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Synthesis and applications of secondary amine derivatives of (+)-dehydroabietylamine in chiral molecular recognition[†]

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(+)-Dehydroabietylamine (1a), the novel derivatives (2a–6a) and their NTf₂ salts (1b–6b) were tested as chiral NMR solvating agents for the resolution of enantiomers of the model compound Mosher's acid (7) and its *n*-Bu₄N salt (8). Best enantiomeric discrimination of 7 was obtained using bisdehydroabietyl-amino- N^1 , N^2 -ethane-1,2-diamine (6a), and of 8 using *N*-(dehydroabietyl)-2-(dehydroabietylamino)ethana-minium bis((trifluoromethyl)-sulfonyl)-amide (6b). For the maximal resolution of enantiomers of 8, 1.0 eq. of 6b were needed. However, 0.5 eq. of 6a sufficed for the maximal resolution of enantiomers of 7. Enantiomeric excess studies were successfully conducted using 6a and 6b. The capability of 6a and 6b to recognize the enantiomers of various α -substituted carboxylic acids and their *n*-Bu₄N salts were examined. Best resolutions were observed for aliphatic and aromatic carboxylic acids bearing an electronegative α -substituent. Now the ee studies on such non-aromatic carboxylic acids are also feasible.

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Introduction

Analytical enantiomeric purity determinations are of great interest particularly in organic, medicinal and biological chemistry, where stereocontrol is important. Compared to commonly used techniques such as HPLC, NMR is more versatile, and the development of more sensitive instruments has made it a potential competitor for the traditional methods in chiral recognition. As NMR can provide fast and easy enantiomeric excess (ee) measurements (up to 94–99% ee),¹ it is the ideal tool for quick ee determinations when developing new asymmetric synthesis or when studying the efficacy of a new chiral catalyst. Also, if the enantiomeric resolution cannot be efficiently performed with traditional methods, NMR can be used as an alternative.²

In NMR, two general methods to investigate the enantiomeric purity of a compound may be applied. One is to use an enantiomerically pure chiral derivatising agent to produce two diastereomers. However, this method is time consuming and also may cause concerns of kinetic resolution and racemization. The second, more convenient and faster method is provided by chiral solvating agents (CSAs) where the resolving ability is based on the supramolecular complexation between

In this study we have used the readily available softwood resin derivative (+)-dehydroabietylamine⁷ (**1a**, Scheme 1) as a starting material to create novel CSAs for the enantiomeric resolution of racemic carboxylic acids by NMR. As only few of the reported amine based CSAs are ionic, and it being thought advisable to see if ionic functionalities might provide better resolution, protonated forms of our amines were also tested.

Results and discussion

Five secondary amine derivatives **2a–6a** of **1a** were prepared and converted along with **1a** to bis(trifluoromethane)-sulfoni-



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two enantiomers of a chiral guest and a chiral host.^{3,4} Since complex formation is strongly dependent on interactions between a host and a guest, CSAs may contain hydrogen bond acceptor and donor groups (such as -NH₂, -OH, -COOH), aromatic functionality for π - π stacking, and ionic and dipolic groups for ion-ion, dipole-dipole and ion-dipole interactions.4,5 However, the functional groups of the host and guest are not solely responsible for an efficient enantiomeric discrimination, but also the deuterated solvent used, concentration, molar ratio of host and guest, temperature and the anion (if present) of the chiral host⁶ have an effect on the resolution.³ The non-ionic and ionic CSAs are often derived from chiral natural compounds such as amino acids, menthol or mandelic acid. These compounds are generally not only chiral but also contain suitable functionalities for complex formation.

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Scheme 1 Preparation of (+)-dehydroabietylamine based secondary amines and their corresponding NTf₂ salts. (DAB = (+)-dehydroabietylamine, BrR = BrEt, Br(CH₂)₂OH, Br(CH₂CH₂O)₂Me, Br(CH₂)₂Br).

mide (NTf₂) salts (**1b–6b**) to give CSAs with ionic functionality. NTf₂ was chosen for a counter anion as it has been found to provide better enantiomeric resolution with an ionic CSA.^{7,8} Compounds **3a–6a** were readily prepared by an expedient one step reaction with suitable alkyl bromides in a microwave reactor (Scheme 1). Compound **2a** was synthesized in two steps by the conversion of **1a** to formamide followed by reduction. Physical data of the compounds are listed in Table 1, showing that when the amines are converted to NTf₂ salts the melting points increase and the optical rotations decrease.

The ability of compounds **1–6a** and **b** to recognize the chirality of ionic and non-ionic racemic carboxylic acids was examined using Mosher's acid 7 and its *n*-Bu₄N salt **8**. The effect of concentration of CSA was also investigated, as according to literature, the magnitude of non-equivalence ($\Delta\delta$) increases when the concentration of host is higher than that of the guest.^{3,4} CDCl₃ was chosen as solvent for the experiments because it is known that polar solvents can solvate ions and protic solvents may interfere in hydrogen bond formation which are important for complex formation.⁹ NMR experiments were performed by taking 0.5 mL (1.0 eq., 22.0 mM) of a stock solution containing 7 or **8** (guest) and dissolved CSA (host) (1.0 or 2.0 eq.). Both ¹H and ¹⁹F NMR spectra were recorded (Table 2). Results indicate that **1–6a** and **b** form a dia-

Table 1 (+)-Dehydroabietylamine derivatives and their physical data

No.	R	Anion	mp (°C)	$[\alpha]^{22 a}_{\mathrm{D}}$	$[M]_D^{22 b}$	
1a	_	_	44.2	+44.35	+126.60	
1b	_	NTf_2	197.2	+17.11	+96.96	
2a	Me		Liquid at rt.	+50.64	+151.65	
2b	Me	NTf_2	180.3	+10.86	+63.06	
3a	Et		Liquid at rt.	+49.47	+155.10	
3b	Et	NTf_2	180.9	+9.80	+58.35	
4a	$(CH_2)_2OH$	_	74.0	+42.05	+138.57	
4b	$(CH_2)_2OH$	NTf_2	160.7	+7.03	+42.92	
5a	$(CH_2CH_2O)_2Me$	_	Liquid at rt.	+34.07	+132.05	
5b	$(CH_2CH_2O)_2Me$	NTf_2	Viscous liquid	+7.03	+47.00	
	· · · ·		at rt.			
6a	$(CH_2)_2 DAB^c$	_	63.8	+43.32	+258.58	
6b	$(CH_2)_2 DAB^c$	NTf_2	237.3	+13.54	+118.93	

 ${}^{a}c = 1.0$, CHCl₂. b Molar rotation calculated from $[a]_{D}^{22} \times M/100$, where *M* is the molar mass. c DAB = (+)-Dehydroabietylamine.

