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Cross-Metathesis Reactions as an Efficient Tool in the Synthesis of Fluorinated Cyclic β-Amino Acids[§]

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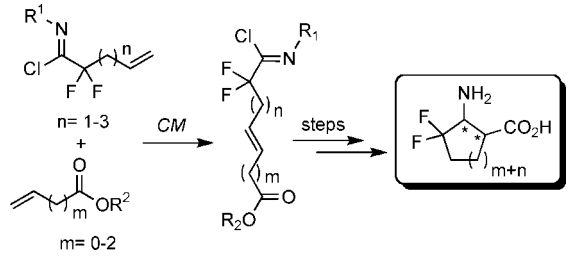

The synthesis of enantiomerically pure, cyclic, γ,γ-difluorinated β-amino acids with various ring sizes has been carried out with a cross-metathesis (CM) reaction being one of the key steps, followed by a Dieckmann-type condensation to bring about the cyclization. Subsequent catalytic hydrogenation under microwave irradiation with (−)-8-phenylmenthol as a chiral auxiliary led to the successful chemo- and diastereoselective chemical reduction of the resulting cyclic β-enamino esters. The efficiency and scope of the CM reaction with different types of fluorinated imidoyl chlorides and unsaturated esters has also been studied in order to determine the optimal reaction conditions with regard to selectivity and reactivity.

Introduction

The main drawback with using bioactive peptides as drugs is their metabolic lability, which results in poor bioavailability. This problem can be addressed, however, by introducing nonproteinogenic amino acids, such as β-amino acids,[1] into the peptidic structure, which enhances the stability of the resulting compounds by rendering their amide bonds unrecognizable to proteolytic enzymes.[2] Moreover, non-natural oligomers of β-amino acids (β-peptides)[3] are able to adopt well-defined secondary structures (helices, turns, and sheets) and usually remain stable toward enzymatic attack. In addition, many of these compounds have been reported to be antibiotics and antifungals[4] as well as potential inhibitors of protein−protein interactions.[5]

Of particular interest are those amino acids in which both the β-amino and the acid functionalities are attached to an aliphatic ring, e.g., β[2,3]-amino acids or 2-aminocycloalkanecarboxylic acids (2-ACACs).[6] Among these, several five- and six-membered derivatives have been shown to exhibit antibacterial activity. Examples include cispentacin,[7] a naturally occurring antifungal agent against *Candida albicans* infections, its synthetic derivative PLD-118, which is currently in clinical trials,[8] and the 2-aminocyclohexenecarboxylic acid BAY 9379 (Chart

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§ Dedicated to Prof. Josep Font on the occasion of his 70th birthday.

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(1) (a) Cardillo, G.; Tomasini, C. *Chem. Soc. Rev.* **1996**, *25*, 117–128. (b) Ojima, I.; Lin, S.; Wang, T. *Curr. Med. Chem.* **1999**, *6*, 927–954.

(2) Adessi, C.; Soto, C. *Curr. Med. Chem.* **2002**, *9*, 963–978.

(3) (a) Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219–3232. (b) Seebach, D.; Beck, A. K.; Bierbaum, D. J. *Chem. Biodiversity* **2004**, *1*, 1111–1239. (c) Seebach, D.; Hook, D. F.; Glättli, A. *Biopolymers (Pept. Sci.)* **2006**, *84*, 23–37. (d) Wu, Y. D.; Han, W.; Wang, D. P.; Zhao, Y. L. *Acc. Chem. Res.* **2008**, *41*, 1418–1427. (e) Seebach, D.; Gardiner, J. *Acc. Chem. Res.* **2008**, *41*, 1366–1375.

(4) (a) Porter, E. A.; Wang, X.; Lee, H.; Weisblum, B.; Gellman, S. H. *Nature (London)* **2000**, *404*, 565–565. (b) Karlsson, A. J.; Pomerantz, W. C.; Weisblum, B.; Gellman, S. H.; Palecek, S. P. *J. Am. Chem. Soc.* **2006**, *128*, 12630–12631.

(5) Kritzer, J. A.; Stephens, O. M.; Guarracino, D. A.; Reznik, S. K.; Schepartz, A. *Biorg. Med. Chem.* **2005**, *13*, 11–16.

(6) Fülöp, F. *Chem. Rev.* **2001**, *101*, 2181–2204.

(7) (a) Oki, T.; Hirano, M.; Tomatsu, K.; Numata, K.; Kamei, H. *J. Antibiot.* **1989**, *42*, 1756–1762. (b) Kawabata, K.; Inamoto, Y.; Sakane, K.; Iwamoto, T.; Hashimoto, S. *J. Antibiot.* **1990**, *43*, 513–518. (c) Benedek, G.; Palkó, M.; Wéber, E.; Martinek, T. A.; Forró, E.; Fülöp, F. *Eur. J. Org. Chem.* **2008**, 3724–3730.

(8) Mittendorf, J.; Benet-Buchholz, J.; Fey, P.; Mohrs, K.-H. *Synthesis* **2003**, 136–140.

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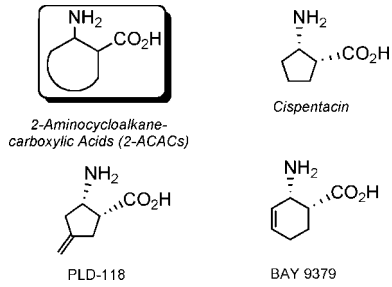
CHART 1. Biologically Active Cyclic β-Amino Acids



1). However, in contrast to linear β-amino acids,[9] the synthesis of cyclic β-amino acids has been explored to a much lesser extent.[10]

The chemistry of fluorinated analogues of β-amino acids is receiving more and more attention as the benefits conferred to organic molecules when fluorine is substituted for hydrogen become clearer.[11] So far, however, most of the reported examples focus on the synthesis of acyclic compounds.[12] In fact, the only examples of cyclic derivatives that have been described to date are a racemic difluorinated analogue of cispentacin[13] and a fluoropyranose containing a $\beta^{2,2}$-amino acid unit.[14] The lack of a general synthetic strategy, coupled with our current interest in obtaining various types of fluorinated nitrogen-containing heterocycles with the aid of metathesis reactions,[15] led us to embark on the development of two complementary

SCHEME 1. Two Synthetic Strategies for the Preparation of Cyclic Fluorinated β-Amino Acid Derivatives

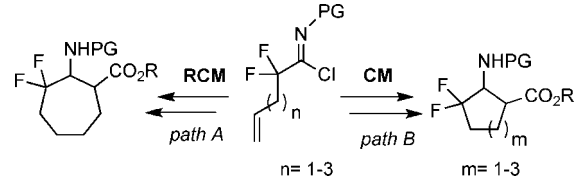
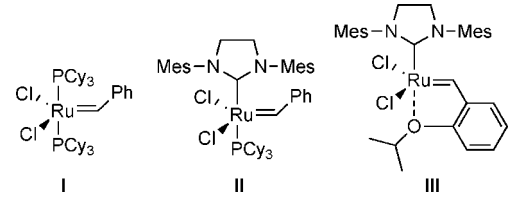


CHART 2. Structures of Ruthenium Catalysts I−III



synthetic routes for the preparation of five- to seven-membered difluoro $\beta^{2,3}$-amino acid derivatives with a CF_2 group next to the amino group. To this end, we used unsaturated fluorinated imidoyl chlorides and esters as starting materials.[16] In a first approach, a ring-closing metathesis (RCM)-based protocol (path A) efficiently led to the preparation of seven-membered rings.[17] A second strategy employing a cross-metathesis (CM) reaction (path B) followed by chemoselective hydrogenation and a Dieckmann-type cyclization proved to be more flexible in accessing different ring sizes (Scheme 1).[18]

Cross-metathesis (CM) reactions are currently witnessing a tremendous rise in popularity since new and more reactive catalysts such as **I**−**III** (Chart 2) have become available.[19] This reaction, however, has two main drawbacks, namely the lack of control in product selectivity when using two different olefins and the low stereoselectivity associated with the newly formed double bond. Recently, a general model for predicting product selectivity has been proposed by Grubbs and co-workers based on the ability of the olefins to homodimerize as well as on the reactivity of the corresponding homodimers under metathesis conditions.[20] According to this model, olefins can be classified into four types (I−IV), each with decreasing reactivity toward CM reactions.

A wide variety of nitrogen-containing olefins has been employed in CM reactions,[19c] including protected amines and amino acids,[21] amides,[22] ureas,[23] nitriles,[24] and nitro compounds.[25] In contrast, unsaturated imidoyl halides have not been

(9) (a) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991–8035. (b) Cole, D. C. *Tetrahedron* **1994**, *50*, 9517–9582. (c) *Enantioselective Synthesis of β-Amino Acids*; 2nd ed.; Juaristi, E. C., Soloshonok, V. A., Eds.; Wiley-VCH Ltd.: New York, 2005.

(10) (a) Kuhl, A.; Hahn, M. G.; Dumié, M.; Mittendorf, J. *Amino Acids* **2005**, *29*, 89–100. (b) Fülöp, F.; Martinek, T. A.; Tóth, G. K. *Chem. Soc. Rev.* **2006**, *35*, 323–334. (c) Miller, J. A.; Nguyen, S. B. T. *Mini-Rev. Org. Chem.* **2005**, *2*, 39–45.

(11) See, for example: (a) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308–319. (b) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881–1886.

