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Stereoselective Synthesis of Functionalized Trisubstituted Olefins via Palladium(0)-Catalyzed Cross-Coupling Reaction

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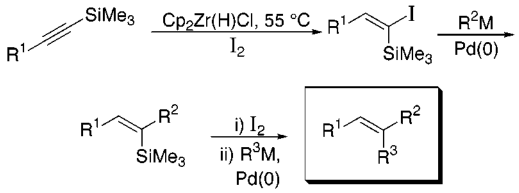
ABSTRACT



A highly flexible and stereoselective protocol for the synthesis of branched (*E*)- and (*Z*)-trisubstituted alkenes has been developed. The key steps are hydrozirconation-iodination of (1-alkynyl)trimethylsilane followed by Negishi-type cross-coupling. The resultant (*Z*)-vinyl silane is iododesilylated and subjected to a second cross-coupling reaction to give the trisubstituted olefin. Model studies aimed at the construction of the C14–C15 (*Z*)-trisubstituted olefin of discodermolide and the C8–C9 (*Z*)-trisubstituted olefin of callystatin A and analogues are also described.

Construction of trisubstituted olefins with a high degree of stereocontrol remains a formidable challenge in organic synthesis. Traditional phosphorus-based olefination methods such as the venerable Wittig[1] and Horner−Wadsworth−Emmons[2] protocols often give mixtures of (*E*)- and (*Z*)-isomers. In many instances these reactions have limited ability to vary substituents on the double bond. Recently, ring-closing metathesis (RCM)[3] and intermolecular cross-metathesis[4] have emerged as useful strategies for the construction of unsaturated ring systems and substituted olefins.

Palladium-catalyzed cross-coupling of vinyl halides with organozinc reagents (Negishi reaction)[5] represents a powerful method for carbon−carbon bond formation. The ready availability and functional group compatibility of organozinc[6] reagents significantly enhance the utility of the cross-coupling process. Hydrozirconation of silyl acetylenes has been shown to proceed with useful levels of regio- and stereoselectivity to give the α-silyl alkenyl zirconium complexes.[7] Electro-

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[2] (a) Horner, L.; Hoffmann, H.; Wippel, H. G. *Chem. Ber.* **1958**, *91*, 61−63. (b) Wadsworth, W. S.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733−1738. For a review, see: (c) Wadsworth, W. S. *Org. React.* **1977**, *25*, 73−253.

[3] (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450. (b) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18−29.

[4] Arduango, A. J. *Acc. Chem. Res.* **1999**, *32*, 913−921.

[5] For a review, see: Negishi, E.-i. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998; Chapter 1.

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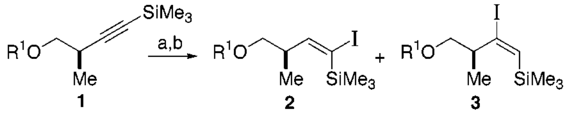
philic iodination of vinyl zirconium species proceeds with retention of double bond configuration to afford the corresponding vinyl iodides.[8] When taken collectively, these individual reactions could be merged in the correct order to afford a flexible sequence that gives stereochemically well defined trisubstituted olefins. Herein we describe a flexible reaction sequence that is useful for the stereoselective synthesis of functionalized trisubstituted olefins. The sequence is based on the formation (and use) of geminally substituted iodo-vinylsilanes, which are synthetic equivalents to 1,1-diiodoalkenes, where each iodide can be cross-coupled independently. The order in which one performs cross-coupling reactions determines the configuration of the resulting olefin.

This modular approach allows significant flexibility in accessing olefin fragments of different stereochemistries, as well as high functional group compatibility limited only by the reactivity of Schwartz reagent.

The use of Pd(0)-mediated cross-coupling reactions of 1-iodo-1-(trimethylsilyl)-1-alkenes with organozinc and organotin reagents results in the synthesis of nearly configurationally pure functionalized trisubstituted olefins.

