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Efficient Synthesis of Trifluoromethyl and Related Trisubstituted Alkene Dipeptide Isosteres by Palladium-Catalyzed Carbonylation of Amino Acid Derived Allylic Carbonates

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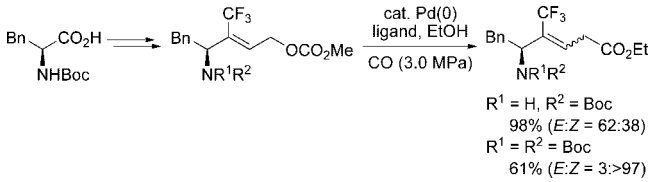

A novel stereoselective synthetic approach to (*Z*)-trifluoromethylalkene dipeptide isosteres (CF_3-ADIs) is described. Starting from readily available *N*-Boc-L-phenylalanine, Phe-Gly type CF_3-ADIs were obtained through palladium-catalyzed carbonylation of allylic carbonates under CO. While the reaction of *N*-Boc derivatives proceeds in excellent yields but lower stereoselectivity (*E*:*Z* = 62:38–43:57), the reaction of the *N*,*N*-diBoc derivative exclusively affords the desired (*Z*)-isomer in 61% yield. We also present a highly stereoselective synthesis of several Phe-Gly type trisubstituted alkene dipeptide isosteres by palladium-catalyzed carbonylation.

Peptides constitute attractive and useful drug leads because a large number of bioactive peptides have already been isolated and identified. However, peptidase-mediated digestion of peptides as well as lower membrane permeability of generally hydrophilic peptides decrease their bioavailability in clinical use. The backbone modification of amide bonds in bioactive peptides is one of the most promising approaches to solving these problems.[1] Among the known isosteric units, (*E*)-alkene dipeptide isosteres (EADIs, Figure 1) have been studied extensively because the (*E*)-carbon−carbon double bond closely resembles the planar structure of the parent amide bond.[2] Fluoroalkene dipeptide isosteres (FADIs) can be considered as more ideal surrogates than nonpolar EADIs due to the presence of a highly electronegative fluorine substituent. This substituent mimics a carbonyl oxygen atom and might contribute to both the electrostatic nature and the three-dimensional structure of bioisosteres.[3] However, our recent studies on stereoselective synthesis and evaluation of functionalized (*Z*)-FADIs have revealed that the (*Z*)-FADI of Phe-Gly showed lower binding affinity for peptide transporter PEPT1 compared with the corresponding EADI.[4] Moreover, when compared to the parent peptide, the EADI analogue of the GPR54 agonistic peptide expressed similar agonist activity,[5] whereas the (*Z*)-FADI analogue showed significantly lower potency. These results suggest that FADIs are not always effective as dipeptide mimetics, even though some examples of bioactive compounds containing FADIs have been reported.[3b,c,6]

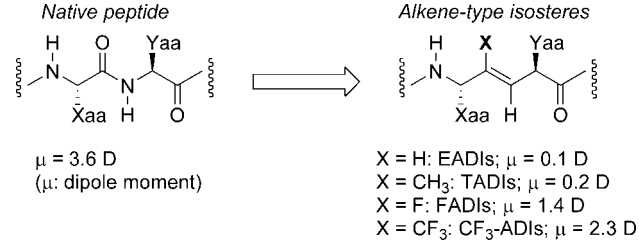

FIGURE 1. Structures of native peptides and corresponding alkene-type isosteres. Xaa, Yaa = Amino acid side chains.

We next turned our attention to trifluoromethylalkene dipeptide isosteres (CF_3-ADIs, Figure 1) that possess a dipole moment (2.3 D) closer to a native peptide bond (3.6 D) than do other alkene-type isosteres (FADI, 1.4 D; EADI, 0.1 D).[7] CF_3-ADIs could serve as more favorable dipeptide isosteres than FADIs due to the presence of fluorine atoms on the sp^3 carbon atoms.[8] Although several asymmetric syntheses of CF_3-ADIs have been reported,[7,9] stereoselective synthesis of optically pure Xaa-Gly

(1) (a) Burgess, K. *Acc. Chem. Res.* **2001**, *34*, 826–835. (b) Bursavich, M. G.; Rich, D. H. *J. Med. Chem.* **2002**, *45*, 541–558. (c) Hruby, V. J. *J. Med. Chem.* **2003**, *46*, 4215–4231.

