

An atom efficient synthesis of Tamoxifen

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

^a *Stratingh Institute for Chemistry, University of Groningen, Nijenborgh 4, 9747 AG, Groningen, The Netherlands*

[‡] These authors made equal contribution to this work

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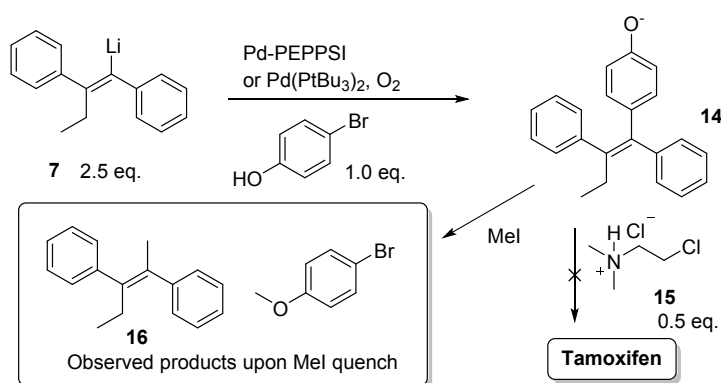
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1. Experimental section

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(P *t*-Bu₃)₂, was purchased from Strem chemicals and stored under nitrogen at -25 °C. 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.

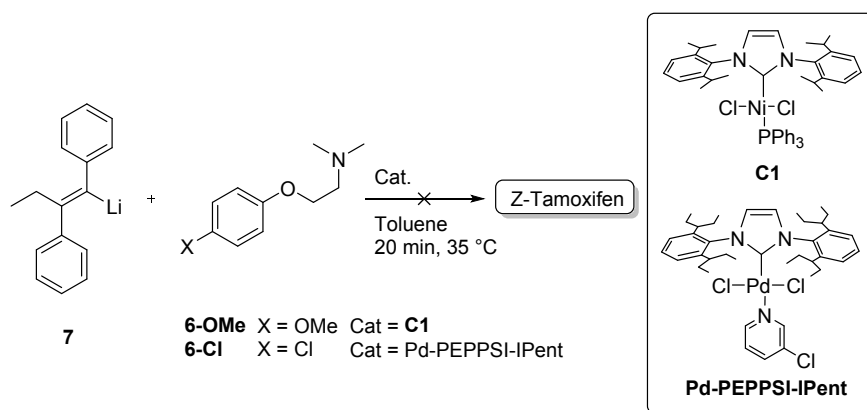
2. Attempted alternatives for the synthesis of Tamoxifen

We have previously described the cross coupling with free phenol electrophiles, that led to the corresponding cross coupled phenol derivatives.¹ 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 **15** of reaction intermediate **14** 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 **16**, as well as products arising from lithium halogen exchange as determined by GC-MS analysis.



Scheme 1: Attempted one pot synthesis of Tamoxifen

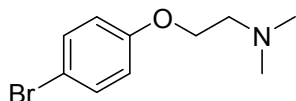
In order to increase the atom economy even further, and omit the need for a heavy halogen coupling partner, the electrophile **2** was also substituted by the lighter, less waste producing corresponding chloride (**6-Cl**) or methyl ether (**6-OMe**)(Scheme 2). Pd-PEPPSI complexes have previously shown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



Scheme 2: Attempted one pot synthesis of Tamoxifen with alternative electrophiles

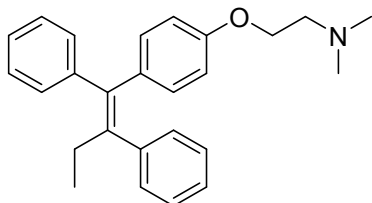
3. Characterization of compounds

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.⁴

Tamoxifen ((Z)-1-(p-Dimethylaminoethoxyphenyl)-1,2-diphenyl-1-butene,



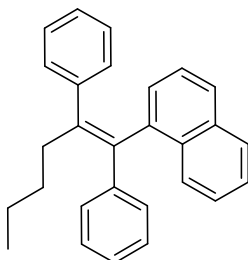
Preparation of lithio-stilbene: In a dry Schlenk flask (A) equipped with a stirring bar under nitrogen atmosphere, 160 mg of diphenylacetylene (0.9 mmol) were dissolved in 1 mL of dry THF, and the solution was cooled to 0 °C by means of an ice bath. To this solution 1.85 mL of 0.5 M ethyllithium in cyclohexane/benzene (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 1 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 C₂₆H₃₀N₁O₁ 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.

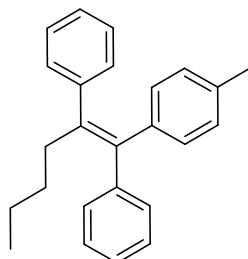
(Z)-1-(1,2-diphenylhex-1-en-1-yl)naphthalene (11)



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 (103.5 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*. Pure 11 was isolated after flash column chromatography on SiO₂ (Pent, R_f = 0.85, 124 mg,

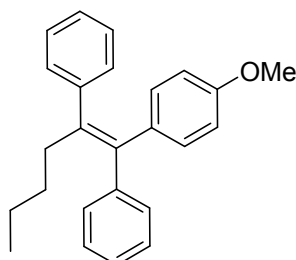
68 %). ^1H NMR (400 MHz, CDCl_3) δ 8.14 – 8.04 (m, 1H), 7.69 (dd, $J = 7.9, 1.6$ Hz, 1H), 7.59 – 7.54 (m, 1H), 7.43 – 7.15 (m, 10H), 7.12 – 7.02 (m, 2H), 6.98 – 6.91 (m, 2H), 2.75 (ddd, $J = 13.4, 9.4, 6.4$ Hz, 1H), 2.61 (ddd, $J = 13.5, 9.3, 6.4$ Hz, 1H), 1.56 – 1.43 (m, 2H), 1.42 – 1.29 (m, 2H), 0.87 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 143.99, 143.33, 142.66, 142.56, 140.92, 137.32, 133.53, 132.06, 128.88, 128.68, 128.30, 128.07, 127.98, 127.34, 126.72, 126.54, 126.36, 125.99, 125.50, 125.15, 125.05, 34.92, 31.46, 22.89, 13.94.

(Z)-(1-(p-tolyl)hex-1-ene-1,2-diyl)dibenzene (12a)



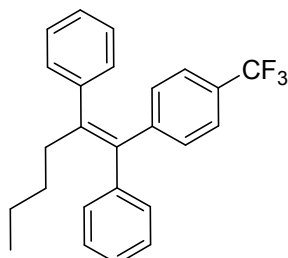
To a dry Schlenk flask (B) equipped with a stirring bar was added $\text{Pd}(t\text{-Bu}_3\text{P})_2$ (7.66 mg, 15 μmol , 5%) and 1 mL of dry toluene. By means of a syringe, 6 mL of dry oxygen were bubbled through the solution which was left stirring vigorously overnight, generating a deep red color. 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 SiO_2 (Pentane, $R_f = 0.2$, 55.1 mg, 56%). The spectral data is in accordance with literature.⁶ ^1H -NMR (400 MHz, CDCl_3) δ 7.35 (m, 2H), 7.24 (m, 3H), 7.14 (m, 5H), 6.82 (d, $J = 8.2$ Hz, 2H), 6.67 (d, $J = 8.2$ Hz, 2H), 2.43 (m, 2H), 2.19 (s, 3H), 1.31 (m, 2H), 1.23 (m, 2H), 0.78 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 157.58, 143.97, 142.92, 140.36, 138.57, 135.66, 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 $\text{Pd}(t\text{-Bu}_3\text{P})_2$ (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 **12a** was isolated after flash column chromatography on SiO_2 (Pentane/DCM 8:2, $R_f = 0.5$, 52.6 mg, 51 %). ^1H -NMR (400 MHz, CDCl_3) 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), 3.69 (s, 3H), 2.44 (m, 2H), 1.32 (m, 2H), 1.22 (m, 2H), 0.79 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) 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, 35.87, 31.27, 22.94, 21.20, 14.03. HRMS (ESI) m/z : $[M + 1]^+$ Calcd for $\text{C}_{25}\text{H}_{25}\text{O}_1$ 341.18999, Found 341.18987.

