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Technical Note

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A Practical Synthesis of an Aminopyridine as a Component of a BTK Inhibitor

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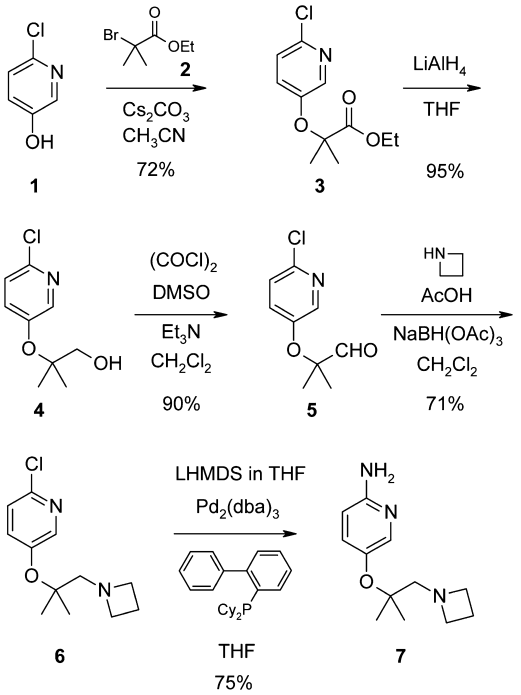
ABSTRACT: Development of a new route to the BTK intermediate, 5-(1-(azetidin-1-yl)-2-methylpropan-2-yloxy)pyridin-2-amine (**7**), has resulted in significant improvements in terms of yield, purity, and operability over the previously known synthesis. The new route was demonstrated on a multihundred-gram scale, and the overall yield of **7** from 2-chloro-5-hydroxypyridine (**1**) was improved to 72%. Lithium aluminum hydride, a Swern oxidation, cesium carbonate, azetidine free base, and four chromatographic purifications used in the earlier synthesis were eliminated.

INTRODUCTION

Bruton's tyrosine kinase (BTK) plays a key role in multiple cell-signaling pathways, and small-molecule BTK inhibitors are currently being pursued for the treatment of autoimmune diseases.[1] Several BTK inhibitors were under investigation at Roche for the treatment of rheumatoid arthritis in which aminopyridine **7** is a common component.[2]

Scheme 1 depicts the route developed by colleagues in Discovery Chemistry to prepare gram quantities of amino-

Scheme 1. Discovery route for preparing 7[2]



pyridine **7** for initial screening. With the need to rapidly prepare larger quantities of this key intermediate, the scalability of the original route was evaluated. Several of the reagents and conditions are undesirable for large scale, including the reduction with lithium aluminum hydride, oxidation using a Swern protocol (odor, cryogenic temperatures), alkylation with cesium carbonate (cost, hygroscopicity), and reductive amination using azetidine free base (cost). In addition, chromatographic purifications of compounds **3**, **5**, **6**, and **7** were required to control the purity. Consequently, a new and improved route to **7** was developed that addressed the scalability issues associated with the initial route. The new process was demonstrated on a multihundred-gram scale to provide **7** in 72% overall yield. The lithium aluminum hydride reduction, Swern oxidation, cesium carbonate alkylation, azetidine free base, and all of the chromatographic purifications were eliminated. Minimization of a side product in a borane reduction, as well as optimization of a Buchwald–Hartwig animation, is discussed.

RESULTS AND DISCUSSION

The first approach investigated was based on a nucleophilic substitution of 5-chloro-2-nitropyridine with 1-(azetidin-1-yl)-2-methylpropan-2-ol. However, instead of displacement of the chlorine atom, the reaction occurred with loss of the nitro group. A second approach using a Weinreb amide was then studied to circumvent the undesirable reduction–oxidation sequence to generate aldehyde **5**. The corresponding Weinreb amide of ester **2** was prepared, but the nucleophilic substitution with hydroxypyridine **1** was not clean under several conditions tried.

The successful, large-scale route to **7** (Scheme 2) proceeded through hydrolysis of ester **2**, amide formation, and reduction to amine **6**, replacing the original sequence of lithium aluminum hydride reduction, Swern oxidation, and reductive amination.

