trans-Stilbene as a Starting Material for the Synthesis of Tamoxifen Based on Palladium-Catalyzed Cross-Coupling Reactions

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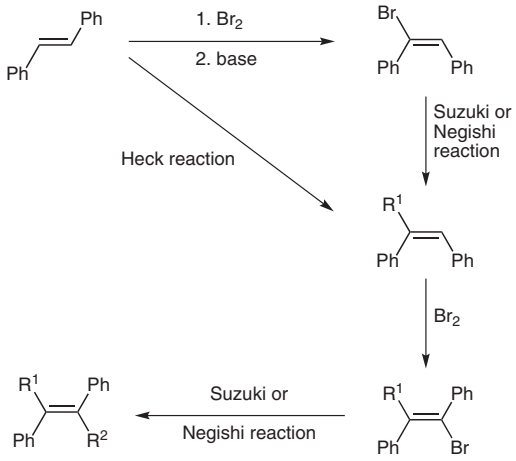
Abstract: (*Z*)-Tamoxifen was synthesized from a simple olefin (*trans*-stilbene) in 5 steps and 40% overall yield (*Z*/*E* = 74:26). The phenyl substituted group (4-$Me_2NCH_2CH_2OC_6H_4$) was attached by a bromination–dehydrobromination–Suzuki reaction sequence. Subsequently, the ethyl group was attached to the triarylated olefin by a bromination–Negishi reaction sequence. Both the Suzuki and Negishi cross-coupling processes are stereospecific, and the stereoselectivity depends only on the bromination–dehydrobromination reactions. (*Z*)-Tamoxifen was also obtained from *trans*-stilbene in only 3 steps by using Heck reaction–bromination–Negishi reaction sequence in 57% overall yield (*Z*/*E* = 65:35).

Key words: tamoxifen, cross-coupling, stilbene, substituted olefins, palladium

The construction of tetrasubstituted olefins with a high degree of stereocontrol remains a significant challenge in organic synthesis.[1] One example of important tetrasubstituted olefin is (*Z*)-tamoxifen, which is a selective estrogen receptor modulator (SERM) used in the treatment of breast cancer.[2,3] It is important to mention that the antiestrogenic activity of tamoxifen is highly dependent on the olefin geometry, and several syntheses of tamoxifen and its derivatives have been reported. The basic approach for the synthesis of tamoxifen and derivatives is the coupling of functionalized ketones by low-valent titanium (McMurry reaction), which, unfortunately, results in a mixture of the desired hetero-ketone coupling and the undesired homo-ketone coupling.[4] Multistep synthesis, involving dehydration[5] and double-bond migration[6,7] reactions, has been used to produce tamoxifen (*Z*/*E* = ~1:1). Palladium-catalyzed reactions are versatile methods for carbon–carbon bond formation, and most of the selective syntheses of (*Z*)-tamoxifen have at least one step involving a Pd-catalyzed cross-coupling reaction.[8–22] One powerful strategy used to obtain tetrasubstituted olefin selectively is to create a substituted vinylic metal substrate by a selective carbometalation of disubstituted alkynes, followed by quenching with an electrophile (iodine or bromine), and then a Pd-cross-coupling reaction or a direct cross-coupling reaction of the vinylic metal substrate.[8–14] On the other hand, Pd-catalyzed three-component coupling of aryl iodides, internal alkynes, and arylboronic acids provides a one-step, selective route to tetrasubstituted olefins including tamoxifen.[15] Disubstituted alkynes are also starting materials for the synthesis of tamoxifen, using a Ni-catalyzed arylative carboxylation.[23] We have recently reported that tri- and tetrasubstituted olefins can be obtained in high yields and regioselectivities, using stilbene as the starting material and a Pd-catalyzed cross-coupling process.[24,25] *trans*-Stilbene is cheaper than alkynes and can be obtained by a Heck cross-coupling reaction of halobenzene and styrene. Therefore, we wish to report here the application of this approach for the synthesis of (*Z*)-tamoxifen (Scheme 1). The substituted phenyl group (R^1 = 4-$Me_2NCH_2CH_2OC_6H_4$) can be attached by a bromination–dehydrobromination–Suzuki reaction sequence or by a Heck reaction. Finally, the ethyl group (R^2) can be attached to the triarylated olefin by a bromination–Negishi reaction sequence. Alternatively, we also investigated the possibility of first inserting the ethyl group (R^1) by a Negishi reaction and then the phenyl substituted group (R^2 = 4-$Me_2NCH_2CH_2OC_6H_4$) by a Suzuki reaction.



