Design, synthesis, and application of tartaric acid derived *N*-spiro quaternary ammonium salts as chiral phase-transfer catalysts†,‡

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Abstract

A novel class of tartaric acid-derived *N*-spiro quaternary ammonium salts was synthesised starting from known TADDOLs. These compounds were found to catalyse the asymmetric α-alkylation of glycine Schiff bases with high enantioselectivities and in good yields.

The use of chiral phase-transfer catalysts (PTCs) for asymmetric reactions has attracted considerable interest over the last three decades.[1] Among the different catalytically active structural motifs like crown ethers, ammonium salts, and phosphonium salts, chiral quaternary ammonium salts have found the most widespread applications.[1] Following the seminal reports of Wynberg[2] and a group of Merck scientists[3] describing the successful use of chiral quaternary ammonium salts for asymmetric epoxide formation[2] or methylation of a phenylindanone derivative,[3] cinchona-based PTCs have been thoroughly investigated in the 1990s.[4-6] Due to their high catalytic potential and broad application scope, these catalysts still belong to the most commonly employed and most powerful PTCs as shown in several recent reports.[7,8]

In 1999, Maruoka *et al.* introduced *C*$_2$-symmetric binaphthyl-based spiro ammonium salts as chiral PTCs.[9] These Maruoka catalysts proved to be very efficient even at low catalyst loadings (<1 mol%) for a variety of asymmetric transformations.[1,9,10] In addition, also Shibasaki's tartaric acid-derived bidentate PTCs[11] and Lygo's spirocyclic catalysts[12] were found to be highly efficient in asymmetric catalysis.

However, considering the fact that asymmetric phase-transfer catalysis using quaternary ammonium salts has been investigated for three decades now, it is somewhat surprising that besides the already mentioned privileged catalyst structures only a few other, (most of them significantly less powerful) ammonium salt-based PTCs have been reported so far.[13,14]

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One of the main demands for novel catalysts is easy accessibility from sufficiently available chiral starting materials. Tartaric acid (**1**) has obtained a prominent position in asymmetric catalysis as both enantiomers are readily available in ample quantities. Although Shibasaki *et al.* have demonstrated the high potential of tartaric acid-derived bidentate PTCs,[11] others were less successful in their attempts to synthesize powerful tartaric acid-derived catalytically active quaternary ammonium salts.[13]

Considering the high potential of tartaric acid-derived TADDOLs (**2**) as chiral ligands in (transition−) metal catalysis,[15] we targeted the use of TADDOLs as starting materials for the synthesis of a new class of quaternary ammonium salts. Inspired by Maruoka's success using axially-chiral C_2-symmetric binaphthyl based *N*-spiro quaternary ammonium ions,[1,9,10] and keeping in mind that TADDOLs represent a unique moiety with electronic and steric properties different from other chiral motives, we inferred that the centro-chiral C_2-symmetric *N*-spiro ammonium compounds **3** would be interesting targets with respect to the development of novel chiral PTCs (Scheme 1).

Catalyst syntheses

The syntheses of TADDOL derivatives were carefully investigated and described in the past, especially by the Seebach group.[15,16] While different aryl substituents have to be introduced early in the synthesis from **1**, modifications of the hydroxyl groups are most commonly achieved *via* conversion of **2** to dichloro compounds **4**, which can then be reacted with different nucleophiles.[15-17]

Initial experiments to develop a suitable synthesis route were carried out using the dichloride **4a** (Ar = Ph)[16a] as the starting material. Subsequent carbon-chain elongation could be achieved using TMSCN (2.5 eq.) in the presence of catalytic amounts of $SnCl_4$ (25%).[18] With the dinitrile **5a** in hand, conversion into the *sec*-amine **6a** was thought to be just a matter of standard functional group manipulations. However, neither attempts to saponify **6a**, nor conversion into the corresponding dialdehyde upon treatment with DIBAL-H were feasible due to the low reactivity of **5a** (under harsher conditions partial decomposition but no product formation was observed). Using $LiAlH_4$ at room temperature in different ethereal solvents also did not affect the cyano groups, whereas a partial decomposition was observed at higher temperatures. In addition, using other hydride donors (combined with different additives) did not give any products either.

Surprisingly, upon refluxing **5a** with an excess of $LiAlH_4$ (10 eq.) in toluene for 2 h, full consumption of **5a** was observed. Besides mainly unidentified decomposition products also 10% of the *sec*-amine **6a** could be isolated. After careful optimization of the reaction conditions, it was found that refluxing a mixture of **5a** and 20 eq. $LiAlH_4$ in mesitylene for 30–45 min gave access to **6a** in 37% isolated yield. Although only modest in yield, the reaction was found to be scalable to several grams, giving the key-intermediate **6a** in sufficient quantities for further elaborations. The final quaternarization could be achieved upon refluxing with 1,4-dibromobutane (CH_3CN, K_2CO_3).

