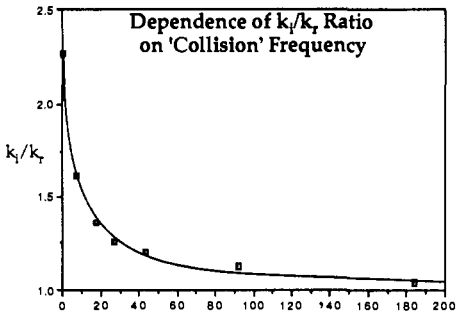

	trans-Decalin		*cis*-Decalin		Dibenzyl ether	
	T °C	k_i/k_r	T °C	k_i/k_r	T °C	k_i/k_r
	129.7	1.96±0.10	129.7	1.73±0.13	130.8	1.69±0.07
	140.2	2.05±0.06	140.2	1.79±0.05	140.0	1.77±0.14
	149.8	2.12±0.11	150.3	1.70±0.12	150.5	1.61±0.37
	161.8	2.06±0.09	161.8	1.88±0.07	159.8	1.66±0.06
	170.5	2.03±0.09	170.5	1.80±0.12	170.1	1.77±0.34
	186.5	2.22±0.22	180.3	1.76±0.13	176.0	1.76±0.13
					182.5	1.71±0.28
$\Delta\Delta H^{\ddagger}$		0.56±0.38		0.24±0.24		0.16±0.23
F		0.859		0.821		0.836
F_0		0.800		0.800		0.833

Figure 3. Theoretical (graph) and experimental (table) results for the reaction run in solution. See ref 4 for the explanation of $\Delta\Delta H^{\ddagger}$, F, and F_0.

fair, reproducing the preference for inversion and the lack of temperature dependence of k_i/k_r (within our experimental error) but not fitting the observed ratio quantitatively. The preference for inversion was found to be due to the planarization at the carbon to which nitrogen is attached, as the nitrogen departs from the diazenyl biradical. This set of atomic motions favors trajectories leading from the transition state to **2x** because of the requirement for conservation of momentum.[6]

The effect of running the reaction in solution was simulated by adding a randomizing component to the trajectories, in the form of pseudocollisions with an adjustable average frequency. The k_i/k_r ratio was calculated for a range of frequencies of these "collisions" (graph in Figure 3). This simulation suggested that, while a reduction in the k_i/k_r value should be expected for reactions in solution, impossibly high "collision" frequencies would be needed to erase the preference for inversion completely.

Experimentally k_i/k_r was determined in three solvents. Reasonable agreement with the theoretical expectations was found (table in Figure 3).

The difference in k_i/k_r between *cis*- and *trans*-decalin is significant within a 97% confidence interval (one-way ANOVA test[7]). We hypothesize that, since vibrational energy exchange in polyatomic liquids appears to occur primarily by a V–V mechanism,[8] the lower ratio in *cis*-decalin might reflect the higher density of vibrational states available in a solvent consisting of more flexible molecules with larger numbers of low-frequency vibrations.[9]

In summary, the combined application of theoretical and experimental techniques appears to favor a dynamic explanation for the stereochemical preference in the title reaction. The resulting picture is quite similar to that proposed by Freeman, Pucci, and Binsch for a related reaction.[10]

(5) Relative potential energies for the key species were assumed to be equal to relative heats of formation, which came from the following: (i) Turner, B. B.; Goebel, P.; Mallon, B. J.; Doering, W. von E.; Coburn, J. F.; Pomerantz, M. *J. Am. Chem. Soc.* **1968**, *90*, 4315. (ii) Reference 3. (iii) Engel, P. S. *Chem. Rev.* **1980**, *80*, 99. (iv) Engel, P. S.; Wood, J. L.; Sweet, J. A.; Margrave, J. L. *J. Am. Chem. Soc.* **1974**, *96*, 2381. (v) Adam, W.; Oppenländer, T.; Zang, G. *J. Org. Chem.* **1985**, *50*, 3033. Other points were determined by AM1 calculation (Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902) or Benson group additivity (Benson, S. W. *Thermochemical Kinetics*, 2nd ed.; Wiley-Interscience: New York, 1976). A polynomial interpolation function was used.

