RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2020, **10**, 25029

One-pot method for the synthesis of 1-aryl-2-aminoalkanol derivatives from the corresponding amides or nitriles†

Jan Otevrel, ‡* David Svestka‡ and Pavel Bobal *

Received 15th May 2020
Accepted 9th June 2020

DOI: 10.1039/d0ra04359a

rsc.li/rsc-advances

We have identified a novel one-pot method for the synthesis of β-amino alcohols, which is based on C–H bond hydroxylation at the benzylic α-carbon atom with a subsequent nitrile or amide functional group reduction. This cascade process uses molecular oxygen as an oxidant and sodium bis(2-methoxyethoxy) aluminum hydride as a reductant. The substrate scope was examined on 30 entries and, although the respective products were provided in moderate yields only, the above simple protocol may serve as a direct and powerful entry to the sterically congested 1,2-amino alcohols that are difficult to prepare by other routes. The plausible mechanistic rationale for the observed results is given and the reaction was applied to a synthesis of a potentially bioactive target.

Introduction

A 1,2-amino alcohol moiety is one of the most prominent structural components in a vast group of naturally occurring and synthetic molecules. The majority of the *vic*-amino alcohol-containing molecules are chiral and, although they are often used in their racemic forms, the desired properties or activities are usually associated with a single enantiomer.[1] The above compounds in their enantiopure forms provide attractive synthetic intermediates for the bioactive agents and also important subunits for construction of the chiral auxiliaries, ligands or scaffolds for stereoselective syntheses.[2] Hence the actively pursued research area of novel, more efficient, and selective synthetic transformations of these potent building blocks represents one of the ultimate goals in current organic chemistry.

As the research in this field is vibrant, a number of possible routes for the β-amino alcohol synthesis including their enantioselective versions have been described and well-reviewed in the literature.[2b,3] Accordingly, five general protocols have been established: (1) functional group interconversions of compounds with both heteroatoms already present in the molecule, such as a reduction of nitroaldols, cyanohydrins, azidohydrins, amino acids, amino ketones, hydroxy imines, *etc.*;[4] (2) ring-opening of epoxides and aziridines;[5] (3) addition of a single heteroatom to a molecule already containing oxygen or nitrogen functionality;[2b] (4) introduction of both heteroatoms in a single process, *i.e.* by aminohydroxylation or oxidative nitration;[6] (5) C–C bond-forming reactions including 1,2-additions to α-hydroxy imines and α-amino aldehydes.[7]

Compared to other methods, the introduction of oxygen to a molecule already containing a nitrogen functionality is not a common approach for the synthesis of β-amino alcohols and hence remained considerably underexplored. Several reactions providing entry into this interesting pathway mainly comprise of the addition of *O*-nucleophiles to α,β- or β,γ-unsaturated amines[3a,8] and nitroolefins,[9] hydroboration–oxidation of enamines[8] or the Schlenck ene reaction.[10] Herein we disclose another, conceptually different method, which is based on a protocol including α-carbon atom hydroxylation and amide or nitrile functional group reduction.

In connection with our interest in the development of organocatalysts for the asymmetric aldol-type reactions, we have been continuously compelled to explore novel chiral auxiliaries for the catalyst design and screening. As part of the above synthetic efforts, we have prepared many chiral non-racemic amine scaffolds by reductions of the corresponding enantiopure amides.[11]

For such transformations, we normally utilized sodium bis(2-methoxyethoxy)aluminum hydride (SMEAH) as a reductant.[12] In comparison to lithium aluminum hydride (LAH), SMEAH is much better soluble, easier to handle, insensitive to dry air, thermally stable (<205 °C), and non-violently reacting with water, which makes it an invaluable reducing agent for both laboratory and industrial use.[13] Although it has been documented that SMEAH exhibited a unique reactivity and selectivity in some cases,[13,14] we have been using it as an equivalent reagent to LAH for numerous amide reductions.

Department of Chemical Drugs, Faculty of Pharmacy, Masaryk University, Palackeho 1946/1, 612 42 Brno, Czech Republic. E-mail: pbobal@icloud.com; otevrel@icloud.com

† Electronic supplementary information (ESI) available: ESI contains optimization, mechanistic experiments, HPLC, NMR, GC/MS, and HRMS data for compounds **1–10**. See DOI: 10.1039/d0ra04359a

‡ These authors contributed equally.

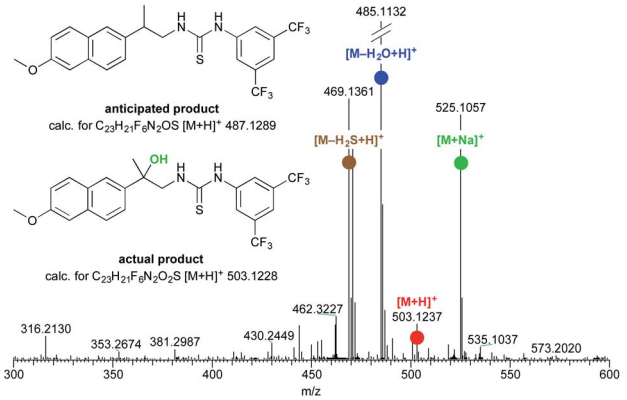


Fig. 1 Partial HRMS spectrum showing the formation of the unexpected product.

However, (*S*)-naproxamide subjected to the above reaction conditions gave a curious product, which was then, to our surprise, identified as 1,2-amino alcohol derivative (Fig. 1). From the initial insights, the formation of this unexpected substance seemed to be favored by a longer reaction time together with a large excess of SMEAH. As this represented, to the best of our knowledge, the only example of the organic transformation that enabled a direct conversion of the primary amide to the appropriate *vic*-amino alcohol derivative, it stimulated us into a research of this interesting phenomenon in more detail.

Results and discussion

The naproxamide was chosen as a model substrate for a further optimization study (Tables S1–S3†). At first, we investigated the loading of the hydride. Although the maximum yield of the β-amino alcohol was achieved with 20 equiv. of SMEAH, 15 equiv. were used in further optimization protocol as it represented the best balance between the hydride consumption and the product yield. Simultaneously the optimal reaction temperature was established to 25 °C. We found that either elevated or diminished reaction temperature led to a drop in the product yield. Moreover, even a slightly elevated reaction temperature (55 °C) caused a significant decrease in the **3a**/**4a** product ratio. Next, several different complex metal hydrides were screened under the above reaction conditions. Accordingly, SMEAH provided the highest ratio of **3a**/**4a** (84 : 16) and DIBAH gave almost pure **4a** (>99%), whereas reductions with LAH and lithium dimethoxyaluminum hydride (LMAH) proceeded with the selectivity somewhere in between the two above-mentioned extremes (Fig. 2). Such results indicate the unique properties of SMEAH in this particular reduction, which justified its selection for further optimization steps.

Further, we examined other reaction solvents besides toluene, such as diethyl ether, glyme, dioxane, and THF. The highest selectivity towards the 1,2-amino alcohol formation was reached by performing the reduction in anhydrous THF (**3a**/**4a** = 92 : 8). Although a pretty good selectivity was obtained at this stage, we were still discouraged by a poor yield (21%) and a very long reaction time, which was necessary for completion of the reaction (>48 h). Finally, the optimization of the reaction atmosphere proved to be the major turning point. The switching of the previously used argon atmosphere to dry air and then oxygen dramatically enhanced both the reaction rate and the yield.

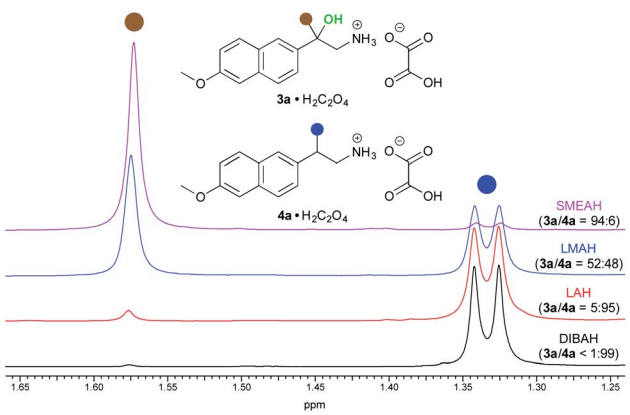
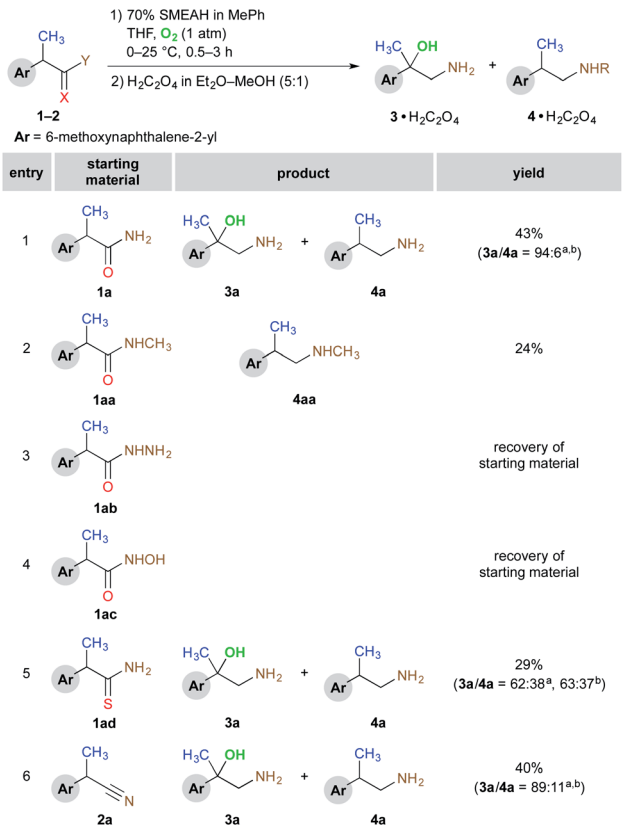
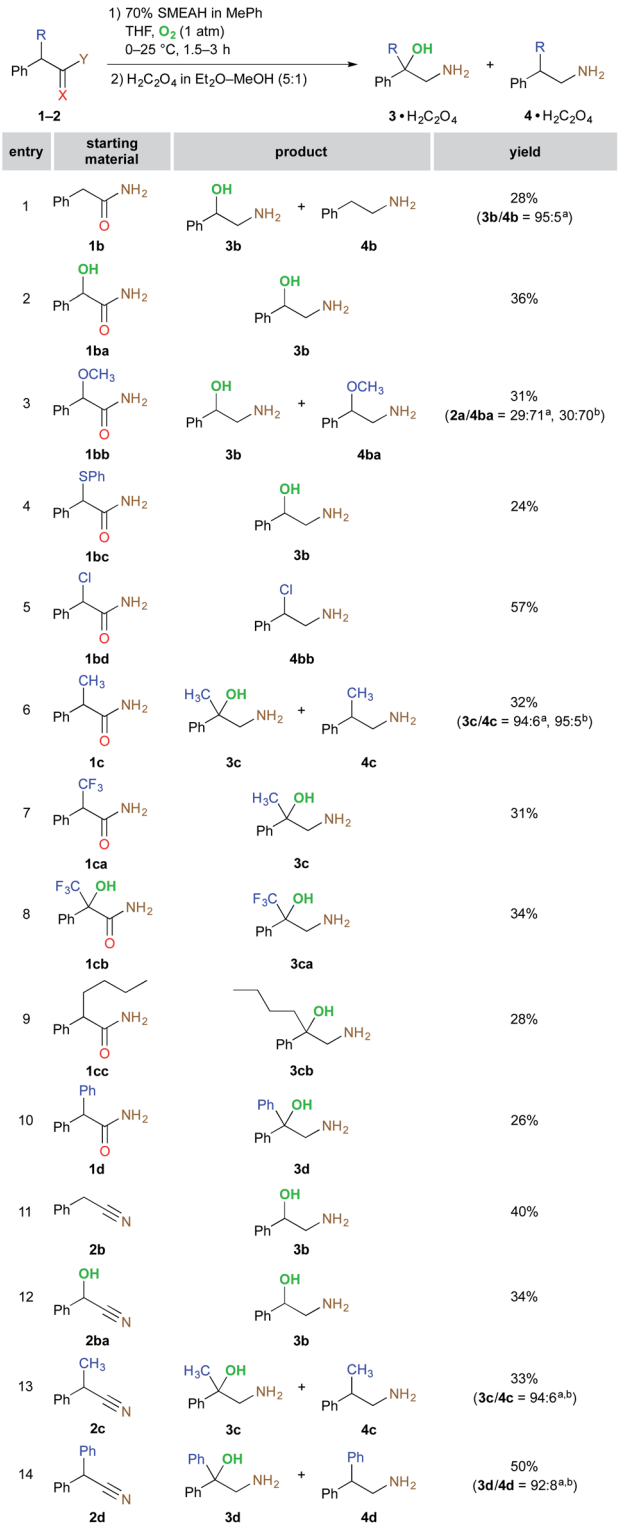


Fig. 2 Partial ^{1}H NMR (400 MHz, DMSO-d_6, 35 °C) spectra showing the **3a**/**4a** ratio affected by the type of the complex metal hydride.



Scheme 1 The functional group scope of the SMEAH-mediated process. Notes: the reductions were performed at the 1.3 mmol scale; the yields refer to the isolated products; [a]the product ratio determined by RP-HPLC analysis; [b]the product ratio determined by ^{1}H NMR analysis.

Consequently, the desired product was furnished in 43% yield in less than 3 h even with the slightly improved selectivity (**3a**/**4a** = 94 : 6). Further attempts to increase the product yield were unsuccessful. Nevertheless, according to our experience, the analogous LAH reductions of 2-arylalkanoic acid amides or nitriles to amines also barely exceeded isolated yields of 50–60%.



entry	starting material	product	yield
1	**1b**	**3b** + **4b**	28% (**3b**/**4b** = 95:5[a])
2	**1ba**	**3b**	36%
3	**1bb**	**3b** + **4ba**	31% (**2a**/**4ba** = 29:71[a], 30:70[b])
4	**1bc**	**3b**	24%
5	**1bd**	**4bb**	57%
6	**1c**	**3c** + **4c**	32% (**3c**/**4c** = 94:6[a], 95:5[b])
7	**1ca**	**3c**	31%
8	**1cb**	**3ca**	34%
9	**1cc**	**3cb**	28%
10	**1d**	**3d**	26%
11	**2b**	**3b**	40%
12	**2ba**	**3b**	34%
13	**2c**	**3c** + **4c**	33% (**3c**/**4c** = 94:6[a,b])
14	**2d**	**3d** + **4d**	50% (**3d**/**4d** = 92:8[a,b])

Scheme 2 Variation of the α-substituent of substrates. Notes: the reductions were performed at the 1.3 mmol scale; the yields refer to the isolated products; [a]the product ratio determined by RP-HPLC analysis; [b]the product ratio determined by ^{1}H NMR analysis.

In the following task, we investigated the scope of possible functional groups that undergo the β-amino alcohol-forming process. The obtained data is summarized in Scheme 1. Accordingly, the appropriate *N*-methylamide (**1aa**), hydrazide (**1ab**), hydroxamic acid (**1ac**), thioamide (**1ad**), and nitrile (**2a**) derivatives of the model compound were tested under the optimized reaction conditions. The above *N*-methylamide (**1aa**) provided a regular *N*-methylamine (**4aa**) instead of the desired *N*-methylamino alcohol, while the respective reaction of hydrazide (**1ab**) or hydroxamic acid (**1ac**) resulted only in a complete recovery of starting material. These experiments have confirmed that the corresponding *N*-substituted derivatives failed to provide β-amino alcohol products under the screening conditions. Amongst other tested functional groups, the best results in terms of the selectivity towards the formation of **3a** were obtained with the amide (**1a**) and nitrile (**2a**) functions. Therefore these types of substrates were selected for the tests henceforth.

