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Structure Elucidation

Design of Selenium-Based Chiral Chemical Probes for Simultaneous Enantio- and Chemosensing of Chiral Carboxylic Acids with Remote Stereogenic Centers by NMR Spectroscopy

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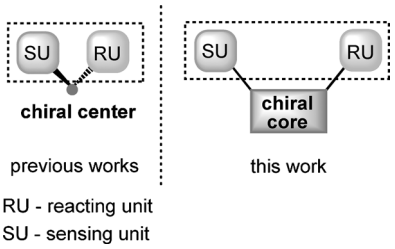
In the memory of our colleague and friend Dr. P. A. Belyakov

Abstract: Selenium-based enantiopure chiral chemical probes have been designed in a modular way starting from available amino alcohols. The probes developed were found to be efficient in chemoselective interaction with carboxylic functions of chiral substrates leading to diastereomeric amide formation and in sensing α-, β-, and remote (up to seven bonds away from the carboxylic group) chiral centers by using ^{77}Se NMR spectroscopy. As a result, it was possible to determine the enantiomeric ratio of structurally diverse individual chiral acids including polyfunctional compounds and drugs with high accuracy. An approach to analyzing the crude reaction mixtures has been successfully developed by using bifunctional selenium- and fluorine-containing chiral probes. More importantly, it was revealed that, based on the ^{77}Se NMR data obtained, it is possible to obtain primary information about the location and nature of the substituents at the chiral center (chemo- and enantiosensing), which can simplify the structural elucidation of complex compounds. The derivatization procedure takes as little as 5 min and can be performed directly in an NMR tube followed by NMR measurements without any isolation and purification steps.

Introduction

Development of asymmetric synthesis and catalysis has seen tremendous progress in recent decades.[1] The new trend in this field is multi-bond forming one-pot reaction cascades that open access to nature-mimicking chiral compounds.[2] To achieve these in a rational way, a demand arises to monitor the chemo-, regio-, diastereo-, and enantioselectivity at different steps in the one-pot sequence, thus requiring efficient, reliable, and quick analytical methods to be used. In addition, it is highly desirable to gain structural information concerning the products formed. Although chiral HPLC and GC are widely used nowadays to determine enantiomeric excess of the chiral compounds, they have some limitations in the case of analysis of crude reaction mixtures especially those containing transition metals. Individually, they can provide no data about the structure of the products formed and combined use of HPLC or GC and HRMS is required. Keeping these in mind, rapidly improving spectral methods (NMR, UV, UV/Vis) can be considered as an attractive and more powerful alternative. As these methods are achiral themselves, auxiliary enantiopure chiral compounds are required to selectively react with an analyzed sample for enantiodiscrimination to be generated. Although this is less convenient compared with chromatographic methods, on another hand it opens wide possibilities to variate the structures of the probes, reaching the highest selectivity and sensitivity. Numerous fluorescent and colorimetric chiral chemical probes have been designed for this purpose, which so far have shown promising results in the determination of enantiomeric excess (*ee*) and absolute configuration of different chiral compounds.[3] The probes are constructed in a modular way so various reacting units, responsible for selective recognition of a molecule or molecular fragment, and sensing units are attached to a chiral core (Scheme 1). Different to the numerous chiral derivatizing agents previously developed in which the chiral center had to be created upon introduction of the reacting and sensing units into a molecule (singular design), modification of chiral probes does not require any impact on a chiral center, which already exists in a suitable chiral core. As a result, the methods of synthesis of the probes are simplified and do



Scheme 1. Modular versus singular design of chiral chemical probes for analysis of chiral compounds by using NMR spectroscopy.

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not require asymmetric steps. What is more important is that it becomes extremely easy to perform fine tuning to reach the best selectivity for definite compounds to be analyzed and sensitivity of the response. Such an approach can be highly beneficial if used in NMR spectroscopy. The method has been shown to provide accurate and reliable data on chirality sensing,[4] but, until recently, it has been lacking easily variable chiral probes and required time- and reagent-consuming derivatization procedures. However, continuous improvement of derivatization procedures and introduction of new chiral auxiliaries during the last decade has resulted in the development of fast methods (within minutes) to form diastereomers directly in an NMR tube, thus avoiding isolation and purification steps before NMR analysis (so-called "mix and shake" protocols).[5]

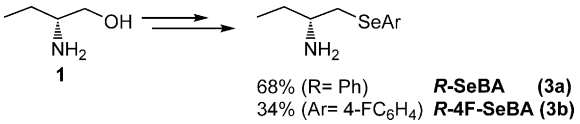
Based on our previous investigations, we envisaged the development of a modular chiral chemical probe that can be easily modified for selective recognition of various functionalized chiral organic compounds by NMR spectroscopy. In addition, introduction of NMR-active heteronuclei (such as ^{19}F, ^{31}P, ^{77}Se) can improve the sensitivity of the analysis and simplify assignment of the diastereomers formed as only the signals of analyzed compounds bound to the probe are observed in the spectra.[6] In this paper, we describe the design of new selenium-based and dual selenium/fluorine chiral probes used for enantio- and chemosensing of chiral carboxylic acids, which are of high demand in laboratory organic synthesis and catalysis[7] as well as in the pharmaceutical industry, perfumery, and agriculture.[8]

Results and Discussion

Design criteria and synthesis of the probes

For an efficient chiral probe for carboxylic functions to be created, first the choice of suitable reacting unit should be considered. Among various types of functional groups able to react with carboxylic acids, the NH_2 group seems to be the most suitable. Given appropriate promoters, it quickly reacts with acids to form amides. It is also important that many chiral amines are commercially available in enantiopure form and thus can be used as a ready chiral core to develop sensitive and selective chiral probes. Although formation of salts can also be used for recognition of enantiomers simply upon mixing of an acid and amine, we did not consider such a possibility. Indeed, diastereomeric amides usually give much better discrimination of signals in NMR spectra (i.e., enantiosensitivity of a sensor) compared with diastereomeric solvation complexes and for the former the value of enantiodiscrimination does not depend on the concentration of the chiral sensor.[9]

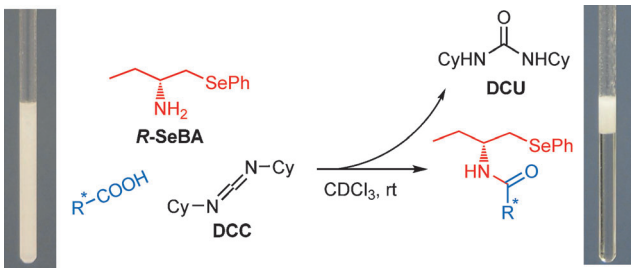
Besides the reacting site, a second functionality should be present in the molecule to provide the possibility for easy introduction of various sensing units depending on the particular analytical needs. α-Amino alcohols fulfill both these criteria so commercially available (*R*)-2-amino-1-butanol **1** was chosen as a chiral core for the synthesis of selenium-based chiral chemical probes—(*R*)-1-(phenylselanyl)butan-2-amine ((*R*)-SeBA) **3a** and (*R*)-1-((4-fluorophenyl)selanyl)butan-2-amine ((*R*)-4F-SeBA) **3b**. The choice of selenium-containing sensing unit was determined by the high NMR sensitivity of this nucleus to structural changes in the molecular environment[5g,6o,p] so it gives the possibility to probe even challenging remote stereogenic centers, which are often present in natural products and drugs. Thus, the target selenium-based chiral probes **3a** and **3b** were obtained on a gram scale in four steps starting from readily available and inexpensive enantiopure amino alcohol **1** (Scheme 2).[10] The key step—introduction of a chirality sensing SeAr group—was performed by using in situ reduced Ar_2Se_2 (Ar = Ph for **3a** and 4-FC_6H_4 for **3b**) followed by one-pot amino-group deprotection with concentrated HCl solution added to the reaction mixture. The original extraction method for isolation and purification developed gave 68% isolated yield (starting from **1**) of free base **3a** of high chemical purity. In a similar manner, pure **3b** was obtained in 34% unoptimized yield. As the stereogenic center was not involved in the reaction, the products were obtained in enantiopure form, which was confirmed by NMR analysis of the corresponding diastereomeric amides formed upon interaction with enantiopure (*R*)-methoxyphenylacetic acid. Thus, the fact that there was no decrease in enantiomeric purity after isolation indicated that the products are stable under acidic and basic conditions. It should be mentioned that the purification procedure developed is much faster than other methods used, such as chromatography, and gave better isolated yields (in the case of other methods, the isolated yield was less than 40%).



Scheme 2. Synthetic approach to chiral NMR probes (*R*)-SeBA **3a** and (*R*)-4F-SeBA **3b**.[10]

Investigation of the probe's enantiosensing capacity

First of all, we tested the enantiosensing ability of (*R*)-SeBA **3a** in $CDCl_3$ as the most common deuterated solvent used in NMR spectroscopy to analyze the vast majority of organic compounds. Mixing the different chiral carboxylic acids and promoter *N*,*N*′-dicyclohexylcarbodiimide (DCC) in $CDCl_3$ directly in an NMR tube resulted in immediate formation of a white suspension upon shaking (Scheme 3, left). After that, chiral probe **3a** (as little as 10 mg) was added and insoluble particles of dicyclohexylurea (DCU) were formed in 1–2 min, which were removed to the top of the solution by centrifugation directly in the NMR tube (Scheme 3, right).[11] The ^1H NMR spectrum was measured after centrifugation and formation of diastereomers was confirmed.[12] It should be emphasized that insoluble particles did not affect quality of the NMR spectra so no additional purification or isolation of diastereomers formed was necessary prior to NMR analysis. Thus, DCC-promoted derivati-



Scheme 3. DCC-promoted "in tube" derivatization of chiral carboxylic acids with chiral probe (*R*)-SeBA **3a**.

zation using the chiral probe (*R*)-SeBA **3a** can be performed directly in an NMR tube and it takes less than 5 min to prepare samples suitable for NMR analysis.

