

*With compliments of the Author*

# Pyrido[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-diones: Synthesis, Cyclometalation, and Protein Kinase Inhibition

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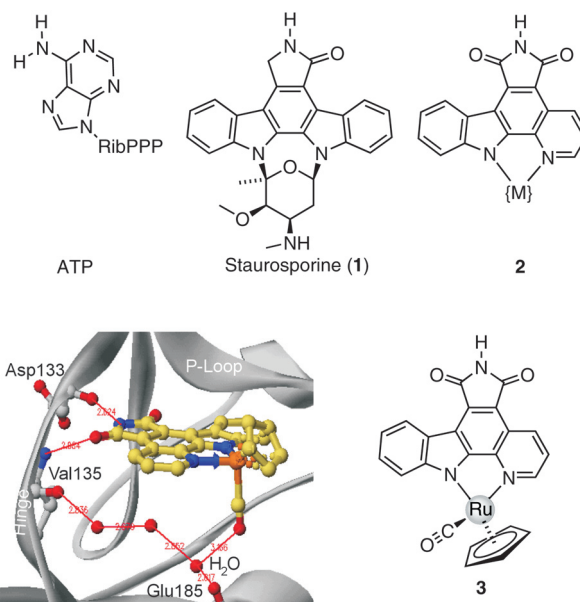
Dedicated to the occasion of the 65th birthday of Prof. Bernd Giese

**Abstract:** Synthetic routes to pyrido[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-diones are disclosed and examples for their subsequent transformations into cyclometalated protein kinase inhibitors are presented.

**Key words:** pyridocarbazoles, photocyclization, cyclometalation, ruthenium, protein kinase inhibitors

We recently started a research program that aims in exploring the versatility of organometallic and inorganic compounds as structural scaffolds for the design of enzyme inhibitors.<sup>1–5</sup> In these molecules, the metal center plays a solely structural role by organizing the organic ligands in the three-dimensional receptor space. We believe that this approach has potentially two important advantages compared to the traditional design of organic inhibitors. First, it gives access to new areas of chemical space that may not be easily accessible with purely organic scaffolds. In this respect, we like to think of a chemically inert metal center as a ‘hypervalent carbon’ with extended structural opportunities. Second, metal complexes are built from a central core and thus may have an advantage in building shape and functional group diversity in an economical fashion.

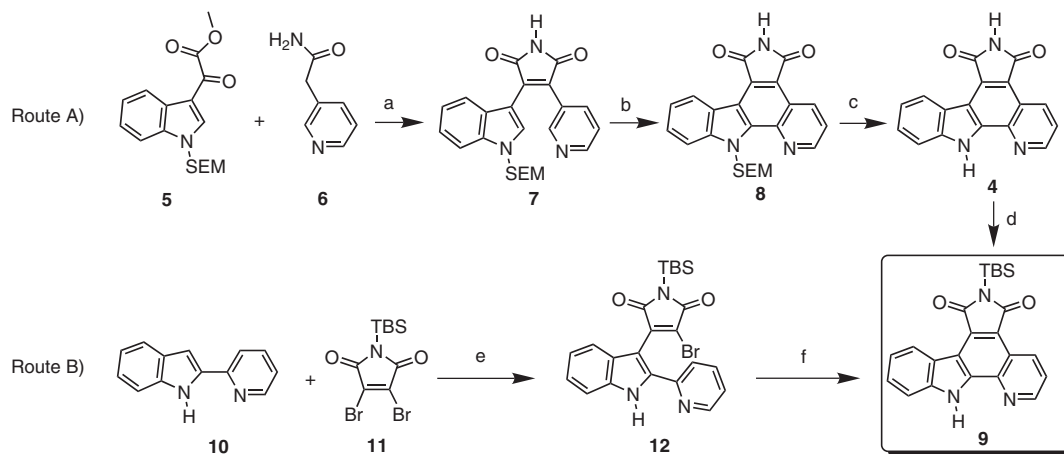
Our design of metal complexes as protein kinase inhibitors uses the class of indolocarbazole alkaloids [e.g. staurosporine (**1**)] as a lead structure.<sup>4,5</sup> Metal complexes such as **2** bear a pyrido[2,3-*a*]carbazole bidentate ligand which retains the structural features of the indolocarbazole heterocycle (Figure 1).<sup>5</sup> This targets the metal complexes to the ATP-binding site by enabling two H-bonds to the backbone of the hinge between the N-terminal and C-terminal kinase domain, analogous to ATP and conventional organic indolocarbazole inhibitors.<sup>6,7</sup> The remaining ligand sphere of the metal gives the opportunity to create interactions with other parts of the ATP-binding site. Potent and specific inhibitors for a particular kinase can now be obtained by assembling elaborate structures around the metal center. For example, the half-sandwich ruthenium complex **3** is a low nanomolar inhibitor for glycogen synthase kinase 3 (GSK-3) (Figure 1).<sup>5</sup>



**Figure 1** Designing ruthenium complexes **2** as protein kinase inhibitors by mimicking ATP-competitive indolocarbazoles such as staurosporine (**1**). For example, ruthenium compound **3** is a low nanomolar inhibitor for glycogen synthase kinase 3 (GSK-3). Bottom left: Modeled interactions (CAChE, Fujitsu) of one enantiomer of **3** with the ATP binding site of GSK-3β (PDB code 1Q3D).

In this article, we describe two syntheses of pyrido[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-dione (**4**) (Scheme 1) and highlight the versatility of our current synthetic strategy by applying it to derivatives in which the indole or pyridine unit is modified. We further demonstrate that these ligands can undergo cyclometalation with ruthenium, leading to molecular scaffolds for the design of highly potent protein kinase inhibitors.

Our initial synthetic strategy to the pyrido[2,3-*a*]carbazole scaffold **4** is based on the methodology developed by Faul et al. and Andersen et al. (Route A in Scheme 1).<sup>8–10</sup> Accordingly, potassium *tert*-butoxide induced condensation of SEM-protected indole-3-methyl glyoxylate **5** with pyridine-3-acetamide (**6**) furnishes maleimide **7** in 50% yield. Subsequent oxidative photo-induced cyclization with a medium pressure mercury lamp in a quartz reactor under air and in the presence of catalytic amounts of iodine provides **8** in 63% yield. We observed almost exclusively the illustrated isomer **8**, resulting from C–C bond formation between the indole and the *ortho*-position at the



**Scheme 1** Two synthetic routes to pyrido[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-dione (**4**) and its TBS-protected derivative **9**.