The alkylation of 2-chloro-5-hydroxypyridine (**1**) was first optimized. Screening experiments showed that potassium carbonate in DMF at 85 °C could replace cesium carbonate in acetonitrile at room temperature. However, switching to the less expensive base[3] required an adjustment in the stoichiometry of the bromoester. A reaction run with 1.5 equiv of the bromide still showed over 20% of **1**, even after the addition of a further 0.2 equiv of the reagent. Fortunately, with 2 equiv the reaction could be driven to ~94% completion (Table 1, entry 2).[4]

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Scheme 2. Borane reduction route to 7

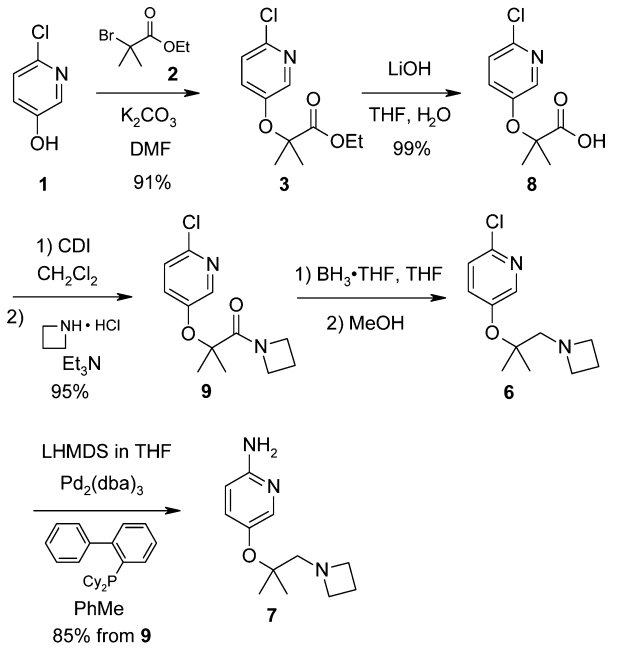


Table 1. Alkyation of hydroxypyridine 1

entry	bromoester (equiv)	**1** (%)[a]	**3** (%)[a]
1	1.5 + 0.2	20.5	79.5
2	2.0	5.6	94.4
3	2.2[b]	5.2	94.8

[a]Normalized to **1** and **3**. [b]Slow addition of bromoester.

As the reaction is exothermic, in order to enable better temperature control on a larger scale, a slow addition of the bromide to a preheated mixture of **1** and potassium carbonate in DMF was used. The reaction was scaled up using 2.2 equiv of halide and 2.6 equiv of potassium carbonate. Workup with heptane, MTBE, and water was followed by solvent exchange into heptanes to obtain **3** as a white solid in 91% yield and 99% purity.[5]

Hydrolysis of ester **3** was carried out with lithium hydroxide in aqueous THF.[6] No displacement of the chlorine atom was observed under these conditions. The hydrolysis required 1.5 equiv of base to reach completion in a reasonable time frame. Acidification, extraction with MTBE, and solvent exchange into heptanes provided 99% pure **8** in 99% yield.

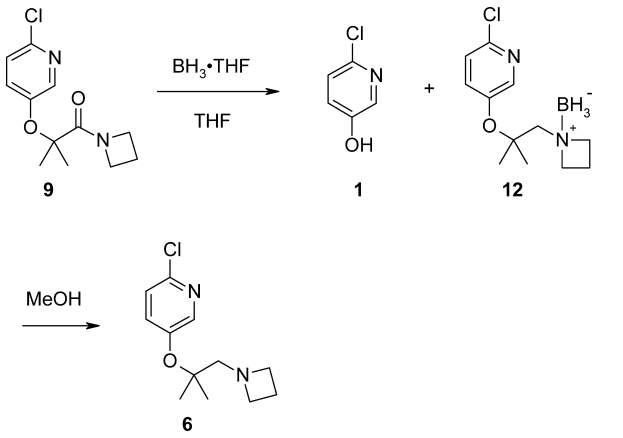
Although propane phosphonic acid anhydride (T3P)[7] was initially used for converting the acid to amide **9**, carbonyldiimidazole (CDI)[8] produced fewer side products by HPLC analysis. Small-scale experiments gave **9** in over 90% isolated yield, but upon initial scale-up to 18 g the yield fell to 80%. Samples from these early experiments also showed several small peaks in the ^{1}H NMR which were attributed to urea **10** and imidazole **11** (Figure 1).[9]

Figure 1.

