Heck–Matsuda Arylation as a Strategy to Access Kavalactones Isolated from *Polygala sabulosa*, *Piper methysticum*, and Analogues

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Herein, we describe the total syntheses of three bioactive pyrones isolated from *Polygala sabulosa* (i.e., **1**, **4**, and **7**) and eight isolated from *Piper methysticum* (i.e., **8–10**, **13**, **15**, and **18–20**) using the Heck–Matsuda arylation as the key strategy. The evaluation of this methodology by employing different arenediazonium tetrafluoroborates revealed that the Heck arylation was more efficient when the olefin undergoing arylation possessed the vinyl-2-pyrone structural unit instead of the vinyl dihydro-2-pyrone moiety. The Heck–Matsuda arylation of many of the examined olefins proceeded in a practical manner with total regio- and stereocontrol.

Introduction

Polygala sabulosa (Polygalaceae) is a perennial herb widely distributed in the South of Brazil. Historically, it was used in regional folk medicine as a topical anesthetic. Phytochemical studies have revealed dihydrostyryl-4-methoxy-2-pyrones **1**–**3** and styryl-4-methoxy-2-pyrones **4**–**7** as its main constituents (Figure 1).[1] The basic skeleton of these natural products greatly resembles that of the kavalactones, isolated from kava (*Piper methysticum*, Piperaceae), which are known for their anxiolytic and antidepressant effects.[2] The major constituents of the kava rhizome are (+)-kavain (1.8%), (+)-methysticin (1.2%), yangonin (1.0%), demethoxyyangonin (1.0%), (+)-dihydrokavain (0.6%), and (+)-dihydromethysticin (0.5%) (Figure 1).[3] Beverages made from the extracts of kava roots have been commonly used to treat fatigue, to reduce anxiety, as a tranquilizer, and as an antidepressant.[4] However, in 2003, kava extracts were banned mainly in Europe and Canada, because of hepatic injuries associated with patients who consumed kava extracts.[2b,5]

In fact, dihydrostyryl-2-pyrones (DST) and styryl-2-pyrones (STY) isolated from *P. sabulosa* have shown anxiolytic-like, hypnosedative, and anticonvulsant effects. These natural 2-pyrones have shown partial binding to the benzodiazepine site, which probably mediates the anxiolytic-like and anticonvulsant effects. In an elevated plus maze test, the intracerebroventricular administration of compounds **1**, **3**, **4**, and **7** were active at doses of 5.0 pmol, 0.3 fmol, 5.0 pmol, and 0.2 pmol, respectively, which is lower than that found with diazepam (7 nmol).[6] In addition, toxicological studies with crude extracts, hexane-, ethyl acetate-, and chloroform-soluble fractions, in mice found neither macroscopic anomalies nor histopathological changes in the vital organs. These studies used standard protocols including macroscopic, microscopic, and biochemical analyses to evaluate plant toxicity after acute and subchronic treatment. Furthermore, no changes in the biochemical parameters or toxic effects were noticed, indicating a good, confident, and safe level for consuming beverages made from extracts of this species.[7]

The potent effect of these compounds on the central nervous system has attracted the attention of organic chemists who search for new strategies to synthesize these bioactive compounds.[8] In this context, we became interested in the development of a flexible strategy that would allow the total synthesis, through a common approach, of several members of this class of compounds. The main differences between these 2-pyrones are the bonds connecting C-5–C-6 and C-7–C-8, which can be saturated or unsaturated, and the substitution pattern on the aromatic ring. Toward this end, the Heck–Matsuda reaction was chosen for the key step in the syntheses of natural kavalactones and their analogues (Scheme 1). The Heck–Matsuda arylation, which uses arenediazonium salts, offers several advantages over conventional aryl halides and triflates.[9] Arenediazonium salts undergo an extremely facile oxidative addition with Pd⁰ under "ligand-free" conditions to generate a highly reactive cationic ArPdII species. These oxidative additions are also greener, faster, very simple to carry out, and usually performed under very mild conditions. Therefore, these arylation reactions are often very efficient, providing the arylated products in a faster and more economical way, as arenediazonium salts can be readily prepared from anilines.[10] Recently, we demonstrated the feasibility of this approach

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Lactones isolated from *Polygala sabulosa*

1 R^1 = R^2 = H
2 R^1 = OMe, R^2 = H
3 R^1 = R^2 = OMe

4 R^1 = R^2 = H
5 R^1 = OMe, R^2 = H
6 R^1 = R^2 = OMe

7 11-methoxyangonin

Lactones isolated from *Piper methysticum*

8 R^1 = OMe, R^2 = R^3 = H; yangonin
9 R^1 = R^2 = R^3 = H; demethoxyangonin
10 R^1 = R^3 = OMe, R^2 = H
11 R^1 = OMe, R^2 = OH, R^3 = H

12 R^1 = H; kavain
13 R^1 = OMe

14 R^1 = R^2 = H; 7,8-dihydrokavain
15 R^1 = OMe, R^2 = H
16 R^1 = R^2 = OMe
17 R^1 = OMe, R^2 = OH

18 methysticin

19 dihydromethysticin

20
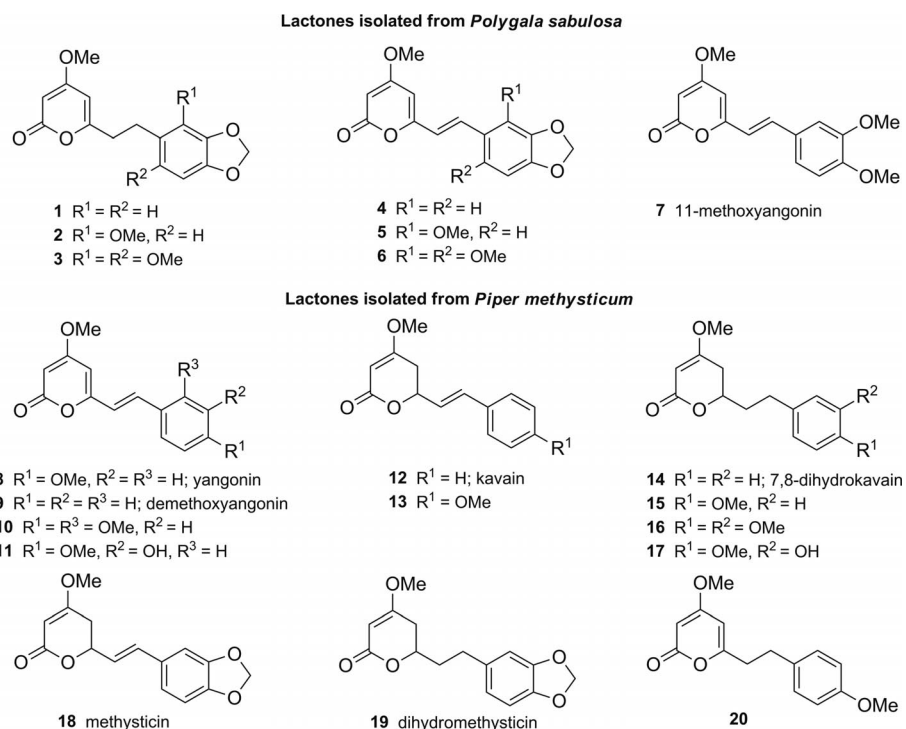
Figure 1. Lactones isolated from *P. sabulosa* (i.e., **1**–**7**) and *P. methysticum* (i.e., **8**–**20**).

in the arylation of allylic esters which proceeds in high yields providing the Heck adducts with excellent regio- and stereochemical control. Also, the methodology was extended to more restricted allylic esters (i.e., vinyl lactones) leading to the total syntheses of the natural products yangonin, methysticin, and dihydromethysticin.[11] Herein, we report a full account of this work, expanding our approach to the syntheses of several other members of the natural kavalactones family as well as of some related analogues.
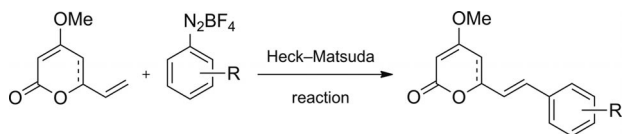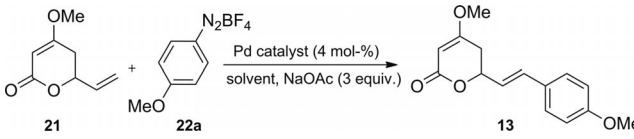

Scheme 1.

Results and Discussion

Initially, we designed the synthesis of the natural kavalactone **13** by using a Heck–Matsuda reaction between 4-methoxybenzenediazonium tetrafluoroborate (**22a**) and olefin **21**. To produce kavalactone **13**, we applied the conditions used in the Heck arylation of allylic esters, featuring Pd$_2$(dba)$_3$·dba as the catalyst, NaOAc as the base, and benzonitrile as the solvent.[11] Unfortunately, at room temperature under these conditions, the Heck product **13** was obtained in only 30% isolated yield (Table 1, Entry 1). In view of the low efficiency of the arylation process, a series of reaction conditions (palladium catalyst, solvent, and microwave heating) were examined to improve the yield of kavalactone **13** (Table 1).

