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Development of an Improved Route for the Synthesis of an Abemaciclib Intermediate

Michael P. Carroll[1], Harold Moloney[1], Olivia Gowran[2], Aoibheann O'Connor[1], Eoin M. Wilson[1], Michael M. Murray[1], Mark A. Pietz[3], Douglas P. Kjell[3], C. Brad Held[3], Michael O. Frederick*[3].*

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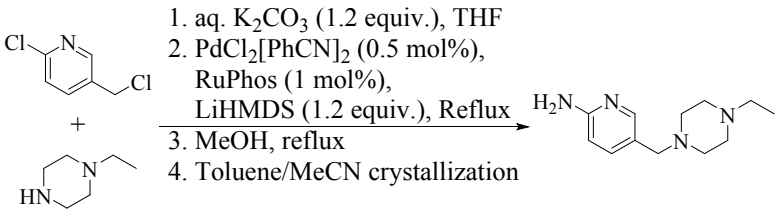
TOC Figure.


1. aq. K2CO3 (1.2 equiv.), THF
2. PdCl2[PhCN]2 (0.5 mol%),
RuPhos (1 mol%),
LiHMDS (1.2 equiv.), Reflux
3. MeOH, reflux
4. Toluene/MeCN crystallization

ABSTRACT: A new synthesis for an intermediate of abemaciclib is described. Keys to this route are: use of inexpensive starting materials; biphasic amine alkylation for mild C–N bond formation; anhydrous coupling of a 2-chloropyridine derivative with LiHMDS to avoid a hydroxy impurity; and neutral, fluoride-free conditions to affect desilylation. Scale-up of the optimized conditions are described on kilogram scale.

KEYWORDS: Abemaciclib, CDK 4/6 Inhibitor, Pd-catalyzed C-N coupling, TMS removal

Abemaciclib (brand name Verzenio) is a small molecule CDK4/6 inhibitor approved for the treatment of hormone-receptor-positive, HER2-negative metastatic or advanced-stage breast cancer as a monotherapy, in combination with fulvestrant,[1] or a non-steroidal aromatase inhibitor.[2]

A recent publication has described a route towards the synthesis of abemaciclib (**1**) by first breaking the molecule into two roughly equal pieces (**2** and **3**) which are joined through a palladium-catalyzed amination (Figure 1).[3] Fragment **3** was derived from ethyl

piperazine (**4**) and bromoaldehyde **5** via a Leuckart–Wallach reductive amination[4] in flow followed by a copper-catalyzed Ullmann-type amination.

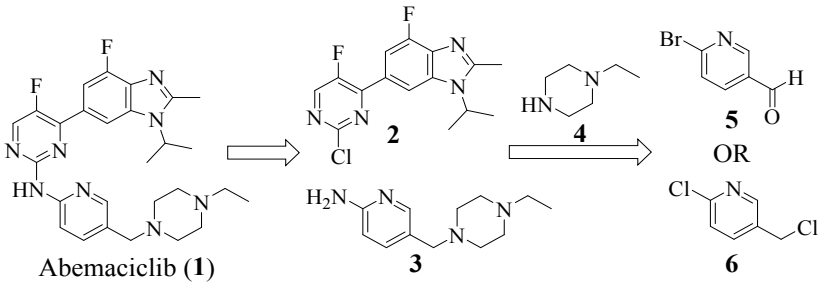
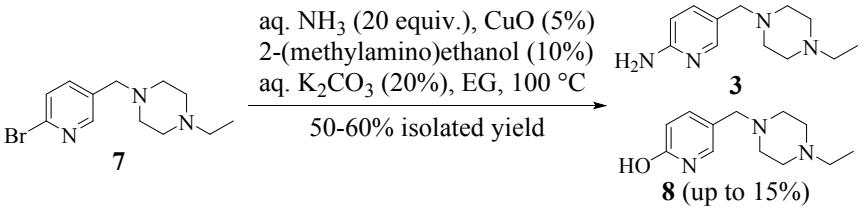


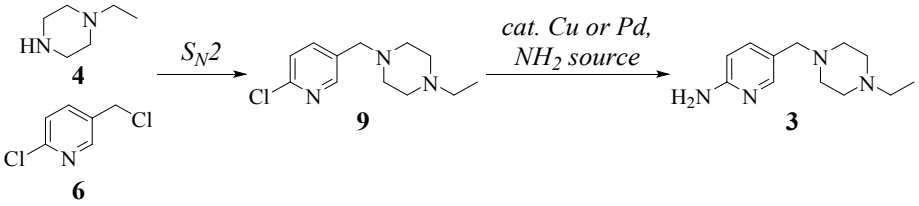
Figure 1. Retrosyntheses of abemaciclib (**1**).

The process is robust and affords high quality **3**. The route, however, employs a relatively expensive starting material **5**, requires high-pressure amination conditions, high temperature/vacuum distillations and is relatively low yielding due to the need for two crystallizations. Aqueous ammonia is employed for safety reasons and significant yield is lost because of the formation of alcohol impurity **8** (up to 15%, Scheme 1).[3] The high solubility of **3** in water also complicates product isolation; high temperature/high vacuum distillations and a hot salt filtration are employed to furnish the desired product.



Scheme 1. Previously reported synthesis of **3** with up to 15% of hydroxy-impurity **8** formed.

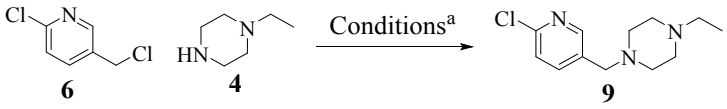
The route to **3** described herein joins ethyl piperazine (**4**) with 2-chloro-5-chloromethylpyridine (CCMP, **6**)[5] through an S_N2 coupling followed by amination on the now less activated chloropyridine (**9**, Scheme 2). Proposed starting material CCMP is readily available in large quantities and at low cost as it is used in the synthesis of large volume agricultural chemicals such as imidacloprid.[5] As the palladium-mediated Buchwald–Hartwig amination uses anhydrous conditions,[6] the formation of impurity **8** can be reduced or eliminated.



