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Asymmetric Recognition of TRISPHAT Anion. Unusually High Difference in Reactivity of the Pseudoenantiomers of *Cinchona* Alkaloids.

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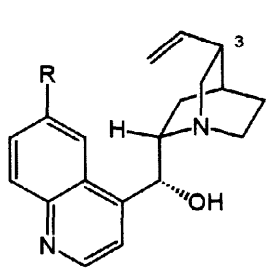
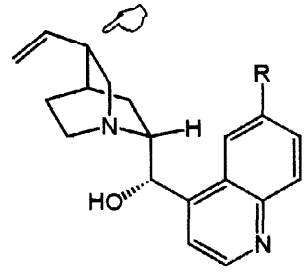
Abstract: Ammonium cations of cinchonidine- and NOT cinchonine-based alkaloids exert high selectivity towards chiral hexacoordinated TRISPHAT anion.

Cinchonidine and cinchonine-based derivatives play a major role in asymmetric chemistry as resolving agents, catalytic or stoichiometric chiral reagents leading usually to high levels of induction or recognition in molecular or supramolecular processes.[1] In most successful asymmetric applications of these derivatives, the enantiomer of a product realised with a cinchonidine-based reagent can be obtained with the cinchonine-derived reagent instead and this usually with only a *small* but reproducible difference in the enantioselectivity of the process. Although cinchonidine **1** and cinchonine **2**, quinine **3** and quinidine **4** are diastereomers and not enantiomers respectively, their main chiral recognition elements, with the exception of the olefin at C3, are mirror-image to each other leading to enantiomer-like reactivity for these two pairs of diastereomers. These compounds are thus called sometimes 'pseudoenantiomers'.[2] Herein, we report an unusually high difference of reactivity and selectivity of the pseudoenantiomers of *cinchona* alkaloids for the asymmetric recognition of TRISPHAT anion.

Cinchonidine (R=H) **1**
Quinine (R=OMe) **3**





Cinchonine (R=H) **2**
Quinidine (R=OMe) **4**

Recently, we have shown that the chiral D_3-symmetric tris(tetrachlorobenzenediolato)phosphate(V) anion **5** (or TRISPHAT) is configurationally stable in solution associated with ammonium counterions.[3,4] Anion **5** is an efficient NMR chiral shift agent and a valuable host in molecular recognition studies conferring unique properties to its ion pairs.[5] For the preparation of enantiomerically pure *P* or enriched *M* TRISPHAT salts, we have used to our benefit the selectivity of the cinchonidinium cation[3,6] towards hexacoordinated anions (Scheme 1):[5a] Addition of 0.5 equiv. of cinchonidine **1** to a solution of racemic tri-*n*-butylammonium TRISPHAT salt (±)-**6** ≡ [^{n}Bu$_3$NH$^+$, (±)-**5**], in CH_2Cl_2 leads, after proton exchange between the tri-*n*-butylammonium cation and **1**, to the precipitation of a white solid **7** containing essentially the

