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First Stereospecific Synthesis of (*E*)- or (*Z*)-α-Fluoroenones via a Kinetically Controlled Negishi Coupling Reaction

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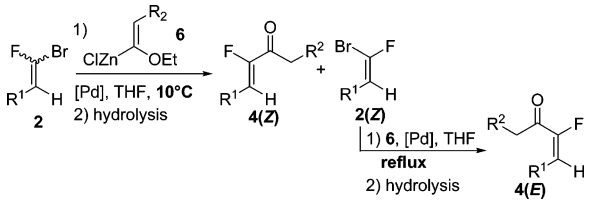

A highly stereospecific synthesis of (*E*)- or (*Z*)-α-fluoro-α,*β*-unsaturated ketones **4**, via a kinetically controlled Negishi palladium-catalyzed coupling reaction, was developed, providing an easy and general access to valuable fluorinated intermediates (pharmaceutical, peptide mimic, and so on). The synthesis involved a reaction between E/Z *gem*-bromofluoroolefins **2** and alkoxyvinylzinc species **6** under controlled reaction temperature. At 10 °C, **(*Z*)-4** (70 to 99% yields) was obtained along with unreacted **(*Z*)-2** (66 to 99% yields). At THF reflux, the recovered olefin was transformed into **(*E*)-4** (up to 98% yield).

The development of efficient and mild methods for the synthesis of organofluorine compounds represents a broad area in organic chemistry, because the incorporation of a fluorine-containing group into an organic molecule dramatically alters its physical, chemical, and biological properties.[1] Among them, monofluorinated olefins have attracted a great deal of attention because of their wide range of applications.[1,2] Especially, fluoroolefins (—CF═CH—) can act as ideal amide bond mimics (—CO—NH—) as a result of steric and electronic similarities.[3] Fluoroolefins have been used in peptide chemistry as hydrolytically stable mimics of peptidic bonds.[4] Depending on the initial configuration of the double bond (*E* or *Z*), an access to blocked cisoide or transoide peptidic bond conformation mimics is made possible. Since the pioneering study in the peptide area by Allmendinger et al.,[4a] some useful methods for the synthesis of fluoroalkenes have been reported.[5,6] Nevertheless, despite these methods, several problems remain to be tackled, in particular with respect to the control of the *Z* or *E* configuration of the double bond, the stereochemistry of the chiral center α to the double bond, and the versatility of the syntheses.

Our initial project aimed to propose a stereospecific and mild method to obtain both isomers of dipeptide mimics **5**. Our strategy was based on the reaction of easily accessible bromofluoroalkenes **2**[7] to set up the carbon skeleton, followed by a Nozaki—Hiyama—Kishi reaction (Scheme 1).[8] Unfortunately, under these conditions, we were unable to access to the *E* isomer, probably because of the instability of the chromium intermediate derived from (*Z*)-bromofluoroalkenes **2**.

To provide straightforward access to both isomers from the same precursor **2**, we decided to investigate the palladium-catalyzed coupling reactions, which are known to react with hindered *Z* vinylhalides.[9] Another advantage of these methods is the potential difference in reactivity between *E* and *Z* isomers, which allows a selective coupling of the *E* isomer in the presence of the *Z* isomer by kinetic control.[10] To anticipate further

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(1) (a) Kirsch, P., Ed. *Modern Fluoroorganic Chemistry*; Wiley-VCH: Weinheim, Germany, 2004. (b) Chambers, R. D., Ed. *Fluorine in Organic Chemistry*; Blackwell Publishing CRC Press: Boca Raton, FL, 2004. (c) Banks, R. E., Smart, B. E., Tatlow, J. C., Eds. *Organofluorine Chemistry: Principle and Principal Applications*; Plenum Press: New York, 1994.

(2) (a) Fieler, R.; Kobayashi, Y. *Biomedical Aspects of Fluorine Chemistry*; Elsevier: Amsterdam, 1982. (b) Ojima, I. *ChemBioChem* **2004**, *5*, 628—635. (c) Jeschke, P. *ChemBioChem* **2004**, *5*, 570—579. (d) Resnati, G., Soloshnok, V. A., Eds.; *Fluoroorganic Chemistry: Synthetic Challenges and Biomedical Rewards*; Tetrahedron Symposia-in-print No. 58 *Tetrahedron* **1996**, *52*, 1—330.

