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A general preparation of (*Z*)-1-fluorostilbene derivatives for the design of conformationally restricted peptidomimetics

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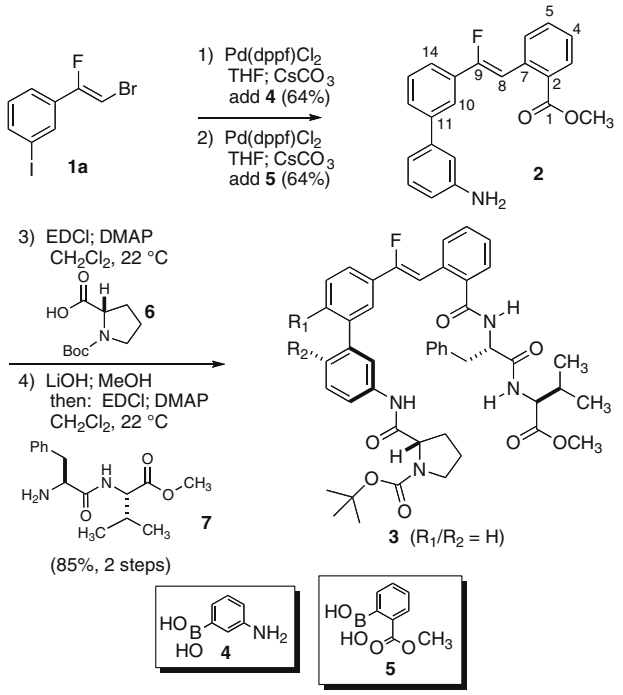
ABSTRACT

The preparation of (*Z*)-1-fluoro-2-bromostyrenes provides a general route for the formation of (*Z*)-1-fluorostilbene derivatives as configurationally stable spacial linkers for the design of conformationally restricted peptidomimetics. Palladium-catalyzed aryl Suzuki and Stille cross-coupling reactions have been surveyed to proceed with complete retention of fluoroalkene geometry, and permit the direct incorporation of a variety of aryl and heteroaromatic substituents.

The role of fluorine-containing compounds in medicinal chemistry is an important area of investigation for drug design and development.[1,2] The electronegativity and the van der Waals radius of the fluoro-substituent has led to effective replacements of oxygen as well as hydrogen.[3] These aspects may provide for enhanced binding affinities or may inhibit biological oxidation processes which result in improved metabolic stability. The inclusion of fluorine may also significantly alter the characteristic properties of potential drug candidates by addressing issues of uptake and bioavailability.

The design of peptidomimetics has led to the consideration of alkenyl fluorides as conformationally rigid surrogates for the amide bond in which the polarity introduced by fluorine in the olefin linkage would provide an electronic effect analogous to the carbonyl oxygen.[3,4] In fact, vinylic fluorides can participate as hydrogen bond acceptors within a peptide skeleton as well as with sequestered solvent molecules.[5] Our interest in the preparation of functionalized *trans*-stilbenes as configurationally rigid spatial linkers for the design of peptidomimetic substances as has led to studies of palladium-catalyzed cross-coupling reactions of (*Z*)-1-fluoro-2-bromostyrenes. In this regard, our investigations complement a previous study by McCarthy and coworkers[6] describing cross-coupling reactions of the regioisomeric *E*- and *Z*-β-bromo-β-fluorostyrenes.

Our studies have defined a general pathway for the preparation of functionalized stilbenes, such as **2**, from readily available 2-bromostyrenes (**1**) (Scheme 1) which can be sequentially linked via N- and C-terminal operations for the construction of conformationally restricted peptide derivatives. As exemplified by the amide **3**, the introduction of aryl linker **2** presents two elements of stereochemical bias which can be harnessed to investigate conformational states available to small chains of tethered peptides. Firstly, the peptide segments may be synclinal, as displayed in **3**. Since the C- and N-terminals of the linker **2** are in close proximity



Scheme 1. Formation of (*Z*)-1-fluorostilbene analogs.

