Cooperative Al(Salen)-Pyridinium Catalysts for the Asymmetric Synthesis of trans-Configured β-Lactones by [2+2]-Cyclocondensation of Acylbromides and Aldehydes: Investigation of Pyridinium Substituent Effects

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Abstract: The trans-selective catalytic asymmetric formation of β-lactones constitutes an attractive surrogate for anti-aldol additions. Recently, we have reported the first catalyst which is capable of forming trans-β-lactones with high enantioselectivity from aliphatic (and aromatic) aldehyde substrates by cyclocondensation with acyl bromides. In that previous study the concepts of Lewis acid and organic aprotic ion pair catalysis were combined in a salen-type catalyst molecule. Since a pyridinium residue on the salen periphery is essential for high trans- and enantioselectivity, we were interested in the question of whether substituents on the pyridinium rings could be used to further improve the catalyst efficiency, as they might have a significant impact on the effective charges within the heterocycles. In the present study we have thus compared a small library of aluminum salen/bispyridinium catalysts mainly differing in the substituents on the pyridinium residues. As one result of these studies a new catalyst was identified which offers slightly superior stereoselectivity as compared to the previously reported best catalyst. NBO calculations have revealed that the higher stereoselectivity can arguably not be explained by the variation of the effective charge.
Keywords: aluminum; cooperative catalysis; ion pair catalysis; ketene; 2-oxetanone; pyridinium

1. Introduction

β-Lactones (systematic name 2-oxetanones), are attracting the interest of scientists for mainly two reasons: (1) a number of natural and synthetic β-lactones are known to act as specific enzyme inhibitors [1–4]. Tetrahydrolipstatin (Xenical®, orlistat), for instance, is used for the treatment of obesity and has recently received renewed attention due to the finding that it is capable of specifically inhibiting fatty acid synthase (FAS-TE), an approved drug target for cancer treatment [5–7]; (2) as a result of their inherent ring strain [8] β-lactones are useful synthetic building blocks. Ring opening with hard nucleophiles offers the possibility to a divergent access to aldol products [9–13], whereas treatment with soft nucleophiles can be utilized to synthesize β-functionalized carboxylic acid derivatives [9,10,12]. In both cases the stereoinformation of the β-lactone ring can be completely transferred into the ring opening product and the acyl-oxygen bond cleavage with hard nucleophiles typically proceeds with retention of configuration. Cis- and trans-configured β-lactones thus behave as masked and activated syn- and anti-aldol equivalents, respectively.

The catalytic asymmetric formation of ester or amide aldol derivatives via β-lactones is not only attractive for the high divergency of accessible aldol structures, but also for the high atom-economy of the overall process, since no preformation of silylketene acetals or related nucleophiles is necessary [14]. Instead an acyl halide is usually used to generate a ketene in situ as a reactive intermediate by dehydrohalogenation induced by a base [15–19]. The ketene then undergoes a cycloaddition with an aldehyde, either catalyzed by a Lewis acid [20–29] or by a Lewis base [30–37] or by a combination of both [38–42]. Particularly appealing appears the development of trans-selective catalytic asymmetric β-lactone formations as a surrogate for anti-aldol additions, since for the latter reaction type only few efficient catalytic asymmetric protocols exist to date [43–46].

Unfortunately, the catalytic asymmetric [2+2] cycloaddition approach of ketenes and aldehydes provides in general only cis-diastereomers as the major products [47–49]. In 2008, Calter et al. described the first catalytic enantioselective access to trans-configured β-lactones by a formal [2+2] cycloaddition [39]. However, this method is so far limited to the use of aromatic aldehydes, whereas the large majority of bioactive compounds such as tetrahydrolipstatin carry an aliphatic chain at the 4-position of the 3,4-disubstituted 2-oxetanone core [50–52].

Recently, we have reported a conceptually new approach which is applicable to both aliphatic and aromatic aldehydes [53,54]. Aluminum salen complexes carrying aprotic organic ion pairs in the periphery of the salen core were investigated. The most useful described catalyst 4aA in terms of enantioselectivity and reactivity was equipped with two pyridinium bromide functionalities connected via benzylic methylene linkers to the ortho-position of the phenolate O atoms (3/3’-position, Scheme 1).
**Scheme 1.** Application of bispyridinium Al-salen complex 4aA for the *trans*-selective catalytic asymmetric synthesis of 3,4-disubstituted 2-oxetanones 3 [53,54].

By the choice of a Lewis acid with only one available coordination site a cyclic Zimmerman-Traxler-type transition state leading to the *cis*-configured product would be avoided. Our catalyst combines the cooperative action of a Lewis acid and of an aprotic onium halide ion pair Q^+X^- (in the case of 4aA pyridinium bromide), the latter being arguably used to generate the acyl halide enolate 6 in the catalyst sphere (Scheme 2). Q^+ might stabilize the otherwise unstable enolate [55–58] by ion pair formation to increase the lifetime of the enolate species and to direct the enolate to the aldehyde–Lewis acid complex 7 via an open transition state 8 adopting a staggered conformation around the generated C–C bond [54]. In the reactive conformation the disubstituted enolate C-1 atom should be oriented *gauche* to the aldehyde function’s H atom and the C-2-enolate-H atom would be expected to direct toward the sterically demanding Lewis acid-ligand complex, so as to minimize repulsive interactions. The initial aldol adduct could then cyclize to form the heterocyclic product 3.

**Scheme 2.** Rationale of the catalyst design for the *trans*-selective catalytic asymmetric synthesis of 3,4-disubstituted 2-oxetanones 3 [54].

The general catalyst principle, utilizing the cooperative action of a Lewis acid and an aprotic organic ion pair, is illustrated in Figure 1.
Figure 1. Cooperative action of a Lewis acid and an aprotic organic ion pair within a single catalyst entity: the Lewis-acid serves to activate an electrophile, whereas the \textit{in situ} generated anionic nucleophile forms an ion pair with an aprotic organic cation (Q\textsuperscript{+}), which stabilizes and directs the nucleophile towards the electrophile [53,54].

Salen ligands were chosen due to their modular nature and their ready and rapid accessibility [59–61]. As a result of the proposed stabilizing electrostatic interaction of Q\textsuperscript{+} and the acyl halide enolate 6, the charge density of Q\textsuperscript{+} was expected to play a decisive role on the reaction outcome, in particular in terms of \textit{trans}/\textit{cis}-diastereoselectivity and enantioselectivity, because neutral substituents at the 3/3\texttextsuperscript{'}-position lead predominantly to the undesired almost racemic \textit{cis}-diastereomer [53,54].

In our continuing efforts to utilize ketenes [62–65] and related reactive intermediates [66–71] for a rapid and practical access to chiral building blocks we have therefore investigated a series of Al-salen catalysts 4 (Figure 2) carrying different substituents Z on the pyridinium moiety (acting as Q\textsuperscript{+}) to study electronic effects on the catalyst performance. The results are compared to NBO calculations which have revealed the charge distribution within the pyridinium rings.

Figure 2. Structure of the investigated aluminum-bispyridinium catalysts 4 carrying different residues R\textsuperscript{1} and pyridinium substituents Z.

2. Results and Discussion

2.1. Ligand Preparation

In our previous studies we found that a major limitation of catalyst 4aA results from its relatively low solubility at low reaction temperatures. For that reason we were also interested in derivatives in which the phenolic \textit{t}-Bu-substituents have been formally replaced by \textit{n}-pentyl groups in order to
increase the rotational freedom of the alkyl substituents $R^1$ and hence the catalyst solubility. To investigate the steric influence of the $R^1$ substituent on the stereoselectivity, $R^1 = \text{Me}$ was also studied. Based on our previously established protocol [53,54] the ligands 14 could be prepared via a general 4-step procedure (Scheme 3). Phenols 9 were formylated with paraformaldehyde in the presence of NEt$_3$ and MgCl$_2$ [72,73]. A subsequent bromomethylation of 10 with paraformaldehyde, HBr and catalytic amounts of sulfuric acid gave benzyl bromides 11 in high yields [74]. The latter were then treated with different commercially available pyridine derivatives in a nucleophilic substitution reaction in acetonitrile (Table 1). The pyridinium salts 12 could be isolated and purified by precipitation and washing with diethyl ether. Nucleophilic substitution proceeded smoothly in most cases. Only the 4-Cl derivative 12bH was prone to releasing the starting pyridine in the back reaction (entry 11). This is ascribed to the electron-withdrawing character of the Cl-substituent, which reduces the nucleophilicity of the pyridine N and leads to a more potent leaving group. The chloro- and iodo-substituents at the 4-position of the pyridine were also found to be sensitive to a partial halogen exchange with bromide (entries 10 and 11).

**Scheme 3.** Synthesis of a salen ligand library 14 with different residues $R^1$ and $R^2$.

Treatment of two equivalents of the corresponding aldehyde 12 with enantiopure ($R,R$)-1,2-diaminocyclohexane (13) in EtOH at room temperature for 15 h in the presence of 4 Å molecular sieves provided the salen ligands 14 (Scheme 3 and Table 1). The diimine formation from aldehydes 12 usually furnished 14 in high yields, with the exception of the 4-chloro- and the 4-cyanopyridine derivatives 14bH and 14bI (entries 11 and 12). In both cases none of the desired ligands was obtained, again arguably due to the pronounced leaving group properties of the more electron poor pyridines.
Table 1. Preparation of pyridinium aldehydes 12 and the ionic salen ligands 14.

| Entry | R<sup>1</sup> | R<sup>2</sup> | 12 | Yield 12 [%]<sup>a</sup> | 14 | Yield 14 [%]<sup>a</sup> |
|-------|--------------|--------------|----|------------------|----|------------------|
| 1     | tBu          | ![Pyridine](image) | 12aA | 92               | 14aA | 100             |
| 2     | n-Pent       | ![Pyridine](image) | 12bA | 62               | 14bA | 91              |
| 3     | Me           | ![Pyridine](image) | 12cA | 79               | 14cA | 84              |
| 4     | t-Bu         | ![Pyridine](image) | 12aB | 67               | 14aB | 89              |
| 5     | n-Pent       | ![Pyridine](image) | 12bB | 91               | 14bB | 93              |
| 6     | n-Pent       | ![Pyridine](image) | 12bC | 96               | 14bC | 82              |
| 7     | n-Pent       | ![Pyridine](image) | 12bD | 54               | 14bD | 91              |
| 8     | n-Pent       | ![Pyridine](image) | 12bE | 47               | 14bE | 86              |
| 9     | n-Pent       | ![Pyridine](image) | 12bF | 81               | 14bF | 92              |
| 10    | n-Pent       | ![Pyridine](image) | 12bG | 65               | 14bG | 77              |
| 11    | n-Pent       | ![Pyridine](image) | 12bH | 29               | 14bH | 0               |
| 12    | n-Pent       | ![Pyridine](image) | 12bI | 80               | 14bI | 0               |

<sup>a</sup> Yield of isolated product.
2.2. Catalysis

To examine the impact of the different pyridinium residues $R^2$, all accessible ligands were investigated in the cyclocondensation of propionylbromide (1A) and dihydrocinnamaldehyde (2a, Table 2). Due to the air and moisture sensitivity of the investigated aluminum complexes 4, the catalysts were generated in situ from 10 mol% of the corresponding ligand 14 and 10 mol% AlMe$_3$ in CH$_2$Cl$_2$ at room temperature. We have previously already reported that the yields of $\beta$-lactone formation are generally higher with isolated catalysts, but isolation has only a small impact on enantio- and diastereoselectivity [53,54]. The catalyst solution was cooled to −70 °C and treated with both reagents and finally with iPr$_2$NEt. After stirring for 24 h at −70 °C, the reaction was terminated by addition of hydrochloric acid.

