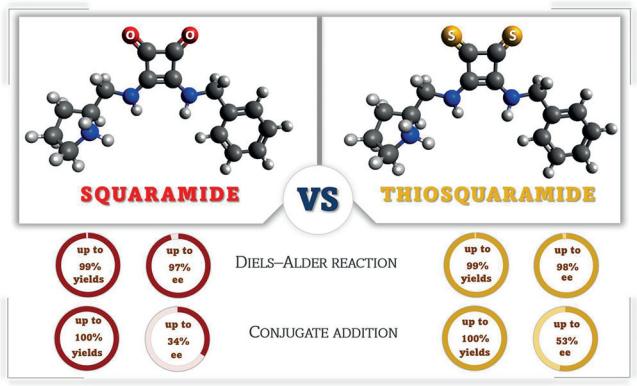
Synthesis G. Dargó et al. Special Topic

# Application of Proline-Derived (Thio)squaramide Organocatalysts in Asymmetric Diels–Alder and Conjugate Addition Reactions

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**Abstract** The synthesis of chiral proline-derived squaramide and thiosquaramide organocatalysts, which are capable of the dual activation in asymmetric reactions is reported. The (thio)squaramide moiety can form hydrogen bonds to activate the substrates and to stereocontrol the reaction, while the pyrrolidine unit can form enamines to activate carbonyl compounds via aminocatalysis. Comparing the performance of thiosquaramide to squaramide, the Diels–Alder reaction of (anthracen-9-yl)acetaldehyde and *trans*-β-nitrostyrene was examined, which has been investigated in the literature using quantum chemical calculations. Both squaramide and thiosquaramide gave excellent yields (up to 99%) and enantiomeric excess values (up to 98%). Moreover, their catalytic performance was compared in conjugate addition of lawsone to β,γ-unsaturated α-keto ester.

**Key words** asymmetric organocatalysis, aminocatalysis, proline, thiosquaramide, Diels–Alder reaction, conjugate addition

Very recently, organocatalysis has received a great deal of attention due to the award of the Nobel Prize[1] to David MacMillan and Benjamin List for their pioneering work in this research area.[2,3] Since the foundation of this attractive synthetic tool, many organocatalyst families have evolved, such as the proline-derived Jørgensen–Hayashi[4] or Corey–Bakshi–Shibata[5] catalysts. These can be derived from the well-known, renewable, natural amino acid L-proline, which can be considered as the simplest 'enzyme' in nature.[6] Proline and proline-derived organocatalysts opened the door to asymmetric aminocatalysis.[7–11] Fülöp and co-workers successfully applied solid-supported proline-based catalysts in asymmetric Michael additions with excellent enantiomeric excess values (up to 95%).[12,13] Moreover, proline derivatives can be also applied in aldol,[3] Michael,[14] Mannich,[15] and Diels–Alder reactions,[2] etc. Considering the stereocontrol of the proline catalysts in asymmetric reactions, they can be divided into two main groups. In one of them, the stereoinduction can be achieved by steric hindrance, in the other by hydrogen-bond interactions.[16]

In the latter group of catalysts, the utilization of hydrogen-bond donors still plays a crucial role in asymmetric organocatalysis.[17,18] After the widespread applications of dual hydrogen-bond donors, such as urea, and thiourea,[19] significant advances have been made in this emerging field by Rawal and co-workers. First, in 2008 they introduced chiral squaramides as novel hydrogen-bonding catalysts.[20] Squaramides have a significantly greater distance between the donor hydrogens than found in thioureas, moreover, the acidity of the NH protons is greater, which can further increase their hydrogen-bonding capability.[21,22]

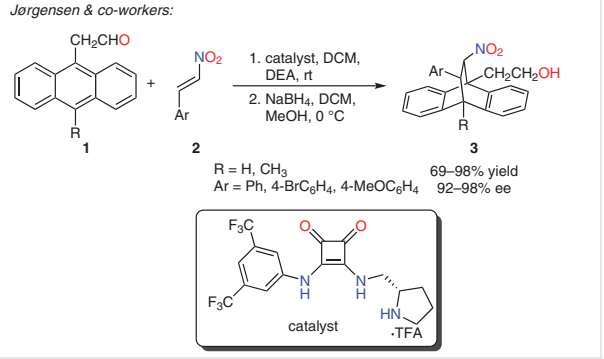
Later, in 2017 the same research group published the first application of chiral thiosquaramides in conjugate addition reaction of the barbituric acid pharmacophore to nitroalkenes.[23] Thiosquaramides, the thio analogues of squaramides, are members of a new class of hydrogen-bonding catalysis, which have greater acidity and increased solubility in nonpolar solvents.[22,24] In contrast to squaramides, which assemble into head-to-tail ladder networks, in the

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case of thiosquaramides the formation of this framework is presumably disrupted, therefore, thiosquaramides have better solubility.[25–29]

Before the first application of thiosquaramides in enantioselective reactions in 2017,[23] their superior performance over squaramides was predicted by using modern tools of computational quantum chemistry.[30] Lu and Wheeler used density functional calculations to examine the Diels–Alder cycloaddition reaction of (anthracen-9-yl)acetaldehydes **1** and *trans*-β-nitrostyrene derivatives **2** catalyzed by a pyrrolidine-based squaramide, which was previously reported by Jørgensen and co-workers (Scheme 1).[31]




**Scheme 1** Diels–Alder reaction of (anthracen-9-yl)acetaldehydes **1** and *trans*-β-nitrostyrene derivatives **2**;[31] DEA = *N*,*N*-diethylacetamide

