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Synthesis of novel NHC–Rh complexes with anti-tumor activity against MCF-7 human breast cancer cells

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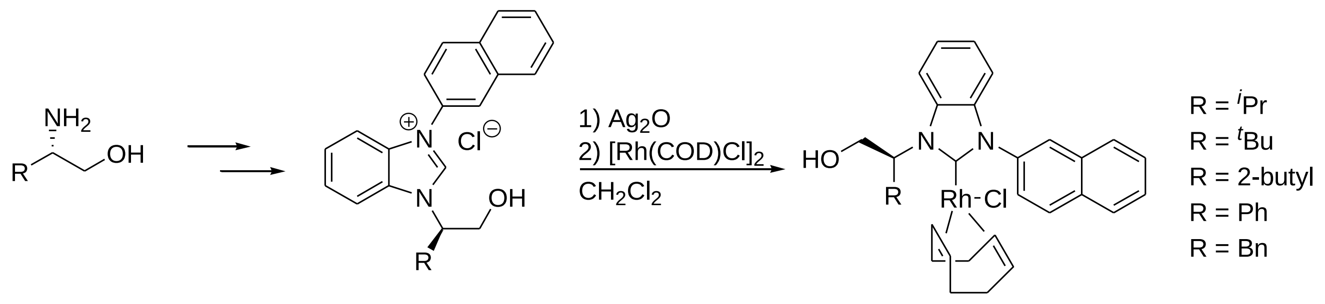
Abstract

A series of novel N-heterocyclic carbene rhodium complexes (NHC–Rh), containing benzimidazole framework, were prepared smoothly by a five-step route. Their structures were elucidated based on spectral techniques, including NMR and MS spectrometry. Along with several NHC–Rh complexes we prepared before, the compounds prepared herein were evaluated for their cytotoxicities against MCF human breast cancer cells and several of them showed strong activities with IC_{50} values ranging from 0.38 to 1.18μM, which were better than the positive control paclitaxel.



Keywords: N-heterocyclic carbene; benzimidazolium; cytotoxic activity; MCF-7 cell lines

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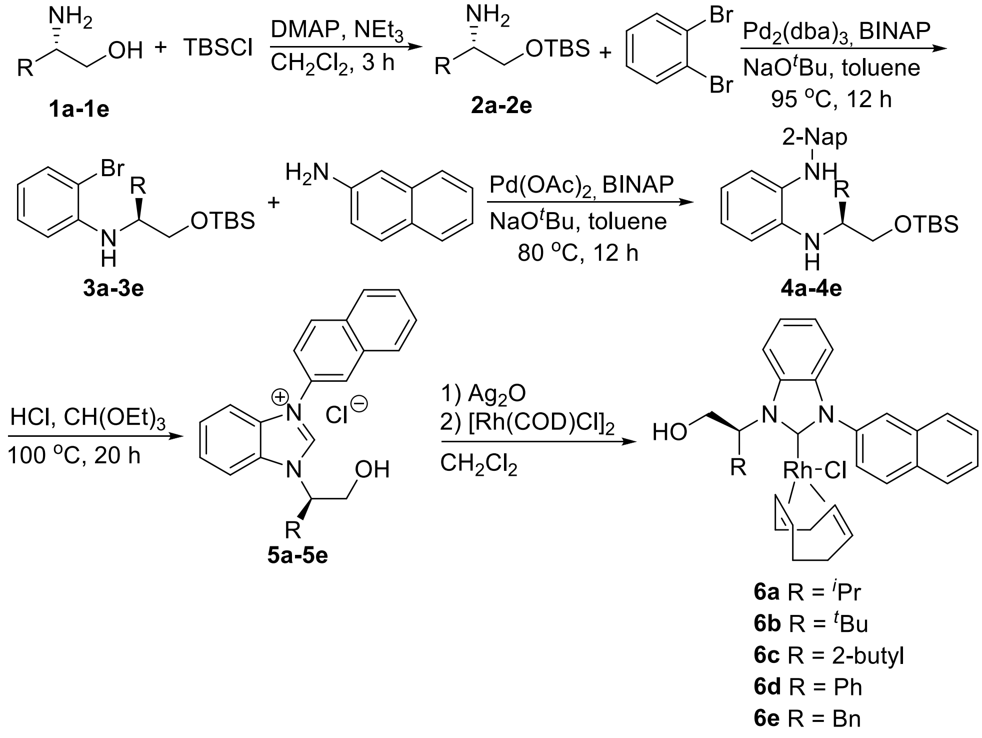
Introduction

In 1960s, Öfele and Wanzlick reported the first example of N-heterocyclic carbenes (NHCs).[1–2] However, little attention was paid to these kind of ligands until Arduengo and co-workers prepared the first isolable carbene in 1991.[3] NHCs are famous for their powerful σ-donating ability due to the adjacent nitrogen atoms around carbene C atom. Therefore, employment of N-heterocyclic carbenes (NHCs) as ligands to generate coordination compounds have attracted considerable attention in homogeneous metal catalysis.[4–13] Due to their excellent σ-donating ability, increasing NHCs appeared as ligands to construct complexes in metal medicine.[14] In this respect, NHC ligands may substantially stabilize metal complexes to resist degradation under physiological conditions. Notably, the modification at ^{1}N and ^{3}N positions of NHC ligands is facile and a variety of functional groups could be introduced to these ligands to increase the selectivity to biomolecules.[15] Since Berners-Price reported the anticancer properties of Au(I)-NHC complexes in 2004,[16] considerable efforts have been dedicated to the investigation of metal NHC complexes, such as Au, Ag, Pd, Pt, Cu, Ru, and Ir, as antineoplastic agents.[17–22] In combination of our interest in the development of novel NHCs ligands[23–28] and our experience with benzimidazole carbenes,[29–31] we herein report a new route for the synthesis NHC–Rh complexes with benzimidazole backbone using simple 1,2-dibromobenzene as starting material. Considering the promising potential of rhodium complexes as therapeutic molecules,[32–39] these new complexes were evaluated for cytotoxicity against MCF-7 human breast cancer cells and most of the synthesized complexes showed excellent activities.

