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trans-1,2-Diaminocyclohexane-based sulfonamides as effective hydrogen-bonding organocatalysts for asymmetric Michael-hemiacetalization reaction

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Maciej Dajek,[a] Rafał Kowalczyk,[a]* and Przemysław J. Boratyński [a]*

An easily attainable bifunctional monosulfonamide derivative of DACH was an effective catalyst for Michael addition-hemiacetalization reactions providing products with ees exceeding 99% under optimized conditions. High enantioselectivities were achieved with just 0.2 %mol catalyst loading. The sulfonamide outperformed analoguous thiourea and squaramide-based organocatalysts.

Introduction

Hydrogen bonds are of primary relevance to metal-free catalysis including enzymatic reactions as well as that of many small molecules known as organocatalysts. The strength of these interactions is collective and the most effective organocatalysts often contain congeners capable of multiple H-donations such as thiourea and squaramide motifs. In general, such planar units donating two or more hydrogens are effective in a wide variety of reactions.[1] While the increase in acidity translates to stronger binding to the reactants, the transition state interactions determine the outcome of the catalyzed processes. Also, there is no direct relationship between the acidity of the catalyst and the obtained enantioselectivity. Therefore, application of otherwise overlooked classes of hydrogen bond donors may be effective in certain types of enantioselective reactions.

In bifunctional compounds with a sulfonamide group, the hydrogen-bonding unit is not planar (as observed in the X-ray structures of most sulfonamides in CCDC database) and thus stereogenic center can be induced at the nitrogen atom much closer to the reaction site. Also, computational work suggests that in such compounds the stabilization of an electrophile in the transition state can be accomplished with only a single hydrogen-bonding site.[2] Furthermore, the additional basic nitrogen atom in close proximity to the reaction site can facilitate nucleophile activation and, with the appropriate geometry, could provide effective chirality transfer. However, there are very few successful applications of sulfonamides in asymmetric catalysis, and these are mostly limited to rather intricate catalysts derived from *Cinchona* alkaloids (aminoquinine and aminocupreine) where the sulfonamide NH is additionally activated by a quinoline-8-sulfonyl residue.[3]

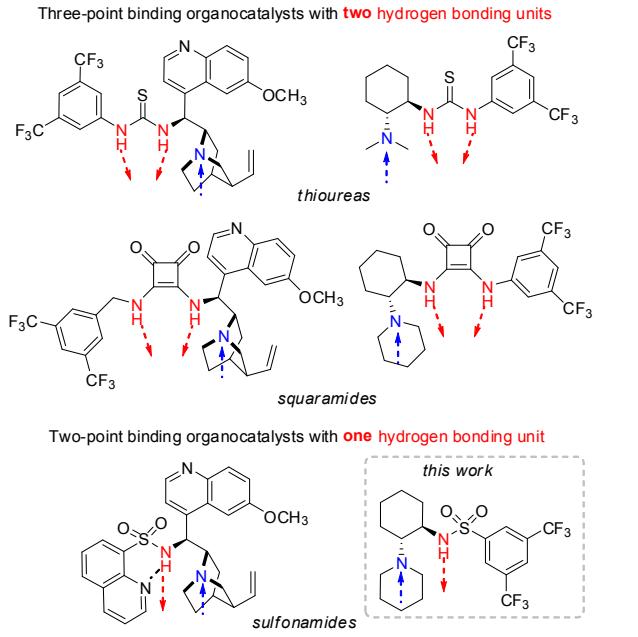

Figure 1. Structures of classical bifunctional thiourea and squaramide catalysts and sulfonamides derived from *Cinchona* alkaloids and diaminocyclohexane. Hydrogen bond donor and basic sites are marked with arrows.

Sulfonamides of chiral amines without aromatic groups, such as 1,2-*trans*-diaminocyclohexane (DACH), have not been exploited in asymmetric catalysis despite their wide availability.[4] These scaffolds were however remarkably successful when modified with other hydrogen binding units.[1,5] Therefore, we decided to explore the applicability of DACH sulfonamides in asymmetric organocatalytic processes.