(6) (a) Carpenter, B. K. *J. Am. Chem. Soc.* **1985**, *107*, 5730. (b) Newman-Evans, R. H.; Simon, R. J.; Carpenter, B. K. *J. Org. Chem.* **1990**, *55*, 695.

(7) Miller, J. C.; Miller, J. N. *Statistics for Analytical Chemistry*, 2nd ed.; Ellis Horwood Ltd.: Chichester, 1988.

(8) Oxtoby, D. W. *Adv. Chem. Phys.* **1981**, *47* (*part 2*), 487 and references therein.

(9) The dependence of the ratio of exo:endo products on the reaction medium has been seen previously (Oslowski, H. J., dissertation, Ruhr-Universität, Bochum, 1984) but the k_i/k_r ratio could not be determined from this work since no correction for epimerization of the products was applied.

(10) Freeman, J. P.; Pucci, D. G.; Binsch, G. *J. Org. Chem.* **1972**, *37*, 1894.

A Selectivity Control Element for Palladium-Catalyzed Trimethylenemethane Cycloaddition

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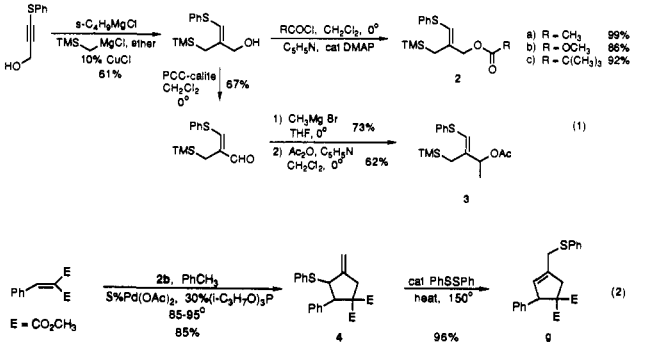
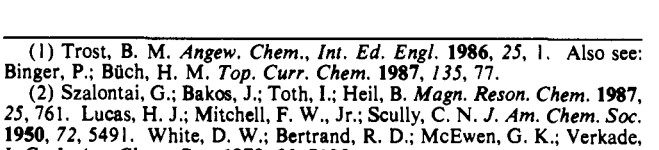
The utility of synthetic reactions depends upon the ability to direct formation of a desired regio- and diastereoisomer. Introduction of such control in Pd-catalyzed trimethylenemethane (TMM) [3 + 2], [4 + 3], and [6 + 3] cycloadditions will expand their utility in general ring-construction methodology.[1] We record that, contrary to the expectation that a sulfur substituent will be a catalyst poison, a phenylthio group serves as an effective selectivity control element especially when used with 2,4-bis[(4,6-dimethyl-1,3,2-dioxaphosphorinan-2-yl)oxy]pentane (**1**)[2] as an exceptional new ligand.

The requisite bifunctional conjunctive reagents are prepared as outlined in eq 1.[3,4] For the carbacuprations, use of the chloride salts and ether as solvent proves important. Equations 2–6 illustrate a cycloaddition with each major class of acceptor.[5–9] The





(1) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1. Also see: Binger, P.; Büch, H. M. *Top. Curr. Chem.* **1987**, *135*, 77.

(2) Szalontai, G.; Bakos, J.; Toth, I.; Heil, B. *Magn. Reson. Chem.* **1987**, *25*, 761. Lucas, H. J.; Mitchell, F. W., Jr.; Scully, C. N. *J. Am. Chem. Soc.* **1950**, *72*, 5491. White, D. W.; Bertrand, R. D.; McEwen, G. K.; Verkade, J. G. *J. Am. Chem. Soc.* **1970**, *92*, 7125.

