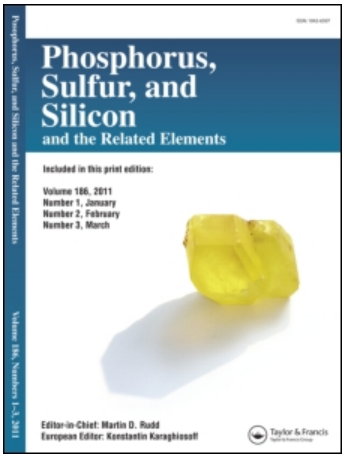

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Enantioselective Phase Transfer Catalytic Reactions. A Comparative Study on the Use of Cinchonidine Salts and Glucose-Based Lariat Ethers Including Phosphinoxidomethyl Derivatives

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Enantioselective Phase Transfer Catalytic Reactions. A Comparative Study on the Use of Cinchonidine Salts and Glucose-Based Lariat Ethers Including Phosphinoxidomethyl Derivatives

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Five model reactions including an epoxidation by alkylhydroperoxide or Darzens condensation, as well as Michael additions were accomplished under phase transfer catalytic conditions using cinchonidine salts or lariat ethers with side arms having HO or $Ph_2P(O)$ endgroups as the catalysts. In almost all cases, the use of lariat ethers with either hydroxyalkyl- or phosphinoxido N*-substituents led to better enantioselectivities than that of the three cinchonidine derivatives studied.*

Keywords *P*-functionalized lariat ethers; cinchonidine salts; phase transfer catalytic reactions; enantioselectivity

INTRODUCTION

From the point of view of "green chemistry," it is a real challenge to elaborate enantioselective procedures. Enantiopure products are especially

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important in the pharmaceutical and in the fine chemical industry; and, the application of antipodes is spreading in the agrochemical and cosmetical industry.

In earlier investigations, we developed *D*-glucose-based lariat ethers with a variety of side arms and tested them in enantioselective reactions.[1–5]

This article is a comparative study on the use of cinchonidine salts[6–8] and lariat ethers, selected as phase transfer catalysts, in model reactions that may be important from the point of view of the pharmaceutical industry.

RESULTS AND DISCUSSION

The phase transfer catalysts selected included three widely used cinchonidine salts—the 4-trifluoromethylbenzyl derivative **1**, the *N*-benzyl derivative **2**, and the *N*-anthracenylmethyl-cinchodinium salt **3**—representing the three generations of this prominent family of compounds, as well as four methyl-4,6-*O*-benzylidene-α-*D*-glucopyranoside-based lariat ethers **4–7** (Figure 1). Compounds **4** and **5** contain a hydroxyalkyl *N*-substituent,[1] while compounds **6** and **7** incorporate a diphenylphosphinoxidoalkyl side chain.[2] The phase transfer reactions were carried out in liquid-liquid (LL) and solid-liquid (SL) systems using 5 mol % of the catalysts. After the usual work-up procedure, the products were isolated by preparative TLC; the enantiomeric excess (ee %) was determined by optical rotation and by ^{1}H NMR spectroscopy using (+)-Eu(hfc)$_3$. For comparison purposes, our earlier results are also included in Tables I–V.

The first model reaction was the epoxidation of chalcone with *tert*-butylhydroperoxide in a liquid-liquid two-phase system using toluene and 20% aqueous sodium hydroxide, at 3–5°C. From the point of view

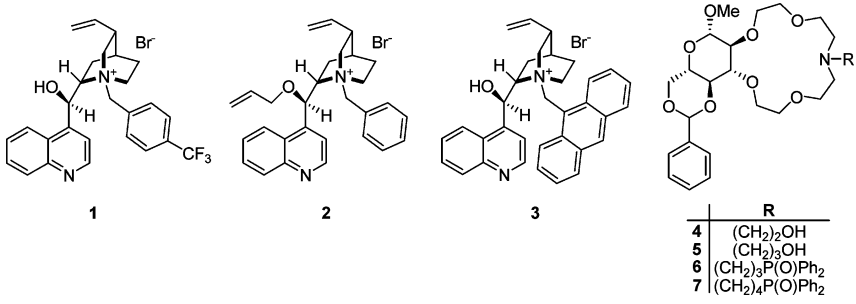
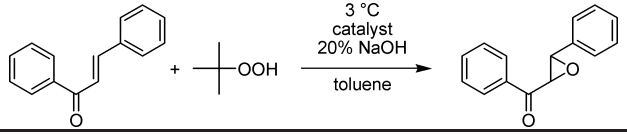