Results and Discussion

As shown (Scheme 1), the novel NHC–Rh complexes were synthesized by a five-step route. To protect the hydroxyl group, the commercial available amino alcohols **1a–1e** were firstly treated with *t*-butyldimethylsilyl chloride, affording the silylanization products **2a–2e** in good yields (74–88%). The corresponding products were then underwent a Buchwald–Hartwig coupling with 1,2-dibromobenzene, giving the monosubstituted products **3a–3e** in 68–93% yields. A second Buchwald–Hartwig coupling was then conducted with 2-naphthylamine, furnishing the differentially substituted diamines **4a–4e** in excellent yields (88–98%). Finally, the benzimidazolium salts **5a–5e** were prepared smoothly by treatment of the corresponding diamines with concentrated hydrochloric acid in $CH(OEt)_3$, giving the products in 80–87% yields. Interestingly, the TBS group was deprotected simultaneously in this cyclization step.

With benzimidazolium precursors in hand, the NHC–Rh complexes **6a–6e** were prepared without difficulty using a transmetalation method developed by Lin and co-workers,[40] and the procedure was depicted as follow. The benzimidazolium salts **5a–5e** were treated with Ag_2O in CH_2Cl_2 at room temperature for 2 hours in the darkness. The resulting reaction mixture was used directly with the addition of $[Rh(COD)Cl]_2$, and the NHC–Rh complexes **6a–6e** were constructed upon workup. The target product is air stable and could be purified by chromatography on silica gel without decomposition.



Scheme 1. Synthesis of new NHC–Rh complexes **6a–6e**.

In our previous work, we have prepared a series of NHC–Rh complexes **7a–7g** with benzimidazole backbone through a different method.[29,31] The NHC–Rh complexes prepared herein distinguish from compounds **7a–7g** for incorporating hydroxyl group in one of the *N*-substituents, which may stabilize the metal center by hydrogen bond. Using paclitaxel as a positive control, the NHC–Rh complexes **7a–7g** (Figure 1), along with the novel complexes **6a–6e** in this study, were subjected to evaluate cytotoxicity against MCF-7 human breast cancer cells. As shown in Table 1, compounds **6a**, **6b**, **6c**, **6e**, **7c**, **7d**, and **7g** exhibited strong activities with IC_{50} values ranging from 0.385 to 1.18 μM, which is better than paclitaxel. The promising results indicated the following primary structure activity relationship: (1) introduction of hydroxyl group at *N*-substituents is beneficial for the antitumor activity of these NHC–Rh complexes. (2) the alkyl groups at C-2' is essential to maintain the biological activity. Overall, the results presented herein may contribute a growing list of bioactive rhodium complexes and provide lead compounds for development of more effective antineoplastic agents.

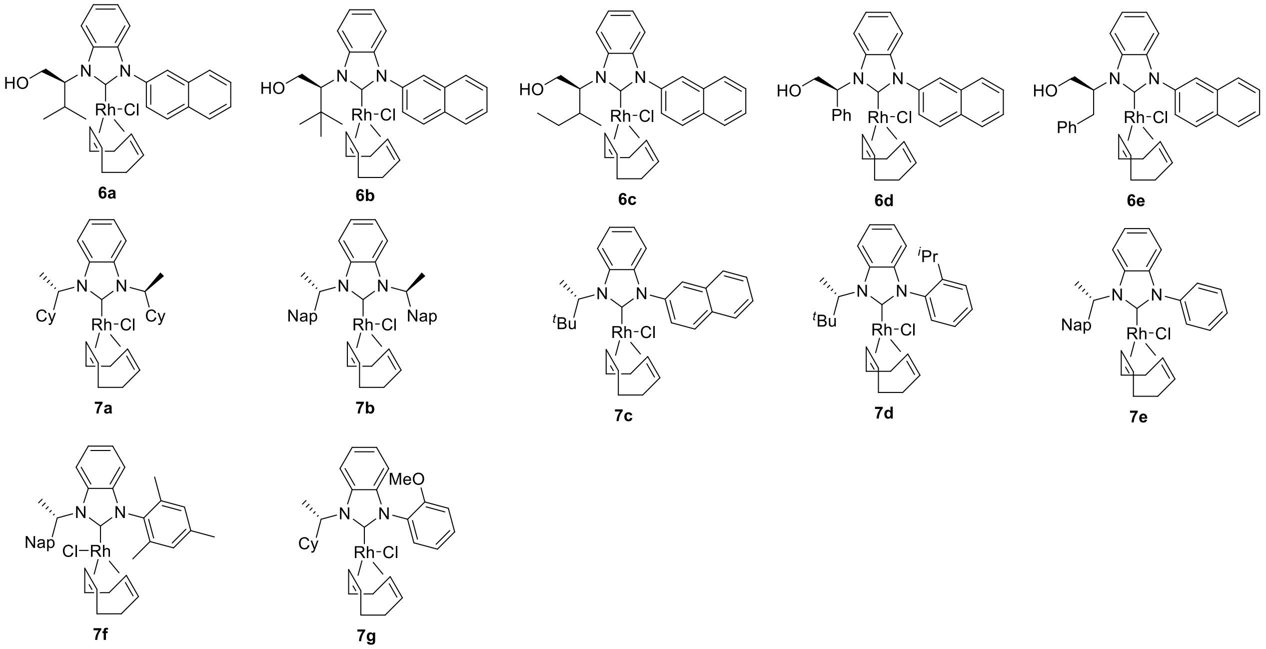

6a 6b 6c 6d 6e
7a 7b 7c 7d 7e
7f 7g

Figure 1. Structure of NHC–Rh complexes **6a–6e** and **7a–7g.**

Table 1. IC_{50} values of NHC–Rh complexes against MCF-7 human breast cancer cell

Entry	Compound	IC_{50} (μM)
1	**6a**	0.38
2	**6b**	0.45
3	**6c**	0.72
4	**6d**	> 10
5	**6e**	1.02
6	**7a**	> 10
7	**7b**	> 10
8	**7c**	0.54
9	**7d**	1.18
10	**7e**	> 10
11	**7f**	> 10
12	**7g**	0.61
13	Paclitaxel	1.38

Conclusions

In summary, we described herein a facile route for the synthesis of novel NHC–Rh compexes with benzimidazole framework. This approach enables the preparation of a series of complexes **6a–6e** bearing similar backbone but incorporating different N-substituents. Comparing to our reported complexes **7a–7g**, the newly complexes which incorporating hydroxyl group showed better result in the test for their biological activity against MCF-7 human cancer cell lines. This study provides the promising compounds for further drug candidate development. Further application of these Rh-complexes in asymmetric catalysis are currently underway and will be reported in due course.