[a] Department of organic Chemistry, Wrocław University of Technology, Wyspiańskiego 27, Wrocław, 50-370 Poland, tel. +4871-3203058, e-mail: Rafal.kowalczyk@pwr.edu.pl; and Przemyslaw.boratynski@pwr.wroc.pl

Electronic Supplementary Information (ESI) available: experimental details, compound characterization, supporting Figures and Tables, NMR spectra, HPLC chromatograms. See DOI: 10.1039/x0xx00000x

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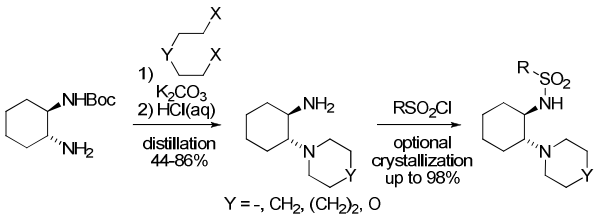
Results and Discussion

Sulfonamides are usually easy to obtain from many commercially available sulfonyl chlorides and are quite resistant to various reaction conditions. A simple synthesis was devised for an array of sulfonamides **1**-**4** by simplification of literature precedents (Scheme 1). DACH was monoprotected with a Boc group,[6] and cyclized with α,ω-dihalides[7] to form pyrrolidine, piperidine, azepane, and morpholine rings. Without purification of the intermediates, the Boc group was removed with aqueous HCl and primary-tertiary diamines were obtained by distillation. The process was rather efficient (70-86% yield), with the exception for seven-membered ring where the yield was moderate (44%). Subsequent reactions with an array of sulfonyl chlorides were nearly quantitative. Most products were obtained as solids which could be further purified by crystallization. The exclusion of chromatography makes the entire process easily scalable. Additionally, compounds **5**-**8** were obtained to serve as reference (Figure 2).



Scheme 1. Syntheses of DACH-based bifunctional sulfonamides

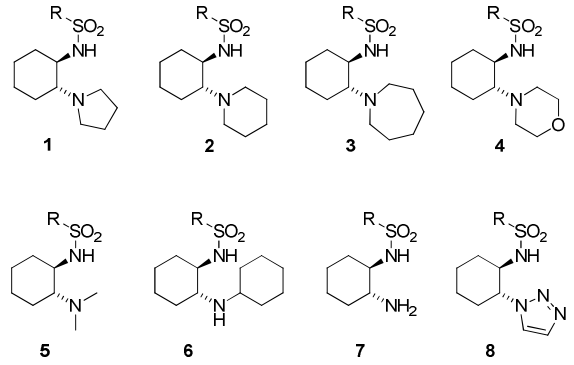
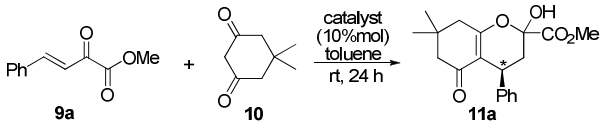


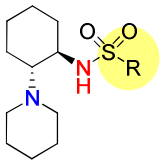
Figure 2. Studied DACH sulfonamide classes

A Michael-hemiacetalization cascade reaction (Scheme 2) was used for the screening of chiral sulfonamide performance (Figure 1). This reaction leads to intermediates relevant to the synthesis of amino acids and hydropyridine derivatives.[8,9] The chosen dicarbonyl Michael acceptor **9a** could interact with a catalyst through two sites.[10] The process can be catalyzed either by a base or a Lewis acid.[9] Nevertheless, substantial enantioselectivity has been achieved using elaborate derivatives of alkaloids.[11] However, bifunctional catalysis exploiting tertiary amines and hydrogen bond donating sites was also effective. Successful examples of such catalysts include thiourea derivatives of aliphatic amino acids, as opposed to more complex *Cinchona* alkaloids.[12] Therefore the chosen model reaction was expected to allow comparison of various types of hydrogen bond donating sites and the interplay of structural components in the catalyst.