**Reagents and conditions:** Route A: (a) *t*-BuOK (3 equiv), DMF, 4 Å mol. sieves (50%); (b) photolysis in MeCN with a medium pressure mercury lamp in the presence of air and catalytic amounts of I<sub>2</sub> (63%); (c) LiBF<sub>4</sub>, MeCN–H<sub>2</sub>O, reflux (ca. 100%); (d) reflux in MeCN with *tert*-butyldimethylsilyloxymethoxyethene (93%); Route B: (e) addition of LiHMDS to **10**, THF, –15 °C, 45 min, then addition of **11** in THF, –15 °C, 15 min, then r.t., 45 min (68%); (f) hv, pyrex filter, MeCN, 3 h, (64%). SEM = CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub>SiMe<sub>3</sub>, TBS = *tert*-butyldimethylsilyl.

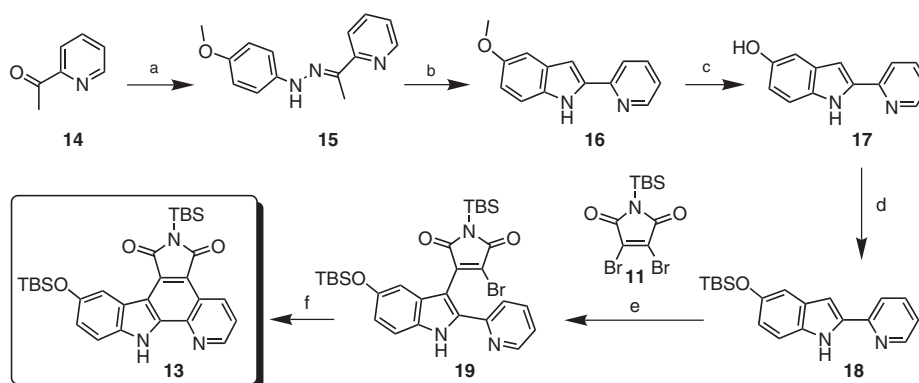
pyridine. The isomeric product that would have resulted from C–C bond formation between the indole and the *para*-position at the pyridine was detected only in trace amounts. Finally, SEM-deprotection with LiBF<sub>4</sub> yielded pyridocarbazole **4** in almost quantitative yield. Unfortunately, **4** has a very poor solubility in most organic solvents and is therefore not suitable as a substrate for direct coordination chemistry.

Currently, the TBS-protected pyrido[2,3-*a*]carbazole **9** (see Scheme 1) is our first choice. It can be synthesized in high yields of 93% starting from **4** by refluxing it with *tert*-butyldimethylsilyloxymethoxyethene in acetonitrile.<sup>11</sup>

We subsequently developed a shorter and more convenient route which would directly yield the TBS-protected pyrido[2,3-*a*]carbazole **9**. The synthesis is shown in Scheme 1 (Route B). Pyridoindole **10**,<sup>12</sup> upon lithiation with LiHMDS, undergoes monosubstitution with TBS-protected dibromomaleimide **11** to afford monobromide

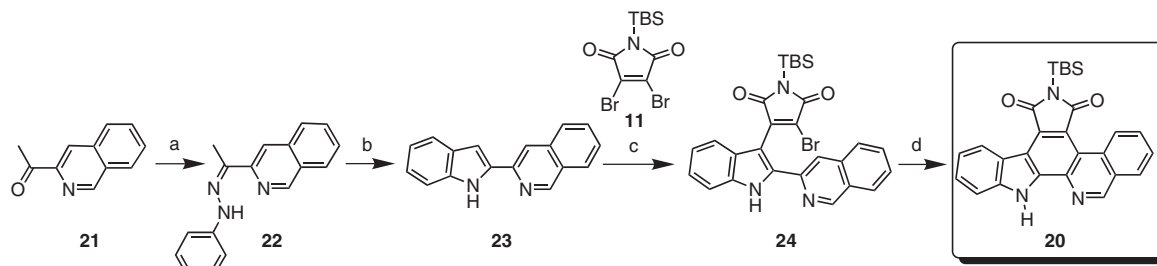
**12** in 68% yield.<sup>13</sup> The key step is the following smooth anaerobic photocyclization to pyridocarbazole **9** upon release of HBr (64%).<sup>14</sup> As a side product, a pyridinium salt is formed which results from nucleophilic substitution of the bromide by the pyridine nitrogen. This cationic by-product is easily separable from the desired compound by silica gel chromatography.

This synthetic route is general and can be applied to substituted pyridocarbazole derivatives. For example, the indole substituted derivative **13** was synthesized starting from 2-acetylpyridine **14** (Scheme 2). Hydrazone formation to **15** was followed by Fischer indole synthesis yielding 5-methoxypyridoindole **16**<sup>15</sup> in 63% yield over the two steps. For this Fischer indole synthesis we found trimethylsilyl polyphosphate the Lewis acid of choice. Demethylation to **17** with BBr<sub>3</sub> followed by TBS protection yielded **18**. Lithiation of **18**, followed by reaction with one equivalent of dibromomaleimide **11** furnished monobromide **19** in 58% yield. Subsequent photolysis under argon provided **13** in a good yield of 78%.



**Scheme 2** Synthesis of **13**.

**Reagents and conditions:** (a) 4-methoxyphenylhydrazine HCl, *t*-BuOH, reflux 4 h (ca. 100%); (b) trimethylsilyl polyphosphate, 120 °C, 18 h (63%); (c) BBr<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, –60 °C, then r.t., overnight (87%); (d) Hünig's base, DMF, 0 °C for 40 min, then TBSOTf, 0 °C for 1 h (71%); (e) LiHMDS, THF, –15 °C for 45 min, then **11** in THF, –15 °C for 15 min, then r.t. for 45 min (58%); (f) hv, pyrex filter, MeCN, 3 h, (78%).



**Scheme 3** Synthesis of **20**.

*Reagents and conditions:* (a) phenylhydrazine, EtOH, reflux, 1.5 h (85%); (b) trimethylsilyl polyphosphate, 150 °C, 12 h (47%); (c) first LiHMDS (2.1 equiv), -15 °C, then **11**, -15 °C to r.t. for 1 h (d) hv, pyrex filter, MeCN, 3 h, (84%, 2 steps).

The synthetic route is also applicable to derivative **20** in which the pyridine ring is replaced by an isoquinoline. Starting with 3-acetylisoquinoline (**21**),<sup>16</sup> hydrazone formation to **22** and subsequent Fischer indole synthesis provided the isoquinolinoindole **23** in yields of 40% over the two steps. Compound **23** was lithiated with LiHMDS and reacted with one equivalent of dibromomaleimide **11** to yield the monobromide substitution product **24** which was directly photocyclized under argon to **20** (84% yield over both steps) (Scheme 3).

