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PALLADIUM-CATALYZED REACTION OF ORGANIC HALIDES WITH ORGANOTIN COMPOUNDS INVOLVING OLEFIN INSERTION: SYNTHESIS OF 2,3-DISUBSTITUTED NORBORNANES

Masanori Kosugi,* Hiroyuki Tamura, Hiroshi Sano and Toshihiko Migita*
Department of Chemistry, Faculty of Engineering, Gunma University, Kiryu, Gunma 376, Japan

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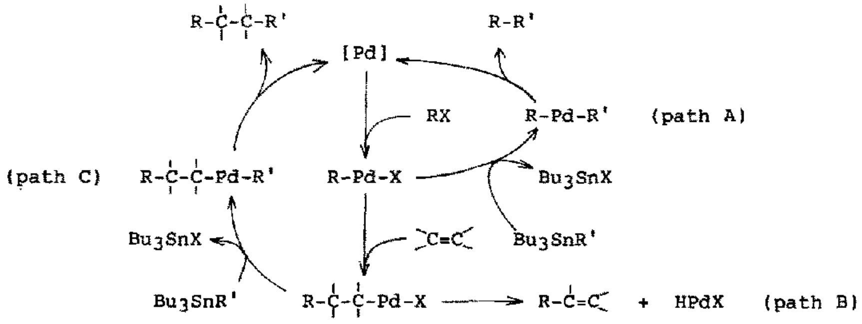
Summary: 2,3-Disubstituted norbornanes were prepared by the palladium-catalyzed reaction of a ternary system composed of organic halide, organotin compound, and norbornene. The scope and limitations of this reaction are described.

Introduction

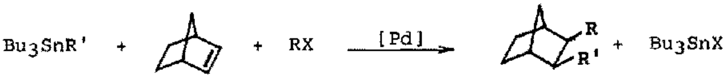
Organotin compounds are versatile reagents for organic synthesis, especially the palladium-catalyzed cross-coupling reaction of various organotin compounds with electrophiles, such as organic halides, triflates, and diazonium salts are useful for C-C bond formation.1) The combination of a Heck-type reaction2) with the palladium catalyzed cross-coupling reaction of organic halides with organotin compounds, that is, a cross-coupling reaction involving insertion of olefin, is a promising simple procedure for the construction of more complex molecules directly (path C in Scheme 1). Unfortunately, however, the fast β-elimination of the palladation product, derived from olefin and the palladium(II) complex (path B in Scheme 1), and the direct coupling between the organic halide and the organotin compound (path A in Scheme 1) make this potentially useful synthetic route unsuccessful.3)

Scheme 1



In 1982, Chiusoli et al. reported the one-pot synthesis of 2,3-disubstituted norbornanes by the reaction of vinyl bromides, terminal acetylene, and norbornene in the presence of a palladium complex.[4] More recently, Larock et al. reported that norbornene could be inserted into a palladium complex and the resulting adduct did not suffer from the undesirable β-elimination.[5] According to Chiusoli[4] and Larock,[5] norbornene is thought to be a promising olefin for the palladium-catalyzed cross-coupling involving the insertion of the olefin. Since the palladium-catalyzed 1,4-arylation/alkylation of 1,3-butadiene[6] and the palladium-catalyzed insertion of allenic hydrocarbon[7] were also reported, 1,3-butadiene and allenes also might be promissing olefins.

In our earlier communication, we reported the palladium-catalyzed reaction of organic halides with organotin compounds involving the insertion of norbornene.[8]



The reaction was carried out with a solution of bromobenzene (3 mmol), norbornene (3 mmol) and vinyltributyltin (3 mmol) in benzene (3 ml) in the presence of a 1 mol % of tetrakis(triphenylphosphine)palladium at 100°C for 10 hr., and gave the expected 2-phenyl-3-vinylnorbornane in 59% yield. Use of double amounts of norbornene improved the yield to 87%. Under these conditions, bromobenzene was completely consumed and styrene was not detected in the reaction mixture. These findings imply that insertion of norbornene into phenylpalladium bromide is much faster than the direct coupling. This paper describes the further survey on the scope and limitations of the reaction.

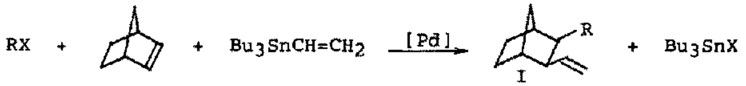
Results and Discussion

Reaction with various halides.

