Cross-Coupling

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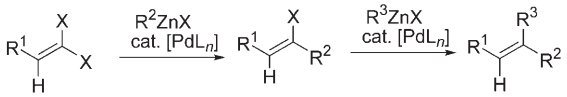
Widely Applicable Pd-Catalyzed *trans*-Selective Monoalkylation of Unactivated 1,1-Dichloro-1-alkenes and Pd-Catalyzed Second Substitution for the Selective Synthesis of *E* or *Z* Trisubstituted Alkenes**

*Ze Tan and Ei-ichi Negishi**

Dedicated to Professor P. L. Fuchs on the occasion of his 60th birthday

Since the discovery of the Pd-catalyzed highly *trans*-selective monosubstitution of 1,1-dihalo-1-alkenes and the subsequent second substitution to produce trisubstituted alkenes [Eq. (1)],[1] its development as a method for not only the



(1)

X = Cl, Br, I, so forth

selective synthesis of monosubstitution products[2] but also for disubstitution products[1,2c,e,3–5] has attracted considerable attention from synthetic chemists.

Although the development of the monosubstitution reaction with aryl,[3] alkenyl,[4] and alkynyl metals[5] and related nucleophiles has been reasonably successful, the Pd- or Ni-catalyzed monoalkylation has not been,[6] except in one isolated example, which consists of the Pd-catalyzed stepwise double alkylation of β,β-dichlorostyrene with *n*BuZnCl (81% yield) and then *n*HexMgBr (77% yield).[1] These results were reproducible in our hands but could not be extended to a similar stepwise dialkylation of alkyl-substituted 1,1-dichloro-1-alkenes, such as 1,1-dichloro-1-octene. Under the influence of 5 mol% of [$PdCl_2$(dppb)] (dppb = 1,4-bis(diphenylphosphino)butane), its reaction with *n*OctZnBr produced only a trace amount, if any, of (*Z*)-8-chloro-7-hexadecene, with (*Z*)-8-(*n*-octyl)-7-hexadecene as practically the only product. The tendency to produce dialkylation products is even more pronounced in the corresponding reactions of 1,1-dibromo-1-alkenes. Thus, even β,β-dibromostyrenes would produce only

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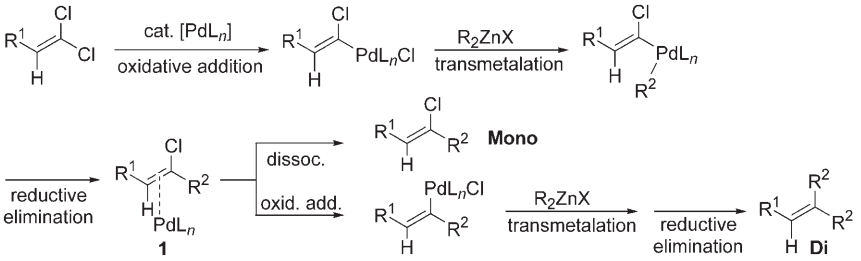
their dialkylation products. Despite these disappointing results, a systematic screening of Pd catalysts, additives, and solvents was conducted, which led to an optimized set of conditions that involve 5 mol% of [$PdCl_2$(dpephos)] (dpephos = bis(*o*-diphenylphosphanylphenylether))[7] and dimethylformamide (DMF). In some cases, the use of one molar equivalent of *N*-methylimidazole (NMI)[8] relative to an alkyl zinc reagent has been shown to further improve the yields. The results of the *trans*-selective monoalkylation are summarized in Table 1.

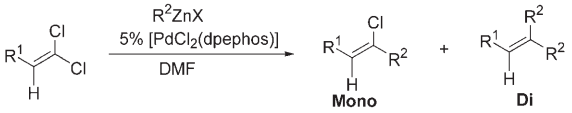


Scheme 1. Putative mechanistic scheme for the competitive formation of the mono- and dialkylation products.

Although the intricate mechanistic details remain unclear, the following features are worth mentioning: First, as long as the combination of [$PdCl_2$(dpephos)] and DMF, along with one molar equivalent of NMI for some cases of monomethylation, is used, various types of 1,1-dichloro-1-alkenes that contain alkyl, aryl, alkenyl, and alkynyl groups as the R^1 group can be satisfactorily monoalkylated for the first time with alkyl zinc compounds containing Me, Et, and higher linear and β-branched primary alkyl groups. Second, the difference between dppb and dpephos ligands in the selective monoalkylation of alkyl-substituted 1,1-dichloro-1-alkenes is striking, and it is clear that competitive formation of the disubstitution products is the major side reaction to be minimized. This goal may be attained by suppressing the second substitution through promotion of catalyst dissociation from the putative monosubstituted alkene–Pd π-complex **1** (Scheme 1).[9] The success observed with 1,1-dichloro-1-alkenes but not with 1,1-dibromo-1-alkenes can also be readily understood in these terms. Third, although unwanted, the formation of the disubstitution product must undoubtedly be responsible for the high stereoselectivity (≥98–99%) attainable by Pd-catalyzed *trans*-selective monosubstitution through kinetic resolution in the second stage of disubstitution, in which the undesired *cis*-monosubstituted isomer of **1** must be significantly more reactive than **1** itself. In this sense, the observed formation of the disubstitution products must be a blessing in disguise to a certain extent.

