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Novel Potential Enantioselective Phase Transfer Catalysts Based on Lupinine [1]

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Abstract. Ten *N*-alkylated lupininium derivatives **5**–**8** were prepared as potential enantioselective phase transfer catalysts. Compounds **5a**–**d**, **6a**–**d** contain four asymmetric centers (including one in the side chain) with known configuration resting on an X-ray structure. Preliminary PT catalytic experiments in several reactions gave high chemical yields but relatively disappointing enantioselectivities.

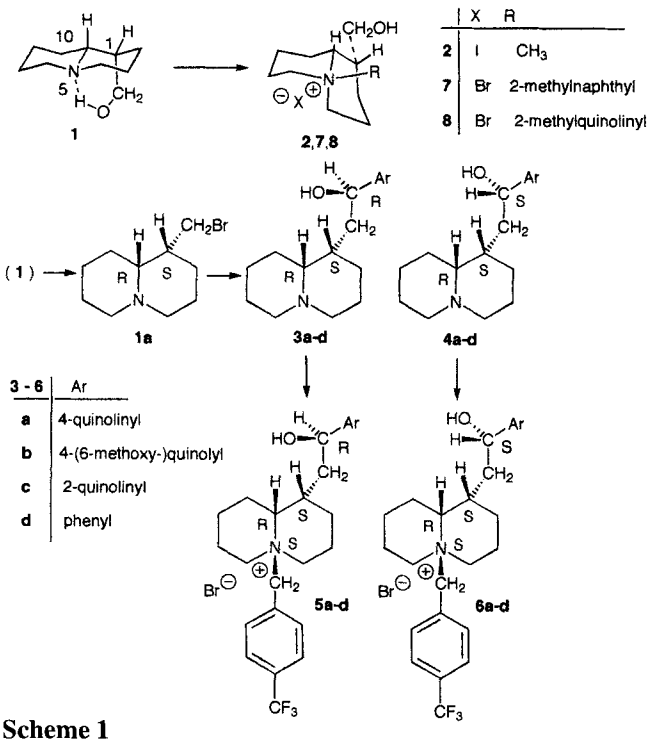
Many chiral quaternary ammonium salts have been tested as enantioselective phase transfer catalysts. Multipoint interactions between catalyst cation and substrate anion proved to be essential, and benzylated quinine and cinchonine derivatives proved to be the most useful catalysts for a number of reactions (reviews [2]). Highlights of catalytic conversions with such "tailor made" catalysts are C alkylations of diphenylmethyleneglycine esters as developed by the O'Donnell [2c, f],Lygo [3a] and Corey [3b] groups with *e.e.*s up to 99.5% [3b]. Important structural features of these Cinchona alkaloid derivatives are: a) an ammonium nitrogen in an asymmetric polycyclic environment, b) two flat aromatic regions for π–π complexation (one of these possibly a quinolinyl residue), and c) a polar group, hydroxyl or ether, positioned opposite to the aromatics. Models for catalyst–substrate interactions stress shielding of three of the four tetrahedral faces of the ammonium cation and complexing by Van der Waals attraction. To find out which partial structures are essential, we started a program of structural variations. In the present report natural lupinine is used as the core structure.

(–)-Lupinine (**1**) can be easily isolated from shredded seeds of *Lupinus luteus* [4] (content ca. 0.5%). There is some ambiguity as to the configurations at N in derivatives. The absolute configuration of the free base was established by X-ray crystallography [5] to be (1*R*, 5*R*, 10*R*). In solution there is an intramolecular and in the crystal an intermolecular N···H-O hydrogen bond, so that the quinolizidine system is chair–chair-*trans* with an axial hydroxymethyl. Protonation at nitrogen does not change its stereochemistry [6], but lupinine is *N*-methylated under inversion at nitrogen giving the *cis* quinolizidine (**2**) with an equatorial hydroxymethyl group (1*R*, 5*S*, 10*R*), at least in the crystal [7]. We planned to fix aromatic rests to the 1-methyl group of **1** and to its *N*-benzylated derivatives. We reasoned that the flexible nature of a *cis* quinolizidine system would allow an "induced fit" with a substrate anion. This might be provided by chair–chair interconversion to the other conformation with axial side chain and subsequent hydrophobic interaction of substrate and aromatic catalyst side groups.

