Mechanochemical Nucleophilic Substitution of Alcohols via Isouronium Intermediates

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Abstract: An expansion of the solvent-free synthetic toolbox is essential for advances in the sustainable chemical industry. Mechanochemical reactions offer a superior safety profile and reduced amount of waste compared to conventional solvent-based synthesis. Herein we report a new mechanochemical method for nucleophilic substitution of alcohols using fluoro-N,N,N',N'-tetramethylformamidinium hexafluorophosphate (TFFH) and K_2HPO_4 as an alcohol-activating reagent and a base, respectively. Alcohol activation and reaction with a nucleophile were performed in one milling jar via reactive isouronium intermediates. Nucleophilic substitution with amines afforded alkylated amines in 40–91% yields. The complete stereoinversion occurred for the S_N2 reaction of (R)- and (S)-ethyl lactates. Substitution with halide anions (F^-, Br^-, I^-) and oxygen-centered (CH_3OH, PhO^-) nucleophiles was also tested. Application of the method to the synthesis of active pharmaceutical ingredients (APIs) has been demonstrated.

Introduction

The synthesis of active pharmaceutical ingredients (APIs) driven by green chemistry concepts plays a pivotal role en route to a cleaner and safer pharmaceutical industry.[1,2] Notably, a great deal of waste and safety concerns commonly originate from the use of solvents, typically responsible for 80–90% of total mass consumption in a given industrial process.[3] Besides environmental and safety issues, solvents can also generate dangerous contaminants in the produced APIs, such as cancerogenic nitrosamines derived from trace secondary amine impurities in N,N-dimethylformamide.[4,5] In this regard, mechanochemistry[6–8] as an essentially solvent-free technique can beneficially contribute to the ongoing green renovation of the pharma industry.[9–11] Despite the rapid development of

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mechanochemical organic synthesis over the past decades,[12–15] its synthetic portfolio still does not entirely cover the diverse range of transformations required for API production and needs to be expanded.

Nitrogen-containing functional groups prevail in the existing immense number of bioactive molecules, including APIs.[16] As a consequence, almost 80% of heteroatom alkylation and arylation reactions used in the synthesis of drug candidates involve the formation of C–N bonds.[17] In addition to the mainstream developments like amide synthesis,[18–23] the state-of-the-art mechanochemical synthetic toolbox offers several opportunities to construct C–N bonds[24] in amines via alkylation[25–27] and arylation[28–30] with organic halides. However, the use of alcohols as ubiquitous starting materials remains nearly untapped.[31] Nucleophilic substitution of the hydroxyl group in alcohols is one of the most fundamental and widespread chemical transformations. Applied to amine synthesis, alcohols can serve as safer replacements to lacrimatic and potentially genotoxic organic halides. However, the direct nucleophilic substitution of alcohols remains a challenge,[2,32–36] and prior transformation of hydroxyl into a better leaving group (e.g., sulfonate ester) is commonly required.

Recently, our group reported a new mechanochemical amidation approach based on the use of reactive uronium-type amide coupling reagents such as (1-cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethylaminomorpholinocarbenium hexafluorophosphate (COMU) or N,N,N',N'-tetramethylchloroformamidinium hexafluorophosphate (TCFH) and K_2HPO_4 as a base (Scheme 1, A).[37] The reaction proceeded via the generation of activated derivatives of carboxylic acids, such as acyl uroniums and acyl phosphates.

