Pergamon

Tetrahedron: *Asymmetry* 14 (2003) 1063–1072

TETRAHEDRON: *ASYMMETRY*

First synthesis of (1*S*,2*S*)- and (1*R*,2*R*)-1-amino-2-isopropylcyclobutanecarboxylic acids by asymmetric Strecker reaction from 2-substituted cyclobutanones☆

Molika Truong, Frédéric Lecornué and Antoine Fadel*

Laboratoire des Carbocycles (Associé au CNRS), Institut de Chimie Moléculaire et des Matériaux d'Orsay, Bât. 420, Université Paris-Sud, 91405 Orsay, France

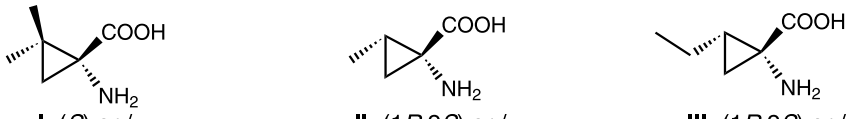
Received 6 December 2002; accepted 14 January 2003

Abstract—An efficient and easy one-pot reaction from readily available racemic 2-substituted cyclobutanones gave, by means of asymmetric Strecker synthesis in the presence of an amine chiral auxiliary, two major aminonitriles with excellent diastereoselectivity. After separation, the major *cis*-aminonitriles were hydrolysed and hydrogenolysed to lead for the first time to pure non-racemic (+)-1-amino-2-isopropylcyclobutanecarboxylic acid (ACBC) and its antipode.

1. Introduction

In the last few years, a variety of interesting biological properties of α-amino acids have been described. 1-Aminocyclopropanecarboxylic acid (ACPC), 1-aminocyclobutanecarboxylic acid (ACBC), and 1-aminocyclopentanecarboxylic acid (ACPentC) are known to be partial agonists at the strychnine insensitive glycine binding site of the NMDA receptor complex.[1] Recently, it was shown that ACPC acts concurrently as a glycine site partial agonist and as a glutamate site antagonist,[2] thus protecting against neural cell death and exhibiting antipsychotic-like effects in animal models.[3] Moreover, α-tetrasubstituted α-amino acids such as ACPC are also able to function as enzyme inhibitors by covalently binding to pyridoxal phosphate-dependent enzymes such as decarboxylases[4a] and transaminases.[4b] Methods for the synthesis of enantiopure ACBCs have not received the same attention as those for the preparation of ACPCs and as far as we are aware, only a few methods for the synthesis of optically active 1-amino-2-alkylcyclobutanecarboxylic acids have been described by recrystallisation with tartaric acid.[5–7] In the course of our work on asymmetric syntheses of cyclic analogues of naturally occuring α-amino acids we have previously published the aminocyclopropanecarboxylic acids methanovalines **I**,[8] *allo*-norcoronamic acids **II**, and *allo*-coronamic acids **III**,[9] by means of asymmetric Strecker reactions (Scheme 1).[10,11]

Herein, we report on the preparation of homochiral 1-amino-2-substituted cyclobutanecarboxylic acids **1**—in four steps—starting from the racemic cyclobu-



I- (*S*) or / and (*R*) **II**- (1*R*,2*S*) or / and (1*S*,2*R*) **III**- (1*R*,2*S*) or / and (1*S*,2*R*)

Scheme 1.

☆ Part of this study was previously reported at the Organic Chemistry Symposium at Palaiseau (SFC, Sept., 2001), France.

* Corresponding author. Fax: +33-(1)-691-56278; e-mail: antfadel@icmo.u-psud.fr

0957-4166/03/$ - see front matter
doi:10.1016/S0957-4166(03)00073-9

tanones **3** and chiral benzylic amine as a chiral auxiliary, proceeding via the amino nitriles **2** by asymmetric Strecker reaction (Scheme 2).

2. Results and discussion

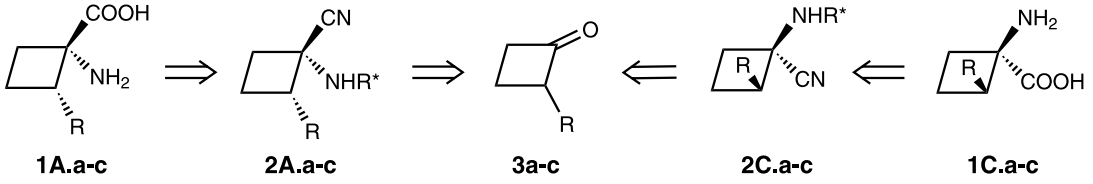
2.1. α-Aminonitrile synthesis

The racemic starting 2-substituted cyclobutanones **3a**–**c**, were prepared from cyclopropyl aldehyde **4**, by a modified ring enlargement according to our previously reported method.[12] Thus, aldehyde **4** underwent, in a 'one-pot' reaction, addition of alkyllithium or Grignard reagent, followed by acidic hydrolysis, to give by ring enlargement[13] of the intermediate **5**, the desired ketone **3b**–**c** with good yields (Scheme 3); **3a** is available commercially.

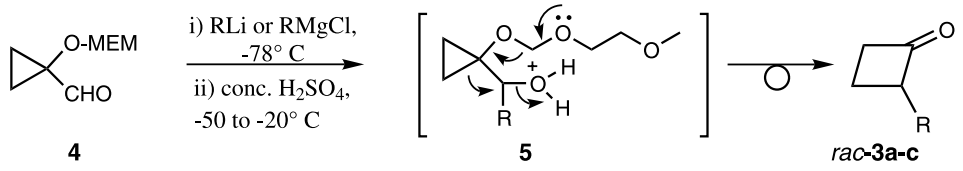
For the synthesis of the α-aminonitriles **2a**–**c**, the alkylated ketones (±)-**3a**–**c** were subjected to a one-pot procedure previously developed in our group[8,9] (Scheme 4). We anticipated that, under acidic conditions, the ketone condensations with the chiral auxiliary (*S*)-1-phenylethylamine or derivatives **6** give the corresponding iminium mixtures **7.a**–**c** (each as a mixture of the (*E*/*Z*,α*S*,2*S*) and (*E*/*Z*,α*S*,2*R*) stereoisomers), which by in situ addition of sodium cyanide to the C=N bond would predominantly afford one diastereomer of the four possible α-aminonitrile isomers **2.a**–**c**.

By changing the solvent, the amine and the R group of the ketones, we could make some interesting observations. Our results of these investigations are summarised in Table 1. It shows that, from the cyclobutanone **3a** the use of DMSO solvent,[14] increases the rate reaction (entries 1 and 2). Whereas, from the 2-alkyl- or 2-arylcyclobutanones **3b**, there are a slight difference (entries 3–8). However in all cases, only a slight difference in the major *cis* configurated α-aminonitriles **2A** and **2C** ratio was observed, 51–56 and 42–44, respectively. Thus the selective synthesis of only a single α-aminonitriles failed. The *trans* configured α-aminonitriles **2B** and **2D** were the minor products only obtained in negligible amounts <1–2.5%.

Heating a mixture of nitriles **2A.b**/**2C.b** (3/7) for 24 h in *i*PrOH in the presence of TFA does not change their stereochemical composition. Furthermore, the amount of **A** increases by changing the R-substituent from 51%

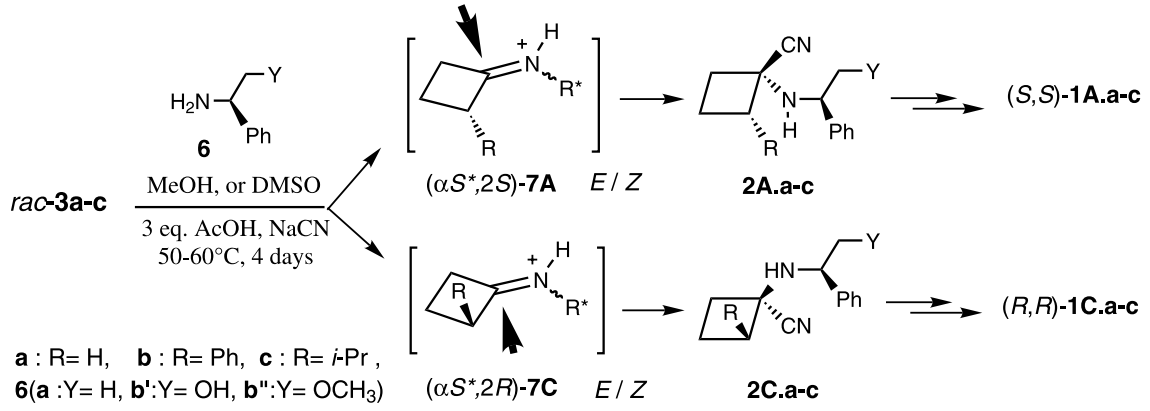


Scheme 2.



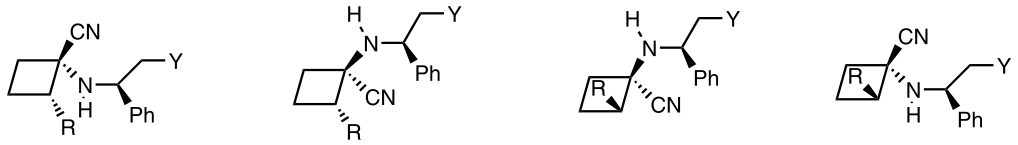
a : R= H, b : R= Ph (50%), c : R= *i*-Pr (82%),

Scheme 3. Synthesis of racemic cyclobutanones **3a**–**c**.



