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Copper(II) Triflate-Catalyzed and Tosyl Isocyanate-Mediated Three-Step Tandem Synthesis of 9-Arylfluorenes

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Graphic Abstract

Abstract

A $Cu(OTf)_2$-catalyzed and TsNCO-mediated three-step tandem synthesis of 9-arylfluorenes was developed from biphenyls and aryl aldehydes, by which the electron-poor 9-aryl substituted fluorenes were synthesized smoothly. Its success is mainly attributed to use an anhydrous synthesis of *N*-tosyl arylaldimines as a key step, which was achieved *in situ* from the reaction of TsNCO and aryl aldehydes.

Keywords: Lewis Acid; Catalysis; *N*-Tosylimines; Tandem Synthesis; 9-Arylfluorenes.

1. Introduction

Since the fluorene molecule has a nearly planar tricyclic structure, its derivatives usually exhibit unique properties. Many 9-arylfluorenes **1** and the synthetic compounds containing the structural unit of **1** have been found creative material applications [1,2]. As shown in Figure 1, the polycyclic compound **2** served as a precursor to produce open-shell polyradicals with fascinating photoelectric properties [2a]. Recently, these compounds also were found novel biological applications. For example, the polymethoxylated compounds **3** showed unprecedented inhibitory activities against tubulin polymerization [3].

Many methods have been developed for the synthesis of 9-arylfluorenes **1** in literature. As shown in Scheme 1, they can be divided into three major methods: (a) direct arylation at C9 of fluorene derivatives **4** [4]; (b) coupling of alkyne/alkyne or alkyne/alkene [5]; (c) annulation of 2-substituted biphenyls **5-7** [6-8]. Although each method has their own advantages, the multi-step synthesis of starting materials remains a common and serious challenge. Therefore, it is necessary to develop new methods to use the accessible starting materials and to increase the structural diversity of products **1**.

Herein, we would like to report a novel tandem synthesis of 9-arylfluorenes **1** from biphenyls **8** and aryl aldehydes **9**. The method was efficiently catalyzed by $Cu(OTf)_2$ and mediated by TsNCO, by which a series of structurally novel 9-arylfluorenes **1** were synthesized conveniently.

2. Experimental

2.1. General. All melting points were determined on a Yanaco melting point apparatus and are uncorrected. IR spectra were recorded as KBr pellets on a Nicolet FT-IR 5DX spectrometer. The ^{1}H NMR (300 or 400 MHz) and ^{13}C NMR (75 or 100 MHz) spectra were recorded on JEOL JNM-ECA spectrometers 300 or 400 in $CDCl_3$ or DMSO-d_6. TMS was used as an internal reference and *J* values are given in Hz. HRMS were obtained on a Bruker micrOTOF-Q II spectrometer. The biphenyls (**8a-d**) were prepared by reported procedures in literature [15].

*2.2. A Typical Procedure for the Preparation of 1,2,3-Trimethoxy-9-(4-chlorophenyl)fluorene (**1a**).* To a suspension of 3,4,5-trimethoxy-biphenyl (**8a**, 122 mg, 0.5 mmol) and 4-chlorobenzaldehyde (**9a**, 84 mg, 0.6 mmol), $Cu(OTf)_2$ (18 mg, 0.05 mmol) in DCE (2 mL) was added tosyl isocyanate (118 mg, 0.6 mmol) in a Schlenk tube under a balloon pressure of N_2. The resultant mixture was stirred at 80 ^{o}C for 15 h. It was directly subjected to flash chromatography [silica gel, 5% EtOAc in petroleum ether (60−90 ^{o}C)] to give 170 mg (93%) of product **1a** as colorless oil; IR (KBr) ν 3062, 2846, 1581, 1100 cm^{-1}; ^{1}H NMR (300 MHz) δ 7.67 (d, J = 7.6 Hz, 1H), 7.35−7.32 (m, 1H), 7.20−7.18 (m, 4H), 7.10 (s, 1H), 7.03−7.00 (m, 2H), 5.02 (s, 1H), 3.97 (s, 3H), 3.86 (s, 3H), 3.44 (s, 3H); ^{13}C NMR (75 MHz) δ 154.5, 150.6, 148.3, 141.9, 140.8, 140.4, 136.8, 132.3, 132.1, 129.5 (2C), 128.5 (2C), 127.3, 126.9, 125.1, 119.3, 99.0, 60.9, 60.0, 56.3, 51.8; HRMS (ESI-TOF) (*m/z*): calcd for $C_{22}H_{19}ClO_3$, $[M+H]^+$ 367.1095; found 367.1100.

The products **1b**−**1w** were prepared by the similar procedure.