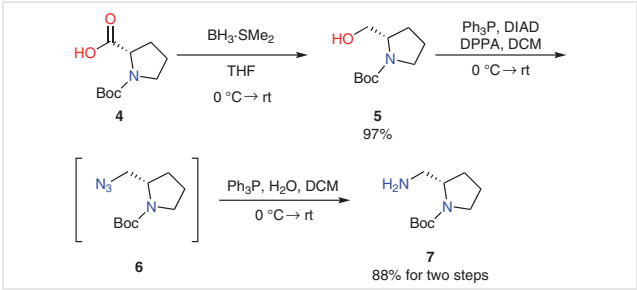
The Diels–Alder reaction is a powerful tool for carbon–carbon bond formation, especially when several new stereocenters arise. Additionally, in the above-mentioned Diels–Alder reaction the obtained aldehydes can be converted to novel, chiral maprotiline or benzoctamine analogues[32–34] by Mannich reaction or reductive amination, respectively, which derivatives could be biologically active. Comparing the activity of squaramide with the corresponding urea, thiourea, and thiosquaramide catalysts, the lowest free-energy barrier can be observed in the case of thiosquaramide.[30]

Another relevant asymmetric reaction, where thiosquaramides proved to possess higher catalytic activity than their oxo analogues, is the conjugate addition of lawsone to β,γ-unsaturated α-keto ester.[35] In our recent study,[36] in this conjugate addition, the application of binaphthyl-cinchona thiosquaramide derivatives resulted in up to 12% higher enantioselectivities (up to 92%) than by using the corresponding oxo analogues.

In the present study, we report the synthesis of a chiral benzyl-pyrrolidine squaramide and its thio analogue. Moreover, we decided to investigate the differences in performance of squaramide and thiosquaramide organocatalysts in asymmetric Diels–Alder reaction of (anthracen-9-yl)acetaldehyde and *trans*-β-nitrostyrene, and in asymmetric conjugate addition of lawsone to β,γ-unsaturated α-keto ester.

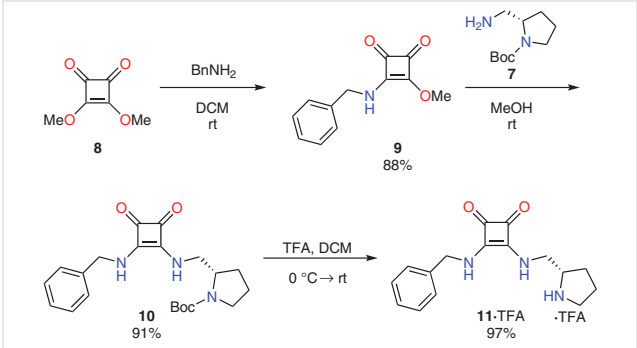
**Synthesis of Benzyl Pyrrolidine-(Thio)squaramide Catalysts**

For the synthesis of squaramide and thiosquaramide catalysts, *N*-Boc-protected pyrrolidine amine **7** was obtained from *N*-Boc-protected naturally occurring amino acid (*S*)-proline **4**, applying the method reported by Fülöp, Juaristi, and their co-workers with minor modifications.[37] First, the reduction of (*S*)-proline derivative **4** with borane dimethyl sulfide complex ($BH_3{\cdot}SMe_2$) gave prolinol **5** in an excellent yield. In the next step, prolinol **5** was converted into the corresponding amine derivative **7** by a one-pot method involving the combination of Mitsunobu and Staudinger reactions (Scheme 2).




**Scheme 2** Synthesis of *N*-Boc-protected pyrrolidine amino derivative **7**

Benzyl half-squaramide **9** was prepared by reacting dimethyl squarate (**8**) with benzylamine.[38] Then benzyl half-squaramide **9** was reacted with (*S*)-pyrrolidine amine **7** affording *N*-Boc-protected squaramide **10**. Finally, after the deprotection step by trifluoroacetic acid (TFA), the TFA salt of the squaramide (**11**·TFA) was obtained (Scheme 3).

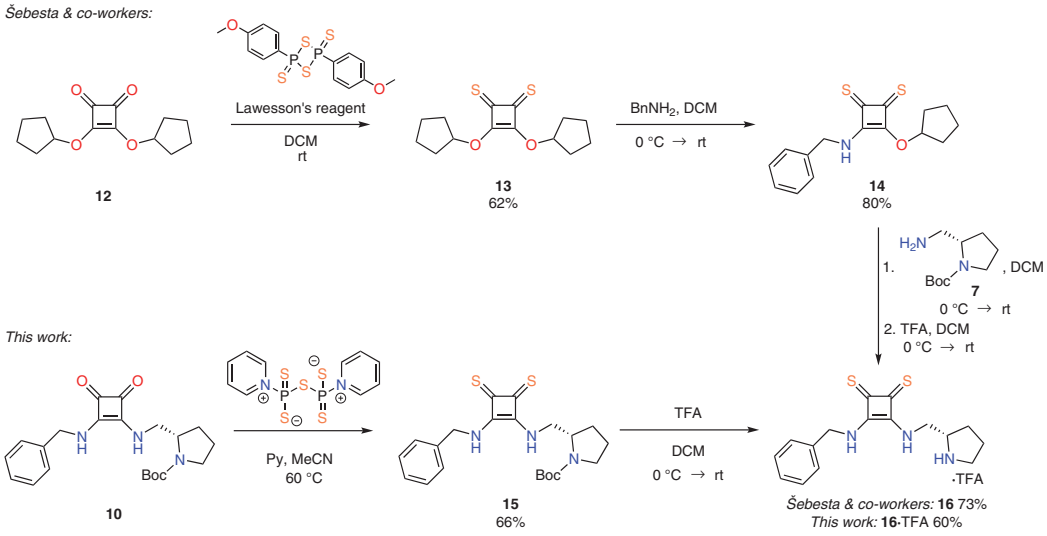



**Scheme 3** Synthesis of proline-derived squaramide organocatalyst **11**·TFA

For the synthesis of thiosquaramides, two generally applied methods exist. Rawal and co-workers developed a user-friendly procedure via dicyclopentyl thiosquarate intermediate **13**, which has appropriate stability at room temperature.[35] Šebesta and co-workers prepared benzyl pyrrolidine-thiosquaramide **16** by using this strategy.[39] In our work, however, we prepared thiosquaramide organo-