(3) (a) Welch, J. T.; Lin, J.; Boros, L. G.; De Corte, B.; Bergmann, K.; Gimi, R. H. In *Biomedical Frontiers of Fluorine Chemistry*; The American Chemical Society: Washington, DC, 1996; Chaper 10, pp 129—142. (b) Cieplak, P.; Kollman, P. A.; Radomski, J. P. In *Biomedical Frontiers of Fluorine Chemistry*; The American Chemical Society: Washington, DC, 1996; Chapter 11, pp 143—156 (c) Abraham, R. J.; Ellison, S. L. R.; Schonholzer, P.; Thomas W. A. *Tetrahedron* **1986**, *42*, 2101—2110.

(4) (a) Allmendiger, T.; Furet, P.; Hungerbühler, E. *Tetrahedron Lett*. **1990**, *31*, 7297—7300 and 7301—7304. (b) Boros, L. G.; De Corte, B.; Gimi, R. H.; Welch, J. T.; Wu, Y.; Handschumacher, R. E. *Tetrahedron Lett.* **1994**, *35*, 6033—6036. (c) Zhao, K.; Lim, D. S.; Funaki, T.; Welch, J. T. *Bioorg. Med. Chem.* **2003**, *11*, 207—215. (d) Van der Veken, P.; Senten, K.; Kertèsz, I.; De Meester, I.; Lambeir, A.-M.; Maes, M.-B.; Scharpé, S.; Haemers, A.; Augustyns, K. *J. Med. Chem.* **2005**, *48*, 1768—1780.

(5) (a) Welch, J. T.; Lin, J. *Tetrahedron* **1996**, *52*, 291—304. (b) Van der Veken, P.; Kertèsz, I.; Senten, K.; Haemers, A.; Augustyns, K. *Tetrahedron Lett.* **2003**, *44*, 6231—6234. (c) Veenstra, S. J.; Hauser, K.; Felber, P. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 351—354. (d) Hollenstein, M.; Leumann, C. J. *J. Org. Chem.* **2005**, *70*, 3205—3217. (e) Bartlett, P. A.; Otake, A. *J. Org. Chem.* **1995**, *60*, 3107—3111.

(6) (a) Nakamura, Y.; Okada, M.; Sato, A.; Horikawa, H.; Koura, M.; Saito, A.; Taguchi, T. *Tetrahedron* **2005**, *61*, 5741—5753. (b) Otaka, A.; Watanabe, H.; Mitsuyama, E.; Yukimasa, A.; Tamamura, H.; Fujii, N. *Tetrahedron Lett.* **2002**, *43*, 5845—5847. (c) Otaka, A.; Watanabe, H.; Yukimasa, A.; Sasaki, Y.; Watanabe, H.; Kinoshita, T.; Oishi, S.; Tamamura, H.; Fujii, N. *J. Org. Chem.* **2004**, *69*, 1634—1645.

(7) (a) Lei, X.; Dutheuil, G.; Pannecoucke, X.; Quirion, J.-C. *Org. Lett.* **2004**, *6*, 2101—2104. (b) Burton, D. J.; Yang, Z.-Y.; Qiu, W. *Chem. Rev.* **1996**, *96*, 1641—1715.

(8) Dutheuil, G.; Lei, X.; Pannecoucke, X.; Quirion, J.-C. *J. Org. Chem.* **2005**, *70*, 1911—1914.

(9) (a) Andrei, D.; Wnuk, S. F. *J. Org. Chem.* **2006**, *71*, 405—408. (b) Eddarir, S.; Francesh, C.; Mestdagh, H.; Rolando, C. *Tetrahedron Lett.* **1990**, *31*, 4449—4452. (c) Chen, C.; Wilcoxen, K.; Strack, N.; McCarthy, J. R. *Tetrahedron Lett.* **1999**, *40*, 827—830. (d) Xu, J.; Burton, D. J. *Tetrahedron Lett.* **2002**, *43*, 2877—2879.

(10) (a) Xu, J.; Burton, D. J. *J. Org. Chem.* **2005**, *70*, 4346—4353. (b) Shimizu, M.; Nakamaki, C.; Shimono, K.; Schelper, M.; Kurahashi, T.; Hiyama, T. *J. Am. Chem. Soc.* **2005**, *127*, 12506—12507. (c) Tan, Z.; Negishi, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 762—765. (d) Zeng, X.; Quian, M.; Hu, Q.; Negishi, E. *Angew. Chem., Int. Ed.* **2004**, *43*, 2259—2263.

