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Synthesis of Fluorenes via the Palladium-Catalyzed 5-Exo-dig Annulation of *o*-Alkynyl Biaryls

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Abstract

The direct Pd-catalyzed intramolecular hydroarylation of *o*-alkynyl biaryls proceeded in highly stereoselective manner producing fluorenes **2**, the products of 5-*exo-dig* cyclization, in excellent yields. The cascade intermolecular arylation, incorporated in this transformation, allowed for efficient synthesis of fully-substituted fluorenes **12**. These cyclizations proceed more rapidly with electron-deficient benzene ring, which, in combination with a substantial isotope effect observed, strongly supports a C-H activation mechanism for the key annulation step.

Keywords

alkynes; arylation; annulations; C-H activation; palladium

Introduction

The palladium-catalyzed annulation reactions serve as a powerful tool for the construction of fused polycyclic aromatic and heteroaromatic compounds.¹ Activation of the C-C triple bond by π -philic metals, followed by cyclization with the adjacent aromatic ring, proved efficient for construction of fused five and six membered ring systems.² One of the representative examples of this approach is the intramolecular hydroarylation of alkynyl biaryls. The palladium-catalyzed version of it was first reported by Fujiwara.³ The other transition metal^{4,5}- and Lewis acid-catalyzed⁶ versions of this reaction quickly emerged shortly after. Generally, this reaction proceeds via the Friedel-Crafts-type electrophilic aromatic substitution pathway and is most efficient with electron-rich aromatic rings. Thus, as reported by Fürstner, *o*-alkynyl biaryls possessing an electron-rich aryl ring in the presence of transition metals undergo a facile intramolecular hydroarylation reaction leading to the exclusive or predominant formation of the phenantrene frameworks via a 6-*endo-dig* carbocyclization pathway (Scheme 1, A). In contrast, we have recently found that employment of neutral Pd(OAc)₂/d-*i*-Prpf catalytic system triggered the exclusive 5-*endo-dig* cyclization leading to the fluorene derivatives (Scheme 1, B). We have shown that this reaction is most efficient with electron-neutral and electron-poor arenes.⁷ In this paper, we discuss the previously communicated intramolecular hydroarylation of *o*-alkynyl biaryls in more details, as well as the extension of this methodology to the cascade arylation of *o*-alkynyl biaryls with aryl halides, followed by cyclization into the polysubstituted fluorenes (Scheme 1, C).

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Dedicated to Prof. Armin de Meijere on the occasion of his 70th birthday.

Results and Discussion

We were intrigued by the palladium-catalyzed intramolecular hydroarylation of alkynyl biaryls that proceeds under ligand free acidic conditions and produced predominantly 6-*exo-dig* cyclization products. Initially, it was believed that this reaction proceeds via a C-H activation path.³ However, recently an electrophilic substitution path for the key annulation step of this transformation was unambiguously established.⁸ We hypothesized that switching from acidic to neutral catalytic conditions may affect the mechanism of this reaction. Accordingly, the cyclization of *o*-alkynyl biaryl **1** under the acid-free conditions has been investigated. It was found that biaryl **1a** in the presence of catalytic amounts of Pd(OAc)₂/dppf in toluene at 120°C underwent a facile 5-*exo-dig* cyclization to produce the fluorene **2a** in 70 % yield. Switching to a bulkier 1,1'-bis(diiso-propylphosphino)ferrocene (*d-i*-Prpf) led to even more efficient cyclization producing fluorene **2a** virtually quantitatively (Table 1, entry 1).

With these conditions in hand, we explored the generality of this transformation. Thus, a variety of *o*-alkynyl biaryls possessing electron-neutral and, most surprisingly, electron-deficient aryl rings underwent smooth 5-*exo-dig* carbocyclization to produce fluorenes **2a-j** in good to excellent yields (Table 1). It was found that a variety of substituents, such as F (entries, 5, 6, 7, 10, 16), NO₂ (entry 12) CO₂Me (entries 5 and 14) and CN (entry 8) were perfectly tolerated under these reaction conditions. It deserves mentioning that in contrast to the reported intramolecular hydroarylations of alkynes,^{3-6,8} *o*-alkynyl biaryls, possessing electron-deficient substituents (R²=F, CF₃, CO₂Me), underwent the carbocyclization reaction faster compared to the biaryls bearing electron-neutral aryl rings. Although no substituents effect at the alkyne moiety (R¹) on the reaction yields was observed, biaryls bearing electron-deficient alkynes reacted slightly faster than their non-activated analogues (entries 5, 8, 9, and 12). Most importantly, all cyclization reactions of **1a-r** proceeded with high *cis*-stereoselectivity, producing fluorenes **2a-r** as single geometrical isomers.⁹ It was found that contrary to the previous reports on hydroarylations under acidic conditions,^{3-6,8} cyclizations of biaryls containing electron-donating groups in the presence of Pd(OAc)₂/*d-i*-Prpf proceeded substantially slower. Thus, the cyclization of *o*-alkynylbiaryl **1q**, possessing methyl groups at the adjacent aromatic ring, was extremely slow, producing fluorene **2q** in 48 hr in 30% only (Table 1, entry 17). Likewise, annulation of tolyl-substituted alkynylbiaryl **1s** proceeded quite sluggishly. Initially, *E*-**2s**, the “normal” stereoisomer of hydroarylation, was produced in trace amounts. However, towards completion of the reaction (20 hours), increased amounts of *Z*-**2s** were produced, suggesting the *E/Z*-isomerization under the prolong heating (Scheme 2).¹⁰

Toward better understanding of the mechanism of this hydroarylation reaction, the kinetic isotope effect studies were performed. The experiments on cyclization of **3**, together with its protio analog **1b**, and **5** revealed a substantial intermolecular ($k_H/k_D=2.6$) and intramolecular ($k_H/k_D=3.5$) kinetic isotope effect (Scheme 3). These data are in the range of the isotope effects found in the Pd-catalyzed arylations proceeding via a C-H activation pathways.¹¹ Based on these observations, we propose the following mechanism for this reaction (Scheme 4). According to the path **a**, upon the ortho-palladation of **1**, the intermediate **8** is produced, which undergoes a migratory insertion to the triple bond to give a vinylpalladium species **9**. Protodepalladation of intermediate **9** produces fluorene **2** and regenerates the catalyst. Alternative pathway (path **b**) involves the formation of palladium hydride species **10**, which upon carbopalladation of the triple bond produces intermediate **11**. Consecutive reductive elimination gives the desired fluorenone **2**. However, this pathway is considered to be less likely due to a substantial loss of the deuterium observed in the cyclization of **3**.¹² The Friedel-Crafts-type mechanism, which potentially could account for the cyclization of **1**, was ruled out based on both the higher propensity of the electron-deficient biaryls in this

hydroarylation reaction and the high values of the obtained kinetic isotope effects. The observed stereoselectivity of reaction also contradicts with the electrophilic mechanism. It should be mentioned that according to the literature reports,^{3–6,8} the Friedel-Crafts cyclization of biaryl **1** should proceed in *trans*-fashion, resulting in the formation of (*Z*)-fluorene (Scheme 5). However, the hydroarylation reaction, described herein, produces fluorenes with the alternative geometry of the double bond, thus strongly supporting the *cis*-cyclization pathway (Table 1, Scheme 4).

Encouraged by the successful hydroarylation of *o*-alkynyl biaryls leading to the fluorene frameworks, we envisioned the cascade intermolecular arylation/annulations of *o*-alkynyl biaryls with aryl halides as an attractive approach toward densely substituted fluorenes. It should be mentioned that the Pd-catalyzed arylation/annulation approach has been extensively explored by Larock for the synthesis of polycyclic aromatic compounds.¹³ However, the annulation step in most of the reported transformations followed the electrophilic path.¹⁴ Consequently, we were eager to learn whether a possible cascade arylation/annulation reaction of *o*-alkynyl biaryls would follow the C-H activation reaction path. Accordingly, the transformation of different *o*-alkynyl biaryls **1**, in the presence of phenylbromide, was studied under one of the typical conditions for Pd-catalyzed arylation reactions.^{14,15} Thus, cyclization of **1a** produced a 58:42 mixture of the 5-*exo-dig* cyclization product **12** and 6-*endo-dig* adduct **13** in 90% combined yield (Table 2, entry 1). Similarly, cyclization of *o*-alkynyl biaryls **1m**, **1t**, and **1u** produced comparable mixtures of regioisomers **12** and **13** (Table 2, entries 2–4). Notably, arylation/annulation of alkyl derivative **1v** was highly regioselective, producing fluorene **12** as a sole reaction product in good yield (entry 5). In contrast, cyclization of **1w**, possessing an ester functionality at the alkyne moiety, exhibited reverse regiochemistry¹⁶ producing phenanthrene **13** selectively, albeit in low yield (Table 2, entry 6).

Next, we performed optimization of the reaction conditions aiming at the development of selective cascade arylation/annulation protocol toward **12** (Table 3). Aryl-substituted **1a**, which produced nearly equal amounts of regioisomeric products (Table 2), was chosen for optimization studies. It was found that employment of bidentate phosphine ligands caused much more selective cyclization of **1a** into **12a**. Expectedly, performing reactions in the presence of Pd(OAc)₂/*d-i*-Prpf led to a more selective reaction. Finally, use of this catalyst system in the presence of DABCO allowed for obtaining **12a** as a sole regioisomer in nearly quantitative yield (Table 3).

After the efficient conditions for cascade arylation of **1** into **12** were identified, the generality of this transformation was examined (Table 4). It was found that the cascade arylation/annulation appeared to be quite general with respect to both *o*-alkynyl biaryl and aryl halide used producing fluorenes **12** in high yields. Introduction of electron-withdrawing substituents at either of reactants usually slightly facilitated the reaction (entries 8, 9, 10, and 11), whereas more electron-rich substrates reacted somewhat slower (entries 2, 4, and 7). Pyridine-containing substrate **1o** reacted comparably well producing hetaryl-substituted fluorenes **12d,e** (entries 5, 6). The reaction was substantially slower with sterically more hindered **1x**, possessing a methyl group at the *ortho*-position (entry 3).