As expected, two baseline resolved signals of diastereomers were observed in the ^{77}Se NMR spectrum, thus proving the utility of the method. Different model chiral carboxylic acids were successfully analyzed by using (*R*)-SeBA **3a** and the high enantiosensitivity of the chiral probe developed, expressed in baseline resolved signals of diastereomers **4**–**32** (Scheme 4). In addition, the protocol developed well tolerated different functional groups on the acids analyzed (hydroxyl, keto, ether, ester, sulfide, halogen, nitro, and secondary amino groups), thus excluding side reactions leading to acid degradation or formation of complex mixtures of diastereomers. This allowed correct assignment and accurate quantitative measurements of enantiomeric purity to be made (see below). It should be mentioned that less than 5 min is required to register ^{77}Se NMR spectra suitable for correct recognition and assignment of diastereomers although longer time is needed to perform accurate quantitative measurements.

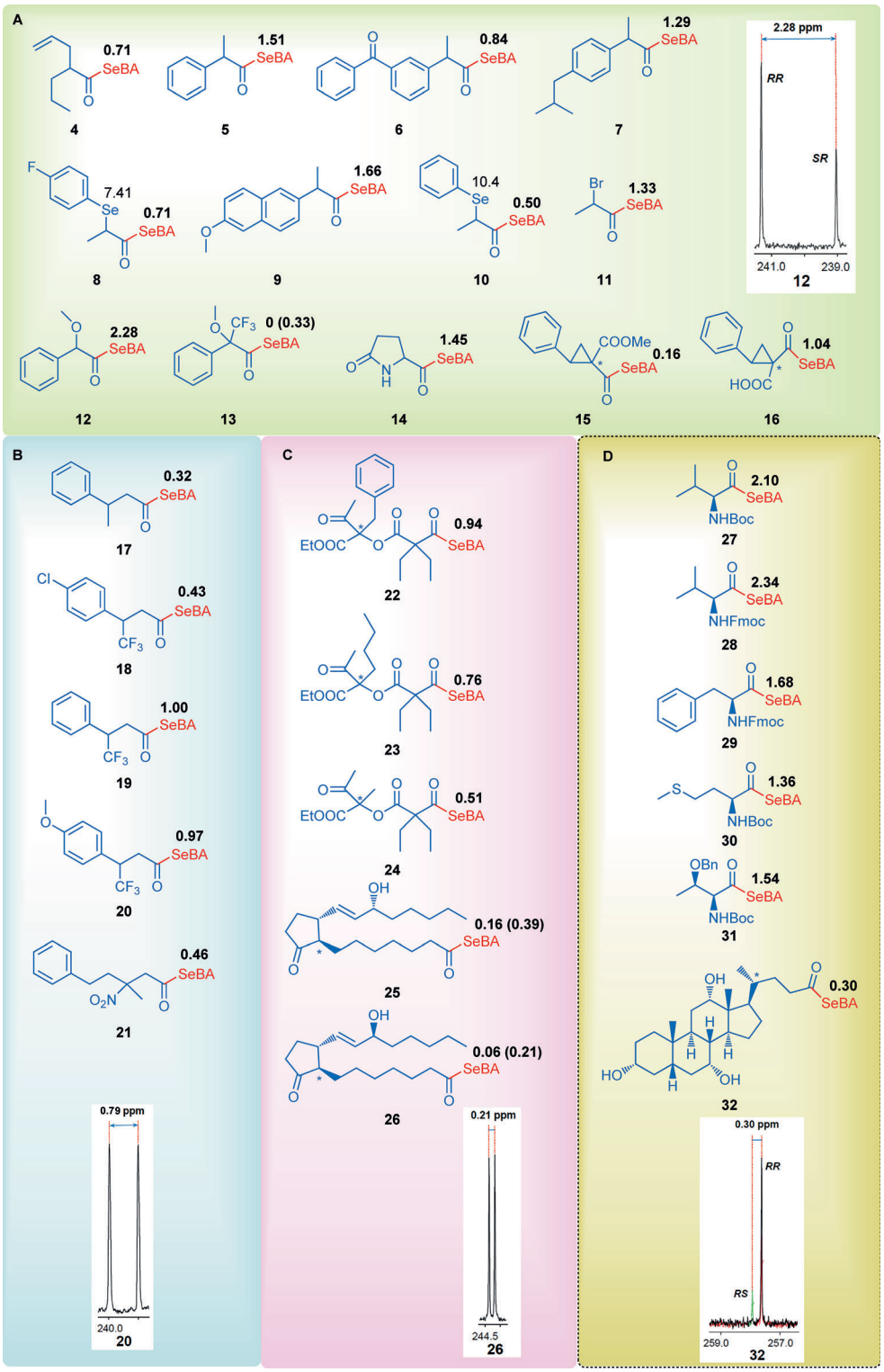
Excellent results were obtained for α-chiral carboxylic acids **4**–**16** (Scheme 4, part A): the average difference in chemical shifts was 0.5–1.5 ppm, with the maximum difference being 2.28 ppm for diastereomeric amides **12** (Scheme 4, part A). The only exceptions were the diastereomeric amides of Mosher's acid **13** with quaternary stereogenic center, which gave no split of signals in $CDCl_3$. However, when derivatization was performed in [D_8]toluene, two separate signals of diastereomers **13** with a difference of 0.33 ppm were observed.[13] In the case of other analyzed acids possessing quaternary stereocenters, no such problems were encountered and signals of corresponding diastereomers **15**, **16**, **21**–**24** were baseline resolved even in $CDCl_3$. We have found that chiral probe (*R*)-SeBA **3a** is efficient for sensing not only stereogenic centers in the α-position of the carboxylic acids analyzed but also for acids with more remote chiral centers. Diastereomers of β-carboxylic acids **17**–**21** were easily recognized and the difference in the chemical shifts was still enough for baseline resolution of signals in the ^{77}Se NMR spectra (Scheme 4, part B). To determine the enantiosensitivity threshold of the probe developed, we have analyzed two racemic prostaglandines **25** and **26** with the closest chiral center seven bonds away from the carboxylic group (the stereocenter under consideration is marked with an asterisk in Scheme 4, part C). Although chiral molecules with such remote centers are challenging for recognition, chiral probe **3a** showed remarkable enantiosensitivity and two baseline resolved signals of the diastereomers with the difference in chemical shift being 0.39 and 0.21 ppm, respectively, were observed in the ^{77}Se NMR spectra (representative example of ^{77}Se NMR spectrum of **26** is shown in the insert of Scheme 4, part C). Again, the resolution of signals observed in [D_8]toluene was better than in $CDCl_3$ (Scheme 4). It should be mentioned that despite free OH groups being present in the analyzed prostaglandines **25** and **26** no side reaction of ester formation occurred, thus the developed chiral probe **3a** is highly chemoselective for carboxylic groups.

As expected, removing the chiral center one or more bond away from the carboxylic group resulted in a decrease in the enantiodiscrimination capacity of the probe (compare homologous acids **5** and **17**, Scheme 4). However, in the case of acids **18**–**24** the difference in chemical shifts of the signals in the ^{77}Se NMR spectra was compatible to α-chiral carboxylic acids (Scheme 4). This fact indicates that the difference in ^{77}Se chemical shifts of diastereomers depends not only on the structural but also on the conformational composition of the considered diastereomers in solution and can be caused by intra- or intermolecular weak interactions stabilizing a particular conformation of a diastereomer. Consideration and prediction of such weak interactions is still a challenging task and is a matter of numerous studies.[14]

Finally, analysis of α-amino acids **27**–**31** and polyfunctional compounds such as bile acid **32** has been successfully performed by using probe **3a** (Scheme 4, part D).[15] Although free amino acids could not be analyzed by using the derivatization protocol developed, use of Boc- and Fmoc-protected derivatives allowed us to overcome solubility limitations. Both protecting groups were tolerant to the derivatization conditions. The differences in chemical shifts obtained for **27**–**31** were comparable to α-chiral carboxylic acids and the value obtained for **32** was in the range of chiral acids with remote stereogenic centers (compare part D with parts A and C in Scheme 4). The only modification in experimental derivatization procedure was the necessity to add a polar co-solvent to the $CDCl_3$ solution to obtain a narrow peaks for the diastereomers in the ^{77}Se NMR spectra.[10]

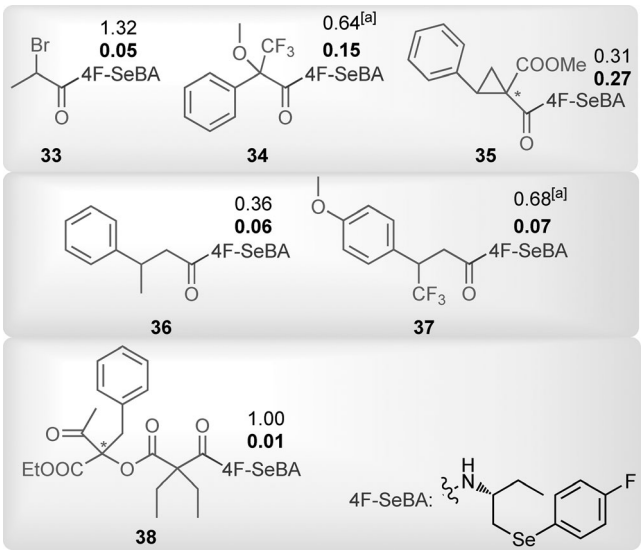
A representative range of chiral carboxylic acids has been used to test the enantiosensing capacity of probe **3b**. Derivatization was performed in an NMR tube in a similar manner as for **3a** (see Scheme 3) and the diastereomers obtained were analyzed by ^{77}Se and ^{19}F NMR spectroscopy (Scheme 5).

