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# Synthesis and Catalytic Activity of 1,2-Benzenediamine-Derived Organocatalysts Based on (1*R*,2*R*)-Cyclohexane-1,2-Diamine

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**Abstract:** A four-step synthesis process of bifunctional, noncovalent organocatalysts based on the chiral (1*R*,2*R*)-cyclohexane-1,2-diamine scaffold containing a 1,2-benzenediamine H-bond donor was developed. Nucleophilic aromatic substitution of the 2-fluoronitrobenzene derivative with the commercial (1*R*,2*R*)-cyclohexane-1,2-diamine was followed by selective alkylation of the primary amino group, reduction of the aromatic nitro group and final derivatization of the primary aromatic amino group, i.e., acylation, sulfonation, reductive alkylation and arylation, leading to the four subtypes of organocatalysts. All new compounds were fully characterized. The prepared organocatalysts (32 examples) were tested in the Michael addition of acetylacetone to *trans*-β-nitrostyrene, yielding the addition product with incomplete conversions (up to 93%) and enantioselectivities of up to 41% *ee*.

**Keywords:** asymmetric organocatalysis; H-bond donor organocatalysts; (1*R*,2*R*)-cyclohexane-1,2-diamine; benzene-1,2-diamines; reduction; nucleophilic aromatic substitution; reductive alkylation; arylation; acylation; sulfonation



**Citation:** Ciber, L.; Klemenčič, K.; Golob, A.; Brodnik, H.; Požgan, F.; Svete, J.; Štefane, B.; Grošelj, U. Synthesis and Catalytic Activity of 1,2-Benzenediamine-Derived Organocatalysts Based on (1*R*,2*R*)-Cyclohexane-1,2-Diamine. *Catalysts* **2024**, *14*, 274. https://doi.org/10.3390/catal14040274

Academic Editors: Antonio M. Romerosa, Luca Bernardi, Adriana Maria da Silva and Arlene Gonçalves Corrêa

Received: 28 February 2024
Revised: 1 April 2024
Accepted: 17 April 2024
Published: 18 April 2024



## 1. Introduction

Since the introduction of the noncovalent bifunctional organocatalyst with the thiourea double H-bond donor by Takemoto in 2003 [1,2], followed by a squaramide analogue developed by Rawal in 2008 [3,4], this class of catalysts has become the workhorses of noncovalent organocatalysis [5–10], as it enables the simultaneous activation and coordination of both nucleophilic and electrophilic reactants [10,11]. A typical and most commonly used organocatalyst of this type is a derivative of a chiral 1,2-diamine based on privileged cinchona alkaloids [12–14] or cyclohexane-1,2-diamine (Figure 1a) [15]. While several double H-bond donors such as diaminomethylenemalononitrile (DMM) [16,17] and (heterocyclic)guanidines [18], as well as single H-bond donors, such as (thio)amides [19], sulfonamides [20] and phosphoramides [21], have been described in the literature, thiourea and squaramide remain the most common and best H-bond donors [5–10,22,23]. They have also been very successfully introduced into noncovalent bifunctional quaternary ammonium salt phase-transfer organocatalysts [24–27].

Recently, we reported the facile two- and three-step synthesis of 24 novel bifunctional noncovalent organocatalysts based on a chiral (*S*)-quininamine scaffold and enaminone or benzene-1,2-diamine as novel H-bond donors (Figure 1b). Their catalytic activity was evaluated in the Michael addition of acetylacetone to *trans*-β-nitrostyrene. The catalysts were characterized by low to moderate enantioselectivity (up to 72% *ee*) at low conversions (up to 41%) [28]. Furthermore, no *N*-arylated (3,5-bis(trifluoromethyl)phenyl) and *N*-benzylated (3,5-bis(trifluoromethyl)benzyl) catalysts could be prepared. In extension of this study, we report here the synthesis of benzenediamine-derived bifunctional organocatalysts based

on chiral cyclohexane-1,2-diamine prepared in four simple steps starting from commercially available (1*R*,2*R*)-cyclohexane-1,2-diamine and *ortho*-fluoronitrobenzene derivatives. The common aromatic primary amine intermediates enabled the preparation of four subclasses of catalysts, i.e., sulfonamides, amides, benzylated amines and arylated amines (Figure 1c). Although structurally similar compounds have been reported, they have never been tested as organocatalysts [29–31]. Their organocatalytic activity was investigated in the 1,4-addition of acetylacetone to *trans*-β-nitrostyrene. Dimethylamine and piperidine were evaluated as tertiary amines, while trifluoromethyl (i.e., 3,5-bis(trifluoromethyl)phenyl group) and/or cyano groups were introduced into the catalysts at strategic positions to increase the H-bond donor acidity and thus hopefully increase the rate and enantioselectivity of the catalysts [32–35]. The electron-donating groups (Me and OMe) on the benzenediamine catalysts of the (*S*)-quininamine series, which were previously investigated [28], performed extremely poorly and were therefore not considered in the present study.

