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Application of novel sulfonamides in enantioselective organocatalyzed cyclopropanation

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Abstract—Three novel aryl sulfonamides derived from (2*S*)-indoline-2-carboxylic acid have been obtained and used as organocatalysts. The catalysts incorporate diverse functionality on the phenyl ring, enabling steric, and electronic fine tuning of the catalysts. The catalysts facilitate the reaction between a range of α,β-unsaturated aldehydes and sulfur ylides, thus providing cyclopropane products in enantiomeric excesses of up to 99%.

1. Introduction

The cyclopropane unit is a common structural constituent in many naturally occurring compounds. Currently over 4000 natural isolates are known and more than a hundred are known to be therapeutically active.[1] Development in the synthetic methodology that allows the construction of these structures in a stereo-controllable manner has attracted the attention of many research groups over the last twenty years.[2] Early synthetic methodology development focused on the stereoselective formation of functionalized cyclopropane adducts; however, the most recent synthetic development has focused on enantioselective construction of diversely substituted cyclopropane adducts.[3]

Early development in stereoselective cyclopropanation reactions utilized Simmons–Smith type of reagents.[4] An increasingly important reaction type features a nucleophile containing an internal leaving group moiety. Here, the nucleophile undergoes an intermolecular Michael addition to a α,β-unsaturated carbonyl compound, and thus forms an enolate; this step is followed by an intramolecular ring closure with loss of a leaving group, present either on the Michael acceptor or on the initial nucleophile, thus furnishing a cyclopropanated product.[5] The most commonly employed nucleophiles in this kind of reaction are α-halocarbanions,[6] sulfur ylides,[7] phosphorous ylides,[8] arsenium ylides,[9] and telleronium ylides.[10] This methodology allows for a wide range of structurally divergent substrates to be reacted and may thus be used to create a plethora of cyclopropane architectures.

Herein we wish to report our results concerning the enantioselective organocatalyzed cyclopropanation reaction. The reaction was initially disclosed by Ley et al., utilizing modified cinchona alkaloids,[11] while MacMillan et al. made use of a dihydroindol carboxylic acid as a catalyst.[12]

We reasoned that substitution of the carboxylic acid of (*S*)-(−)-indoline-2-carboxylic acid to the corresponding (*S*)-(−)-indoline-2-aryl sulfonamide should allow fine tuning of the catalyst structure by varying the substitution on the phenyl ring of the aryl sulfonamide.

2. Results and discussion

To investigate the potential of aryl sulfonamides in enantioselective cyclopropanation we synthesized three different catalysts, that is, **1**–**3**, containing differently substituted phenyl rings.

Catalyst **1** was synthesized by converting (*S*)-(−)-indoline-2-carboxylic acid **4** to the Boc protected derivative **5**, followed by direct coupling with *p*-nitrophenyl sulfonamide to give **6**, which was further Boc deprotected to give catalyst **1** (Scheme 1). Direct coupling was necessary due to the poor nucleophilicity of *p*-nitrophenyl sulfonamide.

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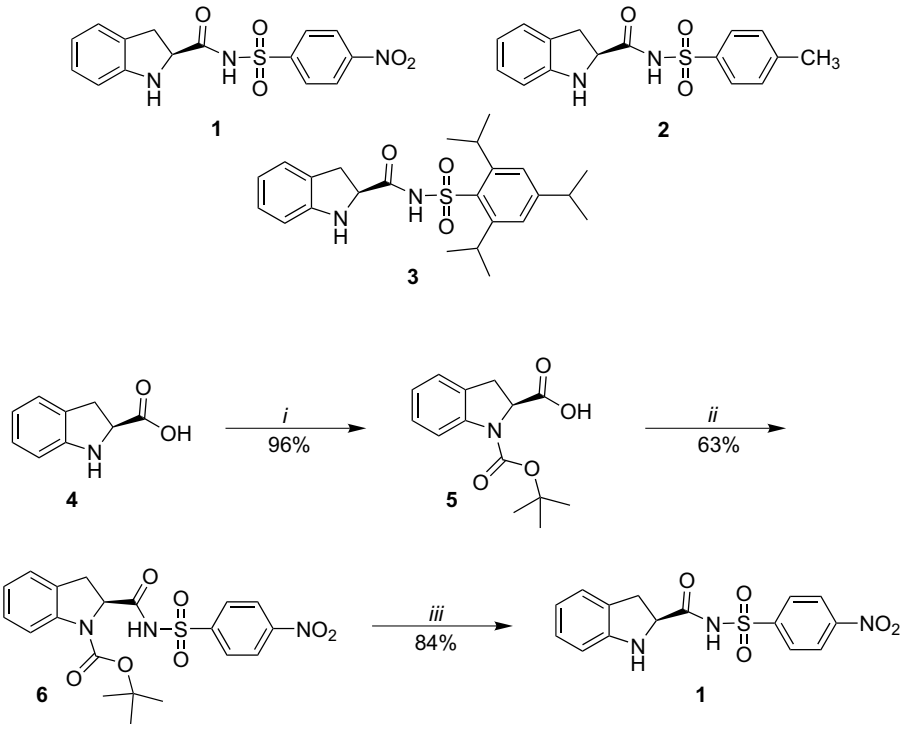