These issues were addressed by minimizing the excess of CDI while maintaining a high level of conversion. This was accomplished in two ways. First, the reaction rate was accelerated by increasing the concentration from 0.063 to 0.17 g/mL. Second, formation of the acylimidazole of **8** was monitored by quenching an aliquot with *n*-butylamine. Initially, CDI was added as a solid to a solution of **8** in dichloromethane. However, for ease of operation on a large scale this was modified to adding the solution of **8** to a slurry of CDI (1.1 equiv). Typically, after 2 h the acylimidazole formation was complete. Then, azetidine hydrochloride was added. This reagent has a significant cost advantage over azetidine free base and was also available in larger pack sizes.[10] The acylimidazole can be added to a slurry of azetidine hydrochloride in dichloromethane, but this mode of addition resulted in considerably higher solvent volumes. Addition of triethylamine and refluxing for 2 h provided amide **9**. While azetidine hydrochloride is hygroscopic, this reaction is not sensitive towards moisture; material containing 8−13 wt % of water can be used without negatively affecting the reaction.[11] Workup with 1 M sulfuric acid[12] and water, solvent exchange to heptanes, and filtration provided **9** as a white solid in 95% yield and 98% purity.

The amide reduction of **9** was investigated using $LiAlH_4$, Red-Al, and borane−THF complex, of which the last gave the best result (Scheme 3). HPLC analysis of the reaction samples

Scheme 3. Amide reduction



showed an additional peak which was identified as **12** by LC/MS. Treatment of these samples with a small amount of concentrated hydrochloric acid conveniently converted **12** to **6**. The major byproduct from the reduction was hydroxypyridine **1**. A considerable amount of **1** (24 area % by HPLC) formed when 2.4 equiv of borane−THF complex was added to a THF solution of **9** at room temperature and the mixture was allowed to heat to 44 °C (Table 2, entry 1). Although removal of **1** was not an issue, there was an obvious impact on yield.

Table 2. Minimization of the formation of 1

entry	BH_3−THF (equiv)	*T* (°C)	**1** (%)[a]	**6** (%)[a]
1[b]	2.4	20−44	24	75
2[b]	2.0 + 1.0	20−29	18	82
3[b]	1.5 + 0.5 + 0.5	45−55	8	92
4[b]	1.0 + 0.5 + 0.5 + 0.5	45	4	96

[a]Determined by HPLC analysis of a reaction sample treated with hydrochloric acid. [b]All reactions proceeded to <1% starting material.

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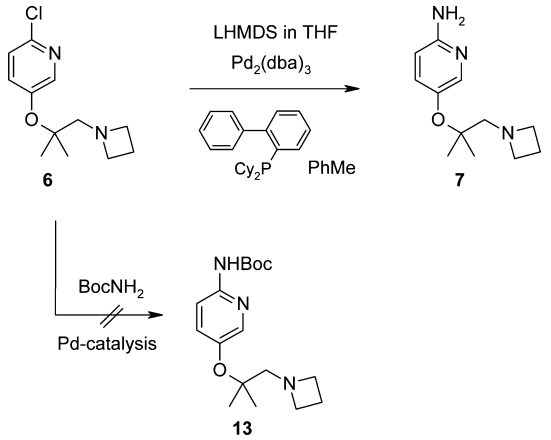
Adding the borane in two portions (Table 2, entry 2) led to a reduction in the amount of the side product formed. Although there is no direct evidence, it seemed likely that the amide **9** and not the azetidine **6** was the source of **1**. We reasoned that, by using a slow addition and limiting the excess of borane present at any given time, the level of **1** could be reduced. Such an approach was expected to have a negative impact on the overall reaction rate, but this could be compensated for by increasing the reaction temperature. Making these changes led to a significant reduction in the level of the production of **1** to 8% (Table 2, entry 3). The final conditions (Table 2, entry 4), used for the larger batches, employed four additions each over 3/4 to 1 h at approximately 1-h intervals. Heating at 45 °C for an additional 6 h was required to complete the reaction. After cooling to room temperature, excess borane−THF was quenched by the slow addition of methanol so as to control the extensive gas evolution. The mixture then required heating under reflux for at least 3 h in order to break the boramine complex **12**. After concentration, the residue was partitioned between MTBE and 0.5 M sodium hydroxide. The organic layer was separated and washed with water. In order to recover the remaining **6** in the aqueous layers, a back extraction was required. The solvent was exchanged for toluene, and the resulting solution of 98% pure **6** was used directly in the next step.

