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Enantioselective alkylation of aminoacid derivatives promoted by cyclic peptoids under phase-transfer conditions

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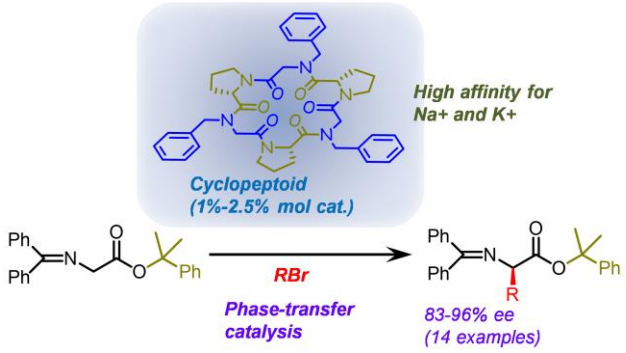

ABSTRACT: The effects of substituents and cavity size on catalytic efficiency of proline-rich cyclopeptoids under phase-transfer conditions were studied. High affinity constants (K_a) for the sodium and potassium cations, comparable to those reported for crown ethers, were observed for an alternated *N*-benzylglycine/L-proline hexameric cyclopeptoid. This compound was found to catalyze the alkylation of *N*-(diphenylmethylene)glycine cumyl ester in values of enantioselectivities comparable with those reported for the *Cinchona* alkaloid ammonium salts derivatives (83-96% ee), and with lower catalyst loading (1%-2.5% mol), in the presence of a broad range of benzyl, allyl and alkyl bromides.

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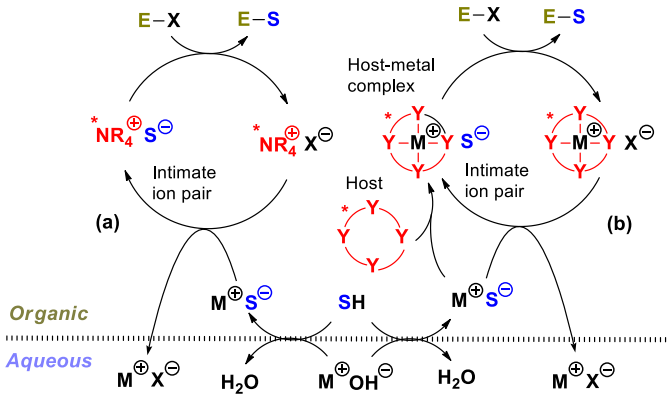
INTRODUCTION

In the intricate and fecund realm of the enantioselective organocatalysis, the asymmetric phase transfer catalysis is gaining an increasing popularity. The advantages of this methodology are multiple: the operational simplicity, the variety of the organic transformations involved, the mild and environmentally friendly experimental conditions employed, and the inexpensiveness of the reagents are some of those.[1]

Most of the recent contributions in the asymmetric phase transfer field, profit of the traditional chiral quaternary onium salts. The *Cinchona* alkaloids-derived and biaryl-based quaternary ammonium salts being the preferred phase transfer catalysts. The reaction mechanism is generally assumed to proceed through the formation, in the organic phase, of an intimate ion pair between the chiral quaternary cation and the anion generated by deprotonation of the weakly acidic substrate[1c,2] The enantioselectivity is presumed to be induced by the proximity of the chiral onium cation and the prochiral nucleophilic anion (Scheme 1 (a)).



Scheme 1. Mechanism of enantioselective phase transfer catalysis promoted by a quaternary ammonium salt (a) and a nonionic metal-complexing macrocycle (b).

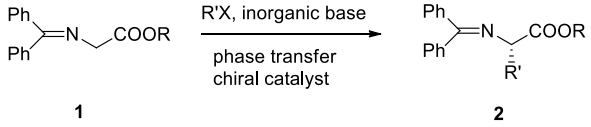
An intriguing alternative to the onium salts as phase transfer catalysts, are the nonionic metal complexing chiral macrocycles. Those efficient hosts, for their inherent structural and recognition

properties, can behave as synthetic enzymes and exert, in phase transfer catalysis conditions, asymmetric induction through complexation (Scheme 1(b)).

However, although crown ethers, calixarenes and cryptands proved to be efficient phase transfer catalysts,[3] chiral macrocycles still have not fulfilled their potentials. The first applications of macrocycles as phase transfer catalysts were originally devised by Cram and co-workers who studied the effect of chiral binaphthyl-modified crown ethers on Michael additions (in particular, in the reaction of methyl vinyl ketone with 2-methoxycarbonyl-1-indanone, and of methyl acrylate with methyl 2-methylphenylacetate and methyl phenylacetate in the presence of insoluble strong bases).[4] The addition of methyl phenylacetate to methyl acrylate was subsequently probed by other groups using different chiral crown ethers. The resulting enantioselectivities were good, but the studies remained limited to few substrates.[5,6] Promising enantioselectivities were achieved in the Michael addition of 2-nitropropane to *trans*-chalcone, in the presence of β-D-glucopyranoside derived aza-crown ethers.[7,8] Further studies revealed the strong influence of the chalcone substituents on the enantioselectivities (17-94% ee).[9] The same catalysts were employed in the Darzens condensation of phenacyl chloride with aromatic aldehydes[7] and the nucleophilic epoxidations of α,β-unsaturated ketones.[10] The addition of methyl phenylthioacetate to 2-cyclopentenone, promoted by a D-mannose-derived crown ether, has also been reported.[11] Moderate enantioselectivities were obtained in the α-hydroxylation of cyclic ketones catalyzed by a chiral aza-crown ether.[12]

Since its first introduction by O'Donnell and co-workers,[13] the asymmetric synthesis of α-amino acids by phase-transfer enantioselective monoalkylation of benzophenone imines of glycine esters **1** (Scheme 2) has become one of the most important application of quaternary ammonium salt catalysts, and it has gained the status of a benchmark reaction for testing the performance of new phase-transfer catalysts (PTCs).[1,14] The leading class of catalysts currently employed for this reaction are *Cinchona* alkaloids-derived and binaphtyl-derived quaternary ammonium salts.[15,16] Efficient catalysts based on

different chiral scaffolds are less common.[17] Surprisingly, chiral crown ethers afforded only poor enantioselectivities in the alkylation of benzophenone imines of glycine esters.[18,19] Better results were obtained in the enantioselective reaction of prochiral substrates **1**[19,20] and of the analogue α-aminophosphonates[21] with Michael acceptors.



Scheme 2. Enantioselective phase-transfer catalyzed alkylation of *N*-(diphenylmethylene)glycine esters.

Cyclopeptoids, cyclic oligomers of *N*-substituted glycines, are macrocyclic compounds whose abilities to host[22] and transport[23] metal cations are well-defined.[24] The introduction of proline residues generates macrocyclic architectures characterized by a reduced conformational freedom and the presence of a "chiral cavity".[25] Moreover, the modular nature of these compounds allows a quick (often automated) preparation of libraries, making them ideal candidates for the easy construction of morphologically diverse PTCs. However, despite these enormous advantages at present exist very few examples of peptoids that function as catalysts.[26] The nucleophilic substitution of *p*-nitrobenzyl bromide with NaSCN and KSCN represented the first example of cyclopeptoids used in PT catalysis.[27] The enantioselective monoalkylation of *N*-(diphenylmethylene)glycine *t*-butyl ester, in the presence of chiral cyclopeptoids, was subsequently probed, giving promising results.[28]

In the present paper we expand the scope of the preliminary studies[28] reporting the synthesis and the application of a library of structurally diverse peptoid-based chiral macrocycles for the enantioselective monoalkylation of benzophenone imines of glycine esters **1**. We also describe the dependence of the catalytic activity and enantioselectivity on the macrocycles' constitution, reaction conditions and substrate's structures.

