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Palladium-catalyzed and organozinc-promoted synthesis of dienes from allylic esters possessing an acyloxy or alkoxy group

Hatsuhiko Hattori, Masahiro Katsukawa and Yuichi Kobayashi*

Department of Biomolecular Engineering, Tokyo Institute of Technology, Box B-52, Nagatsuta-cho 4259, Midori-ku, Yokohama 226-8501, Japan

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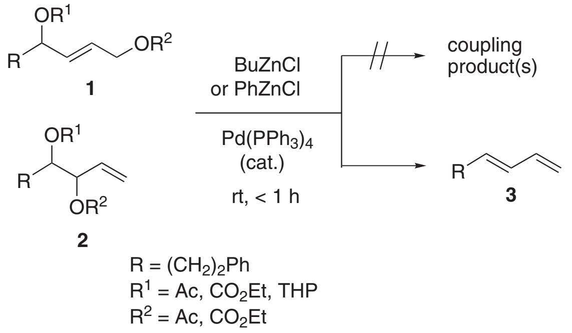
Abstract—Organozinc and a Pd catalyst promoted formation of dienes from allylic esters possessing a leaving group such as acyloxy and alkoxy groups next to the allyl moiety. The reaction proceeded with high regio- and stereoselectivity when applied to secondary allylic substrates.

Recently, we reported a palladium-catalyzed coupling reaction of the hydroxy-cyclopentenyl acetate with RMgCl, in which the hydroxyl group directs the reaction to follow an unusual stereochemical course.[1] However, when the reaction was examined with an acyclic substrate, the expected coupling did not take place. Instead, the reagent promoted formation of diene in low yield with other products (the corresponding diol and reduction products). Herein, we present optimization of the diene formation with a modified reagent system consisting of an organozinc reagent and a Pd catalyst, which proceeds well with allylic esters **1** and **2** possessing a leaving group such as acyloxy and alkoxy groups next to the allyl moiety (Scheme 1). The reaction is in sharp contrast to reactions of similar substrates with vinylstannanes and with soft nucleophiles producing normal coupling products.[2,3] In the mechanistic point of view, the allylpalladium species generated herein from **1** or **2**, Pd(0) cat. and RZnCl (R = Bu, Ph) is formally of anionic character which triggers elimination of the proximate acyloxy or alkoxy group, and thus is different from the normal cationic allylpalladium intermediates.[4]



Scheme 1.

Previously, similar substrates possessing an epoxy or $MeOCO_2$ group next to the allylic system have been converted to dienes with palladium complexes.[5,6] The reaction ends up with production of Pd^{2+} and diene. The Pd^{2+} species in the latter case is recycled to active Pd(0) species by reduction with $P(O\text{-}i\text{-}Pr)_3$ used as a ligand and/or methoxide derived from $MeOCO_2$.[6] On the contrary, the present reaction is promoted by a palladium catalyst and, more importantly, is applicable to substrates of secondary allylic esters[7] with regio- and stereoselective manners.

The present investigation was initiated with reaction of diacetate **1a** ($R^1 = R^2 = Ac$) with Bu-(or Ph-)MgCl (3 equiv) and $Pd(PPh_3)_4$ (10 mol %) to furnish diene **3** ($E/Z = 79\text{–}87{:}21\text{–}13$) in moderate to good yields (Table 1, entries 1 and 2). None of the anticipated coupling product was observed by ^1H NMR spectroscopy, while the corresponding diol was obtained in 20% yield (entry 1). These results prompted examination of other organometallics. Use of Bu- and PhZnCl provided somewhat higher yields of **3** (entries 3 and 4), while Et_2Zn and Me_3Al were less effective (entries 5 and 6).

Keywords: Palladium catalyst; Organozinc; Diene; *p*-Allylpalladium.

