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TECHNICAL NOTE

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The Development of Scalable and Efficient Methods for the Preparation of Dicyclopropylamine HCl Salt

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ABSTRACT: The unique chemical properties of dicyclopropylamine (DCPA) **1** render its synthesis a challenge for process chemists despite its structural simplicity. Chemical instability and high aqueous solubility further complicate the process for DCPA's preparation, isolation, and purification. In this note we describe the development of three strategies for the synthesis of DCPA **1**, all of which provide material with excellent purity profiles (>99 GC area %). Our final route provides significant improvements in terms of cost-efficiency, safety, scalability, and impurity content. Highlights of this strategy include two chemo-selective, Pd-catalyzed, deallylation reactions and an efficient reductive amination protocol. To circumvent the chemical instability of DCPA **1**, an innovative isolation procedure was developed which reliably reduced the amount of Pd residue to less than 20 ppm. Following this protocol, impurities such as *N*-propylcyclopropyl-, *mono*-cyclopropyl-, and *N*-ethyl-cyclopropylamines (**3**, **4**, and **17**) were minimized to 0.06, not detectable, and 0.02%, respectively.

INTRODUCTION

Dicylopropylamine (DCPA)[1] **1** is a deceptively difficult molecule to prepare, presenting a number of challenges in the synthesis and isolation of this structurally unique molecule. In this note we describe our work on developing an efficient and scalable process for the formation of the hydrochloride salt of DCPA **1** with high quality.

Retrosynthetically, limited options for the disconnection of DCPA present themselves, illustrated in Scheme 1. Simple S_N1- or S_N2-based approaches are inherently flawed due to the cyclopropyl framework;[2] Pd-catalyzed cross-coupling is a challenging transformation[3] for current coupling methods;[4] and the known Cu-catalyzed *N*-centered displacement on *O*-benzoyl hydroxylamine failed in our hands.[5] Other known approaches, such as the conversion of *N*-formyl compounds to the corresponding cyclopropyl derivative [with EtMgBr/Ti(II)],[6] were judged undesirable from a process standpoint.

The unusual instability of DCPA **1** to a variety of reaction conditions presents another significant challenge (Scheme 1). The cyclopropyl groups are labile to hydrogenolysis, yielding the *N*-propyl reduction product **3**.[7] Also, rather surprisingly, DCPA **1** is unstable to aqueous base or elevated temperature in chlorinated solvents such as DCE, undergoing facile cleavage of one cyclopropane to give *mono*-cyclopropylamine **4**.[8] Presumably, this is an artifact of the stability of the cyclopropyl cation, increasing the rate of elimination or fragmentation.[9] These instabilities complicate not only protecting group strategy but also the isolation and purification of high-quality DCPA **1**.

Given these issues, reductive amination of a suitably protected amine and a cyclopropanone synthon[10] appeared to present the most viable strategy for development (Scheme 2). Indeed, in order to prepare initial samples of DCPA our Discovery colleagues employed the $NaCNBH_3$-mediated bis-reductive amination protocol developed by Gillaspy,[11] which utilizes commercially available 1-ethoxy-1-[(trimethylsilyl)oxy]cyclopropane (**5**)[12] as the cyclopropanone synthon and benzhydrylamine (Ph_2CHNH_2) as the nitrogen source. Acceptable yields of the corresponding amine were obtained; however, during the hydrogenolytic deprotection of the benzyhydryl group the cyclopropyl ring-opened product **3** was observed in significant amounts (~5% as noted in Scheme 1).[7,13]

Our retrosynthetic design (Scheme 2) focused on direct isolation of DCPA·HCl (**2**), with the aim of aiding both purification and chemical stability. The sensitivity of the cyclopropyl framework to hydrogenolysis required an alternate deprotection strategy, as we required tighter control over other secondary amine isomers (<0.1%). We therefore directed our efforts towards the development of a mild and efficient deprotection protocol that would ensure the survival of the sensitive DCPA skeleton; to this end, conditions involving reduction or oxidation were avoided, as well as exposure to strong base or aqueous workup conditions.

RESULTS AND DISCUSSION

Our first approach to the synthesis of DCPA·HCl (**2**) was to evaluate an alternate protecting group to benzhydryl (Scheme 3). We envisaged using a Von Braun dealkylation[14] of *N*-*p*-methoxybenzyl-bis(cyclopropylamine), **7**, in the hope that deprotection under acidic conditions would afford greater stability to the DCPA via *N*-protonation. In practice the reductive amination of commercially available PMB-amine **6**[15] with 1-ethoxy-1-[(trimethylsilyl)oxy]-cyclopropane, **5**, was readily achieved following the literature protocol ($NaCNBH_3$ in AcOH/MeOH).[11] Although the yield was modest (~75%), the tertiary amine **7** was easily isolated and purified as its crystalline HCl salt. Since the HCl salt of amine **7** proved unreactive in the Von Braun deprotection due to *N*-protonation, freebasing (with aq NaOH) was required to give the free-amine **7** in 75% yield and high purity. The modified Von Braun deprotection, using

