

Chemosselective Ruthenium-Catalyzed C–O Bond Activation: Orthogonality of Nickel- and Palladium-Catalyzed Reactions for the Synthesis of Polyaryl Fluorenones

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Published as part of the Cluster C–O Activation

Received: 05.10.2017

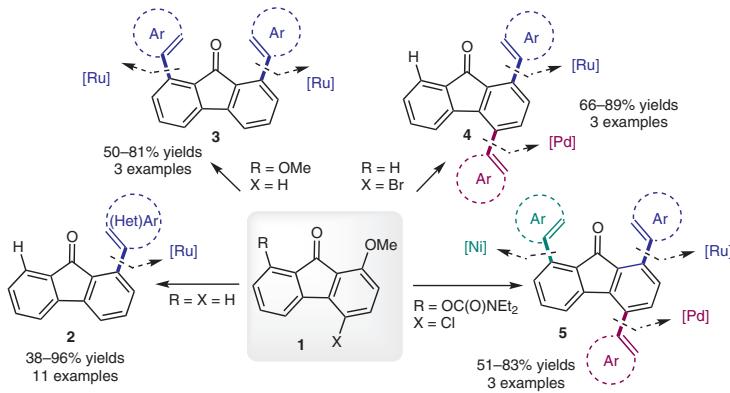
Accepted after revision: 31.10.2017

Published online: 14.11.2017

DOI: 10.1055/s-0036-1590985; Art ID: st-2017-r0772-c

Abstract Ruthenium-catalyzed C–O bond activation/arylation of methoxy and O-carbamoyl-substituted fluorenones is reported. Established are new reactions of compound **1** ($X = H$) to aryl (**2**) and 1,8-diaryl (**3**) fluorenones. Orthogonal ruthenium-, palladium- and nickel-catalyzed reactions with Suzuki–Miyaura reactions to afford 1,4-diaryl (**4**) and 1,4,8-triaryl fluorenones (**5**) are also described. The ready availability of starting methoxy fluorenones by directed *ortho* and remote metalation tactics confers facility to the presented reactions which may find application in material science areas. DFT calculations have been performed to rationalize the lack of C–H bond reactivity in the ruthenium-catalyzed reaction.

Key words C–O activation, fluorenone, ruthenium catalysis, nickel catalysis, palladium catalysis, polyarylation, orthogonal cross-coupling



Over the past decade, fluoren-9-one derivatives have attracted considerable attention due to their presence in natural products¹ with a range of biological activities (e.g., dengibisin,^{1d,g} dengibisinin,^{1d} dendroflorin,^{1b} cauliphin)^{1j} and in pharmaceutically important agents (anticancer, antioxidant, and anti-HIV).² Furthermore, fluorenones, arylated fluorenones, and benzofluorenones have been incorporated in oligomers and polymers which have been examined for potential applications of their optical and electrochemical properties as organic light-emitting devices³ and liquid crystals⁴ (Figure 1).

As a result, the synthetic chemistry community has voiced considerable interest in fluorenones and, in addition to the traditional routes,⁵ new routes have been discovered and generalized based on a Directed *ortho* Metalation (DoM)/Suzuki–Miyaura cross-coupling/Directed remote

