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Efficient formylation of alcohols and thiols by means of formamides and benzoyl chloride

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Dedicated to Professor Hans-Günther (Hagga) Schmalz, an outstanding teacher, mentor and role model

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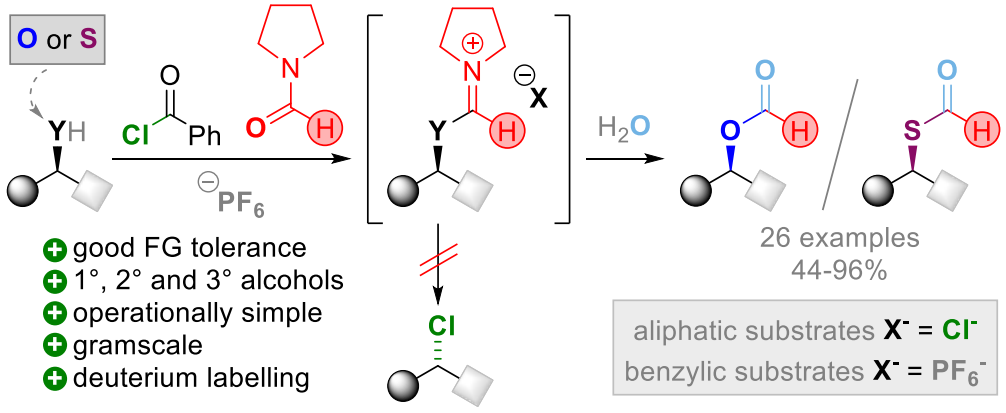
Abstract

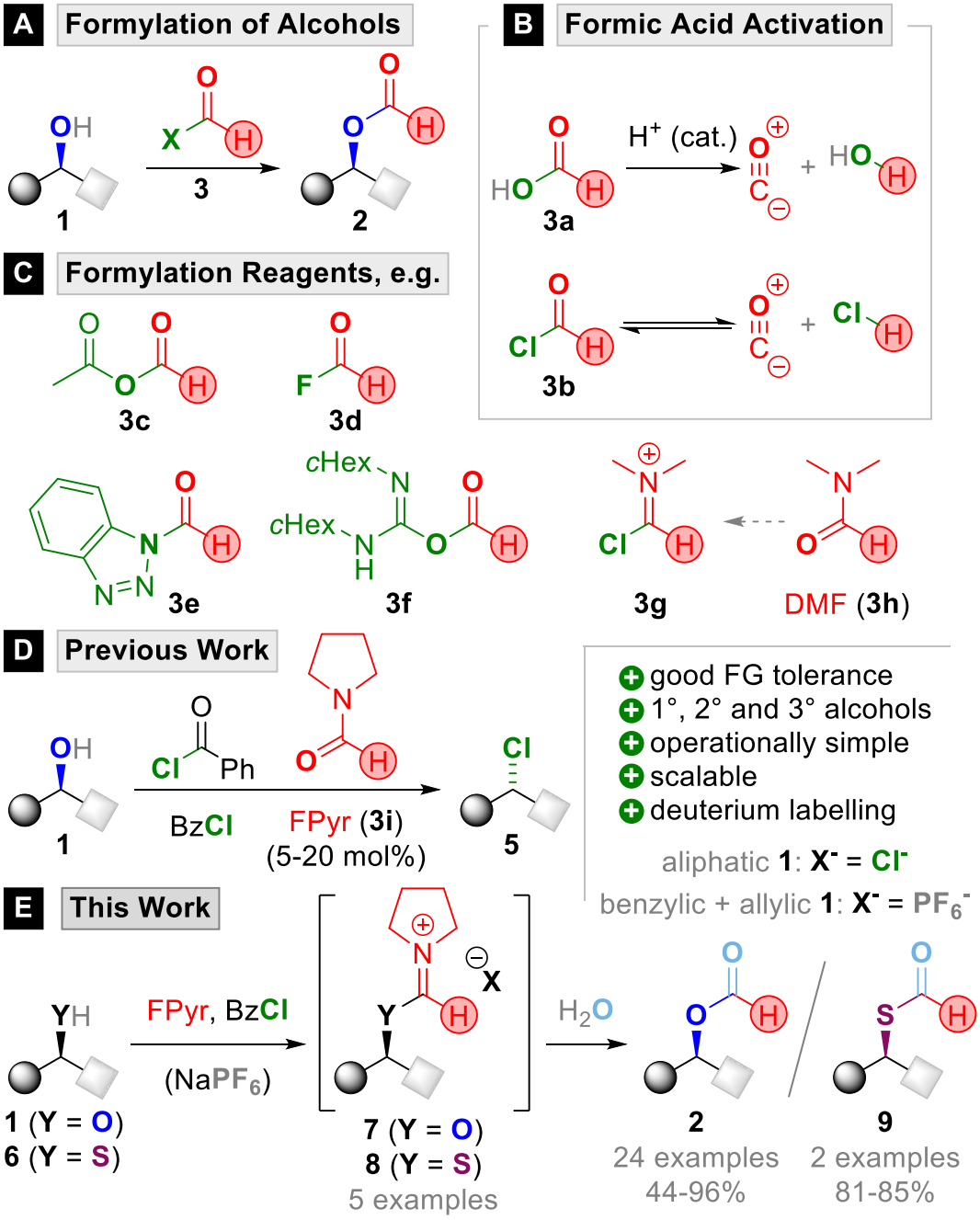
Esters derived from formic acid are frequently found in fragrances and perfumes and are popular as protective groups, for instance. Against this background, a novel method for the transformation of both, alcohols and thiols into the respective formates under mild conditions with formyl pyrrolidine and benzoyl chloride is introduced. These reagents enable the formation of (thio)amidate salts, which yield formate esters upon hydrolysis. Remarkably, the current approach also allows for the synthesis of benzylic and allylic formates with hexafluorophosphate, which constitute a limitation of preceding protocols based on formamides as agents. The value of the operationally simple and straightforward procedure is highlighted by application of terpenes, steroids and amino acid derivatives as substrates and the tolerance of substrates with both, acid- and base-sensitive functional groups. Finally, a simplified access towards thioamidate salts, which are of interest as ionic liquids, is disclosed.



Keywords: Formylation, formamides, formic acid, amidate salts

Introduction

Formate esters are valuable compounds for the flavour and fragrance industry[1,2] and are exploited as protective groups.[3] In addition, they are substrates for formate dehydrogenases, a class of enzyme that promotes the oxidation of formate (HCO_2^-) to CO_2 in nature.[4-6] These enzymes allow for the regeneration of the coenzyme NADH, which is mediated by formic acid esters,[7,8] the chemoselective cleavage of formates beside other ester protection groups,[9] and potentially also kinetic resolutions of chiral substrates. However, the synthesis of esters of formic acid (**3a**) can be more challenging than of other carboxylic acids, because activated derivatives of HCO_2H of type **3** are often labile and decompose to CO (Scheme 1 **A** and **B**).[10-12]



Scheme 1. Synthesis of formates: A Formylation of Alcohols, **B** activation of formic acid, **C** common reagents for formylation, **D** previous and **E** this work.