Following the optimization of the functional groups, the feasible substituents of the α-position of substrates were evaluated (Scheme 2). The α-oxidation of the compound **1b** lacking the α-substituent turned out to be even more sensitive to the reaction atmosphere than **1a** as the selectivity towards the 1,2-amino alcohol formation (**3b**/**4b**) was improved from 81 : 19 to 95 : 5 by replacing Ar by O_2 (Fig. S10–11†). The control α-OH bearing substrate **1ba** was reduced under the identical reaction conditions to the sole **3b** in 36% yield. The SMEAH-mediated reduction of the α-methoxy and α-phenylsulfanyl functionalized derivatives **1bb** and **1bc** led at least partially to a displacement of the original α-substituent by OH group. On the contrary, the α-chlorine was preserved and **1bd** yielded the regular 1,2-chloroamine **4bb** in 57%. The α-alkyl and α-aryl derivatives **1c**, **1cc**, and **1d** afforded the respective β-amino alcohols in excellent selectivities and modest yields. Surprisingly, reduction of the α-CF_3 substituted **1ca** provided the completely hydrodefluorinated derivative **3c** identical to the product of the reaction of **1c**. On the other hand, the corresponding α-OH analog thereof (**1cb**) did not exhibit any detectable defluorination under the above reaction conditions. According to these observations and the available literature,[14d,15] we have postulated a plausible hypothesis that defluorination of the CF_3 group of **1ca** could be driven by a series of fluoride β-elimination – hydride addition events of the intermediary α-carbanion leading to **1c** that is then converted to the β-amino alcohol **3c**. This is also supported by the fact that the respective α,α-disubstituted derivative **1cb** did not lose any of the fluorine atoms during the reduction.

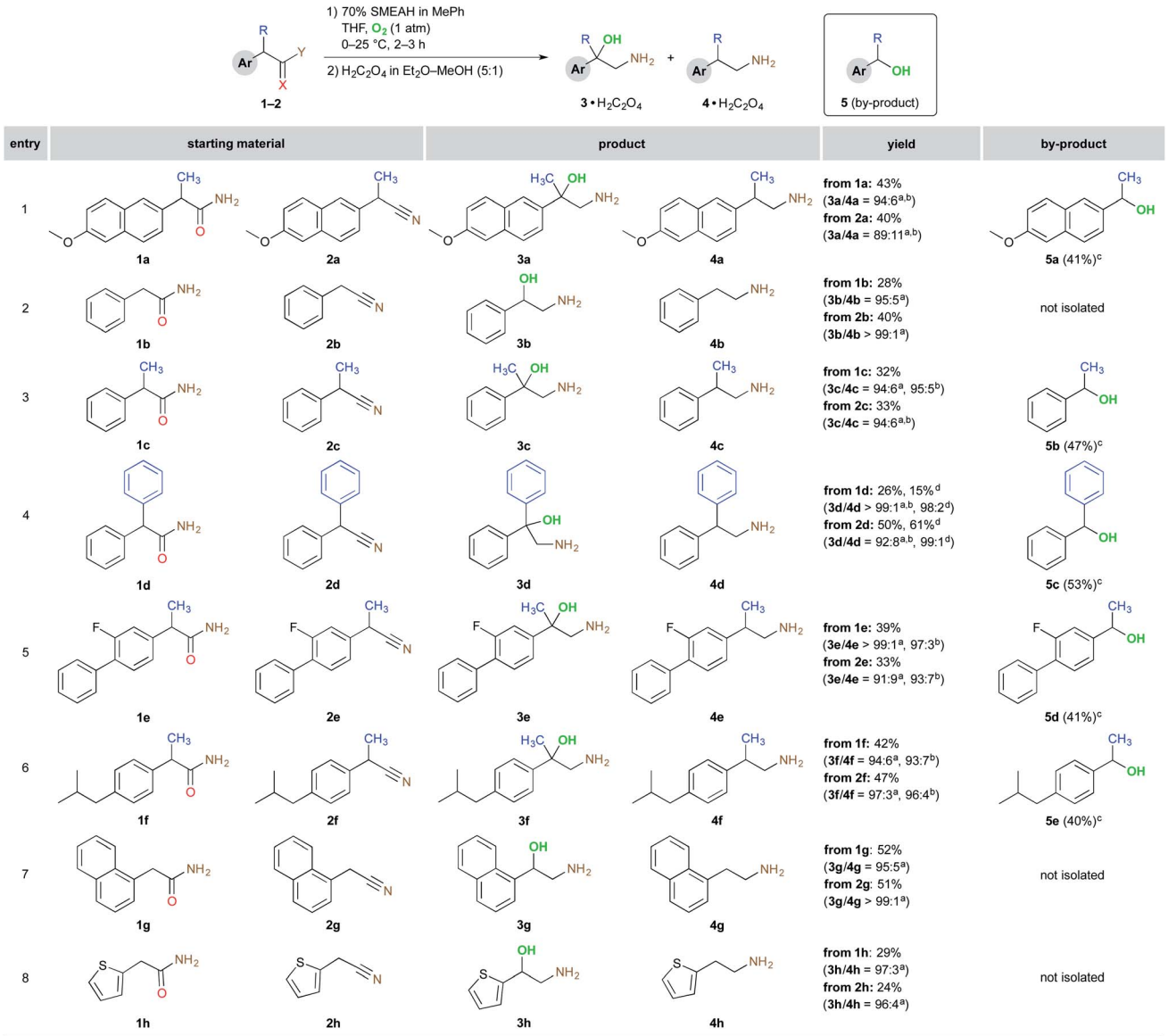
Next, we tested also several nitrile derivatives **2b**, **2ba**, **2c**, and **2d**, which gave the results comparable with the amide partners regarding both the yield and the selectivity. The remaining amides **1e–h** and also their nitrile counterparts **2e–h** together with **1a–d** and **2a–d** are presented in Scheme 3.

In all the described experiments, the corresponding 1,2-amino alcohols were isolated by simple filtration of their oxalic

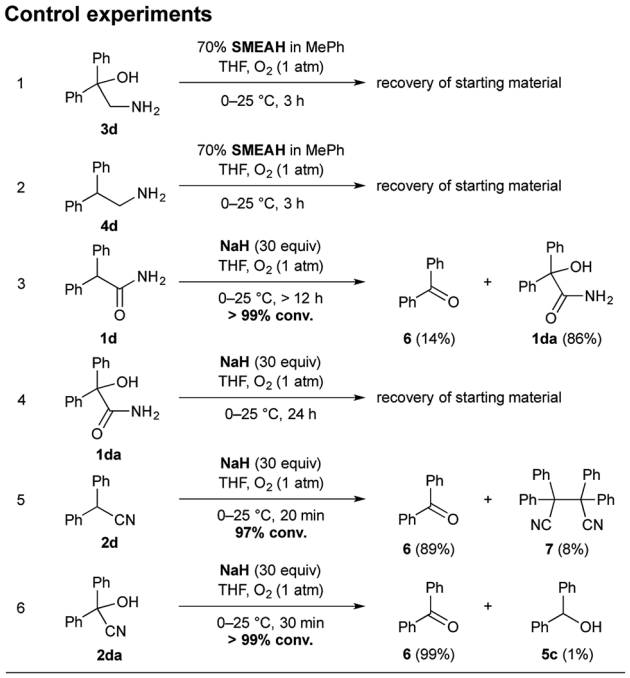
acid salts. After isolation of the respective ammonium salts, the filtrate afforded the one-carbon-shorter alcohol as a predominant by-product in all the displayed entries. However, the corresponding dehomologated alcohols were isolated and purified only in the instance of the α-substituted derivatives (entries 1 and 3–6), where this method, in contrast to the α-unsubstituted **1b** and **1g–h**, can constitute at least an interesting route for the synthesis thereof.

As depicted in Schemes 1–3, the reaction tolerated well hydrogen, alkyl or aryl substituents at the benzylic position. Aromatic substitution may comprise alkyl and alkoxy groups. Aryl halides such as fluorine also remained practically untouched, however, in the case of aryl chloride, we have encountered dehalogenation on a significant level,[16] which was also documented in the literature.[17] In summary, it should be emphasized that although the reduction power of SMEAH is attenuated in comparison with the parent LAH due to the presence of two bulky and electron-withdrawing alkoxy groups, it is still a very powerful reducing agent and, as such, it is incompatible with almost any reducible functional group in a molecule. Thus, these properties considerably limit the chemoselectivity of the present process.[13b,13c]

To establish a plausible mechanistic proposal, a series of experiments with **1d**, **2d**, and other diphenyl substituted derivatives were performed. Initially, the respective products **3d** and **4d** were subjected to the standard reaction conditions (entries 1–2, Scheme 4). The full recovery of the unchanged material in both the cases supported that, according to our expectations, there is no detectable interconversion between the



Scheme 3 The substrate scope of the SMEAH-mediated process. Notes: the reductions were performed at the 1.3 mmol scale; the yields refer to the isolated products; [a]the product ratio determined by RP-HPLC analysis; [b]the product ratio determined by ^{1}H NMR analysis; [c]the product yield isolated from the reaction involving substrate **1**; [d]the product yield and ratio obtained from the reaction with added NaCN (10 equiv.).



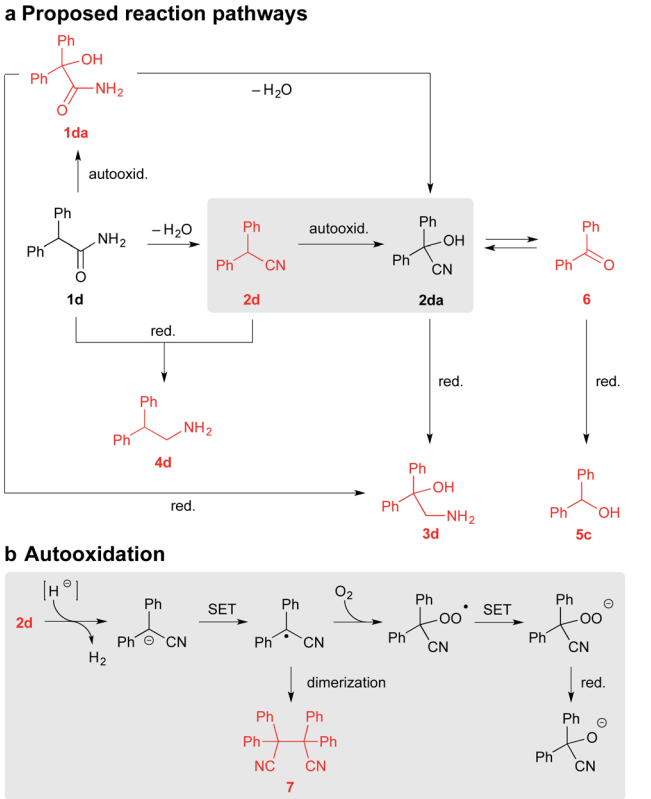
Scheme 4 Control experiments with **3d**, **4d**, **1d**, **1da**, **2d**, and **2da**. Notes: the yields were determined by RP-HPLC analysis using the external standard calibration.

products and that the oxidation of the α-carbon precedes the functional group reduction step.

As mentioned above, the SMEAH-mediated reduction of **1d** provided the oxalic acid salt of **3d** as a sole product in the precipitate and **5c** as a predominant side product in the filtrate.[18]

The subsequent analysis of the filtrate and particularly the fore fractions obtained during the purification of **5c** by column chromatography (SiO_2) *n*-heptane–EtOAc (9 : 1), revealed the minor and trace components **1da**, **2d**, **6**, and 7, which were further confirmed by comparison with the authentic samples. The presence of **2d** and 7 in the reaction mixture of **1d** led us to assume that reduction of the primary amide likely involved intermediacy of the nitrile (Scheme 5).[4] Moreover, if we consider that the respective nitrile **2d** gave a similar product profile with the comparable selectivity in even better yield and shorter reaction time than the corresponding amide **1d** (Scheme 4), it seems plausible to suppose that both **1d** and **2d** could share a common reduction pathway. The above hypothesis is also in connection with the aforementioned incapability of the secondary amides to undergo the present process.

It has been reported earlier that a striking difference between the reduction properties of SMEAH and LAH towards nitriles was found with reductions of compounds carrying hydrogen atom at α-carbon, which proceeded unsatisfactorily with SMEAH. Hence the majority of the starting nitrile was always recovered on workup.[19] These findings were also validated by us when the above reaction was conducted under the strictly oxygen-free conditions.



Scheme 5 The working hypothesis of the possible reduction and oxidation pathways (a) and the plausible autooxidation process under basic conditions (b). Notes: the intermediates shown in red were successfully isolated from the reaction mixture of **1d**; metal counter-ions were omitted for clarity.

Therefore we have hypothesized that the nitrile intermediate **2d**, which can be only α-deprotonated but not efficiently further reduced by SMEAH, is present in the reaction mixture as a colored resonance-stabilized nitrile anion. The small portion of the reduced substrate **2d** is likely responsible for a formation of the minor by-product **4d**, which can become more significant under elevated temperature.[20] Under basic conditions, the electron-rich nitrile anions are susceptible to autooxidation *via* single-electron transfer (SET).[21] Hence, the anion of **2d** is probably trapped by O_2 to the corresponding α-hydroperoxy nitrile, which is then rapidly reduced to the cyanohydrin **2da** and the successive species (Scheme 5). This presumption was supported by the identification of the corresponding radical homocoupling product 7 from the above reaction mixture.

Since cyanohydrins are formed reversibly, they are considered to be unstable in basic media (entry 6, Scheme 4). Especially for cyanohydrins that are sterically hindered, the position of the equilibrium is unsatisfactory for the effective synthesis thereof. Therefore, cyanohydrins encumbered with bulky substituents are rather prone to the elimination of cyanide ion and the formation of the corresponding dehomologated carbonyl compounds.[22]

Our findings indicate that the moderate yields of β-amino alcohols in the present transformation are probably caused by

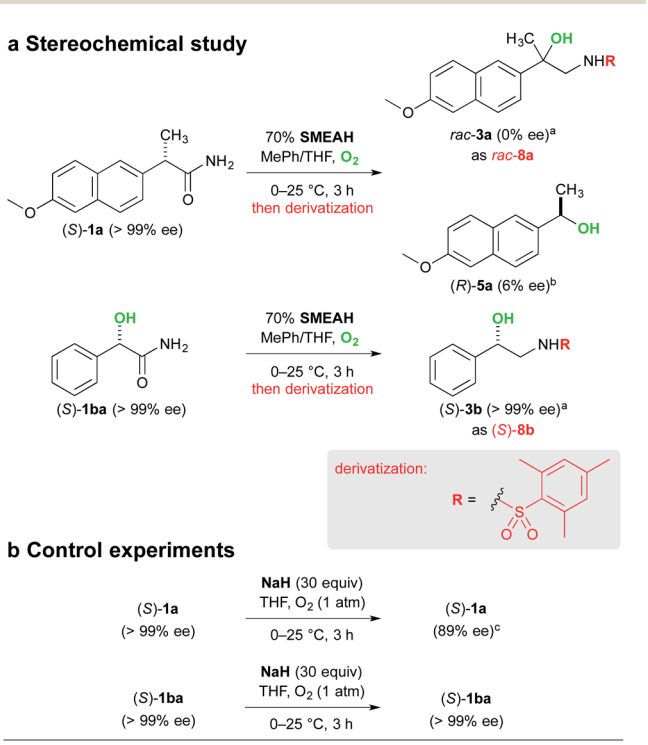
the previously mentioned retro-cyanohydrination (Scheme 5). These speculations were also supported by isolation of traces of the ketone **6** from the SMEAH-driven reductions of **1d**, **1da**, **2d**, and **2da**.[23]

Under the above conditions, the presumptive α-hydroxy nitrile intermediate **2da** can undergo either reduction to the desired β-amino alcohol **3d** or expulsion of cyanide anion to **6**. The resulting degraded carbonyl compound **6** is then readily reduced to the alcohol **5c** by the hydride. To further prove this hypothesis, the separately prepared cyanohydrin **2da** was subjected to identical reaction conditions. Accordingly, **4d** and **5c** were isolated as the major products. However, in comparison with the reaction starting from **1d** or **2d**, the desired β-amino alcohol **4d** was obtained in a somewhat decreased yield (21%). Expectably, the yield of the corresponding alcohol **5c** was slightly increased in this case (63%). Thus we suppose that the continuous reduction of cyanohydrin generated *in situ* during the present process is likely beneficial to the batch reduction of **2da**, as it eliminates the excessive decomposition of this relatively labile compound by retro-cyanohydrination. Besides that, we have found that the formation of **5c** was favored over **3d** mainly under a diminished reaction temperature (<0 °C). This likely corresponds to the instability of **2da** in a basic environment for the extended period necessary for the slower reduction thereof under a decreased temperature.