Although the results in Table 4 indicate faster reaction of biaryls possessing electron-withdrawing substituents at the adjacent phenyl ring (entries 1, 7, and 8), we found clarification of this question quite important and thus set up a competitive reactivity studies (Figure 1). It was found that, at early stage of the reaction (ca 25% conversion), MeO-containing **1y** reacted about 1.5 times slower and CF₃-containing **1c** 1.4 times faster than the unsubstituted substrate **1a** (Figure 1). This trend, alike that in the hydroarylation reaction (*vide supra*), strongly contradicts with possible electrophilic character of the cyclization

step.^{3-6,8} Furthermore, the intermolecular deuterium-/hydrogen isotope effect studies of the cascade arylation of **1a** and its deuterated analog with phenyl bromide revealed a profound isotope effect of 5.2 (Scheme 6). This value is in a good agreement with the reported data of the isotope effect in the Pd-catalyzed arylations proceeding via a C-H activation mechanism.
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Based on the above-mentioned results, we propose the following rationale for the Pd-catalyzed cascade arylation/annulation of *o*-alkynyl biaryls **1** into fluorenes **12** (Scheme 7). ArPdX, upon regioselective carbopalladation of triple bond 17 of **1**, produces a vinylpalladium species **14**. The latter, upon a direct¹⁸ or a ligand-assisted¹⁹ C-H activation (**15**) with subsequent loss of HX produces the palladacycle **17**. Reductive elimination of **17** furnishes the fluorene product **12** (Scheme 7, path **a**). Alternatively, the vinylpalladium species **14** may undergo an electrophilic aromatic substitution (**16**) to give palladacycle **17**. However, on the basis of a substantial isotope effect values and higher propensity of electron-deficient arenas toward cyclization (*vide supra*), this path was considered to be less likely. Although less plausible, a triple bond-coordinated^{20,21} ArPdX (**18**) entity may undergo a direct insertion into the C-H bond to produce a bis-arylpalladium species **19** (path **b**). Intramolecular migratory insertion of either of the Ar-Pd bonds into the triple bond (**20** or **17**), followed by reductive elimination, produces **12**.

We were intrigued to learn whether the observed exclusive 5-*exo-dig* annulation for this cascade reaction is specific for the Pd(OAc)₂/*d*-i-Prpf catalytic system. By other words, what would happen if by design, the vinylpalladium intermediate of type **14** would have a choice to cyclize into 5- and 6-membered ring? To this end, a bis-biphenyl alkyne **21** was synthesized. It was reasoned that, upon carbopalladation of the triple bond, a vinylpalladium intermediate **22** would form. It can undergo a C-H insertion into the adjacent phenyl ring to form the pallacycle **23**, which, after reductive elimination, would produce the fluorene derivative **24**. Alternatively, **22**, via a well-precedented double bond isomerization,²² may form **25**, which is set for an insertion into the C-H bond of a distinct aryl ring to produce **26**, and, upon reductive elimination, the phenanthrene derivative **27** (Scheme 8). The experiment showed that, upon standard reaction conditions, the fluorene **24** was formed as a single reaction product, thus supporting a strong preference of this catalytic system for 5-*exo-dig* reaction pathway.

Conclusions

In conclusion, we have developed a set of methodologies for efficient construction of fluorene framework from *o*-alkynyl biaryls in the presence of Pd(OAc)₂/*d*-i-Prpf catalytic system. The intramolecular hydroarylation of *o*-alkynyl biaryls provides easy access to fluorenes with defined geometry. Alternative intermolecular cascade arylation/annulation method allows for efficient synthesis of fluorenes, fully substituted at C-10. It was shown that, regardless of the substitution pattern, these methods proceed exclusively via a 5-*exo-dig* cyclization motif. Mechanistic studies, including product and hydrogen/deuterium isotope effect studies, strongly support a C-H activation path for the key annulation step in both transformations.

Experimental Section

NMR spectra were recorded on a Bruker Avance DRX-500 (500 MHz) or DPX-400 instruments. (+) and (-) represent positive and negative signals in ¹³C DEPT-135 experiments. GC/MS analysis was performed on a Hewlett Packard Model 6890 GC interfaced to a Hewlett Packard Model 5973 mass selective detector (15 m × 0.25 mm capillary column, HP-5MS). HPLC analysis was performed using Gilson 321 pump

interfaced with Gilson Holochrome variable band UV-detector tuned for 254 nm. Chiralcel OD-H column (250 × 4.6 mm) was used for chiral HPLC analysis. Column chromatography was carried out employing Silicycle Silia-P Flash silica gel (40–63 μm). Precoated silica gel plates F-254 were used for thin-layer analytical chromatography. Anhydrous solvents were purchased from Aldrich and stored over calcium hydride. Alkynes and metal catalysts were commercially available and purchased from Aldrich, Strem Chemicals Inc. or Acros Organics, or synthesized via known literature procedures.

General Procedure Synthesis of *o*-Alkynyl Biaryl Compounds 1a-z (Table 1)

Round bottom flask containing stirring bar was charged with (Ph₃P)₂PdCl₂ (70.1 mg, 0.1 mmol), arylboronic acid (2.6 mmol), *o*-alkynyl arylbromide (2 mmol) and Na₂CO₃ (424 mg, 4 mmol). The flask was sealed with rubber septum, evacuated and backfilled with argon. Toluene (10 mL) was added through the septum via syringe together with EtOH (5 mL) and water (5 mL). The reaction mixture was placed into 700C preheated oil bath and heated at this temperature for 1 to 3 hrs until judged complete by GC/MS analysis. The content was cooled down to room temperature, diluted with 10 mL of EtOAc and 10 mL of water and transferred into separatory funnel. The organic layer was separated, washed with water (2 × 20 mL), dried over MgSO₄. The solvent was evaporated under reduced pressure and resulting residue was purified by column chromatography on a silica gel with hexanes or 20:1 hexanes/DCM system to afford *o*-alkynyl biaryl.

2[(4methylphenyl)ethynyl]-4'-(trifluoromethyl) biphenyl (1d)—¹H NMR (500 MHz, CDCl₃) δ ppm: 7.75 – 7.83 (m, 2 H), 7.71 (s, 2 H), 7.67 (d, *J*=7.52 Hz, 1 H), 7.34 – 7.47 (m, 3 H), 7.17 – 7.23 (m, 2 H), 7.12 (s, 2 H), 2.35 (s, 3 H); ¹³C NMR (126 MHz, CDCl₃) δ ppm: 144.2, 142.2, 138.6, 132.9 (+), 131.2 (+), 129.7 (+), 129.3 (+), 129.1 (+), 128.5 (+), 127.8 (+), 124.8 (+), 121.9, 120.0, 93.1, 88.0, 21.5 (+).

5-fluoro-2-methyl-2'-(4-methylphenyl)-ethynylbiphenyl (1f)—¹H NMR (500 MHz, CDCl₃) δ ppm: 7.64 (dd, *J*=6.60, 1.65 Hz, 1 H), 7.33 – 7.42 (m, 3 H), 7.31 (dd, *J*=7.15, 1.65 Hz, 1 H), 7.16 (s, 3 H), 7.04 – 7.11 (m, 3 H), 2.38 (s, 3 H), 2.33 (s, 3 H); ¹³C NMR (126 MHz, CDCl₃) δ ppm: 159.0, 157.1, 138.4, 138.2, 132.8, 132.4 (+), 132.1 (+), 131.3 (+), 130.1 (+), 129.8 (+), 129.7 (+), 129.0 (+), 127.9 (+), 127.6 (+), 123.1, 120.3, 115.3 (+), 115.1 (+), 92.5, 88.1, 21.5 (+), 20.0 (+).

3',5'-difluoro-2-(4-methylphenyl)ethynylbiphenyl (1g)—¹H NMR (500 MHz, CDCl₃) δ ppm: 7.65 (d, *J*=6.97 Hz, 1 H), 7.34 – 7.44 (m, 3 H), 7.27 (s, 2 H), 7.20 – 7.25 (m, 2 H), 7.14 (s, 2 H), 6.85 (s, 1 H), 2.36 (s, 3 H); ¹³C NMR (126 MHz, CDCl₃) δ ppm: 163.6 (d, *J*=12.9 Hz), 161.6 (d, *J*=12.9 Hz), 143.7, 141.2, 138.6, 133.0, 132.8 (d, *J*=90.6 Hz, +), 131.6 (+), 131.2 (+), 129.2 (+), 128.5 (+), 128.0, 120.9 (d, *J*=232.1 Hz), 112.4 (d, *J*=25.9 Hz, +), 102.7 (t, *J*=25.4 Hz, +), 93.5, 87.8, 21.5 (+).

4-(3',5'-bis(trifluoromethyl)biphenyl-2-yl) ethynylbenzonitrile (1h)—¹H NMR (500 MHz, CDCl₃) δ ppm: 8.12 (s, 2 H), 7.93 (s, 1 H), 7.73 (s, 1 H), 7.59 (s, 2 H), 7.50 – 7.56 (m, 1 H), 7.48 (s, 3 H); ¹³C NMR (126 MHz, CDCl₃) δ ppm: 142.2, 140.8, 140.4, 133.7 (+), 132.0 (+), 131.8 (+), 131.6 (+), 131.4 (+), 129.8 (+), 129.5 (+), 128.7, 127.4, 124.4, 121.4 (+), 120.7(+), 118.5(+), 118.4(+), 111.9(+), 92.0, 91.5(+).

2(4methylphenyl)ethynyl-3',5'-bis(trifluoromethyl) biphenyl (1k)—¹H NMR (500 MHz, CDCl₃) δ ppm: 8.16 (s, 2 H), 7.91 (s, 1 H), 7.70 (s, 1 H), 7.40 – 7.48 (m, 3 H), 7.23 (d, *J*=8.07 Hz, 2 H), 7.12 (d, *J*=7.89 Hz, 2 H), 2.35 (s, 3 H); ¹³C NMR (126 MHz, CDCl₃) δ ppm: 142.5, 140.3, 138.8, 133.3 (+), 131.3 (+), 130.3 (+), 129.9 (+), 129.5 (+), 129.3 (+), 129.1 (+), 128.7 (+), 128.5, 124.5, 122.4, 122.0, 121.2, 119.5, 93.7, 87.1, 21.5 (+).

3-(4'-(trifluoromethyl)biphenyl-2-yl)ethynyl)pyridine (1o)—¹H NMR (500 MHz, CDCl₃) δ ppm: 8.57 (s, 1 H), 8.52 (d, *J*=5.68 Hz, 1 H), 7.67 – 7.80 (m, 4 H), 7.55 – 7.60 (m, 1 H), 7.38 – 7.50 (m, 3 H), 7.21 – 7.29 (m, 2 H); ¹³C NMR (126 MHz, CDCl₃) δ ppm: 152.0 (+), 148.7 (+), 144.0, 142.6, 138.1 (+), 133.2 (+), 129.7 (+), 129.5 (+), 129.2 (+), 127.9 (+), 124.9 (+), 123.2, 123.0, 121.0, 91.9, 89.3.

Pd-Catalyzed Cyclization of *o*-Alkynyl Biaryls

Representative Procedure—An oven dried 3 mL Wheaton vial containing a stirring bar was charged with **1** (0.5 mmol), Pd(OAc)₂ (5.6 mg, 0.025 mmol) and 1,1'-bis(di-*i*-propylphosphino)ferrocene (146 mg, 0.035 mmol) under N₂ atmosphere. Dry toluene (1 mL) was added and the reaction vessel was capped with pressure screw cap. Reaction was heated at 120°C for 2 hrs (when judged complete by GC/MS analysis). The resulting mixture was cooled down to room temperature and filtered through short SiO₂ plug with the aid of DCM. The filtrate was concentrated under the reduced pressure and the residue was purified by chromatography on a silica gel column (20:1 hexanes/DCM) affording benzylidene-9*H*-fluorene.