Inspired by these findings, we planned to extend the same activation methodology towards nucleophilic substitution of alcohols (Scheme 1, B). Indeed, O-alkyl isouronium salts can be obtained by the reactions of alcohols with halouronium salts (e.g., TCFH or its fluoro-analog TFFH), a process commonly utilized for the preparation of amide coupling reagents.[38,39] Similarly to O-alkyl isoureas generated from alcohols and carbodiimides,[40–44] isouronium salts can act as reactive intermediates in nucleophilic displacement reactions.[45,46] However, none of these alcohol-activation techniques have been previously attempted under solvent-free conditions or utilized for the synthesis of amines. Here we report for the first time the application of an air-stable and non-hygroscopic solid TFFH reagent[46–48] for activation of alcohols towards nucleophilic substitution with amines, halogens and some oxygen nucleophiles under essentially solvent-free conditions provided by mechanochemistry.
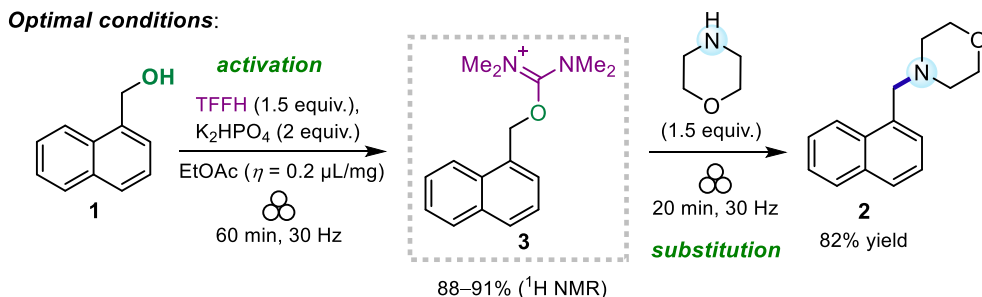
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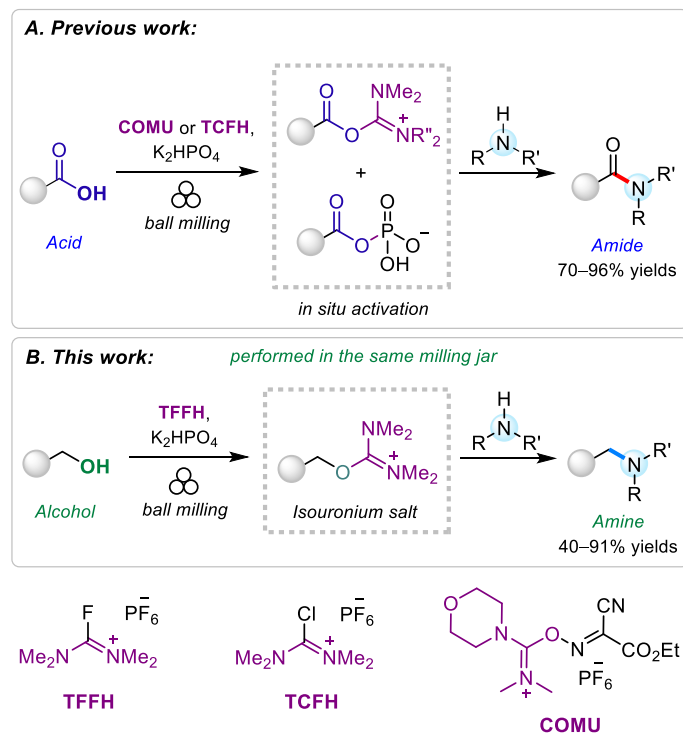
Scheme 1. Mechanochemical synthesis of amides via *in situ* activation of carboxylic acids[37] and preparation of amines from alcohols.

Results and Discussion

Optimization of coupling of alcohols with amines. The reaction between 1-naphthalenemethanol (**1**) and morpholine as a nitrogen nucleophile was selected as a model transformation to find the optimal reaction conditions leading to tertiary amine product **2** (Scheme 2). Ball milling experiments were performed in a Form-Tech Scientific FTS1000 shaker mill operating at 30 Hz using a 14 mL zirconia-coated milling jar and a single 10 mm milling ball. In contrast to amide synthesis,[37] attempted *in situ* activation of alcohol **1** with TCFH and TFFH reagents in the presence of morpholine resulted in a very low yield of **2** (less than 8%; see Table S1 in the Supporting Information). This result is a likely outcome of a faster competitive reaction of halouronium reagents with morpholine itself.[48,49] To overcome the problem, a stepwise reaction in a single milling jar was considered, which involved the generation of isouronium salt **3** by the reaction of **1** with a halouronuim reagent before adding morpholine. To our delight, this technique afforded high 88–91% conversions to **3** by milling alcohol **1** with TFFH reagent in the presence of K_2HPO_4 as a base for 1 h (Scheme 2). The addition of morpholine to the same reaction jar resulted in fast (less than 20 min) and quantitative transformation of **3** into amine **2**, which was isolated in 82% yield. The same reaction sequence

