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An improved synthesis of 3-aminoestrone

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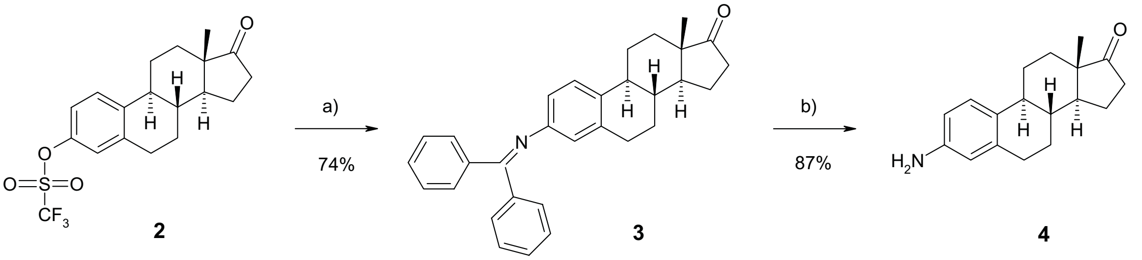
Abstract—An efficient Pd(0)-catalyzed protocol for the rapid and efficient preparation of 3-aminoestrone via 3-benzylaminoestrone from estrone–triflate is described. The three step synthesis proceeds with an overall yield of about 55% using X-Phos as optimal ligand for the Pd(0)-catalyzed Buchwald–Hartwig amination.

3-Aminoestrone (**4**), a non-natural C-18 steroid, has been described as a key intermediate for the synthesis of biologically active steroid derivatives which can be used, for example, for the treatment of prostate and breast cancers.[1] Unfortunately, the compound is not commercially available and the classical and the recent synthetic methods described so far[2–4] have some drawbacks, such as high reaction temperature, long reaction time, poor yields, low product purity and high costs. Thus, we were interested to develop a simple and efficient way to overcome these drawbacks.

In two recent publications about the transformation of estrone (**1**) into 3-aminoestrone (**4**), Pd(0)-catalyzed amination was used as a key reaction. In 2002, as shown in Scheme 1, Poirier and co-workers[4] reported a new efficient pathway starting with estrone–triflate (**2**). To introduce the nitrogen atom at position C-3 of estrone, they used benzophenone imine as a convenient ammonia equivalent. Their optimized conditions required three days of reaction time at 120 °C in a Schlenk tube [estrone–triflate, benzophenone imine, $Pd_2(dba)_3$, *S*(−)-BI-NAP, Cs_2CO_3, toluene (74%)] and, finally, by acidic hydrolysis 3-aminoestrone was isolated in 87% yield.

In 2003, Zhang and Sui reported[5] the preparation of 3-aminoestrone by using benzylamine as ammonia equivalent and slightly modified amination conditions [$Pd(OAc)_2$, BINAP, and NaO-*t*-Bu in toluene at 100 °C, 24 h] (Scheme 2). However, the reaction resulted in very low yield of desired amino derivative (**4**) (~15%) with mostly recovering estrone, generated by the hydrolysis



Scheme 1. 3-Aminoestrone synthesis via benzophenone imine. Reagents and conditions: (a) benzophenone imine, $Pd_2(dba)_3$, *S*(−)-BINAP, Cs_2CO_3, toluene, Schlenk tube, 120 °C, 3 days; (b) cat. HCl, wet THF, rt.

Keywords: Microwave; Buchwald–Hartwig amination; X-Phos; Palladium; 3-Aminoestrone; Steroids.

