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Axially Chiral Trifluoromethylbenzimidazolylbenzoic Acid: A Chiral Derivatizing Agent for α-Chiral Primary Amines and Secondary Alcohols to Determine Absolute Configuration

Michal Kriegelstein[a], David Profous[a], Antonín Lyčka[b], Zdeněk Trávníček[c], Adam Přibylka[a], Tereza Volná[d], Sandra Benická[d], Petr Cankař*[a]

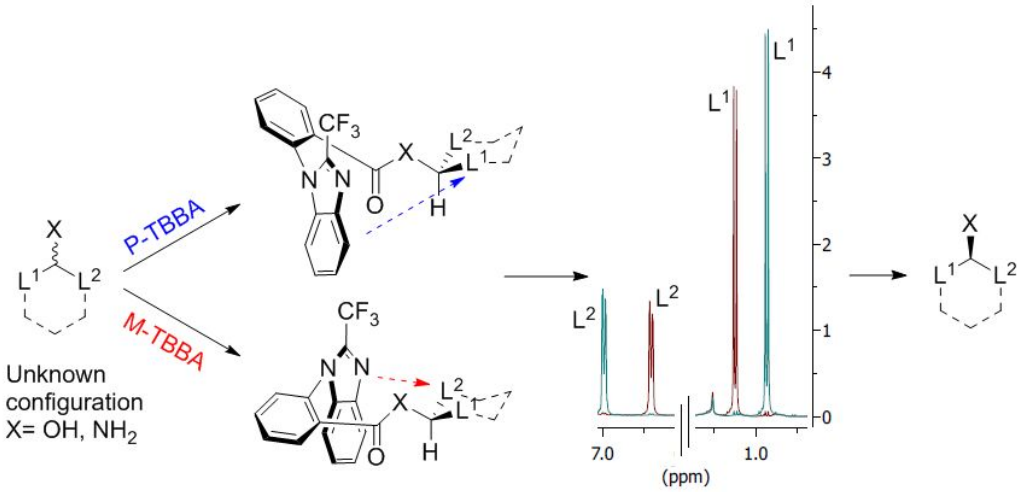
[a] Department of Organic Chemistry, Faculty of Science, Palacký University, 17 listopadu 12, 771 46 Olomouc, Czech Republic

[b] University of Hradec Králové, Faculty of Science, Rokitanského 62, CZ-500 03, Hradec Králové 3, Czech Republic

[c] Division of Biologically Active Complexes and Molecular Magnets, Regional Centre of Advanced Technologies and Materials, Faculty of Science, Palacký University, Šlechtitelů 27, 783 71 Olomouc, Czech Republic

[d] Institute of Molecular and Translation Medicine, Faculty of Medicine and Dentistry, Palacký University, Hněvotínská 5, 779 00, Olomouc, Czech Republic

Email: petr.cankar@upol.cz



ABSTRACT:

Racemic 2-(2-trifluoromethyl)-1*H*-benzo[*d*]imidazol-1-yl)benzoic acid (TBBA) was synthesized in three steps from 1-fluoro-2-nitrobenzene. Target (*P*)- and (*M*)-TBBA atropisomers were stable with a racemization barrier above 30 kcal/mol. As a chiral derivatizing agent, TBBA showed much higher differences in chemical shifts ($\Delta\delta^{PM}$) than the conventional Mosher's acid.

INTRODUCTION

The determination of absolute configuration and/or enantiomeric purity is an important task for organic chemists. NMR spectroscopy[1–5] is suitable for this purpose and readily available compared with other methods.[6] Usually, a sample is converted into diastereomers by a suitable enantiomerically pure chiral derivatizing agent (CDA) and the NMR spectra of the diastereomers are compared. Differences in the chemical shifts ($\Delta\delta^{RS}$) and knowledge of the conformation model provide information about the spatial orientation of substituents attached to a stereogenic center with an unknown configuration.[4] The most widely known CDA is Mosher's acid (MTPA), which was introduced in late 70s (Figure 1).[7,8]

Other CDA reagents, such as 9-anthrylmethoxyacetic acid (9-AMAA),[9] methoxyphenylacetic acid (MPA)[10] or Boc-Phenylglycine (BPG)[11] were introduced later. The methodology is not limited only to primary amines and secondary alcohols, but was successfully used for the other classes of compounds such as thiols, cyanohydrins, primary and tertiary alcohols, diols, triols, and aminoalcohols.[12]

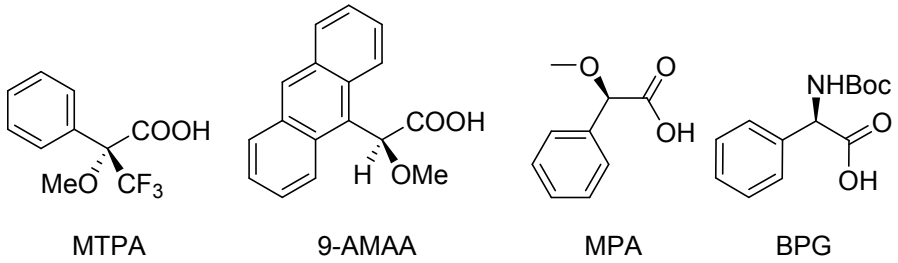


Figure 1: Structures of Mosher's acid (MTPA), 9-anthrylmethoxyacetic acid (9-AMAA), methoxyphenylacetic acid (MPA), and Boc-Phenylglycine (BPG).

Although MTPA is commonly used, it has some limitations. Sometimes the distribution of the signs is not consistent within the substituent[13,14] and the $\Delta\delta^{RS}$ values can be very small[13] and near or under the experimental error, which could lead to incorrect assignment of the configuration. This was demonstrated for a set of amines of known configurations, which were analyzed as their MTPA amides and had $\Delta\delta^{RS}$ values below 0.1 ppm in most cases.[15] These discrepancies were explained in more detail by examination of conformational equilibria. As a consequence, a revised conformational model was proposed and other CDA such as methoxyphenylacetic acid (MPA) and 9-AMAA were recommended.[16]

Previously, we prepared axially chiral benzimidazolone **1** (Figure 2),[17] which inspired us to design a similar compound, 2-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-1-yl)benzoic acid (**2**, TBBA), with trifluoromethyl and carboxylate groups to serve as a novel CDA. We hypothesized that the energy barrier might be sufficiently high to restrict C-N bond rotation, which would make the molecule stable with a low risk of racemization.

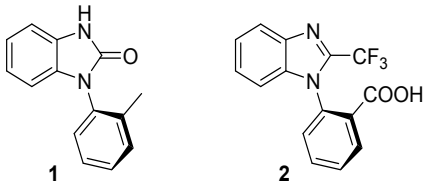


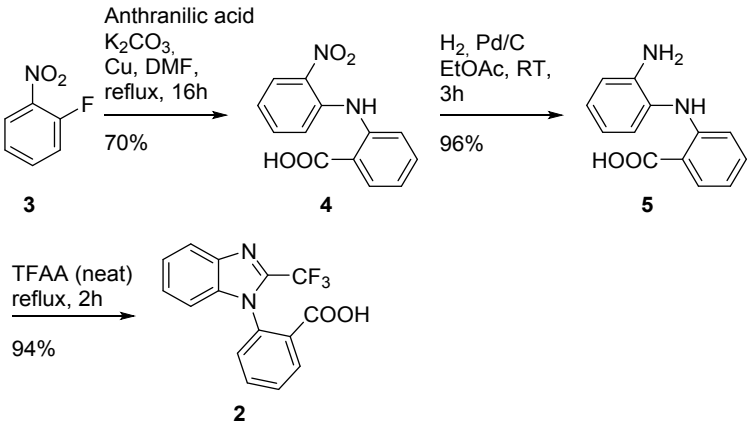
Figure 2: Benzimidazolone **1** and TBBA **2** (only one atropisomer is shown).

To explore whether the anisotropic effect of the benzimidazole cycle could be efficiently and selectively space-oriented towards a potentially unknown stereogenic carbon, we focused on the synthesis of both TBBA atropisomers and the corresponding TBBA amides and esters prepared from α-chiral primary amines and secondary alcohols.

RESULTS AND DISCUSSION

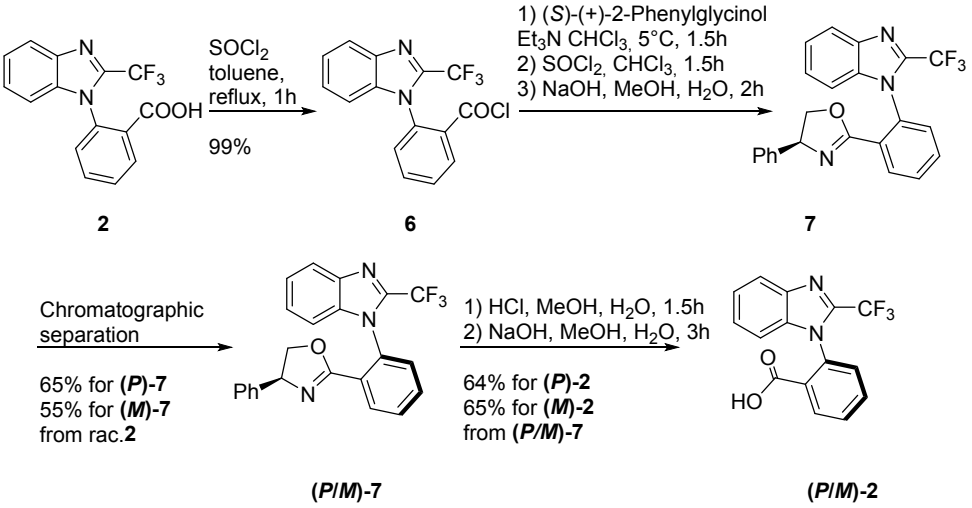
The synthesis started with a copper-powder-catalyzed reaction of fluorobenzene **3** with anthranilic acid to yield diphenyl amine **4**,[18] followed by catalytic hydrogenation to give phenylenediamine **5** in nearly quantitative yield (Scheme 1). The final cyclization in refluxing concentrated trifluoroacetic acid[19] gave a complex mixture containing the desired product. The use of more reactive trifluoroacetic anhydride prevented undesired side reactions and produced racemic **2** (TBBA) in excellent yield.

Scheme 1: Synthesis of racemic acid **2** (TBBA).



After conversion of acid **2** into chloride **6**, phenylglycinol was added and the resulting diastereomeric oxazolines **7** were separated by chromatography (Scheme 2).[20] Subsequent two-step hydrolysis of (***P/M***)-**7** with hydrochloric acid and sodium hydroxide[28] recovered enantiopure acid **2**. The absolute configuration of (***P***)-**2** was confirmed by X-ray diffraction analysis of (***R,P***)-**8** (CCDC 1871600, see SI for more details).

Scheme 2: Chiral resolution of racemic acid **2** (only one atropisomer is shown).



The conformational stabilities of the atropisomers of **2** were tested in ethylene glycol at 100°C and 140°C (see SI for more details). The energy barrier for racemization, calculated according to Eyring's equation,[21,22] was always higher than 30 kcal/mol, which means that atropisomers **2** are sufficiently stable for practical use.

Comparison of the ^{1}H chemical shifts of diastereomeric pairs of (***P***)- and (***M***)-TBBA amides (Figure 3) and esters (Figure 4), which were prepared by conventional methods,[23,24] showed significant differences. Phenylethylamine **8** was chosen as a model compound to prove our concept even though the aromatic ring at the α position can cause irregular distribution of $\Delta\delta^{PM}$ signs.[25] The $\Delta\delta^{PM}$ between the most relevant proton signals — the methyl group and the aromatic hydrogens at the *ortho* positions were −0.18 and +0.27, respectively, and decreased to +0.09 at the *meta* positions, which was expected. Moreover, the $\Delta\delta^{PM}$ of the methyl group with TBBA was substantially higher than the reported values (absolute values shown) for the derivatives with MTPA (0.04), MPA (0.07), or MPA in complex with barium perchlorate (0.09).[10,26,27]

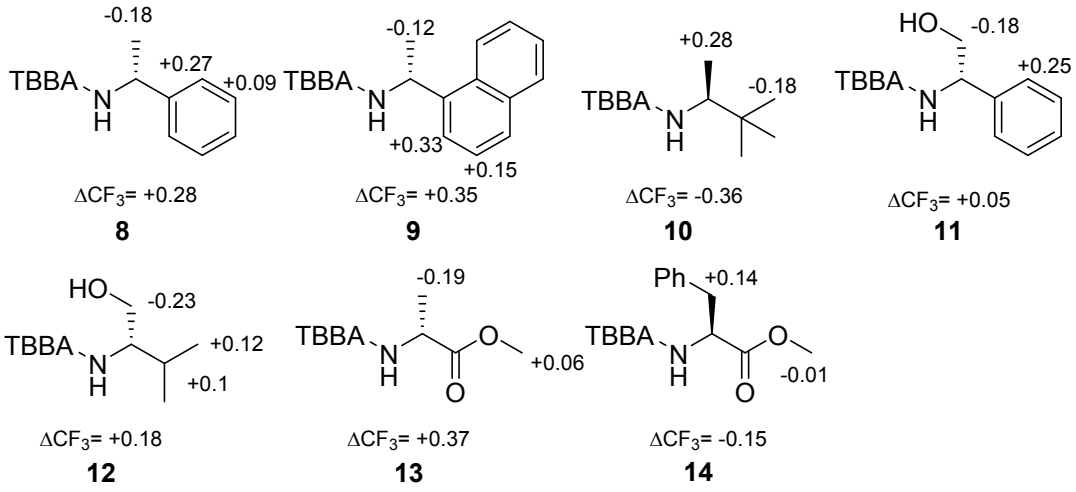


Figure 3: ^{1}H and ^{19}F chemical shift differences ($\Delta\delta^{PM}$, $\Delta\delta^{PM} = \delta L(P) - \delta L(M)$) of diastereomeric TBBA-amides. ^{19}F chemical shift differences are shown as ΔCF_3.