(3) Cutting, I.; Parsons, P. J. *J. Chem. Soc., Chem. Commun.* **1983**, 1209.

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(5) For enoates, etc., see: Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1983**, *105*, 2315.

(6) For aldehydes, see: Trost, B. M.; King, S. A.; Schmidt, T. *J. Am. Chem. Soc.* **1989**, *111*, 5902.

(7) For imines: Marrs, C., unpublished observations in these laboratories.

(8) For pyrones, see: Trost, B. M.; Schneider, S. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 213.

(9) For tropones, see: Trost, B. M.; Seoane, P. R. *J. Am. Chem. Soc.* **1987**, *109*, 615.

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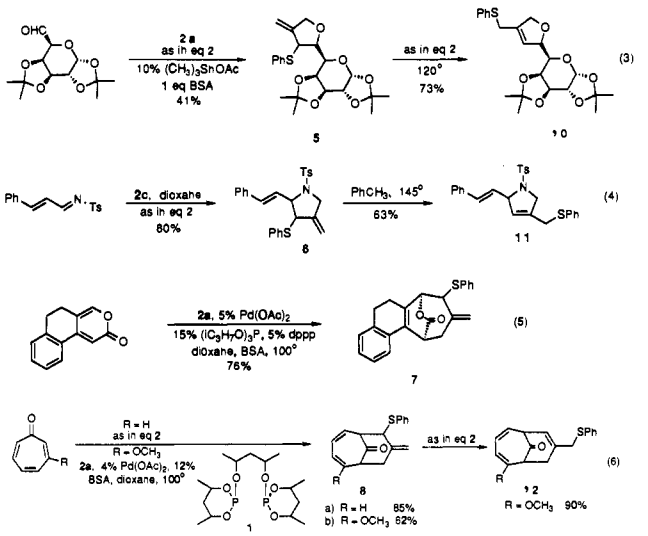
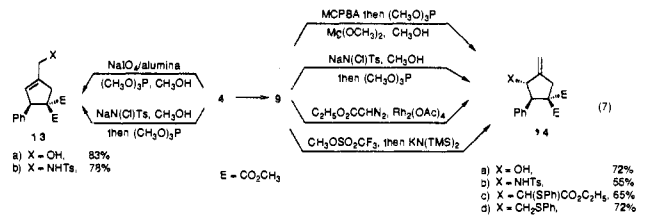
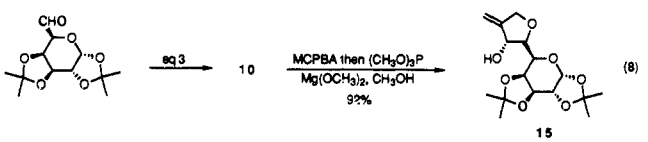


aldehyde acceptor requires a tin cocatalyst (eq 3).[6] The extreme sensitivity of the bifunctional conjunctive reagent under the reaction conditions frequently required introduction of *O,N*-bis(trimethylsilyl)acetamide (BSA). Most noteworthy, the ligand choice proves critical. While triisopropyl phosphite proves most general,[10] the pyrone acceptor requires a stronger donor ligand, dppp (eq 5). The tropone acceptor (R = OCH_3) requires the introduction of a new bidentate phosphite **1**, a ligand which subsequently proved to be more generally efficacious (vide infra).