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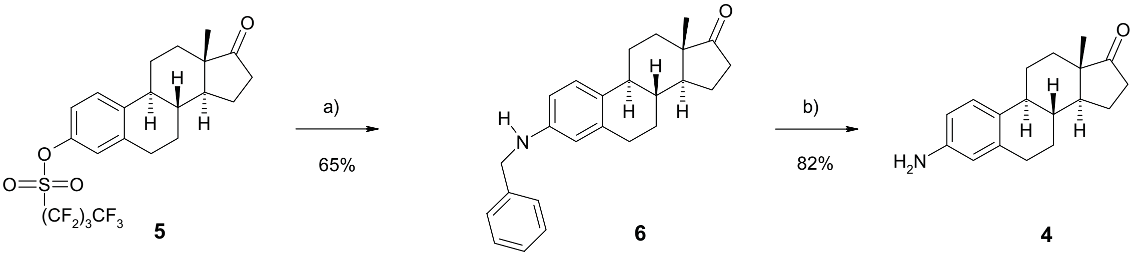
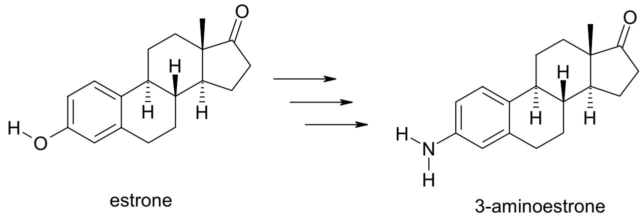


Scheme 2. 3-Aminoestrone synthesis via nonaflate. Reagents and conditions: (a) $Pd(OAc)_2$, BINAP, NaO-*t*-Bu, benzylamine, toluene, 100 °C, 24 h; (b) H_2, Pd/C.

of triflate (**2**) under alkaline reaction conditions. As a consequence, the authors replaced triflate by the corresponding nonaflate (**5**) possessing stronger stability toward base hydrolysis. Finally, 3-aminoestrone (**4**) was obtained by hydrogenation of the benzyl-protected amino derivative (**6**) in 82% yield.

As we were interested in larger amounts of 3-aminoestrone for different research programs, we wanted to improve this method, especially because of the high cost of $CF_3(CF_2)_3SO_2F$, by using triflic anhydride.

In recent years, the Pd(0)-catalyzed amination of aryl halides, triflates or tosylates (independently developed by the groups of Buchwald and Hartwig) has been widely used as methodology of choice for the synthesis of substituted anilines.[6] Thus, given the distinct advantages of Pd(0)-catalyzed amination reaction, we started a program to optimize the reaction conditions for the transformation of estrone–triflate to 3-benzylamino estrone using different ligands, palladium sources, solvents and bases at different temperatures. Our experimental results are presented and discussed below (Scheme 3).

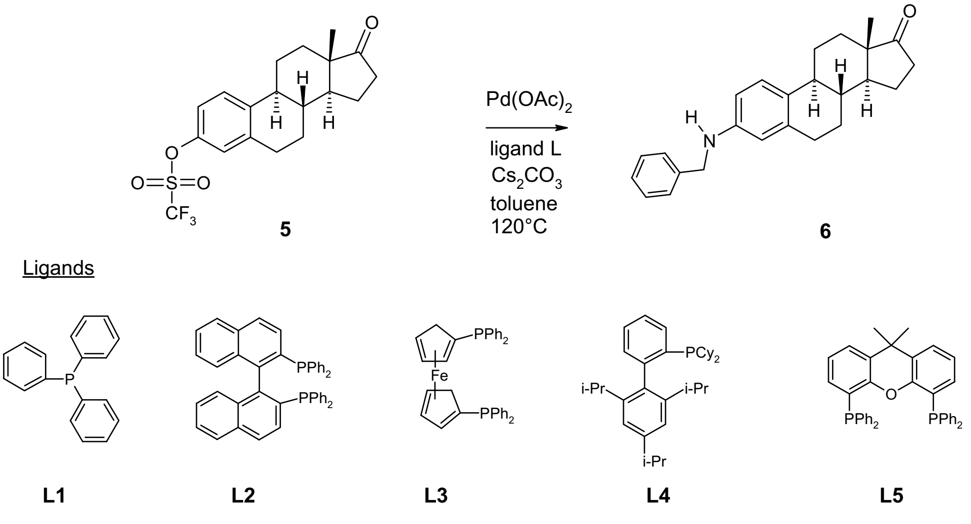


Scheme 3. Goal optimization.

Our work began with the intention to identify the best phosphine ligand required in the synthesis of 3-benzylamino estrone. In a typical experiment, estrone–triflate was subjected to Pd(0)-catalyzed amination in the presence of five different phosphine ligands, Cs_2CO_3 in toluene at 120 °C for 15 h using benzylamine as a NH_2 equivalent (Scheme 4).