As can be seen, introduction of fluorine into the probe did not significantly influence the difference in chemical shifts of diastereomers in the ^{77}Se NMR spectra (compare the data in Schemes 4 and 5). Again, chiral carboxylic acids containing stereogenic centers in the α-, β-, and more remote positions were successfully analyzed. The only difference from **3a** was in the case of diastereomers **34** and **37**, which contained fluorine substituents in the chiral acid analyzed. In this case, broadening of the signals of the diastereomers in the ^{77}Se NMR spectra was observed when $CDCl_3$ was used as a solvent. The picture observed was quite similar to that obtained for the diastereo-



Scheme 4. The difference in the ^{77}Se NMR chemical shifts (in ppm) of the signals of diastereomers **4**–**32** obtained from the corresponding chiral carboxylic acids and (*R*)-SeBA **3a** in $CDCl_3$ (data in $[D_8]$toluene are given in parenthesis) and representative fragments of ^{77}Se NMR spectra of selected diastereomers. **A**: α-carboxylic acids; **B**: β-carboxylic acids; **C**: carboxylic acids with remote stereogenic centers; **D**: polyfunctional carboxylic acids (mixture of $CDCl_3/CD_3OD$ is used as a solvent, see text for details). Detailed data for the experimental NMR parameters of the spectra presented are given in the Supporting Information.

mers **27**–**32** of polyfunctional chiral acids with the probe **3a** and may result from weak interactions in solution (see above). Again, addition of a polar co-solvent, $[D_4]$MeOH, to the $CDCl_3$ solution allowed us to obtain narrow peaks for the diastereomers in the ^{77}Se NMR spectra. In addition, excellent results were obtained in the ^{19}F NMR spectra. Despite the fact that the fluorine atom is located in an even more remote position of the probe compared to selenium, baseline resolved signals



Scheme 5. The difference in ^{77}Se and ^{19}F (bold) NMR chemical shifts (in ppm) of the signals of diastereomers **33**–**38** obtained from the corresponding chiral carboxylic acids and (*R*)-4F-SeBA **3b** in $CDCl_3$. [a] Mixture of $CDCl_3/CD_3OD$ used as a solvent, see text for details.

were observed even for diastereomers **38**. More importantly, the ^{19}F NMR spectra could be obtained using one scan only so NMR analysis took less than 1 min. Thus, the whole procedure from sample preparation to spectrum obtained took less than 10 min for the ^{19}F NMR spectra. This is of high importance for high-throughput screening of numerous samples and can be useful in asymmetric synthesis and catalysis.

Determination of enantiomeric purity of chiral carboxylic acids by using the probes developed

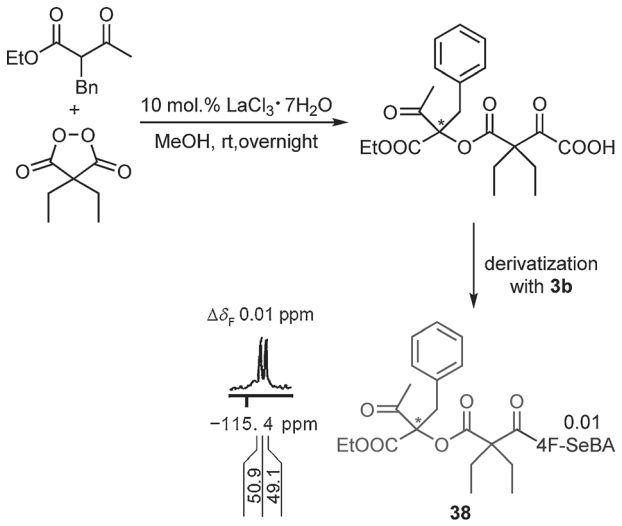
In addition to excellent enantiodiscrimination in ^{77}Se NMR spectra, the diastereomeric ratio (d.r.) of amides **4**–**32** formed was measured with high accuracy (usually within 1%).[10] Provided no racemization, kinetic resolution, or side reactions take place during the derivatization process, the diastereomeric ratio measured will be equal to the enantiomeric ratio (e.r.) of the initial chiral acids.

As the chiral probes developed have been found to be stable to racemization in basic and acidic conditions as well as during the storage in air in the cold, we studied possible side reactions during the derivatization process. In the studied derivatization system, chiral acids can form stable salts with **3** or unreactive adducts with DCC. All these side reactions can consume enantiomers of acids in different amounts, thus leading to kinetic resolution and special precautions should be made to exclude them. To prevent salt formation, the chiral acid to be analyzed was mixed with DCC first to form the activated adduct so no free acid was present in the system (confirmed by ^{1}H NMR spectroscopy). After that, chiral probe **3a** or **3b** was added to the mixture, resulting in the formation of the diastereomers. To study side reactions in the presence of DCC, special NMR monitoring was performed by using probe **3a**, which revealed that no kinetic resolution took place during the derivatization even at incomplete conversion of the analyzed acid.[10] As the difference in the chemical shifts of the diastereomers does not depend on their concentration, we were sure of the accuracy of assignment and determination of the d.r. of the diastereomers regardless of the completeness of the transformation of the analyzed chiral acids into the corresponding amides.

Thus, the chiral probe **3a** was used to analyze the enantiomeric purity of several chiral drugs containing carboxylic functions (such as profens **6**, **7**, **9** isolated directly from pills and bile acid **32** in Scheme 4).[15] Given the chemical shifts of both diastereomers, the acids to be analyzed were derivatized with enantiopure (*R*)-SeBA **3a** and ^{77}Se NMR spectra were recorded. When the conversion of the analyzed acid was full, approximately 6000–8000 scans were enough to obtain a good signal-to-noise ratio and precisely determine the intensity of the signal of a minor diastereomer. However, up to 40000 scans (overnight acquisition) were required to perform accurate d.r. determinations in the case of low conversions. The spectra obtained revealed the presence of only one diastereomer of the bile acid with the second being out of the detection limit of the NMR method (that is, less than 1%). In the case of profens, racemates were detected for diastereomers of ketoprofen **6** and ibuprofen **7** and 98% *ee* was detected in the case of (*S*)-naproxen **9**, which is in full agreement with that reported. A representative example of the ^{77}Se NMR spectra with enantiopure diastereomer of cholic acid **32** (black spectrum) and a mixture of both diastereomers (*R*/*S* = 3:1, green spectrum) is shown in the insert of Scheme 4, part D (for other examples, see the Supporting Information).

In addition to the analysis of pure samples, we have extended the derivatization procedure of chiral carboxylic acids in crude reaction mixtures. The possibility to perform NMR monitoring of enantiomeric excess of chiral products in crude reaction mixtures is of high practical importance nowadays. As we have shown that diastereomers can be formed directly in an NMR tube followed by NMR analysis without isolation and purification steps, we considered that the derivatization protocol developed can be implemented with a crude reaction mixture as well. To test this, we chose the formation of chiral carboxylic acids by lanthanide-catalyzed oxidative C–O coupling of 1,3-dicarbonyl compounds with diacyl peroxide recently developed by Terent'ev et al. (Scheme 6).[16] After the completion of the reaction, an aliquot of the crude reaction mixture was taken, the solvent was evaporated under reduced pressure, and the residue was derivatized by using the typical protocol discussed above.[10]

Unfortunately, it was difficult to completely remove moisture from the analyzed sample. This resulted in very low conversion of the acid to amide with both chiral probes **3a** and **3b**, thus no signals were detected in the ^{77}Se NMR spectra even after overnight acquisition. However, this problem was overcome when the ^{19}F NMR spectrum was registered by using the probe **3b** for derivatization. Despite low conversion of the acid into amide, signals of the diastereomers were definitely observed in the ^{19}F NMR spectrum even after one scan acquisition and these could be easily assigned.[10] The presence of other com-



Scheme 6. ^{19}F NMR monitoring of the enantiomeric ratio of the chiral acid in crude reaction mixtures by using (*R*)-4F-SeBA **3b**. Fragment of ^{19}F NMR spectrum with signals of diastereomers **38**.

ponents in the reaction mixture (including metal salt) did not influence the derivatization procedure or quality of the NMR spectrum so the product in the crude reaction mixture was successfully analyzed within several minutes and a 1:1 ratio of signals for the diastereomers was observed in the ^{19}F NMR spectrum (see insert in Scheme 6).