The catalytic cyclopeptoids examined in this work are made of alternating units of L-proline and *N*-arylmethylsubstituted glycines. While the L-proline has the role to induce chirality and conformational rigidity to the macrocycle frame, the substituted glycines tune the complexing abilities and the consequent catalytic efficiency.[25a]

In our preliminary investigations[28] we demonstrated that arylmethyl side chains were an essential prerequisite for good enantioselectivities. This finding prompted us to generate a library of structurally related *N*-methylaryl cyclopeptoids **3** and **4** (Figure 1) whose catalytic properties and structural features are fully described in this paper. It must be noted that while the complexing abilities of cyclic hexameric peptoids are well known (and even exalted in the presence of alternated L-proline units),[22,25] the chelating properties of prolinated cyclotetrapeptoids have rarely been studied before.[29]

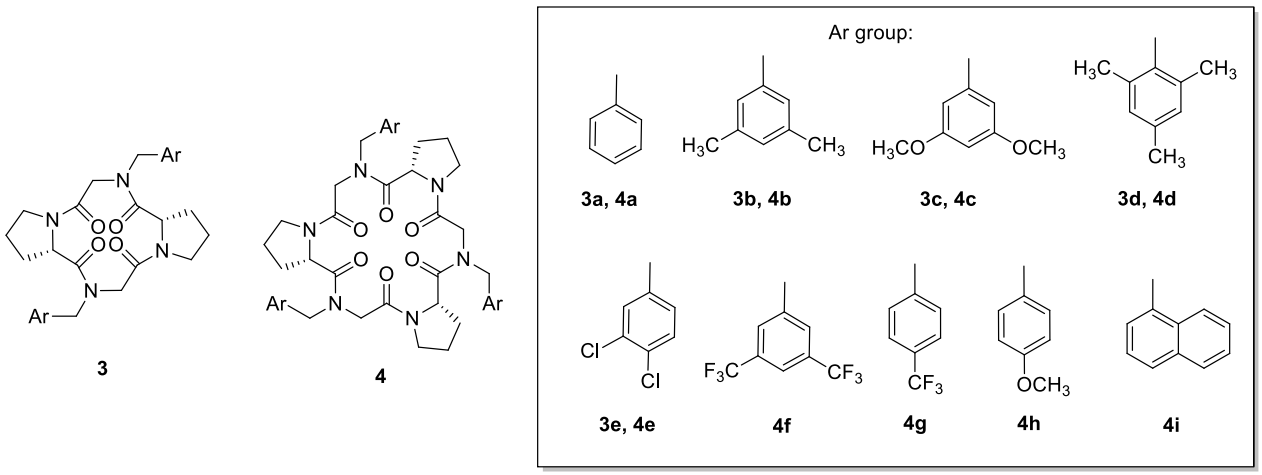
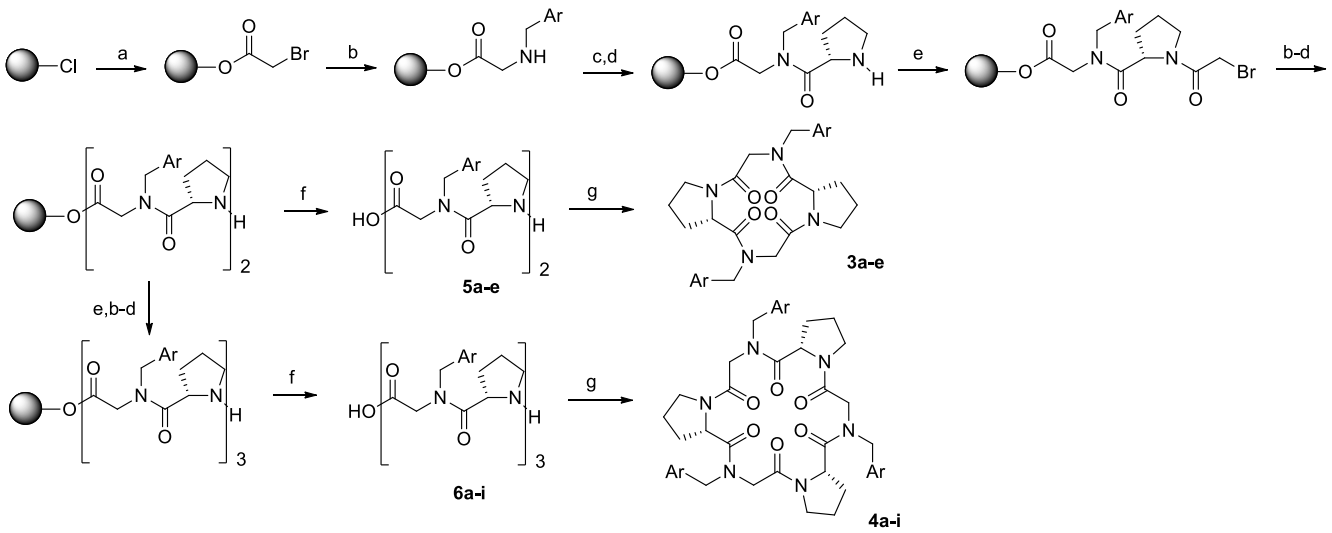


Figure 1. Structures of cyclopeptoids used in the present study.

The catalysts' syntheses followed the well-established mixed "sub-monomer/monomer approach" (Scheme 3).[25a,30] In particular, the *N*-alkyl glycine monomers were prepared on the chlorotrityl resin and subsequently coupled with Fmoc-L-proline (in the presence of HATU as condensing agent). The oligomeric chains were elongated repeating the above steps, with DIC or

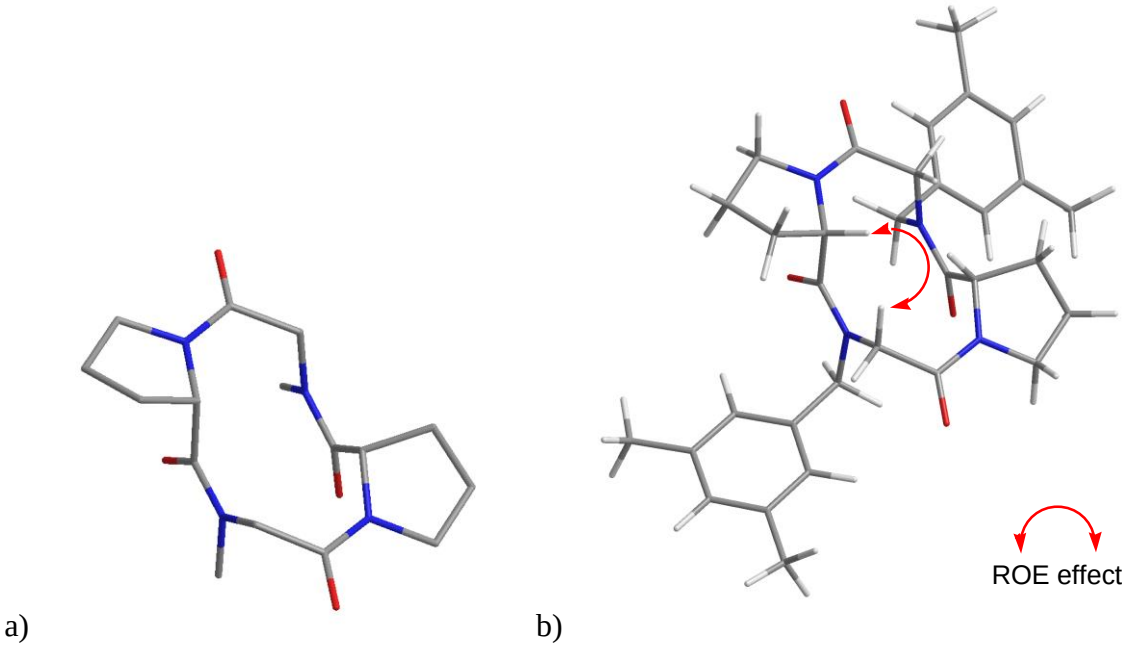
HATU as coupling reagents, until the desired length was achieved. Cleavage from the resin afforded the linear peptoids in 75-99% yield for the tetrameric series **5** and 40-55% yield for the hexameric series **6**. HATU-induced high dilution head-to-tail macrocyclization produced the expected cyclic peptoids **3a-e** (11-62% yield) and **4a-i** (10-57% yield).



