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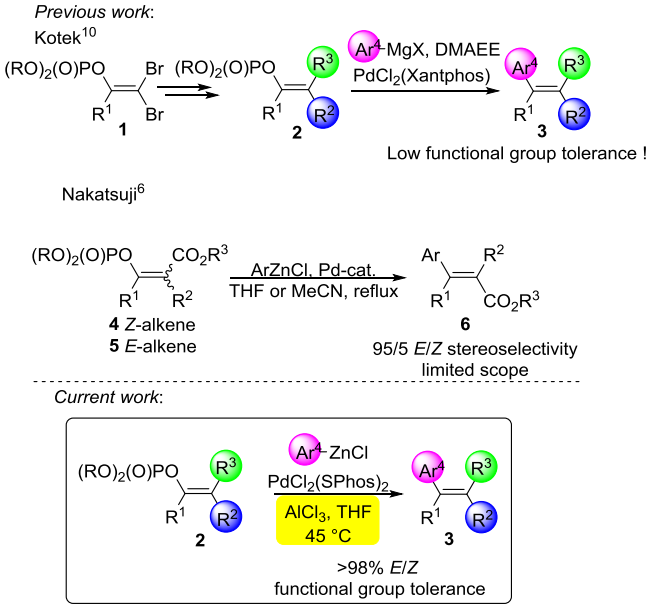
Aluminum chloride promoted cross-coupling of trisubstituted enol phosphates with organozinc reagents en route to stereoselective synthesis of tamoxifen and its analogues

Vladislav Kotek,[a] Peter Polák,[a] Hana Dvořáková,[b] and Tomáš Tobrman*[a]

Abstract: A new methodology for the stereoselective cross-coupling reaction of aryl zinc chlorides with trisubstituted enol phosphates is described. The developed methodology requires aluminum chloride as a promoter, and the reaction conditions tolerate various functional groups. The observed reactivity pattern of trisubstituted enol phosphates was used for the stereoselective preparation of tamoxifen and its analogues.

Introduction

Substrates bearing acyclic tetrasubstituted double bond form an important structural motif that has found many applications, for instance as biologically active compounds. The importance of tetrasubstituted alkenes can be illustrated by increasing effort placed on the stereoselective synthesis of tetrasubstituted alkenes.[1] The diversity of building blocks used for the synthesis of substituted alkenes has been reviewed.[2] Among these templates, mono-, di-, and trisubstituted enol phosphates play an important role, mainly due to their availability and variability. Thus, a wide variety of cross-coupling reactions of di- and trisubstituted enol phosphates have been reported.[3] Quite surprisingly, acyclic trisubstituted enol phosphates have found only a few applications in transition metal-catalyzed cross-coupling reactions. Their typical applications include copper(I) catalyzed methylation,[4] the Kumada-Corriu reaction,[5] and Suzuki and Negishi cross-coupling.[6] In addition to the above reports, transformations of trisubstituted enol phosphates, including elimination reactions,[7] radical processes[8] and heterocycle synthesis have been reported.[9] In a paper by Nakatsuji,[6] the stereoselective synthesis of tetrasubstituted alkenes was performed via the reaction of phosphates **4** or **6** with organozinc reagents under harsh reaction conditions (Scheme 1). Similarly, Brown[5] described the cross-coupling reactions of enol phosphates with Grignard reagents in THF at 70 °C.



Scheme 1. Overall scheme of the $AlCl_3$ promoted Negishi reaction of enol phosphates.

As part of our synthetic efforts, we have disclosed that the triply electrophilic template **1** can be transformed to the trisubstituted enol phosphates **2** in a highly stereoselective fashion (≥ 98% *E* or *Z*) using a two-fold Suzuki reaction.[10] Next, the introduction of the alkyl group was accomplished by coupling with the trialkylaluminum reagent, and aryl substituents were installed by the Kumada-Coriu coupling reaction using $PdCl_2(SPhos)_2$ and 2-[2-(dimethylamino)ethoxy]ethanol (DMAEE). Compared to the work of Nakatsuji, our protocol possesses several key advantages, including an improved stereochemical outcome of the process as well as a virtually general scope that would enable the synthesis of almost any tetrasubstituted alkene starting from simple and easily available dibromo enol phosphates. However, the high reactivity of Grignard reagents conflicts with the preparation of functionalized tetrasubstituted alkenes.

Results and Discussion

Therefore, we looked for a more convenient methodology for the introduction of aryl substituents into the molecule of phosphate **2** by a cross-coupling reaction with organometallic reagents. Similar to our first report,[10] dialkyl enol phosphates were used as the starting compounds because of their simple synthetic availability and better atom economy compared to diaryl enol

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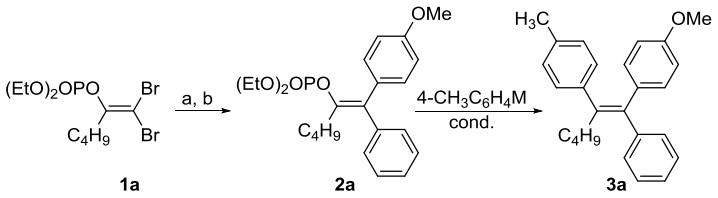
phosphates. Thus, the starting dibromo enol phosphate **1a** was converted to the phosphate **2a** using a two-fold cross-coupling reaction with phenylboronic acid and 4-methoxyphenylboronic acid.[10] Then, the phosphate **2a** reacted with 4-methylphenylboronic acid. A Pd-catalyzed reaction in toluene at 110 °C using various phosphine ligands gave yields of **3a** lower than 10% (Table 1, entries 1- 3). Decomposition of the starting compound was observed upon heating the reaction to 140 °C in *N*,*N*-dimethylacetamide (Table 1, entry 4). Ni catalysis was successful, leading to 100% conversion of **2a** to **3a**; however, a mixture of stereoisomers (*E*:*Z*/1:1) was formed according to the detailed ^{1}H NMR analysis of the crude reaction mixture. The Negishi cross-coupling reaction of **2a** with 4-methylphenylzinc chloride in THF at 70 °C was also unsuccessful, no matter what catalytic system was used (Table 1, entries 6-9). A considerably higher isolated yield of **3a** was observed if aluminum chloride[11] was used as an additive (Table 1, Entry 10). Careful ^{1}H and ^{13}C NMR spectra inspection showed that no changes in the double bond geometry occurred. The other tested Lewis acids, i.e. aluminum triflate, titanium chloride, boron trifluoride diethyl etherate, and tin chloride, failed to give the expected product **3a** (Table 1, entries 11-14). Application of a Grignard reagent as well as an organozinc reagent in the presence of magnesium chloride with aluminum chloride failed to give the alkene **3a** in high yield (Table 1, entries 15 and 16). On the other hand, treating **2a** with 4-$CH_3C_6H_4AlCl_2$ in the presence of $ZnCl_2$ gave the final product **3a** in 75% yield (Table 1, entry 17). Based on the findings presented in Table 1, (Entry 10) we reason that in the abovementioned case (Table 1, entry 17), an equilibrium transmetallation process must be operating in order to enable the cross-coupling reaction.

