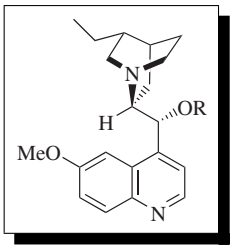
# Dihydroquinine Acetate[1]




(R = Ac)
*[75917-54-3]* $C_{22}H_{28}N_2O_3$ (MW 368.47)
InChI = 1/C22H28N2O3/c1-4-15-13-24-10-8-16(15)11-21(24)22(27-14(2)25)18-7-9-23-20-6-5-17(26-3)12-19(18)20/h5-7,9,12,15-16,21-22H,4,8,10-11,13H2,1-3H3/t15-,16-,21+,22+/m0/s1
InChIKey = ZVEDOOXEZTUEBN-RZTYQLBFBQ
(R = *p*-$ClC_6H_4C(O)$–)
*[113162-88-9]* $C_{27}H_{29}ClN_2O_3$ (MW 464.99)
InChI = 1/C27H29ClN2O3/c1-3-17-16-30-13-11-19(17)14-25(30)26(33-27(31)18-4-6-20(28)7-5-18)22-10-12-29-24-9-8-21(32-2)15-23(22)24/h4-10,12,15,17,19,25-26H,3,11,13-14,16H2,1-2H3/t17-,19-,25+,26+/m0/s1
InChIKey = TXVNNFDXQZFMBQ-IPFQZCJUBZ
(R = H)
*[522-66-7]* $C_{20}H_{26}N_2O_2$ (MW 326.44)
InChI = 1/C20H26N2O2/c1-3-13-12-22-9-7-14(13)10-19(22)20(23)16-6-8-21-18-5-4-15(24-2)11-17(16)18/h4-6,8,11,13-14,19-20,23H,3,7,9-10,12H2,1-2H3/t13-,14-,19+,20+/m0/s1
InChIKey = LJOQGZACKSYWCH-AFHBHXEDBO

(asymmetric dihydroxylation;[2] conjugate additions;[3] carbonyl additions[3])

*Alternate Name:* DHQ-Ac.

*Physical Data:* *p*-$ClC_6H_4C(O)$–: mp 130–133 °C; $[\alpha]_D$ +150° (*c* = 1, EtOH).

*Solubility:* *p*-$ClC_6H_4C(O)$–: sol $CH_2Cl_2$, $Et_2O$, EtOH, EtOAc.

*Form Supplied in:* the *p*-chlorobenzoate is available as a white foam.

*Preparative Methods:* the acetate is prepared from dihydroquinine[4] and the *p*-chlorobenzoate is commercially available. The phthalazine-derived bis(dihydroquinine) ligand is commercially available.[5] A formulation of the standard reactants for the asymmetric dihydroxylation (AD-mix-$\alpha$) on the small scale has been developed and is commercially available.[6] AD-mix-$\alpha$ (1 kg) consists of potassium osmate (0.52 g), the phthalazine-derived ligand (5.52 g), $K_3Fe(CN)_6$ (700 g), and powdered $K_2CO_3$ (294 g).

*Purification:* dihydroquinine *p*-chlorobenzoate is recovered after a dihydroxylation reaction using the same method as that described for ***Dihydroquinidine Acetate***.

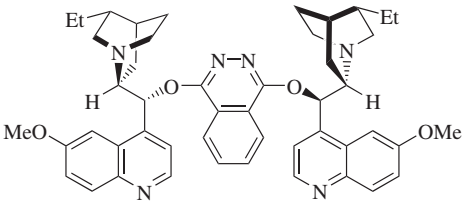
*Handling, Storage, and Precautions:* toxic; use in a fume hood.