Experimental Section

General. ^{1}H- and ^{13}C-NMR spectra were obtained on Bruker AVANCE III 500 MHz and 600 MHz spectrometers (Bruker Co., Billerica, MA, USA) with TMS as the internal standard; MS spectra were measured on a Finnigan LCQDECA XP instrument and an Agilent Q-TOF 1290 LC/6224 MS system (Santa Clara, CA, USA); silica gel GF$_{254}$ and H (10–40 mm, Qingdao Marine Chemical Factory, Qingdao, China) were used for TLC and CC. Unless otherwise noted, all reactions were carried out under an atmosphere of nitrogen.

Procedure for the synthesis of compounds 2a–2e. A solution of *t*-butylchlorodimethylsilane (TBSCl) (1.5 g, 10 mmol) in CH_2Cl_2 (50 mL) was dropped to a stirred solution of (S)- valinol (**1a**) (1.03 g, 10 mmol), Et_3N (2.02 g, 20 mmol), and 4-(dimethylamino)pyridine (DMAP) (0.244 g, 2.0 mmol) in CH_2Cl_2 (16 mL). After stirring at room temperature for 18 h, the mixture was poured into water, and extracted with CH_2Cl_2 (30 mL × 3). The solvents were removed under reduced pressure and the residue was purified by column chromatography (CH_2Cl_2:MeOH = 70:1) to give the product **2a** as colorless oil (74% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.64 (dd, J 9.8, 4.0 Hz, 1H), 3.40 – 3.37 (m, 1H), 2.59 – 2.56 (m, 1H), 0.92 (d, *J* 4.4, 6H), 0.90 (s, 9H), 0.06 (s, 6H). The ^{1}H NMR data of **2a** was identical to those reported in the literature.[41]

Analogous compounds **2b–2e** were prepared according to the similar procedure for **2a**. **2b**: 75% yield; ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 3.76 (dd, *J* 9.8, 3.2 Hz, 1H), 3.37 – 3.34 (m, 1H), 2.57 (dd, *J* 8.8, 3.2 Hz, 1H), 0.92 (s, 9H), 0.91 (s, 9H), 0.07 (s, 6H). **2c**: 78% yield; ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 3.66 (dd, *J* 9.8, 3.7 Hz, 1H), 3.40 – 3.37 (m, 1H), 2.68 – 2.65 (m, 1H), 1.55 – 1.50 (m, 1H), 1.42 – 1.37 (m, 1H), 1.22 – 1.13 (m, 1H), 0.92 – 0.87 (m, 15H), 0.06 (s, 6H). **2d**: 85% yield; ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 7.38 (dd, *J* 8.3, 1.3 Hz, 2H), 7.35 – 7.32 (m, 2H), 7.28 – 7.25 (m, 1H), 4.08 (dd, *J* 8.4, 3.9 Hz, 1H), 3.73 (dd, *J* 9.8, 4.0 Hz, 1H), 3.53 (dd, *J* 9.8, 8.4 Hz, 1H), 0.91 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H). The ^{1}H NMR data of **2d** was identical to those reported in the literature.[42] **2e**: 88% yield; ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 7.32 – 7.29 (m, 2H), 7.24 – 7.21 (m, 3H), 3.59 (dd, *J* 9.7, 4.4 Hz, 1H), 3.45 (dd, *J* 9.7, 6.5 Hz, 1H), 3.13 – 3.08 (m, 1H), 2.80 (dd, *J* 13.4, 5.3 Hz, 1H), 2.52 (dd, *J* 13.4, 8.4 Hz, 1H), 0.92 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H). The ^{1}H NMR data of **2e** was identical to those reported in the literature.[43]

Procedure for the synthesis of compounds 3a–3e. $Pd_2(dba)_3$ (18 mg, 0.02 mmol), (±)-BINAP (25 mg, 0.04 mmol), and sodium tert-butoxide (250 mg, 2.6 mmol) were dissolved in toluene (6 ml) and the solution degassed for three times before being heated at 95 °C for 15 min. Upon cooling to room temperature, **2a** (521 mg, 2.4 mmol) and 1,2-dibromobenzene (241 mg, 2.0 mmol) were added and the reaction mixture heated at 95 °C for 2 h. The solution was allowed to cool and filtered through a pad of celite. Solvents were removed under reduced pressure and the crude material purified by column chromatography eluting with light petroleum/ethyl acetate (99/1). Colorless oil (692 mg, 93%); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.41 (d, *J* 7.9, 1.5 Hz, 1H), 7.15 – 7.12 (m, 1H), 6.65 (dd, *J* 8.2, 1.0 Hz, 1H), 6.52 – 6.49 (m, 1H), 4.60 (d, *J* 9.1 Hz, 1H), 3.74 (dd, *J* 10.1, 3.7 Hz, 1H), 3.63 (dd, *J* 10.1, 5.0 Hz, 1H), 3.28 – 3.23 (m, 1H), 2.10 – 2.03 (m, 1H), 1.01 (d, *J* 7.0 Hz, 3H), 1.00 (d, *J* 7.0, 3H), 0.90 (s, 9H), 0.03 (d, *J* 1.5 Hz, 6H).

