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New enantiopure imidazolinium carbene ligands incorporating two hydroxy groups for Lewis acid-catalyzed diethyl zinc addition to aldehydes

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ABSTRACT

New enantiopure imidazolinium carbene ligands incorporating two hydroxy functions have been synthesized from commercially available chiral amino alcohols and diamines. These ligands in combination with different metallic salts have been investigated in the diethylzinc addition to aldehydes with good yields and enantioselectivity.

1. Introduction

The family of enantiopure *N*-heterocyclic carbenes has emerged as an important class of ligands with many applications in organometallic chemistry[1] and as organocatalysts.[2] In general the carbenes are mainly prepared from the corresponding salts via deprotonation. The latter can also be considered to be part of the class of chiral ionic liquids[3] depending on their melting points. For example, chiral imidazolinium-based ionic liquids have recently been reported.[3b,4] The number of highly selective enantiopure carbene ligands in a few reactions is increased, but remains small compared to the many other applications of chiral phosphine ligands, this makes it desirable to expand upon the library of chiral carbene ligands.[1f]

A limited number of chiral imidazol(in)ium salts incorporating hydroxy groups have been reported. The salts are precursors for bidentate ligands and for example salt **3** has also been used as an ionic liquids.[4a] A very successful bidentate hydroxy-carbene ligand prepared from salt **1** was described by Hoveyda et al.[5] giving up to 96% ee in an asymmetric olefin metathesis and 98% ee in a copper-catalyzed allylic alkylation. Arnold et al. prepared from salt **2** a Cu^{I} complex for the diethylzinc conjugate addition to cyclohexenone, resulting in up to 51% ee.[6] Mauduit et al. used various analogues of salt **4** in the Cu^{II}-catalyzed addition of diethylzinc to cyclohexenone obtaining ees of up to 93% (Fig. 1).[7]

In addition, Alexakis and Mauduit also used analogues of **4** and other chiral imidazolinium salts as carbene precursors in a copper-catalyzed conjugate Grignard addition to 3-substituted cyclohexenones to obtain quaternary chiral centers in up to 96% ee.[8]

Recently, we explored the behavior of a few new imidazolinium salts of type **5** with two hydroxy groups as potential tridentate ligands in the diethyl zinc addition to aldehydes giving up to 66% ee and 67% yield without the addition of an additional metal salt.[4c] In order to explore this group of ligands further, we herein report an expansion of the library of these ligands and a study of the influence of various Lewis acidic metals. In particular oxophilic metals, related to zinc, were explored with these carbene ligands in the diethyl zinc addition[9] to aldehydes in order to prepare optically active secondary alcohols, which are important intermediates in synthesis.

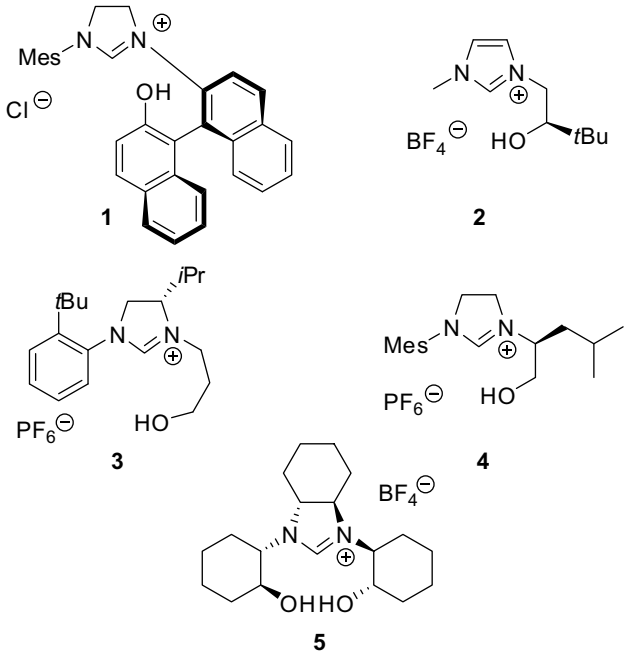

Figure 1. Hydroxy-containing imidazol(in)ium salts.

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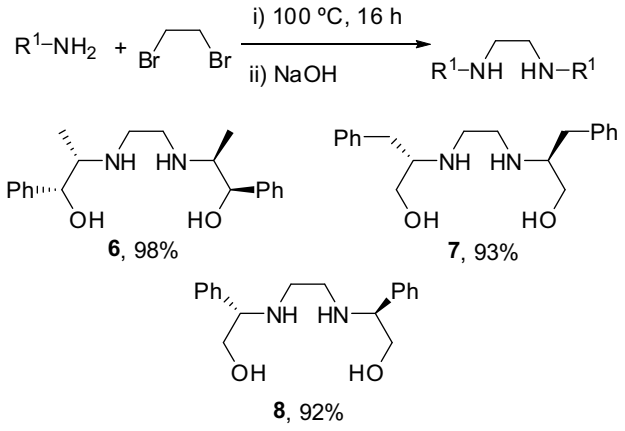
2. Results and discussion

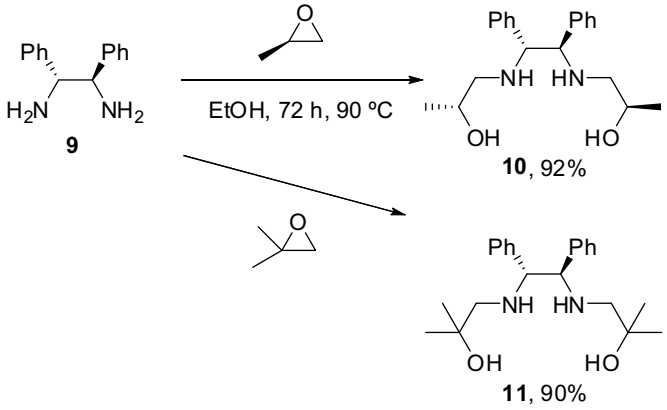
2.1. Preparation of the salts

The synthesis started with the preparation of C_2 symmetric diamines. Two routes were employed for their synthesis. First, diamines bearing hydroxy groups were prepared by simple alkylation of the corresponding amino alcohols with 1,2-dibromoethane via a literature procedure.[10] The reaction was neat and gave excellent yields of the diamines (Scheme 1). The HBr salt of the corresponding diamine was precipitated as a yellow solid in the reaction mixture, which was dissolved in water. After removal of impurities by solvent extraction with chloroform, the aqueous phase was basified with NaOH to obtain pure bis-amino alcohol which was free of acid contents.