# Original Commentary

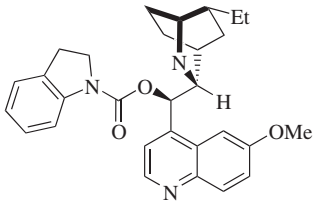
André B. Charette
*Université de Montréal, Québec, Canada*

**Chiral Ligand for the Asymmetric Dihydroxylation of Alkenes.** Dihydroquinine-derived chiral ligands have been used as pseudoenantiomers of the dihydroquinidine analog in the catalytic asymmetric dihydroxylation of alkenes. In general, the enantioselectivities with these ligands are as good as or slightly lower than those obtained with the dihydroquinidine ligand. For example, styrene could be dihydroxylated in 62% ee using a mixture of dihydroquinidine *p*-chlorobenzoate (DHQD-CLB, 0.13 equiv), ***Osmium Tetroxide*** (0.13 equiv), and ***N-Methylmorpholine N-Oxide***, whereas the analogous reaction with dihydroquinine *p*-chlorobenzoate produced the diol of opposite absolute stereochemistry in 54% ee.[7]

As in the dihydroquinidine series, the phthalazide cinchona derivative [$(DHQ)_2$-PHAL] (**1**)[6] is the best ligand for the asymmetric dihydroxylation of terminal, *trans*, 1,1-disubstituted, and trisubstituted alkenes, and enol ether,[8] whereas the DHQ-IND ligand (**2**)[9] turns out to be superior for *cis*-alkenes (Table 1). The addition of ***Methanesulfonamide*** to enhance the rate of osmate(VI) ester hydrolysis is recommended for all nonterminal alkenes.




(**1**)
$(DHQ)_2$-PHAL
(ligand used in AD-mix-α)

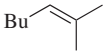
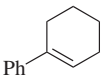
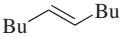
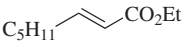
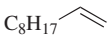
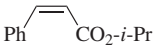
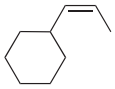
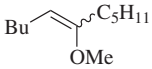



(**2**)
DHQ-IND

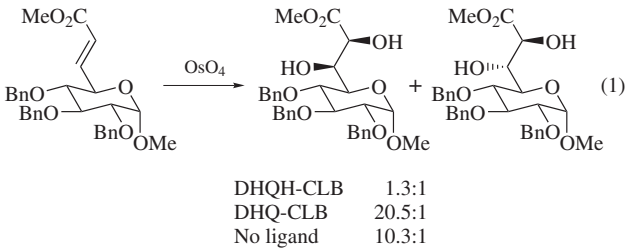
For additional examples of regioselective asymmetric dihydroxylations, see ***Dihydroquinidine Acetate***.

**Double Diastereoselection in the Dihydroxylation Reaction.** The dihydroxylation reaction of chiral nonracemic substrates using the cinchona-derived ligand leads to a matched and mismatched pair.[10] The dihydroquinine-derived ligand was found to be superior to its pseudoenantiomer in the dihydroxylation of

**Table 1** Alkenes dihydroxylated using DHQ ligands

|  |  |  |
|---|---|---|
| $(DHQD)_2$-PHAL<br>98% ee<br>$(DHQ)_2$-PHAL<br>95% ee | $(DHQD)_2$-PHAL<br>99% ee<br>$(DHQ)_2$-PHAL<br>97% ee | $(DHQD)_2$-PHAL<br>97% ee<br>$(DHQ)_2$-PHAL<br>93% ee |
|  |  |  |
| $(DHQD)_2$-PHAL<br>99% ee<br>$(DHQ)_2$-PHAL<br>96% ee | $(DHQD)_2$-PHAL<br>94% ee<br>$(DHQ)_2$-PHAL<br>93% ee | $(DHQD)_2$-PHAL<br>84% ee<br>$(DHQ)_2$-PHAL<br>80% ee |
|  |  |  |
| DHQD-IND<br>80% ee<br>DHQ-IND<br>72% ee | DHQD-IND<br>56% ee<br>DHQ-IND<br>44% ee | $(DHQD)_2$-PHAL<br>95% ee<br>$(DHQ)_2$-PHAL<br>96% ee |

carbohydrate derivatives (eq 1).[11]



(1)

| | |
|---|---|
| DHQH-CLB | 1.3:1 |
| DHQ-CLB | 20.5:1 |
| No ligand | 10.3:1 |

For additional examples and an extensive discussion on the use of these ligands in asymmetric dihydroxylation reactions, see ***Dihydroquinidine Acetate***.

