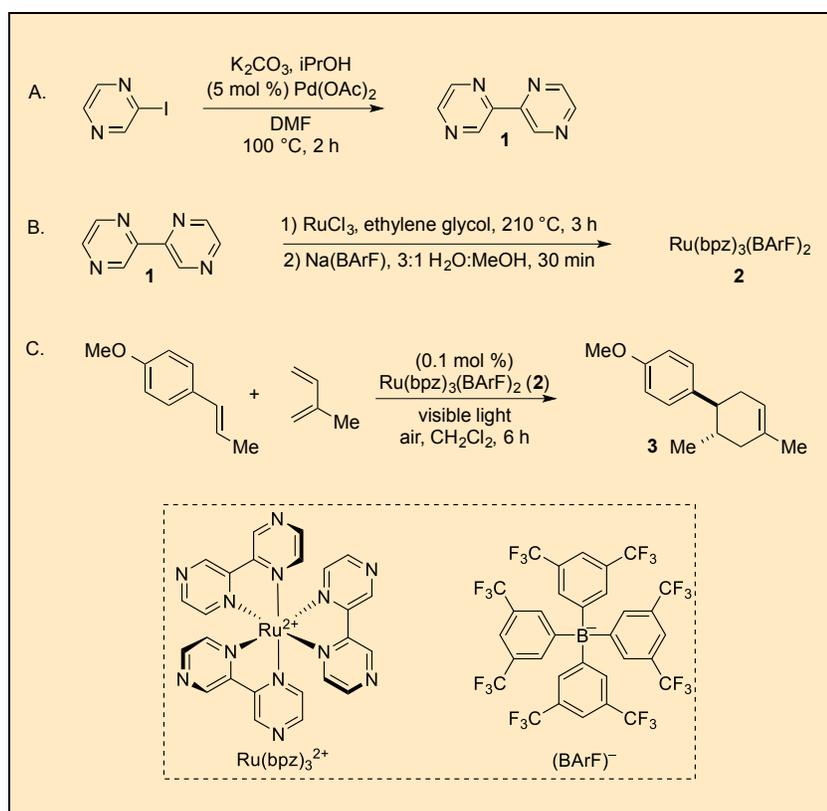


Visible Light Photocatalysis of Radical Cation Diels–Alder Cycloadditions: Preparation of Tris(2,2'-bipyrazyl) Ruthenium(II) Bis(tetrakis(3,5-bis(trifluoromethyl)phenyl)borate)

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Checked by Stanley Chang and Richmond Sarpong



Procedure

A. *2,2'-Bipyrazine (1)*. A 250-mL, three-necked, round-bottomed flask open to air is equipped with a magnetic stir bar (15 x 31 mm, egg-shaped, Teflon-coated), glass stopper, and thermometer. The reaction vessel is charged with 2-iodopyrazine (4.01 g, 19.5 mmol, 1.0 equiv) (Note 1) and *N,N*-dimethylformamide (55.0 mL) (Note 2). To this solution are added potassium carbonate (4.03 g, 29.1 mmol, 1.5 equiv) (Note 3), palladium (II) acetate (218 mg, 0.973 mmol, 0.05 equiv) (Note 4), and 2-propanol (3.0 mL, 39.2 mmol, 2.0 equiv) (Note 5), resulting in a heterogeneous light-orange mixture. A reflux condenser is attached (Figure 1), and the mixture is heated to 100 °C with a silicone oil bath under nitrogen atmosphere and stirred (500 rpm) for 2 h (internal temperature = 101–103 °C) (Note 6). The oil bath is removed, and the reaction is allowed to cool to 30 °C (internal



Figure 1. Reaction Apparatus used in Step A (provided by Checker)

temperature) over 60 min. A saturated aqueous solution of ammonium chloride (40 mL) is added drop-wise using a glass pipette to the reaction mixture over 5 min (Note 7). The reaction mixture is again cooled to 30 °C (internal temperature) over 15 min, then the mixture is transferred to a 500-mL separatory funnel and diluted with ethyl acetate (75 mL) and water (10 mL). After extraction and separation, the aqueous phase is extracted with ethyl acetate (3 x 75 mL). The combined organic fractions are washed with saturated aqueous solution of NH_4Cl (3 x 75 mL), and dried over Na_2SO_4 (15 g). The brown solution is filtered through a 150-mL coarse-porosity sintered glass funnel into a 500-mL recovery flask, and the solvent removed by rotary evaporation (35 °C, *ca.* 200 mmHg) in two portions to furnish 1.26 g of light brown solid. The residue is recrystallized from EtOAc (30 mL) (Note 8) to afford 1.11–1.17 g (mp 186–188 °C, 7.00–7.39 mmol, 72–76%) of 2,2'-bipyrazine as light brown flakes (Note 9).

B. $\text{Ru}(\text{bpz})_3(\text{BARF})_2$ (**2**). A 100 mL, three-necked, round-bottomed flask is equipped with magnetic stir bar (17 x 7 mm, egg-shaped, Teflon-coated), glass stopper, thermometer, and charged with ruthenium(III) chloride (294 mg, 1.42 mmol, 1.0 equiv) (Note 10). 2,2'-Bipyrazine (**2**) (1.00 g, 6.33 mmol, 4.5 equiv) and ethylene glycol (25.0 mL) (Note 11) are added to the flask, resulting in a turbid dark-brown mixture. A reflux condenser is attached (Figure 2), and the mixture is heated under nitrogen atmosphere to 214 °C with a silicone oil bath (Note 12). The stirred solution (500 rpm) is refluxed for 3 h (internal temperature = 195–197 °C), after which time the oil bath is removed and the reaction is allowed to cool to 60 °C (internal temperature) (Note 13). Upon further cooling over 30 min, the reaction mixture is added drop-wise using glass pipette over 15 min to a 500-mL Erlenmeyer flask containing acetone (200 mL) (Note 14), which results in the precipitation of an orange solid. The round-bottomed flask is rinsed with acetone (2 x 25 mL) and sonicated (15 s) each time, and the combined mixtures are stored at 3 °C for 14 h. The resulting precipitates are collected by vacuum filtration (Note 15) to afford tris(2,2'-bipyrazyl)ruthenium(II) chloride as a dark-red powder (Note 16).



Figure 2. Reaction Apparatus used in Step B (provided by Checker)

The precipitate is transferred to a 250-mL, single-necked, round-bottomed flask equipped with a magnetic stir bar (37 x 17 mm, egg-shaped, Teflon-coated) and water (52.5 mL) (Note 17) is added to afford an opaque dark-red solution. A 24-mL vial is charged with NaBARF (2.48 g, 2.80 mmol, 2.0 equiv) (Note 18) and methanol (17.5 mL) (Note 19), capped (Teflon lining), and inverted until fully mixed. The resulting cloudy white mixture is added to the round-bottomed flask using a glass pipette over 1.5 min, causing a light-brown semisolid precipitate to form. The mixture is stirred for 30 min, and the solid is collected by vacuum filtration (Note 20) to afford a brown powder. The powder is dissolved in acetone (10 mL) and loaded onto a column (4.5 x 18.5 cm) of alumina (250 g) (Note 21) that has been conditioned with dichloromethane. The top of the alumina column is protected with a thin layer of sand (1.5 cm), and the loaded material is eluted by gravity elution with CH_2Cl_2 (450 mL) (Note 22). The eluent is

collected in 17.5 mL fractions, and the dark colored product is obtained in fractions 12–18. Concentration of these fractions by rotary evaporation (35 °C, *ca.* 200 mmHg) furnishes a dark-brown slurry. The slurry is dissolved in acetone (8 mL) and the chromatography procedure is repeated. The eluent is collected in 17.5 mL fractions, and the dark-brown product is obtained in fractions 12–18. Concentration of these fractions by rotary evaporation (35 °C, *ca.* 200 mmHg) furnishes a dark-brown slurry (Note 23).

