Truncated *Cinchona* alkaloids as catalysts in enantioselective monobenzoylation of *meso*-1,2-diols†

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Readily synthesised quincorine and quincoridine derived chiral diamines efficiently catalyse the asymmetric monobenzoylation of cyclic and acyclic *meso*-1,2-diols.

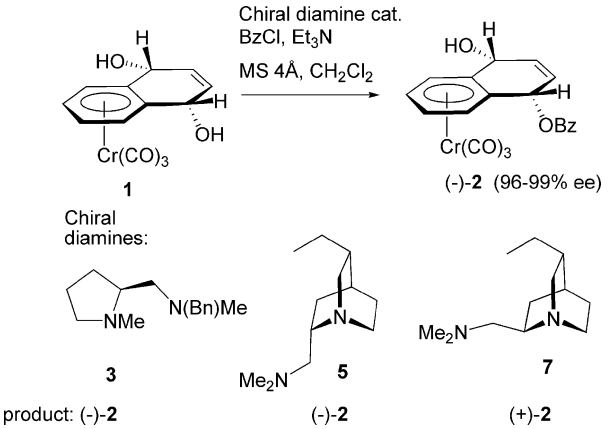
Chiral diamines are widely used in organocatalytic, metal-mediated and -catalysed asymmetric reactions.[1] They are accessible by asymmetric synthesis or from abundant natural sources such as amino acids, ephedrine, and *Cinchona* alkaloids, to name but a few. In this *communication* we report our study on the desymmetrisation of *meso*-diols by the quincorine- and quincoridine-derived diamines **5** and **7**.

Our interest in this field started with the search for a simple and efficient method for the desymmetrisation of the *meso*-complex **1** to give enantiomerically enriched **2**. A number of chiral acyl transfer catalysts have been successfully developed in recent years for the desymmetrisation of *meso*-diols.[2,3] Although not previously used for the desymmetrisation of *meso*-1,4-diols, Oriyama's proline derived catalyst **3**[3] turned out to be a good choice for the reaction in question (Scheme 1).[4] Assuming that the role of one amine function is acyl activation, that of the second tertiary amine would be to engage in hydrogen bonding to a hydroxy group and discriminate between the two enantiotopic alcohol moieties in **1**, thus setting up the system for stereoselective acyl delivery. Pursuing this line of reasoning, we felt that other chiral diamines incorporating a highly nucleophilic amine such as the quinuclidine fragment may be good catalysts.

Indeed the diamines **5** and **7**, readily synthesised by reductive Eschweiler–Clark reaction and hydrogenation from the precursor diamines **4** and **6** (Scheme 2), were excellently suited for this task. Compounds **4** and **6** are accessible in a two step sequence from quinine and quinidine, respectively.[5]‡

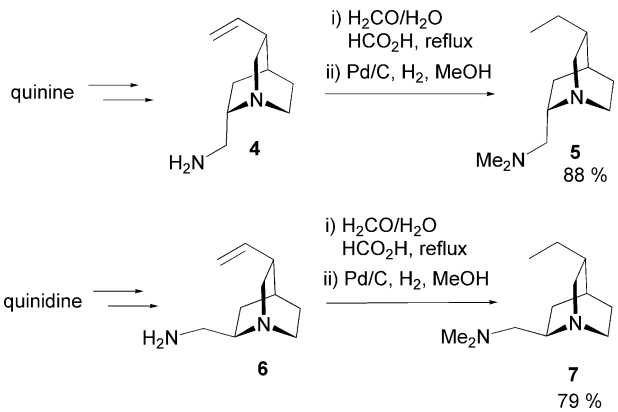
Another advantage of **5** and **7** is their low molecular mass. By stripping the alkaloids to the core function of the chiral quinuclidine with a second amine function reduces the molecular weight of the catalysts by 40%.

The two pseudo-enantiomeric diamine catalysts afforded **2** in ees of 95–99% (Scheme 1).[4] The same reaction was also applied equally successfully to [$Cr(CO_3)$(5,8-dihydroxytetralin)].[6]



Scheme 1 Asymmetric acylation of the *meso*-diol **1**.

