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Remarkable tolerance of ethynyl steroids to air and water in microwave-assisted hydrophosphinylation: Reaction scope and limitations

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Abstract

The microwave-assisted hydrophosphinylation of propargyl alcohols has been investigated using group 9 catalysts under solvent-free conditions as well as with pure water, ethyl lactate, or THF as the solvent. Reactions involving simple propargyl alcohols gave mixtures containing significant amounts of elimination products. In contrast, analogous reactions involving ethynyl steroids afforded a single species with only trace amounts of elimination products. The molecular structures of several derivatives have been determined and are discussed.

Keywords: Hydrophosphinylation; Rhodium; Microwave-assisted; Aqueous

1. Introduction

The development of organometallic reactions that proceed in water as well as other "green" solvents is a current and challenging goal [1,2]. Recent developments include the synthesis of small molecules and polymeric materials through Suzuki-type coupling reactions [3,4], the aqueous phase reduction of ketones and aldehydes [5], and the use of a sulfonated XANTPHOS ligand for a regioselective hydroformylation reaction in water [6]. Additionally, water is an attractive solvent for microwave-assisted chemistry due to its high absorption of microwave radiation.

The transition metal catalyzed addition of P(O)–H bonds to alkenes and alkynes is a powerful way to generate P–C bonds [7–11]. Despite the intense amount of research that has been devoted to this chemistry, a number of challenges still remain. For example, propargyl alcohols are a particularly problematic class of compounds for metal catalyzed hydrophosphinylation reactions due to the generation of a wide range of products. This product distribution often depends upon the metal catalyst and additives (Fig. 1). Recently, Uemura et al. found that dinuclear ruthenium catalysts promoted the conversion of propargyl alcohols to ethynyl phosphine oxides in 1,2-dichloroethane [12]. Han et al. recently reported that a nickel catalyst generated mixtures of phosphinoyl 1,3-butadienes and alkenyl phosphine oxides in THF [13]. Tanaka et al. has shown that Wilkinson's catalyst promoted the addition of a pinacol derived hydrogen phosphonate to 2-methyl-3-butyn-2-ol in THF [14].

Ethynyl steroids are a particularly attractive class of propargyl alcohols. The development of methodology for the functionalization of ethynyl steroids is an important

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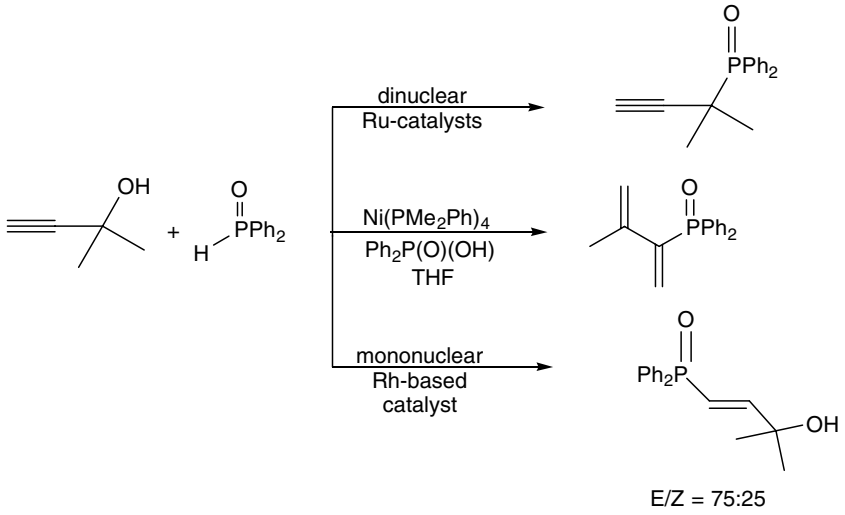


Fig. 1. Addition of diphenylphosphine oxide to 2-methyl-3-butyn-2-ol with different catalysts and additives.

area of research since steroid derivatives often exhibit a high degree of biological activity [15,16]. For example, sulfonylpyrazole and related derivatives of ethisterone are *anti*-androgenic agents [17,18] and arylated ethisterone species are modulators of ion channels in the mammalian brain (γ-aminobutyric acid receptors) [19]. Recent reports on ethynyl steroid functionalization have focused on the reactivity of the acetylenic hydrogen and include the Sonogashira coupling of ethynyl steroids with aryl halides [20], the palladium catalyzed amination of estrone [21], and the synthesis of estradiol-based pincer compounds [22]. The latter are attractive agents for the targeted cellular delivery of platinum to cancerous tissues that are rich in estrogen receptors. As part of our continuing studies on the development of microwave-assisted approaches for the formation of carbon-heteroelement bonds [23], we have investigated the addition of P(O)–H bonds to simple propargyl alcohols as well as ethynyl steroids under solvent-free conditions and with water, THF, or ethyl lactate as the solvent.

2. Results and discussion

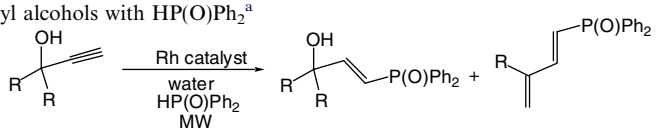
To determine an effective catalyst system for the microwave-assisted addition of P(O)–H bonds to propargyl alcohols using water as the solvent, a number of group 9 catalysts were screened for activity. Palladium, nickel, and dinuclear ruthenium catalysts were not selected for the microwave-assisted reactions since significant amounts of competing elimination, dehydration, and rearrangement reactions were observed in conventionally heated reactions (Fig. 1) using these catalysts. Cyclic and acyclic propargyl alcohols as well as secondary systems were investigated using $HP(O)Ph_2$ as the source of the $R_2P(O)$–H unit (Table 1). Using microwave heating, reactions involving simple substrates such as 1-ethynyl-1-cyclohexanol and 2-methyl-3-butyn-2-ol gave mixtures of addition and elimination products when common homogenous catalysts such as $[Rh(cod)Cl]_2$ and $(Ph_3P)_3RhCl$ were used. Similar results were obtained when the Rh(III) precatalyst $(Me_2PhP)_3RhMe_3$ [24] was employed. Extensive manipulation of the catalyst loading, reaction temperature, and the presence or absence of solvent only changed the ratio of the products. Propargyl alcohol does not have the problem of elimination, however, analogous reactions using this substrate afforded a reaction mixture with 12 resonances in the $^{31}P\{^1H\}$ NMR spectrum with less than 40% conversion into the desired phosphine oxide. In contrast to the problematic addition/elimination chemistry exhibited by simple propargyl alcohols, an ethynyl steroid (ethisterone) was cleanly hydrophosphinylated using $(Me_2PhP)_3RhMe_3$ as the precatalyst. While the precise rationale for this observation is unknown, the conformational restriction of the steroid ring system as well as the *syn*-methyl group is likely to play a role. Remarkably, the reactions could be carried out under an atmosphere of air with no precautions for the removal of oxygen. High yielding solvent-free reactions were also carried out using the model system of ethisterone and $HP(O)Ph_2$. Similar to the aqueous reactions, the solvent-free processes could be carried out under an atmosphere of air without significant decreases in yield. Analysis of the crude reaction mixture by ^{31}P NMR spectroscopy revealed only small amounts of rearrangement, dehydration, or elimination products (totaling less than 5%). For comparison, the addition reaction was carried out using conventional heating in water as well as THF. After dunking the reaction mixtures into a preheated oil bath at 150 °C and stirring for 10 min, analysis of the crude reaction mixtures revealed the desired alkenyl phosphine oxide (water, 64%; THF, 72%). As part of the preliminary investigation, analogous reactions were carried out using $(Ph_3P)_3RhBr$ according to Tanakas

protocol.[8] After stirring ethisterone with $HP(O)Ph_2$ using $(Ph_3P)_3RhBr$ as the catalyst in toluene for 1 h, analysis of the reaction mixture revealed only a 5% conversion into the desired alkenyl phosphonate. This lack of reactivity could be due to the limited solubility of the ethynyl steroid in toluene. Control reactions revealed no consumption of $HP(O)Ph_2$ in reactions without a metal catalyst.

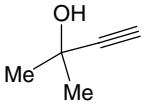
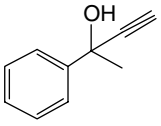
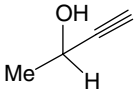
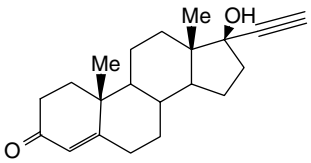
Since the hydrophosphinylation reactions were selective and high yielding with ethisterone, these atom-efficient transformations were extended to mestranol and ethynyl estradiol as well as 6H-dibenz[*c*,*e*][1,2]oxaphosphorin,6-oxide (DOPO) and ethyl phenylphosphinate (Table 2). Similar to reactions with $HP(O)Ph_2$, the microwave-assisted additions of DOPO to ethynyl steroids were rapid and moderate yields of the desired alkenyl phosphinates were obtained. For comparison, reactions were carried out under solvent-free conditions as well as with THF or (−)-ethyl L-lactate as the solvent. (−)-Ethyl L-lactate is a biodegradable solvent with an attractive temperature range (boiling point = 154 °C) that has replaced a number of solvents such as methyl ethyl ketone and methyl isobutyl ketone in organic transformations [25]. The addition reactions were rapid and high yielding with diphenylphosphine oxide and DOPO using $(Me_2PhP)_3RhMe_3$ as the precatalyst with microwave heating. Similar to reactions carried out in water, the reactions were insensitive to air and moderate to high yields of the alkenyl phosphine oxides and phosphinates were obtained. The solvent-free reactions were successful using $(Ph_3P)_3RhCl$ as the catalyst. A simple trituration was the only purification step that was needed to isolate the desired addition product. Analogous reactions using ethyl phenylphosphinate were challenging, and after an extensive number of catalysts and solvents were screened, moderate yields of the addition products were observed when THF was used as the solvent with $[Rh(cod)Cl]_2$ as the catalyst. However, lower yields were obtained in pure water or under solvent-free conditions.