For example, solutions of formyl chloride (**3b**) are only stable for an hour at -60 °C.[13,14] The capability to form carbon monoxide upon activation has been harnessed also in carbonylative transformations by reaction formic acid with methanesulfonyl chloride,[15] sulfuric acid,[16-18] and cyanuric chloride,[19] for example. As highlighted in Scheme 1 **C**, several less labile derivatives of formic acid have been applied for the formylation of alcohols **1** (and thiols) including the mixed anhydride of formic and acetic acid **3c**,[20] formyl fluoride (**3d**),[21] formyl benzotriazol **3e**,[22,23] and non-symmetrical anhydrides derived from carbodiimides such as dicyclohexyl carbodiimide (see **3f**).[24,25] Moreover, also the Vilsmeier Haack reagent **3g** and related compounds have been engaged for the production for formate esters.[26,27] These electrophilic iminium salts are typically prepared *in situ* from dimethylformamide (DMF) and highly reactive acid halides like phosgene,[28] thionyl chloride,[29] phosphoryl chloride,[30] and sulfuryl fluoride,[31] and benzoyl chloride (BzCl), respectively.[32] As an alternative, activation of DMF is also possible by means of phosphines in combination with an oxidant.[33,34] Finally, alkylation of DMF with iodoalkanes also furnished formates.[35] Alongside, thioformates are accessible from thiols and the mixed anhydride of formic and acetic acid[36,37] and CO_2, for instance.[38,39]

Indeed, the generation of formates from Vilsmeier Haack reagents and alcohols has been explained by the hydrolysis of cationic esters of imidic acid such as **7**, which are obtained as intermediates (see Scheme 1 **E**).[40,41] Both, amidate and thioimidate salts like compound **8** have been prepared by alkylation of amides and thioamides, respectively, with Meerwein trialkyl onium salts and alkyl triflates and applied as ionic liquids.[42-55]

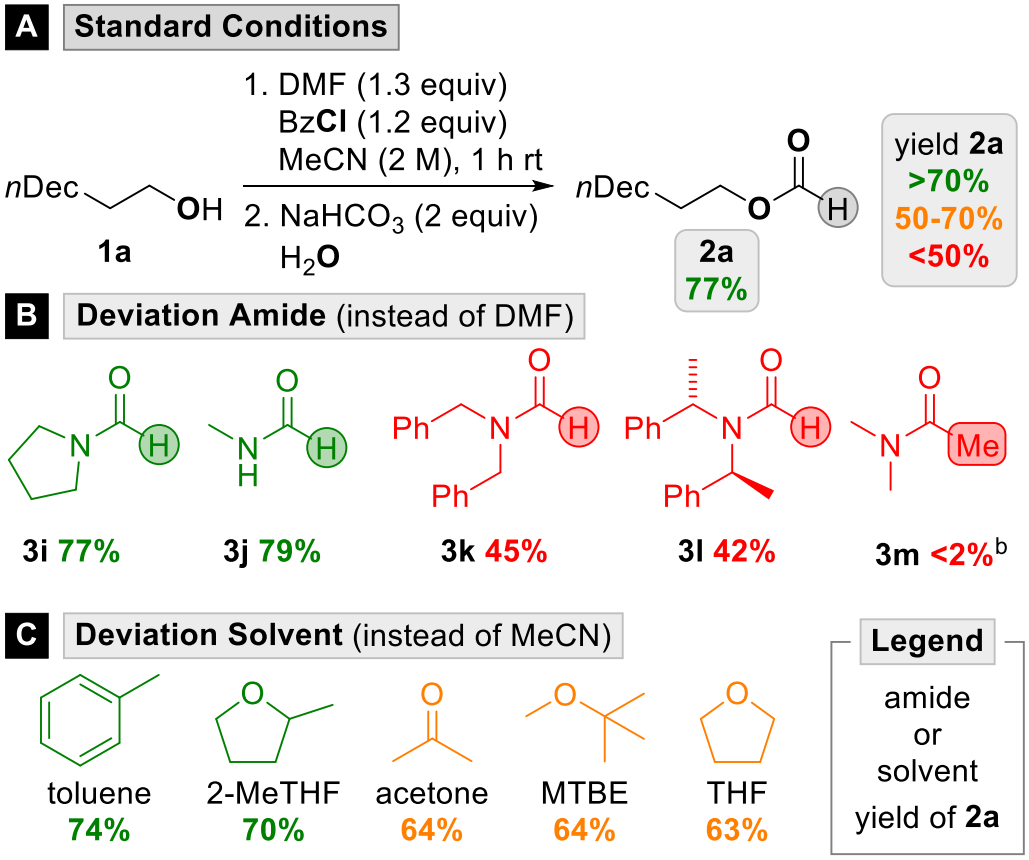
Recently, our group has disclosed several organocatalytic approaches for nucleophilic substitutions (S_N)[56]to transform alcohols into alkyl chlorides of type **5** (Scheme 1 **D**),[57,58,59] aldehydes into 1,1-dichlorides,[60] carboxylic acids into acid chlorides,[61] and formic acid into CO.[19] In these approaches, the C–Cl bond formation has been facilitated by the mild acid chlorides BzCl, cyanuric chloride and phenyl chloroformate in the presence of the catalysts DMF and formyl pyrrolidine **3i** (FPyr).[62,63] In fact, we have verified in mechanistic elucidations that these S_N-type conversions proceed via imidate salts of type **7**, in which the amide moiety is replaced by the counteranion (chloride).[57,64] During these investigations we observed formation of formates as side-products in small traces and wondered, if the chemoselectivity could be shifted in favour of formylation.

