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Convenient Conditions for the Enantioselective Synthesis of α-Methyl-α-amino Acids with the Use of *Cinchona* Ammonium Salts as Phase-Transfer Organocatalysts

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Dedicated to Prof. Jan-E. Bäckvall on the occasion of his 60th birthday

Keywords: Enantioselective synthesis / Phase-transfer catalysis / Amino acids / Ammonium salts / Organocatalysis

The enantioselective α-alkylation of 2-naphthalenecarbaldehyde aldimine alanine *tert*-butyl ester is carried out by using *N*-anthracenylmethyl ammonium salts from the simple and unmodified cinchonidine and cinchonine alkaloids as phase-transfer organocatalysts, which affords (*S*)- and (*R*)-enantioenriched α-methyl-α-amino acid (AMAA) derivatives in 71–98 % yield and 79–96 % *ee*. The employed reaction conditions, rubidium hydroxide as base and toluene/chloroform as solvent at –20 °C, allows higher enantioselectivities to be obtained than those previously obtained by using other *Cinchona* alkaloid-derived ammonium salts, even with a lower catalyst loading (5 mol-%).

Introduction

The enantioselective synthesis of natural and nonproteinogenic amino acids is a topic of high interest due to their remarkable pharmacological and conformational properties, both as free amino acids and as components of biologically active peptides. Among them, α-alkyl- and especially α-methyl-α-amino acids (AMAAs) are valuable tools for restricting the conformational mobility of a peptide backbone and promote particular structures in the design of peptides and proteins.[1] This effect can be of great importance, for instance, in preventing the ability of amyloidogenic proteins, responsible for diseases such as Alzheimer's and Parkinson's, from adopting a β-sheet conformation by interfering with the amyloid self-assembly process.[2] Moreover, they can make peptides resistant to degradation,[3] and they are present in natural antibiotics[4] and act as enzyme inhibitors.[5] The asymmetric synthesis of AMAAs has been traditionally achieved by diastereoselective α-alkylation of an enolate obtained from chiral alanine-derived templates.[6] However, more recently their enantioselective syntheses by employing easily available chiral catalysts has revealed clear synthetic advantages for large-scale preparations.[7]

Phase-transfer catalysis (PTC) applied to the asymmetric alkylation of amino acid derived Schiff bases by using chiral phase-transfer organocatalysts is nowadays one of the most simple and easy to scale up procedures for the enantioselective synthesis of α-amino acids.[7,8] Thus, the advent in the early 1990s of the enantioselective alkylation of amino acid imines under PTC conditions catalyzed by quaternized *Cinchona* alkaloids, pioneered by O'Donnell[9] by using ammonium salts such as *N*-benzylated cinchonidinium chloride **1**, and further improved by Lygo[10] and Corey[11] by using *N*-anthracenylmethylated analogues such as **2a** and **2d**, respectively, allowed impressive degrees of enantioselectivity to be introduced into the products by using a very simple procedure. This procedure allows reversal of the enantioselectivity by using the corresponding pseudoenantiomeric cinchoninium-derived ammonium salts such as **3**[9] or **4**[12] as organocatalysts.

These asymmetric PTC procedures have been mainly employed for the α-alkylation of benzophenone-derived glycine Schiff base derivatives **5**, although applications to the enantioselective synthesis of AMAA derivatives by alkylation of aromatic aldehyde-derived alanine Schiff base derivatives **6** (R^1 = Me) can also be found. This change in the nature of the imine group from glycine to alanine is important, as the benzophenone imine, used for the monoalkylation of glycine derivatives **5**, does not allow a second alkylation process because of the decreased acidity of the α-methine proton in the monoalkylated derivative.[13]

The enantioselective synthesis of α,α-dialkylamino acids by subsequent α-alkylation of derivatives of type **6** is con-

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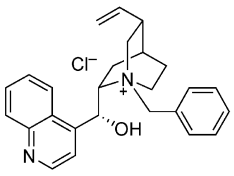