Chemosensing of chiral centers by using chiral probe 3a

Usually, the only difference in the chemical shifts or the relative position of signals of diastereomers in NMR spectra are taken into consideration to determine enantiomeric excess or the absolute configuration of the analyzed compounds.[4a,h,j] However, the values of chemical shifts of the diastereomers' signals can also give important information about the structure of the analyzed compound owing to the high sensitivity of heteronuclei to structural changes in a molecule. Such data are of primary importance for structural elucidation in modern organic and bioorganic chemistry.[17] Usually, a wide range of 2D NMR experiments is used for this purpose, so it would be highly desirable to develop simple, quick, and reliable methods to gain primary information about a studied structure. For this purpose, we have analyzed two parameters from the ^{77}Se NMR spectra of diastereomers obtained with the chiral probe **3a**: chemical shifts of the signals of diastereomers of different carboxylic acids (δ_{Se}) and the difference between the signals of diastereomers of these acids ($\Delta\delta_{Se}$). As solvents can cause large shifts in signals in ^{77}Se NMR spectra, data for structures **27**–**32** obtained in $CDCl_3/CD_3OD$ were excluded from consideration. The combined data for diastereomers **4**–**26** are represented in a plot in Figure 1 (see Scheme 4, parts A–C for the structures of the diastereomers). As can be seen from the plot, the signals of the diastereomers of structurally different chiral acids are located across a wide range of the ^{77}Se NMR scale, thus confirming the high chemosensitivity of the selenium nucleus (Figure 1, horizontal axis). A correlation is observed between chemical shifts of signals in the ^{77}Se NMR spectrum and electronic effects of substituents at chiral centers of the model chiral acids analyzed. In general, *the greater the electronegativity of the substituents at the chiral center, the more the signals of the diastereomers are shifted downfield on the ^{77}Se NMR scale*. Thus, the most upfield signals resulted from the acids containing aliphatic or aromatic substituents at the α-chiral center (**4**–**10**) and are located in the region 235–239 ppm. It should be noted that electron-withdrawing groups or atoms located far from the chiral center have almost no influence on the chemical shift (compare **5**, **6**, and **7**, Figure 1). When heteroatoms (Br, O, N, with Se being an exception) or electron-withdrawing groups (NO_2, CF_3) are introduced at the chiral center of the acids, the signals of the diastereomers are shifted downfield and are found in the region 239–245 ppm (**11**–**14**, Figure 1). Although a similar trend is observed for β-chiral centers (**17**–**21**), the substituent effect is less pronounced in this case and all

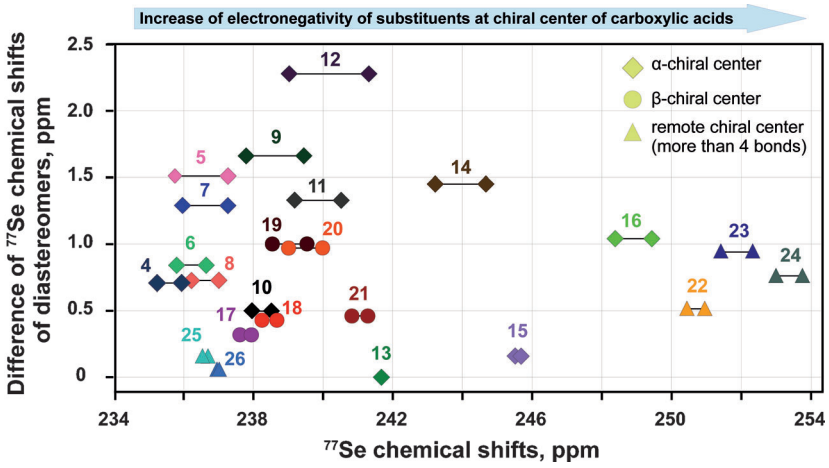


Figure 1. Chemosensitivity and enantiosensitivity of the chiral probe **3a** on the ^{77}Se NMR scale in $CDCl_3$ (α-chiral centers for diastereomers **4**–**16** are marked with diamonds, β-chiral centers for diastereomers **17**–**21** are marked with circles, and more remote chiral centers for diastereomers **22**–**26** are marked with triangles).

the signals are located in a narrow range, 238–241 ppm, of the ^{77}Se NMR scale. Finally, the diastereomers of acids with carboxylic substituents at the chiral center (**15**, **16**, **22**–**24**, Figure 1) are the most downfield ones (246–254 ppm).[18] In this case, remoteness of the chiral center from the carboxylic group did not influence the value of the chemical shift, δ_{Se}, with amides **22**–**24** being more downfield compared with **15** and **16**. Hence, based on these results obtained from routine 1D NMR experiments, it is possible to suggest what type of substituents is located at the chiral center of the studied molecule.

When we consider the correlation between the difference in the ^{77}Se chemical shifts of the diastereomers $\Delta\delta_{Se}$ and the nature of substituents at the chiral center, it is clear that the closer the analyzed chiral center is to the carboxylic function, the larger the difference in the chemical shifts of diastereomers observed in the ^{77}Se NMR spectra (compare **5** and **17** in Figure 1, vertical axis). Another thing that influences the $\Delta\delta_{Se}$ parameter is the nature of the substituents at the chiral center. When aromatic substituents or electron-withdrawing heteroatoms are bound to the α-chiral center of the acid, the difference in the chemical shifts increases (compare **5**, **7**, and **12** in Figure 1, vertical axis). This can be caused by the anisotropic current of the aromatic ring, the influence of which will be different for a pair of diastereomers.[19] The most pronounced effect is observed for amides **15** and **16** with rigid locations of the phenyl ring: when the phenyl substituent is located *cis* to the amide group, the difference observed is almost an order of magnitude larger than for *trans*-orientation of the substituents (Figure 1, Scheme 4). It is clear that in the case of flexible conformations, this effect on the difference in the chemical shifts of diastereomers can vary significantly, thus in some cases the influence of the aromatic ring may be neglected. Most likely, this is the case for diastereomers **13**, which show no enantiodiscrimination in $CDCl_3$ (Figure 1, Scheme 4).

Upon removing the chiral center from the reacting site, the difference in the chemical shifts of the diastereomers decreases (Figure 1, Scheme 4). In the case of α-chiral carboxylic acids **4**–**16**, the minimum difference observed was more than 0.5 ppm (with the diastereomers **13** and **15** being the only exceptions), with a maximum difference of $\Delta\delta_{Se}$ 2.28 ppm being obtained for amide **12**. However, $\Delta\delta_{Se}$ values were not more than 1.0 ppm for carboxylic acids with β- or remote stereogenic centers, **17**–**26** (Figure 1, Scheme 4).

Thus, taking into consideration these two parameters (δ_{Se} and $\Delta\delta_{Se}$), it is possible to make primary assumptions about the structure of the chiral acid analyzed. Although some complications may arise when acids with different locations of chiral center (α-, β-, or remote) are compared, it is clear from the plot presented that the region above 1.0 ppm on the vertical axis ($\Delta\delta_{Se}$) is specific for α-chiral carboxylic acids. Hence, if the signals of the diastereomers of an unknown structure are located in this region, unambiguous assignment to an α-chiral carboxylic acid can be made and the nature of the substituents at the chiral center can be proposed. Data from the complicated region (less than 1 ppm) can be still valuable to distinguish between structurally similar compounds (such as homologous acids **5** and **17**). We believe that the development of new selenium-based chiral probes with improved chemo- and enantiosensing capacities will allow better differentiation of signals of structurally diverse chiral acids and will be of high importance for quick and reliable structure elucidation.

Conclusion

Novel selenium-based chiral chemical probes (*R*)-SeBA and (*R*)-4F-SeBA have been synthesized and were found to be efficient for selective and quick interaction with carboxylic functions, giving diastereomers directly in an NMR tube without the need to isolate and purify the amides formed prior to NMR analysis. The derivatization method developed is general and can be implemented for structurally diverse chiral carboxylic acids as well as amino acids and polyfunctional compounds containing carboxylic functions (including drugs); different functional groups are tolerated. Both ^{77}Se and ^{19}F NMR spectroscopy have shown excellent results in the enantiodiscrimination of chiral carboxylic acids with stereogenic centers situated in the α-, β-, or even more remote (up to seven bonds away from the carboxylic group) positions. In addition to easy assignment of the signals of diastereomers, this method is suitable for the accurate determination of enantiomeric ratios (equal to the observed diastereomeric ratio) of pure samples as well as of crude reaction mixtures (by ^{19}F NMR spectroscopy), which is very useful for monitoring reactions for asymmetric synthesis and catalysis. Finally, by using the probe (*R*)-SeBA, we have revealed that it is possible to gain primary information about the nature of the chiral center of the analyzed acids based on the chemical shifts of the diastereomers δ_{Se} and the difference in the chemical shifts of diastereomers $\Delta\delta_{Se}$ in the ^{77}Se NMR spectra. Excellent empirical correlation between the position of the signals of diastereomers on the ^{77}Se NMR scale and the acid structure is observed for α-chiral carboxylic acids. Reliable assumptions about the nature of substituents at the chiral center of the acid can be made for diastereomers possessing $\Delta\delta_{Se}$ values more than 1.0 ppm, whereas for those with smaller enantiodiscrimination it is still possible to distinguish between homologous structures. The development of a range of chiral chemical probes with improved properties for the NMR analysis of chiral functionalized compounds is in progress in our laboratory.

