4-Aryl- and 4-Vinyl-2,2-Dialkyl-3-chromenes from Tertiary 3-(*o*-Bromophenyl)propynols via a Palladium-Catalyzed Hydroarylation/Hydrovinylation–Cyclization Sequence

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Abstract: 4-Aryl- and 4-vinyl-2,2-dialkyl-3-chromenes were prepared from tertiary 3-(*o*-bromophenyl)propynols and aryl iodides or vinyl triflates through a one-pot process, which involves the addition of *t*-BuONa, dppf and, where appropriate, fresh $Pd(OAc)_2$ to the crude mixture resulting from the hydroarylation or hydrovinylation step [$Pd(OAc)_2$, Et_3N, HCOOH, Bu_4NCl, toluene]. In general, 4-aryl- and 4-vinyl-2,2-dialkyl-3-chromenes are obtained with high regioselectivity and overall yields range from satisfactory to high. Vinyl triflates tend to give higher yields than aryl iodides.

Key words: chromenes, palladium catalysis, cyclization, hydrovinylation, hydroarylation

The palladium-catalyzed hydroarylation and hydrovinylation of disubstituted alkynes with aryl and vinyl halides or triflates represents a valuable tool for the addition of a carbon sp^2 unit and a hydrogen to a carbon–carbon triple bond.[1] With unsymmetrical alkynes, steric and coordinating effects appear to play a major role in controlling the regioselectivity of the process. Solvents[2] and other reaction parameters such as temperature, the presence or absence as well as the nature of phosphine ligands, and the nature of the sp^2 donor have also been found to influence the regiochemical outcome. In general, the reaction is stereoselective and overall *cis*-addition derivatives are usually obtained as the main products. Therefore, the addition to alkynes with suitable nucleophilic and electrophilic centers close to the acetylenic system can be followed by a cyclization step. We have taken advantage of this addition–cyclization strategy to develop new versatile routes to substituted butenolides,[3] quinolines,[4] coumarins, and chromanols.[5]

More recently, we reported the synthesis of chromene derivatives through the hydroarylation/hydrovinylation–cyclization of tertiary 3-(*o*-acetoxyaryl)- and 3-(*o*-benzoyloxyaryl)propynols.[6] Though this process gives good overall yields with a variety of aryl iodides and vinyl triflates, it requires a stepwise protocol involving the protection of the starting material, isolation of hydroarylation/hydrovinylation products, deprotection of the phenolic oxygen, and cyclization. Therefore, considering the general trend towards improving the environmental acceptability of synthetic processes and that one of the more convenient strategies is limiting the number of distinct steps, we decided to investigate the development of a simplified one-pot procedure, with beneficial effects on costs, time, energy, raw materials, and waste.

The presence of the 2,2-dimethyl-3-chromene motif in a variety of biologically active compounds has led to a continuing interest in the chromene ring system.[7] The 2,2-dimethyl-3-chromene motif is commonly found in potassium channel activators with smooth-muscle relaxant activity in a variety of cardiovascular and bronchopulmonary diseases (cromakalim,[8] Ro 31-6930,[9] and several other compounds with the 2,2-dimethyl-3-chromene moiety have been tested[10]). The chromene scaffold is present in a novel class of selective non-steroidal glucocorticoid receptor (GR) antagonists.[11] Moreover, chromenes containing substituents at the C-4 position may act as potent retinoic acid receptor α-selective antagonists[12] and 4-aryl-4*H*-chromenes have been recently identified as potent apoptosis inducers.[13]

This justifies efforts to develop new more efficient synthetic procedures towards this class of compounds from readily available starting materials by simple procedures. Herein we report the results of this study.

Readily available tertiary 3-(*o*-bromophenyl)propynols **1** appeared to us particularly suited for the development of a one-pot protocol for the preparation of chromene derivatives containing 4-aryl and 4-vinyl substituents. The whole process would proceed through a palladium-catalyzed hydroarylation/hydrovinylation–cyclization, with the cyclization step involving an intramolecular Buchwald–Hartwig C–O bond-forming reaction (Scheme 1).

