Synthetic Methods

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Development of a Catalytic Platform for Nucleophilic Substitution: Cyclopropenone-Catalyzed Chlorodehydration of Alcohols**

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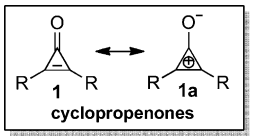
The nucleophilic substitution of alcohols is one of the most commonly executed and strategically important transformations in organic chemistry.[1] These reactions have long been used to transfer the structural and stereochemical complexity of alcohols to a myriad of other products.[2] Despite this importance, the traditional reagents for alcohol substitution leave much to be desired. Such reagents often produce problematic by-products or suffer from a narrow scope or poor reactivity. Most importantly, many of these processes are not amenable to catalysis or enantioselection (for example, kinetic resolution or desymmetrization), with two recent exceptions.[3,4]

As a powerful alternative to the established methods, we recently reported a new strategy for promoting nucleophilic substitution and other dehydration reactions, based on the facile formation of aromatic cyclopropenium ions.[5] We have demonstrated the effectiveness of this "cyclopropenium activation" approach in a number of dehydration reactions, including alcohol[5a] and carboxylic acid[5b] chlorodehydration, diol cyclodehydration,[5c] and the Beckmann rearrangement.[5d] This strategy offers potent reactivity, adaptable reagents, and significant operational convenience. Herein, we report the development of a catalytic platform for the nucleophilic substitution of alcohols through simple cyclopropenone catalysts. This work provides a new means to prepare alkyl chlorides from alcohols and sets the conceptual framework for developing cyclopropenones into a new class of organocatalysts.

Cyclopropenones were first prepared by Breslow et al.[6] and Volpin and co-workers[7] more than 50 years ago. These compounds have a number of useful qualities for applications in catalysis, which include straightforward preparation[8] in one or two steps from commercially available materials, and the ability to tune their physical and electronic properties (Figure 1).[9] In terms of reactivity, the pseudo-aromatic character of the cyclopropenone ring (c.f. resonance form **1a**) manifests itself in a remarkably large dipole moment,[6d] and a relatively high carbonyl basicity.[6d,9b] This substantial

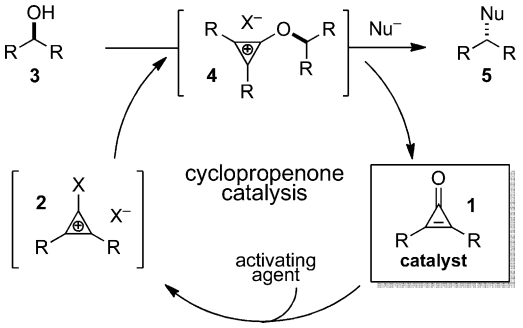


· First prepared by Breslow and Volpin in 1959
· Polarized due to aromatic resonance form
· Stable precursor to cyclopropenium ions
· High tunability of electronic and steric profile

Figure 1. Cyclopropenones.

polarization is also responsible for the unusual nucleophilicity of the cyclopropenone carbonyl,[10] which is the reactivity we have exploited in previous studies on the activation of cyclopropenium ions. In those studies, cyclopropenones served as the precursors to activated cyclopropenium ions, and were the eventual by-products of dehydration. Therefore, we hypothesized that a catalytic process that involves the concurrent activation of cyclopropenone and substitution of an alcohol could be realized.

Under our proposed design, cyclopropenone catalyst **1** would react rapidly with an activating agent, to produce cyclopropenium salt **2** (Scheme 1). This cyclopropenium ion



Scheme 1. General design of cyclopropenone-catalyzed nucleophilic substitution.

would then react with an alcohol substrate **3**, to generate the key cyclopropenium-activated intermediate **4**. Nucleophilic displacement by the cyclopropenium counterion, or other exogenous nucleophile, would then furnish the substitution product **5**, and return cyclopropenone **1** to the catalytic cycle. The viability of this process depends on favorable competition between the catalyst and the substrate in the reaction with the activating agent. As a factor in this competition, the turnover of the catalyst must also be facile. We were optimistic that such selectivity could be achieved through tuning the electronic profile of the cyclopropenone.