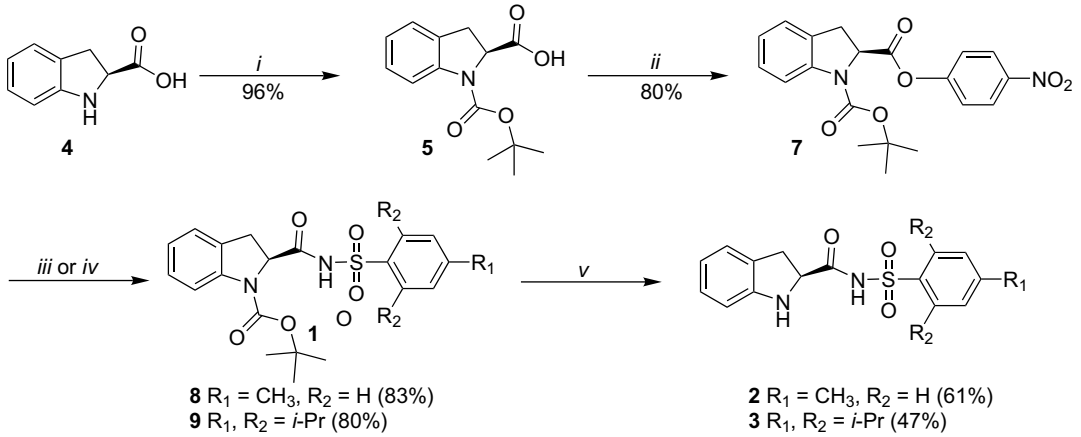
Scheme 1. Reagents and conditions: (i) Boc_2O, Na_2CO_3, H_2O, *t*-BuOH, rt, 12 h; (ii) DMAP, EDCI, 4-nitrophenyl sulfonamide, *t*-BuOH–1,2-dichloroethane (1:1), rt, 12 h; (iii) 50% TFA in DCM, rt, 1 h.

Catalysts **2** and **3** could, however, be synthesized by reacting **5** with *p*-nitrophenol yielding the active ester **7** in high yield. Catalysts **2** and **3** were then prepared by reacting the active ester with suitable sulfonamides, which after Boc-deprotection furnished the final catalysts products **2** and **3** (Scheme 2).

Catalysts **1**–**3** were assessed in the enantioselective organocatalytic cyclopropanation reaction between 2-(dimethyl-λ^4-sulfanylidene)-1-phenyl-ethanone and crotonaldehyde.[2]

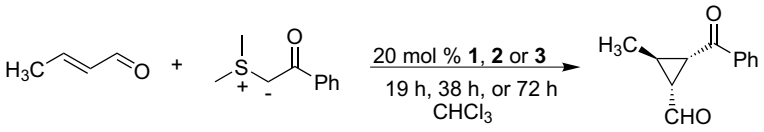
The results, as presented in Table 1, show that while catalysts **1** and **2** provide products with high enantiomeric excess catalyst **3** gave less good results. This result clearly demonstrates that the nature of the aryl group affects the reaction outcome, and that the large 2,4,6-tri-isopropylbenzene moiety in **3** is too bulky to provide good stereoselectivity in the current reaction. The fact that identical stereoselectivities were obtained independent of the reaction time concludes that no epimerization occurred during the course of the reaction.

After this initial catalyst and time screening, the optimal reaction conditions were employed in an expanded substrate study where both the enal and sulfur ylide structure were varied. The results of this investigation are shown in Table 2. It can be seen that catalyst **2** gives products in slightly higher enantiomeric excess than catalyst **1**,



Scheme 2. Reagents and conditions: (i) Boc_2O, Na_2CO_3, H_2O, *t*-BuOH, rt, 12 h; (ii) *p*-nitrophenol, DIPCDI, Pyridine; (iii) *p*-toluene sulfonamide, DMF, NaH, rt, 12 h; (iv) 2,4,6-tris(isopropylbenzene) sulfonamide, DMF, NaH, rt, 12 h; (v) 50% TFA in DCM, rt, 1 h.