Table 1. Optimization of the cross-coupling reaction of the phosphate **2a** with 4-methylphenylboronic acid and 4-methylphenylzinc chloride. Reagents and conditions:(a) $PhB(OH)_2$, $Pd(OAc)_2$, $PPPh_3$, 2M K_3PO_4, toluene 45 °C; (b) 4-$MeOC_6H_4B(OH)_2$, $Pd(OAc)_2$, RuPhos, 2M K_3PO_4, toluene, 50 °C.



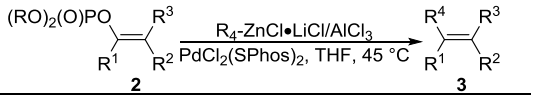
1a **2a** **3a**

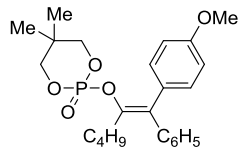
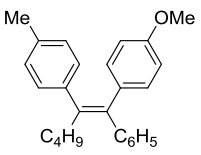
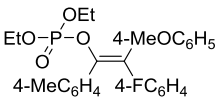
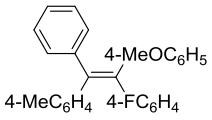
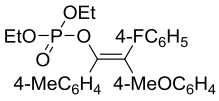
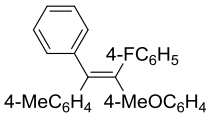
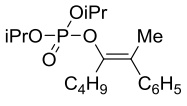
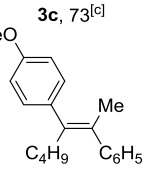
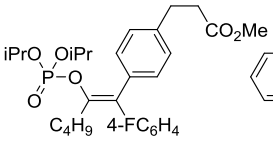
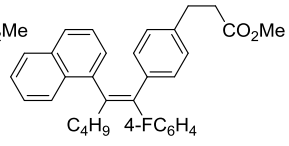
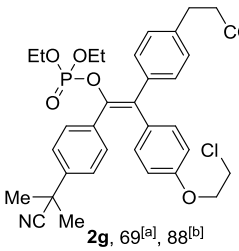
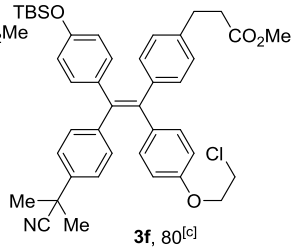
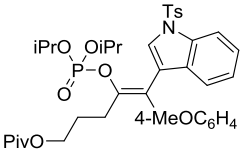
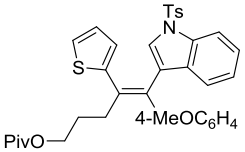
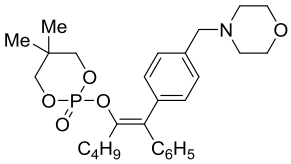
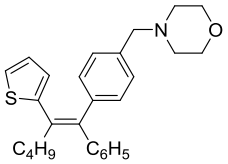
Entry	M[a]	Catalyst	Cond.	**3a** (%)
1	$B(OH)_2$	$PdCl_2(PPh_3)_2$	toluene, 110 °C, K_3PO_4	0
2	$B(OH)_2$	$PdCl_2(PCy_3)_2$	toluene, 110 °C, K_3PO_4	<10
3	$B(OH)_2$	$PdCl_2(SPhos)_2$	toluene, 110 °C, K_3PO_4	<10
4	$B(OH)_2$	$PdCl_2(SPhos)_2$	DMA, 140 °C, K_3PO_4	–[b]
5	$B(OH)_2$	$NiCl_2(PCy_3)_2$	toluene, 90 °C, K_3PO_4	100[c,d]
6	ZnCl•LiCl	$PdCl_2(PPh_3)_2$	THF, 70 °C	0
7	ZnCl•LiCl	$PdCl_2(PtBu_3)_2$	THF, 70 °C	<10
8	ZnCl•LiCl	PEPPSI-IPr	THF, 70 °C	<10
9	ZnCl•LiCl	$PdCl_2(SPhos)_2$	THF, 70 °C	<10
10	ZnCl•LiCl	$PdCl_2(SPhos)_2/AlCl_3$	THF, 45 °C	77
11	ZnCl•LiCl	$PdCl_2(SPhos)_2/Al(OTf)_3$	THF, 45 °C	0
12	ZnCl•LiCl	$PdCl_2(SPhos)_2/BF_3•Et_2O$	THF, 45 °C	–[b]
13	ZnCl•LiCl	$PdCl_2(SPhos)_2/TiCl_4$	THF, 45 °C	–[b]
14	ZnCl•LiCl	$PdCl_2(SPhos)_2/SnCl_4$	THF, 45 °C	0
15	MgCl	$PdCl_2(SPhos)_2/AlCl_3$	THF, 45 °C	<10
16	$ZnCl•MgCl_2•LiCl$	$PdCl_2(SPhos)_2/AlCl_3$	THF, 45 °C	<20
17	$AlCl_2•LiCl$	$PdCl_2(SPhos)_2/ZnCl_2$	THF, 45 °C	75

[a] Phosphate **2a** was prepared in 70% yield in two steps starting from **1a**[10] [b] Decomposition of starting compound was observed. [c] Conversion of the phosphate **2a** to the alkene **3a** [d] A mixture of *E*:*Z* (1:1) was obtained.