* Corresponding author. Tel./fax: +81 45 924 5789; e-mail: ykobayas@bio.titech.ac.jp

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Table 1. Palladium-catalyzed diene formation[a]

Entry	Substrate No	R^1	R^2	Organometallic or reagent[b]	Time	Yield[c] (%)	Ratio of *E*:*Z*
1	**1a**	Ac	Ac	BuMgCl	1.5 h	58[d]	79:21
2	**1a**	Ac	Ac	PhMgCl	1 h	90	87:13
3	**1a**	Ac	Ac	BuZnCl	1 h	92	85:15
4	**1a**	Ac	Ac	PhZnCl	1 h	100	89:11
5	**1a**	Ac	Ac	Et_2Zn	24 h	<5	—
6	**1a**	Ac	Ac	Me_3Al	24 h[e]	65	77:23
7	**1a**	Ac	Ac	Pd(0)/P(O-*i*-Pr)$_3$[f]	6 h	0[g]	—
8	**1b**	CO_2Et	CO_2Et	BuZnCl	<30 min	100 (99)	73:27
9	**1b**	CO_2Et	CO_2Et	PhZnCl	<30 min	99 (84)	60:40
10	**1b**	CO_2Et	CO_2Et	Et_2Zn	<30 min	81	82:18
11	**1b**	CO_2Et	CO_2Et	Pd(0)/P(O-*i*-Pr)$_3$[f]	3 h	47	79:21
12	**1c**	THP	Ac	BuZnCl	1.5 h	85	91:9
13	**1d**	TBS	Ac	BuZnCl	24 h	46	72:28
14	**2a**	Ac	Ac	BuZnCl	<30 min	100 (98)	81:19
15	**2a**	Ac	Ac	PhZnCl	<30 min	100 (99)	86:14
16	**2b**	C(=O)		BuZnCl	<30 min	100 (99)	73:27
17	**2b**	C(=O)		PhZnCl	<30 min	100 (98)	75:25

[a] Reactions were carried out with organometallic (3 equiv) and Pd(PPh$_3$)$_4$ (10 mol %) in THF at rt, unless otherwise noted.

[b] Zinc reagents in entries 3, 4, 8, 9, and 12–17 were prepared in situ from Bu(or Ph)MgCl and $ZnCl_2$.

[c] Referred to ^{1}H NMR yields, while isolated yields are given in parentheses.

[d] Diol (**1** with $R^1 = R^2 = H$) was co-produced with **3** in ca. 20% yield.

[e] 30–40 °C.

[f] Pd$_2$(dba)$_3$·CHCl$_3$ (5 mol %) and P(O-*i*-Pr)$_3$ (0.8 equiv) at rt.

[g] **1a** (48%) was recovered.

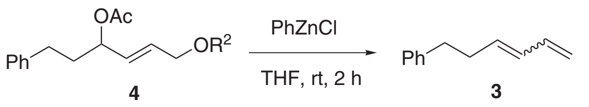
The previous reagent system,[6] P(O-*i*-Pr)$_3$/Pd$_2$(dba)$_3$·CHCl$_3$, was ineffective (entry 7)[8] (for more reactions, see below).

The RZnCl/Pd cat. was applied to dicarbonate **1b**, which produced diene **3** cleanly within 30 min (usually ca. 15 min) (entries 8 and 9). The Et_2Zn/Pd cat. reagent also afforded diene **3** (entry 10), reflecting high reactivity of the carbonate moiety compensating the rather low reactivity of Et_2Zn in the diene formation (cf. entry 5).

Examination was continued to find an alkoxy leaving group (OR^1 group) in monoacetate **1** ($R^2 = Ac$). Among THP, TBS and TBDPS groups examined as R^1, THP showed a similar potency to the acetoxy group ($R^1 = Ac$) (entry 12).

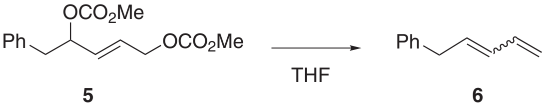
Substrates of type **2** (R^1, $R^2 = Ac$, cyclic carbonate) underwent the reaction within 30 min to give the same diene **3** in good yields (entries 14–17).

Next examined is the substrate of type **4** in which the allylpalladium is generated at the secondary position (Scheme 2). Reactions of **4** with the THP or TBS group as R^2 completed within 2 h to afford diene **3** in good yields with similar *E*/*Z* ratios. Noteworthy with the substrate is that the TBS-oxy group which was unsuccessful in **1d** (Table 1, entry 13) played its role as the leaving group sufficiently. Diene **3** was also formed from benzyloxy and methoxy substrates **4** ($R^2 = Bn$, Me), but in somewhat lower yields. These results imply that the rate-determining step is the elimination of the acyloxy or alkoxy group and not the formation of an allylpalladium species.