Scheme 2. Proposed alternative synthesis of **3** starting from CCMP (**6**) and ethyl piperazine (**4**).

The S_N2-coupling between **4** and **6** proceeded well under a variety of conditions. To settle on optimized conditions, we focused on three areas: 1. high conversion of **6** as it has a negative impact on color and purity in the subsequent steps; 2. Use of a base that would be soluble without insoluble by-product salts; and 3. Use of a solvent that would allow telescoping into the subsequent amination. Table 1 summarizes these efforts and optimal conditions were found to be a biphasic reaction with THF/H_2O (5:3) with 1.20 equiv. of both **4** and K_2CO_3 at reflux for 6 hours.

Table 1. S_N2 reaction between CCMP (**6**) and ethyl piperazine (**4**).



6 **4** **9**

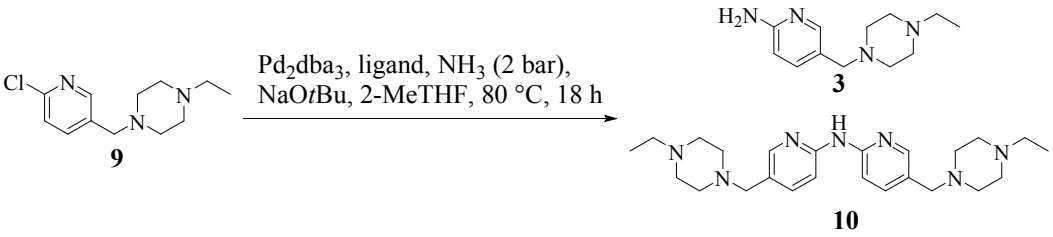
Entry	Equiv. of **4**	Solvent (ratio)	Temp.	Time (h)	Conversion %[a]
1	1.15	Toluene	70 °C	6	74.4
2	1.15	Toluene/H_2O (2:1)	70 °C	13	98.8
3	1.15	Toluene/THF (2:1)	70 °C	7	99.4
4	1.15	Toluene/THF/H_2O (4:1:2)	75 °C	8.5	90.6
5	1.15	THF	Reflux	6	92.3
6	1.15	THF/H_2O (2:1)	Reflux	7	91.2
7	1.15	THF/H_2O (4:1)	45 °C	7	95.2
8	1.15	THF/H_2O (4:1)	Reflux	4	99.6

Entry	Equiv. of **4**	Solvent (ratio)	Temp.	Time (h)	Conversion %[a]
9	1.15	THF/H_2O (8:1)	Reflux	3	99.5
10	1.15	THF/H_2O (5:1)	Reflux	3	99.6
11	1.00	THF/H_2O (5:3)	Reflux	6	91.8
12	1.10	THF/H_2O (5:3)	Reflux	6	98.5
13	1.20	THF/H_2O (5:3)	Reflux	6	>99.9

[a]1.2 equiv. K_2CO_3 used for all reactions. Numbers listed indicate conversion which were assessed by HPLC analysis of the organic layer. Reactions conducted on 1 mmol scale.

With conditions to arrive at intermediate **9**, attention turned to the amination reaction. Initial exploration with copper-based systems under an ammonia atmosphere led to very poor conversion, leading us to explore palladium-catalyzed variants. Screening of various ligands and additives led us to BrettPhos and *t*-BuBrettPhos-based ligands in 2-MeTHF. The results described in Table 2, were promising, but lacking in utility. In addition to incomplete conversion, bis-adduct **10** was consistently formed. At this stage, screening with ammonia was halted, as overcoming this side-reaction was deemed difficult.

Table 2. Conditions for the amination of intermediate **9**. Reactions conducted on 1 mmol scale with 4 mol% Pd, 8 mol% ligand.

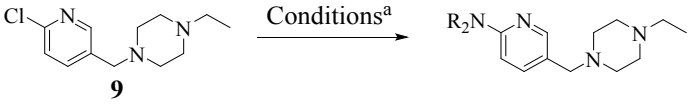


Entry	Ligand	Additive	%**3**	%**9**	%**10**[a]
1	BrettPhos	none	17	67	16
2	*t*-BuBrettPhos	none	55	29	16
3	*t*-BuBrettPhos	LiBr	64	23	13
4	*t*-BuBrettPhos	NaBr	54	24	22
5	*t*-BuBrettPhos	KBr	74	14	12
6	*t*-BuBrettPhos	$ZnBr_2$	59	24	17

[a]Reactions conducted on 1 mmol scale with 4 mol% Pd_2dba_3, 8 mol% ligand. Area % listed are based on HPLC analysis.

To avoid the bis-amination by-product, the use of protected amines was explored. A 96-reaction screen was set up exploring 8 different protected amines, 4 catalyst systems, 4 different bases/additives and three different solvents heated to 80 °C for 16 hours (Table 3). Analysis showed multiple hits, but LiHMDS was consistently the best amine, working well with most every set of conditions explored. Not only was complete conversion obtained, but it was assumed subsequent TMS cleavage would be easier than the alternatives.

Table 3. Results of a 96-well plate screening amines, additives, ligands, catalysts and solvents.



