Improved Access to Cyclopropanol via Supply-Centered Synthesis

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Baeyer-Villiger Oxidation • Continuous Flow • Slurry • Active Pharmaceutical Ingredient

Abstract Access to cyclopropanol is improved by developing a route from highly available, cyclopropyl methyl ketone. The Baeyer-Villiger oxidation inserts oxygen between the cyclopropyl and ketone functionalities, and the alcohol is subsequently unmasked by cleaving the ester with an amine. Optimization resulted in high yield (>90% for each step), isolation of volatile and water soluble cylopropanol, selection of a peroxide with improved safety profile (urea hydrogen peroxide, UHP), and implementation of continuous flow to handle an exotherm. The urea present in the peroxide unexpectedly enhanced conversion of the ketone to the ester, and the addition of a rheology modifier to a 20 wt% suspension of UHP in DCM facilitated continuous delivery of an otherwise difficult to pump slurry.

■ Introduction

MRTX1719 is a clinical drug candidate for cancer treatment.[1] The compound contains several structural features of note, including an axis of chirality, a penta-substituted benzene ring, and a pendant cyclopropyl ether. Cyclopropanol derivatives are present in a number of biologically active compounds (Figure 1).[2] None of these clinical candidates have moved to commercial stage, however, and as a result, cyclopropanol (**5**) has a limited supply chain and high cost. MRTX1719 consumes large quantities of the alcohol since it is used as a reactant early in the synthetic sequence, and this proved to be a significant cost driver for the program. An improved route to cyclopropanol is therefore highly desirable.

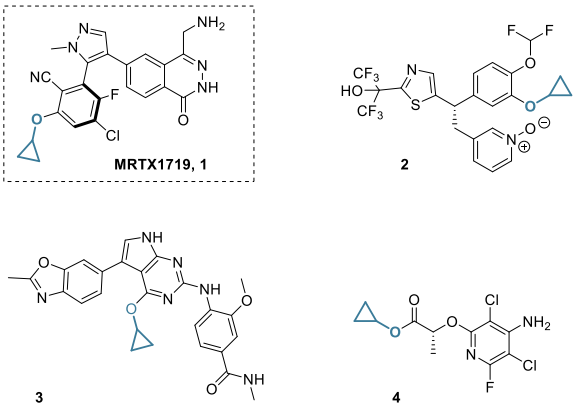


Figure 1: Biologically active molecules incorporating cyclopropanol.

Current production relies upon oxidative cleavage of a boronic acid.[3] The parent compound of this acid is cyclopropyl bromide. While this appears to be a simple starting point for the synthesis, supply is surprisingly limited resulting in high cost (Figure 2).

Supply-centered synthesis ensures robust and economical access to targets through identification of a highly available building blocks.[4] Several candidates which fit this criteria emerged, including cyclopropylamine, epichlorohydrin, cyclopropanecarboxylic acid, and cyclopropyl methyl ketone (**6**). Initial attempts to make cyclopropanol from the amine, epoxide,[5] and acid were not promising, but oxidation of the ketone appeared to have high potential. Emmons and Lucas made acetate **7** in 53% yield by combining the ketone with 90% peroxide in trifluoroacetic anhydride,[6] and though sensitivity to ring opening is reported,[7] Depuy reductively cleaved the ester to reach cyclopropanol also in 53% yield albeit with the

