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Imine Additions of Internal Alkynes for the Synthesis of Trisubstituted (*E*)-Alkene and Cyclopropane Peptide Isosteres

Peter Wipf,* Jingbo Xiao, Steven J. Geib

Department of Chemistry and Center for Chemical Methodologies & Library Development, University of Pittsburgh, 219 Parkman Avenue, Pittsburgh, Pennsylvania 15260, USA
Fax: (+1)-412-624-0787, e-mail: pwipf@pitt.edu

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Abstract: Divergent multi-component reactions (DMCR) involving C–C bond formations can provide large increases in structural diversity and allow the rapid assembly of complex products from readily available starting materials. Cascade hydrozirconation-Zr/Zn transmetalation-imine addition of alkynes represents a versatile methodology for the synthesis of (*E*)-alkene and cyclopropane dipeptide isosteres. Appropriate substitutions at the sp^2-carbon of (*E*)-alkene peptide isosteres allow a range of Pd-catalyzed cross-coupling reactions, which can be used for the fine-tuning of the conformational and electronic properties of the parent peptide bond mimic. C–C bond formation by microwave-accelerated Stille coupling of stannylalkenes represents a fast, convergent synthetic approach toward trisubstituted (*E*)-alkene dipeptide isosteres.

Keywords: (*E*)-alkene; C–C bond formation; cyclopropanes; palladium; peptide isosteres; zirconocenes

Introduction

While the past success of peptide mimicry in pharmaceutical R&D has been mixed,[1] the recent worldwide surge in marketed peptides as well as peptides in clinical testing bodes well for the future of this field. Most current peptidic drugs such as insulin, oxytocin, and cyclosporin are of natural origin,[2] but synthetically produced structures such as fuzeon (enfuvirtide) and integrilin (eptifibatide) are also taking hold.[3] The broad application of peptides as drugs is still limited since they are rapidly metabolized *in vivo*, exhibit poor oral bioavailability, and are not easily transported across cellular and nuclear membranes.[4] Many of these shortcomings can be attributed to the polar amide bonds which comprise the peptide backbone.[5] The design of isosteric replacements of the amide bond offers an attractive strategy to overcome these limitations.[6] In particular, the replacement of the scissile peptide bond with non-hydrolyzable analogues is an important design motif in medicinal and bioorganic chemistry due to enhanced stability against enzymatic degradation. The rigid (*E*)-alkene peptide isostere design, based on the concept of amide ω-angle planarity, has proven to yield useful, conformationally pre-organized structural mimetics of hydrolytically labile amide bonds.[7,8] The main rationale for this strategy is the accurate mimicry of the geometry of the peptide bond and the $\alpha C_{(i+1)}-\alpha C_{(i+2)}$ distance (Figure 1).[7,9]

In order to generate a closer correlation between the conformational and electrostatic properties of peptide bonds and the corresponding alkene isosteres, we have begun a systematic study of trisubstituted (*E*)-alkene peptide isosteres (ψ[XC=CH], TEADIs) where X = aryl, alkyl, Me, H, F, and CF_3.[7b,10,11] However, alkenes can suffer from potential isomerization, oxidation and general chemical lability.[12] Accordingly, we are also investigating novel cyclopropane dipeptide isosteres (ψ[RCp], CPDIs),[11] which are expected to display increased metabolic stability compared to the corresponding TEADIs.[13] Furthermore, we have developed an approach to backbone-extended α,β-cyclopropyl-γ-amino acids,[14] which were inspired by the natural occurrence and conformational properties of vinylogous amino acids.[15]

The divergent multi-component cascade reaction (DMCR)[16] of alkenylzirconocenes **1** allows a convenient access to allylic amines,[17,18] homoallylic amines,[19] *C*-cyclopropylalkylamines,[17,18] and *C,C*-dicyclopropylalkylamines by stereoselective formation of multiple C–C bonds (Figure 2).[20]

We now report an extension of this methodology using internal alkynes as readily available precursors of *in situ* prepared alkenylzirconocenes for the convergent syn-

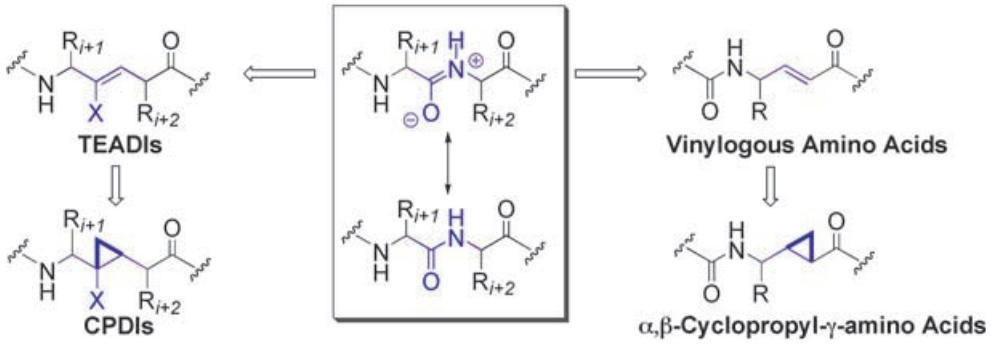


Figure 1. The structural and electronic features of peptide bonds served as inspiration for the design of trisubstituted (*E*)-alkene peptide isosteres (TEADIs) and cyclopropane dipeptide isosteres (ψ[Cp], CPDIs), which are related to backbone-extended vinylogous amino acids and α,β-cyclopropyl-γ-amino acids.

