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A short and efficient synthetic approach to hydroxy (*E*)-stilbenoids via solid-phase cross metathesis

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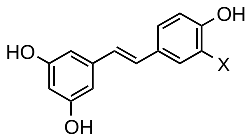
Abstract—Solid-phase cross metathesis of supported styrenyl ether with styrene derivatives afforded stilbenoids in high yields with complete (*E*)-selectivity, and this approach could be readily applied for a facile synthesis of a biologically important natural product, resveratrol. © 2002 Elsevier Science Ltd. All rights reserved.

Stilbenoids have been found in a number of plant species and they are of interest in many cases from a pharmacological point of view.[1] In particular, some hydroxy substituted (*E*)-moieties such as resveratrol or piceatannol display certain biological activities including anti-inflammatory, platelet antiaggregation, heart protection, herpes simplex virus inhibition, and anticarcinogenic effects.[2]



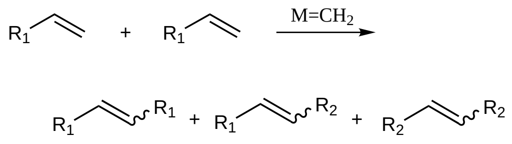
Resveratrol (X = H)
Piceatannol (X = OH)

Although the stilbenoids have been accessed through some conventional synthetic methods such as Wittig reactions[3] and Pd-catalyzed Heck or Negishi cross-couplings,[4] the syntheses in many cases suffer from low selectivities for the forming double bonds. Therefore, a more general, convenient, and selective preparative method would be highly desirable for the synthesis of stilbeneoid derivatives with desired stereochemistry. During the course of our studies on the synthetic application of olefin metathesis,[5] we have established a facile and highly stereoselective synthetic route to hydroxy substituted (*E*)-stilbenoids on the basis of a solid-phase cross metathesis, which is described herein.

Although ring-closing olefin metathesis has attracted widespread attention as a versatile tool for C–C bond formation,[6] cross metathesis has been much less utilized compared to RCM largely due to inherent difficulties of controlling selectivities. Minimization of unproductive self-coupled alkenes and subsequent maximization of a crossed-product is a crucial issue to be optimized in this chemistry as well as stereocontrol of the newly generated double bonds (Scheme 1).

As can be seen in Table 1, when one styrene moiety was allowed to react under standard metathesis conditions with a recently developed Ru-carbene catalyst $(Im)Cl_2PCy_3RuCHPh$ (**1**),[7] corresponding symmetric stilbene derivatives were produced in excellent yields with almost complete control of the double bond (E/Z >99:1).

Electronic variation within the olefinic substrates has little influence on the stereoselectivity as can be seen in entries 1–5. When two different styrenes were allowed to couple by the Ru catalyst **1**, however, no preferential formation of any one type of stilbene was obviously observed, and instead all three kinds of stilbenes were



Scheme 1.

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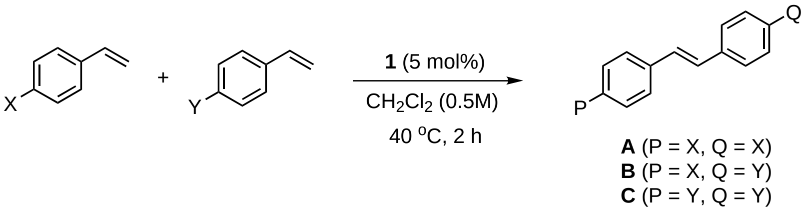
Table 1. Solution-phase cross metathesis of various styrene derivatives



