Asymmetric Phase-Transfer Catalysis

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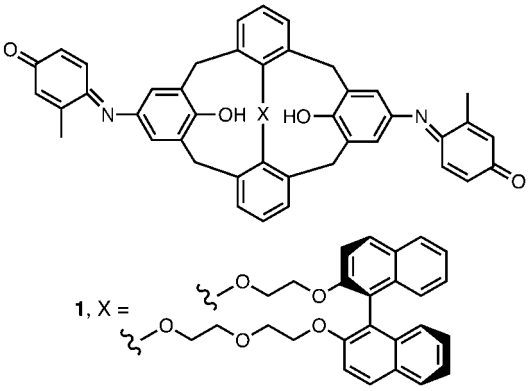
The selective recognition of enantiomeric ions and the efficient transmission of stereochemical information between contacting ions remain important goals for many chemists.[1–3] For example, the molecular sensor[1] **1** can distinguish between the enantiomers of primary ammonium ions **2** and reports this

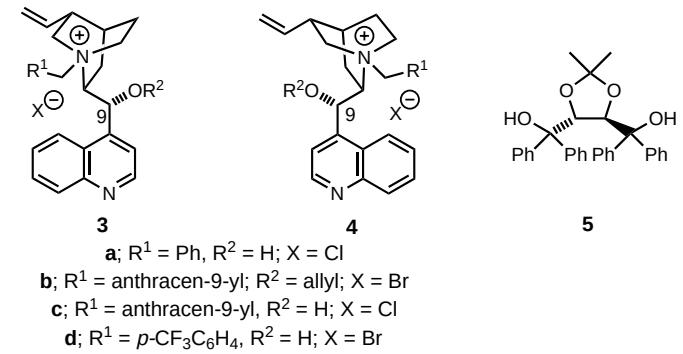


2

information as a discernible color change; (*S*)-camphor-10-sulfonate can direct the enantioselective folding of a protonated polyguanine into helices of predominantly one handedness.[2]

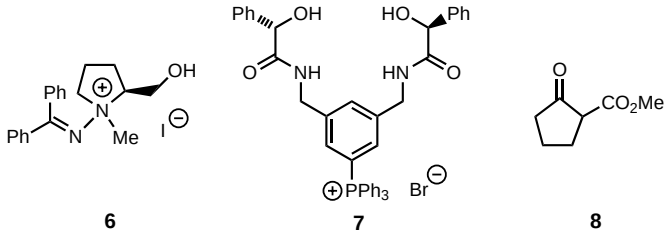
Phase-transfer catalysts can be effective tools for accelerating[4] and controlling the regiochemistry[5] of synthetic reactions. Although isolated examples of highly enantioselective phase transfer catalyzed reactions have been known for many years,[6] some "high" enantioselectivities claimed by early workers have been attributed to trace impurities with high optical rotations.[7] Recently, however, the structural features of cinchonidinium (**3**) and cinchoninium salts (**4**) which are necessary for effective asymmetric phase-transfer catalysis (PTC) have been unravelled.[3]

A key discovery was that the size of the R^1 substituent of salts **3** and **4** has a profound effect on the enantioselectivity of alkylation of the glycine derivative **9** (Scheme 1, Table 1). The benzyl cinchoninium salt **3a** induces a modest level of enantioselectivity in the reaction of **9** with benzyl bromide

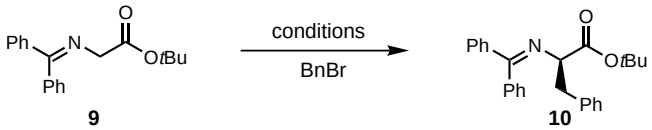


3 **4** **5**

a; R^1 = Ph, R^2 = H; X = Cl
b; R^1 = anthracen-9-yl; R^2 = allyl; X = Br
c; R^1 = anthracen-9-yl, R^2 = H; X = Cl
d; R^1 = *p*-$CF_3C_6H_4$, R^2 = H; X = Br



6 **7** **8**



9 **10**

Scheme 1. Alkylation of **9** under PTC conditions; see Table 1 for details.

