Communication

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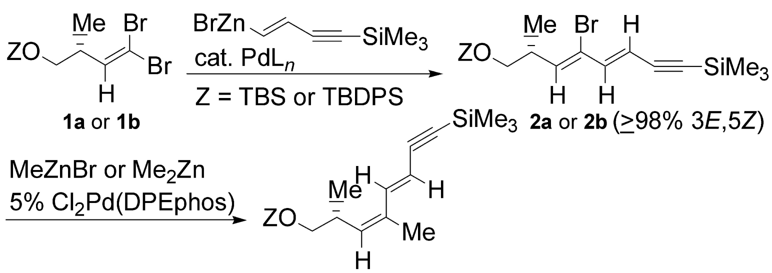

1a or **1b** **2a** or **2b** (≥98% 3*E*,5*Z*)

3a or **3b** (90-95% yield, ≥97% 3*E*,5*Z*)

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Clean Inversion of Configuration in the Pd-Catalyzed Cross-Coupling of 2-Bromo-1,3-dienes

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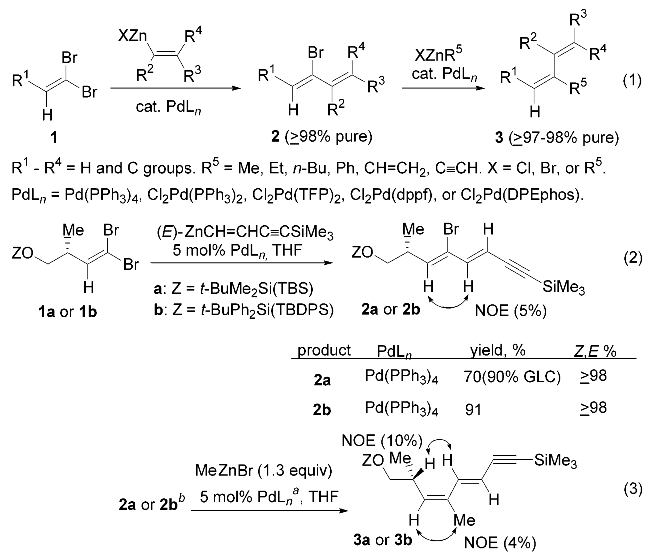
Aside from examples of unwanted, partial stereoisomerization, the Pd-catalyzed alkenylation with alkenyl halides has been known to proceed with retention of configuration.[1] We now report some unprecedented examples exhibiting ≥97−98% inversion at halogen-bearing C_{sp^2} centers that can be represented by eq 1 in Scheme 1. Besides being novel, the reaction promises to provide an attractive and useful route to conjugated dienes present in a number of complex natural products, such as (−)-callystatin A,[2] (−)-leptomycin B,[3] and (+)-ratjadone.[4]

In a project directed toward natural products synthesis, we recently ran the Pd-catalyzed alkenylation−methylation of 1,1-dibromo-1-alkenes **1a** and **1b**[1b] with (*E*)-BrZnCH═CHC≡CSiMe$_3$[5] and then with either MeZnBr or Me$_2$Zn[6] in the presence of a Pd-phosphine catalyst in one pot without isolation of **2a** or **2b**. Under these conditions, clean and highly stereoselective disubstitution reactions took place in excellent yields. To our surprise, detailed analysis of the both crudely isolated product mixtures and purified products by NMR spectroscopy including NOE measurements has established that the essentially single stereoisomer formed is the unexpected (3*E*,5*Z*)-diene **3a** or **3b** rather than the expected (3*E*,5*E*)-isomer (eqs 2 and 3, Scheme 1). Very high stereoselectivities of ≥97−98% have been observed by using Cl$_2$Pd(DPEphos) or Cl$_2$-Pd(dppf), while the use of Cl$_2$Pd(TFP)$_2$ or Pd(PPh$_3$)$_4$ has led to a slightly lower stereoselectivity level of about 95% (eq 3, Scheme 1).[7]

Scheme 1



R^1 - R^4 = H and C groups. R^5 = Me, Et, *n*-Bu, Ph, CH=CH$_2$, C≡CH. X = Cl, Br, or R^5.
PdL_n = Pd(PPh$_3$)$_4$, Cl$_2$Pd(PPh$_3$)$_2$, Cl$_2$Pd(TFP)$_2$, Cl$_2$Pd(dppf), or Cl$_2$Pd(DPEphos).

product	PdL_n	yield, %	*Z,E* %
2a	Pd(PPh$_3$)$_4$	70(90% GLC)	≥98
2b	Pd(PPh$_3$)$_4$	91	≥98

product	PdL_n	yield, %	*Z,E* %
3a	Cl$_2$Pd(DPEphos)	76	≥97
3b	Cl$_2$Pd(DPEphos)	91	≥97
3b	Cl$_2$Pd(dppf)	85	≥97
3b	Cl$_2$Pd(TFP)$_2$	87	95
3b	Pd(PPh$_3$)$_4$	90	95

[a] In the stepwise process either one or two different catalysts were used. [b] In the one-pot process **2a** or **2b** was not isolated. The results shown below **3a** or **3b** were obtained via one-pot process.