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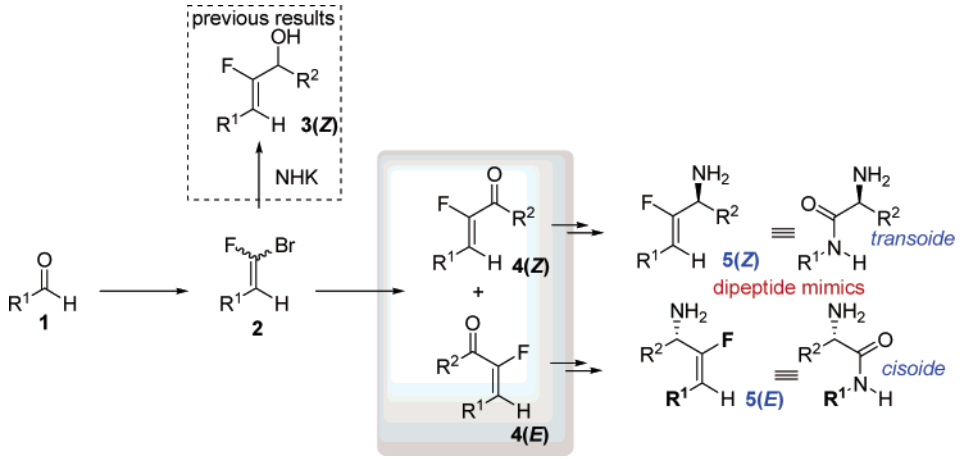
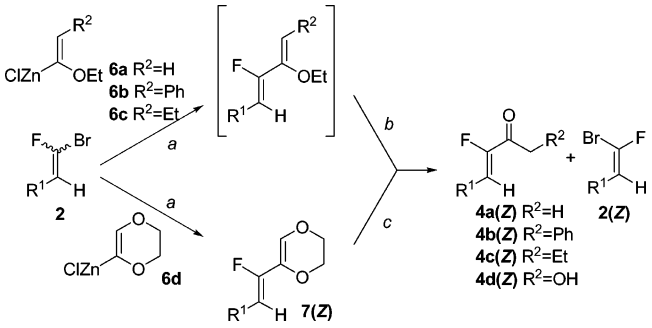
SCHEME 1. Fluoroolefins as Amide Mimics; General Method Envisioned



SCHEME 2. Stereospecific Synthesis of (*Z*)-α-Fluoroenones from an *E*/*Z* Mixture of Bromofluoroolefins 2[a]



[a] Reagents and conditions: (a) **6a**−**d** (0.85 equiv), $Pd(OAc)_2$ 2.5%/PPh_3 5%, THF, 10 °C; (b) 1 N HCl, rt; (c) *i*. *m*CPBA, CH_2Cl_2, MeOH; *ii*. $NaBH_4$, EtOH; *iii*. pTsOH in 1% aq acetone (R^1 = 4-MeOPh 38%).

transformations into dipeptide mimics, a functionalized carbon is to be introduced α to the fluorovinyl moiety. Only a few examples of palladium-catalyzed coupling reactions with bromofluoroolefins affording α-functionalized fluoroalkenes have been described to date: the carbonylation, affording the corresponding conjugated esters or amides[10a] (transformation into chiral amines **5** appeared to be rather complicated as shown by Allmendinger et al.[4a] and Welch and Lin[5a]) and the reaction with aromatic acyl chloride, affording fluoroenones **4**.[11] Surprisingly, and despite their interest in organic synthesis (Michael addition, Diels−Alder reaction) and the fact that these ketones should be easily converted into dipeptide mimics, only a few routes to α-fluoro-α,*β*-enones were described.[11,12] These ones revealed to be inadapted to our peptidomimetic program in terms of substrate diversity, yields or reaction conditions. To overcome these limitations we, therefore, turned our attention toward the Negishi-type coupling reaction (Scheme 2). Additionally, the good availability of zinc derivatives makes this approach highly attractive.[13] Herein, we report the first stereospecific synthesis of (*E*)- or (*Z*)-α-fluoro-α,*β*-unsaturated ketones **4** via a kinetically controlled palladium-catalyzed coupling reaction.

Stereospecific Preparation of (*Z*)-α-Fluoro-α,*β*-unsaturated Ketones. We reasoned that 1-bromo-1-fluoroolefins **2** (*E*/*Z* ≈ 1/1),[7] could serve as precursors for the preparation of both *E*- and *Z*-α-fluoroenones, provided sufficient kinetic differences can be exploited. Based on the Hegedus and Russel[13a] and Negishi and Luo[13b] procedure, we first optimized the preparation of the α-ethoxyvinylzinc chloride **6a**. The best results were obtained reacting ethoxyethene with 1 equiv of the Lochmann−Schlosser superbase (*n*-BuLi/*t*-BuOK) and 2 equiv of zinc chloride in THF from −78 °C to rt. After optimization of the reaction conditions (temperature, palladium catalyst, and reaction time), the *E*/*Z* mixture of bromofluoroalkenes **2** was reacted under Negishi coupling conditions with 0.85 equiv of α-ethoxyvinylzinc chloride **6a**, 2.5% of $Pd(OAc)_2$, and 5% of PPh_3 in THF at 10 °C, yielding the enolether intermediates (Scheme 2). After hydrolysis, the α-fluoro-α,*β*-unsaturated ketones **4a** were isolated in high yields. Aldehyde-derived bromofluoroolefins led to a totally stereospecific coupling; at 10 °C, only bromofluoroolefins **(*E*)-2** reacted, affording ketones **(*Z*)-4a** along with the unreacted **(*Z*)-2**. The reaction was versatile and mild enough to be compatible with various substituents: aromatic, aliphatic, functionalized (ester, nitrile, halogen, protected alcohol). The coupling product and the recovered bromofluoroolefins **(*Z*)-2** were isolated in excellent yields (79 to 99% and 66 to 98%, respectively; Table 1 entries 1−8). Actually, temperature was revealed to play a crucial role: rising the medium above 10 °C led to an *E*/*Z* mixture of ketones **4a**.