Scheme 4. Synthesis of α-amino acids **1a**–**c**.

Table 1. Preparation of amino nitriles **2A–D** from racemic 2-substituted cyclobutanones **3a–c**



Entry	Amine **6**	Ketone **3**	Solvent	Time	Yield (%)	**2** Diastereomers ratio[a]					
	Y	R					**A**	**B**	**C**	**D**	*cis*/*trans*
1	H	**a** H	DMSO	6 h	57	**2.a**	100	–	–	–	–
2	H	**a** H	MeOH	3 days	55	**2.a**	100	–	–	–	–
3	H	**b** Ph	DMSO	4 days	54	**2.b**	51	<2.5	45	<1.5	96/4
4	H	**b** Ph	MeOH	4 days	43	**2.b**	52	2.5	44	<1.5	96/4
5	OH	**b** Ph	DMSO	4 days	42.5	**2.b′**	54	<2	43	<1	97/3
6	OMe	**b** Ph	DMSO	4 days	44.5	**2.b″**	53	<2	44	<1	97/3
7	H	**c** *i*Pr	DMSO	4 days	46	**2.c**	56	1	42	<1	98/2
8	H	**c** *i*Pr	MeOH	4 days	42	**2.c**	54	<1	44	<1	98/2

All reactions of racemic acetal **4** were carried out in the presence of 1.5 equiv. of amine, 1.5 equiv. of NaCN and 3 equiv. of AcOH in DMSO at 55°C.

[a] Diastereoisomeric ratios were measured by GC analysis using a chiral column.

for **2A.b** (R = Ph) to 56% for **2A.c** (R = isopropyl). In parallel, the amount of the second *cis* nitrile **C** decreases slightly from 45% to 42% under these conditions. These major *cis* nitriles **2A.a–c**/**2C.a–c** are readily separated from the minor *trans* isomers by chromatography on silica gel. But infortunately isolation of pure **2A.a–c** from **2C.a–c** required exhaustive chromatography.

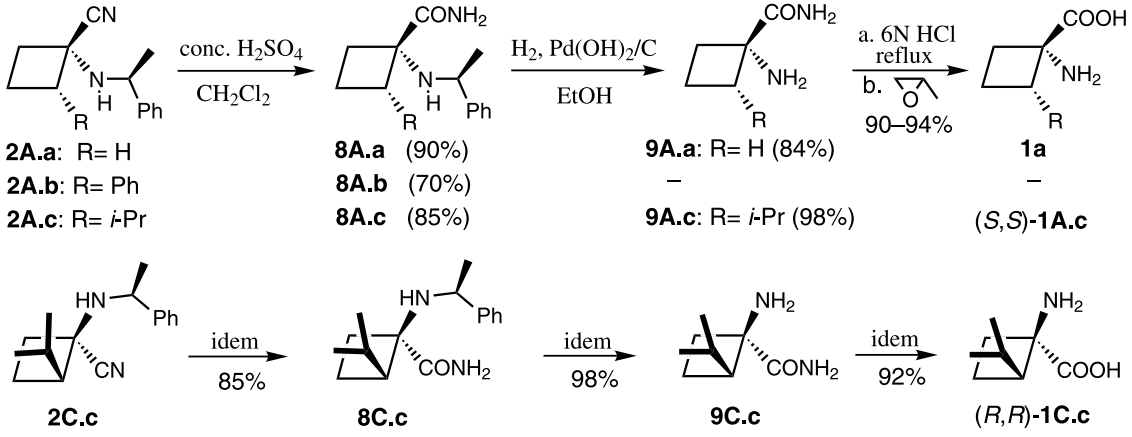
2.2. Acidic hydrolysis

Subsequently, the α-aminonitriles mixtures **2A.a,c**/**2C.a,c** or each one were subjected to hydrolysis in the concentrated sulfuric acid in methylene chloride at 0°C to rt for 10 h, to afford the amides (1*S*,2*S*)-**8A.a–c** and (1*R*,2*R*)-**8C.c** in 70–90% yields after easy chromatographic separation.

Hydrogenolysis of pure α-aminocarboxamides **8A.a–c** and **8C.c**, separately in the presence of a catalytic amount of 20% $Pd(OH)_2$ on activated carbon (w/w, 20%) in AcOH under hydrogen (1 atm, 10 h) gives after flash chromatography the free amino amides **9a**, **9A.c** and **9C.c** in 84, 98 and 98% yields, respectively. These latters were finally hydrolysed with 6N HCl at reflux followed by the addition of propylene oxide in ethanol, to furnish the target α-amino acid **1.a**, and for the first time optically active **1A.c** and **1C.c** with 90–94% yields (Scheme 5).

2.3. Absolute configuration

Following Mosher derivatization[15] the resulting (*R*)- and (*S*)-methoxy-α-trifluoromethylphenylacetic acid amides (MTPA) of **9A.c** showed positive chemical shift differences ($\Delta\delta = \delta_S - \delta_R$) for the 2-$H^1$ and $H_{isopropyl}$ protons located on the right side of the MTPA plane



Scheme 5. Synthesis of amino acids via free amino amides.

and negative values for the 4-H_2 and 3-H^2 protons located on the left side of the cyclobutane. The protons 3-H^3 and CH_3 protons were found to reside virtually in the plane of the MTPA moiety, thus their δ values were nearly equal ($\Delta\delta \approx 0$ ppm). The optimized structure obtained by molecular mechanics (MM2) calculations on the (*S*)-MTPA amide of (1*S*,2*S*)-**9A.c** was wholly consistent with these results (Fig. 1).

In addition, the (*S*)-configuration at C-1 was also assigned by means of Kelly's empirical method[16] as follows. For (*R*)-MTPA (*u*) and (*S*)-MTPA amide (*l*) of **9A.c**, the δ values (^{1}H NMR) for their methoxy groups appears at 3.47 and 3.43 ppm, respectively taking into account that the isopropyl group shield the methoxy group in the *l*-diastereoisomer, but not in the *u*-diastereoisomer. Consequently the $\Delta\delta_{OMe} = u - l = +0.04$ indicating an (*S*)-configuration at C-1.

Moreover, we assume that the configuration in the present case (*major* nitrile) is *cis* and consequently the absolute configuration at C-2 must be (*S*). Unfortunately, we were unable to confirm these conclusion by X-ray crystallographic analyses since the compounds could not be obtained in crystalline form.

In all cases the 1,2-induction mechanism is favorable, and the cyanide addition occurs *anti* to the bulky group with an unlike approach to the iminium intermediates.

For example, in the (*E*,α*S*,2*S*)- and (*Z*,α*S*,2*S*)-iminiums the isopropyl group hampers the nucleophilic *si*-face attack, thus leading to a high *re*-face selectivity of (A:B ≈ 56:1). While for the (*E*,α*S*,2*R*)- and (*Z*,α*S*,2*R*)-iminiums the *re*-face is completely blocked by both isopropyl group and the phenyl group of amine, in addition, in (*Z*,α*S*,2*R*)-iminium the *si*-face is partially favored, thus leading to high *si*-face selectivity of (C:D = 42:1) (Fig. 2). In some cases, we cannot exclude C-2 epimerisation under the applied reaction conditions of the iminium intermediate, which occurs most likely via a carbanion intermediate.

3. Conclusion

We have developed an easy and efficient four-step synthesis of new enantiopure (+)-(1*S*,2*S*)-1-amino-2-isopropylcyclobutanecarboxylic acid (+)-**1A.c** and its antipode (−)-**1C.c** starting from readily available

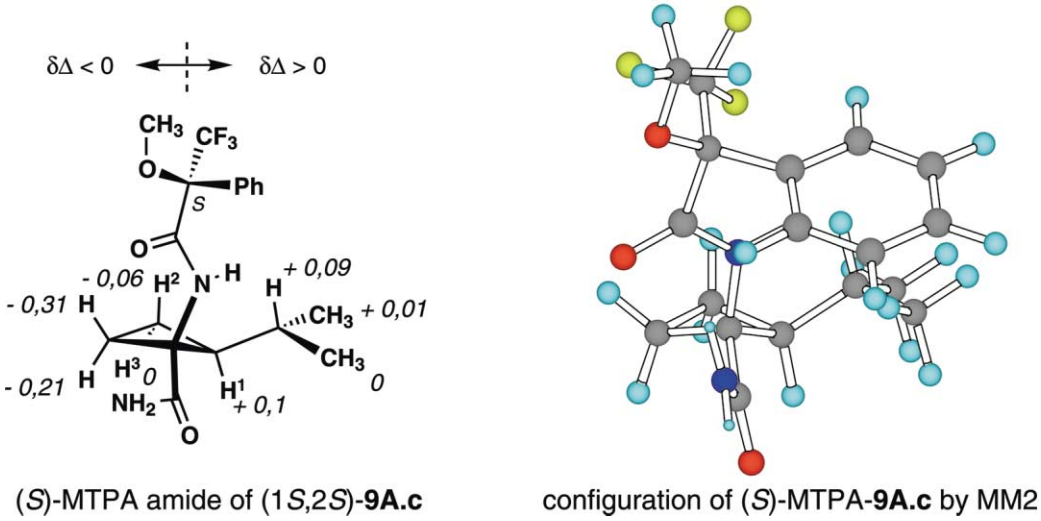


Figure 1. $\Delta\delta = (\delta_S - \delta_R)$ for (*S*)- and (*R*)-MTPA amides of **9A.c** by ^{1}H NMR spectroscopy at 250 MHz.