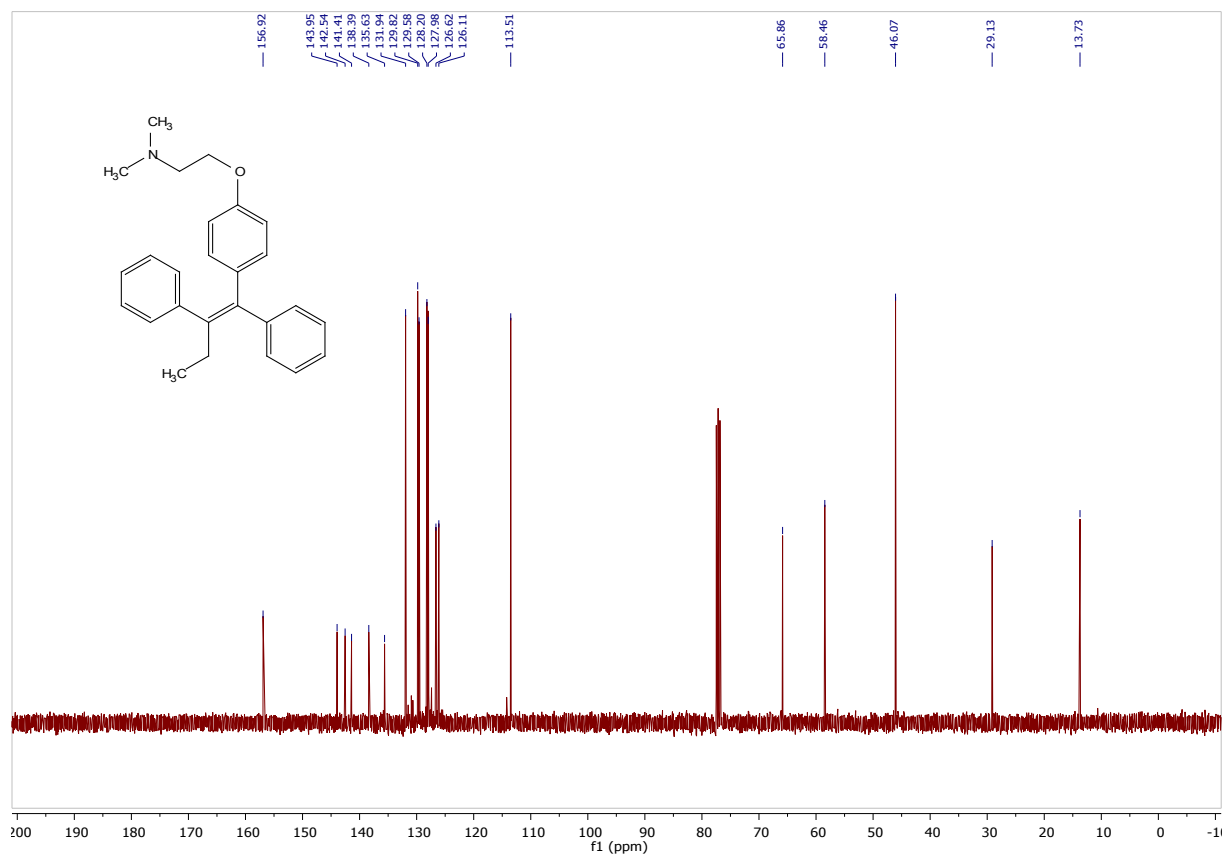
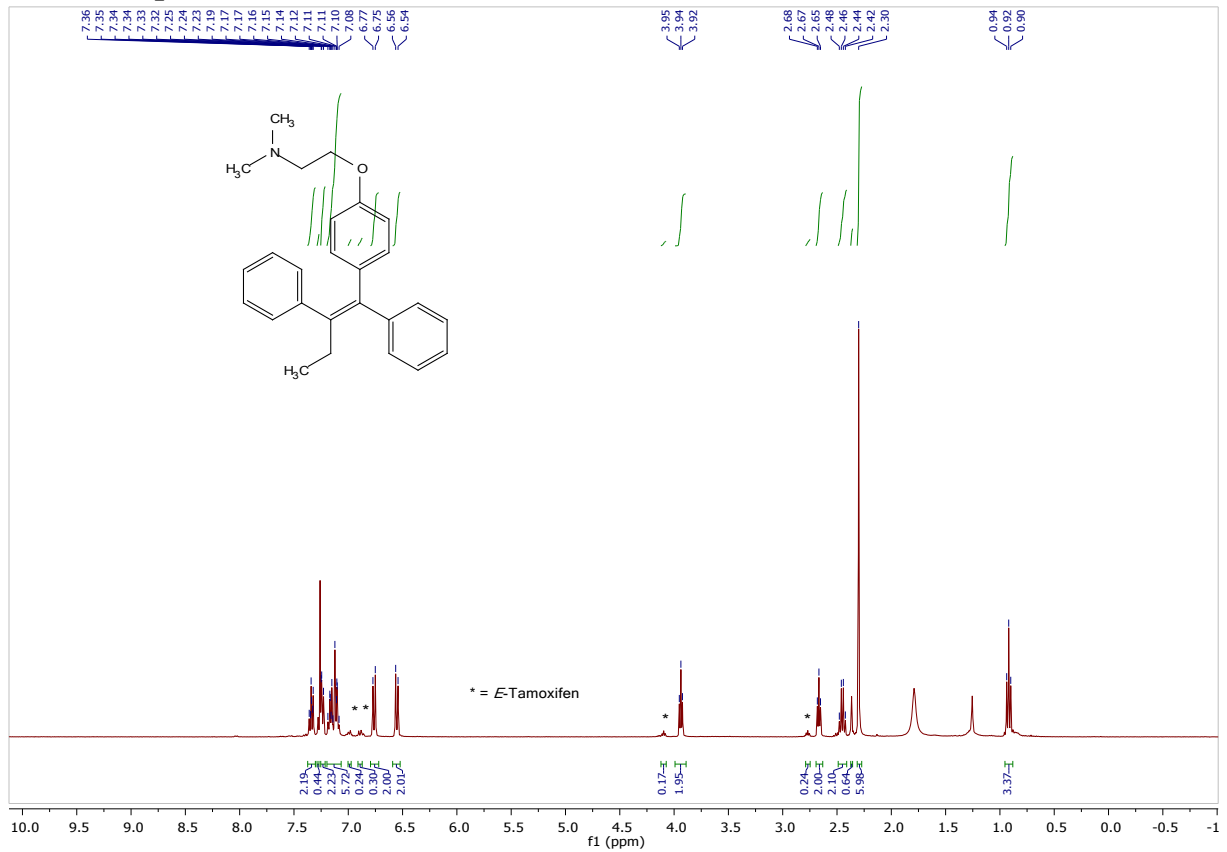
(Z)-(1-(4-(trifluoromethyl)phenyl)hex-1-ene-1,2-diyl)dibenzene (12c)

