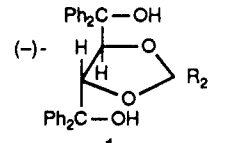
Table I. Enantioselective Wittig Reactions of Cyclohexanone Derivatives (4-6) in the 1:1 Inclusion Complex with Optically Active Hosts (1, 2)

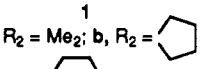
host	ketone	reaction conditions		product		
		reaction temp, °C	reaction temp, h		yield, %	optical purity,[a] % ee
1a	4a	70	4	5a	50.8	42.8
1b	4a	70	4	5a	73.0	42.3
1c	4a	80	4	5a	47.5	39.0
2	4a	70	4	5a	30.0	8.6
1b	4b	70	4	5b	72.5	45.2
1c	4b	80	4	5b	58.0	44.4
1c	6	80	2	7	58.0	56.9
2	6	80	8	7	28.1	5.5

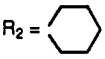
[a] All optical purities were determined by ^{1}H NMR analysis in $CDCl_3$ by using the chiral shift reagent, tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III), Eu(hfc)$_3$.[8]

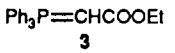
The absolute configuration of **5a** was determined to be *R*, because its hydrolysis gave the (*R*)-carboxylic acid derivative.[9]



1

a, $R_2 = Me_2$; b, R_2 = 

c, R_2 = 



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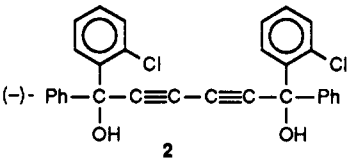

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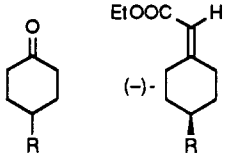
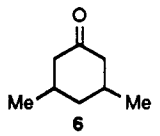


4 5

a, R = Me; b, R = Et



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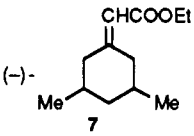

7

Although the host (−)-*trans*-3,5-bis(hydroxydiphenylmethyl)-2,2-dimethyl-1,3-dioxacyclopentane (**1a**)[10] and (−)-*trans*-2,3-bis(hydroxydiphenylmethyl)-1,4-dioxaspiro[5.4]decane (**1c**)[11] are also effective for the enantioselective Wittig–Horner reaction of **4a**, **2** is not effective (Table I). The enantioselective reaction is also applicable to 3-ethylcyclohexanone (**4a**) and 3,5-dimethylcyclohexanone (**6**), and (−)-4-ethyl-1-(carbethoxymethylene)cyclohexane (**5b**) and (−)-3,5-dimethyl-1-carbethoxymethylene)cyclohexane (**7**) were obtained, respectively (Table I). The optical purity of **5b** and **7** was also determined by measuring ^{1}H NMR spectra in the presence of Eu(hfc)$_3$.[12] The absolute configuration of **5b** was also determined to be *R*, but that of **7** was not determined. In the reactions of **4b** and **6**, **2** is again not effective (Table I). The enantioselectivity of the Wittig–Horner reaction is not very high; however, it may be valuable because the procedure is very simple.

To the best of our knowledge, only three enantioselective variants of the Wittig reaction have been reported. Tomoskoz and Janzso have reported that the reaction of **4a** with a Wittig reagent bearing an optically active substituent gives optically active 4-methyl-1-methylenecyclohexane of about 50% ee.[13] Bestmann and Lienert have reported that the reaction of **4a** with **3** in the presence of a chiral carboxylic acid gives optically active **5a** of less than 10% ee.[14] Hanessian and his co-workers have reported that the reaction of **4a** and its derivatives with optically active bicyclic phosphonamide reagents gives optically active cyclohexene derivatives of up to 90% ee.[15] In comparison with these precedents, our method using the host–guest inclusion compound is much simpler. Furthermore, our results suggest that the method is applicable to many other organic reactions.

Acknowledgment. We wish to thank the Ministry of Education, Science and Culture, Japan, for Grant-in-Aid for Scientific Research on Priority Areas, No. 63840017.