9

Amine	Base/ Additive	XPhos pre-cat			Pd_2dba_3/Xantphos			$(tBu_3P)_2Pd(0)$			Pd_2dba_3/CyJohnPhos		
		MeTHF	PhMe	Dioxane	MeTHF	PhMe	Dioxane	MeTHF	PhMe	Dioxane	MeTHF	PhMe	Dioxane
H_2NBoc	Cs_2CO_3	67	64	34	20	24	38	30	42	32	20	9	15
Benzamide	Cs_2CO_3	35	32	21	14	22	27	0	2	0	7	9	8
diMe-Pyrrole	Cs_2CO_3	0	0	0	0	0	0	0	0	0	0	0	0
Allyl amine	NaO*t*Bu	0	14	15	74	72	88	70	65	51	89	85	93
Benzophenone imine	NaO*t*Bu	33	10	33	58	23	85	0	1	0	54	28	63
Benzyl amine	NaO*t*Bu	56	27	28	98	88	100	89	84	83	98	93	100
LiHMDS	None	100	100	100	100	100	100	99	94	91	100	100	100
$Zn(HMDS)_2$	LiCl	0	0	0	0	0	0	57	45	38	0	0	0

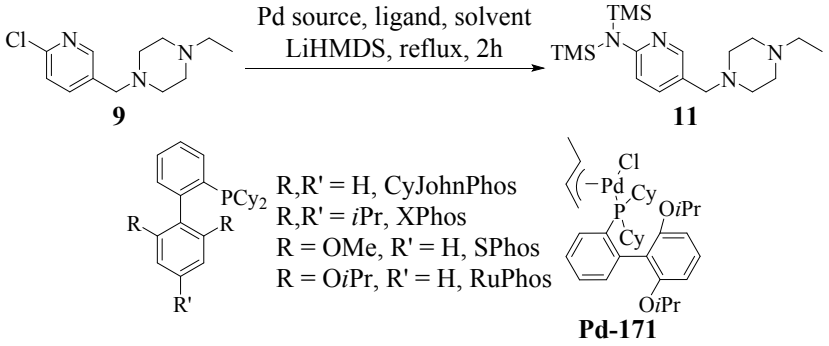
[a]Numbers listed indicate conversion. Reactions conducted at 80 °C for 16 hours with 2 mol% Pd and 4 mol% ligand. Area % listed are based on HPLC analysis.

A subsequent round of optimization was then conducted using LiHMDS as the protected amine and exploring different palladium catalysts and phosphine ligands (Table 4). The initial aim of this round of optimization was to retain the excellent conversions observed in earlier screening while also reducing the palladium loading. Our screening efforts focused on the Buchwald class of ligands due to literature precedent[6] and our earlier success with these ligands in this transformation (Table 2). Attempting to halve the initial palladium loading using CyJohnPhos resulted in poor conversion but by employing

XPhos, up to a 4-fold reduction in catalyst was possible (Entries 1–3). When trying to rationalize the difference in reactivity between these two ligands it was observed that XPhos contained substituents in the *ortho* positions of the lower aryl ring of the ligand which CyJohnPhos lacked. This led to screening other ligands containing similar substitution patterns. Applying SPhos and RuPhos in the transformation also resulted in excellent conversions with RuPhos matching the performance of XPhos (Entries 4 & 5). Cy_3P, was also screened and found to provide excellent conversions (Entry 6). Further lowering the palladium loading to 0.5 mol %, revealed that RuPhos was the only ligand capable of giving full conversion at this loading (Entries 7–9). For manufacturing purposes it was desirable, if possible, to use a Pd(II) source as palladium (0) sources such as Pd_2dba_3 have been shown to degrade over time.[7] $Pd(OAc)_2$ was screened and although it showed excellent conversions at higher loadings, reducing the palladium loading to 0.5 mol % resulted in poor conversions (entries 10 – 13). Further it was noted that running the reaction in toluene resulted in cleaner impurity profile than 2-MeTHF. Toluene also allows for more efficient water removal *via* distillation in the previous steps solvent swap, ensuring the LiHMDS does not get quenched prior to reacting (entry 14). Further

palladium (II) salts were then screened with RuPhos (Entries 15–17) and pleasingly, it was found that $PdCl_2(PhCN)_2$ was capable of providing complete conversion at 0.5 mol % loading.[8] The Pd-allyl RuPhos complex, Pd-171[9] was also screened (entry 18) and allowed a further reduction in catalyst loading to 0.25 mol %, however the RuPhos/$PdCl_2(PhCN)_2$ was chosen going forward due to its wide availability from multiple sources. Finally prompted by a recent report,[10] the nickel catalyst $NiCl_2(PPh_3)_2$ was screened under the reaction conditions but was found be ineffective (entry 19).

Table 4. Optimization of the amination with LiHMDS.



Entry	Pd source	Ligand	Solvent	% conversion[a]
1	Pd_2dba_3 1 mol%	CyJohnPhos 4 mol%	2-MeTHF	33
2	Pd_2dba_3 1 mol%	XPhos 4 mol%	2-MeTHF	96
3	Pd_2dba_3 0.5 mol%	XPhos 2 mol%	2-MeTHF	94
4	Pd_2dba_3 0.5 mol%	SPhos 2 mol%	2-MeTHF	87
5	Pd_2dba_3 0.5 mol%	RuPhos 2 mol%	2-MeTHF	94
6	Pd_2dba_3 0.5 mol%	Cy_3P 2 mol%	2-MeTHF	99
7	Pd_2dba_3 0.25 mol%	RuPhos 1 mol%	2-MeTHF	100
8	Pd_2dba_3 0.25 mol%	XPhos 1 mol%	2-MeTHF	95

Entry	Pd source	Ligand	Solvent	% conversion[a]
9	Pd_2dba_3 0.25 mol%	Cy_3P 1 mol%	2-MeTHF	31
10	$Pd(OAc)_2$ 1 mol%	RuPhos 3 mol%	2-MeTHF	92
11	$Pd(OAc)_2$ 1 mol%	XPhos 3 mol%	2-MeTHF	99
12	$Pd(OAc)_2$ 0.5 mol%	RuPhos 1.5 mol%	2-MeTHF	65
13	$Pd(OAc)_2$ 0.5 mol%	XPhos 1.5 mol%	2-MeTHF	16
14	Pd_2dba_3 0.25 mol%	RuPhos 1 mol%	Toluene	100
15	$PdCl_2$ 0.5 mol%	RuPhos 1 mol%	Toluene	1
16	$PdCl_2(MeCN)_2$ 0.5 mol%	RuPhos 1 mol%	Toluene	68
17	$PdCl_2(PhCN)_2$ 0.5 mol%	RuPhos 1 mol%	Toluene	100
18	Pd-171 0.25 mol%	-	Toluene	100
19[b]	$NiCl_2(PPh_3)_2$ 1 mol%	-	Toluene	2

[a]Determined by HPLC. [b] Reaction was run for 3.5 hours.

