Highly Stereoselective Synthesis of 2-Methyl-1,3-dienes by Palladium-Catalyzed Cross-Coupling Reaction with Trimethylaluminum

Masahiro Miyazawa,* Risa Takehana, Takao Sanga, Aoi Hosomori, Hajime Yokoyama, Yoshiro Hirai

Graduate School of Science and Engineering, University of Toyama, 3190 Gofuku, Toyama 930-8555, Japan
Fax +81(76)4456614; E-mail: miyazawa@sci.u-toyama.ac.jp

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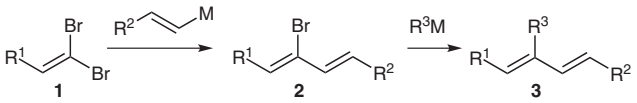
This work is dedicated to Dr. Masanori SAKAMOTO, Professor Emeritus of Meiji Pharmaceutical University, on the occasion of his 77th birthday (KIJU).

Abstract: Palladium-catalyzed cross-coupling reaction using tricyclohexylphosphine can be used to convert a range of 2-bromo-1,3-dienes efficiently and selectively to the corresponding methyl-branched conjugated dienes.

Key words: palladium catalyst, alkylation, isomerization, cross-coupling, conjugated diene

Conjugated dienes are an important structural unit of biologically active organic compounds, including carotenoids, antibiotics, and antitumor agents, and have been synthesized by cross-coupling reaction of haloalkenes with alkenyl metal compounds.[1] However, stereoselective construction of alkyl-branched conjugated dienes remains an important problem. Differentiation of the two carbon–halogen bonds of 1,1-dibromo-1-alkenes **1** in metal-catalyzed reactions has been achieved in Suzuki coupling, Stille coupling, and Negishi coupling (Scheme 1),[2] but it is remarkably difficult to introduce a second alkyl group stereoselectively, because isomerization often occurs to give regioisomers.[3] Negishi and co-workers reported a stereoselective coupling reaction of the alkenyl halide **2** with alkylzinc reagent using $Pd(P\textit{t}\text{-}Bu_3)_2$ catalyst.[4]



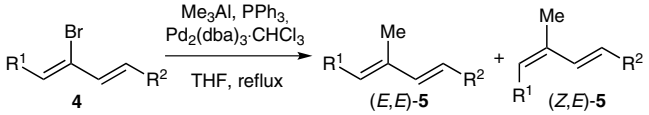
Scheme 1 Synthesis of alkyl-branched conjugated dienes

We have also independently developed a stereoselective coupling reaction of alkenyl halide **2** with trialkylaluminum reagents.[5]

Here, we report a stereoselective construction of trisubstituted 1,3-butadiene via palladium-catalyzed alkylation of 2-bromo-1,3-butadiene with Me_3Al. Initially, we examined the reaction of (*E*,*E*)-2-bromo-1,3-butadiene **4a**–**d** and trimethylaluminum in the presence of 5 mol% of $Pd(PPh_3)_4$ in THF under reflux. Isomerization of the olefin was observed when R^1 was an alkyl group (Table 1, entries 1 and 2). However, when the R^1 was a phenyl moiety, little isomerization was observed.

Next, we focused on the reaction of (1*Z*,3*E*)-2-bromo-1-cyclohexyl-4-phenyl-1,3-butadiene (**4e**) with trimethylaluminum in the presence of various ligands (Table 2). Indeed, treatment of **4e** with Me_3Al (2 equiv) in the presence of $Pd_2(dba)_3CHCl_3$ (5 mol%) and PPh_3 (20 mol%) in THF under reflux afforded the methylated product **5e** in 92%

Table 1 Palladium-Catalyzed Methylation of 2-Bromo-1,3-diene **4a**–**4d**



Entry	Diene	R^1	R^2	Me_3Al (equiv)	Time (h)	Yield (%)[a]	*E*,*E*/*Z*,*E*[b]
1	**4a**	*n*-C_9H_{19}	Ph	2	5	39	32:68
2	**4b**	*n*-C_9H_{19}	CH_2CH_2OTBS	4	19	95	36:64
3	**4c**	Ph	*n*-C_7H_{15}	2	3	48	95:5
4	**4d**	Ph	Ph	2	3	90	>95:<5

[a] Isolated yield.
[b] Determined by GLC.