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(11) Toda, F.; Satō, A.; Tanaka, K.; Mak, T. C. W. *Chem. Lett.* **1989**, 873. Seebach, D.; Beck, A. K.; Imwinkelried, R.; Roggo, S.; Wonnacott, A. *Helv. Chim. Acta* **1987**, *70*, 954.
(12) The methylene proton signal of the carbethoxy group of **5b** and its (+)-enantiomer appeared at δ 3.72 and 3.78 ppm in $CDCl_3$, respectively, in the presence of 0.1 molar equiv of Eu(hfc)$_3$. The same signal of **7** and its (+)-enantiomer appeared at δ 4.81 and 4.86 ppm, respectively, under the same conditions.
(13) Tomoskoz, I.; Janzso, G. *Chem. Ind.* **1962**, 2085.
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Palladium-Catalyzed Heteroannulation of 1,3-Dienes by Functionally Substituted Aryl Halides

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Summary: Heteroatom-containing aryl iodides react with 1,3-dienes in the presence of a palladium catalyst and an appropriate base to afford a variety of oxygen and nitrogen heterocycles.

The ability to append a heteroatom-containing unit onto existing functionality (heteroannulation) is one of the most important routes to heterocyclic compounds. Many such palladium-based processes have recently been reported,[1]

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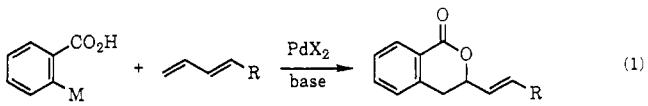
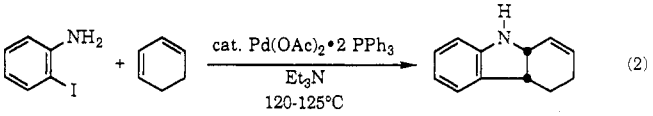
but few are general in scope. We recently disclosed very versatile palladium-based methodology for the heteroannulation of 1,3-dienes which employed arylmercury[2] or -thallium[3] intermediates (eq 1). The disadvantage of



(1)

M = HgX, TlX_2

having to prepare toxic aryl organometallics and in some cases employ stoichiometric amounts of expensive palladium salts encouraged us to seek improvements in this methodology. During the course of our work, Dieck and co-workers published analogous palladium-catalyzed annulation chemistry employing *o*-iodoaniline and two different 1,3-dienes (eq 2).[4] This approach suggested a



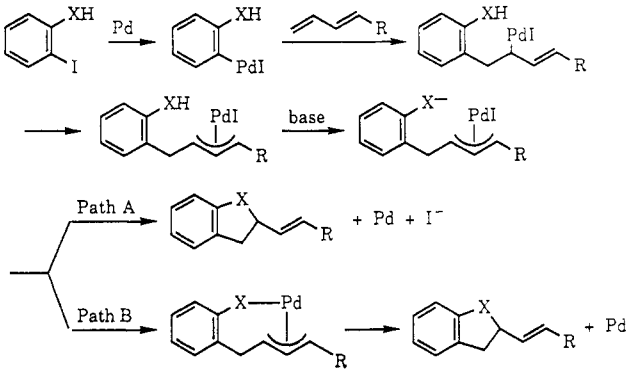
(2)

convenient solution to our problems. At this time we report our successful efforts to generalize this heteroannulation methodology to the synthesis of a wide variety of oxygen- and nitrogen-containing heterocycles.

In our initial work, we attempted to extend Dieck's basic procedure to a variety of other heterocyclic systems, but with very little success. We subsequently turned to a palladium catalyst system[5] with which we have recently had considerable success[6] [5% $Pd(OAc)_2$ or $Pd(dba)_2$, *n*-Bu_4NCl, DMF and 3.5 equiv of an appropriate base, with or without 5% PPh_3]. This approach to the heteroannulation of 1,3-dienes has proven very versatile as indicated by the results summarized in Table I.

In general, similar results are observed using either $Pd(OAc)_2$ or $Pd(dba)_2$ as the catalyst. The yield of heterocycle can vary significantly, however, with the base employed, with best results usually being obtained using either NaOAc or Na_2CO_3. We have recently observed a dramatic effect in the ability of palladium-catalyzed processes to accommodate functionality when adding 1 equiv of PPh_3 per palladium.[6f] Indeed, in some of our heteroannulation reactions, the addition of PPh_3 was observed to dramatically improve the yield. In others, the yield dropped upon addition of PPh_3. At present we have no rational explanation for this phenomenon.