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**Scheme 4** Synthesis of benzyl pyrrolidine-thiosquaramides **16** and **16**·TFA

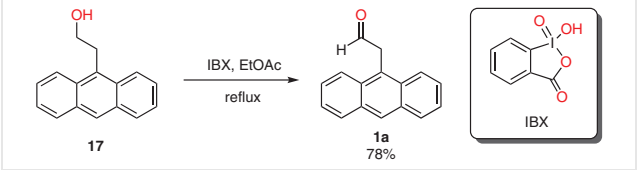
catalyst **16**·TFA by the direct thionation of squaramide analogue **10** using $P_4S_{10}$-pyridine complex, which thionating agent was successfully applied previously in the literature.[22,36] Since thiosquaramides are usually unstable on silica gel, by using the direct thionation of squaramides, several purification steps of thio intermediates can be avoided (Scheme 4).

During the thionation of *N*-Boc protected benzyl pyrrolidine-squaramide **10** at higher temperature than 80 °C, the decomposition of thiosquaramide **15** was observed, therefore, in contrast to that reported,[22,36] the thionation was carried out at 60 °C.

**Diels–Alder Reaction of (Anthracen-9-yl)acetaldehyde and *trans*-β-Nitrostyrene**

For the comparison of the catalytic activity of squaramide **11**·TFA and thiosquaramide **16**·TFA in Diels–Alder cycloaddition, (anthracen-9-yl)acetaldehyde (**1a**) was synthesized from the commercially available 2-(anthracen-9-yl)ethanol (**17**). For this selective oxidation, 2-iodoxybenzoic acid (IBX) was chosen as an oxidizing agent (Scheme 5). The solubility of IBX is poor in the most common organic solvents at room temperature, therefore, IBX is usually applied in DMSO. Due to the inconvenient application of DMSO, the oxidation was carried out in refluxing EtOAc, in which case the solubility of IBX is sufficient. Furthermore, using EtOAc as a solvent is advantageous, because all products formed from IBX are insoluble in this solvent at room temperature, hence, they can be removed by simple filtration.[40]

Benzyl pyrrolidine-squaramide **11**·TFA and -thiosquaramide **16**·TFA were applied in the Diels–Alder cycloaddition of *trans*-β-nitrostyrene (**2a**) with (anthracen-9-yl)acetaldehyde (**1a**). The main difficulty in the application of pyrrolidine-squaramide type organocatalysts is their low solubility in common organic solvents, therefore, the use of additives is usually inevitable.




**Scheme 5** Selective oxidation of 2-(anthracen-9-yl)ethanol (**17**) with 2-iodoxybenzoic acid (IBX)

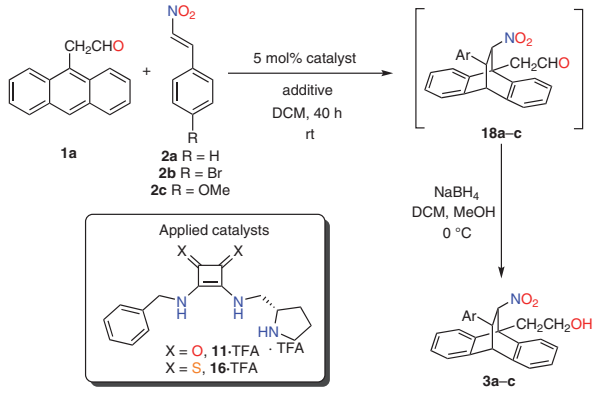
Without any additives in dichloromethane, only low conversion was achieved with both squaramide **11**·TFA and thiosquaramide **16**·TFA as catalysts after 40 hours (Table 1, entries 1, 2).

Surprisingly, the use of additives was also necessary in the case of the thiosquaramide catalyst **16**·TFA, despite the fact that it was totally soluble in pure dichloromethane. Using dimethylacetamide (DMA) as an additive, the Diels–Alder product was obtained with excellent enantioselectivities (96–97% ee), however, the yield was lower in the case of benzyl pyrrolidine-thiosquaramide (**16**·TFA), since the full conversion of the aldehyde was not achieved after 40 hours (Table 1, entries 3, 4). Using pyridine as an additive, both squaramide **11**·TFA and thiosquaramide **16**·TFA catalysts led to the desired adduct in excellent yields (up to 99%), and enantiomeric excess values (96–98% ee, entries 5, 6). In order to investigate the effects of electron-donating and electron-withdrawing groups on the aromatic ring of dienophile, we evaluated the reaction of *trans*-4-methoxy-β-nitrostyrene and *trans*-4-bromo-β-nitrostyrene by using pyridine as additive (entries 7–10). Both electron-rich and electron-defi-

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**Table 1** Investigation of Diels–Alder Reaction[a]



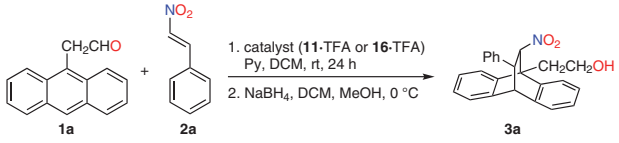

| Entry | Catalyst | R | Additive | Yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|---|
| 1 | **11**·TFA | H | – | traces | |
| 2 | **16**·TFA | H | – | traces | |
| 3 | **11**·TFA | H | DMA (2 equiv) | 98 | 96 |
| 4 | **16**·TFA | H | DMA (2 equiv) | 83 | 97 |
| 5 | **11**·TFA | H | Py (10 mol%) | 99 | 96 |
| 6 | **16**·TFA | H | Py (10 mol%) | 99 | 98 |
| 7 | **11**·TFA | Br | Py (10 mol%) | 99 | 97 |
| 8 | **16**·TFA | Br | Py (10 mol%) | 98 | 98 |
| 9 | **11**·TFA | OMe | Py (10 mol%) | 87 | 97 |
| 10 | **16**·TFA | OMe | Py (10 mol%) | 99 | 97 |