Based on the above findings, we investigated the reaction of various halides with norbornene and vinyltributyltin in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium. Results are shown in Table 1.

As Table 1 shows, aryl bromide and vinyl bromide were good substrates, but allyl and benzyl chloride were not. The difference in the behavior of these halides seems to be due to the difference in the ability to insert norbornene into the oxidative-addition adducts derived from the halides and palladium. It was reported that the π-allyl palladium complex derived from allyl chloride did not insert norbornene.[5] The reaction of benzoyl chloride gave the product in 36% yield, while the reaction of acetyl chloride did not produce any product. It should be noted that the reactions of aryl bromide having an electron-withdrawing group and of benzoyl chloride gave considerable amounts of the direct coupling products (entries 5 and 12). These findings show that the direct coupling reactions of acyl chloride or negatively substituted aryl bromide with vinyltin are considerably fast, in other words, transmetallation of acyl or negatively substituted aryl palladium complex with vinyltin is so much effective as competing with olefin insertion.

Table 1. Palladium-catalyzed reaction of halides, norbornene, and vinyltributyltin

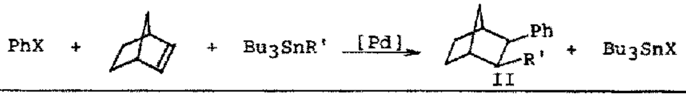


Entry	R-X	Temp./°C	hr.	Isolated Yield of I/%		
1	Ph-Br	100	10	Ia	87	
2	p-$MeOC_6H_4$-Br	100	10	Ib	99	
3	o-MeC_6H_4-Br	100	10	Ic	87	
4	p-AcC_6H_4-Br	100	10	Id	73	
5	p-NCC_6H_4-Br	100	10	Ie	56	[p-$NCC_6H_4CH=CH_2$ 15%]
6	$CH_2=CH$-Br	100	10	If	64	
7	PhCH=CH-Br	100	10	Ig	91	
8	$Me(CH_2)_5CH=CH$-Br	100	10	Ih	83	
9	$CH_2=CHCH_2$-Cl	120	20		0	
10	$PhCH_2$-Cl	120	20		0	
11	MeCO-Cl	80	20		0	
12	PhCO-Cl	80	12	Ii	36	[$PhCOCH=CH_2$ 39%]

Reaction with various organotin compounds

Table 2 shows the results with various organotins in this ternary reaction system. Thus, in the reaction of phenylethynyl-, phenyl-, allyl-, and vinyltins, the expected 2,3-disubstituted norbornanes were obtained in moderate yields accompanied by small amounts of direct coupling products. On the other

Table 2. Reaction with various organotin compounds



Entry	Ph-X	Bu_3SnR'	Temp./°C	Time/	Isolated Yield of II/%		
13	-Br	-C≡CPh	100	12	IIa	28	[RC≡CPh 44%]
14	-I	-C≡CPh	60	20	IIa	52	[RC≡CPh 13]
15	-Br	-Ph	100	20	IIb	60	[R'Ph 10]
16	-Br	$-CH_2CH=CH_2$	100	20	IIc	47	[$RCH_2CH=CH_2$ 9]
17	-Br	$-C(OEt)=CH_2$	100	20	IId	73*	
18	-Br	$-CH_2COCH_3$	100	20		0	
19	-Br	$-CH_2OCH_3$	100	20		0	
20	-Br	-CN	100	20		0	
21	-Br	-OMe	100	20		0	
22	-Br	-SMe	100	20		0	
23	-Br	$-NEt_2$	100	20		0	

*Isolated as ketone.

hand, acetonyl, methoxymethyl, cyano, methoxy, methylthio, and N,N-diethylaminotin compounds did not give the expected products. Introduction of an allyl group could be accomplished by using the allyltin compound, but not an allyl halide (see above). α-Ethoxyvinyltin was found to behave as a good masked acetylating agent (entry 17), indicating that this is a good tool for the introduction of acyl group in norbornane. In the reaction with phenylethynyltin, iodobenzene was a better substrate than bromobenzene, giving a higher yield of 2,3-disubstituted norbonane and a lower yield of direct coupling product under milder conditions (entry 14).