Table 1. Catalyst assessment using catalysts **1**–**3** in the representative reaction between 2-(dimethyl-λ-sulfanylidene)-1-phenyl-ethanone and crotonaldehyde



Entry[a]	Time (h)	Catalyst	Yield[b] (%)	ee[c] (%)
1	19	**1**	36	88
2	19	**2**	53	88
3	19	**3**	18	80
4	38	**1**	45	88
5	38	**2**	55	88
6	38	**3**	30	80
7	72	**1**	57	88
8	72	**2**	61	88

[a] Reaction was conducted at 4 °C.
[b] Isolated yield.
[c] Enantiomeric excess was determined by correlation through GC–MS analysis of a reference sample.[12]

although the difference is small as might be expected from the similar steric nature of the substituents. Somewhat more surprising is that the electronic properties of the two different catalysts, that is, the electron withdrawing properties of the *p*-nitro substituent in catalyst **1**, do not affect the reaction outcome in a more positive way. One might expect that the reaction rate, and possibly also the stereoselectivity, should benefit from a postulated tighter binding of the transition state comprising catalyst **1**, which is expected to have a more acidic sulfonamide proton than catalyst **2** in $CHCl_3$. Such effects were seen with sulfonamide substituted proline derivatives in other organocatalyzed reactions.[13] The lack of such correlations in the present reaction remains unclear, but it should be noted that the observed differences are small, and relates to isolated yields.

Still, as seen in Table 2 both aliphatic and aromatic aldehydes were transformed into the corresponding cyclopropanated products in fair yields and high enantiomeric excesses. The results show that the allylether substituted α,β-unsaturated aldehydes react slower, only giving 25% and 21% isolated yield after 38 h with catalyst **2** (Table 2, entries 9–12), whereas straight carbon chain α,β-unsaturated aldehydes constitute more reactive substrate giving products in 52–58% isolated yield (Table 2, entries 1–6 and 13–16). Also the investigated aromatic *trans*-cinnamaldehyde gave the product in quite low yield (Table 2, entries 7 and 8), but very high enantioselectivities. The results collected suggest that catalyst **2** is the most suitable of these two catalysts to be employed in the enantioselective organocatalytic cyclopropanation reaction, as it generally provides the products in some 10% higher yield and enantioselectivity.

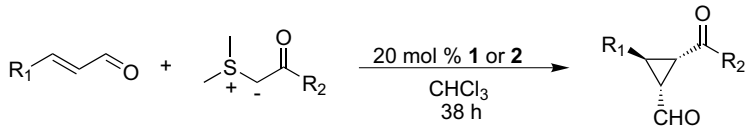
3. Conclusion

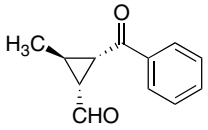
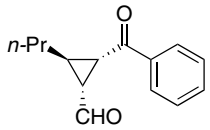
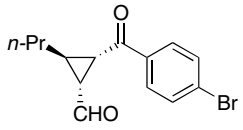
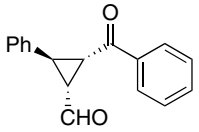
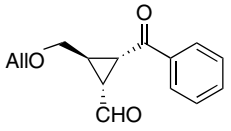
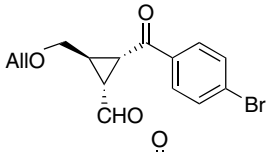
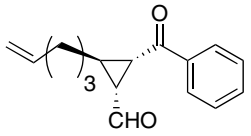
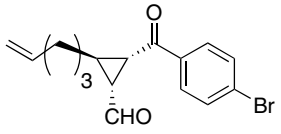
Structurally diverse aryl sulfonamide containing catalysts were synthesized in order to investigate the utility of these catalysts in the enantioselective organocatalytic cyclopropanation reaction. The mechanistic postulate of this reaction highlights the role of directed electrostatic activation between the negatively charged catalyst carboxylate and the thionium part of the sulfur ylide. We have shown that substitution of the carboxylic acid to the corresponding aryl sulfonamide retains the structural requirements in respect to the directed electrostatic activation model, thus enabling highly stereoselective reactions. Although none of these catalysts perform as well as the indolin-2-carboxylic acid used in MacMillan's first disclosure on this reaction sequence,[12] this study has still demonstrated the potential of sulfonamide modified indole derivatives as novel kinds of modular catalyst structures, most likely of use in a variety of organocatalytic processes.

4. Experimental

Chemicals and solvents were either purchased puriss p.A from commercial suppliers or purified by standard techniques. For thin layer chromatography (TLC), precoated 0.25 mm silica plates (Macherey–Nagel 60 Alugram® Sil G/UV254) were used and spots were visualized either by UV light or by a solution composed of *p*-anisaldehyde (2.3 ml), concentrated H_2SO_4 (3.5 ml), acetic acid (1 ml), and 100 ml ethanol followed by heating. ^1H NMR 500 MHz spectra were recorded on a Varian Unity 500 MHz and ^{13}C NMR 75 MHz spectra were recorded with a Varian Unity 300 MHz spectrometer at ambient temperature using deuterated chloroform, methanol, or dimethylsulfoxide as solvents. Chemical shifts (δ) are reported in parts per million using residual chloroform, methanol or dimethylsulfoxide as internal reference (^1H δ 7.26, 3.34, and 2.49, respectively) or (^{13}C δ 77, 49.9, and 39.5, respectively) and coupling constants (J) are given in Hertz. Infrared spectra was recorded on a Perkin–Elmer Spectrum 100 FT/IR spectrometer. Enantiomeric excesses were determined using a high pressure liquid chromatography (HPLC) system equipped with a column consisting of a chiral stationary phase. The HPLC system consisted of a Gilson 322 pump, Gilson 233 XL autosampler, and an