The results of the ligand screening are depicted in Figure 1 and it can be seen that the extent of amination depends on the ligand used. Of the five ligands screened, the highest isolated yield was achieved by using X-Phos (L4) while the other ligands such as BINAP (L2) and DPPF (L3) gave much lower yields and $P(C_6H_5)_3$ (L1) and the bidentate ligand Xantaphos (L5) were observed to be highly ineffective.

Recently, Buchwald and co-workers reported that X-Phos (L4) was an excellent supporting ligand for the Pd-catalyzed amination of arylbenzene sulfonates as well. They also reported that the catalyst system based



Scheme 4. Ligand screening.

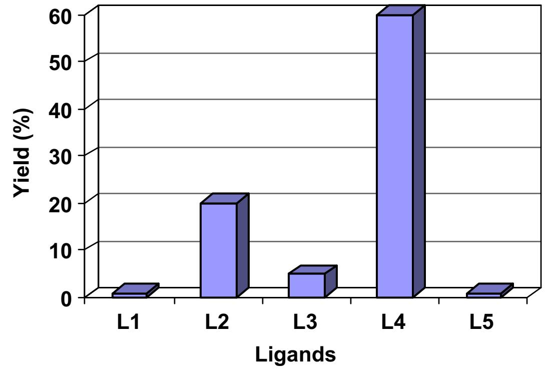


Figure 1. Ligand effect on palladium-catalyzed amination reaction of estrone–triflate with benzylamine. Estrone–triflate (1 equiv), Cs_2CO_3 (1 equiv), $BnNH_2$ (1.5 equiv), $Pd(OAc)_2$ (10 mol %), ligand (5 mol %), toluene, 120 °C, 15 h.

on X-Phos exhibits both dramatically increased activity and stability relative to those based on simple biaryl phosphine ligands.[7] However, our best results were still only 60% yield so we proceeded to further optimize the reaction by varying other parameters, like palladium source, solvent system, base and temperature.

As the Pd source has been described to affect the amination step[8] in a crucial way, reactions with two different Pd sources were investigated and the results are compared in Table 1.

Reactions with both the catalysts successfully gave the desired product in almost comparable yields (Table 1). Due to a slightly higher yield and for economical reasons, we decided to use the pre-catalyst $Pd(OAc)_2$ for further investigations.

We also wanted to explore the different solvent systems (see Table 2). Toluene and 1,4-dioxane are often used for aryl amination, while the mixture of toluene/*tert*-butyl alcohol has been used for the amination of aryl sulfonates.[9]

Table 1. Pd source effects on palladium-catalyzed amination reaction of estrone–triflate with $BnNH_2$[a]

Entry	Pd source	Yield[b] (%)
1	$Pd_2(dba)_3$	54.1
2	$Pd(OAc)_2$	60.0

[a] Reagents: estrone–triflate (1 equiv), $BnNH_2$ (1.1 equiv), Cs_2CO_3 (1 equiv), Pd(0) (10 mol %), ligand X-Phos (5 mol %), toluene at 120°C for 15 h in a sealed tube.

[b] Isolated yield.

Table 3. Effect of ligand amount on palladium-catalyzed amination of estrone–triflate with $BnNH_2$ in toluene[a]

X-Phos (mol %)	$Pd(OAc)_2$ (mol %)	Temp (°C)	Time (h)	**6** (%)[b]	**2** (%)[b]
5	10	120	15	60	29.4
10	10	120	15	74.5	17.2

[a] Reagents and conditions: estrone–triflate (1 equiv), $BnNH_2$ (1.1 equiv), Cs_2CO_3 (1 equiv), $Pd(OAc)_2$ (10 mol %), X-Phos.

[b] LC yield.

As summarized in Table 2, it was found that toluene and the mixture of toluene/*tert*-butyl alcohol (5:1) could be used as appropriate solvent systems, whereas 1,4-dioxane gave mainly or exclusively estrone, which might have been formed by hydrolysis of starting material, without any traces of the desired product. It may be here mentioned that similar results are reported for Buchwald couplings under microwave-reaction conditions.[10]

In order to improve the yield of **6**, either increasing amounts of ligand, palladium or raising temperature or a longer reaction time are considered. Thus, at first to ensure higher conversion we repeated the amination reaction by increasing the amount of X-Phos (10 mol %, see Table 3) and observed better yields. The reaction was scaled up to 20 g without yields getting affected.