performed in acetonitrile solution with trimethylamine as a base (see Table S5 in the Supporting Information) produced **2** in noticeably lower yield (did not exceed 50% according to ^{1}H NMR analysis).
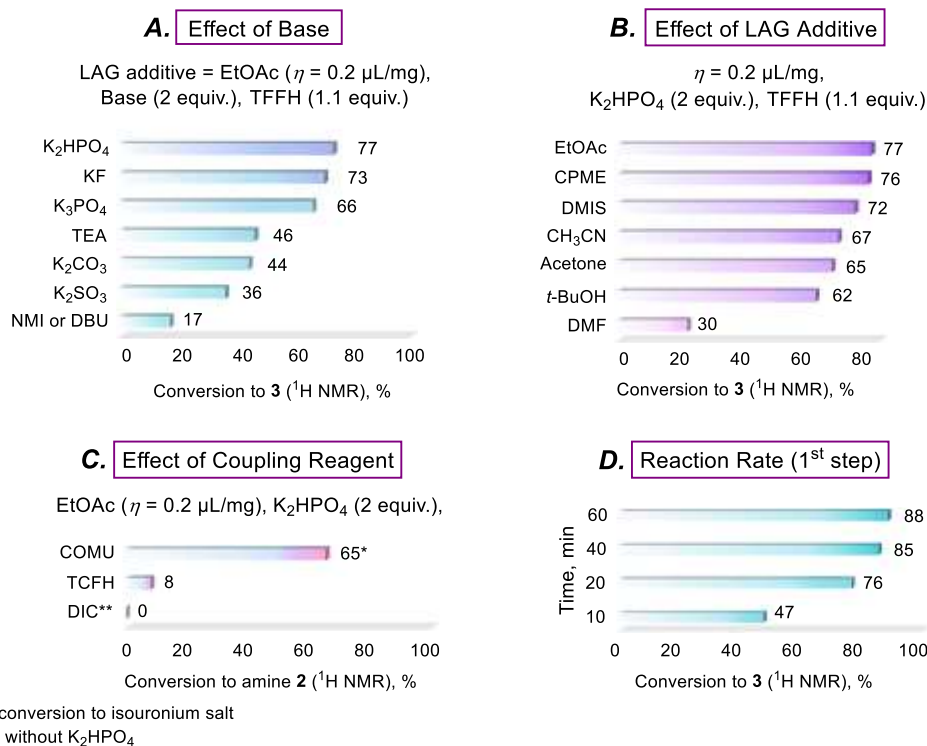
Scheme 2. Selected optimization experiments (performed with 0.16 mmol of alcohol **1** as a limiting substrate) and kinetic studies. TEA = trimethylamine, NMI = *N*-methylimidazole, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DIC = *N,N′*-diisopropylcarbodiimide, CPME = cyclopentyl methyl ether; DMIS = dimethyl isosorbide. The complete dataset of optimization experiments is provided in the Supporting Information (Table S2).

Selection of base, liquid additive for liquid-assisted grinding (LAG)[6,7] and coupling reagent were identified as a trio of most crucial parameters affecting the reaction efficiency. No reaction of **1** and TFFH occurred without a basic additive. Concerning the choice of base (Scheme 2, A), replacement of organic bases like triethylamine (TEA), *N*-methylimidazole (NMI) and diazabicyclo(5.4.0)undec-

7-ene (DBU) with inexpensive and less hazardous inorganic salts was superior (e.g., K_2HPO_4 or K_3PO_4) or at least as efficient (K_2CO_3 *vs.* TEA). Potassium fluoride (KF) and dipotassium phosphate (K_2HPO_4) were identified as the most efficient bases during the initial screening, affording 73% and 77% conversions to **3**, respectively. In the case of K_2HPO_4, a slight increase of TFFH amount (1.5 equiv.) to compensate for pyrophosphate formation (see the Supporting Information, Fig. S2) delivered the highest conversion values (88–91%).

A minor amount of liquid additive usually accelerates mechanochemical reactions, a technique known as liquid-assisted grinding (LAG). It is empirically characterized by the parameter η, expressing the ratio of the volume of liquid (µL) added to the total amount of solid (mg).[50] Although LAG requires a subtle amount of liquid (fixed at 0.2 µL/mg in our experiments), we preferred to screen several green solvents as LAG additives,[51,52] in addition to several conventional polar solvents (Scheme 2, B; see Table S2 in the Supporting Information for additional data). In our hands, green solvents like ethyl acetate (EtOAc), cyclopentyl methyl ether (CPME) and dimethyl isosorbide (DMIS) served as excellent LAG additives offering the best conversions in the 72–77% range and outperforming other polar solvents.

Among the activating reagents, TFFH was identified as the best activator, producing isouronium salt **3** in the highest yield. In comparison, COMU delivered lower 65% yield of the corresponding isouronium intermediate (Scheme 2, C). In contrast to TFFH, the corresponding chlorine reagent TCFH was found almost unreactive towards alcohol **1**, with the same order of reactivity also observed in acetonitrile solution (see Table S5 in the Supporting Information). The use of TFFH is also preferable to TCFH or COMU in view of the lowest molecular weight and, therefore, better atom economy for the former. The reaction of alcohol **1** with *N,N′*-diisopropylcarbodiimide (DIC) led to the formation of the corresponding *O*-alkyl isourea[42] but did not result in any further nucleophilic substitution reaction (see Table S2 in the Supporting Information for the details). Note that at least 60 min milling time was required to achieve the highest conversion (88–91%) of starting alcohol **1** into intermediate **3**, as a kinetic study revealed (Scheme 2, D).