1 was transformed into 1-bromomethylquinolizidine (**1a**) with phosphorus tribromide [8]. The corresponding Grignard compound was treated with the following aldehydes: quinoline-4-carbaldehyde, 6-methoxyquinoline-4-carbaldehyde, quinoline-2-carbaldehyde, and benzaldehyde. In each case two diastereomers (**3** and **4**) were obtained which could be separated by crystallization. Quaternization by 4-trifluoromethylbenzyl bromide presented problems in some cases because of competing *N*-alkylation of the heteroaromatic rings and formation of unpleasant mixtures as a consequence, but eventually compounds **5** and **6** could be obtained (Scheme 1).

Thus, the reaction between **1a** and quinoline-4-carbaldehyde gave **3a** and **4a** which were converted into two salts with melting points of 234 °C and 255 °C, respectively (later found to be **5a** and **6a**) when treated

[1]) X-ray analyses



Scheme 1

with 4-(trifluoromethyl)benzyl bromide. To ascertain the stereochemistry both at nitrogen and in the side chain, the compound with *m.p.* 234 °C was subjected to an X-ray structural analysis [9] (Figure 1). It turned out that it was **5a** with the absolute configuration (1*S*, 2'*R*, 5*S*, 10*R*). Thus, trifluoromethylbenzyl *N*-alkylates the quinolizidine system from the same face as methyl. The known stereostructure of **5a** then allows assignment of **3a**, **4a**, and **6a**. In the NMR spectra, chemical shifts of the HCOH multiplet centers are δ/ppm = 5.70 in **3a** and 5.58 in **4a**. Similar shift differences are present in the other cases, and we assign therefore the (2'-(*R*) = **5**) configurations to the isomers with the larger δ values for the respective signals (Table 1).

Table 1 NMR signals of H–COH protons and configurational assignments at C-2' in compounds **5** and **6**

Compound	δ (center of multiplett)
5a	5.69
6a	5.58
5b	5.60
6b	5.22
5c	5.04
6c	4.95
5d	4.87
6d	4.83

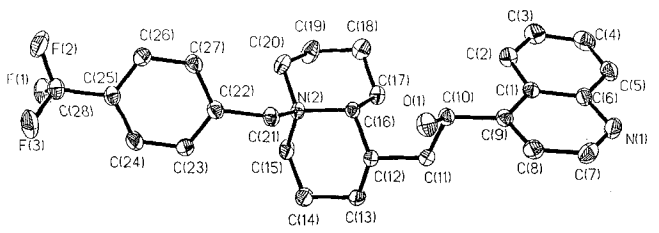


Fig. 1 Structure of compound **5a** by X-Ray

Catalysts **7** and **8** were prepared by quaternization of **1** with 2-bromomethylnaphthalene and 2-bromomethylquinoline.

The new catalysts were tested in a number of model reactions known to show enantioselectivity under certain PTC conditions: 1) Benzylation of ethyl diphenylmethyleneglycinate according to O'Donnell [2f], 2) borohydride reduction of pivalophenone in water/dichloromethane, 3) Michael addition of butenone to 2-ethoxycarbonylcyclohexanone [10] 4) kinetic racemate resolution of phthalimide with ethyl bromopropionate [11]. All conversions exhibited satisfactory chemical yields, but disappointingly low enantiomeric excesses. These were close to zero in the reactions 3) and 4). Somewhat better results were found in the reaction (1) only with the following catalysts (% *e.e.*): **7** (23, *R*-isomer), **8** (13, *R*), **6b** (13, *S*). **5b**, in contrast, gave no *e.e.* under the same conditions. In reaction (2), these maximal *e.e.*s were observed: **5b** (17, *R*), **6b** (3, *R*), **5d** (10, *R*), **6d** (9, *R*). It can be seen, that there are influences of the substituents and their configurations, but the observed effects are not large enough.