Scheme 3. Synthesis of tetracyclopeptoids **3a-e** and hexacyclopeptoids **4a-i**. Reagents and conditions: (a) bromoacetic acid, DIPEA, DCM; (b) $ArCH_2NH_2$, DMF; (c) *N*-Fmoc-L-proline, HATU, DIPEA; (d) 20% piperidine/DMF; (e) bromoacetic acid, DIC; (f) HFIP/CH_2Cl_2 1:4; (g) HATU, DIPEA, DMF, DIPEA = *N*,*N* diisopropylethylamine; HATU = 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium hexafluorophosphate 3-oxide; DIC = *N*,*N*'-diisopropyl carbodiimide; HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol.

While metal-free cyclic hexameric peptoids appear as a complex mixture of conformers (r.t. ^{1}H-NMR analysis),[22b] cyclic tetrapeptoids show a locked conformation. In particular, non-prolinated cyclic tetrameric peptoids assume a *cis-trans-cis-trans* peptoid sequence[22b,25b,31] and the corresponding alternated *bis*-prolinated present a rigid all-*cis* peptoid bond conformation.[32,33] The C_2-symmetric morphology, previously found by Shimizu and co-workers for *cyclo*(L-Pro-Sar)$_2$ and reported in Figure

2 (a),[32,33] in our case was confirmed by a ROESY[34] experiment (Figure 2 (b)) made on compound **3b**. The key cross peak between the Pro-H_α (d, 5.52 ppm) and the Gly-H (d, 4.67 ppm) corroborated a *cis* peptoid bond junction for the Pro-*N*(alkyl)-Gly sequence.



a) b)

Figure 2. (a) Representation of the X-ray structure for the all-*cis cyclo*(L-Pro-Sar)$_2$ as reported by Shimizu[33] (hydrogen atoms omitted for clarity) (b) Picture of the predicted lowest energy conformation for the cyclotetrapeptoid **3b** displaying an all-*cis* geometry, located by Density Functional Theory calculations[35] (see supporting material) (atom type: C gray, N blue, O red, H white). The ROE effect is depicted by the red arrow. Gaussian 08 Software Package.[35]

Once established the structural features of the smaller cyclopeptoid, we determined the complexing abilities of the simplest members of the two cyclic peptoid series (the *N*-benzyl-substituted **3a** and **4a**). The association constants (K_a), $-\Delta G°$ and R_{CHCl_3}, in the presence of Na^+ and K^+, were calculated following the Cram's method[36] and are reported in Table 1. In the case of the hexameric

macrocycle **4a** we recorded the highest K_a values for a cyclic peptoid (both for the Na^+ and the K^+).[22b,27] In particular, for the sodium ion the calculated K_a value was one order of magnitude higher than that determined for the commercially available 15-crown-5, a well known sodium complexing agent.[27] To our surprise, we also observed high K_a values for the tetrameric peptoid **3a** (even higher than those reported for most of the non prolinated cyclic hexameric peptoids).[22b,27]

Table 1: Parameters for association between hosts and picrate salts in $CHCl_3$ at 25°C for cyclopeptoids **3a** and **4a**

entry	complexing agent	M^+	R_{CHCl_3} [a]	$K_a \times 10^{-4}/M^{-1}$	-ΔG°/Kcal/mol
1	**3a**	Na^+	0.38	530	9.1
2		K^+	0.34	206	8.5
3	**4a**	Na^+	0.73	10000	10.8
4		K^+	0.62	2000	9.9

[a] [Guest]/[Host] in $CHCl_3$ layer at equilibrium obtained by direct measurement, or calculated by difference from measurement made on aqueous phase at 25 °C (figures within ±10% in multiple experiments). Guest : host stoichiometry for extractions was assumed as 1 : 1.

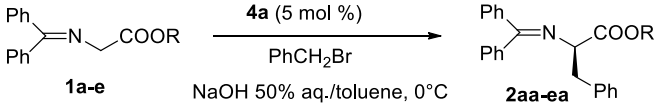
Considering the promising results recently obtained by us in the enantioselective alkylations of glycine ester derivatives catalyzed by cyclopeptoids (using toluene/50% NaOH liquid biphasic system at 0°C under anaerobic conditions, at catalyst loading of 5 mol %)[28,37] we chose the above conditions as a starting point to fully explore the potentials of this reaction.

We started studying the reaction catalyzed by the hexacyclopeptoid **4a** evaluating the effect of the ester group in the substrates **1** (Table 2). The C-2 benzylation of the *tert*-butyl ester **1a** afforded the (*R*)-phenylalanine ester derivative **2aa** with an encouraging 91% yield and 75% ee (entry 1). We assumed that the good catalytic activity and enantioselectivity were the result of the rigid macrocycle's

host properties. In fact, when the acyclic version of **4** was used in the same reaction, an almost racemic product was isolated (Scheme 4).

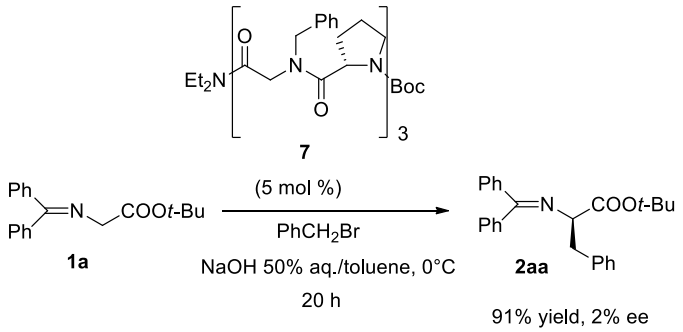
Ethyl and benzyl ester groups (present in **1b** and **1c**) gave lower performances (entries 2 and 3). Although we previously reported a complete degradation of **1b** under the above alkylation conditions for 20 h,[28] the reduction of reaction time to 4 h allowed smooth conversion to **2ba**, albeit with a moderate enantioselectivity (entry 2). Similarly, a clean conversion of benzyl ester **1c** to product **2ca** was obtained in 4 h with only a 49% ee (entry 3). A significant improvement, up to 81% ee, was obtained with the cumyl ester **1d** (entry 4). The cumyl residue can stabilize the transition state through π-π interactions with the catalyst and increase the ee. A bulkier ester group (as the benzhydryl in **1e**) lowers the ee (entry 5).

Table 2: Screening for the best ester group in the phase transfer benzylation of **1** promoted by **4a**.[a]



entry	R	product	time (h)	yield (%)[b]	ee (%)[c,d]
1	*t*-Bu– (**1a**)	**2aa**	20	91	75
2	Et– (**1b**)	**2ba**	4	88	41
3	Bn– (**1c**)	**2ca**	4	89	49
4	$Ph(Me)_2C$– (**1d**)	**2da**	20	74	81
5	Ph_2CH– (**1e**)	**2ea**	3	70	18

[a] All reactions were performed in a liquid-liquid system with 0.08 mmol of **1**, benzyl bromide (1.2 equiv.), and catalyst **4a** (5 mol %) in toluene (0.8 mL) and NaOH 50% aq (0.5 mL). [b] Isolated yields. [c] Determined by HPLC using a Chiralcel OD-H chiral stationary phase. [c] The absolute configuration of the products was determined by comparison of the HPLC retention time and optical rotation with literature values.[15a,e,38-40]

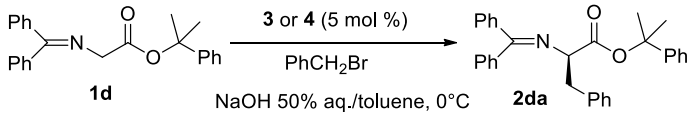


Scheme 4. Phase transfer benzylation of **1a** catalyzed by the acyclic peptoid **7**.

After the identification of **1d** as the optimal substrate, we screened differently substituted arylmethyl cyclopeptoids **3** and **4** under the above mentioned reaction conditions (Table 3) and found that the parent hexacyclopeptoid **4a** gave the best enantioselectivity (entry 1). *Meta*- and *para*-substituents, regardless of their electronic properties, have a slight effect on the catalytic activity and enantioselectivity (entries 2 and 6-8). Exceptions were the 3,5-dimethoxy derivative **4c** (entry 3) and even more the 3,4-dichlorobenzyl derivative **4e** (entry 5), for which very low yield and ee were obtained. The introduction of *ortho*- substituents resulted in lower catalytic activity and enantioselectivity as well (entries 4 and 9).