Scope and Limitations. With the optimal conditions established, the substrate scope of various alcohols was examined (Scheme 3). In addition to the above-mentioned amine **2**, analogous morpholine derivatives **4**–**6** were flawlessly prepared in 61–91% yields from the corresponding benzylic-type primary alcohols. Substitution of the aromatic ring with electron-donating (OMe) or electron-withdrawing (CF_3) groups did not substantially affect the reaction efficacy (**5** and **6**, Scheme 3).
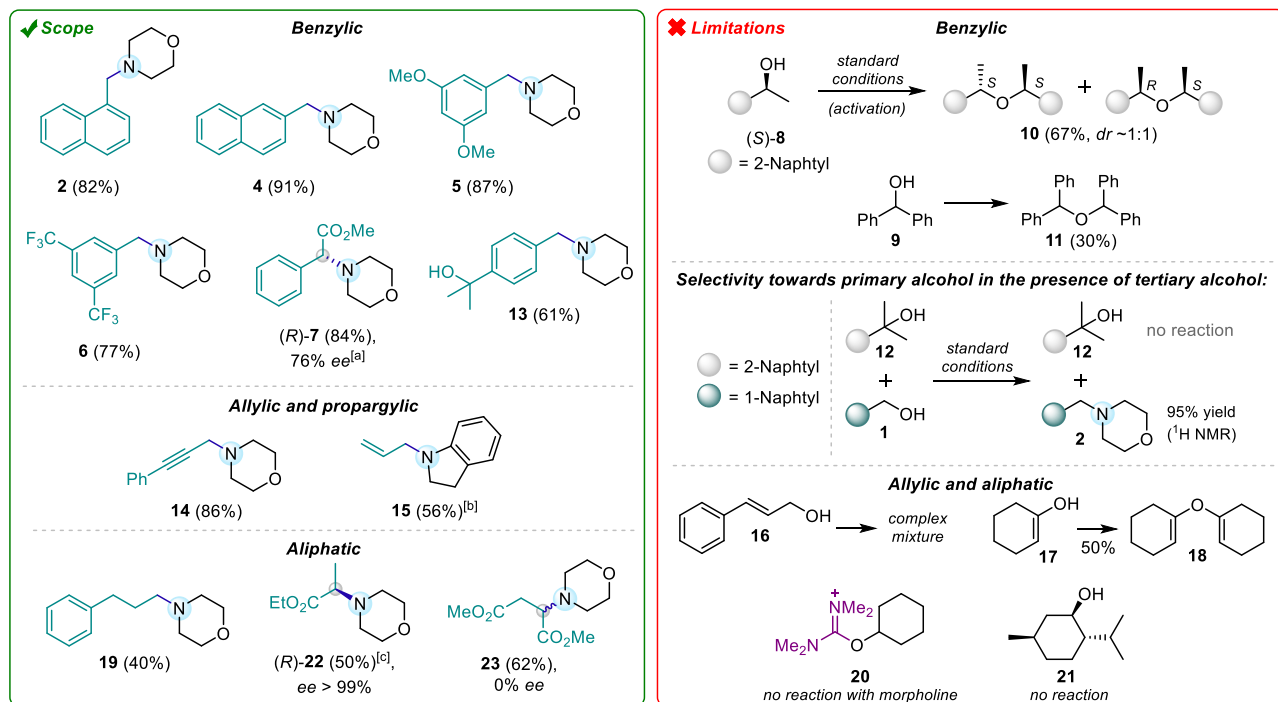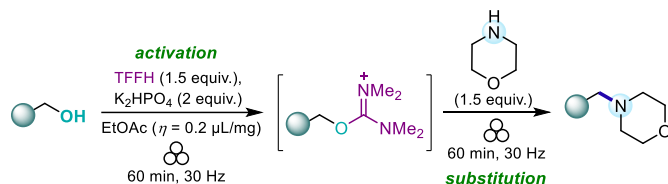
Scheme 3. Scope of alcohols and limitations of amine synthesis (performed with 0.25–0.60 mmol of alcohols as limiting substrates). [a] 85% *ee* after 15 min milling with TFFH/K$_2$HPO$_4$. [b] Indoline was used instead of morpholine. [c] Milling time with morpholine 3 h. (*S*)-**22** was prepared from (*R*)-lactate with the same yield and optical purity.

