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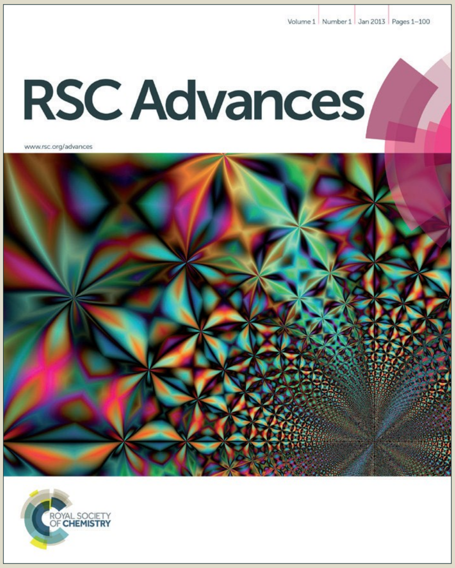

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ARTICLE

Design of Chiral Urea-Quaternary Ammonium Salt Hybrid Catalysts for Asymmetric Reactions of Glycine Schiff Bases

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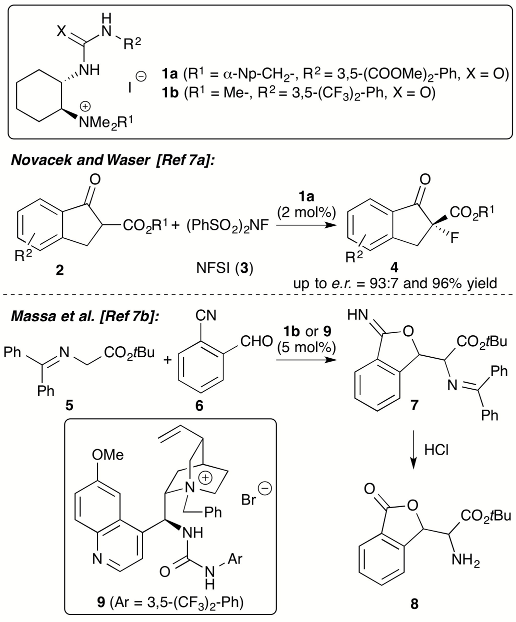
Bifunctional chiral urea-containing quaternary ammonium salts can straightforwardly be synthesised in good yields and with a high structural diversity via a scalable and operationally simple highly telescoped sequence starting from *trans*-1 cyclohexanediamine. These novel hybrid catalysts were systematically investigated for their potential to control glycine Schiff bases in asymmetric addition reactions. It turned out that Michael addition reactions and the herein presented aldol-initiated cascade reaction can be carried out with enantiomeric ratios up to 95:5 and in 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 contains an additional OH-group as the second coordination site,[2-4] the design and application of ammonium salts containing alternative H-bonding motives has so far been less exhaustively investigated.[2,5-7] While the groups of Lassaletta and Fernandez,[5a] Dixon,[5b] Smith[5c] and Lin and Duan[5d] 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-cyclohexane diamine-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 the asymmetric α-fluorination of β-ketoesters **2**.[7a] In addition, catalyst **1b** was found to be promising for the 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 cyclohexane diamine-based catalyst **1** was tested and it also turned out that the Cinchona alkaloid-based catalyst **9** introduced by Dixon[5b] and Smith[5c] gave the highest e.r. of 85:15 among the so far tested existing bifunctional ammonium salt motives (Scheme 1, lower reaction).[7b]



1b: *d.r.* = 3:2, *e.r.* = 77:23 (major) and 60:40 (minor), 82% yield
(no other salts **1** tested)
9: *d.r.* = 4:1, *e.r.* = 85:15 (major) and 73:27 (minor), 89% yield
(no further improvement with existing catalysts possible)

Scheme 1: Hybrid ammonium salts **1** and their applications reported previously.