[a] Reaction conditions: aldehyde **1a** (0.068 mmol), *trans*-β-nitrostyrenes **2a–c** (0.102 mmol), and catalyst (5 mol%) were dissolved in DCM (375 μL). Subsequently, additive was added, and stirred at rt for 40 h. In the next step, MeOH (0.5 mL) was added, and for reduction $NaBH_4$ (2 equiv) was used.
[b] Yield of isolated product, purified by preparative TLC.
[c] Determined by chiral HPLC.

cient dienophiles provided the Diels–Alder products **3a–c** in good yields (87–99%) with excellent stereocontrol (97–98% ee).

Finally, we aimed to optimize the amount of the catalyst in the presence of pyridine additive, which gave the best result with both catalysts **11**·TFA and **16**·TFA, furthermore, our plan was to decrease the reaction time from 40 hours to 24 hours. In shorter time, the yields and enantiomeric excess values did not change significantly in the presence of 5 mol% catalysts (Table 1 entries 5, 6 vs Table 2 entries 3 and 8). Both the squaramide **11**·TFA and the thiosquaramide **16**·TFA catalysts gave excellent results (up to 99% yield, and up to 98% ee) when the catalyst loading was at least 5 mol%. Below 5 mol% catalyst, only a slight decrease was observed regarding enantiomeric excess values, however, the yields were drastically decreased in the presence of only 1 mol% catalyst (Table 2, entries 5 and 10).

**Table 2** Effects of Catalyst Amounts in Diels–Alder Reaction[a]




| Entry | Catalyst | Amount of catalyst (mol%) | Amount of pyridine (mol%) | Yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|---|
| 1 | **11**·TFA | 20 | 40 | 99 | 96 |
| 2 | **11**·TFA | 10 | 20 | 99 | 96 |
| 3 | **11**·TFA | 5 | 10 | 99 | 97 |
| 4 | **11**·TFA | 2 | 4 | 48 | 95 |
| 5 | **11**·TFA | 1 | 2 | 19 | 94 |
| 6 | **16**·TFA | 20 | 40 | 91 | 96 |
| 7 | **16**·TFA | 10 | 20 | 99 | 97 |
| 8 | **16**·TFA | 5 | 10 | 99 | 98 |
| 9 | **16**·TFA | 2 | 4 | 66 | 98 |
| 10 | **16**·TFA | 1 | 2 | 30 | 98 |

[a] Reaction conditions: aldehyde **1a** (0.068 mmol), *trans*-β-nitrostyrene (**2a**; 0.102 mmol), and catalyst were dissolved in DCM (375 μL). Subsequently, pyridine was added, and stirred at rt for 24 h. In the next step, MeOH (0.5 mL) was added, and for reduction $NaBH_4$ (2 equiv) was used.
[b] Yield of isolated product, purified by preparative TLC.
[c] Determined by chiral HPLC.

### Conjugate Addition of Lawsone to β,γ-Unsaturated α-Keto Ester

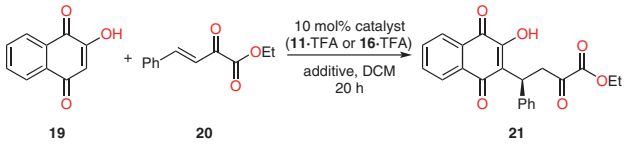
For further examination of the difference in catalytic activity, we investigated the conjugate addition of lawsone (**19**) to β,γ-unsaturated α-keto ester **20** in dichloromethane, which was one of the first asymmetric reactions of chiral thiosquaramides.[35,36] Without any additives only low conversion was achieved with both squaramide **11**·TFA and thiosquaramide **16**·TFA after 20 hours (Table 3, entries 1,2). Therefore, the conjugate addition was carried out in the presence of different additives: DMA and three common organic bases (pyridine, DIPEA, and TEA). The reactions were studied at 0 °C, 40 °C, and room temperature. Both catalysts **11**·TFA and **16**·TFA in the presence of DMA additive at 0 °C gave low yields and enantiomeric excess values (entries 3 and 6). In addition, only a slight increase was observed at room temperature (entries 4 and 7). At elevated temperature (40 °C) quantitative yields were achieved, however, the ee values were not improved (entries 5 and 8).

The use of pyridine or DIPEA as additive resulted in a modest increase in yields and ee values (Table 3, entries 9–14), while the addition of TEA led to higher yields at room temperature with no significant change in ee values (Table 3, entries 15–16). Moreover, we tested the reaction in six additional solvents, which may influence the stereoselectivity (Table 4). Unfortunately, in most solvents nearly racemic product **21** was obtained. However, thiosquaramide

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**Table 3** Effects of Various Additives in Conjugate Addition[a]

