EurJOC European Journal of Organic Chemistry

SHORT COMMUNICATION

DOI: 10.1002/ejoc.201403224

Cyclopeptoids as Phase-Transfer Catalysts for the Enantioselective Synthesis of α-Amino Acids

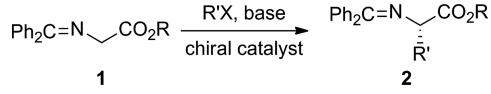
Rosaria Schettini,[a] Brunello Nardone,[a] Francesco De Riccardis,[a] Giorgio Della Sala,*[a] and Irene Izzo*[a]

Keywords: Organocatalysis / Asymmetric catalysis / Phase-transfer catalysis / Peptidomimetics / Cyclopeptoids

The first application of cyclopeptoids in asymmetric phase-transfer catalysis was examined. A small library of nine alternating *N*-substituted-glycine and proline hexacyclopeptoids was tested in the enantioselective alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester. The presence of an *N*-arylmethyl side chain in the catalyst was found to be crucial for the synthesis of α-amino acids with up to 73 % *ee*.

Introduction

Phase-transfer catalysis is green methodology that is largely employed in industry and organic synthesis.[1,2] The preparation of optically active α-amino acids derivatives, for its simplicity and intrinsic formal elegance, represents one of the most reliable applications of phase-transfer catalysis.[3] The asymmetric approach introduced by O'Donnell and co-workers[3d] based on the selective monoalkylation of benzophenone imines of glycine alkyl esters **1** (Scheme 1) is paradigmatic and has gained the status of a benchmark reaction for testing the performance of new phase-transfer catalysts (PTCs).



Scheme 1. Alkylation of glycine anion equivalents.

Generally, quaternary ammonium salts have been proven to be the catalysts of choice for such reactions and both natural and non-natural derivatives have been utilized to afford products with moderate to excellent enantiomeric excess values.[2,3] Since their first report in 1989,[4] the *Cinchona* quaternary ammonium salts have been the leading class of chiral catalysts employed for this reaction and excellent enantioselectivities have been reported by the groups of O'Donnell,[4] Lygo,[5] and Corey.[6] These results drove several groups to test ingeniously modified *Cinchona* alkaloids as catalysts.[7] Valid alternatives are the efficient binaphthyl- and biphenyl-modified Maruoka quaternary ammonium salts.[8,9] Quaternary ammonium salts based on different chiral scaffolds have rarely gained the status of efficient catalysts.[10–13] An accurate survey of the pertinent literature shows that, in most cases, the alkylation of glycine ester derivatives results in modest enantioselectivities.[14] Moreover, thermal lability in the presence of bases/nucleophiles seriously limits the application of quaternary ammonium salts for industrial purposes.[15] More stable metal complexing catalysts, such as crown ethers and open-chain polyethers, could offer a valid alternative;[15] however, this type of catalyst has been poorly investigated in asymmetric phase-transfer catalysis[16–19] and very few examples are reported for the asymmetric alkylation of glycine derivatives. In one case, an achiral crown ether was successfully used as a co-catalyst in the presence of chiral ammonium salts,[20] whereas more recently, Takizawa and co-workers developed spiro chiral crown ethers that promoted benzylation with low to moderate enantioselectivities.[19] In other examples, different macrocyclic catalysts, such as calixarenes, have been used merely as scaffolds for anchoring an ammonium salt group without exploiting potential metal complexing properties.[21] Considering the vivacity of this intellectual arena and pondering the well-explored complexation,[22] bilayer transport,[23] and phase-transfer catalysis abilities[24] of cyclopeptoids (cyclic oligomers of *N*-substituted glycines),[25] we decided to test them as possible PTCs for the enantioselective synthesis of amino acids. Compared to other catalysts, the core structures of which are fixed by nature or human inventiveness, cyclopeptoids, for their modular synthesis, have the advantage to display a potentially immense degree of diversity. Moreover, the solid-phase synthetic approach that we used for their construction allows quick preparation, no tedious workup/purification, and a potentially automated process. These properties make cyclopeptoids ideal candidates for the exploration of