(2) (a) For EADIs and TADIs, see: Christos, T. E.; Arvanitis, A.; Cain, G. A.; Johnson, A. L.; Pottorf, R. S.; Tam, S. W.; Schmidt, W. K. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1035−1040. (b) Tamamura, H.; Hiramatsu, K.; Ueda, S.; Wang, Z.; Kusano, S.; Terakubo, S.; Trent, J. O.; Peiper, S. C.; Yamamoto, N.; Nakashima, H.; Otaka, A.; Fujii, N. *J. Med. Chem.* **2005**, *48*, 380–391. (c) Oishi, S.; Miyamoto, K.; Niida, A.; Yamamoto, M.; Ajito, K.; Tamamura, H.; Otaka, A.; Kuroda, Y.; Asai, A.; Fujii, N. *Tetrahedron* **2006**, *62*, 1416–1424. (d) Xiao, J.; Weisblum, B.; Wipf, P. *Org. Lett.* **2006**, *8*, 4731–4734.

(3) (a) Abraham, R. J.; Ellison, S. L. R.; Schonholzer, P.; Thomas, W. A. *Tetrahedron* **1986**, *42*, 2101–2110. (b) Allmendinger, T.; Felder, E.; Hungerbühler, E. *Tetrahedron Lett.* **1990**, *31*, 7301–7304. (c) Lin, J.; Toscano, P. J.; Welch, J. T. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 14020–14024. (d) Narumi, T.; Niida, A.; Tomita, K.; Oishi, S.; Otaka, A.; Ohno, H.; Fujii, N. *Chem. Commun.* **2006**, 4720–4722.

(4) Niida, A.; Tomita, K.; Mizumoto, M.; Tanigaki, H.; Terada, T.; Oishi, S.; Otaka, A.; Inui, K.; Fujii, N. *Org. Lett.* **2006**, *8*, 613–616.

(5) (a) Tomita, K.; Niida, A.; Oishi, S.; Ohno, H.; Cluzeau, J.; Navenot, J.; Wang, Z.; Peiper, S. C.; Fujii, N. *Bioorg. Med. Chem.* **2006**, *14*, 7595–7603. (b) Tomita, K.; Narumi, T.; Niida, A.; Oishi, S.; Ohno, H.; Fujii, N. *Biopolymers* **2007**, *88*, 272–278.

(6) Bartlett, P. A.; Otake, A. *J. Org. Chem.* **1995**, *60*, 3107–3111.

(7) Wipf, P.; Henninger, T. C.; Geib, S. J. *J. Org. Chem.* **1998**, *63*, 6088–6089.

(8) Howard, J. A. K.; Hoy, V. J.; O'Hagan, D.; Smith, G. T. *Tetrahedron* **1996**, *52*, 12613–12622.

(9) (a) Xiao, J.; Weisblum, B.; Wipf, P. *J. Am. Chem. Soc.* **2005**, *127*, 5742–5743. (b) Wipf, P.; Xiao, J.; Geib, S. J. *Adv. Synth. Catal.* **2005**, *347*, 1605–1613.

(10) (a) For further discussion of palladium-catalyzed carbonylation of allylic carbonates, see: Tsuji, J.; Sato, K.; Okumoto, H. *Tetrahedron Lett.* **1982**, *23*, 5189−5190. (b) Tsuji, J.; Sato, K.; Okumoto, H. *J. Org. Chem.* **1984**, *49*, 1341–1344. (c) Ozawa, F.; Son, T.; Ebina, S.; Osakada, K.; Yamamoto, A. *Organometallics* **1992**, *11*, 171–176. (d) Narumi, T.; Fujii, M.; Adachi, T.; Shimizu, I. *Pept. Sci.* **2003**, 417–420.

