ometry than other routes (e.g., a Wadsworth–Emmons reaction on the mono dimethyl acetal of malondialdehyde). Reduction of the enal **4** gave the allylic alcohol **5** in 87% crude yield (70% after chromatography).[6] The chirality necessary for the final product was introduced by a Sharpless epoxidation, namely, treatment of **5** with D-(−)-diisopropyl tartrate, *tert*-butyl hydroperoxide, and titanium tetraisopropoxide at −20 °C for 2 days to afford, after workup and chromatography, the desired epoxy alcohol **6** in 74% yield.[7] The optical purity of **6** was shown by examination of the ^{1}H NMR of the Mosher ester to be >95% ee (the corresponding ester of racemic **6** was prepared for comparison). The key step of this synthesis involves the regioselective opening of the epoxy alcohol **6** with azide. After much experimentation with a wide variety of reagents and conditions,[8-10] we found that diethylaluminum fluoride[11] cleanly promoted the desired regioselective opening of **6** with trimethylsilyl azide to furnish, after quenching with bicarbonate and chromatography, the desired azido diol **7** in 64% yield. We see no evidence for the production of any of the opposite regioisomer in this reaction, although not all of the material can be accounted for. With the two non-anomeric stereocenters set, all that remained in the synthesis was to cyclize to the methyl furanoside and attach the thymine base. Cyclization was accomplished quite easily by stirring a mixture of the azido diol **7** in dichloromethane with a few drops of 1.5% HCl in aqueous methanol for 5 min at 23 °C to give, after silica gel chromatography, the desired methyl furanoside **8** as a mixture of α and β anomers in 81% yield.[12] These anomers could be separated by further chromatography or preparative TLC and their ^{1}H NMR and ^{13}C NMR spectra matched the published data.[3i] Silylation of the alcohol **8** under standard conditions gave the *tert*-butyldiphenylsilyl (TPS) ether **9** in 90% yield. The final attachment of the base has already been carried out by Fleet,[3i] namely, Vorbrüggen coupling[13] of **9** with bis(trimethylsilyl)thymine and treatment with fluoride to give, after flash chromatographic separation, D-AZT (**1**) (32%) and its α-epimer **10** (29%). This ends a nine-step synthesis of optically pure D-AZT (**1**) from crotonaldehyde, which should be applicable for the production of other 3′-substituted 2′,3′-dideoxynucleosides (via addition of other nucleophiles to **6**) as well as 2′,3′-dideoxynucleosides (via regioselective reduction of **6**).[14]

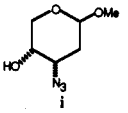
Since the asymmetry is introduced from an external chiral catalyst or promoter, one can prepare the enantiomeric series as well. Epoxidation of **5** using L-(+)-diisopropyl tartrate gave the enantiomer of **6** in comparable yield and purity. This epoxy alcohol was converted via the identical sequence of steps into the enantiomer of **9**. L-AZT should be readily available from this methyl L-furanoside by the standard Vorbrüggen coupling. This route to L nucleosides may be of use in the preparation of substrates for antisense oligonucleotide therapy.[15]

We have thus synthesized the important antiviral agent D-AZT (**1**) from crotonaldehyde (**2**) by a route that should be general enough for the preparation of analogues and that should allow the preparation of the enantiomeric series as well from the same starting material.

Acknowledgment. We thank the National Institutes of Health (AI-26692) for their generous support.

Supplementary Material Available: Experimental details and compound characterization data for compounds prepared (6 pages). Ordering information is given on any current masthead page.

(6) Hughes, P.; Clardy, J. *J. Org. Chem.* **1989**, *54*, 3260.
(7) We have only used the stoichiometric version of the Sharpless asymmetric epoxidation procedure and have not attempted to carry out this reaction by the catalytic procedure.
(8) For example, treatment of **6** with trimethylsilyl azide and titanium tetraisopropoxide under the normal conditions[9] for nucleophilic opening of an epoxy alcohol gave the corresponding trimethylsilyl ether of **6** as the major product in only moderate yield (50–67%). Use of diazido titanium diisopropoxide[9,10] as the catalyst in refluxing benzene gave the desired azido diol **7** in poor yield again along with the trimethylsilyl ether of **6** as the major product.
(9) Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1560.
(10) (a) Choukroun, R.; Gervais, D. *J. Chem. Soc., Dalton Trans.* **1980**, 1800. (b) Blandy, C.; Choukroun, R.; Gervais, D. *Tetrahedron Lett.* **1983**, *24*, 4189.
(11) Maruoka, K.; Sano, H.; Yamamoto, H. *Chem. Lett.* **1985**, 599.
(12) Treatment of a more concentrated solution of **7** under similar conditions leads mainly to the methyl pyranoside i rather than **8** for as yet unknown reasons. Isomerization of i into **8** is also possible under acidic conditions.