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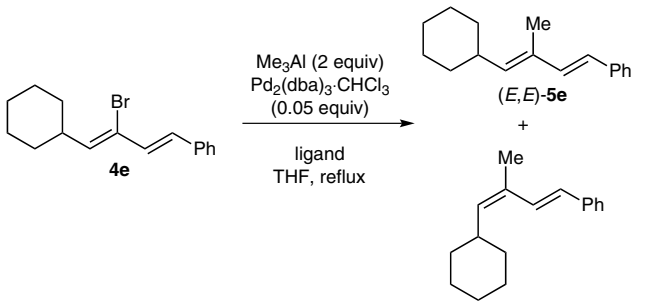
yield as a diastereomeric mixture [(*E*,*E*)-**5e**/(*Z*,*E*)-**5e** = 67:33; Table 2, entry 1]. The reaction rate and stereoselectivity of the reaction products decreased as the amount of triphenylphosphine was increased (Table 2, entries 1 and 2). The reaction using bidentate DPPE showed no stereoselectivity (entry 3). Although 2,2′-bis(diphenylphosphanyl)-1,1′-biphenyl (DPBP)[6] afforded the retention product (*E*,*E*)-**5e** as the major isomer (94% selectivity), the catalyst was easily deactivated[7] (Table 2, entry 4). The use of a very bulky ligand such as tri-*o*-tolylphosphine or tricyclohexylphosphine, furnished the cross-coupling product in good yield with retention of stereochemistry (Table 2, entries 5 and 6). Although the isomerization product was not observed using triphenylphosphite, the reaction was not completed, because the catalyst was easily deactivated (Table 2, entry 8). Negishi and co-workers reported that $PdCl_2$(DPEphos) was the best catalyst for alkylation of 2-bromo-1,3-diene by Me_2Zn with inversion of configuration.[3] In our case, $PdCl_2$(DPEphos) also afforded the inversion product (*Z*,*E*)-**5e** as a major isomer, but the stereoselectivity was only 87% (Table 2, entry 9). On the other hand, Negishi reported that Pd(P*t*-$Bu_3)_2$ exclusively afforded the retention product.[4] In our case, Pd(P*t*-$Bu_3)_2$ afforded the retention product (*E*,*E*)-**5e** as the major isomer, but the stereoselectivity was only 89% (Table 2, entry 10). The reactions using tri(2-furyl)phosphine and triphenylarsine were not completed, because the catalysts were easily deactivated (Table 2, entries 11 and 12).

Table 2 Optimization of Palladium-Catalyzed Methylation of 2-Bromo-1,3-diene **4e**

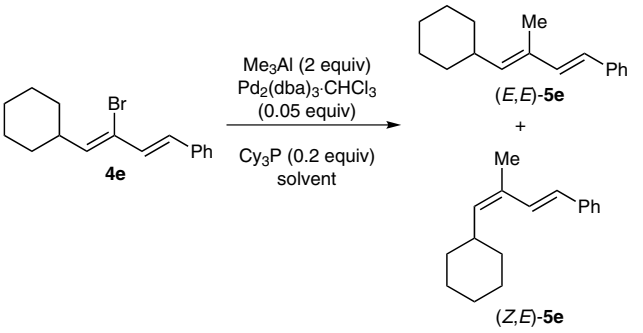


Entry	Ligand	Time (h)	Yield (%)[a]	*E*,*E*/*Z*,*E*[a]
1	Ph_3P (0.2 equiv)	1.5	92	67:33
2	Ph_3P (0.4 equiv)	4	90	26:74
3	dppe (0.1 equiv)	14	81	53:47
4	dpbp (0.1 equiv)	2	32	94:6
5	*o*-tolyl$_3$P (0.2 equiv)	0.5	81	95:5
6	Cy_3P (0.2 equiv)	3	95	>95:<5
7	*n*-Bu_3P (0.32 equiv)	13	87	88:12
8	$(PhO)_3P$ (0.3 equiv)	3	69	>95:<5
9	DPEphos (0.1 equiv)[b]	3	65	13:87
10	*t*-Bu_3P (0.2 equiv)[c]	3	77	89:11
11	(2-furyl)$_3$P (0.2 equiv)	2	39	81:19
12	Ph_3As (0.2 equiv)	1	29	85:15

[a] Determined by GLC analysis.
[b] Amount of $PdCl_2$(DPEphos) used was 0.1 equiv.
[c] Amount of Pd(P*t*-$Bu_3)_2$ used was 0.1 equiv.