The slurry is dissolved in dichloromethane (75 mL) (Note 24), transferred to a 250-mL Erlenmeyer flask, and layered with benzene (60 mL) (Note 25) by slow pouring from a 50-mL graduated cylinder (2 x 30 mL portions) over 5 min. The solution is cooled to 3 °C for 16 h, and the resulting crystals are collected by vacuum filtration (air aspirator, *ca.* 300 mmHg) on a 60-mL medium-porosity sintered glass funnel. The crystals are washed with ice-cold benzene (2 x 30 mL) and air-dried for 1 h. Residual dichloromethane (*ca.* 7–8%) is observed from recrystallization (Note 26). The recrystallized product is dried under vacuum (0.3 mmHg) for 4 h to furnish 1.47 g (0.64 mmol, 45%) of Ru(bpz)₃(BArF)₂ as orange needles (Notes 27, 28, and 29).

C. *1-(4,6-Dimethyl-3-cyclohexen-1-yl)-4-methoxybenzene* (3). A 1 L, three-necked, round-bottomed flask open to air, equipped with a magnetic stir bar (20 x 40 mm, egg-shaped, Teflon-coated) and a thermometer, is charged with *trans*-anethole (5.06 mL, 5.01 g, 33.8 mmol, 1.0 equiv) (Note 30). Dichloromethane (420 mL) (Note 22), Ru(bpz)₃(BArF)₂ (2) (78.9 mg, 0.034 mmol, 0.001 equiv), and isoprene (9.9 mL, 6.73 g, 98.8 mmol, 2.9 equiv) (Note 31) are transferred into the flask under air, resulting in a clear yellow solution. The mixture is placed 5 cm in front of a 26 W compact fluorescent light bulb (Note 32), stirred (500 rpm) and irradiated open to air (Figure 3) (Note 33). The progress of the reaction is monitored by gas chromatography (Note 34). Upon completion (6 h), the stir-bar and thermometer are removed and rinsed with dichloromethane (5 mL), and the clear dark-orange mixture is transferred to a 500-mL recovery flask, and the three-necked flask is rinsed with dichloromethane (15 mL). The clear, dark-orange mixture is concentrated by rotary evaporation (35 °C, *ca.* 200 mmHg) to afford a brown oil containing dark brown precipitates. The residue is eluted through a column (4.5 x 4.0 cm) of silica (25 g) (Note 35) using a 50:1 mixture of pentanes:ethyl acetate (350 mL) (Note 36) into a 500-mL recovery flask. The clear solution is concentrated by rotary evaporation (35 °C, *ca.* 200 mmHg) to provide a colorless oil. The crude product is transferred to a 25-mL, round-bottomed flask equipped with a magnetic stir bar (12.5 x 9 mm,

Teflon-coated). The desired product is obtained by distillation through a short-path distillation apparatus at 108–110 °C (0.5 mmHg) to afford 6.67 g (31 mmol, 91%, run 1) and 6.78 g (31 mmol, 93%, run 2) of the title compound as a clear, colorless oil (Note 37).



Figure 3. Reaction Apparatus used in Step C (provided by Checker)

Notes

1. 2-Iodopyrazine (97%) was purchased from Sigma-Aldrich and distilled immediately prior to use. The Checker also performed one run using 2-iodopyrazine (97%+) that was purchased from Ark Pharm and distilled immediately prior to use. The starting material is distilled under vacuum through a short-path distillation apparatus at 41–42 °C (1.2 mmHg) and provided a light yellow oil.
2. *N,N*-Dimethylformamide ($\geq 99.8\%$) was purchased from Sigma-Aldrich and used as received.
3. Potassium carbonate ($\geq 99.0\%$) was purchased from Sigma-Aldrich and used as received.
4. Palladium(II) acetate (99+% [99.95+% Pd]) was purchased from Strem Chemicals Inc. and used as received.

- 2-Propanol ($\geq 99.8\%$) was purchased from Sigma-Aldrich and used as received.
- The Submitter and Checker observed that during heating, the heterogeneous mixture turns orange, then dark reddish-purple, and the solid changes from white to brown.

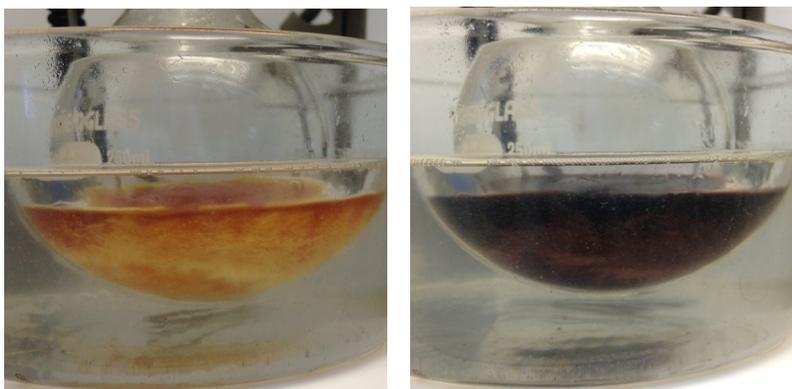


Figure 4. Color changes observed in Step A (provided by Submitter)

The Checker follows progress of the reaction by TLC analysis on silica gel (first placed under 0.3 mmHg vacuum for 5 min) with 50% EtOAc-hexane as eluent. Visualization is performed with UV irradiation, where the 2-iodopyrazine starting material has $R_f = 0.52$ and the 2,2'-bipyrazine product has $R_f = 0.27$.

- An exotherm of *ca.* 12 °C was observed upon the addition of saturated aqueous solution of NH_4Cl .
- The Checker performed recrystallization as follows. The residue is suspended in EtOAc (25 mL) and transferred open to air into a 100-mL round-bottomed flask. Following removal of EtOAc *in vacuo* (35 °C, *ca.* 200 mmHg), a magnetic stir bar (14 x 27.5 mm, egg-shaped, Teflon-coated) and EtOAc (30 mL) are added to the flask. A reflux condenser is attached and the solution is heated to reflux in a silicone oil bath (95 °C). After dissolution of the solid and 15 min at reflux, the flask was removed from the oil bath and the stir bar was removed using a magnetic rod. The flask is allowed to cool under ambient conditions over 1 h, the condenser replaced with a glass stopper, and then placed in a refrigerator at 7 °C for 13 h. The resulting crystals are collected by vacuum filtration (air aspirator, *ca.* 300 mmHg) through a Büchner

funnel (68 mm diameter; fitted with filter paper) with a 250-mL Erlenmeyer flask with side-arm, washed with hexanes (4 x 5 mL), and air-dried by vacuum (air aspirator, *ca.* 300 mmHg) for 30 min. The mother liquor is concentrated by rotary evaporation (35 °C, *ca.* 200 mmHg) to furnish a light-brown solid. The residue is transferred to a 100-mL round-bottomed flask with magnetic stir bar (14 x 27.5 mm, egg-shaped, Teflon-coated). Crystallization was carried out as described for the first crop, using 5 mL EtOAc. The two crops are combined and used in the next step. The Submitter performed recrystallization using a 50-mL Erlenmeyer flask, heated to 75 °C on a hot plate with occasional swirling, and using the same volume of EtOAc for each recrystallization.