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 hybrid salts **1** for stereoselective transformations. Thus w

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Electronic Supplementary Information (ESI) available: experimental details and copies of NMR spectra and HPLC analyses. See DOI: 10.1039/x0xx00000x especially focused on the optimisation of the existing synthesis route[7a] to fuel the demand for larger quantities of readily tuneable catalysts **1** and on the 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 compounds **8** was considered to be particularly interesting, as our modular catalyst synthesis approach should allow us to overcome the limitations of the existing catalyst motives. Interestingly, the groups of Liu and Soloshonok recently achieved the highly asymmetric synthesis of the analogous lactams in a complementary approach by employing an asymmetric auxiliary-based approach using chiral glycine Schiff base Ni(II) complexes.[8] This report once again proves the high potential of this robust auxiliary approach for the synthesis of chiral α-amino acid derivatives.[9]

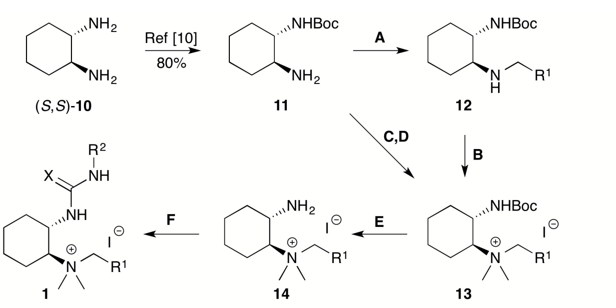
Results and Discussion

Catalyst Syntheses

In contrast to recent reports by others who described incorporation of the H-bonding donor first, followed by a final quaternarization step,[5,6] we have chosen to use the opposite assembly strategy by carrying out the quaternarization of mono-protected diamine **11** first, followed by deprotection and coupling with an iso(thio)cyanate (Scheme 2).[7a] This strategy allowed us to overcome some of the challenges of the commonly used protocols,[5,6] as side reactions of the nucleophilic heteroatoms of the H-bonding donor with the alkylating agent can be avoided, thus resulting in a broader and more functional group tolerant synthesis route.

As outlined in Scheme 2, catalysts **1** can be obtained from the known Boc-protected diamine **11**[10] in four chemical steps. First, the introduction of bulkier (aromatic) residues R^1 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 of any further purification. However, the subsequent quaternarization (step B, Scheme 2) was found to be the major bottleneck in the initial protocol.[7a] 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 R^1. 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 quaternarization 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** (R^1 = H). Formation of the latter can be explained by a nucleophilic substitution of the benzylic ammonium groups of compounds **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 R^1 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 MeI (6 eq.) and solid K_2CO_3 (1.1 eq.) in DMF (60 °C) gave the target ammonium salts **13** in reliably high yields (around 70% *in situ*) and sufficient purities to be telescoped further in the sequence without any purification. Noteworthy, 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 R^1 being electron-rich, -neutral, and –poor giving access to derivatives that were not accessible by the initial route (e.g. 3,5-(CF_3)-C_6H_3-). Unfortunately, when using sterically demanding R^1 groups (e.g. naphthyl or *ortho*-substituted aromatics) this route was still not very satisfactory (hereby the reactions mainly stalled on the *tert*-amine intermediates). However, these ammonium salts could be obtained in reasonable yields by first carrying out the dimethylation of **11** (step C) and then a final quaternarization with the appropriate benzylic halides (step D). Again the products were obtained in sufficient purities for direct further use. Thus, these newly developed quaternarization conditions allowed us to obtain a much more diverse assembly of ammonium salts **13** which were then transferred into the catalysts **1** in two more steps. The only limitations in the present synthesis are the fact that only one sterically demanding group R^1 can be introduced and that groups bigger than a naphthyl group (e.g. anthracenyl) can only very slowly be incorporated.



Initial Protocol [Ref 7a]:
Two tedious purifications by column chromatography and limitations in the quaternarization!
(10-30% overall yield from **11**)

Optimized Protocol(s):
Final step column chromatography only, high yield and control of impurities in the quaternarization!
(40-50% yield from **11** on up to 3 mmol scale)

Scheme 2: Catalyst syntheses: A) R^1CHO (1 eq.), $NaBH_4$ (1.5 eq.), MeOH/THF, r.t., 15 h (no purification, > 90% conversion); B) MeI (6 eq.), K_2CO_3 (1.1 eq.), DMF, 60 °C, 30 h (no purification, around 70% crude yield over 2 steps); C) CH_2O (2 eq.), $Na(OAc)_3BH$ (2 eq.), DCE, r.t., 15 h (no purification, > 90% conversion); D) R^1CH_2X, DMF, 60 °C, 30 h (no purification, 60-80% crude yield over 2 steps); E) HI (10 eq.), DCM, r.t., 2 h (extractive work-up with Na_2CO_3); F) R^2NCX (1.2 eq.), DCM, r.t., 2-6 h (simple purification by column chromatography, 60-80% yield over 2 steps).

