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The Heck Reaction of Protected Hydroxychromones: on route to Natural Products

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The Heck reaction has been successfully extended to the bromochromones with an adjacent protected phenolic hydroxy group which offers a new methodology to various naturally occurring derivatives including tricyclic O-heterocycles. Phosphine-free coupling conditions are found to be effective. Surprisingly, the methoxymethyl protecting group is unstable in several cases but benzyl proved to be an ideal protecting group which could be selectively cleaved by boron trihalides in good yields.

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Introduction

The Heck reaction, the palladium-catalyzed alkenylation of aryl or vinyl halides or triflates, has become a versatile tool in organic synthesis.[1] Although it is also widely used in the field of heterocyclic compounds, our literature survey showed only a few applications in the synthesis of O-heterocycles, particularly chromonoids, flavonoids, and coumarins.[2] Therefore, we have initiated a research program to introduce this valuable methodology to the synthesis of these compound families with the final goal to develop new approaches to naturally occurring targets. In a previous contribution we have demonstrated that bromochromones **1** having the halogen in positions 3, 6, 7, and 8 could be successfully coupled with various terminal olefins.[3] Styrene, acrylonitrile, ethyl acrylate, 2,2-dimethylbut-3-en-1-ol, and acrolein diethyl acetal were used as model alkenes and alkenyl derivatives **2** were formed in good to excellent yields under either traditional or phosphine-free conditions. In the reaction of acrolein diethyl acetal aldehydes **3** or propionates **4** were obtained as products of the competing β and β′ hydride eliminations, the product ratio was highly depended on the applied conditions (Scheme 1).[3]

After this successful optimization we focussed on the Heck reaction of 6- and 8-bromo-7-hydroxychromones to verify its usefulness in the synthesis of naturally occurring and frequently biologically active products. Some of representative examples are shown in Fig. 1. Torosaflavone D (**5**) was isolated from the leaves of *Cassia torosa*.[4] Anadanthoflavone (**6**) was isolated from *Anadenanthera colubrine* and showed lipoxygenase inhibitory effect, it was active against both human platelet 12-lipoxygenase and human reticulocyte 15-lipoxygenase.[5] Isoartocarpesin (**7**) was obtained from *Artocarpus incisus* and showed tyrosinase inhibitory activity.[6] These three compounds exemplify natural products with C-alkenyl functionality in position 6. 7-Aryl-5*H*-furo[3,2-*g*]chromen-5-ones **8** having the same core unit were isolated from *Pongamia* species[7a,7b] or *Ochna squarrosa* L.[7c] Some derivatives were analgesic and anti-inflammatory agents[7c] while others showed good inhibitory activity against protein tyrosine phosphatase 1B enzyme, which has a critical role in the downregulation of insulin signalling.[8] Visnagin (**9**), a similar furochromone, was obtained from *Ammia visnaga*.[9] Various activities, among others antiviral phototoxicity[10a] and a vasodilator effect,[10b,10c] were reported, this latter interpreted in terms of its action on cyclic nucleotide phosphodiesterases.[10c] Erythrinin-A (**10**) isolated from *Erythrina variegate* represents a tricyclic structure with two six-membered oxygen heterocycles.[11] A similar flavone derivative, carpachromene (**11**) was isolated from *Atalantia monophylla*,[12a] *Ficus formosana f. formosana*,[12b] and *Erythrina vogelii*,[12c] the compound had significant cytotoxicity agains various cell lines.[12b] Candidin (Isopongaflavone, **12**) is a representative of the angular tricyclic systems, it was first isolated from *Tephrosia candida* seeds[13] and was reported to show cAMP phosphodiesterase inhibiting activity.[14] Cneorum-Chromone-G (**13**) obtained from *Cneorum pulverulentum* is an interesting example of the simultaneous presence of a ring-closed and an open-chain alkenyl unit.[15]

In this contribution we present our results on the palladium-catalyzed cross-coupling reaction of 6- or 8-bromo-7-hydroxychromones and the optimization of the necessary protecting group opening the way to alkenylated hydroxychromones with a resacetophenone-type substitution pattern.

Results and Discussion

Keeping in mind the structures of the naturally occurring products exemplified in the Introduction, 8-bromo-7-hydroxychromone (**5**) and 6-bromo-7-hydroxychromone (**6**) were

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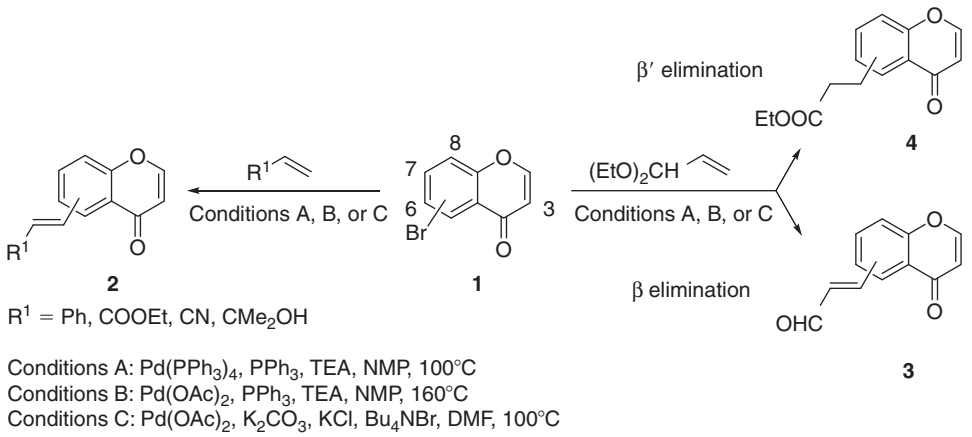


Scheme 1. The Heck reaction of bromochromones **1**.

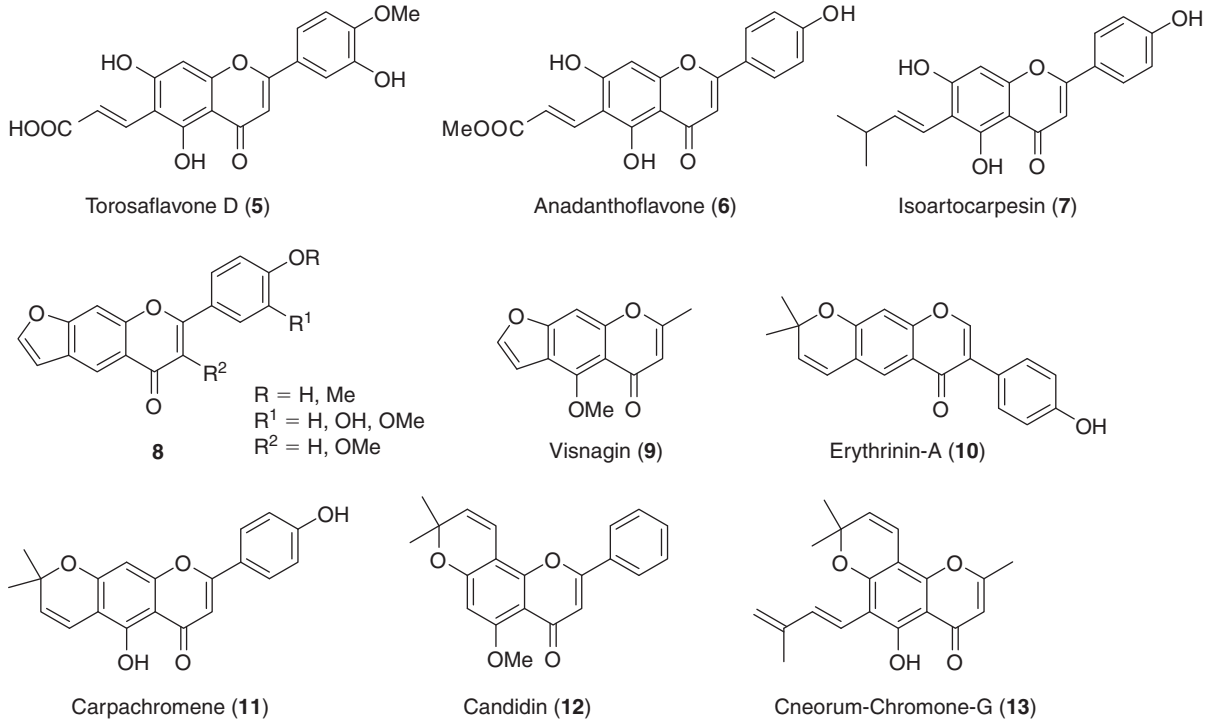
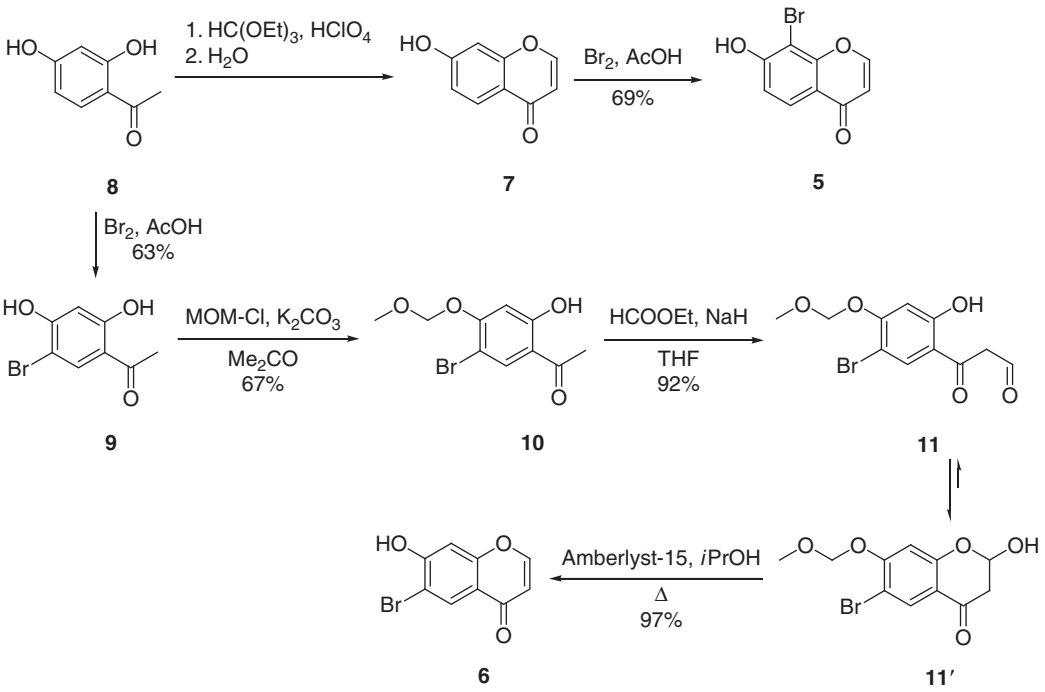
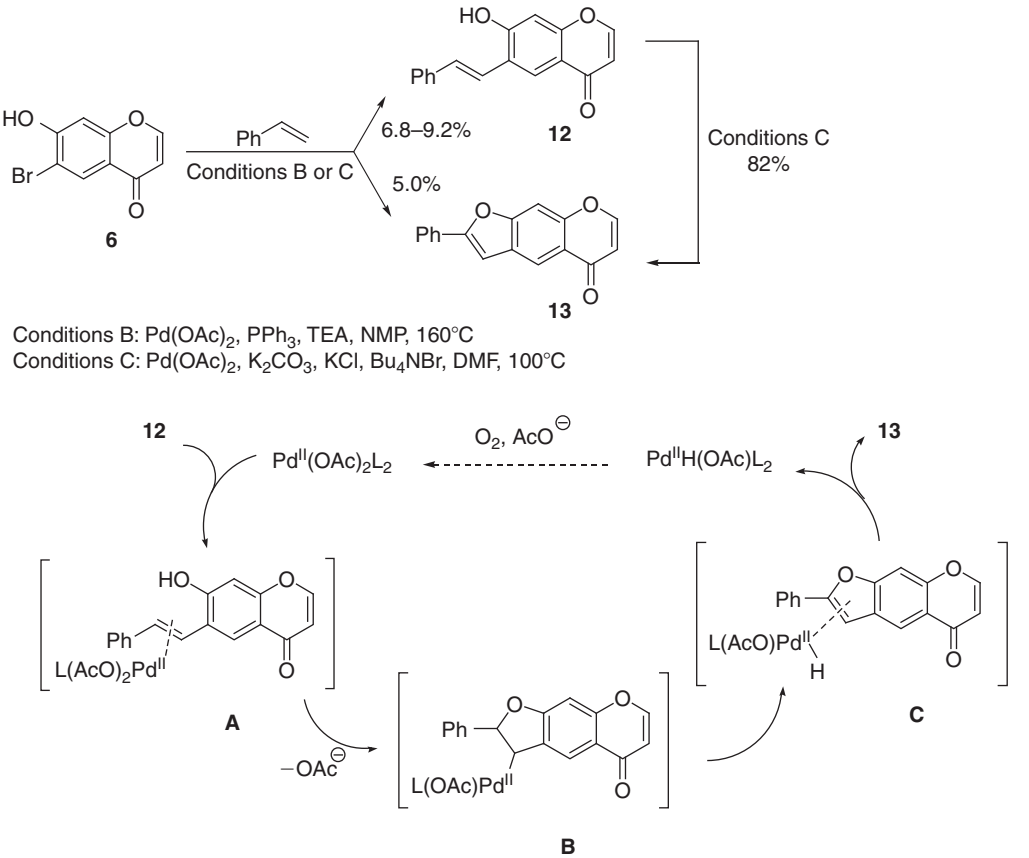