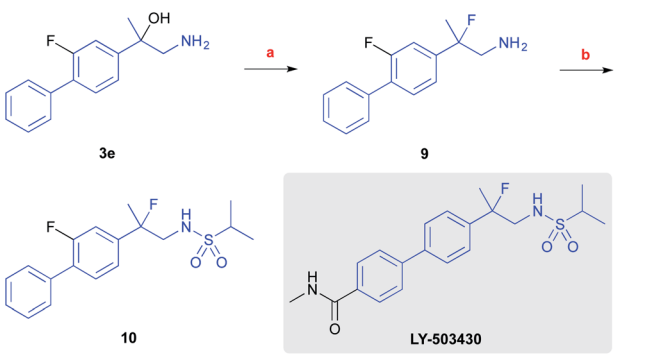
We further speculated whether the hypothetically employed decyanation of **2da** might be suppressed by raising the concentration of free cyanide in the reaction medium according to Le Chatelier's principle. Indeed, the addition of powdered NaCN (10 equiv.) to the reaction mixture of **2d** furnished a slightly increased yield of **3d** (50% → 61%) after the prolonged reaction time (3 h) with the improved selectivity expressed by **3d**/**4d** (92 : 8 → 99 : 1, Fig. S35–37†).

Although the residues of **1da** were also detected in the SMEAH-mediated reduction involving **1d**, the autooxidation of **1d** to **1da** presumably constitutes only a less important path in the overall process. Based on the control experiment with sodium hydride, the reaction time longer than 12 h was required for completion in this case, which is in contrast to the rapid autooxidation of **2d** under the same conditions (entries 3 and 5, Scheme 4). Moreover, the analogous reaction of **1a** with NaH under O_2 atmosphere did not provide any product even after 24 h, which suggests that α-oxidation of nitriles is considerably faster in comparison with the parent primary amides. The subjection of α-hydroxy amide **1da** to the control experiment with NaH resulted in the complete recovery of starting material (entry 4, Scheme 4). On the other hand, the SMEAH-driven reaction thereof afforded both **3d** and **5c** as the major products in accordance with **1d**, **2d**, and **2da**. Hence we suppose that the possible reaction pathways of all the aforementioned derivatives with SMEAH can plausibly proceed as depicted in Scheme 5.

The analysis of the stereochemical course of the reaction involving (*S*)-naproxamide (*S*)-**1a** gave us evidence for complete racemization of the optically pure substrates lacking the α-hydroxy group during the reaction. It is in agreement with our assumption that the initial α-proton abstraction and mainly the subsequent radical isomerization led to the loss of the stereochemical integrity (Scheme 6).[24] The respective alcohol **5a** was isolated from the reaction mixture of (*S*)-**1a** as a slightly enriched (*R*)-isomer (6% ee).[25] This phenomenon is not yet clearly understood by us but might be attributed to the asymmetric reduction of the corresponding ketone **6** by a non-racemic complex of the hydride with the substrate or some chiral intermediate. To the contrary, (*S*)-mandelamide (*S*)-**1ba** subjected to identical reaction conditions furnished (*S*)-**3b** with



Scheme 6 Analysis of the stereochemical outcome of the SMEAH-mediated process. Notes: [a]determined by the CSP-HPLC of the 2-mesitylenesulfonyl derivative **8** (Chiralpak IA); [b]determined by the CSP-HPLC (Chiralpak IB); [c]specific optical rotation decreased from +18 to +16 (*c* 0.5, MeOH).



Scheme 7 Synthesis of the LY-503430 analog. Conditions: (a) 65% HF-pyridine, CH_2Cl_2, rt, 24 h (y. 69%); (b) i-$PrSO_2Cl$, Et_3N, DMAP, CH_2Cl_2, 0 °C, 3 h (y. 37%).

retention of its configuration, which suggests that the α-hydroxy-substituted stereocenter remained unaffected.

To showcase the synthetic utility of the developed process, we have prepared the racemic fluoro-analog of the biarylpropylsulfonamide potentiator of AMPA receptors, LY-503430, by our reaction (Scheme 7).[26] Accordingly, the respective β-amino alcohol product **3e** was subjected to the fluorodehydroxylation reaction with the Olah's reagent to afford the respective 1,2-fluoroamine **9** in 69% yield. This intermediate was further converted to the sulfonamide **10** using isopropylsulfonyl chloride (y. 37%).

Conclusions

In summary, we have demonstrated that amides and nitriles bearing hydrogen atoms at benzylic α-carbon exhibit a unique reactivity towards SMEAH under O_2 atmosphere. Performing the reaction under dry oxygen allows radical α-hydroxylation to precede amide or nitrile functional group reduction and thus both these steps can take place in a single cascade process. Although the respective products were isolated in the modest yields only with somewhat limited chemoselectivity, the above one-pot protocol could be used as a powerful entry to the 1,2-amino alcohols, especially the sterically encumbered ones, that are often difficult to prepare by other routes. The present method may also open up attractive prospective routes for future developments in ^{18}O-labeling strategies or stereoselective synthesis thereof. The plausible mechanistic proposal for the observed results was given based on the isolation and identification of the stable intermediates and stereochemical evidence. Finally, the process was applied to the synthesis of a potentially bioactive target.

Experimental

Materials and methods

If not stated otherwise, all experiments were performed standardly under open-vessel conditions. Moisture and air-sensitive reactions were done in oven-dried glassware (140 °C) under Ar atmosphere in anhydrous solvents. Solvents and reagents were purchased from commercial suppliers and used as received, if not stated otherwise. Flurbiprofen and naproxen were extracted from the commercially available formulations. Naproxamide (**1a**) and lithium dimethoxyaluminum hydride (LMAH) were prepared according to the literature.[11c,27] Anhydrous solvents and reagents were absolutized as usual and distilled prior to use. The specific rotation was determined by an automatic polarimeter AA-10 (Optical Activity). Melting points were measured by a Böetius apparatus (Franz Küstner Nachf.) and are uncorrected. HPLC data were recorded on a Dionex UltiMate 3000 LC System and a Spectra-System (ThermoFisher Scientific). IR spectra were collected on a SmartMIRacle ATR (diamond) for a Nicolet Impact 410 FT-IR (ThermoFisher Scientific). NMR spectra were obtained from a JEOL ECZR-400 MHz (Jeol). NMR experiments were standardly performed at 25 °C ($CDCl_3$) or 35 °C (DMSO-d_6), chemical shifts are reported in δ parts per million (ppm) and J values in Hz, the signal of TMS or the residual solvent signals of $CDCl_3$ or DMSO-d_6 were used as a reference. GC/MS data were collected on a system consisting of a gas chromatograph Agilent 7890A and a mass spectrometer Agilent 5975C inert XL with TAD (Agilent Technologies). HRMS measurements were performed using a LTQ Orbitrap XL high-resolution mass spectrometer (ThermoFisher Scientific) and a Bruker Impact II Q-TOF high-resolution mass spectrometer (Bruker Daltonics).

Synthetic procedures

2-(6-Methoxynaphthalen-2-yl)-*N*-methylpropanamide (1aa). Naproxen (1.15 g, 5.1 mmol) was treated with oxalyl chloride (2.2 mL, 5.0 equiv.) and the resulting solution was left to stir for 30 min at rt under Ar. The excess of oxalyl chloride was evaporated *in vacuo*. The obtained acyl chloride was added to the ice-cold aqueous $MeNH_2$ (25%, 15 mL) portionwise and the resulting mass was left to stir for 30 min at rt. Then the mixture was repetitively extracted with EtOAc, the combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, filtered, and evaporated *in vacuo*. Yield: 1.09 g (89%). Physical state: white powder. Mp 105–107 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 7.81–7.80 (m, 1H), 7.78–7.70 (m, 3H), 7.43 (dd, J = 8.5, 1.7 Hz, 1H), 7.26 (d, J = 2.3 Hz, 1H), 7.14 (dd J = 8.9, 2.5 Hz, 1H), 3.86 (s, 3H), 3.69 (q, J = 7.0 Hz, 1H), 2.57 (d, J = 4.6 Hz, 3H), 1.41 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 173.6, 156.9, 137.4, 133.0, 128.9, 128.3, 126.4, 126.3, 125.1, 118.4, 105.7, 55.0, 45.0, 25.5, 18.5; IR (neat) $\tilde{\nu}$/cm^{-1}: 3298m, 1645s, 1606m, 1552m, 1504m, 1390m, 1263m, 1210s, 1162m, 1030s, 924m, 892m, 855s, 812s, 690m; HRMS (ESI-Q-TOF) m/z: calcd for $C_{15}H_{18}O_2N$ $[M + H]^+$ 244.1332, found 244.1339.

2-(6-Methoxynaphthalen-2-yl)propanehydrazide (1ab).[28] Prepared from naproxen (1.00 g, 4.4 mmol), oxalyl chloride, and aqueous N_2H_4 (25%, 15 mL) analogously to **1aa**. Yield: 0.87 g (81%). Physical state: white powder. Mp 94–96 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 9.17 (s, 1H), 7.78–7.72 (m, 3H), 7.46–7.44 (m, 1H), 7.26 (s, 1H), 7.15–7.13 (m, 1H), 4.20 (s, 2H), 3.86 (s, 3H), 3.66 (q, J = 6.9 Hz, 1H), 1.42 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 172.8, 156.9, 137.1, 133.1, 129.0, 128.3, 126.43, 126.39, 125.2, 118.4, 105.7, 55.1, 43.2, 18.3; IR (neat) $\tilde{\nu}$/cm^{-1}: 3277m, 2958w, 1633s, 1606m, 1527w, 1480w, 1392m, 1263m, 1213s, 1162w, 1036m, 985w, 882m, 845s, 815m, 693s; HRMS (ESI-Orbitrap) m/z: calcd for $C_{14}H_{17}N_2O_2$ $[M + H]^+$ 245.1285, found 245.1285.

***N*-Hydroxy-2-(6-methoxynaphthalen-2-yl)propanamide (1ac).**[29] A suspension of methyl naproxenate (1.00 g, 4.1 mmol) and $NH_2OH \cdot HCl$ (0.57 g, 8.2 mmol) in dry MeOH (10 mL) was treated dropwise with a freshly prepared solution of sodium methoxide (0.66 g, 12.3 mmol) in MeOH (7 mL). The resulting mixture was left to stir at rt for 24 h under Ar. Then the suspension was poured into water (50 mL) and acidified with glacial acetic acid. The precipitate was filtered off, washed with water and dried. Yield: 0.76 g (76%). Physical state: white powder. Mp 152–153 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 10.64 (br s, 1H), 8.75 (br s, 1H), 7.79–7.72 (m, 3H), 7.45 (dd, J = 8.4, 1.3 Hz, 1H), 7.27 (d, J = 2.2 Hz, 1H), 7.14 (dd, J = 8.9, 2.4 Hz,

1H), 3.86 (s, 3H), 3.58 (q, $J = 7.0$ Hz, 1H), 1.42 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 170.4, 157.0, 137.0, 133.2, 129.1, 128.3, 126.6, 126.5, 125.3, 118.6, 105.7, 55.1, 42.1, 18.2; IR (neat) $\tilde{\nu}$/cm^{-1}: 2900br, 1605s, 1503w, 1484m, 1392m, 1261m, 1213s, 1163m, 1068w, 1027s, 940w, 890w, 858s, 809s; HRMS (ESI-Orbitrap) m/z: calcd for $C_{14}H_{16}NO_3$ $[M + H]^+$ 246.1125, found 246.1131.

2-(6-Methoxynaphthalen-2-yl)propanethioamide (1ad).[30] Prepared from naproxenamide (**1a**, 1.00 g, 4.4 mmol) according to the literature.[30] Product was purified by column chromatography (SiO_2) CH_2Cl_2. Yield: 0.30 g (28%). Physical state: white powder. Mp 140–142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.75–7.70 (m, 3H), 7.65 (br s, 1H), 7.41 (dd, $J = 8.5$, 1.9 Hz, 1H), 6.69 (br s, 1H), 4.20 (q, $J = 7.2$ Hz, 1H), 3.93 (s, 3H), 1.79 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 213.0, 158.0, 136.0, 134.0, 129.3, 128.9, 127.8, 126.1, 126.0, 119.3, 105.8, 55.3, 53.6, 21.3; IR (neat) $\tilde{\nu}$/cm^{-1}: 3404w, 3140w, 1621s, 1600m, 1480m, 1425s, 1394m, 1264m, 1232m, 1207m, 1160m, 1025s, 962w, 852s, 817s, 763m, 696w; HRMS (ESI-Orbitrap) m/z: calcd for $C_{14}H_{14}ONS$ $[M - H]^-$ 244.0802, found 244.0804.

Phenylacetamide (1b).[31] Methyl 2-phenylacetate (1.50 g, 10.0 mmol) in aqueous NH_3 (25%, 15 mL) was left to stir for 24 h at rt. Then the reaction mixture was repetitively extracted with EtOAc, the combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, filtered, and evaporated *in vacuo*. Yield: 0.89 g (66%). Physical state: white powder. Mp 131–133 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 7.46 (br s, 1H), 7.32–7.19 (m, 5H), 6.88 (br s, 1H), 3.37 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 172.2, 136.5, 129.1, 128.1, 126.3, 42.3; IR (neat) $\tilde{\nu}$/cm^{-1}: 3348m, 3164m, 1633s, 1497w, 1413s, 1284w, 1184w, 1073w, 747m, 697s; HRMS (ESI-Orbitrap) m/z: calcd for $C_8H_{10}NO$ $[M + H]^+$ 136.0757, found 136.0756.

2-Hydroxy-2-phenylacetamide (1ba).[32] Prepared from methyl mandelate (1.66 g, 10.0 mmol) analogously to **1b**. Yield: 0.70 g (47%). Physical state: white powder. Mp 127–128 °C (*rac*), 121–122 °C (*S*); $[\alpha]_D^{25}$ +55 (*c* 1.0, THF); lit.[33] +54.5 (*c* 1.0, THF); ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 7.44–7.42 (m, 2H), 7.40 (br s, 1H), 7.35–7.24 (m, 3H), 7.19 (br s, 1H), 6.01 (d, $J = 4.7$ Hz, 1H), 4.85 (d, $J = 4.7$ Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 174.6, 141.4, 127.9, 127.3, 126.5, 73.5; IR (neat) $\tilde{\nu}$/cm^{-1}: 3367m, 3170m, 1633s, 1496w, 1454w, 1411m, 1285w, 1182w, 1058w, 922w, 748m, 694s; HRMS (ESI-Orbitrap) m/z: calcd for $C_8H_8NO_2$ $[M - H]^-$ 150.0561, found 150.0566.

2-Methoxy-2-phenylacetamide (1bb).[34] Prepared from methyl 2-methoxy-2-phenylacetate (1.8 g, 10.0 mmol) analogously to **1b**. Yield: 1.04 g (63%). Physical state: white powder. Mp 105–106 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 7.51 (br s, 1H), 7.41–7.30 (m, 5H), 7.26 (br s, 1H), 4.55 (s, 1H), 3.28 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 172.2, 138.2, 128.1, 127.9, 127.0, 83.3, 56.7; IR (neat) $\tilde{\nu}$/cm^{-1}: 3461m, 3176w, 1695m, 1652s, 1466w, 1411m, 1327w, 1197m, 1086s, 983m, 950w, 813m, 769m, 704s; HRMS (ESI-Orbitrap) m/z: calcd for $C_9H_{12}NO_2$ $[M + H]^+$ 166.086, found 166.0865.

2-Phenyl-2-(phenylsulfanyl)acetamide (1bc).[35] Prepared from methyl 2-phenyl-2-(phenylsulfanyl)acetate (2.58 g, 10.0 mmol) analogously to **1b**. Yield: 1.60 g (66%). Physical state: white powder. Mp 153–155 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 7.71 (br s, 1H), 7.50–7.48 (m, 2H), 7.34–7.19 (m, 8H), 7.17 (br s, 1H), 5.10 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 170.5, 137.5, 135.0, 129.7, 128.9, 128.2, 128.1, 127.6, 126.6, 55.4; IR (neat) $\tilde{\nu}$/cm^{-1}: 3362m, 3174w, 1657s, 1481w, 1454w, 1439w, 1387m, 1237w, 1089w, 805w, 745m 733m; HRMS (ESI-Orbitrap) m/z: calcd for $C_{14}H_{12}ONS$ $[M - H]^-$ 242.0645, found 242.0646.

2-Chloro-2-phenylacetamide (1bd).[36] Prepared from 2-chloro-2-phenylacetyl chloride (0.79 mL, 5.0 mmol) and aqueous NH_3 (25%, 15 mL) analogously to **1aa**. Yield: 0.71 g (84%). Physical state: white powder. Mp 95–97 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 7.80 (br s, 1H), 7.53–7.50 (m, 2H), 7.43 (br s, 1H), 7.41–7.35 (m, 3H), 5.53 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 168.7, 137.5, 128.6, 128.4, 127.8, 59.8; IR (neat) $\tilde{\nu}$/cm^{-1}: 3396m, 3191m, 1650s, 1607m, 1497w, 1453w, 1405m, 1215m, 1178w, 1076w, 851m, 781w, 691m; HRMS (ESI-Orbitrap) m/z: calcd for C_8H_9NOCl $[M + H]^+$ 170.0367, found 170.0374.

