Stereoselective Synthesis of (*E*)-Hydroxystilbenoids by Ruthenium-Catalyzed Cross-Metathesis

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An efficient and highly stereoselective synthetic procedure is reported for the construction of symmetrical and unsymmetrical (*E*)-polymethoxystilbene and (*E*)-polyhydroxystilbene derivatives. The strategy rests on a cross-metathesis reaction catalyzed by stable, well-defined (alkylidene)ruthenium complexes, in particular the second-generation Grubbs catalyst [$RuCl_2$(=CHPh)(SIMes)(PCy_3)] [SIMes = 1,3-bis(2,4,6-trimethylphenyl)imidazolidin-2-ylidene]. The metathesis of unprotected phenolic styrenes is illustrated by the synthesis of the important phytoalexins (*E*)-3,4′,5-trihydroxystilbene (resveratrol) and (*E*)-3,3′,4,5′-tetrahydroxystilbene (piceatannol).
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Introduction

Naturally occurring stilbenoid compounds usually display significant biological activities. Among them, resveratrol (3,4′,5-trihydroxystilbene) and its derivatives have recently attracted a great deal of attention because of their physiological properties and potential therapeutic values.[1] Resveratrol is part of a class of molecules called phytoalexins, which are defense compounds produced by higher plants in response to pathogens and stresses (Figure 1). Phytoalexins are present, inter alia, in grape skins and in peanuts, but only in minute amounts that vary widely with the growth conditions. For these reasons, they cannot be obtained in large quantities by extractive procedures. Hence, the search for reliable and efficient chemical syntheses of resveratrol and related stilbene derivatives has sparked an ongoing research effort in the organic chemistry community.

From a historical point of view, Wittig or Horner–Wadsworth–Emmons reactions were the initial methods of choice for assembling a stilbenoid unit from two appropriately functionalized aromatic building blocks.[2] However, these reactions are not catalytic and usually afford poor control over the configuration of the newly formed C=C double bonds, thereby yielding mixtures of (*E*)- and (*Z*)-alkenes. Owing to the development of transition-metal-assisted organic synthesis, several catalytic approaches have been proposed to achieve better selectivities in the preparation of stilbene derivatives.[3] Most strategies developed so far involve palladium-mediated coupling reactions. Among them, methods based on the Heck[4,5] and Suzuki[6] reactions stand out for their synthetic versatility and efficiency. Other transition-metal-promoted stilbene syntheses rely on the McMurry coupling of aldehydes and ketones upon treatment with low-valent titanium species[7,8] or on olefin metathesis.[9,10] Thanks to the development of well-defined (alkylidene)metal complexes based on ruthenium (see structures **1**–**4** in Figure 2), this latter reaction has emerged as a powerful tool for exchanging substituents across carbon–carbon double bonds in the presence of many other functional groups.[11]

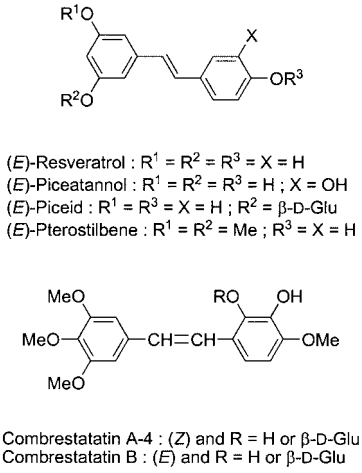

Figure 1. Structures of selected phytoalexins.

Alkene cross-metathesis (CM) can, indeed, provide a convenient access to stilbenoid compounds (Scheme 1). The reaction has attracted much attention recently,[12] although it has not yet attained the same level of synthetic usefulness as ring-closing metathesis (RCM) or ring-opening metathe-

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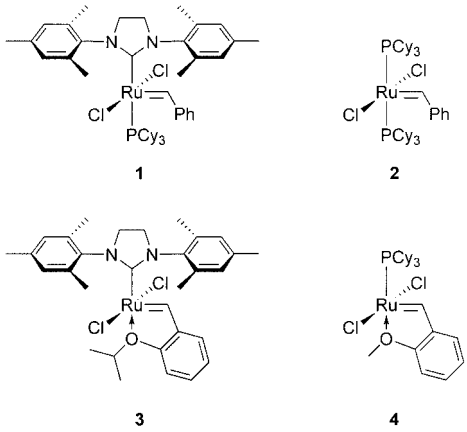
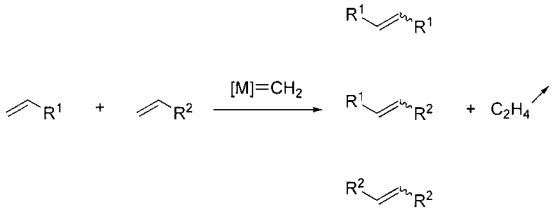


Figure 2. Structures of the ruthenium catalysts used in this study.

sis polymerization (ROMP). This is largely due to inherent difficulties in controlling selectivities toward cross-coupling instead of homodimerization in a process that is not favored either by a strong enthalpic driving force (like ROMP) or by entropic factors (like RCM).[13] Thus, to the best of our knowledge, reports of stilbene formation by cross-metathesis are still scarce in the literature.[9,10]



Scheme 1. Olefin cross-metathesis reaction.

