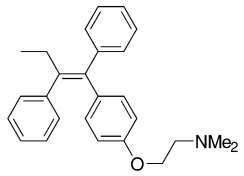
Organofluorine Compounds

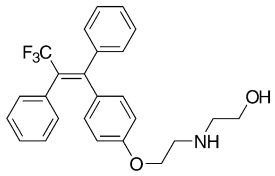
A Facile Stereocontrolled Approach to CF_3-Substituted Triarylethenes: Synthesis of Panomifene**

Xinyu Liu, Masaki Shimizu, and Tamejiro Hiyama*

Triaryl ethenes is a key structure in nonsteroidal antiestrogens.[1] In particular, tamoxifen (**1**) has been widely used for clinical treatment of breast cancer.[2] The antiestrogenic activity is known to depend on the olefin geometry of the triaryl ethene component.[3] On the other hand, selective replacement of C–H bonds with C–F bonds in biologically active compounds has been proved to be the most effective and powerful strategy in the optimization of parent compounds.[4] This strategy, when applied to the exploration of highly potent triaryl ethenes,[5,6] led to discovery of panomifene (**2**),[6] which exhibits antiestrogenic and tumor-inhibiting



Tamoxifen (**1**)



Panomifene (**2**)

activities superior to those of **1**. In view of this history, a general, convenient, and stereoselective synthetic method for the preparation of CF_3-substituted triaryl ethenes should definitely open a new entry to highly potent nonsteroidal antiestrogens.

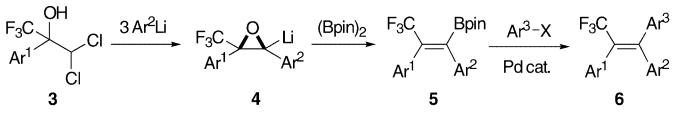
We recently found that treatment of CF_3-substituted dichlorohydrin **3** ($Ar^1 = PhC{\equiv}C$) with BuLi or PhLi (3 equiv) in THF at −98 °C generated the corresponding CF_3-substituted lithio-oxirane **4** ($Ar^1 = PhC{\equiv}C$, $Ar^2 = Bu$ or Ph), which reacted with bis(pinacolato)diboron, $(Bpin)_2$, to afford **5** ($Ar^1 = PhC{\equiv}C$, $Ar^2 = Bu$ or Ph) in high yields with excellent diastereoselectivity (Scheme 1).[7] We envisioned that the stereospecific cross-coupling reaction of β-CF_3-substituted alkenyl boronates **5** with Ar^3X, if feasible, would give rise to a series of compounds **6** conveniently and stereoselectively. Herein we describe the success of this

[*] X. Liu, Dr. M. Shimizu, Prof. Dr. T. Hiyama
Department of Material Chemistry
Graduate School of Engineering, Kyoto University
Katsura Campus, Nishikyo-ku, Kyoto 615-8510 (Japan)
Fax: (+81) 75-383-2445
E-mail: shimizu@npc05.kuic.kyoto-u.ac.jp

[**] This work was supported by a Grant-in-Aid for COE Research on Elements Science, no. 12CE2005, from the Ministry of Education, Culture, Sports, Science, and Technology, Japan. 1,1-Difluoro-3,3,3-trifluoropropan-2-one was kindly donated by Central Glass Co. Ltd. We are grateful to Dr. Yi-Chou Tsai for a helpful literature survey.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

 DOI: 10.1002/anie.200353032



Scheme 1. Novel approach to CF_3-substituted triarylethenes **6**. Bpin = (pinacolato)boryl.

approach and demonstrate the versatility of the sequence through the total synthesis of panomifene (**2**).

Following our original protocol, we first treated a solution of **3**[8] in THF with Ar^2Li (3 equiv) at low temperatures and soon found that the corresponding lithio-oxiranes **4** could be generated at −78 °C. The 3-aryl derivatives **4** (Ar^2 = aryl) are stable at −78 °C, in sharp contrast to 3-alkyl-substituted lithio-oxiranes **4** (Ar^2 = alkyl) whose reactions had to be conducted at −98 °C. The enhanced stability of lithio-oxiranes **4** may be ascribed to the anion-stabilizing effect of an Ar^2 group in **4**,[9] which smoothly reacted with $(Bpin)_2$ at −78 °C to room temperature to give the corresponding compounds **5** in moderate to good yields with high *E* selectivity (Table 1). Fluorine, chlorine, methoxy, and methoxymethoxy (MOMO) substituents on Ar^1 and Ar^2 were tolerated under these conditions. The *E* configuration of **4** was confirmed by conversion of **5a** into a deborylated product (see below).

