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

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Supporting Information

ABSTRACT: A new synthesis for an intermediate of abemaciclib is described. Keys to this route are the 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 a 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 nonsteroidal aromatase inhibitor.[2]

A recent publication has described a route toward 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 (see 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.

The process is robust and affords high-quality **3**. However, the route employs a relatively expensive starting material **5**, requires high-pressure amination conditions and high-temperature/vacuum distillations, and is relatively low yielding, because of 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%; see Scheme 1).[3] The high solubility of **3** in water also complicates product isolation; high-temperature/high-vacuum distillations and hot salt filtration are employed to furnish the desired product.

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**; see Scheme 2). Proposed starting material CCMP is readily available in large quantities and at low cost, since 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.

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**, because it has a negative impact on color and purity in the subsequent steps;
(2) use of a base that would be soluble without insoluble byproduct 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 tetrahydrofuran and water (THF/H_2O = 5:3) with 1.20 equiv of both **4** and K_2CO_3 at reflux for 6 h.

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.

To avoid the bis-amination byproduct, the use of protected amines was explored. A 96-reaction screen was set up exploring eight different protected amines, four catalyst systems, four different bases/additives, and three different solvents heated to 80 °C for 16 h (see 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 that subsequent TMS cleavage would be easier than the alternatives.

A subsequent round of optimization was then conducted using LiHMDS as the protected amine and exploring different palladium catalysts and phosphine ligands (see Table 4). The initial aim of this round of optimization was to retain the

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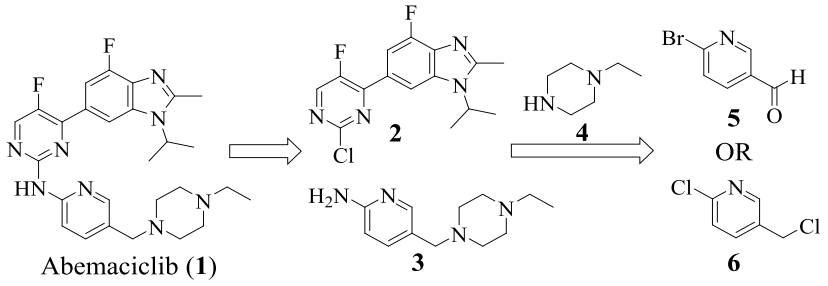
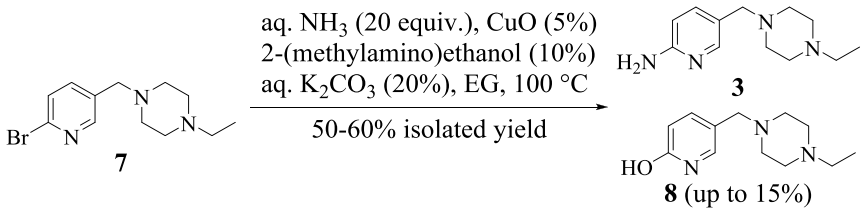


Figure 1. Retrosyntheses of abemaciclib (**1**).

Scheme 1. Previously Reported Synthesis of 3 with up to 15% of Hydroxy-Impurity 8 Formed



Scheme 2. Proposed Alternative Synthesis of 3 Starting from CCMP (6) and Ethyl Piperazine (4)

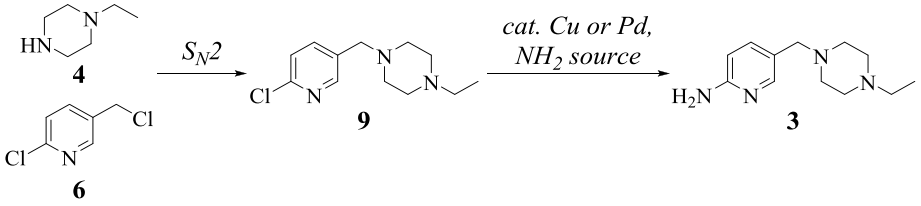
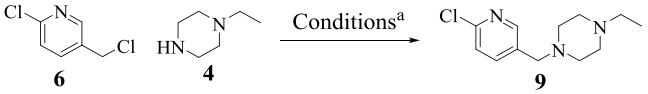


