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Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 15 (2004) 2603–2607

The counterion effect in the phase-transfer catalyzed asymmetric synthesis of α-amino acids promoted by anthryl-derived dimeric *Cinchona* ammonium salts

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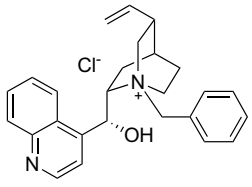
Received 13 July 2004; accepted 16 July 2004
Available online 21 August 2004

Dedicated to the memory of Dr. Juan C. del Amo

Abstract—Dimeric ammonium salts derived from cinchonidine or cinchonine and a bridging (anthracen-9,10-yl)dimethyl moiety bearing different counter-anions are used as chiral phase-transfer catalysts in the asymmetric alkylation reaction of a benzophenone-imine *tert*-butyl glycinate. The counterion generally has a great influence on the final enantioselectivity, the tetrafluoroborate or hexafluorophosphate anion giving place to higher ee's compared to the chloride or bromide anions. The more noticeable differences are generally observed when the hexafluorophosphate salts of *O*-allylated dimeric catalysts are employed.

1. Introduction

Optically active α-amino acids are well-known interesting compounds, their synthesis being an important synthetic challenge, which has boosted the development of many methodologies.[1] Amongst all of them, the phase-transfer catalysis (PTC)[2] applied to the asymmetric alkylation[1r] of glycine and alanine Schiff bases is probably the most simple and easy to scale-up. Thus, the enantioselective alkylation of amino acid imines under PTC conditions catalyzed by quaternized *Cinchona* alkaloids,[3] such as the cinchonidine-derived ammonium salts of the type **1** and **2**, pioneered by O'Donnell **1**[4] and improved by Lygo **2a**[5] and Corey **2b**,[6] has allowed high degrees of enantioselection using a very simple procedure to be obtained. In addition, dimeric,[7] trimeric,[8] dendrimeric[9] *Cinchona* alkaloid-derived catalysts, and even polymer-supported *Cinchona*-derived species have been employed.[10] Moreover, catalysts such as spiro ammonium[11] and phosphonium salts,[12] TADDOL[13a,b] and other tartaric derivatives,[13c,d] guanidinium salts,[13e] binaphthyl-derived amines[13b,14] and salen–metal complexes[15] have also been used.



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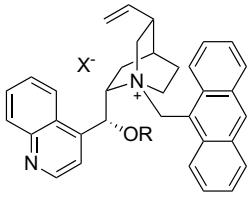

2a, R = H, X = Cl
2b, R = Allyl, X = Br

The counter-anion present in these ammonium salts is usually a halogenide, a logical consequence of the common use of a halogenated compound for the *N*-quaternization, this anion always being considered irrelevant. However, in a recently reported synthesis of the tetrapeptide aeruginosin 298-A,[16] the influence of the counter-anion in an asymmetric PTC alkylation reaction of *tert*-butyl *N*-(diphenylmethylene)glycinate using a homochiral two-center tartrate-derived bis-ammonium salt[13c] was observed. Thus, by changing the iodide counter-anion to a tetrafluoroborate, the enantioselectivity was improved from 74% to 81% ee, this effect being the first example of such an influence in PTC reactions.[16] Inspired by this observation, we decided to study the counterion effect in the asymmetric PTC alkylation reaction

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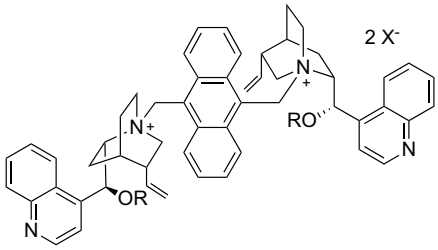
doi:10.1016/j.tetasy.2004.07.025

of iminic glycine esters when using our previously prepared dimeric cinchonidinium and cinchoninium salts **3a** and **4a**, respectively.[7c] This type of ammonium salt has shown good ee's combined with the possibility of catalyst recovering by simple precipitation. An improvement in the enantioselectivity of the chiral PTC catalysts achieved by just changing their accompanying counterion would be more simple and straightforward than by modifying their structural features.