As expected, based on the good metal affinities exhibited, also the tetracyclopeptoids **3a-e** were able to catalyse the benzylation reaction. The catalytic activities and enantioselectivities, however, were generally lower than those promoted by the hexameric counterparts (compare entry 1 and 10, 2 and 11, 3 and 12, 4 and 13, 5 and 14). Lower reaction rates, with concomitant formation of decomposition byproducts, decreased the yields and eroded the stereoselectivity. A similar trend was observed in the C-2 benzylation of *tert*-butyl ester **1a** (see supporting material).

Table 3. Screening of the catalysts **3** and **4** in the phase transfer benzylation of **1d**

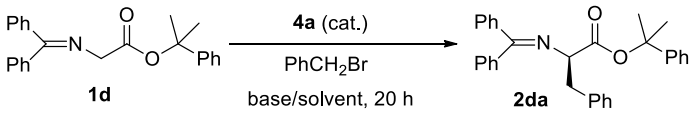


entry	catalyst	yield (%)[b]	ee (%)[c,d]
1	**4a**	74	81
2	**4b**	92	77
3	**4c**	54	45
4	**4d**	60	12
5	**4e**	50	5
6	**4f**	89	77
7	**4g**	71	65
8	**4h**	86	77
9	**4i**	61	48
10	**3a**	55	52
11	**3b**	50	*rac*
12	**3c**	54	46
13	**3d**	54	10
14	**3e**	55	46

[a] All reactions were performed in a liquid-liquid system with 0.08 mmol of **1d**, benzyl bromide (1.2 equiv.), and catalyst (5 mol %) in toluene (0.8 mL) and NaOH 50% aq (0.5 mL). [b] Isolated yields. [c] Determined by HPLC using a Chiralcel OD-H chiral stationary phase. [d] The absolute configuration of **2da** was determined by comparison of the HPLC retention time and optical rotation with literature values.[40]

A deeper study of the reaction parameters (solvent, concentration, catalyst loading, aqueous or solid base and temperature) was then performed in order to fully assess the potential of the studied reaction (Table 4).

Table 4: Screening of different reaction parameters in the phase transfer benzylation of **1d** promoted by **4a**.[a]



entry	solvent	base	catalyst loading (% mol)	temp (°C)	yield (%)[b]	ee (%)[c,d]
1	toluene	NaOH 50% aq.	5	0	74	81
2	Et_2O	NaOH 50% aq.	5	0	63	49
3	*p*-xylene	NaOH 50% aq.	5	0	72	62
4	toluene/$CHCl_3$ 9:1	NaOH 50% aq.	5	0	72	17
5	toluene/CH_2Cl_2 9:1	NaOH 50% aq.	5	0	69	78
6	toluene [e]	NaOH 50% aq.	5	0	73	75
7	toluene	NaOH 50% aq.	10	0	70	73
8	toluene	NaOH 50% aq.	2.5	0	75	86
9	toluene	NaOH 50% aq.	1	0	68	46
10	toluene	NaOH 50% aq.	5	–20	71	82
11	toluene	NaOH 50% aq.	2.5	–20	50	74
12	toluene	KOH 50% aq.	5	0	71	78
13	toluene	KOH 50% aq.	5	–20	70	87
14	toluene	KOH 50% aq.	2.5	–20	75	93
15	toluene	KOH 50% aq.	1	–20	76	92
16	toluene	CsOH 66% aq.	5	0	65	78
17	toluene	CsOH 66% aq.	5	–20	77	18
18	toluene	CsOH·OH (s) [f]	5	0	69	*rac*

[a] All reactions were performed in a liquid-liquid system with 0.08 mmol of **1d**, benzyl bromide (1.2 equiv.), and catalyst **4a** in the appropriate solvent (0.8 mL) and aqueous base (0.5 mL). [b] Isolated yields. [c] Determined by HPLC using a Chiralcel OD-H chiral stationary phase. [d] The absolute configuration of **2da** was determined by comparison of the HPLC retention time and optical rotation with literature values.[40] [e] 1.6 mL of toluene were used. [f] 5.0 equiv. of solid base were used.

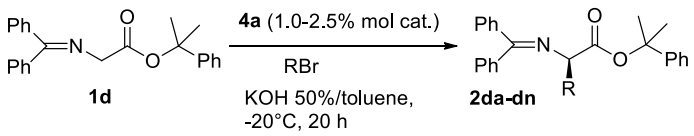
As previously reported by us, toluene is the best solvent for this reaction. Lower enantioselectivities were obtained in diethyl ether and *p*-xylene (entries 2 and 3, Table 3). A 10% amount of $CHCl_3$ in toluene caused a dramatic decrease of the ee (entry 4) while, surprisingly, only a

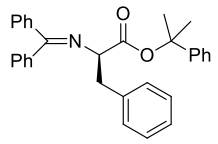
minor decrement was observed in the presence of the same amount of CH_2Cl_2 (entry 5). More dilute conditions also resulted in a worse performance of catalyst **4a** (entry 6). We also examined the effect of the catalyst loading. Interestingly, while a decrease of the enantioselectivity was obtained doubling the amount of catalyst (10 mol %, entry 7), a slight improvement to 86% ee was observed by using 2.5 mol % of catalyst loading (entry 8). A further reduction of catalyst loading to 1 mol % (entry 9) resulted in a substantial loss of enantioselectivity (the background uncatalyzed reaction becames competitive). At −20°C a little decrease of the stereoselectivity was observed with both 5 mol % and 2.5 mol % of catalyst loading (entries 10 and 11). The effect of the base was then studied. With a 5 mol % of catalyst loading the use of aqueous KOH 50% caused a very small decrease of the ee compared to NaOH 50% at 0 °C (entry 12). However a better performance of this system, probably due to the better solubility of KOH compared to NaOH, was observed at –20 °C (entry 13). The product **2da** was formed in 87% ee, 93% ee with 2.5 mol % of catalyst loading (entry 14) and 92% ee with 1 mol % of catalyst loading (entry 15).

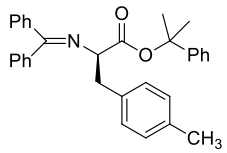
With the optimized reaction conditions in hand we explored the phase transfer reaction of **1d** catalysed by the cyclopeptoid **4a** (Table 5) in the presence of different alkylating agents. Catalyst loading (2.5% or 1.0% mol) was adjusted for each substrate in order to maximize the enantioselectivity. High enantioselectivities and good yields were consistently obtained with different benzyl, allyl and alkyl bromides (83-96% ee). The introduction of methyl groups in the *para*- and *meta*- positions of the benzyl bromide left the enantioselectivity values almost unchanged (Table 5, **2db** and **2dc**). A small increase, up to 96% ee, was achieved with the introduction of an *ortho*-methyl group (Table 5, **2dd**). The presence of different groups in *para*- position gave high enantioselectivities as well (Table 5, **2de-2di**). Comparable levels of enantioselectivities were achieved with allyl, propargyl, and ethyl bromides (Table 5, **2dk-dn**).

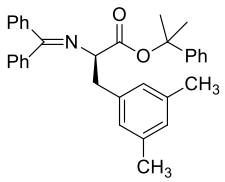
Kodanko and coauthors suggested the use of cumyl group as a valid alternative to the *tert*-butyl group as ester (the former can be cleaved by hydrogenolysis without affecting side chain acid-labile groups).[40] A single example of phase-tranfer α-alkylation of *N*-(diphenylmethylene)glycine cumyl ester **1d** has been reported to date, using *O*-allyl-*N*-(9-anthracenylmethyl)cinchonidinium bromide (in a 10 mol% catalyst loading).[40] In our study, a significantly lower amount of catalyst **4a** induced levels of enantioselectivities comparable to those previously reported, in the case of products **2da**, **2dk**, **2dm** and **2dn.**

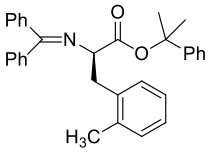
Table 5: Scope of the phase transfer alkylation of **1d** promoted by **4a**.[a-d]

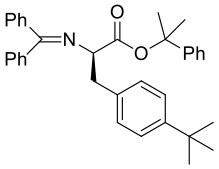


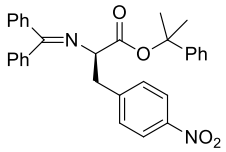

2da, 75% yield, 93% ee (2.5% mol cat.)