The optimized reaction conditions were used for the introduction of diverse aryl substituents. In contrast to the optimized results (Table 1, entry 10), a 4-tolyl substituent was introduced by the coupling reaction of the neopentyl glycol phosphate **2b** in 91% yield (Scheme 2, entry 1). Both *E* and *Z* stereoisomers **3b**,**c** were prepared by using phosphates **2c**,**d** as the starting compound. Thus, the present methodology enabled the regio- and stereoselective introduction four different aryl substituents while retaining the stereoselective configuration of the double bond (Scheme 2, entries 2 and 3). The methodology also tolerates sensitive ester and nitrile functional groups, as demonstrated by the preparation of alkenes **3e**,**f** (Scheme 2, entries 5 and 6). The $AlCl_3$-mediated coupling reaction also

allowed the introduction of hetaryl substituents, providing access to heteroaromatic tetrasubstituted alkenes (Scheme 2, Entry 7,8).

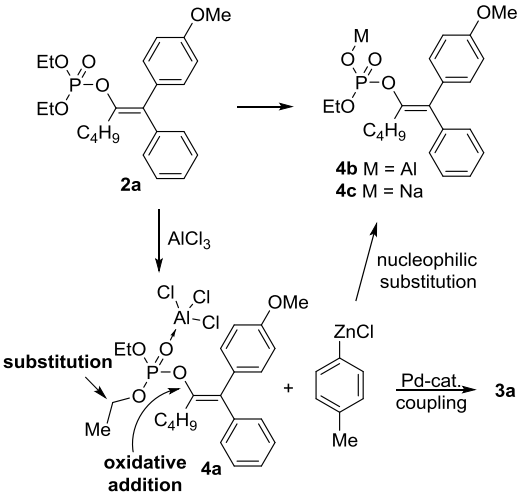


Entry	2	3
1	 **2b**, 83[a], 78[b]	 **3a**, 91[c]
2	 **2c**, 68[a], 89[b]	 **3b**, 74[c]
3	 **2d**, 71[a], 90[b]	 **3c**, 73[c]
4	 **2e**, 90[a], 88[b]	 **3d**, 78[c]
5	 **2f**, 86[a], 87[b]	 **3e**, 88[c]
6	 **2g**, 69[a], 88[b]	 **3f**, 80[c]
7	 **2h**, 88[a], 91[b]	 **3g**, 91[c]
8	 83[a], 81[b]	 **3h**, 90[c]

[a] Isolated yield of the first Suzuki reaction (%). [b] Isolated yield of the second Suzuki reaction (%). [c] Isolated yield (%).

Scheme 2. The $AlCl_3$ mediated reaction of trisubstituted enol phosphates **2**.

The significant yield dependence of the cross-coupling outcome on the structure of the phosphate ester during the preparation of alkenes **3a** drove us to study the reaction course in detail. Analogously to the McKenna reaction,[12] we reasoned that aluminum chloride is responsible for the cleavage of the Et–O bond, affording the product **4b** and lowering the yield of the coupling reaction. Thus, a model phosphate **2a** was mixed with 4-$CH_3C_6H_4ZnCl$•LiCl, and the resultant mixture was heated to 60 °C. No conversion of the starting phosphate **2a** to the product **4b** was observed within two days. When aluminum chloride was added to the reaction mixture, complete conversion to the product **4b** was observed. The structure of the observed product **4b** was confirmed as the sodium salt **4c** using HR MS. However, the cyclic phosphate **2b** was inert to decomposition even if heated to 60 °C in the presence of 4-$CH_3C_6H_4ZnCl$•LiCl and $AlCl_3$. Based on observed experimental evidence, we reasoned that the side product **4b** is formed via aluminum chloride-mediated nucleophilic substitution at the methylene center (Scheme 3). On the other hand, tris(*p*-tolyl)aluminum, and dichloro(*p*-tolyl)aluminum do not react with phosphate **2a** in the presence of $PdCl_2(SPhos)_2$ at 45 °C, excluding Zn–Al transmetalation as an alternative route of the coupling reaction. Therefore, analogously to the above case, we believe that coordination of $AlCl_3$ to the phosphate moiety facilitates oxidative addition of Pd(0) to O–C_{sp2} bond. However, precise role of aluminum chloride for the cross-coupling of trisubstituted enol phosphates is a subject of further studies.

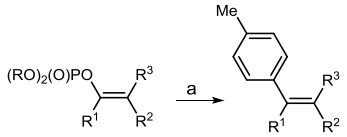


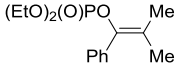
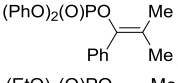
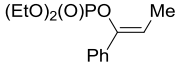
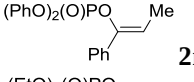
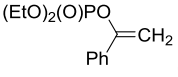
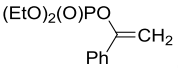
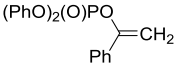
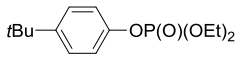
Scheme 3. A tentative role for $AlCl_3$ in the cross-coupling of trisubstituted phosphates with organozinc reagents.

Next, we investigated the reactivity of variously substituted diethyl enol phosphates **2j**-**l** in the aluminum chloride promoted cross-coupling reaction. In accordance with our previous observations, 100% conversion of the trisubstituted enol phosphate **2j** was observed in case of coupling with 4-tolylzinc

chloride in the presence of $AlCl_3$, giving the target alkene **3i** in 71% isolated yield (Table 2, entry 1). Running the reaction without $AlCl_3$ resulted in less than 30% conversion of the starting alkene **2j**. Moreover, the diphenyl enol phosphate **2k** coupled with an organozinc reagent without any additive afforded the alkene **3i** in 90% yield (Table 2, entry 2). The coupling reaction of disubstituted enol phosphate **2l** catalyzed by $PdCl_2(SPhos)_2$ or $PdCl_2$(dppf) did not proceed without aluminum chloride. The presence of $AlCl_3$ accelerated the reaction and the product **3j** was obtained in 86% isolated yield (Table 2, entry 3). However, diphenyl enol phosphate **2m** smoothly reacted with p-tolylzinc chloride without $AlCl_3$ if the reaction was catalyzed by $PdCl_2$(dppf) (Table 2, entry 4). A similar reactivity trend was also observed in the case of the 1,1-disubstituted enol phosphate **2n**. When the starting diethyl phosphate was coupled with 4-MeC_6H_4ZnCl•LiCl in $PdCl_2$(dppf) catalysis, incomplete conversion of the starting material was observed (Table 2, entry 5). The presence of $AlCl_3$ increased the conversion to 100%, although the yield of **3k** was 51% (Table 2, entry 6). In contrast, diphenyl phosphate **2o** was smoothly coupled without $AlCl_3$ at rt, affording the alkene **3k** in 90% isolated yield (Table 2, Entry 7). The aromatic phosphate **2p** did not react under the tested conditions (Table 2, entry 8).