Analogous compounds **3b–3e** were prepared according to the similar procedure for **3a**. **3b**: 68% yield; ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 7.40 (d, *J* 6.5 Hz, 1H), 7.12 (t, *J* 7.2 Hz 1H), 6.70 (d, *J* 7.8 Hz, 1H), 6.49 (t, *J* 7.0 Hz, 1H), 4.70 (d, *J* 9.7 Hz, 1H), 3.76 – 3.73 (m, 2H), 3.21 – 3.19 (m, 1H) 1.26 (s, 9H), 0.86 (s, 9H), 0.01 (s, 6H). **3c**: 80% yield; ^{1}H

NMR (500 MHz, $CDCl_3$) *δ*: 7.41 (d, *J* 7.8 Hz, 1H), 7.13 (t, *J* 7.7 Hz, 1H), 6.64 (d, *J* 8.2 Hz, 1H), 6.51 (t, *J* 7.5 Hz, 1H), 4.65 (d, *J* 8.9 Hz, 1H), 3.75 (dd, *J* 10.1, 3.6 Hz, 1H), 3.67 (dd, *J* 10.2, 4.6 Hz, 1H) 3.34 – 3.31 (m, 1H), 1.82 – 1.77 (m, 1H), 1.65 – 1.60 (m, 1H), 1.24 – 1.19 (m, 1H), 0.98 – 0.93 (m, 6H), 0.90 (s, 9H), 0.03 (s, 6H). **3d**: 75% yield; ^1H NMR (500 MHz, $CDCl_3$) *δ*: 7.43 (dd, *J* 7.9, 1.5 Hz, 1H), 7.38 – 7.37 (m, 2H), 7.34 – 7.31 (m, 2H), 7.28 – 7.26 (m, 1H), 6.98 – 6.94 (m, 1H), 6.54 – 6.50 (m, 1H), 6.33 (dd, *J* 8.2, 1.4 Hz, 1H), 5.42 (br s, 1H), 4.44 – 4.41 (m, 1H), 3.95 (dd, *J* 10.1, 4.2 Hz, 1H), 3.72 (dd, *J* 10.2, 7.3 Hz, 1H), 0.91 (s, 9H), 0.05 (s, 3H), 0.01 (s, 3H). **3e**: 77% yield; ^1H NMR (500 MHz, $CDCl_3$) *δ*: 7.43 (dd, *J* 7.9, 1.5 Hz, 1H), 7.33 – 7.30 (m, 2H), 7.25 – 7.22 (m, 3H), 7.19 – 7.16 (m, 1H), 6.70 (dd, *J* 8.2, 1.3 Hz, 1H), 6.57 – 6.53 (m, 1H), 4.78 (d, *J* 8.9 Hz, 1H), 3.68 – 3.58 (m, 3H), 2.94 (d, *J* 6.7 Hz, 2H), 0.97 (m, 9H), 0.08 (s, 3H), 0.07 (s, 3H).

Procedure for the synthesis of compounds 4a–4e. $Pd(OAc)_2$ (34 mg, 0.15 mmol) and (±)-BINAP (93 mg, 0.15 mmol) were dissolved in toluene (10 mL) under a nitrogen atmosphere, the mixture was heated to 60 °C for 10 min. After cooling to room temperature, **2a** (556 mg, 1.5 mmol), 2-naphthylamine (258 mg, 1.8 mmol), and of NaO^tBu (360 mg 3.75 mmol) were added successively under N_2. After stirring at 80 °C for 12 h, the solution was allowed to cool and filtered through a pad of celite. Solvents were removed under reduced pressure and the crude material purified by column chromatography eluting with light petroleum/ethyl acetate (50/1). **4a**: yellow oil (566 mg, 87%); ^1H NMR (500 MHz, $CDCl_3$) δ: 7.70 (t, *J* 9.3 Hz, 2H), 7.56 (d, *J* 8.3 Hz, 1H), 7.35 (t, *J* 7.5 Hz, 1H), 7.24 (t, *J* 7.4 Hz, 1H), 7.18 – 7.12 (m, 2H), 7.04 (d, *J* 8.8 Hz, 1H), 6.91 (s, 1H), 6.79 (d, *J* 7.9 Hz, 1H), 6.68 (t, *J* 7.3 Hz, 1H), 4.43 (br s, 1H), 3.68 (dd, *J* 10.0, 3.6 Hz, 1H), 3.55 (dd, *J* 10.0, 5.3 Hz, 1H), 3.27 (d, *J* 4.2 Hz, 1H), 2.01 – 1.97 (m, 1H), 0.92 (d, *J* 6.7 Hz, 3H), 0.87 (d, *J* 6.7 Hz, 3H), 0.80 (s, 9H), –0.03 (s, 3H), –0.08 (s, 3H).
Analogous compounds **4b–4e** were prepared according to the similar procedure for **4a**. **4b**: 91% yield; ^1H NMR (500 MHz, $CDCl_3$) *δ*: 7.70 – 7.67 (m, 2H), 7.55 (d, *J* 8.3 Hz, 1H), 7.34 (t, *J* 7.1 Hz, 1H), 7.22 (t, *J* 7.0 Hz, 1H), 7.16 – 7.10 (m, 2H), 7.04 (dd, *J* 8.7, 2.1 Hz, 1H), 6.91 (s, 1H), 6.82 (d, *J* 8.1 Hz, 1H), 6.67 – 6.64 (m, 1H), 3.71 – 3.64 (m, 2H), 3.18 – 3.16 (m, 1H), 0.91 (s, 9H), 0.79 (s, 9H), –0.04 (s, 3H), –0.09 (s, 3H). **4c**: 98% yield; ^1H NMR (500 MHz, $CDCl_3$) *δ*: 7.70 (t, *J* 8.5 Hz, 2H), 7.57 (d, *J* 8.1 Hz, 1H), 7.36 (t, *J* 7.4 Hz, 1H), 7.28 – 7.23 (m, 3H), 7.09 – 7.06 (m, 2H), 6.99 (s, 1H), 6.84 – 8.82 (m, 1H), 3.72 – 3.68 (m, 2H), 3.44 – 3.37 (m, 1H), 1.85 – 1.76 (m, 1H), 1.65 – 1.56 (m, 1H), 1.53 – 1.46 (m, 1H), 0.96 – 0.86 (m, 6H), 0.81 (s, 9H), –0.02 (s, 3H), –0.06 (s, 3H). **4d**: 99% yield; ^1H NMR (500 MHz, $CDCl_3$) *δ*: 7.73 (dd, *J* 8.2, 5.2 Hz, 2H), 7.61 (d, *J* 8.2 Hz, 1H), 7.40 – 7.38 (m, 3H), 7.32 (t, *J* 7.4 Hz, 2H), 7.27 – 7.24 (m, 2H), 7.19 (d, *J* 7.3 Hz, 1H), 7.11 (dd, *J* 8.7, 2.0 Hz, 1H), 6.98 (s, 1H), 6.95 (t, *J* 7.9 Hz, 1H), 6.72 (t, *J* 7.4 Hz, 1H), 6.52 (d, *J* 7.3 Hz, 1H), 4.44 – 4.41 (m, 1H), 3.85 (dd, *J* 10.1, 4.1 Hz, 1H), 3.65 – 3.61 (m, 1H), 0.70 (s, 9H), –0.13 (s, 3H), –0.19 (s, 3H). **4e**: 97% yield; ^1H NMR (500 MHz, $CDCl_3$) *δ*: 7.72 – 7.68 (m, 2H), 7.55 (d, *J* 8.2 Hz, 1H), 7.36 (t, *J* 7.1 Hz, 1H), 7.26 – 7.14 (m, 8H), 6.99 (dd, *J* 8.7, 1.8 Hz, 1H), 6.87 – 6.86 (m, 2H), 6.74 (t, *J* 7.1 Hz, 1H), 3.67 (br s, 1H), 3.59 (dd, *J* 9.9, 3.1 Hz, 1H), 3.50 (dd, *J* 9.9, 4.8 Hz, 1H), 2.90 – 2.84 (m, 2H), 0.80 (s, 9H), –0.04 (s, 3H), –0.10 (s, 3H).

