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# Aromatic Cation Activation: Nucleophilic Substitution of Alcohols and Carboxylic Acids

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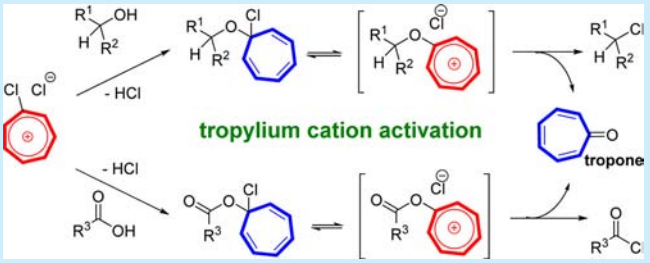
Supporting Information

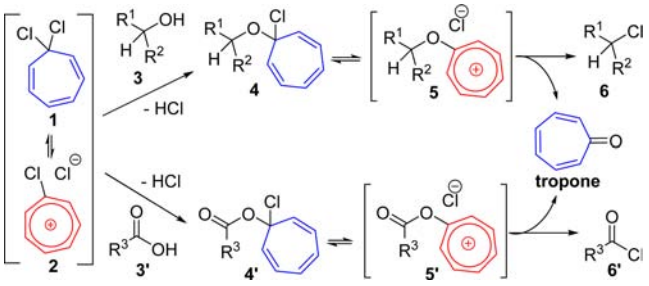
**ABSTRACT:** A new method for the nucleophilic substitution of alcohols and carboxylic acids using aromatic tropylium cation activation has been developed. This article reports the use of chloro tropylium chloride for the rapid generation of alkyl halides and acyl chlorides under very mild reaction conditions. It demonstrates, for the first time, the synthetic potential of tropylium cations in promoting chemical transformations.




The history of carbocations started in 1891 with Merling's discovery of cycloheptatrienylium (tropylium) bromide,[1] which was confirmed spectroscopically by Doering and Knox more than 60 years later.[2] It is no surprise that a salt of the tropylium cation was discovered first among the vast pool of carbocations because the tropylium ion is one of the most stable carbocations known. Having 6$\pi$-electrons delocalized on seven carbons, tropylium ions obey Hückel's rule for aromaticity[3] and therefore possess remarkable stability. Tropylium salts are known to be stable in their solid and solution states. In general, stable carbocations such as the trityl[4] or cyclopropenium[5] ions are known to promote numerous chemical transformations due to their ability to act as Lewis acids. However, despite being the 'first discovered' stable carbocation, tropylium cations have rarely been utilized in practical synthetic chemistry.[6] Herein, we report the first study of the use of tropylium cations to activate alcohols for dehydrative nucleophilic chlorination and bromination. Carboxylic acids can also be activated for nucleophilic acyl substitution in the same manner (Scheme 1).

Tropylium and cyclopropenium[7] ions are the two simplest members of Hückel's aromatic carbocations. The former is predicted to be relatively more stable than the latter,[8] presumably due to the lack of ring constraint energy. Recently, Lambert and co-workers established a novel method to activate several types of substrates for nucleophilic substitution reactions via the dearomatization/rearomatization of cyclopropenium systems.[5a,b,f] We envisioned that tropylium cations would possess a similar capability. The positively charged aromatic system of the tropylium ion can conveniently and reversibly convert to its neutral cycloheptatriene state by association with a negatively charged species.[5a] It is known that 1-substituted 2,4,6-cycloheptatrienes with a substituent capable of turning into a good leaving group, such as a halogen, can dissociate to form aromatic tropylium halide salts,[2,9] similar to those reported with *gem*-dichlorocyclopropenes[5a] and chlorotriphenyl phosphonium chloride.[10] This intriguing property encouraged us to examine the synthetic value of tropylium cations in organic chemistry, as the dearomatization/rearomatization process can provide an apposite driving force for chemical reactions.

**Scheme 1. Proposed Design for Tropylium-Promoted Nucleophilic Substitution Reaction**




1,1-Dichlorocycloheptatriene (**1**) was easily prepared *in situ* by treating tropone with a chlorinating reagent, preferably oxalylchloride.[11] In a preliminary series of experiments, **1** successfully converted benzyl alcohol to benzyl chloride. The reaction occurred rapidly at room temperature in several different solvents.[11] The optimized reaction conditions utilized dichloromethane solvent with 1.1 mol equiv of 1,1-dichlorocycloheptatriene (**1**) (Table 1, entry 1). These conditions were employed in nucleophilic chlorination reactions with a range of alcohol substrates to afford products in good to excellent yields.[12] As expected, the reactivity decreased from activated (benzylic/allylic) primary alcohols to nonactivated primary alcohols and then nonactivated secondary alcohols (Table 1). Electron withdrawing and donating groups on the aromatic rings of the benzylic alcohols seemed to have no significant