Disubstituted alkyne **1a** ($R^1 = R^2 = Me$) and 1-chloro-3-iodobenzene **2a** were selected as the model system. Compound **1a** – prepared in 93% yield by chemoselective Sonogashira cross-coupling of commercially available 1-bromo-2-iodobenzene with 2-methyl-3-butyn-2-ol at room temperature, in DMF, in the presence of $PdCl_2(PPh_3)_2$, CuI and *i*-Pr_2NH as the base – was reacted with 2.4 equivalents of **2a** under conditions previously developed by us to give regio- and stereoselectively the hydroarylated alkene **3a** (Scheme 2).

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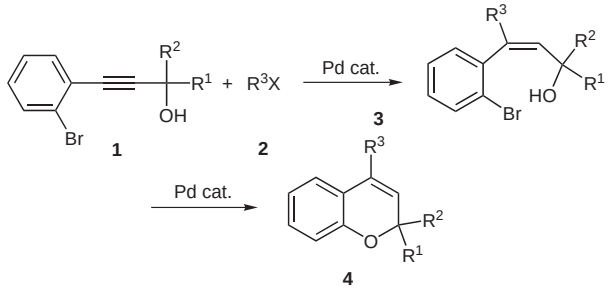
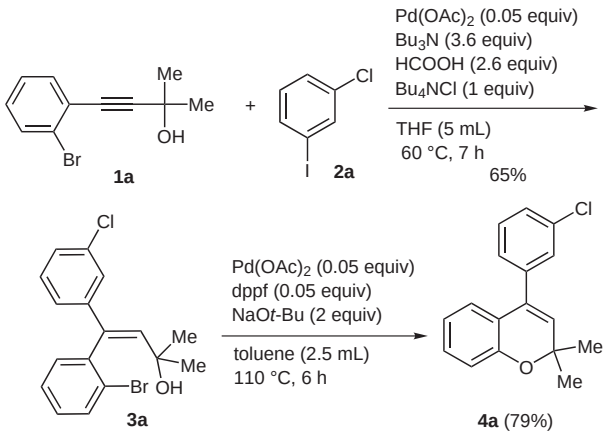


Scheme 1

Compound **3a** was isolated as a single isomer. Its stereochemistry (*Z*; *cis* adduct) and regiochemistry are in agreement with our previous studies[1] and were assigned by NOESY experiments. Compound **3a** (0.29 mmol) was next converted to the corresponding chromene derivative **4a** under the conditions developed by Buchwald et al.[14] for intramolecular C–O bond formation (Scheme 2).

Subsequently, we found that **4a** could be conveniently prepared through a process in which the cyclization step is carried out on the crude mixture resulting from the hydroarylation step, after extraction and evaporation of the solvent. Using this procedure, **4a** was isolated in a slightly higher overall yield (56%) than that obtained via the stepwise protocol (51%).



Scheme 2

This procedure, which omits the isolation of addition products, was extended to include other substrates (Table 1). Two different procedures were used for the hydroarylation/hydrovinylation step; Procedure A[15] (applied to aryl iodides): $Pd(OAc)_2$, Bu_3N, HCOOH, Bu_4NCl, THF, 60 °C and Procedure B[16] (applied to vinyl triflates): $Pd(OAc)_2$, HCOOK, DMF, 40 °C.

Table 1 Palladium-Catalyzed Synthesis of 4-Aryl- and 4-Vinyl-2,2-dialkyl-3-chromenes **4**[a]

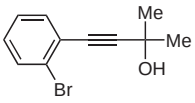
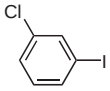
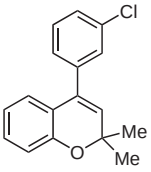
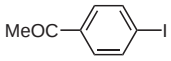
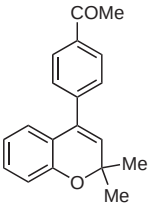
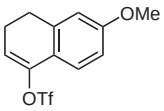
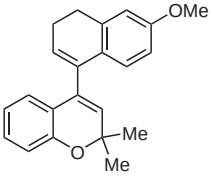
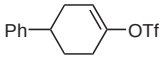
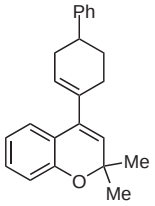
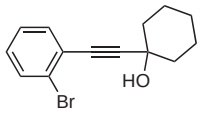
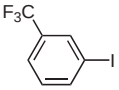
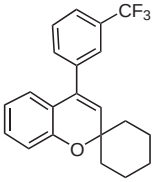
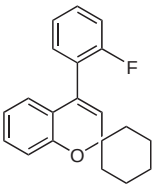
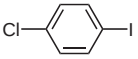
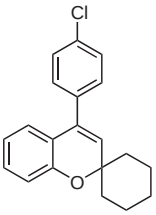
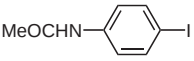
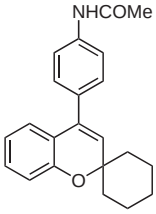
Entry	Alkyne **1**		R^3X **2**		Procedure	Time (h)[b]	Chromene **4**		Yield (%)[c]
1		**1a**		**2a**	A	7 (6)		**4a**	56
2		**1a**		**2b**	A	16 (7)		**4b**	57
3		**1a**		**2c**	B	19 (22)		**4c**	40
4		**1a**		**2d**	B	17 (5)		**4d**	40