Table 2. Investigation of salen ligands 14 carrying different pyridinium moieties $R^2$ in the cyclocondensation reaction of propionylbromide (1A) and dihydrocinnamaldehyde (2a) $^a$.

| Entry | 14 | $R^1$ | $R^2$ | Conversion [%] $^b$ | Yield 3Aa [%] $^b$ | $dr$ 3Aa [trans/cis] $^c$ | ee 3Aa [%] $^d$ |
|-------|----|------|------|-----------------|-----------------|-------------------|-------------|
| 1     | 14aA | t-Bu | | >95 | 91 | 93:7 | 89 |
| 2     | 14bA | n-Pent | | >98 | 98 | 93:7 | 88 |
| 3     | 14cA | Me | | n.d. | 71 | 91:9 | 88 |
| 4     | 14aB | t-Bu | | 71 | 29 | 97:3 | 89 |
Table 2. Cont.

| Entry | 14 | R¹ | R² | Conversion [%] b | Yield 3Aa [%] b | dr 3Aa [trans/cis] c | ee 3Aa [%] d |
|-------|----|----|----|-----------------|-----------------|----------------------|-------------|
| 5     | 14bB | n-Pent |     | 88              | 60              | 97:3                 | 90          |
| 6     | 14bC | n-Pent |     | 75              | 56              | 92:8                 | 80          |
| 7     | 14bD | n-Pent |     | 82              | 39              | 88:12                | 80          |
| 8     | 14bE | n-Pent |     | 62              | 38              | 88:12                | 77          |
| 9     | 14bF | n-Pent |     | 73              | 37              | 94:6                 | 82          |
| 10    | 14bG | n-Pent |     | 78              | 45              | 92:8                 | 81          |

a The catalyst was prepared in situ from 14 and AlMe₃; b Determined by ¹H-NMR using mesitylene as standard; c Determined by ¹H-NMR; d Determined by HPLC on a chiral stationary phase.

In most cases, conversion of the aldehyde was good and yields of β-lactone 3Aa were moderate to good. Catalysts generated from 14bA and 14bB with R¹ = n-Pent (entries 2 and 5) resulted in higher conversions and yields than their direct counterparts derived from 14aA and 14aB, respectively, carrying a t-Bu residue R¹ (entries 1 and 4). This is attributed to a higher solubility in CH₂Cl₂ at −70 °C with a more flexible alkyl chain [75]. 14cA with R¹ = Me resulted in poor solubility, explaining the lower yield (entry 3) compared to the results with 14aA and 14bA, respectively (entries 1 and 2). For that reason additional Me derivatives were not studied.

Interestingly, the nature of R¹ was found to have only a minor effect on both enantio- and diastereoselectivity (compare entries 1, 3, 4 and 5), whereas most salen catalyzed reactions require enhanced steric demand at that position for an efficient transfer of chirality [76]. In the present case, the stereoselectivity is much more dependent on the pyridine substituents. The best combination of enantioselectivity (ee = 90%) and diastereoselectivity (trans/cis = 97:3) was attained with ligand 14bB carrying a 4-Me substituent as a weak σ-donor on the pyridine ring (entry 5). This ligand also allowed for a useful product yield.

Increasing the steric demand of the pyridine by a 4-t-Bu substituent had only a minor impact on the reactivity, but both the dr (92:8) and the ee (80%) were negatively affected (entry 6). Reduced
diastereoselectivity data were also noticed with a 3,5-dimethyl substitution pattern on the pyridine (entry 7) or with a quinoline residue (entry 8).

The DMAP derivative 14bF (entry 9) carrying the potent \( \pi \)-donor group NMe\(_2\) at the pyridine 4-position and the derivative 14bG (entry 10) carrying an iodo atom as a weak \( \sigma \)-acceptor at the 4-position resulted in similar reactivity and stereoselectivity. For 14bF, a lower diastereoselectivity was expected as a consequence of the +M-effect which should result in a wider charge distribution thereby weakening the postulated contact ion pair with the acyl halide enolate 6. Consequently, \( \sigma \)-acceptors like in 14bG should result in a more efficient ion pair formation and improved stereoselectivity, but steric effects as well as the poor solubility of 14bG even at room temperature might have overwritten this effect. Unfortunately, it appears to be difficult to study the effect of \( \sigma \)-acceptors in ligands 14, as they result in a lower stability of the catalysts.

In contrast, the 4-Me group does not only lead to an improved catalyst stability (the ligand 14bB can be stored for at least two months at room temperature with no decomposition detected) and solubility, but might also have a positive effect on a uniform reactive conformation of the generated acyl halide enolate, whereas larger residues might hamper an efficient ion pair formation of the enolate and the pyridinium residue.

The most stereoselective catalyst 4bB was applied to different substrates (Table 3). For the investigated aldehydes and acyl bromides 4bB gave always slightly higher enantioselectivities compared to our previously reported system 4aA.

**Table 3.** Asymmetric synthesis of trans-configured \( \beta \)-lactones 3 catalyzed by the aluminum bis-picolinium catalyst 4bB.

| Entry | 1 | R\(^1\) | 2 | R\(^2\) | 3 | Yield [%] \(^a\) | dr [trans/cis] \(^b\) | ee [%] \(^c\) |
|-------|---|--------|---|--------|---|---------------|-----------------|----------|
| 1 \(^d\) | 1A | Me | 2a | (CH\(_2\))\(_2\)Ph | 3Aa | 60 | 97:3 (97:3) | 90 (88) |
| 2 \(^e\) | 1A | Me | 2a | (CH\(_2\))\(_2\)Ph | 3Aa | 69 | 97:3 (97:3) | 90 (88) |
| 3 \(^d\) | 1A | Me | 2b | Et | 3Ab | 59 | 98:2 (95:5) | 90 (87) |
| 4 \(^d\) | 1A | Me | 2c | Ph | 3Ac | 37 | 98:2 (94:6) | 96 (91) |
| 5 \(^d\) | 1B | n-Pr | 2a | (CH\(_2\))\(_2\)Ph | 3Ba | 59 | 99:1 (98:2) | 95 (94) |

\(^a\) Yield of isolated product; \(^b\) Diastereomeric ratio determined by \(^1\)H-NMR (data in brackets refer to the reported data obtained with 10 mol% catalyst 4aA); \(^c\) Determined by HPLC on a chiral stationary phase (data in brackets refer to the reported data obtained with 10 mol% catalyst 4aA); \(^d\) The catalyst was formed in situ; \(^e\) The catalyst was isolated prior to use.
Moreover, the trans-selectivity was equal (entries 1 and 2) or better (entries 3 and 5) than with catalyst 4aA. Entry 2 shows that improved yields can be obtained with the isolated catalyst 4bB. However, the more convenient protocol with in-situ catalyst formation allows for similar diastereo- and enantioselectivity (compare entries 1 and 2). The highest enantioselectivity was attained with the aromatic benzaldehyde (entry 4, ee = 96%), but the yield is significantly lower than for aliphatic aldehydes. This is mainly a consequence of the marked sensitivity towards elimination of 4-aryl substituted 2-oxetanones explaining a partial decomposition during the workup [77].

2.3. Mechanistic and Theoretical Investigations

Reactions catalyzed by salen complexes are known to proceed in several cases via bimetallic reaction pathways [78]. As part of our programme on bimetallic cooperative catalysis [79–82], we were therefore interested if two salen units might also cooperate to form the β-lactone products 3. In that case the presence of a non-linear effect (NLE) would be expected [78,83]. The absence of a NLE in the present case (Figure 3) indicates that a major product formation pathway involving two salen molecules is most likely no realistic scenario. Our mechanistic considerations thus focus on reaction pathways involving a single catalyst molecule.

Figure 3. Investigation of a potential nonlinear effect for the formation of 3Ad catalyzed by 4bA.

As mentioned above, we have previously shown that a cationic residue on the salen periphery is essential for high trans-selectivity, but also for high enantioselectivity and reactivity [53,54]. In the case of standard Al-salen complexes carrying a H atom or an isobutyl residue at the 3/3’-position, reactivity was poor and almost racemic product was formed favoring the cis-isomer. With a t-Bu residue no product was formed at all. In the initial study a pyridinium residue was found to be superior
compared to ammonium residues [53,54]. We have tentatively explained this preference by a more efficient contact ion pair formation of the planar enolate moiety with the planar pyridinium system as compared to tetrahedral ammonium moieties.

As the positive charge of the substituent at the 3/3’-position is essential for a successful reaction outcome, we were interested in the effective charges for the derivatives described above. For that reason we accomplished a series of NBO analyses using the MOLPRO package of ab initio programmes [84]. For the electronic structure calculations we chose density functional theory in combination with a double-ζ basis set, i.e., B3LYP/cc-pVDZ. Our original idea was that an acceptor substituent in the 4-position of the pyridinium ring might amplify the effect of the positive charge and could further stabilize the contact ion pair. In agreement with the literature [85], our calculations revealed a negative partial charge for the nitrogen atoms, for both tetramethylammonium and pyridinium cation systems (see Table 4). The positive partial charges in the tetramethylammonium reference are distributed over the nine hydrogen atoms. In contrast the pyridinium cation has positive partial charges on the α-carbon atoms, which might stabilize the enolate in the proposed contact ion pair more efficiently than in the case of quaternary ammonium cations, since the positive charge is wider distributed in the latter case. Pyridinium derivatives with substituents in the 4-position give nearly identical partial charges for the nitrogen and the α-carbon atoms as the parent system with a H atom in 4-position. Only the partial charge of the carbon in the 4-position shows a noticeable change on substitution.