Table 1. S_N2 Reaction between CCMP (6) and Ethyl Piperazine (4)



entry	equiv of 4	solvent (ratio)	temperature (°C)	time (h)	conversion[a] (%)
1	1.15	toluene	70	6	74.4
2	1.15	toluene/H_2O (2:1)	70	13	98.8
3	1.15	toluene/THF (2:1)	70	7	99.4
4	1.15	toluene/THF/H_2O (4:1:2)	75	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	7	95.2
8	1.15	THF/H_2O (4:1)	reflux	4	99.6
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 high-performance liquid chromatography (HPLC) analysis of the organic layer. Reactions conducted on 1 mmol scale.

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 (see 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 (Table 4, 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 that 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 (Table 4, entries 4 and 5). Cy_3P was also screened and found to provide excellent conversions (Table 4, 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 (Table 4, entries 7−9). For manufacturing purposes, it was desirable, if possible, to use a Pd(II) source, because 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 (Table 4, entries 10−13). Furthermore, it was noted that performing the reaction in toluene resulted in a cleaner impurity profile than 2-MeTHF. Toluene also allows for more-efficient water removal via distillation in the previous steps solvent swap, ensuring that the LiHMDS does not get quenched prior to reacting (Table 4, entry 14). Further palladium(II) salts were then screened with RuPhos (Table 4, 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 (Table 4, entry 18) and allowed a further

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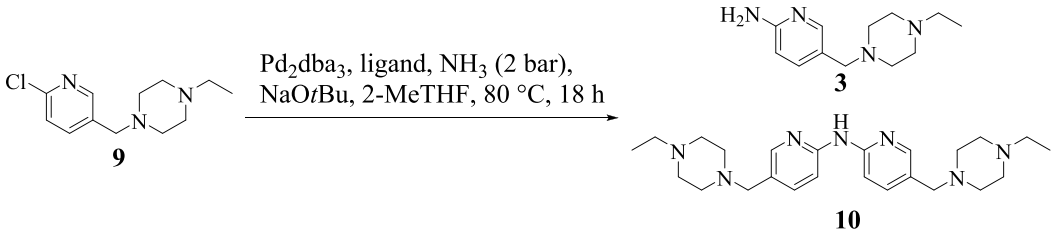
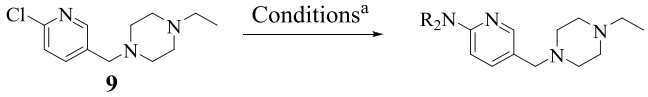
Table 2. Conditions for the Amination of Intermediate 9[a]



			Area (%)		
entry	ligand	additive	3	9	10[b]
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, 8 mol % ligand. [b]Reactions conducted on 1 mmol scale with 4 mol % Pd_2dba_3, 8 mol % ligand. Area % listed are based on HPLC analysis.

Table 3. Results of a 96-Well Plate Screening Amines, Additives, Ligands, Catalysts, and Solvents[a]



		XPhos precat			Pd_2dba_3/Xantphos			(tBu_3P)$_2$Pd(0)			Pd_2dba_3/CyJohnPhos		
amine	base/additive	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 h with 2 mol % Pd and 4 mol % ligand. Area % values listed are based on HPLC analysis.

reduction in catalyst loading to 0.25 mol %; however, the RuPhos/$PdCl_2(PhCN)_2$ was chosen going forward, because of 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 (Table 4, entry 19).

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 (see Table 5).

Of the salts and surfactants screened, three were able to provide an improvement in separation over using water alone: potassium pyrophosphate, ammonium phosphate, and sodium sulfate. Of these three, sodium sulfate was chosen for further development, because of its cost, stability,, and availability.[12] For operational reasons, it was desirable to use a more dilute sulfate solution, to prevent any salt precipitation at lower temperatures, and employing a more dilute sodium sulfate solution (40% saturated) 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, because of the high solubility of **3** in water.[11] Furthermore, because of 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, because of the amount of fluoride waste that 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 (bp 57 °C) and could be removed by distillation.

