Selective Diene Synthesis

Highly Stereoselective Synthesis of (1*E*)-2-Methyl-1,3-dienes by Palladium-Catalyzed *trans*-Selective Cross-Coupling of 1,1-Dibromo-1-alkenes with Alkenylzinc Reagents**

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Methyl-branched conjugated dienes and oligoenes represent a wide variety of natural products including carotenoids, antibiotics, and antitumor agents. Consequently, a number of synthetic methods have been devised for their synthesis. The Wittig and other carbonyl olefination reactions[1] have played a dominant role in these syntheses. However, these reactions often fail to display high stereoselectivities ($\geq 98\,\%$). An alternative methodology based on hydrometalation[2] and carbometalation[2b,c,3,4] of alkynes is more highly stereoselective, with typical values being $\geq 98\,\%$. However, it has often been difficult to synthesize trisubstituted alkenes in a highly regioselective manner by hydrometalation of internal alkynes. Carbometalation-based methods,[3,4] on the other hand, have often been shown to be not only highly regio- and stereoselective but also very efficient, as exemplified by recently developed novel, general, and highly selective methods for the synthesis of carotenoids[5] and terpenoids containing 1,5-diene units[6] by involving the Zr-catalyzed carboalumination of terminal alkynes. However, the "head-to-tail" construction[7] of the critical trisubstituted alkene unit has not been a

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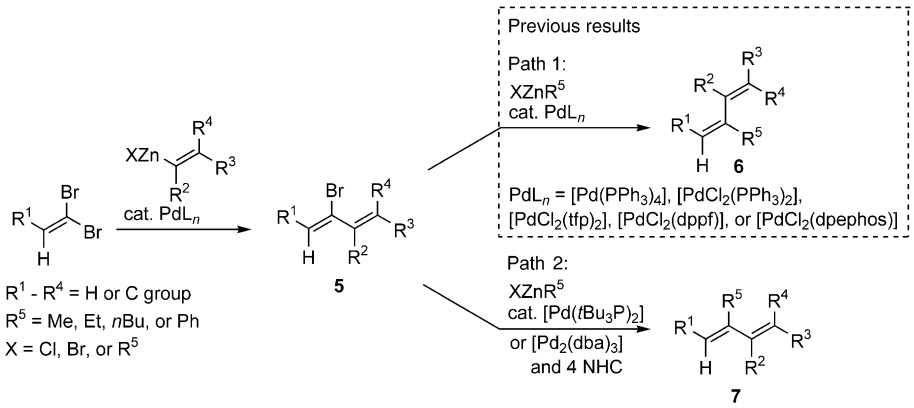
convenient route to (*E*)-2-methyl-1,3-dienes **1** with an Me-branched chiral carbon atom bonded to C-1[8]—a group of compounds that represent a variety of natural products of biological and medicinal interest, such as apoptolidin (**2**),[9] callystatin A (**3**),[10] and stipiamide (**4**)[11] (Scheme 1).