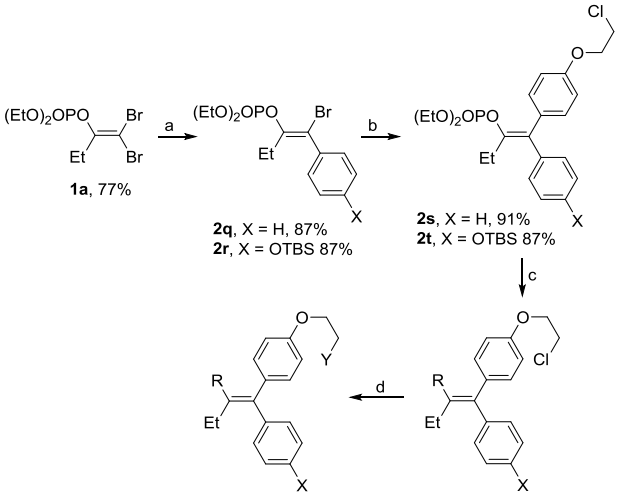
Table 2. The influence of enol phosphate double bond steric hindrance on the course of the Negishi cross-coupling reaction. Reagents and conditions: (a) 4-$CH_3C_6H_4ZnCl$•LiCl, $PdCl_2(SPhos)_2$, THF.



Entry	Phosphate	Temp. [°C], Time [h]	Conv.[a] [%]
1	 **2j**	45[b], 24	**3i**, 100,71[d](30[e])
2	 **2k**	45[c], 24	**3i**, 100, 90[d]
3	 **2l**	45[b], 8	**3j**,100, 86[d](0[e])
4	 **2m**	45[c], 9	**3j**, 100, 94[d]
5	 **2n**	rt[c], 24	**3k**, 80
6	 **2n**	rt[b,c], 24	**3k**, 100, 51[d]
7	 **2o**	rt[c], 24	**3k**, 100, 90[d]
8	 **2p**	45, 24	–[f]

[a] Conversion of starting phosphates [b] $AlCl_3$ was used as an additive. [c] $PdCl_2$(dppf) was used as a catalyst. [d] Isolated yield. [e] Conversion of starting phosphate in the reaction without $AlCl_3$.[f] No reaction.

In addition to an effort of other groups,[13] we performed the synthesis of tamoxifen (**3r**) and its analogues **3p**,**q** (Scheme 4). Following a previous report,[10] we prepared dibromo enol phosphate **1a** starting from propanal and bromoform. Then, the Suzuki reaction of **1a** with phenylboronic and 4-TBSO phenylboronic acid afforded substituted alkenes **2q**,**r** as the sole *Z*-stereoisomers. The second bromine atom substitution by the Suzuki reaction of **2q**,**r** with para substituted boronic acid was used for the introduction of a 2-chloroethoxyphenyl substituent to the *cis*-position. Subsequently, a Lewis acid-catalyzed Negishi reaction or the cross-coupling reaction with tribenzylaluminum, phenyl zinc chloride and ferrocenyl zinc chloride led to the tetrasubstituted alkenes **3l**-**o**. The overall synthesis of tamoxifen and its analogues **3p**-**r** was finished by a simple chlorine displacement using dimethylamine or pyrrolidine. Thus, the preparation of alkenes **3p**-**r** was accomplished in four simple steps starting from the dibromo enol phosphate **1a** in overall yields ranging from 47-73%. Moreover, the prepared compounds were >98% (*E*) or (*Z*), as deduced from the ^1H and ^{13}C NMR spectra of the isolated compounds.



Scheme 4. Stereoselective approach to tamoxifen-type estrogen receptors antagonists. Reagents and conditions:(a) $PhB(OH)_2$ or 4-$TBSOC_6H_4B(OH)_2$, $Pd(OAc)_2$, PPh_3, 2M K_2CO_3, toluene, 45 °C; (b) $Cl(CH_2)_2OC_6H_4B(OH)_2$, $Pd(OAc)_2$, RuPhos, 2M K_2CO_3, toluene, 50 °C; (c) Bn_3Al or PhZnCl•LiCl/$AlCl_3$ or FcZnCl•LiCl/$AlCl_3$, $PdCl_2(SPhos)_2$, THF 45 °C

Conclusions

In conclusion, we have shown that developed methodology for the aluminum chloride-promoted cross-coupling reaction of trisubstituted enol phosphates catalyzed by $PdCl_2(SPhos)_2$ in THF at 45 °C is a valuable method for the cross-coupling

reaction of acyclic trisubstituted dialkyl enol phosphates. The methodology tolerates diverse functional groups, including ester and nitrile groups. Moreover, the combination of a previously developed methodology for the three-fold cross-coupling synthesis of tetrasubstituted alkenes with a Lewis acid-promoted coupling reaction provides simple and efficient access to the highly stereoselective synthesis of tamoxifen and its derivatives. Further experiments to explore benefits of $AlCl_3$ promoted cross-coupling reactions of phosphates are ongoing in our laboratory.

Experimental Section

All reactions were performed under an argon atmosphere. NMR spectra were measured on a Varian Gemini 300 (^{1}H, 300.07 MHz; ^{13}C, 75.46 MHz), a Agilent Technologies 400-MR (^{1}H, 399.80 MHz and ^{13}C, 100.51 MHz) spectrometer at 298 K. Mass spectra were measured on ZAB-SEQ (VG Analytical). The solvents were dried and degassed by standard procedures; silica gel (Merck, Silica Gel 60, 40-63 μm) was used for column chromatography. BuLi (2.5 M solution in hexane), and other compounds were purchased. Compounds **2a**,**c**,**d**,**e**,**f**, **1a** were prepared according to the literature procedure.[10] Concentration of BuLi was determined by titration using menthol and 1,10-phenanthroline before use. Arylzinc reagents were prepared by the reaction of arylzinc iodides/bromides with butyllithium in dry THF at -78 °C followed by the reaction with $ZnCl_2$.

*General procedure for $AlCl_3$ promoted cross-coupling reaction of phosphates **2** with organozinc reagents*

A solution of organozinc reagent (1.2 equiv, 0.7 mmol) in dry THF (1 mL) was added to a solution of phosphate (1.0 equiv, 0.5 mmol) and $PdCl_2(SPhos)_2$ (4 mol %) in dry THF (1 mL/mmol). Then a solution of aluminum chloride in dry THF (1 mL, 0.7 M solution in dry THF) was added. The resultant mixture was stirred for 24 hours at 45 °C. The reaction mixture was diluted with ether and 1M tartaric acid or 1M potassium sodium tartrate was added. Clear organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduce pressure. Column chromatography afforded the title compound.