The resulting functionalized steroids were isolated as successful white solids. The retention of the 17α-OH was the most important factor when catalyst systems were screened since previous studies demonstrated that this group was critical to the binding of the steroid to the estrogen receptor hormone binding domain [26]. The 17-OH group remained intact in these reactions and was observed

Table 1
Microwave-assisted reaction of propargyl alcohols with $HP(O)Ph_2$[a]

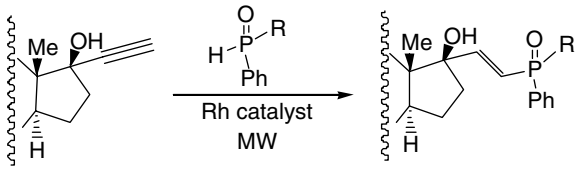


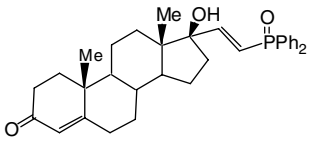
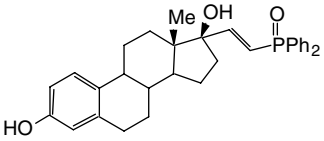
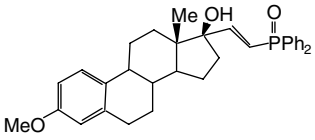
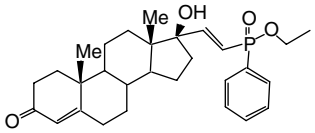
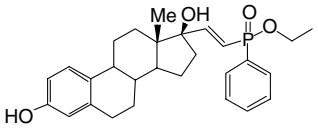
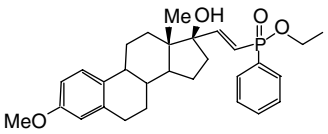
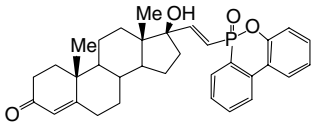
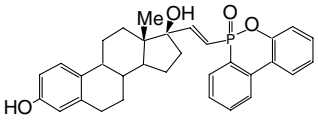
A B

#	Propargyl alcohol	Catalyst[b]	Product A[c]	Product B[c]
1		$(Ph_3P)_3RhCl$	40	25
		$[Rh(cod)Cl]_2$	31	22
		$(Me_2PhP)_3RhMe_3$	26	30
2		$(Ph_3P)_3RhCl$	48	32
		$[Rh(cod)Cl]_2$	25	19
		$(Me_2PhP)_3RhMe_3$	31	25
3		$(Ph_3P)_3RhCl$	58	20
		$[Rh(cod)Cl]_2$	41	30
		$(Me_2PhP)_3RhMe_3$	55	21
4		$(Ph_3P)_3RhCl$	35	10
		$[Rh(cod)Cl]_2$	39	5
		$(Me_2PhP)_3RhMe_3$	86	1

[a] Reactions carried out in pure water (1.5 mL) using 0.32 mmol of propargyl alcohol and $HP(O)Ph_2$.
[b] 3 mol% (stable Rh). The reactions were irradiated for 15 min at 150 °C using 70–100 W of microwave power.
[c] The listed yields of the products in these screening reactions were determined by integration of the appropriate resonances in the ^1H and ^{31}P NMR spectra using hexamethylbenzene and triphenylphosphine oxide as internal standards.

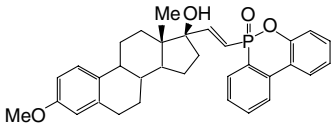
Table 2
Microwave-assisted functionalization of ethynyl steroids



#	Steroid	Product		Solvent-free[a,f]	Water[b,f]	THF[c,f]	Ethyl lactate[d,f]
1	Ethisterone		**1**	80	79	86	80
2	Ethynyl estradiol		**2**	83	75	85	71
3	Mestranol		**3**	85	81	80	73
4	Ethisterone		**4**	21[e] (1:1.1)	11[e] (1:1.1)	55[g] (1:1.2)	25[e] (1:1.1)
5	Ethynyl estradiol		**5**	17[e] (1:1.3)	12[e] (1:1.1)	41[g] (1:1)	21[e] (1:1.2)
6	Mestranol		**6**	35[e] (1:1.2)	25[e] (1:1.1)	58[g] (1:1.5)	34[e] (1:1.1)
7	Ethisterone		**7**	35 (1:1.5)	42 (1:1.4)	53 (1:1.3)	50 (1:1.5)
8	Ethynyl estradiol		**8**	41 (1:1.2)	57 (1:1.3)	65 (1:1)	49 (1:1.5)

(*continued on next page*)

Table 2 (*continued*)

#	Steroid	Product		Solvent-free[a,f]	Water[b,f]	THF[c,f]	Ethyl lactate[d,f]
9	Mestranol		**9**	45 (1:1.3)	50 (1:1.7)	60 (1:1.2)	45 (1:1.2)

Equimolar ratios of phosphine oxide and ethynyl steroid were used in all experiments.

[a] Neat reagents (60 min, 125 °C), $(Ph_3P)_3RhCl$ (1.7 mol%).

[b] 1.5 mL of water as the solvent (10–15 min, 150 °C), $(Me_2PhP)_3RhMe_3$ (3.1 mol %).

[c] 1.0–3.0 mL of THF as the solvent (10–15 min, 150 °C), $(Ph_3P)_3RhCl$ (1.7 mol%).

[d] 0.4–1.0 mL of (−)-ethyl L-lactate as the solvent (20 min, 120–150 °C), $(Me_2PhP)_3RhMe_3$ (3.1 mol%).

[e] Determined by ^1H or $^{31}P\{^1H\}$ NMR spectroscopy using appropriate internal standards.

[f] Yields are based upon isolated material.

[g] $[Rh(cod)Cl]_2$ (1.3 mol%) was used as the catalyst in these reactions. The numbers in parenthesis refer to the ratio of diastereomers as determined by quantitative $^{31}P\{^1H\}$ NMR spectroscopy. The microwave power levels needed to maintain the desired temperatures were: solvent-free (70–90 W), water (70–80 W), THF (210–280 W), ethyl lactate (20–75 W).

as a singlet in the ^1H NMR spectrum (5.04 ppm for **1**; DMSO-d_6). Compounds **1**–**9** gave strong $M + H^+$ peaks for the title compounds in electrospray ionization mass spectrometric (ESI-MS) studies. Analysis of the ^1H NMR spectra revealed that only the (*E*)-1,2 substituted compounds were formed [27,28]. No dehydrated, vinylidene, or *Z*-isomers were isolated from these experiments. Due to the chiral phosphorus centers in **4**–**9**, diastereomers resulted from the addition reaction. The diastereomeric ratio was readily determined from the $^{31}P\{^1H\}$ NMR spectrum. Although the resolved (−)-ethyl L-lactate was used as the solvent in several reactions, the addition process was not diastereoselective.

3. Molecular structures of hydrophosphinylated steroids

Long needles of **1** and **2** were obtained by slow diffusion of pentane into solutions containing **1** and **2**. Compound **1** crystallizes in the chiral space group $P2_1$ with one molecule of crystallization solvent (C_6H_6) per **1**. The molecular structures of **1** and **2** are shown in Fig. 2, and the extended structures are displayed in Figs. 3 and 4. The crystallographic parameters are listed in Table 3. For **1**, the *E* stereochemistry and regioselectivity about the alkene fragment are evident from the diagrams, and the –C=C– distance (1.314(5) Å) is lengthened relative to free ethisterone (1.171 Å) [29] and mestranol (1.176 Å) [30]. An analysis of the packing revealed that **1** crystallized as

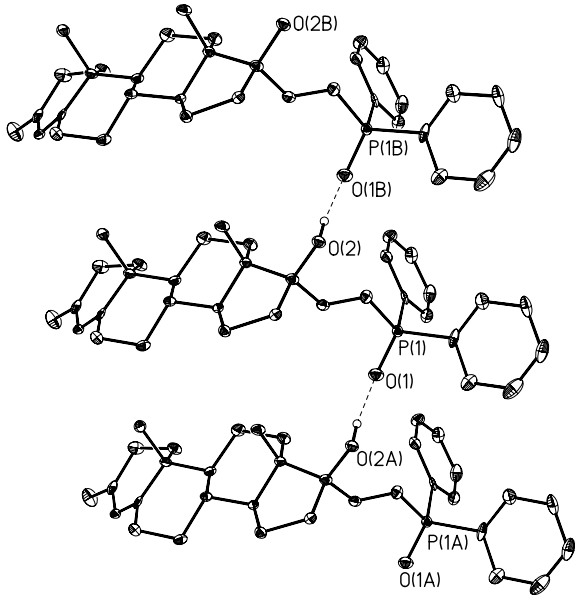


Fig. 3. The polymeric structure of **1** showing the hydrogen bonding between the phosphoryl oxygen and the 17-OH. Thermal ellipsoids are shown at 50% probability.