[a] Dipartimento di Chimica e Biologia, Università degli Studi di Salerno,
Via Giovanni Paolo II, 132
E-mail: gdsala@unisa.it
iizzo@unisa.it
http://www.unisa.it/dipartimenti/dip_chimica_e_biologia/index

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201403224.

vast chemical spaces for the discovery of new catalysts. Notwithstanding all the reported advantages, and to the best of our knowledge, there is only one example of a peptoid that has been used in asymmetric catalysis.[26] In this communication, we report the first example of chiral cyclopeptoids as PTCs and highlight their potential in asymmetric synthesis.

Results and Discussions

In our previous investigation, chiral hexameric cyclic peptoid **3** containing alternating L-proline and *N*-methoxyethyl glycine residues (Figure 1) showed very high affinity for alkali metals, and in the solid state, it formed an intriguing triple decker Na^+ complex.[22b] Taking advantage of the same synthetic scheme, cyclohexameric peptoids **4**–**6** (Figure 1) containing L-proline residues were prepared. Lipophilicity (benzyl and *n*-hexyl appendages) or cation affinity (methoxyethyl and methoxyethoxyethyl pendant groups) dictated the choice of *N*-alkyl side chains.[24]

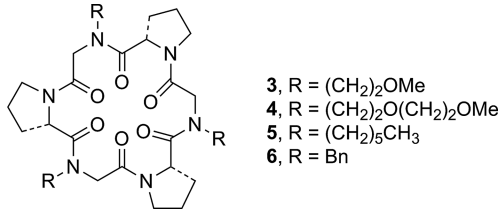
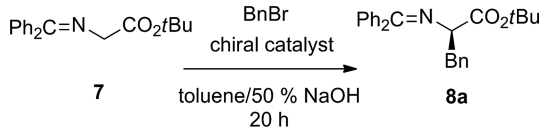


Figure 1. First-generation catalysts.

The ability of cyclopeptoids **3**–**6** to serve as PTCs was tested in the benzylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester (**7**, Table 1). Initially, the reactions were performed for 20 h in a toluene/50% NaOH liquid–liquid biphasic system under aerobic conditions at a catalyst loading of 5 mol-%. The studies started with cyclopeptoid **6**. At room temperature, the (*R*)-α-amino acid derivative was obtained with low enantiomeric excess (*ee*; Table 1, entry 1), whereas a racemic product was recovered under liquid–solid conditions (Table 1, entry 2). To improve the low *ee* observed in the liquid–liquid biphasic system, the reaction was conducted at 0 °C. As expected, the lower temperature had a beneficial effect on the enantioselectivity, possibly owing to a decrease in the conformational flexibility of the catalyst (Table 1, entry 3). In any case, at both room temperature and 0 °C, partial decomposition of the starting material was observed and benzophenone was recovered as a side product.[27] For this reason, in a subsequent trial, an inert atmosphere and deoxygenation of the organic and aqueous phases was performed by taking advantage of anaerobic conditions (Table 1, entry 4). In this way, both the yield and the *ee* were improved. Aliphatic cyclopeptoids **3**–**5** were tested under the same conditions (Table 1, entries 5–7). Unfortunately, even if the *N*-methoxyethoxyethyl chain proved to be beneficial in terms of yield, for all the macrocycles low *ee* values resulted. Interestingly, enantioselectivity inversion was observed in the presence of these catalysts. This behavior reveals the decisive role played by the aromatic groups in the selection of the appropriate enantioface of the substrate, for example, through the formation of π–π interactions.