**Chiral Ligand for Other Stereoselective Reactions.** The effect of the addition of dihydroquinine-derived alkaloids on the product enantioselectivity has also been investigated in the addition reaction of ***Diethylzinc*** to aldehydes,[12] in the addition of aromatic thiols to conjugated cycloalkenones,[13] and in the heterogeneous hydrohalogenation of $\alpha,\alpha$-dichlorobenzazepinone-2.[14]

# First Update

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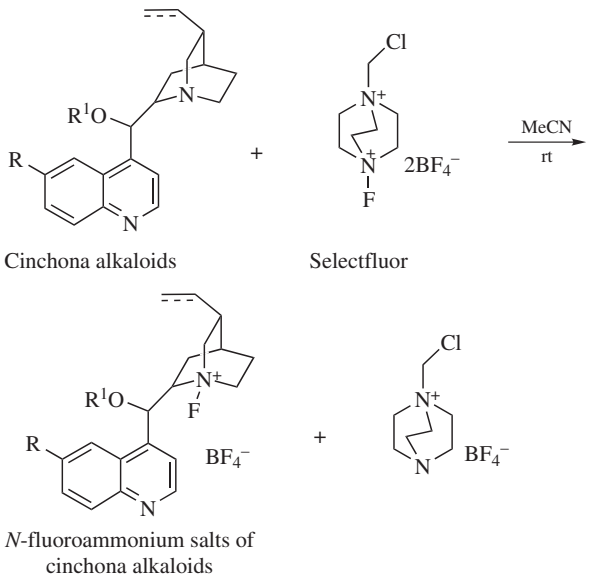
*Nagoya Institute of Technology, Nagoya, Japan*

**Enantioselective Fluorination.** The synthesis of enantiomerically pure fluorinated molecules is an important topic in pharmaceutical and material sciences. Chiral *N*-fluoro-camphorsultam derivatives had been developed for this purpose; however, they were far from ideal because of low yields and ee's of the fluorinated products. In 2000, a fundamentally new approach for enantioselective fluorination based on cinchona alkaloid derivatives combined with the commercially available fluorinating reagent Selectfluor® was disclosed. [15–17] The chiral C-F unit in the target compounds can be conveniently constructed from appropriate C-H substrates using cinchona alkaloid/Selectfluor® combinations. In general, in situ generated cinchona alkaloid/Selectfluor® combinations efficiently fluorinate a variety of carbonyl compounds in a highly enantioselective manner to furnish chiral $\alpha$-fluorocarbonyl compounds in high yields. It should be stressed that the enantioselectivity of the fluorination is highly substrate and reagent dependent; thus, high enantioselectivity requires screening of the cinchona alkaloids. Dihydroquinine acetate (DHQ-Ac) is one of the first-line cinchona alkaloids for enantioselective fluorination of silyl enol ethers. Namely, the silylenol ether of 2-benzyl-1-indanone was treated with a stoichiometric amount of DHQ-Ac/Selectfluor® in MeCN at $-20\,^{\circ}C$ to give 2-benzyl-2-fluoroindanone in 67% yield with 86% ee. When dihydroquinine-4-nitrobenzoate was used instead of DHQ-Ac for this reaction, 91% ee was observed (Table 2). The structures of the cinchona alkaloid *N*-fluoroammonium salts were proven by X-ray crystallographic analyses.[16,17] The reagent is prepared by mixing equimolar amounts of the cinchona alkaloids and Selectfluor® in MeCN at ambient temperature and is used directly as a MeCN solution (eq 2). The enantioselective fluorination can also employ the isolated cinchona alkaloid *N*-fluoroammonium salts.[17]