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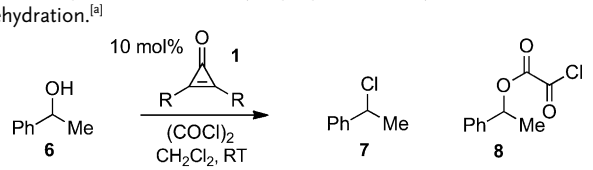
Initially, we chose to examine the chlorodehydration of 1-phenylethanol (**6**) with oxalyl chloride and catalytic amounts of various cyclopropenones **1** (Table 1). In the absence of any cyclopropenone, no alkyl chloride **7** was obtained, and chloroxalate **8** was the only product (Table 1, entry 1). In contrast, adding 10 mol% of 2,3-diphenylcyclopropenone and a single aliquot of neat oxalyl chloride to the reaction at room temperature increased the percentage of **7** obtained to 68% (Table 1, entry 2). Adding the oxalyl chloride over one hour by syringe pump increased the amount of **7** obtained to 75% (Table 1, entry 3).

We expected that changing the substituents of the cyclopropenone ring would have a significant impact on the efficiency of the reaction. Therefore, we screened a range of cyclopropenones bearing different R groups. Increasing the size of the aryl substituents made little impact on the ratio of **7**:**8** produced (Table 1, entries 4 and 5). On the other hand, changing the electronic properties of the aryl substituents significantly affected the outcome of the reaction. The presence of an electron-withdrawing substituent (*m*-NO_2) was detrimental to the formation of **7** (Table 1, entry 6). In contrast, the electron-donating substituents *p-tert*-butyl (Table 1, entry 7) and *p*-methoxy (Table 1, entry 8) increased the ratio of **7**:**8** to approximately 9:1. A further increase in the electron-donating character of the cyclopropenone substituents was counterproductive (Table 1, entries 9 and 10), although good selectivity was achieved with alkyl substituents (Table 1, entries 11 and 12).

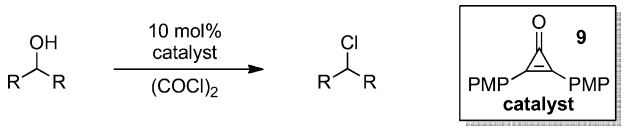
Table 1: Optimization of the cyclopropenone-catalyzed alcohol chlorodehydration.[a]

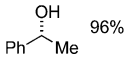
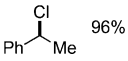
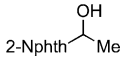
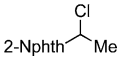
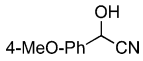
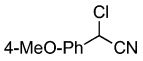
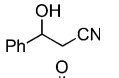
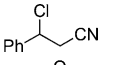
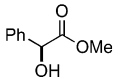
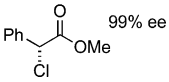
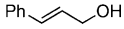
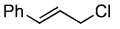
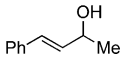
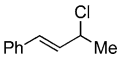
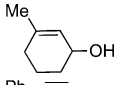
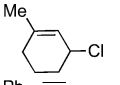
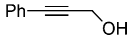
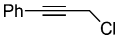
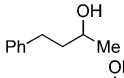
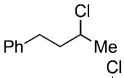
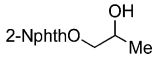
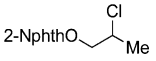
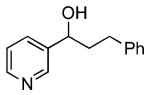
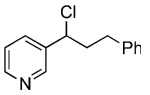
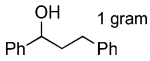
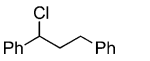
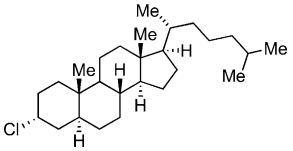


Entry	R	Catalyst conc. [M]	$(COCl)_2$ Addition time [h][b]	**7** [%][c]	**8** [%][c]
1	no catalyst	–	0	0	100
2	Ph	0.1	0	68	32
3	Ph	0.1	1	75	25
4	2,4-xylyl	0.1	1	75	25
5	Mes	0.1	1	67	33
6	*m*-NO_2Ph	0.1	1	14	86
7	*p*-*t*Bu-Ph	0.1	1	87	13
8	*p*-MeO-Ph	0.1	1	91	9
9	2,4-$(MeO)_2$-Ph	0.1	1	38	62
10	Ph, *i*Pr_2N	0.1	1	17	83
11	*i*Pr	0.1	1	89	11
12	adamantyl	0.1	1	92	8
13	*p*-MeO-Ph	0.2	1	33	67
14	*p*-MeO-Ph	0.05	1	96	4
15	***p*-MeO-Ph**	**0.03**	**1**	**>98**	**<2**
16	*p*-MeO-Ph	0.03	0.25	94	6