*2.2.1. 1,2,3-Trimethoxy-9-(3-chlorophenyl)fluorene (**1b**).* Yellow oil; IR (KBr) ν 2938, 2827, 1581, 1112 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.68 (d, J = 7.8 Hz, 1H), 7.37−7.33 (m, 1H), 7.24−7.20 (m, 2H), 7.17−7.15 (m, 2H), 7.11 (s, 1H), 7.06 (s, 1H), 7.00−6.97 (m, 1H), 5.02 (s, 1H), 3.98 (s, 3H), 3.86 (s, 3H), 3.45 (s, 3H); ^{13}C NMR (100 MHz) δ 154.6, 150.5, 148.0, 143.9, 141.9, 140.8, 136.9, 134.0, 132.0, 129.6, 128.2, 127.4, 127.0, 126.7, 126.4, 125.1, 119.4, 99.1, 60.9, 60.0, 56.3, 52.0; HRMS (ESI-TOF) (*m/z*): calcd for $C_{22}H_{19}ClO_3$, $[M+H]^+$ 367.1095; found 367.1092.

*2.2.2. 1,2,3-Trimethoxy-9-(2-chlorophenyl)fluorene (**1c**).* White solid, 111−112 ^{o}C; IR (KBr) ν 2962, 2930, 2828, 1579, 1109 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.67 (d, J = 7.8 Hz, 1H), 7.47 (d, J = 7.8 Hz, 1H), 7.34−7.31 (m, 2H), 7.19−7.15 (m, 1H), 7.11−7.07 (m, 2H), 6.94−6.90 (m, 1H), 6.45−6.43 (m, 1H), 5.78 (s, 1H), 3.97 (s, 3H), 3.85 (s, 3H), 3.50 (s, 3H); ^{13}C NMR (100 MHz) δ 154.4, 150.3, 148.3, 141.9, 140.7, 139.4, 137.2, 134.3, 132.2, 129.3, 128.3, 127.7, 127.2, 126.9, 126.8, 125.0, 119.3, 98.9, 60.9, 59.9, 56.2, 48.0; HRMS (ESI-TOF) (*m/z*): calcd for $C_{22}H_{19}ClO_3$, $[M+H]^+$ 367.1095; found 367.1089.

*2.2.3. 1,2,3-Trimethoxy-9-(4-fluorophenyl)fluorene (**1d**).* Yellow oil; IR (KBr) ν 2831, 1636, 1113 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.67 (d, J = 7.6 Hz, 1H), 7.35−7.31 (m, 1H), 7.20−7.19 (m, 2H), 7.11 (s, 1H), 7.06−7.02 (m, 2H), 6.93−6.89 (m, 2H), 5.04 (s, 1H), 3.97 (s, 3H), 3.86 (s, 3H), 3.42 (s, 3H); ^{13}C NMR (100 MHz) δ 161.6 (d, J = 243.1 Hz, 1C), 154.4, 150.6, 148.6, 141.9, 140.7, 137.4, 136.7, 132.5, 129.5 (d, J = 7.6 Hz, 2C),

127.0 (d, *J* = 35.3 Hz, 2C), 125.0, 119.3, 115.2, 115.0, 99.0, 60.9, 60.0, 56.2, 51.7; HRMS (ESI-TOF) (*m/z*): calcd for $C_{22}H_{19}FO_3$, $[M+H]^+$ 351.1391; found 351.1390.

*2.2.4. 1,2,3-Trimethoxy-9-(4-bromophenyl)fluorene (**1e**).* Yellowish oil; IR (KBr) ν 2825, 1583, 1110 cm^{-1}; ^1H NMR (400 MHz) δ 7.67 (d, *J* = 7.2 Hz, 1H), 7.36−7.32 (m, 3H), 7.20 (d, *J* = 4.4 Hz, 2H), 7.11 (s, 1H), 6.96 (d, *J* = 8.8 Hz, 2H), 5.01 (s, 1H), 3.98 (s, 3H), 3.85 (s, 3H), 3.44 (s, 3H); ^{13}C NMR (100 MHz) δ 154.5, 150.5, 148.3, 141.9, 140.9, 140.7, 136.9, 132.2, 131.4 (2C), 129.9 (2C), 127.3, 126.9, 125.1, 120.2, 119.4, 99.0, 60.9, 60.1, 56.3, 51.9; HRMS (ESI-TOF) (*m/z*): calcd for $C_{22}H_{19}BrO_3$, $[M+H]^+$ 411.0590; found 411.0590.

*2.2.5. 1,2,3-Trimethoxy-9-(2-bromophenyl)fluorene (**1f**).* White solid, mp 115−116 ^oC; IR (KBr) ν 2837, 1595, 1103 cm^{-1}; ^1H NMR (400 MHz) δ 7.66 (t, *J* = 7.3 Hz, 2H), 7.35−7.31 (m, 2H), 7.19−7.15 (m, 1H), 7.11 (s, 1H), 7.02−6.93 (m, 2H), 6.43−6.41 (m, 1H), 5.78 (s, 1H), 3.97 (s, 3H), 3.85 (s, 3H), 3.50 (s, 3H); ^{13}C NMR (100 MHz) δ 154.4, 150.3, 148.3, 141.9, 141.2, 140.6, 137.1, 132.6, 132.3, 128.4, 128.0, 127.5, 127.2, 126.9, 125.1, 124.9, 119.3, 98.8, 60.9, 59.9, 56.2, 50.8; HRMS (ESI-TOF) (*m/z*): calcd for $C_{22}H_{19}BrO_3$, $[M+H]^+$ 411.0590; found 411.0593.