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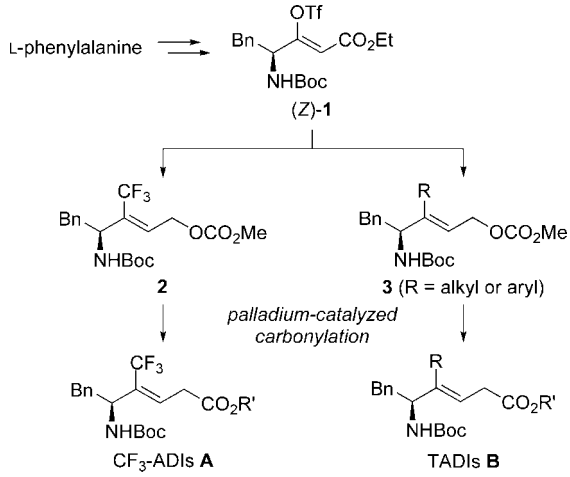
SCHEME 1. Palladium-Catalyzed Synthesis of CF_3-ADIs A and TADIs B via a Single Intermediate



type CF_3-ADIs by use of the reported methodologies would be extremely difficult because the construction of a stereogenic center at the δ-position relies upon the chirality of the α-carbon.

We proposed that palladium-catalyzed carbonylation of allylic carbonates **2**[10d] derived from α-amino acids would provide a general and convenient approach to enantiopure Xaa-Gly type CF_3-ADIs **A** (Scheme 1). This strategy could also be applied to facile synthesis of trisubstituted alkene dipeptide isosteres (TADIs) **B**, which are known as useful hydrolytically stable structural surrogates of dipeptides[2d] as well as potent β-turn promoters in acyclic sequences.[9,11] To evaluate the utility of CF_3-ADIs and TADIs, development of a simple and efficient methodology for the preparation of both isosteres by way of the same intermediate is highly desirable. Herein, we describe a novel synthetic approach to Phe-Gly type CF_3-ADIs **A** and TADIs **B** (R = *n*-Bu, Me, *i*-Pr, or Ph) by palladium-catalyzed carbonylation of allylic carbonates such as **2** and **3**. These approaches enable a facile synthesis of enantiomerically pure dipeptide isosteres by retention of the asymmetric centers of the starting amino acids.

Our synthesis started from commercially available *N*-Boc-L-phenylalanine **4** as illustrated in Scheme 2. After conversion to β-keto ester **5** by the reaction with carbonyldiimidazole and ethyl acetate lithium enolate,[12] treatment with Tf_2O in the presence of $(i\text{-Pr})_2NH$ afforded the triflate **1** as a separable mixture of *E*- and *Z*-isomers (*E*:*Z* = 1:4). Next, we investigated the tributylstannylation of (*Z*)-**1** under various conditions. Representative results are shown in Table 1. While the reactions with bis(tributyltin) in the presence of a catalytic amount of $Pd(PPh_3)_2Cl_2$ or $PdCl_2[P(o\text{-tol})_3]_2$ gave a mixture of unidentified products (entries 1 and 2), the reaction with cyano Gilman reagent [n-$Bu_3Sn(n\text{-Bu})Cu(CN)Li_2$], a well-known stannylating reagent for cross-coupling reaction,[13] afforded the desired

SCHEME 2. Synthesis of Carbonate 2 Bearing a CF_3 Group

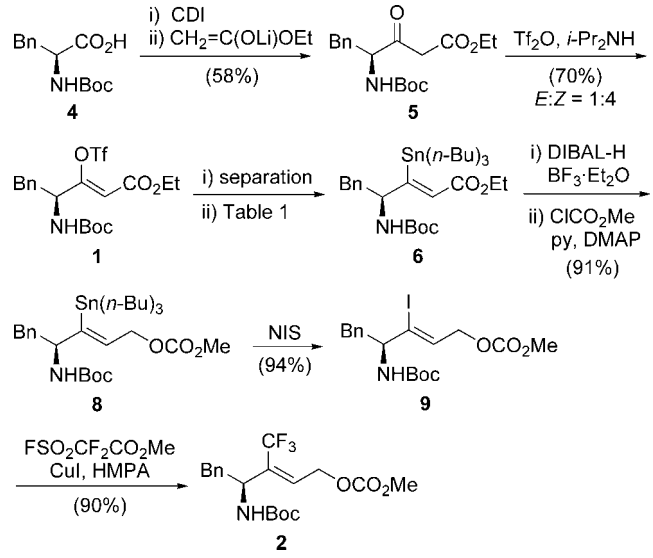
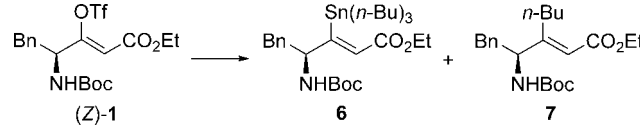