Fig. 1. Some representatives of naturally occurring chromones and flavones with C-alkenyl functionality.

chosen as starting materials. 7-Hydroxy-2-methylchromone,[16] 7-hydroxy-2,3-dimethylchromone, and 3-ethyl-7-hydroxy-2-methylchromone[17] were reported to give the corresponding 8-bromo derivatives upon treatment with bromine in glacial acetic acid, and no other regioisomer was mentioned. Direct bromination of 7-acetoxy-2-methylchromone in acetic acid or carbon tetrachloride resulted in 8-bromo-7-hydroxy-2-methylchromone, which was also synthesized by treating 7-hydroxy-2-methylchromone with *N*-bromosuccinimide.[18] Based on these reports we tested the bromination of 7-hydroxychromone (**7**), prepared from 2′,4′-dihydroxyacetophenone (**8**) according to literature methods,[19] in glacial acetic acid and to our delight the expected 8-bromo-7-hydroxychromone (**5**) was obtained in good yield as a sole product (Scheme 2). The other isomer 6-bromo-7-hydroxychromone (**6**) was synthesized by using our previously reported methodology based on the Claisen condensation of methoxymethyl-protected acetophenones with ethyl formate.[20] The desired starting material, 5′-bromo-2′,4′-dihydroxyacetophenone (**9**) was apparently available by the bromination of 2′,4′-dihydroxyacetophenone (**8**) but the possible formation of two regioisomers and the dibromo derivative as a result of the highly activated aromatic ring makes this reaction difficult. Bromination of acetophenone **8** by using pyridinium bromochromate was reported to give the dibromo compound in excellent (89%) yield,[21] while its treatment with copper(II) bromide resulted in a mixture of 3′- and 5′-bromo isomers.[22] Contradictory results were published for the reaction of acetophenone **8** with bromine in acetic acid. Seshadri and Vasadarajan[23] reported on a mixture of the 5-bromo derivative **9** and the dibromo compound, whereas only the desired product **9** was communicated by others.[24,25] In our hands the bromination of resacetophenone **8** in glacial acetic acid at room



Scheme 2. Synthesis of bromochromones **5** and **6**.



Scheme 3. Cross-coupling of unprotected 6-bromo-7-hydroxychromone (**6**) and the suggested mechanism of the formation of furochromone **13**.

temperature with 1.07 equivalents of bromine led to the needed compound **9** in 63% yield (Scheme 2). The short reaction period and the quick workup were crucial for the high yield of the monobrominated product.

The 4′-hydroxy group of acetophenone **9** was selectively methoxymethylated under standard conditions and the obtained product **10** was coupled with ethyl formate and sodium hydride to give 3-oxopropanal **11** in excellent yield. According to the

^{1}H NMR spectrum this compound exists exclusively in its ring-closed form **11′** in deuteriochloroform. In the final step a simultaneous dehydration and cleavage of the protecting group took place under acidic conditions and the desired starting material **6** was obtained (Scheme 2). However, the attempted cross-coupling reaction of 6-bromo-7-hydroxychromone (**6**) with styrene by using either Conditions B or C gave the expected 7-hydroxy-6-styrylchromone (**12**) only in very poor yields. In addition, a low conversion of the starting material **6** was observed using Conditions C which previously proved to be very effective[3] (Scheme 3, Table 1, entries 1 and 2).

In this latter case an interesting by-product, the hitherto unknown tricyclic 2-phenyl-5*H*-furo[3,2-*g*]chromen-5-one (**13**) was also isolated in a low yield. No formation of this by-product from bromochromone **6** was observed under Condition B. Apparently, furochromone **13** originates from the primary product styryl derivative **12** by a palladium-catalyzed intramolecular oxypalladation,[26] which was also verified by a control experiment. When primary product **12** was reacted under Condition C for 2.5 h, tricyclic compound **13** was obtained in good yield (82%). Similar reactions of 2-vinylphenols were reported for the first time in the 1970s although the yields of the resultant benzofurans were low in some cases.[27] The probable mechanism of the ring-closure is shown by Scheme 3. In the first step the double bond coordinates to the palladium(II) ion, and then the resultant complex **A** transforms into the cyclic σ-bonded palladium intermediate **B**. In the final step the β-elimination of a palladium-hydrogen species from the complex **C** leads to the tricyclic product **13**. The exact catalytic cycle is not known but the incorporation of molecular oxygen followed by the leaving of a hydroperoxo anion seems to be probable.[26b] As mentioned in the Introduction, 7-aryl-5*H*-furo[3,2-*g*]chromen-5-ones having the same tricyclic core unit were isolated from *Pongamia* species or *Ochna squarrosa*.[7]

Based on the observed low efficiency of the cross-coupling of compound **6** we decided upon the synthesis of O-protected analogues to achieve acceptable yields for the Heck products. 7-Acetoxy- (**14a**) and 7-acryloyloxy-6-bromochromone (**14b**) were prepared by standard methods (Scheme 4). This latter derivative was prepared because its structure would have allowed an intramolecular Heck reaction leading to the tricyclic 2*H*,6*H*-benzo[1,2-*b*:5,4-*b*′]dipyran-2,6-dione. Methoxymethylation and benzylation of the intermediate **6** gave the corresponding derivatives **14c** and **14d**. A shorter but more efficient three-step approach to the compound **14d** was also developed (Scheme 4).

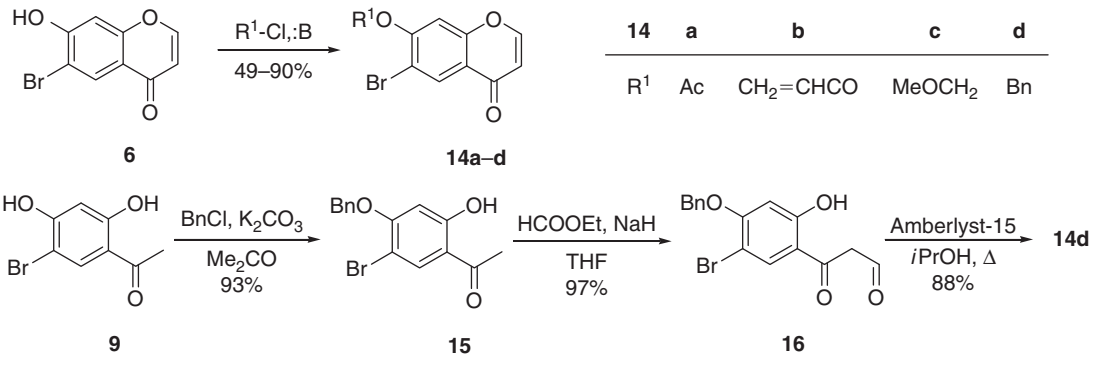
Next, we tested the Heck reaction of the protected derivatives **14a**–**d** with various alkenes under different conditions. Acetyl and acryloyl protecting groups turned out to be unstable and cleaved to give the 6-bromo-7-hydroxychromone (**6**) (Table 1, entries 3, 4). In one case, 2-phenyl-5*H*-furo[3,2-*g*]chromen-5-one (**13**) (see above) was also isolated (Table 1, entry 3).