The napthylethylamine **9** behaved similarly, the magnitude ($\Delta\delta^{PM}$) of the methyl group was slightly higher compared to MPA (0.07)[27] but lower in comparison to BPG (0.17).[11] The values ($\Delta\delta^{PM}$) of methyls of nonaromatic amine **10** were comparable to aromatic amines **8** and **9**. Phenylglycinol **11** and valinol **12** showed approximately the same differences even though the polar hydroxyl group could change the population of conformers by hydrogen bonding with the TBBA carbonyl. Substitution of the phenyl group with isopropyl in valinol **12** slightly increased the chemical shift difference at the hydroxymethyl group; however, the $\Delta\delta^{PM}$ values of the isopropyl hydrogens decreased.

The methyl group in alanine derivatives **13** showed a difference of the same magnitude, but the $\Delta\delta^{PM}$ value of the remote methyl ester group was reduced as the shielding effect decreased with distance. However, the $\Delta\delta^{PM}$ is still higher compared to the reported alanine–MTPA amide (0.08 and 0.03 for the methyl and methylester group respectively).[26] Phenylalanine derivative **14** showed slightly lower difference than **13.** Compared to BPG and MPA, the difference at the benzylic methylene group is roughly the same (0.14 vs 0.18 and 0.08 ppm), however, the difference at remote methylester is significantly lower (0.01 vs 0.11 and 0.07).[11]

The chemical shift difference of methyl group of **15** was higher compared to azaanalog **8**, MPA and MTPA esters (0.06 and 0.08 ppm), and similar to 9-AMAA ester (0.3).[28] Substitution of the aromatic ring for ethyl or ethynyl side chain in **16** and **17** slightly lowered the $\Delta\delta^{PM}$ and the more remote terminal protons showed $\Delta\delta^{PM}$ 0.33 and 0.28 respectively, higher than those reported for the MPA esters (0.207 and 0.086 respectively).[29] The chemical shift differences of (***S***)-lactic acid TBBA-esters **18** were comparable to the values reported for the MPA derivatives.[27,] Interestingly, substitution of methyl for phenyl in **19** had a considerable effect on $\Delta\delta^{PM}$ of the methyl ester group, which showed only 0.02 ppm difference. This value is lower in comparison to **18** and both MPA and 9-AMAA esters (0.12)[28,29].

Additionally, L-menthol-TBBA esters **20** were prepared, since L-menthol has been frequently studied as a benchmark model with other CDAs.[13,30–32] The $\Delta\delta^{PM}$ between the diastereomers **20** were generally higher than those for the MTPA and MPA esters.[28] Surprisingly, one difference exceeded 1 ppm. The $\Delta\delta^{PM}$ of the isopropyl methyls was lower compared the 9-AMAA menthol ester (0.1 and 0.36 vs 0.79 and 0.75 for 9-AMAA) while the difference of the methyl group at position 5 was slightly higher for TBBA compared to 9-AMAA (0.2 vs 0.1).[9] Borneol ester **21** showed slightly lower differences compared to menthol ester **20,** but at the same level as the MPA ester and lower compared to 9-AMAA ester.[28]

Finally, we analyzed the more complex natural compounds betulinic acid **22** and cholesterol **23**. Comparison of the TBBA diastereomeric esters of betulinic acid **22** showed significant differences on the A-ring which were distinguishable even at remote positions 6 (0.04 and 0.05 ppm) and 25 (methyl, 0.02 ppm)., The sign distribution was inconsistent only at remote position 5, however, this value was relatively small compared with the largest

and qualitatively most important differences and could be ignored in the analysis. In a previous study, cholesterol was derivatized with MTPA but the reported differences were all lower than 0.1 ppm.[33] TBBA diastereomers **23** showed much higher differences, and even the chemical shift difference at remote position 6 (olefinic hydrogen) exceeded 0.1 ppm. Moreover, the sign distribution was consistent.

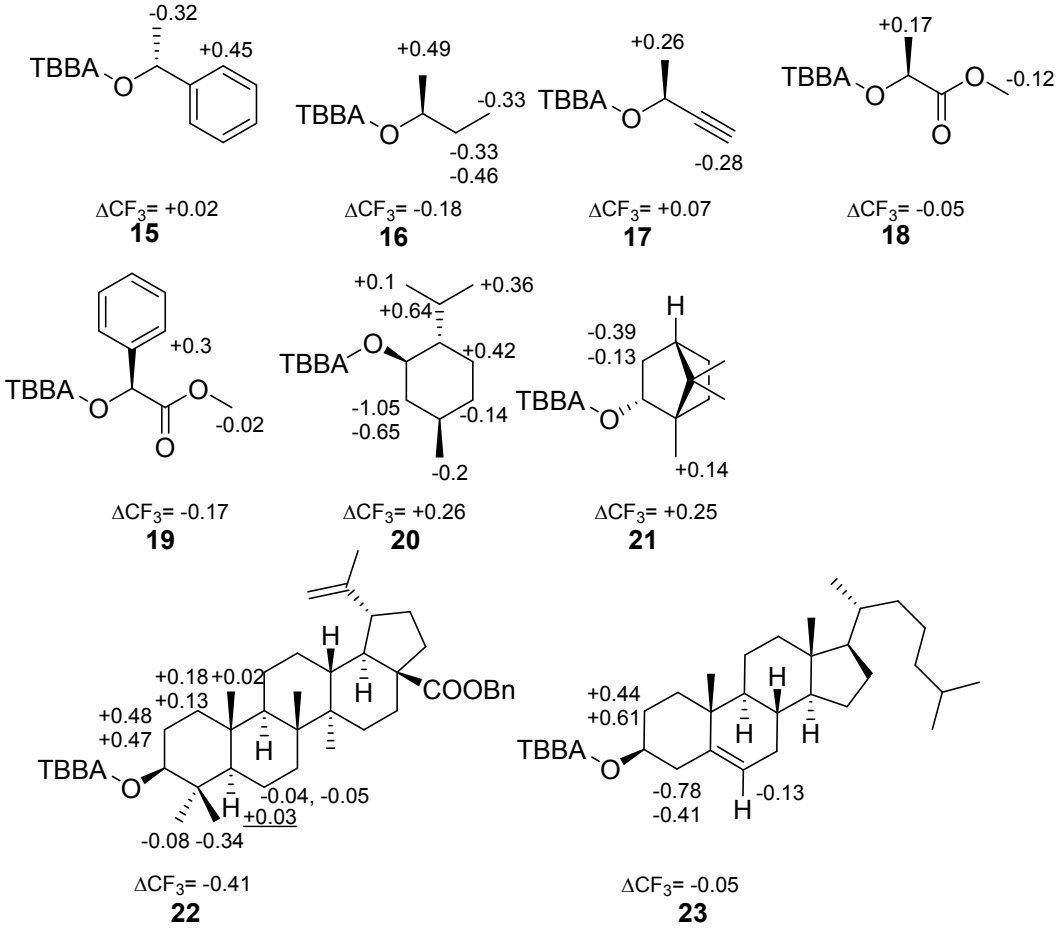


Figure 4: ^{1}H and ^{19}F chemical shift differences ($\Delta\delta^{PM}$, $\Delta\delta^{PM} = \delta L(P) - \delta L(M)$) of diastereomeric TBBA-esters. ^{19}F chemical shift differences are shown as ΔCF_3. Anomalous value (^{1}H differences) is underlined

In addition, the preliminary study of the carbon spectra was performed as well. To our delight, analyzed $^{13}C\Delta\delta^{PM}$ data were in accordance with the general model. The easily distinguishable methyl groups in compounds **8**-**10**, **13,** and **15**-**18** showed $^{13}C\Delta\delta^{PM}$ absolute values between 0.14-0.4 ppm. The methylene signals in **11** and **12** displayed differences 0.3 and 0.33 ppm. On the other hand, the methylene carbons in **14** were shifted by 0.08 ppm. Most importantly, the alkynyl carbon in **17** without protons, demonstrated a difference 0.45 ppm. Furthermore, in accordance with the general trend, the more remote methylester signals in **13**,**14**,**18,** and **19** displayed only minimal $^{13}C\Delta\delta^{PM}$ values ranging from 0.04 (**13**, **14**) to 0.06 (**18**,**19**) ppm. Despite observed values are small when the entire ^{13}C NMR chemical shift range is considered, in most cases, the $\Delta\delta^{PM}$ value was high enough to assign the absolute configuration, especially, when results were coupled with ^{1}H chemical shifts data.

To correlate the differences in the NMR chemical shifts (Figure 3 and 4) with the absolute configuration, we searched for a general NMR-significant conformational model. Initially, we performed a series of calculations with the diastereomers **8** using Spartan 16 software. The populations of theoretical conformers were calculated with the molecular mechanics model MMFF. Depending on the total number of theoretical conformers, this was followed by sorting of the conformation candidates with relative energies lower than 10–20 kJ/mol. The energies

of sorted candidates at the ground state in the nonpolar solvent were calculated using density functional theory (B3LYP, 6-31G*) to find the lowest energy conformer.

The calculation revealed that over 99% of diastereomer (***P***)**-8** was distributed over four conformers with Boltzmann weights of 0.414, 0.276, 0.186, and 0.120. We assumed the second most stable theoretical conformer of ***(P)*-8** (Boltzmann weight = 0.276) was the most NMR-significant one since the anisotropic effect of the benzimidazole moiety is preferentially space-oriented and efficient towards the methyl group (see SI for more details).

The data obtained by the calculation suggest that the conformational equilibrium of diastereomer (***M***)**-8** practically depends only on two conformers that make up over 97% of the population. As previously stated, we assumed the less stable conformer (by 1.15 kJ/mol) was the most NMR-significant one, and the phenyl group was selectively exposed to the anisotropic effect of the benzimidazole group.

These conformers are very likely further stabilized by interaction between the NH and CF_3 functionalities, which was confirmed by ^{1}H-^{19}F HOESY (see SI for more details).

Despite the NMR-significant conformers being minor components in the conformational equilibrium, their impacts on the chemical shifts enabled us to devise general NMR-significant conformational models for (***P***)- and (***M***)-TBBA amides (from α-chiral primary amines) or esters (from α-chiral secondary alchohols) with the TBBA carbonyl group syn-periplanar to the C-H bond of the chiral carbon atom (Figure 5a and 5b). We subtracted the chemical shift of (***M***)-TBBA from that of (***P***)-TBBA (Figure 5c). In the conformational model, a substituent with a negative difference is above the plane of the coplanar nitrogen/oxygen, chiral carbon, and hydrogen atom, and a substituent with a positive difference is below the plane (Figure 5d). The suggested conformational model agrees with the experimental $\Delta\delta^{PM}$ values given in Figures 3 and 4.

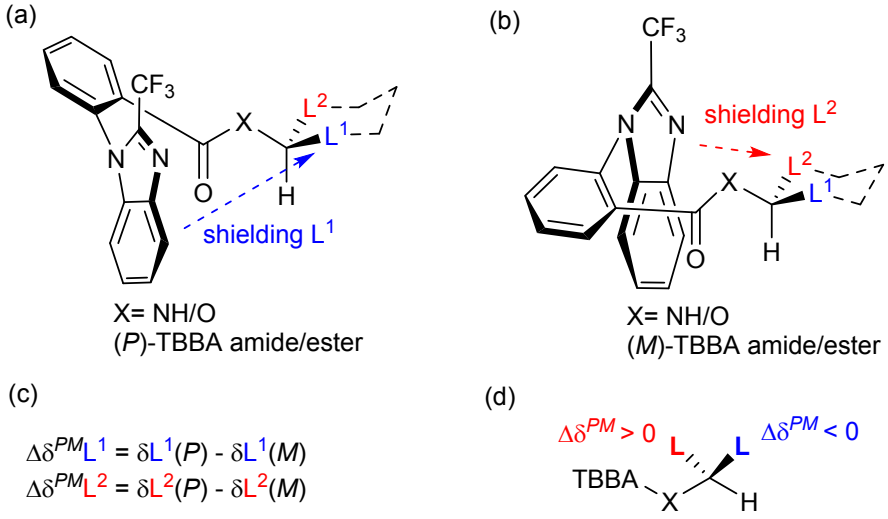


Figure 5: General conformational model for α-chiral primary amines and secondary alcohols. (a) NMR-significant conformer of the (*P*)-TBBA amide/ester. (b) NMR-significant conformer of the (*M*)-TBBA amide/ester. (c) Equations for differences in the chemical shifts between (*P*)- and (*M*)-TBBA amide/esters. (d) Simplified projection for the absolute configuration assignment.

One possible explanation for the higher differences of the chemical shifts between (***P***)- and (***M***)-TBBA amides/esters compared with the MTPA derivatives is the population of NMR significant conformers. For this purpose, we chose menthol as a frequently studied model compound. The set of calculations (see previously described parameters for the energy calculation) performed by Spartan 16 software showed that more than 90% of the conformational equilibrium was made up of one conformer in the case of (***M***)-**20** and two conformers in the case of ***(P)*-2**0. By comparison, six conformers of (***R***)-MTPA and two conformers of (***S***)-MTPA menthol

ester made up more than 90% of their populations. The complex conformational equilibrium of MTPA esters was previously confirmed in theoretical calculations.[16] These findings indicate that less flexible TBBA conformers are probably, on average, able to project the anisotropic effect of the benzimidazole moiety in a more efficient and space-oriented manner towards the analyzed ligands.

The TBBA trifluoromethyl group can provide additional information if ^{19}F NMR spectra are recorded (ΔCF_3 values, Figures 3 and 4). We did not find a conformational model for the ^{19}F method as was suggested for MTPA,[34] but we observed a simple relationship. If a sterically more demanding substituent has a negative difference (^{1}H NMR), then the value of $\Delta\delta^{PM}(^{19}F)CF_3$ will be negative and *vice versa* for the opposite configuration. However, this trend was broken for the TBBA esters **17** and **21**. The ^{19}F NMR difference is at most indicative, since some values are relatively small with regard to the ^{19}F NMR chemical shift scale. Furthermore, only two data points (one for each diastereomer) are obtained, which leads to a configuration assignment with no space for self-correction. This was shown by Kakisawa *et al.*[13] on a set of marine terpenoids. In this case, the reliability of the ^{19}F NMR method was less than 50% compared with the ^{1}H-NMR method. Nevertheless, the ^{19}F NMR spectra of TBBA esters or amides can provide valuable information about enantiomeric purity.