Experimental Section

NMR spectroscopy

^{1}H and ^{77}Se NMR measurements were performed by using Bruker Avance 400 and 600 MHz spectrometers, ^{19}F NMR measurements were performed by using a Bruker Avance 400 MHz spectrometer. All spectra were recorded in $CDCl_3$ (unless otherwise noted) at 303 K without spinning of the NMR tube. ^{1}H and ^{19}F NMR measurements were carried out with a single 90° pulse. The spectra were processed with a Linux workstation using the TopSpin 2.1 software package. ^{1}H chemical shifts are reported relative to the corresponding solvent signals used as internal reference; $CFCl_3$ (0 ppm) and Ph_2Se_2 (463 ppm) were used for ^{19}F and ^{77}Se NMR spectrosco-

py, respectively, as external references. The detailed description of the NMR data is given in the Supporting Information.

Experimental setup and processing of 1D ^{77}Se NMR data

The spectrum was collected in the ^{77}Se observation and ^{1}H decoupling mode. A standard waltz16 decoupling was applied in this ^{77}Se{^{1}H} experiment. Spectral parameters: ^{77}Se 30° pulses, a relaxation delay of 3.0 s, a 1.0 s acquisition time, 2400–40000 scans, and 46000 Hz spectral window. The data was zero filled to 32k matrix and processed with exponential multiplication (LB = 1).

General

Unless otherwise noted, all experiments were performed in air. Reagents were obtained from Acros and Aldrich and used as supplied (checked by NMR spectroscopy and GC before use). The acids to prepare diastereomers **18**–**24**, **37**, and **38** can be synthesized according to published procedures.[16,20] The acids to prepare diastereomers **4**, **8**, and **10** were synthesized according to published procedures.[5g,7d] Solvents were purified according to published methods. The samples for analysis with the chiral chemical probes developed were prepared by using chiral compounds of known enantiomeric content. For the experiments shown in Tables S1 and S2 in the Supporting Information deuterated solvents were used as received.

High-resolution mass spectra were recorded with a Bruker maXis instrument equipped with an electrospray ionization (ESI) ion source. All measurements were performed in a positive (+MS) ion mode (interface capillary voltage: 4500 V) with scan range m/z = 50–3000. External calibration of the mass spectrometer was performed with Electrospray Calibrant Solution (Fluka). Direct syringe injection was used for the all analyzed solutions in MeCN (flow rate: 3 μL min^{-1}). Nitrogen was used as the nebulizer gas (0.4 bar) and dry gas (4.0 L min^{-1}); the interface temperature was set at 180 °C. All the spectra were processed by using the Bruker DataAnalysis 4.0 software package.

Synthesis of (*R*)-2-((*tert*-butoxycarbonyl)amino)butyl methanesulfonate (2)

N-Boc-protected (*R*)-2-amino-1-butanol was synthesized according to the modified literature procedure[21] with quantitative yield (stirring at 40 °C for 2 h was used instead of room temperature).

The crude adduct obtained was dissolved in CH_2Cl_2 (20 mL), which was followed by addition of Et_3N (1.2 equiv) and cooling to 0 °C. A solution of $MeSO_2Cl$ (1.1 equiv) in CH_2Cl_2 (20 mL) was added dropwise to the reaction mixture under stirring. The reaction temperature was increased slowly to room temperature and the reaction mixture was stirred overnight. The product was washed with H_2O (5×20 mL), dried with Na_2SO_4, and the solvent was removed under reduced pressure. Mesylate **2** was obtained in quantitative yield as a light-yellow solid. The product was identified according to the literature data.[22]

Synthesis of (*R*)-1-(phenylselanyl)butan-2-amine ((*R*)-SeBA, 3 a)

A mixture of mesylate **2** (2.0 g, 7.5 mmol) and Ph_2Se_2 (1.168 g, 3.7 mmol) was placed in a 150 mL round-bottomed flask followed by addition of argon-flushed ethanol (50 mL); a yellow suspension was formed. The mixture was cooled to −5 °C and $NaBH_4$ (0.849 g, 22.0 mmol) was added portion-wise under an argon atmosphere under stirring. The mixture was stirred for an additional 10 min and the color of the suspension changed to light yellow. The reaction temperature was increased slowly to room temperature and the reaction mixture was stirred overnight.

The reaction was quenched with water (10 mL). Then, concentrated HCl (20 mL) was added to the reaction vessel to remove the Boc group and stirring was continued for an additional 2 h at room temperature. The solution was gently concentrated under reduced pressure. H_2O (20 mL) was added to the residue and the solution was washed with CH_2Cl_2 (6×20 mL). Excess KOH was added to the water layer (a white suspension was formed upon neutralization of the **3**·HCl adduct). The pure product was extracted with Et_2O (2×25 mL). The combined organic layers were washed with H_2O (4×20 mL), dried with Na_2SO_4, and the solvent was removed under reduced pressure. Isolated yield 68% (1.159 g). Light-yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.92 (t, J = 7.5 Hz, 3H, Me), 1.35–1.41 (m, 1H, CH_2), 1.45 (br. s, 2H, NH_2), 1.50–1.57 (m, 1H, CH_2), 2.78 (dd, J = 11.5, 3.4 Hz, 1H, CH_2Se), 2.79–2.85 (m, 1H, CHN), 3.10 (dd, J = 11.5, 3.4 Hz, 1H, CH_2Se), 7.19–7.26 (m, 3H, Ph), 7.51 ppm (dd, J = 7.9, 1.8 Hz, 2H, Ph); ^{13}C{^{1}H} NMR (150.9 MHz, $CDCl_3$, 25 °C, TMS): δ = 10.6, 30.7, 37.3 (J_{Se} = 63.7 Hz), 52.3, 126.8, 129.0, 130.3, 132.7 ppm; ^{77}Se{^{1}H} NMR (114.5 MHz, $CDCl_3$, 25 °C, Ph_2Se_2): δ = 247.92; HRMS (ESI): calcd for $C_{10}H_{16}NSe$ $[M+H]^+$: 230.0443; found: 230.0447.

Synthesis of (*R*)-1-((4-fluorophenyl)selanyl)butan-2-amine ((*R*)-4F-SeBA, 3 b)

The product was synthesized by using the same procedure as for **3 a**. Isolated yield (unoptimized) 34% (0.204 g). Yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.92 (t, J = 7.5 Hz, 3H, Me), 1.34–1.43 (m, 1H, CH_2), 1.43–1.48 (br. s, 2H, NH_2), 1.49–1.57 (m, 1H, CH_2), 2.76 (dd, J = 11.8, 3.6 Hz, 1H, CH_2Se), 2.76–2.81 (m, 1H, CHN), 3.05 (dd, J = 11.8, 3.6 Hz, 1H, CH_2Se), 6.94–6.99 (m, 2H, Ph), 7.49–7.54 ppm (m, 2H, Ph); ^{13}C{^{1}H} NMR (150.9 MHz, $CDCl_3$, 25 °C, TMS): δ = 10.8, 30.5, 38.4 (J_{Se} = 63.3 Hz), 52.5, 116.4 (J_F = 21.3 Hz), 124.6, 135.5 (J_F = 8.1 Hz), 162.5 ppm (J_F = 246.4 Hz); ^{77}Se{^{1}H} NMR (114.5 MHz, $CDCl_3$, 25 °C, Ph_2Se_2): δ = 246.67 ppm (J_F = 4.3 Hz); ^{19}F{^{1}H} NMR (376.5 MHz, $CDCl_3$, 25 °C, $CFCl_3$): δ = −115.40 ppm; HRMS (ESI): calcd for $C_{10}H_{15}FNSe$ $[M+H]^+$: 248.0348; found: 248.0352.

To obtain *rac*-**3**, a similar synthetic procedure was used starting from commercially available *rac*-2-amino-1-butanol.

Typical procedure for the analysis of the samples of chiral carboxylic acids with chiral probe (*R*)-SeBA

The acid to be analyzed (4.0×10^{-5} mol) and DCC (0.0098 g, 4.7×10^{-5} mol) were dissolved in 0.1 mL of an appropriate deuterated solvent ($CDCl_3$ or [D_8]toluene) in an NMR tube and the mixture was shaken for 1–2 min.[11] A white suspension was formed. (*R*)-SeBA **3 a** (0.0075 mL, 0.0100 g, 4.4×10^{-5} mol) was subsequently added and the mixture was shaken for 1–2 min. After that, the same deuterated solvent (0.5 mL, $CDCl_3$ or [D_8]toluene) was added into the NMR tube. The insoluble particles were separated to the top of the $CDCl_3$ solution (to the bottom in the case of [D_8]toluene) by centrifugation of the NMR tube for 1 min at 1500 rpm.[10] The ^{1}H and ^{77}Se NMR spectra were recorded directly without any further purification steps.

Typical procedure for the analysis of the samples of polyfunctional chiral carboxylic acids with chiral probe SeBA

The acid to be analyzed (4.0×10^{-5} mol) and DCC (0.0098 g, 4.7×10^{-5} mol) were dissolved in 0.2 mL of $CDCl_3$ in an NMR tube and the mixture was shaken for 1–2 min.[11] A white suspension was formed. SeBA **3a** (0.0075 mL, 0.0100 g, 4.4×10^{-5} mol, *R*- or a mixture of *R*- and *S*-enantiomers 3:1 depending on the aim of the analysis)[15] was subsequently added and the mixture was shaken for 1–2 min. After that, CD_3OD (0.4 mL) was added into the NMR tube. A clear solution was formed, thus negating the need for the centrifugation procedure. The ^{1}H and ^{77}Se NMR spectra were recorded directly without any further purification steps.