**Table 4. Results of the NBO analysis.**

| atom     | charge | atom     | charge | atom     | charge | atom     | charge |
|----------|--------|----------|--------|----------|--------|----------|--------|
| N        | −0.36  | C (1)    | +0.11  | C (1)    | +0.12  | C (1)    | +0.11  |
| C        | −0.41  | N (2)    | −0.35  | N (2)    | −0.36  | N (2)    | −0.36  |
| H        | +0.25  | C (3)    | +0.11  | C (3)    | +0.11  | C (3)    | +0.10  |
|          |        | C (4)    | −0.22  | C (4)    | −0.24  | C (4)    | −0.22  |
|          |        | C (5)    | −0.12  | C (5)    | +0.02  | C (5)    | +0.07  |
|          |        | C (6)    | −0.22  | C (6)    | −0.24  | C (6)    | −0.23  |
|          |        | C (7)    | −0.41  | C (7)    | −0.40  | C (7)    | −0.41  |
|          |        | H (8)    | +0.26  | H (8)    | +0.26  | H (8)    | +0.26  |
|          |        | H (9)    | +0.28  | H (9)    | +0.29  | H (9)    | +0.27  |
|          |        | H (10)   | +0.27  | Cl (10)  | +0.14  | C (10)   | −0.67  |
|          |        | H (11)   | +0.28  | H (11)   | +0.29  | H (11)   | +0.27  |
|          |        | H (12)   | +0.26  | H (12)   | +0.26  | H (12)   | +0.26  |
|          |        | H (13–15)| +0.25  | H (13–15)| +0.25  | H (13–15)| +0.25  |
|          |        |          |        |          |        |          |        |
Exemplarily, the 4-chloropyridinium cation is shown in Table 4 as an example of a $\sigma$-acceptor substituent and the 4-methylpyridinium cation bearing a $\sigma$-donor substituent. Hence the most important effects of the substituents are presumably: (1) the (de)stabilization of the bond between the pyridinium and the salen framework, since electron acceptors result in a higher leaving group tendency of the corresponding pyridine, whereas donor substituents have the opposite effect, and (2) the steric influence on the enolate.

For the cooperative contact ion pair/Lewis acid activation two reaction pathways appear to be feasible (Scheme 4), both leading to the observed absolute and relative $\beta$-lactone configurations. The two reaction mechanisms differ in the reactive conformations of the coordinated aldehyde and in the pyridinium unit involved. In path A presented in Scheme 4, the aldehyde group’s H atom is expected to point toward the C=N imine bond in 15 connected to phenolate ring A. Pyridinium ring A forms the reactive contact ion pair with the acylbromoenolate. The depicted aldehyde conformation appears to be required to get the aldehyde in close distance to the reactive enolate in a transition state adopting the above proposed staggerd conformation (see Scheme 2) to form the trans-$\beta$-lactone with a (3S,4S)-configuration.

**Scheme 4.** Two plausible reaction pathways via cooperative contact ion pair directed Lewis acid activation leading to the observed absolute and relative configuration of $\beta$-lactones 3.
In path B the same aldehyde H atom would point away from the chiral salen backbone. To form the product with the observed absolute configuration again the Re-face of the aldehyde has to react and this would require the action of the other pyridinium moiety B.

We favor this scenario because the repulsive interactions of the aldehyde and the salen core would be minimized. An aldehyde conformation like in path B is often hampered in salen-complex catalyzed reactions by the presence of tBu groups at the 3/3'-position [76,86]. However, the aldehyde conformation in path A appears more unfavorable in the present case given the folding of chiral salen metal complexes derived from trans-1,2-diaminocyclohexane which describes the ligand deviation from a planar arrangement [87–89]. In the present case phenolate ring B is expected, based on literature precedent for related Al salen complexes [90], to fold downward toward the Me-Al bond in a stepped conformation. That means, the B-half offers more available space for substrate accomodation.

3. Experimental

3.1. General

$^1$H-NMR and $^{13}$C-NMR spectra were measured on a Bruker Avance spectrometer (300 or 500 MHz, Rheinstetten, Germany) in CDCl$_3$ or DMSO as solvent using TMS as internal standard and chemical shifts are expressed as $\delta$ in ppm. Molecular masses were determined with the electron spray ionization (ESI) method on a MicroTOFQ (Bruker, Bremen, Germany) spectrometer. IR spectra were recorded on a Bruker Vector 22 FT-IR spectrometer (Bremen, Germany) with an ATR module (Golden Gate). Melting points are uncorrected and were measured on a Büchi Melting Point B-535 analysis device. The enantiomeric excesses were determined by HPLC on an Elite LaChrom system equipped with Hitachi modules. A chiral stationary phase Daicel column of the Chiracel OD-H type was used.

3.2. General Procedure for the Synthesis of 10 (GP1)

This procedure was according to a published protocol [72,73]. To a solution of the phenol derivative 9 (1 eq., 15.0 mmol) in acetonitrile, paraformaldehyde (6.7 eq.), magnesium chloride (1.5 eq.) and triethylamine (3.8 eq.) were added and the mixture was heated under reflux for 24 h. After cooling to ambient temperature, 1 M hydrochloric acid was added till the yellow residue dissolved, followed by extraction with diethyl ether (3 $\times$ 20 mL). The organic layers were dried over MgSO$_4$, filtered and the solvent was removed in vacuo. Purification by column chromatography (petroleum ether/ethyl acetate 10:1) gave the aldehyde 10.

2-Hydroxy-5-tert-butylbenzaldehyde (10a) was prepared according to GP1 using 4-tert-butylphenol (1 eq., 15.0 mmol, 2.25 g) and paraformaldehyde (6.7 eq., 101 mmol, 3.02 g). The product was formed as a yellow oil (13.5 mmol, 2.40 g, 90%). C$_{11}$H$_{14}$O$_2$, MW: 178.23 g/mol. $^1$H-NMR (300 MHz, CDCl$_3$, 20 °C): $\delta = 10.87$ (s, 1H, Ar-\text{OH}), 9.89 (s, 1H, Ar-\text{CHO}), 7.58 (dd, $J = 8.8$, 2.5, 1H, $p$-Ar-\text{H}), 7.51 (d, $J = 2.5$, 1H, o-Ar-\text{H}), 6.94 (d, $J = 8.7$, 1H, m-Ar-\text{H}), 1.33 (s, 9H, Ar-C(CH$_3$)$_3$). The analytical data were in agreement with the literature values [72].

2-Hydroxy-5-pentylbenzaldehyde (10b) was prepared according to GP1 using 4-n-pentylphenol (1 eq., 8.0 mmol, 1.31 g, 1.4 mL) and paraformaldehyde (6.7 eq., 53.6 mmol, 1.61 g). The product was
formed as a yellow oil (6.7 mmol, 1.29 g, 84%). C₁₂H₁₆O₂, MW: 192.25 g/mol. ¹H-NMR (300 MHz, CDCl₃, 20 °C): δ = 10.85 (s, 1H, Ar-OH), 9.87 (s, 1H, Ar-CHO), 7.33–7.37 (m, 2H, Ar-, p-Ar-H), 6.91 (d, J = 8.5, 1H, m-Ar-H), 2.59 (t, J = 7.7, 2H, Ar-CH₂(CH₂)₂CH₃), 1.65–1.55 (m, 2H, Ar-CH₂CH₂(CH₂)₂CH₃), 1.36–1.28 (m, 4H, Ar-(CH₂)₂(C₂H₅)₂CH₃), 0.90 (t, J = 6.9, 3H, Ar-(CH₂)₆CH₃). The analytical data are in agreement with the literature [91].

2-Hydroxy-5-methylbenzaldehyde (10c) was prepared according to GP1 using 4-methylphenol (1 eq., 14.0 mmol, 1.50 g) and paraformaldehyde (6.7 eq., 93.0 mmol, 2.80 g). The product was formed as a slightly yellow oil (10.5 mmol, 1.43 g, 76%) after Kugelrohr distillation (no column chromatography in this case). C₈H₈O₂, MW: 136.15 g/mol. ¹H-NMR (300 MHz, CDCl₃, 20 °C): δ = 10.84 (s, 1H, Ar-OH), 9.86 (s, 1H, Ar-CO), 7.35–7.33 (m, 2H, o-, p-Ar-H), 6.90 (d, J = 9.2, 1H, m-Ar-H), 2.34 (s, 3H, C₃H₃). The analytical data are in agreement with the literature [72].

3.3. General Procedure for the Synthesis of 11 (GP2)

This procedure was according to a published protocol [74]. To the corresponding aldehyde 10 (1 eq., 10.5 mmol) were added aq. hydrobromic acid (48%, 7.5 eq., 78.9 mmol, 8.6 mL), paraformaldehyde (1.5 eq., 15.8 mmol, 0.47 g) and a catalytic amount of sulfuric acid (3 drops). Depending on the alkyl chain R¹, the mixture was stirred at 70 °C for 1 to 5 days. After cooling to ambient temperature, water (10 mL) was added followed by extraction with methylene chloride (3 × 10 mL). The collected organic layers were dried over Na₂SO₄, filtered and the solvent was removed in vacuo.

3-(Bromomethyl)-2-hydroxy-5-tert-butylbenzaldehyde (11a) was prepared according to GP2 using 10a (1 eq., 13.5 mmol, 2.40 g), paraformaldehyde (1.5 eq., 20.2 mmol, 0.61 g) and aq. hydrobromic acid (48%, 7.5 eq., 101.1 mmol, 11.5 mL). After 1 day reaction time a brown oil (13.3 mmol, 3.61 g, 98%) was isolated. C₁₂H₁₅BrO₂, MW: 271.15 g/mol. ¹H-NMR (300 MHz, CDCl₃, 20 °C): δ = 11.32 (s, 1H, Ar-OH), 9.90 (s, 1H, Ar-CO), 7.64 (d, J = 2.5, 1H, Ar-H), 7.51 (d, J = 2.5, 1H, Ar-H), 4.59 (s, 2H, CH₂Br), 1.34 (s, 9H, C(CH₃)₃). The analytical data are in agreement with the literature [74].

3-(Bromomethyl)-2-hydroxy-5-pentylbenzaldehyde (11b) was prepared according to GP2 using 10b (1 eq., 10.5 mmol, 2.02 g), paraformaldehyde (1.5 eq., 15.8 mmol, 0.47 g) and aq. hydrobromic acid (48%, 7.5 eq., 78.9 mmol, 8.6 mL). After 5 days reaction time a brown oil (9.77 mmol, 2.79 g, 93%) was isolated. C₁₃H₁₇BrO₂, MW: 285.18 g/mol. m.p.: 32–34 °C. ¹H-NMR (300 MHz, CDCl₃, 20 °C): δ = 11.31 (s, 1H, Ar-OH), 9.87 (s, 1H, Ar-CHO), 7.43 (d, J = 2.1, 1H, Ar-H), 7.33 (d, J = 2.1, 1H, Ar-H), 4.57 (s, 2H, CH₂Br), 2.59 (t, J = 7.8, 2H, Ar-CH₂-C₄H₉), 1.61 (m, 2H, (CH₂)₅pentyl), 1.33 (m, 4H, (CH₂)₅pentyl), 0.90 (t, J = 6.9, 3H, CH₃). ¹³C-NMR (75 MHz, CDCl₃, 21 °C): δ = 196.5 (1C, CHO), 157.6 (1C, C₅H-OH), 138.3 (1C, C₅H-H), 134.5 (1C, C₅H-C₂H₁₁), 133.6 (1C, C₅H-H), 126.0 (1C, C₅H-CH₂Br), 120.5 (1C, C₅H-CHO), 34.6 (1C, C₅H-CH₂-C₄H₉), 31.3 (1C, (CH₂)₅pentyl), 31.0 (1C, (CH₂)₅pentyl), 26.8 (1C, C₅H-CH₂Br), 22.5 (1C, (CH₂)₅pentyl), 14.0 (1C, CH₃). IR (solid): ν = 3046, 2954, 2930, 2854, 2753, 2185 (b), 1967 (b), 1811, 1646, 1438, 1209, 760. HRMS (EI) m/z: Anal. Calcd. for [C₁₃H₁₁BrO₂⁺]: 284.0412, found 284.0412.
3-(Bromomethyl)-2-hydroxy-5-methylbenzaldehyde (11c) was prepared according to GP2 using 10c (1 eq., 9.0 mmol, 1.23 g), paraformaldehyde (1.5 eq., 13.5 mmol, 0.407 g) and aq. hydrobromic acid (48%, 7.5 eq., 67.5 mmol, 7.8 mL). After 70 h reaction time a beige-colored solid (5.8 mmol, 1.58 g, 76%) was isolated. C₉H₉BrO₂, MW: 229.07 g/mol. ¹H-NMR (300 MHz, CDCl₃, 20 °C): δ = 11.28 (s, 1H, Ar-CH=O), 9.84 (s, 1H, Ar-CHO), 7.42 (d, J = 1.9, 1H, o-Ar-H), 7.31 (d, J = 1.9, 1H, p-Ar-H), 4.54 (s, 2H, Ar-CH₂-Br), 2.33 (s, 3H, CH₃). The analytical data are in agreement with the literature [74].