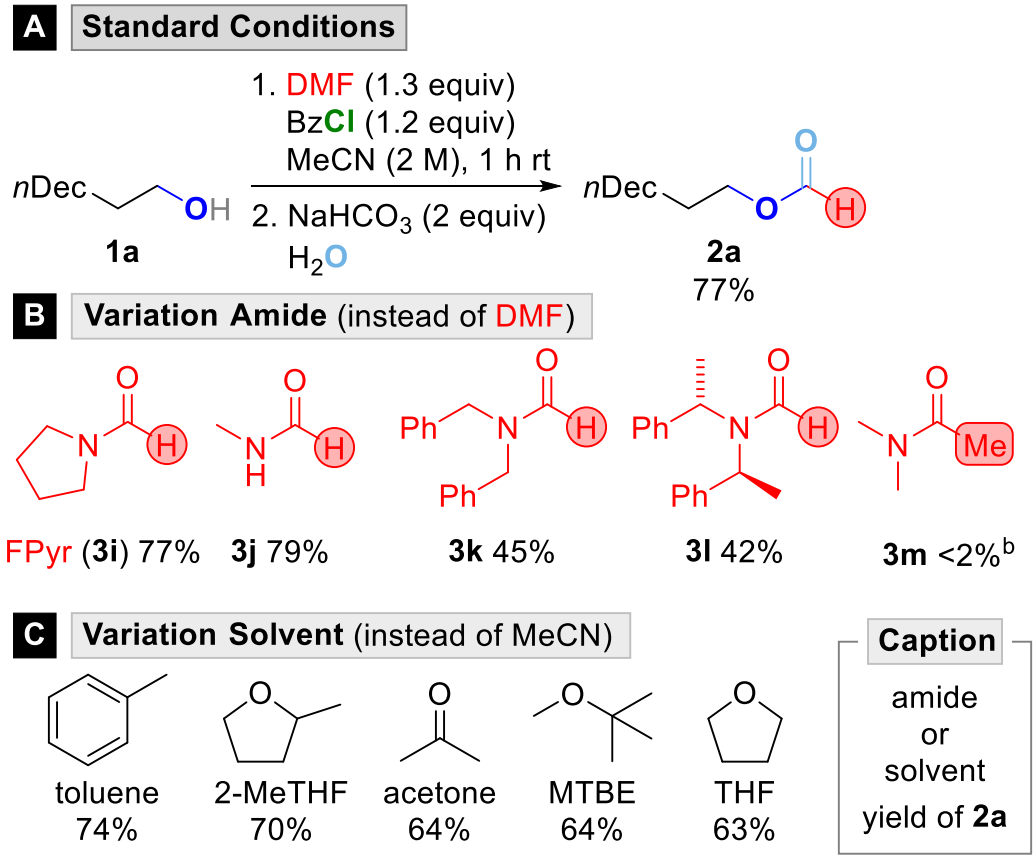
Interestingly, in previous reports regarding formylations of alcohols with DMF the substrate scope mainly encompasses aliphatic alcohols. Only in a few selected cases formates derived from (electron-deficient) benzylic and allylic starting materials have been included, the production of which required low reaction temperatures of -10 to -20 °C.[29,32] Imidate salts of type **7** with an aliphatic rest at the O atom, which are amenable from aliphatic alcohols, are rather stable and can even be isolated. In contrast, O-benzylic and allylic imidate cations quickly react further to alkyl halides.[57,64] To the best of our knowledge, we have described such reactive imidates for the first time by means of an exchange of the nucleophilic chloride against a non-nucleophilic hexafluorophosphate counter ion.[64]

Despite of a related reported using DMF and BzCl for the formylation of alcohols,[32] we were curious to explore the formamide mediated synthesis of formic acid esters in particular with regard to challenging benzylic and allylic esters further and extend the scope to thiols. Against this backdrop, we present an enhanced method for the transformation of alcohols and thiols into alkyl, benzyl and allyl formates and thioformates based on the formamide FPyr and benzoyl chloride (BzCl) with the support by counterion exchange (Scheme 1 **E**).

Results and Discussion

The method development was commenced with 1-dodecanol (**1a**) as model substrate based on our previous protocol for the chlorination of alcohols (Scheme 2 **A**).[57,64] Stoichiometric amounts of DMF and BzCl in MeCN allowed the production of dodecyl formate **2a** at room temperature in 77% yield after quenching with aqueous $NaHCO_3$ solution.