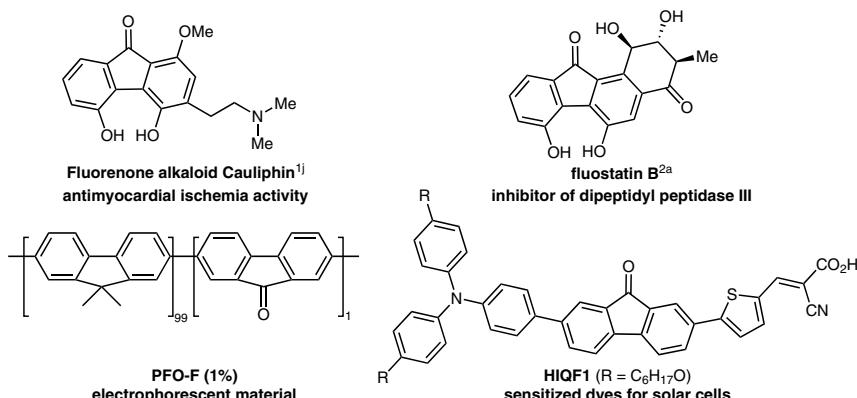


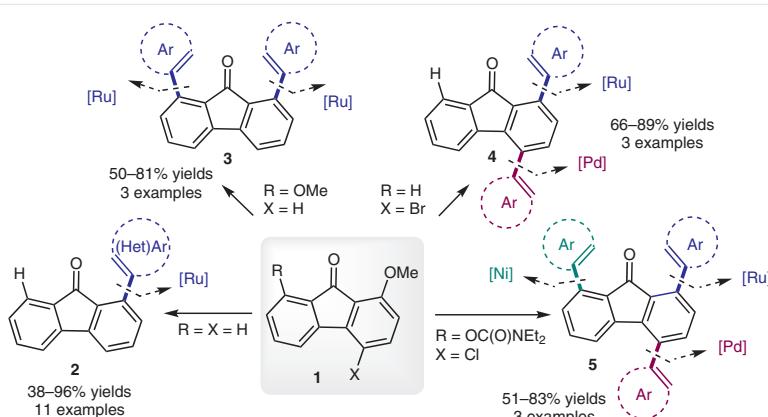
Figure 1 Natural products, pharmaceutical and photoelectronic materials containing the fluorenone framework

Metalation (DreM) strategy^{6–8} which complements, in the site selectivity of reaction, the classical Friedel–Crafts method. Recently, new metal-catalyzed strategies have been reported including radical cyclization,⁹ direct C–H coupling,¹⁰ decarboxylative coupling,¹¹ and CO insertion¹² processes. Specifically, with respect to the synthesis of polarylated fluorenones, the literature is very limited despite their current interest in the area of organic electronics due to their highly rigid π-conjugated systems.³ Indeed, only Diels–Alder cycloaddition/aromatization,¹³ [2+2+2]-cycloaddition,¹⁴ and radical cycloisomerization¹⁵ strategies have been reported. Recently, Langer and co-workers described the first site-selective arylation of the bis triflate of a 5,10-dihydroxybenzo[*b*]fluorenone to furnish the corresponding diarylated derivative by a Suzuki–Miyaura cross-coupling reaction.¹⁶ While advances in synthesis of 2-, 3-, and 4-substituted fluorenones are evident over several decades, few methods for the preparation of 1-substituted fluorenones, and particularly for the 1-arylated fluorenones, have been reported.^{10i,17}

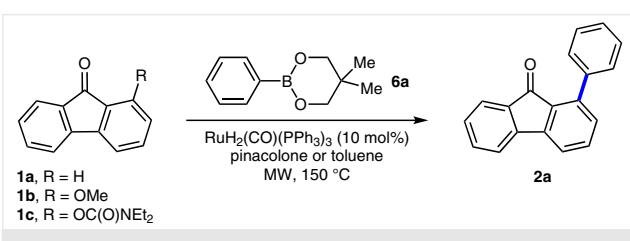
In the past decade, C–C bond-forming reactions based on aryl C–O bond activation/cross-coupling using transition-metal catalysis have been discovered which constitutes a fundamental and powerful alternative to the aryl halide/cross-coupling tactic.^{18–21} Following Wenkert's seminal observation,^{20a} Ni-catalyzed processes (Kumada–Corriu,^{20a,b} Suzuki–Miyaura,^{20f,22} and Negishi^{20c} reactions) have historically dominated the process for C–O bond cleavage of aryl alkyl ethers. In 2004, Kakiuchi, Chatani, and Murai triggered a new area of synthetic methodology by the discovery of the Ru-catalyzed cross-coupling reaction of aryl ethers with boronates by *ortho*-ketone-assisted chelation.^{20e} Shortly thereafter, Kakiuchi and coworkers overcame competitive C–O and C–H activation by use of a bulky ketone group or a fused aromatic ketone to achieve a regioselective C–OMe bond-activation reaction.^{23,24}