R^2 = THP, 99%; TBS, 87%

Scheme 2.

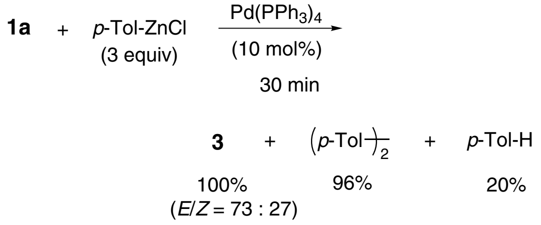


P(O-*i*-Pr)$_3$/Pd cat.	rt	56% (*E* only) (lit. 6)
	rt, 60 h	ca. 30% (*E*/*Z* = 75 : 25) by us
PhZnCl/Pd cat.	rt, 0.5 h	85% (*E*/*Z* = 70 : 30)

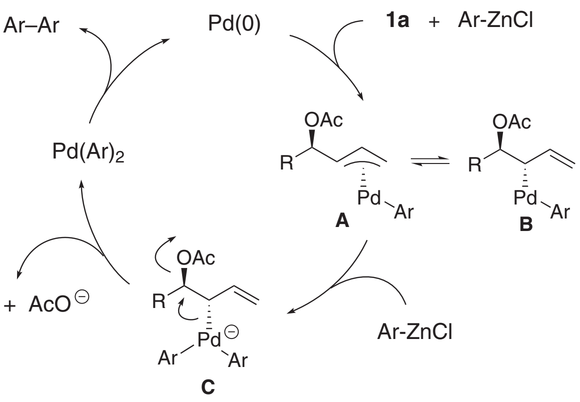
Scheme 3.

We then compared the present reaction system and that in the literature[6] by using the literature substrate **5** (Scheme 3). Although **5** is reported to afford diene **6** stereoselectively, the same reaction repeated by us two times produced **6** with a 75:25 *E*/*Z* ratio in low yields (the second line of the results in Scheme 3). On the other hand, reaction with PhZnCl (3 equiv) and Pd(PPh$_3$)$_4$ (10 mol %) for 30 min afforded **6** in 85% yield with the *E*/*Z* ratio of 70:30. The same tendency in reactivity is described in the above paragraph with one-carbon long substrate **1b** (Table 1, entries 8 and 9 vs 11). Different reactivity in these reagent systems was also observed with slightly less reactive diacetate **1a** as mentioned above (Table 1, entries 3 and 4 vs 7).

In order to understand the reaction at the mechanistic level, diacetate **1a** was subjected to reaction with



Scheme 4.

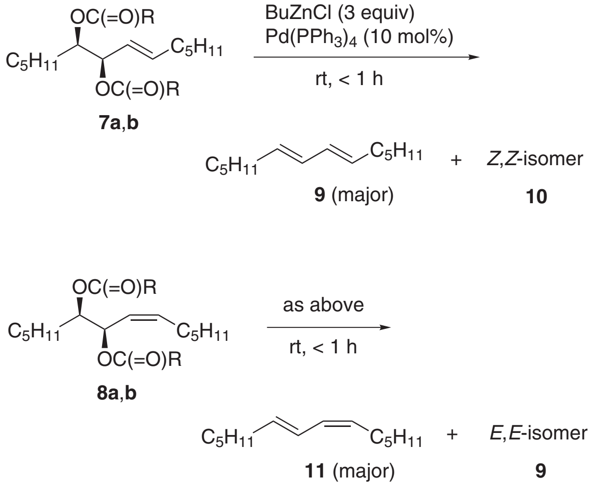


Scheme 5. Plausible pathways of the reaction. Ar = *p*-Tol.