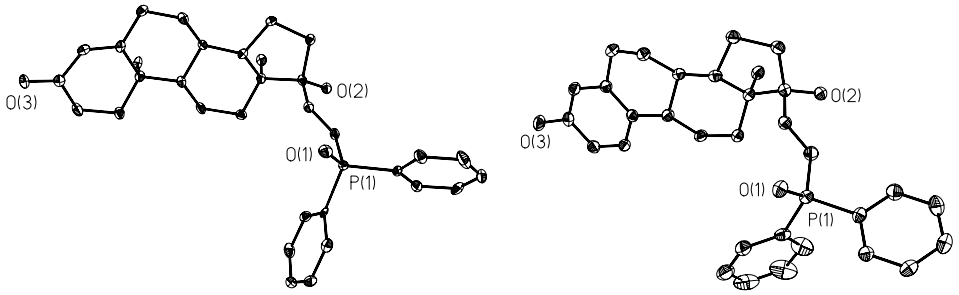


Fig. 2. Molecular structures of **1** and **2**. Thermal ellipsoids are shown at 50% probability.

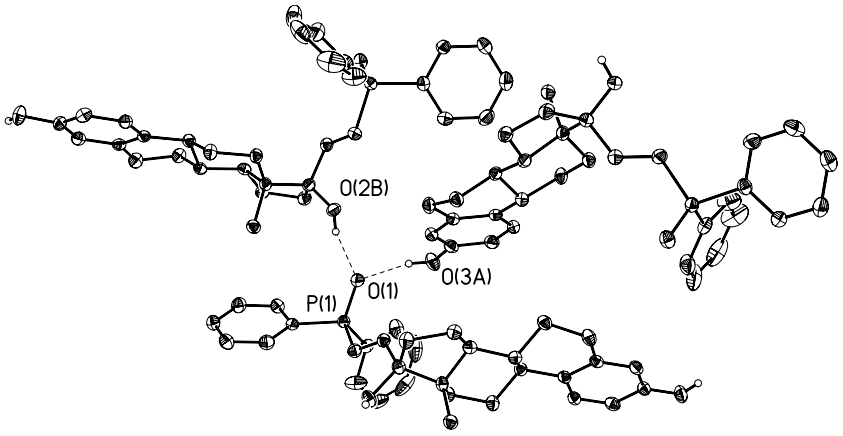


Fig. 4. The repeat unit from the polymeric framework of **2**. Thermal ellipsoids are shown at 50% probability.

a 1-dimensional polymer linked by hydrogen bonds between the phosphoryl oxygen and the 17-OH of an adjacent molecule. Compound **2** crystallizes in the non-centrosymmetric space group $P2_12_12_1$ with no solvent of crystallization. In contrast to the packing found in **1**, compound **2** exists as a 3-dimensional framework with each repeat unit comprised of three molecules of **2**. The individual units are held together by a bifurcated hydrogen bond between the phosphoryl oxygen, the 17-OH, and the 3-OH of the 3 adjacent molecules of **2** [31].

In summary, although simple propargyl alcohols generated mixtures of products in microwave-assisted hydrophosphinylation reactions, analogous reactions involving ethynyl steroids cleanly generated a single product under a variety of conditions. The aqueous catalytic reactions involving ethynyl steroids were also remarkably tolerant to oxygen and could be carried out under an atmosphere of air with no precaution for the removal of oxygen.

Table 3
Crystal data and structure refinement for **1** and **2**

Compound	**1**	**2**
Formula	$C_{39}H_{45}O_3P$	$C_{32}H_{35}O_3P$
Formula weight	592.72	498.57
Crystal system	Monoclinic	Orthorhombic
Space group	$P2_1$	$P2_12_12_1$
a (Å)	6.1340(13)	9.1595(11)
b (Å)	24.554(5)	13.2685(16)
c (Å)	10.957(2)	22.093(3)
α (°)	90	90
β (°)	104.523(3)	90
γ (°)	90	90
Temperature (K)	100(2)	100(2)
V (Å^3)	1597.6(6)	2685.1(6)
Z	2	4
θ_{max} (°)	26.43	26.41
D(calcd) (Mg m^{-3})	1.232	1.233
No. of reflections collected	18220	14767
No. of independent reflections	6411	5476
R ($I > 2\sigma(I)$)	0.0644	0.0381
Absolute structure parameters	−0.01(13)	−0.04(8)
GOF	0.996	1.030

4. Experimental

General considerations. Coupling reactions were carried out under an atmosphere of air. Diethyl ether, dichloromethane, and hexane were dried using a Grubbs-style solvent purification system. THF was dried by distillation from Na/benzophenone. Mestranol, ethynyl estradiol, ethisterone, diphenylphosphine oxide, DOPO, and ethyl phenylphosphinate were obtained from Aldrich and used as received. All yields are based upon isolated material unless specified. Electrospray ionization mass spectrometric (ESI-MS) data were recorded on a SCIEX Model API III+ operating in positive ion mode using acetonitrile as the solvent. Elemental analyses were performed by Midwest Microlabs. ^{1}H and ^{13}C{^{1}H} chemical shifts were determined by reference to residual protonated solvent resonances. All coupling constants are given in Hertz. ^{31}P{^{1}H} NMR spectra were referenced to external H_3PO_4 (0 ppm). Quantitative ^{31}P{^{1}H} NMR spectra were collected using an inverse-gated decoupling sequence with a recycle delay of 30 s. Ionizable hydrogens were identified using acetone-d_6 or DMSO-d_6 as the solvent. Microwave catalyzed reactions were carried out in 10 mL pressure tubes using a CEM Discover microwave reactor.

4.1. Preparation of **1** (solvent-free)

A microwave reactor vial was charged with ethisterone (0.10 g, 0.32 mmol), $(Ph_3P)_3RhCl$ (0.005 g, 5.4 μmol), a magnetic stirring bar, and $HP(O)Ph_2$ (0.065 g, 0.32 mmol). The vial was sealed, placed in the reactor, and irradiated. The microwave power was maintained between 70 and 75 W for the duration of the experiment. The desired temperature (125 °C) was reached after 5.0 min. After a total of 60 min irradiation, the vial was cooled to ambient temperature and triturated twice with diethyl ether (6 mL)

containing 9 drops of CH_2Cl_2. The solid was collected and dried under vacuum to afford 0.13 g (80%) of the title compound. Anal. Calc. for $C_{33}H_{39}O_3P$: C, 77.02; H, 7.64. Found: C, 76.70; H, 7.46. ESI-MS: $m/z = 515$ ($M + H^+$). ^1H NMR ($CDCl_3$, 25 °C): δ 7.70–7.64 (m, 4H, Ar-H), 7.52–7.41 (m, 6H, Ar-H), 7.05 (dd, 1H, $J = 20.2$, 16.4, =CH–), 6.51 (dd, 1H, $J = 27.0$, 16.3, =CH–), 5.72 (s, 1H, =CH–), 2.37–2.29 (m, 6H, –CH– or $–CH_2–$), 2.00–1.33 (m, 11H, –CH– or $–CH_2–$), 1.17 (m, 3H, $–CH_3$), 0.98 (s, 3H, $–CH_3$), 0.98–0.80 (m, 2H, –CH– or $–CH_2–$). ^1H NMR (acetone-d_6, 25 °C, only alcohols listed): δ 5.04 (br s, –OH). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 25 °C): δ 199.5 (s, C=O), 170.9 (s, quat), 155.6 (d, $J = 2.4$, *–C*=CP(O)–), 133.2 (d, $J = 105.3$, *ipso–*C_6H_5), 133.18 (d, $J = 105.3$, *ipso–*C_6H_5), 131.8 (d, $J = 3.1$, Ar-C), 131.7 (d, $J = 3.1$, Ar-C), 131.2 (d, $J = 5.4$, Ar-C), 131.1 (d, $J = 5.2$, Ar-C), 128.5 (d, $J = 11.5$, Ar-C), 123.9 (s, =CH–), 117.9 (d, $J = 101.9$, –C=*C*P(O)–), 84.8 (d, $J = 14.5$, quat), 53.1 (s, –CH–), 50.0 (s, –CH–), 47.3 (d, $J = 1.0$, quat), 38.5 (s, $–CH_2–$), 37.3 (s, quat), 36.3 (s, –CH–), 35.6 (s, $–CH_2–$), 33.9 (s, $–CH_2–$), 32.7 (s, $–CH_2–$), 32.3 (s, $–CH_2–$), 31.5 (s, $–CH_2–$), 23.8 (s, $–CH_2–$), 20.6 (s, $–CH_2–$), 17.4 (s, $–CH_3$), 14.2 (s, $–CH_3$). $^{31}P\{^1H\}$ NMR ($CDCl_3$, 25 °C): δ 22.9 (s).