At this stage, we had only considered α-ethoxyvinylzinc chloride **6a** in the Negishi coupling reaction. To probe the scope and limitations of the reaction, we extended our investigation to *β*-substituted α-ethoxyvinylzinc derivatives, both in aromatic and in aliphatic series. The access to phenylalanine-type mimics required coupling substrates such as **6b** (R^2=Ph).[14] A convenient introduction of various aliphatic chains, aimed to build common amino acid moiety, was also desired. Accordingly, we first attempted to prepare *β*-methyl-α-ethoxyvinylzinc derivatives **6** (R^2=Me). However, the addition of 1 equiv of the Lochmann−Schlosser base and 2 equiv of zinc chloride to 1-ethoxypropene in THF led exclusively to the more stable allylic zinc deriva-

(11) (a) Chen, C.; Wilcoxen, K.; Zhu, Y. F.; Kim, K.; McCarthy, J. R. *J. Org. Chem.* **1999**, *64*, 3476−3482. (b) Chen, C.; Wilcixen, K.; Huang, C. Q.; Strack, N.; McCarthy, J. R. *J. Fluorine Chem.* **2000**, *101*, 285−290.

(12) (a) Bainbridge, J. M.; Corr, S.; Kanai, M.; Percy, J. M. *Tetrahedron Lett.* **2000**, *41*, 971−974. (b) Kanai, M.; Percy, J. M. *Tetrahedron Lett.* **2000**, *41*, 2453−2455.

(13) (a) Russel, C. E.; Hegedus, L. S. *J. Am. Chem. Soc.* **1983**, *105*, 943−949. (b) Negishi, E.-I.; Luo, F.-T. *J. Org. Chem.* **1983**, *48*, 1560−1562. (c) Su, M.; Kang, Y.; Yu, W.; Hua, Z.; Jin, Z. *Org. Lett.* **2002**, *4*, 691−694.

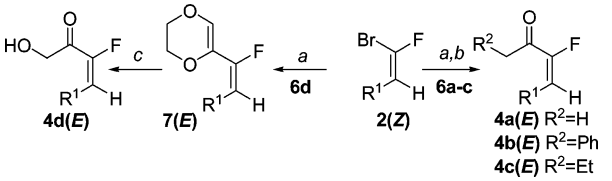
(14) (a) Tzalis, D.; Koradin, C.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 6193−6195. (b) Soderquist, J. A.; Hsu, G. J.-H. *Organometallics* **1982**, *1*, 830−833.

TABLE 1. Reaction of an *E*/*Z* Mixture of Bromofluoroolefins 2 under Negishi Coupling Conditions

entry	substrate: R^1 (*E*/*Z* ratio)	organo-zinc	product: yield[a] (%)	(*Z*)-2 yield[b] (%)
1	**2$_1$**: 4-MeO−C_6H_4 (51/49)	**6a**	(*Z*)-**4a$_1$**: 85	86
2	**2$_2$**: 2-naphthyl (48/52)	**6a**	(*Z*)-**4a$_2$**: 86	85
3	**2$_3$**: 4-NC−C_6H_4 (45/55)	**6a**	(*Z*)-**4a$_3$**: 85	70
4	**2$_4$**: 4-MeO_2C−C_6H_4 (45/55)	**6a**	(*Z*)-**4a$_4$**: 92	90
5	**2$_5$**: 4-O_2N−C_6H_4 (42/58)	**6a**	(*Z*)-**4a$_5$**: 99	88
6	**2$_6$**: 4-Br−C_6H_4 (45/55)	**6a**	(*Z*)-**4a$_6$**: 91	66
7	**2$_7$**: $PhCH_2CH_2$ (51/49)	**6a**	(*Z*)-**4a$_7$**: 79	98
8	**2$_8$**: $TBDPSOCH_2CH_2$ (47/53)	**6a**	(*Z*)-**4a$_8$**: 94	93
9	**2$_1$**: 4-MeO−C_6H_4 (51/49)	**6b**	(*Z*)-**4b$_1$**: 93[c]	99
10	**2$_7$**: $PhCH_2CH_2$ (51/49)	**6b**	(*Z*)-**4b$_2$**: 95[c]	71
11	**2$_1$**: 4-MeO−C_6H_4 (51/49)	**6c**	(*Z*)-**4c$_1$**: 75[c]	84
12	**2$_7$**: $PhCH_2CH_2$(51/49)	**6c**	(*Z*)-**4c$_2$**: 70[c]	69
13	**2$_1$**: 4-MeO−C_6H_4 (51/49)	**6d**	(*Z*)-**7$_1$**: 95	90
14	**2$_7$**: $PhCH_2CH_2$(51/49)	**6d**	(*Z*)-**7$_2$**: 79	85