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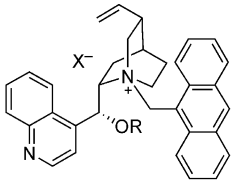
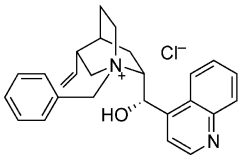


2a: R = H, X = Cl **2d**: R = Allyl, X = Br
2b: R = H, X = BF_4 **2e**: R = Allyl, X = BF_4
2c: R = H, X = PF_6 **2f** : R = Allyl, X = PF_6



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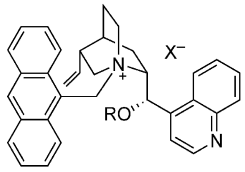

4a: R = H, X = Cl
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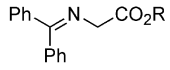

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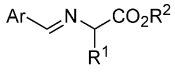

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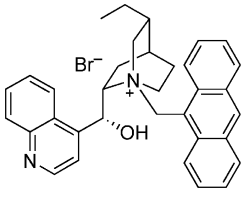
sidered to be a more difficult process in comparison to the α-monoalkylation of glycine derivatives **5**; generally, lower enantioselectivities are observed. Thus, the only example in which a chiral ammonium salt was prepared directly from a natural, simple, and cheap chiral source was reported by O'Donnell who employed *N*-benzyl cinchoninium chloride **3** as a phase-transfer organocatalyst for the enantioselective α-alkylation of 4-chlorobenzaldehyde-derived iminic alaninate **6** (Ar = 4-ClC_6H_4, R^1 = Me, R^2 = *t*Bu); however, low *ee* values were obtained such as the 40%*ee* for the α-benzylation reaction.[13] This result was improved up to 87%*ee* by Lygo who used *N*-anthracenylmethyl dihydrocinchonidinium bromide **7** as a catalyst, which was obtained after hydrogenation of cinchonidine and further *N*-quaternization.[14] Related to this hydrocinchonidine-incorporating structure is trifluorinated catalyst **8**, which was developed recently by Jew and Park. They obtained even higher enantioselectivities in the α-alkylation of a 2-naphthyl aldimine Schiff base of alanine *tert*-butyl ester **6** (Ar = 2-naphthyl, R^1 = Me, R^2 = *t*Bu) and achieved 95%*ee* for the benzylation reaction.[15] Other non-*Cinchona* catalysts have been used for the enantioselective synthesis of AMAA derivatives by alkylation of alanine-derived imines **6** under PTC conditions, such as metal–salen complexes,[16,17] binaphthol derivatives,[18] and C_2-symmetric ammonium salts.[19–21]



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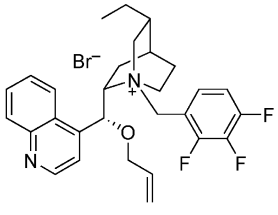

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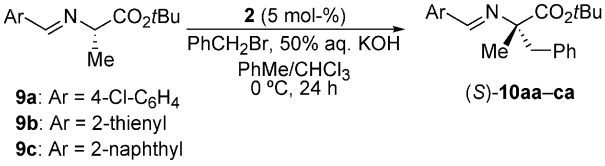
Recently, we demonstrated that the enantioselectivity in the alkylation reaction of benzophenone imine glycinates under PTC conditions with the use of common, simple, and inexpensive cinchonidine and cinchonine ammonium salts **2a**,**d** or **4** as organocatalysts can be considerably improved. Simple changes in the reaction conditions and some fine tuning of the catalysts were all that was needed. This included the exchange of the chloride anion of **2a** for tetrafluoroborate or hexafluorophosphate anions to afford **2b**,**c**, respectively, and exchange of the bromide anion of the *O*-allylated derivatives to afford fluorinated derivatives **2e**,**f**.[22] In this work we describe that simple *Cinchona* catalysts **2** or **4** can be used for the efficient enantioselective alkylation of imine alaninates under PTC conditions to afford enantioenriched AMAA derivatives.