The reaction of **1a** and **1b** with 1.5 mol equiv of BrZnCH═CHC≡CSiMe$_3$ in the presence of 5 mol % of Pd(PPh$_3$)$_4$ produced in high yields **2a** and **2b**, respectively, that were ≥98% 3*E*,5*Z* (eq 1, Scheme 1) in accordance with the well-documented high *trans*-selectivity in Pd-catalyzed monosubstitution of 1,1-dihalo-1-alkenes with alkenylmetals containing Zn,[8a−c] B,[8d,e] Sn,[8f] and Zr.[8b] Consequently, the observed stereoinversion must occur in the second step for the conversion of **2** into **3**. To further probe the nature of this unprecedentedly clean and virtually full stereoinversion in the Pd-catalyzed cross-coupling of alkenyl halides, **2a**−**2m**, prepared as stereoisomerically ≥98% pure compounds in the presence of 5 mol % of Pd(PPh$_3$)$_4$ according to eq 2 in Scheme 1, were further substituted with organozinc derivatives containing Me, Et, *n*-Bu, Ph, H$_2$C═CH, and HC≡C in the presence of 5 mol % of Cl$_2$Pd-(DPEphos) in THF. The experimental results summarized in Table 1 indicate the following.

First, as long as (a) alkyl aldehydes are used as precursors to 1,1-dibromo-1-alkenes (**1**) and (b) its cross-coupling partners are (*E*)-β-monosubstituted alkenylzinc derivatives, the stereoinversion in the second substitution occurs predictably and in high stereoselectivity (entries 1−14). Stereoinversion in all of these cases is strictly confined to the trisubstituted alkene moiety, and the *E* geometry of the disubstituted alkenyl group remains intact. Irrespective of mechanistic details, this novel tandem disubstitution should offer an efficient and selective route to various complex natural products, such as those mentioned earlier.

Second, these results clearly indicate that the class and structural details of the R^5 group introduced as R^{5}ZnX, where X = R^5 or Br, have little or nothing to do with the observed stereoinversion. These results strongly suggest that the observed stereoinversion is a phenomenon pertaining only to the putative dienylpalladium intermediates generated via oxidative addition.

The observed stereoinversion has to do primarily with relative thermodynamic stabilities of various possible alkenylidene-substituted π-allylpalladium derivatives (**4** and **5**, Scheme 2).[9] It can be reasoned on steric ground that the *trans* relationship[10] between R^1 and Pd would be thermodynamically more favorable than the starting *cis* relationship. In this context, however, it is to be noted that the widely accepted, fully orbital interaction controlled $\pi-\sigma-\pi$ rearrangement mechanism for stereoinversion of ordinary allylpalladium derivatives may not operate in the observed stereoinversion, as it would require double *E*−*Z* stereoinversions.[10] Thus, interconversion between **4** and **5** must involve an as yet unclear nonconcerted transformation.

For both exploring the synthetic scope and further probing mechanistic details, substitution pattern of the alkenyl groups introduced as alkenylzinc derivatives was varied, while employing the same R^1 and R^5, i.e., (*S*)-TBSOCH$_2$(Me)CH and Me, respec-

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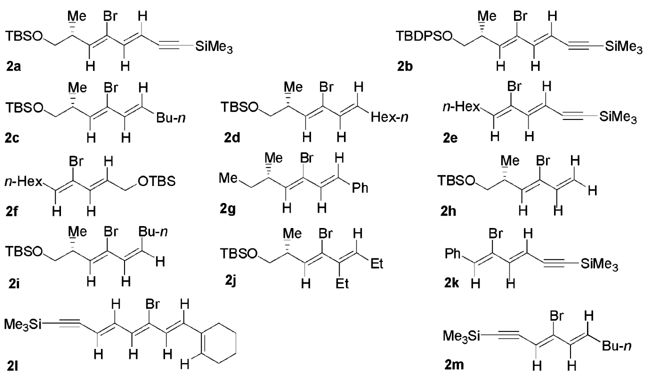
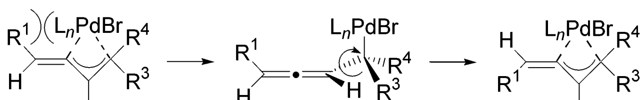
Table 1. Reaction of (*Z*)-2-Bromo-1,3-dienes with Organozinc Derivatives in the Presence of 5 mol % of $Cl_2Pd(DPEphos)$