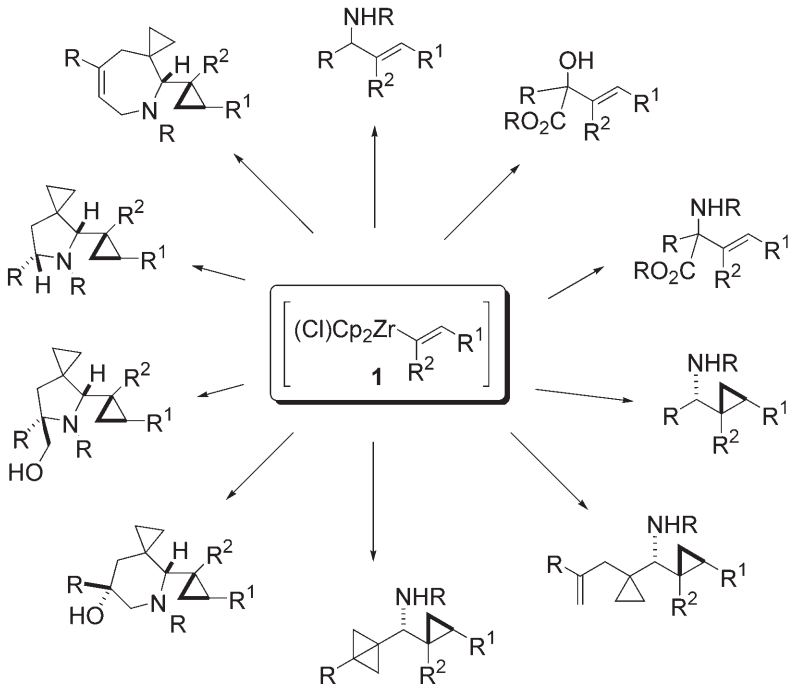
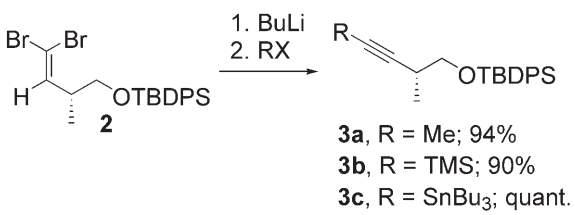


Figure 2. Examples for synthetic scaffolds that are available by addition of alkenylzirconocenes to imines and carbonyl compounds.

thesis of TEADIs and CPDIs, and the use of Pd-catalyzed cross-couplings for a variation of the X substituent on TEADIs.[21]



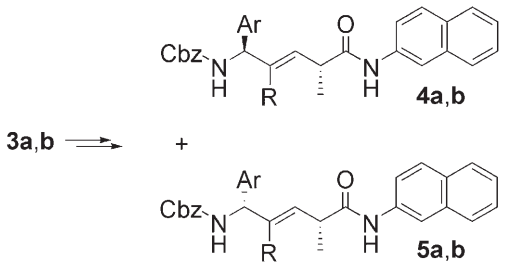
Scheme 1. Synthesis of chiral internal alkynes.

Results and Discussion[22]

Treatment of the (*S*)-(+)-Roche ester derived dibromoalkene **2**[11] with *n*-BuLi, and quenching of the reaction mixture with methyl iodide, trimethylchlorosilane or tributyltin chloride afforded the key internal alkynes **3a**–**c** in high yields (Scheme 1).

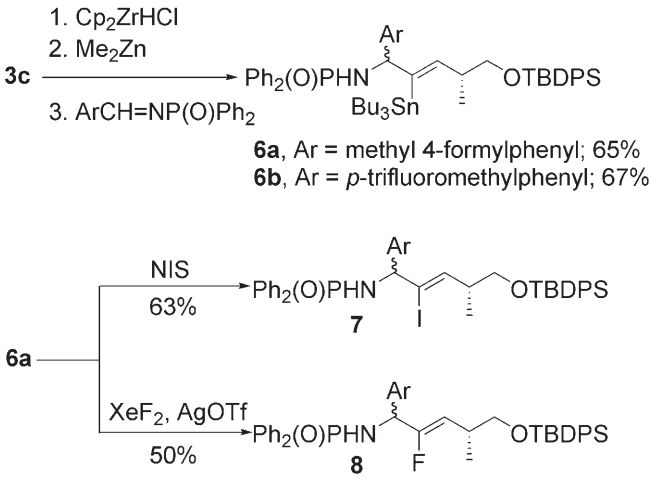
1st Generation Approach to Trisubstituted (*E*)-Alkene Dipeptide Isosteres (TEADIs)

