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Development of a Robust Process for the Preparation of High-Quality Dicyclopropylamine Hydrochloride

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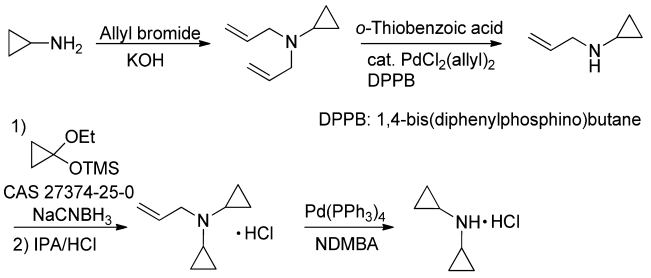
ABSTRACT: A short and efficient process for the preparation of high-quality dicyclopropylamine HCl salt is described. An oxygen-mediated Chan−Lam coupling of *N*-cyclopropyl 4-nitrobenzenesulfonamide with cyclopropylboronic acid was followed by an optimized *p*-nosyl deprotection with 1-decanethiol, providing the title compound in high chemical yield. This process addresses many of the challenges and liabilities inherent in previous synthetic approaches to this challenging molecule. The collection of key safety data enabled implementation of an oxygen-mediated process on-scale and ensured safe operation throughout development, optimization, and processing.

INTRODUCTION

The cyclopropylamino group, with its unique electronic and steric properties, has become an important structural motif in medicinal chemistry, as evidenced by its presence in numerous drugs and drug candidates.[1] Compared to cyclopropylamine, dicyclopropylamine-containing compounds are relatively rare.[2] This may be partially attributed to the difficulty of preparing this system, which, despite its structural simplicity, presents a number of synthetic challenges. For example, dicyclopropylamine (DCPA) has unique electronic properties that impact both its chemical compatibility and stability in addition to the challenging bond disconnections required for installation of the cyclopropyl rings.[3] Our requirements for this compound came with high-quality specifications and necessitated the preparation of DCPA largely free of other secondary or primary amine impurities, a significant complicating factor in developing an approach to the bulk supply of this complex small molecule.

In 2011, we reported several synthetic approaches to DCPA.[3] The most efficient process at that time was based on a reductive amination/allyl deprotection strategy (Scheme 1). Although

Scheme 1. Previous Synthetic Route to DCPA·HCl[3]



that route provided multikilogram quantities of the material, it had several drawbacks. For example, one of the key reagents, the cyclopropyl ketal, is expensive and difficult to source on a large scale, the process involves palladium chemistry in two steps, and the product is prone to contamination with several difficult to purge impurities, such as other secondary amines (*N*-propyl- and *N*-ethyl-cyclopropylamines). Additional issues with the use of sodium cyanoborohydride and allyl bromide are well-known.

Here, we describe the development of a new, robust, shorter, and more efficient process for the preparation of dicyclopropylamine hydrochloride. This approach is based on a Chan−Lam coupling[4] of *N*-cyclopropyl sulfonamide **2** with cyclopropylboronic acid (CPBA) followed by a S_NAr-type deprotection of the *p*-nosyl (Ns) protecting group by a thiolate (Scheme 2).

Considering our previous experience with this system,[3] we realized that the selection of the proper protecting group would be a critical success factor to ensure the delivery of high-quality DCPA. We desired a protecting group that could be removed under conditions in which the DCPA itself would remain chemically stable. Our previous strategy (allylation) lacked the appropriate deprotection practicality for large-scale synthesis, and the allyl group was suboptimal in terms of its own stability. Benzylation was not an option because of the known liabilities associated with that approach.[3] A critical area of concern was the observed sensitivity of DCPA under strongly basic conditions, resulting in degradation of DCPA to cyclopropylamine.[5] To obviate these issues, we envisioned that the Ns group would provide the appropriate balance of chemical compatibility and stability. Deprotection could be accomplished through an aromatic nucleophilic substitution using a weakly basic but highly nucleophilic thiolate anion, whereas the Ns group would provide appropriate reactivity upstream.[6] The precursor to the Ns-protected DCPA could, in turn, be prepared by a Chan−Lam coupling between the Ns-protected cyclopropylamine and CPBA, leveraging conditions recently described in the literature for other alkyl cyclopropyl amines.[7] The Ns group would then be both the protecting and activating group, enabling one cyclopropane ring to be derived from readily available cyclopropylamine.[8] It was apparent from inception that this Chan−Lam approach would have several technical and safety challenges in its development and