entry	**2**[a]	R^5ZnX	3	yield, %[b]	*Z,E*, %[c]
1	**2a**	Me_2Zn	**3a**	90	≥97[d]
2	**2a**	Me_2Zn	**3a**	93	≥99
3	**2b**	MeZnBr	**3b**	95	≥98
4	**2a**	EtZnBr	**3c**	93	≥98
5	**2a**	*n*-BuZnBr	**3d**	91	≥98
6	**2a**	PhZnBr	**3e**	92	≥98(*E,E*)
7	**2a**	$H_2C{=}CHZnBr$	**3f**	96	≥98
8	**2a**	$HC{\equiv}CZnBr$	**3g**	96	≥98(*E,E*)
9	**2c**	MeZnBr	**3h**	85	≥98
10	**2d**	MeZnBr	**3i**	70	≥98
11	**2d**	EtZnBr	**3j**	95	≥98
12	**2e**	MeZnBr	**3k**	84	≥98
13	**2f**	Me_2Zn	**3l**	88	≥97
14	**2g**	Me_2Zn	**3m**	87	≥98
15	**2h**	Me_2Zn	**3n**	72	≥97(*Z*)
16	**2i**	Me_2Zn	**3o**	92	≥98(*Z,Z*)
17	**2j**	Me_2Zn	**3p**	90	≥98
18	**2k**	MeZnBr	**3q**	92	50[e]
19	**2l**	Me_2Zn	**3r**	61	≤3[f]
20	**2m**	Me_2Zn	**3s**	95	≤1[g]



[a] Fully identified as ≥98% *Z,E* isomer. [b] Isolated yield. [c] Percentage of the *Z,E* isomer unless otherwise indicated in parentheses. [d] $Pd(PPh_3)_4$ was used as a catalyst. [e] *Z,E*/*E,E* = 50/50. [f] *E,Z,E*/*E,E,E* ≤ 3/97. [g] *Z,E*/*E,E* ≤ 1/99.

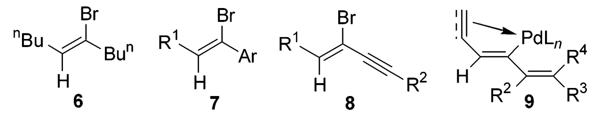
Scheme 2



4 (*cis*) **5** (*trans*)

tively (entries 1, 2, 9, 10, 15−17). All alkenyl groups were introduced in good yields in ≥98% *trans*-selectivity to produce the corresponding **2**. Their subsequent reaction with Me_2Zn or MeZnBr in the presence of 5 mol % of $Cl_2Pd(DPEphos)$ proceeded with clean stereoinversion (≥97−98%) in high yields. Particularly noteworthy and puzzling is the fact that stereoisomerization was confined to the Br-bearing C═C bond even in the case in which (*Z*)-1-hexenylzinc bromide was used, and yet, it is definitely not a phenomenon observable with any types of bromoalkenes. Thus, the corresponding reaction of **6** showed no sign of stereoinversion. Furthermore, our recent studies have shown that the corresponding reactions of α-bromostyrenes **7** underwent stereoisomerization only to the extent of <5%,[11] while those of 2-bromo-1-en-3-ynes **8** were accompanied by significant but partial stereoisomerization.[1b] It is therefore clear that the observed clean and essentially full stereoinversion is induced by the presence of the C═C bond that is in conjugation with the Br-bearing C═C bond and allylic to Br.

Although electronic effects of R^5 were insignificant (entries 6−8), those of R^1 were of crucial importance. Thus, alkenyl and alkynyl[12] groups as R^1 can totally inhibit stereoisomerization (entries 19 and 20), while Ph as R^1 led to partial stereoinversion (entry 18). These results may tentatively be attributed to chelation shown in **9**.



In summary, the Pd-catalyzed cross-coupling reaction of 2-bromo-1,3-dienes derived from alkyl aldehydes, especially with Cl_2Pd(DPEphos) as a catalyst, proceeds with clean stereoinversion of the Br-bearing C═C bond to produce in high yields and in high stereoselectivity (≥97−98%) conjugated *Z,E* dienes of potentially high utility in the synthesis of complex natural products. The observed stereoinversion cannot be readily accommodated by the widely accepted $\pi-\sigma-\pi$ rearrangement mechanism for isomerization of ordinary allylpalladium derivatives.

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Supporting Information Available: Experimental procedures, spectroscopic data, and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) Comparable results were obtained with Me_2Zn or MeZnBr derived from either MeLi or MeMgBr.

(7) All ligands used in this study are commercially available. DPEphos = bis(2-diphenylphosphinophenyl) ether. TFP = tris(2-furyl)phosphine.

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