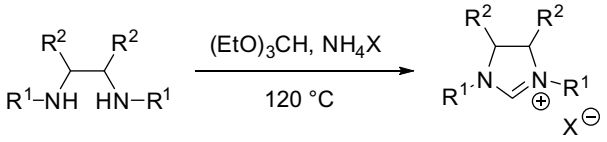
Scheme 1. Alkylation of amino alcohols.

In addition C_2 symmetric amino alcohols were also synthesized by the ring opening of epoxides. Here, chiral diamine **9** was reacted with chiral and achiral epoxides giving rise to β-amino alcohols (Scheme 2). The mixture was refluxed in EtOH for 72 h. The solvent was removed, after which the solid was dissolved in water and acidified to pH 2 with 2 M hydrochloric acid. The aqueous layer was extracted with chloroform which was discarded. The aqueous layer was then basified to pH 11 with 2 M NaOH solution and the product was obtained by extracting the aqueous layer with chloroform. The amino alcohols **10** and **11** were obtained in excellent yields with high purity.



Scheme 2. Ring opening of epoxides.

The salts were then prepared by the direct reaction of the diamines and triethyl orthoformate in the presence of ammonium salts according to a literature procedure.[11] The latter were used as a Brønsted acid source for the activation of the orthoester. These ammonium salts also acted as a source of the anion for the corresponding imidazolinium salts (Scheme 3).

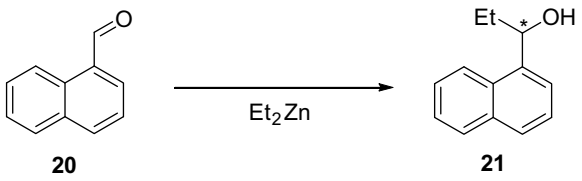


Scheme 3. Synthesis of imidazolinium salts.

Salt **12** has been synthesized from amino alcohol **6** with a yield of 74%.[4c] Salts **13**, **14**, and **15** have the same cation but different anions. Chloride, bromide, and iodide salts were synthesized in order to investigate the influence of harder anions in the diethylzinc addition to aldehydes. Salts **18** and **19** have additional steric information in their backbone, and have been synthesized in excellent yields of 80% and 90%, respectively. The results are summarized in Table 1.

Table 1
Preparation of salts

Entry	Diamine	Cation	Anion	Salt	Yield (%)
1			BF_4^-	**12**	74
2	**6**		Cl^-	**13**	42
3			Br^-	**14**	66
4			I^-	**15**	67
5	**7**		BF_4^-	**16**	57
6	**8**		BF_4^-	**17**	66
7	**10**		BF_4^-	**18**	80
8	**11**		BF_4^-	**19**	90



Scheme 4. Diethylzinc addition to aldehydes.

Table 2
Investigation of the salts: 2.5 mol % $Cu(OTf)_2$, 5 mol % salt, 15 mol % KO*t*Bu, 46 h, rt, toluene

Entry	Salt	Yield (%)	ee (%)	Conf.
1	**12**	42	84	(*R*)
2[a]	**13**	37	44	(*R*)
3	**14**	43	42	(*R*)
4[a]	**15**	31	22	(*R*)
5	**16**	16	0	—
6	**17**	13	0	—
7	**18**	62	12	(*S*)
8	**19**	55	34	(*R*)

[a] 5 mol % $Cu(OTf)_2$, 10 mol % salt, 30 mol % KO*t*Bu.

2.2. Investigation in catalysis

The imidazolinium salts were applied in the diethylzinc addition to 1-naphthaldehyde **20** as shown in Scheme 4 in order to evaluate their efficiency in terms of yield and stereoselectivity.

Therefore, the carbene ligands were employed along with copper(II) triflate (Table 2). It was found that ligand **12** gave the highest ee of 84% with a moderate yield of 42%. Among the other ligands, **18** gave a higher yield of 62% but with a lower ee of 12%. The large influence of the counter-anion on the ee can be attributed to the fact that BF_4, at least in comparison to Cl, Br, and I, is a non-coordinating anion. The halide anions could co-ordinate a metal center and therefore change the catalytic species.

Since the carbene based on salt **12** gave the best results, further optimization was performed with this ligand. Since different metal cations can influence the reaction due to their size, co-ordination sphere, and charge density, several metal salts were investigated in the reaction. The results are summarized in Table 3. $Cu(OTf)_2$ was found to give the highest enantiomeric excess of 84%, but with a moderate yield of 42%. Cupric ions with different counter-anions such as chloride gave 80% ee. However, the yield decreased to 32% indicating the influence of the metallic halide counter-anion, which coordinates to the metal in the catalytic species.

Titanium(IV)chloride gave an ee of 15% while titanium(IV)tetraisopropoxide resulted in 51% ee. This marked difference can be attributed to the fact that these anions also take part in the transition state formed, depending on their binding strength to the metal cation. Calcium chloride proved to be a better Lewis acid as compared to $MgBr_2$, as can be seen from entries 9 and 10 of Table 3. The results obtained with calcium are remarkable as this metal has not often been used in such a type of catalysis, and is an environmentally friendly cation.