3.4. General Procedure for the Synthesis of 12 (GP3)

This procedure was according to a published protocol [92]. To a solution of 11 (1 eq., 3.0 mmol) in acetonitrile (8 mL) was added the corresponding pyridine derivative (1.1 eq., 3.3 mmol). The mixture was stirred for 15 h at ambient temperature. For the workup the solvent was removed in vacuo till a volume of ca. 5 mL was reached and the product was precipitated with diethyl ether (10 mL). After drying in vacuo the salt 12 was obtained.

1-(5-tert-Butyl-3-formyl-2-hydroxybenzyl)pyridinium bromide (12aA) was prepared according to GP3 using 11a (1 eq., 1.50 mmol, 406.7 mg) and pyridine (1.1 eq., 1.65 mmol, 130.5 mg, 133 µL). The product was formed as a white solid (1.39 mmol, 483.2 mg, 92%). C₁₉H₂₂BrNO₂, MW: 350.25 g/mol. ¹H-NMR (300 MHz, CDCl₃, 20 °C): δ = 11.37 (s, 1H, Ar-CH=O), 9.83 (s, 1H, Ar-CHO), 9.62 (d, J = 6.6, 2H, o-Py-H), 8.70 (d, J = 2.5, 1H, Ar-H), 8.38 (t, J = 7.9, 1.3, 1H, p-Py-H), 7.97 (t, J = 7.0, 2H, m-Py-H), 7.57 (d, J = 2.5, 1H, Ar-H), 6.30 (s, 2H, Ar-CH₂-Py), 1.32 (s, 9H, C(CH₃)₃). The analytical data are in agreement with the literature [54].

1-(3-Formyl-2-hydroxy-5-pentylbenzyl)pyridinium bromide (12bA) was prepared according to GP3 using 11b (1 eq., 9.8 mmol, 2.79 g) and pyridine (1.1 eq., 10.7 mmol, 0.85 g, 866 µL). The product was formed as a beige-colored solid (6.1 mmol, 3.56 g, 62%). C₁₈H₂₂BrNO₂, MW: 364.28 g/mol. M.p.: 146–147 °C. ¹H-NMR (300 MHz, CDCl₃, 20 °C): δ = 14.45 (s, 1H, Ar-CH=O), 9.87 (s, 1H, Ar-CHO), 9.63 (d, J = 6.1, 2H, o-Py-H), 8.43 (d, J = 2.5, 1H, Ar-H), 8.39 (t, J = 7.9, 1.3, 1H, p-Py-H), 7.99 (t, J = 7.2, 2H, m-Py-H), 7.47 (d, J = 2.1, 1H, Ar-H), 6.35 (s, 2H, Ar-CH₂-Py), 2.67 (t, J = 8.0, 2H, Ar-CH₂-C₄H₉), 1.64 (m, 2H, (CH₂)₅pentyl), 1.33 (m, 4H, (CH₂)₅pentyl), 0.89 (t, J = 6.9, 3H, CH₃). ¹³C-NMR (75 MHz, CDCl₃, 21 °C): δ = 196.6 (1C, CHO), 157.9 (1C, C₅Ar-OH), 145.6 (1C, α-C₅Py), 145.6 (1C, α-C₅Py), 145.1 (1C, γ-C₅Py), 140.2 (1C, C₅Ar-H), 136.2 (1C, C₅Ar-C₅H₁₁), 135.0 (1C, C₅Ar-CHO), 127.8 (2C, β-C₅Py), 121.1 (1C, C₅Ar-H), 120.6 (1C, C₅Ar-CH₂-N₅Py), 95.2 (1C, C₅Ar-CH₂-N₅Py), 34.5 (1C, C₅Ar-CH₂-C₄H₉), 31.4 (1C, (CH₂)₅Pentyl), 31.0 (1C, (CH₂)₅Pentyl), 22.5 (1C, (CH₂)₅Pentyl), 14.1 (1C, CH₃). IR (solid): ν = 3046, 2949, 2860, 2196, 1966, 1641, 1627, 1154, 690. HRMS (ESI) m/z: Anal. Calcd. for [[C₁₈H₂₂NO₂]⁺]: 284.1645, found 284.1641.

1-(3-Formyl-2-hydroxy-5-methylbenzyl)pyridinium bromide (12cA) was prepared according to GP3 using 11c (1 eq., 7.0 mmol, 1.62 g) and pyridine (1.1 eq., 7.7 mmol, 597 µL). The product was formed as a colorless solid (6.5 mmol, 1.99 g, 92%). C₁₄H₁₄BrNO₂, MW: 308.17 g/mol. M.p.: 189–192 °C. ¹H-NMR (300 MHz, CDCl₃, 20 °C): δ = 11.39 (s, 1H, Ar-CH=O), 9.84 (s, 1H, Ar-CHO), 9.63 (d, J = 5.7, 2H, o-Py-H), 8.44 (m, 2H, p-C₅Py-H und C₅Ar-H), 8.02 (t, J = 7.2, 2H, m-Py-H), 7.44 (d, J = 1.9, 1H, o-Ar-H), 6.33 (s, 2H, Ar-CH₂-Py), 2.39 (s, 9H, CH₃). ¹³C-NMR (75 MHz, CDCl₃, 20 °C): δ = 196.6
1-(5-tert-Butyl-3-formyl-2-hydroxybenzyl)-4-methylpyridinium bromide (12aB) was prepared according to GP3 using 11a (1 eq., 3.00 mmol, 813.5 mg) and picoline (1.1 eq., 3.30 mmol, 307.3 mg, 321 µL). The product was formed as a white solid (2.02 mmol, 734.9 mg, 67%). C_{18}H_{22}BrNO_{2}, MW: 364.28 g/mol. M.p.: 247.2–248.0 °C. ¹H-NMR (300 MHz, DMSO, 20 °C): δ = 11.16 (s, 1H, Ar-OH), 10.66 (s, 1H, Ar-CHO), 8.99 (d, J = 6.7, 2H, o-Py-H), 8.09 (d, J = 2.4, 1H, Ar-H), 7.98 (d, J = 6.5, 2H, m-Py-H), 7.89 (d, J = 2.6, 1H, Ar-H), 5.82 (s, 2H, Ar-CH$_{2}$-Py), 2.59 (s, 3H, Py-CH$_{3}$), 1.32 (s, 9H, C(CH$_{3}$)$_{3}$). ¹³C-NMR (125 MHz, DMSO, 20 °C): δ = 196.5, 159.3, 156.7, 143.9, 142.8, 136.1, 130.8, 128.3, 122.0, 121.2, 58.2, 34.1, 31.0, 21.4. IR (solid): ν = 3419, 3018, 2951, 2864, 1639, 1473, 1379, 1280, 1226, 1151, 1018, 826, 761, 700, 617. MS (ESI) m/z: 284.2 (57%, [M]$^+$), 191.1 (100%, [M]$^+$–[Py]), 94.1 (15%, [PyH]$^+$). HRMS (ESI) m/z: Anal. Calcd. for [(C$_{18}$H$_{22}$NO$_{2}$)$^+$]: 284.1645, found: 284.1634.

1-(3-Formyl-2-hydroxy-5-pentylbenzyl)-4-methylpyridinium bromide (12bB) was prepared according to GP3 using 11b (1 eq., 14.0 mmol, 4.0 g) and picoline (1.1 eq., 15.4 mmol, 1.4 g, 1.5 mL). The product was formed as a yellow solid (12.8 mmol, 4.8 g, 91%). C$_{19}$H$_{24}$BrNO$_{2}$, MW: 378.30 g/mol. M.p.: 118.2–120.6 °C. ¹H-NMR (300 MHz, CDCl$_{3}$, 20 °C): δ = 11.41 (s, 1H, Ar-OH), 9.86 (s, 1H, Ar-CHO), 9.40 (d, J = 6.7, 2H, o-Py-H), 8.39 (d, J = 2.0, 1H, Ar-H), 7.72 (d, J = 6.4, 2H, m-Py-H), 7.45 (d, J = 2.1, 1H, Ar-H), 6.24 (s, 2H, Ar-CH$_{2}$-Py), 2.68–2.63 (m, 5H, Ar-CH$_{2}$-C$_{4}$H$_{9}$ and Py-CH$_{3}$), 1.68–1.58 (m, 2H, (CH$_{2}$)$_{3}$pentyl), 1.38–1.25 (m, 4H, (CH$_{2}$)$_{3}$pentyl), 0.89 (t, J = 6.8, 3H, CH$_{3}$). ¹³C-NMR (75 MHz, CDCl$_{3}$, 20 °C): δ = 196.6, 158.9, 157.9, 144.6, 140.3, 134.9, 128.2, 121.3, 120.5, 58.3, 34.5, 31.4, 31.0, 22.5, 22.3, 14.1. IR (solid): ν = 3013, 2927, 2855, 1637, 1466, 1278, 1151, 1016, 830, 748, 699. MS (ESI) m/z: 298.2 (100%, [M]$^+$), 205.1 (13%, [M]$^+$–[Py]). HRMS (ESI) m/z: Anal. Calcd. for [(C$_{19}$H$_{24}$NO$_{2}$)$^+$]: 298.1802, found: 298.1793.