4.2. Preparation of **2** (in water)

A microwave reactor vial was charged with ethynyl estradiol (0.10 g, 0.34 mmol), $(Me_2PhP)_3RhMe_3$ (0.006 g, 10 μmol), a magnetic stirring bar, $HP(O)Ph_2$ (0.068 g, 0.34 mmol), and water (1.5 mL). The vial was sealed, placed in the reactor, and irradiated. The microwave power was held at 150 W until the desired temperature (150 °C) was reached (2.0 min). The microwave power was decreased to 70–85 W for the remainder of the experiment in order to maintain the temperature. After a total irradiation time of 10 min, the reaction mixture was cooled and extracted with CH_2Cl_2. After drying the organic layer with $MgSO_4$, the volatiles were removed under vacuum, and the residue was triturated twice with diethyl ether (6 mL) containing 9 drops of CH_2Cl_2. The solid was collected and dried under vacuum to afford 0.126 g (75%) of the title compound. Anal. Calc. for $C_{32}H_{35}O_3P$: C, 77.09; H, 7.08. Found: C, 77.15; H, 7.09. ESI-MS: $m/z = 499$ ($M + H^+$). ^1H NMR ($CDCl_3$, 25 °C): δ 7.78–7.70 (m, 4H, Ar-H), 7.57–7.47 (m, 6H, Ar-H), 7.31 (dd, 1H, $J = 20.3$, 16.8, =C*H*–), 6.84 (d, 1H, $J = 8.4$, Ar-H), 6.70 (dd, 1H, $J = 8.4$, 2.4, Ar-H), 6.60 (m, 1H, Ar-H), 6.59 (dd, 1H, $J = 30.3$, 16.8, =C*H*–), 2.80–2.62 (m, 2H, –CH– or $–CH_2–$), 2.09–1.64 (m, 5H, –CH– or $–CH_2–$), 1.44–1.20 (m, 6H, –CH– or $–CH_2–$), 0.99 (m, 2H, –CH– or $–CH_2–$), 0.87 (s, 3H, $–CH_3$). ^1H NMR (acetone-d_6, 25 °C, only –OH groups): δ 8.87 (br s, –OH), 4.17 (s, –OH). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 25 °C): δ 156.5 (d, $J = 2.5$, *C*=CP–), 155.3 (s, quat), 137.5 (s, quat), 132.9 (d, $J = 110.2$, Ar-C), 132.8 (d, $J = 110.1$, Ar-C), 132.0 (d, $J = 2.9$, Ar-C), 131.9 (d, $J = 3.1$, Ar-C), 131.2 (d, $J = 10.1$, Ar-C), 131.0 (s, quat), 128.8 (d, $J = 7.5$, Ar-C), 128.6 (d, $J = 7.5$, Ar-C), 125.6 (s, Ar-C), 116.1 (d, $J = 102.6$, –C=*C*P–), 115.3 (s, Ar-C), 112.4 (s, Ar-C), 85.3 (d, $J = 14.3$, quat), 49.5 (s, –CH–), 47.6 (s, quat), 41.8 (s, –CH–), 38.8 (s, –CH–), 38.1 (s, $–CH_2–$), 32.3 (s, $–CH_2–$), 29.6 (s, $–CH_2–$), 27.1 (s, $–CH_2–$), 25.7 (s, $–CH_2–$), 23.5 (s, $–CH_2–$), 14.1 (s, $–CH_3$). $^{31}P\{^1H\}$ NMR ($CDCl_3$, 25 °C): δ 24.2 (s).

4.3. Preparation of **3** (in water)

A microwave reactor vial was charged with mestranol (0.10 g, 0.32 mmol), $(Me_2PhP)_3RhMe_3$ (0.006 g, 10 μmol), a magnetic stirring bar, $HP(O)Ph_2$ (0.064 g, 0.32 mmol), and water (1.5 mL). The reactor vial was sealed, placed in the reactor, and irradiated. The microwave power was held at 150 W until the desired temperature (150 °C) was reached (2.2 min). The microwave power was reduced to 70–80 W for the remainder of the experiment in order to maintain the temperature. After a total irradiation time of 10 min, the reaction mixture was cooled to ambient temperature and extracted with CH_2Cl_2. After drying the organic layer with $MgSO_4$, the volatiles were removed under vacuum, and the residue was triturated twice with diethyl ether (6 mL) containing 9 drops of CH_2Cl_2. The solid was collected and dried under vacuum to afford 0.134 g (81%) of the title compound. Anal. Calc. for $C_{33}H_{37}O_3P$: C, 77.32; H, 7.28. Found: C, 77.08; H, 7.15. ESI-MS: $m/z = 513$ ($M + H^+$). ^1H NMR ($CDCl_3$, 25 °C): δ 7.74–7.67 (m, 4H, Ar-H), 7.54–7.43 (m, 6H, Ar-H), 7.17 (d, 1H, $J = 9.0$, Ar-H), 7.13 (dd, 1H, $J = 19.8$, 16.7, –*H*C=CHP(O)–), 6.70 (dd, 1H, $J = 8.5$, 2.7, Ar-H), 6.63 (d, 1H, $J = 2.7$, Ar-H), 6.54 (dd, 1H, $J = 27.2$, 16.8, –HC=C*H*P(O)–), 3.78 (s, 3H, –OMe), 2.84 (m, 2H, $–CH_2–$), 2.27–1.21 (m, 13H, $–CH_2–$, –CH–), 0.97 (s, 3H, $–CH_3$). ^1H NMR (acetone-d_6, 25 °C, only –OH groups): δ 3.90 (br s, –OH). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 25 °C): δ 157.4 (s, quat), 155.9 (d, $J = 2.6$, *–C*=CHP(O)–), 137.9 (s, quat), 133.3 (d, $J = 105.1$, *ipso*-C_6H_5), 133.27 (d, $J = 105.1$, *ipso*-C_6H_5), 132.4 (s, quat), 131.8 (d, $J = 3.0$, Ar-C), 131.6 (d, $J = 3.0$, Ar-C), 131.3 (d, $J = 6.9$, Ar-C), 131.2 (d, $J = 6.6$, Ar-C), 128.6 (d, $J = 12.2$, Ar-C), 126.3 (s, Ar-C), 118.0 (d, $J = 102.1$, =*C*HP(O)–), 113.8 (s, Ar-C), 111.5 (s, Ar-C) 85.1 (d. $J = 14.5$, –*C*OH), 55.2 (s, –OMe), 49.6 (s, –CH–), 47.7 (s, quat), 43.4 (s, –CH–), 39.4 (s, –CH–), 37.5 (s, $–CH_2–$), 32.7 (s, $–CH_2–$), 29.7 (s, $–CH_2–$), 27.4 (s, $–CH_2–$), 26.2, (s, $–CH_2–$), 23.5 (s, $–CH_2–$), 14.2 (s, $–CH_3$). $^{31}P\{^1H\}$ NMR ($CDCl_3$, 25 °C): δ 23.2 (s).

4.4. Preparation of **4** (in THF)

A microwave reactor vial was charged with ethisterone (0.10 g, 0.32 mmol), $[Rh(cod)Cl]_2$ (0.002 g, 4.1 μmol), HP(O)(OEt)Ph (48.3 μL, 0.32 mmol), a magnetic stirring bar, and THF (3.0 mL). The vial was sealed, placed in the reactor, and irradiated for a total of 10 min. The microwave power was held at 220 W (3.0 min) until the desired

temperature was reached (150 °C). The microwave power decreased to 200–210 W for the remainder of the run to maintain the temperature. The vial was cooled to ambient temperature and the volatiles were removed under vacuum. The title compound was isolated as a colorless solid (0.085 g, 55%; 1:1.2 ratio of diastereomers) after purification of the reaction residue by column chromatography (silica gel, 30% THF in Et_2O). Anal. Calc. for $C_{29}H_{39}O_4P$: C, 72.18; H, 8.15. Found: C, 71.90; H, 8.14. ESI-MS: $m/z = 484$ ($M + H^+$). ^1H NMR (both diastereomers, $CDCl_3$, 23 °C): δ 7.80 (m, 2H, Ar-H), 7.49 (m, 3H, Ar-H), 6.99 (dd, 1H, $J = 20.8$, 17.0, =CH–), 6.16 (dd, $J = 17.0$, 23.5, =CH–), 6.14 (dd, $J = 17.0$, 24.0, =CH–), 5.74 (s, 1H, =CH–), 4.05 (m, 2H, –O*C*H_2CH$_3$), 2.37 (m, 4H, –CH_2–, –CH–), 2.10–0.85 (m, 15H, –CH_2–, –CH–), 1.32 (t, 3H, $J = 7.0$, –OCH$_2$*C*H$_3$), 1.19 (s, –CH_3), 1.17 (s, –CH_3), 0.97 (s, –CH_3), 0.95 (s, –CH_3). ^1H NMR (acetone-d_6, 25 °C, only alcohols listed): δ 4.11 (br s, –O*H*, one diastereomer), 3.79 (br s, –O*H*, second diastereomer). $^{13}C\{^1H\}$ NMR (both diastereomers, $CDCl_3$, 25 °C): δ 199.4 (s, –C=O), 170.7 (s, quat), 155.9 (d, $J = 4.9$, –*C*=CP(O)), 155.8 (d, $J = 4.7$, –*C*=CP(O)), 132.1 (d, $J = 2.6$, Ar-C), 131.54 (d, $J = 136.4$, quat), 131.51 (d, $J = 136.7$, quat), 131.3 (d, $J = 10.2$, Ar-C), 131.2 (d, $J = 10.2$, Ar-C), 128.5 (d, $J = 13.2$, Ar-C), 123.9 (s, Ar-C), 117.3 (d, $J = 136.3$, –C=*C*P(O)), 84.6 (d, $J = 16.1$, quat), 84.5 (d, $J = 16.4$, Ar-C), 60.7 (d, $J = 5.9$, –O*C*H$_2$CH$_3$), 53.2 (s, –CH–), 53.1 (s, –CH–), 50.0 (s, –CH–), 47.2 (s, quat), 47.1 (s, quat), 38.5 (s, quat), 37.2 (m, –CH_2–), 36.3 (s, –CH–), 35.6 (s, –CH_2–), 33.9 (s, –CH_2–), 32.7 (s, –CH_2–), 32.3 (s, –CH_2–), 32.2 (s, –CH_2–), 31.5 (s, –CH_2–), 23.7 (s, –CH_2–), 20.6 (s, –CH_2–), 20.5 (s, –CH_2–), 17.3 (s, –CH_3), 16.51 (d, $J = 7.7$, –CH$_2$*C*H$_3$), 16.48 (d, $J = 6.7$, –CH_2CH$_3$), 14.2 (s, –CH_3). $^{31}P\{^1H\}$ NMR (both diastereomers, $CDCl_3$, 25 °C): δ 30.14 (s, one diastereomer), 30.10 (s, second diastereomer).