9-benzylidene-9*H*-fluorene (2a)23—¹H NMR (500 MHz, CDCl₃) δ ppm: 7.81 (1 H, d, *J*=7.52 Hz) 7.70 – 7.77 (4 H, m) 7.60 (4 H, s) 7.48 (3 H, t, *J*=7.43 Hz) 7.38 – 7.44 (3 H, m) 7.30 – 7.38 (3 H, m) 7.08 (1 H, dt); ¹³C NMR (126 MHz, CDCl₃) δ ppm 141.27, 139.50, 139.21, 136.92, 136.57 (+) 136.50 (+) 129.28 (+) 128.56 (+) 128.23 (+) 128.04 (+) 127.29 (+) 127.00 (+) 126.68 (+) 124.43 (+) 120.26 (+) 119.73 (+) 119.61 (+).

9-(4-methylbenzylidene)-9*H*-fluorene (2b)24—¹H NMR (500 MHz, CDCl₃) δ ppm: 7.80 (d, *J*=7.34 Hz, 1 H), 7.73 (d, *J*=7.52 Hz, 2 H), 7.68 (s, 2 H), 7.51 (s, 2 H), 7.36 – 7.41 (m, 1 H), 7.30 – 7.36 (m, 2 H), 7.28 (s, 3 H), 7.06 – 7.12 (m, 1 H), 2.45 (s, 3 H); ¹³C NMR (126 MHz, CDCl₃) δ ppm 141.17, 139.63, 139.08, 138.00, 136.64 (+), 135.99 (+) 133.87 (+) 129.28 (+) 129.23 (+) 128.39 (+) 128.03 (+) 127.54 (+) 126.93 (+) 126.61 (+) 124.38 (+) 120.17 (+) 119.68 (+) 119.55 (+) 21.46 (+).

(9*E*)-9-benzylidene-2-(trifluoromethyl)-9*H*-fluorene (2c)—¹H NMR (500 MHz, CDCl₃) δ ppm 8.03 (1 H, s) 7.76 – 7.83 (3 H, m) 7.47 – 7.52 (2 H, m) 7.41 – 7.46 (1 H, m) 7.35 – 7.39 (1 H, m) 7.13 – 7.18 (1 H, m); ¹³C NMR (126 MHz, CDCl₃) δ ppm: 142.09, 139.81, 139.69, 137.11, 136.27, 135.42, 129.23, 129.03(+), 128.82(+), 128.66(+), 128.46(+), 127.81(+), 125.07(+), 125.04(+), 124.53(+), 120.44(+), 119.69(+), 117.32 (+); HRMS (EI) calcd. for C₂₁H₁₃F₃: 322.09694, Found: 322.09712.

(9*E*)-9-(4-methylbenzylidene)-2-(trifluoromethyl)-9*H*-fluorene (2d)—¹H NMR (400 MHz, CDCl₃) δ ppm: 8.02 (s, 1 H), 7.70 – 7.85 (m, 4 H), 7.63 (d, 1 H), 7.51 (d, *J*=7.89 Hz, 2 H), 7.36 (t, *J*=7.45 Hz, 1 H), 7.29 (d, *J*=7.75 Hz, 2 H), 7.16 (t, *J*=7.60 Hz, 1 H), 2.45 (s, 3 H); ¹³C NMR (126 MHz, CDCl₃) δ ppm: 141.94, 139.81, 139.73, 138.55, 137.20, 134.89 (+), 131.75, 129.34 (+), 129.27 (+), 127.74 (+), 124.87 (+), 124.48 (+), 120.39 (+), 119.64 (+), 117.23 (+), 21.48 (+); HRMS (EI) calcd. for C₂₂H₁₅F₃: 336.1126, Found: 336.1128.

Ethyl (2*E*)-(1,3-difluoro-9*H*-fluoren-9-ylidene)acetate (2e)—¹H NMR (500 MHz, CDCl₃) δ ppm: 8.83 (d, *J*=7.89 Hz, 1 H), 7.61 (d, *J*=7.34 Hz, 1 H), 7.41 – 7.46 (m, 1 H), 7.36 – 7.40 (m, 1 H), 7.16 (dd, *J*=7.79, 2.11 Hz, 1 H), 7.09 (d, *J*=4.03 Hz, 1 H), 4.35 (q, *J*=7.15 Hz, 2 H), 1.40 (t, *J*=7.15 Hz, 3 H); ¹³C NMR (126 MHz, CDCl₃) δ ppm: 166.3, 165.4, 163.3, 161.1, 159.1, 144.6, 140.5(+), 135.8 (+), 130.6 (+), 129.2 (+), 128.8 (+), 120.0 (+), 119.3 (+), 103.4 – 103.9, 103.2 (+), 60.9 (+), 14.3 (+); HRMS (EI) calcd. for C₁₇H₂₂F₂O₂: 286.0806, Found: 286.0813.

(9E)-4-fluoro-1-methyl-9-(4-methylbenzylidene)-9H-fluorene (2f)—¹H NMR (500 MHz, CDCl₃) δ ppm: 7.93 (d, *J*=7.52 Hz, 1 H), 7.83 (s, 1 H), 7.40 (s, 3 H), 7.29 (s, 3 H), 6.92 – 7.10 (m, 3 H), 2.68 (s, 3 H), 2.46 (s, 3 H); ¹³C NMR (126 MHz, CDCl₃) δ ppm: 158.14 (+), 156.17 (+), 138.45 (+), 138.32 (+), 137.91 (+), 136.72 (+), 134.49 (s, 1 C), 133.22 (+), 131.39 (s, 1 C), 131.34 (s, 1 C), 129.91 (s, 1 C), 129.56 (s, 1 C), 129.35 (s, 1 C), 128.95 (s, 1 C), 128.42 (s, 1 C), 126.42 (s, 1 C), 124.39 (s, 1 C), 114.48 (s, 1 C), 114.32 (s, 1 C), 21.81 (s, 1 C), 21.42 (s, 1 C); HRMS (EI) calcd. for C₂₂H₁₇F: 300.1314, Found: 300.1313.

(9E)-1,3-difluoro-9-(4-methylbenzylidene)-9H-fluorene (2g)—¹H NMR (500 MHz, CDCl₃) δ ppm: 7.98 (d, *J*=2.75 Hz, 1 H), 7.67 (d, *J*=7.52 Hz, 1 H), 7.56 (d, *J*=7.89 Hz, 1 H), 7.45 (d, *J*=7.89 Hz, 2 H), 7.32 (dt, *J*=7.52, 0.92 Hz, 1 H), 7.28 (s, 1 H), 7.24 (dd, *J*=7.98, 2.11 Hz, 1 H), 7.12 (dd, *J*=15.22, 1.10 Hz, 1 H), 6.78 (dt, *J*=11.00, 9.17, 2.20 Hz, 1 H), 2.45 (s, 3 H); ¹³C NMR (500 MHz, CDCl₃) δ ppm: 162.8 (dd, *J*=248.8, 11.1 Hz), 159.4 (dd, *J*=253.4, 12.9 Hz), 142.9, 139.6, 138.2, 137.4 (+), 134.0 (+), 133.5 (+), 129.8(+), 129.3(+), 129.0(+), 128.3(+), 127.8(+), 124.6 (+), 121.5 (+), 120.1 (+), 10.8 (+), 21.4 (+); HRMS (EI) calcd. for C₂₁H₁₄F₂: 305.1151, Found: 305.1142.

4-(E)-[1,3-bis(trifluoromethyl)-9H-fluoren-9-ylidene]methylbenzotrile (2h)—¹H NMR (500 MHz, CHLOROFORM-*d*) δ ppm: 8.1 (d, *J*=13.9 Hz), 7.9 (s), 7.8 (s), 7.6 – 7.7 (m), 7.4 (s), 7.0 – 7.2 (m); ¹³C NMR (126 MHz, CDCl₃) δ ppm: 143.19, 141.74, 138.55, 138.24, 136.47, 135.92, 134.17, 132.64 (+), 129.53 (+), 129.39 (+), 128.56 (+), 124.81 (+), 122.09 (+), 120.17 (+), 119.84 (+), 118.51 (+), 112.33 (+), 91.16 (+); HRMS (EI) calcd. for C₂₃H₁₁F₆N: 415.0795, Found: 415.0798.

(9Z)-3-(trifluoromethyl)-9-[4-(trifluoromethyl) benzylidene]-9H-fluorene (2i)—¹H NMR (500 MHz, CDCl₃) δ ppm: 7.94 (br. s., 1 H), 7.82 (d, *J*=7.34 Hz, 1 H), 7.72 – 7.79 (m, 4 H), 7.68 (s, 2 H), 7.45 – 7.51 (m, 2 H), 7.38 – 7.45 (m, 1 H), 7.34 (s, 1 H); ¹³C NMR (126 MHz, CDCl₃) δ ppm: 141.9, 140.1, 138.8, 139.4, 138.1, 137.0, 130.6 (+), 129.5 (+), 129.1 (+), 128.1 (+), 127.3, 125.7 (+), 124.4 (+), 123.7 (+), 123.1, 122.9, 121.0 (+), 120.6 (+), 116.7 (+); HRMS (EI) calcd. for C₂₂H₁₂F₆: 390.0843, Found: 390.0841.

(9E)-9-benzylidene-1,3-difluoro-9H-fluorene (2j)—¹H NMR (500 MHz, CDCl₃) δ ppm: 8.0 (d, *J*=2.9 Hz), 7.7 (d, *J*=7.7 Hz), 7.5 (s), 7.4 – 7.5 (m), 7.3 (s), 7.2 (s), 7.1 (s), 6.7 – 6.8 (m); ¹³C NMR (126 MHz, CDCl₃) δ ppm: 139.66, 137.31, 137.03, 134.07, 133.14, 133.04, 128.98 (+), 128.58 (+), 128.45 (+), 128.21 (+), 128.15 (+), 127.93 (+), 127.83 (+), 124.67 (+), 120.14 (+), 103.09 (+), 102.88 (+), 102.74 (+), 102.53; HRMS (EI) calcd. for C₂₀H₁₂F₂: 290.09071, Found: 290.09019.

(9-(4-methylbenzylidene)-1,3-bis(trifluoromethyl)-9H-fluorene (2k)—¹H NMR (400 MHz, CDCl₃) δ ppm: 8.22 (s, 1 H), 8.16 (s, 1 H), 7.90 (s, 1 H), 7.78 (d, *J*=7.60 Hz, 1 H), 7.39 – 7.48 (m, 3 H), 7.32 – 7.39 (m, 1 H), 7.27 – 7.32 (m, 2 H), 7.12 (s, 1 H), 2.46 (s, 3 H); ¹³C NMR (101 MHz, CDCl₃) δ ppm: 142.7 (s), 139.2 (s), 138.8 (s), 138.0 (s), 138.0 (s), 137.9 (s), 137.8 (s), 137.2 (s), 133.9 (s), 133.8 (s), 129.5 (s), 128.9 (s), 128.5 (s), 128.2 (s), 124.8 (s), 122.4 (s), 121.8 (s), 119.7 (s), 119.6 (s), 21.5 (s); HRMS (EI) calcd. for C₂₃H₁₄F₆: 404.1000, Found: 404.0998.

