledge, Ru-carbene intermediate **5** is the very first carbene that is isolated from reaction systems that lead to indolizine heterocycles. It is also worth noting that complex **5** has excellent thermal stabilities despite the unsaturated Ru coordination center. Solid samples of **5** remain nearly unchanged at 120 °C under air for 5 h. Such remarkable thermal stabilities may be related to the bulky PPh_3 ligand and quaternary phosphonium salt.[13] The high thermal stability of the Ru-carbene does not effect its reactivity, which may be related to the unsaturated ruthenium coordination center.

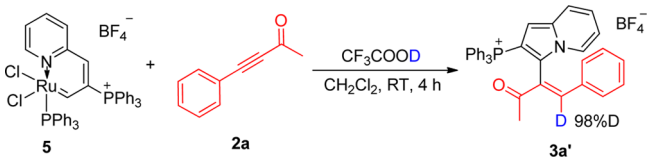
Scheme 4. Preparation of Indolizines from Ru-Carbene 5



Deuterium-Labeling Experiement. In order to gain more insight into the mechanism for the formation of **3**, we performed a deuterium-labeling experiment by means of isotopically homogeneous CF_3COOD. Accordingly, treatment of **5** and **2a** with CF_3COOD all together in CH_2Cl_2 afforded the compound **3a′**, in which a deuterium is incorporated in a defined position next to the phenyl group (Scheme 5). This result reveals that this proton derives mechanistically from the acid rather than from the Ru-carbene **5**.

On the basis of the structures of the Ru-vinyl **4** and Ru-carbene **5** intermediates and the result of the deuterium-labeling experiment, we here propose a possible mechanism of the formation of indolizines (Scheme 6). According to this

Scheme 5. Deuterium-Labeling Experiment for Synthesizing 3a′



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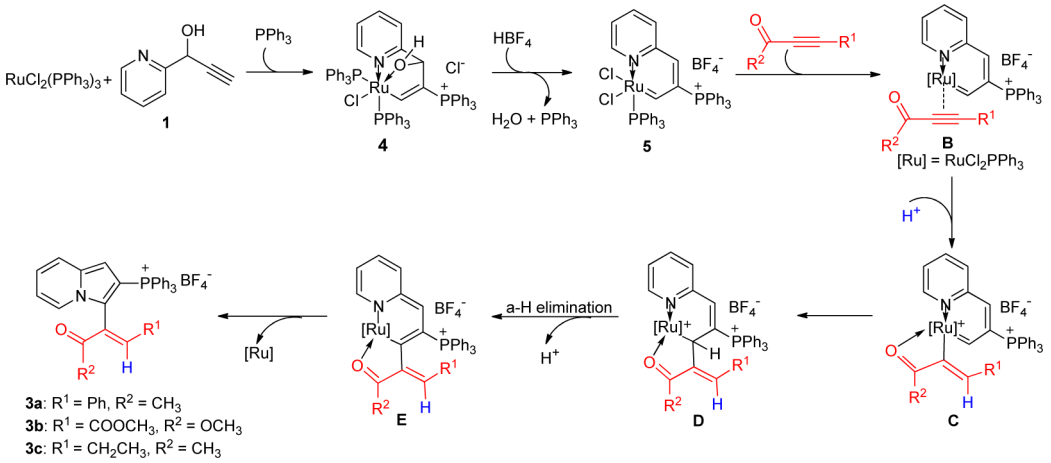
Scheme 6. Possible Mechanism for the Formation of Indolizines



mechanism, $RuCl_2(PPh_3)_3$ reacts with **1** affording the ruthenium vinyl complex **4**. In the presence of HBF_4, vinyl complex **4** is then transformed into ruthenium carbene complex **5** by dehydroxylation.[14] Subsequently, ruthenium coordinates to the alkyne of the alkynone to form the π-alkyne intermediate **B**, which then rearranges to **C** by a net proton of acid adding to an alkyne carbon. Similar roles played by acid have already been postulated for the reaction of $C_5(CH_3)_5(CO)_2Re(\eta^2\text{-}CH_3C{\equiv}CCH_3)$ with HBF_4.[14,15] Next, insertion of the alkyne into the Cα bond of the alkenylcarbene group gives **D**. Compound **E** then forms by α-H elimination of **D**.[16] Finally, through a 6π-electrocyclization and subsequent reductive elimination, the product indolizine **3** is furnished.