Table 1. Benzylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester (**7**) by using first-generation catalysts.[a]

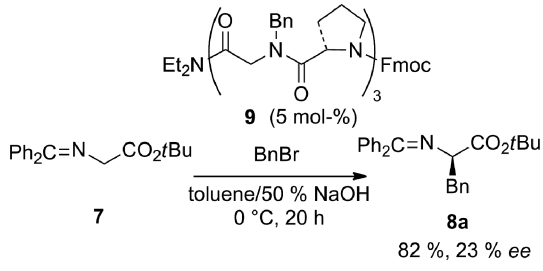


Entry	Catalyst	*T* [°C]	Yield [%]	*ee* [%][b,c]
1	**6**	r.t.	29	14 (*R*)
2[d]	**6**	r.t.	28	*rac*
3	**6**	0	36	29 (*R*)
4[e]	**6**	0	54	38 (*R*)
5[e]	**3**	0	11	8 (*S*)
6[e]	**4**	0	66	10 (*S*)
7[e]	**5**	0	36	10 (S)

[a] All reactions were performed in a liquid–liquid system for 20 h on a 0.08 mmol scale by using **7** (1.0 equiv.), benzyl bromide (1.2 equiv.), and catalyst (5 mol-%) in toluene (0.8 mL), with 50% aq. NaOH (0.5 mL), unless otherwise stated. [b] Determined by HPLC by using a Chiralcel OD-H chiral stationary phase. [c] The absolute configuration of **8a** was determined by comparison of the HPLC retention time and optical rotation with literature values.[6,7b] [d] Solid NaOH (3 equiv.) was used. [e] The reaction was performed under an inert atmosphere after deoxygenation of the two phases.

To prove the necessity of the base-stable *tert*-butyl ester in the glycine substrate, we submitted commercially available glycine ethyl ester benzophenone imine **1** (R = Et) to the alkylation conditions developed for **7**. However, after the canonical 20 h reaction (in the presence of catalyst **6**), complete hydrolysis of the ethyl ester was observed.

Moreover, with the purpose of demonstrating the relevance of the peptoid cyclization for the catalytic activity and enantioselectivity, we performed C_α-alkylation in the presence of acyclic peptoid **9** (Scheme 2). Although the reaction proceeded in good yield, the enantioselectivity was low. This observation served to point out the significance of the conformational restrictions of the macrocycle in the facial stereodifferentiation.



Scheme 2. Benzylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester (**7**) catalyzed by acyclic peptoid **9**. Fmoc = 9-fluorenylmethoxycarbonyl.

Considering the promising performance of compound **6** containing the *N*-benzyl pendant group, it was decided to graft the aromatic ring with groups inducing different steric

and electronic effects. In this way, a second generation of catalysts was designed and promptly synthesized (see compounds **10**–**14**, Figure 2).

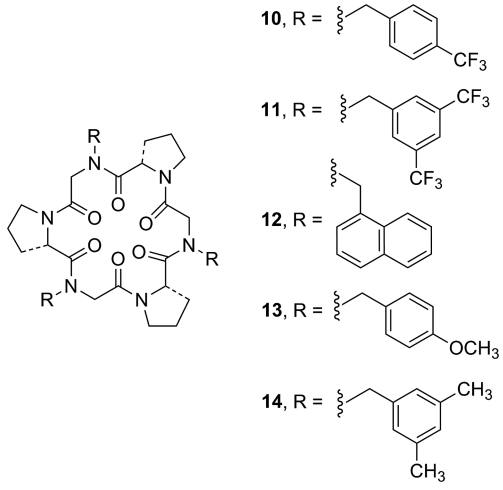


Figure 2. Second-generation catalysts.