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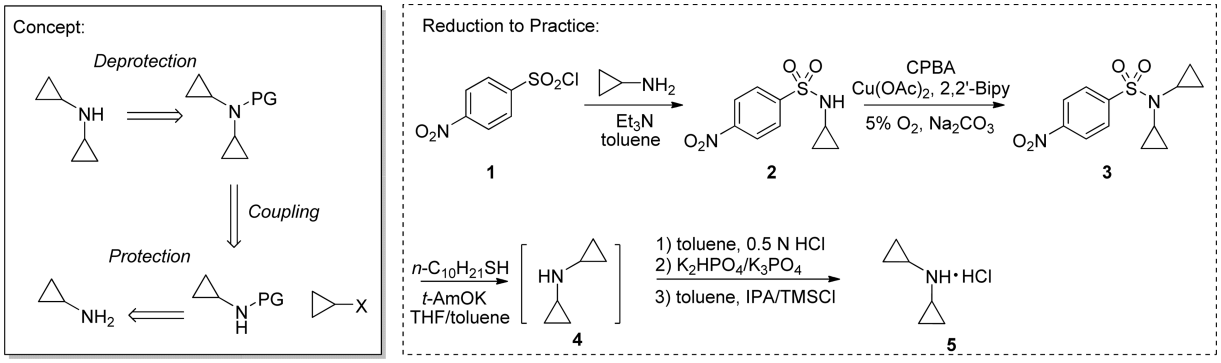
Scheme 2. New Synthesis of DCPA·HCl



implementation; thus, a proactive approach to chemical safety would be needed should proof of concept be achieved.

RESULTS AND DISCUSSION

Nosylation of Cyclopropylamine. Preparation of sulfonamide **2** via nosylation of cyclopropylamine was straightforward and readily generated **2** as a highly crystalline solid in high yield and quality. Our initial process to prepare **2** on a lab scale employed *i*-Pr_2NEt as the base and dichloromethane as the solvent followed by an aqueous workup to remove the resulting *i*-Pr_2NEt·HCl salt. However, because of the limited solubility of the sulfonamide in dichloromethane, addition of a secondary solvent, such as 2-methyl THF, was required to solubilize the sulfonamide during the acidic workup. After examining other common solvents, the sulfonamide was found to have greater solubility in ethyl acetate, allowing the use of a single solvent. After a solvent exchange from ethyl acetate to *n*-heptane and crystallization, sulfonamide **2** was produced in excellent yield and quality (>99.5 AP, 95% yield).

A more efficient one-drop process was later developed and adopted for larger scale preparation. The extractive workup and the solvent exchange were eliminated by introducing toluene as the reaction solvent with triethylamine as the base. In this system, the product precipitated directly from the reaction mixture. Addition of water to dissolve the triethylamine hydrochloride byproduct produced a triphasic system. Filtration of the triphasic system was rapid, and after washes with water and toluene, the dried product was isolated with comparable yield and quality. The use of triethylamine was preferred over *i*-Pr_2NEt to prevent contamination of the product with the corresponding amine hydrochloride because triethylamine hydrochloride easily purged to the aqueous phase during isolation. This straightforward process was successfully performed on up to a 110 kg scale without any issues, providing product **2** in 90% yield and >99.5 AP purity.

Chan–Lam Coupling. The Chan–Lam coupling to generate dicyclopropyl sulfonamide **3** plays a central role in the preparation of DCPA and, as predicted, proved to be the most challenging step to develop, optimize, and implement. Following a recently reported procedure for the coupling of simple alkyl toluenesulfonamides with boronic acids,[7b] our initial results were encouraging, with >90% conversion to the desired product being obtained after 3–5 h on the 50–100 mg scale. However, when the reaction was carried out on 1 g scale, the coupling became very sluggish and reached only 50% yield after 24 h, presumably because of a less efficient mass transfer of the oxidant. Oxygen is the stoichiometric oxidant in this process; we therefore utilized air on a small scale (<100 mg) rather than performing the trials under a controlled atmosphere. As the scale increased, the use of air appeared to reduce reaction performance. An additional concern was the formation of a gummy residue during the reactions in either 1,2-dichloroethane (DCE) or toluene, typical solvents reported in the literature for this transformation.[7a−c] Thus, extensive screening was initiated to identify conditions that would address these challenges and result in a robust process that is amendable for the preparation of sulfonamide **3** on scale.

We first screened various solvents to improve the efficiency of oxygen mass transfer and to address the solubility issues, using DCE and toluene as our initial reference for reactivity. The results are summarized in Table 1.

Table 1. Conversions[a] of Chan–Lam Reactions[b] at 1 and 18 h in Various Solvents

entry	solvent	1 h (2/3)	18 h (2/3)
1	DCE	32/67	2/96
2	toluene	30/68	3/93
3	$PhCF_3$	48/49	12/83
4	PhCl	2/95	0.2/94
5	DMF	82/6	47/35
6	MeCN	26/74	0.6/99
7	acetone	22/77	0/96
8	*t*-AmOH	43/52	18/78
9	THF	60/35	2/89
10	*i*-PrOAc	48/51	5/94
11	IPA	98/2	93/7

[a]HPLC area percent of **2**/**3**. [b]Reactions were carried out on a 50 mg scale with 1.0 mL of the solvent, 0.5 equiv of $Cu(OAc)_2$, 0.5 equiv of 2,2′-bipyridyl, 2.0 equiv of CPBA, and 2.0 equiv of Na_2CO_3 at 55 °C under an atmosphere of air.