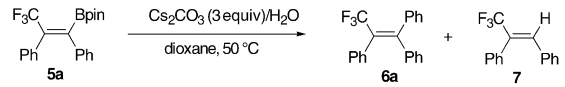
Table 1: Stereoselective preparation of **5** from **3** with Ar^2Li.[a]

Entry	3	Ar^1	Ar^2	5	Yield [%][b]	*E*/*Z*[c]
1	**a**	Ph	Ph	**a**	63	98:2
2	**a**	Ph	*p*-Cl-C_6H_4	**b**	73	97:3
3	**a**	Ph	*p*-MeO-C_6H_4	**c**	78	94:6
4	**a**	Ph	*p*-MOMO-C_6H_4[d]	**d**	75	92:8
5	**b**	*p*-F-C_6H_4	Ph	**e**	65	99:1
6	**c**	*p*-Cl-C_6H_4	Ph	**f**	80	99:1
7	**d**	*p*-MeO-C_6H_4	Ph	**g**	63	>99:<1

[a] A THF solution of **3** (5 mmol) was treated with Ar^2Li (15 mmol) at −78 °C for 0.5–2 h, and then with $(Bpin)_2$ (5.25 mmol) at −78 °C. The mixture was gradually warmed to room temperature before quenching with saturated aqueous NH_4Cl solution. [b] Yields of isolated products. [c] *E*/*Z* ratio was determined by ^{19}F NMR spectroscopic analysis. [d] MOM = methoxymethyl.

With **5** in hand, we next examined the Pd-catalyzed cross-coupling reaction with aryl iodide Ar^3I.[10] To the best of our knowledge, no examples of cross-coupling reactions of β-CF_3-substituted alkenyl boron reagents is available.[11,12] The reaction conditions were first optimized with iodobenzene as a typical coupling partner. The results are summarized in Table 2. When a dioxane solution of **5a** (*E*/*Z* = 98:2) and iodobenzene was heated in the presence of $[Pd(PPh_3)_4]$ (10 mol %) and Cs_2CO_3 (3 equiv) at 50 °C for 12 h, only protodeborylation took place to give (*E*)-1,2-diphenyl-3,3,3-trifluoropropene (**7**)[13] as the sole product (Table 2, entry 1).[14] The formation of **7** indicated that the Bpin group in **5a** was positioned *cis* to the CF_3 group. $[PdCl_2(PPh_3)_2]$ or $[Pd(tBu_3P)_2]$ catalyst produced **6a** as the major product though very slowly; fair amounts of **7** were still obtained (Table 2, entries 2 and 3). The use of TlOEt as base

Table 2: Coupling reaction of **5a** with iodobenzene.[a]



Entry	Catalyst	H_2O [equiv]	*t* [h]	Conv. [%][b]	**6a**/**7**[c]
1	$[Pd(PPh_3)_4]$	–	12	100	0:100
2	$[PdCl_2(PPh_3)_2]$	–	12	25	84:16
3	$[Pd(tBu_3P)_2]$	–	12	37	70:30
4[d]	$[Pd(tBu_3P)_2]$	–	2	100	22:78
5	$[PdCl_2(PPh_3)_2]$	3	4	100	77:23
6	$[Pd(tBu_3P)_2]$	3	1.5	100	82:18
7	$[Pd(tBu_3P)_2]$	6	2	100	91:9
8	$[Pd(tBu_3P)_2]$	15	5	100	93:7
9	$[Pd(tBu_3P)_2]$	[e]	6	100(94)[f]	98:2

[a] Reaction conditions: **5a** (0.5 mmol), iodobenzene (0.75 mmol), palladium catalyst (0.05 mmol), Cs_2CO_3 (1.5 mmol), H_2O (indicated amount), dioxane (0.1 mL), 50 °C. [b] For entries 1–3, reaction was terminated after 12 h. For entries 4–9, reaction was monitored by TLC and terminated when **5a** was completely consumed. [c] The ratio was determined by ^{19}F NMR analysis of crude product. [d] TlOEt was used instead of Cs_2CO_3. [e] A 5 M aqueous solution of Cs_2CO_3 was employed. [f] The value in parentheses is the yield of isolated **6a**.