Table 1. Reaction of 6-bromo-7-(protected)hydroxychromones 6 and 14a–d with various alkenes

Conditions A: $Pd(PPh_3)_4$ (6 mol-%), Et_3N, NMP, PPh_3, 100°C; Conditions B: $Pd(OAc)_2$ (6 mol-%), Et_3N, NMP, PPh_3, 160°C; Conditions C: $Pd(OAc)_2$ (7 mol-%), K_2CO_3, KCl, Bu_4NBr, DMF, 100°C

Entry	Starting material	R^1	R^3	Cond.	Reaction period	Conv. [%]	Product(s) (Yield[A] [%])
1	**6**	H	Ph	B	36.5 h	93	**12** (9.2)
2	**6**	H	Ph	C	5 h	48	**12** (6.8) + **13** (5.0)
3	**14a**	Ac	Ph	C	30 min	100	**6** (41) + **13** (7.0)
4	**14b**	Acryloyl	—	C	5 min	100	**6** (70)
5	**14c**	MOM	Ph	C	1 h	100	**17c** (70)
6	**14c**	MOM	COOEt	A	4 h	76	**18c** (22)
7	**14c**	MOM	COOEt	C	4 h	73	**18c** (8.1) + **21** (15) + **6** (40)
8	**14c**	MOM	CHO	C	35 min	93	**19c** (18) + **22c** (36) + **6** (19)
9	**14d**	Bn	Ph	C	30 min	100	**17d** (82)
10	**14d**	Bn	COOEt	C	90 min[B]	100	**18d** (54)
11	**14d**	Bn	CHO	C	420 min	100	**19d** (21) + **22d** (31)
12	**14d**	Bn	CN	A	24 h	100	(*E*)-**20d** (26) + (*Z*)-**20d** (2.9)

[A]Yields refer to isolated pure products. In the case of incomplete conversion the value was corrected with the recovered starting material.
[B]90 min at 100°C, and then 2.5 h 130°C.



Scheme 4. Synthesis of protected bromochromones **14a**–**d**.

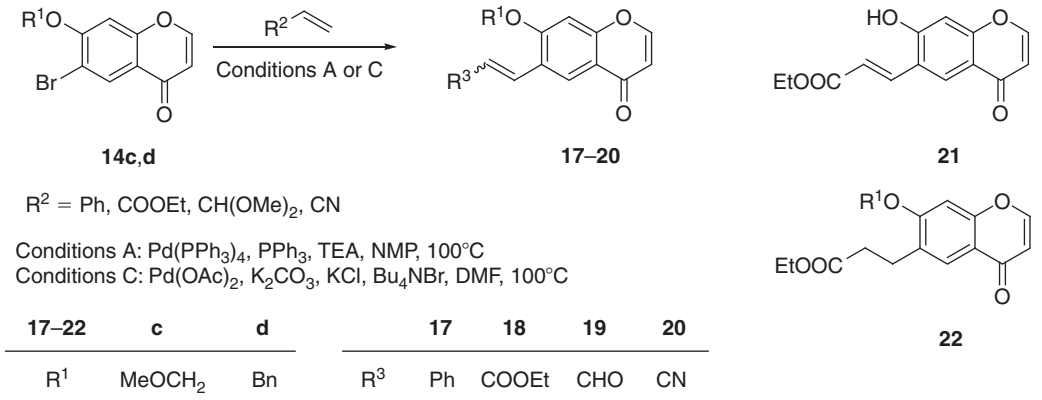
Therefore, we also tested the cross-coupling reaction of derivatives **14c** and **14d** having ether-type protecting groups. The reaction of methoxymethyl-protected substrate **14c** with styrene afforded the desired product in good yield (Scheme 5, Table 1, entry 5). On the contrary, the coupling reaction of bromochromone **14c** with ethyl acrylate resulted in an incomplete conversion and low yield of the expected product **18c** (Scheme 5, Table 1, entries 6, 7). Under Condition C the alkenylated product **21** with a free phenolic hydroxy function and the unprotected derivative **6** have also been isolated in addition to the expected product **18c** (Scheme 5, Table 1, entry 7). Similarly, the reaction of bromochromone **14c** with acrolein diethyl acetal under Condition C gave a mixture of aldehyde **19c**, ethyl 3-[7-(methoxymethoxy)-4-oxo-4*H*-1-benzopyran-6-yl]-propanoate (**22c**), and 6-bromo-7-hydroxychromone (**6**) (Scheme 5, Table 1, entry 8). The formation of aldehyde **19c** and the by-product **22c** can be interpreted in terms of the competing β and β′-hydride elimination[3] but the formation of product **6** shows again the cleavage of the protecting group. To prove this observation we reacted the starting material **14c** under Condition C without any alkene for 4 h and obtained the unprotected **6** in 53% yield, in addition to some unreacted starting material **14c** (32%). The instability of the methoxymethoxy functionality under basic conditions or in the presence of palladium(II) or palladium(0) species is unprecedented,[28] and further studies on this unusual reactivity and its exploitation to develop a new methodology to cleave acetal-type protecting groups are in progress.

When we investigated the cross-coupling reactions of the benzyl-protected substrate **14d** with styrene, ethyl acrylate, and acrolein diethyl acetal, the desired derivatives **17d**, **18d**, and **19d** were obtained in moderate to good yield using Conditions C (Scheme 5, Table 1, entries 9–11). In the case of ethyl acrylate, a higher temperature was needed to achieve the complete conversion but no decomposition was observed and the protecting group was found to be stable (Table 1, entry 10). The products formed with complete *E*-diastereoselectivity in each case. As expected, ethyl 3-(7-benzyloxy-4-oxo-4*H*-1-benzopyran-6-yl) propanoate (**22d**), the product of the competing β′-hydride elimination, was isolated as the major product from the reaction of **14d** with acrolein diethyl acetal.[3] The only exception of these modified Jeffery's conditions failing to give the desired Heck product was the reaction of bromochromone **14d** with acrylonitrile, when only a strong decomposition was observed. However, successful cross-coupling reaction was found using Conditions A, even if the yield of the product **20d** was moderated. It is worth noting that this reaction resulted in the formation of not only the more stable *E*-diastereomer but also the *Z*-isomer (Scheme 5, Table 1, entry 12). Similar changes of the diastereoselectivity were also observed previously during the cross-coupling of simple bromochromones[3] but in this case the diastereomers could be separated by column chromatography.

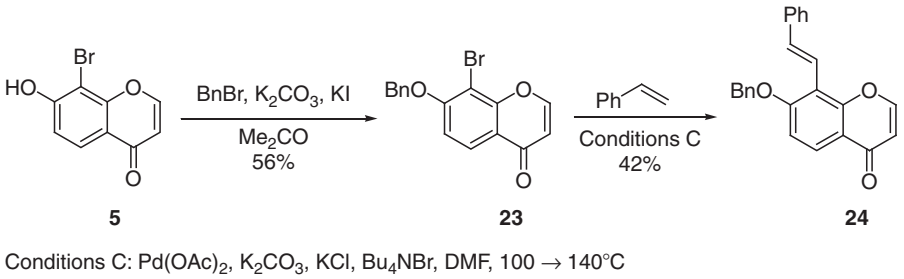
Conditions C were also effective in the coupling of 7-benzyloxy-8-bromochromone (**23**) with styrene, although an elevated temperature was also needed for the completion of the transformation (Scheme 6).

Since our final goal is to develop a new approach to natural products with a free phenolic hydroxy group or to create a new O-heterocycle by using this hydroxy functionality, we investigated the selective deprotection of the benzyloxy derivatives **17d** and **18d** with various Lewis acids (Scheme 7, Table 2).

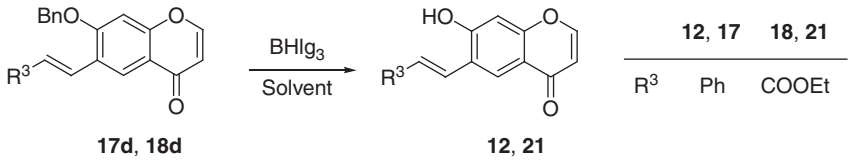
Boron trihalides were found to effectively cleave the protecting group, and the highest reactivity and the shortest reaction periods were observed in the case of boron trichloride



Scheme 5. Cross-coupling reactions of protected bromochromones **14c**,**d** with various terminal alkenes.



Scheme 6. Synthesis and cross-coupling reaction of protected 7-bromo-8-benzyloxychromone **23** with styrene.



Scheme 7. Removal of the benzyl protecting group of the alkenylated chromones **17d** and **18d**.

Table 2. Cleavage of the benzyl protecting group of chromones 17d and 18d

Entry	Starting material	R^3	Reagent	Solvent	Temperature [°C]	Product (Yield[A] [%])
1	**17d**	Ph	$BF_3 \cdot Et_2O$	PhMe	55	**12** (62)
2	**17d**	Ph	$BF_3 \cdot Et_2O$	MeCN	Reflux	**12** (58)
3	**17d**	Ph	BCl_3	PhMe	$-100 \rightarrow -75$	**12** (92)
4	**17d**	Ph	BBr_3	CH_2Cl_2	$0 \rightarrow$ RT	**12** (66)
5	**17d**	Ph	$SnCl_4$	CH_2Cl_2	Reflux	No reaction
6	**18d**	COOEt	$BF_3 \cdot Et_2O$	MeCN	Reflux	**21** (59)
7	**18d**	COOEt	BCl_3	PhMe	$-100 \rightarrow -75$	**21** (77)
8	**18d**	COOEt	BBr_3	CH_2Cl_2	$0 \rightarrow$ RT	**21** (78)

[A]Yields refer to isolated pure products.