[a] The reactions were performed by combining 1-phenylethanol (**6**) with the cyclopropenone catalyst **9** (10 mol%) in CH_2Cl_2, then adding a solution of oxalyl chloride (1 equiv) in CH_2Cl_2 (0.5 mL) through a syringe pump, over the time indicated. [b] 0 Indicates $(COCl)_2$ was added as one aliquot at the beginning of the reaction. [c] Percent conversion was determined by ^{1}H NMR spectroscopy. The text in bold highlights the conditions giving the highest yield of **7**.

Table 2: Substrate scope of the cyclopropenone-catalyzed chlorodehydration.



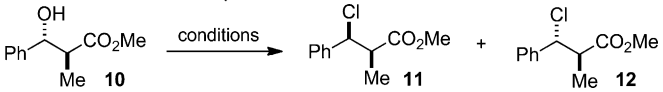
Entry, Cond.	Alcohol	Product	Yield [%][b]
1, A			84
2, A			90
3, A			99
4, A			86
5, B			75
6, B			82
7, B			72[c]
8, A			94
9, A			90
10, A			99
11, A			81
12, A			96
13, B			67[c]
14, B			67
15, C			77
16, A			91
17, A	cholestanol		62 >98:2 d.r.

[a] Reaction conditions A: The alcohol substrate was combined with cyclopropenone **9** (10 mol%, 0.03 M in CH_2Cl_2) and a solution of oxalyl chloride (1 equiv) in CH_2Cl_2 (0.5 mL) was added through a syringe pump, over 1 h. Reaction conditions B: The same as reaction conditions A, except $PhCF_3$ was used as the solvent and the reaction was performed at 80°C. Reaction conditions C: The same as reaction conditions A, except the oxalyl chloride solution was added over 8 h and 20 mol% of **9** was used. [b] Percent yield was determined after the products were isolated and purified, except for entries 1 and 11, which were determined by ^{1}H NMR spectroscopy versus Bn_2O as an internal standard. [c] The oxalyl chloride solution was added over 4 h. PMP = *p*-methoxyphenyl.

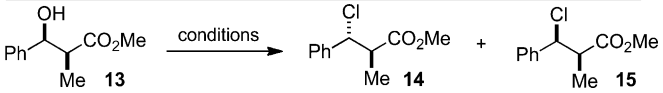
Since it is readily available, we chose 2,3-bis-(*p*-methoxyphenyl)cyclopropenone for further optimization studies. Interestingly, a twofold increase in the concentration of the catalyst favored the production of **8** by a 2:1 ratio (Table 1, entry 13), whereas a twofold dilution increased the selectivity for chlorination to 96% (Table 1, entry 14). Diluting the catalyst further almost completely suppressed the production of **8** (Table 1, entry 15). The oxalyl chloride addition time could also be reduced to 15 min, which did not significantly affect the selectivity of the reaction (Table 1, entry 16).

A range of benzylic (Table 2, entries 1–8), allylic (Table 2, entries 9–11), and propargylic alcohols (Table 2, entry 12) were efficiently chlorodehydrated using cyclopropenone catalysis. Notably, with some modifications to the reaction conditions, α- and β-hydroxynitriles (Table 2, entries 5 and 6), as well as an α-hydroxyester (Table 2, entry 7), were also viable substrates. The modified reaction conditions, which also included a higher temperature, were also effective for converting aliphatic alcohols to the corresponding alkyl chlorides (Table 2, entries 13 and 14). Moreover, this catalytic method was rendered compatible with basic functional groups, such as a pyridine ring (Table 2, entry 15). To demonstrate the cyclopropenone-catalyzed procedure on a preparative scale, we conducted the reaction with one gram of 1,3-diphenyl-1-propanol. This reaction produced the corresponding chloride product in 91% yield (Table 2, entry 16). Importantly, we determined that the chlorination occurs with inversion of stereochemistry at chiral centers (entries 3, 7, and 17; see also Table 3).

Table 3: Comparison of the cyclopropenone-catalyzed and thionyl chloride mediated chlorodehydrations.



