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Lowering the symmetry of difunctionalized coordination compounds via nucleophilic aromatic substitutions

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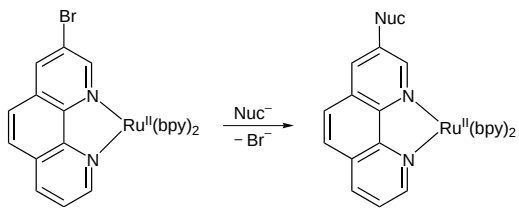
Abstract—Ru^{II}-coordinated 3,8-dibromo-1,10-phenanthroline undergoes nucleophilic aromatic substitutions with simple nucleophiles (e.g. thiolate) to give the disubstituted products in high yields. When a fluorenyl anion is used, a mono-substituted product is exclusively obtained. The highly acidic nature of this mono-substituted complex results in deprotonation under the reaction conditions and deactivation toward a second substitution reaction. A complex of lower symmetry that can be further functionalized using other transformations is obtained.

The consequences of metal complexation on substitution reactions that take place on the coordinated organic moiety have been of interest for decades.[1] Although significant advances have been made with organometallic species,[2] less attention has been given to polypyridine coordination compounds.[3,4] Early work by Tobe demonstrated enhanced reactivity of 5-chloro-1,10-phenanthroline in displacement reactions upon metal complexation;[5] and elegant work by Constable illustrated similar behavior in Ru^{II}-coordinated 4-halopyridines,[1] 4,4′-dichloro-2,2′-bipyridines[6] as well as 4′-chloro-2,2′:6′,2″-terpyridines.[7,8] Recognizing the need to derivatize 1,10-phenanthroline along the strategic long axis of the molecule, we have recently established a convenient approach for the modification of metal-coordinated 3-bromo-1,10-phenanthroline by nucleophilic aromatic substitutions (Scheme 1).[9] Thus, under conditions where the free ligand is not sufficiently reactive, the metal-coordinated 3-bromo-1,10-phenanthroline smoothly reacts with various soft and hard nucleophiles. This unprecedented reactivity of *meta*-substituted 1,10-phenanthroline was attributed to the increased electrophilicity of the complexed ring upon metal coordination and the effective resonance stabilization of the anionic addition intermediate.[9] This simple methodology facilitates the preparation of uniquely modified and useful bioinorganic building blocks, such as metal-containing amino acids.[10]

The efficiency of the substitution reactions of **1** with various nucleophiles has led us to examine the reactivity of the corresponding 3,8-dibromo-1,10-phenanthroline complex **2** under similar conditions (Scheme 2). This C_2 symmetric functionalized metal complex is synthesized by treating 3,8-dibromo-1,10-phenanthro-



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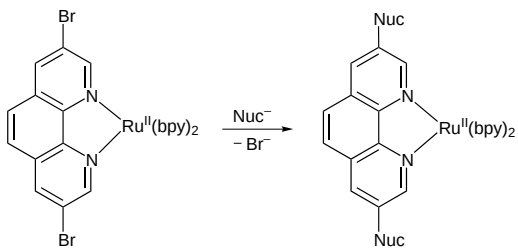
Scheme 1. Nucleophilic aromatic substitution on Ru^{II}-coordinated 3-bromo-1,10-phenanthroline **1** (see Ref. 9).



2

3a Nuc=SCH_3
3b Nuc=$SCH_2CH(NHBoc)CO_2H$

Scheme 2. Nucleophilic aromatic disubstitution on Ru^{II}-coordinated 3,8-dibromo-1,10-phenanthroline **2** with thiolate nucleophiles.