4-tert-Butyl-1-(3-formyl-2-hydroxy-5-pentylbenzyl)-pyridinium bromide (12bC) was prepared according to GP3 using 11b (1 eq., 1.0 mmol, 285.2 mg) and 4-tert-butylpyridine (1.1 eq., 1.1 mmol, 148.7 mg, 107 µL). The product was formed as a yellow solid (0.96 mmol, 403.4 mg, 96%). C$_{22}$H$_{36}$BrNO$_{2}$, MW: 420.38 g/mol. M.p.: 188.6–189.8 °C. ¹H-NMR (300 MHz, CDCl$_{3}$, 20 °C): δ = 11.45 (s, 1H, Ar-OH), 9.87 (s, 1H, Ar-CHO), 9.50 (d, J = 6.8, 2H, o-Py-H), 8.46 (d, J = 2.0, 1H, Ar-H), 7.86 (d, J = 6.8, 2H, m-Py-H), 7.45 (d, J = 2.0, 1H, Ar-H), 6.24 (s, 2H, Ar-CH$_{2}$-Py), 2.67 (t, J = 7.7, 2H, Ar-CH$_{2}$-C$_{4}$H$_{9}$), 1.69–1.59 (m, 2H, (CH$_{2}$)$_{3}$pentyl), 1.39 (s, 9H, Py-(CH$_{2}$)$_{3}$). ¹³C-NMR (75 MHz, CDCl$_{3}$, 20 °C): δ = 196.7, 157.9, 144.8, 140.5, 136.3, 134.8, 124.7, 121.3, 120.5, 58.0, 36.6, 34.5, 31.4, 31.0, 30.0, 22.5, 14.1. IR (solid): ν = 3035, 2956, 2928, 2857, 1643, 1462, 1384, 1270, 1219, 1169, 1109, 1015, 849, 749, 712, 647, 561. MS (ESI) m/z: 340.2 (15%, [M]$^+$), 205.1 (100%, [M]$^+$–[Py]). HRMS (ESI) m/z: Anal. Calcd. for [(C$_{22}$H$_{36}$NO$_{2}$)$^+$]: 340.2271, found: 340.2255.
3,5-Dimethyl-1-(3-formyl-2-hydroxy-5-pentylbenzyl)-pyridinium bromide (12bD) was prepared according to GP3 using 11b (1 eq., 1.0 mmol, 285.2 mg) and 3,5-dimethylpyridine (1.1 eq., 1.1 mmol, 117.9 mg, 126 μL). The product was formed as a yellow solid (0.54 mmol, 211.4 mg, 54%). C20H26BrNO2, MW: 392.33 g/mol. M.p.: 187.6–188.9 °C. 1H-NMR (300 MHz, DMSO, 20 °C): δ = 196.6, 157.8, 156.2, 143.0, 139.7, 135.7, 134.2, 122.4, 120.5, 107.8, 55.3, 40.4, 34.5, 31.4, 31.0, 22.5, 18.6, 15.3, 14.1. IR (solid): ν = 2994, 2924, 2852, 1644, 1620, 1527, 1449, 1370, 1278, 1224, 1158, 1012, 821, 785, 709. MS (ESI) m/z: 334.2 (32%, [M]+), 205.1 (100%, [M]+−[Py]), 108.1 (52%, [PyH]+). HRMS (ESI) m/z: Anal. Calcd. for [[C22H26NO2]⁺]: 334.1802, found: 334.1802.

1-(3-Formyl-2-hydroxy-5-pentylbenzyl)-quinolinium bromide (12bE) was prepared according to GP3 using 11b (1 eq., 1.0 mmol, 285.2 mg) and quinoline (1.1 eq., 1.1 mmol, 142.1 mg, 129 µL). The product was formed as a white solid (0.47 mmol, 194.0 mg, 47%). C22H24BrNO2, MW: 414.34 g/mol. M.p.: 215.1–216.4 °C. 1H-NMR (300 MHz, DMSO, 20 °C): δ = 11.20 (s, 1H, Ar-OH), 10.04 (s, 1H, Ar-CHO), 9.68 (d, J = 5.8, 1H, quinoline-H), 9.37 (d, J = 8.3, 1H, quinoline-H), 8.58–8.50 (m, 2H, quinoline-H), 8.29–8.19 (m, 2H, quinoline-H), 8.03 (m, J = 7.6, 1H, quinoline-H), 7.65 (d, J = 1.8, 1H, Ar-H), 7.57 (d, J = 1.8, 1H, Ar-H), 6.32 (s, 2H, Ar-CH2-quinoline), 2.52 (m, 2H, Ar-CH2-C4H9), 1.50 (m, 2H, (CH2)pentyl), 1.20 (m, 4H, (CH2)pentyl), 0.80 (m, J = 6.9, 3H, CH3). 13C-NMR (125 MHz, DMSO, 20 °C): δ = 196.2, 156.3, 150.7, 148.1, 137.6, 137.0, 135.7, 134.3, 133.1, 130.9, 129.9, 129.7, 122.1, 121.7, 121.3, 118.9, 55.7, 33.6, 30.5, 30.3, 21.8, 13.9. IR (solid): ν = 3024, 2924, 2852, 1644, 1620, 1527, 1449, 1370, 1278, 1224, 1158, 1012, 821, 785, 709. MS (EI) m/z: 343.2 (32%, [M]+), 205.1 (100%, [M]+−[quinoline]). HRMS (ESI) m/z: Anal. Calcd. for [[C22H26NO2]⁺]: 343.1802, found: 343.1796.

4-Dimethylamino-1-(3-formyl-2-hydroxy-5-pentylbenzyl)-pyridinium bromide (12bF) was prepared according to GP3 using 11b (1 eq., 1.0 mmol, 285.2 mg) and 4-dimethylaminopyridine (1.1 eq., 1.1 mmol, 134.4 mg). The product was formed as a beige-colored solid (0.81 mmol, 330.2 mg, 81%). C20H26BrN2O2, MW: 407.34 g/mol. M.p.: 206.6–208.9 °C. 1H-NMR (300 MHz, CDCl3, 20 °C): δ = 11.29 (b, 1H, Ar-OH), 9.85 (s, 1H, Ar-CHO), 8.68 (d, J = 7.8, 2H, o-Py-H), 8.08 (d, J = 2.2, 1H, Ar-H), 7.38 (d, J = 2.2, 1H, Ar-H), 6.88 (d, J = 7.8, 2H, m-Py-H), 6.55 (s, 2H, Ar-CH2-Py), 3.22 (s, 6H, Py-CH3), 2.61 (t, J = 7.8, 2H, Ar-CH2-C4H9), 1.60 (m, 2H, (CH2)pentyl), 1.29 (m, 4H, (CH2)pentyl), 0.86 (t, J = 6.8, 3H, CH3). 13C-NMR (75 MHz, CDCl3, 20 °C): δ = 196.6, 157.8, 156.2, 143.0, 139.7, 135.7, 134.2, 122.4, 120.5, 107.8, 55.3, 40.4, 34.5, 31.4, 31.0, 22.5, 14.1. IR (solid): ν = 3065, 2955, 2927, 2855, 1560, 1443, 1402, 1384, 1261, 1164, 1013, 943, 838, 820, 770, 715, 702. MS (EI) m/z: 327.2 (68%, [M]+), 205.1 (70%, [M]+−[Py]), 123.1 (100%, [PyH]+). HRMS (ESI) m/z: Anal. Calcd. for [[C20H26N2O2]⁺]: 327.2067, found: 327.2069.

1-(3-Formyl-2-hydroxy-5-pentylbenzyl)-4-iodopyridinium bromide (12bG) was prepared according to GP3 using 11b (1 eq., 1.0 mmol, 285.2 mg) and 4-iodopyridine (1.1 eq., 1.1 mmol, 225.5 mg). The
product was formed as a green solid (0.68 mmol, 332.7 mg, 65%). C_{18}H_{21}BrINO₂, MW: 490.17 g/mol. M.p.: 182.5–183.3 °C (decomposition). ¹H-NMR (300 MHz, CDCl₃, 20 °C): δ = 11.36 (s, 1H, Ar-OH), 9.89 (s, 1H, Ar-CHO), 4.95 (d, J = 6.9, 2H, o-Py-H), 8.29 (m, 1H, Ar-H), 7.22 (d, J = 6.6, 3H, Ar-C), 2.56 (t, J = 7.5, 2H, Ar-CH₂-C₄H₉), 1.59–1.56 (m, 2H, (CH₂)₅pentyl), 1.33–1.30 (m, 4H, (CH₂)₅pentyl), 1.29 (s, 3H, CH₃). IR (solid): ν = 3012, 2959, 2856, 1645, 1615, 1448, 1275, 1261, 1123, 1017, 837, 807, 703. MS (ESI) m/z: 390.1 (9%, [M⁺]), 205.1 (100%, [M⁺]=[Py]). HRMS (ESI) m/z: Anal. Calcd. for [C₁₉H₂₁N₂O₂⁺]: 318.1598, found: 318.1596.

4-Chloro-1-(3-formyl-2-hydroxy-5-pentylbenzyl)-pyridinium bromide (12bH) was prepared according to GP3 using 11b (1 eq., 1.0 mmol, 285.2 mg) and 4-chloropyridine (1.1 eq., 1.1 mmol, 187.3 mg, 156 µL). The product was formed as a beige-colored solid (0.67 mmol, 267.2 mg, 29%). C₁₈H₂₁BrClNO₂, MW: 398.72 g/mol. M.p.: 151.6–153.2 °C. ¹H-NMR (500 MHz, CDCl₃, 20 °C): δ = 11.36 (s, 1H, Ar-OH), 9.88 (s, 1H, Ar-CHO), 9.50 (d, J = 6.8, 2H, o-Py-H), 8.29 (m, 1H, Ar-H), 7.96 (d, J = 6.8, 2H, m-Py-H), 7.36 (m, 1H, Ar-H), 5.81 (s, 2H, Ar-CH₂-Py), 2.58 (t, J = 7.8, 2H, Ar-CH₂-C₄H₉), 1.58 (m, 2H, (CH₂)₅pentyl), 1.30 (m, 4H, (CH₂)₅pentyl), 0.86 (s, J = 6.6, 3H, CH₃). ¹³C-NMR (125 MHz, CDCl₃, 20 °C): δ = 196.5, 157.9, 54.0, 139.9, 128.1, 121.0, 120.6, 58.9, 30.7, 21.8, 16.8, 11.4. IR (solid): ν = 3012, 2959, 2856, 1645, 1615, 1448, 1275, 1261, 1153, 1017, 837, 807, 703. MS (ESI) m/z: 410.1 (9%, [M⁺]), 205.1 (100%, [M⁺]=[Py]). HRMS (ESI) m/z: Anal. Calcd. for [C₁₈H₂₁BrINO₂⁺]: 410.0611, found: 410.0609.

