(9) with benzyl alcohol under phase-transfer conditions (C_6H_6, NaOH, n-Bu_4NHSO_4 (5%), 25 °C, 40 h) smoothly affords monobromide **10**[8] in 80% yield. Conversion of **10** to the Grignard reagent (Mg, THF, 4 h 35 °C), followed by addition of triethyl orthoformate (2 equiv, 18 h, reflux) and hydrolytic workup (5% HCl/THF), provides aldehyde **11**[8] in 66% yield. (3) Treatment of phosphonate **8** in THF with sodium hydride (catalytic H_2O required[10]) followed by addition of aldehyde **11** (4 h, 25 °C) and extractive workup results in the highly selective[11] generation of vinyl ester **12**[8] (87%). Reduction of the ester moiety of **12** (DIBAL, CH_2Cl_2, 25 °C, 24 h) afforded alcohol **13**[8] (89%) which was protected[12] to afford acetal **14**[8] in 91% yield (Scheme II).

Conversion of allylstannane **14** to the requisite "trimethylenemethane[13,14a]" reagent was accomplished by treatment with n-butyllithium in THF at −78 °C to produce allyllithium species **6a**[15] which was treated with freshly prepared copper(I) bromide–dimethyl sulfide complex[16] in the presence of lithium bromide (3 equiv) providing bromocuprate **6b**.[17] Reaction of **6b** (1.1 equiv) with optically active **5**[6,7] (THF, −55 °C, 30 min) affords **15**[8] (Scheme III) (74%) as a single stereoisomer as assayed by HPLC and NMR.[18] Deprotection of **15** with 3 equiv of dimethylboron bromide[19] in dichloromethane at −78 °C for 1 h provides alcohol **16**[8] in 85% yield. Conversion of **16** to allyl chloride **3**[8] (98% yield) was smoothly accomplished by using the Corey–Kim protocol.[20] Reaction of **3** with the chiral vinyllithium reagent **4**[5] (THF, −78 °C, 15 min; −50 °C, 10 min) affords the bicyclic sulfone **17**[8,14] (95% yield) which is subsequently desilylated by treatment with 10 equiv of tetrabutylammonium fluoride[21] in THF for 24 h at 25 °C providing diol **18**[8] in 80% yield. Treatment of **18** with 20 equiv of lithium in liquid ammonia containing 4 equiv of *tert*-butyl alcohol (THF cosolvent, −78 °C, isoprene quench after 15 min) affords the desulfonylated, debenzylated triol **19**[8] in 88% yield. Completion of the synthesis was conveniently achieved by a method first utilized by Fried for oxidation of a PGF triol.[22] Oxidation of triol **19** with Pt/O_2 in 1:10 acetone–water containing 19 equiv of sodium bicarbonate at 57 °C for 2 h afforded a 57% yield of **2**.[23] Comparison of the synthetic material with an authentic sample of (*E*)-carbacyclin[24] reveals the stereochemistry at C5,6 to be >96% *E*, consistent with the stereochemical purity of the "trimethylenemethane" reagent.[11] Thus the overall yield from cyclopentadiene for this triply-convergent process is 4.7%, including the resolution step.

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(10) (a) Pietrusiewicz, K. M.; Monkiewicz, J. *Tetrahedron Lett.* **1986**, *27*, 739. (b) Pietrusiewicz, K. M.; Monkiewicz, J.; Bodalski, R. J. *J. Org. Chem.* **1983**, *48*, 788 and references cited therein.

(11) The stereoselectivity of this process is 96:4 as assayed by HPLC. Use of the triethoxy reagent gave an 85:15 mixture of vinyl esters which were effectively inseparable by preparative chromatography.

(12) Stork, G.; Takahashi, T. *J. Am. Chem. Soc.* **1977**, *99*, 1275.

(13) The parent 2-oxygenated 3-allylstannanes have been utilized by the Trost group as trimethylenemethane precursors (*J. Am. Chem. Soc.* **1985**, *107*, 719, 1778.), and a trisubstituted reagent has recently been utilized by Schlessinger and Wood for 1,2-addition to an aldehyde by using Lewis acid catalysis (see: Schlessinger, R. H.; Wood, J. L. *J. Org. Chem.* **1986**, *51*, 2621.), but apparently **14** represents the first example of an oxygenated allylstannane bearing a stereodefined trisubstituted olefin being used for allyl anion generation.