Methylated alkyne **3a** and silylated alkyne **3b** were hydrozirconated with Cp_2ZrHCl,[23] transmetalated to



4a, **5a**, Ar = Ph, R = Me
4b, **5b**, Ar = methyl 4-formylphenyl, R = TMS

Scheme 2. Synthesis of methyl- and TMS-substituted TEADIs.



Scheme 3. Introduction of the fluoro- and iodoalkene moieties by electrophilic halogenation of stannylated alkenes.

Me_2Zn and added to (diphenylphosphinylimino)methylarenes to provide the corresponding allylic amides, which were converted to the desired TEADIs **4** and **5** using standard protocols (Scheme 2).[11,24] Naphthylamine was selected as a coupling component due to the relative ease of crystallization of the resulting amides. The assignment of the configuration of the diastereomers was based on chemical degradation and further secured by X-ray structural analyses of **5a** and **5b** (Figure 3).

2nd Generation Approach to TEADIs

We initially planned to access the halogen-substituted TEADIs as common intermediates generated from the corresponding silylated alkenes in order to establish a convergent approach toward TEADIs bearing different functional groups on the conformation-controlling[10] double bond. Interestingly, we were unable to convert the trimethylsilyl group into the corresponding vinyl halides using a variety of halodesilylation methods.[25] The unusual stability of the TMS-alkene to electrophilic attack is most likely due to the steric shielding effect of the bulky substituents flanking the double bond and the relatively rigid conformation due to $A^{1,3}$- and $A^{1,2}$-strain on this system.

The difficulties of the TMS-halogen exchange could be circumvented by the selection of stannylated alkyne **3c** as a substrate. The 1,1-heterobimetallic species[26] derived from hydrozirconation/transmetalation of stannylalkyne **3c** readily added to the electron-poor aldimine, and no regioisomeric addition products were detected (Scheme 3). This reaction represents the first example of a vinylstannylzinc addition to an aldimine.

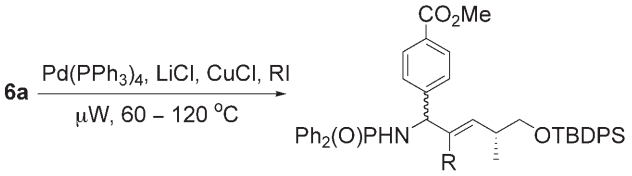
The higher reactivity of the C–Sn bond *vs.* a C–Si bond and the longer C–Sn bond distance both worked in concert to facilitate the halogen exchange reaction. In contrast to the TMS substrates, stannyl intermediate **6a** rapidly succumbed to NIS to give vinyl iodide **7** in 63% yield. Furthermore, fluorination of **6a** was possible with the protocol developed by Tius et al. (XeF_2/AgOTf/DMAP) to afford the vinyl fluoride **8** in 50% yield.[27] Alkene **8** served as the substrate for the synthesis of fluorine-substituted TEADIs, which have been used as mimics of the dipolar properties of amide groups and as potential hydrogen bond acceptors.[28,29]

The microwave-accelerated Stille coupling[30] of stannyl intermediate **6a** proved to be a versatile method for installment of substituents on the alkene sp^2-carbon (Table 1). Under monomode microwave irradiation conditions, the reaction time was shortened from 24 h to less than 1 h and the scope was extended to sterically hindered substrates like 2,6-dimethyliodobenzene. Both π-electron-rich and -deficient heterocycles such as thiophene, pyrazole, pyridine, and pyrazine could be coupled in high yields. This methodology thus enabled us to pursue a convergent approach for the attachment of a broad selection of aromatic groups to the alkene moiety of TEADIs.[31]

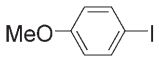
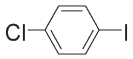
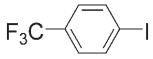
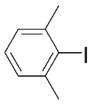
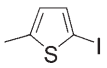
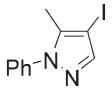
Alternatively, Negishi coupling[32] of vinyl iodide **7** with phenylzinc bromide can also be used to install aromatic groups on the double bond (Scheme 4). Moreover, this coupling variant provides a way to introduce aliphatic groups like methyl or ethyl.[33] For example, phenyl-substituted TEADIs **11** and **12** were obtained from **9a** after separation by chromatography on SiO_2 (Scheme 4). The configuration of these coupling products was assigned by X-ray structural analysis of **11**, which was shown to have the *anti*-[$(L_{i+1}L_{i+2})$]-configuration (Figure 3).