The coupling of terminal alkenes into symmetrical internal olefins has been investigated by Schrock and coworkers using a range of (alkylidene)(imido)molybdenum(VI) complexes as catalysts.[9] Only (*E*)-stilbene was obtained when styrene was used as substrate, but the yields remained low except when [Mo(CHCMe$_2$Ph)(N-2,6-Me$_2$C$_6$H$_3$){OCMe$_2$(CF$_3$)}$_2$] was employed as catalyst under carefully adjusted conditions.

In 2002, Chang et al. reported that the cross-metathesis of a polymer-grafted styrenyl ether with substituted styrenes affords stilbenoid derivatives in good yields and with complete (*E*)-selectivity using complex **1** as catalyst.[10] The advantages of this solid-phase metathesis approach lie in the expected inhibition of the supported substrate self-coupling, as well as the ease of product separation from the reaction mixture. However, the reaction rates are significantly lower than under homogeneous conditions, despite the fact that 20 mol-% of the expensive catalyst **1** was used.

We have recently launched a study of the formation of stilbenoid derivatives by ruthenium-catalyzed cross-metathesis of styrene derivatives. Herein, we disclose our results demonstrating the ability of ruthenium complexes **1**–**3** to act as catalysts for the preparation of polyhydroxy- and polymethoxystilbenes by CM. The underlying objective that guided us in this research was to achieve the mixed coupling of unprotected phenolic styrenes into the important phytoalexin resveratrol.

Results and Discussion

To begin our investigations, we first examined the homocoupling of styrene and 4-methoxystyrene catalyzed by complexes **1**[14] and **2**.[15] With the second-generation Grubbs catalyst **1** (5 mol-%), the reactions in toluene at 110 °C were quantitative after 15 min and afforded 99.8% of (*E*)-stilbene and 98.9% of (*E*)-4,4′-dimethoxystilbene, respectively. The kinetics were slower with the first-generation Grubbs catalyst **2**, leading to partial conversions, i.e., about 85% for both substrates, after 72 h under the same experimental conditions. These results are in line with the olefin categorization recently proposed by Grubbs et al. for predicting reactivity in CM.[13] Indeed, styrenes bearing no large *ortho* substituents are classified as olefins of type I (rapid homodimerization, secondary metathesis on homodimers) with catalyst **1**, and as olefins of type II (slow homodimerization, homodimers sparingly consumable) with complex **2**.

It is noteworthy that catalyst **1** does not promote the metathesis of 2-methoxystyrene under the same experimental conditions. This may be due to the formation of a less active carbene species possessing a chelated methoxy ligand. To probe the validity of this hypothesis, we prepared the chelated methoxy complex [(PCy$_3$)Cl$_2$Ru{=CH(C$_6$H$_4$-*o*-OMe)}] (**4**), which has previously been described by Hoveyda and co-workers,[16] and assessed its catalytic efficiency toward styrene CM. It was found to be a very poor catalyst, since only 10% of styrene was consumed after 24 h in refluxing toluene.

Next, the cross-metathesis of 4-methoxystyrene and 3,5-dimethoxystyrene was investigated using a 1:1 mixture of the two olefins in the presence of catalyst **1** (Scheme 2). As expected, the time required to reach completion was shorter when the reaction was carried out in refluxing toluene than in refluxing dichloromethane. In both solvents, however, the reaction mixtures had the same final composition. With a 5 mol-% catalyst loading, complete conversion occurred within 1 h in refluxing toluene and the three coupling products were obtained in a close to statistical distribution, i.e., about 50% of the cross-product (*E*)-3,4′,5-trimethoxystilbene (**6**) and 25% each of homoproducts **5** and **7** (Table 1). In refluxing dichloromethane under the same conditions, 24 h were needed to fully consume the starting materials. When the proportion of complex **1** was reduced to 1 mol-%, conversion levelled off at 85% after 2 h in refluxing toluene and did not further increase when the reaction time was extended to 24 h. Rather similar kinetics and proportions of products **5**–**7** were obtained when the Hoveyda–Grubbs catalyst **3**[17] (5 mol-%) was substituted for its parent **1** (Table 1). Complex **2**, on the other hand, did not lead to any reaction in dichloromethane, even at reflux. In toluene, it eventually promoted CM between 4-methoxystyrene and 3,5-dimethoxystyrene, but full conversion of the substrates

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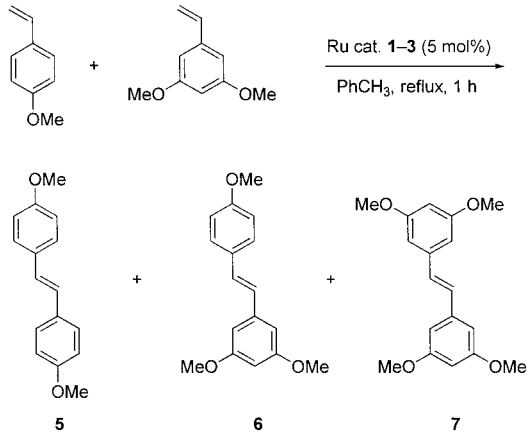
could not be achieved, even when the reaction time and the proportion of catalyst were increased. Therefore, we decided to carry out all further experiments with 3–5 mol-% of complex **1** in refluxing toluene (or THF, vide infra).



Scheme 2. Cross-metathesis of 4-methoxystyrene and 3,5-dimethoxystyrene catalyzed by ruthenium complexes **1**–**3**.

Table 1. Cross-metathesis of 4-methoxystyrene and 3,5-dimethoxystyrene catalyzed by ruthenium complexes **1**–**3** (5 mol-%) in refluxing toluene for 1 h.