Scheme 1 Possible syntheses of (*Z*)-tamoxifen (R^1 = 4-$Me_2NCH_2CH_2OC_6H_4$, and R^2 = Et) from *trans*-stilbene

trans-Stilbene was submitted to a sequence of bromination–dehydrobromination to give the monobrominated product (*E*)-bromostilbene (Scheme 2). The bromination was performed in CH_2Cl_2 at 0 °C, affording the *anti*-addition product *meso*-1,2-dibromo-1,2-diphenylethane in good yield (ca. 71%).[26,27] The yield was improved to 92% by using room-temperature ionic liquid 1-butyl-3-methylimidazolium hexafluorophosphate (BMI·PF_6) as the

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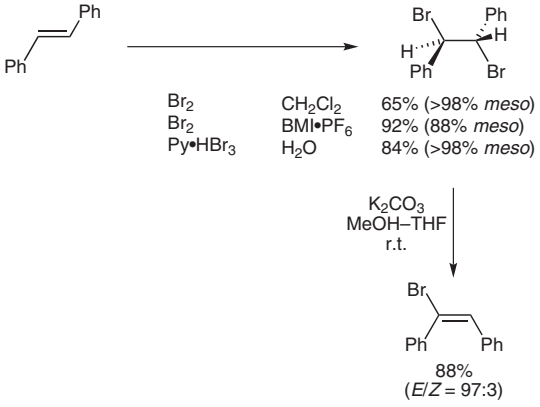
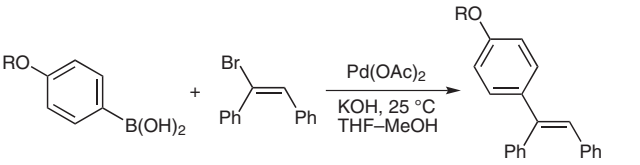
solvent.[28] A faster reaction was observed in BMI·PF_6, but the dibrominated product was obtained as a mixture of 88% *meso* and 12% *rac*. It is important to mention that after extraction of the products, the ionic liquid could be recovered and reused for further bromination reactions. The best compromise between yield and selectivity was obtained when the reaction was carried out in a water suspension with pyridinium hydrobromide perbromide as the brominating agent (84% yield and >98% *meso* compound, as judged by GC-MS analysis).[29] Then, a screening of bases and solvents for the dehydrobromination of *meso*-1,2-dibromo-1,2-diphenylethane was performed. By using K_2CO_3 as the base and a mixture of THF and methanol as the solvent, (*E*)-bromostilbene was obtained in a yield of 88% (Scheme 2). The high stereoselectivity obtained for the dehydrobromination product (*E*/*Z* = 97:3) is related to the strong preference for the *anti*-elimination process.[30] It is worthwhile to mention that the overall bromination–dehydrobromination process results in an inversion of the configuration of the two phenyl groups from *trans* to *cis*.



Scheme 2 Synthesis of (*E*)-bromostilbene from *trans*-stilbene

For the synthesis of triarylethylene product by Pd-catalyzed Suzuki reaction, we chose the cross-coupling of (*E*)-bromostilbene with 4-methoxyphenylboronic acid as a reaction model. The optimization results are summarized in Table 1. As the initial condition, we used an optimized protocol obtained for the coupling of arylboronic acids with vinyl bromide, generated in situ from 1,2-dibromoethane (Table 1, entry 1).[31] (*E*)-Bromostilbene is more active than vinyl bromide, and the substrate was completely converted after 1 hour at room temperature, affording **1a** in almost quantitative yield (Table 1, entry 2). In addition, lower catalyst loading was used, giving a turnover number of 1960 in 1 hour (Table 1, entries 1,2,5). The phosphine-free system also gave the expected coupling product in good yields (Table 1, entries 3 and 4). However, incomplete conversions were obtained even when using higher reaction times and palladium loadings. In all cases, the Suzuki reaction proceeded while retaining the configuration (97%). By using the best conditions, (*E*)-l-{4-[2-(dimethylamino)ethoxy]phenyl}-1,2-diphenylethene (**1b**) was obtained in 94% yield and 98% selectivity for the *E*-isomer (Table 1, entry 5).