Table 2. Scope of the enantioselective organocatalytic cyclopropanation using sulfonamide based catalysts **1** and **2**



Entry[a]	R_1	R_2	Catalyst	Product	Yield[c] (%)	de[d] (%)	ee[e] (%)
1[b]	CH_3	Ph	**1**		45	95	88
2[b]	CH_3	Ph	**2**		55	95	88
3	C_3H_7	Ph	**1**		25	96	94
4	C_3H_7	Ph	**2**		52	97	98
5	C_3H_7	PhBr	**1**		50	96	95
6	C_3H_7	PhBr	**2**		58	96	99
7	Ph	Ph	**1**		20	95	92
8	Ph	Ph	**2**		28	94	97
9	$C_3H_5OCH_2$	Ph	**1**		16	97	93
10	$C_3H_5OCH_2$	Ph	**2**		25	96	99
11	$C_3H_5OCH_2$	PhBr	**1**		20	95	91
12	$C_3H_5OCH_2$	PhBr	**2**		21	94	99
13	C_5H_9	Ph	**1**		43	96	90
14	C_5H_9	Ph	**2**		52	95	99
15	C_5H_9	PhBr	**1**		48	97	92
16	C_5H_9	PhBr	**2**		57	98	94

[a] Reaction performed at −10 °C for 38 h.
[b] Reaction performed at 4 °C for 38 h.
[c] Isolated yield after column chromatography.
[d] Diastereomeric excess was determined by ^{1}H NMR or GLC analysis.
[e] Enantiomeric excess was determined by GLC or HPLC analysis and correlated to a reference sample generated with (*S*)-(−)-indoline-2-carboxylic acid **4**.

Agilent 1100 diodo-array detector. Details concerning mobile phase compositions and column types are presented below individually for each compound. GC–MS determination of enantiomeric excesses was done using a Varian CP-8410 auto injector and a Varian Satum 2100T GC–MS system equipped with a chiral stationary phase column, using helium at 10 psi as carrier gas. Details concerning the columns and temperature programs used are given specifically for each compound below. Purity confirmations of the prepared catalysts were assessed using a HPLC system coupled to an MS detector and an evaporative light-scattering detector (ELSD); the system consisted of a Gilson 322 pump, Gilson 233 XL autosampler and a Gilson UV/VIS 152 detector, coupled in series with a Finnigan AQA mass spectrometer and an ELSD (Sedex 85 CC) from Sedere. The reverse phase HPLC analysis was done using a Phenomenex Gemini C18 (3 m, 3.0U150 mm) column employing acetonitrile–water (both containing 0.1% formic

acid) as mobile phase (gradient: 5–95% acetonitrile in 6 min+6 min at 95%, flow 1.0 mL/min). High-resolution ESI mass spectra were recorded on a Bruker micrOTOFQ. These data were collected in positive ion mode. The spectrometer was calibrated with the standard tune mix. The sample was dissolved in the mixture acetonitrile–water 1:1 containing 0.1% of formic acid and infused at a flow rate of 3 μl/min, the endplate voltage was set to −500 V and the capillary to +4500 V.

4.1. (*S*)-Boc-indoline-2-carboxylic acid[14] 5

(*S*)-(−)-Indolin-2-carboxylic acid (1 g, 6.13 mmol) was added to a solution of 0.5 g of sodium carbonate in 100 ml water. To the mixture was added di-*tert*-butyl dicarbonate (1.65 g, 7.32 mmol) solubilized in 20 ml of *t*-butyl alcohol after which the mixture was stirred overnight at ambient temperature. The solution was then washed with *n*-pentane followed by cooling of the aqueous phase to 0 °C and a 40% aqueous solution of $KHSO_4$ was added until pH 3 was reached. The cloudy mixture was extracted with ethyl acetate followed by washing of the organic phase with water. The organic phase was dried with magnesium sulfate followed by filtration and concentration under reduced pressure to give a colorless solid (1.55 g; 96%). The product was considered sufficiently pure and used directly in next steps. ^{1}H NMR (CD_3OD, 500 MHz): δ 1.53 (s, 9H), 3.85 (dd, $J = 16.6$, 3.9 Hz, 1H), 3.55 (dd, $J = 11.7$, 4.9 Hz, 1H), 4.81 (d, $J = 10.5$ Hz, 1H), 6.94 (td, $J = 7.6$, 1.0 Hz, 1H), 7.12 (d, $J = 7.3$ Hz, 1H), 7.17 (t, $J = 7.8$ Hz, 1H), 7.82 (d, $J = 6.8$ Hz, 1H).