Scandium triflate gave a poor yield of 8% with an ee of 57%. $Ni(acac)_2$ and silver oxide led to an ee of 18% and 10%, respectively. The best yield was 70%, obtained by using zinc triflate with an ee of 63%. Fe^{+2} proved to be superior to Fe^{+3} as the former gave 53% yield with an ee of 63%, while the latter gave 32% yield and 49% ee. It can be seen that the ligand based on salt **12** has a wide range of interaction with several metallic cations.

Table 3
Investigation of salt **12** with different metals: (metal salt:salt **12**:KO*t*Bu) (1:1:3), 46 h, rt, toluene

Entry	Metal salt	Ligand (mol %)	Yield (%)	ee (%)
1	CuI	5	53	80
2	$CuCl_2$	3	32	80
3	$Cu(OTf)_2$	5	42	84
4	$Cu(acac)_2$	10	15	28
5	$FeCl_2$	2	53	63
6	$FeCl_3$	2	32	49
7	$Ti(iPrO)_4$	3	41	51
8	$TiCl_4$	3	34	15
9	$CaCl_2$	5	60	43
10	$MgBr_2$	5	52	25
11	$Sc(OTf)_3$	5	8	57
12	$Ni(acac)_2$	10	52	18
13	Ag_2O	10	14	10
14	$Zn(OTf)_2$	5	70	63
15	$CrCl_3$	5	45	86

Table 4
Investigation of salt **12** with different metals concentrations: (metal salt:salt **12**:KO*t*Bu) (1:1:3), 46 h, rt, toluene

Entry	Metal salt	Ligand (mol %)	Yield (%)	ee (%)
1	CuI	20	21	80
2		10	22	80
3		5	53	84
4		3	55	82
5		1	51	63
6	$Cu(OTf)_2$	10	12	80
7		5	42	84
8		3	44	77
9		1	24	6

In these experiments, three parts of KO*t*Bu were added to one part of the imidazolinium salt in toluene. As shown in Table 5, this was important in order to deprotonate the C2 position and both hydroxyl groups. After 30 min, metallic salt was added and the mixture left to stir for 1 h. Next 1-naphthaldehyde **20** was added, followed by the addition of Et_2Zn (1.1 equiv). The reaction was stirred for 46 h at rt and then quenched with 1 M HCl. Considering the fact that the ligand contains two hard oxygen ligator atoms and one soft carbene moiety, one could explain why these metals (being in the middle of the hard-soft scale) gave the best results. As catalytic active species, a tridentate ligand arrangement can be assumed, as has been reported for tris-oxazoline ligands,[12] which were able to coordinate to a copper center to give a hexacoordinated stereo-discriminating complex containing the tridentate ligand, and one water molecule, leaving two co-ordination sites for the substrate.

Table 5
Investigation of base: (metal salt:salt **12**) (1:1), 46 h, rt, toluene

Entry	Base	Base (equiv)	Yield (%)	Ee (%)
1	KO*t*Bu	0.3	42	80
2		0.2	26	80
3		0.1	Traces	—
4	KHMDS	0.3	44	28
5		0.2	31	5
6		0.1	Traces	—

The concentration of the catalyst in the diethyl zinc addition to 1-naphthaldehyde could play a pivotal role on the yield and enantiomeric excess of the product. In order to evaluate the effect of concentration of catalyst, CuI and $Cu(OTf)_2$ were employed as these catalysts prove the best candidates for further investigation as shown in Table 4. When the salt to ligand ratio was 1:1, CuI with 20 mol % of ligand gave 21% yield with 80% ee. Moreover, 10 mol % of ligand gave 22% yield and 80% ee, while 5 mol % of ligand gave 53% yield and 84% ee. A yield of 55% and 82% ee was

found when 3 mol % of the ligand was used. With $Cu(OTf)_2$, 5 mol % of ligand was the best concentration as it gave 42% yield and 84% ee. It is rare but not unknown that lower catalyst loading gives better yield and higher ee.[13] In the present case the drop of ee at lower catalyst loading and therefore lower concentration can be explained by a competitive, ligand-free background reaction. On the other hand, at a higher catalyst loading and therefore higher concentration, it may be possible that an inactive dimer with two copper atoms and two ligands could be formed.

In addition, the influence of the bases KHMDS and KO*t*Bu to generate the carbenes was investigated. The latter gave the best results. KHMDS resulted in 28% ee when 3 equiv was used with a yield of 44% (Table 5, entry 4), while 31% yield was obtained with a low ee of 5%, when 2 equiv of base was applied. KO*t*Bu proved to be the best choice. It can also be concluded from entries 1–3 of Table 5 that 3 equiv of KO*t*Bu is necessary in order to achieve a yield of 42% and an ee of 84%. For all these reactions, $Cu(OTf)_2$ was used and the ligand to salt ratio was 1:1. The need for 3 equiv of KO*t*Bu strongly supports that a tridentate ligand is present in the active catalyst. In addition the enhanced ee resulting in KO*t*Bu can be attributed to the fact that the released *t*BuOH is also participating in the formation of the catalytically active species and could coordinate the metal center. That the alcohol plays such a role is also shown later, when the sterically less hindered ethanol was added, which increased the ee.

In order to further optimize the diethylzinc addition to 1-naphthaldehyde, the reaction was carried out at different temperatures. It was found that by lowering the temperature to 0 °C, the yield decreased markedly to 8% and also a slightly lower ee of 73% was observed (Table 6, entry 5). A further decrease in temperature also decreased the ee to 9% (Table 6, entry 4). For this experiment, *n*-BuLi was used as a base instead of KO*t*Bu, showing again the importance of the presence of *t*BuOH for the enantioselective reaction. When the reaction was carried out at 40 °C, the results were almost similar to those obtained when the reaction was performed at rt (Table 6, entries 1 and 2). Increasing the temperature to 60 °C led to a decrease in yield and in ee of the product, respectively (Table 6, entry 3). The decrease of the ee at higher temperature is obvious since an enantioselective-catalyzed reaction is kinetically controlled. The decrease of the yield and more important the ee at lower temperatures could be explained by the formation of different catalytic copper species and clusters. Similarly, unusual relationships have been observed by Hoveyda[14] and Leighton[15] in the copper-catalyzed enantioselective conjugate addition with chiral phosphine ligands.