(Scheme 7, Table 2, entries 3, 7). However, boron tribromide showed a quite similar efficiency (Scheme 7, Table 2, entries 4, 8) and, because of its easier handling, we prefer it to boron trichloride. We have also tested tin(IV) chloride[29] but no reaction was observed even at reflux temperature (Scheme 7, Table 2, entry 5).

Conclusions

We have demonstrated that the Heck reaction could be successfully applied for the alkenylation of chromones with adjacent hydroxy group but the protection of the phenolic functionality is essential to achieve good yields in the cross-coupling reactions. Phosphine-free conditions (modified Jeffery's conditions) were found more effective. Because of the surprising instability of the methoxymethyl group under the conditions of the coupling reaction, benzyl proved to be the protecting group of choice. By the successful cleavage of the benzyl protecting group we opened the way to a new synthetic methodology of naturally occurring derivatives with free phenolic hydroxy groups or to their ring-closed tricyclic analogues. Experiments on the extension of this methodology to the derivatives with a phloroacetophenone-type substitution pattern, occurring in natural sources more often than the resacetophenone-type, are in progress and will be disclosed soon.

Experimental

Melting points were determined on a Boetius hot-stage apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker AM 360 (360 MHz for ^{1}H, 90 MHz for ^{13}C nuclei) spectrometer (internal standard TMS, $\delta = 0$ ppm). IR spectra were recorded with a Perkin–Elmer 16 PC-FT-IR instrument in KBr disks. The mass spectra were determined on an AutoSpecEQ EI+ spectrometer. Elemental analyses were performed in house with a Carlo Erba 1106 EA instrument. chromatographic separations were performed using silica gel (Merck, 70–230 mesh). TLC was carried out on Kieselgel 60 F_{254} (0.25 mm layer thickness, Merck). Triethylamine was distilled over lithium aluminium hydride.

7-Hydroxychromone (**7**) was prepared according to the literature method.[19]

*8-Bromo-7-hydroxychromone (**5**)*

To the stirred solution of **7** (405 mg, 2.498 mmol) in glacial acetic acid (5.5 mL), a solution of bromine (0.13 mL, 2.537 mmol) in glacial acetic acid (5 mL) was added dropwise at room temperature, the mixture was stirred for 20 min and was poured over crushed ice. The precipitate was filtered off, dried, and submitted to column chromatography (eluent: toluene/ethyl acetate, 1/1, v/v) to yield 413 mg (69%) of product **5** as white powder. mp 275–277°C. ν_{max} (KBr)/cm^{-1} 3432 (OH), 3071, 1627 (C=O), 1577, 1545, 1426, 1415, 1308, 1061, 872, 816. δ_H ($CDCl_3$ + (D6)DMSO) 6.27 (d, *J* 5.9, 1H, 3-H),7.08 (d, *J* 9.1, 1H, 6-H), 7.87 (d, *J* 9.1, 1H, 5-H), 8.23 (d, *J* 5.9, 1H, 2-H). δ_C ($CDCl_3$ + (D6)DMSO) 95.2 (C-8), 110.3 (C-3), 112.5 (C-6), 116.2 (C-4a), 123.2 (C-5), 152.6 (C-8a), 154.2 (C-2), 157.9 (C-7), 173.5 (C-4). Anal. Calc. for $C_9H_5BrO_3$: C 44.85, H 2.09. Found: C 44.97, H 1.98%.

*5′-Bromo-2′,4′-dihydroxyacetophenone (**9**)*

To the stirred solution of 2′,4′-dihydroxyacetophenone (**8**) (5.000 g, 32.869 mmol) in glacial acetic acid (120 mL), bromine (1.8 mL, 35.13 mmol) was added at room temperature and stirred for 10 min. The reaction mixture was poured into 1% sodium thiosulfate solution (250 mL) and neutralized with 8% sodium hydroxide solution. The precipitate was filtered off, washed with water, dried, and re-crystallized to yield 4.859 g (63%) of product **9**. mp 170–172°C (hexane/ethanol), lit.[23] 166–167°C. ν_{max} (KBr)/cm^{-1} 3285 (OH), 1631 (C=O), 1488, 1369, 1288, 1271, 1225, 1161. δ_H ($CDCl_3$) 2.53 (s, 3H, 2-H), 6.81 (s, 1H, 3′-H), 7.83 (s, 1H, 6′-H), 10.82 (s, 1H, 4′-OH), 12.47 (s, 1H, 2′-OH). δ_C ($CDCl_3$) 25.5 (C-2), 99.7 (C-3′), 103.3 (C-5′), 113.6 (C-1′), 134.5 (C-6′), 160.6 (C-2′), 163.1 (C-4′), 201.1 (C-1). Anal. Calc. for $C_8H_7BrO_3$: C 41.59, H 3.05. Found: C 41.35, H 2.89%.

*5′-Bromo-2′-hydroxy-4′-(methoxymethoxy) acetophenone (**10**)*

To a mixture of 5′-bromo-2′,4′-dihydroxyacetophenone (**9**) (500 mg, 2.164 mmol), anhydrous potassium carbonate (358 mg, 2.590 mmol), and dry acetone (10 mL), a solution of methoxymethyl chloride (215 mg, 2.277 mmol) in dry acetone (3 mL)

was added dropwise. After stirring at room temperature for 3 h another batch of methoxymethyl chloride (120 mg, 1.243 mmol) was added and it was repeated after a further 3 h stirring. This mixture was stirred for 4 h and then the solids were filtered off, washed with acetone, and the filtrate was concentrated. The solid residue was dissolved in dichloromethane (80 mL), washed with saturated sodium hydrocarbonate solution, dried ($MgSO_4$), and evaporated. The white solid was triturated with hexane and filtered to give the pure protected acetophenone **10** (400 mg, 67%) as a white powder. mp 71–73°C. ν_{max} (KBr)/cm^{-1} 3442 (OH), 2918, 1634 (C=O) 1574, 1556, 1484, 1416, 1360, 1324, 1250 (C–O–C), 1220, 1152 (C–O–C), 1088, 1014 (C–O–C), 942. δ_H ($CDCl_3$) 2.55 (s, 3H, 2-H), 3.50 (s, 3H, CH_3), 5.27 (s, 2H, CH_2), 6.70 (s, 1H, 3′-H), 7.86 (s, 1H, 6′-H), 12.49 (s, 1H, 2′-OH). δ_C ($CDCl_3$) 26.3 (C-2), 56.6 (CH_3), 94.8 (CH_2), 101.7 (C-5′), 103.8 (C-3′), 115.4 (C-1′), 134.8 (C-6′), 159.5 (C-2′), 163.8 (C-4′), 202.0 (C-1). Anal. Calc. for $C_{10}H_{11}BrO_4$: C 43.66, H 4.03. Found: C 43.82, H 4.19%.

*6-Bromo-2-hydroxy-7-(methoxymethoxy)chromanone (**11** ⇆ **11′**)*

In a flame-dried apparatus, sodium hydride (4.252 g, ~0.114 mol, 60% dispersion in mineral oil) rinsed with dry hexane was suspended in absolute tetrahydrofuran (THF, 60 mL) and a mixture of 5′-bromo-2′-hydroxy-4′-(methoxymethoxy)acetophenone (**10**) (7.555 g, 27.463 mmol) and ethyl formate (5.5 mL, 68.34 mmol) was added dropwise in 30 min. After stirring for 10 min the mixture was poured into icy water and acidified by concentrated hydrochloric acid. The precipitate was filtered off. The aqueous phase was extracted with ethyl acetate (2 × 100 mL), and the extract was combined with the previous solid compound, dried ($MgSO_4$), and evaporated. The residue was triturated with diisopropyl ether to give pure chromanone **11′** (7.625 g, 92%) as a white powder. mp 106–108°C. ν_{max} (KBr)/cm^{-1} 3412 (OH), 2924, 1620, 1599 (C=O), 1566, 1432, 1256 (C–O–C), 1211, 1156 (C–O–C), 1089, 1011 (C–O–C), 948. δ_H ($CDCl_3$) 2.82 (dd, J_{AB} 16.8, $J_{2H,3Heq}$ 4.5, 1H, 3-H_{eq}), 2.97 (dd, J_{AB} 16.8, $J_{2H,3Hax}$ 3.5, 1H, 3-H_{ax}), 3.50 (s, 3H, CH_3), 4.35 (br s, 1H, OH), 5.27 (s, 2H, CH_2), 5.85 (m, 1H, 2-H), 6.73 (s, 1H, 8-H), 8.05 (s, 1H, 5-H). δ_C ($CDCl_3$) 43.3 (C-3), 56.7 (CH_3), 94.8 (CH_2), 95.4 (C-2), 104.2 (C-8), 106.0 (C-6), 116.4 (C-4a), 103.9 (C-5), 158.8, 159.6 (C-8a, C-7), 188.8 (C-4). Anal. Calc. for $C_{11}H_{11}BrO_5$: C 43.59, H 3.66. Found: C 43.74, H 3.79%.