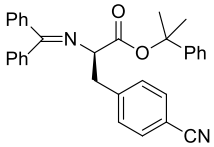

2db, 75% yield, 94% ee (1% mol cat.)

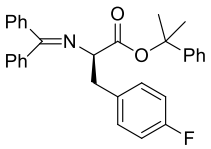

2dc, 82% yield, 89% ee (1% mol cat.)

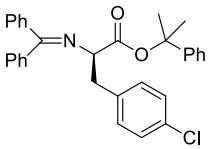

2dd, 89% yield, 96% ee (2.5% mol cat.)

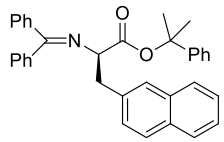

2de, 74% yield, 88% ee (2.5% mol cat.)

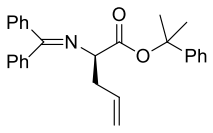

2df, 89% yield, 89% ee (2.5% mol cat.)

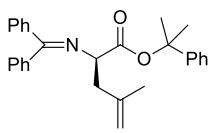

2dg, 80% yield, 93% ee (1% mol cat.)

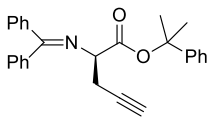

2dh, 75% yield, 91% ee (2.5% mol cat.)

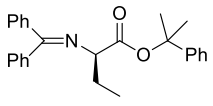

2di, 87% yield, 94% ee (1% mol cat.)


2dj, 97% yield, 95% ee (2.5% mol cat.)


2dk,[e] 90% yield, 93% ee (2.5% mol cat.)


2dl,[e] 93% yield, 86% ee (2.5% mol cat.)


2dm,[e] 91% yield, 83% ee (2.5% mol cat.)


2dn,[f] 86% yield, 86% ee (1% mol cat.)

[a] Reactions were performed in a liquid-liquid system on a 0.5 mmol scale by using **1d**, alkyl bromide (1.2 equiv.), and catalyst **4a** in the appropriate solvent (5.0 mL) and KOH 50% aq (3.0 mL), unless otherwise noted. [b] The yields are referred to the isolated products. [c] The ee values are determined by HPLC using a Chiralcel OD-H chiral stationary phase.[d] The absolute configurations of products **2da**, **2dk**, **2dm** and **2dn** were assigned by

comparison of the HPLC retention times and optical rotations with literature values.[40] For the other products the same (*R*) absolute configuration was assumed. [e] 1.5 equiv. of alkyl bromide were used. [f] 3.0 equiv. of alkyl bromide were used.

In conclusion, a library of proline-containing cyclopeptoids was prepared and characterized. Evaluation by Cram's method demonstrated the conspicuous complexing ability of these macrocycles, comparable to the best crown ether derivatives. The hexacyclopeptoid **4a** has been successfully utilized as phase-transfer catalyst in the alkylation of *N*-(diphenylmethylene)glycine cumyl ester **1d**, affording chiral α-aminoacid cumyl esters with high levels of enantioselectivity (83-96%) and high yields (74-97%). Only small catalyst loading (1% or 2.5% mol) is required. This is the first example of an efficient macrocyclic neutral phase-transfer catalyst employed in the alkylation of glycine derivatives with alkyl bromides. The complexing abilities and the catalytic efficiency, combined with their modular structure and the ease of preparation by solid-phase methodology, make these proline-containing cyclopeptoids a promising class of novel macrocyclic phase-transfer catalysts, potentially applicable to different processes.

EXPERIMENTAL SECTION

General remarks. Starting materials and reagents purchased from commercial suppliers were generally used without purification unless otherwise mentioned. Reaction temperatures were measured externally; reactions were monitored by analytical thin layer chromatography (TLC) on precoated silica gel plates (0.25 mm) and visualized by UV light. Flash chromatography was performed on silica gel 60 (particle size: 0.040-0.063 mm) and the solvents employed were of analytical grade. Cyclopeptoids **3a-e** and **4a-i** were purified by reversed-phase chromatography on C_{18} bonded silica (particle size 0.040-0.063 mm) and the purity grade were checked by HPLC analysis using a C_{18} reversed-phase analytical column (Bondapak, 10 μm, 125 Å, 3.9 mm × 300 mm) run with linear gradients of ACN (0.1% TFA) into H_2O (0.1% TFA) over 30 min, at a flow rate of 1.0 mL/min, with an UV detector set at 220 nm. Enantiomeric excesses of products **2da-dn** were determined by chiral HPLC using Chiralcel AD-H

columns with an UV detector set at 260 nm. All ultraviolet (UV) measurements were made at 24–26 °C, using spectrophotometric grade solvents. Low-resolution ESI-MS analysis in positive ion mode were performed using a Bio-Q triple quadrupole mass spectrometer equipped with an electrospray ion source. High-resolution mass spectra (HRMS) in positive ion mode were recorded on a Fourier transform ion cyclotron resonance mass spectrometer (FTICR-MS) using electrospray ionization (ESI). Optical rotation values were measured at λ = 589 nm, corresponding to the sodium D line, at the temperatures indicated. ^{1}H NMR and ^{13}C spectra were recorded on a 600 MHz, 400 MHz and 300 MHz instruments. Chemical shifts (δ) are reported in ppm relative to the residual solvent peak ($CHCl_3$, δ = 7.26; $^{13}CDCl_3$, δ = 77.0; ^{1}H-DMSO-d_6, δ = 2.50; ^{13}C-DMSO- d_6, δ = 39.5) and the multiplicity of each signal is designated by the following abbreviations: s, singlet; d, doublet; t, triplet; m, multiplet; bs, broad singlet; bd, broad doublet. Coupling constants (*J*) are quoted in Hertz. COSY and ROESY spectra of compound **3b** were measured on a 600 MHz instrument.

General procedure for the mixed monomer/submonomer solid-phase synthesis of linear peptoids 5 and 6. Linear peptoids were synthesized by alternating submonomer solid-phase method using standard manual Fmoc solid-phase peptide synthesis protocols. Typically 0.40 g of 2-chlorotrityl chloride resin (Fluka; 2, α-dichlorobenzhydryl-polystyrene crosslinked with 1% DVB; 100-200 mesh; 1.20 mmol/g) was swelled in dry DCM (4 mL) for 45 min and washed twice in dry DCM (3 mL). Bromoacetic acid (107 mg, 0.77 mmol) and DIPEA (310 mg, 2.4 mmol) in dry DCM (4 mL) were added to the resin and the vessel was stirred on a shaker platform for 40 min at room temperature, and then washed with dry DCM (3 × 4 mL) and then with DMF (3 × 4 mL). Then the arylmethylamine (4.80 mmol) in dry DMF (4 mL) was added to the bromoacetylated resin. The mixture was left on a shaker platform for 40 min at room temperature, then the resin was washed with DMF (3 × 4 mL). The resin was incubated with a solution of *N*-Fmoc-L-proline (486 mg, 1.44 mmol), HATU (529 mg, 1.39 mmol) and DIPEA (248 mg, 1.92 mmol) in dry DMF (4 mL) on a shaker platform for 1 h, followed by

extensive washes with DMF (3 × 4 mL), DCM (3 × 4 mL) and DMF (3 × 4 mL). Chloranil test was performed and once the coupling was complete the Fmoc group was deprotected by sequential additions of two aliquots of 20% piperidine/DMF (v/v, 3 mL), stirring on a shaker platform for 3 min and 7 min respectively, followed by extensive washes with DMF (3 × 3 mL), DCM (3 × 3 mL) and DMF (3 × 3 mL). Subsequent bromoacetylation reactions were accomplished by reacting the oligomer with a solution of bromoacetic acid (690 mg, 4.8 mmol) and DIC (666 mg, 5.28 mmol) in DMF (4 mL), stirring on a shaker platform for 40 min at room temperature. Then, reaction with arylmethylamine, with *N*-Fmoc-L-proline, Fmoc deprotection and bromoacetylation steps were repeated as described above. Generally, addition of the proline at the fourth position required longer reaction time (3 h). The synthesis was stopped for the tetramer or proceeded until the desired hexaoligomer was obtained. The oligomer-resin was cleaved by treatment with three aliquots of a solution of 20% HFIP in DCM (v/v; 3 × 4 mL), with stirring each time on a shaker platform for 30 min at room temperature, and filtering the resin away after each treatment. The combined filtrates were concentrated in vacuo. The final product was analysed by ESI mass spectrometry and RP-HPLC and used for the cyclization step without further purification.