Table 6
Investigation of temperature: (metal salt:salt **12**) (1:1), 46 h, rt, toluene

Entry	Salt	*t* (°C)	Yield (%)	ee (%)
1	CuI	rt	53	80
2		40	43	83
3		60	29	56
4[a]	$Cu(OTf)_2$	−50	47	9
5		0	8	73

[a] *n*-BuLi was used as a base.

Table 7
Effect of salt to ligand ratio

Entry	Metal salt	Metal:ligand	Yield (%)	ee (%)
1	$Cu(OTf)_2$	1:1	42	84
2		1:2	76	73
3		2:1	35	11
4		1:4	60	70
5	$Ti(iPrO)_4$	1:1	41	51
6		1:2	54	75

It is known that the salt to ligand ratio can play a crucial role in controlling the outcome of the reaction particularly in terms of yield. In the case of $Cu(OTf)_2$ the yield of the product was maximized to 76% from 42% as the salt to ligand ratio was changed from 1:1 to 1:2. The enantiomeric excess experienced a slight drop from 84% to 73% (Table 7, entries 1 and 2). The reversal of this optimized M:L ratio gave 35% yield and 11% ee (Table 7, entry 3). This can be explained by a ligand-free background reaction. In case of $Ti(iPrO)_4$, when the salt to ligand ratio was changed from 1:1 to 1:2, the yield improved from 41% to 54% and the ee rose from 51% to 75%.

The catalytic system was then examined to determine if a nonlinear effect was present, since the best results were obtained with a metal:ligand ratio of 1:2. Both enantiomers of norephedrine-based imidazolinium salt **12** were mixed in different ratios. The graph obtained shows a slight deviation from linearity, as can be seen from the following graph (Fig. 2). However, taking the error range into consideration no nonlinear effect is present, and the benefit of using a larger amount of ligand is in order to suppress a ligand-free catalyzed background reaction.

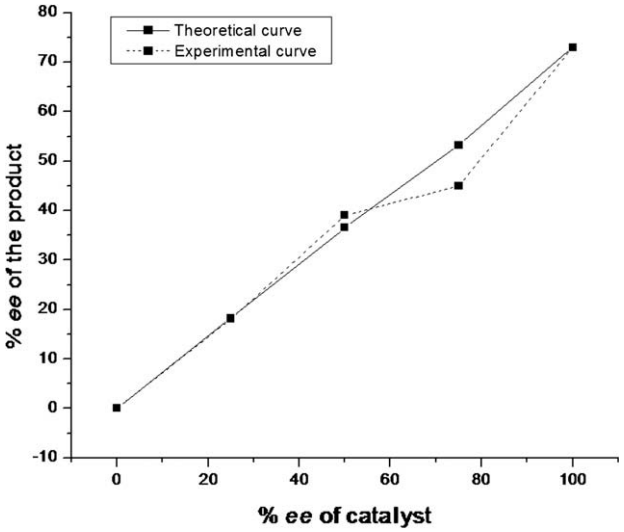


Figure 2. Absence of a nonlinear effect.

The influence of ethanol, as an additive, was also explored. It was seen that addition of ethanol as an additive in the diethylzinc addition to 1-naphthaldehyde showed a marked increase in the ee of the product, that is, 85% as compared with 73% ee, which was obtained without the addition of any additive. However, the yield decreased slightly from 76% to 65%. Furthermore, exploring other solvents revealed that toluene is the best solvent for this system.

In addition, the new bis-amino alcohols *ent*-**10** and **11** were also evaluated as ligands in the diethyl zinc addition to 1-naphthaldehyde. The product was obtained in 77% and 90% yield with an ee of 53 (*S*) and 43% (*R*), respectively.

Finally, different aldehydes were used under the optimized conditions as shown in Table 8. The results were comparable to those of 1-naphthaldehyde.

Table 8
Enantioselective diethylzinc addition to aldehydes[a]

Entry	Aldehyde	Yield (%)	ee (%)	Conf.
1	2-Naphthaldehyde	57	50	(*R*)
2	Benzaldehyde	59	75	(*R*)
3	*p*-Chlorobenzaldehyde	60	78	(*R*)
4	*p*-Methylbenzaldehyde	50	71	(*R*)

[a] $Cu(OTf)_2$:**12**:KO*t*Bu/1:2:3, 46 h, rt, toluene.

Table 9
Chemical shifts δ of Mosher's carboxylate in ppm and $\Delta\delta$ values in Hz (400 MHz ^{1}H NMR, 375 MHz ^{19}F NMR)

Entry	Salt	δ(1H) (*S*)/(*R*)	δ(^{19}F) (*S*)/(*R*)	$\Delta\delta$(^{1}H)	$\Delta\delta$(^{19}F)
1	—	3.57/3.57	−71.19/−71.19	0	0
2	**13**	3.56/3.56	−70.75/−70.75	0	0
3	**14**	3.57/3.54	−70.73/−71.04	12	117
4	**15**	3.56/3.53	−70.68/−70.99	12	117
5	**16**	3.56/3.56	−71.06/−71.06	0	0
6	**17**	3.60/3.61	−71.17/−71.17	4	0
7	**18**	3.60/3.60	−70.97/−71.03	0	22
8	**19**	3.62/3.62	−71.07/−71.07	0	0

2.3. Use as a shift reagent

The newly synthesized salts were investigated for their ability to interact with Mosher's carboxylate, by examining the differences in the chemical shifts of the MeO group and the CF_3 group of the two enantiomers of Mosher's carboxylate. In order to assign the signals of the corresponding enantiomers, enantioenriched (12% ee) Mosher's carboxylate was mixed with the chiral imidazolinium salts in a 1:1 ratio. The mixture was dissolved in acetone-d_6 and ^{1}H and ^{19}F NMR spectra were recorded. The results are summarized in Table 9.