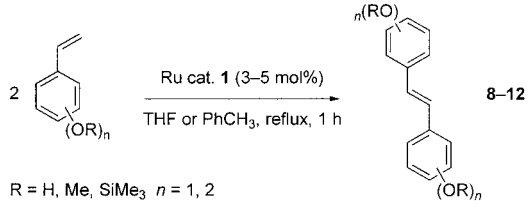
Catalyst	Isolated yield [%]	Product distribution **5/6/7** [%]
1	83	19:63:18
2	78[a]	22:62:16
3	81	20:52:28

[a] GC yield after 2 h of reaction.

Although ruthenium complexes **1**–**3** afford only (*E*)-double bonds, they obviously lack selectivity by giving a close to statistical mixture of three different coupling products. This is probably due to their ability to perform secondary metathesis on the newly formed C=C double bond of the stilbenoid compounds.[13] In order to confirm this hypothesis, pure trimethoxylated compound **6** was mixed with 5 mol-% of complex **1**. After about 1 h in refluxing toluene, the reaction mixture contained the three substituted (*E*)-stilbenes **5**–**7** in an 18:55:27 ratio. Additional unidentified products were also detected by gas chromatography and accounted for 9% of the mass balance.

A way to improve the selectivity for the unsymmetrical cross-product is to introduce one substrate in excess. Thus, when the coupling of 3,5-dimethoxystyrene with 10 equiv. of commercially available 4-methoxystyrene was performed in toluene at 110 °C using 5 mol-% of complex **1**, cross-product **6** was isolated in 94% yield. The workup was particularly easy to carry out, since the (*E*)-4,4′-dimethoxystilbene (**5**) present as a side-product precipitated from the reaction mixture upon cooling to room temperature. Protected resveratrol **6** could therefore be obtained by a simple filtration followed by flash-chromatographic purification. Demethylation of (*E*)-3,4′,5-trimethoxystilbene by treatment with boron tribromide[18] or with the recently described boron trichloride/tetra-*n*-butylammonium iodide reagent[19] cleanly afforded pure resveratrol in 80% overall yield.

A more direct access to resveratrol, and to polyhydroxystilbene derivatives in general, would be available if cross-metathesis could be accomplished without protection/deprotection of the styrenyl substrate hydroxy groups. This would constitute a significant advance since, to the best of our knowledge, all the synthetic routes devised so far involve a preliminary etherification and a subsequent cleavage step.[3] A quick survey of the literature revealed that the second-generation Grubbs catalyst might be suitable for the task. Indeed, compared to its predecessor **2**, complex **1** tolerates a wider range of functional groups, including amines, sulfides, and phenols.[20] It has been successfully used for the preparation of oxazolylphenol ligands by CM,[20] for the cross-coupling of eugenol with (*Z*)-1,4-butenediol,[21] and for the total synthesis of resorcylic macrocycles by RCM.[22] We therefore investigated the reactions of several (poly)hydroxystyrenes in the presence of this (carbene)ruthenium complex. The homocouplings of 4-hydroxystyrene, 3,5-dihydroxystyrene, and 3,4-dihydroxystyrene were first examined using 3–5 mol-% of catalyst **1** (Scheme 3). To our great satisfaction, the reactions proceeded very cleanly, and quantitative conversions were achieved within 1 h in refluxing THF. Recourse to this solvent as the reaction medium was dictated by the poor solubility of the polar phenolic substrates in toluene. After purification by flash chromatography, (*E*)-hydroxystilbenes **8**–**10** were isolated in high yields (Table 2).



Scheme 3. Homocoupling of various (poly)hydroxystyrene derivatives catalyzed by ruthenium complex **1**.

Additionally, the ruthenium-catalyzed homocouplings of 4-hydroxy-3-methoxystyrene and of 3,4-bis(trimethylsilyloxy)styrene were carried out in refluxing toluene with 5 mol-% of complex **1**. The consumption of both alkoxy and silyloxy derivatives was total after 30–60 min and led to (*E*)-4,4′-dihydroxy-3,3′-dimethoxystilbene (**11**) and to (*E*)-3,3′,4,4′-tetrakis(trimethylsilyloxy)stilbene (**12**), respectively, in close to quantitative yields (Table 2).

In another experiment designed to obtain stilbene derivatives bearing both hydroxy and methoxy functional groups, the ruthenium-catalyzed heterocoupling of 4-hydroxystyrene and 4-methoxystyrene was carried out in refluxing toluene. The two coupling partners were introduced in 1:1 stoichiometric proportions together with 5 mol-% of complex **1**. The consumption of both substituted styrenes was total after 30 min and led to a mixture of the three products **5**, **13**, and **8** in 13:65:22 molar proportions (Scheme 4). These products were easily separated by column chromatography. Thus, a recycling process involving ruthe-

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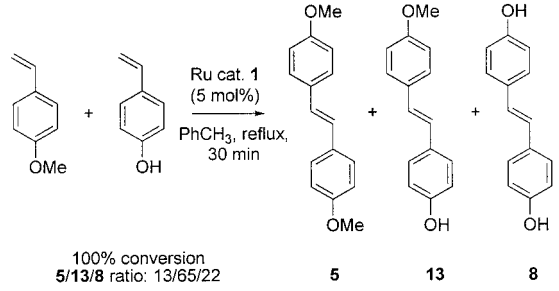
Table 2. Homocoupling of various (poly)hydroxystyrene derivatives catalyzed by ruthenium complex **1**.