2-Phenylpropanamide (1c).[37] Prepared from 2-phenylpropanoic acid (0.75 g, 5.0 mmol), $SOCl_2$ (5 equiv.), and aqueous NH_3 (25%, 15 mL) analogously to **1aa**. Yield: 0.63 g (84%). Physical state: white powder. Mp 84–86 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 7.41 (br s, 1H), 7.33–7.19 (m, 5H), 6.83 (br s, 1H), 3.57 (q, $J = 7.0$ Hz, 1H), 1.30 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 175.4, 142.4, 128.2, 127.3, 126.4, 44.9, 18.5; IR (neat) $\tilde{\nu}$/cm^{-1}: 3349m, 3176m, 1629s, 1496w, 1452w, 1403m, 1287w, 1030w, 850w, 694s; HRMS (ESI-Orbitrap) m/z: calcd for $C_9H_{12}NO$ $[M + H]^+$ 150.0913, found 150.0914.

3,3,3-Trifluoro-2-phenylpropanamide (1ca).[38] Prepared from 3,3,3-trifluoro-2-hydroxy-2-phenylpropanamide (**1cb**, 1.10 g, 5.0 mmol) according to the literature.[38] Yield: 0.75 g (74%) over two steps. Physical state: white powder. Mp 106–107 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 7.72 (br s, 1H), 7.52–7.50 (m, 2H), 7.42–7.40 (m, 3H), 7.33 (br s, 1H), 4.54 (q, $^3J_{HF} = 9.4$ Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 166.5, 130.9, 129.2, 128.6, 128.5, 124.6 (q, $^1J_{CF} = 279.4$ Hz), 53.5 (q, $^2J_{CF} = 26.3$ Hz); ^{19}F NMR (376 MHz, DMSO-d_6) δ/ppm: −65.88 (d, $^3J_{HF} = 8.7$ Hz); IR (neat) $\tilde{\nu}$/cm^{-1}: 3448m, 3322w, 3193w, 1674s, 1616m, 1461w, 1403w, 1357m, 1325w, 1259s, 1149s, 1116s, 1097s, 1035w, 957w, 901m, 851m; HRMS (ESI-Orbitrap) m/z: calcd for $C_9H_7NOF_3$ $[M - H]^-$ 202.048, found 202.0485.

3,3,3-Trifluoro-2-hydroxy-2-phenylpropanamide (1cb).[39] Prepared from 2,2,2-trifluoroacetophenone (2.16 g, 12.2 mmol) according to the literature.[39] Yield: 1.97 g (74%) over two steps. Physical state: white powder. Mp 93–95 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.69–7.66 (m, 2H), 7.45–7.42 (m, 3H), 6.25 (s, 1H), 6.19 (s, 1H), 4.82 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 169.4, 134.0, 129.7, 128.9, 126.2, 123.6 (q, $^1J_{CF} = 285.8$ Hz), 78.1 (q, $^2J_{CF} = 29.2$ Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ/ppm: −74.27 (s); IR (neat) $\tilde{\nu}$/cm^{-1}: 3503m, 3386w, 1697s, 1567m, 1258m, 1194m, 1167s, 1125s, 1080w, 983m, 943m, 769m, 745m; HRMS (ESI-Orbitrap) m/z: calcd for $C_9H_7NO_2F_3$ $[M - H]^-$ 218.0434, found 218.0436.

2-Phenylhexanamide (1cc).[40] Prepared from 2-phenylhexanoic acid (1.06 g, 5.0 mmol), $SOCl_2$ (5 equiv.), and aqueous NH_3 (25%, 15 mL) analogously to **1aa**. Yield: 0.74 g (77%). Physical state: white powder. Mp 93–94 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.36–7.25 (m, 5H), 5.64 (br s, 1H), 5.39 (br s, 1H),

3.37 (t, J = 7.6 Hz, 1H), 2.20–2.11 (m, 1H), 1.83–1.74 (m, 1H), 1.37–1.18 (m, 4H), 0.87 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 176.2, 140.0, 128.8, 127.9, 127.3, 52.8, 32.6, 29.8, 22.5, 13.9; IR (neat) $\tilde{\nu}$/cm^{-1}: 3381m, 3174w, 2933m, 1651s, 1455w, 1413m, 1301w, 1126w, 816w, 755w, 719m, 697s; HRMS (ESI-Orbitrap) m/z: calcd for $C_{12}H_{17}NO$ $[M + H]^+$ 192.1383, found 192.1386.

2,2-Diphenylacetamide (1d).[37] Prepared from 2,2-diphenylacetic acid (1.06 g, 5.0 mmol), $SOCl_2$ (5 equiv.), and aqueous NH_3 (25%, 15 mL) analogously to **1aa**. Yield: 0.78 g (74%). Physical state: white powder. Mp 169–171 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 7.69 (br s, 1H), 7.33–7.28 (m, 8H), 7.24–7.21 (m, 2H), 7.09 (br s, 1H), 4.94 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 173.0, 140.5, 128.5, 128.2, 126.6, 56.3; IR (neat) $\tilde{\nu}$/cm^{-1}: 3386w, 3172w, 1651s, 1496m, 1405m, 1260m, 1103w, 1034w, 845w, 738m, 722m, 697s; HRMS (ESI-Orbitrap) m/z: calcd for $C_{14}H_{14}NO$ $[M + H]^+$ 212.1070, found 212.1075.

2-Hydroxy-2,2-diphenylacetamide (1da).[32] Prepared from methyl benzilate (2.42 g, 10.0 mmol) analogously to **1b**. Yield: 1.29 g (57%). Physical state: white powder. Mp 153–155 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 7.42–7.39 (m, 5H), 7.36 (br s, 1H), 7.33–7.24 (m, 6H), 6.52 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 175.1, 144.2, 127.4, 126.9, 80.2; IR (neat) $\tilde{\nu}$/cm^{-1}: 3384w, 1682s, 1494w, 1445m, 1155w, 1049m, 903w, 755m, 696s; HRMS (ESI-Orbitrap) calcd for $C_{14}H_{12}O_2N$ $[M - H]^-$ 226.0874 m/z, found 226.0873 m/z.

2-(2-Fluoro-[1,1′-biphenyl]-4-yl)propanamide (1e).[37] Prepared from flurbiprofen (1.22 g, 5.0 mmol), $SOCl_2$ (5 equiv.), and aqueous NH_3 (25%, 15 mL) analogously to **1aa**. The precipitated product was filtered off, washed with a saturated solution of $NaHCO_3$, water, toluene, and dried *in vacuo*. Yield: 1.07 g (87%). Physical state: white powder. Mp 125–126 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 7.54–7.37 (m, 7H), 7.26–7.23 (m, 2H), 6.95 (br s, 1H), 3.65 (q, J = 7.0 Hz, 1H), 1.35 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): 174.8, 158.8 (d, J = 245.6 Hz), 144.4 (d, J = 7.7 Hz), 135.1, 130.5, 128.7, 128.6, 127.8, 126.3 (d, J = 12.5 Hz), 123.9, 114.9 (d, J = 23.1 Hz), 44.5, 18.2; ^{19}F NMR (376 MHz, DMSO-d_6): −118.76 to −118.82 (m, 1F); IR (neat) $\tilde{\nu}$/cm^{-1}: 3360m, 3181m, 1656s, 1482m, 1422m, 1397s, 1282m, 1130w, 1090w, 1011w, 932m, 869w, 830w, 764m, 694s; HRMS (ESI-Orbitrap) m/z: calcd for $C_{15}H_{15}NOF$ $[M + H]^+$ 244.1132, found 244.1138.

2-(4-Isobutylphenyl)propanamide (1f).[37] Prepared from ibuprofen (1.03 g, 5.0 mmol), $SOCl_2$ (5 equiv.), and aqueous NH_3 (25%, 15 mL) analogously to **1aa**. The precipitated product was filtered off, washed with a saturated solution of $NaHCO_3$, water, toluene, and dried *in vacuo*. Yield: 0.98 g (95%). Physical state: white powder. Mp 112–113 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 7.33 (br s, 1H), 7.22–7.20 (m, 2H),7.08–7.06 (m, 2H), 6.77 (br s, 1H), 3.52 (q, J = 7.0 Hz, 1H), 2.40 (d, J = 7.1 Hz, 2H), 1.85–1.75 (m, 1H), 1.29 (d, J = 7.0 Hz, 3H), 0.85 (d, J = 6.6 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 175.4, 139.7, 139.1, 128.7, 127.0, 44.5, 44.3, 29.6, 22.2, 18.5; IR (neat) $\tilde{\nu}$/cm^{-1}: 3342m, 3164m, 2958m, 1633s, 1515w, 1460m, 1406m, 1367m, 1265w, 1115w, 1070w, 999w, 841w; HRMS (ESI-Orbitrap) m/z: calcd for $C_{13}H_{20}NO$ $[M + H]^+$ 206.1539, found 206.1545.

2-(Naphthalen-1-yl)acetamide (1g).[31] Prepared from 2-(naphthalen-1-yl)acetic acid (0.93 g, 5.0 mmol), $SOCl_2$ (5 equiv.), and aqueous NH_3 (25%, 15 mL) analogously to **1aa**. Yield: 0.80 g (86%). Physical state: white powder. Mp 162–165 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 8.09 (d, J = 7.7 Hz, 1H), 7.93–7.91 (m, 1H), 7.81 (dd, J = 6.7, 2.5 Hz, 1H), 7.56–7.44 (m, 5H), 6.93 (br s, 1H), 3.87 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 172.0, 133.3, 132.8, 132.0, 128.2, 127.7, 126.9, 125.8, 125.5, 125.4, 124.2, 39.7; IR (neat) $\tilde{\nu}$/cm^{-1}: 3361w, 3178w, 1659m, 1620m, 1512w, 1397m, 1291w, 1261w, 775s; HRMS (ESI-Orbitrap) m/z: calcd for $C_{12}H_{12}NO$ $[M + H]^+$ 186.0913, found 186.0916.

2-(Thiophen-2-yl)acetamide (1h).[41] Prepared from 2-(thiophen-2-yl)acetic acid (0.71 g, 5.0 mmol), $SOCl_2$ (5 equiv.), and aqueous NH_3 (25%, 15 mL) analogously to **1aa**. Yield: 0.42 g (60%). Physical state: white powder. Mp 115–117 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 7.44 (br s, 1H), 7.33 (dd, J = 5.1, 1.3 Hz, 1H), 6.95–6.90 (m, 3H), 3.60 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 171.2, 137.8, 126.5, 126.0, 124.8, 36.4; IR (neat) $\tilde{\nu}$/cm^{-1}: 3347m, 3157m, 1633s, 1405s, 1287m, 1258m, 1128w, 1040w, 828w, 760w, 694s; HRMS (ESI-Orbitrap) m/z: calcd for C_6H_8NOS $[M + H]^+$ 142.0321, found 142.0325.

2-(6-Methoxynaphthalen-2-yl)propanenitrile (2a).[42] Phosgene (15% in toluene, 4.3 mL, 6 mmol) was added dropwise to a suspension of naproxamide (**1a**, 0.46 g, 2.0 mmol) in dry toluene (6 mL) and THF (2 mL) at rt under Ar. After the TLC (SiO_2) n-hexane–EtOAc (3 : 1) revealed a complete consumption of starting material (*ca.* 4 h), the reaction was quenched with water. The layers were separated, the organic phase was washed with a saturated aqueous solution of $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, filtered, and evaporated *in vacuo*. Yield: 0.34 g (80%). Physical state: white powder. Mp 90–91 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.87–7.84 (m, 3H), 7.48 (dd, J = 8.5, 1.9 Hz, 1H), 7.34 (d, J = 2.5 Hz, 1H), 7.20 (dd, J = 9.0, 2.5 Hz, 1H), 4.40 (q, J = 7.2 Hz, 1H), 3.88 (s, 3H), 1.62 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 157.5, 133.6, 132.5, 129.2, 128.2, 127.6, 125.2, 125.1, 122.3, 119.1, 105.8, 55.2, 29.8, 20.5; IR (neat) $\tilde{\nu}$/cm^{-1}: 2962w, 1727w, 1602m, 1505w, 1482w, 1448w, 1393w, 1258m, 1212m, 1085w, 1022m, 927w, 890m, 856s, 816m; HRMS (ESI-Orbitrap) m/z: calcd for $C_{14}H_{12}NO$ $[M - H]^-$ 210.0924, found 210.0926.

2-Hydroxy-2-phenylacetonitrile (2ba).[43] The solution of benzaldehyde (0.41 mL, 4.0 mmol) and acetic acid (0.57 mL, 10 mmol) in dry Et_2O (6 mL) was added dropwise to a suspension of KCN (0.65 g, 10 mmol) in dry Et_2O (30 mL) at −5 °C under Ar. The resulting reaction mixture was allowed to warm to rt slowly and stirred overnight. Then the reaction mass was diluted with water (30 mL), the organic phase was separated and washed repetitively with a 20% aqueous solution of $NaHSO_3$ to remove residues of the starting aldehyde. Next, it was washed with a saturated aqueous solution of $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, filtered, and evaporated *in vacuo*. Yield: 0.43 g (83%). Physical state: colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.53–7.43 (m, 5H), 5.52 (s, 1H), 3.25 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 135.1, 129.8, 129.2, 126.6, 118.8, 63.5; IR (neat) $\tilde{\nu}$/cm^{-1}: 3413br, 1494w, 1455m, 1261w,

1192w, 1025s, 932w, 819w, 762m, 698s; HRMS (ESI-Orbitrap) *m*/*z*: calcd for C_8H_8ON $[M + H]^+$ 134.0600, found 134.0598.

2-Phenylpropanenitrile (2c).[42] Prepared from 2-phenylpropanamide (**1c**, 0.30 g, 2.0 mmol) analogously to **2a**. Yield: 0.21 g (82%). Physical state: colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.39–7.28 (m, 5H), 3.87 (q, J = 7.3 Hz, 1H), 1.60 (d, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 136.9, 128.9, 127.8, 126.5, 121.5, 31.0, 21.3; IR (neat) $\tilde{\nu}$/cm^{-1}: 2241w, 1484w, 1452m, 1030w, 756m, 697s; HRMS (ESI-Orbitrap) *m*/*z*: calcd for $C_9H_{10}N$ $[M + H]^+$ 132.0808, found 132.0805.

2-Hydroxy-2,2-diphenylacetonitrile (2da).[32] Prepared from benzophenone (1.0 g, 5.5 mmol) according to the literature.[44] Yield: 0.90 g (78%) over two steps. Physical state: white powder. Mp 125–127 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.55–7.53 (m, 4H), 7.43–7.38 (m, 6H), 3.51 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 140.2, 129.2, 128.8, 125.8, 120.6, 75.4; IR (neat) $\tilde{\nu}$/cm^{-1}: 3364m, 2249w, 1492w, 1450m, 1410w, 1198w, 1177w, 1052m, 1032m, 769s, 746s; HRMS (ESI-Orbitrap) *m*/*z*: calcd for $C_{14}H_{10}NO$ $[M - H]^-$ 208.0768, found 208.0774.

2-(2-Fluoro-[1,1′-biphenyl]-4-yl)propanenitrile (2e).[42] Prepared from flurbiprofenamide (**1e**, 0.47 g, 2.0 mmol) analogously to **2a**. Yield: 0.33 g (73%). Physical state: white solid. Mp 67–68 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.55–7.52 (m, 2H), 7.48–7.43 (m, 3H), 7.44–7.36 (m, 1H), 7.23–7.16 (m, 2H), 3.94 (q, J = 7.3 Hz, 1H), 1.68 (d, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 159.8 (d, $^1J_{CF}$ = 249.5 Hz), 138.1, 134.9, 131.5, 128.9, 128.9 (d, $^2J_{CF}$ = 13.5 Hz), 128.5, 128.0, 122.7, 121.0, 114.7 (d, $^2J_{CF}$ = 24.0 Hz), 30.7, 21.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ/ppm: −116.16 to −116.20 (m, 1F); IR (neat) $\tilde{\nu}$/cm^{-1}: 2239w, 1563w, 1484m, 1450w, 1414w, 1375w, 1270w, 1215w, 1127w, 1085w, 1011w, 928w, 869w, 838m, 765m, 697s; HRMS (ESI-Orbitrap) *m*/*z*: calcd for $C_{15}H_{13}NF$ $[M + H]^+$ 226.1027, found 226.1026.

