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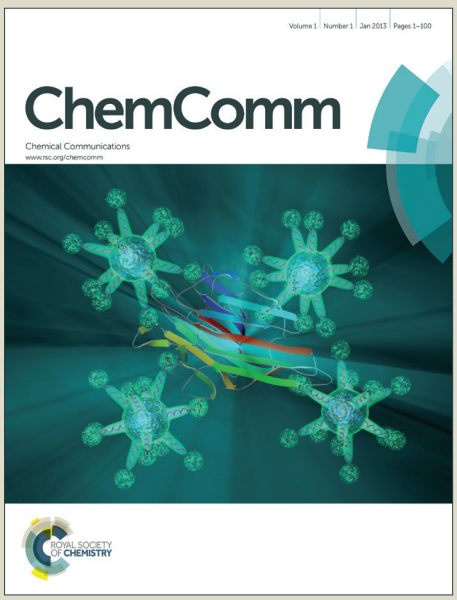

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An alternative synthesis of the breast cancer drug Fulvestrant (Faslodex®): Catalyst control over C-C bond formation

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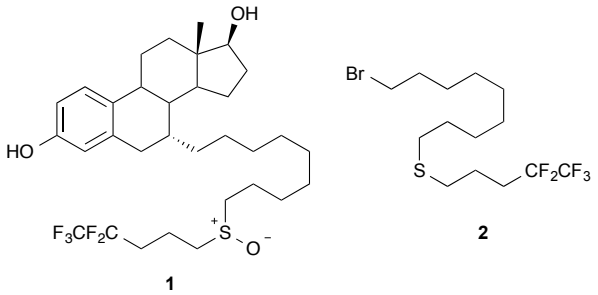
Fulvestrant (Faslodex®) was synthesized in four steps (35% overall yield) from 6-dehydronandrolone acetate. Catalyst controlled, room temperature, diastereoselective 1,6-addition of the zirconocene derived from commercially available 9-bromonon-1-ene was used in the key C-C bond forming step.

Breast cancer is the most frequently diagnosed cancer and is common in women from all regions of the world.[1] Faslodex® (active ingredient, fulvestrant, **1**) is a breast cancer drug with a unique mechanism of action; it is a selective estrogen receptor (ER) downregulator with antiestrogenic and antiproliferative, but not estrogen agonist, activity.[2] Approved by the FDA in 2002[3] and more recently in Europe (2010)[4] and Japan (2011),[5] Faslodex® had 2014 sales of US$720 million.[6] The drug is prescribed to postmenopausal women with advanced, tamoxifen resistant, or metastatic ER-positive breast cancer. It may also be used as a first-line treatment[2,7] with results comparable to tamoxifen and anastrozole.[8] **1** has no significant adverse effects and the efficacy and ease of fulvestrant administration (three times 1st month, then once per month) is attractive[9] and offers options for combination treatments.[10,11] Around 1990, ICI (now part of AstraZeneca) pharmaceuticals research on 7α-alkylated estradiol analogues with pure antiestrogenic activity[12] led to **1**,[13] which is used as a mixture of sulfoxide isomers.[12,14]



1 **2**

Figure 1 Structures of Fulvestrant (**1**) and Fulvestrant bromide (**2**).

The commercial-scale manufacturing route to **1** (Scheme 1) represents a tour-de-force in process development, and has produced tonne quantities of material.[15] The synthesis relies on selective addition of a Grignard reagent, which raised significant practical challenges. While these were ultimately overcome in the AZ manufacturing route, we became intrigued by the possibility of simplifying the synthesis of **1** by avoiding the use of highly reactive premade organometallic species. The route to **1** could (at least potentially) be improved by: A) shortening the length of the synthesis of (or finding an alternative to) **2**; B) improving the stereoselectivity, and conditions used, in the key C-C bond forming step; and C) eliminating impurities observed in the final product, which are generated by use of impure **2** and by side-reactions resulting from the use of the Grignard reagent derived from **2**.