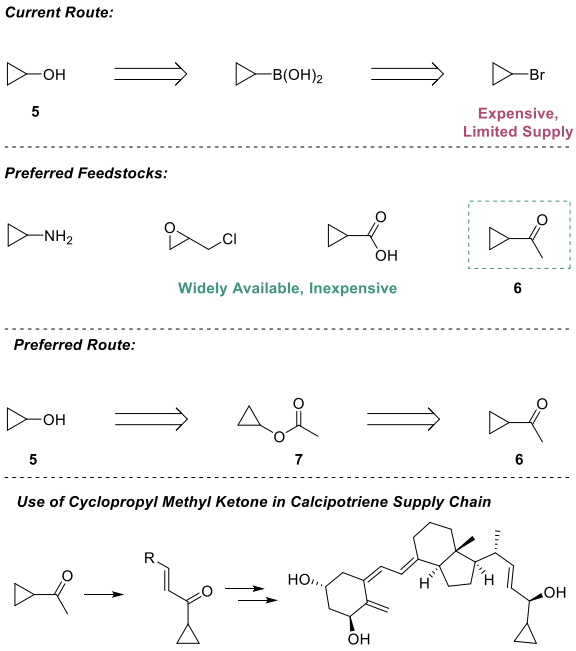


Figure 2: Cyclopropanol route selection based upon availability of chemical feedstocks.

coproduction of ethanol.[7a]

Optimization of the yield and peroxide risk mitigation would enable commercial viability. This work describes the search for a safer peroxide source, the unexpected finding that peroxide stabilizer accelerated the oxidation, peroxide risk mitigation *via* continuous flow, and a novel solution for handling slurries in flow. Considerations upon isolation of cyclopropanol are also addressed.

■ Route Scouting and Optimization

The investigation commenced with identification of a 90% H_2O_2 alternative. Even at lab scale, such high peroxide concentrations are not available, and there is considerable concern with storage and handling at commercial quantities. Urea hydrogen peroxide (UHP) is an attractive alternative because complexation with urea renders a safer form of hydrogen peroxide.[8] It is also anhydrous and highly concentrated, and it is not listed as shock sensitive on safety data sheets. Thus it was particularly gratifying that the reaction to form acetates **7** and **8** not only proceeded but also gave a combined assay yield (AY) much higher than what was previously reported.

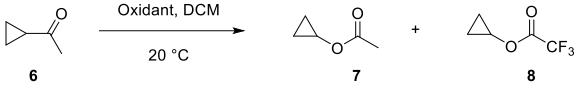


Table 1: Identification of peroxide source for oxidation.

Entry	Oxidant (Equiv.)	Time (hr)	Additive	AY Yield (%, 6, 7, 8)
1	BVMO	24	-	0%
2	*m*CPBA	96	-	2%
3	UHP (10), Ac_2O (2.5)	24	-	0%
4	UHP (10), TFAA (2.5)	2	-	91% (57%, 17%, 17%)
5	30% H_2O_2 (1), TFAA (6)	16	-	27%
6	30% H_2O_2 (1), TFAA (6)	16	Urea (1 equiv.)	55% (45%, 8%)
7	30% H_2O_2 (1) TFAA (6)	16	Urea (4 equiv.)	63% (31%, 32%)

This *in situ* formation of trifluoroperacetic acid (TFPAA) appeared to be critical. Attempts to use lower strength peracetic acid, and *meta*-chloroperbenzoic acid failed to yield substantial ester. Yields with aqueous peroxide were also not as high as with UHP, and the role of urea appears to be non-trivial. Addition of urea to the aqueous hydrogen peroxide significantly increased yield. The Baeyer-Villiger oxidation is accelerated by acidic catalysts which activate intermediates through hydrogen bonding in both the formation of the tetrahedral Criegee-intermediate, and in the oxidative rearrangement.[9] Perhaps, the urea serves as a hydrogen-bond donor to activate the system, and indeed there is precedence for use of catalysts with urea or amide functionality in the asymmetric transformation.[10] Interestingly, the typical prescription of dibasic hydrogen phosphate buffer lowered assay yield and caused the reaction to be a thick and difficult to stir gum. Removal of the phosphate results in either a clear biphasic mixture or a well-behaved slurry based on the amount of DCM incorporated. Attempts to render the system catalytic in either TFA or TFAA did not proceed to desired levels of conversion unfortunately, and no product was observed in a screen with commercial Baeyer-Villiger monooxygenase (BVMO) enzymes.[11]

The peroxide loading of initial results were quite high (10 equivalents) since these trials merged the conditions of Emmons and TFPAA generation from UHP. Such high peroxide consumption increases risk and cost. Optimization identified safer conditions using much less peroxide (≤ 2.5 equiv., Table X)). Balancing the ratio of UHP to TFAA was important and yield decreased with less than 2 equivalents of UHP.