Cinchona alkaloids Selectfluor

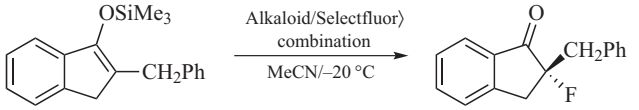
*N*-fluoroammonium salts of cinchona alkaloids

(2)

**Preparation of cinchona alkaloids/selectfluor combination**

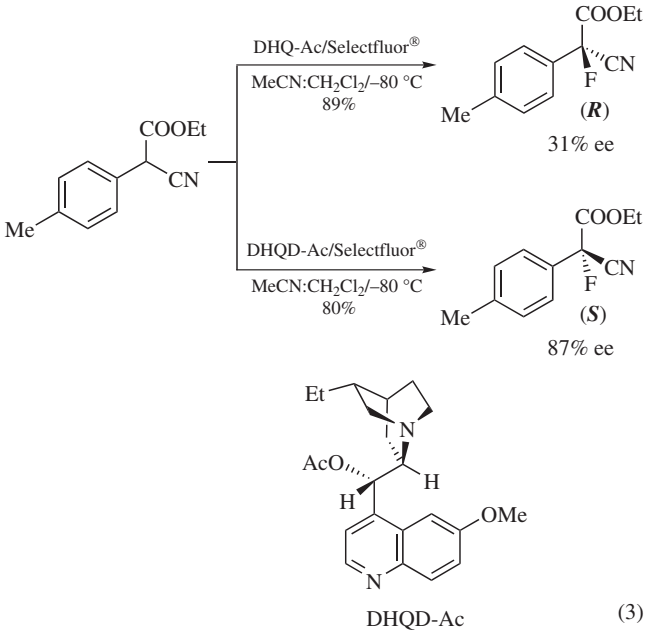
Optically active $\alpha$-cyano-$\alpha$-fluoro-aryl acetates, which are themselves efficient chiral derivatizing reagents, were synthesized by the enantioselective fluorination of $\alpha$-cyano-aryl acetates using the cinchona alkaloid/Selectfluor® combination. Treatment of ethyl $\alpha$-cyano-tolyl acetate with DHQ-Ac/Selectfluor® in MeCN/$CH_2Cl_2$ at $-80\,^{\circ}C$, afforded ethyl $\alpha$-cyano-$\alpha$-fluoro-tolyl acetate in 89% yield with 31% ee with the (*R*)-configuration (eq 3).[16] Dihydroquinidine acetate (DHQD-Ac), a pseudoenantiomer of DHQ-Ac, was found to be a superior partner with Selectfluor®

**Table 1** Enantioselective fluorination of silyl enol ether by cinchona alkaloid/selectfluor combination




| Entry | Alkaloid | Yield(%) | ee(%) |
|---|---|---|---|
| 1 | DHQ-Ac | 67 | 86 |
| 2 | DHQ-benzoate | 82 | 90 |
| 3 | DHQ-4-nitrobenzoate | 61 | 91 |
| 4 | DHQ-4-methoxybenzoate | 80 | 87 |
| 5 | DHQ-1-napthalenecarboxylate | 61 | 87 |
| 6 | DHQ-anthraquinone-2-carboxylate | 100 | 86 |
| 7 | DHQ-trifluoroacetate | 43 | 31 |

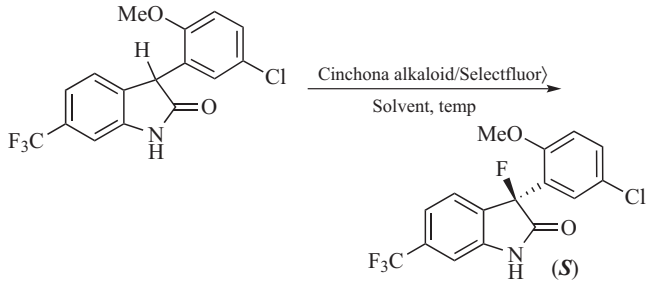
providing (*S*)-$\alpha$-cyano-$\alpha$-fluoro-tolyl acetate in 80% yield with 87% ee (eq 3).



