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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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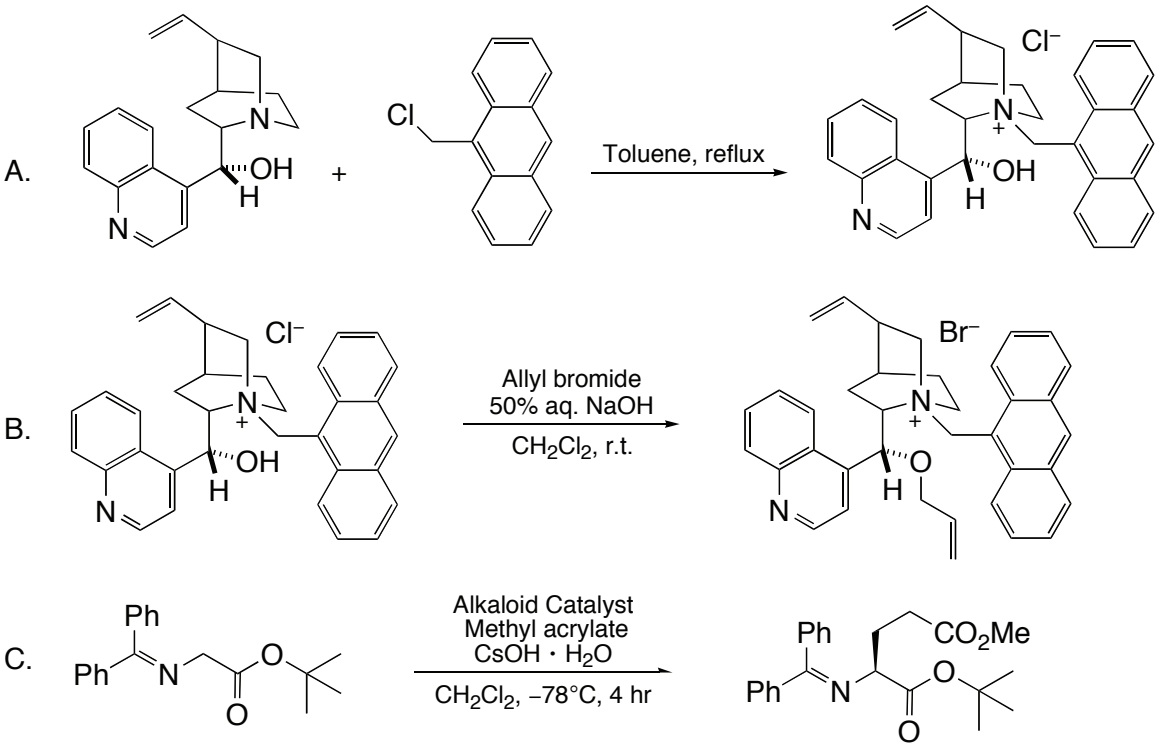
PREPARATION OF *O*-ALLYL-*N*-(9-ANTHRACENYLMETHYL)CINCHONIDINIUM BROMIDE AS A PHASE TRANSFER CATALYST FOR THE ENANTIOSELECTIVE ALKYLATION OF GLYCINE BENZOPHENONE IMINE *tert*-BUTYL ESTER: (4*S*)-2-(BENZHYDRYLIDENAMINO)PENTANEDIOIC ACID, 1-*tert*-BUTYL ESTER-5-METHYL ESTER

[[Cinchonanium, 1-(9-anthracenylmethyl)-9-(2-propenyloxy)-, bromide, (8*α*,9*R*)-and L-Glutamic acid, *N*-(diphenylmethylene)-, 1-(1,1-dimethylethyl) 5-methyl ester]]



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1. Procedure

A. N-(9-Anthracenylmethyl)cinchonidinium chloride (Note 1). A 2-L, three-necked flask, equipped with an overhead stirrer, reflux condenser and nitrogen inlet, is charged with 78.2 g (266 mmol) of cinchonidine (Note 2), 63.0 g (278 mmol) of 9-chloromethylanthracene (Note 3), and 800 mL of toluene (Note 4). The mixture is stirred and heated to reflux employing a bath temperature of ~130 °C for 3 h. Within 30 min all of the material dissolves, then the product begins to crystallize. At the end of the reflux period the mixture is cooled to ~30 °C and 800 mL of diethyl ether is added over 10 min. The slurry is stirred for 20 min, filtered through a coarse sintered glass, fritted funnel, washed with 250 mL of diethyl ether and dried at 50 °C under vacuum overnight to afford 144.4 g (235 mmol, 88%) of *N*-(9-anthracenylmethyl)cinchonidinium chloride as a crystalline, light yellow solid (Notes 1, 5), which is sufficiently pure for use in the next step.

