Organocatalytic asymmetric direct vinylogous Michael addition of \( \alpha,\beta \)-unsaturated \( \gamma \)-butyrolactam to nitroolefins

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SUPPORTING INFORMATION: PART A

General: Unless stated otherwise, all reactions were carried out with distilled and dried solvents under an atmosphere of \( \text{N}_2 \) or argon, oven (120 °C) dried glassware with standard vacuum line techniques. Organic solvents used for carrying out reactions were dried using standard methods. All work up and purification were carried out with reagent grade solvents in air. Thin-layer chromatography was performed using Merck silica gel 60 F\textsubscript{254} pre-coated plates (0.25 mm). Column chromatography was performed using silica gel (230-400 or 100-200 mesh). Infrared (FT-IR) spectra were recorded on a Perkin Elmer Spectrum BX spectrophotometer in cm\textsuperscript{-1} and the bands are characterized as broad (br), strong (s), medium (m), and weak (w). NMR spectra were recorded on Bruker Ultrashield spectrometer at 400MHz (\( ^1\text{H} \)) and 100 MHz (\( ^{13}\text{C} \)). Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as internal standard (CDCl\textsubscript{3}: \( \delta \) 7.26, CD\textsubscript{3}OD: \( \delta \) 3.31 for \( ^1\text{H-NMR} \) and CDCl\textsubscript{3}: \( \delta \) 77.16 for \( ^{13}\text{C NMR} \)). For \( ^1\text{H} \) NMR, data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz) and integration. High-resolution mass spectrometry was performed on Micromass Q-TOF Micro instrument. Optical rotations were measured on JASCO P-1020 polarimeter. Melting points were measured using ANALAB µ-Thermocals 10 melting point apparatus. All melting points were measured in open glass capillary and values are uncorrected. Enantiomeric ratios were determined by HPLC analysis using Daicel chiral columns (4.6 mm × 250 mm) in comparison with authentic racemic materials.
Preparation of N-Boc-α,β-unsaturated-γ-butyrolactam (1):

N-Boc-α,β-unsaturated-γ-butyrolactam 1 was prepared according to a modified literature procedure.¹

In a 500 mL round-bottom flask, barium carbonate (1.5 g, 7.6 mmol) and pyrrole (5 mL, 72 mmol) was taken in 300 mL of distilled water. A solution of 30% hydrogen peroxide (9 mL) was added and the reaction mixture was refluxed at 120 °C for 5h. The reaction mixture was then allowed to attain r.t. While cooling, lead dioxide was added to quench the remaining hydrogen peroxide till the effervescence cease. It was filtered through filter paper and concentrated under reduced pressure to obtain reddish yellow solid. Dioxane (50 mL) was added and filtered again through filter paper and washed with 50 mL dioxane. The filtrate was dried over anh. Na₂SO₄ and concentrated in vacuo to obtain reddish residue which was used for subsequent step without any further purification.

¹H-NMR (400 MHz, CDCl₃): δ 4.00-4.01 (m; 2H), 6.09-6.10 (m; 1H), 7.10-7.11 (m; 1H), 8.17 (br s; 1H);
¹³C-NMR (100 MHz, CDCl₃): δ 49.1, 127.6, 146.1, 175.7.
¹H-NMR and ¹³C-NMR data are in agreement with literature.²

In a 100 mL round-bottom flask, the residue (3.40 g, 40.92 mmol) and Boc₂O (8.93 g, 40.92 mmol) was taken in 20 mL of CH₃CN at r.t. DMAP (249.9 mg, 2.05 mmol) was added and the resulting brownish solution was stirred at r.t. for 2 h. The solvent was then evaporated in vacuo. The resulting residue was dissolved in 50 mL of EtOAc. Silica gel (3.4 g) was added and the resulting mixture was allowed to stir at r.t. for 20 min. It was filtered through filter paper and the filtrate was concentrated in vacuo to obtain dark brown solid which was purified by silica gel (100-200 mesh) column chromatography using 50% EtOAc in petroleum ether as eluent to obtain N-Boc-α,β-unsaturated-γ-butyrolactam 1 as yellow solid (6.37 g, 34.78 mmol; 48% yield over two steps).¹H-NMR (400MHz, CDCl₃): δ 1.53 (s; 9H), 4.33 (br t, J = 1.8 Hz; 2H), 6.13 (dt, J = 1.9, 6.1 Hz; 1H), 7.17 (dt, J = 2.0, 6.1 Hz; 1H); ¹³C-NMR (100 MHz, CDCl₃): δ 28.0, 51.6, 82.9, 127.8, 145.1, 149.5, 169.1. ¹H-NMR and ¹³C-NMR data are in agreement with literature.¹