We first examined hydrozirconation of the α-branched alkynes **1a**,**b** with zirconocene hydrochloride (Schwartz reagent), Table 1.[9] Maximum conversion and selectivity were obtained in the presence of stoichiometric amounts of $Cp_2Zr(H)Cl$ in THF at 55 °C with reaction times around 1 h. The hydrozirconation reactions of substrate **1a** (benzyl ether) proceed with higher regioselectivity than for **1b** (silyl ether), which suggests that the reversible nature of the second hydrozirconation is slower for **1b**, producing the kinetic product **3** in greater amounts.[10]

Table 1. Hydrozirconation of Silylacetylenes



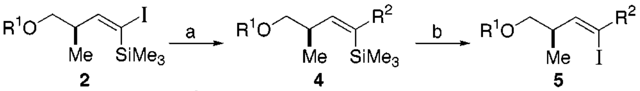
(a) $Cp_2Zr(H)Cl$ (2.5 equiv.), THF, 55 °C, 1h; (b) I_2, CH_2Cl_2, rt, 15 min.

1	R	time (h)	T (°C)	**2**/**3**[a]	**2** (yield)[b]
1a	CH_2PH	0.5	rt	>30:1	**2a** (50%)
		1	rt	>30:1	**2a** (65%)
		1	55	>30:1	**2a** (87%)
1b	TBDPS	2	rt	2:1	**2b** (74%)[c]
		1	50	5:1	**2b** (71%)[d]
		1	55	12:1	**2b** (82%)

[a] Ratio determined by ^{1}H NMR analysis. [b] Isolated yield of the desired isomer. [c] Undesired isomer also present. [d] Two equivalents of the Schwartz reagent was used.

The use of 1-iodo-1-(trimethylsilyl)-1-alkenes as synthons of 1,1-diodoalkenes was demonstrated by converting these α-iodo vinyl silanes to (*Z*)-vinyl iodides via a two-step procedure (Table 2). Initially, we investigated the palladium(0)-catalyzed cross-coupling reactions with organozinc reagents generated from the commercially available Grignard reagents. High yields and selectivities were obtained with in situ generated *n*-alkyl, *sec*-alkyl, benzyl, vinyl, and alkynylzinc chlorides. In general, the reactions were complete within 0.5 h, affording isomerically pure vinyl silanes **4**. The resulting cross-coupled vinyl silanes **4** were converted to vinyl iodides **5** by treatment with 1 equiv of I_2 in methylene chloride at room temperature. In agreement with literature precedent,[11] iododesilylation occurs with retention of configuration at the double bond and with good yields for the alkyl or benzyl substituents. However, attempts at iododesilylation for the substrates with vinyl or alkynyl substituents were unsuccessful.[12]

Table 2. Synthesis of (*Z*)-Vinyl Iodides



(a) R^2ZnCl, $Pd(Ph_3P)_4$, THF, rt; (b) I_2, CH_2Cl_2

entry	**2** (R^1)	R^2	product (yield)	
1	**2a** (CH_2Ph)	Me	**4a** (95%)	**5a** (75%)
2		Et	**4b** (97%)	**5b** (77%)
3		^{i}Pr	**4c** (80%)	**5c** (69%)[a]
4		Bn	**4d** (80%)	**5d** (68%)[a]
5		$CH{=}CH_2$	**4e** (95%)	
6		$C{\equiv}CH$	**4f** (94%)	
7	**2b** (TBDPS)	Me	**4g** (95%)	**5g** (74%)
8		Et	**4h** (96%)	**5h** (78%)
9		^{i}Pr	**4l** (86%)	**5i** (68%)
10		Bn	**4j** (82%)	**5j** (64%)
11		$CH{=}CH_2$	**4k** (93%)	
12		$C{\equiv}CH$	**4l** (88%)	

[a] (Z)-Configuration was assigned by NOE measurements.

Since vinyl and alkynyl substituents on the vinylsilane are incompatible with iododesilylation conditions, the trisubstituted olefin synthesis is limited to cases where *trans*-substituent R^2 is an alkyl or benzyl group.[13] Having established high yields and complete stereoselectivity for the conversion of 1-iodo-1-(trimethylsilyl)-1-alkenes to (*Z*)-vinyl iodides via a two-step sequence, we explored Pd(0)-catalyzed cross-coupling reactions for the construction of the trisubstituted olefins.