(12) (a) Soloshonok, V. A.; Soloshonok, I. V.; Kukhar, V. P.; Svedas, V. K. *J. Org. Chem.* **1998**, *63*, 1878–1884. (b) Fustero, S.; Pina, B.; García de la Torre, M.; Navarro, A.; Ramírez de Arellano, C.; Simón, A. *Org. Lett.* **1999**, *1*, 977–980. (c) Marcotte, S.; Pannecoucke, X.; Feasson, C.; Quirion, J.-C. *J. Org. Chem.* **2001**, *64*, 8461–8464. (d) Fustero, S.; Salavert, E.; Pina, B.; Ramírez de Arellano, C.; Asensio, A. *Tetrahedron* **2001**, *57*, 6475–6486. (e) Crousse, B.; Narizuka, S.; Bonnet-Delpon, D.; Bégué, J.-P. *Synlett* **2001**, 679–681. (f) Ohkura, H.; Handa, M.; Katagiri, T.; Uneyama, K. *J. Org. Chem.* **2002**, *67*, 2692–2695. (g) Fustero, S.; Pina, B.; Salavert, E.; Navarro, A.; Ramírez de Arellano, M. C.; Simón Fuentes, A. *J. Org. Chem.* **2002**, *67*, 4667–4679. (h) Staas, D. D.; Savage, K. L.; Homnick, C. F.; Tsou, N. N.; Ball, R. G. *J. Org. Chem.* **2002**, *67*, 8276–8279. (i) Soloshonok, V. A.; Ohkura, H.; Sorochinsky, A.; Voloshin, N.; Markovsky, A.; Belik, M.; Yamazaki, T. *Tetrahedron Lett.* **2002**, *43*, 5445–5448. (j) Vidal, A.; Nefzi, A.; Houghten, R. A. *J. Org. Chem.* **2002**, *67*, 8268–8272. (k) Sorochinsky, A.; Voloshin, N.; Markovsky, A.; Belik, M.; Yasuda, N.; Uekusa, H.; Ono, T.; Berbasov, D. O.; Soloshonok, V. A. *J. Org. Chem.* **2003**, *68*, 7448–7454. (l) Hook, D.; Gessier, F.; Noti, C.; Kast, P.; Seebach, D. *ChemBioChem* **2004**, *5*, 691–706. (m) Chung, W. J.; Omote, M.; Welch, J. T. *J. Org. Chem.* **2005**, *70*, 7784–7787. (n) Fustero, S.; Jiménez, D.; Sanz-Cervera, J. F.; Sánchez-Roselló, M.; Esteban, E.; Simón-Fuentes, A. *Org. Lett.* **2005**, *7*, 3433–3436. (o) Huguenot, F.; Brigaud, T. *J. Org. Chem.* **2006**, *71*, 2159–2162. (p) Shimada, T.; Yoshioka, M.; Konno, T.; Ishihara, T. *Chem. Commun.* **2006**, 3628–3630. (q) Edmonds, M. K.; Graichen, F. H. M.; Gardiner, J.; Abell, A. D. *Org. Lett.* **2008**, *10*, 885–887. (r) Michaut, V.; Metz, F.; Paris, J.-M.; Plaquevent, J.-C. *J. Fluorine Chem.* **2007**, *128*, 500–506. (s) Boyer, N.; Gloanec, P.; De Nanteuil, D.; Jubault, P.; Quirion, J.-C. *Tetrahedron* **2007**, *63*, 12352–12366.

(13) Mittendorf, J.; Kunisch, F.; Matzke, M.; Militzer, H.-C.; Schmidt, A.; Schönfeld, W. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 433–436.

(14) Vera-Ayoso, Y.; Borrachero, P.; Cabrera-Escribano, F.; Diánez, M. J.; Estrada, M. D.; Gómez-Guillén, M.; López-Castro, A.; Pérez-Garrido, S. *Tetrahedron: Asymmetry* **2001**, *12*, 2031–2041.

(15) (a) Fustero, S.; Sánchez-Roselló, M.; Jiménez, D.; Sanz-Cervera, J. F.; del Pozo, C.; Aceña, J. L. *J. Org. Chem.* **2006**, *71*, 2706–2714. (b) Fustero, S.; Catalán, S.; Piera, J.; Sanz-Cervera, J. F.; Fernández, B.; Aceña, J. L. *J. Org. Chem.* **2006**, *71*, 4010–4013. (c) Fustero, S.; Sánchez-Roselló, M.; Rodrigo, V.; del Pozo, C.; Sanz-Cervera, J. F.; Simón, A. *Org. Lett.* **2006**, *8*, 4129–4132. (d) Fustero, S.; Sánchez-Roselló, M.; Rodrigo, V.; Sanz-Cervera, J. F.; Piera, J.; Simón-Fuentes, A.; del Pozo, C. *Chem.*−*Eur. J.* **2008**, *14*, 7019–7029.

(16) It should be noted that fluorinated imidoyl halides constitute readily available building blocks for the synthesis of a variety of fluorine-containing molecules: (a) Uneyama, K. *J. Fluorine Chem.* **1999**, *97*, 11–25. (b) Uneyama, K.; Amii, H.; Katagiri, T.; Kobayashi, T.; Hosokawa, T. *J. Fluorine Chem.* **2005**, *126*, 165–171.

(17) Fustero, S.; Bartolomé, A.; Sanz-Cervera, J. F.; Sánchez-Roselló, M.; García Soler, J.; Ramírez de Arellano, C.; Simón Fuentes, A. *Org. Lett.* **2003**, *5*, 2523–2526.

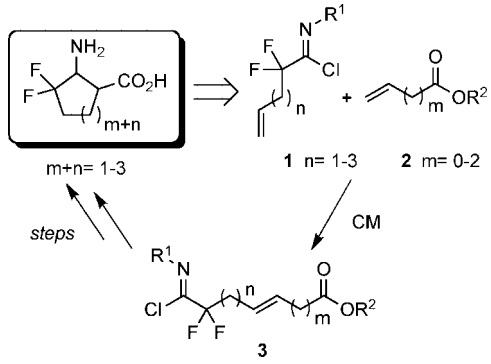
(18) For a preliminary communication, see: Fustero, S.; Sánchez-Roselló, M.; Sanz-Cervera, J. F.; Aceña, J. L.; del Pozo, C.; Fernández, B.; Bartolomé, A.; Asensio, A.; Ramírez de Arellano, C. *Org. Lett.* **2006**, *8*, 4633–4636.

(19) For reviews, see: (a) Schrodi, Y.; Pederson, R. L. *Aldrichimica Acta* **2007**, *40*, 45–52. (b) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900–1923. (c) Vernall, A. J.; Abell, A. D. *Aldrichim. Acta* **2003**, *36*, 93–105. For leading references, see: (d) Crowe, W. E.; Zhang, Z. J. *J. Am. Chem. Soc.* **1993**, *115*, 10998–10999. (e) Blackwell, H. E.; O'Leary, D. J.; Chatterjee, A. K.; Washenfelder, R. A.; Bussmann, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 58–71. (f) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783–3784.

(20) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370.

(21) Biagini, S. C. G.; Gibson, S. E.; Keen, S. P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2485–2499.

SCHEME 2. Synthetic Strategy for the Preparation of Cyclic Fluorinated β-Amino Acids based on the CM Reaction between Imidoyl Chlorides 1 and Esters 2



viewed as suitable coupling partners in CM processes up to this point, mostly due to their instability. Nevertheless, α-fluorinated imidoyl halides are relatively stable[16] and have thus been employed as starting substrates for the synthesis of different types of fluorinated molecules.[26] We anticipated that, according to Grubbs' model,[20] these imidoyl halides would behave as either type I or II olefins in CM reactions, depending on the catalyst employed. In fact, in a previous communication, we described the use of unsaturated α,α-difluoroimidoyl chlorides in selective CM reactions with acrylates and the further application of the resulting cross-coupled products to the synthesis of fluorinated cyclic β-amino acid derivatives.[18] This paper describes in full the scope and limitations of this methodology for the preparation of enantiomerically pure, cyclic, fluorinated β-amino acids.

Results and Discussion

The first step in our strategy to synthesize cyclic fluorinated β-amino acids was the cross-metathesis (CM) reaction between imidoyl chlorides **1** and unsaturated esters **2** to afford cross-coupling products **3** (Scheme 2).

Given the various possible reaction pathways (due to the use of chains with different lengths in both imidoyl chloride and ester starting materials), we first decided to examine the CM reaction between imidoyl chlorides and esters in order to find the best route to products **3** in terms of selectivity and reactivity.

A number of unsaturated fluorinated imidoyl chlorides **1** was prepared from the corresponding carboxylic acids **5** through treatment with a primary amine and $PPh_3/CCl_4/Et_3N$.[27] The synthesis of carboxylic acids **5a**−**c** by means of a sigmatropic rearrangement of allyl chlorodifluoroacetates **4a**−**c** was carried out as previously reported,[28] whereas the preparation of the longer analogues **5d**,**e** was achieved by subjecting the starting α-ketoesters **6a**,**b**[29] to difluorination with Deoxofluor[30] and subsequent hydrolysis. Carboxylic acids **5a**−**e** were then transformed into the corresponding imidoyl chlorides **1a**−**e**, in accordance with the methodology described above[27] (Scheme 3).

We initially tested the cross-metathesis reaction of imidoyl chloride **1a** with unsaturated esters **2** bearing a remote olefin in the α-, β-, or γ-position in relation to the ester functionality. For this we used second-generation Grubbs catalyst **II**, obtaining the corresponding cross-coupled products **3** with a varied degree of efficiency depending on the ester used and the reaction conditions. These results are summarized in Table 1. When using CH_2Cl_2 as solvent, for example, the reaction with an excess (2 equiv) of ethyl 4-pentenoate **2a** ($m = 2$), benzyl 3-butenoate **2b**, or methyl 3-butenoate **2c** ($m = 1$) (type I olefins, rapid homodimerization) afforded the homodimers of reactants **7** and **8a**−**c**, therefore decreasing the yield of the desired products **3a**−**c** (entries 1−3).[31] A longer reaction time only caused a slight alteration in the product ratio (entry 4). The *E*/*Z* selectivity was moderate in all cases, as determined with the aid of ^{19}F NMR. Increasing the reaction temperature and changing the solvent to toluene likewise failed to improve the results due to the fact that the ester double bond in **2c** ($m = 1$) partially isomerized under the reaction conditions, either before[32] or after[15a] the metathesis process, thus affording a complex mixture of products (entry 5). The best results with regard to yield and selectivity came with the use of less reactive olefins such as acrylates (type II olefins, with a slower homodimerization than type I). Thus, the reaction with ethyl acrylate **2d** ($m = 0$) was quite slow in refluxing CH_2Cl_2, affording compound **3d** in yields ranging from 40 to 70% and with almost complete *E* selectivity (entries 6−8). In this case ($m = 0$), no ester homodimer formation was observed. Moreover, the use of toluene as a solvent along with a higher reaction temperature and a greater amount of acrylate led to the isolation of **3d** in excellent yield (entry 9).[33] Under these conditions, the imidoyl chloride homodimer **7** probably reacted with acrylate **2d** through a secondary metathesis process, thus affording the desired cross-coupled product **3d**. Most importantly, the imidoyl chloride function withstood the metathesis conditions, thus providing a route for its further functionalization.