*6-Bromo-7-hydroxychromone (**6**)*

A mixture of 6-bromo-2-hydroxy-7-(methoxymethoxy)chromanone (**11′**) (1.751 g, 5.777 mmol), Amberlyst-15 (H^+) (1.444 g), and propan-2-ol (30 mL) was stirred at reflux temperature for 1 h. The resin was filtered off and washed a few times with hot methanol. The combined filtrates were concentrated under reduced pressure and the solid residue was filtered off and washed with plenty of hexane to give pure chromone **6** (1.256 g, 90%) as a white powder. mp 293°C (dec). ν_{max} (KBr)/cm^{-1} 3152 (OH), 1651 (C=O), 1617 (C=C), 1575, 1463, 1400, 1307, 1249 (C–O), 1233, 868, 844, 829. δ_H ($CDCl_3$ + (D6)DMSO) 6.22 (d, *J* 5.9, 1H, 3-H), 7.02 (s, 1H, 8-H), 7.90 (d, *J* 5.9, 1H, 2-H), 8.20 (s, 1H, 5-H), 11.18 (s, 1H, 7-OH). δ_C ((D6)DMSO) 104.3 (C-8), 109.7 (C-6), 112.8 (C-3), 119.0 (C-4a), 129.8 (C-5), 157.4 (C-8a), 157.5 (C-2), 159.8 (C-7), 175.6 (C-4). Anal. Calc. for $C_9H_5BrO_3$: C 44.85, H 2.09. Found: C 45.02, H 2.01%.

*7-Acetoxy-6-bromochromone (**14a**)*

A mixture of 6-bromo-7-hydroxychromone (**6**) (2.000 g, 8.285 mmol), acetic anhydride (30 mL), and anhydrous sodium acetate (2.000 g, 24.381 mmol) was heated under stirring for 0.5 h and then poured into icy water. The precipitate was filtered off, washed with water, dried and re-crystallized from a mixture of hexane and ethyl acetate (20 mL, 1/1, v/v) to give acetate **14a** (1.369 g, 58%), mp 131–132°C. ν_{max} (KBr)/cm^{-1} 3091, 1780, 1766 (C=O, ester), 1654 (C=O, chromone), 1612 (C=C), 1433, 1287 (C–O–C), 1220, 1194, 1140, 1031 (C–O–C), 905, 834. δ_H ($CDCl_3$) 2.42 (s, 3H, CH_3), 6.35 (d, *J* 5.9, 1H, 3-H), 7.33 (s, 1H, 8-H), 7.86 (d, *J* 5.9, 1H, 2-H), 8.46 (s, 1H, 5-H). δ_C ($CDCl_3$) 20.7 (CH_3), 113.0, 113.6 (C-3, C-8), 113.8 (C-6), 123.8 (C-4a), 130.4 (C-5), 151.8 (C-8a), 155.5 (C-2), 155.6 (C-7), 167.7 (CH_3**C**=O), 175.5 (C-4). Anal. Calc. for $C_{11}H_7BrO_4$: C 46.67, H 2.49. Found: C 46.88, H 2.29%.

*7-Acryloyloxy-6-bromochromone (**14b**)*

6-Bromo-7-hydroxychromone (**6**) (301 mg, 1.249 mmol) and triethylamine (0.22 mL, 1.55 mmol) were dissolved in dry dichloromethane (15 mL) and a solution of acryloyl chloride (0.1 mL, 1.25 mmol) in dry dichloromethane (5 mL) was added in dropwise in 0.5 h at room temperature. After 1.5 h another batch of acryloyl chloride (37 µL, 0.37 mmol) was added in one portion and the mixture was stirred for 10 min. It was washed with water (2 × 50 mL), and the organic phase was dried ($MgSO_4$) and concentrated. The solid residue was triturated with hexane and filtered to afford pure ester **14b** (297 mg, 81%) as a white powder, mp 117–119°C. ν_{max} (KBr)/cm^{-1} 3093, 1748 (C=O, ester), 1666 (C=O, chromone), 1614, 1436, 1407, 1291 (C–O–C), 1234, 1217, 1153, 1036 (C–O–C), 866, 836. δ_H ($CDCl_3$) 6.15 (d, *J* 10.7, 1H, 3′-H_{cis}), 6.35 (d, *J* 5.7, 1H, 3-H), 6.37 (dd, *J* 17.0, 10.7, 1H, 2′-H), 6.73 (d, *J* 17.0, 1H, 3′-H_{trans}), 7.39 (s, 1H, 8-H), 7.85 (d, *J* 5.7, 1H, 2-H), 8.47 (s, 1H, 5-H). δ_C ($CDCl_3$) 113.1, 113.5 (C-3, C-8), 113.7 (C-6), 123.8 (C-4a), 126.6 (C-2′), 130.4 (C-5), 134.5 (C-3′), 151.6 (C-8a), 155.6 (C-7), 162.7 (C-1′), 175.6 (C-4). Anal. Calc. for $C_{12}H_7BrO_4$: 48.84, H 2.39. Found: C 48.89, H 2.25%.

*6-Bromo-7-(methoxymethoxy)chromone (**14c**)*

To a mixture of 6-bromo-7-hydroxychromone (**6**) (3.000 g, 12.446 mmol), potassium carbonate (2.060 g, 14.905 mmol) and absolute acetone (120 mL), methoxymethyl chloride (1.44 mL, 18.96 mmol) was added dropwise at room temperature. After 80 min another batch of methoxymethyl chloride (0.77 mL, 9.48 mmol) was added in one portion, the mixture was stirred for 100 min and concentrated. Water (150 mL) was added to the solid residue, the mixture was extracted with dichloromethane (2 × 150 mL), dried ($MgSO_4$), and evaporated. The solid residue was triturated with hexane and filtered off to give pure product **14c** (3.194 g, 90%) as a light brown powder, mp 119–121°C. ν_{max} (KBr)/cm^{-1} 3088, 2943, 1640 (C=O), 1595, 1435, 1292 (C–O–C), 1250 (C–O–C), 1231, 1157 (C–O–C), 1085, 1036 (C–O–C), 987, 942, 921, 866, 850. δ_H ($CDCl_3$) 3.54 (s, 3H, CH_3), 5.35 (s, 2H, CH_2), 6.30 (d, *J* 6.0, 1H, 3-H), 7.19 (s, 1H, 5-H), 7.80 (d, *J* 6.0, 1H, 2H), 8.39 (s, 1H, 8-H). δ_C ($CDCl_3$) 56.7 (CH_3), 95.0 (CH_2), 103.6 (C-3), 110.7 (C-6), 112.9 (C-8), 120.1 (C-4a), 130.0 (C-5), 155.1 (C-2), 156.7, 157.5 (C-7, C-8a), 175.8 (C-4). Anal. Calc. for $C_{11}H_9BrO_4$: C 46.34, H 3.18. Found: C 46.11, H 3.33%.

*7-Benzyloxy-6-bromochromone (**14d**)*

(a) A mixture of 6-bromo-7-hydroxychromone (**6**) (1.000 g, 4.149 mmol), benzyl bromide (0.73 mL, 6.14 mmol), potassium carbonate (573 mg, 4.146 mmol), potassium iodide (27 mg, 0.162 mmol), and absolute acetone (30 mL) was refluxed for 1.5 h. Another batch of benzyl bromide (0.73 mL, 6.14 mmol) was added and heated for 160 min. The reaction mixture was allowed to cool to room temperature, and the inorganic salts were filtered off and washed with acetone (2 × 10 mL). The combined organic fractions were concentrated, the residue was washed with water and then hexane to give chromone **14d** (675 mg, 49%) as off-white crystals, mp 186–188°C. ν_{max} (KBr)/cm^{-1} 3063, 1644 (C=O), 1618 (C=C), 1594, 1441, 1384, 1298 (C–O–C), 1255, 1226, 1038 (C–O–C), 867, 825, 727. δ_H ($CDCl_3$) 5.24 (s, 2H, CH_2), 6.28 (d, *J* 5.9, 1H, 3-H), 6.90 (s, 1H, 8-H), 7.36–7.49 (m, 5H, Ph), 7.76 (d, *J* 5.9, 1H, 2-H), 8.40 (s, 1H, 5-H). δ_C ($CDCl_3$) 71.2 (CH_2), 101.4 (C-8), 110.6 (C-6), 112.9 (C-3), 119.5 (C-4a), 126.9 (C-2′,6′), 128.4 (C-4′), 128.7 (C-3′,5′), 130.0 (C-5), 134.9 (C-1′), 154.9 (C-2), 156.9 (C-8a), 158.8 (C-7), 175.7 (C-4). Anal. Calc. for $C_{16}H_{11}BrO_3$: C 58.03, H 3.35. Found: C 57.81, H 3.20%.

(b) A mixture of 7-benzyloxy-6-bromo-2-hydroxychromanone (**16′**) (7.164 g, 20.517 mmol) and Amberlyst-15 (H^+) (2.58 g) in propan-2-ol (150 mL) was heated and stirred for 140 min, and then a further portion of Amberlyst-15 (H^+) (2.04 g) was added. After the consumption of the starting material (TLC, 4 h), the resin was filtered off and washed several times with hot methanol. The methanolic solution was concentrated under vacuum, the solid residue was triturated with methanol, filtered off, and washed with hexane and a small amount of cold methanol to give pure product **13d** (6.010 g, 88%).

*4′-Benzyloxy-5′-bromo-2′-hydroxyacetophenone (**15**)*

A mixture of 5′-bromo-2′,4′-dihydroxyacetophenone (**9**) (2.000 g, 8.656 mmol), potassium carbonate (1.195 g, 8.646 mmol), potassium iodide (57 mg, 0.343 mmol), and benzyl bromide (1.53 mL, 12.892 mmol) in absolute acetone (20 mL) was heated and stirred for 50 min, and then a further portion of benzyl bromide (1.53 mL, 12.892 mmol) was added. After 1 h the potassium carbonate was filtered off and washed with acetone (2 × 20 mL). The combined filtrates were evaporated, the solid residue was triturated with hexane and filtered to give 2.004 g (72%) of pure acetophenone **15**. The mother liquor was concentrated and submitted to column chromatography. The excess benzyl bromide was removed by eluting with hexane, and then the elution was continued with ethyl acetate to give a second crop of product as a light brown crystalline powder (589 mg, 21%), mp 157–158°C, lit. mp[30]: 154–155°C. ν_{max} (KBr)/cm^{-1} 3066, 1632 (C=O), 1616, 1367, 1329, 1256 (C–O–C), 1192, 810, 740. δ_H ($CDCl_3$) 2.54 (s, 3H, 2-H), 5.15 (s, 2H, CH_2), 6.49 (s, 1H, 3′-H), 7.34–7.44 (m, 5H, Ph), 7.87 (s, 1H, 6′-H), 12.63 (s, 1H, 2′-OH). δ_C ($CDCl_3$) 26.2 (C-2), 70.8 (CH_2), 101.5 (C-5′), 101.9 (C-3′), 114.7 (C-1′), 126.9 (C-2′,6′), 128.2 (C-4′), 128.6 (C-3′,5′), 134.7 (C-6′), 135.2 (C-1′), 160.8 (C-2′), 164.1 (C-4′), 201.9 (C-1). Anal. Calc. for $C_{15}H_{13}BrO_3$: C 56.10, H 4.08. Found: C 55.87, H 4.27%.

