to attain an axial orientation on six-membered rings when flanked by an oxygen atom and a carbonyl group.[14]

In addition, oxidized forms of 1,6-dioxaspiro[4.5]decanes can be synthesized by an analogous sequence starting with γ-lactones. The hemispiroketals **14a–c** were synthesized in good overall yield and again isolated as mobile mixtures of diastereomers containing one predominant species, which has been tentatively assigned conformations analogous to the six-membered ring cases.

The method has been applied to the synthesis of trioxadispiroketals, key structural units of the narasin–salinomycin polyether antibiotics.[15] Sequential alkylation (Scheme II) of furan with the iodide **15** followed by the lactone **17** results in the 2-furyl ketone **18**. Oxidation–rearrangement of **18** with 2 equiv of NBS in THF/H_2O (2:1) at 0 °C gives an equilibrium mixture of hemispiroketals **19**, which were not further purified. Desilylation and spiroketalization with 5% HF in CH_3CN provided a 1:1 mixture of the two diastereomeric trioxadispiroketals **20a** and **20b**, which were readily separated by chromatography on silica. Isomer **20a** was assigned the stereochemistry and conformation shown on the basis of weak (1–5%) inter-annular nuclear Overhauser enhancement of one of the hydrogens on C-4 when the C-9 axial hydrogen is irradiated. Isomer **20b** was assigned the structure and conformation shown on the basis of a 6% enhancement of a methyl group attached to C-2 when the C-9 axial hydrogen was irradiated. Although isomer **20b** possesses what appears to be the maximum anomeric effect stabilization, it does not greatly predominate in the product mixture. This may be due to unfavorable dipole–dipole interaction at the two spiro carbons.[16]

Reduction of each isomer with $LiBH(Et)_3$ in THF gave rise to a single allylic alcohol in each case. Isomer **21b** possesses the configuration of the trioxadispiroketal present in salinomycin[8a] and narasin[8b] while **21a** matches that of deoxy (O-8)-epi-17-salinomycin.[17]

In summary, efficient syntheses of hemispiroketals and trioxadispiroketals have been accomplished. The route is convergent, utilizing sequential alkylation of 2-lithiofuran derivatives as the key C–C bond forming steps. Oxidation–rearrangement of the 2-furylketones followed by thermodynamic cyclization leads to highly oxidized spiroketals modeling those present in **4–6**, as well as the narasin–salinomycin polyether antibiotics. Further studies involving the application of this method are in progress.

Acknowledgment. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work. We also acknowledge the support of the American Cancer Society, the National Institutes of Health (Biomedical Research Support Grant), and the Wayne State University Research Committee. F.P. thanks Wayne State University for a Thomas F. Rumble Fellowship.

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Received February 6, 1989

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(14) (a) Preferred axial disposition of anomeric C–O bonds is frequently encountered. This tendency is considerably enhanced by adjacent carbonyl groups: Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: New York, 1983. Kirby, A. J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Springer-Verlag: New York, 1983.

(15) Other methods of trioxadispiroketal synthesis: (a) Baker, R.; Brimble, M. A. *J. Chem. Soc., Perkin Trans. 1* **1988**, 125. (b) Horita, K.; Nagato, S.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron Lett.* **1987**, *28*, 3253. (c) Cottier, L.; Descotes, G. *Tetrahedron* **1985**, *41*, 409.

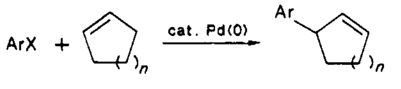
(16) Kishi, Y.; Hatakeyama, S.; Lewis, M. D. *Front. Chem. Plenary, Keynote Lect. IUPAC Congr. 28th, 1981*; Laidler, K. J., Ed.; Pergamon Press: Oxford, 1982; pp 287–304. For general discussions and examples see ref 3, Vol. 2, Chapters 3, 5, and 6.

(17) Westley, J. W.; Blount, J. F.; Evans, R. H., Jr.; Liu, C.-H. *Bull. Soc. Chim. Belg.* **1981**, *90*, 471.

Palladium-Catalyzed Intermolecular Vinylation of Cyclic Alkenes

Summary: Vinylic halides or triflates and cyclic alkenes undergo facile, palladium-catalyzed, intermolecular, allylic cross-coupling under mild reaction conditions to afford excellent yields of 1,4-dienes.