[a] Based on starting **(*E*)-2** isomer. [b] Based on starting **(*Z*)-2** isomer. [c] Zinc derivatives **6** are needed in the amount of 2 equiv.

SCHEME 3. Stereospecific Synthesis of (*E*)-α-Fluoro-α,β-unsaturated Ketones from (*Z*)-2[a]



[a] Reagents and conditions: (a) **6** (2 equiv), $Pd(OAc)_2$ 5%/PPh_3 10%, THF, reflux; (b) 1 N HCl, rt (c) *i*. *m*CPBA, CH_2Cl_2, MeOH; *ii*. $NaBH_4$, EtOH; *iii*. pTsOH in 1% aq acetone (R^1 = 4-MeOPh, 42%).

tive.[15] We then tried to prepare **6c** (R^2 = Et). As predicted from the work of Sebastian and Power,[15] in the case of **6c**, due to the presence of an allylic methylene group, a mixture of allylic and vinylic zinc chlorides was recovered. Two equivalents of this mixture were coupled in the condition described above with olefins **2**. Only the more reactive vinylic zinc derivatives **6c** gave rise to the coupling product **4c**. We also tried the functionalized coupling reagent **6d**[16] (2,3-dihydro-1,4-dioxine zinc chloride) en route to serine-type peptide mimics.

With these three organozinc derivatives, **6b**−**d**, the coupling reactions proceeded smoothly and stereospecifically with the isomeric mixture of trisubstituted bromofluoroolefins **2** (aliphatic or aromatic); at 10 °C, only bromofluoroolefins **(*E*)-2** reacted, providing in high yields **(*Z*)-7** (from **6d**) or after hydrolysis **(*Z*)-4b**, **(*Z*)-4c** (from **6b** and **c**, respectively). In all cases, the recovery of the unreacted isomers **(*Z*)-2** was achieved in high yield (Table 1, entries 9−14). A known, purification-free, three-step procedure[17] allowed us to transform coupling products **(*Z*)-7** into the desired functionalized α-fluoro-α,β-unsaturated ketone **(*Z*)-4d** (38% overall yield, 72% per step).

Stereospecific Preparation of (*E*)-α-Fluoro-α,β-unsaturated Ketones. The recovered bromofluoroolefins **(*Z*)-2** were submitted, at higher temperature (reflux of THF), to similar Negishi reaction conditions. Thus, **6a**−**d** (Scheme 3) afforded, stereospecifically and after hydrolysis, α-fluoro-α,β-unsaturated ketones **(*E*)-4** in very good coupling yields (70 to 90%, Table 2, entries 1−3, 7−8, and 10−14). Note that to prevent coupling of the allylic zinc reagent present in the mixture with **6c** and to get higher yields, the palladium-catalyzed Negishi reaction had to be run at 55 °C, with 4 equiv of the zinc mixture.