Procedure for the synthesis of compounds 5a–5e. Diamine **4a** (781 mg, 1.8 mmol) was dissolved in 70 mL triethylorthoformate, then concentrated hydrochloric acid (37% w/w, 10.8 mmol, 896 µL of solution) was added at room temperature and the mixture was stirred for 30 mins. Then the mixture was heated to 80 °C under air atmosphere for 12 h. After cooling to room temperature, solvents were removed under reduced pressure and the crude material purified by column chromatography eluting with CH_2Cl_2/MeOH = 45:1, giving the product **5a** as white solid (560 mg, 85%). ^1H NMR (500 MHz, DMSO) δ: 10.47 (s, 1H), 8.55 (s, 1H), 8.33 (d, J 8.7 Hz, 2H), 8.16 (d, *J* 2.7 Hz, 2H), 8.02 – 7.96 (m, 2H), 7.81 – 7.73 (m, 4H), 5.46 (t, *J* 5.8 Hz, 1H), 4.82 – 4.81 (m, 1H), 4.12 – 4.07 (m, 1H), 3.92 – 3.90 (m, 1H), 2.56 – 2.50 (m, 1H), 1.15 (d, *J* 6.5 Hz, 3H), 0.88 (t, *J* 7.8 Hz, 3H);

^{13}C NMR (125 MHz, DMSO) δ: 142.3, 133.2, 130.7, 128.9, 128.5, 128.4, 128.2, 128.0, 127.5, 125.1, 123.3, 114.9, 114.2, 67.5, 60.7, 19.8, 19.7; HR-ESIMS*: m/z* 331.1823 [M–Cl]$^+$ (calcd for $C_{22}H_{23}N_2O$, 331.1805).

Analogous compounds **5b−5e** were prepared according to the similar procedure for **5a**. **5b**: 83% yield; ^{1}H NMR (500 MHz, DMSO) *δ*: 10.52 (s, 1H), 8.57 (s, 1H), 8.42 (d, *J* 8.4 Hz, 1H), 8.32 (d, *J* 8.8 Hz, 1H), 8.17 – 8.15 (m, 2H), 8.02 (dd, *J* 8.7, 1.9 Hz, 1H), 7.95 (d, *J* 8.2 Hz, 1H), 7.81 – 7.76 (m, 1H), 7.75 – 7.72 (m, 3H), 5.38 (t, *J* 5.6 Hz, 1H), 4.96 – 4.94 (m, 1H), 4.26 (br s, 1H), 4.11 – 4.07 (m, 1H), 1.07 (s, 9H); ^{13}C NMR (125 MHz, DMSO) *δ*: 142.2, 134.3, 133.6, 133.2, 131.3, 131.1, 130.6, 128.9, 128.5, 128.5, 128.2, 127.9, 127.5, 125.3, 123.5, 115.2, 114.1, 70.1, 59.5, 55.4, 35.0; HR-ESIMS: *m/z* 345.1972 [M–Cl]$^+$ (calcd for $C_{23}H_{25}N_2O$, 345.1961). **5c**: 87% yield; ^{1}H NMR (500 MHz, DMSO) *δ*: 10.44 (s, 1H), 8.52 (s, 1H), 8.33 –8.30 (m, 2H), 8.16 – 8.15 (m, 2H), 8.00 – 7.96 (m, 2H), 7.81 – 7.72 (m, 4H), 5.40 (t, *J* 5.9 Hz, 1H), 4.88 – 4.85 (m, 1H), 4.11 – 4.06 (m, 1H), 3.91 – 3.87 (m, 1H), 2.37 – 2.35 (m, 1H), 1.36 – 1.32 (m, 1H), 1.16 – 1.13 (m, 1H), 1.11 (d, *J* 6.7 Hz, 3H), 0.83 (t, *J* 7.3 Hz, 3H); ^{13}C NMR (125 MHz, DMSO) *δ*: 142.3, 133.6, 133.2, 132.7, 131.7, 131.2, 130.7, 128.9, 128.5, 128.4, 128.2, 128.0, 127.5, 125.1, 123.3, 114.9, 114.3, 65.9, 60.6, 35.1, 25.4, 15.6, 11.0; HR-ESIMS: *m/z* 345.1974 [M–Cl]$^+$ (calcd for $C_{23}H_{25}N_2O$, 345.1961). **5d**: 93% yield; ^{1}H NMR (500 MHz, DMSO) *δ*: 10.69 (s, 1H), 8.59 (d, *J* 2.0 Hz, 1H), 8.33 (d, *J* 8.9 Hz, 1H), 8.18 – 8.15 (m, 2H), 8.08 – 8.04 (m, 2H), 7.98 – 7.96 (m, 1H), 7.75 – 7.71 (m, 4H), 7.69 – 7.68 (m, 2H), 7.46 – 7.40 (m, 3H), 6.29 – 6.27 (m, 1H), 5.90 (t, *J* 5.7 Hz, 1H) 4.60 – 4.54 (m, 1H), 4.23 – 4.18 (m, 1H); ^{13}C NMR (125 MHz, DMSO) *δ*: 142.4, 135.5, 133.6, 133.2, 131.9, 131.8, 131.1, 130.7, 129.4, 128.9, 128.5, 128.5, 128.4, 128.2, 128.2, 128.1, 127.7, 125.2, 123.2, 114.9, 114.4, 112.5, 64.6, 62.5, one resonance was not observed due to coincidental overlap; HR-ESIMS: *m/z* 365.1652 [M–Cl]$^+$ (calcd for $C_{25}H_{21}N_2O$, 365.1648) **5e**: 93% yield; ^{1}H NMR (500 MHz, DMSO) *δ*: 10.63 (s, 1H), 8.48 (d, *J* 2.0 Hz, 1H), 8.32 (d, *J* 8.8 Hz, 1H), 8.22 (d, *J* 7.8 Hz, 1H), 8.17 – 8.15 (m, 2H), 7.93 (dd, *J* 8.7, 2.2 Hz, 1H), 7.90 (d, *J* 7.6 Hz, 1H), 7.75 – 7.67 (m, 4H), 7.36 (d, *J* 7.3 Hz, 2H), 7.27 – 7.24 (m, 2H), 7.19 – 7.16 (m, 1H), 5.62 (t, *J* 6.2 Hz, 1H), 5.39 – 5.37 (m, 1H), 4.01 – 3.96 (m, 1H), 3.92 – 3.87 (m, 1H), 3.54 – 3.50 (m, 1H), 3.46 – 3.42 (m, 1H); ^{13}C NMR (125 MHz, DMSO) *δ*: 142.5, 137.2, 133.6, 133.2, 132.3, 131.3, 131.0, 130.8, 129.6, 129.0, 128.9, 128.5, 128.5, 128.3, 127.9, 127.4, 127.3, 124.9, 123.0, 114.8, 114.0, 79.8, 62.6, 61.9, 36.1; HR-ESIMS: *m/z* 379.1812 [M–Cl]$^+$ (calcd for $C_{26}H_{23}N_2O$, 379.1805).