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(7.06 Å), hydrogen-bonding interactions of the tethered moieties may be designed to further stabilize the synclinal conformers. On the other hand, bond rotation (C_7–C_8) of the stilbene can preorganize the attached peptide chains on opposite sides of the planar alkenyl fluoride in an *anti* conformation. Calculations indicate that synclinal **3** is more stable than the *anti* conformer by 4.5 kcal/mol. Secondly, biphenyl atropisomers may be prepared via selected R_1 and R_2 substituents in **3** as a further refinement of stereochemistry. A torsional angle of 50° is calculated for the aniline moiety in Figure 1.

Initial efforts have documented a stepwise assembly of **3** in Scheme 1 via the Suzuki coupling of boronic acid **4** with the aryl iodide of **1** followed by a second palladium insertion reaction of the alkenyl bromide with **5** to yield (*Z*)-stilbene **2**. Subsequent attachment of the amino acid side chains **6** and **7** yields peptidomimetic **3**.

An additional feature is illustrated by the sequential Pd(0) cross-coupling reactions of fully elaborated components (Scheme 2). Thus, the facile Stille coupling of the aryl iodide of **1a** selectively occurs with **8** under neutral conditions followed by the alkenyl bromide coupling to install the intact dipeptide of stannane **9**. In similar fashion the coupling reactions of **1a** with 5′-pyrimidyl **10** and stannane **9** have provided a direct route to **11**. Thus, readily available components can be utilized to access focused libraries.

To broaden the flexibility of the approach and accommodate a general design of probes for biological process, we have explored the preparation of a variety of substituted (*Z*)-1-fluoro-2-bromostyrenes, and we have surveyed Suzuki and Stille cross-coupling reactions to access electron-rich and electron-deficient derivatives, as well as heterocyclic analogs of (*Z*)-1-fluorostilbenes. Three methods were examined to prepare substituted 1-bromo-2-arylethylenes (Scheme 3). Nucleophilic displacement of bromide **12** with lithiodibromomethane at −78 °C resulted in elimination upon warming to room temperature to give **13** (*E*/*Z* ratio 20:1) in 87%

