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Formamides as Lewis Base Catalysts in S_N Reactions—Efficient Transformation of Alcohols into Chlorides, Amines, and Ethers

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Abstract: *A simple formamide catalyst facilitates the efficient transformation of alcohols into alkyl chlorides with benzoyl chloride as the sole reagent. These nucleophilic substitutions proceed through iminium-activated alcohols as intermediates. The novel method, which can be even performed under solvent-free conditions, is distinguished by an excellent functional group tolerance, scalability (>100 g) and waste-balance (E-factor down to 2). Chiral substrates are converted with excellent levels of stereochemical inversion (99 %→≥95 % ee). In a practical one-pot procedure, the primary formed chlorides can be further transformed into amines, azides, ethers, sulfides, and nitriles. The value of the method was demonstrated in straightforward syntheses of the drugs rac-Clopidogrel and S-Fendiline.*

Nucleophilic substitutions at sp^3-hybridized carbon centers belong to the most fundamental transformations in organic chemistry.[1] Especially, the conversion of alcohols into other important functional groups, such as chlorides, amines, and ethers is an indispensable task in chemical synthesis. Examples of chlorinated natural products[2] and blockbuster pharmaceuticals potentially accessible through S_N2 bond formation are shown in Figure 1 A (see also Scheme 2). However, conventional methods for S_N reactions give rise of vast amounts of waste (e.g. the Appel[3] and Mitsunobu[4] reaction), which hamper their sustainability significantly.[5,6] Some substitution procedures employing simple acid chlorides, such as thionyl chloride ($SOCl_2$) and phosgene ($COCl_2$), as reagents formally exhibit a better atom economy. Nevertheless, functional group tolerance, as well as regio- and stereoselectivity in the case of allylic and/or non-racemic substrates are poor,[1c–e] due to the formation of hydrochloric acid as a strongly acidic by-product.

To improve the original methods, Lewis base-catalyzed nucleophilic substitutions have been developed.[1a,7–9] However, in these catalytic approaches HCl is still liberated as a by-product and the compatibility with acid-sensitive functional groups remains limited.[7,8] Therefore, the development

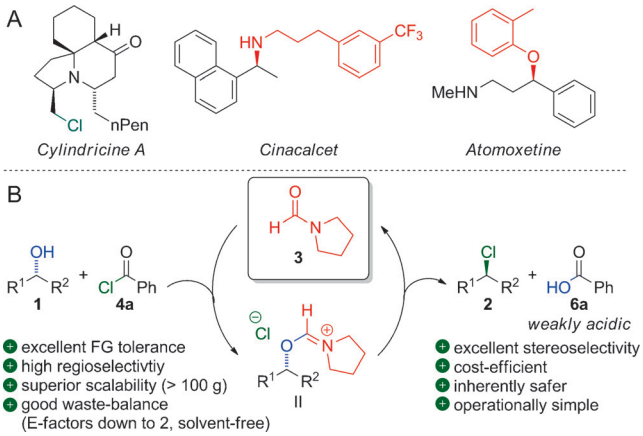

Figure 1. Selected chloride-containing natural products and pharmaceuticals containing amino and ether functionalities (A); presented method (B).

of efficient methods for the nucleophilic substitution of OH groups, which combine a good waste balance with high levels of regio- and stereoselectivity and functional group tolerance, are highly desirable and would meet one of the major demands of the chemical industry.[10]

In this context, we realized that the formation of stoichiometric amounts of HCl could be avoided, if a carboxylic acid chloride **4** is applied as a reagent (Figure 1 B). In this case a carboxylic acid **6** (e.g. benzoic acid **6a**) would be formed as the sole and only weakly acidic by-product. We envisioned that the less-acidic conditions could result in improved functional group compatibility and selectivity. While the reaction of alcohols with carboxylic acid chlorides usually provides the corresponding esters,[11] we herein present a first and highly efficient method for the chlorination of alcohols employing inexpensive benzoyl chloride (BzCl, **4a**) as the exclusive reagent in the presence of a simple formamide as catalyst.[12,13]