i

(13) (a) For other examples of this coupling to give AZT, see: Dyatkina, N. B.; Kraevskii, A. A.; Azhaev, A. V. *Bioorg. Khim.* **1986**, *12*, 1048. (b) Reference 3h.
(14) We have not yet examined in a systematic way the addition of other nucleophiles to the epoxy alcohol **6** but based on the Sharpless work,[9] we would expect nucleophiles to add well. We have carried out the reduction of **6** with DIBAL, which gave in about 60% yield a mixture of regioisomers in which the desired 5,5-dimethoxypentane-1,2-diol was the major isomer. We are currently studying the conversion of this compound into 2′,3′-dideoxynucleosides.
(15) For reviews, see: (a) Miller, P. S.; Ts'O; P. O. *Ann. Rep. Med. Chem.* **1988**, *23*, 295. (b) Uhlmann, E.; Peyman, A. *Chem. Rev.* **1990**, *90*, 543. (c) For a specific example of the use of enantio-DNA, see: Fujimori, S.; Shudo, K.; Hashimoto, Y. *J. Am. Chem. Soc.* **1990**, *112*, 7436.

Regioselective, Palladium-Catalyzed Hetero- and Carboannulation of 1,2-Dienes Using Functionally Substituted Aryl Halides

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Received January 18, 1991

Summary: Aryl halides bearing heteroatom- or potential carbanion-containing functionality in the ortho position react regioselectively with 1,2-dienes in the presence of a palladium catalyst and a carbonate base to afford five- and six-membered ring hetero- and carbocycles in high yield.

Annulation processes are among the most important reactions in organic chemistry.[1] Few, however, have

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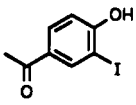
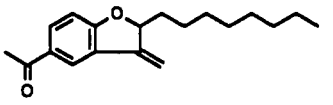
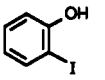
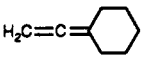
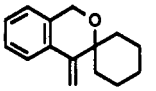
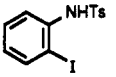
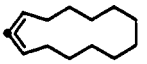
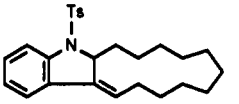
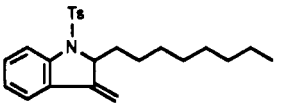
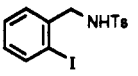
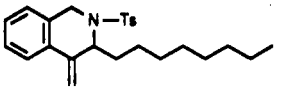
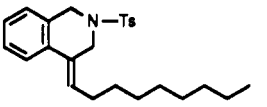
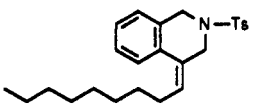
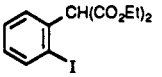
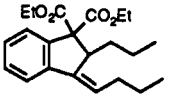
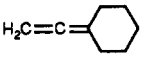
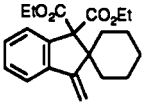
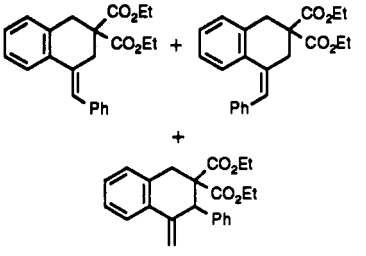
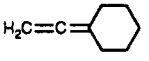
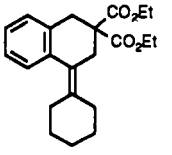
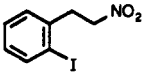
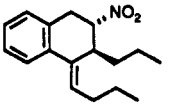
Table I. Palladium-Catalyzed Annulation of 1,2-Dienes[a]

