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Improved conditions for the asymmetric synthesis of α-amino acids using *Cinchona*-derived anthracenylmethyl ammonium salts as chiral phase-transfer organocatalysts

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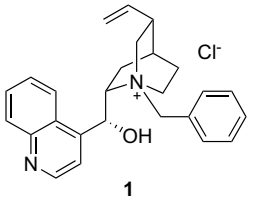
Abstract—Cinchonidine and cinchonine-derived monomeric anthracenylmethyl ammonium salts bearing different counter-anions are used as chiral organocatalysts in the enantioselective alkylation of a benzophenone-imine *tert*-butyl glycinate under phase-transfer conditions. Generally, an improvement of the enantioselectivity is observed when the counterions are tetrafluoroborate and hexafluorophosphate using 50% aqueous KOH as the base and toluene/chloroform as the solvent. The enantioselectivities achieved are comparable and frequently higher, even working under simpler and less-strict reaction conditions and with lower organocatalyst loading, than those reported previously.

1. Introduction

The asymmetric synthesis of α-amino acids has always been always considered as a synthetic challenge due to their biological properties, therefore boosting the development of many methodologies.[1] Especially interesting from an industrial point of view are those which include the use of a catalyst, and amongst them the phase-transfer catalysis (PTC)[2] applied to the asymmetric alkylation 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 salts from *Cinchona* alkaloids[3] pioneered by O'Donnell with benzylated ammonium salts, such as the cinchonidine-derived **1**[4] and its *pseudoenantiomeric* cinchonine-derived counterpart **2**,[4f] and improved by Lygo (**3a**)[5] and Corey (**3d**)[6] by changing the benzyl by an anthracenylmethyl group, allowed high degrees of enantioselection using a very simple procedure to be achieved. Encouraged by these results, dimeric,[7] trimeric,[8] dendrimeric[9] *Cinchona* alkaloid-derived catalysts and even polymer-supported *Cinchona*-derived species have been developed.[10] In addition, catalysts such as spiro ammonium[11] and phosphonium salts,[12] TADDOL[13a,b] and other tartaric derivatives,[13c–e] guanidinium salts,[13f] binaphthyl-derived amines,[13b,14] and salen-metal complexes[15] have also been used.



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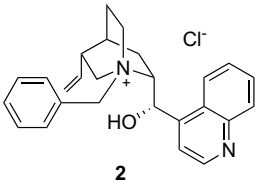

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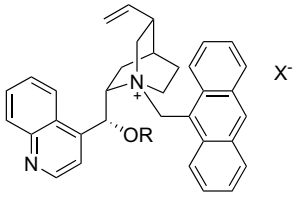

3a, R = H, X = Cl
3b, R = H, X = BF_4
3c, R = H, X = PF_6
3d, R = Allyl, X = Br
3e, R = Allyl, X = BF_4
3f, R = Allyl, X = PF_6

Amongst this array of PTC catalysts, and considering large-scale use, the cinchonidine-derived monomeric ammonium salts developed by Lygo[5] (**3a**) and Corey[6] (**3d**) are the most simple, easily available, and economical.

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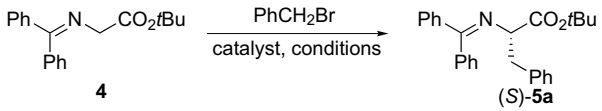
Comparing their performance in the alkylation of *tert*-butyl *N*-(diphenylmethylene)glycinate, the cinchonidine-derived ammonium salt **3a** has been used in the synthesis of (*S*)-α-amino acid derivatives under liquid–liquid PTC condition with economical bases, such as KOH and at room temperature, although the higher ee's achieved are only close to 90%. Ammonium salt **3d** affords generally higher ee's than **3a** (even higher than 99%), although these results were achieved under solid–liquid PTC conditions, using relatively expensive CsOH as a base and low reaction temperatures (generally at or below −60 °C) in CH_2Cl_2 as a solvent. In spite of the use of this rather strict reaction conditions, the asymmetric alkylation of *tert*-butyl *N*-(diphenylmethylene)glycinate using **3d** as a PTC catalysts has frequently been used in the preparation of many α-amino acids of interest.[16]

Recently, a certain influence of the counter anion accompanying the chiral ammonium salt in the enantioselectivity of this reaction has been observed in a two-center tartrate-derived bis-ammonium salt,[17] this influence being even larger when using the dimeric cinchonidinium and cinchoninium salts developed by our group,[18] as well as in enantioselective Michael addition reactions.[19] These observations are especially interesting, as an improvement in the enantioselectivity of these chiral PTC catalysts can be achieved just by changing their accompanying counterion, which is more simple and straightforward than by modifying their structural features. A subsequent question is, if a counter-anion exchange in the more simple monomeric salts **3a** and **3d**, perhaps also combined with a modification of the reaction conditions, would positively affect their performance as chiral PTC catalysts. Thus, an anion-exchanged salt from the less-derivatized **3a** might be more suitable for achieving the high enantioselectivities required, whereas an exchanged salt from its allylated derivative **3d** could keep its high-performing properties although avoiding the use of strict reaction conditions.

