Communication

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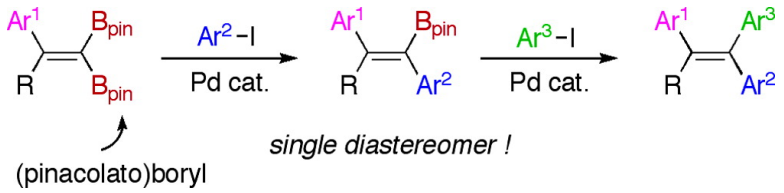

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Stereoselective Cross-Coupling Reaction of 1,1-Diboryl-1-alkenes with Electrophiles: A Highly Stereocontrolled Approach to 1,1,2-Triaryl-1-alkenes

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Triarylated alkenes (TAA) constitute an important class of nonsteroidal antiestrogens, as exemplified by tamoxifen, which is currently used clinically for breast cancer treatment.[1] Since antiestrogenic activity of TAA depends on configuration of the double bond, stereocontrolled synthesis of TAA gains much interest for exploration and improvement of TAA-based pharmaceuticals.[2]

Stepwise and 2-fold cross-coupling reaction of 1,1-dimetalated-1-alkenes $R^1R^2C{=}CM^1M^2$ (**1**, $R^1 \neq R^2$)[3] with electrophiles provides a promising approach for stereoselective synthesis of such unsymmetrical tetrasubstituted alkenes as TAA.[4] Both diastereomers can be prepared simply by reversing the order of employed electrophiles, and furthermore, the whole transformation could be effected in a one-pot procedure. When M^1 and M^2 in **1** are different, stereocontrol of tetrasubstituted ethenes relies definitely on stereoselective preparation of **1**. Accordingly, structural variation in **1** is quite limited.[5] On the other hand, preparation of **1** ($M^1 = M^2$) is much more easily achieved to provide a broader scope of starting *gem*-dimetalated alkenes **1**. The intrinsic issue in the use of **1** ($M^1 = M^2$) for the coupling reaction is whether the first coupling takes place stereoselectively or not. Although *gem*-dizincio and -distannyl reagents **1** leading to stereodefined nonarylated and diarylated alkenes, respectively, have a few precedents,[6] to our best knowledge, there is no example of the present approach applied to TAA. In this communication, we report a solution for the synthetic problem. Namely, palladium-catalyzed cross-coupling reaction of 1,1-diboryl-1-alkenes **2** with $Ar^2{-}I$ proceeds stereoselectively to give monocoupled product **3** with R and Ar^2 being cis as a single diastereomer (Scheme 1). Further coupling reaction of **3** with another iodide $Ar^3{-}I$ allows us to establish a stereocontrolled approach to a diverse kind of TAA **4**.[7] The whole transformation is applicable to facile synthesis of both (*Z*)- and (*E*)-tamoxifen and can be carried out sequentially in one pot, if desired.

Diboryl reagents **2** were readily prepared by *gem*-diborylation of 1,1-dibromo-1-alkenes with bis(pinacolato)diboron[8] or ketone addition of tris(pinacolato)borylmethyllithium.[9] At first, when **2a** (Ar^1 = Ph; R = Et) was treated with *p*-F$-C_6H_4-$I in the presence of Pd_2dba_3 (5 mol %)/P(*t*-Bu)$_3$ (20 mol %) and 3 M KOH aqueous solution in THF at room temperature, coupling product **3b** was isolated in 86% yield as a sole diastereomer (Table 1, entry 2). The *E*-stereochemistry of **3b** was determined by X-ray analysis of its single crystal.[10] Thus, the coupling reaction was found to take place selectively with the boryl moiety cis to the ethyl group. The scope of the stereoselective cross-coupling reaction is summarized in Table 1. Perfect discrimination of two geminal boryl groups in **2a**−**2c** (R = Et) is general regardless of a substituent at the *para*-position of Ar^1 and Ar^2 (entries 1−11 except for 9). The *ortho*-methyl group in Ar^2 also did not influence the stereoselectivity (entry 9). In addition to **2a**−**2c**, coupling reaction of **2d**−**2g** bearing Me, *i*-Pr, *t*-Bu, or CF_3 as R also proceeded stereoselectively to give **3l**−**3s** as a single diastereomer with the same stereochemical outcome,[11] although **2f** reacted slower than others and gave **3q** and **3r** in lower yields.