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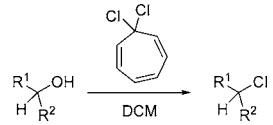
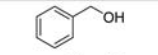
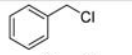
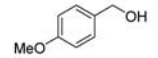
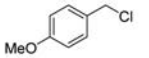
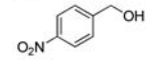
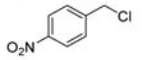
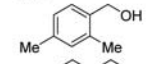
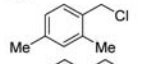
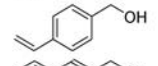
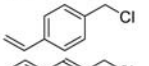
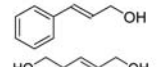
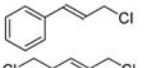
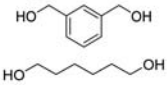
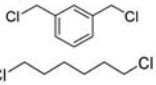
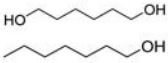
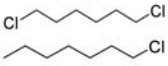
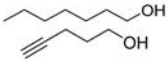
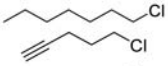
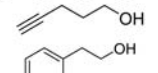
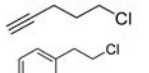
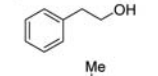
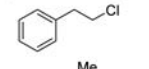
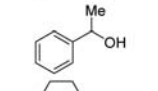
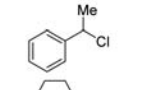
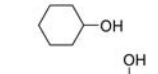
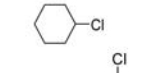
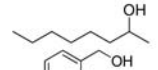
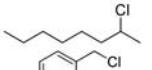
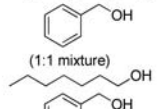
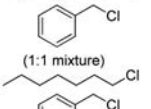
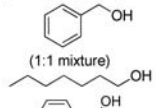
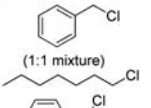
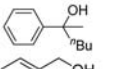
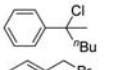
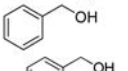
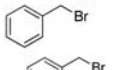
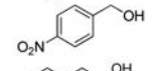
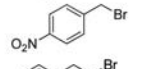
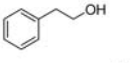
**Table 1. Nucleophilic Substitution Reactions of Alcohols**




| entry[a] | substrate | product | temp[b] | time[c] | yield[d] |
|---|---|---|---|---|---|
| 1 |  |  | rt | 15 | 91 |
| 2 |  |  | rt | 15 | 93 |
| 3 |  |  | rt | 15 | 90 |
| 4 |  |  | rt | 25 | 86 |
| 5 |  |  | rt | 15 | 84 |
| 6 |  |  | rt | 10 | 90 |
| 7[e] |  |  | rt | 25 | 76 |
| 8[e] |  |  | 75[f] | 40 | 63 |
| 9 |  |  | 75[f] | 30 | 81 |
| 10 |  |  | 75[f] | 30 | 84 |
| 11 |  |  | 75[f] | 30 | 88 |
| 12 |  |  | rt | 30 | 89 |
| 13 |  |  | 75[f] | 40 | 85 |
| 14 |  |  | 75[f] | 40 | 78 |
| 15[e] |  (1:1 mixture) |  (1:1 mixture) | rt | 20 | 86<br><3 |
| 16[e] |  (1:1 mixture) |  (1:1 mixture) | 75[f] | 40 | 81<br>73 |
| 17 |  |  | 75[f] | 30 | - |
| 18[g] |  |  | rt | 5 | 73 |
| 19[g] |  |  | rt | 5 | 70 |
| 20[g] |  |  | rt | 720 | 81 |
| 21[g] |  |  | rt | 720 | 79 |