4-Cyano-1-(3-formyl-2-hydroxy-5-pentylbenzyl)-pyridinium bromide (12bI) was prepared according to GP3 using 11b (1 eq., 1.0 mmol, 285.2 mg) and 4-cyanopyridine (1.1 eq., 1.1 mmol, 114.5 mg). The product was formed as a yellow solid (0.80 mmol, 312.5 mg, 80%). C₁₉H₂₂BrN₂O₂, MW: 389.29 g/mol. M.p.: 131.6–133.2 °C. ¹H-NMR (300 MHz, CDCl₃, 20 °C): δ = 11.36 (s, 1H, Ar-OH), 9.88–9.85 (m, 3H, Ar-CHO and o-Py-H), 8.30 (m, 1H, Ar-H), 8.23 (d, J = 6.5, 2H, m-Py-H), 7.59 (m, 1H, Ar-H), 6.56 (s, 2H, Ar-CH₂-Py), 2.66 (t, J = 7.8, 2H, Ar-CH₂-C₄H₉), 1.63 (m, 2H, (CH₂)₅pentyl), 1.33 (m, 4H, (CH₂)₅pentyl), 0.89 (s, J = 6.8, 3H, CH₃). ¹³C-NMR (125 MHz, CDCl₃, 20 °C): δ = 196.5, 157.9, 147.3, 139.9, 136.2, 135.3, 130.1, 128.1, 120.7, 120.4, 113.7, 60.8, 34.5, 31.4, 31.0, 22.5, 14.1. IR (solid): ν = 3012, 2959, 2856, 1645, 1615, 1448, 1275, 1261, 1153, 1017, 837, 807, 703. MS (ESI) m/z: 318.1 (100%, [M⁺]), 205.1 (54%, [M⁺]=[Py]). HRMS (ESI) m/z: Anal. Calcd. for [C₁₉H₂₁N₂O₂⁺]: 318.1255, found: 318.1255.

3.5. General Procedure for the Synthesis of 14 (GP4)

This procedure is according to a published protocol [54]. To a solution of (1R,2R)-(−)-1,2-diaminocyclohexane (1 eq., 0.15 mmol, 17.1 mg) in ethanol (0.7 mL) at ambient temperature molecular sieves (4 Å) and the corresponding salt 12 (2 eq., 0.30 mmol) were added. The mixture was stirred for 15 h at ambient temperature. For workup the mixture was filtered and washed with ethanol. The solvent was removed in vacuo till a volume of 5 mL was reached and the ligand was precipitated with diethyl ether (30 mL). The solid product was then dried in vacuo.
(R,R)-(−)-N,N′-Bis(3-tert-butyl-5-(pyridinium-1-ylmethyl)salicylidene)-1,2-cyclohexanediamine dibromide (14aA) was prepared according to GP4 using 12aA (2 eq., 1.06 mmol, 371.3 mg) and (1R,2R)-(−)-1,2-diaminocyclohexane (1 eq., 0.53 mmol, 60.5 mg). The product was formed as an orange solid (0.53 mmol, 438.0 mg, 100%). C_{39}H_{38}Br_{2}N_{4}O_{2}, MW: 778.66 g/mol. 1H-NMR (300 MHz, CD_{2}Cl_{2}, 20 °C): δ = 14.16 (b, 2H, Ar-CH=), 9.55 (d, J = 5.5, 4H, o-Py-H), 8.46 (t, J = 7.8, 2H, p-Py-H), 8.38 (s, 2H, Ar-CH=N-Cy), 8.22 (d, J = 2.5, 2H, Ar-H), 7.99 (m, 4H, m-Py-H), 7.32 (d, J = 2.5, 2H, Ar-H), 6.13 (m, 4H, Ar-CH_{2}-Py), 3.43 (d, J = 9.5, 2H, Cy-H), 1.90 (m, 4H, Cy-H_{2}), 1.67 (m, 2H, Cy-H_{2}), 1.47 (m, 2H, Cy-H_{2}), 1.27 (s, 18H, C(CH_{3})_{3}). The analytical data are in agreement with the literature [54].

(R,R)-(−)-N,N′-Bis(3-pentyl-5-(pyridinium-1-ylmethyl)salicylidene)-1,2-cyclohexanediamine dibromide (14bA) was prepared according to GP4 using 12bA (2 eq., 0.90 mmol, 328.0 mg) and (1R,2R)-(−)-1,2-diaminocyclohexane (1 eq., 0.45 mmol, 51.4 mg). The product was formed as an orange solid (0.41 mmol, 329.3 mg, 91%). C_{43}H_{54}Br_{2}N_{4}O_{2}, MW: 806.71 g/mol. M.p.: 128.4–129.6 °C. 1H-NMR (300 MHz, CD_{2}Cl_{2}, 21 °C): δ = 164.8 (2C, C_{Ar}-CH=N), 159.4 (2C, C_{Ar}-OH), 145.6 (2C, α-C_{Py}), 145.6 (2C, α-C_{Py}), 145.4 (2C, γ-C_{Py}), 135.5 (2C, C_{Ar}-C_{H}(1)), 134.0 (2C, C_{Ar}), 133.5 (2C, C_{Ar}), 128.2 (4C, β-C_{Py}), 120.8 (2C, C_{Ar}-CH_{2}-N_{Py}), 118.9 (2C, C_{Ar}-CHN), 71.7 (2C, C_{Cy}HN), 60.4 (2C, Ar-CH=Py), 35.0 (2C, C_{Ar}-CH_{2}-C_{H}(3)), 33.2 (2C, C_{Cy}H_{2}), 31.8 (2C, (CH_{2})_{Pentyl}), 24.5 (2C, C_{Cy}H_{2}), 22.9 (2C, (CH_{2})_{Pentyl}), 14.2 (2C, C_{H}). IR (solid): ν = 3396, 2925, 2854, 2561, 2374, 2186, 1967, 1627, 1472, 683. HRMS (ESI) m/z: Anal. Calcd. for [(C_{43}H_{54}Br_{2}N_{4}O_{2})⁺]: 725.3413, found 725.3422.

(R,R)-(−)-N,N′-Bis(3-methyl-5-(pyridinium-1-ylmethyl)salicylidene)-1,2-cyclohexanediame dibromide (14cA) was prepared according to GP4 using 12cA (2 eq., 6.5 mmol, 2.0 g) and (1R,2R)-(−)-1,2-diaminocyclohexane (1 eq., 3.2 mmol, 370 mg). The product was formed as a slightly yellow solid (2.7 mmol, 1.89 g, 84%). C_{34}H_{38}Br_{2}N_{4}O_{2}, MW: 694.50 g/mol. M.p.: Decomp. at T > 200 °C. [α]^{20^oC}_{D} (c = 10 mg/mL, CH_{2}Cl_{2}) = −296.0. 1H-NMR (300 MHz, CD_{2}Cl_{2}, 20 °C): δ = 14.09 (b, 1H, Ar-CH=), 9.48 (d, J = 9.7, 4H, o-Py-H), 8.42 (t, J = 7.9, J = 1.4, 2H, p-Py-H), 8.31 (s, 2H, Ar-CH=N-Cy), 7.96 (t, J = 7.2, 4H, m-Py-H), 7.84 (d, J = 2.2, 2H, Ar-H), 7.12 (d, J = 1.9, 2H, Ar-H), 6.08 (q, J = 13.7, Ar-CH_{2}-Py), 3.42 (m, 2H, C_{Cy}HN=CHR), 2.26 (s, 6H, C_{H}), 1.98–1.48 (m, 8H, (CH_{2})_{Cy}). 13C-NMR (75 MHz, CDCl_{3}, 21 °C): 164.8 (2C, CHN), 159.2 (2C, C_{Ar}-OH), 145.6 (2C, C_{Cy}HN), 145.6 (2C, C_{Ar}-Me), 134.1 (2C, C_{Ar}), 128.6 (2C, C_{Ar}), 128.3 (4C, β-Py-C), 120.9 (2C, C_{Ar}-CH_{2}-Py), 118.9 (2C, C_{Ar}-CHN), 71.8 (2C, C_{Cy}HN), 60.1 (2C, Ar-CH=Py), 33.1 (2C, C_{Cy}H_{2}), 24.5 (2C, C_{Cy}H_{2}), 20.4 (2C, C_{H}). IR (solid): ν = 3381, 3123, 3044, 2928, 2857, 2054, 1627, 1476. MS (ESI) m/z: 613.2 (20%, M^{+}), 597.1 (60%, M^{−}-OH), 518.0 (100%, M^{−}-Br), 454.2 (90%, M^{−}-pyridine). HRMS (ESI) m/z: Anal. Calcd. for [(C_{34}H_{38}Br_{2}N_{4}O_{2})^{+}]: 613.2173, found: 613.2182.

(R,R)-(−)-N,N′-Bis(3-tert-butyl-5-(4-methylpyridinium-1-ylmethyl)salicylidene)-1,2-cyclohexane-diamine dibromide (14aB) was prepared according to GP4 using 12aB (2 eq., 0.30 mmol, 109.3 mg) and
(1R,2R)-(−)-1,2-diaminocyclohexane (1 eq., 0.15 mmol, 17.1 mg). The product was formed as a yellow solid (0.13 mmol, 107.3 mg, 89%). C42H54N4O2, MW: 806.71 g/mol. M.p.: 198.2–200.3 °C (decomposition). [α]D20°C = 14.00 (b, 2H, Ar-OH), 9.31 (d, J = 6.4, 4H, o-Py-H), 8.37 (s, 2H, Ar-CH=N-Cy), 8.08 (d, J = 3.3, 2H, Ar-H), 7.78 (d, J = 6.3, 4H, m-Py-H), 7.28 (d, J = 2.3, 2H, Ar-H), 6.07–5.94 (m, 4H, Ar-CH2-Py), 3.42 (m, 2H, Cy-HN=CHR)), 2.59 (s, 6H, Py-CH3), 1.94–1.84 (m, 4H, Cy-H2), 1.67 (m, 2H, Cy-H2), 1.46 (m, 2H, Cy-H2), 1.25 (s, 18H, C(CH3)3). 13C-NMR (125 MHz, CDCl3, 20 °C): δ = 164.7, 158.9, 158.7, 144.4, 142.1, 132.7, 130.2, 128.4, 120.5, 118.0, 71.4, 59.4, 34.3, 33.1, 31.5, 24.1, 22.3. IR (solid): ν = 3387, 2946, 2862, 1628, 1469, 1280, 1204, 1149, 1019, 824, 787. MS (ESI) m/z: 725.3 (1%, [M]−[Br]), 552.4 (7%, [M]+[Py]), 459.3 (100%, [M]+2×[Py]), 323.2 (1%, [M]+2), 276.7 (93%, [M]+2−[Py]). HRMS (ESI) m/z: Anal. Calcd. for [[C42H54N4O2]2+]: 323.2118, found: 323.2097.