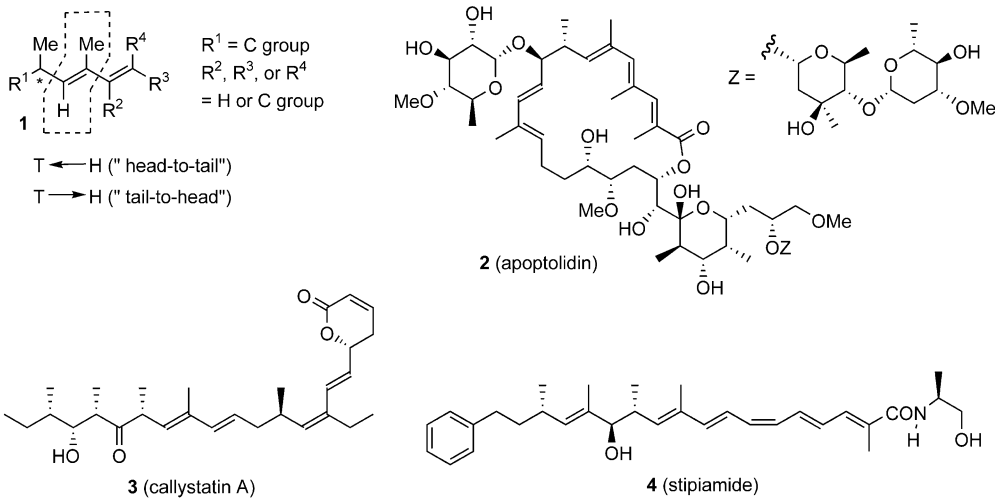
We have recently reported Pd-catalyzed two-step protocols for regio- and stereoselective synthesis of conjugated enynes[7] and styrenes[12] that are structurally related to **1**. However, the development of a related route to conjugated dienes including those represented by **1** has proved to be unpredictable and challenging. Thus, the reaction of 2-bromo-1,3-dienes **5**[13] with various types of organozinc reagents containing Me, Et, higher alkyl, Ph, vinyl, and ethynyl groups in the presence of a variety of Pd–phosphane catalysts, such as $[Pd(PPh_3)_4]$, $[PdCl_2(PPh_3)_2]$, $[PdCl_2(TFP)_2]$,[14] $[PdCl_2(dppf)]$,[14] and $[PdCl_2(dpephos)]$,[14] led to previously unprecedented and essentially complete ($\geq$97–98%) stereoinversion at the Br-bearing C=C bond, thereby providing a synthetically attractive route to the otherwise difficult-to-access conjugated dienes **6**[15] (path 1, Scheme 2). However, this reaction failed to produce the desired dienes **7**.

We now report that the use of tBu_3P[16] or NHCs[17] as ligands can almost completely prevent the above-mentioned stereoinversion and produce dienes **7** with the same skeletal arrangement as the initial bromodienes **5** (path 2, Scheme 2), thereby nicely complementing the reaction shown in path 1. The contrast between paths 1 and 2 is very striking and points to the unexpected significance of ligand development and selection for altering and controlling the stereochemistry of Pd-catalyzed alkenylation.



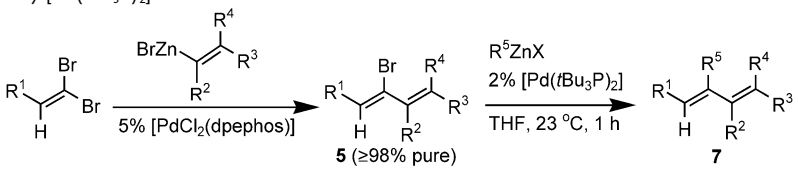
Scheme 2. Stereoselective generation of (1*Z*)-2-bromo-1,3-dienes **5** and their stereospecific conversions into either (1*Z*)- or (1*E*)-1,3-dienes by Pd-catalyzed cross-coupling. dba = *trans*,*trans*-dibenzylideneacetone, NHC = nitrogen-heterocyclic carbene.

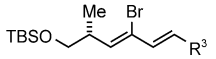
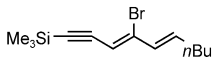
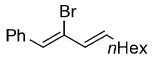
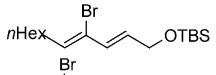
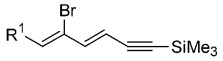
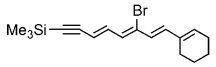
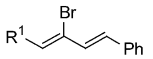
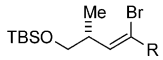
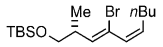
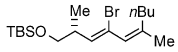
The experimental results summarized in Table 1 indicate the following. In cases where R^4 in the initial 2-bromo-1,3-dienes **5** is H, both yield and stereoselectivity of the Pd-catalyzed substitution of Br with Me, Et, *n*Bu, and Ph are uniformly high. By using (*E*)-1-alkenylzinc derivatives as the alkenylating agent for the generation of **5**, the corresponding conjugated (*E*,*E*)-dienes **7**, where R^4 is H, can be obtained in $\geq$98% stereoselectivity (entries 1–19). Only traces, if any, of the other three possible dienes were detected. The R^3 group can be an alkyl (including CH_2OTBS; entries 1–7), alkynyl (entries 8–13), alkenyl (entry 14), or aryl (entries 15 and 16) group. Similarly, R^1 can be an alkyl (including α-chiral alkyl; entries 1–4, 7–12, 15–21), aryl (entries 6 and 13), alkenyl (entry 14), or alkynyl (entry 5) group. Furthermore, a carbon group in the R^2 position does not appear to exert any noticeable ill effects (entries 17 and 18). Although tBu_3P was a satisfactory ligand, leading to $\geq$98% stereoselectivity in entries 1–19 in Table 1, some side reactions were observed in cases where ethylation and butylation were performed in the second step (entries 3 and 4). On the other hand, the extent of



Scheme 1. (1*E*)-2-Methyl-1,3-dienes **1** with an Me-branched chiral carbon atom bonded to C-1 and natural products represented by **1**.