Scheme 2. Asymmetric Michael hemiacetaization reaction

Table 1. Enantioselectivities in asymmetric reaction catalyzed by various sulfonamides **2a**-**y**: the role of sulfonyl group[a)]



Entry	Catalyst	R	ee, %[a)]
		Aryl sulfonamides	
1	**2a**	3,5-$(CF_3)_2C_6H_3$	99.4[b)]
2	**2a**	3,5-$(CF_3)_2C_6H_3$	93
3	*ent*-**2a**[4b]	3,5-$(CF_3)_2C_6H_3$	90[c)]
4	**2b**	3-FC_6H_4	87
5	**2c**	3,5-$(MeSO_2)_2C_6H_3$	84
6	**2d**	3,5-$F_2C_6H_3$	84
7	**2e**	3,5-$Cl_2C_6H_3$	83
9	**2f**	4-$CH_3C_6H_4$	79
9	**2g**	3-$NO_2C_6H_4$	78
10	**2h**	4-$NO_2C_6H_4$	78[d)]
11	**2i**	C_6H_5	74
12	**2j**	4-FC_6H_4	70
13	**2k**	3,5-$(CH_3)_2C_6H_3$	68
14	**2l**	2-Naphthyl	68[d)]
15	**2m**	2-FC_6H_4	53
16	**2n**	2,3,4-$F_3C_6H_2$	44
17	**2o**	2,4-$F_2C_6H_3$	41[d)]
18	**2p**	C_6F_5	33[d)]
19	**2q**	8-quinolinyl	4[d)]
20	**2r**	2,6-$Cl_2C_6H_3$	3[d)]
21	**2s**	2,4,6-(*i*Pr)$_2C_6H_3$	2[c)d)]
		Alkyl sulfonamides	
22	**2t**	CH_3	72
23	**2u**	CF_3	44[d)]
24	**2v**	cyclohexyl	39[d)]
		Dimeric sulfonamides	
25	**2w**	benzene-1,3-diyl	86
26	**2x**	biphenyl-4,4'-diyl	72
27	**2y**	sulfamide	63

[a)]Reaction conditions: 10 %mol catalyst in toluene at room temperature for 24 h, catalytic product (4*S*)-**11a**. [b)]Under optimized conditions: 1 %mol catalyst in PhCl at −20°C for 72h. [c)]Major product (4*R*)-**11a**. [d)]Incomplete conversions

For the entire class of the catalysts the obtained enantioselectivities were good, and with few exceptions exceeded 65%, also in most cases complete conversions were observed (Table 1). The most effective catalysts **2a**[4b]-**2e** had inductively electron-withdrawing substituents at positions 3 and 5 of the benzenesulfonamide residue. At these *meta*

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positions, the substituent's size had very little effect on the enantioselectivity as judged by the similar performance of catalysts with fluorine and methylsulfonyl substituents (**2d** vs. **2c**). The 3,5-substitution with methyl groups in **2k** had no effect compared to unmodified benzenesulfonate **2i**. Thereby any steric interactions involving substituents at the *meta* positions did not affect the chirality transfer. On the other hand, *ortho*-substitution of the benzenesulfonamides had a detrimental effect on the obtained enantioselectivities. The 2,6-disubstituted catalysts **2r**-**s** and 8-quinoline sulfonamide **2q** gave mostly racemates. Consequence of *ortho* substitution was less pronounced for fluorine, thus, it indicates that steric interactions were involved. Methanesulfonamide **2t** was comparable in performance to benzenesulfonamide **2i**; however, both bulkier and more electron withdrawing aliphatic sulfonamides **2u**-**v** exhibited inferior catalytic performance.