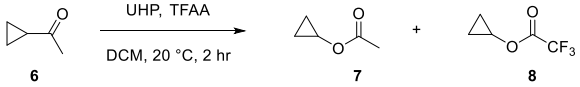
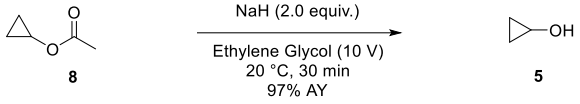


Table 2: Optimization of UHP and TFAA charge.

Entry	UHP (Equiv.)	TFAA (Equiv.)	AY Yield (%, 6, 7, 8)
1	10	2.5	91% (57%, 17%, 17%)
2	5	5	95% (63%, 32%)
3	2.5	5	37% (29%, 8%)
4	5	2.5	86% (53%, 12%, 21%)
5	2.5	2.5	92% (63%, 21%, 8%)
6	2	2	93% (70%, 17%, 6%)
7	1.5	1.5	77% (60%, 12%, 5%)

Cleavage of cyclopropylacetate's ester gives cyclopropanol. Transesterification with methanol was sluggish under acidic or neutral conditions. However the cleavage proceeded with assay yield above 90% when conducted with NaH in ethylene glycol. This is notable because there are presumptions of product instability based on the reported instability under highly acidic or basic conditions.[7] Ethylene glycol was chosen as the alcohol since it has a boiling point much higher than that of cyclopropanol (197 °C vs. 101 °C),

presenting a likely means of isolating the cyclopropanol without cross-contamination of a structurally similar alcohol which could interfere with downstream synthetic sequence. This gives high confidence in the chemistry underlying these transformations since both oxidation and ester cleavage can be conducted with yields above 90%, and thus route-scouting was concluded.



■ Isolation of Cyclopropanol

Isolation of cyclopropanol is non-trivial. It is a volatile, water soluble, liquid. Moreover, cyclopropanol is prone to decomposition upon heating in strongly acidic or basic medium. Further, cyclopropanol's boiling point is quite similar to that of its chemical precursors. The next downstream step is a S_NAr reaction in the presence of water, but other alcohols or nucleophiles need to be absent from the isolated cyclopropanol.

The trifluoroacetate has a boiling point similar to that of DCM. Isolation of the esters from DCM is thus challenging since concentration would render a major loss of material which could be converted to cyclopropanol. Indeed, even gentle evaporation of DCM at this stage resulted in nearly complete co-distillation of the trifluoroacetate.

The above considerations also suggest that the use of NaH in alcoholic medium might not be suitable. Ethylene glycol is a high-boiling solvent and so it can be separated from cyclopropanol; however, attempts to distill cyclopropanol from this basic mixture led to decomposition based on oligomerization of the ring-opened product, propionaldehyde. The milder ester cleavage with a high boiling amine might be more appropriate.

The following work-up strategy was devised (Figure 3, Table 4). After carrying out the oxidation, inorganic material from UHP and acid was removed by addition of water and phase separation. These materials inhibit the ester cleavage with base. Since the product is still in the ester form, it is not water soluble and yield is not lost (AY typically 80%). The product can now be carried forward to the alcohol by simply adding a more mildly basic amine (diethylene triamine, ammonium hydroxide or ethanolamine) to the DCM layer without evaporation of the volatile acetates. Cyclopropanol is generated (AY: 75%) and needs to be separated from the nucleophilic amine residuals and the majority of the DCM. The difference in boiling point