Table 1: Pd-catalyzed *trans*-selective monoalkenylation of 1,1-dibromo-1-alkenes followed by a second substitution with retention of configuration with organozinc reagents catalyzed by $[Pd(tBu_3P)_2]$.[a]



Entry		5[b]		yield [%]	R^5ZnX[c]	yield[d] [%]	7 stereoselectivity[e] [%]
			category A (≥98% stereoselective)				
1		**5a**	(R^3 = *n*Bu)	90	Me_2Zn	93	≥98 (*E*,*E*)
2		**5b**	(R^3 = *n*Hex)	72	Me_2Zn	62	≥98 (*E*,*E*)
3		**5b**	(R^3 = *n*Hex)	72	Et_2Zn	65	≥98 (*E*,*E*)
					Et_2Zn[f]	89	≥98 (*E*,*E*)
4		**5b**	(R^3 = *n*Bu)	72	*n*BuZnBr	78	≥98 (*E*,*E*)
					*n*BuZnBr[f]	94	≥98 (*E*,*E*)
5		**5c**		90	Me_2Zn	95	≥98(*E*,*E*)
6		**5d**		63	Me_2Zn	94	≥98 (*E*,*E*)
7		**5e**		76	Me_2Zn	86	≥98 (*E*,*E*)
8		**5f**	(R^1 = *n*Hex)	87	Me_2Zn	68	≥98 (*E*,*E*)
9		**5g**	(R^1 =)	70	Me_2Zn	90	≥98 (*E*,*E*)
10		**5g**	(R^1 =)	70	Et_2Zn	86	≥98 (*E*,*E*)
11		**5g**	(R^1 =)	70	PhZnBr	91	≥99 (*E*,*E*)
12		**5h**	(R^1 =)	91	Me_2Zn	95	≥98 (*E*,*E*)
13		**5i**	(R^1 = Ph)	86	Me_2Zn	94	≥98 (*E*,*E*)
14		**5j**		61	Me_2Zn	62	≥98 (*E*,*E*,*E*)
15		**5k**	(R^1 = *n*Hex)	76	Me_2Zn	95	≥98 (*E*,*E*)
16		**5l**	(R^1 =)	64	Me_2Zn	92	≥98 (*E*,*E*)
17		**5m**	(R^1 =)	71	Me_2Zn[g]	69	≥98 (*E*,*E*)
18		**5n**	(R^1 =)	90	Me_2Zn	87	≥98 (*E*,*E*)
19		**5o**	(R^1 =)	71	Me_2Zn	89	≥98 (*E*,*E*)
			category B (94–95% stereoselective)				
20		**5p**		72	Me_2Zn[h]	84	95 (*E*,*Z*)
21		**5q**		67	Me_2Zn[h]	85	94 (*E*,*Z*)

[a] Unless otherwise stated, the reactions were run in tetrahydrofuran at 23 °C. The preparation of **5** was performed as reported previously.[15] For the conversion of **5** into **7**, either R_2^5Zn (R^5 = Me or Et; 1 mol equiv) or R^5ZnBr (R^5 = *n*Bu or Ph; 1.3 mol equiv) was used. [b] See ref. [15]. Stereoselectivity was ≥98% *Z*. [c] Commercially available Me_2Zn and Et_2Zn in toluene, as well as neat Et_2Zn, were used. Other R^5ZnBr compounds were prepared by treating R^5Li with dry $ZnBr_2$. [d] Yield of purified product. [e] The stereoselectivity values indicated are those of the reaction mixtures (GLC analysis) and the crude product before chromatographic purification (^{13}C NMR spectroscopy analysis). [f] 5% $[Pd(dba)_2]$, 5% NHC, and 10% Cs_2CO_3 were used as the components of the catalyst. [g] The reaction time was 4 h. [h] This reaction was run in diethyl ether (see Table 2).