TABLE 1. Synthesis of Tributylstannylated Enoate 6 via Organocopper-Mediated Stannylation of (*Z*)-1[a]



entry	reagents	solvent	products (yield)	
1	$(n\text{-}Bu_3Sn)_2$, $Pd(PPh_3)_2Cl_2$	THF	ND[b]	
2	$(n\text{-}Bu_3Sn)_2$, $PdCl_2[P(o\text{-tol})_3]_2$	DMF	ND[b]	
3	$n\text{-}Bu_3Sn(n\text{-Bu})Cu(CN)Li_2$	THF	**6** (35%)	**7** (17%)
4	$n\text{-}Bu_3SnCu(CN)Li$[c]	THF	**6** (23%)	**7** (62%)
5	$n\text{-}Bu_3SnCu(CN)Li$[d]	THF	**6** (80%)	**7** (trace)

[a] Catalytic reactions (entries 1 and 2) were carried out with $(n\text{-}Bu_3Sn)_2$ (1.2 equiv) in the presence of a palladium catalyst (5 mol %) and LiCl (6.0 equiv). [b] Not determined (a complex mixture of unidentified products was obtained). [c] Prepared by stirring at 0 °C for 10 min. [d] Prepared by stirring at 0 °C for 60 min.

product **6** in 35% yield along with 17% of the butylated enoate **7** (entry 3). The reaction with a lower-order cuprate [n-Bu_3-SnCu(CN)Li] gave **7** as a major product (entry 4). In sharp contrast, the cyanocuprate with the same constituent of the reagents with a prolonged reaction time gave the desired stannylated product **6** in 80% yield (entry 5). Stannyl ester **6** was then reduced with DIBAL-H to the corresponding allylic alcohol, which was converted to the allylic carbonate **8** under standard conditions. After treatment of **8** with NIS,[9] the resulting vinyl iodide **9** was subjected to copper-mediated trifluoromethylation using $FSO_2CF_2CO_2Me$/CuI[14] as a trifluoromethyl anion equivalent to give the requisite allylic carbonate **2** containing a CF_3-alkene unit in high yield.[15]

Next, allylic carbonates **3** for the syntheses of several Phe-Gly type TADIs **B**, Boc-Phe-Ψ[(*E*)-CR═CH]-Gly-OR' (Scheme 1), were prepared from the key intermediate (*Z*)-**1** through

(11) Tyndall, J. D. A.; Pfeiffer, B.; Abbenante, G.; Fairlie, D. P. *Chem. Rev.* **2005**, *105*, 793–826.

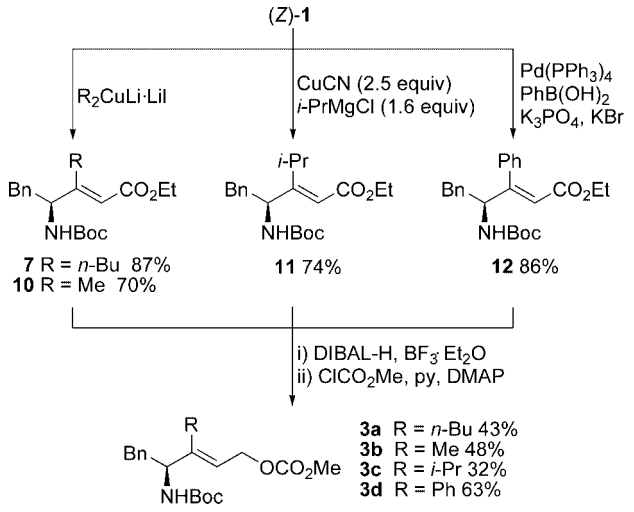
(12) The ketone **5** with >95% ee (Chiralcel OD-RH, MeCN/H_2O = 53:47) was obtained according to Hoffman's protocol: Hoffman, R.V.; Maslouh, N.; Cervantes-Lee, F *J. Org. Chem.* **2002**, *67*, 1045−1056. It should be noted that a prolonged reaction time for CDI treatment caused serious racemization.