Table 1 Pd-Catalyzed Suzuki Cross-Coupling Reaction of (*E*)-Bromostilbene with Arylboronic Acids[a]



1a (R = Me)
1b (R = $CH_2CH_2NMe_2$)

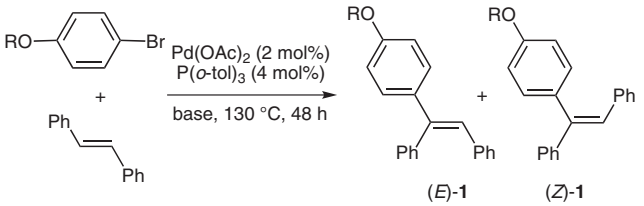
Entry	Pd (mol%)	L	Time (h)	Product	Conv. (%)	Yield (%)
1	0.5	Ph_3P	1	**1a**	100	99
2	0.05	Ph_3P	1	**1a**	99	98
3	2	–	72	**1a**	92	93
4	0.05	–	72	**1a**	99	98
5	0.5	Ph_3P	1	**1b**	100	94

[a] Reaction conditions: (*E*)-bromostilbene (1 mmol), arylboronic acid (1.5 mmol), KOH (2 mmol), $Pd(OAc)_2$/L ratio = 2, MeOH (3 mL), THF (3 mL).

The synthesis of triarylalkenes by Heck vinylation of aryl halides with stilbene is a very attractive alternative to bromination–dehydrobromination–Suzuki reaction sequence since it could produce the desired (*E*)-1-(4-methoxyphenyl)-1,2-diphenylethene from stilbene in only one step. This reaction was investigated by Doucet and Santelli, who used a catalyst composed of $[Pd(C_3H_5)Cl]_2$ and *cis*,*cis*,*cis*-1,2,3,4-tetrakis(diphenylphosphanylmethyl)cyclopentane (Tedicyp) as the phosphine ligand.[32] The addition of 4-bromoanisole to *trans*-stilbene in the presence of 0.2% catalyst led to the corresponding coupled products in 75% yield with an *E*/*Z* ratio of 61:39. We decided to investigate the Heck reaction of 4-bromoanisole with stilbene, using a catalyst system composed of $Pd(OAc)_2$ and P(*o*-tol)$_3$ (Table 2). Classical bases for the Heck reaction, such as Et_3N or NaOAc, gave only moderate yields and selectivities (Table 2, entries 1 and 2). However, higher activity and stereoselectivity for the *E*-isomer was obtained by using K_2CO_3 (Table 2, entry 3). We were delighted to see that by replacing 4-bromoanisole with 1-bromo-4-[2-(dimethylamino)ethoxy]benzene and using this aryl bromide as limiting reagent, the coupling product **1** was obtained in almost quantitative yield with an *E*/*Z* ratio of 87:13 (Table 2, entry 4).

The bromination of triarylethylenes directly produces the bromotriarylethylenes, since dibrominated products are not stable, and undergo HBr elimination in the reaction media.[33,34] A nonselective bromination of (*E*)-**1a** was observed when the reaction was carried out in CH_2Cl_2 at 0 °C (*E*/*Z* = 45:55, Table 3, entry 1). More interestingly, under the same conditions, bromination with a reasonable stereoselectivity was observed for the substrate (*E*)-**1b** possessing a 2-(dimethylamino)ethoxy group (*E*/*Z* = 73:27, Table 3, entry 2). In view of these results, we ex-

Table 2 Pd-Catalyzed Heck Cross-Coupling Reaction of Aryl Bromides with (*E*)-Bromostilbene[a]