A two-step procedure, namely the self-dimerization of imidoyl chloride **1a** followed by a CM with unsaturated esters, was also evaluated. In this way, homodimer **7** was prepared in good yield (75%) and with 9:1 *E*/*Z* selectivity under the initially tested conditions (catalyst **II**, CH_2Cl_2, reflux).[34] A small amount of compound **9** was also obtained, resulting from the phenyl group being incorporated from the catalyst. Next, compound **7** reacted with methyl 3-butenoate **2c** in the presence of catalyst **II** and refluxing toluene to give the coupled product **3c** in moderate yield and with moderate selectivity. In contrast, the reaction with ethyl acrylate **2d** afforded enoate **3d** in the same way as

(22) Choi, T. L.; Chatterjee, A. K.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1277–1279.
(23) Formentín, P.; Gimeno, N.; Steinke, J. H. G.; Vilar, R. *J. Org. Chem.* **2005**, *70*, 8235–8238.
(24) Hoveyda, H. R.; Vézina, M. *Org. Lett.* **2005**, *7*, 2113–2116.
(25) Marsh, G. P.; Parsons, P. J.; McCarthy, C.; Corniquet, X. G. *Org. Lett.* **2007**, *9*, 2613–2616.
(26) See, for example: (a) Fustero, S.; Salavert, E.; Pina, B.; Ramírez de Arellano, C.; Asensio, A. *Tetrahedron* **2001**, *57*, 6475–6486. (b) Fustero, S.; Pina, B.; Salavert, E.; Navarro, A.; Ramírez de Arellano, M. C.; Simón Fuentes, A. *J. Org. Chem.* **2002**, *67*, 4667–4679. (c) Fustero, S.; García Soler, J.; Bartolomé, A.; Sánchez-Roselló, M. *Org. Lett.* **2003**, *5*, 2707–2710.
(27) Uneyama, K.; Tamura, K.; Mizukami, H.; Maeda, K.; Watanabe, H. *J. Org. Chem.* **1993**, *58*, 32–35.
(28) Greuter, H.; Lang, R. W.; Romann, A. J. *Tetrahedron Lett.* **1988**, *29*, 3291–3294.
(29) Macritchie, J. A.; Silcock, A.; Willis, C. L. *Tetrahedron: Asymmetry* **1997**, *8*, 3895–3902.
(30) Lal, G. S.; Pez, G. P.; Pesaresi, R. J.; Prozonic, F. M.; Cheng, H. *J. Org. Chem.* **1999**, *64*, 7048–7054.
(31) Purification of cross-coupled products **3a**−**c** by means of column chromatography was hampered by the difficult separation of ester homodimers **8**.
(32) For a review, see: Schmidt, B. *Eur. J. Org. Chem.* **2004**, 1865–1880.
(33) The isomerization of the double bond in the reaction of **1a** with acrylates was thwarted by an electronic effect of the CF_2 group. For a mechanistic explanation, see ref 15a.
(34) The same reaction in the presence of first-generation Grubbs catalyst **I** afforded only 20% of homodimer **7** after 48 h.

SCHEME 3. Synthesis of Fluorinated Imidoyl Chlorides 1a−e

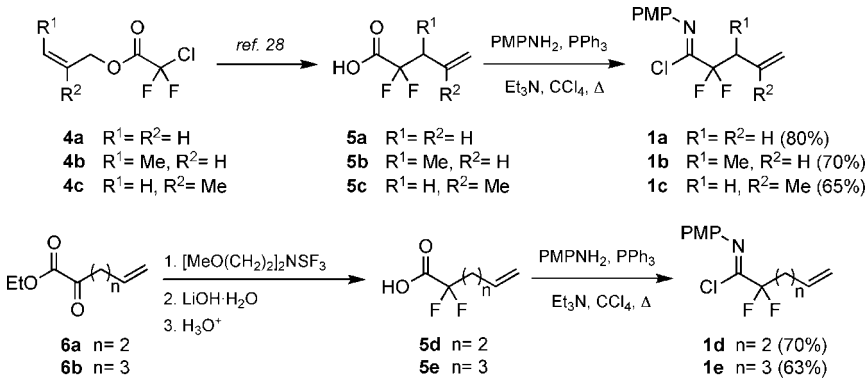
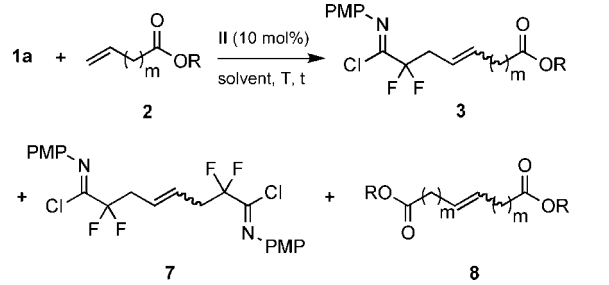


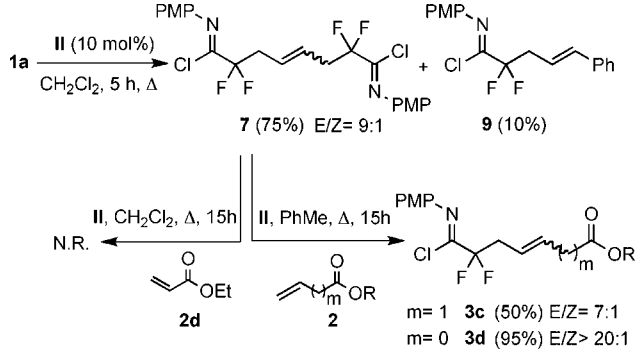
TABLE 1. CM of Imidoyl Chloride 1a with Unsaturated Esters 2



entry	*m*	R	**2** (equiv)	solvent/ *T* (°C)	time (h)	**3**[a] (%)	*E*/*Z* ratio[b]	**7** (%)	**8** (%)
1	2	Et	**2a** (2)	CH_2Cl_2/Δ	3	**3a** (70)	3:1	13	**8a** (10)
2	1	Bn	**2b** (2)	CH_2Cl_2/Δ	4	**3b** (60)	10:1	10	**8b** (13)
3	1	Me	**2c** (2)	CH_2Cl_2/Δ	4	**3c** (60)	10:1	10	**8c** (25)
4	1	Me	**2c** (2)	CH_2Cl_2/ Δ	15	**3c** (70)	7:1	14	**8c** (19)
5	1	Me	**2c** (2)	PhMe/Δ	15	*c*			
6	0	Et	**2d** (2)	CH_2Cl_2/Δ	5	**3d** (40)[d]	>20:1	16	
7	0	Et	**2d** (2)	CH_2Cl_2/Δ	15	**3d** (60)[d]	>20:1	8	
8	0	Et	**2d** (3)	CH_2Cl_2/Δ	48	**3d** (70)	>20:1	6	
9	0	Et	**2d** (5)	PhMe/Δ	15	**3d** (95)	>20:1		**8d** (4)[e]

[a] Isolated yields after flash chromatography purification. [b] Ratio calculated from signal integration in the ^{19}F NMR spectra and/or with the aid of GC−MS. [c] Complex mixture. [d] Starting material was recovered (30−40%) after purification. [e] Determined with the aid of GC−MS.

SCHEME 4. Synthesis and Reactivity of Imidoyl Chloride Homodimer 7



when starting from **1a** (see Table 1, entry 9). It is worth noting that the identical reaction carried out in refluxing CH_2Cl_2 only produced recovered starting material **7** (Scheme 4).

While homodimer **7** of **1a** is easily formed in refluxing dichloromethane (conditions for which olefins were categorized),[20] it does not react with other olefins in this solvent. This means that, in the presence of second generation catalyst **II**, imidoyl chloride **1a** acts as a type II olefin according to Grubbs' model. However, in refluxing toluene, **1a** could be regarded as a type I olefin because its homodimer **7** is able to react selectively with other olefins under these conditions.

SCHEME 5. CM of 1a with Ethyl Methacrylate

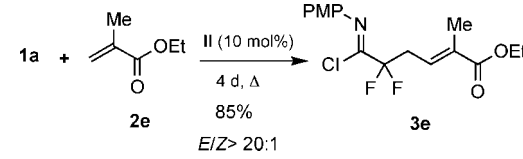
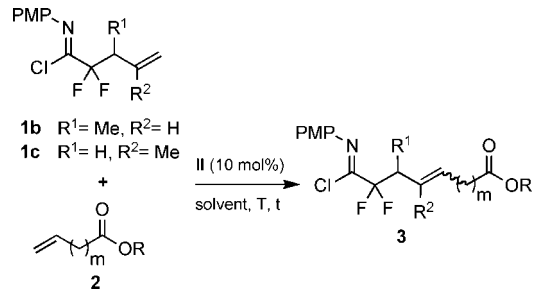


TABLE 2. CM of Imidoyl Chlorides 1b,c with Unsaturated Esters 2



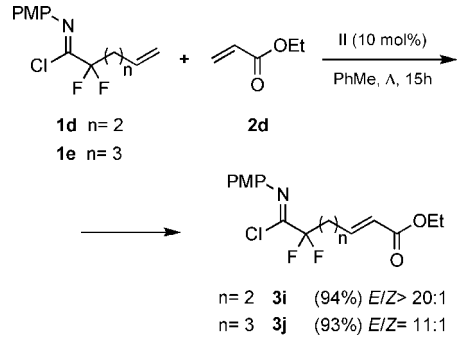
entry	**1**[a] (%)	*m*	R	**2** (equiv)	solvent/ *T* (°C)	time (h)	**3**[b] (%)	*E*/*Z* ratio[c]
1	**1b** (10)	1	Me	**2c**(2)	CH_2Cl_2/Δ	15	**3f** (75)[d]	6:1
2	**1b** (36)	0	Et	**2d**(3)	CH_2Cl_2/Δ	48	**3g** (40)	>20:1
3	**1b** (30)	0	Et	**2d**(5)	PhMe/Δ	15	**3g** (50)	>20:1
4	**1c** (32)	1	Me	**2c**(2)	CH_2Cl_2/Δ	15	**3h** (40)[e]	5:1
5	**1c**	0	Et	**2d**(3)	CH_2Cl_2/Δ	48	*f*	

[a] Starting imidoyl chloride recovered. [b] Isolated yields after flash chromatography purification. [c] Ratio calculated from integration in the ^{19}F NMR spectra and/or with the aid of GC−MS. [d] 15% of ester homodimer **8c** was also detected with the aid of GC−MS. [e] 27% of ester homodimer **8c** was also detected with the aid of GC−MS. [f] Complex mixture.