2. Results and discussion

Attending to different counter-anions for these types of salts, the tetrafluoroborate and hexafluorophosphate where considered promising, as they could form less tight ionic pairs than chloride or bromide, thus allowing a more easy and rapid complexation of the chiral ammonium cation with the glycine-derived enolate, therefore driving to a higher enantioselection. Thus, dimeric chloride salt **3a** was obtained by the reaction of 9,10-di(chloromethyl)anthracene with cinchonidine as described,[7c] and the chloride anion exchanged by the tetrafluoroborate and the hexafluorophosphate anions after the reaction of **3a** with 2.5 equiv of either sodium tetrafluoroborate or potassium hexafluorophosphate, respectively, in acetonitrile as the solvent for 1 day at room temperature. After the addition of ether and filtration, the resulting solids were washed with water and dried to give the corresponding salts **3b** and **3c** in 62% and 86% yield, respectively (Scheme 1). Similarly were prepared the *O*(9)-allylated tetrafluoroborate and hexafluorophosphate cinchonidine-derived salts **3e** and **3f** in 50% and 61% yield, respectively, now starting from the *O*-allylated dimeric bromide **3d**.[7c] These new tetrafluoroborates **3b** and **3e** and hexafluorophosphates **3c** and **3f** showed identical ^{1}H and ^{13}C NMR spectra than the corresponding parent chloride **3a** or bromide **3d**.[7c] However, their infrared spectra revealed new strong absorption bands at 1066 cm^{-1} for **3b** and **3e** and 842 cm^{-1} for **3c** and **3f** cm^{-1}, corresponding to the tetrafluoroborate and hexafluorophosphate anions, respectively.

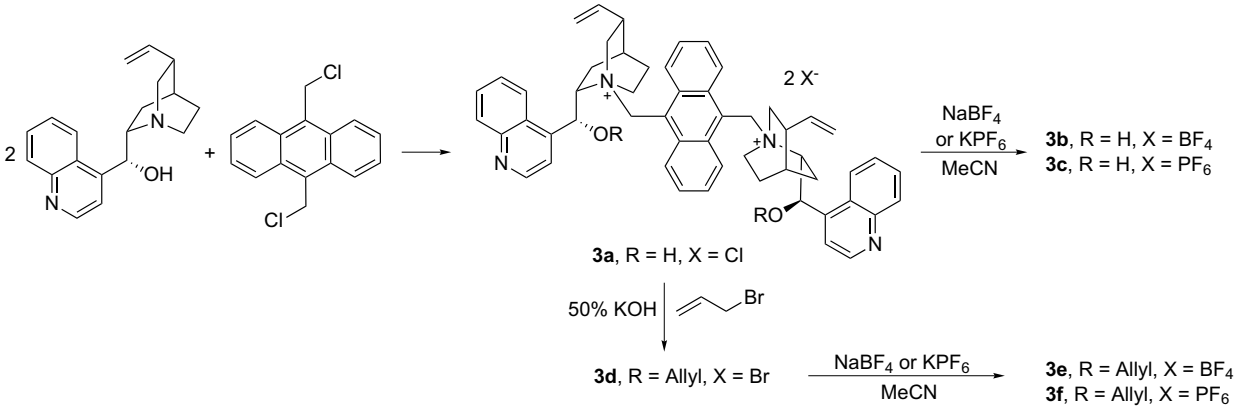
Furthermore, by taking into account the consideration of cinchonine-derived ammonium salts as *pseudoenantiomers* of their cinchonidine counterparts, and hence being a simple way of achieving an opposite enantioselection,[4f] the cinchonine-derived series **4** was also prepared following the same methodology described in Scheme 1. Thus, starting from chloride **4a**, obtained from cinchonine similarly to **3a**,[7c] the corresponding tetrafluoroborate **4b** and hexafluorophosphate **4c** were obtained in 60% and 63% yield, respectively, whereas identical anion exchange from the *O*-allylated bromide **4d** gave place to the corresponding salts **4e** and **4f** in 68% and 76% yield, respectively. These anion exchanges were also confirmed by IR spectroscopy.



4a, R = H, X = Cl
4b, R = H, X = BF_4
4c, R = H, X = PF_6
4d, R = Allyl, X = Br
4e, R = Allyl, X = BF_4
4f, R = Allyl, X = PF_6

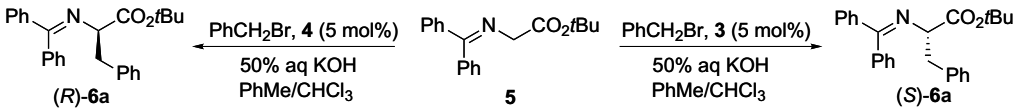
These dimeric ammonium salts bearing different counter-anions were employed as chiral PTC catalysts (5 mol%) in the model benzylation reaction of *tert*-butyl *N*-(diphenylmethylene)glycinate **5** to give compound **6a** (Table 1). The aqueous base selected for these PTC reactions was 50% KOH whereas the solvent employed was a mixture of toluene/chloroform (7/3 v/v), these reaction conditions were previously found as more appropriate when working with these dimeric PTC catalysts.[7c] The enantioselectivity of the reaction was measured by chiral GLC analysis[17] of the corresponding *N*-trifluoroacetamide esters from **6a**,[18] whereas the absolute configuration was determined by the sign of the specific rotation of the phenylalanine, obtained by hydrolysis of **6a** under refluxing 6 M HCl and treatment with propylene oxide.[19] The catalysts could be recovered by precipitation with ether after the reaction.[7c]

When the cinchonidine-derived OH-free chloride **3a** was employed as the PTC catalyst, the reaction showed a



Scheme 1. Preparation of chiral dimeric PTC catalysts **3**.