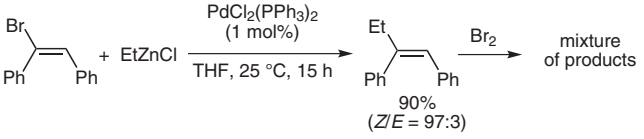


Entry	R	Base	Conv. (%)	Yield (%)	*E*/*Z*
1	Me	Et_3N	51	47[b]	73:27
2	Me	NaOAc	74	54[b]	72:28
3	Me	K_2CO_3	100	79[b]	83:17
4	$CH_2CH_2NMe_2$	K_2CO_3	100	98[c]	87:13

[a] Reaction conditions (entries 1–3): 4-bromoanisole (1 mmol), *trans*-stilbene (0.5 mmol), base (1 mmol), $Pd(OAc)_2$ (0.01 mmol), P(*o*-tol)$_3$ (0.02 mmol), DMF (4 mL), 130 °C, 48 h; (entry 4): 1-bromo-4-[2-(dimethylamino)ethoxy]benzene (1 mmol), *trans*-stilbene (1.5 mmol), base (2 mmol), $Pd(OAc)_2$ (0.02 mmol), P(*o*-tol)$_3$ (0.04 mmol), DMF (4 mL), 130 °C, 48 h.
[b] GC yield.
[c] Isolated yield (average of two runs).

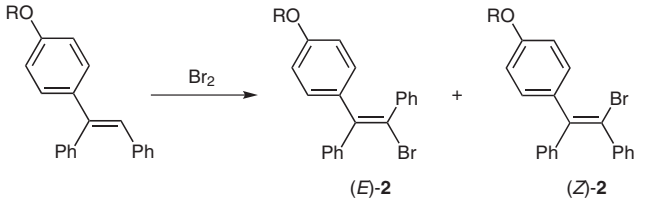
amined the effect of different bases on the bromination of (*E*)-**1a** (Table 3, entries 1, 3–8). A stereoselectivity of 78% was obtained using Et_3N as the base (Table 3, entry 8), which has a structure similar to that of the (dimethylamino)ethoxy group. Indeed, Et_3N has no effect on the bromination of (*E*)-**1b** (Table 3, entries 9 and 10). The amine group can be involved in the elimination step by assisting with the selective *anti*-elimination process or by forming a milder bromination reagent from the reaction with HBr and Br_2, which can assist in the formation of the bromonium ion.[35] No improvement was observed using BMI·PF_6 as the solvent (Table 3, entries 11 and 12) or when the reaction was carried out in a water suspension with pyridinium hydrobromide perbromide as the brominating agent (Table 3, entry 13). Therefore, (*E*)-**2b** was obtained in 78% yield and 74% stereoselectivity (Table 3, entry 10).

Alternatively, we also investigated the possibility of inserting first the ethyl group by Negishi reaction and then the aryl group by Suzuki reaction (Scheme 3). We examined the coupling of (*E*)-bromostilbene with ethylzinc chloride in THF at room temperature using different catalyst precursors and phosphine ligands. Using $PdCl_2(PPh_3)_2$ as a catalyst precursor at room temperature, the (*Z*)-1,2-diphenylbut-1-ene was obtained in 90% isolated yield.[24] Once again, the stereoselectivity was main-



Scheme 3 Synthesis and bromination of (*Z*)-1,2-diphenylbut-1-ene

Table 3 Bromination of Triarylethylenes **1a**,**b**[a]



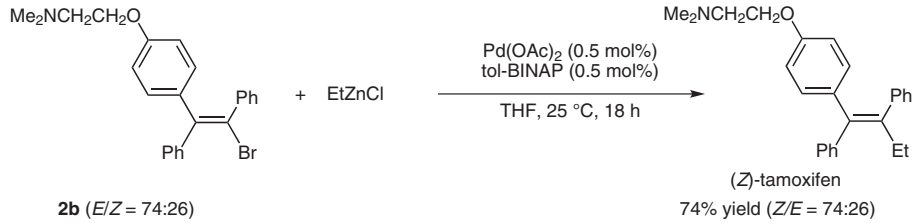
Entry	Solvent	Base	Product	Yield (%)	*E*/*Z*
1	CH_2Cl_2	–	**2a**	94	45:55
2	CH_2Cl_2	–	**2b**	88	73:27
3	CH_2Cl_2	NaO*t*-Bu	**2a**	95	45:55
4	CH_2Cl_2	*i*-Pr_2NEt	**2a**	88	48:52
5	CH_2Cl_2	*i*-Pr_2NH	**2a**	87	47:53
6	CH_2Cl_2	DMAP	**2a**	90	49:51
7	CH_2Cl_2	Et_3N	**2a**	90	78:22
8[b]	CH_2Cl_2	Et_3N	**2a**	90	78:22
9	CH_2Cl_2	Et_3N	**2b**	73	73:27
10[b]	CH_2Cl_2	Et_3N	**2b**	78	74:26
11	BMI·PF_6	–	**2a**	86	55:45
12	BMI·PF_6	Et_3N	**2a**	82	55:45
13[c]	H_2O	–	**2a**	82	56:44