entry	aryl halide	1,2-diene	base	reaction conditions	product(s)[b]	% isolated yield (ratio)
1		n-$C_8H_{17}CH{=}C{=}CH_2$	K_2CO_3	100 °C, 1 day		71
2			Na_2CO_3	100 °C, 2 days		63
3			Na_2CO_3	100 °C, 2 days		83
4		n-$C_8H_{17}CH{=}C{=}CH_2$	Na_2CO_3	100 °C, 1 day		85
5		n-$C_8H_{17}CH{=}C{=}CH_2$	Na_2CO_3	100 °C, 1 day	 **1** +  **2** +  **3**	87 (44:36:20)
6		n-$C_3H_7CH{=}C{=}CH$-n-C_3H_7	Na_2CO_3	80 °C, 2 days		86
7			Na_2CO_3	80 °C, 2 days		82
8		$H_2C{=}C{=}CHPh$	Na_2CO_3	80 °C, 6 days		93 (54:35:11)
9			Na_2CO_3	80 °C, 2 days		87
10		n-$C_3H_7CH{=}C{=}CH$-n-C_3H_7	Li_2CO_3	80 °C, 2 days		86

[a] All reactions were run by heating 5% palladium acetate and PPh_3, 1 equiv of aryl iodide and n-Bu_4NCl, 5 equiv of 1,2-diene, and 3 (heteroannulation) or 5 (carboannulation) equivs of base in DMF (1 mL/0.50 mmol of aryl iodide for heteroannulation and 1 mL/0.25 mmol for carboannulation). [b] All products gave appropriate ^1H and ^{13}C NMR, IR and mass spectral or elemental analysis data.

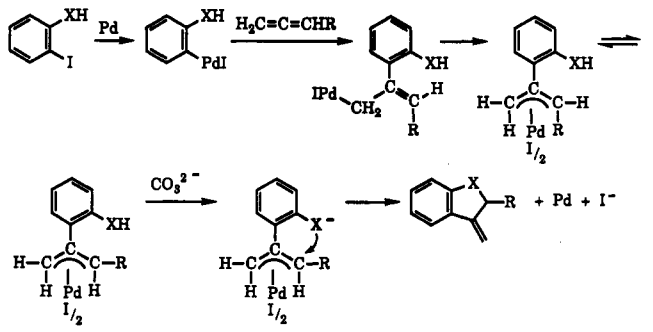
proven very general in scope. We and others have recently reported palladium-catalyzed methodology that allowed the facile hetero- and carboannulation of 1,3-dienes[2-4] and vinylic cyclopropanes or cyclobutanes.[5] We report here the success of this same methodology for the regioselective

(1) For a general review, see: Jung, M. E. *Tetrahedron* **1976**, *32*, 3.

(2) Larock, R. C.; Berrios-Peña, N.; Narayanan, K. *J. Org. Chem.* **1990**, *55*, 3447.

(3) Larock, R. C.; Fried, C. A. *J. Am. Chem. Soc.* **1990**, *112*, 5882.

Scheme I



annulation of 1,2-dienes. Our results are summarized in Table I.

A variety of reaction conditions have been examined, and some variations in our earlier procedures have proven desirable. In the annulation of 1,2-dienes, best results have been obtained with use of carbonate bases and catalytic amounts of PPh_3. Heteroannulation can usually best be effected by running the reactions at 100 °C, while carboannulation is best carried out at the lowest temperature at which reaction occurs in a convenient period of time. Functionally substituted aryl halides with substituents as diverse as phenols, alcohols, tosyl amides, malonates, and nitro groups can effect annulation in high yield. Acyclic, cyclic, terminal, and internal 1,2-dienes have all been successfully employed in this annulation process with little variation in yield.

The regioselectivity of this annulation process is generally very high. Indeed, with most unsymmetrically substituted 1,2-dienes, only one regioisomer is observed. Several factors appear to play an important role in determining the regioselectivity. The formation of five-membered rings involves exclusive annulation across the more highly substituted carbon–carbon double bond (entries 1, 4, and 7). Even carbanions, which generally undergo intermolecular π-allylpalladium attack at the less substituted termini, afford exclusively the products of attack at the more substituted end of the 1,2-diene when a five-membered ring is formed. On the other hand, six-membered rings are generally formed by annulation primarily across the less substituted carbon–carbon double bond (entries 5, 8, and 9), although exceptions have been observed (entry 2). Clearly, the nature of the functional group plays an important role as well. Only six-membered ring formation using monosubstituted 1,2-dienes (entries 5 and 8) leads to mixtures of regioisomers. This annulation process offers an exciting new way to generate quaternary carbon centers, even adjacent quaternary centers (entry 7).[6]