Next, we focused on screening of solvent conditions (Table 3). The reaction using diethyl ether and hexane did not afford the cross-coupling product, because the catalyst hardly dissolved in these solvents (Table 3, entries 2 and 3). The reaction using toluene and dichloromethane afforded **5e** in moderate yield and the catalyst was easily deactivated (Table 3, entries 4 and 5).

Table 3 Screening of Solvent Conditions for Palladium-Catalyzed Methylation of 2-Bromo-1,3-diene **4e**



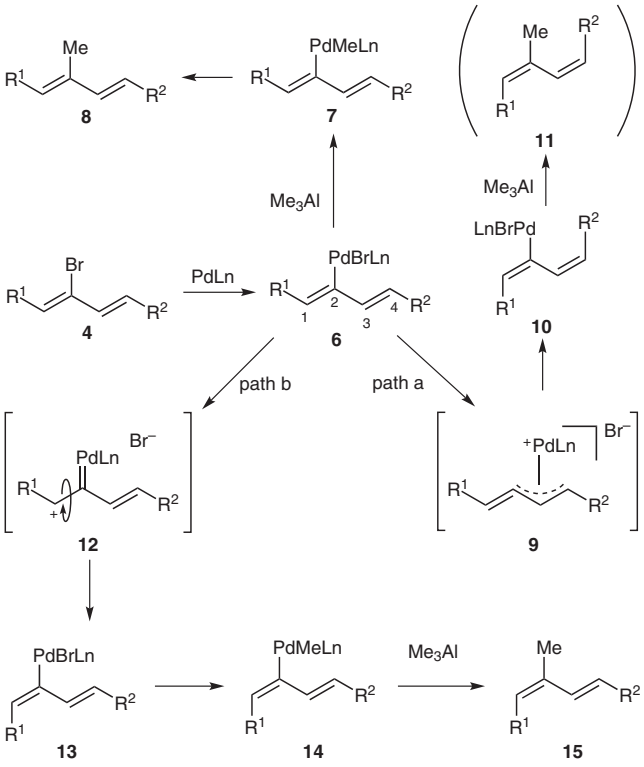
Entry	Solvent	Temp (°C)	Time (h)	Yield (%)[a]	*E*,*E*/*Z*,*E*[a]
1	THF	reflux	3	95	>95:<5
2	Et_2O	reflux	–	–	–
3	hexane	reflux	–	–	–
4	toluene	60	4.5	54	94:6
5	CH_2Cl_2	reflux	5	46	89:11
6	dioxane	60	1	87	>95:<5
7	dioxane	27	4	12	72:28

[a] Determined by GLC analysis.

The reaction using 1,4-dioxane at 60 °C afforded **5e** in 87% yield and excellent stereoselectivity, but the catalyst was rapidly deactivated (Table 3, entry 6). At 27 °C, the cross-coupling reaction of **4e** afforded **5e** in only 12% yield and low stereoselectivity (Table 3, entry 7).

A plausible mechanism of the olefin isomerization is shown in Scheme 2. There are two plausible mechanisms for the olefin isomerization. The first one is the π–σ–π rearrangement mechanism via alkylidene-π-allyl palladium species **9** (path a). The alkylidene-π-allyl palladium species **9**, which were prepared from 2-bromo-1,3-dienes have been previously reported.[6,8] Although the π–σ–π rearrangement product should be (*Z*,*Z*)-diene **11**, the isomerization products were (*Z*,*E*)-diene **15**. At least, **15** was not formed via π-σ-π rearrangement mechanism. The oth-