9. Characterization data for **1** obtained by Checker: ^1H NMR (400 MHz, CDCl_3) δ : 8.66 (s, 4H), 9.60 (s, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ : 143.6, 143.9, 145.3, 149.4; FT-IR (ATR) 3077, 3051, 3015, 1465, 1383, 1092, 1028, 1019, 846 cm^{-1} ; Exact mass EI-MS: calculated m/z for $[\text{C}_8\text{H}_6\text{N}_4]^+$: 158.0592, found: 158.0591; Anal. calcd for $\text{C}_8\text{H}_6\text{N}_4$: C, 60.75; H, 3.82; N, 35.42. Found: C, 60.60; H, 3.94; N, 35.15. Picture provided by Checker.



Figure 5. Product of Step A (provided by Checker)

10. Ruthenium(III) chloride hydrate (40-43% Ru [99.9%-Ru]) was purchased from Strem Chemicals and used as received.
11. Ethylene glycol ($\geq 99\%$) was purchased from Sigma-Aldrich and used as received.
12. The oil bath and reaction vessel was wrapped with aluminum foil during the course of the reaction to prevent radiative heat loss.

13. The Submitter reported isolation of 681 mg of crude $\text{Ru}(\text{bpz})_3\text{Cl}_2$ (~2.5% by mass of residual ethylene glycol) following the submitted procedure for precipitation. The Checker observed that precipitation following Submitter's procedure consistently led to low isolated mass (251 mg and 248 mg for 2 separate runs).

The Checker observed that consistent yield of crude $\text{Ru}(\text{bpz})_3\text{Cl}_2$ may be obtained when excess ethylene glycol is removed at this stage by distillation using the procedure as follows. The condenser of the three-necked round-bottomed flask is replaced with a short-path distillation apparatus, and the thermometer is replaced with a glass stopper. The distillation apparatus is fitted with a 100-mL round-bottomed flask (with marking at 20 mL volume). Ethylene glycol is distilled under vacuum by heating in a silicone oil bath to 125 °C. Following removal of 20 mL of ethylene glycol at 70–78 °C (2.9 mmHg), the reaction mixture was cooled again prior to precipitation. Note: the distilled ethylene glycol also contains white precipitates that are identified as 2,2'-bipyrazine by analysis of the corresponding ^1H NMR spectrum.



Figure 6. Distillation Apparatus for Removal of Ethylene Glycol (provided by Checker)

14. Acetone ($\geq 99.9\%$) was purchased from Sigma-Aldrich and used as received.
15. The Checker performed isolation of tris(2,2'-bipyrazyl)ruthenium(II) chloride as follows. The 500-mL Erlenmeyer flask is first sonicated for 15 s with swirling. The precipitates are collected by vacuum filtration

(air aspirator, *ca.* 300 mmHg) using a 60-mL medium-porosity sintered glass funnel with a 500-mL Erlenmeyer flask with side-arm. The 500-mL Erlenmeyer flask containing crude material is rinsed with ice-cold acetone (2 x 15 mL). Any solid deposited on the sides of the flask can be collected by scraping during rinsing. Vacuum is turned off and the collected solid is stirred in ice-cold acetone (2 x 15 mL), then vacuum is reapplied, resulting in a dark-red paste. The solid is air dried for 30 min, agitating by scraping (once every 10 min) to furnish red-brown powder (670 and 658 mg for 2 separate runs).



Figure 7. Tris(2,2'-bipyrazyl)ruthenium(II) chloride (provided by Checker)

16. Data for crude tris(2,2'-bipyrazyl)ruthenium(II) chloride: ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 10.21 (m, 6H), 8.71 (d, $J = 3.0$ Hz, 6H), 8.03 (d, $J = 3.0$ Hz, 6H); ^{13}C NMR (101 MHz, $\text{DMSO-}d_6$) δ 150.3, 148.5, 147.0, 145.5; FT-IR (ATR) 2999, 2974, 1585, 1407 (s), 1269, 1157 (s), 828, 660 (s), 468 cm^{-1} ; Exact mass ESI-MS: calculated m/z for $[\text{C}_{24}\text{H}_{18}\text{N}_{12}\text{ClRu}]^+$: 611.0504, found: 611.0500.
17. The Checker used water (HPLC grade, submicron filtered) that was purchased from Fisher Scientific and used as received.
18. Sodium tetrakis[bis(3,5-trifluoromethyl)phenyl]borate (97%) was purchased from Alfa Aesar and used as received.
19. Methanol (absolute) was purchased from Macron Fine Chemicals and used as received.
20. The Checker performed vacuum filtration of the crude solid product as follows. The crude reaction mixture is transferred to a 150-mL medium-porosity sintered glass funnel with a 250-mL Erlenmeyer flask with side-arm. Vacuum (air aspirator, *ca.* 300 mmHg) is applied for 16 h until clumps of catalyst are obtained, and the crude solid is agitated then

rinsed with water (10 mL). After drying for 12 h, the crude solid is again agitated, then rinsed with water (10 mL). Additional drying for 12 h affords 2.49 g of a brown powder (picture provided by Checker).



Figure 8. $\text{Ru}(\text{bpz})_3(\text{BArF})_2$ as isolated after filtration (provided by Checker)

The Submitter performed vacuum filtration using procedure as follows. The crude reaction mixture is transferred to a 150-mL medium-porosity sintered glass funnel with a 250-mL round-bottomed receiving flask. Vacuum (water aspirator) is applied for 24–48 h (filtration time varies by aspirator pressure), and the crude solid is rinsed with water (2×10 mL) then dried to afford a dark brown powder.

21. Alumina (puriss., $\geq 98\%$ Al_2O_3 basis) was purchased from Sigma-Aldrich and used as received.

The Submitter dissolved the powder in acetone (10 mL) and loaded onto a column (4.5 x 20 cm) of alumina (200 g). The Submitter and Checker performed the column by gravity elution. The Submitter suggests running columns using nitrogen or air positive pressure may reduce the resolution between the product and the brown impurity.

22. The Submitter used dichloromethane ($\geq 99.5\%$) that was purchased from Sigma-Aldrich and used as received. The Checker used dichloromethane ($\geq 99.5\%$) that was purchased from Fisher Scientific and used as received.
23. The Checker observed oiling out of product during recrystallization if only two alumina columns were performed. In these cases, the dark-brown slurry is dissolved in acetone (6 mL) and loaded onto a column (4.5 x 18.5 cm) of alumina (250 g) that had been conditioned with dichloromethane. The top of the alumina column is protected with a

thin layer of sand (1.5 cm), and the loaded material is eluted by gravity filtration with CH_2Cl_2 (450 mL). The eluent is collected in 17.5 mL fractions, and the colored product in fractions 12–18 are collected (2.2–2.3 g) (Note 24). For improved reproducibility, a minimum total of four alumina columns may be necessary.