"Fulvestrant bromide" **2** is precursor to Grignard reagent **3** which undergoes substrate controlled diastereoselective 1,6-conjugate addition to the steroidal dienone **4**.[15] The industrial scale routes, initially mediated by stoichiometric copper, and later refined into a catalytic process, require high purity **2**. Bromide **2** is produced in several steps followed by vacuum distillation using a wiped film evaporator (Scheme 1A).[15] Generation of Grignard reagent **3** requires temperature sensitive (maintaining ~45 ºC) portion-wise addition, and the optimized conjugate 1,6-addition to form **5** involves slow addition of **4** in THF over 3.5 h at –34 ºC. Using this procedure, **5** is produced in 90-95% yield with an α:β ratio of 2.5:1 (yield of **5**α ~64-68%), with the isomers being separated at the end of the synthesis.

As detailed elsewhere,[16,17] such Cu-catalyzed reactions are extremely sensitive to solvent, temperature, concentration, method of addition and the presence of additives. Additionally, compatibility of the Grignard reagent with other functional groups limits the options available for

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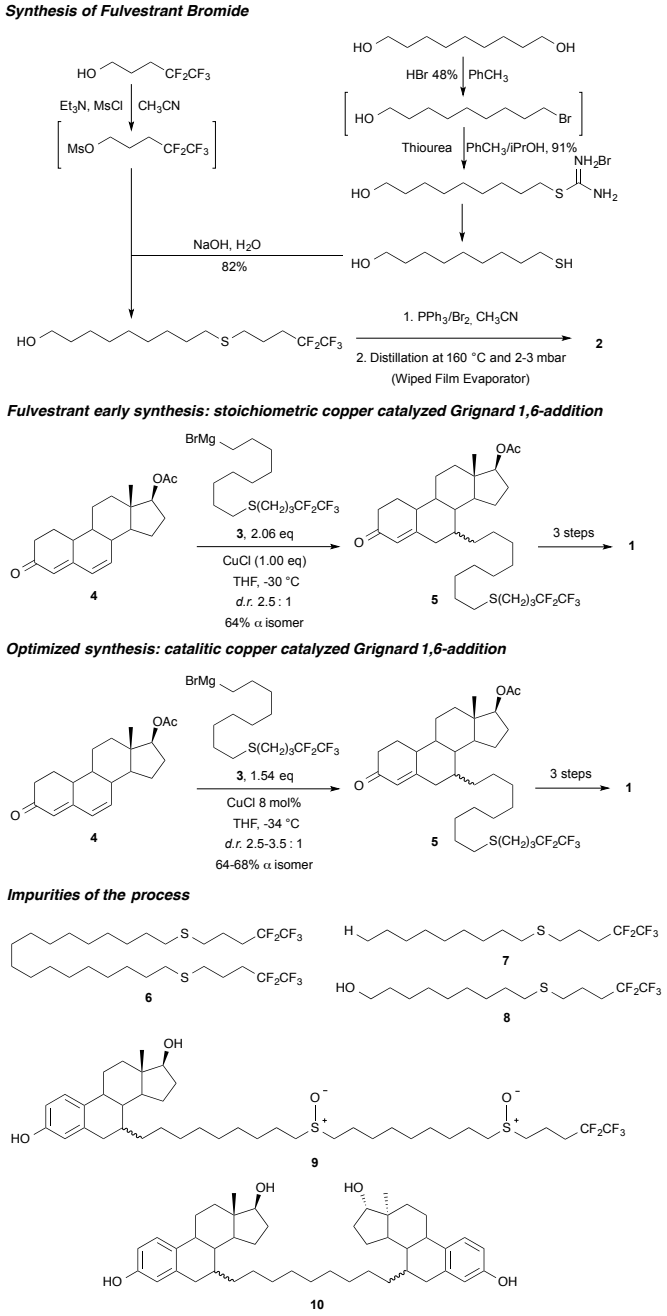
reaction/sequence design. In this case, a delicate purification of **2** is required to obtain high purity material, which is essential to both generating **3** effectively, and minimizing the formation of several impurities (**6** to **10**).[16]