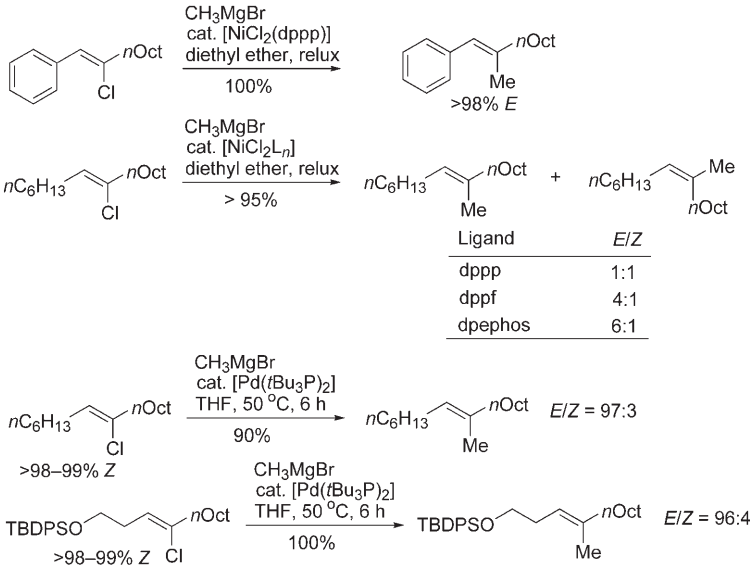
With the development of a widely applicable and satisfactory protocol for the *trans*-selective monoalkylation of 1,1-dichloro-1-alkenes, the second substitution of relatively unreactive internal *Z* chloroalkenes was investigated. In the only reported case of a stepwise dialkylation using β,β-dichlorostyrene,[1] the second alkylation was achieved by using *n*HexMgBr and 1 mol% [$NiCl_2$(dppp)] (dppp = 1,3-bis(diphenylphosphino)propane). This procedure was very satisfactory for the methylation of (*Z*)-2-chloro-1-phenyl-1-decene with MeMgBr, thus providing the desired methylation product in almost quantitative yield and with >98% stereoisomeric purity. Its application to the methylation of (*Z*)-8-chloro-7-hexadecene was also high yielding, but the product was essentially a 1:1 mixture of the *E* and *Z* isomers (Scheme 2).[10] The use of some other chelating ligands containing the diphenylphosphino group, such as dppf and dpephos, did improve the stereoisomeric ratio, but the highest *E*/*Z* ratio never exceeded 6:1 (Scheme 2). Fortunately, a recent development of satisfactory procedures for the Pd-catalyzed cross-coupling of organochlorides through the use of bulky trialkylphosphines[8,11] and dialkylarylphosphines[12] came to the rescue. Thus, when (7*Z*)-8-chloro-7-hexadecene was treated with MeMgBr in the presence of 5 mol% [Pd(*t*Bu_3P)$_2$] at 50°C for 6 h, the desired product of (7*E*)-8-methyl-7-hexadecene was obtained in 90% yield and with high stereoselectivity (*E*/*Z* = 97:3). Under the

Table 1: Pd-catalyzed *trans*-selective monoalkylation of 1,1-dichloro-1-alkenes with alkyl zinc compounds and a catalytic amount of [$PdCl_2$(dpephos)].

