Supporting Information

Copper-Catalyzed Enantioselective 1,4-Addition of Alkyl Groups to N-Sulfonyl Imines

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1) Experimental Section

**General:** $^1$H and $^{13}$C NMR spectra were recorded at 300 or 500 MHz (75.5 or 125 MHz) on a Bruker AV-300, an AV-500, or a DRX-500 instrument in CDCl$_3$, using the residual peak of CHCl$_3$ ($^1$H NMR: $\delta =$ 7.26 ppm, $^{13}$C NMR: $\delta =$ 77.36 ppm) as internal standard. IR spectra were recorded on a Bruker Alpha-P FT-IR spectrometer. Optical rotations were measured on a Perkin-Elmer 241 polarimeter, $[\alpha]_D^{20}$ values are given in $10^{-1}$ deg cm$^2$ g$^{-1}$. Electron impact (EI) mass spectra were recorded on a Finnigan MAT 95S spectrometer (70 eV); electrospray ionisation (ESI) mass spectra on a Finnigan LTQ FT spectrometer. Melting points are uncorrected. Gas chromatograms were recorded on a Shimadzu GC-2010 Plus with an AOC-20i autosampler. Enantiomeric excesses were determined with a Chiral-Separations Cyclodextrin TA column (6-TBDMS-2,3-acetyl-ß-cyclodextrin, 50% in PS086, 25 m, 0.25 mm i.d., 0.125 µm film). Helium was used as the carrier gas. Method A: 4 min 80 °C isothermal → 10 K min$^{-1}$ to 130 °C → 20 K min$^{-1}$ to 170 °C → 5 min isothermal; 45 cm s$^{-1}$ gas flow. Method B: 2 min 100 °C isothermal → 2 K min$^{-1}$ to 140 °C → 20 min isothermal → 1 K min$^{-1}$ to 160 °C → 50 min isothermal; 45 cm s$^{-1}$ gas flow. Method C: 2 min 100 °C isothermal → 2 K min$^{-1}$ to 140 °C → 20 min isothermal → 0.5 K min$^{-1}$ to 160 °C → 50 min isothermal; 30 cm s$^{-1}$ gas flow. HPLC chromatograms were recorded on a JASCO instrument equipped with a JASCO MD-2010 Plus multiwavelength detector. Method A: Daicel Chiralpak IA column, isocratic elution: $n$-hexane/2-propanol 98:2, flow rate 1.0 mL min$^{-1}$. Method B: Daicel Chiralpak IC column, isocratic elution: $n$-hexane/2-propanol 95:5, flow rate 1.0 mL min$^{-1}$. Method C: Daicel Chiralpak IA column coupled with a Daicel Chiralpak IB column, isocratic elution: $n$-hexane/2-propanol 98:2, flow rate 1.0 mL min$^{-1}$. Method D: Daicel Chiralpak IC column, isocratic elution: $n$-hexane/2-propanol 99:1, flow rate 1.5 mL min$^{-1}$. Method E: Daicel Chiralpak IC column, isocratic elution: $n$-hexane/2-propanol 98:2, flow rate 1.0 mL min$^{-1}$. Method F: Daicel Chiralpak IC column, isocratic elution: $n$-hexane/2-propanol 98:2, flow rate 1.5 mL min$^{-1}$. Method G: Daicel Chiralpak IC column, isocratic elution: $n$-hexane/2-propanol 85:15, flow rate 1.0 mL min$^{-1}$. Diastereomeric ratios were determined by $^1$H NMR spectrometry at 300 or 500 MHz; the relative configuration of the products was determined by NOESY. Solvents used for extraction and chromatography were of technical grade and distilled prior to use. All moisture-sensitive reactions were carried out under argon in oven- and/or flame-dried glassware. Column chromatography was carried out on MN Kieselgel 60 M (Machery-Nagel, 0.040-0.063 mm). Diethyl ether, THF, and toluene were distilled from sodium benzenophene ketyl; triethyl amine and CH$_2$Cl$_2$ were distilled from CaH$_2$. $N$-(Cyclohex-2-en-1-ylidene)-4-methylbenzenesulfonamide (1a),$^1$ $N$-(4,4-dimethylcyclopent-2-en-1-ylidene)-4-methylbenzenesulfonamide (1b),$^1$ $N$-(4,4-dimethylcyclohex-2-en-1-ylidene)-4-methylbenzenesulfonamide (1c),$^1$ (E)-$N$-(5,5-dimethylcyclopent-2-en-1-ylidene)-4-
methylbenzenesulfonamide (1d),

(E)-N-(6,6-dimethylcyclohex-2-en-1-ylidene)-4-methylbenzenesulfonamide (1e),

N-(5,5-dimethylcyclohex-2-en-1-ylidene)-4-methylbenzenesulfonamide (1f),

N-(3-methylcyclohex-2-en-1-ylidene)-4-methylbenzenesulfonamide (1g),

N-(1,3-diphenylprop-2-en-1-ylidene)-4-methylbenzenesulfonamide (1h),

N-(5R-methylcyclohex-2-en-1-ylidene)-4-methylbenzenesulfonamide (1i),

N-(cyclohex-2-en-1-ylidene)-tart-butanesulfonamide (5a),

N-(cyclopent-2-en-1-ylidene)-tart-butanesulfonamide (5b),

N-(cyclohept-2-en-1-ylidene)-tart-butanesulfonamide (5c),

and N-(cyclohex-2-en-1-ylidene)diphenylphosphinamide (7a),

the racemic ligand $O,O'-(1,1'-dinaphthyl-2,2'-diyl)-N,N-di-iso-propylphosphoramide,$

$O,O'-(S)-(1,1'-dinaphthyl-2,2'-diyl)-N,N-di-(R,R)-1-phenylethylphosphoramide (L1)$ and $O,O'-(R)-(1,1'-dinaphthyl-2,2'-diyl)-N,N-di-(S,S)-1-phenylethylphosphoramide (ent-L1),$

$\text{RuCl(p-cymene)}[(S,S)-\text{Ts-DPEN}] (3),$

copper(I)-thiophen-2-carboxylate (CuTC) were prepared according to literature. All other chemicals were of commercial origin and used as received.

General Procedure for the Optimization of the Conjugate Addition (GP 1):

A mixture of the respective copper salt (10.0 μmol, 2.00 mol%), ligand $L1$ (10.8 mg, 20.0 μmol, 4.00 mol%), and ketimine $1a$ (125 mg, 501 μmol) was dissolved in the respective solvent (4 mL), stirred for 0.5 h at rt, and then cooled to the given temperature. ZnEt$_2$ (0.50 mL, 0.75 mmol, 1.5 M in toluene) was added slowly, and the resulting yellow solution was stirred for the given time at the given temperature. The solution was then poured into a mixture of methyl tert-butyl ether (MTBE, 20 mL), H$_2$O (0.5 mL), and NaHCO$_3$ (0.5 g), stirred for 10 min, dried over MgSO$_4$, filtered, and concentrated under reduced pressure.

For determination of the yield by $^1$H NMR spectrometry, a precise amount of diphenylmethane (about 50 mg) was added to the crude enamide $2a-Et$, which was then dissolved in CH$_2$Cl$_2$ (20 mL). The solvent was then carefully removed under reduced pressure to give the crude product with internal standard, and a $^1$H NMR spectrum was recorded in CDCl$_3$. Signals at δ = 5.37 (1H, 2a-Et) and δ = 3.99 (2H, diphenylmethane) were used for determination of the yield.

General Procedure for the Hydrolysis of Enamide 2a-Et (GP 2):

THF (5 mL) and aqueous HCl (1 mL, 6 M) were added to the crude enamide 2a-Et, and the solution was stirred for 1 h at rt. The reaction mixture was then diluted with pentane (5 mL), and sat. aqueous NaHCO$_3$ solution was added until the gas evolution ceased. The organic phase was separated, dried over MgSO$_4$, filtered, and concentrated under reduced pressure. Purification was performed by column chromatography over silica gel ($R_f$ 0.31, pentane/Et$_2$O 5:1), and the ee of the 3-ethylcyclohexanone thus obtained was measured by GC, method A, retention times 9.54 min (minor enantiomer), 9.67 min (major enantiomer). The (S)-configuration of enamide 2a-Et was
determined by comparison with a sample of authentic (S)-3-ethylcyclohexanone, which was prepared according to literature.⁷

General Procedure for the Asymmetric Conjugate Addition (GP 3):
A mixture of copper(I)-thiophene-2-carboxylate (1.91 mg, 10.0 µmol), ligand L1 (10.8 mg, 20.0 µmol), and the respective ketimine 1, 5, or 7 (500 µmol) was dissolved in toluene (4 mL), stirred for 0.5 h at rt, and then cooled to the given temperature. ZnEt₂ (0.50 mL, 0.75 mmol, 1.5 M in toluene) was slowly added, and the resulting yellow solution was stirred for the given time at the given temperature. The reaction mixture was then poured into a mixture of MTBE (20 mL), H₂O (0.5 mL), and NaHCO₃ (0.5 g), stirred for 10 min, dried over MgSO₄, filtered, and concentrated under reduced pressure.