*2.2.6. 1,2,3-Trimethoxy-9-phenylfluorene (**1g**).* Colorless oil; IR (KBr) ν 2834, 1461, 1109 cm^{-1}; ^1H NMR (400 MHz) δ 7.67 (d, *J* = 7.6 Hz, 1H), 7.32 (t, *J* = 7.2 Hz, 1H), 7.23−7.16 (m, 5H), 7.11−7.07 (m, 3H), 5.06 (s, 1H), 3.96 (s, 3H), 3.85 (s, 3H), 3.37 (s, 3H); ^{13}C NMR (100 MHz) δ 154.3, 150.6, 148.8, 141.9, 141.7, 140.7, 136.9, 132.9,

128.3 (2C), 128.1 (2C), 127.1, 126.8, 126.5, 125.1, 119.2, 99.0, 60.8, 59.9, 56.2, 52.5; HRMS (ESI-TOF) (*m/z*): calcd for $C_{20}H_{20}O_3$, $[M+H]^+$ 333.1485; found 333.1480.

*2.2.7. 1,2,3-Trimethoxy-9-(4-methylphenyl)fluorene (**1h**).* Colorless oil; IR (KBr) ν 2934, 2850, 1461, 1110 cm^{-1}; ^1H NMR (400 MHz) δ 7.66 (d, J = 7.2 Hz, 1H), 7.31 (t, J = 7.6 Hz, 1H), 7.23−7.15 (m, 2H), 7.11 (s, 1H), 7.03 (d, J = 8.4 Hz, 2H), 6.97 (d, J = 8.0 Hz, 2H), 5.04 (s, 1H), 3.97 (s, 3H), 3.86 (s, 3H), 3.41 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz) δ 154.2, 150.6, 149.0, 141.9, 140.7, 138.5, 136.9, 136.0, 132.9, 129.0 (2C), 127.9 (2C), 127.0, 126.8, 125.1, 119.2, 99.0, 60.9, 60.0, 56.3, 52.2, 21.1; HRMS (ESI-TOF) (*m/z*): calcd for $C_{23}H_{22}O_3$, $[M+H]^+$ 347.1642; found 347.1637.

*2.2.8. 1,2,3-Trimethoxy-9-(3,4,5-trimethoxyphenyl)fluorene (**1i**).* White solid, mp 181−182 °C; IR (KBr) ν 2933, 2836, 1588, 1117 cm^{-1}; ^1H NMR (400 MHz) δ 7.67 (d, J = 7.8 Hz, 1H), 7.36−7.26 (m, 2H), 7.23−7.19 (m, 1H), 7.12 (s, 1H), 6.32 (s, 2H), 5.00 (s, 1H), 3.99 (s, 3H), 3.87 (s, 3H), 3.80 (s, 3H), 3.74 (s, 6H), 3.48 (s, 3H); ^{13}C NMR (100 MHz) δ 167.6, 154.3, 153.0, 150.6, 148.4, 141.9, 140.5, 137.2, 136.9, 136.6, 132.2, 127.2, 126.8, 125.0, 119.2, 105.0 (2C), 98.9, 60.9, 60.8, 60.1, 56.2, 56.0 (2C), 52.8; HRMS (ESI-TOF) (*m/z*): calcd for $C_{25}H_{26}O_6$, $[M+Na]^+$ 445.1622; found 445.1618.

*2.2.9. 1,2,3-Trimethoxy-9-(4-nitrophenyl)fluorene (**1j**).* White solid, mp 113−114 °C; IR (KBr) ν 2939, 2837, 1595, 1346 cm^{-1}; ^1H NMR (400 MHz) δ 8.09 (d, J = 8.0 Hz, 2H), 7.71 (d, J = 7.6 Hz, 1H), 7.39−7.35 (m, 1H), 7.24−7.17 (m, 4H), 7.13 (s, 1H), 5.13 (s, 1H), 3.99 (s, 3H), 3.85 (s, 3H), 3.48 (s, 3H); ^{13}C NMR (75 MHz) δ 154.9,

150.3, 150.0, 147.3, 146.7, 141.7, 140.8, 136.8, 131.2, 128.9 (2C), 127.7, 127.0, 125.0, 123.6 (2C), 119.6, 99.0, 60.9, 59.9, 56.2, 51.9; HRMS (ESI-TOF) (*m/z*): calcd for $C_{22}H_{19}NO_5$, $[M+H]^+$ 378.1336; found 378.1338.