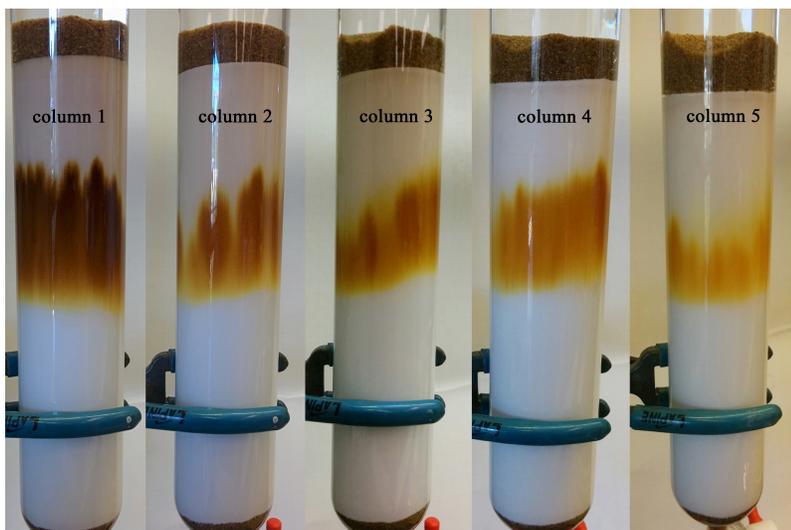


Figure 9. Alumina Columns (provided by Checker)

24. The Checker observed that the crude product may begin to precipitate during dilution with dichloromethane when using a crude product that has been concentrated to complete dryness. This leads to problematic recrystallization, which traps dichloromethane that is difficult to remove at a later stage. To prevent unwanted precipitation, the Checker recommends concentrating to a viscous oil, and immediately adding dichloromethane. In cases where precipitation occurs, the Checker adds acetone (2 mL) (Note 14) to re-dissolve precipitates, then re-attempts concentrating to a viscous oil by rotary evaporation (35 °C, *ca.* 200 mmHg).
25. Benzene ($\geq 99.0\%$) was purchased from Sigma-Aldrich and used as received.
26. The Submitter's ^1H NMR spectrum indicates that the Submitter's sample may contain a non-negligible amount of dichloromethane and a small amount of benzene. The Checker used 10 mg dimethyl fumarate

- (Sigma-Aldrich, TraceCERT[®]) as internal standard with 48 mg recrystallized product **2** to calculate weight percent of desired product by Q NMR.
27. Q NMR results for run 1: 1.58 g isolated mass (92.9% pure by Q NMR; 10.2 mg dimethyl fumarate, 47.8 mg analyte), 1.47 g adjusted mass (45% adjusted yield); run 2: 1.70 g isolated mass (92.3% pure by Q NMR; 10.2 mg dimethyl fumarate, 47.7 mg analyte), 1.57 g adjust mass (48% adjusted yield).
28. Characterization data for **2** (anhydrous catalyst, based on EA result and absence of OH absorption in IR spectrum) obtained by Checker: mp = 273–276 °C; ¹H NMR (400 MHz, Acetone-*d*₆) δ: 7.67 (br s, 8H), 7.78 (m, 16H), 8.47 (dd, *J* = 3.1, 0.8 Hz, 6H), 8.79 (d, *J* = 3.2 Hz, 6H), 10.21 (br s, 6H); ¹³C NMR (101 MHz, Acetone-*d*₆) δ: 118.5 (app. p, ³*J*_{C-F} = 3.8 Hz), 125.4 (q, ¹*J*_{C-F} = 272.0 Hz), 130.0 (qq, ²*J*_{C-F} = 31.4 Hz, ³*J*_{C-B} = 2.9 Hz), 135.6, 146.6, 148.2, 149.8, 151.9, 162.6 (1:1:1:1 q, ¹*J*_{C-B} = 49.8 Hz); ¹⁹F NMR (376 MHz, Acetone-*d*₆) δ -62.1; UV (CH₂Cl₂); λ_{max} nm (ε): 294 (5.71 × 10⁴); FT-IR (ATR) 1698, 1409, 1354 (s), 1275 (s), 1117 (br, s), 932, 887, 744, 712, 682 cm⁻¹; Exact mass ESI-MS: calculated *m/z* for [C₂₄H₁₈N₁₂Ru]²⁺: 288.0405, found: 288.0409; Exact mass ESI-MS: calculated *m/z* for [C₃₂H₁₂BF₂₄]⁻: 863.0654, found: 863.0627; Anal. calcd for C₈₈H₄₂B₂F₄₈N₁₂Ru: C, 45.92; H, 1.84; N, 7.30. Found: C, 45.71; H, 1.53; N, 7.26. Note: elemental analysis obtained using solvent-free sample of **2**.



Figure 10. Color of Product Formed in Step B (provided by Checker)

The Submitter reported that the product is isolated as the trihydrate, but can be dried *in vacuo* over P₂O₅ for 48 h. For the subsequent procedure, drying the catalyst is not necessary. μ

29. A second run by the Checkers provided 1.57 g (0.68 mmol) of $\text{Ru}(\text{bpz})_3(\text{BARF})_2$ as orange needles with $\text{mp} = 274\text{--}277\text{ }^\circ\text{C}$.
30. *trans*-Anethole ($\geq 99\%$, FCC, FG) was purchased from Sigma-Aldrich and purified by silica gel flash chromatography and vacuum distillation. The Submitter observed generation of an oxidized impurity (*p*-anisaldehyde) upon ambient storage conditions, and performed flash chromatography due to similar boiling points of *trans*-anethole and *p*-anisaldehyde. Distillation further removes residual solvent following flash chromatography. Purified *trans*-anethole can be stored for several days when stored in a refrigerator. Purification is performed as follows: 10 g of *trans*-anethole is charged onto a column (4.5 x 12.5 cm) of silica gel (75 g) that had been conditioned with a 50:1 mixture of hexanes:ethyl acetate. The top of the silica column is protected with a thin layer of sand (1.5 cm) and the loaded material is eluted with a 50:1 mixture of hexanes:ethyl acetate (510 mL). The eluent is collected in 17.5 mL fractions and the UV-active fractions (fractions 9–19) are combined into a 500-mL recovery flask and concentrated by rotary evaporation (35 $^\circ\text{C}$, *ca.* 200 mmHg). The residue is transferred to a 50 mL round-bottomed flask equipped with a magnetic stir bar (12.5 x 9 mm, Teflon-coated) and distilled immediately prior to use. The starting material is distilled at 59–61 $^\circ\text{C}$ under vacuum (0.7 mmHg) through a short-path distillation apparatus to provide a colorless oil.
31. The Checker used isoprene ($\geq 99\%$) that was purchased from Sigma-Aldrich and distilled under a prior to use. Isoprene (30 g) is distilled through a short-path distillation apparatus at 34–35 $^\circ\text{C}$ (760 mmHg) to provide a colorless liquid. The Submitter distilled isoprene under nitrogen prior to use.
32. Both the Submitter and Checker used 26 W compact fluorescent light bulb with the following specifications: GE Reveal[®] (product code 67454, model number FLE26HT3) 1570-lumen T3 spiral CFL bulb.
33. The Checker observed that during the first 10 min of reaction, the mixture turns from yellow to dark orange.



Figure 11. Color Change Observed in Step C (provided by Checker)

The Checker also observed an increase in internal temperature to 27.5–28.5 °C during the course of the reaction.