Table 1 Palladium-Catalyzed Synthesis of 4-Aryl- and 4-Vinyl-2,2-dialkyl-3-chromenes **4**[a] (continued)

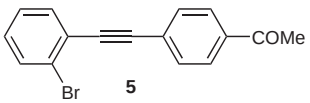
Entry	Alkyne **1**	R^3X **2**	Procedure	Time (h)[b]	Chromene **4**	Yield (%)[c]
6	 **1b**	 **2e**	A	40 (15)	 **4e**	50
5	**1b**	 **2f**	A	25 (9)	 **4f**	58
6	**1b**	 **2g**	A	3 (16)	 **4g**	55
7	**1b**	 **2h**	A	20 (24)	 **4h**	77

[a] All reactions were conducted under a nitrogen atmosphere. Procedure A (aryl iodides): **1** (1 equiv), **2** (2.4 equiv), Bu_3N (3.6 equiv), HCOOH (2.6 equiv), Bu_4NCl (1 equiv), $Pd(OAc)_2$ (0.05 equiv), THF, 60 °C, work-up, then *t*-BuONa (2 equiv), $Pd(OAc)_2$ (0.05 equiv), dppf (0.05 equiv), toluene, 110 °C. Procedure B (vinyl triflates): **1** (1.2 equiv), **2** (1 equiv), HCOOK (2 equiv), $Pd(OAc)_2$ (0.05 equiv), DMF, 40 °C, work-up, then as for procedure A.

[b] Figures in parentheses refer to the cyclization step.

[c] Overall isolated yields for isolated products.

Though the results shown in Table 1 were interesting, providing distinct advantages over our previous procedure,[6] to simplify further the synthetic protocol, we attempted the preparation of chromenes **4** from **1** through a pseudo-domino process[17] which would avoid the work-up step. However, under the best hydroarylation conditions developed, no cyclization products were observed with our model system even with prolonged reaction times or increasing the temperature after completion of the hydroarylation step. Even attempts to combine cyclization with hydroarylation conditions met with failure, for example, when **1a** was treated with 2 equivalents of *p*-iodoacetophenone, 2 equivalents of HCOOK, 2 equivalents of *t*-BuONa, 0.05 equivalents of $Pd(OAc)_2$, 0.05 equivalents of dppf in toluene at 110 °C for 18 hours, no evidence of the chromene product was observed, the main product being the diarylalkyne **5** (formed via removal of the alcohol group as acetone followed by a coupling reaction)[18] in 36% isolated yield. It is very likely that incompatibilities between the two mechanistically unrelated catalytic cycles prevent any pseudo-domino process.



5

Figure 1

Therefore, we decided to return to the procedure requiring a work-up between the two transformations with the task of making it more attractive synthetically by omitting the work-up step. After some experimentation we were pleased to find that the reaction of **1a** with 2 equivalents of *p*-iodoacetophenone **2b**, 3 equivalents of Et_3N, 2 equivalents of HCOOH, and 0.025 equivalents of $Pd(OAc)_2$ in toluene at 60 °C for 16 hours, in the absence of phosphine ligands,[19] resulted in the formation of the hydroarylation product with almost complete conversion of the starting alkyne and that the direct addition of 4 equivalents of *t*-BuONa, 0.025 equivalents of $Pd(OAc)_2$, and 0.05 equiv of dppf to the reaction mixture (without work-up) led to the isolation of **4b** in 57% overall yield after 6 hours at 110 °C.