(14) The overall synthetic strategy is formally equivalent to a regiospecific, stepwise trimethylenemethane 3 + 2 cycloaddition to a vinyl sulfone. For examples of trimethylenemethane 3 + 2 cycloadditions with vinyl sulfones, see: (a) Little, R. D.; Brown, L. *Tetrahedron Lett.* **1980**, *21*, 2203. (b) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1982**, *104*, 3733.

(15) Seyferth has shown that simple allylstannanes undergo transmetalation with methyllithium at 0 °C to afford allyllithium reagents (Seyferth, D.; Mammarella, R. E. *J. Organomet. Chem.* **1979**, *177*, 53.). The ability of nearby oxygen functionality to promote this exchange process, as seen with **14**, has also been reported by Carpenter (Newman-Evans, R. H.; Carpenter, B. K. *Tetrahedron Lett.* **1985**, *26*, 1141).

(16) (a) House, H. O.; Chu, C.-Y.; Wilkins, J. M.; Umen, M. J. *J. Org. Chem.* **1975**, *40*, 1460. (b) Theis, A. B.; Townsend, C. A. *Synth. Commun.* **1981**, *11*, 157.

(17) Hutchinson, D. K.; Hardinger, S. A.; Fuchs, P. L. *Tetrahedron Lett.* **1986**, *27*, 1425.

(18) A survey of the reaction of **5** with a series of allylic organometallic reagents (α/γ ratios; C-9/C-11 stereocontrol; trisubstituted olefin stereointegrity) will be described in detail subsequently in a full paper.

(19) Guindon, Y.; Yoakim, C.; Morton, H. E. *J. Org. Chem.* **1984**, *49*, 3912.

(20) Corey, E. J.; Kim, C. U.; Tadeka, M. *Tetrahedron Lett.* **1972**, *13*, 4339.

(21) (a) Corey, E. J.; Venkatswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190. (b) Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1975**, *53*, 2975.

(22) Fried, J.; Sih, J. C. *Tetrahedron Lett.* **1973**, *14*, 3899. In contrast to Fried's substrate, we were able to use a 1:1 PtO_2/substrate ratio.

(23) Although the "crude" carbacyclin obtained as an oil from this reaction was found to be >96% pure, with an *E*:*Z* = >99:1 by HPLC [25 cm × 4.6 mm Hi-chrom reversible HPLC column ODS-II (Regis Chemical Co.), mobile phase 45/55 (acetonitrile/0.01 M KH_2PO_4 adjusted to pH 2.5 with concentrated H_2SO_4), flow rate 1 mL/min, detection at 205 nm], and provided an essentially superimposable 470-MHz ^1H NMR spectra with that of an authentic sample;[24] it could not be made to crystallize, even by addition of a seed crystal. An analytical sample was prepared by treatment of the carbacyclin with diazomethane and then with acetic anhydride and triethylamine in the presence of catalytic 4-(dimethylamino)pyridine. The methyl ester diacetate was purified by medium pressure liquid chromatography by using a Merck size C lobar column. The purified material was saponified and chromatographed over Mallincrodt CC-4 special acid washed silica gel, followed by recrystallization from ether–hexane. The crystalline carbacyclin thus obtained in 34% yield (1.6% overall from cyclopentadiene) had an identical HPLC profile with that of the oily material under the aforementioned conditions. The carbacyclin obtained had the following physical data: mp 60–62.3 °C (lit. mp 62.4–63.3 °C,[3j] 64.5–66.5 °C,[3a] 61–62.5 °C[3c]), $[\alpha]_D^{25}$ +95.2° (*c* 0.520, MeOH) (lit. $[\alpha]_D^{25}$ + 90° (*c* 0.810, MeOH),[3l] $[\alpha]_D^{25}$ + 92.2° (*c* 0.515, MeOH),[3a] $[\alpha]_D^{25}$ + 91° (*c* 0.964, MeOH)[3c]).