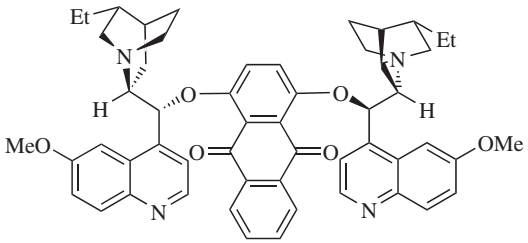

(3)

**Synthesis of BMS-204352.** BMS-204352 (MaxiPost®) is a potent, effective opener of maxi-K potassium channels developed by Bristol–Myers Squibb. BMS-204352 is a chiral, nonracemic compound bearing an (*S*)-configured fluorine atom at the asymmetric quaternary carbon center. Employing cinchona alkaloid/Selectfluor®-mediated enantioselective fluorination of 3-(5-chloro-2-methoxyphenyl)-6-(trifluoromethyl)indolin-2-one achieved the first direct enantioselective synthesis of BMS-204352.[18] In this study, the DHQ-Ac/Selectfluor® was first attempted for the fluorination of the staring oxindole in MeCN at 0 °C to furnish BMS-204352 in 93% yield; however, the optical purity of the product was 16% ee. The use of *bis*-cinchona alkaloid, $(DHQ)_2AQN$/Selectfluor® combination in place of DHQ-Ac considerably improved enantioselectivity. The enantioselective synthesis of BMS-204352 was also achieved by the use of isolated *N*-fluoroammonium salt of napthoyl-QN (*N*F-QNN, Table 3).[19]

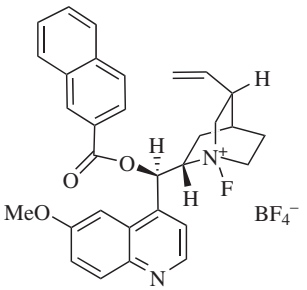
**Table 2** Synthesis of BMS-204352 by enantioselective fluorination using cinchona alkaloid/Selectfluor combination




| Entry | Cinchona alkaloid | Solvent | Temp (°C) | Yield (%) | ee (%) |
|---|---|---|---|---|---|
| 1 | DHQ-Ac | MeCN | 0 | 93 | 16 |
| 2 | $(DHQ)_2AQN$ | $MeCN:CH_2Cl_2$ | −80 | 94 | 84 |
| 3 | *N*F-2-NaphtQN (isolated) | $THF:MeCN:CH_2Cl_2$ | −78 | 96 | 88 |



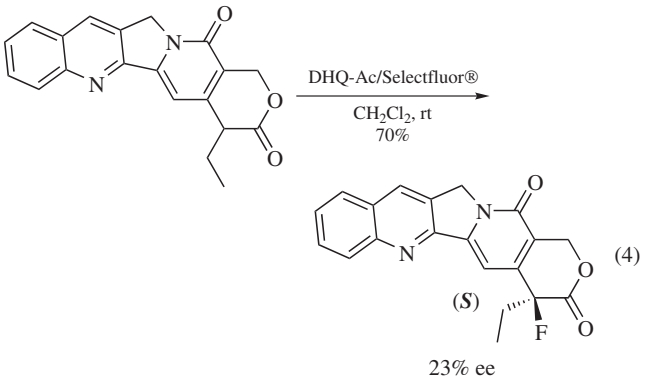

$(DHQ)_2AQN$




*N*F-QNN

**Synthesis of 20-Deoxy-20-fluorocamptothecin.** Camptothecin, a natural product isolated from extracts of the Chinese tree Camptothea acuminate in 1958, possesses impressive activity against leukemias and a variety of solid tumors. However, severe toxicities such as myelosuppression, vomiting, and diarrhea necessitated cessation of clinical trials. To overcome these intrinsic difficulties of camptothecin, 20-deoxy-20-fluorocamptothecin was designed as an isosteric analogue.[20,21] Direct enantioselective fluorination of the lactone moiety of 20-deoxycamptothecin by cinchona alkaloid/Selectfluor® was examined. The DHQ-Ac/Selectfluor® combination in dichloromethane at 25 °C gave the 20-deoxy-20-fluorocamptothecin in 70% yield with 23% optical purity (eq 4). High levels of enantioselection in the fluorination of 20-deoxycamptothecin were achieved using *bis*-cinchona

