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Synthesis of 2,3,6,8-Tetrasubstituted Chromone Scaffolds

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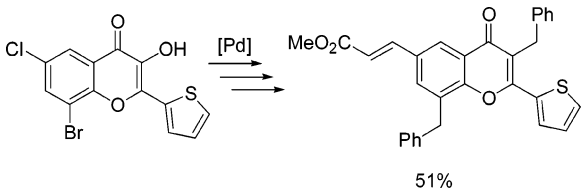

A useful and efficient synthetic strategy to 2,3,6,8-tetrasubstituted chromone derivatives has been developed. 2-Aryl/styryl-8-bromo-6-chloro-3-hydroxychromone derivatives were synthesized and used as scaffolds by introducing a variety of substituents in the 3-, 6-, and 8-positions using palladium-mediated reactions. Excellent regioselectivity in all positions could be obtained by performing reactions in the 8-position first, in which Stille, Heck, Suzuki, and Sonogashira reactions gave good to excellent yields of product (63−98%). Stille and Heck reactions in the 6-position also gave the desired products in good yields (64−86%). The hydroxy group in the 3-position was activated as a triflate and used in productive Stille reactions (63−94%). This hydroxyl group was also used in O-alkylation reactions with different functionalized alkyl bromides (57−88%). The flavonoids, which are based on the chromone structure, and other related ring systems, have several interesting biological activities. The chromones are also interesting structural scaffolds, and they have for example been designed to be used as mimetics of short peptides. The versatile applicability of chromone derivatives and especially their potential use in drug discovery implicates the importance of access to efficient synthetic routes to such compounds.

Introduction

The flavonoids represent one of the largest groups of natural products known; several thousand derivatives have been identified.[1] The flavonoids are based on the flavone (2-phenyl-4-chromone) and related ring systems and constitute an important class of widely distributed plant secondary metabolites. In addition to the various functions of flavonoids in plants, their widespread distribution in nature, their structural variability, their relatively low toxicity, and their antioxidant activities have increased the interest in flavonoids as beneficial for human health.[2] Several therapeutically interesting biological activities of certain flavonoids have been reported including anticancer,[3−8] anti-HIV,[9−11] and antioxidant[12−14] properties.

The chromones are also interesting as structural scaffolds and have been assigned as privileged structures for drug development.[15] Chromone derivatives, with different functionalized substituents, have for example been designed to be used as mimetics of short peptides.[16] Furthermore, the flavonols (3-hydroxy-2-phenyl-chromones) have been demonstrated to have excellent fluorescent properties,[17−21] which could be exploited

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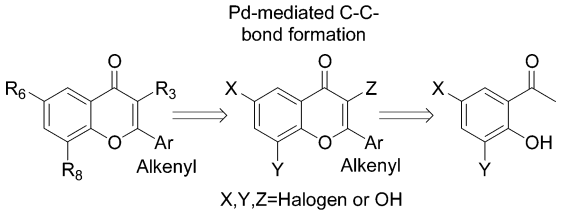


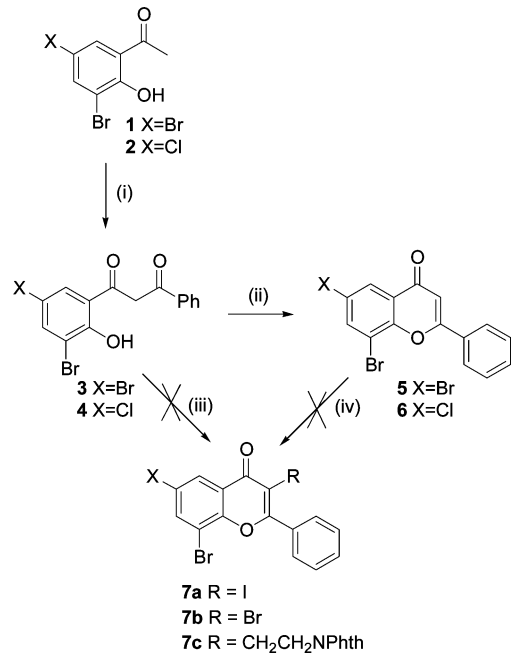
FIGURE 1. Retrosynthetic analysis of 2,3,6,8-tetrasubstituted chromones.

in various applications, e.g. as probes to study lipid membranes and proteins.[22−24] The versatile biological applicability of chromone derivatives and their potential use in drug discovery implicate the importance of access to efficient synthetic routes to well designed substituted chromone derivatives.

The focus of the present study is the synthesis of 2,3,6,8-tetrasubstituted chromones (Figure 1). A literature search revealed that only a few chromone derivatives with this substitution pattern have been reported previously.[25−29] In addition, the published compounds were cyclized to the chromone after the substituents had been introduced, and only undemanding substituents (e.g. Me, $COCH_3$ and OH) had been used.

The aim of the present study was therefore to develop a general synthetic route to 2,3,6,8-tetrasubstituted chromones with functionalized substituents using a scaffold approach. The study was started with the development of a scaffold for 3,6,8-trisubstituted flavones; however, other aryl groups than phenyl can also be introduced in the 2-position. As the substituents are connected to the ring system through carbon−carbon bonds and the substituents will contain various functional groups, the most effective and versatile chemistry was believed to be accomplished using palladium-mediated reactions. Some initial results were published recently by our group, where the general synthetic strategy was also presented.[30]

SCHEME 1. Synthesis of 3,6,8-Trisubstituted Flavones[a]



[a] Reagents and conditions: (i) (a) Benzoyl chloride, pyridine, rt, 1 h; (b) KOH, pyridine, 50 °C, 2 h; (ii) HCl, HOAc, reflux, 14 h; (iii) (a) ICl, DMF; or (b) Br_2, dioxane/DMF; (iv) (a) NIS or NBS, $CHCl_3$ or DMF; or (b) NIS or NBS, AIBN, benzene; or (c) NaH, LDA or K_2CO_3, $BrCH_2CH_2NPhth$, THF or acetone. Phth = Phthalimide.

Results and Discussion

To introduce substituents in the 3-, 6-, and 8-positions of the flavone ring system, palladium-mediated chemistry was used. For such reactions to proceed, either halogens or triflates at these positions are needed.

Halogens at the 6- and 8-positions can easily be introduced in the starting material before the cyclization of the chromone ring (Scheme 1). The chosen scaffold approach required a working strategy for regioselectivity. Therefore, the difference in reactivity between the 6- and 8-positions was first studied. A Heck reaction with methyl acrylate on 6,8-dibromoflavone (**5**) gave mixtures of products, as both 6- and 8-monosubstituted and 6,8-disubstituted flavones were formed. Thus, the difference in reactivity at the 6- and 8-positions in flavones was not sufficient to provide regioselectivity; instead, the use of two different halogens (e.g. Br and Cl) was needed.

Several strategies to introduce halogens at the 3-position of flavones are available in the literature.[31−33] However, in our hands these reactions proved to be difficult. Reactions of **4** with ICl in refluxing DMF to obtain **7a** or with Br_2 in dioxane/DMF to afford **7b** did not result in any product formation (Scheme 1). We also failed to introduce iodide or bromide in the 3-position of flavone **6**, as reactions with NIS or NBS, respectively, in different solvents did not give any of the desired products. Alternatively, the 3-position has also been directly alkylated.[34,35] Alkylation of **6** with different alkyl bromides (e.g.

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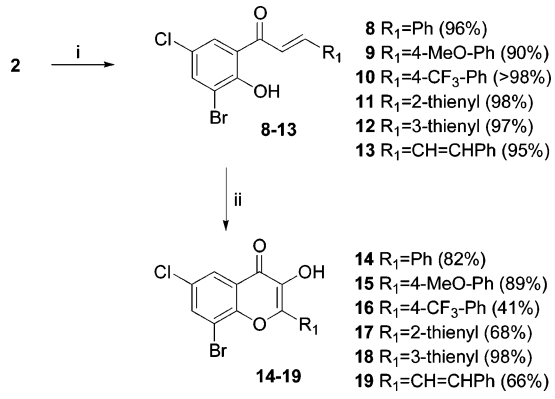
SCHEME 2. Synthesis of 8-Bromo-6-chloro-3-hydroxy-chromones[a]



[a] Reagents and conditions: (i) Aldehyde, KOH, EtOH, 50 °C→RT, 14 h; (ii) NaOH, H_2O_2, MeOH/THF, 0 °C→RT, overnight.

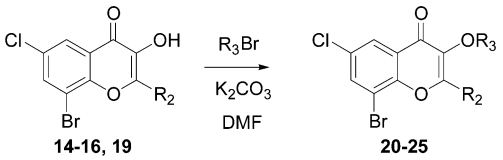
N-(2-bromoethyl)phthalimide) in the present of a base (NaH, LDA, or K_2CO_3) did not, however, result in any product formation.

Due to problems in introducing halogens or performing alkylation reactions in position 3, another synthetic strategy starting from the flavonol (3-hydroxyflavone) was adopted. The 3-hydroxyl group can when needed be transformed to a triflate which is also a good leaving group in Pd-mediated reactions.[36−39] In addition, the 3-hydroxyl group can be utilized in O-alkylation reactions which is an easy alternative to palladium-mediated chemistry if an ether link can be tolerated in the target compound. Variations in the substitution pattern in the 2-position to obtain 2,3,6,8-tetrasubstituted chromones can be accomplished by introducing different aryl/styryl groups before cyclization of the chromone ring.