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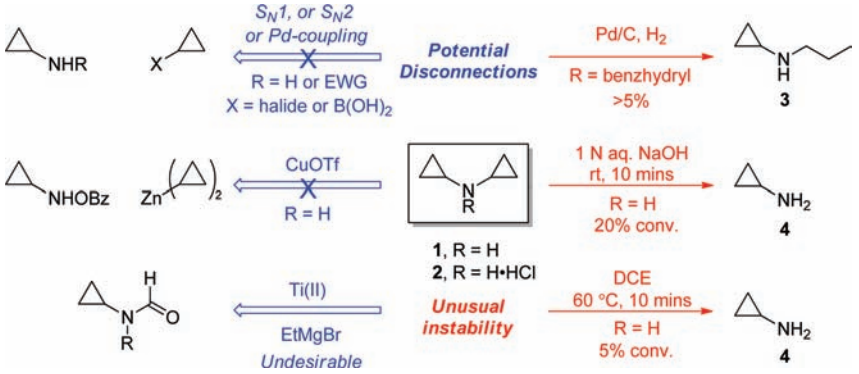
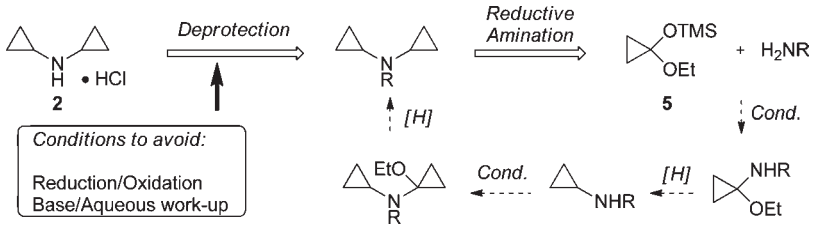
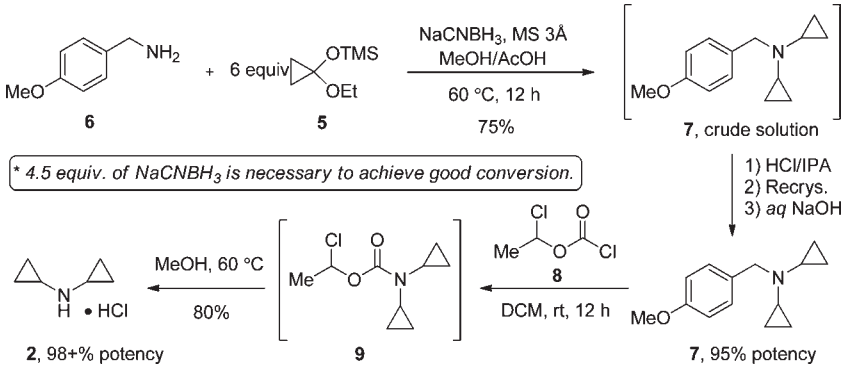
Scheme 1. Attempted approaches towards DCPA 1 and the observed instability of DCPA 1



Scheme 2. Analysis of retrosynthetic strategy for DCPA·HCl 2



Scheme 3. First route to DCPA·HCl 2



1-chloroethylchloroformate (**8**) (ACE-Cl),[16] then proceeded smoothly in dichloromethane (DCM) at room temperature. Methanolysis of the intermediate chloro-carbamate **9** cleanly gave the DCPA·HCl **2**, with excellent purity (98+%) and in good chemical yield (~80%). It is worth noting that utilization of the electron-rich PMB group is key to the successful implementation of such a method, as both benzyl and benzhydryl analogues failed to afford DCPA under identical reaction conditions, leaving starting material unchanged. The low reactivity of these derivatives under the Von Braun deprotection conditions is surprising; literature precedent suggests that the reaction of a tertiary amine with 1-chloroethylchloroformate, **8**, normally proceeds at very low temperature to give the corresponding carbamate (benzylamine at −10−0 °C, PMB amine at as low as −78 °C).[17] The significantly decreased *N*-reactivity of the alkylated DCPA analogues is hypothesized to be due to the extent of delocalization of the nitrogen electron density into the appended cyclopropane framework.

While this approach gave us access to DCPA·HCl **2** with a suitable purity profile, the utilization of hazardous ACE-Cl **8** and the need to develop controls for the CO_2 off-gassing (observed during the thermal cleavage of the chlorocarbamate **9**) were both scale-up concerns. Furthermore, during the course of optimization, we noticed that the quality of ACE-Cl **8**, which was variable from vendor to vendor, played a major role in the efficiency of the deprotection. For example, hydrogen chloride (a common impurity in ACE-Cl) would stall the reaction by generating the unreactive HCl salt of amine **7**. As HCl is a degradant of ACE-Cl, we sought alternative synthetic strategies.