CONCLUSION

In summary, we developed a simple synthesis of axially chiral TBBA. This stable CDA can be used to assign the absolute configuration of α-chiral primary amines and secondary alcohols more reliably than the conventional MTPA. Much higher $\Delta\delta^{PM}$ values of up to 1.05 ppm are observed for several compounds. We also propose a conformational model using NMR spectra and density functional theory calculations of the lowest energy conformers. In addition, the TBBA derivatives can be utilized to determine enantiomeric purity by ^{19}F NMR analysis.

EXPERIMENTAL SECTION

General methods. All reactions were carried out under air unless otherwise stated. Reaction workup and column chromatography were performed with commercial grade solvents without further purification. ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were measured on Jeol ECA400II (400 MHz) or Jeol ECX-500SS (500 MHz) in $CDCl_3$ or DMSO-D_6 as a solvent. ^{1}H and ^{13}C spectra were calibrated using residual non-deutertated solvent as an internal reference (7.26 ppm and 77.16 ppm for $CDCl_3$ and 2.50 ppm and 39.52 ppm for DMSO-D_6) ^{19}F spectra were calibrated by addition of $CFCl_3$ as an internal reference (δ= 0.0 ppm). ^{15}N NMR spectra were calibrated to external reference (CH_3NO_2, δ= 0.0 ppm) All ^{13}C NMR spectra were measured with broad band ^{1}H decoupling. ^{1}H NMR data are reported as follows: δ, chemical shift; coupling constants (J are given in Hertz, Hz) and integration. Abbreviations to denote the multiplicity of a particular signal were s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad singlet).

Analytical thin-layer chromatography (TLC) was performed using precoated silica gel plates. Flash chromatography was performed using silica gel (35 - 70 μm particle size).

High-resolution mass spectral analyses were performed using electrospray ionisation and time of flight detector. Analytical high performance liquid chromatography (HPLC) was performed on a C-18 column using ammonium acetate buffer/acetonitrile as a mobile phase. Eluents were detected by using UV/VIS detector and mass detector with electrospray ionisation (ESI) and Orbitrap analyzer.

SFC chiral analyses were performed using an Acquity UPC^2 system (Waters) consisting of a binary solvent manager, sample manager, column manager, column heater, convergence manager, PDA detector 2998, QDa mass detector and chiral analytical columns CHIRALPAK IA3 4,6x100mm, 3 um particle size. The chromarographic runs were performed at a flow rate of 2,2 ml/min, column temperature of 38°C and ABPR 2000 psi.

Synthesis of rac-2

2-((2-Nitrophenyl)amino)benzoic acid (4): Anthranilic acid (16.8 g, 120 mmol) was dissolved in DMF (30 mL). 2-fluoronitrobenzene (12.75 mL, 120 mmol, 1 eq.), K_2CO_3 (16.5 g, 120 mmol, 1 eq.) and copper (0.16 g, 0.8 mmol, 0.02 eq.) were added respectively. The suspension was refluxed for 17 hrs. Then, the reaction mixture was cooled down to room temperature. A formed muddy solid was suspended in cold water (150 ml). Resulting suspension was acidified using glacial acetic acid (150 mL). A precipitate was stirred until a fine suspension was formed, filtered, washed with water, and recrystallized from glacial acetic acid (125 mL). A filtered solid was washed thoroughly with water and dried in an oven (90 °C). Yield: 22 g (70%), brown solid. **^{1}H NMR** (400 MHz, DMSO-D_6) δ 13.46 (s, 1H), 11.11 (s, 1H), 8.13 (dd, *J* = 8.4, 1.4 Hz, 1H), 8.00 – 7.95 (m, 1H), 7.67 – 7.58 (m, 2H), 7.56 – 7.49 (m, 2H), 7.13 – 7.05 (m, 2H). **^{13}C{^{1}H} NMR** (101 MHz, DMSO-D_6) δ 168.8, 142.1, 138.1, 137.2, 135.5, 133.6, 131.8, 126.3, 121.7, 120.7, 119.2, 118.6, 118.3. **HRMS** (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{13}H_{11}O_4N_2$: 259.0713, found: 259.0712 **Mp**: 218-221°C.

2-((2-Aminophenyl)amino)benzoic acid (5): A two liter three-necked flask was charged with 2-((2-nitrophenyl)amino)benzoic acid **4** (16.8 g, 65 mmol, 1 eq.) and 10% Pd/C (1.3 g, 0.01 eq.). A solid mixture was suspended in ethylacetate (1 L). The flask was fitted with a large stir bar, rubber balloon, valve and rubber septa, and flushed with nitrogen and vacuum multiple times to remove air. To an evacuated aparatus, a hydrogen gas was introduced and the reaction mixure was rapidly stirred at room temperature (500 rpm). The reaction was monitored by TLC (hexane:ethyl aceate 1:1, UV and nynhydrin detection) (a sample can be taken via syringe through rubber septum). After two hours, the mixture was filtered through pad of celite. Celite was washed twice with ethylacetate and a filtrate was evaporated. Yield 14.3 g (96%), a yellow to brown solid. **^{1}H NMR** (400 MHz, DMSO-D_6) δ 9.02 (s, 1H), 7.86 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.28 (ddd, *J* = 8.5, 7.2, 1.5 Hz, 1H), 7.03 (dd, *J* = 7.7, 1.1 Hz, 1H), 6.99 – 6.93 (m, 1H), 6.80 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.66 (td, *J* = 7.6, 0.9 Hz, 1H), 6.62 – 6.56

(m, 2H). **^{13}C{^{1}H} NMR** (101 MHz, DMSO-D_6) δ 170.6, 149.7, 144.7, 134.6, 132.1, 126.8, 126.6, 125.3, 117.1, 116.4, 115.9, 113.7, 111.8, **HRMS** (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{13}H_{13}O_2N_2$: 229.0972, found: 229.0973, **Mp**: 195-200°C.

1-Carboxyphenyl(2-trifluoromethy)benzimidazole (rac-2): To 2-((2-aminophenyl)amino)benzoic acid **5** (11.4 g, 49.9 mmol, 1 eq.) trifluoroacetic anhydride was added (100 mL, c= 0,5 mmol/mL). After effervescence ended, a solution was refluxed for 70 minutes. The reaction mixture was then cooled to room temperature and added dropvise into ice-cold water (2.7 L) with rapid stirring by overhead stirrer. A white precipitate was collected by filtration and dried in vacuum at 90°C. Yield 14.5 g (94%), a pale yellow solid. **^{1}H NMR** (400 MHz, DMSO-D_6) δ 13.19 (d, *J* = 84.5 Hz, 1H), 8.18 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.92 – 7.89 (m, 1H), 7.88 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.81 (td, *J* = 7.6, 1.3 Hz, 1H), 7.74 (dd, *J* = 7.7, 0.8 Hz, 1H), 7.44 – 7.38 (m, 2H), 7.06 – 7.02 (m, 1H). **^{13}C{^{1}H} NMR** (101 MHz, DMSO-D_6) δ 165.2, 140.2, 140. (q, *J* = 38.9 Hz), 137.4, 133.8, 133.3, 131.9, 130.94 130.2, 129.4, 126.0, 123.7, 120.8, 118.8 (q, *J* = 272.2 Hz), 111.1. **^{19}F NMR** (376 MHz, DMSO-D_6) δ -60.52 **HRMS** (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{15}H_{10}O_2N_2F_3$: 307.0689, found: 307.0685, **Mp:** 218-220 °C

Resolution of rac-2

(*P*/*M*)-(*S*)-4-Phenyl-2-(2-(2-(trifluoromethy)-1*H*-benzo[*d*]imidazol-1-yl)phenyl)-4,5-dihydrooxazole (*P/M*-7) Racemic 2-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-1-yl)benzoic acid **rac-2** (1.8 g, 6 mmol, 1 eq.) was suspended in toluene (90 mL) and $SOCl_2$ (2.2 mL, 30 mmol, 5 eq.) was added. A mixture was refluxed for 20 minutes (all solids dissolved). After cooling to RT, the solvent was evaporated yielding a dark oily residue. This residue was twice dissolved in $CHCl_3$ (25 mL) and evaporated to remove all residual $SOCl_2$.

The resulting oil was dissolved in $CHCl_3$ (25 mL) and after cooling to 5°C (ice/water bath), a solution was added dropvise into a cooled solution of (*S*)-(+)-phenylglycinol (904 mg, 6.6 mmol, 1.1 eq.) and triethylamine (910 µL, 6.6 mmol, 1.1 eq.) in $CHCl_3$ (12 mL). This mixture was stirred on an ice bath for 90 min. After 90 min., the solution was washed with 10% (v/v) aq. HCl (2 x 30 mL) and 10% (m/m) aq. K_2CO_3 (2 x 30 mL) and dried over $MgSO_4$.

Afterwards, the drying agent was removed by filtration and $SOCl_2$ (2.2 mL, 30 mmol, 5 eq.) was added to the filtrate. The solution was stirred at room temperature in an open flask for 90 minutes (monitored by TLC, hexane:EtOAc 2:1; Rf= 0.75). After the reaction was completed, the solution was evaporated, redissolved in $CHCl_3$, and evaporated again to yield a dark oily residue.

This residue was dissolved in MeOH (32 mL) and solution of NaOH (1.2 g, 30 mmol, 5 eq.) in water (12 mL) was added dropwise and the reaction was stirred for 2 hrs (monitored by TLC, hexane:EtOAc 2:1, Rf= 0.62 or Hex:EtOAc 5:1, Rf= 0.32 and 0.22). After completion of the reaction, methanol was evaporated using RVO and H_2O (50 mL) was added. A cloudy solution was extracted with $CHCl_3$ (50 and 2x 30 mL). Organic layers were combined and dried over $MgSO_4$ and evaporated to yield 1.94 g of an oily mixture of diastereomers. The mixture was purified by column chromatography (10x6 cm, petrolether: ethyl acetate 6:1) yielding 807 mg (65% from rac. acid) of (***P***)-**7** and 676 mg (55% from rac. acid) of (***M***)-**7** as yellow oils.

(***P***)-**7** **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.24 (dd, *J* = 7.6, 1.9 Hz, 1H), 7.90 (d, *J* = 7.3 Hz, 1H), 7.76 – 7.65 (m, 2H), 7.54 (dd, *J* = 7.4, 1.3 Hz, 1H), 7.43 – 7.33 (m, 2H), 7.16 – 7.08 (m, 3H), 7.02 (dd, *J* = 7.3, 1.2 Hz, 1H), 6.63 (td, *J* = 7.4, 3.2 Hz, 2H), 5.06 (dd, *J* = 9.9, 9.1 Hz, 1H), 4.28 (dd, *J* = 10.3, 8.4 Hz, 1H), 3.83 (t, *J* = 8.6 Hz, 1H). **^{13}C NMR{^{1}H}** (101 MHz, $CDCl_3$) δ 161.2, 141.7, 141.5 (q, *J* = 40.7 Hz), 141.0, 137.6, 133.6, 132.4, 131.6, 130.5, 130.0, 128.6, 127.3, 126.6, 126.2, 125.6, 123.7, 121.5, 119.0 (q, *J* = 271.7 Hz), 111.0, 74.4, 69.7 **^{19}F NMR** (376 MHz, $CDCl_3$) δ -61.52 **HRMS** (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{23}H_{17}ON_3F_3$: 408.1318, found: 408.1320 $[\alpha]_D^{26}$ = -82.31° (c= 0.39 MeOH).

(*M*)-7 ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.95 – 7.89 (m, 1H), 7.77 – 7.65 (m, 2H), 7.53 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.43 – 7.33 (m, 2H), 7.25 – 7.18 (m, 3H), 7.08 – 7.02 (m, 1H), 6.88 – 6.82 (m, 2H), 5.02 (t, *J* = 9.4 Hz, 1H), 4.40 (dd, *J* = 10.2, 8.5 Hz, 1H), 3.50 (t, *J* = 8.7 Hz, 1H). **^{13}C NMR{^{1}H}** (101 MHz, $CDCl_3$) δ 162.3, 141.5 (q, *J* = 39.9 Hz), 141.3, 140.9, 137.7, 133.4, 132.4, 131.9, 130.5, 129.7, 128.7, 127.7, 127.1, 126.7, 125.8, 123.9, 121.5, 119.0 (q, *J* = 272.1 Hz), 111.1, 75.0, 69.8. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -61.34 **HRMS** (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{23}H_{17}ON_3F_3$: 408.1318, found: 408.1323 $[\alpha]_D^{26}$ = +82.50° (c= 0.44 MeOH).

Hydrolysis of (*P*)-7 to (*P*)-1-carboxyphenyl(2-trifluoromethy)benzimidazole (*P*)-2: (***S,P***)-4-phenyl-2-(2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)phenyl)-4,5-dihydrooxazole (***P*)-7** (807 mg, 2 mmol, 1 eq.) was dissolved in MeOH (20 mL) and 10% (v/v) HCl (7.2 mL) was added. The solution was stirred at room temperature for 90 minutes when HPLC analysis showed complete ring opening. After 90 minutes, NaOH (1.6g, 40 mmol, 20 eq.) was added as a 10% aq. solution (16 mL). The reaction was stirred for another 3 hours until HPLC analysis showed a complete conversion. The solution was then diluted with water (15 mL), methanol was evaporated using RVO and a resulting solution was extracted with DCM (3x20 mL). The alkaline aq. phase was then added dropvise to ice cold 10% (v/v) HCl (30 mL) with rapid stirring. A white precipitate was collected by filtration and dried on air to give 393 mg of a white solid (64%). The compound was identical as racemic acid **rac-2** (with regards to spectrocsopic properties NMR, MS, MP). $[\alpha]_D^{24}$ = -46.02° (c= 1, MeOH). Enantiomeric purity was determined by chiral SFC: isocratic elution with 90% CO_2, 10% MeOH 0.1% TFA, column CHIRALPAK 1A3.