4.2. (*S*)-*N*-[(4-Nitrophenyl)sulfonyl]indoline-2-carboxamide 1

Boc-(*S*)-(−)-indolin-2-carboxylic acid (300 mg, 1.83 mmol), DMAP (673 mg, 5.49 mmol), EDCI (707 mg, 3.66 mmol), and 4-nitrobenzenesulfonamide (557 mg, 2.75 mmol) were dissolved in 15 ml of a 1:1 mixture of *tert*-butyl alcohol and 1,2 dichloroethane. The solution was stirred 12 h at ambient temperature. Ethyl acetate (10 ml) and Amberlyst-15 (protonated form, 3.0 g) were added, and stirring was continued for 2 h. The mixture was passed through a plug of silica gel (1 cm) and washed with ethyl acetate. The filtrate was concentrated under reduced pressure followed by purification of the residue by means of column chromatography (silica gel, 100% ethyl acetate) to give pure Boc protected *N*-sulfonylcarboxamide (0.52 g; 63%). Deprotection of the Boc group was done using 50% TFA in DCM, which after concentration under reduced pressure gave a brown oil that was further purified by a catch and release procedure utilizing solid-state bound MP-TsOH. A mixture of the product and MP-TsOH (0.5 g) was stirred overnight followed by filtration of the resin. The resin was washed with methanol and subsequently the product was released from the resin by addition of a saturated ammonia solution of methanol. This provided the product as a light brown oil after concentration (0.3 g; 47% overall yield). ^{1}H NMR (CD_3OD, 500 MHz) δ 3.15 (dd, $J = 16.1$, 5.8 Hz, 1H), 2.26 (dd, $J = 16.1$, 10.0 Hz, 1H), 4.11 (m, 1H), 6.64 (m, 2H), 6.93 (t, $J = 7.6$ Hz, 1H), 6.98 (d, $J = 8.0$ Hz, 1H), 8.06 (m, 2H), 8.22 (m, 2H); ^{13}C NMR (CD_3OD, 75 MHz): δ 36.7, 65.1, 111.9, 112.5, 121.3, 125.2, 126.1, 129.1, 129.4, 130.3, 130.4, 183.2; IR (neat): ν_{max} 3230, 1680, 1600, 1535, 1276, 1189, 865, 740 cm^{-1}; $[\alpha]_D^{23} = +5.5$ (*c* 1.0, MeOH); HR ESI-MS: *m*/*z*: calcd for $C_{15}H_{13}N_3O_5S$: 347.0575; found: 348.0658 $[M+H]^+$.

4.3. (*S*)-*N*-[(4-Methylphenyl)sulfonyl]indoline-2-carboxamide 2

Boc-(*S*)-(−)-indolin-2-carboxylic acid (1.4 g, 5.4 mmol) was dissolved in 15 ml dry pyridine and (0.93 ml, 1.11 g, 8.8 mmol) DIPCDI was added. Afterwards (1.24 g, 8.8 mmol) *p*-nitrophenol was added. The solution was stirred overnight at ambient temperature and then diluted by 20 ml ethyl acetate. The solution was extracted by 2% ice cold sulfuric acid until the aqueous phase became acidic after extraction. The organic layer was dried with $MgSO_4$ and purified by means of column chromatography on silica gel with dichloromethane as mobile phase resulting in Boc-(*S*)-(−)-indolin-2-nitrophenyl ester (1.39 g; 68%). To a solution of *p*-toluenesulfonamide (0.32 g, 1.87 mmol) in 10 ml of absolute DMF was added sodium hydride (134 mg, 3.34 mmol). After stirring for approximately 1 h at ambient temperature, Boc-(*S*)-(−)-indolin-2-nitrophenyl ester (0.41 g, 1.44 mmol), dissolved in 5 ml of absolute DMF, was added. The yellow solution was stirred overnight at room temperature. The mixture was then poured onto crushed ice and the pH was adjusted to 3 by citric acid addition. During the addition a white precipitate appeared, which was filtered and washed with water. The white solid was dried under high vacuum resulting in the Boc protected toluenesulfonamide (0.5 g; 83%). The deprotection was performed by addition of a mixture of 50% TFA in DCM (10 ml). The mixture was stirred for an hour at room temperature followed by concentration under reduced pressure to give a yellow oil, which was dissolved in methanol followed by addition of 0.5 g of a MP-TsOH resin. The mixture was stirred overnight followed by filtration of the resin. The resin was washed with methanol and subsequently the product was released from the resin by addition of a saturated ammonia solution of methanol, which furnished the product as a yellow oil after concentration (0.20 g; 44% overall yield). ^{1}H NMR (CD_3OD, 500 MHz): δ 2.34 (s, 3H), 3.13 (dd, $J = 15.9$, 5.9 Hz, 1H), 3.26 (m, 1H), 4.13 (m, 1H), 6.66 (m, 2H), 6.96 (t, $J = 7.6$ Hz, 1H), 6.99 (d, $J = 7.3$ Hz, 1H), 7.22 (d, $J = 8.1$ Hz, 2H), 7.77 (m, 2H); ^{13}C NMR (CD_3OD, 75 MHz): δ 22.2, 36.7, 64.9, 112.5, 121.3, 126.1, 129.0, 129.1, 130.4, 130.6, 142.8, 143.9, 152.9, 182.4; IR (neat): ν_{max} 3200, 1650, 1535, 1485, 1230, 1134, 890, 725 cm^{-1}; $[\alpha]_D^{23} = -5.4$ (*c* 1.0, MeOH); HR ESI-MS: *m*/*z*: calcd for $C_{16}H_{16}N_2O_3S$: 316.0881; found: 317.0936 $[M+H]^+$.