Preparation of nitroolefins (2):

Nitroolefins 2a-o are prepared according to the literature procedure.³⁻⁴ The spectral data obtained are in accordance with those described in the literature.³⁻⁵
**Preparation of catalysts (III–VIII, IX, XII):**

**Cupreinidine (III) and 6'-Isobutoxy-cinchonine (IV):**

6'-Isobutoxy-cinchonine **IV** was prepared according to a modified literature procedure.⁶

In a dry 50 mL round-bottom flask, quinidine **I** (500 mg, 1.54 mmol) & sodium hydride (246 mg, 6.16 mmol) was taken under argon atmosphere with 10 mL DMF. Ethane thiol (0.44 mL, 6.16 mmol) was added dropwise over a period of 10 min at r.t. It was then allowed to stir at 100 °C for 24 h. The reaction mixture was cooled to r.t., sat. NH₄Cl solution was added and stirred at r.t. for 1 h. It was extracted with EtOAc (3 × 20 mL), the organic layer was dried over anh. Na₂SO₄ and concentrated in vacuo to obtain a yellowish oil which was purified by silica gel column chromatography using 100:5:2 CH₂Cl₂/MeOH/Et₃N as eluent to obtain cupreinidine (III) as a pale yellow solid (400 mg, 1.29 mmol; 84% yield). ¹H-NMR (400 MHz, CDCl₃): δ 0.87-0.89 (m; 1H), 1.27-1.38 (m; 2H), 1.69 (br s; 1H), 2.04 (s; 1H), 2.24-2.34 (m; 2H), 2.67 (br s; 1H), 2.87 (t, J = 10.8 Hz; 1H), 3.05 (s; 1H), 3.80-3.82 (m; 1H), 4.98-5.05 (m; 2H), 6.01-6.08 (m; 2H), 7.04 (br s; 2H), 7.30 (s; 1H), 7.42 (s; 1H), 7.57 (d, J = 4.3 Hz; 1H), 7.90 (d, J = 9.2 Hz; 1H), 8.61 (d, J = 4.4 Hz; 1H). The spectral data are consistent with those reported in the literature.⁷

In a dry 10 mL round-bottom flask equipped with reflux condenser, cesium carbonate (142 mg, 0.44 mmol) was taken and dried for 2 h in vacuo at 150 °C. It was then cooled to r.t. under argon atmosphere and cupreinidine (III) (90 mg, 0.29 mmol) was added followed by the addition of 0.9 mL NMP. It was allowed to stir at r.t. for 5 min followed by the addition of isobutyl bromide (47 μL, 0.44 mmol). It was allowed to stir at 130 °C for 26 h and the solvent was removed. The residue was cooled to r.t., and 5 mL CHCl₃ and 5 mL water was added. The organic phase was collected and the aqueous phase was extracted with CHCl₃ (3 × 5 mL). The collective organic layer was dried over anh. Na₂SO₄ and concentrated in vacuo to obtain a reddish liquid which was purified by silica gel column chromatography using 100:5:2 CH₂Cl₂/MeOH/NH₄OH as eluent to obtain 6'-isobutoxy-cinchonine (IV) as a off-white solid (76 mg, 0.21 mmol; 47% yield).
$^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 1.01 (d, $J = 6.8$ Hz; 6H), 1.09-1.16 (m; 1H), 1.25 (s; 1H), 1.45-1.52 (m; 2H), 1.75 (br s; 1H), 2.01-2.11 (m; 2H), 2.23 (q, $J = 8.4$ Hz; 1H), 2.73-2.81 (m; 1H), 2.87-2.93 (m; 2H), 3.02-3.08 (m; 1H), 3.37 (dd, $J = 8.0$, 13.4 Hz; 1H), 3.72 (d, $J = 6.4$ Hz; 2H), 5.02-5.06 (m; 2H), 5.61 (d, $J = 3.8$ Hz; 1H), 5.98-6.07 (m; 1H), 7.14 (d, $J = 2.2$ Hz; 1H), 7.28 (dd, $J = 2.4$, 9.2 Hz; 1H), 7.50 (d, $J = 4.5$ Hz; 1H), 7.93 (d, $J = 9.2$ Hz; 1H), 8.59 (d, $J = 4.5$ Hz; 1H); $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 19.2, 21.1, 26.2, 28.2, 39.9, 49.5, 50.1, 59.6, 71.7, 74.6, 101.8, 114.6, 118.4, 121.8, 121.9, 126.5, 131.3, 140.4, 143.9, 147.3, 147.4, 157.3; HRMS (ESI$^+$): Calculated for C$_{23}$H$_{31}$N$_2$O$_2$ $^+$ ([M+H]$^+$): 367.2386, Found: 367.2387.