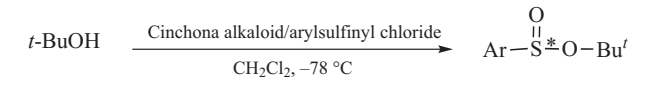
alkaloids/Selectfluor® combinations derived from $(DHQ)_2PHAL$ and $(DHQD)_2PHAL$ in 81–88% ee's (eq 5).[20]



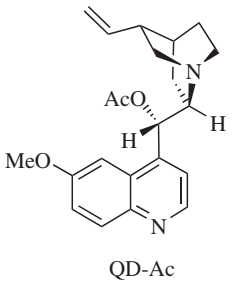

(4)

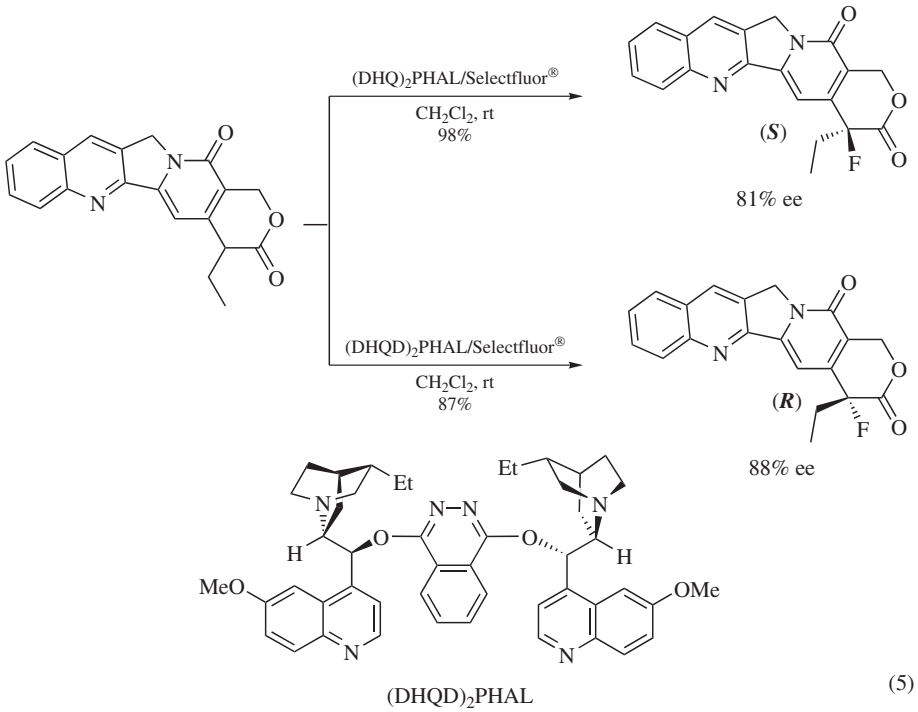
**Chiral Reagent for Enantioselective Sulfinylation of Alcohols.** Chiral sulfinates play an important role in organic chemistry and useful building blocks for biologically active molecules and natural products. Similar to the case in the enantioselective fluorination reactions, cinchona alkaloid/sulfinyl chloride was developed for enantioselective sulfinylation of alcohols.[22] Treatment of *tert*-butyl alcohol with the combination prepared in situ from cinchona alkaloid and arylsulfinyl chloride in dichloromethane at −78 °C for 1 hour afforded chiral *tert*-butyl arylsulfinates in high yields with high enantioselectivities. The screening of the cinchona alkaloid revealed that the best alkaloid for the preparation of (*R*)-arylsulfinates is DHQ-Ac, while the antipode, (*S*)-arylsulfinates, can be accessed by the use of QD-Ac/sulfinyl chloride with enantioselectivities up to 99% ee (QD-Ac; quinidine acetate, Table 4). In the case of enantioselective preparation of chiral alkyl sulfinates, a catalytic version of the reaction is available.[23,24] The enantioselective sulfinylation of the 9-fluorenol catalyzed by either quinidine 2-naphtoate (QDN) or QNN (qunine-2-naphtoate) delivers both enantiomers of optically active alkylsulfinates with very high enantioselectivities (eq 6). *N*-Sulfinylammonium salts of cinchona alkaloids are proposed as the reactive species (eq 7).