34. The Checkers performed gas chromatography using a Shimadzu GCMS-QP2010 SE Gas Chromatograph. Column: Shimadzu SHRXI-5MS (cat no. 220-94764-02), –60 to 330/350 °C; 30 m length x 0.25 mm ID x 0.25 μm thickness; 5% diphenyl 95% dimethyl polysiloxane. Injector: 200 °C; detector: 200 °C. Oven program: 80 °C for 1 min, then 20 °C/min to 250 °C for 8.5 min, then 250 °C for 2.5 min. Retention times: *trans*-anethole (5.8 min), 1-(4,6-Dimethyl-3-cyclohexen-1-yl)-4-methoxybenzene (8.5 min). The Submitters performed gas chromatography using a Shimadzu GC-2010 Gas Chromatograph. Column: Restek RTX-5: 350 °C; 15 m x 250 μm x 0.25 μm ; 5% diphenyl 95% dimethyl polysiloxane. Injector: 300 °C; detector FID: 300 °C. Oven program: 50 °C for 0 min then 15 °C/min to 130 °C for 0 min then 30 °C/min to 250 °C for 5.0 min. Retention times: anethole (5.0 min), 1-(4,6-Dimethyl-3-cyclohexen-1-yl)-4-methoxybenzene (7.4 min), anethole homodimer (9.5 min). Reaction is complete when anethole is consumed and ratio of product to anethole homodimer is $\geq 100:1$.
35. Silica (60 Å, 230-400 mesh, 40-63 μm particle size) was purchased from Sigma-Aldrich and used as received.
36. Pentanes (98%) was purchased from Sigma-Aldrich and used as received. Ethyl acetate ($\geq 99.5\%$) was purchased from Sigma-Aldrich and used as received. The Submitter notes that hexanes can be used as an alternative to pentanes.
37. Characterization data for **3**: ^1H NMR (400 MHz, CDCl_3) δ : 0.70 (d, $J = 6.3$ Hz, 3H), 1.69 (br s, 3H), 1.74–1.94 (m, 2H), 2.03–2.25 (m, 3H), 2.30 (ddd, $J = 10.5, 10.5, 5.2$ Hz, 1H), 3.79 (s, 3H), 5.44 (br s, 1H), 6.84 (d, $J = 8.5$ Hz, 2H), 7.08 (d, $J = 8.5$ Hz, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ :

20.4, 23.5, 34.1, 35.4, 40.0, 47.1, 55.3, 113.8, 121.0, 128.6, 133.9, 138.3, 157.9; FT-IR (ATR) 2949, 2888, 2833, 1611, 1511 (s), 1440, 1270 (s), 1242, 1175, 1108, 1038, 823, 801 cm^{-1} ; Exact mass EI-MS: calculated m/z for $[\text{C}_{15}\text{H}_{20}\text{O}]^+$: 216.1514, found: 216.1518; Anal. calcd for $\text{C}_{15}\text{H}_{20}\text{O}$: C, 83.28; H, 9.32. Found: C, 83.17; H, 9.27.

38. A second run by the Checkers provided 6.78 g (31 mmol, 93%) of the product as a clear, colorless oil.

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The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

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Discussion

The Diels–Alder reaction ranks among the most important reactions for the synthesis of complex organic molecules. One major limitation of classical Diels–Alder methodology, however, arises from electronic considerations; efficient [4+2] cycloadditions generally require the reaction of one electron-rich reaction component (typically the diene) and one electron-deficient component (typically the dienophile). In this regard, radical cation Diels–Alder reactions initiated by single-electron oxidation of an electron-rich dienophile can overcome this fundamental limitation and enable the efficient [4+2] cycloaddition of two electron-rich reaction partners that would otherwise be electronically mismatched.

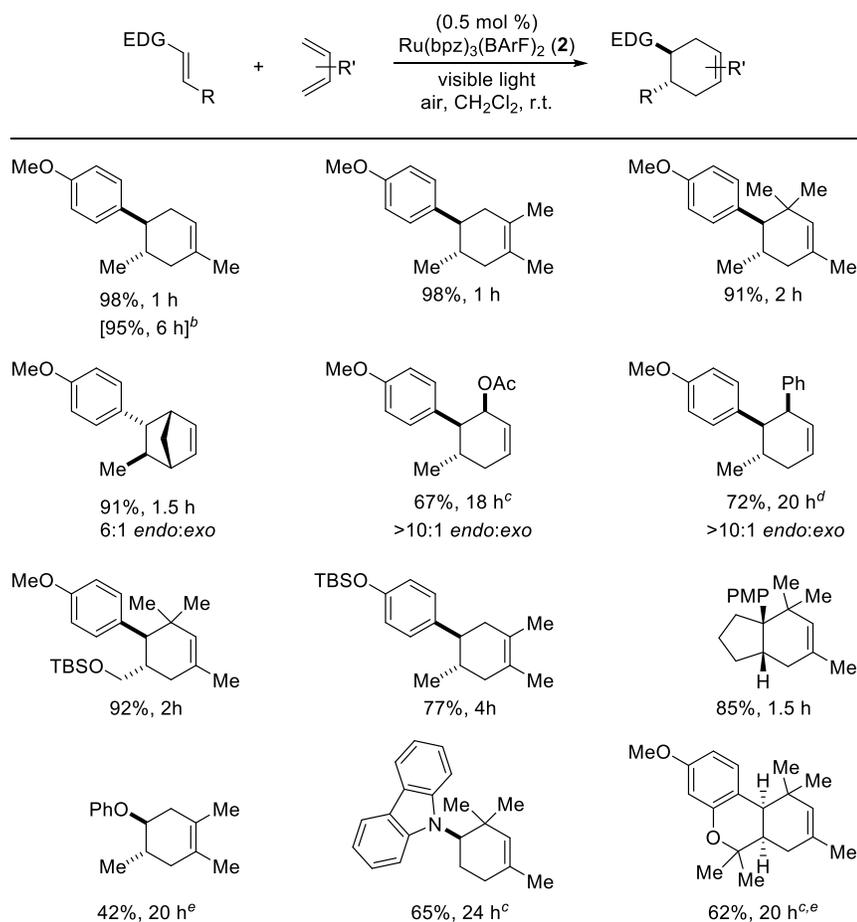
A variety of one-electron oxidation methods have been used to initiate radical cation Diels–Alder reactions. The most common classical methods use chemical oxidants such as aminium salts,² although somewhat high loadings of the oxidant are typically required to achieve complete conversion. The radical cation intermediates can also be generated by photoinitiated electron transfer (PET). A variety of organic photosensitizers have been utilized for this purpose, although the poor chemical stability and relatively short excited state lifetimes again necessitate somewhat high loadings of the photooxidant.

We have recently described a highly efficient and versatile method for radical cation Diels–Alder reactions. The highly oxidizing $\text{Ru}(\text{bpz})_3^{2+}$ photocatalyst utilized in this method absorbs strongly in the visible range, enabling the reaction to be conducted with variety of conveniently available visible light sources, including ambient sunlight.³ This catalyst also exhibits excellent chemical stability and a long-lived redox-active excited state, enabling loadings of the photocatalyst as low as 0.1 mol%. The procedure described here is adapted from our initial communication.