CONCLUSION

We here presented a mechanistic study on a ruthenium-assisted reaction for the synthesis of indolizines. By successfully isolating and characterizing two important intermediates and an additional deuterium-labeling experiment, we were able to propose a reasonable mechanism for the formation of the indolizine salt products. A key component of this mechanism is a thermally stable but reactive ruthenium carbene intermediate. These insights might pave the way to the development of a ruthenium-catalyzed indolizine synthesis.

EXPERIMENTAL SECTION

General Information. All syntheses were carried out in a dry nitrogen atmosphere using standard Schlenk techniques, unless otherwise stated. Solvents were distilled from sodium/benzophenone (diethyl ether) or calcium hydride (CH_2Cl_2, $CHCl_3$) under N_2 prior to use. The starting material (2-Py)CH(OH)C≡CH (**1**)[5d] was synthesized according to a literature procedure. Other reagents were used as received from commercial sources without further purification. Column chromatography was performed on alumina gel (200−300 mesh) in air. NMR spectra were performed on a Bruker AVIII-500 (^{1}H, 500.1 MHz; ^{13}C, 125.8 MHz; ^{31}P, 202.5 MHz), AVIII-400 (^{1}H, 400.13 MHz; ^{13}C, 100.63 MHz; ^{31}P, 161.96 MHz), and AVIII-300 (^{1}H, 300.1 MHz; ^{13}C, 75.48 MHz; ^{31}P, 121.5 MHz) spectrometer at room temperature. ^{1}H and ^{13}C NMR chemical shifts (δ) are relative to tetramethylsilane, and ^{31}P NMR chemical shifts are relative to 85% H_3PO_4. The absolute values of the coupling constants are given in hertz (Hz). Multiplicities are abbreviated as singlet (s), doublet (d), triplet (t), multiplet (m), and broad (br). High-resolution mass spectra (HRMS) experiments were recorded on a Bruker En Apex Ultra 7.0T FT-MS.