[a]See the Supporting Information for experimental details. [b]Reaction temperature (°C) after the addition. [c]Reaction time (minutes) after the addition. [d]Yield of isolated product. [e]2.5 mmol of **1** were used. [f]Reaction was performed in chloroform in a sealed tube. [g]2.5 equiv of $[Br]^-$ were added before the alcohol.[11]

effect on the reactivity (Table 1, entries 2−3). Nonactivated primary alcohols and secondary alcohols required an elevated temperature (75 °C, $CHCl_3$), affording the corresponding alkyl chloride products in slightly lower yields (Table 1, entries 8−11, 13−14). Reactions for these alcohols at room temperature were rather sluggish, requiring up to 24 h to achieve full conversion. In contrast, an activated secondary alcohol reacted quickly with 1,1-dichlorocycloheptatriene at room temperature to form the chloride products in high yield (Table 1, entry 12). Based on the difference in reaction rate, a benzylic alcohol can be selectively chlorinated from the mixture of it with a nonactivated alcohol (Table 1, entries 15−16). For a tertiary alcohol with an available $\beta$-hydrogen, a competing elimination reaction was observed to give alkene products while a substitution product was only found in a trace amount (Table 1, entry 17).[13] Bisalcohols were converted to dichlorides smoothly with an excess of 1,1-dichlorocycloheptatriene (**1**) (Table 1, entries 7, 8). C−C double and triple bonds seemed to tolerate the reaction conditions (Table 1, entries 5, 6, 10). NMR control experiments were performed with 2-phenyl ethanol in $CDCl_3$ to confirm that the reaction indeed proceeded via the formation of tropylium alkoxy **5**.[14]

By adding a nucleophile stronger than chloride, such as bromide, to the reaction mixtures before the addition of alcohols, competing nucleophilic substitution reactions occurred to predominantly afford alkyl bromide derivatives (Table 1, entries 18−21).[15] These bromination reactions occurred more rapidly than the analogous chlorination reactions, and high reaction temperatures were not required for nonactivated alcohols (Table 1, entries 20, 21). These preliminary results serve as the basis for the development of a new method to substitute the hydroxyl group of alcohols with *nucleophiles other than chloride or bromide*, which will be reported shortly.

The formation of 1,1-dichlorocycloheptatriene (**1**) by treating tropone with oxalylchloride was confirmed by $^1H$ and $^{13}C$ NMR. 1,1-Dichlorocycloheptatriene was sufficiently stable, as a solution of **1** in dichloromethane can be evaporated to dryness at 25 °C under reduced pressure. The compound in its solid form is deliquescent, but it could be stored under nitrogen in a refrigerator for weeks or on the bench for days without significant decomposition. The compound is miscible with water but sparingly soluble in nonpolar organic solvents such as hexanes or carbon tetrachloride. The NMR spectra show that the carbon−chlorine bonds of 1,1-dichlorocycloheptatriene are partially covalent,[9,11] while mass spectrometry analysis (Figure 1) reveals the ionic nature of these bonds. The EI-




**Figure 1.** Pertinent mass range from the EI-HRMS of 1,1-dichlorocycloheptatriene **1**.

HRMS spectrum of 1,1-dichlorocycloheptatriene (**1**) shows only traces of $[M(Cl_2C_7H_6)]^+$, and the predominant signals are 125.0158 ($[(^{35}ClC_7H_6)]^+$) and 127.0128 ($[(^{37}ClC_7H_6)]^+$), which have a ratio of ~3:1, approximately the natural chlorine isotope ratio ($^{35}Cl/^{37}Cl$ = 75.77%:24.23%).[16]

1,1-Dichlorocycloheptatriene (**1**) was then employed to convert carboxylic acids to acid chlorides. The optimal reaction conditions were similar to those for the alcohol dehydrative chlorination, except that an organic base such as triethylamine was necessary to quench the resulting hydrogen chloride and increase the reaction rate.[5b,17] The conversions of carboxylic acids to acid chlorides using this method were mild, rapid, and clean and provided good to high yields (Table 2).[18] To demonstrate the synthetic value of this pathway, the acid


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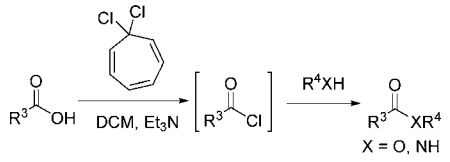
**Table 2. Acyl Substitution of Carboxylic Acids**