Results and Discussion

Initially, the model enantioselective PTC for α-benzylation of (*S*)-alanine was performed on 4-chlorobenzaldimine alanine *tert*-butyl ester **9a** by using the simple and less derivatized cinchonidium-derived ammonium salt **2a** (5 mol-%) as the organocatalyst (Table 1, Entry 1). We employed 50% aqueous KOH as a cheap base in a toluene/chloroform (7:3) mixture as the solvent at 0 °C for 1 d. These conditions afforded high selectivity in the enantioselective α-alkylation of benzophenone glycine imines **6** when these types of organocatalysts were used.[22] Jew and Park had found that the use of this particular mixture of organic solvents in this PTC alkylation process afforded high enantioselectivities with the use of dimeric cinchonidinium salts as organocatalysts.[23] The incorporation of a certain amount of a more polar solvent to the toluene solution probably allows higher solubility of the organocatalyst, even at low temperatures, in the organic reaction phase.[24] Thus, under these reaction conditions, 50% aqueous KOH,

Table 1. Enantioselective benzylation of alanine imine derivatives **9** with the use of catalysts **2** under PTC conditions.



9a: Ar = 4-Cl-C_6H_4
9b: Ar = 2-thienyl
9c: Ar = 2-naphthyl

(*S*)-**10aa–ca**

Entry	Aldimine	Catalyst	Product	Yield[a] [%]	*ee*[b,c] [%]
1	**9a**	**2a**	(*S*)-**10aa**	83	82[d]
2	**9a**	**2b**	(*S*)-**10aa**	56	74
3	**9a**	**2c**	(*S*)-**10aa**	60	75
4	**9a**	**2d**	(*S*)-**10aa**	56	60
5	**9a**	**2e**	(*S*)-**10aa**	29	51
6	**9a**	**2f**	(*S*)-**10aa**	31	51
7	**9b**	**2a**	(*S*)-**10ba**	55	82
8	**9c**	**2a**	(*S*)-**10ca**	57	87

[a] Crude yield as determined by ^{1}H NMR (300 MHz) spectroscopy. [b] Determined by chiral HPLC from the corresponding *N*-benzoyl amides.[14] [c] Configuration assigned on the basis of the relative reported retention times of the (*R*/*S*) isomers.[15] [d] A 87%*ee* was reported with the use of catalyst **7** (K_2CO_3/KOH, toluene, r.t.).[14]

toluene/chloroform, 0 °C, a 82%*ee* for corresponding AMAA derivative (*S*)-**10aa** was obtained (Table 1, Entry 1). Attempts to improve this result by exchanging the chloride anion of **2a** for the tetrafluoroborate and hexafluorophosphate anions,[22] were not successful (Table 1, compare Entry 1 with Entries 2 and 3). The use of Corey's cinchonidine ammonium salt **2d** as the organocatalyst under these reaction conditions gave a rather poor value of 60%*ee* (Table 1, Entry 4), and even lower values were obtained with the use of the corresponding tetrafluoroborate (**2e**) and hexafluorophosphate (**2f**) salts (Table 1, compare Entry 4 with Entries 5 and 6).

After observing that the more simple catalyst **2a** afforded the highest degree of enantioselectivity, we next investigated the influence of the aldimine group in the alanine derivative. Thus, we performed the benzylation reaction on 2-thienyl aldimine alanine *tert*-butyl ester **9b** by using ammonium salt **2a** as the catalyst. No influence on the enantioselectivity was observed in comparison to that achieved with 4-chlorobenzaldehyde-derived alanine ester **9a**; the *ee* value remained at 82% for (*S*)-**10ba**. (Table 1, compare Entries 1 and 7). However, when the alkylation substrate was changed to 2-naphthyl aldimine alanine *tert*-butyl ester **7c**,[15] the enantioselectivity for (*S*)-**10ca** rose from 82 up to 87%*ee* (Table 1, compare Entries 1 and 8).