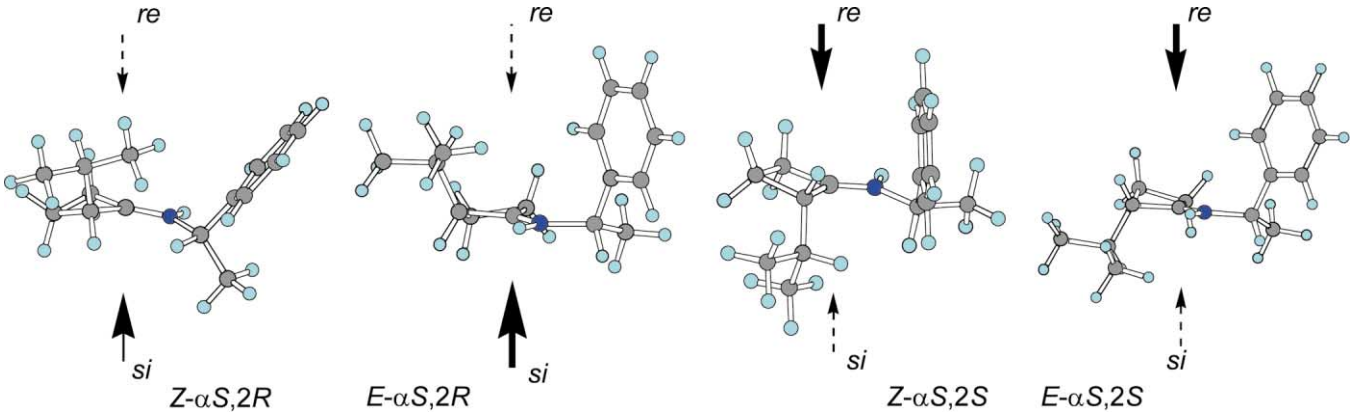


Figure 2. Proposed nucleophilic attack to *Z* and *E* iminiums **7.c**.

racemic α-alkylcyclobutanones, prepared from cyclopropylcarboxaldehyde.[10] These acids were obtained from separable major *cis*-amino nitriles **2A** and **2C** which were prepared by asymmetric Strecker reaction with excellent selectivity (dr>97:3). This approach should constitute an efficient method for the synthesis of a wide variety of aminocyclobutanecarboxylic acids. Efforts to obtain one major *cis*-amino nitrile are currently in progress in our laboratory.

4. Experimental

The general experimental procedures and the analytical instruments employed have been described in detail in a previous paper.[17] Enantiomeric excess were also performed on a GC (Fisons 9130) chiral column Cydex B (SGE) (25 m, 155°C, 1 bar).

4.1. (±)-2-Phenylcyclobutanone, 3b

To a cold solution (−78°C) of 1-(methoxyethoxymethoxy)cyclopropanecarboxaldehyde **4** [12] (2.61 g, 15 mmol) in THF (15 mL) was added dropwise a solution of phenyllithium (1.5 M, 12 mL, 18 mmol). After stirring at −78°C for 1 h, concentrated H_2SO_4 (3 mL) was slowly added. The reaction mixture was stirred at −78°C for 1 h and allowed to warm to rt (1 h). Recooled to 0°C, the acidic medium was neutralised very slowly by Na_2SO_3 (solid). After adding water (20 mL) the mixture was extracted with ether (3×100 mL), and the combined organic layers, dried, filtered then concentrated under partial vacuum (bath <35°C). The residue purified by FC (eluent, CH_2Cl_2/petrol ether: 1/1) gave 1.095 g (50%) of pure 2-phenylcyclobutanone **3b**.

^{1}H NMR ($CDCl_3$): δ 2.15–2.42 (m, 1H), 2.41–2.69 (m, 1H), 2.95–3.16 (m, 1H), 3.16–3.40 (m, 1H), 4.44–4.65 (m, 1H-C_2), 7.12–7.46 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 17.4 (C_3), 44.6 (C_4), 64.3 (C_2) [6 arom. C: 126.7, 126.8 (2C), 128.4 (2C), 136.3], 207.7 (C_1). All spectra are identical with those of lit. [13a]

4.2. (±)-2-Isopropylcyclobutanone, 3c

Following the procedure described above: From carboxaldehyde **4** (2.61 g, 15 mmol), THF (15 mL), *i*PrMgCl 1 M solution (18 mL), then concentrated H_2SO_4, gave after FC (eluent, CH_2Cl_2/pentane: 70/30) 1.353 g (82%) of pure 2-*iso*-propylcyclobutanone **3c**.[18] IR (neat): ν 1778 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.91 (d, J=6.4 Hz, 3H), 1.01 (d, J=6.4 Hz, 3H), 1.62–1.84 (m, 1H), 1.90 (dq, J=6.4 Hz, J=7.3 Hz, 1H, C*H*-(Me)$_2$), 1.99–2.20 (m, 1H), 2.75–2.97 (m, 2H-C_4), 2.97–3.18 (m, 1H-C_2); ^{13}C NMR ($CDCl_3$): δ 14.6 (C_3), 19.9 (CH_3), 20.3 (CH_3), 28.9 ($CH_{isopropyl}$), 44.2 (C_4), 67.4 (C_2), 212.1 (C_1).

4.3. General procedure A: aminonitriles formation by modified Strecker reaction

To a solution of alkylcyclobutanone **3.a**–**c** (3 mmol), in MeOH or DMSO (4 mL) was added successively (*S*)-α-phenylethylamine (525 μL, 500 mg, 4.5 mmol), AcOH (540 μL, 9 mmol) and finally NaCN (220 mg, 4.5 mmol). The reaction mixture was stirred and heated at 55–60°C for 3–4 days. Monitored by TLC, the reaction mixture was concentrated, then eluted with EtOAc (100 mL) and neutralised with $NaHCO_3$ solution to pH 8. After extraction with EtOAc (2×50 mL) the combined organic layer was dried, filtered, then concentrated. The residue was purified by FC to give two major and two minor diastereoisomers **2.a**–**c** with acceptable yields.

4.3.1. (1′*S*)-1-[(1′-Methylbenzyl)amino]cyclobutanecarbonitrile, 2.a. Following procedure A: From cyclobutanone **3a** (210 mg, 3 mmol), DMSO (4 mL), (*S*)-α-phenylethylamine (525 μL, 500 mg, 4.5 mmol), AcOH (9 mmol) and NaCN (220 mg) heated at 55°C for 6 h, we isolated after FC (EtOAc/petrol ether: 5→25%), 343 mg (57%) of pure aminonitrile **2.a**. $[\alpha]_D^{20}=-126$ (c 1, $CHCl_3$); R_f=0.4 (AcOEt/petrol ether: 2/8); IR (neat): ν 3420 and 3300 cm^{-1} (NH), 2210 (CN); ^{1}H NMR ($CDCl_3$): δ 1.40 (d, J=6.5 Hz, 3H), 1.56–1.82 (m, 1H and NH), 1.80–2.15 (m, 3H), 2.15–2.35 (m, 1H), 2.48–2.62 (m, 1H), 4.07 (q, J=6.5 Hz, 1H), 7.20–7.50 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 15.4 (t, C_3), 24.1 (q), 34.3 (t, C_4), 34.9 (t, C_2), 54.0 (s, C_1), 55.8 (d), 122.4 (s, CN) [6 arom. C: 127.0, (2C), 127.3, 128.3 (2C), 144.4]; MS (70 ev) m/z (%): 174 (1) (M^+−CN), 106 (20), *105* (100), 104 (10), 79 (13), 77 (16); ES$^+$MS m/z: 223.1 [M+Na]$^+$.

4.3.2. (1*S,2*S**,1′*S*)-1-[(1′-Methylbenzyl)amino]-2-phenylcyclobutanecarbonitrile, (1*S*,2*S*,1′*S*)-2A.b and (1*R*,2*R*,1′*S*)-2C.b**. Following procedure A: From phenylcyclobutanone **3b** (438 mg), DMSO (4 mL), (*S*)-α-phenylethylamine **6a** (525 μL), AcOH (540 μL) and NaCN (220 mg) heated at 55°C for 4 days, were obtained 1.5 g of crude nitriles as a mixture of four diastereoisomers in 51:45:2.5:1.5 ratio (determined by chiral GC). Purified twice by FC (eluent, Et_2O/pentane: 25/75) gave 228 mg (27.5%) of nitrile **2A.b**, 200 mg (24.3%) of nitrile **2C.b**, 11 mg (1.3%) and 7 mg (0.8%) of nitriles **2B.b** or **2D.b**.