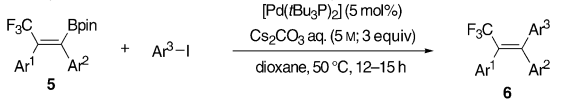
accelerated the reaction remarkably, but led to preferential formation of **7** (Table 2, entry 4).[15] After several attempts, we found that the addition of water also accelerated the coupling reaction and was quite effective for the selective production of **6a** (Table 2, entries 5–9).[16] In particular, aqueous solution of Cs_2CO_3 (5 M) in combination with $[Pd(tBu_3P)_2]$ allowed the reaction to go to completion in 6 h, and **6a** was isolated as a single stereoisomer in 94 % yield (**6a**/**7** = 98:2; Table 2, entry 9). The minor stereoisomer of **5a** (*Z* isomer) did not undergo the coupling reaction under these conditions, although the reason is not clear at present.

The optimized conditions were applied to the synthesis of several CF_3-substituted triaryl ethenes **6** (Table 3). The yields and selectivity of **6** were uniformly high. Both electron-withdrawing and -donating group at *para*-position of any of the aryl groups did not affect the performance of the coupling reaction. Notably, the coupling reaction cleanly discriminates Cl from I in **5** and Ar^3-I (Table 3, entries 3, 6, 7, 11, 12). The remaining Cl substituent can be elaborated for further transformation (see below). In all cases, the *Z* isomer of **5** did not undergo reaction, as determined by ^{19}F NMR spectroscopic and GC-MS analysis of the crude products, so that **6** was always obtained as a single diastereomer.

Synthetic transformations of chlorine-substituted **6** are illustrated in Scheme 2. The remaining Cl functionality in **6l** and **6g** was subjected to palladium-catalyzed C–N or C–O coupling reactions[17,18] to introduce nitrogen or oxygen functionality. Thus, aniline **8** and phenyl ether **9** were isolated in 83 % and 52 % yields, respectively.

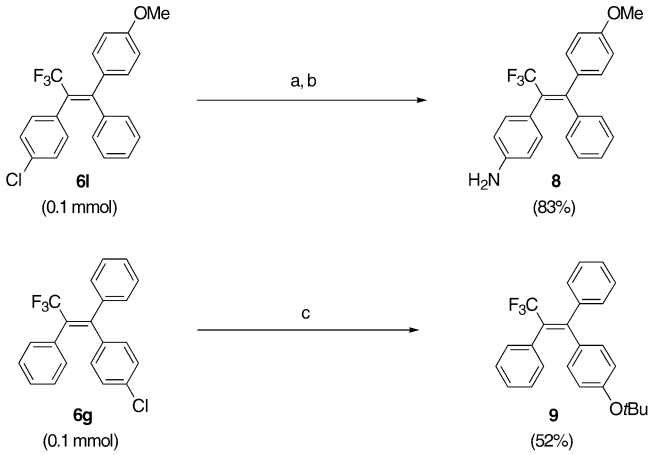
Finally, we demonstrated the synthetic potential of the methodology described herein by conversion of **6i** into panomifene (**2**). Demethylation of **6i** with NaSEt proceeded without any isomerization of the double bond in **6i** to give **10**,[19] which was treated with $Cl(CH_2)_2OTs$ and then with ethanolamine to give rise to **2** as shown in Scheme 3.

Table 3: Synthesis of CF_3-substituted triarylethenes **6**.[a]



Entry	**5**	Ar^1	Ar^2	Ar^3	**6**	Yield [%][b]
1	**a**	Ph	Ph	*p*-EtO_2C-C_6H_4	**b**	92
2	**a**	Ph	Ph	*p*-F-C_6H_4	**c**	91
3	**a**	Ph	Ph	*p*-Cl-C_6H_4	**d**	96
4	**a**	Ph	Ph	*p*-MeO-C_6H_4	**e**	95
5	**a**	Ph	Ph	*p*-$Me_2N(CH_2)_2O$-C_6H_4	**f**	95
6	**b**	Ph	*p*-Cl-C_6H_4	Ph	**g**	92
7	**b**	Ph	*p*-Cl-C_6H_4	*p*-MeO-C_6H_4	**h**	89
8	**c**	Ph	*p*-MeO-C_6H_4	Ph	**i**	90
9	**d**	Ph	*p*-MOMO-C_6H_4	Ph	**j**	92
10	**e**	*p*-F-C_6H_4	Ph	*p*-F-C_6H_4	**k**	91
11	**f**	*p*-Cl-C_6H_4	Ph	*p*-MeO-C_6H_4	**l**	91
12	**f**	*p*-Cl-C_6H_4	Ph	*p*-F-C_6H_4	**m**	90
13	**g**	*p*-MeO-C_6H_4	Ph	*p*-F-C_6H_4	**n**	94