All the new macrocycles were used under the best conditions observed for compound **6** (Table 1, entry 4). As can be seen in Table 2, compounds **10** and **11** containing electron-withdrawing groups proved to be less efficient, and they gave lower *ee* values (Table 2, entries 1 and 2). The steric hindrance of the 1-naphthyl group on the side chain (catalyst **12**; Table 2, entry 3) gave a better *ee* value and a better yield. On the other hand, the presence of the weak electron-donating *p*-methoxy substituent (catalyst **13**; Table 2, entry 4) proved to ameliorate only the *ee* value. Finally, and to our delight, the *ee* was improved by using compound **14** containing two methyl groups on the benzyl group, and although the value was moderate, this result is significant if compared with those observed for the few macrocyclic catalysts reported to date.[19] Then, an exhaustive study of the reaction parameters was performed. The use of more dilute conditions resulted in a worse performance of catalyst **6** (Table 2, entry 6). An extensive screening of the solvents was performed (Table 2, entries 7–17), and toluene was the optimal solvent. In addition, some experiments performed with aqueous KOH and CsOH revealed a relevant effect of the base (Table 2, entries 18 and 19). NaOH gave a better *ee* value than the other two hydroxides. Very low *ee* values were also obtained with solid $CsOH·H_2O$ both at 0 and –20 °C (Table 2, entries 20 and 21).

Other alkylating agents were tested to expand the scope of the alkylation reaction. As shown in Table 3, yields and *ee* values were comparable to those obtained with benzyl bromide (and in some cases were improved). The best *ee* value was achieved with 4-methylbenzyl bromide (Table 3, entry 5).

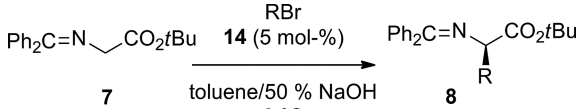
Finally, we checked the stability of our macrocyclic catalyst to possible base-induced epimerization (conscious of the strongly basic reaction conditions). After running the reaction in toluene/50% NaOH we performed an accurate flash chromatography and recovered C_3 symmetric cyclo-

Table 2. Benzylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester (**7**) by using second-generation catalysts with different bases and solvents.[a,b]

Entry	Cat.	Solvent	Base	Yield [%]	*ee* [%][c,d]
1	**10**	toluene	50% NaOH	7	30 (*R*)
2	**11**	toluene	50% NaOH	65	28 (*R*)
3	**12**	toluene	50% NaOH	77	61 (*R*)
4	**13**	toluene	50% NaOH	53	48 (*R*)
5	**14**	toluene	50% NaOH	64	67 (*R*)
6[e]	**14**	toluene	50% NaOH	53	37 (*R*)
7	**14**	CH_2Cl_2	50% NaOH	38	8 (*R*)
8	**14**	$CHCl_3$	50% NaOH	14	8 (*R*)
9	**14**	mesitylene	50% NaOH	68	*rac*
10	**14**	*o*-xylene	50% NaOH	51	16 (*R*)
11	**14**	*m*-xylene	50% NaOH	12	2 (*R*)
12	**14**	*p*-xylene	50% NaOH	16	35 (*R*)
13	**14**	chlorobenzene	50% NaOH	63	4 (*S*)
14	**14**	ethyl ether	50% NaOH	11	30 (*R*)
15	**14**	toluene/$CHCl_3$ (7:3)	50% NaOH	50	14 (*R*)
16	**14**	toluene/$CHCl_3$ (9:1)	50% NaOH	54	33 (*R*)
17	**14**	toluene/CH_2Cl_2 (7:3)	50% NaOH	54	11 (*R*)
18	**14**	toluene	50% KOH	50	50 (*R*)
19[f]	**14**	toluene	66% CsOH	7	5 (*R*)
20[g]	**14**	toluene	$CsOH·H_2O$ (s)	86	14 (*R*)
21[f,g]	**14**	toluene	$CsOH·H_2O$ (s)	7	16 (*R*)

[a] All reactions were performed in a liquid–liquid system for 20 h at 0 °C on a 0.08 mmol scale by using **7** (1.0 equiv.), benzyl bromide (1.2 equiv.), and catalyst (5 mol-%) in organic solvent (0.8 mL), with 50% aq. NaOH (0.5 mL), unless otherwise stated. [b] All reactions were performed under an inert atmosphere by deoxygenating the two phases. [c] Determined by HPLC by using a Chiralcel OD-H chiral stationary phase. [d] The absolute configuration of **8a** was determined by comparison of the HPLC retention time and optical rotation with literature values.[6,7b] [e] Toluene (1.6 mL). [f] The reaction was performed at –20 °C. [g] $CsOH·H_2O$ (5.0 equiv.).