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line with $[Ru(bpy)_2Cl_2]$, in an analogous fashion to the synthesis of **1**.[11] Treating complex **2** with excess sodium thiomethoxide in degassed DMF resulted in a rapid conversion to the disubstituted product **3a** that was isolated in 80% yield.[12] Similar reaction conditions were employed for the derivatization of this complex with the nucleophilic sulfhydryl side-chain of *N*-Boc-L-cysteine. Thus, reaction of **2** with 3 equiv. of *N*-Boc-L-cysteine in degassed Na_2CO_3 DMF–H_2O (1:1) at 55°C gives the bis-*N*-Boc-L-cysteine Ru^{II} complex **3b** in 82% yield.[12]

An intriguing challenge is the conversion of a coordinated 3,8-dibromo-1,10-phenanthroline to an asymmetrically substituted ligand by a single substitution reaction. Such reactions would provide attractive complexes, where the coordinated phenanthroline ligand can be substituted with two electronically distinct substituents. We hypothesized that certain nucleophiles may facilitate such transformations by deactivating the remote brominated ring after a single substitution. Such nucleophiles should possess an additional acidic hydrogen. Upon the first substitution reaction, the acidity of the remaining hydrogen would dramatically increase, generating a stable anion under the reaction conditions. Resonance structures show that such an anion would substantially decrease the electrophilicity of the remote brominated ring. This scenario is illustrated in Scheme 3. A single substitution reaction of **2** with a fluorenyl anion should give **5**, a product with a very acidic hydrogen. Under the reaction conditions, deprotonation by excess base should generate the anion **7**. Delocalization of the negative charge reduces the electrophilicity of the 1,10-phenanthroline skeleton and attack at the 8-position should be suppressed. Quenching is expected to afford the 3-bromo-8-substituted product **5** that can be further functionalized using other transformations (e.g. cross-coupling reactions).[11,13]

To explore this route, we first investigated the reactivity of the fluorenyl anion with $[Ru(bpy)_2(3\text{-bromo-1,10-phenanthroline})]^{2+}$ **1**, a singly functionalized complex (Scheme 3). Thus, when **1** is treated with 5 equiv. of the fluorenyl anion in anhydrous degassed DMF at slightly elevated temperature (55–60°C), the 3-fluorenyl Ru^{II} complex **4** is isolated in 60% yield.[14] Under the basic reaction conditions, product **4** exists as the anion **6**, whose formation is easily monitored by electronic absorption spectroscopy (Fig. 1). Upon deprotonation of the isolated **4** by triethylamine in degassed DMF or CH_2Cl_2, an intense low energy band appears at 680 nm in the visible spectrum ($\varepsilon = 1.2\times10^4$ M^{-1} cm^{-1}), corresponding to the highly delocalized anion **6**. The solution turns from the typical orange–red color of Ru^{II} polypyridyl complexes to a dark green color in the deprotonated form (Fig. 1).[15] The efficient generation of anion **6** by triethylamine (triethylammonium: pK_a 10.7) indicates that the pK_a of the acidic methine proton in **4** is likely to be less than 10, making it a potent carbon acid.[16]

In a similar fashion, the asymmetrically substituted Ru^{II} complex **5** is obtained in 40–60% yield by the reaction of a fluorenyl anion with $[Ru(bpy)_2(3,8\text{-dibromo-1,10-phenanthroline})]^{2+}$ **2** in degassed DMF (Scheme 3).[17] No bis-fluorenyl Ru^{II} complex is observed or isolated. This is in marked contrast to the reaction with thiolate nucleophiles, which readily substitute the bromines at both the 3- and 8-positions of the coordinated phenanthroline ligand (Scheme 2). This observation strongly supports our proposed mechanism that suggests deactivation of the remotely substituted ring