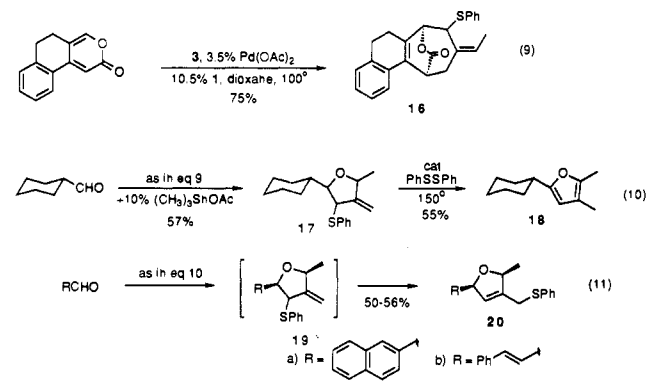
Accessibility to the allylically related thermodynamically more stable sulfides derives from a surprisingly facile 1,3-sulfide shift thermally (eq 4) or, better, catalyzed by diphenyl disulfide (eqs 2, 3, and 6).[11] The availability of both allylic sulfides can be used to transform these cycloadducts into a wide array of both regio- and diastereoselective substitution products (eq 7).[12-15] In each



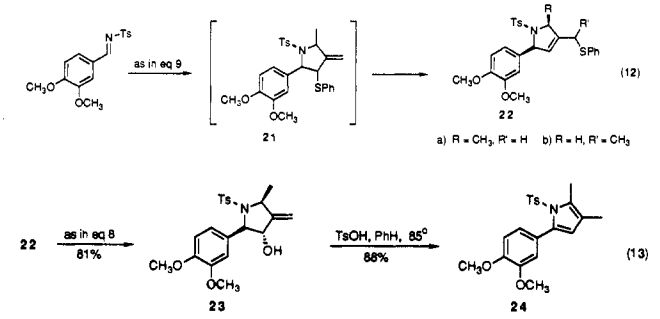
case, adduct **14** is isolated as a single diastereomer assigned as *E*. The assignment of **14a** as *E* is confirmed by preparation of the epimeric alcohol by oxidation [$(COCl_2)_2$, DMSO, $(C_2H_5)_3N$, CH_2Cl_2, 100%] and reduction [$NaBH_4$, $CeCl_3$, CH_3OH, 64%]. Metamorphosis of the sulfide **10** into its allylically rearranged alcohol **15** represents a useful carbohydrate homologation for ionophore synthesis (eq 8).



The phenylthio group functions as a regioselectivity control element even in the cycloadditions of disubstituted conjunctive reagents which contain opposing directing substituents as in **3** (eqs 9–11).[16] In each case, initial bond formation occurs between the



electrophilic terminus of the acceptor and the sulfide bearing carbon of the TMM intermediate.[17] The final disposition of the methyl substituent is a result of the conflict between the steric demands of the nucleophilic terminus of the acceptor (eq 9) and the electronic bias for attack at the less electron rich allyl terminus of the intermediate π-allylpalladium complex (eqs 10–12). *All cycloadditions of substrate 3 require the special bidentate phosphite ligand 1.* The aldehyde adduct **17** eliminates the elements of thiophenol on attempted allyl rearrangement, the overall process becoming a cycloaddition approach to furans (eq 10). On the other hand, the kinetic adduct **19** from cinnamaldehyde undergoes sulfide shift during cycloaddition to give cycloadduct **20** in a 9.6:1 diastereomeric ratio in which the major isomer is assigned as *Z* on the basis of NOE experiments (eq 11). A similar sulfide shift accompanied cycloaddition to the imine acceptor to give the *Z* cycloadduct **22a** contaminated with a minor amount of the regioisomer **22b** (eq 12). Equation 13 illustrates the utility of this cycloadduct in terms of a synthesis of the allyl alcohol **23**, a pyrrolidine related to the antihypotensive agent codonopsine,[18] and a pyrrole synthesis (i.e., **24**).