(R,R)-(−)-N,N'-Bis(3-pentyl-5-(4-methylpyridinium-1-ylmethyl)salicylidene)-1,2-cyclohexanedicarboximide dibromide (14bB) was prepared according to GP4 using 12bB (2 eq., 0.30 mmol, 113.5 mg) and (1R,2R)-(−)-1,2-diaminocyclohexane (1 eq., 0.15 mmol, 17.1 mg). The product was formed as a beige-colored solid (0.14 mmol, 116.9 mg, 93%). C44H58Br2N2O2, MW: 834.76 g/mol. M.p.: 143.7–146.8 °C. [α]D20°C = 9.5 mg/mL, CH2Cl2 = −289.1. 1H-NMR (300 MHz, CDCl3, 20 °C): δ = 13.97 (b, 2H, Ar-OH), 9.26 (d, J = 6.7, 4H, Ar-OH), 8.33 (s, 2H, Ar-CH=N-Cy), 7.78 (m, 2H, Ar-H), 7.76 (m, 4H, m-Py-H), 7.11 (m, 2H, Ar-H), 6.08–5.91 (m, 4H, Ar-CH2-Py), 3.41 (m, 2H, Cy-HN=CHR)), 2.59 (s, 6H, Py-CH3), 2.48 (t, J = 7.8, 4H, Ar-CH2CH3), 1.93–1.84 (m, 4H, Cy-H2), 1.71–1.62 (m, 2H, Cy-H2), 1.55–1.43 (m, 6H, (CH2)pentyl und Cy-H2), 1.29–1.19 (m, 8H, (CH2)pentyl), 0.81 (t, J = 6.8, 6H, C3H6CH3). 13C-NMR (125 MHz, CDCl3, 20 °C): δ = 164.4, 159.0, 158.7, 144.3, 135.0, 133.6, 133.1, 128.4, 120.6, 118.4, 71.4, 59.2, 34.6, 33.0, 31.5, 31.3, 24.1, 22.5, 22.3, 14.1. IR (solid): ν = 3380, 2926, 2855, 1629, 1468, 1276, 1152, 1028, 829, 787. MS (ESI) m/z: 487.3 (5%, [M]+2×[Py]), 337.2 (1%, [M]+2), 290.7 (100%, [M]+2−2×[Py]), 244.2 (8%, [M]+2−2×[Py]). HRMS (ESI) m/z: Anal. Calcd. for [[C44H58N4O2]2+]2: 337.2274, found: 337.2294.

(R,R)-(−)-N,N'-Bis(3-pentyl-5-(4-tert-butylpyridinium-1-ylmethyl)salicylidene)-1,2-cyclohexanediamide dibromide (14bC) was prepared according to GP4 using 12bC (2 eq., 0.30 mmol, 126.1 mg) and (1R,2R)-(−)-1,2-diaminocyclohexane (1 eq., 0.15 mmol, 17.1 mg). The product was formed as a beige-colored solid (0.12 mmol, 113.1 mg, 82%). C50H70Br2N2O2, MW: 918.92 g/mol. M.p.: 154.7–157.3 °C. [α]D20°C = 10.2 mg/mL, CH2Cl2 = −289.1. 1H-NMR (300 MHz, CDCl3, 20 °C): δ = 13.97 (b, 2H, Ar-OH), 9.44 (d, J = 6.7, 4H, Ar-OH), 8.33 (s, 2H, Ar-CH=N-Cy), 7.89 (d, J = 6.8, 4H, m-Py-H), 7.84 (m, 2H, Ar-H), 7.11 (m, 2H, Ar-H), 6.13–5.95 (m, 4H, Ar-CH2-Py), 3.42 (m, 2H, Cy-HN=CHR)), 2.48 (t, J = 7.8, 4H, Ar-CH2CH3), 1.92–1.85 (m, 4H, Cy-H2), 1.72–1.61 (m, 2H, Cy-H2), 1.55–1.44 (m, 6H, (CH2)pentyl und Cy-H2), 1.34 (s, 18H, Py-(CH3)), 1.29–1.19 (m, 8H, (CH2)pentyl), 0.81 (t, J = 6.8, 6H, C3H6CH3). 13C-NMR (125 MHz, CDCl3, 20 °C): δ = 170.6, 164.5, 158.9, 144.7, 135.2, 133.7, 133.1, 124.9, 120.7, 118.4, 71.5, 58.8, 36.5, 34.6, 33.1, 31.5, 30.5, 30.0, 24.0, 22.5, 14.1. IR (solid): ν = 3380, 2927, 2857, 1630, 1459, 1275, 1167, 1109, 1025, 850, 815. MS (ESI) m/z: 379.3 (27%, [M]+2), 311.7 (100%, [M]+2−[Py]). HRMS (ESI) m/z: Anal. Calcd. for [[C50H70N2O2]2+]2: 379.2744, found: 379.2770.
(R,R)-(−)-N,N′-Bis(3-pentyl-5-(3,5-dimethylpyridinium-1-ylmethyl)salicylidene)-1,2-cyclohexanediamine dibromide (14bD) was prepared according to GP4 using 12bD (2 eq., 0.30 mmol, 117.8 mg) and (1R,2R)-(−)-1,2-diaminocyclohexane (1 eq., 0.15 mmol, 17.1 mg). The product was formed as a yellow solid (0.14 mmol, 117.9 mg, 91%). C_{46}H_{52}Br_{2}N_{4}O_{2}, MW: 862.82 g/mol. M.p.: 139.3–141.2 °C. [α]D20°C c = 10.7 mg/mL, CH₂Cl₂ = −271.0. ¹H-NMR (300 MHz, CDCl₃, 20 °C): δ = 13.91 (b, 2H, Ar-OH), 9.13 (m, 4H, o-Py-H), 8.33 (s, 2H, Ar-CH=N-Cy), 7.92 (m, 2H, p-Py-H), 7.80 (d, J = 2.0, 2H, Ar-H), 7.08 (d, J = 2.0, 2H, Ar-H), 6.06–5.91 (m, 4H, Ar-CH₂-Py), 3.43 (m, 2H, Cy-HN=CHR), 2.54–2.47 (m, 16H, Ar-CH₂Cy₃ and Py-CH₃), 1.93–1.85 (m, 4H, Cy-H₂), 1.73–1.60 (m, 2H, Cy-H₂), 1.55–1.43 (m, 6H, (CH₂)₅pentyl und Cy-H₂), 1.29–1.20 (m, 8H, (CH₂)₅pentyl), 0.82 (t, J = 6.8, 6H, C₆H₄(CH₂)₅). ¹³C-NMR (125 MHz, CDCl₃, 20 °C): δ = 164.5, 158.8, 146.0, 142.0, 138.3, 135.4, 133.7, 133.0, 130.6, 118.4, 71.6, 59.4, 34.6, 33.2, 31.5, 31.2, 24.1, 22.5, 18.7, 14.1. IR (solid): ν̃ = 3386, 2924, 2855, 1627, 1468, 1277, 1171, 1030, 863, 783, 700. MS (ESI) m/z: 487.3 (52%, [M]−2 × [Py]), 351.2 (34%, [M]²−), 595.4 (100%, [M]²−+[Py]). HRMS (ESI) m/z: Anal. Calcd. for [C_{46}H_{62}N_{4}O_{2}]²⁺: 351.2431, found: 351.2424.

(R,R)-(−)-N,N′-Bis(3-pentyl-5-(quinolinium-1-ylmethyl)salicylidene)-1,2-cyclohexanediamine dibromide (14bE) was prepared according to GP4 using 12bE (2 eq., 0.30 mmol, 124.3 mg) and (1R,2R)-(−)-1,2-diaminocyclohexane (1 eq., 0.15 mmol, 17.1 mg). The product was formed as an orange solid (0.14 mmol, 127.9 mg, 94%). C₅₀H₅₈Br₂N₄O₂, MW: 906.83 g/mol. M.p.: 146.2–147.8 °C. [α]D20°C c = 10.4 mg/mL, CH₂Cl₂ = −193.3. ¹H-NMR (300 MHz, CDCl₃, 20 °C): δ = 14.15 (b, 2H, Ar-OH), 10.32 (d, J = 5.5, 2H, quinoline-H), 9.17 (d, J = 8.3, 2H, quinoline-H), 8.59 (d, J = 8.9, 2H, quinoline-H), 8.39 (s, 2H, Ar-CH=N-Cy), 8.23 (d, J = 7.8, 2H, quinoline-H), 8.08 (m, 2H, quinoline-H), 7.83 (m, 2H, quinoline-H). 7.73 (m, 2H, quinoline-H), 7.43 (m, 2H, Ar-H), 7.11 (m, 2H, Ar-H), 6.48–6.36 (m, 4H, Ar-CH₂-quinolinium), 3.47 (m, 2H, Cy-HN=CHR), 2.59 (s, 6H, Py-CH₂), 2.44 (t, J = 7.8, 4H, Ar-CH₂Cy₃), 1.96–1.84 (m, 4H, Cy-H₂), 1.73–1.61 (m, 2H, Cy-H₂), 1.54–1.38 (m, 6H, (CH₂₅pentyl und Cy-H₂), 1.28–1.12 (m, 8H, (CH₂₅pentyl), 0.77 (t, J = 6.8, 6H, C₆H₄(CH₂₅)). ¹³C-NMR (125 MHz, CDCl₃, 20 °C): δ = 164.5, 158.6, 150.8, 147.6, 137.9, 135.7, 133.7, 133.3, 132.9, 129.9, 122.0, 119.5, 119.0, 118.5, 71.1, 56.6, 34.6, 32.9, 31.3, 31.2, 24.1, 22.4, 14.1. IR (solid): ν̃ = 3385, 2924, 2854, 1562, 1526, 1465, 1373, 1230, 1020, 769. MS (ESI) m/z: 616.4 (10%, [M]−[quinoline]), 487.3 (80%, [M]−2×[quinoline]), 373.2 (14%, [M]²−), 308.7 (100%, [M]²−+[quinoline]). HRMS (ESI) m/z: Anal. Calcd. for [[C₅₀H₅₈N₄O₂]²⁺]: 373.2274, found: 373.2284.

(R,R)-(−)-N,N′-Bis(3-pentyl-5-(4-(dimethylamino)pyridinium-1-ylmethyl)salicylidene)-1,2-cyclohexanediamine dibromide (14bF) was prepared according to GP4 using 12bF (2 eq., 0.30 mmol, 122.2 mg) and (1R,2R)-(−)-1,2-diaminocyclohexane (1 eq., 0.15 mmol, 17.1 mg). The product was formed as a yellow solid (0.14 mmol, 123.1 mg, 92%). C₄₆H₆₄Br₂N₄O₂, MW: 892.85 g/mol. M.p.: 145.9–147.1 °C. [α]D20°C c = 10.2 mg/mL, CH₂Cl₂ = −269.1. ¹H-NMR (300 MHz, CDCl₃, 20 °C): δ = 13.91 (b, 2H, Ar-OH), 8.51 (d, J = 7.7, 4H, o-Py-H), 8.35 (s, 2H, Ar-CH=N-Cy), 7.73 (d, J = 1.9, 2H, Ar-H), 7.09 (d, J = 2.0, 2H, Ar-H), 6.89 (d, J = 7.8, 4H, m-Py-H), 5.50–5.37 (m, 4H, Ar-CH₂-Py), 3.42 (m, 2H, Cy-HN=CHR), 3.21 (s, 12H, Py-N(CH₃)₂), 2.47 (t, J = 7.8, 4H, Ar-CH₂Cy₃), 1.96–1.86 (m, 4H, Cy-H₂), 1.74–1.59 (m, 2H, Cy-H₂), 1.54–1.45 (m, 6H, (CH₂₅pentyl und Cy-H₂), 1.33–1.20 (m, 8H, (CH₂₅pentyl), 0.82 (t, J = 6.7, 6H, C₆H₄(CH₂)). ¹³C-NMR (125 MHz, CDCl₃, 20 °C): δ = 164.5, 158.4,
(R,R)-(−)-N,N′-Bis(3-pentyl-5-(4-iodopyridinium-1-ylmethyl)salicylidene)-1,2-cyclohexanediamine dibromide (14bG) was prepared according to GP4 using 12bG (2 eq., 0.30 mmol, 147.1 mg) and 
(1R,2R)-(−)-1,2-diaminocyclohexane (1 eq., 0.15 mmol, 17.1 mg). The product was formed as a brown solid (0.14 mmol, 142.4 mg, 77%). C42H52Br2I2N4O2, MW: 1058.50 g/mol. M.p.: 221.2–223.7 °C (decomposition).