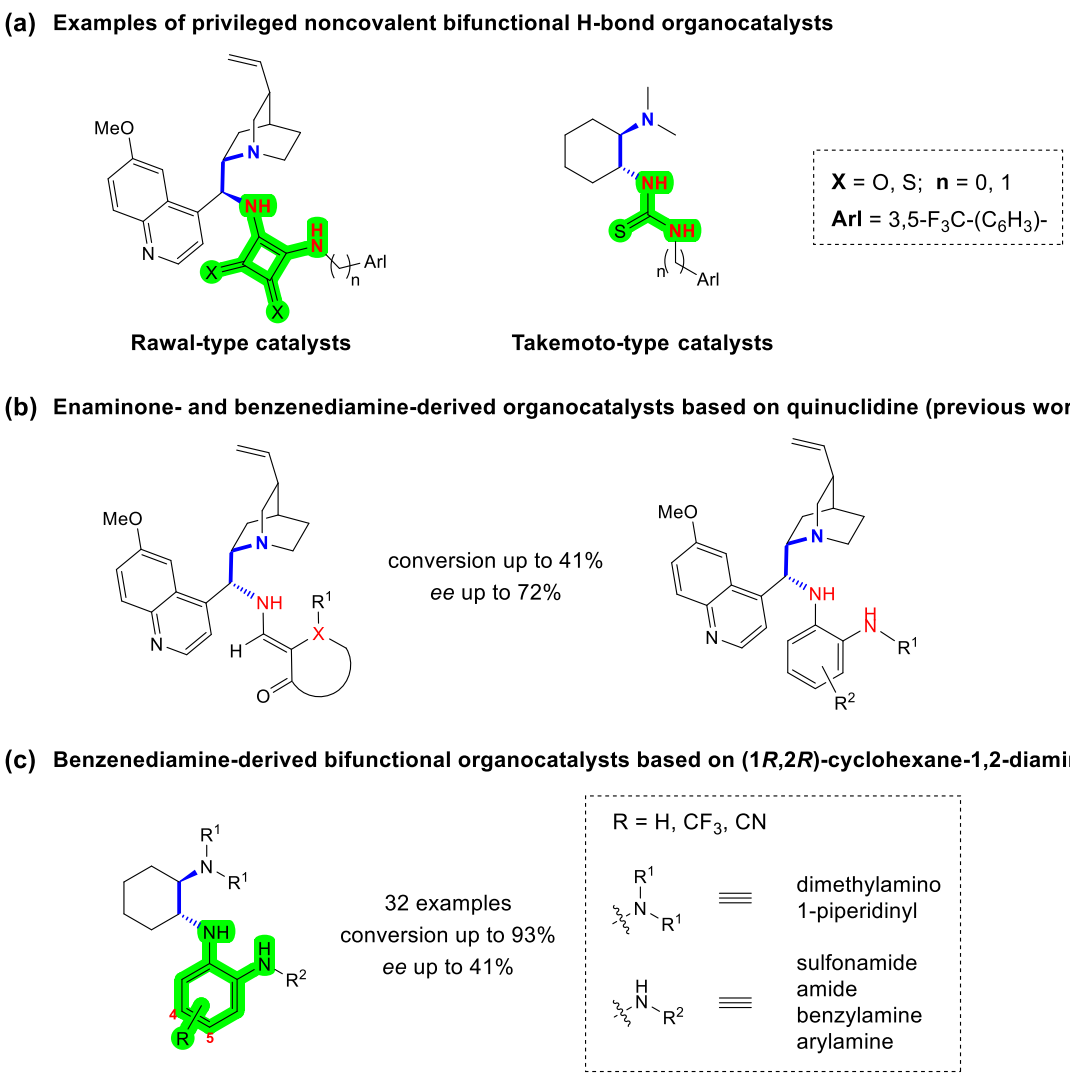



**Figure 1.** (**a**) Typical examples of the most commonly used bifunctional noncovalent 1,2-diamine-derived organocatalysts containing (thio)urea or (thio)squaramide as double H-bond donors and chiral quinuclidine or cyclohexane-1,2-diamine scaffolds. (**b**) Enaminone- and benzenediamine-derived organocatalysts based on quinuclidine. (**c**) Benzenediamine-derived bifunctional organocatalysts based on (1*R*,2*R*)-cyclohexane-1,2-diamine.