*2.2.10. 1,2,3-Trimethoxy-9-(3-nitrophenyl)fluorene (**1k**).* Yellow oil; IR (KBr) ν 3000, 2840, 1524, 1353, 1106 cm^{-1}; ^1H NMR (300 MHz) δ 8.08−8.04 (m, 1H), 8.00 (s, 1H), 7.71 (d, *J* = 7.8 Hz, 1H), 7.40−7.35 (m, 3H), 7.22−7.20 (m, 2H), 7.13 (s, 1H), 5.14 (s, 1H), 3.99 (s, 3H), 3.85 (s, 3H), 3.48 (s, 3H); ^{13}C NMR (75 MHz) δ 154.9, 150.4, 148.3, 147.3, 144.1, 141.8, 140.9, 136.8, 134.3, 131.2, 129.2, 127.7, 127.1, 125.0, 123.1, 121.7, 119.0, 99.1, 60.9, 60.0, 56.2, 51.8; HRMS (ESI-TOF) (*m/z*): calcd for $C_{22}H_{19}NO_5$, $[M+H]^+$ 378.1336; found 378.1332.

*2.2.11. 1,2,3-Trimethoxy-9-(4-cyanophenyl)fluorene (**1l**).* Colorless oil; IR (KBr) ν 2870, 2223, 1543, 1110 cm^{-1}. ^1H NMR (400 MHz) δ 7.70 (d, *J* = 7.8 Hz, 1H), 7.53 (d, *J* = 8.3 Hz, 2H), 7.39−7.35 (m, 1H), 7.23−7.17 (m, 4H), 7.12 (s, 1H), 5.08 (s, 1H), 3.99 (s, 3H), 3.85 (s, 3H), 3.45 (s, 3H); ^{13}C NMR (100 MHz) δ 154.8, 150.4, 147.8, 147.4, 141.8, 140.9, 136.9, 132.2 (2C), 131.4, 128.9 (2C), 127.6, 127.1, 125.0, 119.5, 118.9, 110.3, 90.0, 60.9, 60.0, 56.3, 52.2; HRMS (ESI-TOF) (*m/z*): calcd for $C_{23}H_{19}NO_3$, $[M+H]^+$ 358.1438; found 358.1437.

*2.2.12. 1,2,3-Trimethoxy-9-(4-methoxycarbonylphenyl)fluorene (**1m**).* Colorless oil. IR (KBr) ν 2992, 1724, 1590, 1108 cm^{-1}. ^1H NMR (400 MHz) δ 7.92 (d, *J* = 8.7 Hz, 2H), 7.69 (d, *J* = 7.8 Hz, 1H), 7.37−7.33 (m, 1H), 7.19 (d, *J* = 4.1 Hz, 2H), 7.16 (d, *J* = 8.2 Hz, 2H), 7.12 (s, 1H), 5.10 (s, 1H), 3.98 (s, 3H), 3.87 (s, 3H), 3.85 (s, 3H), 3.39

(s, 3H),; ^{13}C NMR (100 MHz) δ166.9, 154.6, 150.5, 148.0, 147.5, 141.8, 140.8, 136.9, 132.0, 129.7 (2C), 128.5 (2C), 128.2, 127.4, 126.9, 125.1, 119.4, 99.0, 60.9, 59.9, 56.2, 52.3, 51.9. HRMS (ESI-TOF) (*m/z*): calcd for $C_{24}H_{22}O_5$, $[M+H]^+$ 391.1540; found 391.1539.

*2.2.13. 1,2,3-Trimethoxy-9-(4-trifluoromethylphenyl)fluorene (**1n**).* Colorless oil. IR (KBr) ν 2933, 2839, 1568, 1116 cm^{-1}. ^{1}H NMR (400 MHz) δ7.69 (d, J = 7.8 Hz, 1H), 7.48 (d, J = 8.2 Hz, 2H), 7.36−7.32 (m, 1H), 7.20−7.18 (m, 4H), 7.12 (s, 1H), 5.09 (s, 1H), 3.97 (s, 3H), 3.85 (s, 3H), 3.43 (s, 3H); ^{13}C NMR (100 MHz) δ154.6, 150.5, 147.9, 146.1, 141.8, 140.8, 136.9, 131.9, 128.7 (q, J = 32.4 Hz), 128.4 (2C), 127.4, 126.9, 125.2 (q, J = 3.8 Hz, 2C), 125.0, 124.2 (q, J = 270.8 Hz, CF_3), 119.4, 99.0, 60.9, 59.9, 56.2, 52.1; HRMS (ESI-TOF) (*m/z*): calcd for $C_{23}H_{19}F_3O_3$, $[M+H]^+$ 401.1359; found 401.1362.

*2.2.14. 1,2,3-Trimethoxy-9-(4-formylphenyl)fluorene (**1o**).* Yellow oil; IR (KBr) ν3055, 2931, 2838, 1698, 1105 cm^{-1}; ^{1}H NMR (400 MHz) δ9.94 (s, 1H), 7.76 (d, J = 7.8 Hz, 2H), 7.71 (d, J = 8.0 Hz, 1H), 7.38−7.34 (m, 1H), 7.26−7.13 (m, 4H), 5.12 (s, 1H), 3.98 (s, 3H), 3.85 (s, 3H), 3.43 (s, 3H); ^{13}C NMR (100 MHz) δ191.8, 154.7, 150.4, 149.4, 147.7, 141.8, 140.8, 136.9, 135.0, 131.8, 129.9 (2C), 128.8 (2C), 127.5, 127.0, 125.0, 119.4, 99.0, 60.9, 59.9, 56.2, 52.4; HRMS (ESI-TOF) (*m/z*): calcd for $C_{23}H_{20}O_4$, $[M+H]^+$ 361.1434; found 361.1435.

