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Synthesis of Unsymmetrically Disubstituted Tetraphenylenes via Carbonyl-Directed C–H Functionalization

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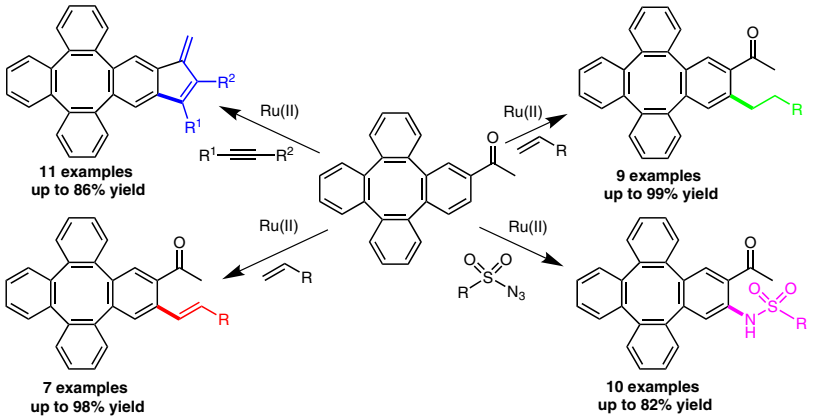

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Abstract A new strategy for the synthesis of unsymmetrically disubstituted tetraphenylenes from 2-acetylbiphenylene has been developed via ruthenium-catalyzed C–H functionalization. Four reactions, including alkenylation–cyclization, alkenylation, alkylation, and amidation, were achieved. The reactions provide easy access to a variety of unsymmetrically disubstituted tetraphenylene derivatives, which could accelerate research on the appliation of tetraphenylenes.

Key words tetraphenylene, C–H activation, palladium, alkenation, alkylation, amidation

Tetraphenylene is a molecule containing four benzene rings that are *ortho*-annulated to form an eight-membered ring (Figure 1).[1] It is nonplanar and adopts a saddle-shaped structure.[2] Although tetraphenylene is achiral, substitution may break the D_{2d} symmetry of the parent tetraphenylene and therefore substituted tetraphenylenes can be chiral molecules.[3,4] Owing to their unique geometry, tetraphenylene and its derivatives are not only of great theoretical interest, more importantly, there exist a wide range of potential applications of these compounds in the fields such as materials science,[5] supramolecular chemistry,[6] and asymmetric catalysis.[7]

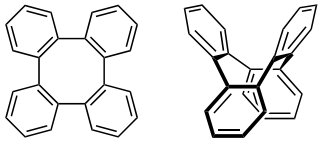

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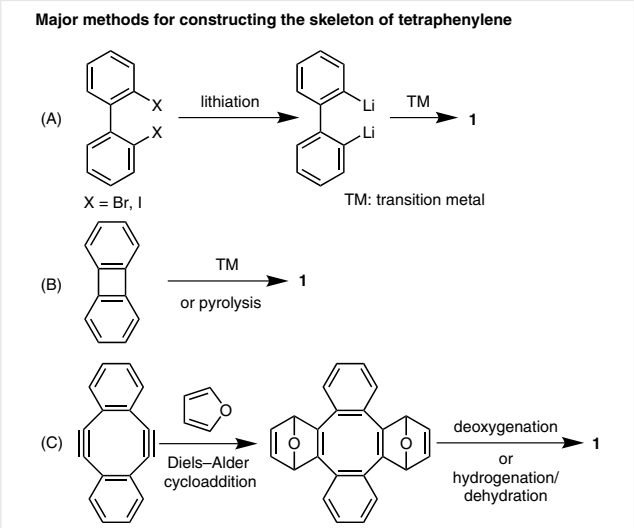
Figure 1 Tetraphenylene and its saddle-shape structure