Salt **13** showed no splitting in either the ^{1}H or ^{19}F spectra. When the anion was changed from chloride to bromide and iodide, a splitting of 12 Hz in ^{1}H NMR and 117 Hz in ^{19}F NMR was observed in each case (Table 9, entries 3 and 4). Salts **16** and **19** showed no splitting at all, while salt **18** showed a splitting of 22 Hz in ^{19}F NMR and salt **17** displayed a splitting of 4 Hz in ^{1}H NMR.

3. Conclusion

In conclusion, enantiomerically pure imidazolinium-based ligands incorporating two hydroxy groups have been synthesized in moderate to excellent yields by following a simple two-step procedure. The ligands have been employed in the diethylzinc addition to 1-naphthaldehyde, and an ee of up to 84% has been achieved. Moreover, extensive optimization allowed us to understand the behavior of the ligands under different reaction conditions, indicating a tridentate ligand and *t*BuOH coordinating to the metal cation. It was found that copper gave the highest ee in the reaction, which is remarkable since it is normally used for the 1,4 addition of diethyl zinc to unsaturated carbonyl compounds.

4. Experimental

4.1. General experimental

All reactions were carried out in anhydrous solvents under nitrogen. All solvents were dried by standard procedures before being used in the reactions. ^{1}H NMR spectra were acquired with Bruker AC 200F (200 MHz) at ambient temperature. Chemical ^{13}C NMR spectra were recorded at ambient temperature with AC 200F (50 MHz) instruments and ^{19}F NMR spectra were recorded at ambient temperature with a Bruker AMX 400 (378 MHz) instrument. Chemical shifts are reported in ppm relative to tetramethylsilane as an internal standard. Mass spectra (ESI) were recorded with a Hewlett–Packard MS LC/MSD Series 1100 MSD instrument, while high-resolution mass spectra were measured with a Bruker Daltonik Tesla–Fourier Transform-Ion Cyclotron Resonance Mass Spectrometer. Elemental analyses were carried out by the Microanalytical Laboratory of the Institut für Pharmazeutische Chemie der Technische Universität Braunschweig with an Elemental Analyzer Model 1106 from Carlo Erba Instrumentazione. Infrared spectra were recorded with a Bruker Vektor 22 FTIR spectrometer, as KBr pellets in case of solid compounds and as thin films between NaCl plates in cases of oils and liquids. Melting points were taken with a Dr. Tottoli apparatus and are uncorrected.

4.2. Preparation of C_2 symmetric diamines

4.2.1. General procedure for the preparation of diamines by alkylation with dibromoethane

An amino alcohol (1.00 mmol) was added in to a dried flask under nitrogen. Dibromoethane (43 μL, 0.50 mmol) was added via syringe under nitrogen. The reaction mixture was heated at 100 °C for 16 h. The mixture was then cooled to room temperature. After dissolving the solid in water, the aqueous phase was washed with chloroform. The aqueous phase was basified with 2 M NaOH and the diamine was extracted with chloroform (3 × 5 mL). The combined organic fractions were dried (Na_2SO_4) and the solvent was evaporated under reduced pressure to give the bis-amino alcohol.

4.2.2. (−)-(1*R*,1′*R*,2*S*,2′*S*)-2,2′-(Ethane-1,2-diylbis(azanediyl))bis(1-phenylpropan-1-ol) 6

This compound was prepared from (−)-norephedrine (3.00 g, 19.84 mmol) and dibromoethane (0.85 mL, 9.92 mmol), after basification with NaOH as a yellow solid (3.18 g, 98%). Spectroscopic data are consistent with literature values.[16]

4.2.3. (−)-(2*S*,2′*S*)-2,2′-(Ethane-1,2-diylbis(azanediyl))bis(3-phenylpropan-1-ol) 7

This compound was prepared from (−)-(*S*)-2-amino-3-phenyl-1-propanol (0.30 g, 1.98 mmol) and dibromoethane (86.0 μL, 0.99 mmol), after basification with NaOH as a yellow solid (0.30 g, 93%). Spectroscopic data are consistent with literature values.[17]

4.2.4. (+)-(2*S*,2′*S*)-2,2′-(Ethane-1,2-diylbis(azanediyl))bis(2-phenylethanol) 8

This compound was prepared from (+)-(*S*)-phenylglycinol (0.30 g, 2.19 mmol) and dibromoethane (95.0 μL, 1.09 mmol), after basification with NaOH as a yellow oil (0.30 g, 92%). Spectroscopic data are consistent with literature values.[18]

4.2.5. General procedure for the preparation of diamines by ring opening of epoxides

To a stirred solution of chiral 1,2-diphenyl-1,2-ethanediamine (0.21 g, 1.0 mmol) in anhydrous ethanol (5 mL) was added epoxide (3.0 mmol) via a syringe dropwise under an inert atmosphere at room temperature. Upon complete addition, the mixture was heated at reflux for 46 h. After refluxing, the mixture was cooled to room temperature whereupon the solvent was evaporated to give a white solid. The solid was dissolved in water that was acidified to pH 2 with 2 M hydrochloric acid and the aqueous layer extracted with chloroform (3 × 5 mL) which was discarded. The aqueous layer was then basified to pH 11 with 2 M aqueous sodium hydroxide and the aqueous layer was again extracted with chloroform (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated, resulting in a white crystalline solid.