9-(4-nitrobenzylidene)-9H-fluorene (2l):25—¹H NMR (400 MHz, CDCl₃) δ ppm: 8.32 (s, 2 H), 7.66 – 7.85 (m, 5 H), 7.60 (s, 1 H), 7.42 (s, 2 H), 7.35 (s, 2 H), 7.07 (t, *J*=7.53 Hz, 1 H); ¹³C NMR (101 MHz, CDCl₃) δ ppm: 147.2, 144.0, 141.8, 139.5, 138.9, 138.9, 135.8, 130.2 (+), 129.5 (+), 129.1 (+), 127.3 (+), 127.0 (+), 124.3 (+), 123.9 (+), 120.6 (+), 120.1 (+), 119.8 (+); HRMS (EI) calcd. for C₂₀H₁₃NO₂: 300.1025, Found: 300.1025.

4-(9H-fluoren-9-ylidenemethyl)phenyl methyl ether (2m):25—¹H NMR (500 MHz, CDCl₃) δ ppm: 7.79 (d, *J*=7.52 Hz, 1 H), 7.73 (s, 3 H), 7.66 (s, 1 H), 7.56 (d, *J*=8.44 Hz, 2 H), 7.29 – 7.42 (m, 3 H), 7.10 (t, *J*=7.61 Hz, 1 H), 7.00 (d, *J*=8.80 Hz, 2 H), 3.90 (s, 3 H); ¹³C NMR (126 MHz, CDCl₃) δ ppm: 159.56, 141.11, 139.70, 138.97, 136.64, 135.48, 130.87(+), 129.12, 128.29(+), 127.89 (+), 127.34 (+), 126.89 (+), 126.59 (+), 124.19 (+), 120.08 (+), 119.70 (+), 119.53 (+), 113.95 (+), 55.36 (+); HRMS (EI) calcd. for C₂₁H₁₆O: 284.1201, Found: 284.1202.

Methyl-(9E)-9-benzylidene-9H-fluorene-2-carboxylate (2n)—¹H NMR (400 MHz, CDCl₃) δ ppm: 8.48 (s, 1 H), 8.09 (d, *J*=8.04 Hz, 1 H), 7.72 – 7.89 (m, 3 H), 7.62 (s, 2 H), 7.30 – 7.56 (m, 3 H), 7.15 (s, 1 H), 3.98 (s, 3 H); ¹³C NMR (101 MHz, CDCl₃) δ ppm: 167.3, 143.2, 140.1, 139.5, 137.5, 136.5 (+), 135.6 (+), 129.7 (+), 129.3 (+), 128.8 (+), 128.6 (+), 128.3 (+), 127.8 (+), 125.8, 124.5 (+), 121.7 (+), 120.6 (+), 120.4, 119.3 (+), 52.2 (+); HRMS (EI) calcd. for C₂₂H₁₆O₂: 312.1150, Found: 312.1149.

3-(9H-fluoren-9-ylidenemethyl)pyridine (2o)—¹H NMR (500 MHz, CDCl₃) δ ppm: 8.87 (s, 1 H), 8.68 (dd, *J*=4.86, 1.38 Hz, 1 H), 8.03 (s, 1 H), 7.82 (d, *J*=7.89 Hz, 1 H), 7.78 (d, *J*=7.70 Hz, 1 H), 7.67 (s, 2 H), 7.48 (d, *J*=7.89 Hz, 1 H), 7.43 (dd, *J*=7.89, 4.95 Hz, 1 H), 7.39 (s, 1 H), 7.12 – 7.18 (m, 1 H); ¹³C NMR (126 MHz, CDCl₃) δ ppm: 150.1 (+), 149.4 (+), 142.3, 140.1, 139.2, 137.4, 136.7 (+), 136.4 (+), 132.3, 129.4 (+), 128.1 (+), 125.6, 124.4 (+), 124.3 (+), 123.4 (+), 120.7 (+), 119.8 (+), 117.5 (+); HRMS (EI) calcd. for C₂₀H₁₃F₃N: 323.09463, Found: 323.09245.

(9E)-2-fluoro-4-methyl-9-(4-methylbenzylidene)-9H-fluorene (2p)—¹H NMR (500 MHz, CDCl₃) δ ppm: 7.80 (d, *J*=7.70 Hz, 1 H), 7.68 (d, *J*=7.70 Hz, 1 H), 7.61 (s, 1 H), 7.48 (d, *J*=7.89 Hz, 2 H), 7.27 – 7.35 (m, 4 H), 7.05 (s, 1 H), 6.88 (s, 1 H), 2.69 (s, 3 H), 2.45 (s, 3 H); ¹³C NMR (126 MHz, CDCl₃) δ ppm: 162.1 (d, *J*=244.1 Hz), 141.5, 138.2, 137.1, 135.5, 134.6, 133.6, 133.1, 129.3 (d, *J*=8.3 Hz, +), 128.5 (+), 128.1 (+), 125.9, 125.6 (+), 124.1 (+), 122.4 (+), 117.2 (d, *J*=22.2 Hz, +), 104.7 (d, *J*=23.1 Hz, +), 21.4 (+), 21.0 (+); HRMS (EI) calcd. for C₂₁H₁₄F₂: 305.1151, Found: 305.1142.

(9E)-9-benzylidene-1,4-dimethyl-9H-fluorene (2q)—¹H NMR (500 MHz, CDCl₃) δ ppm: 7.86 (s, 2 H), 7.51 (s, 2 H), 7.43 – 7.48 (m, 2 H), 7.40 (s, 1 H), 7.29 (s, 2 H), 7.06 (s, 2 H), 6.97 (s, 1 H), 2.71 (s, 6 H); ¹³C NMR (126 MHz, CDCl₂) δ ppm: 141.7, 139.0, 138.2, 137.9, 137.6, 136.5, 131.5 (+), 131.5, 130.7, 130.4 (+), 129.0 (+), 128.6 (+), 128.0 (+), 127.6 (+), 125.6 (+), 124.5 (+), 122.8 (+), 22.5 (+), 21.2 (+); HRMS (EI) calcd. for C₂₂H₁₈: 282.1410, Found: 282.1409.

(9Z)-3-methoxy-9-(4-methoxybenzylidene)-9H-fluorene (2r)—¹H NMR (500 MHz, CDCl₃) δ ppm: 7.77 (d, *J*=7.15 Hz, 1 H), 7.69 (s, 1 H), 7.62 (d, *J*=8.62 Hz, 1 H), 7.53 (s, 3 H), 7.30 – 7.40 (m, 2 H), 7.24 (s, 1 H), 6.99 (d, *J*=8.80 Hz, 2 H), 6.65 (s, 1 H), 3.89 (s, 6 H); ¹³C NMR (126 MHz, CDCl₃) δ ppm: 160.3, 159.4, 142.9, 140.6, 138.7, 135.0, 130.8 (+), 129.6, 129.3, 127.8 (+), 127.0 (+), 125.2 (+), 125.1 (+), 120.1 (+), 119.4 (+), 113.9 (+), 112.7 (+), 104.7 (+), 55.5 (+), 55.4 (+); HRMS (EI) calcd. for C₂₂H₁₈O₂: 314.1307, Found: 314.1308.

Mechanistic Studies

9-(4-methylbenzylidene)-9H-fluorene-d₅ (4)—Round bottom flask containing stirring bar was charged with (Ph₃P)₂PdCl₂ (34 mg, 0.05 mmol), phenylboronic acid-d₅ (200 mg, 3.2 mmol), 1-bromo-2-[(4-methylphenyl)ethynyl]benzene (657 mg, 2.4 mmol) and Na₂CO₃ (424 mg, 4 mmol). The flask was sealed with rubber septum, evacuated and backfilled with argon. Toluene (4 mL) was added through the septum via syringe together with EtOH (1

mL) and water (1 mL). The reaction mixture was placed into 70°C preheated oil bath and heated at this temperature for 2 hrs until judged complete by GC/MS analysis. The mixture was cooled down to room temperature, diluted with 10 mL of EtOAc and 10 mL of water and transferred into separatory funnel. The organic layer was separated, washed with water (2 × 10 mL), dried over MgSO₄. The solvent was evaporated under reduced pressure and resulting residue was purified by column chromatography on a silica gel with hexanes to afford 9-(4-methylbenzylidene)-9*H*-fluorene-*d*₅ (99% incorporated deuterium): ¹H NMR (500 MHz, CDCl₃) δ ppm: 7.65 (dd, *J*=7.70, 0.92 Hz, 1 H), 7.41 – 7.48 (m, 1 H), 7.37 – 7.42 (m, 1 H), 7.30 – 7.36 (m, 1 H), 7.23 (s, 2 H), 7.10 (d, *J*=7.89 Hz, 2 H), 2.34 (s, 3 H); ¹³C NMR (126 MHz, CDCl₃) δ ppm: 143.7, 140.4, 138.2, 132.8 (+), 131.2 (+), 129.4 (+), 129.0 (+), 128.3 (+), 127.0 (+), 121.8, 120.4, 92.4, 88.7, 21.5 (+).

9-benzylidene-9*H*-fluorene-*d*₁ (6)—Round bottom flask containing stirring bar was charged with (Ph₃P)₂PdCl₂ (121 mg, 0.173 mmol), phenylboronic acid-*d*₁ (510 mg, 4.1 mmol), 1-Bromo-2-phenylethynyl-benzene (546 mg, 3.5 mmol) and Na₂CO₃ (424 mg, 4 mmol). The flask was sealed with rubber septum, evacuated and backfilled with argon. Toluene (7 mL) was added through the septum via syringe together with EtOH (3 mL) and water (3 mL). The reaction mixture was placed into 70°C preheated oil bath and heated at this temperature for 2 hrs until judged completed by GC/MS analysis. The mixture was cooled down to room temperature, diluted with 10 mL of EtOAc and 10 mL of water and transferred into separatory funnel. The organic layer was separated, washed with water (2 × 10 mL), dried over MgSO₄. The solvent was evaporated under reduced pressure and resulting residue was purified by column chromatography on a silica gel with hexanes to afford 9-benzylidene-9*H*-fluorene-*d*₁ (99% deuterium incorporated): ¹H NMR (500 MHz, CDCl₃) δ ppm: 7.64 – 7.75 (m, 2 H), 7.39 – 7.53 (m, 5 H), 7.23 – 7.39 (m, 6 H); ¹³C NMR (126 MHz, CDCl₃) δ ppm: 143.9, 140.5, 132.9 (+), 131.4 (+), 129.5 (+), 129.4 (+), 128.6 (+), 128.3 (+), 128.1 (+), 127.9 (+), 127.0 – 127.9 (m), 123.5, 121.6, 92.2, 89.4.