Our second approach again varied the nitrogen protecting group, anticipating the use of a mild Pd-catalyzed deallylation. Although the deallylation of free amines is a very well-precedented

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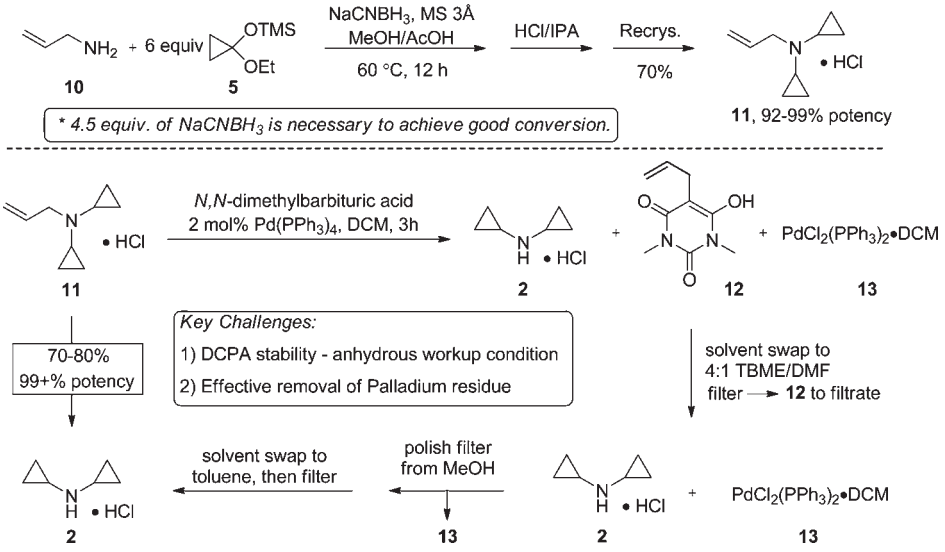
Scheme 4. Second synthesis of DCPA·HCl 2



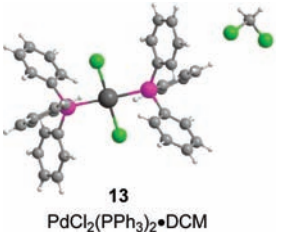


Figure 1. X-ray structure of $PdCl_2(PPh_3)_2$·DCM (**13**).

transformation,[18] there are only a few reported cases which utilize the amine HCl salt directly.[19] Given the instability of DCPA to basic conditions, we set out to pursue a deallylation protocol which would convert the HCl salt **11** directly to the desired DCPA·HCl **2** (Scheme 4). It would also be crucial to replace the standard aqueous workup conditions, commonly utilized in Pd-catalyzed deallylations, and find a new method to remove process-related impurities and residual palladium (vide infra).

The sequence began with the preparation of the HCl salt of *N*-allyl-dicyclopropylamine **11** via the reductive alkylation of allylamine **10** (70% yield), setting the stage for the key deallylation step. After considerable catalyst/condition screening, tetrakis(triphenylphosphine)palladium(0) in the presence of *N,N*-dimethylbarbituric acid[20] proved remarkably effective in promoting the desired transformation; after 3 h at room temperature, the deallylation was complete using less than 2 mol % of $Pd(PPh_3)_4$.

With the deallylation performing reliably, we set out to develop an anhydrous isolation protocol. After significant experimentation an acceptable procedure was developed, which was capable of providing high-quality DCPA·HCl **2** with minimum Pd contamination (Scheme 4). Once deallylation was complete, solvent exchange from DCM to a 4:1 mixture of *tert*-butyl methyl ether (TBME) and DMF facilitated the precipitation of DCPA·HCl **2** and Pd residues from solution, allowing the removal of the soluble barbituric acid byproduct **12**. During the course of development, the Pd residue isolated from this solvent exchange was characterized by X-ray crystallography and shown to be the DCM-solvated Pd(II) salt $PdCl_2(PPh_3)_2$ (**13**) (Figure 1).[21] We found that this Pd-complex was relatively insoluble in MeOH; thus, the mixture of **2** and **13** was slurried in MeOH. Subsequent filtration removed the complex **13** selectively, leaving only the methanolic solution of DCPA·HCl **2**. Lastly, crystallization from toluene afforded DCPA·HCl **2** in 70−80% yield with excellent potency (99+ %). ICP-MS revealed that DCPA·HCl **2** generated by this approach contained less than 20 ppm of palladium. This is, to the best of our knowledge, the first report of a nonaqueous method to reliably purge palladium residue from a Pd-catalyzed deallylation reaction.

The mild and effective nature of the Pd-catalyzed deallylation set the course for the generation of DCPA·HCl **2** with high quality. However, the preparation of the deallylation precursor (amine **11**) was not very efficient due to the need to employ 6 equiv of 1-ethoxy-1-[(trimethylsilyl)oxy]cyclopropane **5** and 4.5 equiv of $NaCNBH_3$ to drive the formation of amine **11** to completion (due to unproductive reduction of the cyclopropanone precursor). Though commercially available, ketal **5** is expensive and nontrivial to prepare.[25] The process was further complicated by the toxicity of $NaCNBH_3$ and the potential off-gassing of HCN under the acidic reaction conditions.[22] Further, allylamine **10** is not an optimal source of nitrogen, since it is often difficult to obtain in high purity (especially with respect to *N*-propylamine content); in addition, shipping restrictions make its use difficult on large scale.[23] The desire to minimize the use of these reagents and other handling considerations led to the development of the third synthetic approach as shown in Scheme 5.