General Procedure for the Hydrogenation Catalyzed by RuCl(p-cymene)[Ts-DPEN] (GP 4)
The crude product of the conjugate addition was dissolved in acetonitrile (3 mL), racemic RuCl(p-cymene)[Ts-DPEN] (3, 15.9 mg, 25.0 µmol) and a 5:2 mixture of formic acid and triethyl amine (314 µL, 0.75 mmol) were added, and the reaction mixture was stirred for 16 h at rt. The solution was then poured into half-saturated brine (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine, dried over MgSO₄, filtered, concentrated under reduced pressure, and purified by flash column chromatography over silica gel.

N-[(1S,3S)-3-Ethylcyclohexyl]-4-methylbenzenesulfonamide (trans-4a-Et)
Preparation according to GP 3 and GP 4 using ketimine 1a (125 mg, 501 µmol), reaction time 1 h at −30 °C, yielded 120 mg (85%) of amide trans-4a-Et as a colorless solid with a dr (trans/cis) >97:3.

R₁ 0.50, CH₂Cl₂. – mp 68 °C. – [α]D²⁰ +7.5 (c 1.0 in CHCl₃). – IR (neat) νmax/cm⁻¹ 3277, 2927, 2872, 2850, 1598, 1421, 1322, 1163, 1142, 818, 708, 552, 515. – δH (500 MHz; CDCl₃) 0.74 (t, ³J = 7.5 Hz, 3H, 2'-H), 0.86-0.93 (m, 1H, 4-H), 1.07-1.17 (m, 3H, 2-H, 1'-H), 1.32 (m, 1H, 3-H), 1.37-1.62 (m, 6H, 2-H, 4-H, 5-H, 6-H), 2.41 (s, 3H, ArCH₃), 3.50 (m, 1H, 1-H), 4.89 (d, ³J = 7.3 Hz, 1H, NH), 7.29 (m, 2H, Ar-H), 7.77 (m, 2H, Ar-H). – δC (125 MHz; CDCl₃) 11.4 (C-2’), 20.4 (C-5), 21.6 (ArCH₃), 28.7 (C-1’), 31.3 (C-4), 31.8 (C-6), 33.7 (C-3), 37.4 (C-2), 49.5 (C-1), 127.1 (C-Ar), 129.7 (C-Ar), 138.4 (C-Ar), 143.2 (C-Ar). – HRMS (ESI) m/z calcd. for C₁₃H₂₃NO₂Sn [M+Na]⁺: 304.1342; found 304.1341. – The enantiomeric excess was measured by HPLC, method A, retention times 33.6 min (major enantiomer), 38.1 min (minor enantiomer): 98% ee. The (S)-configuration at C-3 was assigned based on the configuration of enamide 2a-Et.
Racemic amide \textit{trans}-4a-Et was prepared as follows: CuCl (49.5 mg, 500 µmol) was suspended in THF (2 mL), cooled to −30 °C, and treated dropwise with EtMgBr (344 µL, 750 µmol, 2.18 M in Et₂O). The reaction mixture was stirred for 15 min, a solution of ketimine 1a (125 mg, 501 µmol) in THF (2 mL) was added dropwise, and the reaction mixture was stirred for 1 h at −30 °C. Workup was performed as described in GP 3. Hydrogenation according to GP 4 yielded 42 mg (30%) of the racemic amide \textit{trans}-4a-Et.

**Preparation of Amide trans-4a-Et with 0.01 mol% Cu-catalyst**

A mixture of copper(I)-thiophene-2-carboxylate (1.91 mg, 10.0 µmol) and ligand L1 (10.8 mg, 20.0 µmol) was dissolved in toluene (50 mL) and stirred for 3 h at rt. In a second flask, ketimine 1a (125 mg, 501 µmol) was dissolved in toluene (3.75 mL), an aliquot of the catalyst-containing solution (250 µL) was added, and the reaction mixture was cooled to −30 °C. ZnEt₂ (0.50 mL, 0.75 mmol, 1.5 M in toluene) was slowly added, and the resulting yellow solution was stirred for 1 h at −30 °C. Workup was performed according to GP 3, and hydrogenation according to GP 4 furnished 125 mg (89%) of amide trans-4a-Et. – 87% ee.

\textit{N-[(1R,3S)-3-Ethylcyclohexyl]-4-methylbenzenesulfonamide (cis-4a-Et)}

Conjugate addition was performed according to GP 3 using ketimine 1a (125 mg, 501 µmol), reaction time 1 h at −30 °C. After workup, the crude product was cooled to 0 °C, and a solution of tBuNH₂-BH₃ (91.3 mg, 1.05 mmol) in CH₂Cl₂ (3 mL) was added. The reaction mixture was stirred for 16 h at 0 °C, then poured into half-saturated aqueous NH₄Cl (2 mL), and extracted with MTBE (3 × 10 mL). The combined organic phases were washed with water (10 mL) and brine (10 mL), dried over MgSO₄, filtered, and concentrated under reduced conditions to furnish 125 mg (89%) of amide cis-4a-Et.
pressure. Purification by flash column chromatography over silica gel furnished 90 mg (64%) of amide cis-4a-Et as a colorless solid. – dr (trans/cis) before chromatography: 10:90, after chromatography: <3:97.

\[ R_f 0.25, \text{pentane/EtOAc 10:1.} \]

– mp 54 °C. – \([\alpha]_D^{20} +22.8 \text{ (c 1.0 in CHCl}_3\). – IR (neat) \(\nu_{\text{max}}/\text{cm}^{-1}\)

3277, 2927, 2854, 1599, 1448, 1321, 1155, 1093, 813, 662, 568, 547. – \(\delta_H\) (500 MHz; CDCl\(_3\))

0.63-0.74 (m, 2H, 2-H, 5-H), 0.78 (t, \(J = 7.2 \text{ Hz, 3H, 2'}-\text{H}\)), 1.00 (m, 1H, 6-H), 1.07-1.20 (m, 4H, 3-H, 4-H, 1'-H), 1.59-1.68 (m, 2H, 4-H, 5-H), 1.73-1.83 (m, 2H, 2-H, 6-H), 2.41 (s, 3H, ArCH\(_3\)), 3.06 (m, 1H, 1-H), 4.78 (d, \(J = 7.7 \text{ Hz, 1H, NH}\)), 7.28 (m, 2H, Ar-H), 7.77 (m, 2H, Ar-H). – \(\alpha_c\) (125 MHz; CDCl\(_3\))

11.3 (C-2'), 21.6 (ArCH\(_3\)), 24.9 (C-4), 29.6 (C-1'), 31.5 (C-5), 34.3 (C-6), 38.7 (C-3), 40.6 (C-2), 53.3 (C-1), 127.0 (C-Ar), 129.7 (C-Ar), 138.7 (C-Ar), 143.2 (C-Ar). – HRMS (ESI) \(m/z\) calcd for C\(_{15}\)H\(_{23}\)NO\(_2\)SNa \([M+Na]^+\]: 304.1342; found 304.1341. – The enantio-meric excess was measured by HPLC, method B, retention times 58.6 min (minor enantiomer), 68.0 min (major enantiomer): 96% ee

Racemic preparation was performed as described above using racemic \(O,O'-(1,1'-\text{dinaphthyl-2,2'-diyl})-N,N-\text{di-iso-propylphosphoramidite}\) (8.30 mg, 20.0 µmol) and yielded 51 mg (36%) of racemic amide cis-4a-Et.