stereometric salt pair with the model compound (7 or 8) as no resolution was detected between a non-ionic CSA (1a-6a) and 8, or an ionic CSA (1b-5b) and 7. This is most probably caused by the lack of suitable interactions in forming a salt pair. However, the ionic 6b resolved the non-ionic 7 presumably because the former has a non-ionic amine group to be protonated by 7 and is therefore able to resolve the enantiomers of 7. Due to the poor solubility of **6b** in CDCl₃ the resolution of 7 under 2:1 conditions could not be determined. No significant increase in the chemical shift difference between R and S enantiomers ($\Delta\delta$) was detected when the concentration of host was doubled. In some cases the increase of concentration even led to a decrease in $\Delta \delta$. This was especially notable in the case of compounds 6a and 6b. Among the non-ionic CSAs, 1a, 2a and 6a resolved the enantiomers of 7 highly efficiently. Especially 6a worked exceptionally well (host: guest ratio 1:1) both in ¹H NMR (0.14 ppm, 71.8 Hz) and in ¹⁹F NMR (0.045 ppm, 21.2 Hz). The extent of resolution decreased both in ¹H NMR and in ¹⁹F NMR when the molar ratio was increased to 2:1. For the resolution of 8 the corresponding NTf₂ salts 1b, 2b and 6b gave best results. In this case the highest resolution was obtained with 6b both in ¹H NMR (0.16 ppm, 81.1 Hz) and in ¹⁹F NMR (0.076 ppm, 35.8 Hz). As in the case of **6a**, an increase in concentration lowered $\Delta \delta$ in ¹H NMR; however, in ¹⁹F NMR $\Delta\delta$ was increased to 0.32 ppm (149.9 Hz).

As compounds **6a** and **6b** gave the best results, their enantiomeric discrimination ability in NMR was further investigated. To find out how much guest is needed for maximum resolution and to obtain information about the composition of complex (*e.g.* 2:1 *vs.* 1:1 complex), the guest 7 (0.5 mL, 2.0 mM) was titrated with host **6a** (46.6 mM). Due to the poor solubility of **6b** in CDCl₃, titration was performed in an opposite manner compared to **6a** (*i.e.*, titrating a 2.0 mM solution of host **6b** with a 46.6 mM solution of guest **8**) (Fig. 1). Titration results from both ¹H and ¹⁹F NMR spectra indicate that the maximal resolution with host **6a** occurs at the point where the molar ratio of host and guest was 0.5:1 (0.200 ppm,

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H₃CO CF₃

Table 2 The magnitude of non-equivalence ($\Delta\delta$) between *R* and *S* enantiomers of racemic Mosher's acid (7) and its *n*-Bu₄N salt (8) in the presence of different CSAs (1–6a and b) in CDCl₃ at 27 °C

H₃CO_{CF3}

	Host : Guest	\bigcirc	U OH O	€ (ppm, (Hz))		
		7 (ppm, (Hz))				
CSA		¹ H	¹⁹ F	¹ H	¹⁹ F	
1a	1:1	0.024 (12.1)	0.074 (34.6)	nd	nd	
	2:1	0.022 (10.9)	0.064 (30.3)	nd	nd	
1b	1:1	nd	nd	0.014 (6.8)	0.051(23.9)	
	2:1	nd	nd	0.016 (8.0)	0.059 (27.7)	
2a	1:1	0.037 (18.7)	nd	nd	nd	
	2:1	0.04 (20.0)	0.029(13.5)	nd	nd	
2b	1:1	nd	nd	0.033 (16.6)	0.019(8.7)	
	2:1	nd	nd	0.025 (12.7)	nd	
3a	1:1	0.013 (6.7)	nd	nd	nd	
	2:1	0.016 (7.8)	nd	nd	nd	
3b	1:1	nd	nd	0.014 (6.9)	nd	
	2:1	nd	nd	0.0074 (3.7)	nd	
4a	1:1	0.0059 (3.0)	0.017 (8.0)	nd	nd	
	2:1	0.0092 (4.6)	0.0066 (3.1)	nd	nd	
4b	1:1	nd	nd	0.0051(2.5)	nd	
	2:1	nd	nd	0.0068 (3.4)	nd	
5a	1:1	0.015 (7.5)	nd	nd	nd	
	2:1	0.013 (6.3)	nd	nd	nd	
5b	1:1	nd	nd	0.0082(4.1)	nd	
	2:1	nd	nd	0.014 (6.8)	nd	
6a	1:1	0.14 (71.8)	0.045(21.2)	nd	nd	
	2:1	0.027 (12.3)	0.028 (13.3)	nd	nd	
6b	1:1	0.023 (11.3)	0.035 (16.6)	0.16 (81.1)	0.076 (35.8)	
	2:1	a	a	0.038(22.2)	0.32 (149.9)	

^a Could not be measured since **6b** was not soluble in CDCl₃ at high concentrations. nd (no resolution was detected).



Fig. 1 (a) The chiral resolution of enantiomers of 7 with 6a (1 H NMR) and (b) chiral resolution of enantiomers of 8 with 6b (1 H NMR).

99.9 Hz in ¹H NMR and 0.088 ppm, 41.2 Hz, in ¹⁹F NMR), and with **6b** at the molar ratio 1:1 (0.204 ppm, 101.8 Hz in ¹H NMR and 0.093 ppm, 43.7 Hz in ¹⁹F NMR) (see ESI 3.1 and 3.2†). Commercially available CSAs are often expensive, and the ability of **6a** to resolve enantiomers at the host:guest molar ratio 0.5:1 is a clear improvement as a minimum of 1.0 eq. (and in some cases an excess up to 24 eq.) of host is needed to obtain a maximal resolution.³ Since $\Delta\delta$ between the enantiomers of 7 (and of **8**) decreased in ¹H NMR when the concentration of **6a** (or **6b**) increased, it is assumed that the supramolecular complexation pattern changes when the concentration of host increases.

The suitability of CSAs **6a** and **6b** for enantiomeric excess (ee) NMR measurements was tested with 7 and **8**. Both **6a** and **6b** can be used to detect the enantiomeric composition of samples with excellent reliability (Fig. 2a and b; see ESI 4.1 and 4.2[†]).

The resolution of racemic α -substituted carboxylic acids or their *n*-Bu₄N salts by **6a** and **6b**, respectively, is presented in Table 3 and ESI 5.1 and 5.2.† CSAs **6a** and **6b** discriminate best carboxylic acids having an electronegative atom (*e.g.* O, N, Br) at the α -position (**11–15a** and **b**). Such aromatic or nonaromatic carboxylic acids were discriminated equally well. This is a major improvement as it has been suggested that the presence of an aromatic ring is necessary for good signal separation.¹⁰ In any case the resolution of non-aromatic carboxylic acids, especially using amine based CSAs, has been largely neglected.^{4,9,11}

The carboxylic acids **9a** and **b**, **10a** and **b** were discriminated by the corresponding host only moderately (1–7 Hz). This may be due to the lack of suitable interactions between the host and guest. This, however, is not a problem for ee determination as certain specialized NMR experiments are now available and can be used when the multiplet resolution



Fig. 2 Validation of enantiomeric composition of (a) **7** in the presence of **6a** (expected ee%: (A) 80, (B) 75, (C) 70, (D) 60, (E) 50) and (b) **8** in the presence of **6b** (expected ee%: (F) 50, (G) 58, (H) 67, (I) 75, (J) 79) by ¹H NMR (500 MHz) in CDCl₃ at 27 °C. (The peak of *S* enantiomer is wider due to strong binding with **6a**, see ESI 3.1.1[†])

needs improvement or when the overlapping of CSA and substrate is an issue.¹² Compound **6b** resolves the enantiomers of **9–12b** better than its non-ionic form **6a** resolves those of compounds **9–12a**, indicating that stronger interaction can be obtained between the ionic CSA and ionic substrate. This can be used to advantage if the resolution of non-ionic CSA and substrate is not sufficient. CSA **6a** resolves the enantiomers of **13–15a** better than the corresponding ionic CSA **6b** those of **13–15b**. Interestingly **6a** resolved the prochiral CH₂ hydrogens in compound **9a**. Since CSAs are usually able to resolve α -substituted carboxylic acids at the chiral α -site¹³ only, this is an additional advantage.