Scheme 1. Stereocontrolled Approach to 1,1,2-Triaryl-1-alkenes **4** Based on Sequential Cross-Coupling Reaction of 1,1-Diborylated Alkenes **2** (B_{pin} is pinacolatoboryl)

2 **3** **4**

single diastereomer !

Table 1. Stereoselective Cross-Coupling Reaction of **2** with $Ar^2{-}I$[a]

entry	**2**	R	Ar^1	Ar^2	**3**[b]	yield (%)[c]
1	**2a**	Et	C_6H_5	C_6H_5	**3a**	83
2	**2a**	Et	C_6H_5	*p*-F$-C_6H_4$	**3b**	86
3	**2a**	Et	C_6H_5	*p*-$CF_3-C_6H_4$	**3c**	75
4	**2a**	Et	C_6H_5	*p*-$EtO_2C-C_6H_4$	**3d**	74
5	**2a**	Et	C_6H_5	*p*-$H_2N-C_6H_4$	**3e**	61
6	**2a**	Et	C_6H_5	*p*-MeO$-C_6H_4$	**3f**	60
7[d]	**2a**	Et	C_6H_5	*p*-RO$-C_6H_4$	**3g**	55
8	**2a**	Et	C_6H_5	*p*-Me$-C_6H_4$	**3h**	87
9	**2a**	Et	C_6H_5	*o*-Me$-C_6H_4$	**3i**	78
10	**2b**	Et	*p*-Me$-C_6H_4$	*p*-F$-C_6H_4$	**3j**	67
11	**2c**	Et	*p*-$CF_3-C_6H_4$	*p*-F$-C_6H_4$	**3k**	66
12	**2d**	Me	C_6H_5	C_6H_5	**3l**	69
13	**2d**	Me	C_6H_5	*p*-$CF_3-C_6H_4$	**3m**	66
14	**2d**	Me	C_6H_5	*p*-MeO$-C_6H_4$	**3n**	70
15	**2e**	*i*-Pr	C_6H_5	*p*-$CF_3-C_6H_4$	**3o**	68
16	**2e**	*i*-Pr	C_6H_5	*p*-MeO$-C_6H_4$	**3p**	71
17	**2f**	*t*-Bu	C_6H_5	*p*-$CF_3-C_6H_4$	**3q**	54
18	**2f**	*t*-Bu	C_6H_5	*p*-MeO$-C_6H_4$	**3r**	39
19	**2g**	CF_3	C_6H_5	C_6H_5	**3s**	72

[a] Reaction conditions: **1** (0.1 mmol), $Ar^2{-}I$ (0.1 mmol), Pd_2dba_3 (5.0 μmol), P(*t*-Bu)$_3$ (0.02 mmol), 3 M KOH aq. (0.1 mmol), THF (1 mL), rt. [b] Obtained as a single diastereomer. [c] Isolated yield. [d] R: $(CH_2)_2NMe_2$

At present, the reason the two boryl groups in **2** are completely discriminated is unclear, although the step to be considered appears to be a transmetalation process of the reaction.[12] Considering *A* values of Me (1.74 kcal/mol), Et (1.79), *i*-Pr (2.21), CF_3 (2.4−2.5), *t*-Bu (4.7; 4.9), and Ph (2.8) groups,[13] the stereochemical outcome cannot be explained simply by steric effect. For example, **2f** having a *t*-Bu undergoes the carbon−carbon bond formation at the cis position of the *t*-Bu group that is bulkier than a Ph group.

With stereodefined **3** in hand, we carried out the second cross-coupling reaction with another aryl iodide $Ar^3{-}I$. The reaction proceeded smoothly in the presence of Pd[P(*t*-Bu)$_3$]$_2$ (5 mol %), 3 M NaOH aqueous solution upon heating at 60 °C to afford **4** as a single stereoisomer. The results are summarized in Table 2. Both diastereomers of **4** can be prepared from **2** simply by changing the order of aryl iodides employed. Thus, stereochemically pure (*Z*)-