Entry	Conditions[a]	Yield [%][b]	*syn*/*anti*[c]
1	**9** (10 mol%), $(COCl)_2$	90	>98:2
2	$SOCl_2$	100	93:7
3	$SOCl_2$, pyridine	90	57:43



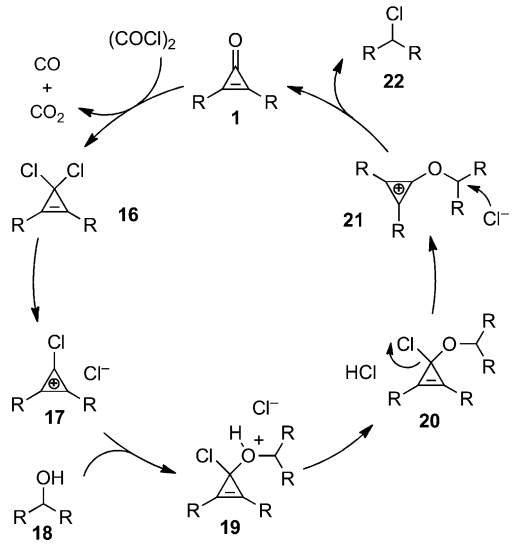
Entry	Conditions[a]	Yield [%][b]	*syn*/*anti*[c]
4	**9** (10 mol%), $(COCl)_2$	79	>98:2
5	$SOCl_2$	0	–
6	$SOCl_2$, pyridine	55	58:42

[a] The reactions in entries 1 and 4 were performed by combining the alcohol substrate with cyclopropenone **9** (10 mol%) in $PhCF_3$ at 80°C, then adding a solution of oxalyl chloride (1 equiv) through a syringe pump, over 1 h. The reactions in entries 2 and 5 were performed by combining the alcohol substrate with thionyl chloride (1.5 equiv) in PhMe at 55°C for 90 min. The reactions in entries 3 and 6 were performed by combining the alcohol substrate with thionyl chloride (1.1 equiv) and pyridine (1.1 equiv) in $CHCl_3$ at 55°C for 90 min. [b] For entries 1 and 4, percent yield was determined after the products were isolated and purified. For entries 2, 3, 5, and 6, percent yield was calculated by ^{1}H NMR spectroscopy versus Bn_2O as an internal standard. [c] Ratios were determined on the crude reaction product by ^{1}H NMR spectroscopy.

To demonstrate the practical benefits of the cyclopropenone-catalyzed strategy, catalyst **9** was compared with the common chlorodehydration reagent, thionyl chloride (Table 3). In the presence of **9**, the *anti*-β-hydroxy ester **10** was converted into the chloride adduct **11** as a single diastereomer, with a 90% yield of isolated product (Table 3, entry 1). The same reaction with thionyl chloride in place of **9** afforded quantitative conversion of **10**; however, the diastereomeric chlorides **11** and **12** were obtained in a 93:7 ratio (Table 3, entry 2). The use of thionyl chloride with pyridine resulted in an approximately 1:1 mixture of the two diastereomers (Table 3 , entry 3).

The same comparison was conducted with the *syn* alcohol substrate **13** (Table 3, entries 4–6). The cyclopropenone-catalyzed method generated the chloride adduct **14** in 79% yield, with complete stereoselectivity (Table 3, entry 4). Interestingly, the reaction with thionyl chloride did not produce any chloride product under the same conditions (Table 3, entry 5). The use of pyridine in addition to thionyl chloride resulted in a modest conversion of the starting material, but almost no stereoselectivity (Table 3, entry 6).

Our proposed mechanism for the cyclopropenone-catalyzed chlorodehydration reaction is shown in Scheme 2. The cyclopropenone catalyst **1** undergoes a rapid reaction with

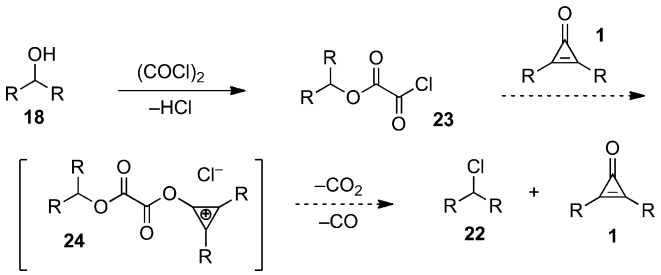


Scheme 2. Proposed mechanism for the cyclopropenone-catalyzed chlorodehydration.