2. Results and discussion

The cinchonidine-derived ammonium salts **3a** and **3d** where employed as chiral PTC catalysts (5 mol %) in the model benzylation reaction of *tert*-butyl *N*-(diphenylmethylene)-glycinate **4** to give the corresponding enantiomerically enriched benzylated compound (*S*)-**5a**. The first experiments focused on a comparison between the enantioselectivities achieved under the previously reported conditions (Table 1, Conditions A and C) and others considered appropriate for further developments (Table 1, Conditions B). The base selected was the economical 50% aqueous KOH. The solvent employed was a mixture of toluene/chloroform (7/3 v/v) at room temperature or at 0 °C with a 5% mol of the phase-transfer catalyst. The use of this particular mixture of organic solvents for this liquid–liquid PTC alkylation process was found to give the highest enantioselectivities originally by Jew and Park using dimeric cinchonidinium salts as catalysts and working at temperatures of 0 and −20 °C.[7a] The incorporation of a certain amount of a more polar solvent than the toluene allows lowering the reaction temperature avoiding a possible insolubility of the catalysts in the organic reaction phase. This problem has been observed in related PTC alkylations carried out in toluene, resulting in a reduction in the effective concentration of the catalyst which therefore gives a lower enantioselection.[20]

Table 1. Enantioselective benzylation of glycine imine **4** under reported and new PTC conditions



Entry	Catalyst			Cond.[a]	*t* (h)	Yield[b] (%)	ee[c] (%)
	No.	R	X				
1	**3a**	H	Cl	A	3	70	91
2	**3a**	H	Cl	B	3	50	91
3	**3a**	H	Cl	B[d]	3	73	90
4	**3d**	Allyl	Br	C	23	90	91
5	**3d**	Allyl	Br	B	1.5	86	93
6	**3d**	Allyl	Br	B[d]	3	93	95

[a] Conditions A: 10 mol % cat., 50% aq KOH, toluene, 25 °C (reported in Ref. 5a: 18 h, 68%, 91% ee); Conditions B: 5 mol % cat., 50% aq KOH, toluene/$CHCl_3$ (7/3 v/v), 25 °C; Conditions C: 10 mol % cat., CsOH·H_2O, CH_2Cl_2, −78 °C (reported in Ref. 6a: 23 h, 87%, 94% ee).
[b] Crude yield determined by ^1H NMR (300 MHz).
[c] Determined by chiral GLC from the corresponding trifluoroacetamides (see Experimental).
[d] The reaction was performed at 0 °C.

The reaction of glycinate **4** with benzyl bromide under PTC conditions using cinchonidine-derived chloride salt **3a** as a catalyst under Conditions B at room temperature or at 0 °C gave 91% and 90% ee, respectively, of the corresponding benzylated product (*S*)-**5** in 3 h reaction time (Table 1, entries 2 and 3), which was similar than the results we obtained for this catalyst when using Conditions A[5a] with a much longer reaction time (Table 1, entry 1). In addition, the allylated cinchonidine bromide **3d** gave rise in our hands to a 94% ee of (*S*)-**5a** under Conditions C during 23 h (Table 1, entry 4).[6a] However, a quite similar 93% ee could be obtained in 1.5 h working at room temperature under Conditions B (Table 1, entry 5). This value increased to 95% ee by lowering the reaction temperature down to 0 °C (Table 1, entry 6). It can be concluded that Conditions B at 0 °C can afford similar enantioselectivities in much lower reaction times than the previously described Conditions A or C and with lower catalyst loading. Therefore, for this benzylation reaction, the O-allylated salt **3d** is a more efficient catalyst than **3a**.

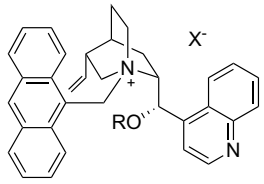
After determining the suitability of the new reaction conditions for performing the model benzylation reaction with, at least, comparable enantioselectivities, the next step was to investigate the influence of the counter anion of the catalyst in the enantioselectivity of the reaction under Conditions B at 0 °C, which gave good enantioselectivities while keeping a non-strict and easy-handling methodology. The tetrafluoroborate and hexafluorophosphate anions were considered appropriate for exchanging the chloride anion of cinchonidine-derived ammonium salt **3a** and the bromide anion of **3d**, as they have proven to give rise to a better enantioselec-

tion,[17–19] probably because they can form less tight ionic pairs than chloride or bromide, thus allowing an easier and rapid complexation of the chiral ammonium cation with the glycine-derived enolate. Thus, the chloride anion of **3a** was exchanged by the tetrafluoroborate and the hexafluorophosphate anions, after the reaction of **3a** with 2.5 equiv of sodium tetrafluoroborate or potassium hexafluorophosphate, respectively, in acetonitrile as a 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 98% and 97% yields, respectively. Similarly the O(9)-allylated tetrafluoroborate and hexafluorophosphate cinchonidine-derived salts **3e** and **3f** were prepared in 96% and 94% yields, respectively, now starting from the O-allylated bromide **3b**. Tetrafluoroborates **3b** and **3e** and hexafluorophosphates **3c** and **3f** showed infrared spectra revealing new strong absorption bands around 1060 **3b** and **3e** and 840 (**3c** and **3f**) cm^{-1}, corresponding to the tetrafluoroborate and hexafluorophosphate anions, respectively.

The results obtained in the benzylation of glycinate **4** using these exchanged salts are shown in Table 2, where the reported values included in Table 1 for **3a** and **3d** are included for a rapid comparison (Table 2, entries 1 and 4). Thus, the reaction of glycinate **4** using the cinchonidine-derived exchanged tetrafluoroborate salt **3b** as a catalyst under Conditions B, afforded (*S*)-**5a** with an enantioselectivity raised up to 94% (Table 2, entry 2) when compared with its counterpart **3a** (Table 2, entry 1); no influence when lowering the temperature down to −20 °C was observed. A similar improvement in the final enantioselection was detected when hexafluorophosphate **3c** was employed as a catalyst under Conditions B, (*S*)-**5a** with 95% ee (Table 2, entry 3) being obtained.

The results observed when working with the new O-allylated cinchonidine-derived exchanged ammonium salts **3d** and **3f** also proved interesting. Thus, under Conditions B at 0 °C, the enantioselectivity achieved was 96% when the exchanged O-allylated tetrafluoroborate **3e** was used as a catalyst, whereas for (*S*)-**5a** a 96% ee was obtained when the O-allylated hexafluorophosphate **3f** was used (Table 2, entries 5 and 6). This value increased to 97% ee when the temperature was lowered to −20 °C.