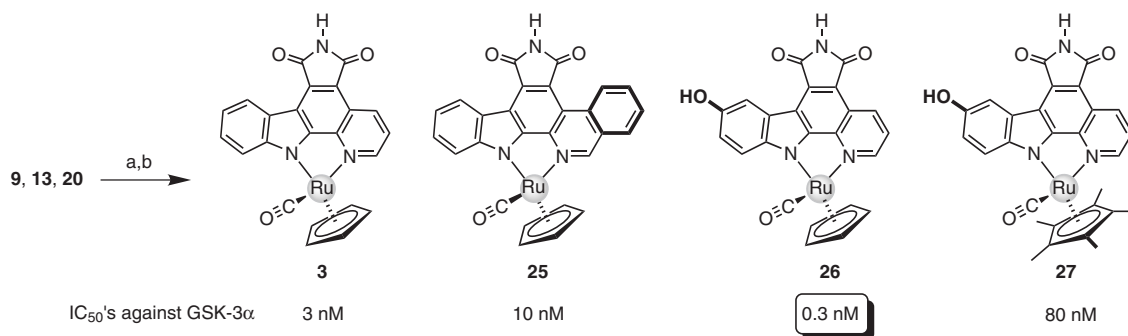
The TBS-protected ligands **9**, **13**, and **20** undergo smooth cyclometalation upon reaction with a suitable metal complex precursor. For example, reaction of **9**, **13**, and **20** with  $[\text{Ru}(\text{Cp})(\text{CO})(\text{MeCN})_2]^+\text{PF}_6^-$ <sup>17</sup> and of **13** with  $[\text{Ru}(\text{Cp}^*)(\text{CO})(\text{MeCN})_2]^+\text{PF}_6^-$ <sup>18</sup> in the presence of one equivalent of  $\text{K}_2\text{CO}_3$  followed by TBAF induced TBS-deprotection, yielded the racemic ruthenium complexes **3**, and **25–27**. Most likely the reaction involves an initial coordination of the pyridyl nitrogen at ruthenium center followed by a nucleophilic attack of the indole nitrogen with subsequent deprotonation. Interestingly, these novel compounds form readily and are very stable. The ruthenium complexes shown in Scheme 4 are completely stable in water, stable in the presence of oxygen, and can withstand millimolar concentrations of thiols.

Ruthenium compounds **3**, and **25–27** are potent inhibitors for glycogen synthase kinase 3 (GSK-3). The concentration at which 50% of the enzyme is inhibited ( $\text{IC}_{50}$ ) is 3 nM for **3** as reported recently (measured against the  $\alpha$ -iso-

form of GSK-3).<sup>5</sup> Interestingly, increasing the hydrophobic surface area by exchanging the pyridine moiety for an isoquinoline in **25** does not improve the affinity but instead leads to a slight increase of the  $\text{IC}_{50}$  to 10 nM. In contrast, the introduction of an hydroxy group at the 5-position of the indole moiety as in **26**, decreases the  $\text{IC}_{50}$  to 300 pM. Ruthenium compound **26** is one of the most potent compounds available for GSK-3 inhibition.<sup>19</sup> In contrast, ruthenium complex **27**, which bears the sterically very demanding pentamethylcyclopentadienyl ligand instead of the plain cyclopentadienyl, shows a reduced activity by more than two orders of magnitude, presumably because it cannot fit properly into the ATP pocket of GSK-3 anymore.

In conclusion, two synthetically viable routes for pyrido[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7(*6H*)-diones have been discussed. The routes include either an oxidative or nonoxidative photocyclization step. The nonoxidative photocyclization route has proven to be especially useful for the preparation of substituted pyridocarbazoles. These ligands serve as important components for the preparation of cyclometalated protein kinase inhibitors.

NMR spectra were recorded on a Bruker AM-500 (500 MHz), DMX-300 (300 MHz), or DMX-360 (360 MHz) spectrometer. Low-resolution mass spectra were obtained on an LC platform from Micromass using ESI technique. High-resolution mass spectra were obtained with a Micromass AutoSpec instrument using either CI or ES ionization. IR spectra were recorded on a Perkin-Elmer 1600 series FTIR spectrometer. Solvents and reagents were used as sup-



**Scheme 4** Synthesis of the racemic ruthenium complexes **3**, **25**, **26**, and **27**.

*Reagents and conditions:* (a)  $[\text{RuCp}(\text{CO})(\text{CH}_3\text{CN})_2]^+\text{PF}_6^-$  or  $[\text{RuCp}^*(\text{CO})(\text{CH}_3\text{CN})_2]^+\text{PF}_6^-$ ,  $\text{K}_2\text{CO}_3$ , MeCN, 55 °C, 12 h; (b) TBAF (1 M solution in THF), then AcOH.

plied from Aldrich or Acros. Reactions were performed under argon unless otherwise specified.

#### Compound 7

To a stirred solution of **5** (6.82 g, 20.45 mmol) and pyridine-3-acetamide (**6**; 2.53 g, 18.59 mmol) in DMF (50 mL) at 0 °C, was added dropwise a solution of *t*-BuOK (6.26 g, 55.77 mmol) in DMF (50 mL). The solution was stirred at 0 °C and was allowed to warm to r.t. The resulting dark red solution was cooled to 0 °C and 20% aq NH<sub>4</sub>Cl (300 mL) was carefully added. This mixture was extracted with EtOAc (3 ×), and the organic layer was dried (MgSO<sub>4</sub>) and concentrated. After drying under vacuum to remove the residual DMF, the residue was subjected to silica gel column chromatography with EtOAc–hexane (2:1) as the eluting solvent. The resulting orange-yellow condensation product **7** was isolated in modest yield (3.88 g, 50%).

IR (film): 3471, 3266, 3200, 3056, 2922, 2712, 1712, 1624, 1513, 1468, 1396, 1337, 1238, 1178, 1078, 838 cm<sup>-1</sup>.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ = 8.74 (dd, *J* = 2.2, 0.5 Hz, 1 H), 8.58 (dd, *J* = 4.9, 1.7 Hz, 1 H), 8.41 (br s, 1 H), 8.05 (s, 1 H), 7.86 (dt, *J* = 8.0, 1.9 Hz, 1 H), 7.50 (d, *J* = 8.2 Hz, 1 H), 7.28 (ddd, *J* = 8.1, 5.1, 0.6 Hz, 1 H), 7.19 (td, *J* = 7.7, 1.0 Hz, 1 H), 6.86 (td, *J* = 7.6, 1.0 Hz, 1 H), 6.41 (d, *J* = 8.1 Hz, 1 H), 5.55 (s, 2 H), 3.57 (t, *J* = 8.1 Hz, 2 H), 0.93 (t, *J* = 8.1 Hz, 2 H), –0.04 (s, 9 H).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ = 171.0, 170.9, 150.7, 149.9, 137.18, 137.15, 133.8, 126.8, 126.7, 125.0, 123.7, 123.3, 122.2, 121.9, 111.2, 105.1, 97.8, 76.5, 66.7, 17.9, –1.2.