*2.2.15. 1,2,3-Trimethoxy-9-(2-bromo-4-chlorophenyl)fluorene (**1p**).* Yellow oil; IR (KBr) ν2937, 2840, 1579, 1118 cm^{-1}; ^{1}H NMR (400 MHz) δ7.66−7.63 (m, 2H),

7.31−7.27 (m, 2H), 7.15−7.10 (m, 1H), 7.09 (s, 1H), 6.93−6.90 (m, 1H), 6.34 (d, *J* = 8.2 Hz, 1H), 5.68 (s, 1H), 3.94 (s, 3H), 3.83 (s, 3H), 3.56 (s, 3H); ^{13}C NMR (100 MHz) δ 154.4, 150.1, 147.6, 141.7, 140.4, 139.9, 136.9, 132.4, 131.9, 131.6, 129.0, 127.7, 127.3, 126.8, 125.1, 124.7, 119.3, 98.7, 60.8, 59.9, 56.1, 50.1; HRMS (ESI-TOF) (*m/z*): calcd for $C_{22}H_{18}BrClO_3$, $[M+H]^+$ 445.0201; found 445.0202.

*2.2.16. 1,2,3-Trimethoxy-9-(2-bromo-4-methoxyphenyl)fluorene (**1q**).* White solid, mp 107−108 °C; IR (KBr) ν 3044, 2935, 2846, 1571, 1119 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.66 (d, *J* = 7.2 Hz, 1H), 7.54 (d, *J* = 9.2 Hz, 1H), 7.37−7.30 (m, 2H), 7.18−7.15 (m, 1H), 7.10 (s, 1H), 6.61−6.58 (m, 1H), 5.97 (d, *J* = 2.8 Hz, 1H), 5.72 (s, 1H), 3.97 (s, 3H), 3.86 (s, 3H), 3.57 (s, 3H), 3.47 (s, 3H); ^{13}C NMR (100 MHz) δ 158.7, 154.4, 150.3, 148.1, 142.3, 141.8, 140.5, 137.2, 133.0, 131.9, 127.2, 126.8, 124.8, 119.3, 115.6, 113.8, 113.7, 99.9, 60.9, 60.0, 56.2, 55.1, 51.0; HRMS (ESI-TOF) (*m/z*): calcd for $C_{23}H_{21}BrO_4$, $[M+H]^+$ 441.0696; found 441.0688.

*2.2.17 1,2,3-Trimethoxy-9-(2-bromo-5-nitrophenyl)fluorene (**1r**).* Yellow solid, mp 140−141 °C; IR (KBr) ν 2997, 2842, 1524, 1359 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.89−7.83 (m, 2H), 7.71 (d, *J* = 7.6 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.30−7.17 (m, 3H), 7.14 (s, 1H), 5.77 (s, 1H), 4.01 (s, 3H), 3.85 (s, 3H), 3.60 (s, 3H); ^{13}C NMR (100 MHz) δ 155.0, 150.0, 147.3, 146.8, 143.8, 141.8, 140.8, 137.1, 133.6, 132.2, 130.6, 127.9, 127.0, 124.6, 123.3, 122.4, 119.8, 99.2, 61.0, 60.1, 56.2, 50.6; HRMS (ESI-TOF) (*m/z*): calcd for $C_{22}H_{18}BrNO_5$, $[M+Na]^+$ 478.0261; found 478.0270.

*2.2.18 1,2,3-Trimethoxy-7-methyl-9-(4-chlorophenyl)fluorene (**1s**).* White solid, mp 112−113 °C; IR (KBr) ν 2928, 2840, 1460, 1108 cm^{-1}; ^{1}H NMR (300 MHz) δ 7.55 (d, J = 7.9 Hz, 1H), 7.21−7.12 (m, 3H), 7.06−7.00 (m, 4H), 4.97 (s, 1H), 3.95 (s, 3H), 3.84 (s, 3H), 3.43 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (75 MHz) δ 154.4, 150.5, 148.5, 141.5, 140.6, 138.1, 137.0, 136.8, 132.0, 131.9, 129.4 (2C), 128.5 (2C), 128.1, 125.7, 119.0, 98.8, 60.9, 60.0, 56.2, 51.6, 21.5; HRMS (ESI-TOF) (*m/z*): calcd for $C_{23}H_{21}ClO_3$, $[M+H]^+$ 381.1252; found 381.1254.