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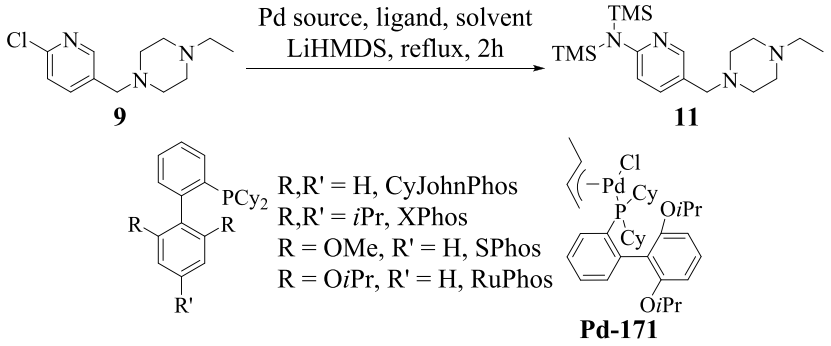
Table 4. Optimization of the Amination with LiHMDS



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
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 h.

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
16	ammonium sulfate	yes
17	lithium sulfate	yes
18	sodium sulfate	no
19	sodium sulfate[b]	no

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

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

Both heterogeneous and homogeneous acids and bases were examined. While bases were shown to be capable of affecting the deprotection (see Table 6, entries 1 and 2), overall, they were inferior to the acids. Several acids were screened with the most effective, acetic acid and trifluoroacetic acid (Table 6, entries 7 and 8), being able to provide complete conversion in 1 h at room temperature. Although reported previously for this transformation,[13] *p*-toluene sulfonic acid (Table 6, entry 6) and silica gel (Table 6, 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 ~5 mol % of an acetate salt of **3**.

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 equiv 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 h and full conversion after 4 h (see Figure 2 for kinetics of some systems).

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Scheme 3. Stepwise Deprotection of Intermediate 11 Giving Amine 3 via Monosilylated Intermediate 12

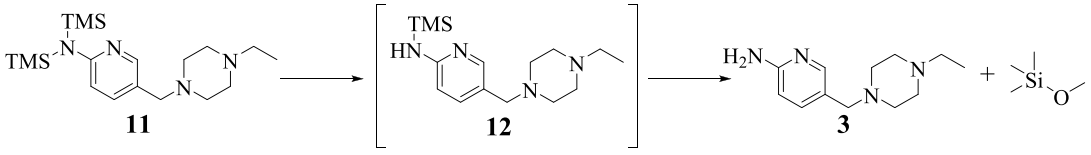
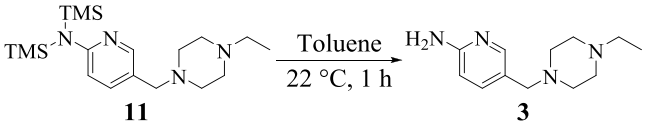


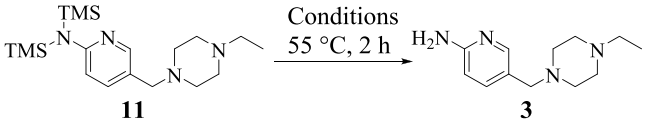
Table 6. Initial Screening of Conditions in the Desilylation Reaction



entry	conditions	conversion after 1 h at room temperature[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.

Table 7. Optimization of Conditions in the Desilylation Reaction



entry	conditions	conversion after 2 h[a] (%)
1	phenol (0.5 mol %), MeOH (5 volumes)	80
2	4-(trifluoromethyl)phenol (0.5 mol %), MeOH (5 volumes)	97
3	4-nitrophenol (0.5 mol %), MeOH (5 volumes)	100
4	2-nitrophenol (0.5 mol %), MeOH (5 volumes)	100
5	2-fluoro-4-nitrophenol (0.5 mol %), MeOH (5 volumes)	100
6	BHT (0.5 mol %), MeOH (5 volumes)	46
7	MeOH (5 volumes)	100[b]
8	AcOH (0.5 mol %), MeOH (5 volumes)	100
9	TFA (0.5 mol %), MeOH (5 volumes)	100
10	AcOH (0.5 mol %)	1
11	TMG (0.5 mol %), MeOH (5 volumes)	82
12	TMG (5 mol %), MeOH (5 volumes)	91