The 2-aryl/styryl-8-bromo-6-chloro-3-hydroxy-chromones were synthesized from 3-bromo-5-chloro-2-hydroxy-acetophenone (**2**) and the appropriate aldehyde using KOH in EtOH, followed by cyclization of the intermediate chalcone using NaOH and H_2O_2 in THF/MeOH (Scheme 2).[40−43] Both reaction steps gave generally good yields. In the formation of the chalcone, *p*-methoxybenzaldehyde showed the lowest reactivity, whereas the cyclization of the chalcone from *p*-trifluoromethylbenzaldehyde gave the lowest yield of flavonol (41%). Thus, electron rich aryl groups decrease the reactivity in the first step, and electron deficient aryl groups decrease the reactivity in the second step. The use of cinnamic aldehyde afforded **19** also in good yield (66%).

O-Alkylation in the 3-Position. O-Alkylation in the 3-position was used to introduce different functionalized substituents (Table 1). Compounds **14**−**16** were alkylated with the appropriate alkyl bromide in the presence of K_2CO_3 in DMF to obtain **20**−**23** and **25** in good yields (71−88%). In the same reaction, compound **19** gave **24** which was isolated in a modest yield (57%). This was most likely a result of the difficulties observed in the separation of unreacted *N*-(2-bromoethyl)-phthalimide from the product by flash chromatography.

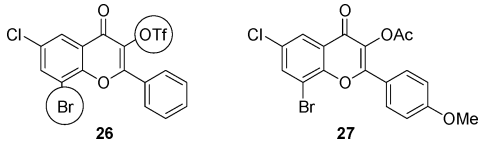
TABLE 1. O-Alkylation Reactions in the 3-Position of the Flavonols 14−16 and 19



compound	R_2	R_3	yield[a] (%)
20	Ph	$(CH_2)_3$NPhth	87[b]
21	4-MeO−Ph	$(CH_2)_3$NPhth	88
22	4-CF_3−Ph	$(CH_2)_3$NPhth	86
23	Ph	$(CH_2)_2$NPhth	71
24	CH═CHPh	$(CH_2)_2$NPhth	57
25	Ph	CH_2CO_2Et	81

[a] Isolated yields. [b] For synthesis of **20**, see ref 30. Phth = phthalimide.

Palladium-Mediated Reactions. Triflates and bromides are known to have similar reactivity in Pd-mediated reactions. To see whether this is true also for the 3- and 8-positions in 8-bromo-6-chloro-3-trifluoromethylsulfonyl-flavone, a Stille cross-coupling reaction on **26** using allyltributyltin was performed. The reaction resulted in a mixture of 3- and 8-monosubstituted and 3,8-disubstituted products which showed that there was no selectivity between a 3-triflate and an 8-bromo substituent in the flavone ring system. However, it showed clearly that the 3-triflate is useful in Pd-coupling reactions. Thus, the synthetic strategy starting from 2-aryl/styryl-8-bromo-6-chloro-3-hydroxy-chromone allows the introduction of a triflate group at the 3-position when needed. Although the 8-position has to be reacted first, this allows flexibility regarding the order that the substituents at the 3- and 6-positions are introduced.



However, the free 3-hydroxyl group could cause solubility problems in typical organic solvents and/or difficulties in flash chromatographic purifications. Acetylation of the hydroxyl group circumvented these problems, e.g. **15** was acetylated to **27** using acetyl chloride and NEt_3 in CH_2Cl_2 in good yield (>99%).

Stille and Heck reactions were used for the introduction of substituents in the 3-, 6-, and 8-positions, whereas Sonogashira and Suzuki reactions were only tested in the 8-position.[44−47] In our initial study we used the Stille cross-coupling with allyl

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tributyltin and the Heck reaction with methyl acrylate, and it was shown that it is possible to obtain the desired products in good yield and with excellent regioselectivity.[30]

The Stille reaction was used to introduce either an allyl or benzyl substituent. The allyl substituent can easily be functionalized using a variety of reactions, e.g. hydroxylation followed by oxidation to an aldehyde or a carboxylic acid. The Heck reaction was used to introduce an α,β-unsaturated ester functionality which can also be modified by further reactions.

The Sonogashira reaction was used to introduce either a TMS-acetylene or a Boc-protected propargylamine. After removing the TMS protecting group, the triple bond can be converted to other functionalities e.g. via oxidation or via reduction to ethylene. A terminal triple bond can also be used in further Sonogashira reactions, in reactions with azides,[48] or in reaction with primary amines to give imines.[49] The Suzuki reaction was used to introduce a sterically demanding naphthyl group in the 8-position.

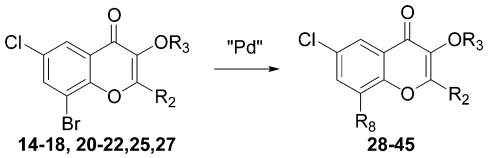
Reactions at Position 8. Stille Cross-Coupling Reactions. The Stille cross-coupling reaction was first performed on **14** and **20** using allylSnBu$_3$ or benzylSnBu$_3$ and Pd(PPh$_3$)$_4$ with thermal heating, to provide **28** and **37** in good yields (89% and 63%, respectively) as was reported earlier.[30] However, when reacting compounds with other groups than phenyl at the 2-position, only fast heating to high temperatures in a sealed vessel using a microwave cavity gave the desired high yields and reproducibility. Therefore, microwave heating at 150−160 °C in DMF was preferable for these reactions.[50] Stille cross-coupling of **14**−**18** in a microwave cavity gave products **29**−**33** in good to excellent yields (64−98%) (Table 2). The free 3-hydroxy groups caused some difficulties in the purification, as repeated flash chromatography was needed. However, when using the 3-acetoxy derivative **27**, the product was easily purified by flash chromatography to give **45** in good yield (78%). Stille reactions on substrates with other substituents present in the 3-position were also investigated, e.g. coupling of **20**-**22** with benzylSnBu$_3$ or allylSnBu$_3$ gave the corresponding products (**37**-**40**) in high yields (63−95%).

Heck Reactions. Heck reactions of **14** with methyl acrylate, Pd(OAc)$_2$, P(*o*-tolyl)$_3$, and NEt$_3$ in DMF gave **34** in 80% yield (Table 2). The same reaction but with **20** as starting material was also productive affording **41** in 87% yield.

Sonogashira Reactions. The Sonogashira reaction was run in a microwave cavity at 120 °C using **14**, TMS-acetylene, PdCl$_2$(PPh$_3$)$_2$, NEt$_3$, and CuI in THF to afford **35** in 71% yield (Table 2). Using **20** as starting material with the same conditions provided **42** (91%). Using **25** as starting material in a Sonogashira coupling with Boc-protected propargylamine gave **44** (83%).

Suzuki Reactions. Suzuki reactions were run using **14**, 2-naphthylboronic acid, Pd(PPh$_3$)$_4$, and Cs$_2$CO$_3$ in DMF heated in a microwave cavity to obtain **36** (79%) (Table 2). However, the crude alcohol was first transferred to its corresponding acetyl ester to simplify the purification. The pure product was directly hydrolyzed to afford **36**. The same reaction conditions were used with **20** as starting material to give **43** (86%).

TABLE 2. Palladium-Mediated Reactions in the 8-Position



compd	method[a]	R_2	R_3	R_8	yield[b] (%)
28	A[c]	Ph	H	allyl	89
29	A[d]	Ph	H	Bn	64
30	A[d]	4-MeO-Ph	H	Bn	77
31	A[d]	4-CF$_3$-Ph	H	Bn	86
32	A[d]	2-thienyl	H	Bn	98
33	A[d]	3-thienyl	H	Bn	89
34	B	Ph	H	CH═CHCO$_2$Me	80
35	C	Ph	H	C≡C-TMS	71
36	D	Ph	H	2-naphthyl	79[e]
37	A[c]	Ph	(CH$_2$)$_3$NPhth	Bn	63
38	A[d]	4-MeO-Ph	(CH$_2$)$_3$NPhth	Bn	81
39	A[d]	4-CF$_3$-Ph	(CH$_2$)$_3$NPhth	Bn	95
40	A[d]	Ph	(CH$_2$)$_3$NPhth	allyl	91
41	B	Ph	(CH$_2$)$_3$NPhth	CH═CHCO$_2$Me	87
42	C	Ph	(CH$_2$)$_3$NPhth	C≡C-TMS	91
43	D	Ph	(CH$_2$)$_3$NPhth	2-naphthyl	86
44	C	Ph	CH$_2$CO$_2$Et	C≡CCH$_2$NHBoc	83
45	A[d]	4-MeO-Ph	COMe	Bn	78

[a] A: AllylSnBu$_3$ or BnSnBu$_3$, Pd(PPh$_3$)$_4$, DMF; B: methyl acrylate, Pd(OAc)$_2$, P(*o*-tol)$_3$, NEt$_3$, DMF, 160 °C, 30 min, microwave heating; C: HC≡C-TMS or HC≡CCH$_2$NHBoc, PdCl$_2$(PPh$_3$)$_2$, NEt$_3$, CuI, THF, 120 °C, 30 min, microwave heating; D: 2-Naphthylboronic acid, Pd(PPh$_3$)$_4$, Cs$_2$CO$_3$, DMF, 150 °C, 30 min, microwave heating. [b] Isolated yields. [c] Thermal heating. [d] Microwave heating. [e] To overcome difficulties in the purification the crude product was acetylated. After the purification the product was deacetylated using NaOMe in MeOH.