*2.2.19. 1,2,3-Trimethoxy-5-methyl-9-(4-chlorophenyl)fluorene (**1t**).* White solid, mp 137−138 °C; IR (KBr) ν 2930, 2840, 1465, 1100 cm^{-1}; ^{1}H NMR (300 MHz) δ 7.28 (s, 1H), 7.19 (d, J = 8.4 Hz, 2H), 7.10−7.08 (m, 2H), 7.06−6.98 (m, 3H), 4.99 (s, 1H), 3.97 (s, 3H), 3.86 (s, 3H), 3.42 (s, 3H) , 2.72 (s, 3H); ^{13}C NMR (75 MHz) δ 154.0, 150.2, 148.8, 141.4, 140.8, 138.7, 137.9, 132.9, 132.1, 132.0, 129.6, 129.5 (2C), 128.4 (2C), 126.7, 122.7, 102.9, 60.8, 60.0, 56.3, 51.6, 20.7; HRMS (ESI-TOF) (*m/z*): calcd for $C_{23}H_{21}ClO_3$, $[M+H]^+$ 381.1252; found 381.1250.

*2.2.20. 1,2,3,6,7,8-Hexamethoxy-9-(4-chlorophenyl)fluorene (**1u**).* White solid, mp 139−140 °C; IR (KBr) ν 2933, 2833, 1405, 1121 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.18 (d, J = 8.4 Hz, 2H), 7.05 (d, J = 8.4 Hz, 2H), 7.00 (s, 2H), 5.07 (s, 1H), 3.97 (s, 6H), 3.84 (s, 6H), 3.39 (s, 6H); ^{13}C NMR (100 MHz) δ 154.4 (2C), 150.2 (2C), 141.5 (2C), 140.4, 136.5 (2C), 133.3 (2C), 131.7, 129.5 (2C), 128.1 (2C), 98.6 (2C), 60.8 (2C), 59.9 (2C), 56.2 (2C), 49.7; HRMS (ESI-TOF) (*m/z*): calcd for $C_{25}H_{25}ClO_6$, $[M+H]^+$ 457.1412; found 457.1406.

*2.2.21. 1,2,3,6,7,8-Hexamethoxy-9-(4-nitrophenyl)fluorene (**1v**).* Yellow solid, mp 152−154 °C; IR (KBr) ν 2832, 1599, 1342, 828 cm^{-1}; ^{1}H NMR (300 MHz) δ 8.10 (d, J = 7.9 Hz, 2H), 7.28 (d, J = 8.3 Hz, 2H), 7.04 (s, 2H), 5.17 (s, 1H), 4.00 (s, 6H), 3.83 (s, 6H), 3.43 (s, 6H); ^{13}C NMR (75 MHz) δ 154.7 (2C), 150.4, 150.1 (2C), 146.4, 141.4 (2C), 136.7 (2C), 132.3 (2C), 128.9 (2C), 123.3 (2C), 98.7 (2C), 60.8 (2C), 59.9 (2C), 56.2 (2C), 49.8; HRMS (ESI-TOF) (*m/z*): calcd for $C_{25}H_{25}NO_8$, $[M+H]^+$ 468.1653; found 468.1656.

*2.2.22. 1,2,3,6,7,8-Hexamethoxy-9-(3-nitrophenyl)fluorene (**1w**).* Yellow solid, mp 135−136 °C; IR (KBr) ν 2940, 2834, 1580, 1347 cm^{-1}; ^{1}H NMR (300 MHz) δ 8.06−8.03 (m, 1H), 7.99−7.97 (m, 1H), 7.46−7.37 (m, 2H), 7.02 (s, 2H), 5.18 (s, 1H), 4.00 (s, 6H), 3.84 (s, 6H), 3.43 (s, 6H); ^{13}C NMR (75 MHz) δ 154.8 (2C), 150.2 (2C), 148.1, 144.3, 141.5 (2C), 136.7 (2C), 134.5, 132.2 (2C), 128.8, 123.1, 121.5, 98.8 (2C), 60.9 (2C), 59.9 (2C), 56.3 (2C), 49.8; HRMS (ESI-TOF) (*m/z*): calcd for $C_{25}H_{25}NO_8$, $[M+H]^+$ 468.1653; found 468.1654.

*2.2.23. Ethyl 2-(4-methylphenylsulfonamido)-2-(3,4,5-trimethoxy-[1,1'-biphenyl] -2-yl)acetate (**12**).* White solid, mp 108−109 °C; IR (KBr) ν 2936, 2846, 1731, 1346, 1113 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.42−7.41 (m, 3H), 7.34−7.32 (m, 2H), 7.29−7.26 (m, 2H), 7.09 (d, J = 8.0 Hz, 2H), 6.51 (s, 1H), 5.93 (d, J = 8.4 Hz, 1H), 4.97 (d, J = 8.4 Hz, 1H), 4.12-4.06 (m, 2H), 3.88 (s, 3H), 3.84 (s, 3H), 3.83 (s, 3H) , 2.35 (s, 3H), 1.14 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz) δ 170.7, 153.2, 151.4, 142.8, 140.8, 140.1, 137.9, 136.9, 129.7 (2C), 129.2 (2C), 128.2, 127.4 (2C), 127.0 (2C), 121.6,

108.5, 62.0, 60.6, 60.5, 55.9, 54.3, 21.4, 13.9; HRMS (ESI-TOF) (*m/z*): calcd for $C_{26}H_{29}NO_7S$, $[M+Na]^+$ 522.1557; found 522.1562.

