An Efficient Approach to Dihydrofuroflavonoids *via* Palladium-Catalyzed Annulation of 1,3-Dienes by *o*-Iodoacetoxyflavonoids

Roman V. Rozhkov, Richard C. Larock*

Department of Chemistry, Iowa State University, Ames, Iowa 50011, USA
Fax: (+1)-515-294-0105, e-mail: larock@iastate.edu

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Abstract: The palladium-catalyzed annulation of 1,3-dienes by *o*-iodoacetoxyflavonoids provides an efficient approach to biologically interesting dihydrofuroflavonoids. This reaction is very general, stereo- and regioselective, and a wide variety of terminal, cyclic and internal 1,3-dienes can be utilized.

Keywords: annulation; catalysis; dihydrofuroflavanone; dihydrofuroflavone; dihydrofuroisoflavone; homogeneous; palladium

Introduction

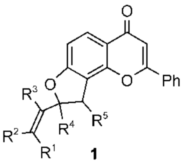
Naturally occurring in plants and fruits, dihydrofuroflavonoids display a broad array of biological properties.[1] For example, dihydrofuroflavones (**1**) have high cytotoxicity against P-388 cells.[2] Dihydrofuroflavanones (**2**) are effective inhibitors of protein kinase,[3] aromatase,[4] and larvae growth,[5] and dihydrofuroisoflavones (**3**) exhibit high antifungal activity.[6]

Recently, we reported an efficient method for the synthesis of dihydrofurocoumarins[7] and dihydrofuroflavonoids.[8] As of today, despite significant interest in dihydrofuroflavonoids, no efficient, general alternative method for the synthesis of dihydrofuroflavonoids has really been developed. Herein, we report our results on the palladium-catalyzed annulation of 1,3-dienes by *o*-iodoacetoxyflavonoids that provides a very general and effective route to a wide variety of dihydrofuroflavonoids.

Results and Discussion

Using our previously developed reaction conditions,[7,8] the scope and limitations of this annulation (Scheme 1) have been studied using various *o*-iodoacetoxyflavonoids and 1,3-dienes, and representative examples are shown in Table 1.

Analogous to the annulation of *o*-iodoacetoxycoumarins,[7] the annulation of various 1,3-dienes by the flavone **4** has given the expected products **5**–**12** in 62 to 96% yields with excellent regioselectivity (entries 1–8). This reaction is pretty general for a wide variety of 1,3-dienes. Highly substituted mono- and disubstituted terminal dienes give excellent yields and even internal double bonds, such as those in 1,3-cyclohexadiene, work well. Running the preparation of **12** on a 2.0-mmol scale resulted in an even higher 90% yield (entry 8), indicating the utility of this procedure for practical applications. The annulation of isoprene gave a 3:2 mixture of regioisomers **13a** and **13b** in an 86% yield (entry 9). The analogous annulation of isoprene by *o*-iodophenol has been shown to be mostly governed by steric factors, favoring addition to the less hindered double bond and thus affording a 7:1 ratio of the corresponding annulation products.[9] The poor regioselectivity in entry 9 presumably results from the higher reactivity of the cationic arylpalladium intermediate (see the later mechanistic discussion) towards the more electron-



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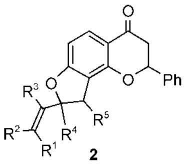

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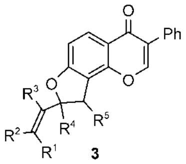

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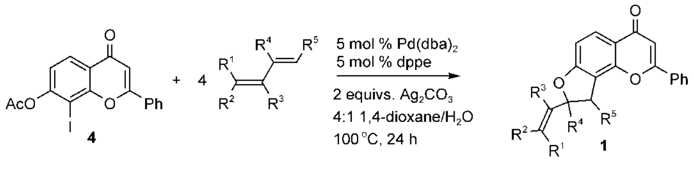

Scheme 1.

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Table 1. Synthesis of dihydrofuroflavonoids by palladium-catalyzed annulation.[a]

