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The scope of the Heck arylation of enol ethers with arenediazonium salts: a new approach to the synthesis of flavonoids

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ABSTRACT

The scope of the Heck arylation of cyclic and acyclic enol ethers with arenediazonium salts was evaluated. Arylation of 2,3-dihydrofuran yielded 2-aryl-2,5-dihydrofurans as the major adducts (>99:1) except when using *n*-Bu_4NHSO_4 as additive or 4-$NO_2PhN_2BF_4$ as arenediazonium salt. 2,3-Dihydropyran provided mixtures of the three possible isomeric Heck adducts. Arylation of *n*-butylvinylether with arenediazonium bearing electron-donating groups resulted in substituted acetophenones as almost exclusive products in good overall yields. Substituted 4*H*-chromenes provided 2-aryl-2*H*-chromenes in moderate yield when applying the $Pd(OAc)_2$/2,6-di-*t*-butyl-4-methylpyridine catalytic system, which were applied in the synthesis of flavonoids.

The Heck reaction promoted by palladium constitutes a versatile and robust methodology in modern organic synthesis.[1] Among the many electrophiles available, the arenediazonium salts are probably the least explored ones. In spite of the increasing awareness of the synthetic advantages of arenediazonium salts in Heck arylations, their use in organic synthesis still remains scarce.[2a] The so-called Heck–Matsuda reaction is operationally simple, usually faster, less costly and greener than traditional protocols.[2]

In an earlier publication,[2c] we reported some initial results dealing with the Heck–Matsuda arylation of endocyclic enol ethers with arenediazonium salts for the synthesis of styryllactones. In view of its synthetic potential, we herein extended considerably the scope of this methodology to other endocyclic and acyclic enol ethers in the construction of α-aryl-oxygenated compounds which has been attracting considerable attention due to their structural and biological features (Fig. 1).

To investigate the actual scope of the Heck arylation of enol ethers with arenediazonium salts, we started our studies using 2,3-dihydrofuran (**1**) and 4-methoxybenzenediazonium tetrafluoroborate (**2a**) using the protocol developed previously for the arylation of endocyclic enecarbamates.[2g] The stoichiometric relationship between the olefin and the arenediazonium salt was evaluated with yields improving significantly when more than 1.0 equiv of dihydrofuran was used (Table 1). This result can be partially rationalized in terms of the higher volatility of dihydrofuran when compared to enecarbamates. The best reaction condition is presented in Table 1, entry 4, where 2-(4-methoxyphenyl)-2,5-dihydrofuran **3a** was obtained as the almost sole product in 95% yield. Independent of the palladium load and the **1**:**2** ratio, only trace amounts of 2-(4-methoxyphenyl)-2,3-dihydrofuran (**4a**) could be detected in the reaction mixture (Table 1, entries 1–4).

A considerable increase in the amount of the regioisomeric adduct **4a** was observed in the presence of tetrabutylammonium hydrogen sulfate (Table 1, entries 5 and 6). Interestingly, regioisomer **4a** was the major Heck adduct when using 5 mol % of $Pd(OAc)_2$ and *n*-Bu_4NHSO_4 as additive in DMF (Table 1, entry 7). Larock[3] and Jeffery[4] previously described the Heck reaction of 2,3-dihydrofuran (**1**) with iodobenzene in the presence of tetrabutylammonium hydrogen sulfate, and they also observed the regioisomer **4** as the major arylation product.

Heck arylation with arenediazonium salts bearing electron-withdrawing groups led to lower yields and more complex reaction mixtures. For example, no Heck arylation is observed when 4-

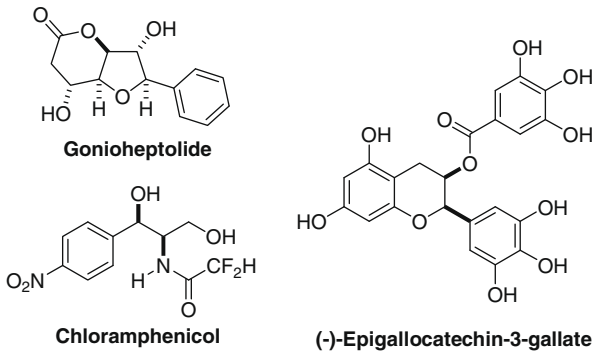

Figure 1. α-Aryl-oxygenated compounds of pharmacological interest.