As shown in Table 1, in addition to DCE and toluene, couplings in chlorobenzene, MeCN, and acetone provided excellent conversions. However, similar to our observations in DCE and toluene, reactions in chlorobenzene produced gummy reaction mixtures, and the conversions declined upon larger-scale experimentation. In contrast, reactions in acetonitrile and acetone performed better, with more consistent reaction profiles across various scales. Eventually, we selected acetonitrile as the solvent for further development because it provided the best balance of reaction rate and impurity profile.

After selecting the solvent, we turned our attention to catalyst optimization. The common copper salts, such as Cu(II) triflate or Cu(II) bromide, were not effective (<30% conversion, Figure 1). Although the less soluble Cu(II) sulfate[9]

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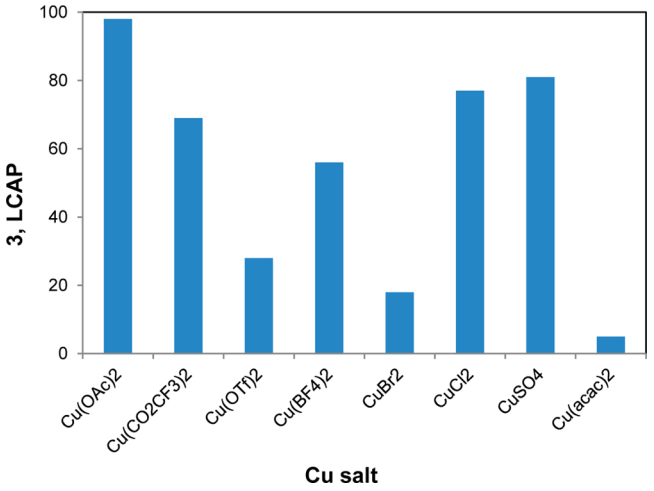

Figure 1. Conversions of the Chan–Lam reactions with copper salts. Conversions are given as the HPLC area percent of **3** excluding the peak of the ligand. Reactions were carried out on a 50 mg scale in 1.0 mL of acetonitrile with 0.5 equiv of the metal precursor, 0.5 equiv of 2,2′-bipyridyl, 2.0 equiv of CPBA, and 2.0 equiv of Na_2CO_3 at 55 °C under an atmosphere of air.

and Cu(II) chloride gave relatively good yields, Cu(II) acetate was found to be the most active copper source for this coupling. In addition, the use of Cu(II) acetate of various purities (97–99.5%) and particle sizes (powder to granular) showed comparable reaction rates under the same reaction conditions, contributing to the processes robustness on scale. Other metal-catalyzed couplings, including the known Ni couplings of boronic acids,[10] were investigated without success.

We also performed an extensive screen of ligands. Four common chemotypes known to coordinate copper were analyzed: 2,2′-bipyridyls, 1,10-phenathrolines, 1,2-diamines, and 1,3-diketones (Figure 2). Among them, both 2,2′-bipyridyls and 1,10-phenathrolines showed better performance than either 1,2-diamines or 1,3-diketones. Because 2,2′-bipyridyl is readily available in bulk quantities and is less expensive than 1,10-phenanthroline, it was our choice for further development.

Consistent with previous reports,[7a−d] we found that a ligand/metal ratio of 1:1 provided the best coupling rates. Although stoichiometric amounts of copper have been generally reported,[11] 0.5 equiv of the optimized catalyst system appeared to be sufficient to reach completion, maintaining a similar kinetic profile to that observed with 1 equiv of catalyst. Reducing the catalyst loading to 0.35 equiv resulted in extended reaction times (11 vs 8 h with 0.5 equiv on a 3 g input scale), and the use of less catalyst led to incomplete conversion, showing the limited number of catalyst turnovers available to this system.

It is known that Chan–Lam couplings require an active oxidant to drive the catalytic cycle.[12] Although the most common oxidant for this transformation is molecular oxygen, which was utilized in our initial work, the use of other oxidants in combination with air have been reported to reduce the loading of the catalyst.[11b] To identify alternative oxidants, we screened numerous reagents,[13] including pyridine *N*-oxide, TEMPO, and $KMnO_4$; however, only MnO_2 produced promising results. Couplings with 2 equiv of MnO_2 reached >95% conversion in 15 h on the scale used in our screening (50 mg); however, the reaction stalled on the 0.5 g input scale, reaching only ∼75% conversion after 24 h. Without a viable alternate oxidant, the use of molecular oxygen seemed inevitable. Thus, understanding the safety implications and controls required for the use of molecular oxygen on scale became critical. It should be noted, however, that despite challenges associated with the use of oxygen on scale, it is the greenest oxidant.