**Dihydroquinidine (V):**

Dihydroquinidine (V) was prepared according to the modified literature procedure.$^8$

In a hydrogenation vessel, quinidine (500 mg, 1.54 mmol) was taken and dissolved in 5 mL of 10% H$_2$SO$_4$. PdCl$_2$ (6 mg, 0.03 mmol) was added to it and it was stirred at r.t. under 4 atmosphere pressure for 4 h. The reaction mixture was filtered through a celite pad and washed with water. 10% aqueous NaOH solution was added to it until white precipitate formed. EtOAc (20 mL) was added and the organic layer was collected after two layers were separated. The aqueous layer was extracted with EtOAc and the collective organic layer was dried over anh. Na$_2$SO$_4$ and concentrated in vacuo to obtain a white solid which was purified by silica gel column chromatography using 100:5:1 CH$_2$Cl$_2$/MeOH/Et$_3$N as eluent to obtain dihydroquinidine (V) as a white solid (412 mg, 1.26 mmol; 82% yield).

$^1$H-NMR (400 MHz, CDCl$_3$): 0.84 (t, $J = 7.2$ Hz; 3H), 0.96-1.03 (m; 1H), 1.34-1.43 (m; 4H), 1.64 (br s; 1H), 1.96 (t, $J = 10.0$ Hz; 1H), 2.64-2.72 (m; 1H), 2.79-2.87 (m; 2H), 2.93-2.96 (m; 1H), 3.09-3.14 (m; 1H), 3.76 (s; 3H), 5.58 (d, $J = 2.5$ Hz; 1H), 7.12 (s; 1H), 7.20 (dd, $J = 2.0$, 9.2 Hz; 1H), 7.48 (d, $J = 4.4$ Hz; 1H), 7.85 (d, $J = 9.1$ Hz; 1H), 8.46 (d, $J = 4.5$ Hz; 1H); HRMS (ESI$^+$): Calculated for C$_{20}$H$_{27}$N$_2$O$_2$ $^+$ ([M+H]$^+$): 327.2073, Found: 327.2073. The
spectral data are consistent with those reported in the literature.9

9-Epiquinidine (VI):

9-Epiquinidine (VI) was prepared according to the literature procedure.10

In a dry 25 mL 2-neck round-bottom flask equipped with an argon inlet and a reflux condenser, quinidine I (200 mg, 0.616 mmol) was taken in 6 mL abs. THF. The solution was cooled to –15 °C and NEt3 (0.69 mL, 4.93 mmol) was added over 10 min. MsCl (72 μL, 0.924 mmol) was added and the resulting mixture was allowed to reflux at 75 °C for 46 h. The reaction mixture was then cooled to r.t. and 5 mL of water was added. It was extracted with Et2O (2 × 10 mL) and the combined ether layer was dried over anh. Na2SO4 and concentrated in vacuo to obtain a liquid which was purified by silica gel column chromatography using 100:2:1 CH2Cl2/MeOH/Et3N as eluent to obtain methanesulphoylquinidine as a colorless oil (62 mg, 0.154 mmol; 25% yield, 73% yield based on the recovered starting material). 1H-NMR (400 MHz, CDCl3): δ 0.85-0.94 (m; 1H), 1.52-1.58 (m; 2H), 1.67 (br s; 1H), 1.86 (br s; 1H), 1.94-2.00 (m; 1H), 2.28 (q, J = 8.0 Hz; 1H), 2.66-2.73 (m; 5H), 2.91 (d, J = 8.4 Hz; 2H), 3.33 (br s; 1H), 3.96 (s; 3H), 5.09-5.15 (m; 2H), 5.99-6.07 (m; 1H), 7.34-7.45 (m; 3H), 8.05 (d, J = 8.2 Hz; 1H), 8.79 (d, J = 4.3 Hz; 1H).