Preparation of Indolizine 3a. Method 1: To a solution of $RuCl_2(PPh_3)_3$ (535 mg, 0.560 mmol), PPh_3 (438 mg, 1.68 mmol), (2-Py)CH(OH)C≡CH (89.1 mg, 0.670 mmol), and HBF_4 (0.20 mL, 1.5 mmol) in 1:1 $CHCl_3/CH_2Cl_2$ (20 mL) was added PhC≡CCOCH$_3$ (0.16 mL, 1.5 mmol). After stirring for 24 h at room temperature, the solution was then concentrated to about 2 mL. The resulting solution was then purified by chromatography over neutral alumina eluting with CH_2Cl_2/CH_3COCH_3 (10:1), affording **3a** as a yellow solid (31 mg, 10%). **Method 2**: To a suspension of compound **5** (450 mg, 0.50 mmol) and HBF_4 (0.20 mL, 1.5 mmol) in CH_2Cl_2 (10 mL) was added PhC≡CCOCH$_3$ (0.16 mL, 1.5 mmol). After stirring for 4 h at room temperature, the solution was concentrated to ca. 2 mL. The resulting solution was purified by chromatography over neutral alumina eluting with CH_2Cl_2/CH_3COCH_3 (10:1), affording **3a** as a yellow solid (253 mg, 83%). Mp: 209−211 °C. ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.74 (t, J = 7.4 Hz, 3 H), 7.59 (s, 1 H, CH_3COCCH), 7.55−7.40 (m, 14 H), 7.23 (t, J = 7.4 Hz, 1 H), 7.12 (t, J = 7.6 Hz, 2 H), 6.89 (dd, J = 6.6, 8.8 Hz, 1 H), 6.72 (d, J(PH) = 5.1 Hz, 1 H, C(PPh$_3$)CH), 6.62 (d, J = 7.3 Hz, 2 H), 6.60 (t, J = 7.1 Hz, 1 H), 2.08 (s, 3 H, CH_3). ^{31}P NMR (161 MHz, CD_2Cl_2): δ 14.5 (s, CPPh$_3$). ^{13}C NMR (100 MHz, CD_2Cl_2): δ 198.3 (s, CO), 149.6 (s, COCCH), 135.2 (d, J(PC) = 2.5 Hz), 135.0, 134.3(d, J(PC) = 10.9 Hz), 132.5, 131.7, 130.4, 130.0 (d, J(PC) = 12.9 Hz), 129.2, 127.0, 126.7, 122.5, 121.3, 120.2, 119.4, 118.4, 114.6 (PPh$_3$, Ph and others carbon atoms), 106.2 (d, ^2J(PC) = 10.9 Hz, C(PPh$_3$)CH), 99.0 (d, ^1J(PC) = 112.1 Hz, C(PPh$_3$)), 26.2 (s, CH_3). HRMS (ESI): m/z calcd for $[C_{36}H_{29}ClORuP]^+$, 522.1981; found 522.1975.

Preparation of [Ru(CHC(PPh$_3$)C(OH)(2-Py)Cl(PPh$_3$)$_2$]Cl (4). $RuCl_2(PPh_3)_3$ (535 mg, 0.560 mmol), (2-Py)CH(OH)C≡CH (89.1 mg, 0.670 mmol), and PPh_3 (663 mg, 2.53 mmol) were dissolved in 15 mL of CH_2Cl_2. A yellow precipitate formed after stirring at room temperature for 7 h. The product was collected by filtration, washed with CH_2Cl_2 (2 × 3 mL), and dried as a yellow solid (458 mg, 75%). Mp = 178−185 °C (dec). ^{1}H NMR (300 MHz, CD_2Cl_2): δ 11.32 (d, J(PH) = 18.0 Hz, 1 H, RuCH), 7.84−6.56 (m, 50 H, other aromatic carbon atoms and OH), 5.96 (d, J(PH) = 4.0 Hz, 1 H, RuCHC(PPh$_3$)CH). ^{31}P NMR (121 MHz, CD_2Cl_2): δ 7.9 (s, CPPh$_3$), 41.0 ppm (d, J(PP) = 26.7 Hz, RuPPh$_3$), 61.1 (d, J(PP) = 26.7 Hz, RuPPh$_3$). ^{13}C NMR plus DEPT 135 and ^{1}H−^{13}C HSQC (75 MHz, CD_2Cl_2): δ 241.6 (br, RuCH), 156.3 (s, CHN), 156.0 (s, C(PPh$_3$)CHC), 136.6−119.7 (m, other aromatic carbon atoms), 105.8 (d, J(PC) = 81.9 Hz, C(PPh$_3$)), 80.57 ppm (d, J(PC) = 29.4 Hz, C(PPh$_3$)CH(OH)). HRMS (ESI): m/z calcd for $[C_{62}H_{52}ClNORuP_3]^+$, 1056.1989; found 1056.1984.