Quenching the amination reaction with water led to emulsions and slow hydrolysis of **11** to **3**, which was subsequently lost to the aqueous layer. Numerous additives were evaluated to improve layer separation (Table 5).

Table 5. Qualitative assessment of different aqueous solutions impacts on layer separations.

Entry	Aqueous solution[a]	Rag Layer/Emulsion
1	Water	Yes
2	Benzalkonium chloride	Yes
3	Benzyltributylammonium chloride	Yes
4	Hexadecylpyridinium chloride	Yes
5	Sodium dodecyl sulfate	Yes
6	Potassium Pyrophosphate	No
7	Ammonium phosphate	Yes
8	Potassium sodium tartrate	No
9	Potassium chloride	Yes
10	Sodium chloride	Yes
11	Potassium carbonate	Yes
12	Ammonium acetate	Yes
13	Ammonium chloride	Yes
14	Ammonium formate	Yes
15	Potassium phosphate dibasic	Yes

Entry	Aqueous solution[a]	Rag Layer/Emulsion
16	Ammonium sulfate	Yes
17	Lithium sulfate	Yes
18	Sodium sulfate	No
19	Sodium sulfate[b]	No

[a]*Solutions were made up to 80% saturation of the respective salt or surfactant. [b]40% saturated solution used.

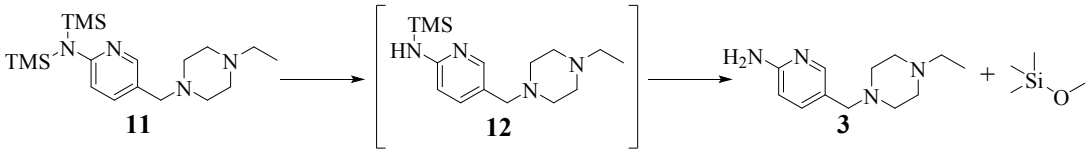
Of the salts and surfactants screened, three (potassium pyrophosphate, ammonium phosphate and sodium sulfate) were able to provide an improvement in separation over using water alone. Of these 3, sodium sulfate was chosen for further development due to its cost, stability and availability.[12] For operational reasons it was desirable to use a more dilute solution of sulfate to prevent any salt precipitation at lower temperatures and employing a more dilute solution (40% saturated) of sodium sulfate maintained a clean phase separation.

Having developed satisfactory conditions to obtain the protected amine **11** we next examined a method for its deprotection. Commonly, the removal of silyl groups from an amine has been accomplished through the use of aqueous acid.[6] In our case we wished to avoid using aqueous solutions owing to the high solubility of **3** in water.[11] Furthermore, due to the presence of several basic nitrogen atoms in the molecule, large

amounts of acid would likely generate a salt of **3** which would require an additional freebasing, followed by back extraction into an organic solvent from which to crystallize. In past cases where acid sensitive functional groups were present tetrabutylammonium fluoride (TBAF) has also been used.[6a] Large scale use of TBAF or other fluoride sources is undesirable due to the amount of fluoride waste which would be produced.

These considerations prompted us to seek a method of deprotection which could be run in an anhydrous homogeneous organic system. It has previously been demonstrated that silyl groups can also be cleaved from amines through the use of an acid catalyst in the presence of an alcohol[13] or by simply stirring in an alcohol solvent.[14] Wishing to avoid long reaction times we first examined the combination of an acid catalyst and alcohol combination in the desilylation reaction of **11**. MeOH was chosen as the alcohol because the side product generated, methoxytrimethylsilane **11**, is volatile (b.p. 57 °C) and could be removed by distillation.

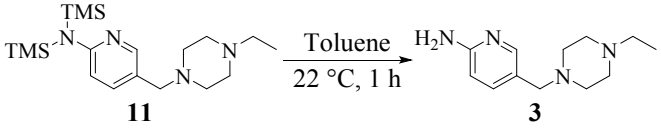
During our initial screen monitoring by ^{1}H NMR revealed that the deprotection proceeds in a stepwise manner first producing a partially deprotected mono-silylated intermediate **11** which then fully deprotects **12** to give **3** (Scheme 3).



Scheme 3. Stepwise deprotection of intermediate **11** giving amine **3** via mono-silylated intermediate **12**.

Both heterogenous and homogenous acids and bases were examined. While bases (Table 6, Entries 1–2) were shown to be capable of affecting the deprotection, overall, they were inferior to the acids. A number of acids were screened with the most effective, acetic and trifluoroacetic acid (Entries 7 & 8), able to provide complete conversion in 1 hour at room temperature. Although reported previously for this transformation,[13] *p*-toluene sulfonic acid (Entry 6) and silica gel (Entry 4) were less effective. ^{1}H NMR analysis of a sample of **3** isolated after using 5 mol% acetic acid and MeOH to deprotect revealed the presence of approximately 5 mol% of an acetate salt of **3**.

Table 6. Initial screening of conditions in the desilylation reaction.