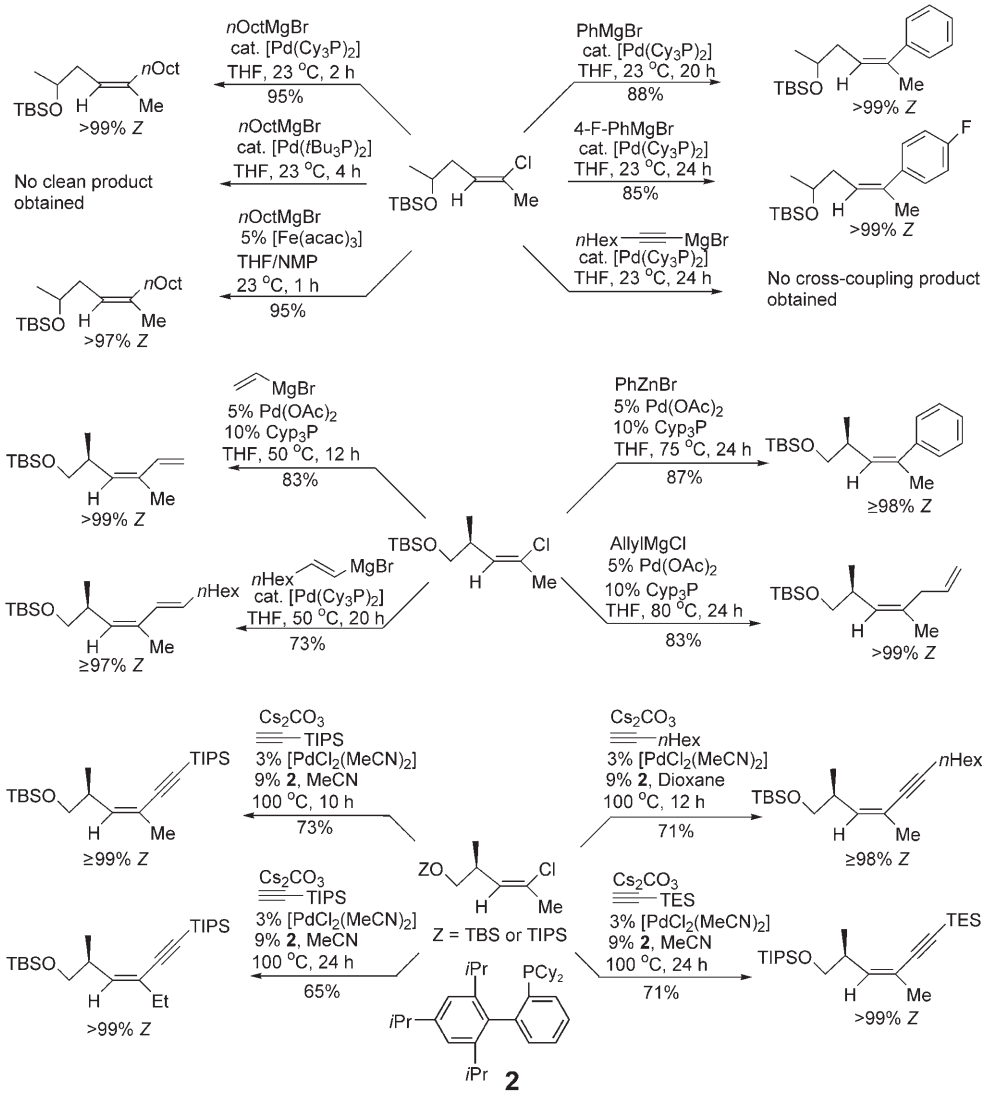


Entry	R^1	R^2ZnX[a] (additive)	Conditions *T* [°C]	Conditions *t* [h]	Yield[b] [%]	
					Mono[c]	Di
1	*n*Hex	Me_2Zn	70	16	50	50
2	*n*Hex	Me_2Zn–NMI[d]	55	10	75	15
3	*n*Hex	Et_2Zn	50	6	76	13
4	*n*Hex	*n*OctZnBr	23	20	85	<3
5	*n*Hex	*n*OctCH(Me)CH_2ZnBr	50	20	70	25
6	TBSOCH$_2$CHMe	Me_2Zn–NMI[d]	60	6	76	15
7	TBSOCH$_2$CHMe	Et_2Zn	23	6	85	5[e]
8	TBDPSO(CH$_2$)$_2$	*n*OctZnBr	50	20	80	12
9	TBSOCH(Me)CH$_2$	Me_2Zn–NMI[d]	65	16	85	12
10	TBSO(CH$_2$)$_3$	*n*OctZnBr	50	24	83	10
11	TMS≡	Me_2Zn	65	7	90	5
12	TMS≡	Me_2Zn	65	5	82	15
13	Ph	Me_2Zn	70	5	80	10
14	Ph	*n*OctZnBr	50	12	90	3

[a] Me_2Zn and Et_2Zn were purchased from Aldrich, R^2ZnBr were prepared from R^2I by lithiation with *t*BuLi (2 equiv) and zincation with dry $ZnBr_2$. [b] Determined by GLC with an internal standard. [c] All monoalkylated products were >98–99% isomerically pure, and their configurations were determined by a combination of NMR techniques, including NOE interaction studies and chemical-shift analysis. [d] NMI (1 equiv relative to Me_2Zn) was added. [e] In addition to the disubstitution product, another by-product identified as the dechlorinated monosubstitution product was produced in 8% yield.



Scheme 2. $[Pd(tBu_3P)_2]$-catalyzed cross-coupling of *Z* chloroalkenes with MeMgBr for the synthesis of *trans*-trisubstituted alkenes.