Conclusions

A number of derivatives (2a-6a) of (+)-dehydroabietylamine (1a) and their NTf_2 salts (1b-6b) were prepared for use in chiral molecular recognition studies, the syntheses being carried out by highly expedient microwave techniques. The ability of the CSAs 1-6a and b to resolve racemic 7 and 8 was examined by ¹H and ¹⁹F NMR. 6a showed excellent discrimination ability for 7 and its corresponding NTf₂ salt 6b for 8. Optimum conditions for enantiomeric discrimination with 6a and 6b were determined by titration. 6b gives best results at a 1:1 host: guest molar ratio whereas 6a gave best resolution at a 0.5:1 host: guest molar ratio. This is a useful result since usually at least 1.0 eq. of CSA are needed for maximum resolution. 6a and 6b are highly useful in ee determination as well. In resolving various α -substituted racemic carboxylic acids using 6a or 6b, best results were given by acids bearing an electronegative α -substituent. In general, acids bearing or lacking an aromatic moiety performed equally well. For carboxylates, somewhat better results were obtained when ionic CSA 6b was used for the resolution than when using 6a for non-ionic substrates. In future, the applicability of compounds **6a** and **6b** in resolution by NMR will be further investigated, and the development of new (+)-dehydroabietylamine based CSAs are being continued.

Experimental

Materials and methods

All reagents and solvents were obtained from commercial suppliers and were used without further purification unless otherwise stated. Dehydroabietylamine was purchased (Sigma Aldrich) as 60% grade and purified by a method described in the literature¹⁴ with slight modifications (see below). Flash chromatography was performed on 40–63 mesh silica gel. Microwave oven reactions were performed using the CEM Focused MicrowaveTM Synthesis System (Model Discover). Melting points were determined on a digital melting point apparatus (Büchi B 545). Optical rotations were determined on a digital polarimeter (JASCO DIP-1000) at 22 °C in CHCl₃ or MeOH as solvent. Exact masses were obtained using highresolution mass spectrometry (Bruker MicroTOF LC) with electrospray ionisation (ESI).

Synthesis of chiral solvating agents

Purification of (+)-dehydroabietylamine 1a 60% (+)-dehydroabietylamine (42.0 g) was dissolved in toluene (70.0 mL) and acetic acid (9.65 g) in toluene (30.0 mL) was slowly added. The salt was let to crystallize in fridge. The product was filtered and washed with hexane. (+)-Dehydroabietylamine acetate was recrystallized from MeOH. (+)-Dehydroabietylamine acetate (21.0 g) was dissolved in hot water and 10% NaOH solution (28.0 mL) was added. (+)-Dehydroabietylamine was extracted by Et₂O and the organic phase was washed with water until neutral. The organic phase was dried over Na₂SO₄. The solvent was evaporated and (+)-dehydroabietylamine was dried under vacuum; mp 44.2 °C (lit. 44–45 °C);¹⁵ HRMS-ESI (m/z) calc. for $C_{20}H_{32}N [M + H]^+$ 286.2529, found 286.2540; $[\alpha]_{D}^{22}$ +44.3480 (c 1.0 in CHCl₃) (lit. +58.0, c 0.2 in DMSO, 20 °C);¹⁵ ¹H NMR (500 MHz, CDCl₃) δ ppm 0.891 (s, 3H, CH₃), 1.220 (s, 3H, CH₃), 1.224 (d, J = 6.98 Hz, 6H, $2 \times CH_3$), 1.331 (m, 2H, CH_2), 1.386 (m, 1H, CHH), 1.521 (dd, J = -11.75, 3.31 Hz, 1H, CH), 1.688 (m, 2H, CH₂), 1.736 (m, 2H, CH₂), 2.289 (dt, J = -13.14, 1.72 Hz, 1H, CHH), 2.395 (d, J = -13.46 Hz, 1H, CHH), 2.607 (d, J = -13.46 Hz, 1H, CHH), 2.822 (sep, J = 6.98 Hz, 1H, CH), 2.884 (m, 2H, CH₂), 6.891 (d, J = 1.94 Hz, 1H, CH_{Ar}), 6.996 (dd, J = 8.08, 1.94 Hz, 1H, CH_{Ar}), 7.183 (d, J = 8.08 Hz, 1H, CH_{Ar}); ¹³C NMR (500 MHz, CDCl₃) δ ppm 18.777 (CH₂), 18.895 (CH₃), 18.895 (CH₂), 24.107 (CH₃), 24.130 (CH₃), 25.374 (CH₃), 30.311 (CH₂), 33.575 (CH), 35.355 (CH₂), 37.355 (C), 37.527 (C), 38.699 (CH₂), 45.003 (CH), 53.998 (CH₂), 123.959 (CH_{Ar}), 124.382 (CH_{Ar}), 126.937 (CH_{Ar}), 134.840 (C_{Ar}), 145.668 (C_{Ar}), 147.626 (C_{Ar}).

Dehydroabietyl-*N*-methanamine 2a. (+)-Dehydroabietylamine (1.82 g, 6.38 mmol, 1.0 eq.) and ethyl formate (1.01 g, 1.10 mL, 12.76 mmol, 2.0 eq.) were measured to a flask and

			$\Delta\delta$					$\Delta\delta$	
Cmpd. ^a	Racemic carboxylic acid		ppm	Hz	Cmpd. ^b	<i>n</i> -Bu ₄ N salt of racemic carboxylic acid		ppm	Hz
9a	OH OH	Me H CH ₂	0.0020 0.0052 0.0062	$1.1 \\ 2.6 \\ 3.1$	9b		Me H CH ₂	0.0099 0.0053 c	5.0 2.6
10a	ОН	Me H	0.014 nd	7.2 nd	10b		Me H	0.01 nd	5.1 nd
11a	ОНОН	Н	0.084	42.1	11b	OH O O	Н	0.10	50.8
12a	ОН ОН	H Me	0.014 0.0062	6.9 3.1	12b	OH O O	H Me	0.038 	19.1 ^c
13a	HN O OH O	H NH Me	0.01 0.052 0.033	5.1 26.1 16.3	13b		H NH Me	nd 0.051 0.033	nd 25.5 16.5
14a	OH O	H Me	0.014 0.077	6.1 38.7	14b		H Me	0.016 c	c
15a	O - OH	H NH	0.016 0.088	8.2 43.8	15b		H NH	0.017 0.072	8.4 36.2