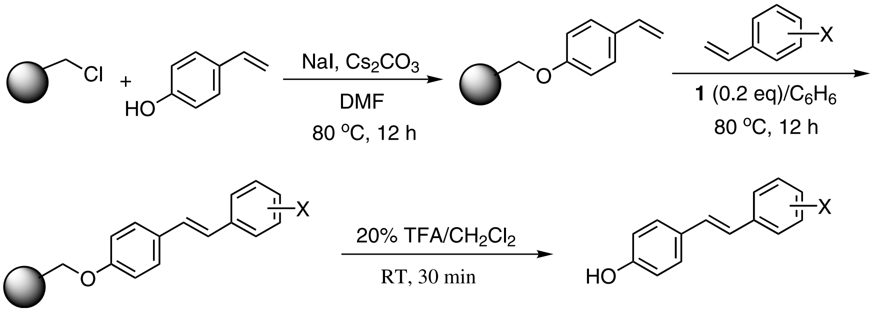
Entry	X	Y	% Yield (**A**:**B**:**C**)[a]
1	H	H	98
2	Cl	Cl	95
3	CF_3	CF_3	91
4	OAc	OAc	98
5	OMe	OMe	94
6	H	Cl	88 (1:1.1:1.2)
7	H	OMe	95 (1:1.5:0.82)
8	OMe	OAc	77 (1:1.4:1.5)
9	Cl	OAc	91 (1:0.9:1.3)

[a] Refer to isolated yields in entries 1–5, and total yields and ratio of **A**:**B**:**C** were determined by ^{1}H NMR based on an internal standard (anisole) in entries 6–9.

generated with a rather statistical ratio as an inseparable mixture (entries 6–9).[8] Poor selectivity for the product distribution was not improved by any changes of electronic properties on substrates in cross metathesis between two different styrenyl compounds demonstrating that this approach is not suitable for obtaining unsymmetrical stilbenes with practical purposes.[9]

Results of the above solution-phase cross metathesis reactions led us to search an alternative approach; a solid-phase counterpart. Apparent advantages of the solid-phase metathesis approach can be expected being inhibition of self coupling of supported substrate as well as ease of product separation from reaction mixtures despite the fact that reaction rate becomes generally lower when compared to that of homogeneous metathesis.[10] Among several solid supports we examined, Merrifield resin turned out to be the most suitable support for anchoring vinylphenol moiety to provide highest yields.[11] As shown in Table 2, 4-vinylphenol was attached to Merrifield resin (0.9 mmol/g) in DMF under standard conditions[12] affording supported

Table 2. Solid-phase approach for cross metathesis of styrenes[a]



Entry	X	Isolated yield (%)[b]
1	H	71
2[c]	H	63
2	4-Cl	81
3	4-CF_3	68
4	4-OAc	72
5	4-Me	61
6	4-OMe	68
7	3,4-$(OCH_2OCH_3)_2$	54
8	3,4-$(OAc)_2$	61

[a] In all metathesis reactions, 10 equiv. of styrenes to the bound styrenyl ether were used except entry 2.

[b] Refer to isolated yields (over three steps) of stilbenoids after cleavage of the resin.

[c] In this case, 4 equiv. of styrene was employed under otherwise identical conditions.

styrenyl ether in 0.75–0.85 mmol/g (83–94% yield based on the initial loading of the resin), which was determined after cleaving the resin. The bound aryl olefin (0.4 g, 0.75–0.85 mmol/g) was next allowed to couple by a Ru carbene (**1**, 20 mol%) with various styrene derivatives (10 equiv.) in benzene (4 mL) at 80°C for 10–12 h.[13] After the reaction, reaction mixture was filtered and washed with hot benzene and DMF several times. From the filtrate only homo-coupled stilbenes of the added styrenes were isolated with complete (*E*)-selectivity, and no unreacted styrenes were recovered. Upon cleavage of the filtered resin bound stilbenoids with 20% trifluoroacetic acid in dichloromethane, desired stilbene derivatives were isolated with high purity (>95%). Although some examples of 'intra-site' olefin metathesis on solid support have been recently reported in both cross and ring-closing reactions,[14] no detectable amounts of the homo-coupled products onto solid-phase were produced in our protocol.[15] Overall yields for the transformations were generally high (54–81% in three steps) and those were not decreased with electronic variations on the styrenyl substrates.[16] The amounts of introduced styrenes could be reduced to 3–4 equiv. with only slight decrease of isolated yield (compare entries 1 and 2). It should be noted that, like in the homogeneous metathesis reaction, stereoselectivity of the generated double bond in this solid-phase approach was excellent in all cases resulting in almost exclusive formation of (*E*)-stilbenoids (*E*/*Z* >99:1). Not only terminal styrenes but also internal styrenyl olefins turned out to be a suitable substrate class.[17]