The results show that different Pd-mediated reactions can be used to successfully introduce a variety of substituents in the 8-position with excellent regioselectivity using standard protocols. No differences in reactivity were observed between the different chromone derivatives used, indicating that the 2-aryl substituents do not influence the Pd-reactions in the 8-position.

Reactions at Position 3. Stille Cross-Couplings. The use of aryl triflates in Pd-chemistry has been well established.[38,45,46] Triflates of **28** and **30**−**33** were synthesized in moderate to good yield (45−77%) using triflic anhydride and NEt$_3$ or pyridine in CH$_2$Cl$_2$. The triflates were used in Stille couplings with allylSnBu$_3$ or benzylSnBu$_3$ and Pd(PPh$_3$)$_4$ in a microwave cavity in high yields (63−94%). This result indicates that the electron-withdrawing or -donating properties in the 2-aryl ring do not influence the reactivity of the triflate group in Stille reactions (Table 3).

Heck Reactions. Heck reactions were attempted using the same conditions as for the reactions in the 8-position; however, only trace amounts of product were observed in reactions at the 3-position. Using standard protocols did also result in trace amounts of product.[51,52] To improve the result, different reaction conditions were tested using a range of Pd-catalysts [Pd(OAc)$_2$, PdCl$_2$(PPh$_3$)$_2$, Pd(PPh$_3$)$_4$], ligands [PPh$_3$, P(*o*-tolyl)$_3$, dppp], additives [LiCl, Tl$_2$CO$_3$], bases [NEt$_3$, Cs$_2$CO$_3$], solvents [DMF, dioxane], and reaction temperatures [80 °C, 160 °C, 180 °C]. Unfortunately, changing the reaction conditions did not improve

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(50) The previously reported syntheses of **28** and **37** were not repeated with microwave heating due to previously satisfying yields using thermal heating.

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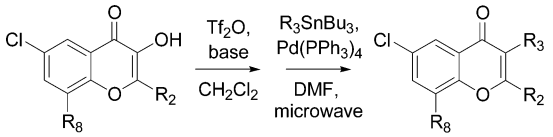
(52) Haaseheld, M.; Hatzis, M.; Mann, J. *J. Chem Soc. Perkin Trans. 1* **1993**, 2907−2911

TABLE 3. Palladium-Mediated Reactions in the 3-Position

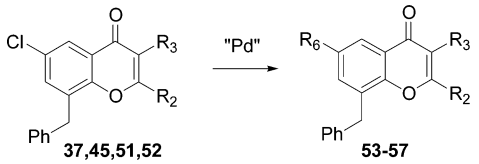


28, 30-33 **46-51**

compd	R_2	R_3	R_8	yield[a] (%)
46	Ph	allyl	allyl	72
47	4-MeO−Ph	allyl	Bn	63
48	4-CF_3−Ph	allyl	Bn	70
49	2-Thienyl	allyl	Bn	78
50	3-Thienyl	allyl	Bn	94
51	2-Thienyl	Bn	Bn	69

[a] Isolated yields using the triflates as starting material.

TABLE 4. Palladium-Mediated Reactions in the 6-Position



37,45,51,52 **53-57**

compd	method[a]	R_2	R_3	R_6	yield[b] (%)
53	A	Ph	$O(CH_2)_3NPhth$	allyl	77
54	B	Ph	$O(CH_2)_3NPhth$	$CH{=}CHCO_2Me$	86
55	B	4-MeO-Ph	OAc	$CH{=}CHCO_2Me$	64
56	B	Ph	$O(CH_2)_3NHBoc$	$CH{=}CHCO_2Me$	85
57	B	2-thienyl	Bn	$CH{=}CHCO_2Me$	76

[a] A: $AllylSnBu_3$, Pd_2dba_3, P(*t*-Bu)$_3$, dioxane, 80 °C, 14 h; B: methyl acrylate, Pd_2dba_3, [P(*t*-Bu)$_3$H]BF_4, NEt_3, dioxane, 160 °C, 30 min, microwave heating. [b] Isolated yields. Phth = phthalimide.

the result. The major side products were found to be the 3-H derivative formed by reduction of the triflate and/or the 3-OH derivative formed by hydrolysis of the triflate.

Reactions at Position 6. The reactivity in the 6-position in the flavone system using Stille and Heck reactions was shown in our previous study.[30] Here the same reactions were used to react the different chromone derivatives to investigate if there was a difference in reactivity depending on substituents in positions 2 or 3. We found that to get the Pd-mediated reactions to proceed in the 6-position, a more electron-rich and sterically hindered phosphine ligand, such as P(*tert*-Bu)$_3$, was necessary.[47]

Stille Cross-Couplings. A Stille cross-coupling of **37** using $AllylSnBu_3$, Pd_2dba_3, and P(*tert*-Bu)$_3$ in dioxane at 80 °C provided **53** in good yield (77%) (Table 4).

Heck Reactions.[53] Also a Heck reaction using methyl acrylate, Pd_2dba_3, [P(*tert*-Bu)$_3$H]BF_4, and NEt_3 in dioxane on **37** or **45** gave the desired products **54** and **55** (86 and 64%, respectively).[54]

It is possible to change the phthalimido protecting group in the substituent in position 3 of **20** to a Boc-group to provide **52** and thereafter run a Pd-coupling reaction in position 6.[55] A Heck reaction of **52** using methyl acrylate, Pd_2dba_3, [P(*tert*-Bu)$_3$H]BF_4, and NEt_3 in dioxane gave **56** in 85% yield. A Boc-group can in many instances, e.g. in solid-phase peptide synthesis, be preferable to a phthalimido protecting group.

A Heck reaction was also performed on **51** using methyl acrylate, Pd_2dba_3, [P(*tert*-Bu)$_3$H]BF_4, and NEt_3 in dioxane in a microwave cavity to afford **57** in 76% yield. This product verifies that three different substituents could be introduced regioselectively in high yield (**57** was formed in 51% yield from **17**).

Conclusions

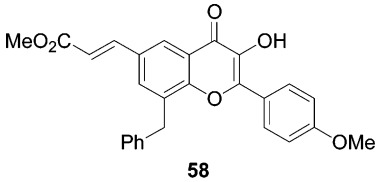
In the present study a useful general synthetic strategy for 2,3,6,8-tetrasubstituted chromones was developed starting from 2-aryl/styryl-8-bromo-6-chloro-3-hydroxychromone. This scaffold approach allows introduction of different substituents in the 3-, 6-, and 8-positions using palladium-mediated reactions. These reactions can without difficulty be performed regioselectively. The 2-substituent consisted of different aryls (phenyl, *p*-methoxyphenyl, *p*-trifluoromethylphenyl, 2-thienyl, 3-thienyl) and styryl which were introduced before the cyclization of the flavonol ring. The results show that the choice of aryl/styryl does not affect the reactivity at the other positions of the chromone ring system. In general, the palladium-mediated reactions gave high yields at all positions. Fast heating to high temperatures in a sealed vessel in a microwave cavity was found to be a more effective form of heating as compared to traditional thermal heating as it at all times gave higher yields of products.

The 8-position was reacted through different palladium-mediated reactions, including Stille, Heck, Sonogashira, and Suzuki reactions, all affording high yields of products. Substituents could thereafter be introduced either in the 3- or 6-position. If the 6-position was reacted before the 3-position, the 3-hydroxyl group was preferably acetylated to ease the purification of the intermediates. The 3-hydroxyl group was activated by formation of the corresponding triflate and reacted in Stille and Heck reactions using the same conditions as for the 8-position. Surprisingly, the Heck reaction failed to afford the desired products; this exception in the series of otherwise successful palladium-mediated reactions could not be fully explained. Also the 6-position was reacted in Stille and Heck reactions, providing the desired products in high yields. The reaction conditions were different from those used in the 3- and 8-positions, due to the lower reactivity of aryl chlorides compared to aryl bromides or triflates.

The palladium-mediated reactions were used to introduce a variety of substituents. Various combinations were also tried

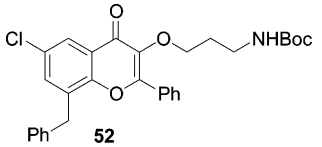
(53) The phosphine was added as the [P(*tert*-Bu)$_3$H]BF_4 salt which is more stable and easier to handle than the phosphine itself. This phosphine is activated when base is added.

(54) Compound **55** could easily be deacetylated using NaOMe in MeOH to obtain **58** in excellent yield (>98%).



58

(55) Deprotection of the phthalimide group in **37** was performed using ethylenediamine in refluxing ethanol for 5 h. The primary amine was not isolated but instead reacted with di-*tert*-butyl dicarbonate in MeOH/THF at reflux for 14 h to obtain the Boc-protected amine **52** (87%).