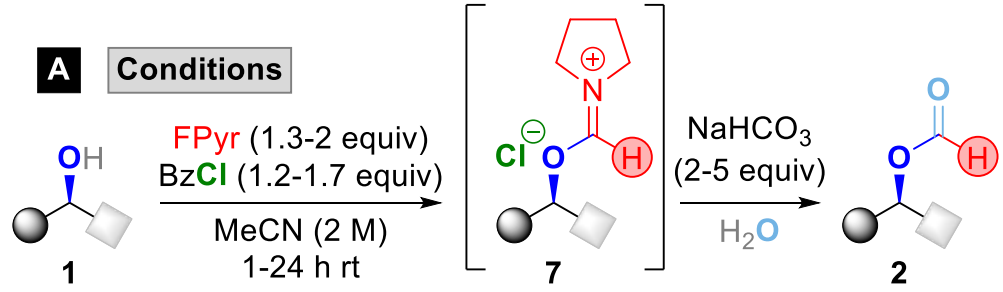


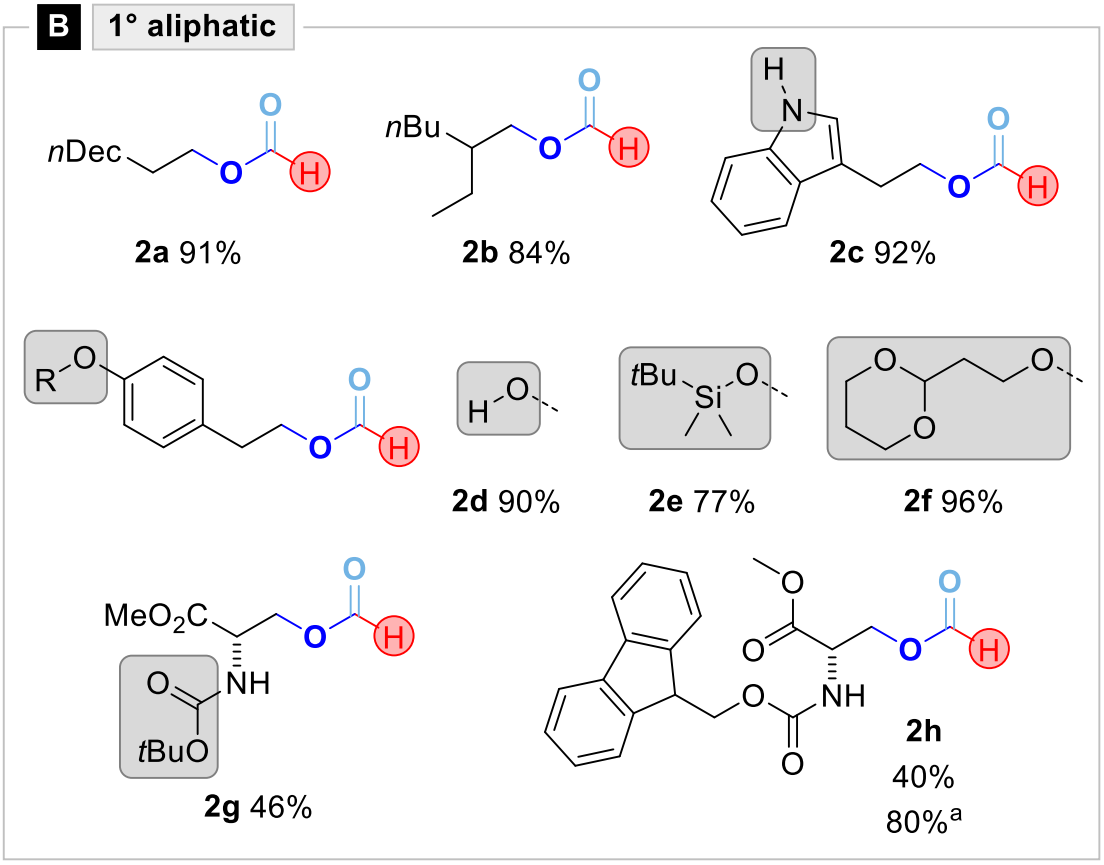


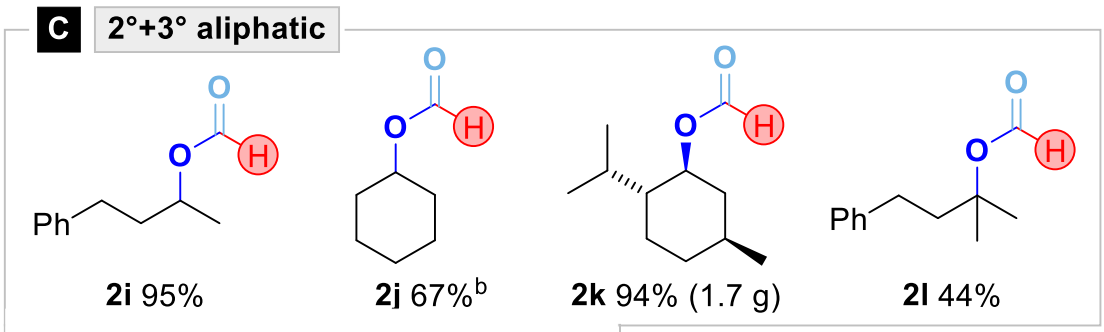
Scheme 2. Optimization of reaction conditions.

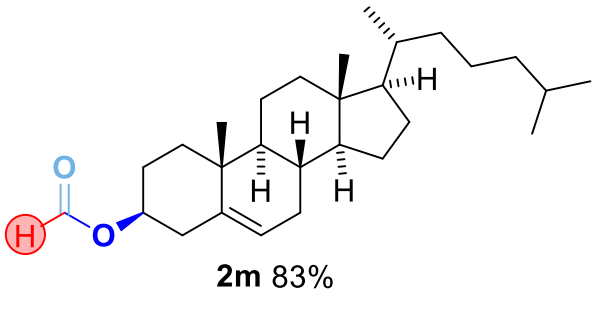
Formyl pyrrolidine (FPyr, **3i**) and methyl formamide (**3j**) both turned out to be similarly efficient formylation agents (Scheme 2 **B**), the latter of which enabled a significant enhancement in terms of atom economy in comparison to DMF.[65] The application of formamides with more sterically demanding substituents such as **3k** and **3l** resulted in moderate yields, most likely because imidate formation is hampered. Indeed, these formamides displayed a much lower catalytic activity in the deoxychlorination of alcohols.[57,64,66] In combination with BzCl other amides like **3m** did not permit access towards the respective amides. A similar trend was observed in the catalytic chlorination of alcohols, in which only amides derived from formic acid were found as potent catalysts.[57] Formation of type **7** imidate salts as productive intermediates is not possible with other amides.[64]

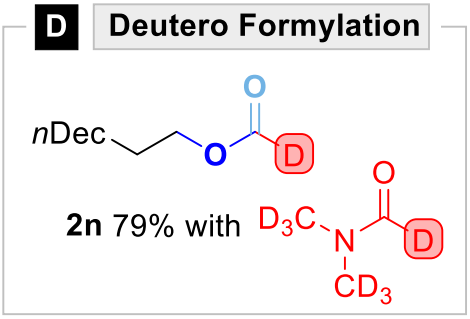
Beside acetonitrile the use of toluene and 2-MeTHF allowed for the preparation of formate **2a** in decent yields (Scheme 2 **C**). Nevertheless, yields were moderate when the formylation was performed in acetone, MTBE and THF, respectively. Furthermore, in a separate solvent evaluation in the esterification of 2-ethyl-1-hexanol MeCN emerged as superior reaction medium (see Table S2 SI). Since diminished yields were attained with methyl formamide in the case benzylic substrates (see Scheme 4 **B**), we decided to explore the substrate scope with FPyr instead.[67] The yield of formate **2a** was enhanced to 91% (referred to isolated material) by an increase of the amount of FPyr and BzCl (Scheme 3 **A**).

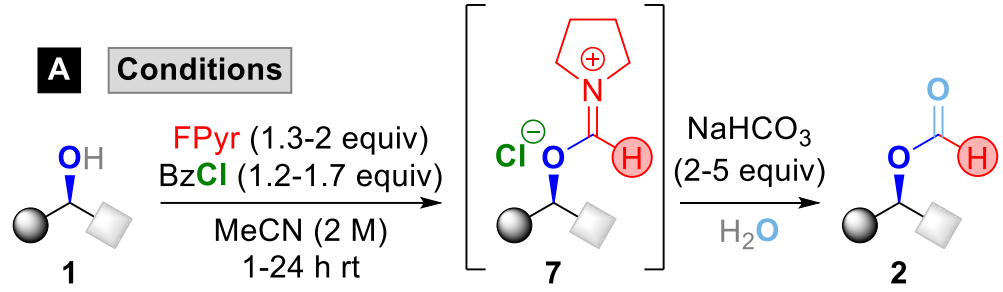

A
Conditions
FPyr (1.3-2 equiv)
BzCl (1.2-1.7 equiv)
MeCN (2 M)
1-24 h rt
NaHCO3
(2-5 equiv)
H2O
1
7
2