When the best combination of substrate/catalyst was settled, that is, **9c** and **2a**, we continued the optimization of the benzylation reaction by changing the base in an attempt to increase the enantioselectivity of the reaction. Thus, we employed solid monohydrated cesium hydroxide in the toluene/chloroform mixture at 0 °C, but the *ee* values for benzylated compound (*S*)-**10ca** dropped dramatically to 59% (Table 2, compare Entries 1 and 2). However, the use of rubidium hydroxide as the base[15] increased the yield to 83% and the enantioselectivity to 90% for (*S*)-**10ca** (Table 2, Entry 3). Moreover, when the reaction temperature was decreased to –20 °C, the yield was similar but the *ee* value increased to 94% (Table 2, Entry 4). This result is quite interesting, as a similar enantioselectivity (95%*ee*) was obtained in the benzylation of **9c** when the more elaborate trifluorobenzylated hydrocinchonidinium ammonium salt **8** was used as the organocatalyst under the same reaction conditions (same base, toluene as solvent) but at –35 °C.[15] In our case, a decrease in the reaction temperature down to –35 °C was not beneficial and a lower enantioselectivity (90%*ee*) was obtained (Table 2, Entry 5).

It is remarkable that these reaction conditions produced such enantioselectivities with the use of only a 5 mol-% loading of phase-transfer organocatalyst **2a**, as a 10 mol-% loading has always been employed with *Cinchona*-related ammonium salts.[13–15] Therefore, we also explored if the amount of catalyst could be diminished even more. Thus, when a 2 mol-% of **2a** was used under the best reaction conditions, an 88%*ee* of (*S*)-**10ca** was obtained; this value dropped slightly to 86%*ee* when only 1 mol-% loading of **2a** was employed (Table 2, compare Entries 4, 6 and 7). We also explored the influence of lowering the reaction temperature when using 50% aqueous potassium hydroxide as base: product (*S*)-**10ca** was obtained with a 90%*ee* at –20 °C with 5 mol-% of catalysts **2a** (Table 2, Entry 8).

Table 2. Enantioselective benzylation of alanine imine derivative **9c** with the use of catalyst **2a** under PTC conditions.

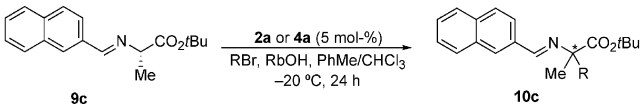
9c (*S*)-**10ca**

Entry	Catalyst [mol-%]	Base	*T* [°C]	*t* [h]	Yield[a] [%]	*ee*[b] [%]
1	5	50% aq. KOH	0	24	57	87
2	5	CsOH	0	8	69	59
3	5	RbOH	0	24	83	90
4	5	RbOH	–20	24	84	94
5	5	RbOH	–35	24	78	90
6	2	RbOH	–20	24	68	88
7	1	RbOH	–20	24	60	86
8	5	50% aq. KOH	–20	24	81	90

[a] Crude yield as determined by ^{1}H NMR (300 MHz) spectroscopy. [b] Determined by chiral HPLC from the corresponding *N*-benzoyl amides.[14]

Once the best substrate (**9c**) organocatalyst (**2a**), and optimal reaction conditions (RbOH as base, toluene/chloroform as solvent at –20 °C) were chosen for the enantioselective PTC benzylation of **9c**, we extended this methodology to the preparation of enantioenriched AMAA derivatives **10c**, and the results are shown in Table 3. In addition to the use of cinchonidinium-derived ammonium salt **2a**, we also employed pseudoenantiomeric cinchonine-derived chloride **4a** as the organocatalyst to obtain the corresponding AMAA enantiomers. Thus, the use of cinchoninium salt **4a** as the organocatalyst in the enantioselective benzylation of

Table 3. Enantioselective alkylation of alanine imine derivative **9c** with the use of catalysts **2a** and **4a** under PTC conditions.