52

out, since different biological applications have different requirements. The use of chromone derivatives as peptide mimetics might require an amino group in one position and a carboxylic acid group at another. As the flavonols are also studied as fluorescent probes, substituents with conjugated unsaturated moieties may be needed to optimize the spectral properties of the compounds, or substituents with different functional groups may be needed to attach the fluorescent flavonol derivative to other compounds.

Flavone and other chromone derivatives have high potential in drug discovery. Synthesis of large compound libraries is a general trend in a modern drug discovery process. Furthermore, computer-aided drug design can be used to perform virtual screening before the compounds are synthesized. Both methodologies require rapid synthesis of the compounds preferably from a limited number of starting materials. The presented scaffold approach in combination with palladium-mediated chemistry meets these requirements.

Experimental Section

1-(3,5-Dibromo-2-hydroxyphenyl)-3-phenyl-propan-1,3-dione (3).[56] Benzoyl chloride (0.4 g, 2.9 mmol) was added to 3,5-dibromo-2-hydroxyacetophenone (**1**) (0.5 g, 1.7 mmol) in pyridine (15 mL) and stirred for 2 h. The solution was acidified with HCl (1 M) and extracted with CH_2Cl_2 (4 × 20 mL). The combined organic phases were dried with $MgSO_4$ before the solvent was removed under vacuum. The residue was dissolved in pyridine (40 mL), KOH (0.2 g, 4.2 mmol) was added, and the mixture was warmed to 50 °C for 4 h. The solution was poured into HCl (1 M), and the precipitate was filtered off and washed with EtOH to give 0.6 g (93%) of **3.** The product was used in the next step without further characterization. Mp 120−121 °C. ^{1}H NMR δ 6.70 (s, 1H), 7.47−7.50 (m, 2H), 7.57−7.59 (m, 1H), 7.78−7.81 (m, 2H), 7.92−7.94 (m, 2H), 12.79 (s, 1H), 15.28 (s, 1H). ^{13}C NMR δ 92.1, 110.7, 113.6, 120.8, 127.2, 129.0, 130.0, 132.3, 133.2, 140.7, 158.1, 179.2, 193.6.

1-(3-Bromo-5-chloro-2-hydroxyphenyl)-3-phenyl-propan-1,3-dione (4).[57] The same procedure as described above using **2** (5.2 g, 20.8 mmol) afforded 6.8 g (93%) of **4.** Mp 113−114 °C. ^{1}H NMR δ 6.77 (s, 1H), 7.50−7.60 (m, 3H), 7.71−7.73 (m, 2H), 7.95−7.98 (m, 2H), 12.80 (s, 1H), 15.32 (s, 1H). ^{13}C NMR δ 92.3, 113.5, 120.4, 124.2, 127.2, 127.3, 129.2, 133.2, 133.3, 138.3, 157.8, 179.4, 193.8.

6,8-Dibromo-flavone (5).[58] A few drops of HCl was added to a solution of **3** (1.2 g, 3.4 mmol) in glacial acetic acid (20 mL). The reaction was refluxed for 14 h. The solution was poured into Na_2CO_3 (10%) and extracted with CH_2Cl_2 (4 × 30 mL). The combined organic phases were washed with H_2O (2 × 20 mL) and dried over anhydrous $MgSO_4$ before the solvent was removed under vacuum. The residue was purified by flash chromatography on silica gel using CH_2Cl_2 as eluent to afford 1.1 g (82%) of **5**. Mp 173−174 °C (lit. 174−175 °C). ^{1}H NMR δ 6.80 (s, 1H), 7.48−7.54 (m, 3H), 7.91−7.96 (m, 3H), 8.22 (d, J = 2.1 Hz, 1H). ^{13}C NMR δ 107.1, 113.1, 118.6, 126.0, 126.5, 127.8, 129.3, 130.8, 132.3, 139.3, 151.8, 163.5, 176.3.

8-Bromo-6-chloro-flavone (6). The same procedure as described above using **4** (1.2 g, 3.4 mmol) afforded 0.9 mg (82%) of **6**. Mp 178−179 °C. ^{1}H NMR δ 6.83 (s, 1H), 7.50−7.56 (m, 3H), 7.86 (d, J = 2.6 Hz, 1H), 7.95−7.98 (m, 2H), 8.11 (d, J = 2.6 Hz, 1H). ^{13}C NMR δ 107.1, 113.0, 124.7, 125.7, 126.5, 129.3, 130.9, 131.4, 132.2, 136.8, 151.4, 163.7, 176.6. Anal. Calcd for $C_{15}H_8BrClO_2$: C, 53.69; H, 2.40. Found: C, 53.75; H, 2.46.

General Procedure for the Synthesis of Chalcones 8−13. KOH (2.9 equiv) was added to a suspension of **2** (1.0 equiv) and the appropriate aldehyde (1.05 equiv) in EtOH (6 mL/mmol acetophenone). The mixture was stirred at 50 °C for 3 h and then at room temperature overnight. The reaction mixture was poured into water and acidified with aqueous HCl (1 M). The product crystallized and was filtered off. The chalcones were used in the next step without any other characterization than ^{1}H and ^{13}C NMR spectroscopy. Spectroscopic and analytical data for some representative examples of **8**−**13** follow.

1-(3-Bromo-5-chloro-2-hydroxyphenyl)-3-phenyl-2-propen-1-one (8). Benzaldehyde (0.45 g, 4.2 mmol) gave 1.3 g (96%) of **8** recrystallized from EtOH. Mp 128−129 °C. ^{1}H NMR δ 7.47−7.50 (m, 3H), 7.57 (d, J = 15.4 Hz, 1H), 7.70−7.72 (m, 2H), 7.78 (d, J = 2.2 Hz, 1H), 7.88 (d, J = 2.2 Hz, 1H), 8.01 (d, J = 15.4 Hz, 1H), 13.51 (s, 1H). ^{13}C NMR δ 113.3, 119.0, 121.1, 124.0, 128.4, 129.2, 129.4, 131.8, 134.3, 139.0, 147.9, 159.0, 192.7.

1-(3-Bromo-5-chloro-2-hydroxyphenyl)-3-(2-thienyl)-2-propen-1-one (11). 2-Thiophenecarboxaldehyde (0.47 g, 4.2 mmol) gave 1.35 g (98%) of **11** (the product was recrystallized by stirring in refluxing EtOH followed by filtration after cooling). Mp 165−167 °C. ^{1}H NMR δ 7.15 (dd, J = 3.5, 5.0 Hz, 1H), 7.31 (d, J = 15.0 Hz, 1H), 7.46 (d, J = 3.5 Hz, 1H), 7.54 (d, J = 5.0 Hz, 1H), 7.76 (d, J = 2.3 Hz, 1H), 7.82 (d, J = 2.3 Hz, 1H), 8.12 (d, J = 15.0 Hz, 1H). ^{13}C NMR δ 113.0, 117.4, 120.8, 123.7, 128.0, 128.8, 130.7, 133.8, 138.6, 139.7, 139.9, 158.8, 191.9.

1-(3-Bromo-5-chloro-2-hydroxyphenyl)-5-phenyl-2,4-pentadien-1-one (13). Cinnamic aldehyde (1.59 g, 12 mmol, 1.2 equiv) gave 3.45 g (95%) of **13**. Mp 148−149 °C. ^{1}H NMR δ 7.06−7.15 (m, 3H), 7.37−7.42 (m, 3H), 7.52−7.54 (m, 2H), 7.74−7.81 (m, 3H), 13.59 (s, 1H). ^{13}C NMR δ 113.1, 120.9, 122.1, 123.7, 126.4, 127.7, 128.1, 129.1, 130.0, 135.7, 138.6, 144.6, 147.6, 158.8, 192.4.

General Procedure for the Synthesis of 2-Aryl/Styryl-8-bromo-6-chloro-3-hydroxychromones 14−19. Aqueous 30% H_2O_2 (8−11 equiv) was added to a solution of the appropriate chalcone (1.0 equiv) and aqueous 4 M NaOH (5.0 equiv) in a 1:1 mixture of MeOH and THF (20 mL/mmol chalcone) at 0 °C. The reaction was stirred at room temperature overnight. The reaction mixture was acidified with aqueous HCl (1 M), and the product was filtered off. Spectroscopic and analytical data for some representative examples of **14**−**19** follow.

8-Bromo-6-chloro-3-hydroxy-flavone (14).[38] The crude product from **8** (440 mg, 1.3 mmol) was recrystallized from EtOH to yield 380 mg (82%) of **14**. Mp 193−194 °C. ^{1}H NMR δ 7.03 (br s, 1H), 7.52−7.59 (m, 3H), 7.93 (d, J = 2.2 Hz, 1H), 8.19 (d, J = 2.2 Hz, 1H), 8.37 (d, J = 7.5 Hz, 2H). ^{13}C NMR δ 113.4, 122.3, 124.4, 128.2 (2 C:s), 129.0 (2 C:s), 130.7, 130.8, 131.0, 136.9, 138.8, 145.9, 150.5, 172.3.