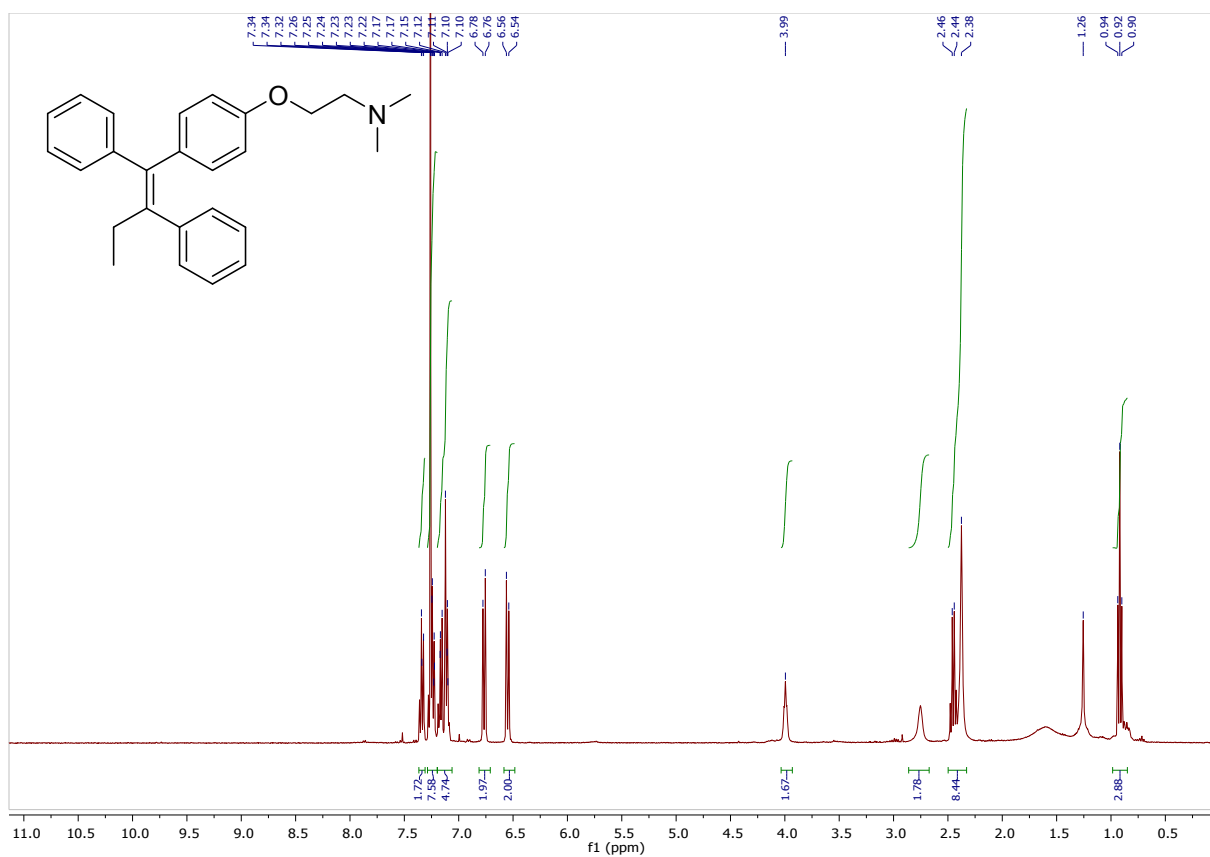


To a dry Schlenk flask (B) equipped with a stirring bar was added $\text{Pd}(t\text{-Bu}_3\text{P})_2$ (12.7 mg, 15 μmol , 5%) and 2 mL of dry toluene. By means of a syringe, 6 mL of dry oxygen were bubbled through the solution which was left stirring vigorously overnight, generating a deep red color. A solution of *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 SiO_2 (Pent, $R_f = 0.9$), and the yield corrected for the impurity (142 mg, 68 %). ^1H NMR (400 MHz, CDCl_3) δ 7.57 – 7.53 (m, 2H), 7.40 – 7.14 (m, 13H)*, 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. ^{13}C NMR (101 MHz, CDCl_3) 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, 124.23, 123.27, 35.75, 30.97, 22.75, 13.83. ^{19}F NMR (376 MHz, CDCl_3) δ -62.43.