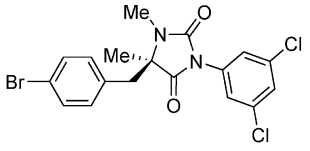


9c **10c**

Entry	RBr	Catalyst	Product	Yield[a] [%]	*ee*[b,c] [%]
1	$PhCH_2Br$	**2a**	(*S*)-**10ca**	84	94
2	$PhCH_2Br$	**4a**	(*R*)-**10ca**	92	94
3	$4\text{-}BrC_6H_4CH_2Br$	**2a**	(*S*)-**10cb**	98	95
4	$4\text{-}BrC_6H_4CH_2Br$	**4a**	(*R*)-**10cb**	67	94
5	$4\text{-}t\text{Bu}C_6H_4CH_2Br$	**2a**	(*S*)-**10cc**	90	91
6	$4\text{-}t\text{Bu}C_6H_4CH_2Br$	**4a**	(*R*)-**10cc**	88	94
7	$3\text{-}MeC_6H_4CH_2Br$	**2a**	(*S*)-**10cd**	84	93
8	$3\text{-}MeC_6H_4CH_2Br$	**4a**	(*R*)-**10cd**	82	96
9	$4\text{-}F_3CC_6H_4CH_2Br$	**2a**	(*S*)-**10ce**	87	93
10	$4\text{-}F_3CC_6H_4CH_2Br$	**4a**	(*R*)-**10ce**	94	93
11	$CH_2{=}CHCH_2Br$	**2a**	(*S*)-**10cf**	79	91
12	$CH_2{=}CHCH_2Br$	**4a**	(*R*)-**10cf**	71	90
13	$CH{\equiv}CCH_2Br$	**2a**	(*S*)-**10cg**	91	93
14	$CH{\equiv}CCH_2Br$	**4a**	(*R*)-**10cg**	82	79

[a] Crude yield as determined by ^{1}H NMR (300 MHz) spectroscopy. [b] Determined by chiral HPLC from the corresponding *N*-benzoyl amides.[14] [c] Configuration assigned on the basis of the relative HPLC reported retention times of the (*R*/*S*) isomers.[15]

9c, under the optimized reaction PTC conditions, gave rise to a value of 94%*ee* for (*R*)-**10ca**, which is identical to that achieved for its enantiomer (*S*)-**10ca** with the use of cinchonidinium-derived organocatalyst **2a** (Table 3, compare Entries 1 and 2). When 4-bromobenzyl bromide was used as the electrophile and cinchonidinium ammonium salt **2a** as the organocatalyst, corresponding 4-bromobenzylalanine ester derivative (*S*)-**10cb** was obtained with a 95%*ee*, whereas a very similar value of 94%*ee* for its enantiomer (*R*)-**10cb** was obtained with the use of cinchoninium-derived organocatalyst **4a** (Table 3, compare Entries 3 and 4). 4-Bromobenzylalanine ester derivative (*R*)-**10cb** can be employed for the synthesis of a precursor of cell adhesion BIRT-377 (**11**).[21]



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Other α-benzylated alanine derivatives were obtained with excellent enantioselectivities by following this methodology. Thus, when 4-*tert*-butylbenzyl bromide was used as the electrophile and ammonium salt **2a** as the organocatalyst, corresponding AMAA derivative (*S*)-**10cc** was obtained with a 91%*ee*, whereas a higher value of 94%*ee* for (*R*)-**10cc** could be achieved by using catalyst **4a** (Table 3, Entries 5 and 6). High enantioselectivities were also obtained by using electrophiles such as 3-methylbenzyl and 4-trifluoromethylbenzyl bromide, which gave rise to 93%*ee* for both (*S*)-**10cd** and (*S*)-**10ce** when **2a** was used as the organocatalyst (Table 3, Entries 7 and 9). Their corresponding enantiomers (*R*)-**10cd** and (*R*)-**10ce** could be prepared in 96 and 93%*ee* by employing cinchoninium salt **4a** as the catalyst (Table 3, Entries 8 and 10).