B. O-Allyl-N-(9-Anthracenylmethyl)cinchonidinium bromide. A 1-L, three-necked flask, equipped with an overhead stirrer and nitrogen inlet, is charged with 49.5 g (80.7 mmol) of *N*-(9-anthracenylmethyl)cinchonidinium chloride-toluene solvate, 400 mL of methylene chloride (CH_2Cl_2), 25 mL of allyl bromide (35.0 g, 289 mmol) (Note 6) and 50 mL of 50% aqueous potassium hydroxide (Note 7). The mixture is stirred vigorously for 4 h, then diluted with 400 mL of water and stirred for 5 min. After separation of the phases, the organic phase is washed with a solution of 25 g of sodium bromide in 250 mL of water and dried over 50 g of sodium sulfate (Na_2SO_4). The solution is filtered using 50 mL of CH_2Cl_2 as a rinse, and 275 mL of ethyl ether is added over 15 min producing a heavy crystalline mass. After stirring for 1 h, the solids are collected by filtration, washed with 250 mL of 1:4 methylene chloride:ethyl ether and dried at 50 °C under vacuum for 1 h to afford 38.1 g (62.9 mmol, 78%) of *O*-allyl-*N*-(9-anthracenylmethyl)cinchonidinium bromide as a crystalline yellow solid (Note 8).

C. Enantioselective Reaction of N-(Diphenylmethylene)glycine tert-Butyl Ester with Methyl Acrylate – (4S)-2-(Benzhydrylidenamino) pentanedioic Acid, 1-tert-Butyl Ester-5-Methyl Ester. A flame-dried, 200-mL, three-necked flask, equipped with a large magnetic stirrer, 50 mL

addition funnel, septum and nitrogen inlet, is charged with 5.0 g (16.9 mmol) of *N*-(diphenylmethylene)glycine *tert*-butyl ester (Note 9), 0.95 g (1.7 mmol) of *O*-allyl-*N*-(9-anthracenylmethyl)cinchonidinium bromide and 40 mL of anhydrous CH_2Cl_2. The mixture is cooled in a dry ice-acetone bath to −78 °C and 29 g (170 mmol) of cesium hydroxide monohydrate ($CsOH·H_2O$) is added to the well-stirred mixture (Note 10). After stirring for 5 min, a solution of 5 mL of methyl acrylate (Note 11) in 10 mL of CH_2Cl_2 is added dropwise over 10 min through the addition funnel. The mixture is stirred vigorously for 3 h, at which point TLC analysis (Note 12) indicates complete reaction. The mixture is diluted with 150 mL of ethyl ether and 50 mL of water and the cooling bath is removed. The mixture is stirred for 5 min, transferred to a separatory funnel, and 650 mL of ethyl ether is added. The organic phase is washed twice with 200 mL of water and once with 50 mL of brine, dried over magnesium sulfate, filtered, and concentrated on a rotary evaporator. The residue is loaded onto a 6-cm column wet-packed with 80 g of silica gel and hexane. Elution with 1 L of 20:1 hexane:ethyl acetate followed by 1 L of 5:1 hexane:ethyl acetate affords 5.8 g of product as a colorless syrup (90% yield, 95.2% ee for the *S*-enantiomer, (Note 13). Recovery of the catalyst as the chloride salt is accomplished by extraction of the aqueous washes with two 50-mL portions of CH_2Cl_2, drying over Na_2SO_4, filtration, and concentration. Trituration of the residue with ethyl ether affords 0.89 g (94% recovery) of the catalyst as a light yellow solid.

2. Notes

1. The cinchona alkaloids and their quaternary salts are photosensitive and should be stored in brown bottles.

2. (−)-Cinchonidine (96%) was purchased from the Aldrich Chemical Co., Inc. and used as received. It typically contains ~5% of the dihydro analog which behaves like cinchonidine throughout this procedure.

3. 9-Chloromethylanthracene (98+%) was purchased from the Aldrich Chemical Co., Inc. and used as received.