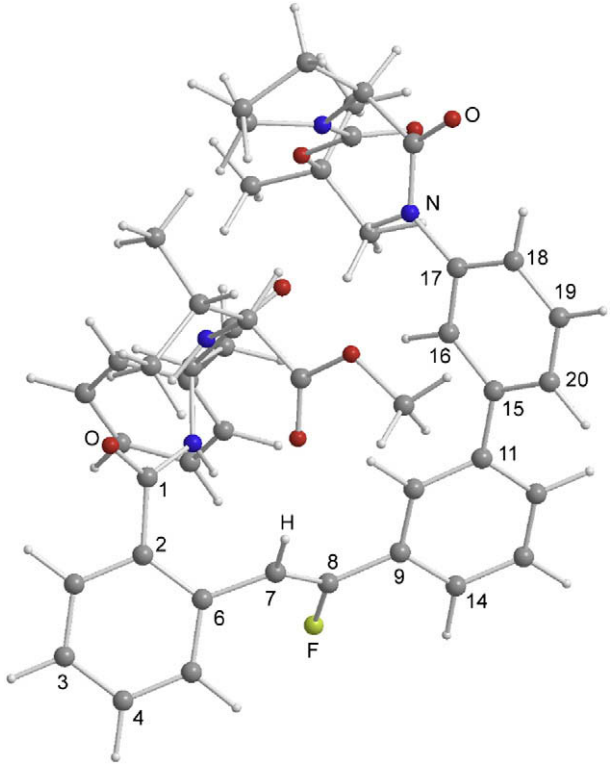
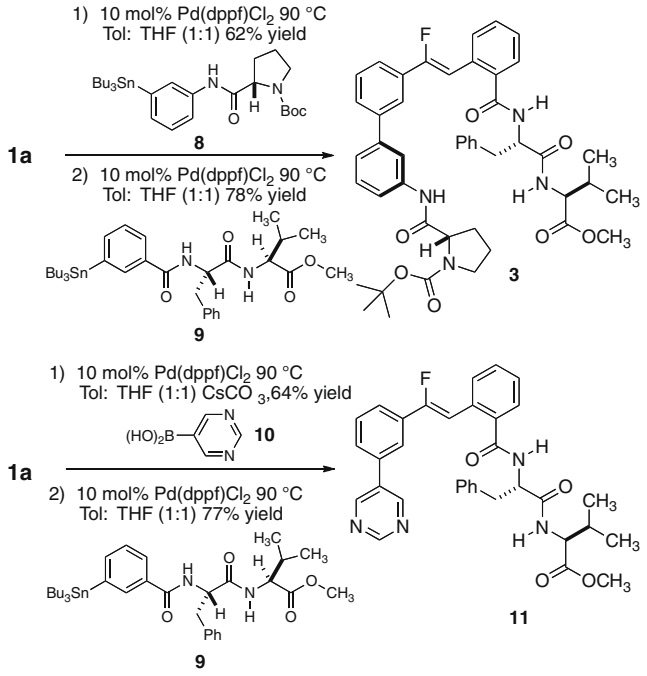
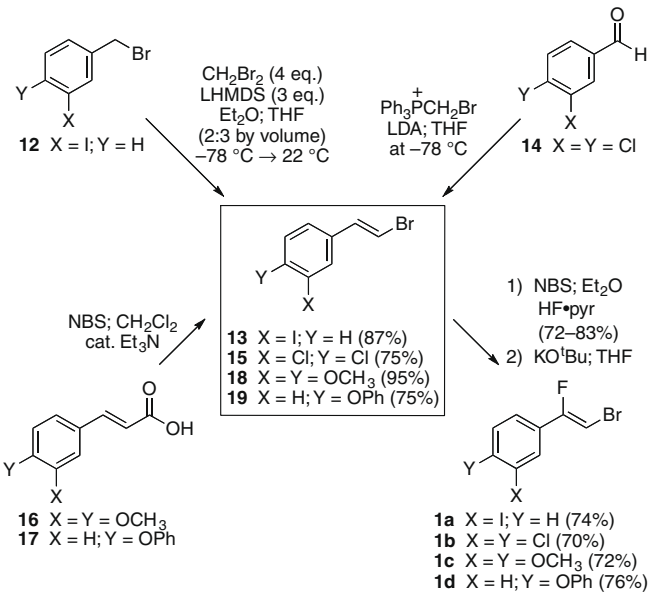


Figure 1. Energy-minimized conformation of **3** using GMMX in PCModel 9.1 (MMX employed with π-calculations enabled).



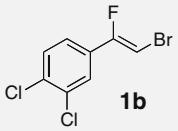
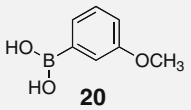
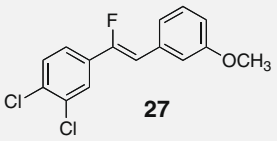
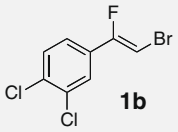
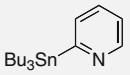
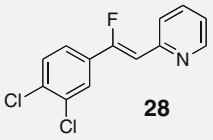
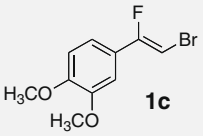
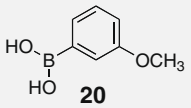
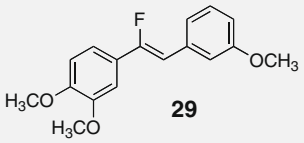
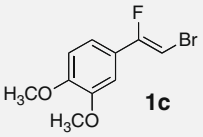
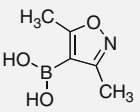
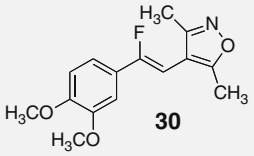
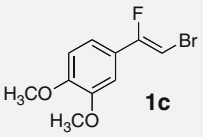
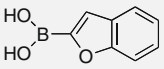
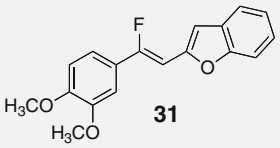
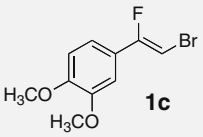
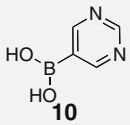
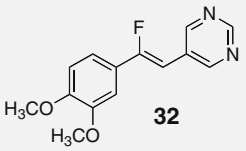
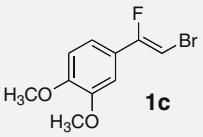
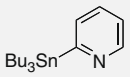
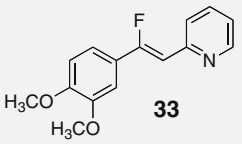
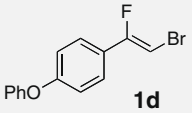
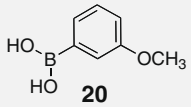
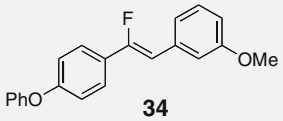
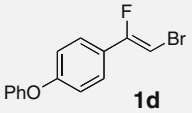
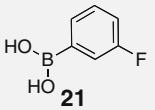
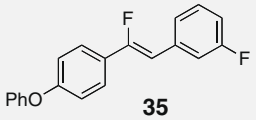
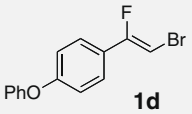
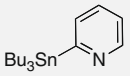
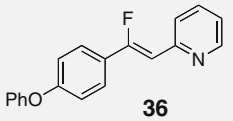
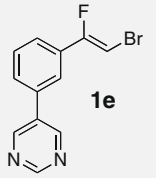
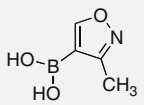
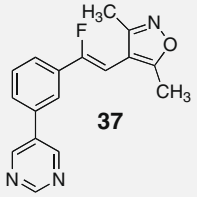
Scheme 2. Direct preparation of peptidomimetics.