[a] Reaction conditions: (*E*)-1-aryl-1,2-diphenylethene (2 mmol), base (8 mmol), CH_2Cl_2 (20 mL), Br_2 (3 mmol in 20 mL of CH_2Cl_2), 0 °C.
[b] At 25 °C.
[c] Pyridinium hydrobromide perbromide as the brominating agent and at 25 °C.

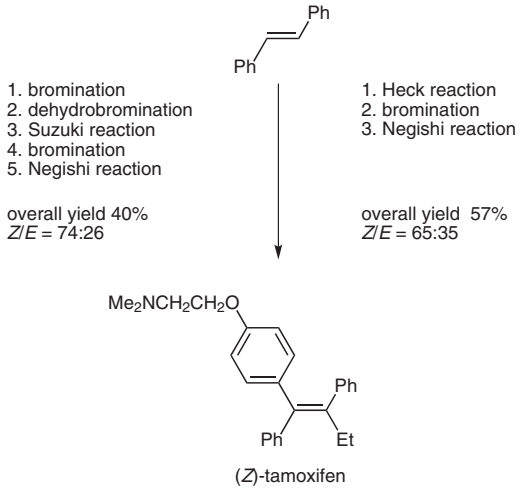
tained in the cross-coupling reaction (*E*/*Z* = 97:3). Unfortunately, due to the presence of the ethyl group, the bromination reaction gave a mixture of regioisomers that discarded this sequence as an alternative to the selective synthesis of tamoxifen.

Finally, (*Z*)-tamoxifen was obtained form a Negishi cross-coupling reaction between (*E*)-**2b** and ethylzinc chloride (Scheme 4). The protocol obtained for the reaction of (*E*)-bromostilbene with ethylzinc chloride was not directly transposable to the coupling of bromotriphenylethylene. In order to achieve a high selectivity in the coupling product (coupling product/reduced product), Ph_3P was replaced by a diphosphine. Thus, using tol-Binap as ligand (*Z*)-tamoxifen was obtained in 74% yield with the same stereoselectivity as the starting **2b** compound (*Z*/*E* = 74:26).

As a more attractive route, (*Z*)-tamoxifen was also obtained from *trans*-stilbene in only 3 steps by using Heck reaction (Scheme 5). Since the synthesis of triarylalkene **1b** by Heck vinylation was less stereoselective (*E*/*Z* = 87:13), the corresponding brominated product (*E*)-**2b** was



Scheme 4 Synthesis of (*Z*)-tamoxifen by Negishi cross-coupling reaction



Scheme 5 *trans*-Stilbene as a starting material for the synthesis of (*Z*)-tamoxifen

obtained in only 65% selectivity. It is important to mention that a simple recrystallization of this product from hexanes afforded pure (*E*)-**2b** with 50% of recovery.

In summary, we have demonstrated that (*Z*)-tamoxifen can be stereoselectively synthesized from *trans*-stilbene in 5 steps in 40% overall yield. The substituted phenyl group (R^1 = 4-$Me_2NCH_2CH_2OC_6H_4$) was attached by a bromination–dehydrobromination–Suzuki reaction sequence. The ethyl group was attached to the triarylated olefin by a bromination–Negishi reaction sequence. Both the Suzuki and Negishi cross-coupling processes are stereospecific, and the stereoselectivity depends only on the bromination–dehydrobromination reactions. (*Z*)-Tamoxifen was also obtained from *trans*-stilbene in only three steps by using Heck reaction–bromination–Negishi reaction sequence in 57% overall yield with a lower selectivity (*Z*/*E* = 65:35). The extension of this protocol for the selective synthesis of tetraarylated olefins is now under investigation in our group.