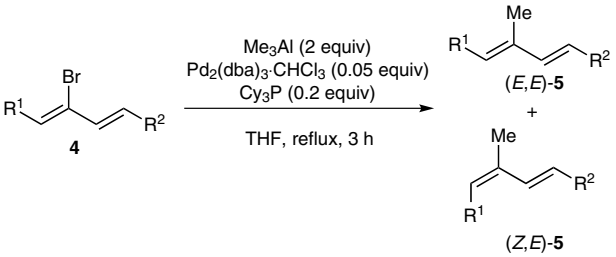
er mechanism involves the isomerization mechanism via palladoene intermediate **12** (path b). In the case of alkylation of 2-bromo-1,3-butadiene with Me_2Zn in the presence of palladium catalyst, Negishi and co-workers proposed that the isomerization proceeded through 2-pallado-3-ene **12** with the loss of bromide ion via coordination of the 3-olefin.[9] In such a cross-coupling reaction, the transmetallation step (**6** → **7** or **13** → **14**) is almost always the rate-determining step. If transmetallation between palladium complex and Me_3Al is easy (**6** → **7**), the retention product would be produced stereoselectively. However, formation of the retention product decreases with increasing amount of phosphine ligand. The reason is probably that phosphine ligands, which are good σ-donors and increase the electron density of the palladium, suppress the transmetallation step. On the other hand, σ-donation of phosphite is lower than that of phosphine, so phosphite ligand facilitates the transmetallation step. When sterically bulky phosphine ligands such as tri-*o*-tolylphosphine or tricyclohexylphosphine were used, isomerization was hardly observed. Bulky ligands probably retard the intramolecular coordination of 3-olefin with palladium, thereby blocking the formation of 2-pallado-3-ene **12**.



Scheme 2 Plausible mechanism for the olefin isomerization

To extend the range applicability of the reaction, various dienyl bromides were subjected to reaction with trimethylaluminum under the optimal conditions.[10] As shown in Table 4, the reaction of dienyl bromides bearing a phenyl group and/or an alkyl group proceeded smoothly to provide the corresponding methyl adducts in good yield with high regioselectivity.

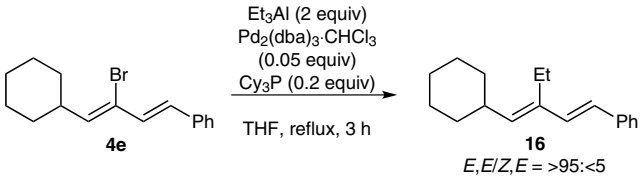
Table 4 Palladium-Catalyzed Methylation of 2-Bromo-1,3-dienes **4a**–**4d**



Entry	Diene	R^1	R^2	Yield (%)[a]	*E*,*E*/*Z*,*E*[b]
1	**4a**	*n*-C_9H_{19}	Ph	57	>95:<5
2	**4b**	*n*-C_9H_{19}	CH_2CH_2OTBS	99	>95:<5
3	**4e**	Cy	Ph	95	>95:<5
4	**4c**	Ph	*n*-C_7H_{15}	93	>95:<5
5	**4f**	Ph	Cy	93	>95:<5
6	**4d**	Ph	Ph	79	>95:<5

[a] Isolated yield.
[b] Determined by GLC.

On the other hand, the reaction of dienyl bromide **4e** with triethylaluminum under the same conditions afforded the ethylated product **16** as the sole product in 88% yield (Scheme 3). Thus, ethylation also proceeded stereoselectively with retention of configuration.



Scheme 3 Palladium-catalyzed ethylation of 2-bromo-1,3-diene **4e**

In conclusion, we have demonstrated a novel and efficient preparation of geometrically pure methyl-branched conjugated dienes from 2-bromo-1,3-dienes with Me_3Al reagent by palladium-catalyzed cross-coupling reaction using tricyclohexylphosphine ligand. This system is as useful as methylation with Me_2Zn reagent in the presence of Pd catalyst containing *t*-Bu_3P, since tricyclohexylphosphine has advantages over *t*-Bu_3P in terms of stability and ease of use. Further investigations into synthetic applications of this reaction are under way.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(7) Palladium mirror was formed and the reaction was stopped.

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(9) Negishi, E.; Hu, Q.; Huang, Z.; Qian, M.; Wang, G. *Aldrichimica Acta* **2005**, *38*, 71.