Table 1 demonstrates that the substrate scope for the photocatalytic radical cation Diels–Alder cycloaddition is quite broad. A variety of structurally diverse dienes react efficiently, including sterically encumbered and cyclic dienes as well as dienes bearing aryl and heteroatom substituents. The regioselectivity in all cases was excellent and consistent with an umpolung polarization of the styryl radical cation, in which the oxidized arene moiety can be considered an electron-withdrawing group. Diastereoselectivity, where relevant, was also excellent and highly *endo* selective. The scope of the reaction with respect to the dienophile is quite

broad as well, so long as the alkene is electron-rich enough to be oxidized by the excited photocatalyst. Thus, a variety of styrenes bearing electron-donating *para* substituents react smoothly. More importantly, non-styrenic alkenes such as enol ethers and enamines are also readily oxidized and are suitable substrates for the radical cation Diels–Alder cycloaddition.

Table 1. Scope of the Radical Cation Diels–Alder Cycloaddition Reaction^a

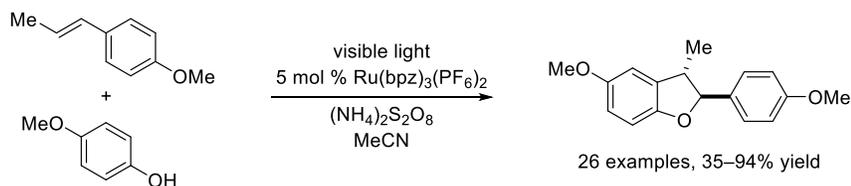


^aConditions, unless specified otherwise: 0.5 mol % Ru(bpz)₃(BArF)₂, 3 equiv. diene, irradiated with a 23 W compact fluorescent bulb. ^b0.1 mol % Ru(bpz)₃(BArF)₂, 25 W CFL, 5 gram scale. ^c3 mol % Ru(bpz)₃(BArF)₂ 2 equiv. diene. ^eYield determined by ¹H NMR analysis using CH₂Br₂ as an external standard.

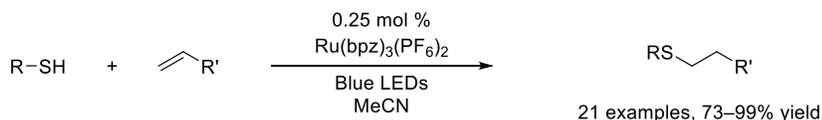
The optimal photocatalyst identified for the radical cation Diels–Alder in our studies was $\text{Ru}(\text{bpz})_3(\text{BARF})_2$. The electron-deficient bipyrazyl ligands render this photocatalyst a substantially more powerful photooxidant than the more common parent tris(bipyridyl) complex. Due to the attractive photoredox properties of $\text{Ru}(\text{bpz})_3^{2+}$ coupled with its chemical stability and long excited state lifetime, this photocatalyst has proven to be powerfully enabling in a variety of photooxidative transformations (Table 2). These have included oxidative [3+2] cycloadditions of phenols,⁴ thiol–ene reactions,⁵ and aerobic cyclooxxygenation reactions,⁶ among others.⁷ However, previously reported methods for the synthesis of the bipyrazyl ligand are not easily scalable or provide poor yields. The improved method described in this manuscript is based upon optimized conditions reported recently by our group.⁸

Table 2. Photooxidative transformations using $\text{Ru}(\text{bpz})_3^{2+}$

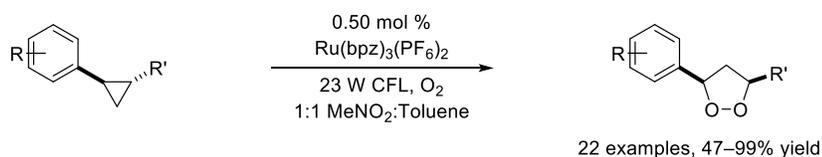
Oxidative [3+2] cycloadditions of phenols



Thiol–ene reactions



Aerobic cyclooxxygenation reactions



References

1. Department of Chemistry, University of Wisconsin–Madison, 1101 University Avenue, Madison, Wisconsin, 5370, United States. E-mail: tyoon@chem.wisc.edu. This publication is based on work supported by NIH-NIGMS (GM095666), the Sloan Foundation, the Beckman Foundation, and Research Corporation. The authors also thank Sigma–Aldrich for a gift of ruthenium(III) chloride used in these studies.
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Appendix

Chemical Abstracts Nomenclature (Registry Number)

2-Iodopyrazine: Pyrazine, 2-iodo-; (32111-21-0)

Potassium carbonate: Carbonic acid, potassium salt (1:2); (584-08-7)

- Palladium (II) acetate: Acetic acid, palladium(2+) salt (2:1); (3375-31-3)
 Ammonium chloride; (12125-02-9)
 2,2'-Bipyrazine; (10199-00-5)
- Ruthenium (III) chloride: Ruthenium chloride (RuCl_3); (10049-08-8)
- $\text{Ru}(\text{bpz})_3\text{Cl}_2$: Ruthenium(2+), tris(2,2'-bipyrazine- $\square N^1, \square N^1$)-, chloride (1:2),
 (OC-6-11)-; (80925-50-4)
- Sodium BArF: Borate(1-), tetrakis[3,5-bis(trifluoromethyl)phenyl]-, sodium
 (1:1); (79060-88-1)
- $\text{Ru}(\text{bpz})_3(\text{BArF})_2$: Ruthenium(2+), tris(2,2'-bipyrazine- $\kappa N^1, \kappa N^1$)-, (OC-6-11)-,
 tetrakis[3,5-bis(trifluoromethyl)phenyl]borate(1-) (1:2); (1350432-81-3)
- trans*-Anethole: Benzene, 1-methoxy-4-(1-propen-1-yl)-; (4180-23-8)
- Isoprene: 1,3-Butadiene, 2-methyl-; (78-79-5)
- 1-(4,6-Dimethyl-3-cyclohexen-1-yl)-4-methoxybenzene: Benzene, 1-[(1*R*,6*R*)-
 4,6-dimethyl-3-cyclohexen-1-yl]-4-methoxy-, *rel*-; (112150-17-1)



Shane Lies was born in Waterloo, Iowa in 1987. He received his B.S. in Biochemistry from the University of Northern Iowa in 2014 where he worked in the laboratory of Prof. Jeffrey Elbert. That year, he began his doctoral studies at the University of Wisconsin–Madison in the laboratories of Prof. Tehshik Yoon. His graduate work has focused on the development of methods for the synthesis of cyclobutane derivatives using photoredox chemistry.



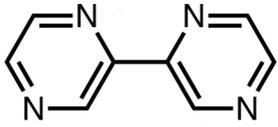
Shishi Lin grew up in sunny Singapore and received her B.Sc. degree in Chemistry from the National University of Singapore in 2009 where she carried out undergraduate research on the enantioselective protonation reactions catalyzed by chiral bicyclic guanidine with Prof. Choon-Hong Tan. She then moved across the globe to the University of Wisconsin-Madison where she completed her Ph.D. degree in Chemistry with Tehshik Yoon. Her graduate research focused on the electronically-mismatched radical cation Diels–Alder cycloaddition reactions by visible light photocatalysis. Currently she is an industrial postdoctoral fellow at Merck Process Chemistry.



Tehshik Yoon received his A.B. in Chemistry from Harvard University in 1996 working with Prof. David Evans. His graduate degrees were received from Caltech, his M.S. under the direction of Prof. Erick Carreira, and his Ph.D. from Prof. David MacMillan. After an NIH postdoctoral fellowship in Prof. Eric Jacobsen's laboratory at Harvard University, Yoon began his independent career at the University of Wisconsin–Madison in 2005. He was promoted to Associate Professor in 2012 and to Professor in 2014.



