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Synthesis of Quaternary Amino Acids Bearing a (2′Z)-Fluorovinyl α -Branch: Potential PLP Enzyme Inactivators

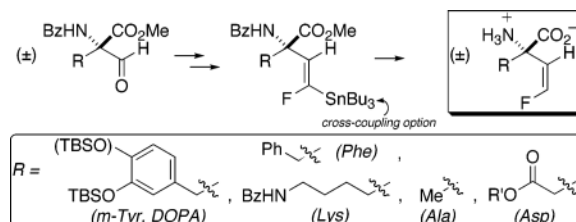
David B. Berkowitz, Roberto de la Salud-Bea, and Wan-Jin Jahng

Department of Chemistry, University of Nebraska, Lincoln, Nebraska 68588-0304

Abstract

Protected α -formyl amino acids, themselves available from the corresponding α -vinyl amino acids, are stereoselectively transformed into the (*Z*)-configured α -(2′-fluoro)vinyl amino acids via a three-step sequence. The route employs McCarthy's reagent, diethyl α -fluoro- α -(phenylsulfonyl)-methyl phosphonate, and proceeds via the intermediate (*E*)- α -fluorovinyl sulfones and (*E*)- α -fluorovinylstannanes. The latter may either be exploited as novel cross-coupling partners for fluorovinyl branch extension or be globally deprotected, to provide the title compounds.

Graphical abstract



Quaternary, α -vinyl amino acids (AA's) are potential mechanism-based inactivators of pyridoxal phosphate (PLP) dependent enzymes, particularly amino acid decarboxylases (AADC's).^{1,2} The "vinylic trigger" is also found in the naturally occurring PLP-enzyme inactivator vinylglycine³ and in the anti-epileptic drug vigabatrin (γ -vinyl-GABA),⁴ which has gained attention more recently for its potential application in the treatment of substance abuse.⁵ Elegant work by Silverman and John has elucidated the mechanism by which the vinylic trigger in vigabatrin functions to inactivate GABA transaminase.^{6,7} Both electrophilic (Michael addition) and nucleophilic (Metzler-type enamine-PLP aldimine condensation⁸) pathways are operative, each of which follows from the normal first two enzymatic steps (transaldimination/ γ -proton abstraction).

Introduction of a 2′-fluorine atom into this trigger might lead to an alternative, potentially more electrophilic,⁹ Michael acceptor, on one hand, and might divert the Metzler enamine pathway into a second Michael addition pathway, on the other. Indeed, in the one case in

Correspondence to: David B. Berkowitz.

Supporting Information **Available:** Complete set of ¹H NMR and selected ¹⁹F NMR spectra, as well as experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

which such a trigger has been reported, for γ -(2'-fluoro)- γ -vinyl-GABA inactivation of GABA transaminase, such changes in mechanism are evident, though multiple pathways are operative.¹⁰ Interestingly, in that case, the (*Z*)- and (*E*)-(2'-fluoro)vinyl triggers give different profiles, highlighting the importance of accessing single geometric isomers.¹¹

Given this, it would be interesting to install such a trigger *at the* α -carbon to probe its effectiveness in an AADC active site. Yet, to our knowledge, no syntheses of quaternary, α -(2'-fluoro)vinyl AA's have yet been reported, though (*E*)- and (*Z*)- α -(2'-fluoro)vinylglycine have been described by McCarthy.¹²

A fluoromethylenation route related to McCarthy's¹³ was attractive, as protected α -formyl AA's might be obtained ozonolytically, from the corresponding quaternary, α -vinyl AA's. The latter were available, with appropriate protecting groups, via a formal α -vinylation sequence that had been developed earlier (Scheme 1).¹⁴ Furthermore, success in the racemic series here would map onto an enantioselective variant, starting from either L- or D- α -vinyl AA's.¹⁵ Pleasingly, the ozonolysis of vinylic AA's (**4**) to formyl AA's (**5**) proceeded in good to excellent yield, across an array of functionalized side chains (Table 1).