Table 3. Reaction of *N*-(diphenylmethylene)glycine *tert*-butyl ester (**7**) with different alkylating agents by using second-generation catalyst **14**.[a,b]



Entry	RBr	Product	Time [h]	Yield [%]	*ee* [%][c,d]
1	benzyl bromide	**8a**	20	64	67 (*R*)
2	4-nitrobenzyl bromide	**8b**	5	86	57 (*R*)
3	4-fluorobenzyl bromide	**8c**	24	62	60 (*R*)
4	4-cyanobenzyl bromide	**8d**	45	62	45 (*R*)
5	4-methylbenzyl bromide	**8e**	24	66	73 (*R*)
6	3,5-dimethylbenzyl bromide	**8f**	18	60	60 (*R*)
7	4-(*tert*-butyl)benzyl bromide	**8g**	24	53	47 (*R*)
8[e]	allyl bromide	**8h**	23	55	55 (*R*)

[a] All reactions were performed in a liquid–liquid system for 20 h at 0 °C on a 0.08 mmol scale by using **7** (1.0 equiv.), benzyl bromide (1.2 equiv.), and catalyst (5 mol-%) in toluene (0.8 mL), with 50% aq. NaOH (0.5 mL), unless otherwise stated. [b] All reactions were performed under an inert atmosphere by deoxygenating the two phases. [c] Determined by HPLC by using a Chiralcel OD-H chiral stationary phase. [d] The absolute configurations of products **8a**–**e**, **8g**, and **8h** were determined by comparison of the HPLC retention times and optical rotations with literature values[6,7b] and for **8f** by analogy with known products. [e] Allyl bromide (1.5 equiv.).

peptoid **14** as a sodium complex (as determined by ^{1}H NMR spectroscopy) with no trace amount of other stereoisomers. The sodium complex showed catalytic efficiency that was similar to that of non-complexed **14** in the benzylation of **7** to afford **8a** in 60% yield with 65%*ee* after 20 h at 0 °C. Moreover, free cyclopeptoid **14** was easily obtained from the complexed form after elution on a reverse-phase HPLC column.[28]

Conclusions

In conclusion, we reported the first example of the use of chiral cyclopeptoids in asymmetric phase-transfer catalysis and showed their potential in enantioselective catalysis. The enantiomeric excess values shown in the alkylation reactions of glycine derivative were moderate, but the results obtained are remarkable considering the very few examples reported with metal-complexing catalysts. Moreover, these macrocycles appear to be promising phase-transfer catalysts, as their modular structure and the solid-phase synthetic approach are especially suitable for constructing libraries of different compounds for combinatorial catalyst screening, for instance, by varying the number, the position, and the nature of each residue.[29] Studies devoted to improve their performances and to clarify the mechanism of the catalysis are currently in progress.

Supporting Information (see footnote on the first page of this article): All experimental procedures, characterization data, and copies of the ^{1}H NMR and ^{13}C NMR spectra and the HPLC traces of the main catalysts.

Acknowledgments

The authors thank the University of Salerno (FARB), the Italian Ministero dell'Università e della Ricerca (MIUR) (PRIN 20109Z2XRJ_006), and the People Programme (Marie Curie Actions) of the European Union's Seventh Framework Programme FP7/2007-2013 under REA grant agreement number PIRSES-GA-2012-319011 for financial support. Dr Patrizia Iannece is thanked for ES-MS and Ms Assunta D'Amato for experimental work.

