Design of chiral urea-quaternary ammonium salt hybrid catalysts for asymmetric reactions of glycine Schiff bases†

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Bifunctional chiral urea-containing quaternary ammonium salts can be straightforwardly synthesised in good yield and with high structural diversity via a scalable and operationally simple highly telescoped sequence starting from trans-1,2-cyclohexanediamine. These novel hybrid catalysts were systematically investigated for their potential to control glycine Schiff bases in asymmetric addition reactions. It was found that Michael addition reactions and the herein presented aldol-initiated cascade reaction can be carried out to provide enantiomeric ratios up to 95 : 5 and good yields under mild conditions at room temperature.

Introduction

Chiral onium salt (phase-transfer) catalysis is one of the fundamental non-covalent activation strategies in asymmetric catalysis.1 Besides monofunctional chiral ammonium salt catalysts, the use of bifunctional derivatives has emerged as a powerful strategy for numerous applications.2 Whereas the vast majority of such catalysts contain an additional OH-group as the second coordination site,2–4 the design and application of ammonium salts containing alternative H-bonding motifs has so far been less exhaustively investigated.2,5–7 While the groups of Lassaletta and Fernández,5e Dixon,5b Smith,5c and Lin and Duan5d introduced powerful Cinchona alkaloid-based (thio)urea containing bifunctional ammonium salt catalysts, Zhao et al.6 recently developed a modular approach to access α-amino acid-based (thio)urea/ammonium salt hybrid catalysts. Simultaneously, our groups introduced trans-1,2-cyclohexanediameine-based bifunctional ammonium salts 1 (Scheme 1).7 An extensive screening of different salts allowed us to identify 1a as the most efficient chiral catalyst for asymmetric α-fluorination of β-ketoesters 2.7a In addition, catalyst 1b was found to be promising for a newly developed aldol-initiated cascade reaction of glycine Schiff base 5 with cyanobenzaldehyde 6.7b In the initial optimisation of this powerful transformation only one cyclohexanediameine-based catalyst 1 was tested and it was also found that the Cinchona alkaloid-based catalyst 9 introduced by Dixon5b and Smith5c gave the highest e.r. of 85 : 15 among the existing bifunctional ammonium salt motifs tested so far (Scheme 1, lower reaction).7b

These encouraging initial results with this novel family of asymmetric catalysts prompted our groups to initiate a joint project focusing on the further development and exploration of

Scheme 1 Hybrid ammonium salts 1 and their applications reported previously.
the hybrid salts 1 for stereoselective transformations. Thus we especially focused on optimisation of the existing synthesis route to fuel the demand for larger quantities of the readily tuneable catalysts 1 and on systematic testing of these catalysts for asymmetric reactions of glycine Schiff bases 5 (i.e. the already mentioned cascade reaction and Michael addition reactions). Hereby a detailed screening of these catalysts to increase the selectivity in the cascade synthesis of compound 8 was considered to be particularly interesting, as our modular catalyst synthesis approach should allow us to overcome the limitations of the existing catalyst motifs. Interestingly, the groups of Liu and Soloshonok recently achieved a highly asymmetric synthesis of analogous lactams in a complementary approach by employing an asymmetric auxiliary-based approach using chiral glycine Schiff base Ni(II) complexes. This report once again proves the high potential of this robust auxiliary approach for the synthesis of chiral z-amino acid derivatives.

Results and discussion
Catalyst synthesis
In contrast to recent reports by others who described incorporation of the H-bonding donor first, followed by a final quaternization step, we have chosen to use an opposite assembly strategy, carrying out the quaternization of mono-protected diamine 11 first, followed by deprotection and coupling with an iso(thio)cyanate (Scheme 2). This strategy allowed us to overcome some of the challenges of the commonly used protocols, as side reactions of the nucleophilic heteroatoms of the H-bonding donor with the alkylation agent can be avoided, thus resulting in a broader and more functional group tolerant synthesis route.