The design of the third approach was to redistribute the origin of the two cyclopropyl moieties in DCPA. Cyclopropylamine **14**, a much less expensive source of nitrogen and a cyclopropyl group, would be an optimal starting material. Thus, bis-allylation of cyclopropylamine **14** with allyl bromide afforded *N,N*-diallylcyclopropylamine **15**, which was purified by acid/base extraction to give a solution of amine **15** in DCM. This stream was then subjected to the deallylation conditions developed by Genet $(Pd_2Cl_2(allyl)_2$/DPPB in the presence of *o*-mercaptobenzoic acid)[24] to give *N*-allyl-cyclopropylamine **16** via selective *mono*-

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Scheme 5. Third synthesis of DCPA·HCl 2

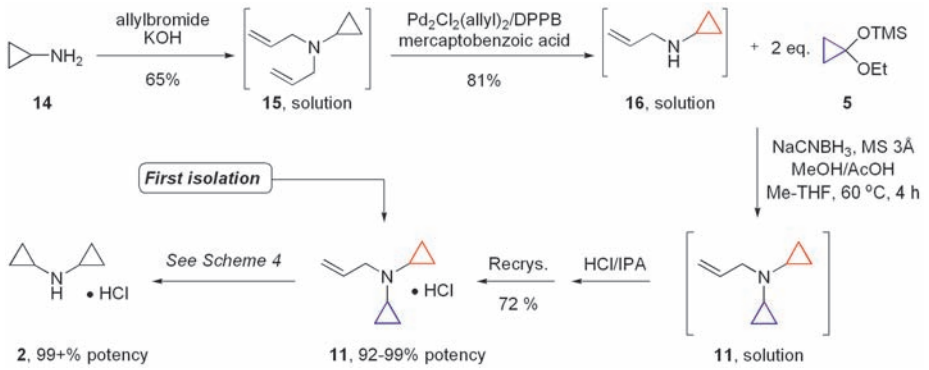
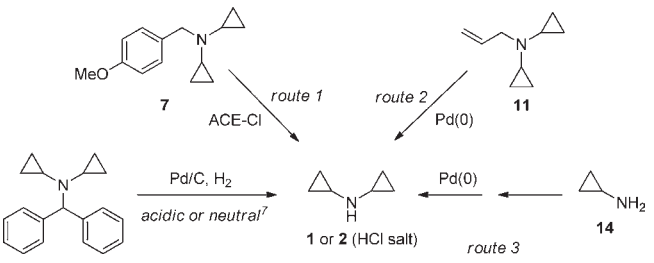


Table 1. Comparison of reductive amination step in the second and third syntheses

	OTMS / OEt (5)	$NaCNBH_3$	MeOH	AcOH	Rx time	Vol*	Yield (%)
NH_2 (10)	6 equiv	4.5 equiv	45 equiv	10 equiv	12 h	140	70
N H (16)	1.2 equiv	1.5 equiv	15 equiv	3 equiv	4 h	30	72

*Reaction volume (L)/amount of isolated product **11** (kg).

Scheme 6. Comparison of impurity content in DCPA (by GC) prepared from three routes and literature precedent



AP of Impurity Content	NH_2 (4)	N H (3)	N H (17)
Hydrogenation (Lit ref)	5[a]; 0[b]	5 -20[c]	*ca.* 0.40
Von Braun (Route 1)	0	0.16	0.41
Pd deallylation (Route 2)	0	0.18	0.36
Route 3	0	0.06	0.02

a. during isolation of DCPA as free amine **1**; *b.* DCPA HCl salt **2** was isolated; *c.* 5 GC-AP under acidic conditions; 20 GC-AP under neutral conditions.

deallylation. After an acid/base extraction, the crude MeTHF solution of **16** was used directly in the reductive amination, resulting in a 72% yield of amine **11**. The deallylation of amine **11** was then performed as previously described in Scheme 4 to afford DCPA·HCl **2**.

We were pleased to find that, under the reductive amination conditions, the more reactive secondary *N*-allyl-cyclopropylamine **16** provided a much more efficient reaction than the previous primary amines **10** or **6** (Table 1). *Gratifyingly, the required amount of 1-ethoxy-1-[(trimethylsilyl)oxy]cyclopropane* **5** *could be reduced by 80% (from 6 to 1.2 equiv); the amount of* $NaCNBH_3$ *was reduced by 67% (from 4.5 to 1.5 equiv); the reaction time decreased by 67% (from 12 to 4 h).* In addition, the volumes of MeOH and AcOH were also significantly reduced, leading to a substantial improvement in the overall volume efficiency of the process (80% reduction in reaction volume).