Scheme 3. Cross-coupling of internal *Z* chloroalkenes with Grignard reagents or terminal alkynes in the presence of Pd catalysts containing bulky trialkylphosphines or **2**.

same conditions, (3*Z*)-1-*tert*-butyldiphenylsilyloxy-4-chloro-3-dodecene gave the desired methylation product in quantitative yield as a 96:4 mixture of the *E* and *Z* isomers (Scheme 2).

Even with the use of $[Pd(tBu_3P)_2]$, however, *Z* chloroalkenes could not be alkylated in useful yields with higher alkyl magnesium halides, such as *n*OctMgBr, with β-dehydrometallation and hydrogenolysis of the *Z* chloroalkenes as the major side reactions. On the other hand, the use of Cy_3P or Cyp_3P as ligands (Cy = cyclohexyl and Cyp = cyclopentyl, respectively)[8,11] led to the formation of the desired alkylation products in high yields (Scheme 3). Satisfactory results were also observed with the use of $[Fe(acac)_3]$ (acac = acetylacetonate)[13] as a catalyst. As indicated by the results summarized in Scheme 3, Pd complexes with Cy_3P and Cyp_3P appear to be generally satisfactory catalysts for the second substitution with Grignard reagents containing alkyl, aryl, alkenyl, and allyl groups. In some favorable cases, even organozinc reagents, such as PhZnBr, can successfully couple with the *Z* chloroalkenes in the presence of a Pd–Cyp_3P complex. Despite all these favorable results, the reaction of (*Z*)-TBSOCH(Me)CH_2CH=C(Cl)Me (TBS = *tert*-butyldimethylsilyl) with *n*HexC≡CMgBr in the presence of 5 mol% of $Pd(Cy_3P)_2$ failed to produce the desired alkynylation product. However, the use of $Et_3SiC{\equiv}CH$ or $iPr_3SiC{\equiv}CH$ in MeCN in the presence of 2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl[12g] (**2**; X-PHOS; purchased from Strem Chemicals) proved to be reasonably satisfactory.

Thus, for the first time, a selective and widely applicable method for the stepwise double substitution of 1,1-dichloro-1-alkenes involving the first *trans*-selective alkylation followed by a second substitution with alkyl-, aryl-, alkenyl-, allyl-, and alkynyl metal compounds has been developed. Although this protocol has not yet been applied to the synthesis of natural products, it promises to be applicable to the synthesis of natural products containing *Z* trisubstituted alkenes, such as hennoxazole A,[14] discodermolide,[15] and ratjadone.[16]

Experimental Section

General procedure for monoalkylation: A flame-dried 25-mL round-bottomed flask under argon was charged with 1,1-dichloro-1-alkene (1 mmol), DMF (3 mL), and $[PdCl_2(dpephos)]$ (35 mg, 0.05 mmol, 5 mol%). After the addition of the organozinc reagent (1.2 mmol), the reaction mixture was stirred at the appro-

priate temperature until gas–liquid chromatographic (GLC) analysis indicated the disappearance of the starting material. The reaction mixture was then quenched with diluted HCl. After extraction with diethyl ether, the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel to give the desired product.

General procedure for the cross-coupling of the *Z* chloroalkenes with Grignard reagents: A flame-dried 25-mL three-neck round-bottomed flask under argon was charged with $Pd(OAc)_2$ (11 mg, 0.05 mmol, 5 mol%), Cyp_3P (24 mg, 0.1 mmol, 10 mol%), and THF (2 mL). The mixture was stirred at 23°C for 10 min and a *Z* chloroalkene (1 mmol) was added followed by the Grignard reagent (1.5 mmol). The flask was stirred at the appropriate temperature until GLC analysis indicated the consumption of the starting material. The mixture was allowed to cool to room temperature, quenched with saturated NH_4Cl, and extracted with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel to give the desired product.

General procedure for the cross-coupling of the *Z* chloroalkenes with terminal alkynes: A flame-dried 25-mL three-neck round-bottomed flask with a reflux condenser under argon was charged with $[PdCl_2(MeCN)_2]$ (8 mg, 0.03 mmol, 3 mol%), **2** (43 mg, 0.09 mmol, 9 mol%), and Cs_2CO_3 (812 mg, 2.5 mmol), followed by anhydrous acetonitrile (3 mL) and the appropriate *Z* chloroalkene (1 mmol). The slightly yellow suspension was stirred at 23°C for 25 min. The alkyne (1.5 mmol) was added by syringe, and the reaction mixture was stirred in a heating bath at the desired temperature for the indicated time. The mixture was allowed to cool to room temperature, quenched with saturated NH_4Cl, and extracted with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel to give the desired product.

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