3. Results and Discussion

During our investigation, the method starting from 2-formyl biphenyls **6** has attracted our attention [7]. As shown in Scheme 2, it actually is a two-step tandem reaction to convert **6** into **1** in one-pot. Its pathway indicated that Ar^3 is introduced first by a nucleophilic addition of aldehyde of **6**. The intermediate **7** then carries out a Friedel-Crafts reaction to give **1**. Since the aldehyde has low electrophilicity, a highly electron-rich Ar^3H is required to initialize this tandem reaction (such as indoles, thiophenes and polyalkyl or polyalkoxy benzenes, etc). Thus, we proposed that the product **1** may be synthesized by a tandem reaction from an electron-rich biphenyl **8** and an aryl aldehyde **9**, wherein two advantages may be expected: (a) the substrates are much more accessible because the preparation of **8** is much easier than **6**; (b) the products **1** bearing electron-poor Ar^3 can be synthesized because EWG-substituted aryl aldehydes have higher electrophilicity.

As shown in Scheme 3, we disappointingly observed that no reaction occurred when the mixture of 3,4,5-trimethoxybiphenyl (**8a**) and 4-chlorobenzaldehyde (**9a**) were treated by various Lewis acids including $FeCl_3$. This result must be caused by the fact that the aldehyde group in **9a** has a low electrophilicity. It is well-known that *N*-tosyl benzaldimines are significantly more electrophilic than the corresponding benzaldehydes (for example: E = –19.92 for PhCHO, E = –11.50 for PhCH=NTs) [9]

and they can efficiently undergo further Lewis acid-catalyzed aza-Friedel-Crafts reactions [10]. Thus, a $FeCl_3$-catalyzed reaction between **8a** and *N*-tosyl 4-chlorobenzaldimine (**10a**) was tested. To our delight, the expected product **1a** was obtained in 64% yield, but the expected intermediate **11a** was not isolated at all. These results indicated that the intermolecular aza-Friedel-Crafts between **8a** and **10a** was a rate-determining step, while the intramolecular Friedel-Crafts of the intermediate **11a** was a fast step.

Since **10a** was pre-made by a $FeCl_3$-catalyzed dehydration between **9a** and $TsNH_2$ [11]. we were encouraged to develop a three-step tandem synthesis of **1a** starting from **9a** as shown in Scheme 4. Unfortunately, when the mixture of **8a**, **9a** and $TsNH_2$ was treated by $FeCl_3$, **1a** and **10a** were isolated in 19% and 47% yields, respectively. This result may be caused by the fact that one molecule of H_2O was formed *in situ* from step 1 and it then functioned as a Lewis base to strongly coordinate with $FeCl_3$, by which the catalytic activity of $FeCl_3$ was reduced significantly. This hypothesis was proved by adding one molecule of H_2O into the reaction described in Scheme 3. As a result, the yield of **1a** was decreased from 64% to 13%.

Therefore, our attention was directed to the anhydrous methods for the synthesis of *N*-tosylimines. Based on the well understanding the pathway of two methods reported by Weinreb [12] and Trost [13], respectively, we recently developed a practical method to convert aryl aldehyde **9** into *N*-tosyl arylaldimines **10** without the

formation of H_2O [14]. As shown in Scheme 5, the reaction was achieved conveniently by heating the mixture of an aryl aldehyde **9** and TsNCO in a solvent or in neat form. Thus, we realized that it is very suitable for our tandem reaction and a group of experiments were tested under the similar conditions. As was expected, the desired product **10a** was obtained in 83% yield when the mixture of **9a** and TsNCO was heated at 80 ^oC for 2 h. In the presence of $FeCl_3$, the same reaction could be finished within 1 h, that indicated that this reaction can be catalyzed by $FeCl_3$ also. To our delight, the target product **1a** was obtained in 61% yield by heating the mixture of **8a**, **9a**, TsNCO and $FeCl_3$ at 80 ^oC for 15 h.

Next, the conditions for the tandem synthesis of **1a** were optimized by using different catalysts. As shown in Table 1, many Lewis acids proved to be unsuitable catalysts (entries 2-6). But, $Sc(OTf)_3$ gave a higher yield of **1a** compared to $FeCl_3$ (entry 7). To our delight, $Cu(OTf)_2$ showed the best catalytic activity to give the highest yield of **1a** (entry 8). The yield of **1a** was not improved by using different ratios of $Cu(OTf)_2$ and different temperatures (entries 9-11). Thus, the entry 8 was assigned as the standard conditions.