**N-[(1S,3S)-3-Methylcyclohexyl]-4-methylbenzenesulfonamide (4a-Me)**

Addition of ZnMe\(_2\): Preparation according to GP 3 and GP 4 using ketimine 1a (125 mg, 501 µmol) and ZnMe\(_2\) (0.63 mL, 0.76 mmol, 1.2 m in toluene), reaction time 1 h at –30 °C, yielded 117 mg (87%) of amide 4a-Me as a colorless solid with a dr (trans/cis) >97:3.
$R_f$ 0.44, CH$_2$Cl$_2$. – mp 112 °C. – $[\alpha]_D^{20}$ -0.7 (c 1.0 in CHCl$_3$). – IR (neat) $\nu_{\text{max}}$/cm$^{-1}$ 3282, 2925, 2867, 1599, 1454, 1422, 1323, 1159, 1141, 1092, 813, 672, 549. – $\delta_{\text{IR}}$ (500 MHz; CDCl$_3$) 0.78 (d, $J$ = 6.5 Hz, 3H, 1'H), 0.84-0.92 (m, 1H, 4'H), 1.09 (ddd, $J$ = 13.5, 10.3, 3.4 Hz, 1H, 2'H), 1.33-1.62 (m, 7H, 2'-H, 3'-H, 4'-H, 5'-H, 6'-H), 2.41 (s, 3H, ArCH$_3$), 3.49 (m, 1H, 1'-H), 5.01 (d, $J$ = 7.3 Hz, 1H, NH), 7.28 (m, 2H, Ar-H), 7.77 (m, 2H, Ar-H). – $\delta_{\text{H}}$ (125 MHz; CDCl$_3$) 20.4 (C-5), 21.6 (Ar-CH$_3$), 21.7 (C-1'), 26.9 (C-3), 31.4 (C-6), 33.7 (C-4), 39.7 (C-2), 49.5 (C-1), 127.1 (C-Ar), 129.7 (C-Ar), 138.3 (C-Ar), 143.2 (C-Ar). – HRMS (ESI) $m/z$ calcd for C$_{14}$H$_{21}$NO$_2$SNa [M+Na]$^+$: 290.1185; found 290.1183. – The enantiomeric excess was measured by HPLC, method A, retention times 39.7 min (major enantiomer), 44.8 min (minor enantiomer): 98% ee. The absolute configuration was assigned in analogy to amide 4a-Et.

Addition of AlMe$_3$: Conjugate addition according to GP 3 using ketimine 1a (125 mg, 501 µmol) and AlMe$_3$ (72 µL, 0.75 mmol) in Et$_2$O (4 mL), reaction time 1.5 h at -30 °C, and hydrogenation according to GP 4 yielded 37 mg (28%) of amide 4a-Me with a dr (trans/cis) >97:3. – 96% ee.
Conjugate addition according to GP 3 using ketimine 1b (65.8 mg, 250 µmol), CuTC (0.96 mg, 5.0 µmol), ligand L1 (5.40 mg, 10.0 µmol), and ZnEt₂ (0.25 mL, 0.38 mmol, 1.5 M in toluene) in toluene (2 mL), reaction time 5 h at −30 °C. The crude product was dissolved in EtOH (2 mL) and cooled to −15 °C, and NaBH₄ (94.5 mg, 2.50 mmol) was added. The solution was stirred for 20 h at this temperature, poured into saturated aqueous NH₄Cl (10 mL), and extracted with CH₂Cl₂ (3 × 10 mL). The combined organic phases were washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure; the crude product was purified by flash column chromatography over silica gel. Amide 4b-Et (52 mg, 70%) was obtained as a viscous, colorless oil that crystallized in the freezer. – dr (trans/cis) before chromatography: 7:93, after chromatography: 7:93.

Rₐ 0.32, CH₂Cl₂. – mp 74-75 °C. – [α]ᵦ²⁰ −11.7 (c 1.0 in CHCl₃). – IR (neat) vₘₐₓ/cm⁻¹ 3274, 2956, 2865, 1598, 1495, 1319, 1304, 1156, 1092, 813, 661, 565, 546. – δ₁H (500 MHz; CDCl₃) 0.78 (s, 3H, 2″-H), 0.79 (t, 3J = 7.4 Hz, 3H, 2'-H), 0.87 (s, 3H, 1″-H), 0.96-1.03 (m, 1H, 1'-H), 1.09-1.15 (m, 1H, 5-H), 1.16-1.22 (m, 1H, 4-H), 1.28 (dd, J = 13.7, 6.1 Hz, 1H, 2-H), 1.37 (m, 1H, 1'-H), 1.72 (dd, J = 13.7, 9.2 Hz, 1H, 2-H), 2.12 (m, 1H, 5-H), 2.42 (s, 3H, ArCH₃), 3.54 (m, 1H, 1H, 1-H), 4.95 (s, 1H, NH), 7.29 (m, 2H, Ar-H), 7.75 (m, 2H, Ar-H). – δ₁C (125 MHz; CDCl₃) 13.6 (C-2′), 21.6 (ArCH₃), 22.6 (C-1′), 24.2 (C-2″), 29.2 (C-1″), 39.36 (C-5), 39.40 (C-3), 49.4 (C-2), 50.6 (C-4), 51.9 (C-1), 127.2 (C-Ar), 129.7 (C-Ar), 137.9 (C-Ar), 143.3 (C-Ar). – HRMS (ESI) m/z calcld for C₁₆H₂₅NO₂SNa [M+Na]⁺: 318.1498; found 318.1500. – The enantiomeric excesses were measured by HPLC, method A; cis-4b-Et: retention times 38.4 min (minor enantiomer), 41.4 min (major enantiomer): 91% ee; trans-4b-Et: retention times 34.3 min (minor enantiomer), 36.2 min (major enantiomer): 91% ee. The absolute configuration was assigned in analogy to amide 4a-Et.
Racemic conjugate addition was performed as follows: CuCl (49.5 mg, 500 µmol) was suspended in THF (2 mL) and cooled to –30 °C, and EtMgBr (344 µL, 750 µmol, 2.18 M in Et₂O) was added dropwise. The reaction mixture was stirred for 15 min, a solution of ketimine 1b (132 mg, 50 µmol) in THF (2 mL) was added dropwise, and the reaction mixture was stirred for 5 h at –30 °C. Workup was performed according to GP 3; hydrogenation according to GP 4 and repeated column chromatography over silica gel yielded an analytical sample of the racemic amide 4b-Et.

\[ N-[(1S,3R)-4,4-Dimethyl-3-ethylcylohexyl]-4-methylbenzenesulfonamide (4c-Et) \]

Conjugate addition according to GP 3 using ketimine 1c (69.3 mg, 250 µmol), CuTC (0.96 mg, 5.0 µmol), ligand L1 (5.40 mg, 10.0 µmol), and ZnEt₂ (0.25 mL, 0.38 mmol, 1.5 M in toluene) in toluene (2 mL), reaction time 18 h at –10 °C. Hydrogenation according to GP 4 with racemic RuCl(p-cymene)[Ts-DPEN] (3, 7.95 mg, 12.5 µmol) and a 5:2 mixture of formic acid and triethyl amine (157 µL, 374 µmol) yielded 67 mg (87%) of amide 4c-Et as a colorless solid with a dr (trans/cis) >97:3.

\( R_f \) 0.37, pentane/EtOAc 10:1. – mp 100 °C. – [α]D²⁰ –23.1 (c 1.0 in CHCl₃). – IR (neat) \( \nu_{\text{max}}/\text{cm}^{-1} \) 3279, 2961, 2939, 2867, 1428, 1325, 1152, 683, 552. – δH (500 MHz; CDCl₃) 0.69 (t, J = 7.4 Hz, 3H, 2'-H), 0.71 (s, 3H, 1''-H*), 0.75-0.84 (m, 1H, 5-H), 0.88 (s, 3H, 2''-H*), 1.02 (m, 1H, 3-H), 1.15-1.21 (m, 2H, 1'-H, 2-H), 1.28 (m, 1H, 2-H), 1.39-1.44 (m, 1H, 6-H), 1.48-1.60 (m, 3H, 1'-H, 5-H, 6-H), 2.42 (s, 3H, ArCH₃), 3.48 (m, 1H, 1-H), 4.66 (d, J = 6.4 Hz, 1H, NH), 7.29 (m, 2H, Ar-H), 7.77 (m, 2H, H-Ar). – δC (125 MHz; CDCl₃) 12.6 (C-2'), 20.6 (C-2''*), 21.6 (ArCH₃), 22.1
(C-5), 27.8 (C-6), 29.8 (C-1"e"), 31.6 (C-1'), 32.9 (C-4), 35.4 (C-2), 43.0 (C-3), 49.4 (C-1), 127.2 (C-Ar), 129.8 (C-Ar), 138.4 (C-Ar), 143.3 (C-Ar). – HRMS (ESI) m/z calcd for C\textsubscript{17}H\textsubscript{27}NO\textsubscript{2}SNa [M+Na]\textsuperscript{+}: 332.1655; found 332.1654. – The enantiomeric excess was measured by HPLC, method A, retention times 35.1 min (minor enantiomer), 42.2 min (major enantiomer): 96% ee. The absolute configuration was assigned in analogy to amide 4a-Et.