General procedure for high dilution cyclization. Synthesis of compounds 3 and 4. To a stirred solution of HATU (178 mg, 0.47 mmol), DIPEA (93.0 mg, 0.72 mmol) in dry DMF (30 mL) at room temperature, a solution of linear precursors (0.12 mmol) in dry DMF (10 mL) was added by syringe pump during 6 h. After 18 h the resulting mixture was concentrated in vacuo, diluted with DCM (20 mL) and washed with 1 M HCl (3 × 7 mL). The mixture was extracted with DCM (2 × 10 mL) and the combined organic phases were washed three times with water (10 mL), dried ($MgSO_4$) and concentrated in vacuo. The crude residues were purified by reversed-phase chromatography on C_{18} bonded silica.

*Cyclic peptoid **4a**:* 43.0 mg, 49% yield, white amorphous solid; $[\alpha]_D^{25}$: 25.5 (c =1.0, $CHCl_3$); RP-HPLC analysis: Bondapak, 5% B in A → 100% B in 30 minutes (A: 0.1% TFA in water, B: 0.1% TFA in acetonitrile), 1.0 ml/min, 220 nm, t_r: 14.8 min.; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers) δ 7.69-6.85 (m, 15H), 5.98-3.04 (m, 21H), 2.59-1.26 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers, broad signals) δ 174.0, 173.8, 173.2, 172.7, 172.6, 172.2, 171.9, 170.9, 169.9 , 168.9, 168.4, 168.1, 167.9, 167.7, 167.3, 167.1, 166.8, 166.7, 165.4, 137.0, 136.7, 136.6, 136.5, 136.4, 136.2, 136.1, 135.7, 129.3, 129.0, 128.7, 128.5, 128.4, 128.3, 128.2, 128.0, 127.8, 127.7, 127.6, 127.5, 127.3, 127.1, 126.9, 126.7, 126.6, 126.4, 126.2, 58.9, 58.8, 57.9, 57.8, 57.3, 56.7, 56.5, 56.1, 53.6, 53.3, 53.1, 53.0, 52.3, 51.7, 51.4, 50.8, 50.1, 50.0, 49.9, 49.8, 49.4, 49.1, 48.8, 48.4, 48.1, 47.8, 47.7, 47.6, 47.4, 47.1, 46.9, 46.8, 46.4, 46.3, 46.2, 32.2, 32.0, 31. 9, 31.4, 31.3, 29.9, 29.6, 29.4, 29.2, 28.9, 28.6, 28.2 , 25.9, 25.4, 25.2 , 25.0, 24.8, 24.6, 22.7, 22.6, 22.0, 21.6 ; MS (ESI) $(M + Na)^+$ 755.2; HRMS (FTICR) $(M + Na)^+$ calcd for $C_{42}H_{48}N_6NaO_6$: 755.3528; found: 755.3510.

General procedure for the phase-transfer alkylation of 2d catalyzed by 4a.

To a solution of *N*-(diphenylmethylene)glycine 1-methyl-1-phenylethyl ester **1d**[36] (178 mg, 0.50 mmol) and cyclopeptoid **4a** (9.2 mg, 0.012 mmol) in toluene (5.0 mL) under nitrogen, the alkyl bromide (1.2-3.0 equiv.) was added. The mixture was degassed and then brought to -20°C. Degassed 50% aqueous KOH (3.0 mL) was then added. The reaction mixture was stirred at -20°C for 20 h. Then the suspension was diluted with CH_2Cl_2 (25 mL) and H_2O (15 mL), and the organic layer was taken. The aqueous layer was extracted twice with CH_2Cl_2 (25 mL × 2) and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether–ethyl acetate: 98:2 to 90:10) afforded the pure alkylated

products. The characterization data of the known products **2da**, **2dk**, **2dm**, **2dn** matched those previously reported.[40]

*(R)-2-phenylpropan-2-yl 2-((diphenylmethylene)amino)-3-phenylpropanoate (**2da**).* Yield 75%, colourless oil; ee 93%; $[\alpha]^{22}_{D}$ +13.4 (*c* 1.0, $CHCl_3$, 93% *ee*); HPLC analysis: Chiralcel OD-H, *i*-PrOH/hexane = 1/99, 0.5 mL/min, 260 nm, t_r (major) = 19.8 min, t_r (minor) = 24.7 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (m, 2H), 7.46−7.13 (m, 14H), 7.07 (m, 2H), 6.60 (bd, *J* = 6.6 Hz, 2H), 4.20 (dd, *J* = 9.3, 4.2 Hz, 1H), 3.28 (dd, *J* = 13.4, 4.2 Hz, 1H), 3.18 (dd, *J* = 13.4, 9.3 Hz, 1H), 2.30 (s, 3H), 1.80 (s, 3H), 1.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 170.0, 145.6, 139.4, 138.3, 136.2, 130.2, 129.9, 128.7, 128.2, 128.2, 128.1, 128.1, 128.0, 127.6, 126.9, 126.2, 124.3, 82.4, 67.9, 39.3, 28.9, 28.3; MS (ESI) $(M + H)^+$ 462.3, $(M + Na)^+$ 484.2; HRMS (FTICR) $[M + H]^+$ calcd for $C_{31}H_{30}NO_2$: 448.2277; found: 448.2268.

*(R)-2-phenylpropan-2-yl 2-((diphenylmethylene)amino)-3-(4-methylphenyl)propanoate (**2db**).* Yield 75%, yellow oil; ee 94%; $[\alpha]^{25}_{D}$ +101.5 (*c* 1.0, $CHCl_3$, 94% *ee*); HPLC analysis: Chiralcel OD-H, *i*-PrOH/hexane = 1/99, 0.5 mL/min, 260 nm, t_r (minor) = 13.9 min, t_r (major) = 17.0 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (m, 2H), 7.44−7.17 (m, 11H), 7.01 (d, *J* = 7.9, 2H), 6.94 (d, *J* = 7.9 Hz, 2H), 6.63 (bd, *J* = 6.8 Hz, 2H), 4.18 (dd, *J* = 9.2, 4.3 Hz, 1H), 3.24 (dd, *J* = 13.4, 4.3 Hz, 1H), 3.13 (dd, *J* = 13.4, 9.2 Hz, 1H), 2.30 (s, 3H), 1.80 (s, 3H), 1.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 170.0, 145.7, 139.5, 136.3, 135.6, 135.1, 130.1, 129.7, 128.7, 128.7, 128.2, 128.2, 128.1, 127.9, 127.7, 126.9, 124.3, 82.3, 68.0, 38.9, 28.9, 28.3, 21.0; MS (ESI) $(M + H)^+$ 462.3, $(M + Na)^+$ 484.2; HRMS (FTICR) $[M + H]^+$ calcd for $C_{32}H_{32}NO_2$: 462.2433; found: 462.2440.