Similar derivatization protocols were used to obtain diastereomers with **3b** (0.0075 mL, 0.0100 g, 4.1×10^{-5} mol).

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Keywords: chiral acids · chiral selenium-containing probes · enantiomeric purity · NMR spectroscopy · structure elucidation

[1] a) P. Chauhan, S. Mahajan, D. Enders, *Chem. Rev.* **2014**, *114*, 8807 – 8864; b) J. Alemán, S. Cabrera, *Chem. Soc. Rev.* **2013**, *42*, 774 – 793; c) B. List, J. W. Yang, *Science* **2006**, *313*, 1584 – 1585; d) K. C. Nicolaou, T. Montagnon, *Molecules that Changed the World*, Wiley-VCH, Weinheim, **2008**; e) J. T. Mohr, M. R. Krout, B. M. Stoltz, *Nature* **2008**, *455*, 323 – 332; f) I. Atodiresei, C. M. R. Volla, M. Rueping, *ACS Catal.* **2015**, *5*, 1972 – 1985; g) K. C. Nicolaou, C. R. H. Hale, *Natl. Sci. Rev.* **2014**, *1*, 233 – 252; h) C. C. J. Loh, D. Enders, *Chem. Eur. J.* **2012**, *18*, 10212 – 10225; i) K. C. Nicolaou, C. R. H. Hale, C. Nilewskia, H. A. Ioannidou, *Chem. Soc. Rev.* **2012**, *41*, 5185 – 5238; j) E. Marqués-López, R. P. Herrera, M. Christmann, *Nat. Prod. Rep.* **2010**, *27*, 1138 – 1167; k) C. Zhong, X. Shi, *Eur. J. Org. Chem.* **2010**, 2999 – 3025; l) S. Bertelsen, K. A. Jørgensen, *Chem. Soc. Rev.* **2009**, *38*, 2178 – 2189; m) S. G. Zlotin, A. S. Kucherenko, I. P. Beletskaya, *Russ. Chem. Rev.* **2009**, *78*, 737 – 784; n) D. Enders, O. Niemeier, A, Henseler, *Chem. Rev.* **2007**, *107*, 5606 – 5655; o) B. List, *Asymmetric Organocatalysis*, Springer, New York, **2009**; p) H. Pellissier, *Chem. Rev.* **2013**, *113*, 442 – 524; q) M. E. Abbasov, D. Romo, *Nat. Prod. Rep.* **2014**, *31*, 1318 – 1327; r) P. I. Dalko, L. Moisan, *Angew. Chem. Int. Ed.* **2004**, *43*, 5138 – 5175; *Angew. Chem.* **2004**, *116*, 5248 – 5286; s) E. N. Jacobsen, A. Pfaltz, H. Yamamoto, *Comprehensive Asymmetric Catalysis, Vols. 1 – 3*, Springer, Berlin, **1999**; t) A. E. Allen, D. W. C. MacMillan, *Chem. Sci.* **2012**, *3*, 633 – 658; u) M. Mahlau, B. List, *Angew. Chem. Int. Ed.* **2013**, *52*, 518 – 533; *Angew. Chem.* **2013**, *125*, 540 – 556.

[2] a) C. M. R. Volla, I. Atodiresei, M. Rueping, *Chem. Rev.* **2014**, *114*, 2390 – 2431; b) G. Eppe, D. Didier, I. Marek, *Chem. Rev.* **2015**, *115*, 9175 – 9206; c) Ł. Albrecht, L. K. Ransborg, K. A. Jørgensen, *Catal. Sci. Technol.* **2012**, *2*, 1089 – 1098; d) D.-F. Chen, Z.-Y. Han, X.-L. Zhou, L.-Z. Gong, *Acc. Chem. Res.* **2014**, *47*, 2365 – 2377; e) R. C. Wende, P. R. Schreiner, *Green Chem.* **2012**, *14*, 1821 – 1849.

[3] a) X. Zhang, J. Yin, J. Yoon, *Chem. Rev.* **2014**, *114*, 4918 – 4959; b) Y. Kubo, S. Maeda, S. Tokita, M. Kubo, *Nature* **1996**, *382*, 522 – 524; c) K. W. Bentley, C. Wolf, *J. Am. Chem. Soc.* **2013**, *135*, 12200 – 12203; d) X. Mei, C. Wolf, *J. Am. Chem. Soc.* **2004**, *126*, 14736 – 14737; e) T. A. Feagin, D. P. V. Olsen, Z. C. Headman, J. M. Heemstra, *J. Am. Chem. Soc.* **2015**, *137*, 4198 – 4206; f) T. D. James, K. R. A. S. Sandanayake, S. Shinkai, *Nature* **1995**, *374*, 345 – 347; g) L. Pu, *Acc. Chem. Res.* **2012**, *45*, 150 – 163; h) L. Pu, *Chem. Rev.* **2004**, *104*, 1687 – 1716; i) C. Wolf, K. W. Bentley, *Chem. Soc. Rev.* **2013**, *42*, 5408; j) H.-L. Liu, Q. Peng, Y.-D. Wu, D. Chen, X.-L. Hou, M. Sabat, L. Pu, *Angew. Chem. Int. Ed.* **2010**, *49*, 602 – 606; *Angew. Chem.* **2010**, *122*, 612 – 616; k) A. Akdeniz, T. Minami, S. Watanabe, M. Yokoyama, T. Ema, P. Anzenbacher, Jr., *Chem. Sci.* **2016**, *7*, 2016 – 2022; l) K. W. Bentley, Y. G. Nam, J. M. Murphy, C. Wolf, *J. Am. Chem. Soc.* **2013**, *135*, 18052 – 18055; m) S. Pagliari, R. Corradini, G. Galaverna, S. Sforza, A. Dossena, M. Montalti, L. Prodi, N. Zaccheroni, R. Marchelli, *Chem. Eur. J.* **2004**, *10*, 2749 – 2758; n) P. Metola, E. V. Anslyn, T. D. James, S. D. Bull, *Chem. Sci.* **2012**, *3*, 156 – 161; o) L. You, G. Pescitelli, E. V. Anslyn, L. Di Bari, *J. Am. Chem. Soc.* **2012**, *134*, 7117 – 7125; p) D. Leung, J. F. Folmer-Andersen, V. M. Lynch, E. V. Anslyn, *J. Am. Chem. Soc.* **2008**, *130*, 12318 – 12327; q) F. Y. Song, G. Wei, L. Wang, J. M. Jiao, Y. X. Cheng, C. J. Zhu, *J. Org. Chem.* **2012**, *77*, 4759 – 4764; r) X. Wu, X.-X. Chen, B.-N. Song, Y.-J. Huang, Z. Li, Z. Chen, T. D. James, Y.-B. Jiang, *Chem. Eur. J.* **2014**, *20*, 11793 – 11799; s) K. Wen, S. Yu, Z. Huang, L. Chen, M. Xiao, X. Yu, L. Pu, *J. Am. Chem. Soc.* **2015**, *137*, 4517 – 4524.

[4] a) J. M. Seco, E. Quinoa, R. Riguera, *Chem. Rev.* **2004**, *104*, 17 – 117; b) G. Uccello-Barretta, F. Balzano, P. Salvadori, *Curr. Pharm. Des.* **2006**, *12*, 4023 – 4045; c) D. Parker, *Chem. Rev.* **1991**, *91*, 1441 – 1457; d) R. Hulst, R. M. Kellogg, B. L. Feringa, *Recl. Trav. Chim. Pays Bas* **1995**, *114*, 115 – 138; e) K. M. Błazewska, T. Gajda, *Tetrahedron: Asymmetry* **2009**, *20*, 1337 – 1361; f) A. P. Kumar, D. Jin, Y.-I. Lee, *Appl. Spectroscopy Rev.* **2009**, *44*, 267 – 316; g) T. Yabuuchi, T. Kusumi, *J. Org. Chem.* **2000**, *65*, 397 – 404; h) T. J. Wenzel, *Top. Curr. Chem.* **2013**, *341*, 1 – 68; i) M. Kaik, J. Gajewy, J. Grajewski, J. Gawronski, *Chirality* **2008**, *20*, 301 – 306; j) J. M. Seco, E. Quinoa, R. Riguera, *Chem. Rev.* **2012**, *112*, 4603 – 4641; k) E. Doyle, J. Parve, M. Kudryashova, S. Tamp, A.-M. Müürisepp, L. Villo, L. Vares, T. Pehk, A. Parve, *Chirality* **2013**, *25*, 793 – 798; l) T. J. Wenzel, C. D. Chisholm, *Progr. Nucl. Magn. Reson. Spectrosc.* **2011**, *59*, 1 – 63; m) T. J. Wenzel, C. D. Chisholm, *Chirality* **2011**, *23*, 190 – 214; n) T. R. Hoye, D. O. Koltun, *J. Am. Chem. Soc.* **1998**, *120*, 4638 – 4643.