[1] a) M. Mąkosza, M. Fedoryński, *Curr. Catal.* **2012**, *1*, 79–87; b) M. Mąkosza, *Pure Appl. Chem.* **2000**, *72*, 1399–1403; c) C. M. Starks, C. L. Liotta, M. Halpern, *Phase-Transfer Catalysis*, Chapman & Hall, New York, **1994**.

[2] For recent reviews on asymmetric phase-transfer catalysis, see: a) S. Shirakawa, K. Maruoka, *Angew. Chem. Int. Ed.* **2013**, *52*, 4312–4348; *Angew. Chem.* **2013**, *125*, 4408–4445; b) T. Ooi, K. Maruoka, *Angew. Chem. Int. Ed.* **2007**, *46*, 4222–4266; *Angew. Chem. Commun.* **2009**, 7090–7103.

[3] a) B. Lygo, B. I. Andrews, *Acc. Chem. Res.* **2004**, *37*, 518–525; b) M. J. O'Donnell, *Acc. Chem. Res.* **2004**, *37*, 506–517; c) K. Maruoka, T. Ooi, *Chem. Rev.* **2003**, *103*, 3013–3028; d) M. J. O'Donnell, *Aldrichim. Acta* **2001**, *34*, 3–15.

[4] M. J. O'Donnell, W. D. Bennett, S. Wu, *J. Am. Chem. Soc.* **1989**, *111*, 2353–2355.

[5] a) B. Lygo, P. G. Wainwright, *Tetrahedron Lett.* **1997**, *38*, 8595–8598; b) B. Lygo, J. Crosby, T. R. Lowdon, J. A. Peterson, P. G. Wainwright, *Tetrahedron* **2001**, *57*, 2403–2409; c) B. Lygo, B. J. Andrews, J. Crosby, J. A. Peterson, *Tetrahedron Lett.* **2002**, *43*, 8015–8018.

[6] E. J. Corey, F. Xu, M. C. Noe, *J. Am. Chem. Soc.* **1997**, *119*, 12414–12415.

[7] For selected examples, see: a) S.-s. Jew, B.-S. Jeong, M.-S. Yoo, H. Huh, H.-g. Park, *Chem. Commun.* **2001**, 1244–1245; b) J.-H. Lee, M.-S. Yoo, J.-H. Jung, S.-s. Jew, H.-g. Park, B.-S. Jeong, *Tetrahedron* **2007**, *63*, 7906–7915; c) H.-g. Park, B.-S. Jeong, M.-S. Yoo, M.-k. Park, H. Huh, S.-s. Jew, *Tetrahedron Lett.* **2001**, *42*, 4645–4648; d) H.-g. Park, B.-S. Jeong, J.-H. Lee, M.-k. Park, Y.-J. Lee, M.-J. Kim, S.-s. Jew, *Angew. Chem. Int. Ed.* **2002**, *41*, 3036–3038; *Angew. Chem.* **2002**, *114*, 3162–3164; e) M.-S. Yoo, B.-S. Jeong, J.-H. Lee, H.-g. Park, S.-s. Jew, *Org. Lett.* **2005**, *7*, 1129–1131; f) S.-s. Jew, M.-S. Yoo, B.-S. Jeong, I. Y. Park, H.-g. Park, *Org. Lett.* **2002**, *4*, 4245–4248; g) R. Chinchilla, P. Mazón, C. Nájera, F. J. Ortega, *Tetrahedron: Asymmetry* **2004**, *15*, 2603–2607; h) J. Lv, L. Zhang, L. Liu, Y. Wang, *Chem. Lett.* **2007**, *36*, 1354–1355; i) W. He, Q. Wang, Q. Wang, B. Zhang, X. Sun, S. Zhang, *Synlett* **2009**, 1311–1314.