During our studies toward the synthesis of the marine natural product discodermolide[14,15] we became particularly

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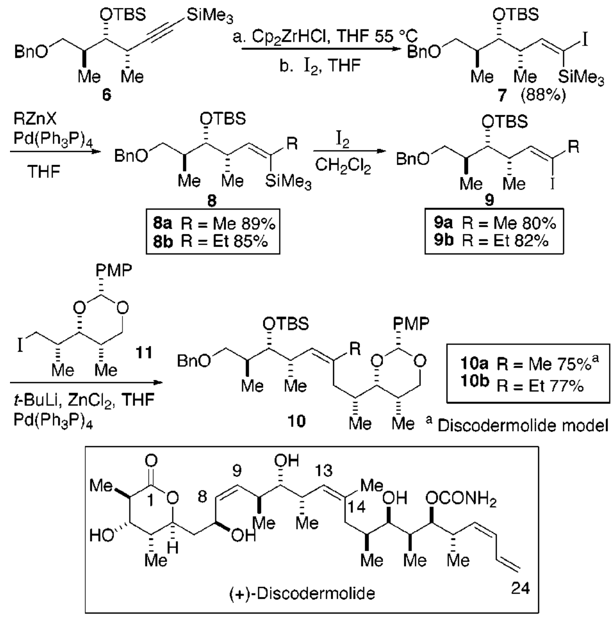
(12) Utilization of *N*-iodosuccinimide in iododesilylation results in isomerization of olefin geometry.

(13) An alternative way to synthesize (*Z*)-vinyl halides with sp^2 or sp types of substituents in geminal position is direct coupling with vinyl dibromide; see refs 16 and 17.

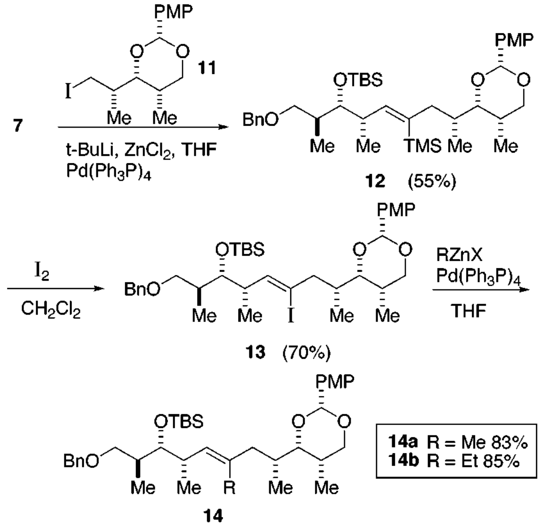
interested in the stereoselective construction of the C13−C14 trisubstituted (*Z*)-olefin of the natural product.

Initially, we investigated the difference in the reactivity between two halogen groups of 1,1-dihalo-1-alkenes in the palladium(0)-catalyzed coupling reactions. Such differentiation of the two halogen groups has been well documented for sp^2-sp^2 and sp^2-sp but not for the sp^2-sp^3 cross-coupling reactions.[16] Our attempts to selectively methylate vinyl dibromide under Negishi, Stille, or Suzuki conditions proved unsuccessful, yielding only dialkylated product.[17] As a result, we searched for a useful synthetic equivalent of 1,1-dihalo-1-alkenes. In studies toward the synthesis of discodermolide, we examined the use of iodo-vinylsilane **7** for the construction of the C13−C14 (*Z*)-olefin of discodermolide (Scheme 1). The vinylsilane **7** was obtained from TMS-terminated alkyne **6** in 90% yield as a single regioisomer under optimized hydrozirconation conditions (2.5 equiv of Schwartz reagent, 55 °C in THF). Cross-coupling with Grignard-derived methyl- and ethylzinc chlorides afforded (*Z*)-vinyl silanes **8a** and **8b**, respectively, in high yields as single stereoisomers. Subsequent iododesilylation and the second cross-coupling under modified Negishi conditions afforded trisubstituted olefin fragments **10a** and **10b** in high yields in (*Z*)-configuration as required for the synthesis of C13−C14 trisubstituted olefin of discodermolide. Flexibility of this procedure was further demonstrated by the synthesis of (*E*)-isomers of compounds **10a**,**b** by reversing the order of cross-coupling reactions (Scheme 2).

