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Stereo- and Regiocontrolled Synthesis of Branched Trisubstituted Conjugated Dienes by Palladium(0)-Catalyzed Cross-Coupling Reaction

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The development of transition metal-mediated intermolecular cross-coupling reactions between vinyl metal species and vinyl halides has been an important achievement in the field of organometallic chemistry.[1] These processes provide an efficient method for the assembly of conjugated diene systems. The original report by Schwartz and co-workers documented that the hydrozirconation of unsymmetrical alkynes proceeds with complete stereoselectivity and high regioselection to produce vinylic Zr(IV) complexes.[2] Subsequent reports by Negishi described highly selective cross-coupling procedures for the synthesis of conjugated olefins involving the reaction of a vinylic zinc intermediate (transmetalated from the vinylic zirconium) with vinyl halides in the presence of a Pd(0)−phosphine complex.[3] This efficient approach to unfunctionalized (*E*,*E*)-dienes remains highly underdeveloped in the synthesis of their (*E*,*Z*)-isomers and functionalized trisubstituted dienes with adjacent nitrogen and oxygen stereogenic centers. This paper reports the use of a Pd(0)-catalyzed cross-coupling reaction of (*E*)-trisubstituted vinyl-zinc intermediates with (*E*)- and (*Z*)-vinyl iodides under modified Negishi conditions. The present study demonstrates the utility of these transition metal-catalyzed reactions in the development of an effective method for the synthesis of configurationally pure (*E,E*)-, (*E,Z*)-, and *(Z,E)*-dienes bearing α- and α,*β*-stereogenic centers adjacent to the olefins (eqs 1 and 2).

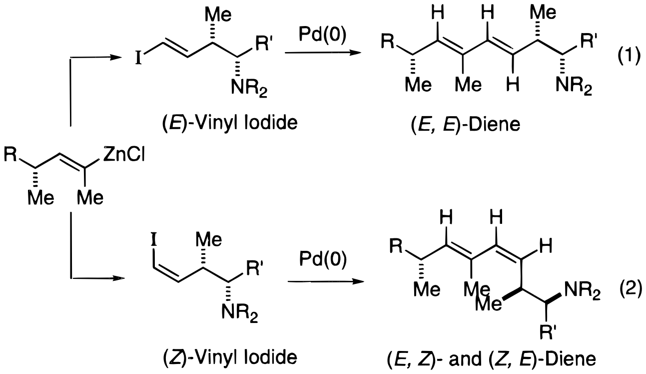
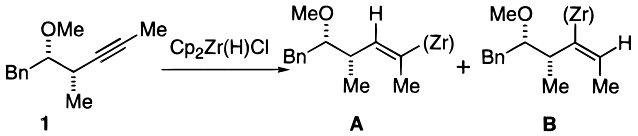


Table 1. Hydrozirconation Selectivity



$Cp_2Zr(H)Cl$[a] (equiv)	solvent	*T* (°C)	time (h)	% concn[b]	regioselectivity **A**/**B**[c]
1.2	toluene	45	2.0	92	63:37
2.5	benzene	rt	3.3	50	72:28
1.5	benzene	45	0.3	90	75:25
√2.0	benzene	50	4.0	100	100:0
2.5	THF	rt	4.0	70	54:46
2.0	THF	50	0.4	100	87:13
√2.0	THF	50	1.0	100	100:0

[a] For the preparation of the Schwartz reagent, see ref 8b. [b] Percent conversion was measured by ^{1}H NMR analysis and is based on remaining alkyne. [c] Regioselectivity (A/B ratio) was determined by ^{1}H NMR analysis.

We anticipated that trisubstituted chiral vinylzirconium derivatives (derived from unsymmetrical internal alkynes) would participate in the cross-coupling reaction with highly functionlized branched (*E*)- and (*Z*)-vinyl iodides.[4−6] Accordingly, initial efforts focused on optimizing the selectivity of the hydrozirconation of the chiral alkyne **1** with zirconocene hydrochloride (Schwartz reagent), Table 1.[7] In agreement with literature precedents concerning hydrozirconation of unsymmetrical alkynes,[8] this study also determined that in the presence of excess Schwartz's reagent this hydrozirconation reaction displays a significant temperature, solvent, and time dependency toward reaction selectivity. Gratifyingly, quantitative conversion of alkyne **1** to the desired hydrozirconated product **A** was obtained in THF or benzene at 50 °C with reaction times ranging from 1 to 4 h. It appears that the hydrozirconation of acetylenes is governed by the amount of Schwartz's reagent employed. With 1 equiv, the kinetic product is obtained as a mixture of isomers **A** and **B**, while an excess of reagent gives the thermodynamic product **A**. This may be rationalized by the reversible addition of a second equivalent of reagent to the initially formed vinylzirconium adduct.[2] *Those crucial results allowed us to execute the hydrozirconation and subsequent cross-coupling reactions in THF as a one-pot reaction sequence, significantly improving the operational aspects of the process.*

Having achieved a high level of conversion and complete regioselectivity in the hydrozirconation reaction of **1**, we explored the transmetalation to the vinylzinc intermediate and Pd(0)-catalyzed cross coupling with a range of functionalized vinyl halides. The results of the preparation of (*E*,*E*)-dienes under the modified Negishi

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(1) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483 and references cited therein. (b) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508−524. (c) Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748−2749. (d) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340−348.

