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Nucleophilic Substitutions of Alcohols in High Levels of Catalytic Efficiency

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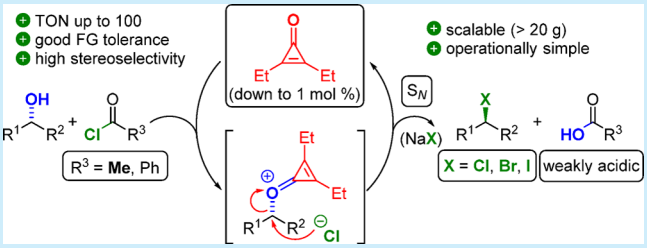
Supporting Information

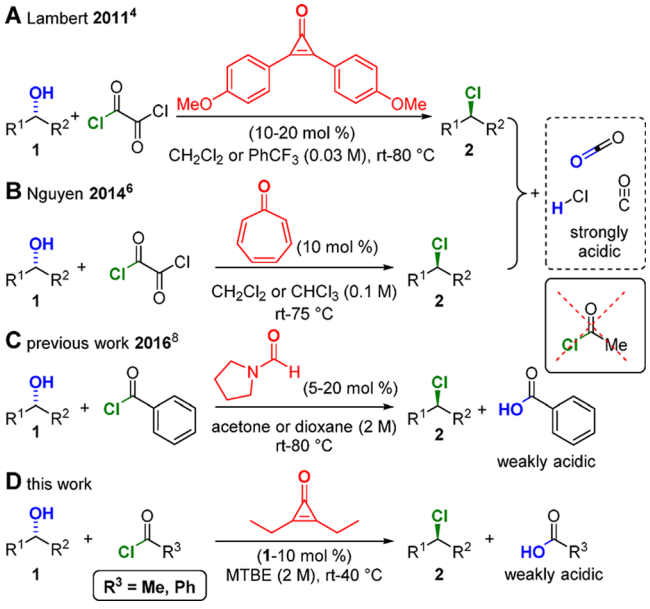
ABSTRACT: A practical method for the nucleophilic substitution (S_N) of alcohols furnishing alkyl chlorides, bromides, and iodides under stereochemical inversion in high catalytic efficacy is introduced. The fusion of diethylcyclopropenone as a simple Lewis base organocatalyst and benzoyl chloride as a reagent allows notable turnover numbers up to 100. Moreover, the use of plain acetyl chloride as a stoichiometric promotor in an invertive S_N-type transformation is demonstrated for the first time. The operationally straightforward protocol exhibits high levels of stereoselectivity and scalability and tolerates a variety of functional groups.



Nucleophilic substitutions (S_N) at sp^3-hybridized carbon centers, in particular those employed on alcohol starting materials, are some of the most fundamental and widely used chemical transformations.[1] Especially, bimolecular nucleophilic substitutions (S_N2), which proceed under stereochemical Walden inversion, provide a straightforward access to a variety of important functional groups, such as alkyl halides, amines, and ethers. To address drawbacks such as (1) low levels of functional group compatibility and (2) stereoselectivity, (3) poor sustainability[2] and (4) low cost-efficiency, there is a high demand for the development of more effective protocols for S_N-type conversions that proceed under chemical inversion.[3]

Despite the significance of invertive S_N-reactions in general, catalytic procedures have only been introduced very recently.[4−11] The first example of a catalytic approach, which engages a Lewis base catalyst with a carbonyl group as the key structural motif, has been reported by Lambert and co-workers (Scheme 1A).[4a] Therein, a cyclopropenone derivative promoted the transformation of alcohols **1** into alkyl chlorides **2**. Subsequently, Nguyen's group introduced tropone as a potent catalyst (Scheme 1B).[6a] Afterward, our group established an efficient catalytic method for conversions of type **1** → **2**, which is based on formamide catalysts like *N*-formylpyrrolidine (FPyr) and utilizes benzoyl chloride (BzCl) as reagent (Scheme 1C).[8] The application of weakly electrophilic BzCl allowed for a significant improvement of the functional group tolerance, cost efficiency, and sustainability because weakly acidic benzoic acid is formed as byproduct instead of strongly acidic HCl. However, a drawback of all approaches so far is a relatively low catalytic efficiency. This is evidenced by (1) high catalyst loadings (typically 10−20 mol %) and hence low turnover numbers (TON ≤ 10),[12] (2) high reaction temperatures of up to 80 °C, and (3) the fact that acetyl chloride (AcCl) could not be employed as a reagent so far.[8,13] Indeed, the low molecular weight of AcCl would facilitate a significant enhancement of the atom efficiency in comparison to conventional reagents such as BzCl, oxalyl and thionyl chloride ($SOCl_2$), and phosgene ($COCl_2$). Against this background, we envisioned that these severe disadvantages could be overcome when carboxylic acid chloride reagents like BzCl and AcCl are merged with cyclopropenones as strong Lewis base catalysts.[14,15]