HRMS: *m/z* calcd for C<sub>23</sub>H<sub>26</sub>N<sub>3</sub>O<sub>3</sub>Si (M + H)<sup>+</sup>: 420.1744; found (M + H)<sup>+</sup>: 420.1761.

#### Compound 8

A stirred solution of **7** (1.0 g, 2.39 mmol) in MeCN (200 mL) with catalytic amounts of I<sub>2</sub> (10 mol%, 0.239 mmol, 60.7 mg) was irradiated with a medium pressure lamp for 2.5 h while air was bubbled through the solution. The resulting suspension was evaporated, and the reaction was repeated three times with this scale. The crude reaction mixtures were combined and purified by silica gel chromatography with CH<sub>2</sub>Cl<sub>2</sub>–MeOH (20:1). The isolated material was further purified by recrystallization from MeCN (300 mL) to yield **8** (2.5 g, 63%).

IR (film): 3178, 3059, 2925, 2845, 1754, 1701, 1601, 1467, 1400, 1340, 1247, 1073, 833 cm<sup>-1</sup>.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ = 9.41 (dd, *J* = 8.5, 1.5 Hz, 1 H), 9.14 (d, *J* = 7.9 Hz, 1 H), 9.05 (dd, *J* = 4.0, 1.8 Hz, 1 H), 7.81 (d, *J* = 8.2 Hz, 1 H), 7.65 (m, 3 H), 7.51 (t, *J* = 7.3 Hz, 1 H), 6.87 (s, 2 H), 3.68 (t, *J* = 7.7 Hz, 2 H), 0.92 (t, *J* = 7.8 Hz, 2 H), –0.17 (s, 9 H).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ = 169.6, 168.7, 150.0, 142.0, 140.0, 139.0, 134.0, 128.6, 127.9, 125.5, 123.0, 122.61, 122.60, 121.6, 119.6, 117.3, 111.4, 74.4, 66.0, 18.2, –1.3.

HRMS: *m/z* calcd for C<sub>23</sub>H<sub>24</sub>N<sub>3</sub>O<sub>3</sub>Si (M + H)<sup>+</sup>: 418.1587; found (M + H)<sup>+</sup>: 418.1566.

#### Pyrido[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-dione (**4**)

A suspension of SEM-protected pyridocarbazole **8** (2.14 g, 5.1 mmol) and LiBF<sub>4</sub> (4.78 g, 51 mmol) in MeCN (605 mL) and H<sub>2</sub>O (26.7 mL) (22.6:1 ratio) was refluxed for 20 h. The resulting suspension was cooled to r.t. and the volume reduced to about 30 mL. The suspension was cooled to –20 °C for 2 h, yielding a yellow precipitate which was isolated via vacuum filtration. The filtrate was washed extensively with H<sub>2</sub>O to remove any excess salt. Drying under vacuum afforded pyridocarbazole **4** (1.47 g, ca. 100%).

IR (KBr): 3237, 2978, 2755, 1755, 1708, 1690, 1531, 1337, 1226, 756, 644 cm<sup>-1</sup>.

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ = 11.26 (s, 1 H), 9.26 (dd, *J* = 8.5, 1.7 Hz, 1 H), 9.14 (dd, *J* = 4.2, 1.5 Hz, 1 H), 8.89 (d, *J* = 7.9 Hz, 1 H), 7.85 (dd, *J* = 8.5, 4.2 Hz, 1 H), 7.77 (d, *J* = 7.7 Hz, 1 H), 7.58 (t, *J* = 7.1 Hz, 1 H), 7.40 (t, *J* = 7.4 Hz, 1 H).

#### Compound 9

**Synthesis from 4**: To a stirred suspension of **4** (1.34 g, 4.7 mmol) in MeCN (134 mL) was added *tert*-butyldimethylsilyloxymethoxyethene (3.05 mL, 14 mmol). The mixture was refluxed for 2 h during which time the yellow suspension became an orange solution. The solution was cooled to r.t. and the solvent was evaporated. The crude yellow solid was subjected to silica gel chromatography (EtOAc–hexanes, 5:1, later 1:1 or CH<sub>2</sub>Cl<sub>2</sub>–MeOH, 20:1) to yield silyl protected imide **9** as a yellow solid (1.73 g, 93%).

**Synthesis from 12**: An orange suspension of **12** (300 mg, 0.59 mmol) in MeCN (200 mL) was irradiated with a medium pressure Hg lamp (pyrex filter) for 4 h with constant argon flow through the suspension. The resulting yellow suspension was dried in vacuo and subjected to silica gel chromatography with CH<sub>2</sub>Cl<sub>2</sub>–MeOH (20:1) as the eluting solvent. Evaporation of the eluents provided **9** as a yellow solid (153 mg, 64%).

IR (film): 2927, 2857, 1752, 1690, 1598, 1528, 1462, 1405, 1339, 1308, 1281, 1260, 1233, 1071, 1044 cm<sup>-1</sup>.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ = 10.36 (br s, 1 H), 9.44 (dd, *J* = 8.5, 1.4 Hz, 1 H), 9.09 (d, *J* = 8.0 Hz, 1 H), 9.01 (dd, *J* = 4.3, 1.5 Hz, 1 H), 7.65 (dd, *J* = 8.5, 4.3 Hz, 1 H), 7.58 (m, 2 H), 7.45 (t, *J* = 8.0 Hz, 1 H), 1.09 (s, 9 H), 0.66 (s, 6 H).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ = 175.6, 174.5, 150.6, 140.1, 139.7, 138.4, 134.7, 130.9, 127.6, 125.8, 123.1, 122.6, 122.1, 122.0, 121.0, 115.5, 111.7, 26.7, 19.4, –3.7.