Coming to secondary benzylic substrates, (*R*)-phenylglycine derivative **7** was obtained from optically pure (> 99% *ee*) methyl (*S*)-mandelate in high 84% yield, but with reduced optical purity (76% *ee*). Although phenylglycine is known as one of the most epimerization-prone amino acids,[53] we found that optical purity of **7** remained almost unchanged over variation of milling time with morpholine (30–120 min; see Table S6 in the Supporting Information). However, shortening the duration of the alcohol activation step to 15 min resulted in a noticeably better 85% *ee*. These results indicate that partial epimerization of the corresponding isouronium intermediate could occur (presumably via enolization[54]) while its S$_N$2 reaction with the amine is faster and dominant. At the same time, secondary benzylic alcohols like (*S*)-α-methyl-2-naphthalenemethanol (**8**) and diphenylmethanol (**9**) produced ethers **10** and **11** during the milling with TFFH/K$_2$HPO$_4$. Ether **10** was obtained as an almost equimolecular mixture of (*S*,*S*)- and (*R*,*S*)-diastereomers according to ^{1}H NMR and HPLC analysis on a chiral stationary phase, indicating that the reaction followed the S$_N$1 mechanism and occurred

via the corresponding benzylic cation. Tertiary benzylic alcohol **12** was unreactive and did not form the corresponding isouronium salt. Notably, highly chemoselective amination of primary alcohol **1** was achieved in the presence of tertiary substrate **12** due to such a high difference in reactivity. This finding was applied in the preparation of amine **13**, which had an intact tertiary alcoholic moiety. Amines **14** and **15** were successfully prepared from the corresponding propargylic and allylic alcohols in 86% and 56% yields, respectively. However, other tested allylic substrates like alcohols **16** and **17** failed to render the corresponding amine products due to several dominant side processes, such as ether formation. Under the standard reaction conditions, 3-phenylpropyl amine **19** was produced from the corresponding alcoholic precursor in a low 40% yield, evidently due to the reduced reactivity of the corresponding isouronium salt with an aliphatic side chain. The yield of **19** was not significantly improved even after extended milling time with an amine (3 h). Secondary aliphatic alcohols either produced unreactive isouronium salts (e.g., **20** obtained from cyclohexanol) or did not react at all (e.g., menthol **21**). Intriguingly, ethyl (*S*)- and (*R*)-lactates were quite reactive under the developed conditions, producing alanine derivative **22** in 50% yield and excellent optical purity (> 99% *ee*). The stereochemical outcome indicates complete stereoinversion via the S_N2 mechanism. Surprisingly, a derivative of aspartic acid **23** was obtained from dimethyl (*S*)-malate with a total loss of optical purity. This result, along with a substantial amount of dimethyl fumarate detected in the reaction mixture (see Figure S6 in the Supporting Information), indicates that substitution of hydroxyl probably occurred via an elimination-addition mechanism in this case.

The scope of amines was explored in the substitution reactions of 2-naphthylmethanol **24** (Scheme 4). Secondary aliphatic amines like thiomorpholine, piperidine and the methyl ester of D-proline delivered corresponding amines **25**–**27** in moderate to high yields (42–79%). Notably, less nucleophilic aromatic amine (indoline) delivered a high 86% yield of the corresponding amine product **28**. Primary amines, for example, 3,5-bis(trifluoromethyl)benzylamine (**29**), were found reacting stepwise under the standard reaction conditions, producing a mixture of mono- and dialkylated products **30** and **31**, respectively. Full conversion into the tertiary amine product can be achieved using stoichiometric amounts (0.5 equiv.) of a primary amine; for example, amine **32** was prepared from benzylamine in 77% yield under these conditions.
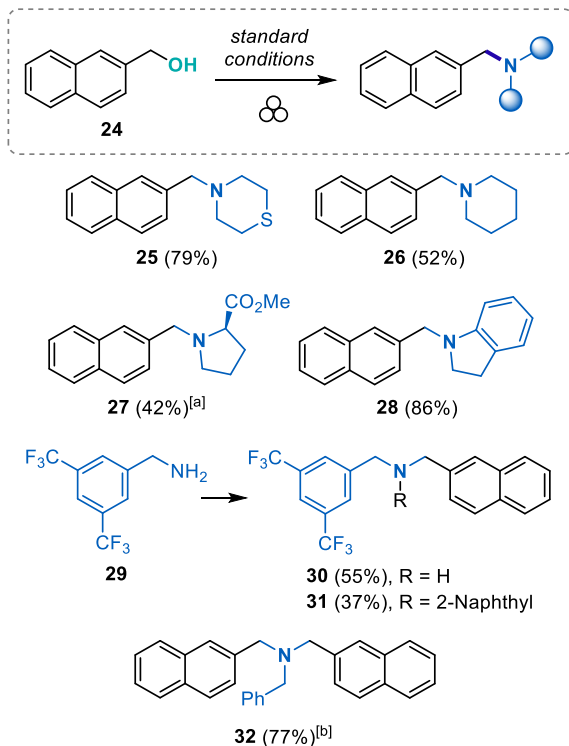
Scheme 4. Scope of amines **25**–**32** prepared from 2-naphthalenemethanol (**24**). (Performed with 0.25 mmol of **24** as a limiting substrate). [a] Amine hydrochloride was used as starting material. [b] With 0.5 equiv. of benzylamine.