Scheme 1. Comparison of This Work with Previous Protocols



Herein, we present a diethylcyclopropenone catalyzed protocol for the conversion of alcohols **1** into chloro, bromo

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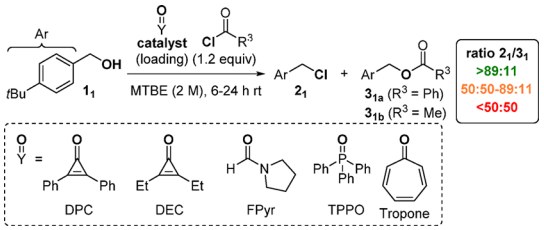
Table 1. Method Development Benzylic Substrates



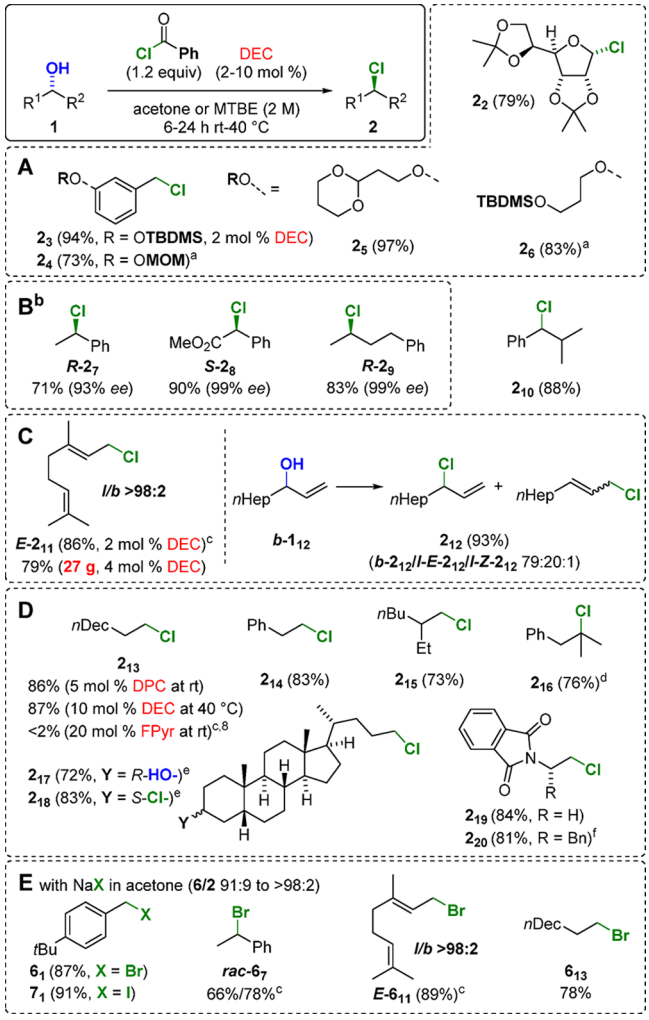
entry	cat. (mol %)	R^3	ratio $2_1/3_1$[a]	yield 2_1 (%)
1	DPC (**2.5**)	Ph	**95:5**	88[c]
2	**DEC** (2.5)	"	**≥98:2**	94[b]
3	DEC (**1**)	"	**≥98:2**	90[b]
4	FPyr (**1**)	"	**21:79**	7[c]
5[d]	DEC (**0.5**)	"	**97:3**	87[c]
6[e]	/	"	**≤2:98**	≤2[c]
7	DEC (10)	Me	**90:10**	86[b]
8[e]	FPyr (10)	"	**7:93**	7[c]
9[e]	TPPO (10)	"	**≤2:98**	≤2[c]
10[e]	Tropone (10)	"	**≤2:98**	≤2[c]
11	/	"	**≤2:98**	≤2[c]

[a]Ratio $2_1/3_1$ determined from the ^{1}H NMR of the crude material. [b]Yields refer to isolated material. [c]Yields were determined by internal NMR standard. [d]Reaction performed at 40 °C. [e]Reaction conducted in dioxane.