Currently, the skeleton of tetraphenylene is constructed primarily via the following methods (Scheme 1).[6b,8] (1) Homocoupling of 2,2′-dihalobiphenyl. This method involves lithiation of dihalobiphenyl and subsequent transition-metal-mediated homocoupling of 2,2′-dimetalbiphenyl.[9] (2) Homocoupling of biphenylene. In this method, 2,2′-dimetalbiphenyls are formed via transition-metal-mediated C–C bond cleavage of biphenylene.[10] In addition, biphenylene can undergo high-temperature pyrolysis to form tetraphenylene.[11] Both of these two methods involve homocoupling reactions, so they are restricted to the synthesis of symmetric tetraphenylene derivatives. Furthermore, these two methods have very limited substrate scopes, because the first reaction suffers from the harsh conditions, and for the second method, the synthesis of substituted biphenylenes is often challenging. Although a method via Diels–Alder reaction has been developed, it is also more suitable for the synthesis of symmetric tetraphenylene derivatives.[12] In summary, the current major methods are primarily applicable to the synthesis of symmetrically substituted tetraphenylene, which hampers research on the properties and application of tetraphenylene derivatives. Although several direct derivatization reactions of teraphenylene (including bromination,[13] nitration,[13] and acylation reaction[14]) have been reported, these reactions are only applicable to the synthesis of monosubstituted tetraphenylene. Furthermore, it is hard to predict the positions of substitution for the bromination and nitration reactions. Therefore, it is important to develop new strategies for the synthesis of tetraphenylene derivatives, especially for unsymmetrically multiple-substituted ones.

In the past decade, C–H functionalization has attracted considerable interest, and a great number of reactions have been developed.[15] C–H functionalization can avoid the use

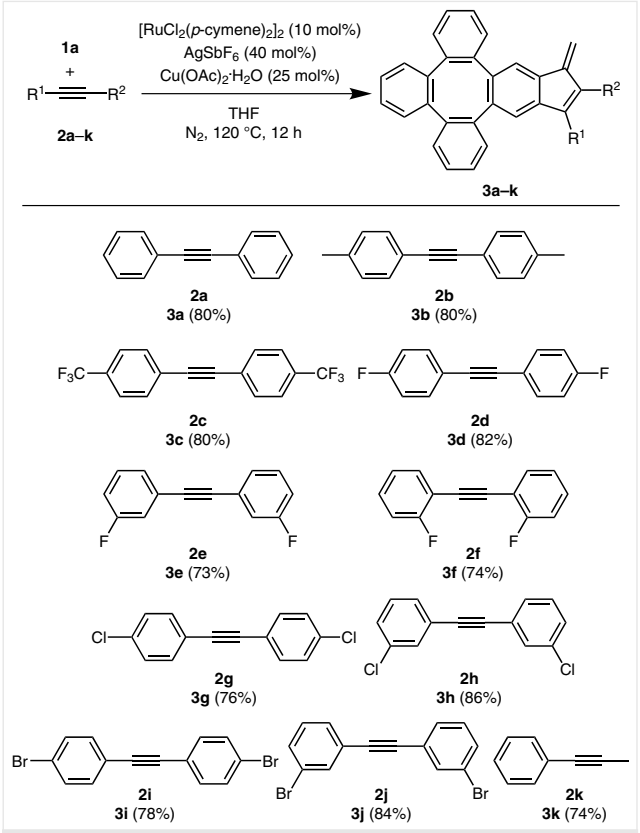


Scheme 1 Synthetic methods for tetraphenylene

of prefunctionalized starting materials and reduce the formation of unnecessary chemical waste. More importantly, it provides novel and efficient strategies for organic synthesis. Attracted to these attractive features, we set out to develop new strategies for the synthesis of unsymmetrically substituted tetraphenylenes via C–H functionalization. Herein, we report novel synthetic protocols for disubstituted tetraphenylenes via ruthenium-catalyzed C–H activation.

Most of the current C–H functionalization reactions rely on the use of directing groups. The directing groups can deliver the catalyst to a desirable C–H bond, and consequently high regioselectivity can be achieved. The directing group strategy offers a great opportunity for the direct derivatization of tetraphenylenes. Currently, a variety of directing groups have been developed.[16] In this context, the carbonyl group is particularly desirable because it is not only a very common functional group in organic molecules, and can also be transformed into other functionalities.[17] Furthermore, 2-acetyltetraphenylene (**1a**) can be readily prepared via the acetylation of tetraphenylene with acetyl chloride.[14] Thus, we selected the acetyl group as the directing group for C–H functionalization of tetraphenylene.