p-Tol-ZnCl (3 equiv)[9] (Scheme 4), which produced (*p*-Tol-)$_2$ in 96% NMR yield with diene **3** (100%) and volatile toluene (20%). *p*-Tol-OAc and/or *p*-Tol-Cl were not detected by ^{1}H NMR and TLC. These results suggest the catalytic cycle delineated in Scheme 5.[10] π-Allyl-Pd-X derived from **1a** and Pd(0) upon transmetalation with Ar-ZnCl produces the π-allyl-Pd-Ar **A**, which is in equilibrium with the σ-allyl species **B**. These species undergo complexation with another Ar-ZnCl at a faster rate than the reductive elimination to afford anionic σ-allyl species **C**, which furnishes diene **3**, AcO$^-$ and (Ar)$_2$Pd through anti-elimination.[11] Reductive elimination of (Ar)$_2$Pd then produces (Ar)$_2$ and an active Pd(0) catalyst. Although syn-elimination is also conceivable for production of **3** from **C**, the anti-fashion (anionic mode of the elimination) is supported by the result obtained with secondary allylic esters (vide infra).

The reagent system established above was applied to secondary allylic diacetates **7a**, **8a** (R: Ac) and cyclic carbonates **7b**, **8b** (R, R: C=O) (Scheme 6).[12] As are summarized in Table 2, trans olefins **7a**,**b** afforded *E*,*E* diene **9** with >91% geometrical purity in good isolated yields. The minor product was *Z*,*Z*-isomer **10**, and the other *E*,*Z*-isomer **11** was not detected. On the other hand, *E*,*Z*-diene **11** was derived from cis olefins **8a**,**b** with the minor *E*,*E*-isomer **9**. Similar results were also obtained with PhZnCl (data not shown).[13]

A reasonable pathway and decisive intermediates for the highly stereoselective conversion of **7a** to *E*,*E*-diene **9** (major) and *Z*,*Z*-diene **10** (minor) are delineated in Scheme 7, in which more and less stable anionic σ-allylpalladium species σ-**12** and -**13** are responsible for the observed production of dienes **9** and **10**, supposing the anti-fashion in the crucial elimination step. Since the supposed syn-elimination from the major σ-**12** should produce *E*,*Z*-diene **11** as the major product, this elimination course is unlikely to proceed. A similar pathway is conceivable for production of *E*,*Z*-diene **11** from **8a**,**b** (pathway not illustrated).

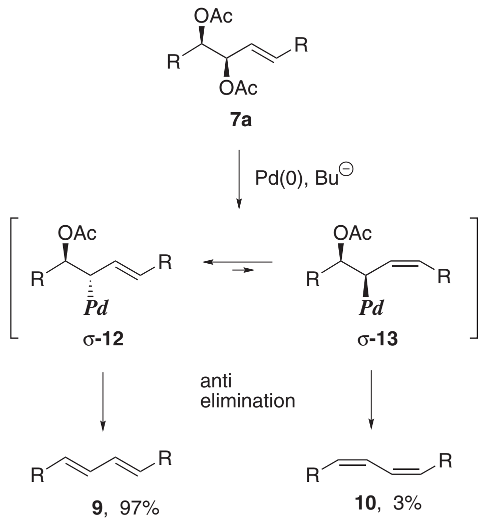


Scheme 6.

Table 2. Diene synthesis from **7a**,**b** and **8a**,**b**

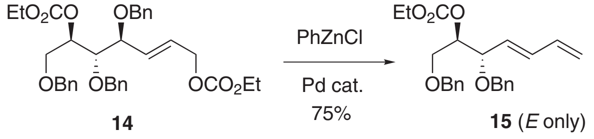
Entry	Substrate	C(=O)R	C(=O)R	Yield[a] (%)	**9**:**10**:**11**
1	**7a**	Ac	Ac	86	97:3:0
2	**7b**	C(=O)		92	91:9:0
3	**8a**	Ac	Ac	74	7:0:93
4	**8b**	C(=O)		70	2:0:98

[a] Isolated yields.