Control experiments were performed to evaluate the effectiveness of this protocol and some of the more significant results are as follows. The presence of dppf was found to hamper the hydroarylation step. Indeed, the hydroarylation derivative, **3b**, was isolated in only 42% yield when the hydroarylation of **1a** with **2b** was carried out using 3 equivalents of Et_3N, 2 equivalents of HCOOH, 0.05 equivalents of $Pd(OAc)_2$, and 0.05 equivalents of dppf in toluene at 60 °C for 24 hours (**1a** was recovered in 45% yield). Higher catalyst loading in both the hydroarylation and cyclization steps did not improve the yield significantly (Table 2, entry 2). Omitting the addition of fresh $Pd(OAc)_2$ in the cyclization step led to the isolation of chromene **4b** in low yield (Table 2, entry 3), most likely due to the irreversible precipitation of the majority of the catalyst during hydroarylation.

Table 2 Palladium-Catalyzed One-Pot Synthesis of 4-Aryl- and 4-Vinyl-2,2-dialkyl-3-chromenes **4**[a]

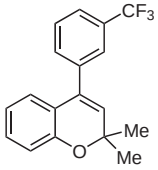
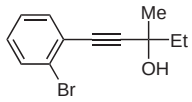
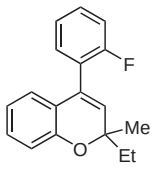
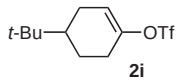
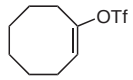
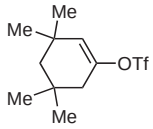
Entry	Alkyne	R^3X	Bu_4NCl (equiv)	Pd 1st step (equiv)	Pd 2nd step (equiv)	Time (h)[b]	Chromene **4**	Yield (%)[c]
1	**1a**	**2b**	–	0.025	0.025	16 (7)	**4b**	57
2	**1a**	**2b**	–	0.05	0.05	16 (24)	**4b**	59
3	**1a**	**2b**	–	0.05	–	16 (7)	**4b**	17
4	**1a**	**2b**	1	0.05	–	16 (7)	**4b**	57
5	**1a**	**2a**	1	0.05	–	5.5 (27)	**4a**	51
6	**1a**	**2a**	–	0.025	0.025	24 (24)	**4a**	56
7	**1a**	**2e**	1	0.05	–	7 (25)	 **4i**	60
8	**1b**	**2e**	1	0.05	–	8 (15)	**4e**	24
9	**1b**	**2e**	–	0.025	0.025	44 (22)	**4e**	50
10	**1b**	**2e**	1	0.025	0.025	18 (6)	**4e**	49
11	**1b**	**2f**	1	0.025	0.025	48 (28)	**4f**	46
12	**1b**	**2g**	1	0.025	0.025	6 (15)	**4g**	57
13	**1b**	**2g**	1	0.05	–	23 (4)	**4g**	16
14	**1b**	**2h**	1	0.025	0.025	8 (15)	**4h**	77
15	 **1c**	**2f**	1	0.025	0.025	24 (7)	 **4j**	50
16	**1b**	**2f**	–	0.025	0.025	16 (–)		–[d]
17	**1a**	**2c**	1	0.05	–	5.5 (18)	**4c**	71
18	**1a**	**2c**	–	0.025	0.025	24 (–)		–[e]
19	**1a**	**2d**	1	0.05	–	4 (17)	**4d**	23
20	**1a**	**2d**	1	0.025	0.025	4 (42)	**4d**	60

Table 2 Palladium-Catalyzed One-Pot Synthesis of 4-Aryl- and 4-Vinyl-2,2-dialkyl-3-chromenes **4**[a] (continued)

Entry	Alkyne	R^3X	Bu_4NCl (equiv)	Pd 1st step (equiv)	Pd 2nd step (equiv)	Time (h)[b]	Chromene **4**	Yield (%)[c]
21	**1a**	 **2i**	1	0.025	0.025	7 (16)	**4i**	85
22	**1a**	 **2j**	1	0.025	0.025	7 (16)	**4j**	82
23	**1b**	 **2k**	1	0.025	0.025	6 (15)	**4k**	81

