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Novel Dimeric Cinchona Alkaloid Ammonium Salts with the 2,7-Naphthalene Ligand: Highly Enantioselective and Practical Phase-Transfer Catalysts for the Synthesis of α-Amino acids**

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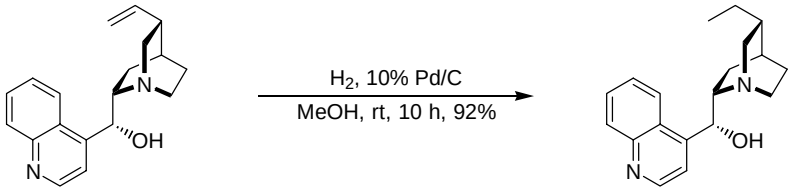
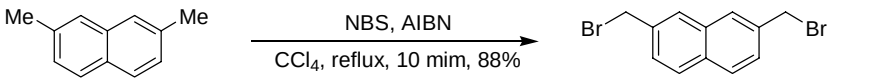


(-)-Cinchonidine (-)-Hydrocinchonidine

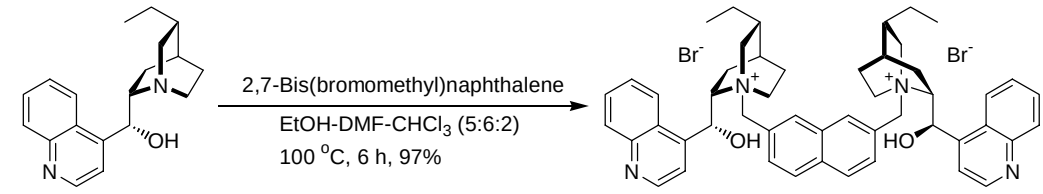
(-)-Hydrocinchonidine: A mixture of (-)-cinchonidine (5.0 g, 16.98 mmol) and 10% Pd/C (1.0 g) in methanol (130 mL) was stirred under hydrogen atmosphere at room temperature for 10 h. The reaction mixture was filtered through Celite pad and the filtrate was concentrated in vacuo. The residue was suspended in hexane (200 mL) and stirred at room temperature for 1 h and then filtered. The solids were collected to afford 4.6 g (92% yield) of the desired product as a white solid. ^{1}H NMR (300 MHz, MeOH-d_4): δ 8.81 (d, J = 4.4 Hz, 1H), 8.22 (d, J = 7.5 Hz, 1H), 8.05 (d, J = 8.3 Hz, 1H), 7.77 (t, J = 7.0 Hz, 1H), 7.71 (d, J = 4.6 Hz, 1H), 7.65 (t, J = 7.0 Hz, 1H), 5.62 (d, J = 3.9 Hz, 1H), 3.63-3.54 (m, 1H), 3.10-3.02 (m, 2H), 2.68-2.59 (m, 1H), 2.37-2.30 (m, 1H), 1.88-1.76 (m, 3H), 1.53-1.40 (m, 3H), 1.28-1.18 (m, 2H), 0.81 (t, J = 7.3 Hz, 3H).



2,7-Dimethylnaphthalene 2,7-Bis(bromomethyl)naphthalene

2,7-Bis(bromomethyl)naphthalene: A mixture of 2,7-dimethylnaphthalene (2.0 g, 12.80 mmol), *N*-bromosuccinimide (5.0 g, 28.16 mmol) and 2,2'-azobisisobutyronitrile (190 mg, 1.152 mmol) in carbon tetrachloride (160 mL) was stirred at reflux for 10 min after which the mixture was cooled to 0 °C. The precipitated succinimide was filtered off and the filtrate evaporated under reduced pressure. The residue was recrystallized from chloroform to give 3.5 g (88% yield) of the desired product as a white solid. ^{1}H

NMR (300 MHz, $CHCl_3$-*d*): δ 7.80 (d, *J* = 8.3 Hz, 2H), 7.78 (s, 2H), 7.49 (d, *J* = 8.3 Hz, 2H), 4.63 (s, 4H).