Table 3 The magnitude of non-equivalencies of aromatic and non-aromatic racemic carboxylic acids in the presence of 6a and their n-Bu₄N salts in the presence of **6b** (¹H 500 MHz NMR, CDCl₃ at 27 °C)

^a 11.0 µL of a 46.6 mM 6a solution was added to 0.5 mL of a 2.0 mM solution of the analyte studied, to give an 0.5:1 host: guest molar ratio. ^b 22.5 µL of a 46.6 mM solution of the analyte studied was added to 0.5 mL of a 2.0 mM solution of **6b**, to give a 1:1 host: guest molar ratio. ^c Peak overlapped with host peaks; nd (no resolution was detected).

refluxed at 65 °C over night. The excess ethylformate was evaporated and product dried under vacuum (yield 99.8%). (+)-Dehydroabietylformamide (2.01 g, 6.41 mmol, 1.0 eq.) in THF (20 mL) was added dropwise to a flask containing LiAlH₄ suspension (0.26 g, 6.74 mmol, 1.05 eq.) in THF (15 mL) at 0 °C, refluxed for 6 h and let to cool to rt. MeOH was added to reaction mixture, which was stirred for 10 min.

General procedure for the preparation of secondary amines under microwave irradiation

The mixture was filtered and solvent evaporated. The crude product was dissolved in Et₂O, dried over MgSO₄ and filtered. The solvent was evaporated and the product dried under vacuum, and purified by column chromatography (1:9 MeOH: DCM). Yield 0.60 g, 42.0%; colourless liquid; calc. for $C_{21}H_{34}N$

 $[M + H]^+$ 300.2686, found 300.2690; $[\alpha]_D^{22}$ +50.6360 (c = 1.0, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ ppm 0.951 (s, 3H, CH₃), 1.223 (s, 3H, CH_3), 1.229 (d, J = 6.90 Hz, 6H, $2 \times CH_3$), 1.406 (m, 1H, CHH), 1.431 (m, 2H, CH_2), 1.543 (dd, J = -12.27, 2.54Hz, 1H, CH), 1.771 (m, 2H, CH₂), 1.789 (m, 2H, CH₂), 2.334 (d, J = -11.72 Hz, 1H, CHH), 2.433 (s, 3H, CH₃), 2.457 (d, J =-11.72 Hz, 1H, CHH), 2.826 (sep J = 6.90 Hz, 1H, CH), 2.893 (m, 2H, CH_2), 6.885 (d, J = 2.11 Hz, 1H, CH_{Ar}), 6.986 (dd, J =8.20, 2.11 Hz, 1H, CH_{Ar}), 7.172 (d, J = 8.20 Hz, 1H, CH_{Ar}); ¹³C NMR (300 MHz, CDCl₃) δ ppm 19.008 (CH₃), 19.091 (CH₂), 19.218 (CH₂), 24.146 (2 × CH₃), 25.409 (CH₃), 30.361 (CH₂), 33.590 (CH), 36.520 (CH₂), 37.094 (C), 37.580 (C), 37.879 (CH₃), 38.664 (CH₂), 46.061 (CH), 64.881 (CH₂), 123.902 (CH_{Ar}), 124.355 (CH_{Ar}), 126.896 (CH_{Ar}), 134.908 (C_{Ar}), 145.582 (C_{Ar}), 147.694 (C_{Ar}).

General procedure for preparation of secondary amines under microwave radiation

(+)-Dehydroabietylamine (1.0 eq.), 1-bromoethane (1.05 eq.) and Na₂CO₃ (0.6 eq.) were added to a microwave tube with isopropanol (in the case of **6a** (+)-dehydroabietylamine (2.0 eq.), 1,2-dibromoethane (1.0 eq.) and Na₂CO₃ (1.0 eq.) were used). The reaction mixture was microwave irradiated (110 W at 110 °C) for 2 h. The solvent was evaporated and the residue triturated with ether, filtered and mixed with Et₂O. The separated phases and organic phase was washed with water until neutral. The organic phase was dried over Na₂SO₄ and filtered, the solvent evaporated and the product dried under vacuum.

Dehydroabietyl-N-ethanamine 3a. Yield 2.47 g 74.9%; colourless liquid; calc. for $C_{22}H_{36}N [M + H]^+$ 314.2842, found 314.2834; $\left[\alpha\right]_{D}^{22}$ +49.4720 (c = 1.0, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ ppm 0.938 (s, 3H, CH₃), 1.082 (t, J = 6.93 Hz, 3H, CH_3), 1.225 (s, 3H, CH_3), 1.235 (d, J = 7.04 Hz, 6H, $2 \times CH_3$), 1.410 (m, 1H, CHH), 1.425 (m, 2H, CH₂), 1.595 (dd, *J* = -12.09, 2.49 Hz, 1H, CH), 1.666 (m, 2H, CH₂), 1.785 (m, 2H, CH₂), 2.277 (dt, J = -12.22 Hz, 3.65, 1H, CHH), 2.327 (d, J = -11.74 Hz, 1H, CHH), 2.512 (d, J = -11.74 Hz, 1H, CHH), 2.626 $(q, J = 6.93, 2H, CH_2)$, 2.832 (sep J = 7.02 Hz, 1H, CH), 2.892 (m, 2H, CH_2), 6.893 (d, J = 2.20 Hz, 1H, CH_{Ar}), 6.993 (dd, J = 8.14, 2.20 Hz, 1H, CH_{Ar}), 7.185 (d, J = 8.14 Hz, 1H, CH_{Ar}); ¹³C NMR (300 MHz, CDCl₃) δ ppm 15.641 (*C*H₃), 18.959 (*C*H₂), 19.040 (CH_3), 19.380 (CH_2), 24.146 (2 × CH_3), 25.466 (CH_3), 30.459 (CH₂), 33.590 (CH), 36.447 (CH₂), 37.054 (C), 37.588 (C), 38.697 (CH₂), 45.324 (CH₂), 45.721 (CH), 61.881 (CH₂), 123.910 (CH_{Ar}), 124.428 (CH_{Ar}), 126.904 (CH_{Ar}), 134.997 (C_{Ar}), 145.557 $(C_{\rm Ar})$, 147.491 $(C_{\rm Ar})$.