As outlined in Scheme 2, the catalysts 1 can be obtained from the known Boc-protected diamine 11 in four chemical steps. First, the introduction of bulkier (aromatic) residues for R2 on the ammonium side can be easily accomplished by means of a reductive amination, giving the corresponding secondary amines 12 in high yields (>90% conversion) and without the need for any further purification. However, the subsequent quaternization (step B, Scheme 2) was found to be the major bottleneck in the initial protocol. It was not possible to introduce any residues that are sterically more demanding than a methyl group, thus allowing the syntheses of dimethyl-containing ammonium salts 13 only. In addition, we found that this exhaustive methylation is strongly dependent on the nature of substituent R1. While smaller, electron rich or electron neutral groups like a phenyl group allowed us to obtain 13 in slightly more than 50% yield starting from 11, electron-poor or sterically more demanding groups performed significantly worse (down to around 25% yield). Hereby we faced two problems: first the final quaternization was rather slow, leading to mixtures of tert-amine intermediates and the quaternary ammonium salts even after long reaction times. In addition, under the rather forcing and prolonged conditions we observed formation of large quantities of the trimethyl ammonium salt 13b (R1 = H). Formation of the latter can be explained by a nucleophilic substitution of the benzylic ammonium groups of compound 13 (e.g. by the base or the iodide counter anion) under the harsh reaction conditions, giving the more reactive dimethyl-containing tert-amine, which was then further methylated. This effect lowered the overall yields significantly and also made purification of the ammonium salts rather difficult. In addition, when using sterically even more demanding R1 residues like an anthracenyl group no product 13 could be obtained.

To overcome these significant limitations, we first tested alternative (sterically less demanding) N-protecting groups (e.g. alloc) but with no success. Also other methylation agents did not improve the outcome. Gratifyingly, after a very careful screening of different conditions we finally found that carrying out the reaction with Mel (6 eq.) and solid K2CO3 (1.1 eq.) in DMF (60 °C) gave the target ammonium salts (13) in reliably high yields (around 70% in situ) and sufficient purity to be telescoped further in the sequence without any purification. It is noteworthy that almost no tert-amine intermediates and no trimethyl ammonium salt 13b were formed (traces of 13b originating from methylation of remaining 11 could be separated in the next step). This strategy was found to be very robust for when R1 is electron-rich, -neutral, and -poor, giving access to derivatives that were not accessible by the initial route (e.g. 3,5-(CF3)2-C6H3-). Unfortunately, when using sterically demanding R1 groups (e.g. naphthyl or ortho-substituted aromatics) this route was still not very satisfactory (hereby the reactions mainly stalled at the tert-amine intermediates). However, the ammonium salts could be obtained in reasonable yields by first carrying out the dimethylation of 11 (step C) and then a final quaternization with the appropriate benzyl halide (step D). Again the products were obtained in sufficient purity for direct further use. Thus, these newly developed quaternization
conditions allowed us to obtain a much more diverse assembly of ammonium salts 13 which were then transformed into the catalysts 1 in two more steps. The only limitations in the present synthesis are the fact that only one sterically demanding group R1 can be introduced and that groups bigger than a naphthyl group (e.g. anthracenyl) can only very slowly be incorporated.

The Boc-deprotection (step E) was initially carried out with TFA and the resulting salt (obtained by evaporation of the TFA and the solvent) was directly used for the final coupling step. However, this deprotection procedure gave mixtures of ammonium trifluoroacetates and iodides, which showed different catalytic properties and were difficult to separate. Use of HI for the deprotection was found to be beneficial for this reaction and, accompanied with an extractive work up, yielded the free amines 14 in good purity and yield. The extraction also allowed us to remove residual trimethyl ammonium salt 14b (R1 = H), which is significantly more hydrophilic than the aryl-containing derivatives. With this optimized procedure in hand, the final coupling could be carried out straightforwardly with different iso(thio)cyanates, requiring only one final (and simple) purification by silica gel column chromatography. Thus, a diversified assembly of different catalysts 1 can now be obtained in a telescoped and operationally simple manner and with satisfying overall yields (>30% based on 10) on a practical scale (up to 3 mmol).