(entry 1, Table 1).[8] Corey et al.[3] as well as Lygo and Wainwright[9] have found that by changing the quaternary ammonium substituent R^1 to the bulkier anthracen-9-ylmethyl group, good to excellent levels of enantioselectivity can be obtained through the use of either solid–organic or aqueous–organic biphasic systems (entries 2–4, Table 1). An important feature of this methodology is that the cinchonidinium salts **3** and the cinchoninium salts **4** induce almost equal levels and opposite senses of enantioselectivity (compare entries 3 and 4, Table 1). Optically active unnatural amino acids[10] can be prepared by alkylation of **9**, and an extended enolate has also been alkylated with high levels of enantioselectivity using this technology.[11]

A new approach to the design of phase-transfer catalysts has recently been reported; Corey et al. studied the X-ray

Table 1. Asymmetric PTC alkylation of **9** with benzyl bromide.

Entry	Cat.[a]	*T* [°C]	*t* [h]	Reagents	Solvent	Product	*ee* [%]	Yield [%]	Ref.
1	**3a**	25	22	NaOH	H_2O	(*R*)-**10**	66	75	[8]
2	**3b**	−78	22	$CsOH \cdot H_2O$	CH_2Cl_2	(*R*)-**10**	99.5	73	[3]
3	**3c**	25	18	KOH	H_2O/PhMe	(*R*)-**10**	89	63	[9]
4	**4c**	25	18	KOH	H_2O/PhMe	(*S*)-**10**	91	68	[9]

[a] In each case 10 mol% of the catalyst was used.

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  1433-7851/99/3811-1583 $ 17.50+.50/0

crystal structures of cinchonidinium salts and formulated a model which explains the highly enantioselective alkylation of the enolate of **9**.[3] The positive charge of ammonium salts is delocalized onto the carbon and hydrogen atoms surrounding the quaternary nitrogen atom; the enolate **11** is in close contact with the chiral ammonium salt and is alkylated highly enantioselectively. A model[3] which has been proposed to explain the efficient transfer of stereochemical information between the ammonium salt **3b** and the enolate **11** is summarized in Figure 1.

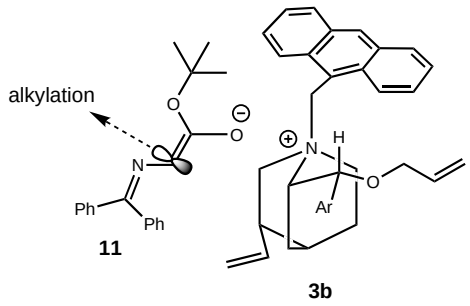
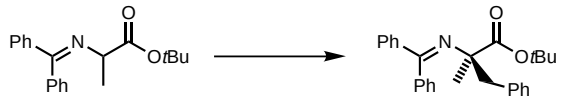


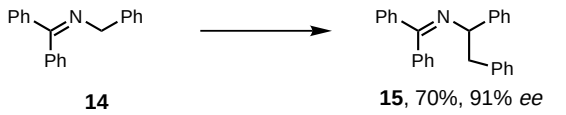
Figure 1. Transition state proposed to explain the enantioselective alkylation of the enolate **11**.

Although alkylations of the glycine derivative **9** have become standards by which chiral phase-transfer catalysts are judged, other asymmetric alkylations under PTC conditions have been studied. For example, 10 mol% of the TADDOL **5** can mediate asymmetric alkylation of **12**, giving the product **13** with up to 82% *ee* (Scheme 2; TADDOL = $\alpha,\alpha,\alpha',\alpha'$-tetraaryl-2,2-dimethyl-1,3-dioxolan-4,5-



Scheme 2. Conditions: 10 mol% of **5**, BnBr, NaOH, PhMe, 15–24 h, room temperature.