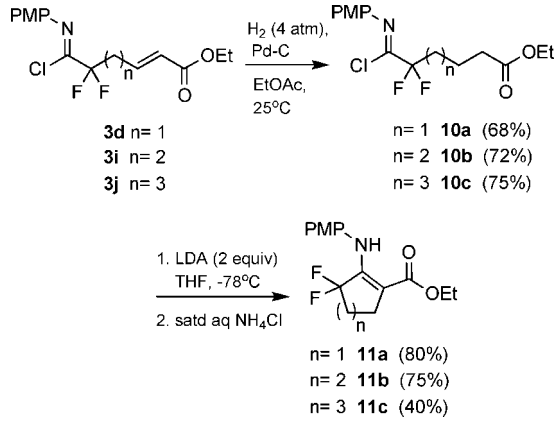
Type III olefins (unable to homodimerize) such as ethyl methacrylate **2e** were less effective under the optimized conditions (catalyst **II**, refluxing toluene), yielding only low conversions (<20%). However, the use of neat methacrylate and prolonged reaction times (4 days) led to the preparation of the trisubstituted cross-coupled product **3e** as a single isomer (Scheme 5).

The introduction of methyl groups into imidoyl chlorides **1b**,**c** decreased their reactivity toward CM reactions in comparison to that of **1a** (Table 2). For instance, **1b**, with a methyl group in allylic position, reacted well with methyl 3-butenoate **2c** to give the corresponding cross-metathesis product **3f** (entry 1), but yields were much lower with ethyl acrylate **2d** in both

SCHEME 6. CM of Imidoyl Chlorides 1d,e with Ethyl Acrylate



SCHEME 7. Synthesis of Cyclic Enamino Esters 11



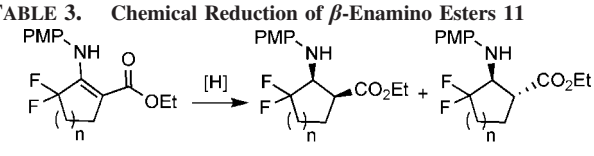
dichloromethane and toluene (entries 2 and 3). As expected, **1c**, with a methyl group on an olefinic carbon, was less reactive, affording the CM product **3h** in moderate yield only after reaction with methyl 3-butenoate **2c** (entry 4). Indeed, reaction with ethyl acrylate **2d** failed to give the CM product (entry 5). Both substrates **1b** and **1c** could thus be regarded as type III olefins, since they did not form the corresponding homodimers and reacted sluggishly with ethyl acrylate (a type II olefin).

Substrates **1d**,**e**, which contain longer unsaturated chains, were used to prepare imidoyl chlorides **3i**,**j** in excellent yields through a CM reaction with ethyl acrylate **2d** under the same conditions that were found to be optimal in the case of **1a** (catalyst **II**, refluxing toluene) (Scheme 6). These results should be compared to the more difficult preparation of CM products **3a**−**c**, which have the same chain length, starting from **1a** and esters other than acrylates (see Table 1, entries 1−5).

Once the cross-metathesis products **3d**,**i**,**j** had been obtained, we were able to prepare 5-, 6-, and 7-membered β-amino acid derivatives, respectively.[18] After undergoing the CM reaction, olefin hydrogenation and a subsequent Dieckmann-type cyclization of these derivatives afforded β-enamino esters **11** (Scheme 7).

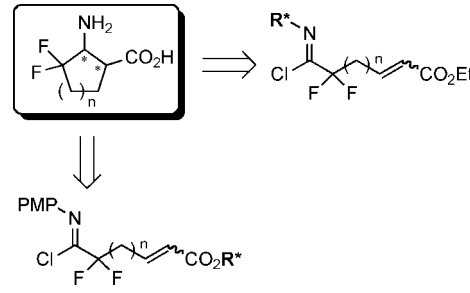
For the crucial stereoselective reduction step, various reducing agents were tested for their efficiency in affording β-amino acid derivatives **12** in racemic form (Table 3). Thus, cyclic compounds **11** were first reduced with $NaCNBH_3$[35] in THF/TFA at 0 °C, producing moderate yields and variable diastereoselectivities, depending on the ring size. Another attempt involved

TABLE 3. Chemical Reduction of β-Enamino Esters 11



		$NaCNBH_3$		$Zn(BH_4)_2$		HCO_2NH_4, Pd−C, microwave	
n	(±)-**12**	*dr* (*cis*/*trans*)	yield (%)	*dr* (*cis*:*trans*)	yield (%)	*dr* (*cis*:*trans*)	yield (%)
1	(±)-**12a**	52:48	70	94:6	90	>99:1	83
2	(±)-**12b**	88:12	70	85:15	80	>99:1	87
3	(±)-**12c**	96:4	60	97:3	87	>99:1	82

SCHEME 8. Strategies for the Asymmetric Synthesis of Cyclic Fluorinated β-Amino Acids



the use of $NaBH_4$ in CH_2Cl_2 in the presence of a Lewis acid (ZnI_2), as we had employed this method successfully in the past for the reduction of acyclic and cyclic fluorinated β-enamino esters.[26a,b] These reactions took place with good yields and better selectivities, which reached 94% de for the seven-membered derivative **12c**. Finally, we attempted a catalytic hydrogenation in order to obtain the corresponding *cis*-diastereoisomers. After several attempts, we found that hydrogenation under microwave irradiation in ethanol with Pd−C and HCO_2NH_4 as the hydrogen source reduced cyclic derivatives **11** in good yields to give *cis*-β-amino esters **12** exclusively, a procedure that worked well with several ring sizes (Table 3).

At this point, the next challenge was to prepare cyclic fluorinated β-amino acids in enantiomerically pure form.

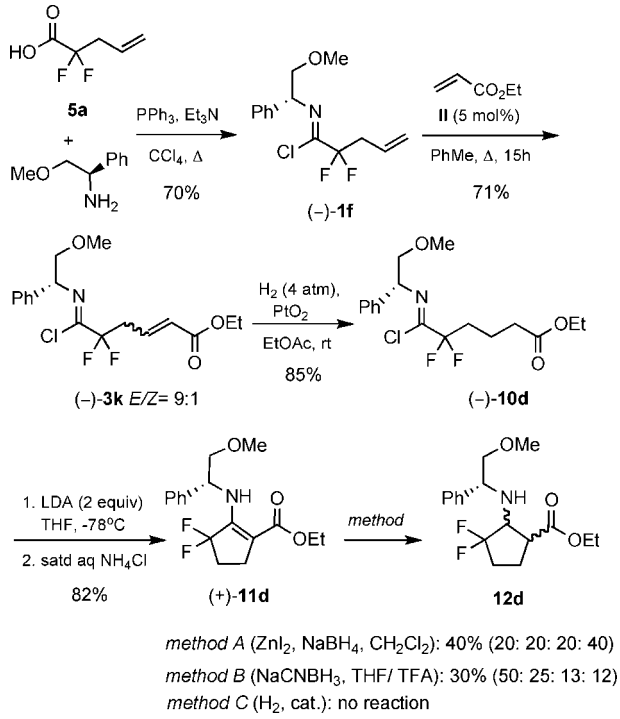
The chemo- and stereoselective reduction of chiral nonracemic β-enamino ester derivatives represents a simple and attractive route for obtaining enantiopure β-amino acids. Two approaches were considered, namely the incorporation of a chiral auxiliary either on the nitrogen atom of the starting imidoyl chloride or in the acrylic ester moiety (Scheme 8).[36] Thus, the CM reaction would give optically pure products, which could then be transformed into *N*-protected chiral β-amino esters. Finally, amine deprotection and ester hydrolysis would lead to the target compounds.

In the first approach, we decided to use the methyl ether of (*R*)-phenylglycinol because it had proven to be extremely efficient in the asymmetric synthesis of fluorinated cyclic α-amino acids.[15c,d] This chiral auxiliary was introduced through the preparation of the corresponding imidoyl chloride **1f** (Scheme 9), which was subjected to a CM reaction with ethyl acrylate under the optimized conditions (catalyst **II**, refluxing toluene). Next, olefin hydrogenation occurred chemoselectively in the presence of PtO_2 under H_2 pressure (4 atm) to give the

(35) (a) *Reduction by the Alumino- and Borohydrides in Organic Synthesis*, 2nd ed.; Seyden-Penne, J., Ed.; Wiley-VCH: New York, 1997. (b) See ref 17.

(36) The enantioselective hydrogenation of five-membered enamino ester **11a** with a ruthenium catalyst [Ru(COD)(Methallyl)$_2$] and a chiral ligand [(*S*)-BINAP] was also attempted with no success.