and iodo alkanes of type **2**, **6** and **7**, respectively, with BzCl and AcCl, respectively (Scheme 1D). The method development was commenced with the simple model substrate $\mathbf{1}_1$, BzCl, and commercially available diphenylcyclopropenone as catalyst (DPC, Table 1). A primary solvent screen revealed environmentally friendly MTBE[2c,d] as optimal (see Table S1 in the Supporting Information, (SI)), and only 2.5 mol % of DPC were necessary for the formation of benzylic chloride $\mathbf{2}_1$ in 88% yield (entry 1). In addition, an excellent level of chemoselectivity was attained, which is reflected in the ratio of the chloro alkane $\mathbf{2}_1$ to the undesired ester $\mathbf{3}_{1a}$ of 95:5. In fact, reaction of alcohol $\mathbf{1}_1$ with BzCl and AcCl, respectively, without an appropriate catalyst, exclusively provides esters of type $\mathbf{3}_{1a}$ and $\mathbf{3}_{1b}$, ($\mathbf{2}_1/\mathbf{3}_1 \leq 2{:}98$, entries 6 and 11).

Next, we discovered that DPC could be replaced by simplified diethylcyclopropenone (DEC), which resulted in an enhancement of the chemoselectivity under otherwise identical conditions ($\mathbf{2}_1/\mathbf{3}_{1a}$ 95:5 → ≥98:2, entry 2). Fortunately, the synthesis of DEC according to Gundersen's group,[16a] which furnished this catalyst reproducibly in multigram quantities and yields >80% (see SI, section 4.3.1), is significantly higher yielding than that of DPC (44%).[16b] Remarkably, the catalyst loading could be minimized to 1 mol %, still affording benzylic chloride $\mathbf{2}_1$ in 90% isolated yield (entry 3).[16c] A comparison reaction with 1 mol % FPyr,[8] which gave $\mathbf{2}_1$ as minor side product in 7% yield, revealed the strongly improved catalytic efficiency (entry 4). Even at levels as low as 0.5 mol % DEC, an excellent selectivity $\mathbf{2}_1/\mathbf{3}_{1a}$ of 97:3 was preserved, although full conversion of $\mathbf{1}_1$ was not achieved within 24 h of reaction time (entry 5). Remarkably, with a yield of 87%, this results in a TON of 174.[13] To our delight, DEC was also able to shift chemoselectivity in favor of substitution product $\mathbf{2}_1$ when AcCl was utilized as reactant (entry 7). The higher electrophilicity of AcCl in comparison to BzCl could explain why less active formamide catalysts like FPyr are unable to promote dehydroxychlorination with AcCl (7% yield for $\mathbf{2}_1$, entry 8). The increased reactivity also called for higher catalyst loadings (10 mol %) to minimize formation of acetate $\mathbf{3}_{1b}$. Interestingly, triphenylphosphine oxide (TPPO) and tropone, which have been reported as potent catalysts for the conversion **1** → **2** mediated by oxalyl chloride,[6,7] failed to deliver $\mathbf{2}_1$ when either AcCl or BzCl were applied as reagents (entries 9 and 10 and ref 8). As illustrated in Scheme 2, the combination of

Scheme 2. Substrate Scope Utilizing Benzoyl Chloride[a]



[a]All yields refer to isolated material if not otherwise specified. (a) With 30 mol % DEC and 1.3 equiv $NiBu_3$. (b) Prepared from the enantiomeric alcohols (99% *ee*). *ee* determined by chiral GC. (c) Yield determined with internal NMR standard. (d) Reaction conducted in MeCN. (e) With 20 mol % DPC in dioxane and 2.3 equiv BzCl for $\mathbf{2}_{18}$. (f) Reaction conducted at 80 °C with 20 mol % DEC in dioxane.

DEC and BzCl allowed the effective transformation of a broad range of primary, secondary, and tertiary alcohols **1** into alkyl chlorides of type **2**. A variety of functional groups was tolerated under the optimized conditions, which includes acid sensitive silyl ethers, a *tert*-butyl ester, and acetals (Scheme 2A). Only in the case of MOM- and aliphatic TBDMS-ether $\mathbf{2}_4$ and $\mathbf{2}_6$, which are highly susceptible toward cleavage through HCl, the reaction had to be conducted in the presence of a base (N-iBu$_3$).