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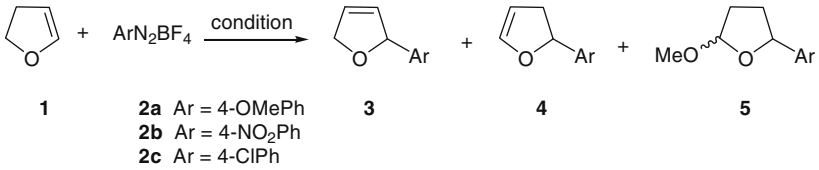
Table 1
Heck reaction of **1** with arenediazonium salts **2**



1 **2a** Ar = 4-OMePh **2b** Ar = 4-NO_2Ph **2c** Ar = 4-ClPh **3** **4** **5**

#	ArN_2BF_4 (equiv of **1**)	Condition	Additive	Product (**3**:**4**:**5**)	Yield (%)
1	**2a** (1.0)	A	—	>99:1:0	60
2	**2a** (2.0)	A	—	>99:1:0	74
3	**2a** (3.0)	A	—	>99:1:0	74
4	**2a** (2.0)	B	—	>99:1:0	95
5	**2a** (5.0)	B[a]	*n*-Bu_4NHSO_4	92:8:0	98
6	**2a** (2.0)	B[b]	*n*-Bu_4NHSO_4	70:30:0	70
7	**2a** (5.0)	C	*n*-Bu_4NHSO_4	38:62:0	76
8	**2b** (2.0)	A	—	—:—:—	0
9	**2b** (5.0)	D	—	48:0:52	48
10	**2b** (5.0)	E	—	27:0:73	45
11	**2c** (5.0)	D and E	—	—:—:—	0
12	**2c** (5.0)	F	—	>99:1:0	32

(A) 0.5 mol % $Pd_2(dba)_3$dba, 4 equiv NaOAc, MeCN, 25 °C, 0.5 h. (B) 1.0 mol % $Pd_2(dba)_3$dba, 4 equiv NaOAc, MeCN, 25 °C, 0.5 h. (C) 5.0 mol % $Pd(OAc)_2$, 2.0 equiv *n*-Bu_4NHSO_4, DMF, 25 °C, 5 h. (D) 5 mol % $Pd_2(dba)_3$dba, 4 equiv NaOAc, MeCN/MeOH (1:1), 25 °C, 0.5 h. (E) 5 mol % $Pd_2(dba)_3$dba, 4 equiv NaOAc, PhCN/MeOH (1:1), 25 °C, 0.5 h. (F) 3.5 mol % $Pd(OAc)_2$, 4 equiv NaOAc, MeCN, CO, 25 °C, 0.5 h.

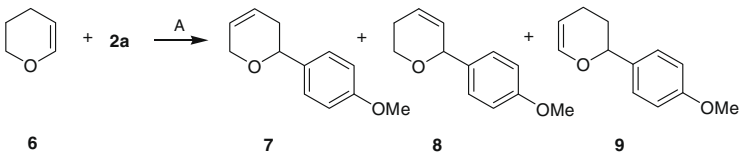
[a] Condition B with 0.5 equiv of *n*-Bu_4NHSO_4, 5.0 h.

[b] Condition B with 2.5 equiv of *n*-Bu_4NHSO_4, 5.5 h.

nitrobenzenediazonium tetrafluoroborate is used in the reaction condition A (Table 1, entry 8). However, when methanol is used as co-solvent with 5 equiv of **1** (Table 1, entry 9) the Heck adduct **3b** and the diastereoisomers **5b** were obtained in 48% yield, as a nearly 1:1 mixture. Most probably, acetals **5b** were generated from the addition of MeOH to enol ether **4b** indicating significant double bond isomerization under these conditions. Arylations performed in a mixture of PhCN/MeOH provided a mixture of **3b** and **5b** diastereoisomers in comparable yields, but with a different product distribution (Table 1, entry 10). Application of the above-mentioned protocols to the reaction of **1** with 4-chlorobenzenodiazonium tetrafluoroborate (**2c**) resulted in no Heck adducts (Table 1, entry 11). The expected Heck product **3c** was obtained in 32% yield only when 3.5 mol % of $Pd(OAc)_2$ was employed as a catalyst in the presence of 4 equiv of NaOAc in MeCN under a CO reducing atmosphere (Table 1, entry 12). Formation of acetal **5c** was not observed in this case.