Procedure for the synthesis of compounds 6a–6e. To a solution of imidazolinium salt **5a** (366.0 mg, 1.00 mmol) in CH_2Cl_2 (25 mL) was added silver(I) oxide (115.9 mg, 0.50 mmol). The suspension was stirred for 3 h in the darkness, during which the black color diminished gradually. The reaction mixture was filtered through a small pad of Celite, $[Rh(COD)Cl]_2$ (246.5 mg, 0.50 mmol) was added, and the reaction mixture was stirred for an additional 16 h. The solvents were removed under reduced pressure, and the residue was purified by flash chromatography on silica gel with CH_2Cl_2 as eluent to give **6a** (379.4 mg, 70% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.73 (br s, 1H), 8.13 – 8.01 (m, 3H), 7.66 – 7.62 (m, 2H), 7.59 – 7.57 (m, 1H), 7.44 – 7.42 (m, 1H), 7.31 – 7.20 (m, 3H), 5.90 – 5.85 (m, 1H), 5.10 – 4.97 (m, 2H), 4.37 – 4.35 (m, 1H), 4.23 (dd, *J* 10.1, 3.1 Hz, 1H), 4.14 – 4.08 (m, 1H), 3.55 – 3.52 (m, 1H), 2.73 – 2.67 (m, 2H), 2.38 – 2.24 (m, 2H), 1.87 – 1.85 (m, 1H), 1.79 – 1.74 (m, 1H), 1.60 – 1.57 (m, 1H), 1.36 (d, *J* 6.5 Hz, 3H), 1.35 – 1.26 (m, 1H), 1.05 (d, *J* 6.5 Hz, 3H), 1.04 – 0.98 (m, 1H); HR-ESIMS: *m/z* 541.1733 [M–Cl]$^+$ (calcd for $C_{30}H_{34}N_2ORh$, 541.1726).