McCarthy had taken a Horner Wadsworth Emmons (HWE) approach, condensing lithio diethyl α -fluoro- α -(phenylsulfonyl)methylphosphonate (**6**) with the Garner aldehyde to obtain an (*E*)/(*Z*) mixture of α -(2'-fluoro)vinylglycinol isomers.¹² In considering the application of this chemistry here, several key issues arose at the outset: (i) Would such sterically encumbered aldehydes (**5**) be amenable to nucleophilic attack by **6**? (ii) If so, would the intermediate β -alkoxyphosphonates follow the desired HWE reaction mode or fragment along a competing "retro-Claisen" mode (Scheme 2)? (iii) Would any such HWE products be formed as an *E/Z* mixture as is typical for this chemistry?¹²

Should these issues be addressable, this synthetic strategy would be redox-efficient in that the α -carboxyl group oxidation state would be preserved throughout. This route would also have the attractive feature of providing intermediate α -fluorovinylstannanes as potential vehicles for fluorovinyl branch extension. Indeed, as can be seen from Table 2, the targeted fluorovinyl sulfones were obtained in each case and *as single geometric isomers*. This level of diastereoselectivity is unusual for carbonyl condensation reactions of **6**, and presumably is a reflection of the steric demand of the quaternary α -center. Furthermore, though the competing "retro-Claisen" manifold is observed, the HWE pathway predominates for all AA's but aspartate.

The subsequent tin-sulfone exchange proceeded smoothly under the agency of Bu_3SnH , generally in very high yield (Table 3). *Surprisingly, only the (E)-stereoisomers were observed in the crude NMR spectra of these reactions.* Previously, McCarthy had observed *E/Z* equilibration in such transformations for fluorovinyl sulfones bearing a single β -substituent.¹² Thus, the transformations **7a-f** \rightarrow **9a-f** may be the first examples of stereospecific tin-sulfonyl exchange for β -monosubstituted, α -fluorovinyl phenyl sulfones.¹⁶ Once again, attachment of a hindered quaternary center directly to the β -vinylic position appears to confer an unexpectedly high degree of stereocontrol.

At this juncture, we selected stannane **9a** as a model compound to examine its potential for chain extension to AA's bearing side chains with embedded fluorovinyl groups (Scheme 3).¹⁷ Stille-type couplings¹⁸ with aryl halides produced α -methylated and homologated analogues of phenylalanine (**11**) and *m*-tyrosine (**13**). A similar Pd-mediated coupling with ethyl chloroformate¹⁹ yielded the α -methylglutamate analogue **10**.

Alternatively, tin-iodine exchange could be effected smoothly to **12**, which could subsequently be engaged in a "ligandless" Suzuki coupling²⁰ with PhB(OH)₂, as an alternative route to **11** (Scheme 4). Pd-mediated Negishi-type coupling²¹ with Me₂Zn or the analogous Ni-mediated procedure of Knoche²² could be applied to the synthesis of **14**, an unusual analogue of α -methylleucine in which a fluorine atom takes the place of a methyl group.

Finally, upon refluxing in 6 N HCl, **7a-f** could be protodestannylated with concomitant ester, ether, and amide hydrolysis to **15a-f**, the free, quaternary, α -(2'-Z-fluoro)-vinyl AA's, bearing side chains relevant to target PLP enzymes. Studies of this new class of potential AADC inactivators are now underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