(24) We thank Dr. John Pike of the Upjohn Company for an authentic sample of (*E*)-carbacyclin (**2**).

Dramatic Rate Enhancement of Suzuki Diene Synthesis: Its Application to Palytoxin Synthesis

Jun-ichi Uenishi, Jean-Marie Beau, Robert W. Armstrong, and Yoshito Kishi*

Department of Chemistry, Harvard University Cambridge, Massachusetts 02138

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In connection with the synthetic studies on the marine natural product palytoxin,[1] we have investigated the possibility to form the C.75–C.76 bond[2] by using the Pd(0)-mediated diene synthesis developed by Suzuki and co-workers.[3] More specifically, we were interested in utilizing this reaction to couple the upper and lower halves in order to assemble the complete carbon backbone of palytoxin. We chose the model system of **1**[4] + **2** → **3** to clarify

(1) For the synthetic studies on palytoxin, see: Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644 and references cited therein.

(2) For the complete structure and numbering of palytoxin, see: Cha, J. K.; Christ, W. J.; Finan, J. M.; Fujioka, H.; Kishi, Y.; Klein, L. L.; Ko, S. S.; Leder, J.; McWhorter, W. W., Jr.; Pfaff, K.-P.; Yonaga, M.; Uemura, D.; Hirata, Y. *J. Am. Chem. Soc.* **1982**, *104*, 7369.

(3) (a) Miyaura, N.; Yamada, Y.; Suzuki, A. *Tetrahedron Lett.* **1979**, *20*, 3437. (b) Miyaura, N.; Suginome, H.; Suzuki, A. *Tetrahedron Lett.* **1981**, *22*, 127. (c) Miyaura, N.; Yamada, K.; Suginome, H.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, *107*, 972.

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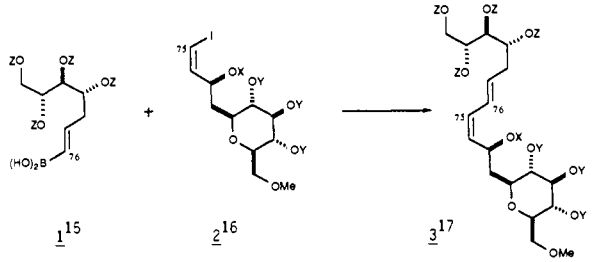
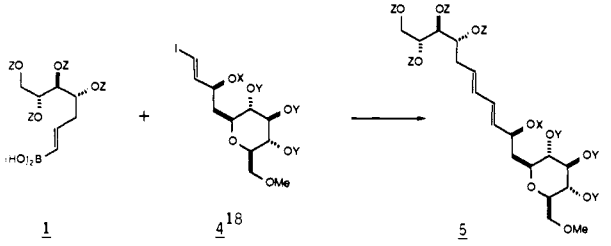
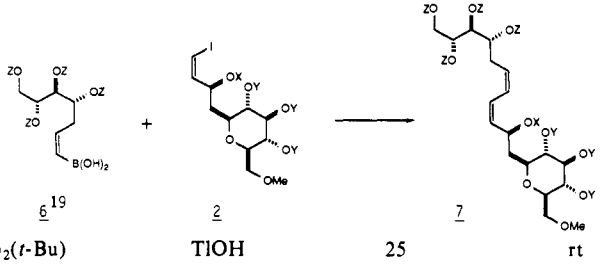
Table I[14]

run	substrate	base	$Pd[P(Ph)_3]_4$ (mol %)	temp (°C)	time	yield (%)
						