Encouraged by our findings, subsequently, in order to reduce the reaction time we decided to investigate other solvents with higher boiling points by comparing thermal heating with microwave-irradiation conditions. Since the introduction of the high-speed microwave-assisted synthesis, a lot of publications documented the rate enhancement under microwave-irradiation conditions.[10] Besides, a better reproducibility often with higher yields and less side reactions has been observed as well. Though several reports of microwave-assisted Pd-catalyzed aryl aminations have appeared in the literature,[11] only recently first results with aryl triflates were reported.[12] In a first stage, we decided to investigate the stability of estrone–triflate with and without the presence of Cs_2CO_3 (see Table 4).

As given in Table 4, up to 160 °C estrone–triflate is stable within the solvents investigated. But, in the presence of Cs_2CO_3 at temperatures higher than 100 °C, the hydrolysis cannot be avoided. Finally, in DMF and DMSO within 30 min at 160 °C estrone–triflate is completely hydrolyzed to estrone, whereas in NMP, 82% of hydrolysis product formation is observed and 17% of the starting material remain unreacted.

Table 2. Solvent effect on palladium-catalyzed amination of estrone–triflate with $BnNH_2$[a]

Solvent	Product[b] **6** (%)	Triflate[b] **2** (%, recovered)	Estrone[b] (%)	Conditions (°C; h)
Toluene	60	29.4		120; 15
Toluene/*t*-BuOH (5/1)	68.4	24.4	3.4	120; 15
1,4-Dioxane			100	100; 6

[a] Reagents: estrone–triflate (1 equiv), $BnNH_2$ (1.1 equiv), Cs_2CO_3 (1 equiv), $Pd(OAc)_2$ (10 mol %), X-Phos (5 mol %).

[b] Isolated and LC data.

Table 4. Aminoestrone synthesis: temperature and solvent effects under thermal conditions[a]

Solvent	Cs_2CO_3	Temp (°C)	Time (h)	Triflate (%)	Estrone (%)	Impurity
Toluene	No	120	16	100	0	0
Toluene	Yes	120	16	92.8	5.8	1.3
DMSO	No	100	16	98	2	0
DMSO	Yes	100	0.5	3.7	91.3	5
DMSO	Yes	160	0.5	4.2	93.9	0.9
DMF	No	160	16	100	0	0
DMF	Yes	160	0.5	0	87.7	12.3
NMP	No	100	16	100	0	0
NMP	Yes	100	3	20.4	68	11.6
NMP	Yes	160	0.5	17.2	82.0	0.7

[a] Reactions performed in sealed tubes. LC–MS data.

Nevertheless, we replaced toluene by DMF in order to investigate the Pd(0)-catalyzed amination in another solvent at 160 °C. To our surprise, in contrast to the above mentioned complete hydrolysis of estrone in DMF, we observed the formation of benzylaminoestrone in good yields. (Reaction conditions: estrone–triflate (1 equiv), $BnNH_2$ (1.1 equiv), Cs_2CO_3 (1 equiv), $Pd(OAc)_2$ (1 mol %), X-Phos (5 mol %) at 160 °C in 10 min, yield 78%.) Obviously, the reactivity of benzylamine at 160 °C is higher than the rate of hydrolysis.

Encouraged by these results, we decided to optimize the reaction conditions in DMF under microwave-irradiation conditions too (Scheme 5).[13] The results are summarized in Table 5.