(*Z*)-1-phenyl-1-(4-methoxyphenyl)-2-(4-methylphenyl)hexene (3a):

Prepared according to the general procedure starting from phosphate **2b** (0.215 g, 0.50 mmol), 4-methylphenylzinc chloride [prepared from 4-bromotoluene (0.120 g, 0.70 mmol), nBuLi (0.28 mL, 0.7 mmol), and zinc chloride (0.7 mL of 1 M solution in THF)], $PdCl_2(SPhos)_2$ (20 mg, 4 mol %, 0.02 mmol) and $AlCl_3$ (1 mL, 0.7M solution in THF). The reaction mixture was stirred for 24 h at 45 °C. Column chromatography (DCM/hexane 1:4, R_f = 0.3) afforded 0.161 g (91%) as a colorless solid, M.p. 77−78 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.33 (m, 2H), 7.31–7.23 (m, 2H, overlapping with $CHCl_3$), 7.00 (d, *J* = 8.3 Hz, 2H) partly overlapping with 7.05 (d, *J* = 8.3 Hz, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 6.59 (d, *J* = 8.7 Hz, 2H), 3.72 (s, 3H), 2.42 (t, *J* = 7.8 Hz, 2H), 2.31 (s, 3H), 1.33 (m, 2H), 1.23 (m, 2H), 0.80 (t, *J* = 7.2 Hz, 3H) ppm, in accordance with reference.[10]

(*Z*)-2-(4-fluorophenyl)-2-(4-methoxyphenyl)-1-(4-methylphenyl)-1-phenylethylene (3b):

Prepared according to the general procedure starting from phosphate **2c** (0.235 g, 0.50 mmol), phenylzinc chloride [prepared from bromobenzene (0.110 g, 0.70 mmol), nBuLi (0.28 mL, 0.7 mmol), and zinc chloride (0.7 mL of 1 M solution in THF)], $PdCl_2(SPhos)_2$ (20 mg, 4 mol %, 0.02 mmol) and $AlCl_3$ (1 mL, 0.7M solution in THF). The reaction mixture was stirred for 24 h at 45 °C. Column chromatography (DCM/hexane 1:4, R_f = 0.3) afforded 0.145 g (74%) of the title compound as a colorless solid, M.p. 164−165 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.17–7.08 (m, 3H), 7.05–6.98 (m, 4H), 6.94-6.86 (m, 6H), 6.83–6.77 (m, 2H), 6.64 (d, *J* = 8.7 Hz, 2H), 3.74 (s, 3H), 2.27 (s, 3H) ppm, in accordance with reference.[10]

(*E*)-2-(4-fluorophenyl)-2-(4-methoxyphenyl)-1-(4-methylphenyl)-1-phenylethylene (3c):

Prepared according to the general procedure starting from phosphate **2d** (0.235 g, 0.50 mmol), phenylzinc chloride [prepared from bromobenzene (0.110 g, 0.70 mmol), nBuLi (0.28 mL, 0.7 mmol), and zinc chloride (0.7 mL of 1M solution in THF)], $PdCl_2(SPhos)_2$ (20 mg, 4 mol %, 0.02 mmol) and $AlCl_3$ (1 mL, 0.7 M solution in THF). The reaction mixture was stirred for 24 h at 45 °C. Column chromatography (DCM-hexane 1:4, R_f = 0.3) afforded 0.143 g (73%) of the title compound product as a colorless solid, M.p. 164−165 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.13-7.07 (m, 3H), 7.03–6.96 (m, 4H), 6.96–6.89 (m, 6H), 6.81–6.75 (m, 2H), 6.66 (d, *J* = 8.7 Hz, 2H), 3.76 (s, 3H), 2.27 (s, 3H) ppm, in accordance with reference.[10]

(*E*)-2-phenyl-3-(4-methoxyphenyl)hept-2-ene (3d):

Prepared according to the general procedure starting from phosphate **2e** (0.260 g, 0.50 mmol), 4-methoxyphenylzinc chloride [prepared from 4-bromoanisole (0.131 g, 0.70 mmol), nBuLi (0.28 mL, 0.7 mmol), and zinc chloride (0.7 mL of 1M solution in THF)], $PdCl_2(SPhos)_2$ (20 mg, 4 mol %, 0.02 mmol) and $AlCl_3$ (1 mL, 0.7 M solution in THF). The reaction mixture was stirred for 24 h at 45 °C. Column chromatography (DCM/hexane 1:9, R_f = 0.3) afforded 0.109 g (78%) of the title compound product as colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.35 (m, 2H), 7.30–7.24 (m, 3H), 7.19 (d, *J* = 8.7 Hz, 2H), 6.94 (d, *J* = 8.7 Hz, 2H), 3.86 (s, 3H), 2.20 (t, *J* = 7.6 Hz, 2H), 1.87 (s, 3H), 1.30–1.14 (m, 4H), 0.73 (t, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.9, 144.8, 137.0, 137.7, 135.1, 133.0, 129.8, 128.10, 128.08, 126.1, 113.4, 55.2, 34.9, 30.8, 22.8, 22.4, 13.8 ppm. HRMS (APCI): Calc. for $C_{20}H_{24}O$ $[M+H]^+$ = 281.1899 Found: 281.1901.

(*Z*)-1-(4-fluorophenyl)-1-(4-(2-carbomethoxyethyl)phenyl)-2-(1-naphthyl)hexene (3e):

