An atom efficient synthesis of Tamoxifen

Dorus Heijnen\textsuperscript{a}, Milan van Zuylen\textsuperscript{a}, Filippo Tosi\textsuperscript{a}, and Ben L Feringa\textsuperscript{* a}

\textsuperscript{*} Stratingh Institute for Chemistry, University of Groningen, Nijenborgh 4, 9747 AG, Groningen, The Netherlands

\textsuperscript{†} These authors made equal contribution to this work

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1. Experimental section
All reactions were carried out under a nitrogen atmosphere using oven dried glassware and using standard Schlenk techniques unless noted otherwise. THF and toluene were dried using an SPS-system. White colored Pd(P₃-t-Bu)₂, was purchased from Strem chemicals and stored under nitrogen at -25 ºC. All alkyllithium reagents and aryl bromides were purchased from Aldrich or TCI and used without further purification, unless noted otherwise. Chromatography: Merck silica gel type 9385 230-400 mesh, TLC: Merck silica gel 60, 0.25 mm, or Grace-Reveleris purification system with Grace cartridges. Components were visualized by UV. Progress and conversion of the reaction were determined by GC-MS (GC, HP6890: MS HP5973) with an HP1 or HP5 column (Agilent Technologies, Palo Alto, CA). PREP-HPLC was performed on a Grace-reveleris PREP with a 5µ Denali silica (15 cm, 10 mm id). ¹H- and ¹³C-NMR were recorded on a Varian AMX400 (400 and 100.59 MHz, respectively) using CDCl₃ as solvent, unless noted otherwise. Chemical shift values are reported in ppm with the solvent resonance as the internal standard (CHCl₃: δ 7.26 for ¹H, δ 77.0 for ¹³C) unless noted otherwise. Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), and integration. An ever present spike in the ¹³C NMR was observed at -5 and 194 ppm, and is therefore ignored. For quantitative analysis using ¹H-NMR, 1,1,2,2-tetrachloroethane was used as an internal standard. RP HPLC column: Denali C18, 200 x 10 mm Flow: 6 ml/min.
2. Attempted alternatives for the synthesis of Tamoxifen

We have previously described the cross coupling with free phenol electrophiles, that led to the corresponding cross coupled phenol derivatives. In order to reduce the step count of this synthetic route, we envisioned that the one pot coupling of free 4-bromophenol, followed by electrophilic quenching with amino-alkyl-chloride of reaction intermediate to give (Z)-Tamoxifen would bring a considerable advantage for the methodology (Scheme 1). Unfortunately, the deprotonation/cross coupling strategy did not lead to significant product formation, and upon MeI quench we could only recover the methylated product, as well as products arising from lithium halogen exchange as determined by GC-MS analysis.

In order to increase the atom economy even further, and omit the need for a heavy halogen coupling partner, the electrophile was also substituted by the lighter, less waste producing corresponding chloride (6-Cl) or methyl ether (6-OMe)(Scheme 2). Pd-PEPPSI complexes have previously shown to be very reactive in the coupling of aryl chlorides with organolithium reagents. Similarly, the Ni-NHC catalysts recently published showed cross coupling with aryl ethers and aryllithium reagents. Unfortunately, the combination of the Pd/Cl and Ni/OMe methodology did not give any observable product formation as determined by GC-MS analysis.
3. Characterization of compounds

2-(4-Bromophenoxy)-N,N-dimethylethylamine (6)

To a dry Schlenk flask equipped with a stirring bar NaH (1.36 g (60%), 34 mmol) was added and washed twice with 5 mL of dry hexane. Subsequently, 5 mL of dry THF were added and the suspension was cooled in an ice bath. In a separate Schlenk flask 4-bromophenol (3.0 g, 17 mmol) was dissolved in 8 mL of dry THF. The resulting solution was added slowly to the flask containing the previously washed NaH as described above. After the addition was complete, the ice bath was removed, 2-chloro-N,N-dimethylethylamine hydrochloride (2.4 g, 17 mmol) was added in portions and the reaction mixture was heated to 40 °C. After 72 h the reaction mixture was allowed to cool to room temperature and the formed precipitate was filtered off. The filtrate was concentrated in vacuo and redissolved in 50 mL of ethyl acetate. The organic layer was extracted three times with 50 mL aq. 1 M HCl. The aqueous layer was then neutralized using aq. sat. Na2CO3, and subsequently extracted three times with 100 mL EtOAc. The organic layer was then dried using Na2SO4 and concentrated in vacuo. The product was obtained without further purification as a colorless liquid (4.2 g, 56%). 1H-NMR (400 MHz, CDCl3) δ 7.36 (d, J = 8.9 Hz, 2H), 6.80 (d, J = 8.9 Hz, 2H), 4.03 (t, J = 5.7 Hz, 2H), 2.72 (t, J = 5.7 Hz, 2H), 2.33 (s, 6H). The spectral data is in accordance with literature.5

Tamoxifen ((Z)-1-(p-Dimethylamoethoxyphenyl)-1,2-diphenyl-1-butene.