#### Compound 12

A solution of pyridoindole **10**<sup>12</sup> (3.36 g, 17.3 mmol) in anhyd THF (45 mL) was stirred at –15 °C under argon. Lithium bis(trimethylsilyl)amide (1 M solution in hexanes) (36.3 mL, 36.6 mmol) was added to the solution over 15 min during which time the pale yellow solution became a bright orange suspension. The suspension was allowed to stir for an additional 30 minutes at –15 °C. A solution of **11** (6.38 g, 17.3 mmol) in anhyd THF (45 mL) was cooled to 0 °C and then added all at once via syringe to the suspension of lithiated pyridoindole. The suspension was allowed to stir for another 15 min at –15 °C and then 45 min at r.t. The dark purple colored slurry was then poured carefully into aq 10% HCl (400 mL) and extracted with EtOAc (3 ×). The combined organics were washed with sat. aq NaHCO<sub>3</sub>, brine, and H<sub>2</sub>O. The organics were dried (MgSO<sub>4</sub>), filtered, and dried in vacuo. The crude material was subjected to silica gel chromatography with hexanes–EtOAc (first 4:1, then increasing polarity until 100% EtOAc) (sample loading using CH<sub>2</sub>Cl<sub>2</sub>). The solvent system was then switched to CH<sub>2</sub>Cl<sub>2</sub>–MeOH (10:1) to flush out the remaining orange product **12** which was isolated upon removal of solvent (5.7 g, 68%).

IR (film): 3334, 2930, 2855, 1704, 1630, 1592, 1529, 1454, 1310, 1252, 911, 821, 784, 736 cm<sup>-1</sup>.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ = 10.06 (s, 1 H), 8.64 (ddd, *J* = 4.8, 1.7, 1.0 Hz, 1 H), 7.64 (td, *J* = 7.8, 1.8 Hz, 1 H), 7.54 (d, *J* = 7.7 Hz, 1 H), 7.46 (d, *J* = 8.2 Hz, 1 H), 7.36 (d, *J* = 7.9 Hz, 1 H), 7.30 (ddd, *J* = 8.2, 7.1, 1.1 Hz, 1 H), 7.24–7.20 (m, 2 H), 1.00 (s, 9 H), 0.50 (s, 6 H).

<sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>): δ = 169.1, 167.1, 149.7, 149.3, 141.0, 137.0, 136.9, 136.4, 126.3, 123.2, 122.7, 122.6, 121.8, 120.6, 120.4, 112.3, 101.4, 25.8, 17.8, –3.2.

HRMS: *m/z* calcd for C<sub>23</sub>H<sub>24</sub>BrN<sub>3</sub>O<sub>2</sub>Si (M + Na)<sup>+</sup>: 504.07189; found (M + Na)<sup>+</sup>: 504.0713.

**Compound 15**

To a stirred suspension of 4-methoxyphenylhydrazine hydrochloride (5.30 g, 30.4 mmol) in *t*-BuOH (100 mL) was added 2-acetylpyridine (**14**; 2.98 mL, 26.4 mmol). The suspension was refluxed for 5 h. After cooling to r.t., the orange precipitate that formed was filtered, washed with cold EtOH and dried under vacuum. The desired product **15** was isolated in quantitative yield (7.33 g) as an orange powder. Characterization data are consistent with a previous report.<sup>15</sup>

**Compound 16**

To hot trimethylsilyl polyphosphate (65 mL), was added **15** (5.1 g) portionwise over 30 min with stirring. The dark orange solution was stirred for 18 h at 120 °C. The solution was cooled to r.t. and became very thick. The reaction mixture was then neutralized with aq 1 M NaOH. This aqueous solution was extracted with EtOAc (4 ×). The combined organic layers were washed with brine, dried (MgSO<sub>4</sub>), and concentrated. The crude product was purified by silica gel chromatography (hexanes–EtOAc, 5:1, later 3:1). The desired product **16** was isolated as a pale yellow solid (2.68 g, 63%). Characterization data are consistent with a previous report.<sup>15</sup>

**Compound 17**

Compound **16** (2.46 g, 11.0 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (75 mL). The solution was purged with argon and cooled to –60 °C. To this stirred solution, was added dropwise a 1 M solution of BBr<sub>3</sub> in CH<sub>2</sub>Cl<sub>2</sub> (24.13 mL, 24.13 mmol). After the addition was complete, the solution was stirred and allowed to warm to r.t. overnight. After TLC analysis, the reaction was quenched with an aq sat. solution of NaHCO<sub>3</sub>. The CH<sub>2</sub>Cl<sub>2</sub> layer was removed and washed with fresh NaHCO<sub>3</sub> solution. The combined aqueous layers were extracted with EtOAc (3 ×). The combined EtOAc layers were dried (MgSO<sub>4</sub>), filtered, and evaporated, yielding **17** as a pale yellow solid (2.01 g, 87%).

IR (film): 3265, 2936, 2854, 1593, 1545, 1440, 1217 cm<sup>-1</sup>.

<sup>1</sup>H NMR (500 MHz, acetone-*d*<sub>6</sub>): δ = 10.54 (br s, 1 H), 8.55 (ddd, *J* = 4.9, 1.7, 0.9 Hz, 1 H), 7.90 (dt, *J* = 8.0, 1.0 Hz, 1 H), 7.78 (td, *J* = 7.5, 1.85 Hz, 1 H), 7.65 (br s, 1 H), 7.38 (d, *J* = 8.7 Hz, 1 H), 7.21 (ddd, *J* = 7.5, 4.9, 1.1 Hz, 1 H), 7.01 (dd, *J* = 1.8, 1.2 Hz, 1 H), 6.95 (dd, *J* = 2.2, 0.8 Hz, 1 H), 6.79 (dd, *J* = 8.6, 2.4 Hz, 1 H).

<sup>13</sup>C NMR (125 MHz, acetone-*d*<sub>6</sub>): δ = 152.3, 151.8, 150.0, 138.4, 137.5, 133.2, 130.9, 122.6, 120.4, 114.2, 113.2, 105.3, 100.7.

HRMS: *m/z* calcd for C<sub>13</sub>H<sub>11</sub>N<sub>2</sub>O (MH)<sup>+</sup>: 211.0871; found (MH)<sup>+</sup>: 211.0878.

**Compound 18**

Compound **17** (1.9 g, 9.05 mmol) was dissolved in DMF (30 mL). The solution was purged with argon and cooled to 0 °C. To this stirred solution, was added carefully *N,N*-diisopropylethylamine (7.9 mL, 45.24 mmol) at 0 °C under vigorous stirring. The mixture was stirred at 0 °C for 40 min followed by the dropwise addition of TBSOTf (2.3 mL, 9.9 mmol). The resulting mixture was stirred for 1 h at 0 °C and allowed to warm to r.t. After TLC analysis, the reaction was quenched with 20% aq NH<sub>4</sub>OAc and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 ×). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated, and further dried *in vacuo* to remove residual DMF. The resulting crude material was subjected to silica gel chromatography with hexanes–EtOAc (10:1, later 5:1) yielding **18** as a pale yellow solid (2.1 g, 71%).