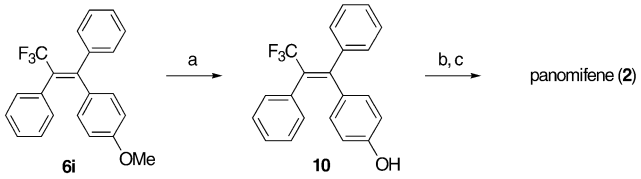
[a] Reaction conditions: **5** (0.2 mmol), Ar^3I (0.22 mmol), [Pd(tBu_3P)$_2$] (0.01 mmol), aqueous Cs_2CO_3 (5 M; 120 μL), dioxane (0.4 mL), 50 °C. [b] Yields of isolated products based on *E* isomer of **5**.



Scheme 2. Synthetic elaboration of chlorine-substituted **6**. Conditions: a) $LiN(SiMe_3)_2$, [$Pd_2(dba)_3$] (2.5 mol%), P(tBu)$_3$ (5 mol%), toluene, 100 °C, 12 h; b) HCl; c) NaO(tBu), [$Pd_2(dba)_3$] (5 mol%), 2-Cy_2P-2′-Me_2N-biphenyl (12 mol%), toluene, 100 °C, 18 h. dba = dibenzylideneacetone.

In summary, we have demonstrated a convenient and versatile synthetic strategy for CF_3-substituted triaryl ethenes through stereoselective preparation of **5** and its Pd-catalyzed cross-coupling. In particular, water was found to be effective in the acceleration of the Pd-catalyzed coupling reaction. This method can be applied to diverse CF_3-substituted triaryl ethenes, including panomifene, a potent nonsteroidal antiestrogen. Further studies on the preparation of organofluorine compounds, taking advantage of CF_3-substituted lithio-oxiranes and alkenyl–metal compounds are in progress.

Received: October 8, 2003 [Z53032]



Scheme 3. Application to the synthesis of panomifene (**2**). Conditions: a) NaSEt, DMF, 150 °C, 10 h, 78% yield; b) $Cl(CH_2)_2OTs$, K_2CO_3, MeCN, reflux, 12 h; c) $H_2N(CH_2)_2OH$, 2-methoxyethanol, reflux, 2 h, 66% (two steps from **10**). DMF = *N*,*N*-dimethylformamide, Ts = *p*-toluenesulfonyl.

Keywords: alkenes · boron · cross-coupling · fluorine · synthetic methods

[1] For a review on antiestrogens, see: a) R. A. Magarian, L. B. Overacre, S. Singh, K. L. Meyer, *Curr. Med. Chem.* **1994**, *1*, 61; b) V. C. Jordan, *J. Med. Chem.* **2003**, *46*, 883; c) V. C. Jordan, *J. Med. Chem.* **2003**, *46*, 1081.

[2] H. Wiseman, *Tamoxifen: Molecular Basis of Use in Cancer Treatment and Prevention*, Wiley, Chichester, **1994**.

[3] M. J. K. Harper, A. L. Walpole, *Nature* **1966**, *212*, 87.

[4] a) T. Hiyama, *Organofluorine Compounds. Chemistry and Applications*, Springer, Berlin, **2000**; b) M. Schlosser, *Angew. Chem.* **1998**, *110*, 1538–1556; *Angew. Chem. Int. Ed.* **1998**, *37*, 1496–1513; c) I. Ojima, J. R. McCarthy, J. T. Welch, *ACS Symp. Ser.* **1996**, *639*; d) M. Hudlicky, A. E. Pavlath in *Chemistry of Organic Fluorine Compounds II. A Critical Review*, American Chemical Society, Washington, DC, **1995**; e) J. T. Welch, *ACS Symp. Ser.* **1991**, *456*; f) J. T. Welch, *Tetrahedron* **1987**, *43*, 3123.

[5] W. J. Middleton, D. Metzger, J. A. Snyder, *J. Med. Chem.* **1971**, *14*, 1193.