Preparation of [Ru(CHC(PPh$_3$)CH(2-Py))Cl$_2$PPh$_3$]BF$_4$ (5). To a suspension of compound **4** (1.1 g, 1.0 mmol) and NH_4Cl (0.16 g, 3.0 mmol) in $CHCl_3$ (15 mL) was added HBF_4/Et_2O (0.41 mL, 3.0 mmol). After 6 h, the resulting green solution was concentrated to ca. 2 mL, and then diethyl ether (20 mL) was added to the solution. The

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Table 1. Crystal Data and Structure Refinement for 3a, 4, and 5

	3a·CH_2Cl_2	4·$3CH_2Cl_2$	5·CH_2Cl_2
formula	$C_{73}H_{60}B_2Cl_2F_8N_2O_2P_2$	$C_{65}H_{58}Cl_8NOP_3Ru$	$C_{45}H_{38}BCl_4F_4NP_2Ru$
M_r	1303.69	1346.70	984.38
color	yellow	yellow	green
temp, K	173(2)	173(2)	173(2)
radiation (Mo Kα), Å	0.71073	0.71073	0.71073
cryst syst	monoclinic	monoclinic	triclinic
space group	$P2_1/c$	$P2_1/c$	$P\bar{1}$
a, Å	22.8041(13)	12.9636(3)	11.3830(3)
b, Å	14.1895(6)	20.3607(7)	12.8300(5)
c, Å	19.9794(9)	23.0029(7)	15.3047(4
α, deg	90	90.00	83.862(3)
β, deg	93.628(5)	94.751(3)	80.728(2)
γ, deg	90	90.00	87.617(3)
V, Å^3	6452.0(5)	6050.7(3)	2192.63(12)
Z	4	4	2
ρ_{calcd}, g cm^{-3}	1.342	1.478	1.491
θ range, deg	3.00−25.00	2.74−25.00	2.74−25.00
$F(000)$	2696	2752	996
cryst size, mm	0.4 × 0.3 × 0.2	0.3 × 0.2 × 0.2	0.25 × 0.15 × 0.1
reflns collected	31 452	30 962	22 325
indep reflns	11 331	10 659	7703
data/restraints/params	11 331/3/820	10 659/0/667	7703/0/523
GOF on F^2	1.025	1.050	0.953
R_1/wR_2	R_1 = 0.0918	R_1 = 0.0573	R_1 = 0.0408
$[I \geq 2\sigma(I)]$	wR_2 = 0.2000	wR_2 = 0.1430	wR_2 = 0.1199
R_1/wR_2 (all data)	R_1 = 0.1462	R_1 = 0.0832	R_1 = 0.0500
	wR_2 = 0.2286	wR_2 = 0.1505	wR_2 = 0.1306
largest peak/hole [e Å^{-3}]	1.584 and −1.007	2.141 and −1.461	1.185 and −0.841

oily precipitate was collected by filtration, washed with $CHCl_3$ (2 × 3 mL), and dried as a green solid (809 mg, 90%). Mp = 185−191 °C (dec). ^{1}H NMR (400 MHz, CD_2Cl_2): δ 17.1 (dd, apprant t, J(PH) = 12.5 Hz, 1 H, RuC*H*), 9.4 (d, J(HH) = 4.7, 1 H, NC*H*), 8.0−7.1 (m, 34 H, other aromatic carbon atoms). ^{31}P NMR (162 MHz, CD_2Cl_2): δ 40.3 (s, Ru*P*Ph_3), 22.0 ppm (s, C*P*Ph_3). ^{13}C NMR (100 MHz, CD_2Cl_2): δ 258.3 (m, RuCH), 151.2 (d, J(PC) = 18.2 Hz, RuCHC(PPh_3)CH), 150.9 (s, NCH), 138.6−125.2 (m, other aromatic carbon atoms), 116.3 (d, J(PC) = 87.4 Hz, *C*(PPh_3)). HRMS (ESI): m/z calcd for $[C_{44}H_{36}Cl_2NRuP_2]^+$, 812.0744; found 812.0739.