The scalability of the palladium-catalyzed amination reaction using LHMDS[13] was of concern as these conditions had previously provided disappointing results (Scheme 4). This has

Scheme 4. Buchwald−Hartwig amination



also been observed by others.[14] In another program, an amidation reaction using *tert*-butyl carbamate[15] had proved to be very successful for an unactivated heteroaromatic chloride.[16] Unfortunately, this previously effective combination of the ligand *t*-BuXPhos, catalytic palladium, and sodium *tert*-butoxide in toluene failed to produce any **13**. Other literature conditions[17] using XPhos as the ligand and cesium carbonate in dioxane were also unsuccessful. Perhaps not surprisingly, aromatic substitution using potassium *tert*-butoxide in NMP also failed. Consequently, optimization of the LHMDS-based system was undertaken (Table 3).

On small scale (Table 3, entry 1), complete conversion was observed after heating for 2 h using $Pd_2(dba)_3$ and 2-(dicyclohexylphosphino)biphenyl. However, on only 4 times the scale, the reaction stalled and required additional charges of reagents to achieve good conversion (Table 3, entry 2). No advantage could be gained from the bulkier 2-(di-*tert*-butylphosphino)biphenyl ligand, which appeared to give a slower reaction (Table 3, entry 3).[18] NaHMDS gave only a trace amount of the desired product, consistent with the lack of literature precedent for the use of this base as an ammonia equivalent. After some adjustment of the ligand/palladium/base amounts, together with the timing of the second catalyst charge, complete consumption of starting material was eventually obtained on a 12-g scale (Table 3, entry 5). A more satisfactory solution came through switching the solvent from THF to toluene and by slowly adding the LHMDS/THF solution (Table 3, entry 6). This change resulted in complete conversion and eliminated the inconvenience of charging additional reagents to an air-sensitive reaction. These conditions were subsequently scaled up over 150-fold with no further issues. Workup with water and concentration of the organic phase were followed by partioning of **7** into dilute acid. Extraction of nonbasic impurities, then addition of sodium hydroxide and extraction with Me-THF provided crude **7**. The crystallization system eventually selected was a mixture of cyclohexane and heptane, due to the high solubility of **7** in many solvents and the propensity of **7** to oil out from other mixed-solvent systems containing heptane. Initial crystallization from cyclohexane, with subsequent slow addition of heptane avoided this last problem, and provided **7** in 98% purity and 85% overall yield from **9**. A total of 520 g, prepared in two runs of 80 and 440 g, respectively, provided sufficient **7** to continue development of the BTK program. No efforts were made to remove residual palladium since downstream processing also had several palladium-catalyzed transformations.

Table 3. Scale-up of Buchwald−Hartwig reaction[a]

entry	scale (g)	ligand (equiv)	$Pd_2(dba)_3$ (equiv)	LHMDS (equiv)	solvent	**6** (%)[b]
1	0.1	0.04	0.02	1.5	THF	<1
2	0.4	0.06 + 0.03	0.02 + 0.01	1.3 + 0.5	THF	2.9
3	0.4	0.06 + 0.03[c]	0.02 + 0.01	1.3 + 0.5	THF	4.1
4	0.3	0.06	0.02	1.5[d]	THF/PhMe	trace **7**
5	12.0	0.03 + 0.03	0.01 + 0.01	1.0 + 0.5	THF	<1
6	4.0	0.03	0.01	1.2	THF/PhMe	<1

[a]Reactions at 65 °C, using 2-(dicyclohexylphosphino)biphenyl unless otherwise noted. [b]HPLC area % at 230 nm. [c]2-(Di-*tert*-butylphosphino)biphenyl was used. [d]NaHMDS (at 110 °C) was used instead of LHMDS.