2-(4-Isobutylphenyl)propanenitrile (2f).[45] Prepared from ibuprofenamide (**1f**, 0.41 g, 2.0 mmol) analogously to **2a**. Yield: 0.34 g (91%). Physical state: colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.28–7.26 (m, 2H), 7.18–7.16 (m, 2H), 3.88 (q, J = 7.3 Hz, 1H), 2.48 (d, J = 7.1 Hz, 2H), 1.92–1.82 (m, 1H), 1.64 (d, J = 7.3 Hz, 3H), 0.91 (d, J = 6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 141.6, 134.2, 129.8, 126.4, 121.8, 44.9, 30.9, 30.2, 22.3, 21.4; IR (neat) $\tilde{\nu}$/cm^{-1}: 2955s, 2868m, 2238w, 1513m, 1455m, 1240w, 1383m, 1168w, 1085m, 1022w, 846s, 797s; HRMS (ESI-Orbitrap) *m*/*z*: calcd for $C_{13}H_{18}N$ $[M + H]^+$ 188.1434, found 188.1431.

2-(Naphthalen-1-yl)acetonitrile (2g).[46] Prepared from 2-(naphthalen-1-yl)acetamide (**1g**, 0.37 g, 2.0 mmol) analogously to **2a**. Yield: 0.30 g (91%). Physical state: yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.94–7.87 (m, 3H), 7.65–7.56 (m, 3H), 7.51–7.47 (m, 1H), 4.14 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 133.7, 130.7, 129.1, 129.0, 127.1, 126.43, 126.35, 125.7, 125.5, 122.4, 117.7, 21.7; IR (neat) $\tilde{\nu}$/cm^{-1}: 2251w, 1598m, 1512m, 1396m, 1262w, 1018w, 792s, 776s; HRMS (ESI-Orbitrap) *m*/*z*: calcd for $C_{12}H_{10}N$ $[M + H]^+$ 168.0808, found 168.0806.

2-(Thiophen-2-yl)acetonitrile (2h).[46] Prepared from 2-(thiophen-2-yl)acetamide (**1h**, 0.28 g, 2.0 mmol) analogously to **2a**. Yield: 0.21 g (84%). Physical state: yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.28 (dd, J = 5.2, 1.2 Hz, 1H), 7.08–7.06 (m, 1H), 7.00 (dd, J = 5.2, 3.5 Hz, 1H), 3.93 (d, J = 1.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 130.9, 127.3, 127.2, 125.9, 116.9, 18.6; IR (neat) $\tilde{\nu}$/cm^{-1}: 2253w, 1412w, 1257w, 1041w, 851m, 831w, 703s; HRMS (ESI-Orbitrap) *m*/*z*: calcd for C_6H_6NS $[M + H]^+$ 124.0215, found 124.0211.

General procedure for a SMEAH-mediated reduction of the carboxylic acid derivatives (GP). A solution of the corresponding substrate **1** or **2** (1.3 mmol) in dry THF (5 mL) was treated with SMEAH (70% in toluene, 5.5 mL, 15 equiv.) dropwise at 0 °C.[47] Then the ice-bath was removed and the resulting mixture was vigorously stirred under dry oxygen atmosphere (rubber balloon) at 25 °C for 3 h. The reaction mixture was carefully quenched by a dropwise addition of an aqueous solution of NaOH (5 M, 1 mL) at 0 °C and further diluted with an aqueous solution of NaOH (5 M, 15 mL). The organic and aqueous layers were separated and the aqueous phase was reextracted with toluene (5 × 15 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and evaporated *in vacuo*. The yellow oily residue was dissolved in 5 mL of Et_2O–MeOH (5 : 1) and a solution of anhydrous oxalic acid (0.13 g, 1.1 equiv.) in 5 mL of Et_2O–MeOH (5 : 1) was added dropwise. The resulting white precipitate was filtered off, washed several times with fresh Et_2O–MeOH (5 : 1), then Et_2O, and dried *in vacuo*. The above filtrate was neutralized by a saturated aqueous solution of $NaHCO_3$ and repetitively extracted with Et_2O. The combined organic extract was dried over anhydrous Na_2SO_4, filtered, and evaporated *in vacuo* to provide alcohol **5**.[48]

*The reduction of **1a**.* The reduction of **1a** (300 mg, 1.3 mmol) was performed according to GP. The precipitated product was obtained as an inseparable mixture of **3a**·$H_2C_2O_4$/**4a**·$H_2C_2O_4$ in a 94 : 6 ratio based on both ^{1}H NMR and RP-HPLC. HPLC conditions: an YMC-Triart C_{18} column (3 μm, 150 × 2.0 mm), MeCN–50 mM $HCOONH_4$ (pH 9.30), 40 : 60, 0.2 mL min^{-1}, 40 °C, 230 nm, t_1 = 3.43 min (**3a**), t_2 = 5.67 min (**4a**). Yield: 180 mg (43%). Physical state: white hygroscopic powder. The crude alcohol **5a** was isolated from the filtrate according to GP. Yield: 111 mg (41%). Physical state: beige solid.

Analytical data for **3a**·$H_2C_2O_4$: Mp 226–228 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 7.94 (s, 1H), 7.82 (dd, J = 8.7, 2.8 Hz, 2H), 7.59 (d, J = 8.6 Hz, 1H), 7.31 (d, J = 1.9 Hz, 1H), 7.17 (dd, J = 8.9, 2.3 Hz, 1H), 3.87 (s, 3H), 3.13, 3.10 (q, AB, J_{AB} = 13.0 Hz, 2H), 1.57 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 164.2, 157.3, 140.3, 133.3, 129.5, 128.0, 126.7, 124.0, 123.5, 118.6, 105.6, 71.0, 55.1, 49.1, 27.4; IR (neat) $\tilde{\nu}$/cm^{-1}: 3459w, 2961w, 1606m, 1515m, 1386w, 1265m, 1179s, 1025m, 898m, 854m, 812m, 702s; HRMS (ESI-Q-TOF) *m*/*z*: calcd for $C_{14}H_{18}NO_2$ $[M + H]^+$ 232.1332, found 232.1328.

Analytical data for **5a**:[49] Mp 93–95 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.75–7.71 (m, 3H), 7.48 (dd, J = 8.6, 1.6 Hz, 1H), 7.18–7.13 (m, 2H), 5.04 (q, J = 6.5 Hz, 1H), 3.93 (s, 3H), 2.26 (br s, 1H), 1.58 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 157.6, 140.9, 140.0, 129.4, 128.7, 127.1, 124.4, 123.7, 118.9, 105.6, 70.4, 55.3, 25.0; IR (neat) $\tilde{\nu}$/cm^{-1}: 3326br, 2961w, 1633w, 1605s, 1485m, 1462m, 1391w, 1260m, 1216m, 1162s, 1072m, 1028s, 961w, 930w, 890m, 853s, 815s, 750w, 673w; HRMS (ESI-Orbitrap) *m*/*z*: calcd for $C_{13}H_{15}O_2$ $[M + H]^+$ 203.1067, found 203.10664.

*The reduction of (S)-**1a**.* The reduction of (*S*)-**1a** (300 mg, 1.3 mmol) was performed according to GP and afforded precipitate of **3a**·$H_2C_2O_4$ and **4a**·$H_2C_2O_4$ in a 94 : 6 ratio and the filtrate containing crude (*R*)-**5a**. The free bases of **3a** and **4a** were liberated from the corresponding oxalic acid salts by aqueous NaOH (2.5 M) and immediately back-extracted to toluene. The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated *in vacuo*. The obtained crude residue (67 mg) was dissolved in anhydrous CH_2Cl_2 (2 mL). DMAP (39 mg, 1 equiv.) and Et_3N (88 μL, 2 equiv.) were added and the resulting solution was treated portionwise with 2-mesitylenesulfonyl chloride (67 mg, 1 equiv.) at 0 °C. The reaction mass was stirred under Ar at the same temperature for 3 h. Then the reaction mixture was diluted with water and repetitively extracted with CH_2Cl_2. The organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to provide the crude **8a**, which was further purified by column chromatography (SiO_2) *n*-hexane–EtOAc (4 : 1).

Analytical data for *rac*-**8a** (0% ee): Yield: 100 mg (45%). Physical state: white powder. Mp 193–194 °C; $[\alpha]_D^{25}$ 0 (*c* 1.0, $CHCl_3$). HPLC conditions: a Hypersil silica column (3 μm, 100 × 4.6 mm) used as a precolumn, which was connected *via* the standard blue PEEK capillary tubing (*L* 300 mm, ID 0.01″, OD 1/16″) to a Daicel Chiralpak IA column (5 μm, 250 × 4.6 mm), i-PrOH–*n*-heptane, 10 : 90, 0.5 mL min^{-1}, 25 °C (230 nm), t_1 = 36.36 min, t_2 = 49.38 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.71–7.69 (m, 2H), 7.60 (d, J = 8.6 Hz, 1H), 7.37 (dd, J = 8.6, 1.7 Hz, 1H), 7.22 (d, J = 2.4 Hz, 1H), 7.12 (dd, J = 9.0, 2.4 Hz, 1H), 6.97 (t, J = 6.2 Hz, 1H), 6.81 (s, 2H), 5.24 (s, 1H), 3.86 (s, 3H), 3.05 (dd, J = 6.2, 1.3 Hz, 2H), 2.40 (s, 6H), 2.18 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 157.0, 141.5, 141.1, 138.0, 134.2, 133.1, 131.4, 129.5, 127.9, 126.1, 124.2, 123.4, 118.3, 105.5, 72.7, 55.1, 53.5, 27.3, 22.5, 20.4; IR (neat) $\tilde{\nu}$/cm^{-1}: 3501w, 3296w, 2930w, 1605m, 1455w, 1378w, 1314s, 1261m, 1199m, 1171m, 1142s, 1084m, 1034m, 960w, 854s, 819s, 739w; HRMS (ESI-Orbitrap) *m*/*z*: calcd for $C_{23}H_{26}NO_4S$ $[M - H]^-$ 412.1588, found 412.1590.

Analytical data for (*R*)-**5a** were in accordance with a compound **5a** reported above. $[\alpha]_D^{25}$ +5 (*c* 0.4, CH_2Cl_2), 6% ee; lit.[49] $[\alpha]_D^{25}$ +26.7 (*c* 0.4, CH_2Cl_2), 70% ee. HPLC conditions: a Hypersil silica column (3 μm, 100 × 4.6 mm) used as a precolumn, which was connected *via* the standard blue PEEK capillary tubing (*L* 300 mm, ID 0.01″, OD 1/16″) to a Daicel Chiralpak IB column (5 μm, 250 × 4.6 mm), i-PrOH–*n*-heptane, 5 : 95, 0.5 mL min^{-1}, 25 °C (230 nm), t_1 = 28.50 min (*S*-isomer), t_2 = 34.07 min (*R*-isomer).

*The reduction of **1aa**.* The reduction of **1aa** (316 mg, 1.3 mmol) was performed according to GP. **4aa**·$H_2C_2O_4$ was obtained in a pure form according to ^{1}H NMR. Yield: 100 mg (24%). Physical state: white hygroscopic powder.

Analytical data for **4aa**·$H_2C_2O_4$: Mp 209–211 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 7.82–7.77 (m, 2H), 7.72 (s, 1H), 7.42 (d, J = 9.0 Hz, 1H), 7.30 (d, J = 2.3 Hz, 1H), 7.16 (dd, J = 8.9, 2.5 Hz, 1H), 3.87 (s, 3H), 3.29–3.17 (m, 3H), 2.54 (s, 3H), 1.34 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 164.3, 157.1, 137.6, 133.4, 129.0, 128.5, 127.2, 125.9, 125.4, 118.6, 105.8, 55.1, 54.4, 36.3, 33.1, 19.5; IR (neat) $\tilde{\nu}$/cm^{-1}: 2970br, 1715m, 1608s, 1485m, 1385w, 1263s, 1218s, 1162m, 1028s, 950w, 849s, 809m; HRMS (ESI-Q-TOF) *m*/*z*: calcd for $C_{15}H_{20}NO$ $[M + H]^+$ 230.1539, found 230.1545.

*The reduction of **1ad**.* The reduction of **1ad** (319 mg, 1.3 mmol) was performed according to GP with a reaction time of 30 min. The precipitated product was obtained as an inseparable mixture of **3a**·$H_2C_2O_4$/**4a**·$H_2C_2O_4$ in a 62 : 38 ratio based on ^{1}H NMR and 63 : 37 according to RP-HPLC. HPLC conditions: an YMC-Triart C_{18} column (3 μm, 150 × 2.0 mm), MeCN–50 mM $HCOONH_4$ (pH 9.30), 40 : 60, 0.2 mL min^{-1}, 40 °C, 230 nm, t_1 = 3.47 min (**3a**), t_2 = 5.69 min (**4a**). Yield: 119 mg (29%). Physical state: white hygroscopic powder. The analytical data for **3a**·$H_2C_2O_4$ were in accordance with the product obtained by the reduction of **1a**.

Analytical data for **4a**·$H_2C_2O_4$ (the authentic sample was prepared by a DIBAH-mediated reduction of **1a**): Mp 225–226 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 7.81–7.78 (m, 2H), 7.70 (s, 1H), 7.42 (dd, J = 8.5, 1.7 Hz, 1H), 7.30 (d, J = 2.5 Hz, 1H), 7.16 (dd, J = 8.9, 2.5 Hz, 1H), 3.87 (s, 3H), 3.19–3.03 (m, 3H), 1.33 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 164.2, 157.1, 137.7, 133.4, 129.0, 128.5, 127.1, 125.9, 125.4, 118.5, 105.8, 55.1, 44.9, 37.4, 19.2; IR (neat) $\tilde{\nu}$/cm^{-1}: 2959br, 1717w, 1606s, 1503m, 1458w, 1392w, 1263m, 1218s, 1197m, 1162m, 1030m, 928w, 849s, 815m, 705s; HRMS (ESI-Q-TOF) *m*/*z*: calcd for $C_{14}H_{18}NO$ $[M + H]^+$ 216.1383, found 216.1379.

*The reduction of **1b**.* The reduction of **1b** (176 mg, 1.3 mmol) was performed according to GP at 0 °C. The precipitated product was obtained as an inseparable mixture of **3b**·$H_2C_2O_4$/**4b**·$H_2C_2O_4$ in a 95 : 5 ratio based on RP-HPLC. HPLC conditions: an YMC-Triart C_{18} column (3 μm, 150 × 2.0 mm), MeCN–50 mM $HCOONH_4$ (pH 9.30), 20 : 80, 0.2 mL min^{-1}, 40 °C, 210 nm, t_1 = 3.09 min (**3b**), t_2 = 5.02 min (**4b**). Yield: 83 mg (28%). Physical state: white hygroscopic powder.

Analytical data for **3b**·$H_2C_2O_4$ (in accordance with the authentic sample):[50] Mp 232–235 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 7.41–7.35 (m, 4H), 7.33–7.28 (m, 1H), 4.81 (dd, J = 9.9, 2.8 Hz, 1H), 3.04 (dd, J = 12.6, 2.8 Hz, 1H), 2.84 (dd, J = 12.6, 9.9 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 163.7, 141.9, 128.3, 127.6, 125.8, 69.1, 45.7; IR (neat) $\tilde{\nu}$/cm^{-1}: 2884br, 1582s, 1446w, 1296m, 1061m, 1020m, 780m, 700m; HRMS (ESI-Orbitrap) *m*/*z*: calcd for $C_8H_{12}NO$ $[M + H]^+$ 138.0913, found 138.0915.

*The reduction of **1ba**.* The reduction of **1ba** (197 mg, 1.3 mmol) was performed according to GP at 0 °C. The precipitated product **3b**·$H_2C_2O_4$ was obtained in a pure form according to RP-HPLC. HPLC conditions: an YMC-Triart C_{18} column (3 μm, 150 × 2.0 mm), MeCN–50 mM $HCOONH_4$ (pH 9.30), 20 : 80, 0.2 mL min^{-1}, 40 °C, 210 nm, t = 3.09 min (**3b**). Yield: 107 mg (36%). Physical state: white hygroscopic powder. The analytical data were in accordance with the product obtained by the reduction of **1b**.