Hydrolysis of (*M*)-*7* to (*M*)-1-carboxyfenyl(2-trifluoromethy)benzimidazole (*M*)-2: Following the above described procedure, starting with 676 mg of oxazoline (***M*)-7**. 324 mg of white solid (64%) $[\alpha]_D^{24}$ = +45.54° (c= 1, MeOH).

General procedure for TBBA-amide formation

(*P*)-(*R*)-*N*-(1-phenylethyl)-2-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-1-yl)benzamide (*P*)-8, Method A: *(P)*-1-Carboxyphenyl(2-trifluoromethy)benzimidazole **(*P*)-2** (40 mg, 0.13 mmol, 1 eq) was suspended in toluene (2 mL) and $SOCl_2$ (48 µL, 0.65 mmol, 5eq) was added. This suspension was put into a pre-heated oil bath (110°C) and refluxed until solids were completely dissolved (aprox. 5 minutes). After that, a mixture was cooled to RT and evaporated, redissolved in $CHCl_3$ and evaporated again. Resulting oil was dissolved in $CHCl_3$ (1 mL) and cooled to 5°C on an ice bath. This solution was then added to an ice cold solution of (*R*)-(+)-1-Phenylethylamine (18.2 µL, 0.143 mmol, 1.1 eq), triethylamine (20 µL, 0.143 mmol, 1.1 eq.) in $CHCl_3$ (1 mL). A solution was stirred on an ice bath for 1 hour, then was washed with 10% (v/v) HCl (2x 2 mL), 10% (m/m) K_2CO_3 (2x 2 mL), and brine (2 mL); dried over $MgSO_4$ and evaporated to yield 25 mg of a white solid (47%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.83 – 7.78 (m, 1H), 7.67 – 7.60 (m, 2H), 7.39 (ddd, *J* = 15.5, 10.2, 6.3 Hz, 3H), 7.26 – 7.19 (m, 3H), 7.09 (d, *J* = 7.7 Hz, 1H), 7.00 – 6.95 (m, 2H), 5.59 (d, *J* = 7.4 Hz, 1H), 4.84 (p, *J* = 7.0 Hz, 1H), 0.92 (d, *J* = 6.8 Hz, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 164.4, 142.1, 140.6, 137.5, 135.3, 131.7, 131.5, 130.8, 129.9, 129.5, 128.8, 127.7, 126.5, 126.05, 124.5, 121.7, 119.0 (q, *J* = 272.0 Hz), 49.4, 20.7 **^{19}F NMR** (376 MHz, $CDCl_3$) δ -61.21 **^{15}N NMR** (50.664 MHz, $CDCl_3$): δ -128.8, -226.4, -247.3 (^{1}J=89.5 Hz) **HRMS** (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{23}H_{19}ON_3F_3$: 410.1475, found: 410.1472, $[\alpha]_D^{22}$ = -21.89° (c= 0.50, MeOH).

Method B: (*P*)-1-Carboxyphenyl(2-trifluoromethy)benzimidazole **(*P*)-2** (40 mg, 0.13 mmol, 1 eq) was dissolved in DMF (0.8 mL). EDCl (51 mg, 0.26 mmol, 2 eq) and then HOBt (40 mg, 0.26 mmol, 2 eq) were subsequently added into the solution. Afterwards, (*R*)-(+)-1-Phenylethylamine (18.2 µL, 0.143 mmol, 1.1 eq) was added into the mixture and the reaction was stirred at room temperature (23-25°C) until a complete conversion of the starting material was detected by HPLC analysis (90-120 min). After completion, the reaction was diluted with 4 ml of EtOAc forming a cloudy white solution, which was extracted with 10% HCl (2x 4ml), sat. $NaHCO_3$ (2x 4 ml), and brine (4 ml). The organic layer was dried over Na_2SO_4 and evaporated to give 24 mg of a white solid (47%). The spectra were identical to those prepared by method A.

(*M*)-(*R*)-*N*-(1-Phenylethyl)-2-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-1-yl)benzamide (*M*)-8, Method A: From 50 mg of **(*M*)-2** and (*R*)-(+)-1-Phenylethylamine, 50 mg of a white solid (77%). **Method B:** From 40 mg of **(*M*)-2** and R-(+)-1-Phenylethylamine, 43 mg of a white solid (81%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.1 Hz, 1H), 7.91 – 7.86 (m, 1H), 7.70 – 7.62 (m, 2H), 7.47 – 7.34 (m, 3H), 7.19 – 7.10 (m, 3H), 7.06 (d, *J* = 8.2 Hz, 1H), 6.73 – 6.69 (m, 2H), 5.48 (d, *J* = 7.0 Hz, 1H), 4.86 (p, *J* = 7.0 Hz, 1H), 1.12 (d, *J* = 6.8 Hz, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 164.3, 141.9, 140.7, 137.5, 135.3, 131.8, 131.3, 130.9, 130.2, 129.5, 128.7, 127.55, 126.5, 125.8, 124.5, 122.0, 118.8 (q, *J* = 272.3 Hz), 111.1, 49.5, 21.1 **^{19}F NMR** (376 MHz, $CDCl_3$) δ -61.49 **^{15}N NMR** (50.664 MHz, $CDCl_3$): δ -129.5, -226.2, -247.4 (^{1}J=89.1 Hz) **HRMS** (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{23}H_{19}ON_3F_3$: 410.1475, found: 410.1475, $[\alpha]_D^{22}$ = +159.59° (c= 0.73, MeOH).

(*P*)-(*R*)-N-(1-(naphthalen-1-yl)ethyl)-2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzamide (*P*)-9 Using method B, from 15 mg of **(*P*)-2** and (*R*)-(+)-1-(1-Naphthyl)ethylamine, 17 mg of oil (74%). Purified by column chromatography (hexane:ethylacetate 3:1, column dimesions 1x10 cm). **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm) = 7.90 (d, *J* = 7.5 Hz, 1H), 7.84 (d, *J* = 7.6 Hz, 1H), 7.75 (dd, *J* = 12.6, 5.3 Hz, 1H), 7.61 (pd, *J* = 7.4, 1.4 Hz, 1H), 7.51 – 7.43 (m, 1H), 7.38 (dt, *J* = 15.5, 7.3 Hz, 1H), 7.20 (d, *J* = 7.1 Hz, 1H), 7.11 (d, *J* = 7.6 Hz, 1H), 5.76 – 5.65 (m, 1H), 1.16 (d, *J* = 6.5 Hz, 1H). **^{13}C{1H} NMR** (126 MHz, $CDCl_3$) δ (ppm) = 164.4, 140.6, 140.6 (app.d, *J* = 38.2 Hz), 137.7, 137.4, 135.6, 134.0, 131.7, 131.0, 130.8, 129.7, 128.9, 128.7, 126.8, 126.4, 126.0, 125.3, 124.4, 123.1, 122.6, 121.7, 119.0 (q, *J* =, 272.0 Hz), 111.5, 45.1, 19.9. **^{19}F NMR** (376 MHz, $CDCl_3$) δ (ppm) = -61.19. **HRMS** (ESI-TOF) m/z: [M+H]+ calculated for $C_{27}H_{21}F_3N_3O$: 460.1637 found: 460.1632, $[\alpha]_D^{22}$ −95.00° (c= 0.1 $CHCl_3$).

(*M*)-(*R*)-N-(1-(naphthalen-1-yl)ethyl)-2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzamide (*M*)-9 Using method B, from 15 mg of **(*M*)-2** and (*R*)-(+)-1-(1-Naphthyl)ethylamine, 15.5 mg of oil (68%). Purified by column chromatography (hexane:ethylacetate 3:1, column dimesions 1x10 cm). **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm) = 7.88 (d, *J* = 8.2 Hz, 1H), 7.86 – 7.81 (m, 1H), 7.80 (d, *J* = 7.9 Hz, 1H), 7.71 (d, *J* = 8.2 Hz, 1H), 7.65 – 7.59 (m, 1H), 7.47 – 7.43 (m, 1H), 7.43 – 7.40 (m, 1H), 7.39 (dd, *J* = 5.9, 3.2 Hz, 1H), 7.37 – 7.33 (m, 1H), 7.27 (dd, *J* = 7.0, 1.0 Hz, 1H), 7.24 (d, *J* = 7.1 Hz, 1H), 6.98 (d, *J* = 8.2 Hz, 1H), 6.86 (d, *J* = 7.1 Hz, 1H), 5.72 (p, *J* = 6.8 Hz, 1H), 5.58 (d, *J* = 7.8 Hz, 1H), 1.26 (d, *J* = 6.7 Hz, 1H). **^{13}C{1H} NMR** (126 MHz, $CDCl_3$) δ (ppm) = 164.1 (s), 141.1 (d, *J* = 38.6 Hz), 140.7, 137.5, 137.40, 135.3, 133.9, 131.8, 131.62, 130.9 , 130.7, 130.0, 129.7, 128.8, 128.5, 126.7, 126.3, 126.0, 125.2, 124.4, 123.0, 122.2, 121.8, 119.0 (q), 110.9, 44.9, 20.3. **^{19}F NMR** (376 MHz, $CDCl_3$) δ (ppm) = -61.54. **HRMS** (ESI-TOF) m/z: [M+H]+ calculated for $C_{27}H_{21}F_3N_3O$: 460.1637 found: 460.1632, $[\alpha]_D^{22}$ +68.00° (c= 0.1 $CHCl_3$).

(*P*)-(*S*)-N-(3,3-dimethylbutan-2-yl)-2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzamide (*P*)-10 Using method B, from 15 mg of **(*P*)-2** and (*S*)-(+)-3,3-dimethyl-2-butylamine, 16.2 mg of oil (83%). Purified by column chromatography (hexane:ethylacetate 4:1, column dimesions 1x10 cm). **^{1}H NMR** (500 MHz, $CDCl_3$) δ(ppm) = 7.96 – 7.93 (m, 1H), 7.91 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.71 – 7.63 (m, 2H), 7.44 – 7.38 (m, 3H), 7.14 – 7.10 (m, 1H), 5.16 (d, *J* = 9.2 Hz, 1H), 3.69 (dq, *J* = 9.5, 6.8 Hz, 1H), 0.70 (d, *J* = 6.8 Hz, 3H), 0.48 (s, 9H). **^{13}C{1H}** (126 MHz, $CDCl_3$) δ 164.7, 141.05 (q, *J* = 39.4 Hz), 140.85, 137.5, 135.9, 131.6, 131.1, 131.0, 130.4 129.6, 126.6, 124.7, 122.0, 118.94 (q, *J* = 272.1 Hz), 111.2, 53.6, 33.6, 25.7, 15.7, **^{19}F NMR** (376 MHz, $CDCl_3$) δ (ppm) = -61.42, **HRMS** (ESI-TOF) m/z: [M+H]+ calculated for $C_{21}H_{23}F_3N_3O$: 390.1788 found: 390.1788, $[\alpha]_D^{22}$ -80.00° (c= 0.1 $CHCl_3$).

(*M*)-(*S*)-N-(3,3-dimethylbutan-2-yl)-2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzamide (*M*)-10 Using method B, from 15 mg of **(*M*)-2** and (*S*)-(+)-3,3-dimethyl-2-butylamine, 14,6 mg of oil (75 %). Purified by column chromatography (hexane:ethylacetate 4:1, column dimesions 1x10 cm). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.94 – 7.90 (m, 1H), 7.88 – 7.85 (m, 1H), 7.67 (pd, *J* = 7.5, 1.7 Hz, 2H), 7.43 – 7.37 (m, 4H), 7.14 – 7.10 (m, 1H), 5.21 (d, *J* = 9.2 Hz, 1H), 3.65 (dq, *J* = 9.6, 6.8 Hz, 1H), 0.66 (s, 9H), 0.42 (d, *J* = 6.8 Hz, 3H). **^{13}C{1H} NMR** (126 MHz, $CDCl_3$) δ 164.9, 140.7, 140.5 (q, *J* = 38.4 Hz), 137.6, 135.9, 131.6, 131.2, 130.9, 130.00,

129.6, 126.6, 124.6, 121.7, 119.1 (q, J = 271.7 Hz), 111.6, 53.5, 33.8, 25.9, 15.1 **^{19}F NMR** (376 MHz, $CDCl_3$) δ (ppm) = -61.06. **HRMS** (ESI-TOF) m/z: [M+H]+ calculated for $C_{21}H_{23}F_3N_3O$: 390.1788 found: 390.1790, $[\alpha]_D^{22}$ = +155.56° (c= 0.09 $CHCl_3$).

(*P*)-(*S*)-*N*-(2-Hydroxy-1-phenylethyl)-2-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-1-yl)benzamide (*P*)-11, Method A: From 40 mg of **(*P*)-2** and (*S*)-(+)-2-Phenylglycinol, 52 mg of oil (94%). **Method B**: From 40 mg of **(*P*)-2** and (*S*)-(+)-2-Phenylglycinol, 41 mg of oil (74%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.93 – 7.85 (m, 2H), 7.70 – 7.64 (m, 2H), 7.41 (dddd, J = 13.4, 8.6, 6.1, 2.8 Hz, 3H), 7.25 – 7.20 (m, 3H), 7.12 (dd, J = 6.9, 1.8 Hz, 1H), 6.23 (d, J = 7.1 Hz, 1H), 4.79 (dt, J = 7.3, 4.6 Hz, 1H), 3.48 – 3.39 (m, 1H), 3.27 (dd, J = 11.0, 4.1 Hz, 1H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 165.5, 140.9 (q, J = 38.1 Hz), 140.6, 138.4, 137.4, 134.9, 131.9, 131.6, 130.9, 130.0, 129.6, 128.5, 128.0, 126.5, 124.5, 121.65, 119.0 (q, J = 272.2 Hz), 111.4, 65.6, 55.6 **^{19}F NMR** (376 MHz, $CDCl_3$) δ -61.29 **HRMS** (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{23}H_{19}O_2N_3F_3$: 426.1424, found: 426.1423, $[\alpha]_D^{24}$ = -32.50° (c= 0.76, MeOH).