4.3.2.1. Data for (1*S*,2*S*,1′*S*)-2A.b major *cis* isomer. $[\alpha]_D^{20}=-155$, $[\alpha]_{365}=-528$ (c 1, $CHCl_3$); mp 108.5°C; t_R=29.75 min (Cydex B, 160°C, 1 bar); R_f=0.44 (ether/pentane: 25/75); IR (neat): ν 3330 and 3300 cm^{-1} (NH), 2220 (CN); ^{1}H NMR ($CDCl_3$): δ 1.40 (d, J=6.6 Hz, 3H), 1.50–1.75 (m, 2H), 1.87 (br s, NH), 1.90–2.13 (m, 1H), 2.13–2.40 (m, 1H), 3.55 (dd, J=11.0 Hz, J=9.0 Hz, 1H-C_2), 4.07 (q, J=6.6 Hz, 1H), 7.15–7.56 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 20.7 (C_3), 24.5 (q, C-$C_{1'}$), 32.6 (C_4), 51.0 (C_2), 55.7 ($C_{1'}$), 62.8 (C_1), 120.35 (CN) [12 arom. C: 127.4, (2C), 127.5 (s, 1C), 127.6 (2C), 127.7 (s), 128.3 (2C), 128.5 (2C), 137.9 (s), 144.3 (s)]; MS (70 ev) m/z (%): no peak parent, 250 (1) (M^+−CN), *105* (100), 124 (25), 79 (18), 77 (24); HRMS m/z: 276.1613 (calcd for $C_{19}H_{20}N_2$: 276.1626). Anal. calcd for $C_{19}H_{20}N_2$: C, 82.57; H, 7.29; N, 10.14. Found: C, 82.19; H, 7.41; N, 9.94%.

4.3.2.2. Data for (1*R*,2*R*,1′*S*)-2C.b major *cis* isomer. $[\alpha]_D^{20}=-85.5$ (*c* 1, $CHCl_3$); $R_f=0.40$ (ether/pentane: 25/75); IR (neat): *v* 3420 and 3300 cm^{-1} (NH), 2220 (CN); ^1H NMR ($CDCl_3$): δ 1.38 (d, $J=6.7$ Hz, 3H), 1.68–2.00 (br s, NH), 2.10–2.50 (m, 3H), 2.50–2.68 (m, 1H), 3.48–3.52 (m, 1H), 4.05 (q, $J=6.7$ Hz, 1H), 7.00–7.60 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 20.9 (C_3), 24.1, 33.5 (C_4), 50.7 (C_2), 55.7 ($C_{1'}$), 62.0 (C_1), 120.1 (CN) [12 arom. C: 126.7, (2C), 127.4, 127.6 (2C), 128.3 (2C), 128.5 (2C), 137.1 (s), 145.1 (s)]; MS (70 ev) *m*/*z* (%): no peak parent, 250 (1) (M^+–CN), *105* (100), 124 (24), 79 (19), 77 (25); HRMS *m*/*z*: 276.1615 (calcd for $C_{19}H_{20}N_2$: 276.1626).

4.3.2.3. Data for (1*R*,2*S*,1′*S*)-2B.b (or (1*S*,2*R*,1′*S*)-2D.b) minor isomer. $R_f=0.62$ (ether/pentane: 25/75); ^1H NMR ($CDCl_3$): δ 1.04 (d, $J=6.7$ Hz, 3H), 1.20–1.60 (m, 3H, $2H_{cycle}$ and NH), 1.90–2.10 (m, $1H_{cycle}$), 2.14–2.41 (m, $1H_{cycle}$), 3.70 (q, $J=6.7$ Hz, 1H), 3.99 (dd, $J=8.5$ Hz, $J=10.7$ Hz, 1H-C_2), 7.10–7.64 (m, 10H).

4.3.2.4. Data for (1*S*,2*R*,1′*S*)-2D.b (or (1*R*,2*S*,1′*S*)-2B.b) minor isomer. $R_f=0.56$ (ether/pentane: 25/75); ^1H NMR ($CDCl_3$): δ 1.15 (d, $J=6.7$ Hz, 3H), 1.25–1.70 (m, 3H, $2H_{cycle}$ and NH), 2.05–2.29 (m, $1H_{cycle}$), 2.30–2.60 (m, $1H_{cycle}$), 3.73 (q, $J=6.7$ Hz, 1H), 3.95–4.12 (m, 1H-C_2), 6.95–7.60 (m, 10H).

4.3.3. (1*S,2*S**,1′*R*)-1-[(1′-Hydroxymethylbenzyl)-amino]-2-phenylcyclobutanecarbonitrile: (1*S*,2*S*,1′*S*)-2A.b′ and (1*R*,2*R*,1′*S*)-2C.b′**. Following procedure A: From 2-phenylcyclobutanone **3b** (292 mg), DMSO (4 mL), (*R*)-α-hydroxymethylbenzylamine **6b′** (548 mg), AcOH (360 μL) and NaCN (196 mg) heated at 55–60°C for 4 days, were obtained after flash chromatography (twice, eluent, EtOAc/petrol ether: 25→75%) 134 mg (23%) of major nitrile **2A.b′**, 107 mg (18.3%) of major **2C.b′**, and 7 mg (1.3%) of a mixture of nitriles **2B.b′** and **2D.b′**.

4.3.3.1. Data for (1*S*,2*S*,1′*R*)-2A.b′ major *cis* isomer. $[\alpha]_D^{20}=-127.3$ (*c* 1, $CHCl_3$); mp 77.7°C; $R_f=0.32$ (EtOAc/petrol ether: 3/7); IR (neat): *v* 3445 and 3313 cm^{-1} (OH and NH), 2222 (CN); ^1H NMR ($CDCl_3$): δ 1.63–1.87 (m, $2H_{cycle}$), 1.98–2.17 (m, $1H_{cycle}$), 2.17–2.40 (m, $1H_{cycle}$), 2.30–2.70 (br s, 2H, NH and OH), 3.54–3.80 (m, 3H, CH_2-O, and $1H_{cycle}$), 4.05 (dd, $J=9.0$ Hz, $J=4.5$ Hz, 1H, CH-N), 7.20–7.57 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 20.6 (C_3), 32.7 (C_4), 50.8 (C_2), 62.1 ($C_{1'}$), 62.6 (C_1), 66.6 (*C*H_2-O), 120.2 (CN) [12 arom. C: 127.5, (2C), 127.7, 128.0 (2C), 128.1, 128.45 (2C), 128.5 (2C), 137.9, 139.6]; MS (70 ev) *m*/*z* (%): no peak parent, 266 (1) (M^+–CN), 237 (32), 161 (91), 120 (50), 118 (80), 117 (35), 104 (67), 103 (69), *91* (100), 92 (56), 90 (32); ES^+MS *m*/*z*: 315.0 $[M+Na]^+$; HR ES^+MS *m*/*z*: 315.1471 (calcd mass for $C_{19}H_{20}NaN_2O$: 315.1473).

4.3.3.2. Data for (1*R*,2*R*,1′*R*)-2C.b′ major *cis* isomer. $[\alpha]_D^{20}=-96.4$ (*c* 1.27, $CHCl_3$); $R_f=0.22$ (EtOAc/petrol ether: 3/7); IR (neat): *v* 3435 and 3315 cm^{-1} (OH and NH), 2230 (CN); ^1H NMR ($CDCl_3$): δ 2.16–2.43 (m, 5H, $3H_{cycle}$ and NH, OH), 2.44–2.68 (m, $1H_{cycle}$), 3.43–3.61 (m, 2H), 3.61–3.78 (m, 1H), 3.93 (dd, $J=4.5$ Hz, $J=8.1$ Hz, 1H), 6.93–7.05 (m, 2H), 7.17–7.47 (m, 8H); ^{13}C NMR ($CDCl_3$): δ 20.5 (C_3), 31.8 (C_4), 51.0 (C_2), 61.3 ($C_{1'}$), 61.9 (C_1), 66.5 (*C*H_2-O), 120.2 (CN) [12 arom. C: 127.5, (3C), 127.6 (3C), 128.2 (2C), 128.6 (2C), 137.9, 140.2].

4.3.3.3. Data for (1*R*,2*S*,1′*R*)-2B.b′ (or (1*S*,2*R*,1′*R*)-2D.b′) minor isomer. $R_f=0.51$ (EtOAc/petrol ether: 3/7); ^1H NMR ($CDCl_3$): δ 1.20-1.42 (m, 1H), 1.42–1.98 (m, 3H, $1H_{cycle}$, NH and OH), 1.98–2.22 (m, $1H_{cycle}$), 2.43–2.70 (m, $1H_{cycle}$), 3.37 (dd, $J_{AB}=11.0$ Hz, $J=8.7$ Hz, 1H-$C_{2'}$), 3.64 (dd, $J_{AB}=11.0$ Hz, $J=4.3$ Hz, 1H-$C_{2'}$), 3.95 (dd, $J=8.7$ Hz, $J=4.5$ Hz, H-$C_{1'}$), 3.97-4.10 (m, 1H, C_2), 7.18–7.70 (m, 10H).

4.3.4. (1*S,2*S**,1′*R*)-1-[(1′-Methoxymethylbenzyl)-amino]-2-phenylcyclobutanecarbonitrile: (1*S*,2*S*,1′*R*)-2A.b′ and (1*R*,2*R*,1′*R*)-2C.b′**. Following procedure A: From 2-phenylcyclobutanone **3b** (219 mg, 1.5 mmol), DMSO (3 mL), (*R*)-α-methoxymethylbenzylamine **6b′** (616 mg, 3 mmol), AcOH (240 μL) and NaCN (150 mg) heated at 55–60°C for 4 days, we obtained after flash chromatography (twice, eluent, ether/pentane: 10→15%) 106 mg (23%) of major nitrile **2A.b′**, 86 mg (18.7%) of major nitrile **2C.b′**, and 11 mg (2.5%) of a mixture of nitriles: (1*R*,2*S*,1′*R*)-**2B.b′** and (1*S*,2*R*,1′*R*)-**2D.b″**.