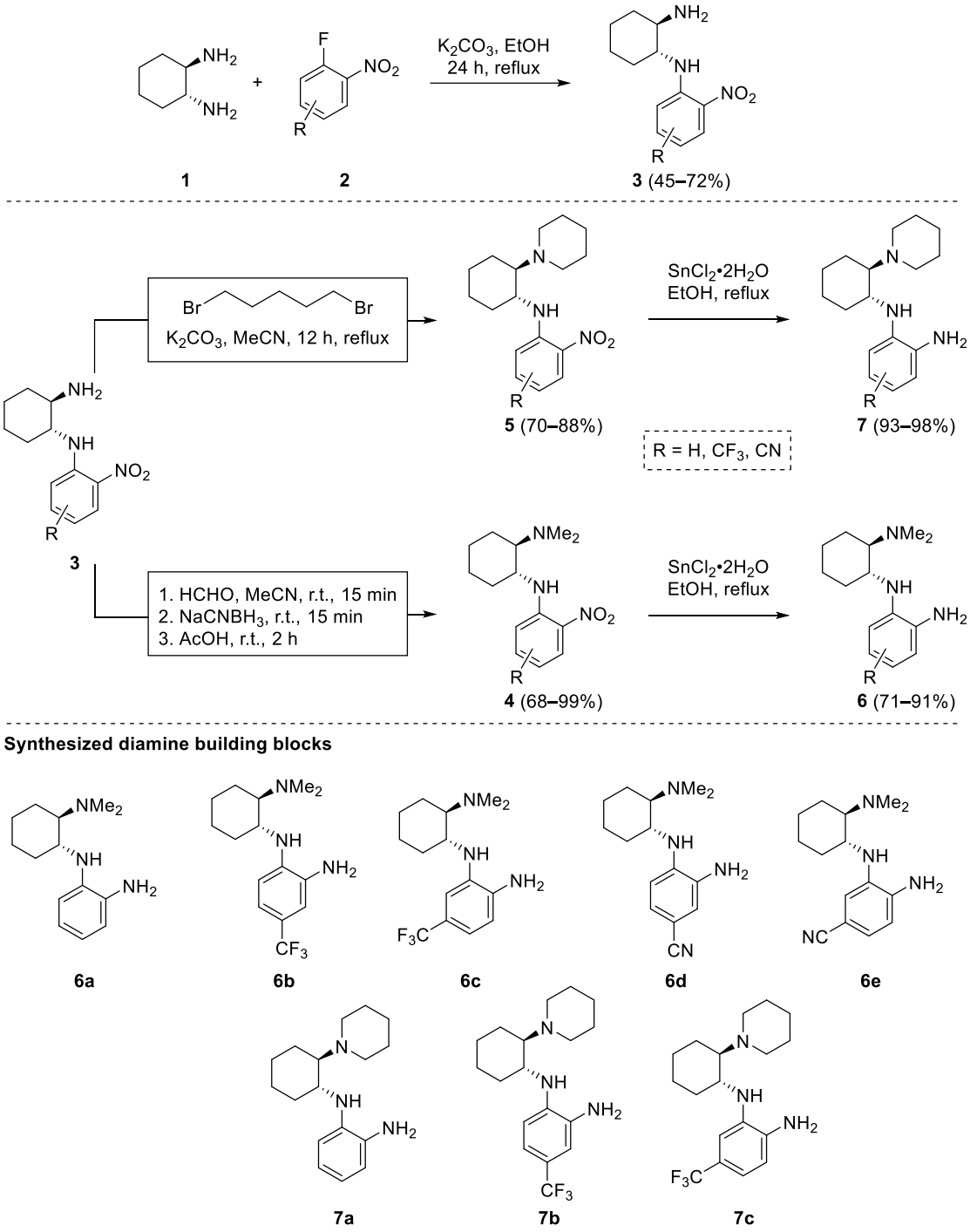
## 2. Results and Discussion

### *2.1. Synthesis*

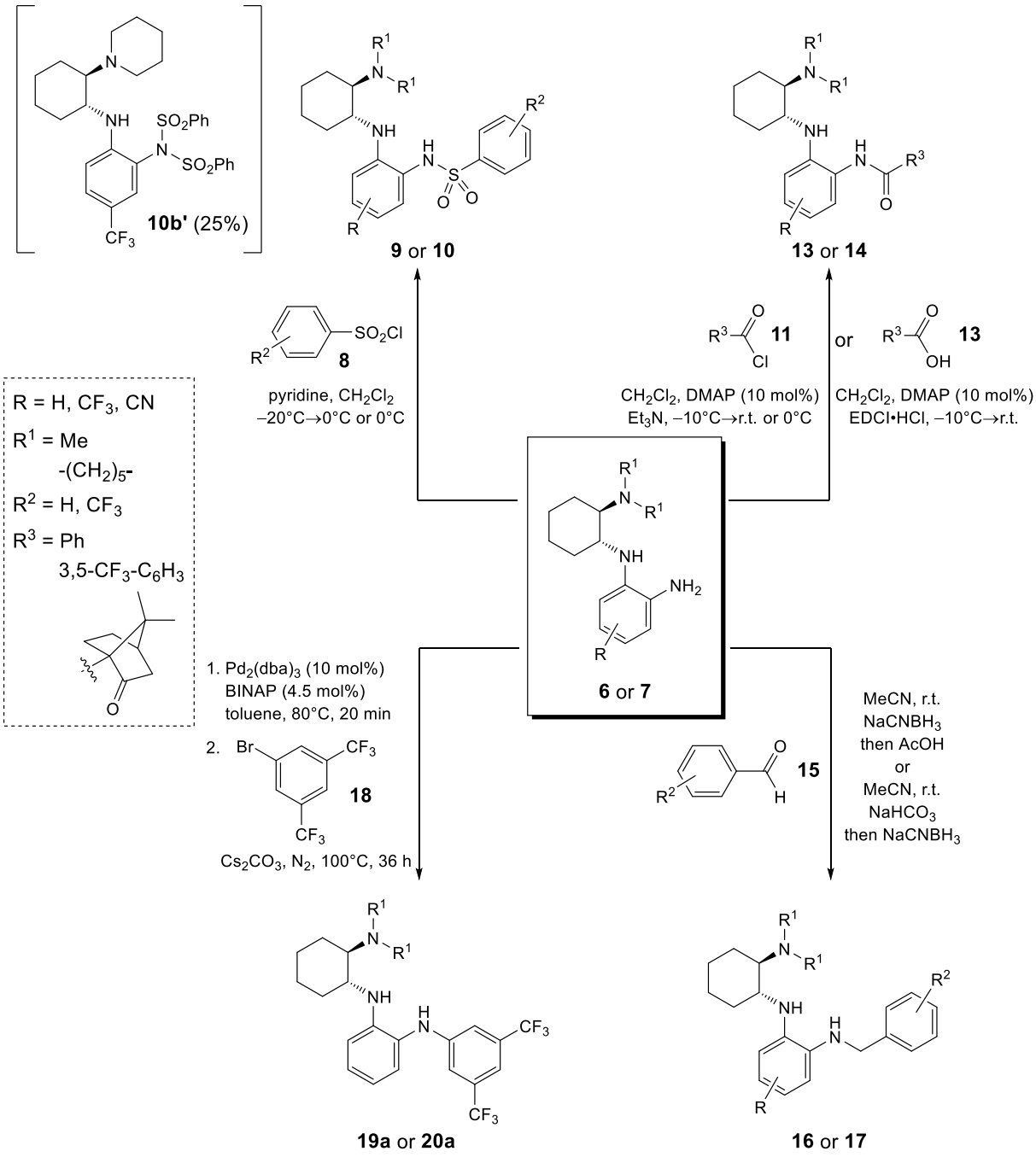
First, a reliable and as straightforward as possible synthesis of the chiral benzene-1,2-diamine building blocks **6** and **7**, which contain a primary aromatic amino group and an aliphatic tertiary amino group, had to be established starting from inexpensive, commercially available (1*R*,2*R*)-cyclohexane-1,2-diamine and *ortho*-fluoronitrobenzene derivatives (Scheme 1). While the introduction of the benzene-1,2-diamine moiety was already developed on a chiral (*S*)-quininamine scaffold [28], the introduction of the aliphatic tertiary amino group had to be considered. Although the initial introduction of the tertiary amino group is well documented in the literature [36–39], this would potentially introduce unwanted additional protection/deprotection steps. Therefore, a nucleophilic aromatic substitution–alkylation–reduction sequence was preferred. First, *ortho*-fluoronitrobenzene **2** was reacted with (1*R*,2*R*)-cyclohexane-1,2-diamine (**1**) in the presence of a base to give nitrobenzene derivatives **3** in 45–72% yields. Only unsubstituted *ortho*-fluoronitrobenzene (**2a**) and *ortho*-fluoronitrobenzene derivatives **2b–e**, substituted with electron withdrawing groups ($CF_3$, CN) were considered. The electron-donating substituents have a detrimental effect on enantioselectivity and yield, as has already been shown [28]. Subsequently, the primary aliphatic amino group of **3** was selectively alkylated. To introduce the dimethylamino group for the preparation of compounds **4**, reductive alkylation with aqueous formaldehyde using $NaCNBH_3$ in acetonitrile worked best (**4** prepared in 68–99% yields), since alkylation with iodomethane was accompanied by numerous side products. In contrast, the initially attempted reductive alkylation of **3** with glutaraldehyde in combination with $NaCNBH_3$ did not give a clean reaction profile; instead, the double nucleophilic $S_N2$ substitution with 1,5-dibromopentane in the presence of $K_2CO_3$ in acetonitrile worked best and gave the desired products **5** in 70–88% yields. Finally, the reduction of the aromatic nitro group of **4** and **5** was carried out with tin(II) chloride in ethanol, giving the desired benzene-1,2-diamines building blocks **6** and **7**, respectively, in 71–98% yields. Surprisingly, all attempts to reduce the aromatic nitro group by catalytic hydrogenation with palladium on charcoal (also in the presence of acetic acid) led to complex product mixtures (Scheme 1). The established three-step synthesis proved to be reproducible and scalable (up to 20 mmol). Compound **3a**, prepared from diamine **1** and *ortho*-fluoronitrobenzene (**2a**), is the only compound described in the literature [29].

Starting from the chiral benzene-1,2-diamines **6** and **7**, four subclasses of noncovalent bifunctional organocatalysts were prepared based on the type of functionalization of the aromatic primary amino group, i.e., the formation of sulfonamides, amides, alkylated amines and arylated amines (Scheme 2, Figures 2 and 3). Sulfonamides **9** and **10** were prepared in 15–65% yield from amines **6** and **7**, respectively, and benzenesulfonyl chloride (**8a**) and 3,5-bis(trifluoromethyl)benzenesulfonyl chloride (**8b**) in the presence of pyridine. The reactions of amines **7** were carried out at −20 °C with a substoichiometric amount of benzenesulfonyl chloride (**8a**) (0.9 equiv.) to minimize the formation of double sulfonamides, such as compound **10b′** (isolated in 25% yield), which was formed as a by-product in the sulfonation of amine **7b**. Amidation of amines **6** and **7** was carried out either with benzoyl chloride (**11**) in the presence of DMAP (4-dimethylaminopyridine) and $Et_3N$ or with EDCI-activated carboxylic acid (3,5-bis(trifluoromethyl)benzoic acid (**12a**) and (1*S*)-(+)-ketopinic acid (**12b**) were used) to produce amides **13** and **14**, respectively, in 23–82% yields. The reductive benzylation of amines **6** and **7** was carried out with benzaldehyde (**15a**) and 3,5-bis(trifluoromethyl)benzaldehyde (**15b**) using $NaCNBH_3$ as a reducing agent in the presence of acetic acid or sodium hydrogencarbonate. The corresponding benzylated secondary amines **16** and **17** were formed in yields of 13–52%. Finally, the Buchwald–Hartwig arylation of amines **6** and 7 with 1-bromo-3,5-bis(trifluoromethyl)benzene (**18**) catalyzed by Pd was carried out using $Pd_2(dba)_3$ and BINAP (2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) in the presence of $Cs_2CO_3$ in anhydrous degassed toluene according to the procedure in [40]. Compounds **19a** and **20a** were isolated in 49% and 40% yield, respectively

(Scheme 2, Figures 2 and 3). All experimental data and procedures can be found in the Supporting Information.




**Scheme 1.** Synthesis of benzene-1,2-diamine building blocks **6** and **7**.




**Scheme 2.** Synthesis of four subclasses of noncovalent bifunctional organocatalysts.

All new compounds **3b–e**, **4a–e**, **5a–c**, **6a–e**, **7a–c**, **9a–d**, **10a–c**, **10b′**, **13a–h**, **14a–f**, **16a–f**, **17a,b**, **19a** and **20a** were characterized by spectroscopic methods ($^{1}$H- and $^{13}$C-NMR, 2D-NMR, HRMS and IR). The structures of compounds **5a** and **10b′** were determined by X-ray single-crystal analysis (Figure 4).