*7-Benzyloxy-6-bromo-2-hydroxychromanone (**16** ⇆ **16′**)*

In a flame-dried apparatus, sodium hydride (3.662 g, ~0.098 mol, 60% dispersion in mineral oil) rinsed with dry hexane was suspended in absolute THF (30 mL) and a mixture of 4′-benzyloxy-5′-bromo-2′-hydroxyacetophenone (**15**) (7.066 g, 22.001 mmol) and ethyl formate (4.58 mL, 57.17 mmol) were added dropwise in 10 min. After stirring for 10 min the mixture was poured into icy water and acidified by concentrated hydrochloric acid. The solid was filtered off, and washed with water and hexane to give 7.441 g (97%) of hemiacetal **16′** as a yellow powder, mp 197–198.5°C. ν_{max} (KBr)/cm^{-1} 3286 (OH), 3063, 1653 (C=O), 1437, 1360, 1266 (C–O–C), 1245, 1187, 1026, 737. δ_H ((D6)DMSO) 2.64 (dd, J_{AB} 16.8, $J_{2H,3Heq}$ 4.9, 1H, 3-H_{eq}), 2.98 (dd, J_{AB} 16.8, $J_{2H,3Hax}$ 3.5, 1H, 3-H_{ax}), 5.30 (s, 2H, PhCH_2), 5.82 (m, 1H, 2-H), 6.82 (s, 1H, 8-H), 7.34–7.49 (m, 5H, Ph), 7.70 (d, *J* 4.2, 1H, 2-OH), 7.84 (s, 1H, 5-H). δ_C ((D6) DMSO) 44.6 (C-3), 71.5 (Ph**C**H_2), 96.5 (C-2), 104.0 (C-8), 104.9 (C-6), 116.6 (C-4a), 128.3 (C-2′,6′), 129.0 (C-4′), 129.5 (C-3′,5′), 130.3 (C-5), 136.8 (C-1′), 160.3, 160.9 (C-7, C-8a), 189.7 (C-4). Anal. Calc. for $C_{16}H_{13}BrO_4$: C 55.04, H 3.75. Found: C 55.19, H 3.79%.

*7-Benzyloxy-8-bromochromone (**23**)*

A mixture of 7-hydroxy-8-bromochromone (**5**) (700 mg, 2.904 mmol), potassium carbonate (400 mg, 2.894 mmol), potassium iodide (19 mg, 0.114 mmol), benzyl bromide (1.02 mL, 8.64 mmol), and absolute acetone (20 mL) was heated and stirred for 5 h. The potassium carbonate was filtered off and washed with acetone (2 × 20 mL). The combined filtrates were evaporated, the solid residue was triturated with hexane and filtered off to give 535 mg (56%) of chromone **22** as a light brown powder, mp 123–125°C. ν_{max} (KBr)/cm^{-1} 3063, 1659 (C=O), 1616 (C=C), 1594, 1420, 1407, 1283, 1247 (C–O–C), 1062 (C–O–C), 810, 725. δ_H ($CDCl_3$) 5.31 (s, 2H, CH_2), 6.31 (d, *J* 5.7, 1H, 3-H), 7.08 (d, *J* 8.9, 1H, 6-H), 7.33–7.50 (m, 5H, Ph), 7.92 (d, *J* 5.7, 1H, 2-H), 8.12 (d, *J* 8.9, 1H, 5-H). δ_C ($CDCl_3$ + (D6) DMSO) 71.1 (CH_2), 100.2 (C-8), 110.8 (C-6), 112.5 (C-3), 119.7 (C-4a), 125.8 (C-4′), 126.8 (C-2′,6′), 128.1 (C-5), 128.5 (C-3′,5′), 135.2 (C-1′), 154.3 (C-8a), 159.4 (C-7), 176.3 (C-4). Anal. Calc. for $C_{16}H_{11}BrO_3$: C 58.03, H 3.35 Found: C 58.22, H 3.23%.

General Procedures for Heck Reactions

Conditions A: A mixture of bromochromone **14c** and **14d** (1.403 mmol), alkene (6.968 mmol), triethylamine (195 µL, 1.399 mmol), triphenylphosphine (37 mg, 0.141 mmol), and tetrakis(triphenylphosphine)palladium(0) (97 mg, 0.084 mmol) in *N*-methylpyrrolidone (15 mL) was heated at 100°C under nitrogen or argon. When the starting material disappeared the reaction was quenched with water, extracted with diethylether (3 × 50 mL), dried ($MgSO_4$), and evaporated to dryness. The solid residue was treated with a hexane/absolute ethanol mixture to give the pure product or was purified by column chromatography.

Conditions B: A mixture of bromochromone **6** (602 mg, 2.498 mmol), alkene (8.030 mmol), triethylamine (390 µL, 2.798 mmol), triphenylphosphine (65 mg, 0.248 mmol), and palladium(II)acetate (39 mg, 0.174 mmol) in *N*-methylpyrrolidone (15 mL) was heated at 160°C under nitrogen or argon. When the starting material disappeared the reaction was worked up as given for Conditions A.

Conditions C: A mixture of bromochromone **6**, **14a–d** (1.000 mmol), alkene (4.970 mmol), anhydrous potassium carbonate (207 mg, 1.498 mmol), potassium chloride (75 mg, 1.006 mmol), tetrabutylammonium bromide (530 mg, 1.644 mmol), and palladium(II)acetate (14 mg, 0.062 mmol) in *N*,*N*-dimethylformamide (10 mL) was heated at 100°C under

nitrogen or argon. When the starting material disappeared the reaction was worked up as given for Conditions A.

Further details of coupling reactions are shown in Table 1.

*(E)-7-Hydroxy-6-styrylchromone (**12**)*

Yield: 9.2% (Conditions B, reaction period: 36.5 h, conversion: 93%, elution: chloroform/acetone, 8/1), 6.8% (Conditions C, reaction period: 5 h, conversion: 48%, elution: chloroform/acetone, 8/1). mp 262–264°C. ν_{max} (KBr)/cm^{-1} 2610 (OH), 1628 (C=O), 1614 (C=C), 1556, 1478, 1400, 1310, 1304, 1260, 848, 820. δ_H ((D6)DMSO) 6.24 (d, *J* 5.5, 1H, 3-H), 6.95 (s, 1H, 8-H), 7.37–7.41 (m, 5H, α-H, β-H, Ph), 7.62 (d, *J* 7.0, 2H, 2′,6′-H), 8.16 (d, *J* 5.5, 1H, 2-H), 8.21 (s, 1H, 5-H), 11.25 (s, 1H, 7-OH). δ_C ((D6)DMSO) 103.5 (C-8), 112.8 (C-3), 118.2 (C-6), 123.0, 123.8 (C-α, C-β), 124.9 (C-4a), 127.5 (C-2′,6′), 128.7 (C-4′), 129.7 (C-3′,5′), 130.9 (C-5), 138.2 (C-1′), 157.0 (C-2), 157.6 (C-8a), 161.0 (C-7), 176.6 (C-4). Anal. Calc. for $C_{17}H_{12}O_3$: C 77.26, H 4.58. Found: C 77.20, H 4.31%.

*2-Phenyl-5H-furo[3,2-g]chromen-5-one (**13**)*

Yield: 5% (from chromone **6**, using Conditions C, reaction period: 5 h, isolated as a by-product in addition to cross-coupled product **12**), 7% (from chromone **14a**, using Conditions C, reaction period: 30 min, isolated as a by-product in addition to the free phenolic product **6**). Yellow crystals, mp 269–272°C. ν_{max} (KBr)/cm^{-1} 1644 (C=O), 1622 (C=C), 1472, 1300, 868, 828, 764. δ_H ($CDCl_3$) 6.35 (d, *J* 6.3, 1H, 3-H), 7.13 (s, 1H, 9-H), 7.39–7.51 (m, 3H, 3′,5′,4′-H), 7.58 (s, 1H, 3-H), 7.89 (overlapping s and d, 3H, 7-H and 2′,6′-H), 8.43 (s, 1H, 4-H). δ_C ($CDCl_3$) 99.8, 101.1 (C-3, C-9), 111.9 (C-6), 117.7 (C-4), 121.6 (C-3a), 125.2 (C-2′,6′), 128.0 (C-4a), 128.9 (C-3′,5′), 129.4 (C-4′), 129.5 (C-1′), 154.5 (C-8a), 155.3 (C-7), 157.4, 158.8 (C-2, C-9a), 177.9 (C-5). Anal. Calc. for $C_{17}H_{10}O_3$: C 77.85, H 3.84. Found: C 77.56, H 3.99%.