Stereochemistry of the product

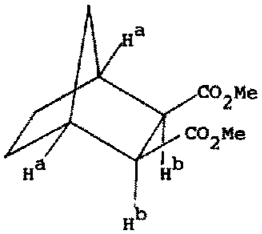
Although there are three potential stereoisomeric 2,3-disubstituted norbornanes, inspection of the ^{13}C NMR spectra showed that only one product was produced. This spectra was identical to that of the exo-cis form described in Chiusoli's report.[4] In order to assign the stereochemistry of the other products, we have synthesized the authentic samples of three isomers of 2,3-dimethoxycarbonyl norbornane and have compared them with those derived from our products by oxidation.

Endo-cis 2,3-dimethoxycarbonylnorbornane was prepared from the Diels-Alder reaction of cyclopentadiene with maleic anhydride, followed by acid-catalyzed methanolysis, and then hydrogenation over palladium on charcoal.[10] The exo-cis isomer was chromatographically collected from the reaction mixtures of the Diels-Alder reaction of cyclopentadiene with dimethyl maleate, followed by hydrogenation over palladium on charcoal.[10] The trans-isomer was prepared by the Diels-Alder reaction of cyclopentadiene with dimethyl fumarate, followed by hydrogenation over palladium on charcoal.[10]

2-(1-Octenyl)-3-vinylnorbornane (obtained by entry 8 in Table 1), for example, was oxidized by potassium permanganate in the presence of dicyclohexyl-18-crown-6-ether, followed by acid-catalyzed esterification by methanol.[11]

Table 3 shows the ^{1}H NMR specra of these compounds. The data of the oxidation product was identical to those of the exo-cis isomer, indicating that the structure of 2-(1-octenyl)-3-vinylnorbornane produced in the reaction of this ternary system is the exo-cis isomer.

Table 3. ^{1}H NMR spectra of 2,3-dimethoxycarbonylnorbornane

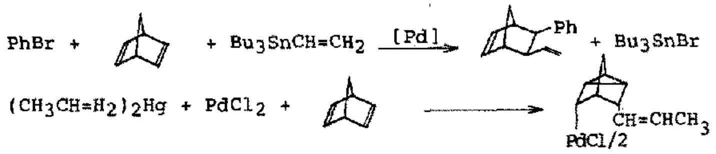


endo-cis	H^a:	2.50 ppm (br. s)
	H^b:	2.87 (br. s)
exo-cis	H^a:	2.50 (br. s)
	H^b:	2.61 (d, J=2Hz)
trans	H^a:	2.53 (br. s)
	H^b:	2.75 (dd, J=2Hz, J=5Hz, endo)
	H^b:	3.13 (t, J=5Hz, exo)
oxidation product	H^a:	2.50 (br. s)
	H^b:	2.58 (d, J=2Hz)

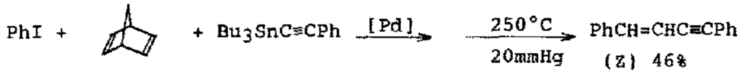
Application to other types of olefin

In order to further explore the full scope and limitations of this newly developed synthetic route, we have applied the reaction to other olefins. Unfortunately, except norbornene and its derivatives, olefins such as cyclopentene, 1,2-diphenylcyclobutene, 3,3-dimethylcyclopropene, bicyclo[2,2,2]-2-octene, phenylacetylene, ethyl vinyl ether etc. did not exhibit any reactivity.

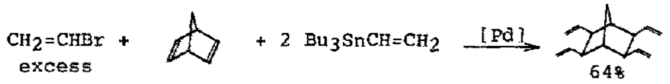
Interestingly, the reaction of bromobenzene and vinyltributyltin with norbornadiene in the presence of palladium complex gave 2-phenyl-3-vinyl-5-norbornene in 87% yield, although Weeks et al. have reported that the reaction of norbornadiene with palladium complex gave tricyclic derivative owing to the coordination of the palladium complex in the endo direction of the diene.[12]



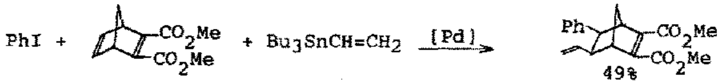
During the isolation of the product of iodobenzene with phenylethynyltributyltin and norbornadiene by distillation, retoro Diels-Alder reaction occurred to give (Z)1,4-diphenyl-1-buten-3-yne.