Substrate	Product	Isolated yield [%]
4-Hydroxystyrene	(*E*)-4,4′-dihydroxystilbene (**8**)	70[a]
3,5-Dihydroxystyrene	(*E*)-3,3′,5,5′-tetrahydroxystilbene (**9**)	89[b]
3,4-Dihydroxystyrene	(*E*)-3,3′,4,4′-tetrahydroxystilbene (**10**)	92[b]
4-Hydroxy-3-methoxystyrene	(*E*)-4,4′-dihydroxy-3,3′-dimethoxystilbene (**11**)	89[c]
3,4-Bis(trimethylsilyloxy)styrene	(*E*)-3,3′,4,4′-tetrakis(trimethylsilyloxy)stilbene (**12**)	97[c]

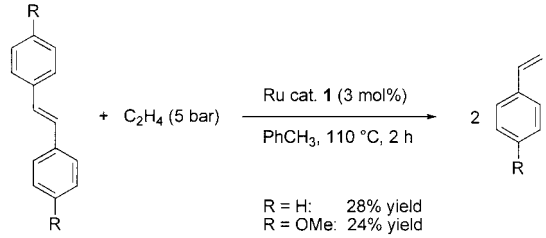
[a] 1 h reaction in refluxing THF using 5 mol-% of Ru catalyst **1**. [b] 1 h reaction in refluxing THF using 3 mol-% of Ru catalyst **1**. [c] 1 h reaction in refluxing toluene using 5 mol-% of Ru catalyst **1**.

nium-catalyzed cleavage of the homodimers **5** and **8** with ethylene or their direct re-equilibration into cross-product **13** is conceivable. We examined these two options using stilbene **5** as a model substrate, since it is the main by-product formed when an excess of 4-methoxystyrene was used in cross-coupling experiments (vide supra).



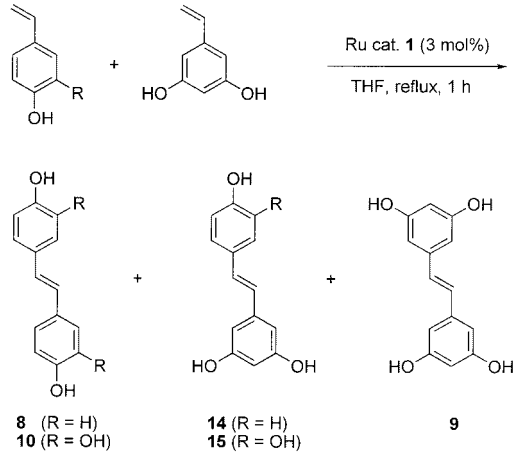
Scheme 4. Cross-metathesis of 4-hydroxystyrene and 4-methoxystyrene catalyzed by ruthenium complex **1**.

First, we carried out the ethenolysis of compound **5** in the presence of complex **1** (Scheme 5). Irrespective of the ethylene pressure applied (1–5 bar) and the solvent used (toluene or THF), large amounts of unconverted starting material were always recovered and the yield of 4-methoxystyrene did not exceed 24% after 2 h at 110 °C. A control experiment with unsubstituted (*E*)-stilbene gave similar results, indicating that the poor solubility of the dimethoxy derivative **5** in organic solvents is not solely responsible for the low reactivity observed. A more likely explanation is the rapid deactivation of the catalyst in the presence of ethylene. Indeed, mechanistic studies by Grubbs and co-workers have shown that (methylidene)ruthenium species are the least stable intermediates in most metathesis reactions initiated by **1** and **2**.[23] Other authors have also pointed out the difficulty in achieving satisfactory conversions in the ethenolysis of methyl oleate using Grubbs' catalysts.[24] In the light of these results, we decided to switch our attention to the recycling of homodimer **5** by CM. Thus, (*E*)-4,4′-dimethoxystilbene was treated with 1 equiv. of 3,5-dimethoxystyrene in refluxing toluene containing 5 mol-% of catalyst **1**. After 1 h, equilibrium was reached and we were pleased to note that protected resveratrol **6** was the major product in the reaction mixture (55%), together with 4-methoxystyrene (12%) and starting materials (26% and 7% of the stilbene and the styrene, respectively).



Scheme 5. Ethenolysis of (*E*)-stilbene and (*E*)-4,4′-dimethoxystilbene (**5**) catalyzed by ruthenium complex **1**.

Finally, since all the indicators were favorable, we examined the direct synthesis of two important phytoalexins starting from unprotected phenolic styrenes (Scheme 6). The cross-metathesis of 1 equiv. of *p*-hydroxystyrene and 1 equiv. of 3,5-dihydroxystyrene in THF led to the formation of resveratrol (**14**) in a close to statistical equilibrium with the two homocoupling products **8** and **9** (Table 3). Under the same conditions, (*E*)-3,3′,4,5′-tetrahydroxystilbene (**15**; piceatannol) was isolated in 45% yield after chromatographic separation from the symmetrical stilbenes **9** and **10**.



Scheme 6. Synthesis of resveratrol (**14**) and piceatannol (**15**) by cross-metathesis catalyzed by ruthenium complex **1**.