Sir: There are a number of examples of the *intermolecular*, palladium-catalyzed, allylic cross-coupling of aryl halides and cyclic alkenes (eq 1).[1-6] We recently reported



(1)

three convenient procedures to effect such reactions. The use of 0.5 mmol of organic halide, 2.5 mmol of cyclic alkene, 2.5% $Pd(OAc)_2$ (3 mg), 3 equiv of KOAc (1.5 mmol), and 1 equiv of n-Bu_4NCl (0.5 mmol) in DMF (1.0 mL) under nitrogen at room temperature or 80 °C (procedure A) generally gives excellent yields,[7] but subsequent work revealed that certain cyclic alkenes afforded mixtures of regioisomers under these conditions and a number of important organic functional groups in the aryl halide could not be accommodated by this procedure.[8] Consequently, we developed two alternative procedures [Procedure B:[9] organic halide (0.5 mmol), cycloalkene (2.5 mmol), 3% $Pd(OAc)_2$ (3.5 mg), 9% PPh_3 (12 mg), 2 equiv of Ag_2CO_3 (1.0 mmol), CH_3CN (6 mL). Procedure C: same as procedure A, plus 2.5% PPh_3]. The former procedure effectively inhibited isomerization and the latter proved particularly useful for functionally substituted aryl halides. These and related arylation procedures have recently proven quite valuable for *intramolecular* cyclizations.[9-15]

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(1) Cortese, N. A.; Ziegler, C. B., Jr.; Hrnjez, B. J.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 2952.

(2) Arai, I.; Daves, G. D., Jr. *J. Org. Chem.* **1979**, *44*, 21.

(3) Andersson, C.-M.; Hallberg, A.; Daves, G. D., Jr. *J. Org. Chem.* **1987**, *52*, 3529.

(4) Harrington, P. J.; DiFiore, K. A. *Tetrahedron Lett.* **1987**, *28*, 495.

(5) Tamaru, Y.; Yamada, Y.; Yoshida, Z. *Tetrahedron* **1979**, *35*, 329.

(6) Arai, I.; Daves, G. D., Jr. *J. Org. Chem.* **1978**, *43*, 4110.

(7) Larock, R. C.; Baker, B. E. *Tetrahedron Lett.* **1988**, *29*, 905.

(8) Larock, R. C.; Gong, W. H.; Baker, B. E. *Tetrahedron Lett.*, submitted.

(9) Abelman, M. M.; Oh, T.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 4130.

(10) Grigg, R.; Sridharan, V.; Stevenson, P.; Worakun, T. *J. Chem. Soc., Chem. Commun.* **1986**, 1697.

(11) Larock, R. C.; Baker, B. E.; Song, H.; Gong, W. H. *Tetrahedron Lett.* **1988**, *29*, 2919.

Table I. Palladium-Catalyzed Intermolecular Vinylation of Cyclic Alkenes

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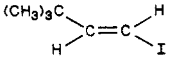
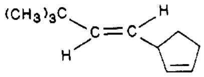
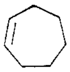
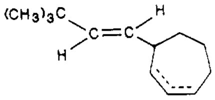
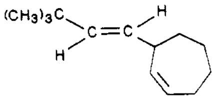
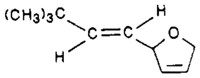
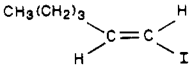
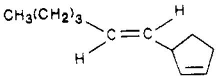
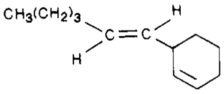
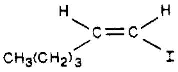
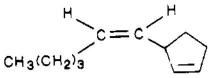
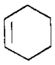
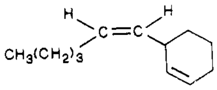
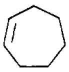
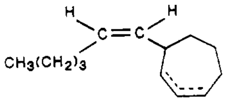
1			A	72 h, 80 °C		62
2			A	48 h, 80 °C	 1:1^a	86
3			B	24 h, 80 °C		65
4			B	24 h, 80 °C		52
5			A	24 h, 80 °C		79
6			B	48 h, 80 °C		51
7			A	216 h, 25 °C		96
8			A	216 h, 80 °C		0
9			B	24 h, 80 °C	 1:1^a	55
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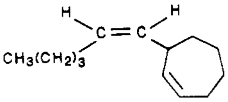
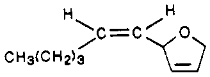
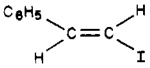
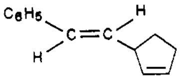
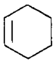
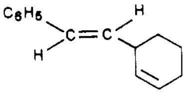
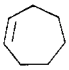
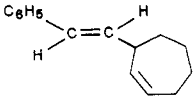
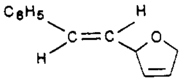
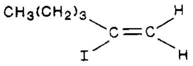
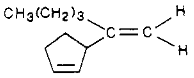
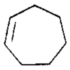
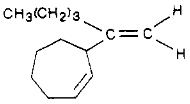
11			B	24 h, 80 °C		81
12			B	24 h, 80 °C		51
13			A	168 h, 25 °C		77, 94^b
14			A	216 h, 25 or 80 °C		0
15			B	48 h, 80 °C		47
16			B	24 h, 80 °C		86
17			B	24 h, 80 °C		52
18			A	216 h, 25 °C		56, 71^b
19			B	24 h, 80 °C		81