8-Bromo-6-chloro-3-hydroxy-2-(2-thienyl)chromone (17). Compound **11** (1.10 g, 3.2 mmol) gave 0.78 g (68%) of **17**. Mp 246−247 °C ^{1}H NMR (DMSO-d_6) δ 7.33−7.35 (m, 1H), 7.94−7.97 (m, 2H), 8.02 (d, J = 2.3 Hz, 1H), 8.26 (d, J = 2.3 Hz, 1H), 10.64 (br s, 1H). ^{13}C NMR (DMSO-d_6) δ 112.4, 123.4, 123.5, 127.8, 128.5, 129.0, 131.6, 131.8, 135.5, 136.7, 143.7, 149.1, 170.3. Anal. Calcd for $C_{13}H_6BrClO_3S$: C, 43.66; H, 1.69. Found: C, 43.78; H, 1.65.

8-Bromo-6-chloro-3-hydroxy-2-styryl-chromone (19). The crude product from **13** (0.87 g, 2.4 mmol) was purified by flash chromatography using a manual gradient of CH_2Cl_2:diethyl ether (100:0→95:5) to yield 0.60 g (66%) of **19**. Mp 173−174 °C. ^{1}H NMR δ 6.51 (br s, 1H), 7.32−7.44 (m, 4H), 7.63−7.67 (m, 3H), 7.89 (d, J = 2.5 Hz, 1H), 8.15 (d, J = 2.5 Hz, 1H). ^{13}C NMR δ 112.9, 115.1, 123.0, 123.9, 124.3, 127.9, 128.5, 128.9, 129.1, 129.8, 130.5, 135.7, 136.3, 136.6, 171.0. Anal. Calcd for $C_{17}H_{10}BrClO_3$: C, 54.07; H, 2.67. Found: C, 53.97; H, 2.72.

General Procedure for the Synthesis of the 3-O-Alkylated Derivatives 21−25. A solution of the 2-aryl-8-bromo-6-chloro-3-hydroxychromone (1 equiv), the appropriate alkyl bromide (1.5−2.0 equiv), and K_2CO_3 (2 equiv) in DMF (volume dependent on the solubility of the starting material) was stirred at 50 °C overnight.

(56) Banerji, K. D.; Poddar, D. *J. Indian Chem. Soc.* **1979**, *56*, 62−65.
(57) Thool, A. W.; Ghiya, B. J. *J. Indian Chem. Soc.* **1988**, *65*, 522−524.
(58) Sandulache, A.; Cascaval, A.; Toniutti, N.; Giumanini, A. G. *Tetrahedron* **1997**, *53*, 9813−9822.

The solution was diluted with water and the solution was acidified with HCl (1 M), and the precipitate was filtered off. Spectroscopic and analytical data for some representative examples of **21**−**25** follow.

8-Bromo-6-chloro-2-(4-methoxyphenyl)-3-[3-(*N*-phthalimido)-propoxy]chromone (21). Compound **15** (0.72 g, 1.9 mmol) gave 0.95 g (88%) of **21**. Mp 207−208 °C. ^{1}H NMR δ 2.14 (m, 2H), 3.85 (t, J = 7.3 Hz, 2H), 3.90 (s, 3H), 4.15 (t, J = 6.3 Hz, 2H), 7.06 (d, J = 9.1 Hz, 2H), 7.70 (dd, J = 3.1, 5.4 Hz, 2H), 7.83 (dd, J = 3.1, 5.4 Hz, 2H), 7.86 (d, J = 2.5 Hz, 1H), 8.13 (d, J = 2.5 Hz, 1H), 8.25 (d, J = 9.1 Hz, 2H). ^{13}C NMR δ 29.3, 35.3, 55.4, 70.0, 112.6, 114.2, 122.7, 123.2, 124.6, 125.7, 130.6, 130.7, 132.1, 133.9, 136.2, 139.7, 150.2, 156.0, 161.9, 168.2, 173.0. Anal. Calcd for $C_{27}H_{19}BrClNO_6$: C, 57.01; H, 3.37; N, 2.46. Found: C, 56.66; H, 3.49; N, 2.59.

8-Bromo-6-chloro-3-ethoxycarbonylmethyl-flavone (25). Compound **14** (0.42 g, 1.2 mmol) gave 0.41 g (71%) of **25**. Mp 124−125 °C. ^{1}H NMR δ 1.20 (t, J = 7.2 Hz, 3H), 4.17 (q, J = 7.2 Hz, 2H). 4.90 (s, 2H), 7.50−7.54 (m, 3H), 7.87 (d, J = 2.5 Hz, 1H), 8.13 (d, J = 2.4 Hz, 1H), 8.29−8.32 (m, 2H). ^{13}C NMR δ 14.3, 61.3, 68.3, 113.0, 124.7, 125.7, 128.8, 129.3, 130.4, 131.1, 131.6, 136.8, 139.7, 150.4, 155.6, 169.0, 173.1. Anal. Calcd for $C_{19}H_{14}BrClO_5$: C, 52.14; H, 3.22. Found: C, 52.00; H, 3.12.

3-Acetoxy-8-bromo-6-chloro-2-(4-methoxyphenyl)chromone (27). Acetyl chloride (0.15 mL, 2.1 mmol) was added to a suspension of **15** (0.38 g, 1.0 mmol) and Et_3N (1.0 mL, 7.2 mmol) in CH_2Cl_2. The reaction was stirred overnight at room temperature. The organic phase was washed twice with 0.2 M HCl and saturated $NaHCO_3$. The organic phase was dried with Na_2SO_2 whereafter the solvent was removed. Yield 0.44 g (>99%). Mp 184−187 °C ^{1}H NMR δ 2.39 (s, 3H), 3.90 (s, 3H), 7.05 (d, J = 9.1 Hz, 2H), 7.90 (d, J = 2.5 Hz, 1H), 8.00 (d, J = 9.1 Hz, 2H), 8.16 (d, J = 2.5 Hz, 1H). ^{13}C NMR δ 20.6, 55.5, 112.7, 114.4, 121.6, 124.8, 125.1, 130.3, 131.2, 132.8, 136.7, 150.5, 156.2, 162.4, 167.6, 170.4. Anal. Calcd for $C_{18}H_{12}BrClO_5$: C, 51.03; H, 2.86. Found: C, 51.26; H, 2.94.

General Procedure for the Synthesis of Triflates Used in the Pd Coupling Reactions. Triflic anhydride (2.0−2.5 equiv) was added dropwise to a solution of the appropriate 3-hydroxychromanone derivative and NEt_3 or pyridine (5−8 equiv) in CH_2Cl_2 at 0 °C. The reaction was stirred overnight at room temperature. The organic phase was washed twice with aqueous 0.1 M HCl and aqueous saturated $NaHCO_3$. The organic phase was dried with $MgSO_4$ or Na_2SO_4 whereafter the solvent was removed. The residue was purified by flash chromatography.

8-Bromo-6-chloro-3-trifluoromethylsulfonyloxy-flavone (26). The triflate from **14** (0.36 g, 1.0 mmol) was purified by flash chromatography using CH_2Cl_2 as eluent to yield 0.33 g (67%) of **26**. ^{1}H NMR δ 7.57−7.67 (m, 3H), 7.95−7.98 (m, 3H), 8.18 (d, J = 2.6 Hz, 1H). ^{13}C NMR δ 113.2, 118.5 (q, $J_{C,F}$ = 321 Hz, CF_3), 125.1, 125.2, 127.9, 129.1, 129.2, 132.4, 133.0, 133.8, 137.9, 150.6, 159.0, 169.7.

General Procedure for Stille Cross-Coupling Reactions of Aryl Bromides and Triflates. Synthesis of 28−33, 37−40, 45−51 (Method A). A solution of the appropriate aryl bromide or triflate (1 equiv), $Pd(PPh_3)_4$ (0.1 equiv), and benzyl- or allylSnBu$_3$ (1.6 equiv) in DMF was reacted (a) under N_2 at 80 °C overnight, or (b) in a microwave cavity at 160 °C for 30 min. The mixture was filtered through Celite with ethyl acetate or a 1:1 mixture of ethyl acetate and CH_2Cl_2. The filtrate was stirred with saturated aqueous KF for 30−60 min. The phases were separated, and the aqueous phase was extracted once with CH_2Cl_2. The combined organic phases were dried over anhydrous $MgSO_4$ or Na_2SO_4, whereafter the solvent was removed. The residue was purified by flash chromatography. Spectroscopic and analytical data for some representative examples of **28**−**33, 37**−**40**, and **45**−**51** follow.

8-Allyl-6-chloro-3-hydroxy-flavone (28). Compound **14** (0.70 g, 2.0 mmol) and allylSnBu$_3$ gave **28** which was purified by flash chromatography using CH_2Cl_2 as eluent to yield 0.56 g (89%) of pure product (method A, procedure a). Mp 176−177 °C. ^{1}H NMR δ 3.76 (d, J = 6.5 Hz, 2H), 5.18−5.25 (m, 2H), 6.01−6.11 (m, 1H), 7.03 (br s, 1H), 7.49−7.57 (m, 4H), 8.10 (d, J = 2.6 Hz, 1H), 8.22−8.24 (m, 2H). ^{13}C NMR δ 33.7, 118.1, 121.6, 122.8, 127.8, 128.8, 130.4, 130.5, 131.1, 132.2, 133.9, 134.3, 138.6, 145.1, 151.9, 172.7. Anal. Calcd for $C_{18}H_{13}ClO_3$: C, 69.13; H, 4.19. Found: C, 68.85; H, 3.97.