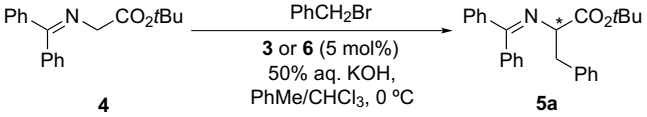
Taking into account the above mentioned consideration of cinchonine-derived ammonium salts as *pseudoenantiomers* of their cinchonidine counterparts, and a simple way of achieving an opposite enantioselection,[4f] a cinchonine-derived series of PTC catalysts **6** bearing different counterions were also prepared following the same methodology as described above. Thus, starting from chloride **6a**, tetrafluoroborate **6b**, and hexafluorophosphate **6c** were prepared in 90% and 87% yields, respectively, whereas O-allylated bromide **6d** gave rise to the corresponding salts **6e** and **6f** in 82% and 85% yields, respectively; these anion exchanges were also confirmed by IR spectroscopy.



6a, R = H, X = Cl **6d**, R = Allyl, X = Br
6b, R = H, X = BF_4 **6e**, R = Allyl, X = BF_4
6c, R = H, X = PF_6 **6f**, R = Allyl, X = PF_6

The use of these cinchonine-derived ammonium salts **6** as PTC catalysts for the standard model benzylation reaction under Conditions B at 0 °C afforded, as expected, the (*R*)-**5a** product. Thus, when chloride **6a** was used as a catalyst, a 93% ee of (*R*)-**5a** was obtained (Table 2, entry 7). This

Table 2. Enantioselective benzylation of glycine imine **4** under PTC conditions



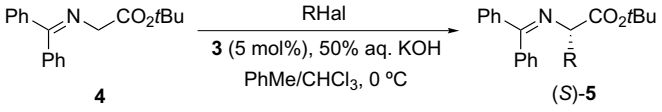
Entry	Catalyst			Time (h)	Product			
	No.	R	X		No.	Yield[a] (%)	*S*/*R* Ratio[b]	ee (%)
1	**3a**	H	Cl	3	(*S*)-**5a**	73	95/5	90
2	**3b**	H	BF_4	2	(*S*)-**5a**	80	97/3	94
3	**3c**	H	PF_6	2.5	(*S*)-**5a**	60	97.5/2.5	95
4	**3d**	Allyl	Br	3	(*S*)-**5a**	93	97.5/2.5	95
5	**3e**	Allyl	BF_4	2.5	(*S*)-**5a**	83	98/2	96
6	**3f**	Allyl	PF_6	1	(*S*)-**5a**	84	98/2	96
7	**6a**	H	Cl	10	(*R*)-**5a**	94	3.5/96.5	93[c]
8	**6b**	H	BF_4	24	(*R*)-**5a**	94	1/99	98
9	**6c**	H	PF_6	24	(*R*)-**5a**	93	3/97	94
10	**6d**	Allyl	Br	6	(*R*)-**5a**	86	4/96	92
11	**6e**	Allyl	BF_4	23	(*R*)-**5a**	75	4/96	92
12	**6f**	Allyl	PF_6	20	(*R*)-**5a**	73	2.5/97.5	95

[a] Crude yield determined by ^1H NMR (300 MHz).
[b] Determined by chiral GLC from the corresponding trifluoroacetamides (see Experimental).
[c] Literature values under Conditions A: 10 mol % cat., 18 h, 63%, 89% ee (Ref. 5a).

value could be increased up to 98% ee when using the tetrafluoroborate counterpart **6b** as a catalyst (Table 2, entry 8), although close to the enantioselection obtained using the exchanged hexafluorophosphate **6c** (Table 2, entry 9). These values were clearly higher than these reported with catalyst **6a** under Conditions A (see footnote c in Table 2). When the O-allylated cinchonine-derived bromide **6d** was used as a catalyst, 92% ee of the benzylated product was obtained, an identical value when using the exchanged tetrafluoroborate **6e** (Table 2, entries 10 and 11). However, when hexafluorophosphate **6f** was used, a higher 95% ee for (*R*)-**5a** was obtained, a value similar than to when using its cinchonidine *pseudoenantiomeric* counterpart **3f** was obtained, although in a longer reaction time (Table 2, entry 12).

The next step was extending the study of the PTC alkylation reaction of glycinate **4** with the anion-exchanged catalysts to other activated and non-activated electrophiles under Conditions B at 0 °C. Thus, when the reaction was performed using allyl bromide as the electrophile and cinchonidine-derived chloride **3a** as the PTC catalyst under these reaction conditions, a 95% ee of the corresponding allylated compound (*S*)-**5b** was obtained (Table 3, entry 2), which is a rather high value, when taking into account that the use of catalyst **3a** under Conditions A is reported to afford an 88% ee for (*S*)-**5b** (Table 3, entry 1).[5a] When this allylation reaction was performed using the exchanged tetrafluoroborate **3b**, the enantioselectivity dropped to 92%. However, a maximum value of 98% ee was achieved using hexafluorophosphate **3c** as a catalyst (Table 3, entries 3 and 4). When the O-allylated cinchonidine-derived bromide catalyst **3d** was employed for this allylation reaction, the enantioselection for the corresponding (*S*)-**5b** was only 85%, which is lower than the 97% ee previously reported using Conditions C[6a] (Table 3, entries 5 and 6). However, in this case, the use of the exchanged tetrafluoroborate and hexafluorophosphate O-allylated salts **3e** or **3f** allowed an increase in the initially rather low enantioselection up to a 96% ee for both catalysts (Table 3, entries 7 and 8).