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Experimental

NMR-Spectra were recorded with DRX-500 or AC 250-P instruments (Bruker) in $CDCl_3$ with TMS as internal standard. Polarimetry was executed with the DIP-360 of Jasco, using methanol as a solvent. Melting points (uncorrected) were measured with the Büchi apparatus 510.

Grignard Reactions with 1-Bromomethylquinolizidine (1a); Preparation of 3a–d and 4a–d

1.57 g (65 mmol) of Mg were covered with 20 ml of absol. diethyl ether, treated with a crystal of iodine and a few drops of the bromide solution (15 g (65 mmol) in 50 ml of ether). Reaction started after warming up the mixture to a soft boil. Thereafter the bromide solution was added dropwise so as to maintain a slow reflux. In the end the reaction was kept refluxing for 1 h, then cooled to r.t. Now 65 mmol of the appropriate carbonyl compound in 20 ml of diethyl ether was added slowly. The mixture was refluxed for 2 h after the end of the addition. Then the mixture was cooled and hydrolyzed with 100 ml of water. Phases were separated and the aqueous one was extracted 4 × with 50 ml of dichloromethane each

time. The combined organic extracts were dried (Na_2SO_4) and concentrated to dryness. The residue was crystallized fractionally from methanol. Repeated crystallization furnished about equal amounts of the two diastereomers.

(1S,2'R,10R)-1-[(2'-hydroxy-2'-quinolin-4-yl)ethyl]quinolizidine (**3a**)

m.p. 181 °C, $[\alpha]_D^{26}$ + 38.1 (c = 1).

$C_{20}H_{26}N_2O$	calcd.:	C 77.38	H 8.44	N 9.02
(310.4)	found:	C 77.38	H 8.65	N 8.96.

(1S,2'S,10R)-isomer (**4a**)

m.p. 246 °C, $[\alpha]_D^{26}$ +144.2 (c = 1).

$C_{20}H_{26}N_2O$	calcd.:	C 77.38	H 8.44	N 9.02
(310.4)	found:	C 77.06	H 8.41	N 8.88.

(1S,2'R,10R)-1-[(2'-hydroxy-2'-(6''-methoxy)quinolin-4''-yl)ethyl]-quinolizidine (**3b**)

m.p. 175 °C, $[\alpha]_D^{26}$ – 149.25 (c = 0.9).

$C_{21}H_{28}N_2O_2$	calcd.:	C 74.08	H 8.29	N 8.23
(340.5)	found:	C 74.05	H 8.54	N 8.16.

(1S,2'S,10R)- isomer (**4b**)

m.p. 184 °C, $[\alpha]_D^{26}$ +79.9 (c = 1).

$C_{21}H_{28}N_2O_2$	calcd.:	C 74.08	H 8.29	N 8.23
(340.5)	found:	C 74.04	H 8.54	N 8.23.

(1S,2'R,10R)-1-[(2'-hydroxy-2'-quinolin-2''-yl)ethyl]quinolizidine (**3c**)

*m.p.*123 °C, $[\alpha]_D^{26}$ – 100.5 (c = 1.1).

$C_{20}H_{26}N_2O$	calcd.:	C 77.38	H 8.44	N 9.02
(310.4)	found:	C 77.32	H 8.77	N 9.00.

(1S,2'S,10R)- isomer (**4c**)

m.p. 115 °C, $[\alpha]_D^{26}$ +73.4 (c = 0.9).

$C_{20}H_{26}N_2O$	calcd.:	C 77.38	H 8.44	N 9.02
(310.4)	found:	C 77.16	H 8.44	N 9.01.

(1S,2'R,10R)-1-[2'-hydroxy-(2'-phenyl)ethyl]quinolizidine (**3d**)

m.p. 122 °C, $[\alpha]_D^{26}$ +44.0 (c = 1).