	1[15] + **2**[16] → **3**[17]					
1.	X = Ac, Y = Z = $Si(Me)_2(t\text{-}Bu)$	KOH	25	50	30 min	87
2.		KOH	25	rt	2 h	86
3.		KOH	150	rt	1 h[a]	53
4.		TlOH	25	rt	<<30 s	92
5.		TlOH	3	rt	30 min	94
6.		Ag_2O	25	rt	5 min	92
7.		TlOEt	25	rt	30 min[b]	74[c]
8.	X = Y = Z = $Si(Me)(t\text{-}Bu)$	KOH	25	50	2 h[b]	57[c]
9.		KOH	25	rt	2 h[b]	11[c]
10.		KOH	150	rt	20 min[a]	8
11.		TlOH	25	rt	60 min	55
12.		TlOH	150	rt	5 min	73
13.	X = MPM, Y = Z = $Si(Me)_2(t\text{-}Bu)$	TlOH	25	rt	ca. 30 s	97
14.	X = Y = MPM, Z = $Si(Me)_2(t\text{-}Bu)$	TlOH	25	rt	ca. 30 s	97
15.	X = Y = Ac, Z = $Si(Me)_2(t\text{-}Bu)$	TlOH	25	rt	ca. 30 s	82
16	X = H, Y = Z = $Si(Me)_2(t\text{-}Bu)$	TlOH	25	50	2 days	0
17.	X = Y = H, Z = $Si(Me)_2(t\text{-}Bu)$	TlOH	25	50	2 days	0
						
	1 + **4**[18] → **5**					
18.	X = H, Y = Z = $Si(Me)_2(t\text{-}Bu)$	TlOH	25	rt	ca. 30 s	43[d]
						
	6[19] + **2** → **7**					
19.	X = Ac, Y = Z = $Si(Me)_2(t\text{-}Bu)$	TlOH	25	rt	10 min	73

[a] The reaction was terminated as soon as **2** was completely consumed (TLC). [b] The catalytic cycle stopped at this point, leaving **1** and **2** not completely consumed. [c] The combined yield of the expected diene with X = $Si(Me)_2(t\text{-}Bu)$ and X = H in **3**. [d] The vinyl compound, derived from **4**, was isolated along with the expected diene.

the applicability and suitability of this process to our synthetic plan and had very promising results. Nonetheless, we have realized that some improvements on this process are highly desirable for our purposes. For example, we have noticed that the rate of coupling slows down severely with an increase in the molecular weight of substrates, resulting in formation by byproducts in substantial, and sometimes exclusive, amounts.[5-7] In this communication, we would like to report a solution to this problem.

Our analysis of the problem began with the mechanism suggested by Suzuki and co-workers, cf. Scheme I.[3] Among several critical steps involved, the oxidative addition of halides to Pd(0), i.e., step a, is unlikely the rate-determining step since, when the coupling is conducted with 1.5 equiv of $Pd[P(Ph)_3]_4$, **2** disappears faster than **3** appears, indicating a possibility that the coupling should be accelerated by enhancing the rate of one of the remaining steps. Related to this point, we are particularly interested in the earlier observation made by Suzuki and co-workers that hydroxide ion seemed to have a special effect,[3] which might suggest that step b is rate determining. We hoped that the rate of this step might be enhanced by using some other bases such as TlOH and Ag_2O, forming water-insoluble salts instead of NaX.

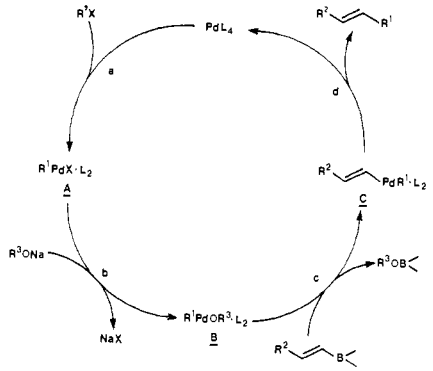
(4) Suzuki and co-workers used both vinyl boranes (disiamyl or catechol) and vinyl boronic acids: see, for example: Miyaura, N.; Suginome, H.; Suzuki, A. *Tetrahedron* **1983**, *39*, 3271. For the present studies, however, only vinyl boronic acids were studied in-depth as they appeared to yield cleaner results than the corresponding catechol boranes particularly for the cases of large molecular weight substrates.

(5) Byproducts isolated and characterized include the *cis*- and *trans*-iodoolefins and the aldehyde, all of which were derived from **1**.