In the dimeric C_2-symmetric sulfonamides (Figure 3, Table 1 entries 25-27) the individual units seem to operate independently and offer no boost in enantioselectivity. The 4,4'-biphenyl disulfonamide **2x** was almost identical in performance to the unsubstituted benzenesulfonamide **2i**. Benzene-1,3-disulfonamide **2w** was a noticeably more selective catalyst, but its increased performance could be equally well explained by the role of the *meta*-sulfonamide group as an electron withdrawing residue. Also, the smallest of the dimers, sulfamide **2y** exhibited moderate enantioselectivity.

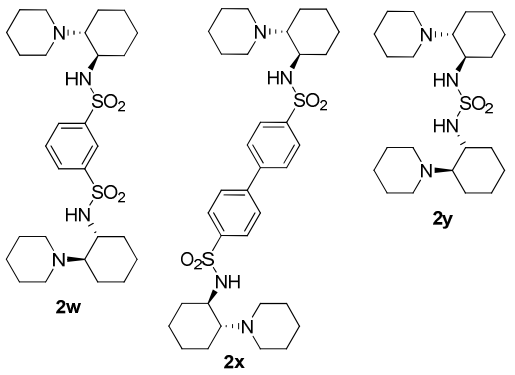
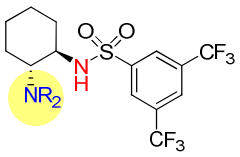


Figure 3. Structures of dimeric sulfonamides and sulfamide

In contrast, the type of tertiary amine had a negligible impact on the enantioselectivity. Nevertheless, the piperidine derivatives **2** were slightly better than all the other groups tested (Table 2). It was surprising to see an almost equal performance by morpholine derivatives **4**, despite their very different basicity. Still, replacement of the tertiary amine with a secondary amine of comparable size or with a triazole ring were both detrimental to the observed enantioselectivity. Also, a catalyst with a primary amine **6a** led to a poor stereochemical outcome. These results indicate that an aliphatic tertiary amine unit was essential for the enantioselectivity, but neither the bulkiness of the surrounding groups nor altering their electronic character affected the enantioselectivity considerably. (However, they did influence the outcome of less successful sulfonamides, for the details, see ESI)

Table 2. Enantioselectivities in asymmetric reaction catalyzed by various sulfonamides **1a**-**8a**: the role of basic center[a)]



Entry	Catalyst	NR_2	Ee, %[a)]
1	**1a**	pyrrolidine	90
2	**2a**	piperidine	93
3	**3a**	azepane	90
4	**4a**	morpholine	90
5	**5a**	dimethylamine	86
6	**6a**	NH_2	31
7	**7a**	cyclohexylamine	11
8	**8a**	1,2,3-triazole	9[b)]

[a)] Reaction conditions: 10 %mol catalyst in toluene at room temperature for 24 h, catalytic product (4*S*)-**11a**, with one exception the conversions were complete. b) In this case conversion of **9a** was approx. 15%.

When **2a** was compared with analogous thiourea and squaramide derivatives (Figure 1) it was found to be a more selective catalyst, although by a narrow margin (93 %ee vs 92 and 90 %ee, respectively). This marks one of the first cases where these classical catalysts are quite effective but still outperformed by a rather simple sulfonamide.

The same configuration of catalytic product (4*S*)-**11a** obtained with different analogues of **2** including three-point binding catalysts suggest related activation pathways.[8c,10] It can be assumed that the role of the tertiary amine is to bind and deprotonate nucleophile **10**, while the acidic NH interacts with the 1,2-dicarbonyl unit of **9a**, arranging it for attack from the *Si* face. Aryl sulfonyl groups may additionally shield **9a** from the *Re* side (Figure 4).