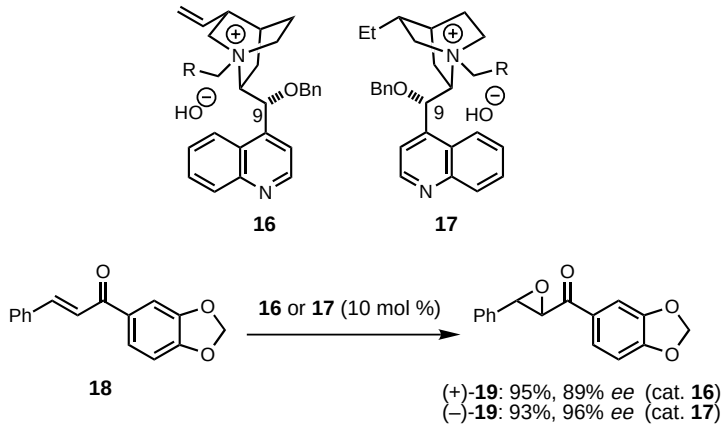
dimethanol).[12] The hydrazonium salt **6** (2 mol%) greatly accelerates the alkylation of the Schiff base **14**, and alkylated products **15** are obtained with high enantiomeric excess (Scheme 3).[13] Manabe has prepared the chiral quaternary



Scheme 3. Conditions: 2 mol% of **6**, BnBr, K_2CO_3, KOH, CH_2Cl_2, 24 h, room temperature.

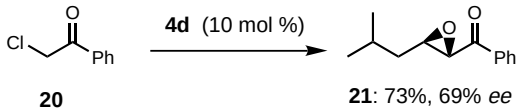
phosphonium salt **7** with a multiple hydrogen bonding site; this salt accelerates the alkylation of the ketoester **8**, giving products with about 40% *ee* at room temperature.[14]

Chiral phase-transfer catalysts have now been exploited in a wide range of reactions with anionic intermediates. For example, the salts **16** and **17** have been used to catalyze the nucleophilic epoxidation of enones (e.g. **18**) to give either enantiomer of epoxides such as **19** (Scheme 4).[15] Once again, the large anthracen-9-ylmethyl substituent is thought to have a profound effect on the enantioselectivity of the process.



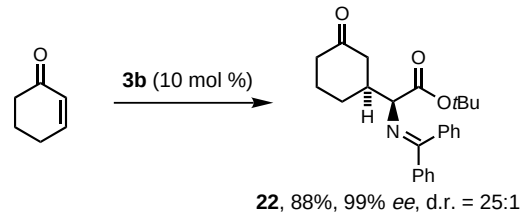
Scheme 4. Conditions: 11% aq. NaOCl, PhMe, 48 h, room temperature. R = anthracen-9-yl.

Epoxides similar to **19** can also be made enantioselectively by an asymmetric Darzens reaction under PTC conditions; here, the cinchoninium salt **4d** allowed the epoxide **21** to be prepared with reasonably high enantiomeric excess (Scheme 5).[16] Michael additions, too, can be rendered



Scheme 5. Conditions: *i*BuCHO, $LiOH \cdot H_2O$, Bu_2O, 134 h, 4 °C.

asymmetric by adding a chiral phase-transfer catalyst. For example, in the presence of 10 mol% of **3b**, the enolate of **9** added to cyclohexenone with excellent diastereoselectivity to give the ketoester **22** with greater than 99% *ee* (Scheme 6).[10]



Scheme 6. Conditions: $CsOH \cdot H_2O$, **9**, CH_2Cl_2, –78 °C.

Several families of efficient chiral phase-transfer catalysts are now available for use in asymmetric synthesis. To date, the highest enantiomeric excesses (>95% *ee*) are the exclusive preserve of salts derived from cinchona alkaloids with an anthracen-9-ylmethyl substituent on the bridgehead nitrogen atom (e.g. **3b**, **4b**). These catalysts will be used to improve the enantioselectivity of existing asymmetric PTC reactions and will be exploited in other anion-mediated processes both in the laboratory and industrially.

German version: *Angew. Chem.* **1999**, *111*, 1685–1687

  1433-7851/99/3811-1584 $ 17.50+.50/0

Keywords: alkylations · asymmetric catalysis · epoxidations · molecular recognition · phase-transfer catalysis

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