Lastly, comparison of the quality of DCPA·HCl **2** from all synthetic approaches was conducted using gas chromatography (analyzed as DCPA free-base, prepared in situ by treatment of the HCl salt with DBU; the degradation observed with aq NaOH is not seen under these conditions). As shown in Scheme 6, the hydrogenolytic deprotection of *N*-benzyhydryl (or *N*-benzyl) generated significant levels of *N*-propyl-cyclopropylamine **3** (ranging from 5 to 20%),[7] resulting from the reductive ring-opening of the cyclopropyl moiety; *N*-ethyl-cyclopropylamine **17** was also observed (~0.40%). While initially surprising, impurity **17** is thought to be related to impurities derived from 1-ethoxy-1-[(trimethylsilyl)oxy]cyclopropane **5** (the key reagent in the reductive amination step).[25] Attempts to isolate DCPA as the free base resulted in the formation of *N*-cyclopropylamine **4** (~5%), but such degradation could be avoided by the direct isolation of the HCl salt **2**. In comparison the three new approaches reported here all provide DCPA·HCl **2** with improved purity profiles vs the initial hydrogenation route. Analysis showed DCPA·HCl **2** generated via route 1 (Von Braun deprotection) contained 0.16% of *N*-propyl-cyclopropylamine **3** and 0.41% of *N*-ethyl-cyclopropylamine **17**. Similar amounts of amines **3** and **17** were observed in the DCPA·HCl from route 2

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(Pd-catalyzed deallylation), where both cyclopropyl groups were introduced by reductive amination. Lastly, by reducing the equivalents of 1-ethoxy-1-[(trimethylsilyl)oxy]cyclopropane **5** and removing allylamine **10** as the nitrogen source, route 3 yielded the highest-purity DCPA·HCl **2** (*N*-propyl-cyclopropylamine **3** observed at 0.06% and *N*-ethyl-cyclopropylamine **17** at 0.02%). The reduced levels of both **3** and **17** produced from this final route suggest that both impurities are related to the use of 1-ethoxy-1-[(trimethylsilyl)oxy]cyclopropane **5**.

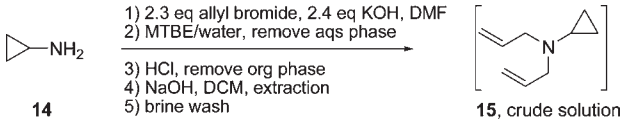
■ CONCLUSION

In conclusion, a high-yielding route to DCPA·HCl (**2**) has been demonstrated that limits the number of isolations, along with the use of hazardous, toxic, and difficult-to-source reactants. Further, an innovative Pd-removal strategy was implemented to assist in the isolation and purification of DCPA·HCl **2**. The final process provides an easy, scalable, and efficient protocol for the synthesis of high-quality DCPA.

■ EXPERIMENTAL SECTION

General. All reactions were performed under a nitrogen atmosphere using anhydrous techniques unless otherwise noted. Reagents were used as received, unless otherwise noted. Quoted yields are for isolated materials or calculated solution yields and have not been corrected for potency. NMR spectra were recorded on Bruker DRX-600 or DRX-500 instruments and are referenced to residual undeuterated solvent. The following abbreviations are used to explain multiplicities: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. High-resolution mass spectra (HRMS) were recorded on a Thermo Orbi-trap Discovery instrument. Melting points were recorded using a Thomas-Hoover melting point apparatus and are uncorrected. The quantitative analysis of residual palladium catalyst was performed with a Perkin-Elmer Optima 4300 DV ICP-AES instrument.

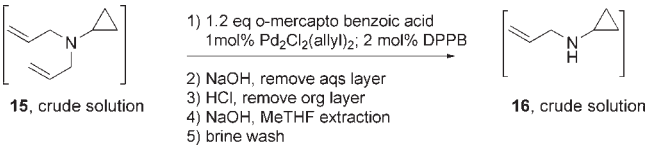
Compound 15.



14 **15**, crude solution

To a 10-L glass reactor was charged with cyclopropylamine **14** (286 g, 5.0 mol, 1.00 equiv), DMF (1.3 L), and potassium hydroxide (664 g, 11.8 mol, 2.35 equiv) with the jacket temperature at 10 °C. The slurry was stirred for 10 min before allyl bromide (1.4 kg, 11.6 mol, 2.31 equiv) was added over 1.5 h, maintaining the internal temperature lower than 55 °C. Upon complete addition, the jacket temp was adjusted to 20 °C. The reaction mass was stirred at 20 °C and monitored by ^{1}H NMR. After completion of the reaction (~2 h), TBME (1.2 L) was charged into the reaction slurry followed by water (2.5 L). The layers were mixed vigorously, and then the bottom layer of aqueous waste was discarded. Aqueous HCl (3 N, 2.4 L) was slowly added to the organic layer while maintaining the internal temperature <35 °C. After addition, the layers were mixed vigorously, and the bottom aqueous layer (~3.0 L) was transferred to a clean reactor. To the HCl solution was added aqueous NaOH (10 N, 0.72 L) maintaining the internal temperature below 30 °C. After addition, the mixture was extracted twice with DCM (1.5 L, then 0.5 L). The combined DCM layers were then washed with aqueous NaCl solution (10%, 660 g). Quantitation by ^{1}H NMR analysis indicated that amine **15** was obtained as a DCM solution (3.05 kg, 14.4 wt %; corrected yield 65%), which was subjected to the next step without further isolation. **Data for Compound 15: ^{1}H NMR:** (500 MHz, $CDCl_3$, 23 °C) δ = 0.42−0.47 (m, 4 H), 1.77−1.83 (m, 1 H), 3.23 (d, J = 6.6 Hz, 4 H), 5.14 (dd, J = 10.1, 17.2 Hz, 4 H), 5.90 (ddd, J = 6.8, 10.1, 16.9 Hz, 2 H).