8-Benzyl-6-chloro-3-hydroxy-2-(2-thienyl)chromone (32). Compound **17** (0.36 g, 1.0 mmol) and benzylSnBu$_3$ gave **32** which was purified by flash chromatography using ethyl acetate, CH_2Cl_2 and hexane (7:7:86) to yield 0.36 g (98%) of pure product (method A, procedure b). Mp 221−222 °C. ^{1}H NMR δ 4.34 (s, 2H), 6.91 (br s, 1H), 7.22−7.36 (m, 6H), 7.40 (d, 1H, J = 2.1 Hz), 7.62 (d, 1H, J = 4.8 Hz), 7.95 (d, 1H, J = 3.4 Hz), 8.09 (d, 1H, J = 2.1 Hz). ^{13}C NMR δ 35.3, 122.0, 122.9, 126.9, 128.4, 128.8, 128.9, 129.8, 130.0, 130.4, 132.78, 132.83, 134.2, 136.3, 138.1, 142.7, 151.3, 171.6. Anal. Calcd for $C_{20}H_{13}ClO_3S$: C, 65.13; H, 3.55. Found: C, 65.26; H, 3.64.

3-Acetoxy-8-benzyl-6-chloro-2-(4-methoxyphenyl)chromone (45). Compound **27** (0.41 g, 0.97 mmol) and benzylSnBu$_3$ gave **45** which was purified by flash chromatography using ethyl acetate, CH_2Cl_2, and hexane (10:10:80) to yield 0.33 g (78%) of pure product (method A, procedure b). Mp 200−201 °C. ^{1}H NMR δ 2.36 (s, 3H), 3.89 (s, 3H), 4.27 (s, 2H), 6.98 (d, J = 9.0 Hz, 2H), 7.21−7.37 (m, 5H), 7.43 (d, J = 2.5 Hz, 1H), 7.66 (d, J = 9.0 Hz, 2H), 8.10 (d, J = 2.5 Hz, 1H). ^{13}C NMR δ 20.6, 35.7, 55.4, 114.2, 122.0, 123.6, 124.7, 126.9, 128.77, 128.81, 130.0, 130.8, 132.6, 132.9, 134.5, 138.0, 152.0, 156.2, 162.0, 167.8, 171.1. Anal. Calcd for $C_{25}H_{19}ClO_5$: C, 69.05; H, 4.40. Found: C, 68.97; H, 4.44.

3,8-Diallyl-6-chloro-flavone (46). The triflate from **28** (0.21 g, 0.66 mmol) was purified by flash chromatography using CH_2Cl_2 as eluent to yield 0.16 g (55%) of pure product. ^{1}H NMR δ 3.68 (d, J = 6.5 Hz, 2H), 5.15−5.25 (m, 2H), 5.95−6.05 (m, 1H), 7.57−7.65 (m, 4H), 7.85−7.87 (m, 2H), 8.10 (d, J = 2.6 Hz, 1H). ^{13}C NMR δ 33.8, 118.4 (q, $J_{C,F}$ = 321 Hz, CF_3), 118.5, 123.9, 124.7, 128.5, 129.0, 129.3, 132.2, 132.4, 132.8, 134.0, 135.2, 137.9, 152.1, 158.8, 170.6. The triflate (0.16 g, 0.36 mmol) and allylSnBu$_3$ gave **46** which was purified by flash chromatography using CH_2Cl_2 as eluent to yield 0.16 g (72%) of pure product (method A, procedure b). Mp 131−132 °C. ^{1}H NMR δ 3.32 (d, J = 5.6 Hz, 2H), 3.59 (d, J = 6.5 Hz, 2H), 5.01−5.19 (m, 4H), 5.92−6.11 (m, 2H), 7.46 (d, J = 2.6 Hz, 1H), 7.51−7.55 (m, 3H), 7.67−7.70 (m, 2H), 8.08 (d, J = 2.6 Hz, 1H). ^{13}C NMR δ 30.2, 33.7, 115.8, 117.8, 119.5, 123.5, 123.9, 128.7, 128.8, 130.6, 130.8, 131.8., 133.1, 133.7, 134.6, 135.9, 152.7, 162.4, 177.3. Anal. Calcd for $C_{21}H_{17}ClO_2$: C, 74.89; H, 5.09. Found: C, 74.76; H, 5.04.

3,8-Dibenzyl-6-chloro-2-(2-thienyl)chromone (51). The triflate from compound **32** was prepared as described for the synthesis of **49**. The triflate (0.26 g, 0.52 mmol) and benzylSnBu$_3$ gave **51** which was purified by flash chromatography using ethyl acetate, CH_2Cl_2, and hexane (5:5:90) to yield 0.16 g (69%) of pure product (method A, procedure b). Mp 171−173 °C. ^{1}H NMR δ 4.24 (s, 2H), 4.30 (s, 2H), 7.10 (m, 1H), 7.20−7.37 (m, 10H), 7.40 (d, J = 2.5 Hz, 1H), 7.43 (d, J = 3.5 Hz, 1H), 7.59 (d, J = 4.9 Hz, 1H), 8.09 (d, J = 2.5 Hz, 1H). ^{13}C NMR δ 31.1, 35.2, 118.6, 123.6, 123.6, 126.2, 126.8, 127.8, 128.1, 128.6, 128.8, 128.9, 130.3, 130.6, 130.6, 132.5, 134.2, 134.6, 138.1, 138.6, 152.1, 156.7, 177.1. Anal. Calcd for $C_{27}H_{19}ClO_2S$: C, 73.21; H, 4.32. Found: C, 73.08; H, 4.19.

General Procedure for Heck Reactions of Aryl Bromides. Synthesis of 34 and 41 (Method B). A solution of the appropriate aryl bromide (1 equiv), $Pd(OAc)_2$ (0.1 equiv), Pd(*o*-tolyl)$_3$ (0.2 equiv), NEt_3 (2 equiv), and methyl acrylate (2 equiv) in DMF (4 mL) in a microwave vial was heated in a microwave cavity for 30 min at 160 °C. The mixture was filtered through Celite with ethyl acetate. The filtrate was acidified with HCl (1 M) and extracted twice with ethyl acetate. The combined organic phases were washed with saturated $NaHCO_3$, and the combined organic phases were dried over anhydrous Na_2SO_4 before the solvent was removed under vacuum. The residue was purified by flash chromatography.

6-Chloro-3-hydroxy-8-(2-methoxycarbonylethenyl)flavone (34). Compound **14** (0.65 g, 1.8 mmol) gave **34** which was purified by flash chromatography using a manual gradient of CH_2Cl_2:diethyl ether (100:0→95:5) to yield 0.53 g (80%) of pure product. Mp 232−233 °C. ^{1}H NMR δ 3.88 (s, 3H), 6.70 (d, J = 16.1 Hz, 1H), 6.97 (br s, 1H), 7.50−7.60 (m, 3H), 7.87 (d, J = 2.5 Hz, 1H), 8.21−8.25 (m, 4H). ^{13}C NMR δ 52.4, 122.5, 122.9, 126.6, 127.0, 128.0, 129.1, 130.7, 130.8, 130.9, 132.0, 135.7, 138.8, 145.8, 151.5, 166.7, 172.4. Anal. Calcd for $C_{19}H_{13}ClO_5$: C, 63.97; H, 3.67. Found: C, 63.94; H, 3.61.

6-Chloro-8-(2-methoxycarbonylethenyl)-3-[3-(*N*-phthalimido)-propoxy]flavone (41). Compound **20** (0.30 g, 0.55 mmol) gave **41** which was purified by flash chromatography using a manual gradient of CH_2Cl_2:diethyl ether (100:0→95:5) to yield 0.26 g (87%) of pure product. Mp 187−188 °C. ^{1}H NMR δ 2.05−2.10 (m, 2H), 3.77 (t, J = 7.3 Hz, 2H), 3.84 (s, 3H), 4.16 (t, J = 6.2 Hz, 2H), 6.67 (d, J = 16.1 Hz, 1H), 7.49−7.57 (m, 3H), 7.67−7.69 (m, 2H), 7.79 (m, 3H), 8.05−8.08 (m, 2H), 8.11 (d, J = 16.1 Hz, 1H), 8.18 (d, J = 2.6 Hz, 1H). ^{13}C NMR δ 29.4, 35.4, 52.2, 70.5, 122.7, 123.4, 126.0, 126.6, 127.0, 128.91, 128.94, 130.5, 130.9, 131.3, 131.8, 132.3, 134.0, 135.8, 140.7, 151.5, 156.3, 166.7, 168.4, 173.6. Anal. Calcd for $C_{30}H_{22}ClNO_7$: C, 66.24; H, 4.08; N, 2.58. Found: C, 66.34; H 3.94; N, 2.53.