IR (film): 3192, 2954, 2930, 2856, 1594, 1544, 1447, 1412, 1286, 1224, 1150, 965, 889, 836, 777 cm<sup>-1</sup>.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ = 9.52 (br s, 1 H), 8.57 (ddd, *J* = 4.9, 1.7, 1.0 Hz, 1 H), 7.77 (dt, *J* = 8.0, 1.1 Hz, 1 H), 7.70 (ddd, *J* = 8.0, 1.8, 0.6 Hz, 1 H), 7.24 (dd, *J* = 8.6, 0.6 Hz, 1 H), 7.15 (ddd, *J* = 7.4, 4.9, 1.2 Hz, 1 H), 7.07 (d, *J* = 2.3 Hz, 1 H), 6.91 (dd, *J* = 2.1,

0.9 Hz, 1 H), 6.80 (dd, *J* = 8.7, 2.3 Hz, 1 H), 1.03 (s, 9 H), 0.23 (s, 6 H).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ = 150.7, 149.8, 149.3, 137.6, 136.8, 132.7, 130.0, 122.0, 120.0, 118.0, 111.9, 110.4, 100.4, 26.0, 18.5, –4.2.

HRMS: *m/z* calcd for C<sub>19</sub>H<sub>25</sub>N<sub>2</sub>O<sub>3</sub>Si (MH)<sup>+</sup>: 325.1736; found (MH)<sup>+</sup>: 325.1736.

**Compound 19**

A solution of **18** (1.8 g, 5.6 mmol) in THF (16 mL) was purged with argon, and cooled to –15 °C. With stirring, a 1 M solution of lithium bis(trimethylsilyl)amide in THF (11.2 mL, 11.2 mmol) was added dropwise over 15 min. During the course of the addition, the color of the solution changed from pale yellow to deep purple. After the addition was complete, the mixture was stirred at –15 °C for 45 min. To this mixture, was added quickly a cold solution of **11** (2.05 g, 5.6 mmol) in THF (16 mL), after which the mixture was stirred for 20 min at –15 °C and 45 min at r.t. The reaction was quenched with 1 M HCl and extracted with EtOAc (3 ×). The combined organic layers were washed with an aq sat. solution of NaHCO<sub>3</sub>, distilled H<sub>2</sub>O, and brine, dried (MgSO<sub>4</sub>), and concentrated. The crude material was further purified by silica gel chromatography with hexanes–EtOAc (10:1, later 5:1) yielding **19** as a bright orange solid (1.96 g, 58%).

IR (film): 3327, 2931, 2858, 1704, 1631, 1583, 1472, 1311, 1261, 1216, 1181, 1081, 971, 897, 830 cm<sup>-1</sup>.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ = 9.78 (br s, 1 H), 8.63 (d, *J* = 4.7 Hz, 1 H), 7.63 (td, *J* = 7.8, 1.7 Hz, 1 H), 7.31 (m, 2 H), 7.21 (m, 1 H), 6.95 (d, *J* = 2.2 Hz, 1 H), 6.86 (dd, *J* = 8.7, 2.8 Hz, 1 H) 1.02 (s, 18 H), 0.50 (s, 6 H), 0.23 (s, 6 H).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ = 173.4, 171.1, 150.5, 149.8, 149.5, 141.7, 137.3, 136.7, 131.7, 128.1, 125.6, 122.9, 122.7, 118.9, 112.6, 110.8, 101.5, 26.5, 26.0, 19.1, 18.4, –4.2.

**Compound 13**

A stirred solution of **19** (334 mg, 0.55 mmol) in MeCN (200 mL) was irradiated with a medium pressure mercury lamp through a pyrex filter for 3 h while argon was bubbled through the solution. The resulting suspension was concentrated and subjected to silica gel chromatography. Some impurity was eluted with 100% CH<sub>2</sub>Cl<sub>2</sub> and the desired product with CH<sub>2</sub>Cl<sub>2</sub>–MeOH (100:1, later 50:1). Compound **13** was isolated as a bright yellow solid (229 mg, 78%).

IR (film): 3287, 2954, 2931, 2858, 1751, 1695, 1472, 1336, 1314, 1280, 1217, 1181, 908, 829 cm<sup>-1</sup>.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ = 10.76 (br s, 1 H), 9.43 (dd, *J* = 8.5, 1.7 Hz, 1 H), 8.98 (dd, *J* = 4.3, 1.7 Hz, 1 H), 8.63 (d, *J* = 2.4 Hz, 1 H), 7.63 (dd, *J* = 8.5, 4.3 Hz, 1 H), 7.37 (d, *J* = 8.7, 1 H), 7.12 (dd, *J* = 8.7, 2.4 Hz, 1 H), 1.09 (s, 9 H), 1.08 (s, 9 H), 0.66 (s, 6 H), 0.34 (s, 6 H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 175.8, 174.1, 151.0, 150.5, 140.7, 138.5, 134.9, 134.6, 131.0, 123.2, 123.0, 122.0, 121.5, 120.3, 115.3, 114.8, 112.0, 26.7, 26.1, 19.3, 18.8, –3.8, –4.1.

HRMS: *m/z* calcd for C<sub>29</sub>H<sub>38</sub>N<sub>3</sub>O<sub>3</sub>Si<sub>2</sub> (MH)<sup>+</sup>: 532.2455; found (MH)<sup>+</sup>: 532.2448.

**Compound 22**

To a suspension of **21** (3.39 g, 19.82 mmol) in absolute EtOH (4.8 mL) was added phenyl hydrazine (4.8 mL, 19.82 mmol). The suspension was refluxed for 2 h during which time the color of the reaction mixture became yellow. Upon cooling, a yellow precipitate was formed. The mixture was cooled to 0 °C for 30 min, and then the yellow precipitate was collected via vacuum filtration. The solid was washed with cold EtOH, then dried under vacuum to provide **22** as a yellow solid (4.4 g, 85%).

IR (film): 3234, 3055, 1596, 1556, 1497, 1452, 1367, 1312, 1252, 1228, 1198, 1063, 993, 949, 889, 749, 690, 465 cm<sup>-1</sup>.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ = 9.25 (s, 1 H), 8.46 (s, 1 H), 7.96 (d, *J* = 8.2 Hz, 1 H), 7.92 (d, *J* = 8.3 Hz, 1 H), 7.69 (t, *J* = 7.5 Hz, 1 H), 7.62 (br s, 1 H), 7.57 (t, *J* = 7.5 Hz, 1 H), 7.35–7.27 (m, 4 H), 6.92 (t, *J* = 7.1 Hz, 1 H), 2.52 (s, 3 H).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ = 151.3, 150.6, 145.1, 142.7, 136.6, 130.6, 129.5, 128.3, 127.7, 127.5, 127.1, 120.7, 116.2, 113.5, 10.9.