2,3,5,6-Tetravinylnorbornane was produced by the reaction of an excess amount of vinyl bromide and two-fold vinyltributyltin with norbornadiene in the presence of a palladium complex as shown below;



This indicates that a stepwise introduction of the vinyl group into olefinic moieties of norbornadiene is possible. The yield of the product tends to decrease when norbornadiene has electron-withdrawing groups on its 2 and 3 positions, for example;



The low yield of the product from the reaction with the olefin bearing the electron-withdrawing groups suggests that an electron-rich olefin is more suitable in this ternary reaction system, that is, the olefins insert electron donatingly into the palladium complex. It is surprising that the reaction fails with bicyclo[2,2,2]-2-octene whose structure resembles that of norbornene, bearing rather mild strain. However, steric strain in the olefin does not seem to be a serious factor in governing the reaction, since both cyclobutene and cyclopropene did not react. Thus, at present, the steric and electronic requirements for the olefin to be a good substrate in this ternary reaction are not clear.

Experimetal

The IR spectra were recorded on a JASCO Model A-100 infrared spectrometer. The ^{1}H NMR spectra (in CCl_3 with Me_4Si as internal standard) were recorded on a Varian Associates Model EM-360 spectrometer. The ^{13}C NMR spectra (in $CDCl_3$ with Me_4Si as internal standard) were taken on a Hitachi Model R-90H spectrometer. MS spectra were recorded on a JEOL Model JMS-DX302 Mass Spectrometer. GLC analyses (10% SF96 or SE30 on Celite 545) were performed on an Ohkura Model 802 instrument.

Materials. Organotin compounds used were prepared by standard methods described in the literatures.[1] Aryl bromides and vinyl bromide were commercially available from Tokyo Kasei Kogyo Co. Ltd. and used directly without further purification. Allyl chloride, benzyl chloride, acetyl chloride, and benzoyl chloride were also available from Tokyo Kasei Kogyo Co. Ltd. and used after distillation. β-Bromostyrene and 1-bromo-1-octene were prepared by the method in literatures.[13] Norbornene, norbornadiene, bicyclo[2,2,2]2-octene, and cyclopentene from Tokyo Kasei Kogyo Co. Ltd. were used without further purification. Endo-cis 2,3-dimethoxycarbonylnorbornane, an exo-cis isomer, and a trans isomer were prepared by the methods described in the text.[10] Their ^{1}H NMR spectra were summerized in Table 3. 2,3-Dimethoxycarbonylnorbornadiene (from cyclopentadiene and dimethyl acetylene dicarboxylate) was prepared by the standard Diels-Alder reactions.[10] 1,2-diphenylcyclobutene[14] and 3,3-dimethylcyclopropene[15] were prepared by the methods described in literatures. Tetrakis(triphenylphosphine)palladium was prepared by the method described in the literature.[16]

Reaction Procedures. A mixture of organotin compound (3 mmol), norbornene (6 mmol), organic halide (3 mmol), tetrakis(triphenylphosphine)palladium (0.03 mmol), and benzene (3 ml) as a solvent was placed in a glass tube and sealed in vacuo. The reaction was carried out in a thermobath at the appropriate temp. for a fixed period of time. The reaction mixture was washed with aqueous potassium fluoride, and then was subjected to column chromatography and Kugelrohr distillation for the isolation of the product.