TABLE 2. Reaction of (*Z*)-Bromofluoroolefins under Negishi Coupling Conditions

entry	substrate: R^1 (*E*/*Z* ratio)	organo-zinc	product: yield (%)
1	**2$_1$**: 4-MeO−C_6H_4	**6a**	(*E*)-**4a$_1$**: 72
2	**2$_2$**: 2-naphthyl	**6a**	(*E*)-**4a$_2$**: 81
3	**2$_3$**: 4-NC−C_6H_4	**6a**	(*E*)-**4a$_3$**: 83
4	**2$_4$**: 4-MeO_2C−C_6H_4	**6a**	(*E*)-**4a$_4$**: 17[a]
5	**2$_5$**: 4-O_2N−C_6H_4	**6a**	(*E*)-**4a$_5$**: 51[a]
6	**2$_6$**: 4-Br−C_6H_4	**6a**	0
7	**2$_7$**: $PhCH_2CH_2$	**6a**	(*E*)-**4a$_7$**: 70
8	**2$_8$**: $TBDPSOCH_2CH_2$	**6a**	(*E*)-**4a$_8$**: 77
9	**2$_1$**: 4-MeO−C_6H_4	**6b**[b]	(*Z*)-**4b$_1$**: 98[c]
10	**2$_7$**: $PhCH_2CH_2$	**6b**[b]	(*E*)-**4b$_2$**: 79
11	**2$_1$**: 4-MeO−C_6H_4	**6c**[b]	(*E*)-**4c$_1$**: 90[d]
12	**2$_7$**: $PhCH_2CH_2$	**6c**[b]	(*E*)-**4c$_2$**: 88[d]
13	**2$_1$**: 4-MeO−C_6H_4	**6d**	(*E*)-**7$_1$**: 71
14	**2$_7$**: $PhCH_2CH_2$	**6d**	(*E*)-**7$_2$**: 78

[a] Along with **(*Z*)-4a** (entry 4, 58%; entry 5, 27%). [b] Zinc derivatives **6** are needed in the amount of 4 equiv. [c] Enoletherhydrolysis conditions: 6 N HCl, 70 °C. [d] The coupling reactions were performed at 55 °C.

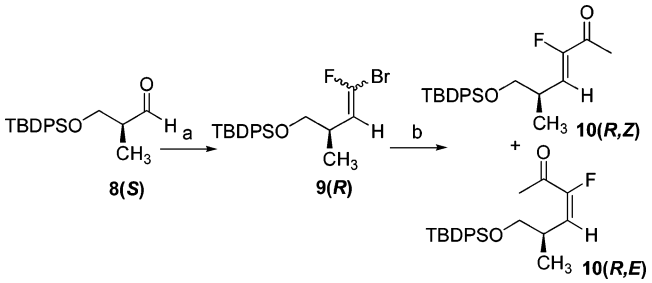
These higher temperature conditions (reflux of THF) led bromoaromatic derivatives to decompose, probably due to side coupling reactions at the aromatic site (Table 2, entry 6). With good electron-withdrawing substituents (CO_2Me and NO_2), a partial isomerization was observed, yielding a chromatographically separable *E*/*Z* mixture of compounds **4** (Table 2, entries 4−5). With aromatic **(*Z*)-2** and **6b** (Table 2, entry 9), ketone **(*Z*)-4b** was even obtained in 98% yield instead of **(*E*)-4b**, probably because of the harsh conditions needed to hydrolyze the conjugated enolether intermediates.[18] In all cases, the isomerization occurred during the enolether hydrolysis, as the enolether intermediates were only present under the *E* configuration ($^3J_{H-F}$ = 17 Hz).

We could use this feature to obtain exclusively **(*Z*)-4** from an *E*/*Z* mixture of bromofluoroolefins **2**. Indeed, running the Negishi reaction under reflux of THF led to an *E*/*Z* mixture of enolether intermediates, which could then be transformed under strong acidic conditions to the pure **(*Z*)-4** isomer. Unfortunately, because of the acidic instability of some conjugated ketones **4** (especially **4a** and **4c**), this improved route was applicable to only a few cases.[19]

Synthesis of Chiral Nonracemic (*E*)- and (*Z*)-α-Fluoro-α,β-unsaturated Ketones. The application of the above strategy to the synthesis of peptidomimetic derivatives required that our coupling reaction did not racemize the stereogenic center borne by the substrates (Scheme 1). To control the mildness of the procedure, enantiomerically pure bromofluoroolefin **(*R*)-9**[7a] was prepared from chiral nonracemic aldehyde **(*S*)-8**.[20] The *E*/*Z* mixture **(*R*)-9** was then subjected to our standard Negishi

(15) Power, T. D.; Sebastian, J. F. *Tetrahedron* **1998**, *54*, 8371−8392.
(16) Fetizon, M.; Goulaouic, P.; Hanna, I. *Tetrahedron Lett.* **1985**, *26*, 4925−4928.
(17) Fetizon, M.; Goulaouic, P.; Hanna, I. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1107−1110.
(18) Strongly acidic conditions such as H_2SO_4, 6 N HCl, and pTsOH were required and led to totally isomerized ketone **(*Z*)-4b**, while milder conditions such as amberlyst 15, $HClO_4$, HCO_2H, 1 N HCl were ineffective. TMSI deprotection led to the decomposition of the enolether intermediates.
(19) **4b** (hydrolysis conditions; 6 N HCl, 70 °C, up to 99% yield based on **(*E*)-2** + **(*Z*)-2**) and **4a**,**c** with R^1 = 4-NO_2−Ph and 4-MeO_2C−Ph (hydrolysis conditions; 1 N HCl, rt, 12h, up to 75% yield based on **(*E*)-2** + **(*Z*)-2**).
(20) Konno, K.; Fujishima, T.; Maki, S.; Liu, Z.; Miura, D.; Chokki, M.; Ishizuka, S.; Yamaguchi, K.; Kan, Y.; Kurihara, M.; Miyata, N.; Smith, C.; DeLuca, H. F.; Takayama, H. *J. Med. Chem.* **2000**, *43*, 4247−4265.