Preparation of lithio-stilbene: In a dry Schlenk flask (A) equipped with a stirring bar under nitrogen atmosphere, 160 mg of diphenylacetylene (0.9 mmol) were dissolved in 1 mL of dry THF, and the solution was cooled to 0 °C by means of an ice bath. To this solution 1.85 mL of 0.5 M ethyllithium in cyclohexane/benzene (0.93 mmol) were added dropwise, causing the solution to turn orange. The solution was allowed to quickly warm to room temperature and stirred for 3 h, during which it changed color to yellow, and eventually light green. The resulting solution was diluted with 2 mL of dry toluene (Solution A).

Procedure for the cross coupling: To a dry Schlenk flask (B) equipped with a stirring bar was added Pd(t-Bu3P)2 (15.4 mg, 30 µmol, 5%) and 2 mL of dry toluene. By means of a syringe, 12 mL of dry oxygen were bubbled through the solution which was left stirring vigorously overnight, generating a deep red color. A solution of compound 2 (146.4 mg, 0.6 mmol) dissolved in 0.5 mL of dry toluene was added to the flask. Solution A (freshly prepared) was added over the course of 20 min by means of a syringe pump. After the addition, the reaction mixture was quenched with 0.5 mL of MeOH, filtered over celite and concentrated in vacuo. The resulting liquid was dissolved in 20 mL of EtOAc and extracted four times with 30 mL of 1 M aq. HCl. The aqueous layer was neutralized using Na2CO3 and subsequently extracted four times with 50 mL of ethyl acetate. The organic layer was dried using Na2SO4* and concentrated in vacuo. The crude yield was determined by 1H-NMR analysis, using 1,1,2,2-tetrachloroethane as an internal standard (in reference with the integration of the doublet signal at δ 6.56 ppm). Pure Tamoxifen mixture ((Z/E): 10:1) was isolated after flash column chromatography on SiO2 (DCM/MeOH 96:4, 127 mg, 57%).

15 mg of the (E/Z)-product were dissolved in a 1:1 mixture of water/acetonitrile and purified by RP (C18 Denali Prep-HPLC chromatography (Water/Acetonitrile/TFA 50:49:1), affording pure (Z)-Tamoxifen. 1H-NMR (400 MHz, CDCl3) δ 7.35 (d, J = 7.5 Hz, 2H), 7.25 (m, 2H), 6.76 (d, J = 8.8 Hz, 2H), 6.56 (d, J = 8.8 Hz, 1H), 3.92 (t, J = 5.8 Hz, 2H), 2.64 (t, J = 5.8 Hz, 2H), 2.46 (q, J = 7.4 Hz, 2H), 2.28 (s, 6H), 0.92 (t, J = 7.4 Hz, 3H). HRMS (ESI) m/z: [M + 1]+ Calcd for C18H13NO1 371.2322, Found 371.2326. The spectral data is in accordance with literature.5

*the use of magnesium sulfate induces the formation of magnesium chelated complexes hampering the purification of the Tamoxifen product.

(Z)-1-(1,2-diphenylhex-1-en-1-yl)naphthalene (11)

To a dry Schlenk flask (B) equipped with a stirring bar was added Pd(t-Bu3P)2 (12.7 mg, 15 µmol, 5%) and 2 mL of dry toluene. By means of a syringe, 6 mL of dry oxygen were bubbled through the solution which was left stirring vigorously overnight, generating a deep red color. A solution of 1-bromonaphthalene (104 mg, 0.5 mmol) dissolved in 0.5 mL of dry toluene was added to the flask. To this flask, a (freshly prepared) solution of lithio-stilbene (as described above) was added over the course of 20 min by means of a syringe pump. After the addition, the reaction mixture was quenched with 0.5 mL of MeOH, filtered over celite and concentrated in vacuo. Pure 11 was isolated after flash column chromatography on SiO2 (Pent, Rf = 0.85, 124 mg,
(Z)-(1-(p-tolyl)hex-1-ene-1,2-diyl)dibenzene (12a)