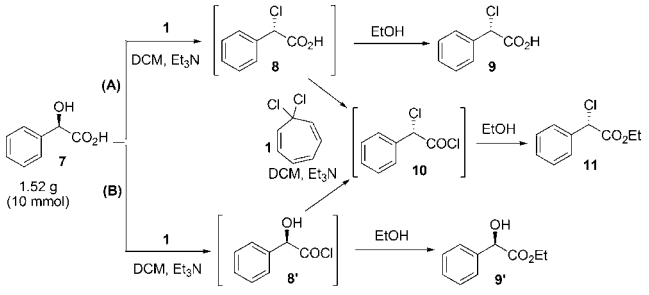

| entry[a] | substrate | product | time[e] | yield[f] |
|---|---|---|---|---|
| 1[b] | $PhCO_2H$ | $PhCO_2Et$ | 30 | 59 |
| 2[b] | $p$-$NO_2C_6H_4CO_2H$ | $p$-$NO_2C_6H_4CO_2Et$ | 45 | traces |
| 3[b] | $p$-$OMeC_6H_4CO_2H$ | $p$-$OMeC_6H_4CO_2Et$ | 25 | 65 |
| 4[c] | $PhCO_2H$ | PhCONHBn | 30 | 61 |
| 5[c] | $p$-$NO_2C_6H_4CO_2H$ | $p$-$NO_2C_6H_4CONHBn$ | 45 | traces |
| 6[c] | $p$-$OMeC_6H_4CO_2H$ | $p$-$OMeC_6H_4CONHBn$ | 25 | 62 |
| 7[d] | AcOH | AcOBn | 20 | 89 |
| 8[d] | $^nC_3H_7CO_2H$ | $^nC_3H_7CO_2Bn$ | 20 | 86 |
| 9[b] | $BnCO_2H$ | $BnCO_2Bn$ | 20 | 88 |
| 10[c] | AcOH | AcNHBn | 20 | 85 |
| 11[c] | $^nC_3H_7CO_2H$ | $^nC_3H_7COBn$ | 20 | 79 |
| 12[c] | $BnCO_2H$ | BnCONHBn | 20 | 84 |

[a]See the Supporting Information for experimental details. [b]$R^4XH$ = ethanol. [d]$R^4XH$ = benzyl alcohol. [c]$R^4XH$ = benzylamine. [e]Reaction time (minutes) after the addition of carboxylic acids and before the addition of $R^4XH$. [f]Yield of isolated product.

chlorides generated were allowed to react with alcohols or amines in the same pot to form the corresponding esters or amides, respectively.[18] Benzoic acids, especially those with electron withdrawing groups (Table 2, entries 2, 5), seemed to be less reactive than aliphatic carboxylic acids (Table 2, entries 7−12) under the investigated reaction conditions, presumably due to the decreased nucleophilicity of the carboxyl groups.[19]

An interesting study was carried out by treating (*R*)-(−)-mandelic acid with 1.0 or 3.0 mol equiv of 1,1-dichlorocycloheptatriene (**1**) followed by the addition of an excess amount of ethanol (Scheme 2). In principle, the

**Scheme 2. Reaction with (*R*)-(−)-Mandelic Acid**

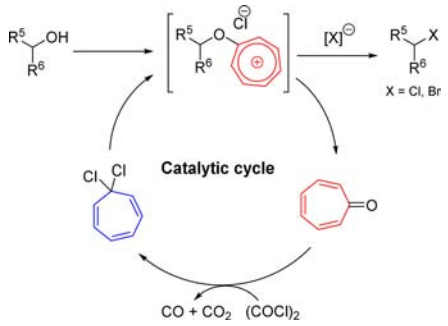



1.0 equiv **1**: **9** (not found), **9'** (66%), **11** (5%)
3.0 equiv **1**: **9** (not found), **9'** (trace), **11** (77%, 94% ee)

nucleophilic chlorination reaction could occur at both the alcohol and carboxylic acid moieties of mandelic acid. The reaction could occur via pathway A to form **8** and then **9** or via pathway B to form **8'** and then **9'**. In the presence of excess 1,1-dichlorocycloheptatriene, **10** and then **11** would be formed. In both cases of using with 1.0 or 3.0 mol equiv of **1**, α-chloro carboxylic acid **9** was not found in the reaction mixtures. With an excess of 1,1-dichlorocycloheptatriene (**1**), **11** was formed predominantly in good yield. The purpose of this study was threefold, as the outcomes of these reactions revealed the following: the reaction preferentially occurred at the carboxylic acid moiety when 1,1-dichlorocycloheptatriene (**1**) was the limiting reagent;[20] the nucleophilic substitution reaction of the hydroxyl group primarily occurred via an $S_N2$ mechanism, as the stereochemistry of the product **11** was inverted after the reaction;[11] and these nucleophilic substitution reactions could be performed on gram scale.