In an initial screening utilizing benzylic alcohol $\mathbf{1_1}$ and various carboxylic acid chlorides in the presence of 10 mol % of DMF, BzCl was identified as the optimum reagent (Table 1, entry 1; see also Schemes S5,S6, in the Supporting Information). Importantly, BzCl is an inexpensive commodity chemical, which is even cheaper than most conventional chlorination agents (see Table S1). In contrast, aliphatic acid chlorides, such as acetyl and pivaloyl chloride, delivered only trace amounts of the desired benzylic chloride $\mathbf{2_1}$ (entries 2 and 3). In the absence of a catalyst no chloride $\mathbf{2_1}$ formed at all, which confirms the crucial catalytic effect of the formamide (entry 5). In contrast, just 1 mol % of DMF was sufficient to switch the chemoselectivity (ratio **2**/**7**) in favor of chloride $\mathbf{2_1}$

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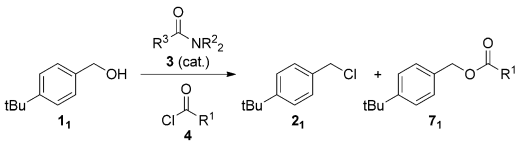
Table 1: Method development.[a]



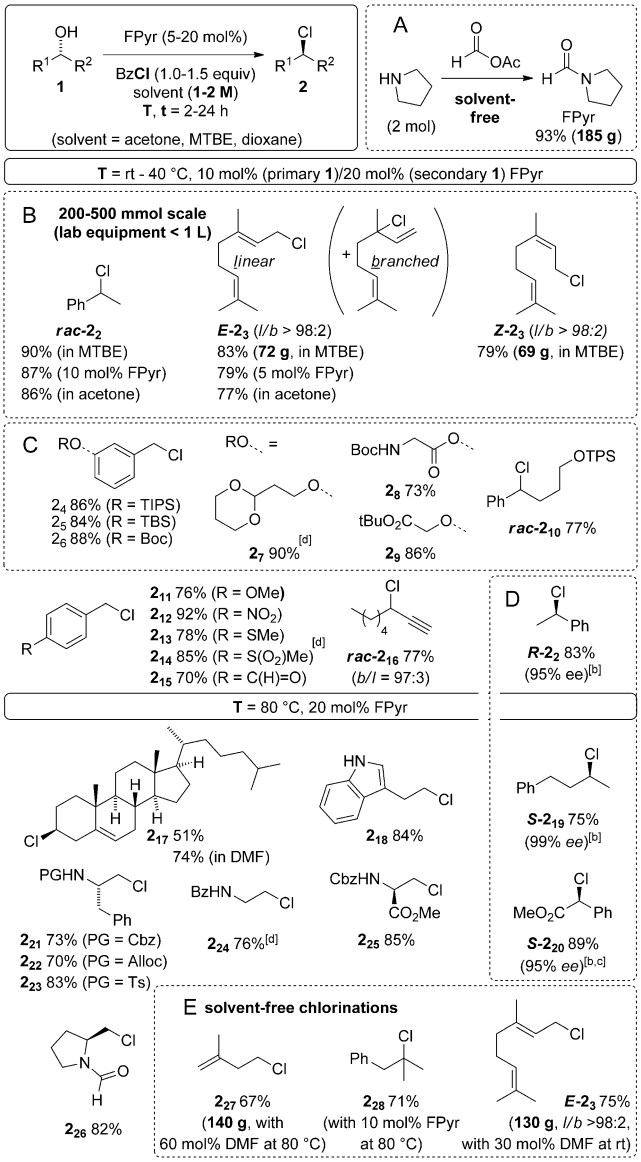
entry	R^1	**3** [mol%]	ratio $\mathbf{2_1}/\mathbf{7_1}$[b]	Yield $\mathbf{2_1}$
1	Ph	DMF (10)	96:4	90%[c]
2	Me	DMF (10)	6:94	6%[d]
3	*t*Bu	DMF (10)	24:76	23%[d]
4	Ph	DMF (1)	69:31	61%[c,e]
5	Ph	/	≤2:98	≤2%
6	Ph	MF (10)	95:5	86%[d]
7	Ph	F (10)	≤2:98	≤2%[d]
8	Ph	DMA (10)	≤2:98	≤2%[d]
9	Ph	FPyr (10)	96:4	96%[d]

[a] Reaction conditions: BzCl (1.2 equiv), dioxane (2 M), 24 h room temperature. MF = methylformamide, F = formamide, DMA = dimethylacetamide. [b] Ratio $\mathbf{2_1}/\mathbf{7_1}$ as determined by ^{1}H NMR spectroscopy of the crude product mixture. [c] Isolated yield after chromatography. [d] Yield determined by NMR spectroscopy with internal standard. [e] 1.5 equiv BzCl were used and the reaction was stirred for additional 2 days at 40 °C.