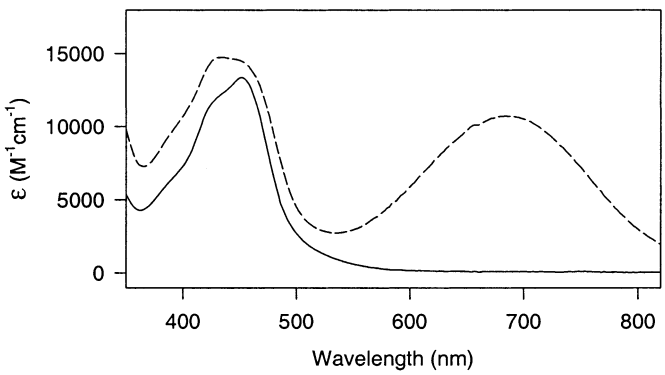
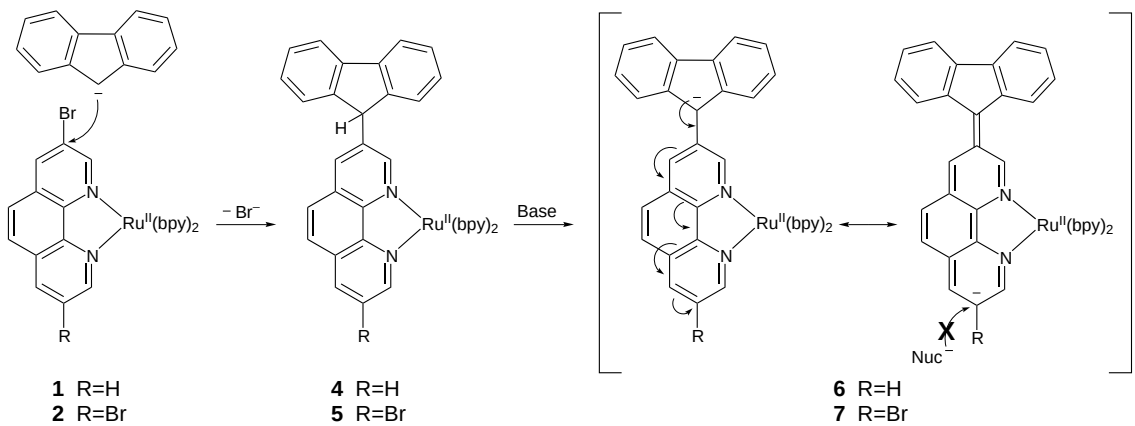


Figure 1. Visible spectra of **4** (—) and the corresponding anion **6** generated with triethylamine (- - -) in deoxygenated DMF.



Scheme 3. Nucleophilic aromatic disubstitution on Ru^{II}-coordinated brominated phenanthrolines **1** and **2** with a fluorenyl anion.

upon the first substitution reaction. As with **4**, **5** is completely deprotonated under the reaction conditions. The orange complex **5** turns dark green upon exposure to organic bases such as triethylamine showing a lower energy absorption band at 720 nm ($\varepsilon = 5\times10^3$ M^{-1} cm^{-1}), corresponding to the highly delocalized anion **7**.[18]

In summary, we have demonstrated that desymmetrization of a disubstituted coordinated ligand can easily be achieved via nucleophilic aromatic substitutions. A prerequisite for this process is the conversion of the monosubstituted intermediate to a highly delocalized anion under the reaction conditions. These observations provide additional experimental support for our proposed mechanism of this family of nucleophilic aromatic substitutions, and further advance the organic chemistry of coordination compounds.