Our first goal was to understand the flammability of the solvent system under the reaction conditions. No flammability data on MeCN at elevated temperatures could be found in the literature; thus, the limiting oxygen concentration (LOC) was experimentally determined.[14] It was found that a LOC of 11 to 12% oxygen in the headspace was required for acetonitrile at either 45 or 55 °C to sustain a flame, which excluded the use of air. However, this provided the possibility of operating below this level using diluted oxygen in nitrogen, and we quickly found that working at levels much lower than 11% were sufficient to drive the reaction to completion. To ensure an ample safety margin, we decided to investigate the use of

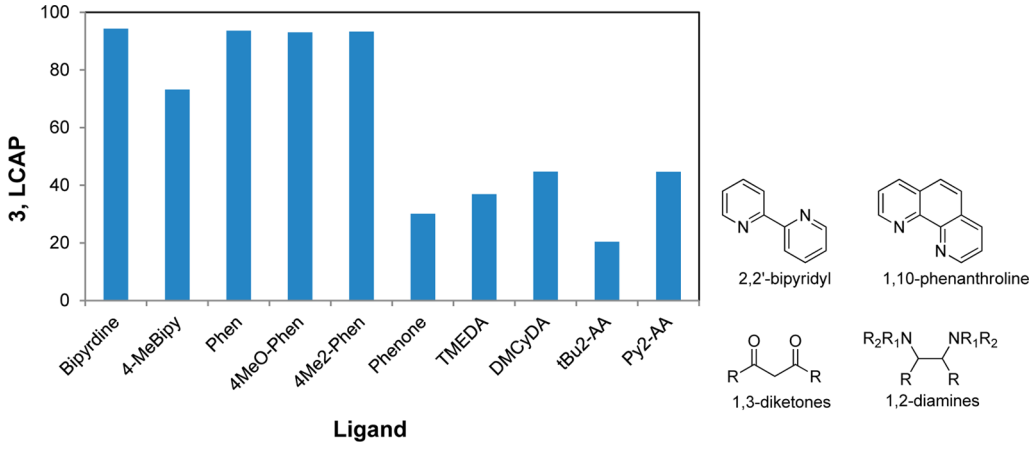

Figure 2. Conversions with various ligands (0.5 equiv) as the HPLC area percent of **3**. Reactions were carried out in acetonitrile (20 v) with 0.5 equiv of $Cu(OAc)_2$, 2.0 equiv of CPBA, and 2 equiv of Na_2CO_3 at 55 °C under an atmosphere of air for 15 h. 4-MeBipy, 4,4′-dimethyl-2,2′-bipyridine; Phen, 1,10-phenathroline; 4MeO-Phen, 4,7-dimethoxy-1,10-phenathroline; 4Me2-Phen, 4,7-dimethyl-1,10-phenathroline; Phenone, 1,10-phenathroline-5,6-dione; DMCyDA, *cis*-N^1,N^2-dimethylcyclohexane-1,2-diamine; tBu2-AA, 2,2,8,8-tetramethylnonane-4,6-dione; and Py2-AA, 1,5-di(pyridin-2-yl)pentane-2,4-dione.

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commercially available 5% oxygen in nitrogen in all future experiments.

With a safe window of operation established,[15] we investigated the impact of base on the reaction profiles, as shown in Figure 3. Sodium carbonate was the most effective

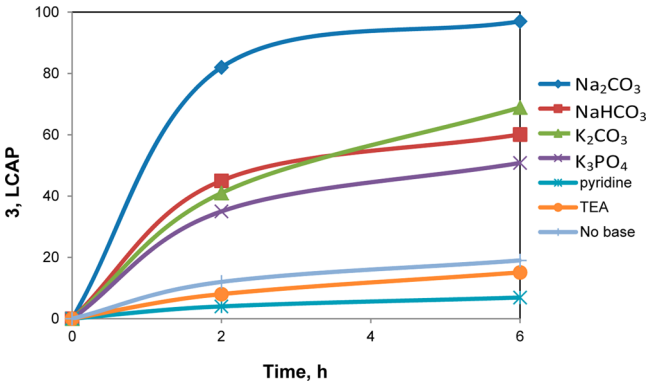

Figure 3. Reaction profiles of Chan–Lam reactions with various bases (2 equiv). Reactions were carried out in acetonitrile (20 v) with 0.5 equiv of $Cu(OAc)_2$, 0.5 equiv of 2,2′-bipyridyl, and 2.0 equiv of CPBA at 55 °C under 5% oxygen in nitrogen.

base, whereas potassium carbonate or phosphate showed lower reactivity. The reactions without base or with organic bases (pyridine, TEA) were much slower or did not reach completion.

The Chan–Lam coupling was found to be sensitive to temperature, with very slow reaction rates being observed at ambient temperature (less than 1% product observed after 15 h). At 45 °C, the reaction proceeded at an appreciable rate and reached completion in 15–20 h. Couplings at 55 °C were more rapid (ca. 5–8 h) but resulted in accelerated and competitive decomposition of CPBA.[16] This side reaction appeared more evident when the impact of a charging protocol was assessed both in terms of rate and conversion (Figure 4). Although an upfront charge of CPBA resulted in stalling, portionwise addition enabled a reduction in overall stoichiometry of CPBA (from 2 to 1.5 equiv) while simultaneously improving the reaction rate (Figure 4). The latter charging CPBA protocol was therefore adopted for further development.