FIGURE 1

TABLE I Epoxidation of Chalcone with *tert*-Butylhydroperoxide in a Toluene-Aqueous NaOH Two-Phase System

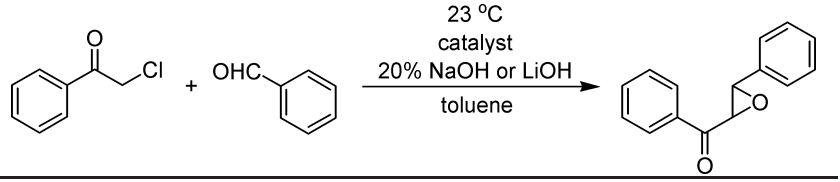


Catalyst	Yield (%)[a]	Opt. purity (ee %)[b] (2R, 3S)[6]
2	70	6
3	42	6
4	65	81[4]
5	72	92[4]
6	60	8
7	64	11

[a]Based on quantity isolated by preparative TLC; [b]Determined by ^{1}H NMR spectroscopy.

of enantioselectivity, we experienced that in this case, the catalysts of choice were the lariat ether with the β-hydroxyethyl side arm (**4**) and the derivative with a hydroxypropyl substituent (**5**), giving ee values of 81% and 92%, respectively. The use of the other catalysts

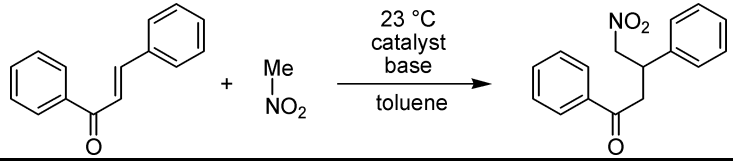
TABLE II *Darzens* Condenzation of α-Chloroacetophenone with Benzaldehyde in a Toluene-Aqueous NaOH Two-Phase System



Catalyst	Base	Yield (%)[a]	Opt. purity (ee %)[b]
1	LiOH	43	42 (2*S*, 3*R*)[6]
2	NaOH	60	25 (2*R*, 3*S*)
3	NaOH	59	20 (2*R*, 3*S*)
4	NaOH	76	65[1] (2*R*, 3*S*)
5	NaOH	49	72[1] (2*R*, 3*S*)
6	LiOH	10	5
6	NaOH	30	5
7	NaOH	35	8

[a]Based on quantity isolated by preparative TLC; [b]Determined by ^{1}H NMR spectroscopy.

TABLE III *Michael* Addition of Nitromethane to Chalcone in a Solid-Liquid System

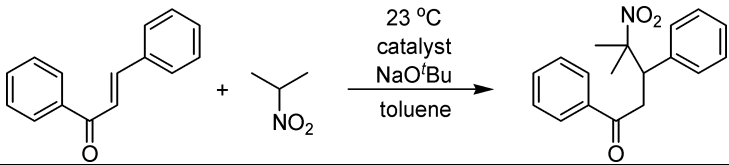


Catalyst	Base	Yield (%)[a]	Opt. purity (ee %)[b](S)[10]
2	NaO^tBu	60	10
3	NaO^tBu	35	39
4	Na_2CO_3	52	15
5	KF	23	16
7	NaO^tBu	50	33
7	KF	26	17
7	Na_2CO_3	44	19

[a]Based on quantity isolated by preparative TLC; [b]determined by ^{1}H NMR spectroscopy.

