Convenient Preparation of *trans*-Arylalkenes via Palladium(II)-Catalyzed Isomerization of *cis*-Arylalkenes

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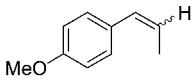
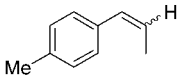
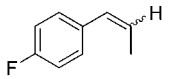
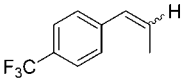
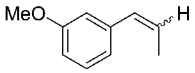
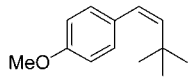
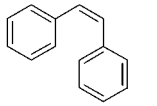
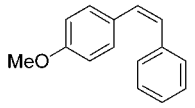
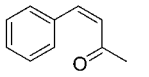
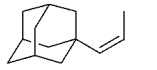
Abstract: A convenient method for the isomerization of *cis*-arylalkenes to their trans isomers using a palladium(II) catalyst is described. The reaction conditions are mild and general across a range of arylalkenes. The synthesis of a *trans*-resveratrol derivative from a mixture of alkene isomers was also completed.

The construction of carbon−carbon double bonds is a fundamental reaction in organic chemistry.[1] A wealth of research has been directed toward the synthesis of geometrically pure alkenes, and many elegant methods have been developed.[2] However, in many reactions, such as the Wittig reaction or alkene metathesis, mixtures of *cis*- and *trans*-alkenes are formed.[2,3] Methods for isomerizing *cis*-alkenes to their trans isomers, such as radical[4a] or photochemical processes,[4b] often involve relatively harsh reaction conditions. Furthermore, in some photochemical procedures the reverse isomerization of trans to cis is observed.[4c] It would therefore be very useful to have a reliable, mild, and facile method for the conversion of alkene mixtures or *cis*-alkenes to geometrically pure *trans*-alkenes. Herein, we report a convenient new method for the preparation of *trans*-arylalkenes via palladium(II)-catalyzed isomerization of *cis*-alkenes under ambient conditions.

Previous studies have demonstrated that palladium(II) salts can promote the migration of terminal double bonds giving a mixture of disubstituted alkenes.[5] This has led to the proposal that the mechanism might involve formation of either a carbocation or a π-allylic complex.[5]

Table 1. Scope of Isomerization Reaction

Entry[a]	Alkene (ratio *c*:*t*)		Time / hrs.	Yield of *trans* isomer **2a-j**[b]
1a		(1:1)	14	**90**
1b		(1:2)	14	**89**
1c		(1:1)	14	**85**
1d		(1.8:1)	14	no reaction
1e		(1:1.4)	14	**96**
1f			24	**90**
1g			14	**91**
1h			14	**93**
1i[c]			0.25	**97**
1j			14	**87**

[a] Reagents and conditions: 10 mol % $(MeCN)_2PdCl_2$, CH_2Cl_2, rt. [b] After purification by flash silica gel chromatography. [c] 10 mol % $PdCl_2(PhCN)_2$ was used as the catalyst.

We felt that this reactivity could be exploited for the preparation of pure *trans*-alkenes from *cis*-alkenes if the double bond could be prevented from migrating. If the mechanism involves a carbocation then we postulated that a stabilizing aryl substituent, conjugated to the double bond, would facilitate the isomerization and prevent the bond from migrating. To test this, a range of alkene substrates were prepared by conventional Wittig olefination. Mixtures of *cis*- and *trans*-alkenes were obtained in each case. Isomerization of these alkene mixtures was carried out with 10 mol % of bis(acetonitrile)palladium(II) chloride in a 0.5 M solution of alkene in dichloromethane under an argon atmosphere. In most cases, the reactions were complete in less than 24 h (Table 1). The mixtures of *cis*- and *trans*-β-methyl

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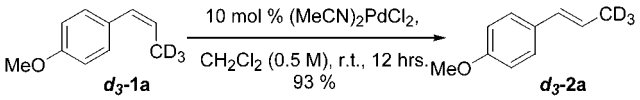
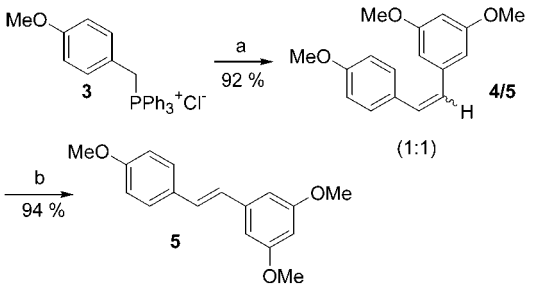
Scheme 1. Isomerization of Deuterium Labeled Styrene