11 **3**

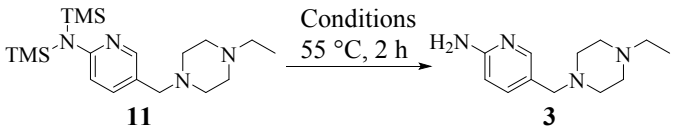
Entry	Conditions	% conversion after 1 h at room temperatute[a]
1	Potassium Carbonate (3 equiv.)	24
2	TMG (5 mol%) MeOH (3 equiv.)	37
3	Bentonite clay (5 mol%) MeOH (3 equiv.)	30
4	Silica Gel (3.5 wt%)	25
5	PPTS (5 mol%) MeOH (3 equiv.)	54
6	PTSA (5 mol%) MeOH (3 equiv.)	72
7	Acetic Acid (5 mol%) MeOH (3 equiv.)	100
8	Trifluoroacetic Acid (5 mol%) MeOH (3 equiv.)	100

[a]Determined by ^{1}H NMR.

In an effort to circumvent salt formation phenols were screened in the deprotection reaction. To improve the rate of reaction the amount of methanol used was increased from 3 equivalents to 5 volumes and the reactions were run at 55 °C. A baseline was first established by running the deprotection reaction in 5 volumes of methanol at 55 °C without any catalyst present. Pleasingly, in the absence of any other catalyst this reaction went to 72% conversion after 2 hours and full conversion after 4 hours (See Figure 2 for kinetics of some systems).

Several phenols were screened with these conditions (Table 7). A trend became apparent whereby the more electron deficient (and thus more acidic) the phenol resulted in a faster rate of deprotection (Entries 1–5). Interestingly in the presence of the electron rich and sterically hindered phenol, butylated hydroxytoluene (BHT, Entry 6), the reaction rate slowed down and was only 46% complete after 2 hours. Both AcOH and TFA (Entries 8–10) were further screened with reduced loadings under these conditions and were still found to give full conversion after 2 hours. Finally 2-*tert*-butyl-1,1,3,3-tetramethylguanidine (TMG, Entries 11–12) was screened under these conditions at two loadings (0.5 and 5 mol %) and could not give full conversion after 2 hours even at the higher loading of 5 mol% further suggesting that the base catalyzed deprotection is slower.

Table 7. Optimization of conditions in the desilylation reaction.



11 **3**

Entry	Conditions	% conversion after 2 hours[a]

1	Phenol (0.5 mol %) MeOH (5 vols.)	80
2	4-(Trifluoromethyl)phenol (0.5 mol %) MeOH (5 vols.)	97
3	4-Nitrophenol (0.5 mol %) MeOH (5 vols.)	100
4	2-Nitrophenol (0.5 mol %) MeOH (5 vols.)	100
5	2-Fluoro-4-nitrophenol (0.5 mol %) MeOH (5 vols.)	100
6	BHT (0.5 mol %) MeOH (5 vols.)	46
7	MeOH (5 vols.)	100[b]
8	AcOH (0.5 mol %) MeOH (5 vols.)	100
9	TFA (0.5 mol %) MeOH (5 vols.)	100
10	AcOH (0.5 mol %)	1
11	TMG (0.5 mol %) MeOH (5 vols.)	82
12	TMG (5 mol %) MeOH (5 vols.)	91

[a]Conversion determined by GC. [b]Reaction was run for 5 hours.

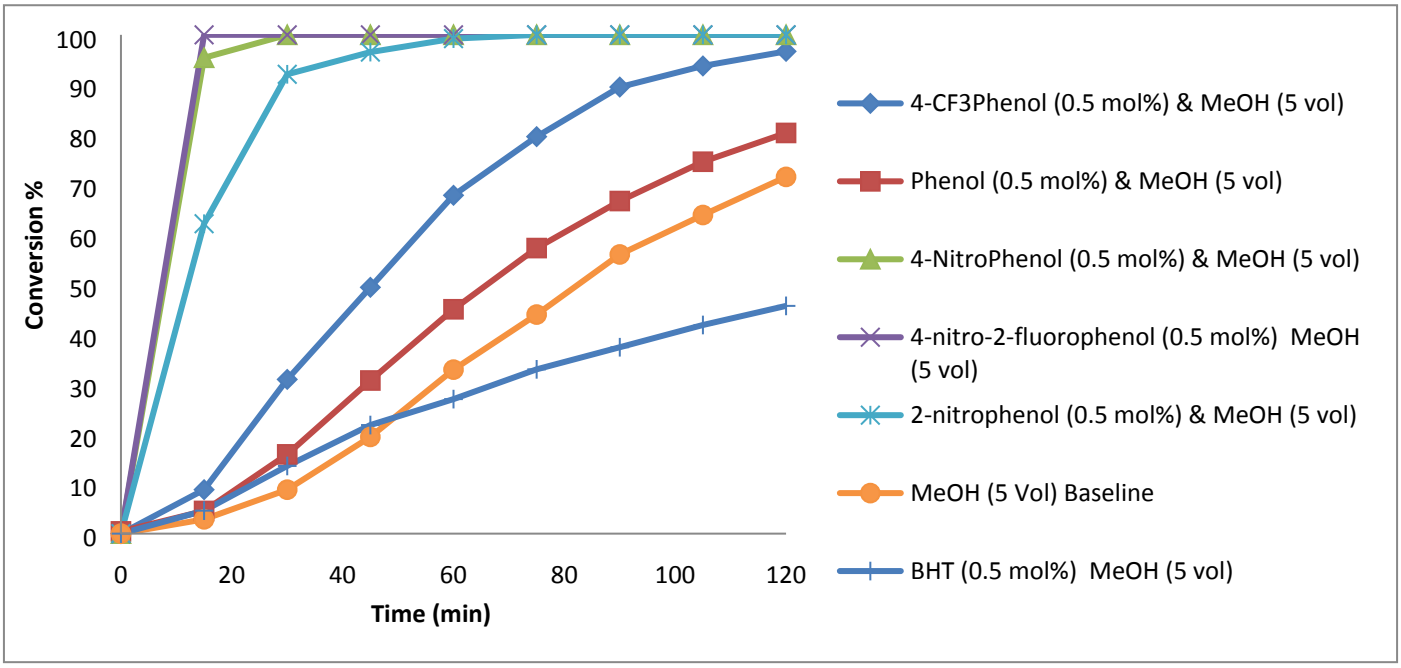


Figure 2. Reaction conversion vs time in the deprotection with various phenols.