4.5. Preparation of **5** (in THF)

A microwave reactor vial was charged with ethynyl estradiol (0.10 g, 0.34 mmol), $[Rh(cod)Cl]_2$ (0.002 g, 4.1 μmol), HP(O)(OEt)Ph (50.1 μL, 0.34 mmol), a magnetic stirring bar, and THF (3.0 mL). The vial was sealed, placed in the reactor, and irradiated for a total of 10 min. The microwave power was held at 220 W (3.0 min) until the desired temperature was reached (150 °C). The microwave power decreased to 200–210 W for the remainder of the run to maintain the temperature. The vial was cooled to ambient temperature and the volatiles were removed under vacuum. The title compound was isolated as a colorless solid (0.065 g, 41%; 1:1 ratio of diastereomers) after purification of the reaction residue by column chromatography (silica gel, 30% THF in Et_2O). Anal. Calc. for $C_{28}H_{35}O_4P$: C, 72.08; H, 7.56. Found: C, 71.90; H, 8.14. ESI-MS: $m/z = 467$ ($M + H^+$). ^1H NMR (both diastereomers, $CDCl_3$, 23 °C): δ 7.90–7.65 (m, 2H, Ar-H), 7.57–7.47 (m, 3H, Ar-H), 7.25–7.08 (m, 2H, =C*H*– and Ar-H), 6.84–6.55 (m, 3H, Ar-H), 4.18–3.99 (m, 2H, –OCH_2–), 2.80–2.62 (m, 2H, –CH– or –CH_2–), 2.09–1.64 (m, 5H, –CH– or –CH_2–), 1.44–0.99 (m, 13H, –CH– or –CH_2–), 0.87 (s, 3H, –CH_3). ^1H NMR (acetone-d_6, 25 °C, only –OH groups): δ 9.00 (br s, –OH), 4.20 (s, –OH). $^{13}C\{^1H\}$ NMR (both diastereomers, $CDCl_3$, 25 °C): δ 157.7 (d, $J = 5.4$, =CH), 157.5 (d, $J = 5.4$, =CH), 154.70 (s, quat), 154.67 (s, quat), 142.8 (s, quat), 137.6 (s, quat), 132.8 (d, $J = 66.8$, quat), 132.7 (d, $J = 66.7$, quat), 132.4 (d, $J = 2.8$, Ar-H), 132.3 (d, $J = 3.7$, Ar-H), 131.18 (d, $J = 10.3$, Ar-H), 131.13 (d, $J = 10.4$, Ar-H), 128.69 (d, $J = 18.5$, Ar-H), 128.5 (d, $J = 18.9$, Ar-H), 125.8 (s, Ar-H), 115.4 (d, $J = 136.9$, =CH), 115.3 (s, Ar-H), 115.2 (d, $J = 136.9$, =CH), 112.4 (s, Ar-H), 84.1 (d, $J = 4.9$, quat), 84.9 (d, $J = 4.8$, quat), 61.33 (d, $J = 5.8$, –OCH_2–), 61.25 (d, $J = 5.8$, –OCH_2–), 49.5 (s, –CH–), 47.6 (s, quat), 47.5 (s, quat), 42.1 (s, –CH–), 42.0 (s, –CH–), 38.9 (s, –CH–), 38.1 (s, –CH_2–), 37.9 (s, –CH_2–), 32.4 (s, –CH_2–), 32.2 (s, –CH_2–), 29.9 (s, –CH_2–), 27.1 (s, –CH_2–), 25.8 (s, –CH_2–), 25.7 (s, –CH_2–), 23.4 (s, –CH_2–), 16.43 (d, $J = 6.7$, –CH_3), 16.39 (d, $J = 6.7$, –CH_3), 14.1 (s, –CH_3). $^{31}P\{^1H\}$ NMR (both diastereomers, $CDCl_3$, 25 °C): δ 32.8 (s, one diastereomer), 31.9 (s, second diastereomer).

4.6. Preparation of **6** (in THF)

A microwave reactor vial was charged with mestranol (0.10 g, 0.32 mmol), $[Rh(cod)Cl]_2$ (0.002 g, 4.1 μmol), HP(O)(OEt)Ph (48.3 μL, 0.32 mmol), a magnetic stirring bar, and THF (3.0 mL). The vial was sealed, placed in the reactor, and irradiated for a total of 10 min. The microwave power was held at 220 W (3.0 min) until the desired temperature was reached (150 °C). The microwave power was decreased to 210 W for the remainder of the run to maintain the temperature. The vial was cooled to ambient temperature and the volatiles were removed under vacuum. The title compound was isolated as a colorless solid (0.090 g, 58%; 1:1.5 ratio of diastereomers) after purification of the reaction residue by column chromatography (silica gel, THF/Et_2O 3:10). Anal. Calc. for $C_{29}H_{37}O_4P$: C, 72.48; H, 7.76. Found: C, 72.26; H, 8.04. ESI-MS: $m/z = 482$ ($M + H^+$). ^1H NMR (both diastereomers, $CDCl_3$, 25 °C): δ 7.80 (m, 2H, Ar-H), 7.47 (m, 3H, Ar-H), 7.18 (m, 1H, Ar-H), 7.08 (dd, 1H, $J = 20.4$, 16.2, =CH–), 6.70 (m, 1H, Ar-H), 6.64 (m, 1H, Ar-H), 6.193 (dd, $J = 23.5$, 16.9, =CH–), 6.190 (dd, $J = 24.3$, 16.8, =CH–), 4.03 (m, 2H, –O*C*H_2CH$_3$), 3.78 (s, –OCH_3), 3.77 (s, –OCH_3), 2.85 (m, 2H, –CH– or –CH_2–), 2.17–1.26 (m, 13 H, –CH–, –CH_2–), 1.34 (t, $J = 7.0$, –OCH$_2$C*H*$_3$), 1.33 (t, $J = 7.0$, –OCH$_2$C*H*$_3$), 0.96 (s, –CH_3), 0.94 (s, –CH_3). ^1H NMR (both diastereomers, acetone-d_6, 25 °C, only –OH groups): δ 4.40 (br s, –OH). $^{13}C\{^1H\}$ NMR (both diastereomers, $CDCl_3$, 25 °C): δ 157.4 (s, quat), 156.4 (d, $J = 4.7$, –*C*=CP(O)), 156.3 (d, $J = 4.6$, –*C*=CP(O)), 137.9 (s, quat), 132.4 (s, quat), 132.3 (s, quat), 132.1 (d, $J = 2.8$, Ar-C), 131.61 (d, $J = 136.9$, quat), 131.59 (d, $J = 137.2$, quat), 131.26 (d, $J = 9.9$, Ar-C), 131.24 (d,

$J = 10.4$, Ar-C), 128.5 (d, $J = 12.9$, Ar-C), 126.2 (s, Ar-C), 117.14 (d, $J = 136.2$, –C=*C*P(O)), 117.05 (d, $J = 135.9$, –*C*=CP(O)), 113.7 (s, Ar-C), 111.4 (s, Ar-C), 84.8 (d, $J = 16.3$, quat), 84.7 (d, $J = 16.3$, quat), 60.7 (d, $J = 5.8$, –O*C*H_2CH$_3$), 55.2 (s, –OMe), 49.6 (s, –CH–), 47.7 (s, quat), 47.6 (s, quat), 43.43 (s, –CH–), 43.37 (s, –CH–), 39.43 (s, –CH–), 39.40 (s, –CH–), 37.3 (s, –CH_2–), 32.6 (s, –CH_2–), 32.5 (s, –CH_2–), 29.7 (s, –CH_2–), 27.4 (s, –CH_2–), 26.2 (s, –CH_2–), 26.1 (s, –CH_2–), 23.5 (s, –CH_2–), 16.52 (d, $J = 6.5$, –OCH$_2$*C*H$_3$), 16.50 (d, $J = 6.7$, –OCH$_2$*C*H$_3$), 14.2 (s, –CH_3). $^{31}P\{^1H\}$ NMR (both diastereomers, $CDCl_3$, 25 °C): δ 30.3 (s, one diastereomer), 30.2 (s, second diastereomer).