*(E)-7-Methoxymethoxy-6-styrylchromone (**17c**)*

Yield: 70% (Conditions C, reaction period: 1 h), mp 129–131°C. ν_{max} (KBr)/cm^{-1} 3050 (sp^2 CH) 2943, 2900, 1640 (C=O), 1618 (C=C), 1594, 1474, 1457, 1300, 1278, 1244 (C–O–C), 1227 (C–O–C), 1203, 1146, 1090 (C–O–C), 1039, 974, 918, 831. δ_H ($CDCl_3$) 3.52 (s, 3H, CH_3), 5.33 (s, 2H, CH_2), 6.27 (d, *J* 5.8, 1H, 3-H), 7.13 (s, 1H, 8-H), 7.22–7.44 (m, α-H, β-H, 3′,5′,4′-H) 7.54 (d, *J* 7.4, 2H, 2′,6′-H), 7.75 (d, *J* 5.8, 1H, 2-H), 8.40 (s, 1H, 5-H). δ_C ($CDCl_3$) 56.5 (CH_3), 94.6 (CH_2), 102.2 (C-8), 112.7 (C-3), 119.2 (C-6), 121.1, 122.7 (C-α, C-β), 126.1 (C-4a), 126.6 (C-2′,6′), 127.8 (C-4′), 128.6 (C-3′,5′), 131.0 (C-5), 137.2 (C-1′), 154.9 (C-2), 157.0, 158.6 (C-7, C-8a), 176.9 (C-4). Anal. Calc. for $C_{19}H_{16}O_4$: C 74.01, H 5.23. Found: C 74.19, H 5.99%.

*(E)-7-Benzyloxy-6-styrylchromone (**17d**)*

Yield: 82% (Conditions C, reaction period: 30 min, elution: ethyl acetate), mp 142–144°C. ν_{max} (KBr)/cm^{-1} 3058, 1648 (C=O), 1618 (C=C), 1595, 1457, 1297, 1260, 1241 (C–O–C), 1057 (C–O–C), 830. δ_H ($CDCl_3$) 5.18 (s, 2H, CH_2), 6.25 (d, *J* 6.3, 1H, 3-H), 6.84 (s, 1H, 8-H), 7.23–7.49 (m, 12H, 2 × Ph, α-H, β-H), 7.71 (d, *J* 6.3, 1H, 2-H), 8.38 (s, 1H, 5-H). δ_C ($CDCl_3$) 70.7 (CH_2), 100.0 (C-8), 112.8 (C-3), 118.6 (C-6), 121.3 (C-β), 122.9 (C-α), 125.9 (C-4a), 126.6, 127.2 (C-2′,6′, C-2′,6′), 127.7, 128.3 (C-4′, C-4′), 128.6, 128.7 (C-3′,5′, C-3′,5′), 131.1 (C-5), 135.5 (C-1′), 137.2 (C-1′), 154.6 (C-2), 157.1 (C-8a), 160.2 (C-7), 176.9 (C-4). Anal. Calc. for $C_{24}H_{18}O_3$: C 81.34, H 5.12. Found: C 81.27, H 5.07%.

*Ethyl (E)-3-[7-(Methoxymethoxy)-4-oxo-4H-1-benzopyran-6-yl]acrylate (**18c**)*

Yield: 22% (Conditions A, reaction period: 4 h, conversion: 76%, elution: toluene/ethyl acetate, 6/1, v/v), 8.1% (Conditions C, reaction period: 4 h, conversion: 76%, elution: toluene/acetic acid, 18/1, v/v). mp 113–114°C. ν_{max} (KBr)/cm^{-1} 2969, 1716 (C=O, ester), 1659 (C=O), 1620 (C=C), 1598, 1448, 1300, 1288, 1261 (C–O–C), 1240, 1210, 1169, 1053 (C–O–C), 923, 832. δ_H ($CDCl_3$) 1.35 (t, *J* 7.0, 3H, CH_2CH_3), 3.53 (s, 3H, OCH_3), 4.28 (q, *J* 7.0, 2H, CH_2CH_3), 5.35 (s, 2H, OCH_2O), 6.30 (d, *J* 5.8, 1H, 3′-H), 6.63 (d, *J* 16.1, 1H, 2-H), 7.18 (s, 1H, 8′-H), 7.79 (d, *J* 5.8, 1H, 2′-H), 8.00 (d, *J* 16.1, 1H, 3-H), 8.39 (s, 1H, 5′-H). δ_C ($CDCl_3$) 14.3 ($CH_2\mathbf{C}H_3$), 56.6 (OCH_3), 60.5 ($\mathbf{C}H_2CH_3$), 94.7 (OCH_2O), 102.6 (C-8′), 113.0 (C-3′), 119.2 (C-6′), 120.6 (C-3), 123.1 (C-4a′), 125.9 (C-5′), 137.8 (C-2), 155.0 (C-2′), 158.4, 159.6 (C-7′, C-8a′), 166.9 (C-1), 176.6 (C-4′). Anal. Calc. for $C_{16}H_{16}O_6$: C 63.15, H 5.30. Found: C 62.97, H 5.17%.

*Ethyl (E)-3-(7-Hydroxy-4-oxo-4H-1-benzopyran-6-yl) acrylate (**21**)*

Yield: 15% (Conditions C, reaction period: 4 h, conversion: 76%, elution: toluene/acetic acid, 18/1, v/v). Isolated as a by-product in addition to the protected product **18c**. mp 239–241°C (dec.). ν_{max} (KBr)/cm^{-1} 3075 (OH), 1711 (C=O, ester), 1617 (C=O, chromone + C=C), 1583, 1465, 1400, 1368, 1350, 1305, 1262 (C–O–C), 1179, 1048 (C–O–C), 870. δ_H ((D6)DMSO) 1.26 (t, *J* 7.0, 3H, CH_2CH_3), 4.19 (q, *J* 7.0, 2H, CH_2CH_3), 6.24 (d, *J* 6.3, 1H, 3′-H), 6.72 (d, *J* 16.2, 1H, 2-H), 6.97 (s, 1H, 8′-H), 7.84 (d, *J* 16.2, 1H, 3-H), 8.15 (d, *J* 6.3, 1H, 2′-H), 8.19 (s, 1H, 5′-H), 11.60 (vbr s, 1H, OH). δ_C ((D6)DMSO) 15.1 ($CH_2\mathbf{C}H_3$), 61.0 ($\mathbf{C}H_2CH_3$), 104.0 (C-8′), 113.0 (C-3′), 118.1 (C-6′), 120.3 (C-3), 121.7 (C-4a′), 127.4 (C-5′), 139.6 (C-2), 158.0 (C-2′), 159.0 (C-8a′), 162.5 (C-7′), 167.3 (C-1), 176.4 (C-4′). Anal. Calc. for $C_{14}H_{12}O_5$: C 64.61, H 4.65. Found: C 64.37, H 4.92%.

*Ethyl (E)-3-(7-Benzyloxy-4-oxo-4H-1-benzopyran-6-yl) acrylate (**18d**)*

Yield: 54% (Conditions C, reaction period: 90 min at 100°C, and then 2.5 h at 135°C), mp 183.5–185.5°C. ν_{max} (KBr)/cm^{-1} 2979, 1710 (C=O, ester), 1655 (C=O, chromone), 1620 (C=C), 1601, 1455, 1294, 1248 (C–O–C), 1175, 1057 (C–O–C), 833. δ_H ($CDCl_3$) 1.33 (t, *J* 6.9, 3H, CH_2CH_3), 4.26 (q, *J* 6.9, 2H, CH_2CH_3), 5.25 (s, 2H, CH_2), 6.29 (d, *J* 5.5, 1H, 3′-H), 6.65 (d, *J* 16.6, 1H, 2-H), 6.90 (s, 1H, 8′-H), 7.37–7.48 (m, 5H, Ph), 7.76 (d, *J* 5.5, 1H, 2′-H), 8.05 (d, *J* 16.6, 1H, 3-H), 8.38 (s, 1H, 5′-H). δ_C ($CDCl_3$) 14.2 (CH_3), 60.5 ($\mathbf{C}H_2CH_3$), 71.0 (Ph$\mathbf{C}H_2$), 100.6 (C-8′), 113.1 (C-3′), 118.6 (C-6′), 120.7 (C-2), 123.0 (C-4a′), 126.1, 128.4 (C-5′, C-4′), 127.2 (C-2′,6′), 128.8 (C-3′,5′), 135.1 (C-1′), 137.8 (C-3), 154.8 (C-2′), 158.6 (C-8a′), 161.0 (C-7′), 166.9 (C-1), 176.5 (C-4′). Anal. Calc. for $C_{21}H_{18}O_5$: C 71.99, H 5.18. Found: C 72.20, H 4.93%.

*(E)-3-[7-(Methoxymethoxy)-4-oxo-4H-1-benzopyran-6-yl]-2-propenal (**19c**)*

Yield: 18% (Conditions C, reaction period: 35 min, conversion: 93%, elution: toluene/ethyl acetate, 12/1, v/v). mp 160–162°C. ν_{max} (KBr)/cm^{-1} 2907, 2828, 1728 (C=O, aldehyde), 1676

(C=O, chromone), 1646, 1623 (C=C), 1599, 1286, 1233 (C–O–C), 1153, 1123, 1044 (C–O–C), 960. δ_H ($CDCl_3$) 3.54 (s, 3H, OCH_3), 5.38 (s, 2H, CH_2), 6.31 (d, *J* 6.5, 1H, 3′-H), 6.92 (dd, $J_{2,3}$ 16.1, $J_{1,2}$ 7.7, 1H, 2-H), 7.21 (s, 1H, 8′-H), 7.75–7.81 (overlapping doublets, 2H, 2-H, 2′-H), 8.40 (s, 1H, 5′-H), 9.72 (d, $J_{1,2}$ 7.7, 1H, 1-H). δ_C ($CDCl_3$) 56.8 (CH_3), 94.9 (CH_2), 102.9 (C-8′), 113.1 (C-3′), 119.4 (C-6′), 122.5 (C-4a′), 127.1 (C-5′), 130.7 (C-2), 146.0 (C-3), 155.2 (C-2′), 159.0, 159.6 (C-7′, C-8a′), 176.5 (C-4′), 193.9 (C-1). Anal. Calc. for $C_{12}H_8O_4$: C 66.67, H 3.73. Found: C 66.47, H 3.93%.