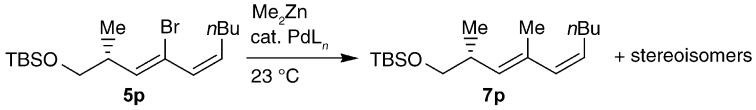
these side reactions was very minor (≤3–4%) and the product yields were significantly higher if an NHC was used instead of tBu_3P. It appears advisable to use and compare NHC ligands with tBu_3P in these demanding cases.

In contrast with the results discussed above, some unprecedentedly capricious and unpredictable reactions have been observed with 2-bromo-1,3-dienes in which R^4 is not H, as vividly indicated by the result for the methylation of

5p ($R^4 = n$Bu), summarized in Table 2. The following points are noteworthy. The reaction of **5p** with Me_2Zn in THF in the presence of 2 mol% of [Pd(tBu$_3$P)$_2$] did produce the desired (3*E*,5*Z*)-diene **7p** in 79% (0.87 × 91) yield. However, it also produced the other three possible stereoisomers: 3*E*,5*E* (6%), 3*Z*,5*E* (4%), and 3*Z*,5*Z* (2%; entry 1). Thus, the stereoselectivity for the formation of the desired (3*E*,5*Z*)-diene **7p** was only 87%. With the hope of improving both yield and stereoselectivity, Pd catalysts generated in situ by treating [$Pd_2(dba)_3$] with four molar equivalents of an NHC, that is, *N*,*N*-bis(2,6-diisopropylphenyl)imidazolium chloride,[17] or tricyclohexylphosphane (Cy_3P)[18] were used in place of [Pd(tBu$_3$P)$_2$]. As indicated in entries 6 and 8, however, the reactions under otherwise identical conditions led to the formation of the 3*E*,5*Z* isomer in yields of 70 and 49% (0.76 × 92 and 0.52 × 94), respectively, even though the respective combined yields were 92 and 94%. Thus, the stereoselectivity values were 76 and 52%, respectively. The capricious nature of these reactions can be most vividly seen in the formation of by-products. Whereas the 3*E*,5*E* isomer was the most abundant by-product when tBu$_3$P was used as a ligand, the 3*Z*,5*E* isomer (24% of the total) and the 3*Z*,5*Z* isomer (48% of the total) were the almost exclusive byproducts in cases where the NHC and Cy_3P, respectively, were used as the ligands. At this point, it is not possible to offer any rationalization for these unpredictable results.

Since none of the ligands used in the reactions in THF led to stereoselectivity exceeding 87%, optimization of solvents was undertaken by screening reactions in diethyl ether, dioxane, toluene, and DMF. The results shown in entries 2 and 7 indicate that diethyl ether used in conjunction with either tBu$_3$P or the NHC permits a stereoselectivity range of 94–95%. Similar stereoselectivity values were also observed in cases where both (*E*)- and (*Z*)-2-methyl-1-alkenylzinc bromides were used to generate **5p** and **5q**, respectively (entries 20 and 21 in Table 1). Fortunately, the isomeric by-products in these reactions were readily separable by column chromatography (silica gel, hexanes). The results presented in this and previous[15] papers have shown that essentially all of the ligands thus far tested are either *E* selective (tBu$_3$P and NHC) or *Z* selective (PPh_3, TFP, dppf, and dpephos). However, Cy_3P can be either *E* selective in diethyl ether, albeit only in 67% (entry 9 in Table 2), or *Z* selective in DMF (92%; entry 10 in Table 2).