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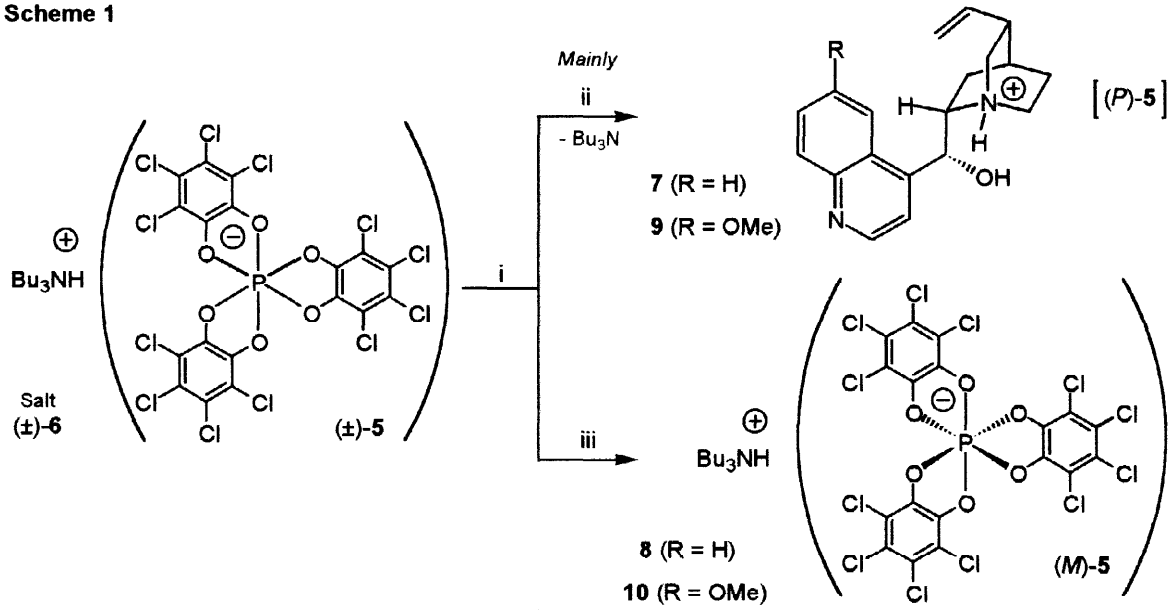
cinchonidinium TRISPHAT salts [1^+, (*P*)-**5**] and [1^+, (*M*)-**5**].[7] This precipitation is coupled to a selective recognition of the cinchonidinium cation towards the *P* enantiomer of **5** (70% de in CH_2Cl_2).[8] Filtration and concentration of the mother liquor *in vacuo* afford a white solid **8** containing essentially enantiomerically enriched **6** ([^{n}Bu$_3$NH$^+$, (*M*)-**5**], 70% ee) along with a minor amount of cinchonidinium salts [1^+, **5**]. Recrystallisation of solid **7** in EtOAc-acetone affords pure cinchonidinium-(*P*-TRISPHAT) salt [1^+, (*P*-**5**)] (78% yield, 38% from (±)-**6**). Recrystallisations of solid **8** in $CHCl_3$ then CH_2Cl_2 afford in the mother liquors, chemically and enantiomerically purified, tri-*n*-butylammonium-(*M*)-TRISPHAT salt (+)-**6** ([^{n}Bu$_3$NH$^+$, (*M*)-**5**], 96% ee, 35% from (±)-**6**).[9]

Scheme 1



Reagents and conditions: i, 0.5 equiv. of **1** or **3**, CH_2Cl_2, 20°C, 6 h; ii, filtration, **7** (49%) or **9** (40%); iii, concentration of the mother liquor *in vacuo* (60°C, 10^{-4} bar, 12 h), **8** (56%, 70% ee) or **10** (65%, 54% ee).

Since *pseudoenantiomeric* reagents give usually similarly good selectivity, we decided to examine, in our case, the reactivity of the cinchoninium and quinidinium cations towards TRISPHAT, expecting to obtain in the mother-liquor the other enantiomer, (-)-**6** ≡ [^{n}Bu$_3$NH$^+$, (*P*)-**5**], with high selectivity.

To our surprise, this was not the case: the resolution procedure performed with cinchonine **2** and quinidine **4** (Table 1, entries 3 and 4), which should have afforded as solids the cinchoninium [2^+, **5**] and quinidinium [4^+, **5**] TRISPHAT salts respectively, led instead to the difficult precipitation of adducts containing the tri-*n*-butylammonium salt **6** [^{n}Bu$_3$NH$^+$, **5**] (!) as the major component with no enantiomeric excess and this, after concentration of the initial volume of CH_2Cl_2 to its half.[10] The added bases, **2** and **4**, and their respective ammonium salts [2^+, **5**] and [4^+, **5**] remain essentially in solution. With quinine **3**, results similar to those of cinchonidine **1** were obtained, although with a lower selectivity (**10**, 54% ee, entry 2), showing nevertheless the net difference of reactivity between the cinchonidine- and cinchonine-based reagents.

This unusually high contrast in reactivity is linked to the high difference in solubility of the respective ammonium TRISPHAT salts:[11] Independently prepared cinchonidine-based [1^+, **5**] and [3^+, **5**] salts are indeed much less soluble than the cinchonine-derived [2^+, **5**] and [4^+, **5**] in CH_2Cl_2 (~0.06 *vs.* 3-6 m*M*). We interpret this large difference as the result of a poor affinity of the cinchoninium and quinidinium cations for TRISPHAT anion.[12]