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. The use of HI for the deprotection was found beneficiary for this reaction and, accompanied with an extractive work up, yielded the free amines **14** in good purities and yields. The extraction also allowed us to remove residual trimethyl ammonium salt **14b** (R^1 = H), which is significantly more hydrophilic than 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).

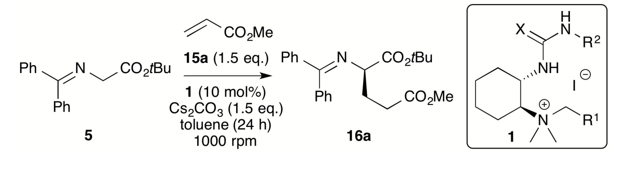
Asymmetric Reactions of Glycine Schiff Bases 5

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-covalent organocatalysis in the past and noteworthy most of the reported catalysts have there own characteristics with respect to their application scope (especially when using β-substituted acceptors).[1,11-13] 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 on the most significant results obtained in a very detailed screening of different catalysts and reactions conditions. We first identified the combination of toluene and solid Cs_2CO_3 (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 these 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 turned out 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 R^1 on the ammonium side (keeping the phenyl-urea group R^2 unchanged) were tested under identical conditions (entries 3-8 give the most significant results). Contrary to our results obtained in the α-fluorination of ketoesters[7a] (compare with Scheme 1), the introduction of bulky naphthyl groups R^1 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 R^1 (i.e. 3,5-$(CF_3)_2$-C_6H_3) in good yields. This catalyst modification turned out to be the most fruitful amongst all the tested R^1 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 R^2. The presence of electron-withdrawing groups lead to reduced selectivities in the case of CF_3-, nitro-, or diester-containing R^2 groups (entries 9-11). Noteworthy, the latter was found to be the urea-modification of choice in our recent α-fluorination protocol.[7a] 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.

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

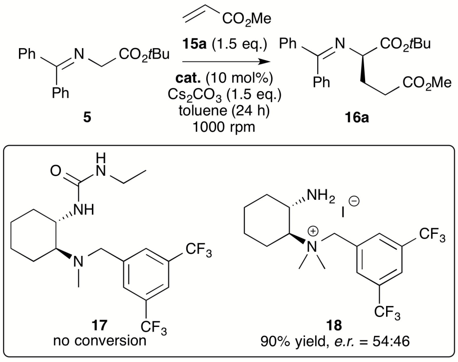


No	R^1	R^2	X	Conc. [M][a]	T [°C]	Yield[b] [%]	e.r.[c] (R:S)
1	H	Ph	O	0.17	25	60	67:33
2			S			69	60:40
3	Ph		O			90	76:24
4	α-Np					72	78:22
5	β-Np					35	74:26
6	4-*t*Bu-C_6H_4					6	79:21
7	4-NO_2-C_6H_4					40	74:26
8	3,5-$(CF_3)_2$-C_6H_3					85	84:16
9		3-NO_2-C_6H_4				83	81:19
10		3,5-$(CO_2Me)_2$-C_6H_3				85	75:25
11		3,5-$(CF_3)_2$-C_6H_3				95	75:25
12		Cy				88	87:13
13					40	90	81:19
14					0	70	92:8
15					-20	5	92:8
16			S		25	91	65:35
17		*t*Bu	O			94	85:15
18		Et				96	89:11
19				0.08		87	90:10
20					0	45	95:5
21	**3,5-$(CF_3)_2$-C_6H_3**	**Et**	**O**	**0.02**	**25**	**85**	**95:5**
22[d]						74	88:12
23				0.01		8	95:5

[a] Based on **5**; [b] isolated yield; [c] determined by HPLC using a chiral stationary phase[11]; [d] using 5 mol% catalyst.

Interestingly, at this stage we found that replacing aryl moieties on the urea side by incorporating a cyclohexyl group R^2 instead resulted in a good selectivity of 87:13 (entry 12). Based on the fact that aliphatic groups were never found to be promising in any of our previously investigated reactions (published[7a] or unpublished) this result came as a big surprise. By testing the influence of reaction temperature we found that the selectivity can be increased by lowering the temperature, however accompanied by a reduced reaction rate (entries 14, 15). Again, the reduced selectivity when using thiourea-moieties was proven by testing the analogous cyclohexyl-thiourea catalyst (entry 16). Finally, additional modifications by introducing different alkyl groups R^2 allowed us to identify an ethyl group as the most powerful urea-substituent giving **16a** with an enantiomeric ratio of 89:11 under standard conditions at room temperature. Further fine-tuning of the reaction conditions showed that the selectivity increases with higher dilutions, however resulting in a stepwise decrease of conversion (entries 18-23). The highest selectivities were obtained either by carrying out the reaction at 0.02M concentration of **5** at 25 °C (entry 21) or at higher concentration (0.08M) at 0 °C (entry 20), albeit with reduced conversion. Furthermore, lowering the catalyst loading resulted in a reduced catalytic performance (entry 22), whereas further dilution did not allow us to improve the selectivity any further (entry 23).