Dehydroabietylamino-N-ethanol 4a. Recrystallized from Et₂O pentane mixture. Yield 0.25 g, 71.0%; white solid; mp. 74.0 °C; calc. for $C_{22}H_{36}NO [M + H]^+$ 330.2791, found 330.2804; $\left[\alpha\right]_{D}^{22}$ +42.0520 (c = 1.0, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ ppm 0.935 (s, 3H, CH₃), 1.225 (s, 3H, CH₃), 1.231 $(d, J = 6.86 \text{ Hz}, 6H, 2 \times CH_3), 1.402 \text{ (m, 1H, CHH)}, 1.410 \text{ (m,})$ 2H, CH₂), 1.636 (dd, J = -11.45, 2.75 Hz, 1H, CH), 1.672 (m, 2H, CH_2), 1.753 (m, 2H, CH_2), 2.289 (dt, J = -12.53 Hz, 3.22, 1H, CHH), 2.307 (d, J = -11.78 Hz, 1H, CHH), 2.512 (d, J = -11.78 Hz, 1H, CHH), 2.763 (m, 2H, CH₂), 2.832 (m, 1H, CH), 2.897 (m, 2H, CH_2), 3.578 (m, 2H, CH_2), 6.892 (d, J = 1.98 Hz, 1H, CH_{Ar}), 6.995 (dd, J = 8.20, 1.98 Hz, 1H, CH_{Ar}), 7.185 (d, J = 8.20 Hz, 1H, CH_{Ar}); ¹³C NMR (300 MHz, $CDCl_3$) δ ppm 18.951 (CH₂), 18.983 (CH₃), 19.485 (CH₂), 24.114 (CH₃), 24.138 (CH₃), 25.490 (CH₃), 30.426 (CH₂), 33.582 (CH), 36.382 (CH₂), 37.151 (C), 37.564 (C), 38.800 (CH₂), 45.397 (CH), 51.661 (CH₂), 60.603 (CH₂), 60.975 (CH₂), 123.975 (CH_{Ar}), 124.404 (CH_{Ar}), 126.961 (CH_{Ar}), 134.859 (C_{Ar}), 145.654 (C_{Ar}), 147.613 $(C_{\rm Ar}).$

Dehydroabietylamino-*N***-2-(2-methoxyethoxy)ethanamine 5a.** Yield 0.23 g, 57.5%; yellow liquid; calc. for $C_{25}H_{42}NO_2 [M + H]^+$ 388.3210, found 388.3214; $[\alpha]_D^{22}$ +34.0680 (*c* = 1.0, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ ppm 0.923 (s, 3H, CH₃), 1.217 (s, 3H, CH₃), 1.228 (d, *J* = 6.95 Hz, 6H, 2 × CH₃), 1.400 (m, 1H, CHH), 1.430 (m, 2H, CH₂), 1.609 (dd, J = -11.58, 2.32 Hz, 1H, CH), 1.662 (m, 2H, CH₂), 1.765 (m, 2H, CH₂), 2.275 (dt, J = -13.08Hz, 3.51, 1H, CHH), 2.305 (d, J = -11.62 Hz, 1H, CHH), 2.532 (d, J = -11.62 Hz, 1H, CHH), 2.778 (t, J = 5.33 Hz, 2H, CH₂), 2.825 (sep J = 6.95 Hz, 1H, CH), 2.880 (m, 2H, CH₂), 3.374 (s, 3H, CH₃), 3.535 (m, 2H, CH₂), 3.561 (m, 2H, CH₂), 3.599 (m, 2H, CH₂), 6.884 (d, J = 2.08 Hz, 1H, CH_{Ar}), 6.986 (dd, J =8.15, 2.08 Hz, 1H, CH_{Ar}), 7.176 (d, J = 8.15 Hz, 1H, CH_{Ar}); ¹³C NMR (300 MHz, CDCl₃) δ ppm 18.935 (CH₂), 19.040 (CH₂), 19.380 (CH₃), 24.138 (2 × CH₃), 25.490 (CH₃), 30.467 (CH₂), 33.582 (CH), 36.334 (CH₂), 37.200 (C), 37.588 (C), 38.680 (CH₂), 45.510 (CH), 50.451 (CH₂), 59.187 (CH₂), 61.809 (CH₂), 70.367 (CH₂), 70.824 (CH₂), 72.078 (CH₂), 123.894 (CH_{Ar}), 124.452 (CH_{Ar}), 126.896 (CH_{Ar}), 135.037 (C_{Ar}), 145.533 (C_{Ar}), 147.783 (C_{Ar}).

Bisdehydroabietylamino-N¹,N²-ethane-1,2-diamine 6a. Purified by flash chromatography (1:9 MeOH: DCM). Yield 0.78 g 74.3%; white solid; mp. 63.8 °C; calc. for $C_{42}H_{65}N_2 [M + H]^+$ 597.5142, found 597.5132; $[\alpha]_{D}^{22}$ +43.3160 (*c* = 1.0, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ ppm 0.914 (s, 6H, 2 × CH₃), 1.204 (s, 6H, $2 \times CH_3$), 1.229 (d, J = 7.02 Hz, 12H, $4 \times CH_3$), 1.336 (m, 2H, 2 × CHH), 1.375 (m, 4H, 2 × CH₂), 1.565 (dd, J = -12.25, 2.66 Hz, 2H, 2 × CH), 1.603 (m, 4H, 2 × CH₂), 1.713 (m, 2H, 2 × CHH), 1.753 (m, 2H, 2 × CHH), 2.233 (dt, J = -12.83, 3.27 Hz, 2H, 2 × CHH), 2.319 (d, J = -11.80 Hz, 2H, 2 × CHH), 2.509 (d, J = -11.80 Hz, 2H, 2 × CHH), 2.696 (s, 4H, 2 × CH₂), 2.824 (sep J = 7.02 Hz, 2H, 2 × CH), 2.876 (m, 4H, 2 × CH₂), 6.872 (d, J =1.85 Hz, 2H, 2 × CH_{Ar}), 6.983 (dd, J = 8.13, 1.85 Hz, 2H, 2 × CH_{Ar}), 7.158 (d, J = 8.13 Hz, 2H, 2 × CH_{Ar}); ¹³C NMR (500 MHz, $CDCl_3$) δ ppm 18.983 (4 × CH_2), 19.348 (2 × CH_3), 24.138 (4 × CH_3), 25.466 (2 × CH_3), 30.459 (2 × CH_2), 33.582 (2 × CH), 36.390 $(2 \times CH_2)$, 37.167 $(2 \times C)$, 37.548 $(2 \times C)$, 38.583 $(2 \times C)$ CH_2), 45.624 (2 × CH), 50.018 (CH_2), 61.606 (2 × CH_2), 123.910 $(2 \times CH_{Ar})$, 124.412 $(2 \times CH_{Ar})$, 126.888 $(2 \times CH_{Ar})$, 134.883 $(C_{\rm Ar})$, 145.541 (2 × $C_{\rm Ar}$), 147.637 (2 × $C_{\rm Ar}$).

General procedure of NTf₂ salts

Primary amine **1a** or secondary amine **2a–6a** (1.0 eq.) was dissolved to DCM (0.5 mL). HNTf₂ (1.0 eq.) was added at 0 °C. Reaction mixture was stirred for 1 h at rt. The layers were separated and the organic phase washed with water (3×2.0 mL). The organic solvent was evaporated and product dried in vacuum.