(6) We have attempted a variety of conditions including $Pd[P(Ph)_3]_4/Na_2CO_3$/aqueous $(CH_2OCH_3)_2$, recommended by Gronowitz and co-workers (*Chem. Scr.* **1984**, *23*, 120), without significant improvements.

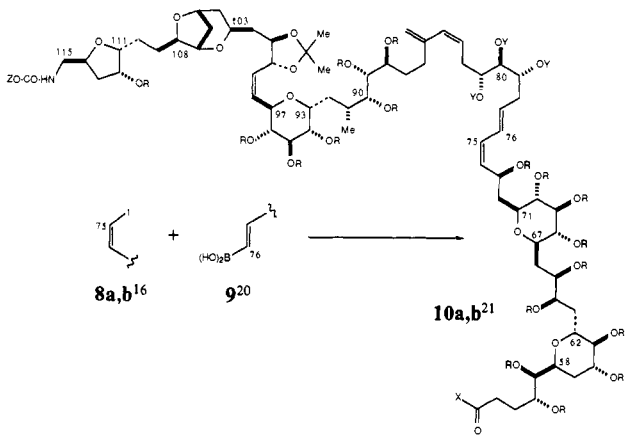
(7) During the preparation of this manuscript, Stille and Groh reported a cross-coupling of vinyl halides with vinyl tin reagents catalyzed by palladium at ambient temperature: *J. Am. Chem. Soc.* **1987**, *109*, 813.

Scheme I.[a] Catalytic Cycle for the Coupling Reaction of Haloalkenes and Haloalkynes with Alkenylboranes[3]



[a] R^1 = alkenyl, aryl, and allylic halides
R^3 = alkyl and H

Scheme II[a,b]



[a] Series: R = $CH_2PhOMe(p)$, X = OMe, Y = $Si(Me)_2(t\text{-}Bu)$, Z = $CH_2CH_2Si(Me)_3$. KOH conditions at 70 °C for 18 h: 36% yield. TlOH conditions at room temperature for 25 min: 75% yield.

[b] Series: R = $CH_2PhOMe(p)$, X = $CH_2P(O)(OMe)_2$, Y = $Si(Me)_2(t\text{-}Bu)$, Z = $CH_2CH_2Si(Me)_3$. KOH conditions at 70 °C for 18 h: 0% yield. TlOH conditions at room temperature for 25 min: 63% yield.

The results summarized in Table I indeed show a dramatic effect of bases on the rate of coupling reactions. Thallium hydroxide is most effective for both *E,Z*- and *Z,Z*-diene preparations thus far.[8] The magnitude of acceleration is roughly estimated to be the following order: KOH (relative rate = 1), TlOEt (5), Ag_2O (30), and TlOH (1000).[9] Under the TlOH conditions, step a appears to be the rate-determining or at least comparable with the rate-determining step since the rate of diene formation is approximately the same as that of iodoolefin consumption.[10] It is interesting to note that the coupling reaction utilizing more than 1 equiv of $Pd[P(Ph)_3]_4$ under the original conditions yields the desired product only in moderate yield, probably due to the side-reaction(s) taking place on the intermediate A, whereas under the TlOH conditions it gives the desired product in excellent yield.[11]

During these studies, we have noticed that the rate of coupling is delicately affected by the protecting group in the case of *cis*-iodoolefin allylic alcohols: *p*-$MeOPhCH_2$ and Ac[12] give approximately the same order of coupling rate whereas (*t*-Bu)-$(Me)_2Si$ gives a much slower rate. In connection with this, it is especially interesting to point out the fact that *trans*-iodoolefin allylic alcohols yield the expected dienes, but the corresponding *cis*-iodoolefin allylic alcohols fail to yield the expected dienes.[13] On the basis of the mechanistic considerations, this observation is not totally unexpected; *cis*-iodoolefin allylic alcohols may yield cyclic intermediates at step b, preventing any further transformation.