oxalyl chloride to generate the 1,1-dichlorocyclopropene **16**.[11] Ionization of **16** affords the cyclopropenium chloride salt **17**. The salt then reacts with the alcohol substrate **18** to produce the protonated cyclopropenyl ether **19**. After deprotonation of **19**, the neutral cyclopropene **20** re-ionizes to give the key alkoxy cyclopropenium salt **21**. Compound **21** is a species we have detected by ^{1}H NMR spectroscopy.[5a] Nucleophilic displacement of the cyclopropenium oxide by a chloride ion then produces the chloride adduct **22**, and regenerates the catalyst **1**.

The mechanism proposed in Scheme 2 is in accordance with our previous studies on the potent reactivity of

dichlorocyclopropenes **16**.[5] However, another plausible pathway by which the reaction might occur must be considered (Scheme 3).[12] Thus, reaction of **18** with oxalyl chloride produces the chloroxalate **23**, which was a by-product detected in our reactions. Theoretically, nucleophilic attack

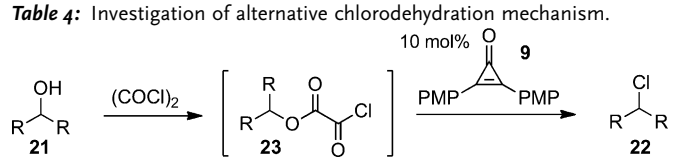


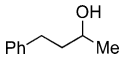
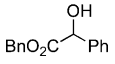
Scheme 3. Alternative mechanism for the cyclopropenone-catalyzed chlorodehydration.

of **1** on **23** could result in the intermediate **24**, which would then decompose into the chloride product **22**, carbon dioxide, and carbon monoxide, while regenerating **1**. This alternative mechanism is analogous to that proposed, and subsequently disproved, by Denton et al. for their triphenylphosphine oxide catalyzed chlorodehydration procedure.[3b]

To determine if the mechanism shown in Scheme 3 was operating in the cyclopropenone-catalyzed process, three different alcohol substrates were treated with one equivalent of oxalyl chloride, to generate a series of chloroxalate esters (**23**), and then with 10 mol% of **9** (Table 4). In the case of a non-activated alcohol (Table 4, entry 1) or an α-hydroxy ester (Table 4, entry 2), no chloride products **22** were observed after 4 h. These results demonstrate that the reaction did not proceed through the mechanism shown in Scheme 3 with these two substrates. On the other hand, the reaction with 1-phenylethanol proceeded to 50% conversion after 1 h (Table 4, entry 3). Therefore, side product **23** may still be a

Table 4: Investigation of alternative chlorodehydration mechanism.



Entry	Alcohol	Conditions[a]	Time [h]	Conv [%][b]
1		$PhCF_3$, 80 °C	4	0 (67)
2		$PhCF_3$, 80 °C	4	0 (88)
3		CH_2Cl_2, 23 °C	1	50 (99)

[a] The reactions were performed by combining the alcohol substrate with oxalyl chloride (1 equiv) in the solvent indicated. After 30 min cyclopropenone **9** (10 mol%) was added, and the reaction stirred at the temperature indicated for 1 or 4 h. [b] Conversion rates were determined by ^{1}H NMR spectroscopy versus Bn_2O as an internal standard. The numbers in parentheses indicate the yield of isolated chloride product obtained by using the corresponding cyclopropenone-catalyzed reaction.

productive intermediate for cyclopropenone-catalyzed chlorodehydration with suitably reactive substrates. However, because our catalytic procedure has a vastly superior rate (99% conv. in 1 h after 1 h addition of oxalyl chloride) to that shown in Table 4, entry 3, we favor the mechanism shown in Scheme 2.

In summary, we have developed a cyclopropenone-based catalyst for nucleophilic substitution in the context of alcohol chlorodehydration. The ability to generate alkyl chlorides from alcohols by using a catalytic amount of a ketone is a major improvement over traditional methods. Broadly speaking, we expect that the concept of cyclopropenone catalysis will be applicable to a wide range of dehydration reactions. Importantly, this work raises the intriguing possibility of applying enantioselective catalysts to kinetic resolutions or desymmetrizations. Efforts in this regard are currently underway in our laboratory.

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