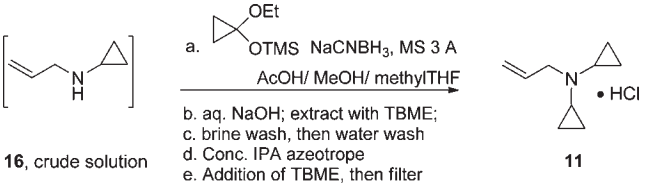
Compound 16.



15, crude solution **16**, crude solution

Diallyl-cyclopropylamine **15** (as DCM solution, 1.8 kg, 26 wt %, 3.4 mol) was charged into a 10-L reactor that had previously been flushed with nitrogen for 90 min. To this solution was added 2-mercaptobenzoic acid (630 g, 4.1 mol, 1.2 equiv), di-μ-chloro-π-allyldipalladium (7.10 g, 38.8 mmol, 0.01 equiv) followed by 1,4-bis(diphenylphosphino)butane (29.0 g, 68.1 mmol, 0.02 equiv). After addition, the reaction mixture was stirred at room temperature under nitrogen. The course of the reaction was monitored by ^{1}H NMR. Upon completion (~3 h), the reaction was quenched with aqueous NaOH solution (2.5 N, 2.7 L) over 20 min. The layers were separated, and the aqueous layer was extracted with DCM (0.5 L). To the combined DCM layers was added HCl solution (4 N, 1.65 L) over 30 min. After addition, the layers were separated, and the aqueous layer was collected. The pH of the aqueous solution was adjusted to 13 by slowly adding aqueous NaOH (2.2 equiv, 5 N, 1.45 L) while maintaining the internal temperature below 45 °C. At the end of addition, product started to oil out. The resulting mixture was extracted with MeTHF (0.8 L), and the extraction solution was washed with brine (26%, 0.6 L). According to quantitation by ^{1}H NMR analysis, compound **16** was obtained as a MeTHF solution (928 g, KF 2.3%, 28.3 wt %; 81% corrected yield), which was directly used in the next transformation, without further purification. **Data for Compound 16: ^{1}H NMR** (500 MHz, $CDCl_3$, 23 °C) δ = 0.33−0.44 (m, 4 H), 2.13−2.18 (m, 1 H), 3.30 (dd, J = 6.1, 1.5, 1.3 Hz, 2 H), 5.06 (ddd, J = 10.1, 1.7, 1.3 Hz, 1 H), 5.17 (ddd, J = 17.2, 1.8, 1.5 Hz, 1 H), 5.86−5.96 (m, 1 H).

Compound 11.



16, crude solution **11**

A 10-L Chemglass reactor was equipped with a nitrogen inlet, a condenser, and an outlet connecting to a NaOH scrubber. To this reactor was charged with allyl-cyclopropylamine **16** (as a MeTHF solution, 1.06 kg, 28.3 wt %, 2.2% water content, 3.1 mol, 1.0 equiv), MeTHF (720 mL), and molecular sieves (3 Å, 1.5 g/g, 450 g). After stirring at 20 °C for 20 min, KF indicated 0.38 wt % water content. [NOTE: allyl-cyclopropylamine **16** was used as a crude MeTHF solution in this step directly. Additional MeTHF was added to adjust the concentration.] Acetic acid (556.0 g, 9.3 mol, 3 equiv) was charged over 10 min, internal