Acknowledgements

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12. Data for **3a**: ^{1}H NMR (CD_3CN, 400 MHz): δ 8.50 (t, $J=7.1$ Hz, 4H), 8.32 (d, $J=1.9$ Hz, 2H), 8.08 (dt, $J=8.0$, 1.7 Hz, 2H), 8.08 (s, 2H), 8.01 (dt, $J=8.2$, 1.7 Hz, 2H), 7.80 (d, $J=5.5$ Hz, 2H), 7.73 (d, $J=1.9$ Hz, 2H), 7.61 (d, $J=5.5$ Hz, 2H), 7.43 (dt, $J=5.8$, 1.4 Hz, 2H), 7.26 (dt, $J=5.5$, 1.4 Hz, 2H), 2.50 (s, 6H); ^{13}C NMR (CD_3CN, 101 MHz): δ 15.06, 125.37, 125.43, 128.50, 128.63, 129.05, 131.21, 132.14, 138.89, 139.01, 140.78, 145.46, 150.53, 153.26, 153.31, 158.07, 158.43, 15.06; UV–vis (CH_3CN): λ_{max} nm ($\varepsilon\times10^{-4}$) 246 (3.5), 286 (7.9), 362 (2.9), 446 (1.5); MALDI MS calcd for $C_{34}H_{28}F_6N_6PRuS_2$ $[M]^+$ 830.793, found 830.2 $[M]^+$. Data for **3b**: ^{1}H NMR (CD_3CN, 300 MHz): δ 8.84 (t, $J=1.7$ Hz, 1H), 8.67 (d, $J=3.3$ Hz, 0.5H), 8.65 (d, $J=3.3$ Hz, 0.5H), 8.47–8.55 (m, 4H), 8.20 (s, 1H), 7.97–8.15 (m, 7H), 7.75–7.79 (m, 2H), 7.57–7.62 (m, 2H), 7.43–7.48 (m, 2H), 7.23–7.29 (m, 2H), 4.21 and 4.13 (dd, $J=8.58$, 4.9 Hz, 1H, H_α), 3.58 and 3.48 (dd, $J=14.2$, 5.0 Hz, 1H, -CH_2-), 3.26 and 3.16 (dd, $J=14.2$, 5.0 Hz, 1H, -CH_2-), 1.35 (d, $J=7.0$, 9H, -^{t}Butyl); UV–vis (MeOH): λ_{max} nm ($\varepsilon\times10^{-4}$) 246 (3.9), 286 (7.5), 352 (2.1), 448 (1.5); ESI MS calcd for $C_{48}H_{50}F_6N_8PRuS_2$ $[M]^+$ 1177.13, found 1177.0 $[M]^+$.
13. (a) Tzalis, D.; Tor, Y. *Chem. Commun.* **1996**, 1043–1044; (b) Tzalis, D.; Tor, Y. *J. Am. Chem. Soc.* **1997**, *119*, 852–853; (c) Hurley, D. J.; Tor, Y. *J. Am. Chem. Soc.* **1998**, *120*, 2194–2195.
14. Data for **4**: ^{1}H NMR (CD_3CN, 400 MHz): δ 8.58 (d, $J=7.3$ Hz, 1H), 8.55 (d, $J=1.5$ Hz, 1H), 8.51 (d, $J=8.1$ Hz, 1H), 8.46 (d, $J=8.8$ Hz), 8.28 (d, $J=8.1$ Hz, 1H), 8.22 (d, $J=8.8$ Hz, 1H), 8.20 (d, $J=8.1$ Hz, 1H), 8.18 (d, $J=8.8$ Hz, 1H), 8.07 (dt, $J=8.1$, 1.5 Hz, 1H), 8.02 (d, $J=5.1$ Hz, 1H), 7.92–7.99 (m, 3H), 7.89 (d, $J=5.1$ Hz, 1H), 7.86 (d, $J=7.3$ Hz, 1H), 7.83 (d, $J=7.3$ Hz, 1H), 7.69 (dd, $J=8.1$, 5.1 Hz, 1H), 7.48–7.53 (m, 3H), 7.39–7.43 (m, 3H), 7.20–7.29 (m, 3H), 7.15–7.20 (m, 3H), 7.00–7.02 (m, 2H), 5.34 (s, 1H); ^{13}C NMR (CD_3CN, 101 MHz): δ 51.71, 121.22, 121.26, 124.78, 124.82, 124.98, 125.03, 125.99, 126.14, 126.69, 128.01, 128.11, 128.16, 128.56, 128.65, 128.77, 129.01, 129.13, 129.25, 131.49, 131.68, 136.29, 137.66, 138.50, 138.52, 138.58, 138.64, 141.51, 141.64, 141.90, 146.92, 147.10, 148.12, 151.86, 152.31, 152.49, 152.53, 153.07, 153.25, 157.31, 157.61, 157.70, 157.91; UV–vis (CH_3CN): λ_{max} nm ($\varepsilon\times10^{-4}$) 208 (8.2), 230 (5.0), 272 (7.1), 280 (6.9), 448 (1.5); MALDI MS calcd for $C_{45}H_{32}F_6N_6PRu$ [M+] 902.810, found 902.4 $[M]^+$.
15. Note that the low energy band (presumably a charge-transfer transition) and the typical metal-to-ligand charge-transfer (MLCT) transitions around 450 nm appear to be orthogonal. The MLCT bands are essentially identical in the neutral complex **4** and the corresponding anion **6** (Fig. 1).