Preparation of Indolizine 3b. To a suspension of compound **5** (450 mg, 0.50 mmol) and HBF_4/Et_2O (0.20 mL, 1.5 mmol) in CH_2Cl_2 (10 mL) was added $CH_3OCOC{\equiv}CCOOCH_3$ (0.19 mL, 1.5 mmol). The resulting solution was concentrated to ca. 2 mL after stirring for 4 h at room temperature and then purified by chromatography over neutral alumina eluting with CH_2Cl_2/CH_3COCH_3 (10:1), affording **3b** as a yellow solid (242 mg, 80%). Mp: 236−238 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85−7.52 ppm (m, 17 H), 6.98 (t, J(HH) = 8.4 Hz, 1 H), 6.80 (s, 1 H, CH_3OCOCH), 6.76 (t, J(HH) = 6.9 Hz, 1 H), 6.74 (d, J(PH) = 4.3 Hz, 1 H, C(PPh_3)C*H*), 3.89 (s, 3 H, CH_3O), 3.85 (s, 3 H, CH_3O). ^{31}P NMR (202 MHz, $CDCl_3$): δ 14.37(s, C*P*Ph_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.8 (s, CH_3OCO), 163.4 (s, CH_3OCO), 136.3 (s, CH_3OCOCH), 135.4 (d, J(PC) = 2.36 Hz), 135.1 (d, J(PC) = 14.7 Hz), 134.4 (d, J(PC) = 10.5 Hz), 131.9, 130.2 (d, J(PC) = 12.8 Hz), 123.5 (d, J(PC) = 19.35 Hz), 122.5, 121.3, 120.1, 119.2, 118.5, 114.6 (other carbon atoms), 106.5 (d, J(PC) = 10.8 Hz, CPPh_3CH), 100.6 (d, J(PC) = 112.5 Hz, CPPh_3), 53.3 (s, CH_3OCO), 52.6 (s, CH_3OCO). HRMS (ESI): m/z calcd for $[C_{32}H_{27}NO_4P]^+$, 520.1672; found 520.1678.

Preparation of Indolizine 3c. To a suspension of compound **5** (450 mg, 0.50 mmol) and CF_3COOH (0.12 mL, 1.5 mmol) in CH_2Cl_2 (10 mL) was added $CH_3CH_2C{\equiv}CCOCH_3$ (0.15 mL, 1.5 mmol). The solution was concentrated to ca. 2 mL after stirring at room temperature for 4 h. The resulting solution was then purified by chromatography over neutral alumina eluting with CH_2Cl_2/CH_3COCH_3 (10:1), affording **3c** as a yellow solid (255 mg, 91%). Mp: 214−216 °C. ^{1}H NMR plus ^{1}H−^{13}C HSQC and ^{1}H−^{1}H COSY (400 MHz, $CDCl_3$): δ 7.76 (t, J = 7.4 Hz, 3 H), 7.64−7.55 (m, 12 H), 7.49 (d, J = 7.2 Hz, 1 H), 7.43 (d, J = 9.5 Hz, 1 H), 6.92 (t, J = 7.3 Hz, 1 H, CH_3CH_2CH), 6.86 (dd, J = 9.1, 6.6 Hz, 1 H), 6.66 (t, J = 6.9 Hz, 1 H), 6.62 (d, J = 5.2 Hz, 1 H, C(PPh_3)C*H*), 1.91 (s, 3 H, CH_3CO), 1.75 (m, 2 H, CH_3CH_2), 0.85 (t, J = 5.2 Hz, 3 H, CH_3CH_2). ^{31}P NMR (162 MHz, $CDCl_3$): δ 14.5 (s, C*P*Ph_3). ^{13}C NMR plus DEPT 135 and ^{1}H−^{13}C HSQC (100 MHz, $CDCl_3$): δ 197.7 (s, CH_3CO), 157.4 (s, CH_3CH_2CH), 105.8 (d, ^2J(PC) = 10.9 Hz, C(PPh_3)C*H*), 99.8 (d, ^1J(PC) = 112.1 Hz, *C*(PPh_3)), 29.2 (s, CH_3CO), 25.8 (s, CH_3CH_2), 12.1 (s, CH_3CH_2), 135.2−114.3 (other carbon atoms). HRMS (ESI): m/z calcd for $[C_{32}H_{29}NOP]^+$, 474.1981; found 474.1984.