In a 10 mL round-bottom flask, methanesulphoylquinidine (62 mg, 0.154 mmol) was taken along with (+)-tartaric acid (24 mg, 0.16 mmol) in 1.5 mL water. The resulting mixture was refluxed at 107 °C for 1 h. The reaction mixture was then cooled to r.t. and 5 mL of sat. NaHCO3 was added. This was extracted with CHCl3 (2 × 10 mL) and the combined organic layer was dried over anh. Na2SO4 and concentrated in vacuo to obtain a yellow liquid which was purified by silica gel column chromatography using 100:2:1 CH2Cl2/MeOH/Et3N as eluent to obtain 9-epiquinidine (VI) as a white solid (49 mg, 0.151 mmol; 98% yield). 1H-NMR (400 MHz, CDCl3): δ 1.09-1.16 (m; 1H), 1.35-1.41 (m; 1H), 1.71-1.81 (m; 3H), 2.47-2.49 (m; 1H), 3.15-3.49 (m; 5H), 3.93 (s; 3H), 5.17-5.23 (m; 2H), 5.36 (d, J = 9.5 Hz; 1H), 5.81-5.89 (m; 1H), 7.36 (dd, J = 2.1, 9.2 Hz; 1H), 7.49 (d, J = 4.2 Hz; 1H), 7.57 (s; 1H), 8.01 (d, J = 9.2 Hz; 1H), 8.73 (d, J = 4.0 Hz; 1H).

The spectral data are consistent with those reported in the literature.11
β-Isocupreidine (VII):

β-Isocupreidine (VII) was prepared according to the literature procedure.12

In a dry 10 mL round-bottom flask, quinidine I (200 mg, 0.62 mmol) & KBr (738 mg, 6.2 mmol) was taken in 3 mL phosphoric acid and stirred at 100 °C for 10 day. The reaction mixture was cooled to r.t. and 25% KOH soln was added until pH~7-8. It was extracted with EtOAc (3 × 10 mL) and the collective EtOAc layer was dried over anh. Na₂SO₄, concentrated in vacuo to obtain a white solid which was purified by silica gel column chromatography using 100:5:1 CH₂Cl₂/MeOH/Et₃N as eluent to obtain β-isocupreidine (VII) as white solid (143 mg, 0.46 mmol; 75% yield).

**¹H-NMR (400 MHz, CDCl₃):** δ 1.02 (t, \( J = 7.4 \) Hz; 3H), 1.27-1.30 (m; 1H), 1.62-1.64 (m; 1H), 1.65-1.73 (m; 3H), 1.80-1.85 (m; 1H), 2.21-2.23 (m; 1H), 2.79 (d, \( J = 13.5 \) Hz; 1H), 2.97-3.04 (m; 1H), 3.09-3.14 (m; 1H), 3.73-3.76 (m; 2H), 5.93 (s; 1H), 7.29 (dd, \( J = 2.3, 9.2 \) Hz; 1H), 7.60 (d, \( J = 4.4 \) Hz; 1H), 7.66 (d, \( J = 1.9 \) Hz; 1H), 7.95 (d, \( J = 9.2 \) Hz; 1H), 8.69 (d, \( J = 4.4 \) Hz; 1H), 9.39 (br s; 1H); **¹³C-NMR (100 MHz, CDCl₃):** δ 7.2, 22.5, 22.9, 27.3, 32.7, 45.8, 50.1, 53.5, 56.4, 72.3, 104.9, 118.7, 122.3, 126.5, 131.4, 140.7, 143.1, 146.7, 156.7; **HRMS (ESI+):** Calculated for C₁₉H₂₂N₂O₂⁺ ([M+H]⁺): 311.1760, Found: 311.1765. The spectral data are consistent with those reported in the literature.12

β-Isoquinidine (VIII):

β-Isoquinidine (VIII) was prepared according to the literature procedure.12
In a dry 10 mL round-bottom flask, quinidine I (200 mg, 0.62 mmol) was taken in 2 mL of methanesulphonic acid and heated at 120 °C for 2 h. The reaction mixture was cooled to r.t. and 20% aqueous KOH solution was added until pH~10 and a white precipitate formed. It was extracted with CH₂Cl₂ (2 × 10 mL) and the collective organic layer was dried over anh. Na₂SO₄, concentrated in vacuo to obtain β-isoquinidine (VIII) as a white solid (191 mg, 0.59 mmol; 95% yield).