(*M*)-(*S*)-*N*-(2-Hydroxy-1-phenylethyl)-2-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-1-yl)benzamide (*M*)-11, Method A: From 40 mg of **(*M*)-2** and (*S*)-(+)-2-Phenylglycinol, 52 mg of oil (94%). **Method B:** From 40 mg of **(*M*)-2** and (*S*)-(+)-2-Phenylglycinol, 39 mg of oil (70%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91 (td, J = 8.3, 1.1 Hz, 2H), 7.70 – 7.63 (m, 2H), 7.45 – 7.39 (m, 2H), 7.36 (dt, 1H), 7.18 – 7.11 (m, 1H), 7.07 (d, J = 8.1 Hz, 2H), 6.71 (dd, J = 7.8, 1.5 Hz, 2H), 6.12 (d, J = 6.9 Hz, 1H), 4.79 (dt, J = 6.9, 5.0 Hz, 1H), 3.55 (dd, J = 5.4, 11.2 Hz, 1H), 3.51 (dd, J = 4.6, 11.2 Hz, 1H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 165.4, 141.0 (q, J = 38.7 Hz), 140.8, 140.8, 138.1, 137.4, 134.8, 132.0, 131.55, 130.95, 130.3, 129.6, 128.9, 127.9, 126.5, 126.4, 124.5, 121.8, 119.5 (q, J = 272.7 Hz), 111.2, 65.8, 55.95 **^{19}F NMR** (376 MHz, $CDCl_3$) δ -61.36 **HRMS** (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{23}H_{19}O_2N_3F_3$: 426.1424, found: 426.1423, $[\alpha]_D^{25}$ = +130.50° (c= 0.8 MeOH).

***(P)*-(*S*)-*N*-(1-Hydroxy-3-methylbutan-2-yl)-2-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-1-yl)benzamide (*P*)-12, Method A**: From 40 mg of **(*P*)-2** and (*S*)-(+)-2-amino-3-methylbutanol, 44 mg of yellow oil (86%). **Method B**: From 40 mg of **(*P*)-2** and (*S*)-(+)-2-amino-3-methylbutanol, 21 mg of white solid (41%) after purification by preparative HPLC **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.94 – 7.90 (m, 1H), 7.89 – 7.85 (m, 1H), 7.71 – 7.64 (m, 2H), 7.45 – 7.38 (m, 3H), 7.15 – 7.09 (m, 1H), 5.70 (d, J = 8.6 Hz, 1H), 3.53 (ddd, J = 11.6, 8.5, 4.2 Hz, 1H), 3.24 (dd, J = 11.0, 4.6 Hz, 1H), 2.96 (dd, J = 11.0, 3.7 Hz, 1H), 1.63 (dq, J = 13.7, 6.9 Hz, 1H), 0.72 (d, J = 6.8 Hz, 3H), 0.67 (d, J = 6.8 Hz, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 165.9, 141.0, 140.6, 137.4, 135.4, 131.8, 131.3, 130.9, 130.0, 129.5, 126.6, 124.6. 121.5, 119.0 (q, J = 272.0 Hz), 111.5, 62.8, 56.8, 28.8, 19.3, 18.5 **^{19}F NMR** (376 MHz, $CDCl_3$) δ -61.18. **HRMS** (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{20}H_{21}O_2N_3F_3$: 392.1580, found: 392.1577, $[\alpha]_D^{22}$ = +99.6° (c= 0.25, MeOH).

(*M*)-(*S*)-*N*-(1-Hydroxy-3-methylbutan-2-yl)-2-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-1-yl)benzamide (*M*)-12, Method A: From 40 mg of **(*M*)-2** and (*S*)-(+)-2-amino-3-methylbutanol, 50 mg of an yellow oil (98%). **Method B:** From 40 mg of **(*M*)-2** and (*S*)-(+)-2-amino-3-methylbutanol, 22 mg of a white solid (41%) after purification by preparative HPLC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.96 – 7.90 (m, 1H), 7.90 – 7.84 (m, 1H), 7.70 – 7.63 (m, 2H), 7.46 – 7.36 (m, 3H), 7.14 – 7.08 (m, 1H), 5.65 (d, J = 8.4 Hz, 1H), 3.60 – 3.52 (m, 1H), 3.33 (ddd, J = 15.0, 11.1, 4.5 Hz, 2H), 1.53 (dq, J = 13.6, 6.8 Hz, 1H), 0.53 (d, J = 6.8 Hz, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 166.1, 141.1 (q, J = 38.5 Hz), 140.8, 137.5, 135.4, 131.8, 131.4, 130.9, 129.9, 129.6, 126.4, 124.5, 118.9 (q, J = 272.1 Hz), 111.2, 63.0, 57.0, 28.7, 19.1, 18.14 **^{19}F NMR** (376 MHz, $CDCl_3$) δ -61.36. **HRMS** (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{20}H_{21}O_2N_3F_3$: 392.1580, found: 392.1581, $[\alpha]_D^{22}$ = +81.63° (c= 0.49, MeOH).

(*P*)-Methyl (2-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-1-yl)benzoyl)-D-alaninate (*P*)-13, Method A: From 40 mg of **(*P*)-2**, D-AlaOMe.HCl and 2.2 eq of triethylamine. 50 mg of oil (98 %). **Method B:** From 40 mg of **(*P*)-2**, D-AlaOMe.HCl and 1.1 eq of triethylamine. 25 mg of white solid (50 %). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.92 (dd, J = 6.5, 2.4 Hz, 1H), 7.86 (dd, J = 5.7, 3.6 Hz, 1H), 7.71 – 7.66 (m, 2H), 7.48 – 7.44 (m, 1H), 7.42 – 7.35 (m, 2H), 7.09 (dd, J = 6.5, 2.4 Hz, 1H), 6.12 (d, J = 6.9 Hz, 1H), 4.35 (p, J = 7.1 Hz, 1H), 3.65 (s, 3H), 0.85 (d, J = 7.2 Hz, 3H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 172.7, 164.7, 140.6 (q, J = 38.6 Hz), 134.7, 132.0, 131.8, 130.9, 129.75, 129.6, 126.4, 124.4, 121.6, 119.0 (q, J = 272.1 Hz), 111.5, 52.7, 48.3, 17.7. **^{19}F NMR** (471

MHz, $CDCl_3$) δ -61.26 **HRMS** (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{19}H_{17}O_3N_3F_3$: 392.1217, found: 392.1211, $[\alpha]_D^{22}$ = -59.03° (c= 0.31 MeOH).

(*M*)-Methyl (2-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-1-yl)benzoyl)-D-alaninate (*M*)-13, Method A: From 30 mg of **(*M*)-2**, D-AlaOMe.HCl and 2 eq. of triethylamine, 31 mg of white foam. (62%). **Method B:** From 40 mg of **(*M*)-2**, D-AlaOMe.HCl and 1.1 eq of triethylamine. 30 mg of white solid (60 %). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.95 – 7.90 (m, 1H), 7.87 – 7.83 (m, 1H), 7.70 – 7.66 (m, 2H), 7.47 – 7.43 (m, 1H), 7.42 – 7.36 (m, 2H), 7.09 (dd, *J* = 5.8, 3.3 Hz, 1H), 6.10 (d, *J* = 6.9 Hz, 1H), 4.35 (p, *J* = 7.1 Hz, 1H), 3.59 (s, 3H), 1.03 (d, *J* = 7.0 Hz, 3H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 172.6, 164.6, 141.2 (q, *J* = 38.7 Hz), 140.7, 137.55, 134.7, 132.0, 132.0, 130.9, 129.7, 129.7, 126.3, 124.4, 121.7, 118.9 (q, *J* = 272.1 Hz), 111.1, 52.6, 48.35, 18.1 **^{19}F NMR** (471 MHz, $CDCl_3$) δ -61.63 **HRMS** (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{19}H_{17}O_3N_3F_3$: 392.1217, found: 392.1219, $[\alpha]_D^{22}$ = +142.09° (c= 0.24 MeOH).

(*P*)-methyl (2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoyl)-L-phenylalaninate (*P*)-14 Using method B, from 15 mg of **(*P*)-2** and L-PheOMe.HCl and 2.2 eq. of triethylamine, 17,5 mg of oil (75 %). Purified by column chromatography (hexane:ethylacetate 3:1, column dimesions 1x10 cm). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.94 – 7.91 (m, 1H), 7.70 – 7.63 (m, 5H), 7.43 – 7.36 (m, 5H), 7.25 – 7.22 (m, 4H), 7.09 – 7.06 (m, 1H), 6.94 (dd, *J* = 7.3, 2.1 Hz, 3H), 6.10 (d, *J* = 7.5 Hz, 1H), 4.68 (dt, *J* = 7.6, 5.8 Hz, 1H), 3.58 (s, 4H), 2.91 (dd, *J* = 5.8, 2.2 Hz, 3H). **^{13}C NMR {1H}** (126 MHz, $CDCl_3$) δ 171.2, 164.8, 141.0 (q, *J* = 39.6 Hz), 140.7, 137.8, 135.6, 134.6, 132.3, 132.0, 130.8, 130.0, 129.3, 129.2, 128.7, 127.3, 126.2, 124.3, 121.6, 119.0 (q, *J* = 271.5 Hz), 111.4, 53.5, 52.5, 37.8. **^{19}F NMR** (376 MHz, $CDCl_3$) δ (ppm) = -61.58., **HRMS** (ESI-TOF) m/z: [M+H]+ calculated for $C_{25}H_{21}F_3N_3O_3$: 468.1535 found: 468.1529, $[\alpha]_D^{22}$ = -75.00°(c= 0.12 MeOH).

(*M*)-methyl (2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoyl)-L-phenylalaninate (*M*)-14 Using method B, from 15 mg of **(*M*)-2** and L-PheOMe.HCl and 2.2 eq. of triethylamine, 19 mg of oil (81 %). Purified by column chromatography (hexane:ethylacetate 3:1, column dimesions 1x10 cm). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.8 Hz, 1H), 7.76 – 7.74 (m, 1H), 7.69 – 7.63 (m, 2H), 7.43 – 7.33 (m, 4H), 7.25 – 7.20 (m, 3H), 7.03 (d, *J* = 7.9 Hz, 1H), 6.90 (dd, *J* = 7.3, 2.0 Hz, 2H), 6.04 (d, *J* = 7.5 Hz, 1H), 4.65 (dt, *J* = 7.6, 6.1 Hz, 1H), 3.59 (s, 3H), 2.84 – 2.75 (m, 2H). **^{13}C NMR{1H}** (126 MHz, $CDCl_3$) δ 171.5, 164.9, 141.1 (q, *J*=38.5 Hz), 140.7, 137.6, 135.5, 134.4, 132.2, 132.1, 130.8, 130.0, 129.5 , 129.1, 128.8, 127.3, 127.3, 126.2, 124.3, 121.7, 119.0 (q, *J* = 272.2 Hz), 111.3., 53.6, 52.4, 37.8., **^{19}F NMR** (376 MHz, $CDCl_3$) δ (ppm) = -61.43, **HRMS** (ESI-TOF) m/z: [M+H]+ calculated for $C_{25}H_{21}F_3N_3O_3$: 468.1535 found: 468.1528, $[\alpha]_D^{22}$ = +33.00°(c= 0.09 MeOH).

General procedure for TBBA-ester formation

***(P)-(S)*-1-Methoxy-1-oxopropan-2-yl 2-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-1-yl)benzoate (*P*)-18:** (*P*)-1-Carboxyphenyl(2-trifluoromethy)benzimidazole **(*P*)-2** (40 mg; 0.13 mmol; 1 eq) and (−)-methyl L-lactate (13µL; 14 mg; 0.13 mmol; 1 eq) were dissolved in dry DCM (2 mL). DCC (27 mg; 0.13 mmol; 1 eq) and then DMAP (16 mg; 0.13 mmol; 1 eq) were subsequently added into the solution. The solution was then stirred at room temperature for 16 hours. After 16 hours, a solid precipitate was filtered-off via syringe filter. The mixture was then adsorbed on celite and purified via column chromatography (hexane:ethylacetate 6:1, column dimensions: 1x10 cm). 46 mg of white foamy solid (88 %) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.32 – 8.28 (m, 1H), 7.93 – 7.88 (m, 1H), 7.79 (td, *J* = 7.6, 1.7 Hz, 1H), 7.72 (td, *J* = 7.7, 1.4 Hz, 1H), 7.49 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.41 – 7.33 (m, 2H), 7.05 – 7.00 (m, 1H), 4.91 (q, *J* = 7.1 Hz, 0H), 3.49 (s, 2H), 0.99 (d, *J* = 5.2 Hz, 1H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 170.2, 163.6, 141.2, 140.8, 140.7, 137.9, 134.1, 134.1, 133.1, 130.8, 130.3, 128.7, 125.9, 124.0, 121.3, 120.3, 117.6, 69.6, 52.3, 16.3 **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.03 **HRMS** (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{19}H_{16}O_4N_2F_3$: 393.1057 found: 393.1058, $[\alpha]_D^{22}$ = −36.7° (c= 0.46 $CHCl_3$).