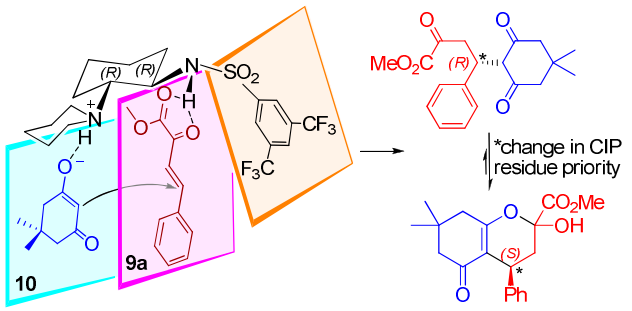


Figure 4. Plausible explanation of stereochemistry observed in the Michael-hemiacetalization sequence

Attempts to observe interaction between the catalyst **2a**, and the substrates of the catalytic reaction using ^{1}H NMR titration were not conclusive. Only the broad resonance attributed to the NH group of **2a** was affected by addition of dimedone,

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while no spectral changes were observed by separate addition of benzylidenepyruvate **9a** (For the details, see: ESI).

We correlated the catalyst performance in terms of selectivity with the highest calculated oscillation frequency, corresponding to the N-H stretching band, at the DFT/B3LYP/CC-pVDZ level of theory. This value can be treated as one of the predictors of intrinsic acidity.[13] It turned out that there exists a trend within this class of catalysts that the lower the calculated frequency the higher the enantioselectivity (Figure 5, for details, see ESI).

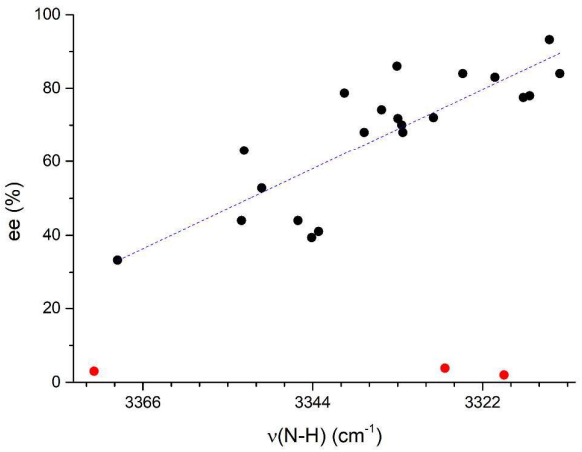


Figure 5. Correlation between enantiomeric excess for 11a and DFT calculated unscaled frequency of the N-H stretching band. The Pearson coefficient for the fitted line is −0.83. Results for 2,6-disubstituted benzenesulfonates and quinoline-sulfonamide providing nearly racemic products were excluded from the fit (marked in red)

The enantioselectivity of the catalytic reaction using **2a** was improved to 96% after replacing solvent with chlorobenzene (Table 3). Also, the amount of catalyst **2a** could be reduced from the original 10 %mol (Figure 6). To our delight, we have found that lowering the catalyst loading down to 0.25 %mol did not significantly affect the enantioselectivity (93%) and yield (90%). A drop in catalyst performance was eventually observed at loadings below 0.1 %mol. Nevertheless, even at 0.05 %mol (500 ppm) moderate enantioselectivity was achieved, albeit after an extended reaction time. The experiments with both 10 and 0.5 %mol catalyst **2a** were repeated using an enantiomer *ent*-**2a** and the enantiomeric ratios were consistently reversed.

Table 3. Effect of solvent on stereoselectivity

Entry	Solvent	Ee, %[a]
1	toluene	93
2	α,α,α-trifluorotoluene	93
3	chlorobenzene	96
4	dichloromethane	96

[a] Reaction conditions: 10 %mol catalyst **2a** at room temperature for 24 h, catalytic product (4*S*)-**11a**, complete conversion

By lowering the reaction temperature down to −20 °C the enantioselectivity increased above 99% for reactions using 1 %mol of the catalyst **2a**. Complete conversions were achieved within 4 days. These results were reproduced on scales ranging from 0.1 to 3 mmoles with 98% preparative yield (Scheme 3). Alternatively, product of such purity could be obtained by enrichment of samples by slow recrystallization from *tert*-butyl methyl ether. However, the efficiency of such crystallization was rather low (ca. 45%).