Scheme 2. Synthesis of Resveratrol Derivative[a]



[a] Reagents and conditions: (a) *n*-BuLi, THF, −78 to 0 °C, 1 h then 3,5-dimethoxybenzaldehyde, THF, −78 °C; (b) 10 mol % $(MeCN)_2PdCl_2$, CH_2Cl_2 (0.5 M), rt, 12 h.

styrenes (entries **1a**−**c**,**e**) were converted to the trans isomer in good yield.

Styrene substrates with sterically bulky substituents (entry **1f**) could also be isomerized to the trans product, although they required extended reaction times (24 h) to reach total conversion. The trans isomer, however, was still isolated in 90% yield. Substituted stilbene derivatives could likewise be isomerized in good yield (entries **1g** and **1h**). When the double bond was further polarized by being conjugated to a carbonyl group the reaction was significantly accelerated (entry **1i**). In contrast the introduction of a trifluoromethyl group in the para position of the aromatic ring (entry **1d**) resulted in no conversion to the *trans*-alkene. This is consistent with the benzylic carbon being electron deficient in the transition state.

It is, however, worth noting that those substrates containing allylic hydrogens could isomerize by bond migration (the double bond moving out of conjugation and back again) with the involvement of a π-allylic complex.[5] To investigate this possibility, deuterated methyl styrene ***d*$_3$-1a** was synthesized and isomerized under similar conditions (Scheme 1). No deuterium was lost from or transferred to the benzylic position, thus ruling out this as a possible mechanism. Another possible explanation for the isomerization is the trans addition of palladium chloride to the double bond followed by rotation and syn-β-elimination of the palladium chloride. At this stage, it is not possible to distinguish between this mechanism and that involving a carbocation.

The synthetic potential of this methodology was demonstrated in the synthesis of trimethoxy resveratrol. Resveratrol is currently attracting a great deal of interest from the scientific community for its biological properties.[6] The synthesis of stilbenes is readily achieved through the Wittig reaction of a benzyl phosphonium salt and benzaldehyde (Scheme 2). However, ylides generated from benzyl phosphonium salts seldom deliver geometrically pure alkenes.[7]

In the present case, a 1:1 mixture of isomers **4/5** was obtained in 92% yield. However, isomerization of this mixture using the palladium catalyst gave only the trans isomer **5** of the resveratrol derivative in 94% yield. In a similar experiment, the pure *cis*-alkene **4** was converted to *trans*-**5** in identical yield.

In summary, isomerization of double bonds conjugated to aromatic systems in the presence of palladium(II) is reported. This reaction should prove an attractive method for the preparation of pure *trans*-arylalkenes due to the mild reaction conditions.

Experimental Section

General Information. ^{1}H NMR spectra were recorded in deuteriochloroform, unless stated otherwise, at 250 MHz at 298 ± 3 K. ^{13}C NMR spectra were recorded at 62.5 MHz. Chemical shifts are quoted relative to residual solvent (7.25 ppm for ^{1}H and 77.0 ppm for ^{13}C of $CDCl_3$), and coupling constants (J) are given in Hz. High-resolution mass spectral (HRMS) analyses were measured by means of EI, FAB, FIB, or ES techniques. All anhydrous solvents were dried by standard techniques and freshly distilled before use or purchased in anhydrous form. All flash chromatography was carried out using silica gel.

General Procedure for the Isomerization of *cis*-Alkenes. A solution of the *cis*-alkene and bis(acetonitrile)palladium(II) chloride (10 mol %) in dichloromethane (2 mL per mmol of substrate) was stirred at room temperature for the appropriate time. The reaction mixture was diluted with diethyl ether and filtered through a short pad of Florisil, eluting with diethyl ether. The solvent was removed under reduced pressure and the residue purified by flash silica gel chromatography to afford the *trans*-alkene.