**Table 3** Enantioselective sulfinylation of tert-butyl alcohol combination




| Entry | Ar | Cinchona alkaloid | Yield (%) | ee (%) |
|---|---|---|---|---|
| 1 | Ph | DHQ-Ac | 88 | 83(*R*) |
| | | QD-Ac | 93 | 88(*S*) |
| 2 | 4-Chlorophenyl | DHQ-Ac | 73 | 84(+) |
| | | QD-Ac | 78 | 88(−) |
| 3 | 4-Methoxyphenyl | DHQ-Ac | 74 | 96(+) |
| | | QD-Ac | 70 | 99(−) |
| 4 | 4-Methoxy-3-methylphenyl | DHQ-Ac | 74 | 94(+) |
| | | QD-Ac | 78 | 93(−) |
| 5 | 2,4,6-Trimethylphenyl | DHQ-Ac | 72 | 92(+) |
| | | QD-Ac | 68 | 92(−) |

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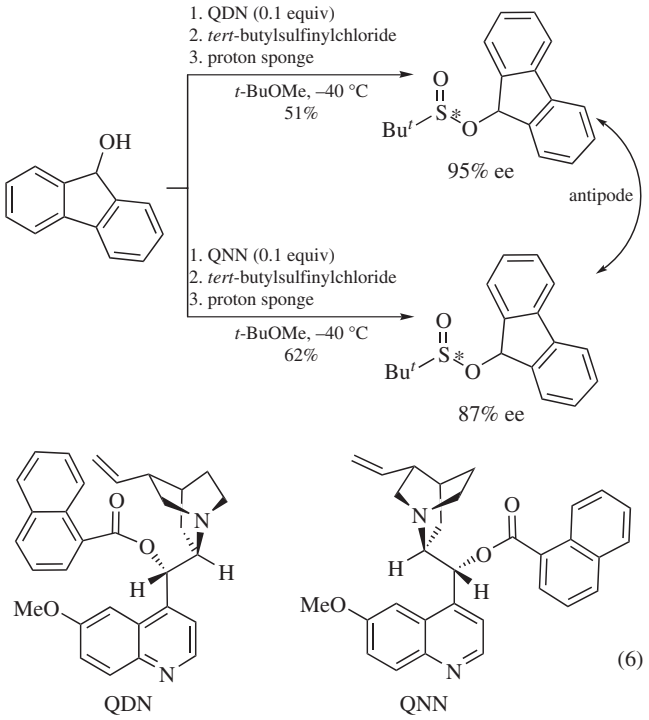


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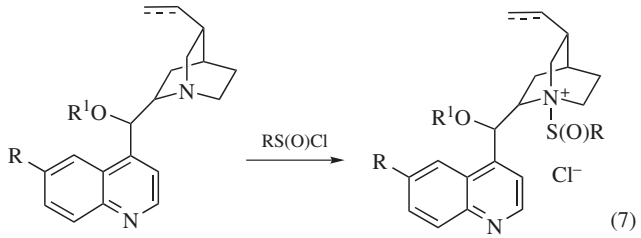


(7)

**Preparation of the cinchona alkaloids/sulfinylchloride combination**


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