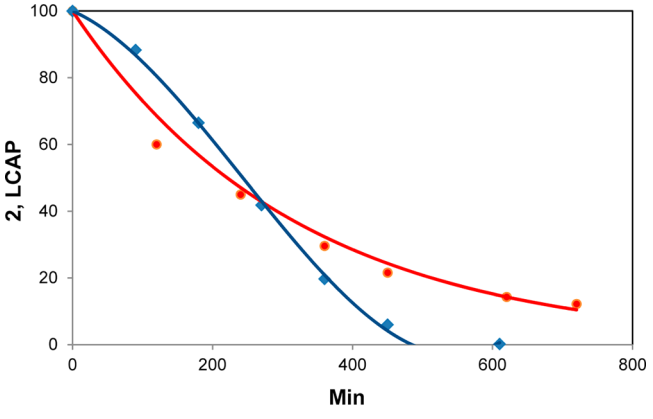

Figure 4. Reaction profiles of Chan–Lam reactions using two CPBA charge protocols (consumption of **2** vs time in min). Red, 1.5 equiv CPBA charged upfront; blue, 1.5 equiv CPBA charged in 5 × 0.3 equiv portions every 1.5 h.

We also investigated the impact of oxygen mass transfer (affected by oxygen concentration, gas flow rate, agitation rate, etc.). Unsurprisingly, this aspect of the process was found to be one of the most critical factors impacting the overall rate of reaction; for example, a reaction fed with 1% oxygen reached only 31% conversion after 8 h, whereas a coupling reaction performed in the presence of 5% oxygen (under otherwise identical conditions) went to completion. Similar observations occurred during the initial scale-up runs, where an initial slow coupling was significantly accelerated once more vigorous agitation and a higher gas flow rate were applied.[17] Interestingly, despite slow conversion, reactions starved of oxygen (such as under of 1% O_2 in N_2) did continue to produce product, indicating that the catalyst system remained active over extended periods of time.

With the transformation itself nearly optimized, our focus turned to development of the workup and isolation, especially with respect to gaining control over the residual copper from the catalyst, as we needed to ensure no Cu contamination in downstream chemistry. In our optimized workup procedure, dichloromethane and water were added to the reaction mixture, and after the phase split, the resulting rich organic phase was washed with 6 wt % aqueous ammonium hydroxide. This extraction transferred the majority of the Cu salts into the aqueous phase. A subsequent wash with aqueous 1 N HCl (mainly to remove the ligand and excess ammonia) removed additional Cu (Table 2). This workup has proved to be very robust, both in the lab and on scale, and always resulted in observed Cu levels in isolated **2** below 10 ppm (proven limit of quantitation).

Table 2. Residual Cu Levels in Various Process Streams

stage of rich DCM stream[a]	after initial phase split	post aqueous NH_4OH wash	post 1 N HCl wash
Cu, ppm	1000	50	<10

[a]Determined by concentrating a sample of the stream to dryness and analyzing the resulting solid residue.

After the aqueous workup, product isolation involved a standard sequence of solvent exchange (from dichloromethane to isopropanol) followed by crystallization and filtration. This protocol proved robust on scale and consistently provided highly crystalline product.

With an optimized process in place, the Chan–Lam step was successfully demonstrated on scales ranging between 60 and 80 kg, producing high yields (85–90%) and excellent quality (>99.5 AP) of sulfonamide **3**.

Deprotection to DCPA. We next investigated the Ns group deprotection, which is usually achieved by simple thiol-based nucleophiles, such as thiophenol.[6] Following several literature procedures, our initial efforts to remove the Ns group used a variety of thiols and provided unsatisfactory results (Table 4). This was largely due to poor selectivity in the competition between the displacement of the sulfonyl (pathway a) versus the nitro group (pathway b) by the thiol (Scheme 3), leading to **6** (desired) or **7** (undesired). The results are summarized in Table 3.

Overall, 1-decanethiol displayed the best impurity profile and was also preferred because of its reduced odor compared to other common thiols (with the exception of thiosalicylic acid).[18] Thus, further optimization of the reaction conditions focused on 1-decanethiol.

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Scheme 3. S_NAr Deprotection of the Nosyl Group

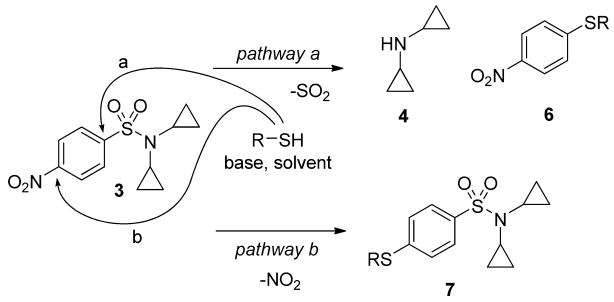


Table 3. Results of Initial Screening with Various Thiols and Bases[a]

thiol	base/solvent	LCAP (3:6:7)[b]
PhSH	3 equiv K_2CO_3/DMF	0:44:32
$HSCH_2CO_2H$	3 equiv K_2CO_3/DMF	55:0:0
p-MeOPhSH	3 equiv K_2CO_3/DMF	5:26:37
o-$HSPhCO_2H$	3 equiv K_2CO_3/DMF	79:0:0
1-$C_{10}H_{21}SH$	3 equiv K_2CO_3/DMF	28:40:19
1-$C_{10}H_{21}SH$	1.5 equiv *t*-BuOK/NMP	0:36:41
o-$HSPhCO_2H$	2.3 equiv *t*-BuOK/NMP	68:0:0
p-MeOPhSH	1.5 equiv *t*-BuOK/NMP	0:27:48