For example, reaction of the bound styrenyl ether with *trans*-β-methylstyrene under the same conditions afforded (*E*)-4-hydroxylstilbene in 59% yield after cleavage. In addition to mono-substituted styrenes, disubstituted styrenes could also be employed as a coupling partner as exemplified in entries 7 and 8. Reaction of the supported styrenyl ether with 3,4-diacetoxystyrene afforded (*E*)-3,4-diacetoxy-4′-hydroxystilbene,[18] a protected form of resveratrol, in 61% overall yield after cleaving the resin demonstrating that the present method is highly efficient and selective for the synthesis of any stilbenoid derivatives (entry 8).

In conclusion, it has been shown that solid-phase cross metathesis of styrenyl ether with substituted styrenes by a ruthenium carbene catalyst is a short and efficient approach for the preparation of hydroxy stilbenoids with complete stereocontrol for generating (*E*)-double bond. Utility of the present method was amply demonstrated in the synthesis of a biologically active stilbenoid, resveratrol.

Acknowledgements

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8. For selected examples of cross metathesis of styrenes, see: (a) Crowe, W. E.; Zhang, Z. J. *J. Am. Chem. Soc.* **1993**, *115*, 10998; (b) Pietraszuk, C.; Marciniec, B.; Fischer, H. *Organometallics* **2000**, *19*, 913; (c) Choi, T.-L.; Chatterjee, A. K.; Grubbs, R. H. *Angew. Chem.*, *Int. Ed.* **2001**, *40*, 1277.
9. It has been recently reported that cross metathesis of protected 2-allylphenols with styrenes afforded 1,3-diarylpropenes with moderate to good yields. See: Forget-Champagne, D.; Mondon, M.; Fonteneau, N.; Gesson, J.-P. *Tetrahedron Lett.* **2002**, *42*, 7229.
10. For some selected examples of metathesis reactions on solid-phase, see: (a) Miller, S. J.; Blackwell, H. E.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 9606; (b) Schuster, M.; Lucas, N.; Blechert, S. *Chem. Commun.* **1997**, 823; (c) Schafmeister, C. E.; Po, J.; Verdine, G. L. *J. Am. Chem. Soc.* **2000**, *122*, 5891.
11. Ring-opening cross metathesis of bicyclic alkenes with styrenes on Wang resin has been reported. See: Cuny, G. D.; Cao, J.; Hauske, J. R. *Tetrahedron Lett.* **1997**, *38*, 5237.
12. For some selected recent reviews on solid phase synthesis, see: (a) Wendeborn, S.; De Mesmaeker, A.; Brill, W. K.-D.; Berteina, S. *Acc. Chem. Res.* **2000**, *33*, 215; (b) Guillier, F.; Orain, D.; Bradley, M. *Chem. Rev.* **2000**, *100*, 2091; (c) Clapham, B.; Reger, T. S.; Janda, K. D. *Tetrahedron* **2001**, *57*, 4637.
13. Higher yields were obtained in this reaction when the solid supported substrate was swelled at least 2 h before addition of the carbene catalyst.
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15. It is assumed that rather long and flexible olefinic moieties on resin allow site–site interactions leading to the intramolecular metathesis as in Ref. 14. However, extents of those interactions may be much less in the bound styrenyl double bonds probably due to steric reasons.
16. All new compounds were fully characterized by spectroscopic means of ^{1}H, ^{13}C NMR, IR and HRMS.
17. Aliphatic olefins (e.g. 1-hexene) were also reacted with the resin bound styrenyl ether with similar efficiency under otherwise identical conditions.
18. For some recent examples for synthesis of resveratrol and its derivatives, see: (a) Orsini, F.; Pelizzoni, F.; Bellini, B.; Miglierini, G. *Carbohydr. Res.* **1997**, *301*, 95; (b) Alonso, E.; Ramón, D. J.; Yus, M. *J. Org. Chem.* **1997**, *62*, 417; (c) Guiso, M.; Marra, C.; Farina, A. *Tetrahedron Lett.* **2002**, *43*, 597.