(**2**, **3**, **6**, and **7**) resulted in ee values below or around 10% (Table I). Remarkably, the *trans* epoxyketone was formed in all cases and the negative optical rotation referred to the enantiomer with 2*R*,3*S* configuration.[9]

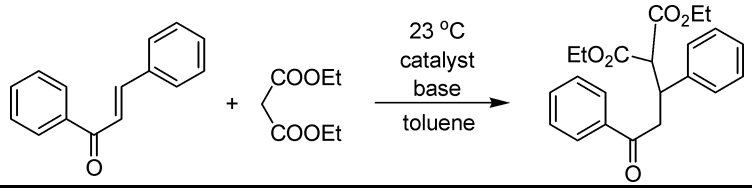
TABLE IV *Michael* Addition of 2-Nitropropane to Chalcone in a Solid-Liquid System



Catalyst	Yield (%)[a]	Opt. purity (ee %)[b] (R)[1]
2	25	16
3	20	23
4	51	62[1]
5	53	85[1]
6	32	77
7	43	95

[a]Based on quantity isolated by preparative TLC; [b]Determined by ^{1}H NMR spectroscopy and optical rotation.

TABLE V Addition of Diethyl Malonate to Chalcone in a Solid – Liquid System



Catalyst	Base	Yield (%)[a]	Opt. purity (ee %)[b] (S)[11]
1	Na_2CO_3	no reaction	
3	NaO^tBu	no reaction	
5	Na_2CO_3	36	42
6	Na_2CO_3	25	26
7	Na_2CO_3	29	30

[a]Based on quantity isolated by preparative TLC; [b]Determined by ^1H NMR spectroscopy.

The second reaction studied led to the same 2,3-epoxy-1,3-diphenyl-1-propanone, but by means of the Darzens condensation of α-chloroacetophenone and benzaldehyde in toluene-aqueous alkalic hydroxide two-phase system. The special attention paid to the Darzens condensations is justified by its pharmaceutical significance. In this case, using sodium hydroxide, the hydroxypropyl- (**5**) and the hydroxyethyl (**4**) lariat ethers proved to be the best catalysts giving ee values of 72% and 65%, respectively. This was followed by the ee value of 42% achieved in the presence of cinchonidine **1** and lithium hydroxide as the base. The other phase transfer catalysts **2**, **3**, **6**, and **7** provided ee values of 25%, 20%, 5%, and 8%, respectively (Table II). Again the *trans* epoxyketone was formed in these experiments and its levorotatory enantiomer (2*R*,3*S*) was found to be in excess,[9] except when catalyst **1** was used, which yielded the enantiomer with 2*S*,3*R* configuration.[6]

The next model reactions involved Michael additions to chalcone carried out in solid-liquid two-phase systems using mainly sodium *tert*-butoxide, sodium carbonate, or potassium fluoride as the base and toluene as the solvent. From the point of view of enantioselectivity, the addition of nitromethane could be best catalyzed using cinchonidine **3** (ee: 39%) and the *P*-functionalized lariat ether **7** (ee: 33%), both in the presence of sodium *tert*-butoxide. The enantioselectivities detected in the presence of other catalysts (e.g., **2**) or using other bases were even lower (10–19%) (Table III). The absolute configuration of the major enantiomer should be *S* on the basis of the optical rotation.[10]

The Michael addition of 2-nitropropane to chalcone was performed in the presence of sodium *tert*-butoxide. In this particular case, the use of diphenylphosphinoxidobutyl lariat ether (**7**) gave the best result; the ee value was as high as 95%. The use of the hydroxypropyl derivative **5** led to a somewhat lower ee value (85%). Moreover, the results obtained with lariat ethers **6** and **4** were also quite good (the ee values were 77 and 62%, respectively). With cinchonidines (**2** and **3**) only ee values around 20% could be achieved (Table IV). In each case, the (+)-*R* enantiomer was found to be in excess.[1]

Michael addition of diethyl malonate to chalcone could only be accomplished in the presence of lariat ethers and sodium carbonate in solid-liquid phase. The ee values fall in the range of 26–42% (Table V). All crown catalysts generated the formation of an excess of the *S* enantiomer.[11]

In summary, our experiments show that in the epoxidation and Darzens condensation studied, the hydroxypropyl lariat ether **5** is the best phase transfer catalyst leading to ee values of 92 and 72%, respectively. Among the Michael additions studied, the addition of 2-nitropropane could be performed in an enantioselectivity of 95% using the phosphinoxido-butyl lariat ether **7**.