*(R)-2-phenylpropan-2-yl 2-((diphenylmethylene)amino)-3-(3,5-dimethylphenyl)propanoate (**2dc**).* Yield 82%, colourless oil; ee 89%; $[\alpha]^{20}_{D}$ +97.9 (*c* 0.9, $CHCl_3$, 89% *ee*); HPLC analysis: Chiralcel OD-H, *i*-PrOH/hexane = 1/99, 0.5 mL/min, 260 nm, t_r (minor) = 14.2 min, t_r (major) = 19.5 min; ^{1}H NMR (400

MHz, $CDCl_3$) δ 7.59 (m, 2H), 7.42−7.14 (m, 11H), 6.80 (s, 1H), 6.66 (s, 2H), 6.61 (bd, J = 6.8 Hz, 2H), 4.18 (dd, J = 9.2, 4.2 Hz, 1H), 3.21 (dd, J = 13.3, 4.2 Hz, 1H), 3.09 (dd, J = 13.3, 9.2 Hz, 1H), 2.19 (s, 6H), 1.80 (s, 3H), 1.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 170.1, 145.7, 139.6, 137.9, 137.4, 136.3, 130.0, 128.7, 128.2, 128.2, 127.9, 127.9, 127.8, 127.7, 127.7, 126.9, 124.3, 82.3, 67.8, 39.1, 28.9, 28.3, 21.1; MS (ESI) $(M + H)^+$ 476.4; HRMS (FTICR) $[M + H]^+$ calcd for $C_{33}H_{34}NO_2$: 476.2590; found: 476.2580.

*(R)-2-phenylpropan-2-yl 2-((diphenylmethylene)amino)-3-(2-methylphenyl)propanoate (**2dd**).* Yield 89%, yellow oil; ee 96%; $[\alpha]^{22}_D$ +111.4 (*c* 1.0, $CHCl_3$, 96% *ee*); HPLC analysis: Chiralcel OD-H, *i*-PrOH/hexane = 1/99, 0.5 mL/min, 260 nm, t_r (major) = 20.8 min, t_r (minor) = 24.1 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (m, 2H), 7.43−7.19 (m, 11H), 7.14−6.98 (m, 4H), 6.49 (m, 2H), 4.23 (m, 1H), 3.32 (m, 1H), 3.20 (m, 1H), 2.08 (s, 3H), 1.83 (s, 3H), 1.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 170.2, 145.7, 139.2, 136.9, 136.3, 136.1, 131.0, 130.1, 130.0, 128.7, 128.2, 128.1, 128.0, 127.9, 127.7, 127.0, 126.4, 125.6, 124.3, 82.4, 66.5, 36.4, 29.0, 28.3, 19.3; MS (ESI) $(M + H)^+$ 462.1, $(M + Na)^+$ 484.1; HRMS (FTICR) $[M + H]^+$ calcd for $C_{32}H_{32}NO_2$: 462.2433; found: 462.2431.

*(R)-2-phenylpropan-2-yl 2-((diphenylmethylene)amino)-3-(4-tert-butyl-phenyl)propanoate (**2de**).* Yield 74%, yellow oil; ee 88%; $[\alpha]^{22}_D$ +38.2 (*c* 1.0, $CHCl_3$, 88% *ee*); HPLC analysis: Chiralcel OD-H, *i*-PrOH/hexane = 1/99, 0.5 mL/min, 260 nm, t_r (minor) = 11.3 min, t_r (major) = 14.1 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (m, 2H), 7.44−7.17 (m, 13H), 6.98 (d, J = 8.1 Hz, 2H), 6.52 (m, 2H), 4.16 (dd, J = 9.3, 4.0 Hz, 1H), 3.25 (dd, J = 13.4, 4.0 Hz, 1H), 3.13 (dd, J = 13.4, 9.3 Hz, 1H), 1.80 (s, 3H), 1.75 (s, 3H), 1.31 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 170.1, 149.1, 145.7, 139.5, 136.2, 135.2, 130.1, 129.5, 128.7, 128.2, 128.2, 128.0, 128.0, 127.6, 126.9, 125.0, 124.3, 82.3, 68.1, 38.7, 34.4, 31.4, 28.9, 28.3; MS (ESI) $(M + H)^+$ 504.2, $(M + Na)^+$ 526.2; HRMS (FTICR) $[M + H]^+$ calcd for $C_{35}H_{38}NO_2$: 504.2903; found: 504.2910.

*(R)-2-phenylpropan-2-yl 2-((diphenylmethylene)amino)-3-(4-nitrophenyl)propanoate (**2df**).* Yield 89%, yellow oil; ee 89%; $[\alpha]^{25}_{D}$ +170.7 (*c* 1.0, $CHCl_3$, 89% *ee*); HPLC analysis: Chiralcel OD-H, *i*-PrOH/hexane = 1/99, 1.0 mL/min, 260 nm, t_r (minor) = 16.6 min, t_r (major) = 35.4 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (m, 2H), 7.61 (m, 2H), 7.45−7.21 (m, 13H), 6.70 (bd, *J* = 7.0 Hz, 2H), 4.26 (dd, *J* = 8.7, 4.5 Hz, 1H), 3.35 (dd, *J* = 13.4, 4.5 Hz, 1H), 3.29 (dd, *J* = 13.4, 8.7 Hz, 1H), 1.80 (s, 3H), 1.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 169.2, 146.6, 146.3, 145.2, 138.9, 135.8, 130.6, 130.5, 128.6, 128.6, 128.3, 128.2, 128.1, 127.4, 127.1, 124.2, 123.2, 82.8, 66.9, 39.1, 28.8, 28.2; MS (ESI) $(M + H)^+$ 493.1, $(M + Na)^+$ 515.0; HRMS (FTICR) $[M + H]^+$ calcd for $C_{31}H_{29}N_2O_4$: 493.2127; found: 493.2138.

*(R)-2-phenylpropan-2-yl 2-((diphenylmethylene)amino)-3-(4-cyanophenyl)propanoate (**2dg**).* Yield 80%, yellow oil; ee 93%; $[\alpha]^{20}_{D}$ +50.8 (*c* 0.9, $CHCl_3$, 93% *ee*); HPLC analysis: Chiralcel OD-H, *i*-PrOH/hexane = 1/99, 1.0 mL/min, 260 nm, t_r (minor) = 18.4 min, t_r (major) = 30.7 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (m, 2H), 7.49 (m, 2H), 7.45−7.21 (m, 11H), 7.18 (m, 2H), 6.66 (bd, *J* = 6.8 Hz, 2H), 4.21 (dd, *J* = 8.9, 4.4 Hz, 1H), 3.30 (dd, *J* = 13.4, 4.4 Hz, 1H), 3.23 (dd, *J* = 13.4, 8.9 Hz, 1H), 1.79 (s, 3H), 1.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 169.3, 145.3, 144.2, 139.0, 135.9, 131.8, 130.7, 130.5, 128.7, 128.6, 128.3, 128.2, 128.1, 127.5, 127.1, 124.2, 119.0, 110.1, 82.8, 67.0, 39.3, 28.8, 28.2; MS (ESI) $(M + H)^+$ 473.2, $(M + Na)^+$ 495.2; HRMS (FTICR) $[M + H]^+$ calcd for $C_{32}H_{29}N_2O_2$: 473.2229; found: 473.2240.

*(R)-2-phenylpropan-2-yl 2-((diphenylmethylene)amino)-3-(4-fluorophenyl)propanoate (**2dh**).* Yield 75%, yellow oil; ee 91%; $[\alpha]^{25}_{D}$ +170.9 (*c* 0.8, $CHCl_3$, 91% *ee*); HPLC analysis: Chiralcel OD-H, *i*-PrOH/hexane = 1/99, 0.5 mL/min, 260 nm, t_r (minor) = 13.9 min, t_r (major) = 20.5 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (m, 2H), 7.43−7.19 (m, 11H), 7.02 (m, 2H), 6.89 (m, 2H), 6.65 (bd, *J* = 6.6 Hz, 2H), 4.17 (dd, *J* = 9.2, 4.2 Hz, 1H), 3.24 (dd, *J* = 13.5, 4.2 Hz, 1H), 3.15 (dd, *J* = 13.5, 9.2 Hz, 1H), 1.79 (s, 3H), 1.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 170.0, 161.5 (d, *J* = 244 Hz), 145.5,

139.3, 136.1, 134.0 (d, J = 2 Hz), 131.3 (d, J = 8 Hz), 130.3, 128.7, 128.3, 128.2, 128.2, 128.0, 127.6, 127.0, 124.3, 114.8 (d, J = 21 Hz), 82.5, 67.8, 38.4, 28.8, 28.3; MS (ESI) $(M + H)^+$ 466.2, $(M + Na)^+$ 488.2; HRMS (FTICR) $[M + H]^+$ calcd for $C_{31}H_{29}FNO_2$: 466.2182; found: 466.2174.