To prove the necessity of the bifunctional nature of catalysts **1** we also tested the simplified catalysts **17** and **18** which performed much less selective or did not give any product at all under the optimized reaction conditions (Scheme 3).

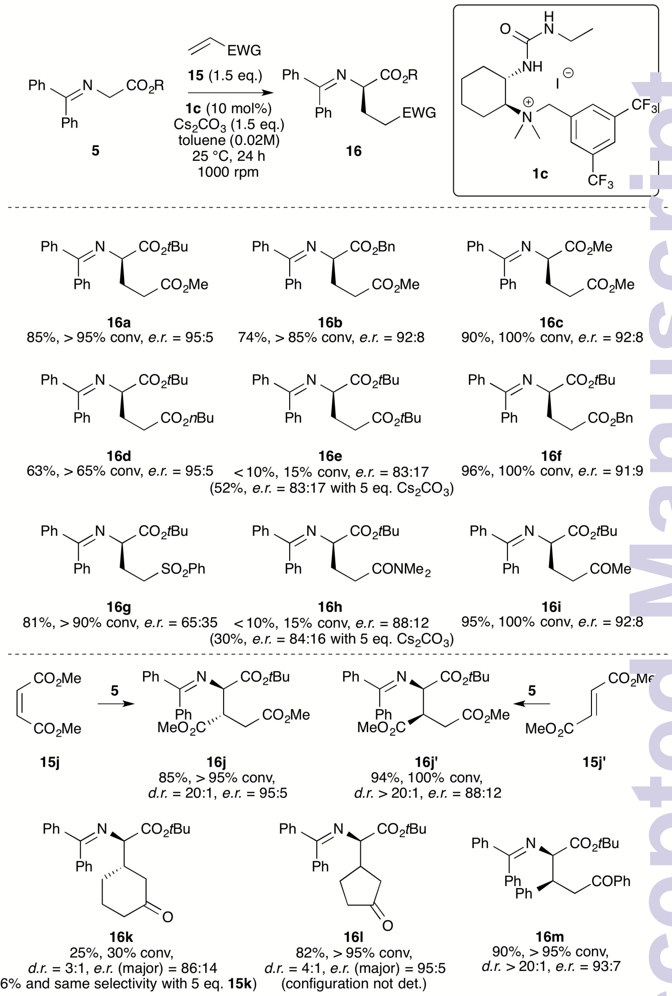


Scheme 3: Control experiments using the simplified catalysts **17** and **18**.

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 used Schlenk flasks 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 selectivity depends on the nature of the ester group, with bulky t-butyl esters **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[14] and the enantioselectivity, were influenced (see products **16d** – **16f**). This was most notable in the syntheses 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 equivalent of base 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**) 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 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 hereby (this substrate was also very difficult to control in an enantioselective manner in a recent project using structurally different TADDOL-based PTCs[11]).

Interesting results where obtained when 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. Noteworthy, Lambert and co-workers recently found that this substrate is unreactive when using their otherwise very powerful and highly selective cyclopropenimine chiral base catalysts.[12] Using dimethyl fumarate **15j’** instead gave the diastereomeric **16j’** in good yield and diastereoselectivity albeit a slightly lower enantioselectivity. Another striking difference to chiral cyclopropenimine base catalysis was also observed when employing s-trans acceptors **15k** and **15l**. Although cyclohexenone **15k** underwent a slowly 1,4-addition under standard conditions (which can be explained by a competing dimerization under basic phase-transfer conditions[15]), the stereoselectivity obtained is still reasonably high.[16] Even more interestingly, when using cyclopentenone **15l** we were able to obtain product **16l** in high yield and with good stereoselectivity.[17] Finally, also chalcone was 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[12] 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.



Scheme 4: Application scope of the Michael addition of glycine Schiff bases **5** to different Michael acceptors **15** using bifunctional catalyst **1c**. The configuration of products **16a**, **16b**, **16d**-**16g**, **16i**, **16j**′, **16k** and **16m** was determined by comparison of analytical details with literature data[11-13, 16, 17] whereas the other products (**16c**, **16h**, **16j** and **16l**) were assigned by analogy.