Table I (Continued)

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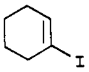
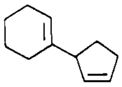
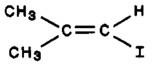
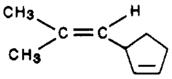
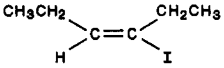
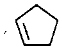
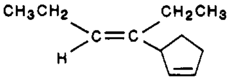
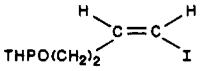
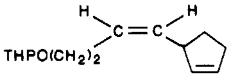
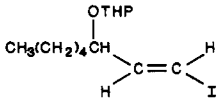
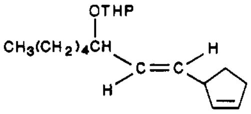
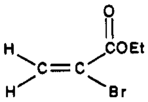
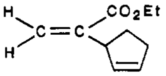
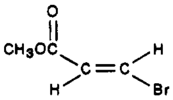
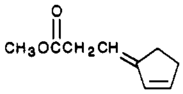
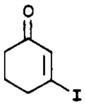
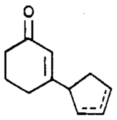
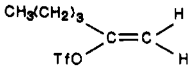
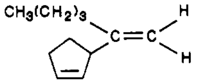
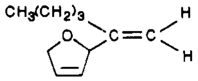
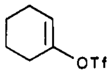
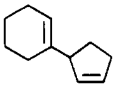
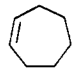
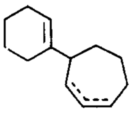
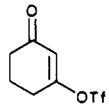
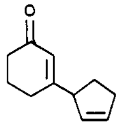
20			A	72 h, 25 °C		66
21			A	96 h, 80 °C		0
22			A	216 h, 25 °C or 24 h, 80 °C		0
23			A	96 h, 80 °C		79
24			A	72 h, 80 °C		74
25			A	24 h, 25 °C		33
26			A	24 h, 25 °C		100
27			A	3 h, 25 °C	 3:1[a]	66[b]
28			B	24 h, 80 °C		65
29			B	24 h, 80 °C		67
30			A	72 h, 25 °C		58
31			B	48 h, 25 °C or 2 h, 80 °C	 3:1[a]	100
32			B	24 h, 25 °C		59

[a] Allylic:homoallylic product. [b] NaOAc used instead of KOAc.

While we have reported the successful, *intramolecular*, palladium-catalyzed vinylation of cyclic alkenes using vinylic halides and procedures A or B,[11] to our knowledge there are only two examples of analogous *intermolecular* reactions. In one reaction the cyclic 1,4-diene was accompanied by significant amounts of an isomer;[16] in the other, the diene was observed as a side product in an entirely different process.[17] We felt that this *intermolecular* process deserved further study and report at this time that our earlier reported procedures A and B afford good to excellent yields of 1,4-dienes via palladium-catalyzed cross-coupling of vinylic halides or triflates and cyclic

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(12) Negishi, E.; Zhang, Y.; O'Connor, B. *Tetrahedron Lett.* **1988**, *29*, 2915.

(13) Zhang, Y.; O'Connor, B.; Negishi, E. *J. Org. Chem.* **1988**, *53*, 5588.