[a] All reactions were run under a nitrogen atmosphere. *Reagents and conditions*: $Pd(OAc)_2$ (0.025 or 0.05 equiv), Et_3N (3 equiv), HCOOH (2 equiv), Bu_4NCl (0 or 1 equiv), alkyne and aryl iodide (1 equiv and 2 equiv; 60 °C) or alkyne and vinyl triflate (1.2 equiv and 1 equiv; 50 °C); then, $Pd(OAc)_2$ (0 or 0.025 equiv), dppf (0.05 equiv), and NaO*t*-Bu (4 equiv) were added and the temperature was increased to 110 °C.
[b] Figures in parentheses refer to the reaction time of the cyclization step.
[c] Overall yields given for isolated products.
[d] No hydroarylation product was observed and **1c** was recovered in 70% yield.
[e] No hydrovinylation product was observed and **1a** was recovered in 84% yield.

Since chloride anions are reported to have a beneficial effect on palladium-catalyzed reactions,[20] stabilizing low-ligated palladium(0) species,[21] the hydroarylation–cyclization sequence was attempted in the presence of one equivalent of Bu_4NCl without further addition of $Pd(OAc)_2$. Only NaO*t*-Bu and dppf were added to the crude mixture resulting from the hydroarylation step. Under these conditions, **4b** was isolated in 57% yield (Table 2, entry 4).

This procedure appeared particularly convenient and was extended to other substrates. However, it was found to give satisfactory results in some cases (Table 2, entries 4, 5, 7 and 17) but to be ineffective in others (Table 2, entries 8 and 13).

Even when Bu_4NCl was omitted and fresh $Pd(OAc)_2$ (along with NaO*t*-Bu and dppf) were added after completion of the hydroarylation step, chromene products were isolated in good yields in some cases (Table 2, entries 1, 2, 6, and 9) and in poor yields in others (Table 2, entries 16 and 18).

Eventually, it appears that the most general procedure requires the presence of Bu_4NCl and the addition of fresh $Pd(OAc)_2$, NaO*t*-Bu, and dppf in the second step.[22] Some of the results obtained by this procedure are shown in Table 2; clearly, there is room for further optimization.

In conclusion, we have demonstrated that tertiary 3-(*o*-bromophenyl)propynols can be useful precursors for the preparation of 4-aryl- and 4-vinyl-2,2-dialkyl-3-chromenes. The synthesis, which can provide a new versatile entry into this class of compounds, involves two unrelated palladium-catalyzed reactions [a hydroarylation or hydrovinylation step followed by an intramolecular C–O bond-forming reaction] and can be conducted as a one-pot process, simply adding NaO*t*-Bu and dppf and, where appropriate, fresh $Pd(OAc)_2$ to the crude mixture resulting from the hydroarylation/hydrovinylation step. In general, 4-substituted 2,2-dialkyl-3-chromenes are obtained with high regioselectivity and overall yields range from satisfactory to high. Vinyl triflates tend to give higher yields then aryl iodides.

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(15) **Hydroarylation/Hydrovinylation–Cyclization of 1; Procedure A**
To a stirred solution of **1a** (0.160 g, 0.67 mmol) and **2b** (0.395 g, 1.61 mmol) in THF (5 mL) were added Bu_3N (0.572 mL, 2.41 mmol), BuN_4Cl (0.198 g, 0.67 mmol), and $Pd(OAc)_2$ (0.008 g, 0.035 mmol). The solution was stirred under nitrogen for 3 min. Then, HCOOH (0.066 mL, 1.74 mmol) was added. The reaction mixture was stirred at 60 °C under nitrogen for 24 h, then cooled, and extracted with 0.1 M HCl (100 mL) and Et_2O (3 × 50 mL). The combined organic layers were washed with 5% $NaHCO_3$ (30 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was dissolved in toluene (5 mL), $Pd(OAc)_2$ (0.008 g, 0.035 mmol), dppf (0.019 g, 0.035 mmol), and *t*-BuONa (0.129 g, 1.34 mmol) were added and the reaction mixture was stirred at 110 °C under nitrogen for 16 h. After cooling, the mixture was extracted with 0.5 M NH_4Cl (100 mL) and EtOAc (3 × 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography (silica gel; *n*-hexane–EtOAc, 98:2) to give **4b** (0.117 g, 61%); mp 113–115 °C. IR (KBr): 1690, 1610, 1270 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.99 (d, *J* = 8.4 Hz, 2 H), 7.45 (d, *J* = 8.4 Hz, 2 H), 7.21–7.13 (m, 1 H), 6.97–6.78 (m, 3 H), 5.67 (s, 1 H), 2.63 (s, 3 H), 1.50 (s, 6 H). ^{13}C NMR ($CDCl_3$): δ = 197.7, 153.3, 143.3, 136.3, 134.1, 130.0, 129.5, 128.9, 128.4, 128.3, 125.3, 120.7, 117.1, 75.7, 27.5, 26.7. EI-MS: *m*/*z* (%) = 263 (100) [$M^+ - CH_3$].