Table 1. Screening of the reaction conditions for the Heck arylation.

Entry	Catalyst	Solvent	T [°C]	Time [h]	Yield [%]
1	Pd$_2$(dba)$_3$·dba	PhCN	25	12	30
2	Pd(OAc)$_2$/CO	PhCN	25	12	20
3[a]	Pd(OAc)$_2$	MeOH	80	12	n.r.[b]
4	Pd$_2$(dba)$_3$·dba	PhCN	80	5	68
5	Pd$_2$(dba)$_3$·dba	PhCN	80 (MW)[c]	0.5	85
6	Pd$_2$(dba)$_3$·dba	MeCN	80 (MW)	0.5	60
7	Pd(OAc)$_2$/CO	PhCN	80 (MW)	0.5	41

[a] Reaction performed without NaOAc. [b] n.r.: no Heck products were observed. [c] MW: reaction was performed under microwave heating.

In general, changing the palladium catalyst to Pd(OAc)$_2$ led to no improvement in the yield of Heck product **13** (Table 1, Entries 2 and 3). On the other hand, when Pd$_2$(dba)$_3$·dba was used as a catalyst with the reaction temperature at 80 °C, **13** was isolated in 68% yield (Table 1, Entry 4). Better results were obtained when the Heck reaction was performed under microwave heating. The desired Heck product **13** was obtained in 85% yield after 30 min (Table 1, Entry 5). Using Pd(OAc)$_2$ under microwave heating yielded the isolation of **13** in only 41% yield.

Other arenediazonium salts were also investigated to target the syntheses of the natural kavalactones **12** and **18** and derivatives **23**–**27** (Scheme 2). In a recent study of a struc-
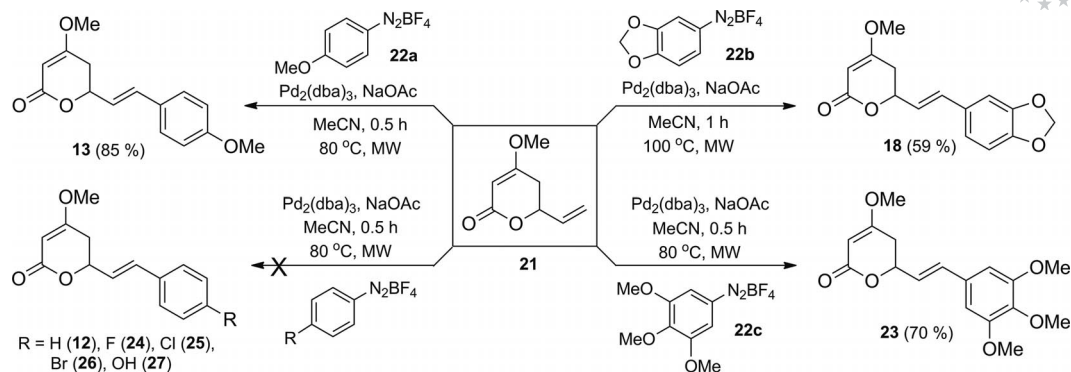
Scheme 2.

ture–activity relationship involving seven naturally occurring kavalactones isolated from *P. sabulosa*, we evaluated the affinity of these compounds to the benzodiazepine binding site.[12] One of the requirements for a good interaction is the presence of electron-releasing groups on the aromatic ring. Therefore, we then envisaged an opportunity to synthesize Heck adduct **23** by using the electron-rich 3,4,5-trimethoxybenzenediazonium salt **22c**. When this arenediazonium salt was employed in the arylation reaction, the desired product **23** was obtained in 70% yield. Moreover, the reaction between arenediazonium salt **22b** − bearing a methylenedioxy group − and olefin **21** at 100 °C, after 1 hour, furnished methysticin (**18**) in 59% yield. The need for a higher temperature hampered the synthesis of kavain (**12**), because of the low thermal stability of the benzenediazonium tetrafluoroborate. Attempts to produce kavain (**12**) at room temperature were unsuccessful. Unfortunately, Heck adducts **24**–**27** could not be obtained using arenediazonium salts with electron-withdrawing substituents or a free phenol OH group (Scheme 2).

Attempts to scale up the reaction between **21** and **22a** to obtain gram quantities of pyrone **13** for biological evaluation were also performed. However, disappointing results were obtained, as scaling up the reaction under microwave conditions did not afford the same results as observed on a small scale (up to 50 mg).

To circumvent the scale-up problem, a new screening of the reaction conditions was performed using 1 mmol of olefin **21**. Gratifyingly, the isolated yields were improved when both the catalyst and the solvent were changed to Pd-(OAc)$_2$ and MeCN (Table 2, Entry 2). Therefore, the arylation of olefin **21** was then performed using 10 mol-% of Pd(OAc)$_2$ at 80 °C for 3 h to synthesize Heck product **13** in 75% yield. On the basis of the assumption that the lactone carbonyl group could be coordinating with the palladium species, we decided to use EtOAc as a cosolvent in MeCN in an attempt to make the active catalyst more stable (Table 2, Entry 4). However, the yields decreased slightly (60% yield) which ruled out the aforementioned coordination.
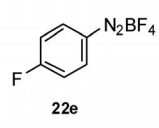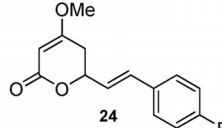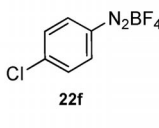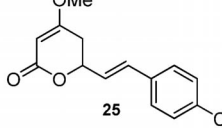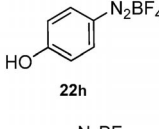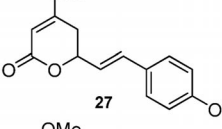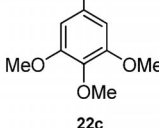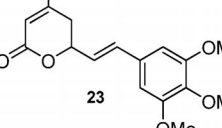
Using the above conditions, Heck adducts **23**–**25** and **27** bearing different substituents on the aryl moiety could be prepared, albeit in low to moderate yields (Table 3). The 12-

Table 2. Screening of the reaction conditions for the Heck arylation.
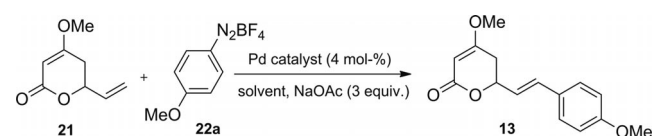
Entry	Catalyst (mol-%)	Solvent	T [°C]	Yield [%]
1	Pd$_2$(dba)$_3$·dba (4)	PhCN	80	23
2	Pd(OAc)$_2$/CO (10)	MeCN	80	75
3	Pd(OAc)$_2$/CO (10)	MeCN	80 (MW)	50
4	Pd(OAc)$_2$/CO (10)	MeCN/EtOAc	80	60

Table 3. Kavalactone derivatives **23**–**25** and **27** synthesized by Heck–Matsuda reaction.
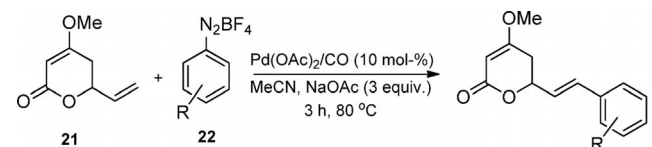
Entry	Diazonium salt	Product	Yield (%)
1	**22e**	**24**	41
2	**22f**	**25**	40
3	**22h**	**27**	35
4	**22c**	**23**	28

chloro-kavalactone **25** was obtained in 40% isolated yield, and the 12-hydroxy derivative **27** was obtained in 35% yield. It is worth mentioning that in all of the cases the only observable product was the *E* isomer. In spite of the low isolated yields for some of the compounds, the present methodology can be considered a valid alternative to access the structures of naturally occurring kavalactones and analogues, mainly because of the high regio- and stereoselectivity of the Heck–Matsuda reaction.

To access the structure of naturally occurring yangonin (**8**) and analogues **28–30**, the oxidation of the Heck–Matsuda adducts was performed with DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) in toluene at reflux. Under these conditions, the oxidation products were isolated in yields ranging from 54 to 90% (Scheme 3).

8	R^1 = OMe, R^2 = H	(85%)
28	R^1 = OH, R^2 = H	(54%)
29	R^1 = Cl, R^2 = H	(90%)
30	R^1 = R^2 = OMe	(56%)
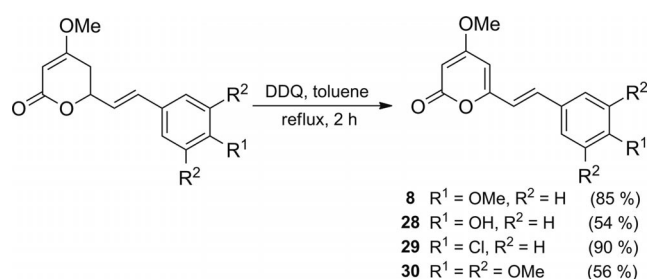
Scheme 3.