4. The toluene was stored over 4 Å molecular sieves prior to use.

5. The product is isolated as a toluene solvate (mp 154-156 °C) and is sufficiently pure for use in the following step. A reference sample of the solvent-free salt can be prepared by dissolving the toluene solvate in CH_2Cl_2 (1 g/5 mL) followed by filtration, washing and drying of the resulting crystals of *N*-(9-anthracenylmethyl)cinchonidinium chloride: $[\alpha]_D^{23}$ −363 (c 0.81, $CHCl_3$); mp 168-171 °C (dec.); FTIR (film) cm^{-1}: 3500-2500, 1625, 1589, 1571, 1509, 1478, 1462, 1451, 1422, 1265, 1062; ^1H NMR (400 MHz, $CDCl_3$): δ 0.99 (m, 1H), 1.09 (m, 1H), 1.68 (bs, 1H), 1.80 (m, 2H), 2.12 (bs, 1H), 2.40 (app. t, 1H, *J* = 11.1), 2.56 (dd, 1H, *J* = 10.7, 12.8), 4.07 (bd, 1H, *J* = 12.9), 4.71 (m, 2H), 4.89 (dd, 1H, *J* = 1.3, 10.5), 5.25 (dd, 1H, *J* = 1.0, 17.3), 5.42 (m, 1H), 6.67 (d, 1H, *J* = 13.6), 6.83 (d, 1H, *J* = 13.5), 7.24 (m, 4H), 7.20 (m, 2H), 7.38 (m, 1H), 7.56 (d, 1H, *J* = 8.2), 7.60 (m, 1 H), 7.63 (d, 1H, *J* = 8.2), 7.96 (s, 1H), 8.02 (d, 1H, *J* = 4.4), 8.21 (d, 1H, *J* = 5.2), 8.71 (d, 1H, *J* = 8.2), 8.85 (m, 2H), 9.06 (d, 1H, *J* = 9.0); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.4, 25.7, 25.9, 38.5, 50.4, 54.8, 61.3, 67.0, 67.3, 117.7, 118.3, 120.1, 124.1, 124.2, 124.7, 124.8, 125.6, 126.3, 126.9, 127.4, 127.6, 128.3, 128.5, 128.6, 129.2, 130.2, 130.4, 131.1, 132.7, 133.2, 136.4, 145.7, 147.1, 149.4; FABMS: 485 $[M\text{-}Cl]^-$; HRMS calcd for $[C_{34}H_{33}N_2OCl\text{-}Cl]^-$: 485.2593, found: 485.2575. Anal. Calcd for $C_{34}H_{33}ClN_2O$: C, 78.37; H, 6.38; Cl, 6.80; N, 5.38. Found: C, 78.04; H, 6.42; Cl, 6.81; N, 5.50.

6. Allyl bromide (99%) was purchased from the Aldrich Chemical Co., Inc. and used as received. Excess reagent is used, as hydrolysis of the allyl bromide is competitive with the *O*-alkylation of *N*-(9-anthracenylmethyl)cinchonidinium chloride.

7. The 50% (w/w) aqueous potassium hydroxide (KOH) solution is prepared immediately before use in a neoprene bottle. *Caution: Cooling with a water bath is necessary since dissolution of KOH is very exothermic.*

8. *O*-Allyl-*N*-(9-anthracenylmethyl)cinchonidinium bromide has the following properties: $[\alpha]_D^{23}$ −320 (c 0.45, $CHCl_3$); mp 194-197 °C; FTIR (film) cm^{-1}: 3504, 3082, 2950, 2907, 2884, 1646, 1641, 1625, 1588, 1509, 1450, 1067, 996; ^1H NMR (400 MHz, CD_3OD); δ 1.60 (m, 2H), 1.96 (d, 1H, *J* = 2.9), 2.17 (m, 1H), 2.48 (m, 2H), 2.61 (m, 2H), 7.79-7.77 (m, 2H), 7.95-7.92 (m, 3H), 8.25-81.9 (m, 3H), 8.44 (d, 1H, *J* = 9.0), 8.57 (m, 1H), 8.76 (d, 1H, *J* = 9.0), 8.89 (s, 1H), 9.02 (d, 1H, *J* = 4.6); ^{13}C NMR (100 MHz, CD_3OD): δ 23.4, 26.2, 27.3, 39.5, 49.9, 53.6, 57.4, 63.4, 69.9, 71.4, 117.8,

119.0, 121.8, 125.7 (2C), 126.5, 126.6, 127.1, 129.2, 129.5, 130.5, 131.1, 131.3, 131.5, 133.0, 133.1, 133.8, 133.9, 134.6, 134.7, 134.8, 138.6, 143.0, 149.3, 151.1; FABMS: 525 $[M\text{-}Br]^-$; HRMS calcd for $[C_{37}H_{37}N_2OBr\text{-}Br]^-$: 525.2906, found: 525.2930. Anal. Calcd for $C_{37}H_{37}BrN_2O$: C, 73.38; H, 6.16; Br, 13.19; N, 4.63. Found: C, 73.40; H, 6.12; Br, 13.19; N 4.47.