Scheme 3. Preparation of 1-fluorostyrenes **1**.

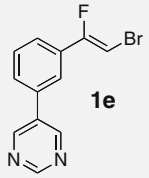
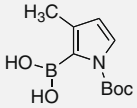
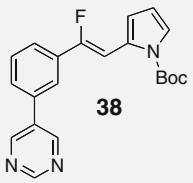
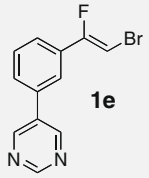
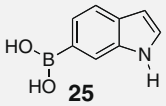
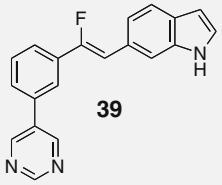
yield.[7] On the other hand, benzaldehydes, such as **14**, were utilized in Wittig olefinations to produce **15** as *Z*/*E*-mixtures (~7:1 ratio) with average yields of approximately 75%.[8] The application of the Hunsdiecker reaction[9] proved to be facile in the case of cinnamic acid derivatives containing aryl electron-donating substituents such as **16** and **17**. In these examples, reactions with recrystallized *N*-bromosuccinimide (NBS) in the presence of a catalytic amount of Et_3N led to a rapid decarboxylation at room temperature yielding the *E*-alkenyl bromides **18** and **19** with high *E*-stereoselectivity (*E*/*Z* ratio >25:1). Hunsdiecker reactions of cinnamic acids containing electron-withdrawing aryl substituents proceeded poorly. Alkenylbromides **13**, **15**, **18,** and **19** were subsequently reacted under conditions of Markonikov addition with recrystallized NBS

Table 1
Formation of (*Z*)-1-fluorostilbene analogs via cross-coupling reactions

Entry	Alkenyl fluoride	Coupling partner[a]	Product[b]	Conditions (yield)[c]
1	 **1b**	 **20**	 **27**	B (79%)
2	 **1b**	 **26**	 **28**	C (80%)
3	 **1c**	 **20**	 **29**	B (78%)
4	 **1c**	 **22**	 **30**	A (50%)
5	 **1c**	 **23**	 **31**	A (85%)
6	 **1c**	 **10**	 **32**	A (70%)
7	 **1c**	 **26**	 **33**	C (70%)
8	 **1d**	 **20**	 **34**	B (80%)
9	 **1d**	 **21**	 **35**	B (78%)
10	 **1d**	 **26**	 **36**	C (73%)
11	 **1e**	 **22**	 **37**	A (73%)

(*continued on next page*)