Application to the synthesis of APIs and bioactive amines. The knowledge acquired during the optimization studies and examination of substrate scope prompted us to implement the synthesis of several bioactive amines (including APIs) using mechanochemical C–N bond-forming reactions as the key steps. Thus, a stimulant drug 1-methyl-4-benzylpiperazine (**33**, MBZP) was prepared by alkylation of *N*-methylpiperazine (**34**) with benzylic alcohol and isolated in 54% yield by crystallization of its hydrochloric salt from methanol (Scheme 5). Antidepressant piberaline (**35**) was prepared from picolinic acid (**36**) via stepwise mechanochemical amide coupling,[37] solvent-free Boc-deprotection[55] and mechanochemical amination steps. Derivatives of 4-(hydroxymethyl)benzoic acid (**39**) have multiple pharmaceutical uses, including anticancer agents (e.g., Imanitib,[56] Masitinib[57]), histone deacetylase inhibitors,[58] histamine receptor antagonists (e.g., Bavisant).[59] The observed low reactivity of TCFH reagent towards alcohols compared to TFFH (see Scheme 2, C) and, conversely, the high amide coupling potency of the TCFH/K_2HPO_4 reagent system[37] was utilized to perform protecting group-free mechanochemical amidation of carboxylic group in **39** (Scheme 6) while leaving the benzylic hydroxyl intact. Switching to the TFFH reagent at the next step resulted in activation of benzylic alcohol **40** and yielded the morpholine derivative[59] **41** in 80% yield.
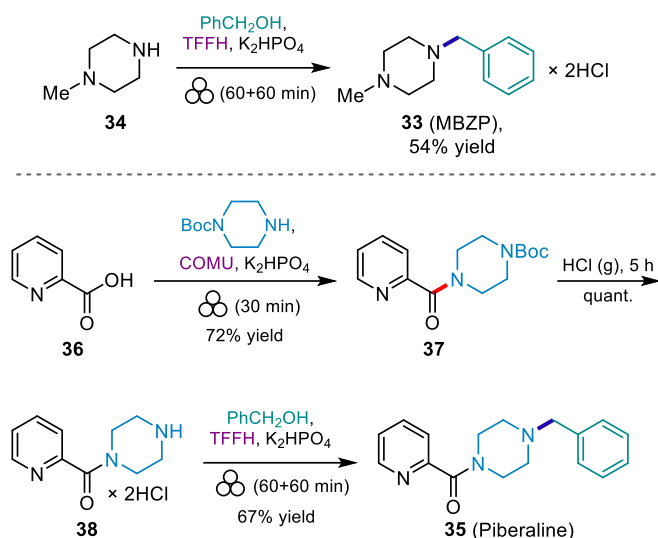
Scheme 5. Mechanochemical C–N bond-forming reactions in the synthesis of antidepressants 1-methyl-4-benzylpiperazine (**33**, MBZP) and piberaline (**35**).
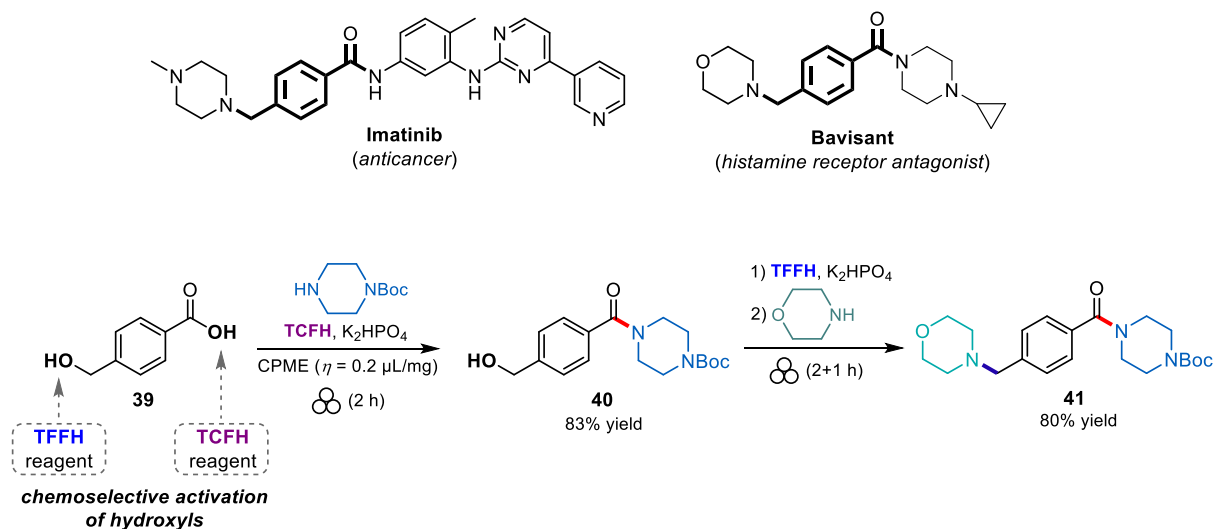
Scheme 6. Examples of pharmacologically active derivatives of 4-(hydroxymethyl)benzoic acid (**39**) and preparation of amine **41** via chemoselective activation of hydroxyls in **39**.

