the latter case also, attempted incorporation of the corresponding free acid, as well as the derived ethyl ester, was unsuccessful. The success of the *N*-acetylcysteamine derivative is presumably related to the ability of the thioester substrate to undergo facile exchange with a thiol residue at the active site of the macrolide synthetase.[19] Taken together, the results from the two laboratories have provided the first direct glimpse of the individual steps leading to generation of the macrolide carbon skeleton and open up the possibility of systematic analysis of the chain-elongation process by stepwise incorporation of successive polyketide intermediates. Further investigations along these lines are in progress.

Acknowledgment. We thank Professor C. Richard Hutchinson for informing us of his results, cited in ref 18, and generously offering to delay publication of his own manuscript so as to allow simultaneous publication of the work from our two laboratories. We also thank Professor David A. Evans for useful discussions. This work was supported by the National Institutes of Health, Grant GM 22172. The Bruker AM-400 used in this work was purchased with funds provided by the NIH Division of Research Resources, RR 02458.

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[19] NAC thioesters are frequently used as substitutes for the corresponding physiologically relevant CoA and ACP esters for in vitro studies of fatty acid biochemistry.

A Remarkable Steric Effect in Palladium-Catalyzed Grignard Coupling: Regio- and Stereoselective Monoalkylation and -arylation of 1,1-Dichloro-1-alkenes[1]

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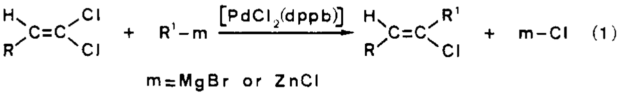
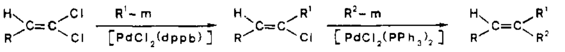
Received September 17, 1986

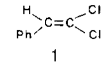
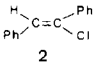
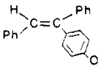
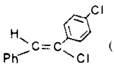
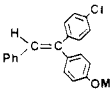
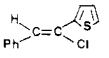
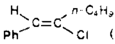
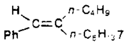
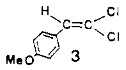
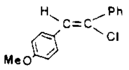
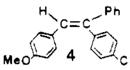
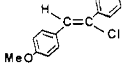
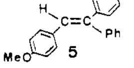
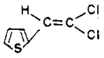
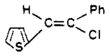
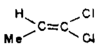
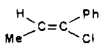
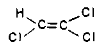
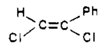
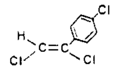
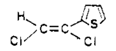
Functionalized carbon chain elongation has been a central concern in transition-metal complex catalyzed carbon–carbon bond-forming reactions.[2] As part of our continued studies on the palladium–phosphine complex catalyzed selective monoalkylation of organic polyhalides,[3] we report here the first success in the regio- and stereoselective monoalkylation and -arylation of 1,1-dichloro-1-alkenes by Grignard or organozinc reagents in the presence of $[PdCl_2(dppb)]$, dppb = $Ph_2P(CH_2)_4PPh_2$, as a catalyst to produce 1-substituted (*Z*)-1-chloro-1-alkenes as shown in eq 1.



(1)

Table I. Stepwise Coupling of 1,1-Dichloro-1-alkenes with Grignard and Organozinc Reagents Catalyzed by Palladium–Phosphine Complexes[a]



Entry	Halide	R^1-m[b]	Product[c]	Yield(%)[d]	R^2-m[b]	Product[c]	Yield(%)[d]
1	 1	A	 2	(98)	B		75
2		C		(94)			
3	1	D		(90)	B		65
4	1	E		80			
5	1	F		0			
6	1	G[e]		(81)[f]	H[g]		77
7	 3	A		97	D	 4	68
8	3	D		81	A	 5	81
9		A		76			
10		A		(90)			
11	 6	A		(55–76)			
12	6	D		90			
13	6	E		87			

[a] Unless otherwise stated, the reactions were carried out under the following conditions. First step: dihalide/R^1-m/$[PdCl_2(dppb)]$ = 1/1/0.01, ether reflux, 2 h. Second step: halide/R^2-MgBr/$[PdCl_2(PPh_3)_2]$ = 1/1.2/0.01, ether reflux, 3 h. [b] A = PhMgBr; B = 4-$MeOC_6H_4MgBr$; C = PhZnCl; D = 4-ClC_6H_4MgBr; E = 2-thienylMgBr; F = *n*-C_4H_9MgBr; G = *n*-C_4H_9ZnCl; H = *n*-$C_6H_{13}MgBr$. [c] All new compounds gave satisfactory spectral (IR, ^1H NMR, ^{13}C NMR, and mass) data and elemental analyses and/or exact mass molecular weights. [d] Isolated yields; yields in parentheses were determined by GLC. [e] Carried out with 2.5 equiv of G in THF at 40 °C for 4 h. [f] Dibutylation product was formed in 11% yield. [g] Performed in the presence of $[NiCl_2(dppp)]$ (1 mol %) under ether reflux for 6 h.