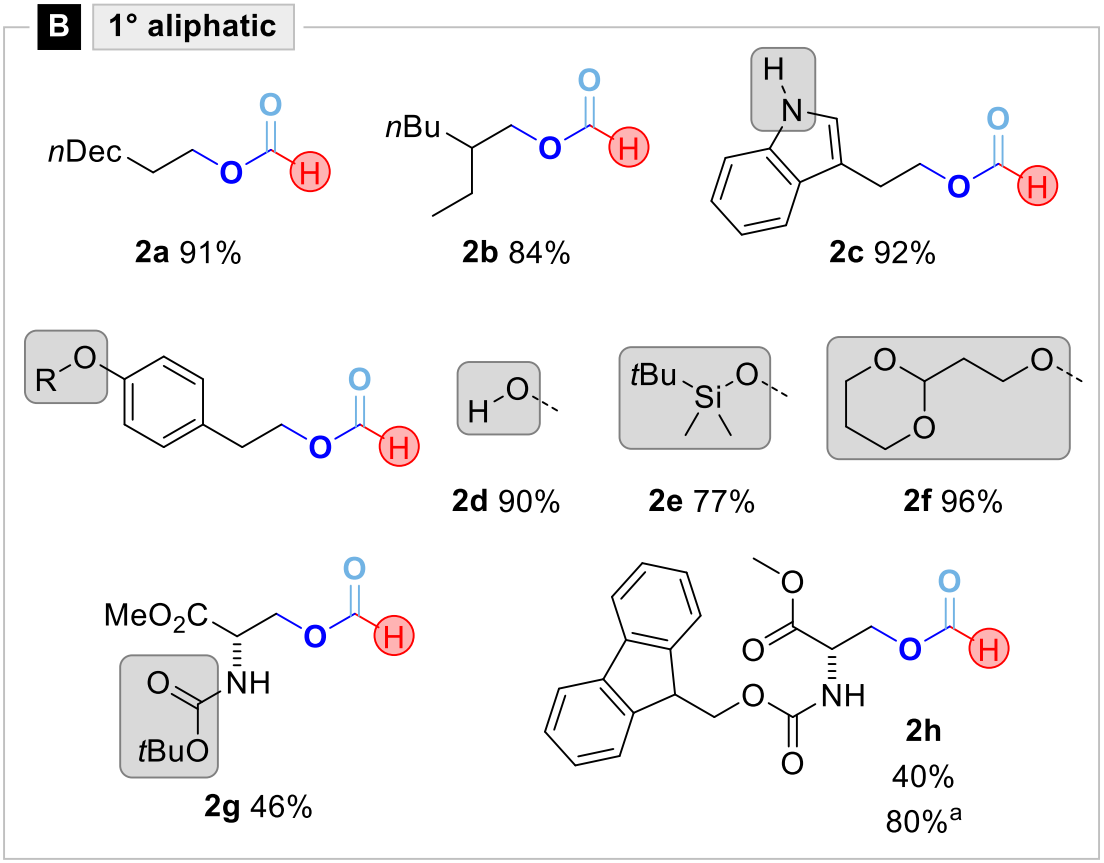

B
1° aliphatic
nDec
nBu
2a 91%
2b 84%
2c 92%
2d 90%
2e 77%
2f 96%
MeO2C
NH
tBuO
2g 46%
2h
40%
80%a

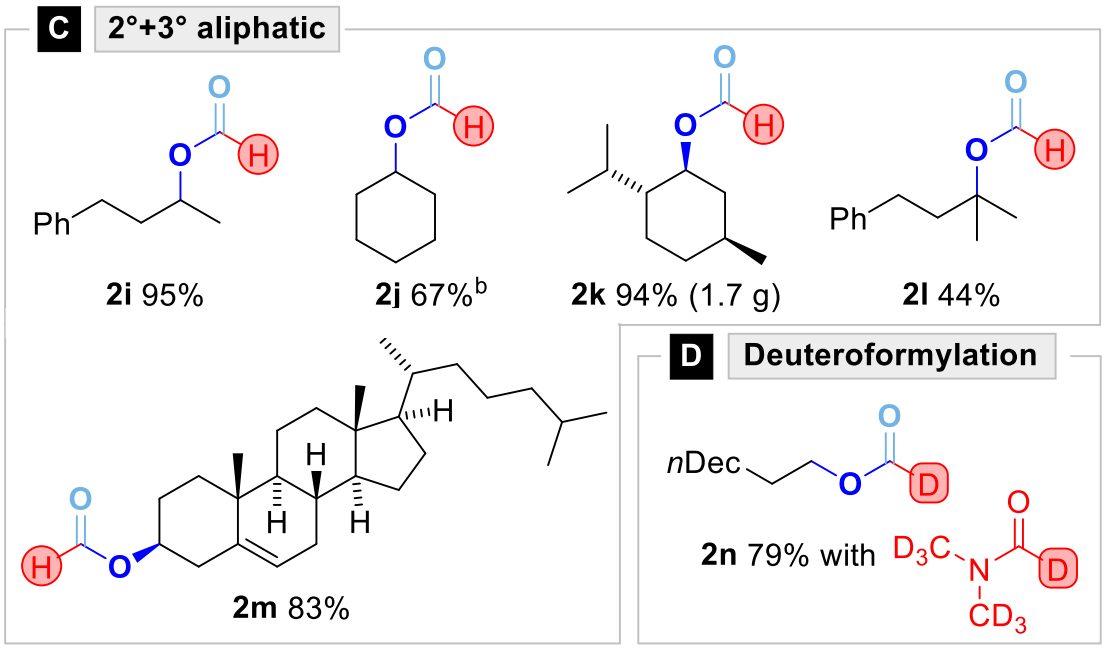

C
2°+3° aliphatic
Ph
2i 95%
2j 67%b
2k 94% (1.7 g)
Ph
2l 44%


2m 83%


D
Deutero Formylation
nDec
2n 79% with
D3C
N
CD3


A
Conditions
FPyr (1.3-2 equiv)
BzCl (1.2-1.7 equiv)
MeCN (2 M)
1-24 h rt
NaHCO3
(2-5 equiv)
H2O
1
7
2

