

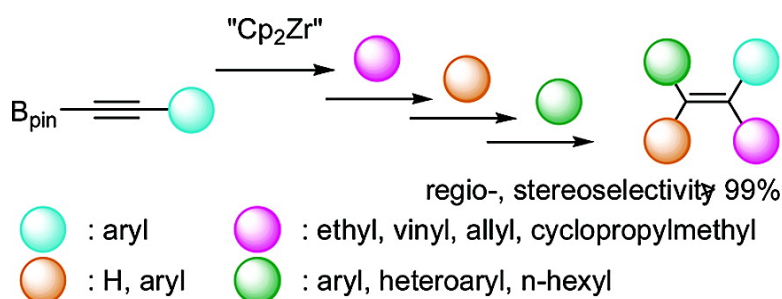
Communication

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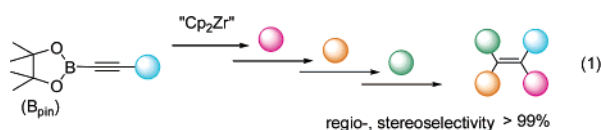
Zirconocene-Mediated Highly Regio- and Stereoselective Synthesis of Multisubstituted Olefins Starting from 1-Alkynylboronates

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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 diarylethyne,⁶ but complete regioselectivity is not observed.⁷ Trimethylsilyl group (Me₃Si-) 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-alkynylboronates⁹ with Schwartz's reagent (Cp₂ZrHCl).¹⁰ One assumes that the reaction of 1-alkynylboronates with Takahashi's reagent (Cp₂ZrCl₂/2EtMgBr)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).



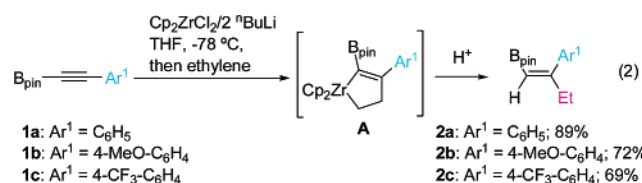
Addition of 1-alkynylboronate **1a** to Takahashi's reagent generated in situ smoothly produced zirconacyclopentene which, upon hydrolysis, afforded (*Z*)-4,4,5,5-tetramethyl-2-(2-phenyl-1-buten-1-yl)-1,3,2-dioxaborolane (**2a**) in 50% GC yield with excellent regio- and stereoselectivities (vide infra). 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 zirconacyclopentenes. To improve the yield of **2a**, we adapted the procedure to prepare the parent zirconacyclopentane (Cp₂ZrC₄H₈) by introduction of atmospheric ethylene gas in situ to Negishi's reagent (Cp₂ZrCl₂/2*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 ¹H 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 geminal to the boron functionality.^{10c} On the other hand, the ¹¹B 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-coupling¹³ with various aryl iodides Ar²-I. The results are summarized in Table 1. The reaction was general and proceeded

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

run	2	Ar ¹	Ar ²	3	% yield ^b
1	2a	C ₆ H ₅	4-MeO-C ₆ H ₄	3a	81
2			4-CF ₃ -C ₆ H ₄	3b	83
3			2-Me-C ₆ H ₄	3c	83
4			4-NH ₂ -C ₆ H ₄	3d	80
5			4-F-C ₆ H ₄	3e	55
6			4-EtOCO-C ₆ H ₄	3f	82
7			2-pyridyl	3g	79
8			4-NC-C ₆ H ₄	3h	86
9			4-NO ₂ -C ₆ H ₄	3i	92
10			2-HO-C ₆ H ₄	3j	58
11			4-MeCO-C ₆ H ₄	3k	56
12			1-naphthyl	3l	94
13			2-thienyl	3m	85
14	2b	4-MeO-C ₆ H ₄	C ₆ H ₅	3n	85
15			4-CF ₃ -C ₆ H ₄	3o	72
16	2c	4-CF ₃ -C ₆ H ₄	C ₆ H ₅	3p	85
17			4-MeO-C ₆ H 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.

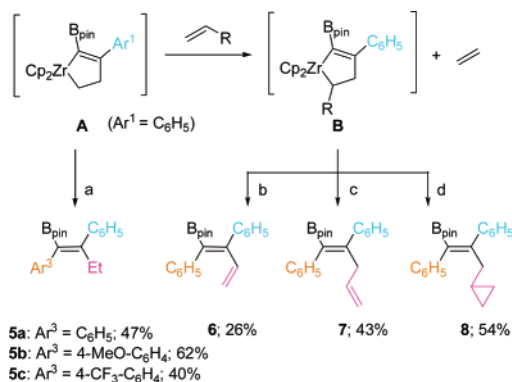


with substituted aromatic iodides across **2a** (runs 1–13). It is noteworthy that the regiochemistry can be readily reversed by interconverting the functionality on the aryl group (Ar¹) in alkenylboronates **1** and the aryl iodide (Ar²). Accordingly, 1-alkynylboronates, **2b** as well as **2c**, successfully 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 [(*IZ*)-1-ethyl-1-octenyl]benzene (**4**) in 44% yield with excellent *Z*-selectivity (eq 3).¹⁵



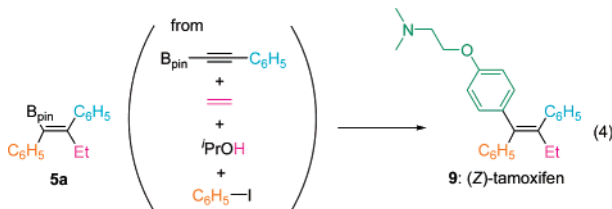
Reagents and conditions: **2a** (2.4 mmol), ⁿC₆H₁₃-I (2.0 mmol), Ni(cod)₂ (4 mol %), bathophenanthroline (8 mol %), KO^tBu (3.2 mmol), 2-butanol (12 mL), 60 °C, 5 h, 44%.

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(PPh₃)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(PPh₃)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(PPh₃)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(PPh₃)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** (Ar¹ = C₆H₅) with the corresponding unsaturated organic molecules afforded zirconacyclopentenenes **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 ¹H NMR spectrum.

In summary, we have developed a versatile direct synthesis of multisubstituted olefins by a regioselective formation of zircona-

cyclopentenenes 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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