[a]Reactions were carried out on a 50 mg input scale with 2.0 equiv of thiols in 1.0 mL of solvent at ambient temperature for 15 h. [b]HPLC area percent of **3**:**6**:**7** excluding the peak of thiol reagents.

With a pK_a value of ca. 10, 1-decanethiol can be deprotonated with mild bases, such as triethylamine or DIPEA. However, the use of organic bases was not desirable because of the complication in separating them from DCPA product. Our next screening with NaOMe in various solvents did not show promising results (Table 4). Although improved selectivity was observed, the deprotections were relatively slow, and the reaction mixtures contained a range of impurities.

Table 4. Results of the Deprotections with 1-Decanethiol and NaOMe[a]

solvent	LCAP (7:3:6)[b]
THF	41:17:0.9
$PhCF_3$	51:26:1.2
DCM	51:4.8:0
toluene	25:59:0.7
MeOH	61:8.7:0.2

[a]Reactions were carried out on a 50 mg input scale with 2.0 equiv of thiols and 1.5 equiv of 25% NaOMe in MeOH at ambient temperature in a solvent (10 mL/g input) for 8 h. [b]HPLC area percent of **3**:**6**:**7**.

A stronger and sterically more hindered base (potassium *tert*-amylate, *t*-AmOK) in combination with 1-decanethiol provided a more efficient deprotection with a vastly improved impurity profile and excellent selectivity for the desired substitution pathway (a). This improvement resulted in a high yield of DCPA, reaching 84 and 79% in toluene and THF, respectively (Table 5).

With deprotection conditions in place, further optimization was required to improve recovery and isolation of high-quality DCPA. A minimal volume of THF was desired to facilitate the phase splits and to reduce the loss of DCPA to the waste stream in the subsequent aqueous workup (vide infra). Because

Table 5. Deprotections with 1-Decanethiol and *t*-AmOK in Various Solvents[a]

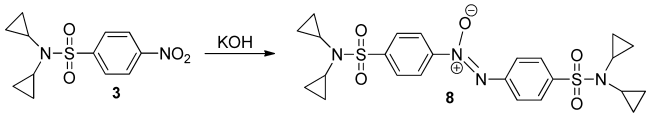
solvent	reaction time (h)	LCAP (3:6:7)[b]	solution yield (%)[c]
toluene	1	62:34:1.2	NA[d]
toluene	7	0.6:89:3.3	84
THF	1	0.5:85:1.6	79
acetone	1	48:31:10	NA[d]
MeCN	1	57:25:13	NA[d]

[a]Reactions were carried out on a 0.1 g scale with 2 equiv of 1-decanethiol and 1.5 equiv *t*-AmOK (1.7 M in toluene). The base was added to the mixture of the substrate and thiol in the solvent (1.0 mL) at ambient temperature. [b]HPLC area percent of **3**:**6**:**7** excluding the peak of toluene. [c]Quantified by derivatizing the resulting DCPA in an aliquot sample with excess TsCl and K_3PO_4 and assaying the amount of the corresponding sulfonamide against a reference standard (by HPLC analysis). [d]Not assayed because of the poor reaction profiles.

DCPA degrades in the presence of a strong base, converting to cyclopropylamine[5] (our main impurity of concern), it is important to ensure the presence of an excess of the thiol over *t*-AmOK at all times. Our optimized procedure involved addition of 1.30 equiv of potassium *tert*-amylate into the solution of the nosyl-protected DCPA **3** and 1.35 equiv of the thiol in the mixed THF and toluene solvent system (1:1, 2.5 mL/g input each) at 5−10 °C. Deprotection was typically complete in 1 to 2 h after the base was added and gave >100:1 selectivity of **6** to **7** and >90% yield of DCPA in solution.

We also found that the quality of *t*-AmOK was critical for the desired reaction rate and impurity profile. The presence of solids, typically KOH in the *t*-AmOK solution, resulted in reaction stalling and competitive reduction of the nitro group in **3** to azoxy byproduct **8** (Scheme 4).[19] A selective titration method for *t*-AmOK and KOH was therefore used[20] along with a visual inspection of the base solution prior to use to ensure acceptable base quality.