Prepared according to the general procedure starting from phosphate **2f** (0.260 g, 0.50 mmol), naphthylzinc chloride [prepared from bromonaphthalene (0.145 g, 0.70 mmol), nBuLi (0.28 mL, 0.7 mmol), and zinc chloride (0.7 mL of 1 M solution in THF)], $PdCl_2(SPhos)_2$ (20 mg, 4 mol %, 0.02 mmol) and $AlCl_3$ (1 mL, 0.7M solution in THF). The reaction mixture was stirred for 24 h at 45 °C. Column chromatography (EtOAc/hexane 1:20, R_f = 0.3) afforded 0.204 g (88%) of the title compound product as a colorless solid, M.p. 78–79 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.05–7.98 (m, 1H), 7.82–7.75 (m, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.49–7.29 (m, 5H), 7.23–7.17 (m, 1H), 7.15–7.04 (m, 2H), 6.74 (d, *J* = 8.4 Hz, 2H), 6.65 (d, *J* = 8.4 Hz, 2H), 3.54 (s, 3H), 2.66 (t, *J* = 8.2 Hz, 2H), 2.38 (t, *J* = 8.2 Hz, 2H) overlapping with 2.57–2.41 (m, 2H), 1.40–1.05 (m, 4H), 0.72 (t, *J* = 7.4 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.2, 161.7 (d, J(C-F) = 245 Hz), 140.3, 140.0, 139.7, 139.4, 138.9 (d, J(C-F) = 3.4 Hz), 137.9, 133.5, 131.6, 131.4 (d, *J*(C-F) = 7.8 Hz), 129.2, 128.3, 127.0, 127.0, 126.7, 125.8, 125.6, 125.4, 125.1, 115.1 (d, *J*(C-F) = 20.9 Hz), 51.5, 36.4, 35.3, 31.2, 30.4, 22.1, 13.8 ppm. ^{19}F NMR: δ -116.28 ppm; IR (ATR): *ν* = 3041 (w), 2951 (m), 2863 (m), 1728 (s), 1600 (w), 1505 (s), 1422 (m), 1255 (m), 1221 (m), 1156 (m), 1014 (m). HRMS (ESI): Calc. for $C_{32}H_{31}FO_2$ $[M+Na]^+$ = 489.2200; Found: 489.2206. Calcd for $C_{32}H_{31}FO_2$: C, 82.37; H, 6.70. Found: C, 82.33; H, 7.05.

(Z)-1-(4-(2-chloroethoxy)phenyl)-1-(4-(2-carbomethoxyethyl)phenyl)-2-(4-(tert-butyldimethylsilyloxy)phenyl)-2-(4-(2-cyano-2-propyl)phenyl)ethene (3f):

Prepared according to the general procedure starting from phosphate **2g** (0.320 g, 0.50 mmol), 4-(tert-butyldimethylsilyloxy)phenylzinc chloride [prepared from tert-butyldimethylsilyloxy)phenyl bromide (0.201 mg, 0.7 mmol) nBuLi (0.28 mL, 0.7 mmol), and zinc chloride (0.7 mL of 1M solution in THF)], $PdCl_2(SPhos)_2$ (20 mg, 4 mol %, 0.02 mmol) and $AlCl_3$ (1 mL, 0.7 M solution in THF). The reaction mixture was stirred for 24 h at 50 °C. Column chromatography (EtOAc/hexane 1:6, R_f = 0.25) afforded 0.276 g (80%) of the title compound product as a colorless solid, M.p. 145–146 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.17 (d, *J* = 8.4 Hz, 2H), 7.02 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H) overlapping with 6.91 (br s, 4H), 6.81 (d, *J* = 8.4 Hz, 2H), 6.64 (d, *J* = 8.8 Hz, 2H), 6.56 (d, *J* = 8.4 Hz, 2H), 4.16 (t, *J* = 5.9 Hz, 2H), 3.78 (t, *J* = 5.9 Hz, 2H), 3.66 (s, 3H), 2.86 (t, *J* = 8.3 Hz, 2H), 2.56 (t, *J* = 8.3 Hz, 2H), 1.67 (s, 6H), 0.95 (s, 9H), 0.15 (s, 6H) ppm=. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.3, 156.6, 154.2, 143.6, 141.9, 139.8, 139.0, 138.9, 138.5, 136.8, 136.7, 132.6, 132.4, 131.7, 131.4, 127.4, 124.6, 124.3, 119.4, 113.8, 67.8, 51.6, 41.9, 36.8, 35.6, 30.6, 29.0, 25.7, 18.2, -4.5 ppm. IR (ATR): *v* = 2956 (m), 2867 (m), 1730 (s), 1605 (m), 1506 (s), 1436 (m), 1363 (m), 1295 (m), 1248 (s), 1167 (s), 1101 (m), 1040 (m). HRMS (ESI): Calc. for $C_{42}H_{48}ClNO_4Si$ [M+Na]+ = 716.2933; Found: 716.2940. Calcd for $C_{42}H_{48}ClNO_4Si$: C, 72.65; H, 6.97; N, 2.02. Found: C, 72.73; H, 7.19; N, 1.97.

(*Z*)-4-(2-thienyl)-5-(4-methoxyphenyl)-5-(1-toluenesulphonylindol-3-yl)-pent-4-enyl pivalate (3g):

Prepared according to the general procedure starting from phosphate **2h** (0.363 g, 0.50 mmol), 2-thienylzinc chloride [prepared from thiophene (0.056 mL, 0.7 mmol) nBuLi (0.28 mL, 0.7 mmol), and zinc chloride (0.7 mL of 1 M solution in THF)], $PdCl_2(SPhos)_2$ (20 mg, 4 mol %, 0.02 mmol) and $AlCl_3$ (1 mL, 0.7M solution in THF). The reaction mixture was stirred for 24 h at 50 °C. Column chromatography (EtOAc/hexane 1:6, R_f = 0.25) afforded 0.284 g (91%) of the title compound product as an amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87 (d, *J* = 8.4 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.26 (s, 1H), 7.19–7.16 (m, 5H), 7.03–6.95 (m, 3H), 6.81 (d, *J* = 8.4 Hz, 2H), 6.73–6.66 (m, 2H), 4.05 (t, *J* = 6.3 Hz, 2H), 3.80 (s, 3H), 2.67 (m, 2H), 2.36 (s, 3H), 2.34 (s, 3H), 1.86 (m, 2H), 1.15 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.5, 158.7, 144.6, 144.0, 135.4, 134.9, 134.2, 134.1, 131.3, 130.4, 129.9, 129.7, 126.8, 126.5, 126.4, 125.9, 125.1, 124.8, 124.3, 123.1, 120.7, 113.7, 113.4, 64.1, 55.2, 38.7, 32.8, 28.8, 27.1, 21.5 ppm. IR (ATR): *v* = 2957 (m), 1721 (s), 1606 (m), 1507 (m), 1445 (m), 1368 (m), 1283 (m), 1243 (m), 1171 (s), 1120 (s), 1034 (m). HRMS (ESI): Calc. for $C_{36}H_{37}NO_5S_2$ $[M+Na]^+$ = 620.2005; Found: 650.2003.