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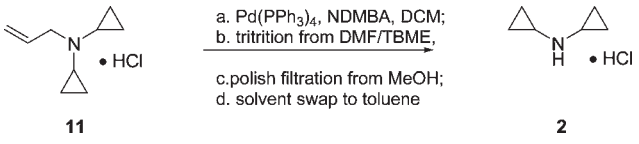
temperature increased from 15 to 39 °C. (1-ethoxycyclopropyl)oxy]trimethylsilane (645.6 g, 3.7 mol, 1.2 equiv) was charged, followed by sodium cyanoborohydride (290.9 g, 4.63 mol, 1.5 equiv) and methanol (1.48 kg, 46.3 mol, 15 equiv). The jacket temperature was set at 65 °C. The course of the reaction was monitored by ^{1}H NMR. Upon completion (~4 h after the internal temperature reached 55 °C), the jacket temperature was cooled to 5 °C. The reaction was carefully quenched with aq NaOH (4 N, 2.8 L, 11.1 mol, 3.6 equiv) over 15 min while the internal temperature was maintained below 30 °C. The jacket temperature was set to 20 °C. The layers were separated, and the bottom aqueous layer was extracted with TBME (5 vol, 1.5 L). The combined organic solution was washed with saturated brine (1 L), then water (1 L).[26] To the TBME solution was added HCl/IPA (5 N, 1.24 L, 6.2 mol, 2 equiv) in one portion. After stirring vigorously for 10 min, the crude product was subjected to distillation (200 Torr with the jacket temperature at 70 °C). After removing 3.5 L of distillate, IPA (30 vol, 9 L) was added for constant-volume distillation (azeotropic removal of water). The moisture content of the distillate (started at ~12 wt %) was constantly monitored. When the distillate KF dropped below 3.0 wt %, the jacket temperature was decreased to 50 °C. TBME (6 L) was charged while maintaining the internal temperature between 35 to 47 °C. A white solid crashed out after the first 500 mL of TBME addition. After addition, the jacket was cooled down from 50 to 20 °C over 3 h. The resulting white slurry was gently stirred at 20 °C for another hour. The solid was filtered, washed with TBME (3 L), and dried in a vacuum oven (45 °C, 15 Torr, nitrogen) to a constant mass. Amine **11** was obtained as a white solid (420 g, potency 92%, corrected yield 72%). **Data for Compound 11: Melting Point** = 135−137 °C; **^{1}H NMR:** (500 MHz, CD_3OD, 23 °C) δ = 0.93−1.25 (m, 8 H), 3.01−3.05 (m, 2 H), 4.01 (d, J = 7.6 Hz, 2 H), 5.58 (ddd, J = 10.1, 1.0, 0.6 Hz, 1 H), 5.67 (ddd, J = 17.0, 1.3, 1.3 Hz, 1 H), 6.16−6.24 (m, 1 H); **^{13}C NMR:** (125 MHz, CD_3OD, 23 °C) δ = 127.9, 126.3, 61.1, 39.7, 4.9, 4.3; **IR (film):** ν_{max} 3047, 2415, 1481, 1410, 1049, 947 cm^{-1}; **HRMS** [M + H] calcd for $C_9H_{16}N$ = 138.1283; found = 138.1274.

Compound 2.



11 **2**

To a 2-L Chemglass reactor flushed with nitrogen was charged with allyl-bis(cyclopropylamine) **11** (185 g, 1.1 mol, 1.0 equiv.), *N*,*N*-dimethylbarbituric acid (166.3 g, 1.1 mol, 1 equiv), tetrakis-(triphenylphosphine)palladium (24.6 g, 21.3 mmol, 2 mol %) and DCM (1.5 L). The crude mixture was stirred at 20 °C under nitrogen while the course of the reaction was monitored by ^{1}H NMR. Upon completion (~1 h), the crude mixture was stirred overnight open to air (to oxidize Pd). DCM (8 vol) was replaced with a mixture of DMF/TBME (0.75 L, 1:4 v/v) via solvent swap with the internal temperature maintained below 30 °C. The resulting light-yellow slurry was filtered and washed with DMF/TBME (0.3 L, 1:9 v/v) then TBME (1 L). The resulting yellow solid (117.4 g, mixture of $PdCl_2(PPh_3)_2$ and amine **2**) was treated with methanol (370 mL) to form a yellow slurry. Filtration through a Whatman Zapcap filter (0.45 μm) and rinsing with extra methanol (200 mL) afforded a colorless solution. Methanol was replaced with toluene (0.75 L) via solvent swap, maintaining internal temperature below 35 °C (50−70 Torr). The resulting white slurry was filtered, rinsed with extra toluene (1 L), and dried in a vacuum oven (20 °C, 15 Torr, nitrogen) to a constant mass. Compound **2** was obtained as a white solid (103 g, 99% potency, corrected yield 72%). **Data for Compound 2: Melting Point** = 130−131 °C; **^{1}H NMR** (500 MHz, CD_3OD, 23 °C) δ = 0.90−1.06 (m, 8 H), 2.86−2.91 (m, 2 H); **^{13}C NMR** (125 MHz, CD_3OD, 23 °C) δ = 31.9, 4.0; **IR (film)** ν_{max}: 2923, 2700, 2464, 2375, 2086, 1597, 1472, 1410, 1209, 1031, 840 cm^{-1}; **HRMS** [M + H] calcd for $C_6H_{12}N$ = 98.0970; found = 98.0957.

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REFERENCES

(1) CAS 73121-95-6 (DCPA as freebase **1**); CAS 246257-69-2 (HCl salt **2**).

(2) For reviews, see: Friedrich, E. C. In *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; Wiley: New York, 1987; Part 1, pp 633−700. Aksenov, V. S.; Terent'eva, G. A.; Savinykh, Yu. V. *Russ. Chem. Rev.* **1980**, *49*, 549.

(3) Standard cross-coupling conditions often led to the formation of the corresponding *N*-allylated product, derived from ring-opening of the cyclopropyl moiety. See: Tsuritani, T.; Strotman, N. A.; Yamamoto, Y.; Kawasaki, M.; Yasuda, N.; Mase, T. *Org. Lett.* **2008**, *10*, 1653–1655.