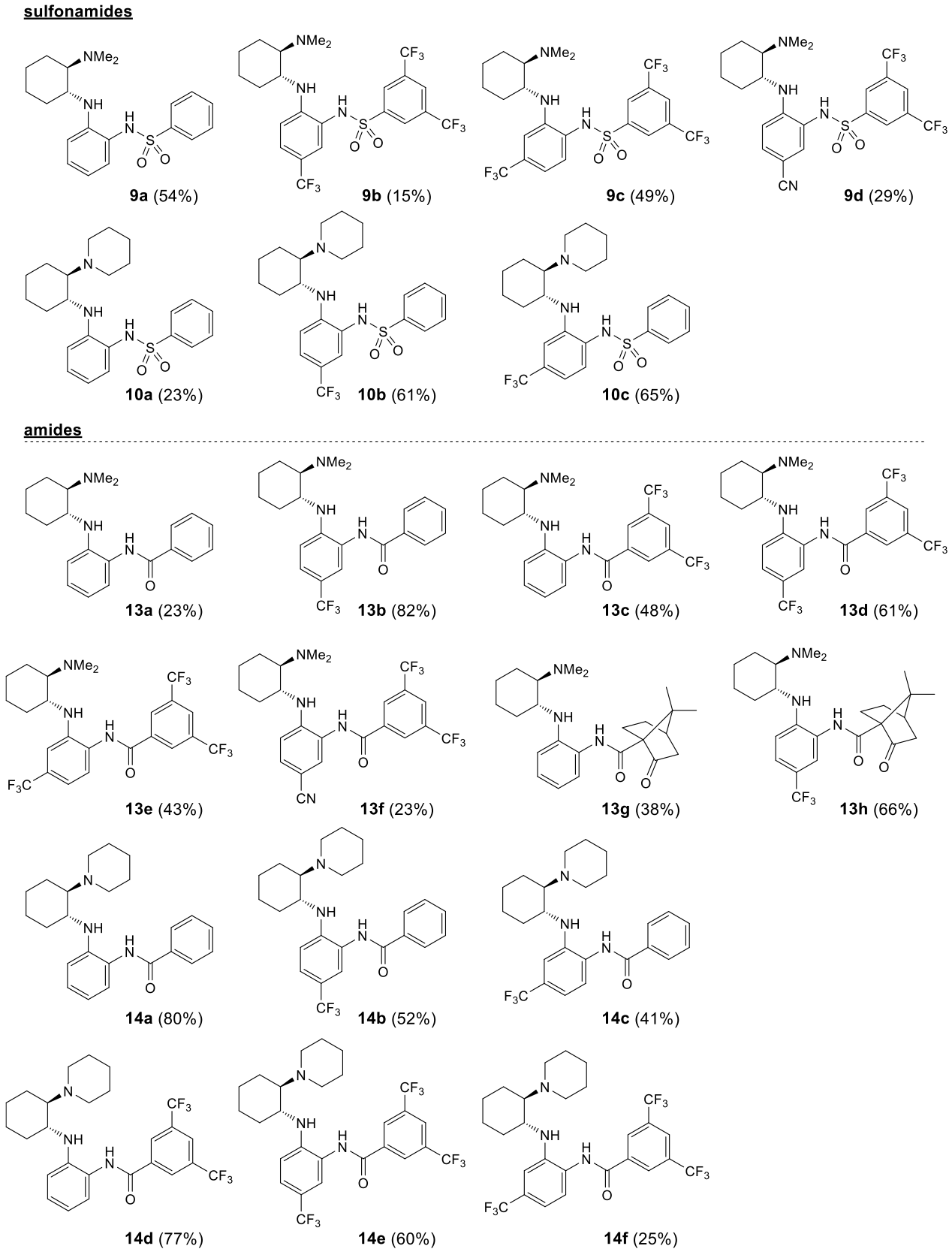



**Figure 2.** Prepared noncovalent bifunctional organocatalysts—sulfonamides and amides.

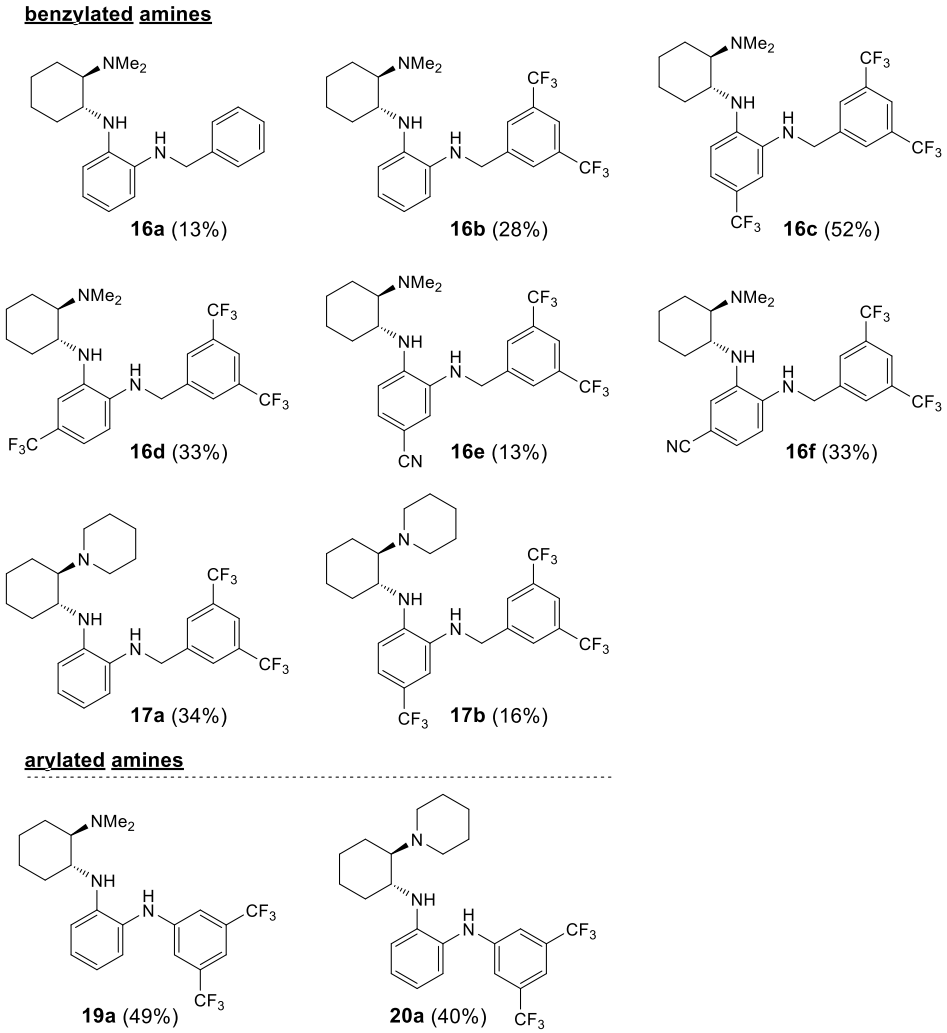



**Figure 3.** Prepared noncovalent bifunctional organocatalysts–arylated and benzylated amines.

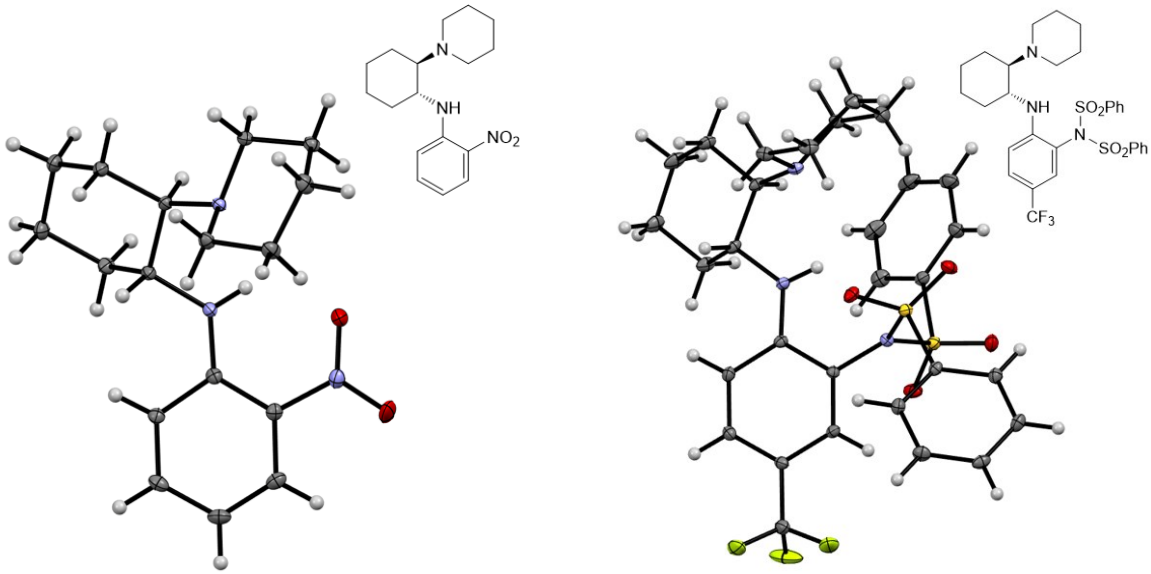
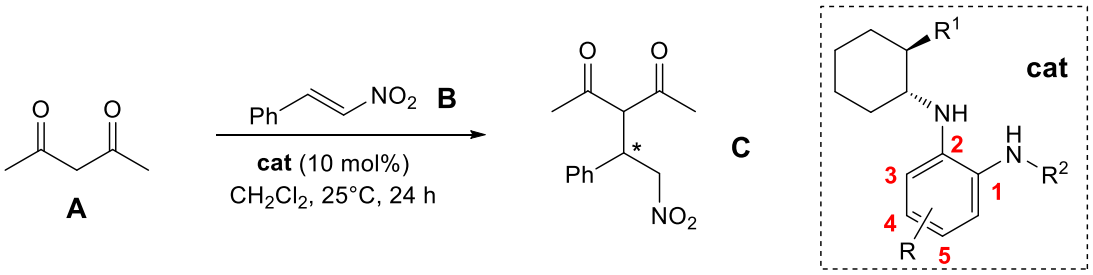


**Figure 4.** Molecular structures of compound **5a** (**left**) and **10b′** (**right**). Thermal ellipsoids are shown at 50% probability.

### 2.2. Organocatalytic Activity

While reactions with a broad combination of Michael acceptors and donors can be catalyzed by bifunctional (non)covalent organocatalysts [41,42], the organocatalytic activity (conversion and enantioselectivity) of 1,2-benzenediamine-derived organocatalysts based on (1*R*,2*R*)-cyclohexane-1,2-diamine was investigated in the chemoselective 1,4-addition of acetylacetone (**A**) to *trans*-β-nitrostyrene (**B**) [11,43,44]. All reactions were carried out in anhydrous dichloromethane at 25 °C for 24 h with 10 mol% of the catalyst (Table 1). Similar to the quinuclidine-derived analogues [28], all of the synthesized subtypes of organocatalysts were characterized by incomplete conversion (up to 93%) and low (*S*)-enantioselectivity (up to 41% *ee*). For comparison, the squaramide organocatalyst **21** [45] yielded the addition product **C** at 98% conversion and with high reversed enantioselectivity (93% *ee*, *R*) (Table 1, Entry 1). In total, 9 of 32 catalysts (**9a**, **10a**, **13a**–**e**, **14d** and **16a**) achieved ≥80% conversion, with the highest conversion (93%) obtained with amide **14d** (Entry 21) and benzylamine **16a** (Entry 24), albeit with low