Table 3. Enantioselective alkylation of glycine imine **4** under PTC conditions



4 (*S*)-**5**

Entry	Catalyst			RHal	Time (h)	Product				Ref.
	No.	R	X			No.	Yield[a] (%)	*S*/*R* Ratio[b]	ee (%)	
1[c]	**3a**	H	Cl	CH_2=$CHCH_2Br$	18	(*S*)-**5b**	76	94/6	88	5a
2	**3a**	H	Cl	CH_2=$CHCH_2Br$	3.5	(*S*)-**5b**	93	97.5/2.5	95	
3	**3b**	H	BF_4	CH_2=$CHCH_2Br$	5	(*S*)-**5b**	84	96/4	92	
4	**3c**	H	PF_6	CH_2=$CHCH_2Br$	5	(*S*)-**5b**	81	99/1	98	
5[d]	**3d**	Allyl	Br	CH_2=$CHCH_2Br$	22	(*S*)-**5b**	87	98.5/1.5	97	6a
6	**3d**	Allyl	Br	CH_2=$CHCH_2Br$	3	(*S*)-**5b**	80	92.5/7.5	85	
7	**3e**	Allyl	BF_4	CH_2=$CHCH_2Br$	5	(*S*)-**5b**	96	98/2	96	
8	**3f**	Allyl	PF_6	CH_2=$CHCH_2Br$	5.5	(*S*)-**5b**	73	98/2	96	
9[e]	**3d**	Allyl	Br	2-$O_2NC_6H_4CH_2Br$	n.r.	(*S*)-**5c**	92	96.25/3.75	92.5	21
10	**3d**	Allyl	Br	2-$O_2NC_6H_4CH_2Br$	12	(*S*)-**5c**	88	95/5	90	
11	**3e**	Allyl	BF_4	2-$O_2NC_6H_4CH_2Br$	12	(*S*)-**5c**	90	97/3	94	
12	**3f**	Allyl	PF_6	2-$O_2NC_6H_4CH_2Br$	12	(*S*)-**5c**	81	97/3	94	
13[c]	**3a**	H	Cl	CH_3I	3	(*S*)-**5d**	41	95.5/5.5	89	5a
14	**3a**	H	Cl	CH_3I	24	(*S*)-**5d**	55	94.5/5.5	89	
15	**3c**	H	PF_6	CH_3I	24	(*S*)-**5d**	52	94.5/5.5	89	
16[d]	**3d**	Allyl	Br	CH_3I	28	(*S*)-**5d**	71	98.5/1.5	97	6a
17	**3d**	Allyl	Br	CH_3I	24	(*S*)-**5d**	50	95/5	90	
18	**3e**	Allyl	BF_4	CH_3I	23	(*S*)-**5d**	58	96.5/3.5	93	
19[f]	**3e**	Allyl	BF_4	CH_3I	28	(*S*)-**5d**	44	96.5/3.5	93	
20	**3f**	Allyl	PF_6	CH_3I	24	(*S*)-**5d**	47	96/4	92	
21[c]	**3a**	H	Cl	$BrCH_2CO_2t$-Bu	18	(*S*)-**5e**	67	84/16	68	5e
22[g]	**3a**	H	Cl	$BrCH_2CO_2t$-Bu	8	(*S*)-**5e**	49	88/12	76	
23	**3a**	H	Cl	$BrCH_2CO_2t$-Bu	8	(*S*)-**5e**	41	90.5/9.5	81	
24	**3b**	H	BF_4	$BrCH_2CO_2t$-Bu	8	(*S*)-**5e**	64	90.5/9.5	81	
25	**3c**	H	PF_6	$BrCH_2CO_2t$-Bu	8	(*S*)-**5e**	56	89/11	78	
26	**3d**	Allyl	Br	$BrCH_2CO_2t$-Bu	8	(*S*)-**5e**	86	90/10	80	
27	**3e**	Allyl	BF_4	$BrCH_2CO_2t$-Bu	8	(*S*)-**5e**	85	89.5/10.5	79	
28	**3f**	Allyl	PF_6	$BrCH_2CO_2t$-Bu	27	(*S*)-**5e**	80	93/7	86	

[a] Crude yield determined by ^{1}H NMR (300 MHz).
[b] Determined by chiral GLC from the corresponding trifluoroacetamides (see Experimental).
[c] Literature results under Conditions A.
[d] Literature results under Conditions C.
[e] Literature results under Conditions C at −30 °C.
[f] The reaction was performed at −20 °C.
[g] The reaction was carried out at 25 °C.

When 2-nitrobenzyl bromide was used as the electrophile in the presence of the O-allylated cinchonidine-derived bromide catalyst **3d**, benzylated compound (*S*)-**5c** was obtained in a 90% ee (Table 3, entry 10). This value was increased up to 94% ee when the exchanged ammonium salts **3e** and **3f** were used as the catalysts (Table 3, entries 11 and 12). This enantioselection was higher than that reported for (*S*)-**5c** employing Conditions C but working at −30 °C (92.5% ee, Table 3, entry 9), in a synthesis of enantiomerically enriched 3-amino-3,4-dihydro-1*H*-quinolin-2-one, a useful building block in the synthesis of many biologically active compounds.[21]

The use of a non-activated electrophile, such as methyl iodide, gave, as expected, longer reaction times and lower yields. When chloride salt **3a** was used as PTC catalysts under Conditions B at 0 °C, the corresponding (*S*)-**5d** was obtained in an 89% ee, an identical value to that detected when the usually enantioselection-increasing tetrafluoroborate salt **3c** was employed (Table 3, entries 14 and 15). This was also identical to the reported value observed under Conditions A[5a] (Table 3, entry 13). In addition, when the O-allylated cinchonidine-derived bromide **3d** was used as a catalyst, a 90% ee of the corresponding methylated product (*S*)-**5d** was obtained. This value could be increased slightly up to 93% and 92% ee when the exchanged tetrafluoroborate and hexafluorophosphate salts **3e** and **3f**, respectively, were employed. No difference when lowering the reaction temperature was detected (Table 3, entries 17–20). This methylation reaction has been previously reported using bromide **3d** as a catalyst, reaching up to 97% ee, although working at −60 °C[6a] (Table 3, entry 16).