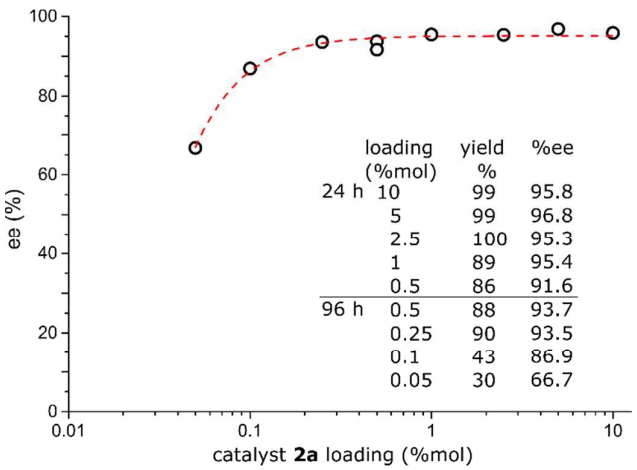
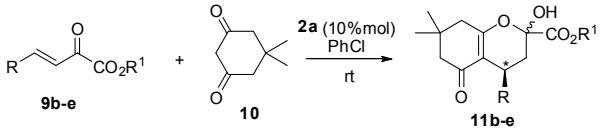


Figure 6. The effect of catalyst **2a** loading on enantioselectivity of (4*S*)-**11a** in chlorobenzene at room temperature. Reactions with 0.5-10 %mol loading were run for 24 h, reactions with 0.05-0.5 %mol loading were run for 96 h.

Also, a short study on the scope of substrates was performed employing the catalyst **2a** (Table 4). High enantioselectivities were achieved with acceptors of varied aromatic substitution (entries 2-5) or with a different ester (entry 6). However, replacement of the phenyl group with cyclohexyl in the acceptor led to a new product **11b** with incomplete conversion (45% isolated yield) and only moderate enantioselectivity.

Table 4. Application of different Michael acceptors



Entry	R	OR[1]	Product	Yield, %	Ee, %[a]
1	cyclohexyl	OMe	**11b**	45	79[b]
2	4-FC_6H_4	OMe	**11c**	92	96 (43)[c]
3[d]	4-FC_6H_4	OMe	**11c**	79	95 [>99][d]
4	4-ClC_6H_4	OMe	**11d**	93	93 (96)[c]
5[d]	4-ClC_6H_4	OMe	**11d**	91	91 [>99][d]
6	Ph	OBn	**11e**	93	96

[a] Reaction conditions: 0.1-mmol scale, 10 %mol **2a** in chlorobenzene at room temperature for 24 h, all products of 4*S* configuration. [b] Reaction run for 96 h up to 50% conversion. [c] Values in parentheses were obtained in reactions run for 120 h at −20°C. [d] Reaction conditions: 3-mmol scale, 1 %mol **2a** in chlorobenzene at room temperature for 96 h, values in square parentheses indicate ee after single recrystallization from *tert*-butyl methyl ether.

A few different nucleophiles were also tested. At room temperature the enantioselectivities achieved starting from coumarins and pyrone were slightly lower compared to

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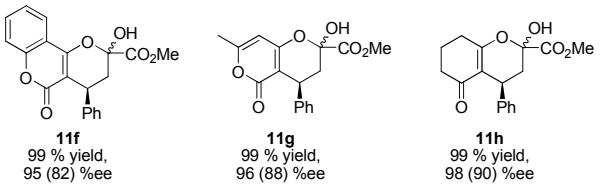
dimedone (Figure 7). However, these could be significantly improved to no less than 95 %ee by lowering the temperature to −40 °C.