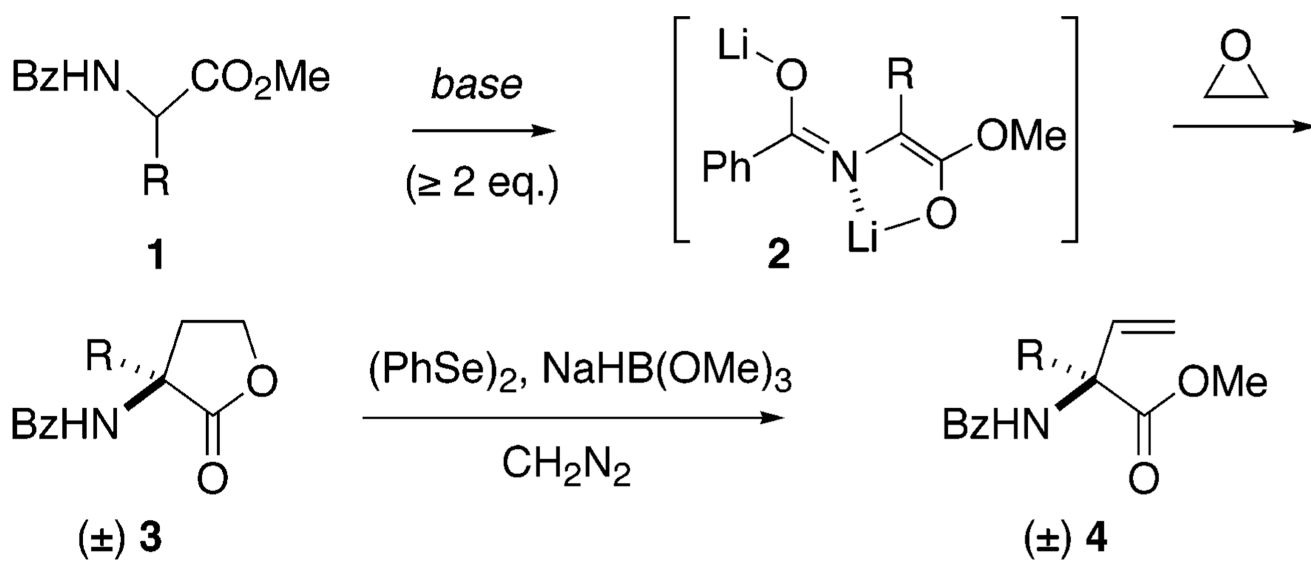
Acknowledgments

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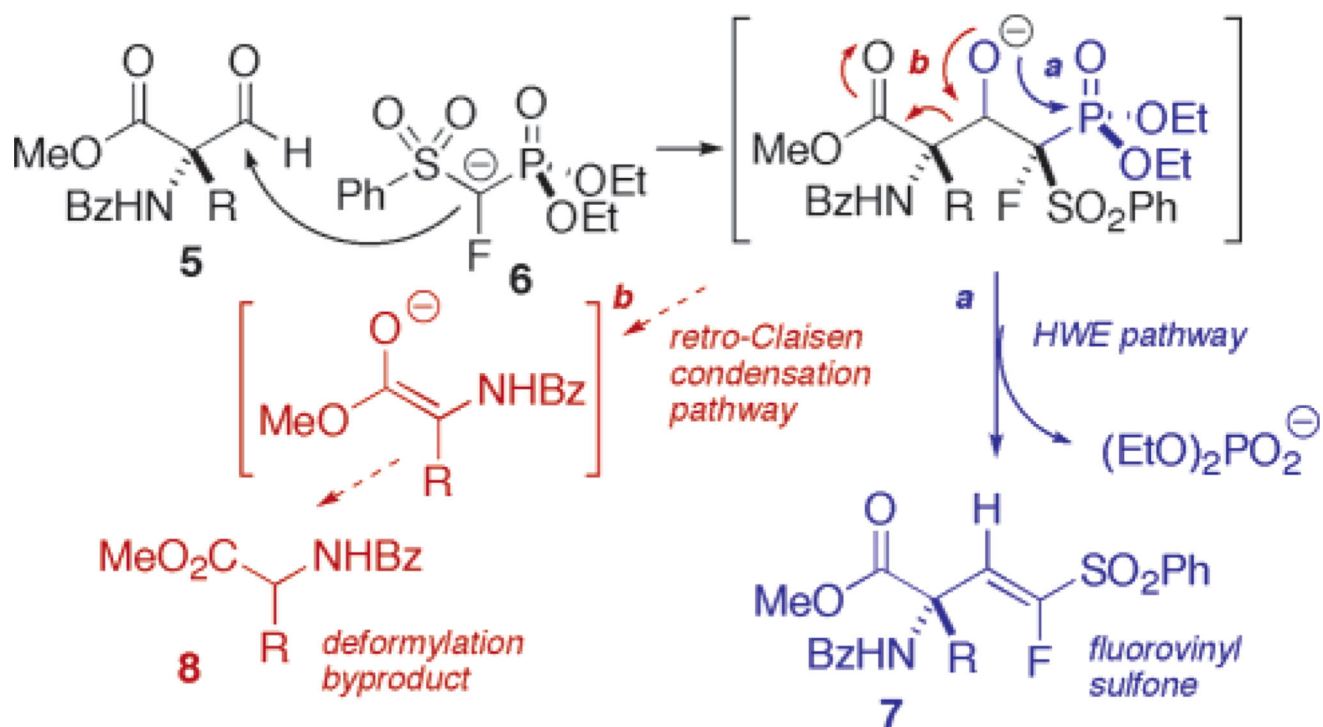
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