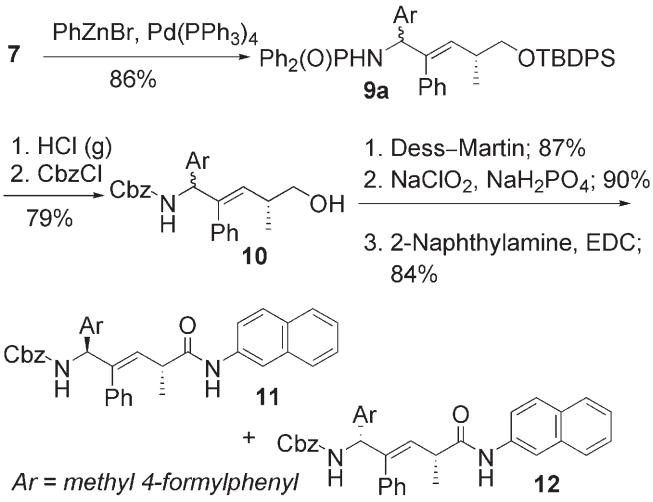
Matching the extraordinary electrostatic and hydrogen-bonding properties of the amide bond represents the most challenging parameter for isostere design and effective peptidomimicry. Our recent study of gramicidin S analogues showed that the trifluoromethyl-substituted (*E*)-alkene was a superior mimetic of the electrostatic effects of the carbonyl group *vs.* its methyl-substi-

Table 1. Microwave-accelerated Stille couplings.

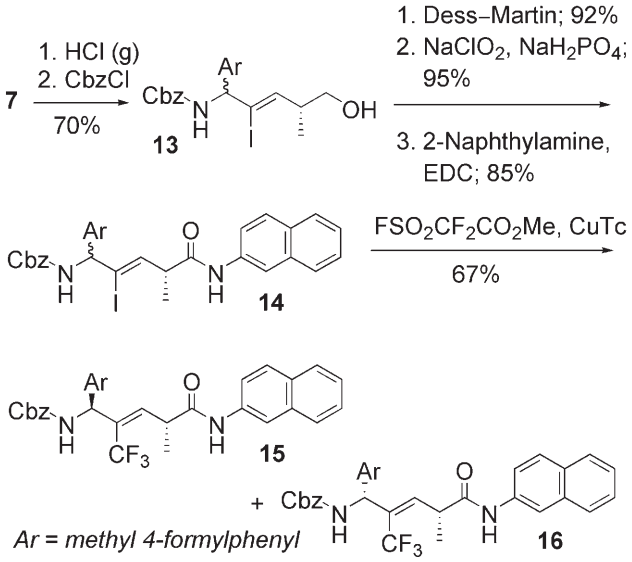


9a – j

Entry	RI	Product	Yield [%]
1		**9a**	63%
2		**9b**	64%
3		**9c**	79%
4		**9d**	77%
5		**9e**	51%
6		**9f**	82%
7		**9g**	58%
8		**9h**	61%
9		**9i**	72%
10		**9j**	95%



Scheme 4. Negishi cross-coupling for the synthesis of phenyl-substituted TEADIs.

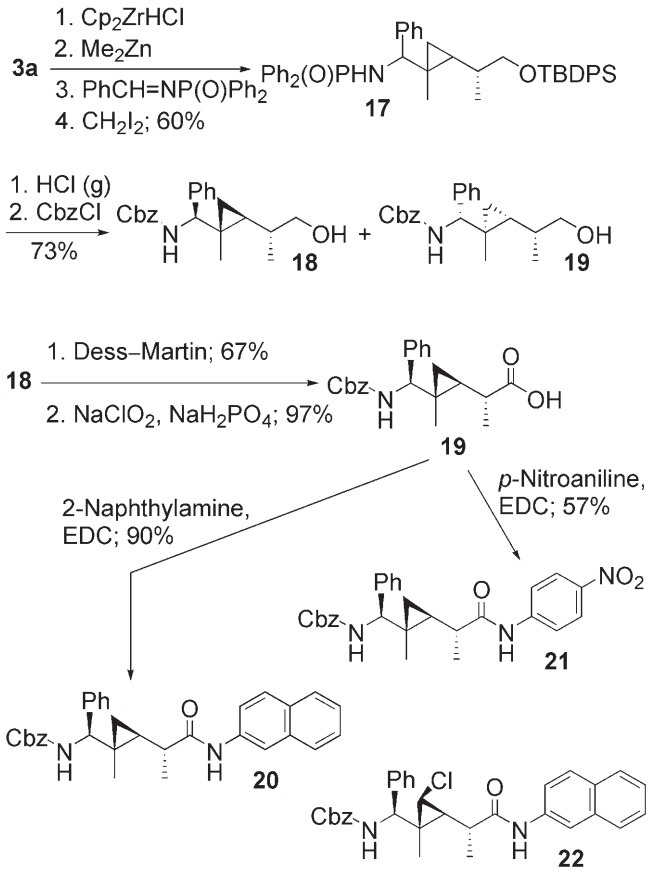


Scheme 5. Synthesis of trifluoromethyl-substituted TEADIs from iodide **14**.