Table 1 (*continued*)

Entry	Alkenyl fluoride	Coupling partner[a]	Product[b]	Conditions (yield)[c]
12	 **1e**	 **24**	 **38**	A (71%)
13	 **1e**	 **25**	 **39**	A (70%)

Reaction conditions: (A) $Pd(dppf)Cl_2$ 10 mol %; $CsCO_3$; THF, sealed tube at 90 °C/8 h. (B) $Pd(PPh_3)_4$ 10 mol %; $CsCO_3$; THF, sealed tube at 90 °C/8 h. (C) $Pd(PPh_3)_4$ 10 mol %; toluene, sealed tube at 90 °C/10 h. *Notes*: (a) All coupling partners are commercially available from Frontier Scientific, Inc. (b) Products were purified by flash silica gel chromatography. (c) Yields are provided for purified products and are based on reactions of 1:1 stoichiometry of coupling reactants.

in the presence of HF·pyridine to regioselectively produce β,β-dibromo-α-fluorophenyl-ethanes.[10] Elimination with potassium *tert*-butoxide in THF proceeded smoothly to give the desired (*Z*)-1-fluoro-2-bromostyrenes **1a**, **1b**, **1c,** and **1d** (yields 70–75%) as the only observed alkene isomers.[11] Substituted (*Z*)-1-fluoro-2-bromostyrenes, such as **1e** of Table 1, are available from aryl iodides as illustrated for **1a** (see Scheme 2). The trans geometry of the fluoro and vinylic hydrogen substituents was confirmed via the characteristically large coupling constants (J_{HF} 38–40 Hz) apparent in the H NMR spectra of the products.

Results of the palladium cross-coupling reactions of the (*Z*)-1-fluoro-2-bromostyrenes **1b**, **1c**, **1d,** and **1e** are compiled in Table 1. Commercially available aryl and heteroaryl boronic acids were surveyed utilizing Suzuki conditions. Reactions proceeded with complete retention of olefin geometry to consistently provide 70–80% yields of cross-coupled (*Z*)-1-fluorostilbenes (Table 1, entries 1–13). Experiments were conducted in resealable Carius tubes in refluxing THF at 90 °C for 8–12 h in the presence of 10 mol % $Pd(dppf)Cl_2$. Reactions were monitored for consumption of the starting alkenyl bromides. Subsequently, we found that 10 mol % $Pd(PPh_3)_4$ could be used in many cases with similar results. The availability of boronic acids provides convenient access to heterocyclic derivatives, and the inclusion of isoxazole, pyrrole, indole, and pyrimidine systems offers opportunities for further elaborations. However, sluggish reactions were observed for cross-coupling of the electron-rich styrene **1c** and 3-fluorophenyl boronic acid giving rise to a modest 40% yield of the desired stilbene product.

In order to incorporate pyridine heterocycles, we examined Stille reactions with 2-tri-*n*-butylstannylpyridine (**26**) (Table 1, entries 2, 7, and 10). Facile reactions were observed with 10 mol % $Pd(PPh_3)_4$, and the complete consumption of the starting alkenyl bromide occurred in refluxing toluene with stereocontrolled generation of the corresponding *Z*-fluorostilbene analogs in 70–80% yields. All of the products of Table 1 proved to be stable at room temperature with purification via flash silica gel chromatography, and have been stored at −10 °C for several months without evidence of isomerization or decomposition.

In summary, we have described a general protocol for the preparation of substituted (*Z*)-1-fluoro-2-bromostyrenes which are utilized in Suzuki and Stille cross-coupling reactions to provide functionalized derivatives of (*Z*)-1-fluorostilbenes. These substances may be incorporated in conformationally restricted amide isosteres for the design of peptidomimetics. The differential reactivity of aryl iodide and alkenylbromide moieties in **1a** facilitates an efficient modular synthesis of peptidomimetics allowing for rapid screening of cross-coupling partners.

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Supplementary data

Supplementary information provides a description of general reaction procedures and a listing of spectral data of products of Schemes 1, 2 and 3, and Table 1. Supplementary data associated with this Letter can be found, in the online version, at doi:10.1016/j.tetlet.2009.10.099.

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