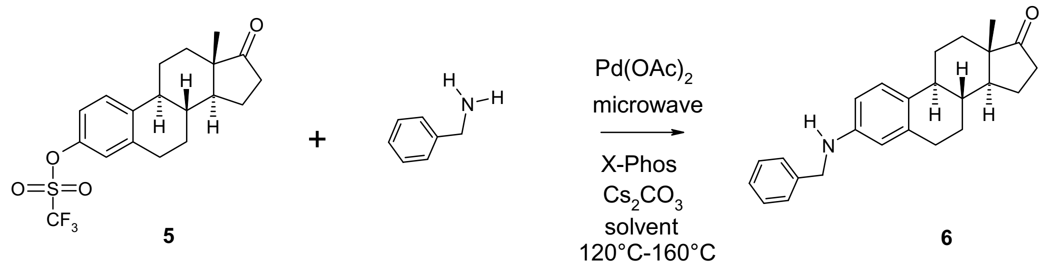
By increasing the temperature to 160 °C within 30 min, the reaction went to completion. Furthermore, the reaction time and the equivalents of $Pd(OAc)_2$, X-Phos and $BnNH_2$ were varied to optimize the reaction conditions. Finally, heating of triflate **5** at 160 °C for 10 min with 1.1 equiv of $BnNH_2$, 5 mol % of X-Phos and 1 mol % of $Pd(OAc)_2$ are observed as optimized conditions. With these data in hand, as mentioned above the Buchwald reaction has been performed under thermal conditions as well, yielding 78% of isolated amino benzyl estrone **6**.[14]

In addition, we explored the use of other bases under microwave-irradiation conditions, such as K_2CO_3, KO-*t*-Bu, Et_3N and K_3PO_4. But, by using K_2CO_3 and KO-*t*-Bu, we observed the formation of only traces of product and by using Et_3N estrone–triflate did not yield formation of any product.

To summarize, we have developed two different approaches for the Pd(0)-catalyzed aminations of estrone–triflate. The reaction can be carried out either in toluene or toluene/*tert*-butanol (5:1) as a solvent mixture at 120 °C for 15 h or the reaction time can be reduced dramatically by using DMF as solvent at 160 °C for 10 min only.

With these optimized conditions for the palladium-catalyzed amination and subsequent hydrogenation, estrone–triflate **5** gives the desired 3-aminoestrone **6** with an overall yield of about 55% (see Scheme 6).[14,15]

In conclusion, we have developed a convenient protocol for the rapid and efficient preparation of 3-aminoestrone via 3-benzylaminoestrone from estrone–triflate. We developed a new methodology which is advantageous over reported methods. Previously described processes either needed long reaction hours or expensive reagents



Scheme 5. Microwave-assisted palladium-catalyzed amination.

Table 5. Optimization of palladium-catalyzed amination of estrone–triflate with $BnNH_2$ under microwave-irradiation conditions[a]

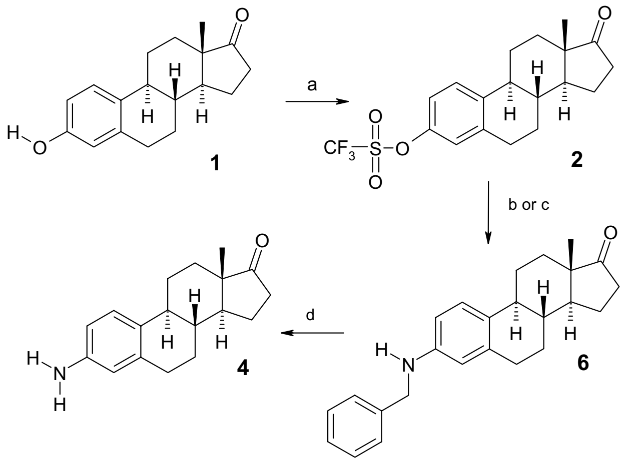
$BnNH_2$ (equiv)	X-Phos (mol %)	$Pd(OAc)_2$ (mol %)	Solvent	Temp (°C)	Time	**6**[b] (%)
1.5	10	10	Toluene	120	15 h	74[c]
1.5	10	10	Toluene	120	0.5 h	51[d]
1.5	10	10	DMF	160	0.5 h	97
1.5	10	2	DMF	160	0.5 h	94
1.5	10	10	DMF	160	5 min	93
1.1	5	1	DMF	160	10 min	93

[a] Reagents and conditions: estrone–triflate (1 equiv), $BnNH_2$, Cs_2CO_3 (1 equiv), $Pd(OAc)_2$, X-Phos.

[b] LC–MS yield.