The best arylation protocol described for the reaction of the dihydrofuran with arenediazonium **2a** (Table 1, entry 4) was also applied to 2,3-dihydropyran **6**. In contrast to the results obtained with dihydrofuran, a mixture of the three possible double bond isomers was observed in all cases (Table 2). In an attempt to improve yields and selectivity, we changed the **6**:**2a** ratio. This strategy increased yields slightly (entries 2 and 3), but it did not change the Heck adducts ratio significantly. Refluxing conditions provided better yields and increased the ratio of enol ether **9** (entry 4). Addition of 0.3 equiv of *n*-Bu_4NHSO_4 at room temperature promoted an effect similar to that observed under reflux regarding product ratio, but caused a significant drop in yield (entry 5). Surprisingly, when 2.0 equiv of *n*-Bu_4NHSO_4 was used, Heck adduct **7** was obtained as

Table 2
Heck reaction of 2,3-dihydropyran **6** with arenediazonium **2a**



6 **7** **8** **9**

	Equiv of **6**	$Pd_2(dba)_3$dba (mol %)	Additive	**7**:**8**:**9**	Yield (%)
1	3.0	1.0	—	52:32:16	80
2	1.5	2.0	—	55:34:11	84
3	1.5	1.5	—	57:30:13	59
4[a]	3.0	1.0	—	20:17:63	88
5	3.0	1.0	*n*-Bu_4NHSO_4[b]	23:11:66	41
6	3.0	1.0	*n*-Bu_4NHSO_4[c]	98:1:1	15

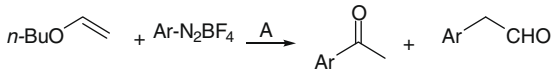
(A) 4 equiv NaOAc, MeCN, 25 °C, 1 h.

[a] MeCN, reflux, 3 h.

[b] Condition A adding 0.3 equiv of *n*-Bu_4NHSO_4.

[c] Condition A adding 2.0 equiv of *n*-Bu_4NHSO_4.

Table 3
Heck reaction of *n*-butylvinylether **10** with arenediazonium salts

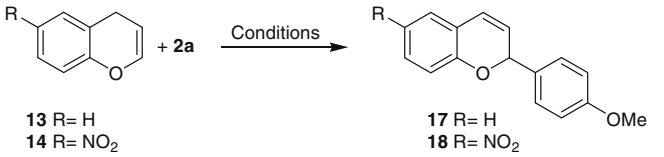


10 **2** **11** **12**

#	Ar	**11**:**12** (α:β)	Yield (%)
1	4-MeOPh	>99:1	80
2	2-MeOPh	>99:1	38
3	4-MePh	98:2[a]	64
4	β-Naphtyl	>99:1[a]	73
5	Ph	95:5[a]	60
6	4-F	72:28[a]	<10[b]
7	4-Cl	36:64[a]	<10[b]
8	4-Br	78:22[c]	<10[b]
9	4-NO_2	—	0

(A) (i) 1.0 equiv of **10**, 1.0 equiv of arenediazonium salt, 2.0 mol % $Pd_2(dba)_3dba$, 4 equiv NaOAc, MeCN, 30 °C, 0.5 h. (ii) 37% HCl (a few drops) at 25 °C followed by stirring for 0.5 h.
[a] Dediazotization and bisaryl homocoupling were detected in less than 5% by GC.
[b] Yields estimated by GC/MS.
[c] $(4\text{-BrPh})_2$ detected in 12% by GC.

Table 4
Heck reaction of **13** and **14** with arenediazonium **2a**



13 R= H
14 R= NO_2

17 R= H
18 R= NO_2

	4*H*-Chromene	Condition	Product	Yield (%)
1	**13**	A	**17**	10
2	**13**	A[a]	**17**	27
3	**13**	A[b]	**17**	54
4	**13**	B	**17**	57
5	**14**	B	**18**	13
6	**14**	C	**18**	53

(A) 1 equiv of **2a**, 1.0 mol % $Pd_2(dba)_3dba$, 4 equiv NaOAc, MeCN, 25 °C, 1.0 h. (B) 1 equiv of **2a**, 10 mol % $Pd(OAc)_2$, 4 equiv 2,6-di-*t*-butyl-4-methylpyridine, EtOH, 55 °C, 2.5 h. (C) 1 equiv of **2a**, 10 mol % $Pd(OAc)_2$, 4 equiv 2,6-di-*t*-butyl-4-methylpyridine, EtOH/MeCN (1:1), 55 °C, 2.5 h.
[a] Reaction performed at 65 °C.
[b] 5 mol % $Pd_2(dba)_3dba$ at 65 °C.