When a nonactivated electrophile such as *n*-butyl iodide was used, no alkylation reaction was observed. However, when allyl bromide was used as the electrophile with the use of organocatalysts **2a** and **4a**, the *ee* value for the (*S*) and (*R*) enantiomers, respectively, of corresponding allylated alanine derivative **10cf** was 91 and 90%, respectively (Table 3, Entries 11 and 12). In addition, the use of propargyl bromide as the electrophile and **2a** as the organocatalyst gave (*S*)-**10cg** with 93%*ee* (Table 3, Entry 13). These values can be considered quite high, as only 85%*ee* for (*S*)-**10cf** and 84%*ee* for (*S*)-**10cg** were recently reported with the use of organocatalyst **8** and the same base, but in toluene as solvent at –35 °C.[15] In the case of the propargylation of **9c**, the use of cinchoninium-derived organocatalyst **4a** did not give a comparable enantioselectivity to that obtained for its enantiomer (*S*)-**10cg**, as (*R*)-**10cg** was obtained with an *ee* value of only 79% (Table 3, Entry 14).

Conclusions

Highly enantioenriched AMAA derivatives can be prepared from aldimine alanine *tert*-butyl esters by alkylation under phase-transfer conditions by using *N*-anthracenylmethyl ammonium salts from simple and easily available nonderivatized OH-free *Cinchona* alkaloids cinchonidine and cinchonine organocatalysts. The most appropriate alkylation substrate is 2-naphthalenecarbaldehyde aldimine alanine *tert*-butyl ester, whereas rubidium hydroxide as base and a mixture of toluene/chloroform as solvent at –20 °C are the most appropriate reaction conditions. Both AMAA enantiomers are accessible by using the cinchonidine or the cinchonine-derived salts. This combination of ammonium salts and reaction conditions shows clear advantages when compared to the previously reported procedure for the enantioselective alkylation of 2-naphthalenecarbaldehyde aldimine alanine *tert*-butyl ester, as a lower loading (from 10 to 5 mol-%) of more simple an economical ammonium salts are used at a higher temperature. The enantioselectivities of the obtained AMMA derivatives are in general the highest achieved to date by using *Cinchona*-derived ammonium salts as organocatalysts under phase-transfer conditions.

Experimental Section

Enantioselective Alkylation of Aldimine Alanine Ester 9c with the Use of Organocatalyst 2a or 4a Under PTC Conditions: A solution of aldimine **9c** (57 mg, 0.20 mmol), catalyst **2a** or **4a** (5.2 mg, 0.01 mmol), and the corresponding alkyl halide (1.0 mmol) dissolved in a mixture of toluene and $CHCl_3$ (7:3, 1.5 mL) was cooled to –20 °C. Rubidium hydroxide (102 mg, 1.0 mmol) was added, and the mixture was stirred vigorously at –20 °C and monitored by GLC. The suspension was diluted with water (10 mL) and extracted with Et_2O (3 × 3 mL). The combined organic layer was dried with $MgSO_4$, filtered, and the solvents evaporated in vacuo to afford crude products **10**, which were analyzed by ^1H NMR (300 MHz) spectroscopy.

The enantioselectivity of the reaction was determined by chiral HPLC of the corresponding *N*-benzoyl derivatives,[14] and the absolute stereochemistry was assigned on the basis of the relative retention times of the enantiomers described in the literature.[15] HPLC reference racemic samples were prepared from corresponding racemic **10**, which were obtained by using *n*-tetrabutylammonium bromide as the PTC catalyst.

Acknowledgments

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