(Z)-1-phenyl-1-(4-(1-morpholinomethyl)phenyl)-2-(2-thienyl)hexene (3h):

Prepared according to the general procedure starting from phosphate **2i** (0.250 g, 0.50 mmol), 2-thienylzinc chloride [prepared from thiophene (0.056 mL, 0.7 mmol) nBuLi (0.28 mL, 0.7 mmol), and zinc chloride (0.7 mL of 1 M solution in THF)], $PdCl_2(SPhos)_2$ (20 mg, 4 mol %, 0.02 mmol) and $AlCl_3$ (1 mL, 0.7M solution in THF). The reaction mixture was stirred for 24 h at 50 °C. Column chromatography (EtOAc/hexane 1:3, R_f = 0.25) afforded 0.186 g (90%) of the title compound product as a colorless solid, M.p. 102-103 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.19 (m, 5H Ph + 1H thiophene), 7.11 (d, *J* = 8.0 Hz, 2H), 7.01 (d, *J* = 8.0 Hz, 2H), 6.79 (m, 1H), 6.68 (m, 1H), 3.68 (t, *J* = 4.8 Hz, 4H), 3.42 (s, 2H), 2.49–2.34 (m, 6H), 1.46 (m, 2H), 1.24 (m, 2H), 0.81 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.7, 143.2, 142.2, 140.0, 135.7, 133.4, 130.0, 129.1, 128.7, 128.1, 126.9, 126.6, 126.2, 124.6, 67.0, 63.2, 53.5, 36.2, 31.6, 22.7, 13.8 ppm. HRMS (ESI): Calc. for $C_{27}H_{31}NOS$ $[M+H]^+$ = 418.2199; Found: 418.2197.

Stereoselective synthesis of SERMs

(*Z*)-2-benzyl-1-(4-(2-chloroethoxy)phenyl)-1-phenylbutene (3l)

Benzylmagnesium chloride (0.65 mL, 0.65 mmol) was added to a solution of $AlCl_3$ (0.086 g, 0.65 mmol) in dry THF (1 mL) cooled to 0 °C. The reaction mixture was stirred 15 min at ambient temperature, the solvents were removed under reduce pressure and formed solid was redissolved in THF (2 mL). Dry diglyme (0.287 g, 2.15 mmol) was added to the precipitated solution and the mixture was stirred 30 min at ambient temperature. Precipitated complex of $MgCl_2$ and diglyme has settled down and supernatant solution of tribenzylaluminum was added to a solution of the phosphate **2s** (0.219 g, 0.50 mmol), $PdCl_2(SPhos)_2$ (0.010 g, 2 mol %) in dry THF (2 mL). The reaction was stirred for 24 h at 45 °C. Then the reaction mixture was quenched with 1M tartaric acid and diluted with ether. After clear biphasic mixture was formed the separated organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduce pressure. Purification by column chromatography (EtOAc/hexane 1:20, R_f = 0.35) afforded 0.173 g (92%) of the title compound as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31–7.20 (m, 10H), 7.18 (d, *J* = 8.7 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 4.19 (t, *J* = 6.3 Hz, 2H), 3.78 (t, *J* = 6.3 Hz, 2H), 3.59 (s, 2H), 2.05 (q, *J* = 7.8 Hz, 2H), 0.98 (t, *J* = 7.8 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.6 143.3, 140.5, 138.8, 138.6, 136.2, 130.4, 129.2, 128.6, 128.3, 128.0, 126.2, 125.8, 114.3, 67.8, 41.9, 37.1, 24.7, 13.3 ppm. HRMS (ESI): Calc. for $C_{25}H_{25}ClO$ $[M+Na]^+$ = 399.1486; Found: 399.1487.

(*Z*)-(1-(4-(2-chloroethoxy)phenyl)-1-(4-(*tert*-butyldimethylsilyloxy)phenyl-2-phenyl) butane (3m):

Prepared according to the general procedure starting from phosphate **2t** (0.284 g, 0.50 mmol), phenylzinc chloride [prepared from bromobenzene (0.110 g, 0.70 mmol), nBuLi (0.28 mL, 0.7 mmol), and zinc chloride (0.7 mL of 1 M in THF) in THF (1 mL)], $PdCl_2(SPhos)_2$ (20 mg, 4 mol %) and $AlCl_3$ (1 mL, 0.7M solution in THF). The reaction mixture was stirred for 24 h at 50 °C. Column chromatography (EtOAc/hexane 1:10, R_f = 0.25) afforded 0.204 g (83%) of the title compound as a colorless glass; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.20–7.09 (m, 7H), 6.84–6.78 (m, 4H), 6.56 (d, *J* = 8.7 Hz, 2H), 4.10 (t, *J* = 6.0 Hz, 2H), 3.73 (t, *J* = 6.0 Hz, 2H), 2.50 (q, *J* = 7.5 Hz, 2H), 1.02 (s, 9H), 0.94 (t, *J* = 7.5 Hz, 3H), 0.24 (s, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.0, 154.3, 142.6, 141.2, 137.8, 136.7, 136.5, 132.0, 130.5, 129.7, 127.8, 125.9, 119.5, 113.4, 67.7, 41.9, 29.0, 25.7, 18.2, 13.6, -4.4 ppm. HRMS (APCI): Calc. for $C_{30}H_{37}ClO_2Si$ $[M+H]^+$ = 493.2324; Found: 493.2323.

(*Z*)-1-(4-(2-chloroethoxy)phenyl)-2-ferrocenyl-1-phenylbutene (3n):

Prepared according to the general procedure starting from phosphate **2s** (0.219 g, 0.50 mmol), ferrocenylzinc chloride [prepared from bromoferrocene (0.185 g, 0.70 mmol), nBuLi (0.28 mL, 0.7 mmol), zinc chloride (0.7 mL, 1M solution in THF), and THF (1 mL)], $PdCl_2(SPhos)_2$ (20 mg, 4 mol %) and $AlCl_3$ (1.0 mL, 0.7M solution in THF). The reaction mixture was stirred for 24 h at 50 °C. Column chromatography (DCM/hexane 1:4, R_f = 0.25) afforded 0.139 g (59%) of the title compound as a rusty red solid, M.p. 118–120 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.17 (m, 5H), 6.99 (d, *J* = 8.7 Hz, 2H), 6.76 (d, *J* = 8.7 Hz, 2H), 4.19 (t, *J* = 5.7 Hz, 2H), 4.11 (s, 5H), 4.09–4.08 (br s, 2H),

3.92–3.91 (m, 2H), 3.79 (t, *J* = 5.7 Hz, 2H), 2.57 (q, *J* = 7.5 Hz, 2H), 1.02 (t, *J* = 7.5 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.5, 144.6, 137.9, 137.3, 137.1, 136.2, 131.0, 129.3, 128.2, 126.1, 114.3, 86.7, 69.3, 69.1, 68.1, 67.8, 41.9, 27.9, 15.5 ppm. HRMS (ESI): Calc. for $C_{28}H_{28}ClOFe$ $[M]^+$ = 470.1094; Found: 470.1098.