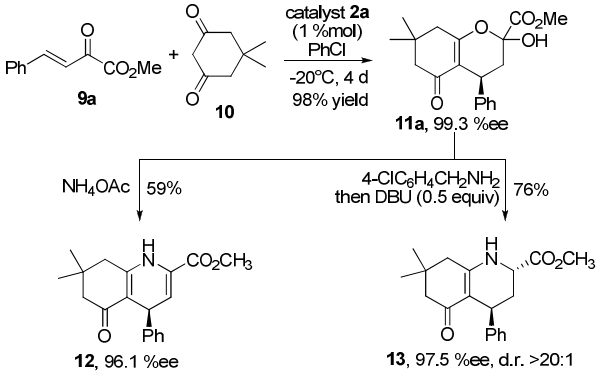
11f
99 % yield,
95 (82) %ee

11g
99 % yield,
96 (88) %ee

11h
99 % yield,
98 (90) %ee

Figure 7. Products obtained from different nucleophiles and **9a** with 10 %mol **2a** in chlorobenzene at −40 °C for 48 h. Values in parentheses indicate %ee obtained for reactions run at room temperature

The synthetic utility of the asymmetric adduct **11a** was proved in reactions leading to enantioenriched dihydropyridine and tetrahydropyridine derivatives **12** and **13** (Scheme 3). Both products are amino acid derivatives analogous to biologically active molecules.[14] The formation of a hydroquinoline ring in **12** was accomplished by heating of the chiral adduct with an excess of ammonium acetate.[11] Compound **13** was obtained from **11a** in a one-pot sequence of transformations involving imine formation, transamination and a final cyclization. Overall, both processes occurred with little erosion of optical purity, and in the case of **13** with high diastereoselectivity.[8a] The relative configuration was established by a combined DFT and NMR approach (for the details, see ESI)



Scheme 3. Further transformation of chiral adducts

Experimental Section

Adduct (4*S*)-**11a**: Benzylidene pyruvate **9a** (0.57 g, 3 mmol) and catalyst **2a** (14 mg, 1 %mol) were dissolved in chlorobenzene (30 mL), then cooled to -20 °C. After 40 min, dimedone (**10**, 0.46 g, 1.1 equiv) was added and the mixture was stirred at −20 °C for 5 days. Then it was diluted with $CHCl_3$ (30 mL) and passed through a pad of silica gel (20g) and washed with 150 mL ethyl acetate. Evaporation and column chromatography (silica gel, hexane/AcOEt/CH_2Cl_2, 7:3:1) gave 0.97 g of product (98% yield, >99 %ee). HPLC (Chiralpak AD-H 4.6×250 mm, hexane/2-propanol 7:3, 0.7 mL/min) t_r (4*R*)-**11a** 7 min, isomer (4*S*)-**11a** 10 min.

Conclusion

We have demonstrated the first successful application of chiral diaminocyclohexane-derived sulfonamides in a catalytic Michael-hemiacetalization reaction. It was proved that a single site hydrogen bond donor in combination with a tertiary amine can provide simple catalysts enabling high stereoselectivity for the Michael-adducts. The best performances were observed when the catalyst benzenesulfonyl group possessed inductively electron withdrawing substituents at the *meta* positions. High enantioselectivity was maintained even at exceptionally low catalyst loadings.

Conflicts of interest

There are no conflicts to declare

Acknowledgements

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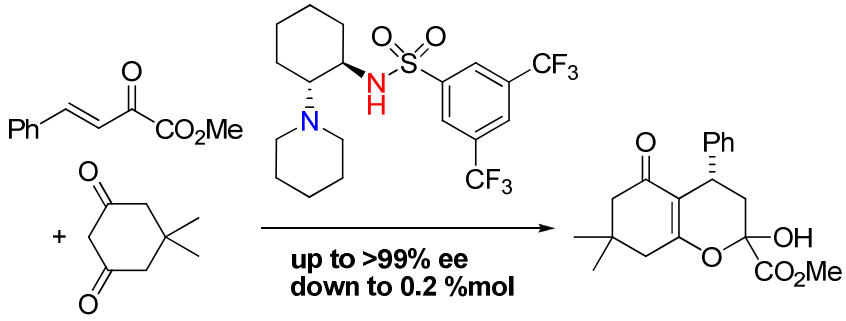

Simple sulfonamide organocatalysts delivers unparalleled efficiency in the asymmetric Michael-hemiacetalization cascade.