Scheme 4. Reduction of 3 to 8



In the isolation of the final product, an acid−base extraction was developed. In this scenario, it was envisaged that all of the nonamine organics would purge to the organic phase, whereas DCPA would transfer to the aqueous phase as its hydrochloride salt. To enable this approach, the stability of DCPA in aqueous acid was quickly determined at ambient temperature and shown to be acceptable. This, however, was not the case once the DCPA salt was liberated and transferred to the organic phase (toluene) as its free base. Because of the sensitivity of DCPA to basic conditions, we developed a salt-liberation protocol with gradual pH adjustment that was accomplished by a two-stage addition of solid dibasic potassium phosphate followed by tribasic phosphate to bring the final pH gradually into the 9−11 range. To provide additional control, the temperature during all quenches and operations during the workup was kept at or below ambient, as decomposition was also shown to be temperature-dependent. At ambient temperature, the stability of the resulting DCPA toluene solution was limited; however, reducing the temperature at which the DCPA solution in toluene was held dramatically enhanced the stability.

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Final isolation was accomplished by precipitation of the hydrochloride salt from toluene. During our initial development studies, this was accomplished by the addition of a 5 to 6 N solution of HCl in isopropanol followed by distillation to remove the alcohol and maximize the recovery of the resulting DCPA·HCl salt. This approach, although providing good yields (ca. 76−85%) and quality on a lab scale, was not robust enough upon scale-up. Again, because of the thermal instability of DCPA·HCl, an elevated level of the cyclopropylamine impurity (3.1 AP) was observed after prolonged distillation. In addition, commercial solutions of 5 to 6 N HCl in IPA typically contain 1−3 wt % water, which adversely impacts both the DCPA recovery and stability.

The above liabilities were addressed by eliminating the distillation and introducing an in situ generation of anhydrous HCl from TMSCl and isopropanol. Thus, a small amount of isopropanol (~7 vol %) was added to the toluene solution prior to addition of TMSCl at 10−15 °C. The product then precipitated as a white crystalline solid, and after isolation, excellent yields (80−89%) and quality of DCPA hydrochloride were obtained (<0.15 AP of cyclopropylamine as the single observable impurity). Although the level of cyclopropylamine was generally extremely well controlled, we also developed an optional reslurry in acetone, which provided additional purging of this impurity.

This deprotection process has been successfully demonstrated on varying scales up to a 30 kg output (Table 6).

Table 6. Scale-Up Data for the Ns Group Deprotection of 3[a]

batch no.	**5** (kg)	yield (%)	LCAP[b]
1	22	79	99.9
2	21	81	99.9
3	22	77	99.9[c]
4	21	78	99.9
5	27	75	99.9
6	30	79	100.0[c]

[a]Combined scale-up summary from two different vendors. [b]Quantified by derivatization of the DCPA by treatment with excess TsCl and K_3PO_4 and assayed as the corresponding sulfonamide against the reference standard by HPLC analysis. [c]The acetone reslurry was implemented.

CONCLUSIONS

We have developed a highly efficient and robust process for large-scale production of dicyclopropylamine hydrochloride in excellent quality, which addressed liabilities of previous synthetic approaches. In the key oxygen-mediated Chan−Lam coupling, the critical LOC safety data was collected, which drove development and optimization of this step in a fundamental way.

EXPERIMENTAL SECTION

General. Sulfonylation and nosyl deprotection were performed under nitrogen, and commercial 5% oxygen in nitrogen was used for the Chan−Lam couplings. Reported yields are for isolated materials or calculated solution yields and are corrected for potency. All transformations were monitored by HPLC at λ = 220 nm using a Zorbax Eclipse Plus C18 1.8 μm 4.6 × 50 mm column at a 1.2 mL/min flow and a 10 μL injection volume using the following gradient method: 15% B (0 min) to 100% B (7 min) and then 100% (15 min). Mobile phase A: 95% water/5% acetonitrile with 0.05% trifluoroacetic acid. Mobile phase B: 5% water/95% acetonitrile with 0.05% trifluoroacetic acid. Dicyclopropylamine and related impurities were analyzed by the HPLC as their tosylated derivatives.

***N*-Cyclopropyl 4-Nitrobenzenesulfonamide 2.**[21] To a solution of 4-nitrobenzenesulfonyl chloride (100 g) in toluene (500 mL, 5 vol) was added cyclopropylamine (38 mL, 1.2 equiv) at 0−15 °C over 15 min. Triethylamine (76 mL, 1.2 equiv) was added at 5−15 °C, and the thick slurry was agitated at 20−25 °C for 30−60 min. A sample was taken to confirm >99% conversion by HPLC. Aqueous 1 N HCl (400 mL) was then added at 20−25 °C, and the triphasic mixture was agitated at 20−25 °C for 4 h. The solids were filtered, washed sequentially with water (300 mL) and toluene (300 mL), and dried under vacuum at 40−50 °C to give 98.3 g (90% yield) of off-white crystalline **2** with 99.7 AP purity by HPLC.