Asymmetric reactions of the glycine Schiff bases

The first transformation that we carefully investigated was the Michael addition of glycine Schiff base 5 to acceptors like methyl acrylate 15a. This has been a thoroughly investigated reaction in asymmetric non-covariant organocatalysis in the past and it is noteworthy that most of the reported catalysts have their own characteristics with respect to their application scope (especially when using β-substituted acceptors).13–15 Thus we were curious to see whether our hybrid catalysts can be used (and systematically optimised) to control this important transformation. Table 1 gives an overview of the most significant results obtained from a very detailed screening of different catalysts and reactions conditions. We first identified the combination of toluene and solid Cs2CO3 (1.5 eq.) as the best-suited solvent–base system for this reaction. Larger amounts of base favoured the racemic background reaction and non-aromatic solvents or aqueous (alternative) bases generally gave significantly lower selectivities (these effects were also carefully double-checked once the most active catalyst was identified).

With the solvent and base conditions set, we focused on the identification of the most active catalyst. All the initial reactions were run for 24 h using the same setup (Schlenk flask, stirring rate, and dilution) and stoichiometric ratio of the reagents to assure reproducible and comparable biphasic reaction conditions.

It immediately became apparent that ureas are better-suited than thioureas (see entries 1 and 2) and that the use of benzylic ammonium salts is beneficial (entry 3 vs. 1). Thus a series of hybrid catalysts with different aryl groups (R1) on the ammonium side (keeping the phenyl-urea R2 unchanged) were tested under identical conditions (entries 3–8 give the most significant results). Contrary to our results obtained in the α-fluorination of ketoesters14 (shown in Scheme 1), the introduction of bulky naphthyl groups as R1 was found to have no beneficial effect. In contrast, increasing the bulk by incorporating a t-butyl group on the aryl moiety (entry 6) significantly reduced the reaction rate. Also, the introduction of nitro substituents did not allow us to increase the selectivity (entry 7). Luckily, as already discussed above, the new synthesis protocol (Scheme 2) allowed us to introduce trifluoromethyl-substituted aryl groups as R1 (i.e. 3,5-(CF3)-C6H3) in good yield. This catalyst modification turned out to be the most fruitful amongst all the tested R1 groups, giving 16a with reasonable selectivity (e.r. = 84 : 16) and in high yield under the standard conditions (entry 8). Based on this encouraging result, we next systematically modified the urea-substituent R2. The presence of electron-withdrawing groups led to reduced selectivities in the case of CF3- or nitro-, or diester-containing R2 groups (entries 9–11). It is noteworthy that the latter was found to be the urea-modification of choice in our recent α-fluorination protocol.14 Accordingly, these results show once more that such reactions always require a detailed and systematic screening of differently modified catalysts, thus illustrating the need for a flexible and functional group-tolerant catalyst synthesis as outlined in Scheme 2.

Interestingly, at this stage we found that replacing the aryl moieties on the urea side by incorporating a cyclohexyl group as R2 instead resulted in a good selectivity of 87 : 13 (entry 12). Based on the fact that aliphatic groups were never found to be promising for any of our previously investigated reactions (published or unpublished) this result came as a big surprise. By testing the influence of the reaction temperature we found that the selectivity can be increased by lowering the temperature, however this is accompanied by a reduced reaction rate (entries 14 and 15). Again, the reduced selectivity when using thiourea-moieties was proven by testing the analogous cyclohexyl-thiourea catalyst (entry 16). Finally, additional modifications introducing different alkyl groups as R2 allowed us to identify an ethyl group as the most powerful urea-substituent, giving 16a with an enantiomeric ratio of 89 : 11 under the standard conditions at room temperature. Further fine-tuning of the reaction conditions showed that the selectivity increases with higher dilution, however this results in a stepwise decrease of conversion (entries 18–23). The highest selectivities were obtained either by carrying out the reaction at a 0.02 M concentration of 5 at 25 °C (entry 21) or at higher concentration (0.08 M) at 0 °C (entry 20), albeit with reduced conversion. Furthermore, lowering the catalyst loading resulted in a reduced catalytic performance (entry 22), and further dilution did not allow us to improve the selectivity any further (entry 23).