EXPERIMENTAL

The cinchonidine derivatives **1**–**3** were purchased from Aldrich, while the lariat ethers **4**–**7** were prepared as described earlier.[1,2] The products of the model reactions, 2,3-epoxy-1,3-diphenyl-1-propanone, 4-nitro-1,3-diphenylbutan-1-one, 4-methyl-4-nitro-1,3-diphenylpentan-1-one, and methyl-3,5-diphenyl-2-methoxycarbonyl-5-oxopentanoate were identified by comparison with authentic samples.[1,4,9–11]

General Procedure for the Epoxidation of Chalcone by *tert*-Butylhydroperoxide

A mixture of chalcone (1.44 mmol) and the appropriate catalyst (0.10 mmol) in toluene (3 mL) and 20% aq. NaOH (1 mL) was treated with 5.5 M *tert*-butyl hydroperoxide in decane (0.5 mL, 2.88 mmol) and the mixture was stirred at 2–5°C. After a reaction time of 1–10 h, a new portion of toluene (7 mL) and water (10 mL) was added, and the mixture was stirred for several minutes. The organic phase was washed with 10% aqueous hydrochloric acid (2 × 10 mL); and, then with water (10 mL), and, finally it was dried (Na_2SO_4). The crude product obtained after evaporating the solvent was purified by preparative TLC (silica gel, hexane/ethyl acetate, 10 : 1 as the eluant) to give pure

(2*R*,3*S*)-2,3-epoxy-1,3-diphenyl-3-propan-1-one. M.p. 64–66°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.02 (d, 2H), 7.63 (t, 1H), 7.50 (t, 2H), 7.38–7.44 (m, 5H), 4.30 (d, $J = 1.9$ Hz, 1H), 4.09 (d, $J = 1.9$ Hz, 1H); the data correspond to those of an authentic sample;[9] HRMS, $M^+_{found} = 224.0830$, $C_{15}H_{12}O_2$ requires 224.0837. Yields and optical purities are listed in Table I; for the best case (92% ee), $[\alpha]^{20}_D = -196$.[4,5]

General Procedure for the Darzens Condensation of α-Chloroacetophenone and Benzaldehyde

30% NaOH solution (1.0 mL) was added to a toluene solution (3 mL) of phenacyl chloride (1.3 mmol), benzaldehyde (1.9 mmol) and the catalyst (0.10 mmol). The mixture was stirred under an argon atmosphere at room temperature for 1–4 h. After completion of the reaction, toluene (7 mL) was added to the mixture and the organic phase was washed with 10% aqueous hydrochloric acid (2 × 10 mL) and then with water (10 mL). Finally, the organic phase was dried (Na_2SO_4) and the solvent was evaporated. The product was isolated by preparative TLC using CH_2Cl_2 as eluant to give, except one case, (2*R*,3*S*)-2,3-epoxy-1,3-diphenyl-3-propan-1-one. Physical and spectroscopic data of the epoxyketone were similar to the data reported above. Yields and enantioselectivities are listed in Table II; for the best case (72% ee), $[\alpha]^{20}_D = -154$.[1]

General Procedure for the Michael Reactions of Chalcone

The corresponding azacrown catalyst (0.10 mmol) was added to a solution of *trans* chalcone (1.44 mmol) and nitromethane, 2-nitropropane or diethylmalonate (3.36 mmol) in dry toluene (3 mL). Sodium *tert*-butoxide (0.5 mmol), dry Na_2CO_3 or KF (2 mmol) was used as the base. The mixture was stirred at room temperature under argon. After a reaction time of 20 to 168 h, a new portion of toluene (7 mL) and water (10 mL) was added, and the mixture was stirred for several minutes. The organic phase was washed with water and dried (Na_2SO_4). The crude product obtained after evaporating the solvent was purified by preparative TLC (silica gel, hexane / ethyl acetate, 10 : 1 as the eluant) to give pure adducts.