Products. Ia: δ: ^{1}H NMR δ: 7.1-6.9(s, 5H, phenyl), 5.4-4.4(m, 3H, vinyl), 3.0-1.2(m, 10H, alkyl): ^{13}C NMR δ: 142.6, 128.2, 127.5, 125.1(phenyl), 140.6, 113.0(vinyl), 53.6, 51.9, 43.0, 41.1, 35.4, 30.9, 29.0(alkyl): MS: M^+ 198: Exact MS: Calcd. for $C_{15}H_{18}$; 198.1409, found; 198.1410.
Ib: ^{1}H NMR δ: 7.1-6.6(ABq, 4H, aryl), 5.5-4.5(m, 3H, vinyl), 3.7(s, 3H, methyl), 3.0-1.2(m, 10H, alkyl): MS: M^+ 228.
Ic: ^{1}H NMR δ: 7.3-6.9(m, 4H, aryl), 5.3-4.4(m, 3H, vinyl), 2.2(s, 3H, methyl), 3.1-1.1(m, 10H, alkyl): MS: M^+ 212.
Id: ^{1}H NMR δ: 8.0-7.1(ABq, 4H, aryl), 5.4-4.5(m, 3H, vinyl), 2.6(s, 3H, methyl), 3.1-1.2(m, 10H, alkyl): Anal. Calcd. for $C_{17}H_{20}O$; C; 8.39, H; 84.96: Found; C; 8.41, H; 85.13.
Ie: ^{1}H NMR δ: 7.7-7.1(ABq, 4H, aryl), 5.3-4.5(m, 3H, vinyl), 3.1-1.2(m, 10H, alkyl): MS: M^+ 223.
If: ^{1}H NMR δ: 6.0-4.7(m, 3H, vinyl), 2.6-1.0(m, 10H, alkyl): MS: M^+ 148.
Ig: ^{1}H NMR δ: 7.3(s, 5H, phenyl), 6.5-4.8(m, 5H, alkenyl), 2.6-0.8(m, 10H, alkyl): MS: M^+ 224.
Ih: ^{1}H NMR δ: 6.3-4.7(m, 5H, alkenyl), 2.6-0.6(m, 23H, alkyl): MS: M^+ 232.
Ii: IR: 1670 cm^{-1}(carbonyl): ^{1}H NMR δ: 8.2-7.2(m, 5H, aryl), 5.8-4.4(m, 3H, vinyl), 3.6-0.9(m, 10H, alkyl): ^{13}C NMR δ: 200.6(carbonyl), 138.0, 132.2, 128.2, 128.0(aryl), 138.2, 115.1(vinyl), 52.7, 54.1, 43.3, 39.1, 35.6, 29.3, 28.9 (alkyl): MS: M^+ 226.
IIa[4]: ^{1}H NMR δ: 7.4-6.8(m, 10H, phenyl), 3.6(d, J=2Hz, 2H, alkyl), 2.5(br s, 2H, alkyl), 2.3-1.1(m, 6H, alkyl): MS: M^+ 272.
IIb: ^{1}H NMR δ: 6.9(s, 10H, phenyl), 3.3(d, J=2Hz, 2H, alkyl), 2.6(br s, 2H, alkyl), 2.4-1.3(m, 6H, alkyl): ^{13}C NMR δ: 141.7, 127.5, 126.1, 123.8(phenyl), 53.8, 41.0, 36.3, 29.8(alkyl): MS: M^+ 248.
IIc: ^{1}H NMR δ: 7.2(s, 5H, phenyl), 6.0-4.6(m, 3H, vinyl), 3.0-0.9(m, 12H, alkyl): MS: M^+ 212.
IId: ^{1}H NMR δ: 7.2(s, 5H, phenyl), 2.1(s, 3H, methyl), 3.3-0.8(m, 10H, alkyl): MS: M^+ 214.
2-Phenyl-3-vinyl-5-norbornene: ^{1}H NMR δ: 7.1(s, 5H, phenyl), 6.2(br.s, 2H, olefine), 5.4-4.5(m, 3H, vinyl), 3.2-1.1(m, 6H, alkyl); ^{13}C NMR δ: 142.4, 141.5, 138.9, 137.4, 128.4, 127.6, 125.1, 113.9(sp^2 C), 48.8, 47.6, 47.3, 46.1, 44.2(alkyl): MS: M^+ 196.

2,3,5,6-Tetravinylnorbornane: ^{1}H NMR δ: 6.3-4.7(m, 3H, vinyl), 2.7-1.4(m, 2H, alkyl). Further identification was not yet done, because easily polymerization occurred.
1,4-diphenyl-1-buten-3-yne: ^{1}H NMR δ: 8.0-7.2(m, 10H, phenyl), 6.7(d, J=12Hz, 1H, olefine), 5.8(d, J=12Hz, 1H, olefine).
2,3-dimethoxycarbonyl-5-phenyl-6-vinyl-2-norbornene: ^{1}H NMR δ: 7.2(br.s, 5H, phenyl), 5.4-3.6(m, 3H, vinyl), 3.8(d, 6H, methyl), 3.6-1.6(m, 6H, alkyl): MS: M$^+$ 312.

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