(*P*)-(R)-1-phenylethyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (*P*)-15 Using general procedure, from 15 mg of **(*P*)-2** and (*R*)-1-Phenylethanol, 18 mg of oil (88 %). Purified by column chromatography (hexane:ethylacetate 10:1, column dimesions 1x10 cm). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.23 – 8.19 (m, 1H), 7.98 – 7.93 (m, 1H), 7.75 (td, *J* = 7.6, 1.8 Hz, 1H), 7.68 (td, *J* = 7.6, 1.4 Hz, 1H), 7.48 – 7.44 (m,

1H), 7.44 – 7.38 (m, 1H), 7.38 – 7.33 (m, 1H), 7.29 – 7.24 (m, 4H), 7.07 – 7.02 (m, 2H), 7.02 – 6.98 (m, 1H), 5.68 (q, *J* = 6.6 Hz, 1H), 0.80 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR {1H}** (101 MHz, $CDCl_3$) δ 163.9, 140.9 (q, *J* = 38.4 Hz), 140.7, 140.2, 137.8, 133.6, 133.5, 132.7, 130.6, 130.0, 129.8, 128.5, 128.2, 126.4, 126.0, 124.0, 121.5, 118.9 (q, *J* = 272.2 Hz), 110.9, 74.1, 20.5, ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) = -62.00, **HRMS** (ESI-TOF) m/z: [M+H]+ calculated for $C_{23}H_{18}F_3N_2O_2$: 411.1320 found: 411.1317, $[\alpha]_D^{22}$ = -131.18°(c= 0.17 $CHCl_3$).

(*M*)-(R)-1-phenylethyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (*M*)-15 Using general procedure, from 15 mg of **(*M*)-2** and (*R*)-1-Phenylethanol, 19 mg of oil (93 %). Purified by column chromatography (hexane:ethylacetate 10:1, column dimesions 1x10 cm). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 – 8.25 (m, 1H), 7.96 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.75 (td, *J* = 7.6, 1.8 Hz, 1H), 7.69 (td, *J* = 7.6, 1.4 Hz, 1H), 7.47 – 7.41 (m, 2H), 7.34 (ddd, *J* = 8.3, 7.2, 1.1 Hz, 1H), 7.16 – 7.11 (m, 1H), 7.06 (ddt, *J* = 8.3, 6.6, 1.4 Hz, 2H), 6.97 – 6.93 (m, 1H), 6.58 – 6.54 (m, 2H), 5.74 (q, *J* = 6.7 Hz, 1H), 1.11 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR {1H}** (101 MHz, $CDCl_3$) δ 163.8, 141.1 (q, *J* = 38.6 Hz), 140.8, 140.4, 138.0, 133.7, 133.2, 130.7, 130.2, 129.9, 128.4, 128.0, 126.1, 126.0, 124.1, 121.6, 119.0 (q, *J* = 272.2 Hz), 111.2, 74.2, 21.3, **^{19}F NMR** (376 MHz, $CDCl_3$) δ (ppm) = -62.02, **HRMS** (ESI-TOF) m/z: [M+H]+ calculated for $C_{23}H_{18}F_3N_2O_2$: 411.1320 found: 411.1317, $[\alpha]_D^{22}$

= +3.64°(c= 0.11 $CHCl_3$).

(*P*)-(S)-sec-butyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (*P*)-16 Using general procedure, from 15 mg of **(*P*)-2** and (*S*)-(+)-2-Butanol, 11.5 mg of oil (64 %). Purified by column chromatography (hexane:ethylacetate 9:1, column dimesions 1x10 cm). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.28 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.94 (d, *J* = 7.8 Hz, 1H), 7.74 (dqd, *J* = 15.0, 7.5, 1.6 Hz, 2H), 7.48 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.37 (tdd, *J* = 15.0, 7.3, 1.1 Hz, 2H), 6.99 (d, *J* = 7.5 Hz, 1H), 4.73 – 4.63 (m, 1H), 0.88 (d, *J* = 6.3 Hz, 3H), 0.87 – 0.80 (m, 1H), 0.77 – 0.64 (m, 1H), 0.35 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR {1H}** (101 MHz,) δ 164.1, 141.1 (q, *J* = 39.4 Hz), 140.7, 138.1, 133.7, 133.5, 132.9, 130.7, 130.2, 125.9, 124.0, 121.5, 119.0 (q, *J* = 271.9 Hz), 111.1, 74.2, 28.1, 18.9, 9.4, **^{19}F NMR** (376 MHz, $CDCl_3$) δ (ppm) = -62.04. **HRMS** (ESI-TOF) m/z: [M+H]+ calculated for $C_{19}H_{18}F_3N_2O_2$: 363.1320 found: 363.1313, $[\alpha]_D^{22}$ = -88.57°(c= 0.07 $CHCl_3$).

(*M*)-(S)-sec-butyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (*M*)-16 Using general procedure, from 15 mg of **(*M*)-2** and (*S*)-(+)-2-Butanol, 10 mg of oil (55 %). Purified by column chromatography (hexane:ethylacetate 9:1, column dimesions 1x10 cm). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.25 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.94 (d, *J* = 7.9 Hz, 1H), 7.76 (td, *J* = 7.6, 1.8 Hz, 1H), 7.71 (td, *J* = 7.6, 1.4 Hz, 1H), 7.49 (d, *J* = 7.5 Hz, 1H), 7.42 – 7.30 (m, 1H), 6.97 (d, *J* = 7.9 Hz, 1H), 4.73 – 4.54 (m, 1H), 1.29 – 1.07 (m, 1H), 0.68 (t, *J* = 7.4 Hz, 1H), 0.39 (d, *J* = 6.3 Hz, 1H). **^{13}C NMR {1H}** (101 MHz, $CDCl_3$) δ 164.3, 141.1 (q, *J* = 38.6 Hz), 140.7, 138.0, 133.6, 133.5, 132.8, 130.7, 130.2, 130.0, 126.0, 124.1, 121.5, 119.0 (q, *J* = 271.9 Hz), 111.0, 74.2, 28.3, 18.1, 9.7, **^{19}F NMR** (376 MHz, $CDCl_3$) δ = -61.86, **HRMS** (ESI-TOF) m/z: [M+H]+ calculated for $C_{19}H_{18}F_3N_2O_2$: 363.1320 found: 363.1315, $[\alpha]_D^{22}$ = +141.67°(c= 0.06 $CHCl_3$).

(*P*)-(S)-but-3-yn-2-yl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (*P*)-17 Using general procedure, from 15 mg of **(*P*)-2** and (*S*)-But-3-yn-2-nol, 15 mg of oil (84 %). Purified by column chromatography (hexane:ethylacetate 7:1, column dimesions 1x10 cm). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.26 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.94 (d, *J* = 7.8 Hz, 1H), 7.76 (dtd, *J* = 15.2, 7.6, 1.0 Hz, 2H), 7.50 (d, *J* = 7.7 Hz, 1H), 7.37 (td, *J* = 14.3, 7.2 Hz, 2H), 6.99 (d, *J* = 8.1 Hz, 1H), 5.21 (qd, *J* = 6.7, 2.0 Hz, 1H), 2.07 (d, *J* = 2.1 Hz, 1H), 1.08 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR {1H}** (101 MHz,) δ 163.4, 141.0 (q, *J* = 39.1 Hz), 140.8, 138.0, 134.0, 133.9, 132.8, 130.7, 130.2, 129.3, 126.0, 124.0, 121.6, 119.0 (q, *J* = 271.9 Hz), 111.0, 80.6, 73.1, 61.4, 20.5, **^{19}F NMR** (376 MHz, $CDCl_3$) δ = -61.99 **HRMS** (ESI-TOF) m/z: [M+H]+ calculated for $C_{19}H_{14}F_3N_2O_2$: 359.1007 found: 359.1001, $[\alpha]_D^{22}$ = -156.67°(c= 0.09 $CHCl_3$).

(*M*)-(S)-but-3-yn-2-yl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (*M*)-17 Using general procedure, from 15 mg of **(*M*)-2** and (*S*)-But-3-yn-2-nol, 16 mg of oil (89 %). Purified by column chromatography (hexane:ethylacetate 7:1, column dimesions 1x10 cm). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.27 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.95 (d, *J* = 7.6 Hz, 1H), 7.76 (dtd, *J* = 25.7, 7.5, 1.5 Hz, 2H), 7.50 (d, *J* = 7.5 Hz, 1H), 7.40

(td, *J* = 7.3, 7.3, 1.3 Hz, 1H), 7.35 (td, *J* = 8.1, 1.3 Hz, 1H), 6.97 (dd, *J* = 7.4, 0.9 Hz, 1H), 5.19 (qd, *J* = 6.7, 2.1 Hz, 1H), 2.35 (d, *J* = 2.2 Hz, 1H), 0.82 (d, *J* = 6.7 Hz, 4H), **^{13}C NMR {1H}** (101 MHz, $CDCl_3$) δ 163.4, 141.2 (q, *J* = 38.6 Hz), 140.8, 137.9, 134.00 (s), 133.93 (s), 132.8, 130.7, 130.2, 129.3, 126.0, 124.0, 121.6, 119.0 (q, *J* = 272.0 Hz), 110.8, 80.9, 73.5, 61.4, 20.1. **^{19}F NMR** (376 MHz, $CDCl_3$) δ = -62.06. **HRMS** (ESI-TOF) m/z: [M+H]+ calculated for $C_{19}H_{14}F_3N_2O_2$: 359.1000 found: 359.1001, $[\alpha]_D^{22}$ = -61.25°(c= 0.08 $CHCl_3$).

(*M*)-(*S*)-1-Methoxy-1-oxopropan-2-yl 2-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-1-yl)benzoate (*M*)-18: (*M*)-1-Carboxyphenyl(2-trifluoromethy)benzimidazole **(*M*)-2** (40 mg, 0.13 mmol, 1 eq) and (−)-methyl L-lactate (13µL, 14 mg, 0.13 mmol, 1 eq) purified via column chromatography (hexane:ethylacetate 6:1, column dimensions: 1x10 cm). 43 mg of a white foamy solid (85 %). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.31 – 8.25 (m, 1H), 7.95 – 7.89 (m, 1H), 7.80 (td, *J* = 7.6, 1.7 Hz, 1H), 7.73 (td, *J* = 7.7, 1.4 Hz, 1H), 7.50 (d, *J* = 7.7 Hz, 1H), 7.43 – 7.30 (m, 1H), 7.01 – 6.95 (m, 1H), 4.86 (q, *J* = 7.1 Hz, 1H), 3.61 (s, 2H), 0.82 (d, *J* = 7.1 Hz, 1H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 170.2, 163.7, 141.1 (q, *J* = 38.6 Hz), 140.6, 137.9, 134.1, 134.0, 133.0, 130.8, 130.3, 128.8, 125.9, 124.0, 121.5, 118.9 (q, *J* = 271.9 Hz), 111.0, 69.5, 52.4, 16.0 **^{19}F NMR** (376 MHz, $CDCl_3$) δ -61.98 **HRMS** (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{19}H_{16}O_4N_2F_3$: 393.1057 found: 393.1057, $[\alpha]_D^{22}$ = +68.14° (c= 0.43 $CHCl_3$).

(*P*)-(S)-2-methoxy-2-oxo-1-phenylethyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (*P*)-19 Using general procedure, from 20 mg of **(*P*)-2** and Methyl-(*S*)-(+)-mandelate, 22 mg of white solid (75 %). Purified by column chromatography (hexane:ethylacetate 7:1, column dimesions 1x10 cm). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.36 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.84 – 7.80 (m, *J* = 2.5, 1.7 Hz, 1H), 7.78 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.73 (td, *J* = 7.6, 1.4 Hz, 1H), 7.44 (dd, *J* = 7.6, 1.0 Hz, 1H), 7.40 – 7.31 (m, 3H), 7.28 – 7.22 (m, 3H), 7.03 – 6.97 (m, 3H), 5.79 (s, 1H), 3.58 (s, 3H), **^{13}C NMR {1H}** (101 MHz, $CDCl_3$) δ 168.5, 163.8, 140.9 (q, *J* = 38.9 Hz), 140.7, 137.6, 134.10, 134.07, 132.8, 130.7, 130.3, 129.4, 128.8, 128.7, 127.7, 126.7, 125.9, 123.9, 121.6, 118.9 (q, *J* = 271.7 Hz), 110.9, 75.5, 52.7, **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.10, **HRMS** (ESI-TOF) m/z: [M+H]+ calculated for $C_{24}H_{18}F_3N_2O_4$: 455.1213 found: 455.1230, $[\alpha]_D^{22}$ = +32.73°(c= 0.22 $CHCl_3$).

(*M*)-(S)-2-methoxy-2-oxo-1-phenylethyl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (*M*)-19 Using general procedure, from 20 mg of **(*M*)-2** and Methyl-(*S*)-(+)-mandelate, 24 mg of white solid (82 %). Purified by column chromatography (hexane:ethylacetate 7:1, column dimesions 1x10 cm). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.32 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.78 (td, *J* = 7.6, 1.7 Hz, 1H), 7.72 (td, *J* = 7.6, 1.4 Hz, 1H), 7.45 (d, *J* = 7.0 Hz, 1H), 7.43 – 7.27 (m, 4H), 7.25 – 7.20 (m, *J* = 10.3, 4.7 Hz, 2H), 6.97 – 6.91 (m, 3H), 5.77 (s, 1H), 3.60 (s, 3H). **^{13}C NMR {1H}** (101 MHz, $CDCl_3$) δ 168.5, 163.6, 140.7, 140.7 (q, *J* = 38.3 Hz), 137.6, 134.3, 134.2, 133.0, 132.8, 130.7, 130.4, 129.5, 128.9, 128.8, 128.4, 127.7, 126.7, 125.9, 123.9, 121.6, 118.9 (q, *J* = 271.9 Hz), 111.0 (s), 75.6, 52.9, **^{19}F NMR** (376 MHz, $CDCl_3$) δ -61.93, **HRMS** (ESI-TOF) m/z: [M+H]+ calculated for $C_{24}H_{18}F_3N_2O_4$: 455.1213 found: 455.1230, $[\alpha]_D^{22}$ = +130.0°(c= 0.24 $CHCl_3$).