SCHEME 9. Use of (*R*)-Phenylglycinol Methyl Ether as Chiral Auxiliary



new imidoyl chloride (−)-**10d**, which was then cyclized to afford chiral enamino ester (+)-**11d** in good yield. Compound **11d** was subsequently reduced with the system $NaBH_4/ZnI_2$ in CH_2Cl_2 (Scheme 9, method A) to give a nonseparable mixture of the four possible diastereoisomers of **12d** in a 20:20:20:40 ratio (GC-MS) and moderate yield (40%). In order to improve these results, we carried out the reduction with $NaCNBH_3$ in THF/TFA (method B), but once again, all four diastereoisomers were detected with the aid of GC−MS (50:25:13:12) in only 30% yield. Finally, we tried the catalytic hydrogenation (method C), but no reaction took place, regardless of whether PtO_2 and H_2 (900 psi) or phase-transfer conditions (HCO_2NH_4 and Pd−C) were used.

In view of these poor results in terms of yield and diastereoselectivity, we decided to change the strategy by incorporating a chiral auxiliary [(+)-8-phenylmenthol] into the ester moiety (Scheme 10). Thus, the synthetic strategy was repeated starting from imidoyl chlorides **1a** and **1d**, which were coupled with the acrylic ester of (−)-8-phenylmenthol, which was previously prepared in the laboratory.[37] The CM reaction, in which Grubbs catalyst **II** in refluxing toluene was used, took place in good yields and with high *E/Z* selectivity. The cross-coupling products (+)-**3l**,**m** were then hydrogenated and cyclized under the conditions outlined above to afford five- and six-membered chiral esters **11e**,**f** in good yields (Scheme 10). While the cyclopentane derivative (+)-**11e** was isolated exclusively in its enamino form, the six-membered analogue (−)-**11f** appeared as a 1:1 mixture of the imino and enamino tautomers, which were separated by means of flash chromatography.

The next step involved the diastereoselective reduction of the imino/enamino moiety. Several reducing agents were tested on the five-membered enamino ester (+)-**11e** (see Table 4). The reduction with $NaCNBH_3$ in THF/TFA gave a

(37) Whitesell, J. K.; Bhattacharya, A.; Buchanan, C. M.; Chen, H. H.; Deyo, D.; James, D.; Liu, C.-L.; Minton, M. A. *Tetrahedron* **1986**, *42*, 2993–3001.

SCHEME 10. Use of (1*R*,2*S*,5*R*)-8-Phenylmenthol as Chiral Auxiliary

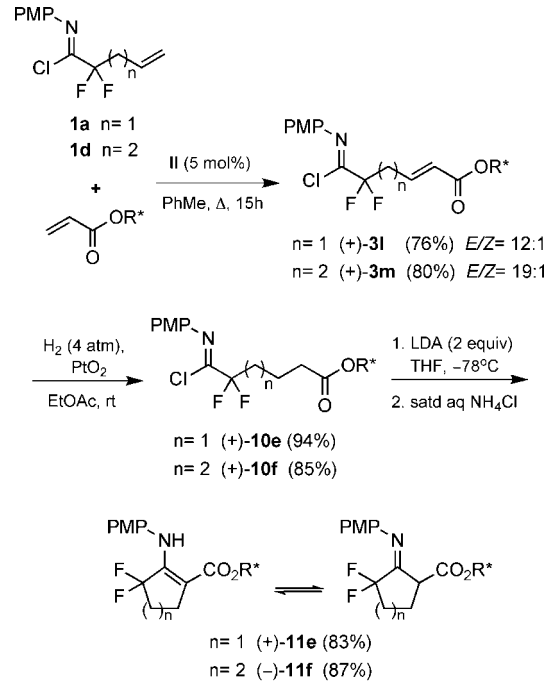
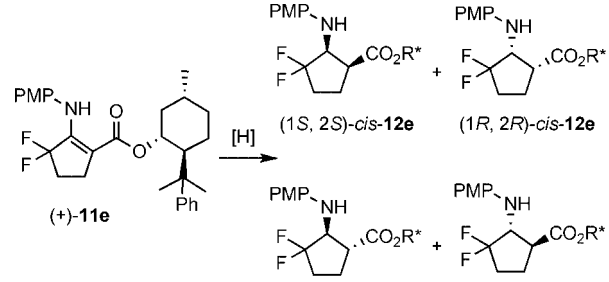


TABLE 4. Chemical Reduction of β-Enamino Ester (+)-11e

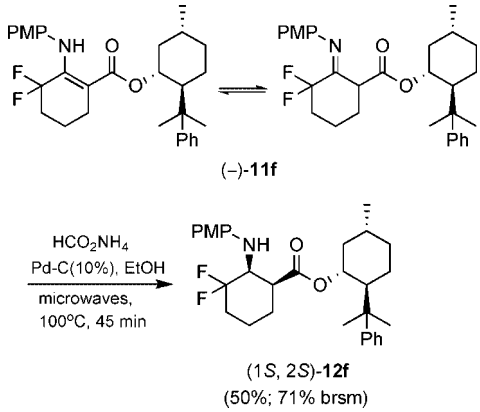


entry	[H]	dr (*cis*:*cis*: *trans*:*trans*)[a]	**12e** overall yield[b] (%)
1	$NaCNBH_3$	48:25:14:13	60
2	$Zn(BH_4)_2$	62:11:15:12	68
3	H_2 (50 atm), PtO_2	88:12:0:0	40[c]
4	HCO_2NH_4, Pd−C, microwave	80:20:0:0	58[d]

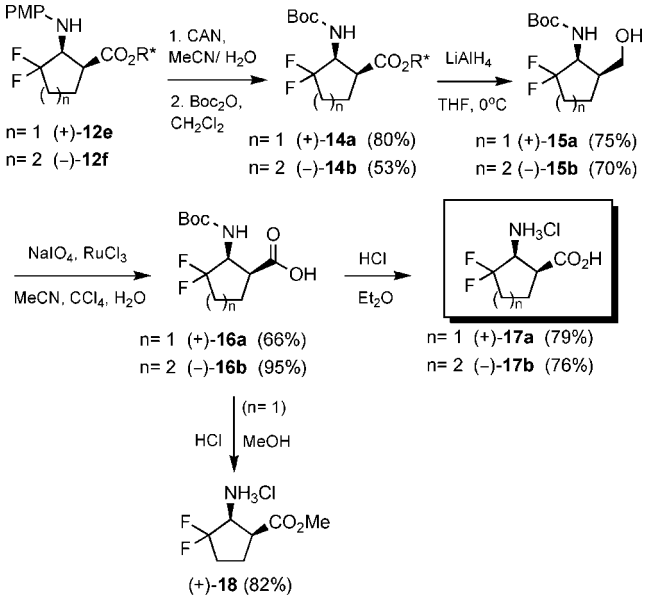
[a] Diastereomeric ratio determined with the aid of GC−MS. [b] Isolated yields after column chromatography. [c] A partial hydrogenation of the PMP group took place, making the purification difficult and lowering the chemical yield. [d] 77% yield based on recovered starting material. (Longer reaction times and higher temperatures led to no significant improvement in the conversion.)

mixture of the four possible diastereoisomers in a 48:25:14:13 ratio (as determined with the aid of GC−MS) and 60% yield (entry 1). With the reducing system $NaBH_4/ZnI_2$ in CH_2Cl_2, the result was similar in terms of chemical yield and stereoselectivity (entry 2), while catalytic hydrogenation under high pressure (50 atm) in the presence of PtO_2 took place with good diastereoselectivity, but only moderate yield (entry 3). The best conditions were again those involving a phase-transfer catalysis hydrogenation under microwave irradiation. Thus, compound (+)-**11e** was reduced after 45 min at 100 °C in the presence of Pd−C and HCO_2NH_4 to

SCHEME 11. Diastereoselective Reduction of Compound (−)-11f



SCHEME 12. Final Deprotection of Chiral Amino Esters 12e,f



R*= (1*R*, 2*S*, 5*R*)-8-phenylmenthyl

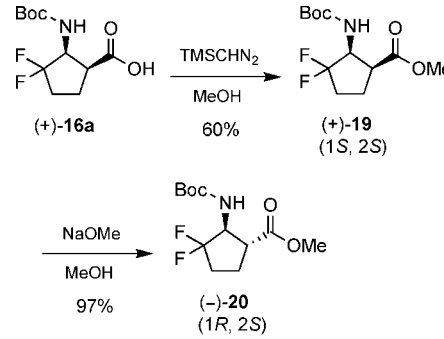
afford an 80:20 mixture of the *cis*-diastereoisomers **12e** in 58% yield (entry 4). These conditions were also applied to the cyclohexene derivative (−)-**11f** to afford the corresponding chiral amino ester (−)-**12f** as the major product (Scheme 11).[38]

In all cases, the major diastereoisomer was separated by means of flash chromatography, and upon X-ray analysis of a *p*-bromobenzoate derivative (+)-**13**, its absolute configuration was found to be (1*S*,2*S*).[39]

To complete the synthesis, we undertook the removal of the amino acid protecting groups on compounds (+)-**12e** and (−)-**12f** (Scheme 12). To achieve this goal, we first changed the nitrogen protecting group from PMP to Boc in order to avoid PMP oxidation in subsequent steps. Thus, treatment of chiral amino esters **12e** and **12f** with CAN and subsequent acylation led to *N*-Boc chiral amino esters **14a** and **14b** in good yields. The removal of the chiral auxiliary was achieved through reduction with $LiAlH_4$ to give alcohols (+)-**15a** and (−)-**15b**,

(38) In this reaction, an 86:14 mixture of the *cis* diastereoisomers was obtained.