[c] Conventional heating in sealed tubes; same conditions as mentioned before.

[d] Reaction incomplete, 49% starting material left.



Scheme 6. Improved synthesis of 3-aminoestrone. Reagents and conditions: (a) Tf_2O, Et_3N, DCM, 0 °C (90–94% yield); (b) estrone–triflate (1 equiv), $BnNH_2$ (1.5 equiv), $Pd(OAc)_2$ (10 mol %), X-Phos (10 mol %), Cs_2CO_3 (1 equiv), toluene, 120 °C, 15 h (74% yield); or estrone–triflate (1 equiv), $BnNH_2$ (1.1 equiv), Cs_2CO_3 (1 equiv), $Pd(OAc)_2$ (1 mol %), X-Phos (5 mol %), DMF, 160 °C, 10 min (yield 78%); (c) $BnNH_2$ (1.1 equiv), $Pd(OAc)_2$ or $Pd_2(dba)_3$ (1 mol %), X-Phos (5 mol %), Cs_2CO_3 (1 equiv) DMF under MW conditions, 160 °C in 10 min (93%); (d) methanol:THF (1:1), acetic acid (1%), 10% palladium over carbon (20% w/w), 55 psi, 30 °C, 6 h (76% yield).

to prepare 3-aminoestrone, our method gives the product in very short reaction times (10 min), in good yields. This compound is not only prepared through conventional heating conditions but also can be synthesized under microwave-irradiation conditions in quantitative yield.

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13. Emrys™ Optimizer from Biotage (formerly Personal Chemistry) was used for all experiments described here (power 300 W).
14. Typical procedure for Pd(0)-catalyzed amination of estrone–triflate **5**: initially, pre-catalyst was prepared by heating palladium acetate (55 mg, 10 mol %), cesium carbonate (0.806 g, 2.4 mmol), X-Phos (118 mg, 10 mol %) and benzylamine (0.298 ml, 2.73 mmol) in DMF (7.5 mL) in a sealed tube under nitrogen gas atmosphere at 70 °C for 10 min and cooled to rt. Then, the triflate **5** (1 g, 2.48 mmol) was dissolved in DMF (2.5 mL) and charged into the tube, purged with nitrogen and heated at 160 °C for 10 min. The reaction mixture was cooled to rt, filtered through a pad of Celite, poured into water (100 mL) and extracted with dichloromethane (50 mL). Organic layer was washed with saturated brine solution (30 mL) and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to get the crude product which was purified on column chromatography using DCM/*n*-hexane (60:40) to yield the desired product **6** as colourless solid (0.7 g, 78%), mp 136–138 °C. Mass spectrum: *m*/*e*: 360.2 (MH^+). ^1H NMR (200 MHz, $CDCl_3$): δ 7.35–6.39 (m, 8H, aromatic), 4.31 (s, 2H, benzylic), 3.00–1.26 (m, 15H, steroid envelope) and 0.91 (s, 3H, $C18\text{-}CH_3$).
15. 3-Aminoestra-1,3,5(10)-trien-17-one **4**: the benzylamino derivative **6** (20 g, 55.7 mmol) was hydrogenated over 10% palladium over carbon (4 g) in a methanol/tetrahydrofuran mixture (100 mL each) containing 1% acetic acid for 6 h at 55 psi at ambient temperature in Parr hydrogenator. The catalyst was filtered over Celite bed and the solvent mixture was removed under reduced pressure. The product was purified on silica gel (230–400 mesh) column chromatography using ethyl acetate/*n*-hexane (5:95) as eluent affording the product in tan crystals form in 11.4 g (76%) quantity, mp 199–200 °C. The characteristics of 3-aminoestrone are identical to those reported in the literature.[16] Mass spectrum: *m*/*e*: 271 (MH^{2+}). ^1H NMR (400 MHz, $CDCl_3$): δ 7.01 (d, 1H, aromatic), 6.47 (d, 1H, aromatic), 6.39 (s, 1H, aromatic), 4.05 (br s, 2H, NH_2), 3.47–1.39 (m, 15H, steroid envelope) and 0.83 (s, 3H, $C18\text{–}CH_3$).
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