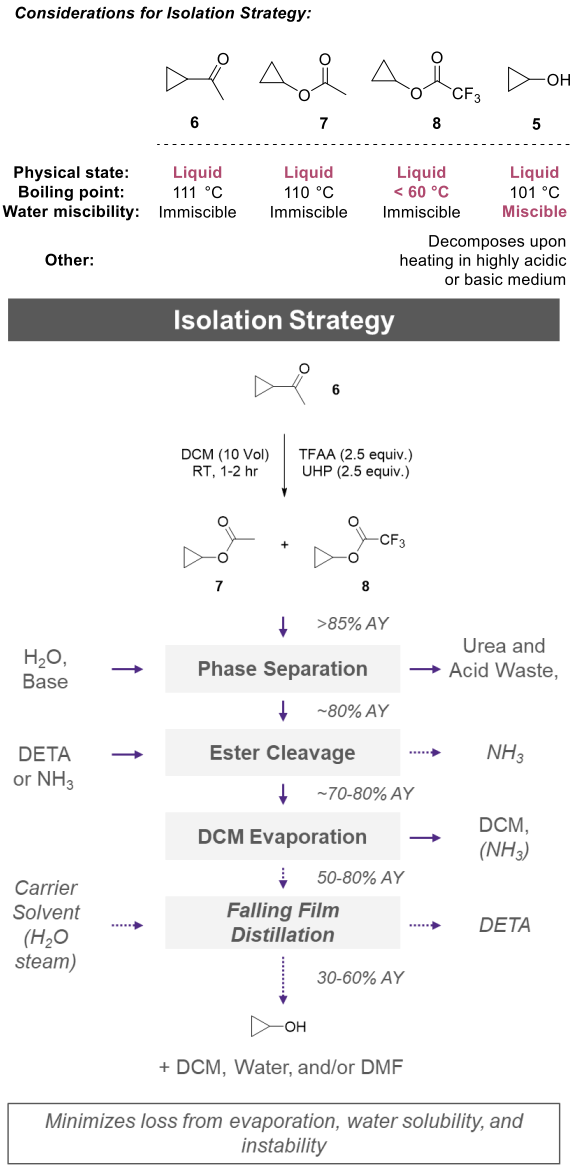


Figure 3: Working around material limitations to design an effective cyclopropanol isolation strategy.

between DCM and cyclopropanol is slightly greater than 50 °C, and so little cyclopropanol is lost (typically < 5%) when gentle evaporation is conducted at pressures > 500 mbar and a temperature of 30 °C (AY: 65%). Use of a falling-film evaporator separates cyclopropanol from the heavier diethylenetriamine and it's acetamides. The continuous nature of the falling film evaporator limits the heat exposure of cyclopropanol, mitigating concerns surrounding stability. Addition of water or dioxane provide a steam of the same boiling point as cyclopropanol which improves recovery (AY of combined fractions: 60%).

Table 4: Mass-Balance of process flow to make cyclopropanol by three different isolation strategies.

Isolation	**Distillation**: Falling Film		**Distillation**: Short Path		**DCM Concentration** (Telescoped to Next Step)	
Amine (Ester Cleavage)	DETA		DETA		NH_3	
Unit Operation	**Wt%**	**AY Total**	**Wt%**	**AY Total**	**Wt%**	**AY Total**
Reaction: IPC	-	87%	-	90%	-	91%
→Phase Separation	3.7%	82%	3.1%	80%	3.6%	77%
→Amine Addition: Ester Cleavage	2.3%	79%	2.8%	75%	2.8%	67%
→Phase Separation	-	-	-	-	2.4%	57%
→DCM Concentration (≥500 mbar)	8.3%	80%	10.5%	67%	**15.1%**	**52%**
→Distillation	**25.0%**	**60%**	**48%**	**32%**	-	-
→*Concentration (Optional)*	*48.4%*	*51%*	-	-	-	-

Alternatively, cyclopropanol can be separated from the amine residuals by short-path distillation to give a more concentrated form, but the isolated yield is lower (32%). This strategy was scaled up from 10 g to 400 g, producing cyclopropanol at 89 wt% in 46% isolated yield. As a third option, ammonium hydroxide can be used. After phase separation and back extraction, the DCM can simply be removed by concentration (AY, 52%).