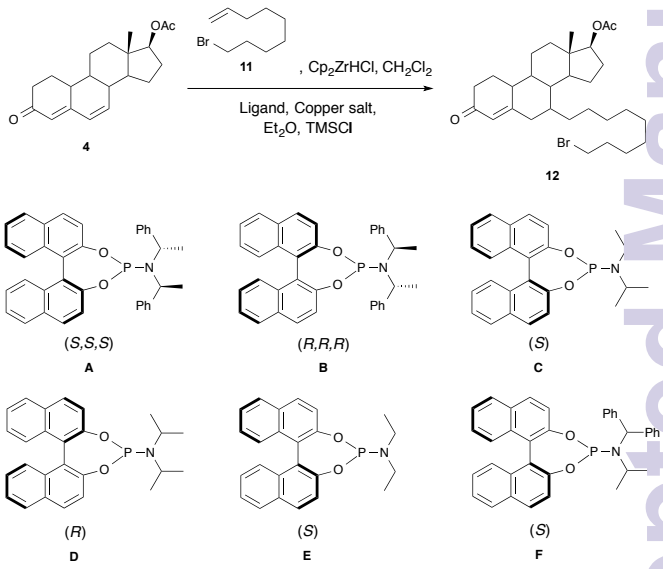


Scheme 1 AstraZeneca's synthesis of Fulvestrant Bromide, diastereoselective additions to form **5**, and then Fulvestrant, and the main impurities of these processes.

As part of research programme aimed at using alkenes as premade alkyl-metal equivalents in catalytic asymmetric additions[18] we have reported that 1,4 and 1,6-additions to steroid derivatives can occur at room temperature.[19] Here we use this approach in a streamlined four-step synthesis of **1** from two commercially available starting materials.

We examined a hydrometallation–copper-catalyzed 1,6-addition sequence using alkene **11**, bearing an alkyl bromide. This functional group is generally incompatible with Grignard reagents and is readily functionalized. Reactions were performed using previously optimized conditions[18a,19] with a combination of CH_2Cl_2 (for hydrometallation) and Et_2O (for conjugate addition), but we have shown that alkylzirconium additions are remarkably tolerant to changes in the solvent system,[18a] so other combinations can likely be used.

Table 1 Diastereoselective hydrometallation–1,6-conjugate addition[a]



Entry	Ligand	Copper source	T	d.r. [b]	Yield
1	-	CuBr•Me_2S	r.t.	1.3 : 1	40% α
2	PPh3	CuCl + AgOTf	r.t.	1.6 : 1	30% α
3	A	CuCl + AgOTf	r.t.	4.6 : 1	60% α
4	B	CuCl + AgOTf	r.t.	1 : 2.3	31% α
5	C	CuCl + AgOTf	r.t.	2.3 : 1	19% α
6	D	CuCl + AgOTf	r.t.	1 : 2.1	20% β
7	E	CuCl + AgOTf	r.t.	1.6 : 1	28% α
8	F	CuCl + AgOTf	r.t.	4.2 : 1	46% α
9	A	CuCl + AgOTf	0 °C	-	0%
10	A	CuCl + AgOTf	40 °C	2.9 : 1	46% α

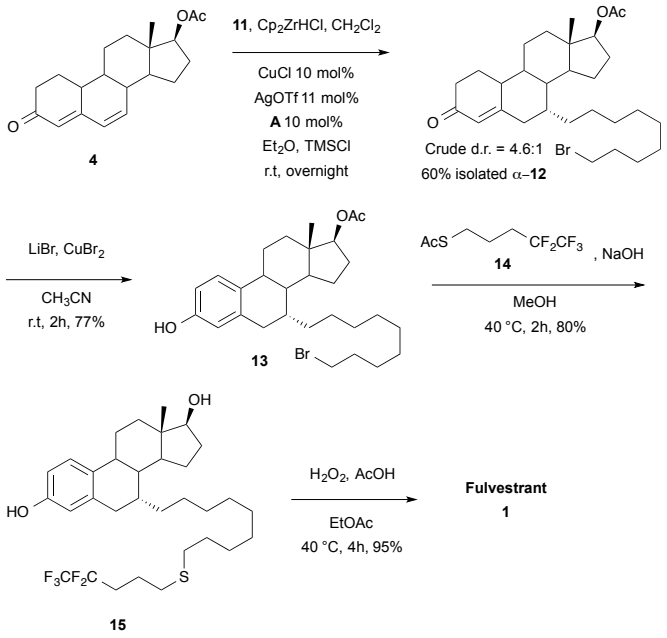
[a] Reaction conditions: Ligand (10% mmol), Copper (10% mmol), **11** (2.5 eq), Cp_2ZrHCl (2.0 eq), TMSCl (5.0 eq) [b] Crude diastereomeric ratio (α:β) determined by ^1H NMR spectroscopy [c] Isolated yield of pure isomer.