4.7. Preparation of **7** (in water)

A microwave reactor vial was charged with ethisterone (0.10 g, 0.32 mmol), $(Me_2PhP)_3RhMe_3$ (0.006 g, 10 μmol), a magnetic stirring bar, DOPO (0.070 g, 0.32 mmol), and water (1.5 mL). The reactor vial was sealed, placed in the microwave, and irradiated. The microwave power held at 150 W (2.0 min) until the desired temperature was reached (150 °C). The microwave power was decreased to 70–80 W for the remainder of the experiment in order to maintain the temperature. After a total irradiation time of 15 min, the vial was cooled and extracted with CH_2Cl_2. After drying with $MgSO_4$ the volatiles were evaporated under vacuum. The crude residue was purified by column chromatography (40% THF in ether) to afford 0.071 g (42%; 1:1.4 ratio of diastereomers) of the title compound as an off-white solid. Anal. Calc. for $C_{33}H_{37}O_4P$: C, 74.98; H, 7.05. Found: C, 74.90, H, 7.06. ESI-MS: $m/z = 529$ ($M + H^+$). ^1H NMR (both diastereomers, $CDCl_3$, 25 °C): δ 8.01–7.92 (m, 2H, Ar-H), 7.82–7.70 (m, 2H, Ar-H), 7.49 (m, 1H, Ar-H), 7.34 (m, 1H, Ar-H), 7.25 (m, 2H, Ar-H), 6.99 (dd, $J = 16.8$, 22.3, =CH–), 6.95 (dd, $J = 17.0$, 22.5, =CH–), 6.18 (dd, $J = 16.8$, 16.8, =CH–), 6.10 (dd, $J = 16.8$, 16.8, =CH–), 5.77 (s, 1H, =CH–), 2.45–2.30 (m, 4H, –CH– or –CH_2–), 2.03 (m, 2H, –CH– or –CH_2–), 1.85 (m, 2H, –CH– or –CH_2–), 1.76–1.34 (m, 8H, –CH– or –CH_2–), 1.20 (s, –CH_3), 1.18 (s, –CH_3), 0.96 (s, –CH_3), 0.94 (s, –CH_3), 0.93 (m, 3H, –CH– or –CH_2–). ^1H NMR (acetone-d_6, 25 °C, only alcohols listed): δ 4.13 (br s, –O*H*, one diastereomer), 4.09 (br s,–O*H*, second diastereomer). $^{13}C\{^1H\}$ NMR (both diastereomers, $CDCl_3$, 25 °C): δ 199.44 (s, –C=O), 199.42 (s, –C=O), 170.9 (s, quat), 170.8 (s, quat), 158.9 (d, $J = 5.6$, –*C*=CP(O)),158.4 (d, $J = 5.1$, –*C*=CP(O)), 149.1 (d, $J = 8.4$, quat), 149.0 (d, $J = 8.5$, quat), 135.6 (d, $J = 5.5$, quat), 133.1 (d, $J = 2.3$, Ar-C), 133.0 (d, 2.4, Ar-C), 130.45 (s, Ar-C), 130.40 (s, Ar-C), 130.4 (d, $J = 11.8$, Ar-C), 130.3 (d, $J = 12.2$, Ar-C), 128.31 (d, $J = 13.9$, Ar-C), 128.27 (d, $J = 14.0$, Ar-C), 125.1 (s, Ar-C), 125.0 (s, Ar-C), 124.8 (d, $J = 129.4$, quat), 124.53 (s, Ar-C), 124.52 (s, Ar-C), 124.0 (s, Ar-C), 123.9 (s, Ar-C), 123.8 (d, $J = 9.58$, Ar-C), 122.5 (d, $J = 11.0$, Ar-C), 122.4 (d, $J = 11.4$, Ar-C), 120.6 (d, $J = 6.0$, Ar-C), 120.5 (d, $J = 6.1$, Ar-C), 115.2 (d, $J = 138.5$, –C=*C*P(O)), 114.9 (d, $J = 139.5$, –C=*C*P(O)), 84.6 (d, $J = 17.2$, quat), 84.5 (d, $J = 17.1$, quat), 53.2 (s, –CH–), 53.1 (s, –CH–), 50.2 (s, –CH–), 49.9 (s, –CH–), 47.2 (d, $J = 1.1$, quat), 47.1 (d, $J = 0.9$, quat), 38.51 (s, quat), 38.50 (s, quat), 37.1 (s, –CH_2–), 37.0 (s, –CH_2–), 36.22 (s, –CH–), 36.19 (s, –CH–), 35.7 (s, –CH_2–), 35.6 (s, –CH_2–), 33.9 (s, –CH_2–), 32.6 (s, –CH_2–), 32.3 (s, –CH_2–), 32.0 (s, –CH_2–), 31.5 (s, –CH_2–), 31.4 (s, –CH_2–), 23.8 (s, –CH_2–), 23.7 (s, –CH_2–), 20.6 (s, –CH_2–), 20.4 (s, –CH_2–), 17.30 (s, –CH_3), 17.2 (s, –CH_3), 14.1 (s, –CH_3), 14.0 (s, –CH_3). $^{31}P\{^1H\}$ NMR (both diastereomers, $CDCl_3$, 25 °C): δ 23.2 (s, one diastereomer), 23.0 (s, second diastereomer).

4.8. Preparation of **8** (in water)

A microwave reactor vial was charged with ethynyl estradiol (0.10 g, 0.34 mmol), $(PhMe_2P)_3RhMe_3$ (0.006 g, 10 μmol), a magnetic stirring bar, water (1.5 mL), and DOPO (0.070 g, 0.32 mmol). The vial was sealed, placed in the microwave, and irradiated. The microwave power was held at 150 W (2.4 min) until the desired temperature was reached (150 °C). The microwave power was decreased to 70–80 W for the remainder of the experiment to maintain the temperature. After a total irradiation time of 15 min, the reaction mixture was cooled and extracted with CH_2Cl_2. After drying with $MgSO_4$ the volatiles were evaporated under vacuum. The crude residue was purified by column chromatography (40% THF in ether) to afford 0.099 g (57%; 1:1.3 ratio of diastereomers) of the title compound as a off-white solid. Anal. Calc. for $C_{32}H_{33}O_4P$: C, 74.98; H, 6.49. Found: C, 75.25, H, 7.02. ESI-MS: $m/z = 513$ ($M + H^+$). ^1H NMR (both diastereomers, $CDCl_3$, 25 °C): δ 8.00 (m, 2H, Ar-H), 7.74 (m, 2H, Ar-H), 7.59–7.26 (m, 5H, Ar-H and =CH–), 6.93 (m, 1H, Ar-H), 6.77 (m, 1H, Ar-H), 6.60 (m, 1H, Ar-H), 6.22 (dd, 1H, $J = 27.7$, 16.8, =CH–), 2.75 (m, 2H, –CH– or –CH_2–), 2.04 (m, 2H, –CH– or –CH_2–), 1.90–1.67 (m, 3H, –CH– or –CH_2–), 1.54–1.15 (m, 6H, –CH– or –CH_2–), 1.00 (m, 2H, –CH– or –CH_2–), 0.87 (s, –CH_3), 0.85 (s, –CH_3–). ^1H NMR (both diastereomers, DMSO-d_6, 25 °C, only –OH groups): δ 9.03 (br s, –OH), 5.01 (br s, –OH). $^{13}C\{^1H\}$ NMR (both diastereomers, $CDCl_3$, 25 °C): δ 160.9 (d, 5.4, *C*=C–P(O)), 160.6 (d, 5.8, *C*=C–P(O)), 154.9 (s, quat), 148.9 (d, $J = 2.4$, quat), 148.8 (d, $J = 2.4$, quat), 137.6 (s, quat), 135.5 (d, $J = 5.0$, quat), 135.4 (d, $J = 5.3$, quat), 133.2 (d, $J = 2.04$, Ar-C), 131.3 (s, quat), 131.2 (s, quat), 130.6 (s, Ar-C), 130.4 (d, $J = 12.8$, Ar-C), 130.2 (d, $J = 13.3$, Ar-C), 128.43 (d, $J = 14.1$, Ar-C), 128.38 (d, $J = 14.8$, Ar-C), 125.9 (s, Ar-C), 125.8 (s, Ar-C), 125.2 (s, Ar-C), 124.7 (s, Ar-C), 124.6 (d, $J = 131.0$, quat), 124.55 (d, $J = 130.6$, quat), 124.0 (d, $J = 10.2$, Ar-C), 123.8 (d, $J = 10.2$, Ar-C), 122.2 (d, $J = 11.3$, Ar-C), 122.1 (d, $J = 11.5$, Ar-C), 120.7 (d, $J = 6.04$, Ar-C), 115.3 (s, Ar-C), 115.2 (s, Ar-C), 113.4 (d, $J = 142.2$, –C=*C*P(O)), 113.2 (d, $J = 141.6$, –C=*C*P(O)), 112.5 (s, Ar-C), 112.4 (s, Ar-C), 85.2 (d, $J = 16.9$, quat), 85.16 (d,

$J = 17.1$, quat), 49.7 (s, –CH–), 49.6 (s, –CH–), 47.7 (s, quat), 42.1 (s, –CH–), 41.9 (s, –CH–), 38.8 (s, –CH–), 38.1 (s, $–CH_2–$), 37.9 (s, $–CH_2–$), 32.4 (s, $–CH_2–$), 32.3 (s, $–CH_2–$), 29.64 (s, $–CH_2–$), 29.59 (s, $–CH_2–$), 27.1 (s, $–CH_2–$), 25.9 (s, $–CH_2–$), 25.7 (s, $–CH_2–$), 23.5 (s, $–CH_2–$), 14.1 (s, –Me), 14.0 (s, –Me). $^{31}P\{^1H\}$ NMR (both diastereomers, $CDCl_3$, 25 °C): δ 25.2 (s, one diastereomer), 24.1 (s, second diastereomer).