**¹H-NMR (400 MHz, CDCl₃):** δ 1.00 (t, J = 7.4 Hz; 3H), 1.23 (dd, J = 5.7, 12.2 Hz; 1H), 1.44-1.51 (m; 1H), 1.59-1.63 (m; 3H), 1.73 (dd, J = 6.6, 12.3 Hz; 1H), 2.10 (t, J = 4.4 Hz; 1H), 2.56-2.61 (m; 1H), 2.93-2.95 (m; 2H), 3.43-3.44 (m; 1H), 3.84-3.85 (m; 1H), 3.94 (s; 3H), 5.87 (s; 1H), 7.13 (s; 1H), 7.32 (d, J = 9.3 Hz; 1H), 7.68 (d, J = 4.2 Hz; 1H), 7.94-8.00 (m; 1H), 8.73 (d, J = 4.4 Hz; 1H); **¹³C-NMR (100 MHz, CDCl₃):** δ 7.3, 23.7, 24.5, 27.4, 32.9, 46.8, 54.9, 55.9, 56.2, 73.2, 77.2, 100.7, 119.4, 121.4, 126.5, 131.8, 143.2, 144.1, 147.7, 157.8; **HRMS (ESI+):** Calculated for C₂₀H₂₄N₂NaO₂⁺ ([M+Na]⁺): 325.1916, Found: 325.1914. The spectral data are consistent with those reported in the literature.¹²

(QD)₂PHAL (IX):

(QD)₂PHAL (IX) was prepared according to the literature procedure.¹³

In a 50 mL round-bottom flask, phthalic anhydride (2 g, 13.5 mmol) was taken in 17 mL EtOH. Hydrazine monohydrate (676 mg, 13.5 mmol) was added and the resulting mixture was refluxed at 85 °C for 1 h. During this time, a white precipitate formed. The reaction mixture was then allowed to attain r.t. The resulting white precipitate was filtered through filter paper and washed with petroleum ether. The product phthalhydrazide (2.10 g, 12.83 mmol; 85% yield) was used for subsequent step without further purification.
A 50 mL 2-neck round-bottom flask, equipped with a condenser and an argon inlet, was dried in vacuo with heating at 200 °C for 1 h. The setup was allowed to cool to r.t. under argon atmosphere. Phthalhydrazide (500 mg, 3.08 mmol) and phosphorous pentachloride (1.35 g, 6.48 mmol) was taken followed by addition of 1 drop of DMF. The argon inlet was replaced by a CaCl₂ guard tube. It was heated to 145 °C with vigorous stirring in which the solids melted to an orange solution which was heated at 145 °C for 4 h. The generated phosphorous oxychloride (colorless liquid) was distilled off and the brownish red residue was dissolved in 20 mL CH₂Cl₂. Alumina (3 g) was added and it was stirred at r.t. for 1 h. It was then filtered through a bed of alumina using sintered funnel. The filtrate was dried over anh. Na₂SO₄ and concentrated in vacuo to obtain 1,4- dichlorophthalazine as a yellowish white solid (559 mg, 3.30 mmol; 75% yield).

**¹H-NMR (400 MHz, CDCl₃):** 8.08-8.10 (m; 2H), 8.33-8.35 (m; 2H).

In a 50 mL 2-neck round-bottom flask equipped with a Dean-Stark apparatus and a condenser, 1,4-dichlorophthalazine (200 mg, 1.00 mmol), quinidine I (638.4 mg, 1.96 mmol) and K₂CO₃ (416.3 mg, 3 mmol) was taken under argon atmosphere. Abs. toluene (12 mL) was added and the reaction mixture was allowed to reflux at 140 °C for 2 h. It was then cooled to r.t. and KOH (169 mg, 3 mmol) was added. The reaction mixture was refluxed at 140 °C under argon atmosphere for 24 h. It was then cooled to r.t. and 10 mL distilled water was added to it followed by addition of 20 mL of EtOAc. The organic layer was collected and the aqueous layer was extracted with EtOAc. The combined organic layer was dried over anh. Na₂SO₄ and concentrated in vacuo to obtain yellowish solid. It was dissolved in EtOH and conc. H₂SO₄ (12.5 mg) in 8 mL EtOH was added dropwise over a period of 10 mins. It was kept at –20 °C for 2 h and the resulting white solid was filtered off and dissolved in water. Sat. NaHCO₃ solution was added until pH ~ 9. EtOAc (20 mL) was added and the organic layer was collected. Aquous layer was extracted with EtOAc. The combined organic layer was dried over anh. Na₂SO₄ and concentrated in vacuo to obtain (QD)₂PHAL (IX) as a white solid (310 mg, 0.40 mmol; 40% yield).