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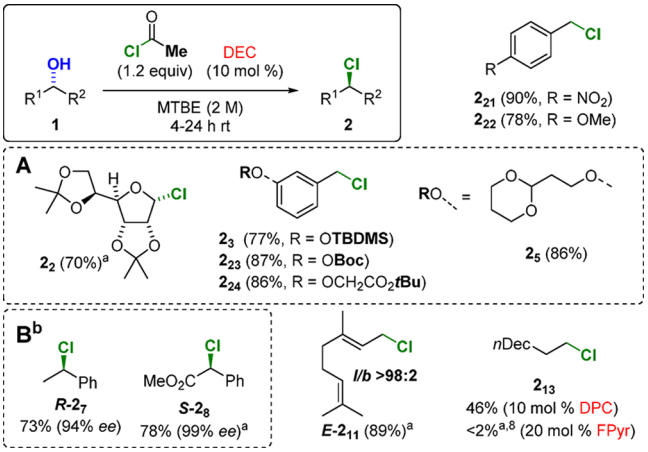
In these cases, to outcompete the condensation of **1** with BzCl (furnishing benzoates of type $\mathbf{3}_a$), which is accelerated by bases, higher catalyst loadings of 30 mol % had to be applied. Notably, our previous formamide catalyzed protocol[8] did not allow access to these products in an efficient manner. In the case of the enantioenriched alcohols $\mathbf{1}_7$−$\mathbf{1}_9$ (99% *ee*), dehydroxychlorination furnished the alkyl halides $\mathbf{2}_7$−$\mathbf{2}_9$ in 93−99% *ee* under stereochemical inversion (Scheme 2B), which strongly suggests that these reactions proceeded via a S_N2 mechanism.[17] Although a small decrease in enantiopurity was observed in the transformation of benzylic alcohol ***S*-1**$_7$, the *ee* of 93% for the product ***R*-2**$_7$ accounts for the highest reported values to date.[4a,8] As an important feature, linear allylic alcohols like geraniol ***E*-1**$_{11}$ could be converted to the corresponding linear chlorides with minimal formation of the undesired branched regioisomer (Scheme 1C). Because chlorinations of ***E*-1**$_{11}$ with simple reagents such as thionyl chloride or phosgene proceed in poor regioselectivities,[8] isomerization sensitive allylic alcohols have not been included in the substrate scopes of previous catalytic protocols.[4,6,7] Additionally, the production of ***E*-2**$_{11}$ on a 27 g scale with just 4 mol % of DEC highlights the excellent scalability and operational simplicity of our method, which uses standard laboratory equipment (volume ≤0.5 L) and does not require rigorous exclusion of water. Furthermore, BzCl can be conveniently added via dropping funnel, whereas literature protocols accomplish addition of the reagent as solution via syringe pump.[4−7] Chlorination of the secondary allylic alcohol ***b*-1**$_{12}$ furnished the branched allylic chloride ***b*-2**$_{12}$ predominantly. Thus S_N2-type attack of chloride is favored over S_N2' in moderate regioselectivities.

While literature protocols demand high reaction temperatures of up to 80 °C for the transformation of aliphatic alcohols **1**,[4−6,8] cyclopropenone catalysis enables milder conditions ≤40 °C (Scheme 1D). For example, dodecyl chloride $\mathbf{2}_{13}$ was prepared at room temperature using just 5 mol % of DPC in good yield, whereas the same reaction with 20 mol % FPyr did not deliver the desired substitution product. In the instance of aliphatic substrates of type **1**, DPC emerged to be more efficient than DEC. This is likely the result of faster decomposition of DEC compared to DPC under the applied reaction conditions. In the case of steroid derived diol $\mathbf{1}_{17}$, the sterically less encumbered primary hydroxyl group could be selectively addressed to furnish product $\mathbf{2}_{17}$, while an excess of BzCl gave rise to the dichloride $\mathbf{2}_{18}$. Moreover, the challenging phthaloyl protected *β*-amino chlorides $\mathbf{2}_{19}$ and $\mathbf{2}_{20}$ could be produced in good yields. In contrast, amino alcohols carrying other protecting groups and an indole moiety bearing substrate, which could be converted to the corresponding chloro alkanes with our previous method,[8] were not feasible (see SI, section 3).[18] Both substrate types have not been included in previous catalytic approaches.[4−7] It is noteworthy that alkyl bromides and iodides **6** and **7**, respectively, are also accessible under Finkelstein-type reaction conditions using sodium halides in acetone (Scheme 1E).