CONCLUSION

The new process to BTK intermediate **7** has provided significant improvements in terms of yield, purity, and operability. The overall yield of aminopyridine **7** from hydroxypyridine **1** was increased to 72% on a multihundred-gram scale. The new route eliminated lithium aluminum hydride, a Swern oxidation, cesium carbonate, azetidine free base, and the four chromatographic purifications used in the previous synthesis.

EXPERIMENTAL SECTION

General Methods. Reactions were monitored by reverse-phase HPLC (Zorbax Eclipse XDB C8 column, 4.6 mm × 50 mm, 1.8 μm particle size, 0.5 mL/min flow, detection at 220 nm, 5−100% acetonitrile/water containing 0.1% TFA over 10 min) or UPLC (Zorbax SB-C8 RRHD column, 2.1 mm × 50 mm, 1.8 μm particle size, 0.7 mL/min, detection at 220 nm, 10−90%

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acetonitrile/water containing 0.1% H_3PO_4 over 3.5 min, hold 0.5 min).

Ethyl 2-(6-Chloropyridin-3-yloxy)-2-methylpropanoate (3). To a mixture of 2-chloro-5-hydroxypyridine (400 g, 3.09 mol) and DMF (3.2 L) was added potassium carbonate (325 mesh; 1.28 kg, 8.05 mol). After heating to 85 °C, ethyl 2-bromoisobutyrate (1.34 kg, 1.01 L, 6.87 mol) was added over 100 min. After heating overnight at 85 °C, the mixture was cooled and diluted with MTBE (4.0 L), *n*-heptane (4.0 L), and water (8.0 L). The aqueous layer was separated and back extracted with 50% MTBE/*n*-heptane (4.0 L). The organic layers were combined and washed with water (2.0 L). The organic layer was then concentrated under vacuum (50 °C water bath); *n*-heptane (3.0 L) was added; the mixture was reconcentrated, diluted with *n*-heptane (3.0 L), and finally concentrated to a thick slurry. The resulting suspension was cooled to 0 °C and filtered, and the collected solids were washed with *n*-heptane (2.0 L) and dried at 40 °C to give 685 g (91% yield) of **3** as a white solid (99.0% HPLC pure): ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.01 (dd, J = 3.01, 0.38 Hz, 1H), 7.43 (dd, J = 8.67, 0.38 Hz, 1H), 7.33 (dd, J = 8.67, 3.01 Hz, 1H), 4.18 (q, J = 7.03 Hz, 2H), 1.55 (s, 6H), 1.17 (t, J = 7.06 Hz, 3H); HRMS calculated for $C_{11}H_{15}NO_3Cl$ $(M + H)^+$ 244.07350, found 244.07291.

2-(6-Chloropyridin-3-yloxy)-2-methylpropanoic Acid (8). To a solution of **3** (865 g, 3.55 mol) in THF (5.39 L) was added aqueous lithium hydroxide (5.39 L of a 1 M solution, 5.39 mol), and the mixture was stirred at room temperature for 2.5 h. Hydrochloric acid (2.7 L of a 2 M solution, 5.4 mol) was added with cooling, and the mixture was diluted with MTBE (6.0 L). The organic layer was separated, washed with water (2.0 L), and concentrated at 35 °C under vacuum to a low volume while adding *n*-heptane (2.0 L), during which time the product crystallized. Additional *n*-heptane (4.0 L) was added, and the slurry was concentrated to dryness to give 756 g (98.8% yield) of **8** as a light-yellow solid (99.0% HPLC pure): ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.31 (br, 1H), 8.01 (d, J = 3.11 Hz, 1H), 7.44 (dd, J = 8.85, 0.38 Hz, 1H), 7.34 (dd, J = 8.76, 3.11 Hz, 1H), 1.54 (s, 6H); HRMS calculated for $C_9H_{11}NO_3Cl$ $(M + H)^+$ 216.04220, found 216.04169.