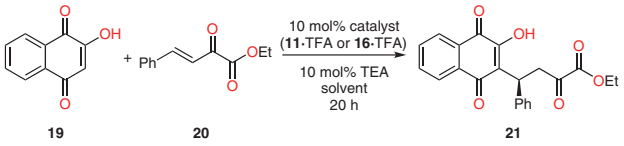



19 20 21

| Entry | Catalyst | Additive | Amount of additive | Temp (°C) | Yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|---|---|
| 1 | **11**·TFA | – | – | rt | trace | |
| 2 | **16**·TFA | – | – | rt | trace | |
| 3 | **11**·TFA | DMA | 2 equiv | 0 | 13 | 14 |
| 4 | **11**·TFA | DMA | 2 equiv | rt | 37 | 24 |
| 5 | **11**·TFA | DMA | 2 equiv | 40 | ~100 | 17 |
| 6 | **16**·TFA | DMA | 2 equiv | 0 | 20 | 32 |
| 7 | **16**·TFA | DMA | 2 equiv | rt | 60 | 37 |
| 8 | **16**·TFA | DMA | 2 equiv | 40 | ~100 | 29 |
| 9 | **11**·TFA | Py | 10 mol% | rt | 41 | 32 |
| 10 | **11**·TFA | Py | 10 mol% | 40 | 96 | 31 |
| 11 | **16**·TFA | Py | 10 mol% | rt | 67 | 32 |
| 12 | **16**·TFA | Py | 10 mol% | 40 | 76 | 31 |
| 13 | **11**·TFA | DIPEA | 10 mol% | rt | 69 | 28 |
| 14 | **16**·TFA | DIPEA | 10 mol% | rt | 96 | 35 |
| 15 | **11**·TFA | TEA | 10 mol% | rt | 82 | 30 |
| 16 | **16**·TFA | TEA | 10 mol% | rt | ~100 | 36 |

[a] Reaction conditions: β,γ-unsaturated α-keto ester **20** (0.055 mmol) was added to the solution of lawsone (**19**; 0.050 mmol), and catalyst (10 mol%) in DCM (0.25 mL). Subsequently, the additive was added and stirred at rt for 20 h.
[b] Yield of isolated product, purified by preparative TLC.
[c] Determined by chiral HPLC.

**Table 4** Effects of Solvents in the Conjugate Addition[a]




19 20 21

| Entry | Catalyst | Solvent | ee (%)[b] | Yield (%)[c] |
|---|---|---|---|---|
| 1 | **11**·TFA | THF | –6 | – |
| 2 | **11**·TFA | MTBE | 4 | – |
| 3 | **11**·TFA | toluene | –4 | – |
| 4 | **11**·TFA | EtOAc | 6 | – |
| 5 | **11**·TFA | 1,4-dioxane | –2 | |
| 6 | **16**·TFA | THF | 16 | – |
| 7 | **16**·TFA | MTBE | 16 | – |
| 8 | **16**·TFA | toluene | –14 | – |
| 9 | **16**·TFA | EtOAc | 22 | – |
| 10 | **16**·TFA | 1,4-dioxane | 4 | |
| 11 | **11**·TFA | MeCN | 32 | 77 |
| 12 | **16**·TFA | MeCN | 51 | 83 |
| 13[d] | **11**·TFA | MeCN | 34 | 100 |
| 14[d] | **16**·TFA | MeCN | 53 | 97 |

[a] Reaction conditions: β,γ-unsaturated α-keto ester **20** (0.055 mmol) was added to a solution of lawsone (**19**; 0.050 mmol) and catalyst (10 mol%) in the corresponding solvent (0.25 mL). Subsequently, 10 mol% TEA was added, and stirred at rt for 20 h.
[b] Determined by chiral HPLC.
[c] Yield of isolated product, purified by preparative TLC. In cases of entries 1–10, yields were not determined.
[d] Catalyst used: 20 mol%.

**16**·TFA provided a higher, but only moderate enantiomer excess (51%) in a good yield (83%) in acetonitrile compared to squaramide **11**·TFA (Table 4, entry 11 vs entry 12). To further improve the selectivity, higher catalyst loading (20 mol%) was applied but only the improvement of yields was achieved (Table 4, entries 13, 14).

To conclude, the conjugate addition product can be prepared in quantitative yields using benzyl pyrrolidine-squaramide **11**·TFA or -thiosquaramide **16**·TFA, respectively, however, only moderate stereoselectivity can be reached. Considering that we have previously presented this conjugate addition with higher enantioselectivities (up to 92% ee) within less than one hour using binaphthyl-cinchona-thiosquaramides,[36] no further attempts for the improvement of selectivity has been done.

In conclusion, we have described the synthesis of two new pyrrolidine-(thio)squaramide organocatalysts and their intermediates starting from commercially available materials. We have tested the performance of squaramide and its thio analogue in asymmetric Diels–Alder reaction of (anthracen-9-yl)acetaldehyde and *trans*-β-nitrostyrene with extensive parameter investigation. This synthesis afforded the adduct in excellent yields (up to 99%), and enantiomeric excess values (96–98% ee). To the best of our knowledge, this is the first application of thiosquaramide derivatives in asymmetric Diels–Alder reaction when aminocatalysis takes place. Furthermore, the obtained aldehyde intermediate can be converted to novel, chiral maprotiline analogues with potential bioactivity by Mannich reaction. Moreover, the new pyrrolidine-(thio)squaramide organocatalysts were applied in asymmetric conjugate addition of 2-hydroxy-1,4-naphthoquinone and ethyl (*E*)-2-oxo-4-phenylbut-3-enoate. These reactions gave the desired product in quantitative yield, but with only low enantiomeric excess values (up to 53% ee). Since the α-oxo ester moiety of the product is a strong electron-withdrawing group, the product can be easily converted into a range of different functionalities, resulting in other useful structures.