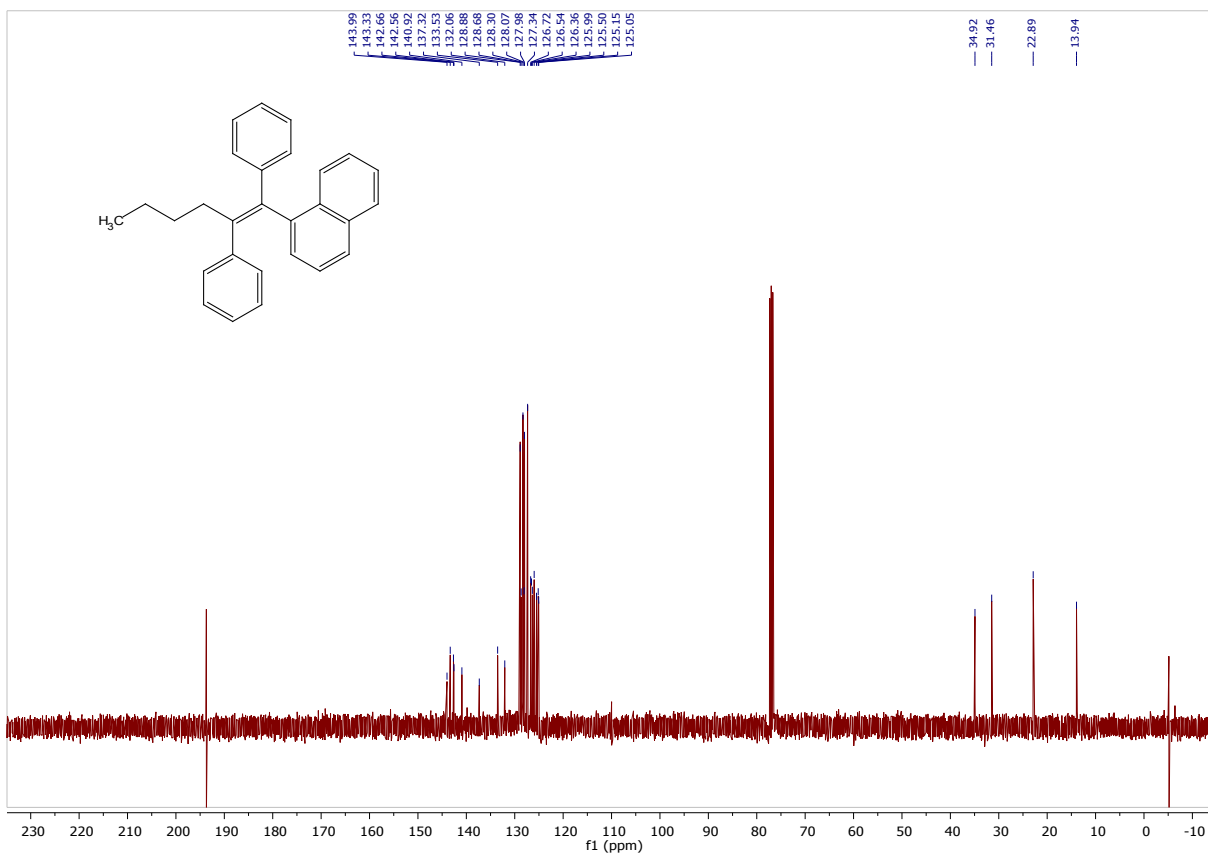
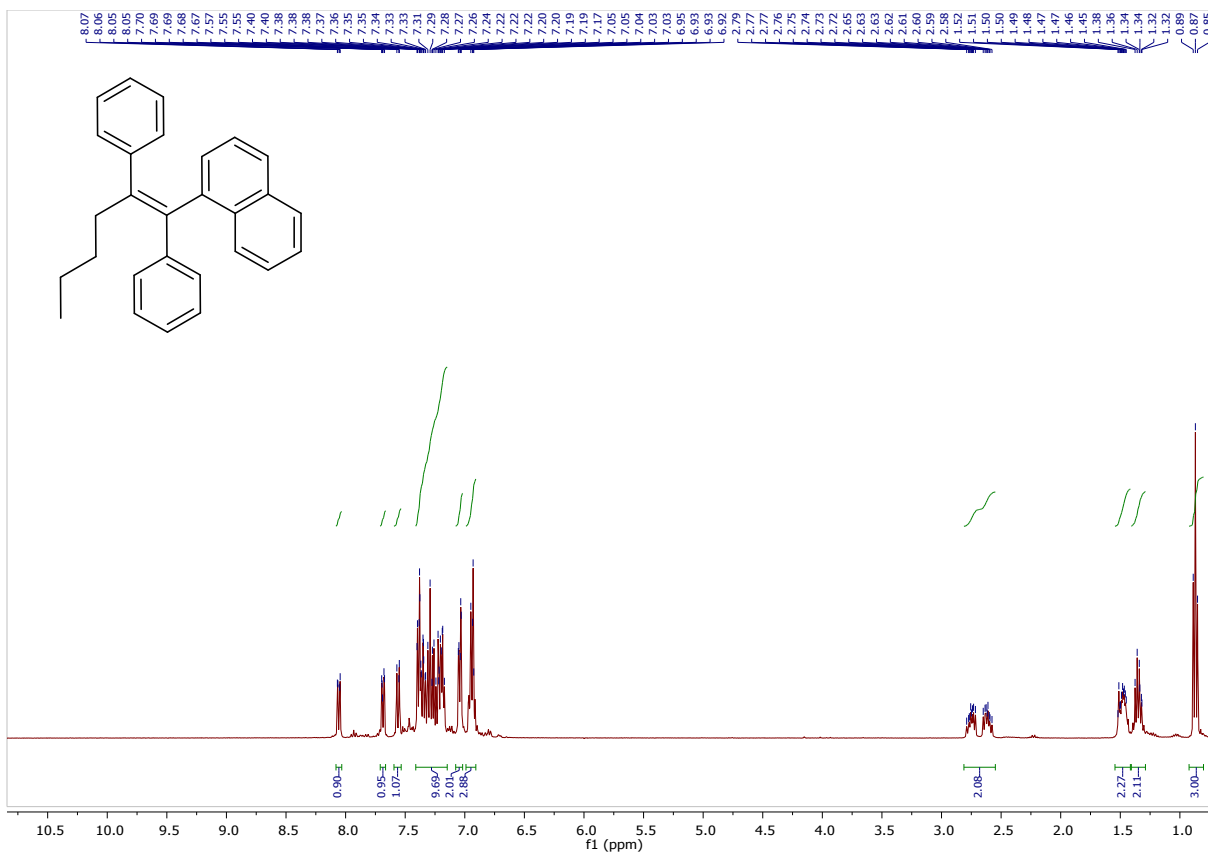
- ¹ D. Heijnen, F. Tosi, C. Vila, M. C. A. Stuart, P. H. Elsinga, W. Szymanski and B. L. Feringa *Angew. Chem. Int. Ed.*, 2017, **56**, 3354–3359.
- ² D. Heijnen, V. Hornillos, B. P. Corbet, M. Giannerini, and B. L. Feringa. *Org. Lett.*, 2015, **17**, 2262–2265.
- ³ D. Heijnen J. Gualtierotti, V. Hornillos, and B. L. Feringa *Chem. Eur. J.*, 2016, **22**, 3991–399.
- ⁴ Sun, P. -P.; Cheng, Y. -C.; Chang, M. -Y. *Synthesis*, 2017, **49**, 2411–2422.
- ⁵ Al-Hassan, M. I.; Miller, R. B. *J. Org. Chem.*, 1985, **50**, 2121–2123.
- ⁶ F. Xue, J. Zhao, T. S. A. Hor, T. Hayashi, *J. Am. Chem. Soc.*, 2015, **137**, 3189–3192.