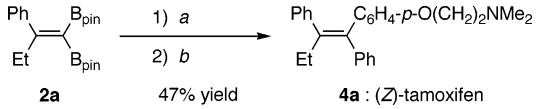
10.1021/ja054484g CCC: $30.25

Table 2. Synthesis of **4** from **3** (Ar^1 = Ph, R = Et) with Ar^3−I[a]

entry	3	Ar^3	4[b]	yield (%)[c]
1	**3a**	*p*-$Me_2N(CH_2)_2O$−C_6H_4	**4a**	59
2	**3b**	*p*-MeO−C_6H_4	**4b**	75
3	**3f**	*p*-CF_3−C_6H_4	**4c**	78
4	**3f**	*p*-Me-C_6H_4	**4d**	89
5	**3g**	C_6H_5	**4e**	75
6	**3h**	C_6H_5	**4f**	89

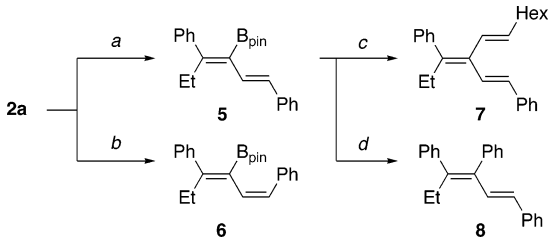
[a] Reaction conditions: **1** (0.1 mmol), Ar^3−I (0.1 mmol), Pd[P(*t*-Bu)$_3$]$_2$ (5.0 μmol), 3 M NaOH aq. (0.1 mmol), THF (1 mL), 60 °C. [b] Obtained as a single diastereomer. [c] Isolated yield.

Scheme 2. One-Pot Synthesis of (*Z*)-Tamoxifen[a]



[a] Reagents and conditions: (a) **2a** (1.0 equiv), Ph-I (1.0 equiv), Pd_2dba_3 (5 mol %), P(*t*-Bu)$_3$ (20 mol %), 3 M KOH aqueous solution, dioxane, rt, 2 h; (b) $Me_2N(CH_2)_2O$−C_6H_4−I (1.0 equiv), 100 °C, 22 h.

Scheme 3. Cross-Coupling Reaction of **2a** with Alkenyl Halides Leading to Polysubstituted 1,3-Dienes and [3]Dendralene[a]



[a] Reagents and conditions: (a) (*E*)-PhHC═C(H)I, Pd(PPh$_3$)$_4$ (5 mol %), 3 M KOH aq., THF, rt, 73% yield (2*E*4*E*:2*E*4*Z* = 98:2); (b) (*Z*)-PhHC═C(H)Br, Pd(PPh$_3$)$_4$ (5 mol %), 3 M KOH aq., THF, 40 °C, 72% yield (2*Z*4*E*:2*Z*4*Z* = 96:4); (c) (*E*)-HexHC═C(H)I, $PdCl_2$(dppf) (5 mol %), 3 M KOH aq., DME, 40 °C, 81% yield; (d) Ph-I, $PdCl_2$(dppf) (5 mol %), 3 M KOH aq., THF, 60 °C, 81% yield.

and (*E*)-tamoxifen (**4a** and **4e**) were synthesized, respectively, as listed in entries 1 and 5.

Moreover, the whole transformation can be carried out sequentially in one pot. A facile synthesis of (Z)-tamoxifen (**4a**) from **2a** is demonstrated in Scheme 2.

Furthermore, the present stereocontrol in the coupling reaction of **2** was extended to the reactions with alkenyl iodides and bromides, giving rise to 3-borylated 1,3-dienes **5** and **6** in good yields with high *E*-selectivity (Scheme 3).[14] Boronates **5** and **6** can serve as versatile precursors of polysubstituted 1,3-dienes. For example, stereocontrolled [3]dendralene **7**[15] and triphenylated 1,3-diene **8** were easily obtained in good yields by successive Pd-catalyzed coupling reactions with alkenyl and aryl iodides, respectively.

In summary, we have demonstrated stereoselective cross-coupling reaction of 1,1-diboryl-1-alkenes with aryl iodides to afford the corresponding (*E*)-alkenylboronates as single diastereomers. In conjunction with the subsequent coupling of the boronates, this approach provides an efficient and completely stereocontrolled access to TAA, including tamoxifen. In addition, this method is applicable to stereoselective preparation of polysubstituted 1,3-dienes. Further studies are in progress to disclose the factors for the stereoselection and to expand this approach to a general stereocontrolled synthesis of π-conjugated molecules.

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Supporting Information Available: Experimental procedures and analytical and spectroscopic data of new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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