1-(Azetidin-1-yl)-2-(6-chloropyridin-3-yloxy)-2-methylpropan-1-one (9). To a slurry of CDI (508 g, 3.13 mol) in dichloromethane (3.07 L) was added a solution of **8** (614 g, 2.85 mol) in dichloromethane (1.84 L) over ~40 min, during which time the temperature rose from 14 to 18 °C. After aging for 2 h, the reaction mixture was cooled to 8 °C, and azetidine hydrochloride (346 g, 3.7 mol) was added in three portions under nitrogen, followed by the slow addition of triethylamine (663 g, 6.55 mol). The mixture was then heated under reflux for 2 h. After cooling to rt, 1 M sulfuric acid (4.5 L) was slowly added (exothermic). The aqueous layer was separated and extracted with dichloromethane (2.0 L). The combined organic layers were washed with water (4.9 L). The organic layer was then concentrated at 40 °C under vacuum to ~5 L, *n*-heptane (2.0 L) was added, and concentration continued to give a thick slurry. Additional *n*-heptane (3.0 L) was added and the mixture reconcentrated. The slurry was cooled to 4 °C and filtered, and the collected solids were washed with *n*-heptane (2 × 1.0 L) and then dried under vacuum at 40 °C to afford 687 g (94.7% yield) of **9**, a white solid (98.1% HPLC pure): ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.01 (dd, J = 3.21 Hz, 0.38 Hz, 1H), 7.46 (dd J = 8.69, 0.38 Hz, 1H), 7.32 (dd, J = 8.69, 3.21 Hz, 1H), 4.18 (t, J = 7.74 Hz, 2H), 3.90 (t, J = 7.74 Hz, 2H), 2.14 (t, J = 7.74 Hz, 2H), 1.46 (s, 6H); HRMS calculated for $C_{12}H_{16}N_2O_2Cl$ $(M + H)^+$ 255.08948, found 255.08910.

5-(1-(Azetidin-1-yl)-2-methylpropan-2-yloxy)-2-chloropyridine (6). To a solution of **9** (665 g, 2.61 mol) in THF (1.0 L) at 45 °C was added borane−THF (2.66 L of a 1 M solution in THF, 2.66 mol) over 45 min. After 45 min, a second portion of borane-THF (1.33 L of a 1 M solution in THF, 1.33 mol) was added over 50 min. After a further 45 min, a third portion of borane−THF (1.33 L of a 1 M solution in THF, 1.33 mol) was added over 90 min. Then, after 60 min, a final portion of borane−THF (1.33 L of a 1 M solution in THF, 1.33 mol) was added over 70 min, and the mixture was heated at 45 °C for 6 h. After the mixture was allowed to cool to rt overnight, methanol (2.66 L) was added over 90 min. The addition of the first 0.6 L caused a vigorous gas evolution and was also exothermic (the temperature increased to 38 °C). The mixture was heated under reflux for 3 h, then concentrated under vacuum to an oil, and diluted with MTBE (4.7 L) and 0.5 M sodium hydroxide (2.2 L). The organic layer was separated and washed with brine (2.2 L) and water (2 × 2.2 L). The water washes were back extracted with MTBE (2.0 L). The combined organic extracts were concentrated under vacuum and then coevaporated with toluene (2 × 1.5 L) to give 615 g (97.9% yield) of **6** as an orange oil (97.8% HPLC pure): ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.07 (dd, J = 2.83, 0.57 Hz, 1H), 7.51 (dd, J = 8.69, 2.83 Hz, 1H), 7.41 (dd, J = 8.69, 0.57 Hz, 1H), 3.22 (t, J = 6.99 Hz, 4H), 2.52 (s, 2H), 1.91−2.03 (m, 2H), 1.19 (s, 6H); HRMS calculated for $C_{12}H_{18}N_2OCl$ $(M + H)^+$ 241.11022, found 241.10979.