Inspired by the discoveries of Kakiuchi, Chatani, and Murai^{20e} and concurrent with our work on the activation of unreactive C–H, C–O, and C–N bonds mediated by ruthenium catalysis²⁵ for the development of new synthetic methodologies competitive or surpassing the DoM–cross-coupling strategies,^{6,8,26} we proposed to test the Ru-catalyzed C–O activation/cross-coupling in the reaction of methoxy-fluorenones with aryl boroneopentylates for the synthesis of aryl-substituted fluorenones. As an additional incentive, we envisaged the potential of S_EAr orthogonal reactivity based on the pendant presence of the strong electron-donating OMe group. Herein we disclose an efficient and straightforward methodology based on conveniently available starting materials **1** which combines DoM/DreM protocols with Ru-, Ni- and Pd-catalyzed cross-coupling reactions of C–OMe and also C–OCONR₂ bonds for the regioselective synthesis of aryl fluorenones **2**, isomeric 1,4- (**4**) and 1,8-diarylated (**3**), and 1,4,8-triarylated (**5**) fluorenones of potential interest in material science areas (Scheme 1).

In view of the successful C–H activation results on 1-tetralone and related aromatic ketones²⁴ and those of Kakiuchi showing nonregioselective C–H and C–O activation,^{24f} we tested commercially available fluorenone to initiate our study. Subjection of fluorenone (**1a**) to reaction with boronic ester **6a** in the presence of 10 mol% of RuH₂(CO)(PPh₃)₃ in pinacolone or dry toluene solution under microwave irradiation at 150 °C led to recovery of starting material even after 12 h reaction time (Scheme 2).²⁷ In contrast, 1-methoxyfluorenone (**1b**), readily available by the combined DoM/Suzuki–Miyaura cross-coupling procedure (see Supporting Information),^{5b,6,28} afforded 1-phenyl-fluorenone (**2a**) in comparable and excellent yields either in pinacolone (86%) or toluene (88%) solution after 2.5 h reaction at 150 °C refluxing conditions.²⁹ Reducing the amount of catalyst (from 5 mol% to 2 mol%) proved to be deleterious to the reaction affording reduced yields of product in both solvents or recovery of starting material (see Supporting Information). Furthermore, to our delight, when 1-O-



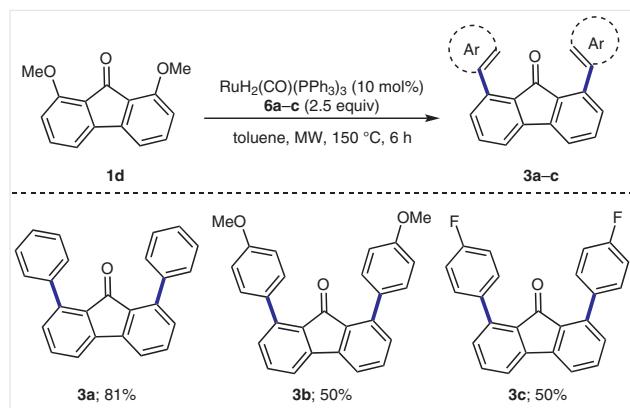
Scheme 1 Proposed strategies for the arylation of the fluorenone skeleton