*(R)-2-phenylpropan-2-yl 2-((diphenylmethylene)amino)-3-(4-chlorophenyl)propanoate (**2di**).* Yield 87%, yellow oil; ee 94%; $[\alpha]^{22}_D$ +109.2 (*c* 1.0, $CHCl_3$, 94% *ee*); HPLC analysis: Chiralcel OD-H, *i*-PrOH/hexane = 1/99, 0.5 mL/min, 260 nm, t_r (minor) = 14.8 min, t_r (major) = 23.6 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (m, 2H), 7.44−7.21 (m, 11H), 7.18 (d, J = 8.3 Hz, 2H), 7.01 (d, J = 8.3 Hz, 2H), 6.67 (bd, J = 6.5 Hz, 2H), 4.19 (dd, J = 9.2, 4.2 Hz, 1H), 3.24 (dd, J = 13.4, 4.2 Hz, 1H), 3.15 (dd, J = 13.4, 9.2 Hz, 1H), 1.80 (s, 3H), 1.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 169.7, 145.5, 139.2, 136.8, 136.1, 132.0, 131.2, 130.3, 128.7, 128.4, 128.2, 128.2, 128.2, 128.0, 127.6, 127.0, 124.3, 82.5, 67.6, 38.6, 28.9, 28.3; MS (ESI) $(M + Na)^+$ 504.1; HRMS (FTICR) $[M + H]^+$ calcd for $C_{31}H_{29}ClNO_2$: 482.1887; found: 482.1878.

*(R)-2-phenylpropan-2-yl 2-((diphenylmethylene)amino)-3-(2-naphthyl)propanoate (**2dj**).* Yield 97%, colourless oil; ee 95%; $[\alpha]^{22}_D$ +50.7 (*c* 1.0, $CHCl_3$, 95% *ee*); HPLC analysis: Chiralcel OD-H, *i*-PrOH/hexane = 1/99, 0.5 mL/min, 260 nm, t_r (minor) = 20.1 min, t_r (major) = 29.8 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (m, 1H), 7.67 (m, 2H), 7.59 (m, 2H), 7.52 (s, 1H), 7.46−7.12 (m, 14H), 6.53 (m, 2H), 4.33 (dd, J = 9.2, 4.3 Hz, 1H), 3.45 (dd, J = 13.5, 4.3 Hz, 1H), 3.33 (dd, J = 13.5, 9.2 Hz, 1H), 1.80 (s, 3H), 1.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 170.0, 145.6, 139.4, 136.1, 135.8, 133.4, 132.1, 130.1, 128.7, 128.3, 128.2, 128.2, 128.0, 127.9, 127.6, 127.5, 127.5, 126.9, 125.8, 125.2, 124.3, 82.4, 67.8, 39.4, 28.9, 28.3; MS (ESI) $(M + H)^+$ 498.2; HRMS (FTICR) $[M + H]^+$ calcd for $C_{35}H_{32}NO_2$: 498.2433; found: 498.2423.

*(R)-2-phenylpropan-2-yl 2-((diphenylmethylene)amino)pent-4-enoate (**2dk**).* Yield 90%, yellow oil; ee 93%; $[\alpha]^{22}_D$ +5.7 (*c* 0.9, $CHCl_3$, 93% *ee*); HPLC analysis: Chiralcel OD-H, *i*-PrOH/hexane = 1/99, 0.5 mL/min, 260 nm, t_r (minor) = 11.1 min, t_r (major) = 12.7 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (m,

2H), 7.48−7.20 (m, 11H), 7.16 (m, 2H), 5.74 (m, 1H), 5.09 (m, 1H), 5.04 (m, 1H), 4.10 (dd, *J* = 7.8, 5.1 Hz, 1H), 2.78−2.60 (m, 2H), 1.80 (s, 3H), 1.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 170.0, 145.7, 139.6, 136.5, 134.6, 130.2, 128.8, 128.5, 128.4, 128.2, 128.0, 127.9, 126.9, 124.3, 117.4, 82.3, 65.8, 37.8, 28.9, 28.3; MS (ESI) $(M + H)^+$ 398.5; HRMS (FTICR) $[M + H]^+$ calcd for $C_{27}H_{28}NO_2$: 398.2120; found: 398.2115.

*(R)-2-phenylpropan-2-yl 2-((diphenylmethylene)amino)-4-methyl-pent-4-enoate (**2dl**).* Yield 93%, colourless oil; ee 86%; $[\alpha]^{22}_D$ +66.9 (*c* 1.0, $CHCl_3$, 86% *ee*); HPLC analysis: Chiralcel OD-H, *i*-PrOH/hexane = 1/99, 0.5 mL/min, 260 nm, t_r (minor) = 10.2 min, t_r (major) = 14.2 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (m, 2H), 7.48−7.20 (m, 11H), 7.16 (m, 2H), 4.77 (m, 1H), 4.74 (m, 1H), 4.18 (dd, *J* = 8.5, 4.9 Hz, 1H), 2.70 (dd, *J* = 13.5, 4.9 Hz, 1H), 2.62 (dd, *J* = 13.5, 8.5 Hz, 1H), 1.81 (s, 3H), 1.77 (s, 3H), 1.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 170.0, 145.7, 141.8, 139.7, 136.3, 130.2, 128.8, 128.5, 128.3, 128.2, 128.1, 128.0, 126.9, 124.3, 113.4, 82.3, 64.8, 41.5, 28.9, 28.3, 22.7; MS (ESI) $(M + Na)^+$ 434.3; HRMS (FTICR) $[M + H]^+$ calcd for $C_{28}H_{30}NO_2$: 412.2277; found: 412.2288.

*(R)-2-phenylpropan-2-yl 2-((diphenylmethylene)amino)pent-4-ynoate (**2dm**).* Yield 91%, colourless oil; ee 83%; $[\alpha]^{22}_D$ +25.4 (*c* 1.0, $CHCl_3$, 83% *ee*); HPLC analysis: Chiralcel OD-H, *i*-PrOH/hexane = 1/99, 0.5 mL/min, 260 nm, t_r (minor) = 17.3 min, t_r (major) = 18.6 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (m, 2H), 7.48−7.19 (m, 13H), 4.27 (dd, *J* = 8.1, 5.1 Hz, 1H), 2.90−2.72 (m, 2H), 1.97 (t, *J* = 2.4 Hz, 1H), 1.79 (s, 3H), 1.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 168.8, 145.4, 139.5, 136.1, 130.4, 128.9, 128.7, 128.4, 128.2, 128.2, 128.0, 127.0, 124.3, 82.8, 81.2, 70.2, 64.7, 28.8, 28.2, 23.2; MS (ESI) $(M + Na)^+$ 418.3; HRMS (FTICR) $[M + H]^+$ calcd for $C_{27}H_{26}NO_2$: 396.1964; found: 396.1955.

*(R)-2-phenylpropan-2-yl 2-((diphenylmethylene)amino)butanoate (**2dn**).* Yield 86%, colourless oil; ee 86%; $[\alpha]^{22}_D$ +33.1 (*c* 1.0, $CHCl_3$, 86% *ee*); HPLC analysis: Chiralcel OD-H, *i*-PrOH/hexane = 1/99, 0.5 mL/min, 260 nm, t_r (minor) = 11.5 min, t_r (major) = 12.9 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (m,

2H), 7.47−7.19 (m, 11H), 7.15 (m, 2H), 3.94 (dd, J = 7.9, 5.0 Hz, 1H), 2.03−1.86 (m, 2H), 1.79 (s, 3H), 1.75 (s, 3H), 0.87 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 170.3, 146.1, 139.9, 136.9, 130.4, 129.0, 128.7, 128.7, 128.4, 128.3, 128.2, 127.2, 124.6, 82.3, 67.6, 29.1, 28.6, 26.9, 10.9; MS (ESI) $(M + H)^+$ 386.3; HRMS (FTICR) $[M + H]^+$ calcd for $C_{26}H_{28}NO_2$: 386.2120; found: 386.2114.

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ASSOCIATED CONTENT:

Supporting Information. Experimental details, optimization tables and copies of ^{1}H NMR and ^{13}C NMR spectra of all the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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