[6] Monograph: a) *Drugs Future* **1985**, *10*, 395; b) *Drugs Future* **1990**, *15*, 532; Biological properties: c) J. Borvendeg, I. Hermann, O. Csuka, *Acta Physiol. Hung.* **1996**, *84*, 405 [*PubMed ID*, **1996**, 9328614]; d) V. Erdelyi-Toth, F. Gyergyay, I. Szamel, E. Pap, J. Kralovanszky, E. Bojti, M. Csorgo, S. Drabant, I. Klebovich, *Anti-Cancer Drugs* **1997**, *8*, 603 [*Chem. Abstr.* **1997**, *127*, 287616]; Synthesis: e) G. Nemeth, R. Kapiller-Dezsofi, G. Lax, G. Simig, *Tetrahedron* **1996**, *52*, 12821; Patents: f) G. Abraham, T. Horvath, L. Toldy, J. Borvendeg, E. Csanyi, E. Kiss, I. Hermann S, K. Tory (Gyogyszerkutato Intezet, Hung.), US 763078, **1989** [*Chem. Abstr.* **1989**, *111*, 77630].

[7] a) M. Shimizu, T. Fujimoto, H. Minezaki, T. Hata, T. Hiyama, *J. Am. Chem. Soc.* **2001**, *123*, 6947; b) M. Shimizu, T. Fujimoto, X. Liu, H. Minezaki, T. Hata, T. Hiyama, *Tetrahedron* **2003**, *59*, 9811.

[8] Dichlorohydrins **3** are readily available by carbonyl addition to 1,1-dichloro-3,3,3-trifluoropropan-2-one with Ar^1MgX (see Supporting Information).

[9] The lithio-oxirane generated from styrene oxide by deprotonation with *s*BuLi/TMEDA in THF at −98 °C was reportedly stable at −98 °C for only 30 min; the presence of a CF_3 group might contribute to the enhanced stability of **4**: V. Capriati, S. Florio, R. Luisi, A. Salomone, *Org. Lett.* **2002**, *4*, 2445.

[10] For reviews on the Suzuki–Miyaura coupling reaction, see: a) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457; b) A. Suzuki, *J. Organomet. Chem.* **1999**, *576*, 147; c) N. Miyaura, *Top. Curr. Chem.* **2002**, *219*, 11.

[11] For reviews on fluorinated organometallic compounds, see: a) D. J. Burton, Z.-Y. Yang, P. A. Morken, *Tetrahedron* **1994**, *50*, 2993; b) D. J. Burton, Z.-Y. Yang, *Tetrahedron* **1992**, *48*, 189.

[12] For the palladium-catalyzed coupling reaction of α-(trifluoromethyl)ethenyl boronic acid with aryl halides, see: a) B. Jiang,

Q.-F. Wang, C.-G. Yang, M. Xu, *Tetrahedron Lett.* **2001**, *42*, 4083. β-CF_3-α,β-diphenylvinylstannane was prepared as a mixture of *E*/*Z* isomers (12:88) and coupled with aryl iodide using a catalyst system of [$Pd(PPh_3)_4$]/CuI to afford the corresponding CF_3-substituted triaryl ethenes as an *E*/*Z* mixture (12:88) in moderate yields: b) I. H. Jeong, Y. S. Park, M. S. Kim, Y. S. Song, *J. Fluorine Chem.* **2003**, *120*, 195.

[13] a) B. S. Nader, J. A. Cordova, K. E. Reese, C. L. Powell, *J. Org. Chem.* **1994**, *59*, 2898; b) J.-P. Begue, D. Bonnet-Delpon, D. Bouvet, M. H. Rock, *J. Org. Chem.* **1996**, *61*, 9111.

[14] Protodeborylation is often observed as a major side reaction; see: a) N. Miyaura, *Top. Curr. Chem.* **2002**, *219*, 20–23; N. Miyaura, *Top. Curr. Chem.* **2002**, *219*, 26–27; b) S. D. Brown, R. W. Armstrong, *J. Org. Chem.* **1997**, *62*, 7076.

[15] J.-i. Uenishi, J.-M. Beau, R. W. Armstrong, Y. Kishi, *J. Am. Chem. Soc.* **1987**, *109*, 4756.

[16] Some Pd-catalyzed coupling reactions of organoboron compounds were reported to be accelerated by the addition of water: a) reference [14a]; b) C. R. Johnson, M. P. Braun, *J. Am. Chem. Soc.* **1993**, *115*, 11014; c) C. Zhou, D. E. Emrich, R. C. Larock, *Org. Lett.* **2003**, *5*, 1579.

[17] S. Lee, M. Jorgensen, J. F. Hartwig, *Org. Lett.* **2001**, *3*, 2729.

[18] C. A. Parrish, S. L. Buchwald, *J. Org. Chem.* **2001**, *66*, 2498.

[19] In reference [6e], acidic demethylation was reported to result in the production of a 1:1 mixture of (*E*)- and (*Z*)-**10**.