As depicted in Scheme 2, a variety of different aryl substituents was introduced successfully. Noteworthy, whereas TADDOLs with aryl groups having electronic properties similar to a phenyl group were easily converted into **6**, more electron-rich as well as more electron-poor aryl group containing ones failed as the corresponding dichlorides **4** could not be obtained. The different amines **6** showed similar quaternarization behaviour as **6a**, giving access to a small set of different quaternary ammonium bromides **3** in reasonable yields.[19]

Application in asymmetric phase-transfer catalysis

Having developed a reliable route for the syntheses of C_2-symmetric *N*-spiro ammonium salts **3**, we next evaluated the catalytic potential of these compounds in the asymmetric α-alkylation of the glycine ester benzophenone Schiff base **7** with benzylbromide (**8**).

Using the *L*-**1** derived ammonium bromides **3aa–3ga** the best-suited aryl substituent was identified first (Table 1, entries 1–8). All reactions were carried out for 20 h under biphasic conditions using 10 mol% catalyst, 25 eq. KOH, and similar dilution. As expected, the choice of the aryl group was crucial not only with respect to enantioselectivity, but also with respect to the reaction rate. Having identified the *p*-biphenyl containing **3ga** as the best among the tested catalysts (entry 8), we next investigated the ammonium bromides **3gb** and **3gc** (entries 9 and 10). Whereas the *o*-xylene-derived catalyst **3gb** gave a reduced enantiomeric excess of 51%, the naphthyl-based **3gc** was found to favour the oppositely configured (*R*)-**9**, albeit in low yield and low ee only.

With the ammonium bromide **3ga** as the most promising among the so far synthesized PTCs we next screened different reaction conditions (entries 11–22 give a representative overview about the most significant results obtained hereby). Interestingly, the use of CH_2Cl_2 gave (*R*)-**9** predominantly (entries 12, 13), whereas no stereodifferentiation could be achieved in THF (entry 14). In addition, liquid–liquid biphasic conditions were found to be superior over liquid-solid ones (entry 8 *vs.* 11). Besides a strong solvent effect, the choice of the base was also found to be crucial (entries 18,19). Lowering the catalyst amount to 1 mol% resulted in a reduced ee and yield (entry 17). Finally, we found that carrying out the reaction with an excess of electrophile in the presence of 10 mol% **3ga** at −35 °C presents a good compromise to obtain (*S*)-**9** in good yield and satisfactory enantioselectivity in a reasonably short reaction time (entry 22). In addition, the catalyst could be recovered (>85%) and reused several times without negatively affecting its efficiency.

Having identified the most active catalyst and the optimum reaction conditions for the asymmetric α-alkylation of **7** with benzylbromide (**8**) we next carried out a short screening of different electrophiles to examine the scope of this protocol. We were glad to find that other electrophiles were tolerated well, giving the corresponding products in good yields and reasonable enantioselectivities (Table 2).

In conclusion, a series of novel C_2-symmetric tartaric acid-derived *N*-spiro quaternary ammonium salts has been successfully synthesized. The catalytic potential of these compounds in the asymmetric α-alkylation of glycine Schiff base strongly depends on their aryl substituent and on the reaction conditions. Under optimised conditions, the α-alkylated

products could be obtained in good yields and up to 93% ee. Further optimizations of the catalyst structures are currently undertaken and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

## Notes and references

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19. A detailed discussion of our efforts to synthesise these PTCs as well as scope and limitations of the developed synthesis route will be reported in a full paper in due course.