*The reduction of (S)-**1ba**.* The reduction of (*S*)-**1ba** (197 mg, 1.3 mmol) was performed according to GP at 0 °C and furnished the precipitate of (*S*)-**3b**·$H_2C_2O_4$. The free base of (*S*)-**3b** was liberated and treated analogously to the product of (*S*)-**1a** to provide (*S*)-**8b**.

Analytical data for (*S*)-**8b** (>99% ee):[51] Yield: 55 mg (48%). Physical state: colorless oil. $[\alpha]_D^{25}$ +40 (*c* 1.0, $CHCl_3$). HPLC conditions: a Hypersil silica column (3 μm, 100 × 4.6 mm) used as a precolumn, which was connected *via* the standard blue PEEK capillary tubing (*L* 300 mm, ID 0.01″, OD 1/16″) to a Daicel Chiralpak IA column (5 μm, 250 × 4.6 mm), i-PrOH–*n*-heptane, 10 : 90, 0.5 mL min^{-1}, 25 °C (230 nm), $t = 57.51$ min (*S*-isomer). ^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 8.08 (s, 1H), 7.35–7.26 (m, 5H), 6.95 (s, 2H), 4.94 (dd, 7.1, 4.2 Hz, 1H), 4.79–4.76 (m, 1H), 3.20 (ddd, $J = 13.2$, 8.5, 4.5 Hz, 1H), 3.00 (ddd, $J = 13.2$, 8.5, 4.5 Hz, 1H), 2.62 (s, 6H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 142.4, 140.9, 139.1, 133.5, 132.1, 128.8, 128.4, 125.9, 72.8, 49.8, 23.0, 21.0; IR (neat) $\tilde{\nu}/cm^{-1}$: 3313w, 1603w, 1453w, 1318m, 1188w, 1149s, 1055m, 917w, 852w, 756w, 700m; HRMS (ESI-Orbitrap) *m*/*z*: calcd for $C_{17}H_{20}O_3NS$ $[M - H]^-$ 318.1169, found 318.1172.

*The reduction of **1bb**.* The reduction of **1bb** (215 mg, 1.3 mmol) was performed according to GP. The precipitated product was obtained as an inseparable mixture of **3b**·$H_2C_2O_4$/**4ba**·$H_2C_2O_4$ in a 30 : 70 ratio based on ^{1}H NMR and 29 : 71 according to RP-HPLC. HPLC conditions: an YMC-Triart C_{18} column (3 μm, 150 × 2.0 mm), MeCN–50 mM $HCOONH_4$ (pH 9.30), 20 : 80, 0.2 mL min^{-1}, 40 °C, 210 nm, $t_1 = 3.10$ min (**3b**), $t_2 = 8.17$ min (**4ba**). Yield: 97 mg (31%). Physical state: white hygroscopic powder. The analytical data for **3b** were in accordance with the product obtained by the reduction of **1b**.

Analytical data for **4ba**·$H_2C_2O_4$: ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 7.44–7.33 (m, 5H), 4.46 (dd, $J = 8.7$, 3.4 Hz, 1H), 3.19 (s, 3H), 3.03–2.94 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 164.0, 133.8, 128.6, 128.4, 126.7, 56.2, 44.3; HRMS (ESI-Orbitrap) *m*/*z*: calcd for $C_9H_{14}NO$ $[M + H]^+$ 152.1070, found 152.1069.

*The reduction of **1bc**.* The reduction of **1bc** (316 mg, 1.3 mmol) was performed according to GP at 0 °C. The precipitated product **3b**·$H_2C_2O_4$ was obtained in a pure form according to RP-HPLC. HPLC conditions: an YMC-Triart C_{18} column (3 μm, 150 × 2.0 mm), MeCN–50 mM $HCOONH_4$ (pH 9.30), 20 : 80, 0.2 mL min^{-1}, 40 °C, 210 nm, $t = 3.09$ min (**3b**). Yield: 71 mg (24%). Physical state: white hygroscopic powder. The analytical data were in accordance with the product obtained by the reduction of **1b**.

*The reduction of **1bd**.* The reduction of **1bd** (220 mg, 1.3 mmol) was performed according to GP at 0 °C. The precipitated product **4bb**·$H_2C_2O_4$ was obtained in a pure form according to ^{1}H NMR. Yield: 182 mg (57%). Physical state: white hygroscopic powder.

Analytical data for **4bb**·$H_2C_2O_4$: Mp 173–175 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 7.48–7.37 (m, 5H), 4.28–4.25 (m, 1H), 3.75–3.66 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 164.2, 135.7, 128.5, 128.4, 127.4, 63.0, 56.0; IR (neat) $\tilde{\nu}/cm^{-1}$: 2968w, 1593m, 1529m, 1202s, 1057s, 765w; HRMS (ESI-Orbitrap) *m*/*z*: calcd for $C_8H_{11}NCl$ $[M + H]^+$ 156.0575, found 156.0570.

The reduction of **1c** (194 mg, 1.3 mmol) was performed according to GP. The precipitated product was obtained as an inseparable mixture of **3c**·$H_2C_2O_4$/**4c**·$H_2C_2O_4$ in a 95 : 5 ratio based on ^{1}H NMR and 94 : 6 according to RP-HPLC. HPLC conditions: an YMC-Triart C_{18} column (3 μm, 150 × 2.0 mm), MeCN–50 mM $HCOONH_4$ (pH 9.30), 30 : 70, 0.2 mL min^{-1}, 40 °C, 210 nm, $t_1 = 2.77$ min (**3c**), $t_2 = 4.76$ min (**4c**). Yield: 101 mg (32%). Physical state: white hygroscopic powder. The crude alcohol **5b** was isolated from the filtrate according to GP. Yield: 75 mg (47%). Physical state: yellowish oil.

Analytical data for **3c**·$H_2C_2O_4$: Mp 126–128 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 7.51–7.49 (m, 2H), 7.38–7.35 (m, 2H), 7.29–7.26 (m, 1H), 3.09, 2.98 (q, AB, $J_{AB} = 12.9$ Hz, 2H), 1.49 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 164.4, 145.6, 128.1, 126.9, 124.9, 70.9, 49.1, 27.2; IR (neat) $\tilde{\nu}/cm^{-1}$: 3438br, 1713w, 1620w, 1514m, 1447w, 1394w, 1211m, 1062m, 760s; HRMS (ESI-Q-TOF) *m*/*z*: calcd for $C_9H_{14}NO$ $[M + H]^+$ 152.1070, found 152.1066.

Analytical data for **5b**:[52] ^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.37–7.32 (m, 4H), 7.29–7.25 (m, 1H), 4.88 (q, $J = 6.5$ Hz, 1H), 2.02 (s, 1H), 1.48 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 145.8, 128.5, 127.4, 125.3, 70.4, 25.1; IR (neat) $\tilde{\nu}/cm^{-1}$: 3329br, 2970w, 1493w, 1452w, 1368w, 1077m, 899m, 761m, 700s; HRMS (ESI) not detected.

*The reduction of **1ca**.* The reduction of **1ca** (264 mg, 1.3 mmol) was performed according to GP. The precipitated product **3c**·$H_2C_2O_4$ was obtained in a pure form based on both ^{1}H NMR and RP-HPLC. HPLC conditions: an YMC-Triart C_{18} column (3 μm, 150 × 2.0 mm), MeCN–50 mM $HCOONH_4$ (pH 9.30), 30 : 70, 0.2 mL min^{-1}, 40 °C, 210 nm, $t = 2.79$ min (**3c**). Yield: 98 mg (31%). Physical state: white hygroscopic powder. The analytical data were in accordance with the product obtained by the reduction of **1c**.

*The reduction of **1cb**.* The reduction of **1cb** (285 mg, 1.3 mmol) was performed according to GP at 0 °C. The precipitated product **3ca**·$H_2C_24_2$ was obtained in a pure form based on both ^{1}H NMR and RP-HPLC. HPLC conditions: an YMC-Triart C_{18} column (3 μm, 150 × 2.0 mm), MeCN–50 mM $HCOONH_4$ (pH 9.30), 30 : 70, 0.2 mL min^{-1}, 40 °C, 210 nm, $t = 8.55$ min (**3ca**). Yield: 130 mg (34%). Physical state: white hygroscopic powder.

Analytical data for **3ca**·$H_2C_2O_4$: Mp 235–237 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 7.61–7.60 (m, 2H), 7.46–7.39 (m, 3H), 3.39, 3.37 (q, AB, $J_{AB} = 14.4$ Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 164.4, 135.1, 128.8, 128.3, 126.8, 125.1 (q, $^1J_{CF} = 287.1$ Hz), 74.7 (q, $^2J_{CF} = 27.0$ Hz), 43.1; ^{19}F NMR (376 MHz, DMSO-d_6) δ/ppm: −77.15 (s); IR (neat) $\tilde{\nu}/cm^{-1}$: 2900w, 1594m, 1506m, 1453m, 1299m, 1197m, 1152s, 1046m, 989m, 763s; HRMS (ESI-Q-TOF) *m*/*z*: calcd for $C_9H_{11}F_3NO$ $[M + H]^+$ 206.0787, found 206.0795.

*The reduction of **1cc**.* The reduction of **1cc** (249 mg, 1.3 mmol) was performed according to GP. The precipitated product **3cb**·$H_2C_2O_4$ was obtained in a pure form based on both ^{1}H NMR and RP-HPLC. HPLC conditions: an YMC-Triart C_{18} column (3 μm, 150 × 2.0 mm), MeCN–50 mM $HCOONH_4$ (pH 9.30), 40 : 60, 0.2 mL min^{-1}, 40 °C, 210 nm, $t = 5.43$ min (**3cb**). Yield: 104 mg (28%). Physical state: white hygroscopic powder.

Analytical data for **3cb**·$H_2C_2O_4$: Mp 138–139 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 7.46–7.44 (m, 2H), 7.38–7.34 (m, 2H), 7.28–7.25 (m, 1H), 3.12, 3.10 (q, AB, $J_{AB} = 13.0$ Hz, 2H), 1.81–1.72 (m, 2H), 1.25–1.13 (m, 3H), 0.85–0.79 (m, 1H), 0.76 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 164.3,

143.1, 128.0, 126.8, 125.5, 73.5, 48.5, 24.7, 22.2, 13.8; IR (neat) $\tilde{\nu}$/cm^{-1}: 2930w, 1587m, 1504m, 1448m, 1218s, 1049w, 764w; HRMS (ESI-Q-TOF) *m*/*z*: calcd for $C_{12}H_{20}NO$ $[M + H]^+$ 194.1539, found 194.1546.

*The reduction of **1d**.* The reduction of **1d** (275 mg, 1.3 mmol) was performed according to GP. The precipitated product **3d**·$H_2C_2O_4$ was obtained in a pure form based on both ^{1}H NMR and RP-HPLC. HPLC conditions: an YMC-Triart C_{18} column (3 μm, 150 × 2.0 mm), MeCN–50 mM $HCOONH_4$ (pH 9.30), 40 : 60, 0.2 mL min^{-1}, 40 °C, 210 nm, t = 5.14 min (**3d**). Yield: 101 mg (26%). Physical state: white hygroscopic powder. The crude alcohol **5c** was isolated from the filtrate according to GP. Yield: 146 mg (53%). Physical state: yellowish waxy solid.

Analytical data for **3d**·$H_2C_2O_4$: Mp 182–184 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 7.50–7.48 (m, 4H), 7.36–7.33 (m, 4H), 7.27–7.24 (m, 2H), 3.68 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 164.1, 144.3, 128.2, 127.2, 125.8, 74.9, 47.3; IR (neat) $\tilde{\nu}$/cm^{-1}: 3443w, 1738m, 1614m, 1417m, 1224s, 715s; HRMS (ESI-Q-TOF) *m*/*z*: calcd for $C_{14}H_{15}NO$ $[M + H]^+$ 214.1226, found 214.1225.

Analytical data for **5c**:[52] Mp 60–61 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.39–7.31 (m, 8H), 7.28–7.24 (m, 2H), 5.84 (s, 1H), 2.23 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 143.8, 128.5, 127.5, 126.5, 76.2; IR (neat) $\tilde{\nu}$/cm^{-1}: 3378w, 1494m, 1446m, 1269w, 1181w, 1017m, 752m, 734s; HRMS (ESI-Orbitrap) *m*/*z*: calcd for $C_{13}H_{13}O$ $[M + H]^+$ 185.0961, found 185.0959.

*The reduction of **1da**.* The reduction of **1da** (295 mg, 1.3 mmol) was performed according to GP. The precipitated product **3d**·$H_2C_2O_4$ was obtained in a pure form based on both ^{1}H NMR and RP-HPLC. HPLC conditions: an YMC-Triart C_{18} column (3 μm, 150 × 2.0 mm), MeCN–50 mM $HCOONH_4$ (pH 9.30), 40 : 60, 0.2 mL min^{-1}, 40 °C, 210 nm, t = 5.11 min (**3d**). Yield: 150 mg (38%). The analytical data were in accordance with the product obtained by the reduction of **1d**.

*The reduction of **1e**.* The reduction of **1e** (316 mg, 1.3 mmol) was performed according to GP. The precipitated product was obtained as an inseparable mixture of **3e**·$H_2C_2O_4$/**4e**·$H_2C_2O_4$ in a 97 : 3 ratio based on ^{1}H NMR and >99 : 1 according to RP-HPLC. HPLC conditions: an YMC-Triart C_{18} column (3 μm, 150 × 2.0 mm), MeCN–50 mM $HCOONH_4$ (pH 9.30), 50 : 50, 0.2 mL min^{-1}, 40 °C, 210 nm, t = 3.89 min (**3e**). Yield: 172 mg (39%). Physical state: white hygroscopic powder. The crude alcohol **5d** was isolated from the filtrate according to GP. Yield: 95 mg (41%). Physical state: white solid.

Analytical data for **3e**·$H_2C_2O_4$: Mp 195–196 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 7.56–7.39 (m, 8H), 3.08 (q, AB, J_{AB} = 13.5 Hz, 2H), 1.50 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 163.6, 158.9 (d, $^1J_{CF}$ = 245.6 Hz), 147.4 (d, $^3J_{CF}$ = 7.7 Hz), 134.8, 130.4, 128.60, 128.56, 127.8, 126.7 (d, $^2J_{CF}$ = 13.5 Hz), 121.6, 113.2 (d, $^2J_{CF}$ = 24.1 Hz), 70.7, 48.8, 27.4; ^{19}F NMR (376 MHz, DMSO-d_6) δ/ppm: −118.12 to −118.17 (m); IR (neat) $\tilde{\nu}$/cm^{-1}: 3465w, 2930w, 1615m, 1501m, 1410m, 1223m, 1107w, 1067m, 1009m, 882w, 831w, 766m; HRMS (ESI-Q-TOF) *m*/*z*: calcd for $C_{15}H_{17}FNO$ $[M + H]^+$ 246.1289, found 246.1290.

Analytical data for **5d**:[53] Mp 65–66 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.58–7.55 (m, 2H), 7.48–7.37 (m, 4H), 7.23–7.20 (m, 2H), 4.96 (q, J = 6.5 Hz, 1H), 2.08 (br s, 1H), 1.54 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 157.7 (d, $^1J_{CF}$ = 248.5 Hz), 147.4 ($^3J_{CF}$ = 6.7 Hz), 135.6, 130.7 ($^3J_{CF}$ = 3.9 Hz), 128.9 ($^3J_{CF}$ = 2.9 Hz), 128.4, 127.9 (d, $^2J_{CF}$ = 13.5 Hz), 127.6, 121.2, 113.1 (d, $^2J_{CF}$ = 24.1 Hz), 69.6, 25.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ/ppm: −117.56 to −117.61 (m); IR (neat) $\tilde{\nu}$/cm^{-1}: 3324br, 1581w, 1484m, 1416m, 1268m, 1153w, 1127w, 1070m, 1010m, 939w, 868m, 839m, 766s; HRMS (ESI-Orbitrap) *m*/*z*: calcd for $C_{14}H_{12}F$ $[M - H_2O + H]^+$ 199.0918, found 199.0917.

*The reduction of **1f**.* The reduction of **1f** (267 mg, 1.3 mmol) was performed according to GP. The precipitated product was obtained as an inseparable mixture of **3f**·$H_2C_2O_4$/**4f**·$H_2C_2O_4$ in a 93 : 7 ratio based on ^{1}H NMR and 94 : 6 according to RP-HPLC. HPLC conditions: an YMC-Triart C_{18} column (3 μm, 150 × 2.0 mm), MeCN–50 mM $HCOONH_4$ (pH 9.30), 50 : 50, 0.2 mL min^{-1}, 40 °C, 210 nm, t_1 = 4.13 min (**3f**), t_2 = 7.23 min (**4f**). Yield: 160 mg (42%). Physical state: white hygroscopic powder. The crude alcohol **5e** was isolated from the filtrate according to GP. Yield: 100 mg (40%). Physical state: yellowish oil.