**Scheme 2** Ru-catalyzed phenylation of fluoren-9-ones **1b** and **1c**

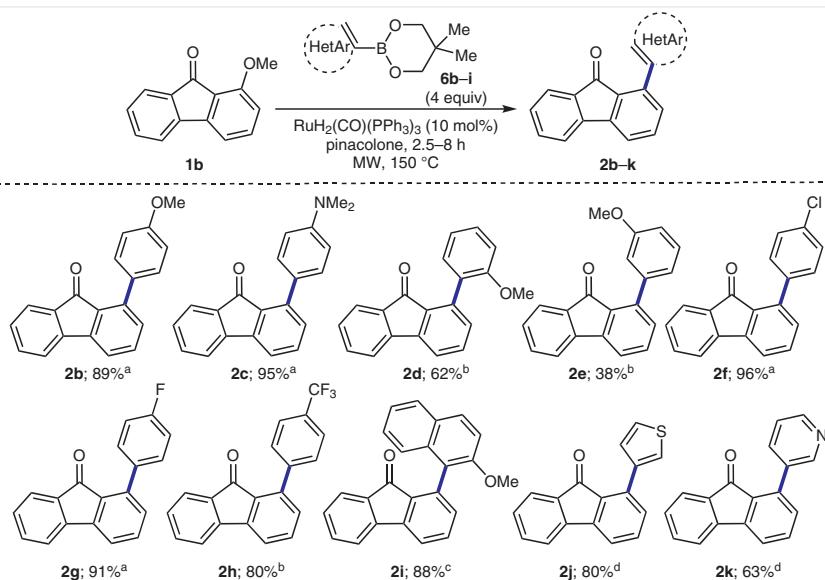
carbamate of fluorenone (**1c**) was subjected to the Ru-catalyzed conditions in pinacolone solvent, the aryl fluorenone **2a** was obtained in 87% yield thus demonstrating the first selective C–O activation/cross-coupling reaction of aryl O-carbamates.³⁰

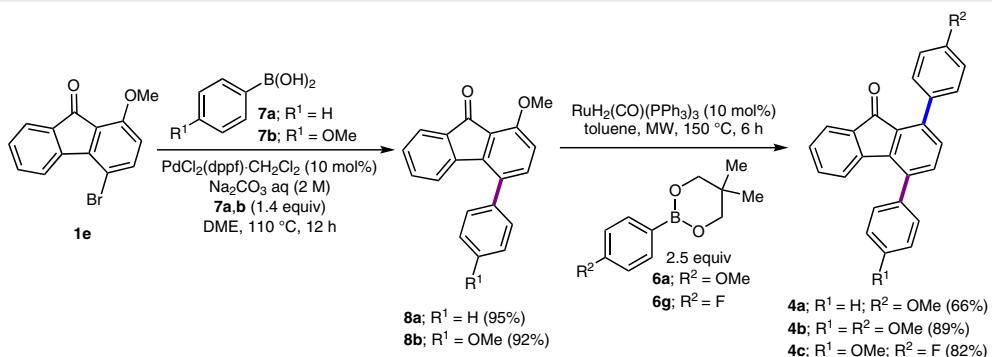
Investigation of the scope of the reaction (Scheme 3) involved the application of commercial (**6b**, **6d**, and **6e**) and readily available³¹ aryl-Bneop compounds. Using the microwave and pinacolone solvent conditions, aryl-Bneop derivatives bearing *para*-EDGs afforded the corresponding products **2b** and **2c** in excellent yields. The *ortho*-substituted aryl boronate (**6d**) was also a suitable substrate, giving product **2d** in 62% yield while, perhaps surprisingly, the *meta*-substituted aryl-Bneop (**6e**) led to a decreased yield of product **2e**. Excellent results were also obtained in the conversion of aryl boronates substituted with *para*-EWG (**6f–h**) to give the corresponding products **2f–h**. Furthermore, the 2-methoxynaphthalene-Bneop **6i** was successfully employed leading to the corresponding product **2i** in 88% yield in spite of potential naphthalene ring C8–H peri interaction.³² Two heterocyclic boronates cases, **6j** and **6k**, were subjected to the coupling conditions to afford products **2j** and **2k**, respectively, in good yields.