In order to obtain resveratrol with a high selectivity compared to the corresponding homoproducts, we performed a cross-metathesis of 3,5-dihydroxystyrene catalyzed by complex **1** using a tenfold excess of *p*-hydroxystyrene (Table 3). This reaction afforded a 94% overall yield of coupling products, out of which resveratrol (**14**) contributed to the remarkable extent of 95% and was therefore isolated in

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Table 3. Synthesis of resveratrol (**14**) and piceatannol (**15**) by cross-metathesis catalyzed by ruthenium complex **1**.

Styrenes	Equiv.	Cross-product	Isolated yield [%]	Product distribution [%]
4-Hydroxystyrene 3,5-Dihydroxystyrene	1 1	**14**	87	**8/14/9** 23:60:17
4-Hydroxystyrene 3,5-Dihydroxystyrene	10 1	**14**	94	**8/14/9** 0:95:5
3,4-Dihydroxystyrene 3,5-Dihydroxystyrene	1 1	**15**	86	**10/15/9** 26:52:22

89% yield after purification. (*E*)-3,3′,5,5′-Tetrahydroxystilbene (**9**) accounted for the remaining 5% of the product distribution, while the formation of (*E*)-4,4′-dihydroxystilbene (**8**) was totally suppressed.

Conclusion

In this study we have shown that the (N-heterocyclic carbene)ruthenium complex **1** efficiently catalyzes the cross-coupling of various substituted styrenes into polymethoxy- and polyhydroxystilbenes with an excellent (*E*)-selectivity for the newly formed C=C double bonds. Selectivity toward the mixed-coupling products can be enhanced by introducing one of the reaction partners in excess. Although the homodimer by-products display interesting biological activities on their own, we have examined the possibility of recycling them. We have also established that the presence of phenolic functions does not hinder the metathesis reaction, thereby allowing the direct synthesis of polyhydroxystilbenes with no preliminary protection step. These results are a good foundation for future developments, and we are currently searching for new catalysts that should be more selective toward the mixed cross-products.

Experimental Section

General Information: All reactions were performed under argon using standard Schlenk techniques. Solvents were freshly distilled from standard drying agents and kept under argon. NMR spectra were recorded with a Bruker AM250 or DSX400 spectrometer. ^{1}H NMR chemical shifts are listed in ppm downfield from TMS. Gas chromatography (GC) was carried out with a Varian 3900 system equipped with a Chrompack CP-Sil 5 CB capillary column (15 m length, 0.25 mm diameter, 0.25 μm film thickness). Microanalyses were performed by the "Centre de Microanalyse du CNRS" at Vernaison, France.

Starting Materials: The ruthenium complexes [$RuCl_2$(=CHPh)(SIMes)(PCy_3)] [second-generation Grubbs catalyst **1**; SIMes = 1,3-bis(2,4,6-trimethylphenyl)imidazolidin-2-ylidene], [$RuCl_2$(=CHPh)-(PCy_3)$_2$] (Grubbs catalyst, **2**), and [$RuCl_2${=C(H)C_6H_4(O*i*Pr)}-(SIMes)] (Hoveyda–Grubbs catalyst, **3**) were purchased from Strem. 4-Hydroxystyrene was obtained by demethylation of 4-methoxystyrene with ethanethiol/sodium hydride in DMF.[25] Other substituted styrene derivatives were obtained by Wittig reaction between the corresponding benzaldehyde and methyltriphenylphosphonium bromide.[26]

Typical Procedure for Homocoupling: A solution of styrene (1 mmol) in dry toluene or THF (2 mL) was added to a solution of ruthenium catalyst **1** (0.03 mmol) in dry toluene or THF (1 mL) under an inert gas. The mixture was refluxed under Ar for 1 h. It was then cooled to room temperature and filtered through Celite®. The filtrate was concentrated under vacuum and purified by flash column chromatography on silica gel using acetone as eluent. The structure of the resulting pure stilbene product was confirmed by ^{1}H NMR spectroscopy.

Typical Procedure for Heterocoupling: A solution of styrene A (1 mmol) and styrene B (1 mmol) in dry toluene or THF (2 mL) was added to a solution of ruthenium catalyst **1** (0.03 mmol) in dry toluene or THF (1 mL) under an inert gas. The mixture was refluxed under Ar for 1 h. It was then cooled to room temperature and filtered through Celite®. The filtrate was concentrated under vacuum and fractioned by column chromatography on silica gel using a 98:2 (v/v) *n*-heptane/acetone mixture as eluent. The structures of the pure homocoupling and cross-coupling products were confirmed by ^{1}H NMR spectroscopy.

Typical Procedure for Ethenolysis: A glass pressure reactor was charged with a stilbene (1 mmol), ruthenium catalyst **1** (0.03 mmol), and dry toluene (2 mL) under an inert gas. It was then pressurized with ethylene (5 bar). The mixture was stirred in an oil bath at 110 °C for 2 h and then cooled to room temperature and filtered by suction. The filtrate was analyzed by GC using *n*-dodecane as an internal standard.

(*E*)-4,4′-Dimethoxystilbene (5):[27,28] White powder. ^{1}H NMR (250 MHz, [D$_6$]acetone, 25 °C): δ = 7.64 (d, $^3J_{H,H}$ = 8.8 Hz, 4 H, Ar), 7.19 (s, 2 H, =CH), 7.07 (d, $^3J_{H,H}$ = 8.8 Hz, 4 H, Ar), 3.95 (s, 6 H, OMe) ppm.