enantioselectivity (≤13% *ee*). In total, 4 of 32 catalysts (**9b**, **13d**–**f**) afforded the product **C** with ≥30% *ee*, with the highest enantioselectivity observed with catalyst **9b** (41% *ee*, Entry 3), although the conversion was low (11%). The best catalysts in terms of both conversion and enantioselectivity were amides **13d** (86% conversion and 32% *ee*; Entry 13) and **13e** (83% conversion and 32% *ee*; Entry 14). The introduction of an electron-withdrawing substituent (R = $CF_3$, CN) onto the benzene-1,2-diamine moiety in either position *4* or *5* generally resulted in lower conversion compared to the unsubstituted derivative (see and compare catalyst series **9a**–**d**, **10a**–**c**, **14a**–**c**, **14d**–**f** and **16a**–**f**), with the exception of amide series **13a**–**e**. The introduction of electron-withdrawing substituents ($CF_3$ and CN) at any position in the catalyst, i.e., the 3,5-bis(trifluoromethyl)phenyl group, did not lead to a significant improvement in enantioselectivity. Both dimethylamino- and piperidine-containing catalysts showed no convincing preference (conversion and enantioselectivity) for one of the two tertiary bases investigated. The double-sulfonated catalyst **10b′** failed to give any addition product (Entry 8), presumably due to steric reasons (see Figure 4).

**Table 1.** The organocatalytic activity tested in a Michael addition of acetylacetone (**A**) to *trans*-β-nitrostyrene (**B**).



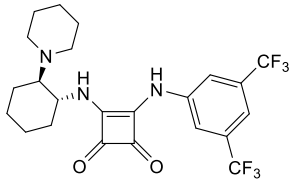

| | Catalyst | R | $R^1$ | $R^2$ | Conversion (%)<br>*ee* (%) [(a)] |
|---|---|---|---|---|---|
| 1 | | |  **21** | | 98<br>93 (*R*) |
| 2 | **9a** | H | $Me_2N$ | Ph-$SO_2$ | 82<br>26 (*S*) |