4.4. (*S*)-*N*-[(2,4,6-Triisopropylphenyl)sulfonyl]indoline-2-carboxamide 3

To a solution of 2,4,6-tris(isopropylbenzene)sulfonamide (0.62 g, 2.197 mmol) were added sodium hydride (150 mg, 8.14 mmol) and Boc-(*S*)-(−)-indolin-2-nitrophenyl ester (0.65 g, 1.69 mmol) (prepared as described above) dissolved in 5 ml of absolute DMF. The light yellow solution

was stirred overnight at room temperature. The mixture was then poured onto crushed ice and the pH was adjusted to 3 by citric acid addition. During the addition a white precipitate appeared, which was filtered and washed with water. The white solid was dried under high vacuum resulting in the Boc protected derivative. Boc-deprotection was performed by addition of a mixture of 50% TFA in DCM to the residue. The mixture was stirred for an hour at room temperature followed by concentration under reduced pressure to give a yellow oil, which was dissolved in methanol followed by addition of 0.5 g MP-TsOH resin. The mixture was stirred overnight followed by filtration of the resin. The resin was washed with methanol and subsequently the product was released from the resin by addition of a saturated ammonia in methanol, which furnished the product as a yellow oil (0.2 g; 27% overall yield). ^{1}H NMR (CD_3OD, 500 MHz): δ 1.62 (d, $J = 6.8$ Hz, 6H), 1.19 (d, $J = 6.8$ Hz, 12H), 2.84 (m, 1H), 3.27 (m, 2H), 4.11 (m, 1H), 4.46 (m, 3H), 6.65 (m, 2H), 6.94 (t, $J = 7.6$ Hz, 1H), 6.98 (d, $J = 7.32$ Hz, 1H), 7.10 (s, 2H). ^{13}C NMR (CD_3OD, 75 MHz): δ 22.7, 23.6, 29.2, 34.2, 61.0, 113.9, 123.9, 124.9, 128.1, 129.3, 132, 151.6, 154.3, 159.4, 182.5; IR (neat): ν_{max} 3150, 1720, 1650, 1535, 1180, 1056, 830, 740 cm^{-1}; $[\alpha]_D^{23} = -47.2$ (c 1.0, MeOH); ESI-MS: m/z: calcd for $C_{24}H_{32}N_2O_3S$: 428.2; found: 429.2 $[M+H]^+$.

4.5. General procedure for the enantioselective organocatalytic cyclopropanation

To a 30 ml flask equipped with a magnetic stirring bar were added chloroform (21 ml), aldehyde (0.5 mmol), and 0.025 mmol of the *N*-arylsulfonamide catalysts **1**, **2**, or **3**. The mixture was cooled to the desired temperature followed by addition of 2-(dimethyl-λ^4-sulfanylidene)-1-phenyl-ethanone (0.127 mmol; 23 mg) or 2-(dimethyl-λ^4-sulfanylidene)-1-(4′-bromophenyl)-ethanone (0.127 mmol; 33 mg). The resulting homogenous yellow mixture was stirred for 38 h after which the cold solution was filtered through a pad of silica. The filtrate was concentrated under reduced pressure to give the crude product as yellow oil, which was further purified by means of column chromatography.

4.6. (1*R*,2*S*,3*R*)-2-Benzoyl-3-methyl-cyclopropanecarbaldehyde (Table 2, entries 1 and 2)

Prepared according to the general procedure. Purification was performed by means of flash chromatography (silica gel, 15% Et_2O in *n*-pentane). The pure products were obtained as light yellow oils. The ^{1}H NMR and ^{13}C NMR spectroscopic data were in good agreement with data reported earlier.[12] The enantiomeric excess was determined by GLC using Astec Chiraldex σ-TA (30 m * 0.25 mm), column (160 °C isotherm for 60 min), ramp to (180 °C by 10 °C/min, hold 0.5 min). *Major* diastereomer: major enantiomer $t_R = 10.9$ min and *minor* enantiomer $t_R = 11.5$ min. MS (EI) m/z (rel. intensity): 187 (M^+, 1), 171 (4), 144 (3), 115 (10), 105 (100), 89 (2), 77 (46), 69 (5), 51 (22). The diastereomeric ratio was determined by ^{1}H NMR analysis on the crude reaction mixture.