Scheme I



A variety of functionally substituted aryl halides have been observed to undergo facile heteroannulation. The majority of our early work has been carried out on phenolic systems (entries 1–9), because of the prevalence of the dihydrobenzofuran products in nature.[7] The reaction of *o*-iodophenol and isoprene affords compound **1** in reasonable yield (entry 4), though a minor amount of a regioisomer is observed. The yield of dihydrofuran **1** is comparable to those of previous syntheses[8] of this compound, and our starting materials are more readily available. With phenols, it has been observed that those bearing electron-withdrawing groups generally afford higher yields of products and even sensitive functional groups, such as aldehydes and ketones, are accommodated (compare entries 1, 2, and 4 with 6, 5, and 7). Thus, the reaction of 3-iodo-4-hydroxyacetophenone and isoprene (entry 7) affords the most direct route to the toxic ketone **2**, previously isolated from "white snakeroot", and known as tremetone.[8a,b] Since many of the naturally occurring dihydrofurans bear an oxygen functionality in the side chain, we have examined the synthesis of allylic alcohol **3** (entry 8). Though the unoptimized yield of alcohol **3** was low, this is at present still the most direct approach to these oxygenated compounds.[8c,e] Finally, our synthesis of fomannoxin, **4** (entry 9), a known phytopathogen, is comparable in yield to previous syntheses[8c,e,9] and certainly more direct.

Other functionality is readily accommodated by our heteroannulation process. Benzylic alcohols can be employed (entry 10), though the displacement of π-allylpalladium intermediates by alcohols[2a,10] has not been terribly successful. Of particular note is the ease with which nitrogen-containing aryl halides undergo heteroannulation. While poor results have been obtained by us using *o*-iodoaniline itself, the addition of an acetyl group

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(5) For early work with this type of catalyst system, see: (a) Jeffery, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1287. (b) Jeffery, T. *Tetrahedron Lett.* **1985**, *26*, 2667. (c) Jeffery, T. *Synthesis* **1987**, 70.

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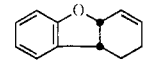
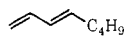
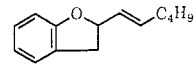
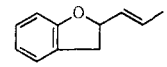
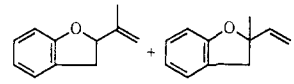
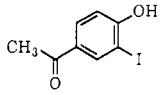
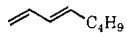
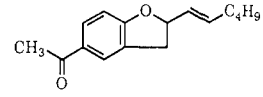
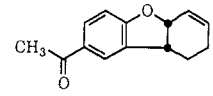
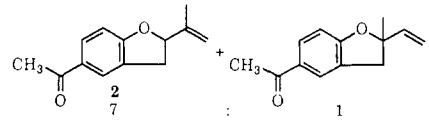
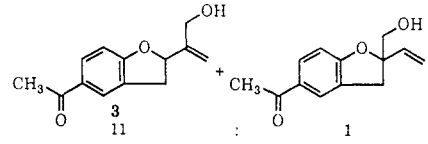
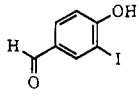
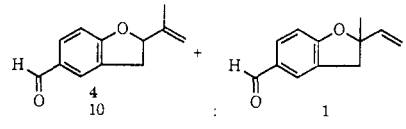
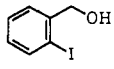
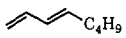
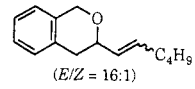
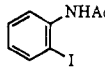
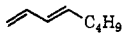
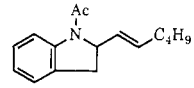
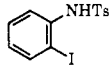
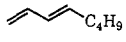
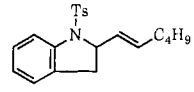
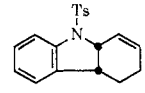
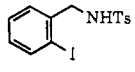
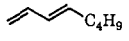
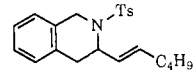
Table I. Palladium-Catalyzed Heteroannulation of 1,3-Dienes[a]