All reactions were carried out under argon in oven dried resealable Schlenk tube. Iodobenzene was purchased from Acros and styrene was purchased from Aldrich and dried before to use. MeOH and THF were degassed and dried, respectively. Arylboronic acids were prepared according to the previously published procedure.[15] Bromination reactions of *trans*-stilbene to afford *meso*-1,2-dibromo-1,2-diphenylethane were performed as described in the literature.[26–29] Chemicals were used without purification. NMR spectra were recorded on a Varian XL300 spectrometer. IR spectra were recorded on a Shimadzu FTIR-8300 spectrometer. Mass spectra were obtained on a GC/MS Shimadzu QP-5050 (EI, 70 eV). Gas chromatography analyses were performed on a HP column DB-17 GC with a FID and 30 meter capillary column with a dimethylsiloxane stationary phase. ESI-(+) HRMS analyses were performed on a Q-Tof (Micromass) mass spectrometer.

Suzuki Coupling of 1-Bromo-1,2-diphenylethene and Arylboronic Acids; General Procedure

An oven-dried resealable Schlenk flask charged with 1-bromo-1,2-diphenylethene (259 mg, 1 mmol) was evacuated and back-filled with argon. Then, $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), Ph_3P (2.6 mg, 0.01 mmol), arylboronic acid (1.2 mmol), KOH (112 mg, 2 mmol), MeOH (2.5 mL), and THF (2.5 mL) were added. The reaction mixture was stirred at r.t. for 1 h. The solution was then taken up in Et_2O (30 mL) and the Et_2O layer was washed with aq 1 M NaOH (10 mL) and brine (2 × 5mL). The organic layer was dried ($MgSO_4$), filtered, concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (Table 1).

(*E*)-l-{4-[2-(dimethylamino)ethoxy]phenyl}-1,2 diphenylethene (1b)[36]

Yield: 94%.

IR (Nujol): 3055, 3022, 1604, 1574, 1508, 1244, 756, 696 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.32 (s, 6 H), 2.71 (t, *J* = 6 Hz, 2 H), 4.05 (t, *J* = 6 Hz, 2 H), 6.84 (s, 1 H), 6.87–7.31 (m, 14 H).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 45.8, 58.2, 65.9, 114.1, 126.3, 126.4, 127.3, 127.8, 128.5, 128.6, 129.3, 130.3, 135.9, 137.5, 140.4, 142.0, 158.4.

GC-MS (EI, 70 eV): *m*/*z* (%) = 343 (68, M^+), 178 (100), 165 (91), 252 (89), 239 (88), 253 (67), 179 (57), 215 (54), 176 (52).

HRMS: *m*/*z* calcd for $C_{24}H_{26}NO$ (M + H^+): 344.2014; found: 344.2035.

Heck Coupling Reaction of *trans*-Stilbene with Aryl Bromides; (*E*)-l-{4-[2-(dimethylamino)ethoxy]phenyl}-1,2 diphenylethene (1b); Typical Procedure

An oven-dried resealable Schlenk flask charged with *trans*-stilbene (270 mg, 1.5 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), and P(*o*-tol)$_3$ (12.2 mg, 0.04 mmol) was evacuated and back-filled with argon. Then, DMF (4 mL), 1-bromo-4-[2-(dimethylamino)ethoxy]benzene (244 mg, 1.0 mmol) and base (276 mg, 2.0 mmol) were added. The reaction mixture was stirred at 130 °C and the conversion and diasteroselectivity were determined by GC analysis. Product **1b** was isolated by acid–base extraction (Table 2).