When using TMG as a catalyst instead of acid, a change in the amount of mono-silylated intermediate which accumulated during the reaction was observed. When the deprotection was carried out using 5 mol% of TMG the amount of the mono-silylated

intermediate observed never rose above 5 area % by GC (Figure 3). When an acid catalyst was used, such as 4-trifluoromethylphenol (Figure 4), the mono-silylated intermediate **12** would rise as high as 48 area % relative to **3** and **11**. This would suggest that there might be different mechanisms at work in the deprotection reaction depending on whether an acid or base is used as the catalyst; this is in agreement with previous reports of the mechanism of desilylation of silyl amines.[14] Desilylating with MeOH led to a similar buildup of **12** during the reaction which could imply that the mechanism of desilylation *via* methanolysis is similar to that of acid catalyzed desilylation.

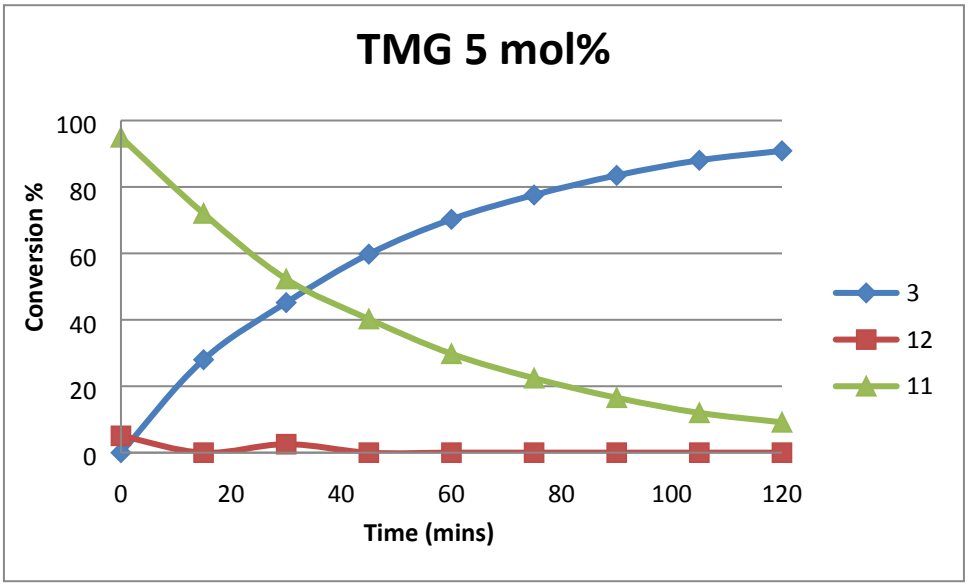


Figure 3. Product, bis-silyl and mono-silyl % during the base catalyzed deprotection.

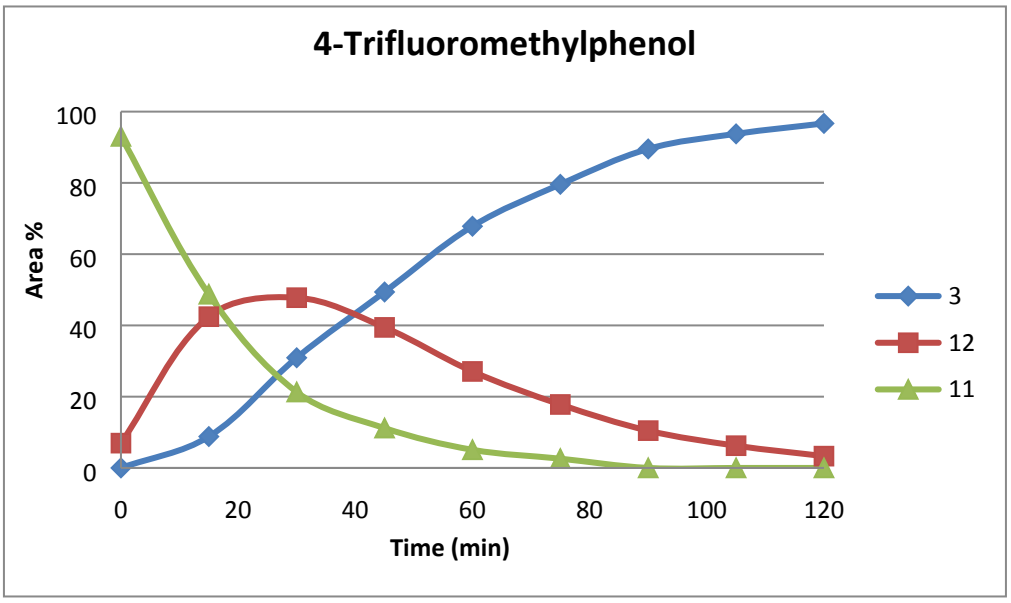


Figure 4. Product **3**, bis-silyl **11** and mono-silyl **12** % during the acid catalyzed deprotection.