the overwhelming major regioisomer (entry 6) in a modest 15% yield. These results are somewhat in contrast to those reported by Schmidt, who observed basically one regioisomer for the Heck arylation of dihydropyrans. However, it should be emphasized that Schmidt used only 6-substituted dihydropyran in his studies.[5]

Cabri,[6] Hallberg and Larhed[7], Xiao,[8] and others[9] have investigated extensively the regioselectivity of the Heck reaction of electron-rich acyclic olefins, such as enol ethers, silanes, and enamides. These olefins tend to afford a mixture of α and β regioisomers, under traditional Heck protocols due to competition between the ionic reaction pathway, leading to α-products, and the neutral reaction pathway, leading to β-products.

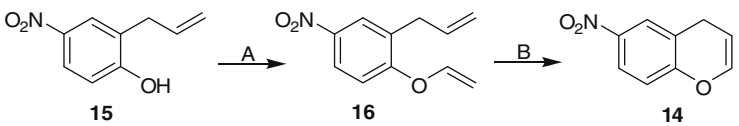
To investigate the scope of the optimized Heck–Matsuda arylation protocols described above, they were also applied to a prototype acyclic enol ether, *n*-butylvinylether **10**. The expected Heck arylations occurred smoothly to afford essentially the α-arylated product in moderate to good yields when arenediazonium salts bearing electron-donating groups (EDGs) are used (Table 3, entries 1–4). These results are supported by the ionic character of the Heck–Matsuda catalytic cycle.[10] In spite of that, the β-arylation pathway was more pronounced when halogen-containing arenediazonium salts were used. These experiments provided low yields of the Heck adducts. Similar results were reported independently by Cabri[6e] and Larhed[11] when phenanthroline ligands were used in the palladium-mediated arylation of acyclic enol ethers using aryltriflates and boronic acids, respectively. As observed for 2,3-dihydrofuran **1** and 2,3-dihydropyran **6**, no arylation products were observed when 4-$NO_2PhN_2BF_4$ was used.

These results prompted us to extend this methodology to the Heck arylation of 4*H*-chromenes aiming at the construction of the catechins and flavans, including (−)-epigallocatechin-3-gallate,[12] which are becoming increasingly important in view of the health-promoting effects found in green tea. The 4*H*-chromene **13** was prepared according to the literature,[13] whereas 4-nitro-4*H*-chromene **14** was prepared from 4-nitro-2-allylphenol **15** in 73% yield (two steps). Vinylation of phenol **15** using tetravinyltin provided diene **16** in 81% yield**,** which was then submitted to ring-closing metathesis (Grubbs-2 catalyst) to give chromene **14** in 91% yield (Scheme 1).

We first investigated the Heck arylation reaction of 4*H*-chromenes **13** and **14** with **2a,** using 1 mol % of $Pd_2(dba)_3dba$, 4 equiv of NaOAc, MeCN, and 1 equiv of **2a** at room temperature, conditions optimized for the arylation of 2,3-dihydrofuran. When the reaction was performed using **13**, the desired Heck product **17** was obtained in only 10% yield (Table 4, entry 1).[14] A significant increase in yield (27%) was obtained when arylation was performed at 65 °C (entry 2). Further increase in yield was observed with a Pd loading of 5 mol % at 65 °C to provide the desired Heck adduct in 54%. The same result was observed when $Pd(OAc)_2$ was employed as a catalyst, EtOH as solvent, and 2,6-di-*tert*-butyl-4-methylpyridine as base at room temperature (entry 4).