More polar alkylating reagents, such as *tert*-butyl bromoacetate, are considered 'difficult' electrophiles for this type of alkylation reactions, usually giving lower enantioselectivities, probably as a consequence of an increased rate of the non-catalyzed background reaction.[5e] Thus, the use of bromide **3a** under Conditions A is reported to afford the corresponding product (*S*)-**5e** in only 68% ee[5e] (Table 3, entry 21). However, just the use of Conditions B at room temperature allowed us to raise this value to 76% ee (Table 2, entry 22), whereas the enantioselectivity achieved was an 81% ee using chloride **3a** or the exchanged tetrafluoroborate **3b** under Conditions B at 0 °C, the hexafluorophosphate **3c** giving place to a 78% ee (Table 2, entries 23–25). The O-allylated bromide **3d** or tetrafluoroborate **3e** performed similarly under Conditions B at 0 °C, to afford the alkylated product in 80% and 79% ee, respectively, whereas a remarkable 86% ee could be achieved when using hexafluorophosphate **3f** as a catalyst (Table 3, entries 22–26).

3. Conclusions

We can conclude that the enantioselectivity of the alkylation reaction of iminic glycinates under PTC conditions using the common, simple, and inexpensive monomeric cinchonidine and cinchonine-derived ammonium salts can be improved, considerably, by using sometimes less-strict reaction conditions. Thus, using 50% aqueous KOH in toluene/chloroform as a solvent, lowering the loading of organocatalyst, and tuning the catalyst efficiency by means of an anion exchange from chloride or bromide to tetrafluoroborate and hexafluorophosphate, can give shorter reaction times, better yields, and higher enantioselectivities.

4. Experimental

4.1. General

All the reagents and solvents employed were of the best grade available and used without further purification. The ammonium salts **3a**,[5a] **3d**,[6a] **6a**,[5a] and **6d**[4e] were prepared as described. Melting points are uncorrected. IR data were collected on a Nicolet Impact 400D-FT spectrometer and only diagnostic bands are given. The ^{1}H NMR spectra were recorded on a Bruker AC-300 at 300 MHz, using $CDCl_3$ as a solvent and TMS as the internal standard. The enantiomeric excesses of products **5** were determined by GLC analyses of the corresponding *N*-trifluoroacetamide esters, obtained after 15% aq citric acid hydrolysis of imines **5** and further reaction with trifluoroacetic anhydride[22] (Crownpack Chirasil-L-Val column, 25 m × 0.25 mm i.d.; conditions for **5a**, **5c**, **5d**, and **5e**: $P = 85$ kPa, 1 min 85 °C, 2 °C/min to 180 °C; conditions for **5b**: $P = 50$ kPa, 1 min 105 °C, 1 °C/min to 180 °C). GLC reference racemic samples were prepared from the corresponding racemic **5**, which were obtained using tetra-*n*-butylammonium bromide as a phase-transfer catalyst. The absolute configuration was determined by the sign of the specific rotation of phenylalanine, obtained by the hydrolysis of (*S*)-**5a** under refluxing 6M HCl and treatment with propylene oxide.[23]

4.2. Preparation of cinchonidine-derived ammonium salts 3b, 3c, 3e, and 3f

To a suspension of **3a** (500 mg, 0.96 mmol) or **3d** (581 mg, 0.96 mmol) in acetonitrile (9 mL) was added sodium tetrafluoroborate (2.4 mmol, 263 mg) or potassium hexafluorophosphate (2.4 mmol, 442 mg). The reaction mixture was stirred at room temperature for 24 h. After this time, the solvent was removed and the mixture diluted with water (10 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated in vacuo to give a crude product, which was washed with water and Et_2O. Filtration and drying afforded **3b** (539 mg, 98%) and **3c** (587 mg, 97%) from **3a**, and **3e** (564 mg, 96%) and **3f** (605 mg, 94%) from **3d**. The ^{1}H NMR of these products were identical to those reported for the starting materials.

4.2.1. *N*-9-Anthracenylmethylcinchonidinium tetrafluoroborate 3b. Mp 173 °C, $[\alpha]_D^{25} = -316$ (*c* 0.7, acetone), IR (KBr) *v* 3419, 1060, 745 cm^{-1}.

4.2.2. *N*-9-Anthracenylmethylcinchonidinium hexafluorophosphate 3c. Mp 167 °C, $[\alpha]_D^{25} = -190$ (*c* 0.5, acetone), IR (KBr) *v* 3522, 839, 557 cm^{-1}.

4.2.3. *O*(9)-Allyl-*N*-anthracenylmethylcinchonidinium tetrafluoroborate 3e. Mp 145 °C, $[\alpha]_D^{25} = -154$ (*c* 0.5, acetone), IR (KBr) *v* 1460, 1066, 743 cm^{-1}.

4.2.4. *O*(9)-Allyl-*N*-anthracenylmethylcinchonidinium hexafluorophosphate 3f. Mp 159 °C, $[\alpha]_D^{25} = -189$ (*c* 0.8, acetone), IR (KBr) *v* 1462, 839, 557 cm^{-1}.

4.3. Preparation of cinchonine-derived ammonium salts 6b, 6c, 6e, and 6f

To a suspension of **6a** (500 mg, 0.96 mmol) or **6d** (581 mg, 0.96 mmol) in acetonitrile (9 mL) was added sodium tetrafluoroborate (2.4 mmol, 263 mg) or potassium hexafluorophosphate (2.4 mmol, 442 mg). The reaction mixture was stirred at room temperature for 24 h. After this time, the solvent was removed and the mixture diluted with water (10 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated in vacuo to give a crude which was washed with water and Et_2O. Filtration and drying afforded **6b** (495 mg, 90%) and **6c** (527 mg, 87%) from **6a**, and **6e** (482 mg, 82%) and **6f** (547 mg, 85%) from **6d**. The ^1H NMR of these products were identical to those reported for the starting materials.