Intermolecular kinetic isotope effect measurements

A mixture of 20 mg of 9-(4-methylbenzylidene)-9*H*-fluorene-*d*₅ (0.0732 mmol) and 19.64 mg of 9-(4-methylbenzylidene)-9*H*-fluorene (0.0732 mmol) was placed into oven dry 1 mL Wheaton vial, with a stir bar. Pd(OAc)₂ (1.6 mg, 0.0074 mmol) and 1,1'-bis(di-*i*-propylphosphino)ferrocene (3.7 mg, 0.009 mmol) were added under N₂ atmosphere. Dry toluene (292 μL) was added and the reaction vessel was capped with pressure screw cap. Reaction was heated at 120°C. Heating stopped at 25%–30% conversion of 9-(4-methylbenzylidene)-9*H*-fluorene as detected by GC/MS analysis. The mixture was allowed to cool down to room temperature, filtered through short SiO₂ plug with aid of DCM. The filtrate was collected and solvent was evaporated under reduced pressure. The resulting mixture was connected to the high vacuum pump, dried, and analyzed by ¹H NMR without any further purification. The above experiment was repeated three more times giving the average of *k*_H/*k*_D = 2.6.

Intramolecular kinetic isotope effect measurements

An oven dried 1 mL Wheaton vial containing a stirring bar was charged with 9-benzylidene-9*H*-fluorene-*d*₁ (30 mg, 0.117 mmol), Pd(OAc)₂ (1.32 mg, 0.006 mmol) and (2.94 mg, 0.007 mmol) under N₂ atmosphere. Dry toluene (240 μL) was added and the reaction vessel was capped with pressure screw cap. Reaction was heated at 120°C. When conversion of 9-benzylidene-9*H*-fluorene-*d*₁ was detected to be 25% – 30% (as judged by GC/MS analysis) heating was stopped. The mixture was cooled down to room temperature and filtered through short SiO₂ plug with the aid of DCM. The filtrate was concentrated under the reduced pressure. The residue was dissolved in 2 mL of MeOH. A spatula tip of 10% Pd on carbon was added and the reaction mixture was subjected to the reduction with

H₂ at atmospheric pressure. The excess of palladium was removed by filtration through celite. The filtrate was concentrated under reduced pressure. The resulting residue was connected to the high vacuum pump, dried and analyzed by ¹H NMR without further purification. The above procedure was repeated two more times, giving the average of $k_H/k_D = 3.5$.

General procedure for aryative cyclization of o-alkynyl biaryls with aryl halides (Table 3)—An oven dried 1 mL Wheaton vial containing a stirring bar was

charged with **1** (0.5 mmol), Pd(OAc)₂ (5.6 mg, 0.025 mmol), d-i-prpf (13 mg, 0.03 mmol), and DABCO (112 mg, 1mmol) under N₂ atmosphere. Dry NMP (1.0 mL) was added followed by the addition of appropriate aryl halide (0.75 mmol) and the reaction vessel was capped with pressure screw cap. Reaction was heated at 120°C until full consumption of starting materials (as judged by GC/MS analysis). The mixture was cooled down to room temperature and filtered through short SiO₂ plug with the aid of EtOAc. The filtrate was diluted with EtOAc and water. The organic layer was separated, washed with water (2 × 10 mL), dried over Na₂SO₄. The solvent was evaporated under reduced pressure, and the resulting crude material was purified by column chromatography on silica gel. The resulting fluorine **12**, was further purified by recrystallization from MeOH.

9-(diphenylmethylene)-9H-fluorene (12a):26—¹H NMR (500 MHz, CDCl₃) δ ppm: 7.71 (d, $J=7.34$ Hz, 2 H), 7.34 – 7.50 (m, 7 H), 7.25 (s, 2 H), 6.94 (t, $J=7.52$ Hz, 2 H), 6.64 (s, 2 H); ¹³C NMR (126 MHz, CDCl₃) δ ppm: 145.50, 142.98, 140.49, 138.70, 134.19, 129.67 (+), 128.82 (+), 128.20 (+), 127.62 (+), 126.41 (+), 124.89 (+), 119.24 (+).

4-[9H-fluoren-9-ylidene(phenyl)methyl]phenyl methyl ether (12b)—¹H NMR (500 MHz, CDCl₃) δ ppm: 7.72 (dd, $J=7.52, 3.12$ Hz, 2 H), 7.35 – 7.46 (m, 4 H), 7.31 (d, $J=8.62$ Hz, 2 H), 7.21 – 7.28 (m, 3 H), 6.90 – 7.02 (m, 4 H), 6.84 (d, $J=7.89$ Hz, 1 H), 6.63 (d, $J=8.07$ Hz, 1 H), 3.88 (s, 3 H); ¹³C NMR (126 MHz, CDCl₃) δ ppm: 159.8, 145.5, 143.3, 140.4, 138.9, 135.3, 133.8, 131.5, 130.0 (+), 128.7 (+), 128.2 (+), 127.4 (+), 127.4 (+), 126.3 (+), 126.3 (+), 124.8 (+), 124.7 (+), 119.2 (+), 114.1 (+), 55.3 (+); HRMS (EI) calcd. for C₂₇H₂₀O: 360.1512, Found: 360.1514.

4-[9H-fluoren-9-ylidene(phenyl)methyl]phenyl methyl ether (12c)—¹H NMR (500 MHz, CDCl₃) δ ppm: 7.70 (m, 2 H), 7.60 – 7.46 (m, 4 H), 7.31 (d, $J=8.62$ Hz, 2 H), 7.21 – 7.28 (m, 3 H), 6.90 – 7.02 (m, 4 H), 6.84 (m, $J=7.89$ Hz, 1 H), 6.63 (d, $J=8.07$ Hz, 1 H), 2.3 (s, 3 H); ¹³C NMR (126 MHz, CDCl₃) δ ppm: 159.8, 145.5, 143.3, 140.4, 138.9, 135.3, 133.8, 131.5, 130.0 (+), 128.7 (+), 128.2 (+), 127.4 (+), 127.4 (+), 126.3 (+), 126.3 (+), 124.8 (+), 124.7 (+), 119.2 (+), 114.1 (+), 21.4 (+); HRMS (EI) calcd. for C₂₇H₂₂: 344.1568, Found: 344.1565.

9-(phenyl(*p*-tolyl)methylene)-9H-fluorene (12d)—¹H NMR (500 MHz, CDCl₃) δ ppm: 7.72 (m, 2 H), 7.35 – 7.46 (m, 4 H), 7.31 (d, $J=8.62$ Hz, 2 H), 7.21 – 7.28 (m, 3 H), 6.90 – 7.02 (m, 4 H), 6.84 (d, $J=7.89$ Hz, 1 H), 6.63 (d, $J=8.07$ Hz, 1 H), 2.3 (s, 3 H); ¹³C NMR (126 MHz, CDCl₃) δ ppm: 159.8, 145.5, 143.3, 140.4, 138.9, 135.3, 133.8, 131.5, 130.0 (+), 128.7 (+), 128.2 (+), 127.4 (+), 127.4 (+), 126.3 (+), 126.3 (+), 124.8 (+), 124.7 (+), 119.2 (+), 114.1 (+), 21.4 (+); HRMS (EI) calcd. for C₂₇H₂₂: 344.1568, Found: 344.1565.

3-[9H-fluoren-9-ylidene(phenyl)methyl]pyridine (12e)—¹H NMR (500 MHz, CDCl₃) δ ppm: 8.67 (s, 2 H), 7.64 – 7.74 (m, 3 H), 7.33 – 7.50 (m, 6 H), 7.23 – 7.31 (m, 2 H), 6.91 – 7.00 (m, 2 H), 6.59 – 6.66 (m, 2 H); ¹³C NMR (126 MHz, CDCl₃) δ ppm: 150.5 (+), 149.2, 142.2, 141.0, 140.8, 140.7, 138.8, 138.3, 138.2 (+), 137.2, 135.7 (+), 129.8 (+),

129.7 (+), 129.2 (+), 129.0 (+), 128.6 (+), 128.2 (+), 126.7 (+), 126.6 (+), 125.0 (+), 124.6 (+), 123.6 (+), 119.5 (+), 119.4 (+); HRMS (EI) calcd. for C₂₅H₁₇N: 331.1357, Found: 331.1361.

3-[9H-fluoren-9-ylidene(3-methylphenyl)methyl] pyridine (12f)—¹H NMR (500 MHz, CDCl₃) δ ppm: 8.68 (s, 2 H), 7.54 – 7.82 (m, 3 H), 7.05 – 7.46 (m, 7 H), 6.96 (s, 2 H), 6.64 (s, 2 H), 2.37 (s, 3 H); ¹³C NMR (126 MHz, CDCl₃) δ ppm: 150.4 (+), 149.2, 142.2, 141.3, 140.8, 140.6, 138.8, 138.4, 138.2, 137.2, 135.5 (+), 130.2 (+), 130.1 (+), 129.3 (+), 129.0 (+), 128.9 (+), 128.1 (+), 126.8 (+), 126.6 (+), 125.1 (+), 124.6 (+), 123.6 (+), 119.5 (+), 119.3 (+), 21.4 (+); HRMS (EI) calcd. for C₂₆H₁₉N: 345.1522, Found: 345.1517.

9-(diphenylmethylene)-2-methoxy-9H-fluorene (12g)—¹H NMR (500 MHz, CDCl₃) δ ppm: 7.72 (dd, *J*=7.52, 3.12 Hz, 2 H), 7.35 – 7.46 (m, 4 H), 7.31 (d, *J*=8.62 Hz, 2 H), 7.21 – 7.28 (m, 3 H), 6.90 – 7.02 (m, 4 H), 6.84 (d, *J*=7.89 Hz, 1 H), 6.63 (d, *J*=8.07 Hz, 1 H), 3.88 (s, 3 H); ¹³C NMR (126 MHz, CDCl₃) δ ppm: 159.8, 145.5, 143.3, 140.4, 138.9, 135.3, 133.8, 131.5, 130.0 (+), 128.7 (+), 128.2 (+), 127.4 (+), 127.4 (+), 126.3 (+), 126.3 (+), 124.8 (+), 124.7 (+), 119.2 (+), 114.1 (+), 55.3 (+); HRMS (EI) calcd. for C₂₇H₂₀O: 360.1513, Found: 360.1514.

9-(phenyl(4-(trifluoromethyl)phenyl)methylene)-9H-fluorene (12h)—¹H NMR (500 MHz, CDCl₃) δ ppm: 7.67 – 7.76 (m, 3 H), 7.53 (d, *J*=8.07 Hz, 2 H), 7.45 (s, 2 H), 7.33 – 7.40 (m, 2 H), 7.22 – 7.31 (m, 3 H), 6.89 – 7.01 (m, 3 H), 6.62 (dd, *J*=7.89, 4.22 Hz, 2 H); ¹³C NMR (126 MHz, CDCl₃) δ ppm: 146.6, 143.2, 142.3, 140.8, 140.6, 138.4, 138.1, 135.2 (+), 130.1 (+), 129.6 (+), 129.1, 128.5 (+), 128.1 (+), 127.2 (+), 126.6 (+), 125.9 (+), 125.0 (+), 124.8 (+), 119.5 (+), 119.4 (+); HRMS (EI) calcd. for C₂₇H₁₇F₃: 398.1285, Found: 398.1282.