General Procedure for Sonogashira Reactions of Bromides. Synthesis of 35, 42, and 44 (Method C). CuI (0.1 equiv) was added to a suspension of the appropriate aryl bromide (1.0 equiv), $PdCl_2(PPh_3)_2$ (0.1 equiv), NEt_3 (10 equiv), and TMS-acetylene or *N*-Boc-propargylamine (2.0 equiv) in THF (15 mL). The mixture was heated in a microwave cavity for 30 min at 120 °C. The solution was filtered through Celite. $NaHCO_3$ was added and extracted four times with CH_2Cl_2. The combined organic phases were dried over anhydrous $MgSO_4$ and the solvent was removed under vacuum. The residue was purified by flash chromatography.

6-Chloro-3-hydroxy-8-(2-trimethylsilylethynyl)flavone (35). Compound **14** (0.24 g, 0.67 mmol) gave **35** which was purified by flash chromatography using CH_2Cl_2 as eluent to yield 0.18 g (71%) of pure product. Mp 248−249 °C. ^{1}H NMR δ 0.37 (s, 9H), 7.01 (br s, 1H), 7.49−7.56 (m, 3H), 7.77 (d, J = 2.5 Hz, 1H), 8.15 (d, J = 2.5 Hz, 1H), 8.38−8.40 (m, 2H). ^{13}C NMR δ −0.1, 97.0, 104.4, 116.3, 121.6, 125.0, 128.2, 128.9, 130.1, 130.8, 131.0, 136.9, 138.9, 145.3, 154.0, 172.5. Anal. Calcd for $C_{20}H_{17}ClO_3Si$: C, 65.12; H, 4.65. Found: C, 65.22; H, 4.62.

6-Chloro-3-[3-(*N*-phthalimido)propoxy]-8-(2-trimethylsilyl-ethynyl)flavone (42). Compound **20** (0.19 g, 0.34 mmol) gave **42** which was purified by flash chromatography using CH_2Cl_2 as eluent to yield 0.18 g (91%). Mp 145−146 °C ^{1}H NMR δ 0.32 (s, 9H), 2.11−2.18 (m, 2H), 3.84 (t, J = 7.3 Hz, 2H), 4.17 (t, J = 6.3 Hz, 2H), 7.49−7.54 (m, 3H), 7.67−7.71 (m, 3H), 7.78−7.82 (m, 2H), 8.08 (d, J = 2.6 Hz, 1H), 8.27−8.29 (m, 2H). ^{13}C NMR δ −0.1, 29.5, 35.4, 70.4, 97.0, 104.1, 115.9, 123.3, 125.2, 125.4, 128.7, 129.1, 130.2, 130.8, 131.3, 132.3, 134.0, 136.6, 140.9, 153.9, 155.5, 168.4, 173.8. Anal. Calcd for $C_{31}H_{26}ClNO_5Si$: C, 66.96; H, 4.71; N, 2.52. Found: C, 67.08; H, 4.63; N, 2.42.

8-[(3-(*tert*-Butoxycarbonylamino)-1-propynyl]-6-chloro-3-[ethoxycarbonylmethyl]flavone (44). Compound **25** (0.10 g, 0.22 mmol) gave **44** which was purified by flash chromatography using CH_2Cl_2 as eluent to yield 0.09 g (83%) of pure product. Mp 158−159 °C ^{1}H NMR δ 1.21 (t, J = 7.1 Hz, 3H), 1.48 (s, 9H), 4.18 (q, J = 7.1 Hz, 2H), 4.28 (d, J = 5.4 Hz, 2H), 4.89 (s, 2H), 4.94 (s, 1H), 7.52−7.58 (m, 3H), 7.66 (d, J = 2.6 Hz, 1H), 8.10 (d, J = 2.6 Hz, 1H), 8.28−8.31 (m, 2H). ^{13}C NMR δ 14.2, 28.5, 31.3, 61.2, 68.3, 75.7, 80.4, 94.5, 115.5, 124.9, 125.1, 128.7, 129.1, 130.3, 130.5, 131.3, 136.5, 139.7, 153.5, 155.2, 155.3, 168.9, 173.3. Anal. Calcd for $C_{27}H_{26}ClNO_7$: C, 63.34; H, 5.12; N, 2.74. Found: C, 63.23; H, 5.01; N, 2.58.

General Procedure for Suzuki Reactions of Aryl Bromides. Synthesis of 36 and 43 (Method D). A mixture of the appropriate aryl bromide (1.0 equiv), 2-naphthylboronic acid (1.2 equiv), Cs_2CO_3 (2.5 equiv), and $Pd(PPh_3)_4$ (0.1 equiv) in DMF (15 mL) was heated in a microwave cavity for 30 min at 150 °C. The solution was filtered through Celite, acidified, and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried over anhydrous $MgSO_4$, and the solvent was removed under vacuum.

6-Chloro-3-hydroxy-8-naphthyl-flavone (36). The crude product from **14** (0.15 g, 0.43 mmol) was dissolved in CH_2Cl_2, acetyl chloride (0.15 mL) and NEt_3 (0.8 mL) were added, and the reaction was stirred for 14 h. HCl (1 M) was added, and the water phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried over anhydrous $MgSO_4$, and the solvent was removed under vacuum. The residue was purified by flash chromatography using a manual gradient of CH_2Cl_2:diethyl ether (100:0→95:5) to afford 3-acetoxy-6-chloro-8-naphthyl-flavone. ^{1}H NMR δ 2.39 (s, 3H), 7.37−7.46 (m, 3H), 7.54−7.58 (m, 2H), 7.69−7.78 (m, 4H), 7.88−7.97 (m, 3H), 8.07 (s, 1H), 8.24 (d, J = 2.6 Hz, 1H). ^{13}C NMR δ 20.8, 124.7, 125.3, 126.9, 127.08, 127.13, 128.0, 128.3, 128.4, 128.5, 128.9, 129.2, 129.8, 131.4, 131.7, 132.1, 133.3, 133.4, 133.8, 134.0, 135.1, 151.3, 156.3, 168.0, 171.5. The resulting 3-acetoxy-6-chloro-8-naphthyl-flavone was directly added to NaOMe (1 M, 2 mL) in MeOH (20 mL) and stirred for 5 h. The solution was acidified HCl (1 M) and extracted with CH_2Cl_2 (4 × 20 mL). The combined organic phases were dried over anhydrous $MgSO_4$, and the solvent was removed under vacuum. The residue was purified by flash chromatography using a manual gradient of CH_2Cl_2:diethyl ether (100:0→95:5) to give 0.14 g (79%) of **36**. Mp 216−217 °C. ^{1}H NMR δ 7.08 (br s, 1H), 7.38−7.40 (m, 3H), 7.57−7.63 (m, 2H), 7.77 (dd, J = 1.4, 8.4 Hz, 1H), 7.81 (d, J = 2.6 Hz, 1H), 7.92−7.98 (m, 2H), 8.01 (d, J = 8.4 Hz, 1H), 8.09−8.11 (m, 2H), 8.15 (s, 1H), 8.26 (d, J = 2.6 Hz, 1H). ^{13}C NMR δ 122.3, 124.0, 127.0, 127.1, 127.3, 128.0, 128.1, 128.4, 128.9, 129.3, 130.6, 130.8, 131.0, 132.3, 133.4, 133.5, 134.2, 134.8, 138.8, 145.5, 151.1, 172.8. Anal. Calcd for $C_{25}H_{15}ClO_3$: C, 75.29; H, 3.79. Found: C, 75.36; H, 3.71.

6-Chloro-8-naphthyl-3-[3-(*N*-phthalimido)propoxy]flavone (43). Compound **20** (0.19 g, 0.34 mmol) gave **43** which was purified by flash chromatography using CH_2Cl_2 as eluent to yield 0.22 g (86%) of pure product. Mp 204−206 °C.^{1}H NMR δ 2.11 (m, 2H), 3.84 (t, J = 7.3 Hz, 2H), 4.21 (t, J = 6.2 Hz, 2H), 7.38−7.41 (m, 3H), 7.56−7.59 (m, 2H), 7.70−7.84 (m, 6H), 7.91−8.03 (m, 5H), 8.13 (s, 1H), 8.24 (d, J = 2.2 Hz, 1H). ^{13}C NMR δ 29.5, 35.5, 70.4, 123.4, 124.4, 125.9, 126.9, 127.0, 127.3, 128.0, 128.3, 128.4, 128.7, 128.9, 129.2, 130.75, 130.83, 131.1, 132.29, 132.34, 133.24, 133.4, 133.8, 134.0, 134.5, 140.7, 150.9, 155.9, 168.4, 174.2. Anal. Calcd for $C_{36}H_{24}ClNO_5$: C, 73.78; H, 4.13; N, 2.39. Found: C, 73.81; H, 4.11; N, 2.33.