tuted counterpart.[7b,34] However, when we subjected iodide **7** to coupling conditions with nucleophilic trifluoromethyl groups,[35] the reaction suffered from unexpected low yield and partial conversion because of competing TBDPS-deprotection and other side reactions. Gratifyingly, when **7** was converted to the corresponding amide **14**, the coupling with $FSO_2CF_2CO_2Me$[36] in the presence of copper(I) thiophenecarboxylate (CuTc) in DMF afforded the corresponding CF_3-substituted TEADIs **15** and **16**, which were separated by chromatography on SiO_2 (Scheme 5).

Methyl-Substituted Cyclopropane Dipeptide Isosteres (CPDIs)

One of the highlights of the coupling of organozirconocenes and imines is its ready combination with Simmons–Smith[37] chemistry for the preparation of cyclopropanated derivatives. CPDI analogues of TEADIs can be obtained by closely related DMCR processes (Scheme 6). A 3:2 *syn*,*syn*:*syn*,*anti* mixture of *N*-phosphinoylaminocyclopropanes **17** was obtained in 60% yield from **3a**. Simultaneous *N*- and *O*-deprotection followed by selective *N*-reprotection with CbzCl afforded a separable mixture of alcohols **18** and **19**. After oxidation to the carboxylic acid, carbodiimide mediated coupling[38] with amines provided CPDIs **20** and **21**.[39] Interestingly, upon scale-up of the preparation of **19** and **20** to the multi-gram level, the chlorocyclopropane by-product **22** was isolated in *ca.* 2% yield as a single diastereomer. While the mechanism of the stereoselective chlorination of the cyclopropane is not completely obvious, a radical process during the sodium chlorite oxidation step is likely involved.



Scheme 6. Synthesis of methyl-substituted CPDIs.

Solid State Structural Analyses of Selected TEADIs and CPDIs

The single crystal X-ray structural analysis plays a very important role in peptide secondary structure determination, even though sometimes solution structures differ from those in the solid state.[6b,40] In order to evaluate the potential of these dipeptide isosteres as β-turn promoters[10] as well as obtain unambiguous assignments of diastereomers, X-ray structures of **5a**, **5b**, **11**, **21** and **22** were procured (Figures 3 and 4). By comparison to typical β-turns,[41] the conformation of isostere **5b** can be assigned as a type II′ β-turn (the four core dihedral angles are $\phi_2 = 65.8°$, $\psi_2 = -121.1°$, $\phi_3 = -101.5°$, and $\psi_3 = 4.2°$) with a characteristic ten-membered hydrogen bonding interaction and a bond length of 2.52 Å. Normally, the length of a typical β-turn hydrogen bond measures around 2.3 Å. Due to the bulk of the TMS substituent, the conformation-anchoring allylic strain interaction is particularly severe for isostere **5b**. It was also interesting to note that the conformations of the other isosteres varied quite broadly. Isostere **5a** could be classified as a type V′ β-turn, a less common relative of the type II′ β-turn with a variable ψ_3 dihedral angle. The larger steric bulk of the TMS *vs.* the methyl group accounts for a narrower tolerance of the ψ_3 dihedral angle and a more compact backbone-side chain packing, facilitating the formation of the intramolecular hydrogen bond. In proteins, type V′ β-turns occur much less frequently than type II′, and they are often not hydrogen-bonded.[42] However, for both types, the $D_{(i+1)}L_{(i+2)}$-configuration at the amino acid α-carbons is preferred, which is the configuration present in both **5a** and **5b**. In contrast, the $L_{(i+1)}L_{(i+2)}$-configuration present in **11**, **21**, and **22** would be expected to stabilize turn types I and III, but maybe due to crystal packing forces two angles (ϕ_2 and ψ_3 for **11**, and ψ_2 and ψ_3 for **21** and **22**) differ by more than 40° from type I (Figure 4). Therefore, the latter reverse turns should be classified as type IV β-turns. The introduction of the chlorine substituent on the cyclopropane ring has almost no effect on the turn conformation (**21** *vs.* **22**). In addition, the distances between $\alpha C_{(i+1)}$ and $\alpha C_{(i+2)}$ were found to be very similar to the parent amide (3.8 Å) for both the trisubstituted (*E*)-alkene isosteres (**5a**, 3.904 Å; **5b**, 4.034 Å; **11**, 3.908 Å) and the cyclopropane isosteres (**21**, 3.909 Å; **22**, 3.881 Å). Significantly, all isosteres thus represent realistic replacements for the amide linkage in peptides.