HRMS: *m/z* calcd for C<sub>17</sub>H<sub>15</sub>N<sub>3</sub> (M)<sup>+</sup>: 261.1266; found (M)<sup>+</sup>: 261.1271.

### Compound 23

A mixture of **22** (1.4 g, 5.36 mmol) and trimethylsilyl polyphosphate was heated to 150 °C for 12 h. The reaction was cooled and added to ice water resulting in the formation of dark solid material. The material was neutralized with aq 25% NaOH, collected via vacuum filtration, and washed extensively with EtOAc. The combined EtOAc filtrates were extracted with H<sub>2</sub>O, dried (MgSO<sub>4</sub>), filtered, and dried in vacuo. The material was subjected to silica gel chromatography with hexanes–EtOAc (5:1) as the eluting solvent yielding **23** as a light yellow solid (615 mg, 47%).

IR (film): 3417, 2920, 2848, 1587, 1402, 1341, 1269, 1233, 1172, 1131, 1044, 961, 931, 879, 854, 797, 736, 700 cm<sup>-1</sup>.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ = 9.71 (br s, 1 H), 9.25 (s, 1 H), 8.16 (s, 1 H), 7.98 (dd, *J* = 8.2, 0.8 Hz, 1 H), 7.88 (d, *J* = 8.3 Hz, 1 H), 7.74–7.67 (m, 2 H), 7.58 (ddd, *J* = 8.1, 6.9, 1.1 Hz, 1 H), 7.47 (dd, *J* = 8.1, 0.9 Hz, 1 H), 7.23 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1 H), 7.16–7.12 (m, 2 H).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ = 152.2, 144.5, 137.4, 136.8, 136.7, 131.0, 129.6, 128.06, 127.98, 127.2, 126.9, 122.9, 121.1, 120.3, 115.8, 111.6, 99.7.

HRMS: *m/z* calcd for C<sub>17</sub>H<sub>12</sub>N<sub>2</sub> (M)<sup>+</sup>: 244.1000; found (M)<sup>+</sup>: 244.0996.

### Compound 20

A solution of **23** (200 mg, 0.82 mmol) was stirred under argon in THF (2.2 mL) and cooled to –15 °C. Lithium bis(trimethylsilyl)amide (1 M in hexanes, 1.72 mL, 1.72 mmol) was added dropwise over 15 min. The solution was stirred at –15 °C for another 15 min, affording a light orange suspension. A solution of **11** (302.5 mg, 0.82 mmol) in THF (2.2 mL) which had been cooled to 0 °C, was added to the lithiated material all at once via syringe. The resulting purple solution was stirred 15 min at –15 °C, then at r.t. for 1 h. The solution was added to aq 10% HCl (30 mL), and washed with EtOAc (3 ×). The combined organic extracts were washed successively with sat. aq NaHCO<sub>3</sub>, brine, and H<sub>2</sub>O, then dried (MgSO<sub>4</sub>), filtered, and dried in vacuo affording crude **24** as an orange solid. The material was not stable to column chromatography and was brought to the next step crude. The material was dissolved in MeCN (220 mL) and photolyzed with a medium pressure quartz lamp with constant argon purge for 4 h. The resulting yellow suspension was dried in vacuo and subjected to silica gel chromatography with CH<sub>2</sub>Cl<sub>2</sub>–MeOH (20:1) to afford **20** as a yellow solid (310 mg, 84%).

IR (film): 2954, 2927, 2855, 1729, 1689, 1603, 1586, 1532, 1452, 1326, 1299, 1255, 1232, 1084, 825, 753, 686, 646, 610, 570, 534, 516 cm<sup>-1</sup>.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ = 10.28 (d, *J* = 8.6 Hz, 1 H), 10.02 (br s, 1 H), 9.38 (s, 1 H), 9.26 (d, *J* = 8.0 Hz, 1 H), 8.15 (d, *J* = 7.9 Hz, 1 H), 8.04 (t, *J* = 7.7 Hz, 1 H), 7.85 (t, *J* = 7.5 Hz, 1 H), 7.68 (d, *J* = 8.0 Hz, 1 H), 7.62 (t, *J* = 7.6 Hz, 1 H), 7.47 (t, *J* = 7.5 Hz, 1 H), 1.11 (s, 9 H), 0.71 (s, 6 H).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>/CD<sub>3</sub>OD): δ = 175.2, 174.0, 154.2, 141.7, 140.7, 134.7, 131.8, 131.4, 131.2, 129.4, 128.6, 128.4, 127.5, 127.4, 125.8, 121.6, 121.2, 121.1, 120.1, 115.9, 111.4, 26.4, 19.1, –3.8.

HRMS: *m/z* calcd for C<sub>27</sub>H<sub>25</sub>N<sub>3</sub>O<sub>2</sub>Si (MH)<sup>+</sup>: 452.1794; found (MH)<sup>+</sup>: 452.1815.

### Compound 3

A suspension of ligand **9** (65 mg, 0.162 mmol), K<sub>2</sub>CO<sub>3</sub> (22.4 mg, 0.162 mmol), and [RuCp(CO)(CH<sub>3</sub>CN)<sub>2</sub>]<sup>+</sup>PF<sub>6</sub><sup>-</sup> (68.2 mg, 0.162 mmol) was heated in MeCN (6.5 mL) to 55 °C overnight. The resulting red/purple solution was then subsequently desilylated with the addition of 1 M solution of TBAF in THF (243 μL, 0.243 mmol) for 15 min at r.t. Glacial AcOH (13.9 μL, 0.243 mmol) was added and the solution stirred at r.t. for 10 min. The solution was then dried in vacuo and purified by silica gel chromatography with EtOAc–hexanes (1:10, later 1:1) as eluents to afford **3** as a pink solid (59 mg, 84%).

IR (film): 2960, 2920, 1949, 1751, 1696, 1522, 1418, 1344, 1264, 1230, 1076 cm<sup>-1</sup>.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ = 9.22 (d, *J* = 8.3 Hz, 1 H), 8.95 (d, *J* = 5.0 Hz, 1 H), 8.87 (d, *J* = 7.9 Hz, 1 H), 7.61 (t, *J* = 7.8 Hz, 1 H), 7.51 (m, 2 H), 7.44 (t, *J* = 7.4 Hz, 1 H), 7.40 (br s, 1 H), 5.25 (s, 5 H).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>/CD<sub>3</sub>OD): δ = 199.6, 171.3, 170.9, 155.4, 154.6, 153.4, 144.7, 133.8, 131.5, 126.3, 124.9, 124.0, 122.2, 122.1, 119.9, 116.0, 115.3, 112.0, 80.6.