4.9. Preparation of **9** (in water)

A microwave reactor vial was charged with mestranol (0.10 g, 0.32 mmol), $(Me_2PhP)_3RhMe_3$ (0.006 g, 10 μmol), a magnetic stirring bar, water (1.5 mL), and DOPO (0.070 g, 0.32 mmol). The vial was sealed, placed in the microwave reactor, and irradiated. The microwave power was held at 150 W (2.2 min) until the desired temperature was reached (150 °C). The microwave power was decreased to 70–76 W for the remainder of the experiment to maintain the temperature. After a total irradiation time of 15 min, the reaction mixture was cooled and extracted with CH_2Cl_2. After drying with $MgSO_4$ the volatiles were evaporated under vacuum. The crude residue was purified by column chromatography (40% THF in ether) to afford 0.084 g (50%; 1:1.7 ratio of diastereomers) of the title compound as a off-white solid. Anal. Calc. for $C_{33}H_{35}O_4P$: C, 75.27; H, 6.70. Found: C, 75.45, H, 7.05. ESI-MS: $m/z = 527$ $(M + H^+)$. ^1H NMR (both diastereomers, $CDCl_3$, 25 °C): δ 7.94 (m, 2H, Ar-H), 7.78 (m, 1H, Ar-H), 7.67 (m, 1H, Ar-H), 7.48 (m, 1H, Ar-H), 7.35 (m, 1H, Ar-H), 7.26–7.05 (m, 4H, Ar-H and =CH–), 6.73 (m, 1H, Ar-H), 6.65 (m, 1H, Ar-H), 6.21 (dd, $J = 16.9$, 24.3, =CH–), 6.13 (dd, $J = 17.0$, 24.8, =CH–), 3.79 (s, 3H, –OMe), 2.85 (m, 2H, $–CH_2–$ or –CH–), 2.30–1.70 (m, 6H, $–CH_2–$ or –CH–), 1.6–1.0 (m, 7H, $–CH_2–$ or –CH–), 0.92 (s, $–CH_3$), 0.91 (s, $–CH_3$). ^1H NMR (both diastereomers, DMSO-d_6, 25 °C, only –OH groups): δ 5.08 (br s, –OH, one diastereomer), 5.03 (br s, –OH, second diastereomer). $^{13}C\{^1H\}$ NMR (both diastereomers, $CDCl_3$, 25 °C): δ 159.3 (d, 5.7, *C*=C–P(O)), 158.8 (d, 5.3, *C*=C–P(O)), 157.41 (s, quat), 157.40 (s, quat), 149.1 (d, $J = 7.9$, quat), 149.0 (d, $J = 7.3$, quat), 137.84 (s, quat), 137.81 (s, quat), 135.63 (d, $J = 5.9$, quat), 135.61 (d, $J = 5.51$, quat), 133.0 (d, $J = 2.3$, Ar-C), 132.9 (d, $J = 2.3$, Ar-C), 130.43 (s, Ar-C), 130.38 (s, Ar-C), 130.38 (d, $J = 11.9$, Ar-C), 130.35 (d, $J = 12.5$, Ar-C), 128.3 (d, $J = 14.0$, Ar-C), 128.2 (d, $J = 14.0$, Ar-C), 126.2 (s, Ar-C), 125.1 (s, Ar-C), 125.0 (s, Ar-C), 124.9 (d, $J = 129.2$, quat),124.5 (s, Ar-C), 123.74 (d, $J = 9.6$, Ar-C), 123.71 (d, $J = 9.7$, Ar-C), 122.6 (d, $J = 11.1$, quat), 122.5 (d, $J = 11.3$, quat), 120.7 (d, $J = 6.0$, Ar-C), 120.5 (d, $J = 6.0$, Ar-C), 115.1 (d, $J = 138.4$, –C=*C*–P(O)), 114.9 (d, $J = 139.5$, –C=*C*–P(O)), 113.7 (s, Ar-C), 111.5 (s, Ar-C), 84.75 (d, $J = 17.2$, quat), 84.73 (d, $J = 17.1$, quat), 55.2 (s, –OMe), 49.7 (s, –CH–), 49.4 (s, –CH–), 47.6 (s, quat), 47.5 (s, quat), 43.33 (s, –CH–), 43.27 (s, –CH–), 39.4 (s, –CH–), 39.3 (s, –CH–), 37.2 (s, $–CH_2–$), 37.0 (s, $–CH_2–$), 32.5 (s, $–CH_2–$), 32.2 (s, $–CH_2–$), 29.7 (s, $–CH_2–$), 27.4 (s, $–CH_2–$), 26.2 (s, $–CH_2–$), 26.1 (s, $–CH_2–$), 23.5 (s, $–CH_2–$), 23.4 (s, $–CH_2–$), 14.1 (s, -Me), 14.0 (s, –Me). $^{31}P\{^1H\}$ NMR (both diastereomers, $CDCl_3$, 25 °C): δ 24.0 (s, one diastereomer), 23.7 (s, second diastereomer).

4.10. Crystallographic studies

*Compounds **1** and **2***. A colorless crystal was selected under oil under ambient conditions and attached to the tip of a nylon loop. The crystal was mounted in a stream of cold nitrogen at 100(2) K and centered in the X-ray beam by using a video camera. The crystal evaluation and data collection were performed on a Bruker CCD-1000 diffractometer with Mo Kα ($\lambda = 0.71073$ Å) radiation and the diffractometer to crystal distance of 4.9 cm. The initial cell constants were obtained from three series of ω scans at different starting angles. The reflections were successfully indexed by an automated indexing routine built in the SMART program. The final cell constants were calculated from a set of strong reflections from the actual data collection. The data were collected by using the hemisphere data collection routine. The reciprocal space was surveyed to the extent of a full sphere to a resolution of 0.80 Å. The highly redundant datasets were corrected for Lorentz and polarization effects. The absorption correction was based on fitting a function to the empirical transmission surface as sampled by multiple equivalent measurements [32]. A successful solution by the direct methods provided most non-hydrogen atoms from the *E*-map. The remaining non-hydrogen atoms were located in an alternating series of least-squares cycles and difference Fourier maps. All non-hydrogen atoms were refined with anisotropic displacement coefficients. All hydrogen atoms were included in the structure factor calculation at idealized positions and were allowed to ride on the neighboring atoms with relative isotropic displacement coefficients. For **1**, the final least-squares refinement of 391 parameters against 6411 data resulted in residuals R (based on F^2 for $I \geqslant 2\sigma$) and wR (based on F^2 for all data) of 0.0644 and 0.1315, respectively. There is also one molecule of solvate (benzene) in the asymmetric unit of **1**. For **2**, the final least-squares refinement of 328 parameters against 5476 data resulted in residuals R (based on F^2 for $I \geqslant 2\sigma$) and wR (based on F^2 for all data) of 0.0381 and 0.0937, respectively. The final difference Fourier maps were featureless.

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Appendix A. Supporting information

Synthetic procedures and characterization data for **1**–**9** as well as representative ^{1}H and $^{31}P\{^{1}H\}$ NMR spectra. The crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center (**1**: 604600, **2**: 604601). This information can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jorganchem.2006.06.007.

References

[1] (a) X. Fu, L. Basickes, B.B. Wayland, Chem. Commun. (2003) 520;
(b) L.J. Higham, M.K. Whittlesey, P.T. Wood, Dalton Trans. (2004) 4202;
(c) S. Ribe, P. Wipf, Chem. Commun. (2001) 299;
(d) F. Joo, G. Laurenczy, L. Nadasdi, J. Elek, Chem. Commun. (1999) 971;
(e) H. Sakurai, T. Tsukuda, T. Hirao, J. Org. Chem. 67 (2002) 2721;
(f) G. Miao, P. Ye, L. Yu, C.M. Baldino, J. Org. Chem. 70 (2005) 2332;
(g) A. Svennebring, N. Garg, P. Nilsson, A. Hallberg, M. Larhed, J. Org. Chem. 70 (2005) 4720;
(h) L. Botella, C. Najera, J. Org. Chem. 70 (2005) 4360;
(i) R.B. DeVasher, L.R. Moore, K.H. Shaughnessy, J. Org. Chem. 69 (2004) 7919.