Nucleophilic substitution with halogens and oxygen nucleophiles. In addition to amines and their derivatives, oxygen- and halogen-containing moieties occupy a spacious fraction of pharmaceutically relevant functional groups.[16] This fact inspired us to examine the efficacy of the developed OH-activation protocol towards incorporating halogens and oxygen-containing functionalities. The corresponding nucleophilic substitution reactions were performed with 1- and 2-naphthalenemethanols (**1** and **24**, Scheme 7). Activation of the hydroxyl in **24** with the TFFH reagent followed by milling the produced isouronium intermediate with solid MgBr$_2$ or KI afforded the

corresponding bromo and iodo derivatives in high yields (**42** and **43**; Eq. 1 and 2). Notably, no fluoro derivative was produced during the milling with TFFH/KF, both serving as a source of a fluoride anion. Only replacing KF with CsF resulted in the generation of fluorine derivative **44** (Eq. 3), although in a moderate 40% yield. This result stays in line with previous observations,[60,61] showing that nucleophilic reactivity of anions under solvent-free conditions is strongly controlled by their counter-ion pairing. The effect was interpreted in the framework of hard–soft acid–base (HSAB) theory,[14] explaining the enhanced nucleophilicity of F^- in CsF as a result of a mismatched soft–hard ion pair. Higher nucleophilic reactivity of F^- in CsF compared to KF also correlates with lower lattice energy for the former (CsF, 740 kJ·mol^{-1}; KF, 821 kJ mol^{-1}).[62] Use of potassium phenolate as the nucleophile resulted in a modest 46% yield of the corresponding substitution product **45** (Eq. 4). At the same time, the isouronium salt generated from 2-naphthalenemethanol was highly sensitive towards solvolysis in a nucleophilic solvent such as methanol and produced methyl ether **46** in high 91% yield (Eq. 5) after 3 h.
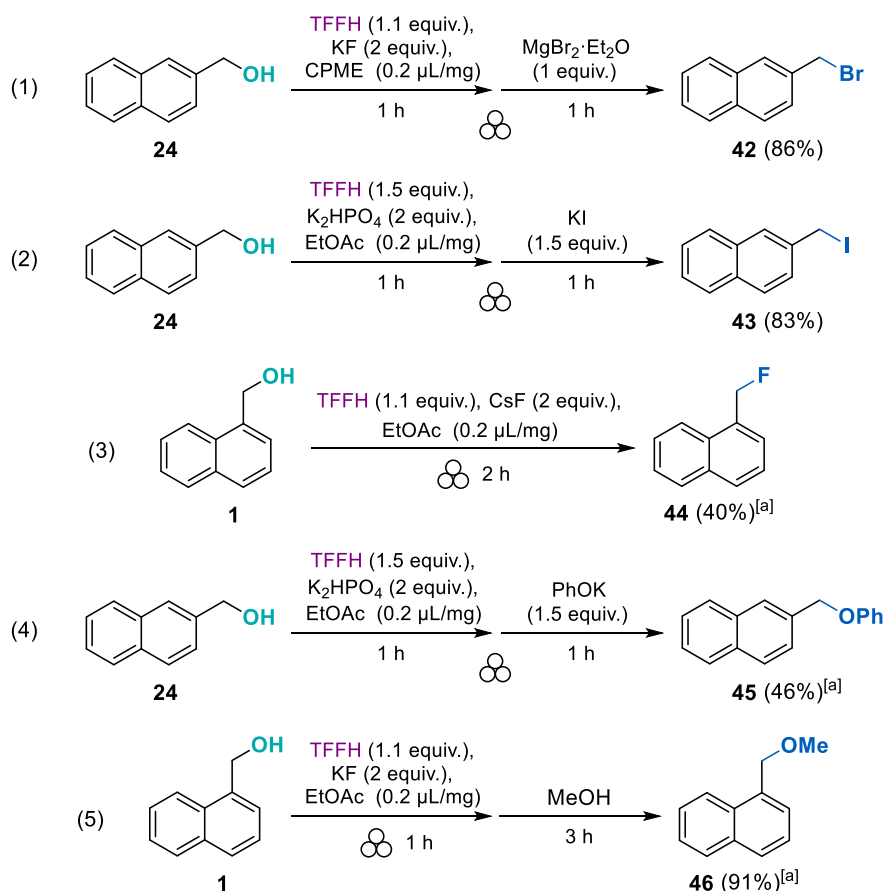
Scheme 7. The substitution reactions of naphthalenemethanols with various nucleophiles. [a] ^{1}H NMR yield.