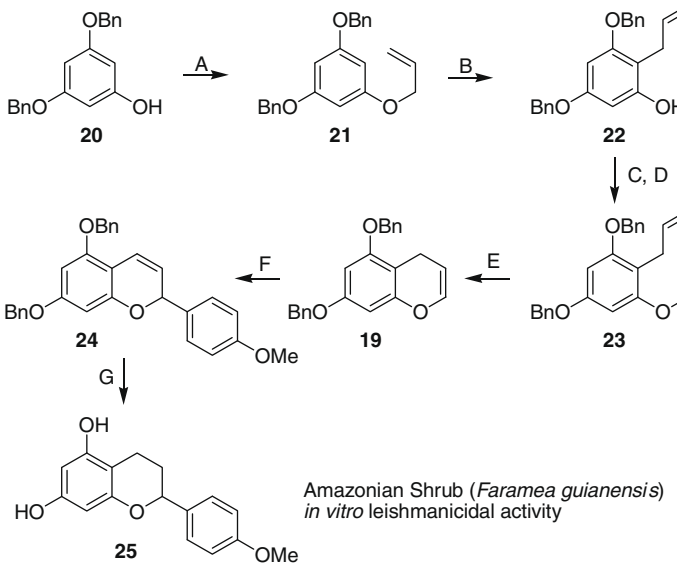
Surprisingly, when the best condition described in Table 4, entry 4, was applied to nitro-chromene **14**, the corresponding Heck adduct **18** was obtained in 13% yield. Much better results were obtain when the reaction was performed in a mixture of EtOH/MeCN (1:1) furnishing the desired Heck adduct **18** in 53% yield (entry 6).

We next turned our attention to the synthesis of the basic skeleton of epigallocatechin-3-gallato (Fig. 1), which has shown antibacterial, antiviral, antioxidant, and antitumoral activities.[12,15] The 4*H*-chromene **19** was synthesized in five steps from 3,5-bis(benzyloxy)phenol **20**, as summarized in Scheme 2. O-Allylation of **20** with allyl bromide in the presence of K_2CO_3 in acetone furnished the desired allylic ether **21** in 77% yield. Claisen rearrangement of **21** under thermal conditions afforded the allyl phenol **22**



15 **16** **14**

Scheme 1. Reagents and conditions: (A) $Cu(OAc)_2$, $Sn(CH{=}CH_2)_4$, O_2, MeCN, 25 °C, 24 h, 81% (30% recovery of **15**); (B) 4 mol % of Grubb's second generation Ru-catalyst, toluene (0.020 M), 60 °C, 1 h, 91%.



Scheme 2. Reagents and conditions: (A) Allyl bromide, K_2CO_3, acetone, 60 °C, 15 h, 77%; (B) 230 °C, 1 h, 80%; (C) 1,2-dibromoethane, K_2CO_3, acetone, 60 °C, 38 h; D) 50% aqueous NaOH, *n*-Bu_4NHSO_4, benzene, 1 h, 80%; (E) 4 mol % Grubbs-2 Ru-catalyst, toluene (0.020 M), 60 °C, 10 min; (F) 1 equiv of **2**, 10 mol % $Pd(OAc)_2$, 4 equiv 2,6-di-*t*-butyl-4-methylpyridine, EtOH, 55 °C, 20 min, 50% (over two steps) (G) H_2, 6 equiv $Pd(OH)_2$, THF/MeOH, 25 °C, 5 h, 65%.

in 80% yield. Next, the vinyl ether function was introduced using 1,2-dibromoethane, followed by base elimination under phase transference catalysis to give diene **23** in 80% yield (two steps). Ring-closing metathesis of diene **23** using 4 mol % of the Grubbs-2 catalyst furnished the desired 4*H*-chromene **19** in 90% yield after flash chromatography. The 4*H*-chromene **19** proved to be a rather unstable compound, and was used just after its purification by column chromatography. With the 4*H*-chromene **19** in hand, we carried out the Heck arylation using arenediazonium salt **2a** by applying conditions as shown in Table 3, entry 4. After some experimentation, the desired Heck adduct **24** was obtained in two steps (RCM and Heck arylation) in 50% yield.

Due to the structural similarities between Heck adduct **24** and natural product **25**, a flavan isolated by Sauvain et al. from the Amazonian shrub (*Faramea guianensis*),[16] we submitted **24** to a catalytic hydrogenation-hydrogenolysis reaction to get the natural product **25** in 65% yield (Scheme 2). This compound displays significant in vitro leishmanicidal activity.

In summary, the Heck arylation of cyclic and acyclic enol ethers using arenediazonium tetrafluoroborates proved to be a viable alternative for the construction of acetophenones, aryl dihydrofuran, aryl dihydropyrans, and aryl benzopyrans (chromenes) with high regiocontrol in moderate to excellent yields. The synthesis of 2*H*-chromene **24** opened up the way for the total synthesis of the natural flavan **25** possessing leishmanicidal activity. Studies are under way to apply the Heck–Matsuda arylation to the synthesis of other flavonoids and cathecins.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.01.017.

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