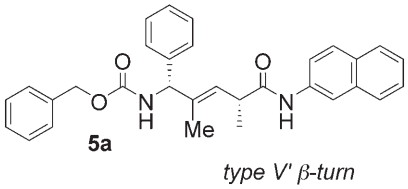
Conclusion

We have developed a new and convergent protocol for the efficient synthesis of trisubstituted (*E*)-alkene dipeptide isosteres (ψ[(*E*)-C(X)=CH], TEADIs). A broad variation of the conformation-determining alkene X-substituent was accomplished that allows the preparation of methyl-, trifluoromethyl-, trimethylsilyl-, stannyl-, iodo-, fluoro-, aryl-, and heteroaryl-functionalized alkenes. Novel trisubstituted cyclopropane dipeptide isosteres (ψ[RCp], CPDIs) were obtained by DMCR methodology. δ-Amino acid scaffolds with (*E*)-alkene or cyclopropane core elements can be used as building blocks for bioorganic and supramolecular chemistry as well as for structure-activity studies of biologically active peptide sequences in medicinal chemistry.[43]

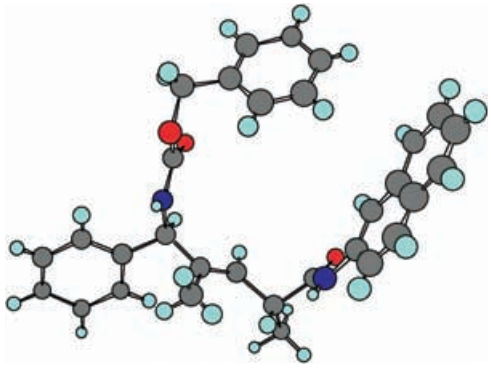
Experimental Section

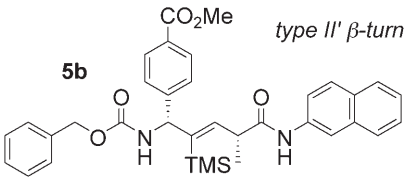
General Remarks

All moisture-sensitive reactions were performed using syringe-septum cap techniques under an N_2 atmosphere and all glassware was dried in an oven at 150 °C for 2 h prior to use. THF was distilled over sodium/benzophenone ketyl; CH_2Cl_2, toluene and Et_3N were distilled from CaH_2. Me_2Zn (2.0 M solution in toluene) was purchased from Aldrich Company. Reactions were monitored by TLC analysis (EM Science pre-coated silica gel 60 F_{254} plates, 250 μm layer thickness) and visualization was accomplished with a 254 nm UV light and by staining with Vaughn's reagent [4.8 g $(NH_4)_6Mo_7O_{24}\cdot 4\,H_2O$, 0.2 g

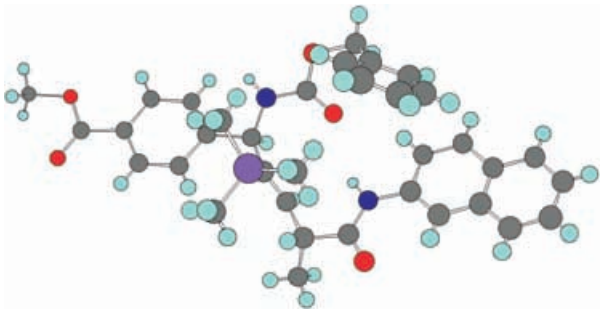


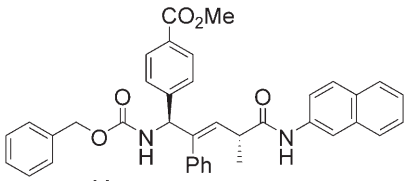
type V' β-turn





type II' β-turn





type IV β-turn

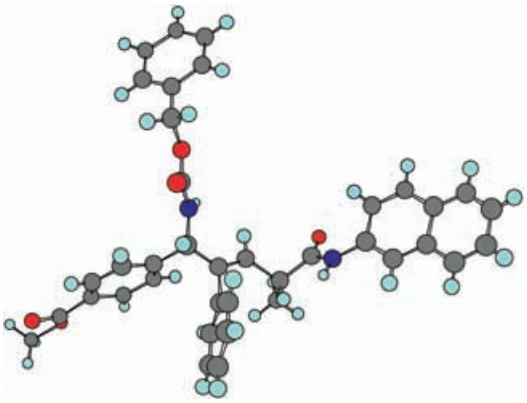
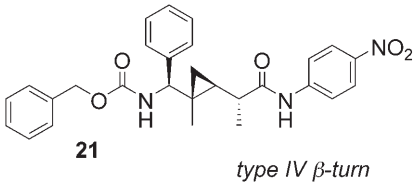
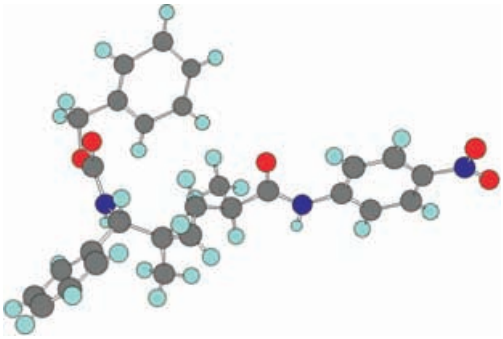
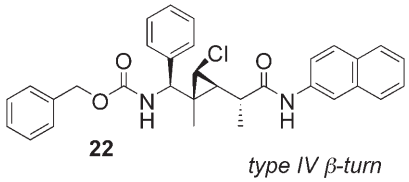