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Starting materials and reagents were purchased from commercially available sources (Sigma-Aldrich, Merck, TCI Europe, and Alfa Aesar). IR spectra were recorded on a Bruker Alpha-T FT-IR spectrophotometer. Optical rotations were measured on a PerkinElmer 241 polarimeter calibrated by measuring the optical rotations of both enantiomers of menthol. Silica gel 60 $F_{254}$ (Merck) plates were used for TLC. Reactions were monitored by TLC and HPLC-MS. $Al_2O_3$ (neutral, activated, Brockman I) and silica gel 60 (70–230 mesh, Merck) were used for column chromatography. Ratios of solvents for the eluents are given in volumes (v/v). Melting points were taken on a Boetius micro-melting point apparatus (VEB Dresden Analytik, Dresden, Germany), and they were uncorrected. NMR spectra were recorded at the Department of Inorganic & Analytical Chemistry, Budapest University of Technology and Economics, on a Bruker DRX-500 Avance spectrometer (at 500 MHz for $^1$H and 125 MHz for $^{13}$C spectra) or on a Bruker 300 Avance spectrometer (at 300 MHz for $^1$H and 75 MHz for $^{13}$C spectra) at the given temperatures. The exact mass measurements were performed using Q-TOF Premier mass spectrometer (Waters Corporation, 34 Maple St, Milford, MA, USA) in positive electrospray ionization mode. HPLC-MS was performed on an HPLC system using Agilent Technologies 1200 Series - Agilent Technologies 6130 Quadrupole; column: Phenomenex Kinetex C18 2.6 µm 100A 50 × 3.00 mm; A eluent: $H_2O$ (1% $HCO_2NH_4$); B eluent: MeCN (8% $H_2O$, 1% $HCO_2NH_4$); gradient: 20–100%, or using a Shimadzu LCMS-2020 (Shimadzu Corp., Kyoto, Japan) device, equipped with a Reprospher (Altmann Analytik Corp., München, Germany) 100 C18 (5 µm; 100 × 3 mm) column and a positive/negative double ion source (DUIS ±) with a quadrupole MS analyzer in a range of 50–1000 *m*/*z*. The samples were eluted with gradient elution, using eluent A (0.1% formic acid in $H_2O$) and eluent B (0.1% formic acid in MeCN). The flow rate was set to 1.5 mL/min. The initial condition was 5% eluent B, followed by a linear gradient to 100% eluent B by 1.5 min; from 1.5 to 4.0 min, 100% eluent B was retained; and from 4 to 4.5 min, it went back by a linear gradient to 5% eluent B, which was retained from 4.5 to 5 min. The column temperature was kept at rt, and the injection volumes were 1–10 µL. The enantiomeric excess (ee) values were determined by chiral HPLC with a PerkinElmer Series 200 instrument. The applied column, eluent, flow rate, column temperature, and detector wavelength are indicated at the corresponding procedure.

**(Anthracen-9-yl)acetaldehyde (1a)**

(Anthracen-9-yl)ethan-1-ol (**17**; 727 mg, 3.27 mmol) was dissolved in EtOAc (30 mL) and 39 wt% 2-iodoxybenzoic acid (3.52 g, 4.91 mmol, stabilized with benzoic acid and isophthalic acid) was added, and the resulting mixture was refluxed for 4 h. After the reaction mixture was cooled to rt, the products formed from IBX were filtered, washed with a small amount of EtOAc, and then the solvent was removed under reduced pressure. Next, the crude product was dissolved in DCM (10 mL), and extracted with sat. aq $NaHCO_3$ (4 × 30 mL) to remove IBX stabilizers. The organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by column chromatography ($SiO_2$, hexane/DCM 3:1 → hexane/DCM 1:1); yield: 565 mg (78%); bright yellow crystals; mp 133–135 °C (Lit.[31] mp 142.4–142.8 °C); $R_f$ = 0.75 (silica gel TLC, hexane/EtOAc 2:1).

Spectroscopic data are fully consistent with those reported in the literature.[31]

HRMS-ESI+: *m*/*z* [M + Na$^+$] calcd for $C_{16}H_{20}ONa$: 243.0780; found: 243.0781.

***tert*-Butyl (*S*)-(–)-2-({[2-(Benzylamino)-3,4-dioxocyclobut-1-en-1-yl]amino}methyl)pyrrolidine-1-carboxylate (10)**

A solution of *tert*-butyl (*S*)-2-(aminomethyl)pyrrolidine-1-carboxylate (**7**; 369 mg, 364 µL, 1.84 mmol) in MeOH (2 mL) was added to a solution of benzyl half-squaramide **9**[38] (400 mg, 1.84 mmol) in MeOH (18 mL). This mixture was stirred overnight at rt. Initially, the mixture became clear, but after 10 min, a white precipitate was formed. After the reaction was complete, the precipitate was filtered, washed with a small amount of ice-cold MeOH and dried. Further purification was not necessary; yield: 644 mg (91%); white crystals; mp 234–237 °C (dec.); $R_f$ = 0.84 (silica gel TLC, DCM/MeOH 10:1); $[\alpha]_D^{25}$ –45.4 (*c* 0.6, DMSO).

IR (KBr): 3162, 3064, 3028, 2972, 2933, 2885, 1800, 1698, 1685, 1645, 1584, 1552, 1476, 1457, 1437, 1395, 1366, 1346, 1330, 1287, 1252, 1170, 1100, 758, 698 cm$^{-1}$.

$^1$H NMR (500 MHz, DMSO-$d_6$): δ = 7.73 (br s, 1 H), 7.37–7.24 (m, overlapping, 6 H), 4.69 (s, 2 H), 3.82 (m, 1 H), 3.70–3.42 (m, overlapping, 2 H), 3.28–3.14 (m, overlapping, 2 H), 1.92–1.56 (m, overlapping, 4 H), 1.34 (s, 9 H).

$^{13}$C NMR (126 MHz, DMSO-$d_6$): δ = 183.1, 182.9, 168.7, 167.9, 154.1, 139.4, 129.1, 128.1, 127.9, 79.1, 57.7, 47.3, 46.9, 46.6, 46.4, 28.5, 27.8, 22.8.

HRMS-ESI+: *m*/*z* [M + Na$^+$] calcd for $C_{21}H_{27}N_3O_4Na$: 408.1894; found: 408.1893.