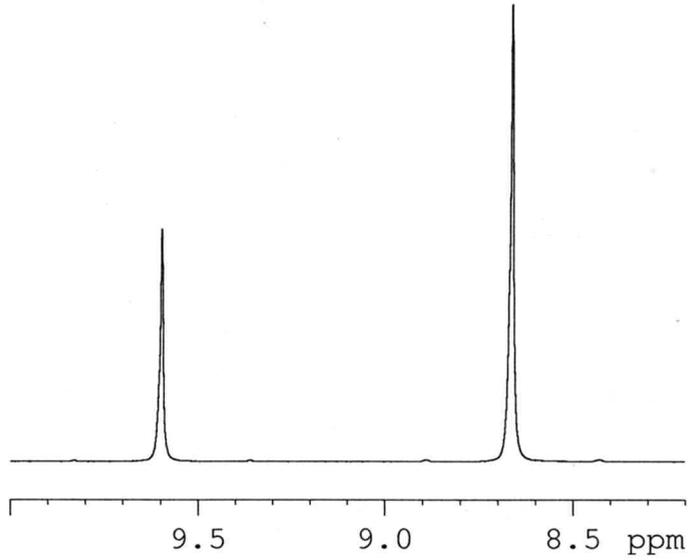
Stanley Chang received his B.Sc. at the University of British Columbia in 2009 and carried out undergraduate research with Prof. Chris Orvig. Later he studied chemistry at Simon Fraser University, obtaining his Ph.D. in 2015 under the direction of Prof. Robert Britton, investigating the total syntheses of 5,5-spiroacetal natural products. He is currently a Postdoctoral Research Fellow with Prof. Richmond Sarpong at UC Berkeley, exploring the total synthesis of complex terpene natural products.



1

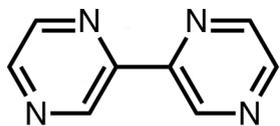
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— 8.66