Figure 3. X-ray structures of TEADIs **5a**, **5b**, and **11**.



type IV β-turn





type IV β-turn

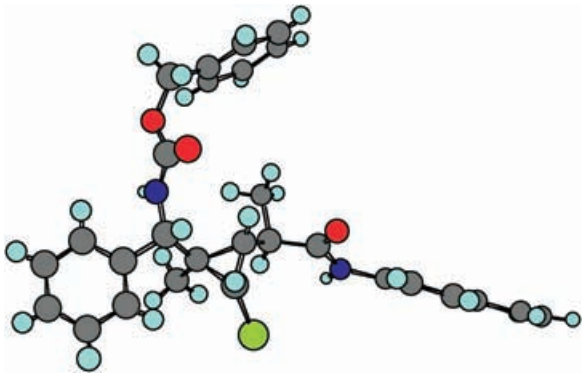


Figure 4. X-ray structures of CPDIs **21** and **22**.

$Ce(SO_4)_2 \cdot 4\,H_2O$ in 10 mL concentrated H_2SO_4 and 90 mL H_2O). Flash chromatography on SiO_2 was used to purify the crude reaction mixtures. An Emrys Optimizer microwave reactor from Personal Chemistry (Biotage) was used for microwave reactions.

N-[5-(*tert*-Butyldiphenylsilanyloxy)-2-tributyltinyl-(4*R*)-methyl-(1*SR*)-(methyl-4-formylbenzoic)pent-(2*Z*)-enyl]-*P*,*P*-diphenylphosphinamide (6a); Typical Protocol for Imine Addition

A suspension of 5.05 g (19.6 mmol) of Cp_2ZrHCl in 50.0 mL of CH_2Cl_2 was treated at room temperature with 6.00 g (9.81 mmol) of **3c**. After 15 min, CH_2Cl_2 was removed on the rotatory evaporator and 50.0 mL of toluene were added. The reaction mixture was cooled to $-78\,^{\circ}C$ and treated over a pe-

riod of 30 min with 4.91 mL (9.82 mmol) of Me_2Zn (2.0 M solution in toluene). The mixture was stirred at $-78\,^{\circ}C$ for 30 min, warmed to room temperature over a period of 5 min and treated in one portion with 2.38 g (6.55 mmol) of methyl 4-[(diphenylphosphinylimino)methyl]benzoate. The mixture was stirred at room temperature overnight, quenched with saturated NH_4Cl, diluted with EtOAc, filtered through Celite, and washed with H_2O and brine. The organic layer was dried ($MgSO_4$), concentrated under vacuum, and purified by chromatography on deactivated SiO_2 (1:1, hexanes/EtOAc containing 1% Et_3N) to afford **6a** as a yellow, oily ~2:1 mixture of diastereomers; yield: 4.18 g (65%); IR (neat). $\nu = 3380, 3314, 3186, 3071, 2956, 2929, 2856, 1724, 1609, 1463, 1438, 1428, 1279, 1192, 1111, 1078, 1020, 824, 741, 726, 702\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.98-7.79$ (m, 6H), 7.72–7.66 (m, 4H), 7.43 (d, 2H, $J = 9.0$ Hz), 7.47–7.28 (m, 12H), 6.21 [d, 0.35H, $J = 9.9$ Hz, dd (^{117}Sn 7.5%, ^{119}Sn 8.6%), $^3J_{H\text{-}Sn} = 118$ Hz, $^3J_{H\text{-}H} = 9.9$ Hz], 6.08 [d, 0.65 H, $J = 10.0$ Hz, dd (^{117}Sn 7.5%, ^{119}Sn 8.6%), $^3J_{H\text{-}Sn} = 119$ Hz, $^3J_{H\text{-}H} = 10.0$ Hz), 4.97–4.86 (m, 1H), 3.91 (s, 3H), 3.71–3.51 (m, 2H), 3.15 (dd, 0.65H, $J =$ 10.6, 6.7 Hz), 3.02 (dd, 0.35H, $J = 10.5$, 6.6 Hz), 2.50–2.40 (m, 1H), 1.26–1.13 (m, 15H), 1.10 (s, 4H), 1.08 (s, 5H), 0.77 (t, 9H, $J = 7.0$ Hz), 0.70–0.60 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 174.8, 166.7, 148.2, 148.0, 144.7, 144.6, 144.4, 144.0, 143.9, 143.2, 135.5, 133.8$ (2C), 133.5, 133.4, 133.3, 132.7, 132.6, 132.5, 132.1 (2C), 131.7, 131.5 (2C), 131.4, 130.9, 130.8, 129.6, 129.5, 128.8, 128.7, 128.4, 128.2, 128.0 (2C), 127.6, 127.5, 68.6, 68.3, 62.3, 61.4, 51.8, 42.0, 29.0, 28.8 (2C), 28.6, 27.5, 27.1, 26.8, 26.7, 19.2 (2C), 18.0 (2C), 13.9, 13.6, 13.4, 10.8, 10.6; EI-MS: $m/z = 976$ (M^+, 0.52), 947 (0.44), 920 (87), 630 (30), 552 (6), 450 (24), 336 (100), 201 (57), 135 (39).