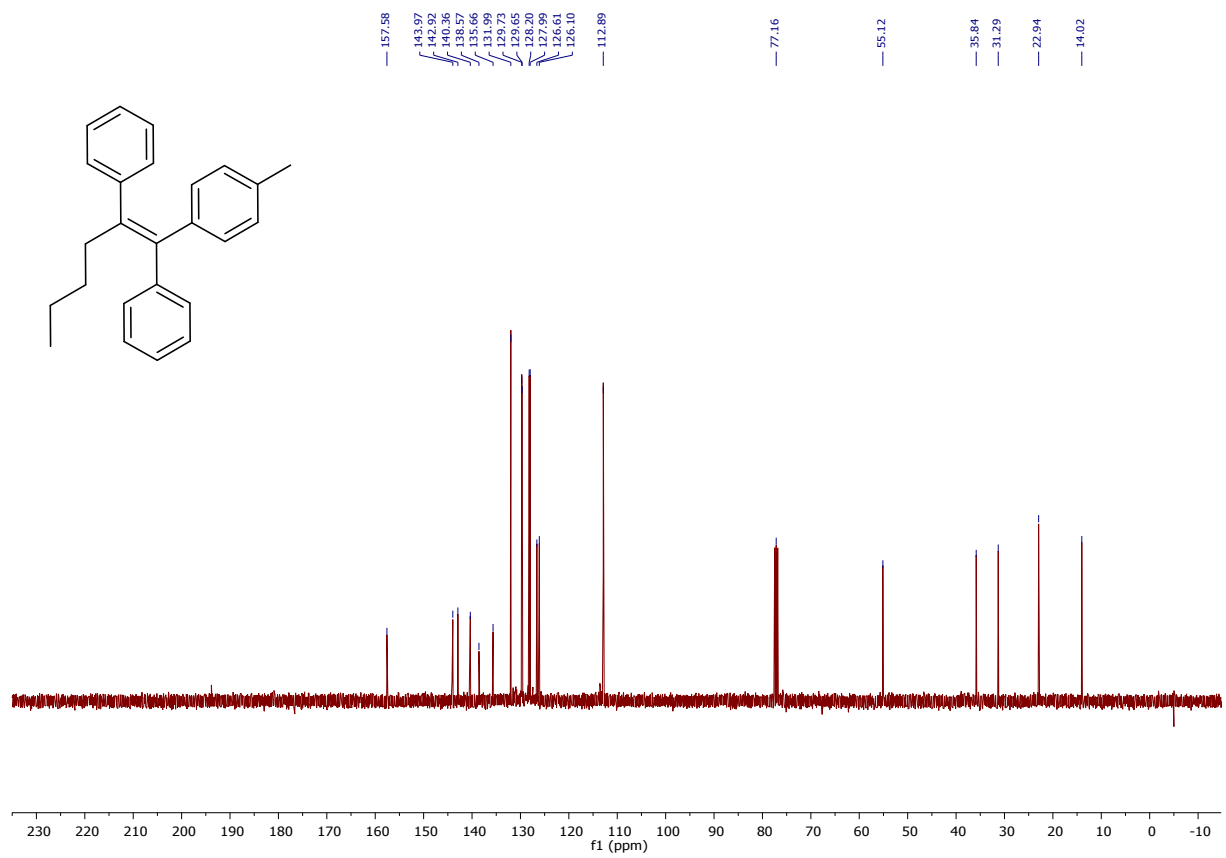
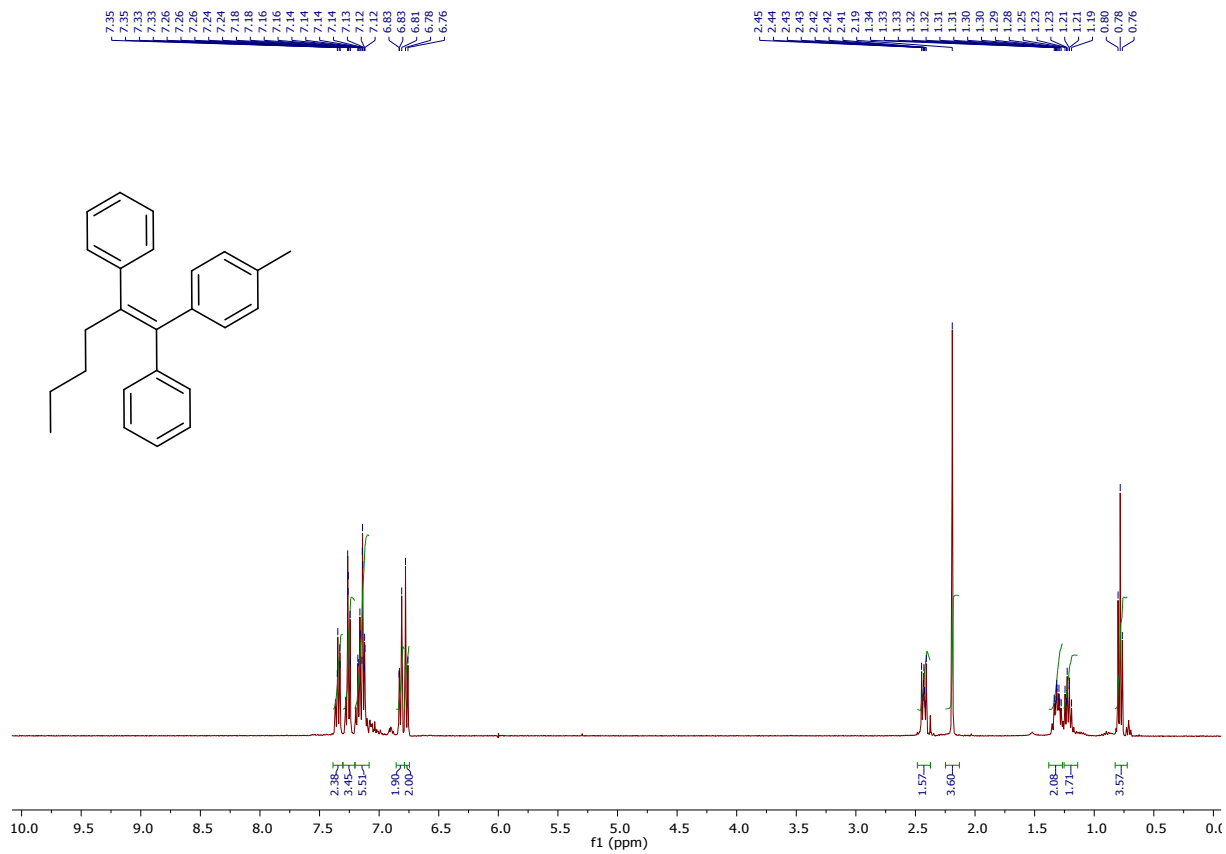
4. NMR Spectra

