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Selective cross-metathesis of 2-allylphenols with styrenes

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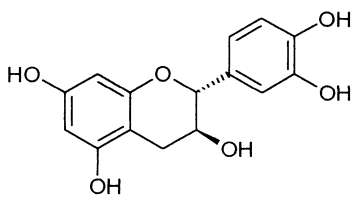
Abstract—A general and efficient preparation of 1,3-diarylpropenes, useful precursors for the synthesis of flavanols, is based on cross metathesis of protected 2-allylphenols with styrenes in presence of the Grubbs catalyst $Cl_2(PCy_3)_2Ru{=}CHPh$.

Flavan-3-ols are naturally occurring phenolic compounds which display various biological activities.[1] A representative example is (+)-catechin **1** (Fig. 1), found in higher woody plants, which is known to have potent antioxidant properties useful against aging diseases such as cancer, cardiovascular and neurodegenerative pathologies.[2] Moreover, flavan-3-ols are constituents of oligomeric proanthocyanidins[3] and condensed tannins[4] which are thought to have health-promoting effects.

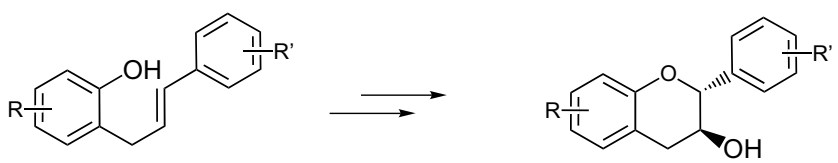
Their synthesis is usually carried out from 1,3-diarylpropenes by intramolecular ring opening of the corresponding epoxide or dihydroxylation followed by cyclization (Scheme 1).[5] In this respect, Ferreira et al.[6] have recently shown that asymmetric dihydroxylation and acid-catalyzed cyclization lead to flavanols in good yield and high enantiomeric excess. Thus, the preparation of appropriately substituted 1,3-diarylpropenes is an important preliminary step. Known methods are based on dehydration of 1,3-diarylpropanols derived from chalcones,[7] metal- or Lewis acid-catalyzed[8] or photochemically induced[9] allylation of aromatics, Pd(0)-catalyzed arylation of allylbenzenes with diazoniums salts,[10] Claisen rearrangement of allyl ethers[11] and olefination of arylacetaldehydes.[12]



(+)-catechin **1**

Figure 1.

We now propose cross metathesis of protected 2-allyl phenols with styrenes as a new, general and efficient route toward *E*-1,3-diarylpropenes (Scheme 2). Indeed, cross metathesis of two different alkenes can be accompanied by metathesis of individual substrates to afford a mixture of *E* and *Z* isomers of symmetrical and unsymmetrical coupling products.[13] One example of such a reaction between allylbenzene and different alkenes (including styrenes) has been recently reported to give all possible isomers.[14] On the other hand, cross metathesis of alkenes bearing allylic (or more distant) groups (ester, amide, silyl…) has been shown to give mainly unsymmetrical coupling products.[15]



Scheme 1.

Keywords: alkenes; metathesis; flavonoids.

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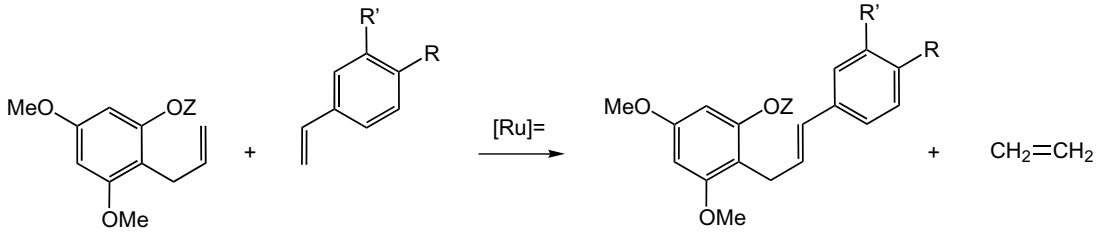

2a-c **3a-f** **4a-h**

Scheme 2.

Table 1. Cross metathesis of allyl derivatives **2** with styrenes **3**

Entry	Allyl compound	Styrene	Diarylpropene	Yield (%)
i	**2a** (Z = Ac)	**3a** (R = R′ = H)	**4a**	75
ii	**2b** (Z = MOM)	**3a**	**4b**	75
iii	**2c** (Z = TPS)	**3a**	**4c**	73
iv	**2a**	**3b** (R = OMe, R′ = H)	**4d**	66
v	**2a**	**3c** (R = Cl, R′ = H)	**4e**	60
vi	**2a**	**3d** (R = CF_3, R′ = H)	**4f**	77
vii	**2a**	**3e** (R = H, R′ = NO_2)	**4g**	79[a]
viii	**2a**	**3f** (R,R′ = benzo fused)	**4h**	72

[a] **2a** (10%) was also isolated.

The starting allyl derivatives **2a–c** were prepared from the known corresponding phenol, itself obtained by Claisen rearrangement of 1-allyloxy-3,5-dimethoxybenzene.[16] Commercially available styrenes **3a–e** and 2-vinylnaphtalene **3f** were chosen for this study. Initial experiments were carried out with **2a** and **3a** in presence of the Grubbs catalyst $Cl_2(PCy_3)_2Ru{=}CHPh$[17] in CH_2Cl_2. The optimum yield of **4a** (75%) was obtained in CH_2Cl_2 (see general procedure[18]) with 2 equiv. of styrene and 18% of this catalyst (under these conditions conversion of **2a** was complete). The use of 1 equiv. of styrene afforded **4a** in 55% yield, further reduced to 28% in presence of only 10% of the catalyst. Shortening the reaction time to 6 h resulted in a 51% yield while conducting the reaction at reflux of CH_2Cl_2 afforded a lower yield of **4a**. In all experiments, no significant amounts of symmetrical cross metathesis products were detected. Then the effect of the protecting group was studied: no significant difference was observed upon replacement of the acetate group by a MOM or TPS ether (Table 1, entries i–iii). Thus, acetate **2a** was used for the study of metathesis reactions with various styrenes. It was found that compounds **4d–h** were isolated in 60–79% in all cases (Table 1, entries iv–viii). Only the *E* configuration was detected in agreement with earlier observations for cross metathesis of styrene.[15]

In conclusion, cross metathesis of protected 2-allylphenols with styrenes is a general route toward 1,3-diarylpropenes useful for the synthesis of flavan-3-ols. Further experiments with more efficient catalysts[19] are needed to lower the amount of catalyst used in order to afford an attractive preparative process. This will be reported in due course.

Acknowledgements

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18. General procedure for cross metathesis reactions: To a 0.15 M solution of **2** in CH_2Cl_2 was added **2** equiv. of styrene **3** and $Cl_2(PCy_3)Ru{=}CHPh$ (0.03 equiv.) at rt under N_2. The solution was stirred for 48 h together with addition of five identical amounts of catalyst at regular periods of time. After concentration in vacuo, purification by flash chromatography on silica gel afforded **4**. All new compounds were characterized by ^1H and ^{13}C NMR, and HRMS.
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