For the chalcone-nitromethane adduct (1,3-diphenyl-4-nitrobutan-1-one): m.p. 87–89°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85 (d, 2H), 7.53 (t, 1H), 7.42 (t, 2H), 7.18–7.32 (m, 5H), 4.46 (q, $J = 17.6$ Hz, 10.4 Hz, 2H), 3.38 (d, $J = 3.2$ Hz, 2H); the data correspond to those of an authentic sample.[10] Yields and optical purities are listed in Table III; for the best case (39% ee), $[\alpha]^{20}_D = +40.2$ (c 1.5, $CHCl_3$).

For the chalcone-2-nitropropane adduct (3-(*R*)-4-Methyl-4-nitro-1,3-diphenylpentan-1-one): m.p. 146–148°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85 (d, 2H), 7.53 (t, 1H), 7.42 (t, 2H), 7.18–7.32 (m, 5H), 4.15 (dd, $J = 10.4$ Hz, 3.3 Hz, 1H), 3.67 (dd, $J = 17.2$ Hz, 10.4 Hz, 1H), 3.27 (dd, $J = 17.2$ Hz, 3.2 Hz, 1H), 1.63 (s, 3H), 1.54 (s, 3H); the data correspond to those of an authentic sample.[1] HRMS, $M^+_{found} = 297.1367$, $C_{15}H_{12}O_2$ requires 297.1365. Yields and optical purities are listed in Table IV; for the best case (95% ee), $[\alpha]_D^{20} = 76.8$ (for pure (+)-(*R*) enantiomer, $[\alpha]_D^{20} = 80.8$ (*c* 1, CH_2Cl_2)[1]).

For the chalcone-diethylmalonathe adduct ((*S*)-Methyl-3,5-diphenyl-2-methoxy-carbonyl-5-oxopentanoate): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88–7.91 (m, 2H), 7.17–7.56 (m, 8H), 4.20 (dt, $J = 5.3$ Hz, 9.2 Hz, 1H), 3.86 (d, $J = 9.2$ Hz, 1H), 3.73 (s, 3H), 3.71 (d, $J = 5.3$ Hz, 1H), 3.52 (dd, $J = 5.3$ Hz, 7.9 Hz, 1H), 3.51 (s, 3H); the data correspond to those of an authentic sample;[11] MS m/z 340 (M^+), 309, 308, 105 (base peak). Yields and optical purities are listed in Table V; for the best case (42% ee), $[\alpha]_D^{20} = +14.0$ (c 2.0, $CHCl_3$).

REFERENCES

[1] P. Bakó, E. Czinege, T. Bakó, M. Czugler, and L. Tőke, *Tetrahedron: Asymmetry,* **10,** 4539 (1999).

[2] T. Novák, J. Tatai, P. Bakó, M. Czugler, Gy. Keglevich, and L. Tőke, *Synlett.*, 424 (2001).

[3] T. Bakó, P. Bakó, Gy. Keglevich, N. Báthori, M. Czugler, J. Tatai, T. Novák, Gy. Parlagh, and L. Tőke, *Tetrahedron: Asymmetry,* **14,** 1917 (2003).

[4] T. Bakó, P. Bakó, Gy. Keglevich, P. Bombicz, M. Kubinyi, K. Pál, S. Bodor, A. Makó, and L. Tőke, *Tetrahedron: Asymmetry,* **15,** 1589 (2004).

[5] P. Bakó, A. Makó, Gy. Keglevich, M. Kubinyi, and K. Pál, *Tetrahedron: Asymmetry,* **16,** 1861 (2005).

[6] S. Arai, Y. Shirai, T. Ishida, and T. Shioiri, *Tetrahedron,* **55,** 6375 (1999).

[7] E. J. Corey, F. Xu, and M. C. Noe, *J. Am. Chem. Soc.,* **119,** 12414 (1997).

[8] H. M. R. Hoffmann and J. Frackenpohl, *Eur. J. Org. Chem.,* 4293 (microreview) (2004).

[9] B. Marsman and H. Wynberg, *J. Org. Chem.,* **44,** 2312 (1979).

[10] A. Sera, K. Takagi, H. Katayama, and H. Yamada, *J. Org. Chem.,* **53,** 1157 (1988).

[11] H. Sasai, T. Arai, Y Satow, K. N. Houk, and M. Shibasaki, *J. Am. Chem. Soc.,* **117,** 6194 (1995).