The convenient availability of the 1,8-dimethoxyfluorenone **1d** by *ortho* and remote metalation–cross-coupling chemistry^{5b,28} prompted the study of its C–O activation/aryl-Bneop coupling behavior and the results are summarized in Scheme 4. Although the reaction failed with pinacolone as solvent, use of toluene and the standard quantity of Ru catalyst afforded product **3a** in good yield and products **3b–c** in moderate yields. Compounds **3a–c** show normal IR $\nu_{C=O}$ absorptions at 1708–1701 cm^{–1} and ¹³C NMR at δ = 192 ppm, suggesting that no anisotropic effects are felt by the carbonyl group and there are minimal resonance effects on the carbonyl due to twisted positioning of the 1,8-aryl groups.

**Scheme 4** Synthesis of 1,8-diaryl-fluorenones **3a–c**

As demonstrated for the *ortho*-methoxy benzamide and –naphthamide systems,^{25a,c} we explored the orthogonal reactivity concept in Ru- and Pd-catalyzed processes (Scheme 5). For this purpose, compound **1b** was easily converted into

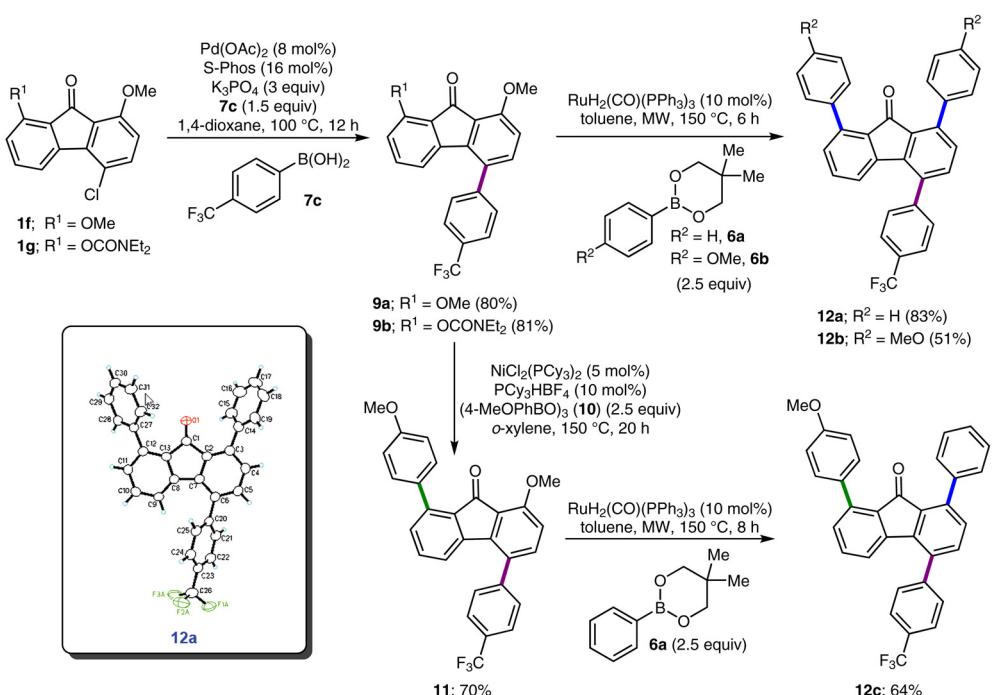
**Scheme 3** Synthesis of 1-aryl fluorenones (**2b–k**). ^a 2.5 h reaction time. ^b 4 h reaction time. ^c 8 h reaction time. ^d 5 h reaction time.

**Scheme 5** Orthogonal Pd- and Ru-catalyzed cross-coupling reactions to 1,4-diaryl-fluorenones

the 4-bromofluorene **1e** (83% yield using NBS) which, upon standard Pd-catalyzed Suzuki–Miyaura coupling with aryl boronic acids **7a** and **7b**, provided 4-aryl fluorenones **8a** and **8b**, respectively. Subsequent coupling of these products with aryl-Bnep derivatives **6a** and **6g** under Ru-catalyzed conditions afforded the 1,4-diaryl-fluorenones **4a–c**, respectively, in high overall yields from 1-methoxyfluorene (**1b**).