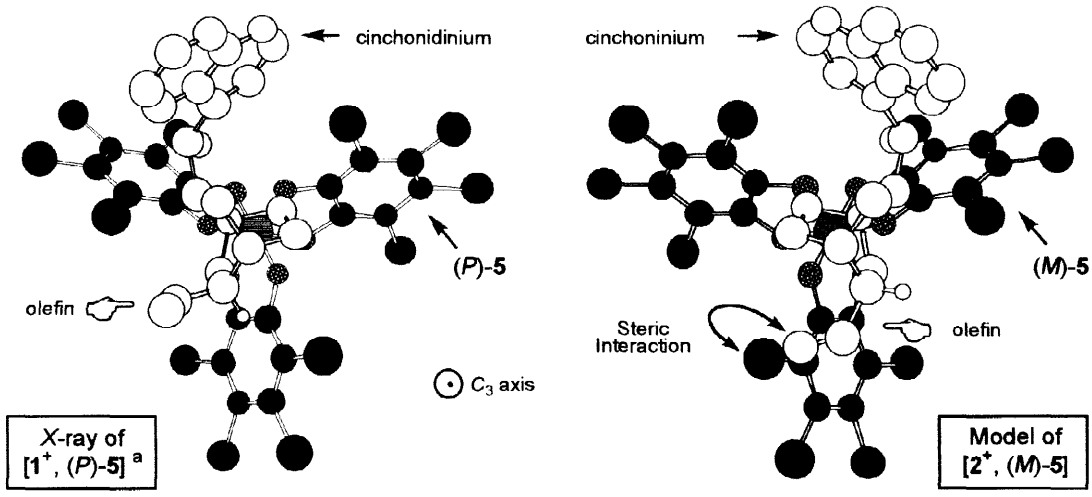
So, the asymmetric recognition of TRISPHAT anion by the ammonium cations of *cinchona* alkaloids is a rare case of high difference in reactivity and selectivity of the *pseudoenantiomeric* reagents.[13] The exocyclic double-bond, which is the only stereogenic element not mirrored, must play an important role in the asymmetric process.

Table 1

		Precipitate		Solid from mother liquor		
Entry	Base	Yield[a]	Ratio	Yield[a]	Ratio	ee
1	**1**	49	[**1**$^+$, **5**] : **6** **7** (97:3)	56	**6** : [**1**$^+$, **5**] **8** (90:10)	70[b]
2	**3**	40	[**3**$^+$, **5**] : **6** **9** (95:5)	65[c]	**6** : [**3**$^+$, **5**] **10** (82:18)	54
3	**2**	33	**2**+[**2**$^+$, **5**] : **6** (36:64)	67	**6** : **2**+[**2**$^+$, **5**] (65:35)	
4	**4**	28	[**4**$^+$, **5**] : **6** (4:96)[d]	75[c]	**6** : **4**+[**4**$^+$, **5**] (59:41)	

[a] Average yield for isolated solids; [b] enantiomeric excess varies from 68 to 74%; [c] excess yield due to remaining Bu_3N and **2**-**4**; [d] no selectivity is observed (0% ee).

X-ray structural analysis of the cinchonidinium-(*P*)-TRISPHAT salt [**1**$^+$, (*P*)-**5**],[3] which has revealed a tight association of *P*-TRISPHAT anion and the cinchonidinium cation, may be used to understand the role of the olefin: The relative positions between anions and cations in the molecular packing are fixed by a hydrogen bond interaction involving the hydrogen atom of the ammonium cation and one oxygen of the phosphate anion (N···O = 3.06(1) Å, N-H···O = 2.27(9) Å, N-H···O = 154°). The quinuclidinium unit of **1** is then aligned along the pseudo-C_3 axis of **5** and two of the three grooves of the D_3-symmetric anion host the quinoline side chain and the exocyclic olefin respectively. The proximity between the ions forces the quinoline side chain of the cinchonidinium cation to adopt an "unnatural" conformation.[1f]



[a] One molecule of EtOAc and most hydrogen atoms have been removed for clarity

On the other hand, a crude model of diastereomeric cinchoninium-(*M*)-TRISPHAT salt [**2**$^+$, (*M*)-**5**], which can be created by an artificial inversion of the configuration of the carbon bearing the olefin on the mirror-image of [**1**$^+$, (*P*)-**5**], shows that the exocyclic olefin is now very close from one of the tetrachlorocatecholate ligand of the phosphate anion. We believe that a negative steric interaction takes place between these residues and is responsible for the difference in reactivity and selectivity observed. Ion pairs of TRISPHAT and ammonium cations of *cinchona* alkaloids are thus best described as *penetrated ion pairs* rather than just *contact ion pairs*.[14]

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References and Notes:

1 a) Wynberg, H. *Top. Stereochem.* **1986**, *16*, 87-129; b) Bhattacharya, A.; Dolling, U.-H.; Grabowski, E. J. J.; Karady, S.; Ryan, K. M.; Weinstock, L. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 476-477; c) Kolb, H. C.; Vannieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483-2547; d) Corey, E. J.; Noe, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 11038-11053; e) Blaser, H. U.; Jalett, H. P.; Muller, M.; Studer, M. In *Catal. Today*, 1997; pp 441-463; f) Winterwerner, B.; Diederich, F.; Gramlich, V. *Helv. Chim. Acta* **1996**, *79*, 1338-1360 and references cited therein.