(13) (a) Gilbertson, S. R.; Challener, C. A.; Bos, M. E.; Wulff, W. D. *Tetrahedron Lett.* **1988**, *29*, 4795–4798. (b) Piers, E.; Chong, J. M.; Morton, H. E. *Tetrahedron* **1989**, *45*, 363–380. (c) Lipshutz, B. H.; Sharma, S.; Reuter, D. C. *Tetrahedron Lett.* **1990**, *31*, 7253–7256. (d) Oehlschlager, A. C.; Hutzinger, M. W.; Aksela, R.; Sharma, S.; Singh, S. M. *Tetrahedron Lett.* **1990**, *31*, 165–168.

(14) (a) Chen, Q. Y.; Wu, S. W. *Chem. Commun.* **1989**, 705–706. (b) Tian, F.; Kruger, V.; Bautista, O.; Duan, J.; Li, A.; Dolbier, W. R., Jr.; Chen, Q. Y *Org. Lett.* **2000**, *2*, 563–564.

(15) The *E*/*Z* stereochemistry of the olefinic compounds was determined by NOE analyses. With the carbonates **2**, **3**, and **15** and (*Z*)-enoates **13**, **16**, and **17**, NOE correlations were observed between the olefinic proton and the proton on the carbon bearing a nitrogen atom. On the other hand, this correlation was not observed with the (*E*)-enoates **13**.

SCHEME 3. Synthesis of Carbonates 3a−d



organocopper-mediated alkylation[16] or Pd-catalyzed Suzuki−Miyaura coupling[17] (Scheme 3). Organocopper-mediated alkylation of (*Z*)-**1** using Gilman reagents (*n*-$Bu_2CuLi\cdot LiI$ or $Me_2CuLi\cdot LiI$) at −78 °C proceeded smoothly to yield the desired *n*-butyl- and methyl-substituted enoates **7** and **10** in 87% and 70% yields, respectively. Although the reactions of (*Z*)-**1** with some typical isopropylcopper reagents [*i*-$Pr_2CuLi\cdot LiI$, *i*-PrCuI·MgCl, *i*-$Pr_2Cu(CN)Li_2$, or *i*-PrCu(CN)MgCl] afforded only a mixture of unidentified compounds, the reaction with the reagent prepared from *i*-PrMgCl (1.6 equiv) and a slight excess of copper cyanide (2.5 equiv) afforded the desired product **11** in 74% yield.[16] Phenylated enoate **12** was prepared in 86% yield by Suzuki−Miyaura coupling of (*Z*)-**1** using $PhB(OH)_2$ in the presence of a catalytic amount of $Pd(PPh_3)_4$.[17] The resulting substituted enoates **7** and **10**−**12** were converted to the allylic carbonates **3a**−**d** by a sequence of reactions similar to the preparation of **2** (Scheme 3).