4.3.1. *N*-9-Anthracenylmethylcinchoninium tetrafluoroborate 6b. Mp 194 °C, $[\alpha]_D^{25} = +250$ (*c* 1.0, $CHCl_3$), IR (KBr) *v* 3448, 1062, 743 cm^{-1}.

4.3.2. *N*-9-Anthracenylmethylcinchoninium hexafluorophosphate 6c. Mp 179 °C, $[\alpha]_D^{25} = +166$ (*c* 0.9, acetone), IR (KBr) *v* 3545, 839, 558 cm^{-1}.

4.3.3. *O*(9)-Allyl-*N*-anthracenylmethylcinchoninium tetrafluoroborate 6e. Mp 159 °C, $[\alpha]_D^{25} = +193$ (*c* 0.7, $CHCl_3$), IR (KBr) *v* 1461, 1060, 744 cm^{-1}.

4.3.4. *O*(9)-Allyl-*N*-anthracenylmethylcinchoninium hexafluorophosphate 6f. Mp 165 °C, $[\alpha]_D^{25} = +152$ (*c* 0.7, acetone), IR (KBr) *v* 1462, 835, 558 cm^{-1}.

4.4. Enantioselective phase-transfer alkylations. General procedure

To a mixture of **4** (74 mg, 0.25 mmol) and chiral catalyst **5** or **6** (0.0125 mmol) in a 7:3 v/v mixture of toluene and $CHCl_3$ (1.5 mL) was added 50% aqueous KOH (0.140 mL, 1.25 mmol) and the corresponding alkyl halide (1.25 mmol). The reaction mixture was stirred vigorously at 0 °C and monitorized by GLC. The suspension was diluted with H_2O (10 mL) and extracted with EtOAc (3 × 3 mL). The organics were dried over $MgSO_4$, filtered, and evaporated in vacuo, affording crude products **5** which were analyzed and identified by their ^1H NMR data (**5a**,**b**,**d**,**e**[5e] and **5c**[21]).

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References

1. (a) Williams, R. M. *Synthesis of Optically Active Amino Acids*; Pergamon Press: Oxford, 1989; (b) Stammer, C. H. *Tetrahedron* **1990**, *46*, 2231–2254; (c) Heimgartner, H. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 238–264; (d) Williams, R. M.; Hendrix, J. A. *Chem. Rev.* **1992**, *92*, 889–917; (e) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1540–1650; (f) Burgess, K.; Ho, K.-K.; Mye-Sherman, D. *Synlett* **1994**, 575–583; (g) Bailey, P. D.; Clayson, J.; Boa, A. N. *Contemp. Org. Synth.* **1995**, 173–187; (h) North, M. *Contemp. Org. Synth.* **1996**, 323–343; (i) Studer, A. *Synthesis* **1996**, 793–815; (j) Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem., Int. Ed.* **1996**, *35*, 2708–2748; (k) Wirth, T. *Angew. Chem., Int. Ed.* **1997**, *36*, 225–227; (l) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517–3599; (m) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645–732; (n) Abellán, T.; Chinchilla, R.; Galindo, N.; Guillena, G.; Nájera, C.; Sansano, J. M. *Eur. J. Org. Chem.* **2000**, 2689–2697; (o) Nájera, C. *Synlett* **2002**, 1388–1403.
2. (a) Dehmlow, E. V.; Dehmlow, S. S. *Phase Transfer Catalysis*, 3rd ed.; VCH: Weinheim, 1993; (b) Starks, C. M.; Liotta, C. L.; Halpern, M. *Phase-Transfer Catalysis*; Chapman & Hall: New York, 1994; (c) *Handbook of Phase-Transfer Catalysis*; Sasson, Y., Neumann, R., Eds.; Blackie Academic & Professional: London, 1997; (d) *Phase-Transfer Catalysis*; Halpern, M. E., Ed. ACS Symposium Series 659; American Chemical Society: Washington, DC, 1997; (e) Nelson, A. *Angew. Chem., Int. Ed.* **1999**, *38*, 1583–1585; (f) Makosza, M. *Pure Appl. Chem.* **2000**, *72*, 1399–1403.
3. (a) Kacprzak, K.; Gawronski, J. *Synthesis* **2001**, 961–998; (b) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013–3028; (c) Lygo, B.; Andrews, B. I. *Acc. Chem. Res.* **2004**, *37*, 518–525; (d) O'Donnell, M. J. *Acc. Chem. Res.* **2004**, *37*, 506–517; (e) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis*; Wiley-VCH: Weinheim, 2005.
4. (a) O'Donnell, M. J.; Bennett, W. D.; Wu, S. *J. Am. Chem. Soc.* **1989**, *111*, 2353–2355; (b) Lipkowitz, K. B.; Cavanaugh, M. W.; Baker, B.; O'Donnell, M. J. *J. Org. Chem.* **1991**, *56*, 5181–5192; (c) O'Donnell, M. J.; Wu, S. *Tetrahedron: Asymmetry* **1992**, *3*, 591–594; (d) O'Donnell, M. J.; Wu, S.; Huffman, J. C. *Tetrahedron* **1994**, *50*, 4507–4518; (e) O'Donnell, M. J.; Delgado, F.; Pottorf, R. S. *Tetrahedron* **1999**, *55*, 6347–6362; (f) O'Donnell, M. J. *Aldrichim. Acta* **2001**, *34*, 3–15.
5. (a) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1997**, *38*, 8595–8598; (b) Lygo, B.; Crosby, J.; Peterson, J. A. *Tetrahedron Lett.* **1999**, *40*, 1385–1388; (c) Lygo, B. *Tetrahedron Lett.* **1999**, *40*, 1389–1392; (d) Lygo, B.; Crosby, J.; Peterson, J. A. *Tetrahedron Lett.* **1999**, *40*, 8671–8674; (e) Lygo, B.; Crosby, J.; Lowdon, T. R.; Peterson, J. A.; Wainwright, P. G. *Tetrahedron* **2001**, *57*, 2403–2409; (f) Lygo, B.; Andrews, B. I.; Crosby, J.; Peterson, J. A. *Tetrahedron Lett.* **2002**, *43*, 8015–8018; (g) Lygo, B.; Allbutt, B. *Synlett* **2004**, 326–328.
6. (a) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414–12415; (b) Corey, E. J.; Noe, M. C.; Xu, F. *Tetrahedron Lett.* **1998**, *39*, 5347–5350; (c) Horikawa, M.; Busch-Petersen, J.; Corey, E. J. *Tetrahedron Lett.* **1999**, *40*, 3843–3846.
7. (a) Jew, S.; Jeong, B.; Yoo, M.; Huh, H.; Park, H. *Chem. Commun.* **2001**, 1244–1245; (b) Park, H.; Jeong, B.; Yoo, M.; Lee, J.; Park, M.; Lee, Y.; Kim, M.; Jew, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 3036–3038; (c) Chinchilla, R.; Mazón, P.;