In order to probe the scope of these acyl transfer catalysts we extended the desymmetrisation from *meso*-1,4-diol complexes to simple *meso*-1,2-diols. Cyclohexanediol **8** was selected for checking conditions for this reaction. The reaction proceeded readily in CH_2Cl_2 in the temperature range −60 °C to 0 °C (Table 1, entries 1–3). Without the addition of catalyst, only 20% of *rac*-**9** was obtained after 22 h at −30 °C, indicating a slow background reaction. (+)-**9** was obtained in excellent enantiomeric purity at −30 °C as seen in entry 2. A drawback with CH_2Cl_2 as solvent was the competitive formation of the diacylation product **10**. Part of this problem could be tracked back to the low solubility of **8** in this solvent at low temperatures. Lowering the concentration improved the result only partially (entry 4). Competitive formation of **10** raises the possibility of kinetic resolution. Indeed, as shown in Scheme 3, this is the case. The product mixture obtained translates into a



Scheme 2 Access to the chiral acyl transfer catalysts **5** and **7**.

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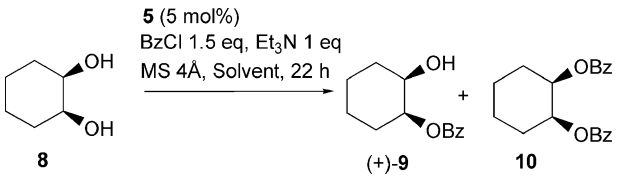
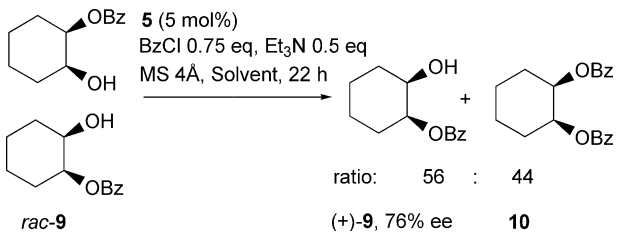
† Electronic supplementary information (ESI) available: Synthesis and spectral data of **5**, **7**, **9**, **19**–**26** plus diacylated products. See DOI: 10.1039/b808268e

Table 1 Asymmetric benzoyl transfer to 1,2-*cis*-cyclohexanediol catalysed by the chiral diamine **5**



Entry	Solvent[a]	Catalyst	T/°C	Conversion[b] (%)	Yield[b] (+)-**9** (%)	ee[c] (+)-**9** (%)	Yield **10** (%)
1	CH_2Cl_2	**5**, 5%	0	91	77	92	14
2	CH_2Cl_2	**5**, 5%	−30	93	74	>99	19
3	CH_2Cl_2	**5**, 5%	−60	87	62	96	25
4[d]	CH_2Cl_2	**5**, 5%	−30	84	75	97	9
5	THF	**5**, 5%	−30	95	89	91	6
6	**THF**	**5**, **2%**	**−60**	**96**	**93**	**93**	**3**
7	THF	**5**, 1%	−60	68	68	85	0
8	THF	**7**, 5%	−30	95	89[e]	91[e]	6
9	EtOAc	**5**, 5%	−30	97	94	92	3
10	EtOAc	**5**, 5%	−60	100	96	97	4
11	**EtOAc**	**5**, **2%**	**−60**	**98**	**94**	**97**	**4**

[a] 0.11 M in **8** unless otherwise noted. [b] From ^{1}H NMR spectra, ratios of crude product. [c] HPLC: Chiralcel OJ-H column, eluent: 95 : 5 hexane–*i*PrOH. [d] 0.055 M in **8**. [e] Product (−)-**9**.



Scheme 3 Kinetic resolution in the asymmetric acylation of *rac* **8**.

selectivity factor of $S = 10.4$.[7] Kinetic resolution due to the faster second acylation of the minor enantiomer thus contributes to the high ee of (+)-**9** in entries 2–3 in Table 1. Another problem with CH_2Cl_2 is that it reacts with diamines **5** and **7** at rt to give the corresponding chloromethylammonium chloride salt by Menshutkin reaction,[7] a consequence of the high nucleophilicity associated to the quinuclidine core.[8]§

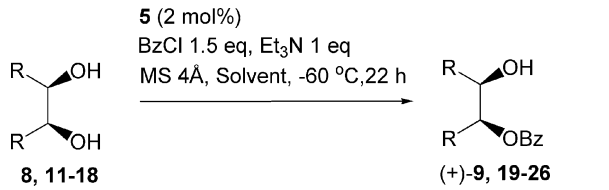
We therefore investigated other solvents. Of the ones tested (chloroform, dichloroethane, acetonitrile, acetone, *tert*-amyl alcohol, diethyl ether, tetrahydrofuran (THF), dimethoxyethane, dioxane, and ethyl acetate (EtOAc)),[9] THF and EtOAc performed better than CH_2Cl_2 and over-acylation could be largely avoided (entries 5–7 and 9–11).