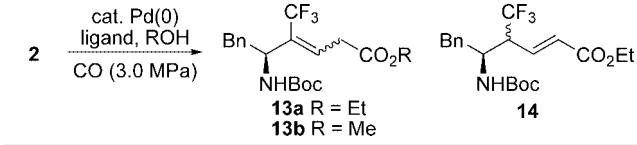
Next, we investigated the palladium-catalyzed carbonylation of allylic carbonate **2** bearing a CF_3 group (Table 2).[10] Treatment of **2** with 10 mol % of $Pd_2(dba)_3\cdot CHCl_3$ and 40 mol % of PPh_3 in EtOH at room temperature under 3.0 MPa of carbon monoxide afforded the desired β,γ-unsaturated ester **13a** in 60% yield with a low *E*/*Z* selectivity (entry 1).[15] Similarly, the reaction proceeded smoothly at 50 °C to give **13a** in 98% combined isolated yield (entry 2). In sharp contrast, when the reaction was carried out at 80 °C, a considerable amount of α,β-unsaturated ester **14** was obtained (26% yield, entry 3). Other palladium sources and ligands were ineffective at improving the *E*/*Z* selectivity (entries 4–7). The reaction in MeOH gave the desired product **13b** in 80% yield within 3 h (compare entries 8 vs 9), but the stereoselectivities were similarly low. Decreased loading of $Pd_2(dba)_3\cdot CHCl_3$ (5 mol %) gave a comparable result, while a slightly lower yield of **13b** was obtained with 2.5 mol % of $Pd_2(dba)_3\cdot CHCl_3$ (entries 9–11). Based on these observations, it was determined that the palladium-catalyzed carbonylation of **2** produces the desired esters in good yields but that improvement of *E*/*Z* selectivity is difficult.

It is worth noting that related palladium-catalyzed allylic carbonylation favors formation of trans-isomers due to the preference for *syn*-π-allylpalladium intermediates.[10b] The observed low *E*/*Z* selectivities with the carbonate **2** can be partly explained by the presence of a sterically demanding CF_3 group. Thus, oxidative addition of **2** to palladium(0) would give π-allylpalladium intermediate **A** via decarboxylation (Figure 2), which is in an equilibrium state with the π-complex **B** and σ-complexes **C** and **D** via $\pi-\sigma-\pi$ rearrangement. Coordination of CO to the palladium atom of **C**, exchange of alkoxide, and reductive elimination would afford (*Z*)-**13**. On the other hand, carbonylation of **D** derived from **B** gives (*E*)-**13** in a similar manner. The bulky CF_3 group would partly destabilize the syn complex **A** because of the unfavorable 1,3-repulsion with a hydrogen atom thus leading to nonselective formation of (*Z*)- and (*E*)-**13**.

To overcome the effect of the CF_3 group and improve the stereoselectivity, we introduced another N-substituent to increase unfavorable 1,3-repulsion in the π-complex **B**, thereby destabilizing **B** and assisting the selective formation of the desired (*Z*)-**13** through the intermediate **A**. Accordingly, we prepared *N*,*N*-diprotected allylic carbonates **15a**,**b** from **2** by the standard protocols and investigated the palladium-catalyzed carbonylation reaction. As expected, the reaction proceeded smoothly to afford the desired (*Z*)-β,γ-enoates **16a**,**b** as single isomers in moderate yields (61% and 60%, respectively) (Scheme 4).

Next, synthesis of TADIs having a *n*-Bu, Me, *i*-Pr, or Ph group on the double bond was investigated. The carbonylation

TABLE 2. Palladium-Catalyzed Carbonylation of CF_3-Containing Allylic Carbonate 2



entry	Pd cat. (mol %)[a]	ligand (mol %)	ROH	temp. (°C)	time (h)	yield (%)[b] (*E*)-**13**	(*Z*)-**13**
1	10	PPh_3 (40)	EtOH	rt	12	26	34
2	10	PPh_3 (40)	EtOH	50	12	61	37
3[c]	10	PPh_3 (40)	EtOH	80	12	16	20
4	10	PCy_3 (40)	EtOH	50	12	ND[d]	
5	10	dppm (40)	EtOH	50	12	ND[d]	
6	10	dppe (40)	EtOH	50	12	20	5
7	10	dppp (40)	EtOH	50	12	12	14
8	10	PPh_3 (40)	EtOH	50	3	27	38
9	10	PPh_3 (40)	MeOH	50	3	32	48
10	5	PPh_3 (20)	MeOH	50	3	35	45
11	2.5	PPh_3 (10)	MeOH	50	3	29	25

[a] Mol % of $Pd_2(dba)_3\cdot CHCl_3$. [b] Isolated yield. [c] α,β-Unsaturated compound **14** was obtained (26%). [d] Starting material was recovered.