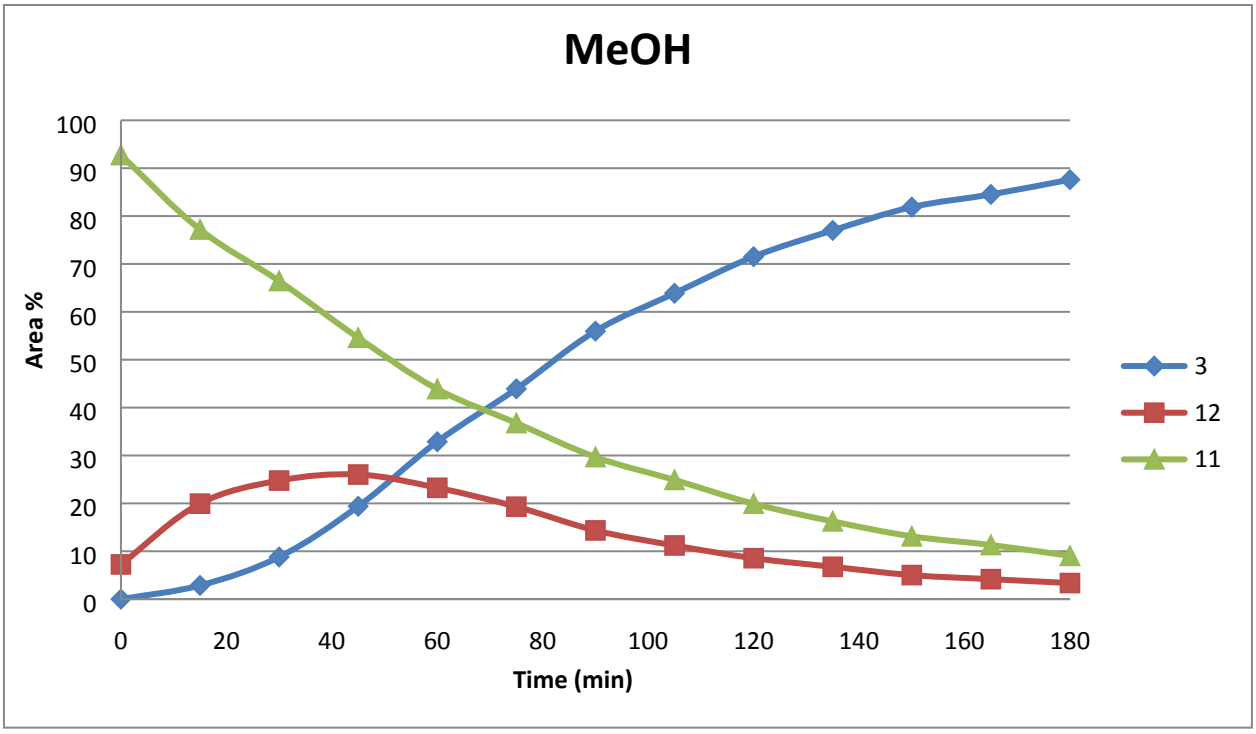
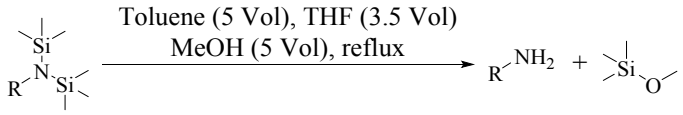


Figure 5. Product **3**, bis-silyl **11** and mono-silyl **12** % during the desilylation using MeOH.

Having screened several successful conditions for the desilylation of **11** it was decided to proceed with desilylation in 5 volumes of MeOH alone. Although slower than the acid catalyzed process (1 h vs 4 h) this route avoided the formation of any product salts and used one less raw material for the process. Intrigued by the simplicity of the methanolysis approach we screened other silyl amines to see if they could be as easily and rapidly desilylated under similar conditions (Table 8). Refluxing several silylated amines in a solvent mixture similar to our process stream resulted in complete

desilylation within 3 hours for all substrates. From this screen and our earlier work, it can be shown that methanolysis is a viable method to desilylate silylamines under anhydrous conditions and in short reaction times.

Table 8. Comparison of the desilylation rates for different substrates with refluxing MeOH (5 volumes).



Entry	R	Time to 100% conversion
1	Hexyl	1 h
2	Benzyl	1.5 h
3	Phenyl	2.5 h
4	**11**	4 h

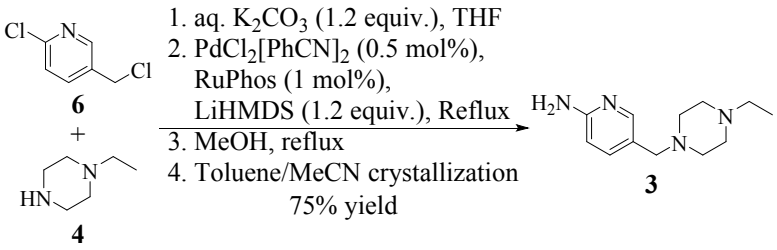
The deprotected product **3** could now be obtained in a process stream containing large quantities of MeOH, THF, Toluene and methoxytrimethylsilane (MTMS). It was found that THF and MeOH needed to be removed from the stream to minimize yield loss as **3** is highly soluble in these solvents.[11] In order to ensure that the MeOH would

always be sufficiently removed a 5 volume toluene add back followed by a second distillation was added to the process.

Crystallization of **3** from the toluene solution was achieved initially through addition of antisolvent. Use of heptane as antisolvent provided poor impurity rejection. While use of MTBE provided acceptable impurity rejection, optimization to prevent occasional oiling was unsuccessful. Use of MeCN as co-solvent provided a system with acceptable impurity rejection and yield which also was not prone to oiling.