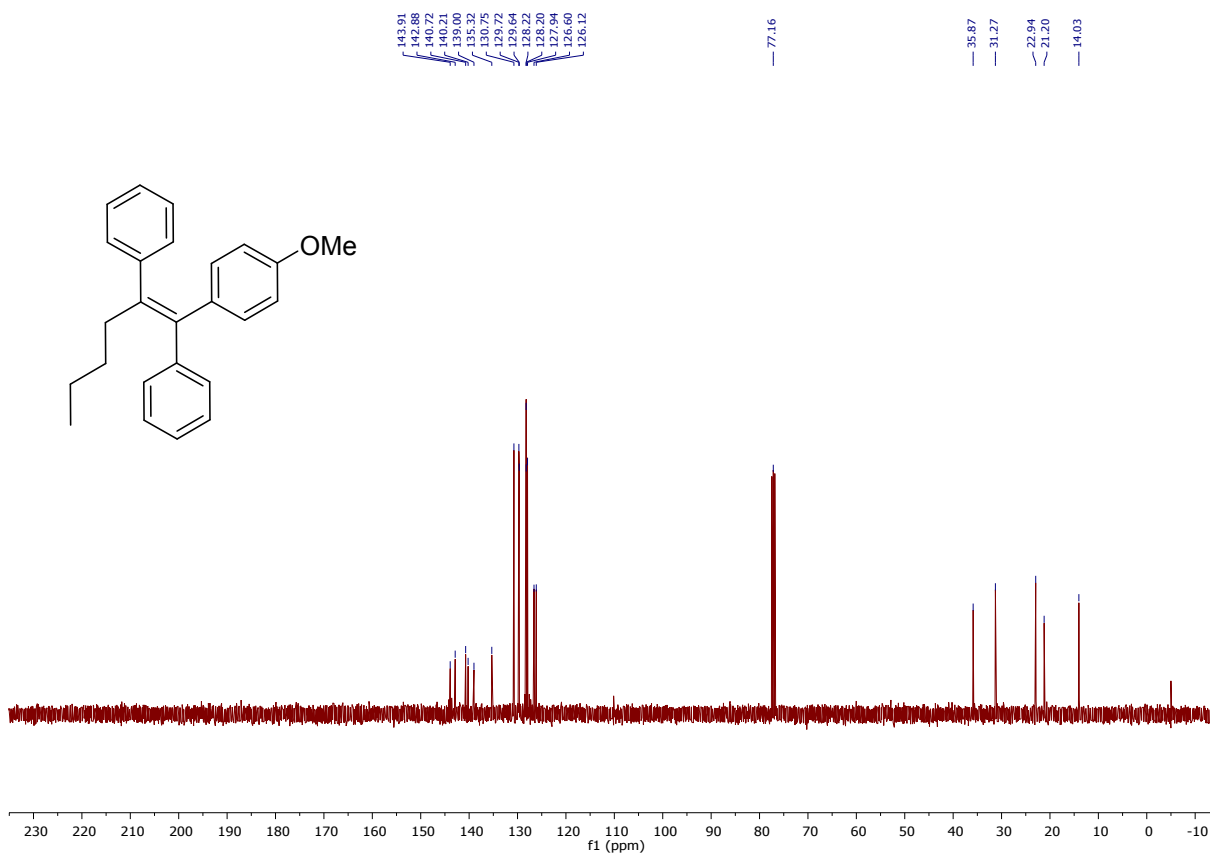
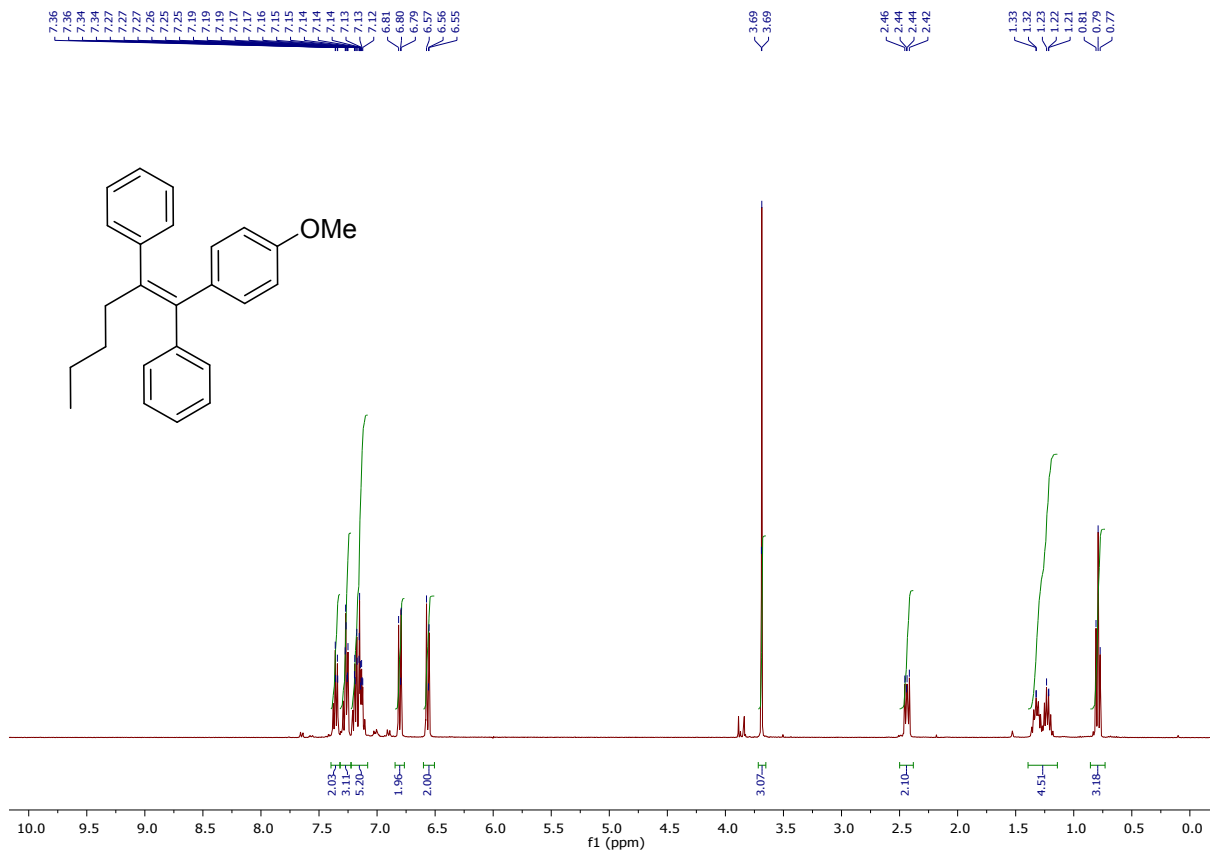