**(*S*)-3-(Benzylamino)-4-[(pyrrolidin-2-ylmethyl)amino]cyclobut-3-ene-1,2-dione Trifluoroacetate (11·TFA)**

To a suspension of squaramide **10** (500 mg, 1.30 mmol) in anhyd DCM (5 mL) was added TFA (1.6 mL, 2.4 g, 20.7 mmol) dropwise at 0 °C, and the resulting mixture was stirred for 30 min at 0 °C. The mixture was stirred further at rt until the reaction was complete based on TLC ($SiO_2$, DCM/MeOH 10:1) analysis. The solvent was removed under reduced pressure. The crude oily product was crystallized from a mixture of DCM and MeOH. The white crystals were filtered, washed with hexane, and dried. Further purification was not necessary; yield: 501 mg (97%); white crystals; mp 198–202 °C (dec.); $R_f$ = 0.19 (silica gel TLC, DCM/MeOH/$NH_4OH$ 5:1:0.01); $[\alpha]_D^{25}$ +12.1 (*c* 0.6, DMSO).

IR (ATR): 3159, 2944, 2525, 1801, 1644, 1570, 1492, 1453, 1430, 1347, 1302, 1277, 1262, 1202, 1173, 1127, 1030, 833, 798, 751, 722, 697, 617, 582, 497, 408 cm$^{-1}$.

$^1$H NMR (500 MHz, DMSO-$d_6$): δ = 9.20 (br s, 1 H), 8.63 (br s, 1 H), 8.23 (br s, 1 H), 7.87 (br s, 1 H), 7.38–7.24 (m, overlapping, 5 H), 4.70 (s, 2 H), 3.81–3.61 (m, overlapping, 3 H), 3.24–3.10 (m, 2 H), 2.07–1.97 (m, 1 H), 1.96–1.79 (m, 2 H), 1.67–1.56 (dt, *J* = 8.2, 20.7 Hz, 1 H).

$^{13}$C NMR (126 MHz, DMSO-$d_6$): δ = 182.9, 182.6, 167.9, 167.7, 158.6 (q, *J* = 32 Hz), 138.9, 128.6, 127.5, 127.4, 116.9 (q, *J* = 298 Hz), 59.7, 46.8, 44.9, 43.8, 27.0, 22.7.

$^{19}$F NMR (282 MHz, DMSO-$d_6$): δ = –73.7 (s).

HRMS-ESI+: *m*/*z* [M + H$^+$] calcd for $C_{16}H_{20}N_3O_2$: 286.1556; found: 286.1554.

***tert*-Butyl (*S*)-2-({[2-(Benzylamino)-3,4-dithiocyclobut-1-en-1-yl]amino}methyl}pyrrolidine-1-carboxylate (15)**

To a suspension of squaramide **10** (500 mg, 1.30 mmol) in anhyd MeCN (25 mL) were added pyridine (1.46 mL, 18.2 mmol) and pyridine complex of $P_2S_5$ (987 mg, 2.60 mmol). The reaction mixture was stirred at 60 °C until the reaction was complete based on HPLC-MS analysis (4 h). Then, the mixture was poured into cold $H_2O$ (20 mL) and extracted with DCM (3 × 15 mL). The combined organic phases

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were dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography ($Al_2O_3$, DCM → DCM/MeOH 150:1). Then, a DCM (1 mL) solution of the crude product was added to hexane (20 mL) dropwise. The precipitated yellow crystals were filtered, washed with hexane, and dried under reduced pressure; yield: 360 mg (66%); mp 82–90 °C (dec.); $R_f$ = 0.68 (silica gel TLC, DCM/MeOH 20:1); $[\alpha]_D^{25}$ +39.2 (*c* 1.0, $CHCl_3$)

IR (KBr): 3233, 3180, 2971, 2930, 2877, 1707, 1659, 1573, 1511, 1497, 1477, 1454, 1415, 1392, 1366, 1334, 1281, 1253, 1230, 1166, 1143, 1109, 1080, 698 $cm^{-1}$.

$^1H$ NMR (500 MHz, DMSO-$d_6$): δ = 8.88 (br s, 1 H), 8.51 (br s, 1 H), 7.49–7.27 (m, overlapping, 5 H), 5.56–5.19 (m, 2 H), 4.41–4.14 (m, 1 H), 4.12–3.49 (m, 2 H), 3.31–3.09 (m, overlapping, 2 H), 1.99–1.63 (m, 4 H), 1.34 (s, 9 H).

$^{13}C$ NMR (126 MHz, DMSO-$d_6$): δ = 204.2, 203.9, 170.9, 170.1, 154.2, 153.7, 137.5, 137.4, 128.8, 128.5, 128.1, 128.1, 127.8, 127.5, 78.8, 78.6, 56.9, 56.7, 46.5, 46.2, 45.9, 45.6, 45.3, 31.0, 28.0, 27.4, 23.2, 22.7, 22.5, 22.1 (signal duplication caused by rotamers).

HRMS-ESI+: *m*/*z* [M + $H^+$] calcd for $C_{21}H_{28}N_3O_2S_2$: 418.1617; found: 418.1613.

HRMS-ESI+: *m*/*z* [M + $Na^+$] calcd for $C_{21}H_{27}N_3O_2S_2Na$: 440.1437; found: 440.1411.

### (*S*)-3-(Benzylamino)-4-[(pyrrolidin-2-ylmethyl)amino]cyclobut-3-ene-1,2-dithione Trifluoroacetate (16·TFA)

A solution of TFA (514 µL, 766 mg, 6.72 mmol) in anhyd DCM (0.5 mL) was added to a solution of thiosquaramide **15** (175 mg, 0.42 mmol) in anhyd DCM (1.5 mL) at 0 °C under argon atmosphere. The reaction mixture was stirred for 1 h at 0 °C and 30 min at rt. After the reaction was complete based on TLC analysis, the volatile components were evaporated under reduced pressure. The crude product was dissolved in a solution of DCM/toluene (3:1, 0.5 mL), and added to hexane (20 mL) dropwise. The precipitated reddish-brown crystals were filtered, washed with hexane, and dried under reduced pressure. Further purification was not necessary; yield: 108 mg (60%); mp 66–70 °C (dec.); $R_f$ = 0.66 (silica gel TLC, DCM/MeOH/$NH_4OH$ 10:1:0.01); $[\alpha]_D^{25}$ +349 (*c* 1.0, $CHCl_3$).