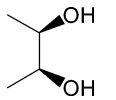
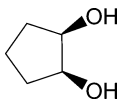
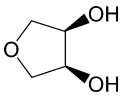
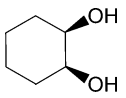
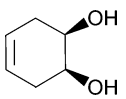
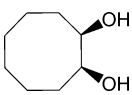
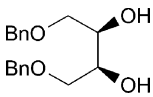
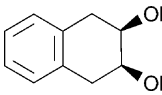
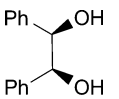
The faster reactions in these solvents allowed the catalyst loading to be lowered to 2% (entries 6 and 11). As previously found[4,6] and as also noted by Mizuta *et al.*[2] with other *Cinchona* alkaloid derived catalysts, the pseudo-enantiomeric quinidine-derived catalysts (in our case **7**) did not quite reach the same level of performance as the quinine-derived catalysts (entry 6).

The optimised conditions established for **9** were then applied to a number of other cyclic and acyclic diols (Table 2).

Cyclic and acyclic diols were efficiently desymmetrised with good to excellent conversions and moderate to excellent enantioselectivities (entries 1 to 18). In most cases, the amount of dibenzoates in the final mixture was <10%. Substrates incorporating phenyl groups afforded products with lower selectivities (entries 13 to 18). In part this is due to their low solubility at low temperature in the two solvents tested.

Table 2 Asymmetric benzoyl transfer to 1,2-diols catalysed by the chiral diamine **5**



Entry	Diol		Solvent	Ratio[a]	Product[b] (% yield)	ee[c] (%)
1		**11**	THF	1 : 93 : 6	**19** (77)	92
2			EtOAc	3 : 95 : 2	**19** (82)	90
3		**12**	THF	3 : 90 : 7	**20** (83)	82
4			EtOAc	2 : 92 : 6	**20** (87)	78
5		**13**	THF	6 : 77 : 17	**21** (77)	75
6			EtOAc	5 : 84 : 11	**21** (84)	77
7		**8**	THF	4 : 93 : 3	**9** (95)	93
8			EtOAc	4 : 91 : 5	**9** (92)	97
9		**14**	THF	10 : 86 : 3	**22** (76)	66
10			EtOAc	10 : 89 : 8	**22** (79)	84
11		**15**	THF	5 : 91 : 4	**23** (87)	72
12			EtOAc	5 : 92 : 3	**23** (86)	77
13		**16**	THF	16 : 64 : 20	**24** (64)	89
14			EtOAc	23 : 51 : 26	**24** (51)	93
15		**17**	THF	13 : 75 : 12	**25** (70)	45
16			EtOAc	17 : 70 : 13	**25** (65)	83
17		**18**	THF	24 : 71 : 5	**26** (68)	34
18			EtOAc	8 : 85 : 7	**26** (82)	13

[a] Product ratio of starting diol : monobenzoylated product : dibenzoylated product. [b] Isolated pure monobenzoylated (+)-products. [c] Determined by HPLC: Chiralcel OJ-H column, eluent: 95 : 5 hexane–^{i}PrOH.

In conclusion, the chiral diamines **5** and **7**, derived from *Cinchona* alkaloids and thus accessible from inexpensive commercially available materials, efficiently desymmetrise *meso*-1,2-diols. On screening conditions, THF or EtOAc emerged as the best solvents, giving highly enantioenriched monobenzoate at low temperature with low 2 mol% catalyst loadings.

Notes and references

‡ **4** and **6** are also commercially available from Aldrich and from Buchler GmbH, Braunschweig, Germany.
§ When using diamines **5** and **7** as catalysts in CH_2Cl_2, the diamine solution should be prepared and rapidly cooled to > -20 °C.

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9. Details will be reported in a forthcoming full paper.