(1S,2'S,10R)- isomer (**4d**)

m.p. 112 °C, $[\alpha]_D^{26}$ +9.6 (c = 1).

$C_{17}H_{25}NO$	calcd.:	C 78.72	H 9.71	N 5.40
(259.4)	found:	C 78.70	H 9.67	N 5.15.

Quaternizations with (4-trifluoromethyl)benzyl bromide or with 2-bromomethylnaphthalene or with 2-bromomethylquinoline

were performed by refluxing in absol. methanol for 3 days to prepare compounds **5a–c**, **6a–c** (16 hours only for **8**) and in refluxing acetonitrile for 2 days to prepare compounds **5d**, **6d** (2 hours only to prepare **7**).

(1S,2'R,5S,10R)-1-[2'-hydroxy-(2'-quinolin-4''-yl)ethyl]-N-(4-trifluoromethyl)benzyl-quinolizidinium bromide (**5a**)

m.p. 234 °C, $[\alpha]_D^{26}$ +96.1 (c = 1). – ^{1}H NMR (250MHz): [typical spectrum] δ/ppm = 1.52 – 2.03 (m, 12 H), 2.42–2.48 (m, 1H), 2.98–3.08 (m, 2H), 3.16–3.19 (m, 1H), 3.67–3.71 (m, 1H), 3.81–3.92 (m, 1H), 5.20 (d, *J*/Hz = 13.2, 1H), 5.30 (d, *J*/Hz = 13.2, 1H), 5.66–5.71 (m, 1H), 7.63–7.84 (m, 7H), 8.11–8.20 (m, 2H), 8.87 (d, *J*/Hz = 4.7, 1 H). – ^{13}C NMR: δ/ppm = 20.6, 20.9, 21.0, 22.65, 24.25 (all CH_2), 31.9 (CH), 41.7, 51.4, 62.8, 63.4 (all CH_2), 68.4, 69.4 (both CH), 119.4, 124.8, 127.0, 127.1, 127.16, 128.2, 130.2, 130.9, 133.2, 135.3, 149.0, 151.3, 153.0 (aromat.).

$C_{28}H_{32}BrF_3N_2O$	calcd.:	C 61.21	H 5.87	N 5.10
(549.5)	found:	C 61.08	H 5.96	N 5.09.

(1S,2'S,5S,10R)- isomer (**6a**)

m.p. 255 °C, $[\alpha]_D^{26}$ – 58.8 (c = 1).

$C_{28}H_{32}BrF_3N_2O$	calcd.:	C 61.21	H 5.87	N5.10
(549.5)	found:	C 61.05	H 6.02	N 5.04.

(1S,2'R,5S,10R)-1-[2'-hydroxy-2'-(6''-methoxy)quinolin-4''-yl)-ethyl]-N-(4-trifluoromethyl)benzylquinolizidinium bromide (**5b**)

m.p. 225 °C, $[\alpha]_D^{26}$ – 20.2 (c = 1).

(1S,2'S,5S,10R)- isomer (**6b**)

m.p. 233 °C, $[\alpha]_D^{26}$ +74.0 (c = 1).

$C_{29}H_{34}BrF_3N_2O_2$	calcd.:	C 60.11	H 5.91	N 4.83
(579.5)	found:	C 60.13	H 6.11	N 4.57.

(1S,2'R,5S,10R)-1-[2'-hydroxy-2'-(quinolin-2''-yl)ethyl]-N-(4-trifluoromethyl)benzylquinolizidinium bromide (**5c**)

m.p. 221°C, $[\alpha]_D^{26}$ – 22.5 (c = 0.8).

$C_{28}H_{32}BrF_3N_2O$	calcd.:	C 61.21	H 5.87	N 5.10
(549.5)	found:	C 60.90	H 5.93	N 5.60.

(1S,2'S,5S,10R)- isomer (**6c**)

m.p. 206 °C, $[\alpha]_D^{26}$ +60.6 (c = 0.9).