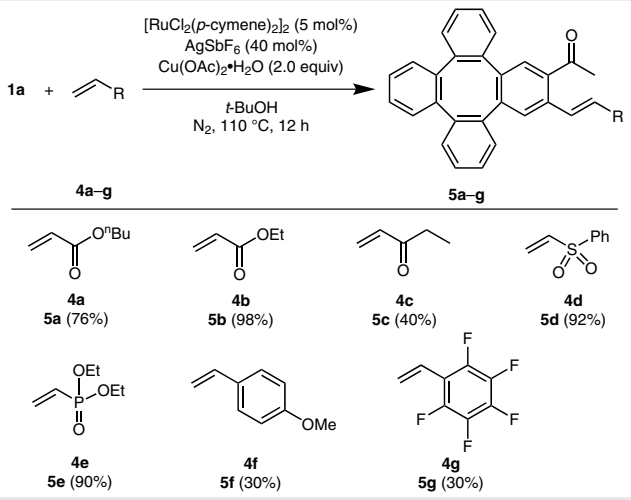
We first investigated the reaction of 2-acetyltetraphenylene with alkynes. Carbonyl-directed C–H functionalization with alkynes has been reported.[18] After surveying different conditions[19] based on the reaction developed by Jeganmohan and coworkers,[18a] we found that **1a** could react with 1,2-diphenylethyne efficiently in the presence of 10 mol% $[RuCl_2(p\text{-cymene})_2]_2$, 40 mol% $AgSbF_6$, and 25% $Cu(OAc)_2{\cdot}H_2O$ in THF at 120 °C, affording a benzofulvene derivative as the final product in 80% yield (Scheme 2). The reaction consists of the following steps: carbonyl-directed C–H alkenylation with the alkyne, cyclization via the insertion of the carbonyl group into the resulting ruthenium–alkenyl bond, and the final dehydration. The C–H activation selectively took place at the less hindered position. This protocol is applicable to other alkynes. Therefore, 1,2-diphenylethynes bearing electron-donating or electron-withdrawing groups (methyl or trifluoromethyl) are suitable, yielding the corresponding benzofulvene derivatives in similar yields. The substrates with two fluoro groups at *ortho*, *meta*, or *para* positions were also reactive. It is noted that the chloro and bromo groups were well tolerated in the reaction. The chloro and bromo groups can be converted into other functionalities, so these reactions provide new tools for the synthesis of tetraphenylene derivatives. An unsymmetrically substituted alkyne was also examined. The C–H functionalization for 1-phenylpropyne occurred at the carbon adjacent to the methyl group selectively, so only one isomer was formed in the reaction.[18a,c]



Scheme 2 Ruthenium(II)-catalyzed C–H functionalization of 2-acetyltetraphenylene with alkynes

Next, we studied the C–H alkenylation of **1a** with alkenes (Scheme 3).[20] Butyl acrylate (**4a**) was chosen as the initial alkene for condition optimization.[19,20a] Compound **1a** was alkenylated using catalyst $[RuCl_2(p\text{-cymene})_2]_2$ with the aid of $AgSbF_6$ and $Cu(OAc)_2{\cdot}H_2O$ in *tert*-butanol, and the alkenylated product **5a** was formed in 76% yield. Other alkenes containing electron-withdrawing groups were also examined. While the reaction with butenone (**4c**) was low-

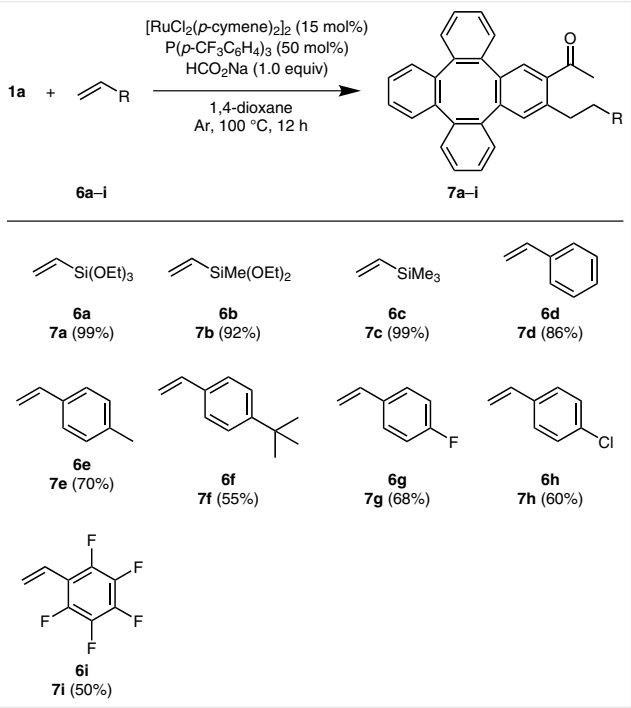
yielding, vinylsulfonylbenzene (**4d**) and diethyl vinylphosphonate (**4e**) were introduced into 2-acetyltetraphenylene in excellent yields. Both electron-rich and electron-deficient styrene derivatives **4f** and **4g** were reactive, albeit in low yields.