**¹H-NMR (400 MHz, CDCl₃):** δ 1.51-1.54 (m; 6H), 1.81 (br s; 2H), 2.06-2.11 (m; 2H), 2.21 (q, J = 7.9 Hz; 2H), 2.64-2.72 (m; 2H), 2.80-2.86 (m; 4H), 2.92-2.97 (m; 2H), 3.37-3.43 (m; 2H), 3.90 (s; 6H), 4.97 (d, J = 13.0 Hz; 4H), 5.89-5.98 (m; 2H), 7.03 (d, J = 5.8 Hz; 2H), 7.36 (dd, J = 1.9, 9.1 Hz; 2H), 7.41 (d, J = 4.5 Hz; 2H), 7.53-7.54 (m; 2H), 7.92-7.94 (m; 2H), 7.99 (d, J = 9.2 Hz; 2H), 8.33-8.35 (m; 2H), 8.63 (d, J = 4.4 Hz; 2H); **¹³C-NMR (100 MHz, CDCl₃):** 23.2, 26.5, 27.8, 39.7
49.5, 49.8, 55.6, 60.1, 76.1, 102.0, 114.6, 118.3, 121.8, 122.4, 123.0, 127.3, 131.5, 132.1, 140.3, 144.7, 144.9, 147.3, 156.4, 157.6; **HRMS (ESI+):** Calculated for C\(_{49}\)H\(_{50}\)N\(_6\)NaO\(_4\)\(^+\) ([M+Na\(^+\)]\(^+\)): 797.3791, Found: 797.3790. The spectral data are consistent with that reported in the literature.\(^{13}\)

6′-Neopentyloxy-dihydroquinine (XII):

In a 250 mL hydrogenation vessel, quinine X (2.0 g, 6.17 mmol) was taken and dissolved in 20 mL of 10% aqueous H\(_2\)SO\(_4\). PdCl\(_2\) (27 mg, 0.15 mmol) was added and the resulting solution was stirred under 4 atmosphere pressure at r.t. for 4 h. The resulting grey solution was filtered through a pad of celite and washed with water. The filtrate was made alkaline by addition of a solution of 10% aqueous NaOH until white precipitate formed. EtOAc (30 mL) was added and the organic layer was collected after separation of two layers. The aqueous phase was back extracted with EtOAc (2 × 15 mL); the combined organic layer was washed with brine, dried over anh. Na\(_2\)SO\(_4\) and concentrated in vacuo to obtain dihydroquinine (2.0 g, 6.12 mmol; 99% yield) as white solid which was used for subsequent step without further purification. **\(^1\)H-NMR (400 MHz, CDCl\(_3\)):** 0.75 (t, \(J = 7.4\) Hz; 3H), 1.15-1.19 (m; 2H), 1.35-1.37 (m; 3H), 1.68-1.72 (m; 3H), 2.31 (d, \(J = 13.3\) Hz; 1H), 2.54-2.59 (m; 1H), 2.96-3.01 (m; 2H), 3.44-3.51 (m; 1H), 3.83 (s; 3H), 5.50 (br s; 1H), 7.20-7.23 (m; 2H), 7.45 (d, \(J = 4.5\) Hz; 1H), 7.85 (d, \(J = 8.9\) Hz; 1H), 8.43 (d, \(J = 4.5\) Hz; 1H); **\(^{13}\)C-NMR (100 MHz, CDCl\(_3\)):** 12.0, 21.0, 25.4, 27.6, 28.1, 37.4, 43.3, 55.6, 58.5, 59.7, 71.5, 101.4, 118.5, 121.2, 126.5, 131.1, 143.8, 147.2, 148.4, 157.6.