Crystallographic Analysis. Crystals suitable for X-ray diffraction were grown from CH_2Cl_2 solutions layered with diethyl ether for **3a**, **4**, and **5**. Data collections were performed on an Oxford Gemini S Ultra or a Rigaku R-AXIS SPIDER IP CCD area detector using graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). Multiscan absorption corrections (SADABS) were applied. All of the data were corrected for absorption effects using the multiscan technique. The structures were solved by direct methods, expanded by difference Fourier syntheses, and refined by full matrix least-squares on F^2 using the Bruker SHELXTL (version 6.10) program package. Non-H atoms were refined anisotropically unless otherwise stated. Hydrogen atoms were introduced at their geometric positions and refined as riding atoms unless otherwise stated. CCDC 941265 (**3a**), 941263 (**4**), and 941264 (**5**) contain the supplementary crystallographic data for this paper. Further details on crystal data, data collection, and refinements are summarized in Table 1.

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■ ASSOCIATED CONTENT

Supporting Information

CIF files giving crystallographic data of compounds **3a**, **4**, and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Singh, G. S.; Mmatli, E. E. *Eur. J. Med. Chem.* **2011**, *46*, 5237. (b) Vemula, V. R.; Vurukonda, S.; Bairi, C. K. *Int. J. Pharm. Sci. Rev. Res.* **2011**, *11*, 159.

(2) (a) Michael, J. P. *Nat. Prod. Rep.* **2001**, *18*, 520. (b) Fan, H.; Peng, J.; Hamann, M. T.; Hu, J. F. *Chem. Rev.* **2008**, *108*, 264. (c) Facompré, M.; Tardy, C.; Bal-Mahieu, C.; Colson, P.; Perez, C.; Manzanares, I.; Cuevas, C.; Bailly, C. *Cancer Res.* **2003**, *63*, 7392.

(3) (a) Wen, J. J.; Zhu, Y.; Zhan, Z. P. *Asian J. Org. Chem.* **2012**, *1*, 108. (b) Basavaiah, D.; Rao, A. J. *Tetrahedron Lett.* **2003**, *44*, 4365. (c) Sonnenschein, H.; Theil, F.; Kreher, T.; Kóeckritz, A. *Chem. Commun.* **1997**, *6*, 551. (d) Kim, I.; Won, H. K.; Choi, J.; Lee, G. H. *Tetrahedron* **2007**, *63*, 12954. (e) Jung, Y.; Kim, I. *Tetrahedron* **2012**, *68*, 8198. (f) Furdui, B.; Dinica, R.; Demeunynck, M.; Druta, I. *Rom. J. Phys.* **2008**, *53*, 369. (g) Furdui, B.; Dinica, R.; Druta, I. I.; Demeunynck, M. *Synthesis* **2006**, *16*, 2640.

(4) (a) Hardin, N. A. R.; Sarpong, R. *Green Chem.* **2010**, *12*, 1556. (b) Smith, C. R.; Bunnelle, E. M.; Rhodes, A. J.; Sarpong, R. *Org. Lett.* **2007**, *9*, 1169. (c) Hardin, A. R.; Sarpong, R. *Org. Lett.* **2007**, *9*, 4547. (d) Chernyak, D.; Skontos, C.; Gevorgyan, V. *Org. Lett.* **2010**, *12*, 3242. (e) Dudnik, A. S.; Sromek, A. W.; Rubina, M.; Kim, J. T.; Kel'in, A. V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2008**, *130*, 1440. (f) Seregin, I. V.; Schammel, A. W.; Gevorgyan, V. *Tetrahedron* **2008**, *64*, 6876. (g) Xia, J. B.; Wang, X. Q.; You, S. L. *J. Org. Chem.* **2009**, *74*, 456. (h) Xia, J. B.; You, S. L. *Org. Lett.* **2009**, *11*, 1187. (i) Chai, D. I.; Lautens, M. *J. Org. Chem.* **2009**, *74*, 3054. (j) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (k) Thansandote, P.; Lautens, M. *Chem.—Eur. J.* **2009**, *15*, 5874.