■ **Safety and Hazard Mitigation**

A strong exotherm was apparent during the oxidation's development. The heat release occurred when either UHP or UHP was added to a mixture containing the other reagents. The reaction was thermally characterized by calorimetry in an RC1 reactor (Table 5). Indeed, the heat release is quite significant as the adiabatic temperature rise is found to be 263 °C. Use of a low boiling solvent (DCM) mitigates risk since evaporative cooling (reflux) keeps the maximum technical temperature below the upper limit of range for thermal stability. However, since the maximum temperature of the synthetic reaction is higher than the thermal stability point, the reaction is classified as a Stoessel Criticality Class 4 hazard.[12]

Table 5: Thermal characterization of Baeyer-Villiger oxidation.

Thermal Properties	
T_P: (Process Temperature)	20 °C
MTT: (Solvent Boiling Point)	40 °C
T_{D24}: (Maximum Temperature for Stability)	69 °C
MTSR: (Maximum Temperature Attainable)	184 °C
ΔH_{adiab}: (Adiabatic Temperature Rise)	263 °C

The thermal hazard can be mitigated by dosing control, cooling from the reactor, evaporative cooling of solvent, and elevation of the reaction's temperature to limit heat accumulation of unreacted materials. Still, further risk mitigation is desirable.

Running the reaction under a continuous regime presents an obvious path toward improved safety. This limits the amount of material reacting at a given time and can enhance heat-transfer as the surface area to volume ratio increases.

The oxidation could be configured either as a:

A. Plug-flow reactor (PFR) if the system is rendered homogenous, or
B. Continuous stirred-tank reactor (CSTR), if the UHP were dosed as a solid or slurry.

Implementation of a continuous platform for this specific system is far from straightforward, however.

In pursuit of Option A, a large variety of highly polar solvents were explored to dissolve the UHP, but none of the combinations performed suitably in the reaction. Even minimal amounts of solvent interfered with the oxidation, causing incomplete conversion. Highly polar solvents were best for dissolving the UHP, yet the oxidation is optimal when performed in less polar solvents such as DCM or hexanes. Perhaps the polar solvents disrupt hydrogen bonding in the transition states. Residual starting material is problematic because of the boiling points between starting material and product are so similar. Solvents explored included water, MeOH, MeCN, nitromethane,

DMF, NMP, DMAc, acetamide, DMPU, diglyme, DMSO, sulfolane, and phosphoric, sulfuric, nitric, and acetic acids. Of these, sulfolane showed the most promise, but the original conditions were far superior.

Option B could present a path to continuous implementation, but dosing of UHP must be solved. Continuous addition of UHP as a solid seems reasonable on first inspection; however, vapor of the highly volatile TFAA (bp: 40 °C) could come in contact with the UHP solids stored in a charging vessel above the reactor. This could cause a serious incident since TFAA and peroxide quickly and exothermically react to form TFPAA.

UHP could be suspended in DCM instead of charging continuously as a solid (Figure 4). Unfortunately, the UHP particles were large and dense. They settled very quickly in DCM and so pumping a slurry with even and representative quantities of UHP was not possible. Attempts to reduce particle size by jet-milling or grinding the UHP as a solid were unsuccessful.

Grinding the UHP in DCM with a rotor-stator homogenizer led to a partially acceptable solution. The smaller particles were much slower to settle than the commercial variant. The suspension could be pumped by a peristaltic pump, but only at flow rates above 20 mL/min. Otherwise, particles settled and let to clogs at pinch-points. Maintaining a steady-state was unreliable.