The representative results are listed in Table I. Typically, when 1,1-dichloro-2-phenylethene (**1**) was allowed to react with 1 equiv of phenylmagnesium bromide in the presence of 1 mol % of $[PdCl_2(dppb)]$ under ether reflux for 2 h, monoarylation product (*Z*)-1-chloro-1,2-diphenylethene (**2**)[4] was obtained exclusively in 98% yield (entry 1): the structure of **2** was unambiguously characterized by converting it into (*E*)-stilbene via $[Pd(PPh_3)_4]$-catalyzed hydrogenolysis.[5] A variety of 1,1-dichloro-1-alkenes coupled with alkyl,[6] aryl, and heteroaryl Grignard and/or

---

[1] Minato, A.; Kawano, S.; Suzuki, K.; Tamao, K.; Kumada, M., presented in part at the Fifth International Conference on Organic Synthesis, Freiburg, FRG, Aug. 27–30, 1984; abstract, p 44.

[2] Recent papers: (a) Negishi, E.-I.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821. (b) Negishi, E.-I. In *Current Trends in Organic Synthesis*; Nozaki, H., Ed.; Pergamon: Oxford, 1983; pp 269–280. (c) Wenkert, E.; Ferreira, T. W. *J. Chem. Soc., Chem. Commun.* **1982**, 840. (d) Kuwajima, I.; Urabe, H. *J. Am. Chem. Soc.* **1982**, *104*, 6831. (e) Russell, C. E.; Hegedus, L. S. *J. Am. Chem. Soc.* **1983**, *105*, 943. (f) Sheffy, F. K.; Stille, J. K. *J. Am. Chem. Soc.* **1983**, *105*, 7175. (g) Baillargeon, V. P.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 452. (h) Sharp, M. J.; Snieckus, V. *Tetrahedron Lett.* **1985**, *26*, 5997. (i) Uno, M.; Seto, K.; Takahashi, S. *J. Chem. Soc., Chem. Commun.* **1985**, 932. (j) Nwokogu, G. C. *J. Org. Chem.* **1985**, *50*, 3900. (k) Satoh, M.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1986**, 1329.

[3] (a) Minato, A.; Tamao, K.; Hayashi, T.; Suzuki, K.; Kumada, M. *Tetrahedron Lett.* **1980**, *21*, 845. (b) Minato, A.; Suzuki, K.; Tamao, K.; Kumada, M. *J. Chem. Soc., Chem. Commun.* **1984**, 511.

[4] Mp 51–52 °C (EtOH); lit. mp 52–54 °C: Cristol, S. J.; Bly, R. S., Jr. *J. Am. Chem. Soc.* **1961**, *83*, 4027.

[5] Helquist, P. *Tetrahedron Lett.* **1978**, *22*, 1913. We have confirmed that this reduction proceeds with retention of configuration of olefin stereochemistry. For example, authentic (*E*)- and (*Z*)-1-chloro-1,2-diphenylethene were reduced to (*Z*)- and (*E*)-stilbene, respectively. Details will be reported in due course.

[6] Selective monobutylation occurred effectively by using organozinc reagent[7] instead of Grignard reagent (entry 6 compared with entry 5). The structure of the monobutylation product was also determined by reduction[5] and a large NOE between the olefin proton and the allylic methylene protons.

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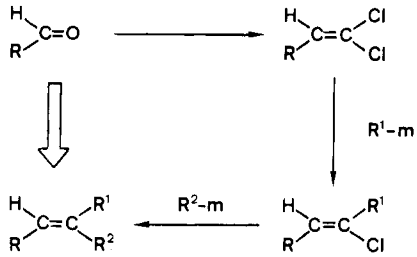
Scheme I



organozinc reagents to give the corresponding substituted (*Z*)-chloroethenes in high yields, showing the wide applicability of the reaction (entries 2–4 and 6–10). Significantly, trichloroethene underwent selective monoarylation similarly at the expected position[8] to give 1-substituted (*Z*)-1,2-dichloroethenes[9] in moderate to excellent yields (entries 11–13).

The following two points deserve comment. (1) The presence of the substituent R in dichloro olefin skeletons was essential for the regio- and stereoselective monocoupling, since parent 1,1-dichloroethene itself produced a comparable amount (ca. 25% yield) of diarylation product and no reaction took place with 1,1-dichloro-2,2-diphenylethene. The significant effect exerted by the vicinal-cis substituent R may be steric, since the electronically different groups, such as alkyl, aryl, heteroaryl, and chlorine, are equally effective. Thus, the chlorine atom cis to hydrogen is preferentially replaced to produce monocoupling product stereoselectively and further reaction is retarded owing to the steric effect of vicinal-cis substituent. (2) A further important point is that the present success depended upon choice of [$PdCl_2$(dppb)] as a catalyst,[10] because the use of the conventional [$PdCl_2(PPh_3)_2$] catalyst resulted mainly in the formation of diarylation products,[11] even when 1 equiv of Grignard reagent was used. The amazing ligand effect strongly suggested that the latter complex would be effective for further coupling reactions.