entry	aryl halide	1,3-diene	Pd catalyst	base	PPh_3	reaction conditions	product(s)[b]	% isolated yield
1			$Pd(dba)_2$	Na_2CO_3	-	100 °C, 1 day		44
2			$Pd(OAc)_2$	NaOAc	-	100 °C, 1 day		75
3			$Pd(OAc)_2$	NaOAc	-	100 °C, 1 day		68
4			$Pd(OAc)_2$	Na_2CO_3	-	100 °C, 1 day	 1 : 7	51
5			$Pd(OAc)_2$	NaOAc	-	100 °C, 2 days		53
6			$Pd(OAc)_2$	NaOAc	-	100 °C, 1 day		65
7			$Pd(dba)_2$	NaOAc	-	100 °C, 1 day	 2 : 7 : 1	83
8			$Pd(OAc)_2$	NaOAc	-	100 °C, 3 days	 3 : 11 : 1	24
9			$Pd(OAc)_2$	NaOAc	-	100 °C, 1 day	 4 : 10 : 1	43
10			$Pd(OAc)_2$	KOAc	+	80 °C, 1 day	 (E/Z = 16:1)	56
11			$Pd(OAc)_2$	Na_2CO_3	+	100 °C, 2 days		63
12			$Pd(OAc)_2$	Na_2CO_3	-	100 °C, 1 day		84
13			$Pd(dba)_2$	Na_2CO_3	-	100 °C, 2 days[c]		87
14			$Pd(OAc)_2$	Et_3N	+	80 °C, 2 days		81

[a] All reactions were run by heating 5% of the palladium catalyst with 1 equiv of the aryl iodide, 3.5 equiv of the base, 1 equiv of n-Bu_4NCl, 2 mL of DMF per mmol of aryl halide, 5% PPh_3 where appropriate, and 5 equiv of 1,3-diene at the indicated reaction temperature and time. [b] All products gave appropriate ^1H and ^{13}C NMR, IR, and mass spectral or elemental analysis data. [c] Reaction run in N,N-dimethylacetamide.

greatly facilitates annulation (entry 11), and excellent results have also been observed with tosyl amides (entries 12–14). The ease with which polycyclic nitrogen groups can be prepared in a single step bodes well for further applications of this methodology in alkaloid synthesis. It is particularly noteworthy that benzylic tosyl amides can be employed to form six-membered ring nitrogen heterocycles (entry 14) in view of the failure of Dieck's process to generate such ring systems.[4]

Our heteroannulation process has also proven quite general for a variety of 1,3-dienes. While best results have generally been achieved with less hindered terminal 1,3-dienes, such as 1,3-octadiene (entries 2, 5, 10–12, and 14), substituted systems such as isoprene (entries 4, 7, and 9) work nearly as well, and internal double bonds such as those present in 1,3-cyclohexadiene (entries 1, 6, and 13)

still afford good yields. It should be noted that *cis*-1,3-pentadiene produces exclusively the trans product (entry 3), consistent with the intermediacy of a syn π-allylpalladium intermediate (see the mechanistic discussion to follow). As noted earlier in entry 8, an allylic alcohol moiety can be accommodated by the process, though a substantial decrease in yield and increase in reaction time was noted.

Mechanistically, heteroannulation no doubt proceeds via intermediate aryl- and π-allylpalladium intermediates as depicted in Scheme I (additional ligands on palladium have been omitted for clarity). While it is impossible with acyclic dienes to tell if intramolecular palladium displacement is proceeding through direct back-side displacement (path A) or via front-side halide displacement and subsequent reductive elimination (path B), it is clear from the 1,3-cyclohexadiene-derived products (entries 1, 6, and 13) that at least where five-membered rings are formed, the latter process predominates.

In conclusion, the palladium-catalyzed heteroannulation of 1,3-dienes is readily effected by a variety of oxygen- and nitrogen-containing aromatic halides. The overall process holds considerable promise for the synthesis of natural products ranging from dihydrobenzofurans to alkaloids.

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

Supplementary Material Available: Physical and spectral data for new compounds (10 pages). Ordering information is given on any current masthead page.