*Ethyl 3-[7-(Methoxymethoxy)-4-oxo-4*H*-1-benzopyran-6-yl]propanoate (**22c**)*

Yield: 36% (Conditions C, reaction period: 35 min, conversion: 93%, elution: toluene/ethyl acetate, 12/1, v/v). Isolated as a by-product in addition to the alkenylated product **19c**. mp 52–54°C. ν_{max} (KBr)/cm^{-1} 2959, 1727 (C=O, ester), 1650 (C=O, chromone), 1625 (C=C), 1480, 1460, 1296, 1238, 1228 (C–O–C), 1153, 1082, 1035 (C–O–C), 972, 851. δ_H ($CDCl_3$) 1.6 (t, *J* 6.9, 3H, CH_2CH_3), 2.64 (t, *J* 8.0, 2H, 2-H), 3.03 (t, *J* 8.0, 2H, 3-H), 3.51 (s, 3H, OCH_3), 4.14 (q, *J* 6.9, 2H, CH_2CH_3), 6.27 (d, *J* 5.8, 2H, 3′-H), 7.10 (s, 1H, 8′-H), 7.77 (d, *J* 5.8, 1H, 2′-H), 7.98 (s, 1H, 5′-H). δ_C ($CDCl_3$) 14.2 ($CH_2\mathbf{C}H_3$), 25.6 (C-3), 34.0 (C-2), 56.5 (OCH_3), 60.5 ($\mathbf{C}H_2CH_3$), 94.4 (OCH_2O), 101.8 (C-8′), 112.9 (C-3′), 119.0 (C-6′), 126.2 (C-5′), 128.4 (C-4a′), 154.9 (C-2′), 156.8 (C-8a′), 159.5 (C-7′), 172.3 (C-1), 177.0 (C-4). Anal. Calc. for $C_{14}H_{14}O_5$: C 64.12, H 5.38. Found: C 63.84, H 5.11%.

*(*E*)-3-(7-Benzyloxy-4-oxo-4*H*-1-benzopyran-6-yl)-2-propenal (**19d**)*

Yield: 21% (Conditions C, reaction period: 260 min, elution: toluene/ethyl acetate, 6/1, v/v). mp 77–80°C. ν_{max} (KBr)/cm^{-1} 2972, 1729 (C=O, aldehyde), 1654 (C=O, chromone), 1624 (C=C), 1458, 1290, 1244 (C–O–C), 1121, 1054 (C–O–C). δ_H ($CDCl_3$) 5.25 (s, 2H, CH_2), 6.30 (d, *J* 5.6, 1H, 3′-H), 6.86–6.95 (m, 2H, 2-H, 8′-H), 7.39–7.45 (m, 5H, Ph), 7.74–7.82 (overlapping doublets, 2H, 3-H, 2′-H), 8.40 (s, 1H, 5′-H), 9.68 (d, *J* 7.6, 1H, 1-H). δ_C ($CDCl_3$) 76.6 (CH_2), 100.8 (C-8′), 113.2 (C-3′), 122.4 (C-6′), 125.0 (C-4a′), 127.0 (C-4′), 127.5 (C-2′,6′), 128.7 (C-5′), 128.9 (C-3′,5′), 130.6 (C-2), 134.8 (C-1′), 145.8 (C-3), 154.9 (C-2′), 158.0 (C-8a′), 160.9 (C-7′), 176.3 (C-4′), 193.9 (C-1). Anal. Calc. for $C_{19}H_{14}O_4$: C 74.50, H 4.61. Found: C 74.77, H 4.59%.

*Ethyl 3-(7-Benzyloxy-4-oxo-4*H*-1-benzopyran-6-yl) propanoate (**22d**)*

Yield: 31% (Conditions C, reaction period: 260 min, elution: toluene/ethyl acetate, 6/1, v/v). Isolated as a by-product in addition to the alkenylated product (**19d**). mp 63.5–65°C. ν_{max} (KBr)/cm^{-1} 2962, 1722 (C=O, ester), 1654 (C=O, chromone), 1602, 1455, 1294, 1261 (C–O–C), 1097, 1055 (C–O–C), 802. δ_H ($CDCl_3$) 1.23 (t, *J* 7.1, 3H, CH_2CH_3), 2.66 (t, *J* 7.7, 2H, 2-H), 3.06 (t, *J* 7.7, 2H, 3-H), 4.11 (q, *J* 7.1, 2H, CH_2CH_3), 5.16 (s, 2H, CH_2), 6.25 (d, *J* 5.9, 1H, 3′-H), 6.85 (s, 1H, 8′-H), 7.35–7.43 (m, 5H, Ph), 7.73 (d, *J* 5.9, 1H, 2′-H), 7.97 (s, 1H, 5′-H). δ_C ($CDCl_3$) 14.1 ($CH_2\mathbf{C}H_3$), 25.5 (C-3), 33.7 (C-2), 60.3 ($\mathbf{C}H_2CH_3$), 70.3 (Ph$\mathbf{C}H_2$), 99.6 (C-8′), 112.8 (C-3′), 118.2 (C-4a′, C-6′), 125.9 (C-4′), 126.9 (C-2′,6′), 128.1 (C-5′), 128.6 (C-3′,5′), 135.5 (C-1′), 154.6 (C-2′), 156.9 (C-8a′), 160.9 (C-7′), 172.6 (C-1), 176.7 (C-4′). Anal. Calc. for $C_{21}H_{20}O_5$: C 71.58, H 5.72. Found: C 71.79, H 5.61%.

*(*E*)-3-(7-Benzyloxy-4-oxo-4*H*-1-benzopyran-6-yl) acrylonitrile [(*E*)-**20d**]*

Yield: 26% (Conditions A, reaction period: 24 h, elution: toluene). mp 187–190°C. ν_{max} (KBr)/cm^{-1} 3094, 2215 (CN), 1644 (C=O), 1621 (C=C), 1599, 1447, 1292, 1271, 1245, 1232, 1058, 972, 838. δ_H ($CDCl_3$) 5.21 (s, 2H, CH_2), 6.13 (d, *J* 16.8, 1H, 2-H), 6.30 (d, *J* 5.7, 1H, 3′-H), 6.95 (s, 1H, 8′-H), 7.44 (s, 5H, Ph), 7.66 (d, *J* 16.8, 1H, 3-H), 7.78 (d, *J* 5.7, 1H, 2′-H), 8.27 (s, 1H, 5′-H). δ_C ($CDCl_3$) 71.4 (CH_2), 98.8 (C-2), 100.8 (C-8′), 113.2 (C-3′), 118.3, 118.6 (C-1, C-4a′), 121.8 (C-6′), 126.5 (C-4′), 127.6 (C-2′,6′), 128.9 (C-5′), 129.0 (C-3′,5′), 134.5 (C-1′), 144.4 (C-3), 155.0 (C-2′), 159.0 (C-8a′), 160.8 (C-7′), 176.2 (C-4′). Anal. Calc. for $C_{19}H_{13}NO_3$: C 75.24, H 4.32, N 4.62. Found: C 75.09, H 4.40, N 4.44%.

*(*Z*)-3-(7-Benzyloxy-4-oxo-4*H*-1-benzopyran-6-yl) acrylonitrile [(*E*)-**20d**]*

Yield: 2.9% (Conditions A, reaction period: 24 h, elution: toluene). mp 177–178°C. ν_{max} (KBr)/cm^{-1} 3071, 2206 (CN), 1649 (C=O), 1622 (C=C), 1595, 1460, 1289, 1256, 1049, 834. δ_H ($CDCl_3$) 5.19 (s, 2H, CH_2), 5.56 (d, *J* 11.9, 1H, 2-H), 6.31 (d, *J* 5.8, 1H, 3′-H), 6.93 (s, 1H, 8′-H), 7.43 (s, 5H, Ph), 7.51 (d, *J* 11.9, 1H, 3-H), 7.76 (d, *J* 5.8, 1H, 2′-H), 8.77 (s, 1H, 5′-H). Anal. Calc. for $C_{19}H_{13}NO_3$: C 75.24, H 4.32, N 4.62. Found: C 75.22, H 4.19, N 4.70%.

*(*E*)-7-Benzyloxy-8-styrylchromone (**24**)*

Yield: 42% (Conditions C, reaction period: 1 h at 100°C, 1.5 h at 140°C), mp 142–144°C. ν_{max} (KBr)/cm^{-1} 1669 (C=O), 1615 (C=C), 1589, 1418, 1276, 1249, 1068, 812, 746. δ_H ($CDCl_3$) 5.28 (s, 2H, CH_2), 6.31 (d, *J* 6.1, 1H, 3-H), 7.09 (d, *J* 9.0, 1H, 6-H), 7.25–7.51 (m, 6H, Ph, α-H), 7.65 (d, *J* 16.7, 1H, β-H), 7.88 (d, *J* 6.1, 1H, 2-H), 8.07 (d, *J* 9.0, 1H, 5-H). δ_C ($CDCl_3$) 71.1 (CH_2), 110.6 (C-6), 112.5 (C-3), 114.9 (C-8), 117.3 (C-α), 119.2 (C-4a), 125.4 (C-β), 126.5, 127.4 (C-2′,6′, C-2′,6′), 127.8, 128.3 (C-4′, C-4′), 128.6, 128.7 (C-3′,5′, C-3′,5′), 134.9 (C-5), 135.9 (C-1′), 138.1 (C-1′), 154.9 (C-2), 155.2 (C-8a), 160.4 (C-7), 177.2 (C-4). Anal. Calc. for $C_{24}H_{18}O_3$: C 81.34, H 5.12. Found: C 81.45, H 5.21%.

*General Procedure for the Cleavage of the Benzyl Group of 6-Alkenyl-7-benzyloxychromones **17d** and **18d** with Boron Tribromide*

To a stirred and cooled (0°C) solution of chromone **17d** or **18d** (0.285 mmol) in dry dichloromethane (3 mL), boron tribromide (55 μL, 0.571 mmol) was added and allowed to react for 30 min, and then for another 1 h at room temperature. The mixture was poured into saturated sodium hydrogen carbonate, extracted with ethyl acetate (3 × 40 mL), dried ($MgSO_4$), and concentrated. The solid residue was triturated with diisopropyl ether and filtered off to give pure hydroxychromones **12** or **21**. Physical and spectroscopic data of the products agreed with those isolated as by-products (see above).

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