Synthesis of *trans*-Anethole, 2a: 1 mmol scale (cis/trans, 1:1), 14 h, gave 133 mg, 90%, R_f = 0.72 diethyl ether−hexane 2:98; colorless oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.30−7.23 (m, 2 H, J = 8.0 Hz), 6.87−6.80 (m, 2 H, J = 8.0 Hz), 6.39−6.30 (m, 1 H, J = 16.0 Hz), 6.18−6.03 (dq, 1 H, J = 16.0, 6.8 Hz), 3.80 (s, 3 H), 1.87−1.83 (dd, 3 H, J = 6.8, 1.9 Hz). ^{1}H NMR spectra were identical to authentic material.

Synthesis of *cis*/*trans*-4-Methoxy-3′,5′-dimethoxystilbene, 4/5. *n*-Butyllithium (3.85 mL of a 1.3 M solution in hexanes, 5.0 mmol) was added dropwise to a stirred suspension of 4-methoxybenzyltriphenylphosphonium chloride (2.10 g, 5 mmol) in anhydrous tetrahydrofuran (10 mL) at 0 °C under an argon atmosphere. After the mixture was stirred for 1 h, the reaction temperature was lowered to −78 °C and the 3,5-dimethoxybenzaldehyde (0.821 g, 4.95 mmol) in tetrahydrofuran (5 mL) was added to the red solution. Stirring was continued at low temperature for another 2 h, allowed to warm to room temperature, and stirred for 12 h.

The reaction mixture was diluted with hexane and poured into dilute hydrochloric acid solution. The solution was extracted with hexane, and the combined organic fractions were washed with water, saturated sodium hydrogen carbonate solution, and water. The organic portions were dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. The residue was purified by flash silica gel chromatography (hexane R_f = cis 0.30, trans 0.23) to afford the stilbene as a 1:1 mixture of isomers as a white solid (0.94 g, 94%).

***cis*-4-Methoxy-3′,5′-dimethoxystilbene 4:** ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.16−7.12 (d, 2 H, J = 8.2 Hz), 6.73−6.68 (d, 2 H, J = 8.2 Hz), 6.50−6.45 (d, 1 H, J = 12.0 Hz), 6.40−6.35 (d, 1 H, J = 120 Hz), 6.38−6.36 (m, 2 H), 6.35−6.22 (m, 1 H), 3.76 (s, 3 H), 3.60 (s, 6 H).

***trans*-4-Methoxy-3′,5′-dimethoxystilbene 5:** ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.72−7.38 (d, 2 H, J = 8.0 Hz), 7.01−6.95 (d, 1 H, J = 17.0 Hz), 6.86−6.79 (d, 1 H, J = 17.0 Hz), 6.83−6.80 (d, 2 H, J = 8.0 Hz), 6.60−6.58 (m, 2 H), 6.33−6.30 (br, 1 H), 3.78 (s, 9 H). ^{1}H NMR spectra were consistent with data in ref 8.

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Isomerization of the Trimethoxyresveratrol Derivative, 4. A solution of the *cis*-alkene **4** (100 mg, 0.5 mmol) and bis-(acetonitrile)palladium(II) chloride (13 mg, 0.05 mmol) in dichloromethane (1 mL) was stirred at room temperature for 14 h. The reaction mixture was diluted with diethyl ether and filtered through a short pad of Florisil, eluting with diethyl ether. The solvent was removed under reduced pressure and the residue purified by flash silica gel chromatography (diethyl ether−hexane 2:98, $R_f = 0.52$) to afford the *trans*-**5** as a white solid (92 mg, 92%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.48−7.45 (d, 2 H, J = 8.7 Hz), 7.11−7.01 (d, 1 H, J = 16.2 Hz), 6.96−6.86 (d, 1 H, J = 16.2 Hz), 6.93−6.90 (d, 2 H, J = 8.7 Hz), 6.69−6.68 (m, 2 H), 6.42−6.41 (br, 1 H), 3.84 (s, 6 H), 3.83 (s, 3 H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 161.0, 159.5, 139.8, 130.0, 128.8, 127.9, 126.6, 114.2, 104.4, 99.7, 55.3. ^{1}H NMR spectra was consistent with data in ref 8.

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Supporting Information Available: Experimental procedures and spectral data for all compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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