Nájera, C. *Tetrahedron: Asymmetry* **2002**, *13*, 927–931; (d) Park, H.; Jeong, B.; Yoo, M.; Lee, J.; Park, B.; Kim, M.; Jew, S. *Tetrahedron Lett.* **2003**, *44*, 3497–3500; (e) Siva, A.; Murugan, E. *J. Mol. Catal. A: Chem.* **2005**, *241*, 111–117.

8. (a) Park, H.; Jeong, B.; Yoo, M.; Park, M.; Huh, H.; Jew, S. *Tetrahedron Lett.* **2001**, *42*, 4645–4648; (b) Siva, A.; Murugan, E. *Synthesis* **2005**, 2927–2933.
9. (a) Mazón, P.; Chinchilla, R.; Nájera, C.; Guillena, G.; Kreiter, R.; Klein Gebbink, R. J. M.; van Koten, G. *Tetrahedron: Asymmetry* **2002**, *13*, 2181–2185; (b) Guillena, G.; Kreiter, R.; van de Coevering, R.; Klein Gebbink, R. J. M.; van Koten, G.; Mazón, P.; Chinchilla, R.; Nájera, C. *Tetrahedron: Asymmetry* **2003**, *14*, 3705–3712.
10. (a) Yongmei, W.; Zhengpu, Z.; Zhen, W.; Jiben, M.; Hodge, P. *Chin. J. Polym. Sci.* **1998**, *16*, 356–361; (b) Zhengpu, Z.; Yongmei, W.; Zhen, W.; Hodge, P. *React. Funct. Polym.* **1999**, *41*, 37–43; (c) Chinchilla, R.; Mazón, P.; Nájera, C. *Tetrahedron: Asymmetry* **2000**, *11*, 3277–3281; (d) Thierry, B.; Plaquevent, J.-C.; Cahard, D. *Tetrahedron: Asymmetry* **2001**, *12*, 983–986; (e) Thierry, B.; Perrard, T.; Audouard, C.; Plaquevent, J.-C.; Cahard, D. *Synthesis* **2001**, 1742–1746; (f) Thierry, B.; Plaquevent, J.-C.; Cahard, D. *Tetrahedron: Asymmetry* **2003**, *14*, 1671–1677; (g) Danelli, T.; Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Tocco, G. *Tetrahedron: Asymmetry* **2003**, *14*, 461–467; (h) Chinchilla, R.; Mazón, P.; Nájera, C. *Molecules* **2004**, *9*, 349–364; (i) Chinchilla, R.; Mazón, P.; Nájera, C. *Adv. Synth. Catal.* **2004**, *346*, 1186–1194.
11. (a) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **1999**, *121*, 6519–6520; (b) Ooi, T.; Tayama, E.; Doda, K.; Takeuchi, M.; Maruoka, K. *Synlett* **2000**, 1500–1502; (c) Ooi, T.; Takeuchi, M.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2000**, *122*, 5228–5229; (d) Ooi, T.; Uematsu, Y.; Maruoka, K. *Adv. Synth. Catal.* **2002**, *344*, 288–291; (e) Ooi, T.; Uematsu, Y.; Maruoka, K. *Tetrahedron Lett.* **2004**, *45*, 1675–1678; (f) Kano, T.; Konishi, S.; Shirakawa, S.; Maruoka, K. *Tetrahedron: Asymmetry* **2004**, *15*, 1243–1245; (g) Shirakawa, S.; Yamamoto, K.; Kitamura, M.; Ooi, T.; Maruoka, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 625–628; (h) Kitamura, M.; Shirakawa, S.; Maruoka, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 1549–1551; (i) Han, Z.; Yamaguchi, Y.; Kitamura, M.; Maruoka, K. *Tetrahedron Lett.* **2005**, *46*, 8555–8558; (j) Ooi, T.; Takeuchi, M.; Kato, D.; Uematsu, Y.; Yamada, E.; Sakai, D.; Maruoka, K. *J. Am. Chem. Soc.* **2005**, *127*, 5073–5083.
12. (a) Manabe, K. *Tetrahedron Lett.* **1998**, *39*, 5807–5810; (b) Manabe, K. *Tetrahedron* **1998**, *54*, 14456–14476.
13. (a) Belokon', Y. N.; Kotchetkov, K. A.; Churkina, T. D.; Ikonnikov, N. S.; Chesnokov, A. A.; Larionov, A. V.; Parmár, V. S.; Kumar, R.; Kagan, H. B. *Tetrahedron: Asymmetry* **1998**, *9*, 851–857; (b) Belokon', Y. N.; Kotchetkov, K. A.; Churkina, T. D.; Ikonnikov, N. S.; Chesnokov, A. A.; Larionov, A. V.; Singh, I.; Parmár, V. S.; Vyskocil, S.; Kagan, H. B. *J. Org. Chem.* **2000**, *65*, 7041–7048; (c) Shibuguchi, T.; Fukuta, Y.; Akachi, Y.; Sekine, A.; Oshima, T.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 9539–9543; (d) Arai, S.; Tsuji, R.; Nishida, A. *Tetrahedron Lett.* **2002**, *43*, 9535–9537; (e) Kowtoniuk, W. E.; MacFarland, D. K.; Grover, G. N. *Tetrahedron Lett.* **2005**, *46*, 5703–5705; (f) Kita, T.; Georgieva, A.; Hashimoto, Y.; Nakata, T.; Nagasawa, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 2832–2834.