4.3.4.1. Data for (1*S*,2*S*,1′*R*)-2A.b″ major *cis* isomer. $[\alpha]_D^{20}=-124.1$ (*c* 1, $CHCl_3$); mp 114.4°C; $R_f=0.38$ (Et_2O/pentane: 25/75); IR (neat): *v* 3290 cm^{-1} (NH), 2230 (CN); ^1H NMR ($CDCl_3$): δ 1.58–1.73 (m, $2H_{cycle}$), 1.95–2.15 (m, $1H_{cycle}$), 2.15–2.40 (m, $1H_{cycle}$), 2.70 (br s, NH), 3.38 (s, 3H, CH_3-O), 3.41 (dd, $J_{AB}=9.7$ Hz, $J=3.8$ Hz, 1H-$C_{2'}$), 3.55 (dd, $J_{AB}=9.7$ Hz, $J=9.7$ Hz, 1H-$C_{2'}$), 3.63 (dd, $J=8.7$ Hz, $J=11.3$ Hz, 1H-C_2), 4.18 (dd, $J=3.8$ Hz, $J=9.7$ Hz, 1H, C*H*-N), 7.20–7.55 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 20.8 (C_3), 32.5 (C_4), 50.6 (C_2), 58.4 ($C_{1'}$), 59.4 (CH_3-O), 62.6 (C_1), 76.4 (CH_2-O), 120.1 (C≡N) [12 arom. C: 127.5, (2C), 127.6, 128.1, 128.3 (4C), 128.5 (2C), 138.0, 139.4]; MS (70 ev) *m*/*z* (%): no peak parent, 280 (1.2) (M^+–CN), 157 (44), 135 (93), 105 (34), 104 (40), *103* (100), 91 (85), 77 (44); ES^+MS *m*/*z*: 329.0 $[M+Na]^+$; HR ES^+MS *m*/*z*: 329.1634 (calcd mass for $C_{20}H_{22}NaN_2O$: 329.1630).

4.3.4.2. Data for (1*R*,2*R*,1′*R*)-2C.b″ major *cis* isomer. $[\alpha]_D=-90$ (*c* 0.40, $CHCl_3$); $R_f=0.30$ (Et_2O/pentane: 25/75); IR (neat): *v* 3325 cm^{-1} (NH), 2230 (CN); ^1H NMR ($CDCl_3$): δ 2.15–2.43 (m, $3H_{cycle}$), 2.43–2.65 (m, $1H_{cycle}$), 2.72 (br s, 1H, NH), 3.39 (s, 3H, CH_3-O), 3.30–3.60 (m, 3H, CH_2-O and 1H-C_2), 4.05 (dd, $J=5.9$ Hz, $J=7.4$ Hz, 1H, CH-N), 6.83–6.98 (m, 2H), 7.14–7.26 (m, 3H), 7.26–7.54 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 20.7 (C_3), 32.0 (C_4), 50.6 (C_2), 58.6 (CH_3-O), 59.0 ($C_{1'}$), 62.0 (C_1), 76.8 (CH_2-O), 120.3 (C≡N) [12 arom. C: 127.2, 127.6 (2C), 127.8 (3C), 128.1 (2C), 128.5 (2C), 138.2, 140.5]; MS (70 ev) *m*/*z* (%): no peak parent, 279 (1.6) (M^+–HCN), 157 (38), 135 (50), 106 (35), 105 (35), 104 (43), 103 (76), *91* (100), 77 (45); ES^+MS *m*/*z*: 329.0 $[M+Na]^+$.

4.3.4.3. Data for (1*R*,2*S*,1′*R*)-2B.b″ and (1*S*,2*R*,1′*R*)-2D.b″) minor *trans* isomers. (Data obtained from mixture): ^{1}H NMR ($CDCl_3$): δ 1.15–1.70 (m, 1H, **B**/**D**), 1.71–1.94 (m, 2H, **D**), 1.94–2.21 (m, 2H, **B**), 2.44–2.72 (m, 1H, **B**/**D**), 3.23 (s, 3H, **B**), 3.34 (s, 3H, **D**), 3.20–3.60 (m, 2H, **B**/**D**), 4.04 (dd, $J=10.0$ Hz, $J=8.0$ Hz, 1H-C_2, **B**), 4.13 (dd, $J=4.8$ Hz, $J=8.8$ Hz, 1H, 1H-$C_{1'}$, **B**), 4.05–4.30 (m, 2H, H-C_2 and H-$C_{1'}$, **D**), 7.20–7.60 (10H, **B**/**D**).

4.3.5. (1*S,2*S**,1′*S*)-1-[(1′-Methylbenzyl)amino]-2-isopropylcyclobutanecarbonitrile: (1*S*,2*S*,1′*S*)-2A.c and (1*R*,2*R*,1′*S*)-2C.c**. According to procedure A: From 2-*iso*propylcyclobutanone **3c** (336 mg, 3 mmol), DMSO (6 mL), (*S*)-α-phenylethylamine **6a** (700 μL, 6 mmol), AcOH (540 μL, 9 mmol) and NaCN (300 mg, 6 mmol). After heating 55–60°C for 4 days and flash chromatography (twice, eluent, ether/CH_2Cl_2, 3/7) we isolated 1.87 mg (56%) of major nitrile *cis*-**2A.c**, 140 mg (52%) of major nitrile *cis*-**2C.c**, and 6.5 mg (2%) of a mixture of nitriles **2B.c** and **2D.c**. The separation of these two major products is better after transformation into their amides **8A.c** and **8C.c**.

4.3.5.1. Data for (1*S*,2*S*,1′*R*)-2A.c major *cis* isomer. $[\alpha]_D^{20}=-100$ (*c* 1, $CHCl_3$); mp 66.2°C; $R_f=0.63$ (MeOH/pentane: 2/98); IR (neat): *v* 3330 cm^{-1} (NH), 2215 (CN); ^{1}H NMR ($CDCl_3$): δ 0.82 (d, $J=6.0$ Hz, 3H), 1.00 (d, $J=6.0$ Hz, 3H), 1.21–1.57 (m, 3H), 1.41 (d, $J=6.8$ Hz, 3H, CH_3-C_1), 1.65–2.02 (m, 3H and NH), 4.13 (q, $J=6.8$ Hz, 1H-$C_{1'}$), 7.21–7.44 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 19.1 (C_3), 20.5 ($CH_{3,isopropyl}$), 21.2 ($CH_{3,isopropyl}$), 24.7 (*C*H_3-$C_{1'}$), 31.9 (*C*H-C_2), 31.95 (C_4), 53.1 ($C_{1'}$), 55.6 (C_2), 59.5 (C_1), 121.1 (CN) [6 arom. C: 127.3 (3C), 128.2 (2C), 144.4]; MS (70 ev) *m*/*z* (%): 242 (0.4) (M^+), 199 (14), 106 (11), *105* (100), 79 (11), 77 (15); HRMS *m*/*z*: 242.1784 (calcd for $C_{16}H_{22}N_2$: 242.1783).

4.3.5.2. Data for (1*R*,2*R*,1′*R*)-2C.c major *cis* isomer. $[\alpha]_D^{20}=-60.3$ (*c* 1, $CHCl_3$); $R_f=0.57$ (MeOH/pentane: 2/98); $t_R=14.88$ min (Cydex B, 155°C/1 bar); ^{1}H NMR ($CDCl_3$): δ 0.79 (d, $J=6.0$ Hz, 3H), 0.90 (d, $J=6.0$ Hz, 3H), 1.36 (d, $J=6.7$ Hz, CH_3-$C_{1'}$), 1.58–1.81 (m, 1H and NH), 1.82–2.23 (m, 4H), 2.45 (dd, $J=9.5$ Hz, $J=7.9$ Hz, 1H–C_2), 4.15 (q, $J=6.7$ Hz, 1H-$C_{1'}$), 7.21–7.48 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 19.1 (C_3), 20.4 ($CH_{3,isopropyl}$), 21.0 ($CH_{3,isopropyl}$), 23.5 (*C*H_3-C_1), 31.2 (*C*H-C_2), 33.5 (C_4), 53.1 ($C_{1'}$), 55.6 (C_2), 58.6 (C_1), 120.5 (CN) [6 arom. C: 126.6 (2C), 127.4, 128.5 (2C), 145.0]; MS (70 ev) *m*/*z* (%): 242 (0.5) (M^+), 199 (11), 106 (11), *105* (100), 77 (14);); HRMS *m*/*z*: 242.1784 (calcd for $C_{16}H_{22}N_2$: 242.1783).

4.4. General procedure B of amide formation from nitrile

A solution of nitrile **2A.a**–**c** or **2C.a**–**c** (3 mmol), in CH_2Cl_2 (12 mL) was cooled to 0°C and concentrated sulphuric acid (5 mL) was added very slowly with efficient stirring. The reaction mixture was allowed to warm to rt and stirred for 5 h. The aqueous layer was separated, washed with CH_2Cl_2 (2 mL), then poured onto crushed ice (10 g), and was slowly basified with concentrated ammonia. The mixture extracted with EtOAc (4×50 mL), dried over $MgSO_4$ then concentrated to give, after flash chromatography (silica gel, 30 g, eluent, EtOAc/petrol ether), the title amide **8A.a**–**c4**.