Bromination of Triarylethylenes; 1-Bromo-2-{4-[[2-(dimethylamino)ethoxy]phenyl}-1,2 diphenylethene (2b);[37] Typical Procedure

A solution of Br_2 (575 mg, 3.6 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a stirred solution of **1b** (1.03 g, 3 mmol) and Et_3N (1.20 g, 12 mmol) in CH_2Cl_2 (10 mL) at r.t. and the reaction mixture was kept overnight in the dark. The bromine color of the mixture was removed by an excess of aq $NaHSO_3$ and the organic layer was washed with aq 10% KOH (20 mL). The organic layer was dried

(Na_2SO_4) and the solvent was evaporated to give 1.01 g (78%) of an *E*/*Z* mixture (74:26) of **2b** as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ (mixture of diasteroisomers) = 2.25 (*E*-isomer, s, 6 H), 2.31 (*Z*-isomer, s, 6 H), 2.62 (*E*-isomer, t, *J* = 5.7 Hz, 2 H), 2.65 (*Z*-isomer, t, *J* = 5.7 Hz, 2 H), 2.72 (*E*-isomer, t, *J* = 5.7 Hz, 2 H), 3.90 (*E*-isomer, t, *J* = 5.7 Hz, 2 H), 4.05 (*Z*-isomer, t, *J* = 5.7 Hz, 2 H), 6.53 (*E*-isomer, d, *J* = 8.7 Hz, 2 H), 6.77 (*E*-isomer, d, *J* = 8.7 Hz, 2 H), 6.83–7.34 (*Z*- and *E*-isomers, m, 10 H).

(*E*)-2b

Recrystallization of the *E*/*Z* mixture of **2b** from hexanes afforded the pure (*E*)-**2b**; mp 116–117 °C (Lit.[37] mp 116–117 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.33 (s, 6 H), 2.72 (t, *J* = 5.7 Hz, 2 H), 3.96 (t, *J* = 5.7 Hz, 2 H), 6.53 (d, *J* = 8.9 Hz, 2 H), 6.77 (d, *J* = 8.9 Hz, 2 H), 7.08–7.34 (m, 10 H).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 45.6, 58.1, 65.3, 114.0, 121.4, 127.7, 128.0, 128.3, 128.4, 129.8, 130.5, 131.9, 134.0, 141.5, 143.2, 144.2, 157.5.

HRMS: *m*/*z* calcd for $C_{24}H_{25}BrNO$ (M + H^+): 422.1119; found: 422.1125.

Negishi Coupling of 1-Bromo-2-{4-[2-(dimethylamino)ethoxy]phenyl}-1,2 diphenylethene (2b) with Ethylzinc Chloride

An oven-dried resealable Schlenk flask was charged with $ZnCl_2$ (273 mg, 2 mmol), THF (3 mL), and Et_2Zn (2 mL of a 1 M solution in hexane, 2 mmol). The mixture was stirred at r.t. for 1 h before use. The mixture was transferred to an oven-dried reseable Schlenk flask containing **2b** (630 mg, 1.5 mmol) in THF (5 mL). Finally, $Pd(OAc)_2$ (6.7 mg, 0.03 mmol) and tol-BINAP (20.3 mg, 0.03 mmol) were added and the mixture was stirred at 30 °C for 2 h. After removal of the solvent, the residue was chromatographed on silica gel (hexanes) to give 412 mg (74%) of an *E*/*Z* mixture (74:26) of tamoxifen. The diastereoisomeric ratio was determined by GC-MS analysis and configuration of the major diasteroisomer established by NMR could be confirmed by GC-analysis of an authentic sample of (*Z*)-tamoxifen.[17]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (*Z*-isomer, t, *J* = 7.3 Hz, 3 H), 0.95 (*E*-isomer, t, *J* = 7.3 Hz, 3 H), 2.29 (*Z*-isomer, s, 6 H), 2.36 (*E*-isomer, s, 6 H), 2.42–2.50 (*Z*- and *E*-isomers, m, 4 H), 2.65 (*Z*-isomer, t, *J* = 5.7 Hz, 2 H), 2.75 (*E*-isomer, t, *J* = 5.7 Hz, 2 H), 3.93 (*Z*-isomer, t, *J* = 5.7 Hz, 2 H), 4.09 (*E*-isomer, t, *J* = 5.7 Hz, 2 H), 6.56 (*Z*-isomer, d, *J* = 9 Hz, 2 H), 6.77 (*Z*-isomer, d, *J* = 9 Hz, 2 H), 6.89–7.37 (*Z*- and *E*-isomers, m, 10 H).

HRMS: *m*/*z* calcd for $C_{26}H_{30}NO$ (M + H^+): 372.2327; found: 372.2328.

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