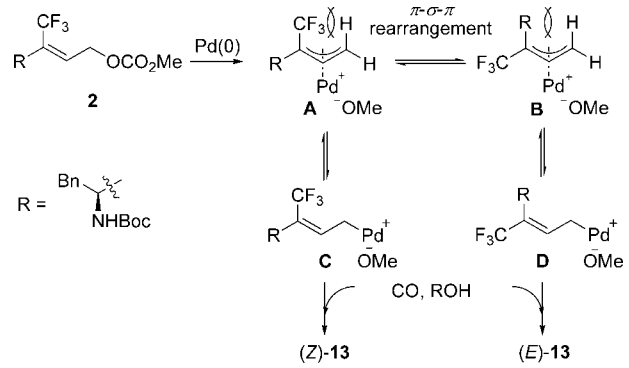
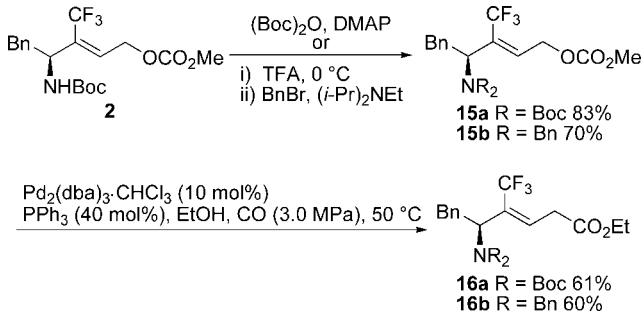


FIGURE 2. Plausible explanation for the observed stereochemical outcome with allylic carbonate **2**.

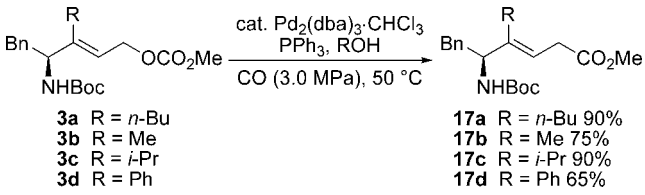
(16) (a) Zahn, T. J.; Weinbaum, C.; Gibbs, R. A. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1763–1766. (b) Rawat, D. S.; Gibbs, R. A. *Org. Lett.* **2002**, *4*, 3027–3030.

(17) (a) Oh-e, T.; Miyaura, N.; Suzuki, A. *J. Org. Chem.* **1993**, *58*, 2201–2208. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483.

SCHEME 4. Carbonylation of *N*,*N*-Diprotected Allylic Carbonates 15



SCHEME 5. Pd-Catalyzed Carbonylation of Allylic Carbonates 3a−d

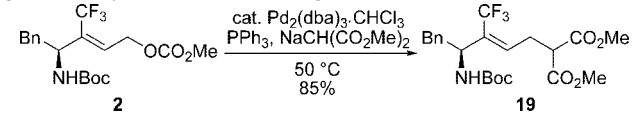


reaction of **3a**−**d** under the same conditions as those with **2** afforded the desired β,γ-unsaturated esters **17a**−**d** in good yields (Scheme 5). In sharp contrast to the reaction of CF_3 derivatives **2** (Table 2), all the *N*-Boc-TADIs, including **17c** having a bulky *i*-Pr group, were obtained as the sole isolable stereoisomer. These results suggest that the CF_3 group would also exert some interesting effects on the formation of (*E*)-**13**, not only as a sterically congested substituent (Figure 2).[18]

Finally, the esters (*Z*)-**13b** and **16a** were converted to the desired deprotected CF_3-ADI **18** by treatment under acidic conditions in 85% and 95% yields, respectively (Scheme 6).[19]

In summary, we have developed a novel synthetic route which is applicable to the general synthesis of CF_3-ADIs and TADIs starting from commercially available *N*-Boc-amino acids. This methodology is useful in that the chiral center at the δ-position of isosteres is derived from α-amino acids, enabling facile evaluation of CF_3-ADIs and several TADIs as peptidomimetics.

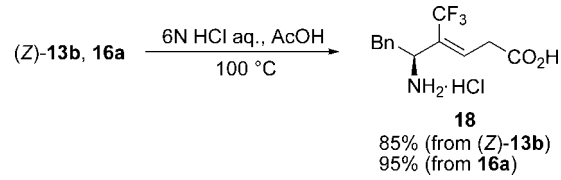
(18) Nucleophilic substitution of allylic carbonate **2** with sodium malonate gave the (*Z*)-γ,δ-malonate **19** as a single isomer.