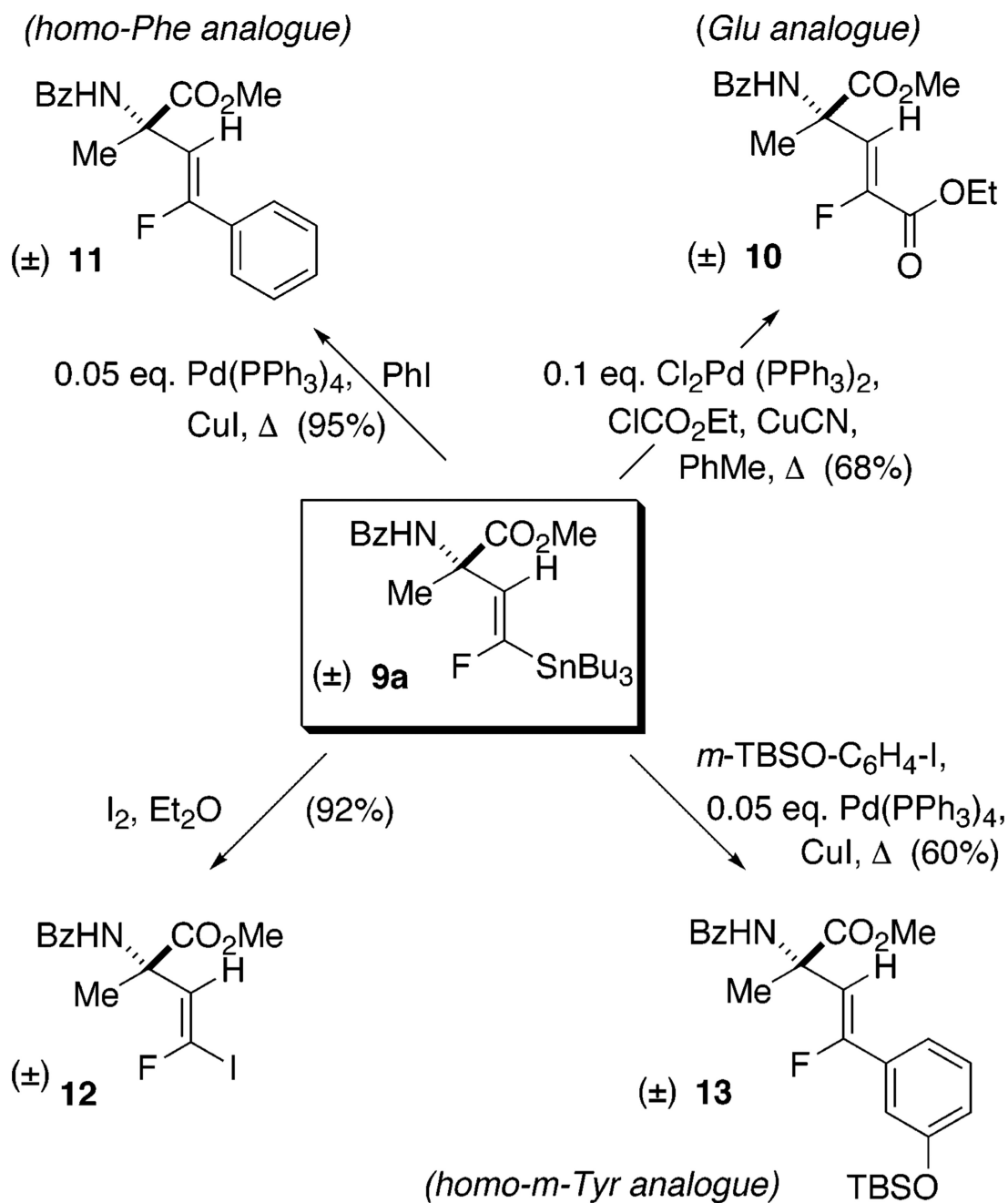
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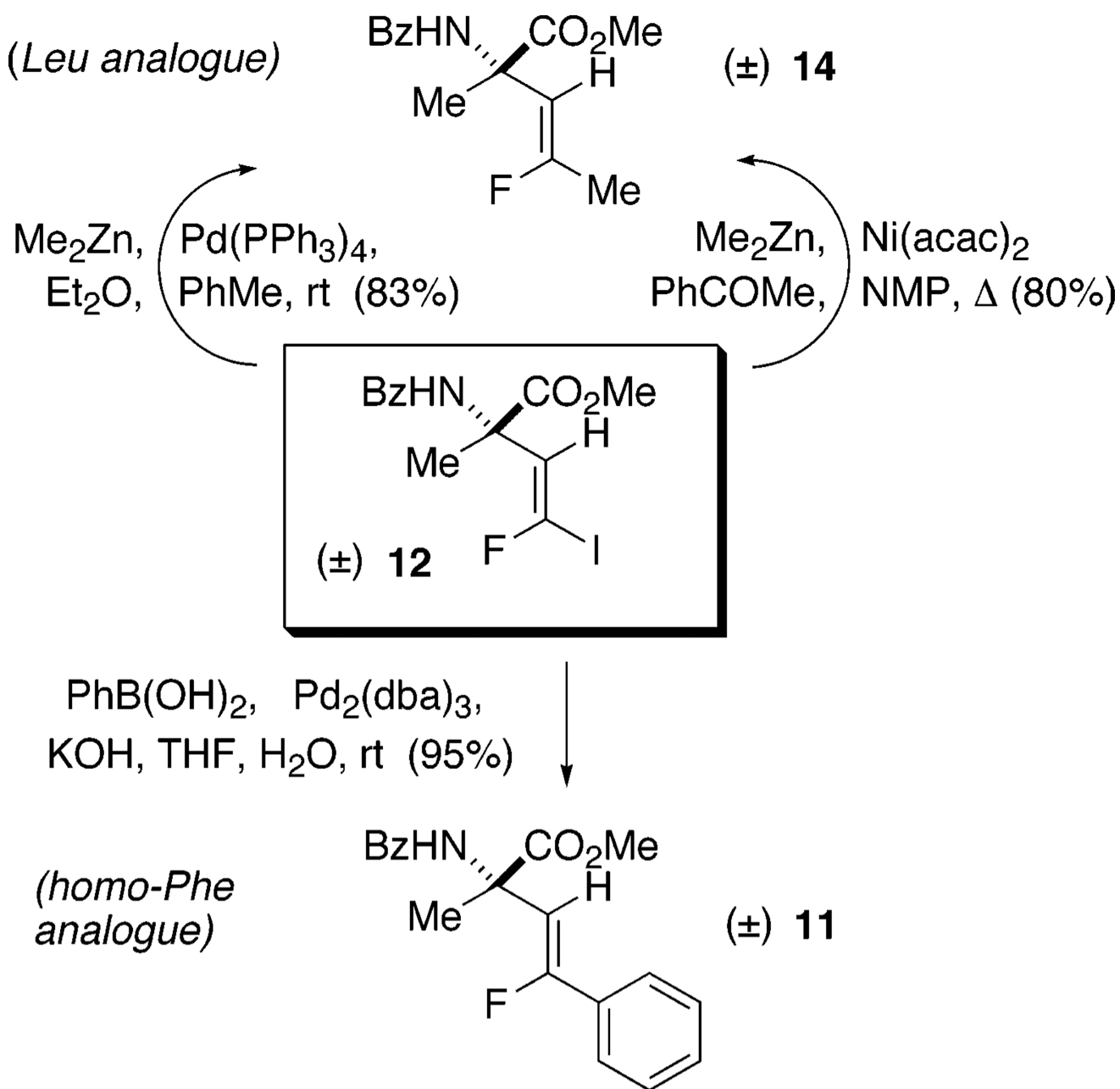
Scheme 1.
Formal α -Vinylation of Amino Acids