To prove the necessity of the bifunctional nature of the catalysts 1 we also tested the simplified catalysts 17 and 18, which performed with much less selectivity or did not give any product at all under the optimized reaction conditions (Scheme 3).
Having identified the best-suited catalyst and the optimum reaction conditions (see entry 21, Table 1) we next investigated the application scope for this reaction (Scheme 4). One important fact that should be mentioned is that this biphasic transformation was found to be rather sensitive (e.r. and conversion) with respect to changes in the reaction setup (i.e. shape of the Schlenk flasks used and stirring rate). Therefore, when investigating the application scope we always carried out each test reaction on a 0.1 mmol scale (based on 5) with exactly the same setup and for comparison also on a smaller scale (0.02 mmol). All the results shown in Scheme 4 were thus carefully double-checked and found to be reproducible in at least two runs with two different setups each.

Testing different esters of the glycine Schiff base 5 first, we found that all gave good conversion within 24 h, but that the selectivity depends on the nature of the ester group, with bulky t-butyl esters of 5 giving the highest enantioselectivity in the addition to methyl acrylate 15a (see results for products 16a – 16c). Interestingly, by changing the ester group of the Michael acceptor 15 both the conversion rate and the enantioselectivity were influenced (see products 16d – 16f). This was most notable in the synthesis of the di-t-butyl containing diester 16e (only 15% conversion under standard conditions and a reduced e.r. of 83 : 17). Here the conversion could be increased by using 5 mol% catalyst without affecting the e.r. (when using other acceptors the use of a larger excess of base usually resulted in a reduced e.r. because of an increased rate of the racemic background reaction). When testing phenyl vinyl sulfone as an acceptor (giving product 16g) the selectivity dropped significantly, whereas N,N-dimethyl acrylamide and methyl vinyl ketone could be employed with reasonable selectivities (16h and 16i). Unfortunately, the acrylamide acceptor was found to

Table 1 Identification of the most active catalyst 1 and the best-suited reaction conditions for the addition of 5 to 15a

<table>
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<th>No</th>
<th>R¹</th>
<th>R²</th>
<th>X</th>
<th>Conc.² [M]</th>
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<td>25</td>
<td>8</td>
<td>95 : 5</td>
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¹ Based on 5. ² Isolated yield. ³ Determined from HPLC using a chiral stationary phase. ⁴ Using 5 mol% catalyst.

Scheme 3 Control experiments using the simplified catalysts 17 and 18.
react rather slowly and in this case the use of more base did not really allow us to overcome this limitation as the selectivity was clearly affected (this substrate was also very difficult to control in an enantioselective manner in a recent project using structurally different TADDOL-based PTCs).49

Interesting results were obtained using prochiral electrophiles 15j–15m (as shown in the lower part of Scheme 4). Using dimethyl maleate 15j, the product 16j could be obtained in good yield and with high diastereo- and enantioselectivity. It is noteworthy that Lambert and co-workers recently found that this substrate was unreactive when using their otherwise very powerful and highly selective cyclopropenimine chiral base catalysts. Using dimethyl fumarate 15j’ instead gave the diastereomeric 16j’ in good yield and diastereo- and enantioselectivity albeit with a slightly lower enantioselectivity. Another striking difference to the chiral cyclopropenimine base catalysts was also observed when employing s-trans acceptors 15k and 15l. Although cyclohexenone 15k underwent a slow 1,4-addition under the standard conditions (which can be explained by a competing dimerization under basic phase-transfer conditions), the stereoselectivity obtained is still reasonably high. Even more interestingly, when using cyclopentenone 15l we were able to obtain product 16l in high yield and with good stereoselectivity. Finally, chalcone was also accepted well in this reaction, providing the product 16k with reasonable selectivity and in good yield. Here it is of course fair to mention that for this substrate again Lambert’s chiral base catalyst was reported to be more selective and therefore the results obtained hereby may illustrate that our catalysts can provide a complementary and useful activation platform for future asymmetric organocatalytic transformations especially for addition reactions to s-trans Michael acceptors.