SCHEME 4. Stereospecific Synthesis of Nonracemic (*E*)- and (*Z*)-α-Fluoro-α,*β*-unsaturated Ketone from Chiral Nonracemic Aldehyde[a]



[a] Reagents and conditions: (a) $CFBr_3$, PPh_3, $ZnEt_2$, THF, rt, 85%; (b) *i*. **6a** (1.5 equiv), $Pd(OAc)_2$ 5%/PPh_3 10%, THF, 10 °C or reflux; *ii*. 1 N HCl, rt, **(*R*,*Z*)-10** 81% based on (*E*)-bromofluoroolefin, **(*R*,*E*)-10** 62% based on (*Z*)-bromofluoroolefin.

coupling conditions with **6a**, affording separately after hydrolysis **(*R*,*Z*)-10** (81%) and **(*R*,*E*)-10** (62%; Scheme 4).

After various unsuccessful attempts to determine the enantiomeric purities of **(*R*,*Z*)-10** and **(*R*,*E*)-10** (Chiral GC or HPLC), the excesses could finally be measured by ^{19}F NMR studies of the crude chiral imines resulting from the condensation of **10** with a chiral nonracemic amine. By comparison with the ^{19}F NMR chemical shift of the imine derived from racemic **10**, the enantiomeric purities were determined to be more than 95% for **(*R*,*Z*)-10** and **(*R*,*E*)-10** (see spectra in the Supporting Information).

In summary, we report the first stereospecific synthesis of (*E*)- or (*Z*)-α-fluoro-α,*β*-unsaturated ketones **4** via a kinetically controlled Negishi palladium-catalyzed coupling reaction. The method is high yielding, mild, versatile, and nonracemizing. Varying the starting aldehydes and the substituted α-ethoxyvinylzinc derivatives (including one with allylic hydrogen atom), a large number of fluoroenones **4** are accessible. These compounds **4** could be relevant intermediates in agro and pharmaceutical chemistry and could also act as peptide bond mimics. In our ongoing chemical−biology program, we are currently concentrating our effort toward the transformation of fluoroolefins **4** into dipeptide analogues **(*Z*)-5** or **(*E*)-5**.

Experimental Section

Representative Procedure for the Obtention of (*Z*)-Fluorinated Methyl Ketones (*Z*)-4 from an E/Z Mixture of Bromofluoroolefins 2: Preparation of (*Z*)-4a$_1$. To a mixture of potassium *tert*-butoxide (1.94 g, 17.3 mmol) ethylvinyl ether (1.65 mL, 17.3 mmol) in anhydrous THF (85 mL) at −78 °C was added *n*-BuLi in hexanes (1.6M, 10.8 mL, 17.3 mmol) dropwise under argon. The mixture was stirred for 30 min at −78 °C, and then a solution of dry zinc chloride (4.7 g, 34.6 mmol) in THF (135 mL) was added dropwise. After 10 min, the cooling bath was removed, and the solution was allowed to warm to room temperature for 30 min. The mixture was then added slowly to a solution of palladiumdiacetate (115 mg, 0.51 mmol), triphenylphosphine (265 mg, 1.02 mmol), and a mixture of bromofluoroolefins **2$_1$** (4.7 g, 20.3 mmol) in anhydrous THF (200 mL) at 10 °C under argon. The mixture was stirred for 1 h. HCl aq (1N, 200 mL) was added, and the solution was stirred for 15 min. The mixture was then extracted with Et_2O (200 mL x 3), washed with brine, and the combined organic layers were dried over $MgSO_4$. After filtration and concentration under reduced pressure, the residue was purified by chromatography on silica gel (eluent: 5% AcOEt in cyclohexane), affording fluorenones **(*Z*)-4a$_1$** (1.72 g, 8.82 mmol, yield = 85%) and unreacted bromofluoroolefin **(*Z*)-2$_1$** (1.98 g, 8.57 mmol, yield = 86%).