As shown in Scheme 6, a $Cu(OTf)_2$-catalyzed three-step tandem reaction for efficient synthesis of **1a** was established thus far, which includes an anhydrous preparation of *N*-tosylimine, an aza-Friedel-Crafts reaction and a normal Friedel-Crafts reaction. It also is a TsNCO-mediated tandem reaction because TsNCO involved in each steps but it did not appeared in molecule of **1a**. In step 1, an anhydrous preparation of **10a** was established by using it as a substrate. In step 2, the

imine group of **10a** was activated by its tosyl group. In step 3, $TsNH_2$ served as a neutral and low nucleophilic leaving group.

Finally, the scope of our tandem method was tested. As shown in Scheme 7, all tested products were obtained smoothly under the standard conditions. The *ortho*-substituted benzaldehydes gave the products (**1c**, **1f**, **1p**-**1r**, and **1t**) in relatively lower yields caused by steric effect. EDG-substituted benzaldehydes gave the products (**1h** and **1i**) in relatively lower yields caused by electronic effects. But, their yields were elevated significantly by using two equivalents of aldehydes and TsNCO. As was expected, EWG-substituted benzaldehydes gave the corresponding 9-arylfluorenes (**1j**-**1n**) in excellent yields because the *in situ* produced imine group was activated by both tosyl group and EWG-substituent. The importance of our method was enhanced greatly by his result because it is a rare method[5e] to synthesize the electron-poor Ar^3 substituted 9-arylflurenes. Almost quantitative yields of **1u**-**1w** were obtained from the substrates bearing trimethoxy-substituted Ar^2. Under the standard conditions, **1a** was prepared in 92% yield on a 5-gram scale.

Like the existed methods in literature, still there are limitations to our method. For example, 4-methoxy-biphenyl (**8e**) or 3,4,5-tirmethylbiphenyl (**8f**) did not carry out the reaction possibly caused by their lower nucleophilicity compared to **8a**. Although 4-nitro- and 3-nitro-benzaldehydes (**9j** and **9k**) were excellent substrates, 2-nitro-benzaldehyde (**9s**) did not carry out the reaction possibly caused by its steric structure. As shown in Scheme 8, the reaction between **8a** and ethyl glyoxylate (**9t**) gave an only partial reaction product **12** in 98% yield. This result gave a strong

support to our hypothesis that **11a** (see: Schemes 3, 4 and 6) was an intermediate in our method.

Conclusions

In conclusion, three works have been made in this article. First, a novel strategy to use aldehyde and biphenyl as substrates for the synthesis of 9-arylfluorenes was proposed. Second, the proposed strategy was realized by using an anhydrous preparation of *N*-tosyl arylaldimines as a key step. Third, a $Cu(OTf)_2$-catalyzed and TsNCO-mediated three-step tandem synthesis of 9-arylfluorenes was developed, by which a series of structurally novel 9-arylfluorenes, especially electron-poor 9-aryl substituted fluorenes, were synthesized conveniently by using much more accessible starting materials. The method is a valuable addition and choice to the synthesis of 9-arylfluorenes.

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Figure Captions

Figure 1. Some important compounds containing the structural unit of **1**.

Scheme 1. Three major methods for the preparation of **1**.

Scheme 2. A proposed strategy for the synthesis of **1** from **8** and **9**.

Scheme 3. Two-step tandem synthesis of **1a** from **8a** and **10a**.

Scheme 4. A failed three-step tandem synthesis from **8a**, **9a** and $TsNH_2$.

Scheme 5. Conditional tests for tandem synthesis of **1a**.

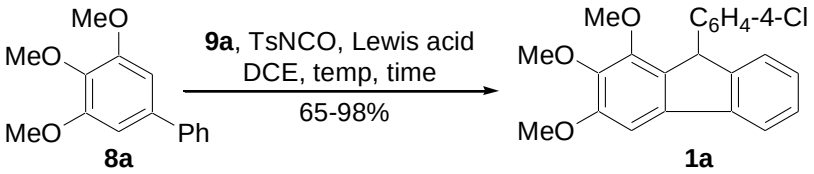
Scheme 6. Proposed pathway for our tandem reaction.

Scheme 7. The scope of our tandem method.

Scheme 8. An indirect evidence for the intermediate **11a**.

Tables

Table 1. Optimization of the reaction conditions [a]



Entry	Lewis acid (mol%)	temp (°C)	time (h)	Yield of **1a** (%)[b]
1	$FeCl_3$ (10)	80	15	64
2	$Ce(OTf)_3$ (10)	80	15	0
3	$Zn(OTf)_2$ (10)	80	15	14
4	$FeBr_3$ (10)	80	15	23
5	$Yb(OTf)_3$ (10)	80	15	25
6	$Bi(OTf)_3$ (10)	80	15	27
7	$Sc(OTf)_3$ (10)	80	15	75
8	$Cu(OTf)_2$ (10)	80	15	93
9	$Cu(OTf)_2$ (20)	80	15	90
10	$Cu(OTf)_2$ (5)	80	15	73
11	$Cu(OTf)_2$ (10)	70	24	61

a The mixture of **8a** (0.5 mmol), **9a** (0.6 mmol) and TsNCO (0.6 mmol) in DCE (2 mL) was heated in the presence of a Lewis acid for 15 h.

b Isolated yields were obtained.