Additionally, the catalytic hydrogenation of the exocyclic double bonds in (±)-methysticin (**18**) and kavalactone **13** allowed the syntheses of the two natural products, (±)-dihydromethysticin (**19**) and kavalactone **15**, in 95 and 89% yield, respectively (Scheme 4).
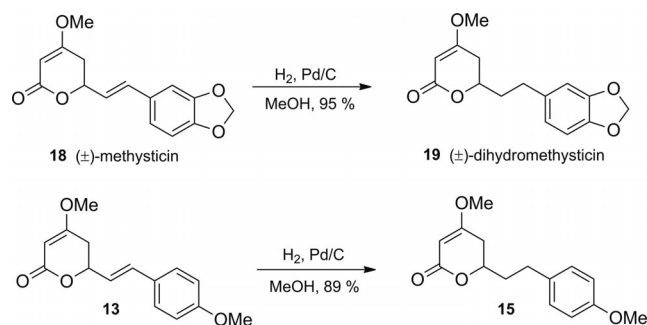
Scheme 4.

In view of the low to moderate reactivity of vinyl dihydropyrone **21** towards the Heck–Matsuda arylations, vinyl pyrone **33** was designed to increase the reactivity of the olefinic system through the conjugation of the π-systems. As we reported previously,[10s] a conjugated system as in olefin **33** should be more reactive in the Heck–Matsuda arylation reaction. In this context, initial attempts to prepare pyrone **33** by oxidizing vinyl lactone **21** with DDQ were unsuccessful (Scheme 5). Other oxidants such as CAN (ceric ammonium nitrate), IBX (*o*-iodoxybenzoic acid), MnO$_2$, and

DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) were also evaluated, but they failed to provide vinyl pyrone **33**. As an alternative, by using dehydroacetic acid **31** as the starting material, we prepared pyrone **33** according to procedures previously reported [deacetylation (H$_2$SO$_4$) and methylation (Me$_2$SO$_4$)].[13] To prepare pyrone aldehyde **32**, the methyl group at C-7 was oxidized with selenium dioxide in 1,4-dioxane in a sealed tube at 180 °C.[14] Finally, the Wittig olefination of aldehyde **32** with methyltriphenylphosphonium iodide in the presence of *n*BuLi in THF (tetrahydrofuran) led to the desired vinyl pyrone **33** in 50% yield.

i. H$_2$SO$_4$, 130 °C, 15 min, 89%
ii. Me$_2$SO$_4$, K$_2$CO$_3$, acetone, reflux, 16 h, 80%
iii. SeO$_2$, dioxane, 180 °C, 4 h, 65%
iv. Ph$_3$PCH$_3$I, *n*BuLi, THF, −78 °C to r.t., 50%

Scheme 5.

Next, we investigated the potential of the new olefin **33** to find the optimum conditions for the syntheses of yangonin and its analogues (Table 4). Initially, we tested the conditions developed by our group for the arylation of styrenes,[10s] that is, at room temperature using benzonitrile as the solvent and Pd(OAc)$_2$ or Pd$_2$(dba)$_3$·dba as the catalyst. Under these conditions, the Heck adduct was obtained in only 47% and 19% yields, respectively (Table 4, Entries 1 and 4). However, carrying out the reaction with Pd$_2$-(dba)$_3$·dba and conventional heating resulted in a significant increase in the yield (77% yield, Table 4, Entry 5).

Table 4. Screening of the reaction conditions for the Heck arylation.

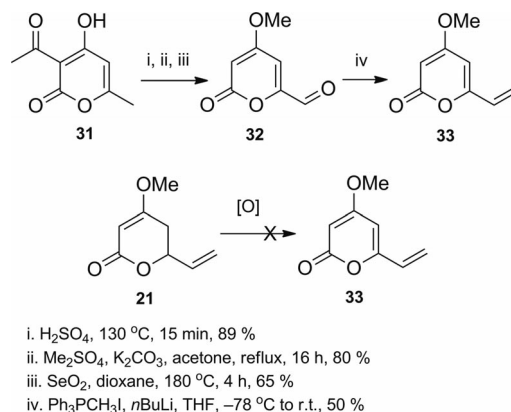| Entry	Catalyst (mol-%)	Solvent	*T* [°C]	Yield [%]
1	Pd(OAc)$_2$/CO (10)	PhCN	25	47
2	Pd(OAc)$_2$/CO (10)	PhCN	80	89
3	Pd(OAc)$_2$ (10)	MeOH	80	59
4	Pd$_2$(dba)$_3$·dba (4)	PhCN	25	19
5	Pd$_2$(dba)$_3$·dba (4)	PhCN	80	77
6	Pd(OAc)$_2$/CO (5)	PhCN	80	90
7	Pd(OAc)$_2$/CO (3)	PhCN	80	80
8	Pd(OAc)$_2$/CO (1)	PhCN	80	25
9	Pd(OAc)$_2$/CO (5)	MeCN	80	96

Even more impressive was the result of the reaction carried out at 80 °C using Pd(OAc)$_2$ under an atmosphere of carbon monoxide (89% yield, Table 4, Entry 2). In the absence of a CO atmosphere, a sharp decrease in yield was observed (Table 4, Entry 3). The catalyst loading was evaluated as well, and we found that the amount of Pd(OAc)$_2$ could be reduced to 5 mol-% without losing the efficiency (Table 4, Entry 6). The further reduction to 3 and 1 mol-% resulted in lower yields of the product (Table 4, Entries 7 and 8). Gratifyingly, when we changed the solvent from benzonitrile to acetonitrile, the optimal conditions were achieved using only 5 mol-% of Pd(OAc)$_2$, and the desired styryl pyrone **8** was obtained in 96% yield (Table 4, Entry 9).
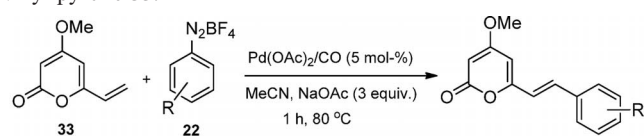
Motivated by the excellent result obtained in the synthesis of yangonin from vinyl pyrone **33**, we extended the protocol to other arenediazonium salts to produce a set of analogues. Nine additional compounds were prepared in good to excellent yields, and their structures are depicted in Table 5. In general, the efficiency of the reaction was not greatly affected by the substitution on the arenediazonium salt, that is, both electron-donating and -withdrawing groups were well tolerated. It is worth pointing out that the reaction can be conducted in the presence of a free phenolic aryldiazonium salt (63% yield, Table 5, Entry 5). However, an exception to our reasoning was found in the arylation using 4-nitrobenzenediazonium tetrafluoroborate which resulted in a low conversion to the Heck adduct (18% yield, Table 5, Entry 11). Finally, the reaction to prepare demethoxyangonin (**9**) was performed at 25 °C because of the thermal instability of benzenediazonium salt **22d**. As expected, the conversion of the starting material into the Heck adduct was low (Table 5, Entry 6). By using ¹H NMR, we found only a 25% conversion. Interestingly, in the synthesis of 12-fluoro-5,6-dehydrokavain (**34**), we observed the formation of 12-acetoxy-5,6-dehydrokavain as a side product in approximately 5% yield.
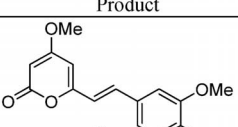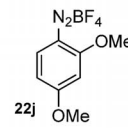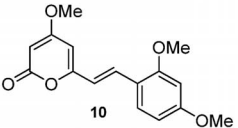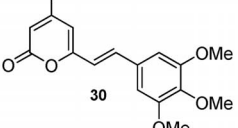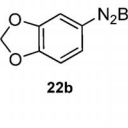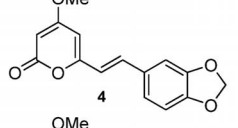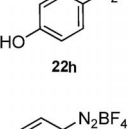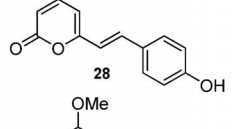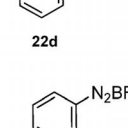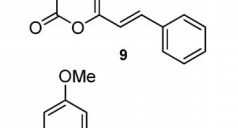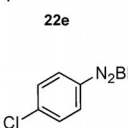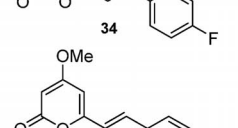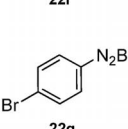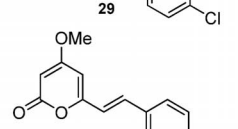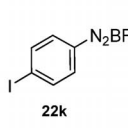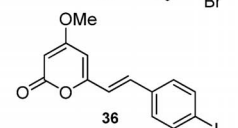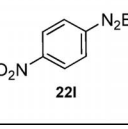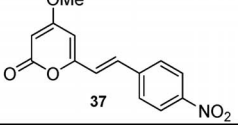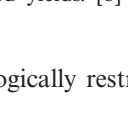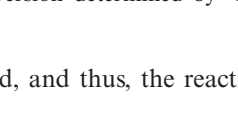
Additional kavalactones possessing a saturated side chain were prepared by the selective hydrogenation of the exocyclic double bond of Heck–Matsuda adducts **4**, **8**, and **30**, allowing the syntheses in good yields of two natural kavalactones (i.e., **1** and **20**) and one synthetic analogue **38** (Scheme 6).