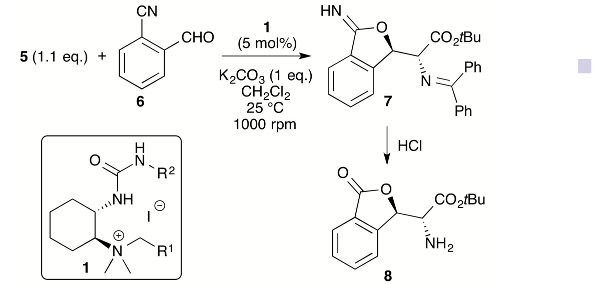
Having shown that catalysts **1** can be systematically fine-tuned to obtain high selectivities for the Michael addition of Schiff bases **5** to different Michael acceptors **15**, we next addressed the recently developed aldol-initiated cascade reaction of **5** with cyanobenzaldehyde **6**.[7b] As already discussed above, the initial screening of existing catalysts showed that the Cinchona alkaloid-based bifunctional ammonium salt **9** introduced by Dixon[5b] and Smith[5c] gave the highest selectivity with d.r. = 4:1 and e.r. of 85:15 for the major diastereomer (see Scheme 1). With our optimized synthesis for catalysts **1** in hand we put our efforts on identifying an even more selective catalyst for this powerful transformation. Table 2 gives an overview on the most significant results obtained thereby. The screening was carried out under the previously developed conditions[7b] using solid K_2CO_3 as the base in CH_2Cl_2 (other solvents and base 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 result[7b] using the trimethylammonium-based catalyst **1b** and it soon turned out 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 dia- 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 R^1 (entries 9 and 10).

In sharp contrast, the introduction of electron-withdrawing groups on the aryl group R^1 on the ammonium side accompanied by the presence of an electron-poor aryl moiety R^2 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 the di-trifluoromethyl-phenyl group R^1 again significantly improved the yield and the selectivity in this transformation (entries 12 and 13). Modifying the R^2 groups 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 only 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). On the other hand the coupling constants of **7** and **8** did also not allow 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 it's corresponding Mosher amides.[18] Subsequent NMR studies of these compounds then indicated that the major diastereomer is most presumably the *anti* isomer as depicted in Table 1.[19]

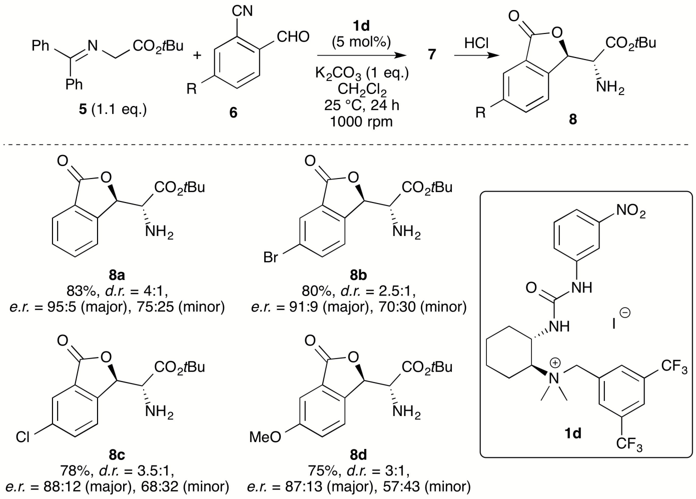
Table 2: Identification of the most active catalyst **1** for the cascade reaction of **5** and **6**.



No	R^1	R^2	t [h]	Yield[a] [%]	d.r.[b]	e.r. major (minor)[c]
1	H	3,5-$(CF_3)_2$-C_6H_3	24	82	1.5:1	77:23 (60:40)
2		3-NO_2-C_6H_4	24	66	1.4:1	77:23 (60:40)
3		4-CF_3-C_6H_4	48	63	1.3:1	76:24 (51:49)
4		Ph	48	52	1.2:1	80:20 (59:41)
5	Ph		48	52	1:1	77:23 (52:48)
6		Cy	72	68	2:1	67:33 (51:49)
7		4-CF_3-C_6H_4	48	60	1:1	80:20 (57:43)
8	β-Np	Ph	48	52	1:1	77:23 (54:46)
9	3,5-F_2-4-MeO-C_6H_2	Ph	96	13	1.1:1	70:30 (57:43)
10	4-MeO-C_6H_3	3-NO_2-C_6H_4	48	59	1.3:1	77:23 (59:41)
11	3-NO_2-C_6H_4	3-NO_2-C_6H_4	26	65	2.4:1	85:15 (63:37)
12	**3,5-$(CF_3)_2$-C_6H_3**	**3-NO_2-C_6H_4**	**24**	**83**	**4:1**	**95:5 (75:25)**
13	3,5-$(CF_3)_2$-C_6H_3	3,5-$(CF_3)_2$-C_6H_3	24	79	3:1	92:8 (73:27)