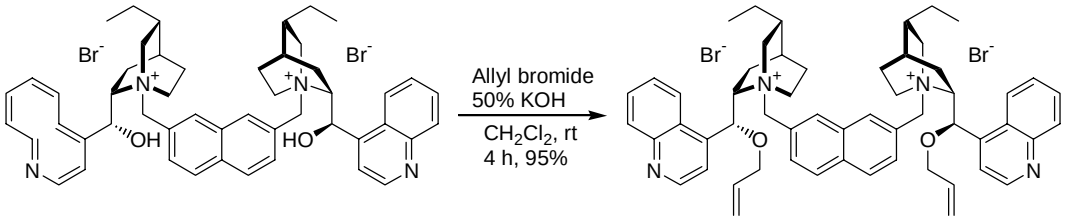


(-)-Hydrocinchonidine

2,7-bis(hydrocinchonidinium-*N*-methyl)naphthalene dibromide

2,7-Bis(hydrocinchonidinium-*N*-methyl)naphthalene dibromide: A mixture of (-)-hydrocinchonidine (2.0 g, 6.75 mmol) with 2,7-bis(bromomethyl)naphthalene (1.04 g, 3.31 mmol) in a mixture of ethanol (5 mL), DMF (6 mL), and chloroform (2 mL) was stirred at 100 °C for 6 h. After cooling the reaction mixture to room temperature, the resulting suspension was diluted with methanol (20 mL) and ether (60 mL) and stirred for 1 h. The solids were filtered, washed with ether. The crude solid was recrystallized from methanol-ether to afford 2.9 g (97% yield) of desired product as a pink solid. m.p. 248 °C (decomp.); $[\alpha]_D^{25}$=-127 (*c*=0.57, CH_3OH); IR (KBr): ν= 3855, 3434, 2960 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.00 (d, *J* = 4.4 Hz, 2H), 8.37-8.31(m, 4H), 8.21 (d, *J* = 8.6 Hz, 2H), 8.12 (d, *J* = 8.6 Hz, 2H), 7.93 (d, *J* = 7.8 Hz, 2H), 7.88-7.82 (m, 4H), 7.76-7.71 (m, 2H), 6.77 (d, *J* = 4.6 Hz, 2H), 6.63 (s, 2H), 5.36 (d, *J* = 12.4 Hz, 2H), 5.15 (d, *J* = 12.7 Hz, 2H), 4.43-4.32 (m, 2H), 4.02-3.96 (m, 2H), 3.54-3.41 (m, 2H), 3.39-3.27 (m, 4H), 2.20-2.05 (m, 4H), 2.01-1.92 (m, 2H), 1.73-1.61 (m, 4H), 1.48-1.36 (m, 2H), 1.31-1.23 (m, 4H), 0.71 (t, *J* = 7.3 Hz, 6H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 150.6, 148.1, 145.7, 136.2, 134.7, 132.6, 132.1, 130.4, 129.9, 128.8, 127.7, 127.0,

124.9, 124.2, 120.6, 68.2, 64.6, 63.2, 62.3, 51.4, 49.5, 35.6, 25.9, 24.1, 11.7; MS (ESI): 373 $[M\text{-}2Br]^{2+}/2$; HRMS (ESI) calcd for $[C_{50}H_{58}N_4O_2]^{2+}/2$: 373.2280, found: 373.2368.



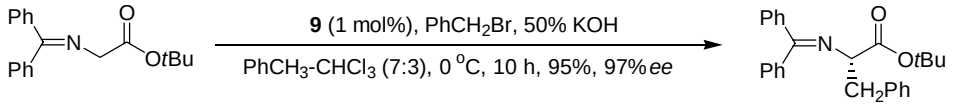
2,7-bis(hydrocinchonidinium-*N*-methyl)naphthalene dibromide

2,7-bis[*O*(9)-allylhydrocinchonidinium-*N*-methyl]naphthalene dibromide (**9**)

2,7-Bis[*O*(9)-allylhydrocinchonidinium-*N*-methyl]naphthalene dibromide (9): To a suspension of 2,7-Bis(hydrocinchonidinium-*N*-methyl)naphthalene dibromide (1.8 g, 1.99 mmol) in dichloromethane (10 mL) was added allyl bromide (1.03 mL, 11.9 mmol) and 50% aqueous KOH (2.23 mL, 19.9 mmol). The resulting mixture was stirred vigorously at room temperature for 4 h, during which time all of solids dissolved. The mixture was diluted with water (20 mL) and was extracted with dichloromethane (2 x 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated in vacuo. The crude solid was recrystallized from dichloromethane-hexane to yield 1.95 g (95% yield) of desired product as a light yellow solid. m.p. 194 °C (decomp.); $[\alpha]_D^{25}$=-196 (*c*=0.62, $CHCl_3$); IR (KBr) ν= 3434, 2959, 1634 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 9.05 (d, *J* = 4.3 Hz, 2H), 8.45 (s, 2H), 8.34 (d, *J* = 7.9 Hz, 2H), 8.25 (d, *J* = 8.2 Hz, 2H), 8.17 (d, *J* = 7.8 Hz, 2H), 7.97 (d, *J* = 7.6 Hz, 2H), 7.90 (t, *J* = 7.2 Hz, 2H), 7.80 (t, *J* = 7.0 Hz, 2H), 7.74 (d, *J* = 4.1 Hz, 2H), 6.54 (s, 2H), 6.25~6.18 (m, 2H), 5.53 (d, *J* = 17.2 Hz, 2H), 5.38~5.33 (m, 4H), 5.14 (d, *J* = 12.2, 2H), 4.46 (d, *J* = 7.8 Hz8 2H), 4.20~4.12 (m, 2H), 4.09~4.01 (m, 4H), 3.60~3.52 (m, 2H),