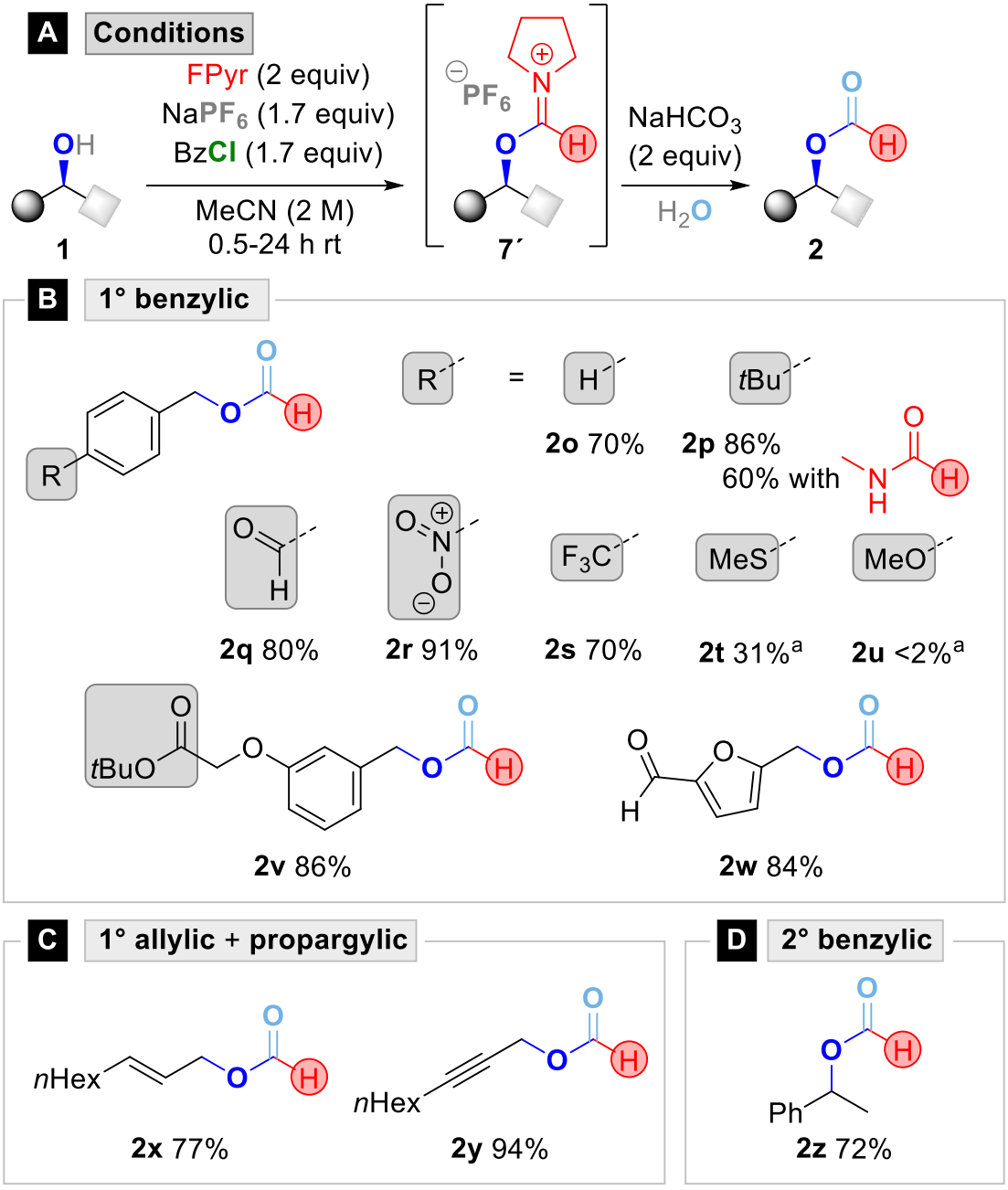

B
1° aliphatic
2a 91%
2b 84%
2c 92%
2d 90%
2e 77%
2f 96%
2g 46%
2h
40%
80%a


C
2°+3° aliphatic
2i 95%
2j 67%b
2k 94% (1.7 g)
2l 44%
2m 83%
D
Deuteroformylation
2n 79% with

Scheme 3. Substrate scope with aliphatic alcohols. a. with $NaPF_6$. b. Yield determined with internal NMR spectroscopy standard.

Subsequently, we evaluated the scope with respect to aliphatic substrates, as the respective imidate cations are relatively stable at room temperature and require heating to 80 °C for conversion to alkyl chlorides.[57-59] Several primary alcohols were transformed into the corresponding formates in moderate to excellent yields (Scheme 3 **B**). Worthy of note, chemoselective formylation was possible in the presence of a nucleophilic NH indole moiety and an aromatic alcohol (examples **2c** and **2d**). Since benzoic acid is generated as by-product, the reaction medium is slightly acidic. Therefore, the compatibility of the current protocol with regard to acid-labile functional groups was probed. Fortunately, the TBDMS ether **2e**, the cyclic acetal **2f** and the Boc protected serine derivate **2g** were isolated in 46% to 96% yield. Indeed, attempts for chlorination of the serine derived alcohol **1g** by our previous protocols (e.g., ref.[57]) were not successful, because C-Cl bond formation necessitates heating to 80 °C. Since formylation is feasible at ambient temperature, levels of functional group tolerance are potentially better than for C-Cl bond construction. Indeed, the moderate yield of **2g** was explained by a deteriorated conversion of 61% and not Boc cleavage. Also, the Fmoc protected serine formate **2h** was accessed in a moderate yield (40%) under standard conditions because of incomplete consumption of the staring material. In fact, addition of $NaPF_6$ to precipitate NaCl improved the yield to 80% because of an increased conversion.

Moreover, a range of secondary (and even one tertiary) alcohol were converted into the respective formic acid esters in 44 to 95% yield (Scheme 4 **C**). Worthy of note are the synthesis of menthyl and of cholesteryl formate **2k** and **2m**, , in excellent yields, both of which are obtained from terpene and steroid natural products, respectively.[68] Moreover, the gram scale preparation of **2k** attested sufficient levels of scalability. Finally, the deuterium labelled formate **2n** was accessed with the aid of d^7-DMF in a yield of 79%, which verifies the ability to prepare isotopically labelled esters (Scheme 3 **D**). In the following, we faced the production of more challenging formates derived from benzylic, allylic and propargylic alcohols (Scheme 4).