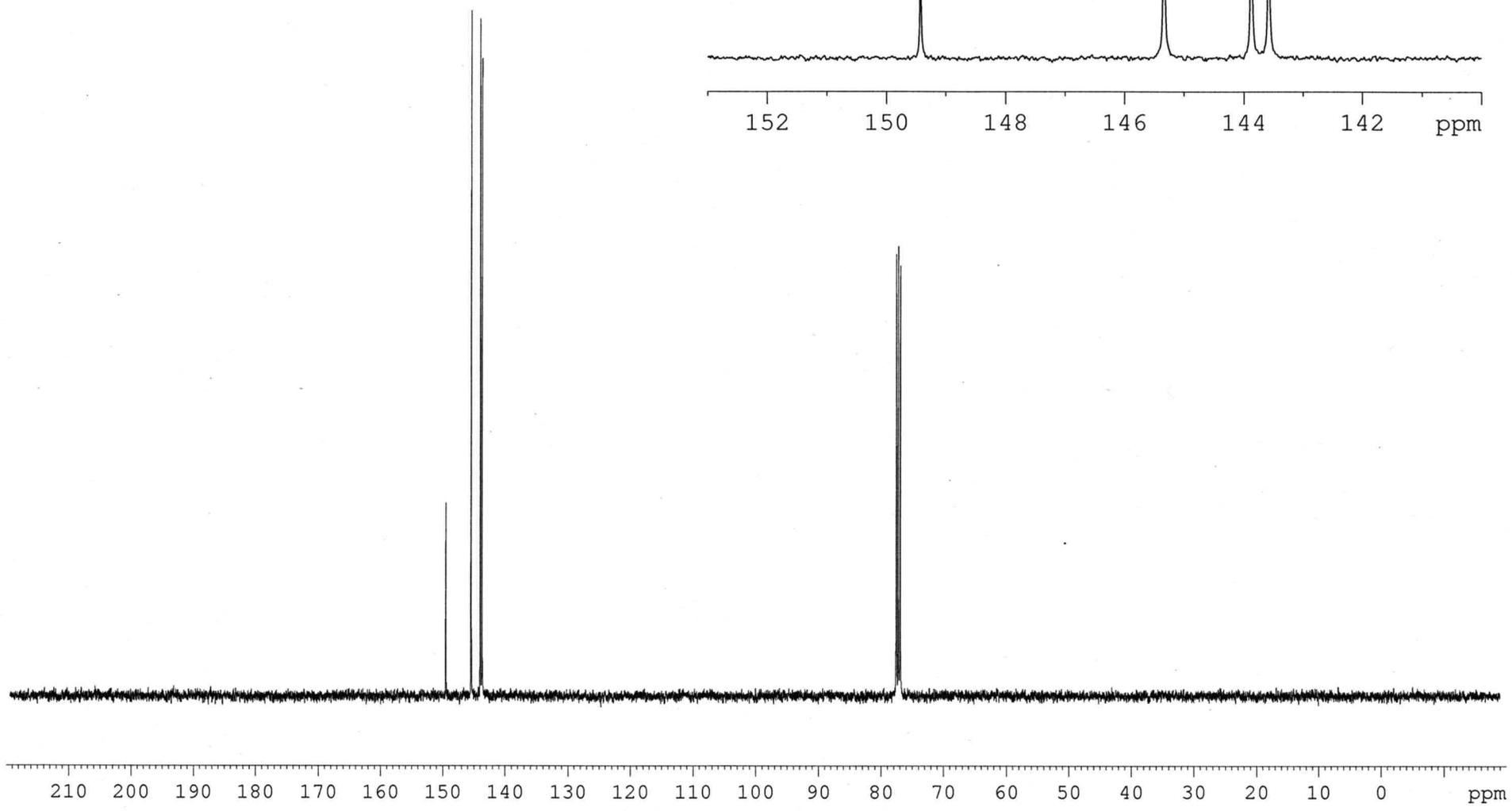
2.00

4.00



1

149.4
145.3
143.9
143.6

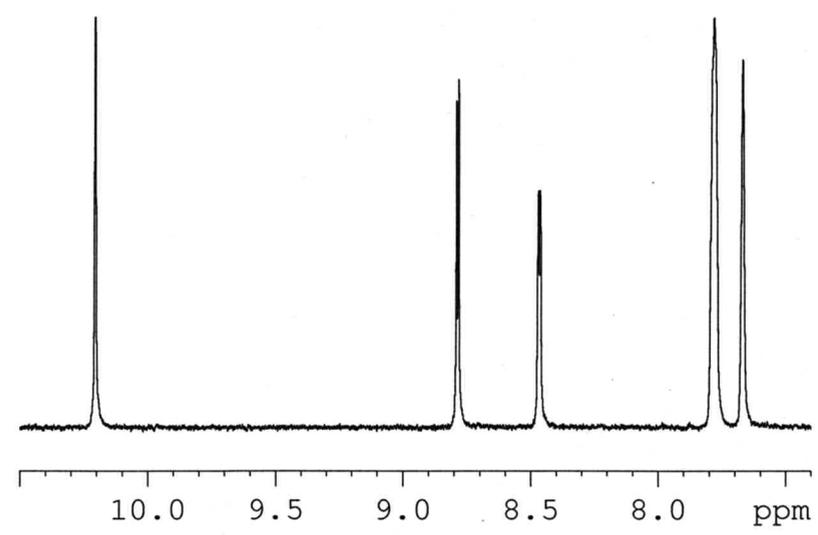


Ru(bpz)₃(BARF)₂

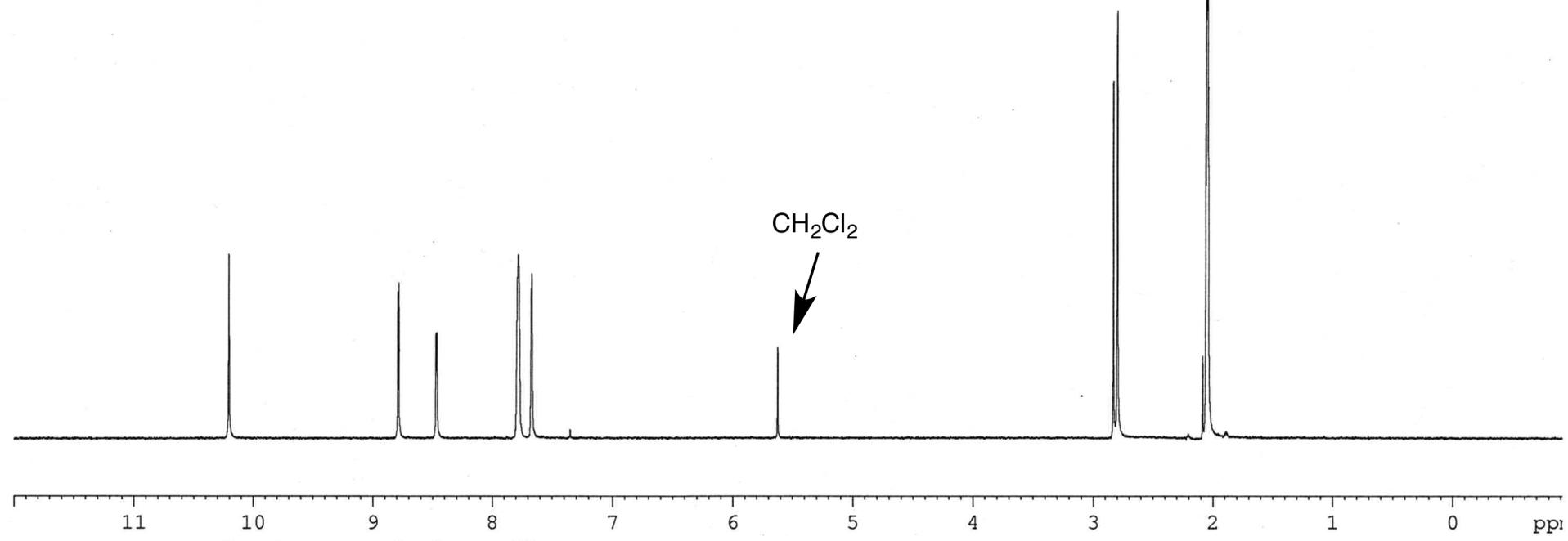
2

— 10.21

8.79
8.78
8.47
8.47
7.78
7.67



CH₂Cl₂



6.00

6.00

6.00

16.00

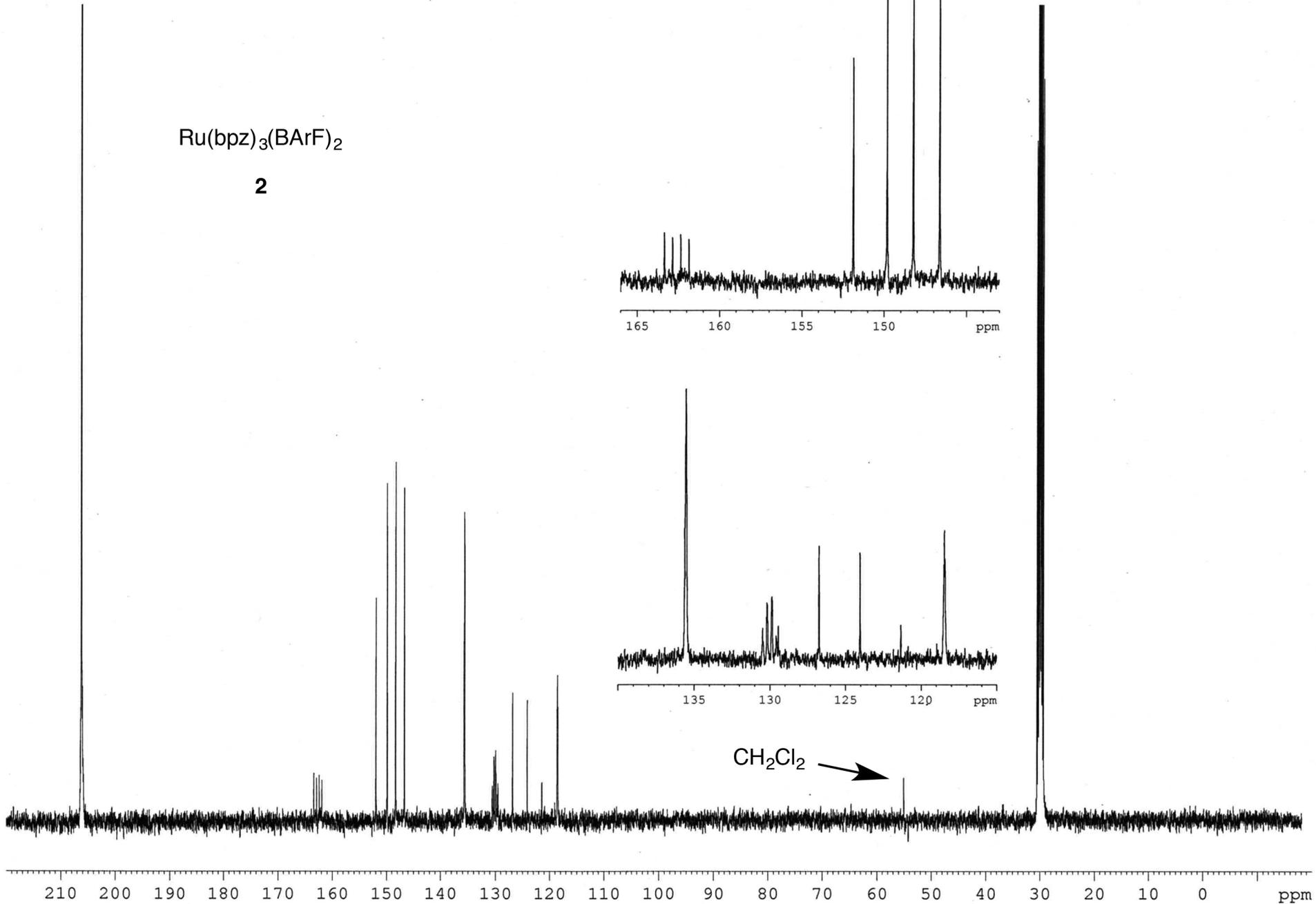
8.00

ppm

Ru(bpz)₃(BARF)₂

2

163.4
162.9
162.4
161.9
151.9
149.8
148.2
146.6
135.6
130.5
130.2
129.9
129.4
126.7
124.0
121.3
118.5



CH₂Cl₂ →

Ru(bpz)₃(BARF)₂

2

+

dimethyl fumarate
(internal standard)