The higher reactivity profile of vinyl pyrone **33** when compared to vinyl lactone **21** is probably a consequence of the conjugation of the two π-systems, making the vinyl pyrone more reactive towards the Heck–Matsuda reaction, analogous to isolated double bonds and styrenes.

On the other hand, the lower reactivity of vinyl dihydropyrone **21**, when compared to the arylation of allylic acetate, as we previously reported,[11] might be due to the lack of coordinating ability of **21** with the cationic arylpalladium intermediate. With allylic acetates, the coordination of palladium to the carbonyl oxygen plays a key role in the reaction outcome, controlling the regio- and stereochemistry of the arylation (Scheme 7). In the case of olefin **21**, which can be viewed as a conformationally restricted allylic ester, the simultaneous coordination of the arylpalladium intermediate with the double bond and the carbonyl oxygen

Table 5. Yangonin analogues by the Heck–Matsuda arylation of vinyl pyrone **33**.

Entry	Diazonium salt	Product	Yield (%)[a]
1	**22i**	**7**	89
2	**22j**	**10**	63
3	**22c**	**30**	81
4	**22b**	**4**	57
5	**22h**	**28**	63
6[b]	**22d**	**9**	25
7	**22e**	**34**	55
8	**22f**	**29**	86
9	**22g**	**35**	71
10	**22k**	**36**	66
11	**22l**	**37**	18

[a] Isolated yields. [b] Conversion determined by ¹H NMR spectroscopy.

is topologically restricted, and thus, the reaction is less efficient.
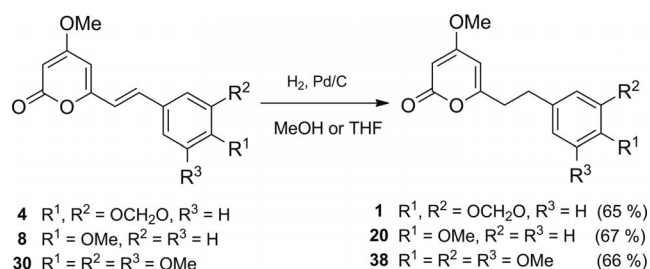
Scheme 6.
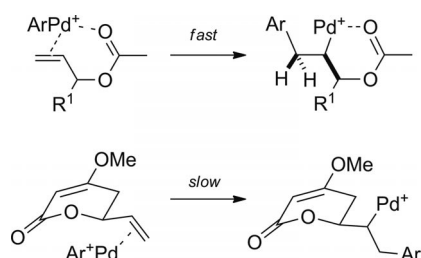
Scheme 7.

Conclusions

Herein, we described the total syntheses of three bioactive pyrones isolated from *P. sabulosa* (i.e., **1**, **4**, and **7**) and eight isolated from *P. methysticum* (i.e., **8**–**10**, **13**, **15**, and **18**–**20**) using the Heck–Matsuda arylation as the key step. Additionally, a number of kavalactone analogues were prepared by simply employing a different arenediazonium salt. This approach allowed the syntheses of several potentially bioactive compounds with a variety of substituents on the aryl moiety and a degree of unsaturation in the lactone moiety and side chain. The broad scope of this adopted methodology will be important for structure–activity studies regarding the affinity of these compounds for the benzodiazepine binding site. Efforts are underway to design synthetic analogues, with lower levels of toxicity, which could be as active as the naturally occurring kavalactones.

Experimental Section

Materials and Methods: The ^{1}H NMR spectroscopic data were recorded at 200 MHz, 250 MHz, and 500 MHz in CDCl$_3$, [D$_6$]-DMSO, and CD$_3$COCD$_3$ solutions. The chemical shifts are reported in ppm and referenced to the residual solvent peak or tetramethylsilane (TMS). The spectroscopic data are reported in the order of chemical shift (δ), multiplicity, coupling constant (J) in Hertz, and integrated intensity. The ^{13}C NMR spectroscopic data were recorded at 50 MHz, 62.5 MHz, and 125 MHz in CDCl$_3$, [D$_6$]DMSO, and CD$_3$COCD$_3$ solutions. The chemical shifts are reported in ppm and referenced to the residual solvent peak. The abbreviations to denote the multiplicity of a particular signal are s (singlet), br. (broad), d (doublet), t (triplet), q (quartet), dd (double doublet), dt (double triplet), ddd (double double doublet), and m (multiplet). The microwave (MW) reactions were conducted with a microwave synthesizer, which consisted of a continuous focus mi-

crowave power delivery system with an operator-selectable power output from 0 to 300 W. These reactions were performed in glass vessels (capacity 10 mL) sealed with a septum. The temperature measurements were conducted with an infrared temperature sensor mounted under the reaction vessel. All of the experiments were performed using a stirring option, whereby the contents of the vessel were stirred by means of both a rotating magnetic plate located below the floor of the microwave cavity and a Teflon-coated magnetic stir bar inside the vessel. All of the experiments were carried out by simultaneously cooling with compressed air passed through the microwave cavity and heating. Column chromatography was performed with silica gel (230–400 mesh) following the methods described by Still.[15] Thin layer chromatography (TLC) was performed using silica gel GF$_{254}$ (0.25 mm thickness). For visualization, the TLC plates were either placed under ultraviolet light or developed with phosphomolybdic acid followed by heating. Air- and moisture-sensitive reactions were conducted in flame- or oven-dried glassware equipped with tightly fitted rubber septa and under a positive atmosphere of dry argon. The reagents and solvents were handled using standard syringe techniques. Temperatures above room temperature were maintained by using a mineral oil bath heated on a hotplate.

Synthesis of 4-Methoxy-6-vinyl-5,6-dihydro-2H-pyran-2-one (21)

First Step: To a solution of lithiumdiisopropylamide (LDA) at 0 °C, freshly prepared from diisopropylamine (2.6 g, 18.5 mmol) in anhydrous THF (35 mL) and nBuLi (18.5 mmol), was added by a syringe pump ethyl acetoacetate (1 mL, 7.7 mmol) over 20 min. Next, freshly distilled acrolein (0.55 mL, 8.5 mmol) was slowly added, and the reaction mixture was stirred at 0 °C for an additional 20 min. Then, cold water (100 mL) was added, and the reaction mixture was warmed to room temperature and stirred for an additional 1 h. After extraction with diethyl ether (60 mL), the aqueous phase was acidified with HCl (3.0 M solution) to pH = 1, and the product was extracted using dichloromethane (3 × 30 mL). The combined dichloromethane layers were dried with MgSO$_4$ and filtered, and then the solvent was removed under reduced pressure. The residue was obtained as a yellow oil (ca. 92% yield), and the product was used in the next step without further purification. ^{1}H NMR (250 MHz, CDCl$_3$): δ = 2.65 (dd, J = 18.0, 9.3 Hz, 1 H), 2.82 (dd, J = 18.0, 3.8 Hz, 1 H), 3.45 (d, J = 19.3 Hz, 1 H), 3.60 (d, J = 19.3 Hz, 1 H), 5.15–5.26 (m, 1 H), 5.40 (d, J = 10.5 Hz, 1 H), 5.47 (dd, J = 17.3, 1.5 Hz, 1 H), 5.94 (ddd, J = 17.3, 10.5, 5.3 Hz, 1 H) ppm. ^{13}C NMR (62.5 MHz, CDCl$_3$): δ = 42.9, 47.0, 75.1, 119.1, 133.3, 166.9, 199.4 ppm.

Second Step: Under argon, to a solution of the above product (1 g, 7.14 mmol) in anhydrous acetone (20 mL) were added anhydrous K$_2$CO$_3$ (1.97 g, 14.3 mmol) and Me$_2$SO$_4$ (1.35 mL, 14.3 mmol) at room temperature. The reaction mixture was stirred for 20 h at room temperature. Then, ethyl acetate (60 mL) was added, and the crude mixture was washed with HCl (0.5 M solution, 60 mL). The organic layer was dried with MgSO$_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/ethyl acetate, 50:50) to provide the methoxy vinyl lactone **21** (0.57 g, 52%) as a slightly yellow oil which precipitated when stored in freezer. ^{1}H NMR (250 MHz, CDCl$_3$): δ = 2.45 (dd, J = 17.0, 5.0 Hz, 1 H), 2.56 (ddd, J = 17.0, 10.0, 1.3 Hz, 1 H), 3.76 (s, 3 H), 4.85–4.94 (m, 1 H), 5.16 (d, J = 1.0 Hz, 1 H), 5.30 (dt, J = 10.0, 1.2 Hz, 1 H), 5.42 (dt, J = 17.0, 1.2 Hz, 1 H), 5.95 (ddd, J = 17.0, 10.0, 5.5 Hz, 1 H) ppm. ^{13}C NMR (62.5 MHz, CDCl$_3$): δ = 32.8, 56.1, 75.8, 90.4, 118.0, 134.7, 166.8, 172.3 ppm. IR (film): $\tilde{\nu}$ = 1739, 1616, 1380, 1229, 1204 cm^{-1}. MS (EI): m/z = 153 [M – 1]$^+$, 125, 110, 98, 79, 68, 55, 40.