4.2.6. (−)-(*R*,*R*)-1,2-Diphenyl-*N*,*N*′-bis((*R*)-2-hydroxyethyl)-3-methyl)ethylenediamine 10

This amino alcohol was synthesized from (+)-(1*R*,2*R*)-1,2-diphenyl-1,2-ethanediamine (0.20 g, 0.94 mmol) and (+)-(*R*)-propylene oxide (0.20 mL, 2.83 mmol) by following the general procedure as a white crystalline solid (0.287 g, 93%). mp 119 °C. $[\alpha]_D^{22} = -30$

(*c* 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 7.07–6.94 (m, 10H), 3.80–3.70 (m, 2H), 3.63 (s, 2H) 2.43–2.16 (m, 4H), 0.98 (d, J = 5.4 Hz, 6H) ^{13}C NMR (50 MHz, $CDCl_3$) δ 140.7, 128.0, 127.7, 127.0, 68.3, 65.9, 54.3, 20.5. IR (KBr): 3303, 2961, 2909, 1646, 1454, 1126, 1051, 864, 772, 700, 625, 575 cm^{-1}. MS (ESI = 0 V): m/z = 351 [M+Na]. HRMS (ESI): calcd for $C_{21}H_{29}N_2O_2$ [M+H]: 329.2229; found 329.2229.

4.2.7. (+)-(*R,R*)-1,2-Diphenyl-*N,N*′-bis(2-hydroxy-2-methylpropyl)ethylenediamine 11

This amino alcohol was synthesized from (+)-(1*R*,2*R*)-1,2-diphenyl-1,2-ethanediamine (0.10 g, 0.47 mmol) and isobutylene oxide (0.13 mL, 1.41 mmol) by following the general procedure as a white crystalline solid (0.148 g, 90%). mp 123 °C. $[\alpha]_D^{22} = +13$ (*c* 0.5, MeOH); ^1H NMR (200 MHz, $CDCl_3$) δ 7.26–6.98 (m, 10H), 3.69 (s, 2H) 2.36 (s, 6H), 1.17 (s, 6H), 1.13 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 141.0, 128.0, 127.6, 127.0, 69.9, 69.6, 58.1, 27.4, 27.3. IR (KBr): 3302, 2962, 2907, 1455, 1405, 1164, 1127, 896, 845, 764, 699, 580 cm^{-1}. MS (ESI = 0 V): m/z (%) = 379 (70%) [M+Na], 357 (60) [M+H]. HRMS (ESI): calcd for $C_{21}H_{33}N_2O_2$ [M+H]: 357.2542; found 357.2542.

4.2.8. General procedure for preparation of imidazolinium salts

A bis-amino alcohol (1.00 mmol) was placed in a flask, and the counteranion source (typically NH_4BF_4, 1.00 mmol) and triethyl orthoformate (148 mg, 165 μL, 1.00 mmol) was added. The reaction vessel was flushed with nitrogen and sealed, and the mixture was heated to 120 °C for 5 h. After cooling, the mixture was dried under vacuum, in order to remove ethanol, formed during the reaction, to give the crude salt in high purity.

4.2.9. (−)-1,3-Bis[(1*S*,2*R*)-2-hydroxy-1-methyl-2-phenylethyl]imidazolinium tetrafluoroborate 12

This compound was prepared from **6** (500 mg, 1.52 mmol), NH_4BF_4 (156 mg, 1.52 mmol), and $CH(OEt)_3$ (250 μL, 1.52 mmol). The reaction mixture was heated to 120 °C in a sealed vessel for 5 h. After removing the ethanol, the crude was washed with hexane, diethyl ether, and dichloromethane giving the title compound as a white solid (481 mg, 74%). Spectroscopic data are consistent with literature values.[4c]

4.2.10. (−)-3-Bis-[(1*S*,2*R*)-2-hydroxy-1-methyl-2-phenyl-ethyl]-imidazolinium chloride 13

This compound was prepared from **6** (300 mg, 0.91 mmol), NH_4Cl (48.8 mg, 0.91 mmol), and $CH(OEt)_3$ (148 μL, 0.91 mmol). The reaction mixture was heated to 120 °C in a sealed vessel for 16 h. After removal of the solvent, the crude was washed with hexane, diethyl ether, and chloroform giving the title compound as a white crystalline solid (143 mg, 42%); mp 199 °C. $[\alpha]_D^{22} = -16$ (*c* 0.4, MeOH); ^1H NMR (200 MHz, CD_3OD) δ 7.90 (s, 1H), 7.17–7.08 (m, 10H), 4.61 (d, J = 4.4 Hz, 2H), 3.71–3.59 (m, 6H), 1.07 (d, J = 7.0 Hz, 6H). ^{13}C NMR (50 MHz, CD_3OD) δ 156.3, 140.6, 128.1, 127.6, 126.0, 73.7, 59.4, 47.0, 11.9; IR (KBr) 3298, 3223, 1246, 1148, 1050, 995, 744, 698 cm^{-1}. MS (ESI = 0 V): m/z (%) = 339 [M]. HRMS (ESI): calcd for $C_{21}H_{27}N_2O_2^+$ 339.2073; found 339.2073.

4.2.11. (−)-1,3-Bis-[(1*S*,2*R*)-2-hydroxy-1-methyl-2-phenyl-ethyl]-imidazolinium bromide 14

This compound was prepared from **6** (100 mg, 0.30 mmol), NH_4Br (32.2 mg, 0.33 mmol), and $CH(OEt)_3$ (56 μL, 0.34 mmol). The reaction mixture was heated to 120 °C in a sealed vessel for 12 h. After the removal of solvent, the crude was washed with hexane and diethyl ether giving the title compound as a yellow crystalline solid (84 mg, 66%); mp 148 °C. $[\alpha]_D^{22} = -17$ (*c* 1.0, MeOH); ^1H NMR (200 MHz, $(CD_3)_2CO$) δ 8.51 (s, 1H), 7.28–7.04 (m, 10H), 5.68 (d, J = 4.0 Hz, 2H), 5.10 (br s, 2H) 4.09–3.86 (m, 6H), 0.85 (d, J = 7.0 Hz, 6H). ^{13}C NMR (50 MHz, $(CD_3)_2CO$) δ 157.2, 142.3, 128.9, 127.7, 126.8, 72.3, 60.3, 48.8, 11.1. IR (KBr) 3344, 1647, 1266, 1151, 753, 704 cm^{-1}: MS (ESI = 0 V): m/z (%) = 339 [M]. HRMS (ESI): calcd for $C_{21}H_{27}N_2O_2^+$ 339.2073; found 339.2070.