[2] (a) H. Akashi, K. Isobe, T. Shibahara, Inorg. Chem. 44 (2005) 3494;
(b) C. Torque, B. Sueur, J. Cabou, H. Bricout, F. Hapiot, E. Monflier, Tetrahedron 61 (2005) 4811.

[3] N.E. Leadbeater, Chem. Commun. (2005) 2881.

[4] J. Terao, A. Tang, J.J. Michels, A. Krivokapic, H.L. Anderson, Chem. Commun. (2004) 56.

[5] L.Y. Kuo, T.J.R. Weakley, K. Awana, C. Hsia, Organometallics 20 (2001) 4969.

[6] L. Leclercq, F. Hapiot, S. Tilloy, K. Ramkisoensing, J.N.H. Reek, P.W.N.M. van Leeuwen, E. Monflier, Organometallics 24 (2005) 2070.

[7] For reviews of hydrophosphinylation reactions and recent reports see:
(a) F. Alonso, I.P. Beletskaya, M. Yus, Chem. Rev. 104 (2004) 3079;
(b) A. Allen, D.R. Manke, W.B. Lin, Tetrahedron Lett. 41 (2000) 151;
(c) S. Deprele, J.L. Montchamp, J. Organomet. Chem. 643 (2002) 154;
(d) S. Deprele, J.L. Montchamp, J. Am. Chem. Soc. 124 (2002) 9386;
(e) P. Ribiere, K. Bravo-Altamirano, M.I. Antczak, J.D. Hawkins, J.L. Montchamp, J. Org. Chem. 70 (2005) 4064;
(f) L.B. Han, C. Zhang, H. Yazawa, S. Shimada, J. Am. Chem. Soc. 126 (2004) 5080;
(g) A. Allen, L. Ma, W.B. Lin, Tetrahedron Lett. 43 (2002) 3707;
(h) L.B. Han, C.Q. Zhao, S.Y. Onozawa, M. Goto, M. Tanaka, J. Am. Chem. Soc. 124 (2002) 3842;
(i) F. Mirzaei, L.B. Han, M. Tanaka, Tetrahedron Lett. 42 (2001) 297;
(j) J.F. Reichwein, M.C. Patel, B.L. Pagenkopf, Org. Lett. 3 (2001) 4303;
(k) C.Q. Zhao, L.B. Han, M. Tanaka, Organometallics 19 (2000) 4196;
(l) L.B. Han, R.M. Hua, M. Tanaka, Angew. Chem. Int. Ed. 37 (1998) 94;
(m) M.R. Douglass, T.J. Marks, J. Am. Chem. Soc. 122 (2000) 1824;
(n) A.M. Kawaoka, M.R. Douglass, T.J. Marks, Organometallics 22 (2003) 4630;
(o) M.R. Douglass, M. Ogasawara, S. Hong, M.V. Metz, T.J. Marks, Organometallics 21 (2002) 283;
(p) S. Gouault-Bironneau, S. Deprele, A. Sutor, J.L. Montchamp, Org. Lett. 7 (2005) 5909;
(q) I. Schlemminger, Y. Saida, H. Groger, W. Maison, N. Durot, H. Sasai, M. Shibasaki, J. Martens, J. Org. Chem. 65 (2000) 4818;
(r) J.R. Moncarz, N.F. Laritcheva, D.S. Glueck, J. Am. Chem. Soc. 124 (2002) 13356;
(s) J.R. Moncarz, T.J. Brunker, D.S. Glueck, R.D. Sommer, A.L. Rheingold, J. Am. Chem. Soc. 125 (2003) 1180;
(t) J.L. Montchamp, J. Organomet. Chem. 690 (2005) 2388;
(u) M. Tanaka, Top. Curr. Chem. 232 (2004) 25.

[8] L.B. Han, C.Q. Zhao, M. Tanaka, J. Org. Chem. 66 (2001) 5929.

[9] L.B. Han, Mirzaei, C.Q. Zhao, M. Tanaka, J. Am. Chem. Soc. 122 (2000) 5407.

[10] F. Jerome, F. Monnier, H. Lawicka, S. Derien, P.H. Dixneuf, Chem. Commun. (2003) 696.

[11] S. Deprele, J.L. Montchamp, Org. Lett. 6 (2004) 3805.

[12] M.D. Milton, G. Onodera, Y. Nishibayashi, S. Uemura, Org. Lett. 6 (2004) 3993.

[13] L.B. Han, Y. Ono, H. Yazawa, Org. Lett. 7 (2005) 2509.

[14] C.Q. Zhao, L.B. Han, M. Goto, M. Tanaka, Angew. Chem. Int. Ed. 40 (2001) 1929.

[15] R. Skoda-Foldes, L. Kollar, Chem. Rev. 103 (2003) 4095.

[16] (a) M.H. Herynk, Endocr. Rev. 25 (2005) 869;
(b) B. Hanstein, S. Djahansouzi, P. Dall, M.W. Beckmann, H.G. Bender, Eur. J. Endocrinol. 150 (2004) 243;
(c) C. Osipo, H. Liu, K. Meeke, V.C. Jordan, Exp. Biol. Med. 229 (2004) 722;
(d) K.R. Barnes, A. Kutikov, S.J. Lippard, Chem. Biol. 11 (2004) 557.

[17] R.G. Christiansen, M.R. Bell, T.E. D'Ambra, J.P. Mallamo, J.L. Herrmann, J.H. Ackerman, C.J. Opalka, R.K. Kullnig, R.C. Winneker, B.W. Snyder, F.H. Batzold, H.P. Schane, J. Med. Chem. 33 (1990) 2094.

[18] T.L. Popper, J.N. Gardner, R. Neri, H.L. Herzog, J. Med. Chem. 12 (1969) 393.

[19] R.B. Upasani, K.C. Yang, M. Acosta-Burruel, C.S. Konkoy, J.A. McLellan, R.M. Woodward, N.C. Lan, R.B. Carter, J.E. Hawkinson, J. Med. Chem. 40 (1997) 73.

[20] E.G. Occhiato, A. Ferrali, G. Menchi, A. Guarna, G. Danza, A. Comerci, R. Mancina, M. Serio, G. Garotta, A. Cavalli, M. De Vivo, M. Recanatini, J. Med. Chem. 47 (2004) 3546.

[21] I.I. Radu, D. Poirier, L. Provencher, Tetrahedron Lett. 43 (2002) 7617.

[22] A. Jackson, J. Davis, R.J. Pither, A. Rodger, M.J. Jannon, Inorg. Chem. 40 (2001) 3964.

[23] (a) R.A. Stockland Jr., R.I. Taylor, L.E. Thompson, P.B. Patel, Org. Lett. 7 (2005) 851;
(b) J.J. Stone, R.A. Stockland Jr., J. Kovach, J. Reyes Jr., C.C. Goodman, E.S. Tillman, J. Mol. Catal. A: Chem. 226 (2004) 11;
(c) G.F. Manbeck, A.J. Lipman, R.A. Stockland Jr., A.L. Freidl, A.F. Hasler, J.J. Stone, I.A. Guzei, J. Org. Chem. 70 (2005) 244.

[24] This complex is an attractive choice for aqueous organometallic chemistry since it was shown to polymerize ethylene in water: L. Wang, R.S. Lu, R. Bau, T.C. Flood, J. Am. Chem. Soc. 115 (1993) 6999.

[25] S.M. Nikles, M. Piao, A.M. Lane, D.E. Nikles, Green Chem. 3 (2001) 109.

[26] (a) F.J. Zeelen, E.W. Bergink, Structure–activity relationships of steroid estrogens, in: J. Raus, H. Martens, G. Leclercq (Eds.), Cytotoxic Estrogens in Hormone Receptive Tumors, Academic Press, London, 1980, pp. 39–48;
(b) J.P. Raynaud, T. Ojasoo, M.M. Bouton, E. Bignon, M. Pons, A. Crastes de Paulet, Structure–activity relationships of steroid estrogens, in: J.A. McLachlan (Ed.), Estrogens in the Environment, Elsevier, Amsterdam, 1985, pp. 24–42.

[27] M. Duncan, M.J. Gallagher, Org. Magn. Reson. 15 (1981) 37.

[28] M. Taillefer, H.J. Crisau, Tetrahedron Lett. 39 (1998) 7857.
[29] J. Reisch, J. Zappel, G. Henkel, N. Ekiz-Gucer, Monatsh. Chem. 124 (1993) 1169.
[30] T. Steiner, B. Lutz, J. van der Maas, N. Veldman, A.M.M. Schreurs, J. Kroon, J.A. Kanters, Chem. Commun. (1997) 191.
[31] This observation is intriguing since bifurcated hydrogen bonds are often critical components of molecular recognition P. Wallimann, T. Marti, A. Furer, F. Diederich, Chem. Rev. 97 (1997) 1567.
[32] Bruker-AXS (2000–2003) SADABS V.2.05, SAINT V.6.22, SHELXTL V.6.10 & SMART 5.622 Software Reference Manuals, Bruker-AXS, Madison, WI, USA.