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Zirconocene-Mediated Highly Regio- and Stereoselective Synthesis of Multisubstituted Olefins Starting from 1-Alkynylboronates

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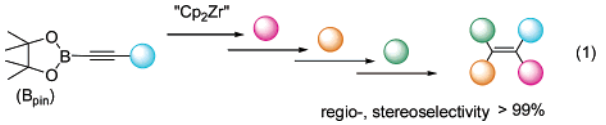
Because the expeditious, regio- and stereoselective synthesis of multisubstituted olefins is one of the most challenging subjects in synthetic organic chemistry,[1] efficient multicomponent couplings of this type are of interest and hold a potential for diversity-oriented syntheses.[2−4] Although it is known that various alkynes are oxidatively coupled on the low-valent zirconium,[5] the complete regiocontrolled formation of zirconacycles is difficult when unsymmetrical alkynes are employed. We also studied the zirconacyclopentene formation using unsymmetrical diarylethynes,[6] but complete regioselectivity is not observed.[7] Trimethylsilyl group (Me_3Si-) can selectively occupy at the α-position of zirconacycles,[8] but the further transformation is rather limited. The pioneering work of Srebnik demonstrated the preparation of highly functionalized vinylboronates by hydrozirconation of 1-alkynylboronates[9] with Schwartz's reagent (Cp_2ZrHCl).[10] One assumes that the reaction of 1-alkynylboronates with Takahashi's reagent (Cp_2ZrCl_2/2EtMgBr)[11] would be useful because the resulting boron-containing zirconacyclopentenes can be converted into various compounds by the subsequent transformation. Herein, we report a versatile procedure for the regioselective formation of zirconacyclopentenes from 1-alkynylboronates and successive transformation to give regio- and stereocontrolled tri- and tetrasubstituted olefins (eq 1; B_{pin} is pinacolatoboryl).

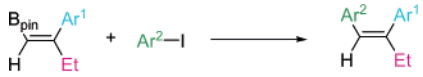


(1)

Addition of 1-alkynylboronate **1a** to Takahashi's reagent generated in situ smoothly produced zirconacyclopentene which, upon hydrolysis, afforded (*Z*)-4,4,5,5-tetramethyl-2-(2-phenyl-1-buten-1-yl)-1,3,2-dioxaborolane (**2a**) in 50% GC yield with excellent regio- and stereoselectivities (vide infra). However, the reaction was always accompanied by the dihydrogenated starting material,[10c] as a byproduct, indicating that some of the zirconacyclopentenes release the ethylene part to form the zirconacyclopropenes. To improve the yield of **2a**, we adapted the procedure to prepare the parent zirconacyclopentane ($Cp_2ZrC_4H_8$) by introduction of atmospheric ethylene gas in situ to Negishi's reagent (Cp_2ZrCl_2/2*n*BuLi). This compound is reported to react cleanly with various alkynes.[12] Accordingly, new classes of alkenylboronates **2a**−**c** were obtained exclusively in good to high yields by hydrolysis of the formed zirconacyclopentenes **A** (eq 2). The regioselectivity of **2** was determined by ^{1}H NMR spectra. The presence of a highly shifted singlet in the double bond region (5.38−5.53 ppm) is indicative that the hydrogen atom located gemenal to the boron functionality.[10c] On the other hand, the ^{11}B NMR chemical shift in the region (29.8−30.1 ppm) is appropriate to vinylboronates.

With stereodefined **2a**−**c** in hand, we performed the Suzuki−Miyaura cross-coupling[13] with various aryl iodides Ar^2-I. The results are summarized in Table 1. The reaction was general and proceeded with substituted aromatic iodides across **2a** (runs 1−13). It is noteworthy that the regiochemistry can be readily reversed by interconverting the functionality on the aryl group (Ar^1) in alkynylboronates **1** and the aryl iodide (Ar^2). Accordingly, 1-alkynylboronates, **2b** as well as **2c**, successfully reacted with iodobenzene to produce the desired products **3n** (run 14) and **3p** (run 16), respectively. Respectively, they are regioisomers of **3a** and **3b**. Furthermore, the present coupling reaction of **2a** was extended to the reaction with an alkyl iodide,[14] giving rise to [(*1Z*)-1-ethyl-1-octenyl]benzene (**4**) in 44% yield with excellent *Z*-selectivity (eq 3).[15]

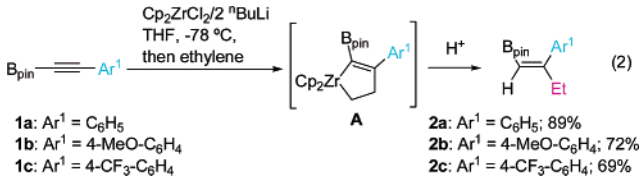
Table 1. Synthesis of Trisubstituted Ethenes **3** via Stereocontrolled Suzuki−Miyaura Cross-Coupling Reactions of Alkenylboronates **2** with Aryl Iodides[a]



2a-2c **3a-3q**

run	2	Ar^1	Ar^2	3	% yield[b]
1	**2a**	C_6H_5	4-MeO-C_6H_4	**3a**	81
2			4-CF_3-C_6H_4	**3b**	83
3			2-Me-C_6H_4	**3c**	83
4			4-NH_2-C_6H_4	**3d**	80
5			4-F-C_6H_4	**3e**	55
6			4-EtOCO-C_6H_4	**3f**	82
7			2-pyridyl	**3g**	79
8			4-NC-C_6H_4	**3h**	86
9			4-NO_2-C_6H_4	**3i**	92
10			2-HO-C_6H_4	**3j**	58
11			4-MeCO-C_6H_4	**3k**	56
12			1-naphthyl	**3l**	94
13			2-thienyl	**3m**	85
14	**2b**	4-MeO-C_6H_4	C_6H_5	**3n**	85
15			4-CF_3-C_6H_4	**3o**	72
16	**2c**	4-CF_3-C_6H_4	C_6H_5	**3p**	85
17			4-MeO-C_6H_4	**3q**	75

[a] The reactions were carried out at room temperature for 12 h by using **2** (2 mmol), aryl iodides (2.2 mmol), KOH (6.0 mmol), $Pd(dba)_2$ (10 mol %), and P(*t*-Bu)$_3$ (20 mol %) in THF (20 mL). [b] Isolated yield.