Procedure for the Heck Arylation of Olefin 21

Condition A − Using Pd₂(dba)₃·dba as Catalyst: To a microwave test tube were added Pd₂(dba)₃·dba (4 mol-%, 6 mg), sodium acetate (40 mg, 0.45 mmol, 3 equiv.) and benzonitrile (2 mL). To the resulting suspension were added olefin **21** (23.5 mg, 0.15 mmol) and the arenediazonium salt (0.17 mmol, 1.1 equiv.). The reaction mixture was stirred in a microwave reactor at 300 W and 80 °C for 1 h. After this time, the crude reaction mixture was filtered through a plug of silica, and the filtrate was concentrated under reduced pressure. The product was purified by flash chromatography (hexanes/ethyl acetate, 50:50) to provide the corresponding Heck adduct as a homogeneous material by TLC.

Condition B − Using Pd(OAc)₂ as Catalyst: To a 10-mL tube were added Pd(OAc)₂ (10 mol-%, 3 mg), sodium acetate (35.6 mg, 0.39 mmol, 3 equiv.) and olefin **21** (20.0 mg, 0.13 mmol). Acetonitrile (0.5 mL) was added, and the tube was filled with a carbon monoxide atmosphere. After 10 min, the arenediazonium salt (0.156 mmol, 1.2 equiv.) was added to the resulting suspension. The reaction was heated at 60 °C for 3 h. After this time, the crude reaction mixture was filtered through a plug of silica, and the filtrate was concentrated under reduced pressure. The product was purified by flash chromatography (hexanes/ethyl acetate, 50:50) to provide the corresponding Heck adduct as a homogeneous material by TLC.

(E)-4-Methoxy-6-(4-methoxystyryl)-5,6-dihydro-2H-pyran-2-one (13):[8a] Condition A (85%), Condition B (75%). Obtained as a white solid, m.p. 122–123 °C. ^{1}H NMR (250 MHz, CDCl₃): δ = 2.52 (dd, J = 17.0, 4.7 Hz, 1 H), 2.67 (ddd, J = 17.0, 10.0, 1.2 Hz, 1 H), 3.76 (s, 3 H), 3.80 (s, 3 H), 4.98–5.07 (m, 1 H), 5.18 (d, J = 1.2 Hz, 1 H), 6.11 (dd, J = 17.0, 6.5 Hz, 1 H), 6.66 (d, J = 17.0 Hz, 1 H), 6.86 (d, J = 8.7 Hz, 2 H), 7.32 (d, J = 8.7 Hz, 2 H) ppm. ^{13}C NMR (62.5 MHz, CDCl₃): δ = 33.6, 55.5, 56.3, 76.2, 90.8, 114.3, 123.4, 128.2, 128.6, 133.1, 160.0, 167.1, 172.6 ppm. IR (film): ṽ = 1704, 1623, 1247, 1225, 1022 cm⁻¹. MS (EI): m/z = 260 [M]⁺, 232, 161, 134, 121, 98, 68.

(E)-6-[2-(Benzo[d][1,3]dioxol-5-yl)vinyl]-4-methoxy-5,6-dihydro-2H-pyran-2-one (18):[16] Condition A (59%). ^{1}H NMR (250 MHz, CDCl₃): δ = 2.52 (dd, J = 17.0, 4.5 Hz, 1 H), 2.66 (ddd, J = 17.0, 10.7, 1.2 Hz, 1 H), 3.77 (s, 3 H), 4.98–5.07 (m, 1 H), 5.19 (d, J = 1.2 Hz, 1 H), 5.97 (s, 2 H), 6.08 (dd, J = 15.7, 6.2 Hz, 1 H), 6.64 (dd, J = 15.7, 1.0 Hz, 1 H), 6.76 (d, J = 8.0 Hz, 1 H), 6.83 (dd, J = 8.0, 1.5 Hz, 1 H), 6.92 (d, J = 1.5 Hz, 1 H) ppm. ^{13}C NMR (62.5 MHz, CDCl₃): δ = 33.3, 56.1, 76.0, 90.5, 101.2, 105.8, 108.3, 121.7, 123.6, 130.1, 132.9, 147.8, 148.1, 166.8, 172.3 ppm. IR (film): ṽ = 1706, 1624, 1249, 1220, 1031 cm⁻¹.

(E)-4-Methoxy-6-(3,4,5-trimethoxystyryl)-5,6-dihydro-2H-pyran-2-one (23):[17] Condition A (70%), Condition B (28%). Obtained as a yellow solid, m.p. 119–120 °C. ^{1}H NMR (250 MHz, CDCl₃): δ = 2.54 (dd, J = 17.2, 4.5 Hz, 1 H), 2.67 (ddd, J = 17.2, 10.5, 1.0 Hz, 1 H), 3.76 (s, 3 H), 3.84 (s, 3 H), 3.87 (s, 6 H), 5.00–5.07 (m, 1 H), 5.19 (d, J = 1.0 Hz, 1 H), 6.16 (dd, J = 16.0, 6.0 Hz, 1 H), 6.61 (s, 2 H), 6.65 (d, J = 16.0 Hz, 1 H) ppm. ^{13}C NMR (62.5 MHz, CDCl₃): δ = 33.3, 56.09, 56.12, 60.9, 75.7, 90.5, 103.7, 125.0, 131.4, 133.0, 138.3, 153.3, 166.7, 172.3 ppm. IR (film): ṽ = 1704, 1624, 1241, 1223, 1127, 1021 cm⁻¹. MS (EI): m/z = 320 [M]⁺, 194, 181, 179.

(E)-6-(4-Fluorostyryl)-4-methoxy-5,6-dihydro-2H-pyran-2-one (24):[8a] Condition B (41%). Obtained as a white, crystalline solid. m.p. 190–191 °C. ^{1}H NMR (250 MHz, CDCl₃): δ = 2.53 (dd, J = 17.0, 4.7 Hz, 1 H), 2.67 (ddd, J = 17.0, 10.5, 1.0 Hz, 1 H), 3.77 (s, 3 H), 5.00–5.11 (m, 1 H), 5.20 (d, J = 1.0 Hz, 1 H), 6.18 (dd, J = 16.0, 6.2 Hz, 1 H), 6.71 (d, J = 16.0 Hz, 1 H), 7.02 (t, J = 8.7 Hz, 2 H), 7.32–7.40 (m, 2 H) ppm. ^{13}C NMR (62.5 MHz, CDCl₃): δ = 33.3, 56.1, 75.7, 90.5, 115.6 (d, J = 21.9 Hz), 125.2 (d, J = 2.5 Hz), 128.3 (d, J = 8.1 Hz), 131.9 (d, J = 3.1 Hz), 132.0, 162.7 (d, J = 246.2 Hz), 166.6, 172.2 ppm. IR (KBr): ṽ = 1699, 1622, 1229, 1022 cm⁻¹. MS (EI) m/z = 248 [M]⁺, 220, 204, 146, 133, 122, 109, 98, 68. HRMS: calcd. for C₁₄H₁₃FO₃ 248.0849; found 248.0849.

(E)-6-(4-Chlorostyryl)-4-methoxy-5,6-dihydro-2H-pyran-2-one (25): Condition B (40%). Obtained as a white, crystalline solid, m.p. 179–180 °C. ^{1}H NMR (250 MHz, CDCl₃): δ = 2.54 (dd, J = 17.0, 4.7 Hz, 1 H), 2.67 (ddd, J = 17.0, 10.2, 1.0 Hz, 1 H), 3.77 (s, 3 H), 5.00–5.10 (m, 1 H), 5.20 (d, J = 1.0 Hz, 1 H), 6.23 (dd, J = 16.0, 6.0 Hz, 1 H), 6.72 (dd, J = 16.0, 1.0 Hz, 1 H), 7.31 (s, 4 H) ppm. ^{13}C NMR (62.5 MHz, CDCl₃): δ = 33.2, 56.1, 75.6, 90.6, 126.1, 127.9, 128.9, 131.9, 134.0, 134.2, 166.6, 172.2 ppm. IR (KBr): ṽ = 1695, 1622, 1385, 1230, 1020 cm⁻¹. MS (EI): m/z = 264 [M]⁺, 236, 138, 125, 98, 68. HRMS: calcd. for C₁₄H₁₃ClO₃ 264.0553; found 264.0580.