(entry 4). An investigation in the structure–activity relationship of the catalyst revealed, that at least one N-alkyl substituent is mandatory and that the formyl H atom cannot be replaced by an alkyl group (entries 6–8). A broader screening of various small molecules bearing a Lewis basic oxygen atom (including ureas and triphenylphosphine oxide) uncovered the unique catalytic activity of certain formamides (see Scheme S7,S8). During evaluation of the substrate scope we realized, that formyl pyrrolidine (FPyr) is an even more efficient catalyst than DMF (entry 9) as it improved both reaction time and yield. Furthermore, the catalyst loading could be decreased from 40 mol% (DMF) to 20 mol% (FPyr) with aliphatic substrates and higher stereoselectivities were obtained in the case of non-racemic alcohols. Noteworthy, the three best formamide catalysts (DMF, MF, and FPyr) are all commercially available at low costs and, in contrast to the majority of established nucleophilic catalysts,[7,8] have exceptionally low molecular weights (59–99 g mol^{-1}). Additionally, FPyr is also easily accessible on a mol scale (Scheme 1 A, see chap. 2.5 of the Supporting Information). With the optimized conditions in our hands we set out to explore the substrate scope. As shown in Scheme 1 structurally diverse primary, secondary, tertiary(!), allylic, benzylic, propargylic, and aliphatic alcohols **1** were efficiently converted into the corresponding chlorides **2**.

In general, aliphatic alcohols require higher temperatures to ensure catalyst turn over. Depending on the nucleophilicity of the starting alcohols either 10 or 20 mol% of the catalyst (FPyr) was used. However, it was possible to halve the catalyst loading (5–10 mol%), if the reaction time or the temperature was increased, as illustrated by examples ***rac*-2$_2$** and ***E*-2$_3$** (Scheme 1 B).

As an important aspect we found, that our chlorinations even proceed efficiently in the absence of any solvent (Scheme 1 E).[14] Nevertheless, utilization of a solvent, such as MTBE (methyl-*tert*-butylether) or acetone improved the



Scheme 1. Chlorination of various alcohols (for detailed reaction conditions see Supporting Information). Yields refer to isolated material. Deviation from standard reaction conditions are given in parentheses. [a] *ee* of starting materials ***S*-1$_2$**, ***R*-1$_{19}$**, and ***R*-1$_{20}$** ≥ 99%. [b] *ee* determined by chiral GC. [c] With 2-FBzCl. [d] With 4-MeOBzCl.

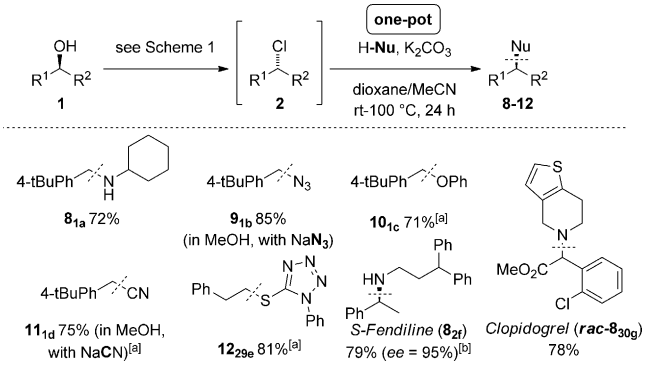
chemoselectivity (ratio **2**/**7**) and allowed the catalyst loading to be reduced. Notably, acetone is the most desired solvent (after water) in industrial processes[5c,d] and cannot be used in conventional substitution methods, which require highly reactive chlorination agents.[1d,e] In accordance to our initial reaction design, BzCl also represents an inherently safer (less toxic and hazardous) reagent than classical chlorination agents, such as $SOCl_2$, $COCl_2$, and oxalyl chloride. This can be mainly attributed to the lower volatility and reactivity of BzCl for instance towards water (producing HCl). A broad range of functional groups was found to be tolerated under the optimized reaction conditions: Among them are various esters, amides, carbamates, aldehydes, ethers, sulfides, sulfones, heterocycles, and nitro groups. As a proof of concept

we were able to verify that acid-sensitive functionalities, such as Boc-carbamates, cyclic acetals, *tert*-butyl esters and silylethers, which would be rapidly cleaved by HCl, are compatible with the reaction conditions (Scheme 1 C).