IR (ATR): 3188, 2953, 1708, 1666, 1571, 1497, 1478, 1453, 1431, 1360, 1275, 1256, 1238, 1193, 1179, 1128, 1058, 1028, 929, 835, 796, 751, 720, 695, 598, 533, 515, 487, 437, 409 $cm^{-1}$.

$^1H$ NMR (500 MHz, $CDCl_3$): δ = 9.57 (br s, 1 H), 9.41 (br s, 1 H), 9.06–8.86 (m, 2 H), 7.45–7.27 (m, 5 H), 5.40–5.24 (dd, *J* = 5.7, 14.5 Hz, 1 H), 5.16–4.97 (dd, *J* = 5.7, 14.5 Hz, 1 H), 4.48–4.28 (m, 2 H), 4.21–4.04 (m, 1 H), 3.70–3.45 (m, overlapping, 2 H), 2.37–2.09 (m, overlapping, 3 H), 1.83–1.74 (m, overlapping, 1 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 204.5, 202.2, 171.0, 170.2, 161.8 (q, *J* = 38 Hz), 136.0, 129.0, 128.2, 127.9, 115.7 (q, *J* = 289 Hz), 61.8, 47.7, 46.0, 44.3, 27.8, 23.9.

$^{19}F$ NMR (282 MHz, $CDCl_3$): δ = –75.7 (s).

HRMS-ESI+: *m*/*z* [M + $H^+$] calcd for $C_{16}H_{20}N_3S_2$: 318.1099; found: 318.1103.

### One-Pot Diels–Alder Reaction; General Procedure

In a small vial, the catalyst **11**·TFA or **16**·TFA, (anthracen-9-yl)acetaldehyde (**1a**; 15 mg, 0.068 mmol), and *trans*-β-nitrostyrene **2a** or **2b** or **2c** (0.102 mmol, 1.5 equiv) were dissolved in anhyd DCM (375 µL). Subsequently, the additive *N*,*N*-dimethylacetamide or pyridine was added, and the reaction mixture was stirred at rt for 24 or 40 h. Next, the solution was diluted with MeOH (500 µL), cooled to 0 °C in an ice bath, and $NaBH_4$ (5.2 mg, 0.136 mmol) was added. After 15 min of stirring, the mixture was quenched with sat. aq $NH_4Cl$ (2 mL) at 0 °C and extracted with EtOAc (3 × 2 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by preparative TLC ($SiO_2$, hexane/1,4-dioxane 1:1) to afford product **3a** or **3b** or **3c** as a white foamy solid.

#### 3a

Yields are shown in Table 1 and Table 2. Mp 74–76 °C (Lit.[31] mp 78.2–80.2 °C); $R_f$ = 0.40 (silica gel TLC, hexane/EtOAc 2:1).

HPLC: Phenomonex Lux® Cellulose-2 column (5 µm, 250 × 4.6 mm); eluent: hexane/EtOH (85:15); isocratic mode at 20 °C; 0.8 mL·$min^{-1}$, UV detector 254 nm; $t_R$ = 12.4 min (minor), $t_R$ = 14.0 min (major).

Spectroscopic data are fully consistent with those reported in the literature.[31]

#### 3b

Yields are shown in Table 1. Mp 78–80 °C; $R_f$ = 0.39 (silica gel TLC, hexane/EtOAc 2:1).

HPLC: Phenomonex Lux® Cellulose-4 column (3 µm, 250 × 4.6 mm); eluent: hexane/EtOH (85:15); isocratic mode at 20 °C; 0.8 mL·$min^{-1}$, UV detector 254 nm; $t_R$: 11.9 min (major), $t_R$: 14.3 min (minor).

Spectroscopic data are fully consistent with those reported in the literature.[31]

#### 3c

Yields are shown in Table 1. Mp 69–71 °C; $R_f$ = 0.30 (silica gel TLC, hexane/EtOAc 2:1).

HPLC: Phenomonex Lux® Cellulose-4 column (3 µm, 250 × 4.6 mm); eluent: hexane/EtOH (85:15); isocratic mode at 20 °C; 0.8 mL·$min^{-1}$, UV detector 254 nm; $t_R$: 17.1 min (major), $t_R$: 18.4 min (minor).

Spectroscopic data are fully consistent with those reported in the literature.[31]

### Asymmetric Conjugate Addition; General Procedure

In a small vial, the catalyst **11**·TFA or **16**·TFA and lawsone (**19**; 8.7 mg, 0.050 mmol) were dissolved in the corresponding solvent (250 µL). Then β,γ-unsaturated α-keto ester **20** (11.3 mg, 0.055 mmol) was added to this solution. Subsequently, the additive *N*,*N*-dimethylacetamide or pyridine or DIPEA or TEA was added, and the resulting reaction mixture was stirred for 20 h at rt. Next, the volatile components were removed under reduced pressure, and the crude product was purified by preparative TLC ($SiO_2$, hexane/EtOAc 3:2); see Tables 3 and 4 for yield; yellow crystals; mp 119–121 °C; $R_f$ = 0.30 (silica gel TLC, hexane/EtOAc 2:1).

HPLC: Phenomonex Lux® Cellulose-1 column (3 µm, 250 × 4.6 mm); eluent MeCN/$H_2O$ (40:60) (0.1% AcOH), isocratic mode; 0.8 mL·$min^{-1}$; UV detector 222 nm; 5 mL or 10 mL injection, 25 °C; $t_R$: 9.1 min (*R*), and $t_R$: 10.9 min (*S*).

Spectroscopic data are fully consistent with those reported in the literature.[41]

## Conflict of Interest

The authors declare no conflict of interest.

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## Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1719886.

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