(14) O'Connor, B.; Zhang, Y.; Negishi, E.; Luo, F.-T.; Cheng, J.-W. *Tetrahedron Lett.* **1988**, *29*, 3903.

(15) Negishi, E.; Nguyen, T.; O'Connor, B.; Evans, J. M.; Silviera, A., Jr. *Heterocycles*, in press.

(16) Kim, J.-I. I.; Patel, B. A.; Heck, R. F. *J. Org. Chem.* **1981**, *46*, 1067.

(17) Karabelas, K.; Hallberg, A. *J. Org. Chem.* **1988**, *53*, 4909.

alkenes. Our preliminary results are summarized in Table I.

The following observations have been made during the course of this work. Simple alkyl-containing vinylic bromides do not react at 25 °C or 80 °C by procedure A. The corresponding vinylic iodides react slowly at room temperature and generally need to be heated to 80 °C in order to get the reaction to go to completion. Under these conditions, good to excellent yields of 1,4-dienes can be obtained from cyclopentene. Cycloheptene has proven less reactive and tends to give mixtures of allylic and homoallylic products. Cyclooctene is equally unreactive and gives bad mixtures, usually containing several products. Cyclohexene is essentially inert. Dihydrofuran exhibits reactivity similar to cyclopentene, but isomeric mixtures are the general rule. The more highly substituted the vinylic iodide is, the lower the yield of 1,4-diene (see entries 21 and 22). This may be due to either a steric or an electronic phenomena. The more electron-rich the double bond of the vinylic halide is, the slower the resulting reaction. Certain functional groups may be accommodated by this procedure. While (*E*)-1-iodo-1-octen-3-ol proved unreactive, the corresponding tetrahydropyranyl ether (entry 24) gave a good yield of 1,4-diene. Vinylic iodides bearing electron-withdrawing groups are generally quite reactive. In fact, even the corresponding bromides react smoothly (entries 25 and 26). However, in some cases these halides simply dimerize to the corresponding symmetrical 1,3-diene or decompose, and in other cases the desired product apparently isomerizes (entries 26 and 27).

Procedure B solves many of the difficulties encountered when using procedure A. Reactions employing less reactive cyclic alkenes, such as cyclohexene, give far better results with procedure B (compare entries 8 and 9, and 14 and 15). Isomerization problems are also virtually eliminated with the Ag_2CO_3 procedure. However, vinylic iodides bearing electron-withdrawing groups tend to dimerize to symmetrical 1,3-dienes when using this procedure.

We have briefly examined procedure C to see if it might overcome any of the difficulties encountered with the other two procedures. With the use of cyclohexene and (*E*)-1-iodo-1-hexene, 2-iodo-1-hexene, or methyl (*E*)-β-iodoacrylate, none of the desired 1,4-dienes could be obtained. The first two vinylic iodides gave only symmetrical 1,3-dienes, while the latter appeared to polymerize.

Sometimes it is easier to prepare vinylic triflates than the corresponding iodides. Therefore, we have examined the use of triflates in these cross-coupling processes (entries 28–32). Vinylic triflates tend to be more reactive than the corresponding iodides (compare entries 18 and 28), but they do not give as consistently good results as the iodides. Best results with triflates have generally been obtained when using procedure B. However, reactions of triflates and less reactive alkenes, such as cyclohexene, fail to give any 1,4-diene with either procedure A or procedure B. Unlike the analogous iodide reactions, the reactions of triflates and procedure B occasionally afford isomerized products (entry 31).

In conclusion, procedures A and B provide the first generally useful procedures for the catalytic, allylic cross-coupling of vinylic halides or triflates and cyclic alkenes. A wide variety of cyclic alkenes and vinylic substrates, including functionally substituted compounds, can be employed in this process. This chemistry has recently afforded a novel, extremely efficient approach to prostaglandins, which will be communicated shortly.

Acknowledgment. We gratefully acknowledge the National Institutes of Health (Grants GM 24254 and 40036) for their generous financial support and Johnson Matthey, Inc., and Kawaken Fine Chemicals Co., Ltd., for the palladium reagents.

Supplementary Material Available: Details of procedures A and B and spectroscopic data for entries in Table I (8 pages). Ordering information is given on any current masthead page.

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Received January 23, 1989