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

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

When using TMG, instead of an acid, as a catalyst, a change in the amount of monosilylated intermediate that accumulated during the reaction was observed. When the deprotection was performed using 5 mol % of TMG, the amount of the monosilylated intermediate observed never rose above 5 area % by gas chromatography (GC) (see Figure 3). When an acid catalyst was used, such as 4-trifluoromethylphenol (Figure 4), the monosilylated intermediate **12** would rise as high as 48 area %, relative to **3** and **11**. This would suggest that there

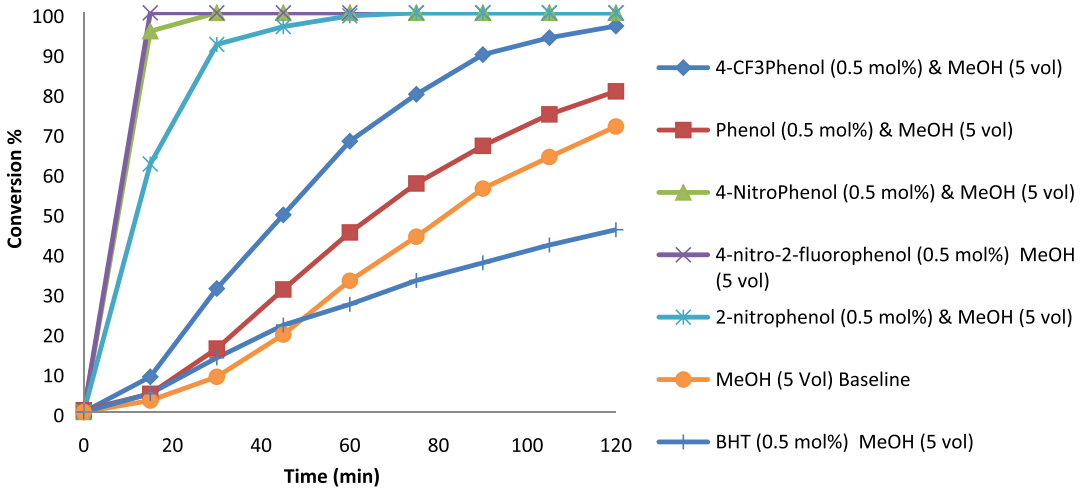


Figure 2. Reaction conversion versus time in the deprotection with various phenols.

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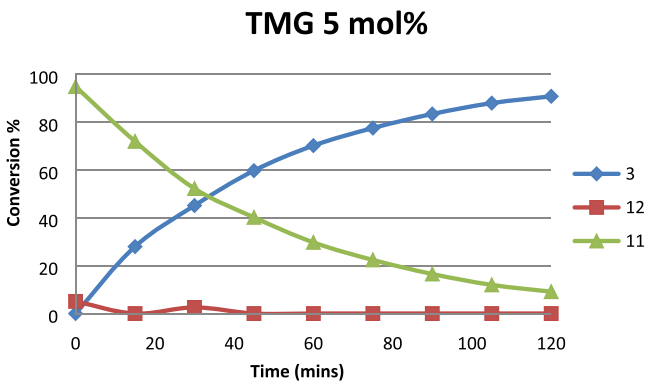


Figure 3. Product (**3**), bis-silyl (**11**), and monosilyl (**12**) conversion (%) during the base-catalyzed deprotection.

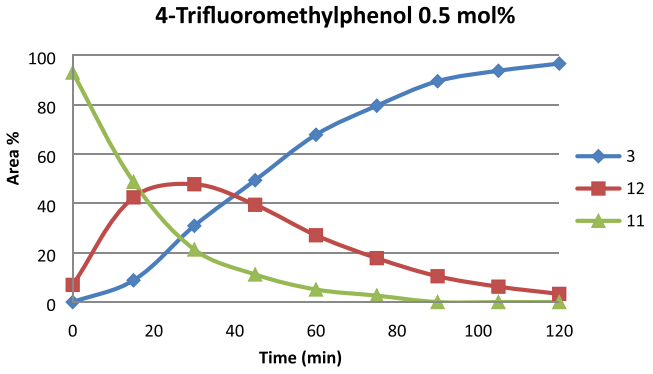
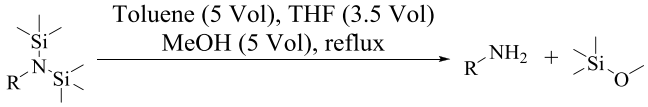


Figure 4. Product (**3**), bis-silyl (**11**), and monosilyl (**12**) conversion (%) during the acid-catalyzed deprotection.