14. (a) Belokon', Y. N.; Kotchetkov, K. A.; Churkina, T. D.; Ikonnikov, N. S.; Vyskocil, S.; Kagan, H. B. *Tetrahedron: Asymmetry* **1999**, *10*, 1723–1728; (b) Belokon', Y. N.; Kotchetkov, K. A.; Churkina, T. D.; Ikonnikov, N. S.; Larionov, O. V.; Harutyunyan, S. R.; Vyskocil, S.; North, M.; Kagan, H. B. *Angew Chem., Int. Ed.* **2001**, *40*, 1948–1951; (c) Casas, J.; Nájera, C.; Sansano, J. M.; González, J.; Saá, J. M.; Vega, M. *Tetrahedron: Asymmetry* **2001**, *12*, 699–702.
15. (a) Belokon', Y. N.; North, M.; Kublitski, V. S.; Ikonnikov, N. S.; Krasik, P. E.; Maleev, V. L. *Tetrahedron Lett.* **1999**, *40*, 6105–6108; (b) Belokon', Y. N.; Davies, R. G.; North, M. *Tetrahedron Lett.* **2000**, *41*, 7245–7248; (c) Belokon', Y. N.; Bhave, D.; D'Addario, D.; Groaz, E.; North, M.; Tagliazucca, V. *Tetrahedron* **2004**, *60*, 1849–1861.
16. (a) Jotterand, N.; Pearce, D. A.; Imperiali, B. *J. Org. Chem.* **2001**, *66*, 3224–3228; (b) Boisnard, S.; Carbonnelle, A.-C.; Zhu, J. *Org. Lett.* **2001**, *3*, 2061–2064; (c) Boeckmann, R. K., Jr.; Clark, T. J.; Shook, B. C. *Org. Lett.* **2002**, *4*, 2109–2112; (d) Berthelot, A.; Piguel, S.; Le Dour, G.; Vidal, J. *J. Org. Chem.* **2003**, *68*, 9835–9838; (e) Shults, M. D.; Pearce, D. A.; Imperiali, B. *J. Am. Chem. Soc.* **2003**, *125*, 10591–10597; (f) Armstrong, A.; Scutt, J. N. *Chem. Commun.* **2004**, 510–511; (g) De Paolis, M.; Chen, X.; Zhu, J. *Synlett* **2004**, 729–731; (h) Lin, L. S.; Lanza, T. J.; Castonguay, L. A.; Kamenecka, T.; McCauley, E.; Van Riper, G.; Egger, L. A.; Mumford, R. A.; Tong, X.; MacCoss, M.; Schmidt, J. A.; Hagmann, W. K. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2331–2334; (i) Srinivasan, J. M.; Burks, H. E.; Smith, C. R.; Viswanathan, R.; Johnston, J. N. *Synthesis* **2005**, 330–333; (j) Chen, X.; Chen, J.; De Paolis, M.; Zhu, J. *J. Org. Chem.* **2005**, *70*, 4397–4408; (k) Lepine, R.; Zhu, J. *Org. Lett.* **2005**, *7*, 2981–2984; (l) Van Rompaey, K.; Ballet, S.; Tomboly, C.; De Wachter, R.; Vanommeslaeghe, K.; Biesemans, M.; Willem, R.; Tourwe, D. *Eur. J. Org. Chem.* **2006**, 2899–2911; (m) Couturier, C.; Schlama, T.; Zhu, J. *Synlett* **2006**, 1691–1694.
17. (a) Ohshima, T.; Gnanadesikan, V.; Shibuguchi, T.; Fukuta, Y.; Nemoto, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 11206–11207; (b) Ohshima, T.; Shibuguchi, T.; Fukuta, Y.; Shibasaki, M. *Tetrahedron* **2004**, *60*, 7743–7754.
18. Chinchilla, R.; Mazón, P.; Nájera, C.; Ortega, F. J. *Tetrahedron: Asymmetry* **2004**, *15*, 2603–2607.
19. Chinchilla, R.; Mazón, P.; Nájera, C.; Ortega, F. J. *Arkivoc* **2005**, *vi*, 222–232.
20. Lygo, B.; Andrews, B. I. *Tetrahedron Lett.* **2003**, *44*, 4499–4502.
21. Hulin, B.; Lopaze, M. G. *Tetrahedron: Asymmetry* **2004**, *15*, 1957–1958.
22. Oppolzer, W.; Moretti, R.; Zhou, C. *Helv. Chim. Acta* **1994**, *77*, 2363–2380.
23. (*S*)-Phenylalanine: $[\alpha]_D^{20} = -34.5$ (*c* 1, H_2O) *Dictionary of Organic Compounds*; Chapman & Hall: New York, 1982.