Dehydroabietylaminium bis((trifluoromethyl)sulfonyl)amide 1b. Yield 0.18 g, 93.1%; white solid; mp. 197.2 °C; calc. for $C_{20}H_{32}N [M - NTf_2]^+$ 286.2529, found 286.2537; calc. for $C_2F_6NO_4S_2 [NTf_2]$ 279.9167, found 279.9178; $[\alpha]_D^{22}$ +17.1120 (c = 1.0, CHCl_3); ¹H NMR (500 MHz, CDCl_3) δ ppm 1.062 (s, 3H, CH₃), 1.213 (m, 1H, CHH), 1.225 (d, J = 6.78 Hz, 6H, 2 × CH₃), 1.230 (s, 3H, CH₃), 1.371 (dd, J = -12.42, 2.50 Hz, 1H, CHH), 1.408 (m, 1H, CHH), 1.592 (td, J = -12.74, 3.16 Hz, 1H, CHH), 1.655 (td, J = 7.30, 1.96 Hz, 1H, CHH), 1.681 (td, J = 7.30, 1.96 Hz, 1H, CHH), 1.681 (td, J = -13.01, 3.35 Hz, 1H, CHH), 2.822 (sep J = 6.78 Hz, CH), 2.829 (d, J = -12.89 Hz, 1H, CHH), 2.904 (m, 2H, CH₂), 3.167 (d, J = -12.89 Hz, 2H, CHH), 6.888 (d, J = 1.81 Hz, 1H, CH_{Ar}), 6.998 (dd, J = 8.17, 1.81 Hz, 1H, CH_{Ar}), 7.141 (d, J = 8.17 Hz, 1H, CH_{Ar}); ¹³C NMR (300 MHz, CDCl₃) δ ppm 17.001 (*C*H₃), 18.166 (*C*H₂), 19.089 (*C*H₂), 24.049 (*C*H₃), 24.090 (*C*H₃), 25.174 (*C*H₃), 29.609 (*C*H₂), 33.598 (*C*H), 35.201 (*C*H₂), 35.678 (*C*), 37.572 (*C*), 37.912 (*C*H₂), 47.008 (*C*H), 52.834 (*C*H₂), 119.552 (q, J = 320.75, *C*F₃), 124.137 (*C*H_{Ar}), 124.258 (*C*H_{Ar}), 126.977 (*C*H_{Ar}), 134.074 (*C*_{Ar}), 146.188 (*C*_{Ar}), 146.245 (*C*_{Ar}).

Dehydroabietyl-N-methanaminium bis((trifluoromethyl)sulfonyl)amide 2b. Yield 0.098, g 88.6%; white solid; mp. 180.3 °C; calc. for $C_{21}H_{34}N [M - NTf_2]^+$ 300.2686, found 300.2696 calc. for C₂F₆NO₄S₂ [NTf₂] 279.9167, found 279.9167; $[\alpha]_{D}^{22}$ +10.8600 (c = 1.0, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ ppm 1.102 (s, 3H, CH_3), 1.218 (d, J = 7.06 Hz, 6H, $2 \times CH_3$), 1.227 (s, 3H, CH_3), 1.278 (m, 1H, CHH), 1.371 (dd, J = -12.49, 2.30 Hz, 1H, CH), 1.408 (m, 1H, CHH), 1.656 (m, 1H, CHH), 1.662 (m, 1H, CHH), 1.753 (m, 2H, CH₂), 1.824 (m, 1H, CHH), 2.332 (dt, J = -13.14, 3.08 Hz, 1H, CHH), 2.717 (d, J = -12.06Hz, 1H, CHH), 2.823 (sep J = 7.06 Hz, CH), 2.827 (s, 3H, CH₃), 2.906 (m, 2H, CH₂), 3.142 (d, J = -12.06 Hz, 1H, CHH), 6.887 (d, J = 1.68 Hz, 1H, CH_{Ar}), 6.998 (dd, J = 8.29, 1.68 Hz, 1H, CH_{Ar}), 7.138 (d, J = 8.29 Hz, 1H, CH_{Ar}); ¹³C NMR (300 MHz, CDCl₃) δ ppm 17.106 (CH₃), 18.118 (CH₂), 19.291 (CH₂), 24.057 (CH₃), 24.082 (CH₃), 25.198 (CH₃), 29.666 (CH₂), 33.598 (CH), 35.719 (CH₂), 36.059 (CH₃), 36.334 (C), 37.588 (C), 37.823 (CH_2) , 47.445 (CH), 63.694 (CH₂), 119.658 (q, J = 321.38, CF_3), 124.315 (CH_{Ar}), 124.112 (CH_{Ar}), 126.961 (CH_{Ar}), 133.945 (C_{Ar}), 146.221 ($2 \times C_{Ar}$).

Dehydroabietyl-N-ethanaminium bis((trifluoromethyl)sulfonyl)amide 3b. Yield 0.18 g, 96.9%; white solid; mp. 180.9 °C; calc. for $C_{22}H_{36}N [M - NTf_2]^+$ 314.2842, found 314.2847; calc. for $C_2F_6NO_4S_2$ [NTf₂] 279.9167, found 279.9167; $[\alpha]_D^{22}$ +9.8120 $(c = 1.0, \text{ CHCl}_3);$ ¹H NMR (500 MHz, CDCl₃) δ ppm 1.113 (s, 3H, CH_3), 1.222 (d, J = 7.05 Hz, 6H, $2 \times CH_3$), 1.233 (s, 3H, CH₃), 1.241 (m, 1H, CHH), 1.371 (dd, *J* = -13.00, 2.33 Hz, 1H, *CH*), 1.400 (t, *J* = 7.32 Hz, 3H, *CH*₃), 1.415 (m, 1H, *CH*H), 1.664 (m, 1H, CHH), 1.719 (m, 1H, CHH), 1.752 (m, 2H, CH₂), 1.829 (m, 1H, CHH), 2.332 (dt, J = -12.75, 3.31 Hz, 1H, CHH), 2.696 (d, J = -12.34 Hz, 1H, CHH), 2.825 (sep J = 7.05 Hz, CH), 2.864(m, 1H, CHH), 2.944 (ddd, J = -17.16, 7.27, 1.28 Hz, 1H, CHH) 3.163 (d, J = -12.34 Hz, 1H, CHH), 3.206 (dq, J = 7.32, 4.51 Hz, 2H, CH_2), 6.889 (d, J = 1.94 Hz, 1H, CH_{Ar}), 7.005 (dd, J = 8.22, 1.94 Hz, 1H, CH_{Ar}), 7.146 (d, J = 8.22 Hz, 1H, CH_{Ar}); ¹³C NMR (300 MHz, CDCl₃) δ ppm 10.697 (CH₃), 17.041 (CH₃), 18.085 (CH₂), 19.323 (CH₂), 24.057 (CH₃), 24.090 (CH₃), 25.174 (CH₃), 29.706 (CH₂), 33.598 (CH), 35.767 (CH₂), 36.204 (C), 37.612 (C), 37.855 (CH₂), 45.697 (CH₂), 47.606 (CH), 60.749 (CH₂), 119.662 $(q, J = 320.21, CF_3)$, 124.128 (CH_{Ar}) , 124.323 (CH_{Ar}) , 126.945 (CH_{Ar}) , 133.912 (C_{Ar}) , 146.221 (C_{Ar}) , 146.261 (C_{Ar}) .