Having shown that the catalysts 1 can be systematically fine-tuned to obtain high selectivities for the Michael addition of the Schiﬀ bases 5 to different Michael acceptors 15, we next addressed the recently developed aldol-initiated cascade reaction of 5 with cyanobenzaldehyde 6.78 As already discussed above, the initial screening of existing catalysts showed that the Cinchona alkaloid-based bifunctional ammonium salt 9 introduced by Dixon5b and Smith15 gave the highest selectivity with a d.r. = 4 : 1 and an e.r. of 85 : 15 for the major diastereomer (see Scheme 1). With our optimized synthesis for the catalysts 1 in hand we put our efforts into identifying an even more selective catalyst for this powerful transformation. Table 2 gives an overview of the most significant results obtained thereby. The screening was carried out under the previously developed conditions78 using solid K2CO3 as the base in CH2Cl2 (other solvents and bases were tested too but found to be less useful). In addition, initial tests showed that again ureas are more active and selective than thioureas and thus the optimization was carried out with ureas only.

Entry 1 shows the initially reported result78 using the trimethylammonium-based catalyst 1b and it was soon found that variation of the urea group alone does not signiﬁcantly change the catalytic performance (entries 1–4). Introducing electron-neutral or bulky aryl groups on the ammonium side (entries 5–8) did not result in any improvement either. In contrast, the introduction of a naphthyl group even reduced the diastereo- and enantioselectivity (entry 8). Also the presence of aliphatic groups on the urea side (which was beneficial for our Michael reaction) did not allow us to improve the catalyst performance (entry 6) and a similar selectivity was obtained upon incorporation of more electron-rich aryl groups as R1 (entries 9 and 10).

In sharp contrast, the introduction of electron-withdrawing groups on the aryl group R1 on the ammonium side accompanied by the presence of an electron-poor aryl moiety R2 on the urea side resulted in significantly superior catalysts (entries 11–13). First, the dinitro-substituted catalyst used in entry 11 almost matched the result previously obtained with the Cinchona catalyst 9, both in terms of reactivity and selectivity. Gratifyingly, as already observed for the Michael addition, the introduction of a di-trifluoromethyl-phenyl group as R1 again signiﬁcantly improved the yield and the selectivity in this transformation (entries 12 and 13). Modifying the R2 group finally resulted in the most promising catalyst, shown in entry 12, which gave product 8 in 83% isolated yield and with a good
d.r. of 4 : 1 and excellent enantioselectivity for the major diastereoisomer (e.r. = 95 : 5; the minor diastereoisomer was always obtained with a lower enantiomeric ratio and no further improvement was possible).

Determination of the relative and absolute configuration of 8 turned out to be rather difficult as both diastereomers only crystallized as amorphous solids and thus X-ray structural analysis was not possible (the same was the case for the other derivatives shown in Scheme 5). The coupling constants of 7 and 8 also did not enable us to unambiguously determine the relative configuration (NOESY experiments were also not clear). However, it was possible to assign the absolute configuration of the amino acid stereogenic center of the major diastereomer to be (R) by analysis of the Mosher amide derivatives of 8a.

Subsequent NMR studies of the compounds then indicated that the major diastereomer is most probably the anti isomer as depicted in Table 2.

With the most active catalyst 1d in hand we quickly tested two halide- and one methoxy-containing cyanobenzaldehydes (6) under the same conditions and found that these substrates were also well tolerated, albeit the stereoselectivities slightly decreased in these cases, especially for the minor diastereoisomers (Scheme 5). Nevertheless, a first proof-of-principle for the generality of this reaction was clearly made, thus illustrating the potential of these catalysts for such cascade-reactions and providing a complementary approach to the recently reported analogous auxiliary-based protocol.