In a dry 100 mL round-bottom flask, dihydroquinine (1 g, 3.06 mmol) and NaH (294 mg, 12.25 mmol) was taken in 20 mL of DMF. The resulting solution was stirred at r.t. for 10 min followed by addition of EtSH (0.9 mL, 12.25 mmol). The resulting mixture was allowed to stir at 110 °C for 32 h under argon atmosphere. The resulting mixture was then cooled to r.t. and quenched with sat. NH\(_4\)Cl. EtOAc (40 mL) was added and the organic layer was separated. The aqueous layer was extracted with EtOAc (2 × 15 mL) and the combined organic layer was
washed with brine, dried over anh. Na₂SO₄ and concentrated in vacuo to obtain dihydrocupreine as yellow solid (940 mg, 3.01 mmol; 98% yield) which was used for subsequent step without further purification. **¹H-NMR (400 MHz, MeOH-d₄):** 0.79 (t, J = 7.4 Hz; 3H), 1.21-1.27 (m; 2H), 1.35-1.41 (m; 1H), 1.53-1.59 (m; 2H), 1.81 (br s; 1H), 1.89-1.94 (m; 2H), 2.45-2.49 (m; 1H), 2.75-2.79 (m; 1H), 3.13-3.19 (m; 2H), 3.78-3.83 (m; 1H), 5.59 (s; 1H), 7.27-7.28 (m; 1H), 7.33 (d, J = 9.1 Hz; 1H), 7.63 (d, J = 4.5 Hz; 1H), 7.90 (d, J = 9.2 Hz; 1H), 8.59 (d, J = 4.5 Hz; 1H); **¹³C-NMR (100 MHz, MeOH-d₄):** 12.2, 20.9, 26.6, 28.2, 28.3, 38.1, 44.5, 59.0, 60.9, 71.5, 105.1, 119.9, 123.5, 128.3, 131.5, 143.9, 147.3, 149.2, 158.3.

In a dry 10 mL 2-neck round-bottom flask equipped with a condenser, Cs₂CO₃ (156 mg, 0.48 mmol) was taken and dried in vacuo at 150 °C for 4 h. The flask was then cooled to r.t. under argon atmosphere followed by addition of 1 mL of NMP. Dihydrocupreine (100 mg, 0.32 mmol) was added and the resulting mixture was allowed to stir at r.t. for 10 min. Neopentyl bromide (49 μL, 0.38 mmol) was added and the resulting mixture was stirred at 100 °C for 30 h under argon atmosphere. The solvent was distilled off and the residue was cooled to r.t. The residue was dissolved in CHCl₃ and washed with brine. The organic layer was dried over anh. Na₂SO₄ and concentrated in vacuo to obtain crude reddish liquid which was purified by silica gel column chromatography using 100:3:1 CH₂Cl₂/MeOH/Et₃N as eluent to obtain 6'-neopentyloxy-dihydroquinine XII as a reddish solid (50 mg, 0.13 mmol; 41% yield). **¹H-NMR (400 MHz, CDCl₃):** 0.77 (t, J = 7.3 Hz; 3H), 1.05 (s; 9H), 1.17-1.25 (m; 4H), 1.63-1.70 (m; 2H), 1.90-1.92 (m; 1H), 1.96-2.01 (m; 1H), 2.06-2.11 (m; 1H), 2.53-2.61 (m; 1H), 2.90-2.96 (m; 1H), 3.20 (t, J = 8.7 Hz; 1H), 3.31 (t, J = 11.0 Hz; 1H), 3.51 (d, J = 9.1 Hz; 1H), 3.62 (d, J = 8.9 Hz; 1H), 4.21 (br s; 1H), 6.08 (s; 1H), 6.88 (s; 1H), 7.05 (dd, J = 2.0, 9.2 Hz; 1H), 7.57 (d, J = 4.4 Hz; 1H), 7.68 (d, J = 9.0 Hz; 1H), 8.58 (d, J = 4.4 Hz; 1H); **¹³C-NMR (100 MHz, CDCl₃):** 11.6, 24.8, 26.7, 27.1, 31.8, 36.1, 43.8, 46.1, 57.3, 58.6, 59.9, 78.4, 100.4, 118.6, 122.2, 125.5, 131.1, 143.5, 145.0, 146.8, 157.7.
Optimization of ratio of the nucleophile and nitroalkene:

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<sup>a</sup> Time required for complete consumption of nitrostyrene.  
<sup>b</sup> Determined by 1H-NMR of crude reaction mixture.  
<sup>c</sup> Determined by chiral HPLC.

References: