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Rapid access to *N*-Boc phenylglycine derivatives via benzylic lithiation reactions

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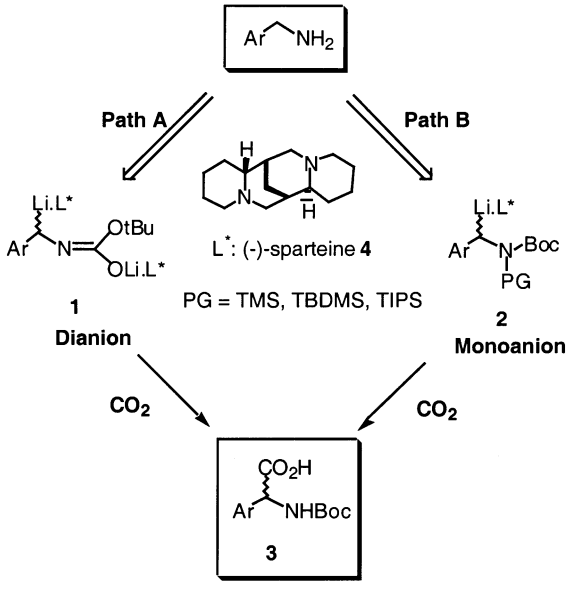
Abstract—We report a novel and efficient method for the enantioselective synthesis of *N*-Boc protected phenylglycines. Yields and enantiomeric ratios vary widely depending on the nature of the solvent, the substrate and on the method of forming the chiral complex. Results show that the major reaction pathway is an enantioselective deprotonation/substitution process. The enantioselectivity appears to be limited by the chiral discrimination ability of the *s*-BuLi–(−)-sparteine complex. The synthetic method described is one of the shortest route to useful enantioenriched *N*-Boc phenylglycine derivatives. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Due to the widespread occurrence of α-amino acids in biologically active compounds, the development of efficient methods for their enantioselective synthesis has been a challenge of considerable practical importance.[1] More specifically, arylglycines constitute an important class of non-proteogenic amino acids. They are present in many biologically active compounds[2] and are also important as chiral building blocks or as precursors of chiral ligands for asymmetric synthesis.[3] Elegant synthetic methods have been developed for the preparation of phenylglycine derivatives, but there is still a need for efficient, rapid procedures toward these compounds. Notably, the formation and reactions of dipole-stabilized anions adjacent to nitrogen have been studied extensively and were shown to be a useful approach for the synthesis of amino acid derivatives.[4]

As part of our research program on the development of peptide based supramolecular devices,[5] we required the preparation of *N*-*t*-Boc protected phenylglycine derivatives. Therefore, we sought to develop a rapid and efficient method to synthesize these compounds, generalized by **3**, using the strategy shown in Scheme 1. We envisioned at first that the protected phenylglycines could be made by the two strategies shown in Scheme 1. Path A involves the formation of a chiral dianionic species **1**, whereas path B implies the generation of a dipole stabilized chiral anion **2**. The intermediates **1** and **2** could in turn react stereoselectively with an electrophilic source of CO_2 to generate enantioenriched amino acids **3**. Therefore, the key steps involve an asymmetric deprotonation and a selective carboxylation. We used (−)-sparteine **4**–*s*-BuLi complex as a chiral base.[6] This versatile chiral complex has been used successfully in several processes, especially by Hoppe[7] and Beak.[8] The latter reported asymmetric syntheses of α-, β-, and γ-aryl aminoacids[8a,b] from *N*-Boc *N*-protected benzylamine derivatives using *n*-BuLi–(−)-sparteine complex as chiral base.

Herein, we demonstrate that *N*-Boc-protected phenylglycines **3** can be prepared efficiently and enantioselectively through path B.



Scheme 1. Strategies for the synthesis of *N*-protected arylglycines.

Keywords: enantioselective deprotonation; (−)-sparteine; organolithium; carboxylation; phenylglycine.

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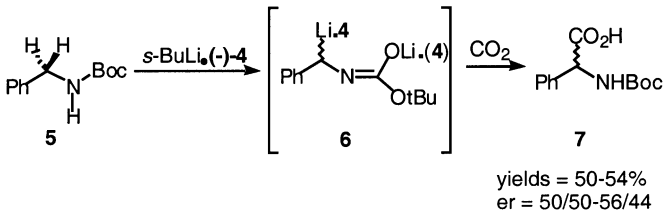


Scheme 2.

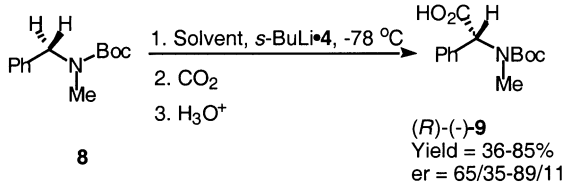
2. Results and discussion

2.1. Synthesis via dianionic species

Pathway A (Scheme 1) which involves a dianionic intermediate **1** was first investigated. As precedent, Tischler,[9] Greene,[10] and Schlosser[11] have reported results on dianionic species. Schlosser's group demonstrated the importance of having a carbamate moiety as stabilizing factor. Using *s*-BuLi–(−)-sparteine, we prepared **7** by the route shown in Scheme 2. In Et_2O or THF, we have been able to obtain **7** in 50–54% yields similar to the reported yields. However, the maximum enantioselectivity observed topped at an enantiomeric ratio (er) of 56/44 using a warm–cool protocol.[12] We attributed the lack of enantioselectivity to the presence of a negative charge on the carbamate, which decreases the configurational stability of the benzylic organolithium **6**. These results brought us to focus our efforts on pathway B, in which the carbamate proton is replaced by a protecting group.

2.2. Synthesis via monoanionic species

Pathway B (Scheme 1) requires a double 'protection' of the amino group. In this approach, the *s*-BuLi–(−)-sparteine complex would stereoselectively deprotonate the benzylic center to generate chiral intermediate **2**, and stereoselective electrophilic substitution with CO_2 was expected to lead to enantioenriched *N*-protected α-amino acid **3**. We initiated the study with the *N*-methyl *N*-Boc derivative **8** (Scheme 3), thereby, replacing the carbamate proton by a methyl group. The deprotonation–carboxylation sequence was performed on compound **8** [13] leading to enantioenriched *N*-Boc phenylsarcosine **9**.[14]



Scheme 3.

Table 1. Yields and enantiomeric ratios of (*R*)-(−)/(*S*)-(+)-**9** using (−)-**4**–*s*-BuLi, pre-formed or formed in situ as chiral base

Entry	Complex	Solvent	Yield (%)	er[a]
1	In situ	Hexane	55	89/11
2	Preformed	Hexane	85	69/31
3	In situ	Et_2O	54	79/21
4	Preformed	Et_2O	36	65/35

[a] Enantiomeric ratios were determined by polarimetry (see Section 4).

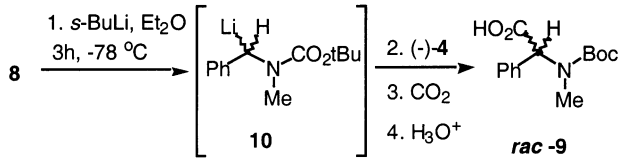
Two different strategies were investigated for the deprotonation procedure of **8**. In the first one, the chiral complex was formed in situ, and in the second, it was preformed separately, then cannulated at −78°C onto the substrate. The results obtained are summarized in Table 1.

Generally, better yields and enantioselectivities were observed in hexane as compared with Et_2O. It has been reported that the selectivity of the deprotonation and carboxylation steps is solvent-dependent.[7] In addition, the methodology involved in the deprotonation process was also shown to influence the degree of enantioselectivity, which was higher when the chiral complex was formed in situ. It is legitimate to presume that different organolithium complexes are produced by the two methodologies, hence leading to different levels of enantioselectivity.

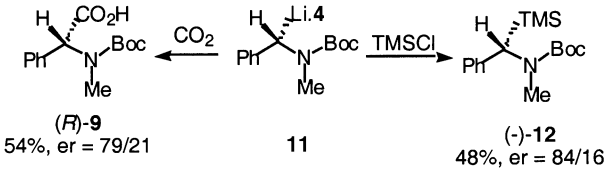
On the other hand, Beak and co-workers[16] observed the introduction of the chirality proceeded either by an enantioselective deprotonation or by an enantioselective substitution in related benzylic organolithiums. Hence, to define our mechanism, the racemic intermediate **10** (Scheme 4) was generated with *s*-BuLi, then (−)-sparteine was added at −78°C before CO_2 was bubbled through the reaction mixture. The acid **9** was obtained in 39% yield in a racemic form. This result suggests that the reaction proceeds most likely via an enantioselective deprotonation step, although it is possible that the ligand exchange reaction with (−)-sparteine is very slow at −78°C.

Studies on the mechanism of deprotonation–substitution sequence with benzylic organolithiums have been reported. Carboxylation with retention[17] or inversion[18] have been discussed extensively and reported. Therefore, it is difficult to assess unambigously which prostereogenic proton is abstracted by the chiral complex at this point.

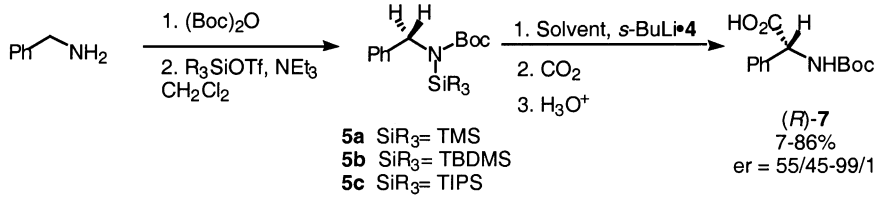
The stereoselectivity of the addition of CO_2 was demonstrated by quenching the intermediate **11** with TMSCl (Scheme 5). On the basis of earlier work, we assumed that the reaction of TMSCl with organolithiums proceeds with retention.[18,19] The silyl-substituted benzylamine **12** was



Scheme 4.



Scheme 5.



Scheme 6.

obtained in an er of 84/16, a level of enantioselectivity sligthly higher than the one obtained in Et_2O with CO_2 (Scheme 5). Therefore, it can be concluded that the carboxylation of the benzylic organolithium derived from **8** is stereoselective. Thus, the enantioselectivity of the overall process is limited by the selectivity of the deprotonation step.

Based on this groundwork, we decided to approach the synthesis of phenylglycines by 'protecting' temporarily the carbamate proton by a silyl group. Our approach to the asymmetric synthesis of aryl glycine derivatives **7** requires only three chemical steps from commercially available benzylic amines and is shown in Scheme 6. The silylation of the Boc-nitrogen atom was done efficiently using a versatile procedure we have described recently.[20]

To evaluate the influence of steric hindrance of the silyl protecting group on the reactivity and the stereoselectivity of the monoanionic species generated by the deprotonation step, different silyl groups were used. The importance of the silyl group variation was demonstrated earlier using *N*-Boc benzylic substrates.[6d] The results are reported in Table 2. These results indicate that the size of the silyl group impedes the approach of the large chiral complex and the deprotonation step. Indeed, the use of bulkier silyl groups leads to lower yields of **7**.

The enantiomeric ratios observed varied from 55/45 to 99/1,

Table 2. Yields and enantiomeric ratios of (*R*)-(+)/(*S*)-(−)-**7** obtained using *s*-BuLi–(−)-**4**, preformed or formed in situ as chiral base

Entry	Solvent	Substrate	Preformed		In situ	
			Yield (%)	er[a]	Yield (%)	er[a]
1	Et_2O	**5a**	86	71/39	49	76/24
2	Et_2O	**5b**	25	75/25	19	69/31
3	Et_2O	**5c**	11	59/41	7	99/1
4	Hexane	**5a**	10	81/19	37	70/30
5	Hexane	**5b**	–	–	13	55/45
6	Hexane	**5c**	–	–	–	–
7	Toluene	**5a**	11	79/21	52	80/20
8	THF	**5a**	12	50/50	18	57/43

[a] Enantiomeric ratios were determined by polarimetry (see Section 4).

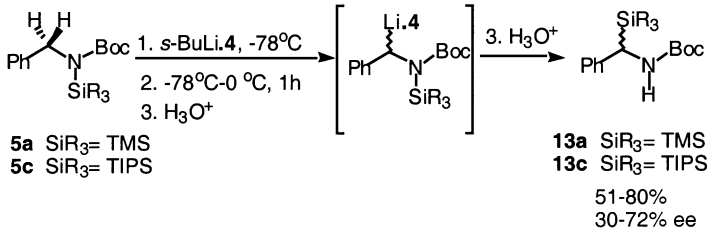
and the best chemical yields were observed with substrates having a TMS group. As the presence of the silyl protecting group influences the yield and the stereoselectivity, we reverified the reaction mechanism, as described previously, by generating the racemic intermediates of **5a**, then adding sparteine. We obtained an er of 55/45 for **7** as compared with 81/19 and 70/30 (Entry 4) when using hexane as solvent. This result indicates that the mechanism proceeds mainly through an enantioselective deprotonation, but a kinetic resolution appears to compete partially. Results in Table 2 demonstrate again that the carboxylation and the deprotonation steps are solvent-dependent as described above for **8**. Comparing results with **5a** (TMS group), the best yields were obtained in Et_2O when the chiral complex was preformed (Entry 1) and in toluene when the complex was formed in situ (Entry 7). As for the enantiomeric ratios, the highest one was observed when using the preformed complex in hexane, although the yield was low (10%; Entry 4). The best combination of yield and enantioselectivity was obtained in toluene with the chiral complex formed in situ (Entry 7). In addition, reactions in THF lead to low yields and enantioselectivity (Entry 8), in agreement with results from Schlosser.[11]

It is important to note that the enantiomeric ratios reported in Tables 1 and 2 are the ones measured on crude Boc-protected acids **7** and **9** obtained after one simple acid-base extraction work-up. In the case of **7** though, the enantiomeric purity could be increased to over 90% (er=96/4) by crystallizing out the mismatched dimer in an ether/hexane mixture (see Section 4 for details).

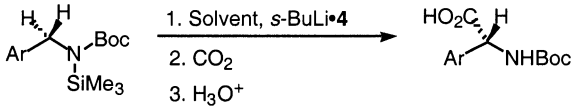
From Table 2, it is clear that the yields decreased dramatically with the size of the protecting group. This phenomena is mainly due to a competitive [1,2] silyl rearrangement of the organolithium intermediates as shown in Scheme 7.[21,22]

Further studies on that rearrangement[22] showed that it proceeds faster with the larger silyl group. Indeed, the TIPS substituted benzylamine **13c** was formed in an 80% yield by this process from **5c**. Notably, the rearrangement is stereoselective and leads to enantioenriched products like **13a** and **13c**.[22] Therefore, there is a competition between the intermolecular carboxylation and the intramolecular [1,2] silicon rearrangement even at −78°C with substrates bearing large silyl groups.

In light of these results, the remaining of the carboxylation studies were conducted with the monoanion of *N*-Boc *N*-trimethylsilylbenzylamine derivatives. To better understand the reactivity of this specific anion, we investigated



Scheme 7.



14 Ar= 2-fluorophenyl
15 Ar= 3-fluorophenyl
16 Ar= 4-fluorophenyl
20 Ar= 4-methylphenyl
21 Ar= 4-biphenyl
22 Ar= 1-naphthyl

(*R*)-**17** Ar= 2-fluorophenyl
(*R*)-**18** Ar= 3-fluorophenyl
(*R*)-**19** Ar= 4-fluorophenyl
(*R*)-**23** Ar= 4-methylphenyl
(*R*)-**24** Ar= 4-biphenyl
(*R*)-**25** Ar= 1-naphthyl

Scheme 8.

Table 3. Yields and enantiomeric ratios for **17**, **18**, **19**, **23**, **24**, **25** using *s*-BuLi–(−)-**4** formed in situ as chiral base

Entry	Ar	Solvent	Yield (%)	er[a]
1	2-Fluorophenyl	Et_2O	87	57/43
2	2-Fluorophenyl	Hexane	79	72/28
3	2-Fluorophenyl	Toluene	95	74/26
4	3-Fluorophenyl	Et_2O	95	60/40
5	3-Fluorophenyl	Hexane	84	75/25
6	3-Fluorophenyl	Toluene	80	85/15
7	4-Fluorophenyl	Et_2O	52	64/36
8	4-Fluorophenyl	Hexane	44	79/21
9	4-Fluorophenyl	Toluene	84	84/16
10	4-Methylphenyl	Et_2O	14	58/42
11	4-Methylphenyl	Hexane	80	82/18
12	4-Methylphenyl	Toluene	92	80/20
13	*p*-Biphenyl	Et_2O	28	87/13
14	*p*-Biphenyl	Hexane	41	98/2
15	*p*-Biphenyl	Toluene	95	90/10
16	1-Naphthyl	Et_2O	26	62/38
17	1-Naphthyl	Hexane	87	81/19
18	1-Naphthyl	Toluene	94	82/18

[a] Enantiomeric ratios were determined by ^1H NMR in $CDCl_3$ and by polarimetry (see Section 4).

the influence of different aromatic substituents as shown in Scheme 8. Results are summarized in Table 3.

The yields are excellent in all solvents for ortho and meta isomers **17** and **18** ranging from 79–95%. However for the *para* isomer **19**, yields are moderate in ether and hexane but very good in toluene. The enantiomeric ratios still top at a maximum around 85/15. The best enantioselectivity was obtained in toluene, and the worst in ether. Thus, the enantioselectivity and yields are generally higher in non-coordinating solvents, which either enhance the selectivity of the deprotonation or the electrophilic substitution. The latter phenomena has been reported by Hoppe.[7]

The inductive effect of the fluorine seems to be responsible for the increased chemical yields observed for the *ortho* and *meta* isomers **17** and **18**. The enantiomeric ratios however are not influenced by the fluorine position. These observations could also be explained, in that specific case, by the propensity of the carbanionic center to become planar more easily in the presence of a fluorine substituent. So the enantioselectivity could therefore originate from a restoration of the chirality after a rapid racemization (kinetic resolution).

Results with fluorine substituted substrates (Entries 1–9, Table 3) suggested that the mechanism of the reaction could go through a rapid racemization followed by restoration of chirality. But results with 4-methyl substituted benzylamine (Entries 10–12, Table 3) are in contradiction with that hypothesis. If there was a specific substituent effect, a simple methyl substituent on the phenyl moiety should have the same reactivity as the unsubstituted phenyl group. However, the yield increased to 92% in toluene (Entry 12) and decreased to 14% yield in Et_2O (Entry 10) as compared with the unsubstituted substrate **5a** (Table 2; Entries 1 and 7). In addition, if the electron delocalization on the aromatic system was responsible for the increased yields in **17**–**19**, the 4-biphenyl substrate **21** would confirm that hypothesis. But we only got a 41% yield in hexane (Entry 14) minimizing the importance of charge delocalization in the chemical yields. It is noteworthy, however, that a very high enantioselectivity (er=98/2) was observed in the case of **21** in hexane (Entry 14). This unusually high selectivity can be rationalized by a more selective approach of the chiral base complex favored by some π-cation interaction between the large aromatic surface and Li^+.[23] However, this phenomena was not observed with the naphthyl substrate **22**. Indeed, the enantiomeric ratio tops at 81/12 with **22** just like with the other substrates (Entries 17 and 18). It is likely that the solubility of the chiral intermediates formed during the process plays an important role in the outcome. We proposed that, in general, the enantioselectivity is limited by the discrimination ability of the chiral complex. Nevertheless, a simple crystallization could be used to generate easily (*R*)-Boc-protected phenylglycine derivatives with high enantiomeric purity making them suitable for a direct use as chiral building blocks. In addition, yields strongly depend on the solubility of the intermediates and the prevalence of the [1,2] silicon rearrangement described. Furthermore, it is possible that a kinetic resolution pathway competes in some cases with the enantioselective deprotonation–substitution sequence. In summary, the best conditions to yield rapidly enantioenriched arylglycine derivatives is to use toluene as solvent and to form the chiral complex *s*-BuLi–(−)-sparteine in situ. Although in certain cases other conditions give better results due to the complex interplay of solubility, substituent effects, and aggregation states.

3. Conclusions

We have described a new, enantioselective, and practical method to synthesize *N*-Boc arylglycines. These useful enantioenriched acids can be obtained at a low cost and the chiral source is also recovered at the end of the synthesis. The enantiomeric ratios obtained vary from 56/44 to 98/2 but could eventually be increased substantially by one simple crystallization. We demonstrated that the intermolecular carboxylation was in competition with an intramolecular [1,2] silicon shift, favored with larger silyl groups. The synthetic methodology reported gives access rapidly and efficiently to *N*-Boc protected aryl glycine analogs ready to use in medicinal or combinatorial chemistry. Current efforts are devoted to elucidate in more detail the mechanistic aspects of the process.

4. Experimental

4.1. General

Organolithiums were handled under dry nitrogen. All reagents were obtained from commercial sources and were used without further purification unless otherwise noted. (−)-Sparteine was distilled under vacuum from KOH. Toluene, hexane, and dichloromethane were distilled from calcium hydride under a nitrogen atmosphere. Et_2O was distilled from sodium and benzophenone under nitrogen. Solutions of *s*-BuLi in cyclohexane were titrated using the method of Suffert.[24] Melting points are uncorrected. Purity of all synthetic intermediates was established by TLC and ^{1}H- and ^{13}C NMR. Purity of the final amino acids was also confirmed by HRMS.

4.2. General procedure for the preparation of Boc-benzylamines

To a solution of primary amine (1.0 equiv., 0.5 M) in anhydrous DCM was added NEt_3 (1.5 equiv.). After cooling to 0°C $(Boc)_2O$ (1.2 equiv.) was added dropwise and the resulting mixture was stirred for about 3 h. After quenching with HCl 0.5 N, the organic phase was washed twice with 20 mL of HCl 0.5 N and twice with brine. The organic phase was then dried with anhydrous $MgSO_4$. After filtration and evaporation to dryness, the white solid was recrystallized in hexane to give white crystals of the Boc-protected amines.

4.2.1. *N*-(*tert*-Butyloxycarbonyl)-*N*-methylbenzylamine (8). See Refs. 14b, 25.

4.2.2. *N*-(*tert*-Butyloxycarbonyl)-2-fluorobenzylamine.[11] Yield: 98%, colorless oil; R_f=0.37 (hexane/15%AcOEt); ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) 1.34 (s, 9H), 4.23 (d, 2H, J=5.9 Hz), 5.42 (s br, 1H), 6.84–7.24 (m, 4H); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm) 162.1, 158.9, 155.8, 129.3, 128.5, 126.0, 123.9, 115.0, 114.7, 79.0, 38.1, 28.1; IR ($CHCl_3$, ν) 3500–3200, 2982, 2920, 1710 cm^{-1}; MS (*m*/*z*) 226 (MH^+), 170 ($M^+-C_4H_9$), 124 (M^+-Boc).

4.2.3. *N*-(*tert*-Butyloxycarbonyl)-3-fluorobenzylamine.[11] Yield: 85%; white solid; R_f=0.37 (hexane/15%AcOEt); mp: 53–54°C; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) 1.44 (s, 9H), 4.29 (d, 2H, J=5.85 Hz), 4.91 (s br, 1H), 6.89–7.04 (m, 3H), 7.23–7.30 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm) 164.5, 161.2, 155.7, 141.5, 129.9, 129.8, 122.6, 114.1, 113.8, 79.5, 44.0, 28.2; IR ($CHCl_3$, ν) 3500–3200, 2982, 2920, 1710 cm^{-1}; MS (*m*/*e*) 226 (MH^+), 170 ($M^+-C_4H_9$), 124 (M^+-Boc).

4.2.4. *N*-(*tert*-Butyloxycarbonyl)-4-fluorobenzylamine.[6c,11] Yield: 80%; white solid; R_f=0.37 (hexane/15%AcOEt); mp: 68–70°C; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) 1.50 (s, 9H), 4.24 (d, 2H, J=5.7 Hz), 4.97 (s, 1H), 7.24–7.94 (m, 4H); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm) 129.1, 115.5, 115.2, 44.0, 28.4, 27.9; IR ($CHCl_3$, ν) 3452, 2982, 1710 cm^{-1}; MS (*m*/*e*): 226 (MH^+), 170 ($M^+-C_4H_9$), 124 (M^+-Boc).

4.2.5. *N*-(*tert*-Butyloxycarbonyl)-4-methylbenzylamine. Yield=70%; white solid; R_f=0.46 (hexane/15% AcOEt); mp: 73–74°C (Lit. 72.5–73°C).[26]

4.2.6. *N*-(*tert*-Butyloxycarbonyl)-4-phenylbenzylamine. Yield=65%; white solid; mp: 101–103°C; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) 1.48 (s, 9H), 4.38 (d, J=5.9 Hz, 2H), 4.90 (s, 1H), 7.25–7.61 (m, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm) 156.8, 128.8, 127.9, 127.3, 127.1, 81.0, 44.4, 28.5; IR ($CHCl_3$, ν): 3454, 3020, 2980, 1710 cm^{-1}; MS (*m*/*e*) 284 (MH^+), 227 ($MH^+-C_4H_9$), 182 (M^+-Boc); HRMS (CI) calcd for $C_{18}H_{21}NO_2$ (MH^+) 284.1650 found 284.1648.

4.2.7. *N*-(*tert*-Butyloxycarbonyl)-1-naphthylmethylamine. Yield=79%; white solid; R_f=0.50 (hexane/15% AcOEt); mp: 99–100°C; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) 1.47 (s, 9H), 4.77 (s br, 2H), 7.38–7.57 (m, 4H), 7.76–7.88 (m, 2H), 8.03–8.06 (d br, 1H, J=7.9 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm) 155.5, 134.0, 131.2, 128.6, 126.3, 125.7, 125.2, 123.3, 79.4, 76.9, 76.5, 42.7, 28.3; IR ($CHCl_3$, ν) 3500–3000, 1775, 1600 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{19}NO_2$ (M^+) 257.1416 found 257.1420.

4.3. General procedure for the silylation of carbamates

To a solution of carbamate (14 mmol) in anhydrous DCM at 0°C was added 1.1 equiv. of NEt_3, then dropwise 1.1 equiv. of R_3SiOTf. The mixture was stirred for 5 min at 0°C then warmed to rt. After quenching with saturated sodium bicarbonate, the organic phase was washed twice with saturated $NaHCO_3$, then dried with anhydrous $MgSO_4$. Filtration and evaporation lead to the crude compound (oil), which was purified by flash chromatography (hexane/ethyl acetate 95/5+1% NEt_3) to give the pure compound. Spectroscopic data for *N*-Silyl *N*-Boc protected amines are following.

4.3.1. *N*-(Trimethylsilyl)-*N*-(*tert*-butyloxycarbonyl)benzylamine (11).[20] Yield=92%; colorless oil; R_f=0.73 (hexane/15%AcOEt/1%Et_3N).

4.3.2. *N*-(*tert*-Butyldimethylsilyl)-*N*-(*tert*-butyloxycarbonyl)benzylamine (12).[20] Yield=89%; colorless oil; R_f=0.89 (hexane/15%AcOEt/1%Et_3N).

4.3.3. *N*-(Triisopropylsilyl)-*N*-(*tert*-butyloxycarbonyl)-benzylamine (13).[20] Yield=98%; colorless oil; R_f=0.90 (hexane/15%AcOEt/1%Et_3N).

4.3.4. *N*-(Trimethylsilyl)-*N*-(*tert*-butyloxycarbonyl)-2-fluorobenzylamine (14). Yield=80%; colorless oil; R_f=0.64 (hexane/15%AcOEt/1% NEt_3); ^1H NMR (300 MHz, C_6D_6, δ ppm) 0.18 (s, 9H), 1.38 (s, 9H), 4.55 (s br, 2H), 6.69–6.88 (m, 3H), 7.35 (m br, 1H); ^{13}C NMR (75.5 MHz, C_6D_6, δ ppm) 162.1, 158.9, 158.1, 128.8, 127.6, 124.1, 115.27, 79.8, 41.5, 28.3, 0.5; IR ($CHCl_3$, ν) 2978, 1688, 1210 cm^{-1}; HRMS (CI) calcd for $C_{15}H_{24}NO_2SiF$ (MH^+) 298.1639 found 298.1635.

4.3.5. *N*-(Trimethylsilyl)-*N*-(*tert*-butyloxycarbonyl)-3-fluorobenzylamine (15). Yield=62%; colorless oil; R_f=0.64 (hexane/15%AcOEt/1% NEt_3); ^1H NMR (300 MHz, C_6D_6, δ ppm) 0.10 (s, 9H), 1.24 (s, 9H), 4.14 (s br, 2H), 6.51–6.58 (m, 1H), 6.73–6.85 (m, 3H); ^{13}C NMR (75.5 MHz, C_6D_6, δ ppm) 165.1, 161.8, 158.1, 130.0, 122.1, 113.8, 113.4, 79.9, 47.4, 28.2, 0.7; IR ($CHCl_3$, ν) 2978, 1688, 1230 cm^{-1}; HRMS (CI) calcd for $C_{15}H_{24}NO_2SiF$ (MH^+) 298.1639 found 298.1635.

4.3.6. *N*-(Trimethylsilyl)-*N*-(*tert*-butyloxycarbonyl)-4-fluorobenzylamine (16). Yield=80%, colorless oil; R_f=0.64 (hexane/15%AcOEt/1% NEt_3); ^1H NMR (300 MHz, C_6D_6, δ ppm) 0.14 (s, 9H), 1.40 (s, 9H), 4.26 (s, 2H), 6.74–7.03 (m, 4H); ^{13}C NMR (75.5 MHz, C_6D_6, δ ppm) 163.8, 115.2, 114.9, 80.0, 47.0, 28.1, 0.6; IR ($CHCl_3$, ν) 2978, 1688, 1230 cm^{-1}; HRMS (CI) calcd for $C_{15}H_{24}NO_2SiF$ (MH^+) 298.1639 found 298.1635.

4.3.7. *N*-(Trimethylsilyl)-*N*-(*tert*-Butyloxycarbonyl)-4-methylbenzylamine (20). Yield=74%; white solid; R_f=0.68 (hexane/15% AcOEt, 1% NEt_3); mp: 41–42°C; ^1H NMR (300 MHz, C_6D_6, δ ppm) 0.17 (s, 9H), 1.41 (s, 9H), 2.09 (s, 3H), 4.37 (s br, 1H), 6.96–6.93 (dd, 2H, J=6.9 Hz), 7.08–7.11 (dd, 2H, J=7.9 Hz); ^{13}C NMR (75.5 MHz, C_6D_6, δ ppm) 158.0, 138.2, 135.7, 129.0, 128.6, 128.1, 127.8, 127.5, 126.6, 79.4, 47.5, 28.2, 20.8, 0.7; IR ($CHCl_3$, ν) 3100–3000, 1775, 1600, 1270 cm^{-1}; HRMS (CI) calcd for $C_{16}H_{27}NO_2Si$ (MH^+) 294.1889 found 294.1886.

4.3.8. *N*-(Trimethylsilyl)-*N*-(*tert*-Butyloxycarbonyl)-4-phenylbenzylamine (21). Yield=60%; white solid; mp: 84–88°C; ^1H NMR (300 MHz, C_6D_6, δ ppm) 0.21 (s, 9H), 1.44 (s, 9H), 4.47 (s, 2H), 7.08–7.46 (m, 9H); ^{13}C NMR (75.5 MHz, C_6D_6, δ ppm) 159.0, 141.0, 126.5–129, 79.5, 47.7, 28.4, 0.9; IR ($CHCl_3$, ν) 2980, 2922, 2850, 1688 cm^{-1}; MS (*m/e*): 356 (MH^+), 300 ($M^+-C_4H_9$), 256 (M^+−Boc); HRMS (CI) calcd for $C_{21}H_{29}NO_2Si$ (MH^+) 356.2046 found 356.2029.

4.3.9. *N*-(Trimethylsilyl)-*N*-(*tert*-butyloxycarbonyl)-1-naphthylmethylamine (22). Yield=79%; colorless oil; R_f=0.68 (hexane/15%AcOEt/1% NEt_3); ^1H NMR (300 MHz, C_6D_6, δ ppm) 0 (s, 9H), 1.24 (s, 9H), 4.68 (s br, 2H), 7.04–7.09 (m, 3H), 7.24–7.26 (m, 1H), 7.31–7.34 (m, 1H), 7.44–7.47 (m, 1H), 7.55–7.58 (m, 1H); ^{13}C NMR (75.5 MHz, C_6D_6, δ ppm) 158.1, 136.3, 134.1, 131.1, 129.0, 127.6, 127.2, 125.7, 122.4, 79.7, 45.4, 28.2, 0.6; IR ($CHCl_3$, ν) 3100–3000, 1775, 1600, 1270 cm^{-1}; HRMS (CI) calcd for $C_{19}H_{27}NO_2Si$ (MH^+) 330.1889 found 330.1878.

4.4. General procedure for the asymmetric deprotonation of *N*-silylcarbamates forming the chiral complex in situ

To a 0.1 M solution of a silylcarbamate (1 equiv.) under a N_2 atmosphere, was added (−)-sparteine (1.1 equiv.) and the solution was cooled to −78°C. After 15 min at that temperature, 1.1 equiv of *s*-BuLi (1.3 M in cyclohexane) was added, and the yellow solution was allowed to stir at −78°C for 3 h before CO_2 was bubbled through (20 min). The mixture was warmed to rt and then quenched with 2N HCl. The organic layer was separated and extracted with 1 N NaOH. The alkaline layer was acidified with 2N HCl and extracted back with ether. The organic phase was separated, dried over anhydrous $MgSO_4$, filtrated and evaporated to give the crude Boc-protected acid. Trituration with hexane yielded pure compound as white powder, which was characterized by ^1H, ^{13}C NMR, and mass spectrometry.

4.5. General procedure for the asymmetric deprotonation of *N*-silylcarbamates using the preformed chiral complex

At −78°C, 1.24 mmol of *s*-BuLi (1.3 M solution in cyclohexane) was added to freshly distilled (−)-sparteine (1.1 equiv.) in 3 mL of solvent. The mixture was stirred for 15 min then cannulated to a solution of substrate (1.13 mmol) in 1.5 mL of solvent. The resulting mixture was stirred at −78°C for 3 h before CO_2 was bubbled through (20 min). After warming to 0°C and quenching with 2N HCl, the organic layer was separated and extracted with 1N NaOH. The alkaline layer was acidified with 2N HCl and extracted back with ether. The organic phase was separated, dried over $MgSO_4$, filtered and evaporated to give the crude Boc-protected acid. Trituration with hexane yielded pure compound as a white powder, which was characterized by ^1H, ^{13}C NMR, and mass spectrometry.

4.5.1. *N*-(*tert*-Butyloxycarbonyl)phenylsarcosine (9). Yield= 36–85% (see text for details), white solid; mp: 111–114°C (Lit. 112–113°C).[14b,15]

4.5.2. *N*-(*tert*-Butyloxycarbonyl)phenylglycine (7). Yield= 7–86% (see text for details), white solid; mp: 90–94°C (lit. 88–91°C).[29]

4.5.3. *N*-(*tert*-Butyloxycarbonyl)-2-fluorophenylglycine (17). Yield=79–95% (see text for details), white solid; mp: 90–91°C (Lit. 121–124°C);[27] ^1H NMR (300 MHz, $CDCl_3$, δ ppm) major conformer: 1.00–1.17 and 1.21–1.42 (2s br, 9H), 5.12 and 5.35 (2d, J=4.6 and 6.5 Hz, 1H), 5.71 and 8.11 (2d, J=6.4 and 5.1 Hz, 1H), 6.97–7.34 (m, 4H), 11.40 (s, br, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm) 172.8, 164.3, 161.0, 158.6, 156.6, 129.5, 129.4, 127.9, 126.0, 125.8, 124.1, 115.3, 115.0, 81.7, 51.5, 28.1, 27.7, 26.3; IR ($CHCl_3$, ν) 3296, 2500–3100, 1724, 1660 cm^{-1}; HRMS (CI) calcd for $C_{13}H_{16}NO_4F$ (MH^+) 270.1142 found 270.1137.

4.5.4. *N*-(*tert*-Butyloxycarbonyl)-3-fluorophenylglycine (18). Yield=80–95% (see text for details); white solid; mp: 90–93°C; ^1H NMR (300 MHz, $CDCl_3$, δ ppm) major conformer: 1.00–1.21 and 1.39–1.51 (2s br, 9H), 5.12 and

5.35 (2d, J=4.6 and 6.2 Hz, 1H), 5.71 and 8.11 (2d, J=6.2 and 5.2 Hz, 1H), 6.90–7.45 (m, 4H), 11.30 (s br, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm) 172.6, 164.3, 161.0, 156.7, 154.8, 140.5, 134.2, 128.9, 116.0, 115.5, 115.2, 82.0, 81.4, 58.1, 56.8, 28.2, 28.0; IR ($CHCl_3$, δ) 3296, 2500–3100, 1724, 1660 cm^{-1}; HRMS (CI) calcd for $C_{13}H_{16}NO_4F$ (MH^+) 270.1142 found 270.1137.

4.5.5. *N*-(*tert*-Butyloxycarbonyl)-4-fluorophenylglycine (19). Yield=44–84% (see text for details); white solid; mp: 44–48°C; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) major conformer 1.22 (s, 9H), 5.11 and 5.32 (2d, J=5.0 and 6.3 Hz, 1H), 5.63 and 8.15 (2d, J=5.0 and 6.3 Hz, 1H), 7.00–7.43 (m, 4H), 11.81 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm) 173.2, 164.1, 160.8, 157.0, 134.2, 128.9, 116.0, 115.5, 115.2, 82.0, 81.4, 58.1, 56.8, 28.2, 28.0; IR ($CHCl_3$, ν) 3296, 2500–3100, 1724, 1660 cm^{-1}; HRMS (CI) calcd for $C_{13}H_{16}NO_4F$ (MH^+) 270.1142 found 270.1137.

4.5.6. *N*-(*tert*-Butyloxycarbonyl)-4-methylphenylglycine (23). Yield=14–92% (see text for details); white solid; mp: 111–112°C; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) major conformer 1.24 (s, 9H), 2.34 (s, 3H), 5.11 (d, 1H, J=7.01 Hz), 7.14–7.16 (m, 2H), 7.25–7.34 (m, 2H), 7.97–7.98 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm) 173.7, 156.6, 137.6, 135.0, 129.0, 126.0, 81.3, 77.3, 58.4, 27.8, 21.0; IR ($CHCl_3$, ν) 3540–2900, 1750, 1600, 1170 cm^{-1}; HRMS (CI) calcd for $C_{14}H_{19}NO_4$ (MH^+) 266.1392 found 266.1397.

4.5.7. *N*-(*tert*-Butyloxycarbonyl)-4-biphenylglycine (24). Yield=28–41% (see text for details); white solid; mp: 71–75°C; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) 1.20 (s, 9H), 5.14 and 5.35 (2s, 1H), 7.20–7.54 (m, 9H), 5.49 and 7.78 (2s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm) 174.0, 138.0, 128.8, 127.6, 127.1, 81.0, 57.3, 28.1; IR ($CHCl_3$, ν) 3200, 2500–3100, 1722, 1658 cm^{-1}; MS (*m/e*): 328 (MH^+), 372 ($M^+-C_4H_9$), 228 (M^+-Boc); HRMS (CI) calcd for $C_{14}H_{21}NO_4$ (MH^+) 328.1549 found 328.1541.

4.5.8. *N*-(*tert*-Butyloxycarbonyl)-1-naphthylglycine (25). Yield=26–94% (see text for details); white solid; mp: 153–155°C (Lit. 182–183°C).[28]

4.5.9. α-Trimethylsilyl-*N*-methyl-*N*-(*tert*-butyloxycarbonyl)benzylamine (12). After deprotonation under the above conditions, TMSCl (2 equiv.) was introduced at −78°C and the reaction mixture was stirred at this temperature for 30 min. After quenching at 0°C with 2N HCl, the organic layer was separated, dried over anhydrous $MgSO_4$, and evaporated to give a yellow oil. Pure **12** was obtained after flash chromatography with hexane/ethylacetate (95/5) as eluant. Yield=48%; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) 0.09 (s, 9H), 1.47 (s, 9H), 2.88 (s, 3H), 3.74 (s, 1H), 7.10–7.35 (m, 5H); MS (*m/e*): 294 (M^+), 237 ($M^+-C_4H_9$), 222 ($M^+-(C_4H_9+CH_3)$).

4.6. Determination of er's by polarimetry

When optical rotations were known in the literature, the enantiomeric ratios were calculated from polarimetry measurements (**7**: $[\alpha]_D^{25}=-144°$ (c=1 in EtOH);[29] **9**: $[\alpha]_D^{25}=-134°$ (c=1 in EtOH).[15] **23**: $[\alpha]_D^{25}=-144°$ (c=0.25 in 1 N HCl).[30] **25**: $[\alpha]_D^{25}=-147°$ (c=1 in MeOH)[28]).

4.7. Determination of er's by NMR spectroscopy

In the cases of **17**, **18**, **19**, **21**, the enantiomeric ratios were determined by ^{1}H NMR in $CDCl_3$ by forming diastereomeric salts in situ with (*S*)-(+)-mandelic acid and the methyl ester of phenylglycines obtained after treatment of **17**, **18**, **19**, **21** with CH_2N_2 and 4 N HCl/dioxane. A typical procedure is as follows: Compound **17** was esterified by an excess of diazomethane in Et_2O. After evaporation, the crude *N*-Boc methyl ester was treated at 0°C with 5 equiv. of 4N HCl in dioxane. The resulting mixture was stirred at rt for 1 h. Volatile compounds were removed under reduced pressure. The crude material was diluted in $CDCl_3$, washed three times with a saturated $NaHCO_3$ solution and dried over K_2CO_3. After filtration, ^{1}H NMR measurement of the diastereomeric ratio was performed by adding 1 equiv. of (*S*)-(+)-mandelic acid. The signals of the α-CH groups of the two diastereomeric complexes formed in situ are easily integrated at 4.96 (major) and 5.08 (minor) ppm.

4.8. Enantiomeric enrichment procedure for 7 by recrystallization

N-*t*-Boc phenylglycine **7** (er=84/16; 68% ee; $[\alpha]_D^{25}=-97.9°$ (c=0.91, EtOH)) was dissolved in a minimum amount of boiling Et_2O. To the clear solution was added dropwise boiling hexane until appearance of cloudiness. The solution was allowed to cool to rt and then to 5°C for 3 days (crystallization begun after 12 h). White crystals were filtered off, dried and submitted to polarimetry measurement. The er observed was 55/45. The mother liquor was evaporated and dried under vacuum. The resulting white powder was then submitted to polarimetry measurement, and was shown to contain pure **7** with an er of 96/4 (93% ee; $[\alpha]_D^{25}=-133.9°$ (c=1, EtOH)).

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References

1. (a) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539. (b) Williams, R. M. *Synthesis of Biologically Active α-Amino-Acids*; Pergamon: New York, 1989.
2. (a) Kukolja, S.; Draheim, S. E.; Cooper, R. D. G.; Graves, B. J.; Holmes, R. E.; Neel, D. A.; Huffmann, G. W.; Webber, J. A.; Kinnick, M. D.; Vasilieff, R. T.; Foster, B. J. *J. Med. Chem.* **1985**, *28*, 1886. (b) Townsend, C. A.; Brown, A. M. *J. Am. Chem. Soc.* **1983**, *105*, 913.
3. North, M. *Contemp. Org. Synth.* **1996**, *3*, 323 and references cited therein.
4. Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552.

5. (a) Voyer, N. *Top. Curr. Chem.* **1996**, 184. (b) Voyer, N.; Lamothe, J. *Tetrahedron* **1995**, *51*, 9241.
6. (a) Park, Y. S.; Beak, P. *J. Org. Chem.* **1997**, *62*, 1574. (b) Park, Y. S.; Boys, M. L.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 3757. (c) Voyer, N.; Roby, J.; Chénard, S.; Barberis, C. *Tetrahedron Lett.* **1997**, *38*, 6505. (d) Barberis, C.; Voyer, N. *Synlett* **1999**, 1106.
7. Hoppe, D.; Hense, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2282 and references.
8. (a) Kim, B. J.; Park, Y. S.; Beak, P. *J. Org. Chem.* **1999**, *64*, 1705. (b) Curtis, M. D.; Beak, P. *J. Org. Chem.* **1999**, *64*, 2996. (c) Serino, C.; Stehle, N.; Park, Y. S.; Florio, S.; Beak, P. *J. Org. Chem.* **1999**, *64*, 1160. (d) Faibish, N. C.; Park, Y. S.; Lee, S.; Beak, P. *J. Am. Chem. Soc.* **1997**, *119*, 11561. (e) Pippel, D. J.; Weisenburger, G. A.; Wilson, S. R.; Beak, P. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2522. See also Ref. 4.
9. Tischler, A. N.; Tischler, M. H. *Tetrahedron Lett.* **1978**, *19*, 3407.
10. Kanazawa, A. M.; Correa, A.; Denis, J. N.; Luche, M. J.; Greene, A. E. *J. Org. Chem.* **1993**, *58*, 255.
11. Katsoulos, G.; Schlosser, M. *Tetrahedron Lett.* **1993**, *34*, 6263.
12. Roby, J., Ph.D. Thesis, Université de Sherbrooke, 1996.
13. Bold, G.; Steiner, H.; Moesh, L.; Walliser, B. *Helv. Chim. Acta* **1990**, *73*, 405.
14. (a) Voyer, N.; Roby, J. *Tetrahedron Lett.* **1995**, *36*, 6627. The same results were reported simultaneously. (b) Schlosser, M.; Limat, D. *J. Am. Chem. Soc.* **1995**, *117*, 12342.
15. Kinoshita, H.; Shintani, M.; Saito, T.; Kotabe, H. *Bull. Chem. Soc. Jpn* **1971**, *44*, 286.
16. (a) Thayumanavan, S.; Lee, S.; Liu, C.; Beak, P. *J. Am. Chem. Soc.* **1994**, *116*, 9755. (b) Beak, P.; Du, H. *J. Am. Chem. Soc.* **1993**, *115*, 2516.
17. Kaufmann, E.; Sieber, S.; Schleyer, P.; Von, R. *J. Am. Chem. Soc.* **1989**, *111*, 4005 and references cited therein.
18. Hoppe, D.; Hintze, F.; Tebben, P.; Paetow, M.; Ahrens, H.; Schwerdtfeger, J.; Sommerfeld, P.; Haller, J.; Guarnieri, W.; Kolczewski, S.; Hense, T.; Hoppe, D. *Pure Appl. Chem.* **1994**, *66*, 1479.
19. (a) Hoppe, D.; Carstens, A.; Kramer, T. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1424. (b) Haller, J.; Hense, T.; Hoppe, D. *Synlett* **1993**, 726.
20. Roby, J.; Voyer, N. *Tetrahedron Lett.* **1997**, *38*, 191.
21. Barberis, C.; Voyer, N.; Toupet, L. In preparation.
22. Barberis, C.; Voyer, N. *Tetrahedron Lett.* **1998**, *39*, 6807.
23. Dougherty, D. *Science* **1996**, *271*, 1163.
24. Suffert *J. Org. Chem.* **1989**, *54*, 509.
25. (a) Yasuyuki, K.; Haruta, J. I.; Hitoshi, Y.; Kukumaga, K.; Shirouchi, Y.; Tamura, Y. *J. Org. Chem.* **1982**, *47*, 2697. (b) see Ref. 14b
26. (a) Tanaka, K. I.; Yoshifuji, S.; Nitta, Y. *Chem. Pharm. Bull.* **1988**, *36*, 3125. (b) Dessolin, M.; Guillerez, M. G.; Thieriet, N.; Guibe, F.; Loffet, A. *Tetrahedron Lett.* **1995**, *36*, 5741.
27. Mitsuko, M.; Kawasaki, K.; Taguchi, T.; Kobayashi, Y.; Yamamoto, Y. *Chem. Pharm. Bull.* **1994**, *42*, 1658.
28. Medina, E.; Vidal-Ferran, A.; Moyano, A.; Pericas, M.; Riera, A. *Tetrahedron: Asymmetry* **1997**, *8*, 1581.
29. *Fluka Catalog* (Chemica-Biochemica) Edition, **1995–1996**, US, 238pp.
30. Garcia, M. J.; Azerad, R. *Tetrahedron: Asymmetry* **1997**, *8*, 85.