To further pursue the orthogonality concept, chloro derivatives **1f** and **1g**, prepared by the DoM/Suzuki–Miyaura coupling/DreM strategy, were subjected to Suzuki–Miyaura coupling under conditions suitable for aryl chlorides³³ to give the 8-methoxy and 8-O-carbamates **9a** and **9b**, respectively (Scheme 6). Compound **9a** underwent Ru-catalyzed coupling with Ph-Bnep (**6a**) and 4-methoxy-phenyl-Bnep

(**6b**) to afford the first cases of 1,4,8-triarylfluorenones **12a** and **12b**, respectively. The structure of **12a** was established by X-ray crystallography analysis (see Supporting Information). In the case of the O-carbamate **9b**, Ni-catalyzed cross-coupling conditions using the triphenylboroxine partner **10** was selective for the O-carbamate over the methoxy C–O bond activation to give the new diaryl fluorenone **11**. To complete the triumvirate metal orthogonality reactions, compound **11** was exposed to our Ru-catalyzed conditions in the coupling with aryl-Bnep **6a** to afford 1,4,8-triaryl-fluorenone **12c**, bearing three different aryl groups. Attempts to prepare 1,4,5,8-tetraaryl fluorenones by further bromination of **1d** and independent synthesis of 1,4,5,8-tetramethoxy fluorenone have been thwarted to date (see Supporting Information).

**Scheme 6** Combined Pd-, Ru-, and Ni-catalyzed cross-coupling reactions to triaryl fluorenones

In order to rationalize the lack of reactivity of the *ortho*-C–H bond of fluorenone (**1a**) and its 1-methoxy derivative **1b**, we performed calculations at the DFT level (see Supporting Information for details) of the square-planar Ru(0) complexes of these compounds and those derived from 2-methoxyacetophenone (**13**) for comparison (Figure 2). In addition, for comparison purposes, geometric data resulting from calculations reported for **13** by Lin and coworkers³⁴ at a different level of theory (PBE/LanL2DZ, plus f-type and d-type polarization functions for Ru and P, and 6-31G* for H, C and O) are also shown in Figure 2. Our results show a significant difference in Ru…H distance and C–H elongation in fluorenone complexes (**1aa**, **1ba**) when compared with that of acetophenone (**13a**). In **13a**, the distance Ru…H is significantly shorter (ca. 0.5 Å) than in **1aa** and **1ba**, while there is a greater degree of C–H elongation in **13a** than in **1aa** and **1ba** (ca. 0.020 Å, 0,003 Å, and 0.003 Å, respectively) with respect to other C–H bonds. Such differences lead us to the hypothesis of absence of agnostic activation in the oxidative addition step of C–H bonds in fluorenones.³⁴ On the other hand, the distance Ru…O(–C) is also significantly smaller in **1bb** (ca. 2.75–2.90 Å) than in **13b** (ca. 3.04–3.21 Å). These features may imply a lower reactivity of the *ortho*-C–H bond in the fluorenones to the oxidative addition of the C–O bond to Ru(0), justifying our experimental results. Additional studies are being conducted in order to test these and other hypotheses.

In conclusion, the present work establishes a new general methodology for the construction of polyarylated fluorophenones which constitutes new experimental evidence for the value of the C–O activation/cross-coupling reaction accumulatively documented for alkoxy aromatics reactions^{19–25} and complements C–H activation/coupling methods reported for anthraquinones.^{24c,d} The methodology highlights the orthogonal Pd-, Ni-, and Ru-catalyzed concept coupled with S_FAr reactions leading to convenient syntheses of 1,

1,4-, 1,4,8-aryl substituted fluorenones. The coupling of O-carbamate fluorenones **1c** and **9b** constitute, to the best of our knowledge, a new site-selective Ru-catalyzed aryl C–O activation/cross-coupling reaction on substrates which offer alternative C–H bond-coupling possibility.³⁰ In view of the ready availability of the starting fluorenones by the *ortho* and remote-directed metalation/cross-coupling protocol and the convenience of the chemistry, the application of the methodology, paralleling that established by Kakiuchi for anthraquinones,^{24b,c} may be anticipated. DFT calculations suggest that C–O oxidative addition over C–H bond activation is the preferred reaction path.