9-(diphenylmethylene)-2-(trifluoromethyl)-9H-fluorene (12i)—¹H NMR (500 MHz, CDCl₃) δ ppm: 7.67 – 7.76 (m, 3 H), 7.53 (d, *J*=8.07 Hz, 2 H), 7.45 (s, 2 H), 7.33 – 7.40 (m, 2 H), 7.22 – 7.31 (m, 3 H), 6.89 – 7.01 (m, 3 H), 6.62 (dd, *J*=7.89, 4.22 Hz, 2 H); ¹³C NMR (126 MHz, CDCl₃) δ ppm: 147.6, 143.2, 143.6, 141.8, 140.6, 139.0, 138.1, 135.2 (+), 131.1 (+), 129.0 (+), 128.8, 128.5 (+), 128.1 (+), 127.2 (+), 126.6 (+), 125.9 (+), 125.0 (+), 124.9 (+), 120.5 (+), 119.4 (+); HRMS (EI) calcd. for C₂₇H₁₇F₃: 398.1285, Found: 398.1283.

9-(1,3-difluoro-9(4methylphenylphenyl)methylene)-9H-fluorene (12k)—¹H NMR (500 MHz, CDCl₃) δ ppm: 7.69 (d, *J*=7.70 Hz, 1 H), 7.40 – 7.50 (m, 1 H), 7.30 – 7.38 (m, 3 H), 7.24 – 7.29 (m, 2 H), 7.21 (s, 2 H), 7.12 (d, *J*=6.97 Hz, 2 H), 6.99 (s, 1 H), 6.58 – 6.64 (m, 1 H), 6.43 – 6.55 (m, 2 H), 2.47 (s, 3 H); ¹³C NMR (126 MHz, CDCl₃) δ ppm: 148.5, 145.0, 144.1, 143.2, 142.0, 140.7, 140.1, 139.1, 138.6, 138.3 (+), 130.9 (+), 130.7 (+), 129.5 (+), 128.9, 128.7 (+), 128.5 (+), 128.2 (+), 127.8 (+), 127.6 (+), 127.2 (+), 124.2 (+), 119.7 (+), 102.8 (+), 102.6 (+), 102.4 (+), 21.5 (+); HRMS (EI) calcd. for C₂₇H₁₈F₂: 380.1380, Found: 380.1377.

4-[9H-fluoren-9-ylidene(4-trifluoromethyl)phenyl)methyl]phenyl methyl ether (12l)—¹H NMR (500 MHz, CDCl₃) δ ppm: 7.71 (d, *J*=7.52 Hz, 2 H), 7.67 (d, *J*=8.07 Hz, 2 H), 7.50 (d, *J*=8.07 Hz, 2 H), 7.22 – 7.31 (m, 4 H), 6.91 – 7.01 (m, 4 H), 6.81 (d, *J*=8.07 Hz, 1 H), 6.59 (d, *J*=7.89 Hz, 1 H), 3.88 (s, 3 H); ¹³C NMR (126 MHz, CDCl₃) δ ppm: 160.0, 146.9, 143.2, 140.6, 140.5, 138.6, 138.3, 134.8, 134.6, 131.5 (+), 130.5 (+), 130.3, 127.9 (+), 127.9 (+), 126.5 (+), 126.5 (+), 125.7 (+), 124.8 (+), 124.6 (+), 119.4 (+), 119.3 (+), 114.3 (+), 55.4 (+); HRMS (EI) calcd. for C₂₈H₁₉F₃O: 428.1387, Found: 428.1387.

4-chloro-9-(phenyl(*p*-tolyl)methylene)-9*H*-fluorene (1j)—¹H NMR (500 MHz, CDCl₃) δ ppm: 8.50 (s, 1 H), 7.39 – 7.45 (m, 3 H), 7.32 – 7.38 (m, 2 H), 7.18 – 7.32 (m, 6 H), 6.99 – 7.04 (m, 1 H), 6.80 – 6.89 (m, 1 H), 6.67 – 6.74 (m, 1 H), 6.58 (dd, *J*=7.98, 0.83 Hz, 1 H), 2.45 (s, 3 H); ¹³C NMR (126 MHz, CDCl₃) δ ppm: 146.9, 143.2, 141.4, 140.0, 139.2, 139.1, 138.5, 136.6, 133.3, 130.8 (s), 130.8 (s), 129.9 (s), 129.8 (s), 129.6 (s), 129.0 (s), 128.9 (s), 128.5, 128.4 (s), 127.5 (s), 126.7 (s), 126.6 (s), 124.5 (s), 123.4 (s), 123.1 (s), 21.5 (s); HRMS (EI) calcd. for C₂₇H₁₉Cl: 378.1179, Found: 380.1175.

9-((2-phenyl)phenylmethylene)-9*H*-fluorene (24)—¹H NMR (500 MHz, CDCl₃) δ ppm: 7.77 (d, *J*=7.15 Hz, 1 H), 7.73 (d, *J*=7.52 Hz, 1 H), 7.47 – 7.56 (m, 2 H), 7.41 – 7.46 (m, 2 H), 7.32 (t, *J*=7.52 Hz, 1 H), 7.21 – 7.27 (m, 2 H), 7.08 – 7.21 (m, 6 H), 7.04 (s, 2 H), 6.81 – 6.92 (m, 3 H), 6.62 (d, *J*=8.07 Hz, 1 H), 6.52 (d, *J*=7.52 Hz, 1 H); ¹³C NMR (126 MHz, CDCl₃) δ ppm: 145.9, 142.1, 141.4, 141.3, 141.2, 140.6, 140.4, 139.0, 138.4, 135.3, 130.7 (s), 130.6 (s), 130.5 (s), 128.9 (s), 128.5 (s), 128.4 (s), 128.2 (s), 127.8 (s), 127.8 (s), 127.6 (s), 127.4 (s), 127.2 (s), 126.9 (s), 126.8 (s), 126.4 (s), 125.1 (s), 124.7 (s), 119.4 (s), 119.2 (s). HRMS (EI) calcd. for C₃₂H₂₂: 406.1718, Found: 406.1722.

Acknowledgments

The financial support of the National Institutes of Health (GM-64444) and the National Science Foundation (Grant CHE-0710749) is gratefully acknowledged.

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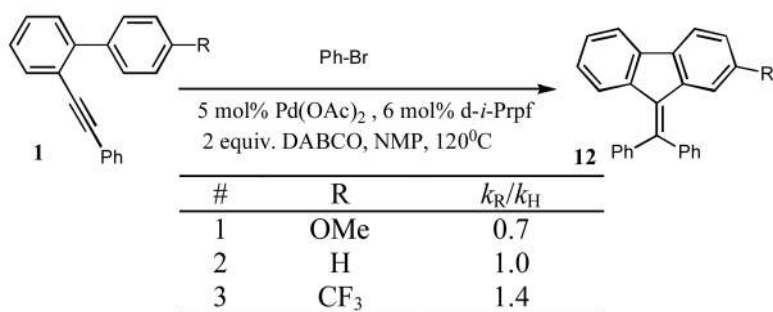
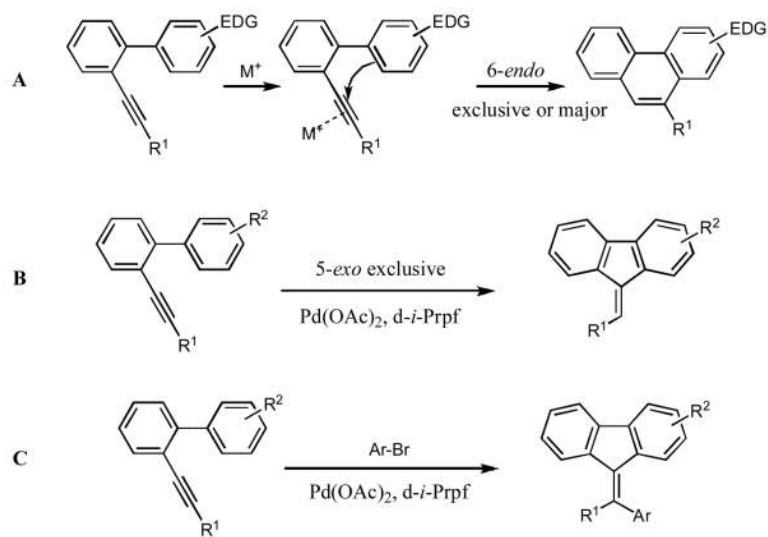
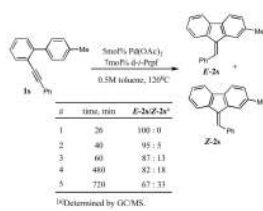


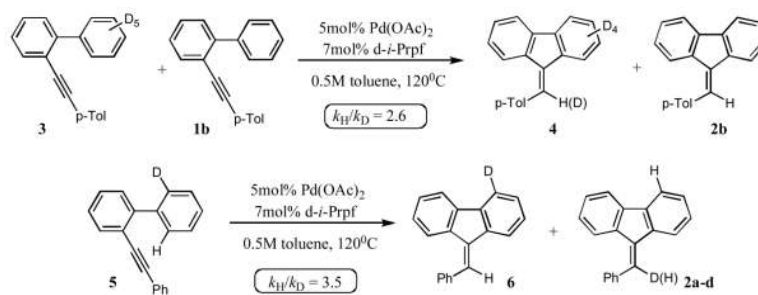
Figure 1.