(4) For selected reviews, see: Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046–2067. Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131–209. Kienle, M.; Dubbaka, S. R.; Brade, K; Knochel, P. *Eur. J. Org. Chem.* **2007**, 4166–4176.

(5) Berman, A. M.; Johnson, J. S. *J. Org. Chem.* **2006**, *71*, 219–224.

(6) De Maijere, A.; Chaplinski, V.; Gerson, F.; Pascal, M.; Haselbach, E. *J. Org. Chem.* **1999**, *64*, 6951–6959.

(7) In our experience hydrogenation of either *N*-benzyl- or *N*-benzhydryl-dicyclopropylamine over Pd/C or $Pd(OH)_2$ gave significant quantities of the ring-opened *N*-propyl-cyclopropylamine **3**. Removal of *N*-benzyl was slower and produced more *N*-propyl-cyclopropylamine **3** than cleavage of *N*-benzyhydryl; carrying out the hydrogenolysis under acidic conditions also reduced this impurity—though never below 5%. These results are in slight contrast to literature precedent (ref 6), although they may be related to differences in reaction time and/or more sensitive analytical methods.

(8) For a similar phenomenon, see: Li, D.; Wang, Y.; Yang, C.; Han, K. *Dalton Trans.* **2009**, 291–297.

(9) Dewar, M. J. S.; Kirschner, S. *J. Am. Chem. Soc.* **1971**, *93*, 4290–4291.

(10) For the instability of cyclopropanone, see: Rothgery, E. F.; Holt, R. J.; McGee, H. A., Jr. *J. Am. Chem. Soc.* **1974**, *97*, 4971–4973.

(11) Gillaspy, M. L., Lefker, B. A., Hada, W. A. Hoover, D. J. *Tetrahedron Lett.*, **1995**, **36**, *41*, 7399-7402.

(12) CAS 27374-25-0.
(13) Crystallization was not effective in our hands at removing the *N*-propyl isomer. Oxidative cleavage methods were investigated; however, the DCPA framework proved unstable to oxidants such as DDQ or CAN. Decomposition occurred most likely via ring fragmentation.
(14) Von Braun, J. *Ber. Dtsch. Chem. Ges.* **1907**, *40*, 3914.
(15) CAS 2393-23-9, used as supplied.
(16) Olofson, R. A.; Martz, J. T.; Senet, J.-P.; Piteau, M.; Malfroot, T. *J. Org. Chem.* **1984**, *49*, 2081.
(17) Olofson, R. A.; Abbott, D. E. *J. Org. Chem.* **1984**, *49*, 2795. Yang, B. V.; O'Rourke, D.; Li, J. *Synlett* **1993**, 195–196.
(18) Tsuji, J.; Mandai, T. *Synthesis* **1996**, 1.Tsuji, J. *Palladium Reagents and Catalysts: Innovation in Organic Synthesis*. John Wiley & Sons: Chichester, 1995.
(19) Xu, F.; Murry, J. A; Simmons, B.; Corley, E.; Fitch, K.; Karady, S.; Tschaen, D. *Org. Lett.* **2006**, *8*, 3885–3888 (included in the SI).
(20) Garro-Helion, F.; Merzouk, A.; Guibe, F. *J. Org. Chem.* **1993**, *58*, 6109–6113 Other palladium sources, such as allylpalladium chloride dimer, proved significantly less effective.
(21) CAS 13965-03-2.
(22) Other reducing reagents were tested, including $NaBH_4$ and $NaBH(OAc)_3$ under various conditions, but $NaCNBH_3$ was the only effective reagent in promoting the desired reductive amination reaction.
(23) For MSDS and safety data regarding allylamine **10**, see: http://progdata.umflint.edu/EHS/MSDS/100300.PDF.
(24) Lemaire-Audoire, S.; Savignac, M.; Genet, J. P.; Bernard, J.-M. *Tetrahedron Lett.* **1995**, *36*, 1267. Bailey, W. F.; Jiang, X.-L. *J. Org. Chem.* **1996**, *61*, 2596. Baldwin, I. C.; Briner, P.; Eastgate, M. D.; Fox, D. J.; Warren, S. *Org. Lett.* **2002**, *4*, 4381.
(25) The commercially available 1-ethoxy-1-[(trimethylsilyl)oxy]-cyclopropane **5** is synthesized from a dissolving metal reduction of ethyl-3-chloropropionate (For reference, see: Salaun, J.; Marguerite, J. *Org. Synth.* **1985**, *63*, 147). The industrial preparation of ethyl-3-chloropropionate often starts from the oxidation of 1-propene to afford acrylic acid, which then reacts with ethanol and $SOCl_2$ to give ethyl-3-chloropropionate; the presence of small amounts of acetaldehyde or related intermediates from such process would be difficult to exclude, which likely contribute to the formation of the *N*-ethyl- and *N*-propyl-cyclopropylamines.
(26) The aqueous layer was treated with aqueous sodium hydroxide (2 N), in order to maintain a basic pH, before being disposed of as cyanide-containing waste.