[5] a) S. Porto, J. M. Seco, J. F. Espinosa, E. Quinoa, R. Riguera, *J. Org. Chem.* **2008**, *73*, 5714 – 5722; b) S. Porto, J. Duran, J. M. Seco, E. Quinoa, R. Riguera, *Org. Lett.* **2003**, *5*, 2979 – 2982; c) T. Arnauld, A. G. M. Barrett, B. T. Hopkins, F. J. Zecri, *Tetrahedron Lett.* **2001**, *42*, 8215 – 8217; d) M. Adamczyk, J. R. Fishpaugh, *Tetrahedron Lett.* **1996**, *37*, 7171 – 7172; e) J. M. Seco, L.-H. Tseng, M. Godejohann, E. Quinoa, R. Riguera, *Tetrahedron: Asymmetry* **2002**, *13*, 2149 – 2153; f) F. Freire, E. Quinoa, R. Riguera, *Chem. Commun.* **2008**, 4147 – 4149; g) N. V. Orlov, V. P. Ananikov, *Chem. Commun.* **2010**, *46*, 3212 – 3214; h) N. V. Orlov, V. P. Ananikov, *Green Chem.* **2011**, *13*, 1735 – 1744; i) J. G. Ferreira, S. M. C. Gonçalves, *J. Braz. Chem. Soc.* **2010**, *21*, 2023 – 2026; j) Y. Perez-Fuertes, A. M. Kelly, J. S. Fossey, M. E. Powell, S. D. Bull, T. D. James, *Nat. Protoc.* **2008**, *3*, 210 – 214; k) A. M. Kelly, Y. Perez-Fuertes, J. S. Fossey, S. L. Yeste, S. D. Bull, T. D. James, *Nat. Protoc.* **2008**, *3*, 215 – 219.

[6] For ^{19}F-based chiral derivatizing agents (CDAs), see: a) G. Helmchen, R. Ott, K. Sauber, *Tetrahedron Lett.* **1972**, *13*, 3873 – 3878; b) S. Sambasivan, D. Kim, K. H. Ahn, *Chem. Commun.* **2010**, *46*, 541 – 542; c) J. A. Dale, H. S. Mosher, *J. Am. Chem. Soc.* **1973**, *95*, 512 – 519; d) J. A. Dale, D. L. Dull, H. S. Mosher, *J. Org. Chem.* **1969**, *34*, 2543 – 2549; e) S. Rodrıguez-Escrich, D. Popa, C. Jimeno, A. Vidal-Ferran, M. A. Pericas, *Org. Lett.* **2005**, *7*, 3829 – 3832; ^{31}P-based CDAs: f) V. M. Mastranzo, L. Quintero, C. A. de Parrodi, *Chirality* **2007**, *19*, 503 – 507; g) A. Alexakis, A. Chauvin, *Tetrahedron: Asymmetry* **2001**, *12*, 1411 – 1415; h) A. Alexakis, J. C. Frutos, S. Mutti, P. Mangeney, *J. Org. Chem.* **1994**, *59*, 3326 – 3334; i) A.-S. Chauvin, G. Bernardinelli, A. Alexakis, *Tetrahedron: Asymmetry* **2006**, *17*, 2203 – 2209; j) A.-S. Chauvin, G. Bernardinelli, A. Alexakis, *Tetrahedron: Asymmetry* **2004**, *15*, 1857 – 1879; k) S. Reymond, J. M. Brunel, G. Buono, *Tetrahedron: Asymmetry* **2000**, *11*, 1273 – 1278; l) R. Hulst, N. K. Devries, B. L. Feringa, *Tetrahedron: Asymmetry* **1994**, *5*, 699 – 708; m) J. Bravo, C. Cativiela, J. E. Chaves, R. Navarro, E. P. Urriolabeitia, *Inorg. Chem.* **2003**, *42*, 1006 – 1013; n) M. Amberg, U. Bergsträsser, G. Stapf, J. Hartung, *J. Org. Chem.* **2008**, *73*, 3907 – 3910; ^{77}Se-based CDAs: o) L. A. Silks, R. B. Dunlap, J. D. Odom, *J. Am. Chem. Soc.* **1990**, *112*, 4979 – 4982; p) J. Peng, M. E. Barr, D. A. Ashburn, L. Lebioda, A. R. Garber, R. A. Martinez, J. D. Odom, R. B. Dunlap, L. A. Silks, *J. Org. Chem.* **1995**, *60*, 5540 – 5549; q) R. Wu, J. D. Odom, R. B. Dunlap, L. A. Silks, *Tetrahedron: Asymmetry* **1999**, *10*, 1465 – 1470.

[7] a) L. S. Liebeskind, P. Gangireddy, M. G. Lindale, *J. Am. Chem. Soc.* **2016**, *138*, 6715 – 6718; b) V. N. Wakchaure, B. List, *Angew. Chem. Int. Ed.* **2010**,

49, 4136 – 4139; *Angew. Chem.* **2010**, *122*, 4230 – 4233; c) E. C. Cherney, J. C. Green, P. S. Baran, *Angew. Chem. Int. Ed.* **2013**, *52*, 9019 – 9022; *Angew. Chem.* **2013**, *125*, 9189 – 9192; d) B. Peng, D. Geerdink, N. Maulide, *J. Am. Chem. Soc.* **2013**, *135*, 14968 – 14971; e) C. Najera, J. M. Sansano, *Chem. Rev.* **2007**, *107*, 4584 – 4671; f) D. Enders, T. Gasperi, *Chem. Commun.* **2007**, 88 – 90; g) W. Notz, F. Tanaka, C. F. Barbas III, *Acc. Chem. Res.* **2004**, *37*, 580 – 591; h) R. A. Hill, A. Sutherland, *Nat. Prod. Rep.* **2014**, *31*, 414 – 418; i) H. M. L. Davies, D. Morton, *Chem. Soc. Rev.* **2011**, *40*, 1857 – 1869; j) M. Luparia, M. T. Oliveira, D. Audisio, F. Frbault, R. Goddard, N. Maulide, *Angew. Chem. Int. Ed.* **2011**, *50*, 12631 – 12635; *Angew. Chem.* **2011**, *123*, 12840 – 12844; k) T. Schmidt, A. Kirschning, *Angew. Chem. Int. Ed.* **2012**, *51*, 1063 – 1066; *Angew. Chem.* **2012**, *124*, 1087 – 1091; l) B. List, I. Coric, O. O. Grygorenko, P. S. J. Kaib, I. Komarov, A. Lee, M. Leutzsch, S. Chandra Pan, A. V. Tymtsunik, M. van Gemmeren, *Angew. Chem. Int. Ed.* **2014**, *53*, 282 – 285; *Angew. Chem.* **2014**, *126*, 286 – 289; m) S. Chang, S. Hur, R. Britton, *Chem. Eur. J.* **2015**, *21*, 16646 – 16653; n) P. Lu, J. J. Jackson, J. A. Eickhoff, A. Zakarian, *J. Am. Chem. Soc.* **2015**, *137*, 656 – 659; o) E. Geist, A. Kirschning, T. Schmidt, *Nat. Prod. Rep.* **2014**, *31*, 441 – 448; p) A. D. Yamaguchi, K. M. Chepiga, J. Yamaguchi, K. Itami, H. M. L. Davies, *J. Am. Chem. Soc.* **2015**, *137*, 644 – 647; q) M. C. Pischl, C. F. Weise, M.-A. Müller, A. Pfaltz, C. Schneider, *Angew. Chem. Int. Ed.* **2013**, *52*, 8968 – 8972; *Angew. Chem.* **2013**, *125*, 9138 – 9142; r) Z.-J. Du, J. Guan, G.-J. Wu, P. Xu, L.-X. Gao, F.-S. Han, *J. Am. Chem. Soc.* **2015**, *137*, 632 – 635; s) N. A. Petasis, I. A. Zavialov, *J. Am. Chem. Soc.* **1997**, *119*, 445 – 446; t) J. Hansen, H. M. L. Davies, *Coord. Chem. Rev.* **2008**, *252*, 545 – 555; u) K. Dong, Y. Li, Z. Wang, K. Ding, *Angew. Chem. Int. Ed.* **2013**, *52*, 14191 – 14195; *Angew. Chem.* **2013**, *125*, 14441 – 14445.

[8] a) R. Kourist, P. Dominguez de Maria, K. Miyamoto, *Green Chem.* **2011**, *13*, 2607 – 2618; b) V. Farina, J. T. Reeves, C. H. Senanayake, J. J. Song, *Chem. Rev.* **2006**, *106*, 2734 – 2793; c) Yu. A. Knirel, S. D. Shevelev, A. V. Perepelov, *Mendeleev Commun.* **2011**, *21*, 173 – 182; d) V. Mascitti, E. J. Corey, *J. Am. Chem. Soc.* **2006**, *128*, 3118 – 3119; e) P. J. Harrington, E. Lodewijk, *Org. Process Res. Dev.* **1997**, *1*, 72 – 76; f) M. E. Kopach, U. K. Singh, M. E. Kobierski, W. G. Trankle, M. M. Murray, M. A. Pietz, M. B. Forst, G. A. Stephenson, V. Mancuso, T. Giard, M. Vanmarsenille, T. DeFrance, *Org. Process Res. Dev.* **2009**, *13*, 209 – 224; g) G. Dannhardt, W. Kiefer, *Eur. J. Med. Chem.* **2001**, *36*, 109 – 126; h) F. Müller, *Agrochemicals*, Wiley-VCH, Weinheim, **2000**; i) T. Angata, A. Varki, *Chem. Rev.* **2002**, *102*, 439 – 470; j) A. R. Bogdan, S. L. Poe, D. C. Kubis, S. J. Broadwater, D. T. McQuade, *Angew. Chem. Int. Ed.* **2009**, *48*, 8547 – 8550; *Angew. Chem.* **2009**, *121*, 8699 – 8702, ; k) H. Raj, W. Szymanski, J. de Villiers, H. J. Rozeboom, V. Puthan Veetil, C. R. Reis, M. de Villiers, F. J. Dekker, S. de Wildeman, W. J. Quax, A.-M. W. H. Thunnissen, B. L. Feringa, D. B. Janssen, G. J. Poelarends, *Nature Chem.* **2012**, *4*, 478 – 484; l) W. A. Velema, M. J. Hansen, M. M. Lerch, A. J. M. Driessen, W. Szymanski, B. L. Feringa, *Bioconjugate Chem.* **2015**, *26*, 2592 – 2597; m) K. C. Nicolaou, K. K. Pulukuri, S. Rigol, P. Heretsch, R. Yu, C. I. Grove, C. R. H. Hale, A. El-Marrouni, V. Fetz, M. Brönstrup, M. Aujay, J. Sandoval, J. Gavrilyuk, *J. Am. Chem. Soc.* **2016**, *138*, 6550 – 6560.