4.4.1. (1′*S*)-1-[(1′-Methylbenzyl)amino]cyclobutanecarboxamide, 8A.a-c. According to general procedure B: From nitrile **2.a** (220 mg, 1.1 mmol), concentrated H_2SO_4 (1.5 mL), and stirring at rt for 4 h gave after FC (eluent, EtOAc/petrol ether: 4/6→6/4) 216 mg (90%) of pure amide **8A.a**. $[\alpha]_D^{20}=-16.0$ $[\alpha]_{365}=65.8$ (*c* 1, $CHCl_3$); $R_f=0.45$ (EtOAc); IR (neat): *v* 3420 and 3300 cm^{-1} (NH), 1670 (CON); ^{1}H NMR ($CDCl_3$): δ 1.34 (d, $J=6.7$ Hz, 3H), 1.60–2.10 (m, $4H_{cycle}$ and NH), 2.35–2.67 (m, $2H_{cycle}$), 3.82 (q, $J=6.7$ Hz, 1H), 5.29 (br s, $1H_{amide}$), 6.80 (br s, $1H_{amide}$), 7.12–7.45 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 14.5 (C_3), 24.2 (*C*-$C_{1'}$), 30.2 (C_4), 34.1 (C_2), 54.5 ($C_{1'}$), 63.0 (C_1) [6 arom. C: 126.3 (2C), 126.9, 128.3 (2C), 146.0], 179.4 (CON); MS (70 ev) *m*/*z* (%): 218 (0.5) (M^+), 190 (28), 174 (18), *105* (100), 104 (21), 70 (32); HRMS *m*/*z*: 218.1412 (calcd for $C_{13}H_{18}N_2O$: 218.1419)

4.4.2. (1*S*,2*S*,1′*S*)-1-[(1′-Methylbenzyl)amino]-2-phenylcyclobutanecarboxamide, 8A.b. According to procedure B: From nitrile **2A.b** (120 mg, 0.43 mmol), CH_2Cl_2 (4 mL), concentrated H_2SO_4 (1 mL) reacted for 8 h at rt, we isolated after FC (eluent, EtOAc/petrol ether: 3/7) 88 mg (70%) of pure amide **8A.b**. $[\alpha]_D^{20}=+29.0$ (*c* 1, $CHCl_3$); mp 175.0°C; $R_f=0.20$ (EtOAc/petrol ether: 3/7); IR (neat): *v* 3500, 3380 and 3280 cm^{-1} (NH), 1670 (CON); ^{1}H NMR ($CDCl_3$): δ 1.32 (d, $J=6.7$ Hz, 3H), 1.40–1.68 (m, $1H_{cycle}$), 1.75–2.20 (m, 2H, $1H_{cycle}$ and NH), 2.26–2.57 (m, 2H), 3.38 (dd, $J=9.4$ Hz, $J=9.5$ Hz, 1H), 3.88 (q, $J=6.7$ Hz, 1H, C*H*-CH_3), 4.93 (br s, $1H_{amide}$), 6.55 (br s, $1H_{amide}$), 7.10–7.45 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 19.4 (d, C_4), 24.0 (CH_3-$C_{1'}$), 27.5 (t, C_5), 54.3 ($C_{1'}$), 55.1 (C_2), 70.4 (C_1) [12 arom. C: 126.5 (2C), 126.9, 127.3, 127.8 (2C), 128.1 (2C), 128.6 (2C), 138.7, 146.4], 175.5 (*C*ON); ES$^+$MS *m*/*z*: 295.1 $[M+H]^+$; HR ES$^+$MS *m*/*z*: 317.1630 (calcd mass for $C_{19}H_{22}NaN_2O$: 317.1630).

4.4.3. (1*S*,2*S*,1′*S*)-1-[(1′-Methylbenzyl)amino]-2-isopropylcyclobutanecarboxamide, 8A.c. According to general procedure B: From nitrile **2A.c** (122 mg, 0.5 mmol), CH_2Cl_2 (4 mL), H_2SO_4 (1.5 mL) stirring at rt for 8 h, we isolated after FC (eluent, EtOAc/CH_2Cl_2: 5→20%), 110 mg (85%) of pure amide **8A.c**.

$[\alpha]_D^{20}=+29.5$ (*c* 0.85, $CHCl_3$); $R_f=0.58$ (EtOAc/CH_2Cl_2: 3/7); $t_R=62.63$ min (Cydex B, 155°C/1 bar); IR (neat): *v* 3445 and 3322 cm^{-1} (NH), 1676 (CON); ^{1}H NMR ($CDCl_3$): δ 0.72 (d, $J=6.3$ Hz, 3H), 0.90 (d, $J=6.3$ Hz, 3H), 1.27 (d, $J=6.7$ Hz, CH_3-$C_{1'}$), 1.47–1.97 (m, $5H_{cycle}$ and NH), 2.18–2.35 (m, $1H_{cycle}$), 3.90 (q, $J=6.7$ Hz, 1H-$C_{1'}$), 5.70 (br s, $1H_{amide}$), 7.10–7.37 (m, 5H), 7.42 (br s, $1H_{amide}$); ^{13}C NMR ($CDCl_3$): δ 19.4 (C_3), 20.6 ($CH_{3,isopropyl}$), 22.4 ($CH_{3,isopropyl}$), 24.0 (CH_3-$C_{1'}$), 26.4 (*C*H-C_2), 30.0 (C_4), 54.9 ($C_{1'}$), 57.7 (C_2), 67.3 (C_1) [6 arom. C: 126.3 (2C), 127.1, 128.5 (2C), 146.6], 178.1 (*C*ON); MS (70 ev) *m*/*z* (%): 260 (1) (M^+), 190 (61), 175

(17), 145 (30), *105* (100), 77 (15); HRMS m/z: 260.1885 (calcd for $C_{16}H_{24}N_2O$: 260.1888).

4.4.4. (1*R*,2*R*,1′*S*)-1-[(1′-Methylbenzyl)amino]-2-isopropylcyclobutanecarboxamide, 8C.c. According to general procedure B: From amino nitrile **2C.c** (120 mg, 0.5 mmol), H_2SO_4 (1 mL), CH_2Cl_2, (4 mL) stirring at rt for 8 h, we isolated after FC (eluent, EtOAc/CH_2Cl_2: 5→20%), 111 mg (85%) of pure amide **8C.c**. $[\alpha]_D^{20}=-119.5$ (c 0.9, $CHCl_3$); $R_f=0.64$ (EtOAc/CH_2Cl_2: 3/7); $t_R=55.77$ min (Cydex B, 155°C/1 bar); IR (neat): ν 3445 and 3322 cm^{-1} (NH), 1676 (CON); ^1H NMR ($CDCl_3$): δ 0.75 (d, $J=6.2$ Hz, 3H), 0.91 (d, $J=6.2$ Hz, 3H), 1.41 (d, $J=6.6$ Hz, CH_3-$C_{1'}$), 1.48–2.00 (m, $5H_{cycle}$ and NH), 2.51–2.68 (m, $1H_{cycle}$), 3.77 (q, $J=6.6$ Hz, 1H-$C_{1'}$), 5.10 (br s, $1H_{amide}$), 6.60 (br s, $1H_{amide}$), 7.15–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 19.5 (C_3), 20.4 ($CH_{3,isopropyl}$), 22.2 ($CH_{3,isopropyl}$), 26.2 (CH_3-$C_{1'}$), 28.3 (CH-C_2), 29.9 (C_4), 54.2 ($C_{1'}$), 57.5 (C_2), 67.9 (C_1) [6 arom. C: 126.3 (2C), 126.8, 128.4 (2C), 146.3], 176.7 (CON); MS (70 ev) m/z (%): 232 (2) (M^+-28), 190 (55), 175 (19), 145 (32), *105* (100), 77 (18); HRMS m/z: 260.1885 (calcd for $C_{16}H_{24}N_2O$: 260.1888).

4.5. Procedure C: hydrogenolysis of benzylic amine

Amino amide adduct **8.a–c** (1.00 mmol) obtained as described above, was dissolved in a mixture of AcOH/EtOH (3 mL/3 mL), and 20% $Pd(OH)_2/C$ (Pearlman's catalyst, 120 mg) was added. The flask was connected to a hydrogenation apparatus equipped with a graduated burette containing water that allowed the uptake of hydrogen to be monitored. TLC control showed that under 1 atm H_2 at rt the reaction was complete within 3 h. The mixture was then degassed under a stream of argon, filtered through Celite, and the collected solid was washed with EtOH (3×10 mL). The combined filtrate and washings were concentrated and the residue was subjected to FC (eluent, MeOH/CH_2Cl_2: 5→20%) to afford pure free amino amides **9.a–c**.