In situ hydrozirconation of commercially available 9-bromonon-1-ene **11** provides an alkylzirconium species which undergoes copper catalysed 1,6-addition to **4**. Using CuBr•Me_2S or PhP_3 as achiral ligands, allows addition (Table 1, Entries 1 and 2) at room temperature but poor crude ratios (~1.3:1 and ~1.6:1) of isomers of **12**. However, pure desired 7α-isomer was easily isolated by flash chromatography with yields of 40 and 30% respectively.

We found we could increase the stereoselectivity in the 1,6-addition using phosphoramidite ligands in combination with

situ generated Cu(I)OTf (Table 1, Entries 3-8). Of the ligands examined, **A** gave best *d.r.* and yield (4.6:1, 60% isolated yield). The use of TMSCl is essential to obtain good levels of conversion, without TMSCl, **12**α was obtained in 30% yield (not shown) together with 66% recovered starting material. We can also reverse the diastereoselectivity by using ligand **B** with the opposite absolute stereochemistry (*c.f.* Entry 3 with 4-6) but overall lower selectivity and yields were observed due to the inherent stereochemical control provided by dienone **4**. No improvements were observed when changing the reaction temperature (Entries 9-10).

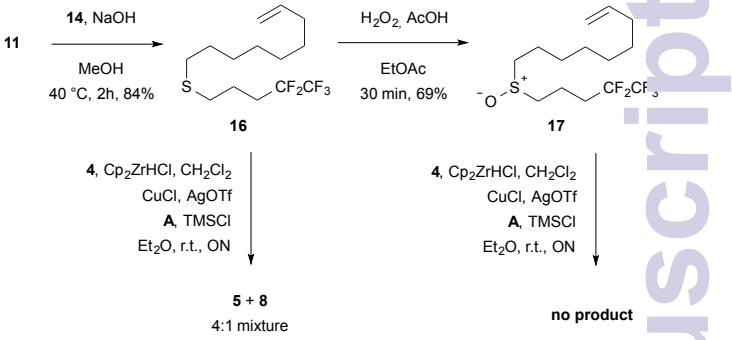
We have run the formation of **12** on a gram scale with no loss of yield or selectivity. With **12** in hand (Scheme 2), we used a mixture of $CuBr_2$ and LiBr to aromatize the enone to **13** (77%) without any observable over-bromination products;[15] aromatization is required at this stage to avoid conjugate addition of thiol to the enone unit in the next step.



Scheme 2 Synthesis of Fulvestrant

In situ hydrolysis of (4,4,5,5,5)-pentafluoropentyl ethanthiolate **14**[20] at 40 ºC liberates the thiol, displacing the bromide and giving **15** (80%); these conditions avoid isolation of malodorous (4,4,4,5,5)-pentafluoropentanthiol and remove the acetate protecting group on the 17β alcohol moiety.

Oxidation to sulfoxides **1** (35% H_2O_2, AcOH, EtOAc, 40 ºC) gave no observable overoxidation, and Fulvestrant **1** as a ~ 1 : 1 mixture of isomers (observable by ^{13}C NMR) in 95% yield.



Scheme 3 1,6-addition of alkyl chains bearing a sulphur atom. Reaction conditions: **4** (1.0 eq), **A** (20 mol%), CuCl (20 mol%), AgOTf (22 mol%), alkene (2.5 eq), Cp_2ZrHCl (2.0 eq), TMSCl (5 eq).

We also examined hydrometallation-addition of alkenes bearing a sulphide and sulfoxide (scheme 3). In both cases unsatisfactory results were obtained. 1,6-addition of **16** to give **5** provided 40% of the desired 7α-isomer, but it was obtained as an inseparable 4:1 mixture with alcohol **8**. Hydrometallation of **17** was not effective and 1,6-additon products were not obtained.

In conclusion, an alternative synthetic route to Fulvestrant involving hydrozirconation of a commercially available alkene and copper-catalyzed 1,6-addition has been developed. As the reaction tolerates an alkylbromide the 1,6-addition product can be readily functionalized, avoiding use of **2** and streamlining the synthesis. The main cause of source of impurities in previous routes was the use of **7**. Diastereoselectivity of 4.6:1 in favour of the desired α-anomer is observed using 10 mol% of a chiral copper catalyst. The overall yield of the four-step sequence is 35%.

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