### Compound 25

A suspension of ligand **20** (15 mg, 0.033 mmol), K<sub>2</sub>CO<sub>3</sub> (5 mg, 0.033 mmol), and [RuCp(CO)(CH<sub>3</sub>CN)<sub>2</sub>]<sup>+</sup>PF<sub>6</sub><sup>-</sup> (13.9 mg, 0.033 mmol) was heated in MeCN (1.5 mL) to 55 °C overnight. The resulting red/purple solution was then subsequently desilylated with the addition of 1 M solution of TBAF in THF (50 μL, 0.050 mmol) for 15 min at r.t. Glacial AcOH (2.9 μL, 0.050 mmol) was added and the solution stirred at r.t. for 10 min. The solution was then dried in vacuo and purified by silica gel chromatography using EtOAc–hexanes (1:3) as eluent to afford **25** as a purple solid (11 mg, 62%).

IR (film): 3041, 1941, 1739, 1699, 1576, 1558, 1536, 1465, 1438, 1377, 1340, 1324, 1300, 1269, 1232 cm<sup>-1</sup>.

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ = 11.29 (s, 1 H), 10.53 (d, *J* = 8.6 Hz, 1 H), 10.04 (s, 1 H), 8.84 (d, *J* = 7.6 Hz, 1 H), 8.35 (d, *J* = 7.6 Hz, 1 H), 8.12 (t, *J* = 7.7 Hz, 1 H), 7.96 (t, *J* = 7.7 Hz, 1 H), 7.60–7.55 (m, 2 H), 7.33 (t, *J* = 7.1 Hz, 1 H), 5.56 (s, 5 H).

<sup>13</sup>C NMR (90 MHz, DMSO-*d*<sub>6</sub>): δ = 202.0, 171.5, 170.5, 161.7, 155.8, 153.8, 139.7, 133.1, 131.9, 131.7, 129.7, 129.3, 129.0, 128.0, 127.3, 125.2, 123.5, 120.5, 119.5, 116.7, 115.8, 114.4, 82.6.

### Compound 26

A suspension of ligand **13** (51 mg, 0.096 mmol), K<sub>2</sub>CO<sub>3</sub> (13.3 mg, 0.096 mmol) and [RuCp(CO)(CH<sub>3</sub>CN)<sub>2</sub>]<sup>+</sup>PF<sub>6</sub><sup>-</sup> (40.5 mg, 0.096 mmol) was heated in MeCN (5 mL) to 55 °C overnight. The resulting red/purple solution was then dried in vacuo, redissolved in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) and subsequently desilylated with the addition of 1 M solution of TBAF in THF (288 μL, 0.288 mmol) for 30 min at r.t. Glacial AcOH (16.5 μL, 0.288 mmol) was added and the mixture was stirred at r.t. for 10 min. The mixture was then dried in vacuo and purified by silica gel chromatography using CH<sub>2</sub>Cl<sub>2</sub>–MeOH (50:1) as eluent to afford **26** as a purple solid (62 mg, 75%).

IR (film): 3438, 3274, 2926, 2849, 1949, 1747, 1698, 1601, 1501, 1471, 1424, 1342, 1214, 795 cm<sup>-1</sup>.

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ = 11.04 (s, 1 H), 9.25 (dd, *J* = 5.1, 1.1 Hz, 1 H), 9.22 (s, 1 H), 9.04 (dd, *J* = 8.3, 1.1 Hz, 1 H), 8.10 (d, *J* = 2.6 Hz, 1 H), 7.69 (dd, *J* = 8.1, 5.1 Hz, 1 H), 7.45 (d, *J* = 8.7 Hz, 1 H), 7.08 (dd, *J* = 8.7, 2.6 Hz, 1 H), 5.52 (s, 5 H).

$^{13}\text{C}$  NMR (extracted from hmbc and hmqc two-dimensional experiments) (600 MHz/150 MHz,  $\text{DMSO-}d_6$ ):  $\delta = 170.0, 155.0, 150.9, 146.3, 143.4, 132.1, 130.5, 123.2, 122.1, 120.5, 115.7, 113.7, 110.2, 107.5, 80.9$ .

#### Compound 27

A suspension of ligand **13** (27 mg, 0.052 mmol),  $\text{K}_2\text{CO}_3$  (7 mg, 0.052 mmol) and  $[\text{RuCp}^*(\text{CO})(\text{CH}_3\text{CN})_2]^+\text{PF}_6^-$  (25 mg, 0.052 mmol) was heated in MeCN (3 mL) to 55 °C overnight. The resulting red/purple solution was then dried in vacuo, redissolved in  $\text{CH}_2\text{Cl}_2$  (3 mL) and subsequently desilylated with the addition of 1 M solution of TBAF in THF (156  $\mu\text{L}$ , 0.156 mmol) for 30 min at r.t. The reaction was then quenched by the addition of glacial AcOH (8.5  $\mu\text{L}$ , 0.156 mmol) and stirred at r.t. for 10 min. The solution was then dried in vacuo and purified by silica gel chromatography using  $\text{CH}_2\text{Cl}_2$ -MeOH (50:1) as eluent to afford **27** as a purple solid (25 mg, 54%).

IR (film): 3310, 2920, 1923, 1742, 1694, 1591, 1532, 1499, 1472, 1423, 1342, 1213, 1010  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (360 MHz,  $\text{DMSO-}d_6$ ):  $\delta = 10.95$  (br s, 1 H), 9.16 (s, 1 H), 9.07 (dd,  $J = 8.3, 1.0$  Hz, 1 H), 8.91 (dd,  $J = 5.0, 1.0$  Hz, 1 H), 8.15 (d,  $J = 2.3$  Hz, 1 H), 7.79 (dd,  $J = 8.3, 5.1$  Hz, 1 H), 7.47 (d,  $J = 8.8$  Hz, 1 H), 7.10 (dd,  $J = 8.8, 2.5$  Hz, 1 H), 1.70 (s, 15 H).

$^{13}\text{C}$  NMR (90 MHz,  $\text{DMSO-}d_6$ ):  $\delta = 202.8, 170.77, 170.70, 153.4, 152.2, 151.3, 145.7, 143.8, 132.6, 131.1, 124.7, 123.1, 120.9, 116.1, 115.6, 114.4, 110.6, 108.5, 93.1, 9.7$ .

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