Scheme 2.
Competition between HWE and “Retro-Claisen” Condensation Manifolds

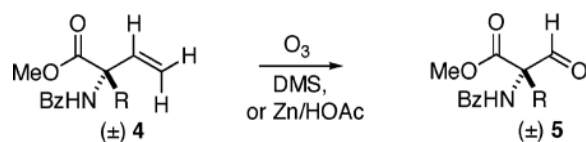
**Scheme 3.**


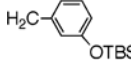
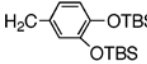


Introduction of Fluoroalkene-Embedded Side Chain Functionality via Stille-Type Coupling



Scheme 4.
Negishi and Suzuki-Type Couplings on α -Fluorovinyl Iodide **12**

Table 1

From Vinyl AA's to Formyl AA's^a

entry	R	AA	reduction method ^b	yield of 5 ^c
a	Me	Ala	A1	87%
b		Phe	A2	93%
c		<i>m</i> -Tyr	A2	66%
d		DOPA	A2	99%
e		Lys	A2	84%
f		Asp	A1	65%


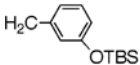
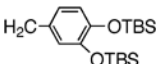

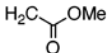
^aProcedure: Ozone was bubbled into a solution of the protected vinyl-AA (**4a-f**) in CH₂Cl₂ at -78 °C, until a light blue color persisted. After several minutes, oxygen was then bubbled through to remove excess ozone (decolorizes).