(*E*)-3,4′,5-Trimethoxystilbene (6):[5,7,29,30] White powder. ^{1}H NMR (250 MHz, [D$_6$]acetone, 25 °C): δ = 7.66 (d, $^3J_{H,H}$ = 8.7 Hz, 2 H, Ar), 7.34 [d, $^3J_{H,H}$ (*E*) = 16.4 Hz, 1 H, =CH], 7.16 [d, $^3J_{H,H}$ (*E*) = 16.3 Hz, 1 H, =CH], 7.07 (d, $^3J_{H,H}$ = 8.8 Hz, 2 H, Ar), 6.91 (d, $^4J_{H,H}$ = 2.2 Hz, 2 H, Ar), 6.57 (t, $^4J_{H,H}$ = 2.2 Hz, 1 H, Ar), 3.96 (s, 6 H, OMe), 3.93 (s, 3 H, OMe) ppm.

(*E*)-3,3′,5,5′-Tetramethoxystilbene (7):[7,27,31] White powder. ^{1}H NMR (250 MHz, [D$_6$]acetone, 25 °C): δ = 7.32 (s, 2 H, =CH), 6.91 (d, $^4J_{H,H}$ = 2.2 Hz, 4 H, Ar), 6.56 (t, $^4J_{H,H}$ = 2.1 Hz, 2 H, Ar), 3.95 (s, 12 H, OMe) ppm.

(*E*)-4,4′-Dihydroxystilbene (8):[7] White powder. ^{1}H NMR (250 MHz, [D$_6$]acetone, 25 °C): δ = 8.74 (s, 2 H, OH), 7.53 (d, $^3J_{H,H}$ = 8.6 Hz, 4 H, Ar), 7.10 (s, 2 H, =CH), 6.97 (d, $^3J_{H,H}$ = 8.6 Hz, 4 H, Ar) ppm.

(*E*)-3,3′,5,5′-Tetrahydroxystilbene (9):[7,31,32] Pale-pink powder. ^{1}H NMR (400 MHz, [D$_6$]acetone, 25 °C): δ = 8.27 (br. s, OH), 6.92 (s, 2 H, =CH), 6.54 (d, $^4J_{H,H}$ = 2.1 Hz, 4 H, Ar), 6.28 (t, $^4J_{HH}$ = 2.1 Hz, 2 H, Ar) ppm.

(*E*)-3,3′,4,4′-Tetrahydroxystilbene (10):[32] White powder. ^{1}H NMR (400 MHz, [D$_6$]acetone, 25 °C): δ = 8.35 (br. s, OH), 7.04 (d, $^4J_{H,H}$

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= 2.0 Hz, 2 H, Ar), 6.91 (s, 2 H, =CH), 6.85 (dd, $^3J_{H,H}$ = 8.0, $^4J_{H,H}$ = 2.1 Hz, 2 H, Ar), 6.79 (d, $^3J_{H,H}$ = 8.1 Hz, 2 H, Ar) ppm.

(*E*)-4,4′-Dihydroxy-3,3′-dimethoxystilbene (11):[33] Colorless crystals from CH_2Cl_2/MeOH. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.02 (d, $^4J_{H,H}$ = 2 Hz, 2 H, Ar), 7.00 (dd, $^3J_{H,H}$ = 8.2 Hz, 2 H, Ar), 6.90 (d, $^3J_{H,H}$ = 8 Hz, 2 H, Ar), 6.89 (s, 2 H, =CH), 5.61 (s, 2 H, OH), 3.95 (s, 6 H, OMe) ppm.

(*E*)-3,3′,4,4′-Tetrakis(trimethylsilyloxy)stilbene (12): Pale-green solid. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.94 (m, 4 H, Ar), 6.79 (d, $^3J_{H,H}$ = 8.8 Hz, 2 H, Ar), 6.76 (s, 2 H, =CH), 1.01 (s, 18 H, $SiMe_3$), 0.99 (s, 18 H, $SiMe_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 146.9, 145.6, 131.5, 126.7, 121.2, 119.8, 118.9, 26.03 ($SiMe_3$), 26.00 ($SiMe_3$) ppm. $C_{26}H_{44}O_4Si_4$ (532.97): calcd. C 58.59, H 8.32; found C 58.51, H 8.36.

(*E*)-4-Hydroxy-4′-methoxystilbene (13):[34] Pink powder. ^{1}H NMR (250 MHz, [D$_6$]acetone, 25 °C): δ = 8.51 (br. s, OH), 7.62 (d, $^3J_{H,H}$ = 8.8 Hz, 2 H, Ar), 7.55 (d, $^3J_{H,H}$ = 8.7 Hz, 2 H, Ar), 7.20 [d, $^3J_{H,H}$ (*E*) = 16.2 Hz, 1 H, =CH], 7.08 [d, $^3J_{H,H}$ (*E*) = 16.1 Hz, 1 H, =CH], 7.05 (d, $^3J_{H,H}$ = 8.8 Hz, 2 H, Ar), 7.00 (d, $^3J_{H,H}$ = 8.7 Hz, 2 H, Ar), 3.94 (s, 3 H, OMe) ppm.

(*E*)-3,4′,5-Trihydroxystilbene (Resveratrol, 14):[5,7,29,30] Pale-pink powder. ^{1}H NMR (400 MHz, [D$_6$]acetone, 25 °C): δ = 8.45 (br. s, OH), 8.19 (br. s, OH), 7.41 (d, $^3J_{H,H}$ = 8.5 Hz, 2 H, Ar), 7.01 [d, $^3J_{H,H}$ (*E*) = 16.6 Hz, 1 H, =CH], 6.88 [d, $^3J_{H,H}$ (*E*) = 16.6 Hz, 1 H, =CH], 6.82 (d, $^3J_{H,H}$ = 8.5 Hz, 2 H, Ar), 6.57 (d, $^4J_{H,H}$ = 2.0 Hz, 2 H, Ar), 6.30 (t, $^4J_{H,H}$ = 2.0 Hz, 1 H, Ar) ppm.