Other examples of a CF_3-containing π-allylpalladium complex with a malonate anion have been reported to proceed with retention of configuration. See: (a) Hanzawa, Y.; Ishizawa, S.; Kobayashi, Y. *Chem. Pharm. Bull.* **1988**, *36*, 4209−4212. (b) Hanzawa, Y.; Ishizawa, S.; Kobayashi, Y.; Taguchi, T. *Chem. Pharm. Bull.* **1990**, *38*, 1104−1106. These results as well as the significantly higher stereoselectivity observed with the *i*-Pr derivative **3c** suggest other important influences of the CF_3 group in this reaction system containing carbon monoxide.

(19) Cragoe, E. J., Jr.; Gould, N. P.; Woltersdorf, O. W., Jr.; Ziegler, C.; Bourke, R. S.; Nelson, L. R.; Kimelberg, H. K.; Waldman, J. B.; Popp, A. J.; Sedransk, N. *J. Med. Chem.* **1982**, *25*, 567–579.

SCHEME 6. Conversion to the Desired CF_3-ADI 18 by Deprotection



Further studies including synthesis and evaluation of bioactive peptides with these isosteres as well as EADIs are now in progress.

Experimental Section

General Procedure for Palladium-Catalyzed Carbonylation of Allyl Carbonates: $Pd_2(dba)_3 \cdot CHCl_3$ (12.8 mg, 0.0124 mmol), PPh_3 (13.1 mg, 0.050 mmol), and EtOH (5 mL) were introduced to a 100 mL stainless steel pressure bottle containing the carbonate **2** (50 mg, 0.124 mmol). After evacuating, 3.0 MPa of CO gas was introduced at room temperature, and the mixture was stirred at 50 °C for 12 h. After purging, the mixture was concentrated under reduced pressure followed by flash chromatography over silica gel with *n*-hexane−AcOEt (7:1) to give (*Z*)-**13a** (18.3 mg, 37% yield) and (*E*)-**13a** (30.4 mg, 61% yield).

Compound (*Z*)-**13a**: pale yellow solid; mp 84.0–84.5 °C; $[\alpha]^{24}_D$ –10.4 (*c* 0.930, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, J = 7.1 Hz, 3H), 1.36 (s, 9H), 2.82 (m, 1H), 3.02 (dd, J = 13.6, 5.0 Hz, 1H), 3.28–3.36 (m, 2H), 4.15 (q, J = 7.1 Hz, 2H), 4.42–4.71 (br, 2H), 6.12 (t, J = 7.1 Hz, 1H), 7.13–7.33 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ14.1, 28.2 (3C), 33.2, 40.6, 53.5, 61.1, 79.9, 125.1, 126.8, 128.5 (2C), 128.6, 129.3 (2C), 130.4, 136.5, 154.5, 170.1; ^{19}F NMR (376 MHz, $CFCl_3$) δ –59.0 (3F); HRMS (FAB) calcd for $C_{20}H_{27}F_3NO_4$ (MH^+) 402.1892; found 402.1895.

Compound (*E*)-**13a**: pale yellow oil; $[\alpha]^{24}_D$ +47.1 (*c* 0.950, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, J = 6.8 Hz, 3H), 1.37 (s, 9H), 2.65–2.75 (m, 1H), 2.88–3.02 (br, 2H), 3.18–3.28 (m, 1H), 4.10 (q, J = 6.8 Hz, 2H), 4.82 (br s, 2H), 6.45 (t, J = 6.0 Hz, 1H), 7.18–7.33 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ14.1, 28.2 (3C), 32.4, 40.1, 49.8, 61.1, 79.9, 126.9, 128.4, 128.6 (2C), 129.0, 129.3 (2C), 136.8, 143.3, 154.9, 169.8; ^{19}F NMR (376 MHz, $CFCl_3$) δ –61.6 (3F); HRMS (FAB) calcd for $C_{20}H_{27}F_3NO_4$ (MH^+) 402.1892; found 402.1894.

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

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