Table 1. Enantioselective PTC benzylation of **5**



Entry	Catalyst			Temp. (°C)	Time (h)	Yield (%)[a]	*S*/*R* ratio[b]	Ee (%)
	No.	R	X					
1	**3a**	H	Cl	25	3	95	87/13	74
2	**3a**	H	Cl	0	6	88	93/7	86
3	**3a**	H	Cl	−20	12	75	93/7	86
4	**3b**	H	BF_4	25	2	87	91/9	82
5	**3b**	H	BF_4	0	20	87	94/6	88
6	**3c**	H	PF_6	25	2	80	89/11	78
7	**3c**	H	PF_6	0	16	63	93/7	86
8	**3d**	Allyl	Br	25	1	98	80/20	60
9	**3d**	Allyl	Br	0	1	84	85/15	70
10	**3e**	Allyl	BF_4	25	2	94	87/13	74
11	**3e**	Allyl	BF_4	0	5	78	91/9	82
12	**3f**	Allyl	PF_6	25	2	91	91/9	82
13	**3f**	Allyl	PF_6	0	3	62	92/8	84
14	**3f**	Allyl	PF_6	−20	5	98	93/7	86
15	**3f**	Allyl	PF_6	−50	48	76	96/4	92
16	**4a**	H	Cl	0	3	76	9/91	82
17	**4b**	H	BF_4	0	3	79	8/92	84
18	**4c**	H	PF_6	0	4	80	10/90	80
19	**4d**	Allyl	Br	0	4	85	14/86	72
20	**4e**	Allyl	BF_4	0	8	90	19/81	62
21	**4f**	Allyl	PF_6	0	3	91	6/94	88

[a] Crude yield determined by ^{1}H NMR (300 MHz).
[b] Determined by chiral GLC from the corresponding trifluoroacetamides (see text).

higher ee of the benzylated product (*S*)-**6a** when the reaction temperature was lowered from 25 to 0 °C (Table 1, entries 1 and 2).[7c] No increment in the ee was observed when the reaction was performed at −20 °C (Table 1, entry 3). When the reaction was carried out using the corresponding tetrafluoroborate **3b** at 25 °C, the enantioselectivity increased to 82% ee compared to the result obtained employing **3a** (74% ee) (Table 1, entry 4). Furthermore, only a small difference in ee was observed when working at 0 °C (Table 1, compare entries 2 and 5). The improvement in the enantioselectivity of the catalyst was less noticeable when using the OH-free cinchonidine-derived hexafluorophosphate **3c** when compared to **3a** (Table 1, compare entries 1 and 2 with entries 6 and 7).

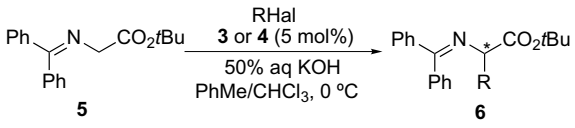
When the *O*-allylated cinchonidine-derived bromide catalyst **3d** was employed at 25 and 0 °C, the resulting ee's were modest (60% and 70%, respectively) (Table 1, entries 8 and 9).[7c]

However, in this case the counter-anion effect was considerable, and the analogous tetrafluoroborate **3e** gave ee values of 74% and 82% working at these temperatures (Table 1, entries 10 and 11). These differences compared to **3d** were even higher when the hexafluorophosphate **3f** was employed (82% ee at 25 °C and 84% ee at 0 °C) (Table 1, entries 12 and 13). Using **3f** at lower reaction temperatures such as −20 °C or even −50 °C gave place to higher enantioselectivities (Table 1, entries 14 and 15), although with longer reaction times, especially in the second case.

When the *pseudoenantiomeric* cinchonine-derived salts **4** were used as PTC catalysts in the benzylation reaction, the expected enantiomer (*R*)-**6** was obtained. In accordance with the previous results, the reaction was now performed at 0 °C, a temperature, which combined good enantioselectivities and yields with not very long reaction times. Almost no effect in the ee was achieved by changing the counter-anion when the OH-free cinchonine-derived system was used, with catalysts **4a**–**c** giving similar results (Table 1, compare entries 16–18). However, the *O*-allylated counterpart shown a counter-anion influence, and up to 88% ee was reached when using the hexafluorophosphate catalyst **4f**, compared to the 72% ee obtained when bromide **4d** was employed (Table 1, entries 19 and 21), whereas only a 62% ee was achieved using tetrafluoroborate **4e** (Table 1, entry 20).