4.5.1. 1-Aminocyclobutanecarboxamide, 9.a. According to procedure C: From amide **8.a** (166 mg, 0.76 mmol), (AcOH/EtOH: 2 mL/2 mL), and 20% $Pd(OH)_2/C$ (80 mg) stirring at rt for 3 h, gave after FC, 73 mg (84%) of pure amino amide **9.a**. $R_f=0.18$ (MeOH/CH_2Cl_2: 1/4); $t_R=3.73$ min (Cydex B, 140°C/1 bar); mp 81.9°C; IR (neat): ν 3420 and 3340 cm^{-1} (NH), 1680 (CON); ^1H NMR ($CDCl_3$): δ 1.75 (s, 2H, NH_2), 1.70–2.10 (m, 4H), 2.60–2.78 (m, 2H), 5.76 (br s, $1H_{amide}$), 7.07 (br s, $1H_{amide}$); ^{13}C NMR ($CDCl_3$): δ 13.9 (C_3), 34.8 (C_2 and C_4), 58.7 (C_1), 179.5 (CON); MS (70 ev) m/z (%): 114 (0.5) (M^+), 86 (44), 70 (21), *42* (100), 41 (21); HRMS m/z: 114.0797 (calcd for $C_5H_{10}N_2O$: 114.0793).

4.5.2. (1*S*,2*S*)-1-Amino-2-isopropylcyclobutanecarboxamide, 9A.c. According to procedure C: Amino amide **8A.c** (130 mg, 0.50 mmol), AcOH/EtOH (2 mL/2 mL), 20% $Pd(OH)_2/C$ (80 mg) stirring at rt for 4 h, gave after FC (eluent, MeOH/EtOAc: 5→10%) 76.5 mg (98%) of pure free amino amide **9A.c.** $[\alpha]_D^{20}=+41$ (c 0.68, $CHCl_3$); mp 45.0°C; $R_f=0.20$ (MeOH/EtOAc: 1/9); $t_R=6.47$ min (Cydex B, 140°C/1 bar); IR (neat): ν 3445 and 3294 cm^{-1} (NH), 1668 (CON); ^1H NMR ($CDCl_3$): δ 0.77 (d, $J=6.2$ Hz, 3H), 0.90 (d, $J=6.2$ Hz, 3H), 1.53–2.05 (m, 5H and NH_2), 2.40–2.70 (m, 1H), 5.56 (br s, $1H_{amide}$), 7.24 (br s, $1H_{amide}$); ^{13}C NMR ($CDCl_3$): δ 19.7 ($CH_{3,isopropyl}$), 20.0 (C_3), 21.1 ($CH_{3,isopropyl}$), 30.0 ($CH_{isopropyl}$), 33.8 (C_4), 58.2 (C_2), 62.3 (C_1), 178.0 (CON);); MS (70 ev) m/z (%): 157 (1.8) [M^++1], 156 (5) [M^+], 111 (11), 96 (10), *86* (100), 83 (16); ES^+MS m/z: 157.1 [M+H]$^+$; HR ES^+MS m/z: 179.1158 (calcd mass for $C_8H_{16}NaN_2O$: 179.1160).

4.5.3. (1*R*,2*R*)-1-Amino-2-isopropylcyclobutanecarboxamide, 9C.c. According to procedure C: Amide **8C.c** (104 mg, 0.40 mmol), AcOH/EtOH (2 mL/2 mL), 20% $Pd(OH)_2/C$ (70 mg) stirring at rt for 4 h, gave after FC (eluent, MeOH/EtOAc: 1/9), 59 mg (≈95%) of pure free amino amide **9C.c**. $[\alpha]_D^{20}=-39.5$ (c 0.7, $CHCl_3$); mp 44.9°C; $R_f=0.20$ (MeOH/EtOAc: 1/9); IR (neat): ν 3445 and 3294 cm^{-1} (NH), 1668 (CON); ^1H NMR ($CDCl_3$): δ 0.77 (d, $J=6.2$ Hz, 3H), 0.90 (d, $J=6.2$ Hz, 3H), 1.56–2.10 (m, 5H and NH_2), 2.42–2.65 (m, 1H), 5.56 (br s, $1H_{amide}$), 7.24 (br s, $1H_{amide}$); ^{13}C NMR ($CDCl_3$): δ 19.7 ($CH_{3,isopropyl}$), 20.0 (C_3), 21.1 ($CH_{3,isopropyl}$), 30.0 ($CH_{isopropyl}$), 33.8 (C_4), 58.2 (C_2), 62.3 (C_1), 178.0 (CON);); MS (70 ev) m/z (%): 157 (1.5) [M^++1], 156 (5) [M^+], 111 (12), 96 (10), *86* (100), 83 (17); HRMS m/z: 179.1159 (calcd for $C_8H_{16}NaN_2O$: 179.1160).

4.6. General procedure D: aminocarboxylic acid formation

A mixture of amide **9X.a–c** (0.50 mmol) and 6N HCl (4 mL) was heated to gentle reflux. The reaction was complete within 20 h as shown by TLC. The solution reaction was cooled to rt, and extracted with ether (5 mL) to remove coloured ether soluble material. The hydrochloric acid was evaporated to dryness under reduced pressure to give amino acids **1.(a–c)**·HCl as a white solid. Recrystallisation from MeOH–ether furnished pure crystalline amino acid·hydrochloride with excellent yield.

To the amino acid salt were added EtOH (2 mL) and propylene oxide (1 mL). The mixture was stirred at rt for 5 h. After complete precipitation the organic solvents were removed under reduced pressure to furnish a solid residue. The latter was dissolved in distilled water then filtered through cotton, to give a clean solution, which was concentrated under reduced pressure leading to pure amino acids **1.(a–c)** with excellent yield.

4.6.1. 1-Aminocyclobutanecarboxylic acid hydrochloride salt, 1a·HCl. Following procedure D: Amino amide **9a** (57 mg, 0.50 mmol), 6N HCl (4 mL), 20 h at reflux, gave after recrystallisation 71 mg (90%) as a white solid of pure **1a**·HCl. Mp 225–226°C (dec.); IR (KBr): ν 3411 cm^{-1} 3024, 1729 (COO), 1592; ^1H NMR (D_2O, HOD, 4.6 ppm): δ 1.99 (s, 4H, NH_3 and H_{acid}), 1.80–2.00 (m, 2H), 2.11–2.30 (m, 2H), 2.33–2.56 (m, 2H); lit.[19] for acid **1a**: mp 295–296 °C (dec.); ^1H NMR (D_2O): δ 1.86–1.97 (m, 2H), 2.07–2.17 (m, 2H), 2.32–2.42 (m, 2H); ^{13}C NMR (D_2O): δ 15.58, 30.96, 60.32, 178.61.

4.6.2. (1*S*,2*S*)-1-Amino-2-isopropylcyclobutanecarboxylic acid, 1A.c. Following procedure D: Amino amide (1*S*,2*S*)-**9A.c** (31.2 mg, 0.20 mmol), 6N HCl (3 mL), 20 h at reflux, gave 36.4 mg (94%) as a white solid of pure (1*S*,2*S*)-**1A.c**·HCl.

4.6.2.1. Data for (1*S*,2*S*)-1A.c·HCl. $[\alpha]_D^{20}=+42$ (*c* 0.75, H_2O); $R_f=0.52$ (MeOH); mp 197–199°C (dec.); IR (KBr): *v* 3401 cm^{-1} 1720 (COO), 1592, 1496, 1404; ^1H NMR (D_2O, HOD: 4.63 ppm): δ 0.58 (d, $J=6.8$ Hz, 3H), 0.62 (d, $J=6.8$ Hz, 3H), 1.39–1.60 (m, 1H, $CH_{isopropyl}$), 1.60–1.80 (m, $1H_{cycle}$), 1.80–2.07 (m, $2H_{cycle}$), 2.07–2.37 (m, $2H_{cycle}$); ^{13}C NMR (D_2O, with $CDCl_3$ as internal reference): δ 18.5 (C_3), 19.6 ($CH_{3,isopropyl}$), 20.5 ($CH_{3,isopropyl}$), 26.2 ($CH_{isopropyl}$), 29.9 (C_4), 51.6 (C_2), 61.0 (C_1), 173.5 (COO).

4.6.2.2. Data for (1*S*,2*S*)-1A.c. $[\alpha]_D^{20}=+51.2$ (*c* 0.51, H_2O); mp 199–202°C (dec.); IR (KBr): *v* 3390 cm^{-1} 1727 (COO), 1453, 1399; ^1H NMR (D_2O, with HOD: 4.63 ppm): δ 0.54 (d, $J=6.5$ Hz, 3H), 0.60 (d, $J=6.5$ Hz, 3H), 1.36–1.55 (m, 1H, $CH_{isopropyl}$), 1.55–1.73 (m, $1H_{cycle}$), 1.73–1.96 (m, $2H_{cycle}$), 2.02 (dd, $J=9.3$ Hz, $J=9.3$ Hz, $1H_{cycle}$),), 2.15 (dd, $J=9.3$ Hz, $J=8.7$ Hz, $1H_{cycle}$); ^{13}C NMR (D_2O, with $CDCl_3$ as internal reference): δ 18.5 (C_3), 19.9 ($CH_{3,isopropyl}$), 20.7 ($CH_{3,isopropyl}$), 26.2 ($CH_{isopropyl}$), 30.1 (C_4), 51.6 (C_2), 62.3 (C_1), 175.4 (COO); ES^+MS *m*/*z*: 158.1 $[M+H]^+$; HR ES^+MS *m*/*z*: calcd for $C_8H_{16}NO_2$ $[M+H^+]$: 158.1181. Found 158.1182.