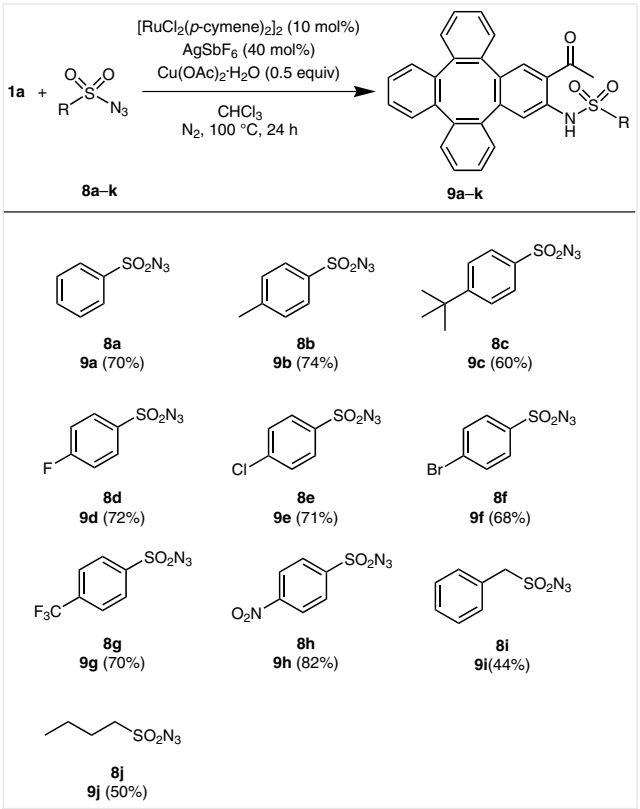
Scheme 3 Ruthenium(II)-catalyzed C–H alkenylation of 2-acetyltetraphenylene with alkenes

C–H bonds can react with alkenes to form alkylation products with ruthenium catalysis.[21] Therefore, we tried to develop a new method for the synthesis of alkylated tetraphenylenes. Gratefully, **1a** could react with triethoxy(vinyl)silane (**6a**) to form the corresponding alkylated product **7a** under the reaction conditions developed by Darses and coworkers,[21b] and the yield was improved to 99% after optimization of reaction conditions (Scheme 4).[19] With the optimal protocol in hand, we probed the substrate scope with regard to alkenes. Therefore, diethoxy(methyl)(vinyl)silane (**6b**) and trimethyl(vinyl)silane (**6c**) underwent the alkylation reaction highly efficiently, and the corresponding alkylated products **7b** and **7c** were formed quantitatively. A range of styrenes, including those containing fluoro and chloro groups, were suitable. It should be mentioned that the alkylation reaction took place selectively at the less hindered positions.

The amino group is ubiquitous in organic molecules and can be modified into various functionalities. The installation of amino groups onto tetraphenylene may endow it with novel properties and allow for further transformation. The carbonyl-directed C–H amidation has been disclosed.[22] On the basis of the amidation protocol reported by the Jiao's and Sahoo's group,[22a,b] we successfully developed an amidation reaction of **1a** with sulfonyl azides. The optimal yield was obtained after the condition survey with benzenesulfonyl azide (**8a**). We first examined the substrate scope of the amidation protocol with arylsulfonyl azides. As shown in



Scheme 4 Ruthenium(II)-catalyzed C–H alkylation of 2-acetyltetraphenylene with alkenes



Scheme 5 Ruthenium(II)-catalyzed C–H amidation of 2-acetyltetraphenylene with sulfonyl azides

Scheme 5, benzenesulfonyl azides bearing a *para*-methyl or *tert*-butyl group (**8b** and **9b**) underwent the amidation reaction in medium yields. Fluoro, chloro, and bromo groups were tolerated in the reaction (**8d**,**e**,**f**), and the substrates bearing trifluoromethyl or nitro group were also reactive under the optimal conditions (**8g**,**h**). The reactivity of aliphatic sulfonyl azides was also examined. Benzyl and butyl sulfonyl azides **8i** and **8j** underwent the amidation reaction with **1a** to form the corresponding amidation products **9i** and **9j**.