Experimental

General information

1H and 13C-NMR spectra were recorded on a Bruker Avance III 300 MHz spectrometer, on a Bruker Avance III 700 MHz spectrometer with a TCI cryoprobe or on Bruker DRX 400, 300 or 250 MHz spectrometers. All NMR spectra were referenced to the solvent peak. High resolution mass spectra were obtained using
an Agilent 6520 Q-TOF mass spectrometer with an ESI source and an Agilent G1607A coaxial sprayer or using a Thermo Fisher Scientific LTQ Orbitrap XL with an Ion Max API Source. Additional mass spectral analyses were carried out using an electrospray spectrometer, a Waters 4 micro quadrupole. Elemental analyses were performed either by using a Waters instrument or using a Dionex Summit HPLC system with a Chiralcel OD-H (250 × 4.6 mm, 5 μm), a Chiralcel OD-R (250 × 4.6 mm, 10 μm), or a Chiralpak AD-H (250 × 4.6 mm, 5 μm) chiral stationary phase. Optical rotations were recorded on a PerkinElmer Polarimeter Model 241 MC and on a Schmidt + Haensch Polarimeter Model Unipol L 1000. All chemicals were purchased from commercial suppliers and used without further purification unless otherwise stated. All reactions were performed under an Ar atmosphere.

A detailed experimental section including all the procedures and analytical data of the catalysts and asymmetric reaction products as well as copies of the NMR spectra and HPLC chromatograms can be found in the ESL†

Synthesis of catalysts 1c and 1d

**Step 2 (Scheme 2).** 3,5-bis(Trifluoromethyl)-benzaldehyde (484 mg, 2 mmol) was added to a solution of 11 (428 mg, 2 mmol) (prepared from (S,S)-cyclohexanediol dihydrochloride in analogy to the literature) in 10 mL of THF–methanol (1 : 1) and the solution was stirred at r.t. overnight. After addition of NaBH₄ (114 mg, 3 mmol, 1.5 eq.), stirring was continued until the reaction was quenched with water, and the solution was basified with saturated Na₂CO₃ solution. The organic phase was dried over Na₂SO₄ and removal of the solvent under reduced pressure gave crude 14c in quantitative yield (689 mg, 1.1 mmol). Compound 14c (R¹ = 3,5-(CF₃)₂-C₆H₄): ¹H NMR (300 MHz, δ, CDCl₃, 298 K): 1.13–1.17 (m, 1H), 1.35–1.40 (m, 1H), 2.67–2.72 (m, 1H), 2.88–2.93 (m, 1H), 3.03–3.05 (m, 1H), 3.10 (s, 3H), 4.08 (d, 1H, J = 14.1 Hz), 4.25 (d, 1H, J = 7.3 Hz), 7.73 (s, 1H), 7.82 (s, 2H) ppm.

**Step 3 (E).** The ammonium salt 13e (1.1 mmol) was dissolved in 12 mL of dichloromethane and hydroiodic acid (57 wt% aqueous solution) (1.45 mL, 11 mmol, 10 eq.) was added. After stirring for 2 h at r.t., the reaction was basified with saturated Na₂CO₃ solution and extracted with dichloromethane. The organic phase was dried over Na₂SO₄ and removal of the solvent under reduced pressure gave crude 14c in quantitative yield (689 mg, 1.1 mmol). Compound 14c (R¹ = 3,5-(CF₃)₂-C₆H₄): ¹H NMR (300 MHz, δ, CDCl₃, 298 K): 1.14–1.18 (m, 1H), 1.35–1.40 (m, 1H), 2.68–2.72 (m, 1H), 2.88–2.93 (m, 1H), 3.03–3.05 (m, 1H), 3.10 (s, 3H), 4.08 (d, 1H, J = 14.1 Hz), 4.25 (d, 1H, J = 7.3 Hz), 7.73 (s, 1H), 7.82 (s, 2H) ppm.