4.2.12. (−)-3-Bis-[(1*S*,2*R*)-2-hydroxy-1-methyl-2-phenyl-ethyl]-imidazolinium iodide 15

This compound was prepared from **6** (200 mg, 0.61 mmol), NH_4I (88.3 mg, 0.61 mmol), and $CH(OEt)_3$ (100 μL, 0.61 mmol). The reaction mixture was heated to 120 °C in a sealed vessel for 5 h. After the removal of the solvent, the crude was washed with hexane and diethyl ether giving the title compound as a white crystalline solid (189 mg, 67%). Compound **15** was recrystallized in acetone for X-ray crystallography. mp 184 °C. $[\alpha]_D^{22} = -4$ (*c* 0.3, MeOH); ^1H NMR (200 MHz, CD_3OD) δ 7.90 (s, 1H), 7.16–7.08 (m, 10H), 4.61 (s, 2H), 3.72–3.60 (m, 6H), 1.00 (d, J = 7.0 Hz, 6H). ^{13}C NMR (50 MHz, CD_3OD) δ 157.8, 142.1, 129.6, 129.1, 127.5, 75.2, 60.9, 47.2, 13.5. IR (KBr): 3438, 3236, 1650, 1496, 1262, 1138, 1029, 1016, 753, 704 cm^{-1}. MS (ESI = 0 V): m/z = 339 [M]. HRMS (ESI): calcd for $C_{21}H_{27}N_2O_2^+$ 339.2073; found 339.2072.

4.2.13. (−)-1,3-Bis[(*S*)-1-(hydroxymethyl)-2-methylbenzyl]-imidazolinium tetrafluoroborate 16

This compound was prepared from **7** (200 mg, 0.61 mmol), NH_4BF_4 (68.6 mg, 0.67 mmol), and $CH(OEt)_3$ (109 μL, 0.67 mmol). The reaction mixture was heated to 120 °C in a sealed vessel for 5 h. After removal of the solvent, the crude was washed with hexane and diethyl ether giving the title yellow gummy compound (147 mg, 57%). $[\alpha]_D^{22} = -71$ (*c* 1.0, $CHCl_3$); ^1H NMR (200 MHz, $(CD_3)_2CO$) δ 8.16 (s, 1H), 7.20–7.14 (m, 10H), 3.57–3.95 (m, 12H), 2.84 (m, 4H). ^{13}C NMR (50 MHz, $(CD_3)_2CO$) δ 158.6, 137.9, 129.9, 129.6, 127.7, 62.8, 61.3, 46.9, 35.6. IR (NaCl): 3054, 2987, 1422, 1265, 896, 739 cm^{-1}. MS (ESI = 0 V): m/z = 339 [M]. HRMS (ESI): calcd for $C_{21}H_{27}N_2O_2^+$ 339.2073; found 339.2075.

4.2.14. (+)-1,3-Bis[(*S*)-1-(hydroxymethyl)-2-methylphenyl]-imidazolinium tetrafluoroborate 17

This compound was prepared from **8** (100 mg, 0.33 mmol), NH_4BF_4 (53.8 mg, 0.49 mmol), and $CH(OEt)_3$ (83 μL, 0.49 mmol). The reaction mixture was heated to 120 °C in a sealed vessel for 16 h. After the removal of the solvent, the crude was washed with hexane and diethyl ether giving a yellow oil (87 mg, 66%). $[\alpha]_D^{22} = +65$ (*c* 0.65, MeOH); ^1H NMR (200 MHz, $(CD_3)_2CO$) δ 8.74 (s, 1H), 7.33–7.24 (m, 10H), 4.97–4.91 (m, 2H), 4.54 (s, br, 2H), 3.90–3.82 (m, 8H). ^{13}C NMR (50 MHz, $(CD_3)_2CO$) δ 158.5, 135.5, 129.9, 129.7, 128.7, 64.9, 62.1, 47.4. IR (NaCl): 3054, 2987, 1422, 1265, 896, 739 cm^{-1}. MS (ESI = 0 V): m/z = 311 [M]. HRMS (ESI): calcd for $C_{19}H_{23}N_2O_2^+$ 311.1760; found 311.1761.

4.2.15. (+)-(4*R*,5*R*)-Diphenyl-1,3-bis((*R*)-2-hydroxyethyl)-3-methyl)-imidazolinium tetrafluoroborate 18

This compound was prepared from **10** (104 mg, 0.32 mmol), NH_4BF_4 (35.8 mg, 0.35 mmol), and $CH(OEt)_3$ (58 μL, 0.35 mmol). The reaction mixture was heated to 120 °C in a sealed vessel for 5 h. After the removal of solvent, the crude was washed with hexane and diethyl ether giving the white crystalline compound (143 mg, 80%). mp 118 °C. $[\alpha]_D^{22} = -51$ (*c* 1.2, $CHCl_3$); ^1H NMR (200 MHz, $(CD_3)_2CO$) δ 8.72 (s, 1H), 7.44–7.33 (m, 10H), 4.48 (d, J = 5.6Hz, 2H), 4.01 (s, br, 2H), 3.52–3.06 (m, 4H), 1.03 (d, J = 6.2 Hz, 6H). ^{13}C NMR (50 MHz, $(CD_3)_2CO$) δ 160.1, 136.9, 130.4, 128.6, 73.4, 63.2, 53.5, 20.9. IR (KBr): 3346, 2971, 1640, 1458, 1211, 1083, 763, 702, 625, 522 cm^{-1}. MS (ESI = 0 V): m/z = 339 [M]. HRMS (ESI): calcd for $C_{21}H_{27}N_2O_2^+$ 339.2073; found 339.2064.