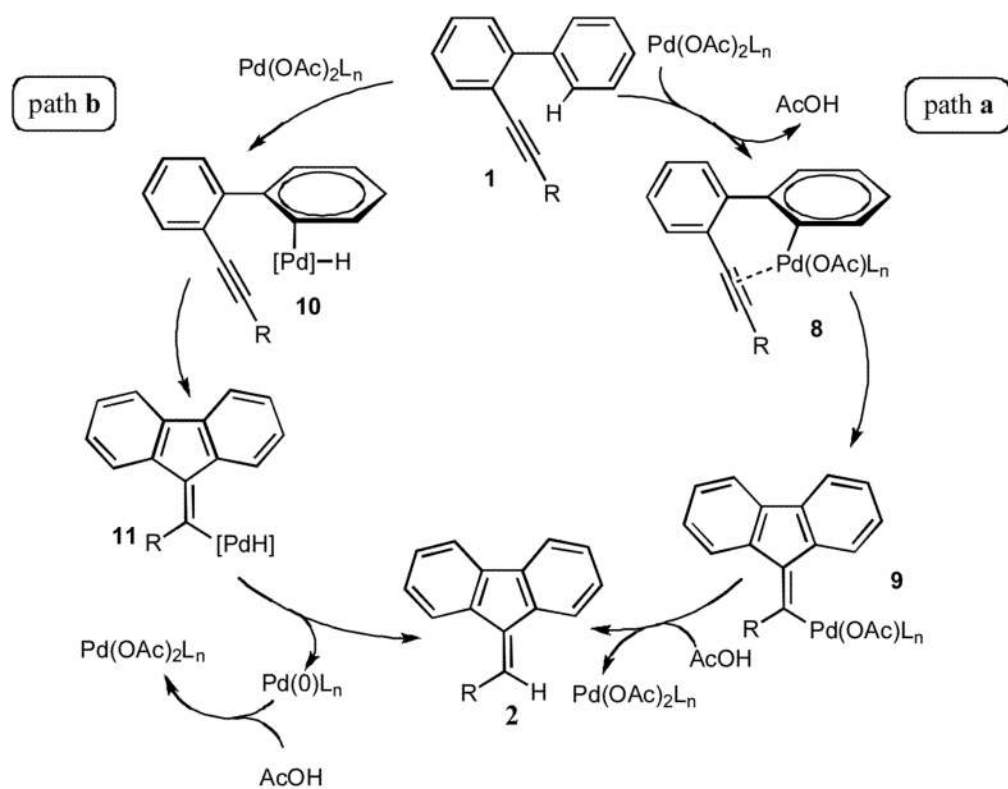
Scheme 1.



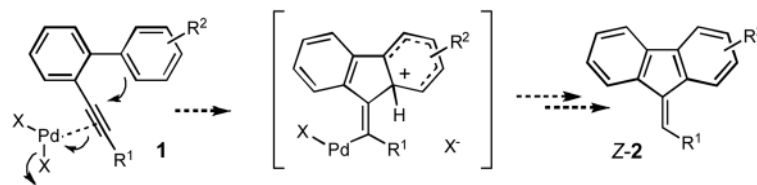
Scheme 2.



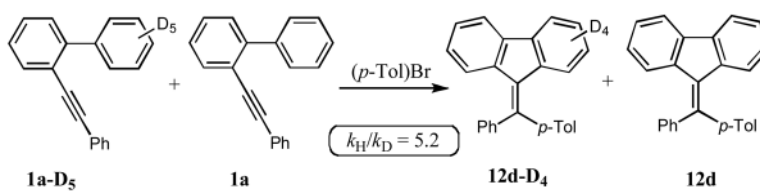
Scheme 3.



Scheme 4.



Scheme 5.



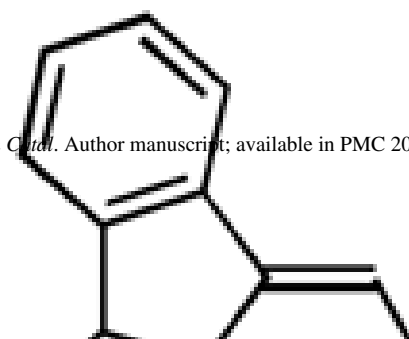
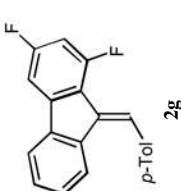
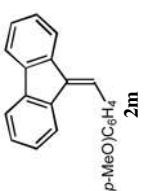
Scheme 6.

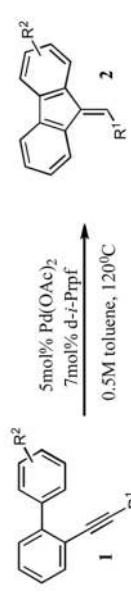
**Scheme 7.**

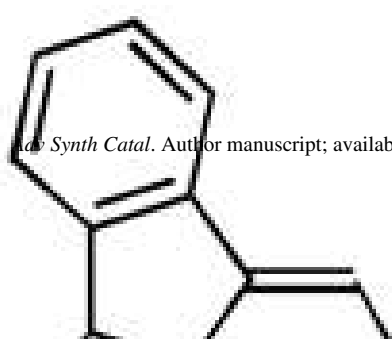
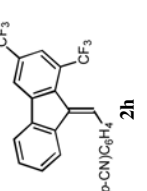
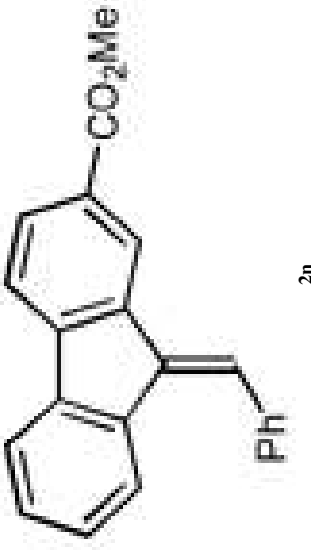
**Scheme 8.**

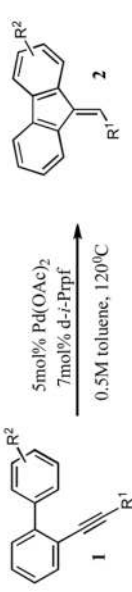
Table 1

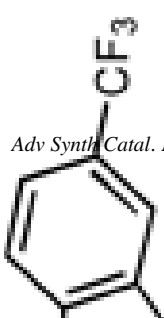
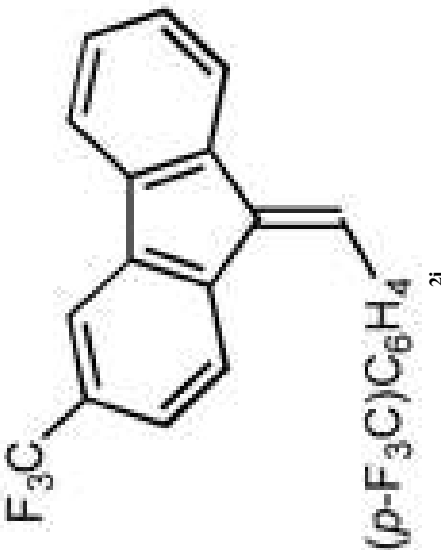
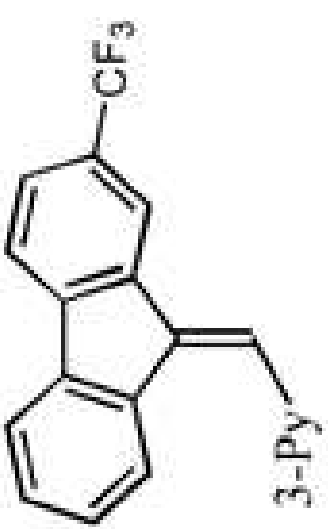
on of *o*-alkynyl biaryls.^a

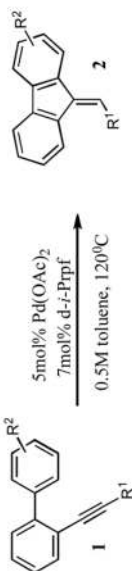
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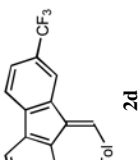
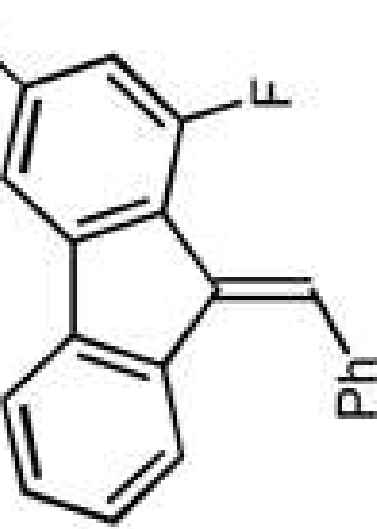
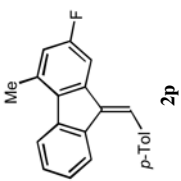
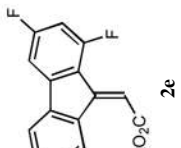
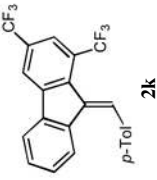
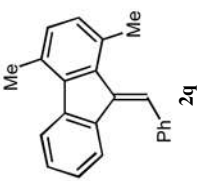


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				1.0	93	14		1.0	85	14					

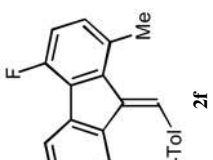
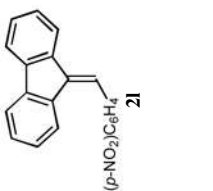
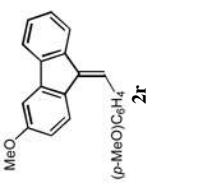


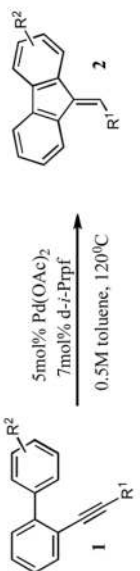
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	1.5	96	9	0.5	98	15		1.5	77	15				



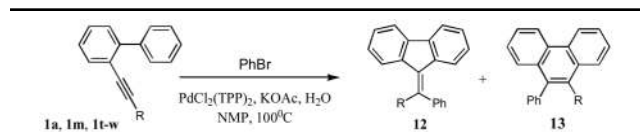
Product	Time, h	Yield, % ^b	#	Product	Time, h	Yield, % ^b	#	Product	Time, h	Yield, % ^b	#
	2.0	96	10		3.0	93	16		24	47	
	0.5	79	11		3.0	94	17		48	30	

Adv Synth Catal. Author manuscript; available in PMC 2010 May 1.

Product	Time, h	Yield, % ^a	#	Time, h	Yield, % ^b	#	Product	Time, h	Yield, % ^b	#	Product	Time, h	Yield, % ^b	#
														
	3.0	92	12					4.0	89	18		6.0	86	



1, 0.025 mmol of Pd(OAc)₂, 0.035 mmol of d-*i*-Prpf, 1 ml of toluene, 120°C.

Table 2Arylative cyclization of *o*-alkynyl biaryls.

#	R	Substrate	12:13 Ratio ^a	Combined yield ^b , %
1	Ph	1a	58:42	90
2	<i>p</i> -OMe(C ₆ H ₄)	1m	72:28	70
3	<i>p</i> -CN(C ₆ H ₄)	1t	51:49	65
4	<i>p</i> -COMe(C ₆ H ₄)	1u	53:47	60
5	<i>n</i> -Bu	1v	100:0	70
6	CO ₂ Et	1w	0:100	30

^aProduct ratios determined by GC/MS analysis.^bIsolated yields.