Racemic conjugate addition was performed as follows: CuCl (24.8 mg, 251 \mu mol) was suspended in THF (1 mL) and cooled to –10 °C, and EtMgBr (172 \mu L, 375 \mu mol, 2.18 M in Et\textsubscript{2}O) was added dropwise. The reaction mixture was stirred for 15 min, a solution of ketimine 1c (69.3 mg, 250 \mu mol) in THF (1 mL) was added dropwise, and the reaction mixture was stirred for 18 h at –10 °C. Workup was performed according to GP 3; hydrogenation according to GP 4 and repeated column chromatography over silica gel yielded an analytical sample of the racemic amide 4c-Et.

\[ \text{N-[(1R,4S)-2,2-Dimethyl-4-ethylcyclopentyl]-4-methylbenzenesulfonamide (4d-Et)} \]

Conjugate addition according to GP 3 using ketimine 1d (65.8 mg, 250 \mu mol), CuTC (0.96 mg, 5.0 \mu mol), ligand L1 (5.40 mg, 10.0 \mu mol), and ZnEt\textsubscript{2} (0.25 mL, 0.38 mmol, 1.5 M in toluene) in toluene (2 mL), reaction time 20 h at –30 °C. The crude product was dissolved in EtOH (2 mL) and cooled to 0 °C, and NaBH\textsubscript{4} (94.5 mg, 2.50 mmol) was added. The solution was stirred for 16 h at this temperature, poured into saturated aqueous NH\textsubscript{4}Cl (10 mL), and extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 \times 10 mL). The combined organic phases were washed with brine, dried over MgSO\textsubscript{4}, filtered, and concentrated under reduced pressure. Purification by flash column chromatography over silica gel yielded 66 mg (89%) of amide 4d-Et as a
viscous, colorless oil that crystallized in the freezer. – dr (trans/cis) before chromatography: 64:36, after chromatography: 64:36.

Rf 0.33, CH₂Cl₂. – mp 102 °C. – [α]D⁰ +0.6 (c 1.0 in CHCl₃). – IR (neat) νmax/cm⁻¹ 3256, 2955, 2930, 2872, 1320, 1156, 1084, 809, 669, 570. – δH (500 MHz; CDCl₃; signals of cis-4d-Et marked with “#”) 0.74 (t, J = 7.4 Hz, 3H, 2'-H), 0.76 (t, J = 7.4 Hz, 2'-H#), 0.81 (s, 3H, 2'-H), 0.85 (s, 3H, 1''-H), 0.87 (s, 3H, 1''-H, 2''-H#), 0.89-0.95 (m, 1H, 3-H), 0.98-1.02 (m, 1H, 5-H#), 1.04-1.08 (m, 1H, 3-H#), 1.14-1.25 (m, 2H, 1'-H), 1.34-1.40 (m, 1H, 5-H), 1.45-1.52 (m, 1H, 5-H), 1.57-1.63 (m, 1H, 3-H, 4-H#), 1.79-1.85 (m, 1H, 5-H#, 4-H), 2.41 (s, 3H, ArCH₃), 3.11-3.18 (m, 1H, 1'-H), 4.79 (d, J = 9.4 Hz, 1H, NH), 4.84 (d, J = 9.4 Hz, 1H, NH#), 7.28 (m, 2H, Ar-H), 7.77 (m, 2H, Ar-H). – δC (125 MHz; CDCl₃; signals of cis-4d-Et marked with “#”) 12.4 (C-2'), 12.8 (C-2#), 21.1 (C-2''), 21.6 (ArCH₃), 24.5 (C-1''#), 26.8 (C-1''), 28.3 (C-2''#), 29.9 (C-1'#), 30.2 (C-1'), 35.4 (C-4), 36.1 (C-4''), 37.2 (C-5), 38.9 (C-5#), 40.2 (C-2''), 41.8 (C-2), 45.3 (C-3#), 46.1 (C-3), 62.0 (C-1), 63.0 (C-1''), 127.2 (C-Ar), 129.6 (C-Ar), 138.3 (C-Ar), 143.2 (C-Ar). – HRMS (ESI) m/z calcd for C₁₆H₂₅NO₂SNa [M+Na⁺]: 318.1498; found 318.1497. – The enantiomeric excesses were measured by HPLC, method C; trans-4d-Et: retention times 45.3 min (major enantiomer), 55.0 min (minor enantiomer): 80% ee; cis-4d-Et: retention times 43.2 min (minor enantiomer), 52.0 min (major enantiomer): 78% ee. The absolute configurations were assigned in analogy to amide 4a-Et.

Racemic conjugate addition was performed as follows: CuCl (24.8 mg, 251 µmol) was suspended in THF (1 mL) and cooled to −30 °C, and EtMgBr (172 µL, 375 µmol, 2.18 M in Et₂O) was added dropwise. The reaction mixture was stirred for 15 min, a solution of ketimine 1d (65.8 mg, 250 µmol) in THF (1 mL) was added dropwise, and the reaction mixture was stirred for 16 h.
at −30 °C. Workup and hydrogenation were performed as described in GP 3 and GP 4 to yield 20 mg (27%) of the racemic amide 4d-Et.

**N-[(1S,5S)-2,2-Dimethyl-5-ethylcyclohexyl]-4-methylbenzenesulfonamide (4e-Et)**

Conjugate addition according to GP 3 using ketimine 1e (138.7 mg, 500.0 µmol), reaction time 16 h at −30 °C. The crude product was cooled to 0 °C, and a solution of tBuNH₂BH₃ (91.3 mg, 1.05 mmol) in CH₂Cl₂ (3 mL) was added. The reaction mixture was stirred for 16 h at 0 °C, poured into half-saturated aqueous NH₄Cl (2 mL), and extracted with MTBE (3 × 10 mL). The combined organic phases were washed with water (10 mL) and brine (10 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. Purification by flash column chromatography over silica gel furnished 118 mg (76%) of amide 4e-Et as a colorless solid with a dr (trans/cis) <3:97.

Rₜ 0.50, CH₂Cl₂. – mp 136 °C. – [α]D²⁰ +17.7 (c 1.0 in CHCl₃). – IR (neat) νmax/cm⁻¹ 3249, 2955, 2920, 2855, 1597, 1451, 1318, 1155, 1092, 812, 660, 573, 549. – δH (500 MHz; CDCl₃) 0.71 (t, J = 7.3 Hz, 3H, 2'-H), 0.76 (s, 3H, 2''-H), 0.79 (s, 3H, 1''-H), 0.84-0.96 (m, 2H, 3-H, 6-H), 1.02-1.21 (m, 4H, 4-H, 5-H, 1'-H), 1.39-1.44 (m, 3H, 3-H, 4-H, 6-H), 2.41 (s, 3H, ArCH₃), 2.90 (ddd, J = 12.2, 9.5, 4.0 Hz, 1H, 1-H), 4.39 (d, J = 9.5 Hz, 1H, NH), 7.28 (m, 2H, Ar-H), 7.76 (m, 2H, Ar-H). – δC (125 MHz; CDCl₃) 11.3 (C-2'), 18.7 (C-2''), 21.6 (ArCH₃), 27.8 (C-3), 29.32 (C-1'), 29.34 (C-1''), 34.6 (C-2), 36.2 (C-6), 38.5 (C-5), 40.1 (C-4), 60.9 (C-1), 127.2 (C-Ar), 129.6 (C-Ar), 138.6 (C-Ar), 143.2 (C-Ar). – HRMS (ESI) m/z calcd for C₁₇H₂₇NO₂SNa [M+Na]⁺: 332.1655; found 332.1652. – The enantiomeric excess was measured by HPLC, method D, retention times 139 min (minor enantiomer), 149 min (major enantiomer): 91% ee. The absolute configuration was assigned in analogy to amide 4a-Et.
Racemic conjugate addition was performed as follows: CuCl (19.8 mg, 200 μmol) was suspended in THF (1 mL) and cooled to −30 °C, and EtMgBr (138 μL, 301 μmol, 2.18 M in Et2O) was added dropwise. The reaction mixture was stirred for 15 min, a solution of ketimine 1e (55.5 mg, 200 μmol) in THF (1 mL) was added dropwise, and the reaction mixture was stirred for 1 h at −30 °C. Workup and hydrogenation were performed according to the preparation of enantiomerically enriched 4e-Et using tBuNH2-BH3 (36.5 mg, 420 μmol). Purification by column chromatography yielded 39 mg (63%) of the racemic amide 4e-Et.