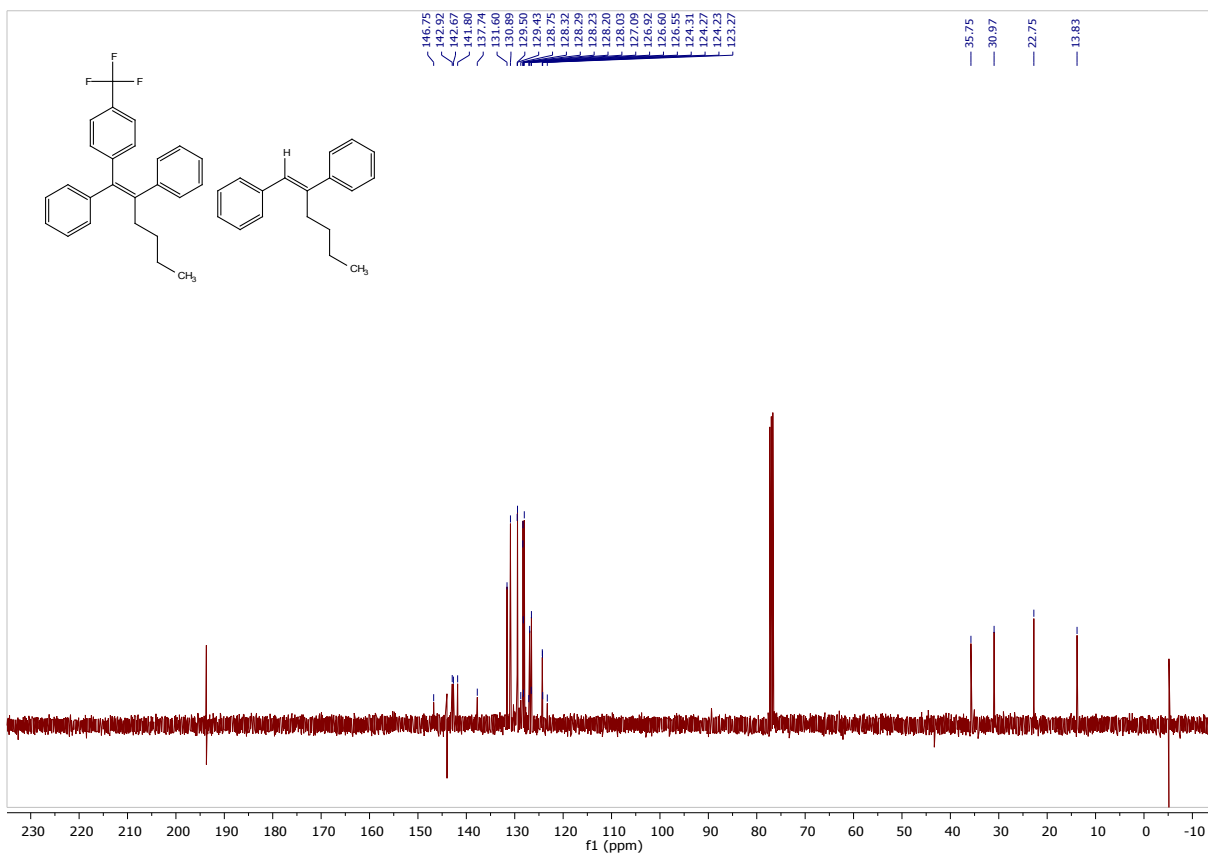
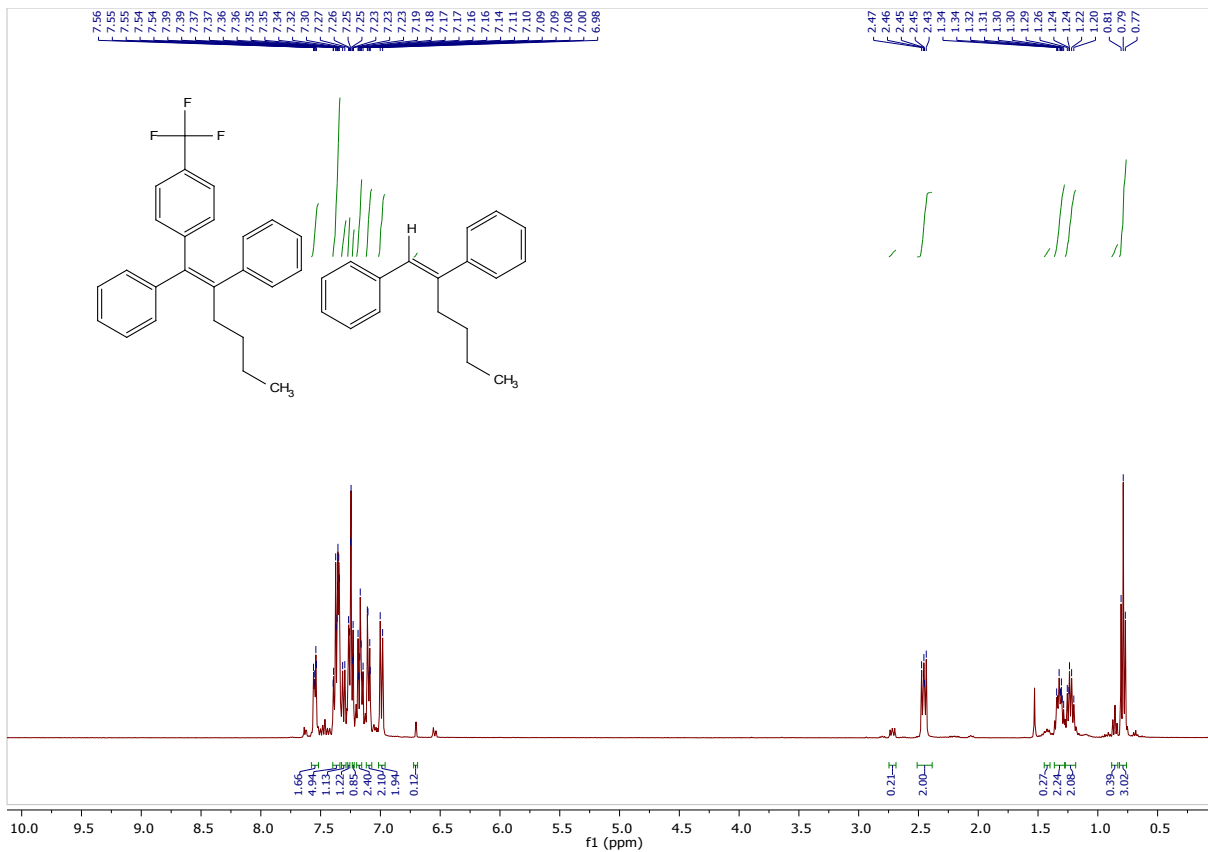


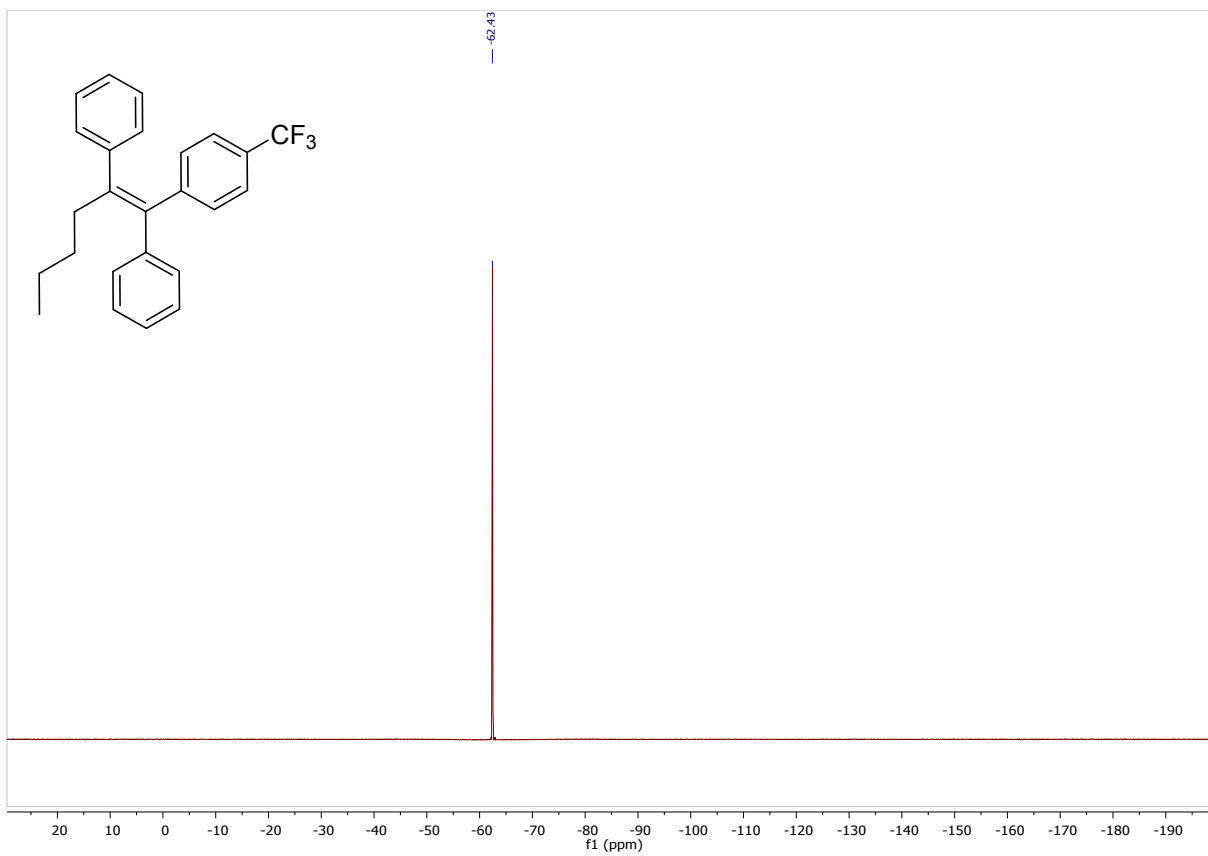
(Z)-Tamoxifen after prep HPLC containing traces of formic acid from the eluent.