4.7. (1*R*,2*S*,3*R*)–2-Benzoyl-3-propyl-cyclopropanecarbaldehyde (Table 2, entries 3 and 4)

Prepared according to the general procedure. Purification was performed by means of flash chromatography (silica gel, 15% Et_2O in *n*-pentane). The pure products were obtained as light yellow oils. The ^{1}H NMR and ^{13}C NMR spectroscopic data were in good agreement with data reported earlier.[12] The enantiomeric excess and diastereomeric excess were determined by GLC using Astec Chiraldex β-DM (30 m * 0.25 mm), column (155 °C isotherm for 90 min), ramp to (175 °C, 5 °C/min and isotherm for 18 min) and ramp to (220 °C, 10 °C/min, hold 0.5 min). *Major* diastereomer: major enantiomer $t_R = 31.8$ min and minor enantiomer $t_R = 33.4$ min. *Minor* diastereomer: major enantiomer $t_R = 20.1$ min and minor enantiomer $t_R = 19.8$ min. MS (EI): m/z (rel intensity): 217 ($[M+H]^+$, 32), 174 (13), 173 (100), 145 (33), 144 (4), 117 (23), 116 (4), 115 (13), 106 (7), 105 (82), 104 (5), 78 (5), 77 (44), 76 (3).

4.8. (1*R*,2*S*,3*R*)-2-(4′-Bromo-benzoyl)-3-propyl-cyclopropanecarbaldehyde (Table 2, entries 5 and 6)

Prepared according to the general procedure. Purification was done by means of flash chromatography (silica gel, 15% Et_2O in *n*-pentane). The pure products were obtained as light yellow oils. The ^{1}H NMR and ^{13}C NMR spectroscopic data were in good agreement with data reported earlier.[12] The enantiomeric excess and diastereomeric excess were determined by GLC using Astec Chiraldex β-DM (30 m * 0.25 mm), column (180 °C isotherm for 110 min), ramp to (220 °C, 10 °C/min, hold 0.50 min). *Major* diastereomer: major enantiomer $t_R = 39.5$ min and minor enantiomer $t_R = 40.6$ min. *Minor* diastereomer: major enantiomer $t_R = 23.1$ min and minor enantiomer $t_R = 22.5$ min. MS (EI) m/z (rel. intensity): 295 ($[M+H]^+$, 4), 294 (M^+, 1), 296 (2), 251 (99), 252 (15), 253 (100), 254 (13), 183 (65), 184 (8), 185 (65), 186 (7), 155 (23).

4.9. (1*R*,2*S*,3*R*)-2-Benzoyl-3-phenyl-cyclopropanecarbaldehyde (Table 2, entries 7 and 8)

Prepared according to the general procedure. Purification was done by means of flash chromatography (silica gel, 15% Et_2O in *n*-pentane). The pure products were obtained as light yellow oils. The ^{1}H NMR and ^{13}C NMR spectroscopic data were in good agreement with data reported earlier.[12] The product (1*R*,2*S*,3*R*)-2-benzoyl-3-phenyl-cyclopropane-carbaldehyde was dissolved in methanol–acetate buffer pH 4.5 (1:1) after which sodium cyano borohydride was added. The reaction was stirred for 8 h after which the mixture was concentrated under reduced pressure. To the residue was added 2 ml of brine followed by extraction of the mixture with ethyl acetate. The ethyl acetate was removed under reduced pressure providing the product as yellow oil. The product was further purified by means of column chromatography (silica gel; 70% EtOAc in *n*-pentane) to give the product as a colorless oil. ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.02–7.98 (m, 2H), 7.60–7.53 (m, 1H), 7.35–7.28 (m, 2H), 7.27–7.14 (m, 5H), 4.15 (m, 2H), 3.90 (dd, $J = 12.1$, 8.3 Hz, 1H), 3.02 (dd, $J = 8.8$, 5.1 Hz, 1H), 2.94 (td, $J = 5.7$, 1.3 Hz, 1H), 2.42–

2.33 (m, 1H). The enantiomeric excess was determined by HPLC equipped with chiral column Chiralcel AD (25% 2-propanol in hexane, 1 ml/min, 254 nm); *Major* diastereomer: major enantiomer $t_R = 21.6$ min and minor enantiomer $t_R = 28.3$ min. *Minor* diastereomer: major enantiomer $t_R = 12.3$ min and minor enantiomer $t_R = 13.8$ min.