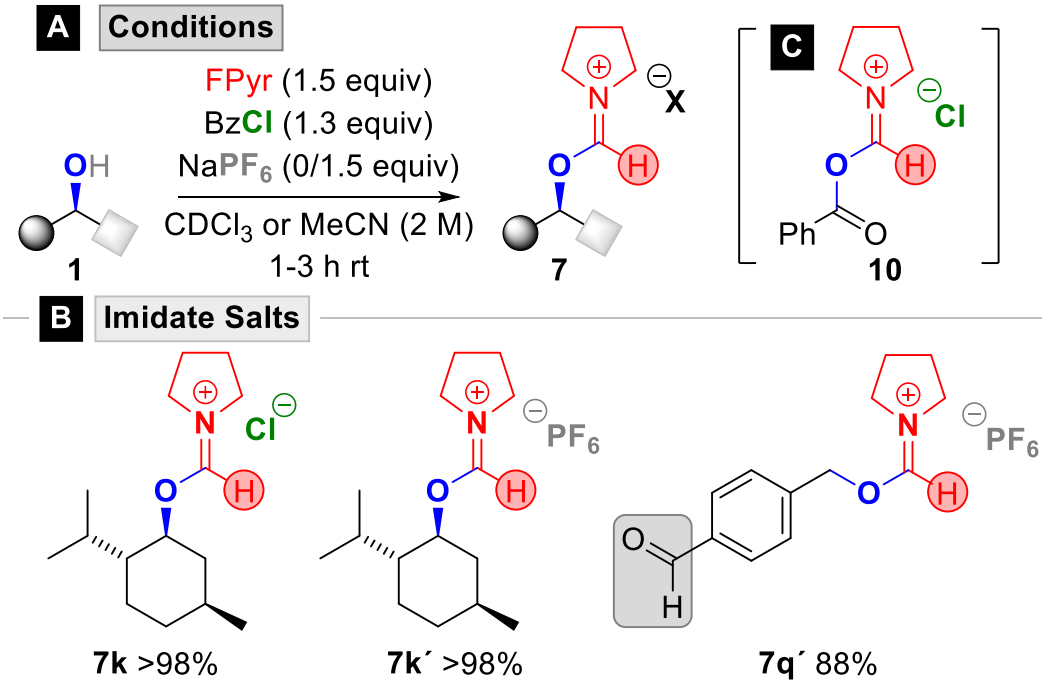


Scheme 4. Substrate scope regarding benzylic, allylic and propargylic alcohols. a. Yields determined by internal NMR standard.

As mentioned in the introduction, in preceding protocols for the preparation of formates by means of DMF benzylic and allylic substrates have rarely been included. This may be rationalized by the high reactivity of the imidate salts of these alcohols, which rapidly react further with the chloride counterion in a nucleophilic substitution to yield chloroalkanes. Recently, we succeeded in stabilizing and characterizing a O-benzyl and allyl imidate by a counterion exchange with non-nucleophilic hexafluorophosphate.[64] This approach enabled the synthesis of a variety of primary benzylic, allylic and propargylic formates in 70 to 94% yield (Scheme 4 **B** and **C**).[69] With methyl formamide instead of FPyr, benzylic formate **2p** was formed in a depleted yield of 60% (in comparison to 88% with FPyr). This result verifies that FPyr is the by far superior formylation reagent than methyl formamide. Notably, are the compatibility of the reaction conditions with aldehydes and acid sensitive *tert*-butyl esters, which are witnessed by the synthesis of formates **2q** and **2v** in 88 to 86% yield, respectively.

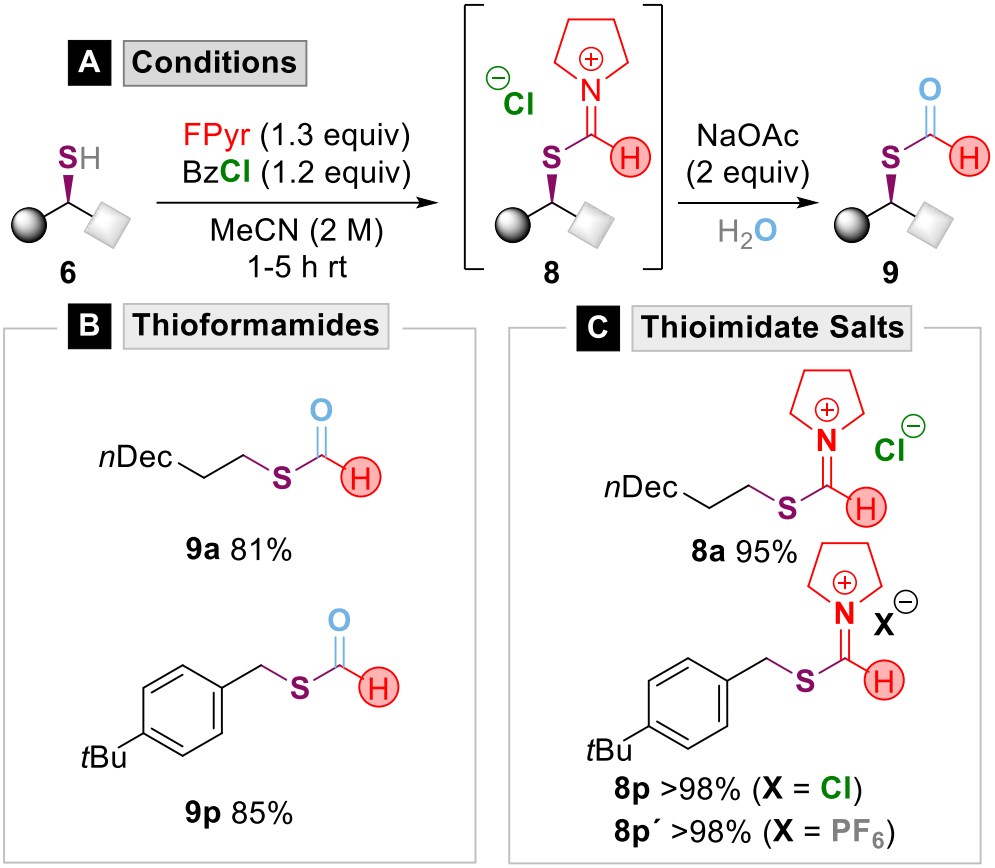
Moreover, hydroxymethyl furfural, which is available from renewable resources such as carbohydrates,[70-72] could be transformed into ester **2w**.

In our hands, the preparation of benzylic and allylic formic acid esters was only possible in synthetically useful yields, when carried out in the presence of $NaPF_6$.[73,74] Without the corresponding alkyl chlorides were formed as main products.[57] Electron-rich benzylic substrates are a limitation of the current protocol. The formates of 4-methylthiobenzyl alcohol was generated in a low yield of 31% and in the case of 4-methoxybenzyl alcohol the desired formate was not observed (esters **2t** and **2u**). These instances may be explained by the good stabilization of positive charges in benzylic position, which increases the reactivity of imidate cations of type **7**. In contrast, the formates **2q**, **2r** and **2s**, which are derived from electron-poor benzylic alcohols, were amenable in reasonable to excellent yields. Probably, the most challenging formate was **2z**, which is based on a secondary alcohol (Scheme 4 **D**). This substrate rapidly reacted to the respective chloride and styrene. Eventually increased amounts of the reagents and $NaPF_6$ and a short reaction duration of 1 h enabled the isolation of **2z** in 72% yield. As shown earlier by our group,[57,64] imidates of type **7** can be produced in $CDCl_3$ at ambient temperature in the case of aliphatic starting materials (Scheme 5 **A**).



Scheme 5. Production of imidate salts. Yields refer to the ratio to not-converted starting material and side-products according to ^{1}H NMR.

In addition, benzylic imidates like **7q´** are amenable by counterion exchange using $NaPF_6$ in MeCN, since the solubility of this sodium salt is too low in $CDCl_3$ (Scheme 5 **B**). According to our previous studies, type **7** imidates are formed by condensation of alcohol **1** with the (proposed) acyl imidate **10** instead of the Vilsmeier Haack reagent type intermediates (Scheme 5 **C**). Next, the methodology was applied to thiols **6**, which furnished thioformates of type **9** (Scheme 6 **A**).