SCHEME 13. Epimerization of Five-Membered Amino Ester (+)-19



again with satisfactory yields for both ring sizes.[40] Oxidation of optically pure compounds **15** was accomplished through treatment with $NaIO_4$ and $RuCl_3$ in a mixture of MeCN, CCl_4, and H_2O. Finally, elimination of the *N*-Boc protecting group on cyclic amino acids (+)-**16a** and (−)-**16b** in acidic conditions (HCl in Et_2O) led to the desired cyclic fluorinated $\beta^{2,3}$-amino acids **17a** and **17b** in enantiomerically pure form. Amine deprotection on compound (+)-**16a** in MeOH as the solvent gave the corresponding methyl ester hydrochloride (+)-**18** (Scheme 12). Monoprotected amino acids **16** and **18** can be regarded as monomeric units for the further construction of fluorinated β-peptides.[41] It is worth noting that compound (+)-**17a** is a fluorinated analogue of the antifungal *ent*-cispentacin.[7]

Finally, we demonstrated that the *cis* β-amino acid (+)-**16a** can be converted into the corresponding *trans* diastereoisomer. Thus, *N*-Boc β-amino ester (+)-**19** was treated with sodium methoxide[42] in MeOH to yield its *trans* epimer (−)-**20** in excellent yield (Scheme 13).

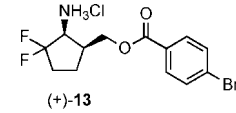
Conclusions

In conclusion, we have shown that fluorinated imidoyl chlorides are useful compounds in cross-metathesis reactions with unsaturated esters, providing an efficient starting point for the preparation of nitrogen-containing organofluorine compounds. In particular, the reaction between imidoyl chlorides **1** with various unsaturated chain lengths and an excess of ethyl acrylate in the presence of second-generation Grubbs catalyst **II** takes place in excellent yields and with high selectivities when toluene is used as the solvent. Thus, the compatibility of the imidoyl chloride functionality with the ruthenium catalyst once again demonstrated the versatility of these complexes. This methodology was then successfully used to synthesize cyclic fluorinated β-amino acids in enantiomerically pure form by using 8-phenylmenthol-derived acrylates as chiral auxiliaries.

Experimental Section

General Procedure for the Synthesis of Fluorinated Imidoyl Chlorides 1. PPh_3 (3.0 equiv) and Et_3N (1.2 equiv) were

(39) For the X-ray structure of (+)-**13**, see ref 18.



(40) In this manner, the chiral auxiliary 8-phenylmenthol was also recovered (70−80%).

(41) (a) Hook, D. F.; Gessier, F.; Noti, C.; Kast, P.; Seebach, D. *ChemBioChem* **2004**, *5*, 691–706. (b) See ref 3.

(42) Tang, W.; Wu, S.; Zhang, X. *J. Am. Chem. Soc.* **2003**, *125*, 9570–9571.

added to a cold (0 °C) solution of the corresponding carboxylic acid **5** (1.0 equiv) in CCl_4 (1 M). After the solution was stirred for 10 min, *p*-anisidine (1.2 equiv) was added, and the mixture was stirred under reflux for 3 h. The solvents were then removed under reduced pressure, and the residue was extracted with hexane and filtered. The filtrate was concentrated and purified through distillation under reduced pressure. Compounds **1a**,[43] **1d**,[18] **1e**,[18] and (−)-**1f**[15c] were previously described.

1-Chloro-2,2-difluoro-3-methyl-*N*-(4-methoxyphenyl)-4-penten-1-imine (1b). By means of the general procedure described above, 1.27 g of **1b** was obtained from 1.00 g (6.67 mmol) of 2,2-difluoro-3-methyl-4-pentenoic acid (**5b**) as a yellow oil (70% yield): bp 88−91 °C (2×10^{-2} Torr); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (d, J = 7.0 Hz, 3H), 3.00−3.10 (m, 1H), 3.61 (s, 3H), 5.02−5.09 (m, 2H), 5.61−5.73 (m, 1H), 6.72 (d, J = 9.0 Hz, 2H), 6.90 (d, J = 9.0 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.0 (t, $^3J_{CF}$ = 4.0 Hz), 43.0 (t, $^2J_{CF}$ = 23.3 Hz), 55.4, 114.1, 118.0 (t, $^1J_{CF}$ = 251.6 Hz), 118.8, 122.8, 124.2, 134.5 (t, $^3J_{CF}$ = 4.3 Hz), 134.5, 137.2 (t, $^2J_{CF}$ = 17.5 Hz), 158.4; ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −104.96 (dd, J_{FF} = 254.1 Hz, J_{FH} = 12.9 Hz, 1F), −106.79 (dd, J_{FF} = 254.1 Hz, J_{FH} = 16.0 Hz, 1F); HRMS (EI) calcd for $C_{13}H_{14}ClF_2NO$ (M^+) 273.0575, found 273.0580.

General Procedure for the Cross-Metathesis Reaction: Synthesis of Imidoyl Chlorides 3, 7, and 9. Unsaturated ester **2** (2.0 or 5.0 equiv) and second-generation ruthenium alkylidene catalyst **II** (5−10 mol %) were added successively to a solution of fluorinated imidoyl chloride **1** (1.0 equiv) in CH_2Cl_2 or PhMe (0.25 M). The mixture was stirred at 95 °C under argon atmosphere overnight. The solvent was then removed under reduced pressure, and the crude reaction mixture was purified by means of flash column chromatography on silica gel with the appropriate solvents. Compounds **3d**, **3i**, **3j**, and (+)-**3l** were previously described.[18]

(+)-(*E*)-(1′*R*,2′*S*,5′*R*)-8′-Phenylmenthyl 7-chloro-6,6-difluoro-7-(4-methoxyphenylimino)-2-heptenoate [(+)-3m]. By means of the general procedure described above, 825 mg of **3m** was obtained from 540 mg (1.97 mmol) of **1d** and 1.10 g (3.94 mmol) of (+)-8-phenylmenthyl acrylate[37] as a yellow oil (80% yield) with an *E*/*Z* isomer ratio of 19:1, as determined by means of signal integration in the ^{19}F NMR. Data for the *E* isomer: R_f= 0.40 (hexane/ethyl acetate, 10:1); $[\alpha]^{25}_D$= +4.9 (*c* 1.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.78 (d, J = 6.4 Hz, 3H), 0.85−1.07 (m, 3H), 1.11 (s, 3H), 1.21 (s, 3H), 1.38−1.42 (m, 1H), 1.55−1.70 (m, 2H), 1.80 (br d, J = 12.2 Hz, 1H), 1.98−2.03 (m, 1H), 2.21−2.34 (m, 4H), 3.74 (s, 3H), 4.75 (dt, J = 10.7, 4.3 Hz, 1H), 5.19 (d, J = 15.6 Hz, 1H), 6.35 (d, J = 15.8 Hz, 1H), 6.86 (d, J = 9.0 Hz, 2H), 6.99−7.18 (m, 7H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.7, 24.2, 24.4 (t, $^3J_{CF}$ = 4.6 Hz), 26.4, 28.5, 31.2, 33.1 (t, $^2J_{CF}$= 24.2 Hz), 34.5, 39.5, 41.6, 50.4, 55.4, 74.1, 114.1, 117.6 (t, $^1J_{CF}$ = 246.7 Hz), 122.5, 123.3, 124.7, 125.3, 127.9, 136.6, 136.7 (t, $^2J_{CF}$ = 37.4 Hz), 145.1, 151.8, 158.7, 165.2. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −107.70 (t, J_{FH}= 15.5 Hz, 2F). HRMS (EI) calcd for $C_{30}H_{36}ClF_2NO_3$ (M^+): 531.2352, found: 531.2361.

General Procedure for the Chemoselective Hydrogenation of Olefins: Synthesis of Imidoyl Chlorides 10. Palladium on active carbon (10 wt %, 0.2 equiv) or platinum dioxide (0.2 equiv) was added to a solution of the enoate (1.0 equiv) in EtOAc (0.05 M). The resulting suspension was stirred in a medium pressure reactor with hydrogen (4 atm) for 24 h. The reaction mixture was then filtered through Celite. The filtrate was concentrated and purified by means of flash chromatography on silica gel with the appropriate solvents. Compounds **10a**, **10b**, **10c**, and (+)-**10e** were previously described.[18]

(+)-(*E*)-(1′*R*,2′*S*,5′*R*)-8′-Phenylmenthyl 7-chloro-6, 6-difluoro-7-(4-methoxyphenylimino)- heptanoate [(+)-10f]. By means of the general procedure described above, 650 mg of **10f** was obtained from 760 mg (1.43 mmol) of (+)-**3m** as a colorless oil (85% yield): R_f = 0.40 (hexane/ethyl acetate, 10:1); $[\alpha]^{25}_D$ = +7.2 (*c* 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.77 (d, J = 6.6 Hz, 3H), 0.80−1.06 (m, 3H), 1.10 (s, 3H), 1.21 (s, 3H), 1.38−1.40 (m, 4H), 1.53−1.60 (m, 2H), 1.64−1.72 (m, 3H), 1.91−1.99 (m, 1H), 2.05−2.19 (m, 2H), 3.73 (s, 3H), 4.73 (dt, J = 10.7, 4.3 Hz, 1H), 6.85 (d, J = 9.1 Hz, 2H), 7.06 (d, J = 9.1 Hz, 2H), 7.02−7.07 (m, 1H), 7.15−7.19 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.3 (t, $^3J_{CF}$ = 3.8 Hz), 21.7, 22.6, 24.0, 26.4, 28.6, 31.2, 31.5, 33.7, 34.5 (t, $^2J_{CF}$ = 23.6 Hz), 39.5, 41.7, 50.2, 55.3, 73.9, 114.1, 118.1 (t, $^1J_{CF}$ = 246.6 Hz), 123.1, 124.9, 125.3, 127.8, 137.0, 137.3 (t, $^2J_{CF}$ = 37.1 Hz), 151.8, 158.5, 172.3; ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −109.24 (t, J_{FH} = 16.4 Hz, 2F); HRMS (EI) calcd for $C_{30}H_{38}ClF_2NO_3$ (M^+) 533.2508, found 533.2504.