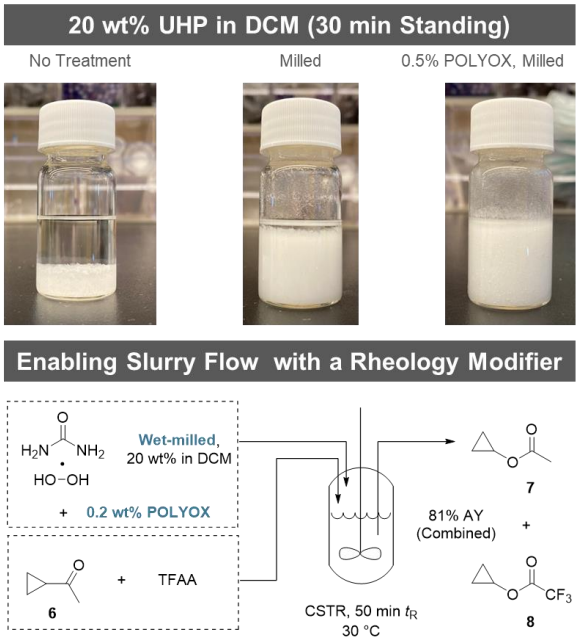


Figure 4: Enabling UHP slurry addition and continuous flow operation by milling and suspending the peroxide solids with a rheology modifier (POLYOX).

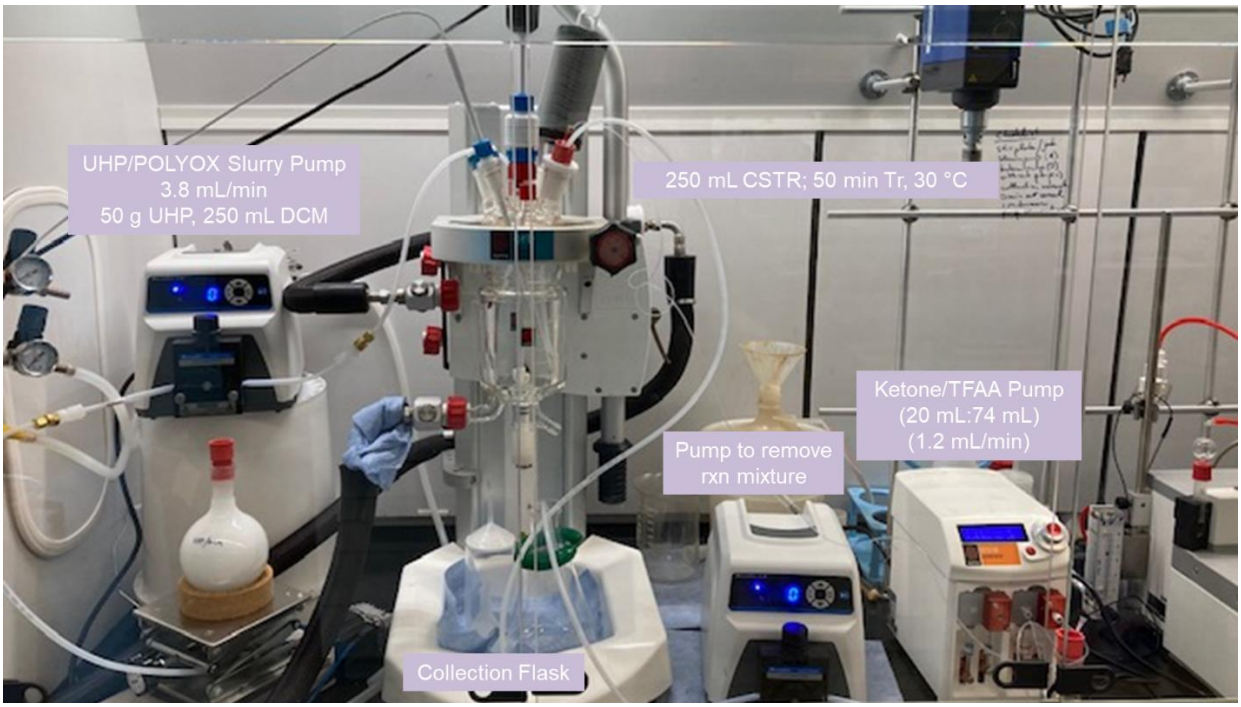


Figure 5: Experimental setup for a 20 g run of the Baeyer-Villiger oxidation in a CSTR.