(E)-6-(4-Hydroxystyryl)-4-methoxy-5,6-dihydro-2H-pyran-2-one (27):[18] Condition B (35%). Obtained as a yellow solid which decomposed at 205 °C. ^{1}H NMR (250 MHz, CD₃COCD₃): δ = 2.55 (dd, J = 17.0, 4.5 Hz, 1 H), 2.68 (ddd, J = 17.0, 10.2, 1.0 Hz, 1 H), 3.77 (s, 3 H), 4.93–5.08 (m, 1 H), 5.15 (d, J = 1.2 Hz, 1 H), 6.20 (dd, J = 16.0, 6.5 Hz, 1 H), 6.68 (d, J = 16.0 Hz, 1 H), 6.82 (d, J = 8.5 Hz, 2 H), 7.33 (d, J = 8.5 Hz, 2 H), 8.53 (br., 1 H) ppm. ^{13}C NMR (125 MHz, CD₃COCD₃): δ = 33.0, 55.7, 76.0, 90.1, 115.4, 123.4, 127.7, 128.0, 132.5, 157.7, 165.6, 172.5 ppm. IR (film): ṽ = 3235, 1682, 1613, 1452, 1269, 1233, 1192, 1075 cm⁻¹. MS (EI): m/z = 246 [M]⁺, 218, 201, 140, 120, 107, 98.

Synthesis of 4-Methoxy-2-oxo-2H-pyran-6-carbaldehyde (32)

First Step: In a 250-mL Erlenmeyer flask open to the air, dehydroacetic acid **31** (10.72 g, 630 mmol) was dissolved in of H₂SO₄ (90% aqueous solution, 34 mL). The mixture was heated at 130 °C for 15 min and then quenched with ice (≈40 g) which led to the precipitation of a white solid. The product was filtered, washed with cold water, and dried under vacuum to yield 4-hydroxy-6-methyl-2H-pyran-2-one (89%) as a white solid, m.p. 175–177 °C. ^{1}H NMR (250 MHz, [D₆]DMSO): δ = 2.13 (s, 3 H), 5.18 (d, J = 1.5 Hz, 1 H), 5.93 (d, J = 1.5 Hz, 1 H), 11.56 (br., 1 H) ppm. ^{13}C NMR (62.5 MHz, [D₆]DMSO): δ = 19.4, 88.1, 100.2, 163.3, 163.9, 170.5 ppm. IR (KBr): ṽ = 1713, 1663, 1583, 1307, 1259 cm⁻¹. MS (EI): m/z = 126 [M]⁺, 111, 98, 85, 69, 55.

Second Step: To a suspension of K₂CO₃ (31.2 g, 226.2 mmol) in anhydrous acetone (200 mL) under argon was added Me₂SO₄ (4.9 mL, 51.6 mmol). The reaction mixture was heated to reflux, and the deacetylated compound 4-hydroxy-6-methyl-2H-pyran-2-one (5.0 g, 39.68 mmol) was added in one portion. The reaction mixture was stirred and heated at reflux overnight. Then, the system was cooled to room temperature and then filtered. The solid was washed with acetone, and the solvent was removed under reduced pressure. After purification by flash chromatography (hexanes/ethyl acetate, 20:80) and recrystallization (ethyl acetate/hexanes), the methylated product 4-methoxy-6-methyl-2H-pyran-2-one (5.0 g, 80%) was obtained as a crystalline, white solid, m.p. 84–84 °C. ^{1}H NMR (250 MHz, CDCl₃): δ = 2.18 (s, 3 H), 3.77 (s, 3 H), 5.37 (d, J = 2.0 Hz, 1 H), 5.75 (d, J = 2.0 Hz, 1 H) ppm. ^{13}C NMR (62.5 MHz, CDCl₃): δ = 19.7, 55.7, 87.2, 100.2, 161.9, 164.8, 171.2 ppm. IR (KBr): ṽ = 1717, 1651, 1568, 1253 cm⁻¹. MS (EI): m/z = 140 [M]⁺, 125, 112, 69, 59, 43.

Third Step: Under argon, 4-methoxy-6-methyl-2H-pyran-2-one (0.56 g, 4 mmol) and selenium dioxide (2.2 g, 20 mmol) were dis-

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solved in dioxane (15 mL) inside a sealed tube. The mixture was heated at 180 °C for 5 h. After this time, the reaction mixture was cooled to room temperature and filtered, and the filter cake was washed with ethyl acetate (30 mL). The crude product was purified by flash chromatography (hexanes/ethyl acetate, 50:50) to provide aldehyde **32** (65 %) as a yellowish solid. ^{1}H NMR (250 MHz, CDCl$_3$): δ = 3.89 (s, 3 H), 5.76 (d, J = 2.2 Hz, 1 H), 6.69 (d, J = 2.2 Hz, 1 H), 9.55 (s,1 H) ppm. ^{13}C NMR (62.5 MHz, [D$_6$]DMSO): δ = 57.5, 95.1, 113.1, 154.2, 161.7, 169.5, 184.8 ppm. IR (KBr): $\tilde{\nu}$ = 1731, 1697, 1336, 1256 cm^{-1}. MS (EI): m/z = 154 [M]$^+$, 125, 69, 59, 53.

4-Methoxy-6-vinyl-2H-pyran-2-one (33): To a solution of methyltriphenylphosphonium iodide (0.55 g, 1.37 mmol) in dry THF (15 mL) under argon at 0 °C was added nBuLi (1.37 mmol). The reaction mixture was stirred at 0 °C for 1 h, and then at –78 °C, a solution of aldehyde **32** (0.152 g, 1 mmol) in THF (10 mL) was added. The reaction was slowly warmed to room temperature and then stirred for 2 h. After this time, a saturated NaCl solution was added, and the mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic phases were dried with MgSO$_4$, filtered, and the solvent was evaporated under reduced pressure. The crude residue was purified by flash chromatography (hexanes/ethyl acetate, 70:30) to give olefin **33** (51 %) as an amorphous, white solid. ^{1}H NMR (250 MHz, CDCl$_3$): δ = 3.80 (s, 3 H), 5.49 (d, J = 2.2 Hz, 1 H), 5.54 (dd, J = 9.7, 1.7 Hz, 1 H), 5.86 (d, J = 2.2 Hz, 1 H), 6.14 (dd, J = 17.2, 1.7 Hz, 1 H), 6.25 (dd, J = 17.2, 9.7 Hz, 1 H) ppm. ^{13}C NMR (62.5 MHz, CDCl$_3$): δ = 55.9, 89.4, 101.4, 121.6, 128.0, 158.0, 163.8, 170.8 ppm. IR (KBr): $\tilde{\nu}$ = 1716, 1561, 1253 cm^{-1}. MS (EI): m/z = 152 [M]$^+$, 124, 81, 69, 59, 55. HRMS: calcd. for C$_8$H$_8$O$_3$ 152.0473; found 152.0471.

Procedure for the Heck Arylation of Olefin 33: To a 10-mL tube were added Pd(OAc)$_2$ (5 mol-%, 1.5 mg), sodium acetate (35.6 mg, 0.39 mmol, 3 equiv.), and olefin **33** (20.0 mg, 0.13 mmol). Acetonitrile (0.5 mL) was added, and the tube was filled with an atmosphere of carbon monoxide. After 10 min, the arenediazonium salt (0.156 mmol, 1.2 equiv.) was added to the resulting suspension. The reaction was heated at 60 °C for 3 h. After this time, the crude reaction mixture was filtered through a plug of silica, and the filtrate was concentrated under reduced pressure. The product was purified by flash chromatography (hexanes/ethyl acetate, 50:50) to provide the corresponding Heck adduct as a homogeneous material by TLC.

(E)-4-Methoxy-6-(4-methoxystyryl)-2H-pyran-2-one (8):[19] Obtained as a yellow solid (96 %), m.p. 152–153 °C. ^{1}H NMR (250 MHz, CDCl$_3$): δ = 3.82 (s, 3 H), 3.83 (s, 3 H), 5.47 (d, J = 2.0 Hz, 1 H), 5.89 (d, J = 2.0 Hz, 1 H), 6.45 (d, J = 16.0 Hz, 1 H), 6.90 (d, J = 8.7 Hz, 2 H), 7.43–7.48 (m, 3 H) ppm. ^{13}C NMR (62.5 MHz, CDCl$_3$): δ = 55.3, 55.9, 88.3, 100.5, 114.3, 116.3, 128.0, 129.0, 135.4, 159.1, 160.7, 164.2, 171.2 ppm. IR (film): $\tilde{\nu}$ = 1706, 1522, 1410, 1256, 1150 cm^{-1}. MS (EI): m/z = 258 [M]$^+$, 230, 215, 187, 159, 115, 89, 69.

(E)-6-(3,4-Dimethoxystyryl)-4-methoxy-2H-pyran-2-one (7):[1b] Obtained as a yellow solid (89 %), m.p. 158–159 °C. ^{1}H NMR (250 MHz, CDCl$_3$): δ = 3.82 (s, 3 H), 3.91 (s, 3 H), 3.92 (s, 3 H), 5.47 (s, 1 H), 5.91 (s, 1 H), 6.45 (d, J = 15.8 Hz, 1 H), 6.87 (d, J = 8.3 Hz, 1 H), 7.02 (s, 1 H), 7.08 (d, J = 8.3 Hz, 1 H), 7.45 (d, J = 15.8 Hz, 1 H) ppm. ^{13}C NMR (62.5 MHz, CDCl$_3$): δ = 55.8 (2 C), 55.9, 88.4, 100.5, 109.3, 111.2, 116.5, 121.6, 128.2, 135.7, 149.2, 150.4, 158.9, 164.1, 171.2 ppm. IR (KBr): $\tilde{\nu}$ = 1710, 1635, 1546, 1516, 1255, 1143, 1030 cm^{-1}. MS (EI): m/z = 288 [M]$^+$, 245, 217, 115, 69. HRMS: calcd. for C$_{16}$H$_{16}$O$_5$ 288.0998; found 288.1009.