***(P)*-(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-1-yl)benzoate (*P*)-20:** (*P*)-1-Carboxyphenyl(2-trifluoromethy)benzimidazole **(*P*)-2** (40 mg, 0.13 mmol, 1 eq) and (1*R*,2*S*,5*R*)-(−)-Menthol (20 mg, 0.13 mmol, 1 eq) purified via column chromatography (hexane:ethylacetate 30:1, column dimensions: 1x10 cm). 49 mg of a white foamy solid (86 %). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.15 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.87 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.69 (ddd, *J* = 7.6, 7.5, 1.7 Hz, 1H), 7.64 (ddd, *J* = 7.6, 7.5, 1.4 Hz, 1H), 7.42 (d, *J* = 7.5 Hz, 1H), 7.32 (ddd, *J* = 8.1, 7.3, 1.2 Hz, 1H), 7.26 (td, *J* = 8.1, 7.3, 1.1 Hz, 1H), 6.89 (dt, *J* = 8.1, 1.0 Hz, 1H), 4.45 (ddd, *J* = 10.8, 10.8, 4.5 Hz, 1H), 1.46 (m, 1H), 1.42 (m, 1H), 1.40 (m, 1H), 1.09 (m,1H), 1.01 (m,1H), 0.76 (m,1H), 0.74 (m,1H), 0.72 (d, *J* = 7.0 Hz, 3H), 0.55 (d, *J* = 6.5 Hz, 3H), 0.50 (d, *J* = 7.0 Hz, 3H), -0.54 (q, *J* = 12.0, 12.0, 11.2 Hz, 1H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 141.1 (q, *J* = 38.4 Hz), 140.8, 138.0, 133.3, 132.6, 130.5, 130.2, 129.9, 125.9, 123.9, 121.5, 118.9 (q, *J* = 272.0 Hz), 110.9, 75.7, 46.3, 39.0, 33.8, 31., 24.6, 22.7, 21.8, 20.7, 15.7 **^{19}F NMR** (376 MHz, $CDCl_3$) δ -61.74 **HRMS** (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{25}H_{28}O_2N_2F_3$: 445.2097.1057 found: 445.2099, $[\alpha]_D^{22}$ = −133.68° (c= 0.19 MeOH).

***(M)*-(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-1-yl)benzoate (*M*)-20:** *(M)*-1-Carboxyphenyl(2-trifluoromethy)benzimidazole **(*M*)-2** (40 mg, 0.13 mmol, 1 eq) and (1*R*,2*S*,5*R*)-(−)-Menthol (20 mg, 0.13 mmol, 1 eq) purified via column chromatography (hexane:ethylacetate 30:1, column dimensions: 1x10 cm). 48 mg of a white foamy solid (85 %). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.24 (dd, *J* = 7.5, 1.9 Hz, 1H), 7.89 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.69 (ddd, *J* = 7.6, 7.5, 1.7 Hz, 1H), 7.65 (ddd, *J* = 7.6, 7.5, 1.4 Hz, 1H), 7.38 (d, *J* = 7.6 Hz, 1H), 7.33 (ddd, *J* = 7.9, 7.3, 1.2 Hz, 1H), 7.38 (ddd, *J* = 8.2, 7.3, 1.3 Hz, 1H), 6.93 (dt, *J* = 8.2, 1.0 Hz, 1H), 4.55 (ddd, *J* = 11.0, 11.0, 4.4 Hz, 1H), 1.66 (m, 1H), 1.45 (m, 1H), 1.34 (m, 1H), 1.23 (m,1H), 0.82 (m,1H), 0.75 (m,1H), 0.75 (d, *J* = 6.5 Hz, 3H), 0.70 (m,1H), 0.58 (m, 1H), 0.40 (d, *J* = 7.0 Hz, 3H), 0.36 (d, *J* = 7.0 Hz, 3H), 0.32 (m, 1H), **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 164.0, 141.0 (q, *J* = 38.3 Hz), 140.7, 138.0, 133.7, 133.4, 133.0, 130.7, 130.2, 130.1, 125.9, 124.0, 121.5, 119.0 (q, *J* = 272.0 Hz), 111.1, 75.8, 46.3, 40.1, 34.0, 31.4, 25.5, 22.7, 21.9, 20.8, 15.5. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -61.38 **HRMS** (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{25}H_{28}O_2N_2F_3$: 445.2097.1057 found: 445.2101, $[\alpha]_D^{22}$ = −3.29° (c= 0.15 MeOH).

(*P*)-(1S,2R,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (*P*)-21 Using general procedure, from 15 mg of **(*P*)-2** and (-)-Borneol, 17 mg of oil (77 %). Purified by column chromatography (hexane:ethylacetate 8.5:1, column dimesions 1x10 cm). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.22 – 8.19 (m, 1H), 7.97 – 7.92 (m, 1H), 7.72 (dqd, *J* = 14.8, 7.5, 1.7 Hz, 2H), 7.42 (dd, *J* = 9.5, 1.4 Hz, 1H), 7.42 – 7.33 (m, 2H), 7.04 – 7.01 (m, 1H), 4.84 (ddd, *J* = 10.0, 3.6, 2.2 Hz, 1H), 2.07 – 1.97 (m, 1H), 1.53 (tdd, *J* = 12.0, 8.0, 4.4 Hz, 1H), 1.46 (t, *J* = 4.5 Hz, 1H), 1.17 (ddd, *J* = 13.8, 9.5, 4.6 Hz, 1H), 1.09 – 1.00 (m, 1H), 0.76 (s, *J* = 4.4 Hz, 3H), 0.75 (s, 3H), 0.74 – 0.67 (m, 1H), 0.64 (s, 3H), 0.24 (dd, *J* = 13.9, 3.6 Hz, 1H). **^{13}C NMR{1H}** (101 MHz, $CDCl_3$) δ 165.3, 140.8 (q, *J* = 38.6 Hz), 140.8, 137.7, 133.4, 133.3, 132.5, 130.6, 130.1, 130.0, 126.1, 124.1, 121.7, 119.0 (q, *J* = 272.0 Hz), 110.9, 82.2, 48.7, 47.9, 44.6, 35.8, 27.8, 26.9, 19.7, 18.8, 13.4, **^{19}F NMR** (376 MHz, $CDCl_3$) δ= -61.65, **HRMS** (ESI-TOF) m/z: [M+H]+ calculated for $C_{25}H_{26}F_3N_2O_2$: 443.1946 found: 443.1941, $[\alpha]_D^{22}$ = -142.5°(c= 0.08 $CHCl_3$).

(*M*)-(1S,2R,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl 2-(2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)benzoate (*M*)-21 Using general procedure, from 15 mg of **(*M*)-2** and (-)-Borneol, 15 mg of oil (68 %). Purified by column chromatography (hexane:ethylacetate 8.5:1, column dimesions 1x10 cm). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.24 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.96 – 7.92 (m, 1H), 7.73 (pd, *J* = 7.5, 1.6 Hz, 2H), 7.44 – 7.33 (m, 3H), 7.08 – 7.02 (m, 1H), 4.95 – 4.90 (m, 1H), 2.14 (ddt, *J* = 14.0, 10.0, 4.0 Hz, 1H), 1.56 – 1.47 (m, 2H), 1.06 – 0.84 (m, 2H), 0.78 (s, *J* = 17.4 Hz, 3H), 0.73 (s, 3H) overalps with 0.75– 0.70 (m, 1H), 0.57 (dd, *J* = 13.8, 3.6 Hz, 1H), 0.50 (s, 3H). **^{13}C NMR {1H}** (101 MHz, $CDCl_3$) δ 165.0, 140.9 (q, *J* = 38.3 Hz), 140.8, 137.7, 133.5, 133.4, 132.6, 130.6, 130.1, 126.1, 124.1, 121.7, 119.0 (q, *J* = 271.9 Hz), 111.1, 81.8, 48.9, 48.00, 44.7, 36.1, 27.9, 26.8, 19.7, 18.8, 13.2, ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) = -61.90, **HRMS** (ESI-TOF) m/z: [M+H]+ calculated for $C_{25}H_{26}F_3N_2O_2$: 443.1946 found: 443.1942, $[\alpha]_D^{22}$ = -3.33°(c= 0.09 $CHCl_3$).

***(P)*-(3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-Dimethyl-17-((*R*)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14, 15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl 2-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-1-yl)benzoate (*P*)-22 :** (*P*)-1-Carboxyphenyl(2-trifluoromethy)benzimidazole **(*P*)-2** (40 mg, 0.13 mmol, 1 eq) and cholesterol (50 mg, 0.13 mmol, 1 eq) purified via column chromatography (hexane:ethylacetate 9:1, column dimensions: 1x10 cm). 64 mg of white foamy solid (72 %). **^{1}H NMR (**500MHz, $CDCl_3$**):** δ 8.20 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.88 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.69 (ddd, *J* = 7.6, 7.5, 1.8 Hz, 1H), 7.64 (ddd, *J* = 7.6, 7.5, 1.5 Hz, 1H), 7.44 (d, *J* = 7.5 Hz, 1H), 7.33 (ddd, *J* = 7.8, 7.5, 1.1 Hz, 1H), 7.28 (td, *J* = 7.8, 7.5, 1.1 Hz, 1H), 6.91 (dd, *J* = 7.8, 1.3 Hz, 1H), 5.04 (m, 1H), 4.34 (dddd, *J* = 10.8, 10.8, 4.5 Hz, 1H), 0.50 (d, *J* = 7.0 Hz, 3H), 0.50 (d, *J* = 7.0 Hz, 3H), 0.50 (d, *J* = 7.0 Hz, 3H), 0.69 (s, 3H), 0.59 (s, 3H), 0.70 - 1.92 (overlapping multiplets) **^{13}C{^{1}H} NMR,** 126MHz, $CDCl_3$**:** δ 163.9, 141.2 (q, *J* =38.5), 140.6, 139.3, 138.1, 133.6, 133.6, 132.9, 130.7, 130.1, 130.0, 126.0, 124.0, 122.6, 121.4, 119.0 (q, *J* = 272.2), 111.0, 75.3, 56.7, 56.2, 50.0, 42.4, 39.8, 39.6, 36.7, 36.6, 36.5, 36.3, 35.9, 31.9, 31.8, 28.3, 29.1, 26.9, 24.4, 23.9, 23.0, 22.7, 21.0, 19.2, 18.8, 11.9 **^{19}F NMR** (376 MHz, $CDCl_3$) δ -61.98 **HRMS** (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{42}H_{54}O_2N_2F_3$: 675.4132, found: 675.4137 $[\alpha]_D^{22}$ = -96.41° (c= 0.64 $CHCl_3$).

***(M)*-(3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-Dimethyl-17-((*R*)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14, 15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl 2-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-**

1-yl)benzoate (*M*)-22: *(M)*-1-Carboxyphenyl(2-trifluoromethy)benzimidazole **(*M*)-2** (40 mg, 0.13 mmol, 1 eq) and cholesterol (50 mg, 0.13 mmol, 1 eq) purified via column chromatography (hexane:ethylacetate 9:1, column dimensions: 1x10 cm). 57 mg of a white foamy solid (64 %). **^{1}H NMR** (500MHz, $CDCl_3$): δ 8.19 (dd, *J* = 7.6, 1.9 Hz, 1H), 7.88 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.69 (ddd, *J* = 7.6, 7.5, 1.7 Hz, 1H), 7.64 (ddd, *J* = 7.6, 7.5, 1.4 Hz, 1H), 7.43 (d, *J* = 7.5 Hz, 1H), 7.33 (ddd, *J* = 7.8, 7.4, 1.2 Hz, 1H), 7.28 (ddd, *J* = 7.6, 7.4, 1.3 Hz, 1H), 6.91 (dt, *J* = 7.6, 1.0 Hz, 1H), 5.17 (ddd, *J* = 11.0, 11.0, 4.4 Hz, 1H), **^{13}C{^{1}H} NMR** (126MHz, $CDCl_3$): δ 163.9, 141.2 (q, *J* =38.4), 140.7, 139.2, 138.1, 133.6, 133.5, 132.8, 130.7, 130.1, 130.1, 126.0, 124.0, 123.0, 122.8, 121.5, 119.0 (q, *J* =272.1), 111.0, 75.3, 56.8, 56.2, 50.0, 42.4, 39.8, 39.6, 37.2, 36.7 36.5, 36.3, 35.9, 31.9, 31.8, 28.3, 28.1, 26.2, 25.7, 24.4, 23.9, 23.0, 22.7, 21.0, 19.3, 18.8, 12.0 **^{19}F NMR** (376 MHz, $CDCl_3$) δ -61.98 **HRMS** (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{42}H_{54}O_2N_2F_3$: 675.4132, found: 675.4132 $[\alpha]_D^{22}$ = +69.83° (c= 0.57 $CHCl_3$).