6-Allyl-8-benzyl-3-[3-(*N*-phthalimido)propoxy]flavone (53). A solution of **37** (0.19 g, 0.35 mmol), allylSnBu$_3$ (0.17 g, 0.52 mmol), Pd_2dba_3 (0.01 g, 0.01 mmol), and P(*tert*-Bu)$_3$ (8 mg, 0.04 mmol) in dioxane (15 mL) under N_2 was warmed to 80 °C for 14 h. The mixture was allowed to cool to RT and filtered through Celite. A saturated aqueous KF solution (10 mL) was added, and the stirring was continued for 30 min. The solution was extracted with CH_2Cl_2 (4 × 20 mL). The combined organic phases were washed with H_2O (2 × 10 mL) and dried over anhydrous $MgSO_4$ before the solvent was removed under vacuum. The residue was purified by flash chromatography using a manual gradient of CH_2Cl_2:diethyl ether (100:0→95:5) as eluent to afford 0.15 g (77%) of **53**. Mp 140−142 °C. ^{1}H NMR δ 2.06−2.13 (m, 2H), 3.47 (d, J = 6.6 Hz, 2H), 3.80 (t, J = 7.2 Hz, 2H), 4.13 (t, J = 6.2 Hz, 2H), 4.29 (s, 2H), 5.09−5.13 (m, 2H), 5.93−6.03 (m, 1H), 7.22−7.34 (m, 6H), 7.45−7.48 (m, 3H), 7.69−7.71 (m, 2H), 7.81−7.83 (m, 2H), 7.87−7.89 (m, 2H), 7.96 (d, J = 2.2 Hz, 1H). ^{13}C NMR δ 29.5, 35.6, 36.2, 39.8, 70.3, 116.8, 120.9, 123.4, 123.5, 126.7, 127.6, 128.6, 128.8, 128.9, 129.8, 130.4, 130.8, 131.3, 132.4, 134.0, 135.4, 136.8, 139.5, 140.5, 152.3, 155.7, 168.4, 175.4. Anal. Calcd for $C_{36}H_{29}NO_5$: C, 77.82; H, 5.26; N, 2.52. Found: C, 77.88; H, 5.22; N, 2.37.

General Procedure for the Heck Reactions of Aryl Chlorides. Synthesis of 54−57. NEt_3 (2.0 equiv) was added to a suspension

of the appropriate aryl chloride (1.0 equiv), $Pd_2(dba)_3$ (0.03 equiv), methyl acrylate (2.5 equiv), and $P(t\text{-}Bu)_3BF_4$ (0.12 equiv) in dioxane (4 mL) under N_2 in a microwave tube. The mixture was heated in a microwave cavity for 30 min at 160 °C. The solution was filtered through Celite with ethyl acetate, and H_2O was added. The mixture was extracted four times with ethyl acetate. The combined organic phases were dried over anhydrous $MgSO_4$ before the solvent was removed under vacuum. The residue was purified by flash chromatography using a manual gradient of CH_2Cl_2:diethyl ether (100:0→95:5). Spectroscopic and analytical data for some representative examples of **54**−**57** follow.

8-Benzyl-3-[3-(*tert*-butoxycarbonylamino)propoxy]-6-(2-methoxycarbonylethenyl)flavone (56). Compound **52** (0.08 g, 0.14 mmol) gave 0.07 g (85%) of **56.** Mp 133−134 °C. ^{1}H NMR δ 1.46 (s, 9H), 1.85−1.88 (m, 2H), 3.37−3.39 (m, 2H), 3.82 (s, 3H), 4.01 (t, J = 5.9 Hz, 2H), 4.32 (s, 2H), 5.66 (s, 1H), 6.48 (d, J = 16.1 Hz, 1H), 7.22−7.36 (m, 5H), 7.46−7.51 (m, 3H), 7.61 (d, J = 2.2 Hz, 1H), 7.73 (d, J = 16.1, 1H), 7.86−7.88 (m, 2H), 8.30 (d, J = 2.2 Hz, 1H). ^{13}C NMR δ 28.7, 30.2, 36.1, 37.3, 52.0, 69.9, 79.0, 119.3, 124.4, 124.7, 127.0, 128.7, 128.8, 128.9, 129.0, 130.8, 131.1, 131.6, 133.3, 138.6, 140.7, 143.2, 154.4, 156.2, 156.4, 167.2, 175.2. Anal. Calcd for $C_{34}H_{35}NO_7$: C, 71.69; H, 6.19; N, 2.46. Found: C, 71.58; H, 6.10; N, 2.38.

3,8-Dibenzyl-6-(2-methoxycarbonylethenyl)-2-thienylchromone (57). Compound **51** (0.09 g, 0.20 mmol) gave 0.08 g (76%) of **57**. Mp 184−185 °C. ^{1}H NMR δ 3.80 (s, 3H), 4.25 (s, 2H), 4.33 (s, 2H), 6.45 (d, J = 16.1 Hz, 1H), 7.09−7.11 (m, 1H), 7.19−7.34 (m, 10H), 7.43 (d, J = 3.3 Hz, 1H), 7.57−7.59 (m, 2H), 7.70 (d, J = 15.8 Hz, 1H), 8.27 (d, J = 1.8 Hz, 1H). ^{13}C NMR δ 31.3, 35.6, 52.0, 119.0, 119.1, 123.0, 124.5, 126.5, 127.0, 128.1, 128.3, 128.9, 129.0, 129.1, 130.5, 130.9, 131.2, 131.4, 133.4, 134.9, 138.7, 138.9, 143.4, 154.8, 156.8, 167.3, 178.0. Anal. Calcd for $C_{31}H_{24}O_4S$: C, 75.59; H, 4.91. Found: C, 75.51; H, 4.90.

8-Benzyl-6-(2-methoxycarbonylethenyl)-2-(4-methoxyphenyl)-chromone-3-ol (58). Compound **55** (0.05 g, 0.10 mmol) was added to a solution of NaOMe (1 M in MeOH, 2 mL) in MeOH and stirred for 5 h. The solution was acidified and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with saturated $NaHCO_3$ (2 × 20 mL) and dried over anhydrous $MgSO_4$ before the solvent was removed under vacuum. The residue was purified by column chromatography (CH_2Cl_2:diethyl ether, 95:5) to give 0.044 g (>98%) of **58**. Mp 220−222 °C**.** ^{1}H NMR δ 3.82 (s, 3H), 3.89 (s, 3H), 4.38 (s, 2H), 6.47 (d, J = 15.7 Hz, 1H), 6.90 (s, 1H), 7.01 (d, J = 9.2 Hz, 2H), 7.21−7.36 (m, 5H), 7.58 (d, J = 1.8 Hz, 1H), 7.72 d, J = 15.7 Hz, 1H), 8.05 (d, J = 9.2 Hz, 2H), 8.29 (d, J = 1.8 Hz, 1H). ^{13}C NMR δ 36.0, 52.1, 55.6, 114.4, 119.2, 123.6, 124.1, 127.1, 129.0, 129.1, 129.7, 130.9, 131.7, 133.1, 138.0, 138.6, 143.3, 145.7, 154.3, 161.4, 167.3, 173.1. Anal. Calcd for $C_{27}H_{22}O_6$: C, 73.29; H, 5.01. Found: C, 73.40; H, 4.88.

8-Benzyl-3-[3-(*tert*-butoxycarbonylamino)propoxy]-6-chloroflavone (52). Ethylenediamine (2 mL) was added to a solution of **37** (0.44 g, 0.8 mmol) in EtOH (30 mL) heated to reflux and stirred for 5 h. The mixture was allowed to cool, and K_2CO_3 (10%) was added to pH > 12. The solution was extracted with diethyl ether (4 × 15 mL), and the combined organic phases were dried over anhydrous Na_2SO_4 before the solvent was removed under vacuum. The residue was dissolved in THF (10 mL) and MeOH (10 mL), di-*tert*-butyl dicarbonate (0.50 g, 2.3 mmol) in THF (5 mL) was added, and the reaction was refluxed for 14 h. The solution was cooled, and H_2O (10 mL) was added. After extraction with CH_2Cl_2 (4 × 15 mL), the combined organic phases were dried over anhydrous Na_2SO_4 before the solvent was removed under vacuum. The residue was purified by flash chromatography with a manual gradient using CH_2Cl_2:diethyl ether (100:0→95:5) as eluent to give 0.36 g (87%) of **52**. Mp 166−167 °C. ^{1}H NMR δ 1.45 (s, 9H), 1.83−1.87 (m, 2H), 3.35−3.39 (m, 2H), 3.99 (t, J = 5.9 Hz, 2H), 4.28 (s, 2H), 5.63 (s, 1H), 7.21−7.36 (m, 5H), 7.41 (d, J = 2.6 Hz, 1H), 7.46−7.51 (m, 3H), 7.85−7.87 (m, 2H), 8.12 (d, J = 2.6 Hz, 1H). ^{13}C NMR δ 28.7, 30.2, 36.0, 37.3, 69.9, 79.1, 123.7, 125.5, 127.1, 128.7, 128.8, 129.0, 129.1, 130.7, 130.9, 131.2, 132.8, 134.5, 138.3, 140.6, 152.0, 156.4, 156.5, 174.5. Anal. Calcd for $C_{30}H_{30}ClNO_5$: C, 69.29; H, 5.81; N, 2.69. Found: C, 69.22; H, 5.74; N, 2.61.

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Supporting Information Available: Compound characterization data for compounds **9**, **10**, **12**, **15**, **16**, **18, 22**−**24**, **29**−**31**, **33**, **37**−**40**, **47**−**50**, **54, 55**. This material is available free of charge via the Internet at http://pubs.acs.org.

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