These reactions most likely proceed as illustrated in Scheme I. The addition of arylpalladium compounds to 1,2-dienes is known to produce π-allylpalladium compounds.[7] Subsequent intermolecular nucleophilic substitution has been reported.[7a–f] Related intramolecular processes employing aryl or vinylic halides and allenic malonates,[7g,h] or ortho-thallated benzoic acids plus simple allenes[7i] are known. The occasional formation (entries 5 and 8) of mixtures of stereoisomers is presumably due to the generation of both syn and anti π-allylpalladium intermediates.

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 acetate.

Supplementary Material Available: General procedures for the annulation reactions and experimental data (^1H and ^{13}C NMR, IR, elemental analyses, and exact mass spectra) for all products shown in Table I (7 pages). Ordering information is given on any current masthead page.

(4) O'Connor, J. M.; Stallman, B. J.; Clark, W. G.; Shu, A. Y. L.; Spada, R. E.; Stevenson, T. M.; Dieck, H. A. *J. Org. Chem.* **1983**, *48*, 807.
(5) Larock, R. C.; Yum, E. K. *Synlett* **1990**, 529.
(6) Krief, A.; Barbeaux, P. *Synlett* **1990**, 511.
(7) (a) Shimizu, I.; Tsuji, J. *Chem. Lett.* **1984**, 233. (b) Ahmar, M.; Cazes, B.; Gore, J. *Tetrahedron Lett.* **1984**, *25*, 4505. (c) Ahmar, M.; Barieux, J.-J.; Cazes, B.; Gore, J. *Tetrahedron* **1987**, *43*, 513. (d) Cazes, B.; Colovray, V.; Gore, J. *Tetrahedron Lett.* **1988**, *29*, 627. (e) Friess, B.; Cazes, B.; Gore, J. *Tetrahedron Lett.* **1988**, *29*, 4089. (f) Kopola, N.; Friess, B.; Cazes, B.; Gore, J. *Tetrahedron Lett.* **1989**, *30*, 3963. (g) Ahmar, M.; Cazes, B.; Gore, J. *Tetrahedron Lett.* **1985**, *26*, 3795. (h) Ahmar, M.; Cazes, B.; Gore, J. *Tetrahedron* **1987**, *43*, 3453. (i) Larock, R. C.; Varaprath, S.; Lau, H. H.; Fellows, C. A. *J. Am. Chem. Soc.* **1984**, *106*, 5274. (j) Shimizu, I.; Sugiura, T.; Tsuji, J. *J. Org. Chem.* **1985**, *50*, 537.

A Novel Concept for Regiochemical and Stereochemical Control in Lewis Acid Promoted [3 + 4] Annulation Reactions

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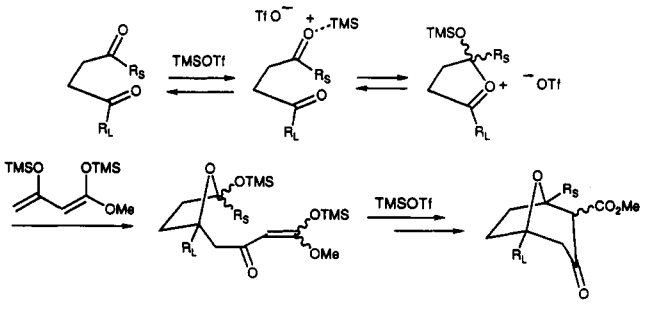
Received January 30, 1991

Summary: Studies on the regioselective and stereoselective formation of a variety of 2-carbalkoxy-8-oxabicyclo-[3.2.1]octan-3-ones by means of a Lewis acid promoted [3 + 4] annulation process leads to a novel concept for selectivity in Lewis acid promoted carbonyl addition reactions.

Development of general annulation strategies for the construction of stereodefined medium-sized carbocycles possessing variable substitution patterns remains a considerable challenge in organic synthesis.[2] Recently, we reported a [3 + 4] annulation process that allowed access to functionalized, unsymmetrical seven- and eight-mem-

Scheme I



(1) Alfred P. Sloan Foundation Fellow, 1987–1991; American Cyanamid Academic Awardee, 1989.

0022-3263/91/1956-2617$02.50/0