Dehydroabietyl-2-hydroxy-*N***-ethanaminium bis**((trifluoromethyl)**sulfonyl)amide** 4b. 0.18 g, 98.26%; white solid; mp. 160.7 °C; calc. for C₂₂H₃₆NO [M – NTf₂]⁺ 330.2791, found 330.2783; calc. for C₂F₆NO₄S₂ [NTf₂] 279.9167, found 279.9165; $[\alpha]_D^{22}$ +7.0280 (c = 1.0, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ ppm 1.114 (s, 3H, CH₃), 1.216 (d, J = 7.05 Hz, 6H, 2 × CH₃), 1.233 (s, 3H, CH₃), 1.300 (m, 1H, CHH), 1.386 (dd, J = -12.42, 2.35 Hz, 1H, CH), 1.411 (m, 1H, CHH), 1.673 (m, 1H, CHH), Organic & Biomolecular Chemistry

1.691 (m, 1H, CH*H*), 1.774 (m, 2H, CH₂), 1.820 (m, 1H, CH*H*), 2.344 (dt, J = -13.08, 3.38 Hz, 1H, CH*H*), 2.815 (d, J = -12.20Hz, 1H, CHH), 2.820 (sep J = 7.05 Hz, CH), 2.872 (m, 1H, CHH), 2.946 (ddd, J = -17.25, 7.02, 1.29 Hz, 1H, CH*H*), 3.177 (d, J = -12.20 Hz, 1H, CH*H*), 3.272 (ddd, J = 6.19 Hz, 1H, CHH), 3.326 (ddd, J = -13.04, 6.19, 4.17 Hz, 1H, CH*H*), 3.932 (m, 2H, CH₂), 6.887 (d, J = 1.95 Hz, 1H, CH_{Ar}), 6.997 (dd, J =8.10, 1.95 Hz, 1H, CH_{Ar}), 7.143 (d, J = 8.10 Hz, 1H, CH_{Ar}); ¹³C NMR (300 MHz, CDCl₃) δ ppm 17.367 (CH₃), 18.127 (CH₂), 19.200 (CH₂), 24.049 (CH₃), 24.083 (CH₃), 25.183 (CH₃), 29.612 (CH₂), 33.594 (CH), 51.202 (CH₂), 36.446 (C), 37.633 (C), 37.847 (CH₂), 47.094 (CH), 51.202 (CH₂), 56.368 (CH₂), 60.758 (CH₂), 119.612 (q, J = 321.32, CF₃), 124.315 (CH_{Ar}), 124.120 (CH_{Ar}), 126.957 (CH_{Ar}), 133.952 (C_{Ar}), 146.196 (C_{Ar}), 146.249 (C_{Ar}).

Dehydroabietylamino-N-2-(2-methoxyethoxy)ethanaminium bis((trifluoromethyl)-sulfonyl)-amide 5b. Yield 0.082 g, 95.1%; yellow liquid; calc. for $C_{25}H_{42}NO_2 [M - NTf_2]^+$ 388.3210 found 388.3216; calc. for C₂F₆NO₄S₂ [NTf₂] 279.9167, found 279.9156; $[\alpha]_{D}^{22}$ +7.0280 (c = 1.0, CHCl₃); ¹H NMR (500 MHz, $\mathrm{CDCl}_3)$ δ ppm 1.118 (s, 3H, CH_3), 1.213 (d, J = 6.82 Hz, 6H, 2 \times CH₃), 1.236 (s, 3H, CH₃), 1.321 (m, 2H, CH₂), 1.386 (dd, J = -12.66, 2.45 Hz, 1H, CH), 1.414 (m, 1H, CHH), 1.685 (m, 1H, CHH), 1.784 (m, 2H, CH₂), 1.834 (m, 1H, CHH), 2.341 (dt, J = -13.73, 3.31 Hz, 1H, CHH), 2.819 (sep J = 6.82 Hz, CH), 2.828 $(d, J = -12.37 \text{ Hz}, 1\text{H}, CH\text{H}), 2.880 \text{ (m, 1H, CHH)}, 2.946 \text{ (m,$ 1H, CHH), 3.109 (d, J = -12.37 Hz, 1H, CHH), 3.260 (s, 3H, CH₃), 3.293 (m, 1H, CHH), 3.407 (m, 1H, CHH), 3.488 (t, J = 4.48 Hz, 2H, CH₂), 3.688 (m, 2H, CH₂), 3.824 (m, 2H, CH₂), 6.884 (d, J = 1.84 Hz, 1H, CH_{Ar}), 6.993 (dd, J = 8.07, 1.84 Hz, 1H, CH_{Ar}), 7.144 (d, J = 8.07 Hz, 1H, CH_{Ar}); ¹³C NMR (300 MHz, CDCl₃) δ ppm 17.585 (CH₃), 18.211 (CH₂), 19.185 (CH₂), 24.072 (CH₃), 24.114 (CH₃), 25.084 (CH₃), 29.482 (CH₂), 33.609 (CH), 35.644 (CH₂), 36.453 (C), 37.602 (C), 37.961 (CH₂), 46.846 (CH), 48.503 (CH₂), 59.006 (CH₃), 59.701 (CH₂), 63.732 (CH₂), 69.643 (CH_2) , 71.257 (CH_2) , 119.766 $(q, J = 322.24, CF_3)$, 124.300 (CH_{Ar}), 124.094 (CH_{Ar}), 126.908 (CH_{Ar}), 133.990 (C_{Ar}), 146.284 $(C_{\rm Ar})$, 146.326 $(C_{\rm Ar})$.