Noteworthy, in these cases no additional base as in previous catalytic approaches[8] was required, which would result in a depleted atom economy and poorer waste balance. Moreover, a range of sterically hindered β-branched amino alcohol derivatives was efficiently converted into the corresponding chlorides (examples $\mathbf{2_{21}}$ to $\mathbf{2_{26}}$). As reported for chlorinations with Vilsmeier–Haack-type reagents,[13a] sterically encumbered cyclohexanol derivatives represent challenging substrates. Nevertheless, catalytic chlorination of cholesterol $\mathbf{1_{17}}$ afforded the steroid analogue $\mathbf{2_{17}}$ (in this case with retention of configuration)[8b] in 51 % yield, which could be improved to 74 % by switching to DMF as the solvent (and catalyst). Besides the excellent functional group compatibility our method is also distinguished by a superior scalability as demonstrated by the mol scale synthesis of geranyl chloride ($\boldsymbol{E}$-$\mathbf{2_3}$) and the non-commercial chlorides $\boldsymbol{Z}$-$\mathbf{2_3}$ and $\mathbf{2_{27}}$ (Scheme 1 B,E). Importantly, these experiments were conducted utilizing standard laboratory equipment (volume ≤ 1 L).

Actually, the synthesis of allylic chlorides such as $\boldsymbol{Z}$- and $\boldsymbol{E}$-$\mathbf{2_3}$, which are important building blocks for natural products, is not trivial at all:[15] In the past specialized and waste-intensive procedures had to be applied, as simple reagents, such as $SOCl_2$ or HCl, only afford complex mixtures of linear and branched regioisomers and *E*/*Z*-diastereomers (see chap. 2.1 and Table S4,S5).[1c–e] In contrast, our catalytic chlorination method not only provides $\boldsymbol{Z}$- and $\boldsymbol{E}$-$\mathbf{2_3}$ with excellent regioselectivity but also displays a superior waste-balance with economy factors (E-factors; that is the mass ratio of waste/isolated product) down to 2. This meets the typical range for industrial bulk chemical production on a multi-ton scale (E-factors of 1–5).[5] According to Metzger's environmental assessment tool for organic synthesis (EATOS)[6] our synthesis of $\boldsymbol{E}$-$\mathbf{2_3}$ generates 89–94 % less waste than the conventional methods (e.g. under Appel-conditions with CCl_4/PPh_3). And due to the low amounts of solvent (or its complete omission) and the non-hazardous nature of the reagents involved the overall environmental impact (which also considers potential human and ecotoxicological effects)[5,6] is minimized to ≤ 7 % (see Figures S1–S3). In contrast, the majority of the previous catalytic methods require rather large solvent amounts to suppress sideproduct formation (e.g. oxalate esters in the case of the reagent oxalyl chloride).[8] A comparative EATOS examination of our method with recent catalytic approaches for the chlorination of 1-phenylethanol ($\mathbf{1_2}$) revealed that the waste amount could actually be reduced to ≤ 4 % (Figure S4).

We could also show that enantioenriched alcohols (99 % *ee*) are converted under inversion into the corresponding chlorides with excellent levels of stereoselectivity (≥ 95 % *ee*, Scheme 1 D). Particularly remarkable is the chlorination of 1-phenylethanol ($\boldsymbol{S}$-$\mathbf{1_2}$) to benzylic chloride ($\boldsymbol{R}$-$\mathbf{2_2}$) with 95 % *ee*. In this representative example other methods such as the Appel-reaction, which is usually the first choice for stereospecific chlorinations,[1c–e] afforded $\boldsymbol{R}$-$\mathbf{2_2}$ with significantly lower *ee* (≤ 88 %, see chap. 2.3). Thus, the present method must be considered as the most efficient approach available today for the stereoselective chlorination of non-racemic alcohols, also with respect to operational simplicity and waste-balance. Furthermore, on dilution of the crude chlorination reaction mixtures with MeCN or MeOH followed by addition of K_2CO_3 as a base and a suitable N-, O-, S-, and C-nucleophile, we were able to obtain a range of amines, azides, ethers, sulfides, and nitriles of type **8**–**12** as shown in Scheme 2.