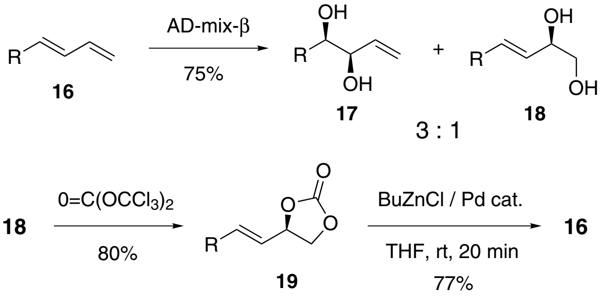


Scheme 7. Plausible mechanism for production of dienes **9** and **10**. R: C_5H_{11}, ***Pd***: -[Pd(Bu)$_2$]$^-$.

To demonstrate the synthetic potential of the present reaction, the reaction was combined with a sugar to



Scheme 8.



Scheme 9. Recycling procedure of minor diol to diene. R = $(CH_2)_4OBn$.

provide a new diene **15** from the sugar-derived compound **14** in 75% yield (Scheme 8).

An application of the present reaction is shown in Scheme 9, which provides a convenient recovery process of unwanted regioisomeric diols produced by the Sharpless AD reaction[14] of 1,3-dienes. Thus, AD reaction of diene **16** (R = $(CH_2)_4OBn$) with AD-mix-β afforded regioisomeric diols **17** and **18** in a 3:1 ratio as expected.[15] After separation of the isomers, the minor 1,2-diol **18** was converted into cyclic carbonate **19**, which produced diene **16** in 77% yield with 95% E-olefin selectivity by using the present reaction with BuZnCl. This protocol would be especially useful when diene is prepared via a long sequence of reactions.

In summary, we have presented that RZnCl/Pd cat. promotes formation of dienes from substrates possessing a leaving group such as acyloxy and alkoxy groups next to the allyl moiety. The use of RZnCl/Pd cat. is unprecedented. Moreover, the reaction is applicable to secondary substrates, thereby producing the dienes regio- and stereoselectively.[16]

Acknowledgements

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8. This result (no reaction) with the less reactive acetoxy leaving group had been predicted from the results of Ref. 6.
9. Reaction proceeded with 2 equiv of *p*-Tol-ZnCl, but took 6 h for the completion.
10. Other possible intermediates responsible for the diene formation would be (1) allylzinc species produced by transmetalation of **A** and/or **B** with ArZnCl; and (2) σ-allylpalladium species **B** as such. These intermediates should produce Ar-Pd-X (X = OAc and/or Cl), which would undergo reductive elimination to afford Ar-X and/or transmetalation with ArZnCl to produce $(Ar)_2Pd$ and thence $(Ar)_2$. However, production of Ar-X was not observed (see text). In relation to this issue, an attempted palladium-catalyzed coupling reaction of *p*-Tol-Cl with *p*-Tol-ZnCl did not take place under otherwise the same reaction conditions for the diene formation, whereas a similar reaction using *p*-Tol-I afforded the coupling product, $(p\text{-Tol})_2$, in 70% yield. These results also support the pathway shown in Scheme 5.
11. cf. β-Carbo-elimination: Harayama, H.; Kuroki, T.; Kimura, M.; Tanaka, S.; Tamau, Y. *Angew. Chem., Int. Ed.* **1997**, *36*, 2352–2354.
12. Isomeric purity of >95% for these substrates was confirmed by ^1H NMR spectroscopy.
13. The literature procedure of Ref. 6 also produces internal diene. However, the reaction takes two days and the diene produced is a mixture of the geometrical isomers with the *E,E* isomer being the major product.
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16. Typical procedure for the palladium-catalyzed diene formation (Table 1, entry 8): To a solution of $ZnCl_2$

(73 mg, 0.535 mmol) dissolved in THF (0.7 mL) was added *n*-BuMgCl (0.505 mL, 0.88 M in THF, 0.444 mmol). After 15 min at rt, $Pd(PPh_3)_4$ (17 mg, 0.015 mmol) and a solution of **1b** (50 mg, 0.148 mmol) in THF (0.3 mL) were added slowly. The reaction was carried out at rt for 30 min and quenched by addition of saturated NH_4Cl solution. The mixture was extracted with Et_2O twice. The combined extracts were dried ($MgSO_4$) and concentrated in vacuo to leave an oil, which was purified by chromatography on silica gel with hexane as an eluent to afford diene **3** (23 mg) in 99% yield.