From the preparative points of view, the dramatic rate enhancement realized by utilization of TlOH will result not only in an enormous economy of time but also several important consequences. For example, the coupling can now be achieved almost instantaneously even at 0 °C, allowing its application to substrates with fragile functional groups as well as with large molecular weights. In addition, under the new conditions described herein, the formation of byproduct(s) is cleanly eliminated. The new coupling conditions have successfully been applied to the palytoxin synthesis. The two examples chosen from the palytoxin area demonstrate the usefulness of the new coupling conditions.

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Supplementary Material Available: ^1H NMR spectra of the diene products and the Pd compound derived from **8b** (17 pages). Ordering information is given on any current masthead page.

(8) For examples of *Z,Z*-diene syntheses by this procedure, see: Miyaura, N.; Satoh, M.; Suzuki, A. *Tetrahedron Lett.* **1986**, *27*, 3745. Satoh, M.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1986**, 1329.

(9) This relative rate was estimated from the runs 2, 7, 6, and 4.

(10) This observation may suggest a possibility to further accelerate the coupling by affecting the rate of step a.

(11) It is interesting to note that a chromatographically isolable Pd compound was formed when **8b** was treated with $Pd[P(Ph)_3]_4$ (2 equiv) and TlOH (6 equiv) in the absence of **1** [Z = $Si(Me)_2(t\text{-}Bu)$]. This substance yielded the expected diene upon further treatment with **1** and TlOH.

(12) There was no indication that the allylic acetate group existing in the vinyl iodides and also in the diene products reacted with the palladium reagent under the reaction conditions used.

(13) We are interested in performing this reaction in an aqueous medium with the hope that the unprotected upper and lower halves of palytoxin, presumably only soluble in water, might be coupled. It is worthy to note that the TlOH conditions are also very effective in water, but the experiment mentioned in the text suggests the need for a proper protecting group at least for the C.73 hydroxyl group for our purposes.

(14) The following is a representative experimental procedure. To a tetrahydrofuran solution of **1** [Z = $Si(Me)_2(t\text{-}Bu)$] (0.14 mmol in 5 mL) was added 10% aqueous TlOH (0.93 mL) under Ar atmosphere, and the mixture was stirred for 2 min at room temperature. Then a tetrahydrofuran solution of **2** [X = Ac, Y = $Si(Me)_2(t\text{-}Bu)$] (0.10 mmol in 1 mL) and $Pd[P(Ph)_3]_4$ (0.025 mmol in 0.7 mL) was added into the reaction mixture. After 1 min the reaction mixture was diluted with ether (10 mL), dried over $MgSO_4$, and filtered through Celite pad. The crude product was purified by silica gel preparative TLC to give **3** [X = Ac, Y = Z = $Si(Me)_2(t\text{-}Bu)$] (92% based on **2**). **Note Added in Proof:** *n*-Hexane is an excellent solvent for this coupling reaction in case substrates are soluble in nonpolar media.

(15) This substance was prepared by catechol hydroboration of the acetylene, followed by aqueous workup.

(16) This substance was prepared by diimide reduction of the iodoacetylene.

(17) Satisfactory spectroscopic data (^1H NMR, MS, UV) were obtained for all the new substances reported in this paper. Their elemental composition was determined by high-resolution mass spectroscopy. The molecular weight of **10a,b** was established by FABMS spectroscopy. The stereochemistry of dienes was established from the spin–spin coupling constants observed in the ^1H NMR spectrum. For the details, see the Supplementary Material.

(18) This substance was prepared from the acetylenic ketone, see: Cheon, S. H.; Christ, W. J.; Hawkins, L. D.; Jin, H.; Kishi, Y.; Taniguchi, M. *Tetrahedron Lett.* **1986**, *27*, 4759.

(19) This substance was the minor product of coupling reaction of the aldehyde and the reagent developed by Matteson and co-workers, see: the papers cited in ref 20.

(20) This substance was prepared from the aldehyde according to the method developed by Matteson and co-workers, see: Matteson, D. S.; Moody, R. J. *Organometallics* **1982**, *1*, 20 and references cited therein. This substance was contaminated with approximately 15% of the corresponding (*Z*)-vinyl boronic acid.

(21) These dienes were contaminated with approximately 10% of the corresponding *Z,Z*-dienes derived from the (*Z*)-vinyl boronic acids.