4.6.3. (1*R*,2*R*)-1-Amino-2-isopropylcyclobutanecarboxylic acid, 1C.c. Following procedure D: amino amide (1*R*,2*R*)-**9C.c** (22 mg, 0.141 mmol), 6N HCl (3 mL), 22 h at reflux, gave 27 mg (98%) as a white solid of pure (1*R*,2*R*)-**1C.c**·HCl.

4.6.3.1. Data for (1*R*,2*R*)-1C.c·HCl. $[\alpha]_D^{20}=-43$ (*c* 0.65, H_2O), $[\alpha]_D^{20}=-44$ (*c* 0.64, MeOH). All spectral data are identical with those of the enantiomer (1*S*,2*S*).

4.6.3.2. Data for (1*R*,2*R*)-1C.c. $[\alpha]_D^{20}=-51.7$ (*c* 0.51, H_2O). All spectral data are identical with those of the (1*S*,2*S*)-enantiomer.

4.7. General procedure for the preparation of Mosher amides of amino amide 9A.c

4.7.1. (1*S*,2*S*,2′*R*)-2-Isopropyl-1-(3′,3′,3′-trifluoro-2′-methoxy - 2′ - phenylpropionylamino)cyclobutanecarboxamide [(*R*)-MTPA-9A.c] (*R*)-MTPA-amide of (1*S*,2*S*)-9A.c. To a stirred suspension of **9A.c** (6 mg, 0.040 mmol) in THF (1 mL) was added (*S*)-(+)-Mosher's acid chloride (7.5 μL, 0.040 mmol, 1 equiv.) and propylene oxide (14 μL, 0.200 mmol, 5 equiv.). The resulting mixture was heated to reflux for 4 h ($T\approx$ 80°C), allowed to cool to room tempearture, and the solvents were completely evaporated. FC (EtOAc/pentane: 8/2) of the residue afforded 13 mg (≈93%) of the pure (*R*)-MTPA amide of **9A.c** [(*R*)-MTPA-**9A.c**]. $[\alpha]_D^{20}=+70.5$ (*c* 0.6, $CHCl_3$); mp 136.1°C; $R_f=0.82$ (MeOH/EtOAc: 1/9); IR (neat): *v* 3620–3352 cm^{-1} (NH), 1670 and 1600 (CON); ^1H NMR ($CDCl_3$): δ 0.80 (d, $J=6.6$ Hz, 3H), 0.86 (d, $J=6.6$ Hz, 3H), 1.26 (br s, NH), 1.62–1.90 (m, $1H_{isopropyl}$), 1.65–1.90 (m, $1H_{cycle}$), 2.13 (m, $1H_{cycle}$), 2.42–2.69 (m, 1H-C_2), 2.45–2.69 (m, $2H_{cycle}$), 3.47 (d, $J=1.6$ Hz, 3H, OMe), 5.80 (br s, $1H_{amide}$), 5.90 (br s, $1H_{amide}$), 7.35–7.67 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 19.2 (C_3), 20.9 ($CH_{3,isopropyl}$), 21.2 ($CH_{3,isopropyl}$), 28.0 (CH-C_2), 30.1 (C_4), 52.1 (C_2), 55.1 (OCH_3), 62.8 (C_1), 83.9 (d, $J=26.2$ Hz, $C_{2'}$), 123.7 (d, $J=289.7$ Hz, CF_3) [6 arom. C: 127.5 (2C), 128.7 (2C), 129.6, 132.3], 165.8 ($C_{1'}$), 173.6 ($CONH_2$).

4.7.2. (1*S*,2*S*,2′*S*)-2-Isopropyl-1-(3′,3′,3′-trifluoro-2′-phenylpropionylamino)cyclobutanecarboxamide (*S*)-MTPA-9A.c, the (*S*)-MTPA-amide of (1*S*,2*S*)-9A.c. Following the procedure described above: From (1*S*,2*S*)-**9A.c** (6 mg, 0.040 mmol), (*R*)-(−)-Mosher's acid chloride (7.5 μL, 0.040 mmol), and propylene oxide (14 μL, 0.200 mmol, 5 equiv.). After evaporation of the solvent and subsequent FC (EtOAc/pentane: 8/2) of the residue, the amide (*S*)-MTPA-**9A.c** (13 mg, 93%) was obtained. $[\alpha]_D^{20}=-47$ (*c* 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 0.80 (d, $J=6.6$ Hz, 3H), 0.87 (d, $J=6.6$ Hz, 3H), 1.26 (br s, NH), 1.79 (m, 1H-C_3), 1.82 (m, CH-C_2), 2.07 (m, 1H-C_3), 2.24 (m, 1H-C_4), 2.41 (m, 1H-C_4), 2.67 (ddd, $J=2.5$ Hz, $J=9.4$ Hz, $J=11.6$ Hz, 1H-C_2), 3.43 (d, $J=1.5$ Hz, OCH_3), 5.89 (br s, $1H_{amide}$), 6.06 (br s, $1H_{amide}$), 7.32–7.67 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 19.2 (C_3), 21.0 ($CH_{3,isopropyl}$), 21.4 ($CH_{3,isopropyl}$), 28.6 (CH-C_2), 29.9 (C_4), 52.5 (C_2), 55.1 (OCH_3), 62.7 (C_1), 83.9 (d, $J=26.2$ Hz, $C_{2'}$), 123.9 (d, $J=290.2$ Hz, CF_3) [6 arom. C: 127.6 (2C), 128.7 (2C), 129.6, 131.9], 165.6 ($C_{1'}$), 173.6 ($CONH_2$).

References

1. (a) Hood, W. F.; Sun, E. T.; Compton, R. P.; Monahan, J. B *Eur. J. Pharmacol.* **1989**, *161*, 281–282; (b) Watson, G. B.; Lanthorn, T. H. *Neuropharmacology* **1990**, *29*, 727–730.
2. Nahum-Levy, R.; Fossom, L. H.; Skolnick, P.; Benveniste, M. *Mol. Pharmacol.* **1999**, *56*, 1207–1218.
3. Karez-Kubicha, M.; Wedzony, K.; Zajaczkowski, W.; Danysz, W. *J. Neural. Transm.* **1999**, *105*, 1189–1204 and references cited therein.
4. (a) Malashkevich, V. N.; Strop, P.; Keller, J. W.; Jansonius, J. N.; Toney, M. D. *J. Mol. Biol.* **1999**, *294*, 193–200; (b) Rhee, S.; Silva, M. M.; Hyde, C. C.; Rogers, P. H.; Metzler, C. M.; Wetzler, D. E.; Arnone, A. *J. Biol. Chem.* **1997**, *272*, 17293–17302.
5. For an excellent review on quaternary amino acids: cyclic compounds, see: Cativiela, C.; Diaz-de-Villegas, M.-D. *Tetrahedron: Asymmetry* **2000**, *11*, 645–732.
6. Burger, A. US Patent p47, 3,345,405, 1967; *CAN* 68: 49173.
7. Gaoni, Y. *Org. Prep. Proced. Int.* **1995**, *27*, 185–212.
8. Fadel, A. *Synlett* **1993**, 503–505.
9. Fadel, A.; Khesrani, A. *Tetrahedron: Asymmetry* **1998**, *9*, 305–320.
10. For a review on asymmetric Strecker synthesis, see: Williams, R. M. *Synthesis of Optically Active α-Amino Acids*, Vol. 7 of the Organic Chemistry Series; Baldwin, J. E.; Magnus, P. D., Eds.; Pergamon Press: Oxford, 1989; Chapter 5, pp. 208–229.

11. For recent work on Asymmetric Strecker synthesis, see: (a) Wede, J.; Volk, F. J.; Frahm, A. W. *Tetrahedron: Asymmetry* **2000**, *11*, 3231–3252 and references cited therein; (b) Ma, D.; Tian, H.; Zou, G. *J. Org. Chem.* **1999**, *64*, 120–125; (c) Corey, E. J.; Grogan, M. *Org. Lett.* **1999**, *1*, 157–160; (d) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901–4902.
12. Salaün, J.; Fadel, A.; Conia, J. M. *Tetrahedron Lett.* **1979**, 1429–1532.
13. For ring enlargement of hydroxymethylcyclopropanol, see: (a) Nemoto, H.; Shiraki, M.; Fukomoto, K. *J. Org. Chem.* **1996**, *61*, 1347–1353 and references cited therein; (b) Krief, A.; Ronvaux, A.; Tuch, A. *Tetrahedron* **1998**, *54*, 6903–6908; (c) Miller, S. A.; Gadwood, R. C. *Org. Synth.* **1989**, *67*, 210.
14. (a) Agami, C.; Couty, F.; Evano, G. *Tetrahedron Lett.* **1999**, *40*, 3709; (b) Tesson, N.; Dorigneux, B.; Fadel, A. *Tetrahedron: Asymmetry* **2002**, *13*, 2267–2276.
15. Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096.
16. Kelly, D. R. *Tetrahedron: Asymmetry* **1999**, *10*, 2927–2934.
17. Fadel, A.; Tesson, N. *Eur. J. Org. Chem.* **2000**, 2153–2159.
18. (a) Lebedew *Zh. Russ. Fiz-Khim.* **1911**, *43*, 830; (b) Hanack, M.; Herterich, I.; Vött, V. *Tetrahedron Lett.* **1967**, 3871.
19. Pirrung, M. C.; Cao, Y.; Chen, J. *J. Org. Chem.* **1995**, *60*, 5790 and references cited therein.