(2) Hart, D. W.; Blackburn, T. F.; Schwartz, J. *J. Am. Chem. Soc.* **1975**, *97*, 679−680.

(3) (a) Negishi, E.; Okukado, N.; King, A. O.; Van Horn, D. E.; Spiegel, B. I. *J. Am. Chem. Soc.* **1978**, *100*, 2254−2256. (b) Ichikawa, J.; Fujiwara, M.; Nawata, H.; Okauchi, T.; Minami, T. *Tetrahedron Lett.* **1996**, *37*, 8799−8802.

(4) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408−7410.

(5) (a) For preparation of (*Z*)-vinyl iodide, see: Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 2173−2174. (b) For preparation of (*Z*)-vinyl bromide, see: Matsumoto, M.; Kuroda, K. *Tetrahedron Lett.* **1980**, *21*, 4021−4024.

(6) To our knowledge, comparison of the reactivity between (*E*)- and (*Z*)-vinyl iodides has been rarely documented, and we are aware of a single report where reactivity differences between (*E*)- and (*Z*)-vinyl bromides have been observed; see: Rossi, R.; Carpita, A. *Tetrahedron Lett.* **1986**, *27*, 2529−2532.

(7) (a) Hart, D. W.; Schwartz, J. *J. Am. Chem. Soc.* **1974**, *96*, 8115−8116. (b) Buchwald, S. L.; La Maire, S. J.; Nielsen, R. B.; Watson, B. T.; King, S. M. *Tetrahedron Lett.* **1987**, *28*, 3895−3898.

(8) (a) Labinger, J. A. In Comprehensive Organic Synthesis; Hydrozirconation of C=C and C≡C and hydrometallation by other metals. Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 8, pp 667−702. (b) Schwartz, J.; Labinger, J. A. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 333−334. (c) Wipf, P.; Jahn, H. *Tetrahedron* **1996**, *52*, 12853−12910.

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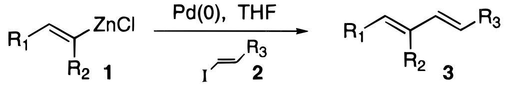
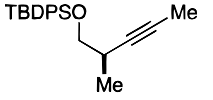
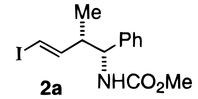
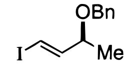
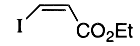
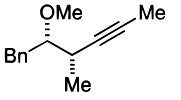
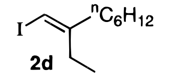
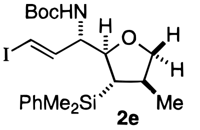
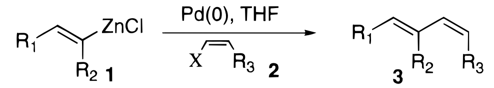
Table 2. Synthesis of Functionalized (*E,E*)-Dienes[a]

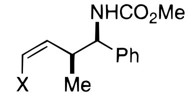
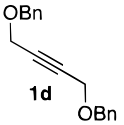
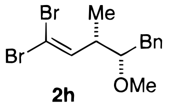
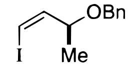
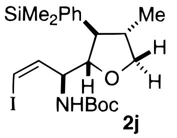


Entry	Alkyne 1[b]	Vinyl Iodide 2[c]	Product 3 (%yield[d])
1	 **1a**		**3a** (77%)
2	**1a**	 **2b**	**3b** (83%)
3	**1a**	 **2c**	**3c** (87%)
4	 **1b**		**3d** (88%)
5	**1b**		**3e** (76%)
6	**1c** (ent of **1b**)	**2a**	**3f** (56%)

[a] Hydrozirconation reactions were conducted at 50 °C (THF, 0.4 M) for 1−2.5 h, cooled to rt before adding a THF solution containing anhydrous $ZnCl_2$ (3.0 equiv) over 3−5 min followed by addition of vinyl iodide (1.0 equiv) and $Pd(PPh_3)_4$ (0.05 equiv) for 5−30 min. [b] For preparation of unsymmetrically substituted internal alkyne **1a**−**c**, see ref 9. [c] Chiral (*E*)-vinyl iodides (**2a**−**e**) were prepared from the corresponding chiral aldehydes with Takai's chromium chloride-mediated homologation (ref 4). Preparation of vinyl indide **2c** and **2d**, see the Supporting Information. [d] Yields refer to configurationally pure materials isolated after SiO_2 chromatography.