**Table 1.** *Cont.*

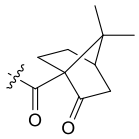
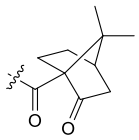
| | | | | | |
|---|---|---|---|---|---|
| 3 | **9b** | 5-$CF_3$ | $Me_2N$ | 3,5-$(CF_3)_2$-$C_6H_3$-$SO_2$ | 11<br>41 (*S*) |
| 4 | **9c** | 4-$CF_3$ | $Me_2N$ | 3,5-$(CF_3)_2$-$C_6H_3$-$SO_2$ | 14<br>26 (*S*) |
| 5 | **9d** | 5-CN | $Me_2N$ | 3,5-$(CF_3)_2$-$C_6H_3$-$SO_2$ | 13<br>19 (*S*) |
| 6 | **10a** | H | 1-piperidyl | Ph-$SO_2$ | 90<br>23 (*S*) |
| 7 | **10b** | 5-$CF_3$ | 1-piperidyl | Ph-$SO_2$ | 16<br>23 (*S*) |
| 8 | **10b′** | 5-$CF_3$ | 1-piperidyl | 2 × $PhSO_2$ [(b)] | 0<br>- |
| 9 | **10c** | 4-$CF_3$ | 1-piperidyl | Ph-$SO_2$ | 40<br>0 |
| 10 | **13a** | H | $Me_2N$ | Ph-CO | 83<br>24 (*S*) |
| 11 | **13b** | 5-$CF_3$ | $Me_2N$ | Ph-CO | 84<br>17 (*S*) |
| 12 | **13c** | H | $Me_2N$ | 3,5-$(CF_3)_2$-$C_6H_3$-CO | 85<br>26 (*S*) |
| 13 | **13d** | 5-$CF_3$ | $Me_2N$ | 3,5-$(CF_3)_2$-$C_6H_3$-CO | 86<br>32 (*S*) |
| 14 | **13e** | 4-$CF_3$ | $Me_2N$ | 3,5-$(CF_3)_2$-$C_6H_3$-CO | 83<br>32 (*S*) |
| 15 | **13f** | 5-CN | $Me_2N$ | 3,5-$(CF_3)_2$-$C_6H_3$-CO | 50<br>33 (*S*) |
| 15 | **13g** | H | $Me_2N$ |  | 13<br>27 (*S*) |
| 17 | **13h** | 5-$CF_3$ | $Me_2N$ |  | 9<br>23 (*S*) |
| 18 | **14a** | H | 1-piperidyl | Ph-CO | 76<br>14 (*S*) |
| 19 | **14b** | 5-$CF_3$ | 1-piperidyl | Ph-CO | 22<br>20 (*S*) |
| 20 | **14c** | 4-$CF_3$ | 1-piperidyl | Ph-CO | 15<br>28 (*S*) |
| 21 | **14d** | H | 1-piperidyl | 3,5-$(CF_3)_2$-$C_6H_3$-CO | 93<br>13 (*S*) |
| 22 | **14e** | 5-$CF_3$ | 1-piperidyl | 3,5-$(CF_3)_2$-$C_6H_3$-CO | 13<br>11 (*S*) |
| 23 | **14f** | 4-$CF_3$ | 1-piperidyl | 3,5-$(CF_3)_2$-$C_6H_3$-CO | 36<br>22 (*S*) |
| 24 | **16a** | H | $Me_2N$ | Ph-$CH_2$ | 93<br>3 (*S*) |

**Table 1.** *Cont.*

| | | | | | |
|---|---|---|---|---|---|
| 25 | **16b** | H | $Me_2N$ | 3,5-$(CF_3)_2$-$C_6H_3$-$CH_2$ | 56<br>3 (*S*) |
| 26 | **16c** | 5-$CF_3$ | $Me_2N$ | 3,5-$(CF_3)_2$-$C_6H_3$-$CH_2$ | 36<br>11 (*S*) |
| 27 | **16d** | 4-$CF_3$ | $Me_2N$ | 3,5-$(CF_3)_2$-$C_6H_3$-$CH_2$ | 20<br>1 (*S*) |
| 28 | **16e** | 5-CN | $Me_2N$ | 3,5-$(CF_3)_2$-$C_6H_3$-$CH_2$ | 11<br>17 (*S*) |
| 29 | **16f** | 4-CN | $Me_2N$ | 3,5-$(CF_3)_2$-$C_6H_3$-$CH_2$ | 27<br>9 (*S*) |
| 30 | **17a** | H | 1-piperidyl | 3,5-$(CF_3)_2$-$C_6H_3$-$CH_2$ | 12<br>- [c] |
| 31 | **17b** | 4-$CF_3$ | 1-piperidyl | 3,5-$(CF_3)_2$-$C_6H_3$-$CH_2$ | 11<br>6 (*S*) |
| 32 | **19a** | H | $Me_2N$ | 3,5-$(CF_3)_2$-$C_6H_3$ | 38<br>27 (*S*) |
| 33 | **20a** | H | 1-piperidyl | 3,5-$(CF_3)_2$-$C_6H_3$ | 39<br>27 (*S*) |

[a] In parentheses, the majority enantiomer is specified in italics. [b] Double-sulfonated amine. [c] The enantiomeric excess could not be reliably determined.

The cyclohexane-1,2-diamine-derived organocatalysts containing benzene-1,2-diamine as the H-bond donor afforded the addition product **C** at a better conversion rate than the chiral (*S*)-quininamine analogues [28] (93% vs. 41% conversion). On the other hand, the enantioselectivity of the cyclohexane-1,2-diamine-derived organocatalysts was disappointingly low (up to 41% *ee*) compared to the (*S*)-quininamine analogues [28] (up to 72% *ee*). The newly introduced benzene-1,2-diamine H-bond donor incorporated in the noncovalent organocatalysts reported here and in the previous publication [28] are no match for the established thiourea (Takemoto-type) [1,2,44] and (thio)squaramide (Rawal-type) organocatalysts [3,4] and their innumerable analogs derived from various chiral scaffolds such as terpenes, cyclohexane-1,2-diamine, 1,2-diphenylethane-1,2-diamine, amino acid-derived catalysts and others [2,5,42,46]. The present catalysts cannot compete with the established bifunctional thiourea and (thio)squaramide organocatalysts in the case of the Michael addition model reaction. However, further mechanistic studies should be performed to better understand and select suitable reactions for enantioselective synthesis.

## 3. Materials and Methods

Solvents for extractions and chromatography were of technical grade and were distilled prior to use. Extracts were dried over technical grade anhydrous $Na_2SO_4$. Melting points were determined on a Kofler micro hot stage and on the SRS OptiMelt MPA100 Automated Melting Point System (Stanford Research Systems, Sunnyvale, CA, USA). The NMR spectra were obtained on a Bruker UltraShield 500 plus (Bruker, Boston, MA, USA) at 500 MHz for $^1H$ and 126 MHz for $^{13}C$ nucleus, using $CDCl_3$ with TMS as the internal standard, as the solvent. Mass spectra were recorded on an Agilent 6224 Accurate Mass TOF LC/MS (Agilent Technologies, Santa Clara, CA, USA), and IR spectra were recorded on a Perkin-Elmer Spectrum BX FTIR spectrophotometer (PerkinElmer, Waltham, MA, USA). Column chromatography (CC) was performed on silica gel (Silica gel 60, particle size: 0.035–0.070 mm (Sigma-Aldrich, St. Louis, MI, USA)). HPLC analyses were performed on an Agilent 1260 Infinity LC (Agilent Technologies, Santa Clara, CA, USA) using CHIRALPAK AD-H (0.46 cm ø × 25 cm) as the chiral column (CHIRAL TECHNOLOGIES, INC., West Chester, PA, USA). The EasyMax 102 Basic Thermostat system reactor (METTLER TOLEDO, Columbus, OH, USA) was used for reactions at low temperatures. All of the

commercially available chemicals used were purchased from Sigma-Aldrich (St. Louis, MI, USA).

### *3.1. Synthesis of (1R,2R)-$N^1$-(2-nitrophenyl)cyclohexane-1,2-diamines **3**—General Procedure 1 (GP1)*

To a solution of (1*R*,2*R*)-cyclohexane-1,2-diamine (**1**) (1.0 equiv.) in anhydrous ethanol, the corresponding 1-fluoro-2-nitrobenzene **2** (1.0 equiv.) and $K_2CO_3$ (1.1 equiv.) were added. The resulting mixture was refluxed for 24 h. The volatiles were evaporated in vacuo, and the residue was dissolved in EtOAc (1.5 mL/1 mmol) and washed with water (0.5 mL/1 mmol). The aqueous phase was extracted twice more with EtOAc (0.5 mL/1 mmol). The combined organic phase was dried over anhydrous $Na_2SO_4$ and filtered and the volatiles were evaporated in vacuo. The residue was purified by column chromatography (Silica gel 60, 1. EtOAc/petroleum ether = 1:1; 2. $CH_2Cl_2$/MeOH = 10:1). The fractions containing the pure product **3** were combined and the volatiles were evaporated in vacuo.