(10) **Typical Procedure for the Synthesis of (*E*,*E*)-5e**: A mixture of $Pd_2(dba)_3CHCl_3$ (26 mg, 0.025 mmol) and PCy_3 (28 mg, 0.100 mmol) was dissolved in THF (5 mL) under a nitrogen atmosphere. To the resultant red solution was added a solution of (1*Z*,3*E*)-2-bromo-1-cyclohexyl-4-phenyl-1,3-butadiene (**4e**; 146 mg, 0.501 mmol) in THF (10 mL). After stirring at r.t. for 5 min, Me_3Al (1.05 M hexane solution, 1.0 mL, 1.0 mmol) was added to the solution and the mixture was refluxed for 3 h. The reaction mixture was allowed to cool to r.t. and quenched with diluted cold HCl. The aqueous layer was extracted with Et_2O (3 ×). The combined organic layers were washed with aq sat. $NaHCO_3$ solution and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using hexane as eluent to afford the title compound [107 mg, 95%, (*E*,*E*)-**5e**/(*Z*,*E*)-**5e** >95:<5]. **(1*E*,3*E*)-1-Cyclohexyl-2-methyl-4-phenylbuta-1,3-diene (*E*,*E*-5e)**: ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.37–7.42 (m, 2 H), 7.27–7.32 (m, 2 H), 7.16–7.20 (m, 1 H), 6.78 (dd, *J* = 16.1, 0.7 Hz, 1 H), 6.45 (d, *J* = 16.1 Hz, 1 H), 5.48 (d, *J* = 9.2 Hz, 1 H), 2.36 (dtt, *J* = 9.1, 11.1, 3.7 Hz, 1 H), 1.88 (d, *J* = 1.1 Hz, 3 H), 1.73 (dquint, *J* = 13.4, 3.4 Hz, 2 H), 1.63–1.71 (m, 3 H), 1.31 (tq, *J* = 3.3, 12.7 Hz, 2 H), 1.20 (tq, *J* = 3.3, 12.5 Hz, 1 H), 1.11 (dq, *J* = 3.0, 12.2 Hz, 2 H). ^{13}C (75 MHz, $CDCl_3$): δ = 140.30, 138.03, 134.29, 131.92, 128.50 (2 × C), 126.76, 126.10 (2 × C), 125.62, 37.40, 33.02 (2 × C), 26.03, 25.92 (2 × C), 12.56. IR (neat): 3079, 3058, 3026, 2924, 2849, 1629, 1598, 1494, 1447, 958, 746, 691 cm^{-1}. MS (EI): *m*/*z* = 226 (64%). HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{17}H_{22}$: 226.1722; found: 226.1731. **(1*E*,3*Z*)-1-Cyclohexyl-2-methyl-4-phenylbuta-1,3-diene (*Z*,*E*-5e)**: ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.43–7.49 (m, 2 H), 7.31–7.37 (m, 2 H), 7.19–7.24 (m, 1 H), 7.19 (d, *J* = 16.1 Hz, 1 H), 6.54 (d, *J* = 16.1 Hz, 1 H), 5.31 (d, *J* = 9.5 Hz, 1 H), 2.54 (dtt, *J* = 9.2, 11.1, 3.7 Hz, 1 H), 1.92 (d, *J* = 1.1 Hz, 3 H), 1.74 (dquint, *J* = 13.6, 3.4 Hz, 2 H), 1.65–1.71 (m, 3 H), 1.34 (tq, *J* = 3.3, 12.7 Hz, 2 H), 1.19 (tq, *J* = 3.5, 12.7 Hz, 1 H), 1.10 (dq, *J* = 3.0, 12.3 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.51, 138.10, 130.06, 128.56 (2 × C), 128.10, 127.12, 126.37, 126.35 (2 × C), 36.52, 33.53 (2 × C), 26.01, 25.93 (2 × C), 20.60. IR (neat): 3080, 3058, 3036, 3024, 2923, 2849, 1632, 1597, 1494, 1446, 957, 747, 691 cm^{-1}. MS (EI): *m*/*z* = 226 (83%). HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{17}H_{22}$: 226.1722; found: 226.1742.