[a] Isolated yield of **8**; [b] determined by 1H NMR of the crude product; [c] determined by HPLC using a chiral stationary phase[7b].

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.[8]



Scheme 5: Use of cyanobenzaldehydes **6** for the cascade reaction.

Experimental

General Information

^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker Avance III 300 MHz spectrometer, on a Bruker Avance III 700 MHz spectrometer with TCI cryoprobe or on Bruker DRX 400, 300, 250 MHz spectrometers. All NMR spectra were referenced on 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, Waters 4 micro quadrupole. Elemental analyses were performed with a FLASHEA 1112 series-Thermo Scientific for CHNS-O apparatus. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer with ATR unit. HPLC analysis were performed either by using a Waters instrument or using a Dionex Summit HPLC system with a Chiralcel OD-H (250 x 4.6 mm, 5 µm), a Chiralcel OD-R (250 x 4.6 mm, 10 µm), or a Chiralpak AD-H (250 x 4.6 mm, 5 µm) chiral stationary phase. Optical rotations were recorded on a Perkin Elmer 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 catalysts and asymmetric reaction products as well as copies of NMR spectra and HPLC chromatograms can be found in the online supporting information.

Syntheses of Catalysts 1c and 1d

Step 1 (Step A in 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*)-cyclohexanediamine-**5**-dihydrochloride in analogy to literature[10]) in 10 mL THF:methanol (1:1) and the solution was stirred at r.t. overnight. After the addition of NaBH$_4$ (114 mg, 3 mmol, 1.5 eq), stirring was continued for another 2 h at r.t.. The reaction was quenched by addition of water and extracted with water/diethyl ether. The organic phase was washed with brine, dried over Na$_2$SO$_4$, and evaporated to dryness to obtain the crude product **12c** in almost quantitative yield (95%, 824 mg, 1.9 mmol), which could be directly used without any purification. **Compound 12c** (R^1 = 3,5-(CF$_3$)$_2$-C$_6$H$_3$): ^{1}H NMR (300 MHz, δ, CDCl$_3$, 298 K): 1.08-1.35 (m, 4H), 1.42 (s, 9H), 1.61-1.85 (m, 2H), 1.96 (s (b), 1H), 1.99-2.15 (m, 2H), 3.31-3.47 (m, 1H), 3.83 (d, 1H, *J* = 14.1 Hz), 4.00 (d, 1H, *J* = 14.1 Hz), 4.48 (d, 1H, *J* = 7.3 Hz), 7.73 (s, 1H), 7.82 (s, 2H) ppm.