The best solution was to use a rheology modifier to thicken the milled UHP suspension.[13] A high molecular weight polyethyleneoxide (PEO), POLYOX, was selected. UHP settling was negligible at only 0.5 wt% loading. The DCM mixture became a thick gel with the PEO additive. Settling of UHP was minimal at loadings as low as 0.1 wt%, and despite the thick, gel-like nature of the heterogeneous mixture containing 20 wt% of UHP solids, it could be pumped at the lowest flow rate of the pump (2 mL/min) indefinitely. The additive did not interfere with the oxidation since it is present in such small quantities, even though the reaction is not compatible with bulk polyether as solvent. The combined yield of esters was 81**%** (Figure 4,5).

Implementation of continuous flow technology which limits the amount of material reacting at a given time greatly improves the risk profile of the oxidative transformation. To the best of my knowledge, this is the first example of use of thickeners to handle solids in flow for continuous flow synthesis, and perhaps its application can be general to flow other slurry based systems.

■ Cyclopropanol Use-Test

Technical grade cyclopropanol made from this process was carried forward to the next step in the synthetic sequence to assess the material's suitability. Cyclopropanol (5% in dioxane) was combined with 4-chloro-2,5-difluorobenzonitrile to form the cyclopropyl ether *via* a S_NAr coupling.[3b] Material made from the new route performed comparably to commercial cyclopropanol (Table 6).

Further, the cyclopropanol made *via* the ammonium hydroxide route could be directly telescoped into the S_NAr reaction, without any distillation of the alcohol (Figure 6). DMF was added to the reaction mixture after phase separation of the ammonium hydroxide. The DCM was then evaporated, and the crude mixture was used to make the aryl ether. This can greatly reduce cycle-time during manufacturing.

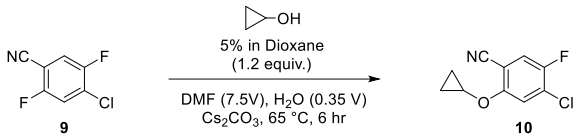


Table 6: Use-test of cyclopropanol made from Baeyer-Villiger oxidation.

Cyclopropanol Source	Yield (%)	Purity (LCAP)	Assay (wt %)
Baeyer-Villiger Route	77%	99.22%	98%
Commercial Cyclopropanol	81%	99.21%	99.5%

■ Conclusions

An improved and economical route to cyclopropanol was developed. Isolation was performed by working around issues related to water solubility, volatility, and stability, and a continuous process was implemented for the oxidation to enable scale-up and mitigate thermal risks. Solids were managed by a novel strategy to suspend the slurry with a rheology modifier which decelerated settling. These improvements debottleneck cyclopropanol supply and reduced raw material costs by more than 50%.

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There are no conflicts of interest to declare

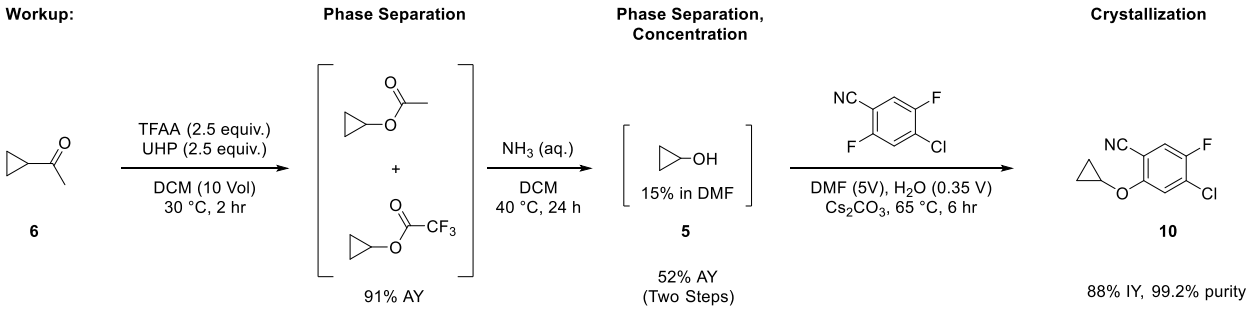

Figure 6: Telescoping crude cyclopropanol into the subsequent S_NAr reaction without distillation.

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