In conclusion, the synthesis of unsymmetrically substituted tetraphenylenes is still challenging, which hampers research on the application of tetraphenylenes. We have developed a new strategy for directly derivatizing tetraphenylene via carbonyl-directed C–H functionalization, and four types of ruthenium-catalyzed reactions have been developed.[23–26] This facile method provides easy access to a variety of tetraphenylene derivatives, which could accelerate research on tetraphenylenes.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561862.

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(23) **Ru(II)-Catalyzed C–H Functionalization of 1a with 2a**

A 25 mL Schlenk-type tube (with a Teflon high-pressure valve and side arm) was charged with compound **1a** (34.6 mg, 0.10 mmol), **2a** (35.6 mg, 0.20 mmol), $Cu(OAc)_2·H_2O$ (5.0 mg, 0.025 mmol), $[RuCl_2(p\text{-cymene})]_2$ (6.1 mg, 0.01 mmol), $AgSbF_6$ (13.7 mg, 0.04 mmol), and THF (1 mL). The reaction tube was evacuated and back-filled with N_2 (3×, ballon). After the reaction mixture was stirred at 120 °C for 12 h, it was allowed to cool down to room temperature. The reaction mixture was diluted with EtOAc (20 mL), and then filtered through a pad of Celite. The filtrate was washed with brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel preparative TLC to give the corresponding product **3a**; yellow solid, 80% yield; mp 161–162 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52 (s, 1 H), 7.31–7.13 (m, 23 H), 6.19 (s, 1 H), 5.69 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.19, 141.85, 141.80, 141.66, 141.62, 141.55, 141.52, 141.46, 139.15, 138.06, 135.18, 134.48, 134.30, 130.61, 129.39, 129.12, 129.09, 129.06, 128.99, 128.22, 128.01, 127.40, 127.29, 127.26, 127.21, 126.95, 120.86, 120.80, 114.44. HRMS (ESI-TOF): *m/z* calcd for $C_{40}H_{26}Na^+$: 529.1927 $[M + Na]^+$; found: 529.1926.

(24) **Ru(II)-Catalyzed C–H Functionalization of 1a with 4a**

A 25 mL Schlenk-type tube (with a Teflon high-pressure valve and side arm) was charged with compound **1a** (34.6 mg, 0.10 mmol), **4a** (25.6 mg, 0.20 mmol), $Cu(OAc)_2·H_2O$ (39.9 mg, 0.20 mmol), $[RuCl_2(p\text{-cymene})]_2$ (6.1 mg, 0.01 mmol), $AgSbF_6$ (13.7 mg, 0.04 mmol), and *t*-BuOH (1 mL). The reaction tube was evacuated and back-filled with N_2 (3×, ballon). After the reaction mixture was stirred at 110 °C for 12 h, it was allowed to cool down to room temperature. The reaction mixture was diluted with EtOAc (20 mL), and then filtered through a pad of Celite. The filtrate was washed with brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel preparative TLC to give the corresponding product **5a**; white solid, 76% yield; mp 195–196 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (d, *J* = 15.9 Hz, 1 H), 7.55 (s, 1 H), 7.42 (s, 1 H), 7.35–7.29 (m, 6 H), 7.21–7.14 (m, 6 H), 6.28 (d, *J* = 15.9 Hz, 1 H), 4.18 (t, *J* = 6.7 Hz, 2 H), 2.58 (s, 3 H), 1.70–1.16 (m, 2 H), 1.44–1.38 (m, 2 H), 0.94 (t, *J* = 7.4 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.38, 166.53, 145.43, 143.35, 142.85, 141.51, 141.28, 140.84, 140.78, 139.82, 139.78, 136.86, 133.84, 130.17, 129.36, 129.31, 129.26, 129.20, 129.16, 128.73, 128.63, 128.07, 128.02, 127.58, 127.54, 127.49, 127.46, 120.99, 64.38, 30.67, 29.14, 19.12, 13.69. HRMS (ESI-TOF): *m/z* calcd for $C_{33}H_{28}O_3Na^+$: 495.1931 $[M + Na]^+$; found: 495.1925.