^bMethod A1: The crude ozonide was reduced with Me₂S at room temperature. Method A2: Ozonide reduction was carried out with Zn, AcOH.

^cIsolated yields.

Table 2

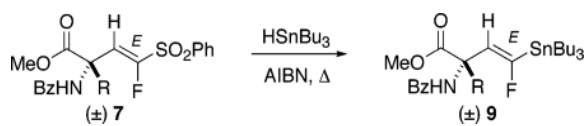
A Stereoselective McCarthy-Type HWE Reaction^a

entry	R	AA	yield of 7 ^b	yield of 8 ^c
a	Me	Ala	74%	trace
b		Phe	44%	nd
c		<i>m</i> -Tyr	55%	5%
d		DOPA	57%	17%
e		Lys	61%	24%
f		Asp	41%	41%

^aProcedure: To a solution of McCarthy's reagent (1.2. equiv) in THF at $-78\text{ }^{\circ}\text{C}$ was added LiHMDS (1.4 equiv, 1 M in hexanes) and stirring was continued for 20 min. Then, a solution of α -formyl AA (**5**) in THF at $-78\text{ }^{\circ}\text{C}$ was added via cannula. The reaction was allowed to warm to room temperature, and quenched with NH_4Cl (aq) once **5** had been consumed and a predominant spot for **7** was visible on TLC.

^bIsolated yields of purified HWE products **7** [assigned as *E* as $J_{1,2}(\text{H-F}) = 33\text{--}34\text{ Hz}$, as opposed to $\approx 22\text{ Hz}$ for *Z*, see ref 12].

^cThe "retro-Claisen" byproducts were not generally isolated. The estimated yields given are based on the ratio of **7**:**8** from the crude NMR spectra and the isolated yields of **7**.

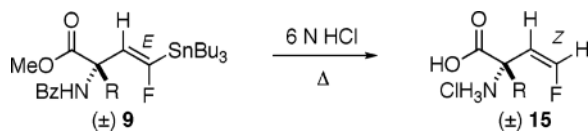
Table 3Sulfone/Stannane Interchange with Retention of Configuration^a


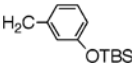
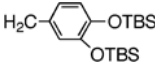
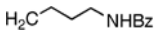
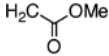
entry	R	AA	yield of 9, ^b %
a	Me	Ala	80
b	CH ₂ Ph	Phe	91
c	CH ₂ (3'-OTBS)C ₆ H ₄	<i>m</i> -Tyr	97
d	CH ₂ (3',4'-bis-OTBS)C ₆ H ₃	DOPA	79
e	(CH ₂) ₄ NHBz	Lys	76
f	CH ₂ CO ₂ Me	Asp	50

^aProcedure: An Ar-purged solution of **7** in benzene containing AIBN (glovebag) and Bu₃SnH (1 equiv) was heated at reflux, until complete conversion to **9** was evident by TLC.

^bIsolated yields of purified substitution products **9** [assigned as *E* as $J_{1,2}(\text{H-F}) = 55\text{--}58$ Hz, as opposed to ≈ 37 Hz for *Z*, see ref 12].

Table 4

Global Deprotection to the Target α -(2'-Z-Fluoro)vinyl-AA's^a

entry	R ^b	AA	yield
a	Me	Ala	89% ^d
b		Phe	85% ^d
c		m-Tyr	88% ^d
d		DOPA	93% ^d
e		Lys	63% ^e
f		Asp	52% ^e

^aProcedure: The fully protected stannylvinyl amino acid (**9**) was suspended in 6 N HCl and refluxed for 12–30 h.

^bR groups are given as they are found in the educts **9**. Under the reaction conditions, the side chain of aspartate is de-esterified, that of lysine is debenzoylated, and those of *m*-Tyr and DOPA are desilylated. Geometry is assigned as *Z* as $J_{1,2}(\text{H-F}) = 43\text{--}46$ Hz, as opposed to ≈ 17 Hz for *E*, see ref 10].

^dThese fluorovinyl AA's were isolated as their hydrochloride salts.

^eFurther purified by Dowex 50 cation exchange chromatography.