Scheme 1



Scheme 2



Under modified Negishi conditions, the vinylsilane **7** was cross-coupled with the organozinc intermediate derived from alkyl iodide **11**. The resulting vinyl silane **12** was iododesilylated and subjected to the second cross-coupling with methyl- and ethylzinc chlorides to afford (*E*)-olefin fragments **14a**,**b**.

Additionally, this methodology has been applied to the synthesis of the C6−C9 (*E*,*Z*)-diene of callystatin A[18,19] (Scheme 3). Hydrozirconation of the (trimethylsilyl)acetylene **14** followed by iododemetalation afforded iodo-vinylsilane

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[17] Cross-coupling reactions of vinyl dibromide with vinyl and alkynyl zinc species selectively afforded products of *trans*-bromo substitution in high yields.

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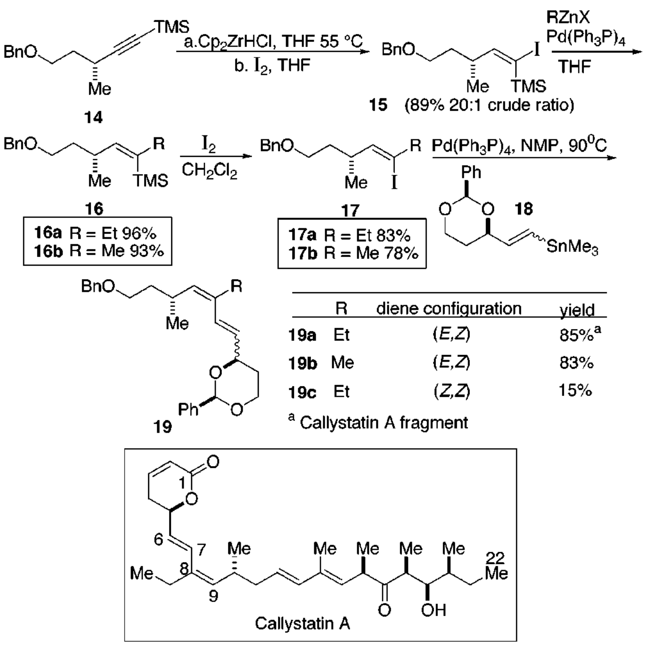
Scheme 3



	R	diene configuration	yield
19a	Et	(*E*,*Z*)	85%[a]
19b	Me	(*E*,*Z*)	83%
19c	Et	(*Z*,*Z*)	15%

[a] Callystatin A fragment

15 in 89% yield as a single isomer after chromatography (SiO_2). Stereoselective cross-coupling with Grignard-derived ethylzinc chloride followed by iododesilylation afforded (*Z*)-vinyl iodide **17a** in high yield as a single stereoisomer. Stille coupling with vinylstannane (*E*)-**18** afforded the requisite C6−C9 (*E*,*Z*)-diene **19a** as a potential synthon for the C1−C12 fragment of callystatin A.

Substituting methyl zinc chloride in the Negishi coupling of this protocol provides an efficient route to the methyl analogue **19b**. Utilization of (*Z*)-**18** provides the synthetically challenging (*Z*,*Z*)-isomer **19c**, albeit in low yield.[20]

In conclusion, we have developed a highly flexible protocol that allows synthesis of configurationally pure (*E*)- and (*Z*)-functionalized trisubstituted olefins. We have described the preparation of trisubstituted olefin fragments as a part of our model studies in the syntheses of natural products discodermolide and callystatin A. Application of this methodology toward the syntheses of these natural products is currently in progress and will be reported at a later time.

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Supporting Information Available: Experimental procedures and spectroscopic characterization (IR, HRMS, and ^1H and ^{13}C NMR data) of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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