Step 2 (B): The amine **12c** (1.7 mmol) was dissolved in 3 ml DMF. After the addition of K$_2$CO$_3$ (287 mg, 2.1 mmol, 1.2 eq) and methyl iodide (646 µl, 10.4 mmol, 6 eq), the suspension was stirred for 30 h at 60 °C. After removal of excess methyl iodide under reduced pressure, the suspension was extracted with dichloromethane/brine. The organic phase was dried over Na$_2$SO$_4$ and removal of the solvent under reduced pressure gives **13c** (70%, 1.13 g, 1.2 mmol), which was used without further purification. **Compound 13c** (R^1 = 3,5-(CF$_3$)$_2$-C$_6$H$_3$): $[\alpha]_D^{21}$ (c = 1.8, CH$_2$Cl$_2$) = -7.4°; ^{1}H NMR (500 MHz, δ, CDCl$_3$, 298 K): 1.32-1.40 (m, 1H), 1.46 (s, 9H), 1.58-1.66 (m, 1H), 1.66-1.74 (m, 1H), 1.77-1.84 (m, 1H), 1.95-2.06 (m, 3H), 2.59-2.64 (m, 1H), 3.22 (s, 3H), 3.28 (s, 3H), 4.11-4.18 (m, 1H), 4.93-5.00 (m, 1H), 5.16 (d, 1H, *J* = 12.8 Hz), 5.36 (d, 1H, *J* = 12.8 Hz), 5.87 (d, 1H, *J* = 9.9 Hz), 8.01 (s, 1H), 8.13 (s, 2H) ppm; ^{13}C NMR (126 MHz, δ, CDCl$_3$, 298 K): 24.8, 24.8, 27.7, 28.5, 35.7, 49.7, 51.1, 51.7, 63.1, 77.8, 81.5, 122.8 (q, *J* = 273 Hz), 124.[illegible], 130.3, 133.0 (q, *J* = 34 Hz), 133.6, 155.9 ppm; ^{19}F NMR (282 MHz, δ, CDCl$_3$, 298 K): -62.8 ppm; IR (film): $\bar{\nu}$ = 3431, 3270, 3011, 2980, 2939, 2867, 1695, 1625, 1516, 1467, 1455, 1393, 1370, 1323, 1281, 1242, 1176, 1138, 1048, 1024, 904, 870, 844, 737, 709, 683 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{22}H_{31}F_6N_2O_2^+$: 469.2284 [M$^+$], found: 469.2281.

Step 3 (E): The ammonium salt **13c** (1.1 mmol) was dissolved in 12 ml dichloromethane and hydroiodic acid (57w% aq. solution, 1.45 ml, 11 mmol, 10 eq) was added. After stirring for 2 h at r.t., the reaction was basified with saturated Na$_2$CO$_3$ solution and extracted with dichloromethane. The organic phase was dried over Na$_2$SO$_4$ and removal of the solvent under reduced pressure gave crude **14c** in quantitative yield (689 mg, 1.1 mmol). **Compound 14c** (R^1 = 3,5-(CF$_3$)$_2$-C$_6$H$_3$): ^{1}H NMR (300 MHz, δ, CDCl$_3$, 298 K): 1.31-1.76 (m, 5H), 1.84-1.95 (m, 1H), 1.96-2.07 (m, 1H), 2.27-2.37 (m, 1H), 3.06 (s, 3H), 3.17 (s, 3H), 3.46 (s (b), 2H), 3.56-3.68 (m, 1H), 4.06-4.17 (m, 1H), 5.12 (d, 1H, *J* = 12.7 Hz), 5.48 (d, 1H, *J* = 12.7 Hz), 7.96 (s, 1H), 8.16 (s, 2H) ppm.

Step 4 (F): A solution of **14** and the corresponding isocyanate (1.2 eq) in dichloromethane (20 ml per mmol **14**) 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 catalysts **1** in the reported yields.

Compound 1c: Obtained in 65% (123 mg, 0.217 mmol starting from 0.33 mmol **13c**) as a colourless oil. $[\alpha]_D^{21}$ (c = 1.3, $CHCl_3$) = 13.0°; ^1H NMR (300 MHz, δ, $CDCl_3$, 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), 4.59-4.52 (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, 2H), ^{13}C NMR (75 MHz, δ, $CDCl_3$, 298 K): 15.5, 24.7, 25.1, 27.4, 35.2, 35.9, 48.1, 50.9, 51.0, 65.3, 78.0, 122.7 (q, *J* = 273Hz), 124.8, 130.5, 133.0 (q, *J* = 34 Hz), 133.4, 157.7 ppm; ^{19}F NMR (282 MHz, δ, $CDCl_3$, 298 K): -62.9 ppm IR (film): $\bar{\nu}$ = 3295, 3021, 2988, 2936, 2864, 2349, 2288, 1656, 1546, 1449, 1373, 1278, 1174, 1130, 904, 843, 751, 719, 682, 663, 593, 463, cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{20}H_{28}F_6N_3O^+$: 440.2131 [M^+]; found: 440.2118.