The compatibility of a phenylthio substituent with Pd-catalyzed TMM cycloaddition opens a new chapter. This substituent dominates the regioselectivity even in bifunctional conjunctive reagents possessing opposing directing substituents. The availability of [2,3] sigmatropic rearrangements permits conversion of the C–S bond into C–O, C–N, and C–C bonds regioselectively. The development of a novel 1,3-allyl transposition of the phenylthio group combines with the [2,3] sigmatropic rearrangement chemistry to create a regio- and diastereoselective approach to a new series of heavily substituted five-, seven-, and nine-membered carbo- and heterocycles that are not accessible by direct cyclo-

(10) Trost, B. M.; Nanninga, T. N. *J. Am. Chem. Soc.* **1985**, *107*, 1293. Trost, B. M.; Renaut, P. *J. Am. Chem. Soc.* **1982**, *104*, 6668.

(11) (a) Cf.: Baechler, R. D.; Bentley, P.; Deuring, L.; Fisk, S. *Tetrahedron Lett.* **1982**, *23*, 2269. Kwart, H.; Johnson, N. A. *J. Am. Chem. Soc.* **1977**, *99*, 3441; *J. Org. Chem.* **1977**, *42*, 2855. (b) Performed by forming an ethereal solution of substrate and diphenyl disulfide, evaporating the solvent, and heating the resulting film.

(12) X = OH: Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 563. Evans, D. A.; Andrews, G. C. *Acc. Chem. Res.* **1974**, *7*, 147.

(13) X = NHTs: Kakimoto, M.; Yamamoto, T.; Okawara, M. *Tetrahedron Lett.* **1979**, 623. Ash, A. S. F.; Challenger, F. *J. Chem. Soc.* **1952**, 2792.

(14) X = $CH(SPh)CO_2C_2H_5$: Davies, H.; Crisco, L. *Tetrahedron Lett.* **1987**, 371. Doyle, M.; Griffin, J.; Chin, M.; vanLeusen, D. *J. Org. Chem.* **1984**, *49*, 1917. Also see ref 15.

(15) X = CH_2SPh: Trost, B. M.; Melvin, L. S., Jr. *Sulfur Ylides. Emerging Synthetic Intermediates*; Academic Press: New York, 1975; Chapter 7.

(16) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1981**, *103*, 5972. Gordon, D. J.; Fenske, R. F.; Nanninga, T. N.; Trost, B. M. *J. Am. Chem. Soc.* **1981**, *103*, 5974.

(17) Trost, B. M.; Miller, M. L. *J. Am. Chem. Soc.* **1988**, *110*, 3687.

(18) Khanov, M. T.; Sultanov, M. B.; Egorova, T. A. *Farmakol. Alkaloidov Serdechnykh Glikozidov* **1971**, 210; *Chem. Abstr.* **1972**, *77*, 135091r. Wang, C.-L. J.; Calabrese, J. C. *J. Org. Chem.* **1991**, *56*, 4341.

addition chemistry. The development of a bidentate phosphite ligand permits successful cycloadditions that otherwise fail and, as such, enlarges significantly the utility of this methodology.

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health, General Medical Sciences Institute, for their generous support of our programs. Mass spectra were provided by the Mass Spectrometry Facility, University of California—San Francisco, supported by the NIH Division of Research Resources.

Supplementary Material Available: Characterization of **2–4**, **6–17**, **20**, **23**, and **24** (6 pages). Ordering information is given on any current masthead page.

Additions and Corrections

Olefin Formation in the Oxidative Deformylation of Aldehydes by Cytochrome P-450. Mechanistic Implications for Catalysis by Oxygen-Derived Peroxide [*J. Am. Chem. Soc.* **1991**, *113*, 5886–5887]. ALFIN D. N. VAZ,* ELIZABETH S. ROBERTS, and MINOR J. COON

The following information was inadvertently omitted during publication: formate, the product formed in the decarbonylation of cyclohexanecarboxaldehyde along with cyclohexene by cytochrome P-450, was derivatized as the *p*-nitrobenzyl ester and identified by mass spectrometry.