A Mild Method for the Synthesis of Furans. Application to 2,5-Bridged Furano Macrocyclic Compounds

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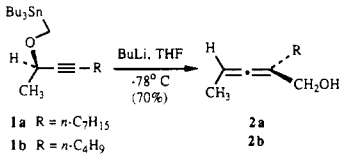
Summary: Upon treatment with $AgNO_3$ or $AgBF_4$ in acetonitrile, allenals **3a** and **3b** and allenones **6** and **8** afford furans **5**, **9**, **10**, and **11** in 72–99% yield. The cyclization is applicable to 2,5-bridged furanocembranoids as well.

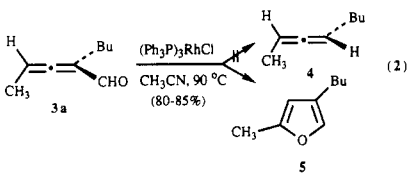
We recently described a stereospecific synthesis of optically active allenes through [2, 3]-Wittig rearrangement of nonracemic propargylic ethers (eq 1).[1] In our efforts



(1)

1a R = *n*-C_7H_{15}
1b R = *n*-C_4H_9 2a 2b

to ascertain the absolute stereochemistry of the allenic products **2** we prepared the formyl derivative **3a**, which we expected to decarbonylate under the influence of $(Ph_3P)_3RhCl$ to the disubstituted allene **4** of known configuration (eq 2).[2] Surprisingly, furan **5** was the sole

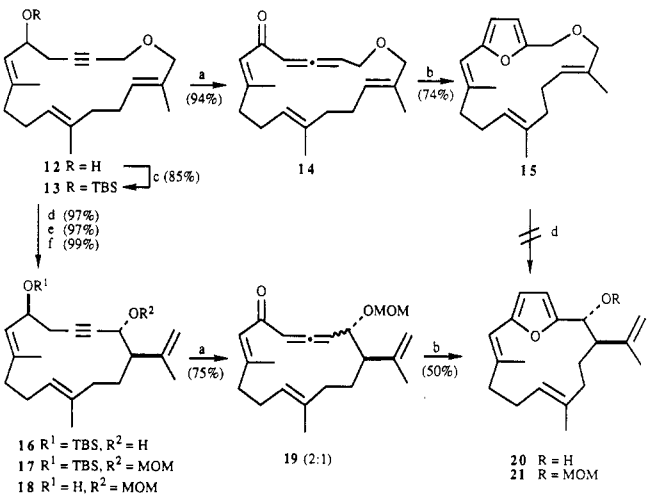


(2)

3a 4 5

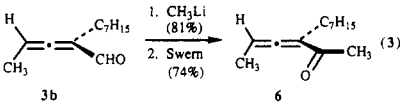
product isolated from the decarbonylation attempt. Furthermore, as little as 10 mol % of catalyst could be employed in this conversion. Assuming that Rh(I) was initiating the cyclization by coordination with the double bond, we briefly examined other π coordinating Lewis acids

Scheme I[a,b]



[a] (a) Dess–Martin periodinane reagent;[6] (b) $AgNO_3$, CH_3CN; (c) TBSCl, Et_3N, DMAP; (d) *n*-BuLi, THF–pentane; (e) MOMCl, CH_2Cl_2, *i*-Pr_2NEt; (f) TBAF, THF. [b] All compounds are racemic.

and found that $AgNO_3$ and $AgBF_4$ were also highly effective. Allenyl aldehyde **3b** and ketones **6** (eq 3) and **8**



(3)

3b 6

afforded furans **9**, **10** and **11** in high yield upon heating with these catalysts in acetonitrile (Table I).[3-5]

(1) Marshall, J. A.; Robinson, E. D.; Zapata, A. *J. Org. Chem.* **1989**, *54*, 5854.

(2) Cf.: Tsuji, J.; Okno, K. *Synthesis* **1969**, 157. Pirkle, W. H.; Boeder, C. W. *J. Org. Chem.* **1978**, *43*, 1950.

(3) A previous report describes the conversion of allenones to furans upon pyrolysis at 800 °C. Jullien, J.; Pechine, J. M.; Perey, F.; Piade, J. J. *Tetrahedron* **1982**, *38*, 1413. For leading references to furan synthesis and furanoid natural products, see: Danheiser, R. L.; Stoner, E. J.; Koyama, H.; Yamashita, D. S.; Klade, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 4407.

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