(E)-6-(2,4-Dimethoxystyryl)-4-methoxy-2H-pyran-2-one (10): 63 % yield. ^{1}H NMR (250 MHz, CDCl$_3$): δ = 3.81 (s, 3 H), 3.84 (s, 3 H), 3.87 (s, 3 H), 5.45 (d, J = 2.0 Hz, 1 H), 5.88 (d, J = 2.0 Hz, 1 H), 6.45 (d, J = 2.2 Hz, 1 H), 6.50 (dd, J = 8.5, 2.2 Hz, 1 H), 6.61 (d, J = 16.0 Hz, 1 H), 7.41 (d, J = 8.5 Hz, 1 H), 7.69 (d, J = 16.0 Hz, 1 H) ppm. ^{13}C NMR (62.5 MHz, CDCl$_3$): δ = 55.40, 55.43, 55.8, 88.0, 98.4, 100.0, 105.2, 117.1, 117.4, 129.6, 131.3, 159.4, 159.9, 162.0, 164.4, 171.3 ppm. HRMS calcd. for C$_{16}$H$_{16}$O$_5$ 288.0998; found 288.0993.

(E)-4-Methoxy-6-(3,4,5-trimethoxystyryl)-2H-pyran-2-one (30):[17] Obtained as a yellow solid (81 %) which decomposed at 185 °C. ^{1}H NMR (250 MHz, CDCl$_3$): δ = 3.83 (s, 3 H), 3.87 (s, 3 H), 3.90 (s, 6 H), 5.50 (d, J = 2.2 Hz, 1 H), 5.95 (d, J = 2.2 Hz, 1 H), 6.48 (d, J = 16.1 Hz, 1 H), 6.73 (s, 2 H), 7.42 (d, J = 16.1 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 56.4, 56.9, 60.6, 89.1, 101.5, 105.6, 119.3, 131.2, 135.0, 139.2, 153.6, 158.9, 163.1, 171.3 ppm. IR (film): $\tilde{\nu}$ = 1705, 1642, 1550, 1252, 1126 cm^{-1}. MS (EI): m/z = 318 [M]$^+$, 303, 243, 148, 69. HRMS: calcd. for C$_{17}$H$_{18}$O$_6$ 318.1103; found 318.1098.

(E)-6-[2-(Benzo[d][1,3]dioxol-5-yl)vinyl]-4-methoxy-2H-pyran-2-one (4):[1b] 57 % yield. ^{1}H NMR (250 MHz, CDCl$_3$): δ = 3.82 (s, 3 H), 5.47 (d, J = 2.0 Hz, 1 H), 5.89 (d, J = 2.0 Hz, 1 H), 5.99 (s, 2 H), 6.40 (d, J = 16.0 Hz, 1 H), 6.80 (d, J = 8.0 Hz, 1 H), 6.97 (d, J = 8.0 Hz, 1 H), 7.00 (s, 1 H), 7.41 (d, J = 16.0 Hz, 1 H) ppm. ^{13}C NMR (62.5 MHz, CDCl$_3$): δ = 55.9, 89.5, 100.7, 101.4, 105.9, 108.6, 116.8, 123.5, 129.7, 135.5, 148.3, 148.9, 158.8, 164.1, 171.1 ppm. IR (film): $\tilde{\nu}$ = 1722, 1635, 1553, 1257, 1031 cm^{-1}. MS (EI): m/z = 272 [M]$^+$, 201, 115, 89, 69, 39. HRMS: calcd. for C$_{15}$H$_{12}$O$_5$ 272.0685; found 272.0682.

(E)-6-(4-Hydroxystyryl)-4-methoxy-2H-pyran-2-one (28):[20] Obtained as a white solid (63 %), m.p. 159–160 °C. ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 3.82 (s, 3 H), 5.59 (d, J = 1.7 Hz, 1 H), 6.22 (d, J = 1.7 Hz, 1 H), 6.77 (d, J = 16.5 Hz, 1 H), 6.78 (d, J = 8.5 Hz, 2 H), 7.24 (d, J = 16.5 Hz, 1 H), 7.52 (d, J = 8.5 Hz, 2 H), 9.91 (br., 1 H) ppm. ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 56.8, 88.6, 100.6, 116.3, 116.6, 126.7, 129.8, 134.9, 159.4 (2 C), 163.2, 171.5 ppm. IR (KBr): $\tilde{\nu}$ = 3231, 1694, 1547, 1454, 1252, 1033 cm^{-1}. MS (EI): m/z = 244 [M]$^+$, 216, 173, 145, 127, 115, 69, 43. HRMS: calcd. for C$_{14}$H$_{12}$O$_4$ 244.0736; found 244.0739.

(E)-4-Methoxy-6-styryl-2H-pyran-2-one (9):[19] 25 % yield. ^{1}H NMR (250 MHz, CDCl$_3$): δ = 3.84 (s, 3 H), 5.50 (d, J = 2.0 Hz, 1 H), 5.95 (d, J = 2.0 Hz, 1 H), 6.60 (d, J = 16.0 Hz, 1 H), 7.31–7.43 (m, 3 H), 7.47–7.55 (m, 3 H) ppm. ^{13}C NMR (62.5 MHz, CDCl$_3$): δ = 55.9, 88.8, 101.3, 118.6, 127.4, 128.9, 129.4, 135.2, 135.7, 158.6, 163.9, 171.0 ppm. IR (KBr): $\tilde{\nu}$ = 1714, 1641, 1533, 1253, 1153 cm^{-1}. MS (EI): m/z = 228 [M]$^+$, 200, 185, 157, 129, 103, 77, 69.

(E)-6-(4-Fluorostyryl)-4-methoxy-2H-pyran-2-one (34): Obtained as a white solid (55 %), m.p. 134–135 °C. ^{1}H NMR (250 MHz, CDCl$_3$): δ = 3.83 (s, 3 H), 5.50 (d, J = 2.0 Hz, 1 H), 5.94 (d, J = 2.0 Hz, 1 H), 6.50 (d, J = 16.0 Hz, 1 H), 7.07 (t, J = 8.5 Hz, 2 H), 7.43–7.51 (m, 3 H) ppm. ^{13}C NMR (125 MHz, CDCl$_3$): δ = 55.9, 88.9, 101.3 (d, J = 0.9 Hz), 116.0 (d, J = 21.7 Hz), 118.4 (d, J = 2.5 Hz), 129.2 (d, J = 8.2 Hz), 131.4 (d, J = 3.5 Hz), 134.5 (d, J = 1.0 Hz), 158.4 (d, J = 0.9 Hz), 163.3 (d, J = 249.0 Hz), 163.9, 171.0 ppm. IR (KBr): $\tilde{\nu}$ = 1721, 1555, 1255, 1157 cm^{-1}. MS (EI): m/z = 246 [M]$^+$, 218, 174, 146, 101, 69. HRMS: calcd. for C$_{14}$H$_{11}$FO$_3$ 246.0692; found 246.0706.

(E)-6-(4-Chlorostyryl)-4-methoxy-2H-pyran-2-one (29):[21] Obtained as a white solid (86 %), m.p. 151–152 °C. ^{1}H NMR (250 MHz, CDCl$_3$): δ = 3.83 (s, 3 H), 5.50 (d, J = 1.7 Hz, 1 H), 5.95 (d, J = 1.7 Hz, 1 H), 6.55 (d, J = 16.0 Hz, 1 H), 7.32–7.48 (m, 5 H) ppm.

^{13}C NMR (62.5 MHz, CDCl$_3$): δ = 55.9, 89.0, 101.7, 119.1, 128.5, 129.1, 133.7, 134.3, 135.2, 158.2, 163.8, 170.9 ppm. IR (KBr): ṽ = 1719, 1642, 1553, 1253 cm^{-1}. MS (EI): m/z = 262 [M]$^+$, 234, 191, 128, 101, 69. HRMS: calcd. for C$_{14}$H$_{11}$ClO$_3$ 262.0397; found 262.0399.