(*Z*)-1-(4-(2-chloroethoxy)phenyl)-1,2-diphenylbutene (3o):

Prepared according to the general procedure starting from phosphate **2s** (0.219 g, 0.50 mmol), phenylzinc chloride [prepared from bromobenzene (0.110 g, 0.70 mmol), nBuLi (0.28 mL, 0.7 mmol), zinc chloride (0.7 mL of 1M in THF), and THF (1 mL)], $PdCl_2(SPhos)_2$ (20 mg, 4 mol %) and $AlCl_3$ (1.0 mL, 0.7M solution in THF). The reaction mixture was stirred for 24 h at 50 °C. Column chromatography (EtOAc/hexane 1:20, R_f = 0.35) afforded 0.148 g of the title compound as a colorless solid, M.p. 64–65 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.11 (m, 10H), 6.78 (d, *J* = 8.8 Hz, 2H), 6.57 (d, *J* = 8.8 Hz, 2H), 4.12 (t, *J* = 5.8 Hz, 2H), 3.76 (t, *J* = 5.8 Hz, 2H), 2.48 (q, *J* = 7.2 Hz, 2H), 0.92 (t, *J* = 7.2 Hz, 3H) ppm, in accordance with reference.[14] HRMS (ESI): Calc. for $C_{24}H_{23}ClO$ $[M+Na]^+$ = 385.1329; Found: 385.1328

General procedure for the synthesis of 3p-r.

A 3M solution of dimethylamine in dry DMF (3.0 equiv, 3.0 mmol) was added to tetrasubstituted alkene (1.0 equiv, 1.0 mmol). The resultant mixture was stirred for 12 h at 65 °C. Then 1 M solution of NaOH (15 mL) and ether (15 mL) was added. The ethereal layer was washed with water (2 x 10 mL/mmol). Organic layer was dried over Na_2SO_4 and solvent evaporations gave a final product.

(*Z*)-2-benzyl-1-phenyl-1-(4-(2-pyrrolidinoethoxy)phenyl)butene (3p):

Preparation following the general procedure starting from alkene **3l** (1.508 g, 4.0 mmol), pyrrolidine (1.6 mL, 20.0 mmol) in DMF (6 mL) affoded 1.640 g (99%) of the title compound as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33–7.20 (m, 10H), 7.13 (d, *J* = 8.7 Hz, 2H), 6.81 (d, *J* = 8.7 Hz, 2H), 4.07 (t, *J* = 6.0 Hz, 2H), 3.57 (s, 2H), 2.88 (t, *J* = 6.0 Hz, 2H), 2.63–2.59 (m, 4H), 2.03 (q, *J* = 7.5 Hz, 2H), 1.83–1.73 (m, 4H), 0.96 (t, *J* = 7.5 Hz, 3H) ppm, in accordance with literature.[15] HRMS (APCI): Calc. for $C_{29}H_{33}NO$ $[M+H]^+$ = 412.2635, Found: 412.2636.

(*Z*)-2-ferrocenyl-1-(4-(2-*N*,*N*-dimethylaminoethoxy)phenyl)-1-phenylbutene (3q):

Preparation following the general procedure starting from alkene **3n** (0.141 g, 0.30 mmol) and dimethylamine (0.50 mL, 1.50 mmol, 3.0M solution in DMF) afforded 0.142 g (99%) of the title compound as a rusty red solid, M.p. 89–90 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.17 (m, 5H), 6.97 (d, *J* = 8.4 Hz, 2H), 6.77 (d, *J* = 8.4 Hz, 2H), 4.11 (s, 5H), 4.08 (br s, 2H), 4.09 (br s, 2H), 4.04 (t, *J* = 5.7 Hz, 2H), 3.90 (br s, 2H), 2.70 (t, *J* = 5.7 Hz, 2H), 2.56 (q, *J* = 7.5 Hz, 2H), 2.27 (s, 6H), 1.02 (t, *J* = 7.5 Hz, 3H) ppm, in accordance with reference.[16] HRMS (APCI): Calc. for $C_{30}H_{33}NOFe$ $[M+H]^+$ = 480.1984; Found: 480.1987.

(*Z*)-1-(4-(2-*N*,*N*-dimethylaminoethoxy)phenyl)-1,2-diphenylbutene (3r):

Preparation following the general procedure starting from alkene **3o** (0.109 g, 0.30 mmol) and dimethylamine (0.50 mL, 1.50 mmol, 3.0M solution in DMF) afforded 0.110 g (99%) of the title compound as a colorless solid, M.p. 98–99 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.09 (m, 10H), 6.77 (d, *J* = 8.7 Hz, 2H), 6.57 (d, *J* = 8.7 Hz, 2H), 3.96 (t, *J* = 5.8 Hz, 2H), 2.73 (t, *J* = 5.8 Hz, 2H), 2.46 (q, *J* = 7.5 Hz, 2H), 2.26 (s, 6H), 0.92 (t, *J* = 7.5 Hz, 3H) ppm, in accordance with reference.[17] HRMS (APCI): Calc. for $C_{26}H_{29}NO$ $[M+H]^+$ = 372.2322; Found: 372.2325 145.

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Keywords: Alkenes • Cross-coupling • Lewis acids • C-C coupling • Synthetic methods

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Layout 1:

FULL PAPER

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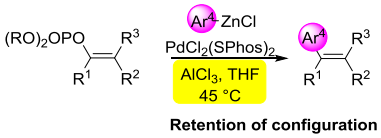
Stereoselective synthesis of tetrasubstituted alkene is achieved via $AlCl_3$ promoted cross-coupling reactions of trisubstituted enol phosphates. The presence of functional groups is tolerated.



Retention of configuration

Stereoselective cross-coupling

*Vladislav Kotek, Peter Polák, Hana Dvořáková, Tomáš Tobrman**

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Aluminum chloride promoted cross-coupling of trisubstituted enol phosphates with organozinc reagents en route to stereoselective synthesis of tamoxifen and its analogues