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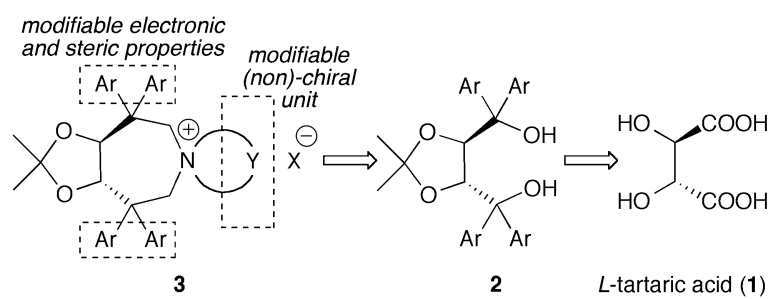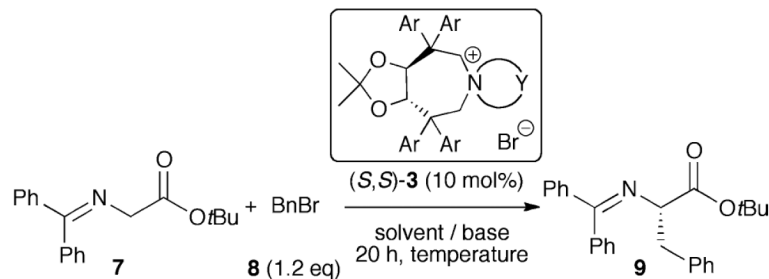
Scheme 1.
Targeted tartaric acid-based C_2-symmetric PTCs.
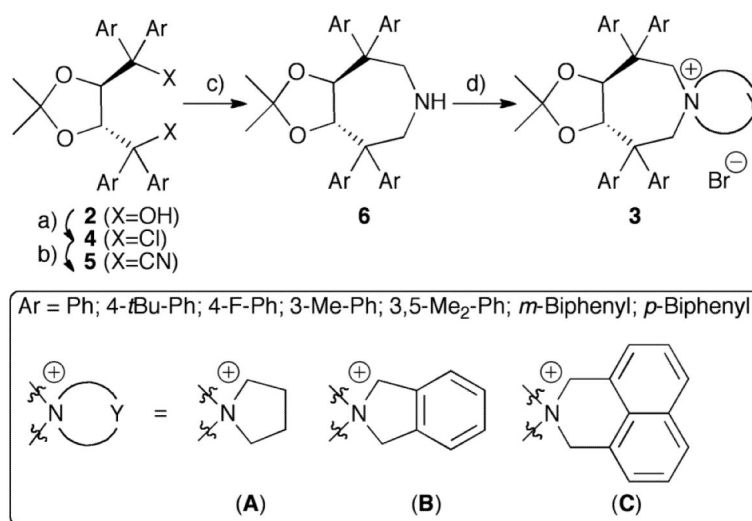
Scheme 2.

Syntheses of azepane-based PTCs **3**. a) $SOCl_2$, Et_3N, CH_2Cl_2, 25 °C b) TMSCN, $SnCl_4$, 25 °C, 47–63% (over two steps) c) $LiAlH_4$, mesitylene, reflux, 29–43% d) Br-Y-Br, K_2CO_3, CH_3CN, reflux, 49–69%.

Table 1

Identification of the most active catalyst for the asymmetric α-alkylation of **7** and of the optimum reaction conditions

Entry	Cat.	Ar	Y^a	Solvent	Base	$T/°C$	Yield[b] (Conv.)[c] (%)	ee (%)[d] (Conf.)[e]
1	**3aa**	Ph	A[a]	PhMe	KOH (50%)	rt	70 (~90)	34 (S)
2						−20	55 (~70)	45 (S)
3	**3ba**	4-*t*Bu-Ph					30(~50)	61 (S)
4	**3ca**	4-F-Ph					35 (~50)	34 (S)
5	**3da**	3-Me-Ph					77 (~90)	55 (S)
6	**3ea**	3,5-Me$_2$-Ph					47 (~60)	5 (S)
7	**3fa**	*m*-Biphenyl					45 (~60)	7 (S)
8	**3ga**	*p*-Biphenyl					65 (~80)	79 (S)
9	**3gb**		B[a]				57 (~80)	51 (S)
10	**3gc**		C[a]				21 (~30)	25 (R)
11	**3ga**	*p*-Biphenyl	A[a]	PhMe	CsOH·H$_2$O	−70	54 (~70)	39 (S)
12				CH$_2$Cl$_2$		−70	35 (~50)	38 (R)
13					KOH (50%)	−20	53 (~70)	28 (R)
14				THF			71 (~90)	7 (S)
15				PhF			82 (>90)	68 (S)
16				benzene: PhMe (2:1)			69 (~80)	82 (S)
17[f]							37 (~50)	57 (S)
18					NaOH (50%)		33 (~50)	19 (S)
19					CsOH (50%)		24 (~40)	65 (S)
20				benzene : PhMe (1 : 1)	KOH (50%)	−35	61 (~75)	84 (S)
21				PhMe			54 (~70)	87 (S)
22[g]							81 (quant)	87 (S)

[a] See Scheme 2.

[b] Isolated yields.

[c] Judged by ^{1}H NMR or TLC of the crude product.

[d] Determined by HPLC using a chiral stationary phase.

[e] Determined by comparison of the HPLC retention time and optical rotation with literature[6,9] values.

^{f}Using 1% catalyst.

^{g}Using 3 eq. **8**.

Table 2

Scope of the α-alkylation of **7** using different electrophiles

Entry	RBr	Electrophile	Product	Yield^a (%)	ee (%)^b (Conf.)^c
1	PhCH$_2$Br	**8**	**9**	81	87 (*S*)
2		**10**	**11**	83	76 (*S*)
3		**12**	**13**	80	85 (*S*)
4		**14**	**15**	79	80 (*S*)
5		**16**	**17**	79	93 (*S*)
6		**18**	**19**	71	78 (*S*)

^{a}Isolated yields

^{b}Determined by HPLC using a chiral stationary phase.

^{c}Determined by comparison of the HPLC retention time and optical rotation with literature values.[6,9,20]