4.10. (1*R*,2*S*,3*R*)-2-Allyloxymethyl-3-benzoyl-cyclopropanecarbaldehyde (Table 2, entries 9 and 10)

Prepared according to the general procedure. Purification was done by means of flash chromatography (silica gel, 15% Et_2O in *n*-pentane) furnishing pure products as light yellow oils. The ^1H NMR and ^{13}C NMR spectroscopic data were in good agreement with data reported earlier.[12] The enantiomeric excess and diastereomeric excess were determined by GLC using Astec Chiraldex β-DM (30 m * 0.25 mm), column (177 °C isotherm for 120 min), ramp to (220 °C by 10 °C/min), hold 220 °C for 0.5 min. *Major* diastereomer: major enantiomer $t_R = 28.1$ min and minor enantiomer $t_R = 29.5$ min. *Minor* diastereomer: major enantiomer $t_R = 13.5$ min and minor enantiomer $t_R = 14.1$ min. MS (EI) *m*/*z* (rel. intensity): 245 ($[M+H]^+$, 52), 244 (M^+, 2), 173 (100), 117 (26), 116 (4), 105 (75), 104 (2), 77 (38), 76 (2).

4.11. (1*R*,2*S*,3*R*)-2-Allyloxymethyl-3-(4′-bromo-benzoyl)-cyclopropanecarbaldehyde (Table 2, entries 11 and 12)

Prepared according to the general procedure. Purification was done by means of flash chromatography (silica gel, 15% Et_2O in *n*-pentane). The pure products were obtained as light yellow oils. The ^1H NMR and ^{13}C NMR spectroscopic data were in good agreement with data reported earlier.[12] The enantiomeric excess and diastereomeric excess were determined by GLC using Astec Chiraldex β-DM (30 m * 0.25 mm), column (200 °C isotherm for 130 min), ramp to (220 °C by 10 °C), hold 0.5 min. *Major* diastereomer: major enantiomer $t_R = 32.2$ min and minor enantiomer $t_R = 33.2$ min. *Minor* diastereomer: major enantiomer $t_R = 21.6$ min and minor enantiomer $t_R = 22.3$ min. MS (EI) *m*/*z* (rel. intensity): 323 ($[M+H]^+$, 7), 283 (5), 281 (8), 280 (1), 253 (97), 252 (16), 251 (100), 250 (4), 185 (53), 184 (8), 183 (55), 182 (2), 157 (22), 156 (4), 155 (21), 154 (1).

4.12. (1*R*,2*S*,3*R*)-2-Benzoyl-3-hex-5-enyl-cyclopropanecarbaldehyde (Table 2, entries 13 and 14)

Prepared according to the general procedure. Purification was done by means of flash chromatography (silica gel, 15% Et_2O in *n*-pentane). The pure products were obtained as light yellow oils. The ^1H NMR and ^{13}C NMR spectroscopic data were in good agreement with data reported earlier.[12] The enantiomeric excess and diastereomeric excess were determined by GLC using Astec Chiraldex β-DM (30 m * 0.25 mm), column (160 °C isotherm for 150 min), ramp to 220 °C by 10 °C/min, 220 °C hold 0.5 min. *Major* diastereomer: major enantiomer $t_R = 60.2$ min and minor enantiomer $t_R = 63.1$ min. *Minor* diastereomer: major enantiomer $t_R = 47.1$ min and minor enantiomer $t_R = 47.3$ min. MS (EI) *m*/*z* (rel. intensity): 256 (M^+, 3), 241 (15), 213 (20), 199 (20), 173 (50), 145 (25), 105 (100), 77 (60).

4.13. (1*R*,2*S*,3*R*)-2-(4′-Bromo-benzoyl)-3-hex-5-enyl-cyclopropanecarbaldehyde (Table 2, entries 15 and 16)

Prepared according to the general procedure. Purification was performed by means of flash chromatography (silica gel, 15% Et_2O in *n*-pentane). The pure products were obtained as light yellow oils. The ^1H NMR and ^{13}C NMR spectroscopic data were in good agreement with data reported earlier.[12] The enantiomeric excess and diastereomeric excess were determined by GLC using Astec Chiraldex β-DM (30 m * 0.25 mm), column (195 °C isotherm for 150 min), ramp to 220 °C by 10 °C/min, 220 °C hold 0.5 min. *Major* diastereomer: major enantiomer $t_R = 41.5$ min and minor enantiomer $t_R = 42.2$ min. *Minor* diastereomer: major enantiomer $t_R = 26.6$ min and minor enantiomer $t_R = 26.2$ min. MS (EI) *m*/*z* (rel. intensity): 334 (M^+, 1), 323 (8), 322 (4), 321 (8), 320 (2), 225 (23), 224 (12), 223 (22), 222 (4), 185 (100), 184 (13), 183 (98), 182 (4), 157 (41), 156 (7), 155 (36), 154 (4).

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