### *3.2. Synthesis of (1R,2R)-$N^1$,$N^1$-dimethyl-$N^2$-(2-nitrophenyl)cyclohexane-1,2-diamines **4**—General Procedure 2 (GP2)*

Formaldehyde (aqueous, 37%, 5.0 equiv.) was added to the corresponding (1*R*,2*R*)-$N^1$-(2-nitrophenyl)cyclohexane-1,2-diamine **3** (1.0 equiv.) dissolved in acetonitrile at room temperature. After stirring for 15 min at room temperature, $NaCNBH_3$ (2.0 equiv.) was added. After 15 min of stirring at room temperature, acetic acid (4.5 equiv.) was added. After stirring at room temperature for 2 h, a solution of 2% MeOH in $CH_2Cl_2$ (14 mL/1 mmol) was added and the mixture was washed three times with NaOH (aqueous; 1 M; 14 mL/1 mmol). The organic phase was dried over anhydrous $Na_2SO_4$ and filtered and the volatiles were evaporated in vacuo. The residue was purified by column chromatography (Silica gel 60, 1. EtOAc/petroleum ether = 1:1). The fractions containing the pure product **4** were combined and the volatiles were evaporated in vacuo.

### *3.3. Synthesis of 2-nitro-N-((1R,2R)-2-(piperidin-1-yl)cyclohexyl)aniline **5**—General Procedure 3 (GP3)*

To a solution of the corresponding (1*R*,2*R*)-$N^1$-(2-nitrophenyl)cyclohexane-1,2-diamine **3** (1.0 equiv.) in anhydrous acetonitrile under argon, 1,5-dibromopentane (1.1 equiv.) and $K_2CO_3$ (2.2 equiv.) were added. The resulting reaction mixture was heated under reflux for 12 h. The volatiles were evaporated in vacuo, and the residue was dissolved in $CH_2Cl_2$ (6 mL/1 mmol) and washed with water (4 mL/1 mmol). The aqueous phase was additionally extracted with $CH_2Cl_2$ (3 mL/1 mmol). The combined organic phase was dried over anhydrous $Na_2SO_4$ and filtered and the volatiles were evaporated in vacuo. The residue was purified by column chromatography (Silica gel 60, EtOAc/petroleum ether = 5:1). The fractions containing the pure product **5** were combined and the volatiles were evaporated in vacuo. The residue was additionally purified by short-path vacuum distillation (120 °C; 2 mbar; several hours) to remove the unreacted 1,5-dibromopentane.

### *3.4. Reduction of the Aromatic Nitro Group—General Procedure 4 (GP4)*

To a solution of the corresponding (2-nitrophenyl)cyclohexane-1,2-diamine **4** or **5** (1.0 equiv.) in ethanol, $SnCl_2 \bullet 2H_2O$ (6 equiv.) was added. The resulting reaction mixture was heated under reflux for 1 h. The reaction mixture was cooled to room temperature and then NaOH (aq., 6 M) was added until a homogeneous solution was obtained (pH = 14). $CH_2Cl_2$ (6 mL/1 mmol) was then added and the mixture was stirred at room temperature for 30 min. The phases were then separated and the organic phase was dried over anhydrous $Na_2SO_4$ and filtered and the volatiles were evaporated in vacuo. If necessary, the resulting product **6** or **7** was additionally purified by column chromatography (Silica gel 60). The fractions containing the pure product **6** or **7**, respectively, were combined and the volatiles were evaporated in vacuo.

### *3.5. Synthesis of Benzenesulfonamides **9** and **10**—General Procedure 5 (GP5)*

To a solution of benzene-1,2-diamine **6** or **7** (1.0 equiv.) in anhydrous dichloromethane, pyridine (1.1 equiv.) (and optionally DMAP (10 mol%)) was added under argon. The reaction mixture was cooled to 0 °C or −20 °C and then benzenesulfonyl chloride **8** was added. The resulting reaction mixture was stirred at 0 °C for 2 h. In the case where the reaction mixture was cooled to −20 °C, the resulting reaction mixture was gradually warmed from −20 °C to 0 °C within 4 h with constant stirring. Then, ethyl acetate (14 mL/1 mmol) was added. The resulting mixture was washed with $NaHCO_3$ (aq. sat., 7 mL/1 mmol) and NaCl (aq. sat., 7 mL/1 mmol). The organic phase was dried over anhydrous $Na_2SO_4$ and filtered and the volatiles were evaporated in vacuo. The residue was purified by column chromatography (Silica gel 60). The fractions containing the pure product **9** or **10**, respectively, were combined and the volatiles were evaporated in vacuo.

### *3.6. Acylation of the Primary Amine with Benzoyl Chloride—General Procedure 6 (GP6)*

To a solution of benzene-1,2-diamine **6** or **7** (1.0 equiv.) in anhydrous dichloromethane, $Et_3N$ (1.2 equiv.) and DMAP (10 mol%) were added under argon. The reaction mixture was cooled to −10 °C or 0 °C and then benzoyl chloride (**11**) (1.2 equiv.) was added. The resulting reaction mixture was stirred at room temperature or 0 °C for 2 h. Then, ethyl acetate (14 mL/1 mmol) was added. The resulting mixture was washed with $NaHCO_3$ (aq. sat., 7 mL/1 mmol) and NaCl (aq. sat., 7 mL/1 mmol). The organic phase was dried over anhydrous $Na_2SO_4$ and filtered and the volatiles were evaporated in vacuo. The residue was purified by column chromatography (Silica gel 60). The fractions containing the pure product **13** or **14**, respectively, were combined and the volatiles were evaporated in vacuo.

### *3.7. Acylation of the Primary Amine with EDCI-Activated Carboxylic Acid—General Procedure 7 (GP7)*

To a solution of benzene-1,2-diamine **6** or **7** (1.0 equiv.) in anhydrous dichloromethane, carboxylic acid **12** (1.0 equiv.) and DMAP (10 mol%) were added under argon. The reaction mixture was cooled to −10 °C, and then, EDCI•HCl (1.2 equiv.) was added. The resulting reaction mixture was stirred at room temperature for 24 h. Then, $CH_2Cl_2$ (35 mL/1 mmol) was added. The resulting mixture was washed with $H_2O$ (7 mL/1 mmol). The organic phase was dried over anhydrous $Na_2SO_4$ and filtered and the volatiles were evaporated in vacuo. The residue was purified by column chromatography (Silica gel 60). The fractions containing the pure product **13** or **14**, respectively, were combined and the volatiles were evaporated in vacuo.

### *3.8. Reductive Alkylation of the Primary Amine—General Procedure 8 (GP8)*

To a solution of $N^1$-((1*R*,2*R*)-2-(dimethylamino)cyclohexyl)benzene-1,2-diamine (**6a**) (1.0 equiv.) in anhydrous acetonitrile at room temperature, aldehyde **15** (2.0 equiv.) and $NaCNBH_3$ (2.0 equiv.) were added. After stirring for 15 min at room temperature, AcOH was added to the reaction mixture. After stirring for 2 h at room temperature, a 2% solution of MeOH in $CH_2Cl_2$ (22 mL/1 mmol) was added. The resulting mixture was washed three times with NaOH (aq., 1 M, 22 mL/1 mmol). The organic phase was dried over anhydrous $Na_2SO_4$ and filtered and the volatiles were evaporated in vacuo. The residue was purified by column chromatography (Silica gel 60). The fractions containing the pure product **16** were combined and the volatiles were evaporated in vacuo.