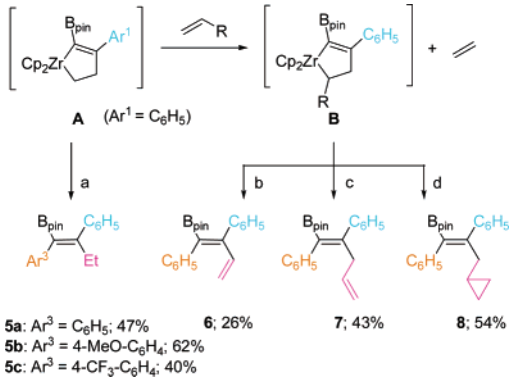
(2)

(3)

Reagents and conditions: **2a** (2.4 mmol), ^{n}C$_6$H$_{13}$-I (2.0 mmol), Ni(cod)$_2$ (4 mol %), bathophenanthroline (8 mol %), KO^{t}Bu (3.2 mmol), 2-butanol (12 mL), 60 °C, 5 h, 44%.

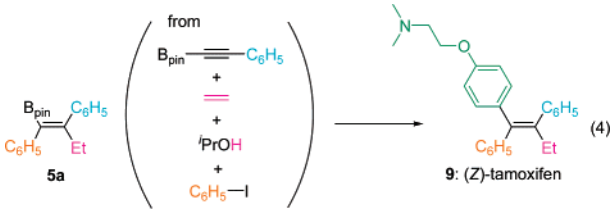
10.1021/ja075234y CCC: $37.00

Scheme 1. Regio- and Stereocontrolled Synthesis of the Boron-Containing Tetrasubstituted Olefins[a]



[a] Reagents and conditions: (a) ^{i}PrOH (0.8 equiv), CuCl (1.0 equiv), $Pd(PPh_3)_4$ (10 mol %), the corresponding aryl iodide (1.0 equiv), THF, room temp, 1 h; (b) ethyl vinyl ether (1.5 equiv), 50 °C, 20 h, then CuCl (1.0 equiv), DMPU (1.5 equiv), $Pd(PPh_3)_4$ (10 mol %), iodobenzene (1.1 equiv), THF, 50 °C, 3 h; (c) allyloxytrimethylsilane (1.5 equiv), 50 °C, 20 h, then CuCl (1.0 equiv), DMPU (1.5 equiv), $Pd(PPh_3)_4$ (10 mol %), iodobenzene (1.1 equiv), THF, 50 °C, 3 h; (d) homoallyl bromide (1.5 equiv), 50 °C, 20 h, then CuCl (1.0 equiv), DMPU (1.5 equiv), $Pd(PPh_3)_4$(10 mol %), iodobenzene (1.1 equiv), THF, 50 °C, 3 h.

Before hydrolysis, zirconacyclopentene **A** formed in situ can serve as versatile precursors of tetrasubstituted olefins bearing the boron functionalities. For example, as shown in Scheme 1, stereocontrolled formation of **5a**−**c** were easily accomplished by sequential one-pot Pd-catalyzed coupling reactions with various aryl iodides. Again, the stereochemistry of **5a**−**c** can be confirmed by comparison of the spectroscopic data with those of the reported authentic compounds of stereochemistry verified by X-ray analyses.[4] Substitution of the ethylene moiety of zirconacyclopentene **A** ($Ar^1 = C_6H_5$) with the corresponding unsaturated organic molecules afforded zirconacyclopentenes **B**, which further reacted with iodobenzene under similar conditions to afford **6**, **7**, and **8**.[16]



An additional motivation for this study is our interest in developing an efficient route to (*Z*)-tamoxifen, which has been widely used for the treatment of breast cancer at all stages. Tamoxifen's anti-estrogen biological activity resides entirely in the *Z*-isomer. Although there are a number of stereoselective syntheses of (*Z*)-tamoxifen,[2,4,17] either they are not regio- and stereoselective or they involve multistep procedures employing starting materials that are not readily available. Our route to (*Z*)-tamoxifen involves a multicomponent reaction of readily available **5a** (from **2a**, ethylene, ^{i}PrOH, iodobenzene), and *N*-[2-(4-iodophenoxy)ethyl]-*N*,*N*-dimethylamine (eq 4). It is noteworthy that the reaction is highly regioselective (possibly >99:1), since the crude tamoxifen obtained is around 99% pure according to ^{1}H NMR spectrum.

In summary, we have developed a versatile direct synthesis of multisubstituted olefins by a regioselective formation of zirconacyclopentenes followed by Cu/Pd cross-coupling and Suzuki−Miyaura coupling with various aryl iodides. Further studies to disclose the factors for the regioselectivity and to expand this approach to a general stereocontrolled synthesis of π-conjugated molecules will be the subjects of forthcoming papers.

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Supporting Information Available: Details of all experimental procedures and spectroscopic data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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