***(P)*-Benzyl (1*R*,3a*S*,5a*R*,5b*R*,7a*R*,9*S*,11a*R*,11b*R*,13a*R*,13b*R*)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-9-((2-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-1-yl)benzoyl)oxy)icosahydro-3a*H*-cyclopenta[*a*]chrysene-3a-carboxylate (*P*)-23:** *(P)*-1-Carboxyphenyl(2-trifluoromethy)benzimidazole **(*P*)-2** (40 mg, 0.13 mmol, 1 eq) and benzyl betulinate (71 mg, 0.13 mmol, 1 eq) purified via column chromatography (hexane:ethylacetate 12:1, column dimensions: 1x10 cm). 37 mg of a white foamy solid (35 %). **^{1}H NMR** (500MHz, $CDCl_3$): δ 8.13 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.86 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.67 (ddd, *J* = 7.6, 7.5, 1.7 Hz, 1H), 7.62 (ddd, *J* = 7.6, 7.5, 1.4 Hz, 1H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.32 (overlap, 1H), 7.29 (overlap, 1H), 7.21-7.30 (m, 5H), 6.96 (dt, *J* = 7.8, 1.3 Hz, 1H), 5.05 (d, 12.3 Hz, 1H), 5.00 (d, 12.3 Hz, 1H), 4.63 (d, 1.8 Hz, 1H), 4.51 (d, 1.8 Hz, 1H), 4.44 (dd, *J* = 11.9, 4.6 Hz, 1H), 2.92 (m, 1H), 2.16 (m, 1H), 2.05 (m, 1H), 1.68 (s, 3H), 0.81 (s, 3H), 0.62 (s, 3H), 0.58 (s, 3H), 0.52 (s, 3H), 0.11 (s, 3H), 0.70 - 1.92 (overlapping multiplets). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$)**:** δ 175.9, 164.4, 150.6, 141.9 (q, *J* =38.6), 140.8, 137.8, 136.60, 133.6, 133.2, 132.4, 130.6, 130.4, 130.0, 128.60 (2C), 128.4 (2C), 128.2, 125.8, 124.0, 121.5, 119.0 (q, *J* =272.1), 111.2, 109.7, 82.7, 65.8, 56.6, 55.4, 50.4, 49.5, 47.0, 42.4, 40.7, 38.4, 38.2, 37.8, 37.0, 34.2, 32.2, 30.7, 29.8, 29.6, 27.7, 25.5, 23.3, 20.9, 19.4, 18.1, 16.1, 15.8 14.7 **^{19}F NMR** (376 MHz, $CDCl_3$) δ -61.86 **HRMS** (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{52}H_{62}O_4N_2F_3$: 835.4656 found 835.4623 $[\alpha]_D^{22}$ = +4.05° (c= 0.37 $CHCl_3$).

(M)*-Benzyl (1*R*,3a*S*,5a*R*,5b*R*,7a*R*,9*S*,11a*R*,11b*R*,13a*R*,13b*R*)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-9-((2-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-1-yl)benzoyl)oxy)icosahydro-3a*H*-cyclopenta[*a*]chrysene-3a-carboxylate (*M*)-23:** **(M*)-1-Carboxyphenyl(2-trifluoromethy)benzimidazole **(*M*)-2** (40 mg, 0.13 mmol, 1 eq) and benzyl betulinate (71 mg, 0.13 mmol, 1 eq) purified via column chromatography (hexane:ethylacetate 12:1, column dimensions: 1x10 cm). 67 mg of white foamy solid (62 %). **^{1}H NMR** (500MHz, $CDCl_3$): δ 8.10 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.86 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.67 (ddd, *J* = 7.6, 7.5, 1.4 Hz, 1H), 7.62 (ddd, *J* = 7.6, 7.5, 1.2 Hz, 1H), 7.39 (d, *J* = 7.5 Hz, 1H), 7.31 (ddd, *J* = 8.0, 7.5, 1.2 Hz, 1H), 7.26 (overlap, 1H), 7.20-7.31 (m, 5H), 6.92 (dt, *J* = 8.0, 1.0 Hz, 1H), 4.63 (d, 1H), 5.06 (d, 12.2 Hz, 1H), 5.00 (d, 12.2 Hz, 1H), 4.63 (d, 1.8 Hz, 1H), 4.51 (d, 1.8 Hz, 1H), 4.33 (dd, *J* = 11.0, 4.9 Hz, 1H), 2.93 (m, 1H), 2.18 (m, 1H), 2.06 (m, 1H), 1.59 (s, 3H), 0.80 (s, 3H), 0.62 (s, 3H), 0.58 (s, 3H), 0.52 (s, 3H), 0.45 (s, 3H), 0.70 - 1.86 (overlapping multiplets). **^{13}C{^{1}H} NMR** (126MHz, $CDCl_3$)**:** δ 175.8, 164.7, 150.7, 140.84, 140.76 (q, *J* =38.5), 137.6, 136.6, 133.4, 133.3, 132.3, 130.5, 130.1, 129.9, 128.6 (2C), 128.4 (2C), 128.5, 126.0, 124.0, 121.6, 119.0 (q, *J* =271.8), 110.9, 109.8, 82.9, 65.8, 56.6, 55.4, 50.4, 49.5, 47.0, 42.4, 40.7, 38.4, 38.2, 37.7, 37.04, 37.00, 34.2, 32.2, 30.7, 29.8, 29.6, 27.9, 25.5, 22.5, 20.9, 19.5, 18.1, 16.3, 16.1, 15.9, 14.7 **^{19}F NMR** (376 MHz, $CDCl_3$) δ -61.45 **HRMS** (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{52}H_{62}O_4N_2F_3$: 835.4656, found: 835.4619, $[\alpha]_D^{22}$ = +100.77° (c= 0.52 $CHCl_3$).

SUPPORTING INFORMATION

^{1}H, ^{13}C and ^{19}F NMR spectra, of **all prepared compounds**, detailed NMR assignment of compounds **(*P*/*M*)-8, (*P*/*M*)-20, (*P*/*M*)-23, (*P*/*M*)-22**, ^{1}H-^{19}F HOESY of compounds **8** , conformational stability of **2**, SFC chromatograms of **2,** X-RAY structure determination of **(*R*,*P*)-8** and relevant conformers calculated using SPARTAN software. This material is available free of charge via the Internet at http://pubs.acs.org.

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REFERENCES

(1) Wenzel, T. J.; Chisholm, C. D. Using NMR Spectroscopic Methods to Determine Enantiomeric Purity and Assign Absolute Stereochemistry. *Prog. Nucl. Magn. Reson. Spectrosc.* **2011**, *59*, 1–63.

(2) Parker, D. NMR Determination of Enantiomeric Purity. *Chem. Rev.* **1991**, *91*, 1441–1457.

(3) Wenzel, T. J.; Wilcox, J. D. Chiral Reagents for the Determination of Enantiomeric Excess and Absolute Configuration Using NMR Spectroscopy. *Chirality* **2003**, *15*, 256–270.

(4) Seco, J. M.; Quiñoá, E.; Riguera, R. The Assignment of Absolute Configuration by NMR. *Chem. Rev.* **2004**, *104*, 17–117.

(5) Seco, J. M.; Riguera, R. NMR Methods for the Assignment of Absolute Stereochemistry of Bioactive Compounds. *eMagRes* **2015**, *4*, 1–30.

(6) Freedman, T. B.; Cao, X.; Dukor, R. K.; Nafie, L. A. Absolute Configuration Determination of Chiral Molecules in the Solution State Using Vibrational Circular Dichroism. *Chirality* **2003**, *758*, 743–758.

(7) Dale, J. A.; Dull, D. L.; Mosher, H. S. α-Methoxy-α-Trifluoromethylphenylacetic Acid, a Versatile Reagent for the Determination of Enantiomeric Composition of Alcohols and Amines'. *J. Org. Chem.* **1969**, *34*, 2543–2549.

(8) Dale, J. A.; Mosher, H. S. Nuclear Magnetic Resonance Enantiomer Reagents. Configurational Correlations via Nuclear Magnetic Resonance Chemical Shifts of Diastereomeric Mandelate, O-Methylmandelate and α-Methoxy-α-Trifluormethylphenylacetate (MTPA) Esters. *J. Am. Chem. Soc.* **1973**, *95*, 512–519.

(9) Latypov, S. K.; Seco, J. M.; Quiñoá, E.; Riguera, R. Conformational Structure and Dynamics of Arylmethoxyacetates: DNMR Spectroscopy and Aromatic Shielding Effect. *J. Org. Chem.* **1995**, *60* (3), 504–515.

(10) Trost, B. M.; Bunt, R. C.; Pulley, S. R. On the Use of *O*-Methylmandelic Acid for the Establishment of Absolute Configuration of α-Chiral Primary Amines. *J. Org. Chem.* **1994**, *59*, 4202–4205.

(11) Seco, J. M.; Quiñoá, E.; Riguera, R. Boc-Phenylglycine : The Reagent of Choice for the Assignment of the Absolute Configuration of α -Chiral Primary Amines by 1 H NMR Spectroscopy. *J. Org. Chem.* **1999**, *64*, 4669–4675.

(12) Seco, J. M.; Quiñoá, E.; Riguera, R. Assignment of the Absolute Configuration of Polyfunctional Compounds by NMR Using Chiral Derivatizing Agents. *Chem. Rev.* **2012**, *112*, 4603–4641.

(13) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. High-Field FT NMR Application of Mosher's Method. The Absolute Configurations of Marine Terpenoids. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096.

(14) Suzuki, M.; Takahashi, Y.; Matsuo, Y.; Guiry, M. D.; Masuda, M. Scanlonenyne, a Novel Halogenated C15 Acetogenin from the Red Alga Laurencia Obtusa in Irish Waters. *Tetrahedron* **1997**, *53*, 4271–4278.

(15) Seco, J. M.; Latypov, S. K.; Quiñoá, E.; Riguera, R. Choosing the Right Reagent for the Determination of the Absolute Configuration of Amines by NMR: MTPA or MPA? *J. Org. Chem.* **1997**, *62*, 7569–7574.

(16) Latypov, S. K.; Seco, J. M.; Quiñoá, E.; Riguera, R. MTPA vs MPA in the Determination of the Absolute Configuration of Chiral Alcohols by ^{1}H NMR. *J. Org. Chem.* **1996**, *61*, 8569–8577.

(17) Janíková, K.; Jedinák, L.; Volná, T.; Cankař, P. Chan-Lam Cross-Coupling Reaction Based on the Cu_2S/TMEDA System. *Tetrahedron* **2018**, *74*, 606–617.

(18) Kalhapure, R. S.; Patil, B. P.; Jadhav, M. N.; Kawle, L. A.; Wagh, S. B. Synthesis of 11-(Piperazin-1-Yl)-5H-Dibenzo[b,e][1,4]Diazepine on Kilo Scale. *E-Journal Chem.* **2011**, *8*, 1747–1749.

(19) René, O.; Souverneva, A.; Magnuson, S. R.; Fauber, B. P. Efficient Syntheses of 2-Fluoroalkylbenzimidazoles and -Benzothiazoles. *Tetrahedron Lett.* **2013**, *54*, 201–204.

(20) Nesper, R.; Pregosin, P. S.; Puentener, K.; Woerle, M. Homogeneous Catalysis with Dicationic Palladium(II) Complexes: Aldol Reaction of Methyl Isocyanoacetate with Benzaldehyde. *Helv. Chim. Acta* **1993**, *76*, 2239–2249.

(21) Wolf, C. *Dynamic Stereochemistry of Chiral Compounds*; Royal Society of Chemistry, 2007.

(22) Bringmann, G.; Mortimer, A. J. P.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. Atroposelective Synthesis of Axially Chiral Biaryl Compounds. *Angew. Chemie - Int. Ed.* **2005**, *44*, 5384–5427.

(23) Neises, B.; Steglich, W. Simple Method for the Esterification of Carboxylic Acids. *Angew. Chemie Int. Ed. English* **1978**, *17*, 522–524.

(24) Carpino, L. A.; El-Faham, A. The Diisopropylcarbodiimide/1-Hydroxy-7-Azabenzotriazole System: Segment Coupling and Stepwise Peptide Assembly. *Tetrahedron* **1999**, *55*, 6813–6830.

(25) Ohtani, I.; Hotta, K.; Ichikawa, Y.; Isobe, M. Application of Modified Mosher´s Method to α-Aromatic Secondary Alcohols. Exception of the Rule and Conformational Analyses. *Chem. Lett.* **1995**, *24*, 513–514.

(26) Omata, K.; Fujiwara, T.; Kabuto, K. Use of a Diamagnetic Lanthanide Complex for Extending the Scope of NMR Determination of Absolute Configuration by the Modified Mosher's Method. *Tetrahedron Asymmetry* **2002**, *13*, 1655–1662.

(27) García, R.; Seco, J. M.; Vázquez, S. A.; Quiñoá, E.; Riguera, R. Role of Barium(II) in the Determination of the Absolute Configuration of Chiral Amines by ^{1}H NMR Spectroscopy. *J. Org. Chem.* **2006**, *71*, 1119–1130.

(28) Seco, J. M.; Latypov, S. K.; Quiñoá, E.; Riguera, R. Determining Factors in the Assignment of the Absolute Configuration of Alcohols by NMR . The Use of Anisotropic Effects on Remote Positions. *Tetrahedron* **1997**, *53*, 8541–8564.

(29) F. Doro, P. Winnertz, W. Leitner, A. Prokofieva, T. E. M. NMR Analysis of Chiral Alcohols and Amines: Development of an Enviromentaly Benign "in Tube" Procedure with High Efficiency and Improved Detection Limit. *Green Chem.* **2011**, *13*, 1735–1744.

(30) Yukibaru, F.; Yaima, C.; Mizutani, J. A New Method for Establishment of Absolute Configurations of Secondary Alcohols by NMR Spectroscopy. *Tetrahedron Lett.* **1994**, *35*, 599–602.

(31) Bautista-Hernández, C. I.; Trejo-Carbajal, N.; Zúñiga-Estrada, E. A.; Aristeo-Dominguez, A.; Meléndez-Rodríguez, M.; Suárez-Castillo, O. R.; Sánchez-Zavala, M.; Cruz-Borbolla, J.; Morales-Ríos, M. S.; Joseph-Nathan, P. 2-Cyano-2-Indolylpropanoic Acid as a Chiral Derivatizing Agent for the Absolute Configuration Assignment of Secondary Alcohols and Primary Amines by ^{1}H NMR and VCD. *Tetrahedron Asymmetry* **2017**, *28*, 762–782.

(32) Hoye, T. R.; Jeffrey, C. S.; Shao, F. Mosher Ester Analysis for the Determination of Absolute Configuration of Stereogenic (Chiral) Carbinol Carbons. *Nat. Protoc.* **2007**, *2*, 2451–2458.

(33) Ovitt, T. M.; Coates, G. W. Stereochemistry of Lactide Polymerization with Chiral Catalysts: New Opportunities for Stereocontrol Using Polymer Exchange Mechanisms. *J. Am. Chem. Soc.* **2002**, *124*, 1316–1326.

(34) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. Correlation of Configuration and F Chemical Shifts of α -Methoxy-α -Trifluoromethylphenylacetate Derivatives. *J. Org. Chem.* **1973**, *38*, 2143–2147.