Name/Year	Overall Yield Tamoxifen	Reagent (equiv.) Weighed mass	Mass Reagent Mass reagent * Equiv.						
Lay 2013	64%	Sm Phenol (1) Weighed mass	173 Base Nah (1) 173 Weighed mass	24 Dim-Amine-Salt HCl (1) 48 Weighed mass	144 144	Buli (1.1)	64		
Larock 2005	68%	Sm Phenol (3) Weighed mass	173 Base Nah (3) 519 Weighed mass	24 Dim-Amine-Salt HCl (3) 144 Weighed mass	144 432		70.4		
Hayashi 2015	41%	Sm Phenol (1) Weighed mass	173 Base Nah (1) 173 Weighed mass	24 Dim-Amine-Salt HCl (1) 48 Weighed mass	144 144	Acetylene (1)	130		
Yoshida 2003	62%	Sm Phenol (1) Weighed mass	173 Base Nah (1) 173 Weighed mass	24 Dim-Amine-Salt HCl (1) 48 Weighed mass	144 144	Pyridine sm (1)	189		
O'Shea 2006	38%	Sm Phenol (1) Weighed mass	173 Base Nah (1) 173 Weighed mass	24 Dim-Amine-Salt HCl (1) 48 Weighed mass	144 144	Etlr (1)	36		
Kochel 1997	65%	Sm Phenol (1) Weighed mass	173 Base Nah (1) 173 Weighed mass	24 Dim-Amine-Salt HCl (1) 48 Weighed mass	144 144	acetylene sm (1)	130		
Brown 2014	31%	Sm Phenol (1) Weighed mass	173 Base Nah (1) 173 Weighed mass	24 Dim-Amine-Salt HCl (1) 48 Weighed mass	144 144	acetylene sm (1)	130		
Hiyama 2005	39%	Sm Phenol (1) Weighed mass	173 Base Nah (1) 173 Weighed mass	24 Dim-Amine-Salt HCl (1) 48 Weighed mass	144 144	bisboron-alkene sm (1)	384		
Takagi 2007	32%	Sm Phenol (1) Weighed mass	173 Base Nah (1) 173 Weighed mass	24 Dim-Amine-Salt HCl (1) 48 Weighed mass	144 144	Zinc-Chloride (1.2)	350.4		
Qiu 2016	48%	Sm Phenol (1) Weighed mass	173 Base Nah (1) 173 Weighed mass	24 Dim-Amine-Salt HCl (1) 48 Weighed mass	144 144	acetylene (1)	102		
Polar 2014	35%	sm (1) Weighed mass	240 Base Nah (1) 240 Weighed mass	24 Dim-Amine-Salt HCl (1) 48 Weighed mass	144 144		102		
Takaki 2012	36%	Sm Phenol (1) Weighed mass	173 Base Nah (1) 173 Weighed mass	24 Dim-Amine-Salt HCl (1) 48 Weighed mass	144 144	acetylene (1)	130		
Hasome 2007	16%	Commercial sm Weighed mass	0 0	0 0	0	TMS s.m. (1.2)	190		
Schren 1986	47%	sm (1) Weighed mass	40 Base (1) 120 Weighed mass	198 Dim-Amine-Salt HCl (1) 198 Weighed mass	144 504	4,4-dihydroxybenzoph. (1)	220		
Ferriga 2018	68%	Sm Phenol (1) Weighed mass	173 Base Nah (1) 173 Weighed mass	24 Dim-Amine-Salt HCl (1) 48 Weighed mass	144 144	Etlr (1.3)	36		

Atom Economy and RME calculatio

For the atom economy, we use stoichiometry), and the mass

For the calculation of the Reaction weight*equivalents) and the reacti (“Yield Key SM”) of the (advanced syntheses, this is “bromo aminoethe preparation was kept identical for al

224	FFAA (2)	210	Et3N (2)	101
268.8	Iodobenzene (3)	420	Acetylene (1)	202
104	Iodobenzene (3)	204	Acetylene (1)	116
312	Arvl Iodide (1.2)	612		116
181	Arvl Iodide (1.2)	291		
217.2		349.2		
228	Arvl Iodide (1.5)	291	BCl3 (2.2)	117
342		436.5		
178	Eriisopropylborate (9)	188	Arvl Iodide (1)	257.4
356		1692		291
220	Iodine (1)	254	aminoether-zn-br (1)	291
440		254		65
254	Arvl Iodide (1.5)	291	NaOtBu (2)	65
381		436.5		96
204	Arvl Iodide (1)	291		192
204		291		
64	Ethylene (1)	26	boralane (1)	228
153.6		26		228
246	Ph-MgBr (1.2)	137	Br2 (1)	160
246		164.4		160
157	Bromine (1.2)	160	Et3N (3)	101
314		192		101
254	BUSSONME (1.3)	321	Arvl Iodide (1.5)	303
330.2		417.3		291
106	dIoro-phenetole (solv)	156	HfCl4 (1)	436.5
106		156		320
107	proplophenone (1)	134	TiCl4 (3)	320
481.5		134		189
178	Br-aminoether (1)			567
231.4				

Name/Year	Total Mass (with stoich)	Tot Mas (No stoich)	371/Total mass	Yield Key SM	Reaction Mass Efficiency	Yield	Atom Ec (No stoich)
Lay 2013		940					
Larock 2005	1326.2	765	0.279746645	0.56	0.100261197	64	0.394680851
Hayashi 2015	2135	943	0.173770492	0.56	0.066171803	68	0.48496732
Yoshida 2003	1061.4	1385	0.349538346	0.56	0.080254004	41	0.393425239
O'Shea 2006	1808.9	1140	0.20509702	0.56	0.071209685	62	0.267870036
Kochel 1997	2846	1010	0.130358398	0.56	0.027740267	38	0.325438596
Brown 2014	1254	1112	0.29585327	0.56	0.109347368	66	0.367326733
Hiyama 2005	1504.5	1220	0.246593553	0.56	0.042808641	31	0.333633094
Takagi 2007	1244	1605	0.298231511	0.56	0.065133762	39	0.304098361
Qiu 2016	2783.5	1450	0.133285432	0.56	0.023884749	32	0.231152648
Polgar 2014	2617.4	862	0.141743715	0.56	0.038100711	48	0.25562069
TAKAKI 2012	1277	1541	0.290524667	1	0.101683634	35	0.430394432
Hasome 2007	1985	929	0.186901763	0.56	0.037679395	36	0.240752758
Schwen 1986	1975	1168	0.187948101	1	0.030055696	16	0.399354144
Feringa 2018	3040.5	555	0.122019405	0.72	0.041291367	47	0.317636986
	643.2		0.5768803483	0.56	0.219646766	68	0.668468468