5-(1-(Azetidin-1-yl)-2-methylpropan-2-yloxy)pyridin-2-amine (7). To a degassed (3 × vac/nitrogen) solution of **6** (607 g, 2.33 mol) in toluene (2.43 L) were added $Pd_2(dba)_3$ (21.4 g, 23.3 mmol) and 2-(dicyclohexylphosphino)biphenyl (24.5 g, 70.0 mmol). The solution was heated to 45 °C, then LHMDS (2.57 L of a 1 M solution in THF, 2.57 mol) was added. The first 0.65 L was added over 5 min; the temperature rose to 48 °C. The mixture was then heated to 62 °C, and the remainder of the LHMDS was added over 90 min. The reaction mixture was heated at 63 °C overnight and then cooled to 30 °C, and ice/water (1.4 L) was added. The organic layer was separated and filtered through a thin layer of Celite to remove palladium black, and the pad was washed with THF. The combined filtrates were concentrated to a dark oil and diluted with MTBE (1.8 L), and 3 N hydrochloric acid (1.6 L) was slowly added while keeping the temperature below 34 °C. The aqueous layer was separated, and the organic layer was extracted with 1 N hydrochloric acid (2.2 L). The combined aqueous layers were diluted with MTBE (3.6 L), and with cooling, the pH was adjusted to 11.5 using 10 N sodium hydroxide (0.82 L). Sodium chloride (1.5 kg) was added and then MTBE (1.0 L) and Me-THF (3.8 L). The aqueous layer was separated and then extracted with Me-THF (3.0 L), and the combined organic extracts were concentrated under vacuum to half volume. After coevaporation with Me-THF (2 × 1.0 L) to ~4 L, the resulting solution was filtered through a Celite pad, and the pad was washed with Me-THF (1.0 L). After concentration under vacuum to a low volume, dilution with cyclohexane (2.0 L) followed by the addition of seed crystals gave a slurry. This slurry was concentrated until near dryness, diluted with cyclohexane (0.6 L), and heated to 45 °C. Then, *n*-heptane (2.4 L) was added slowly, and the resulting mixture was allowed to cool to rt overnight. The slurry was filtered, and the collected solids were washed with 50% cyclohexane/*n*-heptane (1.0 L) and then *n*-heptane (2 × 0.5 L), and the solids were dried under vacuum at 40 °C to give 443 g (85.8% yield) of **7** as a dark-brown solid

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(98.1% HPLC pure): ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.55 (dd, J = 2.83, 0.57 Hz, 1H), 7.04 (dd, J = 8.69, 2.83 Hz, 1H), 6.35 (dd, J = 8.69, 0.57 Hz, 1H), 5.60 (s, 2H), 3.20 (t, J = 6.99 Hz, 4H), 2.43 (s, 2H), 1.88−2.03 (m, 2H), 1.07 (s, 6H); HRMS calculated for $C_{12}H_{20}N_3O$ $(M + H)^+$ 222.16009, found 222.15956.

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Notes

The authors declare no competing financial interest.

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(3) Recent pricing for Cs_2CO_3 was $31/mol (Chem-Impex), and for K_2CO_3, 325 mesh was $8/mol (SigmaAldrich).

(4) Presumably there is competing elimination to ethyl methacrylate.

(5) Purity refers to HPLC area%.

(6) Evans, D. A.; Ellman, J. A.; Dorow, R. L. *Tetrahedron Lett.* **1987**, *28*, 1123.

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(9) A multiplet at δ 3.6 ppm was attributed to **10**, the remaining signals at ∼2 ppm were hidden by those of the product. Signals at δ 8.09 (m), 7.50 (m), 7.10 (m), and 2.30 (m) were attributed to **11**. In addition there were signals at ∼4 ppm but no clear assignment could be made.

(10) Recent catalog pricing for azetidine was $1710/mol (5 g, Oakwood Products) and for azetidine hydrochloride was $636/mol (100 g, Combi-Blocks).

(11) Providing allowance is made for the low assay of the azetidine hydrochloride.

(12) Work-up with citric acid led to a lower yield, whereas hydrochloric acid required additional washes to remove unreacted azetidine from the organic phase.

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(18) Samples taken after 20 min also showed a lower conversion for the bulkier di-*t*-butyl phosphine ligand as compared to the dicyclohexyl analog.