General Procedure for the Dieckmann-Type Cyclization: Synthesis of Imino/Enamino Esters 11. *N*-Butyllithium (2.5 M in hexane, 2.1 equiv) was added dropwise to a cold (−30 °C) solution of diisopropylamine (2.1 equiv) in THF (0.25 M). After being stirred for 30 min, the mixture was cooled to −78 °C and a solution of the corresponding imidoyl chloride **10** (1.0 equiv) in THF (0.12 M) was added slowly. The reaction mixture was stirred for 1 h at −78 °C, and then it was quenched with satd aq NH_4Cl. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The filtrate was concentrated and purified by means of flash chromatography on silica gel with the appropriate solvents. Compounds **11a**, **11b**, **11c**, and (+)-**11e** were previously described.[18]

(−)-(1′*R*,2′*S*,5′*R*)-3,3-difluoro-1-(8′-phenylmenthyloxycarbonyl)-2-(4-methoxyphenylamino)-1-cyclohexene [(−)-11f]. By means of the general procedure described above, from 560 mg (1.05 mmol) of (+)-**10f**, (−)-**11f** was obtained as a mixture of enamino (229 mg, 43% yield) and imino forms (234 mg, 44% yield), both as a yellow oils. Data for the enamino form: R_f= 0.40 (hexane/ethyl acetate, 10:1). $[\alpha]^{25}_D$= −252.3 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81 (d, J = 6.6 Hz, 3H), 0.88−1.08 (m, 3H), 1.16 (s, 3H), 1.29 (s, 3H), 1.56−1.66 (m, 6H), 1.80−1.84 (m, 1H), 1.99−2.11 (m, 4H), 3.71 (s, 3H), 4.92 (dd, J = 10.6, 4.5 Hz, 1H), 6.73−6.78 (m, 2H), 7.06−7.20 (m, 7H), 8.66 (br s, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.8, 22.0 (t, $^3J_{CF}$= 10.3 Hz), 25.3, 26.7, 27.8, 31.4, 33.2 (t, $^2J_{CF}$= 24.4 Hz), 33.3, 34.5, 39.8, 42.2, 50.5, 55.4, 73.4, 101.9 (t, $^3J_{CF}$= 7.5 Hz), 113.9, 124.9, 125.1 (t, $^4J_{CF}$= 2.9 Hz), 125.4, 128.9 (t, $^1J_{CF}$= 248.7 Hz), 131.9, 148.9 (t, $^2J_{CF}$= 23.3 Hz), 151.6, 156.9, 166.9, 172.1. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −97.66 (br, 2F). HRMS (EI) calcd for $C_{30}H_{37}F_2NO_3$ (M^+): 497.2742, found: 497.2755. Data for the imino form: R_f= 0.20 (hexane/ethyl acetate, 10:1). $[\alpha]^{25}_D$= −242.95 (*c* 0.9, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (d, J = 6.6 Hz, 3H), 0.87−0.95 (m, 3H), 1.08 (s, 3H), 1.18 (s, 3H), 1.28−1.47 (m, 4H), 1.60−1.84 (m, 5H), 1.96−2.05 (m, 1H), 2.24−2.33 (m, 1H), 3.15 (br s, 1H), 3.79 (s, 3H), 4.82 (dt, J = 10.8, 4.4 Hz, 1H), 6.85−6.90 (m, 7H), 7.01−7.05 (m, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.0 (t, $^3J_{CF}$= 9.2 Hz), 21.8, 23.0, 26.4, 27.0, 29.2, 31.3, 34.5, 36.2 (dd, $^2J_{CF}$= 25.9, 21.9 Hz), 39.3, 41.3, 45.3, 50.3, 55.5, 75.7, 114.2, 117.9 (dd, $^1J_{CF}$= 255.9, 237.5 Hz), 120.6, 124.8, 125.0, 127.8, 141.4, 152.0, 157.2, 160.4 (dd, $^2J_{CF}$= 27.9, 16.4 Hz), 167.3. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −110.57 (ddd, J_{FF}= 246.7 Hz, J_{FH}= 34.9, 10.8 Hz, 1F), −118.23 (d, J_{FF}= 246.6 Hz, 1F). HRMS (EI) calcd for $C_{30}H_{37}F_2NO_3$ (M^+): 497.2742, found: 497.2732.

General Procedure for the Hydrogenation of Enamino/imino Esters 11: Synthesis of Amino Esters 12. Palladium on active carbon (10 wt %, 0.2 equiv) and NH_4CO_2H (10.0 equiv) were added to a solution of the corresponding enamino/imino ester **11** (1.0 equiv) in EtOH (0.1 M). The mixture was stirred in a sealed tube in a microwave reactor at 100 °C for 45 min. The reaction was then filtered. The filtrate was concentrated and purified by means of flash chromatography on silica gel with the appropriate solvents. Compounds **12a**, **12b**, **12c**, and (+)-**12e** were previously described.[18]

(43) Fustero, S.; Navarro, A.; Pina, B.; García-Soler, J.; Bartolomé, A.; Asensio, A.; Simón, A.; Bravo, P.; Fronza, G.; Volonterio, A.; Zanda, M. *Org. Lett.* **2001**, *3*, 2621–2624.

(−)-(1*S*,2*S*,1′*R*,2′*S*,5′*R*)-3,3-Difluoro- 2-(4-methoxyphenylamino)-1-(8′-phenylmenthyloxycarbonyl)cyclohexane [(−)-12f]. By means of the general procedure described above, from 100 mg (0.20 mmol) of (−)-**11f** was obtained 50 mg of **12f** as a white solid (50% yield), together with 8 mg of its diastereoisomer (8% yield) and 25 mg of recovered (−)-**11f** (25% yield): R_f = 0.25 (hexane/ethyl acetate, 10:1); $[\alpha]^{25}_D$ = −28.6 (*c* 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80 (d, J = 6.6 Hz, 3H), 0.85−0.99 (m, 2H), 1.03 (s, 3H), 1.10 (s, 3H), 1.13 (d, J = 2.9 Hz, 1H), 1.23 (d, J = 3.4 Hz, 1H), 1.55−1.65 (m, 4H), 1.76−1.80 (m, 2H), 1.91−2.08 (m, 4H), 2.46 (q, J = 6.9 Hz, 1H), 3.67 (s, 3H), 3.78 (quint, J = 9.3 Hz, 1H), 4.73 (dt, J = 10.7, 4.3 Hz, 1H), 4.42 (d, J = 8.9 Hz, 1H), 6.61 (d, J = 8.9 Hz, 2H), 6.71 (d, J = 8.9 Hz, 2H), 7.02−7.22 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.2 (t, $^3J_{CF}$ = 5.2 Hz), 21.7, 21.9, 24.5, 26.5, 28.2, 29.8 (t, $^2J_{CF}$ = 23.3 Hz), 31.2, 34.5, 39.5, 41.7, 43.9 (t, $^3J_{CF}$ = 2.9 Hz), 50.0, 55.7, 57.0 (t, $^2J_{CF}$ = 26.7 Hz), 75.2, 114.6, 115.6, 123.4 (t, $^1J_{CF}$= 247.2 Hz), 125.1, 125.3, 127.9, 141.6, 151.7, 152.8, 171.3; ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −115.49 (dt d, J_{FF} = 230.2 Hz, J_{FH} = 15.5, 9.9 Hz 1F), −106.75 (dt d, J_{FF} = 230.2 Hz, J_{FH}= 16.1, 10.8 Hz 1F); HRMS (EI) calcd for $C_{30}H_{39}F_2NO_3$ (M^+) 499.2898, found 499.2892.

General Procedure for the Synthesis of *N*-Boc-Protected Chiral Amino Esters 14. A solution of CAN (3.0 equiv) in H_2O (0.6 M) was added dropwise to a cold (0 °C) solution of **12** (1.0 equiv) in MeCN (0.1 M). After being stirred for 4 h at room temperature, the reaction was quenched with 5% aq $NaHCO_3$ until pH 7, and 20% aq $Na_2S_2O_3$ was added. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4, and the solvents were removed under reduced pressure. Then the resulting brown residue was dissolved in dry CH_2Cl_2, and $(Boc)_2O$ (5.0 equiv) and K_2CO_3 (3.0 equiv) were added at room temperature. After being stirred for 4 h at room temperature, the reaction was quenched with H_2O and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4, and the solvents were removed under reduced pressure. The crude reaction mixture was purified by means of column chromatography on silica gel with the appropriate solvents.

(+)-(1*S*,2*S*,1′*R*,2′*S*,5′*R*)-3,3-Difluoro-2-(*N*-*tert*-butoxycarbonylamino)-1-(8′-phenylmenthyloxycarbonyl)cyclopentane [(+)-14a]. By means of the general procedure described above, 206 mg of **14a** was obtained from 300 mg (0.62 mmol) of (+)-**12e** as a colorless oil (80% yield): R_f = 0.30 (hexane/ethyl acetate, 15:1); $[\alpha]^{25}_D$ = +46.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (d, J = 6.5 Hz, 3H), 0.84−1.06 (m, 2H), 1.12 (s, 3H), 1.22 (s, 3H), 1.37 (s, 9H), 1.41−1.46 (m, 1H), 1.56−1.65 (m, 2H), 1.70−1.75 (m, 2H), 1−87−2.13 (m, 6H), 4.04−4.17 (m, 1H), 4.67 (d, J = 9.2 Hz, 1H), 4.74 (dt, J = 10.7, 4.4 Hz, 1H), 7.03−7.08 (m, 1H), 7.18−7.20 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9, 23.7, 26.3, 28.3, 29.0, 31.3, 31.8 (t, $^2J_{CF}$ = 22.9 Hz), 34.4, 39.5, 41.5, 43.4, 50.0, 56.1 (dd, $^2J_{CF}$ = 31.3, 20.3 Hz), 74.7, 80.0, 125.0, 125.3, 127.9, 128.1 (t, $^1J_{CF}$ = 254.2 Hz), 151.6, 154.8, 171.0; ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −107.25 (dq, J_{FF} = 230.9 Hz, J_{FH} = 14.4 Hz, 1F), −101.02 (dq, J_{FF} = 230.9 Hz, J_{FH} = 12.4 Hz, 1F); HRMS (EI) calcd for $C_{27}H_{39}F_2NO_4$ (M^+) 479.2847, found 479.2831.