Conclusion

In conclusion, we have developed a new mechanochemical protocol for nucleophilic substitution of alcohols by applying TFFH as an activator and K_2HPO_4 as a non-toxic inorganic base. This combination of reagents enables fast (within 1 h) and effective conversion of alcohols into reactive *O*-alkyl isouronium salts under ball milling conditions with sustainable solvents (EtOAc, CPME) as LAG additives. We showed for the first time that *O*-alkyl isouronium salts could act as highly reactive activated derivatives of alcohols in nucleophilic displacement reactions with amines, under mechanochemical conditions or in solution. Thus, mechanochemically generated isouronium intermediates afforded a range of *N*-alkylated amine products in 40–91% yield after ball milling with amines in the same reaction vessel. Complete stereoinversion was attained in the substitution reactions of ethyl (*S*)- and (*R*)-lactates with morpholine, while enolizable α-hydroxy esters could result in reduced or even fully demolished optical purity of the product. The developed substitution protocol is particularly efficient for reactive alcoholic substrates like primary benzylic alcohols. However, steric hindrances (tertiary, secondary substrates) or reduced reactivity in nucleophilic displacement reactions (aliphatic substrates) could substantially reduce the yield of amine products or even prevent the reaction from occurring. These limitations were advantageous when performing chemoselective transformations, such as substituting a primary benzylic alcohol in the presence of a tertiary alcoholic function. A striking difference in the chemoselectivity of fluoro- and chlorouronium coupling reagents (TFFH vs. TCFH) allowed performing amide coupling of 4-(hydroxymethyl)benzoic acid with an unprotected benzylic alcohol moiety. The developed process expands the synthetic portfolio of mechanochemical reactions. It can serve as a beneficial supplement to the existing C–N bond-forming protocols, which are suitable for multistep mechanosynthesis of APIs with a decreased environmental impact and a better safety profile.

Experimental Section

Detailed information about optimization studies, experimental methods and the corresponding structure characterization data are given in the Supporting Information.

Acknowledgements

Conflict of interest

The authors declare no conflict of interest.

Keywords: mechanochemistry • solvent-free chemistry • amines • isouronium • alcohols • pharmaceuticals • nucleophilic substitution

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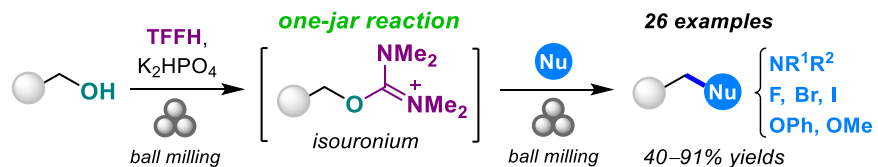
Towards greener amine synthesis: Nucleophilic substitution of alcohols via reactive isouronium salts under mechanochemical one-jar reaction conditions is presented for the first time. The method opens access towards biologically active amines, including active pharmaceutical ingredients.

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