The subsequent reaction of thus obtained monohalo olefins with Grignard reagents in the presence of [$PdCl_2(PPh_3)_2$] as a catalyst indeed gave trisubstituted olefins stereoselectively (entries 1, 3, 7, and 8). The preparation of opposite stereoisomers **4** and **5** was readily attained from the same starting dihalide **3** by merely changing the order of the treatment of two Grignard reagents (entries 7 and 8). Since 1,1-dichloro-1-alkenes are readily obtainable from aldehydes by dichloromethylenation,[12] the present method has opened a new, general transformation of aldehydes to unsymmetrically trisubstituted olefins in a stereoselective manner (Scheme I), showing the synthetic superiority over the Wittig olefination reaction which has almost no ability toward such a transformation.[13,14]

Acknowledgment. We thank Professor Emeritus M. Kumada and Professor Y. Ito for valuable discussion and encouragement and S. Kawano for partial experimental assistance. This research was partially supported by Scientific Research Fund of Kyoto Pharmaceutical University (A.M.).

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(7) The Pd or Ni complex catalyzed cross-coupling reaction of orgnozinc reagents with organic halides was first reported by Negishi and co-workers.[2a]

(8) The present result is quite interesting, because it had been well documented that the oxidative addition of trichloroethene to [$M(PPh_3)_4$] (M = Pd or Ni) occurs at the monosubstituted position: Fitton, P.; McKeon, J. E. *J. Chem. Soc., Chem. Commun.* **1968**, 4. Johnson, F. G.; Lewis, J.; Jones, J. D.; Taylor, K. A. *J. Chem. Soc., Dalton Trans.* **1974**, 34. Carvajal, J.; Muller, G.; Sales, J.; Solans, X.; Miravitlles, C. *Organometallics* **1984**, *3*, 966. Coupling reactions of trichlorethene induced by the same complexes have also been known to occur at the monosubstituted position in contrast to the present results: Moritani, I.; Fujiwara, Y.; Danno, S. *J. Organomet. Chem.* **1971**, *27*, 279. Ratovelomanana, U.; Linstrumelle, G.; Normant, J. F. *Tetrahedron Lett.* **1985**, *26*, 2575.

(9) The structure of (*Z*)-1,2-dichloro-1-phenylethene was fully characterized by comparing retention times on GLC and spectral data with those of authentic samples of all three regio- and stereoisomers.

(10) Comparable results were obtained with [$PdCl_2$(dppf)], dppf = 1,1′-bis(diphenylphosphino)ferrocene, while [$PdCl_2$(dppp)] and [$PdCl_2$(dppe)], dppp = 1,3-bis(diphenylphosphino)propane and dppe = 1,2-bis(diphenylphosphino)ethane, showed less efficiency. For understanding of the relationship between structure and catalytic activity of bidentate phosphine-palladium complexes, see: Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 158.

(11) The reaction of **1** with the phenyl Grignard reagent (1 equiv) under ether reflux for 2 h in the presence of [$PdCl_2(PPh_3)_2$] (1 mol%) gave a mixture of triphenylethene (33%), diphenylchloroethene (3%), and recovered **1** (50%).

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(13) Cadogan, J. I. G. *Organophosphorous Reagents in Organic Synthesis*; Academic: London, 1979.

(14) A stereoselective, stepwise Grignard coupling reaction of 1,1-bis(alkylthio)-1-alkenes has recently been achieved with nickel–phosphine complexes.[2c]

Theoretical Study of Structures and Relative Energies of Isomeric Metalated Acetaldoximes, Models for Metalated Oxime Ethers

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Received September 15, 1986

The regioselective formation of a new carbon–carbon bond in the α-position to a carbonyl group is one of the fundamental reactions of modern synthetic organic chemistry.[2] Metalated enolate equivalents derived from N-derivatives of carbonyl compounds,[3] $R_1R_2C{=}NX$, such as imines,[4-6] hydrazones,[7-11] oximes,[11-17] and oxime ethers,[18-22] have been used for such regioselective reactions. A remarkable preference for the formation of the syn-configured[23] enolate intermediate is generally observed. The role of aggregated intermediates in these reactions is still not

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(1) Fonds-Stipendiat des Verbandes der Chemischen Industrie.

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(23) "Syn" is used to refer to the isomer in which the deprotonated carbon atom and the OH group are cisoid with respect to the CN bond.

0002-7863/87/1509-1258$01.50/0