General Procedure for the Synthesis of *N*-Boc-Protected Chiral Amino Alcohols 15. $LiAlH_4$ (5 equiv) was added to a cold (0 °C) solution of **14** (1 equiv) in THF (0.1 M). After being stirred at room temperature for 6 h, the reaction was quenched with $Na_2SO_4 \cdot 10H_2O$. The organic layer was filtered and concentrated. The crude reaction mixture was purified by means of column chromatography on silica gel with the appropriate solvents.

(+)-(1*S*,5*S*)-2, 2-Difluoro-1-(*N*-*tert*-butoxycarbonylamino)-5-(hydroxymethyl)cyclopentane [(+)-15a]. By means of the general procedure described above, 135 mg of **15a** was obtained from 320 mg (0.72 mmol) of (+)-**14a** as a white solid (75% yield): mp 69−70 °C; R_f = 0.50 (hexane/ethyl acetate, 1:1); $[\alpha]^{25}_D$ = +28.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (s, 9H), 1.75−1.81 (m, 1H), 2.03−2.14 (m, 2H), 2.40−2.46 (m, 1H), 2.70−2.73 (m, 1H), 3.50−3.52 (m, 2H), 4.17−4.22 (m, 1H), 4.87 (d, J = 6.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.1 (t, $^3J_{CF}$ = 4.0 Hz), 28.2, 32.5 (t, $^2J_{CF}$ = 24.3 Hz), 42.5, 56.8 (dd, $^2J_{CF}$ = 25.3, 18.5 Hz), 61.8, 80.7, 129.3 (t, $^1J_{CF}$ = 254.4 Hz), 156.6; ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −98.2 (dq, J_{FH} = 14.4 Hz, J_{FF} = 234.6 Hz, 1F), −108.2 (dm, J_{FF} = 233.2 Hz, 1F); HRMS (FAB) calcd for $C_{11}H_{19}F_2NO_3$ (M^+ + 1) 252.1411, found 252.1416.

General Procedure for the Synthesis of N-Boc-Protected Chiral Amino Acids 16. *N*-Boc-protected amino alcohols **15** (1 equiv) were dissolved in $CCl_4/CH_3CN/H_2O$ (1:2:1.5) under brisk stirring. Then, $NaIO_4$ (10 equiv) and $RuCl_3 \cdot 3H_2O$ (0.05 equiv) were added. After the mixture was stirred at room temperature for 2 h, the reaction salts were filtered off and washed with CCl_4. The organic layer was extracted with EtOAc, washed with brine, and dried over anhydrous Na_2SO_4, and the solvents were removed under reduced pressure. The crude reaction mixture was purified by means of column chromatography on silica gel with the appropriate solvents.

(+)-(1*S*,2*S*)-3,3-Difluoro-2-(*N*-*tert*-butoxycarbonylamino)cyclopentanecarboxylic Acid [(+)-16a]. By means of the general procedure described above, 70 mg of **16a** was obtained from 100 mg (0.40 mmol) of (+)-**15a** as a colorless oil (66% yield) as a 1:1 mixture of rotamers: R_f = 0.50 (hexane/ethyl acetate, 1:1); $[\alpha]^{25}_D$ = +32.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 (s, 9H), 1.85−1.95 (m, 2H), 2.04−2.21 (m, 2H), 3.15−3.22 (m, 1H), 4.22−4.45 (m, 1H), 5.37 (d, J = 8.9 Hz, 0.5H), 6.75 (d, J = 9.3 Hz, 0.5H), 11.38 (br s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.7, 22.3, 28.0, 31.9 (t, $^2J_{CF}$ = 24.0 Hz), 32.0 (t, $^2J_{CF}$ = 23.3 Hz), 43.8, 44.1, 56.4 (dd, $^2J_{CF}$ = 29.7, 20.0 Hz), 57.4 (dd, $^2J_{CF}$ = 33.1, 20.2 Hz), 80.6, 82.3, 127.5 (t, $^1J_{CF}$ = 252.5 Hz), 128.1 (t, $^1J_{CF}$ = 254.7 Hz), 155.4, 157.6, 175.1, 177.4; ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −99.96 (dd, J_{FH}= 11.1 Hz, J_{FF} = 231.5 Hz, 0.5F), −101.26 (dq, J_{FH} = 12.0 Hz, J_{FF} = 232.4 Hz, 0.5F), −104.52 (dq, J_{FH} = 15.5 Hz, J_{FF} = 230.7 Hz, 0.5F), −109.42 (dd, J_{FH} = 7.8 Hz, J_{FF} = 231.5 Hz, 0.5F); HRMS (FAB) calcd for $C_{11}H_{17}F_2NO_4$ (M^+ + 1) 266.1204, found 266.1204.

General Procedure for the Synthesis of Chiral Cyclic *β*-Amino Acids 17. *N*-Boc-protected amino acids **16** (1 equiv) were dissolved in diethyl ether, and anhydrous HCl (1 M in diethyl ether) was added. The mixture was stirred at room temperature for 6 h and concentrated under reduced pressure to obtain free chiral amino acids **17**, which were purified by washing the solid residue with diethyl ether.

(+)-(1*S*,2*S*)-3,3-Difluorocyclopentanecarboxylic Acid Hydrochloride [(+)-17a]. By means of the general procedure described above, 27 mg of **17a** were obtained from 45 mg (0.17 mmol) of (+)-**16a** as a white solid (79% yield): mp 227−228 °C; $[\alpha]^{25}_D$ = +36.2 (*c* 1.0, H_2O); ^{1}H NMR (300 MHz, D_2O) δ 2.07−2.20 (m, 4H), 3.29−3.31 (m, 1H), 3.95−4.00 (m, 1H); ^{13}C NMR (75.5 MHz, D_2O) δ 23.6 (t, $^3J_{CF}$ = 3.0 Hz), 32.0 (t, $^2J_{CF}$ = 17.7 Hz), 42.7 (t, $^3J_{CF}$ = 3.9 Hz), 55.3 (dd, $^2J_{CF}$ = 23.5, 15.5 Hz), 128.1 (t, $^1J_{CF}$ = 189.3 Hz), 176.1; ^{19}F NMR (282.4 MHz, D_2O) δ −97.90 (br d, J_{FH}= 236.2 Hz, 1F), −103.79 (br d, J_{FF}= 235.5 Hz, 1F); HRMS (FAB) calcd for $C_6H_{10}ClF_2NO_2$ (M^+ − HCl) 166.0679, found 166.0680.

Synthesis of (+)-(1*S*,2*S*)-Methyl 2-(*N*-*tert*-Butoxycarbonylamino)-3,3-difluorocyclopentanecarboxylate [(+)-19]. *N*-Boc-protected amino acid (+)-**16a** (67 mg, 0.26 mmol) was dissolved in MeOH (4 mL), and trimethylsilyldiazomethane (2 M in hexane, 0.5 mL) was added dropwise. The mixture was stirred at room temperature for 10 min and then concentrated under reduced pressure. The crude reaction mixture was purified by means of column chromatography on silica gel (hexane/EtOAc, 4:1) to obtain 40 mg of (+)-**19** as a colorless oil (60% yield): $[\alpha]^{25}_D$ +58.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (s, 9H), 1.87−1.97 (m, 1H), 2.04−2.12 (m, 3H), 3.18 (dt, J = 8.4, 4.5 Hz, 1H), 3.64 (s, 3H), 4.39 (quint, J = 10.5 Hz, 1H), 5.18 (d, J = 8.9, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.5 (t, $^3J_{CF}$ = 4.2 Hz), 27.2, 31.2 (t, $^2J_{CF}$ = 24.1 Hz), 43.0 (d, $^3J_{CF}$ = 6.7 Hz), 51.1, 55.3 (dd, $^2J_{CF}$ = 29.5, 20.0 Hz), 79.2, 114.3, 126.7 (t, $^1J_{CF}$ = 251.5 Hz), 128.5, 154.2, 171.5; ^{19}F NMR (282.4 MHz,

$CDCl_3$) δ −101.85 (ddt, J_{FH} = 11.8, 23.6 Hz, J_{FF} = 230.9 Hz, 1F), −106.01 (ddt, J_{FH} = 16.8, 30.4 Hz, J_{FF} = 231.5 Hz, 1F); HRMS (EI) calcd for $C_{12}H_{19}F_2NO_4$ (M^+) 279.1345, found 279.1332.

Synthesis of (−)-(1*R*,2*S*)-Methyl 2-(*N*-*tert*-Butoxycarbonylamino)-3,3-difluorocyclopentanecarboxylate [(−)-20]. Sodium methoxide (0.5 M in MeOH, 0.9 mL) was added to a solution of (+)-**19** (30 mg, 0.1 mmol) in dry MeOH (1.5 mL). The mixture was stirred at room temperature for 24 h and then concentrated under reduced pressure. The crude reaction mixture was purified by means of column chromatography on silica gel (hexane/EtOAc, 5:1) to obtain 29 mg of (−)-**20** as a white solid (97% yield): mp 86−87 °C; $[\alpha]^{25}_D$ −14.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39 (s, 9H), 1.94−2.22 (m, 4H), 2.63 (q, *J* = 9.3 Hz, 1H), 3.66 (s, 3H), 4.29−4.34 (m, 1H), 4.72−4.80 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) 25.1 (t, $^3J_{CF}$ = 4.7 Hz), 29.6, 34.5 (t, $^2J_{CF}$ = 24.2 Hz), 51.7 (t, $^3J_{CF}$ = 5.4 Hz), 60.9 (dd, $^2J_{CF}$ = 26.7, 19.8 Hz), 81.2, 130.2 (t, $^1J_{CF}$ = 250.8 Hz), 158.7, 181.8; ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −113.76 (ddt, J_{FH} = 10.7, 21.1 Hz, J_{FF} = 227.4 Hz, 1F), −116.54 (ddt, J_{FH} = 17.2, 34.4 Hz, J_{FF} = 239.1 Hz, 1F); HRMS (FAB) calcd for $C_{12}H_{20}F_2NO_4$ (M^+ + 1) 280.1360, found 280.1355.

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Supporting Information Available: Experimental procedures and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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