**Step 4 (F).** A solution of 14c and the corresponding isoyanate (1.2 eq.) in dichloromethane (20 mL per mmol of 14c) was stirred for 4 h at r.t. Evaporation of the solvent under reduced pressure gave crude 1, which was further purified by column chromatography (dichloromethane : methanol = 50 : 1 to 10 : 1) to obtain pure catalyst 1 in the reported yields.

**Catalyst 1c.** Obtained in 65% yield (123 mg, 0.217 mmol starting from 0.33 mmol of 13c) as a colourless oil. [α]⁺²⁵ (c = 1.3, CHCl₃) = 13.0°; ¹H NMR (300 MHz, δ, CDCl₃, 298 K): 1.16 (t, J = 7.2 Hz, 3H), 1.24–1.41 (m, 1H), 1.43–1.66 (m, 2H), 1.67–1.87 (m, 2H), 1.90–2.12 (m, 2H), 1.49–1.61 (m, 1H), 3.06 (s, 3H), 3.18–3.34 (m, 5H), 4.22–4.38 (m, 1H), 4.59–5.42 (m, 1H), 5.32–5.47 (m, 2H), 5.99 (s, 1H), 6.92 (d, J = 9.7 Hz, 1H), 7.97 (s, 1H), 8.00 (s, 1H); ¹³C NMR (75 MHz, δ, CDCl₃, 298 K): 15.5, 24.7, 25.1, 27.4, 28.5, 35.7, 49.7, 51.1, 51.7, 63.1, 77.8, 81.5, 122.8 (q, J = 273 Hz), 124.9, 130.3, 133.0 (q, J = 34 Hz), 133.6, 155.9 ppm; ¹⁹F NMR (282 MHz, δ, CDCl₃, 298 K): –62.8 ppm; IR (film): v = 3341, 3270, 3011, 2980, 2939, 2867, 1695, 1625, 1516, 1467, 1455, 1393, 1370, 1323, 1281, 1242, 1176, 1104, 1024, 904, 870, 844, 737, 709, 683 cm⁻¹; HRMS (ESI) m/z calcd for C₂₂H₁₈F₂N₂O₂⁺: 469.2284 [M⁺]; found: 469.2281.

**Catalyst 1d.** Obtained in 67% yield (96 mg, 0.14 mmol, starting from 0.22 mmol of 13e) as an orange oil. [α]⁺²⁵ (c = 0.75, CH₂Cl₂) = –29.3°; ¹H NMR (300 MHz, δ, CDCl₃, 298 K): 1.29–1.46 (m, 1H), 1.56–2.06 (m, 5H), 2.11–2.23 (m, 1H), 2.55–2.67 (m, 1H), 3.19 (s, 3H), 3.28 (s, 3H), 3.40–4.62 (m, 2H), 3.57 (s, 2H), 7.39 (t, 1H, J = 8.2 Hz), 7.47 (d, 1H, J = 9.2 Hz), 7.73 (dd, 2H, J₁ = 3.3 Hz), 7.84 (dd, 1H, J₁ = 1.5 Hz), 8.74 (dd, 1H, J₁ = 1.5 Hz), 9.74 (s, 1H), 8.03 (s, 2H), 8.69 (s, 1H, J = 2.1 Hz), 9.11 (s, 1H) ppm; ¹³C NMR (75 MHz, δ, CDCl₃, 298 K): 24.5, 25.0, 27.3, 36.0, 49.1, 50.6, 50.9, 50.9, 65.0, 78.4, 113.0, 117.5, 122.5 (q, J = 275 Hz), 124.3, 124.9, 129.6, 130.2, 133.1 (q, J = 34 Hz), 133.3, 140.4, 148.6, 155.1 ppm; ¹⁹F NMR (282 MHz, δ, CDCl₃, 298 K): –63.0 ppm; IR (film): v = 3462, 3254, 3031, 2944, 2866, 1692, 1600, 1548, 1529, 1485, 1451, 1434, 1372, 1352, 1325, 1280, 1206, 1178, 1137, 904, 843, 830, 798, 737, 709, 683 cm⁻¹; HRMS (ESI) m/z calcd for C₃₀H₂₈F₂N₂O₂⁺: 533.1982 [M⁺]; found: 533.1998.
General procedure for the asymmetric Michael reactions of 5