To a dry Schlenk flask (B) equipped with a stirring bar was added Pd(t-Bu)₂P₂ (7.66 mg, 15 µmol, 5%) and 1 mL of dry toluene. By means of a syringe, 6 mL of dry oxygen were bubbled through the solution which was left stirring vigorously overnight, generating a deep red color. A solution of p-bromotoluene (51.3 mg, 0.3 mmol) dissolved in 0.5 mL of dry toluene was added to the flask. To this flask, a (freshly prepared) solution of lithio-stilbene (as described above) was added over the course of 20 min by means of a syringe pump. After the addition, the reaction mixture was quenched with 0.5 mL of MeOH, filtered over celite and concentrated in vacuo. Pure compound 12a was isolated after flash column chromatography on SiO₂ (Pentane, RF = 0.2, 55.1 mg, 56%). The spectral data is in accordance with literature. ¹H-NMR (400 MHz, CDCl₃) δ 7.36 (m, 2H), 7.26 (m, 3H), 7.15 (m, 5H), 6.80 (d, J = 8.8 Hz, 2H), 6.56 (d, J = 8.8 Hz, 2H), 2.61 (s, 3H), 2.19 (s, 3H), 1.32 (m, 2H), 1.23 (m, 2H), 0.78 (t, J = 7.2 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 143.91, 142.88, 140.72, 140.21, 139.00, 135.32, 130.75, 129.72, 129.64, 128.22, 128.20, 127.94, 126.60, 126.12, 125.87, 125.66, 131.99, 129.73, 129.65, 128.20, 127.99, 126.61, 126.10, 112.89, 55.12, 35.84, 31.29, 22.94, 14.02.

(Z)-(1-(4-methoxyphenyl)hex-1-ene-1,2-diyl)dibenzene (12b)

To a dry Schlenk flask (B) equipped with a stirring bar was added Pd(t-Bu)₂P₂ (7.66 mg, 15 µmol, 5%) and 1 mL of dry toluene. By means of a syringe, 6 mL of dry oxygen were bubbled through the solution which was left stirring vigorously overnight, generating a deep red color. A solution of p-bromoanisole (56.1 mg, 0.3 mmol) dissolved in 0.5 mL of dry toluene was added to the flask. To this flask, a (freshly prepared) solution of lithio-stilbene (as described above) was added over the course of 20 min by means of a syringe pump. After the addition, the reaction mixture was quenched with 0.5 mL of MeOH, filtered over celite and concentrated in vacuo. Pure compound 12b was isolated after flash column chromatography on SiO₂ (Pentane/DCM 8:2, RF = 0.5, 52.6 mg, 51%).

(Z)-(1-(4-(trifluoromethyl)phenyl)hex-1-ene-1,2-diyl)dibenzene (12c)

To a dry Schlenk flask (B) equipped with a stirring bar was added Pd(t-Bu)₂P₂ (12.7 mg, 15 µmol, 5%) and 2 mL of dry toluene. By means of a syringe, 6 mL of dry oxygen were bubbled through the solution which was left stirring vigorously overnight, generating a deep red color. A solution of p-bromobenzotrifluoride (112.5 mg, 0.5 mmol) dissolved in 0.5 mL of dry toluene was added to the flask. To this flask, a (freshly prepared) solution of lithio-stilbene (as described above) was added over the course of 20 min by means of a syringe pump. After the addition, the reaction mixture was quenched with 0.5 mL of MeOH, filtered over celite and concentrated in vacuo. 12c was isolated as a mixture with 10% of the impurity arising from protonation of compound 9 after flash column chromatography on SiO₂ (Pent, RF = 0.9), and the yield corrected for the impurity (142 mg, 68%). ¹H NMR (400 MHz, CDCl₃) δ 7.57 – 7.53 (m, 2H), 7.40 – 7.14 (m, 3H)*, 7.10 (dd, J = 7.9, 1.8 Hz, 2H), 6.99 (d, J = 8.1 Hz, 2H), 2.54 – 2.37 (m, 2H), 1.37 – 1.28 (m, 2H), 1.27 – 1.17 (m, 2H), 0.79 (t, J = 7.1 Hz, 3H).*signal originating from product and identified impurity. ¹³C NMR (101 MHz, CDCl₃) δ 146.75, 142.92, 142.67, 141.80, 137.74, 131.60, 130.89, 129.50, 129.43, 128.75, 128.32, 128.29, 128.23, 128.20, 128.03, 127.09, 126.92, 126.60, 126.55, 124.31, 124.27, 123.27, 35.75, 30.97, 22.75, 13.83. ¹⁹F NMR (376 MHz, CDCl₃) δ -62.43.
4. NMR Spectra

[Diagram of NMR spectra with peaks labeled]

* = E-Tamoxifen

[Diagram of chemical structures with peaks labeled]
(Z)-Tamoxifen after prep HPLC containing traces of formic acid from the eluent.
Atom Economy and RME calculations

For the atom economy, we used the total mass of all the reagents (not including stoichiometry), and the mass of Tamoxifen (free amine, mass = 371).

For the calculation of the Reaction Mass Efficiency, we used the weighed mass (molecular weight*equivalents) and the reaction yield. We also incorporated the synthesis and yield ("Yield Key SM") of the advanced syntheses. This is a "bromo amine ether" (6). For most syntheses, this is "bromo amine ether" (6) that is made from the corresponding phenol, and its preparation was kept identical for all routes.