Table 3. Synthesis of Functionalized Trisubstituted (*E,Z*)- and (*Z,E*)-Dienes[a]



Entry	Alkyne 1[b]	Vinyl Halide 2[c]	Product 3 (%yield[d])
1	**1a**	 **2f** X = Br	X = Br (27%)
2	**1a**	**2g** X = I	X = I (63%)
3			**3h** (55%)
4	**1e** (3-Hexyne)	 **2i** *Z/E* = 80 : 20	**3i** (84%) *Z/E* : *E/E* = 80 : 20
5	**1e**	**2g**	**3j** (77%)
6	**1b**		**3k** (80%)

[a] Hydrozirconation reactions were conducted at 50 °C (THF, 0.4 M) for 1−2.5 h and then cooled to rt before adding a THF solution containing $ZnCl_2$ (3.0 equiv) over 3−5 min followed by the addition of the vinyl iodide (1.0 equiv) and *in situ* generated Pd(0) [$PdCl_2(PPh3)_2$-DIBAL] for 5−60 min. [b] (*Z*)-Vinyl halides were prepared from corresponding chiral aldehydes by Wittig olefination, see ref 5. Also see Supporting Information for further details. [c] Yields refer to configurationally pure materials isolated after SiO_2 chromatography.

coupling conditions are summarized in Table 2. Good to excellent yields of the cross-coupling products were obtained with the chiral alkynes **1a**−**1c**.[9] The reactions were effective with either (*E*)- or (*Z*)-vinyl iodides **2**.[10] For the cases studied, the reactions were complete within 0.5 h, affording the (*E,E*)-dienes **3a**−**3f** as isomerically pure materials. It is important to note that various substitutions on each reaction partner did not affect reaction rate or coupling efficiency.

The scope of the reaction was broadened using unsymmetrical (internal) alkynes and (*Z*)-vinyl halides (Table 3). Those experiments provided routes to the complementary (*E,Z*)- and (*Z,E*)-dienes. As illustrated for **3g**, the (*Z*)-vinyl iodides coupled in very good yields (Table 3, entry 2), while the corresponding bromides were less reactive (Table 3, entry 1).[11] Symmetrical alkynes **1d** and **1e** also participated in the cross coupling affording (*E,Z*)- and (*Z,E*)-dienes (Table 3, entries 3 and 4). For example, **3h** derived from the coupling of geminal dibromide **2h** with alkyne **1d** was produced in 55% yield as a single observed (*E,Z*)-isomer. Such discrimination of the two halogen groups with 1,1-disubstituted olefins has only been documented in the Suzuki/Tamao coupling reaction.[12] Interestingly, for reactions involving (*Z*)-isomers, best results were obtained employing $PdCl_2(PPh_3)_2$−DIBAL as the catalytic system,[13] and no significant differences in reactivity between (*E*)- and (*Z*)-vinyl iodides were observed under the reported reaction conditions.

In conclusion, the present paper describes an efficient one-pot sp^2−sp^2 Pd(0)-catalyzed coupling reaction between complex subunits: the *in situ* generated vinylic zinc intermediate and the chiral vinyl halide. In the following paper in this issue, we describe an application of this coupling reaction in the asymmetric synthesis of the β-amino acid Adda.

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Supporting Information Available: Complete physical and spectral data and experimental details for all reaction products (77 pages).

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(9) Chiral internal alkynes **1a**−**1c** were prepared from the corresponding dibromo olefins via the Corey−Fuchs protocol; see: Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769−3772. See Supporting Information for further details.

(10) Satisfactory spectroscopic data (^{1}H and ^{13}C NMR, IR, CIMS, CIHRMS) were obtained for all new compounds. Ratios of diastereomers were determined by ^{1}H NMR (400 MHz).

(11) In this case, the coupling reaction was performed at room temperature for 15 h while an increase in the reaction temperature did not improve the yield of the desired coupling product.

(12) (a) Roush, W. R.; Moriarty, K. J.; Brown, B. B. *Tetrahedron Lett.* **1990**, *31*, 6509−6512. (b) Minato, A.; Suzuki, K.; Tamao, K. *J. Am. Chem. Soc.* **1987**, *109*, 1257−1258.

(13) Okukado, N.; Van Horn, D. E.; Klima, W. L.; Negishi, E. *Tetrahedron Lett.* **1978**, 1027−1030.