(*E*)-3,3′,4,5′-Tetrahydroxystilbene (Piceatannol, 15):[29,35] Pale-yellow powder. ^{1}H NMR (400 MHz, [D$_6$]acetone, 25 °C): δ = 8.20 (br. s, OH), 7.07 (d, $^4J_{H,H}$ = 2.1 Hz, 1 H, Ar), 6.95 [d, $^3J_{H,H}$ (*E*) = 16.2 Hz, 1 H, =CH], 6.90 (dd, $^3J_{H,H}$ = 8.1, $^4J_{H,H}$ = 2.1 Hz, 1 H, Ar), 6.82 [d, $^3J_{H,H}$ (*E*) = 16.2 Hz, 1 H, =CH], 6.80 (d, $^3J_{H,H}$ = 8.1 Hz, 1 H, Ar), 6.52 (dd, $^4J_{H,H}$ = 2.1, $^4J_{H,H}$ = 1.0 Hz, 2 H, Ar), 6.25 (dd, $^4J_{H,H}$ = 2.1, $^4J_{H,H}$ = 1.1 Hz, 1 H, Ar) ppm.

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[1] a) J. Gorham, *Progr. Phytochem.* **1980**, *6*, 203–252; b) S. Renaud, M. de Lorgeril, *Lancet* **1992**, *339*, 1523–1526; c) M. Jang, L. Cai, G. O. Udeani, K. V. Slowing, C. F. Thomas, C. W. W. Beecher, H. H. S. Fong, N. R. Farnsworth, A. D. Kinghorn, R. G. Mehta, R. C. Moon, J. M. Pezzuto, *Science* **1997**, *275*, 218–220; d) M. C. Pinto, J. A. Garcia-Barrado, P. Macias, *J. Agric. Food Chem.* **1999**, *47*, 4842–4846; e) M. Ibern-Gomez, S. Roig-Perez, R. M. Lamuela-Raventos, M. C. de la Torre-Boronat, *J. Agric. Food Chem.* **2000**, *48*, 6352–6354; f) L. Frémont, *Life Sci.* **2000**, *66*, 663–673; g) T. Ito, T. Tanaka, M. Iinuma, I. Iliya, K.-I. Nakaya, Z. Ali, Y. Takahashi, R. Sawa, Y. Shirataki, J. Murata, D. Darnaedi, *Tetrahedron* **2003**, *59*, 5347–5363.

[2] For selected examples applying to phytoalexins, see: a) M. L. Cardona, M. I. Fernandez, M. B. Garcia, J. R. Pedro, *Tetrahedron Lett.* **1986**, *42*, 2725–2730; b) F. Orsini, F. Pelizzoni, L. Verotta, T. Aburjai, *J. Nat. Prod.* **1997**, *60*, 1082–1087; c) R. Shirai, H. Takayama, A. Nishkawa, Y. Koiso, Y. Hashimoto, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1997–2000; d) K. E. Polunin, I. A. Polunina, H.-G. Schmalz, *Mendeleev Commun.* **2002**, 178–180.

[3] For a review, see: K. Ferré-Filmon, L. Delaude, A. Demonceau, A. F. Noels, *Coord. Chem. Rev.* **2004**, *248*, 2323–2336.

[4] a) M. Guiso, C. Marra, A. Farina, *Tetrahedron Lett.* **2002**, *43*, 597–598; b) N. F. Thomas, K. C. Lee, T. Paraidathathu, J. F. F. Weber, K. Awang, D. Rondeau, P. Richomme, *Tetrahedron* **2002**, *58*, 7201–7206; c) M. B. Andrus, J. Liu, E. L. Meredith, E. Nartey, *Tetrahedron Lett.* **2003**, *44*, 4819–4822.

[5] T. Jeffery, B. Ferber, *Tetrahedron Lett.* **2003**, *44*, 193–197.

[6] S. Eddarir, Z. Abdelhadi, C. Rolando, *Tetrahedron Lett.* **2001**, *42*, 9127–9130.

[7] M. A. Ali, K. Kondo, Y. Tsuda, *Chem. Pharm. Bull.* **1992**, *40*, 1130–1136.

[8] Y. Pasturel-Jacopé, G. Solladié, J. Maignan (L'Oréal S.A.), *Fr. Demande* FR 2829759, **2003**; *Chem. Abstr.* **2003**, *138*, 254948.

[9] a) R. R. Schrock, J. S. Murdzek, G. C. Bazan, J. Robbins, M. DiMare, M. O'Regan, *J. Am. Chem. Soc.* **1990**, *112*, 3875–3886; b) H. H. Fox, R. R. Schrock, R. O'Dell, *Organometallics* **1994**, *13*, 635–639.

[10] S. Chang, Y. Na, H. J. Shin, E. Choi, L. S. Jeong, *Tetrahedron Lett.* **2002**, *43*, 7445–7448.

[11] a) *Handbook of Metathesis* (Ed.: R. H. Grubbs), Wiley-VCH, Weinheim, **2003**; b) K. J. Ivin, J. C. Mol, *Olefin Metathesis and Metathesis Polymerization*, Academic Press, San Diego, **1997**.