Analytical data for **3f**·$H_2C_2O_4$: Mp 193–195 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 7.40–7.38 (m, 2H), 7.16–7.14 (m, 2H), 3.05, 2.97 (q, AB, J_{AB} = 12.8 Hz, 2H), 2.44 (d, J = 7.1 Hz, 2H), 1.88–1.78 (m, 1H), 1.48 (s, 3H), 0.87 (d, J = 6.6 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 163.3, 142.7, 139.8, 128.6, 124.7, 70.7, 49.1, 44.1, 29.5, 27.2, 22.1; IR (neat) $\tilde{\nu}$/cm^{-1}: 3467m, 2954m, 1732w, 1615m, 1504s, 1365w, 1184s, 1063s, 1019s, 810w, 794m; HRMS (ESI-Q-TOF) *m*/*z*: calcd for $C_{13}H_{22}NO$ $[M + H]^+$ 208.1696, found 208.1689.

Analytical data for **4f**·$H_2C_2O_4$ (the authentic sample was prepared by a DIBAH-mediated reduction of **1f**): Mp 190–191 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 7.19–7.11 (m, 4H), 3.00–2.95 (m, 3H), 2.43 (d, J = 6.9 Hz, 2H), 1.86–1.79 (m, 1H), 1.25–1.19 (m, 3H), 0.87 (d, J = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 164.0, 140.0, 139.6, 129.1, 126.7, 45.0, 44.1, 37.0, 29.4, 22.1, 19.1; IR (neat) $\tilde{\nu}$/cm^{-1}: 2866m, 1622m, 1574s, 1532s, 1446m, 1300s, 1186w, 1019w, 840w, 799w, 777s; HRMS (ESI-Q-TOF) *m*/*z*: calcd for $C_{13}H_{22}N$ $[M + H]^+$ 192.1747, found 192.1737.

Analytical data for **5e**:[54] ^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.28–7.25 (m, 2H), 7.13–7.11 (m, 2H), 4.86 (q, J = 6.5 Hz, 1H), 2.46 (d, J = 7.1 Hz, 2H), 2.15 (br s, 1H), 1.90–1.80 (m, 1H), 1.48 (d, J = 6.5 Hz, 3H), 0.90 (d, J = 6.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 143.0, 141.0, 129.2, 125.2, 70.2, 45.0, 30.2, 25.0, 22.3; IR (neat) $\tilde{\nu}$/cm^{-1}: 3344br, 2952s, 2923m, 2867m, 1650w, 1513w, 1465m, 1366m. 1077s, 1008m, 898m, 846m; HRMS (ESI-Orbitrap) *m*/*z*: calcd for $C_{12}H_{19}O$ $[M + H]^+$ 179.1430, found 179.1424.

*The reduction of **1g**.* The reduction of **1g** (241 mg, 1.3 mmol) was performed according to GP at 0 °C. The precipitated product was obtained as an inseparable mixture of **3g**·$H_2C_2O_4$/**4g**·$H_2C_2O_4$ in a 95 : 5 ratio based on RP-HPLC. HPLC conditions: an YMC-Triart C_{18} column (3 μm, 150 × 2.0 mm), MeCN–50 mM $HCOONH_4$ (pH 9.30), 30 : 70, 0.2 mL min^{-1}, 40 °C, 230 nm, t_1 = 4.64 min (**3g**), t_2 = 12.88 min (**4g**). Yield: 188 mg (52%). Physical state: white hygroscopic powder.

Analytical data for **3g**·$H_2C_2O_4$: Mp 139–141 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 8.17 (d, J = 8.2 Hz, 1H), 7.99–7.96 (m,

1H), 7.89 (d, J = 8.2 Hz, 1H), 7.73 (d, J = 6.8 Hz, 1H), 7.61–7.53 (m, 3H), 5.60 (dd, J = 9.6, 2.3 Hz, 1H), 3.16 (dd, J = 12.9, 2.3 Hz, 1H), 2.92 (dd, J = 12.6, 9.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 163.6, 137.5, 133.2, 129.7, 128.7, 128.0, 126.3, 125.6, 125.4, 123.4, 122.7, 66.1, 45.4; IR (neat) $\tilde{\nu}$/cm^{-1}: 2899m, 1715w, 1652s, 1580m, 1524m, 1218m, 1150m, 1059m, 772s, 722s; HRMS (ESI-Q-TOF) m/z: calcd for $C_{12}H_{14}NO$ $[M + H]^+$ 188.1070 m/z, found 188.1072.

*The reduction of **1h**.* The reduction of **1h** (184 mg, 1.3 mmol) was performed according to GP at 0 °C. The precipitated product was obtained as an inseparable mixture of **3h**·$H_2C_2O_4$/**4h**·$H_2C_2O_4$ in a 97 : 3 ratio based on RP-HPLC. HPLC conditions: an YMC-Triart C_{18} column (3 μm, 150 × 2.0 mm), MeCN–50 mM $HCOONH_4$ (pH 9.30), 20 : 80, 0.2 mL min^{-1}, 40 °C, 230 nm, t_1 = 2.83 min (**3h**), t_2 = 5.32 min (**4h**). Yield: 87 mg (29%). Physical state: white hygroscopic powder.

Analytical data for **3h**·$H_2C_2O_4$: Mp 168–170 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 7.47 (d, J = 4.8 Hz, 1H), 7.06–7.01 (m, 2H), 5.05 (d, J = 8.1 Hz, 1H), 3.13–3.10 (m, 1H), 2.95–2.90 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 164.5, 145.9, 126.9, 125.0, 123.9, 65.6, 45.8; IR (neat) $\tilde{\nu}$/cm^{-1}: 2892br, 1582s, 1446w, 1296m, 1232m, 1021w, 924w, 867w, 784w, 717m; HRMS (ESI-Orbitrap) m/z: calcd for $C_6H_{10}NOS$ $[M + H]^+$ 144.0478, found 144.0478.

*The reduction of **2a**.* The reduction of **2a** (275 mg, 1.3 mmol) was performed according to GP with a reaction time of 2 h. The precipitated product was obtained as an inseparable mixture of **3a**·$H_2C_2O_4$/**4a**·$H_2C_2O_4$ in a 89 : 11 ratio based on both ^{1}H NMR and RP-HPLC. HPLC conditions: an YMC-Triart C_{18} column (3 μm, 150 × 2.0 mm), MeCN–50 mM $HCOONH_4$ (pH 9.30), 40 : 60, 0.2 mL min^{-1}, 40 °C, 230 nm, t_1 = 3.42 min (**3a**), t_2 = 5.65 min (**4a**). Yield: 167 mg (40%). Physical state: white hygroscopic powder. The analytical data were in accordance with the product obtained by the reduction of **1a**.

*The reduction of **2b**.* The reduction of **2b** (152 mg, 1.3 mmol) was performed according to GP at 0 °C with a reaction time of 2 h. The precipitated product **3b**·$H_2C_2O_4$ was obtained in a pure form based on both ^{1}H NMR and RP-HPLC. HPLC conditions: an YMC-Triart C_{18} column (3 μm, 150 × 2.0 mm), MeCN–50 mM $HCOONH_4$ (pH 9.30), 20 : 80, 0.2 mL min^{-1}, 40 °C, 210 nm, t = 3.10 min (**3b**). Yield: 118 mg (40%). Physical state: white hygroscopic powder. The analytical data were in accordance with the product obtained by the reduction of **1b**.

*The reduction of **2ba**.* The reduction of **2ba** (173 mg, 1.3 mmol) was performed according to GP at 0 °C with a reaction time of 1.5 h. The precipitated product **3b**·$H_2C_2O_4$ was obtained in a pure form based on both ^{1}H NMR and RP-HPLC. HPLC conditions: an YMC-Triart C_{18} column (3 μm, 150 × 2.0 mm), MeCN–50 mM $HCOONH_4$ (pH 9.30), 20 : 80, 0.2 mL min^{-1}, 40 °C, 210 nm, t_R = 3.10 min (**3b**). Yield: 99 mg (34%). Physical state: white hygroscopic powder. The analytical data were in accordance with the product obtained by the reduction of **1b**.

*The reduction of **2c**.* The reduction of **2c** (171 mg, 1.3 mmol) was performed according to GP with a reaction time of 2 h. The precipitated product was obtained as an inseparable mixture of **3c**·$H_2C_2O_4$/**4c**·$H_2C_2O_4$ in a 94 : 6 ratio based on both ^{1}H NMR and RP-HPLC. HPLC conditions: an YMC-Triart C_{18} column (3 μm, 150 × 2.0 mm), MeCN–50 mM $HCOONH_4$ (pH 9.30), 30 : 70, 0.2 mL min^{-1}, 40 °C, 210 nm, t_1 = 2.78 min (**3c**), t_2 = 4.79 min (**4c**). Yield: 103 mg (33%). Physical state: white hygroscopic powder. The analytical data were in accordance with the product obtained by the reduction of **1c**.

*The reduction of **2d**.* The reduction of **2d** (251 mg, 1.3 mmol) was performed according to GP with a reaction time of 2 h. The precipitated product was obtained as an inseparable mixture of **3d**·$H_2C_2O_4$/**4d**·$H_2C_2O_4$ in a 92 : 8 ratio based on both ^{1}H NMR and RP-HPLC. HPLC conditions: an YMC-Triart C_{18} column (3 μm, 150 × 2.0 mm), MeCN–50 mM $HCOONH_4$ (pH 9.30), 40 : 60, 0.2 mL min^{-1}, 40 °C, 210 nm, t_1 = 5.14 min (**3d**), t_2 = 7.90 min (**4d**). Yield: 195 mg (50%). Physical state: white hygroscopic powder. The analytical data were in accordance with the product obtained by the reduction of **1d**.

*The reduction of **2da**.* The reduction of **2da** (272 mg, 1.3 mmol) was performed according to GP with a reaction time of 1.5 h. The precipitated product **3d**·$H_2C_2O_4$ was obtained in a pure form based on both ^{1}H NMR and RP-HPLC. HPLC conditions: an YMC-Triart C_{18} column (3 μm, 150 × 2.0 mm), MeCN–50 mM $HCOONH_4$ (pH 9.30), 40 : 60, 0.2 mL min^{-1}, 40 °C, 210 nm, t = 5.16 min (**3d**). Yield: 83 mg (21%). The analytical data were in accordance with the product obtained by the reduction of **1d**.

*The reduction of **2e**.* The reduction of **2e** (293 mg, 1.3 mmol) was performed according to GP with a reaction time of 2 h. The precipitated product was obtained as an inseparable mixture of **3e**·$H_2C_2O_4$/**4e**·$H_2C_2O_4$ in a 91 : 9 ratio based on ^{1}H NMR, 89 : 11 based on ^{19}F NMR and 93 : 7 according to RP-HPLC. HPLC conditions: an YMC-Triart C_{18} column (3 μm, 150 × 2.0 mm), MeCN–50 mM $HCOONH_4$ (pH 9.30), 50 : 50, 0.2 mL min^{-1}, 40 °C, 210 nm, t_1 = 3.88 min (**3e**), t_2 = 6.50 min (**4e**). Yield: 141 mg (33%). Physical state: white hygroscopic powder. The analytical data were in accordance with the product obtained by the reduction of **1e**.

*The reduction of **2f**.* The reduction of **2f** (243 mg, 1.3 mmol) was performed according to GP with a reaction time of 2 h. The precipitated product was obtained as an inseparable mixture of **3f**·$H_2C_2O_4$/**4f**·$H_2C_2O_4$ in a 96 : 4 ratio based on ^{1}H NMR and 97 : 3 according to RP-HPLC. HPLC conditions: an YMC-Triart C_{18} column (3 μm, 150 × 2.0 mm), MeCN–50 mM $HCOONH_4$ (pH 9.30), 50 : 50, 0.2 mL min^{-1}, 40 °C, 210 nm, t_1 = 4.23 min (**3f**), t_2 = 7.76 min (**4f**). Yield: 182 mg (47%). Physical state: white hygroscopic powder. The analytical data were in accordance with the product obtained by the reduction of **1f**.

*The reduction of **2g**.* The reduction of **2g** (217 mg, 1.3 mmol) was performed according to GP at 0 °C with a reaction time of 2 h. The precipitated product was obtained in a pure form based on RP-HPLC. HPLC conditions: an YMC-Triart C_{18} column (3 μm, 150 × 2.0 mm), MeCN–50 mM $HCOONH_4$ (pH 9.30), 30 : 70, 0.2 mL min^{-1}, 40 °C, 230 nm, t = 4.61 min (**3g**). Yield: 183 mg (51%). Physical state: white hygroscopic powder. The analytical data were in accordance with the product obtained by the reduction of **1g**.

*The reduction of **2h**.* The reduction of **2h** (160 mg, 1.3 mmol) was performed according to GP at 0 °C with a reaction time of 2 h. The precipitated product was obtained as an inseparable mixture of **3h**·$H_2C_2O_4$/**4h**·$H_2C_2O_4$ in a 96 : 4 ratio based on RP-

HPLC. HPLC conditions: an YMC-Triart C_{18} column (3 μm, 150 × 2.0 mm), MeCN–50 mM $HCOONH_4$ (pH 9.30), 20 : 80, 0.2 mL min^{-1}, 40 °C, 230 nm, $t_1 = 2.84$ min (**3h**), $t_2 = 5.54$ min (**4h**). Yield: 74 mg (24%). Physical state: white hygroscopic powder. The analytical data were in accordance with the product obtained by the reduction of **1h**.

2-Fluoro-2-(2-fluoro-[1,1′-biphenyl]-4-yl)propan-1-amine (9). The free base of **3b** (130 mg, 0.53 mmol) in dry CH_2Cl_2 (1 mL) was treated dropwise with HF-pyridine (65%, 0.75 mL) and the resulting mixture was stirred for 24 h at rt. Then it was diluted with CH_2Cl_2 and alkalinized with an excess of aqueous NaOH (2.5 M). The layers were separated and the aqueous phase was repetitively extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and evaporated *in vacuo*. The crude product was subjected to column chromatography (SiO_2) CH_2Cl_2–MeOH (93 : 7). Yield: 90 mg (69%). Physical state: brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.58–7.56 (m, 2H), 7.49–7.45 (m, 3H), 7.41–7.37 (m, 1H), 7.20–7.15 (m, 2H), 3.11–3.05 (AB-part of ABX system, $J_{AB} = 14.5$ Hz, $J_{AX} = 14.8$ Hz, $J_{BX} = 27.8$ Hz, 2H), 1.69 (d, $^3J_{HF} = 22.3$ Hz, 3H), 1.29 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 159.6 (d, $^1J_{CF} = 246.6$ Hz), 144.2 (dd, $J_{CF} = 22.6$, 7.2 Hz), 135.2, 130.8, 128.9, 128.4, 128.0 (d, $^2J_{CF} = 13.5$ Hz), 127.7, 120.2 (dd, $J_{CF} = 9.6$, 2.9 Hz), 112.6 (dd, $J_{CF} = 25.1$, 10.6 Hz), 97.6 (d, $^1J_{CF} = 173.4$ Hz), 52.0 (d, $^2J_{CF} = 25.1$ Hz), 24.9 (d, $^2J_{CF} = 24.1$ Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ/ppm: −117.09 to −117.14 (m, 1F), −156.63 to −156.92 (X-part of ABX system, 1F); IR (neat) $\tilde{\nu}$/cm^{-1}: 1581w, 1484m, 1408m, 1281w, 1184w, 1075w, 1010w, 830m, 767s; HRMS (ESI-Orbitrap) *m*/*z*: calcd for $C_{15}H_{16}N_2F$ $[M + H]^+$ 248.1245, found 248.1254.