Palladium-Mediated Stereocontrolled Reductive Amination of Azido Sugars Prepared from Enzymatic Aldol Condensation: A General Approach to the Synthesis of Deoxy Aza Sugars [*J. Am. Chem. Soc.* **1991**, *113*, 6678]. TETSUYA KAJIMOTO, LIHREN CHEN, KEVIN K. K.-C. LIU, and CHI-HUEY WONG*

The configuration at C-3 of compound **4b** should be inverted. Compound **1b** should have the inverted configuration at the corresponding carbon. This compound was prepared from Fuc-1-P aldolase instead of Rham-1-P aldolase.

*Book Reviews**

The Alkaloids, Chemistry and Pharmacology. Volume 39. Edited by A. Brossi (National Institutes of Health). Academic Press, Inc.: San Diego, CA. 1991. xi + 364 pp. $95.00. ISBN 012-469539-6.

The first extremely well written chapter on the betalains was prepared by W. Steglich and D. Strack. The betalains have, of course, received attention by the food industry for use as nonmutagenic color additives. The present chapter highlights recent findings in the area, critically surveying the present state of betaiain chemistry and describing the distribution of betalains in plants. The chapter is replete with an interesting compilation of isolation methods, chemical degradations, spectroscopic details, reaction mechanisms, and biological facts. An encyclopedic listing of the individual pigments is provided in Part B of this chapter, while synthesis, chemotaxonomy, and biosynthesis are found in the latter sections.

The second chapter, by W. Ross, provides a description of the biogenic benzodiazepine alkaloids. These natural compounds are to be contrasted in terms of biological activity with their synthetic relatives, which possess tranquilizing properties. Structure elucidation, biosynthesis, metabolic conversion to quinolines, physiological aspects, and biological activity are covered. Interestingly, of the various members of this family, only asperlicin and specifically analogues of it appear to hold promise as pharmacological agents. This chapter is again extremely rich in detail.

Chapter 3, by L. Castedo and G. Tojo, concerns a class of alkaloids that lacks a nitrogen heterocycle, the phenanthrene alkaloids. An encyclopedic listing of members of this family together with spectral data make up about 20 pages of the chapter. The synthesis of these compounds is considered next and provides some interesting transformations. The pharmacology of these compounds is covered in one single (the last) page of the chapter.

The vegetable drug khat, which is chewed by habitants of several countries for its stimulant properties, is covered in Chapter 4, prepared by L. Crombie, W. M. L. Crombie, and D. A. Whiting. The synthesis and pharmacology of the khatamines are covered first, then the more complex structures, the cathedulin alkaloids, and synthetic work relevant to these alkaloids is detailed next. The chapter is succinct and ends abruptly.

As stated by the authors, H. Hashimoto, K. Kawanishi, and M. Ichimaru, Chapter 5 reviews biological and biochemical investigations of plants from five families using histochemical and other techniques. The authors also describe their apparatus used for histochemical chromatography and its application to plant and animal tissues. While interesting, this particular chapter seems somewhat out of sync with the foregoing ones, especially in view of the more chemical orientation of the earlier chapters. It would seem that this chapter should have been located at the end of the volume or perhaps better published together with like chapters in a separate volume.

Chapter 6, by S. Blechert and D. Guenard, focuses on the structure and isolation of the taxus alkaloids and updates the earlier review of Suffness and Cordell published in Volume 25 of *The Alkaloids*. Major portions of the chapter are devoted to semisynthesis protocols for producing taxol analogues, as well as synthetic efforts aimed toward constructing the tricyclic taxane framework in the laboratory. Total synthesis in this area is, of course, a difficult feat to achieve in view of both the unusual ring system and complex functionality present in the taxanes. The potential of taxol in the treatment of solid tumors and adult leukemia will undoubtedly lead to continued synthetic pursuits. The problems of obtaining adequate supplies of the compound from the yew tree is discussed in the pharmacology section of the chapter.

The last chapter, by G. W. Gribble, concerns the ellipticine alkaloids and related materials and also updates a chapter appearing in Volume

*Unsigned book reviews are by the Book Review Editor.