(25) **Ru(II)-Catalyzed C–H Functionalization of 1a with 6a**

A 25 mL septum-capped vial equipped with a magnetic stir bar was charged with compound **1a** (34.6 mg, 0.10 mmol), **6a** (57.0 mg, 0.30 mmol), HCO_2Na (13.6 mg, 0.20 mmol), $[RuCl_2(p\text{-cymene})]_2$ (6.1 mg, 0.01 mmol), and $P(p\text{-}CF_3C_6H_4)_3$ (23.3 mg, 0.05 mmol). The vial was closed and evacuated under vacuum during 10 min and placed under an argon atmosphere. Degassed dioxane (1 mL) was added, and the reaction vial was evacuated and back-filled with Ar (3×, ballon). After the reaction mixture was stirred at 100 °C for 12 h, it was allowed to cool down to room temperature. The reaction mixture was diluted with EtOAc (20 mL), and then filtered through a pad of Celite. The filtrate was washed with brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel preparative TLC to give the corresponding product **7a**; amorphous, 99% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 (s, 1 H), 7.33–7.27 (m, 6 H), 7.20–7.14 (m, 6 H), 7.12 (s, 1 H), 3.80 (q, *J* = 7.0 Hz, 6 H), 3.04–2.85 (m, 2 H), 2.54 (s, 3 H), 1.20 (t, *J* = 7.0 Hz, 9 H), 1.01–0.94 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.55, 144.82, 143.87, 141.62, 141.26, 141.19, 141.15, 140.59, 140.48, 139.02, 136.16, 131.53, 130.17, 129.32, 129.30, 129.22, 129.10, 128.87, 127.68, 127.58, 127.39, 127.32, 58.31, 29.75, 26.94, 18.28, 12.48. HRMS (ESI-TOF): *m/z* calcd for $C_{34}H_{36}O_4SiNa^+$: 559.2275 $[M + Na]^+$; found: 559.2270.

(26) **Ru(II)-Catalyzed C–H Functionalization of 1a with 8a**

A 25 mL Schlenk-type tube (with a Teflon high pressure valve and side arm) was charged with compound **1a** (34.6 mg, 0.10

mmol), **8a** (54.9 mg, 0.30 mmol), $Cu(OAc)_2 \cdot H_2O$ (10.0 mg, 0.05 mmol), $[RuCl_2(p\text{-cymene})]_2$ (6.1 mg, 0.01 mmol), $AgSbF_6$ (13.7 mg, 0.04 mmol), and $CHCl_3$ (1 mL). The reaction tube was evacuated and back-filled with N_2 (3×, ballon). After the reaction mixture was stirred at 100 °C for 24 h, it was allowed to cool down to room temperature. The reaction mixture was diluted with EtOAc (20 mL), and then filtered through a pad of Celite. The filtrate was washed with brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel preparative TLC to give the corresponding product **9a**; white solid, 70% yield; mp 244–245 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.35 (s, 1 H), 7.72 (d, *J* = 7.4 Hz, 2 H), 7.56 (s, 1 H), 7.52 (s, 1 H), 7.49 (t, *J* = 7.5 Hz, 1 H), 7.37–7.26 (m, 8 H), 7.20–7.12 (m, 4 H), 7.09–7.07 (m, 1 H), 6.99–6.97 (m, 1 H), 2.46 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.99, 148.46, 141.74, 140.99, 140.90, 140.73, 139.74, 139.58, 139.11, 138.67, 136.64, 132.88, 132.32, 129.32, 129.26, 129.24, 129.00, 128.83, 128.80, 128.26, 128.22, 127.90, 127.51, 127.48, 127.47, 127.28, 121.55, 119.98, 28.08. HRMS (ESI-TOF): *m/z* calcd for $C_{32}H_{23}NO_3SNa^+$: 524.1291 $[M + Na]^+$; found: 524.1294.