9. *N*-(Diphenylmethylene)glycine *tert*-butyl ester was purchased from the Aldrich Chemical Co., Inc. and used as received.

10. Cesium hydroxide monohydrate was purchased from the Aldrich Chemical Co., Inc. and used as received.

11. Methyl acrylate was purchased from the Aldrich Chemical Co., Inc. and used as received.

12. The TLC analysis was performed using silica gel plates, 10% ethyl acetate in hexane and UV detection.

13. Characterization data for the Michael adduct: $[\alpha]_D^{23}$ −100 (c 1.35, CH_2Cl_2); mp 194-196 °C; FTIR (film) cm^{-1}: 3061, 3056, 2977, 2950, 2933, 1735, 1624, 1446, 1368, 1316, 1277, 1254, 1195, 1150; ^1H NMR (400 MHz, $CDCl_3$): δ 1.43 (s, 9H), 2.24-2.18 (m, 2H), 2.39-2.35 (m, 2H), 3.59 (s, 3H), 3.95 (dd, 1H, *J* = 7.2, 5.6), 7.18-7.16 (m, 2H), 7.45-7.25 (m, 6H), 7.63 (d, 2H, *J* = 7.2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 28.3, 28.8, 30.7, 51.8, 65.0, 81.5, 128.1, 128.3, 128.7, 128.9, 129.1, 130.6, 136.6, 139.6, 170.5, 170.9, 173.8; CIMS: 382 $[M+H]^+$, 280, 134; HRMS calcd for $[C_{23}H_{27}NO_4+H]^+$: 382.2018, found: 382.2017. The enantioselectivity was determined by chiral HPLC analysis (Regis Whelk-O1 column, 20% 2-propanol-hexane, 0.5 mL/min, λ = 254 nm, retention times: R (minor): 16.1 min, S (major): 19.1 min).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academic Press; Washington, DC 1998.

3. Discussion

O-Allyl-*N*-(9-anthracenylmethyl)cinchonidinium bromide can be used as a versatile phase transfer catalyst for highly enantioselective alkylation and Michael addition reactions of the benzophenone Schiff base of glycine tert-butyl ester.[3,4,5] The reaction is performed with 10 mol% of the cinchona alkaloid catalyst, 1.5 to 5 equivalents of the electrophile and 10 equivalents of $CsOH{\cdot}H_2O$ in methylene chloride at −60 to −78 °C.[3] The reaction may be performed using 50% aqueous KOH (w/v) at 0 °C instead of $CsOH{\cdot}H_2O$ with a slight reduction in enantioselectivity. The catalyst itself is prepared from inexpensive, readily available starting materials in two steps without chromatography. It is stable at room temperature for many months and can be recovered from the asymmetric alkylation reaction and reused. The alkylation reaction can be performed with a variety of electrophiles, including aliphatic, allylic and benzylic halides as well as cyclic and acyclic α,β-unsaturated esters and ketones, affording convenient access to orthogonally protected, enantiomerically pure amino acid derivatives useful as chiral building blocks in asymmetric synthesis. The use of the 9-anthracenylmethyl group on the cationic nitrogen rigidifies the catalyst and favors reaction through a highly structured contact ion pair.[3,4,5] Similar reactions using previously prepared catalysts are less enantioselective.[6,7,8]

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

O-Allyl-*N*-(9-anthracenylmethyl)cinchonidinium bromide: Cinchonanium, 1-(9-anthracenylmethyl)-9-(2-propenyloxy)-, bromide, (8α,9*R*)- (9); (200132-54-3)

Cinchonidine: Cinchonan-9-ol, (8α, 9R)- (9); (485-71-2)

9-Chloromethylanthracene: Anthracene, 9-(chloromethyl)- (8,9); (24463-19-2)

Allyl bromide:1-Propene, 3-bromo- (9); (106-95-6)

N-(Diphenylmethylene)glycine tert-butyl ester: Glycine, (diphenylmethylene)-, 1,1-dimethylethyl ester (9); (81477-94-3)

Methyl acrylate: 2-Propenoic acid, methyl ester (9); (96-33-3)

(4S)-2-(Benzhydrylidenamino)pentanedioic acid, 1-tert-butyl ester-5-methyl ester: L-Glutamic acid, N-(diphenylmethylene)-, 1-(1,1-dimethylethyl) 5-methyl ester (9); (212121-62-5)