The final crystallization solvent system chosen was a 2:1 MeCN/toluene as a cooling crystallization and possessed excellent rejection capabilities. At the saturation point, the metastable zone width is 12 °C, and given the potential batch-batch variability at scale, considerable levels of supersaturation could exist within the process stream and lead to a lack of control in the crystallization. The chosen seed point limits the maximum supersaturation of the solution prior to crystal growth and mitigates against the risk of oiling. During development and 30 L scale runs, crystals have been observed at the seed point and thus have not required seeding. No impact has been observed to the quality of **3** obtained in unseeded versus seeded crystallizations.

In conclusion, a new set of conditions were developed for the synthesis of abemaciclib intermediate **3**. The new process for the production of **3** has been performed on kilogram scale as a telescoped three step process involving two bond forming steps, one deprotection step, three extractions, two distillations and product isolation by crystallization (Scheme 4). The improvements addressed shortcomings of the previous route (eliminating formation of hydroxy impurity **8** and the use of a simpler, higher yielding process) and make for a good alternative to existing chemistry.



Scheme 3. Summary of the optimized process for the synthesis of **3**.

Supporting Information

An optimized procedure for the synthesis of **3** is provided in the Supporting Information file. In addition to procedures, characterization of new compound (**11**) is also included.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

REFERENCES

1) Goetz, M. P.; et al. MONARCH 3: abemaciclib as initial therapy for advanced breast cancer. *J. Clin. Oncol* **2017**, 35 (32), 3638-3646.

2) Johnston, S.; et al. MONARCH 3 final PFS: a randomized study of abemaciclib as initial therapy for advanced breast cancer. *NPJ Breast Cancer* **2019**, 5 (5), 1-8.

3) Frederick, M. O.; Pietz, M. A.; Kjell, D. P.; Richey, R. N.; Tharp, G. A.; Touge, T.; Yokoyama, N.; Kida, M.; Matsuo, T. Development of a Leuckart-Wallach reaction in flow for the synthesis of abemaciclib. *Org. Process Res. Dev.* **2017**, *21*, 1447.

4) a) Frederick, M. O.; Kjell, D. P. A synthesis of abemaciclib utilizing a Leuckart-Wallach reaction. *Tetrahedron Lett.* **2015**, *56*, 949; b) Leuckart, R. Tribenzylamine. *Ber. Dtsch. Chem. Ges* **1886**, *18*, 2341; c) Leuckart, R.; Bach, E. Action of ammonium formate on benzaldehyde and benzophenone. *Ber. Dtsch. Chem. Ges.* **1886**, *19*, 2128; d) Wallach, O. Menthylamine. *Ber. Dtsch. Chem. Ges.* **1891**, *24*, 3992.

5) a) Zhang, T. Y., Scriven, E. F. V. Cyclocondensation process for the preparation of 2-halo-5-(halomethyl)pyridines. U.S. Patent, 5229519 A 19930720, 20 Jul 1993; b) Shao, X.; Liu, Z.; Xu, X.; Li, Z., Qian, X. Overall status of neonicotinoid insecticides in China: production, application and innovation. *J. Pestic. Sci*. **2013**, *38(1),* 1.

6) a) Huang, X.; Buchwald, S. L. New ammonia equivalents for the Pd-catalyzed amination of aryl halides. *Org. Lett.*, **2001**, *3*, 3417. b) Lee, S.; Jørgensen, M.; Hartwig, J. F. Palladium-catalyzed synthesis of arylamines from aryl halides and lithium bis(trimethylsilyl)amide as an ammonia equivalent. *Org. Lett.* **2001,** *3,* 2729

7) Zalesskiy, S. S.; Ananikov, V. P. Pd2(dba)3 as a precursor of soluble metal complexes and nanoparticles: determination of palladium active species for catalysis and synthesis. *Organometallics*, **2012**, *31*, 2302.

8) The superior performance of $PdCl_2(PhCN)_2$ over the other palladium (II) chloride salts is believed to be due to its greater solubility in the reaction solvent.

9) DeAngelis, A. J.; Gildner, P. G.; Chow, R.; Colacot, T. J, Generating active “L-Pd(0)” via neutral or cationic π-allylpalladium complexes featuring biaryl/bipyrazolylphosphines: synthetic, mechanistic, and structure-activity studies in challenging cross-coupling reactions. *J. Org. Chem.* **2015,** *80*, 6794.

10) Martinez, G. E.; Nugent, J. W.; Fout, A. R., Simple nickel salts for the amination of (hetero)aryl bromides and iodides with lithium bis(trimethylsilyl)amide. *Organometallics* **2018,** *37*, 2941.

11) The solubility of **3** in water was measured to be 72mg/mL at room temperature. Solubility of **3** in THF was measured to be 83 mg/mL at room temperature and in MeOH was measured to be 127 mg/mL at room temperature.

12) Analysis of the aqueous layers revealed an additional benefit from using the sodium sulfate solution as the yield loss to the aqueous layer decreased from 2% using water to 0.5% using the sulfate solution. This decrease in yield loss is likely due to the Hoffmeister "salting out" effect from using a sodium sulfate solution. See Hyde, A. M.; Zultanski, S. L.; Waldman, J. H.; Zhong, Y.; Shevlin, M.; Peng, F. General principles and strategies for salting-out informed by the Hofmeister series. *Org. Process Res. Dev.* **2017**, *21*, 1355 for a paper describing this effect.

13) Morimoto, T.; Takahashi, T.; Sekiya, M. "*N,N*-Bis(trimethylsilyl)methoxymethylamine as a convenient synthetic equivalent for +CH2NH2: primary aminomethylation of organometallic compounds" *J. Chem. Soc., Chem. Commun*, **1984**, 794.

14) Boe, B. The mechanisms of solvolysis of organosilicon compounds containing bonds from silicon to oxygen, nitrogen, and carbon. *J. Organometal. Chem.* **1976**, *107*, 139.