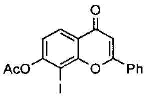
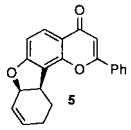
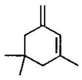
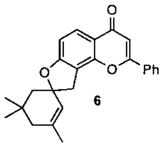
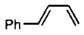
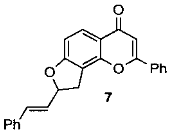
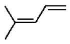
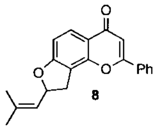
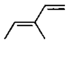
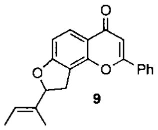
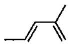
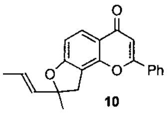
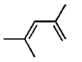
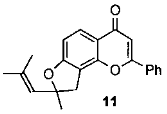
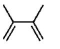
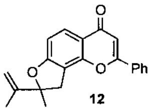
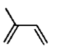
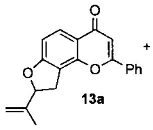
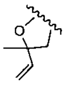
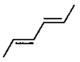
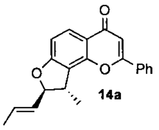
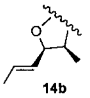
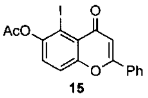
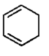
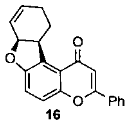
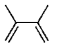
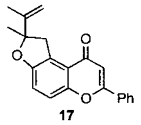
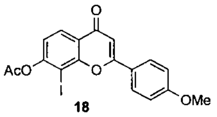
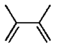
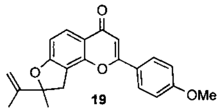
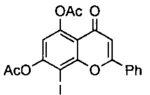
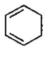
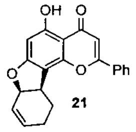
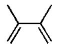
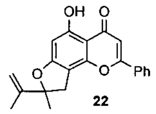
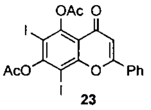
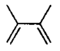
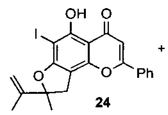
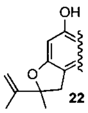
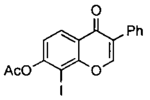
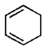
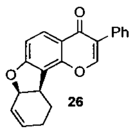
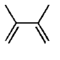
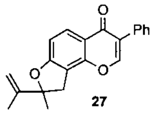
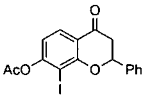
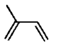
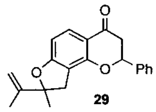
Entry	Flavonoid	1,3-Diene	Product(s)	Yield [%][b] (ratio of isomers)
1	 **4**		 **5**	62
2	”		 **6**	75
3	”		 **7**	80
4	”		 **8**	82
5	”		 **9**	76
6	”		 **10**	96
7	”		 **11**	85
8	”		 **12**	77, 90[c]
9	”		 **13a** +  **13b**	86 (3:2)
10	”		 **14a** +  **14b**	68 (20:1)[d]
11	 **15**		 **16**	25

Table 1 (cont.)

Entry	Flavonoid	1,3-Diene	Product(s)	Yield [%][b] (ratio of isomers)
12	”		 **17**	16
13	 **18**		 **19**	90
14	 **20**		 **21**	60
15	”		 **22**	92
16	 **23**		 **24** +  **22**	72 (2:1)
17	 **25**		 **26**	70
18	”		 **27**	95
19	 **28**		 **29**	88, 96[c]

[a] The iodoacetoxyflavonoid (0.25 mmol), Pd(dba)$_2$ (5 mol %, 0.0125 mmol), dppe (5 mol %, 0.0125 mmol), Ag$_2$CO$_3$ (0.5 mmol), the 1,3-diene (1.0 mmol), and 5 mL of a 4:1 1,4-dioxane/water mixture were stirred at 100 °C for 24 h.

[b] All yields are isolated and based on a single run.

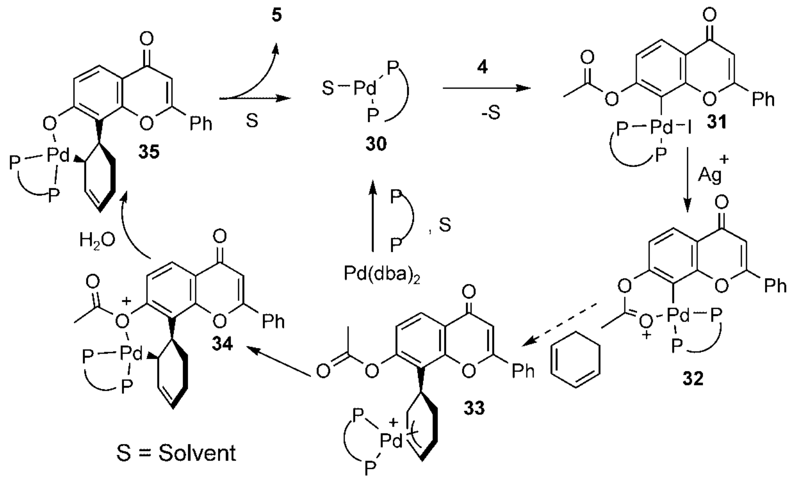
[c] This experiment was performed on a 2.0-mmol scale.