\[ \text{N-[(1R,5S)-3,3-Dimethyl-5-ethylcyclohexyl]-4-methylbenzenesulfonamide (4f-Et)} \]

Preparation according to GP 3 and GP 4 using ketimine 1f (139 mg, 501 μmol), reaction time 1 h at −30 °C, yielded 129 mg (83%) of amide 4f-Et as a colorless solid with a dr (trans/cis) >97:3.

\[ R_f 0.39, \text{pentane/EtOAc 10:1. } \] 
\[ mp 82 °C. \] 
\[ [\alpha]_D^{20} -5.8 (c 1.0 \text{ in CHCl}_3). \] 
\[ \text{IR (neat) } \nu_{\max}/\text{cm}^{-1} 3255, 2957, 2918, 2873, 1347, 1304, 1152, 1120, 773, 666, 597, 527, 498. \] 
\[ \delta_H (500 \text{ MHz; CDCl}_3) 0.72-0.75 (m, 1H, 4-H), 0.76 (t, J = 7.4 Hz, 3H, 2'-H), 0.82 (s, 3H, 2''-H), 0.95 (m, 1H, 6-H), 0.93 (s, 3H, 1''-H), 1.12 (m, 2H, 1'-H), 1.23 (dd, J = 14.2, 4.6 Hz, 1H, 2-H), 1.36-1.46 (m, 3H, 2-H, 4-H, 5-H), 1.57-1.64 (m, 1H, 6-H), 2.41 (s, 3H, ArCH3), 3.50 (m, 1H, 1-H), 4.74 (d, J = 6.2 Hz, 1H, NH), 7.29 (m, 2H, Ar-H), 7.76 (m, 2H, Ar-H). \] 
\[ \delta_C (125 \text{ MHz; CDCl}_3) 11.4 (C-2’), 21.6 (ArCH3), 28.5 (C-1”), 29.4 (C-1’), 30.3 (C-5), 30.8 (C-3), 33.7 (C-2”), 37.1 (C-6), 43.3 (C-2), 45.2 (C-4), 49.8 (C-1), 127.3 (C-Ar), 129.7 (C-Ar), 137.9 (C-Ar), 143.3 (C-Ar). \] 
\[ \text{HRMS (ESI) } m/z \text{ calcd for } C_{17}H_{28}NO_{2}S [M+H]^+: 310.1835; \text{ found 310.1836.} \] 
\[ \text{The enantiomeric excess was measured by HPLC, method E, retention times 71.2 min (major enantiomer), 76.5 min (minor enantiomer): 94% ee. The absolute configuration was assigned in analogy to amide 4a-Et.} \]
Racemic conjugate addition was performed as follows: Ketimine 1f (139 mg, 501 \( \mu \)mol) and CuCl (49.5 mg, 500 \( \mu \)mol) were dissolved in Et\(_2\)O (2 mL) and cooled to –30 °C. EtMgBr (344 \( \mu \)L, 750 \( \mu \)mol, 2.18 M in Et\(_2\)O) was added dropwise, and the reaction mixture was stirred for 1 h at –30 °C. Workup and hydrogenation were performed according to the preparation of enantio-merically enriched 4f-Et, and an analytical sample of the racemic compound was obtained by repeated column chromatography.

\( N\)-[(1R,3R)-3-Ethyl-3-methylcyclohexyl]-4-methylbenzenesulfonamide (4g-Et)

Conjugate addition according to GP 3 using ketimine 1g (131.7 mg, 500 \( \mu \)mol), CuTC (9.55 mg, 50.1 \( \mu \)mol), and ligand ent-L1 (32.4 mg, 60.0 \( \mu \)mol), reaction time 20 h at –15 °C. Hydrogenation according to GP 4 with RuCl\((p\text{-cymene})/[(S,S)-Ts-DPEN]\) and column chromatography furnished 133 mg of 4g-Et with minor impurities from unreacted ketimine 1g. After repeated column chromatography, 80 mg (54\%) of amide 4g-Et were obtained as a colorless oil. – dr (trans/cis) before chromatography: 82:18, after repeated chromatography: 81:19.

\( R_f \) 0.33, pentane/EtOAc 5:1. – mp 55-57 °C. – IR (neat) \( \nu_{\text{max}}/\text{cm}^{-1} \) 3247, 2963, 2929, 2865, 1447, 1319, 1164, 811, 659, 569, 548. – \( \delta_H \) (500 MHz; CDCl\(_3\), signals of cis-4g-Et marked with “#”) 0.64 (t, \( J = 7.5 \) Hz, 3H, 2'-H), 0.72 (t, \( J = 7.6 \) Hz, 3H, 2'-H#), 0.75 (s, 3H, 1'-H), 0.85 (t, \( J = 12.4 \) Hz, 1H, 2-H), 0.89-1.01 (m, 2H, 5-H, 6-H), 1.11-1.26 (m, 2H, 1'-H), 1.32-1.57 (m, 4H, 2-H, 5-H, 4-H), 1.81 (m, 1H, 6-H), 2.42 (s, 3H, ArCH\(_3\)), 3.18 (m, 1H, 1-H), 3.27 (m, 1H, 1-H#), 4.68 (d, \( J = 8.1 \) Hz, 1H, NH), 4.71 (d, \( J = 7.7 \) Hz, 1H, NH), 7.28 (m, 2H, Ar-H), 7.76 (m, 2H, Ar-H), – \( \delta_C \) (125 MHz; CDCl\(_3\), signals of cis-4g-Et marked with “#”) 7.5 (C-2#), 7.7 (C-2'), 20.8 (C-4), 21.2 (C-4#), 21.4
(C-1”,#), 21.6 (ArCH₃), 28.3 (C-1’), 28.6 (C-1”), 34.18 (C-6), 34.24 (C-3), 34.4 (C-3#), 34.6 (C-6#), 35.9 (C-5#), 36.3 (C-5), 38.1 (C-1’#), 44.6 (C-2), 44.9 (C-2#), 49.6 (C-1), 50.2 (C-1#), 127.05 (C-Ar#), 127.07 (C-Ar), 129.7 (C-Ar), 138.6 (C-Ar), 138.7 (C-Ar#) 143.2 (C-Ar). – HRMS (ESI) m/z calcld for C₁₆H₂₅NO₂SNa [M+Na]+: 318.1498; found 318.1499. – The enantiomeric excesses were measured by HPLC, method B; trans-4g-Et: retention times 52.9 min (minor enantiomer), 59.9 min (major enantiomer): 94% ee; cis-4g-Et: retention times 55.4 min (major enantiomer), 65.1 min (minor enantiomer): 19% ee. The absolute configurations were assigned in analogy to amide 4a-Et.

Racemic conjugate addition was performed as follows: Ketimine 1g (65.8 mg, 250 μmol) and CuCl (18.6 mg, 188 μmol) were dissolved in Et₂O (2 mL) and cooled to –15 °C. EtMgBr (172 μL, 375 μmol, 2.18 M in Et₂O) was added dropwise, and the reaction mixture was stirred for 16 h at –30 °C. Workup was performed according to GP 3. Hydrogenation according to GP 4 with racemic RuCl(p-cymene)[Ts-DPEN] (rac-3, 7.95 mg, 12.5 μmol) and a 5:2 mixture of formic acid and triethyl amine (157 μL, 374 μmol) and repeated column chromatography yielded an analytical sample of the racemic amide 4g-Et.