Acknowledgment

NSERC DG is acknowledged for support of our synthetic programs. A.J.M.S. and L.C.R.M.F. are grateful for the financial support from CNPq and CAPES. L.C.R.M.F. thanks CAPES for a fellowship.

Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0036-1590985>.

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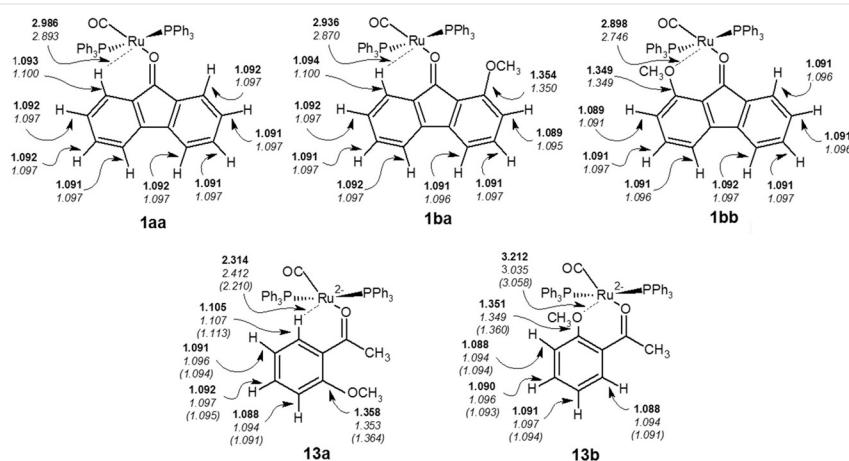


Figure 2 Bond distances (in Å) (PBE/Def2-TZVP (this work); PBE/Def2-SVP (this work); (PBE/LandL2DZ)³⁴).

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A dried Biotage microwave vial equipped with a magnetic stirring bar and a nitrogen inlet was sequentially charged with fluorenone (**1**, 0.5 mmol), boronic ester (**6**, 0.5–1 mmol), pinacolone (0.5 mL), and RuH₂(CO)(PPh₃)₃ (10 mol%). The reaction mixture was heated under MW irradiation at 150 °C for 2.5–8 h. The reaction mixture was extracted with EtOAc (15 mL), washed with brine, subjected to filtration, dried (Na₂SO₄), and concentrated under reduced pressure. Purification using flash column chromatography on silica gel (eluting with 1:9 hexanes/EtOAc) afforded product **2**.
- 1-(4-Fluorophenyl)-9H-fluoren-9-one (2g)**
Yellow solid, 91% yield; mp 156–158 °C (hexanes). ¹H NMR (400 MHz, CDCl₃): δ = 7.59 (d, *J* = 7.4 Hz, 1 H), 7.55 (d, *J* = 7.4 Hz, 1 H), 7.53–7.46 (m, 5 H), 7.29 (t, *J* = 7.2 Hz, 1 H), 7.16 (dd, *J* = 8.7, 1.2 Hz, 1 H), 7.12 (d, *J* = 8.7 Hz, 2 H). ¹³C NMR (101 MHz, CDCl₃): δ = 193.1 (C), 162.9 (d, ¹J_{C-F} = 247.3 Hz, C), 145.6 (C), 143.5 (C), 141.2 (C), 134.6 (CH), 134.3 (CH), 134.2 (C), 133.3 (d, ⁴J_{C-F} = 3.2 Hz, C), 131.5 (CH), 130.9 (d, ³J_{C-F} = 8.26 Hz, 2 CH), 129.6 (C), 129.3 (CH), 124.2 (CH), 120.1 (CH), 119.3 (CH), 114.87 (d, ²J_{C-F} = 21.5 Hz, 2 CH). IR (CH₂Cl₂): 1709, 1159 cm⁻¹. HRMS (ESI): *m/z* calcd for (C₁₉H₁₂FO)⁺: 275.0867; found: 275.0875.
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