[8] a) T. Ooi, M. Kameda, K. Maruoka, *J. Am. Chem. Soc.* **1999**, *121*, 6519–6520; b) T. Ooi, Y. Uematsu, M. Kameda, K. Maruoka, *Angew. Chem. Int. Ed.* **2002**, *41*, 1551–1554; *Angew. Chem.* **2002**, *114*, 1621–1624; c) M. Kitamura, S. Shirakawa, K. Maruoka, *Angew. Chem. Int. Ed.* **2005**, *44*, 1549–1551; *Angew. Chem.* **2005**, *117*, 1573–1575; d) T. Kano, Q. Lan, X. Wang, K. Maruoka, *Adv. Synth. Catal.* **2007**, *349*, 556–560; e) S. Shirakawa, M. Ueda, Y. Tanaka, T. Hashimoto, K. Maruoka, *Chem. Asian J.* **2007**, *2*, 1276–1281; f) M. Kitamura, Y. Arimura, S. Shirakawa, K. Maruoka, *Tetrahedron Lett.* **2008**, *49*, 2026–2030.

[9] a) Y.-G. Wang, K. Maruoka, *Org. Process Res. Dev.* **2007**, *11*, 628–632; b) Y.-G. Wang, M. Ueda, X. Wang, Z. Ha, K. Maruoka, *Tetrahedron* **2007**, *63*, 6042–6050.

[10] a) B. Lygo, B. Allbutt, S. R. James, *Tetrahedron Lett.* **2003**, *44*, 5629–5632; b) B. Lygo, B. Allbutt, D. J. Beaumont, U. Butt, J. A. R. Gilks, *Synlett* **2009**, 675–680; c) B. Lygo, U. Butt, M. Cormack, *Org. Biomol. Chem.* **2012**, *10*, 4968–4976.

[11] T. Kita, A. Georgieva, Y. Hashimoto, T. Nakata, K. Nagasawa, *Angew. Chem. Int. Ed.* **2002**, *41*, 2832–2834; *Angew. Chem.* **2002**, *114*, 2956–2958.

[12] T. Shibuguchi, Y. Fukuta, Y. Akachi, A. Sekine, T. Ohshima, M. Shibasaki, *Tetrahedron Lett.* **2002**, *43*, 9539–9543.

[13] M. Waser, K. Gratzer, R. Herchl, N. Müller, *Org. Biomol. Chem.* **2012**, *10*, 251–254.

[14] a) S. E. Denmark, N. D. Gould, L. M. Wolf, *J. Org. Chem.* **2011**, *76*, 4260–4336; b) T. Ishikawa, K. Nagata, S. Kani, M. Matsuo, D. Sano, T. Kanemitsu, M. Miyazaki, T. Itoh, *Heterocycles* **2011**, *83*, 2577–2588; c) K. Lippur, T. Kanger, K. Kriis, T. Kailas, A.-M. Müürisepp, T. Pehkb, M. Loppa, *Tetrahedron: Asymmetry* **2007**, *18*, 137–141; d) G. N. Grover, W. E. Kowtoniuk, D. K. MacFarland, *Tetrahedron Lett.* **2006**, *47*, 57–60; e) W. E. Kowtoniuk, D. K. MacFarland, G. N. Grover, *Tetrahedron Lett.* **2005**, *46*, 5703–5705; f) N. Mase, T. Ohno, N. Hoshikawa, K. Ohishi, H. Morimoto, H. Yoda, K. Takabe, *Tetrahedron Lett.* **2003**, *44*, 4073–4075.

[15] M. Halpern, *Phase-Transfer Catalysis*, in: *Ullmann's Encyclopedia of Industrial Chemistry*, **2012**, Wiley-VCH, Weinheim, Germany, vol. 26, p. 496.

[16] a) P. Bakó, K. Vizvárdi, Z. Bajora, L. Tõke, *Chem. Commun.* **1998**, 1193–1194; b) P. Bakó, A. Makó, G. Keglevich, M. Kubinyi, K. Pál, *Tetrahedron: Asymmetry* **2005**, *16*, 1861–1871; c) A. Makó, Z. Rapi, G. Keglevich, Á. Szöllősy, L. Drahos, L. Hegedűs, P. Bakó, *Tetrahedron: Asymmetry* **2010**, *21*, 919–925.