Analogous compounds **6b−6e** were prepared according to the similar procedure for **6a**. **6b**: 73% yield; ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 8.82 (br s, 1H), 8.12 – 8.01 (m, 3H), 7.66 – 7.62 (m, 3H), 7.34 – 7.16 (m, 3H), 6.21 – 6.18 (m, 1H), 5.06 – 4.97 (m, 2H), 4.38 – 4.20 (m, 3H), 3.61 – 3.58 (m, 1H), 2.88 – 2.80 (m, 1H), 2.39 – 2.21 (m, 2H), 1.88 – 1.70 (m, 2H), 1.45 – 1.40 (m, 1H), 1.35 (s, 9H), 1.31 – 1.25 (m, 2H), 0.95 – 0.87 (m, 1H); HR-ESIMS: *m/z* 555.1895 [M–Cl]$^+$ (calcd for $C_{31}H_{36}N_2ORh$, 555.1883). **6c**: 71% yield; ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 8.64 (br s, 1H), 8.04 – 7.93 (m, 3H), 7.58 – 7.54 (m, 2H), 7.50 – 7.48 (m, 1H), 7.36 – 7.34 (m, 1H), 7.22 – 7.12 (m, 3H), 5.88 – 5.83 (m, 1H), 5.01 – 4.88 (m, 2H), 4.30 – 4.26 (m, 1H), 4.13 – 4.10 (m, 1H), 4.07 – 4.00 (m, 1H), 3.45 – 3.42 (m, 1H), 2.65 – 2.63 (m, 1H), 2.30 – 2.22 (m, 4H), 1.95 – 1.92 (m, 1H), 1.77 – 1.75 (m, 1H), 1.68 – 1.65 (m, 1H), 1.52 – 1.49 (m, 1H), 1.34 – 1.31 (m, 1H), 1.24 (d, *J* 6.5 Hz, 3H), 1.18 (s, 9H), 0.87 (t, *J* 7.3 Hz, 3H), 0.76 – 0.73 (m, 1H); HR-ESIMS: *m/z* 555.1892 [M–Cl]$^+$ (calcd for $C_{31}H_{36}N_2ORh$, 555.1883). **6d**: 74% yield; ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 8.78 (br s, 1H), 8.16 – 8.14 (m, 1H), 8.09 – 8.03 (m, 2H), 7.85 – 7.82 (m, 1H), 7.67 – 7.64 (m, 2H), 7.51 – 7.49 (m, 1H), 7.44 – 7.38 (m, 5H), 7.25 – 7.15 (m, 3H), 5.17 – 5.13 (m, 1H), 4.98 – 4.94 (m, 1H), 4.78 – 4.74 (m, 1H), 4.48 (dd, *J* 22.5, 11.0 Hz, 1H), 4.21 (dd, *J* 11.0, 2.0 Hz, 1H), 3.37 – 3.34 (m, 1H), 2.70 – 2.68 (m, 1H), 2.15 – 2.00 (m, 2H), 1.72 – 1.59 (m, 4H), 1.32 – 1.25 (m, 1H), 1.07 – 0.99 (m, 1H); HR-ESIMS: *m/z* 575.1586 [M–Cl]$^+$ (calcd for $C_{33}H_{32}N_2ORh$, 575.1570). **6e**: 69% yield; ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 8.70 (br s, 1H), 8.11 – 8.09 (m, 1H), 8.05 – 8.00 (m, 2H), 7.75 – 7.74 (m, 1H), 7.64 – 7.60 (m, 2H), 7.45 – 7.44 (m, 1H), 7.39 – 7.19 (m, 7H), 6.51 – 6.45 (m, 1H), 5.06 – 5.02 (m, 1H), 4.91 – 4.87 (m, 1H), 4.33 – 4.22 (m, 2H), 4.11 (dd, *J* 9.9, 2.7 Hz, 1H), 3.57 (dd, *J* 13.9, 4.8 Hz, 1H), 3.43 (dd, *J* 14.0, 7.2 Hz, 1H), 2.60 – 2.53 (m, 2H), 2.27 – 2.19 (m, 1H), 2.11 – 2.04 (m, 1H), 1.73 – 1.69 (m, 1H), 1.63 – 1.56 (m, 1H), 1.48 – 1.47 (m, 2H), 1.26 – 1.23 (m, 1H), 0.88 – 0.82 (m, 1H); HR-ESIMS: *m/z* 589.1739 [M–Cl]$^+$ (calcd for $C_{34}H_{34}N_2ORh$, 589.1726).

Anti-tumor activity. The MCF-7 cells were purchased from American Type Culture Collection (ATCC, Manassas, VA, USA). They were routinely maintained in the RPMI-1640 with 10% FBS at 37 °C and an atmosphere of 5% CO_2. The antitumor activities of the compounds were determined by MTT assay. Cells were seeded in 96-well cell culture plates at a density of 10000 cells/well in 100 μL of culture medium, incubated at 37 °C and 5% CO_2. After 24 h incubation, they were treated with different concentrations of the candidate compounds for the indicated time periods, respectively. Cell viability was measured by the 3-(4, 5-dimetrylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) assay.

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Supplementary Material

NMR spectra of **5a–5e** and **6a–6e**.

References

1. Öfele, K. *J. Organomet. Chem.* **1968**, *12*, 42–45.
   https://doi.org/10.1016/S0022-328X(00)88691-X
2. Wanzlick, H. W.; Schönherr, H. J. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 141–142.
   https://doi.org/10.1002/anie.196801412
3. Arduengo, A. J.; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1991**, *113*, 361-363.
   https://doi.org/10.1021/ja00001a054
4. Herrmann, W. A.; Köcher, C. *Angew. Chem., Int. Ed.* **1997**, *36*, 2162–2187.
   https://doi.org/10.1002/anie.199721621

5. Bourissou, D.; Guerret, O.; Gabbaï, F. P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39–92. https://doi.org/10.1021/cr940472u
6. Zinn, F. K.; Viciu, M. S.; Nolan, S. P. *Annu. Rep. Prog. Chem. Sect. B* **2004**, *100*, 231–249. https://doi.org/10.1039/B401751J
7. Cavell, K. J.; McGuinness, D. S. *Coord. Chem. Rev.* **2004**, *248*, 671–681. https://doi.org/10.1016/j.ccr.2004.02.006
8. Peris, E.; Crabtree, R. H. *Coord. Chem. Rev.* **2004**, *248*, 2239–2246. https://doi.org/10.1016/j.ccr.2004.04.014
9. Crudden, C. M.; Allen, D. P. *Coord. Chem. Rev.* **2004**, *248*, 2247–2273. https://doi.org/10.1016/j.ccr.2004.05.013
10. Pugh, D.; Danopoulos, A. A. *Coord. Chem. Rev.* **2007**, *251*, 610–641. https://doi.org/10.1016/j.ccr.2006.08.001
11. Mata, J. A.; Poyatos, M.; Peris, E. *Coord. Chem. Rev.* **2007**, *251*, 841–859. https://doi.org/10.1016/j.ccr.2006.06.008
12. Sommer, W. J.; Weck, M. *Coord. Chem. Rev.* **2007**, *251*, 860–873. https://doi.org/10.1016/j.ccr.2006.07.004
13. Hahn, F. E.; Jahnke, M. C. *Angew. Chem., Int. Ed.* **2008**, *47*, 3122–3172. https://doi.org/10.1002/anie.200703883
14. Hopkinson, M. N.; Richter, C.; Schedler, M.; Glorius, F. *Nature* **2014**, *510*, 485–496. https://doi.org/10.1038/nature13384
15. Zou, T.; Hung, F. F.; Yang, C.; Che, C. M. Strongly phosphorescent transition-metal complexes with N-heterocyclic carbene ligands as cellular probes. In Luminescent and Photoactive Transition Metal Complexes as Biomolecular Probes and Cellular Reagents. Structure and Bonding, vol 165. Edited by Kam-Wing Lo K . Berlin Heidelberg: Springer; **2015**:181–203. https://doi.org/10.1007/430_2015_173
16. Barnard, P. J.; Baker, M. V.; Berners-Price, S. J.; Day, D.A. *J. Inorg. Biochem.* **2004**, *98*,1642–1647. https://doi.org/10.1016/j.jinorgbio.2004.05.011
17. Karaca, O.; Meier-Menches, S. M.; Casini, A.; Kuhn, F. E. *Chem. Commun.* **2017**, *53*, 8249–8260. https://doi.org/10.1039/C7CC03074F
18. Liu, W. K.; Gust, R. *Coord. Chem. Rev.* **2016**, *329*, 191–213. https://doi.org/10.1016/j.ccr.2016.09.004
19. Hemmert, C.; Gornitzka, H. *Dalton Trans.* **2016**, *45*, 440–447. https://doi.org/10.1039/C5DT03904E
20. Cisnetti, F.; Gautier, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 11976–11978. https://doi.org/10.1002/anie.201306682
21. Oehninger, L.; Rubbiani, R.; Ott, I. *Dalton Trans.* **2013**, *42*, 3269–3284. https://doi.org/10.1039/C2DT32617E
22. Teyssot, M. L.; Jarrousse, A. S.; Manin, M.; Chevry, A.; Roche, S.; Norre, F.; Beaudoin, C.; Morel, L.; Boyer, D.; Mahiou, R. *Dalton Trans*. **2009**, *35*, 6894–6902. https://doi.org/10.1039/b906308k
23. Li, J.; Xu, L. *Tetrahedron* **2015**, *71*, 2858–2862. https://doi.org/10.1016/j.tet.2015.03.067
24. Zhou, B. H.; Wu, C.; Chen, X. X.; Huang, H. X.; Li, L. L.; Fan, L. M.; Li, J. *Tetrahedron Lett.* 2017, 58, 4157–4161.