N-[5-(*tert*-Butyldiphenylsilanyloxy)-2-phenyl-(4*R*)-methyl-(1*SR*)-(methyl-4-formylbenzoic)pent-(2*E*)-enyl]-*P,P*-diphenylphosphinamide (9a); Typical Protocol for Microwave-Accelerated Stille Coupling

In a 10-mL microwave tube, 16.4 mg (387 μmol) of LiCl was flame fused under vacuum. After cooling to room temperature, 7.45 mg (6.44 μmol) of $Pd(PPh_3)_4$ and 25.4 mg (257 μmol) of CuCl were added. The mixture was degassed 3 times under vacuum with an argon purge. A solution of 47.0 mg (48.1 μmol) of **6a** and 13.1 mg (64.2 μmol) of iodobenzene in DMSO (2.00 mL) was added with stirring. The resulting black mixture was degassed by a freeze-thaw process and heated under microwave irradiation at 60 °C for 40 min. The brown solution was quenched with H_2O, and extracted with EtOAc. The combined organic layers were dried ($MgSO_4$), concentrated under vacuum, and purified by chromatography on SiO_2 (1:1, hexanes/EtOAc) to afford **9a** as a colorless, solid ~ 1:1 mixture of diastereomers; yield: 23.0 mg (63%); mp 72–74 °C (ether); IR (neat): $\nu = 3184, 3054, 2958, 2930, 2858, 1723, 1610, 1437, 1280, 1192, 1111, 1020, 917, 824, 743, 725, 701\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.92-7.86$ (m, 2H), 7.84–7.76 (m, 4H), 7.67–7.63 (m, 2H), 7.59–7.59 (m, 2H), 7.48–7.32 (m, 14H), 7.23–7.17 (m, 3H), 6.84 (dd, 1H, $J = 7.7$, 1.9 Hz), 6.78 (dd, 1H, $J = 7.7$, 1.7 Hz), 5.63 (d, 0.5H, $J = 10.1$ Hz), 5.51 (d, 0.5H, $J = 10.0$ Hz), 5.07 (t, 0.5H, $J = 10.7$ Hz), 5.04 (t, 0.5H, $J = 10.7$ Hz), 3.91 (s, 1.5H), 3.90 (s, 1.5H), 3.58–3.43 (m, 2H), 3.28–3.21 (m, 1H), 2.49–2.44 (m, 0.5H), 2.39–2.33 (m, 0.5H), 1.07 (s, 4.5H), 1.00 (s, 4.5H), 0.98 (d, 1.5H, $J = 7.0$ Hz), 0.95 (d, 1.5H, $J = 6.7$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 166.9, 166.8, 146.8 (2C), 141.5, 141.4, 137.9, 137.3, 135.5 (2C), 135.4, 134.1, 133.6 (2C), 133.5, 133.4, 133.1, 132.6, 132.7, 132.5, 132.4, 132.3 (2C), 131.9, 131.8 (2C), 129.7, 129.6, 129.5, 129.4, 129.1, 128.9, 128.8, 128.5, 128.4, 128.3 (2C), 128.1, 127.6 (2C), 127.5, 127.3, 127.2 (2C), 68.5, 68.3, 61.3, 60.8, 51.9, 35.9, 26.8 (2C), 19.2 (2C), 17.4, 17.3; EI-MS: $m/z = 763$ (M^+, 0.44), 706 (38), 416 (5), 398 (18), 364 (25), 259 (8), 218 (17), 201 (100), 183 (17), 135 (37), 91 (14), 77 (28); HR-MS (EI): *m/z* calcd. for $C_{44}H_{41}NO_4PSi$ ($M - C_4H_9$): 706.2543; found: 706.2509.

Supporting Information

Comprehensive experimental protocols and spectroscopic data for all new compounds.

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