[12] S. J. Connon, S. Blechert, *Angew. Chem. Int. Ed.* **2003**, *42*, 1900–1923.

[13] A. K. Chatterjee, T.-L. Choi, D. P. Sanders, R. H. Grubbs, *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370.

[14] M. Scholl, S. Ding, C. W. Lee, R. H. Grubbs, *Org. Lett.* **1999**, *1*, 953–956.

[15] P. Schwab, M. B. France, J. W. Ziller, R. H. Grubbs, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2039–2041.

[16] J. S. Kingsbury, J. P. A. Harrity, P. J. Bonitatebus, Jr., A. H. Hoveyda, *J. Am. Chem. Soc.* **1999**, *121*, 791–799.

[17] S. B. Garber, J. S. Kingsbury, B. L. Gray, A. H. Hoveyda, *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179.

[18] a) F. L. Benton, T. E. Dillon, *J. Am. Chem. Soc.* **1942**, *64*, 1128–1129; b) J. F. W. McOmie, M. L. Watts, D. E. West, *Tetrahedron* **1968**, *24*, 2289–2292; c) J. Press, *Synth. Commun.* **1979**, *9*, 407–410.

[19] P. R. Brooks, M. C. Wirtz, M. G. Vetelino, D. M. Rescek, G. F. Woodworth, B. P. Morgan, J. W. Coe, *J. Org. Chem.* **1999**, *64*, 9719–9721.

[20] a) F. D. Toste, A. K. Chatterjee, R. H. Grubbs, *Pure Appl. Chem.* **2002**, *74*, 7–10; b) R. H. Grubbs, A. K. Chatterjee, T.-L. Choi, S. D. Goldberg, J. A. Love, J. P. Morgan (California Institute of Technology), WO 02079126, **2002**; *Chem. Abstr.* **2002**, *137*, 295099.

[21] D. F. Taber, K. J. Frankowski, *J. Org. Chem.* **2003**, *68*, 6047–6048.

[22] E. A. Couladouros, A. P. Mihou, E. A. Bouzas, *Org. Lett.* **2004**, *6*, 977–980.

[23] a) M. Ulman, R. H. Grubbs, *J. Org. Chem.* **1999**, *64*, 7202–7207; b) M. S. Sanford, J. A. Love, R. H. Grubbs, *J. Am. Chem. Soc.* **2001**, *123*, 6543–6554; c) S. H. Hong, M. W. Day, R. H. Grubbs, *J. Am. Chem. Soc.* **2004**, *126*, 7414–7415.

[24] a) K. A. Burdett, L. D. Harris, P. Margl, B. R. Maughon, T. Mokhtar-Zadeh, P. C. Saucier, E. P. Wasserman, *Organometallics* **2004**, *23*, 2027–2047; b) G. S. Forman, A. E. McConnell, M. J. Hanton, A. M. Z. Slawin, R. P. Tooze, W. J. van Rensburg, W. H. Meyer, C. Dwyer, M. M. Kirk, D. W. Serefontein, *Organometallics* **2004**, *23*, 4824–4827.

[25] G. I. Feutrill, R. N. Mirrington, *Aust. J. Chem.* **1972**, *25*, 1719–1729.

[26] a) R. Greenwald, M. Chaykovsky, E. J. Corey, *J. Org. Chem.* **1963**, *28*, 1128–1129; b) A. Takano, A. Meguro, T. Kazama, Y. Isono, *React. Funct. Polym.* **1998**, *37*, 39–47.

[27] R. S. Mali, P. G. Jagtap, *Synth. Commun.* **1991**, *21*, 841–848.

[28] a) P. Warner, R. Sutherland, *J. Org. Chem.* **1992**, *57*, 6294–6300; b) M. B. Andrus, K. G. Mendenhall, E. L. Meredith, B. B. V. Soma Sekhar, *Tetrahedron Lett.* **2002**, *43*, 1789–1792; c) M. B. Andrus, C. Song, J. Zhang, *Org. Lett.* **2002**, *4*, 2079–2082.

 © 2005 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

[29] E. Alonso, D. J. Ramon, M. Yus, *J. Org. Chem.* **1997**, *62*, 417–421.
[30] G. Solladié, Y. Pasturel-Jacopé, J. Maignan, *Tetrahedron* **2003**, *59*, 3315–3321.
[31] J. Gerold, U. Holzenkamp, H. Meier, *Eur. J. Org. Chem.* **2001**, 2757–2763.
[32] K. Thakkar, R. L. Geahlen, M. Cushman, *J. Med. Chem.* **1993**, *36*, 2950–2955.
[33] a) J. Gierer, J. Lenic, I. Szabo-Lin, *Acta Chem. Scand., Ser. B* **1974**, *28*, 717–729; b) L. Lonsky, W. Lonsky, K. Kratzl, *Monatsh. Chem.* **1976**, *107*, 685–695; c) Z. Hajdu, E. Varga, J. Hohmann, A. Kalman, G. Argay, G. Guenther, *J. Nat. Prod.* **1998**, *61*, 1298–1299.
[34] J.-E. Dubois, M.-F. Ruasse, *J. Org. Chem.* **1973**, *38*, 493–499.
[35] J. P. Steynberg, D. Ferreira, D. G. Roux, *J. Chem. Soc., Perkin Trans. 1* **1987**, 1705–1712.

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