16. Increased delocalization over an additional aromatic ring is known to have a substantial effect on the pK_a of the 9-fluorenyl proton. Indeed, 9-phenyl-fluorene has a pK_a of 18.5, which is 4–5 pK_a units more acidic than its parent hydrocarbon (Kosower, E. M. *An Introduction to Physical Organic Chemistry*; John Wiley & Sons: New York, 1968. See also: Ritchie, C. D.; Uschold, R. E. *J. Am. Chem. Soc.* **1967**, *89*, 2752–2753). The delocalization of the negative charge onto the strongly electron-withdrawing Ru^{II} metal ion should also substantially lower the pK_a of **4**. Bordwell and co-workers have shown that the pK_a of the 9-fluorenyl proton can be brought to less than 11 with substitution of an electron-withdrawing group such as -CN or -CO_2Me at the 9-position (Bordwell, F. G.; Clemens, A. H.; Cheng, J.-P. *J. Am. Chem. Soc.* **1987**, *109*, 1773–1782).
17. [Ru(bpy)$_2$(3,8-dibromo-1,10-phenanthroline)][PF_6]$_2$ **2** (44 mg, 0.042 mmol) was evaporated with CH_3CN (3×2 mL) to remove traces of moisture, heated at 65°C under vacuum for 1 hr, then dissolved in degassed anhydrous DMF (2 mL). In a separate flask, fluorene (70 mg, 0.42 mmol) was evaporated with CH_3CN (2×3 mL) and dissolved in degassed anhydrous DMF (3 mL). The fluorene solution was degassed using argon for 10 min, then cannulated into the NaH (60% dispersion in mineral oil, 20 mg, 0.50 mmol) to create a dark orange solution. This solution of the fluorenyl anion was cannulated into the Ru^{II} complex solution, which turned immediately from dark red to dark green. The reaction mixture was heated at 65°C for 3 h. [*Note: The product anion generated in situ reacts rapidly with oxygen. Extreme care should be taken to exclude oxygen from this reaction*]. The reaction was quenched with degassed 0.05 M potassium phosphate buffer pH 7.0 (7 mL), turning the green reaction mixture orange. The product was extracted into dichloromethane. The organic layer was dried over Na_2SO_4, filtered, and evaporated. The crude reaction mixture was purified by flash chromatography (silica gel, 0.1% satd aq. KNO_3, 1–4% water in acetonitrile). The product fractions were evaporated, dissolved in 2 mL methanol, then treated with an aqueous 0.05 M KPF_6 solution, followed by extraction into dichloromethane. The organic phase was dried over Na_2SO_4, filtered, and evaporated to yield 27 mg of **5** as a red solid (60% yield). TLC (1% satd aq. KNO_3/10% H_2O/CH_3CN) R_f=0.50; ^{1}H NMR (CD_3CN, 300 MHz): δ 8.81 (d, J=2.2 Hz, 1H), 8.55 (d, J=1.7 Hz, 1H), 8.49 (m, 3H), 8.27 (d, J=7.7 Hz, 1H), 8.20 (m, 2H), 8.13 (d, J=9.3 Hz, 1H), 8.01–8.10 (m, 3H), 7.96 (t, J=7.1 Hz, 2H), 7.81–7.89 (m, 3H), 7.58 (d, J=5.5 Hz, 1H), 7.51 (t, J=7.1 Hz, 1H), 7.43 (m, 2H), 7.39 (t, J=5.0, 1H), 7.17–7.29 (m, 5H), 6.99–7.02 (m, 2H), 5.34 (s, 1H); UV–vis (CH_3CN): λ_{max} nm ($\varepsilon\times10^{-4}$) 206 (10.1), 236 (5.7), 278 (8.8), 448 (1.6); MALDI MS calcd for $C_{45}H_{31}BrF_6N_6PRu$ [M+] 981.706, found 981.3 $[M]^+$. A byproduct in these reactions is the dehalogenated product **4** (10–30%). Longer reaction times (>12 h) at elevated temperatures (60°C) can result in the complete dehalogenation of **5**. In addition, the anions **6** and **7** react rapidly with oxygen (as confirmed by mass spectrometry, which shows the presence of [M+16] peaks for both compounds). Elimination of oxygen, particularly in the quenching buffer, virtually eliminates these side products.
18. Preliminary experiments indicate that the 3-bromo-8-fluorenyl-1,10-phenanthroline Ru^{II} complex **5** is amenable to Pd-catalyzed Sonogashira cross-coupling reactions with aromatic acetylenes.