In order to determine the extension of this counterion effect, we performed the alkylation of **5** with the cinchonidine-derived salts **3d** and **3f** as PTC catalysts although now using other activated electrophiles such as allyl bromide and *tert*-butyl bromoacetate, as well as a nonactivated electrophile such as *n*-butyl iodide, at 0 °C (Table 2). We compared the behavior of these precise dimeric salts because the counterion effect seemed to be more remarkable when using *O*-allylated dimeric species (see above). In general, hexafluorophosphate salt **4f** gave

Table 2. Enantioselective PTC alkylations with *O*-allylated catalysts



Entry	Catatyst		RHal	Time (h)	Product			
	No.	X			No.	Yield[a] (%)	*S*/*R* ratio[b]	Ee (%)
1	**3d**	Br	CH_2=$CHCH_2Br$	8	(*S*)-**6b**	98	90/10	80
2	**3e**	BF_4	CH_2=$CHCH_2Br$	8	(*S*)-**6b**	96	89/11	78
3	**3f**	PF_6	CH_2=$CHCH_2Br$	3	(*S*)-**6b**	70	95/5	90
4	**3d**	Br	$BrCH_2CO_2tBu$	24	(*S*)-**6c**	54	72/28	44
5	**3e**	BF_4	$BrCH_2CO_2tBu$	24	(*S*)-**6c**	56	87/13	74
6	**3f**	PF_6	$BrCH_2CO_2tBu$	36	(*S*)-**6c**	67	93/7	86
7	**3d**	Br	$CH_3CH_2CH_2CH_2I$	46	(*S*)-**6d**	72	82/18	64
8	**3e**	BF_4	$CH_3CH_2CH_2CH_2I$	35	(*S*)-**6d**	83	92/8	84
9	**3f**	PF_6	$CH_3CH_2CH_2CH_2I$	30	(*S*)-**6d**	72	93/7	86
10	**4d**	Br	CH_2=$CHCH_2Br$	8	(*R*)-**6b**	97	15/85	70
11	**4e**	BF_4	CH_2=$CHCH_2Br$	8	(*R*)-**6b**	93	13/87	74
12	**4f**	PF_6	CH_2=$CHCH_2Br$	6	(*R*)-**6b**	74	7/93	86

[a] Crude yield determined by ^{1}H NMR (300 MHz).
[b] Determined by chiral GLC from the corresponding trifluoroacetamides (see text).

place to higher enantioselectivities. Thus, when the alkylation of **5** was carried out with allyl bromide using the *O*-allylated bromide **3d** as catalyst, an 80% ee was obtained of the corresponding (*S*)-**6b** (Table 2, entry 1), with this value remaining very similar when the corresponding tetrafluoroborate **3e** was used (Table 2, entry 2). However, when using hexafluorophosphate **3f** an increased ee of 90% was achieved in a lower reaction time (Table 2, entry 3). In addition, a remarkable increment in the enantioselectivity to compound (*S*)-**6c** was observed when catalyst **3d** was changed by **3e** or especially by **3f** in the case of using *tert*-butyl bromoacetate as electrophile (Table 2, compare entry 4 with entries 5 and 6). When the alkylation of **5** was performed with an unactivated electrophile such as *n*-butyl iodide, the achieved ee of (*S*)-**6d** was considerably higher in shorter reaction times when using **3e** or **3f** as catalysts when compared to using bromide **3d** (Table 2, compare entry 7 with entries 8 and 9). As expected, the *O*-allylated cinchonine-derived bromide **4d** gave the corresponding enantiomer (*R*)-**6b** in 70% ee when using allyl bromide as the electrophile (Table 2, entry 10), a slight increment in the enantioselectivity being achieved when using their tetrafluoroborate **4e** (74% ee) (Table 2, entry 11) whereas the use of the hexafluorophosphate **4f** produced a much higher ee value (86%) (Table 2, entry 12).

3. Conclusion

It can be concluded that the counterion accompanying anthryl-derived *Cinchona* ammonium salts employed as chiral PTC catalysts, can play an important role in the enantioselectivity of the alkylation reaction of glycinate imines. This effect of giving better ee's has been observed more noticeably in the case of using *O*-allylated dimeric catalysts carrying a hexafluorophosphate counter-anion. Although the effect of changing the anion could be very small, it seems worthwhile to investigate it when new chiral quaternary ammonium salts are prepared, even before of thinking in a modification of the catalyst structure. The improvement in enantioselectivities can be very rewarding after performing such a simple transformation.

Acknowledgements

We thank the Spanish Ministerio de Ciencia y Tecnología (BQU2001-0724-C02-01), the Generalitat Valenciana (CTIDIB/2002/320) and the Universidad de Alicante for financial support. F.J.O. thanks the Universidad de Alicante for a grant.

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