(*Z*)-2-1: (*Z*)-1-(2-Bromo-2-fluorovinyl)-4-methoxybenzene.[7a] **(*Z*)-4a-1: (*Z*)-3-Fluoro-4-(4-methoxyphenyl)but-3-en-2-one.** Yellow powder (mp = 72−74 °C), R_f 0.2 (5% AcOEt in cyclohexane). ^1H NMR (300 MHz, $CDCl_3$) δ 7.6 (d, J = 8.9 Hz, 2H, H_4), 6.9 (d, J = 8.9 Hz, 2H, H_5), 6.7 (d, $^3J_{H-F}$ = 36.9 Hz, 1H, H_2), 3.7 (s, 3H, H_7), 2.3 (d, $^4J_{H-F}$ = 3.3 Hz, 3H, H_9). ^{19}F NMR (282.5 MHz, $CDCl_3$) δ −127.1 (dq, $^3J_{H-F}$ = 36.9 Hz, $^4J_{H-F}$ = 3.3 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 192.2 (d, $^2J_{C-F}$ = 32 Hz, C_8), 161.2 (d, J = 4 Hz, C_6), 153.5 (d, $^1J_{C-F}$ = 267 Hz, C_1), 135.5 (d, J = 6 Hz, C_4), 124.0 (d, $^3J_{C-F}$ = 4 Hz, C_3), 116.4 (d, $^2J_{C-F}$ = 6 Hz, C_2), 114.5 (d, J = 18 Hz, C_5), 55.7 (C_7), 25.9 (C_9). MS (EI) 194 (M^+), 179 ($M^+ - CH_3$), 159, 43 (CH_3CO^+). IR (KBr) 3037, 2970, 2937, 2898, 2837, 1672, 1643, 1605, 1570, 1513, 1424, 1343, 1264, 1185, 1177, 1069, 1022, 869, 808, 539 cm^{-1}. Anal. Calcd for $C_{11}H_{11}FO_2$: C, 68.03; H, 5.71. Found: C, 68.06; H, 5.63.

Representative procedure for the obtention of (*E*)-fluorinated methyl ketones **(*E*)-4** from **(*Z*)-2**. Same protocol was used as for **(*Z*)-4a$_1$**, preparing 2 equiv of vinylzinc derivatives **6a** and letting the coupling reaction occur at the reflux of THF with 0.05 equiv of palladiumdiacetate and 0.1 equiv of PPh_3. Bromofluoroolefin **(*Z*)-2** afforded, after purification by chromatography on silica gel (eluent: 5% AcOEt in cyclohexane), (*E*)-methyl ketone **(*E*)-4a$_1$** (1.2 g, 6.17 mmol, yield = 72%).

(*E*)-4a$_1$: (*E*)-3-Fluoro-4-(4-methoxyphenyl)but-3-en-2-one. Yellow solid (mp < 44°C), R_f 0.2 (5% AcOEt in cyclohexane). ^1H NMR (300 MHz, $CDCl_3$) δ 7.6 (d, J = 8.9 Hz, 2H, H_4), 6.9 (d, J = 8.9 Hz, 2H, H_5), 6.7 (d, $^3J_{H-F}$ = 26.1 Hz, 1H, H_2), 3.7 (s, 3H, H_7), 2.3 (d, $^4J_{H-F}$ = 5.1 Hz, 3H, H_9). ^{19}F NMR (282.5 MHz, $CDCl_3$) δ −115.2 (d, $^3J_{H-F}$ = 26.1 Hz, $^4J_{H-F}$ = 5.1 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 193.4 (d, $^2J_{C-F}$ = 39 Hz, C_8), 161.2 (d, J = 2 Hz, C_6), 152.6 (d, $^1J_{C-F}$ = 252 Hz, C_1), 132.6 (d, J = 3 Hz, C_4), 123.5 (d, $^3J_{C-F}$ = 10 Hz, C_3), 121.0 (d, $^2J_{C-F}$ = 29 Hz, C_2), 114.1 (C_5), 55.7 (C_7), 28.6 (d, $^3J_{C-F}$ = 4 Hz, C_9). MS (EI) 194 (M^+), 179 ($M^+ - CH_3$), 159, 43 (CH_3CO^+). IR (KBr) 3005, 2937, 2839, 1729, 1681, 1601, 1513, 1462, 1423, 1371, 1304, 1257, 1177, 1031, 832, 599, 533. Anal. Calcd for $C_{11}H_{11}FO_2$: C, 68.03; H, 5.71. Found: C, 68.09; H, 5.54.

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Supporting Information Available: Complete experimental section and ^1H, ^{13}C, and ^{19}F NMR spectra with atom numbers for the NMR spectra attribution. This material is available free of charge via the Internet at http://pubs.acs.org.

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