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. (See Figure 5.)

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 determine if they could be as easily and rapidly desilylated under similar conditions (see Table 8). Refluxing several silylated amines in a solvent mixture similar to our process stream resulted in complete desilylation within 3 h 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 had to be removed from the stream to minimize yield loss, because **3** is highly soluble in these solvents.[11] In order to ensure that the MeOH would always be sufficiently removed, a quantity of 5 volumes of toluene was added to the process, followed by a second distillation.

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

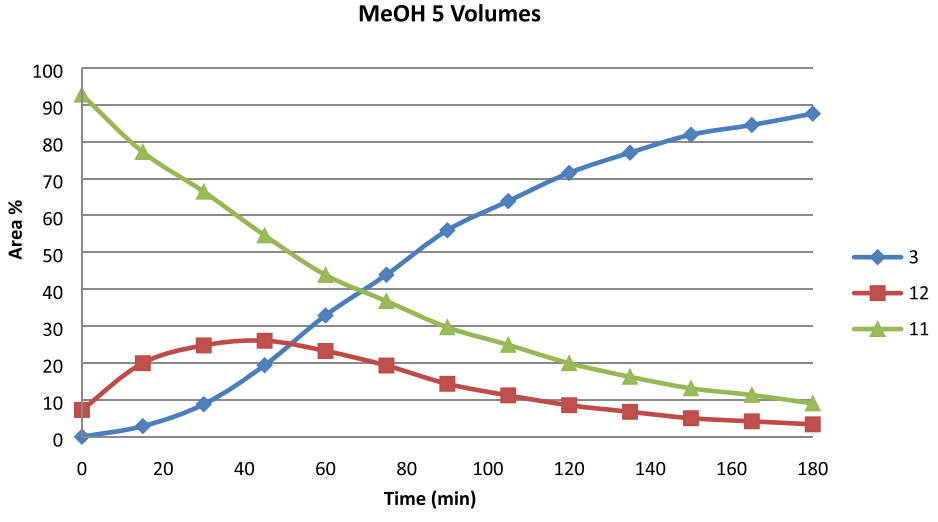


Figure 5. Product (**3**), bis-silyl (**11**), and monosilyl (**12**) conversion (%) during the desilylation using MeOH.

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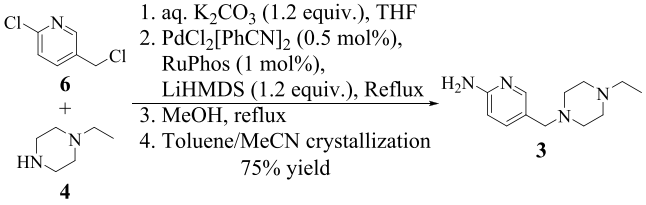
The final crystallization solvent system chosen was a 2:1 MeCN/toluene as a cooling crystallization and possessed excellent rejection capabilities. At the saturation point, the metastable zone width is 12 °C, and given the potential batch-to-batch variability at scale, considerable levels of supersaturation 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, therefore, have not required seeding. No impact to the quality of **3** obtained in unseeded versus seeded crystallizations has been observed.

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 (see Scheme 4).

Scheme 4. Summary of the Optimized Process for the Synthesis of 3



The improvements addressed shortcomings of the previous route (eliminating the formation of hydroxy impurity **8** and the use of a simpler, higher yielding process) and make for a good alternative to existing chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.9b00347.

An optimized procedure for the synthesis of **3**, in addition to procedures and characterization of new compound **11** (PDF)

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

Notes

The authors declare no competing financial interest.

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(11) The solubility of **3** in water was measured to be 72 mg/mL at room temperature. Solubility of **3** in THF was measured to be 83 mg/mL at room temperature, and, in MeOH, the solubility of **3** 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. For a paper describing this effect, 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.

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