4.2.16. (+)-(4*R*,5*R*)-Diphenyl-1,3-bis(2-hydroxy-2-methylpropyl)-imidazolinium tetrafluoroborate 19

This compound was prepared from **11** (150 mg, 0.42 mmol), NH_4BF_4 (47.5 mg, 0.46 mmol), and $CH(OEt)_3$ (78 μL, 0.46 mmol). The reaction mixture was heated to 120 °C in a sealed vessel for 12 h. After removal of the solvent, the crude was washed with hexane and diethyl ether to give a white crystalline compound (170 mg, 90%). mp 108 °C. $[\alpha]_D^{22} = +150$ (*c* 1.1, MeOH); ^{1}H NMR (200 MHz, $(CD_3)_2CO$) δ 8.84 (s, 1H), 7.44–7.33 (m, 10H), 5.43 (s, 2H), 3.68–3.61 (m, 4H) 3.14 (s, 1H), 3.07 (s, 1H) 1.18 (s, 6H), 1.10 (s, 6H) ^{13}C NMR (50 MHz, $(CD_3)_2CO$) δ 157.2, 142.3, 128.9, 127.7, 126.8, 72.3, 60.3, 48.8, 11.1. IR (KBr): 3355, 2976, 1638, 1457, 1379, 1159, 1061, 763, 702, 625 cm^{-1}. MS (ESI = 0 V): *m*/*z* = 367 [M]. HRMS (ESI): calcd for $C_{23}H_{31}N_2O_2^+$ 367.2386; found 367.2383.

4.2.17. General procedure for Et_2Zn addition to aldehydes

An imidazolinium salt (0.017 mmol) and KO*t*Bu (6.1 mg, 0.051 mmol) were placed in a dry Schlenk flask and dry toluene (1 mL) was added. After stirring the mixture for 30 min, $Cu(OTf)_2$ (3.2 mg, 0.009) mmol) was added and left to stir for 1 h. Aldehyde (0.35 mmol) was added and the mixture was stirred for 5 min. Then Et_2Zn (0.5 mL of a 1 0 M solution in hexane) was added dropwise. The mixture was stirred at rt for 46 h, quenched by the addition of 1 M HCl (1 mL), and extracted with Et_2O (3 × 5 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure to give the crude product, which was purified by flash column chromatography (petroleum ether/ethyl acetate, 9:1) to give the corresponding alcohol **21**.

4.2.18. (*R*)-1-(1-Naphthyl)-propan-1-ol 21

$[\alpha]_D^{22} = +35$ (*c* 0.30, $CHCl_3$). For catalysts, bases, yields, and ee see Tables 1–7. Spectroscopic data were consistent with literature values.[4] 73% ee (*R*) by HPLC analysis [OD–H; *i*PrOH/hexane, 5:95; 0.4 mL min^{-1}; $t_1(S) = 35.7$ min, $t_2(R) = 67.6$ min].

4.2.19. (*R*)-1-(2-Naphthyl)-propan-1-ol

Yield = 57%; $[\alpha]_D^{22} = +29$ (*c* 0.50, $CHCl_3$). 50% ee (*R*) by HPLC analysis [OD-H; *i*PrOH/hexane, 10:90; 1.0 mL min^{-1}; $t_1(S) = 10.0$ min, $t_2(R) = 11.0$ min]. Spectroscopic data were consistent with literature values.[4]

4.2.20. (*R*)-1-Phenyl-1-propanol

Yield = 39%; $[\alpha]_D^{22} = +36$ (*c* 0.50, $CHCl_3$). 75% ee (*R*) by HPLC analysis [OD-H; *i*PrOH/hexane, 5:95; 1.0 mL min^{-1}; $t_1(R) = 8.0$ min, $t_2(S) = 9.0$ min]. Spectroscopic data were consistent with literature values.[4]

4.2.21. (*R*)-1-(4-Chlorophenyl)-1-propanol

Yield = 60%; $[\alpha]_D^{22} = +28$ (*c* 1.33, $CHCl_3$). 78% ee (*R*) by HPLC analysis [OD-H; *i*PrOH/hexane, 2.5:97.5; 1.0 mL min^{-1}; $t_1(S) = 11.8$ min, $t_2(R) = 12.5$ min]. Spectroscopic data were consistent with literature values.[4]

4.2.22. (*R*)-1-(4-Methylphenyl)-1-propanol

Yield = 50%; $[\alpha]_D^{22} = +32$ (*c* 1.0, $CHCl_3$). 71% ee (*R*) by HPLC analysis [OD–H; *i*PrOH/hexane, 0.1:99.9; 1.0 mL min^{-1}; $t_1(R) = 67.7$ min, $t_2(S) = 85.0$ min]. Spectroscopic data were consistent with literature values.[4]

4.3. NMR Experiments with Mosher's acid salt

4.3.1. Preparation of racemic potassium Mosher's carboxylate

Racemic Mosher's acid (302 mg, 1.29 mmol) was dissolved in water (1 mL) and a solution of KOH (72 mg, 1.29 mmol) in water (3 mL) was added. The mixture was stirred at rt for 15 min and water was removed under reduced pressure. The remaining solid was further dried under high vacuum to give the potassium Mosher's carboxylate salt as a white solid (351 mg, quant).

4.3.2. NMR experiment with the racemic Mosher's acid salt

The Mosher's acid salt (1 mmol) and the corresponding imidazolinium salt (1 mmol) were dissolved in acetone-d_6 and the ^{1}H NMR and ^{19}F NMR spectra were recorded at rt. For results see Table 8.

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