[17] E. F. J. de Vries, L. Ploeg, M. Colao, J. Brussee, A. van der Gen, *Tetrahedron: Asymmetry* **1995**, *6*, 1123–1132.

[18] K. Hori, M. Tamura, K. Tani, N. Nishiwaki, M. Ariga, Y. Tohda, *Tetrahedron Lett.* **2006**, *47*, 3115–3118.

[19] K. Yonezawa, M. L. Patil, H. Sasai, S. Takizawa, *Heterocycles* **2005**, *66*, 639–644.

[20] S. Shirakawa, K. Yamamoto, M. Kitamura, T. Ooi, K. Maruoka, *Angew. Chem. Int. Ed.* **2005**, *44*, 625–628; *Angew. Chem.* **2005**, *117*, 631–634.
[21] For some examples see: a) S. Bozkurt, M. Durmaz, M. Yilmaz, A. Sirit, *Tetrahedron: Asymmetry* **2008**, *19*, 618–623; b) S. Shirakawa, S. Shimizu, *New J. Chem.* **2010**, *34*, 1217–1222.
[22] a) C. De Cola, G. Fiorillo, A. Meli, S. Aime, E. Gianolio, I. Izzo, F. De Riccardis, *Org. Biomol. Chem.* **2014**, *12*, 424–431; b) I. Izzo, G. Ianniello, C. De Cola, B. Nardone, L. Erra, G. Vaughan, C. Tedesco, F. De Riccardis, *Org. Lett.* **2013**, *15*, 598–601; c) N. Maulucci, I. Izzo, G. Bifulco, A. Aliberti, D. Comegna, C. Gaeta, A. Napolitano, C. Pizza, C. Tedesco, D. Flot, F. De Riccardis, *Chem. Commun.* **2008**, 3927–3929.
[23] a) D. Comegna, M. Benincasa, R. Gennaro, I. Izzo, F. De Riccardis, *Bioorg. Med. Chem.* **2010**, *18*, 2010–2018; b) C. De Cola, S. Licen, D. Comegna, E. Cafaro, G. Bifulco, I. Izzo, P. Tecilla, F. De Riccardis, *Org. Biomol. Chem.* **2009**, *7*, 2851–2854.
[24] G. Della Sala, B. Nardone, F. De Riccardis, I. Izzo, *Org. Biomol. Chem.* **2013**, *11*, 726–731.
[25] For recent reviews on cyclopeptoids, see: a) C. Tedesco, L. Erra, I. Izzo, F. De Riccardis, *CrystEngComm* **2014**, *16*, 3667–3687; b) I. Izzo, C. De Cola, F. De Riccardis, *Heterocycles* **2011**, *82*, 981–1006; c) B. Yoo, S. B. Y. Shin, M. L. Huang, K. Kirshenbaum, *Chem. Eur. J.* **2010**, *16*, 5528–5537.
[26] a) K. Kirshenbaum, G. Maayan, M. D Ward, U. S. Pat. Appl. Publ., US 20140100354 A1 20140410, **2014**; b) G. Maayan, M. D. Ward, K. Kirshenbaum, *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 13679–13684.
[27] The decomposition of a related substrate under aerobic phase-transfer catalysis conditions was previously reported and a radical pathway was suggested: T. Ooi, M. Takeuchi, D. Ohara, K. Maruoka, *Synlett* **2001**, *7*, 1185–1187.
[28] For details, see the Supporting Information. The retention time was the same as that obtained with cyclopeptoid **14**.
[29] In this respect, studies are underway by our group to evaluate the effect of the substitution of proline and *N*-alkylglycine residues with different α-amino acids and derivatives.

Received: September 17, 2014
Published Online: November 10, 2014