### *3.9. Reductive Alkylation of the Primary Amine—General Procedure 9 (GP9)*

Aldehyde **15** (1.0 equiv.) and $NaHCO_3$ (2.0 equiv.) were added to a solution of benzene-1,2-diamine **6** or **7** (1.0 equiv.) in anhydrous acetonitrile at room temperature. After stirring at room temperature for 15 min, $NaCNBH_3$ (4.0–6.0 equiv.) was added to the reaction mixture in portions (1.0–1.5 equiv. per hour). After stirring at room temperature for 4 h, HCl (aq., 2 M) was added to reach pH 1, followed by the addition of NaOH (aq.,

2 M) to reach pH = 12. The resulting mixture was extracted with EtOAc (14 mL/1 mmol). The organic phase was dried over anhydrous $Na_2SO_4$ and filtered and the volatiles were evaporated in vacuo. The residue was purified by column chromatography (Silica gel 60). The fractions containing the pure product **16** or **17**, respectively, were combined and the volatiles were evaporated in vacuo.

### *3.10. Arylation of the Primary Amine—General Procedure 10 (GP10)*

An AC heavy-walled reaction tube was charged with $Pd_2(dba)_3$ (1.5 mol%) and BINAP (4.5 mol%) in anhydrous degassed toluene under argon. The mixture was heated at 80 °C under argon for 20 min. The resulting red mixture, cooled to room temperature, was then transferred to a separate heavy-walled AC reaction tube that had previously been charged with $Cs_2CO_3$ (1.53 equiv.) and 1-bromo-3,5-bis(trifluoromethyl)benzene (**18**) (1 equiv.) in anhydrous degassed toluene under argon. Finally, benzene-1,2-diamine **6** or **7** (1.0 equiv.) was added and the sealed reaction mixture was heated at 100 °C for 36 h. Then, $H_2O$ (20 mL/1 mmol) was added to the cooled reaction mixture (at room temperature) and extracted with $CH_2Cl_2$ (60 mL/1 mmol). The organic phase was dried over anhydrous $Na_2SO_4$ and filtered and the volatiles were evaporated in vacuo. The residue was purified by column chromatography (Silica gel 60). The fractions containing the pure product **12** or **13**, respectively, were combined and the volatiles were evaporated in vacuo.

### *3.11. Organocatalyzed Addition of Acetylacetone to trans-β-nitrostyrene*

To a solution of *trans*-β-nitrostyrene (**B**) (29.8 mg, 0.2 mmol) in anhydrous $CH_2Cl_2$ (1 mL) under argon, the catalyst (10 mol%) was added, followed by the addition of acetylacetone (**C**) (30.8 μL, 0.3 mmol). The resulting reaction mixture under argon was stirred at 25 °C for 24 h. After 24 h, an aliquot of 100 μL of the reaction mixture was withdrawn to determine the reaction conversion by $^1$H NMR (in $CDCl_3$). The remainder of the reaction mixture was used to isolate the addition product **C**. The residue was purified by column chromatography (Silica gel 60, EtOAc/petroleum ether = 1:1—in the case of non-polar catalysts, EtOAc/petroleum ether = 1:3 was used). The reaction mixture was transferred directly to the top of the column without prior evaporation of the volatile components. The fractions containing product **C** were combined and the volatiles were evaporated in vacuo. Enantioselectivity was determined by chiral HPLC analysis (chiral column CHIRALPAK AD-H; mobile phase: *n*-hexane/*i*-PrOH = 90:10; flow rate: 1.0 mL/min; λ = 210 nm).

### *3.12. X-ray Crystallography*

Single-crystal X-ray diffraction data were collected on an Agilent Technologies SuperNova Dual diffractometer with an Atlas detector using monochromated Cu-Kα radiation (λ = 1.54184 Å) at 150 K. The data were processed using CrysAlis PRO [47]. Using Olex2.1.2. [48], the structures were solved by direct methods implemented in SHELXS [49] or SHELXT [50] and refined by a full-matrix least-squares procedure based on F2 with SHELXT-2014/7 [51]. All nonhydrogen atoms were refined anisotropically. Hydrogen atoms were placed in geometrically calculated positions and were refined using a riding model. The drawings and the analysis of bond lengths, angles and intermolecular interactions were carried out using Mercury [52] and Platon [53]. Structural and other crystallographic details obtained from the data collection and refinement for compounds **5a** and **10b′** have been deposited with the Cambridge Crystallographic Data Centre as a supplementary publication number, with CCDC Deposition Numbers 2330833 and 2330834, respectively. These data are available free of charge at https://www.ccdc.cam.ac.uk/structures/, accessed on 4 February 2024 (or from CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk).

## 4. Conclusions

The chiral benzene-1,2-diamine building blocks **6** and **7**, containing a primary aromatic amino group and an aliphatic tertiary amino group, were prepared from commercially

available (1*R*,2*R*)-cyclohexane-1,2-diamine (**1**) and *ortho*-fluoronitrobenzene derivatives **2** in a three-step synthesis involving a nucleophilic aromatic substitution–alkylation–reduction sequence. Subsequent functionalization of the primary aromatic amino group of **6** and **7** led to four subclasses of noncovalent organocatalysts, namely, sulfonamides **9**/**10**, amides **13**/**14**, alkylated amines **16**/**17** and arylated amines **19**/**20**. All new compounds were fully characterized. The organocatalytic activity (conversion and enantioselectivity) of 1,2-benzenediamine-derived organocatalysts based on (1*R*,2*R*)-cyclohexane-1,2-diamine was investigated in the 1,4-addition of acetylacetone to *trans*-β-nitrostyrene in anhydrous dichloromethane at 25 °C for 24 h with 10 mol% of the catalyst. All synthesized subtypes of organocatalysts were characterized by incomplete conversion (up to 93%) and low (*S*)-enantioselectivity (up to 41% *ee*). The alkylated amines **16**/**17** and the arylated amines **19**/**20** have the potential to be converted into benzimidazole N-heterocyclic carbene precursors in one step.

**Supplementary Materials:** The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/catal14040274/s1: Syntheses and characterization; HPLC data; Copies of $^{1}$H- and $^{13}$C-NMR spectra; Copies of HRMS reports; Structure determination using X-ray diffraction analysis.

**Author Contributions:** Conceptualization, K.K., A.G., L.C., U.G., J.S. and B.Š.; methodology, K.K., A.G., L.C. and U.G.; software, K.K., A.G., L.C., H.B., U.G., J.S. and B.Š.; validation, K.K., A.G., L.C., H.B., U.G., J.S., F.P. and B.Š.; formal analysis, K.K., A.G., U.G., H.B. and L.C.; investigation, K.K., A.G., L.C. and U.G.; resources, L.C., U.G. and J.S.; data curation, K.K., A.G., L.C., H.B., U.G., J.S. and B.Š.; writing—original draft preparation, U.G., J.S. and B.Š.; writing—review and editing, L.C., U.G., J.S., F.P. and B.Š.; visualization, L.C., H.B., U.G., B.Š. and J.S.; supervision, U.G.; project administration, U.G. and J.S.; funding acquisition, U.G. and J.S. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research study was funded by the Slovenian Research Agency through grant P1-0179.

**Data Availability Statement:** The data are contained within the article and Supplementary Materials.

**Conflicts of Interest:** The authors declare no conflicts of interest.

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