https://doi.org/10.1016/j.tetlet.2017.09.022

25. Zhou, B. H.; Li, Z. J.; Yang, C.; Li, L. L.; Fan, L. M.; Huang, H. X.; Li, J. *Arkivoc* **2018**, (v), 1–10. https://doi.org/10.1016/j.tetlet.2017.09.022
26. Zhou, B. H.; He, W. P.; Li, L. L.; Fan, L. M.; Li, X. R.; Li, J. *Curr. Org. Syn.* **2018**, *15*, 137–142. https://doi.org/10.2174/1570179414666170830130658
27. Li, J.; Yao, J. Q.; He, W. P.; Yang, F.; Liu, X. M. *Lett. Org. Chem.* **2019**, *16*, 951–954. https://doi.org/10.2174/1570178616666190212125426
28. Li, J.; Zhou, B. H.; Jiang, Y. J.; Liu, X. M. *Catalysts* **2018**, *8*, 46. https://doi.org/10.3390/catal8020046
29. He, W. P.; Zhou, B. H.; Zhou, Y. L.; Li, X. R.; Fan, L. M.; Shou, H. W.; Li, J. *Tetrahedron Lett.* **2016**, *57*, 3152–3155. https://doi.org/10.1016/j.tetlet.2016.06.023
30. He, W. P.; Zhao, W.; Zhou, B. H.; Liu, H. F.; Li, X. R.; Li, L. L.; Li, J.; Shi, J. Y. *Molecules* **2016**, *21*, 742. https://doi.org/10.3390/molecules21060742
31. He, W. P.; Zhou, B. H.; Li, J.; Shi, J. Y. *Catalysts* **2016**, *6*, 132. https://doi.org/10.3390/catal6090132
32. Dorcier, A.; Ang, W. H.; Bolaño, S.; Gonsalvi, L.; Juillerat-Jeannerat, L.; Laurenczy, G.; Peruzzini, M.; Phillips, A. D.; Zanobini, F.; Dyson, P. J. *Organometallics* **2006**, *25*, 4090–4096. https://doi.org/10.1021/om060394o
33. Angeles-Boza, A. M.; Chifotides, H. T.; Aguirre, J. D.; Chouai, A.; Fu, P. K. L.; Dunbar, K. R.; Turro, C. *J. Med. Chem.* **2006**, *49*, 6841–6847. https://doi.org/10.1021/jm060592h
34. Aguirre, J. D.; Angeles-Boza, A. M.; Chouai, A.; Turro, C.; Pellois, J.-P.; Dunbar, K. R. *Dalton Trans.* **2009**, 10806−10812. https://doi.org/10.1039/b915357h
35. Bieda, R.; Dobroschke, M.; Triller, A.; Ott, I.; Spehr, M.; Gust, R.; Prokop, A.; Sheldrick, W. S. *ChemMedChem* **2010**, *5*, 1123−1133. https://doi.org/10.1002/cmdc.201000129
36. Ernst, R. J.; Komor, A. C.; Barton, J. K. *Biochemistry* **2011**, *50*, 10919−10928. https://doi.org/10.1021/bi2015822
37. Geldmacher, Y.; Rubbiani, R.; Wefelmeier, P.; Prokop, A.; Ott, I.; Sheldrick, W. S. *J. Organomet. Chem.* **2011**, *696*, 1023−1031. https://doi.org/10.1016/j.jorganchem.2010.10.034
38. Siu, F. M.; Lin, I. W. S.; Yan, K.; Lok, C. N.; Low, K. H.; Leung, T. Y. C.; Lam, T. L.; Che, C. M. *Chem. Sci*. **2012**, *3*, 1785−1793. https://doi.org/10.1039/c2sc00620k
39. Dieckmann, S.; Riedel, R.; Harms, K.; Meggers, E. Eur. J. *Inorg. Chem*. **2012**, 813−821. https://doi.org/10.1002/ejic.201101175
40. Wang, H. M. J.; Lin, I. J. B. Organometallics **1998**, 17, 972−975. https://doi.org/10.1021/om9709704
41. Palomo, C.; Aizpurua, J. M.; Balentová, E.; Jimenez, A.; Oyarbide, J.; Fratila, R. M.; Miranda, J. I. *Org. Lett.* **2007**, *9*, 101−104. https://doi.org/10.1021/ol0626241
42. Isobe, T.; Fukuda, K.; Yamaguchi, K.; Seki, H.; Tokunaga, T.; Ishikawa, T. *J. Org. Chem.* **2000**, *65*, 7779−7785.

https://doi.org/10.1021/jo000746f

43. Jo, D.; Han, S. *Org. Lett.* **2019**, *21*, 6045−6049.
https://doi.org/10.1021/acs.orglett.9b02203