3.42~3.39 (m, 2H), 2.33~2.29 (m, 2H), 2.17~2.10 (m, 2H), 2.07~1.99 (m, 2H), 1.81~1.76 (m, 4H), 1.56~1.48 (m, 2H), 1.29~1.16 (m, 6H), 0.72 (t, J = 7.1 Hz, 6H; ^{13}C NMR (125 MHz, DMSO-d_6): δ 150.7, 148.5, 141.7, 134.9, 134.8, 132.6, 132.2, 130.4, 130.1, 128.8, 127.9, 126.8, 125.5, 124.2, 120.2, 117.9, 72.5, 69.7, 68.2, 63.9, 61.9, 51.7, 35.4, 25.6, 25.3, 24.1, 21.1, 11.7; MS (ESI): 413 [M-2Br]$^{2+}$/2; HRMS (ESI) calcd for [$C_{56}H_{66}N_4O_2$]$^{2+}$/2: 413.2593, found: 413.2620.

Representative Procedure for Enantioselective Catalytic Alkylation of *N*-(Diphenylmethylene)glycine *tert*-butyl ester 11 under Phase-Transfer Conditions (Benzylation):

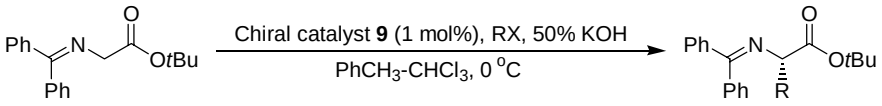


11 **12g**

To a mixture of *N*-(diphenylmethylene)glycine *tert*-butyl ester **11** (50 mg, 0.17 mmol) and chiral catalyst **9** (1.7 mg, 0.0017 mmol) in toluene/chloroform (volume ratio = 7:3, 0.75 mL) was added benzyl bromide (0.1 mL, 0.85 mmol). The reaction mixture was then cooled (0 °C), 50% aqueous KOH (0.25 mL) was added, and the reaction mixture was stirred at 0 °C until the starting material had been consumed (10 h). The suspension was diluted with ether (20 mL), washed with water (2 x 5 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (hexane:EtOAc = 50:1) afforded the desired product **12g** (62 mg, 95% yield) as a colorless oil.

Chiral HPLC Conditions[a]

Determination of enantiopurity of alkylated imines (**12a~m**)[b]



11 **12**

alkylated imine	eluent [hexane:2-propanol]	flow rate [mLmin^{-1}]	retention times [min]		*ee* [%]
			minor (*R*)	major (*S*)	
12a	500:1.0	0.7	17.9	14.4	94
12b	500:2.5	0.5	13.8	11.8	97
12c	500:1.0	1.0	9.5	8.5	>99
12d	500:1.0	1.0	11.8	9.5	97
12e	500:1.0	1.0	17.4	9.6	96
12f	500:1.0	1.0	20.3	18.2	98
12g	500:2.5	1.0	12.2	22.5	97
12h	500:2.5	1.0	11.4	7.5	98
12i	500:5.0	1.0	18.6	11.2	96
12j	500:2.5	0.5	16.7	13.1	98
12k	500:10.0	1.0	16.9	22.9	98
12l	500:2.5	1.0	15.4	11.3	96
12m	500:5.0	1.0	18.8	14.1	99

[a] chiral column: DAICEL CHIRALCEL OD (4.6 X 250 mm), temperature: 23 °C, detection: λ = 254 nm. [b] In this case it was established by analysis of racemate of which the enantioisomers were fully resolved.