Degased toluene (5 mL) was added to a mixture of the Schiff base 5 (0.1 mmol), catalyst 1c (10 mol%), and Cs₂CO₃ (1.5 eq.) in a Schlenk tube. The stirring rate was set to 1000 rpm and the corresponding electrophile 15 (1.5 eq.) was added. After 24 h at 25 °C the reaction mixture was filtered through a plug of Na₂SO₄. The solvent was removed under reduced pressure. The crude products were purified by column chromatography (silica gel, heptanes : EtOAc = 20 : 1 to 2 : 1) giving the Michael addition products (16) in the reported yields.

R(+)–16a. Obtained as a colourless oil in 85% yield (>95% conv.) and with an e.r. = 95 : 5 upon reacting Schiff base 5a with acrylate 15a in the presence of 10 mol% 1c at 25 °C under the general procedure conditions. The analytical data are in full accordance with those reported in the literature. [α]D²⁵ (c = 0.70, CHCl₃) = 74.9°; ¹H NMR (300 MHz, δ, CDCl₃, 298 K): 1.44 (s, 9H), 2.16–2.27 (m, 2H), 2.33–2.41 (m, 2H), 3.59 (s, 3H), 3.93–3.99 (m, 1H), 7.14–7.21 (m, 2H), 7.28–7.47 (m, 6H), 7.60–7.68 (m, 2H) ppm; ¹³C NMR (75 MHz, δ, CDCl₃, 298 K): 28.2, 28.8, 30.5, 51.7, 64.9, 81.3, 127.9, 128.1, 128.6, 128.7, 128.9, 130.5, 136.6, 139.6, 170.8, 170.9, 173.7 ppm; IR (film): v = 2978, 2926, 1738, 1738, 1707, 1661, 1599, 1578, 1449, 1369, 1319, 1279, 1260, 1234, 1153, 943, 849, 812 cm⁻¹; the enantioselectivity was determined using HPLC (Chiralcel AD-H, eluent: n-hexane : i-PrOH = 90 : 10, 0.7 mL min⁻¹, 25 °C, retention times (major diastereomer): 25.3 min (minor), 34.3 min (major)).

Conclusions

A flexible and highly telescoped synthesis strategy for a structurally diverse library of chiral cyclohexanediamine-based urea-containing quaternary cyclohexanediimine bases with cyanobenzaldehyde derivatives. In both cases the flexible catalyst strategy allowed us to systematically fine-tune the catalysts for these reactions, thus resulting in high enantioselectivities and good to excellent yields. Besides the high enantioselectivities, it was also shown that these catalysts are very promising for the control of s-trans Michael acceptors, thus providing a powerful catalyst platform for further challenging asymmetric transformations.

Acknowledgements

This work was supported by the Austrian Science Funds (FWF): Project No. P26387-N28. Financial support from the Federal State Government of Upper Austria (Research Fellowship to J. N.) is kindly acknowledged. We are grateful to Dr Markus Himmelsbach for his support with HRMS analysis. The NMR spectrometers used at JKU Linz were acquired in collaboration with the University of South Bohemia (CZ) with financial support from the European Union through the EFRE INTERREG IV ETC-AT-CZ program (project M00146, “RERI-uasb”).

Notes and references


14 In those cases where the conversion was at least 60–70% after 24 h, stirring for another day was usually sufficient to ensure >95% conversion of starting material 5.


17 For a highly enantioselective but only moderately diastereoselective copper-catalyzed protocol for this reaction see: M. Strohmeier, K. Leach and M. A. Zajak, Angew. Chem., 2011, 123, 12543–12546.


19 Detailed VCD studies to unambiguously prove this assignment will soon be carried out in collaboration with specialists.