(16) **One-Pot Hydroarylation/Hydrovinylation–Cyclization of 1; Procedure B**
To a stirred solution of **1a** (0.143 g, 0.60 mmol) and **2d** (0.153 g, 0.50 mmol) in DMF (2 mL) were added $Pd(OAc)_2$ (0.006 g, 0.026 mmol) and HCOOK (0.084 g, 1.00 mmol). The reaction mixture was stirred at 40 °C under nitrogen for 17 h, then cooled, and extracted with 5% $NaHCO_3$ (100 mL) and Et_2O (3 × 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in toluene (5 mL), $Pd(OAc)_2$ (0.006 g, 0.026 mmol), dppf (0.014 g, 0.026 mmol), and *t*-BuONa (0.096 g, 1.00 mmol) were added and the reaction mixture was stirred at 110 °C under nitrogen for 5 h. After cooling, the mixture was extracted with 0.5 M NH_4Cl (100 mL) and EtOAc (3 × 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography (silica gel; *n*-hexane–EtOAc, 99:1) to give **4d** (0.063 g, 40%); mp 55–57 °C. IR (KBr): 1610, 1480, 1450, 1260 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.32–7.07 (m, 7 H), 6.90–6.81 (m, 2 H), 5.83 (br s, 1 H), 5.47 (s, 1 H), 2.95–2.80 (m, 1 H), 2.38–1.80 (m, 6 H), 1.42 (s, 3 H), 1.40 (s, 3 H). ^{13}C NMR ($CDCl_3$): δ = 153.3, 146.8, 136.3, 135.5, 128.8, 128.4, 126.8, 126.5, 126.3, 126.1, 125.2, 121.9, 120.5, 116.9, 75.5, 39.8, 33.6, 30.0, 29.2, 27.6, 27.5. EI-MS: *m*/*z* (%) = 316 (2) [M^+], 301 (100) [$M^+ - CH_3$].

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(22) **One-Pot Synthesis of Chromenes without Work-up after Hydroarylation/Hydrovinylation**
To a stirred solution of **1a** (0.161 g, 0.67 mmol) and **2j** (0.145 g, 0.56 mmol) in toluene (3 mL) were added Et_3N (0.234 mL, 1.68 mmol), BuN_4Cl (0.166 g, 0.56 mmol), and $Pd(OAc)_2$ (0.003 g, 0.014 mmol). The solution was stirred under nitrogen for 5 min and then HCOOH (0.042 mL, 1.12

mmol) was added. The reaction mixture was stirred at 50 °C under nitrogen for 7 h, then $Pd(OAc)_2$ (0.003 g, 0.014 mmol), dppf (0.016 g, 0.029 mmol), and NaO*t*-Bu (0.216 g, 2.25 mmol) were added, the temperature was raised to 110 °C and the reaction mixture was stirred under nitrogen for 16 h. After cooling, the mixture was extracted with 0.5 M NH_4Cl (100 mL) and EtOAc (3 × 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography (silica gel; *n*-hexane–EtOAc, 99:1) to give **4j** (0.124 g, 82%) as an oil. IR: 1630, 1500, 1470, 1280 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.08–7.01 (m, 2 H), 6.85–6.78 (m, 2 H), 5.68 (t, *J* = 8.2 Hz, 1 H), 5.39 (s, 1 H), 2.34–2.21 (m, 4 H), 1.60–1.44 (m, 8 H), 1.41 (s, 6 H). ^{13}C NMR ($CDCl_3$): δ = 153.3, 139.0, 136.6, 129.5, 128.7, 127.0, 126.9, 125.4, 120.4, 116.7, 75.6, 29.9, 28.6, 28.4, 27.8, 26.6, 26.3. EI-MS: *m*/*z* (%) = 268 (7) [M^+], 253 (100) [$M^+ – CH_3$].