[d] The diene used was 95% *trans, trans*.

rich disubstituted double bond, leading to a competition between steric and electronic factors, which produces a mixture of the two isomeric products. The use of *trans, trans*-2,4-hexadiene (95% purity) gave a 20:1 ratio of isomers **14a** and **14b** in a 68% yield (entry 10). The exclusive generation of *E*-stereochemistry in the newly formed carbon-carbon double bond in products **7**, **9**, **10** and **14** is consistent with the intermediacy of a *syn*-π-allylpalladium intermediate in these reactions.[10]

In order to broaden the scope of this reaction, similar reactions have been performed on flavonoids **15**, **18**, **20**, **23**, **25**, and **28**. Steric hindrance in the vicinity of the iodo group in the flavone **15** gave much lower yields of the desired annulation products **16** and **17**, presumably due to slower oxidative addition to the Pd(0) catalyst or insertion of the diene (entries 11 and 12).

Since annulations of 1,3-dienes with electron-rich *o*-iodophenols have given lower yields of the desired an-



Scheme 2.

nulation products in previous studies in our group,[9] annulations employing the electron-rich flavones **18**, **20** and **23** presented a significant challenge to our methodology. Contrary to our earlier results,[9] using our current reaction conditions, the annulation of 2,3-dimethyl-1,3-butadiene by flavone **18** gave a 90% yield of the expected annulation product **19** (entry 13). Despite a longer reaction time (96 h), the annulation of 1,3-cyclohexadiene and 2,3-dimethyl-1,3-butadiene by flavone **20**, followed by a basic work-up, afforded the annulated products **21** and **22** in 60% and 92% yields, respectively (entries 14 and 15). Our attempts to accomplish a bis-annulation using electron-rich flavone **23** failed, presumably due to significant steric hindrance at the C-6 position of the flavone moiety. Instead, this process gave a 2:1 mixture of monoannulated product **24** and deiodinated monoannulated product **22** in a 72% overall yield (entry 16).

The annulation of 1,3-cyclohexadiene and 2,3-dimethyl-1,3-butadiene by isoflavone **25** produced the desired annulation products **26** and **27** in 70 and 95% yields, respectively (entries 17 and 18). Finally, the annulation of 2,3-dimethyl-1,3-butadiene by flavanone **28** afforded the desired annulation product **29** in an 88% yield (entry 19). Running the latter reaction on a 2.0-mmol scale increased the isolated yield to 96%. Thus, the annulation works well on a variety of substituted flavonoids. Electron-rich systems are readily accommodated, but steric hindrance about the iodide can be a problem.

A proposed mechanism for this annulation process is shown in Scheme 2. Initial oxidative addition of the iodoflavone **4** to palladium intermediate **30** generated *in situ* forms arylpalladium intermediate **31**.[11] Abstraction of the iodide by Ag_2CO_3 leads to a cationic intermediate **32**,[12] presumably stabilized by coordination to the neighboring acetyl group. The higher reactivity of these cationic arylpalladium complexes towards alkenes, compared to the neutral arylpalladium complexes, is presumably responsible for the excellent yields in our annulations,[11b] although it also results in lower regioselectivity in the anulation of isoprene. Next, complex **32** adds to the 1,3-diene in a *cis*-fashion to give a σ-allylpalladium complex, which rapidly forms π-allylpalladium intermediate **33**.[9] Coordination of the acetoxy oxygen to the palladium atom, leading to the formation of intermediate **34**, restricts rotation of the C–C bonds in the allyl moiety, and is, presumably, responsible for the high stereoselectivity when *trans, trans*-2,4-hexadiene is utilized (Table 1, entry 10). Since no hydrolysis of the starting material **4** has been observed under our reaction conditions, the deacylation of intermediate **34** is presumably accelerated by coordination of the acetyl oxygen atom to the cationic palladium center. Finally, complex **35** undergoes reductive elimination to give the final product **5** and simultaneously regenerates the palladium catalyst **30**.

Conclusion

We have developed an efficient palladium-catalyzed approach to dihydrofuroflavonoids including dihydrofuroflavones, dihydrofuroflavanones and dihydroisoflavones. The process is quite general, regio- and stereoselective, and a variety of *o*-iodoacetoxyflavonoids, as well as symmetrical and unsymmetrical 1,3-dienes can be utilized.

Experimental Section

Palladium-Catalyzed Annulation of 1,3-Dienes by *o*-Iodoacetoxyflavonoids

The *o*-iodoacetoxyflavonoid (0.25 mmol), $Pd(dba)_2$ (5 mol %, 0.0125 mmol), dppe (5 mol %, 0.0125 mmol), Ag_2CO_3 (0.5 mmol) and 1,4-dioxane (4 mL) were stirred in a capped vial for 5 min, and then water (1 mL) and the 1,3-diene (1.0 mmol) were added. The resulting reaction mixture was stirred at 100 °C for 24 h, cooled to room temperature, filtered and the filtrate was concentrated to give a yellow residue. This residue was purified by column chromatography using silica gel as a solid phase and 4:1 hexanes/ethyl acetate as the eluent to afford, after solvent removal, the final product. Solid products were then recrystallized from 1:1 ethanol/water. Experimental procedures and spectral data for all newly synthesized flavonoids are available in the Supporting Information.

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