To our delight, DEC (10 mol %) also enabled the utilization of AcCl as reagent for the synthesis of a range of benzylic and allylic chlorides, some of which contain acid-labile groups (Scheme 3A). The preparation of the chiral chlorides ***R*-2**$_7$ and ***S*-2**$_8$ in 94−99% *ee* was accomplished under inversion of the stereochemistry from the respective alcohols ***S*-1**$_7$ and ***R*-1**$_8$ (99% *ee*), which implies a S_N2 mechanism again (Scheme 3B). Aliphatic alcohols, on the other hand, could not be accessed in synthetically useful yields. For instance, dodecyl chloride $\mathbf{2}_{13}$ was obtained in a moderate yield of 46% alongside with dodecyl acetate in similar

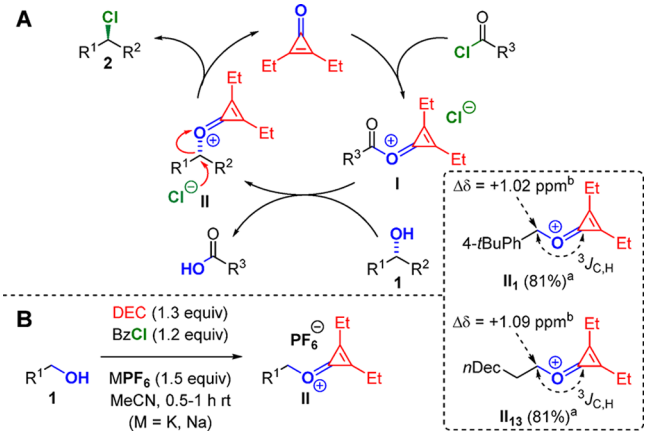
Scheme 3. Substrate Scope Using Acetyl Chloride[a]



[a]All yields refer to isolated material if not otherwise specified. (a) Yield determined with internal NMR-standard. (b) Prepared from the enantiomeric alcohols in (99% *ee*). *ee* determined by chiral GC.

amounts. Nevertheless, the superior catalytic efficiency of cyclopropenones was demonstrated by a comparison reaction with FPyr,[8] which did not furnish the product $\mathbf{2}_{13}$ at all. In alignment to Lambert's[4] and our previous work,[8] a mechanism is proposed in Scheme 4A.[19] Initially, cyclopropenone DEC is

Scheme 4. (A) Tentative Mechanism and (B) Proof of Intermediates II[a]



[a](a) Corresponds to the ratio of **II**, starting material **1** and benzoate $\mathbf{3}_a$ according to ^{1}H NMR. (b) Chemical shift difference in relation to **1**.

expected to be acylated with either BzCl or AcCl to furnish the charged intermediate **I**. Subsequently, the hydroxyl group of alcohol **1** would be activated to an enhanced leaving group by means of intermediate **I**, which delivers cyclopropenium ion **II**. Finally, S_N displacement of the catalyst moiety through the chloride counterion allows for the formation of product **2** and the catalyst. While Lambert already proved intermediate **II** by ^{1}H NMR, we were able to stabilize and fully characterize this transient species by means of NMR spectroscopy after anion exchange with non-nucleophilic hexafluorophosphate (Scheme 4B). Apparent from the ^{1}H NMR spectrum of **II** is the large difference of the chemical shift of the multiplets of the CH_2 group bound to oxygen $\Delta\delta$ of approximately 1 ppm relative to the starting material **1**. The conjunction of the cyclopropenylium fragment and the alkyl group of the starting material could be

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unambiguously proven by $^3J_{C,H}$ couplings in the 2D-NMR. The suggested intermediate **I** could not be verified by this approach.

In summary, the amalgamation of cyclopropenone type catalysts and carboxylic acid chloride reagents facilitated the straightforward transformation of alcohols **1** into chloro, bromo, and iodo alkanes of type **2**, **6**, and **7** in high catalytic efficacy. Remarkably, the present protocol allows (1) catalyst loadings as low as 1 mol % and (2) application of AcCl as reagent for the first time in an S_N process under inversion of the stereochemistry. Additionally, the novel procedure is distinguished by several other important advantages such as high levels of (3) compatibility with acid sensitive functional groups, (4) stereo- and regioselectivity, and (5) scalability. In view of these significant enhancements and the operational simplicity, our novel protocol is expected to have a significant impact on synthetic chemistry laboratories in academia and industry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01023.

Optimization data, experimental procedures, characterization of new compounds, and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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