CδD20[α]20 (c = 9.6 mg/mL, DMSO) = −242.8. 1H-NMR (300 MHz, DMSO, 20 °C): δ = 14.19 (b, 2H, Ar-OH), 8.73 (d, J = 6.4, 4H, o-Py-H), 8.54 (d, J = 6.5, 4H, m-Py-H), 8.48 (s, 2H, Ar-CH=NCy), 7.47 (b, 2H, Ar-H), 7.20 (b, 2H, Ar-H), 5.69–5.60 (m, 4H, Ar-C2-Py), 3.49 (m, 2H, Cy-H=NCHR), 2.46 (m, 4H, Py-C2CH3), 1.93–1.86 (m, 4H, Cy-H2), 1.81–1.74 (m, 4H, (CH2)pentyl), 1.63–1.40 (m, 4H, Cy-H2), 1.33–1.19 (m, 8H, (CH2)pentyl), 0.84 (t, 6H, C4H8CH3). 13C-NMR (125 MHz, DMSO, 20 °C): δ = 165.4, 159.7, 144.0, 137.0, 134.7, 132.8, 132.7, 126.1, 121.1, 118.4, 117.4, 69.4, 58.9, 33.8, 32.2, 30.7, 30.4, 23.5, 21.8, 13.8. IR (solid): ν = 3396, 2923, 2852, 1615, 1441, 1160, 1026, 806. MS (ESI) m/z: 977.1 (1%, [M]+−[Br]), 4.87.3 (31%, [M]+−2×[Py]), 346.6 (100%, [M]+2−[Py]). HRMS (ESI) m/z: Anal. Calcd. for [C42H52I2N4O2]+: 449.1084, found: 449.1105.

3.6. General Procedure for the Catalytic Asymmetric Synthesis of 3 (GP5)

To a solution of the salen ligand 14 (0.1 eq., 75 µmol) in CH2Cl2 (3 mL) a solution of Me3Al in toluene (2 M, 0.1 eq., 75 µmol, 38 µL) was added and the mixture was stirred for 3 h at ambient temperature. Afterwards aldehyde 1 (1 eq., 0.75 mmol), acylbromide 2 (6 eq., 4.5 mmol) and diisopropylethylamine (2.5 eq., 1.88 mmol) were added at −70 °C and the reaction mixture was stirred for 24 h at this temperature. The reaction was quenched by pouring into aqueous 1 M HCl (30 mL) and the product was extracted with CH2Cl2 (2 × 20 mL). The combined organic layers were dried over MgSO4 and filtered through a pad of silica gel. After removing the solvent in vacuo the desired trans-β-lactone 3 was obtained.

(3S,4S)-trans-3-Methyl-4-(2-phenylethyl)-oxetan-2-one (3Aa, 0.45 mmol, yield: 60%, ee = 90%, dr = 97:3) was prepared from propionyl bromide (1A) and 3-phenylpropionaldehyde (2a) according to GP5. The dr value was determined by 1H-NMR and the ee value by HPLC (Chiralcel OD-H, 97:3 n-hexane/iPrOH, 1.0 mL/min, 210 nm). An analytically pure sample was obtained as a colorless oil by flash chromatography (pentane/diethyl ether 20:1). C12H14O2, MW: 190.24 g/mol. 1H-NMR (300 MHz, CDCl3, 20 °C): δ = 7.34–7.17 (m, 5H, Ar-H), 4.16 (ddd, J = 7.5, 5.9, 4.0, 1H, CH-O), 3.20 (qd, J = 7.5, 4.0, 1H, CH-C(O)), 2.77 (m, 2H, CH2-CH2-Ph), 2.13 (m, 2H, CH2-CH2-Ph), 1.32 (d, J = 7.5, 3H, CH3). The analytical data are in agreement with the literature [54].

(3S,4S)-trans-3-Methyl-4-ethylxetan-2-one (3Ab, 0.44 mmol, yield: 59%, ee = 90%, dr = 98:2) was prepared from propionyl bromide (1A) and propanal (2b) according to GP5. The dr value was determined by 1H-NMR and the ee value by GC (Fisons Instruments HRGC Mega 2, Bondex-UN-β-column 20 m × 0.30 mm, 0.5 bar H2, method: 40 °C hold 5 min, ramp @ 2.5 °C/min till 100 °C, ramp
@ 10.0 °C/min till 200 °C). An analytically pure sample was obtained as a colorless oil by flash chromatography (pentane/diethyl ether 20:1). C\textsubscript{6}H\textsubscript{10}O\textsubscript{2}, MW: 162.18 g/mol. 1H-NMR (300 MHz, CDCl\textsubscript{3}, 20 °C): δ = 7.45–7.36 (m, 5H, Ar-H), 5.15 (d, J = 4.2, 1H, CH-O), 3.58 (qd, J = 7.5, 4.2, 1H, CH-C(O)), 1.53 (d, J = 7.5, 3H, CH\textsubscript{3}). The analytical data are in agreement with the literature [54].

(3S,4R)-trans-3-Methyl-4-phenyloxetan-2-one (3Ba, 0.18 mmol, yield 37%, ee = 96%, dr = 98:2) was prepared from propionyl bromide (1B) and benzaldehyde (2c) according to GP5. The dr value was determined by 1H-NMR and the ee value by HPLC (Chiralcel OD-H, 97:3 n-hexane/iPrOH, 0.5 mL/min, 210 nm). An analytically pure sample was obtained as a colorless oil by flash chromatography (CH\textsubscript{2}Cl\textsubscript{2}/pentane 3:1, then pentane/diethyl ether 1:10). The analytical data are in agreement with the literature [54].

Preformation of the catalyst \{[(1R,2R)-1,2-cyclohexanediylbis[fimino-κ\textsuperscript{2}N][5-pentyl-2-(hydroxy-k\textsuperscript{2}O)-3,1-phenylenemethylen]bis[4-methyl-pyridinium]](2-)]-methylaluminum(III)\} dibromide (4bB): To a solution of ligand 4bB (0.13 g, 0.16 mmol, 1.0 equiv.) in CH\textsubscript{2}Cl\textsubscript{2} (3.0 mL) a solution of Me\textsubscript{3}Al in toluene (2 M, 0.10 mL, 0.16 mmol, 1.0 equiv.) was added. The mixture was stirred for 3 h at ambient temperature. The reaction mixture was poured into 20 mL of pentane to precipitate complex 4bB. Subsequently the mixture was centrifuged and the supernatant removed. Washing the catalyst with additional pentane (10 mL) and drying \textit{in vacuo} afforded the active catalyst as orange powder in quantitative yield. C\textsubscript{42}H\textsubscript{59}AlBr\textsubscript{2}N\textsubscript{2}O\textsubscript{2}, MW: 874.77 g/mol. 1H-NMR (500 MHz, CD\textsubscript{2}Cl\textsubscript{2}, 20 °C): δ = 9.48 (m, 2H, o-Py-H), 9.42 (m, 2H, o-Py-H), 8.49 (m, 1H, Ar-CH=N-Cy), 8.15 (m, 1H, Ar-CH=NCy), 7.78 (m, 1H, m-Py-H), 7.74–7.71 (m, 3H, m-Py-H), 7.53 (d, J = 5.5, 2H, Ar-H), 7.28 (m, 1H, Ar-H), 7.24 (m, 1H, Ar-H), 6.52 (d, J = 13.7, 1H, Ar-CH\textsubscript{2}-Py), 6.38 (d, J = 13.5, 1H, Ar-CH\textsubscript{2}-Py), 5.98 (d, J = 13.7, 1H, Ar-CH\textsubscript{2}-Py), 5.86 (d, J = 13.5, 1H, Ar-CH\textsubscript{2}-Py), 3.63 (m, 1H, Cy-HN=CHR), 3.15 (m, 1H, Cy-HN=CHR), 2.61–2.45 (m, 11H, Cy-H\textsubscript{2} and (CH\textsubscript{2}pentyl and Py-CH\textsubscript{2}), 2.34 (m, 1H, Cy-H\textsubscript{2}), 2.05 (m, 2H, Cy-H\textsubscript{2}), 1.66–1.58 (m, 4H), 1.52–1.45 (m, 4H), 1.39–1.26 (m, 8H, (CH\textsubscript{2}pentyl), 0.93–0.87 (m, 6H, (CH\textsubscript{2}pentyl), −1.31 (s, 3H, Al-CH\textsubscript{3}). 13C-NMR (125 MHz, CD\textsubscript{2}Cl\textsubscript{2}, 20 °C):
δ = 168.8, 162.1, 161.3, 160.7, 158.7, 158.4, 144.6, 144.5, 138.5, 136.9, 135.5, 134.5, 131.9, 131.3, 127.9, 127.7, 124.9, 124.3, 119.2, 119.1, 66.2, 62.5, 60.6, 60.1, 34.4, 31.5, 31.4, 31.2, 31.2, 29.7, 26.9, 24.1, 23.7, 22.5, 22.3, 21.9, 13.9, 13.8. MS (ESI) m/z: 793.4 (100%, [M]+–Br) 700.3 (86%, [M]+–Py–Br). HRMS (ESI) m/z: Anal. Calcd. for [C_{45}H_{59}AlBrN_{4}O_{2}]$: 793.3631, found: 793.3620.

4. Conclusions

In summary, we have reported a catalyst which offers the highest enantio- and trans-selectivity known so far for the catalytic asymmetric synthesis of β-lactones by [2+2] cyclocondensation of acyl halides and aldehydes. Catalysts for the asymmetric formation of trans-β-lactones are of major interest, since trans-β-lactones offer a divergent and atom-economic access to the important class of anti-aldol products. In our catalyst, an Al-center (offering a single coordination site) cooperates with a picolinium bromide moiety based on our recently published strategy to combine the concepts of Lewis acid and organic aprotic ion pair catalysis in a single catalyst system. Since cationic residues like pyridinium units have been found to be essential for both high trans- and enantioselectivity (suggesting that the positive charge enables an ion pair catalysis pathway), we have investigated the question, if substituents on the pyridinium rings can be utilized to further improve the catalyst efficiency, as they might display a significant impact on the effective charges. In the present study we have thus compared a small library of aluminum-salen/bispyridinium catalysts, mainly differing in the substituents on the pyridinium rings. NBO calculations have revealed though that the different catalyst efficiencies can arguably not be explained by the variation of the effective charges, since there are only very small differences for σ-donor or σ-acceptor substituted pyridinium systems. However, we have noticed that the substituents have a major impact on the catalyst stability and presumably they have also an impact on the reactive conformation of the proposed acyl halide enolate intermediates.

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