(Z)-N-(1,3-Diphenylpent-1-enyl)-4-methylbenzenesulfonamide (2h-Et)

Preparation according to GP 3 from ketimine 1h (90.4 mg, 250 μmol), CuTC (0.96 mg, 5.0 μmol), ligand L1 (5.40 mg, 10.0 μmol), and ZnEt₂ (0.25 mL, 0.38 mmol, 1.5 M in toluene) in toluene (2 mL), reaction time 2.5 h at –30 °C. The crude product was purified by column chromatography, and 67 mg (68%) of enamide 2h-Et were obtained as a colorless solid.
$R_f$ 0.57, CH$_2$Cl$_2$. – mp 144 °C. – $[\alpha]_D^{20} -39.3$ (c 1.0 in CHCl$_3$). – IR (neat) $v_{\text{max/cm}^{-1}}$ 3279, 2964, 2927, 1597, 1387, 1166, 688. – $\delta_1$ (500 MHz; CDCl$_3$) 0.66 (t, $J = 7.4$ Hz, 3H, 5-H), 1.41-1.49 (m, 1H, 4-H), 1.53-1.60 (m, 1H, 4-H), 2.37 (s, 3H, ArCH$_3$), 2.94 (dt, $J = 9.0$, 7.4 Hz, 1H, 3-H), 5.65 (dd, $J = 9.2$, 0.7 Hz, 1H, 2-H), 6.13 (s, 1H, NH), 6.99 (m, 2H, Ar-H), 7.17-7.19 (m, 3H, Ar-H), 7.22-7.26 (m, 5H, Ar-H), 7.37-7.40 (m, 2H, Ar-H), 7.56 (m, 2H, Ar-H). – $\delta_C$ (125 MHz; CDCl$_3$) 11.9 (C-5), 21.6 (ArCH$_3$), 30.6 (C-4), 45.2 (C-3), 126.7 (C-Ar), 127.39 (C-Ar), 127.41 (C-Ar), 127.5 (C-Ar), 128.1 (C-Ar), 128.4 (C-Ar), 128.9 (C-2), 129.6 (C-Ar), 135.0 (C-1), 136.9 (C-Ar), 137.7 (C-Ar), 143.4 (C-Ar), 143.8 (C-Ar). – HRMS (EI) $m/z$ calcld for C$_{24}$H$_{25}$NO$_2$S [M$^+$]: 391.1606; found 391.1608. – The enantiomeric excess was measured by HPLC, method F, retention times 44.9 min (minor enantiomer), 52.2 min (major enantiomer): 72% ee. The absolute configuration was not determined.

Racemic preparation was performed as described above using racemic $O,O'$-$\text{di}(1,1'$-dinaphthyl-2,2'$-diyl)$-$N,N'$-di-$\text{iso}$-propylphosphoramidite (4.15 mg, 10.0 $\mu$mol) and yielded 96 mg (98%) of the racemic enamide 2h-$\text{Et}$. No purification was performed.

$N$-[(1S,3S,5R)-3-$\text{Ethyl}$-5-$\text{methylcyclohexyl}]$-4-$\text{methylbenzenesulfonamide}$ (4i-$\text{Et}$)

Conjugate addition according to GP 3 from ketimine (R)-11 (131.7 mg, 500 $\mu$mol), reaction time 1 h at -30 °C, furnished the conjugate addition product 2i-$\text{Et}$ with a dr (trans/cis) 48:52. Hydrogenation according to GP 4 yielded 53 mg (36%) of amide (1S,3S,5R)-4i-$\text{Et}$ as a colorless solid.

$R_f$ 0.60, pentane/EtOAc 5:1. – mp 116 °C. – $[\alpha]_D^{20} -6.2$ (c 1.0 in CHCl$_3$). – IR (neat) $v_{\text{max/cm}^{-1}}$ 3276, 2922, 1495, 1162, 1144, 1092, 817, 684, 553. – $\delta_1$ (500 MHz; CDCl$_3$) 0.44 (ddd, $J = 12.5$, 9.0, 7.4 Hz, 1H, 3-H), 1.41-1.49 (m, 1H, 4-H), 1.53-1.60 (m, 1H, 4-H), 2.37 (s, 3H, ArCH$_3$), 2.94 (dt, $J = 9.0$, 7.4 Hz, 1H, 3-H), 5.65 (dd, $J = 9.2$, 0.7 Hz, 1H, 2-H), 6.13 (s, 1H, NH), 6.99 (m, 2H, Ar-H), 7.17-7.19 (m, 3H, Ar-H), 7.22-7.26 (m, 5H, Ar-H), 7.37-7.40 (m, 2H, Ar-H), 7.56 (m, 2H, Ar-H). – $\delta_C$ (125 MHz; CDCl$_3$) 11.9 (C-5), 21.6 (ArCH$_3$), 30.6 (C-4), 45.2 (C-3), 126.7 (C-Ar), 127.39 (C-Ar), 127.41 (C-Ar), 127.5 (C-Ar), 128.1 (C-Ar), 128.4 (C-Ar), 128.9 (C-2), 129.6 (C-Ar), 135.0 (C-1), 136.9 (C-Ar), 137.7 (C-Ar), 143.4 (C-Ar), 143.8 (C-Ar). – HRMS (EI) $m/z$ calcld for C$_{24}$H$_{25}$NO$_2$S [M$^+$]: 391.1606; found 391.1608. – The enantiomeric excess was measured by HPLC, method F, retention times 44.9 min (minor enantiomer), 52.2 min (major enantiomer): 72% ee. The absolute configuration was not determined.
12.3, 12.1 Hz, 1H, 4-H), 0.75 (t, J = 7.5 Hz, 3H, 2'-H), 0.79 (d, J = 6.5 Hz, 3H, 1''-H), 0.92 (m, 2H, 2-H, 6-H), 1.04-1.17 (m, 2H, 1'-H), 1.24-1.33 (m, 1H, 3-H), 1.46-1.55 (m, 1H, 5-H), 1.57-1.64 (m, 2H, 2-H, 6-H), 1.65-1.68 (m, 1H, 4-H), 2.42 (s, 3H, ArCH₃), 3.60 (m, 1H, 1-H), 4.82 (d, J = 7.2 Hz, 1H, NH), 7.29 (m, 2H, H-Ar), 7.77 (m, 2H, H-Ar). – δC (125 MHz; CDCl₃) 11.2 (C-2'), 21.6 (ArCH₃), 22.5 (C-1''), 26.8 (C-5), 29.7 (C-1'), 33.4 (C-3), 36.9 (C-6), 39.6 (C-2), 41.0 (C-4), 50.1 (C-1), 127.2 (C-Ar), 129.7 (C-Ar), 138.3 (C-Ar), 143.3 (C-Ar). – HRMS (EI) m/z calcd for C₁₅H₂₃NO₂S [M]+: 295.1606; found 295.1601.

Additionally, 51 mg (35%) of N-[(3R,5R)-3-ethyl-5-methylcyclohexyl]-4-methylbenzenesulfonamide were obtained as an oil that crystallized in the freezer. This material is an epimeric mixture at C-1 in a 54:46 ratio.

Rf 0.48, pentane/EtOAc 5:1. – δH (500 MHz; CDCl₃, signals corresponding to single diastereomers are marked with “#”) 0.65-0.81 (m, 7H), 0.86 (d, J = 7.3 Hz, 3H#), 0.91-0.98 (m, 1H), 1.08-1.26 (m, 3H), 1.34-1.62 (m, 4H), 1.82 (m, 1H), 1.98 (m, 1H#), 2.42 (s, 3H), 3.22 (m, 1H#), 3.31 (m, 1H#), 4.59 (m, 1H), 7.29 (m, 2H), 7.76 (m, 2H). – δC (125 MHz; CDCl₃) 11.4, 12.4, 18.6, 21.6, 22.5, 24.8, 26.5, 27.9, 29.7, 32.9, 35.4, 37.0, 37.3, 37.6, 39.7, 41.0, 43.3, 49.0, 127.1, 129.7, 138.6, 138.7, 143.2.

N-[(1S,3S)-3-Ethylcyclohexyl]-tert-butylsulfonamide (6a-Et)

Conjugate addition according to GP 3 using ketimine 5a (53.8 mg, 250 μmol), CuTC (0.96 mg, 5.0 μmol), ligand L1 (5.40 mg, 10.0 μmol), and ZnEt₂ (0.25 mL, 0.38 mmol, 1.5 M in toluene) in toluene (2mL), reaction time 20 h at −30 °C. Hydrogenation according to GP 4 with racemic RuCl(p-cymene)[Ts-DPEN] (rac-3, 7.95 mg, 12.5 μmol) and a 5:2 mixture of formic acid and triethyl amine (157 μL, 374 μmol) yielded 37 mg (60%) of amide 6a-Et as a colorless oil that crystallized in the freezer. – dr (trans/cis) >97:3.