***N,N*-Dicyclopropyl 4-Nitrobenzenesulfonamide 3.** Acetonitrile (700 mL, 7 vol), copper(II) acetate (37.6 g, 0.5 equiv), 2,2′-bipyridyl (32.3 g; 0.5 equiv), sodium carbonate (87.6 g, 2.0 equiv), **2** (100 g), and cyclopropylboronic acid (10.6 g, 0.3 equiv) were sequentially charged at rt under an atmosphere of 5% O_2 in N_2. The resulting mixture was heated at 55 °C and vigorously agitated for 3 h while bubbling subsurface 5% O_2 in N_2 through the mixture. Four additional portions of CPBA (10.6 g, 0.3 equiv each) were charged every 3 to 4 h, and the progress of coupling was monitored by HPLC. Desired >98% conversion was typically reached after 16−24 h.

After cooling to rt, 6 wt % aqueous ammonium hydroxide (1.7 L) and dichloromethane (1.5 L) were added, and the biphasic mixture was agitated for a 30 min. The bottom organic (brown) and the top aqueous (blue) phases were separated, and the organic layer was washed with 1 N aqueous HCl (1.5 L) and once with water (1 × 800 mL). The organic layer was then subjected to distillation at atmospheric pressure to bring the final volume to ~500 mL. Isopropanol (500 mL) was added, and the product partially precipitated. The resulting slurry was again concentrated to ~500 mL, and another portion of isopropanol (500 mL) was added. The slurry was reheated to 78 °C and then cooled to 20 °C over 1 h. After agitation for 1 h at 20−25 °C, the solids were filtered, washed with isopropanol (~400 mL), and dried under vacuum at 40−50 °C to give 105 g (90% yield) of **3** as a light yellow crystalline solid with 100 AP purity by HPLC.

Data for compound **3**: mp 168−169 °C. ^{1}H NMR (500 MHz, $CDCl_3$): 0.76 (m, 4H), 0.95 (m, 4H), 1.98 (m, 2H), 8.11 (d, J = 9.0 Hz, 2H), 8.41 (d, J = 9.0 Hz, 2H). ^{13}C NMR ($CDCl_3$): 6.5, 32.4, 124.0, 129.4, 142.3, 150.2. HRMS $[M + H]^+$ calcd for $C_{12}H_{15}N_2O_4S$, 283.0748; found, 283.0753.

***N,N*-Dicyclopropylamine Hydrochloride 5.**[3] THF (310 mL), toluene (310 mL), **3** (100 g), and 1-decanethiol (98 mL, 1.35 equiv) were charged under nitrogen, and the mixture was cooled to 0−5 °C. Potassium *tert*-amylate solution in toluene (25 wt %, 229 g, 1.30 equiv) was added dropwise at 5−10 °C. The mixture was agitated at 5−10 °C for 90 min and sampled to confirm >99% conversion by the HPLC derivatization method. Aqueous 0.5 N HCl (940 mL) and toluene (190 mL) were added to the reaction mixture at 10−15 °C, partitioning **5** into the aqueous phase. The biphasic mixture was stirred for 10 min, and the phases were split. The rich aqueous layer was washed with toluene (500 mL) and cooled to ca. 10 °C. Toluene (500 mL), solid K_2HPO_4 (156 g, pH 7.0 at this point), and solid K_3PO_4 (156 g, pH 9.9) were sequentially added at 10−20 °C, partitioning DCPA free-base **4** into the organic

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phase. After the phase split, isopropanol (36 mL) was charged to the organic layer, and TMSCl (46 mL, 1 equiv) was added at 15−20 °C within 15 min. The resulting white slurry was agitated for 30−60 min at 20−25 °C. The product was filtered, washed with toluene (200 mL), and dried under vacuum at 20−25 °C to give 40.7 g (86% yield) of **5** as a white crystalline solid with 99.9 AP HPLC purity.

Optional Reslurry of 5 in Acetone. The slurry of **5** (40 g) in acetone (160 mL, 4 vol) was agitated for at 1 to 2 h at 20−25 °C. The solids were filtered, washed with acetone (80 mL), and dried under vacuum at 20−25 °C to give 38.4 g (96% recovery) of **5** with upgraded purity.

HPLC Derivatization Method for 5. Two percent (w/v) *p*-toluenesulfonyl chloride (TsCl) in acetonitrile was added into a 50 mL volumetric flask followed by ca. 10 mg of solid **5** or an equivalent amount of **4** or **5** in solution and 10 mL of a 2% (w/v) potassium phosphate (K_3PO_4) solution in water. The flask was filled with 80 vol % acetonitrile/20 vol % water diluent, and the solution was shaken well for a few seconds. After at least 30 min aging at ambient temperature, a sample was taken for UV HPLC analysis.

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Notes

The authors declare no competing financial interest.

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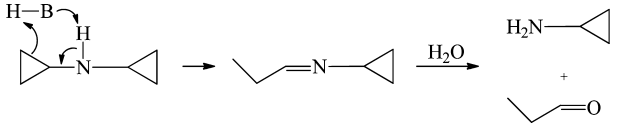

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(14) The safety evaluations were conducted by Chilworth Technology, Inc.

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