Scheme 6. Synthesis of thiofomates and thioimidate salts. Yields of salts **7** refer to ratio with respect to starting material and side-products according to ^{1}H NMR spectroscopy.

The successful synthesis of aliphatic and benzylic thioformate **9a** and **9p** afforded careful quenching with aqueous NaOAc solution (Scheme 6 **B**). Hydrolysis with both aqueous $NaHCO_3$ solution and water delivered the starting thiol as main product (see SI chapter 2.4.2.1 for more details). To the best of our knowledge, formamides have yet not been engaged as reagents for the formylation of thiols. Not only dodecyl thioimidate could be prepared in $CDCl_3$ without $NaPF_6$, but also benzylic cation **8p** (Scheme 6 **C**). Apparently, benzylic thioimidates of type **8** are more stable than the related imidates **7**. To this end, thioimidate salts have been produced by alkylation of thioamides with highly reactive Meerwein´s trialkyl onium salts and alkyl triflates. Therefore, the current approach allows for a significantly simplified entry towards these C=N double bond containing cations, which are important ionic liquids (*vide supra*).

Conclusions

Herein, we have disclosed a novel method for the synthesis of formic acid esters **2** and thioesters **9** from alcohols **1** and thiols **6** by means of formation of imidate salts with formyl pyrrolidine (FPyr) and benzoyl chloride (BzCl) and subsequent hydrolysis. Additionally, benzylic and allylic formates are amenable with the aid of counterion exchange of chloride against hexafluorophosphate. Indeed, imidate salts containing chloride anions rapidly react further to chloro alkanes, when they are derived from benzylic and allylic alcohols. Therefore, the current approach overcomes the limitation towards aliphatic substrates of previous protocols for alcohol formylation with formamides as reagents. Furthermore, the presented methodology exhibits high

levels of functional group tolerance, acid- and base-labile functions such as Boc and Fmoc carbamates (examples **2g** and **2h**), *tert*-butyl esters and acetals (**2v** und **2f**) are compatible. Finally, a simple and straightforward access to thioimidates has been implemented. The synthetic utility of the current protocol has been highlighted by the syntheses of several formates engaging both, natural products and a platform chemical that is available from renewable resources. Based on the current project ongoing research in our lab focuses on the application of thioimidates as starting materials for single electron transfer promoted transformations.

Experimental Section

Representative gram scale preparation of menthyl formate (2k). A 50 mL flask with a stir bar was charged with (1S,2R,5S)-(+)-menthol (**1k**, 1.563 g, 10.0 mmol, 1.00 equiv), FPyr (1.62 mL, 1.685 g, 17.0 mmol, 1.70 equiv) and dry MeCN (5.0 mL, 2.0 M). Then, BzCl (1.74 mL, 2.108 g, 15.0 mmol, 1.50 equiv) was added dropwise with the aid of a syringe and the reaction mixture was stirred at 400 rpm for 3 h. In following, aqueous saturated $NaHCO_3$ (20 mL, 2.0 equiv, 1.1 M) was added and the heterogeneous mixture was stirred for a further 10 min. Finally, the mixture was diluted with MTBE (20 mL) and transferred to a 100 mL extraction funnel. Subsequently, the reaction vessel was rinsed with MTBE/H_2O (2 x 10 mL/10 mL) and additional MTBE (10 mL). Next, the organic phase was separated and washed with brine (1 x 20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. After drying for 5 min on a rotary evaporator at 20 mbar, ^{1}H NMR spectroscopy of the crude material (1.95 g, 106%) verified full conversion of alcohol **1k**. Eventually, purification with the aid of column chromatography on silica gel (25 g, ratio weight crude product/SiO_2 1:13) using MTBE/*n*-heptane 3:97 as eluent mixture afforded formate **2k** in 94% yield (1.732 mg, 9.40 mmol) as a colorless oily liquid after drying in high vacuum.
M ($C_{11}H_{20}O_2$) = 184.28 g/mol; $\mathbf{r_f}$ (SiO_2, MTBE/*n*-heptane 3:97) = 0.47; **^{1}H NMR** (500 MHz, $CDCl_3$) δ [ppm] = 8.08 (s, 1H, 1'-H), 4.81 (ψ-td, ^3J = 11.0, 4.3 Hz, 1H, 1-H), 2.02 (ψ-d, J = 11.8 Hz, 1H, 2-H_a), 1.93-1.87 (m, 1H, 3-H), 1.71-1.68 (m, 2H, 5-H_a, 4-H_a), 1.51-1.49 (m, 1H, 7-H), 1.41 (ψ-t, J = 11.5 Hz, 1H, 6-H), 1.10-1.00 (m, 2H, 2-H_b, 5-H_b), 0.92-0.85 (m, 7H, 4-H_b, 8-H, 9-H; amongst at 0.91 ψ-t, J = 6.6 Hz), 0.77 (d, $^3J_{9,3}$ = 7.0 Hz, 3H, 10-H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ [ppm] = 161.01 (C.1'), 74.30 (C-1), 46.99 (C-6), 41.04 (C-2), 34.27 (C-5), 31.56 (C-7), 26.15 (**C-3**), 23.38 (C-4), 22.12, 20.89 (C-8, C-9), 16.21 (C-10); **GC MS** (EI, 70 eV) m/z [u] (%) = 138 (34, [M-CO_2H-H]$^+$), 123 (44), 109 (9), 95 (100, [methylcyclohexenyl]$^+$), 81 (69), 67 (22), 55 (23, [butenyl]$^+$); **$[\alpha]^D_{20}$** ($CHCl_3$, c = 1.23 g/100 mL, T = 25.9 °C) = +82.5. The NMR data is in good match with literature data of the enantiomer of **2k**.

Acknowledgements

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Supplementary Material

Additional data regarding the optimization of the reaction conditions, procedures for the preparation of all compounds and analytical data are available in the supplementary material file associated with this manuscript.

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67. FPyr was chosen over DMF, because in numerous of our previous assessments FPyr was identified as superior catalyst for C-Cl bond formation (see for example references 57 to 59 and 61).
68. The yield of 67% of cyclohexyl formate (**2j**), which had been determined by internal NMR standard, is likely reasoned by a high volatility of this low molecular weight product.
69. Recently, we implemented an approach for formamide catalyzed chlorination of alcohols based on cyanuric chloride (TCT).[58] Since TCT contains three Cl atoms, 0.4 equiv are sufficient for complete conversion of the starting alcohol. In light of the superior atom efficiency in comparison to BzCl, TCT was also probed as agent in the synthesis of benzylic format **2p**. A depleted yield of 59% verified that BzCl is the superior reagent in the formyl group transfer (see SI for further details).
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