Rf 0.30, CH₂Cl₂. – mp 54 °C. – [α]D²⁰ +1.3 (c 1.0 in CHCl₃). – IR (neat) νmax/cm⁻¹ 3290, 2958, 2927, 2873, 1478, 1294, 1124, 677, 514. – δH (500 MHz; CDCl₃) 0.87 (t, J = 7.4 Hz, 3H, 2'-H), 0.97-1.05 (m, 1H, 5-H), 1.21-1.27 (m, 2H, 1'-H), 1.38-1.47 (m, 12H, 2-H, 3-H, 4-H, C(CH₃)₃), 1.56-1.65 (m, 4H, 4-H, 5-H, 6-H), 1.69-1.74 (m, 1H, 2-H), 3.67 (m, 1H, 1-H), 4.16 (d, J = 9.3 Hz, 1H, NH). – δC (125 MHz; CDCl₃) 11.6 (C-2'), 20.6 (C-4), 24.5 (C(CH₃)₃), 28.3 (C-1'), 31.0 (C-5), 33.3 (C-6), 34.2 (C-3), 38.8 (C-2), 50.7 (C-1), 59.7 (C(CH₃)₃). – HRMS (ESI) m/z calcd for C₁₃H₂₃NO₂SNa [M+Na]+: 270.1498; found 270.1497. – The enantiomeric excess was measured by GC, method B, retention times 41.3 min (major enantiomer), 41.8 min (minor enantiomer): 95% ee. The absolute configuration was assigned in analogy to amide 4a-Et.
Racemic conjugate addition was performed as follows: CuCl (24.8 mg, 251 µmol) was suspended in THF (1 mL) and cooled to –30 °C, then EtMgBr (172 µL, 375 µmol, 2.18 M in Et2O) was added dropwise. The reaction mixture was stirred for 15 min, a solution of ketimine 5a (53.8 mg, 250 µmol) in THF (1 mL) was added dropwise, and the reaction mixture was stirred for 1 h at –30 °C. Workup was performed according to GP 3. Hydrogenation according to GP 4 with racemic RuCl(p-cymene)[Ts-DPEN] (rac-3, 7.95 mg, 12.5 µmol) and a 5:2 mixture of formic acid and triethyl amine (157 µL, 374 µmol) yielded 13 mg (21%) of the racemic amide 6a-Et.

\[ \text{N-[(R,3S)-3-Ethylcyclopentyl]-} \text{tert-butylation} \text{onamid} \text{e (6b-Et)} \]

Conjugate addition according to GP 3 using ketimine 5b (50.3 mg, 250 µmol), CuTC (0.96 mg, 5.0 µmol), ligand L1 (5.40 mg, 10.0 µmol), and ZnEt2 (0.25 mL, 0.38 mmol, 1.5 M in toluene) in toluene (2 mL), reaction time 20 h at –30 °C. Hydrogenation according to GP 4 with RuCl(p-cymene)[(S,S)-Ts-DPEN] (rac-3, 7.95 mg, 12.5 µmol) and a 5:2 mixture of formic acid and triethyl amine (157 µL, 374 µmol) yielded 42 mg (72%) of amide 6b-Et as a colorless oil that crystallized in the freezer. – dr (trans/cis) before chromatography: 23:77, after chromatography: 23:77.

\[ R_1 0.15, \ CH_2Cl_2, \ mp 47–49 °C. \ – [\alpha]_D^{20} +1.3 \ (c 1.0 \ in \ CHCl_3). \ – \ IR (neat) \ \nu_{\text{max}}/\text{cm}^{-1}: 3289, 2958, 2931, 2873, 1477, 1297, 1116, 933, 667. \ – \ \delta_1 (500 \ MHz; CDCl_3, \ signals \ of \ the \ minor \ diastereomer \ marked \ with “#”) \ 0.86 (t, \ J = 7.4 \ Hz, 3H, 2'-H), 1.02 (ddd, \ J = 12.5, 9.7, 9.7 Hz, 1H, 2-H), 1.09 (ddd, \ J = 9.5, 8.1, 4.2 Hz, 1H, 2-H#), 1.23-1.35 (m, 3H, 1'-H, 4-H), 1.37 (s, 9H, C(CH3)3), 1.44-1.54 (m, 1H, 5-H), 1.59 (dt, \ J = 13.4, 7.7 Hz, 1H, 2-H#), 1.67-1.78 (m, 2H, 3-H, 4-H), 1.88 (m, 2H, 3-H#), 1.98-2.05 (m, 1H, 5-H), 2.07-2.13 (m, 1H, 5-H#), 2.25 (ddd, \ J = 12.5, 6.8, 6.8 Hz, 1H, 2-H), 3.75 (m, 1H, 1-H), 3.83 (m, 1H, 1-H#), 4.09 (d, \ J = 9.2 Hz, 1H, NH), 4.14 (d, \ J = 9.2 Hz, 1H, NH#). \ – \ \delta_2 (125 \ MHz; CDCl_3, \ signals \ of \ the \ minor \ diastereomer \ marked \ with “#”) \ 12.8 \ (C-2'), 24.5 \ (C(CH3)3), 29.1 \ (C-1'), 29.3 \ (C-1'), 29.7 \ (C-4), 30.6 \ (C-4#), 33.9 \ (C-5), 35.1 \ (C-5#), 39.4 \ (C-3#), 39.8 \ (C-3), 40.7 \ (C-2'), 41.8 \ (C-2), 56.1 \ (C-1'), 56.4 \ (C-1), 59.61 \ (C(CH3)3), 59.63 \ (C(CH3)3#). \ –
HRMS (ESI) m/z calcd for C_{11}H_{23}NO_{2}SNa [M+Na]^+: 256.1342; found 256.1339. The enantiomeric excess was measured by GC, method B, retention times 46.2 min (major enantiomer), 47.1 min (minor enantiomer): 69% ee. Enantiomers of the minor diastereomer could not be separated; the absolute configuration was assigned in analogy to amide 4a-Et.

Racemic conjugate addition was performed as described above using racemic O,O’-(1,1’-dinaphthyl-2,2’-diyl)-N,N-di-iso-propylphosphoramidite (4.15 mg, 10.0 μmol). The crude conjugate addition product was dissolved in EtOH (2 mL), NaBH₄ (94.5 mg, 2.50 mmol) was added, and the reaction mixture was stirred for 16 h at rt. The reaction mixture was then poured into saturated aqueous NH₄Cl (10 mL), extracted with CH₂Cl₂ (3 × 10 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. Column chromatography over silica gel yielded 17 mg (29%) of the racemic amide 6b-Et.

N-[1S,3S]-3-Ethylcycloheptyl]-tert-butylsulfonamide (6c-Et)

Conjugate addition according to GP 3 using ketimine 5c (57.3 mg, 250 μmol), CuTC (0.96 mg, 5.0 μmol), ligand L1 (5.40 mg, 10.0 μmol), and ZnEt₂ (0.25 mL, 0.38 mmol, 1.5 M in toluene) in toluene (2 mL), reaction time 16 h at –30 °C.

Hydrogenation according to GP 4 with racemic RuCl(p-cymene)[Ts-DPEN] (rac-3, 7.95 mg, 12.5 μmol) and a 5:2 mixture of formic acid and triethyl amine (157 μL, 374 μmol) yielded 43 mg (66%) of amide 6c-Et as a colorless oil that crystallized in the freezer. – dr (trans/cis) before chromatography: 96:4, after chromatography: 97:3.