(5) (a) Seregin, I. V.; Schammel, A. W.; Gevorgyan, V. *Org. Lett.* **2007**, *9*, 3433. (b) Seregin, I. V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2006**, *128*, 12050. (c) Schwier, T.; Sromek, A. W.; Yap, D. M. L.; Chernyak, D.; Gevorgyan, V. *J. Am. Chem. Soc.* **2007**, *129*, 9868. (d) Xia, Y.; Dudnik, A. S.; Li, Y.; Gevorgyan, V. *Org. Lett.* **2010**, *12*, 5538.

(6) (a) Chuprakov, S.; Hwang, F. W.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2007**, *46*, 4757. (b) Chuprakov, S.; Gevorgyan, V. *Org. Lett.* **2007**, *9*, 4463.

(7) Lozano-Vila, A. M.; Monsaert, S.; Bajek, A.; Verpoort, F. *Chem. Rev.* **2010**, *110*, 4865.

(8) Gong, L.; Lin, Y. M.; Wen, T. B.; Xia, H. P. *Organometallics* **2009**, *28*, 1101.

(9) Nguyen, S. T.; Johnson, L. K.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3974.

(10) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **1995**, *34*, 2039.

(11) Zhang, H.; Xia, H. P.; He, G. M.; Wen, T. B.; Gong, L.; Jia, G. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 2920.

(12) (a) Chung, C. P.; Chen, C. C.; Lin, Y. C.; Liu, Y. H.; Wang, Y. *J. Am. Chem. Soc.* **2009**, *131*, 18366. (b) Shaffer, E. A.; Chen, C. L.; Beatty, A. M.; Valente, E. J.; Schanz, H. J. *J. Organomet. Chem.* **2007**, *692*, 5221. (c) Gandelman, M.; Naing, K. M.; Rybtchinski, B.; Poverenov, E.; Ben-David, Y.; Ashkenazi, N.; Gauvin, R. M.; Milstein, D. *J. Am. Chem. Soc.* **2005**, *127*, 15265. (d) Conrad, J. C.; Yap, G. P. A.; Fogg, D. E. *Organometallics* **2003**, *22*, 1986. (e) Volland, M. A. O.; Rominger, F.; Eisentrager, F.; Hofmann, P. *J. Organomet. Chem.* **2002**, *641*, 220.

(13) Zhao, Q. Y.; Gong, L.; Xu, C. F.; Zhu, J.; He, X. M.; Xia, H. P. *Angew. Chem., Int. Ed.* **2011**, *50*, 1354.

(14) (a) Casey, C. P.; Brady, J. T. *Organometallics* **1998**, *17*, 4620. (b) Wolf, J.; Werner, H. *Organometallics* **1987**, *6*, 1164.

(15) (a) Esteruelas, M. A.; Lahoz, F. J.; Lopez, J. A.; Oro, L. A.; Schluenken, C.; Valero, C.; Werner, H. *Organometallics* **1992**, *11*, 2034. (b) Andriollo, A.; Esteruelas, M. A.; Meyer, U.; Oro, L. A.; Sanchez-Delgado, R. A.; Sola, E.; Valero, C.; Werner, H. *J. Am. Chem. Soc.* **1989**, *111*, 7431.

(16) (a) Conejero, S.; Paneque, M.; Poveda, M. L.; Santos, L. L.; Carmona, E. *Acc. Chem. Res.* **2010**, *43*, 572. (b) Rankin, M. A.; McDonald, R.; Ferguson, M. J.; Stradiotto, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3603.