2 a) Pearlstein, R. M.; Blackburn, B. K.; Davis, W. M.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 639-641; b) Zhang, S. Y.; Girard, C.; Kagan, H. B. *Tetrahedron : Asymmetry* **1995**, *6*, 2637-2640; c) Iwashima, M.; Kinsho, T.; Smith, A. B. *Tetrahedron Lett.* **1995**, *36*, 2199-2202

3 J. Lacour, C. Ginglinger, C. Grivet, G. Bernardinelli, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 608-609.

4 For general articles on hexacoordinated phosphorus adducts, see: a) Cherkasov, R. A.; Polezhaeva, N. A. *Uspekhi Khimii* **1987**, *56*, 287-321; *Russ. Chem. Rev.* **1987**, *56*, 163-181; b) Burgada, R.; Setton, R. In *The chemistry of organophosphorus compounds*; Hartley, F. R., Ed.; John Wiley & Sons: New York, 1994; Vol. 3; pp 185-272 and references therein.

5 a) Lacour, J.; Ginglinger, C.; Favarger, F.; Torche-Haldimann, S. *Chem. Commun.* **1997**, 2285-2286; b) Lacour, J.; Barchéchath, S.; Jodry, J. J.; Ginglinger, C. *Tetrahedron Lett.* **1998**, *39*, 567-570.

6 Cinchona alkaloids has been used successfully for the resolution of tris(benzenediolato)arsenate anion: a) Rosenheim, A.; Plato, W. *Chem. Ber.* **1925**, *58*, 2000-2009; b) Craddock, J. H.; Jones, M. M. *J. Am. Chem. Soc.* **1961**, *83*, 2839-2843; c) Mason, J.; Mason, S. F. *Tetrahedron* **1967**, *23*, 1919-1927; d) Ryschkewitsch, G. E.; Garett, J. M. *J. Am. Chem. Soc.* **1968**, *90*, 7234-7238.

7 [**1-4**$^+$, (*P*)-**5**] and [**1-4**$^+$, (*M*)-**5**] represent the diastereomeric salts [ammonium-(*P*)-**5**] and [ammonium-(*M*)-**5**] of the alkaloids **1-4** respectively. Notation [**1-4**$^+$, **5**] designates a mixture of both diastereomeric salts.

8 The use of $CHCl_3$ instead of CH_2Cl_2 improves the selectivity (86% *vs.* 72% de). However, the amount of $CHCl_3$ needed for the resolution (5 x CH_2Cl_2) renders the procedure less practical and economical on a large scale.

9 The enantiomeric excess of the anion is measured by ^{31}P NMR using (-)-bis[(*S*)-1-phenylethyl]amine hydrochloride as chiral shift agent in $CDCl_3$. The absolute *M* configuration is unambiguously determined by its CD spectrum by comparison with [**1**$^+$, (*P*)-**5**] and analogy with the tris(benzenediolato)arsenate anion, see ref. 6c.

10 The lower solubility of **2** *vs.* **6** leads to an important precipitation of **2** (and salts [**2**, **5**]) along with **6**. See Table 1.

11 Solubilities of alkaloids **1-4**, salts [**1-4**$^+$, **5**] and **6** in CH_2Cl_2 are 24, 4.0, >250, >250, 0.06, 5.8, 0.07, 2.9 and 13.3 m*M* respectively.

12 Independently prepared cinchonine-based salts [**2**$^+$, **5**] and [**4**$^+$, **5**] are slightly less soluble than **6** ([Bu_3NH^+, **5**]) in CH_2Cl_2. Equilibria [**2** + **6** ⇆ [**2**$^+$, **5**] + Bu_3N] and [**4** + **6** ⇆ [**4**$^+$, **5**] + Bu_3N] are thus probably shifted towards the starting materials as no or little precipitation of salts [**2**$^+$, **5**] and [**4**$^+$, **5**] is observed.

13 a) Kobayashi, N.; Iwai, K. *J. Am. Chem. Soc.* **1978**, *100*, 7071-7072; b) references 2c and cited therein.

14 a) Pochasky, T. C.; Stone, P. M.; Pochasky, S. S. *J. Am. Chem. Soc.* **1991**, *113*, 1460-1462, b) X. Yang, A. Zaitsev, B. Sauerwein, S. Murphy, G. B. Schuster, *ibid.* **1992**, *114*, 793-794; c) G. Boche, *Angew. Chem.* **1992**, *104*, 742-743; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 731-732.