[9] a) N. H. Pham, T. J. Wenzel, *Chirality* **2012**, *24*, 193 – 200; b) S. Bozkurt, M. Durmaz, H. N. Naziroglub, M. Yilmaz, A. Sirit, *Tetrahedron: Asymmetry* **2011**, *22*, 541 – 549; c) T. P. Quinn, P. D. Atwood, J. M. Tanski, T. F. Moore, J. F. Folmer-Andersen, *J. Org. Chem.* **2011**, *76*, 10020 – 10030; d) K. Tanakaa, Y. Nakai, H. Takahashi, *Tetrahedron: Asymmetry* **2011**, *22*, 178 – 184; e) S. C. Benson, P. Cai, M. Colon, M. A. Haiza, M. Tokles, J. K. Snyder, *J. Org. Chem.* **1988**, *53*, 5335 – 5341; f) G. Bian, S. Yang, H. Huang, H. Zong, L. Song, H. Fan, X. Sun, *Chem. Sci.* **2016**, *7*, 932 – 938.

[10] See the Supporting Information for details.

[11] For practical reasons, it was found more convenient to perform the derivatization in 1.5 mL plastic Eppendorf tubes® (or equivalents). Unless otherwise noted, throughout this paper after mixing all the components (chiral acid, DCC, the chiral probe) in appropriate solvent, the suspension formed was directly transferred into the NMR tube followed by removal of insoluble DCU particles by centrifugation in a common centrifuge using special inserts to prevent tube destruction (see the Supporting Information for details).

[12] Use of ^{1}H NMR spectra for sensing of chiral carboxylic acids with the chiral probes **3a** or **3b** was found to be much less efficient compared with the ^{77}Se NMR spectra. The majority of ^{1}H NMR signals of diastereomers were either non-resolved or overlapped with other signals. Only for a few diastereomeric amides, obtained from α- and β-carboxylic acids, were baseline resolved signals observed, which could be used for quantitative measurements (see the Supporting Information for details). So only ^{77}Se NMR spectra will be discussed throughout the paper. Nevertheless, ^{1}H NMR spectra are given in the Supporting Information.

[13] See the Supporting Information for details concerning solvents effect on difference in the chemical shifts.

[14] For some recent reviews on the topic, see: a) A. S. Mahadevi, G. N. Sastry, *Chem. Rev.* **2016**, *116*, 2775 – 2825; b) K. Müller-Dethlefs, P. Hobza, *Chem. Rev.* **2000**, *100*, 143 – 167; c) M. Erdelyi, *Nat. Chem.* **2014**, *6*, 762 – 764; d) A. S. Christensen, T. Kubar, Q. Cui, M. Elstner, *Chem. Rev.* **2016**, *116*, 5301 – 5337.

[15] When a single enantiomer of a chiral acid to be analyzed is available, the following two-step algorithm can be used: first, the acid is reacted with a mixture of (*R*)- and (*S*)-**3a** or **3b** (a 3:1 molar ratio was used in this study) to assign the chemical shifts of both diastereomers; after that, in a second step, derivatization of the acid with enantiopure **3a** or **3b** is performed to determine the enantiomeric purity.

[16] A. O. Terent'ev, V. A. Vil', E. S. Gorlov, G. I. Nikishin, K. K. Pivnitsky, W. Adam, *J. Org. Chem.* **2016**, *81*, 810 – 823.

[17] a) *Structure Elucidation in Organic Chemistry: The Search for the Right Tools* (Eds.: M.-M. Cid, J. Bravo), Wiley-VCH, Weinheim, **2015**; b) F. V. Toukach, V. P. Ananikov, *Chem. Soc. Rev.* **2013**, *42*, 8376 – 8415; c) M. E. Maier, *Nat. Prod. Rep.* **2009**, *26*, 1105 – 1124; d) P. A. Belyakov, V. I. Kadentsev, A. O. Chizhov, N. G. Kolotyrkina, A. S. Shashkov, V. P. Ananikov, *Mendeleev Commun.* **2010**, *20*, 125 – 131; e) R. L. E. G. Aspers, P. E. T. J. Geutjes, M. Honing, M. Jaeger, *Magn. Reson. Chem.* **2011**, *49*, 425 – 436; f) M. Elyashberg, *Trends Anal. Chem.* **2015**, *69*, 88 – 97; g) K. A. M. Ampt, R. L. E. G. Aspers, M. Jaeger, P. E. T. J. Geutjes, M. Honing, S. S. Wijmenga, *Magn. Reson. Chem.* **2011**, *49*, 221 – 230; h) T. F. Molinski, *Nat. Prod. Rep.* **2010**, *27*, 321 – 329; i) M. Weingarth, M. Baldus, *Acc. Chem. Res.* **2013**, *46*, 2037 – 2046; j) M. Eberstadt, G. Gemmecker, D. F. Mierke, H. Kessler, *Angew. Chem. Int. Ed.* **1995**, *34*, 1671 – 1695; *Angew. Chem.* **1995**, *107*, 1813 – 1838; k) M. Kruck, H. Wadepohl, M. Enders, L. H. Gade, *Chem. Eur. J.* **2013**, *19*, 1599 – 1606; l) E. E. Kwan, G. H. Shaw, *Eur. J. Org. Chem.* **2008**, 2671 – 2688.

[18] Although diastereomers **25** and **26** have carbonyl groups adjacent to the chiral center, the most probable long distance between the chiral center and sensing unit of the probe diminishes the substituent influence on the ^{77}Se chemical shifts.

[19] For studies concerning the topic, see: a) J. M. Seco, S. K. Latypov, E. Quinoa, R. Riguera, *Tetrahedron* **1997**, *53*, 8541 – 8564; b) S. K. Latypov, A. V. Aganov, S. Tahara, Y. Fukushi, *Tetrahedron* **1999**, *55*, 7305 – 7318; c) S. K. Latypov, J. M. Seco, R. Riguera, *J. Org. Chem.* **1995**, *60*, 504 – 515; d) T. R. Hoye, S. E. Erickson, S. L. Erickson-Birkedahl, C. R. H. Hale, E. C. Izgu, M. J. Mayer, P. K. Notz, M. K. Renner, *Org. Lett.* **2010**, *12*, 1768 – 1771; e) Y. Kasai, A. Sugio, S. Sekiguchi, S. Kuwahara, T. Matsumoto, M. Watanabe, A. Ichikawa, N. Harada, *Eur. J. Org. Chem.* **2007**, 1811 – 1826; f) O. Thillaye du Boullay, A. Alba, F. Oukhatar, B. Martin-Vaca, D. Bourissou, *Org. Lett.* **2008**, *10*, 4669 – 4672.

[20] For the synthesis and identification of acids used to obtain diastereomers **18**–**21**, see: a) A. A. Zemtsov, V. V. Levin, A. D. Dilman, M. I. Struchkova, P. A. Belyakov, V. A. Tartakovsky, *Tetrahedron Lett.* **2009**, *50*, 2998 – 3000; b) A. S. Naumova, A. A. Mikhaylov, Yu. A. Khomutova, R. A. Novikov, D. E. Arkhipov, A. A. Korlyukov, S. L. Ioffe, *RSC Advances* **2014**, *4*, 12467 – 12475.

[21] B. I. Morinaka, M. N. Masuno, J. R. Pawlik, T. F. Molinski, *Org. Lett.* **2007**, *9*, 5219 – 5222.

[22] D. B. Damon, R. W. Dugger, S. E. Hubbs, J. M. Scott, R. W. Scott, *Org. Process Res. Dev.* **2006**, *10*, 472 – 480.

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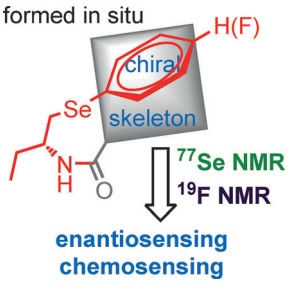
FULL PAPER

α-, β-, and beyond: Selenium-based chiral chemical probes were designed and show high efficiency in sensing chiral centers of structurally diverse and multifunctional chiral carboxylic acids by ^{77}Se NMR spectroscopy. Besides accurate quantitative measurements, it was possible to perform primary analysis of the nature of the stereogenic centers in the compounds analyzed.



Structure Elucidation

*S. A. Shyshkanov, N. V. Orlov**

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Design of Selenium-Based Chiral Chemical Probes for Simultaneous Enantio- and Chemosensing of Chiral Carboxylic Acids with Remote Stereogenic Centers by NMR Spectroscopy