Table 2: Ligand and solvent optimization in the Pd-catalyzed reaction of the TBS-protected (2*R*,3*Z*,5*Z*)-2-methyl-4-bromo-3,5-decadien-1-ol with Me_2Zn.[a]



5p **7p**

Entry	Ligand	Solvent	t [h]	Combined yield[b] [%]	Composition [%] 3*E*,5*Z*	3*E*,5*E*	3*Z*,5*E*	3*Z*,5*Z*
1	tBu$_3$P	THF	1	91	87	7	4	2
2	**tBu$_3$P**	**diethyl ether**	**1**	**90 (84)**	**95**	**2**	**≤1**	**2**
3	tBu$_3$P	toluene	1	87	92	2	4	2
4	tBu$_3$P	dioxane	1	84	86	7	4	3
5	tBu$_3$P	DMF	1	87	78	≤1	22	≤1
6	NHC	THF	1	92	76	≤1	24	≤1
7	**NHC**	**diethyl ether**	**1**	**84**	**94**	**≤1**	**5**	**≤1**
8	Cy_3P	THF	16	94	52	≤1	≤1	48
9	Cy_3P	diethyl ether	16	90	67	6	2	33
10	Cy_3P	DMF	16	57[c]	8	≤1	≤1	92

[a] TBS = *tert*-butyldimethylsilyl, THF = tetrahydrofuran, DMF = *N*,*N*-dimethylformamide, Cy = cyclohexyl. [b] GLC yield. The number in parentheses is the yield after isolation. [c] 39% of the starting compound was recovered.

Despite some room for further improvements and developments, it has now been established, for the first time, that (1*Z*)-2-bromo-1,3-dienes **5**, obtainable by previously reported Pd-catalyzed *trans*-selective monoalkenylation of 1,1-dibromo-1-alkenes,[13,15] can be further substituted with methyl, higher alkyl, and phenyl groups with nearly full *retention* of configuration with the corresponding organozinc reagents in the presence of Pd catalysts containing tBu$_3$P or NHCs. In combination with the recently reported[15] Pd-catalyzed substitution of **5** with nearly full *inversion* by using [$PdCl_2$(dpephos)] and other phosphane ligands, a widely applicable, efficient, and selective methodology for the synthesis of stereodefined conjugated dienes, especially those containing an adjacent asymmetric carbon center, has just been developed. It promises to provide an attractive route to a wide variety of polyketides and related natural products, such as **2**–**4**. Efforts along these lines are currently underway.

Experimental Section

Representative procedure: Preparation of **7g** (R^5 = Me): [Pd(tBu$_3$P)$_2$] (10 mg, 0.02 mmol) and Me_2Zn (0.50 mL, 2.0 M in toluene, 1.0 mmol) were added to a stirred solution of **5g** (402 mg, 1.0 mmol) in THF (5.0 mL) at 0 °C and the resultant dark-red mixture was stirred at 23 °C for 30 min. GLC analysis indicated that a clean and complete reaction had taken place. The reaction mixture was then slowly quenched with water, extracted with diethyl ether, washed with brine and aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (silica gel, hexanes/ethyl acetate (99:1)) afforded **7g** (303 mg, 90%) as an oil: $[\alpha]_D^{23} = +17.1°$ (c = 1.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = -0.01$ (s, 3H; CH_3), 0.00 (s, 3H; CH_3), 0.16 (s, 9H; CH_3), 0.85 (s, 9H; CH_3), 0.94 (d, ^3J(H,H) = 6.9 Hz, 3H; CH_3), 1.70 (d, ^4J(H,H) = 0.9 Hz, 3H; CH_3), 2.55–2.7 (m, 1H; CH), 3.38 (dd, J = 9.8 and 6.5 Hz, 1H; CH_2), 3.43 (dd, J = 9.8 and 6.5 Hz, 1H; CH_2), 5.35 (d, ^3J(H,H) = 9.6 Hz, 1H; CH), 5.50 (d, ^3J(H,H) = 16.2 Hz, 1H; CH), 6.63 ppm (d, ^3J(H,H) = 16.2 Hz, 1H; CH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = -5.41$, −5.34, 0.01 (3C), 12.13, 16.95, 18.28, 25.89 (3C), 35.92, 67.54, 95.32, 105.17, 105.22, 133.43, 139.09, 147.57 ppm; IR (neat): $\tilde{\nu}$ = 2130, 1626, 1472, 1390, 1251, 1123, 954, 847, 776 cm^{-1}; elemental analysis: calcd for $C_{19}H_{36}OSi_2$: C 67.78, H 10.78; found: C 67.39, H 10.53.

Further experimental details are available in the Supporting Information.

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