$C_{28}H_{32}BrF_3N_2O$	calcd.:	C 61.21	H 5.87	N 5.10
(549.5)	found:	C 61.08	H 5.96	N 5.09.

(1S,2'R,5S,10R)-1-[2'-hydroxy-(2'-phenyl)ethyl]-N-(4-trifluoromethyl)benzyl-quinolizidinium bromide (**5d**)

m.p. 244 °C, $[\alpha]_D^{26}$ +51.3 (c = 1).

$C_{25}H_{31}BrF_3NO$	calcd.:	C 60.24	H 6.27	N2.81
(498.4)	found:	C 60.12	H 6.27	N 2.74.

(1S,2'S,5S,10R)- isomer (**6d**)

m.p. 232 °C, $[\alpha]_D^{26}$ +37.5 (c = 1).

$C_{25}H_{31}BrF_3NO$	calcd.:	C 60.24	H 6.27	N 2.81
(498.4)	found:	C 60.78	H 6.50	N 2.86.

(1R,5S,10R)-N-(2-naphthylmethyl)lupininium bromide (**7**)

m.p. 252 °C (dec), $[\alpha]_D^{26}$ + 15.4 (c = 1)

$C_{21}H_{28}BrNO$	calcd.:	C 64.61	H 7.23	N 3.59
(390.4)	found:	C 64.46	H 6.96	N 3.58.

(1R,5S,10R)-N-(2-quinolinylmethyl)lupininium bromide (**8**)

m.p. 228 °C (dec), $[\alpha]_D^{26}$ +41.6 (c = 1).

$C_{20}H_{27}BrN_2O$	calcd.:	C 61.38	H 6.95	N 7.16
(391.4)	found:	C 61.09	H 6.88	N 6.89.

Test Reactions

1) 1 mmol of *N*-diphenylmethyleneglycine ethyl ester and 1 mmol of benzyl bromide and 0.1 mmol of catalyst were dissolved in 10 ml of CH_2Cl_2 and stirred with 5 equiv. of powdered NaOH for 24 h at r.t. (The total consumption of starting

material was shown by t.l.c.). The mixture was filtered, and the solvent was removed. The residue was taken up in petroleum ether (*b.p.* 45–60 °C)/*tert*-butyl methyl ether, filtered, and the solvent was removed again. The remaining mixture consisted of the expected product and some benzophenone formed by hydrolysis. Inspite of that the *e.e.* of the product could be determined by HPLC on a chiral column [Chirasep DNBPG of Merck A.G. with (*R*)-9-*N*-(3,5-dinitrobenzoyl)phenylglycine as stationary phase; hexane/2-propanol 500 : 1; 0.7 ml / min. flow rate].

2) 1mmol of pivalophenone were dissolved in 3 ml of CH_2Cl_2 and stirred with 0.6 mmol of $NaBH_4$ in 0.5 ml of water in the presence of 0.1 mmol of catalyst for 3 h at 0 °C. The *e.e.* was determined by HPLC with a chiral column [Chirasep DNBPG of Merck A.G. with (*R*)-9-*N*-(3,5-dinitrobenzoyl)phenylglycine as stationary phase; hexane/2-propanol 200 : 1; 0.7 ml/min. flow rate].

3) 1.18 mmol of the β-ketoester and 1.18 mmol of butenone were dissolved in 5 ml of toluene and stirred with 1.18 mmol of solid K_2CO_3 and 5 mol % of catalyst for 24 h at r.t. After workup the product was distilled in a kugelrohr apparatus, and the *e.e.* was determined by polarimetry [10].

4) 2.7 mmol of potassium phthalimide were refluxed with 5.4 mmol of ethyl 2-bromopropionate in CH_2Cl_2 for 24 h in the presence of 5 mol % of catalyst. Workup was followed by chromatographic isolation of product, *m.p.* 61 °C. The *e.e.* (4% with **8**) was determined by polarimetry [11].

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