We noted that tropone can be isolated and recovered in 78−95% yield under the alkyl/acyl nucleophilic substitution reaction conditions. The recovery of tropone prompted our interest in its potential use as a catalyst for such transformations.[5f] To confirm this hypothesis, we carried out preliminary experiments using *catalytic amounts of tropone* with slow addition of oxalyl chloride to chlorinate several alcohol substrates (Table 3). Indeed, benzyl alcohol can be

**Table 3. Catalytic Nucleophilic Substitution Reactions**




| entry[a] | product | mol % tropone | $(COCl)_2$ addition time[b] | yield[c] |
|---|---|---|---|---|
| 1 | BnCl | 25 | 1 h | 81 |
| 2 | BnCl | 10 | 1 h | 68 |
| 3 | BnCl | 10 | 3 h | 80 |
| 4[d] | $PhCH_2CH_2Cl$ | 10 | 5 h | 72 |
| 5 | PhCH(Me)Cl | 10 | 3 h | 78 |
| **6**[e] | **BnBr** | **10** | **18 h** | **71** |
| **7**[e] | **$PhCH_2CH_2Br$** | **10** | **18 h** | **74** |

[a]See the Supporting Information for experimental details. [b]Oxalyl chloride was added via syringe pump over the indicated time. [c]Yield of isolated product. [d]75 °C in chloroform. [e]2.5 equiv of $[Br]^-$ were added before oxalyl chloride.

effectively converted to benzyl chloride with catalyst loading of 10 mol % (entries 1−3, Table 3). Other activated secondary alcohols and nonactivated primary alcohols also reacted to form chloride products in good yields (entries 4, 5, Table 3). Most notably, the dehydrative bromination reaction also worked smoothly with 10% tropone catalyst in the presence of an excess of bromide salt (entries 6, 7, Table 3).[11] Thus, tropone can be used as a catalyst for various nucleophilic substitution reactions of alcohol. Further development of this tropone-based catalytic system for alkyl/acyl nucleophilic substitution reactions is currently underway and will be reported in due course.

In conclusion, this work has demonstrated for the first time that the tropylium ion can be effectively used to promote nucleophilic alkyl/acyl substitution reactions via aromatic cation activation. The reagent can be generated *in situ* or premade from readily available starting materials and stored for a long period of time under inert conditions. This new method of activation is generally practical at room temperature, requires short reaction times, and could be utilized on a catalytic scale, thus enriching and diversifying the chemistry associated with aromatic carbocations in particular and stable carbocations in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general. The different stabilization effect of the tropylium ion used in this work compared to that of the reported cyclopropenium ion[5] opens new avenues for the investigation of different chemistry and new reactions. We envisage that structural modification of the seven-membered ring of the tropylium ion could allow optimization of activation for specific reactions and substrates. Work on tuning this tropylium system to activate substitution reactions with other types of nucleophiles other than chloride as well as to activate other types of chemical transformations is currently ongoing and will be reported in due course.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental procedures and product characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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## ■ DEDICATION

This work is dedicated to Professor Dieter Enders on the occasion of his retirement.

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(11) See the Supporting Information for more details.

(12) That the reaction occurred between 1,1-dichloroheptatriene **1** and the alcohol was confirmed by the treatment of alcohols in entries 1−3, Table 1 with oxalyl chloride or HCl. Oxalyl chloride gave predominantly a mixture of oxalate esters whereas reactions with HCl were very slow and low-yielding. See the Supporting Information for more details.

(13) The tendency for an elimination reaction of tertiary alcohol to occur was also reported by Parnes et al.; see ref 6b.

(14) Similar to the control experiment designed by Lambert et al. (ref 5a), the reaction in entry 11, Table 1 was also carried out in $CDCl_3$ and followed by $^1H$ NMR to confirm the presence of the proposed alkoxytropylium intermediate. See the Supporting Information for more details.

(15) The color of the reaction mixture changed from yellow to dark-brown upon addition of the bromide source to the solution of **1** in dichloromethane. We suspected that ion exchange occurred to form tropylium bromide/bromocycloheptatriene species; see ref 2. In these reactions, chloro derivatives were also formed in negligible ratio to bromo derivatives. See the Supporting Information for more details.

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(17) We thank one of the referees for pointing out that it is possible that the more nucleophilic carboxylate group, generated from an acid−base reaction with $Et_3N$, would react faster with the tropylium ion, hence increasing the reaction rate.

(18) Complete conversion of the acid to the acid chloride was confirmed by $^{13}C$ NMR before the addition of amine or alcohol, except for entries 2, 5 (Table 2) where the reaction mixtures were messy.

(19) A conjugated electron withdrawing group will render the carboxylic acid or carboxylate group less nucleophilic or less likely to participate in the formation of the tropylium carboxylate intermediate **5′**; see ref 5b.

(20) The carboxylate $-COO^-$ group is more nucleophilic than the alcohol hydroxyl $-OH$ group. Thus, it is possible that it is easier to form the tropylium carboxylate intermediate **5′** than the tropylium alkoxide intermediate **5**.