(E)-6-(4-Bromostyryl)-4-methoxy-2H-pyran-2-one (35): Obtained as a white solid (71%), m.p. 158–159 °C. ^{1}H NMR (250 MHz, CDCl$_3$): δ = 3.83 (s, 3 H), 5.50 (d, J = 2.0 Hz, 1 H), 5.95 (d, J = 2.0 Hz, 1 H), 6.56 (d, J = 16.0 Hz, 1 H), 7.35 (d, J = 8.5 Hz, 2 H), 7.42 (d, J = 16.0 Hz, 1 H), 7.50 (d, J = 8.5 Hz, 2 H) ppm. ^{13}C NMR (62.5 MHz, CDCl$_3$): δ = 56.0, 89.1, 101.7, 119.2, 123.5, 128.8, 132.1, 134.1, 134.4, 158.2, 163.8, 170.9 ppm. IR (KBr): ṽ = 1728, 1641, 1557, 1252, 1153 cm^{-1}. MS (EI): m/z = 308 [M]$^+$, 306 [M]$^+$, 280, 278, 237, 235, 208, 156, 139, 128, 102, 69. HRMS: calcd. for C$_{14}$H$_{11}$BrO$_3$ 305.9892; found 305.9887.

(E)-6-(4-Iodostyryl)-4-methoxy-2H-pyran-2-one (36): Obtained as an amorphous, white solid (66%). ^{1}H NMR (250 MHz, CDCl$_3$): δ = 3.83 (s, 3 H), 5.50 (d, J = 2.0 Hz, 1 H), 5.95 (d, J = 2.0 Hz, 1 H), 6.57 (d, J = 15.7 Hz, 1 H), 7.22 (d, J = 8.5 Hz, 2 H), 7.40 (d, J = 15.7 Hz, 1 H), 7.71 (d, J = 8.5 Hz, 2 H) ppm. ^{13}C NMR (62.5 MHz, CDCl$_3$): δ = 56.0, 89.1, 95.3, 101.8, 119.3, 128.9, 134.5, 134.7, 138.1, 158.2, 163.8, 170.9 ppm. IR (KBr): ṽ = 1726, 1640, 1557, 1252, 1153 cm^{-1}. MS (EI): m/z = 354 [M]$^+$, 326, 282, 156, 128, 102, 69. HRMS: calcd. for C$_{14}$H$_{11}$IO$_3$ 353.9753; found 353.9776.

Procedure for the DDQ Oxidation of Heck Adducts: To a round-bottomed flask under an argon atmosphere were added the Heck adduct (40 mg, 0.15 mmol) and dry toluene (2 mL). To this solution was added DDQ (42 mg, 0.18 mmol), and the reaction was heated at reflux for 2 h. After this time, the crude reaction mixture was filtered through a plug of Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/ethyl acetate, 50:50). Compounds **8** and **28**–**30** were obtained in yields shown in Scheme 2. For the analytical data, see above.

Procedure for the Hydrogenation of Heck Adducts 18 and 13: To a round-bottomed flask under a hydrogen atmosphere were added the Heck adduct **18** (41 mg, 0.15 mmol) and methanol (3 mL) followed by the addition of 10% Pd/C (9 mg). The reaction was stirred at room temperature for 12 h. After this time, the crude reaction mixture was filtered through a plug of Celite, and the filtrate was concentrated under reduced pressure. The products were purified by flash chromatography (hexanes/ethyl acetate, 50:50).

6-[2-(Benzo[d][1,3]dioxol-5-yl)ethyl]-4-methoxy-5,6-dihydro-2H-pyran-2-one (19):[16] Obtained as colorless crystals (95%). ^{1}H NMR (250 MHz, CDCl$_3$): δ = 1.79–1.93 (m, 1 H), 2.01–2.17 (m, 1 H), 2.28 (dd, J = 17.0, 4.0 Hz, 1 H), 2.50 (ddd, J = 17.0, 12.0, 1.5 Hz, 1 H), 2.64–2.86 (m, 2 H), 3.73 (s, 3 H), 4.29–4.40 (m, 1 H), 5.13 (d, J = 1.5 Hz, 1 H), 5.92 (s, 2 H), 6.64 (dd, J = 7.9, 1.4 Hz, 1 H), 6.68 (d, J = 1.4 Hz, 1 H), 6.72 (d, J = 7.9 Hz, 1 H) ppm. ^{13}C NMR (62.5 MHz, CDCl$_3$): δ = 30.7, 33.0, 36.6, 56.0, 74.6, 90.3, 100.8, 108.3, 108.8, 121.3, 134.6, 145.8, 147.7, 167.3, 172.7 ppm.

4-Methoxy-6-(4-methoxyphenethyl)-5,6-dihydro-2H-pyran-2-one (15):[19] Obtained as colorless crystals (89%). ^{1}H NMR (250 MHz, CDCl$_3$): δ = 1.87–1.94 (m, 1 H), 2.06–2.13 (m, 1 H), 2.29 (dd, J = 16.8, 3.6 Hz, 1 H), 2.50 (dd, J = 16.8, 12.0 Hz, 1 H), 2.71–2.91 (m, 2 H), 3.73 (s, 3 H), 3.78 (s, 3 H), 4.30–4.39 (m, 1 H), 5.13 (s, 1 H), 6.83 (d, J = 8.7 Hz, 2 H), 7.12 (d, J = 8.7 Hz, 2 H) ppm. ^{13}C NMR (62.5 MHz, CDCl$_3$): δ = 30.4, 33.4, 36.9, 55.6, 56.4, 75.2, 90.7, 114.3, 129.8, 133.2, 158.4, 167.7, 173.2 ppm.

Procedure for the Hydrogenation of the Heck Adducts 8, 30, and 4: To a round-bottomed flask under a hydrogen atmosphere were

added the desired Heck adduct (41 mg, 0.18 mmol) and dry THF or methanol (20 mL) followed by the addition of 5% Pd/C (10 mg). The reaction was stirred at room temperature for 1.5 h. After this time, the crude reaction mixture was filtered through a plug of silica, and the filtrate was concentrated under reduced pressure.

4-Methoxy-6-(4-methoxyphenethyl)-2H-pyran-2-one (20):[21] Compound **20** was prepared using methanol as the solvent. The product was purified by recrystallization (ethyl acetate) followed by washing with diethyl ether to furnish the product as colorless crystals (67%), m.p. 101–102 °C. ^{1}H NMR (250 MHz, CD$_3$COCD$_3$): δ = 2.70–2.76 (m, 2 H), 2.86–2.92 (m, 2 H), 3.75 (s, 3 H), 3.82 (s, 3 H), 5.40 (d, J = 2.2 Hz, 1 H), 5.85 (d, J = 2.2 Hz, 1 H), 6.84 (d, J = 8.5 Hz, 2 H), 7.16 (d, J = 8.5 Hz, 2 H) ppm. ^{13}C NMR (62.5 MHz, CDCl$_3$): δ = 31.6, 35.1, 54.5, 55.6, 87.1, 99.6, 113.7, 129.3, 132.1, 158.3, 163.4, 164.6, 171.0 ppm. IR (KBr): ṽ = 1709, 1566, 1513, 1246, 1034 cm^{-1}. MS (EI): m/z = 260 [M]$^+$, 134, 121, 91.

4-Methoxy-6-(3,4,5-trimethoxyphenethyl)-2H-pyran-2-one (38):[8f] Compound **38** was prepared using methanol as the solvent. The product was purified by recrystallization (ethyl acetate) followed by washing with diethyl ether to furnish the product as amorphous solid (66%). ^{1}H NMR (250 MHz, CD$_3$COCD$_3$): δ = 2.73–2.80 (m, 2 H), 2.86–2.93 (m, 2 H), 3.68 (s, 3 H), 3.79 (s, 6 H), 3.83 (s, 3 H), 5.40 (d, J = 2.2 Hz, 1 H), 5.87 (d, J = 2.2 Hz, 1 H), 6.57 (s, 2 H) ppm. IR (KBr): ṽ = 1704 cm^{-1}. MS (EI): m/z = 320 [M]$^+$, 181, 125, 69.

6-[2-(Benzo[d][1,3]dioxol-5-yl)ethyl]-4-methoxy-2H-pyran-2-one (1):[1b] Compound **1** was prepared using THF as the solvent. The product was purified by flash chromatography (hexanes/ethyl acetate, 50:50) to provide the product as colorless crystals (65%). ^{1}H NMR (250 MHz, CDCl$_3$): δ = 2.69 (t, J = 7.0 Hz, 2 H), 2.89 (t, J = 7.0 Hz, 2 H), 3.78 (s, 3 H), 5.41 (d, J = 1.7 Hz, 1 H), 5.71 (d, J = 1.7 Hz, 1 H), 5.92 (s, 2 H), 6.59–6.73 (m, 3 H) ppm. ^{13}C NMR (62.5 MHz, CDCl$_3$): δ = 32.5, 35.7, 55.8, 87.7, 100.3, 100.8, 108.3, 108.6, 121.2, 133.6, 146.0, 147.7, 164.2, 164.8, 171.1 ppm. IR (KBr): ṽ = 1709, 1648, 1568, 1491, 1241, 1033 cm^{-1}. MS (EI): m/z = 274 [M]$^+$, 135. HRMS: calcd. for C$_{15}$H$_{14}$O$_5$ 274.0841; found 274.0854.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra for compounds **1**, **4**, **7**–**10**, **13**, **15**, **18**, **19**, **21**, **23**–**25**, **29**, and **32**–**36**.

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