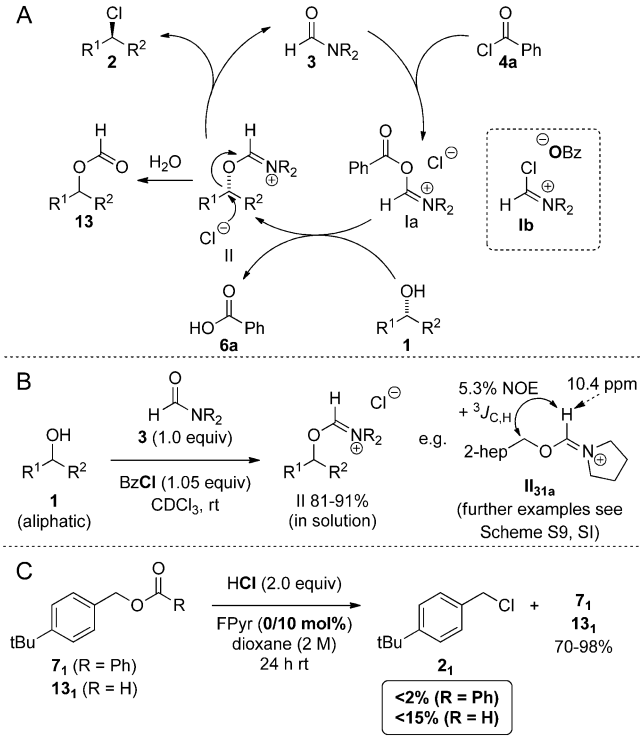


Scheme 2. One-pot chlorination and substitution (for detailed reaction conditions see Supporting Information). All yields refer to isolated products after chromatography. [a] Transformation **2**→**9**–**12** conducted in the presence of 10 mol % of TBAI. [b] *ee* determined by $[\alpha]_D^{25}$-value. As starting material phenylethanol $\boldsymbol{S}$-$\mathbf{1_2}$ in 99 % *ee* was utilized.

Advantageous, this practical one-pot route allows avoiding the isolation of alkyl chlorides **2**, which are prone to (thermal or SiO_2-induced) HCl elimination or hydrolysis in many cases. Again, an excellent stereoselectivity was observed (99 %→95 % *ee*), when the non-racemic alcohol $\boldsymbol{S}$-$\mathbf{1_2}$ was employed as starting material to furnish the drug *S*-Fendiline ($\boldsymbol{S}$-$\mathbf{8_{2f}}$) under overall retention (two-fold S_N2-inversion). To further demonstrate the applicability, racemic Clopidogrel was efficiently prepared (from the racemic precursor). The proposed mechanism for the chlorination **1**→**2** is shown in Scheme 3 A.

First evidence for type **II** intermediates was gained by the identification of formyl esters **13** as side products. On treating aliphatic alcohols **1** with equimolar amounts of a formamide **3** and BzCl at room temperature (in $CDCl_3$), iminium salts of type **II** could be detected by NMR spectroscopy (Scheme 3 B). While hydrolysis of iminium chlorides **II** provided formiates of type **13**, heating to 60 °C effected quantitative conversion into chlorides **2** (Scheme S10). Comparison experiments verified that esters of type **7** and **13** (side products formed in trace amounts) do not occur as productive intermediates in the catalytic chlorination cycle: Exposed to an excess of HCl under the standard reaction conditions, $\mathbf{7_1}$ and $\mathbf{13_1}$, respectively, afforded chloride $\mathbf{2_1}$ only in negligible quantities (Scheme 3 C).

In conclusion, a highly efficient method for the transformation of alcohols **1** into chlorides **2** utilizing BzCl as the sole reagent in the presence of a simple formamide catalyst



Scheme 3. A) Proposed mechanism, B) synthesis of iminium salts **II**, and C) comparison experiments.

was developed. Moreover, a one-pot method for chlorination and subsequent substitution allows the direct conversion of alcohols **1** into amines, azides, (thio)ethers, and cyanides of type **8**–**12**. As demonstrated through the synthesis of *S*-Fendiline, this procedure opens a straightforward access to enantioenriched bioactive compounds. The method provides several advantages (Figure 1 B) such as excellent functional group tolerance, high regio- and stereoselectivity and scalability. In comparison to earlier catalytic and non-catalytic methods waste-balance and environmental impact were significantly improved. Remarkably, these benefits were achieved by replacing the common strongly electrophilic chlorination agents by the weakly electrophilic agent BzCl. Therefore, the present method is of high synthetic utility and expected to find broad application in both academia and industry.

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Keywords: green chemistry · halogenation · homogenous catalysis · nucleophilic substitution · organocatalysis

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[15] Indeed, chlorination of allylic alcohols (other than simple cinnamyl alcohol) have been rarely described in previous catalytic approaches (Ref. [7,8]). In Ref. [8g] chlorination of geraniol ***E*-1$_3$** afforded a 1:1 mixture of regioisomers.

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