N-(Dehydroabietyl)-2-(dehydroabietylamino)ethanaminium bis((trifluoromethyl)-sulfonyl)-amide 6b. Yield 0.16 g, 83.4%; white solid; mp. 237.3 °C; calc. for $C_{42}H_{65}N_2 [M - NTf_2]^+$ 597.5142, found 597.5160; calc. for C₂F₆NO₄S₂ [NTf₂] 279.9167, found 279.9173; $[\alpha]_{D}^{22}$ +13.5440 (*c* = 1.0, MeOH); ¹H NMR (500 MHz, CDCl₃) δ ppm 1.015 (s, 6H, 2 × CH₃), 1.185 (s, 6H, $2 \times CH_3$), 1.208 (d, J = 76.98 Hz, 12H, $4 \times CH_3$), 1.230 (m, 2H, 2 × CHH), 1.314 (m, 2H, 2 × CHH), 1.369 (dd, J = -11.78, 2.27 Hz, 2H, 2 × CH), 1.555 (dt, J = -11.55 Hz, 2H, 2 × CHH), 1.664 (m, 4H, $2 \times CH_2$), 1.769 (m, 4H, $2 \times CH_2$), 2.267 (dt, J = -12.89 Hz, 2H, 2 × CHH), 2.677 (d, J = -11.76 Hz, 2H, $2 \times CHH$), 2.813 (sep J = 7.05 Hz, 2H, $2 \times CH$), 2.832 (m, 2H, $2 \times CHH$), 2.926 (dd, J = -16.91, 6.86 Hz, 2H, $2 \times CHH$), 2.952 (m, 2H, 2 × CHH), 3.269 (s, 4H, 2 × CH₂), 6.866 (d, J = 1.81 Hz, 2H, 2 × CH_{Ar}), 6.987 (dd, J = 8.13, 1.81 Hz, 2H, 2 × CH_{Ar}), 7.113 (d, J = 8.13 Hz, 2H, 2 × CH_{Ar}); ¹³C NMR (500 MHz, CDCl₃) δ ppm 17.908 (2 × CH_3), 18.311 (2 × CH_2), 19.158 (2 × CH_2), 24.099 (4 × CH_3), 25.225 (2 × CH_3), 29.802 (2 × CH_2), 33.601 $(2 \times CH)$, 36.201 $(2 \times CH_2)$, 36.705 $(2 \times C)$, 37.560 $(2 \times C)$,

38.045 (2 × *C*H₂), 46.304 (2 × *C*H₂), 46.945 (2 × *C*H), 61.499 (2 × *C*H₂), 119.606 (q, J = 320.98, *C*F₃), 124.170 (2 × *C*H_{Ar}), 124.246 (2 × *C*H_{Ar}), 126.960 (2 × *C*H_{Ar}), 134.081 (2 × *C*_{Ar}), 146.131 (2 × *C*_{Ar}), 146.501 (2 × *C*_{Ar}).

Synthesis of guests

N-Acetylation of phenylalanine was performed according to literature.¹⁶ Preparation of $[NBu_4]^+$ salts was performed by adding tetrabutylammoniumhydroxide (1.0 M in MeOH, 1.0 eq.) to racemic acid (1.0 eq.) in MeOH. After stirring for 1–3 h, the solvent was evaporated and product was dried in vacuum.

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Notes and references

- (a) H. Bergmann, B. Grosch, S. Sitterberg and T. Bach, J. Org. Chem., 2004, 69, 970; (b) K. S. Heo, M. H. Hyun,
 Y. J. Cho and J. J. Ryoo, Chirality, 2011, 23, 281;
 (c) S. H. Grimm, L. Allmendinger, G. Hoefner and K. T. Wanner, Chirality, 2013, 25, 923.
- 2 M. Suzuki, J. R. Deschamps, A. E. Jacobson and K. C. Rice, *Chirality*, 2015, 27, 287.
- 3 (a) G. Uccello-Barretta and F. Balzano, *Top. Curr. Chem.*, 2013, **341**, 69; (b) K. Bica and P. Gaertner, *Eur. J. Org. Chem.*, 2008, 3235.
- 4 N. Jain, M. B. Mandal and A. V. Bedekar, *Tetrahedron*, 2014, **70**, 4343.
- 5 T. J. Wenzel, *Discrimination of Chiral Compounds Using NMR Spectroscopy*, John Wiley & Sons, Hoboken, New Jersey, 2007.
- 6 V. Kumar, C. E. Olsen, S. J. C. Schaeffer, V. S. Parmar and S. V. Malhotra, *Org. Lett.*, 2007, **9**, 3905.
- 7 First used by N. Guranatne *et al.* for the construction of an enantio-recognizing reagent: M. B. Foreiter, H. Q. N. Gunaratne, P. Nockemann, K. R. Seddon, P. J. Stevenson and D. F. Wassell, *New J. Chem.*, 2013, 37, 515.

- 8 (*a*) T. Heckel, A. Winkel and R. Wilhelm, *Tetrahedron: Asymmetry*, 2013, **24**, 1127; (*b*) B. Altava, D. S. Barbosa, M. Isabel Burguete, J. Escorihuela and S. V. Luis, *Tetrahedron: Asymmetry*, 2009, **20**, 999.
- 9 L. Gonzalez, B. Altava, M. Bolte, M. I. Burguete, E. Garcia-Verdugo and S. V. Luis, *Eur. J. Org. Chem.*, 2012, 4996.
- 10 K. Tanaka and N. Fukuda, *Tetrahedron: Asymmetry*, 2006, 17, 916.
- (a) A. R. Chaudhary, P. Yadav and A. V. Bedekar, Tetrahedron: Asymmetry, 2014, 25, 767; (b) L. Liu, M. Ye, X. Hu, X. Yu, L. Zhang and X. Lei, Tetrahedron: Asymmetry, 2011, 22, 1667; (c) M. Periasamy, M. Dalai and M. Padmaja, J. Chem. Sci., 2010, 122, 561; (d) X. Yang, G. Wang, C. Zhong, X. Wu and E. Fu, Tetrahedron: Asymmetry, 2006, 17, 916; (e) S. Tabassum, M. A. Gilani and R. Wilhelm, Tetrahedron: Asymmetry, 2011, 22, 1632; (f) S. Satishkumar and M. Periasamy, Tetrahedron: Asymmetry, 2009, 20, 2257; (g) S. Bozkurt, M. Durmaz, H. N. Naziroglu, M. Yilmaz and A. Sirit, Tetrahedron: Asymmetry, 2011, 22, 541; (h) W. Wang, F. Ma, X. Shen and C. Zhang, Tetrahedron: Asymmetry, 2007, 18, 832; (i) C. Pena, J. Gonzalez-Sabin, I. Alfonso, F. Rebolledo and V. Gotor, Tetrahedron, 2008, 64, 7709.
- 12 (a) M. Perez-Trujillo, L. Castanar, E. Monteagudo, L. T. Kuhn, P. Nolis, A. Virgili, R. T. Williamson and T. Parella, *Chem. Commun.*, 2014, **50**, 10214; (b) J. A. Aguilar, S. Faulkner, M. Nilsson and G. A. Morris, *Angew. Chem., Int. Ed.*, 2010, **49**, 3901; (c) S. R. Chaudhari and N. Suryaprakash, *Chem. Phys. Lett.*, 2013, **555**, 286; (d) N. Lokesh, S. R. Chaudhari and N. Suryaprakash, *Org. Biomol. Chem.*, 2014, **12**, 993.
- 13 T. J. Wenzel, in *Stereoselective Synthesis of Drugs and Natural Products*, ed. V. Andrushko and N. Andryushko, John Wiley & Sons, Inc., Hoboken, New Jersey, 2014, pp. 1505–1528.
- 14 L. C. Cheney, US Pat, 2787637, 1957.
- 15 G. Su, L. Huo, W. Huang, H. Wang and Y. Pan, *Chin. J. Struct. Chem.*, 2009, **28**(6), 693–698.
- 16 S. Stella and A. Chadha, *Tetrahedron: Asymmetry*, 2010, 21(4), 457–460.