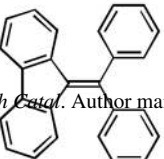
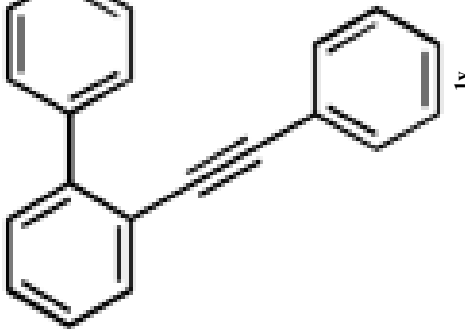
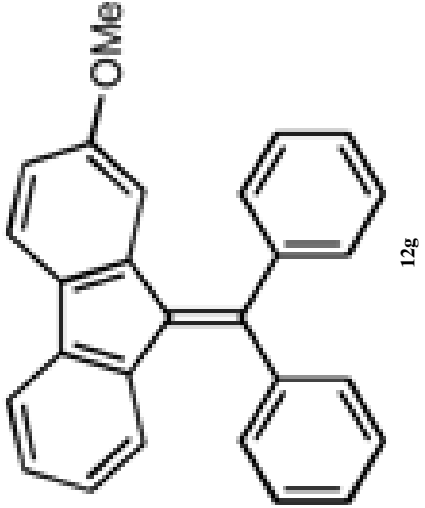
Table 3

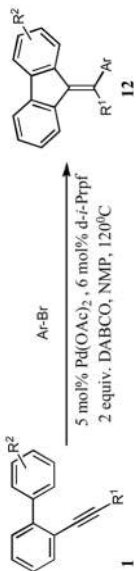
Optimization of conditions for arylyne cyclization of **1a**.

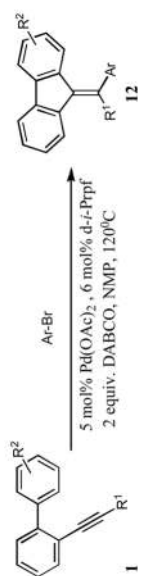
#	[Pd] source	Ligand	Base	Temperature	12a:13a Ratio ^a	Yield of 12a, % ^b
1	Pd(OAc) ₂	dppp	KOAc	120	-	0
2	Pd(OAc) ₂	dppe	KOAc	120	-	0
3	Pd(OAc) ₂	Ph ₂ P(CH ₂) ₃ PPh ₂	KOAc	120	-	0
4	Pd(OAc) ₂	dppf	KOAc	100	90:10	10
5	Pd(OAc) ₂	d- <i>r</i> -Bupf	KOAc	100	90:10	12
6	Pd(OAc) ₂	d- <i>i</i> -Prpf	KOAc	120	95:5	12
7	Pd(OAc) ₂	d- <i>i</i> -Prpf	Cs ₂ CO ₃	120	-	0
8	Pd(OAc) ₂	d- <i>i</i> -Prpf	Et ₃ N	120	99:1	45
9	Pd(OAc) ₂	d- <i>i</i> -Prpf	EtN(<i>i</i> -Pr) ₂	120	100:0	60
10	PdCl ₂	d- <i>i</i> -Prpf	EtN(<i>i</i> -Pr) ₂	120	100:0	31
11	Pd(dba) ₂	d- <i>i</i> -Prpf	EtN(<i>i</i> -Pr) ₂	120	100:0	20
12	PdCl ₂ (CH ₃ CN) ₂	d- <i>i</i> -Prpf	EtN(<i>i</i> -Pr) ₂	120	100:0	30
13	Pd(OAc) ₂	d- <i>i</i> -Prpf	Bu ₄ NBr	120	100:0	20
14	Pd(OAc) ₂	d- <i>i</i> -Prpf	DABCO	100	100:0	70 ^c
15	Pd(OAc) ₂	dppf	DABCO	110	100:0	81
16	Pd(OAc) ₂	d- <i>r</i> -Bupf	DABCO	110	100:0	80
17	Pd(OAc) ₂	d- <i>i</i> -Prpf	DABCO	110	100:0	95
18	Pd(OAc) ₂	d- <i>i</i> -Prpf	DABCO	120	100:0	89 ^d

^aProduct ratios determined by GC/MS analysis.^bYield determined by GC/MS analysis.^cYield after 24 hrs.^dIsolated yield after 6 hrs.

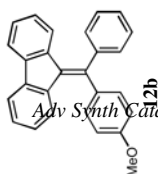
Table 4

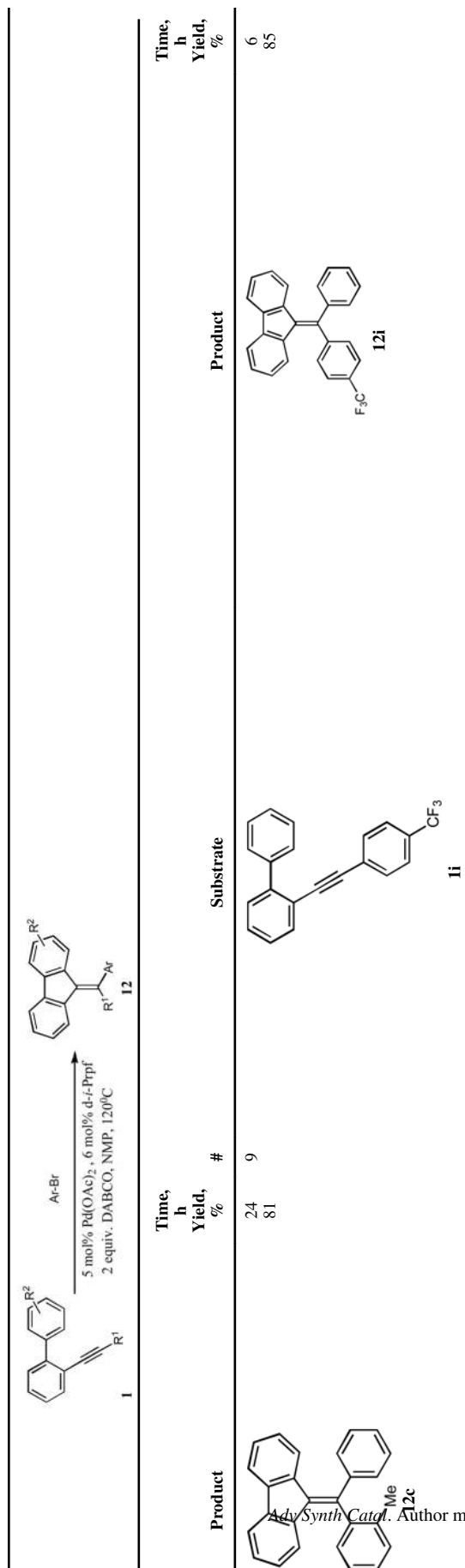
Product	Substrate	Time, h	Yield, %	#	Time, h	Yield, %
		6	89	7	10	76
						

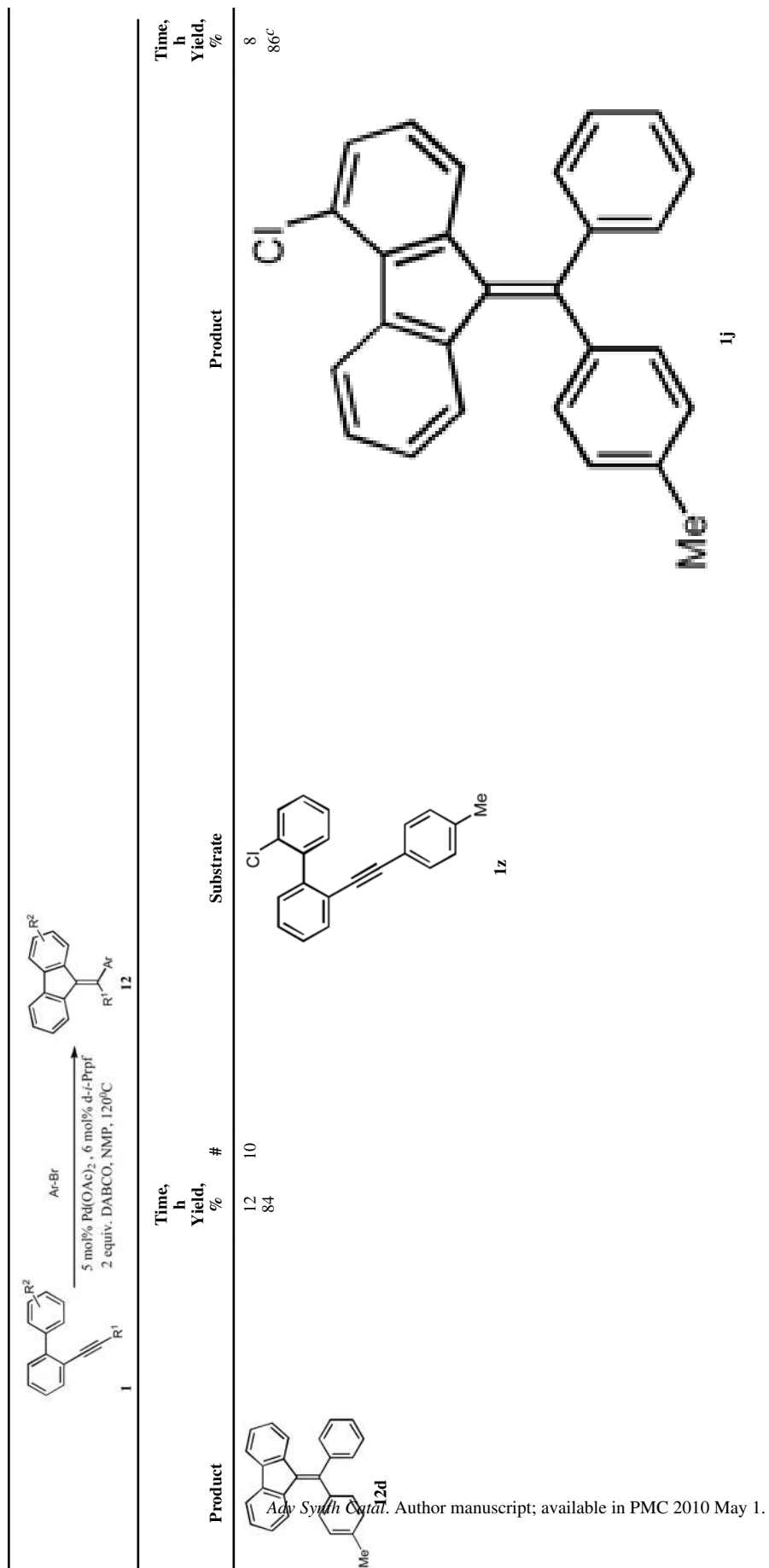
Reaction scheme: 

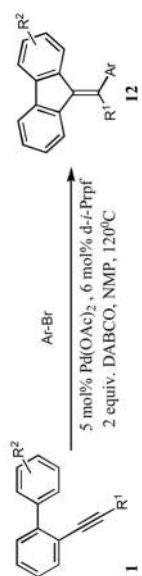


Product	Time, h	Yield, %	#	Substrate	Product	Time, h	Yield, %
 12b	9	86	8			12h	88









Product	Time, h	Yield, %	#	Substrate	Product	Time, h	Yield, %
	12	86	11			8	89 ^c