***N*-(2-Fluoro-2-(2-fluoro-[1,1′-biphenyl]-4-yl)propyl)propane-2-sulfonamide (10).** Propane-2-sulfonyl chloride (55 μL, 430 μmol) was added dropwise to a solution of **9** (90 mg, 360 μmol), DMAP (53 mg, 360 μmol) and Et_3N (100 μL, 720 μmol) in dry CH_2Cl_2 (1 mL). The resulting reaction mass was left to stir at 0 °C under Ar for 3 h. Then the mixture was diluted with CH_2Cl_2, washed with aqueous HCl (2 M), and brine. The organic phase was dried over anhydrous Na_2SO_4, filtered, and evaporated *in vacuo*. The product was further purified by column chromatography (SiO_2) *n*-heptane–EtOAc, (3 : 1). Yield: 47 mg (37%). Physical state: white solid. Mp 86–88 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.56–7.54 (m, 2H), 7.50–7.56 (m, 3H), 7.42–7.38 (m, 1H), 7.22–7.17 (m, 2H), 4.47 (t, $J = 6.3$ Hz, 1H), 3.67–3.51 (m, 2H), 3.09 (sept, $J = 6.8$ Hz, 1H), 1.77 (d, $^3J_{HF} = 22.5$ Hz, 3H), 1.34 (d, $J = 6.8$ Hz, 3H); 1.31 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 159.7 (d, $^1J_{CF} = 248.5$ Hz), 142.9 (dd, $J_{CF} = 22.2$, 7.7 Hz), 135.0, 131.0, 128.9, 128.7 (d, $^2J_{CF} = 13.5$ Hz), 128.5, 127.9, 120.1 (dd, $J_{CF} = 9.6$, 3.4 Hz), 112.5 (dd, $J_{CF} = 25.1$, 10.6 Hz), 96.4 (d, $^1J_{CF} = 176.3$ Hz), 54.0, 52.4 (d, $^2J_{CF} = 23.1$ Hz), 24.5 (d, $^2J_{CF} = 24.1$ Hz), 16.5 (d, $^3J_{CF} = 7.7$ Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ/ppm: −116.42 to −116.52 (m, 1F), −153.04 to −153.33 (m, 1F); IR (neat) $\tilde{\nu}$/cm^{-1}: 3137w, 2933w, 1484w, 1450w, 1409m, 1308s, 1187w, 1116s, 1072m, 915m, 872w, 839m, 770s, 725s; HRMS (ESI-Orbitrap) *m*/*z*: calcd for $C_{18}H_{20}O_2NF_2S$ $[M - H]^-$ 352.1188, found 352.1191.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

CIISB research infrastructure project LM2015043 funded by MEYS CR is gratefully acknowledged for the financial support of the measurements at the Proteomics Core Facility. We wish to thank Peter Zubac for the generous gift of several 2-arylalkanoic acids.

Notes and references

1 (*a*) L. A. Nguyen, H. He and C. Pham-Huy, *Int. J. Biomed. Sci.*, 2006, **2**, 85; (*b*) S. W. Smith, *Toxicol. Sci.*, 2009, **110**, 4; (*c*) W. H. Brooks, W. C. Guida and K. G. Daniel, *Curr. Top. Med. Chem.*, 2011, **11**, 760; (*d*) M. Hyneck, J. Dent, J. B. Hook, E. J. Ariens and D. S. Davies, in *Chirality in Drug Design and Synthesis*, ed. C. Brown, Academic Press, San Diego, 1st edn, 2013, pp. 1–51.

2 (*a*) D. J. Ager, I. Prakash and D. R. Schaad, *Chem. Rev.*, 1996, **96**, 835; (*b*) S. C. Bergmeier, *Tetrahedron*, 2000, **56**, 2561; (*c*) H.-S. Lee and S. H. Kang, *Synlett*, 2004, 1673; (*d*) S. Giorgio Della, R. Alessio and L. Alessandra, *Curr. Org. Chem.*, 2011, **15**, 2147; (*e*) H. Nakano, I. A. Owolabi, M. Chennapuram, Y. Okuyama, E. Kwon, S. Seki, M. Tokiwa and M. Takeshita, *Heterocycles*, 2018, **97**, 647.

3 (*a*) O. K. Karjalainen and A. M. P. Koskinen, *Org. Biomol. Chem.*, 2012, **10**, 4311; (*b*) T. Sehl, Z. Maugeri and D. Rother, *J. Mol. Catal. B: Enzym.*, 2015, **114**, 65; (*c*) P. Gupta and N. Mahajan, *New J. Chem.*, 2018, **42**, 12296.

4 Vol. 8: Reduction, in *Comprehensive Organic Synthesis,* ed. J. Clayden, Elsevier Science, Amsterdam, 2nd edn, 2014.

5 (*a*) J. Cossy, D. Gomez Pardo, C. Dumas, O. Mirguet, I. Déchamps, T.-X. Métro, B. Burger, R. Roudeau, J. Appenzeller and A. Cochi, *Chirality*, 2009, **21**, 856; (*b*) T.-X. Métro, B. Duthion, D. Gomez Pardo and J. Cossy, *Chem. Soc. Rev.*, 2010, **39**, 89; (*c*) C. Weng, H. Zhang, X. Xiong, X. Lu and Y. Zhou, *Asian J. Chem.*, 2014, **26**, 3761; (*d*) D. S. Bhagavathula, G. Boddeti and R. Venu, *J. Chem.*, 2017, **6**, 27.

6 (*a*) T. J. Donohoe, C. K. A. Callens, A. Flores, A. R. Lacy and A. H. Rathi, *Chem.–Eur. J.*, 2011, **17**, 58; (*b*) T. Taniguchi, A. Yajima and H. Ishibashi, *Adv. Synth. Catal.*, 2011, **353**, 2643; (*c*) D. Hofmann, C. de Salas and M. R. Heinrich, *ChemSusChem*, 2015, **8**, 3167; (*d*) M. M. Heravi, T. B. Lashaki, B. Fattahi and V. Zadsirjan, *RSC Adv.*, 2018, **8**, 6634.

7 O. N. Burchak and S. Py, *Tetrahedron*, 2009, **65**, 7333.

8 G. B. Fisher, C. T. Goralski, L. W. Nicholson, D. L. Hasha, D. Zakett and B. Singaram, *J. Org. Chem.*, 1995, **60**, 2026.

9 (*a*) A. Kamimura and N. Ono, *Tetrahedron Lett.*, 1989, **30**, 731; (*b*) S.-C. Tsay, H. V. Patel and J. R. Hwu, *Synlett*, 1998, 939; (*c*) P. Diner, M. Nielsen, S. Bertelsen, B. Niess and K. A. Jørgensen, *Chem. Commun.*, 2007, 3646; (*d*) A. Russo and A. Lattanzi, *Adv. Synth. Catal.*, 2008, **350**, 1991.

10 (*a*) H.-G. Brunker and W. Adam, *J. Am. Chem. Soc.*, 1995, **117**, 3976; (*b*) W. Adam and H.-G. Brunker, *Synthesis*, 1995, 1066.
11 (*a*) J. Otevrel and P. Bobal, *Synthesis*, 2017, **49**, 593; (*b*) J. Otevrel and P. Bobal, *J. Org. Chem.*, 2017, **82**, 8342; (*c*) J. Otevrel, D. Svestka and P. Bobal, *Org. Biomol. Chem.*, 2019, **17**, 5244.
12 J. Vit, B. Casensky and J. Machacek, Patent FR 1515582, Czechoslovak Academy of Sciences, 1968; Chem. Abstr., 1969, 70, 115009.
13 For selected reviews, see: (*a*) O. Strouf, B. Casensky and V. Kubanek, *Sodium Dihydrido-bis(2-methoxyethoxo)-aluminate (SDMA): A Versatile Organometallic Hydride*, Elsevier, Amsterdam, 1985; (*b*) J. Malek, *Org. React.*, 1985, **34**, 1; (*c*) J. Malek, *Org. React.*, 1988, **36**, 249; (*d*) M. Gugelchuk, L. F. Silva III, R. S. Vasconcelos and S. A. P. Quintiliano, Bis(2-methoxyethoxy)aluminum Hydride, in *Encyclopedia of Reagents for Organic Synthesis*, ed. P. Fuchs, J. Bode, A. Charette and T. Rovis, John Wiley, New York, 2007; (*e*) A. Rathi, *Synlett*, 2010, 1140; (*f*) M. B. Smith, *Organic Synthesis*, Elsevier Science, Cambridge, 2016, pp. 339–344.
14 For recent seminal works, see: (*a*) N. Bajwa and M. P. Jennings, *J. Org. Chem.*, 2008, **73**, 3638; (*b*) F. von Kieseritzky and J. Lindstrom, *Tetrahedron Lett.*, 2011, **52**, 4558; (*c*) K. Miyamoto, M. M. Hoque and S. Ogasa, *J. Org. Chem.*, 2012, **77**, 8317; (*d*) J. Wu, J. Xiao, W. Dai and S. Cao, *RSC Adv.*, 2015, **5**, 34498; (*e*) R. Sun, J. Liu, S. Yang, M. Chen, N. Sun, H. Chen, X. Xie, X. You, S. Li and Y. Liu, *Chem. Commun.*, 2015, **51**, 6426.
15 (*a*) H. H. Jeon, J. B. Son, J. H. Choi and I. H. Jeong, *Tetrahedron Lett.*, 2007, **48**, 627; (*b*) T. Konno, M. Kishi, T. Ishihara and S. Yamada, *J. Fluorine Chem.*, 2013, **156**, 144; (*c*) G. Jin, J. Zhang, W. Wu and S. Cao, *J. Fluorine Chem.*, 2014, **168**, 240.
16 *e.g.* 2-(4-chlorophenyl)-2-hydroxyacetonitrile subjected to the standard reaction conditions provided a mixture of 2-amino-1-phenylethan-1-ol and 2-amino-1-(4-chlorophenyl)ethan-1-ol in a 26 : 74 ratio according to RP-HPLC. HPLC conditions: an YMC-Triart C_{18} column (3 μm, 150 × 2.0 mm), MeCN–50 mM $HCOONH_4$ (pH = 9.30), 20 : 80, 0.2 mL min^{-1}, 40 °C, 210 nm.
17 (*a*) M. Kraus, *Collect. Czech. Chem. Commun.*, 1972, **37**, 3052; (*b*) M. Czakoova, J. Hetflejs and J. Vcelak, *React. Kinet. Catal. Lett.*, 2001, **72**, 277.
18 HPLC purity was >93%. HPLC conditions: an YMC-Triart C_{18} column (3 μm, 150 × 2.0 mm), MeCN–H_2O, 50 : 50 → 90 : 10, 0.2 mL min^{-1}, 40 °C, 210 nm.
19 (*a*) V. Bazant, M. Capka, M. Cerny, V. Chvalovsky, K. Kochloefl, M. Kraus and J. Malek, *Tetrahedron Lett.*, 1968, **9**, 3303; (*b*) M. Cerny, J. Malek, M. Capka and V. Chvalovsky, *Collect. Czech. Chem. Commun.*, 1969, **34**, 1033.
20 This was revealed during optimization of the reaction conditions (entry 5, Table S1†).
21 (*a*) M. S. Kharasch and G. Sosnovsky, *Tetrahedron*, 1958, **3**, 97; (*b*) M. S. Kharasch and G. Sosnovsky, *Tetrahedron*, 1958, **3**, 105; (*c*) J. S. Selikson and D. S. Watt, *J. Org. Chem.*, 1975, **40**, 267; (*d*) C. Walling, *Autoxidation in Active Oxygen in Chemistry*, ed. C. S. Foote, J. S. Valentine, A. Greenberg and J. F. Liebman, Springer, Dordrecht, 1995, pp. 24–65.
22 U. Bergstrasser, S. J. Collier, Y. Ito, S. Kanemasa and S. I. Murahashi, *Three Carbon–Heteroatom Bonds: Nitriles, Isocyanides, and Derivatives in Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*, ed. S. I. Murahashi, Georg Thieme, Stuttgart, 2004, vol. 19.
23 Traces of analogous ketones were isolated also from the reaction mixtures of **1a**, **1c**, **1d**, **1e**, and the respective nitriles.
24 M. Moller, M. Husemann and G. Boche, *J. Organomet. Chem.*, 2001, **624**, 47.
25 It is noteworthy that *rac*-**1a** provided **5a** in the racemic form.
26 (*a*) D. M. Bender, B. E. Cantrell, A. H. Fray, W. D. Jones, W. D. Miller, D. Mitchell, R. L. Simon, H. Zarrinmayeh and D. M. Zimmerman, Patent WO 2000066546, Eli Lilly, 2000Chem. Abstr., 2000, 133, 350055; (*b*) J. A. Clemens and D. Lodge, Patent WO 2002032389, Eli Lilly, 2002Chem. Abstr., 2002, 136, 340487.
27 L. H. Sommer, C. L. Frye, G. A. Parker and K. W. Michael, *J. Am. Chem. Soc.*, 1964, **86**, 3271.
28 M. Amir, H. Kumar and S. A. Javed, *Arch. Pharm.*, 2007, **340**, 577.
29 N. Ohtsuka, M. Okuno, Y. Hoshino and K. A. Honda, *Org. Biomol. Chem.*, 2016, **14**, 9046.
30 F. A. J. Kerdesky, C. D. W. Brooks, K. I. Hulkower, J. B. Bouska and R. L. Bell, *Bioorg. Med. Chem.*, 1997, **5**, 393.
31 T. Tu, Z. Wang, Z. Liu, X. Feng and Q. Wang, *Green Chem.*, 2012, **14**, 921.
32 T. Kanda, A. Naraoka and H. Naka, *J. Am. Chem. Soc.*, 2019, **141**, 825.
33 T. Mecca, S. Superchi, E. Giorgio and C. Rosini, *Tetrahedron: Asymmetry*, 2001, **12**, 1225.
34 M. Kimura, A. Kuboki and T. Sugai, *Tetrahedron: Asymmetry*, 2002, **13**, 1059.
35 W. A. Bonner, *J. Am. Chem. Soc.*, 1954, **76**, 6350.
36 N. Iqbal and E. J. Cho, *Adv. Synth. Catal.*, 2015, **357**, 2187.
37 E. V. Bellale, D. S. Bhalerao and K. G. Akamanchi, *J. Org. Chem.*, 2008, **73**, 9473.
38 G. Nemeth, E. Rakoczy and G. Simig, *J. Fluorine Chem.*, 1996, **76**, 91.
39 J. A. Dale, D. L. Dull and S. H. Mosher, *J. Org. Chem.*, 1969, **34**, 2543.
40 F. Li, X. Zou and N. Wang, *Adv. Synth. Catal.*, 2015, **357**, 1405.
41 B. Guo, J. G. de Vries and E. Otten, *Chem. Sci.*, 2019, **10**, 10647.
42 H.-M. Xia, F.-L. Zhang, T. Ye and Y.-F. Wang, *Angew. Chem., Int. Ed.*, 2018, **57**, 11770.
43 N. H. Khan, S. Agrawal, R. I. Kureshy, S. H. R. Abdi, S. Singh and R. V. Jasra, *J. Organomet. Chem.*, 2007, **692**, 4361.
44 P. G. Gassman and J. J. Talley, *Org. Synth.*, 1981, **60**, 14.
45 T. Hiyama, M. Inoue and K. Saito, *Synthesis*, 1986, 645.
46 R. Shang, D.-S. Ji, L. Chu, Y. Fu and L. Liu, *Angew. Chem., Int. Ed.*, 2011, **50**, 4470.
47 The same results were obtained with 60% SMEAH in toluene (6.4 mL, 15 equiv.).

48 The free base of the respective aminoalcohol **3** was liberated from the corresponding oxalic acid salt on demand by addition of an aqueous solution of NaOH (2.5 M) and back-extraction to toluene.
49 J. Xiao, Z. Z. Wong, Y. P. Lu and T. P. Loh, *Adv. Synth. Catal.*, 2010, **352**, 1107.
50 A. Dornow and W. Sassenberg, *Justus Liebigs Ann. Chem.*, 1955, **594**, 185.
51 V. M. Balaramnavar, R. Srivastava, N. Rahuja, S. Gupta, A. K. Rawat, S. Varshney, H. Chandasana, Y. S. Chhonker, P. K. Doharey, S. Kumar, S. Gautam, S. P. Srivastava, R. S. Bhatta, J. K. Saxena, A. N. Gaikwad, A. K. Srivastava and A. K. Saxena, *Eur. J. Med. Chem.*, 2014, **87**, 578.
52 C. P. Casey and H. Guan, *J. Am. Chem. Soc.*, 2007, **129**, 5816.
53 J. V. Castell, M. J. Gomez-Lechon, M. A. Miranda and I. M. Morera, *J. Photochem. Photobiol., B*, 1992, **13**, 71.
54 D. P. Riley, D. P. Getman, G. R. Beck and R. M. Heintz, *J. Org. Chem.*, 1987, **52**, 287.