Rₜ 0.17, pentane/EtOAc 15:1. – mp 35 °C. – [α]_D²⁰^{20} = −9.2 (c 1.0 in CHCl₃). – IR (neat) ν_max/cm⁻¹ 3268, 2921, 2855, 1440, 1306, 1125, 1048, 666. – δ_H (500 MHz; CDCl₃) 0.88 (t, J = 7.4 Hz, 3H, 2’-H), 1.09-1.17 (m, 1H, 4-H), 1.24-1.46 (m, 14H, 1’-H, 3-H, 5-H, 6-H, C(CH₃)₃), 1.53-1.60 (m, 1H, 7-H), 1.65-1.82 (m, 5H, 2-H, 4-H, 5-H, 6-H), 2.01 (m, 1H, 7-H), 3.62 (m, 1H, 1-H), 3.99 (d, J = 9.8 Hz, 1H, NH). – δ_C (125 MHz; CDCl₃) 11.9 (C-2’), 24.4 (C(CH₃)₃), 25.5 (C-5), 28.3 (C-6),
30.5 (C-1'), 34.4 (C-4), 36.2 (C-3), 37.3 (C-7), 42.1 (C-2), 54.2 (C-1), 59.7 (C(CH₃)₃). – HRMS (ESI) m/z calcd for C₁₃H₂₇NO₂SNa [M+Na]⁺: 284.1655; found 284.1651. – The enantiomeric excess was measured by GC, method C, retention times 66.7 min (major enantiomer), 67.1 min (minor enantiomer): ~92% ee. The absolute configuration was assigned in analogy to amide 4a-Et.

Racemic preparation was performed as described above using racemic O,O'- (1,1'-dinaphthyl-2,2'-diyl)-N,N-di-iso-propylphosphoramidite (4.15 mg, 10.0 μmol) and yielded 30 mg (46%) of the racemic amide 6c-Et.

N-Diphenylphosphinoyl-(1S*,3S*)-3-ethylcyclohexylamide (8a-Et)

Conjugate addition according to GP 3 using ketimine 7a (73.8 mg, 250 μmol), CuTC (0.96 mg, 5.0 μmol), ligand L1 (5.40 mg, 10.0 μmol), and ZnEt₂ (0.25 mL, 0.38 mmol, 1.5 mL in toluene) in toluene (2 mL), reaction time 20 h at –30 °C. The crude product was dissolved in THF (2.5 mL), and L-Selectride® (0.55 mL, 0.55 mmol, 1.0 mL in THF) was added. The solution was stirred for 2.5 h and cooled to 0 °C, and H₂O (0.5 mL), aqueous NaOH (0.1 mL, 15 w/w), and H₂O₂ (0.1 mL, 30 w/w in H₂O) were added subsequently. The mixture was stirred for 0.5 h at 0 °C and poured onto a mixture of H₂O (10 mL) and MTBE (10 mL). The organic phase was separated, and the aqueous phase was extracted with MTBE (2 × 10 mL). The combined organic phases were washed with brine (10 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. Purification by flash column chromatography over silica gel yielded 51 mg (62%) of amide 8a-Et as a colorless solid. – dr (trans/cis) >97:3.

Rₚ 0.35, CH₂Cl₂/THF 85:15. – mp 117-118°C. – IR (neat) νmax/cm⁻¹ 3199, 2924, 1437, 1186, 1109, 748, 721, 693, 555, 526. – δH (500 MHz; CDCl₃) 0.83 (t, J = 7.4 Hz, 3H, 2'-H), 0.95-1.02 (m, 1H, 4-H), 1.15-1.24 (m, 2H, 1'-H), 1.30-1.36 (m, 1H, 2-H), 1.42-1.74 (m, 7H, 2-H, 3-H, 4-H, 5-H, 6-H), 3.44 (m, 1H, 1-H), 7.42-7.46 (m, 4H, Ar-H), 7.47-7.51 (m, 2H, Ar-H), 7.88-7.94 (m, 4H, Ar-H). – δC (125 MHz; CDCl₃) 11.6 (C-2'), 20.5 (C-5), 28.5 (C-1'), 31.2 (C-4), 34.0 (C-6), 34.1
(C-3), 39.7 (d, J_{C,P} = 4.8 Hz, C-2), 46.9 (C-1), 128.6 (d, J_{C,P} = 12.5 Hz, C-Ar), 131.9 (C-Ar), 132.2 (d, J_{C,P} = 9.5 Hz, C-Ar), 132.4 (d, J_{C,P} = 9.4 Hz, C-Ar). – HRMS (ESI) m/z calcd for C_{20}H_{26}NOPNa [M+Na]^+: 350.1644; found 350.1633. – The enantiomeric excess was measured by HPLC, method G, retention times 18.7 min (first enantiomer), 20.0 min (second enantiomer): 0% ee.

Racemic preparation was performed as described above using racemic O,O’-(1,1’-dinaphthyl-2,2’-diyl)-N,N-di-iso-propylphosphoramidite (4.15 mg, 10.0 µmol) and yielded 44 mg (54%) of the racemic amide 8a-Et.

tert-Butyl-(1S,3S)-3-ethylcyclohexylcarbamat (9a-Et)

A solution of amide 4a-Et (84 mg, 0.30 mmol) in CH$_3$CN (1 mL) was treated with di-tert-butyl dicarbonate (97.7 mg, 448 µmol) and 4-(dimethylamino)pyridine (3.65 mg, 29.9 µmol) and stirred for 1 h at rt. The reaction mixture was poured onto MTBE (5 mL), washed subsequently with saturated aqueous NH$_4$Cl (5 mL), saturated aqueous NaHCO$_3$ (5 mL), and brine (5 mL), dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The residue was dissolved in MeOH (4 mL), Mg powder (36.3 mg, 1.49 mmol) was added, and the suspension was stirred at rt under ultrasonication. After 48 min, the suspension was filtered through a pad of celite, and the solvent was removed under reduced pressure. Purification by flash column chromatography over silica gel furnished 57 mg (84%) of carbamate 9a-Et as a colorless solid.

$R_f$ 0.58, CH$_2$Cl$_2$. – mp 45 °C. – [α]$_D^{20}$ +2.5 (c 1.0 in CHCl$_3$). – IR (neat) $\nu_{max}$/cm$^{-1}$ 3369, 2924, 1681, 1517, 1162, 1047, 1020, 609. – $\delta_{H}$ (500 MHz; CDCl$_3$) 0.84 (t, J = 7.4 Hz, 3H, 2’-H), 0.96-1.03 (m, 1H, 4-H), 1.20-1.39 (m, 6H, 1’-H, 2-H, 3-H, 5-H, 6-H), 1.43 (s, 9H, C(CH$_3$)$_3$), 1.51-1.58
(m, 2H, 5-H, 6-H), 1.60-1.66 (m, 2H, 2-H, 4-H), 3.80, (m, 1H, 1-H), 4.63 (bs, 1H, NH). – δC (125 MHz; CDCl₃) 11.6 (C-2'), 20.7 (C-5), 28.6 (C(CH₃)₃, C-1'), 31.4 (C-4), 31.5 (C-6), 34.3 (C-3), 37.2 (C-2), 45.9 (C-1'), 79.0 (C(CH₃)₃), 155.3 (CO). – HRMS (ESI) m/z calcd for C₁₃H₂₅NO₂Na [M+Na]⁺: 250.1778; found 250.1780.
2) Monitoring of the 1,4-Addition by Continuous IR Detection

A 10 mL three-necked flask, equipped with the probe of a Mettler-Toledo ReactIR® device, was charged with a mixture of copper(I)-thiophene-2-carboxylate (3.82 mg, 20.0 µmol), ligand L1 (21.6 mg, 40.0 µmol), and ketimine 1a (249 mg, 0.999 mmol). Toluene (8 mL) was added, and the solution was stirred for 0.5 h at rt and then cooled to −30 °C. ZnEt₂ (1.0 mL, 1.5 mmol, 1.5 M in toluene) was added rapidly, and simultaneously, data collection was started (t = 0 min). Then, the resulting yellow solution was stirred at −30 °C for 24 min.

Data analysis was performed using the decreasing IR band at 1320 cm⁻¹ to determine conversion and the increasing IR band at 1129 cm⁻¹ to determine product formation. Raw data is plotted in Fig. 1, while Fig. 2 gives an overview of all IR absorptions within the monitored reaction time.

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**Figure 1:** Monitoring of the 1,4-addition by continuous IR detection, sampling rate >5 Hz.

**Figure 2:** Overview of all IR band intensities over time.
3) $^1$H and $^{13}$C NMR spectra
cis-4a-Et
$4d$-Et, dr (trans/cis) 64:36
4g-Et, dr (trans/cis) 71:29
(1S,3S,5R)-4i-Et
(3R,5R)-4i-Et
6b-Et

dr (trans/cis) 23:77
39
4) References