Catalyst 1d: Obtained in 67% (96 mg, 0.14 mmol, starting from 0.22 mmol **13c**) as an orange oil. $[\alpha]_D^{21}$ (c = 0.75, CH_2Cl_2) = -29.3°; ^1H NMR (300 MHz, δ, $CDCl_3$, 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), 4.40-4.62 (m, 2H), 5.37 (s, 2H), 7.39 (t, 1H, *J* = 8.2 Hz), 7.47 (d, 1H, *J* = 9.2 Hz), 7.73 (dd, 2H, J_1 = 8.1 Hz, J_2 = 1.5 Hz), 7.84 (dd, 1H, J_1 = 8.1 Hz, J_2 = 1.8 Hz), 7.94 (s, 1H), 8.03 (s, 2H), 8.69 (t, 1H, *J* = 2.1 Hz), 9.11 (s, 1H) ppm; ^{13}C NMR (75 MHz, δ, $CDCl_3$, 298 K): 24.5, 25.0, 27.3, 36.0, 49.1, 50.6, 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; ^{19}F NMR (282 MHz, δ, $CDCl_3$, 298 K): -63.0 ppm; IR (film): $\bar{\nu}$ = 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 $C_{24}H_{27}F_6N_4O_3^+$: 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 Cs_2CO_3 (1.5 eq) in a Schlenk tube. 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 over a plug of Na_2SO_4. The solvents were 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 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. Analytical data are in full accordance with those reported in literature.[11,12] $[\alpha]_D^{21}$ (c = 0.70, $CHCl_3$) = 74.9°; ^1H NMR (300 MHz, δ, $CDCl_3$, 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; ^{13}C NMR (75 MHz, δ, $CDCl_3$, 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): $\bar{\nu}$ = 2978, 2926, 1738, 1707, 1661, 1599, 1578, 1449, 1369, 1319, 1279, 1260, 1234, 1153, 943, 920, 849, 812 cm^{-1}. The enantioselectivity was determined by HPLC (Chiralcel AD-H, eluent: *n*-hexane:*i*-PrOH = 95:5, 0.5 mL/min, 10 °C, retention times: 10.9 min (major; *R*-enantiomer), 12.3 min (minor; *S*-enantiomer)); Absolute configuration was determined by comparison of the retention times and $[\alpha]_D$ value with literature data.[12] HRMS (ESI): *m/z* calcd for $C_{23}H_{27}NO_4$: 382.2013 $[M+H]^+$; found: 382.2013.

General Procedure for the Cascade Reactions of 5

In a round-bottom flask, 2-cyanobenzaldehydes **6** (0.10 mmol) were added at room temperature to a stirred solution of glycine Schiff base **5** (1.1 eq., 0.11 mmol), K_2CO_3 (1 eq.), and catalyst **1d** (5% mol) in CH_2Cl_2 (3 mL). The mixture was stirred at r.t. for 24 h (1000 rpm). After, the mixture was purified directly by flash chromatography on silica gel with hexane:ethyl acetate = 8:2 to give the intermediates **7** as mixture of diastereoisomers. The products **7** were dissolved in a cooled solution of 0.5 M HCl (1 mL) and THF (3 mL) (0 °C). The mixtures were stirred at the same temperature for 2 h and then concentrated under vacuum. The resulting residue was treated with saturated $NaHCO_3$ (20 mL), extracted with CH_2Cl_2 (4 x 30 mL), and purified by flash chromatography (silica gel, hexanes:EtOAc = 2:1).

(-)-8a: Obtained as an amorphous solid in 83% yield (22 mg, 0.083 mmol) with d.r. = 4:1 and e.r. = 95:5 for the major diastereoisomer. $[\alpha]_D^{20}$ = (c = 0.5, $CHCl_3$) = - 2.5°. ^1H-NMR (300 MHz, δ, $CDCl_3$, 298 K): 1.40 (s, 9H), 1.61 (br s, 2H), 4.04 (d, *J* = 3.6 Hz, 1H), 5.77 (d, *J* = 3.5 Hz, 1H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.58 (t, *J* = 7.42 Hz, 1H), 7.68 (t, *J* = 6.48 Hz, 1H), 7.92 (d, *J* = 7.6 Hz, 1H); ^{13}C-NMR (100 MHz, δ, $CDCl_3$): 29.1, 58.7, 83.3, 83.9, 123.8, 126.9, 128.3, 130.8, 135.2, 147.5, 171.3, 171.5; MS (ESI): m/z 264.1 $(M+H)^+$; Anal. calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.97; H, 6.41; N, 5.37%. The enantioselectivity was determined by HPLC (Chiralcel OD-H, eluent: *n*-hexane:*i*-PrOH = 90:10, 0.7 mL/min, 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 ammonium salts was developed. The catalysts were successfully employed in asymmetric Michael addition reactions and a new powerful aldol-initiated cascade reaction of glycine Schiff 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 in the control of s-*trans* Michael acceptors, thus providing a powerful catalyst platform for further challenging asymmetric transformations.

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